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IN THE UNITED STATES DISTRICT COURT
DISTRICT OF ALASKA

UNITED STATES OF AMERICA *Ex rel.* Law Project for Psychiatric Rights, an Alaskan non-profit corporation, Plaintiff, vs. OSAMU H. MATSUTANI, MD, *et al*., Defendants.	)	Case No. 3:09-CV-00080-TMB

MOTION FOR PRELIMINARY INJUNCTION AGAINST DEFENDANTS HOGAN AND STREUR

Qui tam relator Law Project for Psychiatric Rights (PsychRights®) moves for a preliminary injunction prohibiting defendants William Hogan and William Streur, their agents, servants, employees and attorneys, and any persons who are in active concert or participation with them, from presenting claims or causing claims to be presented to Medicaid for reimbursement or payment of the United States Government's federal

financial participation (FFP) share[1] of outpatient prescriptions for psychotropic drugs to recipients under the age of 18 (children and youth) that are not for a medically accepted indication.

I. BACKGROUND

This is a case under the federal False Claims Act, 31 U.S.C. §3729, *et seq*., to:

(a) recover for false claims presented to and paid by Medicaid for outpatient psychiatric drugs prescribed to children and youth that were not for a "medically accepted indication;" and

(b) order the defendants to cease and desist from presenting or causing the presentment of such false claims.

This motion seeks to enjoin Defendants William Hogan and William Streur, their agents, servants, employees and attorneys, and any persons who are in active concert or participation with them from presenting claims or causing claims to be presented to Medicaid for outpatient prescriptions for psychotropic drugs to children and youth that are not covered under that program. Defendant Hogan is the Commissioner of the Alaska Department of Health and Social Services (DHSS), and Defendant William Streur is the Director of the Division of Health Care Services (HCS) within DHSS. Defendant Streur is in charge of the administration of the Medicaid program by the State of Alaska under the direction and supervision of Defendant Hogan. In other words, Defendants Hogan and Streur are in charge of the administration of the Medicaid program by the State of Alaska.

Congress restricted reimbursement for outpatient drugs by the federal government under Medicaid to those that are "medically accepted indications," defined as indications approved by the Food and Drug Administration (FDA), or the use of which is supported by one or more citations included or approved for inclusion in (i) American Hospital

[1] "FFP" stands for "Federal Financial Participation," which means "the Federal Government's share of a State's expenditures under the Medicaid program." 42 CFR §400.203.

Formulary Service Drug Information, (ii) United States Pharmacopeia-Drug Information (or its successor publications), or (iii) DRUGDEX Information System (Covered Outpatient Drugs). 42 USC § 1396r-8(k)(3); 42 USC § 1396r-8(k)(6); 42 USC § 1396r-8(g)(1)(B)(i).

The parties sought to be enjoined continue to present claims or cause claims to be presented to Medicaid for payment of prescriptions to children and youth for psychiatric drugs that are not for a medically accepted indication. This motion thus seeks to preliminarily enjoin such continuing violation of federal law.

II. STANDARDS FOR PRELIMINARY INJUNCTIONS

In *California Pharmacists Ass'n v. Maxwell-Jolly*, 563 F.3d 847, 849 (9th Cir. 2009), citing to *Winter v. Natural Res. Def. Council, Inc*., --- U.S. ----, 129 S.Ct. 365, 376, 172 L.Ed.2d 249 (2008), the 9th Circuit, recently had occasion to state the standard for obtaining a preliminary injunction:

> Plaintiffs seeking a preliminary injunction in a case in which the public interest is involved must establish that they are likely to succeed on the merits, that they are likely to suffer irreparable harm in the absence of preliminary relief, that the balance of equities tips in their favor, and that an injunction is in the public interest. .

These factors will be discussed in turn.

III. THE STANDARDS FOR ISSUANCE OF A PRELIMINARY INJUNCTION ARE MET HERE

A. PsychRights is Likely to Succeed on the Merits

(1) Medicaid Coverage for Outpatient Drugs is Limited to "Medically Accepted Indications

42 USC 1396R-8(k)(3) provides in pertinent part, "The term 'covered outpatient drug' does not include any . . . drug . . . used for a medical indication which is not a medically accepted indication." 42 USC 1396R-8(k)(6) provides:

> The term "medically accepted indication" means any use for a covered outpatient drug which is approved under the Federal Food, Drug, and Cosmetic Act [21 U.S.C.A. § 301 et seq.], or the use of which is supported by one or more citations included or approved for inclusion in any of the compendia described in subsection (g)(1)(B)(i) of this section.

42 USC § 1396R-8(g)(1)(B)(i), in turn, designates the compendia as

> (I) American Hospital Formulary Service Drug Information;
> (II) United States Pharmacopeia-Drug Information (or its successor publications); and
> (III) the DRUGDEX Information System.

(Compendia).

In sum, Medicaid is only permitted by Congress to reimburse the states for expenditures on outpatient drugs for "medically accepted indications," defined as indications approved by the FDA or "supported" by a citation in any of the three Compendia. This was recognized in *US ex rel Rost v. Pfizer*, 253 F.R.D. 11, 13-14 (D.Mass 2008) where the Court held:

> Medicaid can only pay for drugs that are used for a "medically accepted indication," meaning one that is either approved by the FDA or "supported by citations" in one of three drug compendia, including DRUGDEX. See 42 U.S.C. § 1396r8 (k)(3), (6); 42 U.S.C. § 1396r-8 (g)(1)(B)(I).

Similarly, in *U.S. ex rel. Franklin v. Parke-Davis*, 147 F.Supp. 2d 39, 44,45 (D.Mass 2001), the Court held:

> Whether a drug is FDA-approved for a particular use will largely determine whether a prescription for that use of the drug will be reimbursed under the federal Medicaid program. Reimbursement under Medicaid is, in most circumstances, available only for "covered outpatient drugs." 42 U.S.C. § 1396b(i)(10). Covered outpatient drugs do not include drugs that are "used for a medical indication which is not a medically accepted indication." Id. §1396r-8(k)(3). A medically accepted indication, in turn, includes a use "which is approved under the Federal Food Drug and Cosmetic Act" or which is included in specified drug compendia. Id. § 1396r-8(k)(6). See also id. § 1396r-8(g)(1)(B)(i) (identifying compendia to be consulted). Thus, unless a particular off-label use for a drug is included in one of the

> identified drug compendia, a prescription for the off-label use of that drug is not eligible for reimbursement under Medicaid.

(footnote omitted)

The Department of Justice concurs as shown by its news release announcing the $2.3 Billion settlement with Pfizer, in which it stated, "[Pfizer] caused false claims to be submitted to government health care programs for uses that were not medically accepted indications and therefore not covered by those programs." Exhibit A.

(2) Defendants Hogan and Streur Are Personally Liable for Presenting or Causing False Claims to be Presented to Medicaid.

Under *Stoner v. Santa Clara County Office of Education*, 502 F.3d 1116, 1124-5 (9th Cir. 2007), Defendants Hogan and Steur are personally liable for presenting or causing the presentment of false claims to Medicaid:

> The district court also held that Stoner failed to state an FCA [False Claims Act] claim against the individual defendants in their personal capacities because Stoner could not allege that the defendants' actions exceeded the scope of their official responsibilities. As explained below, this was an error. The plain language of the FCA subjects to liability "any person" who, among other things, knowingly submits a false claim or causes such a claim to be submitted to the United States. 31 U.S.C. § 3729. Although the FCA does not define the term "person," the Supreme Court has made clear that the term includes "natural persons." . . . Therefore, state employees sued in their personal capacities are "persons" who may be subject to liability for submitting a false claim to the United States. . . .
>
> To state a claim against Wilcox, Fimiani, and Wong in their personal capacities, Stoner need show only that the individual employees "knowingly present[ed], or cause[d] to be presented, to an officer or employee of the United States Government ... a false or fraudulent claim for payment or approval."

(citations omitted).

(3) Defendants Hogan and Streur Are Flouting Medicaid Requirements By Presenting or Causing the Presentment of Claims for Prescriptions of Psychotropic Drugs to Children and Youth That Are Not For A Medically Accepted Indication

In *ex rel Rost*, 253 F.R.D. at 14 the district court noted, "Each prospective Medicaid provider must agree that he will comply with all Medicaid requirements." States must similarly agree to abide by Medicaid requirements as a condition of participation. Attached hereto as Exhibit B is a copy of the State of Alaska's agreement to comply with all Medicaid requirements.

Among these requirements, under 42 USC §1396r-8 (g)(1)(A), the State of Alaska is required to have a drug use review program (DUR) "designed to educate physicians and pharmacists to identify and reduce the frequency of patterns of fraud."

Under 42 CFR §456.703, the DUR is required to include "prospective drug review." 42 CFR §456.705 in turn provides in pertinent part:

> **42 CFR §456.705 Prospective drug review.**
>
> (a) General. Except as provided in Sec. Sec. 456.703 (b) and (c), the State plan must provide for a review of drug therapy before each prescription is filled or delivered to a recipient . . . . The State must provide pharmacies with detailed information as to what they must do to comply with prospective DUR requirements . . . . The pharmacies, in turn, must provide this information to their pharmacists.

In other words, through this prospective drug review, before each prescription is filled, the state Medicaid agency is required to review it to determine if it is eligible for reimbursement by Medicaid.

42 CFR §456.722 allows for this prospective review of prescriptions to occur through a computerized system:

> **42 CFR §456.722 Electronic claims management system.**
>
> (a) Point-of-sale system. Each Medicaid agency, at its option, may establish, as its principal (but not necessarily exclusive) means of processing claims for covered outpatient drugs, a point-of-sale electronic claims management (ECM) system to perform on-line, real-time (that is,

immediate) eligibility verifications, claims data capture, adjudication of claims, and to assist pharmacists and other authorized persons (including dispensing physicians) in applying for and receiving payment. . . . If the State exercises this option and wishes to receive FFP for its ECM system, the system must meet the functional and additional procurement and system requirements in paragraphs (b) and (c) of this section.

(b) Functional requirements. The ECM system developed by the State must include at least the on-line, real-time capabilities specified in paragraphs (b)(1) through (3) of this section. . . .

(2) Claims data capture, including the following: . . .

(iii) Minimum data set (as defined in Part 11 of the State Medicaid Manual).

(3) Claims adjudication, including the following:

(i) Performing all edits and audits contained in the State's Medicaid Management Information System (MMIS) applicable to prescription drugs.

(ii) Notifying the pharmacist (or other authorized person, such as the dispensing physician) about the claim status.

(iii) Taking steps up to, but not including, payment of the claim.

Included in the data set of Part 11 of the State Medicaid Manual[2] are:

*6. Recipient's Date of Birth:

The date of birth of the recipient. . .

*61. Principal Diagnosis Code:

a. The diagnosis code for the principal condition requiring medical attention. . . .

62. Other Diagnosis Code:

a. The diagnosis code of any condition other than the principal condition which requires supplementary medical treatment. . . .

88. Drug Code:

Codes identifying particular drugs; e.g., National Drug Code, drug tables.

89. Diagnosis Code:

A table of codes identifying medical conditions; i.e., ICD-9-CM.

[2] Exhibit C, downloaded from http://www.cms.hhs.gov/manuals/downloads/P45_11.zip on March 17, 2010.

90. Drug Name:
The generally accepted nomenclature for a particular drug.
91. Drug Classification:
The therapeutic group in to which a drug is categorized.
92. Minimum Days Supply of Drugs:
The minimum units of a drug prescription eligible for payment.
93. Maximum Days Supply of Drug:
The maximum units of a drug prescription eligible for a particular drug. . . .
95. Diagnosis Name:
The generally accepted nomenclature for a diagnosis. Name is required only if not encoded by provider. (See Data Element No. 61.)

These statutory and regulatory provisions require the State of Alaska to screen prescriptions for compliance with the requirement that it not seek federal Medicaid payment for outpatient prescriptions to children and youth for psychotropic drugs that are not for a medically accepted indication.

To summarize: 42 USC §1396r-8 (g)(1)(A) requires a DUR program, 42 CFR §456.703 requires the DUR program to include prospective drug review, and 42 CFR §456.705 requires such prospective review to verify eligibility before the prescription is filled. Under 42 CFR §456.722, the State's electronic claims management system is required to collect the minimum data specified in Part 11 of the State Medicaid Manual, relevant elements of which are set forth above. These elements can determine whether psychotropic drugs prescribed to children and youth are or are not for a medically accepted indication.

Under Defendants Hogan's and Steur's administration of Alaska's Medicaid program, these requirements are being flouted.

(4) Injunctive Relief is Available Against Defendants Hogan and Streur

Injunctive relief to enjoin a state official from violating a federal statute is proper and not barred by the 11th Amendment to the United States Constitution. *Armstrong v. Wilson*, 124 F.3d 1019 (9th Cir. 1997); *Independent Living Center of Southern*

California, Inc., v Maxwell-Jolly, 572 F.3d 644 (9th Cir. 2009). Where a district court has the power to issue a permanent injunction, it also has authority to issue preliminary injunctions. *F.T.C. v. H. N. Singer, Inc.*, 668 F.2d 1107, 1111 (9th Cir. 1982).

B. The Plaintiff Will Suffer Irreparable Harm Without the Preliminary Injunction

(1) To the Extent the 11th Amendment Prohibits a Monetary Judgment Against the State of Alaska for its Medicaid Fraud, Irreparable Harm is Established as a Matter of Law.

In *California Pharmacists, supra*., 563 at 852, the 9th Circuit held that to the extent the 11th Amendment prevents a federal court from awarding a damages remedy against a state, irreparable harm is established as a matter of law:

> Because the economic injury doctrine rests only on ordinary equity principles precluding injunctive relief where a remedy at law is adequate, it does not apply where, as here, the Hospital Plaintiffs can obtain no remedy in damages against the state because of the Eleventh Amendment.

(citation and footnote omitted).

In *Stoner*, as set forth above, the Ninth Circuit held that state employees are personally liable under the False Claims Act for Medicaid violations while acting within the scope of their official duties. However, it specifically held open the question of whether the 11th Amendment prevented the district court from awarding money damages against a state under the False Claims Act through its employees:

> With respect to the official capacity claims, the district court held that the individually named defendants could not be sued for damages in their official capacities because such a suit would, in effect, be against the state. . . . The parties do not challenge this ruling and we express no opinion on the merits of the district court's conclusion.

572 F.3d at 1123 (citation omitted).

California Pharmacists does not mention *Stoner*, and the two cases are certainly distinguishable, especially in that *California Pharmacists* is not a False Claims Act case

while *Stoner* is, but it can be read to suggest that even under the False Claims Act, the 11th Amendment bars a federal court from awarding monetary damages against a state.

If Defendants Hogan and Streur, who are being represented by the Alaska Department of Law as to both their individual and official capacities,[3] concede that the State of Alaska is subject to monetary damages by virtue of Defendants Hogan and Streur having been sued in their official capacities as well as individually, then irreparable harm will not have been established on the grounds that the 11th Amendment bars this Court from awarding monetary damages against the State of Alaska through Defendants Hogan and Streur. However, if the State of Alaska, through Defendants Hogan and Streur, does not concede the State is subject to monetary damages, and this Court concludes the State of Alaska is immune, under *California Pharmacists*, irreparable harm has been established as a matter of law.

As will be discussed in the next section, however, even if the Court concludes the State of Alaska through Defendants Hogan and Streur is subject to monetary damages in this case and therefore irreparable harm has not been established for that reason, irreparable harm is established as a matter of law because the continuing violation of a federal statute constitutes irreparable harm as a matter of law.

(2) The Continuing Violation of a Federal Statute is Irreparable Harm as a Matter of Law.

In *New Motor Vehicle Bd. v. Orrin W. Fox Co.*, 434 U.S. 1345, 1351, 98 S.Ct. 359, 363, 54 L.Ed.2d 439 (1977) (Rehnquist, J., in chambers), the U.S. Supreme Court held, "any time a State is enjoined by a court from effectuating statutes enacted by representatives of its people, it suffers a form of irreparable injury." In *Coalition for Economic Equity v. Wilson*, 122 F.3d 718, 719 (9th Cir. 1997), citing *New Vehicle*, the Ninth Circuit held, "it is clear that a state suffers irreparable injury whenever an enactment of its people or their representatives is enjoined." In *Independent Living*

[3] *See*, Docket Nos. 52 & 55.

Center, *supra*., 572 F.3d at 658, the Ninth Circuit clarified, that while that may be true, enforcing federal law pre-empts such irreparable harm suffered by a state, stating:

> As the cited authority suggests, a state may suffer an abstract form of harm whenever one of its acts is enjoined. To the extent that is true, however, it is not dispositive of the balance of harms analysis. If it were, then the rule requiring "balance" of "competing claims of injury," *Winter*, 129 S.Ct. at 376, would be eviscerated. Federal courts instead have the power to enjoin state actions, in part, because those actions sometimes offend federal law provisions, which, like state statutes, are themselves "enactment [s] of its people or their representatives,"

PsychRights respectfully suggests the Ninth Circuit has thus implicitly held that allowing continuing violation of federal law constitutes irreparable harm as a matter of law.

C. The Balance of Equities Tips in Favor of the Plaintiff and the Injunction is in the Public Interest as a Matter of Law

Under California Pharmacists, *supra*., 563 at 852-853, as a matter of law, the balance of equities tips in favor of the plaintiff and a prospective preliminary injunction is in the public interest if the requested preliminary injunction is to enjoin continuing violation of federal law ("it is clear that it would not be equitable or in the public's interest to allow the state to continue to violate the requirements of federal law"). Thus, these two factors are satisfied as a matter of law. Where, as here, the violation of law is clear, the court must not allow it to continue.

IV. SCOPE OF THE REQUESTED PRELIMINARY INJUNCTION

Whether a prescription for a psychotropic drug to a child or youth that is not for an FDA approved indication is nonetheless covered under Medicaid because it is a medically accepted indication, the American Hospital Formulary Service and DRUGDEX compendia citations must be consulted to be if such use is "supported."[4]

[4] It is PsychRights' understanding, after inquiry, that United States Pharmacopeia-Drug Information (or its successor publications), the other compendium specified in 42 U.S.C. 1396r-8(g)(1)(B)(i), is no longer being published.

Attached hereto as Exhibit D are the most recent citations in the American Hospital Formulary Service compendium, and Exhibit E the most recent citations in DRUGDEX[5] available to PsychRights,[6] for specific prescription psychotropic drugs often prescribed to children and youth. These establish the following with respect to medically accepted indications prescribed to children and youth for the specific psychotropic drugs:

1. The following psychotropic drugs have no medically accepted indication for anyone under 18 years of age and should be prohibited entirely:

   a. Clorazil (clozapine)
   b. Cymbalta (duloxetine)
   c. Desyrel (trazadone)
   d. Effexor (venlafaxine)
   e. Geodon (ziprasidone)
   f. Invega (paliperidone)
   g. Paxil (paroxetine)
   h. Symbyax (fluoxetine hydrochloride/olanzapine)

2. The only medically accepted indications for anyone under 18 years of age are as set forth below for the following psychotropic drugs and all other indications should be prohibited:

Drug	**Medically Accepted Indication**	**Notes**
Abilify (Aripiprazole)		
	Bipolar I Disorder - Adjunctive therapy with lithium or valproate for Acute Manic or Mixed Episodes	10 yrs old and up
	Bipolar I Disorder, monotherapy, Manic	10-17 years old for acute therapy

[5] Exhibit F is a copy of the DRUGDEX Recommendation, Evidence and Efficacy Ratings.

[6] PsychRights has requested Defendant Thomson Reuters (Healthcare), the publisher of DRUGDEX, for the most recent citations in DRUGDEX and to keep them current so that any additions to medically accepted indications may be reflected in the requested preliminary injunction. *See*, Exhibit G.

Drug	Medically Accepted Indication	Notes
	or Mixed Episodes	
	Schizophrenia	13-17 years old
Adderall (amphetamine/dextroamphetamine)		
	Attention Deficit Hyperactivity Disorder (ADHD)	3 years old and up for immediate-release and 6 years old and up for extended-release
	Narcolepsy	6 years old and up for immediate release
Anafranil (clomipramine)		
	Obsessive-Compulsive Disorder	10 years and up
Concerta (methylphenidate)		
	Attention Deficit Hyperactivity Disorder (ADHD)	6 years old to 12 years old
	Attention Deficit Hyperactivity Disorder (ADHD)	6 years old and up for ConcertaR
Depakote (valproic acid)		
	Absence Seizure, Simple and Complex and/or Complex Partial Epileptic Seizure	10 years and older
Dexedrine (dextroamphetamine)		
	Attention Deficit Hyperactivity Disorder (ADHD)	3 years to 16 years old (immediate-release) and age 6 years to 16 years old (sustained-release))
	Narcolepsy	6 years old and up
Focalin (dexmethylphenidate)		
	Attention Deficit Hyperactivity Disorder (ADHD)	6 years and older
Haldol (haloperidol)		
	Hyperactive Behavior, (Short-term treatment) after failure to respond to non-antipsychotic medication and psychotherapy	3 years old and up
	Problematic Behavior in Children (Severe), With failure to respond to non-antipsychotic medication or psychotherapy	3 years old and up
	Psychotic Disorder	3 years old and up but ORAL formulations only

Drug	Medically Accepted Indication	Notes
	Schizophrenia	3 years old and up but ORAL formulations only
Lamictal (lamotrigine)		
	Epilepsy, Refractory	
Lexapro (escitalopram)		
	Major Depressive Disorder	12 years old and up
Luvox (fluvoxamine)		
	Obsessive-Compulsive Disorder	8 years old and up and immediate release formula only
Mellaril (thioridazine)		
	Schizophrenia, Refractory	
Neurontin (gabapentin)		
	Partial Seizure; Adjunct	3-12 years old
Orap (pimozide)		
	Gilles de la Tourette's syndrome	12 years and older
Prozac (fluoxetine)		
	Major Depressive Disorder	8 years old and up
	Obsessive-Compulsive Disorder	7 years old and up
Ritalin (methylphenidate)		
	Attention Deficit Hyperactivity Disorder (ADHD)	6 years to 12 years old (extended release)
	Attention Deficit Hyperactivity Disorder (ADHD)	6 years old and up (immediate release)
	Narcolepsy	6 years and up, and Ritalin(R) -SR only
Risperdal (risperidone)		
	Autistic Disorder – Irritability	5 years old and up
	Bipolar I Disorder	10 years old and up
	Schizophrenia	13 years old and up (Orally)
Seroquel (quetiapine)		
	Manic episodes associated with bipolar disorder	10 years old to 17 years old
	Schizophrenia	13 years old to 17 years old
Sinequan (doxepin)		
	Alcoholism - Anxiety – Depression	12 years old and up

Drug	Medically Accepted Indication	Notes
	Anxiety – Depression	12 years old and up
	Anxiety - Depression - Psychoneurotic personality disorder	12 years old and up
Strattera (atomoxetine)		
	Attention Deficit Hyperactivity Disorder (ADHD)	6 years old and up
Tegretol (carbamazepine)		
	Epilepsy, Partial, Generalized, and Mixed types	
Tofranil (imipramine)		
	Nocturnal enuresis	6 years old and up
Trileptal (*oxcarbazepine*)		
	Partial Seizure, monotherapy	4 years old and up
	Partial seizure; Adjunct	2 years old and up
Vyvanse (lisdexamfetamine)		
	Attention Deficit Hyperactivity Disorder (ADHD)	6 years old to 12 years old
Zoloft (sertraline)		
	Obsessive-Compulsive Disorder	6 years old and up
Zyprexa (olanzapine)		
	Schizophrenia	13 years old to 17 years old
	manic or mixed episodes associated with bipolar I disorder	13 years old to 17 years old

For psychotropic drugs not listed, PsychRights respectfully suggests the parties sought to be enjoined should be prohibited from approving for payment or reimbursement by Medicaid of the United States Government's FFP share of outpatient prescriptions for psychiatric drugs to anyone under 18 unless (a) it is for an indication approved by the FDA, or (b) upon application to the Court with notice to the other parties to determine whether such use is for a medically accepted indication.

V. BOND

Under F.R.C.P. 65(c) the United States is not required to give security. Since the United States is the real party in interest in this action, *Stoner*, *supra*, 502 F.3d at 1126, no security is required.

VI. CONCLUSION

For the foregoing reasons PsychRights' motion for a preliminary injunction should be granted.

RESPECTFULLY SUBMITTED this 24th day of March, 2010.

Law Project for Psychiatric Rights, an Alaskan non-profit corporation

By: /s/ James B. Gottstein
JAMES B. GOTTSTEIN
ABA #7811100

Attorney for *relator*, Law Project for Psychiatric Rights

CERTIFICATE OF SERVICE

The undersigned hereby certifies that on March 24 2010, a true and correct copy of this document and accompanying proposed order was served electronically on all parties of record by electronic means through the ECF system as indicated on the Notice of Electronic Filing, or if not confirmed by ECF, by first class regular mail.

/s/ James B. Gottstein
JAMES B. GOTTSTEIN, ABA #7811100
Law Project for Psychiatric Rights

IN THE UNITED STATES DISTRICT COURT
DISTRICT OF ALASKA

UNITED STATES OF AMERICA *Ex rel.* Law Project for Psychiatric Rights, an Alaskan non-profit corporation, Plaintiff, vs. OSAMU H. MATSUTANI, MD, *et al*., Defendants.	)	**CIVIL ACTION NO. 3:09-CV-00080-TMB**

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Department of Justice

FOR IMMEDIATE RELEASE
Wednesday, September 2, 2009
WWW.USDOJ.GOV

AAG
(202) 514-2007
TDD (202) 514-1888

Justice Department Announces Largest Health Care Fraud Settlement in Its History

Pfizer to Pay $2.3 Billion for Fraudulent Marketing

WASHINGTON – American pharmaceutical giant Pfizer Inc. and its subsidiary Pharmacia & Upjohn Company Inc. (hereinafter together "Pfizer") have agreed to pay $2.3 billion, the largest health care fraud settlement in the history of the Department of Justice, to resolve criminal and civil liability arising from the illegal promotion of certain pharmaceutical products, the Justice Department announced today.

Pharmacia & Upjohn Company has agreed to plead guilty to a felony violation of the Food, Drug and Cosmetic Act for misbranding Bextra with the intent to defraud or mislead. Bextra is an anti-inflammatory drug that Pfizer pulled from the market in 2005. Under the provisions of the Food, Drug and Cosmetic Act, a company must specify the intended uses of a product in its new drug application to FDA. Once approved, the drug may not be marketed or promoted for so-called "off-label" uses – *i.e.*, any use not specified in an application and approved by FDA. Pfizer promoted the sale of Bextra for several uses and dosages that the FDA specifically declined to approve due to safety concerns. The company will pay a criminal fine of $1.195 billion, the largest criminal fine ever imposed in the United States for any matter. Pharmacia & Upjohn will also forfeit $105 million, for a total criminal resolution of $1.3 billion.

In addition, Pfizer has agreed to pay $1 billion to resolve allegations under the civil False Claims Act that the company illegally promoted four drugs – Bextra; Geodon, an anti-psychotic drug; Zyvox, an antibiotic; and Lyrica, an anti-epileptic drug – and caused false claims to be submitted to government health care programs for uses that were not medically accepted indications and therefore not covered by those programs. The civil settlement also resolves allegations that Pfizer paid kickbacks to health care providers to induce them to prescribe these, as well as other, drugs. The federal share of the civil settlement is $668,514,830 and the state Medicaid share of the civil settlement is $331,485,170. This is the largest civil fraud settlement in history against a pharmaceutical company.

As part of the settlement, Pfizer also has agreed to enter into an expansive corporate integrity agreement with the Office of Inspector General of the Department of Health and Human Services. That agreement provides for procedures and reviews to be put in place to avoid and promptly detect conduct similar to that which gave rise to this matter.

Whistleblower lawsuits filed under the *qui tam* provisions of the False Claims Act that are pending in the District of Massachusetts, the Eastern District of Pennsylvania and the Eastern District of Kentucky triggered this investigation. As a part of today's resolution, six whistleblowers will receive payments totaling more than $102 million from the federal share of the civil recovery.

The U.S. Attorney's offices for the District of Massachusetts, the Eastern District of Pennsylvania, and the Eastern District of Kentucky, and the Civil Division of the Department of Justice handled these cases. The U.S. Attorney's Office for the District of Massachusetts led the criminal investigation of Bextra. The investigation was conducted by the Office of Inspector General for the Department of Health and Human Services (HHS), the FBI, the Defense Criminal Investigative Service (DCIS), the Office of Criminal Investigations for the Food and Drug Administration (FDA), the Veterans' Administration's (VA) Office of Criminal Investigations, the Office of the Inspector General for the Office of Personnel Management (OPM), the Office of the Inspector General for the United States Postal Service (USPS), the National Association of Medicaid Fraud Control Units and the offices of various state Attorneys General.

"Today's landmark settlement is an example of the Department of Justice's ongoing and intensive efforts to protect the American public and recover funds for the federal treasury and the public from those who seek to earn a profit through fraud. It shows one of the many ways in which federal government, in partnership with its state and local allies, can help the American people at a time when budgets are tight and health care costs are increasing," said Associate Attorney General Tom Perrelli. "This settlement is a testament to the type of broad, coordinated effort among federal agencies and with our state and local partners that is at the core of the Department of Justice's approach to law enforcement."

"This historic settlement will return nearly $1 billion to Medicare, Medicaid, and other government insurance programs, securing their future for the Americans who depend on these programs," said Kathleen Sebelius, Secretary of Department of Health and Human Services**.** "The Department of Health and Human Services will continue to seek opportunities to work with its government partners to prosecute fraud wherever we can find it. But we will also look for new ways to prevent fraud before it happens. Health care is too important to let a single dollar go to waste."

"Illegal conduct and fraud by pharmaceutical companies puts the public health at risk, corrupts medical decisions by health care providers, and costs the government billions of dollars," said Tony West, Assistant Attorney General for the Civil Division. "This civil settlement and plea agreement by Pfizer represent yet another example of what penalties will be faced when a pharmaceutical company puts profits ahead of patient welfare."

"The size and seriousness of this resolution, including the huge criminal fine of $1.3 billion, reflect the seriousness and scope of Pfizer's crimes," said Mike Loucks, acting U.S. Attorney for the District of Massachusetts. "Pfizer violated the law over an extensive time period. Furthermore, at the very same time Pfizer was in our office negotiating and resolving the allegations of criminal conduct by its then newly acquired subsidiary, Warner-Lambert, Pfizer was itself in its other operations violating those very same laws. Today's enormous fine demonstrates that such blatant and continued disregard of the law will not be tolerated."

"Although these types of investigations are often long and complicated and require many resources to achieve positive results, the FBI will not be deterred from continuing to ensure that pharmaceutical companies conduct business in a lawful manner," said Kevin Perkins, FBI Assistant Director, Criminal Investigative Division.

"This resolution protects the FDA in its vital mission of ensuring that drugs are safe and effective. When manufacturers undermine the FDA's rules, they interfere with a doctor's judgment and can put patient health at risk," commented Michael L. Levy, U.S. Attorney for the Eastern District of Pennsylvania. "The public trusts companies to market their drugs for uses that FDA has approved, and trusts that doctors are using independent judgment. Federal health dollars should only be spent on treatment decisions untainted by misinformation from manufacturers concerned with the bottom line."

"This settlement demonstrates the ongoing efforts to pursue violations of the False Claims Act and recover taxpayer dollars for the Medicare and Medicaid programs," noted Jim Zerhusen, U.S. Attorney for the Eastern District of Kentucky.

"This historic settlement emphasizes the government's commitment to corporate and individual accountability and to transparency throughout the pharmaceutical industry," said Daniel R. Levinson, Inspector General of the United States Department of Health and Human Services. "The corporate integrity agreement requires senior Pfizer executives and board members to complete annual compliance certifications and opens Pfizer to more public scrutiny by requiring it to make detailed disclosures on its Web site. We expect this agreement to increase integrity in the marketing of pharmaceuticals."

"The off-label promotion of pharmaceutical drugs by Pfizer significantly impacted the integrity of TRICARE, the Department of Defense's healthcare system," said Sharon Woods, Director, Defense Criminal Investigative Service. "This illegal activity increases patients' costs, threatens their safety and negatively affects the delivery of healthcare services to the over nine million military members, retirees and their families who rely on this system. Today's charges and settlement demonstrate the ongoing commitment of the Defense Criminal Investigative Service and its law enforcement partners to investigate and prosecute those that abuse the government's healthcare programs at the expense of the taxpayers and patients."

"Federal employees deserve health care providers and suppliers, including drug manufacturers, that meet the highest standards of ethical and professional behavior," said Patrick E. McFarland, Inspector General of the U.S.

Office of Personnel Management. "Today's settlement reminds the pharmaceutical industry that it must observe those standards and reflects the commitment of federal law enforcement organizations to pursue improper and illegal conduct that places health care consumers at risk."

"Health care fraud has a significant financial impact on the Postal Service. This case alone impacted more than 10,000 postal employees on workers' compensation who were treated with these drugs," said Joseph Finn, Special Agent in Charge for the Postal Service's Office of Inspector General. "Last year the Postal Service paid more than $1 billion in workers' compensation benefits to postal employees injured on the job."

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09-900

Revision: HCFA-PM-91-4 (BPD) OMB No. 0938-
AUGUST 1991

STATE PLAN UNDER TITLE XIX OF THE SOCIAL SECURITY ACT
MEDICAL ASSISTANCE PROGRAM

State/Territory: ALASKA

Citation

42 CFR
430.10

As a condition for receipt of Federal funds under title XIX of the Social Security Act, the

Department of Health and Social Services
(Single State Agency)

submits the following State plan for the medical assistance program, and hereby agrees to administer the program in accordance with the provisions of this State plan, the requirements of titles XI and XIX of the Act, and all applicable Federal regulations and other official issuances of the Department.

11375 DATA REQUIREMENTS

The minimum data element file requirements for systems approval derive from State plan requirements and Federal reporting requirements. Data elements related to services not covered in the State plan need not be included.

Claim format and content varies depending upon the type of provider that submits a claim and individual State plan requirements.

NOTE: Subtitle F of Public Law 104-191 mandates that the Secretary of the Department of Health and Human Services adopt a wide range of national standards for the electronic exchange of health information. Standards are to be adopted for: 1) electronic transactions and data elements, 2) code sets, 3) unique health identifiers for individuals, providers, health plans, and employers, 4) security of health information, and 5) electronic signatures. The recommended standards for various types of standards mandated under Public Law 104-191 will be made available for public comment via Notices of Proposed Rulemaking in the Federal Register. Once standards are published as Final Rules in the Federal Register, States and all health related providers must implement standards within 2 years from the Federal Register publication date. The final standards will supersede any/all standards currently in place for electronic transactions and data elements.

The Uniform Hospital Discharge Data Set (UHDDS), developed through the National Committee on Vital and Health Statistics (NCVHS) and required by HHS departmental policy, effective January 1, 1975, and which meets current PRO requirements of §11205, contains, for hospital service only, discharge data as a file requirement and is identified in this section as:

* UHDDS as well as MMIS requirement
** UHDDS requirement only

The following data elements contained in the systems files are minimal and not exclusive requirements for source and use within the MMIS.

1. Recipient Identification Number:
   A number that uniquely identifies an individual eligible for Medicaid benefits.

*2. Recipient Social Security Number (SSN):
   The number used by SSA throughout a wage earner's lifetime to identify earnings under the Social Security program.

   For newborns and children not having a SSN but covered under Medicaid use No. 1 above to identify these eligibles.

3. Recipient Social Security Claim Number:
   The number assigned to an individual by the SSA under which monthly cash benefits (and Medicare benefits) are paid or eligibility is established.

4. Recipient's Name:
   The name of the recipient.

*5. Recipient's Address:
The address of the recipient.

*6. Recipient's Date of Birth:
The date of birth of the recipient.

7. Recipient's Race Code:
a. The racial origin of the recipient
** b. Race/Ethnic
White, Black, Hispanic, Asian/Pacific Islander, American/Indian/Alaska Native, and other

*8. Recipient's Sex Code:
The sex of the recipient.

9. Recipient's Aid Category:
The statutory category of public assistance, SSI or State supplementary payment under which a recipient is eligible for Medicaid benefits.

10. Gross Family Income:
The monthly gross income for the family of which this recipient is a member.

11. Family Size:
The number of persons in the family of which this recipient is a member.

12. Eligibility Beginning Date:
A date that begins a period in which a recipient was certified as eligible to receive Medicaid benefits.

13. Eligibility Ending Date:
A date concluding a period in which a recipient is eligible to receive Medicaid benefits.

14. Third Party Liability Code:
a. A code indicating availability to a recipient of potential third party resources.
** b. Expected Principal Source of Payment
(1) Self-pay
(2) Workmen's Compensation
(3) Medicare
(4) Medicaid
(5) Maternal and Child Health
(6) Other Government Payments
(7) Blue Cross
(8) Insurance Companies
(9) No charge (free, charity, special research, or teaching)
(10) Other

15. Buy-In Status Code:
The code indicating a recipient's status with respect to the Medicare Buy- In Program.

16. Recipient Exception Indicator:
A code indicating that all claims for a given recipient are to be manually reviewed prior to payment.

17. Money Payment Code:
A code indicating whether or not the recipient is currently receiving cash assistance.

18. Medicare Type Code:
A code indicating whether the recipient is covered by Medicare, and, if so, whether he/she has Hospital Insurance Benefits (Part A) and/or Supplementary Medical Insurance Benefits (Part B).

19. Buy-In Eligibility Date:
The date from which the recipient is eligible for the Medicare Buy-In Program.

20. Buy-In Premium Date:
The date associated with a Buy-In premium amount.

21. Buy-In Premium Amount:
The amount of money the State pays to HCFA each month per recipient for Buy-In coverage.

22. SSA-Information Exchange Code:
A code scheme consisting of various numerical codes which describe situations that can occur at SSA or at the State level.

23. Recipient's Eligibility Certification Date:
Date recipient was certified as eligible for public assistance, supplemental security income or State supplemental benefits.

24. Recipient's Location Code:
The geographic or geopolitical subdivision of a State in which the recipient resides.

25. Medicaid Premium Amount:
A recurring premium paid by medically needy individuals before they can receive Medicaid services. The amount of the fee is based upon the number of persons in the family and the gross family income.

26. Medicaid Enrollment Fee Amount:
A one-time enrollment fee paid by medically needy individuals before they can receive Medicaid services. The amount of the fee is based on the number of persons in the family and the gross family income.

27. Medicaid Deductible Amount:
The annual (or other period) amount which the recipient must pay toward the cost of medical services before Medicaid will begin to pay.

28. Date of Death:
The date of a recipient's death as indicated in the Social Services or SSI file after an official notice of death has been received.

29. Provider Number (State):
A unique number assigned by the State to each participating provider of services.

30. Provider Name:
The name of the provider of Medicaid services as used on official State records.

31. Provider Address:
The mailing address of the provider.

32. Provider Pay to Address:
The address to which Medicaid payments to a provider are sent.

33. Provider Type:
A code indicating the classification of the provider rendering health and medical services as approved under the State Medicaid plan.

34. Provider Beginning Date of Service:
A date beginning a period in which the provider was authorized to receive Medicaid payments.

35. Provider Ending Date of Service:
A date concluding a period in which the provider is authorized Medicaid payments for services rendered.

36. Provider Group Number:
The number assigned to the group practice of which an individual provider is a member.

37. Provider Type of Practice Organization:
A code identifying the organizational structure of a provider's practice.

38. Provider Employer Identification Number:
The number assigned to an employer by the Internal Revenue Service for tax reporting purposes.

39. Provider Social Security Number:
The number assigned to an individual by SSA.

*40. Medicare Provider Number:
The identification number assigned to a Medicare provider by HCFA (provider means any individual or entity furnishing Medicaid services under a provider agreement with the Medicaid agency (Reference 42 CFR 430.l).

41. Provider Year End Date:
The calendar date on which the provider's fiscal year ends.

42. Provider Specialty Code:
A code used to indicate the medical specialty of a physician.

43. Provider Exception Indicator:
A code indicating that all claims from a given provider are to be manually reviewed prior to payment.

44. Provider Credit Balance Amount:
The amount of money the Medicaid program owes a provider.

45. Provider Credit Balance Date:
The processing date on which the last amount was entered in the Provider Credit Balance amount.

46. Out-of-State Provider Code:
A code indicating that the provider is located out of State.

47. Per Diem Rate:
The payment amount for each day of care in an institution reimbursed on a per diem basis.

48. Percent-of-Charges Factor:
The percent of a provider's charges that constitutes payment for certain categories of service.

49. Rate Effective Date:
The effective date of the accompanying per diem rate or percent-of-charges factor.

50. Provider Location Code:
The geographic or geopolitical subdivision in which the provider's place of business is located.

51. Provider Enrollment Status Code:
A code indicating a provider's certification status with respect to the Medicaid program.

52. Provider Enrollment Status Date:
The effective date of the accompanying provider enrollment status code.

53. Provider Group Name and Address:
The name and mailing address of the provider group.

54. Transaction Control Number:
A unique number identifying each claim transaction received.

55. Category of Service:
A code defining the category of service rendered (e.g., general inpatient, pharmacy, physician, home health).

56. Laboratory, Medicare Certified Indicator:
A code indicating that a laboratory is approved as meeting the requirements for participation in Medicare.

57. Laboratory Service Authorized Code:
A code indicating the services/procedures that a laboratory which meets the requirements for participation in Medicare is authorized to perform.

*58. Physician Identification:
a. Attending Physician Number
The provider number of the physician attending an inpatient in a hospital, nursing home, or other institution.

This is the physician primarily responsible for the care of the patient from the beginning of this institutional episode.

**b. Operating Physician
This is the physician who performed the principal procedure. See Data Element No. 87 below, for definition of principal procedure.

59. Referring Physician Number:
The provider number of the physician referring a recipient to another practitioner or provider.

60. Prescribing Physician Number:
The provider number of the physician issuing a prescription.

*61. Principal Diagnosis Code:
a. The diagnosis code for the principal condition requiring medical attention.

**b. The condition established after study to be chiefly responsible for causing the patient's admission to the hospital for care for the current hospital stay. (HCFA requires the acceptance of ICD-9-CM coding.)

62. Other Diagnosis Code:
a. The diagnosis code of any condition other than the principal condition which requires supplementary medical treatment.

**b. Conditions (up to four) other than the principal condition that coexisted at the time of admission, or developed subsequently, which affected the treatment received and/or the length of stay. Exclude diagnoses that relate to an earlier episode which have no bearing on this hospital stay. (HCFA requires the acceptance of ICD-9-CM coding.)

*63. Admission Date:
The date a recipient was admitted to a medical institution.

64. Beginning Date of Service:
The date upon which the first service covered by a claim was rendered. If a claim is for one service only (e.g., a prescription), this is the only service date.

65. Ending Date of Service:
The date upon which the last service covered by a claim was rendered.

*66. Discharge Date:
The formal release of an inpatient from a hospital.

67. Place of Service:
A code indicating where a service was rendered by a provider.

*68. Patient Number:
Any number assigned by a provider to a recipient or claim for reference purposes, such as a medical record number.

69. Patient Status:
A code indicating the patient's status on the last date of service covered by an institutional claim.

70. Total Claim Charge:
The sum of all charges associated with an individual claim.

71. Units of Service:
A quantitative measure of the services rendered to, or for, a recipient (e.g., days, visits, miles, injections).

72. Third Party Payment Amount:
The amount of payment applied toward a claim by third party sources.

73. Medicare Cash Deductible Amount:
The unmet Medicare deductible subject to payment by Medicaid.

74. Medicare Blood Deductible Amount:
The unmet Medicare deductible for blood subject to payment by Medicaid.

75. Medicare Coinsurance Charge:
The Medicare coinsurance amount subject to payment by Medicaid.

76. Medicare Reasonable Charge:
Payment amount recognized as the reasonable charge for Medicare.

77. Medicaid Co-Payment Amount:
The portion of the claim charge which the recipient must pay, called coinsurance when expressed as a percentage of the payment amount.

78. Prior Authorization Control Number:
A number that uniquely identifies a particular instance of prior authorization.

79. Payment Amount:
The computed amount of payment due a provider for a claim transaction.

80. Date of Adjudication:
The date a claim is approved (or partially approved) or disallowed.

81. Error Code:
A code indicating the nature of an error condition associated with that claim transaction.

82. Date Entered Suspense:
The date a claim transaction was initially suspended.

83. Payment Date:
The date a payment instrument was generated for a claim transaction.

84. Allowable Procedure Payment:
The maximum allowed amount payable for a particular medical procedure, treatment, or service item.

85. Professional Fee:
The amount allowed to a dispenser of drugs as compensation for his professional services.

86. Prescription Number:
The number assigned by a pharmacist to a prescription at the time it is filled.

87. Procedure Codes:
Codes identifying medical procedures (i.e. accept and use exclusively the HCPCS in a physician or outpatient setting). (For an inpatient setting, ICD-9-CM Volume 3 is recommended).

**a. Principal Significant Procedures:
When more than one procedure is reported, designate the principal procedure. In determining which of several procedures is the principal, apply the following criteria:

(1) The principal procedure is the one which was performed for definitive treatment rather than performed for diagnostic or exploratory purposes, or was necessary to take care of a complication.

(2) The principal procedure is that procedure most closely related to the principal diagnosis.

**b. Other Significant Procedures:

(1) One which carries an operative or anesthetic risk, requires highly trained personnel, or requires special facilities or equipment.

(2) Up to four significant procedures can be reported.

(HCFA requires the acceptance of ICD-9-CM coding.)

88. Drug Code:
Codes identifying particular drugs; e.g., National Drug Code, drug tables.

89. Diagnosis Code:
A table of codes identifying medical conditions; i.e., ICD-9-CM.

90. Drug Name:
The generally accepted nomenclature for a particular drug.

91. Drug Classification:
The therapeutic group in to which a drug is categorized.

92. Minimum Days Supply of Drugs:
The minimum units of a drug prescription eligible for payment.

93. Maximum Days Supply of Drug:
The maximum units of a drug prescription eligible for a particular drug.

94. Procedures Names:
The generally accepted nomenclature for medical, surgical, dental, etc., procedure.

95. Diagnosis Name:
The generally accepted nomenclature for a diagnosis. Name is required only if not encoded by provider. (See Data Element No. 6l.)

96. Unit of Measure:
The unit in which a drug is dispensed (e.g., cc, capsule, tablet).

97. Drug Cancellation Date:
The date after which a particular drug is no longer covered under the State Medicaid program.

98. Medicaid Reasonable Charge:
Payment amount recognized as the reasonable charge for Medicaid.

*99. Discharged Patient's Destination:
A code indicating a recipient's destination upon discharge from a medical institution.

a. Discharged to home (routine discharge).
b. Left against medical advice.
c. Discharged to another short term hospital.
d. Discharged to a long term care institution.
e. Died.
f. Other.

100. Billing Date:
The date a provider indicates a claim was prepared.

101. Procedure Charge:
The charge for an individual procedure, treatment, or service item as submitted by the provider.

102. Drug Charge:
The charge submitted by a provider for a given drug prescription.

103. Adjustment Amount:
The amount (plus or minus) by which a provider's account is to be changed.

104. Date Claim Received:
The date on which a claim transaction is received by the claims processing agency.

105. Date of Surgery:
The date on which a surgical procedure(s) was performed on an inpatient.

106. Drug Wholesale Cost:
The generally accepted wholesale cost of a drug.

107. Maximum Allowed Price:
The maximum amount that will be paid for a procedure, treatment, or service item.

108. Valid Sex Indicator:
A code which indicates when a procedure or diagnosis is limited to one sex only.

109. Age Range Indicator:
A code which specifies an age range when a procedure or diagnosis is limited to a particular age group.

110. Budgeted Amount:
The planned expenditures for various Medicaid services over a given period of time.

111. Screening Results Code:
A code indicating the outcome of the various screening tests rendered.

112. Screening Referral Code:
A code indicating the nature of any referrals made as a result of screening.

113. Screening Related Treatment:
A code identifying procedures or services received as a result of screening.

114. Family Planning Code:
A code indicating whether any diagnosis, treatment, drugs, supplies, and devices, counseling service, or other billed services or materials are for the purposes of family planning.

115. Certification Review Indicator:
Indicator showing that review was made of certification of a recipient who has been admitted to institutional care including approval status.

116. Certification/Recertification Date:
The date of certification/recertification of a recipient who has been admitted to institutional care.

117. Certification Status:
An indication of initial certification status of a patient in an institution.

118. Number of Requests for Extension:
The number of times an extension of certification of stay was requested for a patient in an institution.

119. Days Certified Initially:
The number of days stay certified initially for a patient in an institution.

120. Total Days Certified:
The total number of days stay certified for a patient in an institution.

121. Date of Application:
The date that a recipient applied for eligibility status in the Medicaid program.

122. SSN of an Absent Parent:
See 42 CFR 433.138 for the conditions under which this piece of information must be captured.

disorder and other psychiatric disorders. However, FDA also states that depression and certain other psychiatric disorders are themselves associated with an increased risk of suicide. (See Cautions: Pediatric Precautions, in Fluoxetine Hydrochloride 28:16.04.20) Anyone considering the use of mirtazapine in a child or adolescent for any clinical use must therefore balance the potential risks with the clinical need. (See Suicidality Precautions under Dosage and Administration: Dosage.)

■ **Dosage in Renal and Hepatic Impairment** Although clearance of mirtazapine may decrease in patients with hepatic or moderate to severe renal impairment, the manufacturer does not make specific recommendations for dosage adjustment in such patients. However, the manufacturer states that since plasma concentrations of mirtazapine may be increased in patients with hepatic or moderate to severe renal impairment, the drug should be used with caution in such patients.

Description

Mirtazapine is a piperazinoazepine-derivative antidepressant agent. As a tetracyclic antidepressant agent, the drug differs structurally from selective serotonin-reuptake inhibitors (e.g., fluoxetine, sertraline), monoamine oxidase inhibitors, and tricyclic antidepressant agents.

The exact mechanism of antidepressant action of mirtazapine has not been fully elucidated, but the drug appears to act as an antagonist at central presynaptic α_2-adrenergic autoreceptors and heteroreceptors resulting in enhanced central noradrenergic and serotonergic activity. Mirtazapine is a potent antagonist of serotonin type 2 (5-HT_2) and type 3 (5-HT_3) receptors, but the drug does not exhibit high affinity for serotonin type 1A (5-HT_{1A}) or type 1B (5-HT_{1B}) receptors. Mirtazapine is a potent antagonist of histamine H_1 receptors, which may account for the prominent sedative effects of the drug. In addition, the drug exhibits moderate peripheral α_1-adrenergic blocking activity that may explain the occasional orthostatic hypotension that reportedly has been associated with mirtazapine. The drug is a moderate antagonist at muscarinic receptors, which may account for the relatively low incidence of anticholinergic effects associated with mirtazapine.

SumMon® (see Users Guide). For additional information on this drug until a more detailed monograph is developed and published, the manufacturer's labeling should be consulted. It is *essential* that the labeling be consulted for detailed information on the usual cautions, precautions, and contraindications.

Preparations

Excipients in commercially available drug preparations may have clinically important effects in some individuals; consult specific product labeling for details.

Mirtazapine

Oral		
Tablets, film-coated	15 mg*	**Mirtazapine Film-coated Tablets**
		Remeron* (scored), Organon
	30 mg*	**Mirtazapine Film-coated Tablets**
		Remeron* (scored), Organon
	45 mg*	**Mirtazapine Film-coated Tablets**
		Remeron*, Organon
Tablets, orally disintegrating	15 mg*	**Mirtazapine Orally Disintegrating Tablets**
		Remeron* SolTab, Organon
	30 mg*	**Mirtazapine Orally Disintegrating Tablets**
		Remeron* SolTab, Organon
	45 mg*	**Mirtazapine Orally Disintegrating Tablets**
		Remeron* SolTab, Organon

*available from one or more manufacturer, distributor, and/or repackager by generic (nonproprietary) name

ANTIPSYCHOTICS 28:16.08
ATYPICAL ANTIPSYCHOTICS 28:16.08.04

Aripiprazole

■ Aripiprazole is considered an atypical or second-generation antipsychotic agent.

Uses

■ **Psychotic Disorders** Aripiprazole is used for the symptomatic management of psychotic disorders (e.g., schizophrenia). Drug therapy is integral to the management of acute psychotic episodes and accompanying violent behavior in patients with schizophrenia and generally is required for long-term stabilization to sustain symptom remission or control and to minimize the risk of relapse. Antipsychotic agents are the principal class of drugs used for the management of all phases of schizophrenia. Patient response and tolerance to antipsychotic agents are variable, and patients who do not respond to or tolerate one drug may be successfully treated with an agent from a different class or with a different adverse effect profile.

Schizophrenia Aripiprazole is used orally for the acute and maintenance treatment of schizophrenia in adults and adolescents 13–17 years of age. Schizophrenia is a major psychotic disorder that frequently has devastating effects on various aspects of the patient's life and carries a high risk of suicide and other life-threatening behaviors. Manifestations of schizophrenia involve multiple psychologic processes, including perception (e.g., hallucinations), ideation, reality testing (e.g., delusions), emotion (e.g., flatness, inappropriate affect), thought processes (e.g., loose associations), behavior (e.g., catatonia, disorganization), attention, concentration, motivation (e.g., avolition, impaired intention and planning), and judgment. The principal manifestations of this disorder usually are described in terms of positive and negative (deficit) symptoms and, more recently, disorganized symptoms. Positive symptoms include hallucinations, delusions, bizarre behavior, hostility, uncooperativeness, and paranoid ideation, while negative symptoms include restricted range and intensity of emotional expression (affective flattening), reduced thought and speech productivity (alogia), anhedonia, apathy, and decreased initiation of goal-directed behavior (avolition). Disorganized symptoms include disorganized speech (thought disorder) and behavior and poor attention.

Short-term efficacy of oral aripiprazole monotherapy in the acute treatment of schizophrenia in adults was evaluated in 5 placebo-controlled studies of 4 and 6 weeks' duration principally in acutely relapsed, hospitalized patients who predominantly met DSM-III/IV criteria for schizophrenia. Four of the 5 studies were able to distinguish aripiprazole from placebo, but the smallest study did not. In the 4 positive studies, assessment of improvement in manifestations of schizophrenia was based on results of psychiatric rating scales, including the Positive and Negative Syndrome Scale (PANSS), the PANSS positive subscale, the PANSS negative subscale, and the Clinical Global Impressions (CGI) scale. Aripiprazole generally was found to be superior to placebo in improving both positive and negative manifestations in acute exacerbations of schizophrenia in these 4 studies. Efficacy of 10-, 15-, 20-, and 30-mg daily dosages of aripiprazole was established in 2 studies for each dosage; however, there was no evidence that higher dosages offered any therapeutic advantage over lower dosages in these studies. Active controls (haloperidol or risperidone) were used in addition to placebo controls in 3 of these studies, but study design did not allow for comparison between aripiprazole and the active controls. An examination of population subgroups did not reveal any clear evidence of differential responsiveness to the drug based on age, gender, or race.

In a longer-term study, adult inpatients or outpatients who met DSM-IV criteria for schizophrenia and who were, by history, symptomatically stable on other antipsychotic agents for at least 3 months were discontinued from those other agents and randomized to receive either oral aripiprazole 15 mg daily or placebo for up to 26 weeks of observation for relapse in the double-blind phase. Relapse was based on results of the CGI-Improvement and PANSS psychiatric rating scales. Patients receiving aripiprazole experienced a significantly longer time to relapse over the subsequent 26 weeks compared with those receiving placebo. In addition, pooled data from 2 double-blind, multicenter studies in acutely ill patients with schizophrenia in whom therapy with aripiprazole or haloperidol was continued for 52 weeks demonstrated a substantially higher rate of symptomatic remission across 52 weeks in the aripiprazole-treated patients compared with the haloperidol-treated patients; improved tolerability with aripiprazole may have contributed to the higher overall remission rates observed in this pooled analysis.

Short-term efficacy of oral aripiprazole in the acute treatment of schizophrenia in adolescents 13–17 years of age was evaluated in a double-blind, placebo-controlled trial of 6 weeks' duration in 302 outpatients who met DSM-IV criteria for schizophrenia and had a PANSS total score of 70 or more at baseline. Patients were randomized to receive a fixed dosage of aripiprazole 10 mg daily or 30 mg daily or to receive placebo. Both dosages of aripiprazole were found to be superior to placebo in reducing the PANSS total score, which was the primary efficacy measure; the 10-mg daily dosage also demonstrated superiority over placebo on the PANSS negative subscale score at the study

end point. However, the 30-mg daily dosage failed to demonstrate superiority over the 10-mg daily dosage. The drug was generally well tolerated.

Although the efficacy of aripiprazole as maintenance therapy in pediatric patients with schizophrenia has not been systematically evaluated, the manufacturer states that such efficacy can be extrapolated from adult data in addition to comparisons of aripiprazole pharmacokinetic parameters in adults and pediatric patients.

If aripiprazole is used for extended periods, the need for continued therapy should be reassessed periodically. (See Dosage and Administration: Dosage and see also Pediatric Use under Warnings/Precautions: Specific Populations, in Cautions.)

The American Psychiatric Association (APA) considers most atypical antipsychotic agents first-line drugs for the management of the acute phase of schizophrenia (including first psychotic episodes), principally because of the decreased risk of adverse extrapyramidal effects and tardive dyskinesia, with the understanding that the relative advantages, disadvantages, and cost-effectiveness of conventional and atypical antipsychotic agents remain controversial. The APA states that, with the possible exception of clozapine for the management of treatment-resistant symptoms, there currently is no definitive evidence that one atypical antipsychotic agent will have superior efficacy compared with another agent in the class, although meaningful differences in response may be observed in individual patients. Conventional antipsychotic agents may be considered first-line therapy in patients who have been treated successfully in the past with or who prefer conventional agents. The choice of an antipsychotic agent should be individualized, considering past response to therapy, adverse effect profile (including the patient's experience of subjective effects such as dysphoria), and the patient's preference for a specific drug, including route of administration.

For additional information on the symptomatic management of schizophrenia, including treatment recommendations and results of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study, see Schizophrenia and Other Psychotic Disorders under Uses: Psychotic Disorders, in the Phenothiazines General Statement 28:16.08.24.

■ **Bipolar Disorder** Aripiprazole is used as monotherapy or as an adjunct to either lithium or valproate for the acute and maintenance treatment of manic or mixed episodes associated with bipolar I disorder with or without psychotic features in adults and pediatric patients 10–17 years of age. According to DSM-IV criteria, manic episodes are distinct periods lasting 1 week or longer (or less than 1 week if hospitalization is required) of abnormally and persistently elevated, expansive, or irritable mood accompanied by at least 3 (or 4 if the mood is only irritability) of the following 7 symptoms: grandiosity, reduced need for sleep, pressure of speech, flight of ideas, distractability, increased goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation, and engaging in high-risk behavior (e.g., unrestrained buying sprees, sexual indiscretions, foolish business investments).

Efficacy of aripiprazole monotherapy in the treatment of acute manic and mixed episodes has been demonstrated in 4 short-term (i.e., 3 weeks' duration), placebo-controlled trials in hospitalized adults who met DSM-IV criteria for bipolar I disorder with manic or mixed episodes. These studies included patients with or without psychotic features and 2 of the studies also included patients with or without a rapid cycling course. The principal rating instrument used for assessing manic symptoms in these trials was the Young Mania Rating Scale (Y-MRS), an 11-item clinician-rated scale traditionally used to assess the degree of manic symptomatology in a range from 0 (no manic features) to 60 (maximum score). The main secondary rating instrument used in these trials was the Clinical Global Impression-Bipolar (CGI-BP) scale. In these trials, aripiprazole 15–30 mg once daily (with an initial dosage of 15 mg daily in 2 studies and an initial dosage of 30 mg daily in the other 2 studies) was found to be superior to placebo in the reduction of the Y-MRS total score and the CGI-BP Severity of Illness score (mania). In the 2 studies with an initial aripiprazole dosage of 15 mg daily, 48 and 44% of patients were receiving 15 mg daily at the study end point; in the 2 studies with an initial dosage of 30 mg daily, 86 and 85% of patients were receiving 30 mg daily at end point.

Aripiprazole is used as monotherapy for the acute and maintenance treatment of manic and mixed episodes associated with bipolar I disorder with or without psychotic features in pediatric patients 10–17 years of age. Efficacy of aripiprazole in the acute treatment of manic and mixed episodes has been demonstrated in a double-blind, placebo-controlled study of 4 weeks' duration in pediatric outpatients who met DSM-IV criteria for bipolar I disorder manic or mixed episodes (with or without psychotic features) and who had Y-MRS scores of 20 or greater at baseline. Patients in this study received aripiprazole 10 mg daily, aripiprazole 30 mg daily, or placebo. Aripiprazole was initiated at a dosage of 2 mg daily, then titrated to 5 mg daily after 2 days, and to the target dosage of 10 mg daily in 5 days or 30 mg daily in 13 days. Both dosages of aripiprazole were found to be superior to placebo in the reduction of the Y-MRS total score from baseline to week 4.

Efficacy of aripiprazole as an adjunct to lithium or valproate in the treatment of acute manic and mixed episodes has been demonstrated in a placebo-controlled study of 6 weeks' duration in adult outpatients who met DSM-IV criteria for bipolar I disorder manic or mixed type (with or without psychotic features). Patients initially received open-label lithium (dosage producing a serum lithium concentration of 0.6–1 mEq/L) or valproate (dosage producing a serum valproic acid concentration of 50–125 mcg/mL) monotherapy for 2 weeks during the lead-in phase. At the end of 2 weeks, patients demonstrating an inadequate response to lithium or valproate were randomized to receive either aripiprazole (15 mg daily or increased to 30 mg daily as early as day 7) or placebo as adjunctive therapy with open-label lithium or valproate during the 6-week, placebo-controlled phase. Patients who received adjunctive aripiprazole with lithium or valproate demonstrated greater reductions in the Y-MRS total score and the CGI-BP Severity of Illness score (mania) compared with patients who received adjunctive placebo with lithium or valproate.

The use of aripiprazole as an adjunct to lithium or valproate in the acute treatment of manic or mixed episodes associated with bipolar I disorder has not been evaluated in the pediatric population. However, the manufacturer states that such efficacy can be extrapolated from adult data in addition to comparisons of aripiprazole pharmacokinetic parameters in adults and pediatric patients.

For the initial management of less severe manic or mixed episodes in patients with bipolar disorder, current APA recommendations state that monotherapy with lithium, valproate (e.g., valproate sodium, valproic acid, divalproex), or an antipsychotic such as olanzapine may be adequate. For more severe manic or mixed episodes, combination therapy with an antipsychotic and lithium or valproate is recommended as first-line therapy. For further information on the management of bipolar disorder, see Uses: Bipolar Disorder, in Lithium Salts 28:28.

The efficacy of aripiprazole as longer-term therapy (i.e., longer than 3 weeks) in adults with bipolar I disorder was demonstrated in a double-blind, placebo-controlled trial in patients with a recent manic or mixed episode who had been stabilized on aripiprazole (15–30 mg daily) and then maintained on the drug for at least 6 consecutive weeks. Following this 6-week maintenance phase, patients were randomized to receive either placebo or aripiprazole and monitored for manic or depressive relapse. Patients receiving aripiprazole experienced a significant delay in time to relapse and there were fewer relapses among those receiving aripiprazole than among those receiving placebo.

An analysis of these data for possible age- and gender-related effects on treatment outcome did not suggest any difference in aripiprazole's efficacy in bipolar disorder based on the age and gender of the patient; however, there were insufficient numbers of patients in each of the ethnic groups to adequately assess race-related effects.

Although the efficacy of aripiprazole as maintenance therapy in pediatric patients with bipolar disorder has not been evaluated, the manufacturer states that such efficacy can be extrapolated from adult data in addition to comparisons of aripiprazole pharmacokinetic parameters in adults and pediatric patients.

The manufacturer states that the efficacy of aripiprazole in bipolar disorder has not been systematically evaluated for long-term use (i.e., exceeding 6 weeks) and recommends that clinicians who elect to use aripiprazole for extended periods periodically reevaluate the long-term risks and benefits of the drug for the individual patient.

■ **Major Depressive Disorder** Aripiprazole is used orally as an adjunct to antidepressants for the acute treatment of major depressive disorder in adults. The adjunctive efficacy of aripiprazole has been demonstrated in 2 short-term, double-blind, placebo-controlled trials of 6 weeks' duration in adults who met DSM-IV criteria for major depressive disorder and who had an inadequate response to previous antidepressant therapy (1–3 courses) in the current episode and who had also demonstrated an inadequate response during a prospective treatment period to 8 weeks of antidepressant therapy with extended-release paroxetine, extended-release venlafaxine, fluoxetine, escitalopram, or sertraline. The primary instrument used for assessing depressive symptoms was the Montgomery-Asberg Depression Rating Scale (MADRS), a 10-item clinician-rated scale used to assess the degree of depressive symptomatology. The principal secondary instrument was the Sheehan Disability Scale (SDS), a 3-item self-rated instrument used to assess the impact of depression on three domains of functioning (work/school, social life, and family life), with each item scored from 0 (not at all) to 10 (extreme). In both of these trials, aripiprazole was found to be superior to placebo in reducing mean MADRS total scores; aripiprazole was also superior to placebo in reducing the mean SDS score in one study. Patients in both trials initially received an aripiprazole dosage of 5 mg daily; subsequent dosage adjustments, based on efficacy and tolerability, could be made in 5-mg increments 1 week apart. Allowable aripiprazole dosages were 2, 5, 10, and 15 mg daily; patients who were not receiving the potent cytochrome P-450 (CYP) isoenzyme 2D6 inhibitors fluoxetine and paroxetine could also receive 20 mg daily.

An analysis of population subgroups did not reveal evidence of differential response based on age, choice of prospective antidepressant, or race. With regard to gender, a smaller mean reduction in the MADRS total score was observed in males than in females.

■ **Agitation Associated with Schizophrenia or Bipolar Mania** Aripiprazole is used IM for the acute management of agitation associated with schizophrenia or bipolar disorder, mixed or manic, in adults for whom treatment with aripiprazole is appropriate and who require an IM antipsychotic agent for rapid control of behaviors that interfere with diagnosis and care (e.g., threatening behaviors, escalating or urgently distressing behavior, self-exhausting behavior). According to DSM-IV, psychomotor agitation is defined as excessive motor activity associated with a feeling of inner tension.

The efficacy of IM aripiprazole for the management of acute agitation was established in 3 short-term (i.e., single-day), placebo-controlled trials in hospitalized, agitated patients with either schizophrenia or bipolar I disorder (manic or mixed episodes, with or without psychotic features). Each of the 3

trials used a single active comparator treatment of either haloperidol injection (for the schizophrenia studies) or lorazepam (for the bipolar mania study). Patients enrolled in the studies needed to be judged by the investigators as clinically agitated and appropriate candidates for IM therapy. In addition, the patients needed to exhibit a level of agitation that met or exceeded a threshold score of 15 on the 5 items constituting the Positive and Negative Syndrome Scale (PANSS) Excited Component (i.e., poor impulse control, tension, hostility, uncooperativeness, and excitement items) with at least 2 individual item scores of 4 ("moderate") or greater using a 1–7 scoring system, where scores of 1 or 7 indicate absent or extreme agitation, respectively. The primary measure used for assessing efficacy in managing agitation in these trials was the change from baseline in the PANSS Excited Component at 2 hours postinjection. A key secondary measure was the Clinical Global Impression of Improvement (CGI-I) scale. Patients could receive up to 3 injections of IM aripiprazole; however, patients could not receive the second injection until after the initial 2-hour period when the primary efficacy measure was assessed.

In the first placebo-controlled trial, IM aripiprazole was given in fixed single doses of 1, 5.25, 9.75, or 15 mg in agitated hospitalized patients presenting predominantly with schizophrenia. All IM aripiprazole doses, with the exception of the 1-mg dose, were found to be superior to placebo in reducing the PANSS Excited Component score and on the CGI-I scale at 2 hours following injection in this study. In the second placebo-controlled trial in agitated hospitalized patients predominantly with schizophrenia, one fixed IM dose of aripiprazole 9.75 mg was evaluated and found to be superior to placebo on the PANSS Excited Component and on the CGI-I scale at 2 hours following injection. In the third placebo-controlled trial in agitated hospitalized patients with bipolar I disorder (manic or mixed), 2 fixed aripiprazole injection doses of 9.75 mg and 15 mg were evaluated; both doses were found to be superior to placebo in reducing the PANSS Excited Component score at 2 hours postinjection. An analysis of these 3 controlled studies for possible age-, race-, or gender-related effects on treatment outcome did not suggest any difference in efficacy based on these patient characteristics.

Dosage and Administration

■ **Administration** Aripiprazole conventional tablets, orally disintegrating tablets, and oral solution are administered orally once daily without regard to meals. Aripiprazole injection is administered *only* by IM injection.

Patients receiving aripiprazole orally disintegrating tablets should be instructed not to remove a tablet from the blister package until just prior to dosing. With dry hands, the blister package should be peeled open to expose a tablet. The tablet should then be removed and placed on the tongue, where it rapidly disintegrates in saliva. The manufacturer recommends that the orally disintegrating tablets be taken without liquid; however, they may be taken with liquid, if necessary. Orally disintegrating tablets should *not* be split.

Aripiprazole injection should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. The required volume of injection should be withdrawn from the vial into a syringe and then injected slowly IM, deep into the muscle mass. Aripiprazole injection should *not* be administered IV or subcutaneously. Unused portions of the solution should be discarded.

Patients receiving aripiprazole should be monitored for possible worsening of depression, suicidality, or unusual changes in behavior, especially at the beginning of therapy or during periods of dosage adjustment. (See Worsening of Depression and Suicidality Risk under Warnings/Precautions: Warnings, in Cautions.)

■ **Dosage** Aripiprazole oral solution may be given at the same dose on a mg-per-mg basis as the conventional tablet strengths of the drug up to a dose of 25 mg. However, if the oral solution is used in patients who were receiving aripiprazole 30 mg as conventional tablets, a dose of 25 mg of the oral solution should be used.

Since conventional tablets and orally disintegrating tablets of aripiprazole are bioequivalent, dosing for the orally disintegrating tablets is the same as for the conventional tablets. However, IM administration of a dose of the commercially available injection results in maximum plasma aripiprazole concentrations and areas under the plasma concentration-time curve (AUCs) (2 hours post-administration) that are about 19 and 90% higher, respectively, than those resulting from an identical oral dose.

Schizophrenia For the acute management of schizophrenia in adults, the recommended initial and target dosage of aripiprazole is 10 or 15 mg orally once daily. Although dosages ranging from 10–30 mg daily administered as conventional tablets were effective in clinical trials, the manufacturer states that dosages exceeding 10–15 mg daily did not result in greater efficacy. Because steady-state plasma concentrations of aripiprazole and dehydro-aripiprazole, its active metabolite, may not be attained for 2 weeks, dosage adjustments generally should be made at intervals of not less than 2 weeks.

For the acute management of schizophrenia in adolescents 13–17 years of age, the recommended target dosage of aripiprazole is 10 mg orally once daily. Therapy was initiated in a dosage of 2 mg once daily in these patients, with subsequent titration to 5 mg once daily after 2 days and to 10 mg once daily after 2 additional days. The manufacturer recommends that any subsequent dosage increases be made in 5-mg once daily increments. Although aripiprazole dosages of 10 and 30 mg once daily administered as conventional tablets have been studied in adolescents, the 30-mg daily dosage was not found to be more effective than the 10-mg daily dosage.

The optimum duration of oral aripiprazole therapy in patients with schizophrenia currently is not known, but maintenance therapy with aripiprazole 15 mg once daily as conventional tablets has been shown to be effective in preventing relapse for up to 26 weeks in adults. In addition, a combined analysis of data from 2 double-blind, multicenter studies indicates that maintenance therapy with the drug may be effective for up to 52 weeks in adults.

Although the efficacy of oral aripiprazole as maintenance therapy in pediatric patients with schizophrenia has not been systematically evaluated, the manufacturer states that such efficacy can be extrapolated from adult data in addition to comparisons of aripiprazole pharmacokinetic parameters in adults and pediatric patients.

The American Psychiatric Association (APA) states that prudent long-term treatment options in patients with schizophrenia with remitted first episodes or multiple episodes include either indefinite maintenance therapy or gradual discontinuance of the antipsychotic agent with close follow-up and a plan to reinstitute treatment upon symptom recurrence. Discontinuance of antipsychotic therapy should be considered only after a period of at least 1 year of symptom remission or optimal response while receiving the antipsychotic agent. In patients who have had multiple previous psychotic episodes or 2 psychotic episodes within 5 years, indefinite maintenance antipsychotic treatment is recommended.

The manufacturer states that it is generally recommended that patients responding to aripiprazole therapy should continue to receive the drug beyond the acute response, but at the lowest dosage needed to maintain remission. The need for continued therapy with the drug should be reassessed periodically.

There are no systematically collected data to specifically address switching patients with schizophrenia from other antipsychotic agents to aripiprazole or concerning concomitant administration with other antipsychotic agents. Immediate discontinuance of the previous antipsychotic agent may be acceptable in some patients with schizophrenia, and more gradual discontinuance may be most appropriate for other patients. In all patients, the period of overlapping antipsychotic administration should be minimized.

Bipolar Disorder For the management of manic and mixed episodes associated with bipolar I disorder in adults, the recommended initial and target aripiprazole dosage in adults is 15 mg given orally once daily as monotherapy or as adjunctive therapy with lithium or valproate. Based on clinical response, the dosage can be increased to 30 mg daily. However, safety of aripiprazole dosages exceeding 30 mg daily has not been established.

For the management of manic and mixed episodes associated with bipolar I disorder in pediatric patients 10–17 years of age, the manufacturer recommends a target aripiprazole dosage of 10 mg daily given orally as monotherapy or as adjunctive therapy with lithium or valproate. In clinical studies, aripiprazole dosages of 10 or 30 mg daily were found to be effective; initially, pediatric patients received 2 mg daily for 2 days, then 5 mg daily for an additional 2 days, and then the target dosage of 10 mg daily. Subsequent increases in the daily dosage of aripiprazole should be made in 5-mg increments.

The optimum duration of aripiprazole therapy, whether used as monotherapy or as adjunctive therapy, for bipolar I disorder currently is not known. While it is generally agreed that pharmacologic treatment beyond an acute response in mania is desirable, both for maintenance of the initial response and for prevention of new manic episodes, there are no systematically obtained data to support the use of aripiprazole beyond 6 weeks in adults. The manufacturer states that clinicians who elect to use aripiprazole in adults for extended periods should periodically reevaluate the long-term risks and benefits of the drug for the individual patient.

The efficacy of aripiprazole for maintenance therapy of bipolar I disorder in pediatric patients has not been evaluated; however, such efficacy can be extrapolated from adult data along with comparisons of pharmacokinetic parameters of the drug in adults and pediatric patients. It is generally recommended that responding pediatric patients continue to receive aripiprazole beyond the acute response, but at the lowest dosage needed to maintain remission. Pediatric patients should be periodically reassessed to determine the need for maintenance therapy.

Major Depressive Disorder For adjunctive management of major depressive disorder in adults already receiving an antidepressant, the manufacturer recommends an initial aripiprazole dosage of 2–5 mg orally once daily for acute treatment. Subsequent dosage adjustments of up to 5 mg daily should occur gradually at intervals of at least 1 week. Efficacy of the drug was established within a dosage range of 2–15 mg daily in clinical studies.

The manufacturer states that the efficacy of aripiprazole for adjunctive maintenance treatment of major depressive disorder has not been evaluated and the optimum duration of aripiprazole maintenance therapy for major depressive disorder is not known. If aripiprazole is used for maintenance therapy, the need for continued therapy with the drug should be reassessed periodically.

Agitation associated with Schizophrenia or Bipolar Mania For the prompt control of agitation associated with schizophrenia or bipolar mania in adults, the recommended dose of aripiprazole is 9.75 mg given IM as a single dose. In clinical trials, effectiveness of IM aripiprazole in controlling agitation in schizophrenia and bipolar mania was demonstrated with doses of 5.25–15 mg IM; however, no additional benefit was demonstrated for the 15-mg dose compared with the 9.75-mg dose. A lower initial IM dose of 5.25 mg may be considered when clinically warranted.

If agitation persists following the initial dose of aripiprazole, subsequent doses up to a cumulative dose of 30 mg daily may be given. However, the

manufacturer states that the efficacy of repeated doses of IM aripiprazole in agitated patients has not been systematically evaluated in controlled trials. In addition, the safety of total daily IM doses exceeding 30 mg or IM injections given more frequently than every 2 hours has not been adequately evaluated in clinical trials.

If continued aripiprazole therapy is clinically necessary, oral aripiprazole therapy in a dosage of 10–30 mg daily should replace IM therapy as soon as possible.

■ **Special Populations** No dosage adjustment is necessary in patients with renal or hepatic impairment or in geriatric patients. In addition, no dosage adjustment is recommended based on gender or race.

Dosage of aripiprazole should be reduced to one-half the usual dosage in patients receiving concomitant therapy with potent inhibitors of cytochrome P-450 (CYP) isoenzyme 3A4 (e.g., clarithromycin, ketoconazole). Dosage of aripiprazole should be reduced to at least one-half the usual dosage in patients receiving concomitant therapy with potential inhibitors of CYP2D6 (e.g., quinidine, fluoxetine, paroxetine). The aripiprazole dosage may be increased to the usual dosage after discontinuance of the CYP3A4 or CYP2D6 inhibitor. (See Drug Interactions: Ketoconazole and Other CYP3A4 Inhibitors and see also Drug Interactions: Quinidine and Other CYP2D6 Inhibitors.)

Dosage of aripiprazole should be doubled upon initiation of concomitant therapy with drugs that induce CYP3A4 (e.g., carbamazepine); additional dosage escalation should be based on clinical evaluation. The aripiprazole dosage should be decreased to 10–15 mg daily if the CYP3A4 inducer is discontinued. (See Drug Interactions: Carbamazepine and Other CYP3A4 Inducers.)

Cautions

■ **Contraindications** Known hypersensitivity reaction to aripiprazole or any ingredient in the formulation; such reactions have ranged from pruritus/urticaria to anaphylaxis.

■ **Warnings/Precautions** ***Warnings*** **Increased Mortality in Geriatric Patients with Dementia-related Psychosis.** Geriatric patients with dementia-related psychosis treated with antipsychotic drugs appear to be at an increased risk of death compared with patients receiving placebo. Analyses of 17 placebo-controlled trials (modal duration of 10 weeks) revealed an approximate 1.6- to 1.7-fold increase in mortality among geriatric patients receiving atypical antipsychotic drugs (i.e., aripiprazole, olanzapine, quetiapine, risperidone) compared with that observed in patients receiving placebo. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5% compared with a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Observational studies suggest that, similar to atypical antipsychotics, treatment with conventional (first-generation) antipsychotics may increase mortality; the extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients remains unclear. In addition, an increased incidence of cerebrovascular adverse effects (e.g., stroke, transient ischemic attack), including fatalities, has been observed in geriatric patients treated with aripiprazole in several placebo-controlled studies (2 flexible-dose studies and one fixed-dose study) of dementia-related psychosis. A statistically significant dose-response relationship for adverse cerebrovascular effects was observed in patients receiving the drug in the fixed-dose study. In 3 placebo-controlled trials of 10 weeks' duration evaluating aripiprazole in geriatric patients with psychosis associated with Alzheimer's disease, adverse effects reported in 3% or more of patients and with an incidence of at least twice that of placebo included lethargy, somnolence (including sedation), incontinence (primarily urinary incontinence), excessive salivation, and lightheadedness.

The manufacturer states that the safety and efficacy of aripiprazole in the treatment of patients with psychosis associated with dementia have not been established and that the drug is not approved for the treatment of patients with dementia-related psychosis. If the clinician elects to treat such patients with aripiprazole, vigilance should be exercised, particularly for the emergence of difficulty swallowing or excessive somnolence, which could predispose to accidental injury or aspiration. (See Geriatric Use under Warnings/Precautions: Specific Populations, in Cautions.)

Worsening of Depression and Suicidality Risk. Worsening of depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior may occur in both adult and pediatric (see Pediatric Use under Warnings/Precautions: Specific Populations, in Cautions) patients with major depressive disorder or other psychiatric disorders, whether or not they are taking antidepressants. This risk may persist until clinically important remission occurs. Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are the strongest predictors of suicide. However, there has been a long-standing concern that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients during the early phases of treatment. Pooled analyses of short-term, placebo-controlled studies of antidepressants (i.e., selective serotonin-reuptake inhibitors and other antidepressants) have shown an increased risk of suicidality in children, adolescents, and young adults (18–24 years of age) with major depressive disorder and other psychiatric disorders. An increased suicidality risk was not demonstrated with antidepressants compared with placebo in adults older than 24 years of age and a reduced risk was observed in adults 65 years of age or older.

The US Food and Drug Administration (FDA) recommends that all patients being treated with antidepressants for any indication be appropriately monitored and closely observed for clinical worsening, suicidality, and unusual changes in behavior, particularly during initiation of therapy (i.e., the first few months) and during periods of dosage adjustments. Families and caregivers of patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and nonpsychiatric, also should be advised to monitor patients on a daily basis for the emergence of agitation, irritability, or unusual changes in behavior as well as the emergence of suicidality, and to report such symptoms immediately to a health-care provider.

Although a causal relationship between the emergence of symptoms such as anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia, hypomania, and/or mania and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality. Consequently, consideration should be given to changing the therapeutic regimen or discontinuing therapy in patients whose depression is persistently worse or in patients experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, particularly if such manifestations are severe, abrupt in onset, or were not part of the patient's presenting symptoms. FDA also recommends that the drugs be prescribed in the smallest quantity consistent with good patient management, in order to reduce the risk of overdosage.

It is generally believed (though not established in controlled trials) that treating a major depressive episode with an antidepressant alone may increase the likelihood of precipitating a mixed or manic episode in patients at risk for bipolar disorder. Therefore, patients with depressive symptoms should be adequately screened for bipolar disorder prior to initiating treatment with an antidepressant; such screening should include a detailed psychiatric history (e.g., family history of suicide, bipolar disorder, and depression).

Aripiprazole is not approved for use in treating depression in the pediatric population. (See Pediatric Use under Warnings/Precautions: Specific Populations, in Cautions.)

Other Warnings and Precautions **Neuroleptic Malignant Syndrome.** Neuroleptic malignant syndrome (NMS), a potentially fatal syndrome requiring immediate discontinuance of the drug and intensive symptomatic treatment, has been reported in patients receiving antipsychotic agents, including rare cases associated with aripiprazole therapy. If a patient requires antipsychotic therapy following recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. If antipsychotic therapy is reintroduced, the dosage generally should be increased gradually and an antipsychotic agent other than the agent believed to have precipitated NMS generally should be chosen. In addition, such patients should be carefully monitored since recurrences of NMS have been reported in some patients. For additional information on NMS, see Neuroleptic Malignant Syndrome under Cautions: Nervous System Effects, in the Phenothiazines General Statement 28:16.08.24.

Tardive Dyskinesia. Because use of antipsychotic agents, including aripiprazole, may be associated with tardive dyskinesia (a syndrome of potentially irreversible, involuntary, dyskinetic movements), aripiprazole should be prescribed in a manner that is most likely to minimize the occurrence of this syndrome. Chronic antipsychotic treatment generally should be reserved for patients who suffer from a chronic illness that is known to respond to antipsychotic agents, and for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the lowest dosage and the shortest duration of treatment producing a satisfactory clinical response should be sought, and the need for continued treatment should be reassessed periodically. The American Psychiatric Association (APA) currently recommends that patients receiving atypical antipsychotic agents be assessed clinically for abnormal involuntary movements every 12 months and that patients considered to be at increased risk for tardive dyskinesia be assessed every 6 months. For additional information on tardive dyskinesia, see Tardive Dyskinesia under Cautions: Nervous System Effects, in the Phenothiazines General Statement 28:16.08.24.

Hyperglycemia and Diabetes Mellitus. Severe hyperglycemia, sometimes associated with ketoacidosis, hyperosmolar coma, or death, has been reported in patients treated with all atypical antipsychotic agents. While confounding factors such as an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population make it difficult to establish with certainty the relationship between use of agents in this drug class and glucose abnormalities, epidemiologic studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotic agents included in the studies (e.g., clozapine, olanzapine, quetiapine, risperidone); it remains to be determined whether aripiprazole also is associated with this increased risk. Although there have been few reports of hyperglycemia in patients receiving aripiprazole, it is not known whether the paucity of such reports is due to relatively limited experience with the drug.

Precise risk estimates for hyperglycemia-related adverse events in patients treated with atypical antipsychotics currently are not available. While some evidence suggests that the risk for diabetes may be greater with some atypical antipsychotics (e.g., clozapine, olanzapine) than with others (e.g., quetiapine, risperidone) in the class, available data are conflicting and insufficient to provide reliable estimates of relative risk associated with use of the various atypical antipsychotics.

The manufacturers of atypical antipsychotic agents state that patients with preexisting diabetes mellitus in whom therapy with an atypical antipsychotic is initiated should be closely monitored for worsening of glucose control; those with risk factors for diabetes (e.g., obesity, family history of diabetes) should undergo fasting blood glucose testing upon therapy initiation and periodically throughout treatment. Any patient who develops manifestations of hyperglycemia (including polydipsia, polyuria, polyphagia, and weakness) during treatment with an atypical antipsychotic should undergo fasting blood glucose testing. In some cases, patients who developed hyperglycemia while receiving an atypical antipsychotic have required continuance of antidiabetic treatment despite discontinuance of the suspect drug; in other cases, hyperglycemia resolved with discontinuance of the antipsychotic.

For further information on managing the risk of hyperglycemia and diabetes mellitus associated with atypical antipsychotic agents, see Hyperglycemia and Diabetes Mellitus under Cautions: Precautions and Contraindications, in Clozapine 28:16.08.04.

Orthostatic Hypotension. Orthostatic hypotension and associated adverse effects (e.g., postural dizziness, syncope) have been reported in patients receiving oral or IM aripiprazole. The drug should be used with caution in patients with known cardiovascular disease (e.g., heart failure, history of myocardial infarction or ischemia, conduction abnormalities), cerebrovascular disease, and/or conditions that would predispose patients to hypotension (e.g., dehydration, hypovolemia, concomitant antihypertensive therapy).

If parenteral benzodiazepine therapy is necessary in patients receiving IM aripiprazole, patients should be monitored for excessive sedation and orthostatic hypotension. (See Drug Interactions: Lorazepam and Other Benzodiazepines.)

Leukopenia, Neutropenia, and Agranulocytosis. In clinical trial and/or postmarketing experience, leukopenia and neutropenia have been temporally related to antipsychotic agents, including aripiprazole. Agranulocytosis also has been reported.

Risk factors for leukopenia and neutropenia include preexisting low leukocyte count and a history of drug-induced leukopenia and neutropenia. Patients with a history of clinically important low leukocyte count or drug-induced leukopenia and neutropenia should have their complete blood count monitored frequently during the first few months of therapy. Discontinuance of aripiprazole should be considered at the first sign of a clinically important decline in leukocyte count in the absence of other causative factors.

Patients with clinically significant neutropenia should be carefully monitored for fever or other signs or symptoms of infection and promptly treated if such signs and symptoms occur. In patients with severe neutropenia (absolute neutrophil count [ANC] less than 1000/mm^3), aripiprazole should be discontinued and the leukocyte count monitored until recovery occurs. Lithium has reportedly been used successfully in the treatment of several cases of leukopenia associated with aripiprazole, clozapine, and some other drugs; however, further clinical experience is needed to confirm these anecdotal findings.

Seizures. Seizures have occurred in 0.1% of adults treated with oral aripiprazole, in 0.3% of pediatric patients 10–17 years of age, and in 0.2% of adults treated with parenteral aripiprazole. Aripiprazole should be used with caution in patients with a history of seizures or other conditions that may lower the seizure threshold (e.g., dementia of the Alzheimer's type); conditions that lower the seizure threshold may be more prevalent in geriatric patients 65 years of age or older.

Cognitive and Motor Impairment. Like other antipsychotic agents, aripiprazole potentially may impair judgment, thinking, or motor skills. In short-term clinical trials, somnolence (including sedation) was reported in 11 and 9% of adults treated with oral or parenteral aripiprazole, respectively, compared with 6% of those receiving placebo. In pediatric patients 10–17 years of age, somnolence (including sedation) was reported in 21% of aripiprazole-treated patients compared with 5% of those receiving placebo. (See Advice to Patients.)

Body Temperature Regulation. Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. The manufacturer recommends appropriate caution when aripiprazole is used in patients exposed to conditions that may contribute to an elevation in core body temperature (e.g., dehydration, extreme heat, strenuous exercise, concomitant use of anticholinergic agents).

Suicide. Attendant risk with psychotic illnesses, bipolar disorder, and major depressive disorder; high-risk patients should be closely supervised. In 2 clinical trials evaluating aripiprazole as adjunctive therapy in patients with major depressive disorder, there were no reported cases of suicidal ideation or suicide attempt in the aripiprazole-treated patients; the incidence of suicidal ideation and suicide attempt was 0.5% in the placebo recipients. Aripiprazole should be prescribed in the smallest quantity consistent with good patient management to reduce the risk of overdosage. (See Worsening of Depression and Suicidality Risk under Warnings/Precautions: Warnings, in Cautions.)

Dysphagia. Esophageal dysmotility and aspiration have been associated with the use of antipsychotic agents, including aripiprazole. These agents should be used with caution in patients at risk for aspiration pneumonia (e.g., geriatric patients, those with advanced Alzheimer's dementia). (See Increased Mortality in Geriatric Patients with Dementia-related Psychosis under Warnings/Precautions: Warnings, in Cautions and see Geriatric Use under Warnings/Precautions: Special Populations, in Cautions.)

Phenylketonuria. Individuals with phenylketonuria (i.e., homozygous genetic deficiency of phenylalanine hydroxylase) and other individuals who must restrict their intake of phenylalanine should be warned that each aripiprazole 10- or 15-mg orally disintegrating tablet contains aspartame, which is metabolized in the GI tract to provide about 1.12 or 1.68 mg of phenylalanine, respectively, following oral administration. Aripiprazole conventional tablets do not contain aspartame.

Concomitant Illnesses. Experience with aripiprazole in patients with certain concomitant diseases is limited. (See Increased Mortality in Geriatric Patients with Dementia-related Psychosis under Warnings/Precautions: Warnings, in Cautions.)

Aripiprazole has not been adequately evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable cardiovascular disease and patients with these conditions were excluded from premarketing clinical studies. Because of the risk of orthostatic hypotension associated with aripiprazole, the manufacturer states that the drug should be used with caution in patients with cardiovascular disease, cerebrovascular disease, and/or other conditions that would predispose patients to hypotension (e.g., dehydration, hypovolemia, concomitant antihypertensive therapy). (See Orthostatic Hypotension under Warnings/Precautions: Other Warnings and Precautions, in Cautions.)

Specific Populations **Pregnancy.** Category C. (See Users Guide.)

Lactation. Aripiprazole is distributed into milk in rats. Not known whether aripiprazole is distributed into milk in humans. The manufacturer states that women receiving aripiprazole should not breast-feed.

Pediatric Use. Safety and efficacy of oral aripiprazole not established in pediatric patients with major depressive disorder. Safety and efficacy of IM aripiprazole not established for agitation associated with schizophrenia or bipolar mania in pediatric patients.

Safety and efficacy of oral aripiprazole for the acute management of schizophrenia in pediatric patients 13–17 years of age have been established in a placebo-controlled study of 6 weeks' duration. Although the efficacy of oral aripiprazole for maintenance treatment of schizophrenia has not been systematically evaluated, the manufacturer states that such efficacy can be extrapolated from adult data in addition to comparisons of aripiprazole pharmacokinetic parameters in adults and pediatric patients. (See Schizophrenia under Uses: Psychotic Disorders.)

Safety and efficacy of oral aripiprazole monotherapy for the acute management of bipolar mania in pediatric patients 10–17 years of age have been established in a placebo-controlled study of 4 weeks' duration. Although the efficacy of oral aripiprazole for maintenance treatment in bipolar disorder has not been established, such efficacy can be extrapolated from adult data in addition to pharmacokinetic comparisons of aripiprazole between adult and pediatric populations.

The efficacy of oral aripiprazole as an adjunct to lithium or valproate for the management of manic or mixed episodes in pediatric patients has not been evaluated. However, efficacy can be extrapolated from adult data in addition to pharmacokinetic comparisons of aripiprazole between adult and pediatric populations.

Mean weight gain of 0.13 kg was reported in pediatric patients with schizophrenia receiving aripiprazole compared with a mean loss of 0.83 kg in those receiving placebo in a short-term (6-week) study; 5% of aripiprazole-treated patients gained 7% or more of their baseline weight compared with 1% of those receiving placebo.

FDA warns that a greater risk of suicidal thinking or behavior (suicidality) occurred during the first few months of antidepressant treatment compared with placebo in children and adolescents with major depressive disorder, obsessive-compulsive disorder (OCD), or other psychiatric disorders based on pooled analyses of 24 short-term, placebo-controlled trials of 9 antidepressant drugs (selective serotonin-reuptake inhibitors [SSRIs] and other antidepressants). However, a more recent meta-analysis of 27 placebo-controlled trials of 9 antidepressants (SSRIs and others) in patients younger than 19 years of age with major depressive disorder, OCD, or non-OCD anxiety disorders suggests that the benefits of antidepressant therapy in treating these conditions may outweigh the risks of suicidal behavior or suicidal ideation. No suicides occurred in these pediatric trials.

These findings should be carefully considered when assessing potential benefits and risks of aripiprazole in a child or adolescent for any clinical use. (See Worsening of Depression and Suicidality Risk under Warnings/Precautions: Warnings, in Cautions.)

Geriatric Use. In clinical studies, approximately 8% of over 13,000 patients treated with oral aripiprazole were 65 years of age or older and approximately 6% were 75 years of age or older; the majority of these geriatric patients (81%) were diagnosed with dementia of the Alzheimer's type. Experience from placebo-controlled trials with oral aripiprazole in patients with schizophrenia, bipolar mania, or major depressive disorder who are 65 years of age and older is insufficient to determine whether they respond differently than younger adults.

In clinical studies, approximately 13% of over 700 patients treated with IM aripiprazole were 65 years of age or older and approximately 10% were 75 years of age or older. Experience from placebo-controlled trials with aripiprazole injection in patients with agitation associated with schizophrenia or bipolar mania who are 65 years of age and older is insufficient to determine whether they respond differently than younger adults.

Studies in patients with psychosis in association with dementia of the Alz-

heimer's type have suggested that aripiprazole may have a different tolerability profile in patients 65 years of age or older compared with younger patients with schizophrenia. The manufacturer states that the safety and efficacy of aripiprazole in the treatment of dementia-associated psychosis have not been established and that the drug is *not* approved for the treatment of dementia-related psychosis. If a clinician decides to treat geriatric patients with dementia-associated psychosis with aripiprazole, the manufacturer recommends that caution be exercised (see Increased Mortality in Geriatric Patients with Dementia-related Psychosis under Warnings/Precautions: Warnings, in Cautions). For additional information on the use of antipsychotic agents in the management of dementia-related psychosis, see Geriatric Considerations under Uses: Psychotic Disorders, in the Phenothiazines General Statement 28:16.08.24.

In pooled data analyses, a *reduced* risk of suicidality was observed in adults 65 years of age or older with antidepressant therapy compared with placebo. (See Worsening of Depression and Suicidality Risk under Warnings/Precautions: Warnings, in Cautions.)

■ **Common Adverse Effects** Adverse effects occurring in 10% or more of adults receiving oral aripiprazole in clinical trials include nausea, vomiting, constipation, headache, dizziness, akathisia, anxiety, insomnia, and restlessness.

Adverse effects occurring in 10% or more of pediatric patients receiving oral aripiprazole in clinical trials include somnolence, extrapyramidal disorder, headache, and nausea.

In clinical trials, nausea was the only adverse effect that occurred in more than 5% of patients with agitation associated with schizophrenia or bipolar mania receiving IM aripiprazole and at an incidence at least twice that for placebo.

Drug Interactions

■ **Drugs Affecting Hepatic Microsomal Enzymes** Cytochrome P-450 (CYP) isoenzyme 3A4 (CYP3A4) inducers (e.g., carbamazepine), CYP3A4 inhibitors (e.g., clarithromycin, ketoconazole), or CYP2D6 inhibitors (e.g., fluoxetine, paroxetine, quinidine): potential pharmacokinetic interaction (altered aripiprazole metabolism); dosage adjustment generally recommended. (See Dosage and Administration: Special Populations, Drug Interactions: Carbamazepine and Other CYP3A4 Inducers, Drug Interactions: Ketoconazole and Other CYP3A4 Inhibitors, and Drug Interactions: Quinidine and Other CYP2D6 Inhibitors.)

Inhibitors or inducers of CYP isoenzyme 1A1, 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, or 2E1: pharmacokinetic interaction unlikely. (See Drug Interactions: Smoking.)

■ **Drugs Metabolized by Hepatic Microsomal Enzymes** Substrates of CYP isoenzyme 1A2, 2C9, 2C19, 2D6, and 3A4: pharmacokinetic interaction unlikely.

■ **Carbamazepine and Other CYP3A4 Inducers** Concurrent administration of carbamazepine (200 mg twice daily), a potent CYP3A4 inducer, and aripiprazole (30 mg daily) resulted in an approximate 70% decrease in peak plasma concentration and area under the plasma concentration-time curve (AUC) values of both aripiprazole and its active metabolite, dehydro-aripiprazole.

When a potential CYP3A4 inducer such as carbamazepine is added to aripiprazole therapy, the dosage of aripiprazole should be doubled; additional dosage increases should be based on clinical evaluation. When the CYP3A4 inducer is withdrawn from combined therapy, the aripiprazole dosage should be reduced to 10–15 mg daily. (See Dosage and Administration: Special Populations.)

■ **Ketoconazole and Other CYP3A4 Inhibitors** Concurrent administration of ketoconazole (200 mg daily for 14 days), a potent CYP3A4 inhibitor, and a single 15-mg dose of aripiprazole increased the AUCs of aripiprazole and its active metabolite by 63 and 77%, respectively; the effect of a higher ketoconazole dosage (e.g., 400 mg daily) has not been studied.

When concurrent therapy with aripiprazole and a potent CYP3A4 inhibitor such as ketoconazole or clarithromycin is clinically indicated, the dosage of aripiprazole should be reduced to one-half of the usual dosage. Other potent inhibitors of CYP3A4 (e.g., itraconazole) would be expected to have similar effects and require similar dosage reductions; the effect of moderate inhibitors (e.g., erythromycin, grapefruit juice) has not been studied. When the CYP3A4 inhibitor is withdrawn from combined therapy, the aripiprazole dosage should be increased. (See Dosage and Administration: Special Populations.)

■ **Quinidine and Other CYP2D6 Inhibitors** Concomitant administration of a single 10-mg dose of aripiprazole with quinidine (166 mg daily for 13 days), a potent CYP2D6 inhibitor, increased the AUC of aripiprazole by 112% but decreased the AUC of its active metabolite, dehydro-aripiprazole, by 35%. Other drugs that substantially inhibit CYP2D6 (e.g., fluoxetine, paroxetine) would be expected to have similar effects as quinidine.

When aripiprazole is given concurrently with potential CYP2D6 inhibitors such as quinidine, fluoxetine, or paroxetine, the dosage of aripiprazole should be reduced to at least one-half of the usual dosage. When the CYP2D6 inhibitor is withdrawn from combined therapy, the aripiprazole dosage should then be increased. When adjunctive aripiprazole is administered to patients with major depressive disorder, aripiprazole should be given without dosage adjustment. (See Major Depressive Disorder under Dosage and Administration: Dosage, and see also Drug Interactions: Fluoxetine, Paroxetine, and Sertraline.)

■ **Anticholinergic Agents** Potential pharmacologic interaction (possible disruption of body temperature regulation); use aripiprazole with caution in patients concurrently receiving drugs with anticholinergic activity. (See Body Temperature Regulation under Warnings/Precautions: Other Warnings and Precautions, in Cautions.)

■ **Hypotensive Agents** Potential pharmacologic interaction (additive hypotensive effects); use with caution.

■ **Lorazepam and Other Benzodiazepines** Clinically important pharmacokinetic changes not reported during concurrent administration of parenteral lorazepam and IM aripiprazole. The manufacturer states that aripiprazole dosage adjustment is not necessary when aripiprazole is concurrently administered with lorazepam. However, increased sedative and orthostatic hypotensive effects have been reported in patients receiving these drugs in combination. If therapy with IM aripiprazole in conjunction with a parenteral benzodiazepine is considered necessary, the patient should be carefully monitored for excessive sedation and orthostatic hypotension. (See Orthostatic Hypotension and see also Cognitive and Motor Impairment under Warnings/Precautions: Other Warnings and Precautions, in Cautions.)

■ **Other CNS Agents or Alcohol** Potential pharmacologic interaction (additive CNS effects). Use with caution.

■ **Dextromethorphan** Clinically important pharmacokinetic interaction unlikely. Dosage adjustment of dextromethorphan is not necessary when administered concomitantly with aripiprazole.

■ **Famotidine** Potential pharmacokinetic interaction (decreased aripiprazole rate and extent of absorption); not clinically important and no dosage adjustment of aripiprazole is necessary when administered concurrently with famotidine.

■ **Lamotrigine** Combined aripiprazole and lamotrigine therapy appears to be well tolerated in patients with bipolar disorder. Pharmacokinetic interaction unlikely; no dosage adjustment of lamotrigine is necessary when aripiprazole is administered concurrently.

■ **Lithium** Clinically important pharmacokinetic interaction unlikely; no dosage adjustment of aripiprazole or lithium is necessary during concurrent administration.

■ **Omeprazole** Concurrent administration of aripiprazole 10 mg daily for 15 days in healthy individuals did not substantially alter the pharmacokinetics of a single 20-mg dose of omeprazole, a CYP2C19 substrate. Dosage adjustment of omeprazole is not necessary when administered concurrently with aripiprazole.

■ **Escitalopram** Concurrent administration of aripiprazole 10 mg daily for 14 days in healthy individuals did not substantially alter the steady-state pharmacokinetics of 10 mg daily of escitalopram, a CYP2C19 and CYP3A4 substrate. Dosage adjustment of escitalopram is not necessary when aripiprazole is added to escitalopram therapy.

■ **Fluoxetine, Paroxetine, and Sertraline** A population pharmacokinetic analysis in patients with major depressive disorder did not demonstrate substantial changes in the pharmacokinetics of fluoxetine, paroxetine, or sertraline (dosed to steady state) following the addition of aripiprazole therapy.

However, fluoxetine and paroxetine are inhibitors of CYP2D6 and the manufacturer recommends that aripiprazole dosage be reduced to one-half the usual dosage in patients receiving concomitant therapy with inhibitors of CYP2D6, including fluoxetine and paroxetine. When the CYP2D6 inhibitor is withdrawn from combined therapy with aripiprazole, the aripiprazole dosage should be increased. When adjunctive aripiprazole is concurrently administered to patients with major depressive disorder receiving fluoxetine or paroxetine, aripiprazole should be given without dosage adjustment. (See Dosage and Administration: Special Populations and see also Drug Interactions: Quinidine and Other CYP2D6 Inhibitors.)

■ **Smoking** Pharmacokinetic interaction unlikely. Dosage adjustment in patients who smoke is not necessary.

■ **Valproate** Clinically important pharmacokinetic interaction unlikely; no dosage adjustment of aripiprazole or valproate is necessary during concurrent administration.

■ **Venlafaxine** Concurrent administration of aripiprazole 10–20 mg daily for 14 days in healthy individuals did not substantially alter the steady-state pharmacokinetics of venlafaxine and O-desmethylvenlafaxine following 75 mg daily of extended-release venlafaxine, a CYP2D6 substrate. Dosage adjustment of venlafaxine is not necessary when aripiprazole is added to venlafaxine therapy.

■ **Warfarin** Concurrent administration of aripiprazole 10 mg daily for 14 days did not substantially affect warfarin pharmacokinetics or the international normalized ratio (INR), suggesting a lack of a clinically important effect of aripiprazole on CYP2C9 and CYP2C19 metabolism or the binding of highly protein-bound warfarin. Warfarin dosage adjustment is not necessary when administered concurrently with aripiprazole.

Description

Aripiprazole is a quinolinone derivative antipsychotic agent that differs chemically from other currently available antipsychotic agents (e.g., butyro-

phenones, phenothiazines) and has been referred to as an atypical or second-generation antipsychotic agent. The exact mechanism of action of aripiprazole in schizophrenia, bipolar mania, major depressive disorder, and agitation associated with schizophrenia or bipolar mania has not been fully elucidated but, like that of other drugs with efficacy in these conditions (e.g., olanzapine, risperidone, ziprasidone), may involve the drug's activity at dopamine D_2 and serotonin type 1 ($5\text{-}HT_{1A}$) and type 2 ($5\text{-}HT_{2A}$) receptors. However, aripiprazole appears to differ from other atypical antipsychotic agents because the drug demonstrates partial agonist activity at D_2 and $5\text{-}HT_{1A}$ receptors and antagonist activity at $5\text{-}HT_{2A}$ receptors. Antagonism at other receptors (e.g., α_1-adrenergic receptors, histamine H_1 receptors) may contribute to other therapeutic and adverse effects (e.g., orthostatic hypotension, somnolence) observed with aripiprazole.

Aripiprazole is extensively metabolized in the liver principally via dehydrogenation, hydroxylation, and *N*-dealkylation by the cytochrome P-450 (CYP) 2D6 and 3A4 isoenzymes. The major active metabolite of aripiprazole, dehydro-aripiprazole, exhibits affinity for D_2 receptors similar to that of the parent compound and represents approximately 40% of aripiprazole area under the concentration-time curve (AUC) in plasma. Steady-state plasma concentrations of both aripiprazole and dehydro-aripiprazole are achieved within 14 days. The elimination half-lives of aripiprazole and dehydro-aripiprazole are approximately 75 and 94 hours, respectively. Approximately 18% and less than 1% of aripiprazole is excreted unchanged in feces and urine, respectively.

Advice to Patients

Importance of providing copy of written patient information (medication guide) each time aripiprazole is dispensed. Importance of advising patients to read the patient information before taking aripiprazole and each time the prescription is refilled.

Increased mortality in geriatric patients with dementia-related psychosis; importance of advising patients and caregivers that geriatric patients with dementia-related psychosis treated with antipsychotic agents are at an increased risk of death. Patients and caregivers should also be informed that aripiprazole is *not* approved for treating geriatric patients with dementia-related psychosis.

Risk of suicidality; importance of patients, family, and caregivers being alert to and immediately reporting emergence of suicidality, worsening depression, or unusual changes in behavior, especially during the first few months of therapy or during periods of dosage adjustment.

Because somnolence and impairment of judgment, thinking, or motor skills may be associated with aripiprazole, avoid driving, operating machinery, or performing hazardous tasks while taking aripiprazole until the drug's effects on the individual are known. Importance of avoiding alcohol during aripiprazole therapy.

Risk of neuroleptic malignant syndrome (NMS), a rare but life-threatening syndrome that can cause high fever, stiff muscles, sweating, fast or irregular heart beat, change in blood pressure, confusion, and kidney damage. Importance of informing patients to immediately contact a healthcare professional if such symptoms develop.

Importance of clinicians informing patients in whom chronic aripiprazole use is contemplated of risk of tardive dyskinesia. Importance of informing patients to report any muscle movements that cannot be stopped to a healthcare professional.

Importance of informing clinicians of existing or contemplated concomitant therapy, including prescription and OTC drugs, as well as any concomitant illnesses (e.g., diabetes mellitus).

Importance of women informing clinicians if they are or plan to become pregnant or plan to breast-feed.

Importance of avoiding overheating or dehydration.

For patients taking aripiprazole orally disintegrating tablets, importance of not removing a tablet from the blister package until just before administering a dose; importance of peeling blister open with dry hands and placing tablet on tongue to dissolve and be swallowed with saliva.

Importance of informing patients with phenylketonuria that aripiprazole orally disintegrating 10- and 15-mg tablets contain 1.12 and 1.68 mg of phenylalanine, respectively.

Importance of being aware that aripiprazole oral solution contains 400 mg of sucrose and 200 mg of fructose per mL.

Importance of informing patients of other important precautionary information. (See Cautions.)

Overview* (see Users Guide). For additional information on this drug until a more detailed monograph is developed and published, the manufacturer's labeling should be consulted. It is *essential* that the manufacturer's labeling be consulted for more detailed information on usual cautions, precautions, contraindications, potential drug interactions, laboratory test interferences, and acute toxicity.

Preparations

Excipients in commercially available drug preparations may have clinically important effects in some individuals; consult specific product labeling for details.

Aripiprazole

Oral		
Solution	5 mg/5 mL	**Abilify* Oral Solution**, Otsuka (also promoted by Bristol-Myers Squibb)
Tablets	2 mg	**Abilify***, Otsuka (also promoted by Bristol-Myers Squibb)
	5 mg	**Abilify***, Otsuka (also promoted by Bristol-Myers Squibb)
	10 mg	**Abilify***, Otsuka (also promoted by Bristol-Myers Squibb)
	15 mg	**Abilify***, Otsuka (also promoted by Bristol-Myers Squibb)
	20 mg	**Abilify***, Otsuka (also promoted by Bristol-Myers Squibb)
	30 mg	**Abilify***, Otsuka (also promoted by Bristol-Myers Squibb)
Tablets, orally disintegrating	10 mg	**Abilify* Discmelt***, Otsuka (also promoted by Bristol-Myers Squibb)
	15 mg	**Abilify* Discmelt***, Otsuka (also promoted by Bristol-Myers Squibb)
Parenteral		
Injection, for IM use only	7.5 mg/mL (9.75 mg)	**Abilify***, Otsuka (also promoted by Bristol-Myers Squibb)

Clozapine

■ Clozapine has been referred to as an atypical or second-generation antipsychotic agent.

Uses

■ **Psychotic Disorders** Clozapine is used for the symptomatic management of psychotic disorders (e.g., schizophrenia). Drug therapy is integral to the management of acute psychotic episodes and accompanying violent behavior in patients with schizophrenia and generally is required for long-term stabilization to sustain symptom remission or control and to minimize the risk of relapse. Antipsychotic agents are the principal class of drugs used for the management of all phases of schizophrenia and generally are effective in all subtypes of the disorder and subgroups of patients. Patient response and tolerance to antipsychotic agents are variable, and patients who do not respond to or tolerate one drug may be successfully treated with an agent from a different class or with a different adverse effect profile.

Clozapine has been shown to be an effective, relatively rapid-acting, broad-spectrum antipsychotic agent in both uncontrolled and controlled studies of patients with schizophrenia. In these studies, improvement in manifestations of schizophrenia was based on the results of various psychiatric rating scales, principally the Brief Psychiatric Rating Scale (BPRS) that assesses factors such as anergy, thought disturbance, activation, hostility/suspiciousness, and anxiety/depression. In clinical studies, clozapine improved both positive (florid symptomatology such as hallucinations, conceptual disorganization, and suspiciousness) and negative ("deficit" symptomatology such as emotional withdrawal, motor retardation, blunted affect, and disorientation) manifestations of schizophrenia; conventional (typical) antipsychotic agents appear to have lesser effects on negative manifestations of the disorder. In comparative studies, clozapine was at least as effective as, or more effective than several conventional antipsychotic agents, including chlorpromazine, haloperidol, perphenazine, or trifluoperazine.

Unlike conventional antipsychotic agents, however, clozapine generally does not induce extrapyramidal effects and has not been clearly implicated as a causative agent in tardive dyskinesia.

While the risks of adverse neurologic effects with long-term clozapine therapy remain to be fully elucidated, other adverse effects, including some potentially serious effects (e.g., agranulocytosis, seizures), may occur more frequently with clozapine therapy. Consequently, the manufacturers and most clinicians currently state that use of clozapine should be reserved for patients with severe disease that fails to respond adequately to conventional antipsychotic therapy, either because of insufficient effectiveness or the inability to achieve an effective dose due to intolerable adverse effects from those drugs. What constitutes an adequate trial of standard antipsychotic therapy, however, varies widely. The manufacturers and some clinicians recommend that a patient be given an adequate trial of at least 2 different antipsychotic agents from at least 2 different chemical classes (e.g., phenothiazines, butyrophenones, thioxanthenes) before the patient is considered a candidate for clozapine therapy. The American Psychiatric Association (APA), however, currently recommends that a trial of clozapine be considered in patients who fail to respond to adequate trials of at least one antipsychotic agent unless therapy with the drug is specifically contraindicated (e.g., patients with myeloproliferative disorders, preexisting bone marrow depression, or a history of clozapine-induced agranulocytosis or severe granulocytopenia) or patients are unable or unwilling to comply with monitoring requirements. The APA also recommends that clo-

ulating effect of dextroamphetamine is approximately twice that of amphetamine and about three or four times that of levamfetamine (no longer commercially available in the US). Levamfetamine is slightly more potent than dextroamphetamine in its cardiovascular effects. In healthy individuals, therapeutic doses of an amphetamine do not appreciably increase respiratory rate or minute volume, but when respiration is depressed by centrally acting drugs, an amphetamine stimulates respiration. The bronchodilating effect of amphetamines is less than that of ephedrine.

Amphetamines may superimpose psychic stimulation and excitability over fatigue, permitting a temporary increase in mental and physical activity. In healthy individuals, the drugs have not consistently facilitated improved mental performance and in some cases, nervousness produced by amphetamines is a distinct mental hazard. The most striking improvement caused by an amphetamine appears to occur when performance has been reduced by fatigue; such improvement may be due to alteration of unfavorable attitudes toward the task. Psychic stimulation produced by amphetamines is usually followed by depression and fatigue. Psychic effects depend on dose, mental state, and personality of the patient.

Theories of dysfunction in attention deficit hyperactivity disorder (ADHD) focus on the prefrontal cortex, which controls many executive functions (e.g., planning, impulse control). Stimulants have putative effects on central dopamine and norepinephrine pathways that are crucial in frontal lobe function. Stimulants act in the striatum by binding to the dopamine transporter, thus increasing synaptic dopamine. This effect may enhance functioning of executive control processes in the prefrontal cortex, ameliorating deficits in inhibitory control and working memory.

Amphetamines apparently produce an anorexigenic effect, leading to loss of weight. The mechanism of action of amphetamines on appetite suppression has not been elucidated. No primary effect on appetite has been demonstrated in humans and it has been postulated that anorexigenic effects of amphetamines are secondary to increased sympathetic activity resulting from amphetamine-induced release of norepinephrine and dopamine. In addition, amphetamines may cause a loss of acuity of smell and taste, which may contribute to the anorexigenic effect of the drugs. Amphetamines have little or no effect on the basal metabolic rate or on nitrogen excretion.

The anorexigenic effect of fenfluramine (no longer commercially available in the US) and dexfenfluramine (no longer commercially available in the US), amphetamine congeners, may have been associated with a different mechanism than those associated with amphetamines since the drugs appeared to stimulate release of serotonin (5-HT) at synapses and selectively inhibit the reuptake of serotonin at the presynaptic serotoninergic nerve endings, which may have resulted in increased postsynaptic concentrations of serotonin in the CNS. In the past, it has been suggested that combined therapy with fenfluramine and phentermine (an amphetamine congener that inhibits uptake of norepinephrine and dopamine) may provide complementary anorexigenic effects; therefore, such combined therapy has been used in the management of obesity. However, because of accumulated data on adverse effects associated with the drugs, fenfluramine hydrochloride (Pondimin®) and its dextrorotatory isomer dexfenfluramine hydrochloride (Redux®) were withdrawn from the US market in 1997. (See Cautions.)

Pharmacokinetics

Amphetamines are readily absorbed from the GI tract and effects persist for 4–24 hours. Amphetamines are distributed into most body tissues with high concentrations occurring in the brain and CSF.

Amphetamine appears in the urine within about 3 hours following oral administration. Urinary excretion of the amphetamines is pH-dependent and excretion is enhanced in acidic urine. Following oral administration of racemic amphetamine to humans, approximately equal amounts of both isomers were excreted during the first 12 hours; after the first 12 hours, a continually decreasing proportion of the *d*-isomer was excreted. Following oral administration of a 70-mg radiolabeled dose of lisdexamfetamine (a prodrug of dextroamphetamine), 96% of the dose was recovered in the urine; of the recovered radioactivity, 42% of the dose was related to amphetamine, 25% to hippuric acid, and 2% to the parent drug. Dextroamphetamine and levamfetamine (no longer commercially available in the US) appear to have different metabolic fates, but the relationship between the fate of the drugs and their pharmacologic activity has not been determined. There are some data to indicate stereospecific metabolism of amphetamine and its isomers, but stereospecific urinary excretion appears unlikely.

Chemistry

Amphetamine is *d,l*-α-methylphenethylamine, an adrenergic agent of the phenylisopropylamine type. The levo- and dextroisomers, racemic amphetamine, and the salts of the isomers and of racemic amphetamine are used in medical practice. Amphetamine is a noncatechol, sympathomimetic amine and has a greater CNS stimulant activity than epinephrine and other catecholamines. Lisdexamfetamine dimesylate is a prodrug and has little, if any, pharmacologic activity until converted to dextroamphetamine by first-pass intestinal and/or hepatic metabolism.

Inactivation of sympathomimetic noncatecholamines largely depends on breakdown by monoamine oxidase and since substitution of an alkyl group for hydrogen on the α-carbon atom blocks enzymatic inactivation of the amino group, the duration of action of noncatecholamines (but not of catecholamines, which are inactivated largely by a different mechanism) is prolonged by α-substitution. The absence of a hydroxyl group on the aromatic ring of amphetamine reduces inactivation of the drug in the GI tract and the amphetamines are active following oral administration.

Amphetamines are subject to control under the Federal Controlled Substances Act of 1970.

For further information on the chemistry, pharmacology, pharmacokinetics, uses, cautions, drug interactions, and dosage and administration of amphetamines, see the individual monographs in 28:20.04.

†Use is not currently included in the labeling approved by the US Food and Drug Administration

Amphetamine

■ Amphetamine is a noncatechol, sympathomimetic amine with CNS-stimulating activity.

Uses

Amphetamine sulfate and amphetamine aspartate in fixed-combination preparations containing amphetamine aspartate, amphetamine sulfate, dextroamphetamine saccharate, and dextroamphetamine sulfate are used in the treatment of narcolepsy and as adjuncts to psychological, educational, social, and other remedial measures in the treatment of attention deficit hyperactivity disorder (ADHD).

■ Narcolepsy and Attention Deficit Hyperactivity Disorder

Amphetamine sulfate and amphetamine aspartate in fixed-combination preparations containing amphetamine aspartate, amphetamine sulfate, dextroamphetamine saccharate, and dextroamphetamine sulfate are used in the treatment of narcolepsy and as adjuncts to psychological, educational, social, and other remedial measures in the treatment of ADHD (hyperkinetic disorder, hyperkinetic syndrome of childhood, minimal brain dysfunction) in children, adolescents, and adults.

ADHD usually is characterized by developmentally inappropriate symptoms (e.g., moderate to severe distractibility, short attention span, hyperactivity, emotional lability, impulsivity). The final diagnosis of this disorder should not be made if these symptoms are of only comparatively recent origin. Nonlocalizing (soft) neurologic signs, learning disability, and abnormal EEG may or may not be present, and a diagnosis of CNS dysfunction may or may not be warranted. Drug therapy is not indicated in all children with ADHD, and such therapy should be considered only after a complete evaluation including medical history has been performed. The decision to use amphetamines should depend on the age of the child and the clinician's assessment of the severity and duration of symptoms and should not depend solely on one or more behavioral characteristics. When symptoms of ADHD are associated with acute stress reactions, use of amphetamines usually is not recommended. For a more detailed discussion on the management of ADHD, including the use of stimulants such as amphetamine, see Uses: Attention Deficit Hyperactivity Disorder, in Methylphenidate 28:20.92.

Dosage and Administration

■ **Administration** Amphetamine sulfate and amphetamine aspartate in fixed-combination preparations containing amphetamine aspartate, amphetamine sulfate, dextroamphetamine saccharate, and dextroamphetamine sulfate are administered orally. The commercially available extended-release capsules containing amphetamine sulfate and amphetamine aspartate in fixed-combination with dextroamphetamine saccharate and dextroamphetamine sulfate (Adderall® XR) may be swallowed intact with or without food or the entire contents of a capsule(s) may be sprinkled on a small amount of applesauce immediately prior to administration; subdividing the contents of a capsule is not recommended. The pellets contained in the capsules should not be chewed or crushed, and the sprinkle/food mixture must not be stored for use at a later time.

The initial dose of amphetamines (as conventional tablets or extended-release capsules) should be given on awakening; when amphetamines are administered as conventional tablets in divided doses (2 or 3), additional doses are given at intervals of 4–6 hours. Because of the potential for insomnia, administration of conventional tablets in the late evening or extended-release capsules in the afternoon should be avoided.

■ **Dosage** Dosage of amphetamines should be adjusted according to individual response and tolerance; the smallest dose required to produce the desired response should always be used.

Narcolepsy In the treatment of narcolepsy, the usual total dosage of amphetamines given in fixed-combination preparations containing amphetamine aspartate, amphetamine sulfate, dextroamphetamine saccharate, and dextroamphetamine sulfate is 5–60 mg daily, depending upon the patient's age and response, usually given in divided doses. In patients 12 years of age and older, the initial dosage is 10 mg daily; daily dosage is increased by 10 mg at weekly intervals until the optimum response is attained. Although narcolepsy seldom occurs in children younger than 12 years of age, such children also may receive dextroamphetamine alone. In patients 6–12 years of age, the recommended initial dosage is 5 mg daily; daily dosage is increased by 5 mg at

weekly intervals until optimum response is attained. When intolerable adverse effects (e.g., insomnia, anorexia) occur, dosage should be reduced.

Attention Deficit Hyperactivity Disorder As an adjunct in the treatment of attention deficit hyperactivity disorder (ADHD) in children 6 years of age and older, the initial total dosage of amphetamines given in conventional fixed-combination preparations containing amphetamine aspartate, amphetamine sulfate, dextroamphetamine saccharate, and dextroamphetamine sulfate is 5 mg once or twice daily; the daily dosage is increased by 5 mg at weekly intervals until the optimum response is attained. Total daily dosage rarely should exceed 40 mg. In children 3–5 years of age, the initial dosage of amphetamines given in conventional fixed-combination preparations containing amphetamine aspartate, amphetamine sulfate, dextroamphetamine saccharate, and dextroamphetamine sulfate is 2.5 mg daily; the daily dosage is increased by 2.5 mg at weekly intervals until the optimum response is attained. When amphetamines are administered as conventional tablets in divided doses (2 or 3), additional doses are given at intervals of 4–6 hours.

Alternatively, in patients who are receiving drug therapy for ADHD for the first time or are being switched from therapy with another stimulant, amphetamine therapy may be initiated with extended-release capsules containing amphetamine aspartate, amphetamine sulfate, dextroamphetamine saccharate, and dextroamphetamine sulfate in fixed combination (Adderall® XR). In children 6–12 years of age, the initial dosage of amphetamines as extended-release capsules (Adderall® XR) is 10 mg once daily; daily dosage may be increased in increments of 5 or 10 mg at weekly intervals to a maximum dosage of 30 mg daily. Treatment may be initiated with a dosage of 5 mg once daily when, in the opinion of the clinician, a lower initial dosage is appropriate. In adolescents 13–17 years of age, the initial dosage of amphetamines as extended-release capsules (Adderall® XR) is 10 mg once daily. Dosage may be increased to 20 mg once daily after 1 week if symptoms are not adequately controlled. In adults who are receiving drug therapy for ADHD for the first time or are being switched from therapy with another drug, the recommended dosage of amphetamines as extended-release capsules (Adderall XR®) is 20 mg once daily. Although dosages of up to 60 mg daily (as extended-release capsules) have been used in adolescents 13–17 years of age and adults in clinical studies, there is no evidence that dosages exceeding 20 mg daily provide any additional benefit in these patients. When switching from conventional tablets (Adderall®) to extended-release capsules (Adderall® XR), the total daily dosage of amphetamines may remain the same but should be given once daily.

When possible, therapy should be interrupted occasionally to determine if there is a recurrence of behavioral symptoms sufficient to require continued treatment. Long-term use of conventional tablets or long-term use of extended-release capsules (i.e., more than 3 weeks in children or more than 4 weeks in adolescents or adults) has not been studied systematically. If conventional tablets or extended-release capsules are used for extended periods, the usefulness of the drug should be reevaluated periodically.

Chemistry and Stability

■ **Chemistry** Amphetamine, *d,l*-α-methylphenethylamine, occurs as a colorless, mobile liquid with an amine odor and is sparingly soluble in water (1:50) and soluble in alcohol. The base is volatile at room temperature and has been used as an inhalant but is no longer commercially available in the US. Amphetamine sulfate occurs as a white, odorless crystalline powder and has a slightly bitter taste. Amphetamine sulfate is freely soluble in water (1:9) and slightly soluble in alcohol (about 1:500). Amphetamine aspartate and amphetamine sulfate currently are commercially available in the US only as fixed-combination preparations containing amphetamine aspartate, amphetamine sulfate, dextroamphetamine saccharate, and dextroamphetamine sulfate.

■ **Stability** The fixed-combination conventional tablets or extended-release capsules containing amphetamine aspartate, amphetamine sulfate, dextroamphetamine saccharate, and dextroamphetamine sulfate should be stored in tight, light-resistant containers at 25°C but may be exposed to temperatures ranging from 15–30°C.

For further information on chemistry, pharmacology, pharmacokinetics, uses, cautions, chronic toxicity, acute toxicity, and dosage and administration of amphetamine and amphetamine sulfate, see the Amphetamines General Statement 28:20.04.

Preparations

Amphetamine sulfate preparations are subject to control under the Federal Controlled Substances Act of 1970 as schedule II (C-II) drugs.

Excipients in commercially available drug preparations may have clinically important effects in some individuals; consult specific product labeling for details.

Amphetamine Sulfate Combinations

Oral		
Capsules, extended-release	5 mg total amphetamine (as 1.25 mg, with Amphetamine Aspartate 1.25 mg, Dextroamphetamine Saccharate 1.25 mg, and Dextroamphetamine Sulfate 1.25 mg)	**Adderall® XR** (C-II), Shire
	10 mg total amphetamine (as 2.5 mg, with Amphetamine Aspartate 2.5 mg, Dextroamphetamine Saccharate 2.5 mg, and Dextroamphetamine Sulfate 2.5 mg)	**Adderall® XR** (C-II), Shire
	15 mg total amphetamine (as 3.75 mg, with Amphetamine Aspartate 3.75 mg, Dextroamphetamine Saccharate 3.75 mg, and Dextroamphetamine Sulfate 3.75 mg)	**Adderall® XR** (C-II), Shire
	20 mg total amphetamine (as 5 mg, with Amphetamine Aspartate 5 mg, Dextroamphetamine Saccharate 5 mg, and Dextroamphetamine Sulfate 5 mg)	**Adderall® XR** (C-II), Shire
	25 mg total amphetamine (as 6.25 mg, with Amphetamine Aspartate 6.25 mg, Dextroamphetamine Saccharate 6.25 mg, and Dextroamphetamine Sulfate 6.25 mg)	**Adderall® XR** (C-II), Shire
	30 mg total amphetamine (as 7.5 mg, with Amphetamine Aspartate 7.5 mg, Dextroamphetamine Saccharate 7.5 mg, and Dextroamphetamine Sulfate 7.5 mg)	**Adderall® XR** (C-II), Shire
Tablets	5 mg total amphetamine (as 1.25 mg, with Amphetamine Aspartate 1.25 mg, Dextroamphetamine Saccharate 1.25 mg, and Dextroamphetamine Sulfate 1.25 mg)*	**Adderall®** (C-II; double-scored), Shire **Dextroamphetamine Saccharate, Amphetamine Aspartate, Dextroamphetamine Sulfate, and Amphetamine Sulfate Tablets** (C-II; double-scored)
	7.5 mg total amphetamine (as 1.875 mg, with Amphetamine Aspartate 1.875 mg, Dextroamphetamine Saccharate 1.875 mg, and Dextroamphetamine Sulfate 1.875 mg)*	**Adderall®** (C-II; double-scored), Shire **Dextroamphetamine Saccharate, Amphetamine Aspartate, Dextroamphetamine Sulfate, and Amphetamine Sulfate Tablets** (C-II; double-scored)
	10 mg total amphetamine (as 2.5 mg, with Amphetamine Aspartate 2.5 mg, Dextroamphetamine Saccharate 2.5 mg, and Dextroamphetamine Sulfate 2.5 mg)*	**Adderall®** (C-II; double-scored), Shire **Dextroamphetamine Saccharate, Amphetamine Aspartate, Dextroamphetamine Sulfate, and Amphetamine Sulfate Tablets** (C-II; double-scored)
	12.5 mg total amphetamine (as 3.125 mg, with Amphetamine Aspartate 3.125 mg, Dextroamphetamine Saccharate 3.125 mg, and Dextroamphetamine Sulfate 3.125 mg)*	**Adderall®** (C-II; double-scored), Shire **Dextroamphetamine Saccharate, Amphetamine Aspartate, Dextroamphetamine Sulfate, and Amphetamine Sulfate Tablets** (C-II; double-scored)
	15 mg total amphetamine (as 3.75 mg, with Amphetamine Aspartate 3.75 mg, Dextroamphetamine Saccharate 3.75 mg, and Dextroamphetamine Sulfate 3.75 mg)*	**Adderall®** (C-II; double-scored), Shire **Dextroamphetamine Saccharate, Amphetamine Aspartate, Dextroamphetamine Sulfate, and Amphetamine Sulfate Tablets** (C-II; double-scored)
	20 mg total amphetamine (as 5 mg, with Amphetamine Aspartate 5 mg, Dextroamphetamine Saccharate 5 mg, and Dextroamphetamine Sulfate 5 mg)*	**Adderall®** (C-II; double-scored), Shire **Dextroamphetamine Saccharate, Amphetamine Aspartate, Dextroamphetamine Sulfate, and Amphetamine Sulfate Tablets** (C-II; double-scored)

30 mg total amphetamine (as 7.5 mg, with Amphetamine Aspartate 7.5 mg, Dextroamphetamine Saccharate 7.5 mg, and Dextroamphetamine Sulfate 7.5 mg)*	**Adderall** (C-II; double-scored), Shire
	Dextroamphetamine Saccharate, Amphetamine Aspartate, Dextroamphetamine Sulfate, and Amphetamine Sulfate Tablets (C-II; double-scored)

*available from one or more manufacturer, distributor, and/or repackager by generic (nonproprietary) name

Dextroamphetamine

■ Dextroamphetamine is the dextrorotatory isomer of amphetamine.

Uses

Dextroamphetamine sulfate alone and in fixed-combination preparations with dextroamphetamine saccharate, amphetamine aspartate, and amphetamine sulfate is used in the treatment of narcolepsy and as an adjunct to psychological, educational, social, and other remedial measures in the treatment of attention deficit hyperactivity disorder (ADHD).

■ **Narcolepsy and Attention Deficit Hyperactivity Disorder** Dextroamphetamine sulfate alone and in fixed-combination preparations with dextroamphetamine saccharate, amphetamine aspartate, and amphetamine sulfate is used in the treatment of narcolepsy and as an adjunct to psychological, educational, social, and other remedial measures in the treatment of ADHD (hyperkinetic disorder, hyperkinetic syndrome of childhood, minimal brain dysfunction) in children, adolescents, and adults.

ADHD usually is characterized by developmentally inappropriate symptoms (e.g., moderate to severe distractibility, short attention span, hyperactivity, emotional lability, impulsivity). The final diagnosis of this disorder should not be made if these symptoms are of only comparatively recent origin. Nonlocalizing (soft) neurologic signs, learning disability, and abnormal EEG may or may not be present, and a diagnosis of CNS dysfunction may or may not be warranted. Drug therapy is not indicated in all children with ADHD, and such therapy should be considered only after a complete evaluation including medical history has been performed. The decision to use amphetamines should depend on the age of the child and the clinician's assessment of the severity and duration of symptoms and should not depend solely on one or more behavioral characteristics. When symptoms of ADHD are associated with acute stress reactions, use of amphetamines usually is not recommended. For a more detailed discussion on the management of ADHD, including the use of stimulants such as dextroamphetamine, see Uses: Attention Deficit Hyperactivity Disorder, in Methylphenidate 28:20.92.

Dosage and Administration

■ **Administration** Preparations containing dextroamphetamine sulfate are administered orally. The commercially available extended-release capsules containing dextroamphetamine sulfate and dextroamphetamine saccharate in fixed-combination with amphetamine sulfate and amphetamine aspartate (Adderall XR®) may be swallowed intact with or without food or the entire contents of a capsule(s) may be sprinkled on a small amount of applesauce immediately prior to administration; subdividing the contents of a capsule is not recommended. The pellets contained in the capsules should not be chewed or crushed, and the sprinkle/food mixture must not be stored for use at a later time.

The initial dose of dextroamphetamine sulfate (alone or in fixed-combination preparations) is given on awakening; when the drug is given as conventional (short-acting) tablets in divided doses (2 or 3), additional doses are given at intervals of 4–6 hours. Because of the potential for insomnia, administration of dextroamphetamine sulfate conventional tablets (Dexedrine®), dextroamphetamine sulfate extended-release capsules (Dexedrine® Spansules®), or fixed-combination conventional tablets (Adderall®) in the late evening or administration of fixed-combination extended-release capsules (Adderall XR®) in the afternoon should be avoided.

■ **Dosage** Dosage of dextroamphetamines should be adjusted according to individual response and tolerance; the smallest dose required to produce the desired response should always be used.

Narcolepsy In the treatment of narcolepsy, the usual dosage of dextroamphetamine sulfate given alone or the total dosage of amphetamines given in fixed-combination preparations containing dextroamphetamine sulfate, dextroamphetamine saccharate, amphetamine aspartate, and amphetamine sulfate is 5–60 mg daily, depending upon the patient's age and response, usually given in divided doses. In patients 12 years of age and older, the initial dosage is 10 mg daily; daily dosage is increased by 10 mg at weekly intervals until the optimum response is attained. Although narcolepsy seldom occurs in children younger than 12 years of age, in pediatric patients 6–12 years of age, the recommended initial dosage of dextroamphetamine sulfate is 5 mg daily; daily dosage is increased by 5 mg at weekly intervals until the optimum response is attained. When intolerable adverse effects occur (e.g., insomnia, anorexia), dosage should be reduced. Dextroamphetamine sulfate extended-release capsules may be used for once-daily dosing whenever appropriate.

Attention Deficit Hyperactivity Disorder Dextroamphetamine sulfate dosage for the treatment of attention deficit hyperactivity disorder (ADHD) should be individualized based on patient response and tolerance. The first dosage that produces an observable response may not be the optimum dosage to improve function, and titration to higher dosages should continue in an attempt to achieve a better response. Such a strategy may require subsequent lowering of dosage when higher dosages produce adverse effects or no further clinical improvement. The best dosage for a given patient is the one that provides optimum therapeutic effects with minimal adverse effects. Dosing schedules also may vary, although there currently are no consistent controlled studies comparing alternative dosing schedules. Patients who require relief only during school may respond adequately to a 5-day (i.e., school day) regimen while those requiring relief at home and school may need a daily regimen throughout the week.

As an adjunct in the treatment of ADHD in children 6 years of age and older, the initial dosage of dextroamphetamine sulfate given in conventional (short-acting) preparations is 5 mg once or twice daily; daily dosage is increased by 5 mg at weekly intervals until the optimum response is attained. The usual dosage range is 5–15 mg twice daily or 5–10 mg 3 times daily. Total daily dosage rarely should exceed 40 mg. In children 3–5 years of age, the initial daily dosage is 2.5 mg; daily dosage is increased by 2.5 mg at weekly intervals until the optimum response is attained. When the drug is administered as conventional tablets in divided doses (2 or 3), additional doses are given at intervals of 4–6 hours. Dextroamphetamine sulfate extended-release capsules can be substituted for their respective conventional short-acting preparations if less frequent daily dosing is desirable.

Dextroamphetamine sulfate in fixed combination with other amphetamines (dextroamphetamine sulfate, dextroamphetamine saccharate, amphetamine aspartate, and amphetamine sulfate) also is used as an adjunct in the treatment of ADHD in children 6 years of age and older; the initial total dosage of amphetamines is 5 mg once or twice daily. The daily dosage is increased by 5 mg at weekly intervals until the optimum response is attained; total daily dosage rarely should exceed 40 mg. In children 3–5 years of age, the initial daily dosage is 2.5 mg; daily dosage is increased by 2.5 mg at weekly intervals until the optimum response is attained. The manufacturer recommends that the initial dose of dextroamphetamine sulfate in fixed combination with other amphetamines be given on awakening; additional doses (1 or 2) are given at intervals of 4–6 hours. The usual dosage for intermediate-acting preparations (e.g., Dexedrine® Spansules®, Adderall®) in children 6 years of age and older is 5–30 mg once daily or 5–15 mg twice daily.

Alternatively, in patients who are receiving drug therapy for ADHD for the first time or are being switched from therapy with another stimulant, dextroamphetamine therapy may be initiated with extended-release capsules containing dextroamphetamine sulfate in fixed-combination with dextroamphetamine saccharate, amphetamine aspartate, and amphetamine sulfate (Adderall XR®). In children 6–12 years of age, the initial dosage of total amphetamines as fixed-combination extended-release capsules (Adderall XR®) is 10 mg once daily; daily dosage may be increased in increments of 5 or 10 mg at weekly intervals to a maximum dosage of 30 mg daily. Treatment may be initiated with a dosage of 5 mg once daily when, in the opinion of the clinician, a lower initial dosage is appropriate. The usual dosage for such longer-acting preparations (e.g., Adderall XR®) is 10–30 mg daily. In adolescents 13–17 years of age, the initial dosage of total amphetamines as fixed-combination extended-release capsules (Adderall XR®) is 10 mg once daily. Dosage may be increased to 20 mg once daily after 1 week if symptoms are not adequately controlled. In adults who are receiving drug therapy for ADHD for the first time or are being switched from therapy with another drug, the recommended dosage of amphetamines as fixed-combination extended-release capsules (Adderall XR®) is 20 mg once daily. Although dosages of up to 60 mg daily (as fixed-combination extended-release capsules) have been used in adolescents 13–17 years of age and adults in clinical studies, there is no evidence that dosages exceeding 20 mg daily provide any additional benefit in these patients. When switching from fixed-combination conventional tablets (Adderall®) to fixed-combination extended-release capsules (Adderall XR®), the total daily dosage of amphetamines may remain the same but should be given once daily.

When possible, therapy should be interrupted occasionally to determine if there is a recurrence of behavioral symptoms sufficient to require continued treatment. Long-term use of fixed-combination extended-release capsules (i.e., more than 3 weeks in children or more than 4 weeks in adolescents or adults) has not been studied systematically. If fixed-combination extended-release capsules are used for extended periods, the usefulness of the drug should be periodically reevaluated.

Cautions

Dextroamphetamine shares the toxic potentials of amphetamines, and the usual cautions, precautions, and contraindications of amphetamine therapy should be observed. (See Cautions in the Amphetamines General Statement 28:20.04.)

Some commercially available preparations of dextroamphetamine (e.g., DextroStat®, Dexedrine® tablets) contain the dye tartrazine (FD&C yellow No. 5), which may cause allergic reactions including bronchial asthma in susceptible individuals. Although the incidence of tartrazine sensitivity is low, it frequently occurs in patients who are sensitive to aspirin.

Dosage and Administration

■ **Administration** Amoxapine is administered orally. Although amoxapine has been administered in 3 divided doses throughout the day, it is long-acting and, when dosage does not exceed 300 mg daily, the entire daily dose may be administered at one time, preferably at bedtime to avoid daytime sedation. When dosage exceeds 300 mg daily, the daily dose should be given in divided doses.

■ **Dosage** There is a wide range of amoxapine dosage requirements, and dosage of the drug must be carefully individualized.

Patients should be monitored for possible worsening of depression, suicidality, or unusual changes in behavior, especially at the beginning of therapy or during periods of dosage adjustment. (See Cautions: Precautions and Contraindications, in the Tricyclic Antidepressants General Statement 28:16.04.28.)

The usual effective dosage of amoxapine is 200–300 mg daily. The usual initial dosage is 100–150 mg daily. Depending on tolerance and response, dosage may be increased to 200–300 mg daily by the end of the first week of therapy. An initial dosage of 300 mg daily may be given, but considerable sedation may occur in some patients during the first few days of therapy at this dosage level. If no response occurs after administration of 300 mg of amoxapine daily for at least 2 weeks, dosage may be increased to a maximum of 400 mg daily in outpatients. Hospitalized patients under close supervision may generally be given higher dosages than outpatients; dosage may be increased cautiously up to 600 mg daily in divided doses in hospitalized patients who have not responded adequately and do not have a history of seizures. Single doses should not exceed 300 mg.

Geriatric patients should usually be given lower than average dosages. Therapy usually should be initiated with 50–75 mg daily in these patients and may be increased to 100–150 mg daily by the end of the first week of therapy, if tolerated. Some geriatric patients may require further increases in dosage; however, dosage in geriatric patients should not exceed 300 mg daily.

Antidepressant effects usually occur within 2 weeks in most patients who respond to amoxapine therapy and may occur within 4–7 days.

After symptoms are controlled, dosage should be gradually reduced to the lowest level which will maintain relief of symptoms.

Cautions

Amoxapine shares the toxic potentials of the tricyclic antidepressants, and the usual precautions of tricyclic antidepressant administration should be observed. Patients should be fully advised about the risks, especially suicidal thinking and behavior (suicidality), associated with tricyclic antidepressant therapy. For a complete discussion, see Cautions: Precautions and Contraindications and Cautions: Pediatric Precautions, in the Tricyclic Antidepressants General Statement 28:16.04.28.

Extrapyramidal reactions have occurred in less than 1% of patients receiving amoxapine. In addition, tardive dyskinesia has been reported rarely in patients receiving the drug. Like antipsychotic agents, amoxapine has been associated with neuroleptic malignant syndrome (NMS), a potentially fatal syndrome requiring immediate discontinuance of the drug and intensive symptomatic treatment. For additional information on NMS, see Extrapyramidal Reactions in Cautions: Nervous System Effects, in the Phenothiazines General Statement 28:16.08.24.

■ **Pediatric Precautions** Safety and efficacy of amoxapine for the treatment of depression in children younger than 16 years of age have not been established.

The US Food and Drug Administration (FDA) has determined that antidepressants increase the risk of suicidal thinking and behavior (suicidality) in children and adolescents with major depressive disorder and other psychiatric disorders. However, FDA also states that depression and certain other psychiatric disorders are themselves associated with an increased risk of suicide. Anyone considering the use of amoxapine in a child or adolescent for any clinical use must therefore balance the potential risk of therapy with the clinical need. (See Cautions: Precautions and Contraindications and Cautions: Pediatric Precautions, in the Tricyclic Antidepressants General Statement 28:16.04.28.)

Pharmacokinetics

■ **Absorption** Amoxapine is rapidly and almost completely absorbed from the GI tract. Peak plasma concentrations of amoxapine occur within 1–2 hours after a single oral dose.

■ **Distribution** In rats, amoxapine is widely distributed throughout body tissues, with highest concentrations distributed into lungs, spleen, kidneys, heart, and brain and lower concentrations distributed into testes and muscle.

Amoxapine is approximately 90% bound to plasma proteins.

Amoxapine and 8-hydroxyamoxapine have been detected in human milk in concentrations of approximately one-fifth and one-third those of maternal steady-state serum concentrations, respectively.

■ **Elimination** The plasma half-life of amoxapine is approximately 8 hours. Amoxapine is metabolized in the liver principally to 8-hydroxyamoxapine and, to a lesser extent, to 7-hydroxyamoxapine; both metabolites are pharmacologically active and have half-lives of 30 hours and 6.5 hours, respectively.

Approximately 60–69% of a dose of amoxapine is excreted in urine within 6 days principally as conjugated metabolites; approximately 7–18% of the drug is excreted in feces principally as unconjugated metabolites. Less than 5% of amoxapine is excreted in urine as unchanged drug.

Chemistry and Stability

■ **Chemistry** Amoxapine, a tricyclic dibenzoxazepine derivative, is the desmethyl analog of loxapine. Amoxapine differs structurally from the dibenzazepine, dibenzocycloheptene, and dibenzoxepin tricyclic antidepressants in that it has both a nitrogen and an oxygen atom in its 7-membered ring and a piperazinyl ring rather than a propylamino chain attached to the center ring. Amoxapine occurs as a white to pale yellow, crystalline powder and is slightly soluble in water and in alcohol. The drug has an apparent pK_a of 7.6.

■ **Stability** Amoxapine tablets should be stored in tight containers at 15–30°C.

For further information on chemistry, pharmacology, pharmacokinetics, uses, cautions, acute toxicity, drug interactions, and dosage and administration of amoxapine, see the Tricyclic Antidepressants General Statement 28:16.04.28.

Preparations

Excipients in commercially available drug preparations may have clinically important effects in some individuals; consult specific product labeling for details.

Amoxapine

Oral		
Tablets, scored	25 mg*	Amoxapine Tablets
	50 mg*	Amoxapine Tablets
	100 mg*	Amoxapine Tablets
	150 mg*	Amoxapine Tablets

*available from one or more manufacturer, distributor, and/or repackager by generic (nonproprietary) name

Clomipramine Hydrochloride

Chlorimipramine Hydrochloride, Chloroimipramine Hydrochloride, CMI

■ Clomipramine, a dibenzazepine-derivative tricyclic antidepressant, is the 3-chloro analog of imipramine.

Uses

■ **Obsessive-Compulsive Disorder** Clomipramine is used in the treatment of obsessive-compulsive disorder when obsessions or compulsions cause marked distress, are time-consuming (take longer than 1 hour daily), or interfere substantially with the patient's normal routine, occupational or academic functioning, or usual social activities or relationships. Obsessions are recurrent and persistent thoughts, impulses, or images that, at some time during the disturbance, are experienced as intrusive and inappropriate (i.e., "ego dystonic") and that cause marked anxiety or distress but that are not simply excessive worries about real-life problems. Compulsions are repetitive behaviors (e.g., hand washing, ordering, checking) or mental acts (e.g., praying, counting, repeating words silently) performed in response to an obsession or according to rules that must be applied rigidly (e.g., in a stereotyped fashion). Although the behaviors or acts are aimed at preventing or reducing distress or preventing some dreaded event or situation, they either are not connected in a realistic manner with what they are designed to neutralize or prevent or are clearly excessive. At some time during the course of the disturbance, the patient, if an adult, recognizes that the obsessions or compulsions are excessive or unreasonable; children may not make such recognition.

The efficacy of clomipramine for the management of obsessive-compulsive disorder has been established in several multicenter, placebo-controlled, parallel-group studies, including 2 studies of 10 weeks' duration in adults and one study of 8 weeks' duration in children and adolescents 10–17 years of age. In these clinical studies, clomipramine was more effective than placebo in reducing the severity of obsessive-compulsive manifestations in patients with moderate to severe obsessive-compulsive disorder. The drug produced substantial improvement in scores on both the Yale-Brown Obsessive-Compulsive Scale (YBOCS) and the National Institute of Mental Health (NIMH) Clinical Global Obsessive-Compulsive Scale (NIMH-OC), while the response with placebo was clinically insignificant. Scores on the YBOCS decreased by an average of approximately 10 from baseline values of 26–28, representing an average improvement of 35–42% in adults and 37% in children and adolescents treated with clomipramine. Scores on the NIMH-OC were reduced by an average of 3.5 units from a mean baseline of 10 in adults, children, and adolescents treated with clomipramine, which represents an improvement in obsessive-compulsive disorder from severe at baseline to subclinical after treatment with the drug. The maximum dosage of clomipramine hydrochloride was 250 mg daily for most adults and 3 mg/kg (up to 200 mg) daily for children and adolescents.

Although obsessive-compulsive manifestations often persist to some extent

in patients who respond to clomipramine, responders generally find it easier to resist the manifestations and spend less time engaged in the associated behavior. Data from a retrospective analysis suggest that clomipramine may be more effective in patients who developed obsessive-compulsive disorder during middle age (35–62 years of age) than in those in whom onset occurred during early adulthood (16–23 years old), independent of the length of illness.

Therapeutic response to clomipramine in patients with obsessive-compulsive disorder generally is evident within 2–6 weeks but may not be maximal until 3–4 months after beginning therapy with the drug. Thus, it is essential that patients receive an adequate trial of clomipramine at a therapeutic dosage in order to determine efficacy.

Many clinicians consider clomipramine or a serotonin-reuptake inhibitor (e.g., fluoxetine, fluvoxamine) to be the drugs of choice in obsessive-compulsive disorder. In addition, behavior therapy often is recommended in patients with obsessive-compulsive disorder even when pharmacologic therapy alone has been partially effective.

Results from comparative studies to date suggest that clomipramine is more effective than other tricyclic antidepressants (e.g., amitriptyline, desipramine, imipramine, nortriptyline) and as or more effective than selective serotonin-reuptake inhibitors (e.g., fluoxetine, fluvoxamine) in the management of obsessive-compulsive disorder. In a pooled analysis of separate short-term (10–13 weeks) studies comparing clomipramine, fluoxetine, fluvoxamine, or sertraline with placebo, clomipramine was calculated as being more effective (as determined by measures on the YBOC scale) than selective serotonin-reuptake inhibitors, although all drugs were superior to placebo. Like clomipramine, selective serotonin-reuptake inhibitors reduce but do not completely eliminate obsessions and compulsions. The decision whether to initiate therapy with clomipramine or a selective serotonin-reuptake inhibitor often is made based on the adverse effect profile of these drugs. For example, some clinicians prefer clomipramine in patients who may not tolerate the adverse effect profile of selective serotonin-reuptake inhibitors (nausea, headache, overstimulation, sleep disturbances) while selective serotonin-reuptake inhibitors may be useful alternatives in patients unable to tolerate the adverse effects (anticholinergic effects, cardiovascular effects, sedation) associated with clomipramine therapy. Consideration of individual patient characteristics (age, concurrent medical conditions), the pharmacokinetics of the drug, potential drug interactions, and cost of therapy may also influence clinicians when selecting between clomipramine and selective serotonin-reuptake inhibitors as first-line therapy in patients with obsessive-compulsive disorder. Although not clearly established, it has been suggested that the mechanism of action of clomipramine and other drugs (fluoxetine, fluvoxamine) used in the management of obsessive-compulsive disorder may be related to their serotonergic activity. Clomipramine also has been effective when used in combination with clonidine in several patients with obsessive-compulsive disorder; however, additional experience is needed to confirm the safety and efficacy of this combination.

The manufacturers state that the efficacy of clomipramine for long-term use (i.e., longer than 10 weeks) in the treatment of obsessive-compulsive disorder has not been established in placebo-controlled studies. After 36 weeks of treatment with clomipramine, improvement compared with placebo was observed on measures of rituals, mood, and social adjustment, although such effects were more substantial after 18 weeks of treatment. At follow-up 22 weeks after treatment ended, clomipramine differed from placebo on one measure of rituals. Clomipramine was not distinguishable from placebo in efficacy at follow-up 6 years after the conclusion of treatment. The combination of clomipramine or placebo with the same behavioral therapy resulted in greater improvement with clomipramine on measures of rituals, mood, and social adjustment at 8 weeks of treatment, but thereafter through the last 15 weeks of treatment and at follow-up through 52 weeks, clomipramine was indistinguishable from placebo. However, clomipramine has been used in some patients for prolonged periods (e.g., up to 1 year) without apparent loss of clinical effect. If clomipramine is used for extended periods, dosage should be adjusted so that patients are maintained on the lowest effective dosage, and the need for continued therapy with the drug should be reassessed periodically.

Discontinuance of clomipramine frequently results in a progressive recurrence of symptoms in patients with obsessive-compulsive disorder, and therefore long-term continued therapy with the drug may be advisable on an individual basis. In a study conducted under double-blind conditions, most patients with obsessive-compulsive disorder who had improved clinically following 5–27 months of clomipramine therapy experienced profound worsening of manifestations after discontinuance of the drug. This worsening started at 4 weeks and continued for the rest of the 7-week placebo period and appeared to be unrelated to the duration of clomipramine therapy or to the type of obsessive-compulsive manifestations originally present. However, readministration of clomipramine resulted in clinical improvement similar to that obtained prior to discontinuance of the drug.

Disorders with an Obsessive-Compulsive Component Depressive episodes may be associated with obsessive-compulsive disorder. Clomipramine and selective serotonin-reuptake inhibitors are effective antidepressants when obsessive manifestations accompany an episode of major depression. However, the antiobsessional effectiveness of clomipramine does not appear to depend on the presence of depression.

Clomipramine also may reduce obsessive-compulsive manifestations in some patients with schizophrenia and such accompanying manifestations. However, exacerbation of psychosis has been reported in some patients treated with clomipramine. Therefore, the possibility of exacerbating psychosis should be considered in patients with obsessive-compulsive manifestations and schizophrenia, and such patients receiving clomipramine should be observed closely for early signs of worsening psychosis.

There is a high incidence of obsessive-compulsive disorder in patients with Tourette's disorder (Gilles de la Tourette's syndrome), and clomipramine can reduce obsessive-compulsive manifestations associated with Tourette's and suppress associated motor and vocal tics. However, in at least one controlled study, clomipramine did not differ from placebo in the number of tics observed during 4 weeks of treatment.

Obsessive thoughts were decreased with the combination of clomipramine and lithium carbonate in a limited number of patients who had obsessive manifestations that previously failed to respond to clomipramine therapy alone. However, in a study of patients with obsessive-compulsive disorder treated with clomipramine for at least 6 months and who were partial responders to the drug, the addition of lithium carbonate for 4 weeks did not result in improvement in scores on the YBOCS.

■ **Panic Disorder** Clomipramine has been used effectively for the treatment of panic disorder† with or without agoraphobia†. In an uncontrolled study, clomipramine reduced both the weekly frequency and severity of panic attacks when given in an average dosage of 45 mg daily (range: 6.25–75 mg daily). In many patients, complete or nearly complete relief from panic attacks was reported during therapy. The number of days that panic attacks occurred was less with clomipramine (mean dosage of 83 mg daily) than with placebo after 8 weeks of treatment in one study. Therapeutic response generally is seen within about 1–3 weeks but may take up to 6 weeks. Although clomipramine therapy generally is well tolerated, a transient increase in the number and intensity of panic attacks may occur during initial therapy with the drug. (See Dosage and Administration: Dosage.) Clomipramine (mean dosage of 109 mg daily; range: 25–200 mg daily) was at least as effective as imipramine (mean dosage of 109 mg daily; range: 25–200 mg daily) in patients with panic disorder and had a faster onset of action in reducing panic attacks and improving phobic avoidance and associated anxiety.

Clomipramine generally is equally effective in patients with panic disorder with or without agoraphobia. In a limited number of patients whose panic disorder with agoraphobia did not respond to exposure-based behavioral treatment, measures of fear (i.e., fear of bodily incapacitation, fear of losing control), state and trait anxiety, depression, severity of condition, and avoidance of separation situations indicated improvement compared with placebo after receiving clomipramine for about 5 weeks (3 weeks at the maximum dosage of 150 mg daily). Despite such improvement, the efficacy of clomipramine in the treatment of such patients was uncertain. A clinical response, as indicated by improvement by at least 50% on assessment of avoidance of separation situations with the Phobic Avoidance Rating Scale, was produced by clomipramine in 29% of the patients, while such response was observed with behavioral treatment in 47% of the patients.

Preliminary results from an uncontrolled study suggest that clomipramine is effective in patients with panic disorder or agoraphobia with panic attacks who have concurrent mitral valve prolapse.

Although it has been suggested that the mechanism of action of clomipramine in patients with panic disorder may be related to the drug's serotonergic activity, the absence of clear superiority compared with less selective antidepressants (e.g., desipramine) suggests that this may not be the case.

For further information on treatment of panic disorder, see Uses: Panic Disorder, in the Tricyclic Antidepressants General Statement 28:16.04.28.

■ **Major Depressive Disorder** Clomipramine has been used effectively in the treatment of major depressive disorder†. Clinical studies have shown that the antidepressant effect of clomipramine exceeds that of placebo and is comparable to that of usual dosages of other tricyclic antidepressants (e.g., amitriptyline, doxepin, imipramine) or selective serotonin-reuptake inhibitors (e.g., fluoxetine, paroxetine). Several (e.g., 4–6) weeks may be required for optimal antidepressant effect at a given clomipramine dosage. Despite comparable efficacy, the adverse effect profile (e.g., anticholinergic effects) of clomipramine may limit its usefulness relative to other antidepressants, and antidepressant therapy should be individualized based on patient response and tolerance. Clomipramine appears to offer no substantial advantage over other tricyclic antidepressants for the management of typical depression in the absence of obsessive-compulsive manifestations and may be more poorly tolerated, particularly compared with tricyclics exhibiting only mild to moderate anticholinergic effects. Although some clinicians have preferred clomipramine to other tricyclic antidepressants for atypical depression (e.g., because of clomipramine's dopaminergic activity), other agents (e.g., selective serotonin-reuptake inhibitors such as fluoxetine) generally have replaced this preference for clomipramine in such depression.

For further information on treatment of major depressive disorder and considerations in choosing the most appropriate antidepressant for a particular patient, including considerations related to patient tolerance, patient age, and cardiovascular, sedative, and suicidal risks, see Considerations in Choosing Antidepressants under Uses: Major Depressive Disorder, in the Tricyclic Antidepressants General Statement 28:16.04.28.

■ **Chronic Pain** Like other tricyclic antidepressants, clomipramine has been used for the treatment of chronic pain†, including central pain, idiopathic pain disorder, tension headache, diabetic peripheral neuropathy, and pain of other neuropathic origin (e.g., cancer pain). Antidepressants have been used alone or as adjuncts to conventional analgesics in the management of such

pain. In patients with central pain (e.g., phantom or stump pain; post-herpetic neuralgia, deafferentation pain secondary to posttraumatic nerve lesions), reduction in pain intensity, as indicated by scores on a visual analog scale for pain, was greater during treatment with clomipramine for 3 weeks than with placebo. Treatment of idiopathic pain disorder with clomipramine (mean dosage of 97 mg daily) for 6 weeks resulted in improvement, as indicated by the physicians' global assessment, in 63% of patients. The patients' scores on visual analog scales that included assessment of pain also were improved. In patients with tension headache, a greater decrease in headache pain, as indicated by scores on a visual analog scale, occurred with clomipramine administered for 6 weeks than with placebo. Treatment of diabetic peripheral neuropathy with clomipramine for 2 weeks resulted in a greater decrease compared with placebo in the severity of symptoms overall, as evaluated by a physician through use of a scale that quantified pain, paresthesia, dysesthesia, numbness, nightly deterioration, and sleep disturbances.

■ **Cataplexy and Associated Narcolepsy** Clomipramine has been used for the symptomatic management of cataplexy† in a limited number of patients with cataplexy and associated narcolepsy. Cataplexy attacks and sleep paralysis resolved or were reduced in frequency during clomipramine therapy (25–200 mg daily); however, the drug did not consistently improve sleep attacks. Although the precise mechanism of clomipramine's anticataplectic action is not known, it has been suggested that its serotonergic and REM-suppressing activity may be involved.

■ **Autistic Disorder** Clomipramine has been effective in a limited number of patients with autistic disorder†. In a double-blind study, clomipramine therapy (mean dosage: 152 mg daily) was superior to both desipramine and placebo in improving standardized ratings of autistic manifestations, including repetitive and obsessive-compulsive behaviors and hyperactivity in a limited number of pediatric outpatients aged 6–18 years with autistic disorder. However, in an open study involving younger inpatients aged 3–9 years with autistic disorder but with relatively low intellectual functioning and without prominent obsessive-compulsive manifestations, clomipramine was not found to be effective and was commonly associated with adverse effects, including acute urinary retention.

■ **Trichotillomania** Clomipramine has been used in a limited number of patients with trichotillomania† (an urge to pull out one's hair). In one double-blind, crossover study, clomipramine (mean dosage of 181 mg daily; range: 100–250 mg daily) was shown to be more effective than desipramine (mean dosage of 173 mg daily; range: 150–200 mg daily) in the short-term management of trichotillomania. However, relapse has been reported in some patients receiving long-term treatment with clomipramine.

■ **Onychophagia** Clomipramine has been used in a limited number of patients with severe onychophagia† (nail biting) and no history of obsessive-compulsive disorder. In one study, the severity of nail biting decreased in patients treated with clomipramine hydrochloride 25–200 mg daily for 5 weeks. However, the relatively high dropout rate secondary to adverse effects and drug intolerance suggests that clomipramine should not be considered as first-line therapy in most patients with onychophagia.

■ **Stuttering** Clomipramine has been used in a limited number of patients with stuttering†. Following 5 weeks of therapy (mean dosage: 147 mg daily), clomipramine improved the severity of stuttering, preoccupation with thoughts about stuttering, amount of energy spent resisting stuttering, and expectancy of stuttering. Additional study of the efficacy of clomipramine in the management of stuttering is necessary.

■ **Eating Disorders** Clomipramine has been used in a limited number of patients with anorexia nervosa†. In a placebo-controlled study, clomipramine therapy was associated with increased appetite, hunger, and calorie consumption during initial therapy; however, the drug was not associated with improved eating behavior after 8 weeks of therapy or greater weight gain. In addition, body weight did not differ between the clomipramine and placebo groups at 1-year follow-up and a measure of outcome based on nutritional status, sexual adjustment, socioeconomic adjustment, and mental state did not differ between the 2 groups at 4-year follow-up. Few controlled studies on the pharmacotherapy for anorexia nervosa have been published, and results with most drugs have been unimpressive. Because malnourished depressed patients may be particularly susceptible to the adverse cardiovascular effects or other severe toxicities (including death) of tricyclic antidepressants, the American Psychiatric Association (APA) states that tricyclic antidepressants should be avoided in underweight individuals and in those exhibiting suicidal ideation. For further information on use of antidepressants in the treatment of eating disorders see Uses: Eating Disorders, in Fluoxetine Hydrochloride 28:16.04.20.

■ **Premature Ejaculation** Clomipramine has been used with some success in the treatment of premature ejaculation†. In a controlled study, mean ejaculatory latency was prolonged in patients receiving 25 or 50 mg of the drug daily. Sexual and relationship satisfaction also was improved. A trial with drug therapy may be particularly useful in patients who fail or refuse behavioral or psychotherapeutic treatment or when partners are unwilling to cooperate with such therapy.

■ **Premenstrual Syndrome** Clomipramine has been used in the management of premenstrual syndrome†. In a limited number of women with severe premenstrual irritability and/or depressed mood, clomipramine given either continuously or intermittently (i.e., premenstrual administration) during 3 menstrual cycles at a dosage of 25–75 mg daily was more effective than placebo in reducing premenstrual irritability and depressed mood. However, preliminary data suggest that patients with premenstrual syndrome may be particularly sensitive to the adverse effects associated with the drug.

Dosage and Administration

■ **Administration** Clomipramine hydrochloride is administered orally. The drug also has been administered IM† or IV†, but a parenteral dosage form is not commercially available in the US.

During initial therapy when the dosage is being titrated, the manufacturers recommend that clomipramine be given in divided doses with meals to lessen adverse GI effects. After dosage titration, the total daily dose may be given once daily at bedtime to minimize adverse effects such as sedation during waking hours and enhance patient compliance.

■ **Dosage** Dosage of clomipramine hydrochloride is expressed in terms of the hydrochloride.

Because there is wide interindividual variation in dosage and dosage may differ in various disease states, the dosage of clomipramine hydrochloride must be individualized carefully.

Patients receiving clomipramine should be monitored for possible worsening of depression, suicidality, or unusual changes in behavior, especially at the beginning of therapy or during periods of dosage adjustment. (See Cautions: Precautions and Contraindications.)

Obsessive-Compulsive Disorder For the management of obsessive-compulsive disorder in adults, children, or adolescents, the recommended initial dosage of clomipramine hydrochloride is 25 mg daily. During the first 2 weeks of therapy, dosage should be increased gradually as tolerated to approximately 100 mg daily in adults. In children and adolescents, dosage should be increased gradually, as tolerated, during the first 2 weeks of therapy up to a maximum of 3 mg/kg or 100 mg daily, whichever is lower. This initial period of titration is intended to minimize adverse effects by permitting tolerance to develop or allowing the patient time to adapt if tolerance does not develop.

During the next several weeks, the dosage of clomipramine hydrochloride may be increased gradually up to a maximum of 250 mg daily in adults and 3 mg/kg or 200 mg daily (whichever is lower) in children and adolescents. Daily clomipramine hydrochloride dosages exceeding 250 mg in adults or 3 mg/kg (up to 200 mg) in children and adolescents should be avoided because of the increased risk of seizures (see Cautions: Nervous System Effects).

Because of the long elimination half-lives of both clomipramine and its active metabolite, desmethylclomipramine, clinicians should take into consideration that steady-state plasma concentrations may not be achieved for 2–3 weeks or even longer. Therefore, the manufacturers state that it may be appropriate to wait 2–3 weeks between any further dosage adjustments after the initial dosage titration period.

Although the optimum duration of clomipramine therapy has not been established, obsessive-compulsive disorder is a chronic condition and it seems reasonable to consider continuation of therapy in responding patients. Although the manufacturers state that the efficacy of clomipramine when given for periods exceeding 10 weeks has not been established systematically in controlled studies, the drug has been given under double-blind conditions for up to 1 year without loss of clinical efficacy. Pending further accumulation of data, some clinicians recommend that clomipramine therapy be continued for at least 18 months in patients with obsessive-compulsive disorder before attempting to discontinue therapy. However, the dosage should be adjusted during maintenance therapy so that patients are maintained on the minimum effective dosage and patients should be reassessed periodically to determine the need for continued therapy.

Clomipramine should not be used concomitantly with MAO inhibitors and it is recommended that at least 2 weeks elapse between discontinuance of therapy with a MAO inhibitor and initiation of clomipramine therapy and vice versa. A similar interval is recommended between discontinuance of therapy with a selective serotonin-reuptake inhibitor (e.g., citalopram, escitalopram, fluvoxamine, paroxetine, sertraline) and initiation of therapy with a tricyclic antidepressant agent such as clomipramine and vice versa. However, because fluoxetine and its active metabolite have a long half-life, at least 5 weeks should elapse between discontinuance of fluoxetine therapy and initiation of clomipramine therapy.

Abrupt discontinuance of clomipramine therapy should be avoided since a variety of withdrawal symptoms have been reported. (See Cautions: Nervous System Effects and also see Chronic Toxicity.) In addition, patients may experience a worsening of psychiatric status when the drug is discontinued abruptly. Therefore, it is recommended that dosage be tapered gradually (e.g., over a period of approximately 2 weeks) and the patient monitored carefully when clomipramine therapy is discontinued.

Panic Disorder For the management of panic disorder† with or without agoraphobia†, clomipramine hydrochloride usually has been effective in dosages ranging from 12.5–150 mg (maximum: 200 mg) daily. Most patients with panic attacks respond to a clomipramine hydrochloride dosage of less than 50 mg daily; however, patients with agoraphobia may require a higher dosage. Because clomipramine may worsen anxiety symptoms during initial therapy, some clinicians recommend that patients be started on a low dosage initially, and then the dosage can be increased gradually until therapeutic response or bothersome adverse effects occur.

Other Uses For the management of major depressive disorder† or chronic pain†, clomipramine hydrochloride is generally given in dosages ranging from 100–250 mg daily.

For the management of cataplexy and associated narcolepsy†, clomipramine hydrochloride has been given in dosages ranging from 25–200 mg daily.

■ **Dosage in Geriatric Patients** The manufacturers and some clinicians recommend selecting an initial clomipramine dosage at the lower end of the recommended range since decreased hepatic, renal, or cardiac function and concomitant illness and medications are more frequent in geriatric patients.

Cautions

Clomipramine shares the toxic potentials of the tricyclic antidepressants, and the usual precautions of tricyclic antidepressant administration should be observed. (See Cautions in the Tricyclic Antidepressants General Statement 28:16.04.28.)

Common adverse effects of clomipramine are extensions of its pharmacologic activity, principally anticholinergic effects; adverse effects secondary to antihistaminic and α-adrenergic activity also may occur. Like other tricyclics, adverse effects of clomipramine could affect compliance and result in dosage reduction; however, the possibility that such reductions could affect response should be considered.

In controlled studies, the most common adverse effects occurring more frequently in patients receiving clomipramine than in those receiving placebo included GI effects such as dry mouth, constipation, nausea, dyspepsia, anorexia, and increased appetite; nervous system effects such as somnolence, tremor, dizziness, nervousness, fatigue, and myoclonus; genitourinary effects such as changed libido, ejaculatory failure, impotence, and micturition disorder; sweating; weight gain; and visual changes. Approximately 20% of the 3616 patients who participated in US premarketing clinical trials for obsessive-compulsive or other disorders discontinued clomipramine therapy because of an adverse effect. About one-half of those who discontinued therapy (9% of the total) experienced multiple adverse effects, none of which could be classified as the principal reason. However, in the cases in which a principal reason for discontinuing therapy could be identified, most of the patients did so because of nervous system effects (5.4%), mainly somnolence, and GI effects (1.3%), mainly nausea and vomiting.

The incidences of adverse effects reported by the manufacturers to have occurred in at least 1% of clomipramine-treated patients were obtained from pooled data from placebo-controlled clinical trials involving 322 adults and 46 children or adolescents who received clomipramine for the treatment of obsessive-compulsive disorder. However, clinicians prescribing clomipramine should be aware that these figures cannot be used to predict the incidence of adverse effects during usual medical practice, in which patient characteristics and other factors differ from those that prevailed during these trials. Similarly, the cited incidences cannot be compared with the incidences obtained from other trials involving different treatments, uses, and investigators. However, the incidences from these trials provide the clinician with a basis for estimating the relative contribution of both drug and nondrug factors to the incidence of adverse effects in the populations studied. Various other adverse effects have been reported in 3525 out of approximately 3600 individuals who received multiple doses of clomipramine for obsessive-compulsive or other disorders during premarketing trials in the US; however, these adverse effects have not been definitely attributed to the drug.

Some evidence suggests that patients with depression may tolerate clomipramine relative to placebo more poorly than those with obsessive-compulsive disorder.

■ **Nervous System Effects** *Seizures* Seizure is the most clinically important risk associated with clomipramine therapy. However, seizure remains a relatively uncommon adverse effect of clomipramine therapy. The cumulative incidence of seizures in patients treated with clomipramine hydrochloride dosages of up to 300 mg daily was 0.64, 1.12, and 1.45% at 90, 180, and 365 days, respectively. The cumulative rates correct the crude incidence of 0.7% (25 of 3519 patients) for the variable duration of exposure to clomipramine in clinical trials. Seizures also have been associated with abrupt withdrawal of the drug.

Dose appears to be a predictor of the development of seizures. However, the influence of dose is confounded by the duration of exposure to the drug, making independent assessment of the effect of either factor alone difficult. Seizures occurred in about 0.5, or 2% of patients who received a maximum daily dose of 250 mg or higher than 250 mg, respectively, of the drug. The ability to predict seizures with daily doses exceeding 250 mg is limited because plasma concentrations achieved during clomipramine therapy may be dose dependent and vary considerably among individuals administered the same dosage.

Rare reports of fatalities in association with clomipramine-associated seizures have been reported in foreign postmarketing surveillance, but not in US clinical trials. In some of these cases, clomipramine had been administered with other epileptogenic agents, while in other cases the patients had possible predisposing medical conditions. Thus, a causal relationship between clomipramine therapy and these fatalities has not been established. (See Cautions: Precautions and Contraindications.)

Withdrawal Effects Withdrawal syndrome has been reported rarely in patients receiving clomipramine. In a limited number of patients, abrupt discontinuance of clomipramine resulted in a variety of withdrawal manifestations, including dizziness, nausea, vomiting, headache, malaise, sleep disturbance, hyperthermia, sweating, and irritability. Abrupt discontinuance of the drug also reportedly has resulted in seizures. In addition, some patients have experienced a worsening of psychiatric status when the drug was discontinued abruptly. Therefore, abrupt discontinuance of clomipramine therapy should be avoided. (See Cautions: Precautions and Contraindications.)

Serotonin Syndrome The manifestation of a group of adverse effects (e.g., tremor, myoclonus, diaphoresis, shivering, restlessness, fever, mental status changes, diarrhea) that resembles the serotonin syndrome observed in animals has been reported with clomipramine monotherapy. In an open study in which patients received clomipramine 150 mg daily for about 4 weeks for the treatment of depression, tremor of the tongue and myoclonus occurred most commonly (42 and 36% of patients, respectively). Tremor of the tongue or fingers and myoclonus were accompanied by diaphoresis and shivering in over a quarter of the patients. In most cases, these manifestations were transient and resolved despite continued therapy. More severe and sometimes fatal reactions resembling the serotonin syndrome have been reported when clomipramine has been given concurrently with other serotonergic agents such as MAO inhibitors, fluoxetine, lithium, or alprazolam. (See Drug Interactions.)

Other Nervous System Effects In controlled trials, somnolence, dizziness, or tremor was each reported in about 54% of adults and in about 46, 41, or 33%, respectively, of children and adolescents receiving clomipramine. Headache occurred in about 52% of adults and 28% of children and adolescents receiving clomipramine. Fatigue occurred in about 39% of adults and 35% of children and adolescents receiving the drug. Insomnia occurred in about 25% of adults and 11% of children and adolescents and nervousness occurred in about 18% of adults and 4% of children and adolescents treated with clomipramine.

Myoclonus occurred in about 13% of adults and 2% of children and adolescents receiving clomipramine. Motor hyperactivity that included jerking of the arms and legs during nocturnal sleep also has been reported. Memory impairment occurred in about 9 or 7% of adults or children and adolescents, respectively, receiving clomipramine. Paresthesia and anxiety each occurred in about 9 or 2% of adults or children and adolescents, respectively, receiving the drug. Twitching occurred in about 7 or 4% of adults or children and adolescents, respectively, receiving clomipramine. Impaired concentration and depression each occurred in about 5% of adults receiving clomipramine. Sleep disorder occurred in about 4 or 9% of adults or children and adolescents, respectively, treated with the drug. Disturbance of sleep by fright that was accompanied by myoclonus also has been reported in association with clomipramine therapy. Hypertonia occurred in about 4 or 2% of adults or children and adolescents, respectively, receiving the drug.

Confusion occurred in about 3 or 2% of adults or children and adolescents, respectively, receiving clomipramine. Psychosomatic disorder, speech disorder, dream abnormalities, agitation, or migraine occurred in about 3% of adults treated with the drug. Depersonalization or irritability occurred in about 2% of both adults and children or adolescents receiving clomipramine. Emotional lability occurred in about 2% of adults and aggressive reaction occurred in about 2% of children and adolescents treated with the drug. Paresis and asthenia each occurred in about 2% of children and adolescents and panic reaction occurred in about 1 or 2% of adults or children and adolescents, respectively, receiving clomipramine.

During premarketing clinical trials in patients with affective disorder, hypomania or mania was precipitated infrequently in patients receiving clomipramine therapy. Activation of mania or hypomania also has been reported in patients treated with other tricyclic antidepressants.

More than 30 cases of hyperthermia with clomipramine have been reported by foreign postmarketing surveillance systems. Most of these cases occurred in patients receiving clomipramine in combination with other drugs (e.g., antipsychotic agents). When clomipramine and an antipsychotic agent were used concomitantly, the cases sometimes were considered to be examples of neuroleptic malignant syndrome (NMS).

Abnormal thinking and vertigo each occurred in 1% or more of patients receiving clomipramine; however, a causal relationship to the drug has not been established.

Dyskinesia occurred in less than 1% of patients receiving clomipramine, although a causal relationship to the drug has not been established. Persistent tardive dyskinesia has been reported after initiation of clomipramine in a patient who was already receiving dextroamphetamine. A severe tardive dyskinesia-like syndrome consisting of orobuccal movements, choreoathetosis of the arms and other abnormal movements of the extremities, motor restlessness, and incoordination has been reported in another patient who was receiving clomipramine concurrently with thiothixene, buspirone, and trihexyphenidyl.

Other adverse nervous system effects occurring in less than 1% of clomipramine-treated patients include apathy, ataxia, coma, abnormal coordination, delirium, delusions, dysphonia, EEG abnormalities, encephalopathy, euphoria, extrapyramidal disorder, abnormal gait, hallucinations, hostility, hyperkinesia, hypnagogic hallucinations, hypokinesia, neuralgia, paranoia, phobic disorder, psychosis, sensory disturbance, somnambulism, stimulation, and teeth grinding; however, a causal relationship to the drug has not been established.

Rarely reported adverse nervous system effects for which a causal relationship to clomipramine has not been established include anticholinergic syndrome, aphasia, apraxia, catalepsy, cholinergic syndrome, choreoathetosis, hemiparesis, hyperesthesia, hyperreflexia, hypoesthesia, illusion, impaired im-

pulse control, indecisiveness, mutism, neuropathy, nystagmus, oculogyric crisis, oculomotor nerve paralysis, schizophrenic reaction, generalized spasm, stupor, and torticollis. Dystonia has been reported rarely in clomipramine-treated patients, although a causal relationship to the drug has not been established. Acute dystonia that included oculogyric crisis, torticollis, and lead-pipe rigidity has occurred in a patient receiving clomipramine. Exacerbation of motor tics and development of vocal tics also have been reported in a patient receiving the drug.

Suicidal ideation and suicide attempt have been reported in less than 1% of patients receiving clomipramine and suicide has been reported rarely. (See Cautions: Precautions and Contraindications.)

■ **Cardiovascular Effects** During clinical trials, modest orthostatic decreases in blood pressure and modest tachycardia each occurred in about 20% of patients receiving clomipramine, although patients frequently were asymptomatic. Postural hypotension occurred in about 6 or 4% of adults or children and adolescents, respectively, and tachycardia occurred in about 4 or 2% of adults or children and adolescents, respectively, receiving clomipramine in controlled clinical trials. Flushing occurred in about 8 or 7% of adults or children and adolescents, respectively, treated with the drug in controlled clinical trials.

Palpitations occurred in about 4% of both adults and children or adolescents receiving clomipramine in controlled clinical trials. Chest pain occurred in about 4 or 7% of adults or children and adolescents, respectively, and syncope occurred in about 2% of children and adolescents receiving clomipramine in controlled clinical trials.

Among approximately 1400 patients who received clomipramine during the premarketing evaluation, ECG abnormalities were observed in about 1.5% of the patients compared with 3.1% of those who received an active control and 0.7% of those receiving placebo. The most commonly observed ECG changes were ventricular premature contractions, ST-T wave changes, and intraventricular conduction abnormalities. These changes rarely were associated with clinically important symptoms; nevertheless, caution is necessary when treating patients with known cardiovascular disease with clomipramine, and gradual dosage titration is recommended in such patients.

Arrhythmia, bradycardia, cardiac arrest, extrasystoles, and pallor occurred in less than 1% of patients receiving clomipramine, although a causal relationship to the drug has not been established. Aneurysm, atrial flutter, bundle-branch block, cardiac failure, cerebral hemorrhage, heart block, myocardial infarction, myocardial ischemia, peripheral ischemia, thrombophlebitis, vasospasm, and ventricular tachycardia have occurred rarely, but these adverse effects also have not been attributed definitely to the drug. Hypertension also has been reported.

General edema, greater susceptibility to infection, malaise, and parosmia have been reported in less than 1% of clomipramine-treated patients and dependent edema has been reported rarely, although these adverse effects have not been attributed definitely to the drug.

There have been reports of fatigue and dizziness during physical exertion in children and adolescents receiving clomipramine. Because the cardiovascular effects of the drug have not been studied during such stress in this age group, some clinicians state that clomipramine should be used with caution in children and adolescents who participate in active sports.

■ **GI Effects** Adverse GI effects are encountered commonly during initial clomipramine therapy and in some cases can lead to early withdrawal of the drug. Dry mouth occurs in about 84 or 63% of adults or children and adolescents, respectively, and constipation occurs in about 47 or 22% of adults or children and adolescents, respectively, receiving clomipramine.

Nausea has been reported in about 33 or 9% of adults or children and adolescents, respectively, receiving clomipramine. Dyspepsia occurred in about 22 or 13% of adults or children and adolescents, respectively, and diarrhea occurred in about 13 or 7% of adults or children and adolescents, respectively, receiving the drug. Anorexia occurred in about 12 or 22% of adults or children and adolescents, respectively, receiving the drug. Abdominal pain occurred in about 11 or 13% of adults or children and adolescents, respectively, receiving clomipramine. Increase in appetite occurred in 11% of adults treated with the drug. Taste perversion occurred in about 8 or 4% of adults or children and adolescents, respectively, receiving clomipramine. Vomiting occurred in about 7% of clomipramine-treated adults, children, and adolescents. Flatulence has been reported in about 6% of adults receiving the drug. GI disorder or dysphagia occurred in about 2% of clomipramine-treated adults, and eructation, ulcerative stomatitis, or halitosis occurred in about 2% of children and adolescents receiving the drug. Esophagitis occurred in about 1% of adults receiving clomipramine.

Blood in stool, colitis, duodenitis, gastric ulcer, gastritis, gastroesophageal reflux, gingivitis, glossitis, hemorrhoids, increased salivation, irritable bowel syndrome, peptic ulcer, rectal hemorrhage, taste loss, and tongue ulceration were reported in less than 1% of patients receiving clomipramine, but a causal relationship to the drug has not been established. Cheilitis, chronic enteritis, discolored feces, gastric dilatation, gingival bleeding, intestinal obstruction, oral/pharyngeal edema, paralytic ileus, and salivary gland enlargement have occurred rarely but have not been attributed definitely to clomipramine.

■ **Dermatologic and Sensitivity Reactions** In controlled trials, increased sweating occurred in about 29 or 9% of adults or children and adolescents, respectively, receiving clomipramine. Rash occurred in about 8% of adults and 4% of children and adolescents treated with the drug. Pruritus occurred in about 6% of adults and 2% of children and adolescents receiving clomipramine. Dermatitis, acne, or dry skin occurred in about 2% of clomipramine-treated adults. Abnormal skin odor occurred in about 2% of children and adolescents receiving clomipramine therapy. Urticaria occurred in about 1% of adults and allergy occurred in about 3% of adults and 7% of children and adolescents treated with the drug.

Alopecia, cellulitis, cyst, eczema, genital pruritus, psoriasis, and rash that was erythematous, maculopapular, or pustular have been reported in less than 1% of patients receiving clomipramine, but these effects have not been attributed definitely to the drug. Lupus erythematosus rash has occurred rarely. Photosensitivity reaction or skin discoloration has occurred in less than 1% of patients receiving clomipramine, although a causal relationship to the drug has not been established. Pseudocyanotic (e.g., slate-gray, blue-black, purplish) pigmentation that affected areas of the body exposed to sunlight and therefore may have been a photosensitivity reaction also has occurred with clomipramine. Chloasma has been reported rarely. Folliculitis, hypertrichosis, pilocrection, polyarteritis nodosa, seborrhea, skin hypertrophy, or skin ulceration has been reported rarely in patients receiving clomipramine, although a causal relationship has not been established.

■ **Metabolic and Electrolyte Effects** In controlled studies, weight gain occurred in about 18% of adults who received clomipramine therapy for the treatment of obsessive-compulsive disorder compared with 1% of those receiving placebo. In these studies, a weight gain of at least 7% of initial body weight occurred in about 28% of clomipramine-treated patients compared with 4% of those receiving placebo. In several patients, weight gain exceeded 25% of the initial body weight. Conversely, weight losses of at least 7% of initial body weight occurred in about 5% of clomipramine-treated patients compared with 1% of those who received placebo. In controlled studies, weight gain or weight loss occurred in about 2 or 7% of children and adolescents, respectively, receiving clomipramine.

Thirst occurred in about 2% of adults receiving clomipramine. Dehydration, gout, hypercholesterolemia, hyperglycemia, hyperuricemia, and hypokalemia have been reported in less than 1% of patients receiving clomipramine, although a causal relationship to the drug has not been established. Fat intolerance and glycosuria have been reported rarely in patients receiving clomipramine, although these adverse effects have not been attributed definitely to the drug.

■ **Ocular and Otic Effects** Abnormal vision occurred in about 18 or 7% of adults or children and adolescents, respectively, receiving clomipramine. Abnormal lacrimation, mydriasis, and conjunctivitis occurred in about 3, 2, and 1% of adults, respectively, receiving the drug. Anisocoria, blepharospasm, and ocular allergy occurred in about 2% of children and adolescents receiving clomipramine. Adverse ocular effects reported in less than 1% of clomipramine-treated patients include abnormal accommodation, diplopia, ocular pain, foreign body sensation, photophobia, and scleritis; however, a causal relationship to the drug has not been established.

Glaucoma has been reported rarely in patients receiving clomipramine, although a causal relationship to the drug has not been established. Angle-closure glaucoma that presented clinically as amaurosis fugax (transient monocular blindness) attacks that were precipitated by rising from a sitting or supine position has been reported in at least one female patient treated with the drug. Although the precise mechanism is unclear, it was suggested that an abnormally large fall in blood pressure upon standing up combined with an increase in intraocular pressure may have been responsible. Blepharitis, chromatopsia, conjunctival hemorrhage, exophthalmos, keratitis, night blindness, retinal disorder, strabismus, and visual field defect occurred rarely in patients receiving clomipramine, but have not been attributed definitely to the drug.

Tinnitus occurred in about 6 or 4% of adults or children and adolescents, respectively, receiving clomipramine. Otitis media or vestibular disorder occurred in about 4 or 2% of children and adolescents, respectively, receiving clomipramine. Adverse otic effects reported in less than 1% of clomipramine-treated patients include hyperacusis, deafness, earache, and labyrinth disorder; however, these effects have not been attributed definitely to the drug.

■ **Musculoskeletal Effects** Myalgia occurred in about 13% of adults receiving clomipramine. Back pain and arthralgia occurred in about 6 and 3% of adults, respectively, receiving clomipramine. Muscle weakness occurred in about 1 or 2% of adults or children and adolescents, respectively, receiving clomipramine. Arthrosis and leg cramps have been reported in less than 1% of patients receiving clomipramine, although a causal relationship to the drug has not been established. Exostosis, bruising, myopathy, and myositis have been reported rarely in clomipramine-treated patients, although these effects have not been attributed definitely to the drug.

■ **Hematologic Effects** Purpura has been reported in about 3% of adults receiving clomipramine. Although no cases of severe hematologic toxicity were reported during the premarketing evaluation of clomipramine, there subsequently have been rare reports of bone marrow depression in patients receiving the drug, including leukopenia, agranulocytosis, thrombocytopenia, anemia, and pancytopenia. In controlled trials, anemia occurred in about 2% of children and adolescents receiving the drug.

■ **Respiratory Effects** Pharyngitis occurred in about 14% of adults receiving clomipramine. Rhinitis occurred in about 12 or 7% of adults or children and adolescents, respectively, receiving clomipramine. Cough occurred in about 6 or 4% of adults or children and adolescents, respectively, receiving clomipramine. Sinusitis occurred in about 6 or 2% of adults or children and

adolescents, respectively, treated with the drug. Yawning occurred in about 3% of adults receiving clomipramine. Bronchospasm occurred in about 2 or 7% of adults or children and adolescents, respectively, receiving clomipramine.

Epistaxis occurred in about 2% of adults receiving clomipramine. Dyspnea or laryngitis occurred in about 2% of clomipramine-treated children and adolescents. The development of adverse respiratory effects (e.g., dry sore throat, cough) severe enough to result in aphonia also has been reported.

Although a causal relationship has not been established, bronchitis, hyperventilation, increased sputum, and pneumonia have been reported in less than 1% of patients receiving clomipramine, and cyanosis, hemoptysis, hiccup, hypoventilation, and laryngismus have been reported rarely.

■ **Genitourinary Effects** ***Sexual Dysfunction*** One characteristic of clomipramine therapy that may be troublesome to some patients is its relatively high incidence of sexual dysfunction. The incidence of sexual dysfunction in male patients receiving clomipramine therapy for obsessive-compulsive disorder during premarketing clinical trials was substantially higher than in those receiving placebo. Normal sexual functioning usually returns within a few days after discontinuing clomipramine therapy.

Libido change occurred in about 21% of adults receiving clomipramine. Ejaculatory failure occurred in about 42% of adult males treated with clomipramine compared with 2% of those receiving placebo, and impotence occurred in 20% of clomipramine-treated adult males compared with about 3% of those receiving placebo. Approximately 85% of adult males who experienced sexual dysfunction during clomipramine therapy chose to continue therapy with the drug. About 6% of adolescent males experienced ejaculation failure while receiving clomipramine. Premature ejaculation has been reported rarely but has not been attributed definitely to the drug. On the other hand, clomipramine has been used in the treatment of premature ejaculation† in a limited number of patients. Painful ejaculation or orgasm has been reported in a limited number of male patients receiving the drug.

Anorgasmy has been reported in both male and female patients receiving clomipramine. In u controlled trial, difficulty or inability to reach orgasm was the most common adverse sexual effect in clomipramine-treated patients; sexual function generally returned to normal within 3 days after discontinuance of the drug. Anorgasmy associated with clomipramine has responded to anticipatory administration of yohimbine in several patients. Orgasm during yawning also has been reported in a limited number of patients receiving clomipramine.

Other Genitourinary Effects Micturition disorder occurred in about 14 or 4% of adults or children and adolescents, respectively, receiving clomipramine. Urinary tract infection and frequent micturition occurred in about 6 and 5%, respectively, of adults receiving the drug. Urinary retention occurred in about 2 or 7% of adults or children and adolescents, respectively, receiving clomipramine while dysuria, including painful urination in men, and cystitis have been reported in about 2% of adults receiving clomipramine.

Dysmenorrhea has been reported in about 12 and 10% of adult and adolescent females, respectively, receiving clomipramine, and menstrual disorder (including irregular menstruation) has been reported in about 4% of adult females receiving the drug. Vaginitis and leukorrhea each occurred in about 2% of adult females receiving clomipramine therapy. Amenorrhea occurred in about 1% of adult females receiving clomipramine.

Although not attributed definitely to the drug, endometriosis, epididymitis, hematuria, nocturia, oliguria, ovarian cyst, perineal pain, polyuria, prostatic disorder, urethral disorder, urinary incontinence, uterine hemorrhage, or vaginal hemorrhage has been reported in less than 1% of clomipramine-treated patients. Albuminuria, cervical dysplasia, endometrial hyperplasia, pyuria, uterine inflammation, and vulvar disorder have occurred rarely; however, a causal relationship to the drug has not been established.

■ **Hepatic Effects** During premarketing evaluation, potentially clinically important elevations in serum ALT (SGOT) and AST (SGPT) concentrations exceeding 3 times the upper limit of normal were reported in approximately 1 and 3%, respectively, of patients receiving clomipramine. In most cases, these elevations in hepatic enzyme concentrations were not associated with other clinical findings suggestive of hepatic injury, and jaundice was not observed. Severe hepatic injury that was fatal in some cases has been reported rarely in foreign postmarketing experience. (See Cautions: Precautions and Contraindications.) Abnormal hepatic function and hepatitis have been reported in less than 1% of patients receiving clomipramine, although a causal relationship to the drug has not been established. Cross hepatotoxicity (e.g., elevated values on hepatic function tests, abdominal pain) involving different tricyclic antidepressants including clomipramine also has been reported.

■ **Other Adverse Effects** Hot flushes occurred in about 5% of adults and 2% of children and adolescents receiving clomipramine. Fever occurred in about 4% of adults and 2% of children and adolescents treated with the drug. Pain has been reported in about 3% of adults and 4% of children and adolescents receiving clomipramine therapy. Chills and local edema each occurred in about 2% of adults receiving the drug.

Tooth disorder occurred in about 5% of clomipramine-treated adults, and dental caries has been reported in less than 1% of patients receiving the drug. Although the exact mechanism for these effects is unclear, it has been suggested that long-term therapy with clomipramine or other antidepressants with prominent anticholinergic activity can lead to dental caries through inhibition of saliva secretion.

Elevations in serum prolactin concentrations have been reported following single and multiple doses of clomipramine. Nonpuerperal lactation has been reported in about 4% of adult females receiving clomipramine therapy. Breast enlargement and breast pain have been reported in about 2 and 1% of adult females, respectively, receiving the drug. Breast engorgement, breast fibroadenosis, and gynecomastia have been reported rarely in patients receiving clomipramine; however, these effects have not been attributed definitely to the drug.

Lymphadenopathy has been reported in less than 1% of clomipramine-treated patients, and leukemoid reaction and lymphoma-like disorder have been reported rarely, although a causal relationship to the drug has not been established.

Diabetes mellitus and hypothyroidism each have been reported in less than 1% of patients receiving clomipramine, and goiter and hyperthyroidism have been reported rarely; however, these effects have not been attributed definitely to the drug.

Oliguria, renal calculus, and renal pain have been reported in less than 1% of patients receiving clomipramine, and pyelonephritis and renal cyst have been reported rarely; however, a causal relationship to the drug has not been established. Hyponatremia also has occurred with clomipramine.

■ **Precautions and Contraindications**

[redacted] changes in behavior may occur in both adult and pediatric (see Cautions: Pediatric Precautions) patients with major depressive disorder or other psychiatric disorders, whether or not they are taking antidepressants. This risk may persist until clinically important remission occurs. Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are the strongest predictors of suicide. However, there has been a long-standing concern that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients during the early phases of treatment. Pooled analyses of short-term, placebo-controlled studies of antidepressants (i.e., selective serotonin-reuptake inhibitors and other antidepressants) have shown an increased risk of suicidality in children, adolescents, and young adults (18–24 years of age) with major depressive disorder and other psychiatric disorders. An increased suicidality risk was not demonstrated with antidepressants compared with placebo in adults older than 24 years of age, and a reduced risk was observed in adults 65 years of age or older. It currently is unknown whether the suicidality risk extends to longer-term use (i.e., beyond several months); however, there is substantial evidence from placebo-controlled maintenance trials in adults with major depressive disorder that antidepressants can delay the recurrence of depression.

The US Food and Drug Administration (FDA) recommends that all patients being treated with antidepressants for any indication be appropriately monitored and closely observed for clinical worsening, suicidality, and unusual changes in behavior, particularly during initiation of therapy (i.e., the first few months) and during periods of dosage adjustments. Families and caregivers of patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and nonpsychiatric, also should be advised to monitor patients on a daily basis for the emergence of agitation, irritability, or unusual changes in behavior as well as the emergence of suicidality, and to report such symptoms immediately to a health-care provider.

Although a causal relationship between the emergence of symptoms such as anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia, hypomania, and/or mania and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality. Consequently, consideration should be given to changing the therapeutic regimen or discontinuing therapy in patients whose depression is persistently worse or in patients experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, particularly if such manifestations are severe, abrupt in onset, or were not part of the patient's presenting symptoms. If a decision is made to discontinue therapy, clomipramine dosage should be tapered as rapidly as is feasible but with recognition of the risks of abrupt discontinuance. (See Dosage and Administration.) FDA also recommends that the drugs be prescribed in the smallest quantity consistent with good patient management, in order to reduce the risk of overdosage.

It is generally believed (though not established in controlled trials) that treating a major depressive episode with an antidepressant alone may increase the likelihood of precipitating a mixed or manic episode in patients at risk for bipolar disorder. Therefore, patients should be adequately screened for bipolar disorder prior to initiating treatment with an antidepressant; such screening should include a detailed psychiatric history (e.g., family history of suicide, bipolar disorder, and depression). Clomipramine is *not* approved for use in treating bipolar depression.

As with closely related tricyclic antidepressants, clomipramine should be used with caution in patients with concurrent cardiovascular disease; hyperthyroidism; increased intraocular pressure, a history of angle-closure glaucoma, or urinary retention; tumors of the adrenal medulla; clinically important renal impairment; or hepatic disease.

In patients with cardiovascular disease, gradual dosage titration of clomipramine is recommended. In hyperthyroid patients or patients receiving thyroid agents, the possibility of cardiac toxicity also should be considered. The manufacturers state that clomipramine should be used with caution in patients with increased intraocular pressure, a history of angle-closure glaucoma, or urinary retention, since its anticholinergic effects may exacerbate these conditions. Caution also should be exercised in patients with tumors of the adrenal medulla

(e.g., pheochromocytoma, neuroblastoma), since hypertensive crises may be provoked by clomipramine.

Clomipramine should be used with caution in patients with known hepatic disease, and the manufacturers recommend periodic monitoring of hepatic enzyme concentrations in such patients.

A variety of neuropsychiatric manifestations, including delusions, hallucinations, psychotic episodes, confusion, and paranoia, have been reported in patients receiving clomipramine. (See Cautions: Nervous System Effects.) However, because of the uncontrolled design of many of these studies, it is not possible to provide a precise estimate of the extent of the risk of such effects in clomipramine-treated patients. In patients whose schizophrenia has been unrecognized, an acute psychotic episode may be precipitated by clomipramine or other antidepressants. Another possibility is that clomipramine, like other antidepressants, may precipitate mania or hypomania in patients with affective disorder.

As with other tricyclic antidepressants, the development of fever and sore throat in any patient receiving clomipramine therapy should prompt the clinician to obtain leukocyte and differential blood cell counts. (See Cautions: Hematologic Effects.)

Male patients for whom clomipramine therapy is considered should be informed about the relatively high incidence of sexual dysfunction associated with the drug. Sexual dysfunction occurred in more males with obsessive-compulsive disorder treated with clomipramine than with placebo in premarketing experience. (See Cautions: Genitourinary Effects.)

As with closely related tricyclic antidepressants, the risks associated with electroconvulsive therapy (ECT) may be increased during concurrent clomipramine therapy. Because of the limited clinical experience to date, the manufacturers recommend that the combination of clomipramine and ECT be limited to those patients for whom it is essential.

Prior to elective surgery with general anesthetics, the manufacturers state that clomipramine therapy should be discontinued for as long as is clinically feasible, and the anesthetist should be so advised.

The withdrawal effects of clomipramine have not been systematically evaluated in controlled studies, although such effects have been reported following abrupt withdrawal of closely related tricyclic antidepressants. (See Cautions: Nervous System Effects and also see Chronic Toxicity in the Tricyclic Antidepressants General Statement 28:16.04.28.) Therefore, gradual tapering of clomipramine dosage and careful monitoring of the patient is recommended during discontinuance of clomipramine therapy.

Clomipramine can produce somnolence and impaired concentration, and patients should be cautioned that the drug may impair the mental and/or physical abilities required for the performance of these complex tasks. Patients also should be cautioned about the use of alcohol, barbiturates, or other CNS depressants because the effects of these agents may be exaggerated during concurrent clomipramine therapy.

The possibility of seizure is the most clinically important risk associated with clomipramine therapy (see Cautions: Nervous System Effects), and the drug should be used with caution in patients with a history of seizures or other predisposing factors (e.g., brain damage of various etiology, alcoholism, concurrent use of other drugs that lower the seizure threshold). The ability to predict the occurrence of seizures with daily doses exceeding 250 mg is limited because plasma concentrations may be dose dependent and may vary considerably among individuals administered the same dosage. Nevertheless, the manufacturers recommend limiting the daily dose of clomipramine to a maximum of 250 mg in adults or 3 mg/kg (up to 200 mg) in children and adolescents. Patients receiving clomipramine should be informed about the risk of seizures associated with the drug. In addition, physicians should discuss with patients the risk and the possibility of serious injury to themselves or other people resulting from sudden loss of consciousness while engaged in certain complex and hazardous activities (e.g., operation of complex machinery, driving a motor vehicle, swimming, climbing).

Clomipramine is contraindicated in patients with known hypersensitivity to the drug or other tricyclic antidepressants. The drug also is contraindicated in patients currently receiving, or having recently received (i.e., within 2 weeks), monoamine oxidase (MAO) inhibitor therapy. (See Drugs Associated with Serotonin Syndrome: Monoamine Oxidase Inhibitors, under Drug Interactions.) Clomipramine also is contraindicated during the acute recovery phase following myocardial infarction.

■ **Pediatric Precautions** Safety and efficacy of clomipramine in children younger than 10 years of age have not been established. Therefore, the manufacturers state that no specific recommendations can be made for the use of the drug in this age group.

Safe use of clomipramine in pediatric patients 10 years of age or older for the treatment of obsessive-compulsive disorder (OCD) is based on relatively short-term studies in this patient population and from extrapolation of experience gained with adult patients. The potential risks associated with long-term clomipramine therapy have not been systematically evaluated in children and adolescents. Although there is no evidence that the drug adversely affects growth, development, or maturation in these patients, the absence of such findings does not rule out a potential for such effects with long-term use.

In a controlled study, clomipramine has been administered for up to 8 weeks to 46 children and adolescents 10–17 years of age. In addition, 150 adolescent patients have received clomipramine therapy for periods ranging from several months to several years in uncontrolled studies. Out of a total of 196 children and adolescents studied, 50 patients were 13 years of age or younger and 146 patients were 14–17 years of age. The adverse effect profile in this age group is similar to that observed in adults.

FDA warns that antidepressants increase the risk of suicidal thinking and behavior (suicidality) in children and adolescents with major depressive disorder and other psychiatric disorders. The risk of suicidality for these drugs was identified in a pooled analysis of data from a total of 24 short-term (4–16 weeks), placebo-controlled studies of 9 antidepressants (i.e., bupropion, citalopram, fluoxetine, fluvoxamine, mirtazapine, nefazodone, paroxetine, sertraline, venlafaxine) in over 4400 children and adolescents with major depressive disorder, OCD, or other psychiatric disorders. The analysis revealed a greater risk of adverse events representing suicidal behavior or thinking (suicidality) during the first few months of treatment in pediatric patients receiving antidepressants than in those receiving placebo. The average risk of such events was 4% among children and adolescents receiving these drugs, twice the risk (2%) that was observed among those receiving placebo. However, a more recent meta-analysis of 27 placebo-controlled trials of 9 antidepressants (SSRIs and others) in patients younger than 19 years of age with major depressive disorder, OCD, or non-OCD anxiety disorders suggests that the benefits of antidepressant therapy in treating these conditions may outweigh the risks of suicidal behavior or suicidal ideation. No suicides occurred in these pediatric trials.

The risk of suicidality in FDA's pooled analysis differed across the different psychiatric indications, with the highest incidence observed in the major depressive disorder studies. In addition, although there was considerable variation in risk among the antidepressants, a tendency toward an increase in suicidality risk in younger patients was found for almost all drugs studied. It is currently unknown whether the suicidality risk in pediatric patients extends to longer-term use (i.e., beyond several months).

As a result of this analysis and public discussion of the issue, FDA has directed manufacturers of all antidepressants to add a boxed warning to the labeling of their products to alert clinicians of this suicidality risk in children and adolescents and to recommend appropriate monitoring and close observation of patients receiving these agents. (See Cautions: Precautions and Contraindications.) The drugs that are the focus of the revised labeling are all drugs included in the general class of antidepressants, including those that have not been studied in controlled clinical trials in pediatric patients, since the available data are not adequate to exclude any single antidepressant from an increased risk. In addition to the boxed warning and other information in professional labeling on antidepressants, FDA currently recommends that a patient medication guide explaining the risks associated with the drugs be provided to the patient each time the drugs are dispensed.

Anyone considering the use of clomipramine in a child or adolescent for any clinical use must balance the potential risk of therapy with the clinical need.

■ **Geriatric Precautions** The manufacturers state that clinical studies with clomipramine did not include sufficient numbers of patients 65 years of age or older to determine whether they respond differently than younger patients. No unusual age-related adverse effects were identified in 152 patients at least 60 years of age participating in US clinical studies who received the drug for periods of several months to several years. In addition, other clinical experience revealed no evidence of age-related differences in response to clomipramine.

In pooled data analyses, a *reduced* risk of suicidality was observed in adults 65 years of age or older with antidepressant therapy compared with placebo. (See Cautions: Precautions and Contraindications.)

Clomipramine is eliminated more slowly in geriatric patients. In addition, older patients may not tolerate the drug's adverse effects as well as younger patients. The manufacturers and some clinicians recommend cautiously selecting a clomipramine dosage regimen in geriatric patients, usually starting at the lower end of the recommended dosage range, since decreased hepatic, renal, or cardiac function and concomitant illnesses and medications are more frequent in this population.

■ **Mutagenicity and Carcinogenicity** No clear evidence of carcinogenicity was seen in rats receiving oral clomipramine hydrochloride dosages of 20 times the maximum recommended human daily dosage in a 2-year bioassay. Hemangioendothelioma was observed in 3 out of 235 rats administered clomipramine; the relationship between this rare tumor and the drug is not known.

■ **Pregnancy, Fertility, and Lactation** Teratogenic effects were not observed in rats and mice receiving clomipramine hydrochloride dosages up to 20 times the maximum human daily dosage. Slight, nonspecific fetotoxic effects were observed in the offspring of pregnant mice receiving 10 times the maximum human daily dosage. Slight, nonspecific embryotoxicity occurred in rats receiving 5–10 times the maximum human daily dosage.

There are no adequate and controlled studies using clomipramine in pregnant women, and the drug should be used during pregnancy only if the possible benefits justify the potential risk to the fetus. Women should be advised to notify their physician if they are or plan to become pregnant during clomipramine therapy. Neonates whose mothers had received clomipramine throughout pregnancy in dosages of 75–250 mg daily have exhibited withdrawal manifestations or adverse effects, including jitteriness, tremor, seizures, twitching, hypertonia, hypotonia, tachypnea, respiratory acidosis, cyanosis, feeding difficulties, hypothermia, lethargy, and diaphoresis. Phenobarbital has been recommended by some clinicians for the management of neurologic withdrawal

symptoms. Abrupt discontinuance of clomipramine at 32 weeks of pregnancy resulted in premature birth of a neonate who developed seizures soon after delivery. Because of the risk of neonatal withdrawal, some clinicians state that clomipramine therapy particularly should be avoided during late pregnancy.

Reproduction studies in rats using clomipramine hydrochloride dosages approximately 5 times the maximum human daily dosage have not revealed evidence of impaired fertility.

Clomipramine is distributed into milk. (See Pharmacokinetics: Distribution.) Adverse effects were absent in an infant who was breast-feeding from a woman who continued treatment with clomipramine at a dosage of 150 mg daily. However, because of the potential for adverse reactions, including concern about the potential for tricyclic antidepressants to affect development of the CNS of infants, a decision should be made whether to discontinue nursing or clomipramine, taking into account the importance of the drug to the woman. Women should be advised to notify their physician if they are breast-feeding.

Drug Interactions

Because of the similarity of clomipramine to other tricyclic antidepressants, all drug interactions that may occur with this class of drugs should be considered when clomipramine is used. (See Drug Interactions in the Tricyclic Antidepressants General Statement 28:16.04.28.) In addition, the possibility that clomipramine may interact with any concomitantly administered drug has not been evaluated systematically but should be considered.

■ **Drugs Associated with Serotonin Syndrome** ***Serotonin Syndrome*** Use of clomipramine concurrently or in close succession with other serotonergic drugs may result in serotonin syndrome. Although the syndrome appears to be relatively uncommon and usually mild in severity, serious complications, including seizures, disseminated intravascular coagulation, respiratory failure, severe hyperthermia, and death occasionally have been reported.

The syndrome most commonly occurs when 2 or more serotonergic agents with different mechanisms of action are administered either concurrently or in close succession. Serotonergic agents include those that increase serotonin synthesis (e.g., the serotonin precursor tryptophan), stimulate synaptic serotonin release (e.g., some amphetamines, dexfenfluramine, fenfluramine), inhibit the reuptake of serotonin after release (e.g., selective serotonin-reuptake inhibitors, tricyclic antidepressants, trazodone, dextromethorphan, meperidine, tramadol), decrease the metabolism of serotonin (e.g., monoamine oxidase [MAO] inhibitors), have direct serotonin postsynaptic receptor activity (e.g., buspirone), or nonspecifically induce increases in serotonergic neuronal activity (e.g., lithium salts).

The combination of selective serotonin-reuptake inhibitors and MAO inhibitors appears to be responsible for most of the recent case reports of serotonin syndrome. The syndrome also has been reported when MAO inhibitors have been combined with tricyclic antidepressants such as clomipramine, tryptophan, meperidine, or dextromethorphan. In rare cases, the serotonin syndrome reportedly has occurred with the recommended dosage of a single serotonergic agent (e.g., clomipramine) or during accidental overdosage (e.g., sertraline intoxication in a child). Some other drugs that have been implicated in certain circumstances include buspirone, bromocriptine, dextropropoxyphene, methylenedioxymethamphetamine (MDMA; ecstasy), selegiline (a selective MAO-B inhibitor), and sumatriptan. Other drugs that have been associated with the syndrome but for which less convincing data are available include carbamazepine, fentanyl, and pentazocine.

Clinicians should be aware of the potential for serious, possibly fatal reactions associated with the serotonin syndrome in patients receiving 2 or more drugs that increase the availability of serotonin in the CNS, even if no such interactions with the specific drugs have been reported to date in the medical literature. Pending further accumulation of data, all drugs with serotonergic activity should be used cautiously in combination and such combinations avoided whenever clinically possible. Some clinicians state that patients who have experienced serotonin syndrome may be at higher risk for recurrence of the syndrome upon reinitiation of serotonergic drugs. Pending further experience in such cases, some clinicians recommend that therapy with serotonergic agents be limited following recovery. In cases in which the potential benefit of the drug is thought to outweigh the risk of serotonin syndrome, lower potency agents and reduced dosages should be used, combination serotonergic therapy should be avoided, and patients should be monitored carefully for symptoms of serotonin syndrome.

For further information on serotonin syndrome, including manifestations and treatment, see Serotonin Syndrome under Drug Interactions: Drugs associated with Serotonin Syndrome, in Fluoxetine Hydrochloride 28:16.04.20.

Monoamine Oxidase Inhibitors Concomitant administration of clomipramine and MAO inhibitors is contraindicated, and at least 2 weeks elapse between discontinuance of clomipramine therapy and initiation of MAO inhibitor therapy and vice versa. Concomitant administration of clomipramine and an MAO inhibitor is potentially hazardous and may result in severe adverse effects associated with serotonin syndrome such as hyperpyrexia, seizures, and coma. Other adverse effects that have occurred with this combination of drugs include confusion, agitation, myoclonus, tremor, diaphoresis, shivering, rigors, rigidity, hypotension, tachycardia, cardiac arrhythmia, and disseminated intravascular coagulation. Some reactions occurring in patients receiving clomipramine and an MAO inhibitor have been fatal.

Clonus, hyperreflexia, tremor, rigidity, and diaphoresis were observed in some patients after administration of clomipramine about 1 month after discontinuance of a selective inhibitor of monoamine oxidase-A. Status epilepticus developed in a patient after treatment with clomipramine was started approximately 24 hours after discontinuance of phenelzine sulfate. Although the mechanism has not been clearly established, the reactions resemble serotonin syndrome and may be caused by excessive serotonergic activity in the CNS.

Other Serotonergic Agents Concurrent administration of clomipramine and other serotonergic drugs (e.g., lithium, alprazolam) has resulted in the development of adverse effects similar to those reported with the combination of clomipramine and an MAO inhibitor and which resemble the serotonin syndrome.

Concurrent administration of clomipramine and fluoxetine has resulted in seizures. Concurrent administration of clomipramine and fluvoxamine has resulted in a severalfold elevation of the plasma clomipramine concentration.

■ **CNS Depressants** Like other tricyclic antidepressants, clomipramine may be additive with or may potentiate the action of other CNS depressants such as alcohol and barbiturates. In addition, concomitant administration of clomipramine with phenobarbital reportedly resulted in an increase in the plasma concentration of phenobarbital.

■ **Drugs Affecting the Seizure Threshold** Caution should be observed with concurrent administration of clomipramine and drugs (e.g., other antidepressants, antipsychotic agents) that lower the seizure threshold. (See Cautions: Nervous System Effects.)

■ **Haloperidol** Concomitant administration of clomipramine with haloperidol reportedly resulted in increases in the plasma concentrations of clomipramine, presumably because of haloperidol-induced inhibition of clomipramine metabolism.

■ **Valproic Acid** The initiation of clomipramine therapy in a patient with a seizure disorder that was well controlled by valproic acid resulted in status epilepticus. The serum clomipramine concentration at the time of the seizures was elevated despite the relatively small dosage of clomipramine received (75 mg daily for 12 days). Although the mechanism has not been established clearly, it was suggested that valproic acid may have inhibited the metabolism and/or elimination of clomipramine. Pending further experience, it should be kept in mind that elevated serum concentrations of clomipramine and possibly its metabolites may occur when clomipramine and valproic acid are used concomitantly and that these changes may precipitate seizures in predisposed individuals.

■ **Other CNS Agents** The risks associated with concurrent administration of clomipramine and other CNS-active agents have not been fully evaluated to date; therefore, caution should be exercised when such agents are administered concomitantly.

■ **Oral Contraceptives** Limited data suggest that oral contraceptives do not interfere with the therapeutic effects of clomipramine. No difference in adverse effects or depression was observed in patients receiving clomipramine and oral contraceptives compared with those receiving clomipramine alone in one study. However, the clomipramine dosage given (25 mg daily) was lower than those commonly used in the treatment of obsessive-compulsive disorder or depression. Further study to confirm the safety and efficacy of combined clomipramine and oral contraceptive therapy is necessary.

■ **Smoking** Substantially lower plasma clomipramine concentrations have been reported in cigarette smokers receiving clomipramine when compared with nonsmokers. The presumed mechanism appears to be induction of clomipramine metabolism by nicotine or other substances present in cigarette smoke.

■ **Protein-bound Drugs** Clomipramine and its active metabolite, desmethylclomipramine, are highly protein bound; therefore, they theoretically could be displaced from binding sites by or could displace from binding sites other protein-bound drugs such as oral anticoagulants (e.g., warfarin) and digoxin. Pending further accumulation of data, patients receiving clomipramine with any highly protein-bound drug should be observed for potential adverse effects associated with combined therapy.

■ **Other Drugs** Concomitant use of clomipramine with anticholinergic or sympathomimetic drugs requires close supervision and careful adjustment of the dosage of clomipramine because of potential additive effects.

Consideration of the structural similarity of clomipramine with other tricyclic antidepressants would suggest that blockade of the pharmacologic effects (such as hypotension) and possibly the adverse effects of guanethidine, clonidine, or other similar hypotensive agents, as has been reported with several other tricyclic antidepressants, may be anticipated with clomipramine.

The plasma concentrations of several tricyclic antidepressants closely related to clomipramine reportedly were increased with concomitant administration of methylphenidate or drugs that inhibit hepatic microsomal enzyme systems (e.g., cimetidine, fluoxetine) and were decreased with concomitant administration of drugs that induce hepatic microsomal enzymes (e.g., barbiturates, phenytoin). Such effects also may be anticipated with clomipramine.

Acute Toxicity

Limited information is available on the acute toxicity of clomipramine.

■ **Pathogenesis** Postmarketing reports from the UK suggest that clomipramine overdosage results in lethality similar to that reported for other closely related tricyclic antidepressants.

In 10 out of 12 patients who overdosed on clomipramine taken alone or with other drugs during US clinical studies, complete recovery occurred with overdosages of up to 5 g that produced plasma concentrations of up to 1010 ng/mL. In the 2 remaining patients, who were suspected of ingesting overdosages of 7 g and 5.75 g, death occurred. Other fatalities have been reported after overdosages of clomipramine were ingested. The lowest dosage of clomipramine associated with fatality outside of the US is 750 mg.

■ **Manifestations** Overdosage with clomipramine produces signs and symptoms similar to that with other tricyclic antidepressants. (See Acute Toxicity: Manifestations, in the Tricyclic Antidepressants General Statement 28:16.04.28.) Acute pancreatitis accompanied by prolonged ileus has occurred following an overdose of clomipramine in one patient.

The signs and symptoms of clomipramine overdosage vary in severity depending on a number of factors, including the amount of drug absorbed, the patient's age, and the amount of time elapsed since ingestion. Plasma concentrations of clomipramine should not guide management of the patient. However, they may be of qualitative value when the diagnosis is not clear. In addition, evidence from one patient who experienced biphasic absorption (delayed) and elimination of clomipramine in which, after an initial decline, the serum concentration of clomipramine and desmethylclomipramine increased to a peak and declined subsequently, suggests that monitoring such concentrations until the patient is stable may be of diagnostic benefit, since manifestations of severe toxicity and the need for aggressive management also were biphasic, recurring 3–4 days after the initial toxic episode. Although clomipramine and desmethylclomipramine have low cross-reactivity (e.g., 40–50% to antibody for clomipramine at concentrations of 189–472 ng/mL) with a fluorescent polarization immunoassay (FPIA) for tricyclic antidepressants, clomipramine concentrations of 100 ng/mL are detectable by the assay, and therefore this nonspecific assay may still be useful in diagnosing overdosage with the drug.

■ **Treatment** For information on the management of tricyclic antidepressant overdosage, see Acute Toxicity: Treatment, in the Tricyclic Antidepressants General Statement 28:16.04.28. In addition, clinicians should consult a poison control center for current information about therapy for overdoses of tricyclic antidepressants because such treatment is complex and changeable.

Chronic Toxicity

Clomipramine has not been evaluated systematically in animals or humans to determine its potential for abuse, tolerance, or physical dependence. Although discontinuance of therapy has been associated with a variety of withdrawal manifestations (see Cautions: Nervous System Effects), there is no evidence of drug-seeking behavior, except for one patient with a history of dependence on codeine, benzodiazepines, and multiple psychoactive drugs. This patient received clomipramine for depression and panic attacks and appeared to become dependent on the drug after hospital discharge.

Although foreign clinical experience has not revealed substantial evidence for abuse potential with clomipramine, it is impossible to predict the extent to which the drug may be misused or abused. Because of such uncertainty, clinicians should carefully evaluate patients for a history of substance abuse and such patients who receive clomipramine should be monitored closely.

Pharmacology

The pharmacology of clomipramine is complex and in many ways resembles that of other antidepressants, particularly those agents (e.g., selective serotonin-reuptake inhibitors, trazodone) that predominantly potentiate the pharmacologic effects of serotonin (5-HT). Although clomipramine's principal pharmacologic effect in vitro is the selective inhibition of serotonin reuptake, in vivo the drug's pharmacologic activity is not so selective because of the action of its demethylated metabolite, desmethylclomipramine, as an inhibitor of norepinephrine reuptake. As a result of this and other effects, clomipramine also shares the pharmacologic profile of other tricyclic antidepressants.

■ **Nervous System Effects** The precise mechanism of action that is responsible for the efficacy of clomipramine in the treatment of obsessive-compulsive disorder is unclear. However, because of its pronounced potency in blocking serotonin reuptake at the presynaptic neuronal membrane and its efficacy in the treatment of obsessive-compulsive disorder, a serotonin hypothesis has been developed to explain the pathogenesis of the condition. The hypothesis postulates that a dysregulation of serotonin is responsible for obsessive-compulsive disorder and that clomipramine is effective because it corrects this imbalance. The potency of clomipramine relative to other tricyclic antidepressants as a serotonin-reuptake inhibitor and its superiority in obsessive-compulsive disorder provide additional support to this hypothesis. Although the available evidence supports the serotonergic hypothesis of obsessive-compulsive disorder (see Pharmacology: Serotonergic Effects), additional studies are necessary to confirm this hypothesis.

Like other tricyclic antidepressants, the exact mechanism of clomipramine's antidepressant action is unclear. Clomipramine and its principal metabolite, desmethylclomipramine, have been shown to block the reuptake of serotonin and norepinephrine, respectively, at the presynaptic neuronal membrane. The effects of serotonin and norepinephrine may thus be potentiated. However, it has been suggested that postsynaptic receptor modification is mainly responsible for the antidepressant action observed during long-term administration of antidepressant agents. During long-term therapy with most antidepressants (e.g., tricyclic antidepressants, monoamine oxidase [MAO] inhibitors), these adaptive changes generally consist of subsensitivity of the noradrenergic adenylate cyclase system in association with a decrease in the number of β-adrenergic receptors; such effects on noradrenergic receptor function commonly are referred to as "down-regulation." In addition, some antidepressants reportedly decrease the number of 5-HT binding sites following chronic administration.

Like other tricyclic antidepressants, clomipramine may produce sedation. The drug also may lower the seizure threshold, particularly at relatively high dosages. (See Cautions: Nervous System Effects.)

Serotonergic Effects Clomipramine is a potent and somewhat selective inhibitor of serotonin reuptake at the presynaptic neuronal membrane. Clomipramine-induced inhibition of serotonin reuptake causes increased synaptic concentrations of the neurotransmitter, resulting in numerous functional changes associated with enhanced serotonergic neurotransmission.

Clomipramine is the most potent inhibitor of serotonin reuptake among currently available tricyclic antidepressants. Data from in vitro studies suggest that clomipramine is approximately equivalent to or more potent than fluoxetine as a serotonin-reuptake inhibitor; however, in vivo studies indicate that the serotonin-reuptake inhibiting effect of fluoxetine may be more potent than that of clomipramine on a weight as well as an equimolar basis. This apparent discrepancy may be explained at least in part by the relatively long elimination half-lives of fluoxetine and its principal metabolite, norfluoxetine. In addition, metabolism by *N*-demethylation decreases the potency and specificity of serotonin-reuptake inhibition by clomipramine but not fluoxetine.

Clomipramine appears to decrease the turnover of serotonin in the CNS, probably as a result of a decrease in the release and/or synthesis of serotonin. Several studies have investigated the effects of clomipramine on serotonin concentrations in patients with obsessive-compulsive disorder. The concentration of serotonin in platelets has been shown to be substantially lower in patients with obsessive-compulsive disorder treated with the drug, and this decrease has been shown to correlate with clinical improvement in obsessive-compulsive manifestations in these patients.

Clomipramine reportedly decreases the concentration of 5-hydroxyindoleacetic acid (5-HIAA), the principal metabolite of serotonin, in the CSF of patients with obsessive-compulsive disorder or depression. Limited data suggest a possible relationship between improvement of obsessive-compulsive manifestations and decreased concentrations of 5-HIAA in the CSF.

Manifestations of obsessive-compulsive disorder worsened after administration of a serotonin agonist, metachlorophenylpiperazine (mCPP), compared with placebo. Manifestations of obsessive-compulsive disorder also appeared to worsen after administration of a nonselective serotonin antagonist, metergoline, compared with placebo in patients receiving clomipramine. In contrast, such exacerbation was not observed with administration of mCPP in patients treated with clomipramine for several weeks or longer. If obsessive-compulsive disorder is related to increased serotonergic responsiveness, then these data suggest that clomipramine's efficacy following long-term administration may be related to induction of subsensitivity in the serotonergic system; such an effect has been referred to as "down-regulation" of serotonin receptors.

Effects on Other Neurotransmitters Clomipramine's principal metabolite, desmethylclomipramine, is an inhibitor of norepinephrine reuptake. Clomipramine decreases the concentration of 3-methoxy-4-hydroxyphenylglycol (MHPG), a metabolite of norepinephrine, in CSF in patients with obsessive-compulsive disorder. Patients with depressive affective (mood) disorders (e.g., major depressive episode) also exhibit decreases in concentrations of 5-HIAA and MHPG in CSF during treatment with clomipramine. The decrease in the concentration of 5-HIAA in CSF was correlated with inhibition of the in vitro uptake of ^{3}H-serotonin in plasma. The change in concentration of MHPG in CSF during clomipramine therapy was correlated with amelioration of depression.

Preliminary evidence suggests that clomipramine may inhibit dopaminergic activity. Unlike many other antidepressants, clomipramine exhibited extensive binding to postsynaptic receptors of dopamine antagonists (^{3}H-spiroperidol) in vitro. In animals, dopamine antagonism has been demonstrated by clomipramine's ability to reduce apomorphine-induced behavioral stereotypy. The drug also increases the CSF concentration of the dopamine metabolite homovanillic acid secondary to increased dopamine turnover. Because obsessive-compulsive disorder is common in patients with certain disorders of dopamine regulation (e.g., Sydenham's chorea, Tourette's disorder [Gilles de la Tourette's syndrome]), additional studies are needed to determine whether these initial findings are clinically important. (See Uses: Obsessive-Compulsive Disorder.)

Like other tricyclic antidepressants, clomipramine binds to cholinergic receptors and exhibits marked anticholinergic activity. As a result, clomipramine therapy may cause adverse effects commonly associated with blockade of muscarinic cholinergic receptors (e.g., dry mouth, blurred vision, urinary retention, constipation, confusion). In addition, clomipramine binds to α_1-adrenergic and histaminergic receptors and consequently exhibits α_1-adrenergic blocking and antihistaminic activity at usual therapeutic dosages. The drug also has been shown to bind to α_2-adrenoceptors and opiate receptors.

CNS Metabolic Effects Brain imaging studies using positron emission tomography (PET) have demonstrated metabolic abnormalities (usually hypermetabolism) in certain regions of the brain (including the orbitofrontal cortex, caudate nucleus, and prefrontal gyri) in patients with obsessive-compulsive disorder. Clomipramine appears to produce a return of metabolism to a more normal level in the regions of the brain that may be involved in the

pathology of obsessive-compulsive disorder (orbitofrontal cortex and the caudate nucleus). For example, the metabolic rate of glucose was decreased in regions of the orbitofrontal cortex and the left caudate nucleus and was increased in other areas of the basal ganglia, including the right anterior putamen, in patients with obsessive-compulsive disorder treated with clomipramine compared with pretreatment measurements.

Other limited data suggest a relationship between decreases in the metabolic rate of glucose in the orbitofrontal cortex and the efficacy of clomipramine in obsessive-compulsive disorder. The decrease from baseline in the metabolic rate of glucose in the left orbitofrontal region was greater in patients whose obsessive-compulsive symptoms improved during clomipramine or fluoxetine therapy than in nonresponders to such therapy. In these patients, the decrease from baseline in the metabolic rate of glucose in the right orbitofrontal region was correlated with improvement in the manifestations of obsessive-compulsive disorder.

Effects on Sleep Like tricyclic and most other antidepressants, clomipramine suppresses rapid eye movement (REM) sleep. The drug appears to be the most potent suppressor of REM sleep in the tricyclic antidepressant class. The REM-suppressing effect may be sustained following discontinuance of clomipramine therapy, and chronic therapy leads to substantial REM rebound upon withdrawal of the drug.

■ **Cardiovascular Effects** Clomipramine shares the cardiovascular effects of other tricyclic antidepressants (see Pharmacology in the Tricyclic Antidepressants General Statement 28:16.04.24) and may produce ECG changes (e.g., increases from baseline in QRS duration, QT interval corrected for rate [QT_c], and QRS axis; inversion or flattening of the T waves), cardiac urrhythmias, tachycardia, and postural hypotension.

■ **Neuroendocrine Effects** Clomipramine affects the endocrine system. IV administration of clomipramine produced a dose-related increase in plasma prolactin and corticotropin (ACTH) concentrations in healthy individuals; an increase in the plasma cortisol concentration also was observed. Patients with depressive affective (mood) disorders (e.g., major depressive episode) also exhibited increases in plasma prolactin, ACTH, and cortisol concentrations following IV administration of clomipramine; however, the increase in plasma prolactin noted in patients with a major depressive episode was less than in nondepressed individuals. Clomipramine-induced increases in prolactin secretion appear to be serotonergically mediated.

Clomipramine appears to affect the CSF concentration of neuropeptides that are elevated in patients with obsessive-compulsive disorder. The concentrations of such neuropeptides (e.g., corticotropin-releasing hormone, vasopressin) are decreased during long-term (e.g., 20 months) therapy with the drug. In addition, an increase in the CSF concentration, corrected for age, of oxytocin has been observed.

For further information on the pharmacology of clomipramine, see Pharmacology in the Tricyclic Antidepressants General Statement 28:16.04.24.

Pharmacokinetics

In all human studies described in the Pharmacokinetics section, clomipramine was administered as the hydrochloride salt.

■ **Absorption** Clomipramine hydrochloride appears to be well absorbed from the GI tract following oral administration. However, extensive first-pass metabolism decreases its oral bioavailability to about 50%. The oral capsules and solution of clomipramine hydrochloride reportedly are bioequivalent. Food does not appear to substantially affect the bioavailability of clomipramine from the capsules.

Peak plasma clomipramine concentrations of approximately 56–154 ng/mL (mean: 92 ng/mL) usually occur within 2–6 hours (mean: 4.7 hours) following oral administration of a single 50-mg dose of clomipramine hydrochloride. Like other tricyclic antidepressants, clomipramine exhibits considerable interindividual variation in plasma concentrations achieved with a given dose due, at least in part, to genetic differences in the metabolism of the drug. (See Pharmacokinetics: Elimination.)

Following multiple-dose oral administration of clomipramine, steady-state plasma concentrations of the drug generally are achieved within about 1–2 weeks. Steady-state plasma desmethylclomipramine (the principal metabolite) concentrations may be achieved at about the same time as steady-state plasma clomipramine concentrations or later. In some cases, plasma desmethylclomipramine concentrations have been observed to continue to increase during 4–6 weeks of administration of a constant dosage of clomipramine hydrochloride. Plasma concentrations of desmethylclomipramine generally exceed those of the parent drug following multiple daily dosing of clomipramine hydrochloride.

The manufacturers state that, after multiple daily dosing of clomipramine hydrochloride 150 mg, the accumulation factors for clomipramine and desmethylclomipramine are approximately 2.5 and 4.6, respectively. However, it may take 2 weeks or more to achieve this extent of accumulation at a constant dosage because of the relatively long elimination half-lives of clomipramine and desmethylclomipramine. At steady state, peak plasma concentrations of 94–339 (mean: 218) and 134–532 (mean: 274) ng/mL of clomipramine and desmethylclomipramine, respectively, were attained following multiple daily doses of 150 mg of clomipramine hydrochloride. Pharmacokinetic data in patients receiving clomipramine hydrochloride dosages ranging from 150–250 mg daily are lacking.

In a dose-proportionality study involving multiple dosing, steady-state plasma concentrations and the areas under the plasma concentration-time curve (AUCs) of clomipramine and desmethylclomipramine were not proportional to dose at dosages ranging from 25–150 mg daily. However, at dosages ranging from 100–150 mg daily there was an approximately linear relationship between these variables and dose. The manufacturers state that the relationship between dose and plasma clomipramine or desmethylclomipramine concentrations has not been systematically evaluated at higher dosages. However, if there is a substantial dose dependency at dosages exceeding 150 mg daily, the potential exists for dramatically higher steady-state plasma concentrations and AUCs of clomipramine and desmethylclomipramine even in patients receiving dosages within the recommended range. Such an effect may pose a potential risk in some patients. (See Cautions: Precautions and Contraindications.)

The effect of age on plasma concentrations of clomipramine and desmethylclomipramine is not fully known. However, substantially lower plasma concentrations of clomipramine and desmethylclomipramine have been reported in younger adults (18–40 years of age) compared with those obtained in individuals older than 65 years of age. Children younger than 15 years of age also had substantially lower plasma concentration-dose ratios of clomipramine when compared with adults. In addition, clomipramine appears to be better tolerated in younger than in older patients.

Substantially lower steady-state plasma clomipramine concentrations have been reported in smokers when compared with nonsmokers. However, smoking appears to have less effect on plasma concentrations of desmethylclomipramine.

The relationship between plasma clomipramine and desmethylclomipramine concentrations and the therapeutic and/or toxic effects of the drug has not been clearly established. The results of studies involving plasma concentration monitoring in patients with obsessive-compulsive disorder and/or depression have been equivocal. In some studies, the sum of plasma clomipramine and desmethylclomipramine concentrations has been used as the drug concentration. In depressed patients, preliminary evidence suggests that lower plasma concentrations of clomipramine plus desmethylclomipramine (less than 150 ng/mL) are associated with nonresponse while higher concentrations (exceeding 450 ng/mL) may be associated with an increased risk of adverse effects and perhaps nonresponse. In patients with obsessive-compulsive disorder, the results of 2 studies in which a relationship between plasma concentration and therapeutic response was found suggested that optimal therapeutic response may be obtained in patients with plasma clomipramine concentrations ranging from 100–250 ng/mL and plasma desmethylclomipramine concentrations ranging from 230–550 ng/mL.

■ **Distribution** Distribution of clomipramine and its metabolites into human body tissues and fluids has not been fully characterized. However, both clomipramine and desmethylclomipramine are highly lipophilic and are widely distributed in body tissues, with moderate to high concentrations occurring in organs such as the lungs, adrenals, kidneys, heart, and brain. The apparent volume of distribution of clomipramine in healthy adults averages 17 L/kg (range: 9–25 L/kg).

Both clomipramine and desmethylclomipramine cross the blood-brain barrier; the manufacturers state that desmethylclomipramine is distributed into CSF at a concentration about 2.6 times higher than in plasma. However, in one study of patients with depression or obsessive-compulsive disorder, the concentration of desmethylclomipramine in CSF was 2.6% that of the plasma concentration, corresponding to the fraction of desmethylclomipramine not bound to plasma proteins.

Clomipramine is approximately 97–98% bound to plasma proteins, principally to albumin and possibly to α_1-acid glycoprotein (α_1-AGP). The extent of protein binding of clomipramine appears to be independent of plasma concentration. Desmethylclomipramine is approximately 97–99% bound to plasma proteins. Because protein binding of both clomipramine and desmethylclomipramine is extensive, the manufacturers state that, while the possibility that clomipramine interacts with other highly protein-bound drugs has not been fully evaluated, such interactions may be important. (See Drug Interactions: Protein-bound Drugs.)

Clomipramine crosses the placenta and also is distributed into human milk. In one case report, plasma clomipramine concentrations were measured in an infant whose mother was receiving clomipramine hydrochloride 125 mg daily during pregnancy. The plasma clomipramine concentration in the infant was 267 ng/mL at birth; subsequently, the plasma concentration in the infant decreased although nursing began 7 days after delivery and continued. After the first week postpartum, the mother's dosage of clomipramine hydrochloride was increased to 150 mg daily and the concentration of clomipramine in milk was 80–160% of the concurrent plasma clomipramine concentration at steady state. The infant's plasma concentration of clomipramine was at the limit of detection (9.8 ng/mL) 35 days postpartum. Serum concentrations of clomipramine and its metabolites (i.e., desmethylclomipramine, 8-hydroxyclomipramine, 8-hydroxydesmethylclomipramine) were not observed or were below the limit of detection in a limited number of healthy, full-term neonates and infants who were breast-fed by mothers whose only medication was clomipramine administered at a constant dosage for at least 3 weeks.

■ **Elimination** Evidence that the steady-state plasma concentrations and AUCs of clomipramine and desmethylclomipramine may increase disproportionately with increasing oral doses of the drug suggests that the metabolism of clomipramine and desmethylclomipramine may be capacity-limited (saturable). The manufacturers caution that this fact should be considered when

evaluating the available data concerning the pharmacokinetic parameters of clomipramine as these data often were obtained in individuals receiving 150-mg daily doses. If clomipramine and desmethylclomipramine exhibit nonlinear pharmacokinetics at dosages exceeding 150 mg daily, their elimination half-lives may be considerably prolonged at dosages near the upper limit of the recommended dosage range (i.e., 200–250 mg daily). At such dosages, clomipramine and desmethylclomipramine may accumulate, which may increase the incidence of any dose- or plasma concentration-dependent adverse effects, particularly seizures.

The elimination half-life of clomipramine averages approximately 32 hours (range: 19–37 hours) and that of desmethylclomipramine averages about 69 hours (range: 54–77 hours) following a single, 150-mg oral dose of the drug.

The exact metabolic fate of clomipramine has not been fully elucidated. Clomipramine appears to be extensively metabolized to desmethylclomipramine and other metabolites and their glucuronide conjugates. Desmethylclomipramine, the principal metabolite, is formed by *N*-demethylation of clomipramine. Other metabolites of clomipramine include 8-hydroxyclomipramine, 2-hydroxyclomipramine, and clomipramine *N*-oxide, which appear to be formed via 8-hydroxylation, 2-hydroxylation, and *N*-oxidation, respectively. The metabolites of desmethylclomipramine include 8-hydroxydesmethylclomipramine and didesmethylclomipramine, which apparently are formed via 8-hydroxylation and *N*-demethylation, respectively. Although desmethylclomipramine is pharmacologically active, its efficacy in obsessive-compulsive disorder is not known. 8-Hydroxyclomipramine and 8-hydroxydesmethylclomipramine also are pharmacologically active but the clinical importance of their presence remains unknown.

The hydroxylation of clomipramine and desmethylclomipramine appears to be under genetic control (similar to that of debrisoquine and sparteine). In healthy adults who were phenotyped for debrisoquine hydroxylation, extensive metabolizers were distinguishable from poor metabolizers with regard to the extent of hydroxylation of desmethylclomipramine. Blood concentrations of desmethylclomipramine were higher than expected in a limited number of patients who subsequently were found to be poor metabolizers. Limited data suggest that CYP2D6, a cytochrome P-450 isoenzyme implicated in the sparteine/debrisoquine oxidation polymorphism, is involved in the 8-hydroxylation of clomipramine and desmethylclomipramine and in the 2-hydroxylation of clomipramine. In addition, demethylation of clomipramine may involve CYP2C, which is implicated in the *S*-mephenytoin oxidation polymorphism, and CYP1A2.

Possible differences in the metabolism of clomipramine among ethnic populations were suggested by a study in a limited number of healthy individuals that showed plasma clomipramine concentrations after a single oral dose of the drug to be higher in Asians (e.g., Indian, Pakistani) than in whites (e.g., British). In Japanese patients treated with clomipramine, substantial interindividual variation in demethylation and hydroxylation was observed; however, the prevalence of possibly poor demethylators and poor hydroxylators of clomipramine was estimated to be 0 and 1%, respectively. Further study is needed to clarify whether the pharmacokinetics of clomipramine truly differ in individuals of various ethnic backgrounds.

Following oral administration, clomipramine and its metabolites are excreted in urine and in feces (via biliary elimination). In 2 healthy individuals, approximately 51–60 and 24–32% of an orally administered, radiolabeled, 25-mg dose of clomipramine hydrochloride were excreted in urine and feces, respectively, after 14 days. Unchanged clomipramine and desmethylclomipramine were excreted in urine in quantities that together comprised approximately 0.8–1.3% of the dose. In a limited number of healthy individuals who received a single oral dose of clomipramine, 8-hydroxyclomipramine glucuronide was the principal metabolite found in urine. Although the urinary recovery of 8-hydroxyclomipramine glucuronide in these individuals who were phenotyped for metabolism of sparteine and mephenytoin was lower in poor metabolizers of sparteine compared with extensive metabolism of sparteine, estimates of clearance via glucuronidation did not differ between phenotypes, suggesting that the capacity for glucuronidation is not contingent on the capacity for 8-hydroxylation of clomipramine.

The effects of renal and hepatic impairment on the disposition of clomipramine have not been fully elucidated.

Limited data suggest that demethylation of clomipramine may be reduced with chronic alcohol consumption. In one study, the clearance of clomipramine via demethylation was decreased substantially and the ratio of blood clomipramine to desmethylclomipramine concentrations at steady state was higher in recently detoxified alcoholic patients (abstinence periods ranged from 4–20 weeks) compared with a control group of patients with no history of alcoholism.

Induction of drug-metabolizing enzymes (as measured by antipyrine half-life) does not appear to occur with clomipramine.

Hemodialysis, peritoneal dialysis, forced diuresis, and/or exchange transfusion are unlikely to remove clomipramine and desmethylclomipramine substantially because of the drug's rapid distribution into body tissues.

Chemistry and Stability

■ **Chemistry** Clomipramine, a dibenzazepine-derivative tricyclic antidepressant, is the 3-chloro analog of imipramine. Clomipramine is commercially available as the hydrochloride salt, which occurs as a white to off-white crystalline powder. The drug is freely soluble in water, methanol, and methylene chloride, and insoluble in ethyl ether and hexane. The drug has a pK_a of 9.5.

■ **Stability** Clomipramine hydrochloride capsules should be stored in tight containers at a temperature of 20–25°C and protected from moisture. When stored as directed, the capsules have an expiration date of 3 years following the date of manufacture.

For further information on chemistry, pharmacology, pharmacokinetics, uses, cautions, acute toxicity, drug interactions, and dosage and administration of clomipramine, see the Tricyclic Antidepressants General Statement 28:16.04.28.

Preparations

Excipients in commercially available drug preparations may have clinically important effects in some individuals; consult specific product labeling for details.

Clomipramine Hydrochloride

Oral		
Capsules	25 mg*	Anafranil*, Mallinckrodt
		Clomipramine Hydrochloride Capsules
	50 mg*	Anafranil*, Mallinckrodt
		Clomipramine Hydrochloride Capsules
	75 mg*	Anafranil*, Mallinckrodt
		Clomipramine Hydrochloride Capsules

*available from one or more manufacturer, distributor, and/or repackager by generic (nonproprietary) name
†Use is not currently included in the labeling approved by the US Food and Drug Administration

Desipramine Hydrochloride

■ Desipramine is a dibenzazepine-derivative tricyclic antidepressant.

Dosage and Administration

■ **Administration** Desipramine hydrochloride is administered orally. Although desipramine has been administered in up to 3 divided doses throughout the day, it is long-acting and the entire daily dose may be administered at one time. Administration of the entire daily dose at bedtime may reduce daytime sedation; patients who experience insomnia and stimulation from the drug may receive the entire daily dose in the morning.

■ **Dosage** There is a wide range of dosage requirements, and dosage of desipramine hydrochloride must be carefully individualized. Initial dosages in adults should be low and generally range from 75–150 mg daily, depending on the severity of the condition being treated. Dosage may be gradually adjusted to the level that produces maximal therapeutic effect with minimal toxicity. In seriously ill patients, desipramine dosage may be gradually increased to 300 mg daily if necessary. Desipramine hydrochloride dosages exceeding 300 mg daily are not recommended. Hospitalized patients under close supervision may generally be given higher doses than outpatients. Geriatric and adolescent patients should usually be given lower than average doses. Manufacturers state that therapy should be initiated with 25–50 mg daily in these patients and that dosages greater than 100 mg daily are usually not necessary. In geriatric and adolescent patients who are seriously ill, desipramine dosage may be further increased to 150 mg daily if necessary. Desipramine hydrochloride dosages exceeding 150 mg daily are not recommended in these age groups. Maximum antidepressant effects may not occur for 2 or more weeks after therapy is begun.

After symptoms are controlled, dosage should be gradually reduced to the lowest level that will maintain relief of symptoms. To avoid the possibility of precipitating withdrawal symptoms, desipramine should not be terminated abruptly in patients who have received high dosages for prolonged periods.

Patients should be monitored for possible worsening of depression, suicidality, or unusual changes in behavior, especially at the beginning of therapy or during periods of dosage adjustment. (See Cautions: Precautions and Contraindications, in the Tricyclic Antidepressants General Statement 28:16.04.28.)

Cautions

Desipramine shares the pharmacologic actions, uses, and toxic potentials of the tricyclic antidepressants, and the usual precautions of tricyclic antidepressant administration should be observed. Patients should be fully advised about the risks, especially suicidal thinking and behavior (suicidality), associated with tricyclic antidepressant therapy. For a complete discussion, see Cautions: Precautions and Contraindications and Cautions: Pediatric Precautions, in the Tricyclic Antidepressants General Statement 28:16.04.28.

■ **Pediatric Precautions** Because collapse and sudden death occurred in at least one child (an 8-year-old boy) receiving desipramine for 2 years for attention deficit hyperactivity disorder (ADHD) and sudden death also has been reported in other children receiving the drug, at least one manufacturer of

phenones, phenothiazines) and has been referred to as an atypical or second-generation antipsychotic agent. The exact mechanism of action of aripiprazole in schizophrenia, bipolar mania, major depressive disorder, and agitation associated with schizophrenia or bipolar mania has not been fully elucidated but, like that of other drugs with efficacy in these conditions (e.g., olanzapine, risperidone, ziprasidone), may involve the drug's activity at dopamine D_2 and serotonin type 1 ($5\text{-}HT_{1A}$) and type 2 ($5\text{-}HT_{2A}$) receptors. However, aripiprazole appears to differ from other atypical antipsychotic agents because the drug demonstrates partial agonist activity at D_2 and $5\text{-}HT_{1A}$ receptors and antagonist activity at $5\text{-}HT_{2A}$ receptors. Antagonism at other receptors (e.g., α_1-adrenergic receptors, histamine H_1 receptors) may contribute to other therapeutic and adverse effects (e.g., orthostatic hypotension, somnolence) observed with aripiprazole.

Aripiprazole is extensively metabolized in the liver principally via dehydrogenation, hydroxylation, and *N*-dealkylation by the cytochrome P-450 (CYP) 2D6 and 3A4 isoenzymes. The major active metabolite of aripiprazole, dehydro-aripiprazole, exhibits affinity for D_2 receptors similar to that of the parent compound and represents approximately 40% of aripiprazole area under the concentration-time curve (AUC) in plasma. Steady-state plasma concentrations of both aripiprazole and dehydro-aripiprazole are achieved within 14 days. The elimination half-lives of aripiprazole and dehydro-aripiprazole are approximately 75 and 94 hours, respectively. Approximately 18% and less than 1% of aripiprazole is excreted unchanged in feces and urine, respectively.

Advice to Patients

Importance of providing copy of written patient information (medication guide) each time aripiprazole is dispensed. Importance of advising patients to read the patient information before taking aripiprazole and each time the prescription is refilled.

Increased mortality in geriatric patients with dementia-related psychosis; importance of advising patients and caregivers that geriatric patients with dementia-related psychosis treated with antipsychotic agents are at an increased risk of death. Patients and caregivers should also be informed that aripiprazole is *not* approved for treating geriatric patients with dementia-related psychosis.

Risk of suicidality; importance of patients, family, and caregivers being alert to and immediately reporting emergence of suicidality, worsening depression, or unusual changes in behavior, especially during the first few months of therapy or during periods of dosage adjustment.

Because somnolence and impairment of judgment, thinking, or motor skills may be associated with aripiprazole, avoid driving, operating machinery, or performing hazardous tasks while taking aripiprazole until the drug's effects on the individual are known. Importance of avoiding alcohol during aripiprazole therapy.

Risk of neuroleptic malignant syndrome (NMS), a rare but life-threatening syndrome that can cause high fever, stiff muscles, sweating, fast or irregular heart beat, change in blood pressure, confusion, and kidney damage. Importance of informing patients to immediately contact a healthcare professional if such symptoms develop.

Importance of clinicians informing patients in whom chronic aripiprazole use is contemplated of risk of tardive dyskinesia. Importance of informing patients to report any muscle movements that cannot be stopped to a healthcare professional.

Importance of informing clinicians of existing or contemplated concomitant therapy, including prescription and OTC drugs, as well as any concomitant illnesses (e.g., diabetes mellitus).

Importance of women informing clinicians if they are or plan to become pregnant or plan to breast-feed.

Importance of avoiding overheating or dehydration.

For patients taking aripiprazole orally disintegrating tablets, importance of not removing a tablet from the blister package until just before administering a dose; importance of peeling blister open with dry hands and placing tablet on tongue to dissolve and be swallowed with saliva.

Importance of informing patients with phenylketonuria that aripiprazole orally disintegrating 10- and 15-mg tablets contain 1.12 and 1.68 mg of phenylalanine, respectively.

Importance of being aware that aripiprazole oral solution contains 400 mg of sucrose and 200 mg of fructose per mL.

Importance of informing patients of other important precautionary information. (See Cautions.)

Overview[a] (see Users Guide). For additional information on this drug until a more detailed monograph is developed and published, the manufacturer's labeling should be consulted. It is *essential* that the manufacturer's labeling be consulted for more detailed information on usual cautions, precautions, contraindications, potential drug interactions, laboratory test interferences, and acute toxicity.

Preparations

Excipients in commercially available drug preparations may have clinically important effects in some individuals; consult specific product labeling for details.

Aripiprazole

Oral		
Solution	5 mg/5 mL	Abilify* Oral Solution, Otsuka (also promoted by Bristol-Myers Squibb)
Tablets	2 mg	Abilify*, Otsuka (also promoted by Bristol-Myers Squibb)
	5 mg	Abilify*, Otsuka (also promoted by Bristol-Myers Squibb)
	10 mg	Abilify*, Otsuka (also promoted by Bristol-Myers Squibb)
	15 mg	Abilify*, Otsuka (also promoted by Bristol-Myers Squibb)
	20 mg	Abilify*, Otsuka (also promoted by Bristol-Myers Squibb)
	30 mg	Abilify*, Otsuka (also promoted by Bristol-Myers Squibb)
Tablets, orally disintegrating	10 mg	Abilify* Discmelt*, Otsuka (also promoted by Bristol-Myers Squibb)
	15 mg	Abilify* Discmelt*, Otsuka (also promoted by Bristol-Myers Squibb)
Parenteral		
Injection, for IM use only	7.5 mg/mL (9.75 mg)	Abilify*, Otsuka (also promoted by Bristol-Myers Squibb)

Clozapine

■ Clozapine has been referred to as an atypical or second-generation antipsychotic agent.

Uses

■ **Psychotic Disorders** Clozapine is used for the symptomatic management of psychotic disorders (e.g., schizophrenia). Drug therapy is integral to the management of acute psychotic episodes and accompanying violent behavior in patients with schizophrenia and generally is required for long-term stabilization to sustain symptom remission or control and to minimize the risk of relapse. Antipsychotic agents are the principal class of drugs used for the management of all phases of schizophrenia and generally are effective in all subtypes of the disorder and subgroups of patients. Patient response and tolerance to antipsychotic agents are variable, and patients who do not respond to or tolerate one drug may be successfully treated with an agent from a different class or with a different adverse effect profile.

Clozapine has been shown to be an effective, relatively rapid-acting, broad-spectrum antipsychotic agent in both uncontrolled and controlled studies of patients with schizophrenia. In these studies, improvement in manifestations of schizophrenia was based on the results of various psychiatric rating scales, principally the Brief Psychiatric Rating Scale (BPRS) that assesses factors such as anergy, thought disturbance, activation, hostility/suspiciousness, and anxiety/depression. In clinical studies, clozapine improved both positive (florid symptomatology such as hallucinations, conceptual disorganization, and suspiciousness) and negative ("deficit" symptomatology such as emotional withdrawal, motor retardation, blunted affect, and disorientation) manifestations of schizophrenia; conventional (typical) antipsychotic agents appear to have lesser effects on negative manifestations of the disorder. In comparative studies, clozapine was at least as effective as, or more effective than several conventional antipsychotic agents, including chlorpromazine, haloperidol, perphenazine, or trifluoperazine.

Unlike conventional antipsychotic agents, however, clozapine generally does not induce extrapyramidal effects and has not been clearly implicated as a causative agent in tardive dyskinesia.

While the risks of adverse neurologic effects with long-term clozapine therapy remain to be fully elucidated, other adverse effects, including some potentially serious effects (e.g., agranulocytosis, seizures), may occur more frequently with clozapine therapy. Consequently, the manufacturers and most clinicians currently state that use of clozapine should be reserved for patients with severe disease that fails to respond adequately to conventional antipsychotic therapy, either because of insufficient effectiveness or the inability to achieve an effective dose due to intolerable adverse effects from those drugs. What constitutes an adequate trial of standard antipsychotic therapy, however, varies widely. The manufacturers and some clinicians recommend that a patient be given an adequate trial of at least 2 different antipsychotic agents from at least 2 different chemical classes (e.g., phenothiazines, butyrophenones, thioxanthenes) before the patient is considered a candidate for clozapine therapy. The American Psychiatric Association (APA), however, currently recommends that a trial of clozapine be considered in patients who fail to respond to adequate trials of at least one antipsychotic agent unless therapy with the drug is specifically contraindicated (e.g., patients with myeloproliferative disorders, preexisting bone marrow depression, or a history of clozapine-induced agranulocytosis or severe granulocytopenia) or patients are unable or unwilling to comply with monitoring requirements. The APA also recommends that clo-

zapine should be considered in patients with a history of chronic and persistent suicidal ideation and behavior and in patients with persistent hostility and aggression.

Schizophrenia Clozapine is used for the symptomatic management of schizophrenia in severely ill patients whose disease fails to respond adequately to other antipsychotic therapy. Schizophrenia is a major psychotic disorder that frequently has devastating effects on various aspects of the patient's life and carries a high risk of suicide and other life-threatening behaviors. Manifestations of schizophrenia involve multiple psychologic processes, including perception (e.g., hallucinations), ideation, reality testing (e.g., delusions), emotion (e.g., flatness, inappropriate affect), thought processes (e.g., loose associations), behavior (e.g., catatonia, disorganization), attention, concentration, motivation (e.g., avolition, impaired intention and planning), and judgment. The principal manifestations of this disorder usually are described in terms of positive and negative (deficit) symptoms, and more recently, disorganized symptoms. Positive symptoms include hallucinations, delusions, bizarre behavior, hostility, uncooperativeness, and paranoid ideation, while negative symptoms include restricted range and intensity of emotional expression (affective flattening), reduced thought and speech productivity (alogia), anhedonia, apathy, and decreased initiation of goal-directed behavior (avolition). Disorganized symptoms include disorganized speech (thought disorder) and behavior and poor attention.

Evidence from both retrospective and controlled prospective studies indicates that clozapine is effective in many patients who fail to respond adequately to other antipsychotic therapy and/or in whom such therapy produces intolerable adverse effects. In a controlled, comparative study in patients with at least moderately severe schizophrenia whose disease was refractory to at least 3 antipsychotic agents from at least 2 different chemical classes during the past 5 years, an adequate clinical response (a 20% or greater decrease in total BPRS score and either a posttreatment Clinical Global Impressions [CGI] scale rating of mildly ill or a posttreatment BPRS score of 35 or less) was noted after 1–6 weeks of therapy in 30% of patients receiving clozapine (mean maximum dosage exceeding 600 mg daily) compared with 4% of patients receiving chlorpromazine (mean maximum dosage exceeding 1200 mg daily) plus benztropine. In addition, clozapine was substantially more effective than chlorpromazine plus benztropine in improving both positive and negative manifestations of schizophrenia. In this study, resistance to antipsychotic treatment prior to entry into the clozapine/chlorpromazine comparative phase was confirmed by a 6-week trial of haloperidol (mean dosage of 61 mg daily) combined with benztropine. This study provides evidence from both categorical and continuous measures not only of clozapine's efficacy as an antipsychotic agent but also of its superiority over conventional antipsychotic drug therapy in a well-defined group of antipsychotic-resistant patients. Similar 6-week response rates in treatment-resistant schizophrenia have been reported in other studies with the drug. Clinically important improvement in quality of life and social functioning, including deinstitutionalization, interpersonal relationships, and ability to hold a job or attend school, also have been reported following initiation of clozapine therapy in patients with antipsychotic-resistant schizophrenia.

For additional information on the symptomatic management of schizophrenia, including treatment recommendations and results of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study, see Schizophrenia and Other Psychotic Disorders under Uses: Psychotic Disorders, in the Phenothiazines General Statement 28:16.08.24.

Pediatric Considerations. Although the safety and efficacy of clozapine in children and adolescents younger than 16 years of age have not been established, the drug has been successfully used for the management of childhood-onset schizophrenia in a limited number of treatment-resistant children and adolescents†. While the lower risk of extrapyramidal adverse effects and tardive dyskinesia during treatment with atypical antipsychotic agents such as clozapine compared with conventional antipsychotic agents represents an advantage in the treatment of childhood-onset schizophrenia, concerns regarding serious adverse effects (e.g., neutropenia; seizures) associated with clozapine limit its use in clinical practice. (See Cautions: Pediatric Precautions.) Therefore, the American Academy of Child and Adolescent Psychiatry (AACAP) states that clozapine is not considered a first-line agent, and the drug is recommended only in patients who have failed to respond to adequate therapeutic trials (i.e., use of sufficient dosages over a period of 4–6 weeks) of at least 2 other antipsychotic agents (at least one of which is an atypical antipsychotic) and/or have experienced substantial adverse effects (e.g., tardive dyskinesia) while receiving other antipsychotic agents. For additional information on the symptomatic management of childhood-onset schizophrenia, see Pediatric Considerations under Psychotic Disorders: Schizophrenia, in Uses in the Phenothiazines General Statement 28:16.08.24.

In one randomized, double-blind, clinical study conducted by the National Institute of Mental Health (NIMH), a limited number of children and adolescents (mean: 14 years of age) with childhood-onset schizophrenia (i.e., development of the disorder by 12 years of age or younger) who were intolerant and/or nonresponsive to at least 2 different antipsychotic agents were treated with either clozapine (up to a 525 mg daily; mean final dosage 176 mg daily) or haloperidol (up to 27 mg daily; mean final dosage 16 mg daily) for 6 weeks. In this study, children and adolescents receiving clozapine had substantially greater reductions in both positive and negative symptoms of schizophrenia than those receiving haloperidol. Additional follow-up of these patients over a 2-year period indicated that, as reported in adults, maximal antipsychotic effects in schizophrenic children and adolescents may not be evident until after 6–9 months of clozapine therapy. For most children and adolescents in the study, clozapine improved interpersonal functioning and enabled a return to a less restrictive setting. However, mild to moderate neutropenia occurred in 24% of the patients, and 29% required therapy with an anticonvulsant.

Suicide Risk Reduction in Schizophrenia and Schizoaffective Disorder Clozapine is used to reduce the risk of recurrent suicidal behavior in patients with schizophrenia or schizoaffective disorder who are judged to be at chronic risk for such behavior, based on history and recent clinical state. Efficacy of clozapine for this indication has been established in a multicenter, randomized, open-label clinical study (the International Suicide Prevention Trial [Inter SePT]) of 2 years' duration comparing clozapine and olanzapine in patients with schizophrenia (62%) or schizoaffective disorder (38%) who were judged to be at risk for recurrent suicidal behavior. These patients either had attempted suicide or had been hospitalized to prevent a suicide attempt within the 3 years prior to their baseline evaluation or had demonstrated moderate-to-severe suicidal ideation with a depressive component or command hallucinations to do self-harm within 1 week prior to their baseline evaluation. Treatment resistance (i.e., resistance to standard antipsychotic drug therapies) was not a requirement for inclusion in this study, and only 27% of the total patient population was identified as being treatment resistant at baseline.

In the Inter SePT study, patients who received flexible dosages of clozapine (mean dosage: 274.2 mg daily) for approximately 2 years had a 26% reduction in their risk for suicide attempts or hospitalization to prevent suicide compared with those who received flexible dosages of olanzapine (mean dosage: 16.6 mg daily); the treatment-resistant status of patients was not predictive of response to clozapine or olanzapine. The cumulative probability of experiencing a suicide attempt, including a completed suicide, or hospitalization due to imminent suicide risk (including increased level of surveillance for suicidal behavior for patients already hospitalized) also was lower for patients receiving clozapine (24%) than for those receiving olanzapine (32%) at year 2. In addition, patients receiving clozapine had a statistically significant longer delay in the time to recurrent suicidal behavior than those receiving olanzapine. These results, however, may have been confounded by extensive use of other treatments to reduce the suicide risk, including concomitant psychotropic agents (84% with antipsychotics; 65% with anxiolytics; 53% with antidepressants, 28% with mood stabilizers), hospitalization and psychotherapy, the contributions of which to clozapine's efficacy are unknown.

Some clinicians state that methodologic problems (e.g., lack of actively suicidal patients in the study, possible bias and unblinding of suicide monitoring board members during the study, use of concomitant psychotropic agents) associated with the Inter SePT study limit definitive conclusions about the efficacy of clozapine for prevention of suicide in patients with schizophrenia or schizoaffective disorder. The US Food and Drug Administration (FDA) currently is advising clinicians to interpret the results of the Inter SePT study only as evidence of the efficacy of clozapine in delaying time to recurrent suicidal behavior, and not as efficacy of the drug for treatment of suicidal behaviors or as a demonstration of the superior efficacy of clozapine over olanzapine. However, the APA states that, based on the available evidence from the Inter SePT study, clozapine should be preferentially considered for schizophrenia patients with a history of chronic and persistent suicidal ideation and behaviors. Decisions to initiate clozapine therapy or switch patients from other antipsychotics to clozapine, therefore, should be individualized. In addition, safety and efficacy of clozapine in actively suicidal patients have yet to be determined.

■ **Parkinsonian Syndrome** Clozapine has been used in a limited number of patients with advanced, idiopathic parkinsonian syndrome for the management of dopaminomimetic psychosis† associated with antiparkinsonian drug therapy, but adverse effects such as sedation, confusion, and increased parkinsonian manifestations may limit the benefit of clozapine therapy in these patients. Attempts to relieve antiparkinsonian drug-induced delusions, paranoia, and hallucinations by reduction of antiparkinsonian drug dosage or administration of typical antipsychotic agents often aggravate parkinsonian symptoms. Limited data suggest that administration of clozapine in dosages of 6.25–400 mg daily can improve psychotic symptoms within a few days, reportedly without exacerbating parkinsonian manifestations. However, in a controlled study in a limited number of patients receiving clozapine dosages up to 250 mg daily, exacerbation of parkinsonian manifestations and development of delirium occurred frequently despite prevention of antiparkinsonian drug-induced deterioration of psychosis; it has been suggested that rapid clozapine dosage escalation may have contributed to the observed negative effect on parkinsonian manifestations and delirium. Clozapine dosages of 100–250 mg daily reportedly have been associated with hypersalivation, hypophonia, bradykinesia, and considerable sedation in patients with idiopathic parkinsonian syndrome, and withdrawal of clozapine therapy or a decrease in dosage also has exacerbated parkinsonian manifestations. Some clinicians suggest that the dosage of clozapine required to treat drug-induced dopaminomimetic psychosis may be substantially less than that required for treatment of psychosis in young, otherwise healthy individuals and that clozapine therapy should be initiated at low dosages (e.g., 6.25–50 mg daily) with cautious upward titration (e.g., to a maximum of 100–200 mg daily). Other clinicians have suggested that clozapine be used only as a last resort in patients with drug-induced dopaminomimetic psychosis.

Dosage and Administration

■ **Administration** Because of the risk of potentially life-threatening agranulocytosis, clozapine is available only through distribution systems that ensure baseline and periodic blood tests prior to delivery of the next supply of medication; dispensing is contingent on the results of the white blood cell (WBC) count and the absolute neutrophil count (ANC). (See Granulocytopenia and Agranulocytosis under Cautions: Hematologic Effects.) Although the amount of clozapine dispensed usually should not exceed a weekly supply, the manufacturers state that additional amounts (up to a 1-week supply) of the drug may be dispensed in exceptional circumstances (e.g., weather, holidays). In addition, patients may receive a supply sufficient for therapy for a period of time equal to that of the monitoring period; patients monitored weekly may receive a 1-week (7 day) supply of medication, patients monitored biweekly may receive a 2-week (14 day) supply, and patients eligible for monitoring every 4 weeks may receive a 28-day supply of medication, depending on WBC count and ANC results.

While availability of clozapine previously was exclusively through Novartis' Clozaril® Patient Monitoring System (CPMS), run jointly with CareMark and Roche Biomedical Laboratories, other distribution systems currently are in place; the individual manufacturers should be contacted for additional information on current mechanisms for obtaining the drug. Before initiating clozapine therapy in any patient, clinicians should check with the Clozaril® National Registry (phone number: [800]448-5938) to ensure that the patient does not have a history of clozapine-induced agranulocytosis or severe leukopenia/granulocytopenia; clozapine should *not* be administered to patients with such a history. (See Cautions: Hematologic Effects.)

Clozapine is administered orally, without regard to meals. Clozapine also has been administered IM†, but a parenteral preparation currently is not commercially available in the US.

Patients receiving clozapine orally disintegrating tablets should be instructed not to remove a tablet from the blister until just prior to dosing. The tablet should not be pushed through the foil; instead, the blister backing should be peeled completely off the blister. The tablet should then be gently removed and immediately placed on the tongue, where it rapidly disintegrates in saliva, and then subsequently swallowed with or without liquid. When clozapine orally disintegrating tablets are divided, the remaining half of the tablet that is not taken should be destroyed.

■ **Dosage** Dosage of clozapine should be carefully adjusted according to individual requirements and response using the lowest possible effective dosage.

Cautious dosage titration and administration of clozapine in divided doses are necessary to minimize the risk of certain adverse effects such as hypotension, seizures, and sedation. (See Cautions: Nervous System Effects and also see Cautions: Cardiovascular Effects.) The sedative effects of the drug may necessitate administration of most or all of the daily dose at bedtime, but some clinicians recommend that doses exceeding 500 mg generally be divided (e.g., a portion in the evening and the remainder at bedtime). Some clinicians also suggest that administration of clozapine in the morning be avoided, particularly in outpatients, at least until the patient has developed tolerance to the sedative effects of the drug.

Schizophrenia **Adult Dosage.** For the management of schizophrenia, the usual initial adult dosage of clozapine is 12.5 mg (one-half of a 25-mg tablet) once or twice daily. (If therapy is initiated with orally disintegrating tablets, the remaining half tablet should be destroyed.) Some clinicians advise that, if practical, consideration should be given to administering the first dose in a setting where facilities for cardiopulmonary resuscitation are available for at least a few hours after the first dose. If the drug is well tolerated, dosage may be increased by 25–50 mg daily over a 2-week period until a dosage of 300–450 mg daily is achieved. Subsequent dosage increases should be made no more frequently than once or twice weekly, in increments not exceeding 50–100 mg. The manufacturers state that cautious titration is necessary to minimize the risks of hypotension, myoclonic jerks, generalized seizures, and sedation. (See Cautions: Nervous System Effects.) If myoclonic jerks or generalized seizures occur, dosage of clozapine should be reduced and, if necessary, anticonvulsant therapy initiated.

Daily administration of clozapine in divided doses should continue until an effective and tolerable dosage is reached, usually within 2–5 weeks. Although many patients may respond adequately to dosages between 200–600 mg daily, a dosage of 600–900 mg daily may be required in some patients. In the multicenter study that provides the principal support for the effectiveness of clozapine in patients resistant to standard antipsychotic therapy, the maximum dosage of clozapine ranged from 100–900 mg daily, which was given in 3 divided doses. The mean and median clozapine dosages in this study both were approximately 600 mg daily. Although some clinicians suggest that dosages exceeding 450–500 mg daily have not been shown to be associated with increased therapeutic benefit, others state that added response is observed at higher dosages in some patients and stress the need for individualized therapy. The manufacturers and most clinicians recommend that the maximum daily dosage of clozapine not exceed 900 mg. Because of the possibility that high dosages of clozapine may be associated with an increased risk of adverse reactions, particularly seizures, patients generally should be given adequate time to respond to a given dosage before dosage escalation is considered.

Pediatric Dosage. The dosage of clozapine for the management of schizophrenia in children and adolescents† has not been established. However, the National Institute of Mental Health (NIMH) protocol used an initial dosage of 6.25–25 mg daily depending on the patient's weight. Dosages could be increased in this study every 3–4 days by 1–2 times the initial dose on an individual basis up to a maximum of 525 mg daily.

Duration of Therapy. The optimum duration of clozapine therapy for the management of schizophrenia currently is not known. While some clinicians state that clozapine therapy should be continued for longer than 6 weeks only in patients who exhibit substantial benefit within this period, others state that even less than substantial degrees of benefit may warrant continued therapy and that an adequate trial of clozapine may require at least 12 weeks (e.g., at 200–600 mg daily) or possibly 5–9 months or longer unless clinical deterioration or intolerable or potentially serious toxicity precludes it. The manufacturers currently recommend that patients who respond continue to receive clozapine therapy but at the lowest dosage needed to maintain remission of symptoms; following effective control of symptoms, dosage may be reduced gradually to determine the minimum therapeutic maintenance dose. In addition, patients should be reassessed periodically to determine the need for continued therapy with the drug. Extended therapy in patients failing to show an acceptable response to clozapine generally should be avoided because of the substantial, continuing risks of agranulocytosis and seizures. (See Cautions: Hematologic Effects and also see Seizures under Cautions: Nervous System Effects.)

Suicide Risk Reduction For suicide risk reduction in schizophrenia and schizoaffective disorder, the usual initial adult dosage of clozapine is 12.5 mg once or twice daily. If the drug is well tolerated, dosage may be increased by 25–50 mg daily over a 2-week period until a dosage of 300–450 mg daily is achieved. Subsequent dosage increases should be made no more frequently than once or twice weekly, in increments not exceeding 50–100 mg. In the multicenter Inter SePT study that provides the principal support for the effectiveness of clozapine for suicide risk reduction, mean dosage was about 300 mg daily (range: 12.5–900 mg daily).

Because efficacy of clozapine for this indication was demonstrated over a 2-year treatment period in this study, clozapine therapy to reduce the risk of suicidal behavior should be continued for at least 2 years. After 2 years, it is recommended that the patient's risk of suicidal behavior be reassessed. If the clinician's assessment indicates that a clinically important risk for suicidal behavior is still present, clozapine therapy should be continued. Thereafter, the need to continue therapy with the drug should be reevaluated at regular intervals, based on thorough assessments of the patient's risk for suicidal behavior during treatment. If the clinician determines that the patient is no longer at risk for suicidal behavior, clozapine therapy may be discontinued gradually (see Dosage: Discontinuance of Therapy) and treatment of the underlying disorder with an antipsychotic agent to which the patient has previously responded may be resumed.

Discontinuance of Therapy In the event of planned termination of clozapine therapy, gradual reduction in dosage over a 1- to 2-week period is recommended. However, should abrupt discontinuance of therapy be required (e.g., because of leukopenia or agranulocytosis), the patient should be observed carefully for recurrence of psychotic symptoms and symptoms related to cholinergic rebound such as headache, nausea, vomiting, and diarrhea. Sudden withdrawal from clozapine therapy can lead to rapid decompensation and rebound psychosis. (See Other Nervous System Effects under Cautions: Nervous System Effects.)

Reinitiation of Therapy If clozapine therapy is restarted in patients who have had even brief interruptions (i.e., 2 days or more) in therapy, dosage generally should be titrated as with initial therapy (i.e., 12.5 mg once or twice daily). If this dosage is well tolerated, dosage may be titrated back to the therapeutic dosage more quickly than during initial treatment. The manufacturers state that clozapine therapy should be reinstituted with extreme caution, even following brief interruptions of only 24 hours, in patients who have previously experienced respiratory or cardiac arrest during initial dosing but subsequently were titrated to a therapeutic dosage.

Because the mechanisms underlying clozapine-induced adverse reactions are unknown and it is conceivable that reexposure might enhance the risk of an adverse effect and/or increase its severity (e.g., when immune-mediated mechanisms are involved), the manufacturers advise additional caution during reinitiation of therapy. When reinitiating therapy, consider WBC count and ANC monitoring recommendations. (See Table 2: WBC and ANC Monitoring for Clozapine Reinitiation under Cautions.)

Patients in whom clozapine therapy is discontinued because of leukocyte counts less than 2000/mm^3 or an ANC less than 1000/ mm^3 must *not* be restarted on the drug. (See Cautions: Hematologic Effects.)

Cautions

Although clozapine differs chemically from the phenothiazines, the drug may be capable of producing many of the toxic manifestations of phenothiazine derivatives. Not all adverse effects of the phenothiazines have been reported with clozapine, but the possibility that they may occur should be considered. Adverse effects of clozapine and the phenothiazines are numerous and may involve nearly all organ systems. Although these effects usually are reversible when dosage is reduced or the drug is discontinued, some effects may be irreversible and, rarely, fatal. In some patients, unexpected death associated with

antipsychotic therapy has been attributed to cardiac arrest or asphyxia resulting from failure of the gag reflex. (See Cautions: Cardiovascular Effects.) In other cases, the cause of death could not be determined or definitely attributed to antipsychotic drug therapy. An increased risk of death has been observed in geriatric patients with dementia-related psychoses receiving atypical antipsychotics. (See Cautions: Geriatric Precautions.)

The most frequent adverse effects of clozapine involve the central and autonomic nervous systems (e.g., drowsiness or sedation, hypersalivation) and the cardiovascular system (e.g., tachycardia, hypotension). While the frequency and severity of some adverse effects (e.g., extrapyramidal reactions, tardive dyskinesia) appear to be less with clozapine than with other antipsychotic agents, other potentially serious adverse effects (e.g., agranulocytosis, seizures) may occur more frequently with clozapine therapy, and the potential risks and benefits should be evaluated carefully whenever therapy with the drug is considered. Because of the substantial risk of clozapine-associated agranulocytosis, which may persist over an extended period of time and be life-threatening or fatal if not detected early and therapy interrupted, clozapine is available for use only through patient-management systems that ensure baseline and periodic blood tests prior to delivery of the next supply of medication; dispensing is contingent on the results of the white blood cell (WBC) count and absolute neutrophil count (ANC). Before initiating clozapine therapy in any patient, clinicians should check with the Clozaril® National Registry to ensure that the patient has no history of clozapine-induced agranulocytosis or severe leukopenia/granulocytopenia; clozapine should *not* be administered to patients with such a history. (See Cautions: Hematologic Effects.)

■ **Hematologic Effects** ***Granulocytopenia and Agranulocytosis***

Agranulocytosis, defined as an absolute neutrophil count (ANC) less than 500/mm³ and characterized by leukopenia (WBC count less than 2000/mm³) and relative lymphopenia, has an estimated cumulative incidence of 1–2% after 1 year of clozapine therapy, as compared with an estimated incidence of 0.1–1% for phenothiazine-induced agranulocytosis. The rate of clozapine-induced agranulocytosis is based on the occurrence of 15 cases out of 1743 patients who received clozapine during clinical trials in the US. Some evidence suggests that the incidence of clozapine-induced agranulocytosis is at least 10 times greater than that of other antipsychotic agents, although it also has been suggested that the incidence of clozapine-induced agranulocytosis may be no higher than that associated with phenothiazines. Of the 149 cases of clozapine-induced agranulocytosis reported worldwide as of December 31, 1989, 32% were fatal. Few of these fatalities have occurred since 1977 when the knowledge of clozapine-induced agranulocytosis became widespread and close monitoring of WBC count became widely practiced. In the US, under a weekly leukocyte monitoring system in premarketing studies and in postmarketing experience with clozapine, 585 cases of agranulocytosis, including 19 fatalities, had occurred as of August 21, 1997; one patient receiving concomitant therapy with carbamazepine and clozapine died following development of an unusual hypoplastic anemia with agranulocytosis, a pancytopenic condition not usually characteristic of clozapine-induced hematologic effects. Based on analysis of data pooled from a confidential national master file of information (the Clozaril® National Registry), the incidence of agranulocytosis appears to rise steeply during the first 2 months of therapy and peaks in the third month. The incidence gradually declines with continued therapy and reaches a rate of 3 per 1000 person-years by 6 months of therapy. After 6 months, the incidence of agranulocytosis declines still further. However, the manufacturer of Clozaril® cautions that a reduction in the frequency of leukocyte monitoring may result in an increase in incidence of agranulocytosis.

The precise mechanism by which clozapine induces agranulocytosis is not known, but both immunologic and toxic mechanisms (including a direct myelotoxic effect of the drug and/or its metabolites) have been implicated. Some evidence suggests that granulocyte antibodies may be involved. Except for the evidence of marked bone marrow depression during initial clozapine therapy and a disproportionate number of females, there are no established risk factors, based on worldwide experience, for developing clozapine-induced agranulocytosis. However, a disproportionate number of US cases have occurred in patients of Eastern European Jewish heritage compared with the overall proportion of such patients exposed to clozapine during domestic trials. Results of genetic typing indicate that genetic factors marked by a major histocompatibility complex haplotype (HLA-B38, DR4, DQw3) may be associated with the susceptibility of certain Jewish patients with schizophrenia to develop agranulocytosis when treated with clozapine; the incidence of some phenotypes common among Ashkenazi Jews has been found to be greatly increased in patients with clozapine-induced agranulocytosis.

Most cases of clozapine-induced agranulocytosis in the US have occurred within 4–16 weeks of exposure to the drug. Although no patient characteristics predictive of an increased risk of agranulocytosis with clozapine have been identified conclusively, agranulocytosis associated with the use of other antipsychotic agents has been reported to occur more frequently in women, geriatric patients, and patients who are cachectic or have serious underlying medical conditions (e.g., immunocompromised patients, patients with human immunodeficiency virus [HIV] infection); such patients also may be at increased risk for developing agranuloeytosis with clozapine therapy.

Investigation of 16 cases of clozapine-associated granuloeytopenia occurring within a 2-month period in 1975 in southwest Finland, including 13 cases of agranulocytosis, revealed characteristics similar to those of phenothiazine-induced agranulocytosis. In all of these cases, the reaction occurred during first exposure to the drug and followed a latent period of 17–109 days at a cumulative dose of 4.5–42 g; reduced values for hemoglobin and peripheral erythrocyte and thrombocyte counts were found infrequently, and granulopoiesis in sternal marrow usually was severely depressed or absent. Erythropoiesis was below normal in only one case, and thrombopoiesis was normal or even increased. Hematologic values returned to baseline within 1–3 weeks after withdrawal of clozapine. All fatalities were attributed to secondary infection in patients in whom granulocytopenia was not diagnosed early or clozapine discontinued promptly. In patients who died, the clinical course typically consisted of fever with tonsillitis, which progressed to pneumonia and septicemia; the immediate cause of death usually was renal or cardiac failure. The frequency of clozapine-induced agranulocytosis or granulocytopenia in the Finnish experience was 7.1 per thousand—approximately 21 times higher than that reported in other countries. Although it has been suggested that a local genetic or environmental factor or factors may have been involved in the Finnish cases, the existence of such a factor has not been documented.

The most likely time of occurrence of granulocytopenia appears to be 4–16 weeks after initiation of treatment with clozapine. However, neither dose nor duration of therapy is a reliable predictor of agranulocytosis. Most patients develop agranulocytosis within the first 10 weeks of therapy, but a latent period of up to 1 year or longer also has been reported. Within the first 18 weeks of therapy, 77–90% of all cases of granulocytopenia and agranuloeytosis have been reported and 85% of fatalities secondary to agranulocytosis have occurred. The latent period between the fall in leukocyte count and the development of a secondary infection usually is moderately long. Leukooyte count usually declines gradually (e.g., over a period of weeks), but it also may decline precipitously. Patients receiving clozapine may have a transient and benign reduction in leukocyte count without progression to agranulocytosis, and may or may not develop manifestations of infection (e.g., fever, sore throat).

Patients in whom granulocytopenia is diagnosed and clozapine therapy discontinued before the occurrence of infection generally have a favorable prognosis. Early diagnosis of granulocytopenia and appropriate medical management can forestall serious consequences and reduce morbidity and mortality substantially since the condition generally is reversible if clozapine is discontinued promptly. In contrast, agranulocytosis is more likely to be fatal in patients in whom clozapine therapy is not halted before the development of infection.

Because of the substantial, persistent risk of agranulocytosis associated with clozapine use, patients must have a WBC count and ANC performed before initiation of therapy with the drug. Clozapine therapy should not be initiated if the baseline WBC count is less than 3500/mm³ or the ANC is less than 2000/mm³. While some clinicians suggest that WBC counts be done weekly during the first 4–12 months of therapy and then less frequently (e.g., every 2 weeks or monthly) thereafter, other clinicians state that patients must have weekly WBC counts for the duration of therapy. However, the manufacturers suggest that the frequency of monitoring depends in part on the duration of therapy, adherence to therapy, and development of adverse hematologic effects. The manufacturers state that patients must have WBC counts and ANC monitored at least weekly for the first 6 months of continuous treatment and then every other week for the next 6 months if WBC counts and ANC remain acceptable (WBC count equal to or exceeding 3500/mm³, ANC equal to or exceeding 2000/mm³). After a further 6 months, if acceptable WBC counts and ANCs continue to be maintained, the frequency of monitoring may be reduced to every 4 weeks for the remainder of clozapine therapy. After discontinuance of therapy, continue to monitor WBC count and ANC weekly for at least 4 weeks from the day of discontinuance or until WBC count is equal to or exceeding 3500/mm³ and ANC is equal to or exceeding 2000/mm³. The current recommendations for WBC count and ANC monitoring based on the stage of therapy and the results from WBC and ANC monitoring are provided in Table 1 below. Dispensing of clozapine is contingent upon compliance with these *required* WBC and ANC tests. (See Dosage and Administration: Administration.)

Table 1. Frequency of Monitoring based on Stage of Therapy or Results from WBC and ANC Monitoring

Situation	Hematological Values	Frequency of WBC and ANC Monitoring
Initiation of therapy	WBC ≥3500/mm³ ANC ≥2000/mm³ Do not initiate in patients with a history of myeloproliferative disorder or clozapine-induced agranulocytosis or granulocytopenia.	Weekly for 6 months.
During 6–12 months of therapy	All results for WBC ≥3500/mm³ and ANC ≥2000/mm³	Every 2 weeks for 6 months.
After 12 months of therapy	All results for WBC ≥3500/mm³ and ANC ≥2000/mm³	Every 4 weeks thereafter.
Immature forms present	Not applicable	Repeat WBC and ANC.

Discontinuance of therapy	Not applicable	Weekly for at least 4 weeks from day of discontinuance or until WBC ≥3500/mm³ and ANC ≥2000/mm³.
Substantial decrease in WBC or ANC	Single decrease or cumulative decrease within 3 weeks of WBC≥3000/mm³ or ANC ≥1500/mm³	Repeat WBC and ANC. Carefully monitor for manifestations of infection.** If repeat values for WBC ≥3000/mm³ and ≤3500/mm³ and ANC <2000/mm³, monitor twice weekly.
Mild leukopenia/mild granulocytopenia	WBC ≥3000/mm³ but <3500/mm³ and/or ANC ≥1500/mm³ but <2000/mm³	Monitor twice weekly until WBC >3500/mm³ and ANC >2000/mm³, then resume previous monitoring frequency. Carefully monitor for manifestations of infection.**
Moderate leukopenia/moderate granulocytopenia	WBC ≥2000/mm³ but <3000/mm³ and/or ANC ≥1000/mm³ but <1500/mm³	Interrupt therapy and carefully monitor for manifestations of infection.** Monitor daily until WBC >3000/mm³ and ANC >1500/mm³, then monitor twice weekly until WBC >3500/mm³ and ANC >2000/mm³. May rechallenge when WBC >3500/mm³ and ANC >2000/mm³. If rechallenged, monitor weekly for 1 year before returning to the usual monitoring schedule of every 2 weeks for 6 months then every 4 weeks indefinitely.
Severe leukopenia/severe granulocytopenia	WBC <2000/mm³ and/or ANC <1000/mm³	Discontinue therapy and *do not rechallenge patient.** Carefully monitor for manifestations of infection.** Monitor until normal and for at least 4 weeks from day of discontinuance as follows: daily until WBC >3000/mm³ and ANC >1500/mm³, twice weekly until WBC >3500/mm³ and ANC >2000/mm³, then weekly after WBC >3500/mm³. Consider bone marrow aspiration to determine granulopoietic status; if granulopoiesis is deficient, protective isolation with close observation may be indicated. If infection develops, perform cultures and institute appropriate anti-infective therapy.
Agranulocytosis	ANC ≤500/mm³	Discontinue therapy and *do not rechallenge patient.** Carefully monitor for manifestations of infection.** Monitor until normal and for at least 4 weeks from day of discontinuance as follows: daily until WBC >3000/mm³ and ANC >1500/mm³, twice weekly until WBC >3500/mm³ and ANC >2000/mm³, then weekly after WBC >3500/mm³. Consider bone marrow aspiration to determine granulopoietic status; if granulopoiesis is deficient, protective isolation with close observation may be indicated. If infection develops, perform cultures and institute appropriate anti-infective therapy.

* Agranulocytosis develops upon rechallenge, often with a shorter latency. Patients who have experienced substantial bone marrow suppression during therapy are listed in a national master file. (See Dosage and Administration: Administration.)

** Carefully monitor for flu-like symptoms or other manifestations of infection; institute appropriate anti-infective therapy if necessary.

If clozapine therapy is reinitiated after interruption of therapy, WBC counts and ANC should be monitored after reinitiating therapy based on the duration of previous therapy, length of interruption of therapy, and previous WBC counts and ANC in the patient according to the schedule in Table 2 below:

Table 2. WBC and ANC Monitoring for Clozapine Reinitiation

Previous therapy duration <6 months, with no abnormal blood event (WBC ≥3500/mm³ and ANC ≥2000/mm³) and interruption in therapy ≥3 days but≤1 month	Continue with weekly WBC and ANC monitoring where left off in schedule; do not restart 6-month period. When 6-month period complete, may decrease monitoring frequency to every other week.
Previous therapy duration <6 months, with no abnormal blood event and interruption in therapy >1 month	Monitor WBC and ANC weekly for *additional* 6 months before decreasing to biweekly testing.
Previous therapy duration <6 months, *with* abnormal blood event (WBC <3500/mm³ or ANC <2000/mm³) but rechallengeable (i.e., WBC ≥2000/mm³ and ANC ≥1000/mm³ during previous therapy)	See Table 1.
Previous therapy duration 6–12 months, with no abnormal blood event and interruption in therapy ≥3 days but ≤1 month	Monitor WBC and ANC weekly for 6 weeks, then resume monitoring every other week for an additional 6 months.*
Previous therapy duration 6–12 months, with no abnormal blood event and interruption in therapy >1 month	Monitor WBC and ANC weekly for 6 months, then resume monitoring every other week for an additional 6 months.*
Previous therapy duration 6–12 months, *with* abnormal blood event (WBC <3500/mm³ or ANC <2000/mm³) but rechallengeable (i.e., WBC ≥2000/mm³ and ANC ≥1000/mm³ during previous therapy)	See Table 1.*
Previous therapy duration >12 months, with no abnormal blood event and interruption in therapy ≥3 days but ≤1 month	Monitor WBC and ANC weekly for 6 weeks, then resume monitoring every 4 weeks.*
Previous therapy duration >12 months, with no abnormal blood event and interruption in therapy >1 month	Monitor WBC and ANC weekly for 6 months, then resume monitoring every other week for an additional 6 months, then resume monitoring every 4 weeks.*
Previous therapy duration >12 months, *with* abnormal blood event (WBC <3500/mm³ or ANC <2000/mm³) but rechallengeable (i.e., WBC ≥2000/mm³ and ANC ≥1000/mm³ during previous therapy)	See Table 1.

*Transition to reduce frequency of monitoring only permitted if all WBC counts are equal to or exceeding 3500/mm³ and ANC values are equal to or exceeding 2000/mm³.

Although some clinicians suggest that body temperature be measured at least once daily for the first 18 weeks of clozapine therapy, others state that such monitoring is not an adequate means of assessing infection in clozapine-treated patients because of the drug's pharmacologic potential for causing temperature elevation. Patients receiving clozapine should be advised to report immediately the appearance of lethargy, weakness, fever, sore throat, or any other potential manifestation of infection.

Supportive therapy with biosynthetic hematopoietic agents, including filgrastim, a recombinant human granulocyte colony-stimulating factor (G-CSF), and sargramostim, a recombinant human granulocyte-macrophage colony-stimulating factor (GM-CSF), has been effective in a limited number of patients with clozapine-induced neutropenia and agranulocytosis. Consultation with a hematologist and infectious disease expert is recommended.

When granulocytopenia is diagnosed and clozapine therapy is discontinued, patients usually recover in 7–28 days. Most of these patients require further antipsychotic therapy because of a recurrence of psychotic symptoms. (See Other Nervous System Effects under Cautions: Nervous System Effects.) Since there appears to be no cross-sensitivity between clozapine and other antipsychotics in terms of hematologic toxicity, other antipsychotic drugs generally may be used without causing further hematologic complications in patients who develop clozapine-induced agranulocytosis. However, patients who develop clozapine-induced agranulocytosis (or those in whom the total WBC count and ANC decrease to less than 2000/mm³ and less than 1000/mm³, respectively) should *not* be rechallenged with clozapine. Patients in whom clozapine therapy has been discontinued due to substantial leukocyte suppression have been found to develop agranulocytosis upon rechallenge with the drug, often with a shorter latency on reexposure. To reduce the chance of rechallenge in patients who

have experienced substantial bone marrow suppression with clozapine therapy, the manufacturer of Clozaril® maintains a confidential national master file of information (the Clozaril® National Registry) on all nonrechallengeable patients.

Eosinophilia Eosinophilia has been reported in approximately 1% of patients who received clozapine therapy in clinical trials. The manufacturers state that if the total eosinophil count exceeds 4000/mm³, clozapine therapy should be temporarily discontinued until the count falls below 3000/mm³.

Other Hematologic Effects Other hematologic effects reported with clozapine therapy include leukopenia, neutropenia, and thrombocytopenia, which have been reported in 1–3% of patients. Anemia, leukocytosis, and increased platelet count have been reported in less than 1% of patients receiving clozapine. Other clozapine-induced hematologic effects reportedly include basophilia, a substantial reduction in B cells, and an increase in hemoglobin concentration. Elevated erythrocyte sedimentation rate (ESR) and sepsis have been reported in patients receiving clozapine during postmarketing surveillance; however, a causal relationship to the drug has not been established.

■ **Nervous System Effects** ***Seizures*** Clozapine lowers the seizure threshold and can cause EEG changes, including the occurrence of spike and wave complexes. Seizures reportedly occurred in approximately 3.5% of patients exposed to the drug during clinical trials in the US (cumulative annual incidence of approximately 5%). In contrast, a seizure incidence of approximately 1% has been reported in patients treated with other antipsychotic agents. The risk of seizures with clozapine therapy appears to be related to dosage and/or plasma concentrations of the drug, with a reported incidence of approximately 0.6–2% at dosages less than 300 mg daily, 1.4–5% at 300–600 mg daily, and 5–14% at high dosages (600–900 mg daily). Clozapine-induced seizures may be associated with rapid dosage escalations, particularly in patients with preexisting epilepsy, and in those receiving concomitant therapy with drugs that may lead to increased plasma concentrations of clozapine. If myoclonic jerks or generalized seizures occur, clozapine dosage should be reduced and, if necessary, anticonvulsant treatment initiated.

One patient receiving clozapine experienced a generalized tonic-clonic (grand mal) seizure following accidental ingestion of an extra dose (total dose ingested within 24 hours: 1050 mg); the same patient had another seizure several weeks later, 2 hours after a usual 450-mg morning dose. Results of plasma clozapine determinations obtained at the time of the seizures revealed plasma clozapine concentrations of approximately 2000 ng/mL in each case. Another patient who had been taking clozapine for 27 months had a generalized tonic-clonic seizure following an apparent intentional overdosage (total dose ingested within 24 hours: approximately 3 g), after which the patient made an uneventful recovery. One hour after the seizure, the patient's plasma clozapine concentration was 1313 ng/mL.

Discontinuance of clozapine therapy, at least temporarily, should be seriously considered in patients who experience seizures while receiving the drug; however, some clinicians state that reduced clozapine dosage and/or, occasionally, addition of anticonvulsant therapy may adequately ameliorate this effect. If clozapine therapy is to be continued in such patients, many clinicians recommend obtaining additional informed consent from the patient. In patients in whom clozapine is withheld, it has been suggested that therapy with the drug can be reinitiated at one-half the previous dosage. Clozapine dosage may then be increased gradually, if clinically indicated, and the need for concomitant anticonvulsant therapy should be considered. Some clinicians recommend that patients who have experienced a clozapine-induced seizure *not* be given clozapine dosages exceeding 600 mg daily unless the results of an EEG performed prior to the anticipated dosage increase are normal; others suggest addition of anticonvulsant therapy and/or consultation with a neurologist in managing such patients. In patients with preexisting seizure disorders who are treated concomitantly with certain anticonvulsants and clozapine, the anticonvulsant dosage may need to be increased. However, clozapine should not be used concomitantly with anticonvulsants (e.g., carbamazepine) or other drugs that potentially may cause bone marrow suppression. (See Drug Interactions: Myelosuppressive Agents.)

Extrapyramidal Reactions In contrast to other antipsychotic agents, clozapine has a low potential for causing certain acute extrapyramidal effects (e.g., dystonias). Such effects, when they occur, have been limited principally to tremor, restlessness, rigidity, and akathisia; these manifestations generally are milder and less persistent than those produced by other antipsychotic drugs. In addition, marked or total remission of such manifestations induced by other antipsychotics has occurred during treatment with clozapine in some patients.

Neuroleptic malignant syndrome (NMS), a potentially fatal symptom complex, has been reported in patients receiving phenothiazines or other antipsychotic therapy. NMS attributable to clozapine therapy alone has been reported in a few patients, and there also have been several reports of NMS in patients treated concomitantly with clozapine and lithium or other CNS drugs; some clinicians suggest that NMS may be more likely to occur when clozapine or other antipsychotic agents are used concomitantly with lithium. Manifestations of NMS (e.g., muscle rigidity, hyperpyrexia, tachycardia, increased serum creatine kinase [CK, creatine phosphokinase, CPK], diaphoresis, somnolence), all of which may not occur in all patients with the condition, have occurred in a few patients treated with clozapine alone or combined with lithium or carbamazepine; resolution of the syndrome occurred following discontinuance of clozapine. However, clozapine also has been used successfully and apparently without recurrence of NMS in at least one patient who developed the syndrome while receiving chlorpromazine.

For additional information on NMS, see Extrapyramidal Reactions in Cautions: Nervous System Effects, in the Phenothiazines General Statement 28:16.08.24.

Tardive Dyskinesia A syndrome consisting of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic agents. However, results of clinical trials in which clozapine was used have demonstrated a virtual absence of acute extrapyramidal reactions (e.g., dystonia), and there reportedly have been no confirmed cases of tardive dyskinesia associated with clozapine therapy alone. Nevertheless, a few cases of tardive dyskinesia have been reported in patients receiving clozapine who had been treated previously with other antipsychotic agents. Although current evidence suggests that clozapine may be less likely than other antipsychotic agents to cause tardive dyskinesia, it cannot yet be concluded, based on current limited experience, that the drug is incapable of causing this syndrome. The possibility of clozapine-induced tardive dyskinesia should be considered in patients receiving long-term therapy with the drug or in those starting clozapine therapy after discontinuance of conventional (typical) antipsychotic agents.

For additional information on tardive dyskinesia, see Tardive Dyskinesia in Cautions: Nervous System Effects in the Phenothiazines General Statement 28:16.08.24.

Other Nervous System Effects Drowsiness and/or sedation occur frequently in patients receiving clozapine. (See Effects on Sleep under Pharmacology: Nervous System Effects.) Somnolence reportedly occurred in 46% of patients receiving clozapine in the International Suicide Prevention Trial (InterSePT) compared with 25% of those receiving olanzapine. The sedative-hypnotic effect of clozapine is most pronounced initially, diminishes after 1–4 weeks, and then generally, but not always, disappears during continued therapy. Daytime sleepiness may be minimized by administration of clozapine at bedtime. (See Dosage and Administration: Dosage.)

Dizziness and vertigo, headache, syncope, disturbed sleep (e.g., insomnia) or nightmares, hypokinesia or akinesia, and agitation have been reported with clozapine therapy. In the International Suicide Prevention Trial (InterSePT), dizziness (excluding vertigo) and insomnia reportedly occurred in 27 and 20% of patients receiving clozapine, respectively, compared with 12 and 33% of those receiving olanzapine, respectively. Clozapine also may cause confusion or delirium, which may be related to central anticholinergic effects, and has been ameliorated in some cases by IV administration of physostigmine. Depression, fatigue, hyperkinesia, weakness or lethargy, and slurred speech also have been reported. Other adverse nervous system effects associated with clozapine therapy include ataxia, epileptiform movements or myoclonic jerks, and anxiety.

Adverse nervous system effects reported in less than 1% of clozapine-treated patients include loss of speech, amentia (deterioration in cognitive function), tics, poor coordination, delusions or hallucinations, stuttering, dysarthria, amnesia, histrionic movements, increased or decreased libido, paranoia, shakiness, parkinsonian syndrome, and irritability. Difficulty in writing, residual daytime effects such as impairment of mental performance, and periodic cataplexy, which is characterized by sudden episodes of dropping objects and may or may not be accompanied by knee buckling, also have been reported infrequently with clozapine therapy. Exacerbation of psychosis, myoclonus, paresthesia, and status epilepticus have been reported in patients receiving clozapine during postmarketing surveillance; however, a causal relationship to the drug has not been established.

Abrupt discontinuance of clozapine (e.g., because of leukopenia or agranulocytosis) may result in recurrence of psychotic symptoms or behavior, including autism, auditory hallucinations, suicide attempts, development of parkinsonian symptoms, anxiety, insomnia, delusions, and violent behavior. It has been suggested that this "rebound psychosis" may result, at least in part, from clozapine-induced supersensitivity of mesolimbic dopamine receptors (see Behavioral Effects in Animals under Pharmacology: Nervous System Effects) and that the essential feature of this phenomenon appears to be recurrence of positive symptoms of schizophrenia. Patients who develop rebound psychosis following discontinuance of clozapine may improve with initiation of other antipsychotic therapy; however, clozapine should *not* be reinstituted in patients in whom severe leukopenia/granulocytopenia or agranulocytosis has occurred. (See Cautions: Hematologic Effects.)

■ **Fever** Fever or transient temperature elevations exceeding 38°C generally have been reported in 5% or more of patients receiving clozapine. The peak incidence of fever occurs within the first 3 weeks of therapy, usually between days 5–20 of treatment. Fever generally is benign and self-limiting and usually diminishes within a few (4–8) days despite continued clozapine therapy; however, it may necessitate discontinuance of the drug. Fever occasionally may be associated with an increase or decrease in leukocyte count, in which case patients should be evaluated for underlying infection or development of agranulocytosis. (See Cautions: Hematologic Effects.) In the presence of high fever, the possibility of neuroleptic malignant syndrome also must be considered. (See Extrapyramidal Reactions under Cautions: Nervous System Effects.)

The mechanism of clozapine-induced fever (other than that occurring secondary to some other factor such as infection) is not yet known. It may result from the drug's pronounced anticholinergic activity (see Anticholinergic Effects under Pharmacology: Nervous System Effects) or a direct effect on the

hypothalamic thermoregulatory center. Clozapine-induced hyperthermia may be a hypersensitivity reaction, a common mechanism underlying drug fevers. It has been suggested that decreasing the dosage of clozapine and then gradually increasing it to the previous level may reverse the hyperthermia and not be accompanied by a recurrence of elevated temperature; however, recurrence is possible despite such dosage adjustment.

■ **Cardiovascular Effects** ***Myocarditis*** Myocarditis (sometimes fatal) has been reported during postmarketing surveillance in patients receiving clozapine. Postmarketing surveillance data from 4 countries employing hematologic monitoring of clozapine-treated patients indicated 30 cases of myocarditis in 205,493 clozapine-treated US patients as of August 2001, 7 cases of myocarditis in 15,600 such Canadian patients as of April 2001, 30 cases of myocarditis in 24,108 such United Kingdom patients as of August 2001, and 15 cases of myocarditis in 8000 such Australian patients as of March 1999, representing an incidence of approximately 5, 16, 43, and 97 cases/100,000 patient-years of clozapine therapy, respectively. Of these 82 cases of myocarditis identified through postmarketing surveillance, 38% resulted in death. Although the overall incidence of myocarditis in patients with schizophrenia receiving antipsychotic agents is unknown, the incidence of myocarditis or fatal myocarditis, respectively, in patients receiving clozapine appears to be 17–322 or 14–161 times greater than the incidence in general population.

These postmarketing surveillance data also suggest that the incidence of myocarditis, including fatal myocarditis, may be highest during the first month of therapy, with 62% of myocarditis cases occurring within the first month of clozapine therapy, 31% of cases occurring after the first month of therapy, and the onset unknown in 7% of cases. Therefore, the possibility of myocarditis should be considered in patients receiving clozapine who present with unexplained fatigue, dyspnea, tachypnea, fever, chest pain, palpitations, other signs or symptoms of heart failure, or ECG findings such as ST-T wave changes or arrhythmias.

It is not known whether eosinophilia is a reliable predictor of myocarditis. However, tachycardia, which has been associated with clozapine therapy, also may be a manifestation of myocarditis. Therefore, tachycardia occurring during the first month of clozapine therapy warrants close monitoring for other manifestations of myocarditis. If myocarditis is suspected, the drug should be discontinued promptly. Because myocarditis recurred in 3 of 5 patients rechallenged with the drug, patients who develop myocarditis while receiving clozapine should *not* be rechallenged with the drug.

Cardiomyopathy Cardiomyopathy has been reported in US patients treated with clozapine at a reporting rate of 8.9 cases/100,000 person-years, which was similar to an estimate of the cardiomyopathy incidence in the US general population derived from the 1999 National Hospital Discharge Survey data (9.7 cases/100,000 person-years). Approximately 80% of clozapine-treated patients in whom cardiomyopathy was reported were younger than 50 years of age; the duration of treatment with clozapine prior to cardiomyopathy diagnosis varied, but exceeded 6 months in 65% of the reports. Dilated cardiomyopathy was most frequently reported, although a large percentage of reports did not specify the type of cardiomyopathy. Signs and symptoms suggestive of cardiomyopathy, particularly exertional dyspnea, fatigue, orthopnea, paroxysmal nocturnal dyspnea, and peripheral edema, should alert the clinician to perform further investigations. If the diagnosis of cardiomyopathy is confirmed, the drug should be discontinued unless the benefit to the patient clearly outweighs the risk.

Thromboembolic Effects Deep-vein thrombosis and pulmonary embolism have been reported in patients receiving clozapine during postmarketing surveillance. As of December 31, 1993, 18 cases of fatal pulmonary embolism were reported in patients 10–54 years of age receiving clozapine therapy. Based on the extent of use observed in the Clozaril National Registry, the mortality rate associated with pulmonary embolism was 1 death per 3450 person-years of use; this incidence is approximately 27.5 times higher than that in the general population. Although a causal relationship between clozapine and these adverse cardiovascular effects has not been established, the possibility of pulmonary embolism should be considered in patients presenting with deep-vein thrombosis or respiratory symptomatology. (See Cautions: Precautions and Contraindications.

Blood Pressure Effects Hypotension and hypertension reportedly occur in less than 10% of patients receiving clozapine. When they occur, changes in blood pressure, principally reductions in systolic pressure, appear soon after initiation of clozapine therapy and may be associated with rapid dosage increases. A decrease in arterial blood pressure below 90 mm Hg was reported in 18% of male patients and 33% of female patients receiving clozapine in one retrospective study. Hypotension may result from clozapine's antiadrenergic effects (see Adrenergic Effects under Pharmacology: Nervous System Effects) and may pose a serious risk for individuals with compromised cardiac function. However, tolerance to the hypotensive effects of clozapine often develops with continued therapy.

Orthostatic hypotension, with or without syncope, has been reported, particularly during initial titration or rapid escalation of clozapine dosage; however, this effect may represent a continuing risk in some patients. Rarely (approximately 1 case per 3000 patients), orthostatic hypotension has been accompanied by profound collapse and respiratory and/or cardiac arrest in patients receiving initial doses as low as 12.5 mg. If clozapine therapy is temporarily discontinued (i.e., for 2 or more days), the manufacturers recommend that the drug be reinitiated at a lower dosage (12.5 mg once or twice daily). In some cases when collapse and cardiac and/or respiratory arrest developed during initial therapy, benzodiazepines or other psychotropic agents were used concomitantly, suggesting a possible adverse interaction between clozapine and these agents. (See Drug Interactions: Benzodiazepines.) Although the clinical importance of this interaction has not been fully established, the manufacturers state that clozapine should be initiated with caution in patients receiving benzodiazepines or other psychotropic agents. Collapse and respiratory and/or cardiac arrest also have been reported in patients receiving initial therapy with clozapine alone. The risk of orthostatic hypotension may be reduced by initiating therapy at lower dosages, followed by only gradual, modest increases as necessary. (See Dosage and Administration: Dosage.) In some cases, withholding the drug for 24 hours and then restarting at a lower dosage has been accomplished without recurrence of orthostatic hypotension.

Tachycardia Tachycardia, which may persist throughout therapy in some cases, reportedly has been observed in 25% of patients receiving clozapine. Patients who experience clozapine-induced tachycardia demonstrate an average increase in pulse rate of 10–15 beats per minute (bpm); with aggressive dosage increases, the mean increase in heart rate ranges from 20–25 bpm. Persistent tachycardia associated with clozapine therapy is not simply a reflex response to hypotension and is present in all positions monitored. Although this effect may lessen once a plateau dosage level is reached, tachycardia may pose a serious risk for individuals with compromised cardiac function.

ECG Effects Some clozapine-treated patients experience ECG repolarization changes, including ST-segment depression, shortening of the PQ interval, and/or flattening, depression, or inversion of T waves. These changes usually normalize after discontinuance of clozapine and are similar to those seen with other antipsychotic agents. The clinical importance of these changes currently is unclear, but some clinicians suggest that they occur infrequently and usually are not serious.

Other Cardiovascular Effects In clinical trials of clozapine, some patients experienced serious cardiovascular events, including ischemic changes, chest pain and angina, hypertension, myocardial infarction, nonfatal arrhythmias, or sudden, unexplained death. Causality assessment was difficult because of serious preexisting cardiac disease in many of the patients and plausible alternative causes.

In addition, postexercise decreases in left ventricular output, which may indicate left ventricular failure, have been reported in patients receiving the drug. Edema, palpitation, phlebitis or thrombophlebitis, cyanosis, ventricular premature complexes, and bradycardia have been reported in less than 1% of clozapine-treated patients. Although a causal relationship has not been established, atrial or ventricular fibrillation, congestive heart failure, pericarditis, and pericardial effusions also have been reported during postmarketing surveillance in patients receiving the drug.

Rare instances of sudden, unexplained death have been reported in psychiatric patients, with or without associated antipsychotic drug treatment, and the relationship between sudden death and antipsychotic drug use is unknown. Some autopsy results have suggested that clozapine-treated patients have died from cardiac arrest and uncompensated cardiac disease, or from other causes such as renal insufficiency or severe alcohol abuse. A causal relationship between clozapine use and sudden death has not been established. (See Cautions: Geriatric Precautions.)

■ **Autonomic Nervous System Effects** Adverse autonomic nervous system effects occur in more than 5% of patients receiving clozapine. Dry mouth occurs frequently, but hypersalivation, an apparently paradoxical effect considering the drug's potent anticholinergic activity, is more common. (See Cautions: GI Effects.)

Other autonomic nervous system effects of clozapine include hyperhidrosis, decreased sweating, visual disturbances, nasal congestion, and pallor. Numbness, polydipsia, hot flushes (flashes), dry throat, and mydriasis have been reported in less than 1% of clozapine-treated patients.

■ **Hepatic Effects** Transient increases in liver function test results, including serum aminotransferases (transaminases), LDH, and alkaline phosphatase, may occur with clozapine therapy, usually with no accompanying physical signs or symptoms. Clozapine-induced changes in liver function test results may be more pronounced than those with other tricyclic antipsychotic agents. Clozapine causes slight liver hyperplasia in rats; hyperplasia was reversible and no histologic changes were detectable. Clozapine occasionally causes slight elevations of bilirubin concentration. Cholestasis, hepatitis, and jaundice have been reported in patients receiving clozapine during postmarketing surveillance; however, a causal relationship to the drug has not been established.

■ **Endocrine and Metabolic Effects** Severe hyperglycemia, sometimes associated with ketoacidosis, hyperosmolar coma, or death, has been reported in patients receiving certain atypical antipsychotic agents, including clozapine. While confounding factors such as an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population make it difficult to establish with certainty the relationship between use of agents in this drug class and glucose abnormalities, epidemiologic studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotic agents included in the studies (e.g., clozapine, olanzapine, quetiapine, risperidone). (See Cautions: Precautions and Contraindications.)

Precise risk estimates for hyperglycemia-related adverse events in patients

treated with atypical antipsychotics currently are not available. While some evidence suggests that the risk for diabetes may be greater with some atypical antipsychotics (e.g., clozapine, olanzapine) than with others (e.g., quetiapine, risperidone) in the class, available data are conflicting and insufficient to provide reliuble estimates of relative risk assoeiated with use of the varions atypieal antipsychotics.

Clozapine causes only a brief, transient elevation of prolactin concentration. (See Pharmacology: Neuroendocrine Effects.) Because the drug's effects on prolactin are only minor, prolactin-dependent effects such as galactorrhea and amenorrheu usually are not associated with clozapine therapy. Breast pain or discomfort has been reported in less than 1% of clozapine-treated patients.

Clozapine may cause increased appetite, polyphagia, and weight gain in a substantial proportion (approximately one-third) of patients. Some clinicians suggest that the potential for weight gain with clozapine therapy may be similar to that with other antipsychotic therapy; others state that they have observed greater weight gain with clozapine in some patients. In the 2-year InterSePT trial, weight gain reportedly occurred in 31% of patients receiving clozapine compared with 56% of those receiving olanzapine. Some clozapine-treated patients reportedly have gained up to 1 kg weekly for 6 weeks. Weight gain may result from the drug's serotonergic-, histaminergic-, and adrenergic-blocking properties. Weight gain has been reported to be a problem for some patients during long-term therapy with clozapine and may be a major cause of outpatient noncompliance. Some clinicians suggest using exercise and active measures (e.g., dietary counseling) to control dietary intake in clozapine-treated patients.

Hyperuricemia, hyponatremia, weight loss, and decreased serum cholesterol concentrations also have been reported in patients receiving clozapine, although a causal relationship to the drug has not been established. In addition, hypercholesterolemia and hypertriglyceridemia have been reported very rarely during postmarketing experience with the drug.

Small decreases in protein-bound iodine or thyroxine concentrations have heen reported in some patients receiving clozapine, but these values remained within normal limits.

■ **GI Effects** Increased salivation may occur in approximately one-third of patients receiving clozapine; in some studies, hypersalivation was reported in up to 75–85% of clozapine-treated patients. In the InterSePT trial, increased salivation reportedly occurred in 48% of patients receiving clozapine compared with 6% of those receiving olanzapine. Salivation may be profuse, very fluid, and particularly troublesome during sleep because of decreased swallowing. Since clozapine exhibits intrinsic anticholinergic properties, hypersalivation is an unexpected paradoxieal effect. A muscle-relaxant effect of the drug may contribute to hypersalivation, but the cause has not been fully elucidated. Difficulty in swallowing has been reported in a few clozapine-treated patients, and it has been suggested that the drug may cause esophageal dysfunction, which may contribute to or exacerbate the nocturnal hypersalivation associated with clozapine therapy. Some clozapine-treated patients develop tolerance to increased salivation within a few weeks. Occasionally, hypersalivation may be ameliorated by reduction of clnzapine dosage or cautious use of a peripherally acting anticholinergic drug; however, some clinicians generally advise against the use of anticholinergic therapy for this adverse effect because of possible potentiation of clozapine's anticholinergic activity.

Other GI effeets associated with clozapine therapy include constipation, diarrhea, nausea and vomiting, dyspepsia or heartburn, abdominal discomfort, and anorexia; some of these effects have been reported in more than 5% of patients. Constipation, nausea, vomiting, and dyspepsia reportedly occurred in 14–25% of patients receiving clozapine in the InterSePT trial compared with 8–10% of those receiving olanzapine. Although some clinicians advocate the use of metoclopramide (e.g., in doses less than 30 mg daily) for the treatment of clozapine-induced nausea, nther clinicians suggest that metoclopramide or other dopamine antagonists not be used or be used with extreme caution for the treatment of clozapine-induced nausea because of their potential for causing parkinsonian manifestations and tardive dyskinesia.

Abdominal distention, gastroenteritis, rectal bleeding, nervous stomach, abnormal stools, hematemesis, gastric ulcer, bitter taste, and eructation have been reported in less than 1% of patients receiving clozapine. Although a causal relationship to the drug has not been established, salivary gland swelling and paralytic ileus also have been reported in patients receiving clozapine.

■ **Genitourinary Effects** Genitourinary effects reported with clozapine therapy include polyuria, incontinence, urinary urgency or frequency, urinary retention, or other urinary abnormalities; enuresis; impotence; abnormal ejaculation; dysmenorrhea; and vaginal itch or infection. Priapism and acute interstitial nephritis also have been reported with clozapine therapy, although a causal relationship to the drug has not been established.

■ **Respiratory Effects** Clozapine-induced respiratory effects include throat discomfort, dyspneu or shortness of breath, coughing, pneumonia or pneumonia-like symptoms, rhinorrhea, hyperventilation, wheezing, bronchitis, laryngitis, and sneezing. Although a causal relationship to the drug has not been established, aspiration and pleural effusion also have been reported with clozapine therapy during postmarketing surveillance.

Respiratory depression or failure, including arrest requiring resuscitation, also has been reported in patients receiving clozapine, usually at initiation of therapy and particularly in patients receiving concomitant benzodiazepine therapy or in those with a history of recent benzodiazepine use. Some evidence indicates that the incidence of respiratory arrest and vascular collapse is about 1–2% of patients receiving clozapine concomitantly with a benzodiazepine. For additional precautionary information about this potential effect, see Benzodiazepines under Drug Interactions: CNS Depressants.

■ **Dermatologic and Sensitivity Reactions** Rash has been reported in 2% of patients receiving clozapine. Pruritus, eczema, erythema, bruising, dermatitis, petechiae, and urticaria have occurred in less than 1% of patients.

Hypersensitivity reactions, including photosensitivity, vasculitis, erythema multiforme, and Stevens-Johnson syndrome, have been reported with clozapine during postmarketing surveillance; however, a causal relationship to the drug has not been established.

■ **Musculoskeletal Effects** Adverse musculoskeletal effects reported in 1% of clozapine-treated patients include muscular weakness (myasthenic syndrome); back, neck, and leg pain; and muscle ache or spasm. Muscle twitching and joint pain have been reported less frequently. Rhabdomyolysis has been reported with clozapine during postmarketing surveillance; however, a causal relationship to the drug has not been established.

■ **Other Adverse Effects** Numb or sore tongue, chills (with or without fever), malaise, ear or eyelid disorder, ocular hyperemia, epistaxis, and nystagmus have been reported in 1% or less of patients receiving clozapine. Periorbital edema and narrow angle glaucoma also have been reported in clozapine-treated patients, although a causal relationship to the drug has not been established.

■ **Precautions and Contraindications** Clozapine shares many of the toxic potentials of other antipsychotic agents (e.g., phenothiazines), and the usual precautions associated with therapy with these agents should be observed. (See Cautions, in the Phenothiazines General Statement 28:16.08.24.)

Sedative Effects Because of initial sedative effects of the drug, patients should be cautioned that clozapine may impair their ability to perform activities requiring mental alertness or physical coordination (e.g., operating machinery, driving a motor vehicle), especially during the first few days of therapy. The recommendation for gradual dosage escalation should be closely followed. (See Dosage and Administration.)

Febrile Reactions During clozapine therapy, patients also may experience transient temperature elevations exceeding 38°C, with the peak incidence within the first 3 weeks of therapy. (See Cautions: Fever.) While this fever generally is benign and self-limiting, it may necessitate discontinuance of therapy. Occasionally, there may be an associated increase or decrease in leukocyte count and patients with fever should be carefully monitored to rule out the possibility of infection or the development of agranulocytosis. In the presence of high fever, the possibility of neuroleptio malignant syndrome also must be considered. (See Extrapyramidal Reactions under Cautions: Nervous System Effects.)

Anticholinergic Effects and Paralytic Ileus Clinical experience with clozapine in patients with concomitant systemic diseases is limited. However, clozapine has potent anticholinergic activity and should therefore be used with caution in individuals whose condition may be aggravated by anticholinergic effects (e.g., patients with prostatic hyperplasia, urinary retention, angle-closure [obstructive, narrow-angle] glaucoma). Clozapine therapy has been associated with varying degrees of impairment of intestinal peristalsis, ranging from constipation to intestinal obstruction, fecal impaction, and paralytic ileus, that rarely have been fatal. The manufacturers state that constipation may be treated initially by maintaining adequate hydration and by using bulk-forming laxatives. Consultation with a gastroenterologist may be necessary in more severe cases. Clozapine is contraindicated in patients with paralytic ileus.

Hepatic Dysfunction Because there have been reports of hepatie dysfunction, including hepatitis, in patients reeeiving clozapine, the drug should be used with caution in patients with preexisting liver disease. Liver function tests should be performed immediately in patients who develop nausea, vomiting, and/or anorexia during clozapine therapy. The manufacturers state that clozapine therapy should be discontinued in patients with marked elevations in serum aminotransferase concentrations or in those presenting with manifestations of jaundice.

Individuals with Phenylketonuria Individuals with phenylketonuria (i.e., homozygous genetic deficiency of phenylalanine hydroxylase) and other individuals who must restrict their intake of phenylalanine should be warned that clozapine 25- or 100-mg orally disintegrating tablets contain aspartame, which is metabolized in the GI tract to provide about 1.74 or 6.96 mg of phenylalanine, respectively, following oral administration.

Hyperglycemia and Diabetes Mellitus Because severe hyperglycemia, sometimes associated with ketoacidosis, hyperosmolar coma, or death, has been reported in patients receiving certain atypical antipsychotic agents, including clozapine, the manufacturers state that patients with preexisting diabetes mellitus in whom therapy with an atypical antipsychotic is initiated should be closely monitored for worsening of glucose control; those with risk factors for diabetes (e.g., obesity, family history of diabetes) should undergo fasting blood glucose testing upon therapy initiation and periodically throughout treatment. Any patient who develops manifestations of hyperglycemia (e.g., polydipsia, polyphagia, polyuria, weakness) during treatment with an atypieal antipsychotic should undergo fasting blood glucose testing. In some cases, patients who developed hyperglycemia while receiving an atypical antipsychotic have required continuance of antidiabetie treatment despite discontinuance of the suspect drug; in other cases hyperglycemia resolved with discontinuance of the antipsychotic.

Various experts have developed additional recommendations for the management of diabetes risks in patients receiving atypical antipsychotics; these include initial screening measures and regular monitoring (e.g., determination of diabetes risk factors; BMI determination using weight and height; waist circumference; blood pressure; fasting blood glucose; hemoglobin A_{1c} [HbA_{1c}]; fasting lipid profile), as well as provision of patient education and referral to clinicians experienced in the treatment of diabetes, when appropriate. Although some clinicians state that a switch from one atypical antipsychotic agent to another that has not been associated with substantial weight gain or diabetes should be considered in patients who experience weight gain (equal to or exceeding 5% of baseline body weight) or develop worsening glycemia or dyslipidemia at any time during therapy, such recommendations are controversial because differences in risk of developing diabetes associated with use of the different atypical antipsychotics remain to be fully established. Many clinicians consider antipsychotic efficacy the most important factor when making treatment decisions and suggest that detrimental effects of switching from a beneficial treatment regimen also should be considered in addition to any potential for exacerbation or development of medical conditions (e.g., diabetes). Decisions to alter drug therapy should be made on an individual basis, weighing the potential risks and benefits of the particular drug in each patient.

Cardiovascular Effects Clozapine should be used with caution in patients with cardiovascular and/or pulmonary disease because the drug may cause tachycardia, hypotension, and cardiac and/or respiratory arrest. In such patients, the recommendation for gradual dosage titration following a low initial dose should be observed carefully. (See Dosage and Administration: Dosage.)

Analyses of postmarketing surveillance data suggest that clozapine is associated with an increased risk of potentially fatal myocarditis, particularly during the first month of therapy. Immediate discontinuance of the drug is recommended in cases of suspected myocarditis. (See Myocarditis under Cautions: Cardiovascular Effects.)

Fatal pulmonary embolism has been reported with clozapine therapy. The possibility of pulmonary embolism should be considered in patients presenting with deep-vein thrombosis, acute dyspnea, chest pain, or other respiratory signs and symptoms.

Because cardiomyopathy has been reported in patients treated with clozapine, signs and symptoms suggestive of cardiomyopathy, particularly exertional dyspnea, fatigue, orthopnea, paroxysmal nocturnal dyspnea, and peripheral edema, should alert the clinician to perform further investigations. If the diagnosis of cardiomyopathy is confirmed, the drug should be discontinued unless the benefit to the patient clearly outweighs the risk.

Orthostatic hypotension with and without syncope can occur with clozapine therapy and may represent a continuing risk in some patients. Orthostatic hypotension is more likely to occur during initial titration of the drug in association with rapid dose escalation, but may even occur with the first dose at clozapine doses as low as 12.5 mg. Rarely, severe hypotension or orthostatic collapse can be profound and be accompanied by respiratory and/or cardiac arrest. Such adverse cardiovascular effects have occurred during initial treatment with the drug alone or in combination with benzodiazepines or other psychotropic agents. (See Drug Interactions: CNS Depressants.) Temporary reduction in dose or interruption of clozapine therapy may be required. Severe hypotensive effects also may be alleviated with standard measures (e.g., IV fluids, placing patient in Trendelenburg's position) and, if required, by the administration of norepinephrine or phenylephrine; epinephrine should *not* be used since a further lowering of blood pressure may occur. (See Drug Interactions: Hypotensive Agents.) Patients should be informed of the risk of orthostatic hypotension associated with use of clozapine, especially during the period of initial dosage titration. In addition, if clozapine therapy has been discontinued for more than 2 days, patients should be advised to contact their clinician for dosing instructions. (See Reinitiation of Therapy under Dosage: Psychotic Disorders, in Dosage and Administration.)

Seizures Clozapine is contraindicated in patients with uncontrolled seizure disorders.

Generalized tonic-clonic (grand mal) seizures have occurred in patients receiving clozapine, particularly in patients receiving high dosages (greater than 600 mg daily) and/or in whom plasma clozapine concentrations were elevated. (See Seizures under Cautions: Nervous System Effects.) Clozapine should be administered with extreme caution to patients having a history of seizure disorder or other factors possibly predisposing to seizure (e.g., abnormal EEG without a history of epilepsy, preexisting CNS pathology, history of electroconvulsive therapy or of perinatal or birth difficulties, family history of seizure or febrile convulsion). Because of the substantial risk of seizures associated with clozapine use, patients should be advised not to engage in any activity where sudden loss of consciousness could cause serious risk to themselves or others (e.g., operating heavy machinery, driving an automobile, swimming, climbing). In addition, the manufacturers recommend that general anesthesia be administered with caution in patients receiving clozapine therapy because of this and other adverse CNS effects associated with the drug. An anesthesiologist should be consulted regarding continuation of clozapine therapy in patients undergoing surgery involving general anesthesia.

Hematotoxicity Because of the substantial risk of agranulocytosis, a potentially life-threatening adverse event, clozapine therapy should be reserved for use in the treatment of severely ill schizophrenic patients who fail to respond to adequate courses of standard antipsychotic therapy or for suicide risk reduction in patients with schizophrenia or schizoaffective disorder who are judged to be at risk for recurrent suicidal behavior. Patients should be warned of this risk and informed that clozapine is available only through distribution systems that ensure baseline and periodic monitoring of leukocyte counts according to a prescribed schedule prior to delivery of the next supply of medication. (See Cautions: Hematologic Effects.) In addition, patients should be advised to report immediately the development of lethargy, malaise, weakness, fever, sore throat, mucous membrane ulceration, or any other potential manifestation of infection. Particular attention should be paid to any flu-like symptoms or other complaints that might suggest infection. Patients who develop agranulocytosis or severe leukopenia/granulocytopenia (leukocyte less than 2000/mm^3 and ANC less than 1000/mm^3) while receiving clozapine should *not* be rechallenged with the drug. Although it is not known whether the risk of agranulocytosis is increased, clozapine generally should be avoided or used with caution in patients with a history of agranulocytosis induced by other drugs.

Clozapine is contraindicated in patients with myeloproliferative disorders, preexisting bone marrow depression, or a history of clozapine-induced agranulocytosis or severe granulocytopenia. The drug also is contraindicated in patients receiving other agents that may cause agranulocytosis or suppress bone marrow function and in those with severe CNS depression or comatose states from any cause. Although the manufacturers do not mention it as a specific contraindication to clozapine therapy, the American Psychiatric Association recommends that clozapine therapy be avoided in schizophrenic patients who are unable or unwilling to comply with the close monitoring that is necessary to detect possible adverse hematologic effects associated with the drug.

Other Precautions and Contraindications Clozapine is contraindicated in patients with a history of hypersensitivity to the drug or any ingredient in the formulation.

■ **Pediatric Precautions** Safety and efficacy of clozapine in children and adolescents younger than 16 years of age have not been established. However, clozapine has been used in a limited number of children and adolescents with treatment-refractory schizophrenia (see Pediatric Considerations under Psychotic Disorders: Schizophrenia, in Uses) and results of at least one randomized, double-blind clinical study indicate that adverse hematologic effects were a major concern for children and adolescents receiving clozapine†. Although no cases of agranulocytosis occurred in this study, 24% of these children and adolescents experienced mild‡ to moderate neutropenia during 2 years of follow-up; compared with an estimated cumulative risk of 1.5–2% of developing neutropenia in adults. The precise mechanism by which clozapine induces agranulocytosis is not known, but a higher concentration of the metabolite norclozapine, which has been associated with hematopoietic toxicity in children and adolescents receiving clozapine, has been suggested as a possible reason for the increased risk in this age group.

In addition to adverse hematologic effects, clinically important seizure activity (e.g., epileptiform spikes, myoclonus, tonic-clonic seizures) also has been reported in children and adolescents with no previous history of epilepsy who received clozapine. In some cases, EEG abnormalities were associated with clinical deterioration (i.e., increased aggression, psychosis, irritability). Because some children and adolescents responded behaviorally to reduced dosages of clozapine and the addition of an anticonvulsant (e.g., valproate), it has been suggested that the EEG may be a sensitive indicator of clozapine toxicity in children as well as in adults.

■ **Geriatric Precautions** Clinical studies of clozapine did not include sufficient numbers of patients 65 years of age and older to determine whether geriatric patients respond differently than younger patients. Because geriatric patients may be at increased risk for certain cardiovascular (e.g., orthostatic hypotension, tachycardia) and anticholinergic effects of the drug (e.g., constipation, urinary retention in the presence of prostatic hypertrophy), clozapine should be used cautiously in this age group. In addition, geriatric patients generally are more sensitive than younger patients to drugs that affect the CNS; data from clinical studies indicate that the incidence of tardive dyskinesia appears to be highest among geriatric patients, especially women. In general, dosage should be titrated carefully in geriatric patients, usually initiating therapy at the low end of the dosage range; the greater frequency of decreased hepatic, renal, and/or cardiac function and of concomitant disease and drug therapy observed in the elderly also should be considered.

Geriatric patients with dementia-related psychosis treated with atypical antipsychotic drugs appear to be at an increased risk of death compared with that among patients receiving placebo. Analyses of 17 placebo-controlled trials (average duration of 10 weeks) revealed an approximate 1.6- to 1.7- fold increase in mortality among geriatric patients receiving atypical antipsychotic drugs (i.e., aripiprazole, olanzapine, quetiapine, risperidone) compared with that in patients receiving placebo. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5% compared with a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Clozapine is not approved for the treatment of dementia-related psychosis.

■ **Mutagenicity and Carcinogenicity** Clozapine did not exhibit carcinogenic potential in long-term studies in mice and rats receiving dosages approximately 7 times (on a mg/kg basis) the usual human dosage. Clozapine also did not exhibit genotoxic or mutagenic effects when assayed in appropriate bacterial and mammalian tests.

■ **Pregnancy, Fertility, and Lactation** Reproduction studies in rats and rabbits using clozapine dosages approximately 2–4 times the usual human dosage have not revealed evidence of harm to the fetus. There are no adequate and controlled studies to date using clozapine in pregnant women, and the drug should be used during pregnancy only when clearly needed. Patients receiving clozapine should notify their physician if they become or plan to become pregnant during therapy.

Reproduction studies in rats and rabbits using clozapine dosages approximately 2–4 times the usual human dosage have not revealed impaired fertility.

Studies in animals suggest that clozapine may be distributed into milk. Because of the potential for serious adverse reactions to clozapine in nursing infants, a decision should be made whether to discontinue nursing or the drug, taking into account the importance of the drug to the woman.

Drug Interactions

The manufacturers state that the potential risks of using clozapine in combination with other drugs have not been evaluated systematically. However, clinical experience and/or theoretical considerations indicate that certain potential drug interactions exist.

■ **Myelosuppressive Agents** The mechanism of clozapine-induced agranulocytosis is unknown; however, the possibility that causative factors may interact synergistically to increase the risk and/or severity of bone marrow suppression warrants consideration. (See Cautions: Hematologic Effects.) Therefore, clozapine should not be used with other agents having a well-known potential to suppress bone marrow function. That clozapine may be directly myelotoxic has been suggested by in vitro study of the serum and bone marrow of a patient who died during multidrug therapy that included clozapine and carbamazepine.

■ **Drugs Affecting the Seizure Threshold** Clozapine may lower the seizure threshold and has caused seizures in some patients (see Seizures under Cautions: Nervous System Effects); therefore, concomitant therapy with other agents that lower the seizure threshold generally should be avoided if possible. If such combined therapy is required, caution should be exercised (e.g., using low initial dosages of clozapine with slow upward titration) and the possible need for anticonvulsant therapy considered.

■ **CNS Depressants** ***Benzodiazepines*** Severe hypotension (including absence of measurable blood pressure), respiratory or cardiac arrest, and loss of consciousness have been reported in several patients who received clozapine concomitantly with or following benzodiazepine (i.e., flurazepam, lorazepam, diazepam) therapy. Such effects occurred following administration of 12.5–150 mg of clozapine concurrently with or within 24 hours of the benzodiazepine, but patients generally have recovered within a few minutes to hours, usually spontaneously; the reactions usually developed on the first or second day of clozapine therapy. Although a causal relationship has not definitely been established and such effects also have been observed in clozapine-treated patients who were not receiving a benzodiazepine concomitantly (see Cautions: Cardiovascular Effects), death resulting from respiratory arrest reportedly has occurred in at least one patient receiving clozapine concomitantly with a benzodiazepine. An increased incidence of dizziness and sedation and greater increases in liver enzyme test results also have been reported with this drug combination.

The manufacturers of clozapine recommend caution when the drug is initiated in patients receiving benzodiazepine therapy. However, some clinicians advise that, pending further accumulation of data, greater precaution should be exercised. These clinicians recommend that since initial titration of clozapine may cause respiratory arrest requiring resuscitation, which may be potentiated by recent benzodiazepine therapy, these latter drugs should be discontinued for at least 1 week prior to initiating clozapine therapy. In addition, these clinicians recommend that clozapine therapy be initiated in a setting where facilities for resuscitation are immediately available for the first few hours after administration of the first dose. Other clinicians, however, state that institutional initiation of clozapine therapy may not be necessary or practical, although they recommend slow and cautious initiation of the drug at low dosages.

Other CNS Depressants Clozapine may be additive with, or may potentiate the action of, other CNS depressants such as opiates or other analgesics, barbiturates or other sedative/hypnotics, general anesthetics, or alcohol. When clozapine is used concomitantly with other CNS-depressant drugs, caution should be exercised to avoid excessive sedation.

■ **Other CNS-active Agents** Although a causal relationship has not been established, at least one death has been reported with concomitant clozapine and haloperidol therapy. A 31-year-old woman with schizophrenia developed respiratory arrest, became comatose, and died 4 days after receiving 10 mg of haloperidol orally and a single 100-mg dose of clozapine IM. The patient had been maintained on oral clozapine 200 mg daily for 2 years and also had received smaller doses of haloperidol concomitantly with clozapine therapy without unusual adverse effect.

Neuroleptic malignant syndrome has been reported rarely with clozapine therapy alone and during concomitant therapy with clozapine and carbamazepine, lithium, or other CNS-active agents. (See Extrapyramidal Reactions under Cautions: Nervous System Effects.)

Concomitant use of clozapine and lithium may also increase the risk of seizures.

Orthostatic hypotension, sometimes accompanied by profound collapse and respiratory and/or cardiac arrest, has been reported rarely with clozapine therapy alone and during concomitant therapy with other psychotropic agents. Although the clinical importance of this interaction has not been fully established, the manufacturers of clozapine state that the drug should be initiated with caution in patients receiving other psychotropic agents.

■ **Drugs Undergoing Hepatic Metabolism or Affecting Hepatic Microsomal Enzymes** Clozapine is a substrate for many cytochrome P-450 (CYP) isoenzymes, in particular 1A2, 2D6, and 3A4. The risk of metabolic interactions caused by an effect on an individual isoform is therefore minimized. However, concomitant use of clozapine with drugs that inhibit the CYP enzyme system (e.g., caffeine, cimetidine, erythromycin, quinidine, certain antidepressants, phenothiazines, type IC antiarrhythmics [e.g., propafenone, flecainide, encainide]) may result in increased plasma concentrations of clozapine. Conversely, concomitant use of clozapine with drugs that induce the CYP enzyme system (e.g., carbamazepine, nicotine, phenytoin, rifampin) may result in decreased plasma concentrations of clozapine. Caution should be observed if clozapine is used concomitantly with these drugs. Dosage adjustments of clozapine and/or other drugs may be necessary in patients receiving concomitant therapy with drugs that inhibit or induce the CYP enzyme system.

Phenytoin Substantial reductions in plasma clozapine concentrations and exacerbation of psychosis have been reported in patients receiving concomitant therapy with clozapine and phenytoin, and an increase in clozapine dosage may be required to reestablish antipsychotic efficacy in patients receiving such combined therapy. In 2 patients stabilized for 1–2 weeks on a given dosage of clozapine, addition of phenytoin for prevention of clozapine-induced seizures resulted in a 65–85% decrease in steady-state plasma clozapine concentrations. Control of psychotic manifestations was regained in both patients by gradually increasing clozapine dosage. Although the mechanism of this potential interaction has not been established, it has been suggested that phenytoin may increase clozapine metabolism via stimulation of the hepatic cytochrome P-450 (microsomal) enzyme system and/or displacement of clozapine from protein binding sites, or that phenytoin may decrease absorption of clozapine from the GI tract. Pending further study, clozapine-treated patients in whom phenytoin therapy is initiated should be monitored carefully for reemergence of psychotic manifestations and clozapine dosage adjusted accordingly.

Carbamazepine Concomitant use of clozapine and carbamazepine has been shown to decrease clozapine concentrations by about 40–50%. In addition, neuroleptic malignant syndrome has been reported rarely with clozapine therapy alone and during concomitant therapy with carbamazepine. (See Extrapyramidal Reactions under Cautions: Nervous System Effects.) Therefore, the manufacturers of clozapine state that concomitant use of these agents generally is not recommended. However, if clozapine and carbamazepine are used concomitantly, it should be considered that discontinuance of carbamazepine may result in increased plasma concentrations of clozapine.

Selective Serotonin-reuptake Inhibitors Concomitant use of clozapine with certain selective serotonin-reuptake inhibitors (SSRIs), including citalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline, can increase plasma concentrations of clozapine and enhance clozapine's pharmacologic effects secondary to suspected inhibition of clozapine metabolism by SSRIs. Modest (less than twofold) elevations in plasma clozapine concentrations have been reported in patients receiving clozapine concomitantly with certain SSRIs (i.e., fluoxetine, paroxetine, sertraline), although substantial (threefold) increases in trough plasma clozapine concentrations have occurred in patients receiving concomitant therapy with clozapine and fluvoxamine. The manufacturers of clozapine state that caution should be exercised and patients should be closely monitored when clozapine is used in patients receiving SSRIs, and a reduction in clozapine dosage should be considered.

■ **Drugs with Anticholinergic Activity** Clozapine has potent anticholinergic effects and may potentiate the actions of other drugs possessing such activity (e.g., antimuscarinics).

■ **Hypotensive Agents** Clozapine may be additive with or potentiate the actions of hypotensive agents. In addition, the administration of epinephrine should be avoided in the treatment of clozapine-induced hypotension because of a possible reversal of epinephrine's vasopressor effects and subsequent further lowering of blood pressure.

■ **Smoking** Some evidence indicates that cigarette smoking may substantially reduce plasma clozapine concentrations. Limited data indicate that average plasma clozapine concentrations following a given dose in smokers average 60–82% of those in nonsmokers. Changes in liver enzyme activity and/or the GI tract induced by nicotine or other substances present in cigarette smoke may explain these reduced concentrations. These effects should be considered when adjusting clozapine dosage in patients who smoke cigarettes.

Acute Toxicity

■ **Pathogenesis** Acute toxicity studies in animals revealed that the LD_{50}s for clozapine administered orally, IV, or intraperitoneally are approximately 145–325, 58–61, and 90 mg/kg, respectively.

Although the acute lethal dose of clozapine in humans remains to be established, fatal overdoses with the drug generally have been associated with doses exceeding 2.5 g. However, there also have been reports of patients surviving overdoses that substantially exceeded 4 g of the drug.

■ **Manifestations** In general, overdosage of clozapine may be expected to produce effects that are extensions of pharmacologic and adverse effects. The most commonly reported signs and symptoms of clozapine overdosage have been altered states of consciousness and CNS depression (e.g., drowsiness, delirium, coma), tachycardia, cardiac arrhythmias, hypotension, respiratory depression or failure, aspiration, pneumonia, and hypersalivation. Seizures have occurred with overdosage in some patients. (See Seizures under Cautions: Nervous System Effects.)

A 24-year-old woman who ingested 2 g in excess of her prescribed daily dosage (i.e., total ingestion approximately 3 g within a 24-hour period) had a tonic-clonic (grand mal) seizure; her plasma clozapine concentration 1 hour after the seizure (1313 ng/mL) was 500 ng/mL higher than usual, but she recovered uneventfully. In a 50-year-old woman who ingested 1 g of clozapine, the only manifestations were confusion and hallucinations lasting about 48 hours. A 26-year-old man who ingested approximately 3 g of clozapine became drowsy, agitated, and disoriented; he also had visual hallucinations, dysarthria, tachycardia, and hypersalivation. The patient was treated with gastric lavage and also received diazepam, digitalis, and anti-infectives, but continued to exhibit manifestations of severe central anticholinergic toxicity. Administration of physostigmine salicylate 2 mg by slow IV injection resulted in improvement in the patient's mental status within minutes; however, symptoms recurred after approximately 1 hour. Symptoms finally remitted 18–24 hours later with no further treatment.

■ **Treatment** Treatment of clozapine overdosage generally requires symptomatic and supportive care, including monitoring of cardiac and vital signs. There is no specific antidote for the management of clozapine overdosage.

The manufacturers recommend establishing and maintaining an airway and ensuring adequate ventilation and oxygenation. Activated charcoal, which may be used with sorbitol, may be as or more effective than emesis or gastric lavage and should be considered in the treatment of clozapine overdosage. Electrolyte and acid-base balance should be monitored and adjusted accordingly. Peritoneal dialysis or hemodialysis is of limited value in the treatment of clozapine overdosage because the drug is almost totally bound to serum protein. Forced diuresis, hemoperfusion, and exchange transfusion also are unlikely to be of benefit. While physostigmine salicylate may be useful as adjunctive treatment if severe anticholinergic toxicity is present, the drug should *not* be used routinely because of its potential adverse effects.

Epinephrine should *not* be used for treating clozapine-induced hypotension, since clozapine can reverse epinephrine's vasopressor effects and cause a further lowering of blood pressure. Because of potential additive anticholinergic effects, quinidine or procainamide should be avoided when treating clozapine-induced arrhythmias. Surveillance of the patient should be continued for several days following overdosage because of the risk of delayed effects. In managing clozapine overdosage, the clinician should consider the possibility of multiple drug involvement.

Chronic Toxicity

Physical and/or psychological dependence have not been reported in patients receiving clozapine.

Chronic toxicity studies in mice, rats, dogs, and monkeys have revealed no specific organ toxicity. After 1 year of treatment with clozapine, a brown discoloration caused by increased lipopigment was observed in various organs in rats; this change normally appears with increasing age. Discoloration was noted in the thyroid, brain, liver, kidney, heart, spleen, and skeletal muscle of rats, but such increased pigmentation was not associated with deleterious changes. The liver did show slight, dose-dependent changes, including centrolobular vacuolation, hepatocyte swelling, and increased weight.

Pharmacology

Clozapine is a dibenzodiazepine-derivative antipsychotic agent. While clozapine shares some of the pharmacologic actions of other antipsychotic agents, the drug has been described as an atypical or second-generation antipsychotic agent since many of its CNS effects differ from those of typical agents (e.g., butyrophenones, phenothiazines). In fact, these apparent differences in actions on neostriatal dopaminergic receptors have led some investigators to question the importance of the dopaminergic system in mediating the therapeutic effects of neuroleptic drugs. The exact mechanism of antipsychotic action of clozapine has not been fully elucidated but appears to be more complex than that of conventional (typical) antipsychotic agents and may involve serotonergic, adrenergic, and cholinergic neurotransmitter systems in addition to more selective, regionally specific effects on the mesolimbic dopaminergic system. Because of differences in the neurologic effects of clozapine, the drug is not considered a classic neuroleptic agent.

■ **Nervous System Effects** Although the precise mechanism of action of antipsychotic drugs has not been fully elucidated, current data suggest that the therapeutic effects of these agents involve antagonism of dopaminergic systems in the CNS. In animals, classic neuroleptic agents increase muscle tone or induce postural abnormalities (catalepsy), antagonize stereotyped behaviors induced by the dopamine agonists apomorphine and amphetamine, accelerate dopamine turnover in various areas of the brain, increase serum prolactin concentrations, and produce dopamine receptor hypersensitivity on repeated administration. These effects, many of which have been attributed to blockade of dopamine receptors in the neostriatum, form the basis for the hypothesis that idiopathic psychoses result from overactivity of dopamine in neostriatal and mesolimbic systems.

Unlike typical antipsychotic agents, clozapine exerts relatively weak antidopaminergic action within the neostriatum and has a low propensity to produce extrapyramidal effects or stimulate prolactin secretion. While some studies have demonstrated that relatively high doses of clozapine suppress the conditioned avoidance response in animals, which is a characteristic of typical antipsychotic agents, this response is not completely blocked by clozapine, and tolerance to this effect develops rapidly with repeated dosing, suggesting that it is not specifically related to clozapine's antipsychotic action. Further research is needed to elucidate fully clozapine's antipsychotic action in terms of the drug's serotonergic, adrenergic, muscarinic, and peptidergic effects and their influences on functional alterations in dopamine receptor systems.

Antidopaminergic Effects The therapeutic effects of antipsychotic drugs are thought to be mediated by dopaminergic blockade in the mesolimbic and mesocortical areas of the CNS, while antidopaminergic effects in the neostriatum appear to be associated with extrapyramidal effects. Several (at least 5) different types or subtypes of dopamine receptors have been identified in animals and humans. The relative densities of these receptors and their distribution and function vary for different neuroanatomical regions, and clozapine's unique effects may be secondary to regionally specific receptor interactions and/or other effects on dopaminergic neurons. Results obtained from receptor binding, behavioral, metabolic, and electrophysiologic studies of clozapine as well as the apparently low incidence of extrapyramidal effects associated with clozapine therapy suggest that the drug is more active in the mesolimbic than the neostriatal dopaminergic system. Results of some studies suggest that clozapine is more effective in increasing dopamine turnover and release in the nucleus accumbens or olfactory tubercle than in the neostriatum with acute administration and that it reduces dopamine release in the accumbens but not in the neostriatum during prolonged administration, which suggests preferential effects on dopaminergic function in the limbic system. However, conflicting data (i.e., no preferential limbic effects) also have been reported with both acute and repeated administration of the drug, which may reflect differences in analytical techniques, regional differences in drug distribution or receptor affinity, or other variables.

Some evidence suggests that the effects of clozapine on dopamine metabolism in the neostriatum are dose related; unlike typical antipsychotic drugs, clozapine appears to increase striatal dopamine turnover only at suprathera-peutic doses. Single high doses (80 mg/kg intraperitoneally) of clozapine in rats interfere with dopaminergic transmission by blocking postsynaptic dopamine receptors and causing a compensatory increase in dopaminergic neuronal firing, while lower doses retard dopamine release. Clozapine appears to increase striatal dopamine content when given either in single high doses or repeated low doses, and low doses of the drug reportedly decrease the degradation of dopamine to 3-methoxy-4-hydroxyphenylacetic acid (homovanillic acid, HVA) in the neostriatum. In a rodent model of tardive dyskinesia, single low doses (up to 1.2 mg/kg intraperitoneally) of clozapine suppressed ketamine-induced linguopharyngeal movements, which resemble symptoms of tardive dyskinesia (e.g., tongue protrusions, retrusions, and swallows), by 15–75% compared with baseline measures. At clozapine doses of 4.8 mg/kg or higher, clozapine caused total suppression of these movements, and duration of suppression became dose dependent. Since suppression of abnormal linguopharyngeal movements occurred at doses substantially lower than those reported to alter dopamine turnover, it has been suggested that doses of the drug lower than those required for antipsychotic activity may be useful for treating antipsychotic-induced tardive dyskinesia.

Current evidence suggests that the clinical potency and antipsychotic efficacy of both typical and atypical antipsychotic drugs generally are related to their affinity for and blockade of central dopamine D_2 receptors; however, antagonism at D_2 receptors does not appear to account fully for the antipsychotic effects of clozapine.

In in vitro studies, clozapine is a comparatively weak antagonist at D_2 receptors. Clozapine's affinity for the D_2 receptor on a weight basis reportedly is approximately one-third (33%) that of loxapine, one-tenth (10%) that of chlorpromazine, and one-fiftieth (2%) that of haloperidol. In oral dosages of 300 mg daily, clozapine produces a 40–65% occupancy of D_1 and D_2 receptors. During long-term clozapine therapy, the relative occupancy of D_1 receptors may become greater than that of D_2 receptors, or the long-term effects of the drug on D_2 receptors may be antagonized by its nondopaminergic properties. Although the in vitro affinity of clozapine for D_1 and D_2 receptors in brain tissue of animals appears to be similar, the drug's in vivo effects in many animals resemble those of D_1 receptor-specific antagonists. Compared with typical antipsychotic agents, clozapine shows greater affinity for and appears to produce greater blockade of neostriatal dopamine D_1 receptors; other data suggest that clozapine preferentially but not selectively antagonizes D_1 receptor-mediated functions. At clinically effective dosages, however, the drug produces comparable blockade of D_1 and D_2 receptors and less D_2 blockade than typical antipsychotic drugs. Long-term administration of clozapine leads to a 35–50% "up-regulation" of D_1 receptors, which is comparable to that observed with administration of selective D_1 antagonists; however, the number of D_2 receptors is not changed, possibly because the proportion of occupied receptors required to elicit a response is less for D_1 than for D_2 receptors. Limited evidence suggests that D_1 receptors may exist either coupled to adenylate cyclase or in uncoupled form. Clozapine appears to be a potent, competitive inhibitor of

dopamine-stimulated adenylate cyclase in vitro, and the adenylate cyclase-coupled state of the D_1 receptor binds clozapine with high affinity; in contrast, typical antipsychotic agents bind preferentially to the uncoupled D_1 receptor.

Although their role in eliciting the pharmacologic effects of antipsychotic agents remains to be fully elucidated, dopamine D_3, D_4, and D_5 receptors also have been identified; clozapine appears to have a much higher affinity for the D_4 receptor than for D_2 or D_3 receptors. Current information on D_3-receptor affinity for antipsychotic drugs suggests that most antipsychotics probably bind to both D_2 and D_3 receptors, although with higher affinity to D_2 receptors; however, the magnitude of the difference in D_3- versus D_2-receptor binding is much less with atypical antipsychotics such as clozapine, suggesting that effects on D_3 receptors may play a more important role in the pharmacologic actions of atypical versus typical antipsychotic drugs. The high affinity of the D_4 receptor for clozapine and its preferential distribution in cortical and limbic areas in animals may explain, in part, the relative lack of tardive dyskinesia and extrapyramidal effects during clozapine therapy. The cloning of a gene for a neuron-specific dopamine D_5 receptor, which binds antipsychotic drugs with similar affinity as the D_1 receptor but has a tenfold higher affinity for dopamine, also has been reported.

Clozapine's clinical potency appears to be twice that of chlorpromazine on a weight basis, although the drug demonstrates considerably weaker D_2-receptor binding affinity than chlorpromazine and appears to be much less potent in elevating dopamine metabolite concentrations in the brain. Clozapine produces a more potent blockade of central serotonergic, adrenergic, histamine H_1, and muscarinic receptors than typical antipsychotic agents; also, long-term administration of clozapine enhances striatal D_1-receptor function in animals and results in "down-regulation" of cortical, type 2 serotonergic (5-HT_2) receptors, suggesting that an interaction between these central neurotransmitter systems may be important for the drug's antipsychotic efficacy. Antagonism at cholinergic and α_1-adrenergic receptors in the mesolimbic system, compensating for dopaminergic blockade in the neostriatum, may explain the apparent selectivity and low incidence of extrapyramidal effects seen with clozapine. The amygdala also may be a site of action for clozapine, since repeated administration of the drug selectively induces supersensitivity to locally applied dopamine in the amygdala, and amygdaloid neurons are excited by clozapine but generally unresponsive to other antipsychotic agents (e.g., haloperidol).

Further studies are needed to elucidate the mechanism of clozapine's antipsychotic effects in various areas of the CNS.

Neurophysiologic Effects In vitro and in vivo electrophysiologic studies in animals demonstrate different sensitivities of various brain areas to clozapine-mediated postsynaptic receptor blockade. While clozapine increases firing rates of both nigrostriatal (A9 pathway) and mesolimbic (A10 pathway) dopaminergic neurons after acute administration, only mesolimbic dopaminergic neurons exhibit prolonged depolarization blockade following repeated exposure to the drug. Repeated administration of typical antipsychotic agents (e.g., haloperidol) concomitantly with an anticholinergic agent (trihexyphenidyl) or an α_1-adrenergic blocking drug (prazosin) mimicked these selective effects of clozapine on mesolimbic versus nigrostriatal dopaminergic neurons, suggesting that α_1-adrenergic blocking and/or anticholinergic effects may be responsible, in part, for the differential effects of clozapine in these midbrain areas. Some evidence suggests that the nucleus accumbens has greater sensitivity for clozapine than do other regions, which may explain why the drug appears to produce depolarization blockade of dopaminergic neurons only in the mesolimbic area. However, some studies have shown that neurons in the neostriatum also may be responsive to clozapine. Clozapine reportedly produces an increase in dopamine metabolites in the neostriatum comparable to or even greater than that in the nucleus accumbens. Demonstrable dopamine-receptor supersensitivity in both striatal and limbic forebrain regions also has been reported with prolonged clozapine administration. Therefore, it has been suggested that there may be a dissociation between the effects of clozapine on synthesis and metabolism of dopamine within nigrostriatal neurons and the drug's effects on neuronal firing rate and dopamine release.

Adrenergic Effects Clozapine has adrenergic-blocking activity, which may be partially responsible for the sedation, muscle relaxation, and cardiac effects observed in patients receiving the drug. (See Cautions: Cardiovascular Effects.) Although the drug appears to have relatively weak α-adrenergic blocking effects compared with typical antipsychotic drugs such as chlorpromazine, clozapine's in vitro affinity (relative to dopamine D_2-receptor affinity) for α_1- and α_2-adrenergic receptors is much higher than that of other antipsychotics, including chlorpromazine, haloperidol, loxapine, and thioridazine. Clozapine increases the number and sensitivity of α_1-adrenergic, but not dopamine D_2, receptors. The turnover rate of epinephrine and norepinephrine also may be increased by clozapine, but to a lesser extent than that of dopamine. Substantial increases in plasma norepinephrine concentrations, which decreased following discontinuance of the drug but remained above basal levels, have been noted in both schizophrenic and healthy individuals receiving clozapine; such increases may be the result of feedback mechanisms activated by adrenergic blockade.

Clozapine's central α_1-adrenergic blocking activity also may be responsible for the dose-related hypothermia observed in mice given the drug. Clozapine also induces ataxia and blocks amphetamine-induced hyperactivity in mice, although repeated administration of the drug results in almost complete tolerance to these effects. It has been suggested that clozapine's α_1-adrenergic blocking properties may, in part, mediate its differential effects on midbrain dopamine receptors and be responsible for its relative lack of extrapyramidal effects. However, the clinical importance of the drug's α_1-adrenergic effects has not been fully elucidated.

Anticholinergic Effects Clozapine possesses potent anticholinergic activity in vitro; the drug's affinity for muscarinic receptors substantially exceeds that of other antipsychotic agents (e.g., 39–50 times greater than that of chlorpromazine and 100 times that of loxapine) and may be similar to that of tricyclic antidepressants and antimuscarinic antiparkinsonian agents (e.g., benztropine, trihexyphenidyl). It has been suggested that clozapine's anticholinergic effects may be more potent centrally than peripherally and that adverse anticholinergic effects generally are not dose limiting; however, peripheral anticholinergic effects such as dry mouth are common and may be troublesome. Clozapine-induced delirium, which reportedly has occurred with rapid dosage escalation, has been reversed by physostigmine; this suggests that clozapine has central antimuscarinic activity. Some evidence also suggests that clozapine's anticholinergic properties may counteract the effects of dopamine receptor blockade in the neostriatum and thus prevent extrapyramidal reactions. Limited data suggest that the propensity of antipsychotic drugs to cause extrapyramidal effects varies inversely with anticholinergic potency and antimuscarinic activity; however, the relatively potent anticholinergic activity of clozapine does not appear to account adequately for its atypical actions.

Serotonergic Effects It has been suggested that schizophrenia may involve a dysregulation of serotonin- and dopamine-mediated neurotransmission, and clozapine may at least partially restore a normal balance of neurotransmitter function, possibly through serotonergic regulation of dopaminergic tone. Clozapine blocks central type 2 serotonergic (5-HT_2) receptors; the drug also antagonizes central and peripheral type 3 serotonergic (5-HT_3) receptors. Long-term and acute administration of clozapine has produced down-regulation of 5-HT_2 receptors in the frontal cortex and neostriatum of male rats; single or repeated daily injections of clozapine also reduced the number of cortical 5-HT_2 receptors but did not change receptor affinity. In contrast to effects caused by typical antipsychotic agents, an increase in brain tryptophan, serotonin, and 5-hydroxyindoleacetic acid (5-HIAA) concentrations generally has been reported with clozapine administration in animals. It has been suggested that these effects might contribute to the pronounced sedative effects of clozapine, although increases in blood serotonin concentrations occurring during clozapine treatment in humans have been inconsistent and variable. (See Effects on Sleep under Pharmacology: Nervous System Effects.) Clozapine's serotonergic effects also reportedly may contribute to the drug's efficacy against negative symptoms of schizophrenia and to the weight gain observed during clozapine therapy. (See Cautions: Endocrine and Metabolic Effects.)

Effects on Other Central Neurotransmitters Clozapine appears to have important activity on the metabolism of γ-aminobutyric acid (GABA), which has inhibitory effects on dopaminergic neurons. In contrast to the effects of typical antipsychotic drugs, clozapine apparently augments GABA turnover in both the neostriatum and nucleus accumbens. Increases in neostriatal GABA turnover and release may attenuate extrapyramidal reactions, while a similar action in the nucleus accumbens may be related to antipsychotic efficacy.

Clozapine appears to have central histamine H_1-receptor blocking activity; such activity reportedly may be associated with sedation, hypotension, and weight gain. The drug's affinity (relative to dopamine D_2-receptor affinity) for histamine H_1-receptors is approximately 30 times that of chlorpromazine and 4 times that of loxapine.

Behavioral Effects in Animals Studies of the effects of clozapine on animal behavior routinely used to detect antipsychotic activity support its classification as an atypical antipsychotic drug. Such studies suggest that the neostriatum is relatively unresponsive to clozapine. Since the drug does not induce catalepsy or inhibit apomorphine-induced stereotypy, which are thought to be mediated principally by the nigrostriatal dopamine system, clozapine's antipsychotic activity appears to result from the drug's activity in other areas. Clozapine also does not block amphetamine-induced hyperactivity or apomorphine-induced emesis in animals as the typical antipsychotic agents do. Long-term administration of clozapine causes supersensitization of behaviors mediated by mesolimbic dopaminergic pathways (e.g., dopamine-induced locomotion) but not those mediated via neostriatal systems (e.g., dopamine-induced stereotypy). Long-term administration of clozapine in male rats caused a marked supersensitivity (of the same magnitude and duration as that of haloperidol) in the mesolimbic but not the nigrostriatal system. It has been suggested that supersensitivity of mesolimbic dopamine receptors may be associated with the apparent rebound psychosis that has been reported following clozapine therapy. (See Cautions: Other Nervous System Effects.)

EEG Effects Clozapine may produce dose-related changes in the EEG, including increased discharge patterns similar to those associated with seizure disorders, and may lower the seizure threshold; seizures have occurred in patients receiving the drug, particularly with high dosages (greater than 600 mg daily), rapid dosage increases, and/or in the presence of high plasma concentrations. (See Seizures in Cautions: Nervous System Effects.) Some EEG changes associated with clozapine administration are atypical of those generally seen with other antipsychotic agents, resembling more closely those produced by antidepressants. Like other drugs with antipsychotic activity, clozapine increases beta-, delta-, and theta-band amplitudes and slows dominant alpha frequencies in clinical EEG studies. However, in patients with severe, treatment-resistant schizophrenia, increases in delta and theta band frequencies are more pronounced with clozapine than with haloperidol or chlorpromazine therapy, a

finding that appears to parallel the drugs' relative antiserotonergic, antihistaminic, and anticholinergic activities. Enhanced EEG synchronization, paroxysmal sharp-wave activity, and spike and wave complexes also may develop during clozapine therapy. Clozapine-induced EEG changes generally appear soon after initiation of the drug and return to baseline upon cessation of therapy. In one study, the EEG showed slight general changes or slight diffuse slowing in 75% of patients receiving clozapine; in another study, clozapine caused marked EEG changes, including a slowing of basal activity, in 5% of patients.

Effects on Sleep Clozapine causes a shift in the sleep-wake pattern toward dozing in animals, with marked reductions in both slow-wave and paradoxical sleep times. However, tolerance to the drug's sedative effect usually occurs, although slowly in some patients, during continuous administration of clozapine. In a controlled study of short-term (3-day) administration in healthy young men, clozapine in dosages of 25 mg nightly substantially increased total sleep time on the first night of administration, but the duration of sleep returned to baseline by the third night. Clozapine did not substantially affect the time spent in stage 1, 2, 3, or slow-wave sleep, nor did it affect latency to the rapid eye movement (REM) period or the percentage of time spent in REM sleep. However, the percentage of time spent in stage 4 sleep was reduced substantially on the second and third nights of drug administration, while a variety of REM indices were increased on the third night of the study.

In a few patients receiving clozapine dosages of 150–800 mg daily, REM sleep increased to 85–100% of total sleep time after several days of drug therapy, with the onset of REM sleep occurring almost immediately after patients fell asleep. Intensification of dream activity also has been reported during clozapine therapy. Some clinicians have suggested that a correlation may exist between increases in body temperature and REM sleep and clozapine-induced improvement in psychosis. Cataplexy has been reported in some patients receiving clozapine.

■ **Neuroendocrine Effects** In contrast to typical antipsychotic drugs, clozapine therapy in usual dosages generally produces little or no elevation of prolactin concentration in humans. Administration of clozapine to rats has produced a transient, dose-related increase in prolactin concentrations that is of much shorter duration than that caused by other antipsychotic agents. Prolactin normally is inhibited by dopamine released from tuberoinfundibular (TIDA) neurons into the pituitary portal circulation. In rats, clozapine acutely increases the activity of TIDA neurons, which inhibit the release of prolactin; activation of TIDA neurons may be mediated by an enhanced release of neurotensin. Clozapine's effect on prolactin appears to be transient, possibly because the drug appears to dissociate from dopamine receptors more rapidly than typical antipsychotic agents and is therefore eliminated from the brain more rapidly.

Clozapine has an effect on corticotropin (ACTH) and corticosterone, possibly through its effects on dopamine metabolism in the hypothalamus. Short-term administration of clozapine (cumulative dose: 200 mg) to a few patients with schizophrenia resulted in marked inhibition of apomorphine-induced somatotropin (growth hormone) response, suggesting that clozapine may block the dopamine receptors responsible for eliciting this response. In contrast to typical antipsychotic agents, clozapine decreases or has no effect on basal cortisol levels. Clozapine markedly increases corticosterone concentrations in a dose-dependent fashion; other antipsychotic agents appear to increase corticosterone concentrations only at doses producing substantial D_2-receptor blockade. Clozapine-induced stimulation of corticosterone secretion may result from stimulation, rather than blockade, of dopamine receptors, but the exact mechanism has not been fully elucidated.

■ **Other Effects** Clozapine produced a dose-dependent delay in initiation of copulation in male rats, which may be related to blockade of mesolimbic dopamine receptors; however, the drug had no effect on copulatory behavior once the behavior had started. Fertility in male and female rats reportedly is not adversely affected by clozapine. (See Cautions: Pregnancy, Fertility, and Lactation.)

In animals, even small oral doses of clozapine cause ptosis, relaxation, and a reduction in spontaneous activity, effects that are consistent with the drug's sedative activity. Inhibition of locomotor activity induced by clozapine diminishes with repeated administration. With increasing doses of the drug, reactions to acoustic and tactile stimuli decline, and disturbances in equilibrium have been reported. Clozapine also inhibits isolation-induced aggression in mice at doses lower than those affecting motor function, suggesting a specific antiaggressive effect.

Studies in animals suggest that clozapine has a weak and variable diuretic effect; the clinical importance of this effect has not been established. In both rats and dogs, low doses of clozapine tend to increase the elimination of water and electrolytes, while higher doses are associated with increases in potassium excretion and sodium retention.

Pharmacokinetics

■ **Absorption** Clozapine is rapidly and almost completely absorbed following oral administration. However, because of extensive hepatic first-pass metabolism, only about 27–50% of an orally administered dose reaches systemic circulation unchanged. Some, but not all, evidence suggests that clozapine may exhibit nonlinear, dose-dependent pharmacokinetics, with oral bioavailability being approximately 30% less following a single 75-mg dose than at steady state following multiple dosing. GI absorption appears to occur principally in the small intestine and is approximately 90–95% complete within 3.5 hours after an oral dose. Food does not appear to affect the rate or extent of GI absorption of the drug. The relative oral bioavailability of clozapine has been shown to be equivalent following administration of commercially available 25-mg and 100-mg conventional tablets, conventional tablets and capsules, and conventional and orally disintegrating tablets of the drug in several studies.

Following oral administration of a single 25- or 100-mg oral dose of clozapine as tablets in healthy adults, the drug is detectable in plasma within 25 minutes, and peak plasma clozapine concentrations occur at about 1.5 hours. Peak plasma concentrations may be delayed with higher single doses and with multiple dosing of the drug. In one multiple-dose study, peak plasma clozapine concentrations at steady state averaged 319 ng/mL (range: 102–771 ng/mL) and occurred on average at 2.5 hours (range: 1–6 hours) after a dose with 100 mg twice daily as conventional tablets in healthy adults; minimum plasma concentrations at steady state averaged 122 ng/mL (range: 41–343 ng/mL). Steady-state plasma concentrations ranging from 200–600 ng/mL generally are achieved with oral dosages of 300 mg daily, and steady-state peak plasma concentrations generally occur within 2–4 hours after a dose. Steady-state plasma concentrations of clozapine are achieved after 7–10 days of continuous dosing.

Following multiple-dose administration of clozapine orally disintegrating tablets at a dosage of 100 mg twice daily in adults, peak plasma clozapine concentrations at steady state averaged 413 ng/mL (range: 132–854 ng/mL) and occurred on average at 2.3 hours (range: 1–6 hours). Minimum plasma concentrations at steady state in this study averaged 168 ng/mL (range: 45–574 ng/mL).

Considerable interindividual variation in plasma clozapine concentrations has been observed in patients receiving the drug, and some patients may exhibit either extremely high or extremely low plasma concentrations with a given dosage. Such variability may be particularly likely at relatively high dosages (e.g., 400 mg daily) of the drug. In one study, a sixfold interindividual variation in steady-state plasma clozapine concentration was observed in patients receiving such dosages. In addition, considerable intraindividual variation, particularly from week to week, may occur in some patients. However, substantial intraindividual variations in pharmacokinetic parameters typically are not observed from day to day. Although the interindividual variability in plasma clozapine concentrations is consistent with that reported for other antipsychotic drugs and may be secondary to differences in absorption, distribution, metabolism, or clearance of the drug, further study is needed to clarify whether such variation results principally from variable pharmacokinetics or other variables.

There is some evidence that interindividual differences in pharmacokinetic parameters for clozapine may result, at least in part, from nonlinear, dose-dependent pharmacokinetics of the drug. However, a linear dose-concentration relationship also has been reported. Results of a study in patients with chronic schizophrenia revealed a correlation between oral clozapine dosages of 100–800 mg daily and steady-state plasma concentrations of the drug. In addition, linearly dose-proportional changes in area under the plasma concentration-time curve (AUC) and in peak and trough plasma concentrations have been observed with oral dosages of 37.5, 75, and 150 mg twice daily in other studies.

Smokers appear to achieve plasma clozapine concentrations that are approximately 60–80% of those achieved by nonsmokers following oral administration of the drug, possibly because of alterations in hepatic metabolism and/or GI absorption of the drug caused by nicotine or other substances (e.g., polycyclic aromatic hydrocarbons) present in cigarette smoke. (See Drug Interactions: Smoking.) There also is limited evidence that gender may affect plasma clozapine concentrations, with concentrations being somewhat reduced, perhaps by as much as 20–30%, in males compared with females. In addition, smoking has a greater effect on clozapine plasma concentrations in men than in women, although this difference could result simply from gender differences in smoking behavior. Plasma concentrations may be increased in geriatric individuals compared with relatively young (e.g., 18–35 years old) individuals, possibly secondary to age-related decreases in hepatic elimination of clozapine.

Pharmacologic effects of clozapine (e.g., sedation) reportedly are apparent within 15 minutes and become clinically important within 1–6 hours. The duration of action of clozapine reportedly ranges from 4–12 hours following a single oral dose. In one study in patients with schizophrenia, the sedative effect was apparent within hours of the first dose of the drug and was maximal within 7 days. (See Effects on Sleep under Pharmacology: Nervous System Effects.) However, antipsychotic activity generally is delayed for one to several weeks after initiation of clozapine therapy, and maximal activity may require several months of therapy with the drug.

Correlations between steady-state plasma concentrations of clozapine and therapeutic efficacy have not been established, and some evidence suggests that the degree of clinical improvement is independent of plasma concentrations ranging from 100–800 ng/mL. However, it also has been suggested that serum clozapine concentrations less than 600 ng/mL may be adequate for therapeutic effect in most patients. Results of one study of 29 patients treated with clozapine 400 mg daily for 4 weeks showed that patients were most likely to respond to therapy when their plasma clozapine concentrations were at least 350 ng/mL and/or when plasma concentrations of clozapine plus norclozapine (an active metabolite) totaled at least 450 ng/mL. Further study is needed to determine whether nonresponding patients with plasma clozapine concentrations less than 350 ng/mL will benefit from increasing their dosage in an attempt to achieve higher concentrations.

Although a relationship between clozapine plasma concentrations and the risk of seizures has been suggested (see Seizures under Cautions: Nervous

System Effects), most clinicians believe that a relationship between plasma concentrations of the drug and the risk of adverse effects has not been established.

■ **Distribution** Distribution of clozapine into human body tissues is rapid and extensive; distribution of metabolites of the drug also appears to be extensive. In mice and rats, clozapine distributes principally into the lung, spleen, liver, kidney, gallbladder, and brain, achieving concentrations in these tissues up to 50 times those in blood. At 8 hours after IV injection, clozapine was still detectable in these organs but not in blood. There is limited evidence in animals that clozapine and its metabolites may be preferentially retained in the lungs by an energy-dependent, carrier-mediated process and by cellular binding. Evidence in animals also suggests that competition between clozapine and other drugs (e.g., chlorpromazine, imipramine, certain tetracycline antibiotics) for pulmonary binding sites may potentially affect plasma and tissue concentrations of clozapine, but the clinical importance, if any, of such an effect has not been established.

The volume of distribution of clozapine has been reported to be approximately 4.65 L/kg. In one study, the volume of distribution at steady state averaged 1.6 L/kg (range: 0.4–3.6 L/kg) in schizophrenic patients. Because the volume of distribution of clozapine is smaller than that of other antipsychotic agents, it has been suggested that clozapine is less sequestered in tissues than the other drugs. Clozapine is approximately 97% bound to serum proteins.

Results of receptor-binding studies in monkeys indicate that clozapine rapidly crosses the blood-brain barrier following IV injection. The highest brain uptake of the drug was in the striatum in these animals; lesser concentrations were achieved in the thalamus and mesencephalon, although they exceeded those in the cerebellum. The pharmacokinetic characteristics of the drug in the CNS paralleled those in plasma in these monkeys, with an elimination half-life from CNS of about 5 hours. Evidence from other animal studies indicates that CNS concentrations of the drug exceed those in blood. Distribution of the drug into the CNS in humans has not been characterized.

Clozapine reportedly is present in low concentrations in the placenta in animals; information on placental transfer of the drug in humans currently is unavailable. Results of animal studies indicate that clozapine distributes into milk. (See Cautions: Pregnancy, Fertility, and Lactation.)

■ **Elimination** The decline of plasma clozapine concentrations in humans is biphasic. The elimination half-life of clozapine following a single 75-mg oral dose reportedly averages 8 hours (range: 4–12 hours); that after a 100-mg oral dose appears to be similar. The elimination half-life of clozapine at steady state following administration of 100 mg twice daily reportedly averages 12 hours (range: 4–66 hours). The rapid elimination phase may represent redistribution and is followed by a slower apparent mean terminal elimination half-life of 10.3–38 hours. Although a study comparing single and multiple dosing of clozapine demonstrated an increase in elimination half-life with multiple dosing, other evidence suggests this finding is not attributable to concentration-dependent pharmacokinetics.

Clozapine is metabolized in the liver prior to excretion. Clozapine may undergo *N*-demethylation, *N*-oxidation, 3′-carbon oxidation, epoxidation of the chlorine-containing aromatic ring, substitution of chlorine by hydroxyl or thiomethyl groups, and sulfur oxidation. A glucuronide metabolite, tentatively identified as a quaternary ammonium *N*-glucuronide of clozapine, also has been identified. Metabolism of clozapine may occur by one or more of these routes.

The rate of formation and biologic activity of clozapine metabolites have not been fully elucidated. The desmethyl metabolite of clozapine (norclozapine) has limited activity while the hydroxylated and *N*-oxide derivatives are inactive. The *N*-oxide and desmethyl derivatives are found in urine and plasma of humans in a proportion of 2:1.

Approximately 32% of a single oral dose of clozapine is found in plasma as the parent compound after 3 hours, 20% in 8 hours, and 10% up to 48 hours following the dose. Only limited amounts (approximately 2–5%) of unchanged drug are detected in urine and feces. Approximately 50% of an administered dose is excreted in urine and 30% in feces; maximum fecal excretion has been estimated at 38%. Approximately 46% of an oral dose of clozapine is excreted in urine within 120 hours.

Total plasma and blood clearance of clozapine reportedly average 217 and 250 mL/minute, respectively, but show considerable interindividual variation.

Chemistry and Stability

■ **Chemistry** Clozapine is a dibenzodiazepine-derivative antipsychotic agent. The drug is a piperazine-substituted tricyclic antipsychotic agent that is structurally similar to loxapine but that differs pharmacologically from this and other currently available antipsychotic agents (e.g., phenothiazines, butyrophenones). Because of these pharmacologic differences, clozapine is considered an atypical or second-generation antipsychotic agent.

While the structure-activity relationships of phenothiazine antipsychotic agents have been well described, these relationships for heterocyclic antipsychotic agents, including clozapine, have not been as fully characterized. Generally, the unsubstituted benzene ring seems to be important for interactions at dopamine receptors, while the chloro-substituted benzene ring seems more important for action at muscarinic receptors. In addition, an open carbon side chain replacing the piperazine moiety of clozapine generally leads to loss of activity.

Clozapine differs structurally from most currently available antipsychotic agents by the presence of a seven- rather than a six-membered central ring and the spatial relationship between the piperazine moiety and the chloro-substituted benzene ring. The core tricyclic ring system of clozapine is nonplanar and allows the piperazine moiety limited freedom of rotation.

Clozapine differs structurally from loxapine by the presence of a diazepine rather than an oxazepine central ring in the tricyclic nucleus and by the presence of a chlorine atom at position 8 rather than 2 of the tricyclic nucleus. The presence of a chlorine atom at position 8 of the tricyclic nucleus of clozapine appears to be associated with its distinct pharmacologic profile and may be responsible for the drug's antimuscarinic activity.

Clozapine occurs as a yellow, crystalline powder and is very slightly soluble in water.

■ **Stability** Commercially available conventional clozapine tablets should be stored in tight containers at a temperature not exceeding 30°C. Clozapine orally disintegrating tablets should be stored in their original sealed blister at a controlled room temperature of 25°C, but may be exposed to temperatures ranging from 15–30°C. The orally disintegrating tablets should be protected from moisture.

Preparations

Clozapine is available only through distribution systems that ensure baseline and periodic testing of white blood cell counts and absolute neutrophil counts as a condition of provision of the patient's next supply of drug. The individual manufacturers should be contacted for additional information on current mechanisms for obtaining the drug.

Excipients in commercially available drug preparations may have clinically important effects in some individuals; consult specific product labeling for details.

Clozapine‡

Oral		
Tablets	25 mg*	**Clozapine Tablets**
		Clozaril* (scored), Novartis
	100 mg*	**Clozapine Tablets**
		Clozaril* (scored), Novartis
Tablets, orally disintegrating	25 mg	**FazaClo*** (scored), Alamo
	100 mg	**FazaClo*** (scored), Alamo

*available from one or more manufacturer, distributor, and/or repackager by generic (nonproprietary) name

‡Use is not currently included in the labeling approved by the US Food and Drug Administration

Olanzapine

■ Olanzapine is considered an atypical or second-generation antipsychotic agent.

Uses

Olanzapine is used for the symptomatic management of psychotic disorders (e.g., schizophrenia). In addition, olanzapine is used alone or in conjunction with lithium or divalproex sodium for the management of acute mixed or manic episodes associated with bipolar I disorder; the drug also is used for longer-term maintenance monotherapy in patients with this disorder. Olanzapine also is used for the management of acute agitation in patients with bipolar disorder or schizophrenia.

■ **Psychotic Disorders** Olanzapine is used for the symptomatic management of psychotic disorders (e.g., schizophrenia). Drug therapy is integral to the management of acute psychotic episodes and accompanying violent behavior in patients with schizophrenia and generally is required for long-term stabilization to sustain symptom remission or control and to minimize the risk of relapse. Antipsychotic agents are the principal class of drugs used for the management of all phases of schizophrenia. Patient response and tolerance to antipsychotic agents are variable, and patients who do not respond to or tolerate one drug may be successfully treated with an agent from a different class or with a different adverse effect profile.

Schizophrenia Olanzapine is used orally for the management of schizophrenia. Schizophrenia is a major psychotic disorder that frequently has devastating effects on various aspects of the patient's life and carries a high risk of suicide and other life-threatening behaviors. Manifestations of schizophrenia involve multiple psychologic processes, including perception (e.g., hallucinations), ideation, reality testing (e.g., delusions), emotion (e.g., flatness, inappropriate affect), thought processes (e.g., loose associations), behavior (e.g., catatonia, disorganization), attention, concentration, motivation (e.g., avolition, impaired intention and planning), and judgment. The principal manifestations of this disorder usually are described in terms of positive and negative (deficit) symptoms, and more recently, disorganized symptoms. Positive symptoms include hallucinations, delusions, bizarre behavior, hostility, uncooperativeness, and paranoid ideation; while negative symptoms include restricted range and intensity of emotional expression (affective flattening), reduced thought and speech productivity (alogia), anhedonia, apathy, and

Methylphenidate Hydrochloride

Methylphenidylacetate Hydrochloride

■ Methylphenidate is a piperidine-derivative CNS stimulant that has pharmacologic actions that are qualitatively similar to those of amphetamines.

Uses

Methylphenidate is used alone or combined with behavioral treatment as an adjunct to psychological, educational, social, and other remedial measures in the treatment of attention deficit hyperactivity disorder (ADHD). Methylphenidate also is used in the symptomatic treatment of narcolepsy.

■ **Attention Deficit Hyperactivity Disorder** Methylphenidate is used alone or combined with behavioral treatment as an adjunct to psychological, educational, social, and other remedial measures in the treatment of ADHD (hyperkinetic disorder, hyperkinetic syndrome of childhood, minimal brain dysfunction) in carefully selected children 6 years of age and older, adolescents, and adults. Although long thought of as a childhood disorder, ADHD is now known to persist into adolescence and/or adulthood in some patients, and adults are increasingly being treated for ADHD. Adults maintaining only some of the manifestations of ADHD are considered by DSM-IV to have ADHD in partial remission. ADHD in adults also has been referred to as simply attention deficit disorder (ADD). Most evidence and experience on the treatment of ADHD has been in children. Almost all studies comparing behavioral therapy versus stimulants alone for ADHD have shown a much stronger therapeutic effect from stimulants than from behavioral therapy.

Diagnostic Considerations ADHD is one of the most commonly diagnosed neurobehavioral disorders of childhood, generally estimated as occurring in 3–12% of US school-age children, although wider ranges of prevalence have been reported. Within this range, reported prevalence rates generally are at the higher end for community samples versus school samples. ADHD also is one of the most prevalent chronic health conditions in school-aged children. Although ADHD has been reported more frequently in boys than in girls (ratio of boys versus girls varies between 3:1 to 9:1), this difference may be artifactual and decrease with age, being skewed in part to boys because of referral bias related to disruptive behavior since boys generally exhibit more hyperactive/impulsive symptoms and more conduct and oppositional symptoms than girls. In addition, when DSM-IV rather than earlier criteria are used, more females have been diagnosed with the predominantly inattentive type.

The diagnosis of ADHD should be made using well-tested diagnostic interview methods; neuropsychologic and/or biologic tests are not recommended for routine clinical use, although they may be useful to researchers investigating links between symptoms and underlying attentional processes and brain functions. To help ensure an accurate diagnosis and decrease the variation in how the diagnosis is made, clinicians should employ DSM-IV criteria in the context of their clinical assessment to diagnose ADHD. However, given the lack of methods to confirm the diagnosis of ADHD through other means, clinicians must recognize the limitations of the DSM-IV definitions (e.g., most of the development and testing of DSM-IV occurred in children evaluated in psychiatric settings, there are no clear empiric data supporting the number of items required for the diagnosis, current criteria do not take into account gender differences nor developmental differences in behavior, behavioral characteristics remain subjective and may be interpreted differently). According to DSM-IV criteria, there are 3 subtypes of ADHD: the principally inattentive type (ADHD/I), the principally hyperactive-impulsive type (ADHD/HI), and the combined inattentive and hyperactive-impulsive type (ADHD/C).

There currently are *no* data establishing that ADHD results from brain malfunction. ADHD is a clinical diagnosis; while the diagnosis can be made reliably using interview methods, there currently is no independent valid test for ADHD nor have laboratory tests, physical examination findings, or general medical conditions been established as aiding in the clinical assessment of this disorder. Diagnostic methods employed in the clinical setting have been variable, and the frequency of diagnosis of ADHD varies widely among type of practitioner (primary care and developmental pediatricians, family physicians, child neurologists, psychologists, and psychiatrists). Pediatricians, family physicians, and psychiatrists tend to rely on parent rather than teacher input, and there is a general disconnect between developmental or educational (school-based) assessments and health-related (medical practice-based) services, including poor communication between diagnosticians and those who implement and monitor treatment in schools, and follow-up may be inadequate and fragmented. School-based clinics with a team approach that includes parents, teachers, school psychologists, and other mental health specialists may improve barriers to appropriate identification, evaluation, and intervention as well as access to assessment and treatment. Current formal diagnostic criteria for ADHD were designed principally for diagnosing this disorder in young children. However, the American Psychiatric Association (APA) and others (e.g., American Academy of Child and Adolescent Psychiatry [AACAP]) have developed diagnostic criteria (e.g., DSM-IV) for ADHD to ages extending through adulthood.

ADHD usually is characterized by developmentally inappropriate symptoms (e.g., moderate to severe distractibility, short attention span, hyperactivity, emotional lability, impulsivity, carelessness, accident-proneness, irresponsibility, failure to complete tasks). The essential feature of ADHD is a persistent pattern of inattention and/or hyperactivity/impulsivity that is more frequent and severe than is observed in individuals with a comparable developmental level, and core symptoms include developmentally inappropriate levels of attention and concentration, activity, distractability, and impulsivity. Some hyperactive/impulsive or inattentive symptoms are present before 7 years of age, although many individuals are diagnosed after the symptoms have been present for many years. In most cases, ADHD becomes apparent (and thus comes to medical attention) during the first few years of grammar (grade) school. Some impairment from symptoms is present in at least 2 settings (e.g., at home, school, or work), and there is clear evidence of interference with developmentally appropriate social, academic, and/or occupational functioning. The final diagnosis of this disorder should not be made if these symptoms are of only comparatively recent origin. Nonlocalizing (soft) neurologic signs, learning disability, and abnormal EEG may or may not be present, and a diagnosis of CNS dysfunction may or may not be warranted.

Children with ADHD usually exhibit pronounced difficulties and impairment resulting from the disorder across multiple settings (at school, at home, with peers) as well as resultant long-term adverse effects on later academic, vocational, social-emotional, and psychiatric outcomes. Such children exhibit higher accident rates, and later in life, those with ADHD that is combined with conduct disorders exhibit drug abuse, antisocial behavior, and accidents of all sorts; for many individuals, the long-term effects of ADHD continue into adulthood. Individuals with a history of ADHD consume a disproportionate share of resources and attention from health-care services, the criminal justice system, schools, and other social services, and ADHD, often combined with coexisting conduct disorders, contributes to societal problems including violent crime and teenage pregnancy. Parents of children with ADHD, as with other behavioral disorders and chronic diseases, experience increased levels of parental frustration, marital discord, divorce, and costs for medical care that may not be covered by health insurance. Up to 80% of diagnosed hyperactive children continue to exhibit features of ADHD into adolescence and up to 65% into adulthood, and most experts consider it a chronic disorder that often seems to require ongoing treatment. As a result, ADHD represents a major public health problem with profound impact on individuals, families, schools, and society; however, because there currently are no established means for preventing this disorder, current efforts must be aimed at effectively identifying, diagnosing, and treating ADHD. Comorbid conditions are present in up to two-thirds of clinically referred children with ADHD, including high rates for oppositional defiant disorder, conduct disorder, mood disorders (e.g., depression), and anxiety disorders. Tourette's syndrome and chronic tic disorder also often are present, and speech and language delays are common.

Although some patients continue to experience the full range of ADHD symptoms into adulthood, the occurrence of adult-onset ADHD is unlikely; however, unrecognized cases of ADHD may not be diagnosed until adulthood. A clinical diagnosis of ADHD in adults, according to DSM-IV criteria, requires evidence of symptom onset before 7 years of age, persisting from childhood until the time of evaluation, and with distress and/or impairment in functioning occurring in more than one setting (e.g., home, work). Some symptoms of disinhibition may present differently in adults than children; the physical symptoms of hyperactivity in children may be replaced in adults with fidgetiness or an inner feeling of restlessness, difficulty relaxing, and a feeling of being chronically "on edge". The DMS-IV criteria also state that a diagnosis of ADHD in partial remission may be used for adults who no longer meet the full range of diagnostic criteria that was present in childhood, but still retain some of the manifestations that cause functional impairment. Confirmation of ADHD in previously undiagnosed adults may present challenges such as difficulty in obtaining a longitudinal history, poor insight and underestimation of the severity of symptoms and resulting impairment, and differentiation from other psychiatric conditions (e.g., bipolar disorder, depression, axis II personality disorders, learning disabilities, narcolepsy, undiagnosed borderline intellectual functioning). Rating scales such as the Wender Utah Rating Scale, Brown Attention-Deficit Disorder Scale for Adults, and the Conners Adult ADHD Rating Scale may be useful adjuncts to clinical assessment in confirming the diagnosis of ADHD in adults.

Therapeutic Considerations **Considerations In Choosing a Therapy.** The choice of therapeutic intervention(s) for ADHD will depend on comorbid conditions, specific target symptoms, and the strengths and weaknesses of the patient, family, school, and community. Parents, school personnel, and patients should be included in discussions of treatment options. A wide variety of treatments have been employed for the management of ADHD, including drug therapy with amphetamines and similar stimulants (e.g., methylphenidate, pemoline [no longer commercially available in the US]), psychotropic drugs (e.g., antidepressants such as desipramine or imipramine), and other drugs (e.g., atomoxetine, clonidine); psychosocial treatment; dietary management; herbal and homeopathic treatments; biofeedback; meditation; and perceptual stimulation/training. Drug therapy and psychosocial interventions have been the focus of research to date, and efficacy studies have focused principally on the combined-type of ADHD; meeting criteria for inattention and hyperactivity/impulsivity; most randomized trials have been of short duration (usually not exceeding 3 months), although a large, multicenter study with a treatment duration of 14 months recently was reported. Current evidence from these studies supports the efficacy of stimulants and psychosocial treatment; however, there are no well-designed, long-term studies employing these treatments beyond 14 months nor is there information on long-term outcomes of drug therapy on educational and occupational achievements, involvement with police, or other areas of social functioning. Results of 3 double-blind clinical studies in 416 children 6–

12 years old with ADHD indicate that therapy with methylphenidate hydrochloride extended-release trilayer core tablets (Concerta®) was more effective than placebo in decreasing hyperactive-impulsive or inattentive symptoms based on evaluation by community school teachers using the Inattention/Overactivity with Aggression (IOWA) Conners scale. Stimulant drug therapy generally appears to be more effective than psychosocial therapy overall, including behavioral treatment that includes parent training, intensive child-focused treatment, and school-based interventions.

Drug therapy is not indicated in all children with ADHD, and such therapy should be considered only after a complete evaluation including medical history has been performed. The decision to use stimulants should depend on the age of the child and the physician's assessment of the severity and duration of symptoms and should not depend solely on one or more behavioral characteristics. The decision to initiate drug therapy is based on the diagnostic evidence of ADHD and persistent target symptoms that are sufficiently severe to cause functional impairment at school; functional impairment usually also is evident at home and with peers. The risks of drug therapy must be weighed carefully with the risks of the untreated disorder, and the expected benefits of drug therapy must be weighed relative to other treatment options. Drug therapy should *not* be used as a substitute for appropriate educational curricula, student-to-teacher ratios, or other environmental accommodations. When severe impulsivity, noncompliance, or aggression is present, the need to initiate drug therapy may be more urgent.

Stimulants. Stimulants (e.g., methylphenidate, amphetamines) remain the drugs of choice for the management of ADHD. Methylphenidate is the most extensively studied and frequently prescribed drug for the treatment of ADHD. Few, if any, differences have been found between methylphenidate, dextroamphetamine, or pemoline (no longer commercially available in the US) or various dosage forms (short-, intermediate, or long-acting formulations) of the drugs in short-term clinical studies in children with ADHD, and the choice of stimulant therapy should be individualized. However, because hepatic toxicities have been associated with pemoline, some experts recommended its use *only* in patients who failed to respond to adequate trials of methylphenidate *and* an amphetamine as well as adequate trials of second-line therapies (e.g., tricyclic antidepressants, bupropion). In 2005, the US Food and Drug Administration (FDA) determined that the risk of hepatic toxicity associated with the drug outweighs its benefits.

Short-term and longer-term (up to 14 months' duration) studies have shown unequivocal beneficial effects of the stimulants on the defining core symptoms of ADHD (attention and concentration, activity, distractability, impulsivity) and associated aggressiveness during continued therapy with the drugs. The response rate for any single stimulant drug in ADHD is about 70%, and at least 80% of children will respond to a single stimulant without major adverse effect if therapy is titrated carefully. Children who fail to show positive therapeutic effects or who experience intolerable adverse effects with one stimulant should be tried on an alternative stimulant since most such children will exhibit a positive response to alternative stimulants and current evidence from crossover studies supports the efficacy of different stimulants in the same child; likewise, children who fail an adequate trial of 2 stimulants, should be tried on a third type or formulation of stimulant. Another consideration for trials with alternative stimulants before resorting to a trial with an alternative therapeutic class is the fact that there currently is greater evidence for the safety and efficacy of stimulants in children with ADHD. However, stimulants usually do not normalize the entire spectrum of behavioral problems, and many children effectively treated with these drugs still manifest a higher level of some behavioral problems than children without ADHD or other behavior disturbances. In addition, titration of therapy may result in improvement in one area of functioning while eliciting no or even a detrimental effect in another area. Although stimulants have been shown to remain effective over many years, long-term benefits remain to be established.

Effects on attentional, academic, behavioral, and social domains exhibit substantial interindividual and intraindividual variation, and the principal disappointment with stimulant drug therapy has been the finding that despite improvement in core symptoms of ADHD, there is little consistent improvement in academic or social skills. Stimulants appear to be as effective in patients with ADHD and associated aggression as in those with pure ADHD. It currently is unclear whether patients with comorbid anxiety disorders respond as well to stimulants as other patients with ADHD; however, some evidence suggests that the emphasis for patients with comorbid anxiety should be on increased reliance on psychosocial interventions. For patients whose symptoms are not severe outside the school setting, drug holidays may be attempted for all or part of the summer to assess continuing efficacy and need for such therapy as well as to minimize adverse effects.

Although the abuse potential of stimulants such as amphetamines and methylphenidate is well established, there currently is no evidence that drug abuse is a major problem with properly monitored stimulant therapy for ADHD. In addition, while it has been suggested that the substantial increase in stimulant prescriptions for ADHD in recent years may pose societal risks, the thresbold of drug availability that can lead to oversupply and resultant illicit use is unknown, and there is little evidence that current levels of stimulant production in the US have had a substantial effect on abuse. Drug abuse and cigarette smoking are associated with childhood ADHD, but there has been controversy whether therapy with stimulants increases or decreases the risk of abuse. Some evidence, including a pooled analysis of available prospective and retrospective studies that included information on stimulant use in children, adolescents, and adults with ADHD, indicates that stimulant use does not lead to an increased risk of substance experimentation, use, dependence, or abuse, and effective ADHD stimulant therapy actually may reduce the risk for subsequent drug and alcohol use disorders. Caution in prescribing stimulants may be indicated in patients with comorbid conduct disorder, preexisting dependency, or a chaotic family. If the risk of drug abuse by the patient or their peers or family is considered high, a nonstimulant drug may be preferable to methylphenidate or an amphetamine (e.g., dextroamphetamine).

Multimodal Therapy. Although multimodal therapy, integrating drug therapy with environmental, educational, psychotherapeutic, and school-based approaches, seems intuitively powerful and some studies and clinicians have suggested the superiority of such an approach versus drug therapy or psychosocial interventions, there currently is little evidence from well-designed studies substantiating this assertion, particularly outside a research setting. In addition, data from a large, well-designed study indicates that drug therapy employing systematic intensive monitoring methods over a period of about 1 year is superior to an intensive set of behavioral treatments on core ADHD symptoms; combined behavioral and drug therapy added little benefit overall but did result in greater improvements in social skills and was judged more favorably by parents and teachers. While it remains to be determined, however, whether the addition of behavioral therapy can improve functioning at reduced stimulant dosages, evidence from this study indicates significantly lower total daily dosages of methylphenidate during combined therapy compared with drug therapy alone.

Alternatives to Stimulants. For patients who are intolerant of or unresponsive to stimulants, various other drugs (e.g., tricyclic antidepressants, atomoxetine, bupropion, selective serotonin-reuptake inhibitors, clonidine, guanfacine) have proven useful in clinical practice. However, experience with such alternative drug therapy is far less extensive than with stimulants, and conclusions regarding relative efficacy currently cannot be made.

Most experts recommend use of a tricyclic antidepressant or bupropion for the treatment of ADHD in children who are nonresponsive or partial responders to adequate trials with at least 2 different stimulants. There currently are no data establishing that one of these alternative drugs is more efficacious than the other in the treatment of ADHD. Tricyclic antidepressants generally have been shown to be effective in the management of ADHD in children and adolescents, but are associated with a narrower margin of safety. In addition, although a causal relationship has not been established, several recent cases of sudden death in children receiving desipramine have raised concerns about the use of this tricyclic. (See Cautions: Pediatric Precautions in Desipramine 28:16.04.28.) Therefore, some experts no longer recommend use of desipramine for the treatment of ADHD in children. Tricyclic antidepressants appear to be less effective than stimulants in improving attentional and cognitive symptoms, but may be useful for impulsive or hyperactive behavior. Tricyclic antidepressant therapy may be indicated as second-line therapy in patients who do not respond to stimulants or who develop clinically important depression or otherwise do not tolerate the drugs; these antidepressants also may be useful for patients with tics or Tourette's disorder or in whom these conditions are exacerbated or not adequately controlled during stimulant therapy. Regardless of which tricyclic antidepressant is considered for use in the management of ADHD, the drugs should be used only if clearly indicated and with careful monitoring, including baseline and subsequent determinations of ECG and other parameters.

Atomoxetine, a selective norepinephrine-reuptake inhibitor, is used in the treatment of ADHD in children 6 years of age and older, adolescents, and adults. Efficacy of atomoxetine for this indication was established in short-term controlled clinical studies in children and adolescents 6–18 years of age and in adults who met DSM-IV criteria for ADHD; efficacy also was established in one longer-term (12 months) controlled clinical study in children and adolescents 6–15 years of age. In one of the short-term studies, atomoxetine and methylphenidate produced comparable results in the reduction of ADHD symptoms in children and adolescents; however, further evaluation in placebo-controlled clinical studies are needed to determine comparative efficacy and tolerance of atomoxetine and other therapies in the treatment of ADHD.

Therapeutic Considerations for Patients with Comorbid Conditions. Alternative drug therapies also may be used alone or in combination with stimulants in patients with ADHD and comorbid conditions (e.g., aggression, anxiety, depression, tic disorders) that are unresponsive to stimulants alone. For the management of anxiety or depression in children with ADHD, selective serotonin-reuptake inhibitors (SSRIs) are considered by some experts the drugs of choice usually to be used in combination with a stimulant. In one clinical study, combined use of methylphenidate and fluoxetine in 32 children with ADHD and a comorbid mood or conduct disorder resulted in marked improvement in school grades and behavior as rated by parents, with no serious adverse effects reported. However, some experts recommend a conservative approach to such combined use of these drugs because of suggestions of rare but potentially serious drug interactions between SSRIs and stimulants. (See Drug Interactions: Antidepressants.)

Some experts state that in the absence of contraindications, α-adrenergic agents (e.g., clonidine) are considered the drugs of choice for the treatment of tic disorders in children with ADHD who were intolerant of stimulants. Clonidine's use has been documented principally in children with ADHD and comorbid conditions, especially sleep disturbances. Antipsychotic agents (e.g., haloperidol, pimozide, risperidone) are recommended by some experts as alternative therapies.

For the management of comorbid intermittent explosive disorder in children with ADHD, mood stabilizing agents (e.g., lithium or valproic acid) are recommended as adjuncts to stimulant therapy. Clonidine, an α-adrenergic agonist, also has been used in the management of comorbid aggressive symptoms as an adjunct to methylphenidate therapy; however, this use is controversial and further study is needed to evaluate efficacy of such concomitant therapy and the potential risk of development of serious cardiovascular effects. Although carbamazepine has been widely used for the treatment of aggression in adults, its efficacy in children remains to be established. In one controlled study, use of the drug failed to reduce aggression in children. Further studies are needed to evaluate the relative role of carbamazepine in the treatment of intermittent explosive disorder in children with ADHD. In addition, some experts no longer recommend use of typical antipsychotic (neuroleptic) agents because of the possible risk of withdrawal and tardive dyskinesia. However, use of risperidone (an atypical antipsychotic agent) may be considered in severely aggressive children with ADHD in whom other treatments have failed.

Adolescents and Adults. Stimulants have been used effectively in the management of ADHD in adolescents and adults, but experience is far less extensive than in children and potential age-related differences in response remain to be elucidated. Children and adults appear to share a similar treatment-responsive, underlying disorder. Although reported rates of stimulant efficacy have varied widely in adults, this variation may have resulted from use of inadequate dosages, diagnostic differences, and/or high rates of comorbid disorders. Stimulants should be used cautiously in adults with comorbid substance abuse disorders.

■ **Narcolepsy** Methylphenidate is used in the symptomatic treatment of narcolepsy. Methylphenidate has been used with equivocal results in the treatment of apathetic or withdrawn senile behavior and mild depression, but the drug should not be used in the treatment of endogenous depression or agitated depressive states since anxiety may be aggravated.

Dosage and Administration

■ **Administration** Methylphenidate hydrochloride is administered orally. Methylphenidate is administered percutaneously by topical application of a transdermal system.

Oral Administration To avoid insomnia, the last daily dose of conventional (immediate-release) preparations should be given several hours before retiring.

Methylphenidate hydrochloride chewable tablets should be administered with a full glass (i.e., at least 240 mL [8 ounces]) of water or other fluid to avoid choking. (See Precautions Associated with Specific Methylphenidate Formulations under Cautions: Precautions and Contraindications.)

The extended-release tablets and extended-release trilayer core tablets of methylphenidate hydrochloride should be swallowed intact and should *not* be crushed or chewed. The extended-release capsules (Metadate® CD, Ritalin® LA) may be swallowed intact or the entire contents of a capsule(s) may be sprinkled onto a small amount (e.g., one tablespoonful) of applesauce immediately prior to administration. The manufacturer of Ritalin® LA states that the capsule contents should not be mixed with warm applesauce because the release properties of the formulation could be affected. The sprinkle/applesauce mixture should be taken immediately; the sprinkle/applesauce mixture must not be stored for use at a later time. One manufacturer suggests that the patient should drink fluids immediately after swallowing the intact capsule or sprinkle/applesauce mixture. Subdividing the contents of a capsule is not recommended, and crushing or chewing of the extended-release capsule or the capsule contents should be avoided.

Patients receiving methylphenidate hydrochloride extended-release trilayer core tablets (Concerta®) should be instructed *not* to become concerned if they notice a tablet-like substance in their stools; this is normal since the tablet containing the drug is designed to remain intact and slowly release the drug from a nonabsorbable shell during passage through the GI tract. The manufacturer states that it is possible that the extended-release trilayer core tablets may be visible on abdominal radiographs under certain circumstances, particularly when digital enhancing techniques are utilized.

Transdermal Administration Patients receiving transdermal methylphenidate should be carefully instructed in the proper use and disposal of the transdermal system.

The methylphenidate transdermal system should be applied once daily in the morning, 2 hours before an effect is needed, and should be removed 9 hours after application. The system should be applied immediately after opening the package and removing the protective liner; the system should not be used if the package seal is broken. The adhesive side of the transdermal system should be placed on a clean, dry area of the hip that is not oily, damaged, or irritated; application of the transdermal system to the waistline or to areas under tight clothing should be avoided, since clothing may cause the system to rub off. The system should be pressed firmly in place with the palm of the hand for approximately 30 seconds, making sure that there is good contact with the skin, particularly around the edges of the system. Application sites should be alternated daily (e.g., opposite hip) if possible.

Following proper application of the transdermal system, bathing, swimming, or showering has not been shown to affect adherence to the skin. If a system becomes dislodged during the intended period of use, it should be replaced with a new system applied at a different site, but the total wear time should not exceed 9 hours per day.

After removal, used systems should be folded so that the adhesive side adheres to itself and then should be flushed down the toilet or disposed of in an appropriate lidded container. Any unused systems that are no longer needed should be removed from their packaging, separated from the protective liner, folded so that the adhesive side adheres to itself, and then flushed down the toilet or disposed of in an appropriate lidded container.

The manufacturer encourages parents to record on the administration chart included with each carton the time that each transdermal system was applied and removed. If a system was removed without the parent's or caregiver's knowledge, or if a system is missing from the tray, the parent or caregiver should be encouraged to ask the child when and how the system was removed.

■ **Dosage** Dosage of methylphenidate hydrochloride must be carefully adjusted according to individual requirements and response. The extended-release tablets should not be used for initiating therapy nor until the daily dosage is titrated using the conventional tablets; the extended-release tablets may be used and given at 8-hour intervals when the 8-hour dosage of the extended-release preparation corresponds to the titrated 8-hour dosage of the conventional tablets. Alternatively, dosage may be initiated with the methylphenidate hydrochloride extended-release capsules or the extended-release trilayer core tablets for patients who are not currently taking methylphenidate starting with the lowest daily dose and increasing at approximately weekly intervals.

Patients receiving intermediate- or long-acting preparations also may require supplemental therapy with methylphenidate conventional tablets to increase the efficacy, particularly in the morning, or to extend the duration of therapeutic effects later in the day.

Attention Deficit Hyperactivity Disorder Methylphenidate hydrochloride dosage for the treatment of attention deficit hyperactivity disorder (ADHD) should be individualized based on patient response and tolerance. The first dosage that produces an observable response may not be the optimum dosage to improve function, and titration to higher dosages should continue in an attempt to achieve a better response. Such a strategy may require subsequent lowering of dosage when higher dosages produce adverse effects or no further clinical improvement. The best dosage for a given patient is the one that provides optimum therapeutic effects with minimal adverse effects. Dosing schedules also may vary, although there currently are no consistent controlled studies comparing alternative dosing schedules. Patients who require relief only during school may respond adequately to a 5-day (i.e., school day) regimen while those requiring relief at home and school may need a daily regimen throughout the week.

The optimum duration of treatment with methylphenidate has not been established; however, pharmacologic treatment may be required for extended periods. The long-term usefulness of the drug should be reevaluated periodically in patients receiving methylphenidate for extended periods. In patients who have responded to methylphenidate therapy, the drug should be discontinued periodically to assess the patient's condition; improvement may be maintained temporarily or permanently after the drug is discontinued.

Immediate-release Oral Preparations. As an adjunct in the treatment of ADHD in children 6 years of age and older, the usual initial dosage of methylphenidate hydrochloride as conventional (immediate-release) preparations is 5 mg before breakfast and lunch. Dosage may be increased by 5–10 mg daily at weekly intervals and can be administered in twice- or thrice-daily regimens. Although some clinicians have recommended weight-based dosing in children, dosage of methylphenidate, unlike most drugs, generally can be adjusted without regard to the child's weight. When weight-based dosing was employed, an initial dosage of 0.25 mg/kg daily was used. If adverse effects were not observed, the daily dose could be doubled each week until the optimum dosage of 2 mg/kg daily is reached.

Oral dosage in children generally ranges from 5–20 mg 2 or 3 times daily and should not exceed 60 mg daily. Although dosages for older adolescents and adults are similar to those for children, total daily dosages may be increased up to 65 mg since more doses are required to medicate these patients throughout a longer active day. Some clinicians have employed a regimen that included systematic intensive monitoring (referred to as "medical management") in the treatment of ADHD, and such a regimen was shown to be more effective than less intensively titrated and monitored regimens (referred to as "community management"). In the medical management regimen, methylphenidate dosage was titrated over a 28-day period via daily-switch titration involving 5 randomly ordered repeats each of placebo and 5-, 10-, 15-, or 20-mg (higher for children weighing more than 25 kg) daily dosages; each dose was repeated at breakfast and lunch, with a half dose (rounded to nearest 5 mg) given in the afternoon. Based on clinical assessment of response, a best dose was chosen for initial maintenance. In addition to the systematic dosage titration, patients underwent 30-minute monthly drug therapy assessment visits during maintenance. Pharmacotherapists could increase or decrease therapy during such visits by 10 mg daily. In general, patients received higher than typical dosages of the drug when this titration and monitoring method was employed. Dosage at the end of a 14-month study period averaged 37.7 mg daily administered in 3 unequally divided doses daily as noted above.

Children whose dosage is excessive or who are overly sensitive to the drug may become overfocused or appear dull or overly restricted; a dosage reduction may obviate such effects. Rarely, some children may experience psychotic reactions, mood disturbances, or hallucinations at relatively high dosages. If a beneficial effect is not attained after appropriate dosage adjustment over a one-month period, methylphenidate therapy should be discontinued.

Intermediate-acting Oral Preparations. Methylphenidate hydrochloride extended-release tablets (Metadate® ER, Methylin® ER, Ritalin-SR®) may be used as an adjunct in the treatment of ADHD in children 6 years of age and older in patients whose ADHD symptoms are controlled with conventional methylphenidate hydrochloride tablets. The manufacturers suggest that extended-release methylphenidate hydrochloride tablets can be substituted for the conventional tablets at the nearest equivalent total daily dosage. For example, patients receiving 10 mg of conventional tablets in the morning and at noon can be switched to 20 mg of methylphenidate hydrochloride extended-release tablets administered once daily in the morning. In some patients, supplemental doses of a short-acting (conventional) preparation may be needed. The usual dosage of methylphenidate hydrochloride administered as an intermediate-acting oral preparation is 20–40 mg once daily or 40 mg in the morning and 20 mg in the early afternoon.

Long-acting Oral Preparations. Methylphenidate hydrochloride extended-release capsules (Metadate® CD, Ritalin® LA) also may be used as an adjunct in the treatment of ADHD in children 6 years of age and older. The initial dosage of methylphenidate hydrochloride extended-release capsules is 20 mg once daily in the morning. Alternatively, when a lower initial daily dosage is appropriate, therapy with Ritalin® LA may be initiated at a dosage of 10 mg once daily. The manufacturer states that Metadate® CD extended-release capsules should be administered before breakfast. Dosage of Metadate® CD may be increased by 10–20 mg daily at weekly intervals, until an optimum response is achieved or adverse effects are observed. Dosage of Ritalin® LA may be increased by 10 mg daily at weekly intervals. Dosages of methylphenidate hydrochloride extended-release capsules exceeding 60 mg daily are not recommended.

Alternatively, as an adjunct in the treatment of ADHD, methylphenidate hydrochloride extended-release trilayer core tablets (Concerta®) may be used. The usual initial dosage of the drug as extended-release trilayer core tablets is 18 mg once daily, in the morning. If adequate response does not occur, dosage may be increased at approximately weekly intervals. The maximum dosage of Concerta® recommended by the manufacturer is 54 mg daily for children 6–12 years of age or 72 mg daily (not to exceed 2 mg/kg daily) for adolescents 13–17 years of age; however, some clinicians state that dosage in children 6–12 years of age may be increased to a maximum dosage of 72 mg daily.

Some clinicians state that patients currently receiving methylphenidate hydrochloride conventional tablets may be switched to Metadate® CD extended-release capsules. Patients being transferred from methylphenidate therapy using conventional tablets at a dosage of 10 mg twice daily can be switched to a dosage of 20 mg every morning as Metadate® CD extended-release capsules. Patients receiving methylphenidate hydrochloride therapy using conventional tablets at a dosage of 20 mg twice daily can be switched to a dosage of 40 mg every morning as Metadate® CD extended-release capsules.

The manufacturer of Ritalin® LA extended-release capsules states that patients receiving conventional or extended-release methylphenidate hydrochloride tablets may be switched to Ritalin® LA extended-release capsules. Patients being transferred from methylphenidate hydrochloride therapy using a conventional tablet at a dosage of 5 mg twice daily can be switched to a dosage of 10 mg every morning as Ritalin® LA extended-release capsules. Patients receiving methylphenidate hydrochloride therapy using a conventional tablet at a dosage of 10 mg twice daily or a 20-mg dosage of an extended-release tablet can be switched to a dosage of 20 mg every morning as Ritalin® LA extended-release capsules. Patients being transferred from methylphenidate hydrochloride therapy using a conventional tablet at a dosage of 15 mg twice daily can be switched to a dosage of 30 mg every morning as Ritalin® LA extended-release capsules. Patients receiving methylphenidate hydrochloride therapy using a conventional tablet at a dosage of 20 mg twice daily or a 40-mg dosage of an extended-release tablet can be switched to a dosage of 40 mg every morning as Ritalin® LA extended-release capsules. Patients being transferred from methylphenidate hydrochloride therapy using a conventional tablet at a dosage of 30 mg twice daily or a 60-mg dosage of an extended-release tablet can be switched to a dosage of 60 mg every morning as Ritalin® LA extended-release capsules. For other conventional or extended-release tablet regimens, the nearest daily dosage can be substituted based on clinical judgment.

The manufacturer of Concerta® extended-release methylphenidate hydrochloride trilayer core tablets states that patients receiving conventional methylphenidate hydrochloride tablets may be switched to Concerta® extended-release trilayer core tablets. Patients being transferred from methylphenidate hydrochloride therapy using a conventional tablet at a dosage of 5 mg 2 or 3 times daily can be switched to a dosage of 18 mg every morning as the extended-release trilayer core tablets. Patients receiving methylphenidate hydrochloride therapy using a conventional tablet at a dosage of 10 mg 2 or 3 times daily can be switched to 36 mg every morning of the methylphenidate hydrochloride extended-release trilayer core tablets. Patients receiving methylphenidate hydrochloride therapy using a conventional tablet at a dosage of 15 mg 2 or 3 times daily can be switched to 54 mg every morning as the extended-release trilayer core tablets. The initial dosage of methylphenidate hydrochloride as extended-release trilayer core tablets in patients being switched from conventional tablets should not exceed 54 mg daily. A 27-mg extended-release trilayer core tablet also is available for patients who require a more gradual titration or who can not tolerate a dosage of 36 mg daily. For other conventional or extended-release tablet regimens, the nearest equivalent daily dosage can be substituted based on clinical judgment. Subsequent titration to higher or lower dosages may be necessary and should occur at approximately weekly intervals, guided by the patient's clinical response and tolerance; however, the manufacturer states that daily dosages exceeding 72 mg are not recommended.

In some patients receiving long-acting methylphenidate preparations, supplemental doses of a short-acting (conventional) preparation may be needed.

Transdermal System. Dosage titration, final dosage, and wear time of the transdermal system should be individualized according to the needs and response of the patient.

The recommended initial dosage of methylphenidate in patients who are receiving the transdermal formulation as their initial methylphenidate regimen is 1 system delivering 10 mg/9 hours applied once daily. If adequate response is not achieved, dosage may be increased at weekly intervals by advancing to the next larger dosage system (i.e., a dosage system delivering 15 mg/9 hours applied once daily during week 2, followed by a dosage system delivering 20 mg/9 hours applied once daily during week 3, and then a dosage system delivering 30 mg/9 hours applied once daily during week 4).

Because differences in bioavailability exist between the methylphenidate transdermal system and other methylphenidate formulations, patients being transferred from therapy with other methylphenidate formulations to transdermal therapy with the drug should receive the same initial transdermal dosage and follow the same dosage titration schedule recommended for patients receiving transdermal methylphenidate as their initial methylphenidate regimen.

The methylphenidate transdermal system may be removed earlier than 9 hours if a shorter duration of effect is desired or if late-day adverse effects occur. If aggravation of symptoms or other adverse events occur, the dosage or wear time should be reduced, or, if necessary, the drug should be discontinued.

Narcolepsy In the treatment of narcolepsy, the usual oral adult dosage of methylphenidate hydrochloride is 10 mg 2 or 3 times daily, given 30–45 minutes before meals. Some patients may require 40–60 mg daily; in others, 10–15 mg daily may be adequate.

Cautions

Methylphenidate generally is well tolerated. Common adverse effects of the drug include nervous system (insomnia, delayed sleep onset, headache, nervousness, jitteriness, social withdrawal) and GI (anorexia) effects. Most adverse effects of methylphenidate can be managed successfully by adjustment in dosage and/or schedule. About 15–30% of children with ADHD experience tics while receiving stimulants such as methylphenidate, but such tics usually are transient. About half of children with ADHD have underlying Tourette's syndrome, and the effects of stimulants on tics are unpredictable; the presence or emergence of tics is not an absolute contraindication to stimulant therapy and some evidence indicates that the incidence of tics is not increased with such therapy.

Discontinuance of methylphenidate therapy, because of sadness and an increase in tics, respectively, was required in 0.9% of patients receiving extended-release trilayer core tablets and 1% of patients receiving placebo in a 4-week controlled study in children. In a 2-week controlled study in adolescents, discontinuance of methylphenidate therapy (because of increased mood irritability) was required in 0% of patients receiving extended-release trilayer core tablets and 1.1 % of patients receiving placebo. In uncontrolled clinical trials, adverse effects requiring discontinuance of methylphenidate therapy occurred in 6.7% of patients receiving the extended-release trilayer core tablets. The principal reasons for discontinuance were insomnia in 1.5% of patients, twitching in 1% of patients, and nervousness, emotional lability, abdominal pain, and anorexia each in 0.7% of patients. Discontinuance of methylphenidate therapy also occurred in 2 patients (1%) receiving extended-release capsules (Metadate® CD) in controlled clinical trials, principally because of rash and pruritus in one patient and headache, abdominal pain, and dizziness in the other patient. In addition, discontinuance of methylphenidate therapy because of depression occurred in a child with ADHD (1.5%) receiving extended-release capsules (Ritalin® LA) in a double-blind controlled clinical trial. Discontinuance also occurred in 6 patients (3.7%) receiving the drug in this trial during the initial single-blind titration period; the reasons for discontinuance were anger (2 patients), hypomania, anxiety, depressed mood, fatigue, migraine, and lethargy. In a 7-week controlled trial in children, adverse effects requiring discontinuance of therapy occurred in 7.1% of patients receiving transdermal methylphenidate and 1.2% of those receiving placebo; reasons for discontinuance of transdermal methylphenidate therapy included erythema or other reactions at the application site, confusional state, crying, headache, irritability, tics, viral infection, or infectious mononucleosis.

Loss of appetite, abdominal pain, weight loss during prolonged therapy, insomnia, and tachycardia may occur more frequently in children than in adults receiving methylphenidate.

■ **Nervous System Effects** The most frequent adverse effects of methylphenidate appear to be dose related and include nervousness and insomnia. Insomnia has been reported in 4–5% of children and adolescents with ADHD receiving methylphenidate hydrochloride extended-release trilayer core tablets, in 5% of children with ADHD receiving Metadate® CD extended-release capsules, in about 3% of children with ADHD receiving Ritalin® LA extended-release capsules, and in 13% of children with ADHD receiving the drug as a transdermal system in clinical trials. Nervousness and insomnia usually can be controlled by reducing dosage and not administering the drug in the afternoon or evening. Headache has been reported in 9–14% of children and adolescents with ADHD receiving methylphenidate hydrochloride extended-release trilayer

core tablets and in 12% of children with ADHD receiving extended-release capsules of the drug in clinical trials. Affect lability (including emotionality and emotional sensitivity, instability, and lability) has been reported in 6% of children with ADHD receiving methylphenidate as a transdermal system in clinical trials. Dizziness was reported in 2% of children with ADHD receiving extended-release trilayer core tablets in clinical trials. In 2 uncontrolled studies, the cumulative incidence of new-onset tics in children receiving methylphenidate hydrochloride extended-release trilayer core tablets was reported to be 9% after 27 months of treatment (first study) and 1% after up to 9 months of treatment (second study). Ties were reported in 7% of children with ADHD receiving methylphenidate as a transdermal system in clinical trials.

Toxic psychosis and Tourette's syndrome have been reported rarely in patients receiving methylphenidate. Neuroleptic malignant syndrome (NMS) also has been reported rarely in patients receiving methylphenidate; most of these patients also were receiving other drugs that have been associated with NMS. An NMS-like syndrome developed in one 10-year old boy (who had been receiving methylphenidate for about 18 months) 45 minutes after ingesting the first dose of venlafaxine. It is not known if such a reaction was associated with administration of either drug alone or if it represented a drug interaction between methylphenidate and venlafaxine or, alternatively, if the reaction was of unknown etiology.

Other adverse effects of methylphenidate include akathisia, dyskinesia, drowsiness, and aggressive behavior. Depression, anxiety, abnormal behavior, irritability, and suicidal behavior (including completed suicide) have been reported in patients receiving methylphenidate, but a causal relationship to the drug has not been definitely established.

■ **GI and Growth Effects** Abdominal pain and anorexia have been reported in 7 and 2–4%, respectively, of children and adolescents with ADHD receiving methylphenidate hydrochloride extended-release trilayer core tablets in clinical trials and in 7 and 9%, respectively, of children with ADHD receiving methylphenidate extended-release capsules (Metadate® CD) in clinical trials. Anorexia also has been reported in about 3% of children with ADHD receiving extended-release capsules (Ritalin® LA) and in 5% of children with ADHD receiving methylphenidate as a transdermal system in controlled clinical trials. Although appetite suppression and weight loss are common with stimulant therapy, there is no apparent difference in their occurrence between methylphenidate or amphetamine (e.g., dextroamphetamine) therapy in children. Results of one study suggest that prolonged methylphenidate hydrochloride therapy (30–40 mg daily) may cause suppression of normal weight gain in children. Results of an analysis of weight and height patterns in children 7–13 years of age suggested that treatment with methylphenidate for up to 3 years was associated with a temporary slowing in growth rate (on average, height gain was suppressed by about 2 cm and weight gain was suppressed by 2.7 kg over 3 years), without evidence of growth rebound during this period of development. Published data are inadequate to determine whether long-term use of amphetamines may cause similar suppression of growth; however, it is anticipated that amphetamines, like methylphenidate, also cause temporary growth suppression. Therefore, the manufacturers of stimulant preparations state that growth should be monitored during therapy with stimulants, and children who are not growing or gaining height or weight as expected may require temporary discontinuance of therapy. Although concerns about potential dose-related growth delays in children have been raised, a prospective follow-up study into adulthood found no significant impairment in height achieved. In general, studies of stimulants in children have found little or no decrease in expected height, with any decrease in growth early in treatment being compensated for later on. Although drug holidays during summers have been suggested to minimize weight loss and other potential adverse effects, there currently are no data from controlled studies establishing whether such holidays are beneficial or associated with risks.

Vomiting was reported in 3–4% and diarrhea was reported in 2% of children and adolescents with ADHD receiving methylphenidate hydrochloride extended-release trilayer core tablets in clinical trials. Nausea and vomiting were reported in 12 and 10%, respectively, of children with ADHD receiving methylphenidate as a transdermal system in clinical trials. Other adverse GI effects of methylphenidate include weight loss during prolonged therapy and dryness of the throat.

■ **Hepatic Effects** Abnormal liver function, ranging from serum aminotransferase (transaminase) elevations to hepatic coma, has been reported in patients receiving methylphenidate, although a definite causal relationship has not been established. Hepatotoxicity was associated with methylphenidate therapy in at least one patient.

■ **Dermatologic and Sensitivity Reactions** Hypersensitivity reactions including rash, urticaria, fever, arthralgia, exfoliative dermatitis, erythema multiforme with histopathologic findings of necrotizing vasculitis, and thrombocytopenic purpura may occur in patients receiving methylphenidate. Stevens-Johnson syndrome has been reported rarely. Fixed drug eruption has been reported in patients receiving methylphenidate, although a definite causal relationship has not been established. Erythema occurs in a majority of patients receiving methylphenidate as the transdermal system but generally causes minimal or no discomfort.

In a study evaluating the potential for methylphenidate transdermal system to cause contact sensitization, continuous exposure of the same skin site to transdermal methylphenidate for 3 weeks resulted in contact sensitization; contact sensitization was confirmed by rechallenge in some individuals. Contact sensitization has not been reported in patients who used the transdermal system as prescribed (i.e., alternating application sites on the hip). However, because sensitization was not specifically assessed in efficacy studies, the incidence of contact sensitization associated with appropriate use of the transdermal system is currently not known. (See Precautions Associated with Specific Methylphenidate Formulations under Cautions: Precautions and Contraindications.)

■ **Hematologic Effects** Thrombocytopenia and/or easy bruisability, epistaxis, and gingival bleeding; leukopenia; anemia; and eosinophilia have been reported rarely in patients receiving methylphenidate, but a causal relationship to the drug has not been definitely established. (See Other Precautions and Contraindications under Cautions: Precautions and Contraindications.)

■ **Cardiovascular Effects** Sudden death, stroke, myocardial infarction, angina, tachycardia, cardiac arrhythmias, palpitation, and increase or decrease in blood pressure and pulse rate may occur in patients receiving stimulants, including methylphenidate. (See Cardiovascular Precautions under Cautions: Precautions and Contraindications.) Isolated cases of cerebral arteritis and/or occlusion have been reported in patients receiving methylphenidate. Cardiac arrest, Raynaud's phenomenon, peripheral coldness, and reversible ischemic neurologic deficit have been reported in patients receiving methylphenidate, although a definite causal relationship has not been established.

■ **Ocular Effects** Blurred vision and difficulty with accommodation have been reported in patients receiving methylphenidate.

■ **Respiratory Effects** Upper respiratory tract infection, increased cough, pharyngitis, sinusitis, and rhinitis were reported in 8, 4, 2–4, 3, and 3%, respectively, of children and adolescents receiving methylphenidate hydrochloride extended-release trilayer core tablets in clinical trials. Nasal congestion and nasopharyngitis were reported in 6 and 5%, respectively, of children receiving methylphenidate as a transdermal system in clinical trials.

■ **Other Adverse Effects** Pulmonary talc granulomata, superficial abscesses, other foreign body reactions, and eosinophilia have been reported in drug abusers who have dissolved methylphenidate hydrochloride tablets in water and injected the resulting solution.

Scalp hair loss has been reported rarely in patients receiving methylphenidate, but a causal relationship to the drug has not been definitely established.

Dysmenorrhea has been reported in adolescents receiving methylphenidate hydrochloride extended-release trilayer core tablets.

■ **Precautions and Contraindications** ***Psychiatric Precautions*** Aggressive behavior and hostility frequently are observed in children and adolescents with ADHD and have been reported in patients receiving drug therapy for the disorder. Although a causal relationship to stimulants has not been established, patients beginning treatment for ADHD should be monitored for the onset or worsening of aggressive behavior or hostility.

Psychotic or manic symptoms (e.g., hallucinations, delusional thinking, mania) have been reported in children and adolescents without prior history of psychotic illness or mania who received usual dosages of stimulants. In a pooled analysis of multiple short-term, placebo-controlled studies, such symptoms occurred in about 0.1% of patients receiving usual dosages of stimulants (i.e., methylphenidate, amphetamine) compared with 0% of those receiving placebo. If psychotic or manic symptoms occur during stimulant therapy, a causal relationship to stimulants should be considered, and discontinuance of therapy may be appropriate.

Stimulants should be used with caution in the management of ADHD in patients with comorbid bipolar disorder because of the potential for precipitation of mixed or manic episodes in such patients. Prior to initiating stimulant therapy, patients with ADHD and comorbid depressive symptoms should be carefully screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history (e.g., family history of suicide, bipolar disorder, or depression).

Stimulants may exacerbate symptoms of behavior disturbance and thought disorder in patients with a preexisting psychotic disorder.

Each time methylphenidate is dispensed, a medication guide should be provided to the patient or caregiver, alerting them to the risks associated with stimulant therapy (e.g., adverse psychiatric effects, possible cardiovascular risks) and advising them of necessary precautions. (See Other Precautions and Contraindications under Cautions: Precautions and Contraindications.) Patients or caregivers should be instructed to inform clinicians of preexisting illnesses or conditions, including suicidal ideation or behaviors of mental or psychiatric disorders. They also should be instructed to inform clinicians immediately if adverse psychiatric effects (e.g., hallucinations, delusional thinking, mania) occur during stimulant therapy.

Cardiovascular Precautions Stimulants, including methylphenidate, cause modest increases in average blood pressure (i.e., by about 2–4 mm Hg) and heart rate (i.e., by about 3–6 beats/minute); larger increases may occur in some patients. Although modest increases would not be expected to have short-term sequelae, all patients should be monitored for larger changes in blood pressure and heart rate. Caution is advised in patients with underlying medical conditions that might be affected by increases in blood pressure or heart rate (e.g., hypertension, heart failure, recent myocardial infarction, ventricular arrhythmia).

Although a causal relationship to stimulants has not been established, sudden unexplained death, stroke, and myocardial infarction have been reported in adults receiving usual dosages of stimulants for the treatment of ADHD.

Sudden unexplained death also has been reported in children and adolescents with structural cardiac abnormalities or other serious cardiac conditions receiving usual dosages of CNS stimulants. Results of one retrospective, case-control epidemiologic study showed that there may be an association between use of stimulant medications (e.g., methylphenidate) and sudden unexplained death in healthy children and adolescents. (See Cautions: Pediatric Precautions.) Given the study limitations, the US Food and Drug Administration (FDA) is unable to conclude that these data affect the overall risk and benefit profile of stimulant medications used to treat ADHD in children and adolescents. Amphetamines or other stimulants should not be discontinued by parents of children or patients receiving these medications for ADHD before consulting with their clinician. Because of postmarketing reports and the results of this and other epidemiologic studies, FDA is conducting an ongoing review of the safety of amphetamines and other stimulants to evaluate a possible link between use of these agents and sudden death in children. To determine whether there is a direct causal relationship between use of stimulants and serious adverse cardiovascular events, the Agency for Healthcare Research and Quality (AHRQ) and FDA announced in 2007 that they are collaborating on a large study evaluating clinical data on approximately 500,000 adults and children who received these drugs for management of ADHD during a 7-year period ending in 2005; data collection for the study is expected to be completed in 2009.

Children, adolescents, and adults who are being considered for stimulant therapy should undergo a thorough medical history review (including evaluation for a family history of sudden death or ventricular arrhythmia) and physical examination to detect the presence of cardiac disease, and should receive further cardiac evaluation (e.g., ECG, echocardiogram) if initial findings suggest such disease. Although some serious cardiac conditions are independently associated with an increased risk of sudden death, CNS stimulants generally should *not* be used in children, adolescents, or adults with known serious structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, coronary artery disease, or other serious cardiac conditions. Patients who develop exertional chest pain, unexplained syncope, or other manifestations suggestive of cardiac disease during stimulant therapy should undergo prompt cardiac evaluation.

Each time methylphenidate is dispensed, a medication guide should be provided to the patient or caregiver, alerting them to the risks associated with stimulant therapy (e.g., possible cardiovascular risks, adverse psychiatric effects) and advising them of necessary precautions. (See Other Precautions and Contraindications under Cautions: Precautions and Contraindications.) Patients or caregivers should be instructed to inform clinicians of preexisting illnesses or conditions, including cardiac or cardiovascular disease. They also should be instructed to inform clinicians immediately if adverse cardiovascular effects (e.g., chest pain, shortness of breath, fainting) occur during stimulant therapy.

For further information on screening for cardiac conditions, selecting appropriate candidates for stimulant therapy, and monitoring for treatment-emergent cardiac conditions, see Cardiovascular Precautions under Cautions: Precautions and Contraindications, in the Amphetamines General Statement 28:20.04.

Precautions Associated with Specific Methylphenidate Formulations Administration of methylphenidate hydrochloride chewable tablets without adequate fluid may cause tablet contents to swell, resulting in blockage of the throat or esophagus and, possibly, choking. Therefore, chewable tablets should be taken with a full glass (i.e., at least 240 mL [8 ounces]) of water or other fluid and should *not* be administered in patients with difficulty swallowing. Patients should be advised to immediately seek medical attention if they experience chest pain, vomiting, or difficulty in swallowing or breathing following administration of the chewable tablets.

Individuals with phenylketonuria (i.e., homozygous genetic deficiency of phenylalanine hydroxylase) and other individuals who must restrict their intake of phenylalanine should be warned that each 2.5-, 5-, or 10-mg chewable tablet contains aspartame (NutraSweet®), which is metabolized in the GI tract to provide about 0.42, 0.84, or 1.68 mg, respectively, of phenylalanine following oral administration.

Methylphenidate hydrochloride extended-release capsules (Metadate® CD) contain sucrose and should not be used in patients with hereditary fructose intolerance, glucose-galactose malabsorption, or sucrase-isomaltase insufficiency.

Methylphenidate hydrochloride extended-release trilayer core tablets generally should not be used in patients with preexisting severe GI narrowing since obstruction may occur.

Patients receiving the methylphenidate transdermal system should be advised to avoid exposing the application site to direct external heat sources (e.g., heating pads, electric blankets, heated water beds) while wearing the transdermal system. Release of methylphenidate from the transdermal system is temperature dependent; release may increase more than twofold when the system is exposed to heat. (See Pharmacokinetics: Absorption.)

Use of the methylphenidate transdermal system may result in contact sensitization. Transdermal methylphenidate should be discontinued if contact sensitization is suspected (i.e., if erythema develops and is accompanied by evidence of a more intense local reaction [e.g., edema, papules, vesicles] that does not improve substantially within 48 hours or that spreads beyond the application site). Diagnosis of allergic contact dermatitis should be confirmed by appropriate diagnostic testing. Patients sensitized from use of the methylphenidate transdermal system may develop systemic sensitization or other systemic reactions if methylphenidate-containing products are administered via other routes (e.g., orally). Manifestations of systemic sensitization may include a flare-up of previous dermatitis or of prior positive patch test sites, or generalized skin eruptions in previously unaffected skin. Other systemic reactions may include headache, fever, malaise, arthralgia, diarrhea, or vomiting. Patients who develop contact sensitization to the methylphenidate transdermal system should be under close medical supervision if oral methylphenidate therapy is initiated. Some patients sensitized to methylphenidate by exposure to the methylphenidate transdermal system may not be able to receive methylphenidate in any form.

Other Precautions and Contraindications The manufacturer's patient information (medication guide) should be provided to the patient or caregiver each time methylphenidate is dispensed, and the clinician should discuss and answer questions about its contents (e.g., benefits and risks of stimulant therapy, appropriate use) as needed. The patient or caregiver also should be instructed to read and understand the contents of the medication guide before initiating therapy and each time the prescription is refilled.

Patients or caregivers should be instructed to inform clinicians of preexisting illnesses or conditions (e.g., cardiac or cardiovascular disease, thyroid disease, glaucoma, suicidal ideation or behaviors, mental or psychiatric disorder, seizures, history of substance abuse).

The manufacturers recommend that laboratory tests, including periodic complete blood cell (with differential) and platelet counts, be performed periodically during prolonged methylphenidate hydrochloride therapy. However, the clinical rationale for this precaution has been questioned by some clinicians since adverse hematologic effects have occurred only rarely in patients receiving methylphenidate and a causal relationship to the drug has not been conclusively established in these cases. Most clinicians consider routine hematologic monitoring unnecessary in the absence of clinical signs (e.g., fever, sore throat, unusual bleeding or bruising) suggestive of possible hematologic toxicity, although some clinicians suggest annual hematologic monitoring in any patient receiving prolonged therapy with the drug. In addition, the American Academy of Pediatrics (AAP) states that routine hematologic, serologic, or ECG monitoring is *not* necessary during methylphenidate therapy.

If paradoxical aggravation of symptoms occurs during methylphenidate therapy, dosage should be reduced or the drug discontinued.

Tolerance and psychological dependence with varying degrees of abnormal behavior have been reported in patients chronically taking large doses of methylphenidate. Frank psychotic episodes including hallucinosis can occur, particularly with parenteral abuse. The possibility of psychological or physical dependence should be considered, particularly when methylphenidate is administered to alcoholics, emotionally unstable patients, or those known to have been addicted to other drugs. The drug should be administered with caution to persons with a history of drug or alcohol dependence since such patients may increase dosage on their own initiative.

Abrupt withdrawal of methylphenidate following prolonged administration may unmask severe depression as well as the effects of chronic overactivity; paranoid and suicidal ideation, dysphoric mood (e.g., depression, irritability, anxiety), fatigue, insomnia or hypersomnia, psychomotor agitation, and disturbed sleep also may occur. Therefore, patients should be carefully supervised during withdrawal of the drug; long-term follow-up may be required since some manifestations (e.g., depression) may persist for prolonged periods.

Visual disturbances (difficulty with accommodation, blurred vision) have been reported in patients receiving stimulants, including methylphenidate.

Methylphenidate should be used with caution in patients with a history of seizures and/or EEG abnormalities. There is some clinical evidence that stimulants, including methylphenidate, may lower the seizure threshold in patients with a history of seizures, in those with prior EEG abnormalities in the absence of seizures, and, very rarely, in those without a history of seizures and no prior evidence of EEG abnormalities. Although safe concomitant use of methylphenidate and anticonvulsants has not been established, studies of methylphenidate use have not shown an increase in seizure frequency or severity when the stimulant was used in patients receiving appropriate anticonvulsant therapy. If seizures occur in patients receiving methylphenidate, the drug should be discontinued.

Therapy with CNS stimulants may be associated with at least a temporary suppression of growth in children. (See Cautions: GI and Growth Effects.)

Methylphenidate is contraindicated in patients with a history of marked anxiety, tension, and agitation, since the drug may aggravate these symptoms. Methylphenidate is also contraindicated in patients with glaucoma, in patients with motor tics or a family history or diagnosis of Tourette's syndrome, and in those known to be hypersensitive to the drug. However, AAP states that the presence of tics before or during medical management of ADHD is *not* an absolute contraindication to stimulant drug use. (See the opening discussion in Cautions.) Methylphenidate also is contraindicated during or within 14 days of administration of monoamine oxidase (MAO) inhibitors since hypertensive crisis could result. (See Drug Interactions: Antidepressants.)

■ **Pediatric Precautions** Although safety and efficacy of methylphenidate in children younger than 6 years of age have not been established, the drug has been used in several controlled clinical studies in preschool-aged children up to 6 years of age. Some studies reported higher rates of adverse effects, particularly with higher dosages, than had previously been reported in children 6 years of age and older and the adverse effects reported in preschool-aged children may be different than those reported in older children with

ADHD. Some of the adverse behavioral effects reported in clinical studies in preschool-aged children receiving methylphenidate also were reported in those receiving placebo; some of these behaviors may actually improve in preschool-aged children receiving methylphenidate therapy. Other issues involved with the use of stimulants in children younger than 6 years of age are the lack of established dosage recommendations for this population. Additional study and experience are required to elucidate further the safety and efficacy of the drug in this age group.

Long-term administration of CNS stimulants has been associated with at least a temporary suppression of normal weight and/or height patterns in children; patients requiring long-term therapy with methylphenidate should be carefully monitored and the drug should be discontinued temporarily in children in whom suppression of normal growth or weight gain is observed. However, AAP states that studies of stimulants in children generally have found little or no decrease in expected height, with any decrease in growth early in treatment being compensated for later on. (See Cautions: GI and Growth Effects.)

Sudden death has been reported in children and adolescents with structural cardiac abnormalities or other serious cardiac conditions receiving usual dosages of CNS stimulants. Results of one retrospective, case-control epidemiologic study suggested a possible association between use of stimulant medications and sudden unexplained death in healthy children and adolescents. (See Cardiovascular Precautions under Cautions: Precautions and Contraindications.)

■ **Pregnancy and Lactation** Although there are no adequate and controlled studies to date in humans, methylphenidate hydrochloride has been shown to have teratogenic effects in rabbits when given at dosages 100 and 40 times the recommended human dosage on a mg/kg or mg/m² basis, respectively. Methylphenidate hydrochloride should be used during pregnancy only when the potential benefits justify the possible risks to the fetus.

It is not known whether methylphenidate is distributed into human milk. Because many drugs are distributed into human milk, caution should be exercised if methylphenidate is administered to a nursing woman.

Drug Interactions

■ **Antidepressants** Because monoamine oxidase (MAO) inhibitors potentiate the pressor effects of sympathomimetic drugs, methylphenidate is contraindicated in patients currently receiving, or having recently received (i.e., within 2 weeks), MAO inhibitor therapy. The metabolism of tricyclic antidepressants (e.g., imipramine, clomipramine, desipramine) has been reported to be inhibited when these drugs are used in patients receiving methylphenidate. Some manufacturers state that the metabolism of selective serotonin-reuptake inhibitors (SSRIs) may be inhibited when methylphenidate is used concomitantly. Dosage reduction of tricyclic antidepressants and SSRIs may be required in patients receiving concomitant methylphenidate therapy.

■ **Cardiovascular Agents** Methylphenidate should be used with caution in patients receiving pressor agents. Methylphenidate may antagonize the effects of antihypertensive agents (e.g., guanethidine [no longer commercially available in the US]) or bretylium. Rare cases of serious adverse cardiovascular effects, including death, have occurred in patients receiving methylphenidate and clonidine concomitantly, although due to the presence of possibly confounding risk factors and lack of systematic evaluation, causality has not been established.

■ **Other Drugs** The metabolism of coumarin anticoagulants and anticonvulsants (e.g., phenobarbital, phenytoin, primidone) has been reported to be inhibited when these drugs are administered in patients receiving methylphenidate. Although additional studies did not confirm the reported inhibition of metabolism of anticonvulsants and coumarin anticoagulants, the possibility that methylphenidate may raise the serum concentrations of these drugs to toxic concentrations necessitating a decrease in dosage should be considered. Additionally, metabolism of phenylbutazone (no longer commercially available in the US) has been reported to be inhibited when administered in patients receiving methylphenidate hydrochloride conventional or extended-release tablets. Dosage reduction of coumarin anticoagulants, anticonvulsants, or phenylbutazone may be required in patients receiving concomitant methylphenidate therapy. It may be necessary to monitor plasma drug concentrations (or, in the case of coumarin anticoagulants, prothrombin time [PT]) when methylphenidate is initiated or discontinued.

Studies to evaluate the effects of changes in gastric pH on the absorption of methylphenidate hydrochloride administered as extended-release capsules (Ritalin® LA) have not been performed to date; the manufacturer states that concurrent use of drugs that increase gastric pH (e.g., antacids, H_2-receptor antagonists) could potentially alter the release characteristics of the formulation.

Acute Toxicity

■ **Manifestations** Acute toxicity due to methylphenidate overdosage results in symptoms similar to those of acute amphetamine intoxication and may be manifested by cardiovascular symptoms including flushing, palpitation, hypertension, cardiac arrhythmias, and tachycardia. Mental disturbances such as confusion, delirium, euphoria, hallucinations, and toxic psychosis may also occur. Other symptoms of overdosage include agitation, headache, vomiting, dryness of mucous membranes, mydriasis, hyperpyrexia, sweating, tremors, hyperreflexia, muscle twitching, and seizures which may be followed by coma.

■ **Treatment** In the treatment of methylphenidate overdosage, general physiologic supportive measures, including maintenance of adequate circulation and respiratory exchange should be immediately instituted. The patient should be protected against self-injury and should be isolated to avoid possible external stimuli. In cases of overdosage involving transdermal methylphenidate, all transdermal systems of the drug should be removed immediately and the skin cleansed of any remaining adhesive; the potential for continued absorption of residual drug in the skin following system removal should be considered. If signs and symptoms of acute toxicity are not too severe and the patient is conscious, gastric contents may be evacuated following ingestion of oral dosage forms by induction of emesis or gastric lavage. In patients with severe intoxication, administration of a carefully titrated dose of a short-acting barbiturate may be required before beginning gastric lavage. External cooling procedures may be required for the treatment of hyperpyrexia. Effectiveness of peritoneal dialysis or extracorporeal hemodialysis for the treatment of methylphenidate overdosage has not been established.

Pharmacology

The pharmacologic actions of methylphenidate are qualitatively similar to those of the amphetamines and include CNS and respiratory stimulation and weak sympathomimetic activity. The mechanism of action involved in the central effect of methylphenidate has not been determined. The main sites of CNS action appear to be the cerebral cortex and subcortical structures including the thalamus; stimulation by methylphenidate causes an increase in motor activity, mental alertness, diminished sense of fatigue, brighter spirits, and mild euphoria. Methylphenidate apparently produces an anorexigenic effect. In usual therapeutic oral dosage, methylphenidate exhibits only moderate effects on the peripheral circulatory system.

Pharmacokinetics

■ **Absorption** Methylphenidate hydrochloride appears to be well absorbed from the GI tract; however, oral bioavailability of the drug is low (about 30%; range: 10–52%), which suggests substantial first-pass metabolism. Following oral administration of methylphenidate hydrochloride as conventional tablets, oral solution, or chewable tablets, peak plasma concentrations were attained at approximately 1–2 hours. Methylphenidate hydrochloride oral solution and chewable tablets are bioequivalent to methylphenidate hydrochloride conventional tablets.

Extended-release methylphenidate hydrochloride tablets are absorbed more slowly but to the same extent as the conventional tablets. Following oral administration of methylphenidate hydrochloride extended-release tablets (Methylin® ER, Ritalin-SR®) in children, peak plasma concentrations were attained at 4.7 hours.

After oral administration of methylphenidate hydrochloride 20 or 40 mg as extended-release capsules (Metadate® CD) in children, peak plasma concentrations were attained at 1.5 hours and again at 4.5 hours after a dose. In children, the mean peak plasma concentration and mean area under the plasma concentration-time curve (AUC) for methylphenidate were slightly lower following administration of 20 mg of the drug once daily as Metadate® CD extended-release capsules than following administration of 10 mg twice daily as conventional tablets. In children and adults, the relative bioavailability of Ritalin® LA extended-release capsules administered once daily is comparable to that of the conventional tablets administered twice daily 4 hours apart. The initial rate of absorption of methylphenidate hydrochloride and the time to first and second peak plasma concentrations were similar following administration of 40 mg of the drug once daily as Ritalin® LA extended-release capsules or 20 mg twice daily (given 4 hours apart) as conventional tablets, but greater interindividual variability and a smaller difference between peak and trough plasma concentrations (resulting from a lower second peak concentration and a higher minimum concentration between the 2 peak concentrations) were observed with the extended-release capsules. In adults, the relative bioavailability of the extended-release trilayer core tablets of methylphenidate hydrochloride (Concerta®) administered once daily is comparable to that of the conventional tablets administered 3 times daily. Following oral administration of the extended-release trilayer core tablets of methylphenidate hydrochloride in healthy adults, an initial peak plasma concentration is attained within 1 hour while peak plasma concentrations of about 3.7 ng/mL are achieved within approximately 6–10 hours.

Following application of a single transdermal system (Daytrana®), peak plasma methylphenidate concentrations are attained within 7.5–10.5 hours. Application of the transdermal system to inflamed skin results in shorter time to peak plasma concentration (4 hours) and a threefold increase in peak plasma concentration and AUC compared with application to intact skin. When heat is applied to the transdermal system after application, time to peak plasma concentration occurs 0.5 hour earlier, and median peak plasma concentration and AUC are twofold and 2.5-fold higher, respectively, than those observed following application without heat. Application sites other than the hip can have different absorption characteristics and have not been adequately studied. Some data suggest that transdermal absorption of methylphenidate may be increased with chronic administration.

Effects persist for 3–6 hours after oral administration of conventional tablets, about 3–8 hours after oral administration of certain extended-release tablets (e.g., Metadate® ER, Methylin® ER, Ritalin-SR®), and about 8–12 hours after oral administration of extended-release trilayer core tablets (Concerta®) or extended-release capsules (e.g., Metadate® CD, Ritalin® LA).

Because of substantially greater first-pass metabolism following oral compared with transdermal administration, a lower transdermal dose of methylphenidate may result in greater systemic exposure to *d*-methylphenidate (the more pharmacologically active isomer) than a higher (on a mg/kg basis) oral dose of the drug. Following repeated transdermal administration of methylphenidate, *l*-methylphenidate is systemically available; on average, systemic exposure to *l*-methylphenidate is 27–45% less than exposure to *d*-methylphenidate. Little, if any, *l*-methylphenidate is systemically available following oral administration of the drug.

In adults, administration of methylphenidate hydrochloride 20 mg as an oral solution with a high-fat meal delayed the peak plasma concentration by approximately 1 hour and increased the average peak plasma concentration and AUC for methylphenidate by 13 and 25%, respectively; the magnitude of increase in peak plasma concentration and AUC is similar between methylphenidate hydrochloride oral solution and conventional tablets. Administration of methylphenidate hydrochloride 20 mg as chewable tablets with a high-fat meal in adults delayed the time to peak plasma concentration by approximately 1 hour and increased the AUC by about 20%; the magnitude of food effect is comparable to that observed with conventional tablets. Administration of methylphenidate hydrochloride 40 mg as extended-release capsules (Metadate® CD) with a high-fat meal in adults delayed the first peak plasma concentration by approximately 1 hour and increased the average peak plasma concentration and AUC for methylphenidate by 30 and 17%, respectively. In a single-dose study in healthy adults, administration of Ritalin® LA extended-release capsules with a high-fat breakfast delayed the first and second peak plasma concentrations and decreased the second mean peak plasma concentration by 25% compared with administration in the fasting state. However, the bioavailability of the extended-release capsules (i.e., Metadate® CD, Ritalin® LA) was not affected by opening the capsules and sprinkling the contents onto applesauce.

■ **Distribution** The extent of methylphenidate distribution in humans is unknown.

■ **Elimination** Methylphenidate is metabolized primarily by de-esterification to form α-phenylpiperidine acetic acid (ritalinic acid), which has little or no pharmacologic activity. Some data indicate that clearance of methylphenidate increases with increasing weight, suggesting that patients with higher body weight may have lower exposures to total methylphenidate at similar doses.

Following oral administration of methylphenidate hydrochloride conventional tablets in adults or children, the mean terminal elimination half-life was reported to be 3.5 or 2.5 hours, respectively. The mean terminal elimination half-life following oral administration of methylphenidate hydrochloride as an oral solution in adults is similar to that following administration of conventional tablets. The mean terminal half-life following oral administration of methylphenidate hydrochloride 20 mg as chewable tablets in adults is 3 hours, which is comparable to that following administration of conventional tablets. Following oral administration of methylphenidate hydrochloride conventional (5 mg 3 times daily) or extended-release trilayer core tablets (Concerta®) (18 mg once daily) in adults, the plasma elimination half-life reportedly is 3 or 3.5 hours, respectively. Following oral administration of a single 20-mg dose of methylphenidate hydrochloride as extended-release capsules (Metadate® CD) in adults, the mean terminal half-life of the drug was reported to be 6.8 hours. The mean elimination half-life of methylphenidate following removal of the transdermal system in children 6–12 years was approximately 3–4 hours for *d*-methylphenidate and 1.4–2.9 hours for *l*-methylphenidate.

Following oral administration of 20 mg of radiolabeled methylphenidate hydrochloride as conventional tablets, approximately 50, 80, and 95% of the dose was recovered as metabolites in urine within 6, 24, and 90 hours, respectively.

Chemistry and Stability

■ **Chemistry** Methylphenidate hydrochloride is a piperidine-derivative stimulant. The drug occurs as a fine, white, odorless, crystalline powder and is freely soluble in water and soluble in alcohol. Methylphenidate hydrochloride is commercially available as conventional tablets, chewable tablets, and an oral solution formulated for immediate release of the drug; extended-release tablets (e.g., Metadate® ER, Methylin® ER, Ritalin-SR®) with an intermediate duration of action; and extended-release capsules (e.g., Metadate® CD, Ritalin® LA) and extended-release tablets (e.g., Concerta®) with a longer duration of action. Methylphenidate is commercially available as a transdermal system.

The commercially available methylphenidate hydrochloride extended-release capsules (Metadate® CD) contain 30% of the dose in immediate-release pellets and 70% of the dose in extended-release pellets that slowly release methylphenidate. The commercially available methylphenidate hydrochloride extended-release capsules (Ritalin® LA) contain the drug in equal amounts in immediate- and extended-release pellets.

The commercially available extended-release tablets of methylphenidate hydrochloride (Concerta®) contain the drug in an oral osmotic delivery system formulation. The osmotic delivery system consists of an osmotically active trilayer core (comprised of two layers containing the drug and a push layer containing osmotically active components) surrounded by a semipermeable membrane with an immediate-release drug overcoat and a laser-drilled delivery orifice. When exposed to water in the GI tract, the drug overcoat is solubilized providing an initial dose of methylphenidate; as water enters the formulation, the osmotic layer expands and the drug is pushed out the delivery orifice of the membrane into the GI tract at a controlled rate. The rate of methylphenidate delivery in the GI tract is independent of GI pH or the presence of food in the GI tract. The inert tablet ingredients remain intact and are eliminated in feces.

The commercially available transdermal system of methylphenidate consists of a laminate film backing layer, an adhesive layer containing the drug, and a protective liner attached to the adhesive surface. The methylphenidate dosage delivered is dependent on the size of the transdermal system and the length of time the system is worn.

■ **Stability** Methylphenidate hydrochloride tablets, extended-release tablets, extended-release trilayer core tablets (Concerta®), and extended-release capsules (Metadate® CD, Ritalin® LA) and methylphenidate transdermal systems should be stored at a controlled room temperature of 25°C, but may be exposed to temperatures ranging from 15–30°C. Methylphenidate hydrochloride oral solution and chewable tablets should be stored at 20–25°C.

Preparations

Methylphenidate hydrochloride is subject to control under the Federal Controlled Substances Act of 1970 as a schedule II (C-II) drug.

Excipients in commercially available drug preparations may have clinically important effects in some individuals; consult specific product labeling for details.

Methylphenidate

Topical		
Transdermal System	10 mg/9 hours (27.5 mg/12.5 cm²)	**Daytrana®** (C-II), Shire
	15 mg/9 hours (41.3 mg/18.75 cm²)	**Daytrana®** (C-II), Shire
	20 mg/9 hours (55 mg/25 cm²)	**Daytrana®** (C-II), Shire
	30 mg/9 hours (82.5 mg/37.5 cm²)	**Daytrana®** (C-II), Shire

Methylphenidate Hydrochloride

Oral		
Capsules, extended-release (containing beads)	10 mg (beads, extended-release 7 mg with 3 mg immediate-release)	**Metadate® CD** (C-II), UCB
	10 mg (beads, extended-release 5 mg with 5 mg immediate-release)	**Ritalin® LA** (C-II), Novartis
	20 mg (beads, extended-release 14 mg with 6 mg immediate-release)	**Metadate® CD** (C-II), UCB
	20 mg (beads, extended-release 10 mg with 10 mg immediate-release)	**Ritalin® LA** (C-II), Novartis
	30 mg (beads, extended-release 21 mg with 9 mg immediate-release)	**Metadate® CD** (C-II), UCB
	30 mg (beads, extended-release 15 mg with 15 mg immediate-release)	**Ritalin® LA** (C-II), Novartis
	40 mg (beads, extended-release 28 mg with 12 mg immediate-release)	**Metadate® CD** (C-II), UCB
	40 mg (beads, extended-release 20 mg with 20 mg immediate-release)	**Ritalin® LA** (C-II), Novartis
	50 mg (beads, extended-release 35 mg with 15 mg immediate-release)	**Metadate® CD** (C-II), UCB
	60 mg (beads, extended-release 42 mg with 18 mg immediate-release)	**Metadate® CD** (C-II), UCB
Solution	5 mg/5 mL	**Methylin® Oral Solution** (C-II), Sciele
	10 mg/5 mL	**Methylin® Oral Solution** (C-II), Sciele
Tablets	5 mg*	**Methylin®** (C-II), Mallinckrodt
		Methylphenidate Hydrochloride Tablets (C-II)
		Ritalin® Hydrochloride (C-II), Novartis
	10 mg*	**Methylin®** (C-II; scored), Mallinckrodt
		Methylphenidate Hydrochloride Tablets (C-II)
		Ritalin® Hydrochloride (C-II; scored), Novartis

	20 mg*	Methylin* (C-II; scored), Mallinckrodt
		Methylphenidate Hydrochloride Tablets (C-II)
		Ritalin* Hydrochloride (C-II; scored), Novartis
Tablets, chewable	2.5 mg	Methylin* (C-II), Sciele
	5 mg	Methylin* (C-II), Sciele
	10 mg	Methylin* (C-II; scored), Sciele
Tablets, extended-release	10 mg	Metadate* ER (C-II), UCB
		Methylin* ER (C-II), Mallinckrodt
	20 mg*	Metadate* ER (C-II), UCB
		Methylin* ER (C-II), Mallinckrodt
		Methylphenidate Hydrochloride Tablets (C-II)
		Ritalin-SR* (C-II), Novartis
Tablets, extended-release core	18 mg (core 14 mg with 4 mg immediate-release)	Concerta* (C-II), McNeil
	27 mg (core 21 mg with 6 mg immediate-release)	Concerta* (C-II), McNeil
	36 mg (core 28 mg with 8 mg immediate-release)	Concerta* (C-II), McNeil
	54 mg (core 42 mg with 12 mg immediate-release)	Concerta* (C-II), McNeil

*available from one or more manufacturer, distributor, and/or repackager by generic (nonproprietary) name

Modafinil

■ Modafinil is a CNS stimulant that is structurally and pharmacologically distinct from other currently available CNS stimulants.

Uses

Modafinil is used to improve wakefulness in adults with excessive sleepiness associated with narcolepsy, obstructive sleep apnea/hypopnea syndrome (OSAHS), and shift work sleep disorder (SWSD). Careful attention to the diagnosis and treatment of the underlying sleep disorder is essential whenever modafinil is used in patients with these conditions. (See Diagnosis of Sleep Disorders under Warnings/Precautions: General Precautions, in Cautions.)

■ **Narcolepsy** Modafinil is used in the symptomatic treatment of narcolepsy to improve wakefulness in adults with excessive daytime sleepiness (EDS). Narcolepsy is a CNS disorder characterized by somnolence, often accompanied by sudden attacks of weakness (cataplexy) while awake and disrupted nocturnal sleep, and occasionally by hypnagogic hallucinations and/or sleep paralysis before falling asleep or awakening. The disorder involves dysregulation of wakefulness and sleep.

Efficacy of modafinil has been established in the US in 2 double-blind, multicenter, placebo-controlled clinical trials of 9 weeks' duration. In these and other clinical studies, modafinil 200 or 400 mg daily increased daytime wakefulness and alertness and decreased the number of daytime sleep episodes as determined by several objective (e.g., the Multiple Sleep Latency Test [MSLT], the Maintenance of Wakefulness Test [MWT], the Steer Clear Performance Test [SCPT]) and subjective (e.g., the Epworth Sleepiness Scale [ESS]) measures of sleepiness. Patients showed an enhanced ability to remain awake with both dosages relative to placebo at 3, 6, and 9 weeks, and at study end point (last post-baseline assessment while the patient was in the study) and also greater global improvement in overall disease status (measured by the Clinical Global Impression of Change [CGI-C]). However, despite the clinical improvement, mean objective and subjective measures of sleepiness did not completely normalize with modafinil therapy, with a degree of clinically important physiologic sleepiness persisting despite therapy. The percentage of patients exhibiting any degree of improvement in overall disease status on the CGI-C in the two 9-week studies establishing efficacy in the US was 60–72, 58–64, or 37–38% for the 400-mg regimen, 200-mg regimen, or placebo, respectively. The efficacy of the 2 modafinil dosage regimens was not shown to differ significantly in these studies.

Although the long-term efficacy of modafinil has not been established systematically beyond 9 weeks, improvements in overall disease status on the CGI-C and in subjective measures of sleepiness on the ESS were maintained in a 40-week open-label extension of one of the trials. In this open-label extension, the percentage of patients exhibiting improvement on the CGI-C ranged from 84% after 2 weeks of extension therapy to 91% after 40 weeks. The drug also was well tolerated for up to 40 weeks of therapy, with 11% of patients discontinuing modafinil because of adverse effects and 14% because of inadequate therapeutic effect. Although most patients enrolled in the 2 clinical trials establishing efficacy in the US had histories of cataplexy, those requiring anticataplectic therapy generally were excluded from enrollment. Therefore, current evidence of efficacy for modafinil is limited principally to effects on excessive daytime sleepiness. In one study in a limited number of patients, cataplexy was not affected by modafinil therapy.

Modafinil did not affect the initiation, maintenance, quality, or quantity of nighttime sleep and did not affect the ability to voluntarily sleep (nap) during the daytime. Like other CNS stimulants modafinil can alter mood, perception, thinking, and feelings and can cause psychoactive and euphoric effects. However, in clinical trials, there was no clinically important association between modafinil and the incidence of agitation in patients. In animals, modafinil is reinforcing; however, the somatic effects of the drug were comparable to those of caffeine and differed from those of amphetamine. Although there currently does not appear to be evidence of problems with modafinil abuse, caution is recommended in patients with a history of drug or stimulant abuse. Withdrawal of modafinil has not been associated with any manifestations of dependency.

■ **Obstructive Sleep Apnea/Hypopnea Syndrome** Modafinil is used in the symptomatic treatment of OSAHS to improve wakefulness in adults with excessive sleepiness. The drug should be used as an adjunct to standard treatment(s) for the underlying obstruction (e.g., nasal continuous positive airway pressure [CPAP]). If CPAP is considered the treatment of choice for a patient with OSAHS, every effort should be made to optimize CPAP treatment for an adequate period of time prior to initiating modafinil therapy. When modafinil is used adjunctively with CPAP treatment, the encouragement of and periodic assessment of CPAP compliance is necessary.

Efficacy of modafinil in reducing excessive daytime sleepiness in patients with OSAHS was established principally in 2 multicenter, placebo-controlled clinical trials. In both of these studies, enrolled patients met the International Classification of Sleep Disorders (ICSD) criteria for OSAHS, which also are consistent with DSM-IV criteria. These criteria include either excessive sleepiness or insomnia with frequent episodes of impaired breathing during sleep and associated features (e.g., loud snoring, morning headaches, dry mouth upon awakening) or polysomnography demonstrating more than 5 obstructive apneas (each greater than 10 seconds in duration) per hour of sleep and one or more of the following: frequent arousals from sleep associated with the apneas; bradytachycardia; and arterial oxygen desaturation in association with the apneas. In addition, all patients enrolled in these studies had excessive daytime sleepiness as demonstrated by a score of 10 or higher on the Epworth Sleepiness Scale (ESS) despite treatment with CPAP. Evidence that CPAP was effective in reducing the episodes of apnea/hypopnea also was required along with documentation of CPAP use.

In the first multicenter, placebo-controlled study, which was of 12 weeks' duration, patients were randomized to receive modafinil 200 mg daily, modafinil 400 mg daily, or placebo. The majority of patients (80%) in this study were fully compliant with CPAP (defined as CPAP use for more than 4 hours per night on more than 70% of nights); the remainder of patients were partially CPAP compliant (defined as CPAP use for less than 4 hours per night on more than 30% of nights). Efficacy of modafinil was principally evaluated by measurement of sleep latency as assessed by the Maintenance of Wakefulness Test (MWT) and change in the patient's overall disease status as measured by the Clinical Global Impression of Change (CGI-C) at week 12 or at the final visit. The modafinil-treated patients demonstrated a significant improvement in their ability to remain awake as measured by the MWT at the study end point and in their clinical condition as measured by the CGI-C compared with those receiving placebo. The 200- and 400-mg daily doses produced similar clinical efficacy in this study.

In the second multicenter, placebo-controlled study, which was of 4 weeks' duration, patients were randomized to receive either modafinil 400 mg daily or placebo. Documentation of regular CPAP use (for at least 4 hours each night on 70% of nights) was required for all patients. Efficacy in reducing daytime sleepiness was principally assessed by the change from baseline on the ESS at week 4 or the final visit. Patients who received modafinil demonstrated a significant reduction in their ESS score from baseline (mean scores reduced by 4.6) compared with patients receiving placebo (mean scores reduced by 2). In addition, the percentage of patients with normalized daytime sleepiness (ESS score less than 10) was significantly higher for the modafinil group than for those receiving placebo (51 and 27%, respectively). Nighttime sleep as measured by polysomnography was not affected by modafinil administration in these 2 studies.

The manufacturer states that the long-term efficacy (e.g., longer than 12 weeks) of modafinil in OSAHS has not been systematically evaluated in placebo-controlled studies to date. However, a 12-month, noncomparative extension phase of the 12-week, placebo-controlled trial in which patients received modafinil 200, 300, or 400 mg daily demonstrated substantial reductions in ESS scores compared with baseline following 3, 6, 9, and 12 months of therapy. When modafinil is used for extended periods, the need for continued therapy should be reassessed periodically.

■ **Shift Work Sleep Disorder** Modafinil is used in the symptomatic treatment of SWSD to improve wakefulness in adults with excessive sleepiness. Criteria of the International Classification of Sleep Disorders (ICSD-10) for chronic SWSD (which are consistent with DSM-IV criteria for circadian rhythm sleep disorder: shift work type) require a primary complaint of excessive sleepiness or insomnia that is temporally associated with a work period

ommends avoiding concomitant alcohol consumption during desvenlafaxine therapy.

■ **Electroconvulsive Therapy** The risks and/or benefits of combined use of electroconvulsive therapy and desvenlafaxine have not been evaluated.

Description

Desvenlafaxine succinate, a selective serotonin- and norepinephrine-reuptake inhibitor (SNRI), is an antidepressant. Desvenlafaxine is the principal active metabolite of venlafaxine and is pharmacologically related to duloxetine, another SNRI.

The exact mechanism of antidepressant action of desvenlafaxine has not been fully elucidated but appears to be associated with the drug's potentiation of serotonergic and noradrenergic activity in the CNS. Like venlafaxine and duloxetine, desvenlafaxine is a potent inhibitor of neuronal serotonin and norepinephrine reuptake; however, inhibition of dopamine reuptake at concentrations that inhibit serotonin and norepinephrine reuptake appears unlikely in most patients. The drug does not inhibit monoamine oxidase (MAO) and has not demonstrated significant affinity for muscarinic cholinergic, H_1-histaminergic, α_1-adrenergic, dopaminergic, γ-aminobutyric acid (GABA), glutamate, and opiate receptors in vitro.

Desvenlafaxine is principally metabolized via conjugation by uridine diphosphoglucuronosyltransferase (UGT) isoenzymes and, to a lesser extent, through oxidation (by the cytochrome P-450 [CYP] 3A4 isoenzyme). The drug minimally inhibits the CYP2D6 isoenzyme and does not inhibit the CYP 1A2, 2A6, 2C8, 2C9, or 2C19 isoenzymes. Desvenlafaxine is not an inhibitor of CYP3A4, nor is it an inducer of CYP3A4. The drug exhibits a low degree of protein binding (30%) and has a mean elimination half-life of approximately 11 hours. Approximately 45% of a single oral dose of desvenlafaxine is eliminated unchanged in the urine at 72 hours, approximately 19% of the dose is excreted as the glucuronide metabolite, and less than 5% is excreted as the oxidative metabolite (N,O-didesmethylvenlafaxine).

Advice to Patients

Risk of suicidality; importance of patients, family, and caregivers being alert to and immediately reporting emergence of suicidality, worsening depression, or unusual changes in behavior, especially during the first few months of therapy or during periods of dosage adjustment. (See Worsening of Depression and Suicidality Risk under Warnings/Precautions: Warnings, in Cautions.) FDA recommends providing written patient information (medication guide) explaining risks of suicidality each time the drug is dispensed. Importance of advising patients about importance of reading the patient information before taking desvenlafaxine and each time the prescription is refilled.

Importance of informing patients of potential risk of serotonin syndrome and neuroleptic malignant syndrome (NMS)-like reactions, particularly with concurrent use of desvenlafaxine and 5-HT_1 receptor agonists (also called triptans), tramadol, tryptophan, other serotonergic agents, or antipsychotic agents. Importance of immediately contacting clinician if signs and symptoms of these syndromes develop (e.g., restlessness, hallucinations, loss of coordination, fast heart beat, increased body temperature, muscle stiffness, increased blood pressure, diarrhea, coma, nausea, vomiting, confusion).

Importance of advising patients not to concurrently take other products containing desvenlafaxine or venlafaxine.

Importance of instructing patients not to take desvenlafaxine with a monoamine oxidase (MAO) inhibitor or within 14 days of stopping the drug, and to allow 7 days after stopping desvenlafaxine before starting therapy with an MAO inhibitor.

Importance of advising patients that they should have regular monitoring of blood pressure while taking desvenlafaxine.

Importance of advising patients with raised intraocular pressure or those at risk of acute narrow-angle glaucoma (angle-closure glaucoma) that mydriasis has been reported with desvenlafaxine and that they should be monitored.

Importance of advising patients, their families, and caregivers to observe desvenlafaxine-treated patients for signs of activation of mania/hypomania.

Importance of advising patients that elevations in total cholesterol, LDL, and triglycerides may occur and that measurement of lipid levels may be considered during therapy.

Importance of advising patients to notify their clinician if they develop any allergic signs or symptoms during therapy (e.g., rash, hives, swelling, difficulty breathing).

Risk of cognitive and motor impairment; importance of exercising caution while operating hazardous machinery, including automobile driving, until patients are reasonably certain that desvenlafaxine therapy does not adversely affect their ability to engage in such activities.

Importance of avoiding alcohol during desvenlafaxine therapy.

Importance of informing clinicians of existing or contemplated concomitant therapy, including prescription and OTC drugs or herbal supplements, as well as any concomitant illnesses (e.g., cardiovascular, cerebrovascular, or lipid metabolism disorders; glaucoma) or personal or family history of suicidality or bipolar disorder. Importance of advising patients about the risk of bleeding associated with concomitant use of desvenlafaxine with aspirin or other nonsteroidal anti-inflammatory agents, warfarin, or other drugs that affect coagulation.

Importance of women informing clinicians if they are or plan to become pregnant or plan to breast-feed.

Importance of advising patients that it usually takes several weeks of antidepressant therapy before they will start to feel better. Advise patients not to stop taking the drug if they do not feel the results right away.

Importance of advising patients not to stop taking desvenlafaxine without first talking with their clinician. Importance of patients being aware that discontinuance effects may occur when stopping the drug.

Importance of informing patients to swallow desvenlafaxine extended-release tablets whole, and not to crush, cut, chew, or dissolve the tablets.

Importance of informing patients that they may notice an inert matrix tablet passing in the stool or via colostomy, and that the active medication has already been absorbed by the time the patient sees the inert matrix tablet.

Importance of informing patients of other important precautionary information. (See Cautions.)

Overview* (see Users Guide). For additional information on this drug until a more detailed monograph is developed and published, the manufacturer's labeling should be consulted. It is *essential* that the manufacturer's labeling be consulted for more detailed information on usual cautions, precautions, contraindications, potential drug interactions, laboratory test interferences, and acute toxicity.

Preparations

Excipients in commercially available drug preparations may have clinically important effects in some individuals; consult specific product labeling for details.

Desvenlafaxine Succinate

Oral		
Tablet, extended-release, film-coated	50 mg (of desvenlafaxine)	**Pristiq**†, Wyeth
	100 mg (of desvenlafaxine)	**Pristiq**†, Wyeth

†Use is not currently included in the labeling approved by the US Food and Drug Administration.

Duloxetine Hydrochloride

■ Duloxetine hydrochloride, a selective serotonin- and norepinephrine-reuptake inhibitor (SNRI), is an antidepressant and anxiolytic agent.

Uses

■ **Major Depressive Disorder** Duloxetine hydrochloride is used for the acute and maintenance treatment of major depressive disorder in adults.

Efficacy of duloxetine for the acute treatment of major depression has principally been established by 4 double-blind, placebo-controlled studies of 8–9 weeks' duration in outpatient settings in adults. In these studies, patients receiving duloxetine (40–120 mg daily) had greater improvements in the 17-item Hamilton depression rating scale (HAMD-17) total score than did patients receiving placebo. No age-, race-, or gender-related differences in efficacy were noted in these studies.

Efficacy of duloxetine for the maintenance treatment of major depressive disorder has been established in a randomized, placebo-controlled relapse prevention study in which 533 adult outpatients who met DSM-IV criteria for major depressive disorder initially received duloxetine 60 mg once daily in a 12-week, open-label acute phase. Patients who responded to treatment during the acute phase were then randomized to continue receiving duloxetine at the same dosage or to receive placebo for 26 weeks in the continuation phase. The duloxetine-treated patients experienced a longer time to relapse of depression compared with the placebo recipients. In addition, more placebo recipients relapsed compared with patients receiving duloxetine (approximately 29% and 17%, respectively).

The manufacturer states that if duloxetine is used for extended periods, the need for continued therapy should be reassessed periodically.

Antidepressant efficacy of duloxetine in hospital settings has not been adequately studied to date.

For further information on treatment of major depressive disorder and considerations in choosing the most appropriate antidepressant for a particular patient, including considerations related to patient tolerance, patient age, and cardiovascular, sedative, and suicidal risk, see Considerations in Choosing Antidepressants under Uses: Major Depressive Disorder, in Fluoxetine Hydrochloride 28:16.04.20.

■ **Generalized Anxiety Disorder** Duloxetine hydrochloride is used for the acute management of generalized anxiety disorder in adults. Efficacy of duloxetine for this indication has been established by 3 placebo-controlled trials of 9–10 weeks' duration in outpatient settings in adults who met DSM-IV criteria for generalized anxiety disorder. In these studies, patients receiving duloxetine (60–120 mg daily) had greater improvements in the Hamilton anxiety scale (HAM-A) total score and the Sheehan Disability Scale (SDS) global functional impairment score than did patients receiving placebo. No age- or gender-related differences in efficacy were noted in these studies.

The manufacturer states that the anxiolytic efficacy of duloxetine for long-term use (i.e., exceeding 10 weeks) has not been established by controlled studies to date. If duloxetine is used for extended periods, the need for continued therapy should be reassessed periodically.

■ **Neuropathic Pain** Duloxetine hydrochloride is used for the management of neuropathic pain associated with diabetic peripheral neuropathy in

adults. Efficacy of duloxetine for this indication has been established by 2 controlled studies of 12 weeks' duration in adults with type 1 or 2 diabetes mellitus and a diagnosis of painful distal symmetrical sensorimotor polyneuropathy for at least 6 months. Patients were excluded from the studies if they met DSM-IV-TR criteria for major depressive disorder and dysthymia. In these studies, 51% of patients receiving duloxetine (60–120 mg daily) and up to 4 g of acetaminophen daily (as needed) reported at least a 30% sustained reduction in pain compared with 31% of those receiving placebo plus acetaminophen (as needed). Some patients in the study experienced a decrease in pain as early as week 1, which persisted throughout the study.

■ **Fibromyalgia** Duloxetine hydrochloride is used for the management of fibromyalgia in adults. Efficacy of duloxetine for this indication has been established by 2 randomized, double-blind, placebo-controlled, fixed-dose studies in adults with a diagnosis of fibromyalgia based on the American College of Rheumatology (ACR) criteria (i.e., history of widespread pain for 3 months and pain present in 11 or more of the 18 specific tender point sites). The first study was of 3 months' duration and enrolled female patients only while the second study was of 6 months' duration and enrolled both male and female patients. Approximately 25% of the patients had concurrent major depressive disorder. Both of these studies compared duloxetine 60 mg once daily or 120 mg daily (given in divided doses in study 1 and as a single daily dose in study 2) with placebo. In addition, Study 2 compared duloxetine 20 mg daily with placebo during the initial 3 months of the 6-month study; after 3 months, the duloxetine dosage was titrated up to 60 mg once daily for the remainder of the study. In these studies, duloxetine therapy in dosages of 60 or 120 mg daily significantly improved the endpoint mean pain scores from baseline and increased the number of patients who had at least a 50% reduction in pain score compared with baseline. Although pain reduction was observed in patients both with and without major depressive disorder, the degree of pain reduction may be greater in patients with major depressive disorder. Some patients experienced a reduction in pain as early as week 1, which persisted throughout the study. Improvement also was noted on measures of function as well as on the Patient Global Impression of Improvement (PGI) scale. Neither study demonstrated an additional therapeutic benefit of 120 mg daily compared with 60 mg daily, and the higher dosage was associated with more frequent adverse effects and early discontinuance of therapy.

The manufacturer states that the efficacy of duloxetine for long-term use (i.e., exceeding 3 months) has not been established by controlled studies to date. However, longer-term efficacy of the drug has been demonstrated for up to 6 months in extension phases of 2 controlled studies to date. The manufacturer recommends that the decision to continue therapy with the drug be based on individual patient response.

■ **Stress Urinary Incontinence** Duloxetine has been used for the management of moderate to severe stress urinary incontinence (SUI)† in women. In a number of placebo-controlled clinical trials involving women with predominantly SUI receiving duloxetine or placebo for up to 12 weeks, duloxetine was significantly better than placebo in reducing the frequency of incontinence episodes (which were reduced by approximately 50% in patients receiving duloxetine) and improving patients' quality of life (as assessed by Incontinence Quality of Life questionnaire scores). Therapy with the drug generally was well tolerated in these studies, with nausea being the most commonly reported adverse effect.

Data from one subsequent analysis suggest that the beneficial effects of duloxetine in women with SUI are maintained for up to 30 months. In addition, some data suggest that combining duloxetine and pelvic floor muscle training exercises may be more effective than either treatment alone. The potential role of duloxetine therapy relative to other forms of treatment (including pelvic floor muscle training, management of fluid intake and voiding, weight loss, devices, and surgery) remains to be established and requires additional study.

Dosage and Administration

■ **Administration** Duloxetine hydrochloride is administered orally without regard to meals. Duloxetine hydrochloride delayed-release capsules should be swallowed whole and should *not* be chewed or crushed, nor should the contents be sprinkled on food or mixed with liquids.

■ **Dosage** Dosage of duloxetine hydrochloride is expressed in terms of duloxetine.

Patients receiving duloxetine should be monitored for possible worsening of depression, suicidality, or unusual changes in behavior, especially at the beginning of therapy or during periods of dosage adjustment. (See Worsening of Depression and Suicidality Risk under Warnings/Precautions: Warnings, in Cautions.)

The manufacturer recommends that an interval of at least 2 weeks elapse when switching a patient from a monoamine oxidase (MAO) inhibitor to duloxetine. In addition, an interval of at least 5 days should elapse when switching from duloxetine to an MAO inhibitor.

Because withdrawal effects may occur (see Withdrawal Effects under Warnings/Precautions: Other Warnings and Precautions in Cautions), abrupt discontinuance of duloxetine should be avoided. When duloxetine therapy is discontinued, dosage should be tapered gradually and the patient carefully monitored to reduce the risk of withdrawal symptoms. If intolerable symptoms occur following dosage reduction or upon discontinuance of treatment, duloxetine therapy may be reinstituted at the previously prescribed dosage until such symptoms abate. Clinicians may resume dosage reductions at that time but at a more gradual rate.

Major Depressive Disorder For the management of major depressive disorder, the recommended initial dosage of duloxetine in adults is 40 mg daily (given as 20 mg twice daily) to 60 mg daily (given either as 60 mg once daily or 30 mg twice daily). In some patients, it may be desirable to initiate therapy with a dosage of 30 mg once daily given for 1 week, followed by an increase to 60 mg once daily. Although duloxetine dosages of 120 mg daily have been effective, there is no evidence that dosages exceeding 60 mg daily provide additional therapeutic benefit. Safety of dosages exceeding 120 mg daily has not been adequately evaluated.

While the optimum duration of duloxetine therapy has not been established, it generally is agreed that acute depressive episodes require several months or longer of sustained antidepressant therapy. Systematic evaluation of duloxetine has shown that its antidepressant efficacy is maintained for periods of up to 26 weeks in patients receiving 60 mg daily. The manufacturer recommends a maintenance dosage of 60 mg once daily in adults. The manufacturer also recommends that the usefulness of duloxetine be reevaluated periodically in patients receiving long-term therapy.

Generalized Anxiety Disorder For the management of generalized anxiety disorder, the recommended initial adult dosage of duloxetine is 60 mg once daily. In some patients, it may be desirable to initiate therapy with a dosage of 30 mg once daily given for 1 week, followed by an increase to 60 mg once daily. Dosage may be increased in increments of 30 mg once daily (up to a maximum dosage of 120 mg once daily). However, no additional benefit has been demonstrated from duloxetine dosages exceeding 60 mg once daily.

While the optimum duration of duloxetine therapy has not been established, it generally is agreed that generalized anxiety disorder is a chronic condition. The manufacturer states that the efficacy of duloxetine for long-term use (i.e., exceeding 10 weeks) has not been established by controlled studies and that the usefulness of the drug in patients receiving prolonged therapy should be reevaluated periodically.

Neuropathic Pain For the management of neuropathic pain associated with diabetic peripheral neuropathy, the recommended adult dosage of duloxetine is 60 mg once daily. Duloxetine dosages exceeding 60 mg daily do not appear to provide substantially greater therapeutic benefit and clearly are less well tolerated. For patients for whom tolerability is a concern, a lower initial dosage may be considered. Because progression of diabetic peripheral neuropathy is highly variable and management of pain is empirical, efficacy of the drug must be assessed individually. The manufacturer states that the efficacy of duloxetine for long-term use (i.e., exceeding 12 weeks) has not been established by controlled studies.

Fibromyalgia For the management of fibromyalgia, the recommended adult dosage of duloxetine is 60 mg once daily. The manufacturer states that treatment should be initiated at 30 mg once daily for one week to allow patients to adjust to the drug before increasing the dosage to 60 mg once daily. Some patients may respond to the initial dosage of 30 mg once daily. Duloxetine dosages exceeding 60 mg daily do not appear to provide greater therapeutic benefit, even in patients not responding to a dosage of 60 mg daily, and are associated with a higher incidence of adverse effects.

Fibromyalgia is recognized as a chronic condition. The manufacturer states that efficacy of duloxetine in the management of fibromyalgia has been demonstrated in placebo-controlled studies lasting up to 3 months, and that the efficacy of the drug for longer-term use (i.e., exceeding 3 months) has not been established in controlled studies. However, efficacy of the drug has been demonstrated for up to 6 months in extension phases of 2 controlled studies. The manufacturer recommends that the decision to continue therapy with the drug be based on individual patient response.

Stress Urinary Incontinence Although the optimum dosage and duration of duloxetine therapy for the treatment of stress urinary incontinence† in women remain to be established, the most commonly used dosage in controlled trials has been 80 mg daily, usually given as 40 mg twice daily (dosage range: 20–120 mg daily). Some patients may benefit (i.e., reduced risk of nausea and dizziness) from initiating therapy with a duloxetine dosage of 20 mg twice daily for 2 weeks before increasing to the usual dosage of 40 mg twice daily. If adverse effects are bothersome during the first few weeks of therapy at the usual dosage, the dosage may be reduced to 20 mg twice daily. The safety of higher dosages (i.e., 120 mg daily), which have been used in a limited number of women with more severe cases of stress urinary incontinence, requires additional study.

■ **Special Populations** Although there are no specific dosage recommendations for geriatric patients, extra caution is recommended when the duloxetine dosage is increased in elderly patients.

Although the manufacturer makes no specific dosage recommendation for smoking patients, some clinicians recommend a slightly increased duloxetine dosage (by about 15%) in patients who smoke. (See Drug Interactions: Smoking.)

In patients with mild to moderate renal impairment (creatinine clearance 30–80 mL/minute), a lower initial dosage and gradual increase in dosage may be considered. The manufacturer recommends that duloxetine *not* be administered to patients with end-stage renal disease (requiring dialysis), severe renal impairment (creatinine clearance less than 30 mL/minute), or any hepatic insufficiency. (See Specific Populations under Cautions: Warnings/Precautions.)

Treatment of Pregnant Women during the Third Trimester Because some neonates exposed to duloxetine and other selective serotonin- and norepinephrine-reuptake inhibitors (SNRIs) or selective serotonin-reuptake inhibitors late in the third trimester of pregnancy have developed severe com-

plications, consideration may be given to cautiously tapering duloxetine therapy in the third trimester prior to delivery if the drug is administered during pregnancy. (See Pregnancy under Warnings/Precautions: Specific Populations, in Cautions.)

Cautions

■ **Contraindications** Concurrent or recent (i.e., within 2 weeks) therapy with a monoamine oxidase (MAO) inhibitor. (See Drug Interactions: Monoamine Oxidase Inhibitors.)

Uncontrolled angle-closure glaucoma.

Known hypersensitivity to duloxetine or any ingredient in the formulation.

■ **Warnings/Precautions** ***Warnings*** **Worsening of Depression and Suicidality Risk.** Worsening of depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior may occur in both adult and pediatric (see Pediatric Use under Cautions: Specific Populations) patients with major depressive disorder or other psychiatric disorders, whether or not they are taking antidepressants. This risk may persist until clinically important remission occurs. Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are the strongest predictors of suicide. However, there has been a long-standing concern that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients during the early phases of treatment. Pooled analyses of short-term, placebo-controlled studies of antidepressants (i.e., selective serotonin-reuptake inhibitors and other antidepressants) have shown an increased risk of suicidality in children, adolescents, and young adults (18–24 years of age) with major depressive disorder and other psychiatric disorders. An increased suicidality risk was not demonstrated with antidepressants compared with placebo in adults older than 24 years of age and a reduced risk was observed in adults 65 years of age or older.

The US Food and Drug Administration (FDA) recommends that all patients being treated with antidepressants for any indication be appropriately monitored and closely observed for clinical worsening, suicidality, and unusual changes in behavior, particularly during initiation of therapy (i.e., the first few months) and during periods of dosage adjustments. Families and caregivers of patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and nonpsychiatric, also should be advised to monitor patients on a daily basis for the emergence of agitation, irritability, or unusual changes in behavior as well as the emergence of suicidality, and to report such symptoms immediately to a health-care provider.

Although a causal relationship between the emergence of symptoms such as anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia, hypomania, and/or mania and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality. Consequently, consideration should be given to changing the therapeutic regimen or discontinuing therapy in patients whose depression is persistently worse or in patients experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, particularly if such manifestations are severe, abrupt in onset, or were not part of the patient's presenting symptoms. FDA also recommends that the drugs be prescribed in the smallest quantity consistent with good patient management, in order to reduce the risk of overdosage.

Other Warnings and Precautions **Hepatic Effects.** Hepatic failure, sometimes fatal, has been reported in duloxetine-treated patients. The cases presented as hepatitis accompanied by abdominal pain, hepatomegaly, and markedly elevated serum transaminase concentrations (more than 20 times the upper limit of normal) with or without jaundice, reflecting a mixed or hepatocellular pattern of hepatic injury. Duloxetine should be discontinued in any patient who develops jaundice or other evidence of clinically important hepatic dysfunction; therapy should not be resumed unless another cause for the hepatic dysfunction can be established.

Cases of cholestatic jaundice with minimal elevation of serum transaminase concentrations also have been reported. Postmarketing reports indicate that elevated serum transaminase, bilirubin, and alkaline phosphatase concentrations have occurred in duloxetine-treated patients with chronic hepatic disease or cirrhosis.

Duloxetine has been shown to increase the risk of serum transaminase elevations in clinical trials; such elevations resulted in discontinuance of the drug in 0.3% of patients. The median time to detection of the transaminase elevation was about 2 months. In placebo-controlled trials, elevations in serum ALT concentrations to more than 3 times the upper limit of normal occurred in 1.1% of the duloxetine-treated patients compared with 0.2% of those receiving placebo. There was evidence of a dose-response relationship for ALT (SGPT) and AST (SGOT) elevations of more than 3 times the upper limit of normal and more than 5 times the upper limit of normal, respectively.

Because of the possibility that duloxetine and alcohol may interact to cause hepatic injury or that duloxetine may aggravate preexisting hepatic disease, duloxetine should not ordinarily be prescribed to patients with a history of excessive alcohol consumption or evidence of chronic hepatic disease. Patients and clinicians should be aware of the signs and symptoms of hepatic injury (e.g., pruritus, dark urine, jaundice, right upper quadrant tenderness, unexplained flu-like symptoms), and clinicians should promptly investigate such manifestations in patients receiving the drug.

Orthostatic Hypotension and Syncope. Orthostatic hypotension and syncope reported with therapeutic dosages; although these effects tend to occur within the first week of therapy, they may occur at any time during therapy; particularly following increases in dosage. Risk of decreased blood pressure may be greater in patients concomitantly receiving other drugs that produce orthostatic hypotension (such as antihypertensive agents); in patients receiving potent inhibitors of the cytochrome P-450 (CYP) 1A2 isoenzyme (see Drug Interactions: Drugs Affecting Hepatic Microsomal Enzymes); or in those receiving duloxetine dosages exceeding 60 mg daily. Discontinuance of the drug should be considered in patients experiencing symptomatic orthostatic hypotension and/or syncope during duloxetine therapy.

Serotonin Syndrome. Potentially life-threatening serotonin syndrome reported with selective serotonin- and norepinephrine-reuptake inhibitors (SNRIs), including duloxetine, or selective serotonin-reuptake inhibitors (SSRIs), particularly with concurrent administration of other serotonergic drugs (e.g., serotonin [5-hydroxytryptamine; 5-HT] type 1 receptor agonists ["triptans"]) or drugs that impair serotonin metabolism (e.g., monoamine oxidase [MAO] inhibitors). Symptoms of serotonin syndrome may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination), and/or GI symptoms (e.g., nausea, vomiting, diarrhea).

Concurrent therapy with MAO inhibitors used for treatment of depression is contraindicated. (See Drug Interactions: Monoamine Oxidase Inhibitors.)

If concurrent therapy with duloxetine and a 5-HT_1 receptor agonist is clinically warranted, the patient should be observed carefully, particularly during initiation of therapy, when dosage is increased, or when another serotonergic agent is initiated.

Concomitant use of duloxetine and serotonin precursors (e.g., tryptophan) is not recommended.

Abnormal Bleeding. SSRIs and SNRIs, including duloxetine, may increase the risk of bleeding events. Concurrent administration of aspirin, nonsteroidal anti-inflammatory agents, warfarin, and other anticoagulants may add to this risk. Case reports and epidemiologic studies have demonstrated an association between the use of drugs that interfere with serotonin reuptake and the occurrence of GI bleeding. Bleeding events related to SSRI and SNRI use have ranged from ecchymoses, hematomas, epistaxis, and petechiae to life-threatening hemorrhages. The manufacturer recommends that patients be advised of the risk of bleeding associated with the concomitant use of duloxetine and aspirin or other nonsteroidal anti-inflammatory agents, warfarin, or other drugs that affect coagulation. (See Drug Interactions: Drugs Affecting Hemostasis.)

Withdrawal Effects. Because withdrawal effects (e.g., dysphoric mood, irritability, agitation, nausea/vomiting, dizziness, sensory disturbances, anxiety, confusion, headache, lethargy, emotional lability, insomnia, nightmares, hypomania, tinnitus, seizures) may occur, abrupt discontinuance of duloxetine should be avoided. (See Dosage and Administration: Dosage.)

If intolerable symptoms occur following dosage reduction or discontinuance, reinstitute previously prescribed dosage until symptoms abate, then resume more gradual dosage reductions.

Activation of Mania/Hypomania. Activation of mania and hypomania has occurred in patients with major depressive disorder receiving duloxetine. Use with caution in patients with a history of mania.

Seizures. The risk of seizures associated with duloxetine use has not been systematically evaluated, but seizures have been reported in patients receiving the drug; therefore, use with caution in patients with a history of seizures.

Blood Pressure. May increase blood pressure. Monitor blood pressure prior to and periodically during duloxetine therapy.

Clinically Important Drug Interactions. Because both CYP1A2 and CYP2D6 are responsible for duloxetine metabolism, the potential exists for clinically important drug interactions when duloxetine is concurrently administered with CYP1A2 inhibitors, CYP2D6 inhibitors, and CYP2D6 substrates.

Concurrent therapy with MAO inhibitors used for treatment of depression is contraindicated. (See Serotonin Syndrome under Warnings/Precautions: Other Warnings and Precautions, in Cautions and also see Drug Interactions: Monoamine Oxidase Inhibitors.)

Because of the possibility that duloxetine and alcohol may interact to cause hepatic injury, duloxetine should not ordinarily be prescribed to patients with a history of excessive alcohol consumption or evidence of chronic hepatic disease. (See Hepatic Effects under Warnings/Precautions: Other Warnings and Precautions, in Cautions and also see Drug Interactions: Alcohol.)

Potential pharmacologic interaction when duloxetine is given with or substituted for other centrally acting drugs, including those with a similar mechanism of action; CNS-active drugs should be used with caution in patients receiving duloxetine.

Hyponatremia/Syndrome of Inappropriate Antidiuretic Hormone Secretion. Treatment with SSRIs and SNRIs, including duloxetine, may result in hyponatremia. In many cases, hyponatremia appears to be due to the syndrome of inappropriate antidiuretic hormone secretion (SIADH). Cases with serum sodium concentrations lower than 110 mmol/L have been reported and hyponatremia appeared reversible when duloxetine was discontinued. Geriatric individuals and patients receiving diuretics or who are otherwise volume depleted may be at greater risk of developing hyponatremia. Signs and symptoms of hyponatremia include headache, difficulty concentrating, memory impairment, confusion, weakness, and unsteadiness, which may lead to falls; more severe and/or acute cases have been associated with hallucinations, syncope, seizures, coma, respiratory arrest, and death. Initiate appropriate medical intervention and consider drug discontinuance in patients with symptomatic hyponatremia.

Concomitant Illnesses. Experience with duloxetine in patients with concomitant diseases is limited. (See Hepatic Impairment and see Renal Impairment under Warnings/Precautions: Specific Populations, in Cautions.)

Because alterations in gastric motility may affect the stability of the enteric coating of the pellets contained in duloxetine capsules, the drug should be used with caution in patients with conditions that may slow gastric emptying (e.g., in some patients with diabetes mellitus).

Duloxetine has not been systematically evaluated in patients with a recent history of myocardial infarction or unstable coronary artery disease; such patients were generally excluded from clinical studies. The manufacturer states that duloxetine use was not associated with the development of clinically important ECG abnormalities in controlled clinical studies of up to 13 weeks' duration.

Duloxetine worsens glycemic control in some patients with diabetes. In the 12-week acute treatment phase of 3 clinical studies in patients with diabetic peripheral neuropathy, small increases in fasting blood glucose were observed in the duloxetine-treated patients compared with those receiving placebo. In the extension phase of these studies, which lasted up to 52 weeks, fasting blood glucose increased by 12 mg/dL in the duloxetine-treated patients and decreased by 11.5 mg/dL in the routine care group; increases in glycosylated hemoglobin (hemoglobin A_{1c}) were observed in both groups of patients although the average increase was 0.3% greater in the duloxetine-treated patients compared with those receiving routine care.

Controlled Narrow-Angle Glaucoma. Possible increased risk of mydriasis; use with caution in patients with *controlled* narrow-angle glaucoma. Contraindicated in patients with such glaucoma that is not controlled.

Urinary Hesitation and Retention. Duloxetine belongs to a class of drugs known to affect urethral resistance. If symptoms of urinary hesitation develop during therapy, consider possibility that they may be drug-related. (See Uses: Stress Urinary Incontinence.)

Cases of urinary retention have been reported during postmarketing experience; in some of these cases, hospitalization and/or catheterization has been necessary.

Specific Populations **Pregnancy.** Category C. (See Users Guide.)

Some neonates exposed to selective serotonin- and norepinephrine-reuptake inhibitors (SNRIs) or selective serotonin-reuptake inhibitors late in the third trimester of pregnancy have developed complications that have sometimes been severe and required prolonged hospitalization, respiratory support, enteral nutrition, and other forms of supportive care in special-care nurseries. Such complications can arise immediately upon delivery and usually last several days or up to 2–4 weeks. Clinical findings reported to date in the neonates have included respiratory distress, cyanosis, apnea, seizures, temperature instability or fever, feeding difficulty, dehydration, excessive weight loss, vomiting, hypoglycemia, hypotonia, hyperreflexia, tremor, jitteriness, irritability, lethargy, reduced or lack of reaction to pain stimuli, and constant crying. These clinical features appear to be consistent with either a direct toxic effect of the SNRI or selective serotonin-reuptake inhibitor or, possibly, a drug withdrawal syndrome. It should be noted that, in some cases, the clinical picture was consistent with serotonin syndrome (see Drug Interactions: Drugs Associated with Serotonin Syndrome, in Fluoxetine Hydrochloride 28:16.04.20). When treating a pregnant woman with duloxetine during the third trimester of pregnancy, the clinician should carefully consider the potential risks and benefits of such therapy. Consideration may be given to cautiously tapering duloxetine therapy in the third trimester prior to delivery if the drug is administered during pregnancy. (See Treatment of Pregnant Women during the Third Trimester under Dosage and Administration: Special Populations.)

Lactation. Duloxetine is distributed into human milk. At steady state, concentrations in breast milk are approximately one-fourth the maternal plasma concentrations. Because the safety of duloxetine in infants is not known, use in nursing women is not recommended. However, if the clinician determines that the potential benefits of duloxetine therapy for the mother outweigh the potential risks to the infant, dosage adjustment is not required since lactation does not affect pharmacokinetics.

Pediatric Use. Safety and efficacy of duloxetine in children younger than 18 years of age have not been established.

FDA warns that a greater risk of suicidal thinking or behavior (suicidality) occurred during first few months of antidepressant treatment (4%) compared with placebo (2%) in children and adolescents with major depressive disorder, obsessive-compulsive disorder (OCD), or other psychiatric disorders based on pooled analyses of 24 short-term, placebo-controlled trials of 9 antidepressant drugs (selective serotonin-reuptake inhibitors [SSRIs] and other antidepressants). However, a more recent meta-analysis of 27 placebo-controlled trials of 9 antidepressants (SSRIs and others) in patients younger than 19 years of age with major depressive disorder, OCD, or non-OCD anxiety disorders suggests that the benefits of antidepressant therapy in treating these conditions may outweigh the risks of suicidal behavior or suicidal ideation. No suicides occurred in these pediatric trials.

Carefully consider these findings when assessing potential benefits and risks of duloxetine in a child or adolescent for any clinical use. (See Worsening of Depression and Suicidality Risk under Warnings/Precautions: Warnings, in Cautions.)

Geriatric Use. Approximately 5.9, 33, and 7.9% of patients studied in clinical trials of duloxetine for major depressive disorder, diabetic peripheral neuropathy, and fibromyalgia, respectively, were 65 years of age or older. The generalized anxiety disorder clinical trials did not include sufficient numbers of patients 65 years of age or older to determine whether they respond differently than younger adults. Although no overall differences in efficacy or safety were observed between geriatric and younger patients in the major depressive disorder, diabetic peripheral neuropathic pain, and fibromyalgia clinical trials and other clinical experience has not revealed any evidence of age-related differences, the possibility that some older patients may exhibit increased sensitivity to the drug cannot be ruled out.

Clinically important hyponatremia has been reported in geriatric patients, who may be at greater risk for this adverse effect. (See Hyponatremia/Syndrome of Inappropriate Antidiuretic Hormone Secretion under Warnings/Precautions: Other Warnings and Precautions, in Cautions.)

In pooled data analyses, a *reduced* risk of suicidality was observed in adults 65 years of age or older with antidepressant therapy compared with placebo. (See Worsening of Depression and Suicidality Risk under Warnings/Precautions: Other Warnings and Precautions, in Cautions.)

Hepatic Impairment. Substantially increased exposure to duloxetine; use is not recommended in patients with hepatic insufficiency or with substantial alcohol use. (See Hepatic Effects under Warnings/Precautions: Other Warnings and Precautions, in Cautions.)

Renal Impairment. Increased plasma concentrations of duloxetine and its metabolites; use is not recommended in patients with end-stage renal disease (requiring dialysis) or severe renal impairment (creatinine clearance less than 30 mL/minute).

Population pharmacokinetic analyses suggest that mild to moderate renal impairment has no clinically important effect on duloxetine apparent clearance.

■ **Common Adverse Effects** Adverse effects reported in 5% or more of patients with major depressive disorder receiving duloxetine and at an incidence at least twice that reported with placebo include nausea, dry mouth, constipation, decreased appetite, fatigue, somnolence, and increased sweating.

Adverse effects reported in 5% or more of patients with generalized anxiety disorder receiving duloxetine and at an incidence at least twice that reported with placebo include nausea, fatigue, dry mouth, somnolence, constipation, insomnia, decreased appetite, vomiting, hyperhidrosis, decreased libido, delayed ejaculation, and erectile dysfunction.

Adverse effects reported in 5% or more of patients with diabetic peripheral neuropathy receiving duloxetine and at an incidence at least twice that reported with placebo include nausea, somnolence, dizziness, dry mouth, constipation, hyperhidrosis, decreased appetite, and asthenia.

Adverse effects reported in 5% or more of patients with fibromyalgia receiving duloxetine and at an incidence at least twice that reported with placebo include nausea, dry mouth, constipation, decreased appetite, somnolence, agitation, and hyperhidrosis.

Drug Interactions

■ **Drugs Metabolized by Hepatic Microsomal Enzymes** Substrates of cytochrome P-450 (CYP) 2D6 isoenzyme (e.g., tricyclic antidepressants [TCAs; amitriptyline, desipramine, imipramine, nortriptyline], phenothiazines, class IC antiarrhythmics [flecainide, propafenone]): potential pharmacokinetic (increased AUC of the substrate) interactions. Use with caution. Consider monitoring plasma TCA concentrations and reducing the TCA dosage if a TCA is administered concurrently with duloxetine.

Substrates of CYP1A2, CYP3A, CYP2C9, or CYP2C19 isoenzymes: clinically important pharmacokinetic interaction generally is considered unlikely.

■ **Drugs Affecting Hepatic Microsomal Enzymes** Potent inhibitors of CYP1A2 (e.g., fluvoxamine, some quinolone anti-infective agents [e.g., ciprofloxacin, enoxacin]): potential pharmacokinetic (increased plasma duloxetine concentrations) interaction. Avoid concomitant use.

Potent inhibitors of CYP2D6 (e.g., fluoxetine, paroxetine, quinidine) isoenzymes: potential pharmacokinetic interaction (increased plasma duloxetine concentrations).

Concomitant administration of duloxetine and fluvoxamine, a potent CYP1A2 inhibitor, in poor CYP2D6 metabolizers resulted in a sixfold increase in duloxetine area under the plasma concentration-time curve (AUC) and peak plasma concentrations.

■ **Drugs Affecting Hemostasis** Altered anticoagulant effects, including increased bleeding, have been reported when selective serotonin-reuptake inhibitors (SSRIs) or selective serotonin- and norepinephrine-reuptake inhibitors (SNRIs), including duloxetine, were concurrently administered with warfarin or other anticoagulants. The manufacturer recommends carefully monitoring patients receiving warfarin during initiation and discontinuance of duloxetine therapy.

Potential pharmacologic (increased risk of bleeding) interaction with aspirin or other nonsteroidal anti-inflammatory agents; use with caution.

■ **Drugs that Affect Gastric Acidity** Theoretical risk of altered duloxetine bioavailability if administered with drugs that increase gastric pH. However, no clinically important effect was demonstrated when duloxetine was administered with aluminum- and magnesium-containing antacids or famotidine.

Whether the concomitant administration of proton-pump inhibitors affects duloxetine absorption is currently unknown.

■ **Alcohol** Potential pharmacologic (increased risk of hepatotoxicity) interaction; avoid concomitant use in patients with substantial alcohol use. (See Hepatic Effects under Warnings/Precautions: Other Warnings and Precautions, in Cautions.)

Duloxetine has not been shown to potentiate the impairment of mental and motor skills caused by alcohol.

■ **Antihypertensive Agents** Potential pharmacologic (increased risk of hypotension and syncope) interaction.

■ **Benzodiazepines** Lorazepam does not appear to affect the pharmacokinetics of duloxetine.

Temazepam does not appear to affect the pharmacokinetics of duloxetine.

■ **CNS-active Drugs** Potential pharmacologic interaction when given with or substituted for other centrally acting drugs, including those with a similar mechanism of action; use with caution.

■ **5-HT$_1$ Receptor Agonists ("Triptans")** Pharmacologic interaction (potentially life-threatening serotonin syndrome) if used concurrently with 5-HT$_1$ reeeptor agonists (e.g., almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, zolmitriptan). If concomitant use is clinically warranted, the patient should be observed carefully, particularly during treatment initiation, when dosage is increased, or when another serotonergic agent is initiated. (See Serotonin Syndrome under Warnings/Precautions:Other Warnings and Precautions, in Cautions.)

■ **Monoamine Oxidase (MAO) Inhibitors** Pharmacologic interaction (potentially fatal serotonin syndrome); concomitant use is contraindicated. The manufacturer recommends that at least 2 weeks should elapse between discontinuance of an MAO inhibitor and initiation of duloxetine and that at least 5 days elapse between discontinuance of duloxetine therapy and initiation of MAO inhibitor therapy. (See Serotonin Syndrome under Warnings/Precautions:Other Warnings and Precautions, in Cautions.)

■ **Selective Serotonin-reuptake Inhibitors and Selective Serotonin- and Norepinephrine-reuptake Inhibitors** Potential pharmacologic interaction (potentially life-threatening serotonin syndrome); concurrent administration not recommended. (See Serotonin Syndrome under Warnings/Precautions:Other Warnings and Precautions, in Cautions.)

Concomitant administration of duloxetine and fluvoxamine, a potent CYP1A2 inhibitor, in poor CYP2D6 metabolizers resulted in a six-fold increase in duloxetine AUCs and peak plasma concentrations.

■ **Serotonergic Drugs** Potential pharmacologic interaction (potentially life-threatening serotonin syndrome) with drugs affecting serotonergic neurotransmission, including linezolid (an anti-infective agent that is a nonselective, reversible MAO inhibitor), lithium, tramadol, and St. John's wort (*Hypericum perforatum*); use with caution. Concurrent administration of serotonin precursors (such as tryptophan) is not recommended. (See Serotonin Syndrome under Warnings/Precautions: Other Warnings and Precautions, in Cautions.)

■ **Smoking** Potential pharmacokinetic interaction (reduced duloxetine bioavailability and plasma concentrations). The manufacturer states that routine dosage adjustment is not necessary. However, some clinicians recommend a small increase in duloxetine dosage (about 15%) in patients who smoke.

■ **Theophylline** Although small increases (averaging from 7–20%) in theophylline AUCs have been reported during concurrent administration of theophylline and duloxetine, combined use of these drugs reportedly has been well tolerated and routine theophylline dosage adjustment does not appear to be necessary during concomitant administration.

■ **Thioridazine** Potential pharmacokinetic (increased plasma thioridazine concentrations) interaction with resulting increased risk of serious ventricular arrhythmias and sudden death; concomitant use is not recommended by manufacturer of duloxetine.

Description

Duloxetine hydrochloride, a selective serotonin- and norepinephrine-reuptake inhibitor (SNRI), is an antidepressant and anxiolytic agent. The drug also has demonstrated analgesic activity in animal models of chronic and persistent pain and in clinical trials evaluating the drug's activity in conditions associated with chronic pain (e.g., neuropathic pain, fibromyalgia). Duloxetine hydrochloride is pharmacologically related to venlafaxine hydrochloride and desvenlafaxine succinate.

The exact mechanisms of the antidepressant, anxiolytic, and central pain inhibitory actions of duloxetine have not been fully elucidated, but appear to be associated with the drug's potentiation of serotonergic and noradrenergic activity in the CNS. Like venlafaxine and desvenlafaxine, duloxetine is a potent inhibitor of neuronal serotonin and norepinephrine reuptake and a less potent inhibitor of dopamine reuptake. Duloxetine does not inhibit monoamine oxidase (MAO) and has not demonstrated significant affinity for dopaminergic, adrenergic, cholinergic, γ-aminobutyric acid (GABA), glutamate, histaminergic, and opiate receptors in vitro.

Although the precise mechanism of action of duloxetine in stress urinary incontinence is unknown, it is thought to be related to potentiation of serotonin and norepinephrine activity in the sacral spinal cord, which increases urethral closure forces and thereby reduces involuntary urine loss.

Duloxetine is extensively metabolized in the liver, principally via oxidation by the cytochrome P-450 (CYP) 2D6 and 1A2 isoenzymes. Duloxetine is a moderate inhibitor of CYP2D6 and a somewhat weak inhibitor of CYP1A2. The drug is not an inhibitor of CYP2C9, CYP2C19, or CYP3A, nor is it an inducer of CYP1A2 or CYP3A.

Advice to Patients

Risk of suicidality; importance of patients, family, and caregivers being alert to and immediately reporting emergence of suicidality, worsening depression, or unusual changes in behavior, especially during the first few months of therapy or during periods of dosage adjustment. FDA recommends providing written patient information (medication guide) explaining risks of suicidality each time the drug is dispensed.

Importance of promptly reporting any manifestations of liver dysfunction (e.g., pruritus, dark urine, jaundice, right upper quadrant tenderness, unexplained flu-like symptoms) to clinician.

Importance of informing patient of risk of severe liver injury associated with concomitant use of duloxetine and heavy alcohol intake. (See Hepatic Effects under Warnings/Precautions: Other Warnings and Precautions and also see Drug Interactions: Alcohol.)

Risk of psychomotor impairment; importance of exercising caution while operating hazardous machinery, including automobile driving, until patient gains experience with the drug's effects.

Importance of advising patients of risk of orthostatic hypotension and syncope, particularly during initial therapy and subsequent dosage escalation and during concomitant therapy with drugs that may potentiate the orthostatic effect of duloxetine.

Importance of informing patients of risk of serotonin syndrome with concurrent use of duloxetine and 5-HT$_1$ receptor agonists (also called triptans), tramadol, or other serotonergic agents. Importance of seeking immediate medical attention if symptoms of serotonin syndrome develop.

Importance of taking medication exactly as prescribed by the clinician. Importance of informing patients that the delayed-release capsules should be swallowed whole and should not be chewed or crushed, nor should the capsule contents be sprinkled on food or mixed with liquids.

Importance of continuing duloxetine therapy even if a response is not evident within 1–4 weeks, unless directed otherwise.

Importance of women informing clinicians if they are or plan to become pregnant or plan to breast-feed.

Importance of informing clinicians of existing or contemplated concomitant therapy, including prescription and OTC drugs, as well as any concomitant illnesses (e.g., bipolar disorder, liver disease) or family history of suicidality or bipolar disorder. Risk of bleeding associated with concomitant use of duloxetine with aspirin or other nonsteroidal anti-inflammatory agents, warfarin, or other drugs that affect coagulation.

Importance of informing patients of other important precautionary information. (See Cautions.)

Overview® (see Users Guide). For additional information on this drug until a more detailed monograph is developed and published, the manufacturer's labeling should be consulted. It is *essential* that the manufacturer's labeling be consulted for more detailed information on usual cautions, precautions, contraindications, potential drug interactions, laboratory test interferences, and acute toxicity.

Preparations

Excipients in commercially available drug preparations may have clinically important effects in some individuals; consult specific product labeling for details.

Duloxetine Hydrochloride

Oral		
Capsules, delayed-release (containing enteric-coated pellets)	20 mg (of duloxetine)	**Cymbalta®, Lilly**
	30 mg (of duloxetine)	**Cymbalta®, Lilly**
	60 mg (of duloxetine)	**Cymbalta®, Lilly**

†Use is not currently included in the labeling approved by the US Food and Drug Administration

Venlafaxine Hydrochloride

■ Venlafaxine hydrochloride, a selective serotonin- and norepinephrine-reuptake inhibitor (SNRI), is a phenylethylamine-derivative antidepressant and anxiolytic agent.

Uses

■ **Major Depressive Disorder** Venlafaxine hydrochloride is used in the treatment of major depressive disorder. Efficacy of venlafaxine conventional tablets for the management of major depression has been established in several placebo-controlled studies in outpatient settings in patients who had major depression and in 1 placebo-controlled study in a hospital setting in patients who had major depression with melancholia. Efficacy of venlafaxine extended-release capsules for the treatment of major depression also has been established by controlled studies of 8–12 weeks' duration in outpatient settings; however, the safety and efficacy of venlafaxine extended-release capsules in hospitalized patients with major depression have not been adequately evaluated.

In 4 studies of 6 weeks' duration in adult outpatients with major depression, venlafaxine in dosages of 75–225 mg daily administered in 2 or 3 divided doses as conventional tablets was found to be superior to placebo on at least 2 of the following 3 clinical measures of depression: Hamilton Depression Rating Scale (HAM-D) total score, HAM-D depressed mood item, and the Clinical Global

although differences in certain animal models have been observed and additive effects appear to occur when the drug is combined with these anticonvulsants.

Although the precise mechanism of action of topiramate is unknown, data from electrophysiologic and biochemical studies have revealed 4 properties that may contribute to the drug's efficacy for seizure disorders and migraine prophylaxis. At pharmacologically relevant concentrations, topiramate blocks voltage-dependent sodium channels; augments the activity of γ-aminobutyric acid (GABA) at some subtypes of the GABA-A receptor; antagonizes the AMPA/kainate subtype of the glutamate receptor; and inhibits carbonic anhydrase (particularly CA-II and CA-IV isoenzymes). In general, anticonvulsant drugs are thought to act by one or more of the following mechanisms: modulating voltage-dependent ion (e.g., sodium) channels involved in action potential propagation or burst generation, enhancement of GABA inhibitory activity, and/or inhibition of excitatory amino acid neurotransmitter (e.g., glutamate, aspartate) activity.

Topiramate exhibits effects on cultured neurons similar to those observed with phenytoin and carbamazepine, and such effects are suggestive of an inactive state-dependent block of voltage-dependent sodium channels. Topiramate reduces the duration of epileptiform bursts of neuronal firing and decreases the number of action potentials in studies of cultured rat hippocampal neurons with spontaneous epileptiform burst activity. Topiramate also decreases the frequency of action potentials elicited by depolarizing electric current in cultured rat hippocampal neurons. Depolarization and firing of an action potential results from the rapid inflow of sodium ions through voltage-dependent sodium channels in the neuronal cell membrane. After firing, a neuron enters a period of inactivation during which it is unable to fire again even if the sodium channel is open. A slow action potential firing rate allows the neuron sufficient time to recover from inactivation, and the normal period of inactivation has a minimal effect on low-frequency firing. During a partial seizure, neurons characteristically undergo high-frequency depolarization and firing of action potentials which is uncommon during normal physiologic neuronal activity. Some anticonvulsant drugs (e.g., phenytoin, carbamazepine) preferentially bind to voltage-dependent sodium channels during their inactivated state, slow the rate of recovery of sodium channels from their period of inactivation, and limit the ability of the neuron to depolarize and fire at high frequencies.

Topiramate enhances the activity of the inhibitory neurotransmitter GABA at a nonbenzodiazepine site on $GABA_A$ receptors. Activation of the postsynaptic $GABA_A$ receptor by GABA causes inhibition by increasing the inward flow of chloride ions, resulting in hyperpolarization of the postsynaptic cell; in chloride ion-depleted murine cerebellar granule cells, therapeutic concentrations of topiramate (in combination with GABA) enhance GABA-evoked inward flux of chloride ions in a concentration-dependent manner. Benzodiazepines act at $GABA_A$ receptors to enhance GABA-evoked inward flow of chloride ions, but the benzodiazepine antagonist flumazenil does not appear to inhibit topiramate enhancement of GABA-evoked currents in $GABA_A$ cortical neuronal receptors. Topiramate also does not appear to increase duration of chloride ion channel opening. Therefore, topiramate may potentiate $GABA_A$-evoked chloride ion flux by a mechanism other than $GABA_A$-receptor modulation.

Topiramate antagonizes a non-*N*-methyl-d-aspartate (NMDA) glutamate receptor and the kainate/α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) receptor subtype. Although topiramate had no apparent effect on glutamate receptors of the NMDA subtype in cultured rat hippocampal neurons, topiramate antagonized the ability of kainate to activate the kainate/AMPA glutamate receptor subtype, and these effects were shown to be concentration dependent. Glutamate, the principal excitatory neurotransmitter amino acid in the brain, interacts with specific neuronal membrane receptors, including ion channel coupled (ionotropic) (e.g., NMDA, kainate/AMPA, kainate) receptor subtypes and with G-protein coupled (metabotropic) receptors that modulate intracellular second-messengers. Glutamate is responsible for a variety of neurologic functions, including cognition, memory, movement, and sensation, and excessive activation of glutamate receptors may mediate injury or destruction of neurons in some acute neurologic disorders and chronic neurodegenerative diseases. The pathogenesis of seizures is thought to be mediated at least in part through excessive stimulation of glutamate receptors. In spontaneously epileptic rats, topiramate has reduced extracellular hippocampal concentrations of both glutamate and aspartate, and a correlation existed between reduction in glutamate concentrations and suppression of tonic seizures.

In animals, topiramate exhibits anticonvulsant activity in the maximal electroshock seizure (MES) test, suggesting that, like phenytoin, it may be effective in the management of partial and tonic-clonic (grand mal) seizures in humans. Topiramate also exhibited dose-dependent inhibition of absence-like seizures, which was antagonized by pretreatment with haloperidol. In animals, topiramate was ineffective or weakly effective in blocking clonic seizures induced by pentylenetetrazole, indicating that the drug may not enhance GABA inhibitory activity substantially.

Although the precise mechanism(s) of action of topiramate in the management of alcohol dependence is unclear, topiramate enhances GABA-mediated inhibitory neurotransmission and inhibits glutamatergic stimulatory neurotransmission; such changes appear to decrease dopaminergic activity in the mesocorticolimbic areas of the brain, which have been associated with alcohol dependence.

Topiramate inhibits carbonic anhydrase CA-II and CA-IV isoenzymes and, like other carbonic anhydrase inhibitors (e.g., acetazolamide, dichlorphenamide), the drug may promote the formation of renal calculi by increasing urinary pH and decreasing the excretion of urinary citrates. In premarketing studies, renal calculi were reported to occur in 1.5% of patients receiving topiramate, an incidence 2–4 times that expected in a similar untreated population, but most patients who developed calculi elected to continue therapy with the drug. Use of topiramate with other carbonic anhydrase inhibitors may increase the risk of renal calculi and therefore should be avoided.

Preparations

Excipients in commercially available drug preparations may have clinically important effects in some individuals; consult specific product labeling for details.

Topiramate

Oral		
Capsules	15 mg	**Topamax® Sprinkle, Ortho-McNeil**
	25 mg	**Topamax® Sprinkle, Ortho-McNeil**
Tablets, film-coated	25 mg	**Topamax®, Ortho-McNeil**
	50 mg	**Topamax®, Ortho-McNeil**
	100 mg	**Topamax®, Ortho-McNeil**
	200 mg	**Topamax®, Ortho-McNeil**

†Use is not currently included in the labeling approved by the US Food and Drug Administration.

Valproate Sodium / Valproic Acid / Divalproex Sodium

Sodium Dipropylacetate, Sodium α-Propylvalerate, DPA Sodium / Dipropylacetic Acid, 2-Propylvaleric Acid, DPA / Valproate Semisodium

■ Valproic acid, valproate sodium, and divalproex sodium are carboxylic acid-derivative anticonvulsants that also are used to treat acute manic episodes or for prophylaxis of migraine headache as well as certain other psychiatric disorders.

Uses

■ **Seizure Disorders** Valproic acid, valproate sodium, or divalproex sodium is used alone or with other anticonvulsants (e.g., ethosuximide) in the prophylactic management of simple and complex absence (petit mal) seizures. The drugs also may be used in conjunction with other anticonvulsants in the management of multiple seizure types that include absence seizures. Valproic acid is considered a drug of choice for absence or atypical absence seizures.

Valproic acid, valproate sodium, or divalproex sodium is used alone or with other anticonvulsants (e.g., carbamazepine, phenytoin) in the prophylactic management of complex partial seizures that occur either by themselves or in association with other seizure types. Some clinicians state that valproic acid may be considered a drug of choice for the management of complex partial seizures. Two randomized, placebo-controlled trials, one of valproic acid as monotherapy and one of valproic acid as adjunctive therapy, demonstrated that the drug decreased the frequency of seizures in patients inadequately controlled by other therapies (e.g., carbamazepine, phenytoin, phenobarbital).

Valproic acid has been used and is considered by some clinicians as a drug of choice for management of other generalized seizures, including primary generalized tonic-clonic seizures†, atypical absence†, myoclonic†, or atonic seizures†, especially for those patients with more than one type of generalized seizure. In addition, some clinicians state that valproic acid may be used as a drug of choice for the management of simple partial seizures†. Valproic acid also has been administered rectally† or by intragastric drip† with some success in the management of status epilepticus refractory to IV diazepam†. A parenteral formulation of valproic acid has been studied and has been effective when administered IV† in the management of status epilepticus.

Valproic acid has been used with some success in the treatment of Lennox-Gastaut syndrome and infantile spasms.

■ **Bipolar Disorder** Divalproex sodium is used in the treatment of manic episodes associated with bipolar disorder; valproic acid† and valproate sodium† also have been used. Because there are only minor differences in the pharmacokinetics of the formulations, and because all forms of the drug circulate in plasma as valproic acid, the term "valproic acid" will be used in the following discussion.

Valproic acid has been used as monotherapy or as part of combination therapy (e.g., with lithium, antipsychotic agents [e.g., olanzapine], antidepressants, carbamazepine) in the treatment of acute manic episodes. The American Psychiatric Association (APA) currently recommends combined therapy with valproic acid plus an antipsychotic agent or with lithium plus an antipsychotic agent as first-line drug therapy for the acute treatment of more severe manic or mixed episodes and monotherapy with one of these drugs for less severe episodes. For mixed episodes, valproic acid may be preferred over lithium. Valproic acid or lithium also is recommended for the initial acute treatment of rapid cycling.

A manic episode is a distinct period of abnormally and persistently elevated, expansive, or irritable mood. Typical symptoms include pressure of speech, motor hyperactivity, reduced need for sleep, flight of ideas, grandiosity, poor judgment, aggressiveness, and possible hostility. Efficacy of valproic acid in

the treatment of manic episodes was established in short-term, placebo-controlled, parallel-group trials in patients hospitalized with bipolar disorder, manic (DSM-IIIR); response to therapy was assessed using objective rating scales such as the Young Mania Rating Scale (YMRS), an augmented Brief Psychiatric Rating Scale (BPRS-A), the Mania Rating Scale (MRS), and the Global Assessment Scale (GAS). One study specifically enrolled patients who were intolerant of or unresponsive to previous lithium therapy. Up to 40% of patients fail to respond to or are intolerant of lithium therapy for manic episodes; such patients may demonstrate a response to valproic acid, although response to valproic acid appears to be independent of prior response to lithium therapy. Valproic acid therapy appears to be about as effective as lithium for the treatment of manic episodes. In one placebo-controlled trial, 48% of patients receiving valproic acid demonstrated a response to the drug as measured by changes in the Manic Syndrome subscale of the MRS; 49% of patients receiving lithium responded to therapy, while 25% of patients receiving placebo responded. Antimanic response to valproic acid typically occurs within 1–2 weeks of initiating therapy. Valproic acid therapy also appears to be effective in specific types of mania, including rapid-cycling mania and dysphoric mania, which have been reported to be poorly responsive to lithium.

Although the manufacturer states that safety and efficacy of long-term (i.e., longer than 3 weeks) valproic acid therapy have not been established in the treatment of manic episodes, valproic acid also has been used, alone or in combination therapy, for long-term or maintenance antimanic therapy†, and APA currently considers the best empiric evidence to support the use of valproic acid or lithium for maintenance therapy. Antimanic efficacy has been maintained from several months to more than 10 years, and such long-term therapy appears to decrease the frequency and severity of bipolar episodes over extended periods of time; however, further study is required to establish the efficacy of valproic acid as maintenance therapy of manic episodes. Valproic acid does not appear to be as effective for the management of the depressive component of bipolar disorder†; although some evidence suggests that long-term valproic acid therapy may be moderately effective in the prophylaxis of depressive episodes, its acute effects on depression appear to be limited. Some clinicians recommend that valproic acid therapy be used in patients with bipolar disorder or schizoaffective disorder, bipolar type, who have responded inadequately to or have been unable to tolerate treatment with lithium salts or other therapy (e.g., carbamazepine), particularly if the patient displays residual manic symptoms, or in the presence of rapid cycling, dysphoric mania or hypomania, associated neurologic abnormalities, or organic brain disorder.

■ **Migraine** ***Prophylaxis of Chronic Attacks*** Divalproex sodium is used in the prophylaxis of migraine headache, with or without associated aura; valproic acid† and sodium valproate† also have been used. Because there are only minor differences in the pharmacokinetics of the formulations, and because all forms of the drug circulate in plasma as valproic acid, the term "valproic acid" will be used in the following discussion. Because valproic acid may pose a hazard to the fetus (see Cautions: Pregnancy, Fertility, and Lactation), it should be considered for women of childbearing potential only after this risk has been discussed thoroughly with the patient and weighed against the potential benefits of treatment. Some clinicians state that effective contraception during valproic acid therapy should be strongly encouraged.

The US Headache Consortium states that there is good evidence from multiple well-designed clinical trials that valproic acid has medium to high efficacy for the prophylaxis of migraine headache. Valproic acid was demonstrated to be effective in the prophylaxis of migraine headache in 2 randomized, double-blind, placebo-controlled trials in patients with at least a 6-month history of migraine, with or without associated aura. Patients also had to experience at least 2 migraines per month in the 3 months prior to enrollment in the studies; patients were excluded if they had cluster headaches. Although women of childbearing potential were excluded from one study because of the teratogenic properties of valproic acid, they were included in the other, provided that they were practicing an effective form of contraception. In both studies, after a 4-week single-blind placebo baseline period, patients were randomized to receive either valproic acid or placebo during a 12-week treatment period consisting of a 4-week titration period and an 8-week maintenance period. Assessment of treatment outcome was based on 4-week migraine headache rates during the 12-week treatment period. In the first study, dosage titration was guided by the use of actual or sham trough total serum valproate concentrations for patients receiving valproic acid or placebo, respectively. The mean dosage of valproic acid was 1087 mg daily (range: 500–2500 mg daily), with dosages of more than 500 mg being given in 3 divided doses daily. Patients receiving valproic acid experienced a substantial decrease in the mean 4-week migraine headache rate compared with those receiving placebo (3.5 versus 5.7, respectively). In the second study, patients were randomized to receive (after titration from an initial dosage of 250 mg daily) 500, 1000, or 1500 mg of valproic acid daily or placebo, administered as 2 daily doses. Efficacy of valproic acid in the second study was to be determined by comparing the 4-week migraine headache rate in the combined groups of patients receiving 1000 and 1500 mg of valproic acid to that of patients receiving placebo. However, the manufacturer reports that the mean 4-week migraine headache rates in patients receiving valproic acid 500, 1000, or 1500 mg daily were 3.3, 3, or 3.3, respectively, compared to a rate of 4.5 in patients receiving placebo, and that the rate in the combined groups of patients receiving 1000 or 1500 mg daily was substantially lower than that of the placebo group.

In addition, valproic acid (given once daily as an extended-release tablet) was demonstrated to be effective in the prophylaxis of migraine headache in a 12-week, multicenter, double-blind, placebo-controlled clinical trial in patients with a history of migraine headaches with or without associated aura.

Other studies also have shown valproic acid to be effective in the prophylaxis of migraine. In one comparative single-blind, placebo-controlled, crossover study, valproic acid was shown to be as effective in migraine prophylaxis as propranolol.

Acute Attacks IV† valproate sodium has been used for the acute† management of migraine headache; however, the role of the drug relative to other acute therapies (selective serotonin type 1-like receptor agonists ["triptans"], ergot alkaloids, antiemetics, nonsteroidal anti-inflammatory agents [NSAIAs], butalbital-containing analgesics, opiate analgesics) requires further elucidation. Results of several studies, including open-label, comparative, randomized, prospective, retrospective, and/or double-blind, studies and at least one placebo-controlled study, as well as case reports, indicate that IV valproate sodium may alleviate acute migraine attacks in patients with or without aura and generally appears to be well tolerated. Efficacy generally was evaluated in terms of a reduction in headache severity as rated by the patient (i.e., a reduction in pain from severe or moderately severe to mild or absent usually using a 3- or 4-point scale) or by a visual analog pain score (VAS). Limited data indicate that 300-mg to 1-g IV valproate sodium doses (some of which were repeated at the same initial dose or less) were associated with relief of migraine headache, usually within 1 to several hours.

IV valproate sodium also has been used in the management of chronic daily headache† in a limited number of patients some of whom have had an inadequate response to dihydroergotamine or when dihydroergotamine was contraindicated.

Further study and experience are needed to more clearly define the role of IV valproate sodium in the management of acute migraine attacks and other headaches.

For further information on management and classification of migraine headache, see Vascular Headaches: General Principles in Migraine Therapy, under Uses, in Sumatriptan 28:32.28.

■ **Schizophrenia** Valproic acid or divalproex sodium has been used as an adjunct to antipsychotic agents in the symptomatic management of schizophrenia† in patients who fail to respond sufficiently to an adequate trial of an antipsychotic agent alone. The American Psychiatric Association (APA) and some clinicians state that anticonvulsant agents such as valproic acid or divalproex sodium may be useful adjuncts in schizophrenic patients with prominent mood lability or with agitated, aggressive, hostile, or violent behavior. In general, for such adjunctive therapy, valproic acid or divalproex sodium is administered in the same dosage and with the same resulting therapeutic plasma concentrations as that in the management of seizure disorders. The APA states that, with the exception of patients with schizophrenia whose illness has strong affective components, valproic acid or divalproex sodium alone has not been shown to be substantially effective in the long-term treatment of schizophrenia.

While some evidence suggested potential benefit of valproic acid in relieving tardive dyskinesia in patients receiving long-term antipsychotic drug therapy†, recent systematic review of randomized controlled trials with nonbenzodiazepine γ-aminobutyric acid (GABA) agonists such as valproic acid found the evidence for such benefit unconvincing, and indicated that any possible benefit may be outweighed by adverse effects. For additional information on the management of schizophrenia, see Uses: Psychotic Disorders, in the Phenothiazines General Statement 28:16.08.24.

■ **Other Uses** Some experts recommend use of valproic acid for the treatment of aggressive outbursts in children with ADHD. For a more detailed discussion on the management of ADHD, see Uses: Attention Deficit Hyperactivity Disorder, in Methylphenidate 28:20.04.

Valproic acid used alone or in conjunction with GABA was ineffective in the treatment of chorea† (including Huntington's chorea). Valproic acid has been effective in a limited number of patients with organic brain syndrome†.

Dosage and Administration

■ **Administration** Valproate sodium can be administered orally or by IV infusion and valproic acid and divalproex sodium are administered orally. Valproic acid also has been administered rectally by enema or in wax-based suppositories.

Patients who are currently receiving or beginning therapy with valproic acid, valproate sodium, or divalproex sodium and/or any other anticonvulsant for any indication should be closely monitored for the emergence or worsening of depression, suicidal thoughts or behavior (suicidality), and/or any unusual changes in mood or behavior. (See Cautions: Nervous System Effects and Cautions: Precautions and Contraindications.)

Oral Administration Valproic acid, valproate sodium, and divalproex sodium are administered orally. Valproic acid capsules should be swallowed whole; not chewed, in order to prevent local irritation to the mouth and throat. If GI irritation occurs, the drug may be administered with food. Patients who are unable to tolerate the GI effects of valproic acid or valproate sodium may tolerate divalproex sodium. When switching to divalproex sodium delayed-release tablets in patients receiving valproic acid, the same daily dose and schedule should be used. After stabilization with divalproex sodium therapy, the daily dose may be divided and administered 2 or 3 times daily in selected patients. Extended-release tablets of divalproex sodium are administered once daily; patients should be advised that the extended-release tablets must be swallowed intact and not chewed or crushed. Valproate sodium oral solution should not be administered in carbonated drinks because valproic acid will be liberated and may cause local irritation to the mouth and throat as well as an unpleasant taste.

The commercially available capsules containing coated particles of divalproex sodium (Depakote®) may be swallowed intact or the entire contents of

the capsule(s) may be sprinkled on a small amount (about 5 mL) of semisolid food (e.g., applesauce, pudding) immediately prior to administration. The mixture containing coated particles from the capsules should not be chewed. The mixture of coated particles and semisolid food should not be stored for future use. Patients receiving divalproex sodium capsules containing coated particles should be instructed not to be concerned if they notice coated particles in their stool, because these particles do not completely dissolve and may be passed in the stool.

The manufacturer states that although the extent of GI absorption of valproic acid from capsules containing coated particles or delayed-release tablets of divalproex sodium is equivalent, peak and trough plasma concentrations achieved with these dosage forms may vary (e.g., higher peak valproic acid concentrations generally are achieved with the delayed-release tablets). Although these differences are unlikely to be clinically important, increased monitoring of plasma valproic acid concentrations is recommended if one dosage form is substituted for the other.

The manufacturer states that although it is agreed that pharmacologic treatment beyond an initial response in patients with manic episodes is desirable, both for the maintenance of initial response and for prevention of new manic episodes, the safety and efficacy of long-term (i.e., longer than 3 weeks) valproic acid therapy for manic episodes have not been established in controlled clinical trials and that clinicians who elect to use such therapy for extended periods (i.e., longer than 3 weeks) should continually reevaluate the usefulness of valproic acid therapy in the individual patient. The manufacturer states that the safety of valproic acid for longer-term antimanic therapy is supported by data from record reviews involving approximately 360 patients treated for longer than 3 months.

IV Administration Valproate sodium injection is intended for IV use only.

For IV use, the manufacturer states that the appropriate dose of valproate sodium injection should be diluted with at least 50 mL of a compatible IV solution (e.g., 5% dextrose injection, 0.9% sodium chloride injection, lactated Ringer's injection). Diluted IV solutions of the drug should be infused IV over 60 minutes.

Rapid IV infusion of valproate sodium has been associated with an increased risk of adverse effects and is not currently included in the manufacturer's labeling. However, rates exceeding 20 mg/minute or infusion periods less than 60 minutes have been studied in a limited number of patients with seizure disorders and in patients with acute migraine headaches, and such administration generally appeared to be well tolerated. In a study of the safety of initial 5- to 10-minute IV infusions of valproate sodium (1.5–3 mg/kg per minute of valproic acid), patients generally tolerated such rapid infusions of the drug; the study was not designed to assess the efficacy of the regimen. The drug also appeared to be well tolerated in studies evaluating efficacy in the management of acute migraine attacks† when valproate sodium doses of 300 mg to 1 g were infused IV at rates ranging from 17–250 mg/minute or occasionally by direct rapid ("bolus") IV injection (100-mg doses).

Use of rapid infusions in patients receiving the IV preparation as a parenteral replacement for oral valproic acid has not been established.

Valproate sodium injection and diluted solutions of the drug should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

■ **Dosage** Dosage of valproate sodium and divalproex sodium is expressed in terms of valproic acid. Dosage must be carefully and slowly adjusted according to individual requirements and response.

Seizure Disorders **IV Dosage.** IV valproate sodium therapy may be employed in patients in whom oral therapy is temporarily not feasible, but therapy should be switched to oral administration as soon as clinically possible. IV administration of the drug can be used for monotherapy or as adjunctive therapy in the management of seizure disorders. The manufacturer states that the usual total daily dosages of valproic acid are equivalent for IV or oral administration, and the doses and frequency of administration employed with oral therapy in seizures disorders are expected to be the same with IV therapy, although plasma concentration monitoring and dosage adjustment may be necessary. The use of IV therapy for longer than 14 days has not been studied to date. The manufacturer also states that the use of IV valproate sodium for initial monotherapy has not been systematically studied; however, usual dosages and titration employed with oral therapy can be employed with parenteral therapy. Patients receiving dosages near the maximum recommended dosage of 60 mg/kg daily should be monitored closely, particularly when enzyme-inducing drugs are not used concomitantly.

Oral Dosage. Various valproic acid dosage regimens have been used in published studies. A correlation between plasma valproic acid concentration and therapeutic effect has not been established; however, a therapeutic range of 50–100 mcg/mL has been suggested.

For the management of complex partial seizures, the manufacturers state that the usual initial dosage of valproic acid as monotherapy or as adjunctive therapy, when being added to a current therapeutic regimen, for adults and children 10 years of age and older is 10–15 mg/kg daily. For the management of simple or complex absence seizures, the manufacturer states that the usual initial dosage of valproic acid is 15 mg/kg daily. Dosage may be increased by 5–10 mg/kg daily at weekly intervals until seizures are controlled or adverse effects prevent further increases in dosage. The manufacturers state that the maximum recommended dosage is 60 mg/kg daily. These dosage recommendations also apply when anticonvulsant therapy is being initiated with divalproex sodium as delayed- or extended-release formulations.

When converting a patient from a current anticonvulsant to valproic acid therapy for the treatment of complex partial seizures, valproic acid therapy should be initiated at usual starting doses. The dose of the current anticonvulsant may be decreased by 25% every 2 weeks, either starting concomitantly with the initiation of valproic acid therapy or delayed by 1–2 weeks if there is a concern that seizures are likely to occur with a reduction. The speed and duration of withdrawal of the current anticonvulsant can be highly variable, and patients should be monitored closely during this period for increased seizure frequency. In order to prevent adverse GI effects, the manufacturers state that the drug should be administered in 2 or more divided doses when the dosage exceeds 250 mg daily. When divalproex sodium delayed-release tablets are administered, a twice-daily dosing regimen is suggested whenever feasible and appears to adequately maintain plasma valproic acid concentrations in most patients receiving the drug. The frequency of adverse effects (particularly hepatic effects) may be dose related. The benefit of improved seizure control which may accompany higher dosages should therefore be weighed carefully against the risk of adverse effects.

When converting a patient whose seizure disorder is controlled with delayed-release divalproex sodium tablets to the extended-release tablets, the drug should be administered once daily using a total daily dose that is 8–20% higher than the corresponding delayed-release dosage that the patient was receiving. For patients whose delayed-release daily dosage cannot be directly converted to a corresponding commercially available extended-release dosage, clinicians may consider increasing the delayed-release total daily dosage to the next higher dosage before converting to the appropriate extended-release dosage.

For the management of status epilepticus refractory to IV diazepam†, 400–600 mg of valproic acid was administered rectally† by enema or in wax base suppositories at 6-hour intervals.

Bipolar Disorder The initial dosage of valproic acid in the treatment of manic episodes is 750 mg daily in divided doses. The dose of valproic acid should be increased as quickly as possible to achieve the lowest therapeutic dose producing the desired clinical effect or desired serum concentration; however, the manufacturer recommends that the dose not exceed 60 mg/kg daily. In placebo-controlled studies of valproic acid for the treatment of manic episodes, the trough serum valproic acid concentration that produced the desired clinical effect ranged from 50–125 mcg/mL. Maximum serum concentrations generally were achieved within 14 days after initiating therapy.

Dosing guidelines for maintenance therapy† with valproic acid are less evidence-based than those for acute therapy, and dosages lower than those employed for acute therapy occasionally have been used. A 1-year study with divalproex sodium found an association between higher serum concentrations and increased appetite and decreased platelet and leukocyte counts.

Migraine **Prophylaxis of Chronic Attacks.** In the prophylaxis of migraine, with or without associated aura, the recommended initial dosage of valproic acid is 250 mg twice daily. Some patients may benefit from doses of up to 1 g daily; however, in clinical trials, there was no evidence that doses of valproic acid exceeding this resulted in greater efficacy.

For the prophylaxis of migraine headache in adults, the recommended initial dosage of divalproex sodium as extended-release tablets is 500 mg once daily for 1 week; dosage may then be increased to 1 g once daily. Although maintenance dosages other than 1 g once daily have not been evaluated in patients with migraine headache, the effective dosage range for these patients is 500 mg to 1 g daily. It should be considered that divalproex sodium extended-release tablets and divalproex sodium delayed-release tablets are *not* bioequivalent. If a patient requires smaller dosage adjustment than that available using the extended-release tablets, the delayed-release tablets should be used instead. If a patient misses a dose of divalproex sodium extended-release tablets, the dose should be taken as soon as possible, unless it is almost time for the next dose. However, if the patient skips a dose, a double dose of divalproex sodium extended-release tablets should *not* be taken to make up for the missed dose.

Acute Attacks. For the acute management of migraine headache† in adults and adolescents, the optimum IV dosage, frequency, and rate of administration have not been established. In most reports, IV valproate sodium was given in doses of 300 mg to 1 g diluted in a compatible IV infusion (e.g., 5% dextrose injection, 0.9% sodium chloride injection) solution (usually about 100–250 mL) and infused IV at rates ranging from 17–100 mg/minute. In some patients, the dose was administered more rapidly (e.g., 500 mg over 2 minutes, 100 mg by direct ["bolus"] IV injection). A repeat dose (equal to the initial dose or less) was given to some patients within a few hours, if reduction of pain was not sufficient. In one study, 500-mg doses of valproate sodium were administered every 8 hours for 2 days. Some patients have received direct IV injections of 100-mg doses repeated at 5-minute intervals or infusions of a single 500-mg dose (diluted in 5 mL of 0.9% sodium chloride injection) into a free-flowing IV line of 0.9% sodium chloride injection.

When IV valproate sodium has been used in the management of chronic daily headache, an initial dose of 15 mg/kg was administered over 30 minutes followed by a dose of 5 mg/kg (infused over 15 minutes) given every 8 hours.

Dosage in Geriatric Patients Because of a decrease in unbound clearance of valproic acid, the starting dosage should be reduced. Subsequent dosage should be increased more slowly in geriatric patients. In addition, the manufacturer recommends regular monitoring of fluid and nutritional intake, dehydration, somnolence, and other adverse effects in these individuals. Dosage reduction or discontinuance of valproic acid should be considered in geriatric patients with decreased food or fluid intake and in those with excessive somnolence. The ultimate therapeutic dosage in these patients should be determined on the basis of tolerability and clinical response.

Cautions

The adverse effect profile of parenteral valproate sodium can be expected to include all of the effects associated with oral administration of the drug. In addition, IV infusion of valproate sodium may cause local effects at the injection site and effects associated with the rate of infusion. (See Cautions: Local and Infusion-related Effects.)

■ **GI Effects** Nausea, vomiting, abdominal pain, anorexia, diarrhea, and dyspepsia may occur in patients receiving valproic acid. The most frequent adverse effects of valproic acid following initiation of therapy with the drug are nausea, vomiting, and indigestion. These adverse effects usually are transient, rarely require discontinuance of therapy, and can be minimized by administering the drug with meals or by beginning therapy with low doses and increasing the dose very gradually. While divalproex sodium shares the toxic GI potential of valproic acid, the frequency of adverse GI effects appears to be lower and the effects possibly less severe with divalproex sodium than with valproic acid; patients who are unable to tolerate the GI effects of valproic acid or valproate sodium may tolerate divalproex sodium, but GI intolerance to divalproex sodium can also occur. Both anorexia with some weight loss and increased appetite with weight gain have been reported in patients receiving valproic acid. Eructation, fecal incontinence, gastroenteritis, glossitis, flatulence, hematemesis, periodontal abscess, tooth disorder, dry mouth, stomatitis, and constipation were reported in 1–5% of patients receiving valproic acid in clinical trials. Dysphagia, gum hemorrhage, and mouth ulceration also have occurred in greater than 1% of patients receiving the drug.

■ **Pancreatitis** Cases of life-threatening pancreatitis have been reported in children and adults shortly after initial use or after several years of therapy with valproic acid. Pancreatitis may be hemorrhagic with a rapid progression from initial symptoms to death. Development of manifestations suggestive of pancreatitis (e.g., abdominal pain, nausea, vomiting, and/or anorexia) requires prompt medical evaluation. (See Cautions: Precautions and Contraindications.) It should be considered that patients receiving valproic acid are at greater risk of developing pancreatitis than that expected in the general population and, in addition, pancreatitis recurred on rechallenge with the drug in several patients. In clinical trials involving 2416 patients, 2 cases of pancreatitis without alternative etiology were reported, representing 1044 patient-years experience.

■ **Nervous System Effects** Sedation and drowsiness may occur with valproic acid therapy, especially in patients receiving other anticonvulsants. (See Drug Interactions: CNS Depressants, Antidepressants, and Anticonvulsants.) Somnolence, asthenia, dizziness, and tremor generally are the most frequently reported adverse nervous system effects in patients receiving valproic acid in clinical trials. Ataxia, emotional lability, abnormal thinking, amnesia, and depression have been reported in up to 5–8% of patients receiving the drug. Some patients have reported increased alertness, insomnia, and nervousness during valproic acid therapy. Coma has been reported rarely in patients receiving valproic acid as monotherapy or in combination with phenobarbital. Rarely, patients have developed encephalopathy with or without fever, without evidence of hepatic dysfunction or abnormal valproic acid plasma concentrations, shortly after the introduction of valproic acid therapy. Although this condition can be reversible upon discontinuance of the drug, there have been fatalities in patients with hyperammonemic encephalopathy, often in patients with underlying urea cycle disorder. (See Cautions: Precautions and Contraindications.) Hearing loss, either reversible or irreversible, has been reported in patients receiving valproic acid therapy; however, a causal relationship to the drug has not been established.

Between 1–5% of patients receiving valproic acid in clinical trials experienced anxiety, confusion, headache, myasthenia, abnormal gait, paresthesia, hypertonia, incoordination, abnormal dreams, personality disorder, hallucinations, euphoria, agitation, catatonia, dysarthria, speech disorder, hypokinesia, increased reflexes, tardive dyskinesia, or vertigo. Asterixis, hypesthesia, parkinsonism, hostility, emotional upset, and psychosis/acute psychosis also have occurred rarely. Hyperactivity, aggressiveness, and other behavioral disturbances have been reported in a few children receiving valproic acid. Several reports have noted reversible cerebral atrophy and dementia in association with valproic acid therapy.

The US Food and Drug Administration (FDA) has analyzed suicidality reports from placebo-controlled studies involving 11 anticonvulsants, including valproic acid, and found that patients receiving anticonvulsants had approximately twice the risk of suicidal behavior or ideation (0.43%) compared with patients receiving placebo (0.24%). FDA's analysis included 199 randomized, placebo-controlled studies of 11 anticonvulsants (carbamazepine, felbamate, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, pregabalin, tiagabine, topiramate, valproate, and zonisamide) involving over 43,000 patients 5 years of age or older; the studies evaluated the effectiveness of the anticonvulsants in epilepsy, psychiatric disorders (e.g., bipolar disorder, depression, anxiety), and other conditions (e.g., migraine, neuropathic pain). This increased suicidality risk was observed as early as one week after beginning therapy and continued through 24 weeks. The results were generally consistent among the 11 drugs studied. In addition, patients who were treated for epilepsy, psychiatric disorders, and other conditions were all found to be at increased risk for suicidality when compared with placebo; there did not appear to be a specific demographic subgroup of patients to which the increased risk could be attributed. However, the relative risk for suicidality was found to be higher in patients with epilepsy compared with patients who were given one of the drugs for psychiatric or other conditions. (See Cautions: Precautions and Contraindications.)

■ **Hepatic Effects** Minor elevations in serum concentrations of aminotransferases (transaminases) and lactate dehydrogenase occur frequently in patients receiving valproic acid and appear to be dose related. Occasionally, increases in serum bilirubin concentration and abnormal changes in other hepatic function test results occur; these results may reflect potentially serious hepatotoxicity. (See Cautions: Precautions and Contraindications.) Hepatic failure resulting in death has occurred in patients receiving valproic acid, usually during the first 6 months of therapy. Clinical experience indicates that children younger than 2 years of age, especially those receiving multiple anticonvulsants or those with congenital metabolic disorders, severe seizure disorders accompanied by mental retardation, or organic brain disease, have a considerably increased risk of developing fatal hepatotoxicity compared with older patient groups. (See Cautions: Precautions and Contraindications.) Above 2 years of age, the frequency of fatal hepatotoxicity decreases considerably in progressively older patient groups. Severe or fatal hepatotoxicity induced by valproic acid may be preceded by nonspecific symptoms such as loss of seizure control, malaise, weakness, lethargy, anorexia, and vomiting.

Between 1–5% of patients receiving valproic acid in clinical trials experienced increased ALT (SGPT) and increased AST (SGOT) concentrations.

■ **Endocrine and Metabolic Effects** Hyperammonemic encephalopathy, including some fatalities, has been reported in patients with urea cycle disorders, particularly ornithine carbamoyltransferase deficiency, following initiation of valproic acid therapy. Hyperammonemia may occur in patients receiving valproic acid and may occur in the absence of abnormal hepatic function test results. Development of symptoms of unexplained hyperammonemic encephalopathy (e.g., lethargy, vomiting, changes in mental status) requires prompt medical evaluation. (See Cautions: Precautions and Contraindications.)

Hyponatremia and inappropriate antidiuretic hormone (ADH) secretion also have been reported. Hyperglycinemia has been reported in patients receiving valproic acid and was associated with a fatal outcome in one patient with preexisting nonketotic hyperglycinemia. Between 1–5% of patients receiving valproic acid in clinical trials experienced dysmenorrhea, amenorrhea, vaginitis, metrorrhagia, or vaginal hemorrhage. Breast enlargement, galactorrhea, irregular menses, polycystic ovaries, hyperandrogenism, weight gain, Fanconi's syndrome (principally reported in children), and parotid gland swelling have occurred in some patients receiving valproic acid. Abnormal thyroid function test results and decreased carnitine concentrations also have been reported; however, the clinical importance of these abnormalities has not been elucidated.

■ **Hematologic Effects** Valproic acid inhibits the secondary phase of platelet aggregation and may prolong bleeding time. In one study of valproic acid monotherapy for seizures, 27% of patients receiving approximately 50 mg/kg per day had at least one platelet count of 75,000/mm^3. Approximately half of the patients discontinued therapy, with their platelet counts returning to normal; the remaining patients experienced normalization of their platelet counts with continued valproic acid therapy. In this study, the probability of thrombocytopenia appeared to increase significantly at total valproate serum concentrations of 110 mcg/mL or greater (females) or 135 mcg/mL or greater (males). Ecchymosis, petechiae, bruising, hematoma formation, epistaxis, frank hemorrhage, lymphocytosis, leukopenia, eosinophilia, macrocytosis, acute intermittent porphyria, decreased fibrinogen concentrations, anemia (including macrocytic anemia, with or without folate deficiency), bone marrow suppression, pancytopenia, and aplastic anemia also have been reported.

■ **Dermatologic and Sensitivity Reactions** Between 1–5% of patients receiving valproic acid in clinical trials experienced seborrhea, dry skin, pruritus, furunculosis, rash (including maculopapular), or discoid lupus erythematosus. Transient alopecia, cutaneous vasculitis, generalized pruritus, anaphylaxis, photosensitivity, Stevens-Johnson syndrome, erythema nodosum, and erythema multiforme have been reported in patients receiving valproic acid therapy. Rare cases of toxic epidermal necrolysis have been reported, including a fatal case in a 6-month-old infant receiving valproic acid therapy; however, the infant was receiving other drugs concomitantly. An additional case of fatal toxic epidermal necrosis was reported in a 35-year-old patient with acquired immunodeficiency syndrome (AIDS) who was taking several concomitant drugs and who had a history of multiple cutaneous drug reactions.

■ **Local and Infusion-related Effects** In addition to the usual adverse effects associated with oral therapy, IV infusion of valproate sodium can produce local effects at the site of injection as well as adverse effects associated with the rate of IV infusion. In clinical trials involving healthy adults as well as patients with seizure disorders at total IV dosages of 120–6000 mg daily, adverse local effects at the site of infusion were reported in up to 2.6% of patients and included pain (2.6%), injection site reaction (2.4%), and inflammation (0.6%). In these trials, about 2% of patients discontinued parenteral therapy with the drug because of adverse effects, principally because of nausea and vomiting and elevated amylase. Other reasons for discontinuing parenteral valproate sodium therapy included hallucinations, pneumonia, headache, injection site reaction, and abnormal gait.

Dizziness and injection site pain were reported more frequently when valproate sodium was infused IV at a rate of 100 mg/minute relative to slower rates that ranged up to 33 mg/minute. At an IV infusion rate of 200 mg/minute, dizziness and taste perversion occurred more frequently than at an IV infusion rate of 100 mg/minute. In clinical trials, the maximum IV infusion rate studied was 200 mg/minute.

■ **Ocular and Otic Effects** Diplopia, amblyopia, nystagmus, and tinnitus have been reported in up to 7–16% of patients receiving valproic acid in clinical trials. Other adverse ocular and otic effects reported in patients receiv-

ing valproic acid include abnormal vision, otitis media, conjunctivitis, dry eyes, ocular pain, ocular disorder, photophobia, otic pain, and otic disorder. Reversible and irreversible hearing loss (including deafness) has been reported; however, a causal relationship has not been established.

■ **Other Adverse Effects** Infection has been reported in up to 20% of patients receiving valproic acid in clinical trials. Back pain, fever, flu syndrome, bronchitis, rhinitis, pharyngitis, dyspnea, and peripheral edema have been reported in up to 5–12% of patients receiving the drug in clinical trials. Increased cough, chest pain, tachycardia, hypertension, palpitation, arrhythmia, bradycardia, hypotension, postural hypotension, taste perversion, hiccups, facial edema, pneumonia, sinusitis, dysuria, urinary incontinence, cystitis, urinary frequency, arthralgia, myalgia, arthrosis, leg cramps, twitching, malaise, chills, fever with chills, sweating, vasodilation, cyst, neck pain, neck rigidity, and accidental injury also may occur. Adverse effects reported rarely in patients receiving valproic acid include muscular weakness, interstitial nephritis, enuresis, urinary tract infection, bone pain, lupus erythematosus, and fatigue. A case of reversible skeletal muscle weakness and ventilatory failure also has been reported in a geriatric patient receiving valproic acid therapy.

■ **Precautions and Contraindications** Since divalproex sodium is a prodrug of valproate, it shares the toxic potentials of valproic acid, and the usual cautions, precautions, and contraindications of valproic acid therapy should be observed with divalproex sodium therapy.

Patients should be warned that valproic acid may impair ability to perform hazardous activities requiring mental alertness or physical coordination (e.g., operating machinery or driving a motor vehicle).

FDA has informed healthcare professionals about an increased risk of suicidality (suicidal behavior or ideation) observed in an analysis of studies using various anticonvulsants compared with placebo. (See Cautions: Nervous System Effects.) FDA recommends that all patients who are currently receiving or beginning therapy with any anticonvulsant for any indication be closely monitored for the emergence or worsening of depression, suicidal thoughts or behavior (suicidality), and/or unusual changes in mood or behavior. Symptoms such as anxiety, agitation, hostility, mania, and hypomania may be precursors to emerging suicidality. Clinicians should inform patients, their families, and caregivers of the potential for an increased risk of suicidality so that they are aware and able to notify their clinician of any unusual behavioral changes. Patients, family members, and caregivers also should be advised not to make any changes to the anticonvulsant regimen without first consulting with the responsible clinician. They should pay close attention to any day-to-day changes in mood, behavior, and actions; since changes can happen very quickly, it is important to be alert to any sudden differences. In addition, patients, family members, and caregivers should be aware of common warning signs that may signal suicide risk (e.g., talking or thinking about wanting to hurt oneself or end one's life, withdrawing from friends and family, becoming depressed or experiencing worsening of existing depression, becoming preoccupied with death and dying, giving away prized possessions). If these or any new and worrisome behaviors occur, the responsible clinician should be contacted immediately. FDA also recommends that clinicians who prescribe valproic acid or any other anticonvulsant balance the risk for suicidality with the risk of untreated illness. Epilepsy and many other illnesses for which anticonvulsants are prescribed are themselves associated with an increased risk of morbidity and mortality and an increased risk of suicidal thoughts and behavior. If suicidal thoughts and behavior emerge during anticonvulsant therapy, the clinician must consider whether the emergence of these symptoms in any given patient may be related to the illness being treated.

Results of in vitro studies indicate that valproate appears to stimulate replication of some strains of human immunodeficiency virus (HIV) and cytomegalovirus (CMV) under certain experimental conditions. The clinical importance of these in vitro findings, including any relevance to patients receiving maximally suppressive antiretroviral therapy, is not known. (See Pharmacology: Antiviral Effects.) It has been suggested that these in vitro effects should be considered when interpreting test results concerning the clinical condition of HIV-infected patients (e.g., plasma HIV RNA levels) or patients with CMV infection.

Since valproic acid may cause serious and potentially fatal hepatotoxicity, hepatic function tests should be performed before and at frequent intervals during therapy with the drug, especially during the first 6 months. Since results of hepatic function tests may not be abnormal in all instances, clinicians must also consider the results of careful interim medical history and physical examination of the patient. Valproic acid therapy should be discontinued immediately in the presence of suspected or apparent substantial hepatic dysfunction. In some patients, hepatic dysfunction has progressed despite discontinuance of the drug. Since elevations in hepatic enzyme concentrations may be dose related, the benefit of improved seizure control which may accompany higher doses of the drug must be weighed against the potential risks. Valproic acid should be used with caution in patients with a history of hepatic disease. Children and patients receiving multiple anticonvulsants or those with congenital metabolic disorders, severe seizure disorders accompanied by mental retardation, or organic brain disease may be at particular risk of hepatotoxicity. Because children younger than 2 years of age, especially those with the previously listed conditions, have a considerably increased risk of developing fatal hepatotoxicity compared with older patient groups, valproic acid should be used in these patients only with extreme caution and as a single agent; the benefits of seizure control must be weighed against the potential risks. Above 2 years of age, the frequency of fatal hepatotoxicity decreases considerably in progressively older patient groups. Valproic acid should *not* be used in patients with hepatic disease or substantial hepatic dysfunction.

Because the use of valproic acid has been associated with life-threatening pancreatitis in children and adults (see Cautions: Pancreatitis), patients and guardians should be instructed that if symptoms of pancreatitis (e.g., abdominal pain, nausea, vomiting, anorexia) develop, prompt medical evaluation is needed. If pancreatitis is diagnosed, valproic acid usually should be discontinued and alternative therapy for the underlying medical condition should be initiated as clinically indicated.

Because the use of valproic acid has been associated with hyperammonemic encephalopathy, patients should be advised that if symptoms of this disorder (e.g., lethargy, vomiting, changes in mental status) develop, they should notify their clinician promptly. (See Cautions: Endocrine and Metabolic Effects.) If such symptoms are present, plasma ammonia concentrations should be determined, and, if these concentrations are increased, valproic acid therapy should be discontinued. Appropriate treatment of hyperammonemia should be initiated and the patient should be evaluated for urea cycle disorders. Asymptomatic elevation of ammonia concentrations is more common than hyperammonemic encephalopathy. In patients with asymptomatic elevations, plasma ammonia concentrations should be closely monitored and, if elevations persist, discontinuance of valproic acid therapy should be considered. Prior to the initiation of valproic acid therapy, an evaluation for urea cycle disorders should be considered in patients with a history of unexplained encephalopathy or coma, encephalopathy associated with a protein load, pregnancy-related or postpartum encephalopathy, unexplained mental retardation, or history of elevated plasma ammonia or glutamine concentrations; patients with cyclical vomiting and lethargy, episodic extreme irritability, ataxia, low BUN concentration, or protein avoidance; patients with a family history of urea cycle disorders or unexplained infant deaths (particularly males); and patients with other signs or symptoms of urea cycle disorders.

Anticonvulsant drugs (including valproic acid) should not be discontinued abruptly in patients receiving the drugs to prevent major seizures because of the strong possibility of precipitating status epilepticus with attendant hypoxia and threat to life.

Since valproic acid may cause thrombocytopenia and inhibit platelet aggregation, platelet counts, bleeding time, and coagulation studies should be determined before and periodically during therapy with the drug and before surgery is performed in patients receiving the drug. In one study of the drug as monotherapy for seizures, 27% of patients receiving approximately 50 mg/kg per day of valproic acid had at least one platelet count of 75,000/mm^3 or less; the probability of thrombocytopenia appeared to increase significantly at total serum valproate concentrations of 110 mcg/mL or greater (females) or 135 mcg/mL or greater (males). Some clinicians have recommended thromboelastography as a more reliable method to assess the effects of valproic acid on coagulation. If clinical evidence of hemorrhage, bruising, or a disorder of hemostasis coagulation occurs during valproic acid therapy, dosage should be reduced or the drug withdrawn pending further evaluation.

Valproic acid is contraindicated in patients with known hypersensitivity to the drug. Valproic acid also is contraindicated in patients with known urea cycle disorders. (See Cautions: Endocrine and Metabolic Effects.)

■ **Pediatric Precautions** Experience with valproic acid therapy in the management of seizures indicates that children younger than 2 years of age are at an increased risk of developing fatal hepatotoxicity. (See Cautions: Precautions and Contraindications.) The drug should be used with extreme caution and as single-agent therapy in such children, and the benefits of valproic acid therapy weighed against the risks. The incidence of fatal hepatotoxicity decreases considerably in progressively older patient groups (i.e., older than 2 years of age).

Younger children, especially those receiving enzyme-inducing drugs, will require larger maintenance doses to attain targeted total and unbound valproic acid concentrations for the management of seizures. The variability in free fraction limits the clinical usefulness of monitoring total serum valproic acid concentrations alone. Interpretation of valproic acid concentration in children should include consideration of factors that affect hepatic metabolism and protein binding.

The safety and efficacy of valproic acid for acute manic episodes in patients younger than 18 years of age and for migraine prophylaxis in patients younger than 16 years of age have not been established. In addition, safety and efficacy of divalproex sodium extended-release tablets in pediatric patients have not been established and use of this preparation in this age group is not recommended.

The safety of valproate sodium injection has not been studied in pediatric patients younger than 2 years of age. If a decision is made to use the injection in this age group, the manufacturer states that it should be used with extreme caution and only as monotherapy, and the potential benefits should be weighed against the possible risks. No unusual adverse effects were observed in clinical trials employing IV valproate sodium for the management of seizure disorders in 24 pediatric patients 2–17 years of age.

■ **Geriatric Precautions** The safety and efficacy of valproic acid in geriatric patients (older than 65 years of age) for the treatment of manic episodes associated with bipolar disorder or prevention of migraine headaches have not been established.

In a case review of almost 600 patients treated with valproic acid for manic episodes, approximately 12% of patients were older than 65 years of age. A higher percentage of these patients reported accidental injury, infection, pain, somnolence, or tremor during valproic acid therapy compared with younger patients. Discontinuance of valproic acid therapy occasionally was associated with somnolence or tremor. The manufacturer states that it is unclear whether these events indicate additional risks of drug therapy or whether they result

from preexisting medical conditions or concomitant medication use in these geriatric patients.

Results of a double-blind, multicenter study of geriatric patients (mean age: 83 years) with dementia who were receiving valproic acid (125 mg daily, titrated to a target daily dosage of 20 mg/kg) indicate that the incidence of somnolence was higher in patients receiving valproic acid than in those receiving placebo and discontinuance of therapy because of somnolence was higher in those receiving valproic acid than in those receiving placebo. In about 50% of patients with somnolence, a reduced nutritional intake and weight loss also were observed. The incidence of dehydration also appeared to be higher in geriatric patients receiving valproic acid than in those receiving placebo. In the patients who experienced the mentioned adverse effects, a trend for lower baseline albumin concentration, lower valproic acid clearance, and higher BUN was observed. Therefore, it is recommended that initial dosage of valproic acid be reduced and subsequent dosages be increased more slowly in geriatric patients. In addition, the manufacturer recommends regular monitoring of fluid and nutritional intake, dehydration, somnolence, and other adverse effects in these individuals. Dosage reduction or discontinuance of valproic acid should be considered in geriatric patients with decreased food or fluid intake and in those with excessive somnolence.

■ **Mutagenicity and Carcinogenicity** Studies of valproic acid that used bacterial and mammalian test systems have shown no evidence to date of a mutagenic potential for the drug.

In rats and mice receiving valproic acid dosages of 80 and 170 mg/kg daily for 2 years, an increased incidence of subcutaneous fibrosarcomas occurred in male rats at the higher dosage level and a dose-related trend for an increased incidence of benign pulmonary adenomas was observed in male mice. The importance of these findings to humans is not known.

■ **Pregnancy, Fertility, and Lactation** Safe use of valproic acid during pregnancy has not been established. Adverse fetal effects have been observed in reproduction studies in rats and mice. Valproic acid can cause teratogenic effects in humans, such as neural tube defects (e.g., spina bifida). Several reports suggest an association between use of valproic acid in pregnant, epileptic women and an increased incidence of birth defects (particularly neural tube defects) in children born to these women; such malformations may be associated with high plasma concentrations during the first trimester. Some experts state that prophylactic use of folic acid may prevent or decrease the incidence of neural tube defects. Valproic acid should be used in pregnant women with seizure disorders or women with seizure disorders who might become pregnant only if the drug is clearly shown to be essential in the management of their seizures. Women should be apprised of the potential hazard to the fetus; this is especially important when valproic acid therapy is being contemplated or used for the management of a spontaneously reversible condition not ordinarily associated with permanent injury or risk of death (e.g., prophylaxis of migraine headache). Tests to detect neural tube and other defects using current accepted procedures should be considered a part of routine prenatal care in childbearing women receiving valproic acid for the management of seizure disorders.

Other congenital anomalies (e.g., craniofacial defects, cardiovascular malformations, anomalies involving various body systems) compatible and incompatible with life also have been reported in children of women treated with valproic acid during pregnancy; sufficient data to determine the incidence of these anomalies are not available. The higher incidence of congenital anomalies in the children of women with seizure disorders treated with anticonvulsant drugs during pregnancy cannot be regarded as a direct effect of such therapy. There are intrinsic methodologic problems in obtaining adequate drug teratogenicity data in humans. Genetic factors and/or the epileptic disorder also may contribute to the development of congenital anomalies.

Patients receiving valproic acid may develop clotting abnormalities. A pregnant patient taking multiple anticonvulsant agents, including valproic acid, developed hypofibrinogenemia; the patient then gave birth to an infant with afibrogenemia, who subsequently died of hemorrhage. If valproic acid is to be used during pregnancy, clotting parameters should be monitored closely. Hepatic failure, resulting in the death of a neonate and an infant, also has been reported following the use of valproic acid during pregnancy.

Anticonvulsant drugs should *not* be discontinued in pregnant women in whom the drugs are administered to prevent major seizures because of the strong possibility of precipitating status epilepticus with attendant hypoxia and threat to life. In individual cases when the severity and frequency of the seizure disorder are such that discontinuance of therapy does not pose a serious threat to the patient, discontinuance of the drugs may be considered prior to and during pregnancy; however, it cannot be stated with any certainty that even minor seizures do not pose some hazard to the fetus. The clinician should carefully weigh these considerations in treating or counseling epileptic women of childbearing potential.

The effect of valproic acid on the development of the testes and on sperm production and fertility in humans is not known. Chronic toxicity studies in rats and dogs demonstrated reduced spermatogenesis and testicular atrophy. Further animal studies are ongoing.

Since valproic acid is distributed into milk, the drug should be used with caution in nursing women; the potential effects on a nursing infant are not known.

Drug Interactions

■ **CNS Depressants, Antidepressants, and Anticonvulsants** Additive CNS depression may occur when valproic acid is administered concomitantly with other CNS depressants including other anticonvulsants (particularly phenobarbital and primidone) and alcohol. If valproic acid is used in conjunction with other CNS depressant drugs including alcohol, caution should be used to avoid overdosage.

Valproic acid displaces diazepam from its albumin binding sites and also inhibits its metabolism. In a study in a limited number of healthy individuals, coadministration of valproic acid (1.5 g daily) increased the free fraction of diazepam (10 mg) by 90%; plasma clearance and volume of distribution of free diazepam were decreased by 25% and 20%, respectively. The elimination half-life of diazepam was unaffected by concomitant valproic acid administration.

Concomitant use of amitriptyline (a single 50-mg oral dose) and valproic acid (500 mg twice daily) resulted in a 21% decrease in the plasma clearance of amitriptyline and a 34% decrease in the net clearance of nortriptyline (the pharmacologically active metabolite of amitriptyline). In addition, increased amitriptyline concentrations have been reported rarely in patients receiving amitriptyline concomitantly with valproic acid; concomitant use has rarely been associated with toxicity. The manufacturer states that monitoring of amitriptyline concentrations should be considered for patients receiving valproic acid concomitantly with amitriptyline.

Because valproic acid may potentiate the effects of monoamine oxidase inhibitors and other antidepressants, dosage reduction of these drugs may be necessary if valproic acid is administered to patients receiving antidepressants.

Valproic acid inhibits the metabolism of ethosuximide. Administration of a single 500-mg dose of ethosuximide to a limited number of healthy individuals receiving valproic acid (800–1600 mg daily) resulted in a 25% increase in ethosuximide elimination half-life and a 15% decrease in total ethosuximide clearance when compared with ethosuximide administration alone. Patients receiving concomitant valproic acid and ethosuximide therapy, especially if receiving other concomitant anticonvulsant therapy, should have their serum drug concentrations monitored carefully.

Concomitant administration of valproic acid with felbamate (1.2 g daily) in a limited number of patients with epilepsy resulted in a 35% increase in mean peak serum valproic acid concentration, from 86 to 115 mcg/mL when compared with administration of valproic acid alone. Increasing the felbamate dose to 2.4 g daily resulted in another 16% increase in mean peak valproic acid concentration to 133 mcg/mL. A decrease in valproic acid dosage may be required when initiating concomitant felbamate therapy.

Valproic acid inhibits lamotrigine metabolism. In a steady-state study in healthy individuals, the elimination half-life of lamotrigine increased from 26 to 70 hours when concomitant valproic acid was administered. Lamotrigine dosage should be decreased when valproic acid therapy is initiated.

Concomitant administration of valproic acid and phenobarbital (or primidone which is metabolized to phenobarbital) can result in increased phenobarbital plasma concentrations and excessive somnolence. This combination can produce CNS depression (possibly severe) even without substantial increases in serum concentrations of either drug. A few patients have become comatose during therapy with valproic acid and phenobarbital. In a study of concomitant valproic acid (250 mg twice daily for 14 days) and single-dose phenobarbital (60 mg) administration in a limited number of healthy individuals, a 50% increase in phenobarbital half-life, a 30% decrease in phenobarbital clearance, and a 50% increase in unchanged phenobarbital excreted in the urine were observed. If valproic acid is used with a barbiturate, the patient should be closely observed for possible neurologic toxicity, plasma concentrations of the barbiturate should be monitored if possible, and the dosage of the barbiturate decreased if necessary.

Serum concentrations of carbamazepine have been reported to decrease by 17% and concentrations of the metabolite carbamazepine-10,11-epoxide have been reported to increase by 45% during concomitant therapy with valproic acid; such interaction may result in carbamazepine CNS toxicity (e.g., acute psychotic reaction). In addition, carbamazepine has been reported to decrease plasma valproic acid concentrations by altering its clearance during concomitant therapy, which may be clinically important. Discontinuance of carbamazepine following concomitant carbamazepine/valproic acid therapy has been reported to result in increased valproic acid concentrations. If concomitant therapy is being undertaken, or if a patient currently is receiving concomitant carbamazepine/valproic acid therapy and one agent is to be discontinued, careful therapeutic drug monitoring should be considered.

Concomitant administration of valproic acid and clonazepam has produced absence status; therefore, some clinicians recommend that concomitant use of these drugs be avoided.

Valproic acid has been associated both with decreased plasma phenytoin concentrations and increased seizure frequency and with increased plasma concentrations of free phenytoin and phenytoin intoxication. Therefore, it is important to monitor plasma phenytoin concentrations whenever valproic acid is added to or withdrawn from the patient's therapy and adjust the dosage of phenytoin as required. Since valproic acid also may interact with other anticonvulsants, it is advisable to monitor plasma concentrations of concomitantly administered anticonvulsants during initial valproic acid therapy.

■ **Anti-infective Agents** *Acyclovir* In a child receiving both phenytoin and valproic acid, short-term oral therapy with acyclovir apparently reduced the plasma concentrations of both anticonvulsant agents to subtherapeutic levels; an increase in seizure frequency and a worsening in the EEG were observed. Although further study is needed to confirm the effects of acyclovir on the pharmacokinetics of anticonvulsant agents, such concomitant therapy should be undertaken with caution.

Antiretroviral Agents Concomitant use of valproic acid (250 or 500 mg every 8 hours) and oral zidovudine (100 mg every 8 hours) for 4 days in a limited number of adults with human immunodeficiency virus (HIV) infection resulted in an 80% increase in the area under the concentration-time curve (AUC) of zidovudine. The effect of concomitant zidovudine on the pharmacokinetics of valproic acid was not evaluated. Although the clinical importance of this interaction between zidovudine and valproic acid is not known, patients receiving both drugs should be monitored more closely for zidovudine-related adverse effects. Severe anemia has been reported following initiation of valproic acid therapy (500 mg twice daily) in an HIV-infected adult who was receiving an antiretroviral regimen that contained zidovudine, lamivudine, and abacavir; the patient had stable hematologic status at the time valproic acid was started. The manufacturer of zidovudine states that a reduction in zidovudine dosage may be considered if a patient experiences substantial anemia or other severe adverse effect while receiving zidovudine concomitantly with valproic acid.

Hepatotoxicity was reported in an HIV-infected adult receiving valproic acid concomitantly with an antiretroviral regimen containing ritonavir, saquinavir, stavudine, and nevirapine. It has been suggested that this may have occurred as the result of a pharmacokinetic interaction between valproic acid and ritonavir and/or nevirapine.

Concomitant use of efavirenz and valproic acid in HIV-infected adults does not appear to affect the pharmacokinetics of either drug.

Concomitant use of the fixed combination of lopinavir and ritonavir with valproic acid may result in slightly increased lopinavir concentrations, but does not affect valproic acid concentrations. It has been suggested that this pharmacokinetic interaction is not clinically important.

Rifampin A study of administration of a single dose of valproic acid (7 mg/kg) given 36 hours after short-term rifampin administration (600 mg daily for 5 days) revealed a 40% increase in the clearance of valproic acid. Valproic acid dosage adjustment may be required when rifampin therapy is initiated.

■ **Other Drugs** Since valproic acid may affect bleeding time (see Cautions: Hematologic Effects), it should be administered with caution in patients receiving drugs which affect coagulation such as aspirin or warfarin. In addition, valproic acid potentially may displace warfarin from its plasma albumin binding sites. Although the clinical relevance of this interaction is unknown, coagulation tests should be monitored if concomitant valproic acid and anticoagulant therapy is undertaken.

In a study of a limited number of pediatric patients receiving valproic acid and antipyretic aspirin therapy (11–16 mg/kg), a decrease in valproic acid protein binding and metabolism was observed. Free valproic acid concentration increased fourfold, compared with valproic acid therapy alone. The oxidative metabolic pathway of valproic acid was inhibited, resulting in a decrease in excretion of valproic acid metabolites, from 25% to 8.3% of total metabolites excreted. Concomitant aspirin and valproic acid therapy should be instituted with caution.

In vitro studies demonstrated that addition of tolbutamide to plasma samples of patients receiving valproic acid therapy resulted in an increase in the unbound tolbutamide fraction from 20% to 50%. The clinical importance of this displacement is unknown.

Limited pharmacokinetic studies reveal little to no interaction following concomitant administration of valproic acid with the following drugs: antacids, chlorpromazine, haloperidol, H_2-receptor antagonists (i.e., ranitidine, cimetidine), acetaminophen, clozapine, lithium, lorazepam, or oral contraceptives.

Laboratory Test Interferences

■ **Tests for Urinary Ketones** A ketone metabolite in the urine of patients receiving valproic acid may produce false-positive results for urine ketones.

■ **Tests for Thyroid Function** Valproic acid reportedly alters thyroid function test results, but the clinical importance of this effect is not known.

Acute Toxicity

■ **Manifestations** Overdosage of valproic acid may produce somnolence, heart block, or deep coma. One adult who ingested 36 g of valproic acid (as valproate sodium) in addition to 1 g of phenobarbital and 300 mg of phenytoin experienced deep coma 4 hours after ingestion of the drugs. The patient recovered following supportive therapy. Fatalities have been reported following valproic acid overdosage; however, patients have recovered from serum valproic acid concentrations as high as 2.12 mg/mL.

■ **Treatment** Treatment of valproic acid intoxication consists of general supportive therapy, particularly maintenance of adequate urinary output. Because the drug is rapidly absorbed, gastric lavage may be of limited value; since absorption of divalproex sodium delayed-release tablets is delayed, the value of gastric lavage or emesis will vary with time since ingestion if this form of the drug has been ingested. In overdose situations, the free or unbound serum valproic acid concentration is high. Hemodialysis or tandem hemodialysis with hemoperfusion may result in significant removal of drug. Naloxone has been reported to reverse the CNS depressant effects of valproic acid overdosage; however, naloxone should be used with caution since it could also theoretically reverse the anticonvulsant effects of valproic acid.

Pharmacology

■ **Anticonvulsant Effects** The mechanism of the anticonvulsant effects of valproic acid is not known. Effects of the drug may be related, at least in part, to increased brain concentrations of the inhibitory neurotransmitter, γ-aminobutyric acid (GABA). Animal studies have shown that valproic acid inhibits GABA transferase and succinic aldehyde dehydrogenase, enzymes which are important for GABA catabolism. Results of one study indicate the drug inhibits neuronal activity by increasing potassium conductance. In animals, valproic acid protects against seizures induced by electrical stimulation as well as those induced by pentylenetetrazol.

■ **Antiviral Effects** Valproic acid inhibits histone deacetylase I (HDACI) (an enzyme that maintains latency of human immunodeficiency virus [HIV] in resting $CD4^+$ T-cells) and induces HIV expression from resting $CD4^+$ T-cells ex vivo. It has been suggested that this effect may be useful in depleting latent infection in resting $CD4^+$ T-cells in HIV-infected patients. Although highly active antiretroviral therapy (HAART) suppresses plasma HIV-1 RNA levels and restores immune function, the presence of replication-competent provirus in resting $CD4^+$ T-cells and persistent HIV replication prevent HAART from eradicating HIV infection. Efficacy of valproic acid in depleting HIV from resting $CD4^+$ T-cells has been evaluated in a small proof-of-concept pilot study in 4 HIV-infected adults (plasma HIV-1 RNA levels less than 50 copies/mL for at least 2 years) receiving HAART. Enfuvirtide was added to the HAART regimens (to prevent the spread of virus in the presence of valproic acid) and, after 4–6 weeks of this intensified regimen, valproic acid (500–750 mg twice daily) was added. After 16–18 weeks of combined valproic acid and enfuvirtide-intensified HAART, there was a substantial decline in the frequency of replication-competent HIV in circulating resting $CD4^+$ T-cells. These preliminary findings suggest that use of valproic acid with HAART and enfuvirtide may represent a new therapeutic approach that possibly represents a step toward the elimination of HIV infection in resting $CD4^+$ T-cells and eventual cure of HIV infection. However, it is unclear whether latently infected $CD4^+$ T-cells are the only reservoir for HIV, and larger, controlled studies are needed to investigate the possible benefits of valproic acid in HIV-infected patients.

Pharmacokinetics

■ **Absorption** *Oral Administration* Following oral administration, valproate sodium is rapidly converted to valproic acid in the stomach. Valproic acid is rapidly and almost completely absorbed from the GI tract. Absorption of the drug is delayed but not decreased by administration with meals; administration of the drug with milk products does not affect the rate or degree of absorption. Following oral administration of divalproex sodium extended-release tablets, divalproex sodium dissociates into valproic acid in the GI tract. Following oral administration of divalproex sodium delayed-release tablets and passage of the tablets into the upper small intestine, divalproex sodium dissociates into valproic acid, which is then absorbed; because of the enteric coating, absorption is delayed compared with that following oral administration of valproic acid capsules or valproate sodium solution. The bioavailability of valproate from divalproex sodium delayed-release tablets and capsules containing coated particles has been shown to be equivalent to that of valproic acid capsules. The absolute bioavailability of divalproex sodium extended-release tablets following oral administration of a single dose after a meal is about 90%. The manufacturer states that divalproex sodium extended-release tablets and delayed-release tablets are not bioequivalent. Results of 2 multiple-dose studies indicate that divalproex sodium extended-release tablets (administered either in the fasting state or immediately before small meals) have an average bioavailability of 81–89% relative to divalproex sodium delayed-release tablets given twice daily. Administration of divalproex sodium with food would be expected to slow absorption but not affect the extent of absorption.

Peak plasma concentrations of valproic acid are usually attained 1–4 hours following a single oral dose of the acid or the sodium salt, 3–5 hours following a single oral dose of divalproex sodium, and 7–14 hours following oral administration of multiple doses of divalproex sodium extended-release tablets. There is wide interindividual variation in plasma concentrations of the drug with a specific dose. Results of a multiple-dose study indicate that following oral administration of divalproex sodium extended-release tablets once daily average plasma concentrations of the drug are 10–20% lower than those achieved with twice-daily administration of divalproex sodium delayed-release tablets. Plasma concentrations of valproic acid required for therapeutic or toxic effects have not been definitely established. Some reports indicate that therapeutic plasma concentrations may be 50–100 mcg/mL of total (bound and unbound) valproic acid and that concentrations in this range are maintained in most adults receiving 1.2–1.5 g of valproic acid daily. However, the possibility that some patients may be controlled with lower or higher plasma concentrations and that the free fraction of valproic acid increases with increasing dosage should be considered. (See Pharmacokinetics: Distribution.) The onset of therapeutic effects is several days to more than one week following initiation of valproic acid therapy.

The relationship between dose and total valproic acid concentration is nonlinear; concentration does not increase proportionally with dose, because of saturable protein binding. The pharmacokinetics of unbound drug are linear.

Parenteral Administration Equivalent valproic acid dosages as the IV injection (available as valproate sodium), administered over 1 hour, or various conventional or delayed-release oral formulations (available as valproate sodium or divalproate sodium) are expected to result in equivalent peak and trough plasma concentrations and total systemic exposure to the valproic acid. Although the rate of valproic acid absorption may vary with

the specific formulation, any such differences should be of minor clinical importance under steady-state conditions achieved with chronic therapy for seizure disorders.

When oral divalproate sodium delayed-release tablets or IV valproate sodium (as a 1-hour infusion) was administered at a dosage of 250 mg of valproic acid every 6 hours for 4 days in healthy males, the resulting area under the plasma concentration-time curves (AUCs) and peak and trough plasma concentrations of the drug were equivalent at steady state as well as after the initial dose. However, the time to reach peak plasma concentrations was delayed with the tablets, occurring at approximately 4 hours after an oral dose versus at the end of the 1-hour infusion with the IV dose. Because the pharmacokinetics of unbound valproic acid are linear, bioequivalence between IV valproate sodium and oral delayed-release divalproate sodium can be expected up to maximum dosages of 60 mg/kg daily. The AUCs and peak plasma concentrations also were equivalent in healthy males receiving single 500-mg doses as the IV injection (infused over 1 hour) or valproate sodium oral solution. In addition, patients maintained on valproic acid dosages of 750–4250 mg daily (given in divided doses every 6 hours) as oral delayed-release divalproate sodium tablets alone or while stabilized on another anticonvulsant (e.g., carbamazepine, phenytoin, or phenobarbital) exhibited comparable plasma concentrations when switched from oral divalproate sodium to IV valproate sodium (as 1-hour infusions).

When valproate sodium (at a dosage of 1 g of valproic acid) was administered IV over 5, 10, 30, and 60 minutes in healthy individuals, peak plasma concentrations of the drug averaged 145 mcg/mL after the 5-minute infusion compared with 115 mcg/mL after the 60-minute infusion. However, plasma concentrations measured at 90–120 minutes after initiation of the valproate sodium infusions were similar for the 4 rates of infusion.

■ **Distribution** Valproic acid is rapidly distributed; distribution appears to be restricted to plasma and rapidly exchangeable extracellular water. Volume of distribution of total or free valproic acid is 11 or 92 L/1.73 m^2, respectively. Valproic acid has been detected in CSF (approximately 10% of serum concentrations), saliva (about 1% of plasma concentrations), and milk (about 1–10% of plasma concentrations). The drug crosses the placenta.

Plasma protein binding of valproic acid is concentration dependent; the free fraction of drug increases from 10% at a concentration of 40 mcg/mL to 18.5% at a concentration of 130 mcg/mL. Protein binding of valproic acid is decreased in geriatric patients, in patients with renal impairment or hepatic disease, or in the presence of other protein-bound drugs. Conversely, valproic acid may displace other drugs from protein binding sites. Because of decreased protein binding of the drug in special patient populations (i.e., patients with renal or hepatic disease), monitoring of total drug concentrations may be misleading, owing to the increased free fraction of valproic acid.

■ **Elimination** Valproic acid is eliminated by first-order kinetics and reportedly has an elimination half-life of 5–20 hours (average 10.6 hours). Elimination half-lives in the lower portion of the range are usually observed in patients receiving other anticonvulsants concomitantly. Half-lives of up to 30 hours have been reported following overdosage of valproate sodium.

Mean plasma clearance of total or free valproic acid is 0.56 or 4.6 L/hour per 1.73 m^2, respectively. Drug clearance may be decreased in special patient populations (e.g., patients with renal failure, geriatric patients). Because hemodialysis typically reduces plasma valproic acid concentration by about 20%, generally there is no dosage adjustment required in patients with renal failure (i.e., creatinine clearance less than 10 mL/min). Geriatric patients should receive lower initial doses of the drug. (See Dosage and Administration: Dosage.)

Pediatric patients (i.e., age range 3 months to 10 years) have 50% higher clearance of the drug expressed by weight (i.e., mL/minute per kg); over the age of 10 years, pharmacokinetic parameters of valproic acid approximate those in adults. Neonates (i.e., younger than 2 months) have a markedly decreased clearance of valproic acid compared with older children and adults, possibly because of delayed development of metabolic enzyme systems and an increased volume of distribution. In one study, the elimination half-life in children younger than 10 days old ranged from 10–67 hours, compared with 7–13 hours in children older than 2 months.

Valproic acid is metabolized principally in the liver by *beta* (over 40%) and *omega* oxidation (up to 15–20%). Valproic acid metabolites are excreted in urine; 30–50% of an administered dose is excreted as glucuronide conjugates. Less than 3% of an administered dose is excreted in urine unchanged. The major metabolite in urine is 2-propyl-3-ketopentanoic acid; minor urinary metabolites are 2-propylglutaric acid, 2-propyl-5-hydroxypentanoic acid, 2-propyl-3-hydroxypentanoic acid, and 2-propyl-4-hydroxypentanoic acid. Small amounts of the drug are also excreted in feces and in expired air. Results of studies in rats suggest the drug may undergo enterohepatic circulation.

Liver disease impairs the ability to eliminate valproic acid. In one study, the clearance of free valproic acid was decreased by 50% in a limited number of patients with cirrhosis and by 16% in a limited number of patients with acute hepatitis, compared with healthy individuals. Half-life of valproic acid was increased from 12 to 18 hours.

Chemistry and Stability

■ **Chemistry** Valproic acid, valproate sodium, and divalproex sodium are carboxylic acid-derivative anticonvulsants. Valproic acid is structurally unrelated to other commercially available anticonvulsants; it lacks nitrogen and/or an aromatic moiety found in most anticonvulsants. Divalproex sodium is a stable coordination compound consisting of valproic acid and valproate sodium in a 1:1 molar ratio and is formed during partial neutralization of valproic acid with sodium hydroxide. Divalproex sodium is a prodrug of valproate, dissociating into valproate in the GI tract.

Valproic Acid Valproic acid occurs as a colorless to pale yellow, slightly viscous, clear liquid with a characteristic odor and is slightly soluble in water and freely soluble in alcohol. Valproic acid has a pK_a of 4.8.

Valproate Sodium Valproate sodium occurs as a white, crystalline, very hygroscopic powder with a saline taste and is very soluble in water and in alcohol.

Valproate sodium injection is a sterile solution of the drug in water for injection. The injection occurs as a clear, colorless solution; sodium hydroxide and/or hydrochloric acid may be added to adjust the pH to 7.6.

Divalproex Sodium Divalproex sodium occurs as a white powder with a characteristic odor and is insoluble in water and very soluble in alcohol.

■ **Stability** ***Valproic Acid*** USP recommends that valproic acid capsules be stored in tight containers at 15–30°C; however, the manufacturer of Depakene® recommends that the capsules be stored in tight containers at 15–25°C.

Valproate Sodium Valproate sodium oral solution has a pH of 7–8. Valproate sodium oral solution should be stored in tight containers at a temperature less than 30°C; freezing should be avoided.

Valproate sodium injection should be stored at a controlled room temperature of 15–30°C. Because the injection does not contain a preservative, unused portions of the solution should be discarded. When stored in glass or PVC containers at 15–30°C, valproate sodium injection that has been further diluted with at least 50 mL of 5% dextrose injection, 0.9% sodium chloride injection, or lactated Ringer's injection is stable for at least 24 hours.

Divalproex Sodium Divalproex sodium delayed-release tablets should be stored in tight, light-resistant containers at a temperature less than 30°C; divalproex sodium capsules containing coated particles should be stored at a temperature less than 25°C. Divalproex sodium extended-release tablets should be stored at 25°C, but may be exposed to temperatures ranging from 15–30°C.

For further information on uses and dosage and administration of valproic acid, see the Anticonvulsants General Statement 28:12.

Preparations

Excipients in commercially available drug preparations may have clinically important effects in some individuals; consult specific product labeling for details.

Valproate Sodium

Oral		
Solution	250 mg (of valproic acid) per 5 mL*	Depakene® Syrup, Abbott Valproate Sodium Oral Solution
Parenteral		
Injection, for IV use	100 mg (of valproic acid) per mL*	Depacon®, Abbott Valproate Sodium Injection

*available from one or more manufacturer, distributor, and/or repackager by generic (nonproprietary) name

Valproic Acid

Oral		
Capsules, liquid-filled	250 mg*	Depakene®, Abbott

*available from one or more manufacturer, distributor, and/or repackager by generic (nonproprietary) name

Divalproex Sodium

Oral		
Capsules (containing coated particles)	equivalent to valproic acid 125 mg	Depakote® Sprinkle, Abbott
Tablets, delayed-release	equivalent to valproic acid 125 mg	Depakote®, Abbott
	equivalent to valproic acid 250 mg	Depakote®, Abbott
	equivalent to valproic acid 500 mg	Depakote®, Abbott
Tablets, extended-release	equivalent to valproic acid 250 mg	Depakote® ER, Abbott
	equivalent to valproic acid 500 mg	Depakote® ER, Abbott

†Use is not currently included in the labeling approved by the US Food and Drug Administration

other indications, both psychiatric and nonpsychiatric, should be advised to monitor patients on a daily basis for the emergence of agitation, irritability, or unusual changes in behavior as well as the emergence of suicidality, and to report such symptoms immediately to a health-care provider.

Although a causal relationship between the emergence of symptoms such as anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia, hypomania, and/or mania and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality. Consequently, consideration should be given to changing the therapeutic regimen or discontinuing therapy in patients whose depression is persistently worse or in patients experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, particularly if such manifestations are severe, abrupt in onset, or were not part of the patient's presenting symptoms. FDA also recommends that the drugs be prescribed in the smallest quantity consistent with good patient management, in order to reduce the risk of overdosage.

Bipolar Disorder Precautions It is generally believed (though not established in controlled trials) that treating a major depressive episode with an antidepressant alone may increase the likelihood of precipitating a mixed or manic episode in patients at risk for bipolar disorder. Therefore, patients should be adequately screened for bipolar disorder prior to initiating treatment with an antidepressant; such screening should include a detailed psychiatric history (e.g., family history of suicide, bipolar disorder, and depression).

Pediatric Precautions Safety and efficacy of nefazodone in children have not been established.

FDA has determined that antidepressants increase the risk of suicidal thinking and behavior (suicidality) in children and adolescents with major depressive disorder and other psychiatric disorders. However, FDA also states that depression and certain other psychiatric disorders are themselves associated with an increased risk of suicide. (See Cautions: Pediatric Precautions, in Fluoxetine Hydrochloride 28:16.04.20.) Anyone considering the use of nefazodone in a child or adolescent for any clinical use must therefore balance the potential risks with the clinical need. (See Suicidality Precautions under Dosage and Administration: Administration.)

■ **Dosage** Patients should be monitored for possible worsening of depression, suicidality, or unusual changes in behavior, especially at the beginning of therapy or during periods of dosage adjustment. (See Suicidality Precautions under Dosage and Administration: Administration.)

Major Depressive Disorder For the treatment of major depressive disorder in adults, the recommended initial dosage of nefazodone hydrochloride is 100 mg twice daily. Based on the tolerance and clinical response of the patient, dosage may be increased by increments of 100–200 mg daily at intervals of not less than 1 week up to a maximum of 600 mg daily. While a relationship between dosage and antidepressant effect has not been established, the effective dosage of nefazodone hydrochloride in controlled clinical studies generally ranged from 300–600 mg daily.

Because geriatric or debilitated patients may have reduced nefazodone clearance and/or increased sensitivity to the adverse effects of CNS-active drugs, therapy with nefazodone hydrochloride should be initiated at a dosage of 50 mg twice daily in such patients and subsequent dosage adjustments generally made in smaller increments and at longer intervals than in younger patients. A nefazodone hydrochloride dosage of 200–400 mg daily generally provided optimum therapeutic effect in patients 65 years of age or older in controlled studies.

Although the optimum duration of nefazodone therapy has not been established, acute depressive episodes may require 6 months or longer of sustained antidepressant medication. Whether the dosage of nefazodone required to induce remission of depression would be comparable to that required to maintain euthymia currently is not known.

■ **Dosage in Renal and Hepatic Impairment** While the manufacturer makes no specific recommendations for modification of dosage in patients with hepatic impairment, AUC values for nefazodone and its active metabolite hydroxynefazodone are increased by approximately 25% in patients with cirrhosis; therefore, nefazodone should be used with caution in patients with clinically important hepatic dysfunction. The manufacturer makes no specific recommendations for modification of dosage in patients with renal impairment. Limited data indicate that steady-state plasma concentrations of nefazodone in patients with renal impairment (creatinine clearance: 7–60 mL/minute per 1.73 m^2 body surface area) do not differ from those in healthy individuals.

Description

Nefazodone is a phenylpiperazine-derivative antidepressant agent. While the drug is structurally related to trazodone, nefazodone differs chemically and pharmacologically from selective serotonin-reuptake inhibitors, monoamine oxidase inhibitors, and tricyclic and tetracyclic antidepressant agents. The exact mechanism of antidepressant action of nefazodone has not been fully elucidated but appears more complex than other antidepressant agents and may involve inhibition of reuptake of serotonin (5-hydroxytryptamine [5-HT]) at the presynaptic membrane, antagonism at serotonin type 2 (5-HT_2) receptors, and down-regulation of 5-HT_2 receptor binding sites. Nefazodone also inhibits presynaptic reuptake of norepinephrine and exhibits α_1-adrenergic blocking activity. In vitro studies have demonstrated that the drug possesses little or no affinity for α_2-adrenergic, β-adrenergic, muscarinic, dopaminergic, histamine H_1, 5-HT_{1A}, or GABA-benzodiazepine receptors.

SumMon® (see Users Guide). For additional information on this drug until a more detailed monograph is developed and published, the manufacturer's labeling should be consulted. It is *essential* that the labeling be consulted for detailed information on the usual cautions, precautions, and contraindications.

Preparations

Excipients in commercially available drug preparations may have clinically important effects in some individuals; consult specific product labeling for details.

Nefazodone Hydrochloride

Oral		
Tablets	50 mg*	Nefazodone Hydrochloride Tablets
	100 mg*	Nefazodone Hydrochloride Tablets
	150 mg*	Nefazodone Hydrochloride Tablets
	200 mg*	Nefazodone Hydrochloride Tablets
	250 mg*	Nefazodone Hydrochloride Tablets

*available from one or more manufacturer, distributor, and/or repackager by generic (nonproprietary) name

Trazodone Hydrochloride

■ Trazodone hydrochloride is a triazolopyridine-derivative antidepressant that is chemically and structurally unrelated to tricyclic or tetracyclic antidepressants or to selective serotonin-reuptake inhibitors.

Uses

■ **Major Depressive Disorder** Trazodone is used in the treatment of major depressive disorder. The drug is used in patients who exhibit a prominent and relatively persistent (nearly every day for at least 2 weeks) depressed or dysphoric mood that usually interferes with daily functioning and is manifested as a change in appetite, psychomotor agitation or retardation, a loss of interest in usual activities, a decrease in sexual drive, increased fatigability, a change in sleep, feelings of guilt or worthlessness, slowed thinking or impaired concentration, and/or suicidal ideation or attempts. Trazodone has been used effectively in the treatment of patients who have major depression with or without prominent anxiety. In addition, trazodone has been used effectively in patients with major depression in hospital, institutional, and outpatient settings. Unlike tricyclic antidepressants, trazodone generally has not been reported to precipitate hypomanic or manic attacks in patients with bipolar disorder; however, further study is needed to determine the safety and efficacy of trazodone when used alone as an antidepressant in these patients.

Trazodone is particularly effective in reducing affective and ideational manifestations of depression, especially anxiety, apathy, irritability, and suicidal thoughts. Somatic signs and symptoms associated with depression, including sleep disturbances and fatigue, are also reduced during trazodone therapy. Most clinical studies have shown that the antidepressant effect of usual dosages of trazodone in patients with moderate to severe depression is about equal to that of usual dosages of amitriptyline, imipramine, or doxepin. However, trazodone has reportedly caused fewer adverse effects (e.g., anticholinergic effects) than these tricyclic antidepressants. (See Cautions: Anticholinergic Effects.) Although trazodone has been reported to have a slightly more rapid onset of action than amitriptyline, desipramine, or imipramine, this has not been established.

Trazodone has been used in patients with major depression who have associated anxiety. Based on limited data, the antidepressant effect of usual dosages of trazodone appears to be greater than that of amitriptyline or imipramine in these patients. Trazodone is particularly effective in reducing anxiety, tension, somatic symptoms, insomnia, and psychomotor retardation in these patients.

For further information on treatment of major depressive disorder and considerations in choosing the most appropriate antidepressant for a particular patient, including considerations related to patient tolerance, patient age, and cardiovascular, sedative, and suicidal risk, see Considerations in Choosing Antidepressants under Uses: Major Depressive Disorder, in Fluoxetine Hydrochloride 28:16.04.20.

■ **Schizophrenic Disorder** Although trazodone has been used in the treatment of schizophrenic disorder†, the drug is less effective than chlorpromazine. Depressive symptomatology may improve during trazodone therapy, but the drug does not appear to relieve psychotic symptoms in most schizophrenic patients. Based on limited data, trazodone has little value when used alone in patients with chronic schizophrenic disorder without depression; however, it

may be a useful adjunct to antipsychotic agents (e.g., phenothiazines) in patients with chronic schizophrenic disorder and associated depression. Unlike tricyclic antidepressants, trazodone does *not* appear to worsen psychotic symptoms in these patients.

■ **Alcohol Dependence** Trazodone has been used in the adjunctive treatment of alcohol dependence†. In a limited number of patients with alcohol dependence, oral (50–75 mg daily) or IV (50 mg twice daily) trazodone has reduced tremor, depression, and anxiety. In one study, trazodone was more effective in patients who had pronounced affective symptomatology during periods of intoxication and abstention than in those who only had affective symptomatology during intoxication. Further study is needed to determine the efficacy of trazodone in the treatment of alcohol dependence.

■ **Erectile Dysfunction** Trazodone has been used in a limited number of patients for the treatment of erectile dysfunction† (ED, impotence); however, the American Urological Association (AUA) states that such therapy currently is not recommended. Although some studies indicated that trazodone was more effective than placebo for the treatment of erectile dysfunction, other comparative studies did not. In addition, pooled analysis of these studies failed to show a statistically beneficial effect of the drug on sexual function, although subgroup analysis suggested possible benefit in those with psychogenic erectile dysfunction.

■ **Other Uses** Trazodone may be useful in the treatment of some patients with anxiety states† (anxiety neuroses). In one study, the drug reduced anxiety, tension, somatic symptoms, and insomnia in most of these patients. Based on limited data, trazodone appears to have a greater anxiolytic effect than some other antidepressant agents (e.g., tricyclic antidepressants); however, further study is needed to confirm this finding.

Trazodone has been used in the symptomatic treatment of a limited number of patients with drug-induced dyskinesias†. In one placebo-controlled study in patients with levodopa-induced dyskinesias, oral trazodone (60–120 mg daily) reduced signs and symptoms of dyskinesia by up to 50%. In this study, most patients showed some improvement, with greatest improvement in facial, oro-buccal-facial, and neck dyskinesias. In another study, IV trazodone (50 mg twice daily) eliminated chronic chlorpromazine- and haloperidol-induced tardive dyskinesias in some patients. The decrease in tremor was accompanied by a reduction in anxiety, which may be partly responsible for the favorable effect of trazodone on tremor in these patients. Additional studies are required to determine the efficacy of trazodone in the treatment of drug-induced dyskinesias.

Dosage and Administration

■ **Administration** Trazodone hydrochloride is administered orally. The drug should be taken shortly after a meal or light snack. If drowsiness occurs, a major portion of the daily dose may be given at bedtime or dosage may be reduced.

■ **Dosage** There is a wide range of individual trazodone hydrochloride dosage requirements, and dosage must be carefully adjusted according to individual tolerance and response, using the lowest possible effective dosage.

Patients receiving trazodone should be monitored for possible worsening of depression, suicidality, or unusual changes in behavior, especially at the beginning of therapy or during periods of dosage adjustment. (See Cautions: Precautions and Contraindications.)

Major Depressive Disorder For the treatment of major depressive disorder, the usual initial adult dosage of trazodone hydrochloride is 150 mg daily given in divided doses. Dosage may be increased by 50 mg/day every 3 or 4 days, depending on the patient's therapeutic response and tolerance. The maximum dosage for outpatients usually should not exceed 400 mg daily. Dosages up to 600 mg daily may be required in hospitalized, institutionalized, or severely depressed patients. Dosages up to 800 mg daily have been used in the treatment of some patients with severe depression; however, the manufacturers do not recommend exceeding a dosage of 600 mg daily.

Although symptomatic relief may be seen in some patients during the first week of therapy, optimum antidepressant effect usually occurs within 2 weeks. About 25% of patients who respond to trazodone require up to 4 weeks of therapy to reach optimum response.

To avoid recurrence of depressive symptoms, trazodone therapy may be required for several months following optimum therapeutic response. Dosage during prolonged maintenance therapy should be kept at the lowest effective level; once an adequate response has been achieved, dosage should be gradually reduced and subsequently adjusted according to the patient's therapeutic response and tolerance.

Cautions

Trazodone hydrochloride apparently causes fewer adverse anticholinergic effects than currently available tricyclic antidepressant agents. Other adverse effects, including cardiovascular effects, also appear to occur less frequently with trazodone than with currently available tricyclic antidepressants.

The incidence and severity of adverse reactions to trazodone in relation to dosage and duration of therapy have not been fully characterized; however, adverse effects appear to occur more frequently at dosages greater than 300 mg/day. Total trazodone hydrochloride dosages up to 800 mg daily have been well tolerated by some patients. Adverse effects appear to be mild to moderate in severity and may decrease after the first few weeks of trazodone therapy. Adverse effects may be obviated by a reduction in dosage or alteration in dosage schedule. Serious reactions requiring discontinuance of therapy are relatively rare.

■ **Nervous System Effects** Adverse nervous system effects occur frequently during the first few weeks of therapy with trazodone. The most frequent adverse effect associated with trazodone therapy is drowsiness, which occurs in 20–50% of patients receiving the drug. Other less frequent adverse nervous system effects of trazodone include dizziness and lightheadedness, nervousness, fatigue, malaise, weakness, heaviness or fullness of the head, headache, and insomnia. Confusion, incoordination, anger or hostility, agitation, decreased concentrating ability, impaired memory, impaired speech, disorientation, hallucinations or delusions, and excitement have also occurred. Hypomania, nightmares or vivid dreams, tonic-clonic seizures, tremors, and paresthesias and akathisia occur rarely.

■ **Anticholinergic Effects** Although bothersome anticholinergic effects commonly occur with tricyclic antidepressants, these effects appear to occur less frequently with trazodone. Dry mouth has been reported in about 15–30% of patients during trazodone therapy; it has been suggested that this effect may result from an α-adrenergic blocking effect rather than an anticholinergic effect of trazodone. In several placebo-controlled studies, the incidence of dry mouth was similar in trazodone- and placebo-treated patients. Other anticholinergic effects such as blurred vision, constipation, and urinary retention have been reported less frequently.

■ **Genitourinary Effects** Trazodone therapy has been associated with priapism, with surgical intervention required in approximately one-third of reported cases; in some cases, permanent impairment of erectile function or impotence has resulted. Male patients receiving trazodone who experience prolonged or inappropriate penile erections should immediately discontinue the drug and consult their physician. Decreased or increased libido, retrograde ejaculation, impotence, inhibited female orgasm (anorgasmia), increased urinary frequency, delayed urine flow, and hematuria have also been associated with trazodone therapy.

■ **GI Effects** Adverse GI effects of trazodone include nausea and vomiting, dysgeusia, and abdominal and gastric disorders. Flatulence and diarrhea have also been reported.

■ **Cardiovascular Effects** Trazodone is thought to be less cardiotoxic than currently available tricyclic antidepressant agents. (See Pharmacology: Cardiovascular Effects.) Hypotension (including orthostatic hypotension) is the most frequent adverse cardiovascular effect of trazodone, occurring in about 5% of patients receiving the drug. In most patients, hypotension is mild and not dose related. Syncope, shortness of breath, chest pain, tachycardia, palpitations, and hypertension have also occurred. Bradycardia has occurred in a few patients during long-term therapy.

Various ECG changes have occurred in patients receiving trazodone. In patients with preexisting cardiac disease, trazodone may be arrhythmogenic. PVCs, ventricular couplets, and short episodes (3 or 4 beats) of ventricular tachycardia have occurred in these patients. Arrhythmias have also been reported in patients without preexisting cardiac disease. Cardiac arrest has also been reported. Myocardial infarction has been reported, but this effect has not been attributed directly to trazodone.

■ **Hematologic Effects** Occasional decreases in leukocyte and neutrophil counts have occurred in some patients receiving trazodone. These changes were not considered clinically important and did not require discontinuance of the drug. Anemia has also been associated with trazodone therapy in a few patients.

■ **Other Adverse Effects** Musculoskeletal aches and pains have occurred in about 5% of patients receiving trazodone. A few patients have developed muscle twitches. Pruritus, rash, urticaria, acne, photosensitivity, edema, nasal or sinus congestion, eye irritation, sweating or clamminess, early or absent menses, and tinnitus have been reported in some patients receiving trazodone. Allergic reactions and hypersalivation have rarely occurred. Minimal increases in serum concentrations of alkaline phosphatase, AST (SGOT), and ALT (SGPT) have occurred in some patients receiving trazodone.

■ **Precautions and Contraindications** Worsening of depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior may occur in both adult and pediatric (see Cautions: Pediatric Precautions) patients with major depressive disorder or other psychiatric disorders, whether or not they are taking antidepressants. This risk may persist until clinically important remission occurs. Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are the strongest predictors of suicide. However, there has been a long-standing concern that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients during the early phases of treatment. Pooled analyses of short-term, placebo-controlled studies of antidepressants (i.e., selective serotonin-reuptake inhibitors and other antidepressants) have shown an increased risk of suicidality in children, adolescents, and young adults (18–24 years of age) with major depressive disorder and other psychiatric disorders. An increased suicidality risk was not demonstrated with antidepressants compared with placebo in adults older than 24 years of age, and a reduced risk was observed in adults 65 years of age or older. It currently is unknown whether the suicidality risk extends to longer-term use (i.e., beyond

several months); however, there is substantial evidence from placebo-controlled maintenance trials in adults with major depressive disorder that antidepressants can delay the recurrence of depression.

The US Food and Drug Administration (FDA) recommends that all patients being treated with antidepressants for any indication be appropriately monitored and closely observed for clinical worsening, suicidality, and unusual changes in behavior, particularly during initiation of therapy (i.e., the first few months) and during periods of dosage adjustments. Families and caregivers of patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and nonpsychiatric, also should be advised to monitor patients on a daily basis for the emergence of agitation, irritability, or unusual changes in behavior as well as the emergence of suicidality, and to report such symptoms immediately to a health-care provider.

Although a causal relationship between the emergence of symptoms such as anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia, hypomania, and/or mania and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality. Consequently, consideration should be given to changing the therapeutic regimen or discontinuing therapy in patients whose depression is persistently worse or in patients experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, particularly if such manifestations are severe, abrupt in onset, or were not part of the patient's presenting symptoms. FDA also recommends that the drugs be prescribed in the smallest quantity consistent with good patient management, in order to reduce the risk of overdosage. Because of the possibility of comorbidity between major depressive disorder and other psychiatric and nonpsychiatric disorders, the same precautions observed when treating patients with major depressive disorder should be observed when treating patients with other psychiatric and nonpsychiatric disorders.

It is generally believed (though not established in controlled trials) that treating a major depressive episode with an antidepressant alone may increase the likelihood of precipitating a mixed or manic episode in patients at risk for bipolar disorder. Therefore, patients should be adequately screened for bipolar disorder prior to initiating treatment with an antidepressant; such screening should include a detailed psychiatric history (e.g., family history of suicide, bipolar disorder, and depression).

Patients should be warned that trazodone may impair their ability to perform activities requiring mental alertness or physical coordination (e.g., operating machinery, driving a motor vehicle). Patients also should be warned that trazodone may enhance their response to alcohol, barbiturates, or other CNS depressants. Since the risk of dizziness or lightheadedness may be increased during fasting conditions, patients should be advised to take trazodone shortly after a meal or light snack. In addition, total drug absorption may be up to 20% greater when the drug is taken with food rather than on an empty stomach. Because priapism has been associated with trazodone therapy, patients should be instructed to discontinue the drug and consult a physician if prolonged or inappropriate penile erection occurs.

Until additional clinical experience on the safety of trazodone in patients with cardiovascular disease is obtained, it is recommended that these patients be closely monitored, particularly for arrhythmias, while receiving the drug. (See Cautions: Cardiovascular Effects.) It is also recommended that trazodone *not* be used during the initial recovery phase of myocardial infarction.

Leukocyte and differential counts should be performed in patients who develop fever and sore throat or other signs of infection while receiving trazodone. The drug should be discontinued in patients whose leukocyte or absolute neutrophil count decreases to less than normal levels. (See Cautions: Hematologic Effects.)

Trazodone is contraindicated in patients who are hypersensitive to the drug.

■ **Pediatric Precautions** Safety and efficacy of trazodone in children younger than 18 years of age have not been established.

FDA warns that antidepressants increase the risk of suicidal thinking and behavior (suicidality) in children and adolescents with major depressive disorder and other psychiatric disorders. The risk of suicidality for these drugs was identified in a pooled analysis of data from a total of 24 short-term (4–16 weeks), placebo-controlled studies of 9 antidepressants (i.e., bupropion, citalopram, fluoxetine, fluvoxamine, mirtazapine, nefazodone, paroxetine, sertraline, venlafaxine) in over 4400 children and adolescents with major depressive disorder, obsessive-compulsive disorder (OCD), or other psychiatric disorders. The analysis revealed a greater risk of adverse events representing suicidal behavior or thinking (suicidality) during the first few months of treatment in pediatric patients receiving antidepressants than in those receiving placebo. The average risk of such events was 4% among children and adolescents receiving these drugs, twice the risk (2%) that was observed among those receiving placebo. However, a more recent meta-analysis of 27 placebo-controlled trials of 9 antidepressants (SSRIs and others) in patients younger than 19 years of age with major depressive disorder, OCD, or non-OCD anxiety disorders suggests that the benefits of antidepressant therapy in treating these conditions may outweigh the risks of suicidal behavior or suicidal ideation. No suicides occurred in these pediatric trials.

The risk of suicidality in FDA's pooled analysis differed across the different psychiatric indications, with the highest incidence observed in the major depressive disorder studies. In addition, although there was considerable variation in risk among the antidepressants, a tendency toward an increase in suicidality risk in younger patients was found for almost all drugs studied. It is currently unknown whether the suicidality risk in pediatric patients extends to longer-term use (i.e., beyond several months).

As a result of this analysis and public discussion of the issue, FDA has directed manufacturers of all antidepressants to add a boxed warning to the labeling of their products to alert clinicians of this suicidality risk in children and adolescents and to recommend appropriate monitoring and close observation of patients receiving these agents. (See Cautions: Precautions and Contraindications.) The drugs that are the focus of the revised labeling are all drugs included in the general class of antidepressants, including those that have not been studied in controlled clinical trials in pediatric patients, since the available data are not adequate to exclude any single antidepressant from an increased risk of suicidality. In addition to the boxed warning and other information in professional labeling on antidepressants, FDA currently recommends that a patient medication guide explaining the risks associated with the drugs be provided to the patient each time the drugs are dispensed.

Anyone considering the use of trazodone in a child or adolescent for any clinical use must balance the potential risk of therapy with the clinical need.

■ **Mutagenicity and Carcinogenicity** In vitro tests have *not* shown trazodone to be mutagenic. No evidence of carcinogenesis was seen in animals receiving oral trazodone dosages up to 300 mg/kg daily for 18 months.

■ **Pregnancy, Fertility, and Lactation** Trazodone has been shown to be teratogenic in rats and rabbits when given at dosages 15–50 times the maximum human dosage. The drug also caused increased fetal resorption and other adverse fetal effects in rats when given at dosages approximately 30–50 times the suggested maximum human dosage. There are no adequate and controlled studies to date using trazodone in pregnant women, and the drug should be used during pregnancy only when the potential benefits justify the possible risks to the fetus.

The effect of trazodone on fertility in humans is not known. Impotence, retrograde ejaculation, and decreased or increased libido have occurred in some individuals during trazodone therapy. Reproduction studies in male and female rats using trazodone dosages up to 150 times the usual human dosage have not revealed evidence of impaired fertility.

Because trazodone is distributed into milk, the drug should be used with caution in nursing women.

Drug Interactions

■ **Drugs Affecting Hepatic Microsomal Enzymes** Results of in vitro studies indicate that metabolism of trazodone is mediated by the cytochrome P-450 (CYP) 3A4 isoenzyme, and the possibility exists that drugs that inhibit or induce this isoenzyme may affect the pharmacokinetics of trazodone. Other metabolic pathways that may be involved in the metabolism of trazodone have not been well characterized.

Concomitant use of trazodone with inhibitors of CYP3A4 can result in substantially increased plasma concentrations of trazodone and increase the potential for adverse effects. In one study, concomitant use of ritonavir (200 mg twice daily for 2 days) and trazodone (a single 50-mg dose) in healthy individuals increased maximum plasma concentrations and decreased clearance of trazodone by 34 and 52%, respectively, and increased area under the plasma concentration-time curve (AUC) and half-life of trazodone by greater than two-fold. Adverse effects (e.g., nausea, hypotension, syncope) also were observed with concomitant use of trazodone and ritonavir. The manufacturers of trazodone state that a reduction in trazodone dosage should be considered in patients receiving a potent inhibitor of the CYP3A4 isoenzyme (e.g., indinavir, itraconazole, ketoconazole, nefazodone, ritonavir) concomitantly with trazodone.

Concomitant use of trazodone (100–300 mg daily) with carbamazepine (400 mg daily), an inducer of CYP3A4, decreased plasma concentrations of trazodone and an active metabolite, *m*-chlorophenylpiperazine, by 76 and 60%, respectively. Patients receiving trazodone and carbamazepine concomitantly should be closely monitored and dosage of trazodone increased if necessary.

■ **Serotonergic Agents** ***Fluoxetine*** Elevated plasma trazodone concentrations and adverse effects possibly associated with trazodone toxicity have been reported occasionally during concomitant trazodone and fluoxetine therapy. Although the exact mechanism has not been established, it has been suggested that fluoxetine may inhibit the hepatic metabolism of many antidepressant agents, including trazodone. In addition, both trazodone and fluoxetine possess serotonergic activity; therefore, the possibility of serotonin syndrome also should be considered in patients receiving trazodone and fluoxetine or other selective serotonin-reuptake inhibitor therapy concurrently. For detailed information on serotonin syndrome, see Drug Interactions: Drugs Associated with Serotonin Syndrome in Fluoxetine Hydrochloride 28:16.04.20 and the Monoamine Oxidase Inhibitors General Statement 28:16.04.12. Further study is needed, but current evidence suggests that patients receiving trazodone and fluoxetine concomitantly should be observed closely for adverse effects; monitoring of plasma trazodone concentrations also should be considered and trazodone dosage reduced as necessary.

Monoamine Oxidase Inhibitors It is not known whether interactions between trazodone and monoamine oxidase (MAO) inhibitors can occur. Unlike tricyclic antidepressants, trazodone does not interfere with catecholamine uptake by the adrenergic neuron or the pressor response to tyramine. Therefore, an interaction between trazodone and MAO inhibitors is unlikely. However, both trazodone and MAO inhibitors possess serotonergic activity; therefore, the possibility that serotonin syndrome may occur during concurrent

therapy should be considered. For detailed information on serotonin syndrome, see Drug Interactions: Drugs Associated with Serotonin Syndrome in Fluoxetine Hydrochloride 28:16.04.20 and the Monoamine Oxidase Inhibitors General Statement 28:16.04.12. Because of the absence of clinical experience, if MAO inhibitors are discontinued shortly before or are to be given concomitantly with trazodone, it is recommended that trazodone therapy be initiated cautiously and dosage increased gradually until optimum response is achieved.

Other Serotonergic Agents Trazodone possesses serotonergic activity and rarely has been associated with serotonin syndrome when combined with other serotonergic agents, including buspirone, phenelzine, and dextropropoxyphene. Because severe complications and even fatalities have accompanied the serotonin syndrome, trazodone probably should be used with caution in patients receiving or who recently have received other serotonergic agents. For additional information on potentially serious drug interactions that may occur between trazodone and other serotonergic agents, see Drug Interactions: Drugs Associated with Serotonin Syndrome, in Fluoxetine Hydrochloride 28:16.04.20 and the Monoamine Oxidase Inhibitors General Statement 28:16.04.12.

■ **General Anesthetics** Since little is known about the interaction between trazodone and general anesthetics, it is recommended that trazodone be discontinued for as long as clinically feasible prior to elective surgery.

■ **Electroconvulsive Therapy** Pending further accumulation of clinical data on the concurrent use of trazodone and electroconvulsive therapy (ECT), concurrent use of these therapies should be avoided.

■ **CNS Depressants** Trazodone may be additive with, or may potentiate the action of, other CNS depressants such as opiates or other analgesics, barbiturates or other sedatives, anesthetics, or alcohol. When trazodone is used concomitantly with other CNS depressants, caution should be used to avoid excessive sedation.

■ **Hypotensive Agents** Because trazodone can cause hypotension, including orthostatic hypotension and syncope, concomitant administration of antihypertensive therapy may require a reduction in dosage of the antihypertensive agent(s). Trazodone has been shown to inhibit the hypotensive effect of various antihypertensive agents (e.g., clonidine, methyldopa) in animals; however, this inhibition has not always been reproducible. It is not known whether trazodone can inhibit the hypotensive effect of these agents in humans, and the clinical importance of this potential interaction has not been determined.

■ **Other Drugs** Increased serum digoxin or phenytoin concentrations have reportedly occurred in patients receiving trazodone concurrently with either drug.

■ **Food** The rate and extent of absorption of trazodone are affected by the presence of food. When trazodone is taken shortly after the ingestion of food, there may be a slight increase in the amount of drug absorbed, a decrease in peak plasma concentration of the drug, and a lengthening of the time to reach the peak plasma concentration. Total drug absorption may be up to 20% greater when the drug is taken with food rather than on an empty stomach. In animals, the rate of absorption has been delayed when trazodone was administered concomitantly with food because of a decrease in the rate of transfer of the drug from the stomach to the small intestine.

The effect of food on absorption of trazodone during long-term administration of the drug is not considered clinically important. Concomitant administration of trazodone with food is generally recommended since it appears to decrease the incidence of dizziness or lightheadedness.

Acute Toxicity

Limited information is available on the acute toxicity of trazodone.

■ **Pathogenesis** The acute lethal dose of trazodone in humans is not known. In addition, there is no clearly defined relationship between plasma trazodone concentration and severity of intoxication. The oral LD_{50} of trazodone is 610 mg/kg in mice, 486 mg/kg in rats, 560 mg/kg in rabbits, and 500 mg/kg in dogs. In animals, lethal doses produced dyspnea, salivation, prostration, and clonic seizures.

■ **Manifestations** One patient who intentionally ingested 7.5 g of trazodone experienced only drowsiness and weakness; the patient was aroused at the time of hospitalization and emesis was induced. Another patient had an uneventful recovery after ingesting 9.2 g of trazodone. There have been several reports of accidental ingestion in children; however, the exact amounts ingested are unknown. Each of these children exhibited only lethargy and drowsiness, and recoveries were uneventful. Fatalities have occurred in adults who intentionally ingested trazodone and other drugs (e.g., alcohol, chloral hydrate, amobarbital, chlordiazepoxide, meprobamate) concurrently.

In general, overdosage of trazodone may be expected to produce effects that are extensions of common adverse reactions; vomiting, drowsiness, and lethargy have been the principal effects reported. Other reported effects associated with acute trazodone overdosage have included orthostatic hypotension, tachycardia, coma, headache, tinnitus, dizziness, dyspnea, shivering, aching muscles, incontinence, and dry mouth. Unlike tricyclic antidepressant overdosage, seizures and arrhythmias do not appear to be associated with trazodone overdosage.

■ **Treatment** Treatment of trazodone overdosage generally involves symptomatic and supportive care; there is no specific antidote for trazodone intoxication. In acute overdosage, the stomach should be emptied immediately by inducing emesis or by gastric lavage. If the patient is comatose, having seizures, or lacks the gag reflex, gastric lavage may be performed if an endotracheal tube with cuff inflated is in place to prevent aspiration of vomitus. Although administration of activated charcoal after gastric lavage and/or emesis has been useful in the treatment of acute overdosage with tricyclic antidepressants, the effect of activated charcoal on the absorption of trazodone is not currently known. Appropriate therapy should be instituted if hypotension or excessive sedation occurs. Forced diuresis may be useful in facilitating elimination of the drug. It is not known if trazodone is dialyzable; however, because of extensive protein binding of the drug, hemodialysis is probably *not* effective in enhancing elimination of trazodone.

Pharmacology

The pharmacology of trazodone is complex and in some ways resembles that of tricyclic antidepressants, benzodiazepines, and phenothiazines; however, the overall pharmacologic profile of trazodone differs from each of these classes of drugs.

■ **Nervous System Effects** The precise mechanism of antidepressant action of trazodone is unclear, but the drug has been shown to selectively block the reuptake of serotonin (5-HT) at the presynaptic neuronal membrane. The effects of serotonin may thus be potentiated. Unlike other antidepressant agents (e.g., tricyclic antidepressants), trazodone may have a dual effect on the central serotonergic system. Animal studies indicate that trazodone acts as a serotonin agonist at high doses (6–8 mg/kg), while at low doses (0.05–1 mg/kg), it antagonizes the actions of serotonin. Trazodone does not appear to influence the reuptake of dopamine or norepinephrine within the CNS; however, animal studies indicate that trazodone may enhance release of norepinephrine from neuronal tissue. Trazodone does not cause serotonin release in vitro.

Although the mechanism of action of antidepressant agents may involve inhibition of the reuptake of various neurotransmitters at the presynaptic neuronal membrane, long-term therapy with antidepressant agents also affects postsynaptic neuronal receptor binding sites, resulting in some adaptive changes in neurotransmission. Long-term administration of trazodone reportedly decreases the number of postsynaptic serotonergic (i.e., serotonin$_2$) and β-adrenergic binding sites in the brain of animals. Although the clinical importance of these effects is not known, the decrease in binding sites is associated with a functional increase in serotonergic activity and a reduction in the sensitivity of adenylate cyclase to stimulation by β-adrenergic agonists. It has been suggested that postsynaptic receptor modification is mainly responsible for the antidepressant action observed during long-term administration of trazodone. Further study is needed to determine the role of binding site alteration in the antidepressant action of trazodone and other antidepressants.

In animals, trazodone's effect on various avoidance behaviors is similar to that of phenothiazines. Unlike phenothiazines, however, trazodone potentiates the effects of serotonin. Trazodone does not potentiate the actions of levodopa or alter neuronal concentrations of acetylcholine. Trazodone does not inhibit monoamine oxidase, and unlike amphetamine-like drugs, does not stimulate the CNS.

Unlike many currently available antidepressants, trazodone exhibits little, if any, anticholinergic activity in vitro. Clinical studies show a lower incidence of anticholinergic effects (e.g., dry mouth, blurred vision, urinary retention, constipation) associated with trazodone use than with tricyclic antidepressant use. (See Cautions: Anticholinergic Effects.)

Trazodone produces varying degrees of sedation in normal and mentally depressed patients. The sedative effect is thought to result principally from central α_1-adrenergic blocking activity and possibly from a histamine blocking action of the drug. Trazodone may cause EEG changes, including increased slow-wave and alpha-wave activity. Some increase in fast-wave activity also occurs. Trazodone increases total sleep time, decreases the number and duration of awakenings in depressed patients, and decreases rapid eye movement (REM) sleep. Unlike tricyclic antidepressants, trazodone does not increase stage 4 sleep.

Although the exact mechanism of action has not been determined, trazodone has an anxiolytic effect. This finding is supported by animal studies in which trazodone is active in certain antianxiety test systems. In addition, the drug has demonstrated anxiolytic activity in patients with major depression who also have associated anxiety. (See Uses: Major Depressive Disorder.)

Therapeutic dosages of trazodone do not appear to affect respiration; however, the effect of higher dosages of trazodone in patients with ventilatory insufficiency is not known.

Like many other centrally acting agents, trazodone exhibits analgesic activity in a variety of analgesic test systems. Trazodone also has weak skeletal muscle relaxant activity but lacks anticonvulsant effects.

Trazodone possesses potent peripheral α-adrenergic blocking activity in animals following IV administration of 3–10 mg/kg. In addition, in animals, the drug blocks the peripheral effects of serotonin, epinephrine, norepinephrine, and histamine. The peripheral antihistaminic effects of trazodone are weaker than those of tricyclic antidepressants.

■ **Cardiovascular Effects** The cardiovascular effects of trazodone have been studied in animals and to a limited extent in humans. Unlike other antidepressant agents (e.g., tricyclic antidepressants, monoamine oxidase inhibitors), trazodone has been associated with only minimal cardiovascular effects. (See Cautions: Cardiovascular Effects.) The absence of substantial anti-

cholinergic activity and catecholamine-potentiating effects appears to be the principal reason for the general lack of cardiovascular effects of trazodone.

Trazodone exhibits α-adrenergic blocking activity and does not inhibit catecholamine reuptake. Unlike tricyclic antidepressants, trazodone blocks the pressor response to norepinephrine and lowers arterial blood pressure. However, in one study in normotensive patients with endogenous depression, the effect of trazodone on systemic blood pressure was equivocal. Trazodone does not block the neuronal uptake of tyramine; thus, unlike tricyclic antidepressants, the drug has no effect on the pressor response to this sympathomimetic amine.

Although trazodone does *not* appear to have substantial arrhythmogenic activity, arrhythmias have occurred in some patients with preexisting cardiac disease during trazodone therapy. (See Cautions: Cardiovascular Effects.) In animals, trazodone does *not* affect intra-atrial, ventricular septal, ventricular free-wall, His-Purkinje, or AV nodal conduction. At doses up to 30 mg/kg in animals, trazodone produces only minimal ECG changes, including prolongation of the QT interval and a decrease in heart rate. Unlike tricyclic antidepressants, trazodone does not exert direct quinidine-like cardiotoxic properties. In addition, trazodone does *not* exert a negative inotropic effect at therapeutic dosages; the drug may decrease aortic blood flow as a result of a decrease in heart rate.

To date, there have been no published studies comparing the cardiovascular effects of therapeutic dosages of trazodone with those of antidepressants such as mianserin, nomifensine, or zimelidine. Although available data suggest that trazodone is less cardiotoxic than tricyclic antidepressant agents at therapeutic dosages, the cardiovascular effects of trazodone overdosage have not been well described.

■ **Other Effects** Trazodone may affect the endocrine system. Following oral administration of a single 50-mg dose in one study in healthy adults, trazodone caused a decrease in mean serum prolactin concentration. However, in another study in depressed patients, trazodone did not alter mean serum prolactin concentration following oral administration of 200 mg daily for 2 weeks.

Trazodone-induced antagonism of α_2-adrenergic receptors may relax the tissues and enhance arterial inflow in penile vascular and corporal smooth muscle resulting in an erection.

Pharmacokinetics

In all studies described in the Pharmacokinetics section, trazodone was administered as the hydrochloride salt.

■ **Absorption** Trazodone is rapidly and almost completely absorbed from the GI tract following oral administration. The rate and extent of absorption are affected by the presence of food. When trazodone is taken shortly after the ingestion of food, there may be a slight increase (up to 20%) in the amount of drug absorbed, a decrease in peak plasma concentration of the drug, and a lengthening of the time to reach the peak plasma concentration.

Peak plasma concentrations of trazodone occur approximately 1 hour after oral administration when the drug is taken on an empty stomach or 2 hours after oral administration when taken with food. Following oral administration of multiple doses of trazodone (25 mg 2 or 3 times daily), steady-state plasma concentrations of the drug are usually attained within 4 days and exhibit wide interpatient variation. Following oral administration of a single 25-mg dose of radiolabeled trazodone to healthy adults in one study, mean peak plasma drug concentrations of 650 and 480 ng/mL occurred at 1.5 and 2.5 hours after ingestion, in the fasted and nonfasted state, respectively. Following oral administration of single doses of 25, 50, or 100 mg of trazodone to healthy, fasted adults in another study, mean peak plasma trazodone concentrations were 490, 860, and 1620 ng/mL, respectively. The areas under the plasma concentration-time curves (AUCs) were 3.44, 5.95, and 11.19 mcg-h/mL, for the 25-, 50-, and 100-mg doses, respectively. Limited crossover data are available comparing AUCs in fasted and nonfasted patients; however, it appears that the presence of food slightly increases the AUC for trazodone.

The therapeutic range for plasma trazodone concentrations and the relationship of plasma concentrations to clinical response and toxicity have not been established.

■ **Distribution** Distribution of trazodone into human body tissues and fluids has not been determined. Following oral administration of trazodone in animals, the drug and its metabolites are distributed mainly into the liver, kidneys, small intestine, lungs, adrenal glands, and pancreas, with lower concentrations being distributed into adipose tissue, heart, and skeletal muscle. Trazodone crosses the blood-brain barrier in animals, and concentrations of the drug in the brain are higher than those in plasma during the first 8 hours after oral ingestion.

In vitro, trazodone is 89–95% bound to plasma proteins at plasma trazodone concentrations of 100–1500 ng/mL.

Although it is not known if trazodone crosses the placenta in humans, the drug crosses the placenta in animals. Following a single oral dose of 50 mg, trazodone is distributed into milk in concentrations approximately 10% of maternal plasma concentrations, with a milk-to-plasma ratio (based on areas under the plasma and milk concentration-time curves) of about 0.1–0.2. Based on these data, it is estimated that a nursing infant would ingest less than 0.1% of the dose. It is not known whether trazodone metabolites are distributed into milk.

■ **Elimination** Plasma concentrations of trazodone decline in a biphasic manner. The half-life of trazodone in the initial phase ($t_{1/2\alpha}$) is about 3–6 hours and the half-life in the terminal phase ($t_{1/2\beta}$) is about 5–9 hours. The clearance of trazodone from the body shows wide interindividual variation. The manufacturers state that the drug may accumulate in plasma in some individuals.

Trazodone is extensively metabolized in the liver via hydroxylation, oxidation, *N*-oxidation, and splitting of the pyridine ring. A hydroxylated metabolite and oxotriazolopyridinpropionic acid (an inactive metabolite excreted in urine) are conjugated with glucuronic acid. Results of in vitro studies indicate that metabolism of trazodone to an active metabolite, *m*-chlorophenylpiperazine, is mediated by the cytochrome P-450 (CYP) 3A4 isoenzyme. The manufacturers state that other metabolic pathways involved in metabolism of trazodone have not been well characterized. Results from animal studies indicate that trazodone does not induce its own metabolism.

Approximately 70–75% of an oral dose of trazodone is excreted in urine within 72 hours of administration, principally as metabolites. About 20% of an oral dose of trazodone is excreted in urine as oxotriazolopyridinpropionic acid and its conjugates, and about 10% as a dihydrodiol metabolite; less than 1% of a dose is excreted unchanged. The remainder of an oral dose of the drug is excreted in feces via biliary elimination, principally as metabolites.

Chemistry and Stability

■ **Chemistry** Trazodone hydrochloride is a triazolopyridine-derivative antidepressant. The drug is chemically and structurally unrelated to tricyclic or tetracyclic antidepressants or to selective serotonin-reuptake inhibitors. Trazodone hydrochloride occurs as a white, odorless, crystalline powder with a bitter taste and is freely soluble in water and sparingly soluble in alcohol. The drug has a pK_a of 6.7.

■ **Stability** Commercially available trazodone hydrochloride tablets should be stored at room temperature in tight, light-resistant containers and protected from temperatures greater than 40°C.

Preparations

Excipients in commercially available drug preparations may have clinically important effects in some individuals; consult specific product labeling for details.

Trazodone Hydrochloride

Oral		
Tablets	50 mg*	Trazodone Hydrochloride Tablets
	100 mg*	Trazodone Hydrochloride Tablets
	150 mg*	Trazodone Hydrochloride Dividose* (scored), Sandoz
		Trazodone Hydrochloride Tablets
	300 mg*	Trazodone Hydrochloride Tablets

*available from one or more manufacturer, distributor, and/or repackager by generic (nonproprietary) name
†Use is not currently included in the labeling approved by the US Food and Drug Administration

TRICYCLICS AND OTHER NOREPINEPHRINE-REUPTAKE INHIBITORS 28:16.04.28

Tricyclic Antidepressants General Statement

■ Tricyclic antidepressants contain a 3-ring structure and differ structurally and pharmacologically from other currently available antidepressants (e.g., selective serotonin-reuptake inhibitors, monoamine oxidase inhibitors).

Uses

■ **Major Depressive Disorder** Tricyclic antidepressants are used in the treatment of major depressive disorder. A major depressive episode implies a prominent and relatively persistent depressed or dysphoric mood that usually interferes with daily functioning (nearly every day for at least 2 weeks). According to DSM-IV criteria, a major depressive episode includes at least 5 of the following 9 symptoms (with at least one of the symptoms being depressed mood or loss of interest or pleasure): depressed mood most of the day as indicated by subjective report (e.g., feels sad or empty) or observation made by others; markedly diminished interest or pleasure in all, or almost all, activities most of the day; significant weight loss (when not dieting) or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite; insomnia or hypersomnia; psychomotor agitation or retardation (observable by others, not merely subjective feelings of restlessness or being slowed down); fatigue or loss of energy; feelings of worthlessness or excessive or inappropriate guilt (not merely self-reproach or guilt about being

30 mg total amphetamine (as 7.5 mg, with Amphetamine Aspartate 7.5 mg, Dextroamphetamine Saccharate 7.5 mg, and Dextroamphetamine Sulfate 7.5 mg)*	**Adderall** (C-II; double-scored), Shire
	Dextroamphetamine Saccharate, Amphetamine Aspartate, Dextroamphetamine Sulfate, and Amphetamine Sulfate Tablets (C-II; double-scored)

*available from one or more manufacturer, distributor, and/or repackager by generic (nonproprietary) name

Dextroamphetamine

■ Dextroamphetamine is the dextrorotatory isomer of amphetamine.

Uses

Dextroamphetamine sulfate alone and in fixed-combination preparations with dextroamphetamine saccharate, amphetamine aspartate, and amphetamine sulfate is used in the treatment of narcolepsy and as an adjunct to psychological, educational, social, and other remedial measures in the treatment of attention deficit hyperactivity disorder (ADHD).

■ Narcolepsy and Attention Deficit Hyperactivity Disorder

Dextroamphetamine sulfate alone and in fixed-combination preparations with dextroamphetamine saccharate, amphetamine aspartate, and amphetamine sulfate is used in the treatment of narcolepsy and as an adjunct to psychological, educational, social, and other remedial measures in the treatment of ADHD (hyperkinetic disorder, hyperkinetic syndrome of childhood, minimal brain dysfunction) in children, adolescents, and adults.

ADHD usually is characterized by developmentally inappropriate symptoms (e.g., moderate to severe distractibility, short attention span, hyperactivity, emotional lability, impulsivity). The final diagnosis of this disorder should not be made if these symptoms are of only comparatively recent origin. Nonlocalizing (soft) neurologic signs, learning disability, and abnormal EEG may or may not be present, and a diagnosis of CNS dysfunction may or may not be warranted. Drug therapy is not indicated in all children with ADHD, and such therapy should be considered only after a complete evaluation including medical history has been performed. The decision to use amphetamines should depend on the age of the child and the clinician's assessment of the severity and duration of symptoms and should not depend solely on one or more behavioral characteristics. When symptoms of ADHD are associated with acute stress reactions, use of amphetamines usually is not recommended. For a more detailed discussion on the management of ADHD, including the use of stimulants such as dextroamphetamine, see Uses: Attention Deficit Hyperactivity Disorder, in Methylphenidate 28:20.92.

Dosage and Administration

■ Administration

Preparations containing dextroamphetamine sulfate are administered orally. The commercially available extended-release capsules containing dextroamphetamine sulfate and dextroamphetamine saccharate in fixed-combination with amphetamine sulfate and amphetamine aspartate (Adderall XR®) may be swallowed intact with or without food or the entire contents of a capsule(s) may be sprinkled on a small amount of applesauce immediately prior to administration; subdividing the contents of a capsule is not recommended. The pellets contained in the capsules should not be chewed or crushed, and the sprinkle/food mixture must not be stored for use at a later time.

The initial dose of dextroamphetamine sulfate (alone or in fixed-combination preparations) is given on awakening; when the drug is given as conventional (short-acting) tablets in divided doses (2 or 3), additional doses are given at intervals of 4–6 hours. Because of the potential for insomnia, administration of dextroamphetamine sulfate conventional tablets (Dexedrine®), dextroamphetamine sulfate extended-release capsules (Dexedrine® Spansules®), or fixed-combination conventional tablets (Adderall®) in the late evening or administration of fixed-combination extended-release capsules (Adderall XR®) in the afternoon should be avoided.

■ Dosage

Dosage of dextroamphetamines should be adjusted according to individual response and tolerance; the smallest dose required to produce the desired response should always be used.

Narcolepsy In the treatment of narcolepsy, the usual dosage of dextroamphetamine sulfate given alone or the total dosage of amphetamines given in fixed-combination preparations containing dextroamphetamine sulfate, dextroamphetamine saccharate, amphetamine aspartate, and amphetamine sulfate is 5–60 mg daily, depending upon the patient's age and response, usually given in divided doses. In patients 12 years of age and older, the initial dosage is 10 mg daily; daily dosage is increased by 10 mg at weekly intervals until the optimum response is attained. Although narcolepsy seldom occurs in children younger than 12 years of age, in pediatric patients 6–12 years of age, the recommended initial dosage of dextroamphetamine sulfate is 5 mg daily; daily dosage is increased by 5 mg at weekly intervals until the optimum response is attained. When intolerable adverse effects occur (e.g., insomnia, anorexia), dosage should be reduced. Dextroamphetamine sulfate extended-release capsules may be used for once-daily dosing whenever appropriate.

Attention Deficit Hyperactivity Disorder Dextroamphetamine sulfate dosage for the treatment of attention deficit hyperactivity disorder (ADHD) should be individualized based on patient response and tolerance. The first dosage that produces an observable response may not be the optimum dosage to improve function, and titration to higher dosages should continue in an attempt to achieve a better response. Such a strategy may require subsequent lowering of dosage when higher dosages produce adverse effects or no further clinical improvement. The best dosage for a given patient is the one that provides optimum therapeutic effects with minimal adverse effects. Dosing schedules also may vary, although there currently are no consistent controlled studies comparing alternative dosing schedules. Patients who require relief only during school may respond adequately to a 5-day (i.e., school day) regimen while those requiring relief at home and school may need a daily regimen throughout the week.

As an adjunct in the treatment of ADHD in children 6 years of age and older, the initial dosage of dextroamphetamine sulfate given in conventional (short-acting) preparations is 5 mg once or twice daily; daily dosage is increased by 5 mg at weekly intervals until the optimum response is attained. The usual dosage range is 5–15 mg twice daily or 5–10 mg 3 times daily. Total daily dosage rarely should exceed 40 mg. In children 3–5 years of age, the initial daily dosage is 2.5 mg; daily dosage is increased by 2.5 mg at weekly intervals until the optimum response is attained. When the drug is administered as conventional tablets in divided doses (2 or 3), additional doses are given at intervals of 4–6 hours. Dextroamphetamine sulfate extended-release capsules can be substituted for their respective conventional short-acting preparations if less frequent daily dosing is desirable.

Dextroamphetamine sulfate in fixed combination with other amphetamines (dextroamphetamine sulfate, dextroamphetamine saccharate, amphetamine aspartate, and amphetamine sulfate) also is used as an adjunct in the treatment of ADHD in children 6 years of age and older; the initial total dosage of amphetamines is 5 mg once or twice daily. The daily dosage is increased by 5 mg at weekly intervals until the optimum response is attained; total daily dosage rarely should exceed 40 mg. In children 3–5 years of age, the initial daily dosage is 2.5 mg; daily dosage is increased by 2.5 mg at weekly intervals until the optimum response is attained. The manufacturer recommends that the initial dose of dextroamphetamine sulfate in fixed combination with other amphetamines be given on awakening; additional doses (1 or 2) are given at intervals of 4–6 hours. The usual dosage for intermediate-acting preparations (e.g., Dexedrine® Spansules®, Adderall®) in children 6 years of age and older is 5–30 mg once daily or 5–15 mg twice daily.

Alternatively, in patients who are receiving drug therapy for ADHD for the first time or are being switched from therapy with another stimulant, dextroamphetamine therapy may be initiated with extended-release capsules containing dextroamphetamine sulfate in fixed-combination with dextroamphetamine saccharate, amphetamine aspartate, and amphetamine sulfate (Adderall XR®). In children 6–12 years of age, the initial dosage of total amphetamines as fixed-combination extended-release capsules (Adderall XR®) is 10 mg once daily; daily dosage may be increased in increments of 5 or 10 mg at weekly intervals to a maximum dosage of 30 mg daily. Treatment may be initiated with a dosage of 5 mg once daily when, in the opinion of the clinician, a lower initial dosage is appropriate. The usual dosage for such longer-acting preparations (e.g., Adderall XR®) is 10–30 mg daily. In adolescents 13–17 years of age, the initial dosage of total amphetamines as fixed-combination extended-release capsules (Adderall XR®) is 10 mg once daily. Dosage may be increased to 20 mg once daily after 1 week if symptoms are not adequately controlled. In adults who are receiving drug therapy for ADHD for the first time or are being switched from therapy with another drug, the recommended dosage of amphetamines as fixed-combination extended-release capsules (Adderall XR®) is 20 mg once daily. Although dosages of up to 60 mg daily (as fixed-combination extended-release capsules) have been used in adolescents 13–17 years of age and adults in clinical studies, there is no evidence that dosages exceeding 20 mg daily provide any additional benefit in these patients. When switching from fixed-combination conventional tablets (Adderall®) to fixed-combination extended-release capsules (Adderall XR®), the total daily dosage of amphetamines may remain the same but should be given once daily.

When possible, therapy should be interrupted occasionally to determine if there is a recurrence of behavioral symptoms sufficient to require continued treatment. Long-term use of fixed-combination extended-release capsules (i.e., more than 3 weeks in children or more than 4 weeks in adolescents or adults) has not been studied systematically. If fixed-combination extended-release capsules are used for extended periods, the usefulness of the drug should be periodically reevaluated.

Cautions

Dextroamphetamine shares the toxic potentials of amphetamines, and the usual cautions, precautions, and contraindications of amphetamine therapy should be observed. (See Cautions in the Amphetamines General Statement 28:20.04.)

Some commercially available preparations of dextroamphetamine (e.g., DextroStat®, Dexedrine® tablets) contain the dye tartrazine (FD&C yellow No. 5), which may cause allergic reactions including bronchial asthma in susceptible individuals. Although the incidence of tartrazine sensitivity is low, it frequently occurs in patients who are sensitive to aspirin.

Chemistry and Stability

■ **Chemistry** Dextroamphetamine is the dextrorotatory isomer of amphetamine. Dextroamphetamine sulfate occurs as a white, odorless, crystalline powder and has a bitter taste. Dextroamphetamine sulfate is freely soluble in water (about 1:10) and slightly soluble in alcohol (about 1:800). Dextroamphetamine sulfate also is commercially available as fixed-combination preparations with dextroamphetamine saccharate, amphetamine aspartate, and amphetamine sulfate.

■ **Stability** Preparations containing dextroamphetamine sulfate should be stored in tight, light-resistant containers at 15–30°C.

Preparations

Dextroamphetamine and dextroamphetamine sulfate preparations are subject to control under the Federal Controlled Substances Act of 1970 as schedule II (C-II) drugs.

Excipients in commercially available drug preparations may have clinically important effects in some individuals; consult specific product labeling for details.

Dextroamphetamine Sulfate

Oral		
Capsules, extended-release	5 mg*	**Dexedrine® Spansule® (C-II), GlaxoSmithKline**
		Dextroamphetamine Sulfate Capsules SR (C-II)
	10 mg*	**Dexedrine® Spansule® (C-II), GlaxoSmithKline**
		Dextroamphetamine Sulfate Capsules SR (C-II)
	15 mg*	**Dexedrine® Spansule® (C-II), GlaxoSmithKline**
		Dextroamphetamine Sulfate Capsules SR (C-II)
Tablets	5 mg*	**Dexedrine® (C-II; scored), GlaxoSmithKline**
		Dextroamphetamine Sulfate Tablets (C-II; scored)
		DextroStat® (C-II; scored), Shire
	10 mg*	**Dextroamphetamine Sulfate Tablets (C-II; scored)**
		DextroStat® (C-II; double-scored), Shire

*available from one or more manufacturer, distributor, and/or repackager by generic (nonproprietary) name

Dextroamphetamine Sulfate Combinations

Oral		
Capsules, extended-release	5 mg total amphetamine (as 1.25 mg with Amphetamine Sulfate 1.25 mg, Amphetamine Aspartate 1.25 mg, and Dextroamphetamine Saccharate 1.25 mg)	**Adderall XR® (C-II), Shire**
	10 mg total amphetamine (as 2.5 mg with Amphetamine Sulfate 2.5 mg, Amphetamine Aspartate 2.5 mg, and Dextroamphetamine Saccharate 2.5 mg)	**Adderall XR® (C-II), Shire**
	15 mg total amphetamine (as 3.75 mg with Amphetamine Sulfate 3.75 mg, Amphetamine Aspartate 3.75 mg, and Dextroamphetamine Saccharate 3.75 mg)	**Adderall XR® (C-II), Shire**
	20 mg total amphetamine (as 5 mg with Amphetamine Sulfate 5 mg, Amphetamine Aspartate 5 mg, and Dextroamphetamine Saccharate 5 mg)	**Adderall XR® (C-II), Shire**
	25 mg total amphetamine (as 6.25 mg with Amphetamine Sulfate 6.25 mg, Amphetamine Aspartate 6.25 mg, and Dextroamphetamine Saccharate 6.25 mg)	**Adderall XR® (C-II), Shire**
	30 mg total amphetamine (as 7.5 mg with Amphetamine Sulfate 7.5 mg, Amphetamine Aspartate 7.5 mg, and Dextroamphetamine Saccharate 7.5 mg)	**Adderall XR® (C-II), Shire**
Tablets	5 mg total amphetamine (as 1.25 mg with Amphetamine Aspartate 1.25 mg, Amphetamine Sulfate 1.25 mg, and Dextroamphetamine Saccharate 1.25 mg)*	**Adderall® (C-II; double-scored), Shire**
		Dextroamphetamine Saccharate, Amphetamine Aspartate, Dextroamphetamine Sulfate, and Amphetamine Sulfate Tablets (C-II; double-scored)
	7.5 mg total amphetamine (as 1.875 mg with Amphetamine Aspartate 1.875 mg, Amphetamine Sulfate 1.875 mg, and Dextroamphetamine Saccharate 1.875 mg)*	**Adderall® (C-II; double-scored), Shire**
		Dextroamphetamine Saccharate, Amphetamine Aspartate, Dextroamphetamine Sulfate, and Amphetamine Sulfate Tablets (C-II; double-scored)
	10 mg total amphetamine (as 2.5 mg with Amphetamine Aspartate 2.5 mg, Amphetamine Sulfate 2.5 mg, and Dextroamphetamine Saccharate 2.5 mg)*	**Adderall® (C-II; double-scored), Shire**
		Dextroamphetamine Saccharate, Amphetamine Aspartate, Dextroamphetamine Sulfate, and Amphetamine Sulfate Tablets (C-II; double-scored)
	12.5 mg total amphetamine (as 3.125 mg with Amphetamine Aspartate 3.125 mg, Amphetamine Sulfate 3.125 mg, and Dextroamphetamine Saccharate 3.125 mg)*	**Adderall® (C-II; double-scored), Shire**
		Dextroamphetamine Saccharate, Amphetamine Aspartate, Dextroamphetamine Sulfate, and Amphetamine Sulfate Tablets (C-II; double-scored)
	15 mg total amphetamine (as 3.75 mg with Amphetamine Aspartate 3.75 mg, Amphetamine Sulfate 3.75 mg, and Dextroamphetamine Saccharate 3.75 mg)*	**Adderall® (C-II; double-scored), Shire**
		Dextroamphetamine Saccharate, Amphetamine Aspartate, Dextroamphetamine Sulfate, and Amphetamine Sulfate Tablets (C-II; double-scored)
	20 mg total amphetamine (as 5 mg with Amphetamine Aspartate 5 mg, Amphetamine Sulfate 5 mg, and Dextroamphetamine Saccharate 5 mg)*	**Adderall® (C-II; double-scored), Shire**
		Dextroamphetamine Saccharate, Amphetamine Aspartate, Dextroamphetamine Sulfate, and Amphetamine Sulfate Tablets (C-II; double-scored)
	30 mg total amphetamine (as 7.5 mg with Amphetamine Aspartate 7.5 mg, Amphetamine Sulfate 7.5 mg, and Dextroamphetamine Saccharate 7.5 mg)*	**Adderall® (C-II; double-scored), Shire**
		Dextroamphetamine Saccharate, Amphetamine Aspartate, Dextroamphetamine Sulfate and Amphetamine Sulfate Tablets (C-II; double-scored)

*available from one or more manufacturer, distributor, and/or repackager by generic (nonproprietary) name

Lisdexamfetamine Dimesylate

■ Prodrug of dextroamphetamine; noncatechol, sympathomimetic amine with CNS-stimulating activity.

Uses

■ **Attention-Deficit Hyperactivity Disorder** Lisdexamfetamine dimesylate is used as an adjunct to psychological, educational, social, and other remedial measures in the treatment of attention deficit hyperactivity disorder (ADHD) (hyperkinetic disorder, hyperkinetic syndrome of childhood, minimal brain dysfunction). Safety and efficacy for this indication have been established in controlled clinical trials in children 6–12 years of age and in adults.

Safety and efficacy of lisdexamfetamine dimesylate in the treatment of ADHD in children 6–12 years of age who met DSM-IV-TR criteria for ADHD (combined type or predominantly hyperactive-impulsive type) have been evaluated in 2 randomized, double-blind, placebo-controlled clinical studies (one phase 2 and one phase 3). The phase 2 crossover study was conducted in an analog classroom environment. In this study, dosage of amphetamines was titrated over a 3-week period using an extended-release formulation of mixed amphetamine salts (Adderall XR®) to a final dosage of 10, 20, or 30 mg daily; the children then were assigned to receive, in randomly determined sequence, 1 week each of treatment with extended-release mixed amphetamine salts (continued at the same dosage), lisdexamfetamine dimesylate (30, 50, or 70 mg

■ **CNS-active Drugs** Potential pharmacologic interaction when given with or substituted for other centrally acting drugs, including those with a similar mechanism of action; use with caution.

■ **5-HT$_1$ Receptor Agonists ("Triptans")** Pharmacologic interaction (potentially life-threatening serotonin syndrome) if used concurrently with 5-HT$_1$ receptor agonists (e.g., almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, zolmitriptan). If concomitant use is clinically warranted, the patient should be observed carefully, particularly during treatment initiation, when dosage is increased, or when another serotonergic agent is initiated. (See Serotonin Syndrome under Warnings/Precautions:Other Warnings and Precautions, in Cautions.)

■ **Monoamine Oxidase (MAO) Inhibitors** Pharmacologic interaction (potentially fatal serotonin syndrome); concomitant use is contraindicated. The manufacturer recommends that at least 2 weeks should elapse between discontinuance of an MAO inhibitor and initiation of duloxetine and that at least 5 days elapse between discontinuance of duloxetine therapy and initiation of MAO inhibitor therapy. (See Serotonin Syndrome under Warnings/Precautions:Other Warnings and Precautions, in Cautions.)

■ **Selective Serotonin-reuptake Inhibitors and Selective Serotonin- and Norepinephrine-reuptake Inhibitors** Potential pharmacologic interaction (potentially life-threatening serotonin syndrome); concurrent administration not recommended. (See Serotonin Syndrome under Warnings/Precautions:Other Warnings and Precautions, in Cautions.)

Concomitant administration of duloxetine and fluvoxamine, a potent CYP1A2 inhibitor, in poor CYP2D6 metabolizers resulted in a six-fold increase in duloxetine AUCs and peak plasma concentrations.

■ **Serotonergic Drugs** Potential pharmacologic interaction (potentially life-threatening serotonin syndrome) with drugs affecting serotonergic neurotransmission, including linezolid (an anti-infective agent that is a nonselective, reversible MAO inhibitor), lithium, tramadol, and St. John's wort *(Hypericum perforatum)*; use with caution. Concurrent administration of serotonin precursors (such as tryptophan) is not recommended. (See Serotonin Syndrome under Warnings/Precautions: Other Warnings and Precautions, in Cautions.)

■ **Smoking** Potential pharmacokinetic interaction (reduced duloxetine bioavailability and plasma concentrations). The manufacturer states that routine dosage adjustment is not necessary. However, some clinicians recommend a small increase in duloxetine dosage (about 15%) in patients who smoke.

■ **Theophylline** Although small increases (averaging from 7–20%) in theophylline AUCs have been reported during concurrent administration of theophylline and duloxetine; combined use of these drugs reportedly has been well tolerated and routine theophylline dosage adjustment does not appear to be necessary during concomitant administration.

■ **Thioridazine** Potential pharmacokinetic (increased plasma thioridazine concentrations) interaction with resulting increased risk of serious ventricular arrhythmias and sudden death; concomitant use is not recommended by manufacturer of duloxetine.

Description

Duloxetine hydrochloride, a selective serotonin- and norepinephrine-reuptake inhibitor (SNRI), is an antidepressant and anxiolytic agent. The drug also has demonstrated analgesic activity in animal models of chronic and persistent pain and in clinical trials evaluating the drug's activity in conditions associated with chronic pain (e.g., neuropathic pain, fibromyalgia). Duloxetine hydrochloride is pharmacologically related to venlafaxine hydrochloride and desvenlafaxine succinate.

The exact mechanisms of the antidepressant, anxiolytic, and central pain inhibitory actions of duloxetine have not been fully elucidated, but appear to be associated with the drug's potentiation of serotonergic and norudrenergic activity in the CNS. Like venlafaxine and desvenlafaxine, duloxetine is a potent inhibitor of neuronal serotonin and norepinephrine reuptake and a less potent inhibitor of dopamine reuptake. Duloxetine does not inhibit monoamine oxidase (MAO) and has not demonstrated significant affinity for dopaminergic, adrenergic, cholinergic, γ-aminobutyric acid (GABA), glutamate, histaminergic, and opiate receptors in vitro.

Although the precise mechanism of action of duloxetine in stress urinary incontinence is unknown, it is thought to be related to potentiation of serotonin and norepinephrine activity in the sacral spinal cord, which increases urethral closure forces and thereby reduces involuntary urine loss.

Duloxetine is extensively metabolized in the liver, principally via oxidation by the cytochrome P-450 (CYP) 2D6 and 1A2 isoenzymes. Duloxetine is a moderate inhibitor of CYP2D6 and a somewhat weak inhibitor of CYP1A2. The drug is not an inhibitor of CYP2C9, CYP2C19, or CYP3A, nor is it an inducer of CYP1A2 or CYP3A.

Advice to Patients

Risk of suicidality; importance of patients, family, and caregivers being alert to and immediately reporting emergence of suicidality, worsening depression, or unusual changes in behavior, especially during the first few months of therapy or during periods of dosage adjustment. FDA recommends providing written patient information (medication guide) explaining risks of suicidality each time the drug is dispensed.

Importance of promptly reporting any manifestations of liver dysfunction (e.g., pruritus, dark urine, jaundice, right upper quadrant tenderness, unexplained flu-like symptoms) to clinician.

Importance of informing patient of risk of severe liver injury associated with concomitant use of duloxetine and heavy alcohol intake. (See Hepatic Effects under Warnings/Precautions: Other Warnings and Precautions and also see Drug Interactions: Alcohol.)

Risk of psychomotor impairment; importance of exercising caution while operating hazardous machinery, including automobile driving, until patient gains experience with the drug's effects.

Importance of advising patients of risk of orthostatic hypotension and syncope, particularly during initial therapy and subsequent dosage escalation and during concomitant therapy with drugs that may potentiate the orthostatic effect of duloxetine.

Importance of informing patients of risk of serotonin syndrome with concurrent use of duloxetine and 5-HT$_1$ receptor agonists (also called triptans), tramadol, or other serotonergic agents. Importance of seeking immediate medical attention if symptoms of serotonin syndrome develop.

Importance of taking medication exactly as prescribed by the clinician. Importance of informing patients that the delayed-release capsules should be swallowed whole and should not be chewed or crushed, nor should the capsule contents be sprinkled on food or mixed with liquids.

Importance of continuing duloxetine therapy even if a response is not evident within 1–4 weeks, unless directed otherwise.

Importance of women informing clinicians if they are or plan to become pregnant or plan to breast-feed.

Importance of informing clinicians of existing or contemplated concomitant therapy, including prescription and OTC drugs, as well as any concomitant illnesses (e.g., bipolar disorder, liver disease) or family history of suicidality or bipolar disorder. Risk of bleeding associated with concomitant use of duloxetine with aspirin or other nonsteroidal anti-inflammatory agents, warfarin, or other drugs that affect coagulation.

Importance of informing patients of other important precautionary information. (See Cautions.)

Overview[a] (see Users Guide). For additional information on this drug until a more detailed monograph is developed and published, the manufacturer's labeling should be consulted. It is *essential* that the manufacturer's labeling be consulted for more detailed information on usual cautions, precautions, contraindications, potential drug interactions, laboratory test interferences, and acute toxicity.

Preparations

Excipients in commercially available drug preparations may have clinically important effects in some individuals; consult specific product labeling for details.

Duloxetine Hydrochloride

Oral		
Capsules, delayed-release (containing enteric-coated pellets)	20 mg (of duloxetine)	**Cymbalta®, Lilly**
	30 mg (of duloxetine)	**Cymbalta®, Lilly**
	60 mg (of duloxetine)	**Cymbalta®, Lilly**

†Use is not currently included in the labeling approved by the US Food and Drug Administration

Venlafaxine Hydrochloride

■ Venlafaxine hydrochloride, a selective serotonin- and norepinephrine-reuptake inhibitor (SNRI), is a phenylethylamine-derivative antidepressant and anxiolytic agent.

Uses

■ **Major Depressive Disorder** Venlafaxine hydrochloride is used in the treatment of major depressive disorder. Efficacy of venlafaxine conventional tablets for the management of major depression has been established in several placebo-controlled studies in outpatient settings in patients who had major depression and in 1 placebo-controlled study in a hospital setting in patients who had major depression with melancholia. Efficacy of venlafaxine extended-release capsules for the treatment of major depression also has been established by controlled studies of 8–12 weeks' duration in outpatient settings; however, the safety and efficacy of venlafaxine extended-release capsules in hospitalized patients with major depression have not been adequately evaluated.

In 4 studies of 6 weeks' duration in adult outpatients with major depression, venlafaxine in dosages of 75–225 mg daily administered in 2 or 3 divided doses as conventional tablets was found to be superior to placebo on at least 2 of the following 3 clinical measures of depression: Hamilton Depression Rating Scale (HAM-D) total score, HAM-D depressed mood item, and the Clinical Global

Impression (CGI) Severity of Illness Scale. In these studies, higher dosages (i.e., dosages exceeding 225 mg daily) were not associated with greater response. In 2 short-term (8 or 12 weeks), placebo-controlled, flexible-dose (75–225 mg daily) studies with venlafaxine extended-release capsules in adult outpatients, venlafaxine was found to be superior to placebo on the same clinical measures of depression that were used in the studies of venlafaxine conventional tablets, as well as on the Montgomery-Asberg Depression Rating Scale (MADRS) total score and certain factors of the HAM-D, including the anxiety/somatization factor, the cognitive disturbance factor, the retardation factor, and the psychic anxiety score.

Venlafaxine also has been shown to be superior to placebo in the management of major depression with melancholia in a hospital setting. In a study of 4 weeks' duration, 65% of hospitalized patients with major depressive disorder and melancholia who received venlafaxine 150–375 mg daily (mean dosage of 350 mg daily) administered in 3 divided doses as conventional tablets had at least a 50% reduction in MADRS total score compared with 28% of those who received placebo. Patients who participated in this study had a mean baseline MADRS total score of 35 (range: 26–48); those with a baseline score of 4 or greater on the suicidal thought item of the MADRS were excluded from the study.

Results of long-term, relapse prevention studies in outpatients with major depression indicate that venlafaxine's antidepressant effects are maintained for up to 1 year. In these studies, patients who responded to an initial 8-week course of venlafaxine 75–225 mg once daily (as extended-release capsules) or an initial 26-week course of venlafaxine 100–200 mg daily in 2 divided doses (as conventional tablets) were randomized to receive either venlafaxine (same dosage range) or placebo. Patients receiving venlafaxine experienced substantially lower relapse rates than those receiving placebo. Relapse was defined in clinical studies with venlafaxine conventional tablets as a score of 4 or greater on the CGI Severity of Illness Scale and in clinical studies with venlafaxine extended-release capsules as a reappearance of major depressive disorder as defined by DSM-IV criteria and a CGI Severity of Illness score of 4 or greater (i.e., moderately severe depression), 2 consecutive scores of 4 or greater on the CGI Severity of Illness Scale, or a final CGI Severity of Illness score of 4 or greater for any patient who withdrew from the study for any reason.

For further information on treatment of major depressive disorder and considerations in choosing the most appropriate antidepressant for a particular patient, including considerations related to patient tolerance, patient age, and cardiovascular, sedative, and suicidal risk, see Considerations in Choosing Antidepressants under Uses: Major Depressive Disorder, in Fluoxetine Hydrochloride 28:16.04.20.

■ **Generalized Anxiety Disorder** Venlafaxine hydrochloride is used in the treatment of generalized anxiety disorder. Efficacy of venlafaxine extended-release capsules for the management of generalized anxiety disorder has been established in 4 randomized, multicenter, placebo-controlled studies of 2 or 6 months' duration in adult outpatients who met DSM-IV criteria for generalized anxiety disorder. Three studies employed fixed venlafaxine dosages, and the other employed a flexible dosing schedule. In the flexible-dose study, approximately 69% of patients receiving venlafaxine (75–225 mg daily as extended-release capsules) were categorized as responders (defined as a 40% or greater reduction from baseline in the Hamilton Rating Scale for Anxiety [HAM-A] total score or a score of 1 ["very much improved"] or 2 ["much improved"] on the Clinical Global Impressions [CGI] Global Improvement Scale) during weeks 6–28 of therapy compared with 42–46% of those receiving placebo. In separate clinical studies of 2 or 6 months' duration employing fixed dosages of venlafaxine (37.5, 75, 150, or 225 mg daily as extended-release capsules), venlafaxine was shown to be substantially more effective than placebo on HAM-A total score, both the HAM-A anxiety and tension items, and the CGI Scale. While a relationship between dosage (over the dosage range of 75–225 mg daily) and efficacy in generalized anxiety disorder has not been definitively established, dosages of 37.5 mg daily were not as consistently effective in one study as dosages of 75 or 150 mg daily.

■ **Social Phobia** Venlafaxine hydrochloride is used in the treatment of social phobia (social anxiety disorder). Efficacy of venlafaxine extended-release capsules in the treatment of social phobia has been established in 2 multicenter, placebo-controlled studies of 12 weeks' duration in adult outpatients who met DSM-IV criteria for social phobia. In these studies, venlafaxine (75–225 mg daily administered as extended-release capsules) was substantially more effective than placebo, as determined by change from baseline in the Liebowitz Social Anxiety Scale (LSAS) total score.

Subgroup analysis of these controlled studies in adult outpatients with social anxiety disorder did not reveal any evidence of gender-related differences in treatment outcome; there was insufficient information to determine the effect of age or race on outcome in these studies.

■ **Panic Disorder** Venlafaxine hydrochloride is used in the treatment of panic disorder with or without agoraphobia. Efficacy of venlafaxine extended-release capsules in the treatment of panic disorder has mainly been established in 2 multicenter, double-blind, placebo-controlled studies of 12 weeks' duration in adult outpatients who met DSM-IV criteria for panic disorder with or without agoraphobia. Venlafaxine was given in a fixed dosage of 75 or 150 mg once daily as extended-release capsules in one study and in a fixed dosage of 75 or 225 mg once daily as extended-release capsules in the other study. Venlafaxine was found to be substantially more effective than placebo, as determined by percentage of patients free of full-symptom attacks on the Panic and Anticipatory Anxiety Scale (PAAS), mean change from baseline on the Panic Disorder Severity Scale (PDSS) total score, and the percentage of patients rated as responders on the Clinical Global Impressions (CGI) Improvement Scale. While a relationship between dosage (over the dosage range of 75–225 mg daily) and efficacy in panic disorder has not been definitively established, efficacy was established for each dosage studied in these 2 trials.

Subgroup analysis of these controlled studies in adult outpatients with panic disorder did not reveal any evidence of gender-related differences in treatment outcome; there was insufficient information to determine the effect of age or race on outcome in these studies.

In a longer-term study, patients meeting DSM-IV criteria for panic disorder who had responded during the 12-week open phase of a clinical trial with venlafaxine (75, 150, or 225 mg once daily as extended-release capsules) were randomly assigned to either continue receiving venlafaxine in the same dosage range or be switched to placebo and observed for relapse. Relapse was defined as having 2 or more full-symptom panic attacks per week for 2 consecutive weeks or having discontinued therapy due to loss of effectiveness as determined by the study investigators. Patients who continued receiving venlafaxine therapy experienced a significantly longer time to relapse than those receiving placebo in this study.

■ **Vasomotor Symptoms** Venlafaxine has been used for the management of vasomotor symptoms† in women with breast cancer and in postmenopausal women. Therapy with the drug has improved both the frequency and severity of vasomotor symptoms (hot flushes [flushes]) in these women.

Most women receiving systemic antineoplastic therapy for breast cancer experience vasomotor symptoms, particularly those receiving tamoxifen therapy. In a randomized, double-blind, placebo-controlled study in 191 women with breast cancer (69% were receiving tamoxifen) who were experiencing 2 or more episodes of hot flushes daily, the percentage reductions in hot flush severity score at 4 weeks of treatment were 27% for placebo, 37% for venlafaxine 37.5 mg daily, 61% for venlafaxine 75 mg daily, and 61% for venlafaxine 150 mg daily. Comparisons among treatment groups showed that all 3 venlafaxine dosages were associated with a statistically significant reduction in hot flush frequency and severity; in addition, the 75-mg dosage was more effective than the 37.5-mg dosage, but the 150-mg dosage provided no additional benefit. The role of venlafaxine in managing vasomotor symptoms in women with breast cancer relative to other nonhormonal therapies (e.g., selective serotonin-reuptake inhibitors [SSRIs], gabapentin) remains to be determined. Well-designed, comparative studies are needed to establish optimum nonhormonal therapy, both in terms of efficacy and patient tolerance of adverse effects in these women.

Because of the risks associated with hormone replacement therapy (HRT) for vasomotor symptoms in perimenopausal and postmenopausal women, alternative nonhormonal therapies are being investigated. In a randomized, double-blind, placebo-controlled study in 80 postmenopausal women who were experiencing more than 14 hot flushes weekly, 12 weeks of venlafaxine 75 mg daily was associated with a 51% reduction in hot flush score (patient's perception of hot flush interference with daily living). Although there also was a reduction in hot flush severity, the difference did not reach statistical significance. The role of venlafaxine therapy relative to other nonhormonal therapies (e.g., SSRIs, gabapentin) for postmenopausal vasomotor symptoms, both in terms of efficacy and safety, remains to be established.

Current evidence indicates that venlafaxine is well tolerated in the short-term treatment of vasomotor symptoms associated with breast cancer treatment and with menopause. The principal adverse effects associated with venlafaxine therapy in women with vasomotor symptoms have been dry mouth, decreased appetite, nausea, constipation, and difficulty sleeping. Additional study and experience are needed to further elucidate the role of venlafaxine relative to other nonhormonal therapies and to establish longer-term (i.e., beyond 4–12 weeks) efficacy and safety.

The possible role of venlafaxine in the management of vasomotor symptoms† associated with antiandrogenic therapy in men with prostate cancer remains to be determined.

■ **Obesity** Although substantial changes in appetite and weight have been reported in clinical studies of venlafaxine for the management of major depression, generalized anxiety disorder, social phobia, and panic disorder, the manufacturer states that the drug, alone or in combination with weight loss agents such as phentermine, is *not* indicated for the management of exogenous obesity†. Concomitant use of venlafaxine and weight loss agents also is not recommended by the manufacturer because the safety and efficacy of these agents when used concomitantly have not been established.

Dosage and Administration

■ **Administration** Venlafaxine hydrochloride is administered orally. To minimize GI intolerance (e.g., nausea), the manufacturer recommends that conventional venlafaxine tablets be taken with food. Food does not appear to affect GI absorption of the drug. Venlafaxine extended-release capsules should be administered as a single daily dose with food at approximately the same time each day (in the morning or evening). The extended-release capsules should be swallowed whole with fluid or the entire contents of a capsule(s) may be sprinkled on a small amount of applesauce immediately prior to administration. The extended-release capsules of venlafaxine and their contents should not be divided, crushed, chewed, or placed in water. If the capsule contents are administered by sprinkling on applesauce, the patient should drink some water

after swallowing the entire mixture without chewing to ensure that the pellets are completely swallowed.

Risk of Sustained Hypertension Venlafaxine therapy has been associated with sustained increases in blood pressure in some patients. An analysis of patients with sustained hypertension and patients whose hypertension resulted in discontinuance of the drug revealed that most blood pressure elevations were modest in severity (i.e., 10–15 or 8–28 mm Hg increases in supine diastolic blood pressure among patients receiving conventional or extended-release venlafaxine, respectively). However, sustained blood pressure increases of this magnitude could have adverse consequences in patients receiving the drug. In addition, some cases of elevated blood pressure requiring immediate treatment have been reported during postmarketing surveillance of the drug. Therefore, the manufacturer recommends that preexisting hypertension be controlled before initiating venlafaxine therapy and that regular blood pressure monitoring be performed in patients receiving the drug. In patients who experience a sustained increase in blood pressure during venlafaxine therapy, dosage reduction or discontinuance of the drug should be considered.

Risk of Serotonin Syndrome or Neuroleptic Malignant Syndrome (NMS)-like Reactions Potentially life-threatening serotonin syndrome or neuroleptic malignant syndrome (NMS)-like reactions have been reported with selective serotonin- and norepinephrine-reuptake inhibitors (SNRIs), including venlafaxine, and selective serotonin-reuptake inhibitors (SSRIs) alone, but particularly with concurrent use of other serotonergic drugs (including serotonin [5-hydroxytryptamine; 5-HT] type 1 receptor agonists ["triptans"], drugs that impair the metabolism of serotonin [e.g., monoamine oxidase inhibitors], or antipsychotics or other dopamine antagonists). Manifestations of serotonin syndrome may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination), and/or GI symptoms (e.g., nausea, vomiting, diarrhea). In its most severe form, serotonin syndrome may resemble NMS, which is characterized by hyperthermia, muscle rigidity, autonomic instability with possible rapid fluctuation in vital signs, and mental status changes. Patients receiving venlafaxine should be monitored for the development of serotonin syndrome or NMS-like signs and symptoms.

Serious (sometimes fatal) adverse reactions, possibly related to serotonin syndrome or NMS, have been reported in patients who received a monoamine oxidase (MAO) inhibitor shortly before or after venlafaxine therapy. Therefore, concomitant use of venlafaxine and MAO inhibitors is *contraindicated*. It is recommended that at least 2 weeks elapse between discontinuance of an MAO inhibitor and initiation of venlafaxine and that an interval of at least 1 week elapse between discontinuance of venlafaxine and initiation of an MAO inhibitor.

If concurrent therapy with venlafaxine and a 5-HT$_1$ receptor agonist (triptan) is clinically warranted, the patient should be observed carefully, particularly during initiation of therapy, when dosage is increased, or when another serotonergic agent is initiated. Concurrent use of venlafaxine and serotonin precursors (e.g., tryptophan) is not recommended.

If signs and symptoms of serotonin syndrome or NMS develop during venlafaxine therapy, treatment with venlafaxine and any concurrently administered serotonergic or antidopaminergic agents, including antipsychotic agents, should be discontinued immediately and supportive and symptomatic treatment should be initiated.

For additional information on serotonin syndrome, see Drug Interactions: Serotonergic Drugs, in Fluoxetine Hydrochloride 28:16.04.20.

Risk of Suicidality and Overdosage Worsening of depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior may occur in both adult and pediatric (see Administration: Pediatric Precautions, in Dosage and Administration) patients with major depressive disorder or other psychiatric disorders, whether or not they are taking antidepressants. This risk may persist until clinically important remission occurs. Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are the strongest predictors of suicide. However, there has been a long-standing concern that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients during the early phases of treatment. Pooled analyses of short-term, placebo-controlled studies of antidepressants (i.e., selective serotonin-reuptake inhibitors and other antidepressants) have shown an increased risk of suicidality in children, adolescents, and young adults (18–24 years of age) with major depressive disorder and other psychiatric disorders. An increased suicidality risk was not demonstrated with antidepressants compared with placebo in adults older than 24 years of age and a reduced risk was observed in adults 65 years of age or older. It is currently unknown whether the suicidality risk extends to longer-term use (i.e., beyond several months); however, there is substantial evidence from placebo-controlled maintenance trials in adults with major depressive disorder that antidepressants can delay the recurrence of depression.

The US Food and Drug Administration (FDA) recommends that all patients being treated with antidepressants for any indication be appropriately monitored and closely observed for clinical worsening, suicidality, and unusual changes in behavior, particularly during initiation of therapy (i.e., the first few months) and during periods of dosage adjustments. Families and caregivers of patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and nonpsychiatric, should be advised to monitor patients on a daily basis for the emergence of agitation, irritability, or unusual changes in behavior, as well as the emergence of suicidality, and to report such symptoms immediately to a health-care provider.

Although a causal relationship between the emergence of symptoms such as anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia, hypomania, and/or mania and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality. Consequently, consideration should be given to changing the therapeutic regimen or discontinuing therapy in patients whose depression is persistently worse or in patients experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, particularly if such manifestations are severe, abrupt in onset, or were not part of the patient's presenting symptoms. If a decision is made to discontinue therapy, venlafaxine dosage should be tapered as rapidly as is feasible but with recognition of the risks of abrupt discontinuance. (See Discontinuance of Therapy under Dosage and Administration: Dosage.)

The results of retrospective studies indicate that venlafaxine overdosage may be associated with an increased risk of fatal outcome compared with that observed with SSRIs but lower than that associated with tricyclic antidepressants. Epidemiologic studies have shown that venlafaxine-treated patients have a higher preexisting burden of suicide risk factors than patients treated with SSRIs. The extent to which the finding of an increased risk of fatal outcomes can be attributed to the toxicity of venlafaxine in an overdosage as opposed to other characteristics of these venlafaxine-treated patients is not clear. As with other antidepressants, FDA and the manufacturer of venlafaxine recommend that the drug be prescribed in the smallest quantity consistent with good patient management, in order to reduce the risk of overdosage.

Risk of Bipolar Disorder It is generally believed (though not established in controlled trials) that treating a major depressive episode with an antidepressant alone may increase the likelihood of precipitating a mixed or manic episode in patients at risk for bipolar disorder. Therefore, patients should be adequately screened for bipolar disorder prior to initiating treatment with an antidepressant; such screening should include a detailed psychiatric history (e.g., family history of suicide, bipolar disorder, and depression). Venlafaxine is *not* approved for use in treating bipolar depression.

Risk of Mydriasis Mydriasis has been reported in association with venlafaxine therapy. Therefore, patients with elevated intraocular pressure or those at risk of angle-closure glaucoma should be monitored during treatment with the drug.

Pediatric Precautions Safety and efficacy of venlafaxine in children younger than 18 years of age have not been established.

Although clinical studies designed to primarily assess the effect of venlafaxine on the growth, development, and maturation of children and adolescents have not been conducted to date, the results from available studies suggest that the drug may adversely affect weight, height, and appetite. Should the decision be made to prescribe venlafaxine for unlabeled (off-label) uses in pediatric patients, the manufacturer recommends regular monitoring of height and weight during therapy, particularly during long-term administration of the drug. In addition, the manufacturer states that the long-term safety of therapy with venlafaxine extended-release capsules (beyond 6 months) has not been systematically evaluated to date. Because the results of clinical studies indicate that the occurrence of blood pressure elevations considered to be clinically important in children and adolescents was similar to that observed in adults receiving venlafaxine, the manufacturer advises that the precautions for adults also should apply to pediatric patients receiving the drug. (See Risk of Sustained Hypertension under Dosage and Administration: Administration.)

In placebo-controlled clinical studies in children and adolescents† 6–17 years of age, efficacy of venlafaxine (administered as extended-release capsules) was *not* established for major depressive disorder or generalized anxiety disorder, and there were increased reports of hostility and suicide-related adverse events such as suicidal ideation and self-harm. Hostility and suicidal ideation were the most common adverse effects leading to discontinuance of the drug in clinical studies in pediatric patients with major depressive disorder, each occurring in 2% of children and adolescents receiving venlafaxine extended-release capsules compared with less than 1 or 0% of those receiving placebo, respectively. In addition, abnormal/changed behavior was the most common adverse effect leading to discontinuance of the drug in clinical studies in pediatric patients with generalized anxiety disorder, occurring in 1% of children and adolescents receiving venlafaxine extended-release capsules compared with none of those receiving placebo. There were no suicides reported in any of these clinical studies.

FDA has determined that antidepressants increase the risk of suicidal thinking and behavior (suicidality) in children and adolescents with major depressive disorder and other psychiatric disorders. However, the FDA also states that depression and certain other psychiatric disorders are themselves associated with an increased risk of suicide. (See Cautions: Pediatric Precautions, in Fluoxetine Hydrochloride 28:16.04.20.) Anyone considering the use of venlafaxine in a child or adolescent for any clinical use must therefore balance the potential risks with the clinical need. (See Risk of Suicidality and Overdosage under Dosage and Administration: Administration.)

■ **Dosage** Dosage of venlafaxine hydrochloride is expressed in terms of venlafaxine.

Although no overall differences in efficacy or safety were observed between

geriatrie and younger adults receiving venlafaxine, the possibility that some older patients may exhibit increased sensitivity to the drug cannot be ruled out. No age-related differences in the pharmacokinetics of venlafaxine have been identified and dosage adjustments are not necessary for geriatric patients on the basis of age alone; however, as with any drug used for the treatment of depression, generalized anxiety disorder, social phobia, or panic disorder, caution should be used when treating geriatric patients and dosage should be increased cautiously. In addition, the greater frequency of decreased hepatic and renal function observed in the elderly should be considered. (See Dosage and Administration: Dosage in Renal and Hepatic Impairment.)

Venlafaxine also should be used with caution in patients whose underlying medical condition might be compromised by increases in heart rate (e.g., patients with hyperthyroidism, heart failure, or recent myocardial infarction), particularly when the venlafaxine dosage exceeds 200 mg daily.

Patients should be monitored for possible worsening of depression, suicidality, or unusual changes in behavior, especially at the beginning of therapy or during periods of dosage adjustment. (See Risk of Suicidality and Overdosage under Dosage and Administration: Administration.)

Major Depressive Disorder For the treatment of major depressive disorder in adults, the recommended initial dosage of venlafaxine is 75 mg daily administered in 2 or 3 divided doses as conventional tablets or as a single daily dose when using the extended-release capsules. According to the manufacturer, an initial dosage of 37.5 mg daily (as extended-release capsules) for the first 4–7 days (followed by an increase to 75 mg daily) may be considered for some patients. If no clinical improvement is apparent, the dosage may be increased by increments of up to 75 mg daily at intervals of not less than 4 days. If clinically necessary, dosage can be increased up to 225 mg daily in divided doses as conventional tablets or in a single daily dose when using the extended-release capsules. Although studies with venlafaxine conventional tablets in outpatient settings did not demonstrate additional benefit from dosages exceeding 225 mg daily in moderately depressed patients, patients with more severe depression responded to a mean dosage of 350 mg daily. Whether higher dosages of venlafaxine extended-release capsules are needed for more severely depressed patients is unknown; however, the manufacturer states that experience with dosages of venlafaxine extended-release capsules exceeding 225 mg daily is very limited. The manufacturer states that venlafaxine dosage should not exceed 375 mg daily (usually administered in 3 divided doses) as conventional tablets or 225 mg daily as extended-release capsules.

If desired, patients with depression who are undergoing treatment with a therapeutic dose of conventional tablets may be switched to the extended-release capsules at the nearest equivalent daily venlafaxine dose (e.g., change 37.5 mg twice daily administered as conventional tablets to a 75-mg extended-release capsule administered once daily).

Although the optimum duration of venlafaxine therapy has not been established, the manufacturer states that acute depressive episodes require several months or longer of sustained antidepressant therapy. Results of 2 relapse prevention trials indicate that the antidepressant efficacy of venlafaxine is maintained for up to 6 months in patients receiving 75–225 mg once daily as extended-release capsules and for up to 12 months in those receiving 100–200 mg daily in 2 divided doses as conventional tablets. In these studies, the same dosage of venlafaxine was used for both acute-phase and maintenance treatment. Based on these limited data, it is not known whether the dosage required to induce remission of depression would be comparable to that required to maintain euthymia. The usefulness of the drug in patients receiving prolonged therapy should be reevaluated periodically.

Generalized Anxiety Disorder For the management of generalized anxiety disorder in adults, the initial dosage of venlafaxine as extended-release capsules recommended for most patients is 75 mg once daily. In some patients, it may be desirable to initiate therapy with a dosage of 37.5 mg daily given for the first 4–7 days, followed by an increase to 75 mg daily. Although a dose-response relationship for effectiveness in generalized anxiety disorder was not clearly established in clinical studies, certain patients not responding to a venlafaxine dosage of 75 mg daily may benefit from a higher dosage. Dosage in these patients may be increased in increments of up to 75 mg daily at intervals of not less than 4 days up to a maximum dosage of 225 mg daily.

The optimum duration of venlafaxine therapy for the management of generalized anxiety disorder has not been established. Although the drug has been used for up to 6 months in controlled clinical studies, the usefulness of the drug in patients receiving prolonged therapy should be reevaluated periodically.

Social Phobia For the management of social phobia in adults, the recommended initial dosage of venlafaxine for most patients is 75 mg once daily as extended-release capsules. In some patients, it may be desirable to initiate therapy with a dosage of 37.5 mg daily given for the first 4–7 days, followed by an increase to 75 mg daily. Although a dose-response relationship for effectiveness in social phobia was not clearly established in clinical studies, certain patients not responding to a venlafaxine dosage of 75 mg daily may benefit from a higher dosage. Dosage in these patients may be increased in increments of up to 75 mg daily at intervals of not less than 4 days up to a maximum dosage of 225 mg daily.

The optimum duration of venlafaxine therapy for the management of social phobia has not been established. The efficacy of venlafaxine for long-term therapy (i.e., longer than 12 weeks) has not been demonstrated in controlled clinical studies to date. The usefulness of the drug in patients receiving prolonged therapy should be reevaluated periodically.

Panic Disorder For the management of panic disorder in adults, the recommended initial dosage of venlafaxine is 37.5 mg once daily as extended-release capsules for 7 days, followed by 75 mg once daily as extended-release capsules for another 7 days. In clinical trials, 37.5 mg once daily was given initially for 7 days, then 75 mg once daily for 7 days; thereafter, dosage was increased in increments of 75 mg once daily every 7 days if necessary up to a maximum dosage of 225 mg daily. Although a dose-response relationship for effectiveness in panic disorder was not clearly established in fixed-dose clinical studies, certain patients not responding to a venlafaxine dosage of 75 mg daily may benefit from a higher dosage. Dosage in these patients may be increased in increments of up to 75 mg daily at intervals of not less than 7 days up to a maximum dosage of approximately 225 mg daily.

The optimum duration of venlafaxine therapy for the management of panic disorder has not been established. The efficacy of venlafaxine for long-term therapy (i.e., longer than 12 weeks) in prolonging time to relapse in responding patients has been demonstrated in a controlled clinical trial. However, the usefulness of the drug in patients receiving prolonged therapy should be reevaluated periodically.

Vasomotor Symptoms Although the optimum dosage for the treatment of vasomotor symptoms† in women with breast cancer and in postmenopausal women remains to be established, some clinicians suggest that venlafaxine be initiated at a dosage of 37.5 mg once daily as extended-release capsules, increasing as necessary to 75 mg once daily. In one clinical study, 75 mg once daily as extended-release capsules appeared to be optimal. Further increases in dosage do not appear to provide substantially increased benefit but are potentially more toxic.

Discontinuance of Therapy Because withdrawal effects may occur, abrupt discontinuance of venlafaxine should be avoided. When venlafaxine therapy is discontinued, dosage should be tapered gradually and the patient carefully monitored to reduce the risk of withdrawal symptoms. If intolerable symptoms occur following dosage reduction or upon discontinuance of treatment, venlafaxine therapy may be reinstituted at the previously prescribed dosage until such symptoms abate. Clinicians may resume dosage reductions at that time but at a more gradual rate.

Withdrawal symptoms reported in clinical studies in adults receiving venlafaxine for major depression or generalized anxiety disorder include agitation, anorexia, anxiety, confusion, impaired coordination, diarrhea, dizziness, dry mouth, dysphoric mood, fasciculation, fatigue, headaches, hypomania, insomnia, nausea, nervousness, nightmares, sensory disturbances (including shock-like electrical sensations), somnolence, sweating, tremor, vertigo, and vomiting. Abrupt discontinuance or dosage reduction of venlafaxine has been associated with the appearance of new symptoms, the frequency of which increased with increased dosage and longer duration of treatment.

In clinical studies, venlafaxine hydrochloride extended-release capsules were discontinued by reducing the daily dosage by 75 mg at intervals of 1 week; however, individualized tapering may be necessary.

■ **Dosage in Renal and Hepatic Impairment** Since clearance of venlafaxine is decreased and elimination half-life is increased in patients with renal impairment, the manufacturer states that dosage of the drug should be reduced by 25–50% in patients with mild-to-moderate renal impairment and by 50% in those undergoing hemodialysis and administration of the dose withheld until the dialysis period is complete (4 hours). Venlafaxine dosage also should be reduced by 50% in patients with moderate hepatic impairment. The manufacturer's labeling should be consulted for more detailed information on the dosage modifications in these patient populations.

■ **Treatment of Pregnant Women during the Third Trimester** Some neonates exposed to venlafaxine, other selective serotonin- and norepinephrine-reuptake inhibitors (SNRIs), or selective serotonin-reuptake inhibitors late in the third trimester of pregnancy have developed complications, which have sometimes been severe and required prolonged hospitalization, respiratory support, enteral nutrition, and other forms of supportive care in special care nurseries. (For additional information, see Cautions: Pregnancy, Fertility, and Lactation, in Fluoxetine Hydrochloride 28:16.04.20.) Therefore, the clinician should carefully consider the potential risks and benefits of treating a pregnant woman with venlafaxine during the third trimester of pregnancy. In addition, consideration should be given to cautiously tapering venlafaxine therapy in the third trimester prior to delivery if the drug is administered during pregnancy.

Description

Venlafaxine hydrochloride, a selective serotonin- and norepinephrine-reuptake inhibitor (SNRI), is a phenylethylamine-derivative antidepressant and anxiolytic agent. Venlafaxine differs structurally and pharmacologically from other commercially available antidepressants, including tricyclic and tetracyclic antidepressants, and also differs from other commercially available agents used to treat generalized anxiety disorder.

The exact mechanisms of antidepressant and anxiolytic actions of venlafaxine have not been fully elucidated but appear to be associated with the drug's potentiation of neurotransmitter activity in the CNS. Venlafaxine and its active metabolite, O-desmethylvenlafaxine (ODV), are potent inhibitors of neuronal serotonin and norepinephrine reuptake and weak inhibitors of dopamine reuptake. In vitro studies have demonstrated that venlafaxine and ODV do not possess any significant affinity for muscarinic cholinergic, H_1-histaminergic, or α_1-adrenergic receptors.

SumMon® (see Users Guide). For additional information on this drug until a more detailed monograph is developed and published, the manufacturer's labeling should be consulted. It is *essential* that the labeling be consulted for detailed information on the usual cautious, precautions, and contraindications.

Preparations

Excipients in commercially available drug preparations may have clinically important effects in some individuals; consult specific product labeling for details.

Venlafaxine Hydrochloride

Oral		
Tablets	25 mg (of venlafaxine)*	Effexor® (scored), Wyeth Venlafaxine Hydrochloride Tablets
	37.5 mg (of venlafaxine)*	Effexor® (scored), Wyeth Venlafaxine Hydrochloride Tablets
	50 mg (of venlafaxine)*	Effexor® (scored), Wyeth Venlafaxine Hydrochloride Tablets
	75 mg (of venlafaxine)*	Effexor® (scored), Wyeth Venlafaxine Hydrochloride Tablets
	100 mg (of venlafaxine)*	Effexor® (scored), Wyeth Venlafaxine Hydrochloride Tablets
Capsules, extended-release	37.5 mg (of venlafaxine)	Effexor® XR, Wyeth
	75 mg (of venlafaxine)	Effexor® XR, Wyeth
	150 mg (of venlafaxine)	Effexor® XR, Wyeth

*available from one or more manufacturer, distributor, and/or repackager by generic (nonproprietary) name
†Use is not currently included in the labeling approved by the US Food and Drug Administration

SELECTIVE SEROTONIN-REUPTAKE INHIBITORS 28:16.04.20

Citalopram Hydrobromide

■ Citalopram hydrobromide, a selective serotonin-reuptake inhibitor (SSRI), is an antidepressant.

Uses

Citalopram hydrobromide is used in the treatment of major depressive disorder. In addition, citalopram has been used for the treatment of obsessive-compulsive disorder†, panic disorder†, social phobia† (social anxiety disorder), alcohol dependence†, premenstrual dysphoric disorder†, premature ejaculation†, eating disorders†, diabetic neuropathy†, and posttraumatic stress disorder†.

■ **Major Depressive Disorder** Citalopram hydrobromide is used in the treatment of major depressive disorder. A major depressive episode implies a prominent and relatively persistent depressed or dysphoric mood that usually interferes with daily functioning (nearly every day for at least 2 weeks). According to DSM-IV criteria, a major depressive episode includes at least 5 of the following 9 symptoms (with at least one of the symptoms being either depressed mood or loss of interest or pleasure): depressed mood most of the day as indicated by subjective report (e.g., feels sad or empty) or observation made by others; markedly diminished interest or pleasure in all, or almost all, activities most of the day; significant weight loss (when not dieting) or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite; insomnia or hypersomnia; psychomotor agitation or retardation (observable by others, not merely subjective feelings of restlessness or being slowed down); fatigue or loss of energy; feelings of worthlessness or excessive or inappropriate guilt (not merely self-reproach or guilt about being sick); diminished ability to think or concentrate or indecisiveness (either by subjective account or as observed by others); and recurrent thoughts of death, recurrent suicidal ideation without a specific plan, or a suicide attempt or specific plan for committing suicide.

Treatment of major depressive disorder generally consists of an acute phase (to induce remission), a continuation phase (to preserve remission), and a maintenance phase (to prevent recurrence). Various interventions (e.g., psychotherapy, antidepressant drug therapy, electroconvulsive therapy [ECT]) are used alone or in combination to treat major depressive episodes. Treatment should be individualized, and the most appropriate strategy for a particular patient is determined by clinical factors such as severity of depression (e.g., mild, moderate, severe), presence or absence of certain psychiatric features (e.g., suicide risk, catatonia, psychotic or atypical features, alcohol or substance abuse or dependence, panic or other anxiety disorder, cognitive dysfunction, dysthymia, personality disorder, seasonal affective disorder), and concurrent illness (e.g., asthma, cardiac disease, dementia, seizure disorder, glaucoma, hypertension). Demographic and psychosocial factors as well as patient preference also are used to determine the most effective treatment strategy.

While use of psychotherapy alone may be considered as an initial treatment strategy for patients with mild to moderate major depressive disorder (based on patient preference and presence of clinical features such as psychosocial stressors), combined use of antidepressant drug therapy and psychotherapy may be useful for initial treatment of patients with moderate to severe major depressive disorder with psychosocial issues, interpersonal problems, or a comorbid axis II disorder. In addition, combined use of antidepressant drug therapy and psychotherapy may be beneficial in patients who have a history of poor compliance or only partial response to adequate trials of either antidepressant drug therapy or psychotherapy alone.

Antidepressant drug therapy can be used alone for initial treatment of patients with mild major depressive disorder (if preferred by the patient) and usually is indicated alone or in combination with psychotherapy for initial treatment of patients with moderate to severe major depressive disorder (unless ECT is planned). ECT is not generally used for initial treatment of uncomplicated major depression, but is recommended as first-line treatment for severe major depressive disorder when it is coupled with psychotic features, catatonic stupor, severe suicidality, food refusal leading to nutritional compromise, or other situations when a rapid antidepressant response is required. ECT also is recommended for patients who have previously shown a positive response to or a preference for this treatment modality and can be considered for patients with moderate or severe depression who have not responded to or cannot receive antidepressant drug therapy. In certain situations involving depressed patients unresponsive to adequate trials of several individual antidepressant agents, adjunctive therapy with another agent (e.g., buspirone, lithium) or concomitant use of a second antidepressant agent (e.g., bupropion) has been used; however, such combination therapy is associated with an increased risk of adverse reactions, may require dosage adjustments, and (if not contraindicated) should be undertaken only after careful consideration of the relative risks and benefits. (See Drug Interactions: Serotonergic Drugs, Tricyclic and Other Antidepressants under Drug Interactions: Drugs Undergoing Hepatic Metabolism or Affecting Hepatic Microsomal Enzymes, and Drug Interactions: Lithium.)

The efficacy of citalopram for the management of major depression has been established in short-term (4–6 weeks' duration), placebo-controlled studies in outpatients 18–66 years of age who met DSM-III or -III-R criteria for major depressive disorder. In a 6-week study in which patients received fixed citalopram dosages of 10, 20, 40, or 60 mg daily, the drug was effective at dosages of 40 and 60 mg daily as measured by the Hamilton Depression Rating Scale (HAM-D) Total Score, the HAM-D Depressed Mood Item (Item 1), the Montgomery Asberg Depression Rating Scale, and the Clinical Global Impression (CGI) Severity Scale. This study showed no clear antidepressant effect of the 10 or 20 mg daily dosages, and the 60 mg daily dosage was not more effective than the 40 mg daily dosage.

In a 4-week, placebo-controlled study in depressed adult patients, of whom 85% met criteria for melancholia, those who were treated with citalopram (at an initial dosage of 20 mg daily, titrated to the maximum tolerated dosage or to a maximum daily dosage of 80 mg) showed greater improvement than patients receiving placebo on the HAM-D Total Score, HAM-D Item 1, and the CGI Severity score. In 3 additional placebo-controlled depression trials, the difference in response to treatment between patients receiving citalopram and patients receiving placebo was not statistically significant, possibly due at least in part to a high spontaneous response rate, a high placebo response rate, small sample size, or, in the case of one study, too low a dosage.

In 2 placebo-controlled studies, depressed adult patients who had responded to an initial 6- to 8-week course of citalopram (fixed dosage of 20 or 40 mg daily in one study and flexible dosages ranging from 20–60 mg daily in the second study) were randomized to continue receiving citalopram or placebo for up to 6 months. In both of these studies, patients receiving citalopram experienced substantially lower relapse rates over the subsequent 6 months compared with those receiving placebo. In the fixed-dose study, the decreased rate of depression relapse was similar in patients receiving 20 or 40 mg daily of citalopram. An analysis of these data for possible age-, gender-, and race-related effects on treatment outcome did not suggest any difference in antidepressant efficacy based on the age, gender, and race of the patient. In a placebo-controlled trial, citalopram also was shown to help prevent recurrences of depression in patients with recurrent major depression receiving the drug for up to 6–18 months.

While the optimum duration of citalopram therapy has not been established, many experts state that acute depressive episodes require several months or longer of sustained antidepressant therapy. In addition, some clinicians recommend that long-term antidepressant therapy be considered in certain patients at risk for recurrence of depressive episodes (such as those with highly recurrent unipolar depression). In placebo-controlled studies, citalopram has been shown to be effective for the long-term (e.g., up to 18 months) management of depression. In addition, the drug has been used in some patients for longer periods (e.g., up to 28 months) without apparent loss of clinical effect or increased

Chemistry and Stability

■ **Chemistry** Caffeine, like theobromine and theophylline, is a xanthine derivative. Caffeine occurs naturally in tea and coffee, but is prepared synthetically for commercial drug use. Caffeine is present in amounts of about 100–150 mg/180 mL of brewed coffee; 60–80 mg/180 mL of instant coffee; 40–100 mg/180 mL of tea; and 17–55 mg/180 mL of cola beverage.

Caffeine occurs as a white powder or white, glistening needles that are usually matted together. The drug is odorless and has a bitter taste. Caffeine, which may contain one molecule of water or be anhydrous, is sparingly soluble in water and in alcohol. The hydrate effloresces in air.

Various synthetic mixtures of caffeine have been prepared to increase its solubility. The mixture of caffeine and sodium benzoate contains 45–52% anhydrous caffeine and occurs as a white powder with a slightly bitter taste. The mixture is freely soluble in water and soluble in alcohol. Caffeine and sodium benzoate injection has a pH of 6.5–8.5. Citrated caffeine is a white powder with a bitter taste, obtained by combining caffeine with citric acid. Citrated caffeine is freely soluble in water and soluble in alcohol and contains approximately 50% anhydrous caffeine. Commercially available caffeine citrate injection and oral solution have a pH of 4.7.

■ **Stability** Commercially available caffeine and sodium benzoate injection and caffeine citrate injection and oral solution should be stored at 15–30°C. The commercially available injections and oral solution should be inspected visually for particulate matter and discoloration prior to administration. Vials containing discolored solution or visible particulate matter should be discarded.

Based on compatibility studies, the commercially available caffeine citrate injection is chemically stable for 24 hours at room temperature when mixed with any of the following solutions: 5% dextrose injection; 50% dextrose injection; Intralipid® 20% emulsion; Aminosyn® 20% solution; dopamine hydrochloride injection (diluted to 0.6 mg/mL with 5% dextrose injection); calcium gluconate 10% injection; heparin sodium injection (diluted to 1 unit/mL with 5% dextrose injection); fentanyl citrate injection (diluted to 10 mcg/mL with 5% dextrose injection).

Preparations

Excipients in commercially available drug preparations may have clinically important effects in some individuals; consult specific product labeling for details.

Caffeine

Oral		
Tablets	100 mg*	**Caffeine Tablets**
	200 mg*	**Caffeine Tablets**
Tablets, film-coated	200 mg*	**Caffeine Film-coated Tablets**
		No Doz® Maximum Strength Caplets®, Novartis
		Vivarin®, GlaxoSmithKline

Caffeine also is commercially available in combination with analgesics, antacids, antihistamines, antipyretics, antitussives, belladonna alkaloids, diuretics, ergotamine tartrate, expectorants, nasal decongestants, skeletal muscle relaxants, sympathomimetics, and vitamins.

*available from one or more manufacturer, distributor, and/or repackager by generic (nonproprietary) name

Caffeine and Sodium Benzoate

Parenteral		
Injection	250 mg/mL (equivalent to caffeine anhydrous 125 mg/mL and sodium benzoate 125 mg/mL)*	**Caffeine and Sodium Benzoate Injection**

*available from one or more manufacturer, distributor, and/or repackager by generic (nonproprietary) name

Caffeine Citrate

Oral		
Solution	20 mg/mL (equivalent to 10 mg/mL caffeine anhydrous)*	**Cafcit®**, MeadJohnson
		Caffeine Citrate Oral Solution
Parenteral		
Injection	20 mg/mL (equivalent to 10 mg/mL caffeine anhydrous)*	**Cafcit®**, MeadJohnson
		Caffeine Citrate Injection
Powder†		

*available from one or more manufacturer, distributor, and/or repackager by generic (nonproprietary) name
†Use is not currently included in the labeling approved by the US Food and Drug Administration

Dexmethylphenidate Hydrochloride

■ Dexmethylphenidate hydrochloride, the *d-threo* enantiomer of racemic methylphenidate hydrochloride, is a CNS stimulant that has pharmacologic actions that are qualitatively similar to those of amphetamines.

Uses

Dexmethylphenidate hydrochloride is used alone or combined with behavioral treatment as an adjunct to psychological, educational, social, and other remedial measures in the treatment of attention deficit hyperactivity disorder (ADHD).

■ **Attention Deficit Hyperactivity Disorder** Dexmethylphenidate hydrochloride is used alone or combined with behavioral treatment as an adjunct to psychological, educational, social, and other remedial measures in the treatment of ADHD (hyperkinetic disorder, hyperkinetic syndrome of childhood, minimal brain dysfunction) in carefully selected children 6 years of age and older, adolescents, and adults.

Efficacy of dexmethylphenidate hydrochloride conventional tablets for this indication was established in 2 placebo-controlled clinical trials in patients 6–17 years of age who met DSM-IV criteria for ADHD. In the first controlled clinical trial, improvement in symptom scores from baseline to study end (4 weeks) was greater in children receiving dexmethylphenidate hydrochloride conventional tablets than in those receiving placebo. In the second trial, children who had responded to dexmethylphenidate hydrochloride as conventional tablets in a 6-week open-label trial were randomized to receive this formulation of the drug for an additional 2 weeks or to receive placebo. Treatment failure occurred in 63% of patients receiving placebo compared with 17% of those receiving dexmethylphenidate.

Efficacy of dexmethylphenidate hydrochloride extended-release tablets for this indication was established in clinical trials in children 6 years of age and older, adolescents, and adults who met DSM-IV criteria for ADHD. In a controlled clinical trial in pediatric patients 6–17 years of age, improvement in symptoms from baseline to study end (7 weeks) was greater in children receiving dexmethylphenidate hydrochloride extended-release capsules than in those receiving placebo. Because a limited number of adolescents were enrolled in the trial, data from the trial were insufficient to adequately assess efficacy of the extended-release capsules in adolescents; however, efficacy of dexmethylphenidate hydrochloride extended-release capsules in adolescents is supported by pharmacokinetic data and by evidence of the efficacy of conventional tablets of the drug in this population. In a controlled clinical trial in adults 18–60 years of age, improvement in signs and symptoms of ADHD from baseline to study end (5 weeks) was greater in adults receiving dexmethylphenidate hydrochloride extended-release capsules than in those receiving placebo.

For further information on the management of ADHD, see Uses: Attention Deficit Hyperactivity Disorder, in Methylphenidate Hydrochloride 28:20.92.

Dosage and Administration

■ **Administration** Dexmethylphenidate hydrochloride conventional tablets are administered orally twice daily without regard to meals; the manufacturer recommends that doses be administered at least 4 hours apart.

Dexmethylphenidate hydrochloride extended-release capsules are administered orally once daily in the morning, with or without food. The capsules should be swallowed intact and should *not* be crushed, chewed, or divided. Alternatively, the entire contents of the extended-release capsule(s) may be sprinkled onto a small amount (e.g., a spoonful) of applesauce immediately prior to administration. The entire sprinkle/applesauce mixture should be taken immediately and should not be stored for use at a later time.

■ **Dosage** The recommended initial dosage of dexmethylphenidate hydrochloride as conventional tablets, in patients 6 years of age and older who currently are not receiving racemic methylphenidate or are receiving stimulants other than methylphenidate is 2.5 mg twice daily. In patients 6 years of age and older who are being transferred from racemic methylphenidate to dexmethylphenidate therapy, the initial dexmethylphenidate hydrochloride dosage is one-half the current methylphenidate hydrochloride dosage. Dosage of dexmethylphenidate hydrochloride may be increased by 2.5–5 mg daily at weekly intervals, up to a maximum dosage of 20 mg daily.

The recommended initial dosage of dexmethylphenidate hydrochloride as extended-release capsules in patients who currently are not receiving dexmethylphenidate or racemic methylphenidate or who are receiving stimulants other than methylphenidate is 5 mg once daily for pediatric patients 6 years of age and older or 10 mg once daily for adults. Patients currently receiving dexmethylphenidate hydrochloride conventional tablets may be switched to the extended-release capsules at the same total daily dosage. In patients being transferred from racemic methylphenidate to dexmethylphenidate therapy, the initial dexmethylphenidate hydrochloride dosage is one-half the current methylphenidate hydrochloride dosage. Dosage of dexmethylphenidate hydrochloride may be increased by 5 mg daily in pediatric patients or by 10 mg daily in adults at weekly intervals, up to a maximum dosage of 20 mg daily.

Dosage of dexmethylphenidate must be carefully adjusted according to individual requirements and response. The patient should be observed for a sufficient duration at a given dosage to ensure that maximum benefit has been achieved before dosage adjustment is considered. If a beneficial effect is not

attained after appropriate dosage adjustment over a 1-month period, dexmethylphenidate therapy should be discontinued. If paradoxical aggravation of symptoms or other adverse effects occur during dexmethylphenidate therapy, dosage should be reduced or the drug discontinued if necessary.

The long-term efficacy (i.e., exceeding 6 weeks for conventional tablets or 7 weeks for extended-release capsules) has not been evaluated systematically in controlled studies; therefore, the long-term usefulness of the drug should be reevaluated periodically in patients receiving dexmethylphenidate for extended periods. In patients who have responded to dexmethylphenidate therapy, the drug should be discontinued periodically to assess the patient's condition; improvement may be maintained temporarily or permanently after the drug is discontinued. For children or adolescents whose symptoms are not severe outside the school setting, drug holidays may be attempted for all or part of the summer to assess continuing efficacy and need for such therapy as well as to minimize adverse effects.

■ **Special Populations** No special population dosage recommendations at this time.

Cautions

■ **Contraindications** Marked anxiety, tension, and agitation, since dexmethylphenidate may aggravate these symptoms. Glaucoma. Motor tics or a family history or a diagnosis of Tourette's syndrome; however, the American Academy of Pediatrics (AAP) states that the presence of tics before or during medical management of ADHD is *not* an absolute contraindication to stimulant drug use. (See the opening discussion in Cautions, in Methylphenidate Hydrochloride 28:20.92.) Recent (within 14 days) administration of monoamine oxidase (MAO) inhibitors, since hypertensive crisis could result.

Known hypersensitivity to dexmethylphenidate, methylphenidate, or any ingredient in the formulation.

■ **Warnings/Precautions** ***Warnings*** Dexmethylphenidate hydrochloride shares the toxic potentials of racemic methylphenidate, and the usual precautions of racemic methylphenidate therapy should be observed.

Abuse Potential. Tolerance and psychologic dependence with varying degrees of abnormal behavior can occur with chronic abuse of dexmethylphenidate. Psychotic episodes can occur, particularly with parenteral abuse. Dexmethylphenidate should be used with caution in patients with a history of drug or alcohol dependence. Caution also may be indicated in patients with comorbid conduct disorder or a chaotic family. If the risk of drug abuse by the patient or the patient's peers or family is considered high, a nonstimulant drug may be preferable.

Withdrawal. Abrupt withdrawal of dexmethylphenidate following prolonged administration may unmask severe depression. Long-term follow-up may be required.

Sudden Death and Serious Cardiovascular Events. Although a causal relationship to stimulants has not been established, sudden unexplained death, stroke, and myocardial infarction have been reported in adults receiving usual dosages of stimulants for the treatment of ADHD. Sudden unexplained death also has been reported in children and adolescents with structural cardiac abnormalities or other serious cardiac conditions receiving usual dosages of CNS stimulants. Results of one retrospective, case-control epidemiologic study showed a possible association between use of stimulant medications (e.g., methylphenidate) and sudden unexplained death in healthy children and adolescents. (See Pediatric Use under Warnings/Precautions: Specific Populations, in Cautions.) Given the study limitations, the US Food and Drug Administration (FDA) is unable to conclude that these data affect the overall risk and benefit profile of stimulant medications used to treat ADHD in children and adolescents. Amphetamines or other stimulants should not be discontinued by parents of children or patients receiving these medications for ADHD before consulting with their clinician. Because of postmarketing reports and results of this and other epidemiologic studies, the FDA is conducting an ongoing review of safety of amphetamines and other stimulants to evaluate a possible link between use of these agents and sudden death in children. To determine whether there is a direct causal relationship between use of stimulants and serious adverse cardiovascular events, the Agency for Healthcare Research and Quality (AHRQ) and FDA announced in 2007 that they are collaborating on a large study evaluating clinical data on approximately 500,000 adults and children who received these drugs for management of ADHD during a 7-year period ending in 2005; data collection for the study is expected to be completed in 2009.

Children, adolescents, and adults who are being considered for stimulant therapy should undergo a thorough medical history review (including evaluation for a family history of sudden death or ventricular arrhythmia) and physical examination to detect the presence of cardiac disease, and should receive further cardiac evaluation (e.g., ECG, echocardiogram) if initial findings suggest such disease. Although some serious cardiac conditions are independently associated with an increased risk of sudden death, CNS stimulants generally should *not* be used in children, adolescents, or adults with known serious structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, coronary artery disease, or other serious cardiac conditions. Patients who develop exertional chest pain, unexplained syncope, or other manifestations suggestive of cardiac disease during stimulant therapy should undergo prompt cardiac evaluation.

For further information on screening for cardiac conditions, selecting appropriate candidates for stimulant therapy, and monitoring for treatment-emergent cardiac conditions, see Cardiovascular Precautions under Cautions: Precautions and Contraindications, in the Amphetamines General Statement 28:20.04.

Effects on Blood Pressure and Heart Rate. Stimulants cause modest increases in average blood pressure (i.e., by about 2–4 mm Hg) and heart rate (i.e., by about 3–6 beats/minute); larger increases may occur in some patients. Although modest increases would not be expected to have short-term sequelae, all patients should be monitored for larger changes in blood pressure and heart rate. Caution is advised in patients with underlying medical conditions that might be affected by increases in blood pressure or heart rate (e.g., hypertension, heart failure, recent myocardial infarction, ventricular arrhythmia).

Psychiatric Effects. Stimulants may exacerbate symptoms of behavior disturbance and thought disorder in patients with a preexisting psychotic disorder.

Stimulants should be used with caution in the management of ADHD in patients with comorbid bipolar disorder because of the potential for precipitation of mixed or manic episodes in such patients. Prior to initiating stimulant therapy, patients with ADHD and comorbid depressive symptoms should be carefully screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history (e.g., family history of suicide, bipolar disorder, or depression).

Psychotic or manic symptoms (e.g., hallucinations, delusional thinking, mania) have been reported in children and adolescents without prior history of psychotic illness or mania who received usual dosages of stimulants. In a pooled analysis of multiple short-term, placebo-controlled studies, such symptoms occurred in about 0.1% of patients receiving usual dosages of stimulants (i.e., methylphenidate, amphetamine) compared with 0% of those receiving placebo. If psychotic or manic symptoms occur during stimulant therapy, a causal relationship to stimulants should be considered, and discontinuance of therapy may be appropriate.

Aggressive behavior and hostility frequently are observed in children and adolescents with ADHD and have been reported in patients receiving drug therapy for the disorder. Although a causal relationship to stimulants has not been established, patients beginning treatment for ADHD should be monitored for the onset or worsening of aggressive behavior or hostility.

Growth Suppression. Prolonged administration of stimulants in children with ADHD has been associated with at least a temporary suppression of normal weight and/or height patterns in some patients. Results of an analysis of weight and height patterns in children 7–13 years of age suggested that treatment with methylphenidate for up to 3 years was associated with a temporary slowing in growth rate (on average, height gain was suppressed by about 2 cm and weight gain was suppressed by 2.7 kg over 3 years), without evidence of growth rebound during this period of development. In a 7-week controlled study in children and adolescents, patients receiving placebo gained a mean of 0.4 kg, while those receiving dexmethylphenidate hydrochloride extended-release capsules *lost* a mean of 0.5 kg. Published data are inadequate to determine whether long-term use of amphetamines may cause similar suppression of growth; however, it is anticipated that amphetamines, like methylphenidate, also cause temporary growth suppression. Therefore, the manufacturers of stimulant preparations state that growth should be monitored during therapy with stimulants, and children who are not growing or gaining height or weight as expected may require temporary discontinuance of therapy. However, AAP states that studies of stimulants in children generally have found little or no decrease in expected height, with any decrease in growth early in treatment being compensated for later on. (See Cautions: GI and Growth Effects, in Methylphenidate Hydrochloride 28:20.92.)

Seizures. There is some clinical evidence that stimulants may lower the seizure threshold in patients with a history of seizures, in those with prior EEG abnormalities but no history of seizures, and, very rarely, in those without a history of seizures and no prior evidence of EEG abnormalities. One patient, without a history of seizure disorder, experienced a seizure while receiving dexmethylphenidate during a controlled clinical trial. If seizures occur, the drug should be discontinued.

Visual Effects. Visual disturbances (difficulty with accommodation, blurred vision) have been reported in patients receiving stimulants.

General Precautions **Hematologic Monitoring.** The manufacturer recommends periodic monitoring of complete blood cell count (CBC), with differential, and platelet counts during prolonged therapy; however, AAP and many clinicians consider routine hematologic monitoring unnecessary in patients receiving recommended stimulants (e.g., methylphenidate, amphetamines) in the absence of clinical signs (e.g., fever, sore throat, unusual bleeding or bruising) suggestive of hematologic toxicity.

Specific Populations **Pregnancy.** Category C. (See Users Guide.)

Lactation. Not known whether dexmethylphenidate is distributed into milk; caution if used in nursing women.

Pediatric Use. Safety and efficacy of dexmethylphenidate not established in children younger than 6 years of age, and therefore the manufacturer states that the drug should not be used in this age group.

Therapy with stimulants may be associated with at least a temporary suppression of growth in children. (See Growth Suppression under Warnings/Precautions: Warnings, in Cautions.)

Sudden death has been reported in children and adolescents with structural cardiac abnormalities or other serious cardiac conditions receiving usual dosages of CNS stimulants. Results of one retrospective, case-control epidemio-

logic study suggested a possible association between use of stimulant medications and sudden unexplained death in healthy children and adolescents. (See Sudden Death and Serious Cardiovascular Events under Warnings/Precautions: Warnings, in Cautions.)

Renal Impairment. Safety and efficacy of dexmethylphenidate not established in patients with renal impairment.

Hepatic Impairment. Safety and efficacy of dexmethylphenidate not established in patients with hepatic impairment.

■ **Common Adverse Effects** Abdominal pain, fever, anorexia, and nausea each occurred in 5% or more of patients receiving dexmethylphenidate hydrochloride conventional tablets in clinical trials and were at least twice as frequent in patients receiving the drug as in those receiving placebo. Twitching (motor or vocal tics), anorexia, insomnia, and tachycardia each resulted in discontinuance of dexmethylphenidate hydrochloride conventional tablets in approximately 1% of patients.

Decreased appetite, headache, dyspepsia, dry mouth, anxiety, and pharyngolaryngeal pain each occurred in 5% or more of patients receiving dexmethylphenidate hydrochloride extended-release capsules in clinical trials. Twitching (motor or vocal tics), anorexia, insomnia, and tachycardia each resulted in discontinuance of dexmethylphenidate hydrochloride extended-release capsules in approximately 1% of pediatric patients. In adults, insomnia, jittery feeling, anorexia, and anxiety each resulted in discontinuance of therapy in about 1–2% of patients.

Nervousness and insomnia are the most commonly reported adverse effects in patients receiving racemic methylphenidate preparations.

Drug Interactions

The possibility that drug interactions reported with racemic methylphenidate also could occur with dexmethylphenidate should be considered.

■ **Cardiovascular Agents** Potential pharmacologic interaction (increased hypertensive effects) with concomitant use of pressor agents and dexmethylphenidate; caution advised. Pharmacodynamic interaction (decreased antihypertensive effect) reported with concomitant use of racemic methylphenidate and antihypertensive agents. Serious adverse effects have occurred rarely in patients receiving racemic methylphenidate and clonidine concomitantly; causality not established.

■ **Anticonvulsants** Potential pharmacokinetic interaction (decreased metabolism of anticonvulsant agent) with concomitant use of racemic methylphenidate and anticonvulsants (e.g., phenobarbital, phenytoin, primidone). Monitoring of plasma anticonvulsant concentrations is recommended when methylphenidate is initiated or discontinued in patients receiving anticonvulsants; adjustment of anticonvulsant dosage may be required.

■ **Anticoagulants** Potential pharmacokinetic interaction (decreased metabolism of anticoagulant) with concomitant use of racemic methylphenidate and coumarin anticoagulants. Monitoring of prothrombin time (PT)/international normalized ratio (INR) is recommended when methylphenidate is initiated or discontinued in patients receiving coumarin anticoagulants; adjustment of anticoagulant dosage may be required.

■ **Antidepressants** Pharmacologic interaction (possible hypertensive crisis) with monoamine oxidase (MAO) inhibitors. (See Cautions: Contraindications.) Pharmacokinetic interaction (decreased metabolism of antidepressant agent) reported with concomitant use of racemic methylphenidate and tricyclic antidepressants (e.g., imipramine, clomipramine, desipramine) or selective serotonin-reuptake inhibitors. Adjustment of antidepressant dosage may be required when methylphenidate is initiated or discontinued.

■ **Drugs Metabolized by Hepatic Microsomal Enzymes** Pharmacokinetic interaction unlikely.

■ **Drugs Affecting GI pH** Studies to evaluate the effects of changes in gastric pH on the absorption of dexmethylphenidate hydrochloride administered as extended-release capsules have not been performed to date. However, the potential exists for a pharmacokinetic interaction (altered release of dexmethylphenidate hydrochloride) between Focalin® XR extended-release capsules and drugs that alter gastric pH (e.g., antacids, acid suppressants).

Description

Dexmethylphenidate hydrochloride, the more pharmacologically active (*d-threo*) enantiomer of racemic methylphenidate hydrochloride, is a CNS stimulant. The mechanism of action in the treatment of attention deficit hyperactivity disorder (ADHD) has not been determined.

Dexmethylphenidate hydrochloride is well absorbed following oral administration. Because of first-pass metabolism, mean absolute bioavailability is 22–25%. When dexmethylphenidate hydrochloride is administered orally as conventional tablets in fasting patients, peak plasma concentrations are achieved within 60–90 minutes after a dose. When the drug is administered as extended-release capsules (Focalin® XR), peak plasma concentrations are attained at 1.5 hours and again at 6.5 hours after a dose. Extended-release capsules are absorbed more slowly but to the same extent as conventional tablets. Plasma concentrations of dexmethylphenidate achieved following single-dose oral administration of dexmethylphenidate hydrochloride capsules are comparable to the dexmethylphenidate concentrations achieved following single-dose oral administration of racemic methylphenidate hydrochloride capsules at equimolar doses (twice the total mg amount of dexmethylphenidate hydrochloride). Dexmethylphenidate is metabolized principally by de-esterification to form *d*-ritalinic acid, which has little or no pharmacologic activity. In vitro studies indicate that the drug does not inhibit the cytochrome P-450 (CYP) enzyme system. The mean plasma elimination half-life of dexmethylphenidate is 2–3 hours in children or 2–4.5 hours in adults.

Dexmethylphenidate hydrochloride is commercially available as conventional tablets and extended-release capsules. Each bead-filled dexmethylphenidate hydrochloride extended-release capsule (Focalin® XR) contains one-half of the dose as immediate-release beads and one-half as enteric-coated, delayed-release beads, thus providing an immediate release of dexmethylphenidate hydrochloride followed by a second delayed release of the drug.

Advice to Patients

Importance of providing patient or caregiver with a copy of the manufacturer's patient information (medication guide); discuss and answer questions about its contents (e.g., benefits and risks of stimulant therapy, appropriate use) as needed. Importance of instructing the patient or caregiver to read and understand the contents of the medication guide before initiating therapy and each time the prescription is refilled.

Importance of informing clinicians immediately of any adverse cardiovascular (e.g., chest pain, shortness of breath, fainting) or psychiatric effects (e.g., hallucinations, delusional thinking, mania).

Importance of taking the drug exactly as prescribed.

Importance of not chewing or crushing the beads contained in the capsules and of not storing the sprinkle/food mixture for later use.

Importance of informing clinicians of existing or contemplated concomitant therapy, including prescription and OTC drugs and herbal supplements, as well as any concomitant illnesses/conditions (e.g., glaucoma, cardiac/cardiovascular disease, mental/psychiatric disorder, seizures, suicidal ideation or behaviors, history of substance abuse).

Importance of women informing clinicians if they are or plan to become pregnant or plan to breast-feed.

Importance of informing patients of other important precautionary information. (See Cautions.)

Overview® (see Users Guide). For additional information on this drug until a more detailed monograph is developed and published, the manufacturer's labeling should be consulted. It is *essential* that the manufacturer's labeling be consulted for more detailed information on usual cautions, precautions, contraindications, potential drug interactions, laboratory test interferences, and acute toxicity.

Preparations

Dexmethylphenidate hydrochloride is subject to control under the Federal Controlled Substances Act of 1970 as a schedule II (C-II) drug.

Excipients in commercially available drug preparations may have clinically important effects in some individuals; consult specific product labeling for details.

Dexmethylphenidate Hydrochloride

Oral		
Capsules, extended-release (containing beads)	5 mg (beads, delayed-release, enteric-coated extended-release 2.5 mg with immediate-release 2.5 mg)	Focalin® XR (C-II), Novartis
	10 mg (beads, delayed-release, enteric-coated extended-release 5 mg with immediate-release 5 mg)	Focalin® XR (C-II), Novartis
	15 mg (beads, delayed-release, enteric-coated extended-release 7.5 mg with immediate-release 7.5 mg)	Focalin® XR (C-II), Novartis
	20 mg (beads, delayed-release, enteric-coated extended-release 10 mg with immediate-release 10 mg)	Focalin® XR (C-II), Novartis
Tablets	2.5 mg	Focalin® (C-II), Novartis
	5 mg	Focalin® (C-II), Novartis
	10 mg	Focalin® (C-II), Novartis

mended human dosage on a mg/m² basis have not revealed evidence of fetal malformation. However, risperidone has been shown to cross the placenta in rats, and an increased rate of stillborn rat pups occurred at dosages 1.5 times higher than the maximum recommended human dosage on a mg/m² basis. In 3 reproductive studies in rats, there was an increase in pup deaths during the first 4 days of lactation at dosages 0.1–3 times the human dosage on a mg/m² basis. It is not known whether these deaths resulted from a direct effect on the fetuses or pups or to effects on the dams. In a separate reproductive study in rats, an increased number of pup daths (at birth or by the day after birth) and a decrease in birth weight were observed in pups of dams treated with risperidone dosages that were 3 times the maximum recommended human dosage on a mg/m² basis. Risperidone also appeared to impair maternal behavior, as evidenced by reduced weight gain and decreased survival (from day 1–4 of lactation) in pups born to control dams but reared by risperidone-treated dams.

Although there are no adequate and controlled studies to date in humans, one case of agenesis of the corpus callosum has been reported in an infant exposed to risperidone in utero; however, a causal relationship to risperidone therapy is unknown. Reversible extrapyramidal adverse effects in the neonate also were observed following postmarketing use of risperidone during the third trimester of pregnancy. Risperidone should be used during pregnancy only when the potential benefits justify the possible risks to the fetus. The effect of risperidone on labor and delivery in humans is unknown.

Risperidone (0.16–5 mg/kg) has been shown to impair mating, but not fertility, in Wistar rats in 3 reproductive studies at dosages 0.1–3 times the maximum recommended human dosage on a mg/m² basis. The effect appeared to be in females since impaired mating behavior was not noted in the Segment I study in which males only were treated. Sperm motility and serum testosterone concentrations were decreased in beagles at dosages 0.6–10 times the human dose on a mg/m² basis. Serum testosterone and sperm parameters partially recovered but remained decreased after treatment was discontinued. A no-effect dosage was not found in these studies in either rats or dogs.

Risperidone and its principal active metabolite, 9-hydroxyrisperidone, are distributed into milk. The manufacturer states that women receiving risperidone should avoid nursing.

Description

Risperidone is a benzisoxazole-derivative antipsychotic agent and is chemically unrelated to other antipsychotic agents. While risperidone shares some of the pharmacologic actions of other antipsychotic agents, the drug has been described as an atypical or second-generation antipsychotic agent since many of its CNS effects differ from those of typical or first-generation agents (e.g., butyrophenones, phenothiazines). The exact mechanism of antipsychotic action of risperidone has not been fully elucidated but, like that of clozapine, appears to be more complex than that of most other antipsychotic agents and may involve antagonism of central type 2 serotonergic (5-HT_2) receptors and central dopamine D_2 receptors.

SumMon® (see Users Guide). For additional information on this drug until a more detailed monograph is developed and published, the manufacturer's labeling should be consulted. It is *essential* that the labeling be consulted for detailed information on the usual cautions, precautions, and contraindications concerning potential drug interactions and/or laboratory test interferences and for information on acute toxicity.

Preparations

Excipients in commercially available drug preparations may have clinically important effects in some individuals; consult specific product labeling for details.

Risperidone

Oral		
Solution	1 mg/mL	Risperdal®, Janssen
Tablets	0.25 mg	Risperdal® (scored), Janssen
	0.5 mg	Risperdal® (scored), Janssen
	1 mg	Risperdal® (scored), Janssen
	2 mg	Risperdal® (scored), Janssen
	3 mg	Risperdal® (scored), Janssen
	4 mg	Risperdal® (scored), Janssen
Tablets, orally disintegrating	0.5 mg	Risperdal® M-TAB®, Janssen
	1 mg	Risperdal® M-TAB®, Janssen
	2 mg	Risperdal® M-TAB®, Janssen
	3 mg	Risperdal® M-TAB®, Janssen
	4 mg	Risperdal® M-TAB®, Janssen
Parenteral		
For injectable suspension, extended-release, for IM use	25 mg	Risperdal® Consta® (available as dose pack containing a SmanSite® needle-free vial access device, a Needle-Pro® safety needle, and with 2-mL prefilled syringe diluent), Janssen
	37.5 mg	Risperdal® Consta® (available as dose pack containing a SmanSite® needle-free vial access device, a Needle-Pro® safety needle, and with 2-mL prefilled syringe diluent), Janssen
	50 mg	Risperdal® Consta® (available as dose pack containing a SmanSite® needle-free vial access device, a Needle-Pro® safety needle, and with 2-mL prefilled syringe diluent), Janssen

†Use is not currently included in the labeling approved by the US Food and Drug Administration

Ziprasidone

■ Ziprasidone has been referred to as an atypical or second-generation antipsychotic agent.

Uses

■ **Psychotic Disorders** *Schizophrenia* Ziprasidone is used for the symptomatic management of schizophrenia. Drug therapy is integral to the management of acute psychotic episodes and accompanying violent behavior in patients with schizophrenia and generally is required for long-term stabilization to sustain symptom remission or control and to minimize the risk of relapse. Antipsychotic agents are the principal class of drugs used for the management of all phases of schizophrenia. Patient response and tolerance to antipsychotic agents are variable, and patients who do not respond to or tolerate one drug may be successfully treated with an agent from a different class or with a different adverse effect profile.

Because of ziprasidone's greater capacity to prolong the QT/QT_c-interval compared with that of several other antipsychotic agents, use of ziprasidone may be reserved for patients whose disease fails to respond adequately to appropriate courses of other antipsychotic agents. (See Prolongation of QT interval under Warnings/Precautions: Warnings, in Cautions.) However, it should be noted that patients with a history of resistance to antipsychotic therapy (i.e., failed to respond to adequate courses of 2 or more antipsychotic agents) usually were excluded in clinical studies of ziprasidone.

Efficacy of oral ziprasidone was evaluated in 5 placebo-controlled studies of variable duration (4 short-term [4–6 weeks] and one long-term [52 weeks]), principally in patients with schizophrenic disorders in hospital settings. Ziprasidone appears to be superior to placebo in improving both positive and negative manifestations in acute exacerbations of schizophrenia and in reducing the rate of relapse for up to 52 weeks.

Although results of a limited comparative study suggest that oral ziprasidone hydrochloride dosages of 160 mg daily may be as effective as oral haloperidol 15 mg daily in reducing positive symptoms of schizophrenia, a reliable and valid comparison of ziprasidone and oral haloperidol cannot be made at this time based solely on this study due to its relatively small sample size (90 patients), high dropout rate (51.1%), and brief duration (4 weeks). Data from one unpublished comparative study also suggest that ziprasidone hydrochloride (mean dosage of 130 mg daily) may be as effective as olanzapine (mean dosage of 11 mg daily) in the treatment of schizophrenia.

Ziprasidone is used IM for the management of acute agitation in patients with schizophrenia for whom treatment with ziprasidone is appropriate and who require an IM antipsychotic agent for rapid control of behaviors that interfere with diagnosis and care (e.g., threatening behaviors, escalating or urgently distressing behavior, self-exhausting behavior). The efficacy of IM ziprasidone for the management of acute agitation in schizophrenia was established in single-day controlled trials in hospital settings. Because there is no experience regarding the safety of administering ziprasidone IM to schizophrenic patients already receiving oral ziprasidone, concomitant use of oral and IM formulations of ziprasidone is *not* recommended.

For additional information on the symptomatic management of schizophrenia, including treatment recommendations and results of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE), see Schizophrenia and Other Psychotic Disorders under Uses: Psychotic Disorders, in the Phenothiazines General Statement 28:16.08.24.

■ **Bipolar Disorder** Ziprasidone is used for the treatment of acute manic and mixed episodes (with or without psychotic features) associated with bipolar I disorder. According to DSM-IV criteria, manic episodes are distinct periods lasting 1 week or longer (or less than 1 week if hospitalization is required) of abnormally and persistently elevated, expansive, or irritable mood accompanied by at least 3 (or 4 if the mood is only irritability) of the following 7 symptoms: grandiosity, reduced need for sleep, pressure of speech, flight of ideas, distractibility, increased goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation, and engaging in high risk behavior (e.g., unrestrained buying sprees, sexual indiscretions, foolish business investments).

Efficacy of ziprasidone in the treatment of acute manic and mixed episodes has been demonstrated in 2 short-term (3 weeks' duration), double-blind, pla-

cebo-controlled trials in patients who met the DSM-IV criteria for bipolar I disorder and who met diagnostic criteria for an acute manic or mixed episode (with or without psychotic features). The principal rating instruments used for assessing manic symptoms in these trials were the Mania Rating Scale (MRS), which is derived from the Schedule for Affective Disorders and Schizophrenia-Change Version (SADS-C) with items grouped as the Manic Syndrome subscale (e.g., elevated mood, less need for sleep, excessive energy, excessive activity, grandiosity), the Behavior and Ideation Subscale (irritability, motor hyperactivity, accelerated speech, racing thoughts, poor judgment), and impaired insight, and the Clinical Global Impression-Severity of Illness Scale (CGI-S), which was used to assess the clinical significance of treatment response.

In the first 3-week, placebo-controlled trial, ziprasidone hydrochloride was given at an initial dosage of 40 mg twice daily on the first day and 80 mg twice daily on the second day; dosage adjustment in 20-mg twice daily increments within a dosage range of 40–80 mg twice daily was then permitted for the remainder of the study. The mean daily dosage of ziprasidone hydrochloride in this study was 132 mg. In the second 3-week, placebo-controlled trial, patients also were given an initial dosage of ziprasidone hydrochloride 40 mg twice daily on the first day; subsequent dosage titration in 20-mg twice daily increments within a dosage range of 40–80 mg twice daily was permitted. The mean daily dosage of ziprasidone hydrochloride in this study was 112 mg daily. Ziprasidone was found to be superior to placebo in the reduction of the MRS total score and the CGI-S score in both of these studies.

For the initial management of less severe manic or mixed episodes in patients with bipolar disorder, current American Psychiatric Association (APA) recommendations state that monotherapy with lithium, valproate (e.g., valproate sodium, valproic acid, divalproex), or an antipsychotic such as olanzapine may be adequate. For more severe manic or mixed episodes, combination therapy with an antipsychotic and lithium or valproate is recommended as first-line therapy. For further information on the management of bipolar disorder, see Uses: Bipolar Disorder in Lithium Salts 28:28.

The manufacturer states that efficacy of ziprasidone has not been systematically evaluated for long-term use (i.e., exceeding 3 weeks) or for prophylactic use in patients with bipolar disorder.

Dosage and Administration

■ **Administration** Ziprasidone hydrochloride is administered orally twice daily with food. Ziprasidone mesylate is administered only by IM injection.

The commercially available lyophilized powder of ziprasidone mesylate for injection must be reconstituted prior to administration by adding 1.2 mL of sterile water for injection to single-dose vials of ziprasidone to provide a solution containing 20 mg/mL. Other solutions should not be used to reconstitute ziprasidone mesylate injection, and the drug should not be admixed with other drugs. The vials should then be shaken vigorously to ensure complete dissolution. Strict aseptic technique must be observed since the drug contains no preservative. Following reconstitution, ziprasidone mesylate for injection is stable for 24 hours when protected from light and stored at 15–30°C or for up to 7 days when refrigerated at 2–8°C. Ziprasidone mesylate injection should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

■ **Dosage** Dosage of ziprasidone hydrochloride is expressed in terms of the hydrochloride monohydrate. Dosage of ziprasidone mesylate is expressed in terms of ziprasidone.

Schizophrenia **Oral Dosage.** For the symptomatic management of schizophrenia, the recommended initial adult dosage of ziprasidone hydrochloride is 20 mg orally twice daily. Dosage may be increased after a minimum of 2 days at each dosage up to a maximum recommended dosage of 80 mg twice daily. To ensure use of the lowest effective dosage, however, it is recommended that patients be observed for several weeks prior to upward titrations of ziprasidone dosages. While a relationship between dosage and antipsychotic effect has not been established, the effective dosage of ziprasidone hydrochloride in clinical studies generally ranged from 20–100 mg twice daily. The manufacturer states that dosages exceeding 80 mg twice daily generally are not recommended, and safety of ziprasidone hydrochloride in dosages exceeding 100 mg twice daily has not been established.

The optimum duration of ziprasidone therapy currently is not known, but maintenance therapy with ziprasidone hydrochloride 20–80 mg twice daily has been shown to be effective for up to 52 weeks. However, the manufacturer states that no additional benefit has been demonstrated for ziprasidone hydrochloride dosages beyond 20 mg twice daily. Patients responding to ziprasidone therapy should continue to receive the drug as long as clinically necessary and tolerated, but at the lowest possible effective dosage, and the need for continued therapy with the drug should be reassessed periodically.

IM Dosage. For the prompt control of acute agitation in patients with schizophrenia, the recommended initial adult IM dose of ziprasidone is 10–20 mg given as a single dose. Depending on patient response, doses of 10 or 20 mg may be repeated every 2 or 4 hours, respectively, up to a maximum cumulative dose of 40 mg daily.

Oral therapy should replace IM therapy as soon as possible. Safety and efficacy of administering ziprasidone mesylate IM injection for longer than 3 consecutive days have not been evaluated. Because there is no experience regarding the safety of administering ziprasidone mesylate IM injection to patients with schizophrenia who already are receiving oral ziprasidone hydrochloride, the concomitant use of oral and IM formulations of ziprasidone is not recommended by the manufacturer.

Bipolar Disorder **Oral Dosage.** For the management of acute manic and mixed episodes associated with bipolar disorder (with or without psychotic features), the recommended initial adult dosage of ziprasidone hydrochloride is 40 mg orally twice daily on the first day of therapy. Dosage should then be increased to 60 or 80 mg twice daily on the second day of therapy. Subsequent dosage adjustments based on efficacy and tolerability may be made within a dosage range of 40–80 mg twice daily. In the flexible-dosage clinical trials, the mean daily dosage of ziprasidone hydrochloride was approximately 120 mg.

The optimum duration of ziprasidone hydrochloride therapy for bipolar disorder currently is not known. While it is generally agreed that pharmacologic treatment beyond an acute response in mania is desirable, both for maintenance of the initial response and for prevention of new manic episodes, there are no systematically obtained data to support the use of ziprasidone beyond 3 weeks. Therefore, the manufacturer states that clinicians who elect to use ziprasidone for extended periods should periodically reevaluate the long-term risks and benefits of the drug for the individual patient.

■ **Special Populations** No special population dosage recommendations at this time.

Cautions

■ **Contraindications** Known history of QT prolongation (including congenital long QT syndrome), recent acute myocardial infarction, or uncompensated heart failure. (See Prolongation of QT Interval under Warnings/Precautions: Warnings, in Cautions.) Concomitant therapy with other drugs that prolong the QT interval. (See Drug Interactions: Drugs that Prolong QT Interval.) Known hypersensitivity to ziprasidone.

■ **Warnings/Precautions** ***Warnings*** **Increased Mortality in Geriatric Patients with Dementia-related Psychosis.** Geriatric patients with dementia-related psychosis treated with atypical antipsychotic drugs appear to be at an increased risk of death compared with that among patients receiving placebo. Analyses of seventeen placebo-controlled trials (average duration of 10 weeks) revealed an approximate 1.6 - to 1.7-fold increase in mortality among geriatric patients receiving atypical antipsychotic drugs (i.e., aripiprazole, olanzapine, quetiapine, risperidone) compared with that in patients receiving placebo. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5% compared with a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. The manufacturer states that ziprasidone is not approved for the treatment of patients with dementia-related psychosis. (See Geriatric Use under Warnings/Precautions: Specific Populations, in Cautions.)

Prolongation of QT Interval. Prolongation of the QT interval can result in an occurrence of ventricular arrhythmias (e.g., torsades de pointes) and/or sudden death. In one study, oral ziprasidone prolonged the QT interval on ECG by a mean of 9–14 msec more than that observed in patients receiving risperidone, olanzapine, quetiapine, or haloperidol, but approximately 14 msec less than that observed in patients receiving thioridazine. In a study evaluating the QT/QT_c prolongation effect of IM ziprasidone, the mean increase in QT_c from baseline following 2 IM injections of ziprasidone (20 mg, then 30 mg, which is 50% higher than the recommended therapeutic dose) or haloperidol (7.5 mg, then 10 mg), given 4 hours apart, was 12.8 or 14.7 msec, respectively. Therefore, although torsades de pointes was not associated with ziprasidone therapy when the drug was administered at recommended dosages in premarketing clinical studies, experience with the drug is too limited to rule out the possibility that ziprasidone may be associated with a greater risk of sudden death than other antipsychotic agents. Patients at particular risk of torsades de pointes and/or sudden death include those with bradycardia, hypokalemia, or hypomagnesemia, those receiving concomitant therapy with other drugs that prolong the QT_c interval, and those with congenital prolongation of QT_c interval. The manufacturer states that ziprasidone should be avoided in patients with congenital prolongation of the QT interval or a history of cardiac arrhythmias and in those receiving concomitant therapy with other drugs that prolong the QT_c interval. (See Cautions: Contraindications and Drug Interactions: Drugs that Prolong QT Interval.)

Baseline serum potassium and magnesium concentrations should be determined in patients at risk for substantial electrolyte (i.e., potassium, magnesium) disturbances, particularly those receiving concomitant diuretic therapy, and hypokalemia or hypomagnesemia should be corrected prior to initiating ziprasidone. Clinical and ECG monitoring of cardiac function, including appropriate ambulatory ECG monitoring (e.g., Holter monitoring), is recommended during ziprasidone therapy in patients with symptoms that could indicate torsades de pointes (e.g., dizziness, palpitations, syncope). Ziprasidone therapy should be discontinued if the QT_c interval exceeds 500 msec.

Neuroleptic Malignant Syndrome. Although no cases have been confirmed to date in patients receiving ziprasidone, neuroleptic malignant syndrome (NMS), a potentially fatal syndrome requiring immediate discontinuance of the drug and intensive symptomatic treatment, may occur in patients receiving antipsychotic agents. For additional information on NMS, see Extrapyramidal Reactions under Cautions: Nervous System Effects, in the Phenothiazines General Statement 28:16.08.24.

Tardive Dyskinesia. Like other antipsychotic agents, use of ziprasidone may be associated with tardive dyskinesias, a syndrome of potentially irreversible, involuntary, dyskinetic movements. Although emergence of tardive dyskinesia was not specifically evaluated in clinical studies of ziprasidone, use of the drug was associated with either no change or small reductions in the Abnormal Involuntary Movement Scale (AIMS) scores from baseline in one year-long study of the drug. However, differences among antipsychotic agents in their potential to cause tardive dyskinesia have not been established definitively. For additional information on tardive dyskinesia, see Cautions: Nervous System Effects, in the Phenothiazines General Statement 28:16.08.24.

Hyperglycemia and Diabetes Mellitus. Severe hyperglycemia, sometimes associated with ketoacidosis, hyperosmolar coma, or death, has been reported in patients receiving certain atypical antipsychotic agents (e.g., clozapine, olanzapine, quetiapine, risperidone). While confounding factors such as an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population make it difficult to establish with certainty the relationship between use of agents in this drug class and glucose abnormalities, epidemiologic studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotic agents included in the studies (e.g., clozapine, olanzapine, quetiapine, risperidone); it remains to be determined whether ziprasidone also is associated with this increased risk. Although there have been few reports of hyperglycemia or diabetes in patients receiving ziprasidone, it is not known whether the paucity of such reports is due to relatively limited experience with the drug.

Precise risk estimates for hyperglycemia-related adverse events in patients treated with atypical antipsychotics currently are not available. While some evidence suggests that the risk for diabetes may be greater with some atypical antipsychotics (e.g., clozapine, olanzapine) than with others (e.g., quetiapine, risperidone) in the class, available data are conflicting and insufficient to provide reliable estimates of relative risk associated with use of the various atypical antipsychotics.

The manufacturers of atypical antipsychotic agents state that patients with preexisting diabetes mellitus in whom therapy with an atypical antipsychotic is initiated should be closely monitored for worsening of glucose control; those with risk factors for diabetes (e.g., obesity, family history of diabetes) should undergo fasting blood glucose testing upon therapy initiation and periodically throughout treatment. Any patient who develops manifestations of hyperglycemia during treatment with an atypical antipsychotic should undergo fasting blood glucose testing. In some cases, patients who developed hyperglycemia while receiving an atypical antipsychotic have required continuance of antidiabetic treatment despite discontinuance of the suspect drug; in other cases, hyperglycemia resolved with discontinuance of the antipsychotic.

For further information on managing the risk of hyperglycemia and diabetes mellitus associated with atypical antipsychotic agents, see Hyperglycemia and Diabetes Mellitus under Cautions: Precautions and Contraindications, in Clozapine 28:16.08.04.

Sensitivity Reactions **Rash.** Rash and/or urticaria, possibly related to dose and/or duration of therapy, occurred in about 5% of patients in clinical studies and have necessitated discontinuance of the drug in about 17% of these patients. Adjunctive treatment with antihistamines or steroids and/or drug discontinuance may be required. Discontinue ziprasidone if alternative etiology of rash cannot be identified.

General Precautions **Cardiovascular Effects.** Orthostatic hypotension, particularly during initial dosage titration period, has been reported. Use with caution in patients with known cardiovascular or cerebrovascular disease and/or conditions that would predispose patients to hypotension (e.g., dehydration, hypovolemia, concomitant antihypertensive therapy).

Nervous System Effects. Seizures occurred in about 0.4% of patients receiving ziprasidone in controlled clinical trials. Use with caution in patients with a history of seizures or with conditions known to lower the seizure threshold (e.g., Alzheimer's disease, geriatric patients).

Although not reported in clinical studies with ziprasidone, disruption of the body's ability to reduce core body temperature has been associated with use of other antipsychotic agents. Use caution when ziprasidone is administered in patients exposed to conditions that may contribute to an elevation in core body temperature (e.g., dehydration, extreme heat, strenuous exercise, concomitant use of anticholinergic agents).

GI Effects. Esophageal dysmotility and aspiration have been associated with the use of antipsychotic agents. Use with caution in patients at risk for aspiration pneumonia (e.g., geriatric patients, those with advanced Alzheimer's dementia). (See Increased Mortality in Geriatric Patients with Dementia-related Psychosis under Warnings/Precautions: Warnings, in Cautions and see Geriatric Use under Warnings/Precautions: Special Populations, in Cautions.)

Suicide. Attendant risk with psychotic illnesses; closely supervise high-risk patients. Prescribe in the smallest quantity consistent with good patient management to reduce the risk of overdosage.

Sexual Dysfunction. One case of drug-induced priapism reported in clinical studies of ziprasidone.

Other Metabolic and Endocrine Effects. Prolactin concentrations exceeding 22 ng/mL were reported in about 20% of patients receiving ziprasidone in phase II or III clinical studies compared with about 4, 46, or 89% of those receiving placebo, haloperidol, or risperidone, respectively.

Median weight gain of 0.5 kg occurred in patients receiving ziprasidone compared with no median weight change in those receiving placebo. In clinical studies, ziprasidone reportedly caused less weight gain than clozapine, olanzapine, quetiapine, or risperidone.

For additional information on metabolic effects, see Hyperglycemia and Diabetes Mellitus under Warnings/Precautions: Warnings, in Cautions.

Specific Populations **Pregnancy.** Category C. (See Users Guide.)

Lactation. Not known whether ziprasidone is distributed into milk; use in nursing women is not recommended.

Pediatric Use. Safety and efficacy not established in children younger than 18 years of age.

Geriatric Use. No substantial differences in safety of oral ziprasidone relative to younger adults have been observed in clinical studies. Ziprasidone mesylate IM injections have not been systematically evaluated in geriatric patients. Lower initial dosages, slower titration, and more careful monitoring during the initial dosing period may be advisable in some geriatric patients. (See Increased Mortality in Geriatric Patients with Dementia-related Psychosis under Warnings/Precautions: Warnings, in Cautions.)

Renal Impairment. Commercially available ziprasidone mesylate injections contain sulfobutylether β-cyclodextrin sodium, an excipient that is cleared by renal filtration. Therefore, ziprasidone injection should be used with caution in patients with renal impairment.

■ **Common Adverse Effects** Adverse effects occurring in more than 5% of patients with schizophrenia receiving oral ziprasidone and at least twice the frequency of placebo include somnolence (14%) and respiratory tract infection (8%).

Adverse effects occurring in more than 5% of patients with schizophrenia receiving IM ziprasidone 10 or 20 mg and at a frequency twice that reported among those receiving IM ziprasidone 2 mg include somnolence (20%), headache (13%), and nausea (12%).

Adverse effects occurring in more than 5% of patients with bipolar mania receiving oral ziprasidone and at least twice the frequency of placebo include somnolence (31%), extrapyramidal symptoms (31%), dizziness (16%), akathisia (10%), abnormal vision (6%), asthenia (6%), and vomiting (5%).

Drug Interactions

■ **Drugs that Prolong QT Interval** Potential pharmacologic interaction (additive effect on QT interval prolongation; concomitant use contraindicated) when ziprasidone is used with drugs that are known or consistently observed to prolong the QT_c interval (e.g., dofetilide, sotalol, quinidine, other Class Ia and III antiarrhythmics, mesoridazine, thioridazine, chlorpromazine, droperidol, pimozide, sparfloxacin, gatifloxacin, moxifloxacin, halofantrine, mefloquine, pentamidine, arsenic trioxide, levomethadyl acetate [no longer commercially available in the US], dolasetron mesylate, probucol, tacrolimus). Ziprasidone also is contraindicated in patients receiving drugs shown to cause QT prolongation as an effect and for which this effect is described in the full prescribing information as a contraindication or a boxed or bolded warning. (See Cautions: Contraindications and Prolongation of QT Interval under Warnings/Precautions: Warnings in Cautions.)

■ **Hypotensive Agents** Potential pharmacologic interaction (additive hypotensive effects).

■ **Other CNS Agents** Potential pharmacologic interaction (additive sedative effects).

■ **Levodopa and Dopamine Agonists** Potential pharmacologic interaction (antagonistic effects).

■ **Drugs Affecting Hepatic Microsomal Enzymes** Inhibitors or inducers of cytochrome P-450 (CYP) 3A4 isoenzyme; potential pharmacokinetic interaction (altered metabolism). Inhibitors or inducers of CYP1A2, CYP2C9, CYP2C19, or CYP2D6 isoenzymes: pharmacokinetic interaction unlikely.

■ **Protein-bound Drugs** Pharmacokinetic interaction unlikely.

Description

Ziprasidone is a benzisothiazolyl piperazine-derivative antipsychotic agent that is chemically unrelated to other currently available antipsychotic agents (e.g., butyrophenones, phenothiazines) and has been referred to as an atypical or second-generation antipsychotic agent. The exact mechanism of antipsychotic action of ziprasidone has not been fully elucidated but, like that of other atypical antipsychotic agents (e.g., olanzapine, risperidone), may involve antagonism of central type 2 serotonergic ($5\text{-}HT_2$) receptors and central dopamine D_2 receptors. As with other drugs that are effective in bipolar disorder, the precise mechanism of antimanic action of ziprasidone has not been fully elucidated. Antagonism of various other receptors (e.g., histamine H_1 receptors, α_1-adrenergic receptors) may contribute to other therapeutic and adverse effects (e.g., orthostatic hypotension, somnolence) observed with ziprasidone.

Ziprasidone is extensively metabolized in the liver principally via reduction by aldehyde oxidase with minimal excretion of unchanged drug in urine (less than 1%) or feces (less than 4%). About one-third of ziprasidone's metabolic clearance is mediated by the cytochrome P-450 (CYP) 3A4 isoenzyme. Ziprasidone did not inhibit CYP1A2, 2C9, 2C19, 2D6, or 3A4 isoenzymes in vitro.

Advice to Patients

Importance of reading manufacturer's patient information.

Importance of informing clinicians of existing or contemplated concomitant therapy, including prescription (see Drug Interactions: Drugs That Prolong QT Interval) or OTC drugs, dietary supplements, and/or herbal products, as well as any concomitant illnesses (e.g., cardiovascular disease, diabetes mellitus).

Because somnolence and impairment of judgment, thinking, or motor skills may be associated with ziprasidone, avoid driving, operating machinery, or performing hazardous tasks while taking ziprasidone until gain experience with the drug's effects.

Importance of taking medication exactly as prescribed by the clinician.

Importance of women informing clinicians immediately if they are or plan to become pregnant or plan to breast-feed.

Importance of informing patients of other important precautionary information. (See Cautions.)

Overview (see Users Guide). For additional information until a more detailed monograph is developed and published, the manufacturer's labeling should be consulted. It is *essential* that the manufacturer's labeling be consulted for more detailed information on usual cautions, precautions, contraindications, potential drug interactions, laboratory test interferences, and acute toxicity.

Preparations

Excipients in commercially available drug preparations may have clinically important effects in some individuals; consult specific product labeling for details.

Ziprasidone Hydrochloride

Oral		
Capsules	20 mg	Geodon®, Pfizer
	40 mg	Geodon®, Pfizer
	60 mg	Geodon®, Pfizer
	80 mg	Geodon®, Pfizer

Ziprasidone Mesylate

Parenteral		
For Injection, for IM use only	20 mg (of ziprasidone)	Geodon®, Pfizer

BUTYROPHENONES 28:16.08.08

Haloperidol

■ Haloperidol is a butyrophenone-derivative antipsychotic agent. The drug is considered a conventional or first-generation antipsychotic agent.

Uses

■ **Psychotic Disorders** Haloperidol is used for the symptomatic management of psychotic disorders. Drug therapy is integral to the management of acute psychotic episodes and accompanying violent behavior in patients with schizophrenia and generally is required for long-term stabilization to improve symptoms between episodes and to minimize the risk of recurrent acute episodes. Antipsychotic agents are the principal class of drugs used for the management of all phases of schizophrenia and generally are effective in all subtypes of the disorder and subgroups of patients. Conventional antipsychotic agents, such as haloperidol, generally are considered to exhibit similar efficacy in treating acute psychotic symptoms, although they vary in their potency and adverse effect profile. Haloperidol is a high-potency antipsychotic that has been shown to be effective in the management of acute and stable phases of schizophrenia, but is frequently associated with extrapyramidal reactions such as akathisia, dystonia, or parkinsonian symptoms, even at low dosages.

Results of short-term studies indicate that haloperidol is more effective than placebo and equally or less effective than atypical antipsychotics in the treatment of positive (e.g., delusions, hallucinations) and negative symptoms (e.g., withdrawal from social interaction, blunted emotional expression) of schizophrenia. However, in one clinical study, haloperidol was less effective than the atypical antipsychotic agent risperidone in preventing relapse in adult outpatients with clinically active schizophrenia or schizoaffective disorders who were assigned to receive either drug for a minimum of 1 year. In this study, approximately 40% of patients in the study who received usual dosages of haloperidol had relapsed by the end of the study compared with approximately 25% of those receiving usual dosages of risperidone. Because atypical antipsychotics appear to be at least as effective in the treatment of positive symptoms and possibly more effective in the treatment of negative symptoms of schizophrenia and have fewer extrapyramidal reactions, some clinicians prefer use of atypical antipsychotics rather than conventional antipsychotics, such as haloperidol, for the management of schizophrenia, except in stable patients who have had good response to conventional antipsychotics without major adverse effects, in patients who require IM therapy, which is not yet available for some atypical antipsychotics, and for the acute management of aggression/violence in some patients, particularly those requiring long-acting (depot) parenteral preparations. However, patient response and tolerance to antipsychotic agents are variable, and patients who do not respond to or tolerate one drug may be successfully treated with an agent from a different class or with a different adverse effect profile.

The long-acting decanoate ester of haloperidol is used parenterally principally in patients requiring prolonged antipsychotic therapy (e.g., patients with chronic schizophrenic disorder). Parenteral antipsychotic therapy with a long-acting preparation may be particularly useful in patients with a history of poor compliance. In addition, long-acting antipsychotic preparations may be useful in patients with suspected GI malabsorption or variable GI absorption of the drug. The principal disadvantage of long-acting parenteral antipsychotics is the inability to terminate the drug's action when severe adverse reactions occur. Long-acting antipsychotic preparations should not be used in the acute management of severely agitated patients. Generally, patients should be stabilized on antipsychotic medication prior to conversion to haloperidol decanoate therapy and should have previously received and tolerated a shorter-acting haloperidol preparation so that the possibility of an unexpected adverse reaction that potentially could not be readily reversed following the decanoate can be minimized. For further information on the use of antipsychotic agents in the symptomatic treatment of schizophrenia, see Uses: Psychotic Disorders, in the Phenothiazines General Statement 28:16.08.24.

■ **Tourette's Syndrome** Haloperidol is used for the control of tics and vocal utterances of Tourette's syndrome (Gilles de la Tourette's syndrome) in children and adults. Haloperidol generally has been considered the drug of choice for the management of Tourette's syndrome and pimozide has been be an effective alternative in some patients who have an inadequate response to or do not tolerate haloperidol. Because limited data suggest that pimozide may be more effective than haloperidol in reducing tics and pimozide appears to be better tolerated than haloperidol, some clinicians and experts prefer the use of pimozide in patients with Tourette's syndrome.

In children with tic disorders (e.g., Tourette's syndrome) and comorbid attention deficit hyperactivity disorder† (ADHD) in whom stimulants alone cannot control tics, haloperidol may be used concomitantly with a stimulant.

■ **Delirium** Antipsychotic agents, mainly haloperidol, have been used in the management of delirium†.

General Considerations Delirium is principally a disturbance of consciousness, attention, cognition, and perception but also may affect sleep, psychomotor activity, and emotions. It is a common psychiatric illness among medically compromised patients, particularly hospitalized patients, and may be a harbinger of substantial morbidity and mortality.

Prevalence and Course The prevalence of delirium in hospitalized medically ill patients ranges from 10–30%; in those who are elderly, delirium ranges up to 40%. Up to 25% of hospitalized cancer patients and 30–40% of hospitalized patients with acquired immunodeficiency syndrome (AIDS) develop delirium. Up to about 50% of postoperative patients develop delirium, and up to 80% of terminally ill patients develop it near death. EEG abnormalities, mainly generalized slowing, have fairly good sensitivity for aiding in the diagnosis of delirium, but the absence of such changes does not rule out the diagnosis. Prodromal manifestations may progress to full-blown delirium over 1–3 days; the duration of delirium generally ranges from less than a week to more than 2 months, but typically does not exceed 10–12 days. Symptoms persist for up to 30 days or longer in up to 15% of patients, and frequently persist for longer than 1 month in geriatric patients. Although most patients recover fully, delirium may progress to stupor, coma, seizures, and death, particularly if untreated. Full recovery is less likely in geriatric patients and patients with AIDS, possibly because of underlying dementia in both populations.

Underlying general medical conditions associated with delirium include CNS disorders (e.g., head trauma, seizures, postictal state, vascular or degenerative disease), metabolic disorders (e.g., renal or hepatic failure, anemia, hypoxia, hypoglycemia, thiamine deficiency, endocrinopathy, fluid or electrolyte imbalance, acid-base imbalance), cardiopulmonary disorder (myocardial infarction, congestive heart failure, cardiac arrhythmia, shock, respiratory failure), and systemic illness (e.g., substance intoxication or withdrawal, infection, cancer, severe trauma, sensory deprivation, temperature dysregulation, postoperative state).

Management Overview. Clinicians should undertake an essential array of psychiatric management tasks designed to provide immediate interventions for urgent general medical conditions, identify and treat the etiology of delirium, ensure safety of the patient and others in contact with the patient, and improve the patient's functioning. Environmental (e.g., varying light levels in intensive care units to heighten awareness about time of day and reduce the perception of timelessness) and supportive interventions (e.g., to deal with disorientation, to assure the patient that manifestations are temporary and reversible and do not reflect a persistent psychiatric disorder) also generally are offered to patients with delirium† and are designed to reduce factors that may exacerbate delirium, to reorient patients, and to provide support. Patients may have life-threatening medical conditions that require therapeutic intervention

even before a specific or definitive cause of the delirium is determined. The goal of diagnosis is to identify potentially reversible causes of delirium and prevent complications through prompt treatment of these specific disorders. Psychiatric management is essential and should be undertaken for all patients with delirium. Somatic interventions principally consist of drug therapy. The choice of somatic intervention will depend on the specific features of the patient's clinical condition, the underlying etiology of the delirium, and any associated comorbid conditions.

Drug Therapy. Antipsychotic agents often are the drugs of choice for the management of delirium†. Although other drugs (e.g., phenothiazines, droperidol) have been used, haloperidol generally is considered the antipsychotic of choice for most patients with delirium because of its relatively low risk of anticholinergic activity and of sedative and hypotensive effects. In addition, haloperidol has been studied most extensively, although few studies have used standardized definitions of delirium or reliable and valid delirium symptom rating measures to assess symptom severity before and after initiation of treatment. For drugs other than haloperidol, there have been no large, prospective studies that included a control. Evidence of efficacy for such alternative therapies, including second-generation antipsychotic agents (e.g., olanzapine, quetiapine, risperidone, ziprasidone), is principally from small case series, case reports, or open-label studies. In addition, interpretation of findings from many such case presentations is difficult because of use of nonstandardized delirium definitions and/or informal measures of delirium symptom severity. In general, evidence of the efficacy of antipsychotics, including haloperidol, in the management of delirium comes from numerous case reports and uncontrolled studies. However, evidence from a randomized, double-blind, comparator-drug controlled study (haloperidol, chlorpromazine, and lorazepam) in patients with AIDS that employed standardized clinical measures of delirium demonstrated clinical superiority of antipsychotic agents compared with benzodiazepines. Statistically significant improvement in the Delirium Rating Scale was evident after 2 days in patients receiving haloperidol or chlorpromazine but not in the lorazepam group (mean decreases in the score [i.e., improvement] were 8, 8.5, and 1, respectively). The symptomatic improvement in delirium occurred quickly among patients receiving antipsychotic therapy, usually before initiation of interventions directed at the medical etiologies of delirium.

Although various antipsychotic agents may be given orally, IM, or IV, IV administration is considered most effective in emergency situations or where oral access is limited. In addition, some evidence indicates that IV administration of antipsychotic agents may be associated with less severe extrapyramidal effects.

Special Precautions. Antipsychotic agents, particularly IV† haloperidol, used in the management of delirium have been associated with lengthening of the QT interval, possibly leading to atypical ventricular tachycardia (torsades de pointes), ventricular fibrillation, and sudden death. The manufacturer of Haldol® and the US Food and Drug Administration (FDA) state that although injectable haloperidol is approved *only* for IM injection and *not for IV administration*, there is considerable evidence from the medical literature that IV† administration of the drug is a relatively common, unlabeled ("off-label") clinical practice, principally for the treatment of severe agitation in intensive care units, and recommend ECG monitoring in any patient receiving the drug IV. Many clinicians also recommend that baseline and periodic or continuous ECG monitoring be performed with special attention paid to the length of the QT_c interval. Prolongation of the QT_c interval to greater than 450 msec or to greater than 15–25% over that in previous ECGs may warrant telemetry, a cardiology consultation, and dose reduction or discontinuance. Serum concentrations of magnesium and potassium also should be monitored at baseline and periodically in critically ill patients, especially those with baseline QT_c intervals of 440 msec or longer, those receiving other drugs known to increase the QT interval, and those who have electrolyte disorders. Limited evidence suggests that the incidence of torsades de pointes in patients receiving haloperidol IV is about 0.4–3.6%, but may increase to greater than 10% at relatively high IV doses (e.g., 35 mg or more over 24 hours). (See Cautions: Cardiovascular Effects and also see Cautions: Precautions and Contraindications.)

■ **Disruptive Behavior Disorder and Attention Deficit Hyperactivity Disorder** Haloperidol is used for the treatment of severe behavioral problems in children marked by combativeness and/or explosive hyperexcitable behavior (out of proportion to immediate provocations), and for the short-term treatment of hyperactive children who exhibit exeessive motor activity with accompanying conduct disorders that are manifested as impulsive behavior, difficulty sustaining attention, aggression, mood lability, and/or poor frustration tolerance. However, the possible risks of tardive dyskinesia, withdrawal dyskinesia, and other extrapyramidal reactions shonld be considered. Some experts currently reeommend use of haloperidol only for the treatment of comorbid tics in children with attention deficit hyperactivity disorder (ADHD). Some clinicians recommend routine administration of the Abnormal Involuntary Movement Scale (AIMS) to all children receiving antipsychotic agents.

■ **Nausea and Vomiting** Haloperidol also has been used in the prevention and control of severe nausea and vomiting† (e.g., cancer chemotherapy-induced emesis). Based on limited data, haloperidol appears to be as effective as phenothiazines in the prevention of cancer chemotherapy-induced emesis. Additional studies are required to determine the efficacy of haloperidol in the prevention and control of severe nausea and vomiting.

Dosage and Administration

■ **Administration** Haloperidol is administered orally. Haloperidol lactate is administered orally or by IM injection, and haloperidol decanoate is administered by IM injection. Pending accumulation of further data to establish safety and efficacy, IM administration of haloperidol lactate or decanoate in children is not recommended by the manufacturers. Haloperidol *lactate* also has been administered by IV injection† or infusion†. Haloperidol decanoate injection should *not* be administered IV.

Haloperidol decanoate should be administered by deep IM injection into the gluteal region using a 21-gauge needle. The manufacturers of haloperidol decanoate state that the maximum volume of haloperidol decanoate should not exceed 3 mL per IM injection site.

Haloperidol lactate and decanoate injections should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

■ **Dosage** Dosage of haloperidol lactate and the decanoate is expressed in terms of haloperidol.

There is considerable interindividual variation in optimum dosage requirements of haloperidol, and dosage must be carefully adjusted according to individual requirements and response, using the lowest possible effective dosage. Dosage should be increased more gradually in children and in debilitated, emaciated, or geriatric patients. Because of the risk of adverse reactions associated with cumulative effects of butyrophenones, patients with a history of long-term therapy with haloperidol and/or other antipsychotic agents should be evaluated periodically to determine whether maintenance dosage could be decreased or drug therapy discontinued.

Oral Dosage For the symptomatic management of psychotic disorders or Tourette's disorder in adults with moderate symptomatology and in geriatric or debilitated patients, the usual initial oral dosage of haloperidol is 0.5–2 mg 2 or 3 times daily. Subsequent dosage should be carefully adjusted according to the patient's tolerance and therapeutic response. Dosage during prolonged maintenance therapy should be kept at the lowest effective level.

The usual initial oral dosage of haloperidol for adults with severe symptomatology and/or chronic or resistant disorders is 3–5 mg 2 or 3 times daily. To achieve prompt control, higher dosages may be required in some patients. Patients who remain severely disturbed or inadequately controlled may require dosage adjustment. Oral dosages up to 100 mg daily may be required in some severely psychotic patients. Occasionally, dosages exceeding 100 mg daily have been used for the management of severely resistant disorders in adults; however, the safety of prolonged administration of such dosages has not been demonstrated.

The usual initial oral dosage of haloperidol in children 3–12 years of age and weighing 15–40 kg is 0.5 mg daily given in 2 or 3 divided doses. Subsequent dosage may be increased by 0.5 mg daily at 5- to 7-day intervals, depending on the patient's tolerance and therapeutic response.

For the symptomatic management of psychotic disorders in children 3–12 years of age, the usual oral dosage range is 0.05–0.15 mg/kg daily given in 2 or 3 divided doses; however, severely disturbed psychotic children may require higher dosages. Dosage during prolonged maintenance therapy should be kept at the lowest possible effective level; once an adequate response has been achieved, dosage should be gradually reduced and subsequently adjusted according to the patient's therapeutic response and tolerance.

For the management of non-psychotic behavioral problems and for the control of Tourette's disorder in children 3–12 years of age, the usual oral dosage range is 0.05–0.075 mg/kg daily given in 2 or 3 divided doses. Unlike psychotic disorders for which prolonged therapy is usually required, non-psychotic or hyperactive behavioral problems in children may be acute, and short-term administration of haloperidol may be adequate. A maximum effective dosage of haloperidol for the management of behavioral problems in children has not been established; however, the manufacturers state that there is little evidence that improvement in behavior is further enhanced at dosages greater than 6 mg daily.

IM Dosage For the prompt control of acutely agitated patients with moderately severe to very severe symptoms, the usual initial adult IM dose of haloperidol lactate is 2–5 mg (of haloperidol) given as a single dose. Depending on the response of the patient, this dose may be repeated as often as every hour; however, IM administration of haloperidol lactate every 4–8 hours may be adequate to control symptoms in some patients.

Oral therapy should replace short-acting parenteral therapy as soon as possible. Depending on the patient's clinical status, the first oral dose should be given within 12–24 hours following administration of the last parenteral dose of haloperidol lactate. Since bioavailability studies to establish bioequivalence between oral and parenteral dosage forms of haloperidol have not been conducted to date; the manufacturers suggest that the parenteral dosage administered during the preceding 24 hours be used for initial approximation of the total daily oral dosage required. Since this dosage is only an initial estimate, patients being switched from parenteral haloperidol lactate therapy to oral therapy should be closely monitored, particularly for clinical signs and symptoms of efficacy, sedation, and adverse effects, for the first several days following initiation of oral therapy. Subsequent dosage may be increased or decreased according to the patient's tolerance and therapeutic response, using the lowest possible effective dosage.

For patients requiring prolonged antipsychotic therapy (e.g., patients with

Advice to Patients

Importance of reading manufacturer's patient information.

Importance of informing clinicians of existing or contemplated concomitant therapy, including prescription (see Drug Interactions: Drugs That Prolong QT Interval) or OTC drugs, dietary supplements, and/or herbal products, as well as any concomitant illnesses (e.g., cardiovascular disease, diabetes mellitus).

Because somnolence and impairment of judgment, thinking, or motor skills may be associated with ziprasidone, avoid driving, operating machinery, or performing hazardous tasks while taking ziprasidone until gain experience with the drug's effects.

Importance of taking medication exactly as prescribed by the clinician.

Importance of women informing clinicians immediately if they are or plan to become pregnant or plan to breast-feed.

Importance of informing patients of other important precautionary information. (See Cautions.)

Overview (see Users Guide). For additional information until a more detailed monograph is developed and published, the manufacturer's labeling should be consulted. It is *essential* that the manufacturer's labeling be consulted for more detailed information on usual cautions, precautions, contraindications, potential drug interactions, laboratory test interferences, and acute toxicity.

Preparations

Excipients in commercially available drug preparations may have clinically important effects in some individuals; consult specific product labeling for details.

Ziprasidone Hydrochloride

Oral		
Capsules	20 mg	Geodon®, Pfizer
	40 mg	Geodon®, Pfizer
	60 mg	Geodon®, Pfizer
	80 mg	Geodon®, Pfizer

Ziprasidone Mesylate

Parenteral		
For Injection, for IM use only	20 mg (of ziprasidone)	Geodon®, Pfizer

BUTYROPHENONES 28:16.08.08

Haloperidol

■ Haloperidol is a butyrophenone-derivative antipsychotic agent. The drug is considered a conventional or first-generation antipsychotic agent.

Uses

■ **Psychotic Disorders** Haloperidol is used for the symptomatic management of psychotic disorders. Drug therapy is integral to the management of acute psychotic episodes and accompanying violent behavior in patients with schizophrenia and generally is required for long-term stabilization to improve symptoms between episodes and to minimize the risk of recurrent acute episodes. Antipsychotic agents are the principal class of drugs used for the management of all phases of schizophrenia and generally are effective in all subtypes of the disorder and subgroups of patients. Conventional antipsychotic agents, such as haloperidol, generally are considered to exhibit similar efficacy in treating acute psychotic symptoms, although they vary in their potency and adverse effect profile. Haloperidol is a high-potency antipsychotic that has been shown to be effective in the management of acute and stable phases of schizophrenia, but is frequently associated with extrapyramidal reactions such as akathisia, dystonia, or parkinsonian symptoms, even at low dosages.

Results of short-term studies indicate that haloperidol is more effective than placebo and equally or less effective than atypical antipsychotics in the treatment of positive (e.g., delusions, hallucinations) and negative symptoms (e.g., withdrawal from social interaction, blunted emotional expression) of schizophrenia. However, in one clinical study, haloperidol was less effective than the atypical antipsychotic agent risperidone in preventing relapse in adult outpatients with clinically active schizophrenia or schizoaffective disorders who were assigned to receive either drug for a minimum of 1 year. In this study, approximately 40% of patients in the study who received usual dosages of haloperidol had relapsed by the end of the study compared with approximately 25% of those receiving usual dosages of risperidone. Because atypical antipsychotics appear to be at least as effective in the treatment of positive symptoms and possibly more effective in the treatment of negative symptoms of schizophrenia and have fewer extrapyramidal reactions, some clinicians prefer use of atypical antipsychotics rather than conventional antipsychotics, such as haloperidol, for the management of schizophrenia, except in stable patients who have had good response to conventional antipsychotics without major adverse effects, in patients who require IM therapy, which is not yet available for some atypical antipsychotics, and for the acute management of aggression/violence in some patients, particularly those requiring long-acting (depot) parenteral preparations. However, patient response and tolerance to antipsychotic agents are variable, and patients who do not respond to or tolerate one drug may be successfully treated with an agent from a different class or with a different adverse effect profile.

The long-acting decanoate ester of haloperidol is used parenterally principally in patients requiring prolonged antipsychotic therapy (e.g., patients with chronic schizophrenic disorder). Parenteral antipsychotic therapy with a long-acting preparation may be particularly useful in patients with a history of poor compliance. In addition, long-acting antipsychotic preparations may be useful in patients with suspected GI malabsorption or variable GI absorption of the drug. The principal disadvantage of long-acting parenteral antipsychotics is the inability to terminate the drug's action when severe adverse reactions occur. Long-acting antipsychotic preparations should not be used in the acute management of severely agitated patients. Generally, patients should be stabilized on antipsychotic medication prior to conversion to haloperidol decanoate therapy and should have previously received and tolerated a shorter-acting haloperidol preparation so that the possibility of an unexpected adverse reaction that potentially could not be readily reversed following the decanoate can be minimized. For further information on the use of antipsychotic agents in the symptomatic treatment of schizophrenia, see Uses: Psychotic Disorders, in the Phenothiazines General Statement 28:16.08.24.

■ **Tourette's Syndrome** Haloperidol is used for the control of tics and vocal utterances of Tourette's syndrome (Gilles de la Tourette's syndrome) in children and adults. Haloperidol generally has been considered the drug of choice for the management of Tourette's syndrome and pimozide has been be an effective alternative in some patients who have an inadequate response to or do not tolerate haloperidol. Because limited data suggest that pimozide may be more effective than haloperidol in reducing tics and pimozide appears to be better tolerated than haloperidol, some clinicians and experts prefer the use of pimozide in patients with Tourette's syndrome.

In children with tic disorders (e.g., Tourette's syndrome) and comorbid attention deficit hyperactivity disorder† (ADHD) in whom stimulants alone cannot control tics, haloperidol may be used concomitantly with a stimulant.

■ **Delirium** Antipsychotic agents, mainly haloperidol, have been used in the management of delirium†.

General Considerations Delirium is principally a disturbance of consciousness, attention, cognition, and perception but also may affect sleep, psychomotor activity, and emotions. It is a common psychiatric illness among medically compromised patients, particularly hospitalized patients, and may be a harbinger of substantial morbidity and mortality.

Prevalence and Course The prevalence of delirium in hospitalized medically ill patients ranges from 10–30%; in those who are elderly, delirium ranges up to 40%. Up to 25% of hospitalized cancer patients and 30–40% of hospitalized patients with acquired immunodeficiency syndrome (AIDS) develop delirium. Up to about 50% of postoperative patients develop delirium, and up to 80% of terminally ill patients develop it near death. EEG abnormalities, mainly generalized slowing, have fairly good sensitivity for aiding in the diagnosis of delirium, but the absence of such changes does not rule out the diagnosis. Prodromal manifestations may progress to full-blown delirium over 1–3 days; the duration of delirium generally ranges from less than a week to more than 2 months, but typically does not exceed 10–12 days. Symptoms persist for up to 30 days or longer in up to 15% of patients, and frequently persist for longer than 1 month in geriatric patients. Although most patients recover fully, delirium may progress to stupor, coma, seizures, and death, particularly if untreated. Full recovery is less likely in geriatric patients and patients with AIDS, possibly because of underlying dementia in both populations.

Underlying general medical conditions associated with delirium include CNS disorders (e.g., head trauma, seizures, postictal state, vascular or degenerative disease), metabolic disorders (e.g., renal or hepatic failure, anemia, hypoxia, hypoglycemia, thiamine deficiency, endocrinopathy, fluid or electrolyte imbalance, acid-base imbalance), cardiopulmonary disorder (myocardial infarction, congestive heart failure, cardiac arrhythmia, shock, respiratory failure), and systemic illness (e.g., substance intoxication or withdrawal, infection, cancer, severe trauma, sensory deprivation, temperature dysregulation, postoperative state).

Management Overview. Clinicians should undertake an essential array of psychiatric management tasks designed to provide immediate interventions for urgent general medical conditions, identify and treat the etiology of delirium, ensure safety of the patient and others in contact with the patient, and improve the patient's functioning. Environmental (e.g., varying light levels in intensive care units to heighten awareness about time of day and reduce the perception of timelessness) and supportive interventions (e.g., to deal with disorientation, to assure the patient that manifestations are temporary and reversible and do not reflect a persistent psychiatric disorder) also generally are offered to patients with delirium† and are designed to reduce factors that may exacerbate delirium; to reorient patients, and to provide support. Patients may have life-threatening medical conditions that require therapeutic intervention

even before a specific or definitive cause of the delirium is determined. The goal of diagnosis is to identify potentially reversible causes of delirium and prevent complications through prompt treatment of these specific disorders. Psychiatric management is essential and should be undertaken for all patients with delirium. Somatic interventions principally consist of drug therapy. The choice of somatic intervention will depend on the specific features of the patient's clinical condition, the underlying etiology of the delirium, and any associated comorbid conditions.

Drug Therapy. Antipsychotic agents often are the drugs of choice for the management of delirium†. Although other drugs (e.g., phenothiazines, droperidol) have been used, haloperidol generally is considered the antipsychotic of choice for most patients with delirium because of its relatively low risk of anticholinergic activity and of sedative and hypotensive effects. In addition, haloperidol has been studied most extensively, although few studies have used standardized definitions of delirium or reliable and valid delirium symptom rating measures to assess symptom severity before and after initiation of treatment. For drugs other than haloperidol, there have been no large, prospective studies that included a control. Evidence of efficacy for such alternative therapies, including second-generation antipsychotic agents (e.g., olanzapine, quetiapine, risperidone, ziprasidone), is principally from small case series, case reports, or open-label studies. In addition, interpretation of findings from many such case presentations is difficult because of use of nonstandardized delirium definitions and/or informal measures of delirium symptom severity. In general, evidence of the efficacy of antipsychotics, including haloperidol, in the management of delirium comes from numerous case reports and uncontrolled studies. However, evidence from a randomized, double-blind, comparator-drug controlled study (haloperidol, chlorpromazine, and lorazepam) in patients with AIDS that employed standardized clinical measures of delirium demonstrated clinical superiority of antipsychotic agents compared with benzodiazepines. Statistically significant improvement in the Delirium Rating Scale was evident after 2 days in patients receiving haloperidol or chlorpromazine but not in the lorazepam group (mean decreases in the score [i.e., improvement] were 8, 8.5, and 1, respectively). The symptomatic improvement in delirium occurred quickly among patients receiving antipsychotic therapy, usually before initiation of interventions directed at the medical etiologies of delirium.

Although various antipsychotic agents may be given orally, IM, or IV, IV administration is considered most effective in emergency situations or where oral access is limited. In addition, some evidence indicates that IV administration of antipsychotic agents may be associated with less severe extrapyramidal effects.

Special Precautions. Antipsychotic agents, particularly IV† haloperidol, used in the management of delirium have been associated with lengthening of the QT interval, possibly leading to atypical ventricular tachycardia (torsades de pointes), ventricular fibrillation, and sudden death. The manufacturer of Haldol® and the US Food and Drug Administration (FDA) state that although injectable haloperidol is approved *only* for IM injection and *not for IV administration*, there is considerable evidence from the medical literature that IV† administration of the drug is a relatively common, unlabeled ("off-label") clinical practice, principally for the treatment of severe agitation in intensive care units, and recommend ECG monitoring in any patient receiving the drug IV. Many clinicians also recommend that baseline and periodic or continuous ECG monitoring be performed with special attention paid to the length of the QT_c interval. Prolongation of the QT_c interval to greater than 450 msec or to greater than 15–25% over that in previous ECGs may warrant telemetry, a cardiology consultation, and dose reduction or discontinuance. Serum concentrations of magnesium and potassium also should be monitored at baseline and periodically in critically ill patients, especially those with baseline QT_c intervals of 440 msec or longer, those receiving other drugs known to increase the QT interval, and those who have electrolyte disorders. Limited evidence suggests that the incidence of torsades de pointes in patients receiving haloperidol IV is about 0.4–3.6%, but may increase to greater than 10% at relatively high IV doses (e.g., 35 mg or more over 24 hours). (See Cautions: Cardiovascular Effects and also see Cautions: Precautions and Contraindications.)

■ **Disruptive Behavior Disorder and Attention Deficit Hyperactivity Disorder** Haloperidol is used for the treatment of severe behavioral problems in children marked by combativeness and/or explosive hyperexcitable behavior (out of proportion to immediate provocations), and for the short-term treatment of hyperactive children who exhibit excessive motor activity with accompanying conduct disorders that are manifested as impulsive behavior, difficulty sustaining attention, aggression, mood lability, and/or poor frustration tolerance. However, the possible risks of tardive dyskinesia, withdrawal dyskinesia, and other extrapyramidal reactions should be considered. Some experts currently recommend use of haloperidol only for the treatment of comorbid tics in children with attention deficit hyperactivity disorder (ADHD). Some clinicians recommend routine administration of the Abnormal Involuntary Movement Scale (AIMS) to all children receiving antipsychotic agents.

■ **Nausea and Vomiting** Haloperidol also has been used in the prevention and control of severe nausea and vomiting† (e.g., cancer chemotherapy-induced emesis). Based on limited data, haloperidol appears to be as effective as phenothiazines in the prevention of cancer chemotherapy-induced emesis. Additional studies are required to determine the efficacy of haloperidol in the prevention and control of severe nausea and vomiting.

Dosage and Administration

■ **Administration** Haloperidol is administered orally. Haloperidol lactate is administered orally or by IM injection, and haloperidol decanoate is administered by IM injection. Pending accumulation of further data to establish safety and efficacy, IM administration of haloperidol lactate or decanoate in children is not recommended by the manufacturers. Haloperidol *lactate* also has been administered by IV injection† or infusion†. Haloperidol decanoate injection should *not* be administered IV.

Haloperidol decanoate should be administered by deep IM injection into the gluteal region using a 21-gauge needle. The manufacturers of haloperidol decanoate state that the maximum volume of haloperidol decanoate should not exceed 3 mL per IM injection site.

Haloperidol lactate and decanoate injections should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

■ **Dosage** Dosage of haloperidol lactate and the decanoate is expressed in terms of haloperidol.

There is considerable interindividual variation in optimum dosage requirements of haloperidol, and dosage must be carefully adjusted according to individual requirements and response, using the lowest possible effective dosage. Dosage should be increased more gradually in children and in debilitated, emaciated, or geriatric patients. Because of the risk of adverse reactions associated with cumulative effects of butyrophenones, patients with a history of long-term therapy with haloperidol and/or other antipsychotic agents should be evaluated periodically to determine whether maintenance dosage could be decreased or drug therapy discontinued.

Oral Dosage For the symptomatic management of psychotic disorders or Tourette's disorder in adults with moderate symptomatology and in geriatric or debilitated patients, the usual initial oral dosage of haloperidol is 0.5–2 mg 2 or 3 times daily. Subsequent dosage should be carefully adjusted according to the patient's tolerance and therapeutic response. Dosage during prolonged maintenance therapy should be kept at the lowest effective level.

The usual initial oral dosage of haloperidol for adults with severe symptomatology and/or chronic or resistant disorders is 3–5 mg 2 or 3 times daily. To achieve prompt control, higher dosages may be required in some patients. Patients who remain severely disturbed or inadequately controlled may require dosage adjustment. Oral dosages up to 100 mg daily may be required in some severely psychotic patients. Occasionally, dosages exceeding 100 mg daily have been used for the management of severely resistant disorders in adults; however, the safety of prolonged administration of such dosages has not been demonstrated.

The usual initial oral dosage of haloperidol in children 3–12 years of age and weighing 15–40 kg is 0.5 mg daily given in 2 or 3 divided doses. Subsequent dosage may be increased by 0.5 mg daily at 5- to 7-day intervals, depending on the patient's tolerance and therapeutic response.

For the symptomatic management of psychotic disorders in children 3–12 years of age, the usual oral dosage range is 0.05–0.15 mg/kg daily given in 2 or 3 divided doses; however, severely disturbed psychotic children may require higher dosages. Dosage during prolonged maintenance therapy should be kept at the lowest possible effective level; once an adequate response has been achieved, dosage should be gradually reduced and subsequently adjusted according to the patient's therapeutic response and tolerance.

For the management of non-psychotic behavioral problems and for the control of Tourette's disorder in children 3–12 years of age, the usual oral dosage range is 0.05–0.075 mg/kg daily given in 2 or 3 divided doses. Unlike psychotic disorders for which prolonged therapy is usually required, non-psychotic or hyperactive behavioral problems in children may be acute, and short-term administration of haloperidol may be adequate. A maximum effective dosage of haloperidol for the management of behavioral problems in children has not been established; however, the manufacturers state that there is little evidence that improvement in behavior is further enhanced at dosages greater than 6 mg daily.

IM Dosage For the prompt control of acutely agitated patients with moderately severe to very severe symptoms, the usual initial adult IM dose of haloperidol lactate is 2–5 mg (of haloperidol) given as a single dose. Depending on the response of the patient, this dose may be repeated as often as every hour; however, IM administration of haloperidol lactate every 4–8 hours may be adequate to control symptoms in some patients.

Oral therapy should replace short-acting parenteral therapy as soon as possible. Depending on the patient's clinical status, the first oral dose should be given within 12–24 hours following administration of the last parenteral dose of haloperidol lactate. Since bioavailability studies to establish bioequivalence between oral and parenteral dosage forms of haloperidol have not been conducted to date, the manufacturers suggest that the parenteral dosage administered during the preceding 24 hours be used for initial approximation of the total daily oral dosage required. Since this dosage is only an initial estimate, patients being switched from parenteral haloperidol lactate therapy to oral therapy should be closely monitored, particularly for clinical signs and symptoms of efficacy; sedation, and adverse effects, for the first several days following initiation of oral therapy. Subsequent dosage may be increased or decreased according to the patient's tolerance and therapeutic response, using the lowest possible effective dosage.

For patients requiring prolonged antipsychotic therapy (e.g., patients with

chronic schizophrenic disorder), the long-acting haloperidol decanoate injection may be considered. If the decanoate is used, the patient's condition should initially be stabilized with an antipsychotic agent prior to attempting conversion to haloperidol decanoate. In addition, if the patient is receiving an antipsychotic agent other than haloperidol, it is recommended that the patient initially be converted to oral haloperidol therapy in order to minimize the risk of an unexpected adverse reaction to the drug, which might not be readily reversible following use of the decanoate.

The initial IM dose of haloperidol decanoate should be based on the patient's clinical history, physical condition, and response to previous antipsychotic therapy. To determine the minimum effective dosage, haloperidol decanoate therapy has been initiated at low initial doses and gradually titrated upward as necessary. A precise formula for converting from oral haloperidol dosage to IM haloperidol decanoate has not been established, but an initial adult dose 10–20 times the previous daily dose of oral haloperidol, not exceeding 100 mg (regardless of previous antipsychotic dosage requirements), is suggested, although limited clinical experience suggests that a lower initial dosage of the decanoate may be adequate. If conversion requires an initial dosage of haloperidol decanoate higher than 100 mg daily, such dosage should be administered in 2 injections (i.e., administering a maximum initial dose of 100 mg followed by the balance in 3–7 days). However, some clinicians have converted therapy to the decanoate using a higher initial dosage.

IM haloperidol decanoate usually has been administered at monthly intervals (i.e., every 4 weeks), but individual response may dictate the need for adjusting the dosing interval as well as the dose.

Lower initial dosages (e.g., 10–15 times the previous daily dose of oral haloperidol) and more gradual upward titration are recommended for patients who are geriatric, debilitated, or stabilized on low oral dosages.

Close clinical observation is required during dosage titration in order to minimize the risk of overdosage and of emergence of psychotic manifestations prior to the next dose. If supplemental antipsychotic therapy is necessary during periods of dosage titration or for control of acute exacerbations of psychotic manifestations, a short-acting haloperidol preparation should be used. Experience with haloperidol decanoate dosages exceeding 450 mg (of haloperidol) monthly is limited.

IV Dosage The optimum dosage of haloperidol for the treatment of delirium has not been established. However, initiation of IV† haloperidol with dosages of 1–2 mg every 2–4 hours in adults has been suggested. Lower IV dosages (e.g., 0.25–0.5 mg every 4 hours) have been suggested for geriatric patients with delirium; severely agitated adults may require titration to higher dosages. Although single IV doses up to 50 mg or total daily dosages of 500 mg have been reported in adults, the risk of adverse effects, particularly prolongation of the QT interval and torsades de pointes, must be considered. (See Uses: Delirium and see also Cautions: Cardiovascular Effects and Cautions: Precautions and Contraindications.) Some evidence suggests that the risk of torsades de pointes increases at total daily dosages of 35–50 mg or more. In patients requiring multiple IV injections of the drug to control delirium (e.g., more than eight 10-mg doses in 24 hours or more than 10 mg/hour for more than 5 consecutive hours), consideration can be given to continuous IV infusion† of haloperidol; in such patients, an initial 10-mg dose followed by an infusion of 5–10 mg/hour has been suggested. If agitation persists, repeat 10-mg IV doses at 30-minute intervals, accompanied by a 5 mg/hour increase in the infusion rate, can be considered. ECG should be determined at baseline and periodically or continuously thereafter, with special attention paid to possible prolongation of the QT interval, and dosage should be reduced or the drug discontinued if clinically important QT prolongation (e.g., 15–25% or more over baseline) occurs or the QT_c exceeds 450 msec. (See Uses: Delirium and see also Cautions: Cardiovascular Effects and Cautions: Precautions and Contraindications.)

Cautions

Haloperidol shares the toxic potentials of phenothiazines, and the usual precautions of phenothiazine therapy should be observed. The total incidence of adverse effects associated with haloperidol is similar to that associated with piperazine-derivative phenothiazines. (See Cautions in the Phenothiazines General Statement 28:16.08.24.)

Geriatric patients with dementia-related psychosis treated with antipsychotic agents are at an increased risk of mortality. (See Cautions: Geriatric Precautions.)

■ **Nervous System Effects** The most frequent adverse effects of haloperidol involve the CNS.

Extrapyramidal Reactions Extrapyramidal reactions occur frequently with haloperidol, especially during the first few days of therapy. In most patients, these reactions consist of parkinsonian symptoms (e.g., marked drowsiness and lethargy, drooling or hypersalivation, fixed stare), which are mild to moderate in severity and are usually reversible following discontinuance of the drug. Other adverse neuromuscular reactions have been reported less frequently, but are often more severe, and include feelings of motor restlessness (i.e., akathisia), tardive dystonia, and dystonic reactions (e.g., hyperreflexia, opisthotonos, oculogyric crisis, torticollis, trismus). Generally, the occurrence and severity of most extrapyramidal reactions are dose related, since they occur at relatively high dosages and disappear or become less severe following a reduction in dosage; however, severe extrapyramidal reactions have reportedly occurred at relatively low dosages. Most patients respond rapidly to treatment with an anticholinergic antiparkinsonian drug (e.g., benztropine, trihexyphenidyl). If persistent extrapyramidal reactions occur, haloperidol therapy may have to be discontinued.

Neuroleptic malignant syndrome (NMS) may occur in patients receiving haloperidol or other antipsychotic therapy. NMS is potentially fatal and requires immediate discontinuance of the drug and initiation of intensive symptomatic and supportive care. For additional information on NMS, see Extrapyramidal Reactions in Cautions: Nervous System Effects, in the Phenothiazines General Statement 28:16.08.24.

Tardive Dyskinesia Like other antipsychotic agents (e.g., phenothiazines), haloperidol has been associated with persistent dyskinesias. Tardive dyskinesia may occur in some patients during long-term administration of haloperidol or it may occur following discontinuance of the drug. The risk of developing tardive dyskinesia appears to be greater in geriatric patients receiving high dosages of the drug, especially females. The symptoms are persistent, and in some patients appear to be irreversible. Tardive dyskinesia is characterized by rhythmic involuntary movements of the tongue, face, mouth, or jaw (e.g., protrusion of the tongue, puffing of cheeks, chewing movements, puckering of the mouth), which sometimes may be accompanied by involuntary movements of the extremities and/or trunk. Although not clearly established, the risk of developing the syndrome and the likelihood that it will become irreversible may increase with the duration of therapy and total cumulative dose of antipsychotic agent(s) administered; however, the syndrome may occur, although much less frequently, after relatively short periods of treatment with low dosages. There is no proven or uniformly effective treatment for tardive dyskinesia; antiparkinsonian agents do not alleviate and tend to exacerbate the symptoms of this syndrome. If possible, antipsychotic agents should be discontinued if signs or symptoms of tardive dyskinesia occur. The syndrome may partially or completely remit if antipsychotic agents are discontinued, although some patients may require many months for improvement. Tardive dyskinesia may be masked if therapy is reinstituted, dosage is increased, or therapy with another antipsychotic agent is initiated. The effect that masking of the symptoms may have on the long-term course of the syndrome is not known. Fine vermicular movement of the tongue may be an early sign of the syndrome; prompt discontinuance of haloperidol after this sign occurs may prevent development of the syndrome.

In general, abrupt withdrawal of antipsychotic agents following short-term administration is not associated with adverse effects; however, transient dyskinetic signs have occurred following abrupt withdrawal in patients receiving prolonged maintenance therapy with haloperidol. In some patients, the dyskinetic movements are indistinguishable, except on the basis of their duration, from tardive dyskinesia. It is not known whether gradual withdrawal of antipsychotic agents reduces the incidence of withdrawal-emergent neurologic signs; however, if haloperidol therapy must be discontinued, gradual withdrawal of the drug is recommended, if possible, pending further accumulation of data.

Other Nervous System Effects Tardive dystonia, not associated with tardive dyskinesia, has occurred in patients receiving haloperidol. Tardive dystonia is characterized by delayed onset of choreic or dystonic movements, often is persistent, and potentially can become irreversible.

Other adverse nervous system effects of haloperidol include insomnia, restlessness, anxiety, euphoria, agitation, drowsiness, depression, lethargy, headache, confusion, vertigo, and tonic-clonic seizures. Exacerbation of psychotic symptoms (including hallucinations and catatonic-like behavior), which may subside following discontinuance of therapy or treatment with anticholinergic agents, has also been reported.

Adverse anticholinergic effects of haloperidol include dry mouth (xerostomia), blurred vision, constipation, urinary retention, and diaphoresis. Priapism has also occurred.

■ **Hematologic Effects** Mild and usually transient leukopenia/neutropenia and leukocytosis have been reported in patients receiving antipsychotic agents, including haloperidol. Agranulocytosis (including fatal cases) has also been reported rarely in patients receiving haloperidol, but only when combined with other drugs. Possible risk factors for leukopenia and neutropenia include preexisting low leukocyte count and a history of drug-induced leukopenia or neutropenia. (See Cautions: Precautions and Contraindications.) Other adverse hematologic effects associated with haloperidol include anemia, minimal decreases in erythrocyte count, and a tendency toward lymphomonocytosis.

■ **Endocrine and Metabolic Effects** Moderate engorgement of the breast with lactation has occurred in some females receiving haloperidol. Galactorrhea, mastalgia, gynecomastia, increased libido, impotence, hyperglycemia, hypoglycemia, and hyponatremia have also occurred in some patients. Antipsychotic agents increase serum prolactin concentrations. (See Cautions: Mutagenicity and Carcinogenicity.) Although not reported to date with haloperidol, the manufacturers caution that decreases in serum cholesterol concentration have occurred in patients receiving chemically related drugs.

■ **Cardiovascular Effects** Tachycardia, hypotension, hypertension, ECG changes (including those compatible with QT-interval prolongation and the polymorphous configuration of torsades de pointes), and sudden death have been reported in patients receiving haloperidol. The US Food and Drug Administration (FDA) states that there have been at least 28 case reports of QT-interval prolongation and torsades de pointes, including some that were fatal, in patients receiving the drug IV†. In addition, FDA states that case-control

studies have demonstrated a dose-dependent relationship between IV haloperidol dosage and subsequent development of torsades de pointes. A postmarketing analysis of a worldwide safety database revealed 229 reports of QT-interval prolongation and torsades de pointes with oral or parenteral haloperidol; many of these cases were confounded by concomitant administration of drugs known to prolong the QT interval or medical conditions associated with QT-interval prolongation. The reports included 73 cases of torsades de pointes, 11 of which were fatal. In 8 out of 11 fatal cases, haloperidol was administered IV in various dosages. In another postmarketing analysis of adverse cardiovascular events associated with haloperidol decanoate, 13 cases of torsades de pointes, QT-interval prolongation, ventricular arrhythmias, and/or sudden death were identified.

FDA states that it is not possible to estimate the frequency with which QT-interval prolongation or torsades de pointes occurs following administration of haloperidol based on these case reports alone. However, use of higher than recommended doses of any haloperidol formulation and IV administration of the drug appear to be associated with an increased risk of these effects. Many of the reported cases of QT-interval prolongation and torsades de pointes have occurred in patients receiving relatively high dosages of IV haloperidol (e.g., exceeding 35 mg daily); however, such effects also have been reported in patients receiving lower IV dosages or oral therapy. Although cases of sudden death, torsades de pointes, and QT-interval prolongation have been reported even in the absence of predisposing factors, FDA, the manufacturer of Haldol®, and some clinicians state that particular caution is advised when using any formulation of haloperidol in patients who have other QT-interval prolonging conditions, including electrolyte imbalance (particularly hypokalemia and hypomagnesemia), underlying cardiac abnormalities, hypothyroidism, or familial long QT syndrome, or those who are concomitantly taking medications known to prolong the QT interval. (See Uses: Delirium, Cautions: Precautions and Contraindications, and Acute Toxicity: Manifestations.) FDA states that clinicians should consider this new cardiovascular risk information when making individual treatment decisions for their patients.

Cases of sudden and unexpected death have been reported in haloperidol-treated patients. The nature of the evidence makes it impossible to determine definitively what role, if any, haloperidol played in the outcome of the cases reported to date. Although the possibility that haloperidol played a causative role in these deaths cannot be excluded, it should be kept in mind that sudden and unexpected death may occur in psychotic patients when they remain untreated or when they are treated with other antipsychotic medications.

■ **Other Adverse Effects** Impaired liver function and/or jaundice, maculopapular and acneiform dermatologic reactions, photosensitivity, alopecia, anorexia, diarrhea, hypersalivation, dyspepsia, nausea, vomiting, cataracts, retinopathy, and visual disturbances have also been reported.

Hyperpyrexia and heat stroke, not associated with neuroleptic malignant syndrome (see Extrapyramidal Reactions in Cautions: Nervous System Effects), have been reported in some patients receiving haloperidol.

Laryngospasm, bronchospasm, and increased depth of respiration have occurred in patients receiving haloperidol. Bronchopneumonia, resulting in fatalities in some patients, has occurred following the use of antipsychotic agents, including haloperidol. It has been suggested that lethargy and decreased thirst, resulting from central inhibition, may cause dehydration, hemoconcentration, and reduced pulmonary ventilation.

Hyperammonemia following haloperidol treatment has been reported in at least one child with citrullinemia, an inherited disorder of ammonia excretion.

■ **Precautions and Contraindications** Haloperidol shares the toxic potentials of other antipsychotic agents (e.g., phenothiazines), and the usual precautions associated with therapy with these agents should be observed. (See Cautions in the Phenothiazines General Statement 28:16.08.24.)

Geriatric patients with dementia-related psychosis treated with antipsychotic agents are at an increased risk of mortality. (See Cautions: Geriatric Precautions.)

Patients should be warned that haloperidol may impair their ability to perform activities requiring mental alertness or physical coordination (e.g., operating machinery, driving a motor vehicle). Patients also should be warned that haloperidol may enhance their response to alcohol, barbiturates, or other CNS depressants.

Because of the possibility of transient hypotension and/or precipitation of angina, haloperidol should be used with caution in patients with severe cardiovascular disorders. If hypotension occurs, metaraminol, norepinephrine, or phenylephrine may be used; epinephrine should *not* be used since haloperidol causes a reversal of epinephrine's vasopressor effects and a further lowering of blood pressure.

Since haloperidol may lower the seizure threshold, the drug should be used with caution in patients receiving anticonvulsant agents and in those with a history of seizures or EEG abnormalities. Adequate anticonvulsant therapy should be maintained during administration of haloperidol.

The manufacturers state that haloperidol should be used with caution in patients with known allergies or with a history of allergic reactions to drugs.

When concomitant therapy with an antiparkinsonian drug is necessary to manage haloperidol-induced extrapyramidal symptoms, it may be necessary to continue the antiparkinsonian drug for a period of time after discontinuance of haloperidol in order to prevent emergence of these symptoms.

The manufacturers caution that when haloperidol is used to control mania in patients with bipolar disorder, there may be a rapid mood swing to depression.

Haloperidol should be used with caution in patients with thyrotoxicosis since severe neurotoxicity (e.g., rigidity, inability to walk or talk) may occur in these patients during therapy with an antipsychotic agent.

Cases of leukopenia and neutropenia have been reported in patients receiving antipsychotic agents, including haloperidol; agranulocytosis (including fatal cases) has also been reported. (See Cautions: Hematologic Effects.) Patients with a preexisting low leukocyte count or a history of drug-induced leukopenia or neutropenia should have their complete blood count monitored frequently during the first few months of therapy and haloperidol should be discontinued at the first sign of a decline in the leukocyte count in the absence of other causative factors. Haloperidol-treated patients with neutropenia should be carefully monitored for fever or other signs or symptoms of infection and be treated promptly should such signs and symptoms occur. Patients with severe neutropenia (absolute neutrophil count less than 1000/mm^3) should discontinue haloperidol and have their leukocyte count followed until recovery.

Care should be taken to avoid skin contact with haloperidol lactate oral solution and injection, since contact dermatitis has occurred rarely.

Cases of sudden death, QT-interval prolongation, and torsades de pointes have been reported in patients receiving haloperidol. (See Uses: Delirium and see also Cautions: Cardiovascular Effects.) Use of higher than recommended doses of any haloperidol formulation and IV† administration of the drug appear to be associated with an increased risk of QT-interval prolongation and torsades de pointes. Although these effects have been reported in the absence of predisposing factors, haloperidol should be used with particular caution in patients with other conditions that prolong the QT interval, including electrolyte imbalance (particularly hypokalemia and hypomagnesemia), underlying cardiac abnormalities, hypothyroidism; and familial long QT syndrome, as well as in those concurrently receiving other drugs known to prolong the QT interval. In addition, ECG monitoring is recommended whenever haloperidol is administered IV. (See Uses: Delirium.)

Haloperidol is contraindicated in patients with severe toxic CNS depression or in those who are comatose from any cause. Haloperidol also is contraindicated in patients who are hypersensitive to the drug and in those with parkinsonian syndrome.

■ **Pediatric Precautions** Safety and efficacy of haloperidol decanoate injection in children have not been established, and safety and efficacy of other haloperidol preparations in children younger than 3 years of age have not been established. Hyperammonemia was reported during postmarketing surveillance in a 5.5-year-old child with citrullinemia, an inherited disorder of ammonia excretion, following haloperidol therapy.

■ **Geriatric Precautions** Clinical studies of haloperidol did not include sufficient numbers of geriatric patients 65 years of age and older to determine whether this age group responds differently from younger adults. Other reported clinical experience has not consistently identified differences in responses between geriatric and younger patients. However, the prevalence of tardive dyskinesia appears to be highest among geriatric patients, particularly elderly women. In addition, the pharmacokinetics of haloperidol generally warrant the use of reduced dosages in geriatric patients. (See Dosage and Administration: Dosage.)

Geriatric patients with dementia-related psychosis treated with either conventional or atypical antipsychotic agents are at an increased risk of mortality. Analyses of 17 placebo-controlled trials (modal duration of 10 weeks) in geriatric patients mainly receiving atypical antipsychotic agents revealed an approximate 1.6- to 1.7-fold increase in mortality compared with that in patients receiving placebo. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5% compared with a rate of about 2.6% in those receiving placebo. Although the causes of death were varied in these trials, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Subsequently, 2 observational, epidemiologic studies have indicated that, similar to atypical antipsychotic agents, treatment with conventional antipsychotic agents may increase mortality; the causes of death were not reported in the first study, and cancer and cardiac disease were the causes of death with the highest relative risk in the second study. However, the extent to which these findings of increased mortality in observational studies may be attributed to the antipsychotic agent as opposed to certain patient characteristics remains unclear.

The US Food and Drug Administration (FDA) currently advises clinicians that antipsychotic agents, including haloperidol, are *not* approved for the treatment of dementia-related psychosis. The FDA further advises clinicians that no drugs currently are approved for the treatment of dementia-associated psychosis and that other management options should be considered in patients with this disorder. The decision whether to prescribe antipsychotic agents "off-label" in the treatment of dementia symptoms is left to the discretion of the clinician. Clinicians who prescribe antipsychotic agents for geriatric patients with dementia-related psychosis should discuss the increased mortality risk with patients, their families, and their caregivers. In addition, patients currently receiving antipsychotic agents for dementia-associated symptoms should not abruptly stop taking the drugs; caregivers and patients should discuss any possible concerns with their clinician. For additional information on the use of antipsychotic agents for dementia-associated psychosis and other behavioral disturbances, see Geriatric Considerations under Psychotic Disorders: Schizophrenia and Other Psychotic Disorders, in Uses and see also Cautions: Geriatric Precautions, in the Phenothiazines General Statement 28:16.08.24.

■ **Mutagenicity and Carcinogenicity** Negative or inconsistent positive findings have been reported in vitro and in vivo in studies on the effects of conventional preparations of haloperidol on chromosome structure and number. However, the available cytogenetic evidence is considered too inconsistent to be conclusive at this time.

Although an increase in mammary neoplasms has been found in rodents following long-term administration of prolactin-stimulating antipsychotic agents, no clinical or epidemiologic studies conducted to date have shown an association between long-term administration of these drugs and mammary tumorigenesis in humans. Current evidence is considered too limited to be conclusive, and further study is needed to determine the clinical importance in most patients of elevated serum prolactin concentrations associated with antipsychotic agents. Since in vitro tests indicate that approximately one-third of human breast cancers are prolactin dependent, haloperidol should be used with caution in patients with previously detected breast cancer.

■ **Pregnancy, Fertility, and Lactation** Although there are no adequate and controlled studies to date in humans, 2 cases of limb malformations (e.g., phocomelia) have occurred in offspring of women who were given haloperidol concurrently with other potentially teratogenic drugs during the first trimester of pregnancy; these teratogenic effects have not been directly attributed to haloperidol. Haloperidol has been shown to be teratogenic and fetotoxic in animals at dosages 2–20 times the usual maximum human dosage. Haloperidol should be used during pregnancy or in women likely to become pregnant only when the potential benefits justify the possible risks to the fetus.

The effect of haloperidol on fertility in humans is not known. Impotence, increased libido, priapism, and menstrual irregularities have occurred in some individuals during haloperidol therapy.

Haloperidol is distributed into milk. The manufacturers warn that nursing should not be undertaken by women receiving haloperidol.

Drug Interactions

■ **CNS Depressants** Haloperidol may be additive with, or may potentiate the action of, other CNS depressants such as opiates or other analgesics, barbiturates or other sedatives, anesthetics, or alcohol. When haloperidol is used concomitantly with other CNS depressants, caution should be used to avoid excessive sedation.

■ **Lithium** Although most patients receiving lithium and an antipsychotic agent (e.g., haloperidol, phenothiazines) concurrently do not develop unusual adverse effects, an acute encephalopathic syndrome occasionally has occurred, especially when high serum lithium concentrations were present. Patients receiving such combined therapy should be observed for evidence of adverse neurologic effects; treatment should be promptly discontinued if such signs or symptoms appear. (See Drug Interactions: Antipsychotic Agents, in the monograph on Lithium Salts 28:28.)

■ **Anticoagulants** Haloperidol has been reported to antagonize the anticoagulant activity of phenindione in one patient. Further study is needed to determine the clinical importance of this interaction.

■ **Rifampin** Concomitant oral therapy with rifampin and haloperidol in schizophrenic patients resulted in a mean 70% decrease in plasma haloperidol concentrations and decreased antipsychotic efficacy. Following discontinuance of rifampin in other schizophrenic patients treated with oral haloperidol, mean haloperidol concentrations increased 3.3-fold. Careful monitoring of clinical status and appropriate dosage adjustment are warranted whenever rifampin is initiated or discontinued in patients stabilized on haloperidol.

■ **Drugs with Anticholinergic Effects** The manufacturers caution that increases in intraocular pressure may occur in patients receiving anticholinergic drugs, including antiparkinsonian agents, concurrently with haloperidol.

■ **Drugs that Prolong QT Interval** Cases of QT-interval prolongation and torsades de pointes have been reported in patients receiving haloperidol. Patients receiving higher than recommended dosages of any haloperidol preparation and those receiving the drug IV appear to be at a higher risk of developing these adverse effects. Particular caution is advised when oral or parenteral haloperidol is used in patients concurrently receiving other drugs that prolong the QT interval.

■ **Methyldopa** Dementia has reportedly occurred in several patients who received haloperidol and methyldopa concomitantly. Although the clinical importance of this possible interaction has not been determined, patients should be carefully observed for adverse psychiatric symptoms if the drugs are used concurrently.

Acute Toxicity

■ **Manifestations** In general, overdosage of haloperidol may be expected to produce effects that are extensions of common adverse reactions; severe extrapyramidal reactions, hypotension, and sedation have been the principal effects reported. Coma with respiratory depression and hypotension (sometimes shock-like) may occur.

Substantial prolongation of the QT interval and atypical ventricular tachycardia (torsades de pointes) have occurred following haloperidol overdosage. The possibility of ECG changes associated with torsades de pointes should be considered following haloperidol overdosage, and ECG and vital signs should be monitored for signs of QT prolongation or dysrhythmias, continuing such monitoring until the ECG is normal.

Following accidental overdosage in a 2-year-old child, hypertension, rather than hypotension, reportedly occurred. Extrapyramidal reactions may consist of muscular weakness or rigidity and a generalized or localized tremor. Manifestations of overdosage with haloperidol decanoate injection may be prolonged.

■ **Treatment** Treatment of haloperidol overdosage generally involves symptomatic and supportive care. There is no specific antidote for haloperidol intoxication; however, anticholinergic or antiparkinsonian drugs may be useful in controlling extrapyramidal reactions associated with haloperidol overdosage.

Following acute ingestion of the drug, the stomach should be emptied by inducing emesis or by gastric lavage. If the patient is comatose, having seizures, or lacks the gag reflex, gastric lavage may be performed if an endotracheal tube with cuff inflated is in place to prevent aspiration of gastric contents. Activated charcoal should be administered after gastric lavage and/or emesis.

ECG and vital signs should be monitored, particularly for signs of QT prolongation or dysrhythmias. Severe arrhythmias should be treated with appropriate antiarrhythmic measures. Appropriate therapy should be instituted if hypotension or excessive sedation occurs; epinephrine should *not* be used (see Cautions: Precautions and Contraindications).

Pharmacology

The principal pharmacologic effects of haloperidol are similar to those of piperazine-derivative phenothiazines. The precise mechanism of antipsychotic action of haloperidol is unclear, but the drug appears to depress the CNS at the subcortical level of the brain, midbrain, and brain stem reticular formation. Haloperidol appears to inhibit the ascending reticular activating system of the brain stem (possibly through the caudate nucleus), thereby interrupting the impulse between the diencephalon and the cortex. The drug may antagonize the actions of glutamic acid within the extrapyramidal system. Inhibition of catecholamine receptors may also be important in the mode of action of haloperidol; the drug may also inhibit the reuptake of various neurotransmitters in the midbrain. Haloperidol appears to have strong central antidopaminergic and weak central anticholinergic activity. Like phenothiazines, haloperidol produces catalepsy and inhibits spontaneous motor activity and conditioned avoidance behaviors in animals. Haloperidol inhibits the central and peripheral effects of apomorphine, produces ganglionic blockade, and reduces affective responses. The precise mechanism of antiemetic action of haloperidol is unclear, but like some phenothiazines (e.g., chlorpromazine, prochlorperazine), haloperidol has been shown to directly affect the chemoreceptor trigger zone (CTZ), apparently by blocking dopamine receptors in the CTZ.

Like other dopamine receptor antagonists (e.g., phenothiazines), haloperidol may cause extrapyramidal reactions, and there appears to be a very narrow range between the effective therapeutic dosage for the management of acute psychotic disorders and that causing extrapyramidal symptoms.

Haloperidol produces less sedation, hypotension, and hypothermia than chlorpromazine.

Pharmacokinetics

■ **Absorption** Haloperidol is well absorbed from the GI tract following oral administration, but appears to undergo first-pass metabolism in the liver. Oral bioavailability of the drug has been reported to average 60%. The drug may undergo some enterohepatic circulation. Peak plasma concentrations of haloperidol occur within 2–6 hours following oral administration. Following IM administration of haloperidol lactate, peak plasma haloperidol concentrations occur within 10–20 minutes and peak pharmacologic action occurs within 30–45 minutes; in acutely agitated patients, control of psychotic manifestations may become apparent within 30–60 minutes, with substantial improvement often occurring within 2–3 hours. Haloperidol concentrations are detectable in plasma for several weeks following administration of a single dose of the drug.

Esterification of haloperidol results in slow and gradual release of haloperidol decanoate from fatty tissues, thus prolonging the duration of action; administration of the ester in a sesame oil vehicle further delays the rate of release. Following IM administration of haloperidol decanoate, plasma haloperidol concentrations are usually evident within 1 day and peak concentrations generally occur within about 6–7 days (range: 1–9 days). Steady-state plasma haloperidol concentrations are usually reached in approximately 3 months following once-monthly IM injection of the decanoate. In one group of patients receiving 20–400 mg monthly, data adjusted to 100-mg monthly doses suggested mean trough plasma haloperidol concentrations of 2 ng/mL after the first dose and of 4 ng/mL at steady state; accumulation during 24 months of therapy was not apparent. Within the usual dosage range, plasma haloperidol concentrations following IM administration of the decanoate are approximately proportional and linearly related to dosage; however, there is considerable interindividual and intraindividual variation in plasma concentrations attained with a given dosage.

■ **Distribution** Distribution of haloperidol into human body tissues and fluids has not been fully characterized. Following administration of haloperidol in animals, the drug is distributed mainly into the liver, with lower concentrations being distributed into the brain, lungs, kidneys, spleen, and heart.

Haloperidol is about 92% bound to plasma proteins.

Haloperidol is distributed into milk.

■ **Elimination** Although the exact metabolic fate has not been clearly established, it appears that haloperidol is principally metabolized in the liver. The drug appears to be metabolized principally by oxidative *N*-dealkylation of the piperidine nitrogen to form fluorophenylcarbonic acids and piperidine metabolites (which appear to be inactive), and by reduction of the butyrophenone carbonyl to the carbinol, forming hydroxyhaloperidol. Limited data suggest that the reduced metabolite, hydroxyhaloperidol, has some pharmacologic activity, although its activity appears to be less than that of haloperidol. Urinary metabolites in rats include *p*-fluorophenaceturic acid, *β*-*p*-fluorobenzoylpropionic acid, and several unidentified acids.

Haloperidol and its metabolites are excreted slowly in urine and feces. Approximately 40% of a single oral dose of haloperidol is excreted in urine within 5 days. About 15% of an oral dose of the drug is excreted in feces via biliary elimination. Small amounts of the drug are excreted for about 28 days following oral administration.

Following IM administration of haloperidol decanoate, the esterified compound is initially distributed into fatty tissue stores, from which the drug is then slowly and gradually released and subsequently undergoes hydrolysis by plasma and/or tissue esterases to form haloperidol and decanoic acid. Subsequent distribution, metabolism, and excretion of haloperidol appears to be similar to those of orally administered drug. Following IM administration of the decanoate, the drug has an apparent half-life of approximately 3 weeks.

Chemistry and Stability

■ **Chemistry** Haloperidol is a butyrophenone-derivative antipsychotic agent. The drug is structurally similar to droperidol. Haloperidol is commercially available as the base, decanoic acid ester (decanoate), and lactate salt.

Haloperidol occurs as a white to faintly yellowish, amorphous or microcrystalline powder and has solubilities of less than 0.1 mg/mL in water and of approximately 16.7 mg/mL in alcohol at 25°C. The drug has a pK_a of 8.3.

Haloperidol decanoate occurs as a clear, light amber, oily liquid and is soluble in fixed oils (e.g., sesame oil) and in most organic solvents. The decanoate has a solubility of approximately 0.01 mg/mL in water. Haloperidol decanoate injection is commercially available as a sterile solution of the drug in sesame oil and contains benzyl alcohol as a preservative.

Haloperidol injection is prepared with the aid of lactic acid and contains the drug as the lactate salt; the injection is a sterile solution of the drug in water for injection. Commercially available injections are adjusted to pH 3–3.8 with lactic acid and also *may* contain parabens as preservatives. Haloperidol oral solution also is prepared with the aid of lactic acid and contains the drug as the lactate salt. The commercially available oral solution has a pH of 2.75–3.75.

■ **Stability** Commercially available haloperidol preparations should be stored in tight, light-resistant containers at controlled room temperature between 15–30°C; freezing of the oral solution and injections and refrigeration of the decanoate injection should be avoided.

Haloperidol lactate injection may be compatible with some drugs for a short period of time after mixing, but at least one manufacturer recommends that the lactate not be mixed with other drugs. Haloperidol decanoate injection is incompatible with sterile water for injection or sodium chloride injection and with other aqueous injections. Specialized references should be consulted for specific compatibility information.

Preparations

Excipients in commercially available drug preparations may have clinically important effects in some individuals; consult specific product labeling for details.

Haloperidol

Oral		
Tablets	0.5 mg*	Haloperidol Tablets
	1 mg*	Haloperidol Tablets
	2 mg*	Haloperidol Tablets
	5 mg*	
	10 mg*	Haloperidol Tablets
		Haloperidol Tablets
	20 mg*	Haloperidol Tablets

*available from one or more manufacturer, distributor, and/or repackager by generic (nonproprietary) name

Haloperidol Decanoate

Parenteral		
Injection, for IM use only	50 mg (of haloperidol) per mL*	Haldol* Decanoate, Ortho-McNeil (also promoted by Scios Nova)
		Haloperidol Decanoate Injection
	100 mg (of haloperidol) per mL*	Haldol* Decanoate, Ortho-McNeil (also promoted by Scios Nova)
		Haloperidol Decanoate Injection

*available from one or more manufacturer, distributor, and/or repackager by generic (nonproprietary) name

Haloperidol Lactate

Oral		
Solution	2 mg (of haloperidol) per mL*	Haloperidol Lactate Oral Solution Concentrate
Parenteral		
Injection	5 mg (of haloperidol) per mL*	Haldol*, Ortho-McNeil
		Haloperidol Lactate Injection

*available from one or more manufacturer, distributor, and/or repackager by generic (nonproprietary) name
†Use is not currently included in the labeling approved by the US Food and Drug Administration

PHENOTHIAZINES 28:16.08.24

Phenothiazines General Statement

■ Phenothiazines are conventional (prototypical, first-generation) antipsychotic agents.

Uses

Phenothiazines mainly are used for the management of various psychoneurologic disorders and for the prevention and control of nausea and vomiting. The efficacy of individual phenothiazines varies in different neuropsychiatric and other conditions, and some phenothiazines are not used as antipsychotic agents. Promethazine is used as an antihistamine (see 4:04) and as a sedative (see 28:24.92) and thiethylperazine as an antiemetic. For further information, see the individual monographs on these derivatives.

■ **Psychotic Disorders** ***Schizophrenia and Other Psychotic Disorders*** Phenothiazines are used principally for the symptomatic management of psychotic disorders, especially those characterized by excessive psychomotor activity. The drugs produce substantial improvement in most schizophrenic patients. Phenothiazines are particularly effective in reducing hallucinations and motor and autonomic hyperactivity in patients with schizophrenic disorder; thought disorders, change in affect, and autism are also reduced during phenothiazine therapy. Patient response and tolerance to antipsychotic agents are variable, and patients who do not respond to or tolerate one drug may be successfully treated with an agent from a different class or with a different adverse effect profile.

General Considerations. Schizophrenia, a major psychotic disorder, is a chronic condition that frequently has devastating effects on various aspects of the patient's life and carries a high risk of suicide and other life-threatening behaviors. Manifestations of the disorder involve multiple psychologic processes, including perception (e.g., hallucinations), ideation, reality testing (e.g., delusions), emotion (e.g., flatness, inappropriate affect), thought processes (e.g., loose associations), behavior (e.g., catatonia, disorganization), attention, concentration, motivation (e.g., avolition, impaired intention and planning), and judgment. The behavioral and psychologic characteristics of schizophrenia are associated with a variety of impairments in social and occupational functioning. Although marked deterioration associated with impairments in multiple areas of functioning (e.g., learning, self-care, working, interpersonal relationships, living skills) can occur, the disorder is characterized by great interindividual heterogeneity and by intraindividual variability over time.

The principal manifestations of schizophrenia usually are described in terms of positive and negative (deficit) symptoms and, more recently, disorganized symptoms. Positive symptoms include hallucinations, delusions, bizarre behavior, hostility, uncooperativeness, and paranoid ideation, while negative symptoms include restricted range and intensity of emotional expression (affective flattening), reduced thought and speech productivity (alogia), anhedonia, apathy, and decreased initiation of goal-directed behavior (avolition). Disorganized symptoms include disorganized speech (thought disorder) and behavior and poor attention. Subtypes of schizophrenia include the paranoid, disorganized, catatonic, undifferentiated, and residual types.

Management of schizophrenia usually involves a variety of interventions (e.g., psychiatric management, psychosocial interventions, drug therapy, electroconvulsive therapy [ECT]) aimed at reducing or eliminating symptoms, maximizing quality of life and adaptive functioning, and enabling recovery by assisting patients in attaining personal life goals (e.g., in work, housing, relationships). The long-term outcome of schizophrenia varies along a continuum between reasonable recovery and complete incapacity. Most patients display exacerbations and remissions in the context of experiencing clinical deterioration, although approximately 10–15% of patients are free of further episodes after recovery from a first psychotic episode, and another 10–15% remain chronically severely psychotic.

Disease Phase Overview. Schizophrenia is a disorder that has been described as developing in phases, which have been characterized as premorbid, prodromal, and psychotic. The premorbid phase consists of a period of normal functioning, although certain events (e.g., complications in pregnancy and delivery during the prenatal and perinatal periods, trauma, family stress during

Olanzapine for IM injection should not be combined with diazepam injection in a syringe because precipitation occurs when these drugs are mixed. Olanzapine for injection should not be combined in a syringe with haloperidol injection because the resulting pH has been shown to degrade olanzapine over time. Specialized references should be consulted for additional specific compatibility information.

Preparations

Excipients in commercially available drug preparations may have clinically important effects in some individuals; consult specific product labeling for details.

Olanzapine

Oral		
Tablets, film-coated	2.5 mg	Zyprexa®, Lilly
	5 mg	Zyprexa®, Lilly
	7.5 mg	Zyprexa®, Lilly
	10 mg	Zyprexa®, Lilly
	15 mg	Zyprexa®, Lilly
	20 mg	Zyprexa®, Lilly
Tablets, orally disintegrating	5 mg	Zyprexa® Zydis®, Lilly
	10 mg	Zyprexa® Zydis®, Lilly
	15 mg	Zyprexa® Zydis®, Lilly
	20 mg	Zyprexa® Zydis®, Lilly
Parenteral		
For injection	10 mg	Zyprexa® IntraMuscular, Lilly

Olanzapine Combinations

Oral		
Capsules	6 mg with Fluoxetine Hydrochloride 25 mg (of fluoxetine)	Symbyax®, Lilly
	6 mg with Fluoxetine Hydrochloride 50 mg (of fluoxetine)	Symbyax®, Lilly
	12 mg with Fluoxetine Hydrochloride 25 mg (of fluoxetine)	Symbyax®, Lilly
	12 mg with Fluoxetine Hydrochloride 50 mg (of fluoxetine)	Symbyax®, Lilly

†Use is not currently included in the labeling approved by the US Food and Drug Administration

Paliperidone

9-Hydroxyrisperidone

■ Paliperidone is considered an atypical or second-generation antipsychotic agent.

Uses

■ **Psychotic Disorders** Paliperidone is used for the symptomatic management of psychotic disorders (e.g., schizophrenia). Drug therapy is integral to the management of acute psychotic episodes and accompanying violent behavior in patients with schizophrenia and generally is required for long-term stabilization to sustain symptom remission or control and to minimize the risk of relapse. Antipsychotic agents are the principal class of drugs used for the management of all phases of schizophrenia. Patient response and tolerance to antipsychotic agents are variable, and patients who do not respond to or tolerate one drug may be successfully treated with an agent from a different class or with a different adverse effect profile.

Schizophrenia Paliperidone is used orally for the acute and maintenance treatment of schizophrenia. Schizophrenia is a major psychotic disorder that frequently has devastating effects on various aspects of the patient's life and carries a high risk of suicide and other life-threatening behaviors. Manifestations of schizophrenia involve multiple psychologic processes, including perception (e.g., hallucinations), ideation, reality testing (e.g., delusions), emotion (e.g., flatness, inappropriate affect), thought processes (e.g., loose associations), behavior (e.g., catatonia, disorganization), attention, concentration, motivation (e.g., avolition, impaired intention and planning), and judgment. The principal manifestations of this disorder usually are described in terms of positive and negative (deficit) symptoms, and more recently, disorganized symptoms. Positive symptoms include hallucinations, delusions, bizarre behavior, hostility, uncooperativeness, and paranoid ideation, while negative symptoms include restricted range and intensity of emotional expression (affective flattening), reduced thought and speech productivity (alogia), anhedonia, apathy, and decreased initiation of goal-directed behavior (avolition). Disorganized symptoms include disorganized speech (thought disorder) and behavior and poor attention.

The short-term efficacy of paliperidone in the acute treatment of schizophrenia was established in 3 placebo-controlled and active comparator (olanzapine)-controlled, fixed-dose clinical trials of 6 weeks' duration in 1665 adult patients with schizophrenia. In these 3 studies, patients receiving paliperidone (3–15 mg daily as extended-release tablets) demonstrated substantially greater improvement in the Positive and Negative Syndrome Scale (PANSS) than did patients receiving placebo. The mean effects at all dosages (3, 6, 9, 12, and 15 mg daily) were fairly similar, although higher dosages produced numerically superior results. Paliperidone also was found to be superior to placebo in improving scores on the Personal and Social Performance (PSP) scale in these trials.

In a longer-term study, adult outpatients with schizophrenia who had clinically responded to oral paliperidone and who had received a stable fixed dosage of the drug for 2 weeks entered a 6-week, open-label, stabilization phase where they received a paliperidone dosage from 3–15 mg once daily as extended-release tablets. After the stabilization phase, patients were randomized in a double-blind manner to either continue receiving paliperidone at their stable dosage or to receive placebo until they experienced a relapse of schizophrenia symptoms. The median treatment exposure during this double-blind phase was 45 days for extended-release paliperidone and 29 days for placebo; the mean paliperidone dosage was approximately 11 mg daily throughout the phases of this trial. An interim analysis of the data showed a significantly longer time to relapse in the paliperidone-treated patients compared with those receiving placebo. In addition, 52% of the paliperidone-treated patients experienced a relapse compared with 22% of those receiving placebo. The study was stopped early because maintenance of efficacy was demonstrated. If paliperidone is used for extended periods, the need for continued therapy should be reassessed periodically on an individualized basis. (See Dosage and Administration: Dosage.)

The American Psychiatric Association (APA) considers most atypical antipsychotic agents first-line drugs for the management of the acute phase of schizophrenia (including first psychotic episodes), principally because of the decreased risk of adverse extrapyramidal effects and tardive dyskinesia, with the understanding that the relative advantages, disadvantages, and cost-effectiveness of conventional and atypical antipsychotic agents remain controversial. The APA states that, with the possible exception of clozapine for the management of treatment-resistant symptoms, there currently is no definitive evidence that one atypical antipsychotic agent will have superior efficacy compared with another agent in the class, although meaningful differences in response may be observed in individual patients. Conventional antipsychotic agents may be considered first-line therapy in patients who have been treated successfully in the past with or who prefer conventional agents. The choice of an antipsychotic agent should be individualized, considering past response to therapy, adverse effect profile (including the patient's experience of subjective effects such as dysphoria), and the patient's preference for a specific drug, including route of administration.

For additional information on the symptomatic management of schizophrenia, including treatment recommendations and results of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study, see Schizophrenia and Other Psychotic Disorders under Uses: Psychotic Disorders, in the Phenothiazines General Statement 28:16.08.24.

Dosage and Administration

■ **Administration** Paliperidone is administered orally once daily in the morning with or without food.

Paliperidone extended-release tablets should be swallowed whole with fluids and should *not* be chewed, divided, or crushed. Patients should be advised *not* to become concerned if they notice a tablet-like substance in their stools; this is normal since the tablet is designed to remain intact and slowly release the drug from a nonabsorbable shell during passage through the GI tract.

■ **Dosage** ***Schizophrenia*** For the management of schizophrenia, the usual recommended dosage of paliperidone in adults is 6 mg once daily in the morning; dosage titration is not required. Although it remains to be systematically evaluated whether dosages exceeding 6 mg once daily provide additional clinical benefit, a general trend for greater clinical effects with higher dosages has been observed. However, the potential for increased clinical efficacy at higher dosages must be weighed against the potential for a dose-related increase in adverse effects. Some patients may benefit from higher dosages of up to 12 mg once daily, while a lower dosage of 3 mg once daily may be sufficient for other patients. The manufacturer states that increases beyond a dosage level of 6 mg once daily should be made only after clinical reassessment and generally should be made at intervals of more than 5 days. When dosage increases are necessary, increments of 3 mg daily are recommended. The maximum recommended dosage is 12 mg once daily.

The optimum duration of oral paliperidone therapy in patients with schizophrenia currently is not known, but maintenance therapy with paliperidone 3–15 mg daily as extended-release tablets has been shown to be effective in preventing relapse. Patients responding to paliperidone therapy should continue to receive the drug as long as clinically necessary and tolerated but at the lowest possible effective dosage, and the need for continued therapy with the drug should be reassessed periodically. The American Psychiatric Association (APA) states that prudent long-term treatment options in patients with schizo-

phrenia with remitted first- or multiple-episodes include either indefinite maintenance therapy or gradual discontinuance of the antipsychotic agent with close follow-up and a plan to reinstitute treatment upon symptom recurrence. Discontinuance of antipsychotic therapy should be considered only after a period of at least 1 year of symptom remission or optimal response while receiving the antipsychotic agent. In patients who have had multiple previous psychotic episodes or 2 psychotic episodes within 5 years, indefinite maintenance antipsychotic treatment is recommended.

■ **Special Populations** Dosage adjustment is not necessary in patients with mild to moderate hepatic impairment (Child-Pugh class A and B). (See Hepatic Impairment under Warnings/Precautions: Specific Populations, in Cautions.)

In patients with renal impairment, the maximum recommended dosage of paliperidone is 6 mg once daily in those with mild renal impairment (creatinine clearance of 50–79 mL/minute) and 3 mg once daily in those with moderate to severe renal impairment (creatinine clearance of 10–49 mL/minute). (See Renal Impairment under Warnings/Precautions: Specific Populations, in Cautions.)

Because geriatric patients may have reduced renal function, dosage adjustment may be required based on renal function status. Geriatric patients with normal renal function generally may receive the same dosage recommended for younger adults with normal renal function. In geriatric patients with moderate to severe renal impairment, the maximum recommended paliperidone dosage is 3 mg once daily. (See Renal Impairment under Warnings/Precautions: Specific Populations, in Cautions.)

No dosage adjustment is necessary based on gender or race.

Cautions

■ **Contraindications** Known hypersensitivity to paliperidone, risperidone, or any ingredient in the formulation.

■ **Warnings/Precautions** ***Warnings*** **Increased Mortality in Geriatric Patients with Dementia-related Psychosis.** Geriatric patients with dementia-related psychosis treated with atypical antipsychotic drugs appear to be at an increased risk of death compared with that among patients receiving placebo. Analysis of 17 placebo-controlled trials (average duration of 10 weeks) revealed an approximate 1.6- to 1.7-fold increase in mortality among geriatric patients receiving atypical antipsychotic drugs (i.e., aripiprazole, olanzapine, quetiapine, risperidone) compared with that in patients receiving placebo. Over the course of a typical 10-week controlled study, the rate of death in drug-treated patients was about 4.5% compared with a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. In addition, an increased incidence of cerebrovascular adverse effects (e.g., stroke, transient ischemic attack), including fatalities, has been observed in geriatric patients treated with aripiprazole, olanzapine, and risperidone in placebo-controlled studies of dementia-related psychosis. The manufacturer states that paliperidone is not approved for the treatment of patients with dementia-related psychosis. (See Dosage and Administration: Special Populations and see also Geriatric Use under Warnings/Precautions: Specific Populations, in Cautions.)

Prolongation of QT Interval. Paliperidone causes a modest increase in the corrected QT (QT_c) interval. The risk of torsades de pointes in association with drugs that prolong the QT_c interval may be increased in patients with bradycardia, hypokalemia, or hypomagnesemia; patients receiving other drugs that prolong the QT_c interval; and in those with congenital prolongation of the QT interval. Therefore, the manufacturer states that paliperidone should be avoided in patients concurrently receiving other drugs known to prolong the QT_c interval, patients with congenital long QT syndrome, and those with a history of cardiac arrhythmias. (See Drugs that Prolong QT Interval under Drug Interactions.)

Neuroleptic Malignant Syndrome. Neuroleptic malignant syndrome (NMS), a potentially fatal syndrome requiring immediate discontinuance of the drug and intensive symptomatic treatment, has been reported in patients receiving antipsychotic agents, including paliperidone. If a patient requires antipsychotic therapy following recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. If antipsychotic therapy is reintroduced, the dosage generally should be increased gradually and an antipsychotic agent other than the agent believed to have precipitated NMS generally should be chosen. In addition, such patients should be carefully monitored since recurrences of NMS have been reported in some patients. For additional information on NMS, see Neuroleptic Malignant Syndrome under Cautions: Nervous System Effects, in the Phenothiazines General Statement 28:16.08.24.

Tardive Dyskinesia. Because use of antipsychotic agents may be associated with tardive dyskinesia, a syndrome of potentially irreversible, involuntary, dyskinetic movements, paliperidone should be prescribed in a manner that is most likely to minimize the occurrence of this syndrome. Chronic antipsychotic treatment generally should be reserved for patients who suffer from a chronic illness that is known to respond to antipsychotic agents, and for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought, and the need for continued treatment should be reassessed periodically. The American Psychiatric Association (APA) currently recommends that patients receiving second-generation antipsychotic agents be assessed clinically for abnormal involuntary movements every 12 months and that patients considered to be at increased risk for tardive dyskinesia be assessed every 6 months. For additional information on tardive dyskinesia, see Tardive Dyskinesia under Cautions: Nervous System Effects, in the Phenothiazines General Statement 28:16.08.24.

Hyperglycemia and Diabetes Mellitus. Severe hyperglycemia, sometimes associated with ketoacidosis, hyperosmolar coma, or death, has been reported in patients treated with all atypical antipsychotic agents. While confounding factors such as an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population make it difficult to establish with certainty the relationship between use of agents in this drug class and glucose abnormalities, epidemiologic studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with atypical antipsychotic agents. Because paliperidone was not marketed at the time these studies were performed, it is unknown if the drug is associated with this increased risk; however, there have been 2 cases of hyperglycemia or diabetes reported to date in paliperidone-treated patients in clinical trials.

The manufacturers of atypical antipsychotic agents state that patients with preexisting diabetes mellitus in whom therapy with an atypical antipsychotic is initiated should be closely monitored for worsening of glucose control; those with risk factors for diabetes (e.g., obesity, family history of diabetes) should undergo fasting blood glucose testing upon therapy initiation and periodically throughout treatment. Any patient who develops manifestations of hyperglycemia (e.g., polydipsia, polyphagia, polyuria, weakness) during treatment with an atypical antipsychotic should undergo fasting blood glucose testing. In some cases, patients who developed hyperglycemia while receiving an atypical antipsychotic have required continuance of antidiabetic treatment despite discontinuance of the suspect drug; in other cases, hyperglycemia resolved with discontinuance of the antipsychotic.

For further information on managing the risk of hyperglycemia and diabetes mellitus associated with atypical antipsychotic agents, see Cautions: Endocrine and Metabolic Effects and see also Hyperglycemia and Diabetes Mellitus under Cautions: Precautions and Contraindications, in Clozapine 28:16.08.04.

GI Effects. As with other nondeformable material, extended-release paliperidone tablets do not appreciably change in shape in the GI tract. Therefore, the drug generally should not be administered to patients with severe, preexisting GI narrowing (either pathological or iatrogenic). Rare cases of obstructive symptoms in patients with known strictures have been reported in association with the ingestion of drugs in nondeformable, controlled-release formulations. Because of the extended-release design of paliperidone tablets, the drug should only be used in patients who are able to swallow the tablet whole.

Decreased bioavailability of paliperidone extended-release tablets would be expected in patients with a decreased GI transit time (e.g., those with diarrhea) while an increased bioavailability would be expected in patients with an increased GI transit time (e.g., those with GI neuropathy, diabetic gastroparesis, or due to other causes). Such changes in bioavailability are more likely when changes in transit time occur in the upper GI tract.

General Precautions **Orthostatic Hypotension and Syncope.** Orthostatic hypotension and syncope have been reported. Syncope occurred in about 0.8% of patients receiving paliperidone in controlled clinical trials. Use with caution in patients with known cardiovascular disease (e.g., heart failure, history of myocardial infarction or ischemia, conduction abnormalities) or cerebrovascular disease and/or conditions that would predispose patients to hypotension (e.g., dehydration, hypovolemia, concomitant antihypertensive therapy). Consider monitoring of orthostatic vital signs in patients who may be vulnerable to hypotension (e.g., geriatric patients).

Seizures. Seizures have occurred in approximately 0.2% of patients receiving paliperidone in controlled clinical studies. Use with caution in patients with a history of seizures or other conditions that may lower the seizure threshold (e.g., dementia of the Alzheimer's type, geriatric patients).

Hyperprolactinemia. Similar to other antipsychotic agents, paliperidone causes elevated prolactin concentrations, which may persist during chronic administration. Paliperidone's prolactin-elevating effects are similar to those seen with risperidone, which appears to be associated with a higher level of prolactin elevation than other currently available antipsychotic agents. Clinical disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been associated with prolactin-elevating drugs. In addition, chronic hyperprolactinemia when associated with hypogonadism may lead to decreased bone density in males and females. However, the clinical importance of elevated prolactin concentrations is unknown for most patients.

Dysphagia. Esophageal dysmotility and aspiration have been associated with the use of antipsychotic agents. Use with caution in patients at risk for aspiration pneumonia (e.g., patients with advanced Alzheimer's dementia). (See Increased Mortality in Geriatric Patients with Dementia-related Psychosis under Warnings/Precautions: Warnings, in Cautions and see Geriatric Use under Warnings/Precautions: Special Populations, in Cautions.)

Suicide. Attendant risk with psychotic illnesses; closely supervise high-risk patients. Prescribe in the smallest quantity consistent with good patient management to reduce the risk of overdosage.

Somnolence. Somnolence and sedation have been reported in patients receiving paliperidone therapy.

Sexual Dysfunction. Although priapism has not been reported in clinical trials of paliperidone, the drug possesses α-adrenergic blocking activity and may therefore be associated with this risk.

Hematologic Effects. Thrombotic thrombocytopenic purpura (TTP) has not been reported in clinical trials of paliperidone. TTP has been reported in association with risperidone therapy; however, the relationship of this adverse event to risperidone is unknown.

Body Temperature Regulation. Disruption of the body's ability to reduce core body temperature has been associated with the use of antipsychotic agents. Use caution when paliperidone is administered in patients exposed to conditions that may contribute to an elevation in core body temperature (e.g., dehydration, extreme heat, strenuous exercise, concomitant use of anticholinergic agents).

Antiemetic Effects. Antiemetic effects were observed in preclinical studies with paliperidone; these effects also may occur in humans and mask signs of overdosage of other drugs or obscure cause of vomiting in various disorders (e.g., intestinal obstruction, Reye's syndrome, brain tumor).

Patients with Concomitant Illness. Clinical experience with paliperidone in patients with certain concomitant illnesses is limited.

Patients with parkinsonian syndrome or dementia with Lewy bodies who receive antipsychotics, including paliperidone, reportedly have an increased sensitivity to antipsychotic agents. Clinical manifestations of this increased sensitivity have been reported to include confusion, obtundation, postural instability with frequent falls, extrapyramidal symptoms, and features consistent with NMS. (For additional information on extrapyramidal adverse effects and NMS, see Cautions: Nervous System Effects, in the Phenothiazines General Statement 28:16.08.24.)

Paliperidone has not been adequately evaluated in patients with a recent history of myocardial infarction or unstable cardiovascular disease to date and patients with these conditions were excluded from premarketing clinical trials. Because of the risk of orthostatic hypotension associated with paliperidone, the manufacturer states that the drug should be used with caution in patients with cardiovascular disease. (See Orthostatic Hypotension and Syncope under Warnings/Precautions/General Precautions, in Cautions.)

Specific Populations **Pregnancy.** Category C. (See Users Guide.)

Lactation. Paliperidone is distributed into milk in animals. Both risperidone and 9-hydroxyrisperidone, which is the major active metabolite of risperidone and the same drug as paliperidone, distribute into milk following risperidone administration in humans. The manufacturer states that women receiving paliperidone should not breast-feed.

Pediatric Use. Safety and effectiveness not established in pediatric patients younger than 18 years of age.

Geriatric Use. In clinical studies, approximately 7% of nearly 1800 patients were 65 years of age or older. In addition, the short-term efficacy and safety of paliperidone have been demonstrated in a placebo-controlled trial of 6 weeks' duration in 114 geriatric patients with schizophrenia. While no substantial differences in efficacy or safety relative to younger adults were observed in these studies or in other clinical experience with the drug, increased sensitivity cannot be ruled out.

Because geriatric patients may have reduced renal function, dosage adjustment may be required based on renal function status; consider monitoring renal function. (See Dosage and Administration: Special Populations.)

Geriatric patients with dementia-related psychosis treated with atypical antipsychotic drugs appear to be at an increased risk of death compared with that among patients receiving placebo. Paliperidone is *not* approved for the treatment of dementia-related psychosis. (See Increased Mortality in Geriatric Patients with Dementia-related Psychosis under Warnings/Precautions: Warnings, in Cautions.)

Hepatic Impairment. Patients with moderate hepatic impairment (Child-Pugh class B) exhibited similar plasma concentrations of free paliperidone as healthy individuals, although total paliperidone exposure decreased because of decreased protein binding. Dosage adjustment is not necessary in patients with mild to moderate hepatic impairment (Child-Pugh class A and B). The effect of severe hepatic impairment on paliperidone pharmacokinetics is not known. (See Dosage and Administration: Special Populations.)

Renal Impairment. Clearance decreased by an average of 32, 64, and 71% in patients with mild, moderate, and severe renal impairment, respectively. Dosage adjustment is recommended in patients with moderate or severe renal impairment. (See Dosage and Administration: Special Populations.)

■ **Common Adverse Effects** Adverse effects reported in 5% or more of patients receiving paliperidone include tremor, headache, orthostatic hypotension, tachycardia, somnolence, akathisia, insomnia, anxiety, extrapyramidal reaction, dizziness, dystonia, QT_c interval prolongation, nausea, dyspepsia, and weight gain.

Drug Interactions

■ **Drugs Affecting Hepatic Microsomal Enzymes** Inhibitors or inducers of cytochrome P-450 (CYP) isoenzymes 2D6, 3A4, 1A2, 2A6, 2C9, and 2C19: pharmacokinetic interaction unlikely.

■ **Drugs Metabolized by Hepatic Microsomal Enzymes** Substrates of CYP1A2, CYP2A6, CYP2C8/9/10, CYP2D6, CYP2E1, CYP3A4, or CYP3A5: pharmacokinetic interaction unlikely.

■ **Drugs Inhibiting P-glycoprotein Transport System** At therapeutic concentrations, paliperidone did not inhibit P-glycoprotein; clinically relevant interactions unlikely.

■ **Drugs that Prolong QT Interval** Potential pharmacologic interaction (additive effect on QT-interval prolongation); avoid concomitant use of other drugs known to prolong the QT interval (e.g., amiodarone, quinidine, procainamide, sotalol; other Class Ia and III antiarrhythmics, chlorpromazine, thioridazine, gatifloxacin, moxifloxacin).

■ **Protein-bound Drugs** Pharmacokinetic interaction unlikely.

■ **Alcohol** Potential pharmacologic interaction (additive sedative effects). Avoid alcoholic beverages during paliperidone therapy.

■ **Hypotensive Agents** Potential pharmacologic interaction (additive hypotensive effects).

■ **Levodopa and Dopamine Agonists** Potential pharmacologic interaction (antagonistic effects).

■ **Paroxetine** Concomitant administration of paroxetine (20 mg daily) and a single dose of paliperidone (3 mg as extended-release tablets) caused a small, clinically insignificant increase in paliperidone area under the concentration-time curves (AUCs) compared with paliperidone administration alone. Therefore, dosage adjustment of paliperidone is not neeessary.

■ **Risperidone** Concurrent use of paliperidone with risperidone has not been studied to date. However, because paliperidone is the prineipal active metabolite of risperidone, consideration should be given to additive paliperidone exposure if risperidone and paliperidone are coneomitantly administered.

■ **Other CNS Agents** Potential pharmacologic interaction (additive sedative effeets). Use with caution.

■ **Smoking** Pharmacokinetic interaction unlikely. Dosage adjustment in patients who smoke is not necessary.

Description

Paliperidone is a benzisoxazole-derivative antipsyehotic agent that differs chemieally from other currently available first-generation (typical) antipsychotic agents (e.g., butyrophenones, phenothiazines) and has been referred to as an atypical or second-generation antipsychotie agent. The drug is the major active metabolite of risperidone, another atypical antipsychotic agent.

The exact mechanism of paliperidone's antipsychotic action, like that of other antipsychotic agents, has not been fully elucidated, but may involve antagonism of central dopamine type 2 (D_2) and serotonin type 2 (5-hydroxytryptamine [$5\text{-}HT_{2A}$]) receptors. Antagonism at α_1- and α_2-adrenergic and histamine (H_1) receptors may contribute to other therapeutic and adverse effects observed with the drug. Paliperidone possesses no affinity for eholinergic muscarinic and β_1- and β_2-adrenergic receptors.

In vitro studies have suggested a role for cytochrome P-450 (CYP) isoenzymes 2D6 and 3A4 in the metaholism of paliperidone; however, the results of in vivo studies indicate that these isoenzymes play a limited role in the overall elimination of the drug from the body.

Approximately 80% and 11% of a single 1-mg oral dose of radiolabeled, immediate-release paliperidone is recovered in urine and feces, respectively, within 1 week. About 59% of the administered dose is recovered as unchanged drug and 32% recovered as metabolites. Following single-dose oral administration as extended-release tablets, paliperidone appears to have a mean terminal elimination half-life of about 23 hours.

Advice to Patients

Importance of reading manufacturer's patient information.

Risk of orthostatic hypotension, particularly during initial dosage titration and at times of reinitiation of therapy or increases in dosage. Importance of advising patients who experience dizziness or fainting during therapy to get up slowly when sitting or lying down.

Because somnolenee and impairment of judgment, thinking, or motor skills may be associated with paliperidone, patients should be cautioned about driving, operating machinery, or performing hazardous tasks while taking paliperidone until they gain experience with the drug's effects. Importance of avoiding alcohol during paliperidone therapy.

Importance of informing clinicians of existing or contemplated concomitant therapy, including prescription (see Drug Interactions: Drugs that Prolong QT Interval) and OTC drugs, dietary supplements, and/or herbal products, as well as any concomitant illnesses (e.g., cardiovascular disease, diabetes mellitus, seizures).

Importance of women informing clinicians if they are or plan to become pregnant or plan to breast-feed.

Importance of avoiding overheating or dehydration.

Importance of informing patients that paliperidone tablets should be swallowed whole with the aid of liquids, and should not be chewed, divided or crushed. Patients should not be concerned if they notice a tablet-like substance in their stool.

Importance of informing patients of other important precautionary information. (See Cautions.)

Overview[a] (see Users Guide). For additional information on this drug until a more detailed monograph is developed and published, the manufacturer's labeling should be consulted. It is *essential* that the manufac-

turer's labeling be consulted for more detailed information on usual cautions, precautions, contraindications, potential drug interactions, laboratory test interferences, and acute toxicity.

Preparations

Excipients in commercially available drug preparations may have clinically important effects in some individuals; consult specific product labeling for details.

Paliperidone

Oral

Tablets, extended-release	3 mg	Invega®, Janssen
	6 mg	Invega®, Janssen
	9 mg	Invega®, Janssen

Quetiapine Fumarate

■ Quetiapine is considered an atypical or second-generation antipsychotic agent.

Uses

■ **Psychotic Disorders** Quetiapine is used for the symptomatic management of psychotic disorders (e.g., schizophrenia). Drug therapy is integral to the management of acute psychotic episodes and accompanying violent behavior in patients with schizophrenia and generally is required for long-term stabilization to sustain symptom remission or control and to minimize the risk of relapse. Antipsychotic agents are the principal class of drugs used for the management of all phases of schizophrenia. Patient response and tolerance to antipsychotic agents are variable, and patients who do not respond to or tolerate one drug may be successfully treated with an agent from a different class or with a different adverse effect profile.

Schizophrenia Short-term efficacy of quetiapine for the management of schizophrenia has been established by placebo-controlled studies of 6 weeks' duration principally in hospitalized patients with schizophrenia. Schizophrenia is a major psychotic disorder that frequently has devastating effects on various aspects of the patient's life and carries a high risk of suicide and other life-threatening behaviors. Manifestations of schizophrenia involve multiple psychologic processes, including perception (e.g., hallucinations), ideation, reality testing (e.g., delusions), emotion (e.g., flatness, inappropriate affect), thought processes (e.g., loose associations), behavior (e.g., catatonia, disorganization), attention, concentration, motivation (e.g., avolition, impaired intention and planning), and judgment. The principal manifestations of this disorder usually are described in terms of positive and negative (deficit) symptoms, and more recently, disorganized symptoms. Positive symptoms include hallucinations, delusions, bizarre behavior, hostility, uncooperativeness, and paranoid ideation, while negative symptoms include restricted range and intensity of emotional expression (affective flattening), reduced thought and speech productivity (alogia), anhedonia, apathy, and decreased initiation of goal-directed behavior (avolition). Disorganized symptoms include disorganized speech (thought disorder) and behavior and poor attention.

In clinical studies in patients with schizophrenia, quetiapine was more effective than placebo in reducing the severity of symptoms associated with this disorder. Quetiapine appears to improve both positive and negative manifestations of schizophrenia. Results from comparative clinical studies and meta-analyses suggest that quetiapine is at least as effective as chlorpromazine or haloperidol in reducing positive and negative symptoms of schizophrenia.

The American Psychiatric Association (APA) considers certain atypical antipsychotic agents (i.e., quetiapine, aripiprazole, olanzapine, risperidone, ziprasidone) first-line drugs for the management of the acute phase of schizophrenia (including first psychotic episodes), principally because of the decreased risk of adverse extrapyramidal effects and tardive dyskinesia, with the understanding that the relative advantages, disadvantages, and cost-effectiveness of conventional and atypical antipsychotic agents remain controversial. The APA states that, with the possible exception of clozapine for the management of treatment-resistant symptoms, there currently is no definitive evidence that one atypical antipsychotic agent will have superior efficacy compared with another agent in the class, although meaningful differences in response may be observed in individual patients. Conventional antipsychotic agents may be considered first-line therapy in patients who have been treated successfully in the past with or who prefer conventional agents. The choice of an antipsychotic agent should be individualized, considering past response to therapy, adverse effect profile (including the patient's experience of subjective effects such as dysphoria), and the patient's preference for a specific drug, including route of administration.

Although the efficacy of quetiapine for long-term use has not been established in controlled studies, the manufacturer states that beneficial effects of the drug were maintained for up to 4 years in some patients during an open-label extension study in patients who achieved an initial response to treatment during double-blind clinical studies. If quetiapine is used for extended periods, the need for continued therapy should be reassessed periodically on an individualized basis. (See Dosage and Administration: Dosage.)

For additional information on the symptomatic management of schizophrenia, including treatment recommendations and results of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study, see Schizophrenia and Other Psychotic Disorders under Uses: Psychotic Disorders, in the Phenothiazines General Statement 28:16.08.24.

■ **Bipolar Disorder** Quetiapine is used alone or in conjunction with lithium or divalproex sodium for the management of acute manic episodes associated with bipolar I disorder. Efficacy of quetiapine monotherapy in the treatment of acute manic episodes has been demonstrated in 2 placebo-controlled studies of 12 weeks' duration in patients who met the DSM-IV criteria for bipolar disorder and who met diagnostic criteria for an acute manic episode (with or without psychotic features). Patients with rapid cycling and mixed episodes were excluded from these studies. The principal rating instrument used for assessing manic symptoms in these studies was the Young Mania Rating Scale (YMRS) score, an 11-item clinician rated scale traditionally used to assess the degree of manic symptomatology in a range from 0 (no manic features) to 60 (maximum score). In these studies, quetiapine was shown to be superior to placebo in reduction of the YMRS total score after 3 and 12 weeks of treatment.

Efficacy of quetiapine when used in combination with lithium or divalproex sodium in the management of acute manic episodes has been demonstrated in a placebo-controlled study of 3 weeks' duration in patients who met the DSM-IV criteria for bipolar I disorder with acute manic episodes (with or without psychotic features). Patients with rapid cycling and mixed episodes were excluded from enrollment and patients included in the study may or may not have received an adequate course of therapy with lithium or divalproex sodium prior to randomization. Quetiapine was shown to be superior to placebo when added to lithium or divalproex sodium alone in the reduction of YMRS total score. However, in a similarly designed study, quetiapine was associated with an improvement of YMRS scores but did not demonstrate superiority to placebo.

For the initial management of less severe manic or mixed episodes in patients with bipolar disorder, current APA recommendations state that monotherapy with lithium, valproate (e.g., valproate sodium, valproic acid, divalproex), or an antipsychotic (e.g., olanzapine) may be adequate. For more severe manic or mixed episodes, combination therapy with an antipsychotic and lithium or valproate is recommended as first-line therapy. For further information on the management of bipolar disorder, see Uses: Bipolar Disorder, in Lithium Salts 28:28.

Quetiapine also is used for the treatment of depressive episodes associated with bipolar disorder. Efficacy of quetiapine in the treatment of depressive episodes has been demonstrated in 2 randomized, double-blind, placebo-controlled studies of 8 weeks' duration in patients with bipolar I or II disorder (with or without a rapid cycling course). Patients in these studies received fixed daily quetiapine dosages of 300 or 600 mg once daily. The principal rating instrument used for assessing depressive symptoms in these studies was the Montgomery-Asberg Depression Rating Scale (MADRS), a 10-item clinician-rated scale with scores ranging from 0 to 60. In both studies, quetiapine was found to be superior to placebo in reduction of MADRS scores at week 8, with improvements in scores evident within one week of treatment. In addition, patients receiving 300 mg of quetiapine daily demonstrated significant improvements compared to placebo recipients in overall quality of life and satisfaction related to various areas of functioning.

Dosage and Administration

■ **Administration** Quetiapine is administered orally. While food reportedly can marginally increase the peak concentration and oral bioavailability of quetiapine, the drug generally can be administered without regard to meals.

Dispensing and Administration Precautions Because of similarity in spelling between Seroquel® (the trade name for quetiapine fumarate) and Serzone® (the former trade name for nefazodone hydrochloride, an antidepressant agent; no longer commercially available in the US under this trade name), dispensing errors have been reported to the US Food and Drug Administration (FDA) and the manufacturer of Seroquel® (AstraZeneca). According to the medication error reports, the overlapping strengths (100 and 200 mg), dosage forms (tablets), and dosing intervals (twice daily) and the fact that these 2 drugs were stored closely together in pharmacies also were critical in causing these errors. Therefore, extra care should be exercised in ensuring the accuracy of both oral and written prescriptions for Seroquel® and Serzone®. Although the Serzone brand was discontinued in June 2004, clinicians may continue to refer to nefazodone by the former brand name in prescribing. Some experts recommend that pharmacists assess the measures of avoiding dispensing errors and implement them as appropriate (e.g., by verifying all orders for these agents by spelling both the trade and generic names to prescribers, using computerized name alerts, attaching reminders to drug containers and pharmacy shelves, separating the drugs on pharmacy shelves, counseling patients). (See Dispensing and Administration Precautions under Warnings/Precautions: General Precautions in Cautions.)

■ **Dosage** Dosage of quetiapine fumarate is expressed in terms of quetiapine and must be carefully adjusted according to individual requirements and response, using the lowest possible effective dosage.

in vitro studies have identified a novel gabapentin binding site in the neocortex and hippocampus of rat brain, additional studies are required to fully elucidate the identity and function of this binding site.

In animal test systems, gabapentin exhibits anticonvulsant activity similar to that of other commonly used anticonvulsant drugs. The drug protects against seizures induced in animals by electrical stimulation or pentylenetetrazole, suggesting that it may be effective in the management of tonic-clonic (grand mal) and partial seizures or absence (petit mal) seizures, respectively. However, available data in animals and humans are conflicting regarding the effect of gabapentin on EEG spike and wave activity associated with absence (petit mal) seizures. Gabapentin also prevents seizures in some animals with congenital epilepsy and protects against audiogenic tonic extensions and clonic seizures in mice.

Although the mechanism of action is unknown as yet, gabapentin also has demonstrated analgesic activity. In animals, gabapentin has been shown to prevent allodynia (pain-related behavior in response to normally innocuous stimuli) and hyperalgesia (exaggerated response to painful stimuli) in several models of neuropathic pain. Gabapentin also has been shown to decrease pain-related responses after peripheral inflammation in animals; however, the drug has not altered immediate pain-related behaviors. The clinical relevance of these findings is not known.

Gabapentin does not bind to plasma proteins, is not appreciably metabolized, does not induce hepatic enzyme activity, and does not appear to alter the pharmacokinetics of commonly used anticonvulsant drugs (e.g., carbamazepine, phenytoin, valproate, phenobarbital, diazepam) or oral contraceptives. In addition, the pharmacokinetics of gabapentin are not altered substantially by concomitant administration of other anticonvulsant drugs.

Children younger than 5 years of age have a higher clearance of gabapentin normalized for weight compared with those 5 years of age and older; clearance of the drug in children 5 years of age and older is consistent with that in adults after a single dose. Therefore, a higher daily dosage is required in children 3–5 years of age to achieve average plasma concentrations similar to those in patients 5 years of age and older. (See Dosage and Administration: Dosage.) Infants younger than 1 year of age have a highly variable clearance.

SumMon* (see Users Guide). For additional information on this drug until a more detailed monograph is developed and published, the manufacturer's labeling should be consulted. It is *essential* that the labeling be consulted for detailed information on the usual cautions, precautions, and contraindications concerning potential drug interactions and/or laboratory test interferences and for information on acute toxicity.

Preparations

Excipients in commercially available drug preparations may have clinically important effects in some individuals; consult specific product labeling for details.

Gabapentin

Oral		
Capsules	100 mg*	Gabapentin Capsules
		Neurontin*, Pfizer
	300 mg*	Gabapentin Capsules
		Neurontin*, Pfizer
	400 mg*	Gabapentin Capsules
		Neurontin*, Pfizer
Solution	250 mg/5 mL	Neurontin*, Pfizer
Tablets	100 mg*	Gabapentin Tablets
	300 mg*	Gabapentin Tablets
	400 mg*	Gabapentin Tablets
	600 mg*	Gabapentin Tablets
	800 mg*	Gabapentin Tablets
Tablets, film-coated	600 mg*	Gabapentin Tablets
		Neurontin*, Pfizer
	800 mg*	Gabapentin Tablets
		Neurontin*, Pfizer

*available from one or more manufacturer, distributor, and/or repackager by generic (nonproprietary) name
†Use is not currently included in the labeling approved by the US Food and Drug Administration

Lamotrigine

■ Lamotrigine is a phenyltriazine anticonvulsant.

Uses

■ **Seizure Disorders** ***Partial Seizures*** Lamotrigine is used in combination with other anticonvulsant agents in the management of partial seizures in adults and children. Lamotrigine also is used as monotherapy in patients converting from monotherapy with a hepatic enzyme-inducing anticonvulsant agent (e.g., phenytoin, carbamazepine, phenobarbital, primidone) in the management of partial seizures in adults.

In controlled clinical studies, adjunctive therapy with lamotrigine was effective in reducing seizure frequency in patients with simple and/or complex partial seizures refractory to therapy with one or more conventional anticonvulsant drugs (e.g., phenytoin, carbamazepine, phenobarbital); the median reduction in seizure frequency was 24–36%. In a controlled clinical study in children 2–16 years of age with partial seizures, the median reduction in frequency of all partial seizures was 36 or 7% in patients receiving lamotrigine or placebo, respectively, in addition to their current therapy (up to 2 conventional anticonvulsant drugs).

The effectiveness of lamotrigine monotherapy in adults with partial seizures who are converting from monotherapy with a hepatic enzyme-inducing anticonvulsant drug (e.g., phenytoin, carbamazepine, phenobarbital, primidone) was established in a controlled clinical study of patients who experienced at least 4 simple or complex partial seizures, with or without secondary generalization, during each of 2 consecutive 4-week baseline periods; during the baseline periods, patients were receiving either phenytoin or carbamazepine monotherapy. Patients were randomized either to lamotrigine (target dose: 500 mg daily) or valproic acid (1000 mg daily) therapy, which was added to their baseline regimen over a 4-week period. Patients were then converted to either lamotrigine or valproic acid monotherapy over another 4-week period and monotherapy continued for another 12-week period. Study end points were either successful completion of the 12-week monotherapy period or meeting a study "escape" criterion, relative to baseline. Escape criteria were defined as doubling of the mean monthly seizure count; doubling of the highest consecutive 2-day seizure frequency; emergence of a new seizure type (defined as a seizure that did not occur during the 8-week baseline period) that was more severe than the other seizure types occurring during the study period; or clinically important prolongation of generalized tonic-clonic seizures. The proportion of lamotrigine- or valproic acid-treated patients meeting escape criteria was 42 or 69%, respectively; no differences in efficacy were detected based on age, race, or gender. It was noted that the patients in the valproic acid control arm were treated intentionally with a relatively low valproic acid dosage because the intent of the study was to establish the effectiveness of lamotrigine monotherapy, and that the study results cannot be interpreted to imply the superiority of lamotrigine therapy to adequate valproic acid therapy. In addition, the manufacturer states that the use of lamotrigine therapy for the management of partial seizures has not been established as initial monotherapy; for conversion from monotherapy with anticonvulsant drugs that do *not* induce hepatic enzymes (e.g., valproate); or for simultaneous conversion to monotherapy from 2 or more concomitant anticonvulsant drugs.

Primary Generalized Tonic-Clonic Seizures Lamotrigine is used in combination with other anticonvulsant agents in the management of primary generalized tonic-clonic seizures in adults and children 2 years of age and older. Efficacy of the drug as adjunctive therapy was established in a placebo-controlled trial in adult and pediatric patients at least 2 years of age who had experienced at least 3 primary generalized tonic-clonic seizures during an 8-week baseline phase. Patients were randomized to receive either placebo or lamotrigine in a fixed-dose regimen (target dosages of 200–400 mg daily in adults and 3–12 mg/kg daily in children) for 19–24 weeks, which was added to their current anticonvulsant regimen of up to 2 anticonvulsant drugs. Patients receiving lamotrigine experienced a substantially greater median reduction in seizure frequency compared with baseline than did patients receiving placebo (66 and 34%, respectively).

Seizures Associated with Lennox-Gastaut Syndrome Lamotrigine also is used in combination with other anticonvulsant agents in the management of generalized seizures associated with Lennox-Gastaut syndrome in pediatric patients and adults. In a controlled clinical trial in patients with Lennox-Gastaut syndrome, adjunctive therapy with lamotrigine resulted in a 32, 34, and 36% decrease in major motor seizures, drop attacks, and tonic-clonic seizures, respectively.

■ **Bipolar Disorder** Lamotrigine is used in the maintenance therapy of bipolar I disorder to prevent or attenuate recurrences of bipolar episodes in patients who remain at high risk of relapse following treatment of an acute depressive or manic episode. The American Psychiatric Association (APA) currently recommends use of lamotrigine as an alternative to first-line maintenance therapies (e.g., lithium, valproic acid, or divalproex). The APA also states that both lamotrigine and lithium are effective in the maintenance treatment of bipolar I disorder; however, the results of two randomized, double-blind, placebo-controlled studies of 18 months' duration indicate that lamotrigine may be more effective in preventing depressive episodes while lithium may be more effective in preventing manic episodes.

Although efficacy of the drug in the acute treatment of mood episodes has yet to be fully established, lamotrigine is considered a first-line agent by the APA for the management of acute depressive episodes in patients with bipolar disorder†. The APA also recommends the use of lamotrigine as an alternative to lithium, valproic acid, or divalproex in the management of patients with rapid cycling bipolar disorder†, particularly in those with the bipolar 2 form of rapid cycling.

For further information on the management of bipolar disorder, see Uses: Bipolar Disorder, in Lithium Salts 28:28.

Dosage and Administration

■ **Administration** Lamotrigine is administered orally. The drug may be administered without regard to meals.

Lamotrigine conventional tablets should be swallowed whole. Lamotrigine chewable/dispersible tablets may be swallowed whole, chewed (and consumed with a small amount of water or diluted fruit juice to aid swallowing), or dispersed in water or diluted fruit juice. To disperse the tablets, they should be added to a small volume (i.e., 5 mL or enough to cover the tablet) of liquid and allowed to disperse completely (over approximately 1 minute); the solution then should be swirled and consumed immediately. Administration of partial quantities of the dispersed tablets should *not* be attempted; calculated doses that do not correspond to available strengths of whole tablets should be rounded down to the nearest whole tablet. Lamotrigine orally disintegrating tablets should be placed on the tongue and moved around in the mouth, where the tablet disintegrates rapidly in saliva, and then subsequently can be swallowed with or without water.

Patients who are currently receiving or beginning therapy with lamotrigine and/or any other anticonvulsant for any indication should be closely monitored for the emergence or worsening of depression, suicidal thoughts or behavior (suicidality), and/or any unusual changes in mood or behavior. (See Cautions: Precautions and Contraindications.)

Dispensing and Administration Precautions Dispensing errors have occurred because of the similarity in spelling between Lamictal® (the trade name for lamotrigine) and Lamisil® (terbinafine hydrochloride), lamivudine, labetalol hydrochloride, Lomotil® (the fixed combination of atropine sulfate and diphenoxylate hydrochloride), and Ludiomil® (the former trade name for maprotiline hydrochloride; no longer commercially available under this trade name in the US). Therefore, extra care should be exercised in ensuring the accuracy of both oral and written prescriptions for Lamictal® and these other drugs. The manufacturer recommends that clinicians consider including the intended use of the particular drug on the prescription, in addition to alerting patients to carefully check the drug they receive and promptly bring any question or concern to the attention of the dispensing pharmacist. The manufacturer also recommends that pharmacists assess various measures of avoiding dispensing errors and implement them as appropriate (e.g., by computerized filling and handling of prescriptions, patient counseling). (See Cautions: Precautions and Contraindications.)

■ **Dosage** Because of the possibility of increasing seizure frequency, anticonvulsant drugs, including lamotrigine, should *not* be discontinued abruptly, particularly in patients with preexisting seizure disorders. Discontinuance of lamotrigine therapy should be done gradually over at least 2 weeks, in a stepwise fashion (e.g., achieving a 50% reduction in the daily dosage of lamotrigine each week). However, concerns for patient safety with continued use of lamotrigine may require more rapid withdrawal of the drug.

The dosage regimen of lamotrigine used in combination with other anticonvulsant drugs depends on whether valproic acid or hepatic enzyme-inducing anticonvulsant drugs, or a combination of these, is administered concomitantly. Addition to lamotrigine therapy of an anticonvulsant drug that induces hepatic microsomal enzymes (e.g., carbamazepine, phenobarbital, phenytoin, primidone) may be expected to increase the clearance (i.e., reduce plasma concentrations) of lamotrigine; conversely, discontinuance of such a concomitantly administered anticonvulsant drug may result in decreased clearance (i.e., increased plasma concentrations) of lamotrigine. Addition of valproate sodium to lamotrigine therapy also decreases the clearance (i.e., increases plasma concentrations) of lamotrigine. Therefore, clinicians should be aware that addition of hepatic enzyme-inducing anticonvulsant drugs or valproic acid to, or their discontinuance from, an anticonvulsant regimen including lamotrigine may require modification of the dosage of lamotrigine and/or the other anticonvulsant agent(s). Exceeding the recommended initial dosage and subsequent dosage escalations of lamotrigine may increase the risk of developing a rash and is *not* recommended.

According to the manufacturer, the effect of anticonvulsants other than hepatic enzyme-inducing anticonvulsant drugs or valproic acid on the pharmacokinetics of lamotrigine has not been fully established, and specific dosing recommendations for patients receiving such drugs cannot be made at this time. Conservative initial dosages and dose escalations (as with concomitant valproic acid) are recommended, and an appropriate maintenance dosage probably would be greater than the maintenance dosage with valproic acid and lower than the maintenance dosage with a hepatic enzyme-inducing anticonvulsant drug.

Seizure Disorders **Adjunctive Therapy for Partial Seizures, Primary Generalized Tonic-Clonic Seizures, or Lennox-Gastaut Syndrome.** For adjunctive therapy in the management of partial seizures, primary generalized tonic-clonic seizures, or Lennox-Gastaut syndrome in adults and children older than 12 years of age who are receiving hepatic enzyme-inducing anticonvulsant drugs *without* concomitant valproic acid therapy, the usual initial dosage of lamotrigine is 50 mg once daily for 2 weeks, then 100 mg daily in 2 divided doses for 2 weeks. The daily dosage may then be increased by 100 mg every 1–2 weeks until an effective maintenance dosage of 300–500 mg daily given in 2 divided doses is reached.

For adjunctive therapy in the management of partial seizures, primary generalized tonic-clonic seizures, or Lennox-Gastaut syndrome in adults and children older than 12 years of age who are receiving an anticonvulsant regimen containing valproic acid, the usual initial dosage of lamotrigine is 25 mg every other day for 2 weeks, followed by 25 mg once daily for 2 weeks. The initial dosage of lamotrigine in patients also receiving valproic acid should not exceed 25 mg every other day because of an increased incidence of rash with concomitant lamotrigine and valproic acid therapy. After the initial 4 weeks of therapy, the daily dosage of lamotrigine may be increased by 25–50 mg every 1–2 weeks until an effective maintenance dosage of 100–400 mg daily given in 1 or 2 divided doses is reached. The usual maintenance dosage of lamotrigine when added to valproic acid alone in adults and children older than 12 years of age is 100–200 mg daily.

Although maintenance dosages of lamotrigine as high as 700 mg daily have been used in anticonvulsant drug regimens that included hepatic enzyme-inducing anticonvulsants but *not* valproic acid or as high as 200 mg daily in drug regimens that included valproic acid alone, dosages exceeding 300–500 mg daily (in regimens *not* containing valproic acid) or exceeding 200 mg daily (in regimens containing valproic acid alone) have not been evaluated in controlled studies.

For adjunctive therapy in the management of partial seizures, primary generalized tonic-clonic seizures, or Lennox-Gastaut syndrome in patients 2–12 years of age who are receiving hepatic enzyme-inducing anticonvulsant drugs *without* concomitant valproic acid therapy, the usual initial dosage of lamotrigine is 0.6 mg/kg daily (rounded down to the nearest whole tablet) in 2 divided doses for 2 weeks. During the subsequent 2 weeks of therapy, the usual dosage is 1.2 mg/kg daily (rounded down to the nearest whole tablet) in 2 divided doses. Subsequent daily doses should be increased every 1–2 weeks by 1.2 mg/kg (rounded down to the nearest whole tablet) until an effective daily maintenance dosage of 5–15 mg/kg (maximum of 400 mg/day in 2 divided doses) is reached. In patients weighing less than 30 kg, increases in maintenance dosages of up to 50% may be required based on the response and tolerance of the patient.

For adjunctive therapy in the management of partial seizures, primary generalized tonic-clonic seizures, or Lennox-Gastaut syndrome in patients 2–12 years of age who are receiving an anticonvulsant regimen containing valproic acid, the usual initial dosage of lamotrigine is 0.15 mg/kg daily (rounded down to the nearest whole tablet) in 1 or 2 divided doses for 2 weeks. During the subsequent 2 weeks of therapy, the usual dosage is 0.3 mg/kg daily (rounded down to the nearest whole tablet) in 1 or 2 divided doses. Subsequent daily doses should be increased every 1–2 weeks by 0.3 mg/kg (rounded down to the nearest whole tablet) until an effective daily maintenance dosage of 1–5 mg/kg (maximum of 200 mg/day in 1 or 2 divided doses) is reached. Usual maintenance dosages range from 1–3 mg/kg daily in patients receiving lamotrigine and valproic acid alone. In patients weighing less than 30 kg, increases in maintenance dosages of up to 50% may be required based on the response and tolerance of the patient.

Monotherapy for Partial Seizures. For subsequent monotherapy in the management of partial seizures in patients converted from monotherapy with a hepatic enzyme-inducing anticonvulsant drug, the usual lamotrigine maintenance dosage in adults and children 16 years of age or older is 500 mg daily given in 2 divided doses. The transition regimen for converting patients from monotherapy with a hepatic enzyme-inducing anticonvulsant drug to lamotrigine monotherapy is a 2-step process; the goal of the transition regimen is to ensure adequate seizure control while minimizing the possibility of developing a serious rash associated with the rapid titration of lamotrigine.

In the first step of the process, lamotrigine therapy is added to the current drug regimen (which should be maintained at a fixed dose) at a dosage of 50 mg once daily for 2 weeks, followed by 100 mg daily in 2 divided doses for 2 weeks; the daily dosage is then increased by 100 mg every 1–2 weeks until the maintenance dosage of 500 mg daily (in 2 divided doses) is reached. Once the maintenance lamotrigine dosage is reached, the concomitant hepatic enzyme-inducing anticonvulsant drug can then be withdrawn gradually over a period of 4 weeks; based on experience from the controlled clinical trial, the concomitant drug was withdrawn by 20% decrements each week over a 4-week period.

Bipolar Disorder For monotherapy in the maintenance treatment of bipolar disorder, the recommended initial adult dosage of lamotrigine is 25 mg once daily for 2 weeks, followed by 50 mg once daily for 2 weeks. After the initial 4 weeks of therapy, the daily dosage of lamotrigine may be doubled at weekly intervals until an effective maintenance dosage of 200 mg daily is reached. Because 400-mg daily dosages were shown to be no more effective than 200-mg daily dosages in clinical studies of lamotrigine monotherapy, the manufacturer recommends that daily dosages not exceed 200 mg daily.

For adjunctive therapy in the maintenance treatment of bipolar disorder in patients who are receiving carbamazepine or other hepatic enzyme-inducing drugs *without* concomitant valproic acid therapy, the usual initial adult dosage of lamotrigine is 50 mg once daily for 2 weeks, followed by 100 mg daily in 2 divided doses for 2 weeks; the daily dosage is then increased in 100-mg increments at weekly intervals until the maintenance dosage of 400 mg daily (in 2 divided doses) is reached.

For adjunctive therapy in the maintenance treatment of bipolar disorder in adults who are receiving valproic acid, the usual initial dosage of lamotrigine is 25 mg every other day for 2 weeks, followed by 25 mg once daily for 2 weeks. After the initial 4 weeks of therapy, the daily dosage of lamotrigine may be doubled at weekly intervals until an effective maintenance dosage of 100 mg daily is reached. To minimize the risk of potentially serious rash in patients receiving lamotrigine in conjunction with valproic acid, the recommended initial dosages and subsequent dose escalations of lamotrigine should not be exceeded.

Addition of hepatic enzyme-inducing drugs (e.g., carbamazepine) or hepatic enzyme-inhibiting drugs (e.g., valproic acid) to a regimen including lamotrigine may require modification of the dosage of lamotrigine and/or the hepatic enzyme-inducing or -inhibiting drug. In pivotal clinical studies, dosages of lamotrigine were halved immediately following the addition of valproic acid to treat an acute mood episode and maintained at that dosage as long as valproic acid was administered concomitantly with lamotrigine. Following addition of carbamazepine or other hepatic enzyme-inducing drugs to treat an acute mood episode, dosages of lamotrigine were gradually doubled (e.g., over a period of at least 3 weeks) and maintained at that dosage as long as these drugs were administered concomitantly with lamotrigine. Following the addition of other psychotropic agents with no known clinical pharmacokinetic interactions with lamotrigine, patients were maintained at current maintenance dosages of lamotrigine.

Discontinuance of hepatic enzyme-inducing drugs (e.g., carbamazepine) or hepatic enzyme-inhibiting drugs (e.g., valproic acid) from a regimen including lamotrigine may require modification of the dosage of lamotrigine. For patients discontinuing carbamazepine or other enzyme-inducing agents following resolution of the acute mood episode and achievement of a maintenance lamotrigine dosage, lamotrigine dosage should remain constant for the first week and then should be decreased in 100-mg daily increments at weekly intervals until an effective maintenance dosage of 200 mg daily is reached. For patients discontinuing valproic acid following resolution of the acute mood episode and achievement of a maintenance lamotrigine dosage, lamotrigine dosage should be increased in 50-mg daily increments at weekly intervals until an effective maintenance dosage of 200 mg daily is reached.

The optimum duration of lamotrigine therapy for the management of bipolar disorder has not been established, and the usefulness of the drug during prolonged therapy (i.e., longer than 18 months) should be reevaluated periodically.

■ **Dosage in Renal and Hepatic Impairment** Because clinical experience with lamotrigine is limited in patients with concomitant illness, the drug should be used with caution in patients with conditions (e.g., renal, hepatic, cardiac impairment) that may affect metabolism and elimination of the drug.

The manufacturer states that lamotrigine should be used with caution in patients with severe renal impairment because there is insufficient information from controlled clinical studies to establish the safety and efficacy of therapy with the drug in such patients. The initial dosage of lamotrigine in patients with renal impairment should be based on the patient's existing anticonvulsant drug regimen (see Dosage and Administration: Dosage). The manufacturer states that a reduced maintenance dosage of lamotrigine may be effective and generally should be used in patients with substantial renal impairment; however, the manufacturer currently makes no specific recommendation for dosage adjustment in such patients.

The manufacturer states that experience with lamotrigine therapy in patients with hepatic impairment is limited. Based on a clinical pharmacology study of the drug in a small number of patients with moderate to severe hepatic dysfunction, the manufacturer makes the general recommendation that initial, escalation, and maintenance doses of lamotrigine therapy should be decreased by approximately 50% in patients with moderate (e.g., Child-Pugh class B) and 75% in patients with severe (e.g., Child-Pugh class C) hepatic impairment. Escalation and maintenance dosages should be adjusted according to clinical response.

Cautions

Lamotrigine generally is well tolerated. However, there have been rare reports of serious dermatologic reactions (including some fatalities) in adults and children receiving lamotrigine. Nervous system and dermatologic effects are among the most frequently reported adverse effects of lamotrigine and among those most frequently requiring discontinuance of the drug. The most frequently occurring adverse effects associated with lamotrigine as adjunctive therapy in adults in controlled clinical trials include dizziness, ataxia, somnolence, headache, diplopia, blurred vision, nausea, vomiting, and rash. Discontinuance of lamotrigine because of adverse effects was required in about 11% of adult patients receiving the drug as adjunctive therapy in uncontrolled and controlled clinical trials; the adverse effects most frequently associated with discontinuance of lamotrigine in these trials were rash (3% of patients), dizziness (2.8% of patients), and headache (2.5% of patients). In children receiving lamotrigine as adjunctive therapy in controlled clinical trials, the most commonly reported adverse effects were infection, vomiting, rash, fever, somnolence, accidental injury, dizziness, diarrhea, abdominal pain, nausea, ataxia, tremor, asthenia, bronchitis, flu syndrome, and diplopia. Approximately 11.5% of pediatric patients receiving lamotrigine as adjunctive therapy in clinical trials discontinued the drug because of an adverse effect; the adverse effects most frequently associated with discontinuance of lamotrigine therapy in these patients were rash (4.4% of patients), reaction aggravated (1.7% of patients), and ataxia (0.6% of patients).

The most common adverse effects associated with lamotrigine as monotherapy in adults in the controlled clinical trial were vomiting, coordination abnormality, dyspepsia, nausea, dizziness, rhinitis, anxiety, insomnia, infection, pain, weight decrease, chest pain, and dysmenorrhea; during the conversion period (i.e., when lamotrigine was initially added on to an existing monotherapy regimen consisting of a hepatic enzyme-inducing anticonvulsant drug), the most commonly reported adverse effects were dizziness, headache, nausea, asthenia, coordination abnormality, vomiting, rash, somnolence, diplopia, ataxia, accidental injury, tremor, blurred vision, insomnia, nystagmus, diarrhea, lymphadenopathy, pruritus, and sinusitis. The adverse effects most commonly associated with discontinuance of the drug in this trial were rash (4.5% of patients), headache (3.1% of patients), and asthenia (2.4% of patients).

The adverse effect profiles in males and females in clinical trials of lamotrigine were similar and were independent of age; the rates of discontinuance of lamotrigine for individual adverse effects also were similar for males and females. In general, females receiving adjunctive therapy with lamotrigine or placebo in controlled trials were more likely to report adverse effects than were males; however, dizziness was the only adverse effect reported with at least 10% greater frequency (i.e., 16.5% greater frequency) in females than in males (without a corresponding difference by gender with placebo) in controlled trials.

Because clinical trials of lamotrigine therapy involved specific patient populations and use of the drug as adjunctive therapy or monotherapy following conversion from therapy with another single hepatic enzyme-inducing anticonvulsant drug, it is difficult to determine whether a causal relationship exists for many reported adverse effects, to compare adverse effect frequencies with those in other clinical reports, and/or to extrapolate the adverse effects experience from controlled clinical trials to usual clinical practice.

■ **Nervous System Effects** Nervous system effects were among the most frequent adverse effects reported in patients receiving lamotrigine as adjunctive therapy in controlled clinical trials. Dizziness, headache, and ataxia were the most frequent adverse nervous system effects, occurring in 38, 29, and 22% of adults, respectively, in controlled trials of lamotrigine adjunctive therapy. The frequency of dizziness and ataxia and the rate of discontinuance of lamotrigine because of these adverse effects were dose related in clinical trials; in a dose-response study, dizziness occurred in 54, 31, or 27% of patients receiving lamotrigine 500 mg/day, lamotrigine 300 mg/day, or placebo, respectively, while ataxia occurred in 28, 10, or 10% of those receiving these respective regimens. Limited data also suggest an increased incidence of adverse nervous system effects in patients receiving carbamazepine concomitantly with lamotrigine. (See Cautions: Precautions and Contraindications.)

Somnolence or insomnia occurred in 14 or 6%, respectively, of adults receiving lamotrigine as adjunctive therapy in controlled clinical trials. Incoordination or tremor was reported in 6 or 4%, respectively, of lamotrigine-treated adults; limited evidence suggests that incoordination and tremor may be dose related, and tremor may occur more frequently with concomitant administration of valproic acid and lamotrigine. Depression occurred in 4%, anxiety in 4%, irritability in 3%, speech disorder in 3%, and concentration disturbance in 2% of adults receiving lamotrigine as adjunctive therapy in controlled clinical trials. Seizure or seizure exacerbation has been reported in 3 or 2% of adults, respectively, receiving lamotrigine as adjunctive therapy in controlled trials; an increase in seizure frequency also has been reported with lamotrigine therapy. Treatment-emergent seizures diagnosed unequivocally as status epilepticus were reported in 7 of 2343 adults receiving adjunctive therapy with lamotrigine in clinical trials; however, the manufacturer states that valid estimates of the incidence of treatment-emergent status epilepticus are difficult to obtain because of variations in the definitions used by different investigators to identify such cases.

Coordination abnormality, dizziness, anxiety, and insomnia occurred in 7, 7, 5, and 5%, respectively, of adults receiving lamotrigine as monotherapy in a controlled trial; amnesia, ataxia, asthenia, depression, hypesthesia, libido increase, decreased or increased reflexes, nystagmus, and irritability, each occurred in 2% of such patients. Paresthesia or asthenia occurred in more than 1% of adults receiving lamotrigine as adjunctive therapy in controlled clinical trials but with equal or greater frequency in those receiving placebo.

Somnolence occurred in 17%, dizziness in 14%, ataxia in 11%, tremor in 10%, and asthenia in 8% of children receiving lamotrigine as adjunctive therapy in controlled clinical trials. Emotional lability, gait abnormality, thinking abnormality, seizures, nervousness, and vertigo each occurred in 2–4% of children receiving lamotrigine as adjunctive therapy in controlled clinical trials.

Amnesia, confusion, hostility, decreased memory, nervousness, nystagmus, thinking abnormality, or vertigo was reported in at least 1% of patients receiving lamotrigine in uncontrolled and controlled clinical trials. Abnormal dreams, abnormal gait, agitation, akathisia, apathy, aphasia, CNS depression, depersonalization, dysarthria, dyskinesia, dysphoria, emotional lability, euphoria, faintness, grand mal seizures, hallucinations, hyperkinesia, hypertonia, hypesthesia, increased libido, mind racing, myoclonus, panic attack, paranoid reaction, personality disorder, psychosis, migraine, sleep disorder, or stupor occurred in at least 0.1% but in less than 1% of such patients. Cerebellar syndrome, choreoathetosis, CNS stimulation, delirium, delusions, dystonia, hypoesthesia, hypotonia, hemiplegia, hyperalgesia, hyperesthesia, hypokinesia, hypomania, decreased libido, manic-depressive reaction, movement disorder, neuralgia, neurosis, or paralysis occurred in less than 0.1% of patients.

Suicidal ideation has been reported in 2–5% of adult patients receiving lamotrigine monotherapy for partial seizures in a controlled clinical trial and in less than 1% of pediatric and adult patients receiving the drug in uncontrolled and controlled clinical trials; suicide and/or suicide attempt has been reported rarely. The Food and Drug Administration (FDA) has analyzed suicidality reports from placebo-controlled studies involving 11 anticonvulsants, including lamotrigine, and found that patients receiving anticonvulsants had approximately twice the risk of suicidal behavior or ideation (0.43%) compared with patients receiving placebo (0.24%). (See Cautions: Precautions and Contraindications.)

Exacerbation of parkinsonian manifestations in patients with preexisting parkinsonian syndrome and the occurrence of tics have been reported during postmarketing experience with lamotrigine and/or in worldwide uncontrolled clinical trials; however, the manufacturer states that data are insufficient to provide an estimate of the incidence of such effects or to establish a causal relationship to lamotrigine.

■ **GI Effects** GI effects were among the most frequent adverse effects reported in adults receiving lamotrigine as adjunctive therapy in controlled clinical trials. Nausea was the most frequent adverse GI effect, occurring in 19% of adults in controlled clinical trials; vomiting was reported in 9% of patients in these trials. The frequency of nausea and vomiting appears to be dose related; in a dose-response study, nausea occurred in 25, 18, or 11% of patients receiving lamotrigine 500 mg daily, lamotrigine 300 mg daily, or placebo, respectively, while vomiting occurred in 18, 11, or 4% of those receiving these respective regimens. Diarrhea occurred in 6%, dyspepsia in 5%, abdominal pain in 5%, constipation in 4%, tooth disorder in 3%, and anorexia in 2% of adults receiving lamotrigine as adjunctive therapy in controlled clinical trials. Flatulence was reported in more than 1% of adults receiving lamotrigine as adjunctive therapy in controlled clinical trials but occurred with equal or greater frequency in patients receiving placebo. Vomiting, dyspepsia, and nausea occurred in 9, 7, and 7%, respectively, of adults receiving lamotrigine as monotherapy in a controlled trial; anorexia, dry mouth, rectal hemorrhage, and peptic ulcer each occurred in 2% of such patients.

Vomiting occurred in 20%, diarrhea in 11%, abdominal pain in 10%, and nausea in 10% of children receiving lamotrigine as adjunctive therapy in controlled clinical trials. Constipation, dyspepsia, and tooth disorder each occurred in 2–4% of children receiving lamotrigine as adjunctive therapy in controlled clinical trials.

Halitosis, dry mouth, dysphagia, gingivitis, glossitis, gum hyperplasia, increased appetite, increased salivation, mouth ulceration, stomatitis, taste perversion, thirst, or tooth disorder occurred in at least 0.1% but in less than 1% of patients receiving lamotrigine in uncontrolled and controlled clinical trials. Eructation, gastritis, GI hemorrhage, gum hemorrhage, hematemesis, hemorrhagic colitis, melena, gastric ulcer, taste loss, or tongue edema was reported in less than 0.1% of patients.

Esophagitis and pancreatitis have been reported during postmarketing experience with lamotrigine and/or in worldwide uncontrolled clinical trials; however, the manufacturer states that data are insufficient to provide an estimate of the incidence of such effects or to establish a causal relationship to lamotrigine.

■ **Dermatologic and Sensitivity Reactions** Serious dermatologic reactions (including some fatalities) have been reported in adults and children receiving lamotrigine therapy. Rash occurred in 10% of adults and 14% of children receiving lamotrigine as adjunctive therapy in controlled clinical trials. The incidence of severe rash associated with lamotrigine also appears to be higher in pediatric patients than in adults; the manufacturer states that severe rash, including Stevens-Johnson syndrome, has been reported in 0.8% of children younger than 16 years of age and in 0.3% of adults receiving lamotrigine as adjunctive therapy in clinical trials. There is evidence that most cases of rash associated with lamotrigine therapy are associated with transiently high plasma concentrations of the drug occurring during the initial weeks of therapy or with high plasma concentrations occurring during concomitant valproic acid therapy. Cases of life-threatening rashes associated with lamotrigine almost always have occurred within 2–8 weeks of treatment initiation; however, severe rashes rarely have presented following prolonged treatment (e.g., 6 months). Lamotrigine-associated rashes do not appear to have distinguishing features. Because it is not possible to distinguish benign rashes from those that may become severe and/or life-threatening, lamotrigine generally should be discontinued at the first sign of rash (unless the rash is known not to be drug related). However, a rash may become life-threatening or permanently disabling or disfiguring despite discontinuance of the drug. Discontinuance of lamotrigine because of rash was required in 3% of adults receiving the drug as adjunctive therapy and 4.5% of adults receiving the drug as monotherapy in controlled clinical trials; 4.4% of pediatric patients receiving lamotrigine in controlled clinical trials discontinued the drug because of the development of rash. The potential for development of a rash at the beginning of lamotrigine therapy may be decreased by employing low initial doses and by gradual escalation of dosage to avoid initially high plasma concentrations of the drug.

Rash, including serious and potentially life-threatening rash, appears to be more likely to occur in patients receiving concomitant valproic acid. Valproic acid can decrease clearance and increase plasma concentrations of lamotrigine more than twofold; exceeding the recommended reduced initial dosage of lamotrigine or the subsequent recommended schedule for escalation of lamotrigine dosage (see Dosage and Administration: Dosage and see Cautions: Precautions and Contraindications), particularly in patients receiving valproic acid, may increase the incidence of rash, including serious rash, in such patients. In clinical trials, 1% of adults and 1.2% of children receiving a drug regimen including lamotrigine concomitantly with valproic acid experienced a rash requiring hospitalization, while 0.16% of adults and 0.6% of children receiving a drug regimen of lamotrigine without valproic acid were hospitalized because of rash.

Rashes severe enough to cause hospitalization, including Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme, angioedema, and a hypersensitivity syndrome (usually consisting of fever, rash, facial swelling, and hematologic, hepatic, and/or lymphatic involvement), occurred in 0.3% of adults receiving lamotrigine in premarketing controlled and uncontrolled clinical trials and in about 0.8% of pediatric patients receiving the drug in clinical trials; death associated with rash has been reported rarely in postmarketing use of lamotrigine. Erythema multiforme has been reported in patients receiving lamotrigine in premarketing controlled and uncontrolled clinical trials in the US, while lupus-like syndrome and vasculitis have been reported during postmarketing experience with the drug and/or in worldwide uncontrolled clinical trials.

Pruritus occurred in 3% of adults receiving lamotrigine as adjunctive therapy in controlled clinical trials. Contact dermatitis, dry skin, peripheral edema, and sweating each occurred in 2% of adults receiving lamotrigine as monotherapy in a controlled trial. Eczema, facial edema, photosensitivity, and pruritus each were reported in 2% of children receiving lamotrigine as adjunctive therapy in controlled clinical trials. Acne, alopecia, facial edema, dry skin, erythema, hirsutism, maculopapular rash, peripheral edema, skin discoloration, Stevens-Johnson syndrome, sweating, urticaria, or vesiculobullous rash occurred in at least 0.1% but in less than 1% of patients receiving lamotrigine in uncontrolled and controlled clinical trials. Angioedema, erythema multiforme, fungal dermatitis, herpes zoster, leukoderma, petechial rash, pustular rash, seborrhea, or photosensitivity occurred in less than 0.1% of patients.

Hypersensitivity reactions, which can be fatal or life-threatening, have been reported in patients treated with lamotrigine. In some cases, manifestations of these reactions have included multiorgan dysfunction (including hepatic abnormalities) and disseminated intravascular coagulation (see Cautions: Hepatic Effects). Early signs of a possible hypersensitivity reaction, such as fever and lymphadenopathy, should prompt immediate evaluation of the patient; a rash may or may not be present. Unless another cause for the signs or symptoms is found, lamotrigine should be discontinued.

■ **Cardiovascular Effects** Hemorrhage was reported in 2% of pediatric patients receiving lamotrigine as adjunctive therapy in controlled clinical trials. Chest pain occurred in more than 1% of adults receiving lamotrigine as adjunctive therapy in controlled clinical trials but occurred with equal or greater frequency in patients receiving placebo. Chest pain also occurred in 5% of adults receiving lamotrigine as monotherapy in a controlled clinical trial. Flushing, hot flushes, palpitations, postural hypotension, syncope, tachycardia, or vasodilation occurred in at least 0.1% but in less than 1% of patients receiving lamotrigine in uncontrolled and controlled clinical trials. Cerebrovascular accident, cerebral sinus thrombosis, deep thrombophlebitis, myocardial infarction, atrial fibrillation, angina pectoris, hemorrhage, or hypertension occurred in less than 0.1% of patients receiving lamotrigine in uncontrolled and controlled clinical trials.

■ **Respiratory Effects** Rhinitis occurred in 14%, pharyngitis in 10%, increased cough in 8%, and flu-like syndrome in 7% of adults receiving lamotrigine as adjunctive therapy in controlled clinical trials. Respiratory disorder was reported in more than 1% of adults receiving lamotrigine as adjunctive therapy in controlled clinical trials but occurred with equal or greater frequency in patients receiving placebo. Rhinitis occurred in 7% of adults receiving lamotrigine as monotherapy in a controlled trial; epistaxis, bronchitis, and dyspnea each occurred in 2% of such patients. Pharyngitis, bronchitis, and increased cough occurred in 14, 7, and 7%, respectively, of children receiving lamotrigine as adjunctive therapy in controlled clinical trials. Sinusitis and bronchospasm each were reported in 2% of children in these trials. Dyspnea, epistaxis, or hyperventilation occurred in at least 0.1% but in less than 1% of patients in uncontrolled and controlled clinical trials, and bronchospasm, hiccups, or sinusitis occurred in less than 0.1% of patients. Apnea has been reported during postmarketing experience with lamotrigine and/or in worldwide uncontrolled clinical trials; however, the manufacturer states that data are insufficient to provide an estimate of the incidence of this adverse effect or to establish a causal relationship to lamotrigine.

■ **Ocular and Otic Effects** Ocular effects were among the most frequent adverse effects reported in patients receiving lamotrigine as adjunctive therapy in controlled clinical trials. Diplopia was the most frequent adverse ocular effect reported in adults receiving lamotrigine as adjunctive therapy in controlled trials, occurring in 28% of such patients, and blurred vision occurred in 16% of patients. The frequency of diplopia and blurred vision appears to be dose related; in a dose-response study, diplopia occurred in 49, 24, or 8% of patients receiving lamotrigine 500 mg daily, lamotrigine 300 mg daily, or placebo, respectively, while blurred vision occurred in 25, 11, or 10% of patients receiving these respective regimens. Limited data also indicate an increased incidence of some adverse effects, including diplopia and blurred vision, in patients receiving carbamazepine concomitantly with lamotrigine. (See Cautions: Precautions and Contraindications.)

Vision abnormality occurred in 3% of adults receiving lamotrigine as adjunctive therapy in controlled clinical trials and in 2% of adults receiving lamotrigine as monotherapy in a controlled trial. Diplopia, blurred vision, or vision abnormality occurred in 5, 4, or 2%, respectively, of children receiving lamotrigine as adjunctive therapy in controlled clinical trials. Abnormality of accommodation, conjunctivitis, oscillopsia, or photophobia occurred in at least 0.1% but in less than 1% of patients in uncontrolled and controlled clinical trials, and dry eyes, lacrimation disorder, strabismus, ptosis, or uveitis occurred in less than 0.1% of patients.

Ear disorder was reported in 2% of children receiving lamotrigine as adjunctive therapy in controlled clinical trials. Otic pain or tinnitus occurred in at least 0.1% but in less than 1% of patients in uncontrolled and controlled

clinical trials. Deafness was reported in less than 0.1% of patients in uncontrolled and controlled clinical trials.

■ **Musculoskeletal Effects** Neck pain and arthralgia each occurred in 2% of adults receiving lamotrigiuc as adjunctive therapy in controlled clinical trials. Back pain or myalgia occurred in more than 1% of patients receiving lamotrigine as adjunctive therapy in controlled trials but with equal or greater frequency in patients receiving placebo. Joint disorder, myasthenia, muscle spasm, or twitching occurred in at least 0.1% but in less than 1% of patients in uncontrolled and controlled trials, and arthritis, bursitis, leg cramps, tendinous contracture, or pathological fracture occurred in less than 0.1% of patients. Rhabdomyolysis has been observed in patients experiencing hypersensitivity reactions during postmarketing experience with lamotrigine and/or in worldwide uncontrolled trials; however, the manufacturer states that data are insufficient to provide an estimate of the incidence of this adverse effect or to establish a causal relationship to lamotrigine.

■ **Genitourinary Effects** Dysmenorrhea occurred in 7%, vaginitis in 4%, and amenorrhea in 2% of women receiving lamotrigine as adjunctive therapy in controlled clinical trials. Dysmenorrhea occurred in 5% of women receiving lamotrigine as monotherapy in a controlled trial. Menstrual disorder or urinary tract infection occurred in more than 1% of adults receiving adjunctive lamotrigine therapy in controlled trials but with equal or greater frequency in patients receiving placebo. Urinary tract infection occurred in 3% of children receiving lamotrigine as adjunctive therapy in controlled clinical trials; penis disorder was reported in 2% of male pediatric patients receiving lamotrigine in these trials.

Lactation (in females), vaginal candidiasis, hematuria, polyuria, urinary frequency, urinary incontinence, or urinary retention occurred in at least 0.1% but in less than 1% of patients receiving lamotrigine therapy in uncontrolled and controlled clinical trials. Abnormal ejaculation, impotence, epididymitis, cystitis, urine abnormality, dysuria, kidney pain, kidney failure, acute kidney failure, or menorrhagia occurred in less than 0.1% of patients in uncontrolled and controlled clinical trials.

■ **Endocrine and Metabolic Effects** Goiter or hyperthyroidism occurred in less than 0.1% of patients receiving lamotrigine in uncontrolled and controlled clinical trials. Weight decrease occurred in 5% of adults receiving lamotrigine as monotherapy in a controlled trial. Weight loss or weight gain occurred in at least 0.1% but in less than 1% of patients in uncontrolled and controlled clinical trials. Edema occurred in 2% of children receiving lamotrigine as adjunctive therapy in controlled clinical trials. Edema or hyperglycemia occurred in less than 0.1% of patients in uncontrolled and controlled clinical trials.

■ **Hepatic Effects** Fatalities associated with multiorgan failure and various degrees of hepatic failure have been reported rarely during premarketing trials of lamotrigine as adjunctive therapy. A young woman receiving concomitant valproic acid and carbamazepine developed a possible hypersensitivity syndrome consisting of headache, fever, and a maculopapular rash 3 weeks following addition of lamotrigine to therapy; fulminant hepatic failure and hepatic coma developed within 3 days, and despite subsequent clinical improvement, the patient died of a massive pulmonary embolus 2 months later. Multiorgan (including renal and/or hepatic) failure and disseminated intravascular coagulation associated with frequent generalized seizures or status epilepticus have been reported in several patients receiving lamotrigine; it has been suggested that this syndrome may have resulted from rhabdomyolysis caused by uncontrolled generalized seizures. The majority of these cases of hepatic and/or multiorgan failure occurred in association with other serious medical events (e.g., status epilepticus, overwhelming sepsis), making it difficult to identify the initiating cause. However, disseminated intravascular coagulation, rhabdomyolysis, renal failure, maculopapular rash, ataxia, and increased liver enzymes (e.g., AST [SGOT]) in the absence of generalized seizures also have been reported rarely with lamotrigine as adjunctive therapy. Abnormal liver function test results occurred in at least 0.1% but in less than 1% of patients receiving lamotrigine in uncontrolled and controlled clinical trials, and hepatitis, increased alkaline phosphatase, or bilirubinemia occurred in less than 0.1% of patients.

■ **Hematologic Effects** Blood dyscrasias that may or may not be associated with hypersensitivity reactions, including neutropenia, leukopenia, anemia, thrombocytopenia, pancytopenia, and rarely, aplastic anemia and pure red cell aplasia (PRCA), have been reported with lamotrigine. Lymphadenopathy occurred in 2% of children receiving lamotrigine as adjunctive therapy in controlled clinical trials. Anemia, ecchymosis, petechiae, leukocytosis, leukopenia, or lymphadenopathy occurred in at least 0.1% but in less than 1% of patients receiving lamotrigine in uncontrolled and controlled clinical trials. Eosinophilia, fibrin decrease, fibrinogen decrease, iron deficiency anemia, lymphocytosis, macrocytic anemia, or thrombocytopenia occurred in less than 0.1% of patients receiving lamotrigine in uncontrolled and controlled clinical trials.

Disseminated intravascular coagulation has been reported rarely in conjunction with multiorgan (e.g., renal and/or hepatic) failure in patients receiving lamotrigine as adjunctive therapy. (See Cautions: Hepatic Effects.) Agranulocytosis, aplastic anemia, hemolytic anemia, neutropenia, pancytopenia, red cell aplasia, and progressive immunosuppression have been reported during postmarketing experience with lamotrigine and/or in worldwide uncontrolled clinical trials; however, the manufacturer states that data are insufficient to provide an estimate of the incidence of such effects or to establish a causal relationship to lamotrigine.

■ **Other Adverse Effects** Flu syndrome or fever occurred in 7 or 6%, respectively, of adults receiving lamotrigine as adjunctive therapy in controlled clinical trials. Pain and infection each occurred in 5% and fever in 2% of adults receiving lamotrigine as monotherapy in a controlled trial. Infection occurred in 20%, fever in 15%, accidental injury in 14%, flu syndrome in 7%, and pain in 5% of children receiving lamotrigine as adjunctive therapy in controlled clinical trials. Pain occurred in at least 1% of patients receiving lamotrigine in uncontrolled and controlled clinical trials. Accidental injury, infection, chills, and malaise occurred in at least 0.1% but in less than 1% of patients receiving lamotrigine in uncontrolled and controlled clinical trials. Breast pain, breast abscess, breast neoplasm, enlarged abdomen, increase in serum creatinine concentration, parosmia, or alcohol intolerance occurred in less than 0.1% of patients.

■ **Precautions and Contraindications** Because of the possibility of increased seizure frequency, anticonvulsant drugs, including lamotrigine, should not be discontinued suddenly, particularly in patients with preexisting seizure disorders. Unless safety concerns dictate a more rapid withdrawal of the drug, discontinuance of lamotrigine should be done gradually over a period of 2 weeks. (See Dosage and Administration: Dosage.) Seizure exacerbation and/or status epilepticus have been reported in patients receiving lamotrigine as adjunctive therapy in the management of seizure disorders, although the incidence of these adverse effects has been difficult to determine conclusively. (See Cautions: Nervous System Effects.) The use and dosage of all anticonvulsant drugs in a regimen including lamotrigine should be reevaluated if there is a change in seizure control or appearance or worsening of adverse effects, and patients should be instructed to report immediately any worsening of seizure control.

The US Food and Drug Administration (FDA) has informed healthcare professionals about an increased risk of suicidality (suicidal behavior or ideation) observed in an analysis of studies using various anticonvulsants compared with placebo. FDA's analysis included 199 randomized, placebo-controlled studies of 11 anticonvulsants (carbamazepine, felbamate, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, pregabalin, tiagabine, topiramate, valproate, and zonisamide) involving over 43,000 patients 5 years of age or older; the studies evaluated the effectiveness of the anticonvulsants in epilepsy, psychiatric disorders (e.g., bipolar disorder, depression, anxiety), and other conditions (e.g., migraine, neuropathic pain). The analysis revealed that patients receiving these anticonvulsants had approximately twice the risk of suicidal behavior or ideation (0.43%) compared with patients receiving placebo (0.24%); this increased suicidality risk was observed as early as one week after beginning therapy and continued through 24 weeks. The results were generally consistent among the 11 drugs studied. In addition, patients who were treated for epilepsy, psychiatric disorders, and other conditions were all found to be at increased risk for suicidality when compared with placebo; there did not appear to be a specific demographic subgroup of patients to which the increased risk could be attributed. However, the relative risk for suicidality was found to be higher in patients with epilepsy compared with patients who were given one of the drugs for psychiatric or other conditions.

Based on the current analysis of the available data, FDA recommends that all patients who are currently receiving or beginning therapy with any anticonvulsant for any indication be closely monitored for the emergence or worsening of depression, suicidal thoughts or behavior (suicidality), and/or unusual changes in mood or behavior. Symptoms such as anxiety, agitation, hostility, mania, and hypomania may be precursors to emerging suicidality. Clinicians should inform patients, their families, and caregivers of the potential for an increased risk of suicidality so that they are aware and able to notify their clinician of any unusual behavioral changes. Patients, family members, and caregivers also should be advised not to make any changes to the anticonvulsant regimen without first consulting with the responsible clinician. They should pay close attention to any day-to-day changes in mood, behavior, and actions; since changes can happen very quickly, it is important to be alert to any sudden differences. In addition, patients, family members, and caregivers should be aware of common warning signs that may signal suicide risk (e.g., talking or thinking about wanting to hurt oneself or end one's life, withdrawing from friends and family, becoming depressed or experiencing worsening of existing depression, becoming preoccupied with death and dying, giving away prized possessions). If these or any new and worrisome behaviors occur, the responsible clinician should be contacted immediately. FDA also recommends that clinicians who prescribe lamotrigine or any other anticonvulsant balance the risk for suicidality with the risk of untreated illness. Epilepsy and many other illnesses for which anticonvulsants are prescribed are themselves associated with an increased risk of morbidity and mortality and an increased risk of suicidal thoughts and behavior. If suicidal thoughts and behavior emerge during anticonvulsant therapy, the clinician must consider whether the emergence of these symptoms in any given patient may be related to the illness being treated.

During the premarketing development of lamotrigine, 20 sudden and unexplained deaths were reported among a cohort of 4700 patients with epilepsy receiving adjunctive therapy with the drug (5747 patient-years of exposure). Although the rate of these deaths exceeds that expected to occur in a healthy (nonepileptic) population matched for age and gender, this rate was similar to that occurring in a similar population of epileptic patients receiving a chemically unrelated anticonvulsant agent. This evidence suggests, but does not prove, that the incidence of sudden, unexplained death observed with lamotrigine adjunctive therapy may be reflective of the population itself rather than the effects of lamotrigine.

Some evidence suggests that use of lamotrigine concomitantly with valproic acid increases the risk of serious rash. The incidence of rash also appears to increase with the magnitude of the initial dose of lamotrigine and the subsequent rate of dosage escalation; exceeding the recommended dosage of lamotrigine at initiation of therapy appears to increase the risk of rash requiring withdrawal of therapy. (See Dosage and Administration: Dosage.) A benign initial appearance of a rash in a patient receiving lamotrigine therapy cannot predict an entirely benign outcome. Patients receiving lamotrigine, especially in conjunction with valproic acid, should be cautioned that rash, in some cases potentially life-threatening, may occur, and that any occurrence of rash should immediately be reported by the patient to their clinician.

The concomitant use of valproic acid and/or hepatic enzyme-inducing anticonvulsant drugs (e.g., phenobarbital, primidone, carbamazepine, phenytoin) can increase or decrease the metabolism and elimination of lamotrigine, requiring dosage adjustments to maintain efficacy and/or avoid toxicity. (See Dosage and Administration: Dosage.) Addition of valproic acid to lamotrigine therapy reduces lamotrigine clearance and increases steady-state plasma lamotrigine concentrations by slightly more than 50% whether or not hepatic enzyme-inducing anticonvulsant drugs are given concomitantly. Conversely, steady-state plasma concentrations of lamotrigine are decreased by about 40% when phenobarbital, primidone, or carbamazepine is added to lamotrigine therapy and by about 45–54% when phenytoin is added to lamotrigine therapy; the magnitude of the effect with phenytoin is dependent on the total daily dosage of phenytoin (from 100–400 mg daily). Discontinuance of an enzyme-inducing anticonvulsant drug can be expected to increase, and discontinuance of valproic acid can be expected to decrease, the elimination half-life and plasma concentrations of lamotrigine. Although the manufacturer states that a therapeutic plasma concentration range has not been established for lamotrigine and that dosage should be based on therapeutic response, the change in plasma lamotrigine concentrations resulting from addition or discontinuance of enzyme-inducing anticonvulsant drugs or valproic acid should be considered when these drugs are added to or withdrawn from an existing anticonvulsant drug regimen that includes lamotrigine.

Addition of lamotrigine to existing therapy with phenytoin or carbamazepine generally does *not* appreciably alter the steady-state plasma concentrations of these concomitantly administered drugs. Addition of lamotrigine to carbamazepine therapy reportedly has resulted in increased plasma concentrations of a pharmacologically active metabolite of carbamazepine (carbamazepine-10,11-epoxide) and an increased incidence of some adverse effects (e.g., dizziness, headache, diplopia, blurred vision, ataxia, nausea, nystagmus). However, elevations in carbamazepine-10,11-epoxide plasma concentrations and/or increased toxicity have not been consistently observed with concomitant administration of lamotrigine and carbamazepine, and the mechanism of the interaction between these drugs remains unclear.

Addition of lamotrigine to valproic acid therapy in healthy individuals resulted in a 25% reduction in trough steady-state plasma concentrations of valproic acid over a 3-week period, followed by stabilization of these concentrations.

The manufacturer states that the effects of adding lamotrigine to an existing regimen including valproic acid, phenytoin, and/or carbamazepine may be expected to be similar to those associated with addition of each drug independently (i.e., valproic acid concentrations decrease, phenytoin and carbamazepine concentrations do not change).

Lamotrigine is a weak inhibitor of dihydrofolate reductase. Although clinically important alterations in blood folate concentrations or hematologic parameters have not been documented in clinical studies of lamotrigine therapy of at least 5 years duration, the manufacturer states that clinicians should be aware of this effect when prescribing other drugs that inhibit folate metabolism.

Multiorgan failure and various degrees of hepatic failure, in some cases fatal, have been reported rarely with lamotrigine as adjunctive therapy. (See Cautions: Hepatic Effects.) The possibility of such potentially fatal adverse effects should be considered in patients who exhibit signs and symptoms associated with multiorgan and/or hepatic impairment following initiation of lamotrigine as adjunctive therapy.

Lamotrigine can produce drowsiness and dizziness, and patients should be cautioned that the drug may impair their ability to perform hazardous activities requiring mental alertness or physical coordination (e.g., operating machinery, driving a motor vehicle).

Limited information indicates that the elimination half-life of lamotrigine is prolonged in patients with severe chronic renal failure (mean creatinine clearance of 13 mL/minute) not receiving other anticonvulsant drugs. In a study of a limited number of patients and healthy individuals receiving a single 100-mg dose of lamotrigine, the mean plasma half-life of the drug was 42.9 hours in patients with chronic renal failure, 57.4 hours between treatments in dialysis patients, and 26.2 hours in healthy individuals. The mean plasma half-life of lamotrigine was decreased to 13 hours during hemodialysis; an average of 20% (range: 5.6–35.1%) of the total body load of lamotrigine was eliminated during a 4-hour hemodialysis treatment. The manufacturer states that a reduced maintenance dosage of lamotrigine generally should be used in patients with substantial renal impairment; however, the manufacturer currently makes no specific recommendations for dosage adjustment in such patients. (See Dosage and Administration: Dosage in Renal and Hepatic Impairment.)

The manufacturer states that experience with use of lamotrigine in patients with impaired liver function is limited. Following a single 100-mg dose of lamotrigine, the median half-life of the drug in patients with mild, moderate, or severe hepatic impairment (Child-Pugh class A, B, or C, respectively) was 36, 60, or 100 hours, respectively, compared with 32 hours in healthy individuals. The manufacturer recommends reduction of initial, escalation, and maintenance dosages of lamotrigine in patients with moderate or severe hepatic impairment. (See Dosage and Administration: Dosage in Renal and Hepatic Impairment.)

Because lamotrigine is transformed in the liver principally to glucuronide metabolites, that are eliminated renally, the drug should be used with caution in patients with diseases or conditions (e.g., renal, hepatic, or cardiac impairment) that could affect metabolism and/or elimination of the drug. In dogs, lamotrigine is extensively metabolized to its 2-*N*-methyl metabolite, which has caused dose-dependent prolongations of the PR interval, widening of the QRS complex, and at high dosages, complete AV block. There have been no consistent effects of lamotrigine metabolites on cardiac conduction in humans. Trace amounts of the 2-*N*-methyl metabolite of lamotrigine have been found in urine, but not in plasma, with chronic dosing of lamotrigine in humans. However, the manufacturer states that it is possible that increased plasma concentrations of the 2-*N*-methyl metabolite could occur in patients with hepatic disease who have decreased ability to glucuronidate lamotrigine.

Lamotrigine binds to melanin-containing ocular tissue in pigmented rats and cynomolgus monkeys, but evidence of this manifestation has not been reported in humans. Although ophthalmologic testing was conducted in one controlled clinical trial of lamotrigine therapy, the manufacturer states that it was inadequate to detect subtle effects or injury resulting from long-term administration of lamotrigine and that the ability of available tests to detect potentially adverse effects associated with the binding of lamotrigine to melanin is unknown. The manufacturer further states that while no specific recommendations for periodic ophthalmologic monitoring of patients receiving long-term lamotrigine therapy can be provided, prolonged administration of the drug could potentially result in its accumulation and possible toxic effects in melanin-rich tissues, including those of the eye, and that clinicians should be aware of possible adverse ophthalmologic effects occurring as a result of binding of the drug to melanin.

Because of similarity in spelling between Lamictal® (the trade name for lamotrigine) and labetalol, Lamisil® (terbinafine hydrochloride), lamivudine, Lomotil® (the fixed combination of atropine sulfate and diphenoxylate hydrochloride), and Ludiomil® (no longer commercially available under this trade name in the US; maprotiline hydrochloride), dispensing errors have been reported to the manufacturer of Lamictal® (GlaxoSmithKline). These medication errors may be associated with serious adverse events either due to lack of appropriate therapy for seizures (e.g., in patients not receiving the prescribed anticonvulsant, lamotrigine, which may lead to status epilepticus) or, alternatively, to the risk of developing adverse effects (e.g., serious rash) associated with the use of lamotrigine in patients for whom the drug was not prescribed and consequently was not properly titrated. Therefore, extra care should be exercised in ensuring the accuracy of both oral and written prescriptions for Lamictal® and these other drugs. When appropriate, clinicians might consider including the intended use of the particular drug on the prescription in addition to alerting patients to carefully check the drug they receive and promptly bring any question or concern to the attention of the dispensing pharmacist. The manufacturer also recommends that pharmacists assess various measures of avoiding dispensing errors and implement them as appropriate (e.g., by computerized filling and handling of prescriptions, patient counseling). Medication errors also may occur between the different formulations of lamotrigine. Depictions of Lamictal® conventional tablets, chewable/dispersible tablets, and orally disintegrating tablets may be found in the medication guide; patients are strongly advised to visually inspect their tablets to verify that they are Lamictal® as well as the correct formulation of Lamictal® each time they fill their prescription.

Lamotrigine is contraindicated in patients with known hypersensitivity to the drug or any ingredient in the formulation.

■ **Pediatric Precautions** Safety and efficacy of lamotrigine have not been established in pediatric patients younger than 2 years of age. Safety and efficacy in children 2–16 years of age have not been established for uses other than adjunctive therapy of partial seizures, primary generalized tonic-clonic seizures, or seizures associated with Lennox-Gastaut syndrome.

Safety and efficacy of lamotrigine for the management of bipolar disorder in patients younger than 18 years of age have not been established.

The incidence of severe rashes requiring hospitalization and discontinuance of the drug appears to be higher in pediatric patients compared with adults (about 0.8% versus 0.3%).

Analyses of population pharmacokinetic data for children 2–18 years of age demonstrated that lamotrigine clearance is influenced mainly by total body weight and concomitant anticonvulsant therapy. Oral clearance of lamotrigine is higher in children than adults when calculated on the basis of body weight; patients weighing less than 30 kg have a higher clearance on a weight-adjusted basis than patients weighing more than 30 kg and may require increases in maintenance dosage. (See Dosage and Administration: Dosage.)

■ **Geriatric Precautions** The manufacturer states that clinical trials of lamotrigine did not include sufficient numbers of patients older than 65 years of age to determine whether they respond differently than younger patients. Because of the greater frequency of decreased hepatic, renal, and/or cardiac function and of concomitant diseases and drug therapy in geriatric patients, the manufacturer suggests that patients in this age group receive initial dosages of the drug in the lower end of the usual range.

■ **Mutagenicity and Carcinogenicity** No evidence of mutagenicity was demonstrated by lamotrigine in vitro in the Ames *Salmonella* microbial mutagen test or the mammalian mouse lymphoma assay. Lamotrigine also did not increase the incidence of structural or numerical chromosomal abnormalities in the in vitro human lymphocyte assay and the in vivo rat bone marrow assay.

No evidence of carcinogenicity was demonstrated by lamotrigine in studies in mice receiving 30 mg/kg daily and in rats receiving 10–15 mg/kg daily for up to 2 years. Steady-state plasma lamotrigine concentrations produced by these dosages ranged from 1–4 mcg/mL in mice and from 1–10 mcg/mL in rats. In humans receiving the recommended lamotrigine dosage of 300–500 mg daily, plasma lamotrigine concentrations generally are in the range of 2–5 mcg/mL, although plasma concentrations up to 19 mcg/mL have been reported.

■ **Pregnancy, Fertility, and Lactation** The safety of lamotrigine when used during pregnancy in humans is unknown, and the drug should be used during pregnancy only when the potential benefits justify the possible risks to the fetus. Patients should be advised to notify their clinician if they become pregnant or intend to become pregnant. The manufacturer, in collaboration with the US Centers for Disease Control and Prevention (CDC), maintains a lamotrigine pregnancy registry to monitor fetal outcomes of pregnant women exposed to lamotrigine. Clinicians aware of patients who have received lamotrigine at any time during their pregnancy and who wish to register these cases before fetal outcome is known (e.g., through ultrasound, amniocentesis, birth) may obtain information by calling the Lamotrigine Pregnancy Registry at 800-336-2176. Patients can enroll themselves in the North American Antiepileptic Drug (NAAED) Pregnancy Registry by calling 888-233-2334; registry information also is available on the website at http://www.aedpregnancyregistry.org/.

Preliminary information from the NAAED Pregnancy Registry suggests a possible association between exposure to lamotrigine monotherapy during the first trimester of pregnancy and an increased incidence of cleft lip or cleft palate in infants. Of 564 pregnant women listed in the NAAED Pregnancy Registry who received lamotrigine monotherapy during the first trimester, 5 cases of oral clefts (2 cases of isolated cleft lips, 3 cases of isolated cleft palate) occurred, yielding a total prevalence of 8.9 cases per 1000 exposures compared with a prevalence of 0.5–2.16 reported among infants of nonepileptic women who were not receiving lamotrigine. However, other pregnancy registries of similar size have not replicated this observation, and the validity of this association cannot be established until additional data are collected in NAAED Pregnancy Registry, in other pregnancy registries, or by additional research. The US Food and Drug Administration (FDA) states that the clinical importance of this preliminary report remains uncertain pending further data collection and more research is needed. FDA recommends that women who are pregnant should not begin or discontinue lamotrigine therapy without first talking to their clinician.

Although there are no adequate and controlled studies to date in humans, lamotrigine has been shown to produce maternal toxicity and secondary fetal toxicity (e.g., reduced fetal weight and/or delayed ossification) in mice and rats receiving oral dosages up to 1.2 or 0.5 times (on a mg/m² basis), respectively, the maximum usual human maintenance dosage of 500 mg daily during the period of organogenesis. However, no evidence of teratogenicity was found in mice, rats, or rabbits receiving the drug orally in dosages up to 1.2, 0.5, or 1.1 times (on a mg/m² basis), respectively, the maximum usual human daily maintenance dosage. Maternal toxicity and fetal death occurred in rats receiving lamotrigine orally during late gestation (days 15–20) in dosages of 0.1, 0.14, or 0.3 times (on a mg/m² basis) the maximum usual human daily maintenance dosage; food consumption and weight gain were reduced in dams, and the gestation period was slightly prolonged. Stillborn pups were found in all three groups of rats receiving lamotrigine, with the greatest number of stillborn pups in the group receiving the highest dosage. Postnatal death of pups occurred between days 1 and 20 only in the group of rats receiving 0.14 or 0.3 times (on a mg/m² basis) the maximum usual human daily maintenance dosage. Some of these deaths appeared to be drug related and not secondary to maternal toxicity. No evidence of teratogenicity was demonstrated in rats receiving lamotrigine in dosages 0.4 times (on a mg/m² basis) the maximum usual human daily maintenance dosage prior to and during mating and throughout gestation and lactation. However, the incidence of intrauterine death without signs of teratogenicity was increased in rat dams receiving lamotrigine isethionate by rapid IV injection in a dosage 0.6 times (on a mg/m² basis) the maximum usual human daily maintenance dosage. In a study designed to determine the effects of lamotrigine on postnatal development, pregnant rats received lamotrigine orally in dosages 0.1 and 0.5 times (on a mg/m² basis) the recommended human daily dosage during the period of organogenesis. At day 21 postpartum, pups born to dams receiving the lower dosage (5 mg/kg daily) exhibited a longer latent period for open field exploration and a lower frequency of rearing. Pups born to dams receiving the higher dosage (25 mg/kg daily) demonstrated an increased time to completion of a swimming maze test performed 39–44 days postpartum. No evidence of adverse effects on development of pups was demonstrated by lamotrigine in a group of rats receiving the drug in dosages 0.4 times (on a mg/m² basis) the maximum usual human daily maintenance dosage prior to and during mating, and throughout gestation and lactation.

Because lamotrigine is a dihydrofolate reductase inhibitor, it decreases fetal folate concentrations in rats, an effect known to be associated with teratogenesis in animals and humans. However, there are no adequate and well-controlled studies in pregnant women, and animal reproduction studies are not always predictive of human response. Decreased plasma folate concentrations in rats were partially returned to normal by administration of leucovorin. Clinicians should be aware of lamotrigine's dihydrofolate reductase inhibiting activity, especially when prescribing other drugs that inhibit folate metabolism.

The effect of lamotrigine on labor and delivery in humans is unknown.

Reproduction studies revealed no adverse effects on fertility in rats receiving lamotrigine in oral dosages 0.4 times (on a mg/m² basis) the maximum usual human daily maintenance dosage prior to and during mating, and throughout gestation and lactation. The effect of lamotrigine on human fertility is unknown.

Preliminary data indicate that lamotrigine is distributed into milk. Because of the potential for serious adverse reactions to lamotrigine in nursing infants, a decision should be made whether to discontinue nursing or the drug, taking into account the importance of the drug to the woman.

Description

Lamotrigine is a phenyltriazine anticonvulsant agent. The drug differs structurally from other currently available anticonvulsant agents. Although the precise mechanism of anticonvulsant action of lamotrigine is unknown, studies in animals indicate that the drug may stabilize neuronal membranes by blocking voltage-sensitive sodium channels, which inhibits the release of excitatory amino acid neurotransmitters (e.g., glutamate, aspartate) that play a role in the generation and spread of epileptic seizures. In animal test systems, lamotrigine exhibits anticonvulsant activity similar to that of phenytoin, phenobarbital, and carbamazepine. The drug protects against seizures induced by electrical stimulation or pentylenetetrazole, suggesting that it may be effective in the management of tonic-clonic (grand mal) and partial seizures or absence (petit mal) seizures, respectively. Lamotrigine also is active in electrically evoked afterdischarge tests, indicating activity against simple and complex partial seizures, and in rat cortical kindling tests, which may indicate activity against complex partial seizures. The mechanism(s) of action of lamotrigine in bipolar disorder has not been established.

In vitro studies indicate that lamotrigine has weak inhibitory effects on type 3 serotonergic (5-HT_3) receptors, and does not exhibit high affinity for type 2 serotoninergic (5-HT_2), adenosine A_1 or A_2, α_1- or α_2-adrenergic, β-adrenergic, dopamine D_1 or D_2, γ-aminobutyric acid (GABA) A or B, histamine H_1, opiate κ, or cholinergic muscarinic receptors. The drug has weak agonist effects at opiate σ receptors. Lamotrigine apparently has no effect on dihydropyridine-sensitive calcium channels or *N*-methyl-d-aspartate (NMDA) receptors and does not inhibit the uptake of norepinephrine, dopamine, serotonin, or aspartic acid.

SumMon® (see Users Guide). For additional information on this drug until a more detailed monograph is developed and published, the manufacturer's labeling should be consulted. It is *essential* that the labeling be consulted for detailed information on the usual cautions, precautions, and contraindications concerning potential drug interactions and/or laboratory test interferences and for information on acute toxicity.

Preparations

Excipients in commercially available drug preparations may have clinically important effects in some individuals; consult specific product labeling for details.

Lamotrigine

Oral		
Tablets	25 mg	**Lamictal®** (scored), GlaxoSmithKline
	100 mg	**Lamictal®** (scored), GlaxoSmithKline
	150 mg	**Lamictal®** (scored), GlaxoSmithKline
	200 mg	**Lamictal®** (scored), GlaxoSmithKline
Tablets, chewable/dispersible	2 mg	**Lamictal®**, GlaxoSmithKline
	5 mg	**Lamictal®**, GlaxoSmithKline
	25 mg	**Lamictal®**, GlaxoSmithKline
Tablets, orally disintegrating	25 mg	**Lamictal® ODT**, GlaxoSmithKline
	50 mg	**Lamictal® ODT**, GlaxoSmithKline
	100 mg	**Lamictal® ODT**, GlaxoSmithKline
	200 mg	**Lamictal® ODT**, GlaxoSmithKline

†Use is not currently included in the labeling approved by the US Food and Drug Administration.

■ **Elimination** The elimination half-life of citalopram averages approximately 35 hours in adults with normal renal and hepatic function.

The exact metabolic fate of citalopram has not been fully elucidated; however, metabolism of citalopram is mainly hepatic and involves *N*-demethylation. Citalopram is metabolized to demethylcitalopram, didemethylcitalopram, citalopram-*N*-oxide, and a deaminated propionic acid derivative. In vitro studies have indicated that cytochrome P-450 (CYP) 3A4 and 2C19 isoenzymes are the principal enzymes involved in the *N*-demethylation of citalopram to demethylcitalopram and that demethylcitalopram is further *N*-demethylated to didemethylcitalopram by CYP2D6. Because citalopram is metabolized by multiple enzyme systems, inhibition of a single enzyme is unlikely to appreciably decrease the clearance of citalopram. Unlike some other selective serotonin-reuptake inhibitors, the demethylated metabolites of citalopram, demethylcitalopram and didemethylcitalopram, are substantially less active than the parent compound as inhibitors of serotonin reuptake. Thus, citalopram's metabolites are unlikely to contribute to the antidepressant and other clinical actions of the drug.

In humans, unchanged citalopram is the predominant compound in plasma. At steady state, the concentrations of demethylcitalopram and didemethylcitalopram in plasma are approximately one-half and one-tenth, respectively, that of the parent drug. Following IV (parenteral dosage form not commercially available in the US) administration of citalopram, the fraction of drug recovered in urine as citalopram and demethylcitalopram was about 10 and 5%, respectively.

Following oral administration of a single, radiolabeled dose of citalopram in healthy individuals, approximately 75% of the dose was excreted in urine and approximately 10% was eliminated in feces within 17 days. An analysis of the urinary composition showed that besides the known metabolites of citalopram, 3 glucuronides were present. The relative amounts of citalopram, demethylcitalopram, didemethylcitalopram, and the *N*-oxide metabolite present in urine collected for 7 days were 26, 19, 9, and 7%, respectively, with glucuronidated metabolites accounting for the remainder.

Following IV administration, the mean systemic clearance of citalopram is approximately 330 mL/minute, with approximately 20% of that due to renal clearance.

The effect of age on the elimination of citalopram has not been fully elucidated. Studies in healthy geriatric individuals and depressed geriatric patients have found higher AUC values and longer elimination half-lives compared with younger individuals. (See Pharmacokinetics: Absorption.) In healthy geriatric individuals, the elimination half-life of citalopram was increased by 50% in a single-dose study and by 30% in a multiple-dose study. It has been suggested that these differences in pharmacokinetic parameters may reflect declining liver and kidney function. In addition, the stereoselective metabolism of the enantiomers for citalopram and demethylcitalopram in older individuals appears to differ from that reported in younger patients, suggesting possible age-associated changes in CYP2C19 activities. (See Dosage and Administration: Dosage in Geriatric Patients and see Cautions: Geriatric Precautions.)

Because citalopram is extensively metabolized in the liver, hepatic impairment can affect the elimination of the drug. Following oral administration, the clearance of citalopram in patients with impaired hepatic function was reduced by 37% and the elimination half-life was increased twofold compared with that in healthy individuals. Therefore, the manufacturer recommends that in depressed patients with hepatic impairment, citalopram therapy should be initiated at 20 mg once daily, and titrated to 40 mg once daily *only* in nonresponders. (See Dosage and Administration: Dosage in Hepatic and Renal Impairment and see Cautions: Precautions and Contraindications.)

The effect of renal impairment on the pharmacokinetics of citalopram has not been fully evaluated to date. In patients with moderate renal impairment, the renal clearance of citalopram and its 2 principal metabolites was reduced and the elimination half-life of citalopram was slightly prolonged to an average of about 50 hours. In a study comparing the pharmacokinetics of citalopram in a limited number of patients with severe renal failure undergoing hemodialysis and in healthy individuals, no substantial differences were found between the 2 groups in any of the pharmacokinetic parameters, with the exception of the renal clearance of citalopram, which was significantly lower in the renal failure group than in the control group (11.7 mL/minute versus 66 mL/minute). Therefore, moderate to severe renal failure does not appear to markedly affect the pharmacokinetics of citalopram suggesting that dosage adjustment in such patients may not be necessary. Additional studies evaluating long-term citalopram therapy in patients with severe renal impairment are necessary to confirm these findings. (See Dosage and Administration: Dosage in Hepatic and Renal Impairment.)

Limited data indicate that citalopram and demethylcitalopram are not appreciably removed by hemodialysis. In a limited number of patients, hemodialysis cleared only about 1% of an oral dose of citalopram as the parent drug and 1% as demethylcitalopram. Because of the large volume of distribution of citalopram, hemodialysis, peritoneal dialysis, forced diuresis, hemoperfusion, and/or exchange transfusion also are unlikely to be effective in removing substantial amounts of citalopram from the body.

Chemistry and Stability

■ **Chemistry** Citalopram hydrobromide, a selective serotonin-reuptake inhibitor (SSRI), is a bicyclic phthalane-derivative antidepressant. The drug differs structurally from most other selective serotonin-reuptake inhibitors (e.g., fluoxetine, fluvoxamine, paroxetine, sertraline) and also differs structurally and pharmacologically from tricyclic and tetracyclic antidepressants. The commercially available drug is a 50:50 racemic mixture of the *R*- and *S*-enantiomers. The inhibition of serotonin reuptake by citalopram is principally due to the *S*-enantiomer, escitalopram (see Escitalopram Oxalate 28:16.04.20).

Citalopram hydrobromide occurs as a fine white to off-white powder that is sparingly soluble in water and soluble in ethanol. The drug has a pK_a of 9.5.

Citalopram hydrobromide is commercially available for oral administration as tablets and as an oral solution. Commercially available Celexa® (citalopram hydrobromide) oral solution is a clear, colorless to opalescent solution with a peppermint flavor and containing 10 mg of citalopram per 5 mL. Citalopram hydrobromide oral solution contains methylparahens and propylparahens as preservatives. Citalopram also is commercially available in some countries as an IV injection†; however, this dosage form currently is not available in the US.

■ **Stability** Citalopram hydrobromide tablets and oral solution should be stored at a temperature of 25°C but may be exposed to temperatures ranging from 15–30°C. When stored as directed, the tablets and oral solution have an expiration date of 2 years and 18 months, respectively, following the date of manufacture.

Preparations

Because of similarity in spelling of Celexa® (citalopram hydrobromide), Celebrex® (celecoxib), and Cerebyx® (fosphenytoin sodium), extra care should be exercised in ensuring the accuracy of prescriptions for these drugs.

Excipients in commercially available drug preparations may have clinically important effects in some individuals; consult specific product labeling for details.

Citalopram Hydrobromide

Oral		
Tablets, film-coated	10 mg (of citalopram)*	**Celexa®**, Forest (also promoted by Pfizer)
		Citalopram Hydrobromide Film-coated Tablets
	20 mg (of citalopram)*	**Celexa®** (scored), Forest (also promoted by Pfizer)
		Citalopram Hydrobromide Film-coated Tablets
	40 mg (of citalopram)*	**Celexa®** (scored), Forest (also promoted by Pfizer)
		Citalopram Hydrobromide Film-coated Tablets
Solution	10 mg (of citalopram) per 5 mL*	**Celexa®**, Forest (also promoted by Pfizer)
		Citalopram Hydrobromide Oral Solution

*available from one or more manufacturer, distributor, and/or repackager by generic (nonproprietary) name
†Use is not currently included in the labeling approved by the US Food and Drug Administration

Escitalopram Oxalate

■ Escitalopram, the *S*-enantiomer of citalopram, is a selective serotonin-reuptake inhibitor (SSRI) and an antidepressant.

Uses

■ **Major Depressive Disorder** Escitalopram oxalate is used for the acute and maintenance treatment of major depressive disorder in adults and adolescents 12–17 years of age.

Efficacy of escitalopram for the acute management of major depression in adults was established in 3 placebo-controlled studies of 8 weeks' duration in adult outpatients who met DSM-IV criteria for major depressive disorder. In these studies, 10- and 20-mg daily dosages of escitalopram were more effective than placebo in improving scores on the Montgomery Asberg Depression Rating Scale (MADRS), the Hamilton Rating Scale for Depression (HAM-D), and the Clinical Global Impression Improvement and Severity of Illness Scale. Escitalopram also was more effective than placebo in improving other aspects of depressive disorder, including anxiety, social functioning, and overall quality of life. Substantial improvement in MADRS and HAM-D scores was noted in patients receiving either dosage of escitalopram compared with those receiving placebo after 1–2 weeks of therapy. In addition, escitalopram dosages of 10–20 mg daily appeared to be at least as effective as racemic citalopram dosages of 20–40 mg daily. No age-, race-, or gender-related differences in efficacy were noted in these studies.

Efficacy of escitalopram for the acute management of major depressive disorder in adolescents 12–17 years of age was established in an 8-week, flexible-dose, placebo-controlled study in outpatients who met DSM-IV criteria for major depressive disorder. Escitalopram-treated patients in this study demonstrated substantially greater improvement on the Children's Depression Rating Scale–Revised (CDRS-R) compared with those receiving placebo. Efficacy of

escitalopram in the acute treatment of major depressive disorder in adolescents was also established on the basis of extrapolation from an 8-week, flexible-dose, placebo-controlled study with racemic citalopram 20–40 mg daily. In this outpatient study conducted in children and adolescents 7–17 years of age who met DSM-IV criteria for major depressive disorder, citalopram-treated patients demonstrated substantially greater improvement on the CDRS-R compared with those receiving placebo; the positive results in this trial came largely from the adolescent subgroup. Two additional flexible-dose, placebo-controlled depression studies (one for escitalopram in patients 7–17 years of age and one for citalopram in adolescents) did not demonstrate efficacy.

In a longer-term study, 274 adults with major depressive disorder who had responded to escitalopram 10 or 20 mg daily during an initial 8-week, open-label, flexible dosage treatment phase were randomized to continue escitalopram at the same dosage or receive placebo for up to 36 weeks of observation for relapse in the double-blind phase. Relapse during the double-blind phase was defined as an increase in the MADRS total score to 22 or greater or discontinuance due to insufficient clinical response. Escitalopram-treated patients experienced a substantially longer time to relapse of depression compared with those receiving placebo. In addition, more placebo recipients relapsed compared with patients receiving escitalopram (cumulative relapse rates were approximately 40 and 26%, respectively).

Although efficacy of escitalopram as maintenance therapy in adolescent patients has not been systematically evaluated, such efficacy can be extrapolated from adult data along with comparisons of escitalopram pharmacokinetic parameters in adults and adolescent patients.

The manufacturer states that if escitalopram is used for extended periods, the need for continued therapy should be reassessed periodically.

There is some evidence that escitalopram may offer some clinical advantages compared with citalopram or other selective serotonin-reuptake inhibitors (e.g., increased efficacy, more rapid onset of therapeutic effect, fewer adverse effects); however, additional studies are needed to confirm these initial findings.

Efficacy of escitalopram in hospital settings has not been established to date.

For further information on use of SSRIs in the treatment of major depressive disorder and considerations in choosing the most appropriate antidepressant agent for a particular patient, see Uses: Major Depressive Disorder, in Citalopram Hydrobromide 28:16.04.20.

■ **Generalized Anxiety Disorder** Escitalopram is used in the management of generalized anxiety disorder in adults. Efficacy for the management of generalized anxiety disorder was established in 3 multicenter, flexible-dose, placebo-controlled studies of 8-weeks' duration in adult outpatients who met DSM-IV criteria for generalized anxiety disorder. In these studies, patients receiving 10–20 mg daily of escitalopram had substantially greater mean improvements in scores on the Hamilton Anxiety Scale (HAM-A) than those receiving placebo.

For further information on the treatment of generalized anxiety disorder, see Uses: Anxiety Disorders, in Paroxetine 28:16.04.20.

Dosage and Administration

■ **Administration** Escitalopram oxalate is administered orally once daily, in the morning or evening, without regard to meals. Commercially available escitalopram oxalate tablets and oral solution are bioequivalent.

Patients receiving escitalopram should be monitored for possible worsening of depression, suicidality, or unusual changes in behavior, especially at the beginning of therapy or during periods of dosage adjustment. (See Worsening of Depression and Suicidality Risk under Warnings/Precautions: Warnings, in Cautions.)

The manufacturer recommends that at least 2 weeks elapse between discontinuance of a monoamine oxidase (MAO) inhibitor and initiation of escitalopram and vice versa. (See Serotonin Syndrome or Neuroleptic Malignant Syndrome [NMS]-like Reactions under Warnings/Precautions: Other Warnings and Precautions, in Cautions and see also Drug Interactions: Monoamine Oxidase Inhibitors.)

■ **Dosage** Dosage of escitalopram oxalate is expressed in terms of escitalopram.

Major Depressive Disorder For the acute management of major depressive disorder in adults, the recommended initial dosage of escitalopram is 10 mg once daily. Although efficacy has been established at dosages of 10 or 20 mg once daily, no additional benefit was observed with the 20-mg dosage in a fixed-dose study. If a dosage exceeding 10 mg daily is considered necessary, dosage may be increased to 20 mg daily after a minimum of 1 week.

For the acute management of major depressive disorder in adolescents 12–17 years of age, the recommended initial dosage of escitalopram is 10 mg once daily. Efficacy has been established at dosages of 10–20 mg daily in a flexible-dose study. If dosage is increased to 20 mg daily, this should occur after a minimum of 3 weeks.

While the optimum duration of escitalopram oxalate therapy has not been established, many experts state that acute depressive episodes require several months or longer of sustained antidepressant therapy. In addition, some clinicians recommend that long-term antidepressant therapy be considered in certain patients at risk for recurrence of depressive episodes (such as those with highly recurrent unipolar depression). Whether the dosage of escitalopram oxalate required to induce remission is identical to the dosage needed to maintain and/or sustain euthymia is unknown. Systematic evaluation of escitalopram oxalate has shown that its antidepressant efficacy is maintained for periods of up to 36 weeks in adults receiving 10–20 mg daily. Nevertheless, the manufacturer recommends that the usefulness of escitalopram be reevaluated periodically in patients receiving long-term therapy.

Generalized Anxiety Disorder For the management of generalized anxiety disorder in adults, the recommended initial dosage of escitalopram is 10 mg once daily. If no clinical improvement is apparent, dosage may be increased to 20 mg daily after a minimum of 1 week.

Although the manufacturer states that the efficacy of escitalopram for long-term therapy (i.e., longer than 8 weeks) has not been demonstrated in controlled studies to date, generalized anxiety disorder is a chronic condition. If escitalopram is used for extended periods, the need for continued therapy with the drug should be reassessed periodically.

Discontinuance of Therapy Because withdrawal effects may occur (see Withdrawal of Therapy under Warnings/Precautions: Other Warnings and Precautions, in Cautions), the manufacturer and many experts recommend that dosage of escitalopram and other SSRIs be tapered gradually (e.g., over a period of several weeks) and the patient monitored closely. Abrupt discontinuance of the drug should be avoided.

If intolerable symptoms occur following a decrease in the dosage or upon discontinuance of therapy, escitalopram therapy may be reinstituted at the previously prescribed dosage. Subsequently, the clinician may continue decreasing the dosage but at a more gradual rate.

■ **Special Populations** The recommended dosage of escitalopram in most geriatric patients and those with hepatic impairment is 10 mg daily. Dosage adjustment in patients with mild to moderate renal impairment is not necessary, but the drug should be used with caution in those with severe renal impairment.

Treatment of Pregnant Women during the Third Trimester Because some neonates exposed to escitalopram and other SSRIs or selective serotonin- and norepinephrine-reuptake inhibitors (SNRIs) late in the third trimester of pregnancy have developed severe complications, consideration may be given to cautiously tapering escitalopram therapy in the third trimester prior to delivery if the drug is administered during pregnancy. (See Pregnancy, under Warnings/Precautions: Specific Populations, in Cautions.)

Cautions

■ **Contraindications** Concurrent or recent (i.e., within 2 weeks) therapy with a monoamine oxidase (MAO) inhibitor. (See Serotonin Syndrome or Neuroleptic Malignant Syndrome [NMS]-like Reactions under Warnings/Precautions: Other Warnings and Precautions, in Cautions and see also Drug Interactions: Monoamine Oxidase Inhibitors.)

Concomitant use with pimozide. (See Drug Interactions: Antipsychotic Agents and Other Dopamine Antagonists.)

Known hypersensitivity to escitalopram, citalopram, or any ingredient in the formulation.

■ **Warnings/Precautions** ***Warnings*** **Worsening of Depression and Suicidality Risk.** Worsening of depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior may occur in both adult and pediatric (see Pediatric Use under Warnings/Precautions: Specific Populations, in Cautions) patients with major depressive disorder or other psychiatric disorders, whether or not they are taking antidepressants. This risk may persist until clinically important remission occurs. Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are the strongest predictors of suicide. However, there has been a long-standing concern that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients during the early phases of treatment. Pooled analyses of short-term, placebo-controlled studies of antidepressants (i.e., selective serotonin-reuptake inhibitors [SSRIs] and other antidepressants) have shown an increased risk of suicidality in children, adolescents, and young adults (18–24 years of age) with major depressive disorder and other psychiatric disorders. An increased suicidality risk was not demonstrated with antidepressants compared to placebo in adults older than 24 years of age and a reduced risk was observed in adults 65 years of age or older.

The US Food and Drug Administration (FDA) recommends that all patients being treated with antidepressants for any indication be appropriately monitored and closely observed for clinical worsening, suicidality, and unusual changes in behavior, particularly during initiation of therapy (i.e., the first few months) and during periods of dosage adjustments. Families and caregivers of patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and nonpsychiatric, also should be advised to monitor patients on a daily basis for the emergence of agitation, irritability, or unusual changes in behavior as well as the emergence of suicidality, and to report such symptoms immediately to a health-care provider.

Although a causal relationship between the emergence of symptoms such as anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia, hypomania, and/or mania and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality. Consequently, consideration should be given to changing the therapeutic regimen or discontinuing therapy in patients whose depression is persistently worse or in patients experiencing emergent suicidality or symptoms

that might be precursors to worsening depression or suicidality, particularly if such manifestations are severe, abrupt in onset, or were not part of the patient's presenting symptoms. If a decision is made to discontinue therapy, taper escitalopram dosage as rapidly as is feasible but consider the risks of abrupt discontinuance. (See Discontinuance of Therapy, under Dosage and Administration: Dosage.) FDA also recommends that the drugs be prescribed in the smallest quantity consistent with good patient management, in order to reduce the risk of overdosage.

Other Warnings and Precautions **Serotonin Syndrome or Neuroleptic Malignant Syndrome (NMS)-like Reactions.** Potentially life-threatening serotonin syndrome or neuroleptic malignant syndrome (NMS)-like reactions have been reported with SSRIs, including escitalopram, and selective serotonin- and norepinephrine-reuptake inhibitors (SNRIs) alone, but particularly with concurrent use of other serotonergic drugs (including serotonin [5-hydroxytryptamine; 5-HT] type 1 receptor agonists ["triptans"]), drugs that impair the metabolism of serotonin (e.g., MAO inhibitors), or antipsychotics or other dopamine antagonists. Manifestations of serotonin syndrome may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination), and/or GI symptoms (e.g., nausea, vomiting, diarrhea). In its most severe form, serotonin syndrome may resemble NMS, which is characterized by hyperthermia, muscle rigidity, autonomic instability with possible rapid fluctuation in vital signs, and mental status changes. Monitor patients receiving escitalopram for the development of serotonin syndrome or NMS-like signs and symptoms. (See Contraindications and see also Drug Interactions.)

Concurrent or recent (i.e., within 2 weeks) therapy with MAO inhibitors intended to treat depression is contraindicated. (See Contraindications and see also Drug Interactions: Monoamine Oxidase Inhibitors.)

If concurrent therapy with escitalopram and a 5-HT_1 receptor agonist (triptan) is clinically warranted, the patient should be observed carefully, particularly during initiation of therapy, when dosage is increased, or when another serotonergic agent is initiated.

Concomitant use of escitalopram and serotonin precursors (e.g., tryptophan) is not recommended.

If signs and symptoms of serotonin syndrome or NMS occur, immediately discontinue treatment with escitalopram and any concurrently administered serotonergic or antidopaminergic agents, including antipsychotic agents, and initiate supportive and symptomatic treatment.

Withdrawal of Therapy. Withdrawal symptoms, including dysphoric mood, irritability, agitation, dizziness, sensory disturbances (e.g., paresthesias such as electric shock sensations), anxiety, confusion, headache, lethargy, emotional lability, insomnia, hypomania, tinnitus, and seizures, have been reported during the postmarketing surveillance period for escitalopram and other SSRIs and SNRIs, particularly upon abrupt discontinuance of these drugs. While these events are generally self-limiting, there have been reports of serious discontinuance symptoms. Therefore, patients should be monitored for these symptoms when discontinuing escitalopram therapy. A gradual reduction in the dosage rather than abrupt cessation is recommended whenever possible. (See Discontinuance of Therapy under Dosage and Administration: Dosage.)

If intolerable symptoms occur following dosage reduction or discontinuance, reinstitute the previously prescribed dosage until symptoms abate, then resume more gradual dosage reductions.

Seizures. Although anticonvulsant effects of racemic citalopram have been observed in animal studies, escitalopram has not been systematically evaluated in patients with seizure disorders. Seizures have been reported in patients receiving escitalopram in clinical trials; therefore, as with other antidepressants, initiate therapy with caution in patients with a history of seizure disorder.

Activation of Mania/Hypomania. Activation of mania and hypomania has occurred in patients receiving escitalopram or citalopram. Use with caution in patients with a history of mania.

Hyponatremia/Syndrome of Inappropriate Antidiuretic Hormone Secretion. Treatment with SNRIs and SSRIs, including escitalopram, may result in hyponatremia. In many cases, hyponatremia appears to be due to the syndrome of inappropriate antidiuretic hormone secretion (SIADH). Cases with serum sodium concentrations lower than 110 mEq/L have been reported. Geriatric individuals and patients receiving diuretics or who are otherwise volume depleted may be at greater risk of developing hyponatremia. Signs and symptoms of hyponatremia include headache, difficulty concentrating, memory impairment, confusion, weakness, and unsteadiness, which may lead to falls; more severe and/or acute cases have been associated with hallucinations, syncope, seizures, coma, respiratory arrest, and death. Initiate appropriate medical intervention and consider drug discontinuance in patients with symptomatic hyponatremia.

Abnormal Bleeding. SNRIs and SSRIs, including escitalopram, may increase the risk of bleeding events. Concurrent administration of aspirin, nonsteroidal anti-inflammatory agents, warfarin, and other anticoagulants may add to this risk. Case reports and epidemiologic studies have demonstrated an association between the use of drugs that interfere with serotonin reuptake and the occurrence of GI bleeding. Bleeding events related to SNRI and SSRI use have ranged from ecchymoses, hematomas, epistaxis, and petechiae to life-threatening hemorrhages. The manufacturer recommends that patients be advised of the risk of bleeding associated with the concomitant use of escitalopram with aspirin or other nonsteroidal anti-inflammatory agents, warfarin, or other drugs that affect coagulation. (See Drug Interactions: Drugs Affecting Hemostasis.)

Interference with Cognitive and Motor Performance. In a study in healthy volunteers, escitalopram 10 mg daily did not impair intellectual function or psychomotor performance. However, because any psychoactive drug may impair judgment, thinking, or motor skills, caution patients about operating hazardous machinery, including driving a motor vehicle, until they are reasonably certain that the drug does not affect their ability to engage in such activities.

Concomitant Illnesses. Experience with escitalopram in patients with certain concomitant diseases is limited. (See Renal Impairment and see Hepatic Impairment under Warnings/Precautions: Specific Populations, in Cautions.)

Escitalopram has not been systematically evaluated in patients with a recent history of myocardial infarction or unstable cardiovascular disease; such patients were generally excluded from clinical studies. Use with caution in patients with diseases or conditions that produce altered metabolism or hemodynamic responses.

Specific Populations **Pregnancy.** Category C. (See Users Guide.)

Complications, sometimes severe and requiring prolonged hospitalization, respiratory support, enteral nutrition, and other forms of supportive care, have been reported in some neonates exposed to escitalopram, other SSRIs, or selective serotonin- and norepinephrine-reuptake inhibitors (SNRIs) late in the third trimester; such complications may arise immediately upon delivery. In addition, an increased risk of persistent pulmonary hypertension of the newborn (PPHN) has been observed in infants exposed to SSRIs during late pregnancy; PPHN is associated with substantial neonatal morbidity and mortality.

Clinicians should carefully consider the potential risks and benefits of escitalopram therapy when used during the third trimester of pregnancy. However, clinicians also should be aware that women who discontinued antidepressant therapy during pregnancy were more likely to experience a relapse of depression than those who remained on antidepressant therapy according to results of one longitudinal study involving women with a history of major depressive disorder who were euthymic while receiving antidepressant therapy at the beginning of pregnancy. Clinicians may consider tapering the dosage of escitalopram in women in the third trimester of pregnancy. (See Pregnancy under Cautions: Pregnancy, Fertility, and Lactation, in Citalopram Hydrobromide 28:16.04.20.)

Lactation. Like racemic citalopram, escitalopram is distributed into human milk. Potential for serious adverse effects (e.g., excessive somnolence, decreased feeding, weight loss) in nursing infants exists. Discontinue nursing or the drug, taking into account the potential risk in nursing infants and the importance of the drug to the mother.

Pediatric Use. Safety and efficacy of escitalopram have not been established in pediatric patients younger than 12 years of age with major depressive disorder. Safety and effectiveness have been established in adolescents 12–17 years of age for the acute treatment of major depressive disorder. Although efficacy of escitalopram as maintenance therapy in adolescent patients with major depressive disorder has not been systematically evaluated, such efficacy can be extrapolated from adult data along with comparisons of pharmacokinetic parameters in adults and adolescent patients. (See Uses: Major Depressive Disorder.)

Safety and efficacy of escitalopram have not been established in pediatric patients younger than 18 years of age with generalized anxiety disorder.

FDA warns that a greater risk of suicidal thinking or behavior (suicidality) occurred during first few months of antidepressant treatment compared with placebo in children and adolescents with major depressive disorder, obsessive-compulsive disorder (OCD), or other psychiatric disorders based on pooled analyses of 24 short-term, placebo-controlled trials of 9 antidepressant drugs (SSRIs and other antidepressants). However, a more recent meta-analysis of 27 placebo-controlled trials of 9 antidepressants (SSRIs and others) in patients younger than 19 years of age with major depressive disorder, OCD, or non-OCD anxiety disorders suggests that the benefits of antidepressant therapy in treating these conditions may outweigh the risks of suicidal behavior or suicidal ideation. No suicides occurred in these pediatric trials.

Carefully consider these findings when assessing potential benefits and risks of escitalopram in a child or adolescent for any clinical use. (See Worsening of Depression and Suicidality Risk under Warnings/Precautions: Warnings, in Cautions.)

Geriatric Use. Approximately 6% of patients studied in clinical trials of escitalopram for major depressive disorder and generalized anxiety disorder were 60 years of age or older; geriatric patients in these trials received daily dosages of 10–20 mg daily. Experience in geriatric patients in these trials was insufficient to determine whether they respond differently from younger adults; however, increased sensitivity cannot be ruled out.

SNRIs and SSRIs, including escitalopram, have been associated with clinically important hyponatremia in geriatric patients, who may be at greater risk for this adverse effect. (See Hyponatremia/Syndrome of Inappropriate Antidiuretic Hormone Secretion under Warnings/Precautions: Other Warnings and Precautions, in Cautions.)

In pooled data analyses, a *reduced* risk of suicidality was observed in adults 65 years of age or older with antidepressant therapy compared with placebo. (See Worsening of Depression and Suicidality Risk under Warnings/Precautions: Warnings, in Cautions.)

Renal Impairment. Use with caution in patients with severe renal impairment (i.e., creatinine clearance less than 20 mL/minute). (See Dosage and Administration: Special Populations.)

Hepatic Impairment. In clinical studies, clearance of racemic citalopram was decreased by 37% and elimination half-life was doubled relative to that in patients with normal hepatic function. Dosage reduction recommended for patients with hepatic impairment. (See Dosage and Administration: Special Populations.)

■ **Common Adverse Effects** Adverse effects reported in approximately 5% or more of patients with generalized anxiety or major depressive disorder receiving escitalopram and with an incidence of at least twice that of placebo include insomnia, nausea, increased sweating, sexual dysfunction (ejaculation disorder [primarily ejaculatory delay], decreased libido, anorgasmia), fatigue, and somnolence.

Drug Interactions

■ **Drugs Affecting or Metabolized by Hepatic Microsomal Enzymes** Inhibitors or inducers of cytochrome P-450 (CYP) 3A4 (e.g., carbamazepine, ketoconazole, ritonavir, triazolam) and 2C19 isoenzymes: clinically important pharmacokinetic interaction unlikely since escitalopram is metabolized by multiple enzyme systems. However, possibility that carbamazepine may increase clearance of escitalopram should be considered.

Substrates of CYP2D6 isoenzyme (e.g., desipramine, metoprolol): potential pharmacokinetic (increased peak plasma concentrations and AUC of the substrate) interactions. Use with caution. Increased plasma concentrations of metoprolol have been associated with decreased cardioselectivity.

■ **Drugs Affecting Hemostasis** Pharmacokinetics of warfarin were not affected by racemic citalopram; however, prothrombin time increased by 5%. The effects of escitalopram have not been evaluated, and the clinical importance of this interaction is unknown.

Altered anticoagulant effects, including increased bleeding, have been reported when SSRIs or selective serotonin- and norepinephrine-reuptake inhibitors (SNRIs) were concurrently administered with warfarin or other anticoagulants. The manufacturer of escitalopram recommends carefully monitoring patients receiving warfarin during initiation and discontinuance of escitalopram therapy.

Potential pharmacologic (increased risk of bleeding) interaction with aspirin or other nonsteroidal anti-inflammatory agents; use with caution.

■ **Antipsychotic Agents and Other Dopamine Antagonists** Potential pharmacologic interaction (potentially serious, sometimes fatal serotonin syndrome or NMS-like reactions) if used concurrently with antipsychotic agents or other dopamine antagonists. If signs and symptoms of serotonin syndrome or NMS occur, immediately discontinue treatment with escitalopram and any concurrently administered antidopaminergic or serotonergic agents and initiate supportive and symptomatic treatment. (See Serotonin Syndrome or Neuroleptic Malignant Syndrome [NMS]-like Reactions under Warnings/Precautions: Other Warnings and Precautions, in Cautions.)

Pimozide In a controlled study, concurrent administration of a single, 2-mg dose of pimozide in individuals receiving citalopram (40 mg once daily for 11 days) was associated with mean increases in the corrected QT (QT_c) interval of approximately 10 msec compared with pimozide given alone. Citalopram did not substantially affect the mean area under the plasma concentration-time curve (AUC) or peak plasma concentrations of pimozide. The mechanism for this potential pharmacodynamic interaction is not known. In addition, concomitant use of citalopram and pimozide rarely may result in potentially serious, sometimes fatal serotonin syndrome or NMS-like reactions. The manufacturer of escitalopram states that concurrent use of escitalopram and pimozide is contraindicated.

■ **5-HT_1 Receptor Agonists ("Triptans")** Potential pharmacologic interaction (potentially serious, sometimes fatal serotonin syndrome or NMS-like reactions) if used concurrently with 5-HT_1 receptor agonists (e.g., almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, zolmitriptan). If concomitant use is clinically warranted, the patient should be observed carefully, particularly during treatment initiation, when dosage is increased, or when another serotonergic agent is initiated. (See Serotonin Syndrome or Neuroleptic Malignant Syndrome [NMS]-like Reactions under Warnings/Precautions: Other Warnings and Precautions, in Cautions.)

■ **Monoamine Oxidase Inhibitors** Potential pharmacologic interaction (potentially serious, sometimes fatal serotonin syndrome or NMS-like reactions). Concomitant use of monoamine oxidase (MAO) inhibitors with escitalopram is contraindicated. In addition, at least 2 weeks should elapse between discontinuance of an MAO inhibitor and initiation of escitalopram and vice versa. (See Serotonin Syndrome or Neuroleptic Malignant Syndrome [NMS]-like Reactions under Warnings/Precautions: Other Warnings and Precautions, in Cautions.)

Linezolid Linezolid, an anti-infective agent that is a nonselective and reversible MAO inhibitor, has been associated with drug interactions resulting in serotonin syndrome and should therefore be used with caution in patients receiving escitulopram.

Isoniazid Potential pharmacologic interaction (potentially serious serotonin syndrome) when isoniazid, an antituberculosis agent that appears to have some MAO-inhibiting activity, is used concomitantly with escitalopram.

■ **Selective Serotonin-reuptake Inhibitors and Selective Serotonin- and Norepinephrine-reuptake Inhibitors** Potential pharmacologic interaction (potentially serious, sometimes fatal serotonin syndrome or NMS-like reactions); concurrent administration not recommended. (See Serotonin Syndrome or Neuroleptic Malignant Syndrome [NMS]-like Reactions under Warnings/Precautions: Other Warnings and Precautions, in Cautions.)

■ **Other Serotonergic Drugs** Potential pharmacologic interaction (potentially serious, sometimes fatal serotonin syndrome or NMS-like reactions) with drugs affecting serotonergic neurotransmission, including tramadol and St. John's wort (*Hypericum perforatum*); use concomitantly with caution. If signs and symptoms of serotonin syndrome or NMS occur, immediately discontinue treatment with escitalopram and any concurrently administered serotonergic or antidopaminergic agents and initiate supportive and symptomatic treatment. Concurrent administration of escitalopram and serotonin precursors (such as tryptophan) is not recommended. (See Serotonin Syndrome or Neuroleptic Malignant Syndrome [NMS]-like Reactions under Warnings/Precautions: Other Warnings and Precautions, in Cautions.)

■ **Alcohol** Concomitant use not recommended.

■ **Cimetidine** Potential pharmacokinetic interaction (increased AUC and peak plasma concentrations of citalopram have been observed); effects on escitalopram have not been evaluated. Clinical importance of this interaction is unknown.

■ **Citalopram** Potential pharmacologic interaction (potentially serious, sometimes fatal serotonin syndrome or NMS-like reactions).

Because escitalopram is the more active isomer of racemic citalopram, the 2 agents should not be used concomitantly.

■ **CNS-active Drugs** Potential pharmacologic interaction when given with other centrally acting drugs; use concomitantly with caution.

■ **Digoxin** Pharmacokinetic interaction unlikely based on studies with racemic citalopram.

■ **Lithium** Concurrent administration of racemic citalopram and lithium did not substantially affect the pharmacokinetics of either drug. However, pending further accumulation of data, the manufacturer of escitalopram recommends that plasma lithium concentrations be monitored in patients concurrently receiving escitalopram and that lithium dosage be adjusted accordingly.

Potential pharmacologic interaction (enhanced serotonergic effects of escitalopram and potentially serious, sometimes fatal serotonin syndrome or NMS-like reactions); use concomitantly with caution.

■ **Ritonavir** Combined administration of a single 600-mg dose of ritonavir, a CYP3A4 substrate and potent inhibitor of CYP3A4, and escitalopram 20 mg did not substantially affect the pharmacokinetics of either drug.

■ **Sibutramine** Potential pharmacologic interaction (potentially serious, sometimes fatal serotonin syndrome or NMS-like reactions). Use concomitantly with caution.

■ **Theophylline** Pharmacokinetics of theophylline were not affected by racemic citalopram. The effect of theophylline on the pharmacokinetics of racemic citalopram, however, has not been evaluated.

■ **Electroconvulsive Therapy** The combined use of electroconvulsive therapy and escitalopram has not been evaluated.

Description

Escitalopram, a selective serotonin-reuptake inhibitor (SSRI), is a bicyclic phthalane-derivative antidepressant. Escitalopram is the *S*-enantiomer of citalopram, an SSRI that occurs as a 50:50 racemic mixture of the *R*- and *S*-enantiomers. Escitalopram and citalopram differ structurally from other SSRIs (e.g., fluoxetine, fluvoxamine, paroxetine, sertraline) and other currently available antidepressants (e.g., monoamine oxidase inhibitors, tricyclic and tetracyclic antidepressants). Escitalopram is at least 100-fold more potent as an inhibitor of the reuptake of serotonin (5-hydroxytryptamine [5-HT]) at the presynaptic membranes and the 5-HT neuronal firing rate than the *R*-enantiomer and is twice as potent as the racemic mixture. However, further studies are needed to determine whether these differences result in any clinical superiority of escitalopram compared with citalopram.

Like other SSRIs, escitalopram's antidepressant effect is believed to involve potentiation of serotonin activity in the CNS. Escitalopram appears to have little or no effect on reuptake of other neurotransmitters such as norepinephrine and dopamine. In vitro studies also have demonstrated that escitalopram possesses little or no affinity for α- or β-adrenergic, dopamine D_{1-5}, histamine H_{1-3}, GABA-benzodiazepine, muscarinic M_{1-5}, or 5-HT_{1-7} receptors or various ion channels (e.g., calcium, chloride, potassium, sodium channels).

Escitalopram is extensively metabolized, principally by the hepatic cytochrome P-450 (CYP) 2C19 and 3A4 isoenzymes. The principal metabolites are less potent inhibitors of serotonin reuptake, suggesting that the metabolites do not substantially contribute to the antidepressant activity of escitalopram.

Advice to Patients

Importance of providing copy of written patient information (medication guide) each time escitalopram is dispensed. Importance of advising patients to read the patient information before taking escitalopram and each time the prescription is refilled.

Risk of suicidality; importance of patients, family, and caregivers being alert to and immediately reporting emergence of suicidality, worsening depression, or unusual changes in behavior, especially during the first few months of therapy or during periods of dosage adjustment. (See Worsening of Depression and Suicidality Risk under Warnings/Precautions: Warnings, in Cautions.)

Importance of informing patients of potential risk of serotonin syndrome and neuroleptic malignant syndrome (NMS)-like reactions, particularly with concurrent use of escitalopram and 5-HT_1 receptor agonists (also called triptans), tramadol, tryptophan, other serotonergic agents, or antipsychotic agents. Importance of immediately contacting clinician if signs and symptoms of these syndromes develop (e.g., restlessness, hallucinations, loss of coordination, fast heart beat, increased body temperature, muscle stiffness, labile blood pressure, diarrhea, coma, nausea, vomiting, confusion).

Risk of psychomotor impairment; importance of exercising caution while operating hazardous machinery, including driving a motor vehicle, until the drug's effects on the individual are known.

Importance of patients being aware that withdrawal effects may occur when stopping escitalopram, especially with abrupt discontinuance of the drug.

Risks associated with concomitant use of escitalopram with alcohol or racemic citalopram.

Importance of informing clinicians of existing or contemplated concomitant therapy, including prescription and OTC drugs or herbal supplements, as well as any concomitant illnesses (e.g., bipolar disorder) or personal or family history of suicidality or bipolar disorder. Risk of bleeding associated with concomitant use of escitalopram with aspirin or other nonsteroidal anti-inflammatory agents, warfarin, or other drugs that affect coagulation.

Importance of women informing clinicians if they are or plan to become pregnant or plan to breast-feed.

Importance of advising patients that, although they may notice improvement with escitalopram therapy within 1–4 weeks, they should continue therapy as directed.

Importance of informing patients of other important precautionary information. (See Cautions.)

Overview[r] (see Users Guide). **For additional information on this drug until a more detailed monograph is developed and published, the manufacturer's labeling should be consulted. It is *essential* that the manufacturer's labeling be consulted for more detailed information on usual cautions, precautions, contraindications, potential drug interactions, laboratory test interferences, and acute toxicity.**

Preparations

Excipients in commercially available drug preparations may have clinically important effects in some individuals; consult specific product labeling for details.

Escitalopram Oxalate

Oral		
Solution	5 mg (of escitalopram) per 5 mL	**Lexapro**®, Forest
Tablets, film-coated	5 mg (of escitalopram)	**Lexapro**®, Forest
	10 mg (of escitalopram)	**Lexapro**® (scored), Forest
	20 mg (of escitalopram)	**Lexapro**® (scored), Forest

Fluoxetine Hydrochloride

■ Fluoxetine, a selective serotonin-reuptake inhibitor (SSRI), is an antidepressant.

Uses

Fluoxetine is used in the treatment of major depressive disorder, obsessive-compulsive disorder, premenstrual dysphoric disorder, and bulimia nervosa. In addition, fluoxetine has been used for the treatment of depression associated with bipolar disorder†; obesity†; anorexia nervosa†; panic disorder† with or without agoraphobia; myoclonus†; cataplexy†; alcohol dependence†; and premature ejaculation†.

■ **Major Depressive Disorder** Fluoxetine is used in the treatment of major depressive disorder. The efficacy of fluoxetine for long-term use (i.e., longer than 5–6 weeks) as an antidepressant has not been established by controlled studies, but the drug has been used in some patients for substantially longer periods (e.g., up to 4 years or longer) without apparent loss of clinical effect or increased toxicity. If fluoxetine is used for extended periods, the need for continued therapy should be reassessed periodically.

A major depressive episode implies a prominent and relatively persistent depressed or dysphoric mood that usually interferes with daily functioning (nearly every day for at least 2 weeks). According to DSM-IV criteria, a major depressive episode includes at least 5 of the following 9 symptoms (with at least one of the symptoms being either depressed mood or loss of interest or pleasure): depressed mood most of the day as indicated by subjective report (e.g., feels sad or empty) or observation made by others; markedly diminished interest or pleasure in all, or almost all, activities most of the day; significant weight loss (when not dieting) or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite; insomnia or hypersomnia; psychomotor agitation or retardation (observable by others, not merely subjective feelings of restlessness or being slowed down); fatigue or loss of energy; feelings of worthlessness or excessive or inappropriate guilt (not merely self-reproach or guilt about being sick); diminished ability to think or concentrate or indecisiveness (either by subjective account or as observed by others); and recurrent thoughts of death, recurrent suicidal ideation without a specific plan, or a suicide attempt or specific plan for committing suicide.

Treatment of major depressive disorder generally consists of an acute phase (to induce remission), a continuation phase (to preserve remission), and a maintenance phase (to prevent recurrence). Various interventions (e.g., psychotherapy, antidepressant drug therapy, electroconvulsive therapy [ECT]) are used alone or in combination to treat major depressive episodes. Treatment should be individualized and the most appropriate strategy for a particular patient is determined by clinical factors such as severity of depression (e.g., mild, moderate, severe), presence or absence of certain psychiatric features (e.g., suicide risk, catatonia, psychotic or atypical features), alcohol or substance abuse or dependence, panic or other anxiety disorder, cognitive dysfunction, dysthymia, personality disorder, seasonal affective disorder), and concurrent illness (e.g., asthma, cardiac disease, dementia, seizure disorder, glaucoma, hypertension). Demographic and psychosocial factors as well as patient preference also are used to determine the most effective treatment strategy.

While use of psychotherapy alone may be considered as an initial treatment strategy for patients with mild to moderate major depressive disorder (based on patient preference and presence of clinical features such as psychosocial stressors), combined use of antidepressant drug therapy and psychotherapy may be useful for initial treatment of patients with moderate to severe major depressive disorder with psychosocial issues, interpersonal problems, or a comorbid axis II disorder. In addition, combined use of antidepressant drug therapy and psychotherapy may be beneficial in patients who have a history of poor compliance or only partial response to adequate trials of either antidepressant drug therapy or psychotherapy alone.

Antidepressant drug therapy can be used alone for initial treatment of patients with mild major depressive disorder (if preferred by the patient) and usually is indicated alone or in combination with psychotherapy for initial treatment of patients with moderate to severe major depressive disorder (unless ECT is planned). ECT is not generally used for initial treatment of uncomplicated major depression, but is recommended as first-line treatment for severe major depressive disorder when it is coupled with psychotic features, catatonic stupor, severe suicidality, food refusal leading to nutritional compromise, or other situations when a rapid antidepressant response is required. ECT also is recommended for patients who have previously shown a positive response or a preference for this treatment modality and can be considered for patients with moderate or severe depression who have not responded to or cannot receive antidepressant drug therapy. In certain situations involving depressed patients unresponsive to adequate trials of several individual antidepressant agents, adjunctive therapy with another agent (e.g., buspirone, lithium) or concomitant use of a second antidepressant agent (e.g., bupropion) has been used; however, such combination therapy is associated with an increased risk of adverse reactions, may require dosage adjustments, and (if not contraindicated) should be undertaken only after careful consideration of the relative risks and benefits. (See Drug Interactions: Serotonergic Drugs, see Drug Interactions: Tricyclic and Other Antidepressants, and see Drug Interactions: Lithium.)

Efficacy of fluoxetine for the management of major depression has been established principally in outpatient settings; the drug's antidepressant efficacy in hospital or institutional settings has not been adequately studied to date. Most patients evaluated in clinical studies with fluoxetine had major depressive episodes of at least moderate severity, had no evidence of bipolar disorder, and had experienced either single or recurrent episodes of depressive illness. Limited evidence suggests that mildly depressed patients may respond less well to fluoxetine than moderately depressed patients. There also is some evidence that patients with atypical depression (which usually is characterized by atypical signs and symptoms such as hypersomnia and hyperphagia), a history of poor response to prior antidepressant therapy, chronic depressive symptomatology with or without episodic worsening of depressive symptoms, a longer duration of depression in the current episode, and/or a younger age of onset of depression may be more likely to respond to fluoxetine than to tricyclic antidepressant therapy.

Considerations in Choosing Antidepressants A variety of antidepressant drugs are available for the treatment of major depressive disorder, including selective serotonin-reuptake inhibitors (SSRIs; e.g., citalopram, escitalopram, fluoxetine, paroxetine, sertraline), selective serotonin- and norepinephrine-reuptake inhibitors (SNRIs; e.g., desvenlafaxine, duloxetine, venlafaxine), tricyclic antidepressants (e.g., amitriptyline, amoxapine, desipramine, doxepin, imipramine, nortriptyline, protriptyline, trimipramine), monoamine oxidase (MAO) inhibitors (e.g., phenelzine, tranylcypromine), and other antidepressants (e.g., bupropion, maprotiline, nefazodone, trazodone). Most clinical studies have shown that the antidepressant effect of usual dosages of fluoxetine in patients with moderate to severe depression is greater than that of placebo and comparable to that of usual dosages of tricyclic antidepressants, maprotiline, other selective serotonin-reuptake inhibitors (e.g., paroxetine, sertraline), and other antidepressants (e.g., trazodone). Fluoxetine appears to be

AHFS® DRUG INFORMATION

22 March 2010

Fluvoxamine Maleate

AHFS Class: Selective Serotonin-reuptake Inhibitors (28:16.04.20)

VA Class: CN609

Chemical Name: *O*-(2-aminoethyl)oxime 5-methoxy-1-(4-(trifluoromethyl)phenyl)-1-pentanone (*Z*)-2-butenedioate (1:1)

Molecular Formula: $C_{15}H_{21}F_3N_2O_2 \cdot C_4H_4O_4$

Make a selection below to quickly jump to a specific section.

Choose...

[Posted 11/17/2009] FDA notified healthcare professionals of new safety information concerning an interaction between clopidogrel (Plavix), an anti-clotting medication, and omeprazole (Prilosec/Prilosec OTC), a proton pump inhibitor (PPI) used to reduce stomach acid. New data show that when clopidogrel and omeprazole are taken together, the effectiveness of clopidogrel is reduced. Patients at risk for heart attacks or strokes who use clopidogrel to prevent blood clots will not get the full effect of this medicine if they are also taking omeprazole. Separating the dose of clopidogrel and omeprazole in time will not reduce this drug interaction.

Other drugs that are expected to have a similar effect and should be avoided in combination with clopidogrel include: cimetidine, fluconazole, ketoconazole, voriconazole, etravirine, felbamate, fluoxetine, fluvoxamine, and ticlopidine.

Recommendations for healthcare professionals are provided in the "Information for Healthcare Professionals" sheet. For more information visit the FDA website at: [Web] and [Web].

Introduction

Fluvoxamine maleate, a selective serotonin-reuptake inhibitor (SSRI), is an antidepressant.[1 7]

Uses

Pending revision, the material in this section should be considered in light of more recently available information in the MEDWATCH notification at the beginning of this monograph.

■ Obsessive-Compulsive Disorder

Fluvoxamine is used in the treatment of obsessive-compulsive disorder when obsessions or compulsions cause marked distress, are time-consuming, or interfere substantially with social or occupational functioning.[1 2 4 7 8 9 10 11 12 13 14] Efficacy of fluvoxamine for the management of obsessive-compulsive disorder has been established by controlled studies of 10 weeks' duration principally in outpatient settings.[1 2 14] In a limited number of clinical studies in patients with moderate to severe obsessive-compulsive disorder, fluvoxamine was more effective than placebo in reducing the severity of symptoms associated with this disorder.[1 2 4 7 8 9 10 12] In the studies used to establish efficacy, a positive clinical response (much or very much improved on the Clinical Global Impressions scale) occurred in 43 or 12% of patients receiving fluvoxamine or placebo, respectively.[1 2 14] In these studies, no age- or gender-related differences in efficacy were noted.[1] Results from a limited number of comparative studies suggest that fluvoxamine is as effective as clomipramine in the management of obsessive-compulsive disorder.[2 4 13] Like fluoxetine and clomipramine, fluvoxamine reduces but does not eliminate obsessions and compulsions.[1 2 4 7 12 14] Therapeutic response to fluvoxamine in patients with obsessive-compulsive disorder generally is evident within 2–3 weeks, but may not be maximal until several months after beginning therapy with the drug.[4 8 9 12 14] The efficacy of fluvoxamine for long-term use (i.e., longer than 10 weeks) has not been established in placebo-controlled studies,[1] but the drug has been used in some patients for prolonged periods (e.g., reportedly up to 8 years) without apparent loss of clinical effect.[4 14] If fluvoxamine is used for extended periods, the need for continued therapy should be reassessed periodically.[1]

As with other antidepressants, the possibility that fluvoxamine may precipitate hypomanic or manic attacks in patients with bipolar or other major affective disorders should be considered.[1 4 7 15 16]

■ Bulimia Nervosa

Fluvoxamine has been used in the treatment of bulimia nervosa†.[19 20] In one double-blind placebo-controlled study in patients with bulimia nervosa, maintenance therapy with fluvoxamine following an inpatient treatment program resulted in an attenuated relapse rate compared with treatment with placebo.[20] For further information on use of antidepressants in the treatment of bulimia nervosa, see Bulimia Nervosa under Uses: Eating Disorders, in Fluoxetine Hydrochloride 28:16.04.20.

Dosage and Administration

■ Administration

Pending revision, the material in this section should be considered in light of more recently available information in the MEDWATCH notification at the beginning of this monograph.

Fluvoxamine maleate is administered orally.[1 5] Dosages of 100 mg daily or less in adults or 50 mg or less in pediatric patients generally are given as a single daily dose at bedtime; higher dosages generally are given as 2 divided doses, either as equally divided doses or as unequal doses with the larger dose given at bedtime.[1 5] Since food does not appear to affect GI absorption of fluvoxamine maleate, the drug generally can be administered without regard to meals.[1 17]

Patients receiving fluvoxamine should be monitored for possible worsening of depression, suicidality, or unusual changes in behavior, especially at the beginning of therapy or during periods of dosage adjustment.[23 24 25] (See Suicidality Precautions under Dosage and Administration: Dosage.)

Fluvoxamine should *not* be used concomitantly with thioridazine.[1 22 26] In addition, fluvoxamine should *not* be used concurrently with alosetron, astemizole (no longer commercially available in the US), cisapride, pimozide, terfenadine (no longer commercially available in the US), or tizanidine.[1 34 35 36 42] For additional information on potentially serious drug interactions that may occur between selective serotonin-reuptake inhibitors such as fluvoxamine and these agents, see Drug Interactions in Fluoxetine Hydrochloride 28:16.04.20.

Risk of Serotonin Syndrome

The development of potentially life-threatening serotonin syndrome may occur with fluvoxamine therapy, particularly during concomitant administration of other serotonergic drugs such as other selective serotonin-reuptake inhibitors (SSRIs), selective serotonin- and norepinephrine-reuptake inhibitors (SNRIs), selective serotonin (5-hydroxytryptamine; 5-HT) type 1 agonists used as antimigraine agents (also called triptans), drugs that impair the metabolism of serotonin (e.g., monoamine oxidase [MAO] inhibitors), tramadol, or tryptophan (a serotonin precursor) supplements.[1 43 44] Therefore, patients should be cautioned about the potential risk of serotonin syndrome when fluvoxamine is given concurrently with other serotonergic agents.[43] Symptoms of serotonin syndrome may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination), and/or GI symptoms (e.g., nausea, vomiting, diarrhea).[43 44]

Serious (sometimes fatal) adverse reactions, possibly related to serotonin syndrome, have been reported in patients who received an MAO inhibitor during or after SSRI therapy.[1 44] Therefore, concomitant use of fluvoxamine and MAO inhibitors is contraindicated, and it is recommended that at least 2 weeks elapse between discontinuance of an MAO inhibitor and initiation of fluvoxamine and vice versa.[1 22]

If concurrent therapy with fluvoxamine and an SSRI, SNRI, or 5-HT_1 receptors agonist ("triptan") is clinically warranted, careful observation of the patient is recommended, particularly during treatment initiation, increases in dosage, or following the addition of another serotonergic drug.[42 43] In addition, clinicians should assess the potential risks and benefits of concurrent therapy with fluvoxamine and triptans prior to prescribing these drugs concurrently.[43] Concurrent use of SSRIs with serotonin precursors (such as tryptophan supplements) is not recommended.[44] For additional information on serotonin syndrome, see Drug Interactions: Drugs Associated with Serotonin Syndrome, in the Monoamine Oxidase Inhibitors General Statement 28:16.04.12 and see Drug Interactions: Drugs Associated with Serotonin Syndrome, in Fluoxetine Hydrochloride 28:16.04.20.

■ Dosage

Pending revision, the material in this section should be considered in light of more recently available information in the MEDWATCH notification at the beginning of this monograph.

Obsessive-Compulsive Disorder

Adult Dosage. For the management of obsessive-compulsive disorder in adults, the recommended initial dosage of fluvoxamine maleate is 50 mg at bedtime.[1] Based on the tolerance and clinical response of the patient, dosage may be increased by increments of 50 mg daily at intervals of 4–7 days up to a maximum of 300 mg daily.[1] Because fluvoxamine clearance may be reduced in geriatric patients and/or such patients may have increased sensitivity to the adverse effects of CNS-active drugs, fluvoxamine maleate therapy may be initiated with a lower dosage (i.e., 25 mg daily)[19] and subsequent dosage adjustments made.[1] While a relationship between dosage and therapeutic effect in obsessive-compulsive disorder has not been established, efficacy of fluvoxamine maleate was demonstrated in clinical trials employing 100–300 mg daily.[1] Although the optimum duration of fluvoxamine therapy has not been established, obsessive-compulsive disorder may require several months of sustained drug therapy.[1] If therapy with the drug is prolonged, the lowest possible dosage should be employed and the need for continued therapy reassessed periodically.[1]

Pediatric Dosage. For the management of obsessive-compulsive disorder in pediatric patients 8–17 years of age, the recommended initial dosage of fluvoxamine maleate is 25 mg at bedtime.[1] This dosage may be increased in increments of 25 mg every 4–7 days, as tolerated, until maximum therapeutic benefit is achieved.[1] In one clinical study, dosages for pediatric patients 8–17 years of age were titrated within a range of 50–200 mg daily.[1 21] However, in a multiple-dose, pharmacokinetic study, steady-state plasma fluvoxamine concentrations were found to be twofold to threefold higher in children 6–11 years of age than in adolescents 12–17 years of age, and the area under the plasma concentration-time curve (AUC) and peak plasma concentrations were 1.5-2.7 times higher in children than in adolescents.[1 37] Both children and adolescents exhibited nonlinear pharmacokinetics, and female children exhibited higher AUC values and peak plasma concentrations compared with male children.[1 37] Steady-state plasma concentrations were similar in adults and adolescents receiving 300 mg of fluvoxamine daily, suggesting that fluvoxamine exposure was similar in these two groups.[1 37] Clinicians should consider both age and gender differences when selecting a fluvoxamine dosage in pediatric patients.[1 37] The maximum dosage of fluvoxamine in children up to 11 years of age should not exceed 200 mg daily, and therapeutic effects of the drug in female children may be achieved with a lower dosage than in male children.[1 37] In adolescents, fluvoxamine dosage adjustment up to the maximum daily dosage of 300 mg daily used in adults may be necessary to achieve optimal therapeutic benefit.[1 37]

The optimum duration of fluvoxamine therapy in pediatric patients has not been established.[22] If therapy with the drug is prolonged (i.e., longer than 10 weeks), the lowest possible dosage should be employed and the need for continued therapy reassessed periodically.[22] (See Pediatric Precautions under Dosage and Administration: Dosage.)

Suicidality Precautions. Worsening of depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior may occur in both adult and pediatric (see Pediatric Precautions under Dosage and Administration: Dosage) patients with major depressive disorder or other psychiatric disorders, whether or not they

are taking antidepressants.[23 24 25 45] This risk may persist until clinically important remission occurs.[23] Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are the strongest predictors of suicide.[23 24 25] However, there has been a long-standing concern that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients during the early phases of treatment.[23] Pooled analyses of short-term, placebo-controlled studies of antidepressants (i.e., selective serotonin-reuptake inhibitors and other antidepressants) have shown an increased risk of suicidality in children, adolescents, and young adults (18–24 years of age) with major depressive disorder and other psychiatric disorders.[23 24] An increased suicidality risk was not demonstrated with antidepressants compared with placebo in adults older than 24 years of age, and a reduced risk was observed in adults 65 years of age or older.[23 24]

The US Food and Drug Administration (FDA) recommends that all patients being treated with antidepressants for any indication be appropriately monitored and closely observed for clinical worsening, suicidality, and unusual changes in behavior, particularly duringinitiation of therapy (i.e., the first few months) and during periods of dosage adjustments.[23 24 25] Families and caregivers of patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and nonpsychiatric, should be advised to monitor patients on a daily basis for the emergence of agitation, irritability, or unusual changes in behavior, as well as the emergence of suicidality, and to report such symptoms immediately to a health-care provider.[23 25 47]

Although a causal relationship between the emergence of symptoms such as anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia, hypomania, and/or mania and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality.[1 23 25] Consequently, consideration should be given to changing the therapeutic regimen or discontinuing therapy in patients whose depression is persistently worse or in patients experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, particularly if such manifestations are severe, abrupt in onset, or were not part of the patient's presenting symptoms.[23] If a decision is made to discontinue therapy, fluvoxamine dosage should be tapered as rapidly as is feasible but with recognition of the risks of abrupt discontinuance.[23] FDA also recommends that the drugs be prescribed in the smallest quantity consistent with good patient management, in order to reduce the risk of overdosage.[23]

Bipolar Disorder Precautions. It is generally believed (though not established in controlled trials) that treating a major depressive episode with an antidepressant alone may increase the likelihood of precipitating a mixed or manic episode in patients at risk for bipolar disorder.[23] Therefore, patients should be adequately screened for bipolar disorder prior to initiating treatment with an antidepressant; such screening should include a detailed psychiatric history (e.g., family history of suicide, bipolar disorder, and depression).[23] Fluvoxamine is *not* approved for use in treating bipolar depression.[23]

Pediatric Precautions. Safety and efficacy of fluvoxamine for the treatment of obsessive-compulsive disorder in children younger than 8 years of age have not been established.[22] In addition, the safety and efficacy of fluvoxamine in the management of pediatric patients with conditions other than obsessive-compulsive disorder have not been established.[1]

The safety and efficacy of fluvoxamine in pediatric patients with obsessive-compulsive disorder were established in a 10-week, placebo-controlled trial in children and adolescents 8–17 years of age.[1 21] The majority of these patients continued receiving fluvoxamine therapy for up to 1–3 years longer in an open-label extension of the initial study.[1] Adverse effects generally were similar to those reported in adults.[1 21] Agitation, depression, dysmenorrhea, flatulence, hyperkinesia, and rash were reported in at least 5% of the pediatric patients and with an incidence at least twice that reported with placebo.[1] In addition, abnormal thinking, increased cough, ecchymosis, emotional lability, epistaxis, hyperkinesia, infection, manic reaction, rash, sinusitis, and weight loss were reported in 2 or more of the 57 pediatric patients receiving fluvoxamine and more frequently than among the patients receiving placebo.[1]

The risks, if any, that may be associated with extended use of fluvoxamine in children and adolescents with obsessive-compulsive disorder have not been systematically evaluated.[1] The evidence relied upon to conclude that fluvoxamine is safe for use in children and adolescents was derived from relatively short-term clinical studies and from extrapolation of experience gained with adult patients.[1] In addition, the effects of long-term fluvoxamine use on the growth, development, and maturation of children and adolescents have not been established.[1] Regular monitoring of weight and growth is recommended if treatment of a child with an SSRI is to be continued long term.[1]

FDA has determined that antidepressants increase the risk of suicidal thinking and behavior (suicidality) in children and adolescents with major depressive disorder and other psychiatric disorders.[23 24] However, FDA also states that depression and certain other psychiatric disorders are themselves associated with an increased risk of suicide.[23 25 45] (See Cautions: Pediatric Precautions, in Fluoxetine Hydrochloride 28:16.04.20.) Anyone considering the use of fluvoxamine in a child or adolescent for any clinical use must therefore balance the potential risks with the clinical need.[23 25] (See Suicidality Precautions under Dosage and Administration: Dosage.)

For further information on use of SSRIs in the treatment of major depressive disorder and considerations in choosing the most appropriate antidepressant agent for a particular patient, see Uses: Major Depressive Disorder, in Fluoxetine Hydrochloride 28:16.04.20.

Other Considerations

Pending revision, the material in this section should be considered in light of more recently available information in the MEDWATCH notification at the beginning of this monograph.

Concomitant use of fluvoxamine is contraindicated in patients receiving astemizole (no longer commercially available in the US), cisapride, pimozide, or terfenadine (no longer commercially available in the US), since fluvoxamine may inhibit metabolism of these drugs and increase the potential for serious adverse cardiac effects.[1]

Since mean AUCs of alosetron were increased approximately sixfold and the elimination half-life was increased approximately

threefold during concurrent fluvoxamine administration in one pharmacokinetic study, concurrent use of these drugs is contraindicated.[1 34]

In a limited number of male patients with schizophrenia, concomitant use of thioridazine and low-dosage fluvoxamine (25 mg twice daily for 1 week) resulted in a threefold increase in plasma concentrations of thioridazine and its two active metabolites (mesoridazine and sulforidazine).[1 26] Thioridazine produces a dose-related prolongation of the QT_C interval, which is associated with serious ventricular arrhythmias (e.g., torsades de pointes) and sudden death. [1] The possible effects of combining higher dosages of thioridazine and/or fluvoxamine are not yet known, but may be even more pronounced. [1] Therefore, concurrent administration of fluvoxamine and thioridazine is contraindicated.[1]

In a limited number of healthy individuals, concurrent administration of fluvoxamine (100 mg daily for 4 days) and tizanidine (single 4-mg dose) resulted in a 12-fold increase in peak plasma tizanidine concentrations, a threefold increase in elimination half-life of tizanidine, and a 33-fold increase in the AUC of tizanidine.[1 35 42] The mean cardiovascular effects observed in this study were a decrease in systolic blood pressure of 35 mm Hg, a decrease in diastolic blood pressure of 20 mm Hg, and a decrease in heart rate of 4 beats/minute.[1 35] In addition, drowsiness was substantially increased and psychomotor performance was substantially impaired during concurrent therapy.[1 35] Since fluvoxamine has been shown to markedly affect the pharmacokinetics of tizanidine and to increase the risk of adverse cardiovascular (including substantial hypotension) and CNS (e.g., drowsiness, psychomotor impairment) effects associated with tizanidine use,[1 35 42] concomitant use of tizanidine and fluvoxamine is contraindicated.[1 35 36 42]

Caution should be exercised if fluvoxamine is used concomitantly with benzodiazepines that are metabolized by hepatic oxidation (e.g., alprazolam, midazolam, triazolam).[1] Concomitant use of diazepam and fluvoxamine generally should be avoided.[1] The clearance of diazepam was reduced by 65% and that of its active metabolite *N*-desmethyldiazepam could not be determined during concomitant administration with fluvoxamine in one study.[1] Concomitant use of fluvoxamine (100 mg daily) and alprazolam (1 mg 4 times daily) resulted in plasma alprazolam concentrations that were approximately twice those observed when alprazolam was administered alone.[1] The initial dosage of alprazolam should be reduced by at least 50% if the drugs are administered concomitantly, with subsequent alprazolam dosages titrated to the lowest effective dosage; modification of fluvoxamine maleate is not necessary.[1] The clearance of benzodiazepines that are metabolized by glucuronidation (e.g., lorazepam, oxazepam, temazepam) is unlikely to be affected by fluvoxamine.[1]

Fluvoxamine (50 mg twice daily for 7 days) reduced the clearance of mexiletine (administered as a single dose of 200 mg) by 38% in a limited number of healthy Japanese males in one pharmacokinetic study.[1 38] Pending further accumulation of data, close patient monitoring and monitoring of serum mexiletine concentrations are recommended when fluvoxamine and mexiletine are given concurrently.[1 38]

Since fluvoxamine coadministration decreased theophylline clearance by approximately threefold, the theophylline dosage should be reduced to approximately one-third of the usual daily maintenance dosage and plasma theophylline concentrations should be monitored if the drugs are administered concomitantly.[1]

Epidemiologic case-control and cohort design studies that have demonstrated an association between selective serotonin-reuptake inhibitor therapy and an increased risk of upper GI bleeding also have shown that concurrent use of aspirin or other nonsteroidal anti-inflammatory agents substantially increases the risk of GI bleeding.[1 39 41] Although these studies focused on upper GI bleeding, there is some evidence suggesting that bleeding at other sites may be similarly potentiated.[1] The precise mechanism for this increased risk remains to be clearly established; however, serotonin release by platelets is known to play an important role in hemostasis, and selective serotonin-reuptake inhibitors decrease serotonin uptake from the blood by platelets, thereby decreasing the amount of serotonin in platelets.[1 40 41] Patients receiving fluvoxamine should be cautioned about the concomitant use of drugs that interfere with hemostasis, including aspirin and other nonsteroidal anti-inflammatory agents.[1]

Patients receiving fluvoxamine concomitantly with oral anticoagulants (e.g., warfarin) should have close monitoring of prothrombin times and adjustment of their anticoagulant dosage if indicated.[1] Prothrombin times were prolonged and plasma warfarin concentrations were increased when the drug was administered concomitantly with fluvoxamine.[1]

■ **Dosage in Renal and Hepatic Impairment**

Because patients with hepatic impairment have reduced fluvoxamine clearance, reduction of the initial dosage and modification of subsequent dosage titration may be appropriate; subsequent dosage adjustments generally should be made in smaller increments and at longer intervals in such patients.[1 19] Limited evidence indicates that dosage modification is not necessary in patients with renal impairment.[1 18 19]

■ **Treatment of Pregnant Women during the Third Trimester**

Some neonates exposed to fluvoxamine and other selective serotonin-reuptake inhibitors or selective serotonin- and norepinephrine-reuptake inhibitors (SNRIs) late in the third trimester of pregnancy have developed complications, which have sometimes been severe and required prolonged hospitalization, respiratory support, enteral nutrition, and other forms of supportive care in special-care nurseries.[1 27 28 29 30 31 32 33] Therefore, the clinician should carefully consider the potential risks and benefits of treating a pregnant woman with fluvoxamine during the third trimester of pregnancy.[1 28 29 30 33] In addition, consideration may be given to cautiously tapering fluvoxamine therapy in the third trimester prior to delivery if the drug is administered during pregnancy.[1 30] For additional information on use of selective serotonin-reuptake inhibitors during pregnancy, see Pregnancy, under Cautions: Pregnancy, Fertility, and Lactation, in Fluoxetine Hydrochloride 28:16.04.20.

Description

Fluvoxamine maleate, a selective serotonin-reuptake inhibitor (SSRI), is an aralkylketone-derivative antidepressant agent.[1 7] The drug differs structurally from other SSRIs (e.g., citalopram, escitalopram, fluoxetine, paroxetine, sertraline) and also differs structurally from other currently available antidepressant agents (e.g., monoamine oxidase inhibitors, and tricyclic and tetracyclic antidepressants).[1 3 4 6 46] The exact mechanism of action of fluvoxamine has not been fully elucidated but appears to involve inhibition of reuptake of serotonin (5-hydroxytryptamine [5-HT]) at the presynaptic membrane.[1 3 4 8 9] Data from in vitro studies suggest that fluvoxamine is more potent than clomipramine, fluoxetine, and desipramine as a serotonin-reuptake inhibitor.[3 4 6 7] Although not clearly established, it has been suggested that the mechanism of action of fluvoxamine and other drugs (e.g., clomipramine, fluoxetine, sertraline) used in the management of obsessive compulsive disorder may be related to their

serotonergic activity.[1 2 7 9 47] Fluvoxamine appears to have little or no effect on reuptake of other neurotransmitters such as norepinephrine and dopamine.[3 4 6] In addition, the selectivity of fluvoxamine in inhibiting serotonin versus norepinephrine reuptake appears to be substantially greater than that of other SSRIs (e.g., fluoxetine, paroxetine, sertraline) and tricyclic antidepressants, including clomipramine.[3 4 6 9] In vitro studies have demonstrated that fluvoxamine possesses virtually no affinity for α_1- or α_2-adrenergic, β-adrenergic, muscarinic, dopamine D_2, histamine H_1, GABA-benzodiazepine, opiate, 5-HT_1, or 5-HT_2 receptors.[1 3 4 6]

SumMon® (see Users Guide). For additional information on this drug until a more detailed monograph is developed and published, the manufacturer's labeling should be consulted. It is *essential* that the labeling be consulted for detailed information on the usual cautions, precautions, and contraindications.

Preparations

Excipients in commercially available drug preparations may have clinically important effects in some individuals; consult specific product labeling for details.

Fluvoxamine Maleate

Routes	Forms	Strengths	Brand Names	Manufacturer
Oral	Tablets, film-coated	25 mg*	Fluvoxamine Maleate Tablets	
		50 mg*	Fluvoxamine Maleate Tablets	
		100 mg*	Fluvoxamine Maleate Tablets	

* available from one or more manufacturer, distributor, and/or repackager by generic (nonproprietary) name

■ Comparative Pricing

This pricing information is subject to change at the sole discretion of DS Pharmacy. This pricing information was updated 03/2010. For the most current and up-to-date pricing information, please visit www.drugstore.com. Actual costs to patients will vary depending on the use of specific retail or mail-order locations and health insurance copays.

Fluvoxamine Maleate 100MG Tablets (TEVA PHARMACEUTICALS USA): 50/$104 or 100/$194.98

Fluvoxamine Maleate 25MG Tablets (IVAX PHARMACEUTICALS INC.): 30/$53.99 or 90/$155.98

Fluvoxamine Maleate 50MG Tablets (BAY PHARMA): 100/$166.77 or 200/$332.5

† Use is not currently included in the labeling approved by the US Food and Drug Administration.

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AHFS® DRUG INFORMATION

21 March 2010

Thioridazine

Thioridazine Hydrochloride

AHFS Class: Phenothiazines (28:16.08.24)

VA Class: CN701

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Introduction

Thioridazine is a phenothiazine antipsychotic agent. The drug is considered a conventional or first-generation antipsychotic agent.[100]

See Uses in the associated General Statement for more information.

Uses

■ Psychotic Disorders

Thioridazine is used for the symptomatic management of psychotic disorders. However, because thioridazine has the potential for substantial, and possibly life-threatening, proarrhythmic effects and can precipitate sudden death, use of the drug is reserved for patients with schizophrenia whose disease fails to respond adequately to appropriate courses with at least 2 different antipsychotic agents, either because of insufficient efficacy or the inability to achieve an effective dosage due to intolerable adverse effects. In addition, use of thioridazine in patients with refractory schizophrenia has not been evaluated in controlled clinical trials and efficacy of the drug in such patients is not known.

Drug therapy is integral to the management of acute psychotic episodes and accompanying violent behavior in patients with schizophrenia and generally is required for long-term stabilization to improve symptoms between episodes and to minimize the risk of recurrent acute episodes. Antipsychotic agents are the principal class of drugs used for the management of all phases of schizophrenia and generally are effective in all subtypes of the disorder and subgroups of patients. Patient response and tolerance to antipsychotic agents are variable, and patients who do not respond to or tolerate one drug may be successfully treated with an agent from a different class or with a different adverse effect profile. For additional information on the symptomatic management of schizophrenia, see Uses: Psychotic Disorders, in the Phenothiazines General Statement 28:16.08.24.

■ Other Uses

Thioridazine is used for the short-term treatment of adults with major depression who have varying degrees of associated anxiety, and for the symptomatic management of agitation, anxiety, depressed mood, tension, sleep disturbances, and fears in geriatric patients (see Cautions).

Thioridazine also has been used for the treatment of severe behavioral problems in children marked by combativeness and/or explosive hyperexcitable behavior (out of proportion to immediate provocations), and for the short-term treatment of hyperactive children who exhibit excessive motor activity with accompanying conduct disorders. However, the possible risks of developing tardive dyskinesia, withdrawal dyskinesia, and other extrapyramidal reactions associated with the drug should be considered. Some clinicians recommend routine administration of the Abnormal Involuntary Movement Scale (AIMS) to all children receiving antipsychotic agents for this indication.

See Dosage and Administration in the associated General Statement for more information.

Dosage and Administration

■ Administration

Thioridazine and thioridazine hydrochloride are administered orally. When thioridazine hydrochloride oral concentrate solution is used, the dose should be diluted (e.g., with water or fruit juice) just before administration.

■ Dosage

Dosage of thioridazine and thioridazine hydrochloride is expressed in terms of the hydrochloride salt. Dosage must be carefully adjusted according to individual requirements and response using the lowest possible effective dosage. Dosage should be increased more gradually in debilitated or geriatric patients.

Psychotic Disorders

For the symptomatic management of psychotic disorders, the usual initial adult dosage of thioridazine is 50–100 mg 3 times daily. Dosage may gradually be increased, depending on the patient's therapeutic response and tolerance. The manufacturer recommends that dosages greater than 300 mg daily be reserved for adults with severe neuropsychiatric conditions. Dosages up to 800 mg daily given in 2–4 divided doses may be required in hospitalized, institutionalized, or severely psychotic adults. Dosage during prolonged maintenance therapy with thioridazine should be kept at the lowest effective level; once an adequate response has been obtained, dosage should be gradually reduced and subsequently adjusted according to the patient's therapeutic response and tolerance. Because of the risk of adverse reactions associated with cumulative effects of phenothiazines, patients with a history of long-term therapy with thioridazine and/or other antipsychotic agents should be evaluated periodically to determine whether drug therapy could be discontinued.

For the management of hospitalized, severely disturbed, or psychotic children 2–12 years of age, the usual initial dosage of thioridazine is 0.5 mg/kg daily, administered in divided doses. Dosage may be gradually increased until optimum therapeutic effect is obtained. Dosage for children should not exceed 3 mg/kg daily.

Other Conditions

For the short-term treatment of adults with major depression who also have varying degrees of associated anxiety, or for the symptomatic management of agitation, anxiety, depressed mood, tension, sleep disturbances, and fears in geriatric patients (see Cautions), the usual initial dosage of thioridazine is 25 mg 3 times daily. Dosage ranges from 20–200 mg daily in these patients, depending on the severity of the condition.

See Cautions in the associated General Statement for more information.

Cautions

Thioridazine shares the toxic potentials of other phenothiazines, and the usual precautions of phenothiazine therapy should be observed. (See Cautions in the Phenothiazines General Statement 28:16.08.24.) At recommended dosages, adverse effects of thioridazine are generally mild and transient.

Geriatric patients with dementia-related psychosis treated with either conventional (first-generation) or atypical (second-generation) antipsychotic agents are at an increased risk of mortality.[101 102 103 104] For additional information on the use of antipsychotic agents for dementia-associated psychosis and other behavioral disturbances, see Geriatric Considerations under Psychotic Disorders: Schizophrenia and Other Psychotic Disorders, in Uses and see Cautions: Geriatric Precautions, in the Phenothiazines General Statement 28:16.08.24.

Care should be taken to avoid skin contact with thioridazine oral suspension or thioridazine hydrochloride oral concentrate solution, since contact dermatitis has occurred rarely.

Because a rubbery, orange substance was noticed in the stool of a patient who ingested chlorpromazine oral solution immediately after ingesting carbamazepine oral suspension, and subsequent testing has shown that mixing thioridazine oral liquid with carbamazepine oral suspension also results in a rubbery, orange precipitate, it has been recommended that thioridazine oral liquid not be administered simultaneously with carbamazepine oral suspension. It is not known whether the development of this precipitate results in decreased bioavailability of either thioridazine or carbamazepine.

■ Arrhythmias and Associated Precautions and Contraindications

Dose-related serious cardiac effects, including prolongation of the QT interval corrected for rate (QT_C), arrhythmias (e.g., atypical ventricular tachycardia [torsades de pointes]), and/or sudden death, have been reported in patients receiving thioridazine. A causal relationship to the drug has not been established; however, since thioridazine and its major metabolite mesoridazine have been shown to prolong the QT_C interval, such a relationship is possible. Although, thioridazine has been shown to prolong the QT_C interval in a dose-dependent manner, prolongation of the QT_C interval and sudden death have been reported occasionally at usual dosages. In a crossover study, healthy men receiving a single 50-mg dose of thioridazine hydrochloride had a greater increase in QT_C interval (mean maximum of about 23 msec) than those receiving either a 10-mg dose or placebo; however, the manufacturer states that even further prolongation of the QT_C interval may be observed in clinical practice.

The risk of atypical ventricular tachycardia (e.g., torsades de pointes) and/or sudden death may be increased in patients with bradycardia, hypokalemia, or congenital long QT syndrome and in those receiving thioridazine concomitantly with drugs that can prolong the QT_C interval. Use of antiarrhythmic agents (e.g., disopyramide, procainamide, quinidine) that can prolong the QT_C interval and potentially exacerbate the cardiotoxic effects of thioridazine should be avoided in treating arrhythmias associated with the antipsychotic agent. (See Acute Toxicity: Treatment.) In patients who experience symptoms of possible atypical ventricular tachycardia (torsades de pointes), such as dizziness, palpitations, or syncope, further cardiac evaluation (e.g., Holter monitoring) should be considered.

Cardiotoxic effects may be associated with increased plasma concentrations of thioridazine and its metabolites. Increased plasma concentrations of the drug are most likely to develop in patients with poor metabolizer phenotypes of the cytochrome P-450 (CYP) 2D6 isoenzyme; and in patients receiving drugs known to inhibit the CYP2D6 isoenzyme (e.g., fluoxetine, paroxetine) or reduce the clearance of thioridazine by other mechanisms (e.g., fluvoxamine, pindolol, propranolol).

Because thioridazine may be associated with serious adverse cardiac effects, ECG and serum potassium concentrations should be determined at baseline and periodically thereafter; such monitoring may be particularly useful during a period of dosage adjustment. Serum potassium concentrations should be within the normal range before thioridazine therapy is initiated; patients with a QT_C interval exceeding 450 msec should not receive thioridazine. Thioridazine should be discontinued if the QT_C interval exceeds 500 msec. Patients receiving thioridazine should be informed about the risk of developing adverse cardiac effects and the possibility of switching from thioridazine to another antipsychotic agent should be considered based on the possible risks and likely benefits associated with thioridazine.

Because thioridazine has been shown to be more cardiotoxic in overdosage than other antipsychotic agents, some clinicians caution against its use in actively suicidal patients.

Patients receiving of thioridazine concomitantly with drugs that prolong the QT_C interval, inhibit the CYP2D6 isoenzyme (e.g., fluoxetine, paroxetine), or reduce clearance of the phenothiazine by other mechanisms (e.g., fluvoxamine, pindolol, propranolol); those with poor metabolizer phenotypes of the CYP2D6 isoenzyme; and those with underlying conditions that might prolong the QT_C interval (e.g., congenital long QT syndrome, history of arrhythmias) may be at increased risk of developing cardiac arrhythmias (e.g., atypical ventricular tachycardia [torsades de pointes]) that may be fatal. Therefore, use of thioridazine in such patients is contraindicated.

Drug Interactions

■ Drugs Affecting Hepatic Microsomal Enzymes

Drugs that inhibit the cytochrome P-450 (CYP) 2D6 isoenzyme (e.g., fluoxetine, paroxetine) appear to inhibit the metabolism of the phenothiazine which has resulted in elevated plasma concentrations of the phenothiazine. Since thioridazine has been shown to prolong the QT interval corrected for rate (QT_C) in a dose-dependent manner, increased plasma concentrations of the drug may be expected to augment such prolongation and thus may increase the risk of serious, potentially fatal, cardiac arrhythmias (e.g., atypical ventricular tachycardia [torsades de pointes]). Therefore, concomitant use of thioridazine with drugs that inhibit the CYP2D6 isoenzyme is contraindicated.

■ Other Drugs that Reduce Clearance of Thioridazine

Fluvoxamine

In a limited number of male patients with schizophrenia, concomitant use of thioridazine and fluvoxamine (25 mg twice daily for 1 week) resulted in a threefold increase in steady-state plasma concentrations of thioridazine and its 2 active metabolites (mesoridazine and sulforidazine). Therefore, fluvoxamine and thioridazine should not be used concomitantly.

Propranolol

Concomitant use of propranolol (100–800 mg daily) and thioridazine reportedly resulted in increased plasma concentrations of thioridazine (approximately 50–400%) and its metabolites (approximately 80–300%). Therefore, propranolol and thioridazine should not be used concomitantly.

Pindolol

Concomitant use of pindolol and thioridazine has resulted in moderate, dose-related increases in serum concentrations of thioridazine and 2 of its metabolites in addition to higher than expected serum concentrations of pindolol. Therefore, pindolol and thioridazine should not be used concomitantly.

■ Drugs that Prolong QT_C Interval

Although specific drug interaction studies have not been performed to evaluate the concomitant use of thioridazine with drugs that prolong the QT_C interval, the manufacturers state that additive effects of such concomitant therapy on the QT_C interval can be expected. Therefore, concomitant use of thioridazine with these drugs is contraindicated.

See Lab Test Interferences in the associated General Statement for more information.

Acute Toxicity

■ Pathogenesis

Although the minimum toxic or lethal doses and blood concentrations of thioridazine remain to be definitely established, it has been suggested that blood thioridazine concentrations of 1 mg/dL or greater are toxic, and those of 2–8 mg/dL are potentially lethal.

■ Manifestations

Overdosage of phenothiazines (e.g., thioridazine) may be expected to produce effects that are extensions of common adverse effects. (See Acute Toxicity: Manifestations, in the Phenothiazines General Statement 28:16.08.24.) However, results of case reports and several studies suggest that overdosage of thioridazine may be associated with cardiotoxicity (e.g., prolongation of QT intervals and QRS complex) more frequently than other antipsychotic agents.

■ Treatment

Management of thioridazine overdosage generally involves symptomatic and supportive care with cardiovascular (e.g., ECG) monitoring. A patent airway must be established and maintained, and adequate oxygenation and ventilation must be ensured.

Following acute ingestion of thioridazine, gastric lavage and repeated doses of activated charcoal should be considered. Induction of emesis is less preferable to gastric lavage because of the risk of dystonia and the potential for aspiration of vomitus. In addition, emesis should not be induced in patients expected to deteriorate rapidly or in those with impaired consciousness.

To detect arrhythmias, continuous ECG monitoring may be necessary for at least 24 hours or for as long as the QT_C is prolonged. Management of thioridazine-induced arrhythmias may include ventricular pacing, defibrillation, administration of IV magnesium sulfate, lidocaine, phenytoin, or isoproterenol and correction of electrolyte abnormalities and/or acid-base balance. Lidocaine must be administered with caution in patients with overdosage of thioridazine since use of this antiarrhythmic in such patients may increase the risk of developing seizures. Antiarrhthmic agents that can prolong the QT interval (e.g., class IA [disopyramide, procainamide, quinidine] or III agents) should be *avoided* in treating overdosage-associated arrhthmias in which prolongation of the QT_C is a manifestation. For additional information on treatment of acute toxicity, see Acute Toxicity: Treatment, in the Phenothiazines General Statement 28:16.08.24.

See Pharmacology in the associated General Statement for more information.

Pharmacology

The principal pharmacologic effects of thioridazine are similar to those of chlorpromazine. On a weight basis, thioridazine is about as potent as chlorpromazine. Thioridazine has strong anticholinergic and sedative effects and weak extrapyramidal effects. Thioridazine has little antiemetic activity.

See Pharmacokinetics in the associated General Statement for more information.

See Chemistry and Stability in the associated General Statement for more information.

Chemistry and Stability

■ Chemistry

Thioridazine is a phenothiazine antipsychotic agent. The drug is an alkylpiperidine derivative of phenothiazine which differs structurally from other phenothiazine derivatives in the presence of a thiomethyl group at the 2 position of the phenothiazine nucleus. Thioridazine is commercially available as the base and as the hydrochloride salt. Each 110 mg of thioridazine hydrochloride is approximately equivalent to 100 mg of thioridazine.

Thioridazine occurs as a white or slightly yellow, crystalline or micronized powder, which is odorless or has a faint odor and is practically insoluble in water and freely soluble in dehydrated alcohol. Thioridazine hydrochloride occurs as a white to slightly yellow, granular powder with a faint odor and a very bitter taste, and is freely soluble in water.

■ Stability

Commercially available thioridazine hydrochloride oral concentrate solution should be stored in tight, light-resistant containers at a temperature less than 30°C, preferably between 15–30°C; freezing should be avoided. Thioridazine hydrochloride tablets should be protected from light and stored in well-closed containers at a temperature less than 40°C, preferably at 15–30°C.

Testing has shown that mixing thioridazine oral liquid with carbamazepine oral suspension results in a rubbery, orange precipitate. (See Cautions.) It is not known whether the development of this precipitate results in decreased bioavailability of either thioridazine or carbamazepine. Therefore, it is recommended that thioridazine oral liquid not be administered simultaneously with carbamazepine oral suspension.

For further information on chemistry and stability, pharmacology, pharmacokinetics, uses, cautions, acute toxicity, drug interactions, and dosage and administration of thioridazine, see the Phenothiazines General Statement 28:16.08.24.

Preparations

Excipients in commercially available drug preparations may have clinically important effects in some individuals; consult specific

product labeling for details.

Thioridazine Hydrochloride

Routes	Forms	Strengths	Brand Names	Manufacturer
Oral	Solution, concentrate	30 mg/mL*	Thioridazine Oral Solution	Roxane
		100 mg/mL*	Thioridazine Oral Solution	Actavis, Roxane
	Tablets	10 mg*	Thioridazine Tablets	Mutual, Mylan
		15 mg*	Thioridazine Tablets	Geneva
		25 mg*	Thioridazine Tablets	Mutual, Mylan
		50 mg*	Thioridazine Tablets	Mutual, Mylan
		100 mg*	Thioridazine Tablets	Mutual, Mylan
		150 mg*	Thioridazine Tablets	Geneva
		200 mg*	Thioridazine Tablets	Geneva

* available from one or more manufacturer, distributor, and/or repackager by generic (nonproprietary) name

■ **Comparative Pricing**

This pricing information is subject to change at the sole discretion of DS Pharmacy. This pricing information was updated 03/2010. For the most current and up-to-date pricing information, please visit www.drugstore.com. Actual costs to patients will vary depending on the use of specific retail or mail-order locations and health insurance copays.

Thioridazine HCl 10MG Tablets (MYLAN): 90/$21.99 or 270/$41.96

Thioridazine HCl 100MG Tablets (MYLAN): 90/$34.99 or 270/$87.97

Thioridazine HCl 25MG Tablets (MYLAN): 90/$25.97 or 270/$55.97

Thioridazine HCl 50MG Tablets (MYLAN): 90/$29.99 or 270/$79.97

References

Please see the general statement for a list of references.

Only references cited for selected revisions after 1984 are available electronically.

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clinician of any unusual behavioral changes. Patients, family members, and caregivers also should be advised not to make any changes to the anticonvulsant regimen without first consulting with the responsible clinician. They should pay close attention to any day-to-day changes in mood, behavior, and actions; since changes can happen very quickly, it is important to be alert to any sudden differences. In addition, patients, family members, and caregivers should be aware of common warning signs that may signal suicide risk (e.g., talking or thinking about wanting to hurt oneself or end one's life, withdrawing from friends and family, becoming depressed or experiencing worsening of existing depression, becoming preoccupied with death and dying, giving away prized possessions). If these or any new and worrisome behaviors occur, the responsible clinician should be contacted immediately. FDA also recommends that clinicians who prescribe felbamate or any other anticonvulsant balance the risk for suicidality with the risk of untreated illness. Epilepsy and many other illnesses for which anticonvulsants are prescribed are themselves associated with an increased risk of morbidity and mortality and an increased risk of suicidal thoughts and behavior. If suicidal thoughts and behavior emerge during anticonvulsant therapy, the clinician must consider whether the emergence of these symptoms in any given patient may be related to the illness being treated.

Because steady-state plasma concentrations of concomitantly administered anticonvulsants may be altered in patients receiving combination therapy including felbamate, monitoring of plasma concentrations of other anticonvulsant agents and appropriate adjustment of felbamate and/or other anticonvulsant dosage may be necessary during concomitant therapy; the value of monitoring plasma concentrations of felbamate has not been established. Specialized references and the manufacturer's labeling should be consulted for specific recommendations. Although clinical trials indicate that routine monitoring of laboratory parameters is not necessary for safe use of felbamate, clinicians should exercise clinical judgment regarding monitoring of laboratory parameters during therapy with the drug.

Patients receiving felbamate should be instructed to take the drug only as prescribed and to store the drug in its tightly closed container at room temperature away from excessive heat, direct sunlight, moisture, and children.

Because of the possibility of increasing seizure frequency, anticonvulsant drugs, including felbamate, should not be discontinued suddenly.

Felbamate is contraindicated in patients with known hypersensitivity to the drug or any ingredient in the formulation. The drug also is contraindicated in patients who have demonstrated hypersensitivity reactions to other carbamates. Felbamate should not be used in patients with a history of any blood dyscrasia or hepatic dysfunction.

■ **Pediatric Precautions** Felbamate is indicated as adjunctive therapy for the treatment of partial and generalized seizures associated with Lennox-Gastaut syndrome in children 2–14 years of age; safety and efficacy of the drug for this indication in children younger than 2 years of age have not been established. Safety and efficacy of felbamate for other indications in children have not been established.

■ **Geriatric Precautions** Safety and efficacy of felbamate in geriatric patients have not been evaluated systematically, and clinical trials did not include sufficient numbers of patients older than 65 years of age to determine whether they respond differently than younger patients. Other clinical experience has not identified any differences in responses between geriatric and younger patients. If felbamate is used in geriatric patients, the initial dosage usually should be at the low end of the dosage range and caution should be exercised since renal, hepatic, and cardiovascular dysfunction and concomitant disease or other drug therapy are more common in this age group than in younger patients.

■ **Mutagenicity and Carcinogenicity** No evidence of mutagenicity was demonstrated by felbamate in the Ames *Salmonella* microbial mutagen test, the CHO/HGPRT mammalian cell forward gene mutation assay, the sister chromatid exchange assay in CHO cells, or bone marrow cytogenetics assay.

Studies to determine the carcinogenic potential of felbamate were performed in mice and rats. Mice received felbamate orally in dosages of 300, 600, and 1200 mg/kg daily for 92 weeks, while male rats received the drug orally in dosages of 30, 100, and 300 mg/kg and female rats received 10, 30, and 100 mg/kg daily for 104 weeks. The maximum dosages used in these studies produced steady-state plasma felbamate concentrations that were equal to or less than the steady-state plasma concentrations in patients with epilepsy receiving 3600 mg of the drug daily. There was an increase in hepatic cell adenomas in male and female mice receiving the high dosages as well as in female rats receiving the high dosages. Hepatic hypertrophy also was increased in a dose-related manner in mice, principally in males, but also in females. Hepatic hypertrophy was not found in female rats. The relationship between the occurrence of benign hepatocellular adenomas and the finding of liver hypertrophy resulting from hepatic enzyme induction has not been evaluated. There also was an increase in benign interstitial cell tumors of the testes in male rats receiving high dosages of felbamate. The relevance of these findings to humans is not known.

As a result of the synthetic process involved in producing felbamate, the drug could contain small amounts of two known animal carcinogens, the genotoxic compound ethyl carbamate (urethane) and the nongenotoxic compound methyl carbamate. Theoretically, it is possible that a 50-kg patient receiving 3600 mg of felbamate could be exposed to up to 0.72 mcg of urethane and 1800 mcg of methyl carbamate. These daily doses of urethane and methyl carbamate are approximately 1/35,000 and 1/5500, respectively, on a mg/kg basis (1/10,000 and 1/1600, respectively, on a mg/m² basis) of the dose levels shown to be carcinogenic in rodents. Any presence of these two compounds in felbamate used in the lifetime carcinogenicity studies was inadequate to cause tumors.

■ **Pregnancy, Fertility, and Lactation** Reproduction studies in rats and rabbits receiving felbamate doses of up to 13.9 and 4.2 times, respectively, the human daily dose of the drug on mg/kg basis (3 and less than 2 times, respectively, the human daily dose on a mg/m² basis) did not reveal evidence of teratogenicity; however, in rats, there was a decrease in pup weight and an increase in pup deaths during lactation. The cause of these deaths is not known. The dose at which there was no effect on rat pup mortality was 6.9 times the human dose on a mg/kg basis (1.5 times the human dose on a mg/m² basis). Felbamate crosses the placenta in rats. There are, however, no adequate and controlled studies to date using the drug in pregnant women, and the effect of felbamate on labor and delivery in humans also is not known. Placental disorder, fetal death, microcephaly, genital malformation, and sudden infant death syndrome (SIDS) have been reported with felbamate, usually when used as adjunctive therapy; however, a causal relationship to the drug has not been established. Felbamate should be used during pregnancy only when clearly needed.

Reproduction studies in rats revealed no evidence of impaired fertility in males or females receiving oral felbamate dosages of up to 13.9 times the human total daily dosage of 3600 mg on a mg/kg basis (up to 3 times the human total daily dosage on a mg/m² basis).

Felbamate is distributed into milk. Since the potential effect in nursing infants is not known, felbamate should be used with caution in nursing women.

Description

Felbamate, a dicarbamate, is an anticonvulsant agent. Felbamate is structurally related to but pharmacologically distinct from meprobamate. Felbamate has a unique spectrum of activity compared with other currently available anticonvulsants.

The exact mechanism of action of felbamate is not known, but available data suggest that the drug increases seizure threshold and reduces seizure spread. A predominant effect on any particular cell process has not been demonstrated to date, but felbamate appears to exhibit a spectrum of anticonvulsant activity that is pharmacologically distinct from other currently available agents. In animals, felbamate protects against seizures induced by electrical stimulation, suggesting that it would be effective in the management of tonic-clonic (grand mal) seizures and partial seizures. In animals, felbamate also protects against seizures induced by pentylenetetrazol, indicating that it may be effective in the management of absence (petit mal) seizures. Felbamate also protects against seizures in animals induced by picrotoxin, glutamate, or *N*-methyl-D-aspartic acid; it does not protect against seizures induced by bicuculline or strychnine.

In vitro studies indicate that felbamate has weak inhibitory effects on binding at γ-aminobutyric acid (GABA) receptors and benzodiazepine receptors. The monocarbamate, *p*-hydroxy, and 2-hydroxy metabolites of felbamate appear to contribute little, if any, to the anticonvulsant action of the drug.

SumMon® (see Users Guide). **For additional information on this drug until a more detailed monograph is developed and published, the manufacturer's labeling should be consulted. It is *essential* that the labeling be consulted for detailed information on the usual cautions, precautions, and contraindications concerning potential drug interactions and/or laboratory test interferences and for information on acute toxicity.**

Preparations

Excipients in commercially available drug preparations may have clinically important effects in some individuals; consult specific product labeling for details.

Felbamate

Oral		
Suspension	600 mg/5 mL	Felbatol®, Meda
Tablets	400 mg	Felbatol® (scored), Meda
	600 mg	Felbatol® (scored), Meda

Gabapentin

■ Gabapentin is an anticonvulsant structurally related to the inhibitory CNS neurotransmitter γ-aminobutyric acid (GABA).

Uses

■ **Seizure Disorders** Gabapentin is used in combination with other anticonvulsant agents in the management of partial seizures with or without secondary generalization in adults and children 12 years of age and older and in the management of partial seizures in children 3–12 years of age. Although the comparative efficacy of therapeutically effective dosages of gabapentin versus other anticonvulsants remains to be established, the anticonvulsant potential of

gabapentin has been established in studies in which gabapentin or placebo was administered as adjunctive therapy in adults and children older than 3 years of age with refractory partial seizures.

In several placebo-controlled clinical studies, gabapentin was effective in reducing seizure frequency, including that of secondarily generalized tonic-clonic seizures, in 17–26% of patients with partial seizures refractory to therapy with conventional anticonvulsant drugs (e.g., phenytoin, carbamazepine, phenobarbital, valproic acid). Patients in these studies had a history of at least 4 partial seizures (with or without secondary tonic-clonic generalization) per month despite optimum therapy with one or more anticonvulsants and were eligible for study entry if they continued to have at least 2–4 seizures per month during a 12-week baseline period while receiving their established anticonvulsant regimen. Efficacy of gabapentin in these studies was evaluated principally in terms of the percentage of patients with a reduction in seizure frequency of 50% or greater compared with baseline values (i.e., responder rate) and the change in seizure frequency associated with the addition of gabapentin or placebo to existing anticonvulsant treatment (i.e., response ratio, calculated as treatment seizure frequency minus baseline seizure frequency divided by the sum of the treatment and baseline seizure frequencies). Combined analysis of these response parameters in patients receiving various dosages of gabapentin (600, 900, 1200, or 1800 mg in 3 divided doses daily) or placebo indicated a dose-related reduction in the frequency of partial seizures with gabapentin, although a dose-response relationship was not consistently found in the individual studies. The efficacy of adjunctive therapy with gabapentin for the management of partial seizures does not appear to be affected by patient gender or age, although the influence of these characteristics on efficacy has not been studied systematically.

Gabapentin also is used in combination with other anticonvulsant agents in the management of partial seizures in children 3–12 years of age. Efficacy of gabapentin as adjunctive therapy in children 3–12 years of age with partial seizures was established in a multicenter randomized controlled trial. Response ratios were substantially better in patients receiving gabapentin 25–35 mg/kg daily compared with patients receiving placebo; for the same population, the responder rate for the drug (21%) was not substantially different from placebo (18%). Another study in children 1 month to 3 years of age reported no substantial difference in either the response ratio or responder rate for those receiving gabapentin compared with those receiving placebo.

Because addition of gabapentin to an existing anticonvulsant regimen does not appreciably alter steady-state plasma concentrations of concomitantly administered anticonvulsants, additional monitoring of plasma concentrations of anticonvulsant agents for adjustment of gabapentin and/or other anticonvulsant dosage generally is not necessary during such concomitant therapy; the value of monitoring plasma concentrations of gabapentin has not been established. Although clinical trials indicate that routine monitoring of laboratory parameters is not necessary for the safe use of gabapentin, clinicians should exercise clinical judgment regarding such monitoring during therapy with the drug.

■ **Neuropathic Pain** ***Postherpetic Neuralgia*** Gabapentin is used in the management of postherpetic neuralgia (PHN) in adults. In 2 placebo-controlled clinical studies in patients with postherpetic neuralgia, gabapentin was effective in relieving pain (based on an 11-point numeric rating scale) in patients who continued to experience pain for longer than 3 months after healing of the herpes zoster rash. In these studies, gabapentin dosage was titrated over the first 3 days of therapy to a maximum dosage of 900 mg daily and then was increased further over a period of 3–4 weeks in increments of 600 mg to 1.2 g daily at intervals of 3–7 days to the designated target dosage. In 1 study, 29% of patients receiving a target dosage of 3.6 g daily reported a reduction in pain of at least 50% compared with baseline; in the other study, the same level of pain relief (50% reduction) was achieved in 32 or 34% of patients receiving a target gabapentin dosage of 1.8 or 2.4 g daily, respectively.

Other Neuropathic Uses Gabapentin is used for the treatment of pain associated with diabetic neuropathy†. In an 8-week controlled clinical study in patients with diabetic neuropathy, gabapentin was more effective than placebo in improving pain (based on an 11-point numeric rating scale), sleep, and mood during weeks 2–8 of the study. Most patients in this study (67%) received gabapentin in dosages of 3.6 g daily. In addition, 2 comparative studies reported that gabapentin was at least as effective as amitriptyline in relieving pain associated with diabetic neuropathy. Analysis of data from randomized studies in patients with pain associated with diabetic neuropathy indicates that 40% of patients who received gabapentin for neuropathic pain obtained good pain relief.

Gabapentin also has been used with some evidence of benefit for the relief of chronic neurogenic pain† in a variety of conditions including trigeminal neuralgia†, pain and control of paroxysmal symptoms of multiple sclerosis†, complex regional pain syndromes† (CRPS), HIV-related peripheral neuropathy†, and neuropathic pain associated with cancer†. Limited evidence indicates that gabapentin is not effective for the management of acute pain. Gabapentin also has been used in the treatment of restless legs syndrome† (RLS). Additional study and experience are needed to further elucidate the precise role of gabapentin in the management of these conditions.

■ **Vasomotor Symptoms** Gabapentin has been used for the management of vasomotor symptoms† in women with breast cancer and in postmenopausal women. Therapy with the drug has improved both the frequency and severity of vasomotor symptoms (hot flushes [flashes]) in these women.

Most women receiving systemic antineoplastic therapy for breast cancer experience vasomotor symptoms, particularly those receiving tamoxifen therapy. In a randomized, double-blind, placebo-controlled study in 420 women with breast cancer (68–75% were receiving tamoxifen) who were experiencing 2 or more episodes of hot flushes daily, the percentage reductions in hot flush severity score at 4 and 8 weeks of treatment were 21 and 15%, respectively, for placebo; 33 and 31%, respectively, for gabapentin 300 mg daily (100 mg 3 times daily), and 49 and 46%, respectively, for gabapentin 900 mg daily (300 mg 3 times daily). Comparisons among treatment groups showed that only the 900-mg daily dosage was associated with a statistically significant reduction in hot flush frequency and severity. Whether higher dosages will provide further reductions in vasomotor symptoms remains to be determined. The role of gabapentin in managing vasomotor symptoms in women with breast cancer relative to other nonhormonal therapies (e.g., selective serotonin-reuptake inhibitors [SSRIs], selective serotonin- and norepinephrine-reuptake inhibitors [SNRIs]) remains to be determined. Well-designed, comparative studies are needed to establish optimum nonhormonal therapy, both in terms of efficacy and patient tolerance of adverse effects, in these women.

Because of the risks associated with hormone replacement therapy (HRT) for vasomotor symptoms in perimenopausal and postmenopausal women, alternative nonhormonal therapies are being investigated. In a randomized, double-blind, placebo-controlled study in 59 postmenopausal women who were experiencing 7 or more hot flushes daily, intent-to-treat analysis revealed that 12 weeks of gabapentin 900 mg daily (300 mg 3 times daily) was associated with a 45% reduction in hot flush frequency and a 54% reduction in composite hot flush score (frequency and severity). In a continuation open-label phase in which patients were permitted upward titration of dosage as needed to a maximum of 2.7 g daily (25% received 900 mg or less daily, 61% received 900 mg–1.8 g daily, 14% received 1.8–2.7 g daily), the associated reductions in hot flush frequency and composite score were 54 and 67%, respectively. The role of gabapentin therapy relative to other nonhormonal therapies (e.g., SSRIs, SNRIs) for postmenopausal vasomotor symptoms, both in terms of efficacy and safety, as well as the optimum dosage remain to be established.

Current evidence indicates that gabapentin is effective and well tolerated in the short-term treatment of vasomotor symptoms associated with breast cancer treatment and with menopause. The principal adverse effects associated with gabapentin therapy in women with vasomotor symptoms have been somnolence, fatigue, dizziness, and rash (with or without peripheral edema). Additional study and experience are needed to further elucidate the role of gabapentin relative to other nonhormonal therapies, and to establish longer-term (i.e., beyond 17 weeks) efficacy and safety.

The possible role of gabapentin in the management of vasomotor symptoms† associated with antiandrogenic therapy in men with prostate cancer remains to be established. Current evidence of efficacy is limited; well-designed, controlled studies are under way in this population.

Dosage and Administration

■ **Administration** Gabapentin is administered orally. The drug may be administered without regard to meals.

If Neurontin® film-coated scored tablets containing 600 or 800 mg of gabapentin are to be used in patients requiring a 300- or 400-mg dose, the tablets can be halved to allow administration of the appropriate dose. Patients should be instructed to take one-half tablet; the remaining half-tablet should be used for the next dose. Half-tablets that are not used within several days should be discarded.

Patients who are currently receiving or beginning therapy with gabapentin and/or any other anticonvulsant for any indication should be closely monitored for the emergence or worsening of depression, suicidal thoughts or behavior (suicidality), and/or any unusual changes in mood or behavior. (See Suicidality under Cautions: Nervous System Effects and see Cautions: Precautions and Contraindications.)

■ **Dosage** ***Seizure Disorders*** Because of the possibility of increasing seizure frequency, anticonvulsant drugs, including gabapentin, should *not* be discontinued abruptly. (See Cautions: Precautions and Contraindications.) Discontinuance of gabapentin therapy and/or addition of an alternative anticonvulsant drug to therapy should be done gradually over a minimum of 1 week.

For adjunctive therapy in the management of partial seizures with or without secondary generalization in adults and children older than 12 years of age, the effective dosage of gabapentin is 900 mg to 1.8 g daily administered in 3 divided doses. Gabapentin therapy is initiated at a dosage of 300 mg 3 times daily.

If necessary, the dosage of gabapentin may be increased up to 1.8 g daily in 3 divided doses. Dosages up to 2.4 g daily have been tolerated well as adjunctive therapy by patients in long-term clinical studies, and a small number of patients have tolerated dosages of 3.6 g daily for short periods. With thrice-daily dosing, the interval between doses should not exceed 12 hours. It is not necessary to monitor plasma gabapentin concentrations to optimize therapy.

For adjunctive therapy in the management of partial seizures, the effective dosage of gabapentin in patients 5 years of age and older is 25–35 mg/kg daily administered in 3 divided doses; for patients 3 and 4 years of age, the effective dosage is 40 mg/kg daily administered in 3 divided doses. Gabapentin therapy in patients 3–12 years of age should be initiated at a dosage of 10–15 mg/kg per day in 3 divided doses. Dosages up to 50 mg/kg daily have been well tolerated by patients 3–12 years of age in a long-term clinical study. When

administered 3 times daily, the interval between doses should not exceed 12 hours.

If gabapentin is discontinued and/or an alternative anticonvulsant is added to the regimen, such changes in therapy should be done gradually over a period of at least 1 week.

Postherpetic Neuralgia For the management of postherpetic neuralgia in adults, the initial dosage regimen of gabapentin is 300 mg once daily on the first day, 300 mg twice daily on the second day, and 300 mg 3 times daily on the third day. Subsequently, the dosage may be increased as needed for relief of pain up to a total daily dosage of 1.8 g administered in 3 divided doses. In clinical studies evaluating gabapentin for the treatment of postherpetic neuralgia, dosages of the drug ranging from 1.8–3.6 g daily were effective, but there was no evidence that dosages exceeding 1.8 g daily provided any additional benefit.

Diabetic Neuropathy For the symptomatic treatment of diabetic neuropathy† in adults, gabapentin dosages of 900 mg to 3.6 g daily have been used; however, pain relief generally has been observed in patients receiving dosages exceeding 1.8 g daily.

Vasomotor Symptoms Although the optimum dosage remains to be established, a gabapentin dosage of 300 mg 3 times daily has been effective in reducing both the severity and frequency of vasomotor symptoms† in women with breast cancer and in postmenopausal women. Some clinicians recommend that therapy be initiated with a dosage of 300 mg once daily at bedtime. If needed, the dosage can be increased to 300 mg twice daily, and then to 300 mg 3 times daily, at 3- to 4-day intervals. A dosage of 100 mg 3 times daily appears to be no more effective than placebo, whereas dosages exceeding 900 mg daily (e.g., up to 2.7 g daily administered as 900 mg 3 times daily) may provide additional benefit in some women.

■ **Dosage in Renal Impairment** In adults and children 12 years of age and older with impaired renal function and/or undergoing hemodialysis, dosage and/or frequency of administration of gabapentin should be modified in response to the degree of renal impairment. Such patients with a creatinine clearance of 60 mL/minute or greater may receive 300 mg to 1.2 g of gabapentin 3 times daily (i.e., up to a total dosage of 3.6 g daily), and those with a creatinine clearance of 30–59 mL/minute may receive 200–700 mg of gabapentin twice daily (i.e., up to a total dosage of 1.4 g daily). Patients with a creatinine clearance of 15–29 mL/minute may receive 200–700 mg of gabapentin once daily, and those with a creatinine clearance of 15 mL/minute may receive 100–300 mg of gabapentin daily. In patients with a creatinine clearance of less than 15 mL/minute, dosage of gabapentin should be reduced proportionally (e.g., patients with a creatinine clearance of 7.5 mL/minute should receive one-half the dosage that patients with a creatinine clearance of 15 mL/minute should receive). Anephric patients may receive maintenance doses of gabapentin based on estimates of creatinine clearance, with supplemental doses of 125–350 mg of gabapentin given after each 4-hour hemodialysis session.

The use of gabapentin in children less than 12 years of age with impaired renal function has not been evaluated.

Cautions

Gabapentin generally is well tolerated, and adverse effects of the drug usually are mild to moderate in severity and may be self-limiting. Nervous system effects are the most frequently reported adverse affects of gabapentin and those most frequently requiring discontinuance of the drug. The most frequent adverse effects of gabapentin as adjunctive therapy in the treatment of partial seizures in adults and children 12 years of age and older are somnolence, dizziness, ataxia, fatigue, and nystagmus. Discontinuance of gabapentin because of adverse effects was required in 7% of adults and children 12 years of age and older receiving the drug as adjunctive therapy in the treatment of partial seizures in premarketing uncontrolled and controlled clinical trials; the adverse effects most frequently associated with discontinuance of gabapentin were somnolence (1.2% of patients), ataxia (0.8% of patients), fatigue (0.6% of patients), nausea and/or vomiting (0.6% of patients), and dizziness (0.6% of patients). The most frequent adverse effects of gabapentin as adjunctive therapy in the treatment of partial seizures in patients 3–12 years of age were viral infection, fever, nausea and/or vomiting, somnolence, and hostility. Discontinuance of gabapentin because of adverse effects was required in approximately 7% of patients 3–12 years of age in clinical trials; the adverse effects most frequently associated with discontinuance of gabapentin were emotional lability (1.6%), hostility (1.3%), and hyperkinesia (1.1%).

Because clinical trials of gabapentin therapy in the treatment of partial seizures involved specific patient populations and use of the drug as adjunctive therapy, it is difficult to determine whether a causal relationship exists for many reported adverse effects, to compare adverse effect frequencies with other clinical reports, and/or to extrapolate the adverse effect experience from controlled clinical trials to usual clinical practice.

In placebo-controlled studies, the adverse effects most frequently reported in adults receiving gabapentin for the management of postherpetic neuralgia were dizziness, somnolence, and peripheral edema. Discontinuance of gabapentin because of adverse effects was required in 16% of patients receiving the drug in 2 clinical trials; the adverse effects most frequently associated with discontinuance of gabapentin for the management of postherpetic neuralgia were dizziness, somnolence, and nausea.

■ **Nervous System Effects** Nervous system effects were among the most frequent adverse effects reported in patients with epilepsy receiving gabapentin as adjunctive therapy in controlled clinical trials in adults and children 12 years of age and older. Somnolence was the most frequent adverse nervous system effect, occurring in about 19% of those receiving gabapentin; the incidence and severity of somnolence appear to be dose related. Dizziness or ataxia was reported in about 17 or 12.5%, respectively, of patients receiving gabapentin as adjunctive therapy in controlled trials; the incidence and severity of ataxia also appear to be dose related. Fatigue reportedly occurred in about 11% of adults receiving gabapentin as adjunctive therapy in controlled trials. Nystagmus was reported in about 8%, tremor in about 7%, nervousness in 2.4%, dysarthria in 2.4%, amnesia in 2.2%, depression in 1.8%, abnormal thinking in 1.7%, twitching in 1.3%, and abnormal coordination in 1.1% of patients receiving gabapentin as adjunctive therapy in controlled trials. Other nervous system effects occurring in more than 1% of patients receiving gabapentin as adjunctive therapy, but with equal or greater frequency in patients receiving placebo, were headache, seizures, confusion, insomnia, and emotional lability.

Vertigo, hyperkinesia, paresthesia, decreased or absent reflexes, increased reflexes, anxiety, hostility, asthenia, or malaise was reported in at least 1% of adults and children 12 years of age and older receiving gabapentin as adjunctive therapy in uncontrolled and controlled clinical trials. CNS tumors, syncope, abnormal dreaming, aphasia, hypoesthesia, intracranial hemorrhage, hypotonia, dysesthesia, paresis, dystonia, hemiplegia, facial paralysis, stupor, cerebellar dysfunction, positive Babinski sign, positive Romberg test, decreased position sense, subdural hematoma, apathy, hallucination, decrease or loss of libido, agitation, paranoia, depersonalization, euphoria, feeling high, doped-up sensation, psychosis, or migraine occurred in at least 0.1% but less than 1% of patients receiving gabapentin as adjunctive therapy in uncontrolled and controlled clinical trials. Choreoathetosis, orofacial dyskinesia, encephalopathy, nerve palsy, personality disorder, increased libido, subdued temperament, apraxia, fine motor control disorder, meningismus, local myoclonus, hyperesthesia, hypokinesia, mania, neurosis, hysteria, antisocial reaction, strange feelings, or lassitude occurred in less than 0.1% of patients receiving gabapentin as adjunctive therapy in uncontrolled and controlled clinical trials.

Somnolence, hostility (including aggressive behavior), emotional lability, fatigue, hyperkinesia, and dizziness were reported in 8.4, 7.6, 4.2, 3.4, 2.5, and 2.5% of children 3–12 years of age receiving gabapentin as adjunctive therapy in controlled clinical trials. Headache and convulsions were reported in more than 2% and equally or more frequently than among those receiving placebo in children 3–12 years of age receiving gabapentin as adjunctive therapy in controlled clinical trials. Somnambulism, aura disappeared, and occipital neuralgia were reported during controlled clinical trials in children 3–12 years of age, but were not reported in trials of adults receiving gabapentin. Thought disorders (e.g., concentration difficulty, change in school performance) have been reported in 1.7% of children 3–12 years of age receiving the drug.

Dizziness was reported in 28%, somnolence in 21.4%, asthenia in 5.7%, headache in 3.3%, ataxia in 3.3%, and abnormal thinking in 2.7% of adults receiving gabapentin for the management of postherpetic neuralgia (PHN) in controlled clinical trials. Abnormal gait, incoordination, amnesia, and hypesthesia occurred in 1.2–1.5% of patients receiving the drug. Pain, tremor, and neuralgia were reported in greater than 1% of patients receiving gabapentin in clinical studies for the management of PHN but occurred with equal or greater frequency in patients receiving placebo.

Suicidality The US Food and Drug Administration (FDA) has analyzed suicidality reports from placebo-controlled studies involving 11 anticonvulsants, including gabapentin, and found that patients receiving anticonvulsants had approximately twice the risk of suicidal behavior or ideation (0.43%) compared with patients receiving placebo (0.24%).

FDA's analysis included 199 randomized, placebo-controlled studies of 11 anticonvulsants (carbamazepine, felbamate, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, pregabalin, tiagabine, topiramate, valproate, and zonisamide) involving over 43,000 patients 5 years of age or older; the studies evaluated the effectiveness of the anticonvulsants in epilepsy, psychiatric disorders (e.g., bipolar disorder, depression, anxiety), and other conditions (e.g., migraine, neuropathic pain). The increased suicidality risk was observed as early as one week after beginning therapy and continued through 24 weeks. The results were generally consistent among the 11 drugs studied. In addition, patients who were treated for epilepsy, psychiatric disorders, and other conditions were all found to be at increased risk for suicidality when compared with placebo; there did not appear to be a specific demographic subgroup of patients to which the increased risk could be attributed. However, the relative risk for suicidality was found to be higher in patients with epilepsy compared with patients who were given one of the drugs for psychiatric or other conditions. (See Cautions: Precautions and Contraindications.)

In uncontrolled and controlled clinical trials, suicidal attempt occurred in at least 0.1% but less than 1% of patients receiving gabapentin as adjunctive therapy, and suicide occurred in less than 0.1% of patients receiving the drug as adjunctive therapy.

■ **GI Effects** Dyspepsia was the most frequent adverse GI effect in adults and children 12 years of age and older receiving gabapentin as adjunctive therapy in controlled clinical trials, occurring in 2.2% of such patients. Dry mouth or throat occurred in 1.7%, constipation in 1.5%, dental abnormalities in 1.5%, and increased appetite in 1.1% of patients receiving the drug. Nausea and/or vomiting, abdominal pain, or diarrhea was reported in more than 1% of patients receiving gabapentin as adjunctive therapy in controlled clinical trials but occurred with equal or greater frequency in patients receiving placebo.

Anorexia, flatulence, or gingivitis was reported in at least 1% of adults and children 12 years of age and older receiving gabapentin as adjunctive therapy in uncontrolled and controlled clinical trials. Glossitis, gingival hemorrhage, thirst, stomatitis, increased salivation, taste loss, unusual taste, gastroenteritis, hemorrhoids, bloody stools, or fecal incontinence occurred in at least 0.1% but less than 1% of such patients receiving gabapentin as adjunctive therapy in uncontrolled and controlled clinical trials. Dysphagia, eructation, pancreatitis, peptic ulcer, colitis, blisters in mouth, tooth discolor, perléche, enlarged salivary gland, lip hemorrhage, esophagitis, hiatal hernia, hematemesis, proctitis, irritable bowel syndrome, rectal hemorrhage, or esophageal spasm was reported in less than 0.1% of adults and children 12 years of age or older receiving gabapentin as adjunctive therapy in uncontrolled and controlled clinical trials.

Nausea and/or vomiting was reported in 8.4% of children 3–12 years of age receiving gabapentin as adjunctive therapy in controlled clinical trials. Diarrhea and anorexia were reported in more than 2% of children 3–12 years of age receiving gabapentin as adjunctive therapy in controlled clinical trials.

Diarrhea was reported in 5.7%, dry mouth in 4.8%, constipation in 3.9%, nausea in 3.9%, and vomiting in 3.3% of adults receiving gabapentin for the management of postherpetic neuralgia (PHN) in controlled clinical trials. Abdominal pain and flatulence occurred in 2.7 and 2.1%, respectively, of patients receiving the drug. Dyspepsia and dyspnea were reported in greater than 1% of patients receiving gabapentin in clinical studies of the management of PHN, but occurred with equal or greater frequency in patients receiving placebo.

■ **Cardiovascular Effects** Peripheral edema was reported in 1.7%, and vasodilation in 1.1% of adults and children 12 years of age and older receiving gabapentin as adjunctive therapy in controlled clinical trials. Hypertension occurred in more than 1% of patients receiving the drug as adjunctive therapy in uncontrolled and controlled clinical trials, and hypotension, angina pectoris, peripheral vascular disorder, palpitation, tachycardia, heart murmur, or generalized edema was reported in at least 0.1% but less than 1% of such patients. Atrial fibrillation, heart failure, thrombophlebitis, deep-vein thrombophlebitis, myocardial infarction, cerebrovascular accident, pulmonary thrombosis, ventricular extrasystole, bradycardia, atrial premature contraction, pericardial rub, heart block, pulmonary embolus, hyperlipidemia, hypercholesterolemia, pericardial effusion, or pericarditis occurred in less than 0.1% of patients receiving gabapentin as adjunctive therapy in uncontrolled and controlled clinical trials.

Peripheral edema was reported in 8.3% of adults receiving gabapentin for the management of postherpetic neuralgia (PHN) in controlled clinical trials.

■ **Respiratory Effects** Rhinitis occurred in 4.1%, pharyngitis in 2.8%, and coughing in 1.8% of adults and children 12 years of age and older receiving gabapentin as adjunctive therapy in controlled clinical trials. Pneumonia occurred in more than 1%; epistaxis, dyspnea, or apnea in at least 0.1% but less than 1%; and mucositis, aspiration pneumonia, hyperventilation, hiccup, laryngitis, nasal obstruction, snoring, bronchospasm, hypoventilation, or lung edema in less than 0.1% of patients receiving gabapentin as adjunctive therapy in uncontrolled and controlled clinical trials.

Bronchitis and respiratory infection were reported in 3.4 and 2.5%, respectively, of children 3–12 years of age receiving gabapentin as adjunctive therapy in controlled clinical trials. Pharyngitis, upper respiratory infection, rhinitis, and coughing were reported in more than 2% of children 3–12 years of age receiving gabapentin as adjunctive therapy in controlled clinical trials. Pseudocroup and hoarseness were reported during controlled clinical trials in children 3–12 years of age, but were not reported in trials in adults receiving gabapentin as adjunctive therapy.

Pharyngitis was reported in 1.2% of adults receiving gabapentin for the management of postherpetic neuralgia (PHN) in controlled clinical trials.

■ **Ocular and Otic Effects** Diplopia was reported in 5.9%, and amblyopia in 4.2%, of adults and children 12 years of age and older receiving gabapentin as adjunctive therapy in controlled clinical trials. Abnormal vision was reported in more than 1% of patients receiving gabapentin as adjunctive therapy in uncontrolled and controlled clinical trials.

Cataract, conjunctivitis, dry eyes, ocular pain, visual field defect, photophobia, bilateral or unilateral ptosis, ocular hemorrhage, ocular twitching, or hordeolum (stye) occurred in at least 0.1% but less than 1% of adults and children 12 years of age and older receiving gabapentin as adjunctive therapy in uncontrolled and controlled clinical trials. Ocular itching, abnormal accommodation, ocular focusing difficulty, watery eyes, retinopathy, glaucoma, iritis, corneal disorders, lacrimal dysfunction, degenerative ocular changes, blindness, retinal degeneration, miosis, chorioretinitis, or strabismus was reported in less than 0.1% of patients receiving the drug as adjunctive therapy in uncontrolled and controlled clinical trials.

Hearing loss, earache, tinnitus, inner ear infection, otitis, or otic fullness occurred in at least 0.1% but less than 1% of adults and children 12 years of age and older receiving gabapentin as adjunctive therapy in uncontrolled and controlled clinical trials. Eustachian tube dysfunction, labyrinthitis, otitis externa, perforated eardrum, or sensitivity to noise was reported in less than 0.1% of patients receiving gabapentin as adjunctive therapy in uncontrolled and controlled clinical trials.

Otitis media was reported in more than 2% of children 3–12 years of age receiving gabapentin as adjunctive therapy in clinical studies.

Amblyopia occurred in 2.7%, and conjunctivitis, diplopia, and otitis media each occurred in 1.2% of adults receiving gabapentin for the management of postherpetic neuralgia (PHN) in controlled clinical trials.

■ **Musculoskeletal Effects** Myalgia was reported in 2%, back pain in 1.8%, and fracture in 1.1% of adults and children 12 years of age and older receiving gabapentin as adjunctive therapy in controlled clinical trials. Arthralgia was reported in more than 1% of adults and children 12 years of age and older receiving the drug as adjunctive therapy in uncontrolled and controlled clinical trials, and tendinitis, arthritis, joint stiffness, or joint swelling occurred in at least 0.1% but less than 1% of such patients. Costochondritis, osteoporosis, bursitis, and contracture were reported in less than 0.1% of patients receiving gabapentin as adjunctive therapy in uncontrolled and controlled clinical trials.

Back pain was reported in greater than 1% of adults receiving gabapentin in clinical studies for the management of postherpetic neuralgia (PHN) but occurred with equal or greater frequency in patients receiving placebo.

■ **Endocrine Effects** Hyperthyroidism, hypothyroidism, goiter, hypoestrogenism, and cushingoid manifestations were reported in less than 0.1% of adults and children 12 years of age and older receiving gabapentin as adjunctive therapy in uncontrolled and controlled trials.

■ **Genitourinary Effects** Impotence was reported in 1.5% of patients receiving gabapentin as adjunctive therapy in controlled clinical trials. Hematuria, dysuria, cystitis, urinary frequency, urinary retention, urinary incontinence, vaginal hemorrhage, amenorrhea, dysmenorrhea, menorrhagia, breast cancer, inability to climax, and abnormal ejaculation occurred in at least 0.1% but less than 1% of patients receiving the drug as adjunctive therapy in uncontrolled and controlled clinical trials, and renal pain, renal lithiasis, acute renal failure, anuria, nephrosis, nocturia, pyuria, urinary urgency, leukorrhea, genital pruritus, vaginal pain, ovarian failure, testicular pain, epididymitis, and swollen testicle were reported in less than 0.1% of such patients.

■ **Dermatologic and Sensitivity Reactions** Pruritus or abrasion occurred in 1.3% of adults and children 12 years of age and older receiving gabapentin as adjunctive therapy in controlled clinical trials. Rash or acne were reported in more than 1% of patients receiving the drug in controlled studies but occurred with equal or greater frequency with placebo.

Facial edema was reported in at least 1% of patients receiving gabapentin as adjunctive therapy in uncontrolled or controlled clinical trials. Allergy, alopecia, eczema, dry skin, increased sweating, urticaria, hirsutism, seborrhea, cysts, and herpes simplex occurred in at least 0.1% but less than 1% of patients receiving the drug as adjunctive therapy in uncontrolled and controlled trials. Herpes zoster, skin discoloration, skin papules, photosensitivity reaction, leg ulcer, scalp seborrhea, psoriasis, desquamation, maceration, skin nodule, subcutaneous nodule, melanosis, skin necrosis, or local swelling was reported in less than 0.1% of such patients.

Angioedema, erythema multiforme, and Stevens-Johnson syndrome have been reported during postmarketing experience with gabapentin; however, the manufacturers state that data are insufficient to provide an estimate of the incidence of such effects or to establish a causal relationship to gabapentin.

Rash also was reported in 1.2% of adults receiving gabapentin for the management of postherpetic neuralgia (PHN) in controlled clinical trials.

■ **Hepatic Effects** Hepatomegaly occurred in at least 0.1% but less than 1% of adults and children 12 years of age and older receiving gabapentin as adjunctive therapy in uncontrolled and controlled clinical trials.

Elevated liver function test results and jaundice have been reported during postmarketing experience with gabapentin; however, the manufacturers state that data are insufficient to provide an estimate of the incidence of such effects or to establish a causal relationship to gabapentin.

Hepatitis was reported during controlled clinical trials in children 3–12 years of age, but was not reported in trials in adults receiving gabapentin.

■ **Electrolyte and Metabolic Effects** A decrease in body weight occurred in at least 0.1% but less than 1% of adults and children 12 years of age and older receiving gabapentin as adjunctive therapy in uncontrolled and controlled clinical trials; weight gain also has been reported. Glycosuria was reported in less than 0.1% of patients receiving the drug as adjunctive therapy in uncontrolled and controlled clinical trials.

Weight gain and hyperglycemia were reported in 1.8 and 1.2%, respectively, of adults receiving gabapentin for the management of postherpetic neuralgia (PHN) in controlled clinical trials.

Fluctuation in blood glucose concentrations and hyponatremia have been reported during postmarketing experience with gabapentin; however, the manufacturers state that data are insufficient to provide an estimate of the incidence of such effects or to establish a causal relationship to gabapentin.

Weight increase was reported in 3.4% of children 3–12 years of age receiving gabapentin in controlled clinical trials.

■ **Hematologic Effects** Leukopenia was reported in 1.1% of adults and children 12 years of age and older receiving gabapentin as adjunctive therapy in controlled clinical trials. Purpura (generally described as bruises resulting from physical trauma) was reported in at least 1% of patients receiving gabapentin as adjunctive therapy in uncontrolled and controlled clinical trials.

Anemia, thrombocytopenia, or lymphadenopathy occurred in at least 0.1% but less than 1% of adults and children 12 years of age and older receiving gabapentin as adjunctive therapy in uncontrolled and controlled clinical trials. Increased leukocyte count, lymphocytosis, non-Hodgkin's lymphoma, or increased bleeding time was reported in less than 0.1% of such patients.

Coagulation defect was reported during controlled clinical trials in children 3–12 years of age, but was not reported in trials in adults receiving gabapentin.

■ **Other Adverse Effects** Viral infection or fever occurred in more than 1% of adults and children 12 years of age and older receiving gabapentin as adjunctive therapy in controlled trials but was equally or more frequent with placebo. Odd smell occurred in less than 0.1% of patients receiving the drug in uncontrolled and controlled trials. Alcohol intolerance, hangover effect, or breast pain occurred in less than 0.1% of adults receiving gabapentin as adjunctive therapy in uncontrolled and controlled clinical trials.

Fever has been reported during postmarketing experience with gabapentin; however, the manufacturers state that data are insufficient to provide an estimate of the incidence of such effects or to establish a causal relationship to gabapentin.

Viral infection and fever were reported in 10.9 and 10.1%, respectively, of children 3–12 years of age receiving gabapentin as adjunctive therapy in controlled clinical trials. Dehydration and infectious mononucleosis were reported during controlled clinical trials in children 3–12 years of age, but were not reported in trials in adults receiving gabapentin as adjunctive therapy.

Infection and accidental injury were reported in 5.1 and 3.3%, respectively, of adults receiving gabapentin for the management of postherpetic neuralgia (PHN) in controlled clinical trials. Flu syndrome was reported in greater than 1% of patients receiving gabapentin for the management of PHN but occurred with equal or greater frequency in patients receiving placebo in clinical studies.

■ **Precautions and Contraindications** The US Food and Drug Administration (FDA) has informed healthcare professionals about an increased risk of suicidality (suicidal behavior or ideation) observed in an analysis of studies using various anticonvulsants, including gabapentin, compared with placebo. (See Suicidality under Cautions: Nervous System Effects.) Based on the current analysis of the available data, FDA recommends that all patients who are currently receiving or beginning therapy with any anticonvulsant for any indication be closely monitored for the emergence or worsening of depression, suicidal thoughts or behavior (suicidality), and/or any unusual changes in mood or behavior. Symptoms such as anxiety, agitation, hostility, mania, and hypomania may be precursors to emerging suicidality. Clinicians should inform patients, their families, and caregivers of the potential for an increased risk of suicidality so that they are aware and able to notify their clinician of any unusual behavioral changes. Patients, family members, and caregivers also should be advised not to make any changes to the drug regimen without first consulting with the responsible clinician. They should pay close attention to any day-to-day changes in mood, behavior, and actions; since changes can happen very quickly, it is important to be alert to any sudden differences. In addition, patients, family members, and caregivers should be aware of common warning signs that may signal suicide risk (e.g., talking or thinking about wanting to hurt oneself or end one's life, withdrawing from friends and family, becoming depressed or experiencing worsening of existing depression, becoming preoccupied with death and dying, giving away prized possessions). If these or any new and worrisome behaviors occur, the responsible clinician should be contacted immediately.

FDA recommends that clinicians who prescribe gabapentin or any other anticonvulsant balance the risk for suicidality with the risk of untreated illness. Epilepsy and many other illnesses for which anticonvulsants are prescribed are themselves associated with an increased risk of morbidity and mortality and an increased risk of suicidal thoughts and behavior. If suicidal thoughts and behavior emerge during anticonvulsant therapy, the clinician must consider whether the emergence of these symptoms in any given patient may be related to the illness being treated.

Because of the possibility of increased seizure frequency, anticonvulsant drugs, including gabapentin, should not be discontinued suddenly. In controlled studies, the incidence of status epilepticus was 0.6% in adults and children 12 years of age and older receiving gabapentin and 0.5% in those receiving placebo. In all (uncontrolled and controlled) clinical studies of gabapentin as adjunctive therapy in adults and children 12 years of age and older, the incidence of status epilepticus was 1.5%. Because adequate historical data are unavailable for comparison, it has not been established whether the incidence of status epilepticus in patients with epilepsy treated with gabapentin is higher or lower than would be expected in a similar population of patients not treated with the drug. Discontinuance of gabapentin and/or addition of an alternative anticonvulsant drug to existing therapy should be done gradually over a minimum of 1 week.

Adverse CNS events (emotional lability, hostility [including aggressive behaviors], thought disorders [including concentration problems and change in school performance], and hyperkinesia) have been reported in epileptic children 3–12 years of age. (See Cautions: Nervous System Effects.)

During the premarketing development of gabapentin, 8 sudden and unexplained deaths were reported among a cohort of 2203 patients with epilepsy (2103 patient-years of exposure). Although the rate of these deaths exceeds that expected to occur in a healthy (nonepileptic) population matched for age and gender, this rate was similar to that occurring in a similar population of epileptic patients not receiving gabapentin. This evidence suggests, but does not prove that the incidence of sudden, unexplained death observed with adjunctive gabapentin therapy may be reflective of the population itself rather than the effects of gabapentin.

Gabapentin can produce drowsiness and dizziness, and patients should be cautioned that the drug may impair their ability to perform hazardous activities requiring mental alertness or physical coordination (e.g., operating machinery, driving a motor vehicle).

Concomitant use of morphine in patients receiving gabapentin may result in increased plasma concentrations of gabapentin. Patients experiencing symptoms of CNS depression such as somnolence may require a decrease in dosage of morphine or gabapentin.

Gabapentin is contraindicated in patients with known hypersensitivity to the drug or any ingredient in the formulation.

■ **Pediatric Precautions** Safety and efficacy of gabapentin as adjunctive therapy in the management of partial seizures in children younger than 3 years of age have not been established. Safety and efficacy of gabapentin in the management of postherpetic neuralgia also have not been established in children.

■ **Geriatric Precautions** Safety and efficacy of gabapentin in the management of partial seizures in geriatric patients have not been evaluated systematically, and clinical trials did not include sufficient numbers of patients 65 years of age and older to determine whether they respond differently than do younger patients. However, in clinical studies of the drug in patients ranging from 20–80 years of age, gabapentin plasma clearance, renal clearance, and renal clearance adjusted for body surface area declined with age. Although safety and efficacy of gabapentin in geriatric patients with postherpetic neuralgia have not been established specifically, 30% of the patients receiving the drug in clinical studies were 65–74 years of age and 50% were 75 years of age and older. In these studies, gabapentin appeared to be more effective for the management of postherpetic neuralgia in patients older than 75 years of age than in younger patients. The manufacturers state that the apparent greater efficacy in geriatric patients may be related to decreased renal function in this age group. Although adverse effects reported in older patients generally were similar to those reported in younger adults, the incidence of peripheral edema and ataxia appears to increase with age. If gabapentin is used in geriatric patients, the initial dosage may need to be reduced and caution should be exercised since renal, hepatic, and cardiovascular dysfunction and concomitant disease or other drug therapy are more common in this age group than in younger patients.

■ **Pregnancy, Fertility, and Lactation** ***Pregnancy*** Although there are no adequate and controlled studies to date in humans, gabapentin has been shown to be teratogenic in mice and rats. Delayed ossification of several bones in the skull, vertebrae, forelimbs, and hindlimbs occurred in mice, and hydroureter and hydronephrosis occurred in rat pups when gabapentin was administered prior to and during mating or during organogenesis in dosages 1–4 times or up to 1–5 times (on a mg/m^2 basis), respectively, the maximum human daily dosage of 3.6 g. The dosage at which these effects did not occur in mice was approximately half the human daily dosage on a mg/m^2 basis. The dosages (on a mg/m^2 basis) at which these effects did not occur in rat pups were those equal to the maximum human daily dosage (in a teratogenicity study) or approximately 3 times the maximum human daily dosage (in a fertility and general reproductive performance study). There also was an increased incidence of postimplantation fetal loss in rabbits receiving gabapentin dosages one-fourth to 8 times the maximum human daily dosage (on a mg/m^2 basis). Other than hydroureter and hydronephrosis, the etiologies of which are unclear, the incidence of malformations was not increased compared with controls in offspring of mice, rats, or rabbits given dosages up to 50 times (mice), 30 times (rats), or 25 times (rabbits) the human daily dosage on a mg/kg basis, or 4 times (mice), 5 times (rats), or 8 times (rabbits) the human daily dosage on a mg/m^2 basis. Gabapentin should be used during pregnancy only when the potential benefits justify the possible risks to the fetus.

Reproduction studies revealed no adverse effects on fertility or reproduction in rats receiving gabapentin dosages up to 5 times the maximum recommended human daily dosage on a mg/m^2 basis.

Lactation Gabapentin is distributed into milk following oral administration. Because of the potential for serious adverse reactions to gabapentin in nursing infants, the drug should be administered to nursing women only if the potential benefits justify the risk to the infant.

Description

Gabapentin is an anticonvulsant agent structurally related to the inhibitory CNS neurotransmitter γ-aminobutyric acid (GABA). Although gabapentin was developed as a structural analog of GABA that would penetrate the blood-brain barrier (unlike GABA) and mimic the action of GABA at inhibitory neuronal synapses, the drug has no direct GABA-mimetic action and its precise mechanism of action has not been elucidated.

Results of some studies in animals indicate that gabapentin protects against seizure and/or tonic extensions induced by the GABA antagonists picrotoxin and bicuculline or by GABA synthesis inhibitors (e.g., 3-mercaptopropionic acid, isonicotinic acid, semicarbazide). However, gabapentin does not appear to bind to GABA receptors nor affect GABA reuptake or metabolism and does not act as a precursor of GABA or of other substances active at GABA receptors. Gabapentin also has no affinity for binding sites on common neuroreceptors (e.g., benzodiazepine; glutamate; quisqualate; kainate; strychnine-insensitive or -sensitive glycine; α_1-, α_2-, or β-adrenergic; adenosine A_1 or A_2; cholinergic [muscarinic or nicotinic]; dopamine D_1 or D_2; histamine H_1; type 1 or 2 serotonergic [5-HT_1 or 5-HT_2]; opiate μ, δ, or κ) or ion channels (e.g., voltage-sensitive calcium channel sites labeled with nitrendipine or diltiazem, voltage-sensitive sodium channel sites labeled with batrachotoxinin A 20α-benzoate). Conflicting results have been reported in studies of gabapentin affinity for and activity at *N*-methyl-d-aspartic acid (NMDA) receptors. Although

in vitro studies have identified a novel gabapentin binding site in the neocortex and hippocampus of rat brain, additional studies are required to fully elucidate the identity and function of this binding site.

In animal test systems, gabapentin exhibits anticonvulsant activity similar to that of other commonly used anticonvulsant drugs. The drug protects against seizures induced in animals by electrical stimulation or pentylenetetrazole, suggesting that it may be effective in the management of tonic-clonic (grand mal) and partial seizures or absence (petit mal) seizures, respectively. However, available data in animals and humans are conflicting regarding the effect of gabapentin on EEG spike and wave activity associated with absence (petit mal) seizures. Gabapentin also prevents seizures in some animals with congenital epilepsy and protects against audiogenic tonic extensions and clonic seizures in mice.

Although the mechanism of action is unknown as yet, gabapentin also has demonstrated analgesic activity. In animals, gabapentin has been shown to prevent allodynia (pain-related behavior in response to normally innocuous stimuli) and hyperalgesia (exaggerated response to painful stimuli) in several models of neuropathic pain. Gabapentin also has been shown to decrease pain-related responses after peripheral inflammation in animals; however, the drug has not altered immediate pain-related behaviors. The clinical relevance of these findings is not known.

Gabapentin does not bind to plasma proteins, is not appreciably metabolized, does not induce hepatic enzyme activity, and does not appear to alter the pharmacokinetics of commonly used anticonvulsant drugs (e.g., carbamazepine, phenytoin, valproate, phenobarbital, diazepam) or oral contraceptives. In addition, the pharmacokinetics of gabapentin are not altered substantially by concomitant administration of other anticonvulsant drugs.

Children younger than 5 years of age have a higher clearance of gabapentin normalized for weight compared with those 5 years of age and older; clearance of the drug in children 5 years of age and older is consistent with that in adults after a single dose. Therefore, a higher daily dosage is required in children 3–5 years of age to achieve average plasma concentrations similar to those in patients 5 years of age and older. (See Dosage and Administration: Dosage.) Infants younger than 1 year of age have a highly variable clearance.

SumMon‡ (see Users Guide). For additional information on this drug until a more detailed monograph is developed and published, the manufacturer's labeling should be consulted. It is *essential* that the labeling be consulted for detailed information on the usual cautions, precautions, and contraindications concerning potential drug interactions and/or laboratory test interferences and for information on acute toxicity.

Preparations

Excipients in commercially available drug preparations may have clinically important effects in some individuals; consult specific product labeling for details.

Gabapentin

Oral		
Capsules	100 mg*	**Gabapentin Capsules** **Neurontin®, Pfizer**
	300 mg*	**Gabapentin Capsules** **Neurontin®, Pfizer**
	400 mg*	**Gabapentin Capsules** **Neurontin®, Pfizer**
Solution	250 mg/5 mL	**Neurontin®, Pfizer**
Tablets	100 mg*	**Gabapentin Tablets**
	300 mg*	**Gabapentin Tablets**
	400 mg*	**Gabapentin Tablets**
	600 mg*	**Gabapentin Tablets**
	800 mg*	**Gabapentin Tablets**
Tablets, film-coated	600 mg*	**Gabapentin Tablets** **Neurontin®, Pfizer**
	800 mg*	**Gabapentin Tablets** **Neurontin®, Pfizer**

*available from one or more manufacturer, distributor, and/or repackager by generic (nonproprietary) name
‡Use is not currently included in the labeling approved by the US Food and Drug Administration

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Lamotrigine

■ Lamotrigine is a phenyltriazine anticonvulsant.

Uses

■ **Seizure Disorders** ***Partial Seizures*** Lamotrigine is used in combination with other anticonvulsant agents in the management of partial seizures in adults and children. Lamotrigine also is used as monotherapy in patients converting from monotherapy with a hepatic enzyme-inducing anticonvulsant agent (e.g., phenytoin, carbamazepine, phenobarbital, primidone) in the management of partial seizures in adults.

In controlled clinical studies, adjunctive therapy with lamotrigine was effective in reducing seizure frequency in patients with simple and/or complex partial seizures refractory to therapy with one or more conventional anticonvulsant drugs (e.g., phenytoin, carbamazepine, phenobarbital); the median reduction in seizure frequency was 24–36%. In a controlled clinical study in children 2–16 years of age with partial seizures, the median reduction in frequency of all partial seizures was 36 or 7% in patients receiving lamotrigine or placebo, respectively, in addition to their current therapy (up to 2 conventional anticonvulsant drugs).

The effectiveness of lamotrigine monotherapy in adults with partial seizures who are converting from monotherapy with a hepatic enzyme-inducing anticonvulsant drug (e.g., phenytoin, carbamazepine, phenobarbital, primidone) was established in a controlled clinical study of patients who experienced at least 4 simple or complex partial seizures, with or without secondary generalization, during each of 2 consecutive 4-week baseline periods; during the baseline periods, patients were receiving either phenytoin or carbamazepine monotherapy. Patients were randomized either to lamotrigine (target dose: 500 mg daily) or valproic acid (1000 mg daily) therapy, which was added to their baseline regimen over a 4-week period. Patients were then converted to either lamotrigine or valproic acid monotherapy over another 4-week period and monotherapy continued for another 12-week period. Study end points were either successful completion of the 12-week monotherapy period or meeting a study "escape" criterion, relative to baseline. Escape criteria were defined as doubling of the mean monthly seizure count; doubling of the highest consecutive 2-day seizure frequency; emergence of a new seizure type (defined as a seizure that did not occur during the 8-week baseline period) that was more severe than the other seizure types occurring during the study period; or clinically important prolongation of generalized tonic-clonic seizures. The proportion of lamotrigine- or valproic acid-treated patients meeting escape criteria was 42 or 69%, respectively; no differences in efficacy were detected based on age, race, or gender. It was noted that the patients in the valproic acid control arm were treated intentionally with a relatively low valproic acid dosage because the intent of the study was to establish the effectiveness of lamotrigine monotherapy, and that the study results cannot be interpreted to imply the superiority of lamotrigine therapy to adequate valproic acid therapy. In addition, the manufacturer states that the use of lamotrigine therapy for the management of partial seizures has not been established as initial monotherapy; for conversion from monotherapy with anticonvulsant drugs that do *not* induce hepatic enzymes (e.g., valproate); or for simultaneous conversion to monotherapy from 2 or more concomitant anticonvulsant drugs.

Primary Generalized Tonic-Clonic Seizures Lamotrigine is used in combination with other anticonvulsant agents in the management of primary generalized tonic-clonic seizures in adults and children 2 years of age and older. Efficacy of the drug as adjunctive therapy was established in a placebo-controlled trial in adult and pediatric patients at least 2 years of age who had experienced at least 3 primary generalized tonic-clonic seizures during an 8-week baseline phase. Patients were randomized to receive either placebo or lamotrigine in a fixed-dose regimen (target dosages of 200–400 mg daily in adults and 3–12 mg/kg daily in children) for 19–24 weeks, which was added to their current anticonvulsant regimen of up to 2 anticonvulsant drugs. Patients receiving lamotrigine experienced a substantially greater median reduction in seizure frequency compared with baseline than did patients receiving placebo (66 and 34%, respectively).

Seizures Associated with Lennox-Gastaut Syndrome Lamotrigine also is used in combination with other anticonvulsant agents in the management of generalized seizures associated with Lennox-Gastaut syndrome in pediatric patients and adults. In a controlled clinical trial in patients with Lennox-Gastaut syndrome, adjunctive therapy with lamotrigine resulted in a 32, 34, and 36% decrease in major motor seizures, drop attacks, and tonic-clonic seizures, respectively.

■ **Bipolar Disorder** Lamotrigine is used in the maintenance therapy of bipolar I disorder to prevent or attenuate recurrences of bipolar episodes in patients who remain at high risk of relapse following treatment of an acute depressive or manic episode. The American Psychiatric Association (APA) currently recommends use of lamotrigine as an alternative to first-line maintenance therapies (e.g., lithium, valproic acid, or divalproex). The APA also states that both lamotrigine and lithium are effective in the maintenance treatment of bipolar I disorder; however, the results of two randomized, double-blind, placebo-controlled studies of 18 months' duration indicate that lamotrigine may be more effective in preventing depressive episodes while lithium may be more effective in preventing manic episodes.

Although efficacy of the drug in the acute treatment of mood episodes has yet to be fully established, lamotrigine is considered a first-line agent by the APA for the management of acute depressive episodes in patients with bipolar disorder†. The APA also recommends the use of lamotrigine as an alternative to lithium, valproic acid, or divalproex in the management of patients with rapid cycling bipolar disorder†, particularly in those with the bipolar 2 form of rapid cycling.

For further information on the management of bipolar disorder, see Uses: Bipolar Disorder, in Lithium Salts 28:28.

Preparations

Excipients in commercially available drug preparations may have clinically important effects in some individuals; consult specific product labeling for details.

Molindone Hydrochloride

Oral		
Tablets	5 mg	Moban*, Endo
	10 mg	Moban*, Endo
	25 mg	Moban*, Endo
	50 mg	Moban*, Endo

†Use is not currently included in the labeling approved by the US Food and Drug Administration

Pimozide

■ Pimozide is a diphenylbutylpiperidine-derivative antipsychotic agent. The drug is considered a conventional or first-generation antipsychotic agent.

Uses

■ **Tourette's Syndrome** Pimozide is used for suppression of motor and vocal tics of Tourette's syndrome (Gilles de la Tourette's syndrome).

Pimozide has been used concomitantly with a stimulant in children with tic disorders (e.g., Tourette's syndrome) and comorbid attention deficit hyperactivity disorder (ADHD)† in whom stimulants alone cannot control tics.

Overview Tourette's syndrome is a neurologic genetic disorder with a spectrum of neurobehavioral manifestations that may vary with time and fluctuate in severity and frequency of symptoms during the natural course of the disease. The diagnosis of Tourette's syndrome usually is based on a history and observation of tics often accompanied by behavioral disorders (e.g., ADHD, obsessive-compulsive disorder). Tics may be sudden, brief, intermittent, involuntary, or semivoluntary movements (motor tics) or sounds (phonic or vocal tics). For a diagnosis of Tourette's syndrome, the criteria established by the Tourette Syndrome Classification Study Group may be used. According to this classification, both multiple motor tics and one or more phonic tics must be present at some time during the disease (although not necessarily concurrently), and such tics must occur many times a day and nearly every day, or intermittently, throughout a period of more than 1 year. Motor and phonic tics must be witnessed directly by a reliable examiner some time during the disease or be recorded by video or cinematography. In addition, anatomical location, number, frequency, type, complexity, or severity of tics must undergo a change over time. Involuntary movements and sounds must not be explained by a medical condition other than Tourette's syndrome. Although the onset of the syndrome must occur in patients younger than 21 years of age, in most patients the disease is manifested by 11 years of age, usually beginning in children 2–15 years old. Generally, tics become more severe when patients reach the age of 10 years, and 50% of patients are free from tics by the time they reach the age of 18 years. Severity of tics usually decreases when reaching adulthood. These and other diagnostic criteria are designed to assist clinicians in reaching an accurate diagnosis (e.g., differentiating Tourette's syndrome from other tic disorders) and those investigating the genetic factors associated with the syndrome.

Therapeutic Considerations Initially, management of Tourette's syndrome should include proper education of patients, family members, and teachers in order to provide a proper environment (at home and in school) for children with the disease. Drug therapy usually is considered when symptoms of the disorder begin to interfere with the patient's activities of daily living (e.g., work, school, social activities). Because Tourette's syndrome is associated with a wide variety of neurologic and behavioral manifestations, drug therapy should be individualized and the most severe symptoms should be treated first. The goal in the management of ties is to relieve tic-related discomfort and embarrassment and to achieve a degree of control of tics that allows the patient to function as normally as possible. Dopamine receptor blocking agents are considered the most effective drugs for the management of tics, although only haloperidol and pimozide are approved by the US Food and Drug Administration (FDA) for the treatment of Tourette's syndrome. Haloperidol generally has been considered the drug of choice for the management of Tourette's syndrome and pimozide has been an effective alternative in some patients who have had an inadequate response to or did not tolerate haloperidol. Limited data suggest that pimozide may be more effective than haloperidol in reducing tics. Some clinicians, however, prefer other antipsychotic drugs including molindone, phenothiazines (e.g., fluphenazine, thioridazine, trifluoperazine), risperidone, thiothixene, or tiapride (not commercially available in the US). It is not known whether some other atypical antipsychotics (e.g., clozapine, olanzapine, quetiapine) are effective in the management of tics or other symptoms of Tourette's syndrome; however, limited data indicate that ziprasidone may decrease the severity of tics. Tetrabenazine (not commercially available in the US), a drug that interferes with monoamine neurotransmitters and blocks dopamine receptors, has been effective for the management of tics and, unlike conventional antipsychotic agents, tetrabenazine does not appear to cause tardive dyskinesia. Although several other drugs (e.g., cannabinoids, clonazepam, pergolide, nicotine gum, nicotine transdermal system) have been shown to be effective in the management of tics, these agents have not been evaluated in well-designed, controlled studies. Focal motor and vocal ties have responded to injections of botulinum toxin in the affected muscles.

Pimozide is considered an orphan drug and is used for suppression of motor and vocal tics of Tourette's syndrome (Gilles de la Tourette's syndrome) in children and adults. The drug usually should be reserved for the treatment of those patients with Tourette's syndrome who have an inadequate response to, or who do not tolerate, conventional therapy (e.g., haloperidol) and whose development and/or daily life function is severely compromised by the presence of motor and vocal tics. Pimozide usually is *not* intended as a treatment of first choice for this syndrome, *nor* is it intended for suppression of tics that are only annoying or cosmetically troublesome.

Controlled studies in patients with Tourette's syndrome have shown that pimozide is effective in reducing the number of stimulated and unstimulated motor and vocal tics and the severity of associated symptomatology. Results of several studies suggest that pimozide is at least as effective as haloperidol in the management of Tourette's syndrome and may be associated with fewer and possibly less severe adverse effects, particularly sedation, in some patients. The long-term safety of pimozide in the management of this syndrome, however, remains to be determined, and additional well-controlled studies comparing pimozide and haloperidol are needed to assess their relative efficacy and safety. Haloperidol generally has been considered the drug of choice for the management of Tourette's syndrome, and pimozide has been an effective alternative in some patients who have an inadequate response to or do not tolerate haloperidol. Because limited data suggest that pimozide may be more effective than haloperidol in reducing tics and pimozide appears to be better tolerated than haloperidol, some clinicians and experts prefer the use of pimozide in patients with Tourette's syndrome. Limited data suggest that pimozide may be more effective than clonidine and that pimozide and penfluridol (not commercially available in the US) may have comparable efficacy in the management of Tourette's syndrome. Well-controlled clinical studies comparing the efficacy and safety of pimozide and other agents used in the management of Tourette's syndrome are needed.

Comorbid Conditions Patients with Tourette's syndrome often exhibit comorbid conditions (e.g., ADHD, obsessive-compulsive disorder). Although CNS stimulants, including amphetamines, have been reported to exacerbate motor and vocal tics in patients with Tourette's syndrome, results of several studies indicate that stimulants are effective in the management of ADHD in patients with Tourette's syndrome and the rate of tics is not increased in the majority of patients. In patients in whom the rate of tics increases, some experts recommend addition of an α-adrenergic agonist (e.g., clonidine, guanfacine), risperidone, pimozide, or haloperidol. Clonidine or guanfacine have been used in the management of ADHD. Although less effective than stimulants, clonidine and guanfacine do not increase the frequency or severity of tics. Tricyclic antidepressants (e.g., imipramine, nortriptyline) also may be used for the treatment of mild cases of ADHD and concomitant tics or Tourette's syndrome in patients who do not respond to or otherwise do not tolerate stimulants, in whom tics are exacerbated by stimulants, or those who develop clinically important depression.

In addition, there is a high incidence of obsessive-compulsive disorder in patients with Tourette's syndrome. Many clinicians recommend that patients with Tourette's syndrome and coexisting obsessive-compulsive disorder receive therapy with a selective serotonin-reuptake inhibitor or a selective serotonin- and norepinephrine-reuptake inhibitor (e.g., citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, venlafaxine) alone or, if needed, in combination with buspirone, clonazepam, lithium, or a dopamine receptor antagonist. In a limited number of patients, other drugs (e.g., clomipramine, risperidone) also have been effective in the management of this comorbid condition.

■ **Schizophrenia** Pimozide has been used for the symptomatic management of a variety of psychiatric illnesses†, principally schizophrenia†, but other agents generally are preferred.

Pimozide appears to be as effective as phenothiazines or haloperidol for the symptomatic management of schizophrenia†. The drug is effective in reducing hallucinations, thought disorders, change in affect, and autism. Pimozide also appears to be effective for the management of social adjustment problems, emotional withdrawal, motor retardation, apathy, and conceptual disorganization. Delusions, bizarre mannerisms, chronic paranoia, anxiety, guilt feelings, disorientation, and hostility also may be reduced during therapy with the drug. Pimozide should *not* be used for the management of schizophrenia in patients whose main manifestations include excitement, agitation, or hyperactivity, because the efficacy of the drug in these patients has not been established.

Pimozide also has been used for the symptomatic management of acute schizophrenic episodes†. Results of initial clinical studies were not encouraging, but subsequent uncontrolled clinical studies suggest that pimozide may be effective in the management of acute schizophrenic episodes when used at dosages substantially higher than those used for the management of schizophrenia. Limited data suggest that high-dose pimozide therapy may be as effective as haloperidol or phenothiazines; however, the frequency and severity of pimozide-induced extrapyramidal reactions are increased at high dosages. Pimozide currently is *not* recommended for the management of acute schizo-

phrenic episodes. For further information on the symptomatic management of schizophrenia, see Uses: Psychotic Disorders, in the Phenothiazines General Statement 28:16.08.24.

■ **Mania** Pimozide has been used for the management of manic episodes† (mania) in patients with major affective disorders. Although limited data suggest that pimozide may be as effective as phenothiazines, the efficacy of the drug has not been clearly established, and pimozide currently is *not* recommended for the management of manic episodes.

■ **Behavioral Disorders** The efficacy of pimozide for the management of behavioral disorders in patients with mental retardation has not been established, but limited data suggest that the drug may reduce irritability, anxiety, and hyperactivity and improve social behavior in mentally retarded adolescents, without substantially affecting cognition or learning performance. Further controlled studies are needed.

■ **Dyskinesias** Pimozide has been used for the management of various dyskinesias†, including chronic progressive hereditary chorea (Huntington's chorea), acute chorea (Sydenham's chorea), tardive dyskinesia, and tardive dystonia; however, the usefulness of the drug for the management of dyskinesias is questionable because it has both dyskinesia-ulleviating and dyskinesia-producing properties. Because pimozide tends to worsen parkinsonian symptoms, the drug should not be used for the management of levodopa-induced dyskinesias in patients with parkinsonian syndrome.

■ **Other Uses** Results of uncontrolled clinical studies suggest that pimozide may be useful for the management of phencyclidine-induced psychosis† or various personality disorders† (e.g., paranoid, schizoid, compulsive). Pimozide also has reportedly been beneficial in some patients for the management of pathologic jealousy†, erotomania†, and monosymptomatic hypochondriacal psychosis†, including delusions of parasitosis.

Although pimozide has been used in the treatment of anorexia nervosa†, use of the drug for this purpose does not appear to provide substantial benefit.

Dosage and Administration

■ **Administration** Pimozide is administered orally. The drug may usually be administered once daily but also may be given in divided doses, particularly if once-daily dosing is not well tolerated. Some clinicians recommend administration of the drug as a single dose at bedtime to minimize adverse effects.

■ **Dosage** When pimozide is used for suppression of motor and vocal tics in patients with Tourette's syndrome, the initial dosage of the drug should be low and dosage adjustments should be made gradually. Dosage of pimozide must be carefully adjusted to balance symptomatic relief and the suppression of tics against the adverse effects of the drug. Patients receiving pimozide should have an ECG performed before therapy with the drug is initiated and periodically thereafter, particularly during the period of dosage adjustment. (See Cautions: Precautions and Contraindications.)

Adult Dosage For the suppression of motor and vocal tics in adults with Tourette's syndrome, the usual initial dosage of pimozide is 1–2 mg daily. The manufacturer and some clinicians state that dosage may be increased every other day according to the patient's tolerance and therapeutic response. Because of pimozide's prolonged elimination half-life, other clinicians suggest that dosage be increased at longer intervals (e.g., every 5–7 days) until signs and symptoms of the disorder decrease by at least 70%, adverse effects occur without symptomatic benefit, or symptomatic benefit and adverse effects occur at the same time. If adverse effects are minimal and do not interfere with functioning (e.g., dry mouth, slight sedation) but adequate response has not been achieved, dosage should not be increased further until these adverse effects resolve. If adverse effects interfere with functioning but are not severe, dosage can be reduced by 1-mg increments at weekly intervals until such effects resolve. Dosage should be reduced by 50% immediately or the drug withheld if severe adverse effects occur. (See Cautions: Precautions and Contraindications.) Once serious adverse effects resolve, therapy can be reinstituted with more gradual titration, increasing dosage at intervals ranging from 7–30 days. Most patients are adequately treated with dosages less than 0.2 mg/kg daily or 10 mg daily, whichever is less, and the manufacturer recommends that these dosages not be exceeded.

Pediatric Dosage For the suppression of motor and vocal tics in children with Tourette's syndrome, the usual initial dosage of pimozide is 0.05 mg/kg daily, preferably at bedtime. The dose may be increased every third day to a maximum of 0.2 mg/kg or 10 mg per day. Reliable dose-response data for the effects of the drug on tic manifestations in children younger than 12 years of age are not available.

Dosage of pimozide during prolonged maintenance therapy should be kept at the lowest possible effective level. Once an adequate response has been achieved, periodic attempts (e.g., every 6–12 months) should be made to reduce dosage of the drug to determine whether the initial intensity and frequency of tics persist. When attempting to reduce the dosage of pimozide, consideration should be given to the possibility that observed increases of tic intensity and frequency may represent a transient, withdrawal-related phenomenon rather than a return of the syndrome's symptoms. Before concluding that an increase in tic manifestations is a function of the underlying disorder rather than a response to drug withdrawal, at least 1–2 weeks should be allowed to elapse. If pimozide therapy is to be discontinued, dosage of the drug should be gradually reduced.

Cautions

■ **Nervous System Effects** The most frequent and potentially severe adverse effects of pimozide involve the CNS.

Extrapyramidal Reactions Extrapyramidal reactions occur frequently with pimozide, especially during the first few days of therapy. In most patients, these reactions consist of parkinsonian symptoms (e.g., tremor, rigidity, akinesia) that are mild to moderate in severity and usually reversible following discontinuance of the drug. Dystonic reactions and feelings of motor restlessness (i.e., akathisia) occur less frequently. Generally, the occurrence and severity of most extrapyramidal reactions are dose related because they occur at relatively high dosages and disappear or become less severe following a reduction in dosage; however, severe extrapyramidal reactions have reportedly occurred at relatively low dosages. Extrapyramidal reactions appear to occur in about 10–15% of patients receiving usual dosages of pimozide. Administration of anticholinergic antiparkinsonian agents (e.g., benztropine, trihexyphenidyl) or diphenhydramine may be necessary to control parkinsonian extrapyramidal reactions. If persistent extrapyramidal reactions occur, pimozide therapy may have to be discontinued.

The most common dystonic reaction is torticollis, which generally is accompanied by orofacial symptoms and, in some instances, oculogyric crisis, as well as spasms of the face, tongue, and jaw. Dyskinesias of the mouth and throat areas, trismus, dysarthria, muscle cramps, and athetoid movements have occurred occasionally.

Akathisia occurs relatively frequently in patients receiving pimozide, but usually can be managed by reducing the dosage of pimozide or by concomitant administration of an anticholinergic antiparkinsonian agent, diphenhydramine, a benzodiazepine, or propranolol.

Like other antipsychotic agents, pimozide has been associated with neuroleptic malignant syndrome (NMS), a potentially fatal syndrome requiring immediate discontinuance of the drug and intensive symptomatic treatment. For additional information on NMS, see Extrapyramidal Reactions in Cautions: Nervous System Effects, in the Phenothiazines General Statement 28:16.08.24.

Tardive Dyskinesia Like other antipsychotic agents, pimozide has been associated with persistent dyskinesias. Tardive dyskinesia may occur in some patients during long-term administration of pimozide or possibly following discontinuance of the drug. The risk of developing tardive dyskinesia appears to be greater in geriatric patients receiving high dosages of the drug, especially females. The symptoms are persistent and in some patients appear to be irreversible. Tardive dyskinesia is characterized by rhythmic involuntary movements of the tongue, face, mouth, or jaw (e.g., protrusion of the tongue, puffing of cheeks, chewing movements, puckering of the mouth), which sometimes may be accompanied by involuntary movements of the extremities and trunk. Although not clearly established, the risk of developing the syndrome and the likelihood that it will become irreversible may increase with the duration of therapy and total cumulative dose of antipsychotic agent(s) administered; however, the syndrome may occur, although much less frequently, after relatively short periods of treatment with low dosages. There is no proven or uniformly effective treatment for tardive dyskinesia; anticholinergic antiparkinsonian agents do not alleviate and often exacerbate the symptoms of this syndrome. If possible, antipsychotic agents should be discontinued if signs or symptoms of tardive dyskinesia occur. The syndrome may partially or completely remit if antipsychotic agents are discontinued, although some patients may require many months for improvement. Tardive dyskinesia may be masked if therapy is reinstituted, dosage is increased, or therapy with another antipsychotic agent is initiated. The effect that masking of the symptoms may have on the long-term course of the syndrome is not known. Fine vermicular movement of the tongue may be an early sign of tardive dyskinesia; prompt discontinuance of pimozide after this sign occurs may prevent development of the syndrome.

In general, abrupt withdrawal of antipsychotic agents following short-term administration is not associated with adverse effects; however, transient dyskinetic signs have occurred following abrupt withdrawal in some patients receiving maintenance therapy. In some of these patients, the dyskinetic movements are indistinguishable, except on the basis of duration, from persistent tardive dyskinesia. It is not known whether gradual withdrawal of antipsychotic agents reduces the incidence of withdrawal-emergent neurologic signs; however, if pimozide therapy must be discontinued, gradual withdrawal of the drug is recommended, if possible, pending further accumulation of data.

Other Nervous System Effects Pimozide is generally considered to be relatively nonsedating compared with other antipsychotic agents, but sedation, lethargy, and/or drowsiness appear to be the most common adverse effects of the drug in patients with Tourette's syndrome. Other adverse nervous system effects of pimozide include insomnia, dizziness, excitement, agitation, nervousness, fainting, aggressiveness, irritability, anxiety, tension, headache, depression, decreased attentiveness, confusion, nightmares, hallucinations, phobia, impaired motivation, speech disorder, handwriting change, fatigue, weakness, transient affective disturbance, and aggravation of psychotic symptomatology. Rarely, pimozide has been associated with seizures, including tonic-clonic (grand mal) seizures, in patients without a previous history of seizure disorder.

Adverse anticholinergic effects of pimozide include dry mouth, blurred vision, difficulty with accommodation, urinary retention, constipation, and urinary and fecal incontinence.

■ **Cardiovascular Effects** Various ECG changes, such as prolongation of the QT (including QT_c) interval; flattening, notching, and inversion of the T wave; and appearance of U waves, have occurred in some patients receiving pimozide. The clinical importance of pimozide-induced ECG changes has not been clearly established, but some clinicians believe that the changes are comparable to those induced by phenothiazines. Sudden, unexpected deaths have occurred in some patients receiving high doses of the drug (i.e., exceeding 10 mg; in the range of 1 mg/kg) for conditions other than Tourette's syndrome or in patients receiving concomitant pimozide and clarithromycin. (See Drug Interactions: Drugs and Foods Affecting Hepatic Microsomal Enzymes.) A possible mechanism for these deaths is prolongation of the QT interval, predisposing the patients to ventricular arrhythmia. Patients receiving pimozide should have ECG evaluations before and periodically during therapy with the drug. (See Cautions: Precautions and Contraindications.)

Pimozide rarely may produce hypotension, orthostatic hypotension, hypertension, tachycardia, or palpitations. In some patients, particularly geriatric or debilitated patients, transient hypotension for several hours after administration of the drug has occurred.

■ **Endocrine and Metabolic Effects** Amenorrhea, dysmenorrhea, and mild galactorrhea have occurred in some patients receiving pimozide. Like other antipsychotic agents, pimozide increases serum prolactin concentrations. (See Cautions: Mutagenicity and Carcinogenicity.) Loss of libido, impotence, and weight gain or, more frequently, weight loss, has occurred in patients receiving pimozide.

■ **GI Effects** Adverse GI effects of pimozide include increased salivation, nausea, vomiting, anorexia, GI distress, diarrhea, constipation, and abdominal cramps or pain. Thirst, altered taste, gingival hyperplasia, and increased appetite also have been reported.

■ **Other Adverse Effects** Rash, urticaria, skin irritation, facial edema (may be severe), periorbital edema, sweating, cataracts, visual disturbances or sensitivity to light, chest pain, nocturia, and urinary frequency have been reported in patients receiving pimozide. Hemolytic anemia also has occurred in pimozide-treated patients, although a causal relationship to the drug has not been established. Hyponatremia has occurred in patients receiving the drug following marketing approval.

The possibility that pimozide may cause other adverse effects reported with other antipsychotic agents should be considered. In addition, because clinical experience with pimozide for the management of Tourette's syndrome is limited, uncommon adverse effects may not have been detected to date.

■ **Precautions and Contraindications** Pimozide shares the toxic potentials of other antipsychotic agents (e.g., phenothiazines, butyrophenones), and the usual precautions associated with therapy with these agents should be observed. (See Cautions in the Phenothiazines General Statement 28:16.08.24.) Because treatment with pimozide exposes the patient to potentially serious risks, the decision to use the drug for the long-term management of Tourette's syndrome should be carefully considered by the patient (and/or the patient's family or guardians) and the physician. The use of pimozide for the management of Tourette's syndrome involves different considerations of risks and benefits than the use of other antipsychotic agents for other conditions. Because the goal of treatment is symptomatic improvement, the patient's view of the need for treatment and assessment of response are critical in evaluating the relative benefits and risks of pimozide therapy. Patients should be informed that pimozide has an adverse effect profile similar to that of other antipsychotic agents and that adverse effects associated with these agents may occur with pimozide.

Geriatric patients with dementia-related psychosis treated with either conventional (first-generation) or atypical (second-generation) antipsychotic agents are at an increased risk of mortality. For additional information on the use of antipsychotic agents for dementia-associated psychosis and other behavioral disturbances, see Geriatric Considerations under Psychotic Disorders: Schizophrenia and Other Psychotic Disorders, in Uses and see also Cautions: Geriatric Precautions, in the Phenothiazines General Statement 28:16.08.24.

Because of the likelihood that a proportion of patients receiving long-term therapy with an antipsychotic agent will develop tardive dyskinesia, patients in whom long-term pimozide therapy is considered should be fully informed, if possible, about the risk of developing this syndrome. The decision to inform the patient (and/or the patient's family or guardians) should take into account the clinical circumstances and the competency of the patient to understand the information. Because of the risk of tardive dyskinesia, long-term pimozide therapy should generally be reserved for patients whose syndrome is responsive to the drug and for whom alternative, equally effective, but potentially less toxic therapy is not available or appropriate. In patients requiring long-term treatment, the smallest effective dosage and shortest duration of therapy producing an adequate clinical response should be employed. Patients receiving pimozide should be evaluated periodically to determine whether maintenance dosage could be decreased or the drug discontinued.

Because sudden, unexpected deaths, which may be related to an effect of pimozide on the heart, have occurred in some patients receiving high doses of the drug (i.e., exceeding 10 mg; in the range of 1 mg/kg) for conditions other than Tourette's syndrome, an ECG should be performed before pimozide therapy is initiated and periodically thereafter, particularly during the period of dosage adjustment. Some clinicians recommend that a cardiologist be consulted before initiating therapy with the drug in patients with a baseline QT_c interval exceeding 440 ms. Patients should be instructed *not* to exceed the prescribed dosage and should be aware of the need for the initial ECG and follow-up ECGs during pimozide therapy. Prolongation of the QT_c interval (QT interval corrected for rate) to greater than 470 ms in children or 520 ms in adults, or more than 25% beyond the patient's pretreatment value, or the development of other T-wave abnormalities should be considered a basis for stopping further dosage increases and considering a dosage reduction. Dosage reduction also should be considered if bradycardia (less than 50 bpm) occurs. Some clinicians recommend that pimozide be withheld if T-wave inversion, U waves, or cardiac arrhythmia occurs and reinstituted only after ECG findings are normal. Because pimozide may cause ECG changes, the drug should be used with caution in patients with cardiovascular disorders. Because hypokalemia has been associated with ventricular arrhythmias, potassium insufficiency secondary to diuretics, diarrhea, or other causes should be corrected before pimozide therapy is initiated, and normal serum potassium concentrations should be maintained during pimozide therapy.

The clinical importance is not known, but pimozide has produced a dose-related increase in benign pituitary tumors in female mice. (See Cautions: Mutagenicity and Carcinogenicity.) The tumorigenic potential of pimozide should be given careful consideration by the patient and physician in the decision to use the drug, especially if the patient is young and long-term therapy is anticipated.

Patients should be warned that pimozide may impair their ability to perform activities requiring mental alertness or physical coordination (e.g., operating machinery, driving a motor vehicle), especially during the first few days of therapy.

Because pimozide produces adverse anticholinergic effects, the drug should be used with caution in individuals whose conditions may be aggravated by anticholinergic activity.

Like other antipsychotic agents, pimozide should be used with caution in patients receiving anticonvulsant agents and in those with EEG abnormalities or a history of seizures because the drug may lower the seizure threshold. If necessary, adequate anticonvulsant therapy should be maintained during pimozide therapy.

Pimozide should be used with caution in patients with hepatic or renal impairment.

Because pimozide has an antiemetic effect, the drug should be used with caution when suppression of nausea and vomiting might obscure diagnosis of an underlying physical disorder.

Because increased plasma concentrations of pimozide have occurred following concomitant use of pimozide and sertraline, the manufacturers of pimozide and sertraline state that concomitant use of the drugs is contraindicated. In addition, increased plasma pimozide concentrations were observed during concurrent use with paroxetine. The manufacturers of paroxetine state that concomitant use of these drugs is contraindicated because of the narrow therapeutic index of pimozide and its known ability to prolong the QT interval. Because of the risk of QT-interval prolongation, the manufacturer of citalopram hydrobromide and escitalopram oxalate states that concurrent use of either of these drugs with pimozide is contraindicated. Concurrent use of pimozide and fluoxetine also is contraindicated because of the potential for adverse drug interactions or QT_c prolongation. In addition, fluvoxamine should not be used concurrently with pimozide. (See Drug Interactions: Selective Serotonin-reuptake Inhibitors.)

Because pimozide prolongs the QT interval, the drug also is contraindicated in patients with congenital long QT syndrome or a history of cardiac arrhythmias, and in patients receiving other drugs that prolong the QT interval or that inhibit the metabolism of pimozide by inhibiting the cytochrome P-450 (CYP) 3A4 isoenzyme such as macrolide antibiotics (e.g., clarithromycin, erythromycin, azithromycin, dirithromycin, troleandomycin), azole antifungal agents (e.g., itraconazole, ketoconazole), protease inhibitors (e.g., ritonavir, saquinavir, indinavir, nelfinavir), nefazodone, or zileuton. (See Drug Interactions: Drugs That Prolong the QT Interval, and Drugs and Foods Affecting Hepatic Microsomal Enzymes.)

Pimozide is contraindicated in the treatment of simple tics or tics other than those associated with Tourette's syndrome. Pimozide should not be used in patients receiving drugs that may cause motor and vocal tics (e.g., pemoline [no longer commercially available in the US], methylphenidate, amphetamines) until such drugs have been withdrawn to determine whether the drugs or Tourette's syndrome is responsible for the tics.

Pimozide is contraindicated in patients with known hypokalemia or hypomagnesemia.

Pimozide is contraindicated in patients with severe toxic CNS depression or in those who are comatose from any cause; patients with blood dyscrasias, depressive disorders, or parkinsonian syndrome; and in patients who are hypersensitive to the drug. It is not known whether cross-sensitivity exists among antipsychotic agents; however, pimozide should be used with particular caution in patients with known hypersensitivity to other antipsychotic agents.

■ **Pediatric Precautions** The onset of Tourette's syndrome usually occurs between the ages of 2 and 15 years, but data on the use and efficacy of pimozide in children younger than 12 years of age are limited. Further study is needed to fully evaluate the use and efficacy of the drug for Tourette's syndrome in this age group. Limited clinical evidence suggests that the safety profile of pimozide in children aged 2–12 years generally is comparable to that observed in older patients. Safety and efficacy of pimozide for the management

of other conditions in children have not been evaluated, and use of the drug in children for any condition other than Tourette's syndrome is *not* recommended.

■ **Mutagenicity and Carcinogenicity** No evidence of pimozide-induced mutagenesis was seen in the Ames microbial mutagen test, the micronucleus test in rats, or the dominant lethal assay in mice.

No evidence of carcinogenesis was seen in rats receiving oral pimozide dosages up to 50 times the maximum recommended human dosage for 2 years; however, because of the limited number of rats surviving the study, the meaning of the results is unclear. Reversible gingival hyperplasia has occurred in dogs receiving oral pimozide dosages greater than 1.5 mg/kg daily (about 5 times the maximum recommended human dosage) for 12 months, and has occurred in at least one patient receiving the drug following marketing approval. Following oral administration of pimozide 0.62, 5, or 40 mg/kg daily for 18 months in mice, dose-related increases in the incidence of pituitary adenomas and mammary gland adenocarcinomas were observed in females. Pituitary changes at a dosage of 0.62 mg/kg daily were characterized as hyperplasia, while benign adenomas occurred at the higher dosages. The mechanism of pimozide-induced pituitary tumors in mice and the clinical importance of this finding are not known; however, the tumorigenic potential of pimozide should be given careful consideration by the patient and physician in the decision to use the drug, especially if the patient is young and long-term therapy is anticipated.

Although an increase in mammary neoplasms has been found in rodents following long-term administration of prolactin-stimulating antipsychotic agents, no clinical or epidemiologic studies conducted to date have shown an association between long-term administration of these drugs and mammary tumorigenesis in humans. Current evidence is considered too limited to be conclusive, and further study is needed to determine the clinical importance in most patients of elevated serum prolactin concentrations associated with antipsychotic agents. Because in vitro tests indicate that approximately one-third of human breast cancers are prolactin dependent, pimozide should be used with caution in patients with previously detected breast cancer.

■ **Pregnancy, Fertility, and Lactation** Reproduction studies in rats and rabbits using oral pimozide dosages up to 2.5 mg/kg daily (up to about 8 times the maximum recommended human dosage) have not revealed evidence of fetal malformation; however, in rats receiving oral pimozide dosages of 2.5 mg/kg daily or higher, a decreased pregnancy rate, increased fetal resorption, and retarded development of fetuses occurred. The observed effects may have resulted from delay or inhibition of implantation. In rabbits, dose-related maternotoxicity, mortality, decreased weight gain, and embryotoxicity, including increased fetal resorption, occurred. There are no adequate and controlled studies to date using pimozide in pregnant women, and the drug should be used during pregnancy only when the potential benefits justify the possible risks to the fetus.

Reproduction studies in animals using oral pimozide were not adequate to fully assess potential effects of the drug on fertility. Female rats receiving oral pimozide dosages up to 2.5 mg/kg daily had prolonged estrus cycles.

It is not known whether pimozide is distributed into milk. Because of the potential for serious adverse reactions (e.g., tumorigenicity, unknown cardiovascular effects) to pimozide in nursing infants, a decision should be made whether to discontinue nursing or the drug, taking into account the importance of the drug to the woman.

Drug Interactions

■ **Selective Serotonin-reuptake Inhibitors** ***Citalopram*** In a controlled study, administration of a single 2-mg dose of pimozide in individuals receiving citalopram (40 mg once daily for 11 days) was associated with mean increases in the QT_c interval of approximately 10 msec compared with pimozide given alone. Citalopram did not substantially affect the mean AUC or peak plasma concentrations of pimozide. The mechanism for this potential pharmacodynamic interaction is not known. The manufacturer of citalopram hydrobromide states that concurrent use of citalopram and pimozide is contraindicated.

Escitalopram In a controlled study, administration of a single 2-mg dose of pimozide in individuals receiving racemic citalopram (40 mg once daily for 11 days) was associated with mean increases in the QT_c interval of approximately 10 msec compared with pimozide given alone. Racemic citalopram did not substantially affect the mean AUC or peak plasma concentrations of pimozide. Concurrent pimozide and escitalopram administration has not been specifically evaluated to date. Pending further accumulation of data, the manufacturer of escitalopram states that concurrent use of escitalopram and pimozide is contraindicated.

Fluoxetine Clinical studies evaluating pimozide and other antidepressants have demonstrated an increase in adverse drug interactions or QT_c prolongation during combined therapy. In addition, rare case reports have suggested possible additive cardiovascular effects of pimozide and fluoxetine, resulting in bradycardia. Marked changes in mental status (e.g., stupor, inability to think clearly) and hypersalivation also were reported in one woman who received both drugs concurrently. Although a specific study evaluating concurrent pimozide and fluoxetine has not been performed to date, concurrent use of these drugs is contraindicated because of the potential for adverse drug interactions or QT_c prolongation.

Fluvoxamine Concomitant use of fluvoxamine is contraindicated in patients receiving pimozide, since fluvoxamine may inhibit the metabolism of pimozide and increase the potential for serious adverse cardiac effects.

Paroxetine In a controlled study, concurrent administration of single 2-mg doses of pimozide in healthy individuals receiving paroxetine (dosage titrated up to 60 mg daily) was associated with mean increases of 151 and 62% in the area under the plasma concentration-time curve (AUC) and peak plasma concentrations of pimozide, respectively, compared with pimozide given alone. The manufacturers of paroxetine state that concomitant use of paroxetine and pimozide is contraindicated because of the narrow therapeutic index of pimozide and its known ability to prolong the QT interval.

Sertraline Administration of a single 2-mg dose of pimozide in individuals receiving sertraline 200 mg daily has resulted in a mean increase of about 40% in pimozide AUC and peak plasma concentrations, but was not associated with changes in ECG parameters. The effect on QT interval and pharmacokinetic parameters of pimozide administered in higher doses (i.e., doses exceeding 2 mg) in combination with sertraline is as yet unknown. Concomitant use of sertraline and pimozide is contraindicated because of the low therapeutic index of pimozide and because the reported interaction between the 2 drugs occurred at a low dose of pimozide. The mechanism of this interaction is as yet unknown.

■ **Other CNS Agents** Pimozide may be additive with, or may potentiate the action of, other CNS depressants such as opiates or other analgesics, barbiturates or other sedatives, anxiolytics, or alcohol. When pimozide is used concomitantly with other CNS depressants, caution should be used to avoid excessive CNS depression.

■ **Drugs That Prolong the QT Interval** Because pimozide prolongs the QT interval, an additive effect on the QT interval might occur if the drug is administered with other agents that may prolong the QT interval such as phenothiazines, tricyclic antidepressants, or antiarrhythmic agents. Therefore, the manufacturer states that pimozide is contraindicated in patients receiving dofetilide, quinidine, sotalol, and other class IA and III antiarrhythmics; chlorpromazine, droperidol, mesoridazine (no longer commercially available in the US), and thioridazine; gatifloxacin, moxifloxacin, and sparfloxacin; halofantrine (licensed in the US but not commercially available); mefloquine; pentamidine; arsenic trioxide; levomethadyl acetate (no longer commercially available in the US); dolasetron mesylate; probucol (no longer commercially available in the US); tacrolimus; ziprasidone; and any other drugs that have demonstrated QT prolongation as one of their pharmacodynamic effects. (See Cautions: Cardiovascular Effects and see also Cautions: Precautions and Contraindications.)

■ **Drugs and Foods Affecting Hepatic Microsomal Enzymes** Prolongation of QT interval and, rarely, serious cardiovascular effects, including ventricular arrhythmias and death, have been reported in patients receiving drugs that inhibit the cytochrome P-450 (CYP) 3A4 isoenzyme such as macrolide antibiotics (e.g., clarithromycin, erythromycin, azithromycin, dirithromycin, troleandomycin), azole antifungal agents (e.g., itraconazole, ketoconazole), protease inhibitors (e.g., ritonavir, saquinavir, indinavir, nelfinavir), nefazodone, or zileuton concomitantly with pimozide. Macrolide antibiotics inhibit metabolism of pimozide, which may result in increased plasma concentrations of unchanged drug. Such alterations in pharmacokinetics of pimozide may be associated with prolongation of the QT and QT_c intervals, and, rarely, associated with ventricular arrhythmias. The manufacturer of pimozide states that concomitant administration of pimozide and macrolide antibiotics, azole antifungal agents, protease inhibitors, nefazodone, or zileuton is contraindicated.

Patients receiving pimozide should avoid grapefruit juice because it may inhibit drug metabolism by the CYP3A4 isoenzyme.

Because pimozide also may be metabolized by the CYP1A2 isoenzyme, the manufacturer states the theoretical potential for drug interactions with drugs that inhibit this enzyme system should be considered.

Acute Toxicity

■ **Pathogenesis** The acute lethal dose of pimozide in humans is not known. The oral LD_{50} of pimozide is 228, 5120, 188, and 40 mg/kg in mice, rats, guinea pigs, and dogs, respectively. The IV and subcutaneous LD_{50}s of pimozide are 11.1 and 40 mg/kg, respectively, for mice, and 5 and 40 mg/kg, respectively, for rats.

■ **Manifestations** In general, overdosage of pimozide may be expected to produce effects that are extensions of pharmacologic effects and adverse reactions, predominantly ECG abnormalities (including prolongation of the QT interval and torsades de pointes), severe extrapyramidal reactions, hypotension, seizures, and comatose state with respiratory depression.

A 17-year-old female who reportedly intentionally ingested 100 mg of pimozide and underwent gastric lavage (apparently no drug was recovered) had a complete and uneventful recovery except for slight tremor of the extremities that subsided within a few hours after ingestion. A 2½-year-old male who accidentally reportedly ingested 60 mg of pimozide exhibited mild extrapyramidal symptoms that subsequently subsided, and the patient recovered completely. Delayed-onset dystonia, hypotension, tachycardia, and drowsiness were reported in an 18-month-old female who ingested up to 6 mg (0.5 mg/kg) of pimozide; manifestations developed more than 12 hours after the accidental ingestion. The dystonia subsided over the following 12 hours while the drowsiness and tachycardia persisted for 40 hours. The child recovered fully without sequelae.

■ **Treatment** Treatment of pimozide overdosage generally involves symptomatic and supportive care, with ECG, blood pressure, and respiratory monitoring. There is no specific antidote for pimozide intoxication.

Following acute ingestion of the drug, the stomach should be emptied immediately, preferably by gastric lavage. If the patient is comatose, having seizures, or lacks the gag reflex, gastric lavage may be performed if an endotracheal tube with cuff inflated is in place to prevent aspiration of gastric contents. As in the case of phenothiazine overdosage, induction of emesis should generally *not* be attempted because a pimozide-induced dystonic reaction of the head or neck may result in aspiration of gastric contents during emesis; however, if the ingestion has only recently occurred (i.e., within an hour or so), induction of emesis may be considered. Following gastric lavage and/or emesis, activated charcoal should be administered. A patent airway should be established, using controlled or mechanically assisted respiration as necessary. ECG monitoring should be initiated immediately and continued until ECG parameters are within normal ranges. For hypotension or circulatory collapse, IV fluids, plasma, albumin, and/or vasopressor agents (e.g., norepinephrine) may be used. Epinephrine should *not* be used. For severe extrapyramidal reactions, anticholinergic antiparkinsonian agents or diphenhydramine should be administered. Because of the long elimination half-life of pimozide, patients should be observed for at least 4 days following acute ingestion of the drug. Clinicians should consider contacting a poison control center for additional information on the management of pimozide overdosage.

Pharmacology

The principal pharmacologic effects of pimozide are similar to those of haloperidol and, to a lesser extent, those of phenothiazines. In animal studies that are correlated with antipsychotic activity, pimozide is, on a weight basis, almost as potent as haloperidol and more potent than chlorpromazine following oral or subcutaneous administration.

■ **Nervous System Effects** In the CNS, pimozide has pharmacologic actions similar to those of haloperidol. The precise mechanism(s) of pimozide in suppressing motor and vocal tics in patients with Tourette's syndrome and its antipsychotic action have not been determined, but it may be related principally to the antidopaminergic effects of the drug. Although it has not been clearly established, most evidence suggests that pimozide is a selective dopamine-2 (D_2) receptor antagonist. Like butyrophenones (e.g., haloperidol), pimozide appears to predominantly block postsynaptic dopamine receptor sites, although the drug also may block presynaptic dopamine receptor sites. Blockade of dopamine receptors by pimozide may be accompanied by a series of secondary alterations in central dopamine metabolism and function that may contribute to the drug's therapeutic and adverse effects. Pimozide inhibits electrically induced dopamine release in brain tissue in vitro and increases synthesis and turnover of brain dopamine. Unlike most other currently available antipsychotic agents, pimozide appears to have little effect on catecholamines other than dopamine, although turnover of brain norepinephrine may be increased at high doses. Like other antipsychotic agents, however, pimozide has various effects on CNS receptor systems (e.g., γ-aminobutyric acid [GABA]) that are not fully characterized. Pimozide may decrease brain acetylcholine indirectly via its antidopaminergic effects, but such activity is considered relatively weak. Unlike haloperidol and chlorpromazine, the drug does not provide protection against a lethal dose of norepinephrine in rats.

Pimozide does not affect total sleep time or rapid eye movement (REM) sleep. The drug may cause EEG changes, including an increase in α-wave activity. Although not clearly established, pimozide may also lower the seizure threshold. The drug does not exhibit anticonvulsant activity in rats.

Although the exact mechanism(s) of action has not been elucidated, pimozide has an antiemetic effect. The antiemetic activity may be mediated via a direct effect of the drug on the medullary chemoreceptor trigger zone (CTZ), apparently by blocking dopamine receptors in the CTZ. Pimozide inhibits the central and peripheral effects of apomorphine.

Like haloperidol and phenothiazines, pimozide inhibits conditioned avoidance behaviors and produces catalepsy and ptosis in animals. The drug also antagonizes behavioral effects mediated by amphetamines in animals. In humans, pimozide antagonizes the euphoric response to amphetamines in amphetamine-dependent individuals, but apparently does not antagonize amphetamine-mediated behavioral effects in patients with schizophrenic disorder. Unlike many other centrally acting agents, pimozide does not appear to exhibit analgesic activity. The drug appears to exhibit anxiolytic activity in patients with chronic schizophrenic disorder who exhibit anxiety and in patients with various anxiety states.

In animals, pimozide does not substantially affect body temperature; however, the drug does inhibit apomorphine- and amphetamine-induced fever.

Pimozide exhibits some anticholinergic activity, although it is generally considered to be relatively weak compared with most other antipsychotic agents; however, anticholinergic effects (e.g., dry mouth, urinary retention, constipation) may occur during therapy with the drug.

■ **Cardiovascular Effects** Pimozide exhibits weak α-adrenergic blocking activity. The drug rarely may produce hypotension, orthostatic hypotension, hypertension, or tachycardia. Pimozide may also produce ECG changes, including prolongation of the QT interval; flattening, notching, and inversion of the T wave; and appearance of U waves. (See Cautions: Cardiovascular Effects.)

■ **Endocrine Effects** Pimozide induces secretion of prolactin from the anterior pituitary. The exact mechanism of increased prolactin secretion has not been determined, but it may be related principally to inhibition of dopamine receptors in the pituitary and hypothalamus.

■ **Other Effects** In vitro, pimozide exhibits weak antispasmodic effects, resulting from antagonism of various mediator substances (e.g., histamine, bradykinin, angiotensin). Pimozide also may inhibit transmembrane influx of extracellular calcium ions via slow calcium channels.

Pharmacokinetics

Limited information is available on the pharmacokinetics of pimozide.

■ **Absorption** Pimozide is slowly and variably absorbed from the GI tract following oral administration. Based on limited data, the drug appears to be at least 40–50% absorbed. Pimozide also appears to undergo extensive first-pass metabolism. It is not known whether food, disease, or concomitant administration of other drugs affects the absorption of pimozide.

Following oral administration of an individual dose of pimozide, peak plasma concentrations of the drug and its metabolites generally occur within 6–8 hours (range: 4–12 hours). Following oral administration of a single 6- or 24-mg dose in patients with chronic schizophrenic disorder, peak plasma pimozide concentrations of approximately 4 or 18–19 ng/mL, respectively, were attained. There are considerable interindividual variations in peak plasma concentrations and areas under the plasma concentration-time curves (AUCs) following single or multiple oral doses of pimozide. In a group of patients with chronic schizophrenic disorder receiving 2–10 mg of pimozide daily, steady-state serum concentrations of the drug varied considerably with specific dosages and ranged from undetectable (less than 1 ng/mL) to about 50 ng/mL. Because there is little correlation between plasma pimozide concentrations and clinical response, the clinical importance of interindividual variations is unclear. In a group of adults with acute schizophrenic disorder, a correlation between plasma pimozide concentration and dopamine receptor blocking activity, but not between clinical response and dopamine receptor blocking activity, was reported.

■ **Distribution** Distribution of pimozide into human body tissues and fluids has not been well characterized. Following subcutaneous administration in animals, pimozide is widely distributed, with highest concentrations attained in the liver, lungs, kidneys, and heart; the drug also is distributed into the brain, thymus, adrenals, thyroid, uterus, and ovaries, and apparently into bile. In animals, there is a direct relationship between the administered dose of pimozide and concentrations of the drug attained in the liver and brain. Following subcutaneous administration in animals, pimozide is widely distributed throughout the brain, principally as unchanged drug, with highest concentrations attained in the pituitary and caudate nucleus. The drug appeared to be selectively retained in the pituitary, caudate nucleus, chemoreceptor trigger zone (CTZ), floor of the third ventricle, lateral hypothalamus, and medulla. There was no correlation between concentrations of pimozide in the caudate nucleus and antagonism of effects mediated by amphetamine or apomorphine, but distribution of pimozide into nerve endings in the caudate nucleus was correlated with antagonism of these effects.

The extent of pimozide binding to plasma proteins is not known.

It is not known whether pimozide crosses the placenta or is distributed into milk.

■ **Elimination** Following multiple oral doses in patients with chronic schizophrenic disorder, the elimination half-life of pimozide averaged 55 hours. In one patient who developed a severe dystonic reaction, the elimination half-life of the drug was reportedly 154 hours.

The exact metabolic fate of pimozide is not clearly established, but the drug appears to undergo extensive first-pass metabolism. Pimozide is metabolized principally by oxidative *N*-dealkylation in the liver; this metabolism is catalyzed mainly by the cytochrome P-450 (CYP) 3A4 isoenzyme and, to a lesser extent, by cytochrome P-450 (CYP) isoenzyme 1A2. The major metabolites are 4,4-*bis*(4-fluorophenyl) butyric acid and 1-(4-piperidyl)-2-benzimidazolinone. The pharmacologic activity of these metabolites has not been determined; however, results of animal studies suggest that the metabolites of pimozide are inactive.

Pimozide and its metabolites are excreted principally in urine and, to a lesser extent, in feces. About 40% (range: 25–60%) of a single oral dose of the drug is excreted in urine and about 15% (range: 5–20%) in feces within 7 days; most urinary excretion occurs within 3–4 days, and most fecal excretion occurs within 3–6 days. Pimozide appears to be excreted in urine almost completely, as metabolites, with probably less than 1% excreted as unchanged drug. Fecal excretion has not been well characterized, but pimozide appears to be excreted in feces mainly as unchanged drug and to a small extent as metabolites. It is not known whether fecal excretion of the drug and metabolites represents unabsorbed drug or drug excreted via biliary elimination. In animals, pimozide and its metabolites are excreted in feces following parenteral administration, apparently via biliary elimination.

It is not known if pimozide and/or its metabolites are removed by hemodialysis or peritoneal dialysis.

Chemistry and Stability

■ **Chemistry** Pimozide is a diphenylbutylpiperidine-derivative antipsychotic agent. The drug is structurally similar to butyrophenones (e.g., haloper-

idol). Pimozide occurs as a white microcrystalline powder and has solubilities of less than 0.01 mg/mL in water and approximately 7 mg/mL in alcohol at room temperature. The drug has a pK_a of 7.32.

■ **Stability** Pimozide tablets should be stored in tight, light-resistant containers at 25°C but may be exposed to temperatures ranging from 15–30°C.

Preparations

Excipients in commercially available drug preparations may have clinically important effects in some individuals; consult specific product labeling for details.

Pimozide

Oral		
Tablets	1 mg	Orap® (scored), Gate
	2 mg	Orap® (scored), Gate

†Use is not currently included in the labeling approved by the US Food and Drug Administration

ANOREXIGENIC AGENTS AND RESPIRATORY AND CEREBRAL STIMULANTS 28:20

AMPHETAMINES 28:20.04

Amphetamines General Statement

■ Amphetamines exhibit pharmacologic actions that include CNS and respiratory stimulation and sympathomimetic effects.

Uses

Amphetamines are used as stimulants to decrease daytime sleepiness in the management of narcolepsy. Amphetamines also are used as adjuncts to psychological, educational, social, and other remedial measures in the treatment of attention deficit hyperactivity disorder (ADHD). Certain amphetamines also have been used as adjuncts to caloric restriction and behavioral modification in the short-term treatment of exogenous obesity. However, short-term or intermittent therapy with anorexigenic drugs is unlikely to maintain a long-term benefit, and prolonged administration of amphetamines for the treatment of obesity is not recommended. Amphetamines, particularly methamphetamine, have been misused and abused for their CNS stimulatory effects.

■ **Narcolepsy** Amphetamines are used as stimulants to decrease daytime sleepiness in the management of narcolepsy. Amphetamines should not be used to combat fatigue or exhaustion or to replace sleep in normal individuals.

Amphetamines remain the mainstay of treatment for narcolepsy based on a long record of clinical experience. However, because most clinical trials have involved small numbers of patients, the risk-to-benefit remains to be further established.

In determining the most appropriate stimulant therapy for a given patient, clinicians should consider benefit-to-risk (including adverse effect profile); drug cost, convenience of administration, and cost of ongoing care (including the possible need for laboratory monitoring).

Patients who fail to respond to an adequate trial of stimulant drug therapy should be assessed carefully for other possible causes of excessive sleepiness such as insufficient sleep, inadequate sleep hygiene, circadian rhythm disorders, obstructive sleep apnea syndrome, or periodic limb movement disorder.

Tolerance to the clinical effects may develop with long-term therapy, particularly at high dosages.

Narcolepsy rarely occurs in children, and the relative safety and efficacy of various stimulant drugs in this age group remains to be elucidated. Although amphetamines can be used, methylphenidate appears to be used most commonly based principally on extensive experience with the drug in pediatric patients with ADHD.

■ **Attention Deficit Hyperactivity Disorder** Amphetamines also are used as adjuncts to psychological, educational, social, and other remedial measures in the treatment of ADHD (hyperkinetic disorder, hyperkinetic syndrome of childhood, minimal brain dysfunction) in children, adolescents, and adults. Almost all studies comparing behavioral therapy versus stimulants alone have shown a much stronger therapeutic effect from stimulants than from behavioral therapy, and stimulants (e.g., methylphenidate, amphetamines) remain the drugs of choice for the management of ADHD. For a more detailed discussion on the management of ADHD, including the use of stimulants such as amphetamines, see Uses: Attention Deficit Hyperactivity Disorder, in Methylphenidate 28:20.92.

Few, if any, differences have been found between amphetamines (e.g., dextroamphetamine), methylphenidate, or pemoline (no longer commercially available in the US) or various dosage forms (short-, intermediate-, or long-acting formulations) of the drugs in short-term clinical studies in children with ADHD, and the choice of stimulant therapy should be individualized. Because hepatic toxicities have been associated with pemoline, some experts recommended its use *only* in patients who failed to respond to adequate trials of methylphenidate *and* an amphetamine, as well as adequate trials of second-line therapies (e.g., tricyclic antidepressants, bupropion). However, in 2005, the US Food and Drug Administration (FDA) determined that the risk of hepatic toxicity associated with the drug outweighs its benefits and the drug no longer is commercially available in the US.

Short-term and longer-term (up to 14 months' duration) studies have shown unequivocal beneficial effects of the stimulants on the defining core symptoms of ADHD (attention and concentration, activity, distractibility, impulsivity) and associated aggressiveness during continued therapy with the drugs. Children who fail to show positive therapeutic effects or who experience intolerable adverse effects with one stimulant should be tried on an alternative stimulant since most such children will exhibit a positive response to alternative stimulants and current evidence from crossover studies supports the efficacy of different stimulants in the same child; likewise, children who fail an adequate trial of 2 stimulants should be tried on a third type or formulation of stimulant. However, stimulants usually do not normalize the entire spectrum of behavioral problems, and many children effectively treated with these drugs still manifest a higher level of some behavioral problems than children without ADHD or other behavioral disturbances. Although stimulants have been shown to remain effective over many years, long-term benefits remain to be established.

■ **Exogenous Obesity** Amphetamines also have been used as adjuncts to caloric restriction and behavioral modification in the short-term treatment of exogenous obesity. The anorexigenic effect of sympathomimetic compounds used in the treatment of obesity appears to be temporary, seldom lasting more than a few weeks, and tolerance may occur. To help bring about and maintain loss of weight, the patient must be taught to curtail overeating and to consume a suitable diet. Prolonged administration of amphetamines is not recommended; however, obesity usually is a chronic disease, and short-term or intermittent therapy with anorexigenic drugs is unlikely to maintain a long-term benefit and is not recommended. Other anorexigenic agents (e.g., amphetamine congeners such as phentermine) with better safety profiles, including reduced potentials for misuse and abuse, generally are preferred to prototype amphetamines for the management of obesity. In the past, it was suggested that combined† therapy with fenfluramine (an amphetamine congener that stimulates release of serotonin [5-HT] at synapses and selectively inhibits the reuptake of serotonin at the presynaptic serotonergic nerve endings resulting in increased postsynaptic concentrations of serotonin in the CNS) and phentermine (an amphetamine congener that inhibits uptake of norepinephrine and dopamine) may provide complementary anorexigenic effects; therefore, such combined† therapy had been used widely in the 1990s in the management of obesity. However, because accumulated data on adverse effects associated with the drugs, fenfluramine hydrochloride (Pondimin®) and its dextrorotatory isomer dexfenfluramine hydrochloride (Redux®) were withdrawn from the US market in 1997. (See Cautions.)

Currently, the only legend (prescription) anorexigenic agent labeled by the US Food and Drug Administration (FDA) for use as an adjunct to behavioral modification, caloric restriction, and exercise in the long-term management of exogenous obesity is sibutramine, a β-phenethylamine that is structurally similar to amphetamine. Sibutramine therapy is indicated for patients with no underlying risk factor, but a pretreatment body mass index (BMI) of 30 kg/m² or greater, and for those with an underlying risk factor (e.g., hypertension, diabetes mellitus, hyperlipidemia) and a pretreatment BMI of 27 kg/m² or greater. Safety and efficacy of sibutramine for use exceeding 1 year have not been adequately studied to date. It appears that the anorexigenic effect of sibutramine, similar to dexfenfluramine, is secondary to inhibition of reuptake of norepinephrine and serotonin; however, unlike dexfenfluramine, sibutramine does not cause an increase in release of serotonin from nerve cells. Orlistat (a chemically synthesized derivative of lipostatin) is used as an adjunct to behavioral modification, caloric restriction, and exercise in the management of exogenous obesity. Some clinicians state that orlistat may be used in the long-term management of obesity; however, safety and efficacy of the drug beyond 2 years of therapy have not been established. Orlistat is not an anorexigenic agent, but is a reversible inhibitor of gastric, pancreatic, and pancreatic carboxylester lipases and thus appears to block fat absorption. (See Orlistat 56:92.)

■ **Misuse and Abuse** Misuse and abuse of amphetamines, especially methamphetamine, for CNS stimulatory effects have experienced a resurgence. In large part, this resurgence has resulted from the relative ease with which methamphetamine can be synthesized clandestinely from readily available chemicals such as ephedrine or pseudoephedrine. (See Chronic Toxicity.) Recent restrictions (including enactment of the Comprehensive Methamphetamine Control Act of 1996, the Methamphetamine Anti-Proliferation Act [MAPA] of 2000, and the Combat Methamphetamine Epidemic Act of 2005) on the availability of these compounds are hoped to reverse this resurgence in misuse and abuse. For a more detailed discussion on methamphetamine abuse, see Uses: Misuse and Abuse, in Pseudoephedrine 12:12.12.

Dosage and Administration

■ **Administration** Amphetamines are administered orally. When used in the treatment of narcolepsy or attention deficit hyperactivity disorder, the initial dose is given on awakening. Because of the potential for insomnia, when amphetamines are administered in divided doses, late evening doses should be avoided. When used as an anorexigenic, the dose is usually given 30–60 minutes before meals.

rate of *N*-demethylation of the drug in the liver. The absence of either a bimodal or trimodal distribution of clearance values suggests that the rate of such metabolism may be under polygenic control. The half-life of fluoxetine reportedly is prolonged (to approximately 4–5 days) after administration of multiple versus single doses, suggesting a nonlinear pattern of drug accumulation during long-term administration. Norfluoxetine appears to exhibit dose-proportional pharmacokinetics following multiple dosing, although limited data indicate that the rate of formation of the metabolite is decreased slightly once steady-state plasma concentrations have been achieved.

Following oral administration of single doses of fluoxetine in healthy individuals, total apparent plasma clearances of fluoxetine and norfluoxetine average approximately 346 mL/minute (range: 94–703 mL/minute) and 145 mL/minute (range: 61–284 mL/minute), respectively. Limited data suggest that plasma clearance of fluoxetine decreases by approximately 75% following multiple oral doses of the drug once steady-state plasma fluoxetine concentrations have been achieved. Plasma clearances of fluoxetine and norfluoxetine also reportedly are decreased in patients with chronic liver disease (e.g., cirrhosis). Evidence from single-dose studies indicates that clearances of the drug and its principal metabolite are not altered substantially in patients with renal impairment.

The exact metabolic fate of fluoxetine has not been fully elucidated. The drug appears to be metabolized extensively, probably in the liver, to norfluoxetine and several other metabolites. Norfluoxetine (desmethylfluoxetine), the principal metabolite, is formed by *N*-demethylation of fluoxetine, which may be under polygenic control. The potency and selectivity of norfluoxetine's serotonin-reuptake inhibiting activity appear to be similar to those of the parent drug. Both fluoxetine and norfluoxetine undergo conjugation with glucuronic acid in the liver, and limited evidence from animals suggests that both the parent drug and its principal metabolite also undergo *O*-dealkylation to form *p*-trifluoromethylphenol, which subsequently appears to be metabolized to hippuric acid.

Following oral administration, fluoxetine and its metabolites are excreted principally in urine. In healthy individuals, approximately 60% of an orally administered, radiolabeled dose of fluoxetine is excreted in urine within 35 days, with approximately 72.8% of excreted drug as unidentified metabolites, 10% as norfluoxetine, 9.5% as norfluoxetine glucuronide, 5.2% as fluoxetine glucuronide, and 2.5% as unchanged drug. Approximately 12% of the dose was eliminated in feces within 28 days following oral administration, but the relative proportion of unabsorbed versus absorbed drug that is excreted in feces (e.g., via biliary elimination) is not known.

The effect of age on the elimination of fluoxetine has not been fully elucidated. Single-dose studies suggest that the pharmacokinetics of fluoxetine in healthy geriatric individuals do not differ substantially from those in younger adults. However, because the drug has a relatively long half-life and nonlinear disposition following multiple-dose administration, single-dose studies are not sufficient to exclude the possibility of altered pharmacokinetics in geriatric individuals, particularly those with systemic disease and/or in those receiving multiple medications concomitantly. The elimination half-lives of fluoxetine and norfluoxetine may be prolonged in patients with hepatic impairment. Following a single oral dose of the drug in patients with hepatic cirrhosis, the elimination half-lives of fluoxetine and norfluoxetine reportedly average approximately 7 and 12 days, respectively.

The elimination half-lives of fluoxetine and norfluoxetine do not appear to be altered substantially in patients with renal impairment following oral administration of single doses of the drug, although multiple-dose studies are needed to determine whether accumulation of the parent drug and/or its metabolites occurs during long-term therapy in such patients.

Fluoxetine and norfluoxetine are not removed substantially by hemodialysis. Because of the large volume of distribution and extensive protein binding of the drug and its principal metabolite, peritoneal dialysis, forced diuresis, hemoperfusion, and/or exchange transfusion also are likely to be ineffective in removing substantial amounts of fluoxetine and norfluoxetine from the body.

Chemistry and Stability

■ **Chemistry** Fluoxetine, a selective serotonin-reuptake inhibitor (SSRI) antidepressant, is a phenylpropylamine-derivative. The drug differs structurally from other selective serotonin-reuptake inhibitor antidepressants (e.g., citalopram, paroxetine, sertraline) and also differs structurally and pharmacologically from other currently available antidepressant agents (e.g., tricyclic antidepressants, monoamine oxidase inhibitors).

Fluoxetine contains a *p*-trifluoromethyl substituent that appears to contribute to the drug's high selectivity and potency for inhibiting serotonin reuptake, possibly as a result of its electron-withdrawing effect and lipophilicity. The commercially available drug is a racemic mixture of 2 optical isomers. Limited in vivo and in vitro data suggest that the pharmacologic activities of the optical isomers do not differ substantially, although the dextrorotatory isomer appears to have slightly greater serotonin-reuptake inhibiting activity and a longer duration of action than the levorotatory isomer.

Fluoxetine is commercially available as the hydrochloride salt, which occurs as a white to off-white crystalline solid and has a solubility of 14 mg/mL in water.

■ **Stability** Fluoxetine hydrochloride capsules and the oral solution should be stored in tight, light-resistant containers, both at 15–30°C. Fluoxetine tablets and delayed-release capsules should be stored at 15–30°C.

Preparations

Excipients in commercially available drug preparations may have clinically important effects in some individuals; consult specific product labeling for details.

Fluoxetine Hydrochloride

Oral		
Capsules	10 mg (of fluoxetine)*	**Fluoxetine Hydrochloride Capsules**
		Prozac® Pulvules®, Dista
		Sarafem® Pulvules®, Lilly
	20 mg (of fluoxetine)*	**Fluoxetine Hydrochloride Capsules**
		Prozac® Pulvules®, Dista
		Sarafem® Pulvules®, Lilly
	40 mg (of fluoxetine)*	**Fluoxetine Hydrochloride Capsules**
		Prozac® Pulvules®, Dista
Capsules, delayed-release (containing enteric-coated pellets)	90 mg (of fluoxetine)	**Prozac® Weekly**, Dista
Solution	20 mg (of fluoxetine) per 5 mL*	**Fluoxetine Hydrochloride Oral Solution**
		Prozac®, Dista
Tablets	10 mg (of fluoxetine)*	**Fluoxetine Hydrochloride Tablets** (scored)
		Sarafem®, Warner Chilcott
	15 mg (of fluoxetine)*	**Serafem®**, Warner Chilcott
	20 mg (of fluoxetine)*	**Fluoxetine Hydrochloride Tablets**
		Sarafem®, Warner Chilcott

*available from one or more manufacturer, distributor, and/or repackager by generic (nonproprietary) name

Fluoxetine Hydrochloride Combinations

Oral		
Capsules	25 mg (of fluoxetine) with Olanzapine 6 mg	**Symbyax® (combination)**, Lilly
	25 mg (of fluoxetine) with Olanzapine 12 mg	**Symbyax® (combination)**, Lilly
	50 mg (of fluoxetine) with Olanzapine 6 mg	**Symbyax® (combination)**, Lilly
	50 mg (of fluoxetine) with Olanzapine 12 mg	**Symbyax® (combination)**, Lilly

†Use is not currently included in the labeling approved by the US Food and Drug Administration

Paroxetine

■ Paroxetine hydrochloride and paroxetine mesylate, selective serotonin-reuptake inhibitors (SSRIs), are antidepressant agents.

Uses

Paroxetine is commercially available in the US as paroxetine hydrochloride (e.g., Paxil®, Paxil CR®) and as paroxetine mesylate (i.e., Pexeva®). The US Food and Drug Administration (FDA) considers paroxetine mesylate (Pexeva®) conventional tablets to be a pharmaceutical *alternative* (as described in section 505[b][2] of the Federal Food, Drug, and Cosmetic Act) and not a pharmaceutical (generic) equivalent to paroxetine hydrochloride conventional tablets (e.g., Paxil®), since both contain the same active moiety (paroxetine) but have different salts. The clinical studies that established efficacy of paroxetine in various conditions have been conducted with paroxetine hydrochloride. Because paroxetine hydrochloride and paroxetine mesylate contain the same active moiety (paroxetine), clinical efficacy is expected to be similar between the 2 different salts.

Paroxetine hydrochloride conventional tablets and oral suspension are used in the treatment of major depressive disorder, obsessive-compulsive disorder, panic disorder with or without agoraphobia, social phobia (social anxiety disorder), generalized anxiety disorder, and posttraumatic stress disorder. Paroxetine hydrochloride extended-release tablets are used in the treatment of major depressive disorder, panic disorder with or without agoraphobia, social phobia, and premenstrual dysphoric disorder (PMDD). Paroxetine mesylate conventional tablets are used in the treatment of major depressive disorder, obsessive-compulsive disorder, and panic disorder with or without agoraphobia. In addition, paroxetine has been used in the treatment of premature ejaculation†,

diabetic neuropathy†, chronic headache†, and depression associated with bipolar disorder†.

■ **Major Depressive Disorder** Paroxetine is used in the treatment of major depressive disorder. A major depressive episode implies a prominent and relatively persistent depressed or dysphoric mood that usually interferes with daily functioning (nearly every day for at least 2 weeks). According to DSM-IV criteria, a major depressive episode includes at least 5 of the following 9 symptoms (with at least one of the symptoms being either depressed mood or loss of interest or pleasure): depressed mood most of the day as indicated by subjective report (e.g., feels sad or empty) or observation made by others; markedly diminished interest or pleasure in all, or almost all, activities most of the day; significant weight loss (when not dieting) or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite; insomnia or hypersomnia; psychomotor agitation or retardation (observable by others, not merely subjective feelings of restlessness or being slowed down); fatigue or loss of energy; feelings of worthlessness or excessive or inappropriate guilt (not merely self-reproach or guilt about being sick); diminished ability to think or concentrate or indecisiveness (either by subjective account or as observed by others); and recurrent thoughts of death, recurrent suicidal ideation without a specific plan, or a suicide attempt or specific plan for committing suicide.

Treatment of major depressive disorder generally consists of an acute phase (to induce remission), a continuation phase (to preserve remission), and a maintenance phase (to prevent recurrence). Various interventions (e.g., psychotherapy, antidepressant drug therapy, electroconvulsive therapy [ECT]) are used alone or in combination to treat major depressive episodes. Treatment should be individualized and the most appropriate strategy for a particular patient is determined by clinical factors such as severity of depression (e.g., mild, moderate, severe), presence or absence of certain psychiatric features (e.g., suicide risk, catatonia, psychotic or atypical features, alcohol or substance abuse or dependence, panic or other anxiety disorder, cognitive dysfunction, dysthymia, personality disorder, seasonal affective disorder), and concurrent illness (e.g., asthma, cardiac disease, dementia, seizure disorder, glaucoma, hypertension). Demographic and psychosocial factors as well as patient preference also are used to determine the most effective treatment strategy.

While use of psychotherapy alone may be considered as an initial treatment strategy for patients with mild to moderate major depressive disorder (based on patient preference and presence of clinical features such as psychosocial stressors), combined use of antidepressant drug therapy and psychotherapy may be useful for initial treatment of patients with moderate to severe major depressive disorder with psychosocial issues, interpersonal problems, or a comorbid axis II disorder. In addition, combined use of antidepressant drug therapy and psychotherapy may be beneficial in patients who have a history of poor compliance or only partial response to adequate trials of either antidepressant drug therapy or psychotherapy alone.

Antidepressant drug therapy can be used alone for initial treatment of patients with mild major depressive disorder (if preferred by the patient) and usually is indicated alone or in combination with psychotherapy for initial treatment of patients with moderate to severe major depressive disorder (unless ECT is planned). ECT is not generally used for initial treatment of uncomplicated major depression, but is recommended as first-line treatment for severe major depressive disorder when it is coupled with psychotic features, catatonic stupor, severe suicidality, food refusal leading to nutritional compromise, or other situations when a rapid antidepressant response is required. ECT also is recommended for patients who have previously shown a positive response or a preference for this treatment modality and can be considered for patients with moderate or severe depression who have not responded to or cannot receive antidepressant drug therapy. In certain situations involving depressed patients unresponsive to adequate trials of several individual antidepressant agents, adjunctive therapy with another agent (e.g., buspirone, lithium) or concomitant use of a second antidepressant agent (e.g., bupropion) has been used; however, such combination therapy is associated with an increased risk of adverse reactions, may require dosage adjustments, and (if not contraindicated) should be undertaken only after careful consideration of the relative risks and benefits. (See Drug Interactions: Serotonergic Drugs, see Drug Interactions: Tricyclic and Other Antidepressants, and see Drug Interactions: Lithium.)

The efficacy of paroxetine for the management of major depression has been established by placebo-controlled studies of 6 weeks' duration in adult outpatients from 18–73 years of age who met DSM-III criteria for major depressive disorder. In these studies, paroxetine hydrochloride was found to be more effective than placebo in improving scores by at least 2 on the Hamilton Depression Rating Scale (HDRS) and the Clinical Global Impression and Severity of Illness Scale. Paroxetine hydrochloride also was more effective than placebo in improving HDRS subfactor scores, including the depressed mood item, sleep disturbance factor, and the anxiety factor.

The efficacy of paroxetine hydrochloride extended-release tablets for the management of depression has been established in 2 flexible-dosage, controlled studies of 12-weeks' duration in adults 18–88 years of age who met DSM-IV criteria for major depressive disorder. In these studies, paroxetine was more effective than placebo in improving scores on the HDRS, the Hamilton depressed mood item, and the Clinical Global Impression-Severity of Illness Scale.

In a study of depressed outpatients who had responded by the end of an initial 8-week open treatment phase to paroxetine (mean dosage: approximately 30 mg daily; HDRS total score of less than 8) and were randomized to continue paroxetine or receive placebo for 1 year, the relapse rate in the paroxetine-treated patients (15%) was substantially lower than that in those who received placebo (39%). An analysis of these data for possible gender-related effects on treatment outcome did not suggest any difference in efficacy based on the gender of the patient. In controlled studies of depressed patients who had responded to a 6-week course of paroxetine or imipramine and were randomized to receive either the same antidepressant or placebo for up to 1 year, both paroxetine and imipramine were more effective than placebo in maintaining euthymia; however, paroxetine was better tolerated than imipramine during long-term therapy. While the optimum duration of paroxetine therapy has not been established, many experts state that acute depressive episodes require several months or longer of sustained antidepressant therapy. In addition, some clinicians recommend that long-term antidepressant therapy be considered in certain patients at risk for recurrence of depressive episodes (such as those with highly recurrent unipolar depression). In placebo-controlled studies, paroxetine has been shown to be effective for the long-term (e.g., up to 1 year) management of depression. In addition, the drug has been used in some patients for longer periods (e.g., up to 4 years) without apparent loss of clinical effect or increased toxicity. However, when paroxetine is used for extended periods, the need for continued therapy should be reassessed periodically. (See Dosage and Administration: Dosage.)

The efficacy of paroxetine as an antidepressant in hospital settings has not been studied adequately to date; however, the drug has been shown to be effective in hospitalized patients with severe depression in at least one controlled study.

As with other antidepressants, the possibility that paroxetine may precipitate hypomanic or manic attacks in patients with bipolar or other major affective disorder should be considered. Paroxetine is *not* approved for use in treating bipolar depression.

Considerations in Choosing Antidepressants A variety of antidepressant drugs are available for the treatment of major depressive disorder, including selective serotonin-reuptake inhibitors (SSRIs; e.g., citalopram, escitalopram, fluoxetine, paroxetine, sertraline), selective serotonin- and norepinephrine-reuptake inhibitors (SNRIs; e.g., desvenlafaxine, duloxetine, venlafaxine), tricyclic antidepressants (e.g., amitriptyline, amoxapine, desipramine, doxepin, imipramine, nortriptyline, protriptyline, trimipramine), monoamine oxidase (MAO) inhibitors (e.g., phenelzine, tranylcypromine), and other antidepressants (e.g., bupropion, maprotiline, nefazodone, trazodone). Most clinical studies have shown that the antidepressant effect of usual dosages of paroxetine in patients with depression is greater than that of placebo and comparable to that of usual dosages of tricyclic antidepressants (e.g., amitriptyline, imipramine, doxepin), other SSRIs (e.g., fluoxetine, fluvoxamine, sertraline), and other antidepressants (e.g., nefazodone). The onset of antidepressant action of paroxetine appears to be comparable to that of tricyclic antidepressants and other SSRIs, although there is some evidence that the onset of action may occur slightly earlier with paroxetine than with imipramine and fluoxetine.

In general, response rates in patients with major depression are similar for currently available antidepressants, and the choice of antidepressant agent for a given patient depends principally on other factors such as potential adverse effects, safety or tolerability of these adverse effects in the individual patient, psychiatric and medical history, patient or family history of response to specific therapies, patient preference, quantity and quality of available clinical data, cost, and relative acute overdose safety. No single antidepressant can be recommended as optimal for all patients because of substantial heterogeneity in individual responses and in the nature, likelihood, and severity of adverse effects. In addition, patients vary in the degree to which certain adverse effects and other inconveniences of drug therapy (e.g., cost, dietary restrictions) affect their preferences.

In the large-scale Sequenced Treatment Alternatives to Relieve Depression (STAR*D) effectiveness trial, patients with major depressive disorder who did not respond to or could not tolerate therapy with one SSRI (citalopram) were randomized to switch to extended-release ("sustained-release") bupropion, sertraline, or extended-release venlafaxine as a second step of treatment (level 2). Remission rates as assessed by the 17-item Hamilton Rating Scale for Depression (HRSD-17) and the Quick Inventory of Depressive Symptomatology—Self Report (QIDS-SR-16) were approximately 21 and 26% for extended-release bupropion, 18 and 27% for sertraline, and 25 and 25% for extended-release venlafaxine therapy, respectively; response rates as assessed by the QIDS-SR-16 were 26, 27, and 28% for extended-release bupropion, sertraline, and extended-release venlafaxine therapy, respectively. These results suggest that after unsuccessful initial treatment of depressed patients with an SSRI, approximately 25% of patients will achieve remission after therapy is switched to another antidepressant and that either another SSRI (e.g., sertraline) or an agent from another class (e.g., bupropion, venlafaxine) may be reasonable alternative antidepressants in patients not responding to initial SSRI therapy.

Patient Tolerance Considerations. Because of differences in the adverse effect profile between SSRIs and tricyclic antidepressants, particularly less frequent anticholinergic effects, cardiovascular effects, and/or weight gain with SSRIs, these drugs may be preferred in patients in whom such effects are not tolerated or are of potential concern. The decreased incidence of anticholinergic effects associated with paroxetine and other SSRIs compared with tricyclic antidepressants is a potential advantage, since such effects may result in discontinuance of the drug early during therapy in unusually sensitive patients. In addition, some anticholinergic effects may become troublesome during long-

term tricyclic antidepressant therapy (e.g., persistent dry mouth may result in tooth decay). Although SSRIs share the same overall tolerability profile, certain patients may tolerate one drug in this class better than another. Antidepressants other than SSRIs may be preferred in patients in whom certain adverse GI effects (e.g., nausea, anorexia), nervous system effects (e.g., anxiety, nervousness, insomnia), and/or weight loss are not tolerated or are of concern, since such effects appear to occur more frequently with paroxetine and other drugs in this class.

Pediatric Considerations. The clinical presentation of depression in children and adolescents can differ from that in adults and generally varies with the age and developmental stages of the child. Younger children may exhibit behavioral problems such as social withdrawal, aggressive behavior, apathy, sleep disruption, and weight loss; adolescents may present with somatic complaints, self esteem problems, rebelliousness, poor performance in school, or a pattern of engaging in risky or aggressive behavior.

Data from controlled clinical studies evaluating various antidepressant agents in children and adolescents are less extensive than with adults, and many of these studies have methodologic limitations (e.g., nonrandomized or uncontrolled, small sample size, short duration, nonspecific inclusion criteria). However, there is some evidence that the response to antidepressants in pediatric patients may differ from that seen in adults, and caution should be used in extrapolating data from adult studies when making treatment decisions for pediatric patients. Results of several studies evaluating tricyclic antidepressants (e.g., amitriptyline, desipramine, imipramine, nortriptyline) in preadolescent and adolescent patients with major depression indicate a lack of overall efficacy in this age group. Based on the lack of efficacy data regarding use of tricyclic antidepressants and MAO inhibitors in pediatric patients and because of the potential for life-threatening adverse effects associated with the use of these drugs, many experts consider selective serotonin-reuptake inhibitors the drugs of choice when antidepressant therapy is indicated for the treatment of major depressive disorder in children and adolescents. However, the US Food and Drug Administration (FDA) states that, while efficacy of fluoxetine has been established in pediatric patients, efficacy of other newer antidepressants (i.e., paroxetine, citalopram, desvenlafaxine, duloxetine, escitalopram, fluvoxamine, mirtazapine, nefazodone, sertraline, venlafaxine) was not conclusively established in clinical trials in pediatric patients with major depressive disorder. In addition, FDA warns that antidepressants increase the risk of suicidal thinking and behavior (suicidality) in children and adolescents with major depressive disorder and other psychiatric disorders. (See Cautions: Pediatric Precautions.) FDA currently states that anyone considering using an antidepressant in a child or adolescent for any clinical use must balance the potential risk of therapy with the clinical need. (See Cautions: Precautions and Contraindications.)

Geriatric Considerations. The response to antidepressants in depressed geriatric patients without dementia is similar to that reported in younger adults, but depression in geriatric patients often is not recognized and is not treated. In geriatric patients with major depressive disorder, SSRIs appear to be as effective as tricyclic antidepressants but may cause fewer overall adverse effects than these other agents. Geriatric patients appear to be especially sensitive to anticholinergic (e.g., dry mouth, constipation, vision disturbance), cardiovascular, orthostatic hypotensive, and sedative effects of tricyclic antidepressants. The low incidence of anticholinergic effects associated with paroxetine and other SSRIs compared with tricyclic antidepressants is a potential advantage in geriatric patients, since such effects (e.g., constipation, dry mouth, confusion, memory impairment) may be particularly troublesome in these patients.However, SSRI therapy may be associated with other troublesome adverse effects (e.g., nausea and vomiting, agitation and akathisia, parkinsonian adverse effects, sexual dysfunction, weight loss, and hyponatremia). Some clinicians state that SSRIs including paroxetine may be preferred for treating depression in geriatric patients in whom the orthostatic hypotension associated with many antidepressants (e.g., tricyclics) potentially may result in injuries (such as severe falls). However, despite the fewer cardiovascular and anticholinergic effects associated with SSRIs, these drugs did not show any advantage over tricyclic antidepressants with regard to hip fracture in a case-control study. In addition, there was little difference in the rates of falls between nursing home residents receiving SSRIs and those receiving tricyclic antidepressants in a retrospective study. Therefore, all geriatric individuals receiving either type of antidepressant should be considered at increased risk of falls and appropriate measures should be taken. In addition, clinicians prescribing SSRIs in geriatric patients should be aware of the many possible drug interactions associated with these drugs, including those involving metabolism of the drugs through the cytochrome P-450 system. (See Drug Interactions.)

Patients with dementia of the Alzheimer's type (Alzheimer's disease, presenile or senile dementia) often present with depressive symptoms, such as depressed mood, appetite loss, insomnia, fatigue, irritability, and agitation. Most experts recommend that patients with dementia of the Alzheimer's type who present with clinically important and persistent depressive symptoms be considered as candidates for pharmacotherapy even if they fail to meet the criteria for a major depressive syndrome. The goals of such therapy are to improve mood, functional status (e.g., cognition), and quality of life. Treatment of depression also may reduce other neuropsychiatric symptoms associated with depression in patients with dementia, including aggression, anxiety, apathy, and psychosis. Although patients may present with depressed mood alone, the possibility of more extensive depressive symptomatology should be considered. Therefore, patients should be evaluated and monitored carefully for indices of major depression, suicidal ideation, and neurovegetative signs since safety measures (e.g., hospitalization for suicidal ideation) and more vigorous and aggressive therapy (e.g., relatively high dosages, multiple drug trials) may be needed in some patients.

Although placebo-controlled trials of antidepressants in depressed patients with concurrent dementia have shown mixed results, the available evidence and experience with the use of antidepressants in patients with dementia of the Alzheimer's type and associated depressive manifestations indicate that depressive symptoms (including depressed mood alone and with neurovegetative changes) in such patients are responsive to antidepressant therapy. In some patients, cognitive deficits may partially or fully resolve during antidepressant therapy, but the extent of response will be limited to the degree of cognitive impairment that is directly related to depression. SSRIs such as citalopram, escitalopram, fluoxetine, paroxetine, or sertraline are generally considered as first-line agents in the treatment of depressed patients with dementia since they usually are better tolerated than some other antidepressants (e.g., tricyclic antidepressants, monoamine oxidase inhibitors). Some possible alternative agents to SSRIs include bupropion, mirtazapine, and venlafaxine. Some geriatric patients with dementia and depression may be unable to tolerate the antidepressant dosages needed to achieve full remission. When a rapid antidepressant response is not critical, some experts therefore recommend a very gradual dosage increase to increase the likelihood that a therapeutic dosage of the SSRI or other antidepressant will be reached and tolerated. In a controlled study comparing paroxetine and imipramine in patients with coexisting depression and dementia, both drugs were found to be effective; however, paroxetine was better tolerated (fewer anticholinergic and serious adverse effects).

Cardiovascular Considerations. The relatively low incidence of adverse cardiovascular effects, including orthostatic hypotension and conduction disturbances, associated with paroxetine and other SSRIs may be advantageous in patients in whom the cardiovascular effects associated with tricyclic antidepressants may be hazardous. In a controlled trial comparing paroxetine and nortriptyline in patients with stable ischemic disease, both antidepressants were found to be effective in treating depression and neither drug substantially affected blood pressure or conduction intervals; however, paroxetine did not produce sustained effects on heart rate or rhythm or heart rate variability whereas nortriptyline increased heart rate and reduced heart rate variability. Most clinical studies of paroxetine for the management of depression did not include individuals with cardiovascular disease (e.g., those with a recent history of myocardial infarction or unstable cardiovascular disease), and further experience in such patients is necessary to confirm the relative lack of cardiotoxicity reported with the drug to date. (See Cautions: Cardiovascular Effects and see Cautions: Precautions and Contraindications.)

Sedative Considerations. Because paroxetine and other SSRIs generally are less sedating than some other antidepressants (e.g., tricyclics), some clinicians state that these drugs may be preferable in patients who do not require the sedative effects associated with many antidepressant agents or in patients who are prone to accidents; however, an antidepressant with more prominent sedative effects (e.g., trazodone) may be preferable in certain patients (e.g., those with insomnia).

Suicidal Risk Considerations. Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are the strongest predictors of suicide. However, there has been a long-standing concern that antidepressants may have a role in inducing worsening of depression and the emergence of suicidal thinking and behavior (suicidality) in certain patients during the early phases of treatment. FDA states that antidepressants increased the risk of suicidality in short-term studies in children, adolescents, and young adults (18–24 years of age) with major depressive disorder and other psychiatric disorders. (See Cautions: Pediatric Precautions.) An increased suicidality risk was not demonstrated with antidepressants compared with placebo in adults older than 24 years of age and a reduced risk was observed in adults 65 years of age or older. It is currently unknown whether the suicidality risk extends to longer-term antidepressant use (i.e., beyond several months); however, there is substantial evidence from placebo-controlled maintenance trials in adults with major depressive disorder that antidepressants can delay the recurrence of depression. Because the risk of suicidality in depressed patients may persist until substantial remission of depression occurs, appropriate monitoring and close observation of patients of all ages who are receiving antidepressant therapy are recommended. (See Suicidality under Cautions: Nervous System Effects, and see Cautions: Precautions and Contraindications.)

Other Considerations. Paroxetine has been effective in patients with moderate to severe depression, endogenous depression, reactive depression (including traumatic grief), depression associated with human immunodeficiency virus (HIV) infection, and depression associated with anxiety and/or agitation.

■ **Obsessive-Compulsive Disorder** Paroxetine is used in the treatment of obsessive-compulsive disorder when obsessions or compulsions cause marked distress, are time-consuming (take longer than 1 hour daily), or interfere substantially with the patient's normal routine, occupational or academic functioning, or usual social activities or relationships. Obsessions are recurrent and persistent thoughts, impulses, or images that, at some time during the disturbance, are experienced as intrusive and inappropriate (i.e., "ego dystonic") and that cause marked anxiety or distress but that are not simply excessive worries about real-life problems. Compulsions are repetitive behaviors (e.g., hand washing, ordering, checking) or mental acts (e.g., praying, counting, repeating words silently) performed in response to an obsession or according to rules that must be applied rigidly (e.g., in a stereotyped fashion). Although

the behaviors or acts are aimed at preventing or reducing distress or preventing some dreaded event or situation, they either are not connected in a realistic manner with what they are designed to neutralize or prevent or are clearly excessive. At some time during the course of the disturbance, the patient, if an adult, recognizes that the obsessions or compulsions are excessive or unreasonable; children may not make such recognition.

The efficacy of paroxetine hydrochloride for the management of obsessive-compulsive disorder in adults has been established by 2 multicenter, placebo-controlled studies of 12 weeks' duration. In these clinical studies, paroxetine was more effective than placebo in reducing the severity of obsessive-compulsive manifestations in adult outpatients with moderate to severe obsessive-compulsive disorder (Yale-Brown Obsessive-Compulsive Scale [YBOCS] baseline values of 23–26). In a fixed-dose study of 12 weeks' duration involving paroxetine dosages of 20, 40, or 60 mg daily, patients receiving 40 or 60 mg of the drug daily experienced substantially greater reductions in the YBOCS total score (approximately 6 and 7 points, respectively) than those receiving paroxetine 20 mg daily (approximately 4 points) or placebo (approximately 3 points). The effective dosage of paroxetine was 40 or 60 mg daily. In a 12-week study with flexible dosing of paroxetine (20–60 mg daily) or clomipramine (25–250 mg daily) compared with placebo, paroxetine-treated patients exhibited a mean reduction of approximately 7 points on the YBOCS total score, which was substantially greater than the mean reduction of approximately 4 points in patients receiving placebo. No age- or gender-related differences in outcome were noted in either of these studies.

The efficacy of paroxetine for long-term use (i.e., longer than 12 weeks) has been demonstrated in a 6-month relapse prevention trial, which was an extension of the fixed-dose study of 12 weeks' duration in patients who had responded to paroxetine. Patients who received paroxetine relapsed substantially less frequently than those receiving placebo in a double-blind placebo-controlled study. The manufacturers and many experts state that obsessive-compulsive disorder is chronic and requires several months or longer of sustained therapy. Therefore, it is reasonable to continue therapy in responding patients. If paroxetine is used for extended periods, dosage should be adjusted so that patients are maintained on the lowest effective dosage, and the need for continued therapy with the drug should be reassessed periodically.

Results from comparative studies to date suggest that paroxetine and other SSRIs (e.g., fluoxetine, fluvoxamine, sertraline) are as effective as or somewhat less effective than clomipramine in the management of obsessive-compulsive disorder. In a pooled analysis of separate short-term (10–13 weeks) studies comparing clomipramine, fluoxetine, fluvoxamine, or sertraline with placebo, clomipramine was calculated as being more effective (as determined by measures on the YBOC scale) than SSRIs, although all drugs were superior to placebo. Like clomipramine, SSRIs reduce but do not completely eliminate obsessions and compulsions.

Many clinicians consider an SSRI (e.g., paroxetine, fluoxetine, fluvoxamine, sertraline) or clomipramine to be the drugs of choice for the pharmacologic treatment of obsessive-compulsive disorder. The decision whether to initiate therapy with an SSRI or clomipramine often is made based on the adverse effect profile of these drugs. For example, some clinicians prefer clomipramine in patients who may not tolerate the adverse effect profile of SSRIs (nausea, headache, overstimulation, sleep disturbances) while SSRIs may be useful alternatives in patients unable to tolerate the adverse effects (anticholinergic effects, cardiovascular effects, sedation) associated with clomipramine therapy. Consideration of individual patient characteristics (age, concurrent medical conditions), pharmacokinetics of the drug, potential drug interactions, and cost of therapy may also influence clinicians when selecting between SSRIs and clomipramine as first-line therapy in patients with obsessive-compulsive disorder.

Pediatric Considerations In children† with obsessive-compulsive disorder, cognitive behavioral therapy and/or serotonin-reuptake inhibitors (such as clomipramine and SSRIs) may be beneficial. Controlled studies evaluating paroxetine in this setting currently are lacking and it remains to be established whether one serotonin-reuptake inhibitor is more effective than another. Pending further data, some experts state that the choice of an agent may depend on their adverse effect profile, potential for adverse drug interactions, and the presence of comorbid conditions. Although clomipramine has been more extensively studied to date than SSRI, it has the most prominent anticholinergic effects, requires electrocardiographic (ECG) monitoring, and is the most toxic following acute overdosage. SSRIs do not require ECG monitoring; however, they are associated with headache, nausea, insomnia, and agitation. If a decision is made to initiate SSRI therapy in a child with obsessive-compulsive disorder, some experts recommend starting with a low initial dosage and then gradually increasing the dosage as tolerated. If there is no clinical response after 10–12 weeks, consideration should be given to switching to another SSRI or clomipramine. (See Cautions: Pediatric Precautions.)

Although combined clomipramine and SSRI therapy has been effective in a limited number of children and adolescents with obsessive-compulsive disorder, very close monitoring of the ECG, blood clomipramine concentrations, and vital signs is necessary because of the risks of potentially dangerous drug interactions (including serotonin syndrome) and adverse effects with such combinations. (See Drug Interactions: Serotonergic Drugs.) As in adults, the optimal duration of pharmacologic therapy in children with obsessive-compulsive disorder remains unclear. Although periodic trials of gradual withdrawal from drug therapy are advisable, some children appear to require long-term maintenance therapy to prevent relapse.

■ **Panic Disorder** Paroxetine is used in the treatment of panic disorder with or without agoraphobia. Panic disorder is characterized by the occurrence of unexpected panic attacks and associated concern about having additional attacks, worry about the implications or consequences of the attacks, and/or a clinically important change in behavior related to the attacks.

According to DSM-IV, panic disorder is characterized by recurrent unexpected panic attacks, which consist of a discrete period of intense fear or discomfort in which 4 (or more) of the following symptoms develop abruptly and reach a peak within 10 minutes: palpitations, pounding heart, or accelerated heart rate; sweating; trembling or shaking; sensations of shortness of breath or smothering; feeling of choking; chest pain or discomfort; nausea or abdominal distress; feeling dizzy, unsteady, lightheaded, or faint; derealization (feelings of unreality) or depersonalization (being detached from oneself); fear of losing control; fear of dying; paresthesias (numbness or tingling sensations); and chills or hot flushes.

The efficacy of paroxetine hydrochloride for the management of panic disorder with or without agoraphobia has been established by multicenter, double-blind, placebo-controlled studies in adult outpatients who met DSM-IIIR criteria for panic disorder with or without agoraphobia. In a fixed-dose study of 10 weeks' duration in which paroxetine was given in dosages of 10, 20, and 40 mg daily, a substantially greater reduction in panic attack frequency from placebo was noted only in the patients receiving paroxetine 40 mg daily; at the end of the study, 76% of patients receiving paroxetine 40 mg daily were free of panic attacks compared with 44% of those receiving placebo. In 2 studies of 12 weeks' duration employing a flexible dosing schedule, greater improvement was reported in patients receiving paroxetine 10–60 mg daily than in those receiving placebo. In one study, 51% of the paroxetine recipients compared with 32% of the placebo recipients were free of panic attacks at the end of the study, and in the other study which was conducted in patients receiving standardized cognitive behavioral therapy, 33% of patients receiving paroxetine 10–60 mg daily had a reduction in panic attack frequency to 0 or 1 panic attacks during the study period compared with 14% of those receiving placebo. The mean paroxetine dosage for those completing these 2 flexible-dose studies was approximately 40 mg daily.

In these studies, paroxetine was found to be substantially more effective than placebo in the treatment of panic disorder in at least 2 out of 3 measures of panic attack frequency and on the Clinical Global Impression Severity of Illness Scale. The results of the studies conducted to date demonstrate that paroxetine reduces global anxiety, depressive symptoms, phobic avoidance, and improves overall impairment associated with panic disorder.

The efficacy of paroxetine hydrochloride extended-release tablets for the management of panic disorder with or without agoraphobia has been established in multicenter, placebo-controlled, flexible-dosage studies in patients with panic disorder with or without agoraphobia. In 2 studies, paroxetine extended-release tablets were more effective than placebo, but a third study failed to show any benefit compared with placebo.

The efficacy of paroxetine for long-term use (i.e., longer than 12 weeks) has been demonstrated in controlled studies. In a 3-month relapse prevention trial which was an extension of the 10-week, fixed-dose study, patients who were responders to paroxetine were randomized to receive either paroxetine (10, 20, or 40 mg daily) or placebo. The patients receiving long-term therapy with paroxetine relapsed substantially less frequently than those receiving placebo. In another controlled study, patients receiving paroxetine therapy for 1 year demonstrated not only long-term efficacy but also continued improvement. The manufacturers and some clinicians state that panic disorder is a chronic condition; therefore, it is reasonable to continue therapy in responding patients. Dosage adjustment may be necessary to maintain the patient on the lowest effective dosage, and patients should be reassessed periodically to determine the need for continued therapy.

Subgroup analysis in controlled studies for possible age- or gender-related effects on treatment outcome did not suggest any difference in efficacy based on either the age or sex of the patient.

The results of controlled studies suggest that paroxetine is as effective as and better tolerated than clomipramine in the treatment of panic disorder. In addition, paroxetine was found to have a more rapid onset of action than clomipramine in reducing the number of panic attacks in one study.

Unlike imipramine which reduces heart rate variability in patients with panic disorder (a condition associated with decreased heart rate variability and consequently an increased risk of serious cardiovascular problems including sudden cardiac death), paroxetine has been shown to normalize heart rate variability in a limited number of patients with panic disorder. The clinical importance of these findings with regard to potentially decreasing cardiovascular mortality in patients with panic disorder remains to be determined.

Panic disorder can be treated with cognitive and behavioral psychotherapy and/or pharmacologic therapy. There are several classes of drugs that appear to be effective in the pharmacologic management of panic disorder, including tricyclic antidepressants (e.g., imipramine, clomipramine), monoamine oxidase (MAO) inhibitors (e.g., phenelzine), selective serotonin-reuptake inhibitors (SSRIs; e.g., citalopram, fluoxetine, sertraline, paroxetine), and benzodiazepines (e.g., alprazolam, clonazepam). When choosing among the available drugs, clinicians should consider their acceptance and tolerability by patients; their ability to reduce or eliminate panic attacks, reduce clinically important anxiety and disability secondary to phobic avoidance, and ameliorate other common comorbid conditions (such as depression); and their ability to prevent relapse during long-term therapy. Because of their better tolerability when com-

pared with other agents (such as the tricyclic antidepressants and benzodiazepines), the lack of physical dependence problems commonly associated with benzodiazepines, and efficacy in panic disorder with comorbid conditions (e.g., depression, other anxiety disorders such as obsessive-compulsive disorder, alcoholism), many clinicians prefer SSRIs as first-line therapy in the management of panic disorder. If SSRI therapy is ineffective or is not tolerated, use of a tricyclic antidepressant or a benzodiazepine is recommended.

■ **Social Phobia** Paroxetine hydrochloride is used in the treatment of social phobia (social anxiety disorder). According to DSM-IV, social phobia is characterized by a marked and persistent fear of one or more social or performance situations in which the person is exposed to unfamiliar people or to possible scrutiny by others. Exposure to the feared situation almost invariably provokes anxiety, which may approach the intensity of a panic attack. The feared situations are avoided or endured with intense anxiety or distress. The avoidance, fear, or anxious anticipation of encountering the social or performance situation interferes significantly with the person's daily routine, occupational or academic functioning, or social activities or relationships, or there is marked distress about having the phobias. Lesser degrees of performance anxiety or shyness generally do not require psychotherapy or pharmacologic treatment.

The efficacy of paroxetine hydrochloride in the treatment of social phobia has been established in 3 multicenter, placebo-controlled studies in adult outpatients who met DSM-IV criteria for social phobia. In 2 studies of 12 weeks' duration in which paroxetine was given in dosages ranging from 20–50 mg daily, significant improvement in the Clinical Global Impressions (CGI) Improvement score and Liebowitz Social Anxiety Scale (LSAS) were noted. In these studies, 69 or 77% of paroxetine-treated patients were CGI Improvement responders compared with 29 or 42% of placebo-treated patients. In the third study, paroxetine was given in fixed dosages of 20, 40, or 60 mg daily for 12 weeks. There was significant improvement in the CGI Improvement responder criterion and LSAS Total Score in patients receiving 20 mg daily compared with placebo. Although there were trends in superiority noted in those receiving 40 or 60 mg daily compared with placebo, the results did not reach statistical significance and there was no indication that dosages exceeding 20 mg daily provide any additional benefit.

Subgroup analysis of these controlled studies in adult outpatients with social anxiety disorder did not reveal any evidence of age- or gender-related differences in treatment outcome. Safety and efficacy of paroxetine for the treatment of social phobia in children or adolescents have not been established to date.

■ **Anxiety Disorders** Paroxetine hydrochloride is used in the management of generalized anxiety disorder. According to DSM-IV-TR, generalized anxiety disorder is characterized by excessive anxiety and worry (apprehensive expectation), occurring more days than not for at least 6 months, about a number of events or activities (e.g., work or school performance). Patients with generalized anxiety disorder find it difficult to control the worry. The anxiety and worry are accompanied by at least 3 of the following somatic symptoms in adults and at least 1 of these symptoms in children: restlessness or feeling keyed up or on edge, being easily fatigued, difficulty concentrating or mind going blank, irritability, muscle tension, and sleep disturbance (e.g., difficulty falling or staying asleep, restless unsatisfying sleep). These symptoms cause clinically important distress or impairment in social, occupational, or other important areas of functioning and are not caused by direct physiologic effects of substances (e.g., medications, drugs of abuse, toxin exposure) or by a general medical condition (e.g., hyperthyroidism). Although patients with generalized anxiety disorder may have another underlying mental disorder (axis I disorder), the focus of the anxiety and worry is unrelated to the latter disorder and does not occur only during the course of a mood, psychotic, or pervasive developmental disorder.

Selective serotonin-reuptake inhibitors (SSRIs) are among several classes of antidepressants recommended by some clinicians as first-line treatment for generalized anxiety disorder because of their safety, tolerability (e.g., lack of physical dependence problems commonly associated with benzodiazepines), and proven efficacy in the treatment of depression and other anxiety disorders (e.g., obsessive-compulsive disorder, panic disorder) that frequently present as comorbid conditions in patients with generalized anxiety disorder. Because an estimated 80% of patients with generalized anxiety disorder will have a comorbid mood disorder (e.g., depression) during their lifetime, an SSRI or a drug that predominantly inhibits serotonin and norepinephrine reuptake (e.g., venlafaxine) is preferred by some clinicians for treatment of patients with long-standing generalized anxiety disorder and in those with several comorbid mood or anxiety disorders. However, the efficacy of antidepressants, including paroxetine, in the management of generalized anxiety disorder in patients with comorbid conditions such as depression has yet to be established, since such patients have been excluded from study entry, and therefore further research is needed.

Efficacy of paroxetine hydrochloride for the management of generalized anxiety disorder has been established in 2 randomized, multicenter, placebo-controlled studies of 8 weeks' duration in adult outpatients who met DSM-IV criteria for generalized anxiety disorder. One study employed fixed paroxetine dosages, and the other employed a flexible dosing schedule. In the flexible-dose study, approximately 62% of patients receiving paroxetine (20–50 mg daily; mean dosage of 26.8 mg daily) had a score of 1 ("very much improved") or 2 ("much improved") on the Clinical Global Impressions (CGI) Global Improvement scale, and approximately 36% of these patients had complete or nearly complete resolution of anxiety (defined as a Hamilton Rating Scale for Anxiety [HAM-A] total score of 7 or less), compared with approximately 47 and 23%, respectively, of patients receiving placebo. These results were similar to those seen in the fixed-dose study, in which a score of 1 or 2 on the CGI Global Improvement scale was attained by 62, 68, or 46%, respectively, and a HAM-A total score of 10 or less was attained by 49, 52, or 33%, respectively, of patients receiving paroxetine 20 or 40 mg daily or placebo. However, in a third study, reductions in HAM-A total score attained by patients receiving flexible dosages of paroxetine (20–50 mg daily; mean dosage of 23.8 mg daily) were not substantially different than those attained by patients receiving placebo. Subgroup analysis of these controlled studies in adult outpatients with generalized anxiety disorder did not reveal any evidence of gender- or race-related differences in treatment outcome.

Systematic evaluation of continuing paroxetine for periods of up to 6 months in patients with generalized anxiety disorder who had responded while taking paroxetine during an 8-week acute treatment phase has demonstrated a benefit of such maintenance therapy. In a double-blind, 24-week relapse prevention trial that was an extension of a single-blind, 8-week acute treatment study, patients who had responded to paroxetine 20–50 mg daily were randomized to receive either paroxetine at the same dosage or placebo. Relapse during the double-blind phase was defined as an increase of 2 or more points on the CGI-Severity of Illness scale to a score of 4 or higher or drug discontinuance due to lack of efficacy. The paroxetine-treated patients experienced a significantly lower relapse rate over the 24-week period compared with those receiving placebo. In addition, 73% of patients receiving a total of 32 weeks of paroxetine therapy achieved remission (defined as a HAM-A total score of 7 or less) compared with about 34% of those who received 8 weeks of therapy and then received 24 weeks of placebo. Because generalized anxiety disorder is a chronic condition, it is reasonable to continue therapy in responding patients. Dosage adjustment may be necessary to maintain patients receiving long-term paroxetine therapy on the lowest effective dosage, and patients should be reassessed periodically to determine the need for continued therapy.

Results of a comparative study indicate that the anxiolytic effects of paroxetine are comparable to those of imipramine, a tricyclic antidepressant, and slightly superior to those of 2′-chlordesmethyldiazepam, a benzodiazepine (not commercially available in the US). In this study, during the first 2 weeks of therapy, 2′-chlordesmethyldiazepam displayed greater anxiolytic efficacy, as measured by HAM-A score, than paroxetine or imipramine; however, following 8 weeks of therapy, a 50% or greater decrease in HAM-A score was attained by 68, 72, or 55% of patients receiving paroxetine, imipramine, or 2′-chlordesmethyldiazepam, respectively. Antidepressants such as paroxetine appear to affect predominantly psychic symptoms, whereas benzodiazepines such as 2′-chlordesmethyldiazepam appear to affect predominately somatic symptoms associated with generalized anxiety disorder.

■ **Posttraumatic Stress Disorder** Paroxetine hydrochloride is used in the treatment of posttraumatic stress disorder (PTSD). PTSD is an anxiety disorder that involves the development of certain characteristic symptoms following personal exposure to an extreme traumatic stressor. According to DSM-IV, PTSD requires exposure to a traumatic event(s) that involved actual or threatened death or serious injury, or threat to the physical integrity of self or others, and the response to the event must involve intense fear, helplessness, or horror (in children the response may be expressed by disorganized or agitated behavior). PTSD is characterized by persistent symptoms of *reexperiencing* the trauma (e.g., intrusive, distressing recollections of the event; recurrent distressing dreams of the event; acting or feeling as if the event were recurring including illusions, hallucinations, or flashbacks; intense distress at exposure to internal or external cues that symbolize or resemble an aspect of the event; physiologic reactivity on exposure to internal or external cues that symbolize or resemble an aspect of the event), persistent *avoidance* of stimuli associated with the trauma and numbing of general responsiveness (e.g., efforts to avoid thoughts, feelings, or conversations related to the event; efforts to avoid activities, places, or people that arouse recollections of the event; inability to recall an important aspect of the event; markedly diminished interest or participation in significant activities; feeling of detachment or estrangement from others; restricted emotions and/or range of affect not present before the event; sense of a foreshortened future); and persistent symptoms of *increased arousal* (e.g., difficulty sleeping; irritability/outbursts of anger; difficulty concentrating; hypervigilance; exaggerated startle response). According to DSM-IV, a PTSD diagnosis requires the presence of 1 or more symptoms of *reexperiencing*, 3 or more symptoms of *avoidance*, and 2 or more symptoms of *increased arousal*, all of which must be present for at least 1 month and cause clinically important distress or impairment in social, occupational, or other important areas of functioning. PTSD, like other anxiety disorders, rarely occurs alone, and patients with PTSD often present with comorbid disorders (e.g., major depressive disorder, substance abuse disorders, panic disorder, generalized anxiety disorders, obsessive-compulsive disorder, social phobia); it is unknown whether these comorbid disorders precede or follow the onset of PTSD.

Psychotherapy alone or in combination with pharmacotherapy generally is considered the treatment of choice for PTSD. Pharmacologic therapy may be indicated in addition to psychotherapy for initial treatment of PTSD in patients who have comorbid disorders (e.g., major depressive disorder, bipolar disorder, other anxiety disorders) and also may be indicated in those who do not respond to initial treatment with psychotherapy alone. If pharmacotherapy is indicated in patients with PTSD, selective serotonin-reuptake inhibitors (SSRIs; e.g.,

fluoxetine, paroxetine, sertraline) usually are considered the drugs of choice (except in patients with bipolar disorder who require treatment with mood-stubilizing agents).

Efficacy of paroxetine hydrochloride in the treatment of PTSD has been established in 2 multicenter, placebo-controlled studies of 12 weeks' duration in adult outpatients (66–68% women) with a primary diagnosis (DSM-IV) of PTSD following physical or sexual assault (48–54%), witnessing injury or death (17–19%), serious accident or injury (6–13%), or exposure to combat (5–8%). The mean duration of PTSD for these patients was approximately 13 years and 41 or 40% of patients had secondary depressive disorders or non-PTSD anxiety disorders, respectively. In these studies, patients receiving fixed (20 or 40 mg daily) or flexible (20–50 mg daily; mean: 27.6 mg daily) dosages of paroxetine had substantially greater changes from baseline on the Clinician-Administered PTSD Scale Part 2 (CAPS-2) score, a multi-item instrument that measures 3 aspects of PTSD with the following symptom clusters: reexperiencing/intrusion, avoidance/numbing, and hyperarousal, and were more likely to have a score of 1 (very much improved) or 2 (much improved) on the Clinical Global Impression-Global Improvement Scale (CGI-I) compared with those receiving placebo. Treatment response in the fixed-dose study appeared to be unaffected by patient's gender, type of trauma, duration of PTSD, or severity of baseline PTSD or comorbid conditions. A third study, also a flexible-dose study comparing paroxetine (20–50 mg daily) with placebo, demonstrated paroxetine to be substantially superior to placebo as assessed by improvement from baseline for CAPS-2 total score, but not by proportion of responders on the CGI-I.

Use of paroxetine in the treatment of chronic PTSD did not appear to produce a complete remission in a substantial proportion of patients receiving the drug in clinical studies. Therefore, some clinicians suggest combined use of psychotherapy with pharmacotherapy in order to optimize treatment outcome; however, further studies are needed.

■ **Premenstrual Dysphoric Disorder** Like some other selective serotonin-reuptake inhibitors (SSRIs; e.g., fluoxetine, sertraline), paroxetine is used in the treatment of premenstrual dysphoric disorder (previously late luteal phase dysphoric disorder). In women suffering from severe premenstrual dysphoric disorder treated daily for 3 menstrual cycles with paroxetine, maprotiline, or placebo, paroxetine was found to be superior to maprotiline or placebo in improving symptoms associated with this disorder. In women with severe premenstrual dysphoric disorder receiving paroxetine 5–30 mg daily for 10 consecutive menstrual cycles, paroxetine also markedly reduced symptoms (premenstrual irritability, depressed mood, increase in appetite, anxiety/tension). The improvement in symptoms continued throughout the entire treatment period; sedation, dry mouth, and nausea occurred commonly but declined during therapy whereas adverse sexual effects (reduced libido, anorgasmia) persisted. Additional controlled studies are needed to determine whether the efficacy of the drug is sustained during longer-term, maintenance therapy in women with this condition. For further information on use of SSRIs in the treatment of premenstrual dysphoric disorder, see Uses: Premenstrual Dysphoric Disorder, in Fluoxetine Hydrochloride 28:16.04.20.

■ **Premature Ejaculation** Like some other SSRIs, paroxetine has been used with some success in the treatment of premature ejaculation†. In a placebo-controlled study in men with premature ejaculation, paroxetine (20 mg daily for the first week followed by 40 mg daily for 5 additional weeks) produced substantially greater clinical improvement (increased intravaginal ejaculation latency time, increased number of thrusts before ejaculation) than placebo. Nearly all the patients in this study reported some improvement in ejaculatory latency during the first week of paroxetine therapy. In an open study, paroxetine 20 mg daily improved premature ejaculation within about 14 days with all patients studied reporting a longer interval before ejaculation. When dosages of 20 or 40 mg daily were compared in patients with primary premature ejaculation, 20 mg daily was found to be sufficient; further study is needed to determine whether higher dosages may further increase ejaculation latency. In a study comparing paroxetine 20 mg daily for 6 months with paroxetine 20 mg daily for 14 days followed by 10 mg daily for a total of 6 months, both regimens were found to be similarly effective in improving premature ejaculation and were well tolerated. There is some evidence that paroxetine may be more effective than other SSRIs in terms of increasing intravaginal ejaculation latency time.

Additional studies have investigated the use of paroxetine on an "as needed" basis for the treatment of premature ejaculation. In one study, men with premature ejaculation (mean age: 39.5 years; mean pretreatment ejaculatory latency time: 0.3 minutes) were randomized to receive 20 mg of paroxetine or placebo 3–4 hours before planned intercourse; at 4 weeks, the mean ejaculatory latency time was 3.2–3.5 minutes in those receiving the drug compared with 0.45–0.6 minutes in those receiving placebo. However, mean ejaculatory latency time was even longer in another group of men (mean age: 40.5 years; mean pretreatment ejaculatory latency time: 0.5 minutes) who received an initial regimen of paroxetine 10 mg daily for 3 weeks and then received paroxetine 20 mg on an as needed basis for 4 weeks.

Further controlled studies are necessary to confirm these findings, to determine the optimal dosage regimen, and to evaluate the long-term efficacy of paroxetine in patients with this condition. Some clinicians advise that a trial with drug therapy may be particularly useful in patients with premature ejaculation who fail or refuse behavioral or psychotherapeutic treatment or when partners are unwilling to cooperate with such therapy.

■ **Diabetic Neuropathy** Tricyclic antidepressants generally have been considered a mainstay of therapy for the treatment of diabetic neuropathy. However, because of potentially improved patient tolerability, therapy with selective serotonin-reuptake inhibitors (SSRIs) or selective serotonin- and norepinephrine-reuptake inhibitors (SNRIs; e.g., duloxetine, venlafaxine) has been attempted as an alternative. In a controlled study, paroxetine (40 mg daily) was effective in a limited number of patients in substantially reducing the symptoms associated with diabetic neuropathy† and was somewhat less effective but better tolerated than imipramine. Because patients who did not respond as well to paroxetine as to imipramine had lower plasma paroxetine concentrations, it was suggested that dosage adjustment based on plasma concentration monitoring potentially may be useful in the management of this condition. When compared with earlier results obtained with imipramine in the management of diabetic neuropathy, SSRIs such as citalopram, fluoxetine, paroxetine, and sertraline generally appear to be less effective but better tolerated overall. Additional study and experience are needed to elucidate the relative roles of SSRIs versus tricyclic antidepressants, SNRIs, anticonvulsants (e.g., pregabalin, gabapentin), and other forms of treatment in the management of this condition.

■ **Chronic Headache** Paroxetine has been used in a limited number of patients with chronic headache† with some success. In an open study, patients with chronic daily headache unresponsive to previous therapy were treated with paroxetine 10–50 mg daily for 3–9 months; most of the patients showed reductions in the number of headache days per month. Fatigue, insomnia, and urogenital disturbances were the most common adverse effects reported in this study. In a double-blind, crossover study in nondepressed patients with chronic tension-type headache comparing paroxetine (20–30 mg daily) and sulpiride (a dopamine antagonist; not commercially available in the US), both drugs improved headache although sulpiride appeared to provide greater relief. Additional controlled studies are needed to confirm these preliminary findings.

■ **Bipolar Disorder** Paroxetine has been used for the short-term management of acute depressive episodes in patients with bipolar disorder†. While antidepressants such as selective serotonin-reuptake inhibitors (SSRIs) have shown good efficacy in the treatment of unipolar depression, the drugs generally have been studied as adjuncts to mood stabilizing agents such as lithium or valproate in the management of bipolar disorder; antidepressant monotherapy is *not* recommended, given the risk of precipitating a switch into mania. The American Psychiatric Association (APA) currently recommends that paroxetine be reserved for patients who had an inadequate therapeutic response to optimal therapy with first-line agents (i.e., lithium, lamotrigine) or who do not tolerate these drugs. If paroxetine was effective for the management of an acute depressive episode, including during the continuation phase, then maintenance therapy with the drug should be considered to prevent recurrence of major depressive episodes. For further information on the management of bipolar disorder, see Uses: Bipolar Disorder, in Lithium Salts 28:28.

Dosage and Administration

■ **Administration** Paroxetine hydrochloride and paroxetine mesylate are administered orally.

Paroxetine hydrochloride conventional tablets, extended-release tablets, and suspension usually are administered once daily in the morning. Since food does not appear to substantially affect GI absorption of paroxetine hydrochloride, the drug generally can be administered without regard to meals; however, administration with food may minimize adverse GI effects. The manufacturer of paroxetine hydrochloride makes no specific recommendations about administration of paroxetine with regard to food.

Paroxetine mesylate conventional tablets are administered once daily, usually in the morning, without regard to meals.

Paroxetine hydrochloride oral suspension should be shaken well just prior to administration of each dose.

Extended-release tablets of paroxetine hydrochloride should be swallowed whole and should *not* be chewed or crushed.

■ **Dosage** Paroxetine is commercially available in the US as paroxetine hydrochloride (e.g., Paxil®, Paxil CR®) and as paroxetine mesylate (i.e., Pexeva®). Conventional tablets of Paxil® and Pexeva® are *not* bioequivalent. The US Food and Drug Administration (FDA) considers paroxetine mesylate (Pexeva®) conventional tablets to be a pharmaceutical *alternative* (as described in section 505[b][2] of the Federal Food, Drug, and Cosmetic Act) and *not* a pharmaceutical (generic) equivalent to paroxetine hydrochloride conventional tablets (e.g., Paxil®), since both contain the same active moiety (paroxetine) but have different salts.

Dosages of paroxetine hydrochloride and paroxetine mesylate are expressed in terms of paroxetine.

Patients receiving paroxetine should be monitored for possible worsening of depression, suicidality, or unusual changes in behavior, especially at the beginning of therapy or during periods of dosage adjustment. (See Cautions: Precautions and Contraindications.)

The manufacturers recommend that an interval of at least 2 weeks elapse when switching a patient from a monoamine oxidase (MAO) inhibitor to paroxetine or when switching from paroxetine to an MAO inhibitor. For additional information on potentially serious drug interactions that may occur between paroxetine and MAO inhibitors or other serotonergic agents, see Cautions: Precautions and Contraindications and see also Drug Interactions: Serotonergic Drugs.

Clinical experience regarding the optimal timing of switching from other antidepressants to paroxetine therapy is limited. Therefore, care and prudent medical judgment should be exercised when switching from other antidepressants, particularly from long-acting agents (e.g., fluoxetine), to paroxetine. Because some adverse reactions resembling serotonin syndrome have developed when fluoxetine therapy has been abruptly discontinued and therapy with another serotonin-reuptake inhibitor (sertraline) initiated immediately afterward, a washout period may be advisable when transferring a patient from fluoxetine to another SSRI. However, the appropriate duration of the washout period when switching from other serotonin-reuptake inhibitors to paroxetine has not been clearly established. Pending further experience in patients being transferred from therapy with another antidepressant to paroxetine and as the clinical situation permits, it generally is recommended that the previous antidepressant be discontinued according to the recommended guidelines for the specific antidepressant prior to initiation of paroxetine therapy.

Because withdrawal effects may occur (see Cautions: Nervous System Effects and see Chronic Toxicity), abrupt discontinuance of paroxetine should be avoided. The manufacturers and some clinicians recommend that paroxetine therapy be discontinued gradually (e.g., over a period of several weeks) and the patient monitored carefully when paroxetine therapy is discontinued to prevent the possible development of withdrawal reactions. If intolerable symptoms occur following dosage reduction or upon discontinuance of treatment, paroxetine therapy may be reinstituted at the previously prescribed dosage until such symptoms abate. Clinicians may resume dosage reductions at that time but at a more gradual rate.

Major Depressive Disorder For the management of major depressive disorder in adults, the recommended initial dosage of paroxetine is 20 mg daily as conventional tablets or suspension or 25 mg daily as extended-release tablets. If no clinical improvement is apparent, dosage may be increased in increments of 10 mg daily for conventional tablets or suspension or 12.5 mg daily for extended-release tablets at intervals of not less than 1 week up to a maximum of 50 mg daily for conventional tablets or suspension or 62.5 mg daily for extended-release tablets. While a relationship between dosage and antidepressant effect has not been established, efficacy of the drug was demonstrated in clinical trials employing 20–50 mg daily dosages as conventional tablets or suspension and 25–62.5 daily dosages as extended-release tablets. Like with other antidepressants, the full antidepressant effects may be delayed.

While the optimum duration of paroxetine therapy has not been established, many experts state that acute depressive episodes require several months or longer of sustained antidepressant therapy. In addition, some clinicians recommend that long-term antidepressant therapy be considered in certain patients at risk for recurrence of depressive episodes (such as those with highly recurrent unipolar depression). Whether the dosage of paroxetine required to induce remission is identical to the dosage needed to maintain and/or sustain euthymia is unknown. In a controlled study, a paroxetine dosage of 40 mg daily was more effective in preventing recurrences of depression than 20 mg daily in patients with recurrent, unipolar depression. Systematic evaluation of paroxetine hydrochloride has shown that its antidepressant efficacy is maintained for periods of up to 1 year in patients receiving a mean dosage of 30 mg daily as conventional tablets or suspension, which corresponds to a 37.5 mg dosage of paroxetine extended-release tablets. In addition, the drug has been used in some patients for longer periods (e.g., up to 4 years) without apparent loss of clinical effect or increased toxicity. If paroxetine is used for extended periods, dosage should be adjusted so that the patient is maintained on the lowest effective dosage, and the need for continued therapy should be reassessed periodically.

Obsessive-Compulsive Disorder For the management of obsessive-compulsive disorder in adults, the recommended initial dosage of paroxetine is 20 mg daily as conventional tablets or suspension. If no clinical improvement is apparent, dosage may be increased in 10-mg increments at intervals of not less than 1 week. The manufacturers recommend a paroxetine dosage of 40 mg daily in the treatment of obsessive-compulsive disorder. Efficacy of the drug was demonstrated in clinical trials employing paroxetine dosages of 20–60 mg daily. The manufacturers state that paroxetine dosage should not exceed 60 mg daily.

Although the optimum duration of paroxetine therapy required to prevent recurrence of obsessive-compulsive symptoms has not been established to date, the efficacy of paroxetine for long-term use (i.e., longer than 12 weeks) has been demonstrated in a 6-month relapse prevention trial. Patients who received paroxetine relapsed substantially less frequently than those receiving placebo. The manufacturers and many clinicians state that obsessive-compulsive disorder is chronic and requires several months or longer of sustained therapy. Therefore, it is reasonable to continue therapy in responding patients. If paroxetine is used for extended periods, dosage should be adjusted so that the patient is maintained on the lowest effective dosage, and the need for continued therapy with the drug should be reassessed periodically.

Panic Disorder For the management of panic disorder in adults, the recommended initial dosage of paroxetine is 10 mg daily as conventional tablets or suspension or 12.5 mg daily as extended-release tablets. Dosage should be increased in 10-mg increments for those receiving conventional tablets or suspension or in 12.5-mg increments for those receiving extended-release tablets at intervals of not less than 1 week. The manufacturers recommend dosages of 40 mg daily for paroxetine conventional tablets or suspension in the treatment of panic disorder. Efficacy of the drug was demonstrated in clinical trials employing 10–60 mg daily as conventional tablets or suspension or 12.5–75 mg daily as extended-release tablets. The manufacturers state that paroxetine dosages should not exceed 60 mg daily for conventional tablets or suspension and 75 mg daily for extended-release tablets.

Although the optimum duration of paroxetine therapy required to prevent recurrence of panic disorder has not been established to date, the efficacy of paroxetine for long-term use (i.e., longer than 12 weeks) has been demonstrated in a 3-month relapse prevention trial. Patients who were treated with paroxetine hydrochloride conventional tablets or suspension (10–40 mg daily) relapsed substantially less frequently than those receiving placebo. The manufacturers and some clinicians state that panic disorder is a chronic condition; therefore, it is reasonable to continue therapy in responding patients. Dosage adjustment may be necessary to maintain the patient on the lowest effective dosage, and patients receiving the drug for extended periods should be reassessed periodically to determine the need for continued therapy.

Social Phobia For the management of generalized social phobia (social anxiety disorder) in adults, the recommended dosage of paroxetine (administered as paroxetine hydrochloride) is 20 mg daily as conventional tablets or suspension or 12.5 mg daily as extended-release tablets. Dosage of the extended-release tablets may be increased in increments of 12.5 mg daily at intervals of not less than 1 week. Efficacy of the drug was demonstrated in clinical trials employing dosages of 20–60 mg daily as conventional tablets or suspension or 12.5–37.5 mg daily as extended-release tablets. The manufacturer of paroxetine hydrochloride states that no additional clinical benefit was observed at dosages exceeding 20 mg daily for conventional tablets or suspension and that the maximum dosage for extended-release tablets should not exceed 37.5 mg daily.

Although the efficacy of paroxetine for long-term therapy (i.e., longer than 12 weeks) has not been demonstrated in controlled studies to date, the manufacturer of paroxetine hydrochloride states that it is reasonable to consider continuation of therapy for a patient who responds to the drug. If paroxetine is used for extended periods, dosage should be adjusted so that the patient is maintained on the lowest effective dosage, and the need for continued therapy should be reassessed periodically.

Anxiety Disorder For the management of generalized anxiety disorder in adults, the recommended initial dosage of paroxetine (administered as paroxetine hydrochloride) is 20 mg daily as conventional tablets or suspension. Although dosages of 20–50 mg daily were effective in clinical studies, there is insufficient evidence to indicate that dosages exceeding 20 mg daily provide additional clinical benefit. Dosage of paroxetine should be increased in 10-mg increments at intervals of not less than 1 week.

The optimum duration of paroxetine therapy for the management of generalized anxiety disorder has not been established to date. Because this disorder is chronic, it is reasonable to continue therapy in responding patients. In general, patients with generalized anxiety disorder usually require at least 8 weeks of treatment to achieve a Hamilton Rating Scale for Anxiety (HAM-A) score of 10 or less, which has been shown to be the score at which specific treatment effects can begin to be distinguished from nonspecific placebo effects. However, available data suggest that some patients may require an extended duration of treatment in order to achieve a HAM-A score of 7–10 or less. In a 32-week, multicenter, relapse-prevention study in outpatients with generalized anxiety disorder and a mean baseline HAM-A score of 26.5, about 34% of patients achieved remission (defined as a HAM-A total score of 7 or less) following 8 weeks of paroxetine therapy compared with 73% of patients following 32 weeks of paroxetine therapy. In addition, patients receiving long-term therapy with the drug relapsed substantially less frequently than those receiving placebo.

Because of the prolonged nature of depressive episodes in patients with generalized anxiety disorder and comorbid depression, some clinicians currently recommend that such patients be treated for at least 12 months to ensure remission of both anxiety and depression. If paroxetine is used for extended periods, dosage should be adjusted so that patients are maintained on the lowest effective dosage, and the need for continued therapy with the drug should be reassessed periodically.

Posttraumatic Stress Disorder For the management of posttraumatic stress disorder (PTSD) in adults, the recommended dosage of paroxetine (administered as paroxetine hydrochloride) is 20 mg daily as conventional tablets or suspension. Although efficacy has been established for dosages ranging from 20–50 mg daily, there is insufficient evidence to suggest a greater benefit with 40 mg daily compared with 20 mg daily. If a dosage increase above 20 mg daily is considered necessary, it should be in increments of 10 mg daily at intervals of at least 1 week.

Some clinicians suggest that an adequate trial period for determining the effectiveness of paroxetine in patients with PTSD is 8 weeks; patients who have not achieved at least a 25% reduction in PTSD symptoms at week 8 generally are unlikely to respond to continued paroxetine therapy and use of alternative agents is recommended in such patients. In addition, although the optimum duration of paroxetine therapy required to prevent recurrence of PTSD has not been established to date, some clinicians recommend up to 24 months of drug therapy in patients who achieve good response (i.e., greater than 75% reduction in PTSD symptoms and response maintained for at least 3 months). Although the efficacy of paroxetine for long-term therapy (i.e., longer than 12 weeks) has not been demonstrated in controlled studies to date, PTSD is a chronic condition for which it is reasonable to continue paroxetine therapy as long as a response is maintained. If paroxetine is used for extended periods,

dosage should be adjusted so that the patient is maintained on the lowest possible effective dosage, and the need for continued therapy with the drug should be reassessed periodically.

Premenstrual Dysphoric Disorder For the treatment of premenstrual dysphoric disorder (previously late luteal phase dysphoric disorder), the recommended initial dosage of paroxetine (administered as paroxetine hydrochloride) is 12.5 mg daily as extended-release tablets. Dosage should be increased at intervals of not less than 1 week. In clinical trials, both the 12.5-mg and 25-mg daily dosages were shown to be effective.

Efficacy of paroxetine for long-term therapy (i.e., longer than 3 menstrual cycles) has not been demonstrated in controlled studies to date. However, women commonly report that symptoms worsen with age until relieved by the onset of menopause. Therefore, the manufacturer of paroxetine hydrochloride states that it is reasonable to consider continuation of therapy for a patient who responds to the drug. Patients should be periodically reassessed to determine the need for continued treatment.

Premature Ejaculation For the treatment of premature ejaculation†, paroxetine has been given in a dosage of 10–40 mg daily to increase ejaculatory latency time. Alternatively, patients have taken paroxetine on an "as needed" basis for the treatment of premature ejaculation using 20-mg doses of the drug 3–4 hours before planned intercourse. However, one study noted more prolonged ejaculatory latency time if patients received paroxetine in a dosage of 10 mg daily for 3 weeks prior to using 20-mg doses of the drug on an as needed basis.

Diabetic Neuropathy In patients with diabetic neuropathy†, paroxetine has been given in a dosage of 40 mg daily to reduce the symptoms associated with the disease.

Chronic Headache In the management of chronic headache†, paroxetine has been given in a dosage of 10–50 mg daily for 3–9 months to reduce the number of headaches per month.

■ **Dosage in Geriatric and Debilitated Patients** In geriatric or debilitated patients, an initial paroxetine dosage of 10 mg daily as conventional tablets or suspension or 12.5 mg daily as extended-release tablets is recommended; if no clinical improvement is apparent, dosage may be titrated up to a maximum of 40 mg daily (for conventional tablets or suspension) or 50 mg (for extended-release tablets).

■ **Dosage in Renal and Hepatic Impairment** In patients with severe renal or hepatic impairment, an initial paroxetine dosage of 10 mg daily as conventional tablets or suspension or 12.5 mg daily as extended-release tablets is recommended. If no clinical improvement is apparent, dosage may be titrated with caution up to a maximum of 40 mg daily (for conventional tablets or suspension) or 50 mg (for extended-release tablets). (See Pharmacokinetics: Elimination and see Cautions: Precautions and Contraindications.)

■ **Treatment of Pregnant Women during the Third Trimester** Because some neonates exposed to paroxetine and other SSRIs or selective serotonin- and norepinephrine-reuptake inhibitors (SNRIs) late in the third trimester of pregnancy have developed severe complications, consideration may be given to cautiously tapering paroxetine therapy in the third trimester prior to delivery if the drug is administered during pregnancy. (See Cautions: Pregnancy, Fertility, and Lactation.)

Cautions

The adverse effect profile of paroxetine is similar to that of other selective serotonin-reuptake inhibitors (SSRIs; e.g., citalopram, escitalopram, fluoxetine, fluvoxamine, sertraline). Paroxetine is commercially available in the US as paroxetine hydrochloride (e.g., Paxil®, Paxil CR®) and as paroxetine mesylate (i.e., Pexeva®). The main clinical studies with paroxetine have been conducted with paroxetine hydrochloride, and the incidences of adverse effects reported in this section are from clinical trials using the hydrochloride salt. Because paroxetine hydrochloride and paroxetine mesylate contain the same active moiety (paroxetine), tolerability is expected to be similar between the 2 different salts. However, direct comparison studies have not been conducted to date, and the possibility that differences in tolerability between paroxetine hydrochloride and paroxetine mesylate may exist should be taken into consideration.

Because paroxetine is a highly selective serotonin-reuptake inhibitor with little or no effect on other neurotransmitters, the incidence of some adverse effects commonly associated with tricyclic antidepressants, such as anticholinergic effects (dry mouth, constipation), cardiovascular effects, drowsiness, and weight gain, is lower in patients receiving paroxetine. However, certain adverse GI (e.g., nausea, anorexia) and nervous system (e.g., somnolence, anxiety, nervousness, insomnia) effects appear to occur more frequently with paroxetine and other SSRIs than with tricyclic antidepressants.

Overall, the adverse effect profile of paroxetine in patients with depression, obsessive-compulsive disorder, panic disorder, social phobia, generalized anxiety disorder, or posttraumatic stress disorder (PTSD) appears to be similar. In controlled studies, the most common adverse effects occurring more frequently in patients receiving paroxetine than in those receiving placebo included nervous system effects such as asthenia, somnolence, dizziness, insomnia, tremor, and nervousness; GI effects such as nausea, decreased appetite, constipation, diarrhea, and dry mouth; impotence, ejaculatory dysfunction (principally ejaculatory delay), and other male genital disorders; female genital disorders (principally anorgasmia or difficulty reaching climax/orgasm); and sweating. The incidence of many of these adverse effects appears to be dose related in patients with depression; however, there was no clear evidence of dose-related adverse events in patients with obsessive-compulsive disorder or social phobia. In addition, there was no clear relationship between the incidence of adverse events and dose except for asthenia, dry mouth, anxiety, decreased libido, tremor, and abnormal ejaculation in the treatment of panic disorder and asthenia, constipation, and abnormal ejaculation in the treatment of generalized anxiety disorder.

Patients receiving paroxetine may develop tolerance to some adverse effects (e.g., nausea, dizziness) with continued therapy (e.g., after 4–6 weeks); however, tolerance is less likely to develop to other adverse effects such as dry mouth, somnolence, and asthenia. During short-term (6 weeks or less) studies, nausea was the most common adverse effect, whereas during long-term studies, headache, sweating, weight gain, and constipation were among the most common. Discontinuance of paroxetine therapy was required in 20% of patients with depression, about 16% of patients with social phobia, about 12% of patients with obsessive-compulsive disorder or PTSD, about 11% of patients with generalized anxiety disorder, and about 9% of patients with panic disorder in clinical trials, principally because of adverse psychiatric (e.g., somnolence, insomnia, agitation, tremor), other nervous system (e.g., dizziness, asthenia), GI (e.g., nausea, vomiting, diarrhea, constipation, dry mouth), or male urogenital (e.g., abnormal ejaculation, impotence) effects or because of sweating.

■ **Nervous System Effects** Somnolence, which appears to be dose related, is among the most common adverse effects of paroxetine, occurring in approximately 23% of depressed patients receiving the drug in short-term controlled clinical trials. Somnolence required discontinuance of therapy in about 2% of patients. Headache occurred in about 18 or 15% of patients receiving paroxetine in short- or long-term controlled clinical trials, respectively. In addition, migraine or vascular headache has been reported in up to 1% or less than 0.1% of paroxetine-treated patients, respectively. Asthenia, which also appears to be dose related, occurred in 15% of depressed patients receiving the drug in short-term controlled clinical trials and required discontinuance of therapy in about 2% of patients.

Dizziness, which appears to be dose related, occurred in about 13% of patients receiving paroxetine in short-term controlled clinical trials. Insomnia occurred in about 13 or 8% of patients receiving the drug in short- or long-term controlled clinical trials, respectively. However, because insomnia is a symptom also associated with depression, relief of insomnia and improvement in sleep patterns may occur when clinical improvement in depression becomes apparent during antidepressant therapy. In clinical trials, less than 2% of patients discontinued paroxetine because of insomnia.

Tremor occurred in about 8%, nervousness or anxiety each in about 5%, paresthesia in about 4%, and agitation in about 2% of patients receiving paroxetine in short-term controlled clinical trials. The incidence of tremor and paresthesia may be dose related. Agitation and tremor each resulted in discontinuance of the drug in about 1% of patients receiving the drug in clinical trials. Drugged feeling or confusion occurred in about 2 or 1% of patients, respectively.

The incidence of seizures during paroxetine therapy appears to be similar to that observed during therapy with most other currently available antidepressants. Seizures, including tonic-clonic (grand mal) seizures, occurred in less than 0.1% of patients receiving paroxetine in clinical trials. (See Cautions: Precautions and Contraindications.) In addition, myoclonus has been reported in about 1% of patients receiving the drug.

Hypomania, mania, manic reaction, and manic-depressive reaction have been reported in approximately 1% of patients receiving paroxetine in short- or long-term controlled clinical trials, which is similar to the incidence reported in patients receiving active control agents (i.e., other antidepressants). The incidence of these adverse effects was 0.3% in unipolar patients receiving placebo. In a subset of patients classified as having bipolar disorder, the incidence of manic episodes was 2.2% in patients receiving paroxetine and 11.6% in patients receiving other antidepressants. (See Cautions: Precautions and Contraindications.) Such reactions have occurred in patients receiving other antidepressant agents and may be caused by antidepressant-induced functional increases in catecholamine activity within the CNS, resulting in a "switch" from depressive to manic behavior. There is some evidence that patients with bipolar disorder may be more likely to experience antidepressant-induced hypomanic or manic reactions than patients without evidence of this disorder. In addition, limited evidence suggests that such reactions may occur more frequently in bipolar depressed patients receiving tricyclics and tetracyclics (e.g., maprotiline, mianserin [not commercially available in the US]) than in those receiving SSRIs (e.g., citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline). However, further studies are needed to confirm these initial findings.

Amnesia, CNS stimulation, impaired concentration; precipitation or worsening of depression, emotional lability, and vertigo each have been reported in at least 1% of patients receiving paroxetine; however, a causal relationship to the drug has not been established. Abnormal thinking, lack of emotion, neurosis, paralysis, paranoid reaction, alcohol abuse, depersonalization, delirium, euphoria, hallucinations, hostility, ataxia, dyskinesia, hyperkinesia, hypesthesia, hypokinesia, and incoordination have been reported in up to 1% of patients receiving the drug, although these adverse effects have not been definitely attributed to paroxetine.

Extrapyramidal reactions associated with paroxetine, which are uncommon, appear to be a class effect of SSRIs and dose related. Reactions occurring *early* during therapy with the drug may be secondary to preexisting parkinsonian

syndrome and/or concomitant therapy. Paroxetine and other SSRIs have been associated with the development of akathisia, which is characterized by an inner sense of restlessness and psychomotor agitation such as an inability to sit or stand still usually associated with subjective distress. Akathisia is most likely to occur within the first few weeks of therapy with these drugs. Other extrapyramidal symptoms reported in patients receiving paroxetine include dystonia, bradykinesia, cogwheel rigidity, hypertonia, oculogyric crisis (associated with concomitant use of pimozide), tremor, and trismus; however, a causal relationship to the drug has not been established.

Adverse nervous system effects reported in less than 0.1% of patients receiving paroxetine include akinesia, antisocial reaction, aphasia, choreoathetosis, circumoral paresthesias, delusions, drug dependence, dysarthria, fasciculations, gait abnormalities, hyperalgesia, hyperreflexia, decreased reflexes, hysteria, meningitis, myelitis, neurulgia, neuropathy, nystagmus, psychotic depression, stupor, and torticollis; these effects have not been definitely attributed to the drug. Fatigue also has been reported. Although a causal relationship to the drug has not been established, serotonin syndrome and neuroleptic malignant syndrome (NMS)-like reactions also have been reported rarely in patients receiving paroxetine, other SSRIs, and selective serotonin- und norepinephrine-reuptake inhibitors. (See Cautions: Precautions and Contraindications, Drug Interactions: Serotonergic Drugs, and Acute Toxicity.)

Status epilepticus has been reported during postmarketing surveillance in patients receiving paroxetine, although a causal relationship to the drug has not been established. Guillain-Barré syndrome has been reported rarely in association with paroxetine; however, a causal relationship to the drug has not been clearly established.

Withdrawal Effects Withdrawal syndrome, manifested as dizziness, blurred vision, sweating, nausea, insomnia, tremor, confusion, lethargy, insomnia, sensory disturbances, anxiety or nervousness, headache, paresthesias, hypomanic-like symptoms (including hyperactivity, decreased need for sleep, irritability, agitation, aggressiveness, volatility, explosive vocal und temper outbursts), and ego-dystonic impulsive behavior (including shoplifting, homicidal impulses, suicidal impulses and gestures) following discontinuance of the drug, also has been reported in less than 0.1% of patients receiving paroxetine. Although manifestations of withdrawal generally have been mild, transient and self-limiting, abrupt discontinuance of the drug should be avoided. Some evidence suggests that the risk of withdrawal effects may be somewhat greater with paroxetine than sertraline; fluoxetine appears to be associated with the fewest withdrawal effects, possibly because of its prolonged elimination half-life. Additional clinical experience is necessary to confirm these findings. (See Chronic Toxicity.)

Suicidality The US Food and Drug Administration (FDA) has determined that antidepressants increase the risk of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults (18–24 years of age) with major depressive disorder and other psychiatric disorders. Patients, therefore, should be appropriately monitored and closely observed for clinical worsening, suicidality, and unusual changes in behavior, particularly during initiation of paroxetine therapy (i.e., the first few months) and during periods of dosage adjustments. (See Cautions: Precautions and Contraindications, Cautions: Pediatric Precautions, and Acute Toxicity.)

■ **GI Effects** Like other SSRIs (e.g., citalopram, escitalopram, fluoxetine, fluvoxamine, sertraline), paroxetine therapy is associated with a relatively high incidence of GI disturbances, principally nausea, dry mouth, and bowel abnormalities. The most frequent adverse effect associated with paroxetine therapy is nausea, which occurred in about 26% of patients receiving the drug in controlled clinical trials. Nausea generally is mild to moderate in severity and usually subsides after a few weeks of continued therapy with the drug. The incidence of nausea appears to be dose related. In clinical trials, nausea required discontinuance of paroxetine in about 3% of patients and was the most frequent adverse effect requiring discontinuance of the drug. Overall, adverse GI effects, principally nausea, required discontinuance of paroxetine therapy in about 6% of patients receiving the drug in clinical trials. While the mechanism(s) of paroxetine-induced GI effects has not been fully elucidated, they appear to arise at least in part because of increased serotonergic activity in the GI tract (which may result in stimulation of small intestine motility and inhibition of gastric and large intestine motility) and possibly because of the drug's effect on central serotonergic type 3 ($5\text{-}HT_3$) receptors.

Dry mouth occurred in about 18%, constipation in about 14%, diarrhea in about 12%, and decreased appetite in about 6% of patients receiving paroxetine in short-term controlled clinical trials. Other adverse GI effects associated with paroxetine therapy include flatulence, which occurred in 4%, and vomiting, which occurred in about 2% of patients receiving the drug in short-term controlled clinical trials. Vomiting generally is mild to moderate in severity and required discontinuance of the drug in about 1% of patients receiving the drug in controlled trials. Oropharyngeal disorders (principally lump or tightness in the throat), taste perversion, and dyspepsia were reported in about 2% and abdominal pain and increased appetite were reported in at least 1% of patients receiving paroxetine. The incidence of constipation, anorexia, decreased appetite, and dry mouth appear to be dose related.

Although a causal relationship to paroxetine has not been established, bruxism, colitis, dysphagia, eructation, gastroenteritis, gingivitis, glossitis, increased salivation, rectal hemorrhage, and ulcerative stomatitis have been reported in up to 1% of patients receiving the drug. Aphthous stomatitis, stomatitis, esophagitis, duodenitis, enteritis, peptic or gastric ulcer, ileus, peritonitis, hematemesis, bloody diarrhea, intestinal obstruction, fecal impaction or incontinence, melena, bulimia, cholelithiasis, tongue discoloration, tongue edema, mouth ulceration, loss of taste, gingival hemorrhage, salivary gland enlargement, and dental caries have been reported in less than 0.1% of patients receiving paroxetine. In addition, laryngismus has been reported during postmarketing surveillance. However, these adverse effects have not been definitely attributed to the drug.

Epidemiologic case-control and cohort design studies have suggested that SSRIs may increase the risk of upper GI bleeding. Although the precise mechanism for this increased risk remains to be clearly established, serotonin release by platelets is known to play an important role in hemostasis, and SSRIs decrease serotonin uptake from the blood by platelets thereby decreasing the amount of serotonin in platelets. In addition, concurrent use of aspirin or other nonsteroidal anti-inflammatory drugs was found to substantially increase the risk of GI bleeding in patients receiving SSRIs in 2 of these studies. Although these studies focused on upper GI bleeding, there is evidence suggesting that bleeding at other sites may be similarly potentiated. Further clinical studies are needed to determine the clinical importance of these findings. (See Cautions: Hematologic Effects and see also Drug Interactions: Drugs Affecting Hemostasis.)

■ **Dermatologic and Sensitivity Reactions** Rash, which may be maculopapular or vesiculobullous, has been reported in about 2% of patients receiving paroxetine in short-term controlled clinical trials. Pruritus has been reported in at least 1% of patients receiving the drug. In addition, allergic reactions have been reported in up to 1% of patients in clinical trials, and allergic alveolitis and anaphylaxis have been reported during postmarketing surveillance. However, these adverse effects have not been definitely attributed to paroxetine.

Adverse dermatologic effects reported in up to 1% of patients receiving paroxetine include acne, alopecia, contact dermatitis, dry skin, eczema, herpes simplex, photosensitivity, and urticaria; however, these adverse effects have not been definitely attributed to the drug. Angioedema, erythema nodosum, erythema multiforme, exfoliative dermatitis, fungal dermatitis, furunculosis, herpes zoster, hirsutism, maculopapular rash, seborrhea, skin discoloration, skin hypertrophy, decreased sweating, and skin ulcer have been reported in less than 0.1% of patients receiving the drug. In addition, toxic epidermal necrolysis has been reported rarely.

Sweating occurred in about 11–12% of patients receiving paroxetine in short- or long-term controlled clinical trials and required discontinuance of therapy in approximately 1% of patients. The incidence of sweating appears to be dose related.

■ **Metabolic and Endocrine Effects** Weight gain occurred in at least 1% of patients receiving paroxetine in controlled clinical trials. While clinically important weight loss may occur in some patients, only minimal weight loss (averaging 0.45 kg) generally occurred in up to 17% of patients receiving paroxetine in controlled clinical trials. In addition, while decreased appetite was reported in about 6% of patients receiving paroxetine in short-term clinical trials, the drug, unlike fluoxetine, does not appear to exhibit clinically important anorectic effects.

Ketosis and increased LDH concentrations have also been reported in less than 1% of paroxetine-treated patients, although a causal relationship to the drug has not been established. Thirst has been reported in up to 1% of patients receiving paroxetine, although a causal relationship to the drug has not been established. Adverse effects reported in less than 0.1% of patients receiving the drug include gout, hypercholesterolemia, hyperglycemia, hypoglycemia, and increased creatine kinase (CK, creatine phosphokinase, CPK), gamma globulin and nonprotein nitrogen concentrations; however, these adverse effects also have not been definitely attributed to paroxetine.

Diabetes mellitus, goiter, hyperthyroidism, hypothyroidism, thyroiditis, and symptoms suggestive of prolactinemia and galactorrhea have been reported in less than 0.1% of patients receiving paroxetine; however, these adverse effects have not been definitely attributed to the drug.

■ **Ocular and Otic Effects** Blurred vision, which appears to be dose related, occurred in about 4% of patients receiving paroxetine in controlled clinical trials. Adverse ocular effects reported in up to 1% of patients receiving paroxetine include abnormality of accommodation, conjunctivitis, ocular pain, mydriasis, and keratoconjunctivitis. Although a causal relationship to paroxetine has not been established, amblyopia, blepharitis, diplopia, cataract, conjunctival edema, corneal ulcer, exophthalmos, ocular hemorrhage, glaucoma, photophobia, night blindness, ptosis, retinal hemorrhage, and visual field defect, have been reported in less than 0.1% of patients receiving the drug. Anisocoria and optic neuritis also have been reported in at least one paroxetine-treated patient; these adverse effects have not been definitely attributed to the drug.

Tinnitus occurred in at least 1% of patients receiving paroxetine in controlled clinical trials. Otic pain or otitis media has been reported in up to 1% of patients receiving paroxetine. Deafness, hyperacusis, otitis externa, and parosmia have been reported in less than 0.1% of patients.

■ **Cardiovascular Effects** Paroxetine does not exhibit clinically important anticholinergic activity, and current evidence suggests that paroxetine is less cardiotoxic than most older antidepressant agents (e.g., tricyclic antidepressants, monoamine oxidase inhibitors).

No clinically important changes in vital signs (systolic and diastolic blood

pressure, heart rate) were observed in patients receiving paroxetine in controlled trials. Unlike tricyclic antidepressants, which may cause characteristic ECG changes such as prolongation of PR, QRS, and QT intervals and ST-segment and T-wave abnormalities, clinically important ECG changes have not been reported during controlled clinical trials in paroxetine-treated patients. However, small but statistically significant QRS widening was reported with paroxetine relative to placebo in one study, and ECG changes occasionally have been reported in healthy individuals and patients receiving the drug. In addition, the relative safety of paroxetine in patients with underlying cardiac disease remains to be more fully elucidated.

Palpitation and vasodilation each have been reported in about 3% of patients receiving paroxetine in short-term controlled clinical trials. Unlike tricyclic antidepressants, paroxetine has been associated with hypotension (e.g., orthostatic) infrequently; in short-term controlled clinical trials, orthostatic hypotension occurred in at least 1% of patients receiving the drug. Chest pain also occurred in about 1–2% of patients in such trials. Hypertension, syncope, and tachycardia also have been reported in at least 1% of patients receiving paroxetine. Bradycardia and generalized peripheral and facial edema have been reported in up to 1% of patients receiving the drug, although a definite causal relationship to paroxetine has not been established. Angina pectoris, myocardial ischemia, myocardial infarction, cerebral ischemia, cerebrovascular accident, pallor, congestive heart failure, low cardiac output, arrhythmia nodal, supraventricular or ventricular extrasystoles, atrial fibrillation, heart block, bundle-branch block, pulmonary embolus, thrombosis, phlebitis, and varicose veins have been reported in less than 0.1% of patients receiving paroxetine; these adverse effects have not been definitely attributed to the drug.

In addition, ventricular fibrillation, ventricular tachycardia (including torsades de pointes), and pulmonary hypertension have been reported during postmarketing surveillance; however, these adverse effects have not been definitely attributed to paroxetine.

■ **Musculoskeletal Effects** Myopathy or myalgia occurred in about 2% of patients receiving paroxetine in short-term controlled clinical trials. In addition, arthralgia has been reported in at least 1% of patients receiving the drug. Myasthenia or back pain was reported in about 1% of patients receiving the drug in such trials. Arthritis or neck pain has been reported in up to 1% of patients receiving paroxetine, although a causal relationship to the drug has not been established. Arthrosis, bursitis, myositis, neck rigidity, osteoporosis, generalized spasm, tenosynovitis, and tetany have been reported in less than 0.1% of patients receiving paroxetine; these adverse effects have not been definitely attributed to the drug.

■ **Hematologic Effects** Anemia, eosinophilia, leukocytosis, leukopenia, ecchymosis, and purpura have been reported in up to 1% of patients receiving paroxetine, although a causal relationship to the drug has not been established. Altered platelet function and abnormal bleeding also have been reported. The manufacturers state that there have been several cases of abnormal bleeding (mostly ecchymosis and purpura) and a case of impaired platelet aggregation in patients receiving paroxetine to date. In one woman, widespread bruising developed on the arms, legs, and hips 15 days after paroxetine therapy was begun; the bruising subsided following discontinuance of the drug. In another female patient, spontaneous bruising of the arms and legs and excessive menstrual blood loss developed 2 weeks after starting paroxetine therapy; addition of ascorbic acid 500 mg daily improved the bleeding after 3 weeks but subsequent discontinuance of ascorbic acid led to a gradual recurrence of these symptoms. Similar reactions have been reported in several patients receiving other SSRIs (e.g., fluoxetine, fluvoxamine, sertraline). Although the precise mechanism for these reactions has not been established, it has been suggested that impaired platelet aggregation caused by platelet serotonin depletion and/or increased capillary fragility may contribute to these cases. (See Cautions: GI Effects and see also Drug Interactions: Drugs Affecting Hemostasis.)

Although a causal relationship to the drug has not been established, hemolytic anemia, impaired hematopoiesis (including aplastic anemia, pancytopenia, bone marrow aplasia, and agranulocytosis), porphyria, and thrombocytopenia have been reported during postmarketing surveillance in patients receiving paroxetine. Abnormal erythrocytes or lymphocytes; prolonged bleeding time; hypochromic anemia, iron-deficiency anemia, microcytic anemia, or normocytic anemia; eosinophilia, leukoeytosis, lymphocytosis, and monocytosis each have been reported in less than 0.1% of patients receiving paroxetine; these adverse effects have not been definitely attributed to the drug.

■ **Respiratory Effects** Respiratory disorders (principally cold symptoms and upper respiratory infections), pharyngitis and other oropharyngeal disorders (sensation of having a lump or tightness in the throat), increased cough, rhinitis, and sinusitis have been reported in at least 1% of patients receiving paroxetine in short-term controlled clinical trials. Yawning occurred in about 4% of patients receiving the drug.

Adverse effects reported in up to 1% of patients receiving paroxetine include asthma, dyspnea, epistaxis, hyperventilation, bronchitis, pneumonia, and respiratory influenza; however, a causal relationship to the drug has not been established. Other adverse respiratory effects reported in less than 0.1% of patients receiving paroxetine include emphysema, hemoptysis, hiccups, lung fibrosis, pulmonary edema, increased sputum production, stridor, and voice alteration; these adverse effects have not been definitely attributed to the drug. Pulmonary alveolitis has been reported rarely.

■ **Renal, Electrolyte, and Genitourinary Effects** ***Sexual Dysfunction*** Like other SSRIs, adverse effects on sexual function have been reported in both men and women receiving paroxetine. Although changes in sexual desire, sexual performance, and sexual satisfaction often occur as manifestations of a psychiatric disorder, they also may occur as the result of pharmacologic therapy. It is difficult to determine the true incidence and severity of adverse effects on sexual function during paroxetine therapy, in part because patients and clinicians may be reluctant to discuss these effects. Therefore, incidence data reported in product labeling and earlier studies are most likely underestimates of the true incidence of adverse sexual effects. Recent reports indicate that up to 50% of patients receiving SSRIs describe some form of sexual dysfunction during treatment and the actual incidence may be even higher. Results of some (but not all) studies in men and women suggest that paroxetine may be associated with a higher incidence of sexual dysfunction than some other currently available SSRIs.

Ejaculatory disturbances (principally ejaculatory delay), which appear to be dose related, are the most common adverse urogenital effects associated with paroxetine in males, reported by the manufacturer as occurring in about 13–28% of male patients receiving the drug compared with 0–2% of patients receiving placebo in controlled clinical studies for the treatment of depression, obsessive-compulsive disorder, panic disorder, social phobia, generalized anxiety disorder, or posttraumatic stress disorder. Abnormal ejaculation was a reason for drug discontinuance in up to about 5% of patients in these controlled clinical studies. However, the adverse effect of ejaculatory delay has been used for therapeutic benefit in the treatment of premature ejaculation. (See Uses: Premature Ejaculation.)

Decreased libido was reported in 6–15% of male patients receiving paroxetine in controlled clinical studies for the treatment of depression, obsessive-compulsive disorder, panic disorder, social phobia, generalized anxiety disorder, or PTSD compared with 0–5% of males receiving placebo. In these studies, impotence was reported in 2–9% of male patients receiving paroxetine compared with 0–3% of males receiving placebo.

In female patients receiving paroxetine in controlled clinical studies for the treatment of depression, obsessive-compulsive disorder, panic disorder, social phobia, generalized anxiety disorder, or PTSD, decreased libido was reported in 0–9% of those receiving paroxetine compared with 0–2% of women receiving placebo. In these studies, orgasmic disturbances were reported in 2–9% of female patients receiving the drug compared with 0–1% of female patients receiving placebo.

Increased libido has been reported in up to 1% of patients receiving paroxetine. Other reported adverse sexual effects include anorgasmia, erectile difficulties, and delayed orgasm. Priapism also has been reported in male patients receiving the drug.

Results of some (but not all) studies in men and women suggest that paroxetine may be associated with a higher incidence of sexual dysfunction than some other currently available SSRIs, including citalopram and sertraline. Since it is difficult to know the precise risk of sexual dysfunction associated with serotonin-reuptake inhibitors, clinicians should routinely inquire about such possible adverse effects in patients receiving these drugs.

Management of sexual dysfunction caused by SSRI therapy includes waiting for tolerance to develop; using a lower dosage of the drug; using drug holidays; delaying administration of the drug until after coitus; or changing to another antidepressant. Although further study is needed, there is some evidence that adverse sexual effects of SSRIs may be reversed by concomitant use of certain drugs, including buspirone, 5-hydroxytryptamine-2 (5-HT_2) receptor antagonists (e.g., nefazodone), 5-HT_3 receptor inhibitors (e.g., granisetron), or α_2-adrenergic receptor antagonists (e.g., yohimbine), selective phosphodiesterase (PDE) inhibitors (e.g., sildenafil), or dopamine receptor agonists (e.g., amantadine, dextroamphetamine, pemoline [no longer commercially available in the US], methylphenidate). In most patients, sexual dysfunction is fully reversed 1–3 days after discontinuance of the antidepressant.

Other Renal, Electrolyte, and Genitourinary Effects Treatment with SSRIs, including paroxetine, and selective serotonin- and norepinephrine-reuptake inhibitors (SNRIs) may result in hyponatremia. In many cases, this hyponatremia appears to be due to the syndrome of inappropriate antidiuretic hormone secretion (SIADH) and was reversible when the SSRI or SNRI was discontinued. Cases with serum sodium concentrations lower than 110 mEq/L have been reported. Hyponatremia has been reported following paroxetine overdosage in a geriatric patient. Hyponatremia and SIADH in patients receiving SSRIs usually develop an average of 2 weeks after initiating therapy (range: 3–120 days). Geriatric individuals and patients receiving diuretics or who are otherwise volume depleted may be at greater risk of developing hyponatremia during therapy with SSRIs or SNRIs. Discontinuance of paroxetine should be considered in patients with symptomatic hyponatremia and appropriate medical intervention should be instituted. Because geriatric patients may be at increased risk for hyponatremia associated with these drugs, clinicians prescribing paroxetine in such patients should be aware of the possibility that such reactions may occur. In addition, periodic monitoring of serum sodium concentrations (particularly during the first several months) in geriatric patients receiving SSRIs has been recommended by some clinicians.

Hyperkalemia, hypercalcemia, hyperphosphatemia, dehydration, increased BUN, hypocalcemia, and hypokalemia have been reported in less than 0.1% of patients receiving the drug; however, these adverse effects have not been definitely attributed to paroxetine.

Urinary frequency and urinary disorders (principally difficulty with micturition or urinary hesitancy) have been reported in about 3% of patients receiving paroxetine in short-term controlled clinical trials. Although a definite

causal relationship to paroxetine has not been established, amenorrhea, breast pain, menorrhagia, cystitis, urinary tract infection, dysuria, hematuria, nocturia, polyuria, pyuria, urinary incontinence, urinary retention, urinary urgency, and vaginitis have been reported in up to 1% of patients receiving the drug. In addition, spontaneous abortion, breast atrophy, vaginal hemorrhage, metrorrhagia, uterine spasm, oliguria, urethritis, salpingitis, urinary casts, renal calculus, renal pain, nephritis, vaginal candidiasis, female lactation, fibrocystic breast, mastitis, and epididymitis have been reported in less than 0.1% of patients receiving paroxetine; however, these adverse effects have not been definitely attributed to paroxetine. Breast enlargement also has been reported in some women receiving chronic therapy with paroxetine or other selective serotonin-reuptake inhibitors. In one study, approximately 40% of patients receiving either selective serotonin-reuptake inhibitors or venlafaxine reported some degree of breast enlargement; most patients with breast enlargement also experienced weight gain, and serum prolactin concentrations were increased in the paroxetine-treated women in this study.

In addition, acute renal failure and eclampsia also have been reported during postmarketing surveillance in patients receiving paroxetine; however, these adverse effects have not been definitely attributed to the drug.

■ **Hepatic Effects** Abnormal liver function test results, including elevations in serum ALT (SGOT) and AST (SGPT) concentrations, have been reported in up to 1% of patients receiving paroxetine, and rarely have been a reason for drug discontinuance. Elevated serum alkaline phosphatase concentrations, bilirubinemia, hepatitis, ascites, and jaundice have been reported in less than 0.1% of patients receiving the drug. In addition, death resulting from liver necrosis and substantially elevated serum aminotransferase (transaminase) concentrations associated with severe liver dysfunction have been reported rarely.

■ **Other Adverse Effects** Fever, influenza-like symptoms, infections, and trauma occurred in at least 2% of patients receiving paroxetine. In addition, chills, influenza, lymphadenopathy, and malaise have been reported in up to 1% of patients receiving the drug. Adrenergic syndrome, cellulitis, lymphedema, moniliasis, pelvic pain, and sepsis have been reported in less than 0.1% of patients receiving the drug, but a definite causal relationship to paroxetine has not been established. Pancreatitis also has been reported during postmarketing surveillance in association with paroxetine; however, a causal relationship to the drug has not been clearly established.

■ **Precautions and Contraindications** Worsening of depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior may occur in both adult and pediatric (see Cautions: Pediatric Precautions) patients with major depressive disorder or other psychiatric disorders, whether or not they are taking antidepressants. This risk may persist until clinically important remission occurs. Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are the strongest predictors of suicide. However, there has been a long-standing concern that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients during the early phases of treatment. Pooled analyses of short-term, placebo-controlled studies of antidepressants (i.e., selective serotonin-reuptake inhibitors and other antidepressants) have shown an increased risk of suicidality in children, adolescents, and young adults (18–24 years of age) with major depressive disorder and other psychiatric disorders. An increased suicidality risk was not demonstrated with antidepressants compared with placebo in adults older than 24 years of age and a reduced risk was observed in adults 65 years of age or older. It is currently unknown whether the suicidality risk extends to longer-term use (i.e., beyond several months); however, there is substantial evidence from placebo-controlled maintenance trials in adults with major depressive disorder that antidepressants can delay the recurrence of depression.

The US Food and Drug Administration (FDA) recommends that all patients being treated with antidepressants for any indication be appropriately monitored and closely observed for clinical worsening, suicidality, and unusual changes in behavior, particularly during initiation of therapy (i.e., the first few months) and during periods of dosage adjustments. Families and caregivers of patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and nonpsychiatric, also should be advised to monitor patients on a daily basis for the emergence of agitation, irritability, or unusual changes in behavior, as well as the emergence of suicidality, and to report such symptoms immediately to a health-care provider.

Although a causal relationship between the emergence of symptoms such as anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia, hypomania, and/or mania and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality. Consequently, consideration should be given to changing the therapeutic regimen or discontinuing therapy in patients whose depression is persistently worse or in patients experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, particularly if such manifestations are severe, abrupt in onset, or were not part of the patient's presenting symptoms. If a decision is made to discontinue therapy, paroxetine dosage should be tapered as rapidly as is feasible but with recognition of the risks of abrupt discontinuance. (See Dosage and Administration: Dosage.) FDA also recommends that the drugs be prescribed in the smallest quantity consistent with good patient management, in order to reduce the risk of overdosage.

It is generally believed (though not established in controlled trials) that treating a major depressive episode with an antidepressant alone may increase the likelihood of precipitating a mixed or manic episode in patients at risk for bipolar disorder. Therefore, patients should be adequately screened for bipolar disorder prior to initiating treatment with an antidepressant; such screening should include a detailed psychiatric history (e.g., family history of suicide, bipolar disorder, and depression).

Potentially life-threatening serotonin syndrome or neuroleptic malignant syndrome (NMS)-like reactions have been reported with SSRIs, including paroxetine, and selective serotonin- and norepinephrine-reuptake inhibitors (SNRIs) alone, but particularly with concurrent administration of other serotonergic drugs (including serotonin [5-hydroxytryptamine; 5-HT] type 1 receptor agonists ["triptans"]), drugs that impair the metabolism of serotonin (e.g., monoamine oxidase [MAO] inhibitors), or antipsychotic agents or other dopamine antagonists. Manifestations of serotonin syndrome may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination), and/or GI symptoms (e.g., nausea, vomiting, diarrhea). In its most severe form, serotonin syndrome may resemble NMS, which is characterized by hyperthermia, muscle rigidity, autonomic instability with possible rapid fluctuation in vital signs, and mental status changes. Patients receiving paroxetine should be monitored for the development of serotonin syndrome or NMS-like signs and symptoms.

Concurrent or recent (i.e., within 2 weeks) therapy with MAO inhibitors used for treatment of depression is contraindicated in patients receiving paroxetine. If concurrent therapy with paroxetine and a 5-HT_1 receptor agonist (triptan) is clinically warranted, the patient should be observed carefully, particularly during initiation of therapy, when dosage is increased, or when another serotonergic agent is initiated. Concomitant use of paroxetine and serotonin precursors (e.g., tryptophan) is not recommended. If signs and symptoms of serotonin syndrome or NMS develop during therapy, treatment with paroxetine and any concurrently administered serotonergic or antidopaminergic agents, including antipsychotic agents, should be discontinued immediately and supportive and symptomatic treatment should be initiated. (See Drug Interactions: Serotonergic Drugs.)

Because clinical experience with paroxetine in patients with concurrent systemic disease, including cardiovascular disease, hepatic impairment, or renal impairment, is limited, caution should be exercised when paroxetine is administered to patients with any systemic disease or condition that may alter metabolism of the drug or adversely affect hemodynamic function. (See Dosage and Administration: Dosage.)

Because paroxetine may cause mydriasis, the drug should be used with caution in patients with angle-closure glaucoma.

Paroxetine should be used with caution in patients with severe renal or hepatic impairment, since increased plasma concentrations of the drug may occur in such patients. (See Pharmacokinetics: Elimination and see Dosage and Administration: Dosage in Renal and Hepatic Impairment.)

Although current evidence suggests that paroxetine is less cardiotoxic than most older antidepressant agents (see Cautions: Cardiovascular Effects), the safety of paroxetine in patients with a recent history of myocardial infarction or unstable cardiovascular disease has not been adequately evaluated to date.

Because of the potential for adverse drug interactions, the manufacturers recommend that patients receiving paroxetine be advised to notify their clinician if they are taking or plan to take nonprescription (over-the-counter) or prescription medications or alcohol-containing beverages or preparations. Although paroxetine has not been shown to potentiate the impairment of mental and motor skills caused by alcohol, the manufacturers recommend that patients be advised to avoid alcohol while receiving the drug.

Paroxetine generally is less sedating than most other currently available antidepressants and does not appear to produce substantial impairment of cognitive or psychomotor function nor to potentiate psychomotor impairment induced by other CNS depressants. However, patients should be cautioned that paroxetine may impair their ability to perform activities requiring mental alertness or physical coordination (e.g., operating machinery, driving a motor vehicle), particularly at dosages of 40 mg or more daily, and to avoid such activities until they experience how the drug affects them. In addition, the possibility that paroxetine may potentiate other (i.e., nonpsychomotor) adverse nervous system effects of CNS depressants should be considered.

The manufacturers recommend that patients receiving paroxetine be advised that while they may notice improvement within 1–4 weeks after starting therapy, they should continue therapy with the drug as directed by their physician.

Seizures have been reported in patients receiving therapeutic dosages of paroxetine. Because of limited experience with paroxetine in patients with a history of seizures, the drug should be used with caution in such patients and should be discontinued if seizures occur.

Activation of mania and hypomania has occurred in patients receiving therapeutic dosages of paroxetine. The drug should be used with caution in patients with a history of mania. (See Cautions: Nervous System Effects.)

Paroxetine and other SSRIs have been associated with the development of akathisia, which is characterized by an inner sense of restlessness and psychomotor agitation such as an inability to sit or stand still usually associated with subjective distress. Akathisia is most likely to occur within the first few weeks of therapy with these drugs.

Treatment with SSRIs, including paroxetine, and selective serotonin- and norepinephrine-reuptake inhibitors (SNRIs) may result in hyponatremia. In

many cases, this hyponatremia appears to be due to the syndrome of inappropriate antidiuretic hormone secretion (SIADH) and was reversible when paroxetine was discontinued. Cases with serum sodium concentrations lower than 110 mEq/L have been reported. Geriatric individuals and patients receiving diuretics or who are otherwise volume depleted may be at greater risk of developing hyponatremia during therapy with SSRIs or SNRIs. Signs and symptoms of hyponatremia include headache, difficulty concentrating, memory impairment, confusion, weakness, and unsteadiness, which may lead to falls; more severe and/or acute cases have been associated with hallucinations, syncope, seizures, coma, respiratory arrest, and death. Discontinuance of paroxetine should be considered in patients with symptomatic hyponatremia and appropriate medical intervention should be instituted. (See Cautions: Renal, Electrolyte, and Genitourinary Effects and see also Cautions: Geriatric Precautions.)

The manufacturers state that there have been several cases of abnormal bleeding (mostly ecchymosis and purpura) and a case of impaired platelet aggregation in patients receiving paroxetine. (See Cautions: Hematologic Effects.)

Because paroxetine is the active moiety in both paroxetine mesylate conventional tablets (Pexeva®) and commercially available paroxetine hydrochloride preparations (e.g., Paxil®, nonproprietary [generic] preparations), concurrent administration of paroxetine hydrochloride and paroxetine mesylate should be avoided.

Paroxetine is contraindicated in patients concurrently receiving pimozide. (See Drug Interactions: Pimozide.)

Paroxetine is contraindicated in patients concomitantly receiving thioridazine. (See Drugs Metabolized by Cytochrome P-450 [CYP] 2D6 under Drug Interactions: Drugs Undergoing Hepatic Metabolism or Affecting Hepatic Microsomal Enzymes.)

Paroxetine hydrochloride is contraindicated in patients concurrently receiving linezolid. (See Monoamine Oxidase Inhibitors under Drug Interactions: Serotonergic Drugs.)

Paroxetine also is contraindicated in patients hypersensitive to the drug or any ingredient in the formulation.

■ **Pediatric Precautions** Safety and efficacy of paroxetine in children younger than 18 years of age have not been established.

Paroxetine has not demonstrated efficacy in several placebo-controlled trials in 752 children and adolescents with major depressive disorder. Adverse effects reported in at least 2% of the paroxetine-treated pediatric patients in these trials and that occurred at least twice as frequently as in pediatric patients receiving placebo included emotional lability (including self-harm, suicidal thoughts, attempted suicide, crying, and mood fluctuations), hostility, decreased appetite, tremor, sweating, hyperkinesias, and agitation. Upon discontinuance of paroxetine in these pediatric trials following a taper phase regimen, adverse events that occurred in at least 2% of the paroxetine-treated pediatric patients and occurred at least twice as frequently as in pediatric patients receiving placebo included emotional lability (including suicidal ideation, suicide attempt, mood changes, and tearfulness), nervousness, dizziness, nausea, and abdominal pain.

In June 2003, the United Kingdom (UK) regulatory agency warned clinicians to avoid the off-label use of paroxetine for the treatment of depression in children younger than 18 years of age. This action was taken in response to concern about a possible association between selective serotonin-reuptake inhibitors and suicidal behavior, which includes a broad range of symptoms ranging from episodes of self-harm to attempted suicide. Proprietary data examined by the UK regulatory agency showed a slight increase in suicidal behavior among patients who were randomly assigned to selective serotonin-reuptake inhibitor treatment, as compared with subjects who received placebo.

The US Food and Drug Administration (FDA) determined that the available data at that time were not sufficient either to establish or to rule out an association between the use of these drugs and increased suicidal thoughts or actions by pediatric patients. However, following the results of independent classification and analysis of the suicidal events and behaviors observed in controlled studies, FDA now warns that antidepressants increase the risk of suicidal thinking and behavior (suicidality) in children and adolescents with major depressive disorder and other psychiatric disorders. The risk of suicidality for these drugs was identified in a pooled analysis of data from a total of 24 short-term (4–16 weeks), placebo-controlled studies of 9 antidepressants (i.e., paroxetine, bupropion, citalopram, fluoxetine, fluvoxamine, mirtazapine, nefazodone, sertraline, venlafaxine) in over 4400 children and adolescents with major depressive disorder, obsessive-compulsive disorder (OCD), or other psychiatric disorders. The analysis revealed a greater risk of adverse events representing suicidal behavior or thinking (suicidality) during the first few months of treatment in pediatric patients receiving antidepressants than in those receiving placebo. However, a more recent meta-analysis of 27 placebo-controlled trials of 9 antidepressants (SSRIs and others) in patients younger than 19 years of age with major depressive disorder, OCD, or non-OCD anxiety disorders suggests that the benefits of antidepressant therapy in treating these conditions may outweigh the risks of suicidal behavior or suicidal ideation. No suicides occurred in these pediatric trials.

The risk of suicidality in the FDA's pooled analysis differed across the different psychiatric indications, with the highest incidence observed in the major depressive disorder studies. In addition, although there was considerable variation in risk among the antidepressants, a tendency toward an increase in suicidality risk in younger patients was found for almost all drugs studied. It is currently unknown whether the suicidality risk in pediatric patients extends to longer-term use (i.e., beyond several months).

As a result of this analysis and public discussion of the issue, FDA has directed manufacturers of all antidepressants to add a boxed warning to the labeling of their products to alert clinicians of this suicidality risk in children and adolescents and to recommend appropriate monitoring and close observation of patients receiving these agents. (See Cautions: Precautions and Contraindications.) The drugs that are the focus of the revised labeling are all drugs included in the general class of antidepressants, including those that have not been studied in controlled clinical trials in pediatric patients, since the available data are not adequate to exclude any single antidepressant from an increased risk. In addition to the boxed warning and other information in professional labeling on antidepressants, FDA currently recommends that a patient medication guide explaining the risks associated with the drugs be provided to the patient each time the drugs are dispensed. Caregivers of pediatric patients whose depression is persistently worse or who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality during antidepressant therapy should consult their clinician regarding the best course of action (e.g., whether the therapeutic regimen should be changed or paroxetine discontinued). *Patients should not discontinue use of paroxetine without first consulting their clinician; it is very important that paroxetine not be abruptly discontinued (see Dosage and Administration: Dosage), as withdrawal effects may occur.*

Anyone considering the use of paroxetine in a child or adolescent for any clinical use must balance the potential risk of therapy with the clinical need.

■ **Geriatric Precautions** While safety and efficacy of paroxetine in geriatric patients have not been established specifically, 17% of patients (approximately 700) receiving the drug for depression in clinical trials were 65 years of age or older. Although no overall differences in efficacy or the adverse effect profile of paroxetine were observed between geriatric and younger patients and other clinical experience revealed no evidence of age-related differences, pharmacokinetic studies have revealed a decreased clearance of paroxetine in geriatric patients. (See Pharmacokinetics: Elimination.) For this reason, the manufacturers and some clinicians recommend initiating paroxetine therapy in patients 65 years of age or older at a lower dosage than in younger patients. (See Dosage and Administration: Dosage in Geriatric or Debilitated Patients.)

Geriatric patients appear to be more likely than younger patients to develop paroxetine-induced hyponatremia and transient syndrome of inappropriate secretion of antidiuretic hormone (SIADH). Therefore, clinicians prescribing paroxetine in geriatric patients should be aware of the possibility that such reactions may occur. Periodic monitoring (especially during the first several months) of serum sodium concentrations in geriatric patients receiving the drug has been recommended by some clinicians.

In studies comparing paroxetine and various tricyclic antidepressants, including amitriptyline, clomipramine, and doxepin, in geriatric patients, paroxetine was at least as effective and as well tolerated as or better tolerated than tricyclic antidepressants. In addition, serum anticholinergicity of paroxetine was found to be substantially lower than that of nortriptyline in geriatric depressed patients; complaints of dry mouth and tachycardia also occurred more frequently in nortriptyline-treated patients than in those receiving paroxetine. These findings indicate that, at therapeutic plasma concentrations, paroxetine has approximately 20% the anticholinergic potential of nortriptyline in older patients. Overall, paroxetine was less frequently associated with dry mouth, somnolence, constipation, tachycardia, or confusion than tricyclic antidepressants, although certain adverse effects (e.g., nausea, diarrhea, headache) were more common with paroxetine. In geriatric patients with depression, paroxetine appears to be at least as effective as fluoxetine.

In pooled data analyses, a *reduced* risk of suicidality was observed in adults 65 years of age or older with antidepressant therapy compared with placebo. (See Cautions: Precautions and Contraindications.)

As with other psychotropic drugs, geriatric patients receiving antidepressants appear to have an increased risk of hip fracture. Despite the fewer cardiovascular and anticholinergic effects associated with selective serotonin-reuptake inhibitors (SSRIs), these drugs did not show any advantage over tricyclic antidepressants with regard to hip fracture in a case-control study. In addition, there was little difference in the rates of falls between nursing home residents receiving SSRIs and those receiving tricyclic antidepressants in a retrospective study. Therefore, all geriatric individuals receiving either type of antidepressant should be considered to be at increased risk of falls and appropriate measures should be taken.

■ **Mutagenicity and Carcinogenicity** Paroxetine was not mutagenic in several in vitro tests including the bacterial mutation assay, mouse lymphoma mutation assay, and unscheduled DNA synthesis assay. The drug also was not mutagenic in tests for cytogenetic aberrations in vivo in mouse bone marrow, in vitro in human lymphocytes, and in a dominant lethal test in rats.

Studies to determine the carcinogenic potential of paroxetine were performed in mice receiving oral dosages of 1, 5, and 25 mg/kg daily and in rats receiving dosages of 1, 5, and 20 mg/kg daily for 2 years. In mice, the maximum dosage was up to approximately 2.4 times the maximum human dose for depression, social anxiety disorder, generalized anxiety disorder, and PTSD on a mg/m^2 basis. In rats, the maximum dosage was up to approximately 3.9 times the maximum human dose for depression on a mg/m^2 basis. Because the maximum recommended human dosage for depression, social anxiety disorder, generalized anxiety disorder, and PTSD is slightly lower than that for obses-

sive-compulsive disorder (50 versus 60 mg daily, respectively), the dosages used in these carcinogenicity studies were only about 2 and 3.2 times the maximum recommended human dosage for obsessive-compulsive disorder in mice and rats, respectively. A substantially greater number of male rats in the high-dose group had reticulum cell sarcomas (1/100, 0/50, 0/50, and 4/50 for control, low-, middle-, and high-dose groups, respectively), and a substantially increased linear trend across dose groups was evident for the occurrence of lymphoreticular tumors in male rats. Female rats were not affected. Although there was a dose-related increase in the number of tumors in mice, there was no drug-related increase in the number of mice with tumors. The relationship of these findings to human exposure to paroxetine is not known.

■ **Pregnancy, Fertility, and Lactation** Some neonates exposed to paroxetine and other selective serotonin-reuptake inhibitors (SSRIs) or selective serotonin- and norepinephrine-reuptake inhibitors (SNRIs) late in the third trimester of pregnancy have developed complications that occasionally have been severe and required prolonged hospitalization, respiratory support, enteral nutrition, and other forms of supportive care in special care nurseries. Such complications can arise immediately upon delivery and usually last for several days or up to 2–4 weeks. Clinical findings reported to date in the neonates have included respiratory distress, cyanosis, apnea, seizures, temperature instability or fever, feeding difficulty, dehydration, excessive weight loss, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, lethargy, reduced or lack of reaction to pain stimuli, and constant crying. These clinical features appear to be consistent with either a direct toxic effect of the SSRI or SNRI or, possibly, a drug withdrawal syndrome. It should be noted that, in some cases, the clinical picture was consistent with serotonin syndrome (see Drug Interactions: Serotonergic Drugs). When treating a pregnant woman with paroxetine during the third trimester of pregnancy, the clinician should carefully consider the potential risks and benefits of such therapy. Consideration may be given to cautiously tapering paroxetine therapy in the third trimester prior to delivery if the drug is administered during pregnancy. (See Dosage: Treatment of Pregnant Women during the Third Trimester in Dosage and Administration.)

FDA states that decisions about management of depression in pregnant women are challenging and that the patient and her clinician must carefully consider and discuss the potential benefits and risks of SSRI therapy during pregnancy for the individual woman. Two recent studies provide important information on risks associated with discontinuing or continuing antidepressant therapy during pregnancy.

The first study, which was prospective, naturalistic, and longitudinal in design, compared the potential risk of relapsed depression in pregnant women with a history of major depressive disorder who discontinued or attempted to discontinue antidepressant (SSRIs, tricyclic antidepressants, or others) therapy during pregnancy compared with that in women who continued antidepressant therapy throughout their pregnancy; all women were euthymic while receiving antidepressant therapy at the beginning of pregnancy. In this study, women who discontinued antidepressant therapy were found to be 5 times more likely to have a relapse of depression during their pregnancy than were women who continued to receive their antidepressant while pregnant, suggesting that pregnancy does not protect against a relapse of depression.

The second study suggests that infants exposed to SSRIs in late pregnancy may have an increased risk of persistent pulmonary hypertension of the newborn (PPHN), which is associated with substantial neonatal morbidity and mortality. Persistent pulmonary hypertension of the newborn occurs at a rate of 1–2 neonates per 1000 live births in the general population in the US. In this retrospective case-control study of 377 women whose infants were born with persistent pulmonary hypertension of the newborn and 836 women whose infants were born healthy, the risk for developing persistent pulmonary hypertension of the newborn was approximately sixfold higher for infants exposed to SSRIs after the twentieth week of gestation compared with infants who had not been exposed to SSRIs during this period. The study was too small to compare the risk of persistent pulmonary hypertension of the newborn associated with individual SSRIs, and the findings have not been confirmed. Although the risk of persistent pulmonary hypertension of the newborn identified in this study still is low (6–12 cases per 1000) and further study is needed, the findings add to concerns from previous reports that infants exposed to SSRIs late in pregnancy may experience adverse serotonergic effects.

Reproduction studies in rats receiving oral paroxetine dosages of 50 mg/kg daily and in rabbits receiving 6 mg/kg daily during organogenesis have been conducted. These dosages correspond to approximately 9.7 and 2.2 times the maximum recommended human dose for depression, social anxiety disorder, generalized anxiety disorder, and PTSD and approximately 8.1 and 1.9 times the maximum recommended human dose for obsessive-compulsive disorder on a mg/m^2 basis in rats and rabbits, respectively. Although these studies have not revealed evidence of teratogenicity, an increase in pup deaths was observed in rats during the first 4 days of lactation when dosing occurred during the last trimester of gestation and continued throughout lactation. This effect occurred at a dose of 1 mg/kg daily, which corresponds to 0.19 times the maximum recommended human dose for depression, social anxiety disorder, generalized anxiety disorder, and PTSD and 0.16 times the maximum recommended human dose for obsessive-compulsive disorder on a mg/m^2 basis. The no-effect dose for rat pup mortality has not been determined and the cause of these deaths is not known.

Preliminary analyses from 2 epidemiologic studies have shown that infants born to women exposed to paroxetine during the first trimester of pregnancy had an increased risk of cardiovascular malformations, principally ventricular and atrial septal defects. In one of these studies using Swedish national registry data, infants born to 6896 women exposed to antidepressants during the first trimester of pregnancy were evaluated; 5175 of the infants born to 5123 of these women were exposed to SSRIs, including 822 infants born to 815 women reporting first trimester use of paroxetine. An analysis of these data indicated that infants exposed to paroxetine during early pregnancy had an increased risk of cardiovascular malformations (principally ventricular and atrial septal defects) compared to the entire registry population. The rate of cardiovascular malformations following early pregnancy exposure to paroxetine was approximately 2% compared with 1% in the entire registry population. An analysis of the data from the same paroxetine-exposed infants revealed no increase in the overall risk of congenital malformations.

A separate retrospective cohort epidemiologic study using U.S. United Healthcare data evaluated 5956 infants born to women dispensed paroxetine (822 infants born to 815 women) or other antidepressants during the first trimester of pregnancy showed a trend toward an increased risk for cardiovascular malformations for paroxetine compared with other antidepressants. The prevalence of cardiovascular malformations following first trimester dispensing was 1.5% for paroxetine compared with 1% for other antidepressants; most of the observed cardiovascular malformations (in 9 out of 12 paroxetine-exposed infants) were ventricular septal defects. This study also demonstrated an increased risk of overall major congenital malformations (inclusive of cardiovascular malformations) for paroxetine compared with other antidepressants; the prevalence of all congenital malformations following first trimester exposure was 4% for paroxetine compared with 2% for other antidepressants.

In addition, a smaller study examining pregnancy outcomes in pregnant women exposed to paroxetine or fluoxetine who contacted two teratogen information services in Israel and Italy reported a higher overall rate of congenital malformations in infants exposed to paroxetine in the first trimester compared with infants in the control group with exposures to drugs not known to be teratogenic (5.1% and 2.6%, respectively). A higher rate of cardiovascular anomalies was also observed in the paroxetine group (1.9%) compared with the control group (0.6%) in this study. Similar trends were reported in the fluoxetine group but these did not achieve statistical significance.

Previous epidemiologic studies of pregnancy outcome following first trimester exposure to SSRIs, including paroxetine, had not revealed evidence of an increased risk of major congenital malformations. In a prospective, controlled, multicenter study, maternal use of SSRIs (paroxetine, fluvoxamine, sertraline) in a limited number of pregnant women did not appear to increase the risk of congenital malformation, miscarriage, stillbirth, or premature delivery when used during pregnancy at recommended dosages. Birth weight and gestational age in neonates exposed to the drugs were similar to those in the control group. In addition, an increased risk of major congenital malformations was not observed in infants in 2 small, case-control studies based on prospectively gathered epidemiologic data collected in women exposed to paroxetine during the first trimester of pregnancy. In another small study based on medical records review, the incidence of congenital anomalies reported in infants born to women who were treated with paroxetine and other SSRIs during pregnancy was comparable to that observed in the general population.

Based on the conflicting preliminary findings reported to date from the available studies, the manufacturer of paroxetine hydrochloride states that it is unclear whether a causal relationship exists between these congenital malformations and maternal paroxetine exposure. However, the available data indicates that the individual risk of a mother having an infant with a cardiovascular malformation following first trimester paroxetine exposure is approximately 1/50, compared with an expected rate for such defects of approximately 1/100 infants in the general population. In general, septal defects range from those that are symptomatic and require surgical intervention to those that are asymptomatic and may resolve spontaneously. The final results of recent studies and additional data relating to the use of paroxetine during pregnancy will be analyzed further once they become available to better characterize the risk for congenital malformations with paroxetine.

The manufacturers of paroxetine state that if a woman becomes pregnant while receiving paroxetine, she should be informed of the potential hazard to the fetus. Unless the potential benefits to the mother justify continuing treatment, consideration should be given to either discontinuing paroxetine therapy or switching to another antidepressant. For women who intend to become pregnant or are in their first trimester of pregnancy, the manufacturer of paroxetine hydrochloride states that paroxetine should only be initiated after consideration of the other available treatment options.

The effect of paroxetine on labor and delivery is not known. However, there have been postmarketing reports of premature births in pregnant women who have received paroxetine or other selective serotonin-reuptake inhibitors.

Reproduction studies in rats receiving paroxetine dosages of 15 mg/kg daily, which corresponds to 2.9 times the highest recommended human daily dose for depression, social anxiety disorder, generalized anxiety disorder, and PTSD and 2.4 times the highest recommended human daily dose for obsessive-compulsive disorder on a mg/m^2 basis, revealed evidence of a reduced pregnancy rate. In toxicity studies performed for 2–52 weeks in male rats receiving paroxetine, irreversible lesions in the reproductive tract were reported. These lesions consisted of vacuolation of epididymal tubular epithelium in male rats receiving paroxetine dosages of 50 mg/kg daily (9.8 times the highest recommended human daily dose in major depressive disorder, social anxiety disorder, and generalized anxiety disorder and 8.2 times the highest recommended hu-

man daily dose in obsessive-compulsive disorder and panic disorder on a mg/m² basis). In male rats receiving paroxetine dosages of 25 mg/kg daily (4.9 times the highest recommended human daily dose in major depressive disorder, social anxiety disorder, and generalized anxiety disorder and 4.1 times the highest recommended human daily dose in obsessive-compulsive disorder and panic disorder on a mg/m² basis), atrophic changes in the seminiferous tubules of the testes with arrested spermatogenesis were observed.

Paroxetine is distributed into human milk. (See Pharmacokinetics: Distribution.) Paroxetine should be used with caution in nursing women, and women should be advised to notify their clinician if they plan to breast-feed.

Drug Interactions

■ **Serotonergic Drugs** Use of selective serotonin-reuptake inhibitors (SSRIs) such as paroxetine concurrently or in close succession with other drugs that affect serotonergic neurotransmission may result in serotonin syndrome or neuroleptic malignant syndrome (NMS)-like reactions. Manifestations of serotonin syndrome may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination), and/or GI symptoms (e.g., nausea, vomiting, diarrhea). Although the syndrome appears to be relatively uncommon and usually mild in severity, serious and potentially life-threatening complications, including seizures, disseminated intravascular coagulation, respiratory failure, and severe hyperthermia, as well as death occasionally have been reported. In its most severe form, serotonin syndrome may resemble NMS, which is characterized by hyperthermia, muscle rigidity, autonomic instability with possible rapid fluctuation in vital signs, and mental status changes. The precise mechanism of these reactions is not fully understood; however, they appear to result from excessive serotonergic activity in the CNS, probably mediated by activation of serotonin 5-HT_{1A} receptors. The possible involvement of dopamine and 5-HT_2 receptors also has been suggested, although their roles remain unclear.

Serotonin syndrome most commonly occurs when 2 or more drugs that affect serotonergic neurotransmission are administered either concurrently or in close succession. Serotonin syndrome also has been reported when paroxetine was given together with another drug that impairs the hepatic metabolism of paroxetine. Serotonergic agents include those that increase serotonin synthesis (e.g., the serotonin precursor tryptophan), stimulate synaptic serotonin release (e.g., some amphetamines, dexfenfluramine [no longer commercially available in the US], fenfluramine [no longer commercially available in the US]), inhibit the reuptake of serotonin after release (e.g., SSRIs, selective serotonin- and norepinephrine-reuptake inhibitors [SNRIs], tricyclic antidepressants, trazodone, dextromethorphan, meperidine, tramadol), decrease the metabolism of serotonin (e.g., monoamine oxidase [MAO] inhibitors), have direct serotonin postsynaptic receptor activity (e.g., buspirone), or nonspecifically induce increases in serotonergic neuronal activity (e.g., lithium salts). Selective agonists of serotonin (5-hydroxytryptamine; 5-HT) type 1 receptors ("triptans") and dihydroergotamine, agents with serotonergic activity used in the management of migraine headache, and St. John's wort (*Hypericum perforatum*) also have been implicated in several cases of serotonin syndrome.

The combination of SSRIs and MAO inhibitors may result in serotonin syndrome or NMS-like reactions. Such reactions also have been reported in patients receiving SSRIs concomitantly with tryptophan, lithium, dextromethorphan, sumatriptan, dihydroergotamine, or antipsychotics or other dopamine antagonists. In rare cases, serotonin syndrome reportedly has occurred in patients receiving the recommended dosage of a single serotonergic agent (e.g., clomipramine) or during accidental overdosage (e.g., sertraline intoxication in a child). Some other drugs that have been implicated in precipitating symptoms suggestive of serotonin syndrome or NMS-like reactions include buspirone, bromocriptine, dextropropoxyphene, fentanyl, linezolid, methylenedioxymethamphetamine (MDMA; "ecstasy"), selegiline (a selective MAO-B inhibitor), and sibutramine (an SNRI used for the management of obesity). Other drugs that have been associated with the syndrome but for which less convincing data are available include carbamazepine and pentazocine.

Clinicians should be aware of the potential for serious, possibly fatal reactions associated with serotonin syndrome or NMS-like reactions in patients receiving 2 or more drugs that affect serotonergic neurotransmission, even if no such interactions with the specific drugs have been reported to date in the medical literature. Pending further accumulation of data, drugs that affect serotonergic neurotransmission should be used cautiously in combination and such combinations should be avoided whenever clinically possible. Serotonin syndrome may be more likely to occur when initiating therapy with a serotonergic agent, increasing the dosage, or following the addition of another serotonergic agent. Some clinicians state that patients who have experienced serotonin syndrome may be at higher risk for recurrence of the syndrome upon reinitiation of serotonergic drugs. Pending further experience in such cases, some clinicians recommend that therapy with serotonergic agents be limited following recovery. In cases in which the potential benefit of the drug is thought to outweigh the risk of serotonin syndrome, lower potency agents and reduced dosages should be used, combination serotonergic therapy should be avoided, and patients should be monitored carefully for manifestations of serotonin syndrome. If signs and symptoms of serotonin syndrome or NMS develop during therapy, treatment with paroxetine and any concurrently administered serotonergic or antidopaminergic agents, including antipsychotic agents, should be discontinued immediately and supportive and symptomatic treatment should be initiated.

For further information on serotonin syndrome, including manifestations and treatment, see Serotonin Syndrome under Drug Interactions: Serotonergic Drugs, in Fluoxetine Hydrochloride 28:16.04.20.

Monoamine Oxidase Inhibitors Potentially serious, sometimes fatal serotonin syndrome or NMS-like reactions have been reported in patients receiving SSRIs in combination with an MAO inhibitor. Such reactions also have been reported in patients who recently have discontinued an SSRI and have been started on an MAO inhibitor. While there are no human data to date demonstrating such interactions with paroxetine, limited data from animal studies evaluating the effects of concomitant use of paroxetine and an MAO inhibitor suggest that these drugs may act synergistically to elevate blood pressure and produce behavioral excitation.

Because of the potential risk of serotonin syndrome or NMS-like reactions, concomitant use of paroxetine and MAO inhibitors is contraindicated. At least 2 weeks should elapse between discontinuance of MAO inhibitor therapy and initiation of paroxetine therapy and vice versa.

Linezolid. Linezolid, an anti-infective agent that is a nonselective and reversible MAO inhibitor, has been associated with drug interactions resulting in serotonin syndrome, including some associated with SSRIs, and potentially may also cause NMS-like reactions. The manufacturer of paroxetine mesylate states that the drug should be used with caution in patients receiving linezolid, and some manufacturers of paroxetine hydrochloride state that concurrent administration with linezolid is contraindicated. The manufacturer of linezolid states that, unless patients are carefully observed for signs and/or symptoms of serotonin syndrome, the drug should not be used in patients receiving SSRIs. Some clinicians suggest that linezolid only be used with caution and close monitoring in patients concurrently receiving SSRIs, and some suggest that SSRI therapy should be discontinued before linezolid is initiated and not reinitiated until 2 weeks after linezolid therapy is completed.

Moclobemide. Moclobemide (not commercially available in the US), a selective and reversible MAO-A inhibitor, has been associated with serotonin syndrome, and such reactions have been fatal in several cases in which the drug was given in combination with the SSRI citalopram or with clomipramine. Pending further experience with such combinations, some clinicians recommend that concurrent therapy with moclobemide and SSRIs be used only with extreme caution and that these drugs should have been discontinued for some time (depending on the elimination half-lives of the drug and its active metabolites) before initiating moclobemide therapy.

Selegiline. Selegiline, a selective MAO-B inhibitor used in the management of parkinsonian syndrome, has been reported to cause serotonin syndrome when used concomitantly with SSRIs (e.g., fluoxetine, paroxetine, sertraline). Although selegiline is a selective MAO-B inhibitor at therapeutic dosages, the drug appears to lose its selectivity for the MAO-B enzyme at higher dosages (e.g., those exceeding 10 mg/kg), thereby increasing the risk of serotonin syndrome in patients receiving higher dosages of the drug either alone or in combination with other serotonergic agents. The manufacturer of selegiline recommends avoiding concurrent selegiline and SSRI therapy. In addition, the manufacturer of selegiline recommends that at least 2 weeks elapse between discontinuance of selegiline and initiation of SSRI therapy.

Isoniazid. Isoniazid, an antituberculosis agent, appears to have some MAO-inhibiting activity. In addition, iproniazid (not commercially available in the US), another antituberculosis agent structurally related to isoniazid that also possesses MAO-inhibiting activity, reportedly has resulted in serotonin syndrome in at least 2 patients when given in combination with meperidine. Pending further experience, clinicians should be aware of the potential for serotonin syndrome when isoniazid is given in conjunction with SSRI therapy (such as paroxetine) or other serotonergic agents.

Other Selective Serotonin-reuptake Inhibitors and Selective Serotonin- and Norepinephrine-reuptake Inhibitors Concomitant administration of paroxetine with other SSRIs or SNRIs potentially may result in serotonin syndrome or NMS-like reactions and is therefore not recommended.

Antipsychotic Agents and Other Dopamine Antagonists Concomitant use of antipsychotic agents and other dopamine antagonists with paroxetine rarely may result in potentially serious, sometimes fatal serotonin syndrome or NMS-like reactions. If signs and symptoms of serotonin syndrome or NMS occur, treatment with paroxetine and any concurrently administered antidopaminergic or serotonergic agents should be immediately discontinued and supportive and symptomatic treatment initiated. (See Drugs Metabolized by Cytochrome P-450 [CYP] 2D6 under Drug Interactions: Drugs Undergoing Hepatic Metabolism or Affecting Hepatic Microsomal Enzymes and see Drug Interactions: Clozapine and see Drug Interactions: Pimozide.)

Tryptophan and Other Serotonin Precursors As with other serotonin-reuptake inhibitors, an interaction between paroxetine and tryptophan, a serotonin precursor, may occur during concurrent use. Adverse reactions reported to date during concomitant therapy resembled serotonin syndrome and have consisted principally of headache, nausea, sweating, and dizziness. Because of the potential risk of serotonin syndrome or NMS-like reactions, concurrent use of tryptophan or other serotonin precursors should be avoided in patients receiving paroxetine.

Sibutramine Because of the possibility of developing potentially serious, sometimes fatal serotonin syndrome or NMS-like reactions, sibutramine should be used with caution in patients receiving paroxetine.

5-HT₁ Receptor Agonists ("Triptans") Weakness, hyperreflexia, and incoordination have been reported rarely during postmarketing surveillance

in patients receiving sumatriptan concomitantly with an SSRI (e.g., citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline). Oral or subcutaneous sumatriptan and SSRIs were used concomitantly in some clinical studies without unusual adverse effects. However, an increase in the frequency of migraine attacks and a decrease in the effectiveness of sumatriptan in relieving migraine headache have been reported in a patient receiving subcutaneous injections of sumatriptan intermittently while undergoing fluoxetine therapy.

Clinicians prescribing 5-HT_1 receptor agonists, SSRIs, and SNRIs should consider that triptans often are used intermittently and that either the 5-HT_1 receptor agonist, SSRI, or SNRI may be prescribed by a different clinician. Clinicians also should weigh the potential risk of serotonin syndrome or NMS-like reactions with the expected benefit of using a triptan concurrently with SSRI or SNRI therapy. If concomitant treatment with paroxetine and a triptan is clinically warranted, the patient should be observed carefully, particularly during treatment initiation, dosage increases, and following the addition of other serotonergic agents. Patients receiving concomitant triptan and SSRI or SNRI therapy should be informed of the possibility of serotonin syndrome or NMS-like reactions and advised to immediately seek medical attention if they experience signs or symptoms of these syndromes.

Fentanyl Because cases of serotonin syndrome have been reported in patients concurrently receiving fentanyl and SSRIs, including paroxetine, clinicians should be aware of this potential interaction and monitor patients receiving these drugs in combination for possible signs and symptoms of serotonin syndrome.

Tramadol and Other Serotonergic Drugs Because of the potential risk of serotonin syndrome or NMS-like reactions, caution is advised whenever SSRIs, including paroxetine, and SNRIs are concurrently administered with other drugs that may affect serotonergic neurotransmitter systems, including tramadol and St. John's wort (*Hypericum perforatum*).

■ **Drugs Undergoing Hepatic Metabolism or Affecting Hepatic Microsomal Enzymes** The metabolism and pharmacokinetics of paroxetine may be affected by a number of drugs that induce (e.g., phenobarbital) or inhibit (e.g., cimetidine, tricyclic antidepressants), drug-metabolizing enzymes.

Drugs Metabolized by Cytochrome P-450 (CYP) 2D6 Paroxetine, like many other antidepressants (e.g., other SSRIs, many tricyclic antidepressants), is metabolized by the drug-metabolizing cytochrome P-450 (CYP) 2D6 isoenzyme (debrisoquine hydroxylase). In addition, like many other drugs metabolized by CYP2D6, paroxetine inhibits the activity of CYP2D6 and potentially may increase plasma concentrations of concomitantly administered drugs that also are metabolized by this isoenzyme. Although similar interactions are possible with other SSRIs, there is considerable variability among the drugs in the extent to which they inhibit CYP2D6; fluoxetine and paroxetine appear to be more potent in this regard than sertraline. In most patients (greater than 90%), the CYP2D6 isoenzyme is saturated early during paroxetine therapy. At steady state when the CYP2D6 pathway is essentially saturated, paroxetine is cleared by alternative cytochrome P-450 isoenzymes which, unlike CYP2D6, show no evidence of saturation.

Concomitant administration of paroxetine with risperidone, a CYP2D6 substrate, was evaluated in one study. In 10 patients with schizophrenia or schizoaffective disorder stabilized on risperidone therapy (4–8 mg daily) who also received paroxetine (20 mg daily) for 4 weeks, mean plasma concentrations of risperidone increased approximately fourfold, mean plasma concentrations of 9-hydroxyrisperidone (the active metabolite of risperidone) decreased by approximately 10%, and concentrations of the active moiety (the sum of the plasma concentrations of risperidone and 9-hydroxyrisperidone) increased by approximately 1.4 fold. These drugs were generally well tolerated when administered concurrently, with the exception of one patient who developed parkinsonian symptoms. Although the precise mechanism for this interaction remains to be fully established, it appears that paroxetine may impair the elimination of risperidone, principally by inhibiting CYP2D6-mediated 9-hydroxylation and, to a lesser extent, by simultaneously affecting the further metabolism of 9-hydroxyrisperidone or other pathways of risperidone biotransformation. Pending further accumulation of data, some clinicians recommend careful clinical observation and possible monitoring of plasma risperidone concentrations when paroxetine and risperidone are given concurrently. Consideration also should be given to using a lower initial dosage of paroxetine (10–20 mg daily) since the inhibitory effect of paroxetine on CYP2D6 is concentration dependent.

The steady-state pharmacokinetics of atomoxetine were altered when the drug was administered at a dosage of 20 mg twice daily concurrently with paroxetine 20 mg daily in healthy adults who were extensive CYP2D6 metabolizers. Concurrent administration with paroxetine increased maximum plasma atomoxetine concentrations threefold to fourfold and steady-state area under the plasma concentration curve was increased sixfold to eightfold compared with administration of atomoxetine alone. The pharmacokinetics of paroxetine were not altered. The manufacturers of paroxetine and atomoxetine recommend that atomoxetine be administered at a reduced dosage when the drugs are administered concurrently.

Concomitant use of paroxetine with other drugs metabolized by CYP2D6 has not been systematically studied. The extent to which this potential interaction may become clinically important depends on the extent of inhibition of CYP2D6 by the antidepressant and the therapeutic index of the concomitantly administered drug. The drugs for which this potential interaction is of greatest concern are those that are metabolized principally by CYP2D6 and have a narrow therapeutic index, such as tricyclic antidepressants, class IC antiarrhythmics (e.g., propafenone, flecainide, encainide), risperidone, and some phenothiazines (e.g., perphenazine, thioridazine).

In one study, chronic dosing of paroxetine (20 mg once daily) under steady-state conditions increased single-dose desipramine (100 mg) peak plasma concentrations, AUC, and elimination half-life by an average of approximately two-, five-, and threefold, respectively. (See Drug Interactions: Tricyclic and Other Antidepressants.)

Administration of perphenazine in patients receiving paroxetine 20 mg daily for 10 days increased plasma concentrations and the adverse CNS effects of perphenazine. This interaction appears to result principally from paroxetine-induced inhibition of the CYP2D6 isoenzyme. Pending further experience with combined therapy, a reduction in perphenazine dosage may be necessary to prevent adverse CNS effects in patients receiving paroxetine.

For information on a potential interaction between paroxetine and metoprolol, see Drug Interactions: β-Adrenergic Blocking Agents.

Concurrent use of paroxetine with other drugs metabolized by CYP2D6, including certain antidepressants (e.g., nortriptyline, amitriptyline, imipramine, desipramine, fluoxetine), phenothiazines (e.g., perphenazine), and class IC antiarrhythmics, or drugs that inhibit CYP2D6 should be approached with caution. Because concomitant use of paroxetine and thioridazine may result in increased plasma concentrations of the phenothiazine and increase the risk of serious, potentially fatal, adverse cardiac effects (e.g., ventricular arrhythmias, sudden death), thioridazine should not be used concomitantly with paroxetine (see Cautions: Precautions and Contraindications). The manufacturer of paroxetine states that concurrent use of a drug metabolized by CYP2D6 may necessitate the administration of dosages of the other drugs that are lower than those usually prescribed. Furthermore, whenever paroxetine therapy is discontinued (and plasma concentrations of the drug are decreased) during concurrent therapy with another drug metabolized by CYP2D6, an increased dosage of the concurrently administered drug may be necessary.

Drugs Metabolized by Cytochrome P-450 (CYP) 3A4 Although paroxetine can inhibit the cytochrome P-450 (CYP) 3A4 isoenzyme, results of in vitro and in vivo studies indicate that the drug is a much less potent inhibitor of this enzyme than many other drugs. In an in vivo drug interaction study, concomitant administration of paroxetine and the cytochrome P-450 3A4 substrate, terfenadine (no longer commercially available in the US), had no effect on the pharmacokinetics of terfenadine. In another in vivo interaction study, ketoconazole, which is a potent inhibitor of CYP3A4 activity, was found to be at least 100 times more potent than paroxetine as an inhibitor of the metabolism of several substrates for this enzyme, including terfenadine, astemizole (no longer commercially available in the US), cisapride, triazolam, and cyclosporine. Based on the assumption that the relationship between paroxetine's inhibitory activity in vitro and its lack of effect on terfenadine's clearance in vivo predicts its effect on other CYP3A4 substrates, the manufacturer states that these data suggest that the extent of paroxetine's inhibition of CYP3A4 activity is unlikely to be of clinical importance.

Drugs Metabolized by Other Cytochrome P-450 Isoenzymes Unlike fluvoxamine, in vitro data indicate that paroxetine does not substantially inhibit the CYP1A2 isoenzyme, which is responsible for the metabolism of caffeine and numerous other substances.

Cimetidine Cimetidine is known to inhibit many cytochrome P-450 oxidative enzymes and can affect the pharmacokinetics of paroxetine. In a study in which oral paroxetine (30 mg once daily) was given for 4 weeks, steady-state plasma paroxetine concentrations were increased by approximately 50% during concomitant use of oral cimetidine (300 mg 3 times daily) for the final week. The possible effects of paroxetine on the pharmacokinetics of cimetidine have not been studied. If paroxetine and cimetidine are used concurrently, dosage adjustment of paroxetine after the initial 20-mg dose should be guided by clinical effect.

Phenobarbital Phenobarbital is known to induce many cytochrome P-450 oxidative enzymes and can affect the pharmacokinetics of paroxetine. Following administration of a single 30-mg oral dose of paroxetine in individuals who had achieved steady-state serum phenobarbital concentrations (100 mg of phenobarbital daily for 14 days), the AUC and elimination half-life of paroxetine were reduced by an average of 25 and 38%, respectively, compared with administration of paroxetine alone. The influence of paroxetine on the pharmacokinetics of phenobarbital has not been studied to date. Since paroxetine exhibits nonlinear pharmacokinetics, the results of this study may not apply in situations in which both drugs are administered chronically. The manufacturer of paroxetine states that initial dosage adjustment of paroxetine is not considered necessary in patients receiving phenobarbital, and any subsequent dosage adjustment should be guided by clinical effect.

■ **Tricyclic and Other Antidepressants** The extent to which SSRI interactions with tricyclic antidepressants may pose clinical problems depends on the degree of inhibition and the pharmacokinetics of the serotonin-reuptake inhibitor involved. In one study, daily dosing of paroxetine (20 mg once daily) under steady-state conditions increased single-dose desipramine (100 mg) peak plasma concentrations, AUC, and elimination half-life by an average of approximately 2-, 5-, and 3-fold, respectively. This interaction appears to result from paroxetine-induced inhibition of CYP2D6. Thus, the manufacturers recommend that caution be exercised during concomitant use of tricyclics with

paroxetine since paroxetine may inhibit the metabolism of the tricyclic antidepressant. In addition, plasma tricyclic concentrations may need to be monitored and the dosage of the tricyclic reduced during concomitant use. (See Drugs Metabolized by Cytochrome P-450 [CYP] 2D6 under Drug Interactions: Drugs Undergoing Hepatic Metabolism or Affecting Hepatic Microsomal Enzymes.)

Clinical experience regarding the optimal timing of switching from other antidepressants to paroxetine therapy is limited. Therefore, care and prudent medical judgment should be exercised when switching from other antidepressants to paroxetine. (See Dosage and Administration: Dosage and see also Drug Interactions: Serotonergic Drugs.)

■ **Lithium** In a multiple-dose study, there was no evidence of a pharmacokinetic or pharmacodynamic interaction between lithium and paroxetine. However, because there is little clinical experience with combined therapy and because lithium may enhance the serotonergic effects of paroxetine, potentially resulting in serotonin syndrome or NMS-like reactions, concurrent use of lithium and paroxetine should be undertaken with caution. (See Drug Interactions: Serotonergic Drugs.)

■ **Protein-bound Drugs** Because paroxetine is highly protein bound, the drug theoretically could be displaced from binding sites by, or it could displace from binding sites, other protein-bound drugs such as oral anticoagulants or digitoxin (no longer commercially available in the US). In vitro studies to date have shown that paroxetine has no effect on the protein binding of 2 highly protein-bound drugs, phenytoin and warfarin; however, preliminary data suggest that there may be a pharmacodynamic interaction between paroxetine and warfarin. Pending further accumulation of data, patients receiving paroxetine concomitantly with any highly protein-bound drug should be observed for potential adverse effects associated with combined therapy. (See Warfarin under Drug Interactions: Drugs Affecting Hemostasis.)

■ **Drugs Affecting Hemostasis** ***Warfarin*** In vitro data have shown that paroxetine has no effect on the protein binding of warfarin. However, preliminary data suggest that there may be a pharmacodynamic interaction between these drugs that causes an increased bleeding diathesis while the prothrombin time remains unchanged. An increase in mild but clinically important bleeding was observed in healthy individuals receiving paroxetine and warfarin for several days. Because of limited clinical experience to date, the concurrent use of paroxetine and warfarin should be undertaken with caution. (See Drug Interactions: Protein-bound Drugs.)

Other Drugs that Interfere with Hemostasis Epidemiologic case-control and cohort design studies that have demonstrated an association between selective serotonin-reuptake inhibitor therapy and an increased risk of upper GI bleeding also have shown that concurrent use of aspirin or other nonsteroidal anti-inflammatory drugs substantially increases the risk of GI bleeding. Although these studies focused on upper GI bleeding, there is some evidence suggesting that bleeding at other sites may be similarly potentiated. The precise mechanism for this increased risk remains to be clearly established; however, serotonin release by platelets is known to play an important role in hemostasis, and selective serotonin-reuptake inhibitors decrease serotonin uptake from the blood by platelets, thereby decreasing the amount of serotonin in platelets. Patients receiving paroxetine should be cautioned about the concomitant use of drugs that interfere with hemostasis, including aspirin and other nonsteroidal anti-inflammatory agents.

■ **Digoxin** The steady-state pharmacokinetics of paroxetine were not altered when administered concurrently with digoxin at steady state. The mean AUC of digoxin at steady state decreased by 15% in the presence of paroxetine. Because there is limited clinical experience to date, the manufacturers state that combined therapy with paroxetine and digoxin should be undertaken with caution.

■ **Alcohol** Paroxetine has not been shown to potentiate the impairment of mental and motor skills caused by alcohol. However, the drug's ability to reduce alcohol consumption in animals and humans suggests that there may be a serotonergically mediated, pharmacodynamic interaction between paroxetine and alcohol within the CNS. The manufacturers recommend that patients be advised to avoid alcohol while receiving paroxetine.

■ **Benzodiazepines** Under steady-state conditions, diazepam does not appear to affect the pharmacokinetics of paroxetine. The effect of paroxetine on diazepam pharmacokinetics has not been evaluated to date. Paroxetine does not appear to potentiate the CNS depressant effects of diazepam, lorazepam, or oxazepam.

■ **Clozapine** Concomitant use of SSRIs such as paroxetine in patients receiving clozapine can increase plasma concentrations of the antipsychotic agent. In a study in schizophrenic patients receiving clozapine under steady-state conditions, initiation of paroxetine therapy resulted in only minor changes in plasma concentrations of clozapine and its metabolites; however, initiation of fluvoxamine therapy resulted in increases that were threefold compared with baseline. In other published reports, concomitant use of clozapine and SSRIs (fluvoxamine, paroxetine, sertraline) resulted in modest increases (less than twofold) in clozapine and metabolite concentrations. The manufacturer of clozapine states that caution should be exercised and patients closely monitored if clozapine is used in patients receiving SSRIs, and a reduction in clozapine dosage should be considered. (See Antipsychotic Agents and Other Dopamine Antagonists under Drug Interactions: Serotonergic Drugs.)

■ **Pimozide** In a controlled study, concurrent administration of a single 2-mg dose of pimozide in healthy individuals receiving paroxetine (dosage titrated up to 60 mg daily) was associated with mean increases in the AUC and peak plasma concentrations of pimozide of 151 and 62%, respectively, compared with pimozide given alone. Because of the narrow therapeutic index of pimozide and its known ability to prolong the QT interval, concurrent administration of paroxetine and pimozide is contraindicated. (See Antipsychotic Agents and Other Dopamine Antagonists under Drug Interactions: Serotonergic Drugs.)

■ **Electroconvulsive Therapy** The effects of paroxetine in conjunction with electroconvulsive therapy (ECT) have not been systematically evaluated to date in clinical studies.

■ **β-Adrenergic Blocking Agents** In a study in which propranolol (80 mg twice daily) was given orally for 18 days, the steady-state plasma concentrations of propranolol were not affected when paroxetine (30 mg once daily) was used concurrently during the last 10 days. The manufacturers state that the effect(s) of propranolol on paroxetine have not been systematically evaluated.

Severe hypotension has been reported following the initiation of paroxetine therapy in a patient who had been receiving chronic metoprolol therapy. Metoprolol is metabolized by the CYP2D6 isoenzyme and paroxetine is known to potently inhibit this enzyme. Pending further experience with this combination, caution should be exercised when paroxetine and metoprolol are used concomitantly.

■ **Phenytoin** In vitro studies to date have shown that paroxetine has no effect on the protein binding of phenytoin. When a single 30-mg oral dose of paroxetine was administered in individuals in whom steady-state plasma phenytoin concentrations (300 mg once daily for 14 days) had been achieved, the AUC and elimination half-life of paroxetine were reduced by an average of 50 and 35%, respectively, compared with paroxetine administered alone. In another study, when a single 300-mg oral dose of phenytoin was administered to individuals in whom steady-state plasma paroxetine concentrations (30 mg once daily for 14 days) had been achieved, the AUC of phenytoin was slightly reduced (by an average of 12%) compared with phenytoin administered alone. However, because both paroxetine and phenytoin exhibit nonlinear pharmacokinetics, these studies may not address the case in which both drugs are given chronically. Elevated plasma phenytoin concentration has been reported in one patient 4 weeks after concurrent therapy with paroxetine and phenytoin. Pending further experience, the manufacturers state that initial dosage adjustments are not considered necessary during concurrent use and that any subsequent adjustments in dosage should be guided by clinical effects.

■ **Theophylline** Elevated serum theophylline concentrations associated with paroxetine therapy have been reported. Although this interaction has not been systematically studied to date, the manufacturers recommend that serum concentrations of theophylline be monitored during concomitant paroxetine therapy.

■ **Procyclidine** Multiple oral doses of paroxetine (30 mg once daily) have increased the steady-state AUC, peak concentrations, and trough concentrations of procyclidine (5 mg once daily) by 35, 37, and 67%, respectively, compared with procyclidine alone at steady state. If anticholinergic effects are observed in patients receiving concurrent therapy with these drugs, the manufacturers recommend that the procyclidine dosage be reduced.

■ **Antacids** Limited data indicate that antacids do not substantially interfere with the absorption of paroxetine following oral administration.

■ **Fosamprenavir and Ritonavir** Concurrent administration of fosamprenavir and ritonavir with paroxetine substantially decreased plasma paroxetine concentrations. The manufacturers recommend that dosage adjustments in patients receiving these drugs concurrently be guided by clinical effect (tolerability and efficacy).

Acute Toxicity

Limited information is available on the acute toxicity of paroxetine.

■ **Pathogenesis** The acute lethal dose of paroxetine in humans is not known.

■ **Manifestations** In general, overdosage of paroxetine may be expected to produce effects that are extensions of the drug's pharmacologic and adverse effects. Overdosages of paroxetine may result in somnolence, coma, nausea, tremor, tachycardia, confusion, vomiting, and dizziness. Other signs and symptoms observed in patients who received overdosages of paroxetine alone or in combination with other substances include mydriasis, convulsions (including status epilepticus), ventricular arrhythmias (including torsades de pointes), hypertension, aggressive reactions, syncope, hypotension, stupor, bradycardia, dystonia, rhabdomyolysis, symptoms of hepatic dysfunction (including hepatic failure, hepatic necrosis, jaundice, hepatitis, and hepatic steatosis), serotonin syndrome, manic reactions, myoclonus, acute renal failure, and urinary retention.

The manufacturers state that, since introduction of paroxetine in the US, 48 fatalities involving overdosages of paroxetine alone or in combination with other substances have been reported worldwide. In 145 nonfatal overdosages, most patients recovered without sequelae. One patient recovered after ingesting 2 g of paroxetine (33 times the maximum recommended daily dosage).

In a geriatric woman who ingested 360 mg of paroxetine, the initial sign

of overdosage was excessive vomiting; hyponatremia developed 5 days later and was associated with somnolence, confusion, muscle spasms, dehydration, and slow reflexes. Ecchymoses and myxedema also were observed in this patient.

In 28 children aged 10.5 months to 17 years of age who ingested an overdosage of paroxetine alone, less sedation and fewer adverse cardiovascular effects were observed when compared with tricyclic antidepressant overdosage. In children 5 years of age and younger, ingestions of 120 mg or less of paroxetine were treated with GI evacuation and minimal supportive care with favorable outcomes. In children 12 years of age and younger who ingested 600–800 mg of the drug alone, most of the patients remained asymptomatic.

■ **Treatment** Because fatalities and severe toxicity have been reported following paroxetine overdosage, particularly in large overdosage and when taken with other drugs or alcohol, some clinicians recommend that any overdosage involving the drug be managed aggressively. Because suicidal ingestion often involves more than one drug, clinicians treating paroxetine overdosage should be alert to possible manifestations caused by drugs other than paroxetine. The manufacturers specifically caution about patients who are currently receiving or recently have taken paroxetine who might ingest either accidentally or intentionally excessive quantities of a tricyclic antidepressant. In such cases, accumulation of both the tricyclic and its active metabolite may increase the possibility of clinically important sequelae and lengthen the time needed for close medical supervision. (See Drug Interactions: Tricyclic and Other Antidepressants.)

Clinicians also should consider the possibility of serotonin syndrome or NMS-like reactions in patients presenting with similar clinical features and a recent history of paroxetine ingestion and/or ingestion of other serotonergic and/or antipsychotic agents or other dopamine antagonists. (See Cautions: Precautions and Contraindications and see also Drug Interactions: Serotonergic Drugs.)

Management of paroxetine overdosage generally involves symptomatic and supportive care. A patent airway should be established and maintained, and adequate oxygenation and ventilation should be ensured. An ECG should be taken and monitoring of cardiac function should be instituted if there is any evidence of abnormality. Frequent vital sign monitoring and close observation of the patient is necessary. There is no specific antidote for paroxetine intoxication.

Following recent (i.e., within 4 hours) ingestion of a potentially toxic amount of paroxetine and in the absence of signs and symptoms of cardiac toxicity, the stomach should be emptied immediately by inducing emesis or by gastric lavage. If the patient is comatose, having seizures, or lacks the gag reflex, gastric lavage may be performed if an endotracheal tube with cuff inflated is in place to prevent aspiration of gastric contents. Since administration of activated charcoal (which may be used in conjunction with sorbitol) may be as or more effective than induction of emesis or gastric lavage, its use has been recommended either in the initial management of paroxetine overdosage or following induction of emesis or gastric lavage in patients who have ingested a potentially toxic quantity of the drug. In the past, the manufacturer of paroxetine hydrochloride suggested that 20–30 g of activated charcoal be administered following gastric evacuation every 4–6 hours during the first 24–48 hours following ingestion.

Because of the large volume of distribution of paroxetine and its principal metabolite, peritoneal dialysis, forced diuresis, hemoperfusion, and/or exchange transfusion are unlikely to be effective in removing substantial amounts of paroxetine from the body.

Clinicians should consult a poison control center for additional information on the management of paroxetine overdosage.

Chronic Toxicity

Paroxetine has not been studied systematically in animals or humans to determine whether therapy with the drug is associated with abuse, tolerance, or physical dependence.

The clinical trials conducted with paroxetine did not reveal any tendency for drug-seeking behavior. However, withdrawal syndrome, manifested as dizziness, sensory disturbances, blurred vision, sweating, nausea, insomnia, tremor, confusion, lethargy, insomnia, nervousness or anxiety, headache, paresthesias, hypermanic-like symptoms (including hyperactivity, decreased need for sleep, irritability, agitation, aggressiveness, volatility, explosive vocal and temper outbursts), and egodystonic impulsive behavior (including shoplifting, homicidal impulses, suicidal impulses and gestures), has been reported following discontinuance of paroxetine therapy. Such reactions may emerge after abrupt discontinuance or intermittent noncompliance with therapy and, less frequently, when the dosage is reduced. Although manifestations of withdrawal generally have been mild, transient, and self-limiting, patients should be carefully monitored when paroxetine therapy is discontinued and abrupt discontinuance of the drug should be avoided. (See Dosage and Administration: Dosage:)

Some evidence suggests that the risk of withdrawal effects may be somewhat greater with paroxetine than with sertraline; fluoxetine appears to associated with the fewest withdrawal effects, possibly due at least in part to its prolonged elimination half-life. Additional clinical experience is necessary to confirm these findings.

Experience with paroxetine and with other serotonin-reuptake inhibitors suggests that a withdrawal syndrome may occur within several days following abrupt discontinuance of these drugs. The most commonly observed manifestations are those that resemble influenza, such as fatigue, GI complaints (e.g., nausea), dizziness or lightheadedness, tremor, anxiety, insomnia, chills, sweating, and incoordination. Other reported manifestations include memory impairment, paresthesia, shock-like sensations, headache, palpitations, agitation, and aggression. Although the mechanism(s) for such withdrawal reactions is not fully understood, it has been suggested that they may be caused by a sudden decrease in serotonin availability at the synapse or cholinergic rebound; other neurotransmitters (e.g., dopamine, norepinephrine, GABA) also may be involved. These manifestations may in some cases be mistaken for physical illness or relapse into depression, but generally appear to be self-limiting and improve over one to several weeks. Manifestations of withdrawal also may be improved by restarting therapy with paroxetine or another antidepressant with a similar pharmacologic profile. Paroxetine therapy should be discontinued gradually (e.g., over a period of several weeks) to prevent the possible development of withdrawal reactions.

As with other CNS-active drugs, clinicians should carefully evaluate patients for a history of substance abuse prior to initiating paroxetine therapy. If paroxetine therapy is initiated in patients with a history of substance abuse, such patients should be monitored closely for signs of misuse or abuse of the drug (e.g., development of tolerance, use of increasing doses, drug-seeking behavior).

Pharmacology

The pharmacology of paroxetine is complex and in many ways resembles that of other antidepressant agents, particularly those agents (e.g., citalopram, escitalopram, fluoxetine, fluvoxamine, sertraline, clomipramine, trazodone) that predominantly potentiate the pharmacologic effects of serotonin (5-HT). Like other selective serotonin-reuptake inhibitors (SSRIs), paroxetine is a potent and highly selective reuptake inhibitor of serotonin and has little or no effect on other neurotransmitters.

■ **Nervous System Effects** The precise mechanism of antidepressant action of paroxetine is unclear, but the drug has been shown to selectively inhibit the reuptake of serotonin at the presynaptic neuronal membrane. Paroxetine-induced inhibition of serotonin reuptake causes increased synaptic concentrations of serotonin in the CNS, resulting in numerous functional changes associated with enhanced serotonergic neurotransmission. Like other SSRIs (e.g., citalopram, fluoxetine, fluvoxamine, sertraline), paroxetine appears to have only very weak effects on the reuptake of norepinephrine or dopamine and does not exhibit clinically important anticholinergic, antihistaminic, or adrenergic (α_1, α_2, β) blocking activity at usual therapeutic dosages.

Although the mechanism of antidepressant action of antidepressant agents may involve inhibition of the reuptake of various neurotransmitters (i.e., serotonin, norepinephrine) at the presynaptic neuronal membrane, it has been suggested that postsynaptic receptor modification is mainly responsible for the antidepressant action observed during long-term administration of antidepressant agents. During long-term therapy with most antidepressants (e.g., tricyclic antidepressants, monoamine oxidase [MAO] inhibitors), these adaptive changes mainly consist of subsensitivity of the noradrenergic adenylate cyclase system in association with a decrease in the number of β-adrenergic receptors; such effects on noradrenergic receptor function are commonly referred to as "down regulation". However, in an animal study, long-term administration of paroxetine was not shown to downregulate noradrenergic receptors in the CNS as has been observed with many other clinically effective antidepressants. In addition, some antidepressants (e.g., amitriptyline) reportedly decrease the number of serotonergic (5-HT) binding sites following chronic administration.

The precise mechanism of action that is responsible for the efficacy of paroxetine in the treatment of obsessive-compulsive disorder is unclear. However, because of the potency of clomipramine and SSRIs (e.g., citalopram, fluoxetine, fluvoxamine, sertraline) in inhibiting serotonin reuptake and their efficacy in the treatment of obsessive-compulsive disorder, a serotonin hypothesis has been developed to explain the pathogenesis of the condition. The hypothesis postulates that a dysregulation of serotonin is responsible for obsessive-compulsive disorder and that paroxetine and these other agents are effective because they correct this imbalance. Although the available evidence supports the serotonergic hypothesis of obsessive-compulsive disorder, additional studies are necessary to confirm this hypothesis.

The exact mechanism of action of paroxetine in panic disorder, social phobia, or generalized anxiety disorder has not been fully elucidated but appears to involve inhibition of reuptake of serotonin at the presynaptic membrane.

Animal data indicate that serotonergic mechanisms also appear to be involved at least in part in a number of other pharmacologic effects associated with SSRIs, such as decreased food intake and altered food selection as well as decreased alcohol intake.

Serotonergic Effects Paroxetine is a highly selective inhibitor of serotonin reuptake at the presynaptic neuronal membrane. Paroxetine-induced inhibition of serotonin reuptake causes increased synaptic concentrations of the neurotransmitter, resulting in numerous functional changes associated with enhanced serotonergic neurotransmission.

Data from in vitro studies suggest that paroxetine is more potent than citalopram, clomipramine, fluoxetine, fluvoxamine, and sertraline as a serotonin-reuptake inhibitor. Unlike some other serotonin-reuptake inhibitors, the metabolites of paroxetine have been shown to possess no more than 2% of the potency

of the parent compound as inhibitors of serotonin reuptake; therefore, they are unlikely to contribute to the clinical activity of the drug.

At therapeutic dosages in humans, paroxetine has been shown to inhibit the reuptake of serotonin into platelets.

Effects on Other Neurotransmitters Like other serotonin-reuptake inhibitors, paroxetine has been shown to have little or no activity in inhibiting the reuptake of norepinephrine. Paroxetine appears to have only very weak activity on neuronal reuptake of dopamine. In addition, paroxetine does not inhibit monoamine oxidase (MAO).

Unlike tricyclic and some other antidepressants, paroxetine does not exhibit clinically important anticholinergic, α- or β-adrenergic blocking, or antihistaminic activity at usual therapeutic dosages. As a result, the incidence of adverse effects commonly associated with blockade of muscarinic cholinergic receptors (e.g., dry mouth, blurred vision, urinary retention, constipation, confusion), α-adrenergic receptors (e.g., orthostatic hypotension), and histamine H_1- and H_2-receptors (e.g., sedation) is lower in paroxetine-treated patients than tricyclic-treated patients. In vitro studies have demonstrated that paroxetine does not possess clinically important affinity for α_1- or α_2-adrenergic, β- adrenergic, histaminergic (H_1-, GABA, benzodiazepine, or dopamine D_2-receptors.

Although paroxetine has demonstrated weak affinity for muscarinic cholinergic receptors in vitro and has caused mydriasis in vivo, these effects generally occurred only at dosages greatly exceeding those required for increasing serotonergic activity in the CNS. Limited data indicate that mydriasis may also be serotonergically mediated. In addition, serum anticholinergicity of paroxetine was found to be substantially lower than that of nortriptyline in depressed geriatric patients in one study; complaints of dry mouth and tachycardia also occurred more frequently in the nortriptyline-treated patients than in those treated with paroxetine. These findings indicate that, at therapeutic plasma concentrations, paroxetine has approximately 20% the anticholinergic potential of nortriptyline in older patients. Therefore, it appears unlikely that paroxetine will produce adverse anticholinergic events when given in the usual recommended dosage.

Effects on Sleep Like tricyclic and most other antidepressants, paroxetine suppresses rapid eye movement (REM) sleep. Some evidence suggests that the drug may suppress REM sleep in a dose-dependent manner. Although not clearly established, there is some evidence that the REM-suppressing effects of antidepressant agents may contribute to the antidepressant activity of these drugs. While the precise mechanism has not been fully elucidated, results of animal studies indicate that paroxetine's effects on REM sleep may be serotonergically mediated.

In some studies, paroxetine prolonged REM latency, increased awakenings, increased stage 1 sleep, and/or reduced actual sleep time and sleep efficiency. In one study, administration of single, 40-mg doses of paroxetine in the morning increased sleep latency; however, the drug did not affect sleep latency when given at bedtime. In addition, sleep maintenance parameters (such as nocturnal wake time, total sleep time, and sleep efficiency) deteriorated in a dose-dependent manner both when a single dose of the drug was given in the morning and when given as a single 30-mg dose at bedtime. Overall, the changes in sleep observed with paroxetine are relatively small and are unlikely to be of clinical importance during prolonged administration. In addition, the changes noted with paroxetine are similar to those reported with other SSRIs and suggest an alerting effect on sleep that has not been shown to adversely affect sleep quality.

Effects on EEG Limited data currently are available regarding the effects of paroxetine on the EEG. In animals, EEG studies have revealed an activating effect associated with slight behavioral arousal and weak locomotor stimulation at dosages higher than those required to inhibit serotonin reuptake in the CNS. EEG changes in healthy individuals receiving single, 70-mg oral doses of paroxetine revealed a decrease in delta and theta activity and an increase in beta activity; these changes were still evident after 72 hours. Overall, available data in humans suggest that paroxetine generally does not produce clinically relevant changes on the EEG.

Effects on Psychomotor Function Paroxetine generally does not appear to cause clinically important sedation and generally does not interfere with psychomotor performance. Controlled studies in healthy young individuals and in patients with major depression did not demonstrate any adverse effects on psychomotor performance in those receiving 20-mg doses of the drug. No adverse effects on psychomotor performance or cognitive function were observed in healthy men older than 60 years of age who received single and repeated doses of paroxetine 20 mg in a controlled study; in some tests (e.g., critical flicker fusion thresholds), paroxetine improved information processing ability. In a controlled study evaluating the effects of paroxetine (20 or 40 mg administered daily for 8 days) on psychomotor performance and car driving in healthy males, the 20-mg dosage was found to have no effect while the 40-mg dosage was not found to affect road tracking but slightly impaired performance in some psychomotor tests in a persistent manner. Further study is needed to clarify whether paroxetine may adversely affect psychomotor performance at dosages of 40 mg daily or more.

■ **Cardiovascular Effects** No clinically important changes in vital signs (systolic and diastolic blood pressure, heart rate, temperature) were observed in patients receiving paroxetine in controlled trials. Paroxetine also appears to have little effect on the ECG. In controlled studies, paroxetine did not produce clinically important changes in heart rate, cardiac conduction, or other ECG parameters in patients receiving the drug. In depressed patients with stable ischemic heart disease, paroxetine did not substantially affect blood pressure or conduction intervals and did not produce sustained effects on heart rate, heart rhythm, or indexes of heart rate variability. However, a small but statistically significant QRS widening relative to placebo was reported in one study, and ECG changes occasionally have been reported in healthy individuals and patients receiving the drug. In addition, the relative safety of paroxetine in patients with underlying cardiac disease, particularly those with severe cardiovascular disease and immediately following a myocardial infarction, remains to be more fully elucidated.

Paroxetine did not demonstrate any substantial change in cardiovascular autonomic function tests (such as heart rate variability) in a limited number of depressed patients receiving the drug for 14 days. On the other hand, paroxetine has been shown to increase heart rate variability in a limited number of patients with panic disorder, a condition associated with decreased heart rate variability and consequently an increased risk of serious cardiovascular problems including sudden cardiac death.

■ **Effects on Appetite and Body Weight** Paroxetine appears to possess some anorexigenic activity, although to a lesser degree than certain other serotonergic agents (e.g., fenfluramine [no longer commercially available in the US], fluoxetine, sertraline, zimelidine). Limited data from animal studies suggest that fenfluramine is the most effective inhibitor of food intake followed by fluoxetine, then sertraline, and then paroxetine. Although the precise mechanism has not been clearly established, results from animal studies indicate that the appetite-inhibiting action of these antidepressants may result at least in part from serotonin-reuptake blockade and enhancement of serotonin release thereby increasing serotonin availability at the neuronal synapse.

While clinically important weight loss may occur in some patients receiving paroxetine, only minimal weight loss (averaging 0.45 kg) generally occurred in patients receiving the drug in controlled clinical trials. In addition, while decreased appetite was reported in about 6% of patients receiving paroxetine in short-term clinical trials, the drug, unlike fluoxetine, does not appear to exhibit clinically important anorectic effects. (See Cautions: Metabolic and Endocrine Effects.)

■ **Neuroendocrine Effects** Limited data currently are available regarding the effects of paroxetine on the endocrine system. Elevated serum prolactin concentrations have been reported in some women receiving chronic paroxetine therapy.

Pharmacokinetics

Paroxetine is commercially available in the US as paroxetine hydrochloride (e.g., Paxil®, Paxil CR®) and as paroxetine mesylate (i.e., Pexeva®). Conventional tablets of Paxil® and Pexeva® are *not* bioequivalent. The U.S. Food and Drug Administration (FDA) considers paroxetine mesylate (Pexeva®) conventional tablets to be a pharmaceutical *alternative* (as described in section 505[b][2] of the Federal Food, Drug, and Cosmetic Act) and not a pharmaceutical (generic) equivalent to paroxetine hydrochloride conventional tablets (e.g., Paxil®), since both contain the same active moiety (paroxetine) but have different salts.

In all human studies described in the Pharmacokinetics section, paroxetine was administered as either the hydrochloride or the mesylate salt; dosages and concentrations are expressed in terms of paroxetine.

■ **Absorption** Paroxetine hydrochloride appears to be slowly but well absorbed from the GI tract following oral administration. Although the oral bioavailability of paroxetine hydrochloride in humans has not been fully elucidated to date, the manufacturer states that paroxetine is completely absorbed after oral dosing of a solution of the hydrochloride salt. However, the relative proportion of an oral dose that reaches systemic circulation unchanged appears to be relatively small because paroxetine undergoes extensive first-pass metabolism. The oral tablets and suspension of paroxetine hydrochloride reportedly are bioequivalent.

Paroxetine mesylate is completely absorbed following oral administration of the tablets.

Food does not substantially affect the absorption of paroxetine. In one study, no substantial differences in pharmacokinetic parameters were noted when paroxetine hydrochloride was administered under fasting and nonfasting conditions or with a low- or high-fat diet, milk, water, or antacids. In another study, administration of a single dose of paroxetine hydrochloride with food resulted in a 6% increase in the area under the concentration-time curve (AUC), a 29% increase in peak plasma concentrations of the drug, and a decrease in the time to peak plasma concentrations from 6.4 to 4.9 hours.

In healthy males receiving one 30-mg tablet of paroxetine (administered as paroxetine hydrochloride) once daily for 30 days, steady-state plasma paroxetine concentrations were achieved after approximately 10 days in most patients, although achievement of steady-state concentrations may take substantially longer in some patients. At steady-state, mean peak plasma paroxetine concentrations of 61.7 ng/mL occurred after an average of 5.2 hours following oral administration; corresponding mean trough concentrations of 30.7 ng/mL were reported. However, wide interindividual variation in peak plasma concentrations of paroxetine has been observed in both single- and multiple-dose studies. In geriatric individuals receiving multiple daily doses of 20–40 mg daily of paroxetine (administered as paroxetine hydrochloride), trough plasma concentrations were 70–80% higher than trough concentrations in nongeriatric

individuals. In another multiple-dose study, mean steady-state trough concentrations were approximately 3 times higher in geriatric individuals than in younger adults receiving paroxetine (administered as paroxetine hydrochloride) 20 mg daily, although there was considerable overlap between the 2 groups. Therefore, the manufacturers and some clinicians recommend that paroxetine be administered in a reduced dosage (i.e., 10 mg daily) initially in geriatric patients. (See Cautions: Geriatric Precautions and see Dosage and Administration: Dosage in Geriatric and Debilitated Patients.)

In healthy males receiving one 30-mg tablet of paroxetine (administered as paroxetine mesylate) once daily for 24 days, steady-state plasma paroxetine concentrations were achieved after approximately 13 days in most patients, although achievement of steady-state concentrations may take substantially longer in some patients. At steady-state, mean peak plasma paroxetine concentrations of 81.3 ng/mL occurred after an average of 8.1 hours following oral administration of paroxetine mesylate tablets; corresponding mean trough concentrations of 43.2 ng/mL were reported.

When compared with administration of a single dose of paroxetine hydrochloride, steady-state peak and trough paroxetine concentrations following multiple dosing were approximately 6 and 14 times higher than would be expected from single-dose values. In addition, steady-state drug exposure based on AUC (0–24 hour) was about 8 times greater than would have been predicted based on the single-dose data in these individuals. When compared with administration of a single dose of paroxetine mesylate, steady-state peak and trough paroxetine concentrations following multiple dosing were approximately 7 and 10 times higher than would be expected from single-dose values. In addition, steady-state drug exposure based on AUC (0–24 hour) was about 8 and 10 times greater than would have been predicted based on the single-dose data in these individuals receiving the hydrochloride and mesylate salts of paroxetine, respectively. The manufacturers attributed this excess accumulation to the fact that one of the enzymes that metabolizes paroxetine, the cytochrome P-450 isoenzyme CYP2D6, is saturable.

In steady-state, dose-proportionality studies involving geriatric and nongeriatric patients receiving 20–40 and 20–50 mg daily of paroxetine (administered as paroxetine hydrochloride), respectively, some nonlinearity was observed in both groups, which also suggests a saturable metabolic pathway. When compared with trough paroxetine concentrations after 20 mg of the drug daily, trough concentrations after 40 mg daily were approximately 2–3 times higher than doubled.

As with other serotonin-reuptake inhibitors, the relationship between plasma paroxetine concentrations and the therapeutic and/or toxic effects of the drug has not been clearly established.

■ **Distribution** Distribution of paroxetine and its metabolites into human body tissues and fluids has not been fully characterized. However, limited pharmacokinetic data suggest that the parent drug, which is highly lipophilic, and some of its metabolites are widely distributed throughout body tissues, including the CNS. Only 1% of paroxetine remains in plasma.

Although the apparent volume of distribution of paroxetine has not been determined in humans, values ranging from 3.1–28 L/kg have been reported in animal studies. The drug crosses the blood-brain barrier in humans and animals.

In vitro, approximately 95 and 93% of paroxetine is bound to plasma proteins at plasma concentrations of 100 and 400 ng/mL, respectively. Under usual clinical conditions, plasma paroxetine concentrations would be less than 400 ng/mL. In vitro, paroxetine does not alter the plasma protein binding of 2 other highly protein-bound drugs, phenytoin and warfarin.

Paroxetine is distributed into human milk. In one lactating woman receiving paroxetine (administered as paroxetine hydrochloride) 20 mg daily for 1 week, the concentration of paroxetine in breast milk was 7.6 ng/mL 4 hours after the daily dose; no adverse effects were observed in the infant during lactation. Based on an estimated weight-adjusted dose to the infant of 0.34% of the maternal dose, the exposure of infants during breastfeeding appears to be lower for paroxetine and fluvoxamine than for fluoxetine; however, further study is needed to clarify the clinical importance of these findings.

■ **Elimination** The elimination half-life of paroxetine when administered as paroxetine hydrochloride averages approximately 21–24 hours, although there is wide interpatient variation with half-lives (ranging from 7–65 hours in one study). In healthy males receiving one 30-mg tablet of paroxetine (administered as paroxetine mesylate) once daily for 24 days, the mean paroxetine half-life was 33.2 hours. In geriatric individuals, elimination half-life of paroxetine (administered as paroxetine hydrochloride) may be increased (e.g., to about 36 hours).

The exact metabolic fate of paroxetine has not been fully elucidated; however, paroxetine is extensively metabolized, probably in the liver. The principal metabolites are polar and conjugated products of oxidation and methylation, which are readily cleared by the body. Conjugates with glucuronic acid and sulfate predominate, and the principal metabolites have been isolated and identified. The metabolites of paroxetine have been shown to possess no more than 2% of the potency of the parent compound as inhibitors of serotonin reuptake; therefore, they are essentially inactive.

Like some other serotonin-reuptake inhibitors, paroxetine is partially metabolized by the drug metabolizing isoenzyme CYP2D6 (a cytochrome P-450 isoenzyme implicated in sparteine/debrisoquine polymorphism). Saturation of this enzyme at dosages used clinically appears to account for the nonlinearity of paroxetine kinetics observed with increasing dosage and duration of treatment. The role of the CYP2D6 enzyme in paroxetine metabolism also suggests potential drug-drug interactions. (See Drug Interactions: Drugs Undergoing Hepatic Metabolism or Affecting Hepatic Microsomal Enzymes.)

Following oral administration, paroxetine and its metabolites are excreted in both urine and feces. Following oral administration of a single, 30-mg dose of paroxetine (administered as paroxetine hydrochloride) as an oral solution (not commercially available), approximately 64% of the dose was excreted in the urine within 10 days; unchanged paroxetine accounted for 2% of the dose and metabolites accounted for the remaining 62% of the dose. During the same period, approximately 36% of the dose was eliminated in feces (probably via the bile), mostly as metabolites and less than 1% as the parent drug.

The effect of age on the elimination of paroxetine has not been fully elucidated. In healthy geriatric adults, hepatic clearance of paroxetine was mildly impaired leading to slower elimination and increased plasma concentrations of the drug. (See Pharmacokinetics: Absorption.) Studies in depressed, geriatric patients confirm these findings with higher steady-state concentrations and longer elimination half-lives reported compared with younger individuals. These results suggest that older patients may be more susceptible to saturation of hepatic metabolic activity resulting in nonlinear kinetics and higher plasma concentrations occurring at lower dosages of paroxetine. Therefore, the manufacturers and some clinicians recommend that paroxetine initially be administered in a reduced dosage in geriatric patients. (See Cautions: Geriatric Precautions and see Dosage and Administration: Dosage in Geriatric and Debilitated Patients.)

Because paroxetine is extensively metabolized by the liver, hepatic impairment can affect the elimination of the drug. In cirrhotic patients with moderate hepatic impairment who received a single 20-mg dose of paroxetine (administered as paroxetine hydrochloride), no significant difference in plasma paroxetine concentrations and pharmacokinetic parameters was observed when compared with corresponding data in healthy individuals. However, accumulation potentially may occur in patients receiving multiple daily doses of paroxetine. The manufacturers state that patients with impaired hepatic function have approximately twofold higher peak plasma concentrations and AUC values. Therefore, the manufacturers recommend that paroxetine be administered in a reduced dosage initially in patients with severe hepatic impairment; caution also should be exercised when increasing the dosage of paroxetine in such patients. (See Cautions: Precautions and Contraindications and see Dosage and Administration: Dosage in Renal and Hepatic Impairment.)

The effect of renal impairment on the pharmacokinetics of paroxetine has not been fully evaluated to date. Following oral administration of multiple daily doses of paroxetine as paroxetine hydrochloride in patients with creatinine clearances less than 30 mL/minute, mean plasma concentrations of paroxetine were approximately 4 times greater than those seen in healthy individuals. In patients with creatinine clearances of 30–60 mL/minute, peak plasma concentrations and AUC values were approximately twofold higher when compared with healthy individuals. The influence of renal impairment in patients receiving multiple daily doses of paroxetine has not been evaluated to date. Pending further accumulation of data, the manufacturers and some clinicians recommend that paroxetine be administered in a reduced dosage initially in patients with severe renal impairment. (See Cautions: Precautions and Contraindications and see Dosage and Administration: Dosage in Renal and Hepatic Impairment.)

Because of the large volume of distribution of paroxetine and its principal metabolite, peritoneal dialysis, forced diuresis, hemoperfusion, and/or exchange transfusion are unlikely to be effective in removing substantial amounts of paroxetine from the body.

Chemistry and Stability

■ **Chemistry** Paroxetine, a selective serotonin-reuptake inhibitor (SSRI) antidepressant agent, is a phenylpiperidine-derivative. Paroxetine differs structurally from other SSRIs (e.g., citalopram, fluoxetine, sertraline) and also differs structurally and pharmacologically from other currently available antidepressants (e.g., tricyclic antidepressants, monoamine oxidase inhibitors).

Paroxetine is commercially available in the US as the hydrochloride and mesylate salts. Paroxetine hydrochloride occurs as an odorless, off-white powder and has a solubility of 5.4 mg/mL in water. The drug has a pK_a of approximately 9.9. Paroxetine mesylate also occurs as an odorless, off-white powder but has a solubility of more than 1 g/mL in water.

The commercially available extended-release tablets of paroxetine hydrochloride contain the drug in a biodegradable polymeric delivery system, consisting of a hydrophilic core surrounded by a biodegradable barrier layer. This delivery system is designed to release the drug gradually over a period of 4–5 hours after ingestion; in addition, an enteric coating delays the release of drug until after the extended-release tablet has left the stomach.

■ **Stability** Paroxetine hydrochloride conventional tablets should be stored at 15–30°C. The oral suspension and extended-release tablets of paroxetine hydrochloride should be stored at or below 25°C. When stored as directed, paroxetine hydrochloride conventional tablets and oral suspension have an expiration date of 3 and 2 years following the date of manufacture, respectively.

Paroxetine mesylate conventional tablets should be stored at a temperature of 25°C but may be exposed to temperatures ranging from 15–30°C; the tablets should be protected from humidity.

Preparations

Excipients in commercially available drug preparations may have clinically important effects in some individuals; consult specific product labeling for details.

Paroxetine Hydrochloride

Oral		
Suspension	10 mg (of paroxetine) per 5 mL	Paxil®, GlaxoSmithKline
Tablets, extended-release, film-coated	12.5 mg (of paroxetine)	Paxil CR®, GlaxoSmithKline
	25 mg (of paroxetine)	Paxil CR®, GlaxoSmithKline
	37.5 mg (of paroxetine)	Paxil CR®, GlaxoSmithKline
Tablets, film-coated	10 mg (of paroxetine)*	Paroxetine Hydrochloride Film-coated Tablets
		Paxil® (scored), GlaxoSmithKline
	20 mg (of paroxetine)*	Paroxetine Hydrochloride Film-coated Tablets
		Paxil® (scored), GlaxoSmithKline
	30 mg (of paroxetine)*	Paroxetine Hydrochloride Film-coated Tablets
		Paxil®, GlaxoSmithKline
	40 mg (of paroxetine)*	Paroxetine Hydrochloride Film-coated Tablets
		Paxil®, GlaxoSmithKline

*Available from one or more manufacturer, distributor, and/or repackager by generic (nonproprietary) name

Paroxetine Mesylate

Oral		
Tablets, film-coated	10 mg (of paroxetine)	Pexeva®, JDS Pharmaceuticals
	20 mg (of paroxetine)	Pexeva® (scored), JDS Pharmaceuticals
	30 mg (of paroxetine)	Pexeva®, JDS Pharmaceuticals
	40 mg (of paroxetine)	Pexeva®, JDS Pharmaceuticals

†Use is not currently included in the labeling approved by the US Food and Drug Administration

Sertraline Hydrochloride

■ Sertraline, a selective serotonin-reuptake inhibitor (SSRI), is an antidepressant agent.

Uses

■ **Major Depressive Disorder** Sertraline is used in the treatment of major depressive disorder. A major depressive episode implies a prominent and relatively persistent depressed or dysphoric mood that usually interferes with daily functioning (nearly every day for at least 2 weeks). According to DSM-IV criteria, a major depressive episode includes at least 5 of the following 9 symptoms (with at least one of the symptoms being either depressed mood or loss of interest or pleasure): depressed mood most of the day as indicated by subjective report (e.g., feels sad or empty) or observation made by others; markedly diminished interest or pleasure in all, or almost all, activities most of the day; significant weight loss (when not dieting) or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite; insomnia or hypersomnia; psychomotor agitation or retardation (observable by others, not merely subjective feelings of restlessness or being slowed down); fatigue or loss of energy; feelings of worthlessness or excessive or inappropriate guilt (not merely self-reproach or guilt about being sick); diminished ability to think or concentrate or indecisiveness (either by subjective account or as observed by others); and recurrent thoughts of death, recurrent suicidal ideation without a specific plan, or a suicide attempt or specific plan for committing suicide.

Treatment of major depressive disorder generally consists of an acute phase (to induce remission), a continuation phase (to preserve remission), and a maintenance phase (to prevent recurrence). Various interventions (e.g., psychotherapy, antidepressant drug therapy, electroconvulsive therapy [ECT]) are used alone or in combination to treat major depressive episodes. Treatment should be individualized and the most appropriate strategy for a particular patient is determined by clinical factors such as severity of depression (e.g., mild, moderate, severe), presence or absence of certain psychiatric features (e.g., suicide risk, catatonia, psychotic or atypical features, alcohol or substance abuse or dependence, panic or other anxiety disorder, cognitive dysfunction, dysthymia, personality disorder, seasonal affective disorder), and concurrent illness (e.g., asthma, cardiac disease, dementia, seizure disorder, glaucoma, hypertension). Demographic and psychosocial factors as well as patient preference also are used to determine the most effective treatment strategy.

While use of psychotherapy alone may be considered as an initial treatment strategy for patients with mild to moderate major depressive disorder (based on patient preference and presence of clinical features such as psychosocial stressors), combined use of antidepressant drug therapy and psychotherapy may be useful for initial treatment of patients with moderate to severe major depressive disorder with psychosocial issues, interpersonal problems, or a comorbid axis II disorder. In addition, combined use of antidepressant drug therapy and psychotherapy may be beneficial in patients who have a history of poor compliance or only partial response to adequate trials of either antidepressant drug therapy or psychotherapy alone.

Antidepressant drug therapy can be used alone for initial treatment of patients with mild major depressive disorder (if preferred by the patient) and usually is indicated alone or in combination with psychotherapy for initial treatment of patients with moderate to severe major depressive disorder (unless ECT is planned). ECT is not generally used for initial treatment of uncomplicated major depression, but is recommended as first-line treatment for severe major depressive disorder when it is coupled with psychotic features, catatonic stupor, severe suicidality, food refusal leading to nutritional compromise, or other situations when a rapid antidepressant response is required. ECT also is recommended for patients who have previously shown a positive response or a preference for this treatment modality and can be considered for patients with moderate or severe depression who have not responded to or cannot receive antidepressant drug therapy. In certain situations involving depressed patients unresponsive to adequate trials of several individual antidepressant agents, adjunctive therapy with another agent (e.g., buspirone, lithium) or concomitant use of a second antidepressant agent (e.g., bupropion) has been used; however, such combination therapy is associated with an increased risk of adverse reactions, may require dosage adjustments, and (if not contraindicated) should be undertaken only after careful consideration of the relative risks and benefits. (See Drug Interactions: Serotonergic Drugs, Drug Interactions: Tricyclic and Other Antidepressants, and Drug Interactions: Lithium.)

The efficacy of sertraline for the acute treatment of major depression has been established by 2 placebo-controlled studies in adult outpatients who met DSM-III criteria for major depression. In the first study of 8 weeks' duration, sertraline was administered with flexible dosing in a range of 50–200 mg daily; the mean daily dosage for patients completing the study was 145 mg daily. In the second study of 6 weeks' duration, sertraline was administered in fixed doses of 50, 100, and 200 mg daily. Overall, these 2 studies demonstrated that sertraline was superior to placebo in improving scores on the Hamilton Depression Rating Scale and the Clinical Global Impression Severity and Improvement Scales. However, the second study was not readily interpretable regarding whether there was a dose-response relationship for the drug's efficacy.

In a third study, depressed outpatients who had responded by the end of an initial 8-week open treatment phase to sertraline 50–200 mg daily were randomized to continue sertraline in the same dosage range or placebo for 44 weeks in a double-blind manner. The mean daily dosage of sertraline in those who completed this long-term study was 70 mg daily, and the relapse rate in the sertraline-treated patients was substantially lower than in those who received placebo.

An analysis of these 3 controlled studies for possible gender-related effects on treatment outcome did not suggest any difference in efficacy based on the gender of the patient.

While the optimum duration of sertraline therapy has not been established, many experts state that acute depressive episodes require several months or longer of sustained antidepressant therapy. In addition, some clinicians recommend that long-term antidepressant therapy be considered in certain patients at risk for recurrence of depressive episodes (such as those with highly recurrent unipolar depression). The efficacy of sertraline in maintaining an antidepressant response for up to 1 year without increased toxicity has been demonstrated in a controlled setting. The manufacturers state that the usefulness of the drug in patients receiving prolonged therapy should be reevaluated periodically. (See Dosage and Administration: Dosage.)

The manufacturers state that the drug's antidepressant efficacy in hospital settings has not been adequately studied to date.

As with certain other antidepressants, the possibility that sertraline may precipitate hypomanic or manic attacks in patients with bipolar or other major affective disorder should be considered. Sertraline is *not* approved for use in treating bipolar depression in adults.

Considerations in Choosing an Antidepressant A variety of antidepressant drugs is available for the treatment of major depressive disorder, including selective serotonin-reuptake inhibitors (SSRIs; e.g., citalopram, escitalopram, fluoxetine, paroxetine, sertraline), selective serotonin- and norepinephrine-reuptake inhibitors (SNRIs; e.g., desvenlafaxine, duloxetine, venlafaxine), tricyclic antidepressants (e.g., amitriptyline, amoxapine, desipramine, doxepin, imipramine, nortriptyline, protriptyline, trimipramine), monoamine oxidase (MAO) inhibitors (e.g., phenelzine, tranylcypromine), and other antidepressants (e.g., bupropion, maprotiline, nefazodone, trazodone). Most clinical studies have shown that the antidepressant effect of usual dosages of sertraline in patients with depression is greater than that of placebo and comparable to that of usual dosages of tricyclic antidepressants (e.g., amitriptyline), other SSRIs (e.g., fluoxetine), and other antidepressants (e.g., nefazodone). In geriatric patients with major depression, sertraline appears to be as effective as amitriptyline. The onset of action of sertraline appears to be comparable to that of tricyclic antidepressants.

Risk of suicidality; importance of patients, family, and caregivers being alert to and immediately reporting emergence of suicidality, worsening depression, or unusual changes in behavior, especially during the first few months of therapy or during periods of dosage adjustment. (See Worsening of Depression and Suicidality Risk under Warnings/Precautions: Warnings, in Cautions.)

Importance of informing patients of potential risk of serotonin syndrome and neuroleptic malignant syndrome (NMS)-like reactions, particularly with concurrent use of escitalopram and 5-HT_1 receptor agonists (also called triptans), tramadol, tryptophan, other serotonergic agents, or antipsychotic agents. Importance of immediately contacting clinician if signs and symptoms of these syndromes develop (e.g., restlessness, hallucinations, loss of coordination, fast heart beat, increased body temperature, muscle stiffness, labile blood pressure, diarrhea, coma, nausea, vomiting, confusion).

Risk of psychomotor impairment; importance of exercising caution while operating hazardous machinery, including driving a motor vehicle, until the drug's effects on the individual are known.

Importance of patients being aware that withdrawal effects may occur when stopping escitalopram, especially with abrupt discontinuance of the drug.

Risks associated with concomitant use of escitalopram with alcohol or racemic citalopram.

Importance of informing clinicians of existing or contemplated concomitant therapy, including prescription and OTC drugs or herbal supplements, as well as any concomitant illnesses (e.g., bipolar disorder) or personal or family history of suicidality or bipolar disorder. Risk of bleeding associated with concomitant use of escitalopram with aspirin or other nonsteroidal anti-inflammatory agents, warfarin, or other drugs that affect coagulation.

Importance of women informing clinicians if they are or plan to become pregnant or plan to breast-feed.

Importance of advising patients that, although they may notice improvement with escitalopram therapy within 1–4 weeks, they should continue therapy as directed.

Importance of informing patients of other important precautionary information. (See Cautions.)

Overview[a] (see Users Guide). For additional information on this drug until a more detailed monograph is developed and published, the manufacturer's labeling should be consulted. It is *essential* that the manufacturer's labeling be consulted for more detailed information on usual cautions, precautions, contraindications, potential drug interactions, laboratory test interferences, and acute toxicity.

Preparations

Excipients in commercially available drug preparations may have clinically important effects in some individuals; consult specific product labeling for details.

Escitalopram Oxalate

Oral		
Solution	5 mg (of escitalopram) per 5 mL	**Lexapro®**, Forest
Tablets, film-coated	5 mg (of escitalopram)	**Lexapro®**, Forest
	10 mg (of escitalopram)	**Lexapro®** (scored), Forest
	20 mg (of escitalopram)	**Lexapro®** (scored), Forest

Fluoxetine Hydrochloride

■ Fluoxetine, a selective serotonin-reuptake inhibitor (SSRI), is an antidepressant.

Uses

Fluoxetine is used in the treatment of major depressive disorder, obsessive-compulsive disorder, premenstrual dysphoric disorder, and bulimia nervosa. In addition, fluoxetine has been used for the treatment of depression associated with bipolar disorder†; obesity†; anorexia nervosa†; panic disorder† with or without agoraphobia; myoclonus†; cataplexy†; alcohol dependence†; and premature ejaculation†.

■ **Major Depressive Disorder** Fluoxetine is used in the treatment of major depressive disorder. The efficacy of fluoxetine for long-term use (i.e., longer than 5–6 weeks) as an antidepressant has not been established by controlled studies, but the drug has been used in some patients for substantially longer periods (e.g., up to 4 years or longer) without apparent loss of clinical effect or increased toxicity. If fluoxetine is used for extended periods, the need for continued therapy should be reassessed periodically.

A major depressive episode implies a prominent and relatively persistent depressed or dysphoric mood that usually interferes with daily functioning (nearly every day for at least 2 weeks). According to DSM-IV criteria, a major depressive episode includes at least 5 of the following 9 symptoms (with at least one of the symptoms being either depressed mood or loss of interest or pleasure): depressed mood most of the day as indicated by subjective report (e.g., feels sad or empty) or observation made by others; markedly diminished interest or pleasure in all, or almost all, activities most of the day; significant weight loss (when not dieting) or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite; insomnia or hypersomnia; psychomotor agitation or retardation (observable by others, not merely subjective feelings of restlessness or being slowed down); fatigue or loss of energy; feelings of worthlessness or excessive or inappropriate guilt (not merely self-reproach or guilt about being sick); diminished ability to think or concentrate or indecisiveness (either by subjective account or as observed by others); and recurrent thoughts of death, recurrent suicidal ideation without a specific plan, or a suicide attempt or specific plan for committing suicide.

Treatment of major depressive disorder generally consists of an acute phase (to induce remission), a continuation phase (to preserve remission), and a maintenance phase (to prevent recurrence). Various interventions (e.g., psychotherapy, antidepressant drug therapy, electroconvulsive therapy [ECT]) are used alone or in combination to treat major depressive episodes. Treatment should be individualized and the most appropriate strategy for a particular patient is determined by clinical factors such as severity of depression (e.g., mild, moderate, severe), presence or absence of certain psychiatric features (e.g., suicide risk, catatonia, psychotic or atypical features, alcohol or substance abuse or dependence, panic or other anxiety disorder, cognitive dysfunction, dysthymia, personality disorder, seasonal affective disorder), and concurrent illness (e.g., asthma, cardiac disease, dementia, seizure disorder, glaucoma, hypertension). Demographic and psychosocial factors as well as patient preference also are used to determine the most effective treatment strategy.

While use of psychotherapy alone may be considered as an initial treatment strategy for patients with mild to moderate major depressive disorder (based on patient preference and presence of clinical features such as psychosocial stressors), combined use of antidepressant drug therapy and psychotherapy may be useful for initial treatment of patients with moderate to severe major depressive disorder with psychosocial issues, interpersonal problems, or a comorbid axis II disorder. In addition, combined use of antidepressant drug therapy and psychotherapy may be beneficial in patients who have a history of poor compliance or only partial response to adequate trials of either antidepressant drug therapy or psychotherapy alone.

Antidepressant drug therapy can be used alone for initial treatment of patients with mild major depressive disorder (if preferred by the patient) and usually is indicated alone or in combination with psychotherapy for initial treatment of patients with moderate to severe major depressive disorder (unless ECT is planned). ECT is not generally used for initial treatment of uncomplicated major depression, but is recommended as first-line treatment for severe major depressive disorder when it is coupled with psychotic features, catatonic stupor, severe suicidality, food refusal leading to nutritional compromise, or other situations when a rapid antidepressant response is required. ECT also is recommended for patients who have previously shown a positive response or a preference for this treatment modality and can be considered for patients with moderate or severe depression who have not responded to or cannot receive antidepressant drug therapy. In certain situations involving depressed patients unresponsive to adequate trials of several individual antidepressant agents, adjunctive therapy with another agent (e.g., buspirone, lithium) or concomitant use of a second antidepressant agent (e.g., bupropion) has been used; however, such combination therapy is associated with an increased risk of adverse reactions, may require dosage adjustments, and (if not contraindicated) should be undertaken only after careful consideration of the relative risks and benefits. (See Drug Interactions: Serotonergic Drugs, see Drug Interactions: Tricyclic and Other Antidepressants, and see Drug Interactions: Lithium.)

Efficacy of fluoxetine for the management of major depression has been established principally in outpatient settings; the drug's antidepressant efficacy in hospital or institutional settings has not been adequately studied to date. Most patients evaluated in clinical studies with fluoxetine had major depressive episodes of at least moderate severity, had no evidence of bipolar disorder, and had experienced either single or recurrent episodes of depressive illness. Limited evidence suggests that mildly depressed patients may respond less well to fluoxetine than moderately depressed patients. There also is some evidence that patients with atypical depression (which usually is characterized by atypical signs and symptoms such as hypersomnia and hyperphagia), a history of poor response to prior antidepressant therapy, chronic depressive symptomatology with or without episodic worsening of depressive symptoms, a longer duration of depression in the current episode, and/or a younger age of onset of depression may be more likely to respond to fluoxetine than to tricyclic antidepressant therapy.

Considerations in Choosing Antidepressants A variety of antidepressant drugs are available for the treatment of major depressive disorder, including selective serotonin-reuptake inhibitors (SSRIs; e.g., citalopram, escitalopram, fluoxetine, paroxetine, sertraline), selective serotonin- and norepinephrine-reuptake inhibitors (SNRIs; e.g., desvenlafaxine, duloxetine, venlafaxine), tricyclic antidepressants (e.g., amitriptyline, amoxapine, desipramine, doxepin, imipramine, nortriptyline, protriptyline, trimipramine), monoamine oxidase (MAO) inhibitors (e.g., phenelzine, tranylcypromine), and other antidepressants (e.g., bupropion, maprotiline, nefazodone, trazodone). Most clinical studies have shown that the antidepressant effect of usual dosages of fluoxetine in patients with moderate to severe depression is greater than that of placebo and comparable to that of usual dosages of tricyclic antidepressants, maprotiline, other selective serotonin-reuptake inhibitors (e.g., paroxetine, sertraline), and other antidepressants (e.g., trazodone). Fluoxetine appears to be

as effective as tricyclic antidepressants in reducing most of the signs and symptoms associated with major depressive disorder, including depression, anxiety, cognitive disturbances, and somatic symptoms. However, in some studies, the drug did not appear to be as effective as tricyclic antidepressants or trazodone in reducing sleep disturbances associated with depression. In geriatric patients with major depressive disorder, fluoxetine appears to be as effective as and to cause fewer overall adverse effects than doxepin. The onset of action of fluoxetine appears to be comparable to that of tricyclic antidepressants, although the onset of action has been variably reported to be somewhat faster or slower than that of tricyclic antidepressants in some studies.

Because response rates in patients with major depression are similar for most currently available antidepressants, the choice of antidepressant agent for a given patient depends principally on other factors such as potential adverse effects, safety or tolerability of these adverse effects in the individual patient, psychiatric and medical history, patient or family history of response to specific therapies, patient preference, quantity and quality of available clinical data, cost, and relative acute overdose safety. No single antidepressant can be recommended as optimal for all patients because of substantial heterogeneity in individual responses and in the nature, likelihood, and severity of adverse effects. In addition, patients vary in the degree to which certain adverse effects and other inconveniences of drug therapy (e.g., cost, dietary restrictions) affect their preferences.

In the large-scale Sequenced Treatment Alternatives to Relieve Depression (STAR*D) effectiveness trial, patients with major depressive disorder who did not respond to or could not tolerate therapy with one SSRI (citalopram) were randomized to switch to extended-release ("sustained-release") bupropion, sertraline, or extended-release venlafaxine as a second step of treatment (level 2). Remission rates as assessed by the 17-item Hamilton Rating Scale for Depression (HRSD-17) and the Quick Inventory of Depressive Symptomatology—Self Report (QIDS-SR-16) were approximately 21 and 26% for extended-release bupropion, 18 and 27% for sertraline, and 25 and 25% for extended-release venlafaxine therapy, respectively; response rates as assessed by the QIDS-SR-16 were 26, 27, and 28% for extended-release bupropion, sertraline, and extended-release venlafaxine therapy, respectively. These results suggest that after unsuccessful initial treatment of depressed patients with an SSRI, approximately 25% of patients will achieve remission after therapy is switched to another antidepressant, and either another SSRI (e.g., sertraline) or an agent from another class (e.g., bupropion, venlafaxine) may be reasonable alternative antidepressants in patients not responding to initial SSRI therapy.

Patient Tolerance Considerations. Because of differences in the adverse effect profile between selective serotonin-reuptake inhibitors and tricyclic antidepressants, particularly less frequent anticholinergic effects, cardiovascular effects, and weight gain with selective serotonin-reuptake inhibitors, these drugs may be preferred in patients in whom such effects are not tolerated or are of potential concern. The decreased incidence of anticholinergic effects associated with fluoxetine and other selective serotonin-reuptake inhibitors compared with tricyclic antidepressants is a potential advantage, since such effects may result in discontinuance of the drug early during therapy in unusually sensitive patients. In addition, some anticholinergic effects may become troublesome during long-term tricyclic antidepressant therapy (e.g., persistent dry mouth may result in tooth decay). Although selective serotonin-reuptake inhibitors share the same overall tolerability profile, certain patients may tolerate one drug in this class better than another. In an open study, most patients who had discontinued fluoxetine therapy because of adverse effects subsequently tolerated sertraline therapy. Antidepressants other than selective serotonin-reuptake inhibitors may be preferred in patients in whom certain adverse GI effects (e.g., nausea, anorexia) or nervous system effects (e.g., anxiety, nervousness, insomnia, weight loss) are not tolerated or are of concern, since such effects appear to occur more frequently with fluoxetine and other drugs in this class.

Pediatric Considerations. The clinical presentation of depression in children and adolescents can differ from that in adults and generally varies with the age and developmental stages of the child. Younger children may exhibit behavioral problems such as social withdrawal, aggressive behavior, apathy, sleep disruption, and weight loss; adolescents may present with somatic complaints, self esteem problems, rebelliousness, poor performance in school, or a pattern of engaging in risky or aggressive behavior.

Data from controlled clinical studies evaluating various antidepressant agents in children and adolescents are less extensive than with adults, and many of these studies have methodologic limitations (e.g., nonrandomized or uncontrolled, small sample size, short duration, nonspecific inclusion criteria). However, there is some evidence that the response to antidepressants in pediatric patients may differ from that seen in adults, and caution should be used in extrapolating data from adult studies when making treatment decisions for pediatric patients. Results of several studies evaluating tricyclic antidepressants (e.g., amitriptyline, desipramine, imipramine, nortriptyline) in preadolescent and adolescent patients with major depression indicate a lack of overall efficacy in this age group.

Based on the lack of efficacy data regarding use of tricyclic antidepressants and MAO inhibitors in pediatric patients and because of the potential for life-threatening adverse effects associated with the use of these drugs, many experts consider selective serotonin-reuptake inhibitors, including fluoxetine, the drugs of choice when antidepressant therapy is indicated for the treatment of major depressive disorder in children and adolescents. However, the US Food and Drug Administration (FDA) states that, while efficacy of fluoxetine has been established in pediatric patients, efficacy of other newer antidepressants (i.e., citalopram, desvenlafaxine, duloxetine, escitalopram, fluvoxamine, mirtazapine, nefazodone, paroxetine, sertraline, venlafaxine) was not conclusively established in clinical trials in pediatric patients with major depressive disorder. In addition, FDA now warns that antidepressants increase the risk of suicidal thinking and behavior (suicidality) in children and adolescents with major depressive disorder and other psychiatric disorders. (See Cautions: Pediatric Precautions.) FDA currently states that anyone considering using an antidepressant in a child or adolescent for any clinical use must balance the potential risk of therapy with the clinical need. (See Cautions: Precautions and Contraindications.)

Geriatric Considerations. The response to antidepressants in depressed geriatric patients without dementia is similar to that reported in younger adults, but depression in geriatric patients often is not recognized and is not treated. In geriatric patients with major depressive disorder, SSRIs appear to be as effective as tricyclic antidepressants (e.g., amitriptyline) but may cause fewer overall adverse effects than these other agents. Geriatric patients appear to be especially sensitive to anticholinergic (e.g., dry mouth, constipation, vision disturbance), cardiovascular, orthostatic hypotensive, and sedative effects of tricyclic antidepressants. The low incidence of anticholinergic effects associated with fluoxetine and other SSRIs compared with tricyclic antidepressants is a potential advantage in geriatric patients, since such effects (e.g., constipation, dry mouth, confusion, memory impairment) may be particularly troublesome in these patients. However, SSRI therapy may be associated with other troublesome adverse effects (e.g., nausea and vomiting, agitation and akathisia, parkinsonian adverse effects, sexual dysfunction, weight loss, hyponatremia). Some clinicians state that SSRIs including fluoxetine may be preferred for treating depression in geriatric patients in whom the orthostatic hypotension associated with many antidepressants (e.g., tricyclics) potentially may result in injuries (such as severe falls). However, despite the fewer cardiovascular and anticholinergic effects associated with SSRIs, these drugs did not show any advantage over tricyclic antidepressants with regard to hip fracture in a case-control study. In addition, there was little difference in the rates of falls between nursing home residents receiving SSRIs and those receiving tricyclic antidepressants in a retrospective study. Therefore, all geriatric individuals receiving either type of antidepressant should be considered at increased risk of falls and appropriate measures should be taken. In addition, clinicians prescribing SSRIs in geriatric patients should be aware of the many possible drug interactions associated with these drugs, including those involving metabolism of the drugs through the cytochrome P-450 system. (See Drug Interactions.)

Patients with dementia of the Alzheimer's type (Alzheimer's disease, presenile or senile dementia) often present with depressive symptoms, such as depressed mood, appetite loss, insomnia, fatigue, irritability, and agitation. Most experts recommend that patients with dementia of the Alzheimer's type who present with clinically important and persistent depressive symptoms be considered as candidates for pharmacotherapy even if they fail to meet the criteria for a major depressive syndrome. The goals of such therapy are to improve mood, functional status (e.g., cognition), and quality of life. Treatment of depression also may reduce other neuropsychiatric symptoms associated with depression in patients with dementia, including aggression, anxiety, apathy, and psychosis. Although patients may present with depressed mood alone, the possibility of more extensive depressive symptomatology should be considered. Therefore, patients should be evaluated and monitored carefully for indices of major depression, suicidal ideation, and neurovegetative signs since safety measures (e.g., hospitalization for suicidality) and more vigorous and aggressive therapy (e.g., relatively high dosages, multiple drug trials) may be needed in some patients.

Although placebo-controlled trials of antidepressants in depressed patients with concurrent dementia have shown mixed results, the available evidence and experience with the use of antidepressants in patients with dementia of the Alzheimer's type and associated depressive manifestations indicate that depressive symptoms (including depressed mood alone and with neurovegetative changes) in such patients are responsive to antidepressant therapy. In some patients, cognitive deficits may partially or fully resolve during antidepressant therapy, but the extent of response will be limited to the degree of cognitive impairment that is directly related to depression. SSRIs such as fluoxetine, citalopram, escitalopram, paroxetine, or sertraline are generally considered as first-line agents in the treatment of depressed patients with dementia since they are usually better tolerated than some other antidepressants (e.g., tricyclic antidepressants, monoamine oxidase inhibitors). Some possible alternative agents to SSRIs include bupropion, mirtazapine, and venlafaxine. Some geriatric patients with dementia and depression may be unable to tolerate the antidepressant dosages needed to achieve full remission. When a rapid antidepressant response is not critical, some experts therefore recommend a very gradual dosage increase to increase the likelihood that a therapeutic dosage of the SSRI or other antidepressant will be reached and tolerated. In a randomized, double-blind study comparing fluoxetine and amitriptyline in a limited number of patients with major depression complicating Alzheimer's disease, fluoxetine and amitriptyline were found to be equally effective; however, fluoxetine was better tolerated.

Cardiovascular Considerations. The relatively low incidence of adverse cardiovascular effects, including orthostatic hypotension and conduction disturbances, associated with fluoxetine and other selective serotonin-reuptake inhibitors may be advantageous in patients in whom cardiovascular effects associated with tricyclic antidepressants may be hazardous. However, most

clinical studies of fluoxetine for the management of depression did not include individuals with cardiovascular disease (e.g., those with a recent history of myocardial infarction or unstable heart disease), and further experience in such patients is necessary to confirm the reported relative lack of cardiotoxicity with the drug. (See Cautions: Precautions and Contraindications.)

Sedative Considerations. Because fluoxetine and other SSRIs generally are less sedating than some other antidepressants (e.g., tricyclics), some clinicians state that these drugs may be preferable in patients who do not require the sedative effects associated with many antidepressant agents; however, an antidepressant with more prominent sedative effects (e.g., trazodone) may be preferable in some patients (e.g., those with insomnia).

Suicidal Risk Considerations. Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are the strongest predictors of suicide. However, there has been a long-standing concern that antidepressants may have a role in inducing worsening of depression and the emergence of suicidal thinking and behavior (suicidality) in certain patients during the early phases of treatment. FDA states that antidepressants increased the risk of suicidality in short-term studies in children, adolescents, and young adults (18–24 years of age) with major depressive disorder and other psychiatric disorders. (See Cautions: Pediatric Precautions.) It currently is unknown whether the suicidality risk extends to longer-term antidepressant use (i.e., beyond several months); however, there is substantial evidence from placebo-controlled maintenance trials in adults with major depressive disorder that antidepressants can delay the recurrence of depression. Because the risk of suicidality in depressed patients may persist until substantial remission of depression occurs, appropriate monitoring and close observation of patients of all ages who are receiving antidepressant therapy are recommended. (See Cautions: Precautions and Contraindications.)

Dosing Interval Considerations. Fluoxetine can be administered once weekly as delayed-release capsules for continuing management of major depressive disorder. Whether the weekly regimen is equivalent to daily therapy with conventional preparations for preventing relapse has not been established. In a double-blind study in adults who responded to daily fluoxetine therapy for major depressive disorder, the relapse rate for continuing therapy with fluoxetine 20-mg conventional capsules administered daily, fluoxetine 90-mg delayed-release capsules administered once weekly, or placebo was 26, 37, or 50%, respectively.

Other Considerations. Fluoxetine has been effective for the treatment of depression in adults with human immunodeficiency virus (HIV) infection. In one randomized, placebo-controlled study, analysis of patients who completed the study showed a statistically significant benefit in patients receiving fluoxetine compared with those receiving placebo. However, results of intent-to-treat analysis did not show a statistically significant benefit in those receiving the antidepressant, possibly because of a high attrition rate and substantial placebo response. There was no evidence that the degree of immunosuppression affected the response to antidepressant therapy.

Fluoxetine has been effective when used in combination with lithium in a limited number of patients with refractory depression who had not responded to prior therapy (including tricyclic antidepressants and MAO inhibitors administered alone or in combination with lithium), suggesting that lithium may potentiate the antidepressant activity of fluoxetine. (See Drug Interactions: Lithium.) In the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) level 2 trial, patients with major depressive disorder who did not respond to or could not tolerate therapy with citalopram (another SSRI) were randomized to receive either extended-release ("sustained-release") bupropion or buspirone therapy in addition to citalopram. Although both extended-release bupropion and buspirone were found to produce similar remission rates, extended-release bupropion produced a greater reduction in the number and severity of symptoms and a lower rate of drug discontinuance than buspirone in this large-scale, effectiveness trial. These results suggest that augmentation of SSRI therapy with extended-release bupropion may be useful in some patients with refractory depression.

Fluoxetine has been used safely for the management of depression in at least one patient with established susceptibility to malignant hyperthermia, suggesting that the drug may be useful in depressed patients susceptible to malignant hyperthermia and in whom tricyclics and MAO inhibitors are potentially hazardous; however, additional experience is necessary to confirm this preliminary finding.

Because fluoxetine possesses anorectic and weight-reducing properties, some clinicians state that the drug may be preferred in obese patients and/or patients in whom the increase in appetite, carbohydrate craving, and weight gain associated with tricyclic antidepressant therapy may be undesirable (e.g., potentially hazardous to the patient's health; result in possible discontinuance of or noncompliance with therapy). However, the possibility that some patients with concurrent eating disorders or those who may desire to lose weight may misuse fluoxetine for its anorectic and weight-reducing effects should be considered. (See Uses: Eating Disorders and also see Chronic Toxicity.)

■ **Obsessive-Compulsive Disorder** Fluoxetine is used in the treatment of obsessive-compulsive disorder in adults and pediatric patients 7 years of age and older when the obsessions or compulsions cause marked distress, are time consuming, or interfere substantially with social or occupational functioning. Obsessions are recurrent and persistent ideas, thoughts, impulses, or images that, at some time during the disturbance, are experienced as intrusive and inappropriate (i.e., "ego dystonic") and that cause marked anxiety or distress but that are not simply excessive worries about real-life problems. Compulsions are repetitive, intentional behaviors (e.g., hand washing, ordering, checking) or mental acts (e.g., praying, counting, repeating words silently) performed in response to an obsession or according to rules that must be applied rigidly (e.g., in a stereotyped fashion). Although the behaviors or acts are aimed at preventing or reducing distress or preventing some dreaded event or situation, they either are not connected in a realistic manner with what they are designed to neutralize or prevent or are clearly excessive. At some time during the course of the disturbance, the patient, if an adult, recognizes that the obsessions or compulsions are excessive or unreasonable; children may not make such a recognition.

The efficacy of fluoxetine for the management of obsessive-compulsive disorder has been established in several multicenter, placebo-controlled studies, including 2 studies of 13 weeks' duration in adults and one study of 13 weeks' duration in children and adolescents 7–17 years of age. Patients in these studies had moderate to severe obsessive-compulsive disorder with average baseline total scores on the Yale-Brown Obsessive-Compulsive Scale (YBOCS) of 22–26 in adults and 25–26 in children and adolescents (measured on the Children's Yale-Brown Obsessive-Compulsive Scale [CY-BOCS]).

In 2 fixed-dose studies of 13 weeks' duration, adults receiving fluoxetine dosages of 20, 40 and 60 mg daily experienced substantially greater reductions in the YBOCS total score than those receiving placebo. Mean reductions in total scores on the YBOCS in fluoxetine-treated patients were approximately 4–6 units in one study and 4–9 units in the other study compared with a 1-unit reduction in patients receiving placebo. In these 2 studies, a positive clinical response (much or very much improved on the Clinical Global Impressions improvement scale) occurred in 36–47 or 11% of patients receiving fluoxetine or placebo, respectively. While there was no indication of a dose-response relationship for effectiveness in one study, a dose-response relationship was observed in the other study, with numerically better responses in patients receiving 40 or 60 mg of fluoxetine daily compared with those receiving 20 mg of the drug daily. No age- or gender-related differences in outcome were noted in either of these studies.

In another randomized, placebo-controlled study of 13 weeks' duration, children and adolescents 7–17 years of age with obsessive-compulsive disorder who received mean fluoxetine dosages of approximately 25 mg daily (range: 10–60 mg daily) demonstrated substantially greater reductions in the CY-BOCS total score than those receiving placebo. In this study, a positive clinical response (much or very much improved on the Clinical Global Impressions improvement scale) occurred in approximately 55–58 or 9–19% of patients receiving fluoxetine or placebo, respectively. In addition, 49% of patients who received fluoxetine were classified as responders (i.e., patients with a 40% or greater reduction in their CY-BOCS total score from baseline) compared with 25% of those who received placebo. Subgroup analyses on outcome did not suggest any differential responsiveness on the basis of age or gender.

Results from comparative studies to date suggest fluoxetine and other selective serotonin-reuptake inhibitors (SSRIs; e.g., fluvoxamine, paroxetine, sertraline) are as effective or somewhat less effective than clomipramine in the management of obsessive-compulsive disorder. In a pooled analysis of separate short-term (10–13 weeks) studies comparing clomipramine, fluoxetine, fluvoxamine, or sertraline with placebo, clomipramine was calculated as being more effective (as determined by measures on the YBOC scale) than SSRIs, although all drugs were superior to placebo.

Many clinicians consider an SSRI (e.g., fluoxetine, fluvoxamine, paroxetine, sertraline) or clomipramine to be the drugs of choice for the pharmacologic treatment of obsessive-compulsive disorder. The decision whether to initiate therapy with an SSRI or clomipramine often is made based on the adverse effect profile of these drugs. For example, some clinicians prefer clomipramine in patients who may not tolerate the adverse effect profile of SSRIs (nausea, headache, overstimulation, sleep disturbances) while SSRIs may be useful alternatives in patients unable to tolerate the adverse effects associated with clomipramine therapy (anticholinergic effects, cardiovascular effects, sedation). Consideration of individual patient characteristics (age, concurrent medical conditions), pharmacokinetics of the drug, potential drug interactions, and cost of therapy may also influence decisions regarding use of SSRIs or clomipramine as first-line therapy in patients with obsessive-compulsive disorder. Although not clearly established, it has been suggested that the mechanism of action of fluoxetine and other drugs (e.g., clomipramine) used in the management of obsessive-compulsive disorder may be related to their serotonergic activity.

Other Disorders with an Obsessive-Compulsive Component

Experience in a limited number of patients suggests that fluoxetine also reduces obsessive-compulsive symptoms associated with Tourette's disorder† (Gilles de la Tourette's syndrome); however, the drug did not appear to be effective in suppressing motor and vocal tics associated with the condition.

Trichotillomania† (an urge to pull out one's hair) has some features in common with those of obsessive-compulsive disorder and some studies have suggested that antiobsessional agents such as SSRIs and clomipramine may be useful in treating this condition. Successful treatment with fluoxetine has been reported in some patients with trichotillomania, including in 2 short-term, open studies in which dosages of up to 80 mg daily were given. However, fluoxetine's efficacy in the management of this disorder was not demonstrated in 2 double-blind, placebo-controlled, crossover studies. In addition, behavioral therapy was found to be more effective than fluoxetine in treating trichotillomania in a short-term, controlled study. Further studies are needed to more

clearly determine the role of fluoxetine and other serotonin-reuptake blockers in the management of this condition.

■ **Premenstrual Dysphoric Disorder** Fluoxetine is used in the treatment of premenstrual dysphoric disorder (previously late luteal phase dysphoric disorder). DSM-IV criteria for premenstrual dysphoric disorder (PMDD) require that in most menstrual cycles of the previous year at least 5 of the following 11 symptoms must have been present for most of the time during the last week of the luteal phase (with at least one of the symptoms being the first 4 listed): marked depressed mood, feelings of hopelessness, or self-deprecating thoughts; marked anxiety, tension, feelings of being "keyed up" or on "edge"; marked affective lability (e.g., feeling suddenly sad or tearful or increased sensitivity to rejection); persistent and marked anger or irritability or increased interpersonal conflicts; decreased interest in usual activities (e.g., work, school, friends, hobbies); a subjective sense of difficulty in concentrating; lethargy, easy fatigability, or marked lack of energy; marked change in appetite, overeating, or specific food cravings; hypersomnia or insomnia; a subjective sense of being overwhelmed or out of control; and other physical symptoms, such as breast tenderness or swelling, headaches, joint or muscle pain, or a sensation of "bloating" or weight gain. Such symptoms should begin to remit within a few days of the onset of menses (follicular phase) and are always absent in the week following menses. The presence of this cyclical pattern of symptoms must be confirmed by at least 2 consecutive months of prospective daily symptom ratings. PMDD should be distinguished from the more common premenstrual syndrome (PMS) by prospective daily ratings and the strict criteria listed above.

There is some evidence that serotonergic agents (e.g., fluoxetine, paroxetine) have greater efficacy compared with non-serotonergic agents (e.g., bupropion, maprotiline) in relieving the physical and/or emotional symptoms of PMDD. In published studies, the response rates to fluoxetine therapy in women with PMDD appear to be similar to those described in patients with depression, panic disorder, and obsessive-compulsive disorder. However, unlike the onset of action of fluoxetine in other psychiatric conditions (6–8 weeks), some clinicians have observed a rapid onset of response to fluoxetine (approximately 2–4 weeks) in women with PMDD, suggesting that the mechanism of action of these agents in PMDD is not mediated by the drug's antidepressant or anti-obsessive effects. In addition, use of fluoxetine in the treatment of PMDD does not appear to produce the sustained remission typically seen in the treatment of major depressive disorder. PMDD symptoms recur soon after discontinuance of fluoxetine therapy (e.g., within 2 menstrual cycles), even in women who have received the drug for more than 1 year. It has been suggested that a past history of major depression may be associated with a partial or absent response to lower dosages of fluoxetine therapy. Because patients on oral contraceptives were excluded from most clinical studies to date, efficacy of fluoxetine used in conjunction with oral contraceptives for the treatment of PMDD has not been determined.

The efficacy of fluoxetine for the management of PMDD has been established in 3 randomized, placebo-controlled (1 intermittent- and 2 continuous-dosing) studies of 3 or 6 months' duration in adult women who met DSM-III-R or DSM-IV criteria for PMDD. One study involved over 300 women (20–40 years of age) who were randomized to receive either fluoxetine (at fixed dosages of 20 or 60 mg daily) or placebo continuously throughout the full menstrual cycle, beginning on the first day of their cycle. In this study, fixed doses of fluoxetine were shown to be substantially more effective than placebo in decreasing the mean total of 3 visual analog scale scores (tension, irritability, dysphoria); total scores decreased by 36–39% on 20 or 60 mg of fluoxetine and 7% on placebo. However, marked (greater than 50% reduction from baseline) improvement in total luteal phase visual analog scale scores occurred only in 18% of patients receiving 60 mg of fluoxetine and in 6 or 4% of those receiving 20 mg of fluoxetine or placebo, respectively. Fluoxetine therapy appeared to be well tolerated in patients receiving dosages of 20 mg daily, but approximately 33% of women receiving 60 mg daily discontinued the drug because of adverse reactions and 86% of those receiving this dosage who remained in the study reported one or more adverse effects attributable to the drug.

In a second double-blind, placebo-controlled, crossover study, women with PMDD who received flexible doses of fluoxetine (20–60 mg daily; mean dosage of 27 mg daily) throughout the menstrual cycle for a total of 3 cycles had an average visual analog scale total score (follicular to luteal phase increase) that was 3.8 times lower than that of patients receiving placebo. However, results of another double-blind, parallel study indicated that the response rate in women receiving fluoxetine 20 mg daily or bupropion 300 mg daily continuously for 2 cycles was not substantially superior to placebo on the Clinical Global Impressions scale.

The efficacy of intermittent dosing (defined as initiation of daily dosage 14 days prior to the anticipated onset of menstruation and continuing through the first full day of menses) was established in a double-blind, parallel group study of 3 months' duration. In this study, women receiving intermittent dosing of 20 mg daily dosages of fluoxetine had substantially greater improvements on the Daily Record of Severity of Problems, a patient-rated instrument that mirrors the diagnostic criteria for PMDD as identified in the DSM-IV, than those receiving placebo. Further studies are needed to evaluate the comparative efficacy of continuous and intermittent dosing regimens.

■ **Eating Disorders** Fluoxetine is used in the treatment of bulimia nervosa; the drug also has been used in a limited number of patients with other eating disorders (e.g., anorexia nervosa).

Although DSM-IV criteria provide guidelines for establishing a diagnosis of a specific eating disorder, the symptoms frequently occur along a continuum between those of anorexia nervosa and bulimia nervosa. The primary features in both anorexia nervosa and bulimia nervosa are weight preoccupation and excessive self-evaluation (i.e., disturbed perception) of body weight and shape, and many patients exhibit a mixture of both anorexic and bulimic behaviors.

The American Psychiatric Association (APA) states that psychiatric management forms the foundation of treatment for patients with eating disorders and should be instituted for all patients in combination with other specific treatment modalities (e.g., nutritional rehabilitation and pharmacotherapy). Because patients with eating disorders often exhibit comorbid conditions and/or associated psychiatric features that may compromise clinical outcome, treatment programs should identify and address all comorbid conditions before initiating therapy. Clinicians should recognize that patients with concurrent diabetes mellitus often underdose their insulin in order to lose weight, and that pregnant patients with disturbed eating behaviors (e.g., inadequate nutritional intake, binge eating, purging, abuse of teratogenic medications) may be at high risk for fetal or maternal complications. Results from several studies indicate that patients with associated psychiatric features such as substance abuse/dependence or personality disorder may require longer-term therapy than those without these comorbid conditions. Although the presence of depression at initial presentation has no predictive value for treatment outcome, many clinicians suggest that severe depression can impair the patient's involvement in and/or response to psychotherapy, and such patients should receive initial pharmacologic therapy to improve mood symptoms.

Bulimia Nervosa Fluoxetine is used in the management of binge-eating and self-induced vomiting behaviors in patients with moderate to severe bulimia nervosa (e.g., at least 3 bulimic episodes per week for 6 months).

According to DSM-IV, bulimia nervosa is characterized by recurrent episodes of binge eating and recurrent inappropriate compensatory behaviors to prevent weight gain (e.g., self-induced vomiting; misuse of laxatives, diuretics, enemas, or other medications; fasting; excessive exercise) and binge eating and compensatory behaviors both occur at least twice a week for 3 months.

Treatment strategies for bulimia nervosa include psychosocial interventions, nutritional counseling and rehabilitation, and pharmacotherapy. The primary goals in treating bulimia nervosa are to reduce binge eating and purging. Although antidepressants initially were used only in bulimic patients who were clinically depressed, evidence from recent studies indicates that nondepressed patients also respond to these agents, and that the presence of depression is not predictive of therapeutic response. Therefore, antidepressants are included as one component of initial treatment regimens for patients with bulimia nervosa. Because selective serotonin-reuptake inhibitors have a more favorable adverse effects profile, these drugs usually are preferred and may be especially useful for patients with symptoms of depression, anxiety, obsessions, or certain impulse disorder symptoms or for those who previously failed to achieve optimal response to psychosocial therapy. Other antidepressants also may be used to reduce the symptoms of binge eating and purging and help prevent relapse. However, the APA cautions against the use of tricyclic antidepressants in patients who are suicidal and cautions against use of MAO inhibitors in those with chaotic binge eating and purging.

The APA states that in patients who fail to respond to initial antidepressant therapy, it may be necessary to assess whether the patient has taken the drug shortly before vomiting or to determine whether effective drug concentrations have been achieved. Although only limited data are available regarding use of antidepressants for maintenance therapy, there appears to be a high rate of relapse during the treatment phase and an even higher rate following discontinuance of therapy. However, limited data indicate that the rate of relapse appears to correlate with the time at which drug therapy is initiated. In one small, open-label study, patients who received drug treatment within 13 weeks of diagnosis were more likely to exhibit sustained recovery during the first year than those who did not receive pharmacotherapy. Furthermore, continuing cognitive behavior therapy following discontinuance of drug therapy appears to prevent relapse in patients with bulimia nervosa. Additional study is needed to determine the effects of sequential use of psychotherapy and pharmacotherapy in the treatment of bulimia nervosa.

The efficacy of fluoxetine for the management of bulimia nervosa has been established in several multicenter, placebo-controlled studies, including 2 studies of 8 weeks' duration (using fluoxetine dosages of 20 or 60 mg daily) and one study of 16 weeks' duration (using fluoxetine dosages of 60 mg once daily) in patients with moderate to severe bulimia nervosa with median binge eating and self-induced vomiting of 7–10 and 5–9 times a week, respectively. In these studies, fluoxetine given in dosages of 60 mg daily (but not in dosages of 20 mg daily) was substantially more effective than placebo in reducing the number of binge-eating and self-induced vomiting episodes weekly. The superiority of fluoxetine compared with placebo was evident as early as within 1 week of therapy and persisted throughout each study period. The drug-related reduction in bulimic episodes appeared to be independent of baseline depression as assessed by the Hamilton Depression Rating Scale. The beneficial effect of fluoxetine therapy (compared with placebo), as measured by median reductions in the frequency of bulimic behaviors at the end of therapy compared with baseline, ranged from 1–2 and 2–4 episodes per week for binge eating and self-induced vomiting, respectively. The magnitude of clinical effect was related to baseline frequency of bulimic behaviors since greater reductions in such behaviors were observed in patients with higher baseline frequencies. Although binge eating and purging resolved completely in some patients who received

fluoxetine therapy, the majority of fluoxetine-treated patients only experienced a partial reduction in the frequency of bulimic behaviors.

In an uncontrolled study in patients with bulimia nervosa, fluoxetine substantially reduced the frequency of binge eating and self-induced vomiting but did not affect bodily dissatisfaction in patients receiving 60–80 mg of the drug for 4 weeks; in several patients, therapeutic effects of the drug appeared to be maintained during chronic therapy. In another uncontrolled study, fluoxetine reduced the frequency of binge eating and self-induced vomiting in several patients with bulimia nervosa who were unresponsive to previous therapy with imipramine. The drug also reportedly improved bulimic symptoms, expanded food preferences, and resulted in weight gain in one underweight patient with anorexia nervosa and bulimia who was unresponsive to or unable to tolerate previous therapy for her eating disorder (including tricyclic antidepressants, monoamine oxidase inhibitors, bupropion, nomifensine, or lithium). In addition, fluoxetine used in combination with lithium was effective in improving bulimic symptoms in a patient with major depression and bulimia who was unresponsive to prior therapy.

The efficacy of fluoxetine for long-term use in the treatment of bulimia nervosa has been established in a placebo-controlled study of up to 52 weeks' duration in patients who responded to an initial single-blind, 8-week acute treatment phase with fluoxetine 60 mg daily for bulimia nervosa. In this study, fluoxetine decreased the likelihood of relapse and improved the clinical outcome. However, symptoms of bulimia gradually worsened over time in patients in both the fluoxetine and placebo groups in this study, suggesting that fluoxetine alone may not be an adequate maintenance treatment after acute response in some patients with bulimia nervosa. Additional management strategies, such as psychotherapy, may be required to augment or to sustain initial improvement in this condition.

Pending further accumulation of data, most clinicians recommend that antidepressant therapy, including fluoxetine, be continued for at least 6–12 months in patients with bulimia nervosa before attempting to discontinue therapy. If fluoxetine is used for extended periods, the need for continued therapy with the drug should be reassessed periodically.

Anorexia Nervosa Fluoxetine has been used in a limited number of patients with anorexia nervosa†. According to DSM-IV, anorexia nervosa is characterized by refusal to maintain body weight at or above a minimally normal weight for age and height (e.g., weight loss leading to maintenance of body weight less than 85% of that expected or failure to make expected weight gain during periods of growth, leading to body weight less than 85% of that expected); intense fear of gaining weight or becoming fat (even though underweight); disturbance in the perception of body weight and shape, undue influence of body weight or shape on self-evaluation, or denial of the seriousness of the current low body weight; and amenorrhea in postmenarchal females (i.e., absence of at least 3 consecutive menstrual cycles). Patients with anorexia nervosa often exhibit depressive (e.g., depressed mood, social withdrawal, irritability, insomnia, and diminished interest in sex) and obsessive-compulsive symptoms that may be associated with or exacerbated by undernutrition.

The APA recommends that a program of nutritional rehabilitation, including vitamin (e.g., potassium and phosphorus) supplementation, be established for all patients who are significantly underweight. The APA states that pharmacologic measures (e.g., antidepressants) may be considered in patients with anorexia nervosa to maintain weight and normal eating behaviors; to treat psychiatric symptoms associated with the disorder (e.g., depression, anxiety, or obsessive-compulsive symptoms); and to prevent relapse. However, such therapy should not be used as the sole or primary treatment for anorexia nervosa. Because associated psychiatric symptoms of anorexia nervosa (e.g., depression) often improve with weight gain, the APA states that the decision to initiate antidepressant therapy should be deferred until weight gain has been restored, and that the choice of an antidepressant agent depends on the remaining symptoms. According to the APA, selective serotonin-reuptake inhibitors commonly are considered in patients with anorexia nervosa whose depressive, obsessive, or compulsive symptoms persist in spite of or in the absence of weight gain.

Although there are few well-controlled, clinical studies of antidepressants for the treatment of anorexia nervosa, data from one study indicate that weight-restored patients with anorexia nervosa who received fluoxetine (40 mg daily) after hospital discharge had less weight loss, depression, and fewer rehospitalizations for anorexia nervosa during the subsequent year than those who received placebo. However, it should be noted that fluoxetine has been misused for its anorectic and weight-reducing effects in a patient with a history of chronic depression, anorexia nervosa, and laxative abuse who was receiving the drug for the treatment of depression; therefore, the misuse potential of fluoxetine in depressed patients with concurrent eating disorders or in other patients who may desire to lose weight should be considered. (See Chronic Toxicity.)

■ **Panic Disorder** Fluoxetine is used in the treatment of panic disorder with or without agoraphobia. Panic disorder is characterized by the occurrence of unexpected panic attacks and associated concern about having additional attacks, worry about the implications or consequences of the attacks, and/or a clinically important change in behavior related to the attacks.

According to DSM-IV, panic disorder is characterized by recurrent unexpected panic attacks, which consist of a discrete period of intense fear or discomfort in which 4 (or more) of the following symptoms develop abruptly and reach a peak within 10 minutes: palpitations, pounding heart, or accelerated heart rate; sweating; trembling or shaking; sensations of shortness of breath or smothering; feeling of choking; chest pain or discomfort; nausea or abdominal distress; feeling dizzy, unsteady, lightheaded, or faint; derealization (feelings of unreality) or depersonalization (being detached from oneself); fear of losing control; fear of dying; paresthesias (numbness or tingling sensations); and chills or hot flushes.

The efficacy of fluoxetine for the management of panic disorder with or without agoraphobia has been established by 2 randomized, double-blind, placebo-controlled studies in adult outpatients who met DSM-IV criteria for panic disorder with or without agoraphobia. These studies were of 12 weeks' duration and used a flexible dosing schedule. Fluoxetine therapy in both studies was initiated in a dosage of 10 mg daily for the first week and then the dosage was escalated to 20–60 mg daily depending on clinical response and tolerability. In these studies, 42–62% of patients receiving fluoxetine were free from panic attacks at week 12 compared with 28–44% of those receiving placebo. The mean fluoxetine dosage in one of these studies was approximately 30 mg daily.

The optimum duration of fluoxetine therapy required to prevent recurrence of panic disorder has not been established to date. The manufacturer states that the efficacy of fluoxetine for long-term use (i.e., longer than 12 weeks) has not been demonstrated in controlled studies. However, in a 10-week, placebo-controlled, fixed-dose study, patients responding to fluoxetine 10 or 20 mg daily were randomized to receive continued therapy with their previous fluoxetine dosage or placebo during a 6-month continuation phase. The patients who received an additional 6 months of fluoxetine therapy in this study demonstrated continued clinical improvement. The manufacturer and some clinicians state that panic disorder is a chronic condition and requires several months or longer of sustained therapy. Therefore, it is reasonable to continue therapy in responding patients. The manufacturer recommends, however, that patients be reassessed periodically to determine the need for continued therapy.

Panic disorder can be treated with cognitive and behavioral psychotherapy and/or pharmacologic therapy. There are several classes of drugs that appear to be effective in the pharmacologic management of panic disorder, including tricyclic antidepressants (e.g., imipramine, clomipramine), monamine oxidase (MAO) inhibitors (e.g., phenelzine), selective serotonin-reuptake inhibitors (SSRIs), and benzodiazepines (e.g., alprazolam, clonazepam). When choosing among the available drugs, clinicians should consider their acceptance and tolerability by patients; their ability to reduce or eliminate panic attacks, reduce clinically important anxiety and disability secondary to phobic avoidance, and ameliorate other common comorbid conditions (such as depression); and their ability to prevent relapse during long-term therapy. Because of their better tolerability when compared with other agents (such as the tricyclic antidepressants and benzodiazepines), the lack of physical dependence problems commonly associated with benzodiazepines, and efficacy in panic disorder with comorbid conditions (e.g., depression, other anxiety disorders such as obsessive-compulsive disorder, alcoholism), many clinicians prefer SSRIs as first-line therapy in the management of panic disorder. If SSRI therapy is ineffective or is not tolerated, use of a tricyclic antidepressant or a benzodiazepine is recommended.

■ **Bipolar Disorder** Fluoxetine has been used for the short-term treatment of acute depressive episodes† in a limited number of patients with bipolar depression† (bipolar disorder, depressed). In one poorly controlled study, fluoxetine was more effective than imipramine, and each drug was more effective than placebo in the management of depression in patients with bipolar disorder; fluoxetine appeared to be particularly effective in reducing anxiety and somatic symptoms in these patients. However, because the drug has been reported to cause manic reactions in some patients, the possibility that hypomanic or manic attacks may be precipitated in patients with bipolar disorder must be considered. In addition, some experts have reported an association between use of antidepressants and the development of rapid cycling and mixed affective states in patients with bipolar disorder, suggesting that such use may worsen the overall course of bipolar disorder in these patients. Consequently, the American Psychiatric Association (APA) does not recommend use of antidepressant monotherapy in patients with bipolar disorder. Initiation or optimization of dosages of maintenance agents (i.e., lithium, lamotrigine) are considered first-line therapies for the management of acute episodes of depression in patients with bipolar disorder. While the addition of either lamotrigine, bupropion, or paroxetine currently is recommended as the next step for patients who fail to respond to optimum dosages of maintenance agents, the APA states that other SSRIs (e.g., fluoxetine) can be used as an alternative to these agents. For further information on the management of bipolar disorder, see Uses: Bipolar Disorder, in Lithium Salts 28:28.

Fluoxetine also is used in combination with olanzapine for the treatment of acute depressive episodes in patients with bipolar disorder. In 2 randomized, double-blind studies of 8 weeks' duration comparing a fixed combination of fluoxetine and olanzapine (Symbyax®) with olanzapine monotherapy and placebo, the fixed combination (flexible daily dosages of 6 mg olanzapine and 25 or 50 mg of fluoxetine or of 12 mg of olanzapine and 50 mg of fluoxetine) was more effective than olanzapine monotherapy (5–20 mg daily) or placebo in improvement in depressive symptoms as assessed by the Montgomery-Asberg Depression Rating Scale (MADRS). Although the manufacturer states that efficacy beyond 8 weeks' duration remains to be established, patients have received the fixed combination for up to 24 weeks in clinical trials. Clinicians who elect to extend therapy beyond 8 weeks should reevaluate the risks and benefits of continued therapy periodically.

■ **Obesity** Fluoxetine has been used in a limited number of patients for the short-term management of exogenous obesity†. In a controlled study, obese

(i.e., more than 20% overweight), nondepressed individuals receiving fluoxetine (average dosage: 64.9 mg daily), benzphetamine hydrochloride (average dosage: 97 mg daily), or placebo concurrently with reduced food intake and increased exercise for 8 weeks lost an average of about 4.8, 4, and 1.7 kg, respectively. Fluoxetine-treated patients who usually experienced carbohydrate cravings reportedly lost more weight during this study than those who did not experience such cravings. (See Pharmacology: Effects on Appetite and Body Weight.)

In a study evaluating the safety of fluoxetine therapy in the management of exogenous obesity, the drug was generally well tolerated. The adverse effect profile of the drug in nondepressed obese patients appeared to differ somewhat from that in depressed patients receiving similar dosages of the drug; obese patients reportedly had a higher incidence of fatigue and a lower incidence of nausea, anxiety, and tremor. Unlike amphetamines, the potential for addiction to or abuse of fluoxetine appears to be minimal (see Chronic Toxicity), and tolerance to the drug's anorectic and weight-reducing effects has not been reported to date following short-term administration. However, long-term studies are necessary to fully determine whether tolerance develops during chronic fluoxetine therapy and to fully establish the relative efficacy and safety of fluoxetine in the management of exogenous obesity.

■ **Cataplexy** Fluoxetine has been used for the symptomatic management of cataplexy† in a limited number of patients with cataplexy and associated narcolepsy. In one study, the drug appeared to be as effective as clomipramine in reducing the number of cataplexy attacks in patients concurrently receiving CNS stimulants (e.g., dextroamphetamine) for the symptomatic management of associated narcolepsy.

■ **Alcohol Dependence** Like some other selective serotonin-reuptake inhibitors (SSRIs; e.g., citalopram, zimeldine [not commercially available in the US]), fluoxetine has been used in the management of alcohol dependence†. However, studies of SSRIs have generally shown modest effects on alcohol consumption. In a limited number of early-stage problem drinkers (who drank an average of about 8 drinks daily prior to therapy), alcohol consumption was reduced by an average of 17% in patients receiving 60 mg of fluoxetine daily; however, response showed considerable interindividual variability, and alcohol consumption was not altered substantially in problem drinkers receiving 40 mg of the drug daily. It has been suggested that the clinical effects of SSRIs in the management of alcohol dependence may only be transient. In patients with mild to moderate alcohol dependence, alcohol consumption is substantially decreased for only the first 1–4 weeks of fluoxetine therapy or first 12 weeks of citalopram therapy. Additional study is required to fully determine the safety and efficacy of fluoxetine in the management of alcohol dependence. (See Pharmacology: Effects on Alcohol Intake and also see Drug Interactions: Alcohol.)

■ **Myoclonus** Fluoxetine has been used for the management of intention myoclonus†, including postanoxic action myoclonus† and progressive action myoclonus†, in a limited number of patients. Although fluoxetine alone was not effective in improving myoclonus, speech abnormalities, gait abnormalities, or overall performance on neurological examination in such patients, the drug did appear to potentiate the therapeutic effects of combined oxitriptan (l-5-hydroxytryptophan, l-5HTP) and carbidopa therapy in some patients. In addition, fluoxetine reportedly reduced the dosage requirement of oxitriptan and the incidence of adverse GI effects (e.g., diarrhea, abdominal cramps) associated with such therapy. Fluoxetine used in combination with oxitriptan also has exhibited antimyoclonic activity in animals. (See Pharmacology: Other Effects.) However, because toxic effects have been reported in some patients concurrently receiving fluoxetine and tryptophan, a serotonergic agent that is structurally similar to oxitriptan (see Tryptophan and Other Serotonin Precursors under Drug Interactions: Serotonergic Drugs), further study and experience are needed to fully determine the safety and efficacy of combined therapy with fluoxetine and oxitriptan-carbidopa in the management of intention myoclonus.

■ **Premature Ejaculation** Like some other SSRIs, fluoxetine has been used with some success in the treatment of premature ejaculation†. In a placebo-controlled study, fluoxetine produced substantial improvements compared with placebo in time to ejaculation and was well tolerated in most patients. However, in a comparative study, patients receiving either clomipramine or sertraline reported a greater increase in mean intravaginal ejaculation latency time and a greater patient sexual satisfaction rating than those receiving either fluoxetine or placebo. Although the mechanism of action of SSRIs in delaying ejaculation is unclear, it has been suggested that these drugs may be particularly useful in patients who fail or refuse behavioral or psychotherapeutic treatment or when partners are unwilling to cooperate with such therapy.

Dosage and Administration

■ **Administration** Fluoxetine hydrochloride is administered orally without regard to meals.

Fluoxetine hydrochloride conventional capsules, tablets, and solution are administered once or twice daily; the delayed-release capsules are administered once weekly. For the initial management of depression, obsessive-compulsive disorder, premenstrual dysphoric disorder, or bulimia nervosa, the drug generally is administered once daily in the morning. If the dosage exceeds 20 mg daily, the manufacturer and some clinicians state that fluoxetine should be administered in 2 divided doses daily (preferably in the morning and at noon). However, limited evidence suggests that no clinically important differences in either the efficacy or incidence of adverse effects exist with once-daily (in the morning) versus twice-daily (in the morning and at noon) administration of the drug. If sedation occurs during fluoxetine therapy, administering the second dose at bedtime rather than at noon may be useful. Because fluoxetine and its principal active metabolite have relatively long half-lives, the drug has been administered less frequently than once daily (e.g., every 2–7 days), particularly during maintenance therapy. Fluoxetine delayed-release capsules are administered once weekly as maintenance therapy in the management of major depressive disorder in patients who have responded to daily administration of the drug. Some clinicians have suggested that conventional fluoxetine preparations administered less frequently than once daily (i.e., three 20-mg capsules once weekly) may also be effective as maintenance therapy in the management of major depressive disorder, but such dosing regimens should be considered investigational at this time and require additional study to confirm their safety and efficacy.

Because of the prolonged elimination of fluoxetine and its active metabolite from the body, missing a dose of the drug once steady-state concentrations have been achieved is unlikely to result in substantial alterations in plasma fluoxetine or norfluoxetine concentrations.

■ **Dosage** Dosage of fluoxetine hydrochloride is expressed in terms of fluoxetine.

In titrating dosage of or discontinuing fluoxetine therapy, the prolonged elimination half-life of fluoxetine and norfluoxetine should be considered. Several weeks will be required before the full effect of such alterations is realized.

The manufacturers and some clinicians recommend that an interval of at least 5 weeks elapse between discontinuance of fluoxetine therapy and initiation of monoamine oxidase (MAO) inhibitor therapy, and that at least 2 weeks elapse following discontinuance of an MAO inhibitor prior to initiation of fluoxetine therapy. For additional information on potentially serious drug interactions that may occur between fluoxetine and MAO inhibitors or other serotonergic agents, see Cautions: Precautions and Contraindications and see also Drug Interactions: Serotonergic Drugs.

Withdrawal symptoms, including dysphoric mood, irritability, agitation, dizziness, anxiety, confusion, headache, lethargy, emotional lability, insomnia, hypomania, and sensory disturbances (e.g., paresthesias such as electric shock sensations), have been reported following discontinuance of fluoxetine and other selective serotonin-reuptake inhibitors (SSRIs), particularly upon abrupt discontinuance. While these events are generally self-limiting, there have been reports of serious discontinuance symptoms. If fluoxetine is to be discontinued, the manufacturer recommends that the dosage be tapered gradually and the patient closely monitored for these manifestations. Abrupt discontinuance should be avoided whenever possible. If intolerable symptoms occur following a decrease in the dosage or upon discontinuance of therapy, fluoxetine therapy may be reinstituted at the previously prescribed dosage. Subsequently, the clinician may continue decreasing the dosage but at a more gradual rate. Plasma concentrations of fluoxetine and norfluoxetine (the principal metabolite) decline gradually after cessation of therapy, which may minimize the risk of withdrawal symptoms.

Patients receiving fluoxetine should be monitored for possible worsening of depression, suicidality, or unusual changes in behavior, especially at the beginning of therapy or during periods of dosage adjustment. (See Cautions: Precautions and Contraindications.)

Major Depressive Disorder Adult Dosage. For the management of major depression, the recommended initial dosage of fluoxetine in adults is 20 mg daily. However, some clinicians suggest that fluoxetine therapy be initiated with lower dosages (e.g., 5 mg daily or 20 mg every 2 or 3 days). Although symptomatic relief may be apparent within the first 1–3 weeks of fluoxetine therapy, optimum antidepressant effect usually requires at least 4 weeks or more of therapy with the drug. If insufficient clinical improvement is apparent after several weeks of fluoxetine therapy at 20 mg daily, an increase in dosage may be considered. Efficacy of fluoxetine for major depression was demonstrated in clinical trials employing 10–80 mg daily. Studies comparing fluoxetine 20, 40, and 60 mg daily to placebo indicate that a dosage of 20 mg daily is sufficient to obtain a satisfactory response in most adults with major depression. Fluoxetine dosages up to 80 mg daily have been administered in some patients, and dosages as low as 5 mg daily may be effective in some patients with depression. In addition, in a study in moderately depressed patients, increasing the dosage of fluoxetine from 20 mg to 40 or 60 mg daily did not result in substantial improvement in depression but was associated with an increase in certain adverse effects (e.g., nausea, anxiety, diarrhea, dry mouth, weight loss). The manufacturer states that the maximum dosage of fluoxetine in adults with major depression should not exceed 80 mg daily; however, somewhat higher dosages (e.g., 100–120 mg daily) occasionally have been used in patients who did not respond adequately to lower dosages.

When fluoxetine hydrochloride delayed-release capsules are used for the continuing management of major depressive disorder, the recommended dosage of fluoxetine is 90 mg once weekly beginning 7 days after the last dose of fluoxetine 20 mg daily. If a satisfactory response is not maintained with once weekly administration, consideration may be given to reestablishing a daily dosage schedule.

As with the use of fluoxetine for other indications, lower dosages or less frequent dosing regimens should be considered for geriatric patients, patients with concurrent disease, and patients receiving multiple concomitant drug therapies.

Pediatric Dosage. For the management of major depressive disorder in children and adolescents 8–18 years of age, the recommended initial dosage of fluoxetine is 10 or 20 mg daily. If therapy is initiated at 10 mg daily, it can be increased after 1 week to 20 mg daily. Because higher plasma fluoxetine concentrations occur in lower weight children, the manufacturer states that both the initial and target dosage in lower weight children may be 10 mg daily. An increase in dosage to 20 mg daily may be considered after several weeks in lower weight children if insufficient clinical improvement is observed. Because a rare but serious drug interaction may occur in depressed children and adolescents with comorbid attention-deficit hyperactivity disorder (ADHD) who receive stimulants and selective serotonin-reuptake inhibitors concomitantly, some experts recommend a maximum fluoxetine dosage of 20 mg daily in such patients. (See Tramadol and Other Serotonergic Drugs under Drug Interactions: Serotonergic Drugs.)

Duration of Therapy. The optimum duration of fluoxetine therapy required to prevent recurrence of depressive symptoms has not been established to date. However, many experts state that acute depressive episodes require several months or longer of sustained antidepressant therapy. Systematic evaluation of fluoxetine has shown that its antidepressant efficacy is maintained for periods of up to approximately 9 months following 3 months of open-label acute treatment (12 months total) in adults receiving 20 mg daily as conventional fluoxetine capsules or for periods of up to approximately 6 months with once-weekly dosing of the 90 mg delayed-release fluoxetine capsules following 3 months of open-label treatment with 20 mg once daily as conventional fluoxetine capsules. However, the therapeutic equivalence of once-weekly administration of the 90-mg delayed-release capsules with that of once-daily administration of the 20-mg conventional preparations for delaying time to relapse has not been established. In addition, it has not been determined to date whether the dosage of the antidepressant necessary to treat acute symptoms of depression is the same as the dosage necessary to prevent recurrence of such symptoms. If therapy with the drug is prolonged, the lowest possible dosage should be employed and the need for continued therapy reassessed periodically.

Switching To or From Other Antidepressants. Because concurrent use of fluoxetine and a tricyclic antidepressant may result in greater than two- to 10-fold elevations in plasma tricyclic antidepressant concentrations, dosage of the tricyclic antidepressant may need to be reduced and plasma tricyclic concentrations may need to be monitored temporarily when fluoxetine is administered concurrently or has been recently discontinued. (See Drug Interactions: Tricyclic and Other Antidepressants.)

Because of the potential risk of serotonin syndrome, the manufacturer recommends that an interval of at least 2 weeks elapse when switching a patient from a monoamine oxidase (MAO) inhibitor to fluoxetine. Because both fluoxetine and its principal metabolite have relatively long half-lives, the manufacturers and some clinicians recommend that at least 5 weeks elapse between discontinuance of fluoxetine therapy and initiation of MAO inhibitor therapy. (See Drug Interactions: Serotonergic Drugs.)

Obsessive-Compulsive Disorder **Adult Dosage.** For the management of obsessive-compulsive disorder, the recommended initial dosage of fluoxetine in adults is 20 mg once daily. Because a possible dose-response relationship for effectiveness was suggested in one clinical study, an increase in dosage may be considered following several weeks of therapy if insufficient clinical improvement is observed. The manufacturer recommends fluoxetine dosages of 20–60 mg daily for the treatment of obsessive-compulsive disorder; dosages up to 80 mg daily have been well tolerated in clinical studies evaluating the drug in adults with obsessive-compulsive disorder. The manufacturer states that fluoxetine dosage should not exceed 80 mg daily. Like fluoxetine's antidepressant effect, the full therapeutic effect of the drug in patients with obsessive-compulsive disorder may be delayed until 5 weeks of fluoxetine therapy or longer.

Pediatric Dosage. For the management of obsessive-compulsive disorder, the recommended initial dosage of fluoxetine in children and adolescents 7–17 years of age is 10 mg once daily. In adolescents and higher weight children, the dosage should be increased to 20 mg daily after 2 weeks; additional dosage increases may be considered after several more weeks if insufficient clinical improvement is observed. In lower weight children, dosage increases may be considered after several weeks if insufficient clinical improvement is observed. The manufacturer recommends fluoxetine dosages of 20–60 mg daily for adolescents and higher weight children and fluoxetine dosages of 20–30 mg daily for lower weight children for the treatment of obsessive-compulsive disorder. In lower weight children, the manufacturer states that clinical experience with fluoxetine dosages exceeding 20 mg daily is minimal and that there is no experience with dosages exceeding 60 mg daily in such patients.

Duration of Therapy. Although the efficacy of fluoxetine for long-term use (i.e., longer than 13 weeks) has not been demonstrated in controlled studies, patients have been continued on the drug under double-blind conditions for up to an additional 6 months without loss of benefit. The manufacturer and many experts state that obsessive-compulsive disorder is chronic and requires several months or longer of sustained therapy. Therefore, it is reasonable to continue therapy in responding patients. If fluoxetine is used for extended periods, dosage should be adjusted so that the patient is maintained on the lowest effective dosage, and the need for continued therapy with the drug should be reassessed periodically.

Premenstrual Dysphoric Disorder For the management of premenstrual dysphoric disorder (previously late luteal phase dysphoric disorder), the recommended dosage of fluoxetine is 20 mg once daily given continuously throughout the menstrual cycle or intermittently (i.e., only during the luteal phase, starting 14 days prior to the anticipated onset of menstruation and continuing through the first full day of menses). The intermittent dosing regimen is then repeated with each new menstrual cycle. Decisions regarding which dosing regimen to use should be individualized. In a clinical study evaluating continuous dosing of fluoxetine dosages of 20 or 60 mg once daily for the treatment of premenstrual dysphoric disorder (PMDD), both dosages were effective but there was no evidence that the higher dosage provided any additional benefit. The manufacturer states that dosages exceeding 60 mg daily have not been systematically studied in patients with PMDD and that 80 mg daily is the maximum dosage of fluoxetine for the management of PMDD.

Clinical studies using fluoxetine dosages of 20 mg daily given intermittently or continuously have shown that the efficacy of the drug in the treatment of PMDD is maintained for up to 3 or 6 months, respectively. Patients should be periodically reassessed to determine the need for continued treatment. Discontinuance of the drug (even after more than 1 year of therapy) has resulted in relapse of PMDD within approximately 2 menstrual cycles.

Eating Disorders **Bulimia Nervosa.** For the management of bulimia nervosa in adults, the recommended dosage of fluoxetine is 60 mg daily, administered as a single dose in the morning. The manufacturer states that in some patients, oral dosage of the drug may be carefully titrated up to the recommended initial dosage over a period of several days. However, since 60-mg doses of fluoxetine were found to be well tolerated, the APA states that many clinicians initiate treatment for bulimia nervosa at the higher dosage, titrating downward as necessary to minimize adverse effects. Fluoxetine dosages exceeding 60 mg daily have not been evaluated in patients with bulimia.

Systematic evaluation of fluoxetine has demonstrated that its efficacy in the treatment of bulimia nervosa is maintained for periods of up to 12 months following 2 months of acute treatment in patients receiving 60 mg daily as conventional fluoxetine capsules. Pending further accumulation of data, most clinicians recommend that antidepressant therapy, including fluoxetine, be continued for at least 6–12 months in patients with bulimia nervosa before attempting to discontinue therapy. If fluoxetine is used for extended periods, the manufacturer states that the need for continued therapy should be reassessed periodically.

Anorexia Nervosa. Although safety and efficacy of fluoxetine for the management of anorexia nervosa† and optimal dosage of the drug for this disorder have not been established, fluoxetine has been given in a dosage of 40 mg daily in weight-restored patients with anorexia nervosa.

Panic Disorder For the management of panic disorder, the recommended initial dosage of fluoxetine in adults is 10 mg daily. After 1 week, the dosage should be increased to 20 mg once daily. If no clinical improvement is apparent after several weeks of fluoxetine therapy at 20 mg daily, an increase in dosage may be considered. Efficacy of the drug was demonstrated in clinical trials employing 10–60 mg daily. However, the most frequently administered dosage in flexible-dose clinical studies was 20 mg daily. As with the use of fluoxetine for other indications, lower dosages or less frequent dosing regimens should be considered for geriatric patients and patients with concurrent disease or those receiving multiple concomitant drug therapies. The manufacturer states that fluoxetine dosages exceeding 60 mg daily have not been systematically evaluated in patients with panic disorder.

The optimum duration of fluoxetine therapy required to prevent recurrence of panic disorder has not been established to date. The manufacturer states that the efficacy of fluoxetine beyond 12 weeks of therapy has not been demonstrated in controlled studies. However, the manufacturer and some clinicians state that panic disorder is chronic and requires several months or longer of sustained therapy. Therefore, it is reasonable to continue therapy in responding patients. The manufacturer recommends, however, that patients be reassessed periodically to determine the need for continued therapy.

Bipolar Disorder **Monotherapy.** For the short-term treatment of acute depressive episodes in patients with bipolar disorder†, fluoxetine has been given in a dosage of 20–60 mg daily. Because of the risk of developing manic episodes associated with antidepressant therapy in patients with bipolar disorder, many clinicians recommend using the lowest effective dosage of fluoxetine for the shortest time necessary using the antidepressant in conjunction with a mood-stabilizing agent (e.g., lithium).

Combination Therapy. When used in fixed combination with olanzapine for acute depressive episodes in patients with bipolar disorder, fluoxetine is administered once daily in the evening, usually initiating therapy with a dose of 6 mg of olanzapine and 25 mg of fluoxetine (Symbyax® 6/25). This dosage generally should be used as initial and maintenance therapy in patients with a predisposition to hypotensive reactions, patients with hepatic impairment, or those with factors that may slow metabolism of the drugs(s) (e.g., female gender, geriatric age, nonsmoking status); when indicated, dosage should be escalated with caution. In other patients, dosage can be increased according to patient response and tolerance as indicated. In clinical trials, antidepressive efficacy was demonstrated at olanzapine dosages ranging from 6–12 mg daily and fluoxetine dosages ranging from 25–50 mg daily. Dosages exceeding 18 mg of olanzapine and 75 mg of fluoxetine have not been evaluated in clinical studies.

Cataplexy For the management of cataplexy†, fluoxetine has been given in a dosage of 20 mg once or twice daily in conjunction with CNS stimulant therapy (e.g., methylphenidate, dextroamphetamine).

Alcohol Dependence For the management of alcohol dependence†, fluoxetine has been given in a dosage of 60 mg daily. Studies have shown that reductions in alcohol intake occur only with dosages of selective serotonin-reuptake inhibitors that are higher than the average therapeutic dosages used in depression. Alcohol intake in patients receiving lower dosages of fluoxetine (40 mg daily) was comparable to that of patients receiving placebo.

■ **Dosage in Renal and Hepatic Impairment** The need for modification of fluoxetine dosage in patients with renal impairment has not been fully determined to date, and the drug should be used with caution in such patients. Although the elimination of fluoxetine and norfluoxetine following single-dose administration does not appear to be altered substantially in patients with renal impairment, multiple-dose studies are needed to determine whether accumulation of the parent drug and/or its metabolites occurs during long-term fluoxetine therapy in patients with severe renal impairment. (See Pharmacokinetics.) The manufacturer and some clinicians state that a reduction in dose and/or frequency of administration of fluoxetine should be considered in patients with renal impairment, particularly those with severe renal impairment. Supplemental doses of fluoxetine during hemodialysis do not appear to be necessary since the drug and its active metabolite norfluoxetine are not removed substantially by hemodialysis.

Since fluoxetine is extensively metabolized in the liver, elimination may be prolonged in patients with hepatic impairment. Therefore, the manufacturer and some clinicians recommend a reduction in dose and/or frequency of administration of fluoxetine in patients with hepatic impairment. Some clinicians recommend a 50% reduction in initial fluoxetine dosage for patients with well-compensated cirrhosis; however, patients with more substantial hepatic impairment, particularly those with severe disease, will require careful individualization of dosage. Subsequent dosage adjustment based on the tolerance and therapeutic response of the patient has been recommended in patients with hepatic impairment.

■ **Treatment of Pregnant Women during the Third Trimester** Because some neonates exposed to fluoxetine and other SSRIs or selective serotonin- and norepinephrine-reuptake inhibitors (SNRIs) late in the third trimester of pregnancy have developed severe complications, consideration may be given to cautiously tapering fluoxetine therapy in the third trimester prior to delivery if the drug is administered during pregnancy. (See Pregnancy under Cautions: Pregnancy, Fertility, and Lactation.)

Cautions

The adverse effect profile of fluoxetine is similar to that of other selective serotonin-reuptake inhibitors (SSRIs; e.g., citalopram, escitalopram, fluvoxamine, paroxetine, sertraline). Because fluoxetine is a highly selective serotonin-reuptake inhibitor with little or no effect on other neurotransmitters, the incidence of some adverse effects commonly associated with tricyclic antidepressants, such as anticholinergic effects (dry mouth, dizziness, constipation), adverse cardiovascular effects, drowsiness, and weight gain, is lower in patients receiving fluoxetine. However, certain adverse GI (e.g., nausea) and nervous system (e.g., anxiety, nervousness, insomnia) effects appear to occur more frequently during fluoxetine therapy than during therapy with tricyclic antidepressants.

In controlled studies, the most common adverse reactions occurring more frequently in adults receiving fluoxetine than in those receiving placebo included nervous system effects such as anxiety, nervousness, insomnia, drowsiness, fatigue or asthenia, tremor, and dizziness or lightheadedness; GI effects such as anorexia, nausea, and diarrhea; vasodilation; dry mouth; abnormal vision; decreased libido; abnormal ejaculation; rash; and sweating. Discontinuance of fluoxetine therapy was required in about 15% of adults, principally because of adverse psychiatric (e.g., nervousness, anxiety, insomnia), other nervous system (e.g., dizziness, asthenia, headache), GI (e.g., nausea), and dermatologic (e.g., rash, pruritus) effects. Because of the relatively long elimination half-lives of fluoxetine and its principal metabolite norfluoxetine, the possibility that some adverse effects may resolve slowly following discontinuance of the drug should be considered.

In controlled clinical trials, adverse effects reported in adults with weekly administration of fluoxetine delayed-release capsules were similar to those reported with daily administration of conventional capsules. Diarrhea and cognitive problems occurred more frequently with the delayed-release formulation compared with the conventional capsules.

Common adverse effects associated with fluoxetine therapy for major depressive disorder or obsessive-compulsive disorder in children and adolescents 7 years of age and older are generally similar to those observed in adults and include nausea, tiredness, nervousness, dizziness, and difficulty concentrating. However, manic reactions, including mania and hypomania, were the most common adverse events associated with discontinuance of the drug in 3 pivotal, pediatric, placebo-controlled studies. These reactions occurred in 2.6% of pediatric patients receiving fluoxetine compared with 0% of those receiving placebo and resulted in the discontinuance of fluoxetine in 1.8% of the patients during the acute phases of the studies combined. Consequently, regular monitoring for the occurrence of mania and hypomania is recommended by the manufacturer.

The usual cautions and precautions of olanzapine should be observed when fluoxetine is used in fixed combination with the antipsychotic.

■ **Nervous System Effects** Headache has occurred in approximately 20% of patients receiving fluoxetine and has required discontinuance of therapy in less than 1.5% of patients. Nervousness and anxiety have occurred in about 15 and 9% of patients, respectively, and insomnia has occurred in about 14% of patients receiving the drug; such effects appear to be dose-related and have required discontinuance of therapy in approximately 5% of fluoxetine-treated patients. However, because insomnia is a symptom also associated with depression, relief of insomnia and improvement in sleep patterns may occur when clinical improvement in depression becomes apparent during antidepressant therapy. The manufacturer and some clinicians state that a sedative (e.g., a short-acting benzodiazepine, chloral hydrate) may be administered to patients who experience insomnia or nervousness early in therapy; however, the possibility that fluoxetine may interact with some benzodiazepines (e.g., diazepam) should be considered. (See Drug Interactions: Benzodiazepines.)

Drowsiness and fatigue or asthenia reportedly occur in about 12 and 4%, respectively, of patients receiving fluoxetine therapy. Tremor and dizziness have occurred in about 8 and 6% of patients, respectively; the incidence of dizziness may be dose-related. Adverse nervous system effects reportedly occurring in approximately 1–2% of patients include sedation, sensation disturbance, lightheadedness, confusion, myoclonus, agitation, amnesia, and decreased concentration. Abnormal dreams and agitation have been reported in more than 1% of patients receiving fluoxetine therapy.

Hypomania, mania, and manic reaction have been reported in 1% or less of patients receiving fluoxetine, including those with depression or obsessive-compulsive disorder. In addition, mania reportedly occurred following administration of a higher than recommended dosage (140 mg daily) in a patient with major depression refractory to conventional antidepressant therapy; this patient subsequently responded to a fluoxetine dosage of 60 mg daily without apparent adverse effects. Such reactions have occurred in patients receiving other antidepressant agents and may be caused by antidepressant-induced functional increases in catecholamine activity within the CNS, resulting in a "switch" from depressive to manic behavior. There is some evidence that patients with bipolar disorder may be more likely to experience antidepressant-induced hypomanic or manic reactions than patients without evidence of this disorder. In addition, limited evidence suggests that such reactions may occur more frequently in bipolar depressed patients receiving tricyclics and tetracyclics (e.g., maprotiline, mianserin [not commercially available in the US]) than in those receiving SSRIs (e.g., citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline). However, further studies are needed to confirm these findings.

Extrapyramidal reactions, including acute dystonic reactions, torticollis, buccolingual syndrome, and akathisia, have occurred rarely in patients receiving fluoxetine. An extrapyramidal reaction consisting of torticollis, jaw rigidity, cogwheel rigidity, and loss of fluid motion in gait reportedly occurred in one patient several days after initiation of fluoxetine therapy, but responded rapidly to an anticholinergic antiparkinsonian agent (i.e., trihexyphenidyl) and did not recur despite continued fluoxetine therapy. Serum prolactin concentrations were increased and CSF 3-methoxy-4-hydroxyphenylacetic acid (homovanillic acid, HVA) concentrations were decreased in this patient, suggesting that a decrease in dopaminergic activity (possibly as a result of enhanced serotonergic neurotransmission) may have contributed to the reaction.

Although a causal relationship to the drug has not been established, serotonin syndrome and neuroleptic malignant syndrome (NMS)-like reactions also have been reported rarely in patients receiving fluoxetine, other SSRIs, and selective serotonin- and norepinephrine-reuptake inhibitors. (See Cautions: Precautions and Contraindications and see also Drug Interactions: Serotonergic Drugs.)

The incidence of seizures during fluoxetine therapy appears to be similar to that observed during therapy with most other currently available antidepressants. Seizures or events that were described as possible seizures have been reported in approximately 0.2% of patients receiving fluoxetine therapy to date. (See Cautions: Precautions and Contraindications.) In addition, seizures have occurred following acute overdosage of the drug (see Acute Toxicity) and in at least one patient undergoing electroconvulsive therapy (ECT) concomitantly.

Adverse nervous system effects occurring in less than 1% of fluoxetine-treated patients include ataxia, abnormal gait, incoordination, hyperkinesia, hypoesthesia, neuropathy, neuralgia, and hydrocephalus; however, a causal relationship to the drug has not been established. Migraine, acute brain syndrome, amnesia, CNS stimulation, vertigo, emotional lability, hostility, depersonalization, apathy, malaise, hangover effect, and euphoria also have been reported in less than 1% of patients receiving the drug. Psychosis, paranoid reaction, delusions, and hallucinations have been reported in less than 1% of patients, although these adverse effects have not been definitely attributed to fluoxetine. Rarely reported adverse nervous system effects for which a causal relationship has not been established include antisocial reaction, violent behavior, chronic brain syndrome, confusion, circumoral paresthesia, precipitation or worsening of depression, stupor, coma, EEG abnormalities, dysarthria, hypertonia, hysteria, myoclonus, dyskinesia, nystagmus, paralysis, exacerbation of multiple sclerosis, and decreased reflexes. Interference with facial nerve conduction, manifesting as ocular tics and impaired hearing, also has been reported. In some patients developing movement disorders with fluoxetine, there were underlying risk factors such as predisposing drug therapy and/or the disorder was an exacerbation of a preexisting disorder.

Suicidality The US Food and Drug Administration (FDA) has determined that antidepressants increase the risk of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults (18–24 years of age) with major depressive disorder and other psychiatric disorders. Suicidal ideation, which can manifest as persistent, obsessive, and violent suicidal thoughts,

has emerged occasionally in adults receiving fluoxetine. In a report of several fluoxetine-associated cases, severe suicidal ideation developed within 2–7 weeks after initiation of fluoxetine therapy and resolved within several days to months after discontinuance of the drug; however, the patients were unresponsive to fluoxetine and had received monoamine oxidase inhibitor therapy previously, and most had a history of suicidal ideation, were receiving relatively high dosages (60–80 mg daily) of fluoxetine, and were receiving other psychotropic therapy concomitantly. Suicidal ideation also has been reported in patients who reportedly had no history of such ideation, but the drug also has been used without recurrence of suicidal ideation in a few patients in whom such ideation emerged during tricyclic antidepressant therapy. Because of the possibility of suicidality, patients should be appropriately monitored and closely observed for clinical worsening, suicidality, and unusual changes in behavior, particularly during initiation of fluoxetine therapy (i.e., the first few months) and during periods of dosage adjustments. (See Cautions: Precautions and Contraindications and see Cautions: Pediatric Precautions and see Acute Toxicity.)

■ **GI Effects** The most frequent adverse effect associated with fluoxetine therapy is nausea, which occurs in about 21% of patients. Nausea generally is mild, occurs early in therapy, and usually subsides after a few weeks of continued therapy with the drug. Limited evidence suggests that the incidence of nausea may be dose-related, but additional experience with the drug is necessary to confirm this finding. Adverse GI effects, principally nausea, have required discontinuance of fluoxetine therapy in about 3% of patients receiving the drug. Although the incidence of vomiting appears to be similar in patients receiving fluoxetine or tricyclic antidepressants (e.g., imipramine), the incidence of nausea appears to be higher with fluoxetine. While the mechanism(s) of fluoxetine-induced GI effects has not been fully elucidated, serotonin has been shown to have complex effects on the GI tract (e.g., stimulation of small intestine motility, inhibition of gastric and large intestine motility).

Diarrhea occurs in about 12%, anorexia in about 9%, and dyspepsia in about 6% of patients receiving the drug; limited evidence suggests that the incidence of anorexia may be dose-related. Other adverse GI effects associated with fluoxetine therapy include abdominal pain and change in taste perception, which occur in approximately 3 and 2% of patients, respectively; taste loss has been reported rarely. Vomiting, melena, and flatulence reportedly occur in about 2% and gastroenteritis in about 1% of patients receiving the drug.

Increased appetite has been reported in more than 1% of patients receiving fluoxetine, but has not been definitely attributed to the drug. Other adverse GI effects, including aphthous stomatitis, dysphagia, eructation, esophagitis, gastritis, gingivitis, glossitis, melena, stomatitis, and thirst, have been reported in less than 1% of fluoxetine-treated patients; however, a causal relationship to the drug has not been established. Bloody diarrhea, GI hemorrhage, colitis, duodenal or gastric ulcer, enteritis, pancreatitis, fecal incontinence, hematemesis, hyperchlorhydria, increased salivation, mouth ulceration, salivary gland enlargement, tongue discoloration, and tongue edema have occurred rarely, but have not been definitely attributed to fluoxetine.

Epidemiologic case-control and cohort design studies have suggested that selective serotonin-reuptake inhibitors may increase the risk of upper GI bleeding. Although the precise mechanism for this increased risk remains to be clearly established, serotonin release by platelets is known to play an important role in hemostasis, and selective serotonin-reuptake inhibitors decrease serotonin uptake from the blood by platelets thereby decreasing the amount of serotonin in platelets. In addition, concurrent use of aspirin or other nonsteroidal anti-inflammatory agents was found to substantially increase the risk of GI bleeding in patients receiving selective serotonin-reuptake inhibitors in 2 of these studies. Although these studies focused on upper GI bleeding, there is some evidence suggesting that bleeding at other sites may be similarly potentiated. Further clinical studies are needed to determine the clinical importance of these findings. (See Cautions: Hematologic Effects and see also Drug Interactions: Drugs Affecting Hemostasis.)

■ **Dermatologic and Sensitivity Reactions** Rash (including maculopapular, purpuric, pustular, and vesiculobullous rash; erythema multiforme) and/or urticaria occurs in about 4% and pruritus occurs in about 2% of patients receiving fluoxetine. Adverse dermatologic effects, principally rash and pruritus, generally occur during the first few weeks of therapy and have required discontinuance of the drug in approximately 1% of patients.

Fluoxetine-induced rash and/or urticaria have been associated with systemic signs or symptoms such as fever, leukocytosis, arthralgia, edema, carpal tunnel syndrome, respiratory distress, lymphadenopathy, proteinuria, and mild elevation in serum aminotransferase (transaminase) concentrations in some patients. Serious systemic illnesses have developed rarely in patients with fluoxetine-induced dermatologic reactions to date. Although the diagnosis was equivocal in at least 2 of these patients, one patient was diagnosed as having a leukocytoclastic vasculitis and the other patient exhibited a severe desquamating syndrome that was variably diagnosed as either vasculitis or erythema multiforme. In addition, serum sickness reactions have developed in several other patients who experienced adverse dermatologic effects in association with fluoxetine therapy. Additional cases of systemic reactions possibly related to vasculitis have been reported in patients with rash. Although systemic reactions appear to occur rarely in patients receiving fluoxetine, such reactions may be serious and potentially may involve the lung, kidney, or liver; death reportedly has occurred in association with such reactions. Anaphylactoid reactions (including bronchospasm, angioedema, and/or urticaria) have been reported, and adverse pulmonary effects (including inflammatory processes of varying histopathology and/or fibrosis), which usually occurred with dyspnea as the only preceding symptom, have been reported rarely. It has not been established whether the systemic reactions and associated skin rash in fluoxetine-treated patients share a common underlying cause and represent a true syndrome induced by the drug or whether the temporal association between the rash and other systemic signs and symptoms occurred only by chance; in addition, a specific, underlying immunologic basis for these effects has not been identified. However, such systemic reactions are of potential concern since zimeldine (another selective serotonin-reuptake inhibitor that previously was commercially available outside the US) reportedly was associated with the development of Guillain-Barré syndrome following flu-like, hypersensitivity reactions to the drug; because of such reactions, zimeldine no longer is commercially available. Most patients with fluoxetine-induced rash and/or urticaria improve soon after discontinuance of therapy and/or administration of an antihistamine or corticosteroid, and most patients with such reactions to date have recovered completely without serious adverse sequelae. In addition, several patients who developed hypersensitivity reactions while receiving zimeldine subsequently received fluoxetine with no recurrence of a similar reaction. However, because of associated severe adverse systemic effects with fluoxetine and pharmacologically similar antidepressants (e.g., zimeldine), it is recommended that fluoxetine be discontinued if rash, urticaria, and/or other manifestations of hypersensitivity (e.g., fever, flu-like symptoms), for which alternative etiologies cannot be identified, occur during therapy with the drug.

Excessive sweating occurs in about 8% of patients receiving fluoxetine. Acne and allergic reactions have occurred in approximately 2 and 1% of patients, respectively. Adverse dermatologic and hypersensitivity reactions occurring in less than 1% of patients receiving fluoxetine include acne, cyst formation, dry skin, contact dermatitis, facial edema, alopecia, and herpes simplex; however, these effects have not been definitely attributed to the drug. Although a causal relationship has not been established, eczema, erythema nodosum, epidermal necrolysis, exfoliative dermatitis, Stevens-Johnson syndrome, seborrhea, psoriasis, fungal dermatitis, cellulitis, hirsutism, herpes zoster, skin discoloration, skin hypertrophy, subcutaneous nodules, and ecchymoses have been reported rarely.

■ **Metabolic Effects** Unlike tricyclic antidepressants, which commonly cause weight gain, weight gain occurs in less than 1% of patients receiving fluoxetine. Weight loss, however, frequently occurs during therapy with the drug. Normal-weight and overweight (i.e., body mass index exceeding 25 kg/m^2) depressed patients lost an average of 0.9–1.8 kg and 1.8 kg, respectively, following 6 weeks of therapy with the drug. In addition, weight loss exceeding 5% of body weight has been reported in approximately 13% of fluoxetine-treated patients. Weight loss associated with fluoxetine therapy appears to be reversible, with a gradual increase in body weight occurring following discontinuance of therapy with the drug. Such weight loss appears to result from decreased food consumption rather than adverse GI effects associated with the drug; there is some evidence that fluoxetine-induced weight loss may be dose-related. (See Pharmacology: Effects on Appetite and Body Weight.) In addition, weight loss appears to occur independent of the antidepressant effect of the drug. Although weight loss is commonly associated with fluoxetine therapy, less than 1% of patients discontinue the drug because of this effect. In some cases, however, substantial weight loss may be an undesirable effect of therapy with the drug, particularly in underweight depressed patients.

Fluoxetine potentially may alter blood glucose concentrations. Hypoglycemia has occurred in less than 1% of patients receiving fluoxetine and hypoglycemic reaction has occurred rarely. In addition, hyperglycemia has developed following discontinuance of the drug. Therefore, the possibility that insulin and/or oral sulfonylurea antidiabetic agent dosage adjustments may be necessary when fluoxetine therapy is initiated or discontinued in patients with diabetes mellitus should be considered.

Hypercholesterolemia, hyperlipidemia, and hypokalemia have been reported rarely in fluoxetine-treated patients; these adverse effects have not been definitely attributed to the drug.

■ **Ocular Effects** Visual disturbances, including blurred vision, occur in approximately 3% of patients receiving fluoxetine. Adverse ocular effects reported in less than 1% of fluoxetine-treated patients include amblyopia, conjunctivitis, eye pain, mydriasis, and photophobia. Blepharitis, cataract formation, corneal lesion, diplopia, ocular hemorrhage, glaucoma, iritis, ptosis, and strabismus have been reported rarely.

■ **Cardiovascular Effects** Current evidence suggests that fluoxetine is less cardiotoxic than most antidepressant agents (e.g., tricyclic antidepressants, monoamine oxidase inhibitors). Unlike tricyclic antidepressants, which may cause characteristic ECG changes such as prolongation of PR, QRS, and QT intervals and ST-segment and T-wave abnormalities, clinically important ECG changes (such as conduction abnormalities) have not been reported during controlled studies in fluoxetine-treated patients without preexisting cardiac disease. In addition, while tricyclic antidepressants commonly cause an increase in heart rate, heart rate reportedly is reduced by an average of approximately 3 beats/minute in patients receiving fluoxetine. (See Pharmacology: Cardiovascular Effects.)

Palpitations and hot flushes have been reported in approximately 1 and 2% of patients receiving fluoxetine, respectively. Chest pain occurs in about 1% of patients. Unlike tricyclic antidepressants, fluoxetine has been associated with hypotension (including orthostatic hypotension) relatively infrequently; in con-

trolled studies, orthostatic hypotension was reported in less than 1% of patients receiving the drug. Angina pectoris, cardiac arrhythmia, tachycardia, hemorrhage, hypertension, and syncope have occurred infrequently in fluoxetine-treated patients, although a causal relationship to the drug has not been established. First-degree AV block, bundle-branch block, bradycardia, ventricular arrhythmia, ventricular tachycardia (including torsades de pointes-type arrhythmias), myocardial infarction, thrombophlebitis, cerebral ischemia, vascular headache, and cerebrovascular accident have occurred rarely, but these adverse effects have not been definitely attributed to fluoxetine.

■ **Musculoskeletal Effects** Back, joint, muscle, and limb pain reportedly occur in approximately 1–2% of patients receiving fluoxetine. Arthritis, bursitis, tenosynovitis, muscle twitching, jaw pain, and neck pain or rigidity have occurred in less than 1% of fluoxetine-treated patients, but these adverse effects have not been directly attributed to the drug. Bone necrosis, osteoporosis, pathological fracture, chondrodystrophy, myositis, muscle hemorrhage, and rheumatoid arthritis have been reported rarely, although a causal relationship to fluoxetine has not been established.

■ **Hematologic Effects** Lymphadenopathy or anemia has been reported in 2% or less than 1% of patients receiving fluoxetine, respectively. Blood dyscrasia, leukopenia, thrombocythemia, pancytopenia, aplastic anemia, immune-related hemolytic anemia, lymphocytosis, increased sedimentation rate, increased bleeding time, petechiae, purpura, and iron deficiency anemia have occurred rarely, although a causal relationship to the drug has not been established. Thrombocytopenia also has been reported.

Abnormal bleeding has been reported in several patients receiving selective serotonin-reuptake inhibitors. Bleeding complications (e.g., ecchymosis, purpura, menorrhagia, rectal bleeding) have been reported infrequently in patients receiving selective serotonin-reuptake inhibitors. Although the precise mechanism for these reactions has not been established, it has been suggested that impaired platelet aggregation and prolonged bleeding time may be due at least in part to inhibition of serotonin reuptake into platelets and/or that increased capillary fragility and vascular tone may contribute to these cases. (See Cautions: GI Effects and see also Drug Interactions: Drugs Affecting Hemostasis.)

■ **Respiratory Effects** Upper respiratory infection has been reported in approximately 8% of fluoxetine-treated patients. Flu-like syndrome (see Cautions: Dermatologic and Sensitivity Reactions), pharyngitis, nasal congestion, sinusitis, sinus headache, cough, and dyspnea have occurred in approximately 1–3% of patients receiving the drug. Adverse respiratory effects reportedly occurring in at least 1% of patients but not directly attributable to fluoxetine therapy include bronchitis, rhinitis, and yawning, and those occurring in less than 1% of patients but not attributed to the drug include asthma, hyperventilation, pneumonia, and hiccups. Apnea, hypoxia, pulmonary edema, laryngeal edema, pulmonary fibrosis/alveolitis, eosinophilic pneumonia, pleural effusion, and hemoptysis have occurred rarely in patients receiving fluoxetine; however, these adverse effects have not been definitely attributed to the drug.

■ **Renal, Electrolyte, and Genitourinary Effects** ***Sexual Dysfunction*** Like other selective serotonin-reuptake inhibitors, adverse effects on sexual function have been reported in both men and women receiving fluoxetine. Although changes in sexual desire, sexual performance, and sexual satisfaction often occur as manifestations of a psychiatric disorder, they also may occur as the result of pharmacologic therapy. It is difficult to determine the true incidence and severity of adverse effects on sexual function during fluoxetine therapy, in part because patients and clinicians may be reluctant to discuss these effects. Therefore, incidence data reported in product labeling and earlier studies are most likely underestimates of the true incidence of adverse sexual effects. Recent reports indicate that up to 50% of patients receiving selective serotonin-reuptake inhibitors describe some form of sexual dysfunction during treatment and the actual incidence may be even higher.

Ejaculatory disturbances (principally ejaculatory delay) are the most common adverse urogenital effects associated with fluoxetine in men, occurring in about 7% of men receiving the drug compared with less than 1% of those receiving placebo in controlled clinical studies for the treatment of obsessive-compulsive disorder or bulimia. In some cases, the adverse effect of ejaculatory delay has been used for therapeutic benefit in the treatment of premature ejaculation. (See Uses: Premature Ejaculation.) Other genital disorders reported in patients receiving the drug include impotence, penile (of the glans) anesthesia, and anorgasmy (in both males and females). Decreased or increased libido also reportedly occurs in up to 2% of patients. In addition, clitoral engorgement, sexual arousal, and orgasm reportedly occurred in at least one female patient receiving fluoxetine.

Management of sexual dysfunction caused by selective serotonin-reuptake inhibitor therapy includes waiting for tolerance to develop; using a lower dosage of the drug; using drug holidays; delaying administration of the drug until after coitus; or changing to another antidepressant. Although further study is needed, there is some evidence that adverse sexual effects of the selective serotonin-reuptake inhibitors may be reversed by concomitant use of certain drugs, including buspirone, 5-hydroxytryptamine-2 (5-HT_2) receptor antagonists (e.g., nefazodone), 5-HT_3 receptor inhibitors (e.g., granisetron), or α_2-adrenergic receptor antagonists (e.g., yohimbine), selective phosphodiesterase (PDE) inhibitors (e.g., sildenafil), or dopamine receptor agonists (e.g., amantadine, dextroamphetamine, pemoline [no longer commercially available in the US], methylphenidate). In most patients, sexual dysfunction is fully reversed 1–3 days after discontinuance of the antidepressant. Ejaculatory dysfunction associated with fluoxetine therapy also has responded to concomitant cyproheptadine therapy in a few patients.

Other Renal, Electrolyte, and Genitourinary Effects Treatment with SSRIs, including fluoxetine, and selective serotonin- and norepinephrine-reuptake inhibitors (SNRIs) may result in hyponatremia. In many cases, this hyponatremia appears to be due to the syndrome of inappropriate antidiuretic hormone secretion (SIADH) and was reversible when fluoxetine was discontinued. Cases with serum sodium concentrations lower than 110 mEq/L have been reported. Geriatric individuals and patients receiving diuretics or who are otherwise volume depleted may be at greater risk of developing hyponatremia during therapy with SSRIs or SNRIs. Discontinuance of fluoxetine should be considered in patients with symptomatic hyponatremia and appropriate medical intervention should be instituted. Because geriatric patients may be at increased risk for hyponatremia associated with these drugs, clinicians prescribing fluoxetine in such patients should be aware of the possibility that such reactions may occur. In addition, periodic monitoring of serum sodium concentrations (particularly during the first several months) in geriatric patients receiving SSRIs has been recommended by some clinicians.

Painful menstruation, sexual dysfunction, frequent micturition, and urinary tract infection have occurred in approximately 1–2% of patients receiving fluoxetine. Decreased or increased libido reportedly occur in 1–2% or less than 1% of patients, respectively. Abnormal ejaculation, impotence, penile (of the glans) anesthesia, amenorrhea, leukorrhea, menorrhagia, ovarian disorder, vaginitis, pelvic pain, menopause, urinary incontinence, urinary urgency, impaired urination, cystitis, and dysuria have been reported in less than 1% of fluoxetine-treated patients, although these adverse effects have not been definitely attributed to the drug. Dyspareunia, abortion, hypomenorrhea, metrorrhagia, uterine spasm, uterine hemorrhage, salpingitis, vaginal hemorrhage, and vaginal bleeding (which occurred following discontinuance of therapy) have occurred rarely, although a causal relationship to the drug has not been established. Albuminuria, hematuria, polyuria, pyuria, urinary tract disorder, pyelonephritis, urethritis, epididymitis, orchitis, urethral pain, and urolithiasis (including renal calculus formation) also have been reported rarely in patients receiving fluoxetine therapy, although such effects have not been directly attributed to the drug.

■ **Endocrine Effects** Hypothyroidism has been reported in less than 1% of patients receiving fluoxetine, and goiter and hyperthyroidism have occurred rarely; however, a causal relationship to the drug has not been established.

■ **Anticholinergic Effects** Although bothersome anticholinergic effects occur commonly in patients receiving tricyclic antidepressant agents, such effects occur less frequently with fluoxetine. Dry mouth, dizziness, and constipation have been reported in about 10, 6, and 5% of patients receiving the drug. Urinary retention has occurred in less that 1% of fluoxetine-treated patients; blurred vision also has been reported.

■ **Other Adverse Effects** Viral infection and influenza have been reported in approximately 3 and 1% of patients receiving fluoxetine, respectively. Fever or chills alone have occurred in more than 1% of patients receiving fluoxetine; however, fever with accompanying chills has been reported in less than 1% of patients. (See Cautions: Dermatologic and Sensitivity Reactions.) Hypothermia has occurred rarely; however, a causal relationship to the drug has not been definitely established.

Abnormal liver function test results, lymphadenopathy, and epistaxis have been reported in less than 1% of fluoxetine-treated patients, although such effects have not been definitely attributed to the drug. Adverse effects occurring rarely in patients receiving fluoxetine include hepatitis, hepatomegaly, liver tenderness, jaundice, cholecystitis, cholelithiasis, acute abdominal syndrome, moniliasis, serum sickness, and lupus erythematosus syndrome.

Ear pain and tinnitus have occurred in less than 1% of patients, and deafness has been reported rarely. Although not directly attributed to the drug, generalized and peripheral edema have been reported in less than 1% of fluoxetine-treated patients; dehydration and gout have occurred rarely.

Breast pain and fibrocystic breast disease have occurred in less than 1% of patients, and breast enlargement and female lactation have been reported rarely. Hyperprolactinemia also has occurred in patients receiving the drug. Although a causal relationship to fluoxetine has not been established for these effects, serotonin has been implicated as a possible physiologic factor in the release of prolactin. (See Pharmacology: Neuroendocrine Effects.)

■ **Precautions and Contraindications** Worsening of depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior may occur in both adult and pediatric (see Cautions: Pediatric Precautions) patients with major depressive disorder or other psychiatric disorders, whether or not they are taking antidepressants. This risk may persist until clinically important remission occurs. Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are the strongest predictors of suicide. However, there has been a long-standing concern that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients during the early phases of treatment. Pooled analyses of short-term, placebo-controlled studies of antidepressants (i.e., selective serotonin-reuptake inhibitors [SSRIs] and other antidepressants) have shown an increased risk of suicidality in children, adolescents, and young adults (18–24 years of age) with major depressive disorder and other psychiatric disorders. An increased suicidality risk was not demonstrated with antidepressants compared with placebo in adults older than 24

years of age, and a reduced risk was observed in adults 65 years of age or older. It currently is unknown whether the suicidality risk extends to longer-term use (i.e., beyond several months); however, there is substantial evidence from placebo-controlled maintenance trials in adults with major depressive disorder that antidepressants can delay the recurrence of depression.

The US Food and Drug Administration (FDA) recommends that all patients being treated with antidepressants for any indication be appropriately monitored and closely observed for clinical worsening, suicidality, and unusual changes in behavior, particularly during initiation of therapy (i.e., the first few months) and during periods of dosage adjustments. Families and caregivers of patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and nonpsychiatric, also should be advised to monitor patients on a daily basis for the emergence of agitation, irritability, or unusual changes in behavior, as well as the emergence of suicidality, and to report such symptoms immediately to a health care provider.

Although a causal relationship between the emergence of symptoms such as anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia, hypomania, and/or mania and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality. Consequently, consideration should be given to changing the therapeutic regimen or discontinuing therapy in patients whose depression is persistently worse or in patients experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, particularly if such manifestations are severe, abrupt in onset, or were not part of the patient's presenting symptoms. FDA also recommends that the drugs be prescribed in the smallest quantity consistent with good patient management, in order to reduce the risk of overdosage.

It is generally believed (though not established in controlled trials) that treating a major depressive episode with an antidepressant alone may increase the likelihood of precipitating a mixed or manic episode in patients at risk for bipolar disorder. Therefore, patients should be adequately screened for bipolar disorder prior to initiating treatment with an antidepressant; such screening should include a detailed psychiatric history (e.g., family history of suicide, bipolar disorder, and depression).

Potentially life-threatening serotonin syndrome or neuroleptic malignant syndrome (NMS)-like reactions have been reported with SSRIs, including fluoxetine, and selective serotonin- and norepinephrine-reuptake inhibitors (SNRIs) alone, but particularly with concurrent administration of other serotonergic drugs (including serotonin [5-hydroxytryptamine; 5-HT] type 1 receptor agonists ["triptans"]), drugs that impair the metabolism of serotonin (e.g., monoamine oxidase [MAO] inhibitors), or antipsychotic agents or other dopamine antagonists. Symptoms of serotonin syndrome may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination), and/or GI symptoms (e.g., nausea, vomiting, diarrhea). In its most severe form, serotonin syndrome may resemble NMS, which is characterized by hyperthermia, muscle rigidity, autonomic instability with possible rapid fluctuation in vital signs, and mental status changes. Patients receiving fluoxetine should be monitored for the development of serotonin syndrome or NMS-like signs and symptoms.

Fluoxetine is contraindicated in patients who currently are receiving or recently (i.e., within 2 weeks) have received therapy with MAO inhibitors used for treatment of depression. If concurrent therapy with fluoxetine and a 5-HT_1 receptor agonist (triptan) is clinically warranted, the patient should be observed carefully, particularly during initiation of therapy, when dosage is increased, or when another serotonergic agent is initiated. Concomitant use of fluoxetine and serotonin precursors (e.g., tryptophan) is not recommended. If signs and symptoms of serotonin syndrome or NMS develop during therapy, treatment with fluoxetine and any concurrently administered serotonergic or antidopaminergic agents, including antipsychotic agents, should be discontinued immediately and supportive and symptomatic treatment should be initiated. (See Drug Interactions: Serotonergic Drugs.)

Because clinical experience with fluoxetine in patients with concurrent systemic disease, including cardiovascular disease, hepatic impairment, and renal impairment, is limited, caution should be exercised when fluoxetine is administered to patients with any systemic disease or condition that may alter metabolism of the drug or adversely affect hemodynamic function. (See Dosage and Administration: Dosage.) Fluoxetine should be used with caution in patients with hepatic impairment, since prolonged elimination of the drug and its principal metabolite has been reported to occur in patients with liver cirrhosis. Because the safety of long-term fluoxetine therapy in patients with severe renal impairment has not been adequately evaluated to date, fluoxetine also should be used with caution in patients with severe renal impairment. (See Dosage and Administration: Dosage in Renal and Hepatic Impairment.) Although current evidence suggests that fluoxetine is less cardiotoxic than most older antidepressant agents (see Cautions: Cardiovascular Effects), the safety of fluoxetine in patients with a recent history of myocardial infarction or unstable cardiovascular disease has not been adequately evaluated to date.

Patients receiving fluoxetine should be advised to notify their clinician if they are taking or plan to take nonprescription (over-the-counter) or prescription medications or alcohol-containing beverages or products. (See Drug Interactions.)

Patients receiving fluoxetine should be cautioned about the concurrent use of nonsteroidal anti-inflammatory agents (including aspirin) or other drugs that affect coagulation since combined use of selective serotonin-reuptake inhibitors and these drugs has been associated with an increased risk of bleeding. (See Cautions: GI Effects and see also Drug Interactions: Drugs Affecting Hemostasis.)

Fluoxetine generally is less sedating than many other currently available antidepressants and does not appear to produce substantial impairment of cognitive or psychomotor function. However, patients should be cautioned that fluoxetine may impair their ability to perform activities requiring mental alertness or physical coordination (e.g., operating machinery, driving a motor vehicle) and to avoid such activities until they experience how the drug affects them.

Patients receiving fluoxetine should be advised to notify their clinician if they develop rash or hives during therapy with the drug. Pending further accumulation of data, monitoring for such effects is particularly important since these effects have been associated with the development of potentially serious systemic reactions in patients receiving fluoxetine or pharmacologically similar antidepressants (e.g., zimeldine). (See Cautions: Dermatologic and Sensitivity Reactions.)

Seizures have been reported in patients receiving therapeutic dosages and following acute overdosage of fluoxetine. Because of limited experience with fluoxetine in patients with a history of seizures, therapy with the drug should be initiated with caution in such patients.

Because fluoxetine may alter blood glucose concentrations in patients with diabetes mellitus (see Cautions: Metabolic Effects), the possibility that insulin and/or oral sulfonylurea antidiabetic agent dosage adjustments may be necessary when fluoxetine therapy is initiated or discontinued should be considered.

Because fluoxetine therapy has been commonly associated with anorexia and weight loss, the drug should be used with caution in patients who may be adversely affected by these effects (e.g., underweight patients).

Treatment with SSRIs, including fluoxetine, and selective serotonin- and norepinephrine-reuptake inhibitors (SNRIs) may result in hyponatremia. In many cases, this hyponatremia appears to be due to the syndrome of inappropriate antidiuretic hormone secretion (SIADH) and was reversible when fluoxetine was discontinued. Cases with serum sodium concentrations lower than 110 mEq/L have been reported. Geriatric individuals and patients receiving diuretics or who are otherwise volume depleted may be at greater risk of developing hyponatremia during therapy with SSRIs or SNRIs. Signs and symptoms of hyponatremia include headache, difficulty concentrating, memory impairment, confusion, weakness, and unsteadiness, which may lead to falls; more severe and/or acute cases have been associated with hallucinations, syncope, seizures, coma, respiratory arrest, and death. Discontinuance of fluoxetine should be considered in patients with symptomatic hyponatremia and appropriate medical intervention should be instituted. (See Cautions: Renal, Electrolyte, and Genitourinary Effects and see also Cautions: Geriatric Precautions.)

Fluoxetine therapy is contraindicated in patients currently receiving, or having recently received, thioridazine therapy. In addition, concurrent use of fluoxetine in patients receiving pimozide is contraindicated. (See Thioridazine and also see Pimozide under Drug Interactions: Antipsychotic Agents.)

Fluoxetine is contraindicated in patients with known hypersensitivity to the drug.

■ **Pediatric Precautions** Safety and efficacy of fluoxetine in pediatric patients have not been established in children younger than 8 years of age for the management of major depressive disorder (see Pediatric Considerations under Uses: Major Depressive Disorder) or in children younger than 7 years of age for the management of obsessive-compulsive disorder.

FDA warns that antidepressants increase the risk of suicidal thinking and behavior (suicidality) in children and adolescents with major depressive disorder and other psychiatric disorders. The risk of suicidality for these drugs was identified in a pooled analysis of data from a total of 24 short-term (4–16 weeks), placebo-controlled studies of 9 antidepressants (i.e., fluoxetine, bupropion, citalopram, fluvoxamine, mirtazapine, nefazodone, paroxetine, sertraline, venlafaxine) in over 4400 children and adolescents with major depressive disorder, obsessive-compulsive disorder (OCD), or other psychiatric disorders. The analysis revealed a greater risk of adverse events representing suicidal behavior or thinking (suicidality) during the first few months of treatment in pediatric patients receiving antidepressants than in those receiving placebo. However, a more recent meta-analysis of 27 placebo-controlled trials of 9 antidepressants (SSRIs and others) in patients younger than 19 years of age with major depressive disorder, OCD, or non-OCD anxiety disorders suggests that the benefits of antidepressant therapy in treating these conditions may outweigh the risks of suicidal behavior or suicidal ideation. No suicides occurred in these pediatric trials.

The risk of suicidality in FDA's pooled analysis differed across the different psychiatric indications, with the highest incidence observed in the major depressive disorder studies. In addition, although there was considerable variation in risk among the antidepressants, a tendency toward an increase in suicidality risk in younger patients was found for almost all drugs studied. It is currently unknown whether the suicidality risk in pediatric patients extends to longer-term use (i.e., beyond several months).

As a result of this analysis and public discussion of the issue, FDA has directed manufacturers of all antidepressants to add a boxed warning to the labeling of their products to alert clinicians of this suicidality risk in children and adolescents and to recommend appropriate monitoring and close observation of patients receiving these agents. (See Cautions: Precautions and Contraindications.) The drugs that are the focus of the revised labeling are all drugs

included in the general class of antidepressants, including those that have not been studied in controlled clinical trials in pediatric patients, since the available data are not adequate to exclude any single antidepressant from an increased risk. In addition to the boxed warning and other information in professional labeling on antidepressants, FDA currently recommends that a patient medication guide explaining the risks associated with the drugs be provided to the patient each time the drugs are dispensed. Caregivers of pediatric patients whose depression is persistently worse or who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality during antidepressant therapy should consult their clinician regarding the best course of action (e.g., whether the therapeutic regimen should be changed or the drug discontinued). *Patients should not discontinue use of selective serotonin-reuptake inhibitors without first consulting their clinician; it is very important that the drugs not be abruptly discontinued, as withdrawal effects may occur.* (See Dosage and Administration: Dosage.)

Anyone considering the use of fluoxetine in a child or adolescent for any clinical use must balance the potential risks of therapy with the clinical need.

Important toxicity, including myotoxicity, long-term neurobehavioral and reproductive toxicity, and impaired bone development, has been observed following exposure of juvenile animals to fluoxetine; some of these effects occurred at clinically relevant exposures to the drug. In a study in which fluoxetine (3, 10, or 30 mg/kg) was orally administered to young rats from weaning (postnatal day 21) through adulthood (day 90), male and female sexual development was delayed at all dosages, and growth (body weight gain, femur length) was decreased during the dosing period in animals receiving the highest dosage. At the end of the treatment period, serum levels of creatine kinase (a marker of muscle damage) were increased in animals receiving the intermediate and highest dosage, and abnormal muscle and reproductive organ histopathology (skeletal muscle degeneration and necrosis, testicular degeneration and necrosis, epididymal vacuolation and hypospermia) was observed at the highest dosage. When animals were evaluated after a recovery period (up to 11 weeks after drug cessation), neurobehavioral abnormalities (decreased reactivity at all dosages and learning deficit at the highest dosage) and reproductive functional impairment (decreased mating at all dosages and impaired fertility at the highest dosage) were noted; testicular and epididymal microscopic lesions and decreased sperm concentrations were observed in the high-dosage group indicating that the reproductive organ effects seen at the end of treatment were irreversible. Reversibility of fluoxetine-induced muscle damage was not assessed in this study. Adverse effects similar to those observed in rats treated with fluoxetine during the juvenile period have not been reported after administration of fluoxetine to adult animals. Plasma exposures (AUC) to fluoxetine in juvenile rats receiving the low, intermediate, and high dosages in this study were approximately 0.1–0.2, 1–2, and 5–10 times, respectively, the average exposure in pediatric patients receiving the maximum recommended dosage of 20 mg daily. Exposures to norfluoxetine, the principal active metabolite of fluoxetine, in rats were approximately 0.3–0.8, 1–8, and 3–20 times the pediatric exposure at the maximum recommended dosage, respectively.

A specific effect of fluoxetine on bone development has been reported in mice treated with fluoxetine during the juvenile period. In mice treated with fluoxetine (5 or 20 mg/kg given intraperitoneally) for 4 weeks beginning at 4 weeks of age, bone formation was reduced resulting in decreased bone mineral content and density. These dosages did not affect overall growth (e.g., body weight gain or femoral length). The dosages given to juvenile mice in this study were approximately 0.5 and 2 times the maximum recommended dose for pediatric patients on a mg/m^2 basis.

In a study conducted in mice, fluoxetine administration (10 mg/kg intraperitoneally) during early postnatal development (postnatal days 4 to 21) produced abnormal emotional behaviors (decreased exploratory behavior in elevated plus-maze, increased shock avoidance latency) in adulthood (12 weeks of age). The dosage used in this study was approximately equal to the pediatric maximum recommended dosage on a mg/m^2 basis. Because of the early dosing period in this study, the clinical importance of these findings for the labeled pediatric use in humans is unknown.

As with other SSRIs, decreased weight gain has been observed in association with the use of fluoxetine in children and adolescents. In one clinical trial in pediatric patients 8–17 years of age, height gain averaged about 1.1 cm less and weight gain averaged about 1 kg less after 19 weeks of fluoxetine therapy relative to placebo-treated patients. In addition, fluoxetine therapy was associated with a decrease in plasma alkaline phosphatase concentrations. Because the safety of fluoxetine in pediatric patients has not been systematically assessed for chronic therapy longer than several months in duration and studies that directly evaluate the long-term effects of fluoxetine on the growth, development, and maturation of children and adolescents are lacking, height and weight should be monitored periodically in pediatric patients receiving fluoxetine. The clinical importance of these findings on long-term growth currently is not known, but the manufacturer will conduct a phase IV study to evaluate any potential impact of fluoxetine therapy on long-term pediatric growth. For further information on adverse effects associated with the use of fluoxetine in pediatric patients, see the opening discussion in Cautions.

■ **Geriatric Precautions** The efficacy of fluoxetine has been established in clinical studies in geriatric patients. Although no overall differences in efficacy or safety were observed between geriatric and younger patients, the possibility that some older patients particularly those with systemic disease or those who are receiving other drugs concomitantly (see Pharmacokinetics: Elimination and also see Uses: Major Depressive Disorder) may exhibit increased sensitivity to the drug cannot be ruled out.

In pooled data analyses, a *reduced* risk of suicidality was observed in adults 65 years of age or older with antidepressant therapy compared with placebo. (See Cautions: Precautions and Contraindications.)

Limited evidence suggests that geriatric patients may be more likely than younger patients to develop fluoxetine-induced hyponatremia and transient syndrome of inappropriate secretion of antidiuretic hormone (SIADH). Therefore, clinicians prescribing fluoxetine in geriatric patients should be aware of the possibility that such reactions may occur. In addition, periodic monitoring (especially during the first several months) of serum sodium concentrations in geriatric patients receiving the drug has been recommended by some clinicians.

As with other psychotropic drugs, geriatric patients receiving antidepressants appear to have an increased risk of hip fracture. Despite the fewer cardiovascular and anticholinergic effects associated with SSRIs, these drugs did not show any advantage over tricyclic antidepressants with regard to hip fracture in a case-control study. In addition, there was little difference in the rates of falls between nursing home residents receiving SSRIs and those receiving tricyclic antidepressants in a retrospective study. Therefore, all geriatric individuals receiving either type of antidepressant should be considered at increased risk of falls, and appropriate measures should be taken.

■ **Mutagenicity and Carcinogenicity** Fluoxetine and norfluoxetine did not exhibit mutagenic activity in vitro in mammalian cell (e.g., mouse lymphoma, rat hepatocyte DNA repair) or microbial (the *Salmonella* microbial mutagen [Ames]) test systems, or with the in vivo sister chromatid-exchange assay in Chinese hamster bone marrow cells. No evidence of carcinogenesis was seen in rats or mice receiving oral fluoxetine dosages of about 7.5 or 9 times the maximum recommended human dosage of the drug, respectively, for 24 months.

■ **Pregnancy, Fertility, and Lactation** ***Pregnancy*** Some neonates exposed to fluoxetine and other selective serotonin-reuptake inhibitors (SSRIs) or selective serotonin- and norepinephrine-reuptake inhibitors (SNRIs) late in the third trimester of pregnancy have developed complications that have sometimes been severe and required prolonged hospitalization, respiratory support, enteral nutrition, and other forms of supportive care in special care nurseries. Such complications can arise immediately upon delivery and usually last several days or up to 2–4 weeks. Clinical findings reported to date in the neonates have included respiratory distress, cyanosis, apnea, seizures, temperature instability or fever, feeding difficulty, dehydration, excessive weight loss, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, lethargy, reduced or lack of reaction to pain stimuli, and constant crying. These clinical features appear to be consistent with either a direct toxic effect of the SSRI or SNRI or, possibly, a drug withdrawal syndrome. It should be noted that, in some cases, the clinical picture was consistent with serotonin syndrome (see Drug Interactions: Serotonergic Drugs). When treating a pregnant woman with fluoxetine during the third trimester of pregnancy, the clinician should carefully consider the potential risks and benefits of such therapy. Consideration may be given to cautiously tapering fluoxetine therapy in the third trimester prior to delivery if the drug is administered during pregnancy. (See Dosage and Administration: Treatment of Pregnant Women during the Third Trimester.)

FDA states that decisions about management of depression in pregnant women are challenging and that the patient and her clinician must carefully consider and discuss the potential benefits and risks of SSRI therapy during pregnancy for the individual woman. Two recent studies provide important information on risks associated with discontinuing or continuing antidepressant therapy during pregnancy.

The first study, which was prospective, naturalistic, and longitudinal in design, evaluated the potential risk of relapsed depression in pregnant women with a history of major depressive disorder who discontinued or attempted to discontinue antidepressant (SSRIs, tricyclic antidepressants, or others) therapy during pregnancy compared with that in women who continued antidepressant therapy throughout their pregnancy; all women were euthymic while receiving antidepressant therapy at the beginning of pregnancy. In this study, women who discontinued antidepressant therapy were found to be 5 times more likely to have a relapse of depression during their pregnancy than were women who continued to receive their antidepressant while pregnant, suggesting that pregnancy does not protect against a relapse of depression.

The second study suggests that infants exposed to SSRIs in late pregnancy may have an increased risk of persistent pulmonary hypertension of the newborn (PPHN), which is associated with substantial neonatal morbidity and mortality. PPHN occurs at a rate of 1–2 neonates per 1000 live births in the general population in the US. In this retrospective case-control study of 377 women whose infants were born with PPHN and 836 women whose infants were born healthy, the risk for developing PPHN was approximately sixfold higher for infants exposed to SSRIs after the twentieth week of gestation compared with infants who had not been exposed to SSRIs during this period. The study was too small to compare the risk of PPHN associated with individual SSRIs, and the findings have not been confirmed. Although the risk of PPHN identified in this study still is low (6–12 cases per 1000) and further study is needed, the findings add to concerns from previous reports that infants exposed to SSRIs late in pregnancy may experience adverse serotonergic effects.

Fluoxetine and its principal metabolite norfluoxetine have been shown to cross the placenta in animals. There are no adequate and controlled studies to

date using fluoxetine in pregnant women, and the drug should be used during pregnancy only when clearly needed. Women should be advised to notify their clinician if they are or plan to become pregnant. FDA states that women who are pregnant or thinking about becoming pregnant should not discontinue any antidepressant, including fluoxetine, without first consulting their clinician. The decision whether or not to continue antidepressant therapy should be made only after careful consideration of the potential benefits and risks of antidepressant therapy for each individual pregnant patient. If a decision is made to discontinue treatment with fluoxetine or other SSRIs before or during pregnancy, discontinuance of therapy should be done in consultation with the clinician in accordance with the prescribing information for the antidepressant, and the patient should be closely monitored for possible relapse of depression. In addition, the prolonged elimination of the drug and its active metabolite from the body after discontinuance of therapy should be considered when a woman of childbearing potential receiving fluoxetine plans to become pregnant.

Most epidemiologic studies of pregnancy outcome following first trimester exposure to SSRIs, including fluoxetine, conducted to date have not revealed evidence of an increased risk of major congenital malformations. In a prospective, controlled, multicenter study, maternal use of several SSRIs (sertraline, fluvoxamine, paroxetine) in a limited number of pregnant women did not appear to increase the risk of congenital malformation, miscarriage, stillbirth, or premature delivery when used during pregnancy at recommended dosages. Birth weight and gestational age in neonates exposed to the drugs were similar to those in the control group. In another small study based on medical records review, the incidence of congenital anomalies reported in infants born to women who were treated with fluoxetine and other SSRIs during pregnancy was comparable to that observed in the general population. However, the results of epidemiologic studies indicate that exposure to paroxetine during the first trimester of pregnancy may increase the risk for congenital malformations, particularly cardiovascular malformations. (See Pregnancy, under Cautions: Pregnancy, Fertility, and Lactation, in Paroxetine 28:16.04.20.) Additional epidemiologic studies are needed to more thoroughly evaluate the relative safety of fluoxetine and other SSRIs during pregnancy, including their potential teratogenic risks and possible effects on neurobehavioral development.

The effect of fluoxetine on labor and delivery is not known.

Fertility Reproduction studies in rats using fluoxetine dosages 5–9 times the maximum recommended human daily dosage have not revealed evidence of impaired fertility. However, a slight decrease in neonatal survival that probably was related to reduced maternal food consumption and suppressed weight gain was reported in the offspring. Like some other SSRIs, pretreatment with fluoxetine inhibits methoxydimethyltryptamine-induced ejaculation in rats; this effect is blocked by metergoline, a serotonin antagonist. Alterations in sexual function also have been reported in patients receiving the drug. (See Sexual Dysfunction under Cautions: Renal, Electrolyte, and Genitourinary Effects and see also Cautions: Pediatric Precautions.)

Lactation Fluoxetine and its metabolites distribute into human milk. Limited data indicate that fluoxetine and norfluoxetine concentrations are 20–30% of concurrent maternal plasma drug concentrations. Crying, sleep disturbance, vomiting, and watery stools developed in an infant who nursed from a woman receiving fluoxetine; plasma fluoxetine and norfluoxetine concentrations in the infant on the second day of feeding were 340 and 208 ng/mL, respectively. Therefore, fluoxetine should not be used in nursing women, and women should be advised to notify their physician if they plan to breast-feed. In addition, the slow elimination of fluoxetine and norfluoxetine from the body after discontinuance of the drug should be considered.

Drug Interactions

As with other drugs, the possibility that fluoxetine may interact with any concomitantly administered drug by a variety of mechanisms, including pharmacodynamic and pharmacokinetic interactions, should be considered. The potential for interactions exists not only with concomitantly administered drugs but also with drugs administered for several weeks after discontinuance of fluoxetine therapy due to the prolonged elimination of fluoxetine and its principal metabolite, norfluoxetine. (See Pharmacokinetics: Elimination.)

■ **Serotonergic Drugs** Use of selective serotonin-reuptake inhibitors (SSRIs) such as fluoxetine concurrently or in close succession with other drugs that affect serotonergic neurotransmission may result in serotonin syndrome or neuroleptic malignant syndrome (NMS)-like reactions. Symptoms of serotonin syndrome may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination), and/or GI symptoms (e.g., nausea, vomiting, diarrhea). Although the syndrome appears to be relatively uncommon and usually mild in severity, serious and potentially life-threatening complications, including seizures, disseminated intravascular coagulation, respiratory failure, and severe hyperthermia, as well as death occasionally have been reported. In its most severe form, serotonin syndrome may resemble NMS, which is characterized by hyperthermia, muscle rigidity, autonomic instability with possible rapid fluctuation in vital signs, and mental status changes. The precise mechanism of these reactions is not fully understood; however, they appear to result from excessive serotonergic activity in the CNS, probably mediated by activation of serotonin 5-HT_{1A} receptors. The possible involvement of dopamine and 5-HT_2 receptors also has been suggested, although their roles remain unclear.

Serotonin syndrome most commonly occurs when 2 or more drugs that affect serotonergic neurotransmission are administered either concurrently or in close succession. Serotonergic agents include those that increase serotonin synthesis (e.g., the serotonin precursor tryptophan), stimulate synaptic serotonin release (e.g., some amphetamines, dexfenfluramine [no longer commercially available in the US], fenfluramine [no longer commercially available in the US]), inhibit the reuptake of serotonin after release (e.g., SSRIs, selective serotonin- and norepinephrine-reuptake inhibitors [SNRIs], tricyclic antidepressants, trazodone, dextromethorphan, meperidine, tramadol), decrease the metabolism of serotonin (e.g., monoamine oxidase [MAO] inhibitors), have direct serotonin postsynaptic receptor activity (e.g., buspirone), or nonspecifically induce increases in serotonergic neuronal activity (e.g., lithium salts). Selective agonists of serotonin (5-hydroxytryptamine; 5-HT) type 1 receptors ("triptans") and dihydroergotamine, agents with serotonergic activity used in the management of migraine headache, and St. John's wort (*Hypericum perforatum*) also have been implicated in serotonin syndrome.

The combination of SSRIs and MAO inhibitors may result in serotonin syndrome or NMS-like reactions. Such reactions have also been reported when SSRIs have been used concurrently with tryptophan, lithium, dextromethorphan, sumatriptan, dihydroergotamine, or antipsychotics or other dopamine antagonists. In rare cases, the serotonin syndrome reportedly has occurred in patients receiving the recommended dosage of a single serotonergic agent (e.g., clomipramine) or during accidental overdosage (e.g., sertraline intoxication in a child). Some other drugs that have been implicated in precipitating symptoms suggestive of serotonin syndrome or NMS-like reactions include buspirone, bromocriptine, dextropropoxyphene, linezolid, methylenedioxymethamphetamine (MDMA; "ecstasy"), selegiline (a selective MAO-B inhibitor), and sibutramine (an SNRI used for the management of obesity). Other drugs that have been associated with the syndrome but for which less convincing data are available include carbamazepine, fentanyl, and pentazocine.

Clinicians should be aware of the potential for serious, possibly fatal reactions associated with serotonin syndrome or NMS-like reactions in patients receiving 2 or more drugs that affect serotonergic neurotransmission, even if no such interactions with the specific drugs have been reported to date in the medical literature. Pending further accumulation of data, serotonergic drugs should be used cautiously in combination and such combinations avoided whenever clinically possible. Serotonin syndrome may be more likely to occur when initiating therapy with a serotonergic agent, increasing the dosage, or following the addition of another serotonergic drug. Some clinicians state that patients who have experienced serotonin syndrome may be at higher risk for recurrence of the syndrome upon reinitiation of serotonergic drugs. Pending further experience in such cases, some clinicians recommend that therapy with serotonergic agents be limited following recovery. In cases in which the potential benefit of the drug is thought to outweigh the risk of serotonin syndrome, lower potency agents and reduced dosages should be used, combination serotonergic therapy should be avoided, and patients should be monitored carefully for manifestations of serotonin syndrome. If signs and symptoms of serotonin syndrome or NMS develop during therapy, treatment with fluoxetine and any concurrently administered serotonergic or antidopaminergic agents, including antipsychotic agents, should be discontinued immediately and supportive and symptomatic treatment should be initiated.

Serotonin Syndrome **Manifestations.** Serotonin syndrome is characterized by mental status and behavioral changes, altered muscle tone or neuromuscular activity, autonomic instability with rapid fluctuations of vital signs, hyperthermia, and diarrhea. Some clinicians have stated that the diagnosis of serotonin syndrome can be made based on the presence of at least 3 of the following manifestations: mental status changes (e.g., confusion, hypomania), agitation, myoclonus, hyperreflexia, fever, shivering, tremor, diaphoresis, ataxia, and diarrhea in the setting of a recent addition or an increase in dosage of a serotonergic agent; the absence of other obvious causes of mental status changes and fever (e.g., infection, metabolic disorders, substance abuse or withdrawal); and no recent initiation or increase in dosage of an antipsychotic agent prior to the onset of the signs and symptoms (in order to rule out NMS). In some cases, features of the serotonin syndrome have resembled those associated with NMS, which may occur in patients receiving phenothiazines or other antipsychotic agents. (See Extrapyramidal Reactions in Cautions: Nervous System Effects, in the Phenothiazines General Statement 28:16.08.24.)

Other signs and symptoms associated with serotonin syndrome have included restlessness, irritability, insomnia, aggressive behavior, headache, drowsiness, dizziness, disorientation, loss of coordination, anxiety, euphoria, hallucinations, dilated pupils, nystagmus, paresthesias, rigidity, clonus, seizures, and coma. Nausea, vomiting, abdominal cramping, flushing, hypertension, hypotension, tachycardia, tachypnea, and hyperventilation also have occurred.

The onset of the serotonin syndrome can range from minutes after initiating therapy with a second serotonergic agent to several weeks after receiving a stable dosage. Preliminary evidence to date suggests that neither the occurrence nor the severity of serotonin syndrome is related to the dose or duration of serotonergic drug therapy.

The incidence of serotonin syndrome is unknown, but it is likely that the syndrome is underreported because it is not recognized or appears in various degrees of severity (mild, moderate, or severe). In addition, serotonin syndrome may be confused with or resemble NMS in some cases.

Treatment. Mild cases of serotonin syndrome generally respond within 12–24 hours to the immediate discontinuance of serotonergic agents and general supportive therapy. Symptoms rarely last more than 72–96 hours in the

absence of complications. Supportive therapy in such cases may include hospitalization, adequate hydration, control of myoclonus and hyperreflexia with benzodiazepines such as clonazepam (and possibly propranolol), and control of fever with acetaminophen and external cooling, if necessary. Other possible causes of altered mental status and fever also should be considered and treated accordingly.

Patients with severe hyperthermia (i.e., a temperature of more than 40.5°C) are considered to have more severe cases of serotonin syndrome which are associated with more serious complications and mortality. Muscular rigidity often accompanies hyperthermia and may respond to benzodiazepine therapy. Such patients should be managed with aggressive cooling measures, including external cooling, the institution of muscular paralysis (to decrease body temperature, help prevent rhabdomyolysis and disseminated intravascular coagulation from muscular rigidity refractory to benzodiazepines, and facilitate intubation), and maintenance of a patent airway with endotracheal intubation. Seizures may be treated with benzodiazepines and, if necessary, other anticonvulsants (e.g., barbiturates). Patients who develop hypertension, cardiac arrhythmias, and other serious complications such as disseminated intravascular coagulation or rhabdomyolysis associated with serotonin syndrome should receive appropriate therapy for these conditions.

Although there is no specific therapy for serotonin syndrome, nonspecific serotonin (5-HT_1 and 5-HT_2) receptor antagonists such as cyproheptadine and methysergide and drugs with 5-HT_{1A} receptor affinity such as propranolol have been used with some success in a limited number of patients whose symptoms persisted or were unusually severe. Dantrolene, bromocriptine, and chlorpromazine (for sedation, to help reduce fever, and because of its 5-HT-receptor blocking activity) also have been used in a limited number of patients with serotonin syndrome but with inconsistent results; the possibility that chlorpromazine may lower the seizure threshold in this setting should be considered.

Monoamine Oxidase Inhibitors Potentially serious, sometimes fatal serotonin syndrome or NMS-like reactions have been reported in patients receiving serotonin-reuptake inhibitors in combination with an MAO inhibitor. Such reactions also have been reported in patients who recently have discontinued a selective serotonin-reuptake inhibitor and have been started on an MAO inhibitor.

Probably because of its extensive clinical use and the prolonged elimination half-life of both fluoxetine and norfluoxetine, fluoxetine has been the selective serotonin-reuptake inhibitor most commonly implicated in serotonin syndrome. In at least 2 cases, serotonin syndrome developed when MAO inhibitor therapy was initiated after the discontinuance of fluoxetine therapy. Shivering, diplopia, nausea, confusion, and anxiety reportedly occurred in one patient 6 days after discontinuance of fluoxetine therapy and 4 days after initiation of tranylcypromine therapy; signs and symptoms resolved without apparent sequelae within 24 hours following discontinuance of the MAO inhibitor in this patient. In another case, the initiation of tranylcypromine therapy more than 5 weeks after discontinuance of fluoxetine reportedly resulted in serotonin syndrome.

Concurrent administration of fluoxetine and MAO inhibitors is contraindicated. Because both fluoxetine and its principal metabolite have relatively long half-lives, at least 5 weeks should elapse between discontinuance of fluoxetine therapy and initiation of MAO inhibitor therapy, since administration of an MAO inhibitor prior to elapse of this time may increase the risk of serious adverse effects. Based on clinical experience with concurrent administration of tricyclic antidepressants and MAO inhibitors, at least 2 weeks should elapse following discontinuance of an MAO inhibitor prior to initiation of fluoxetine therapy.

Linezolid. Linezolid, an anti-infective agent that is a nonselective and reversible MAO inhibitor, has been associated with drug interactions resulting in serotonin syndrome, including some associated with SSRIs, and potentially may also cause NMS-like reactions. Therefore, at least one manufacturer of fluoxetine states that linezolid should be used with caution in patients receiving fluoxetine. The manufacturer of linezolid states that, unless patients are carefully observed for signs and/or symptoms of serotonin syndrome, the drug should not be used in patients receiving SSRIs. Some clinicians suggest that linezolid only be used with caution and close monitoring in patients concurrently receiving SSRIs, and some suggest that SSRI therapy should be discontinued before linezolid is initiated and not reinitiated until 2 weeks after linezolid therapy is completed.

Moclobemide. Moclobemide, a selective and reversible MAO-A inhibitor (not commercially available in the US), also has been associated with serotonin syndrome and such reactions have been fatal in several cases in which the drug was given in combination with the selective serotonin-reuptake inhibitor citalopram or with clomipramine. Pending further experience with such combinations, some clinicians recommend that concurrent therapy with moclobemide and selective serotonin-reuptake inhibitors be used only with extreme caution and serotonin-reuptake inhibitors should have been discontinued for some time (depending on the elimination half-lives of the drug and its active metabolites) before initiating moclobemide therapy.

Selegiline. Selegiline, a selective MAO-B inhibitor used in the management of parkinsonian syndrome, also has been reported to cause serotonin syndrome when given concurrently with selective serotonin-reuptake inhibitors (fluoxetine, paroxetine, sertraline). Although selegiline is a selective MAO-B inhibitor at therapeutic dosages, the drug appears to lose its selectivity for the MAO-B enzyme at higher dosages (e.g., those exceeding 10 mg/kg), thereby increasing the risk of serotonin syndrome in patients receiving higher dosages of the drug either alone or in combination with other serotonergic agents. The manufacturer of selegiline recommends avoiding concurrent selegiline and selective serotonin-reuptake inhibitor therapy. In addition, the manufacturer of selegiline recommends that a drug-free interval of at least 2 weeks elapse between discontinuance of selegiline and initiation of selective serotonin-reuptake inhibitor therapy. Because of the long half-lives of fluoxetine and its principal metabolite, at least 5 weeks should elapse or even longer (particularly if fluoxetine has been prescribed chronically and/or at higher dosages) between discontinuance of fluoxetine and initiation of selegiline therapy.

Isoniazid. Isoniazid, an antituberculosis agent, appears to have some MAO-inhibiting activity. In addition, iproniazid (not commercially available in the US), another antituberculosis agent structurally related to isoniazid that also possesses MAO-inhibiting activity, reportedly has resulted in serotonin syndrome in at least 2 patients when given in combination with meperidine. Pending further experience, clinicians should be aware of the potential for serotonin syndrome when isoniazid is given in combination with selective serotonin-reuptake inhibitor therapy or other serotonergic agents.

Tryptophan and Other Serotonin Precursors Adverse nervous system effects (e.g., agitation, restlessness, aggressive behavior, insomnia, poor concentration, headache, paresthesia, incoordination, worsening of symptoms of obsessive-compulsive disorder), adverse GI effects (e.g., nausea, abdominal cramps, diarrhea), palpitation, and/or chills reportedly have occurred in a limited number of patients receiving fluoxetine concurrently with tryptophan, a serotonin precursor. Such symptoms generally resolved within several weeks following discontinuance of tryptophan despite continued fluoxetine therapy. Although the mechanism for this interaction has not been fully elucidated, it has been suggested that these adverse effects resemble the serotonin syndrome observed in animals and therefore may result from a marked increase in serotonin availability when tryptophan and potent serotonin-reuptake inhibitors such as fluoxetine are administered concurrently. Because of the potential risk of serotonin syndrome or NMS-like reactions, concurrent use of tryptophan or other serotonin precursors should be avoided in patients receiving fluoxetine.

Sibutramine Because of the possibility of developing potentially serious, sometimes fatal serotonin syndrome or NMS-like reactions, sibutramine should be used with caution in patients receiving fluoxetine.

5-HT_1 Receptor Agonists ("Triptans") Weakness, hyperreflexia, and incoordination have been reported rarely during postmarketing surveillance in patients receiving sumatriptan concomitantly with an SSRI (e.g., fluoxetine, citalopram, escitalopram, fluvoxamine, paroxetine, sertraline). Oral or subcutaneous sumatriptan and SSRIs were used concomitantly in some clinical studies without unusual adverse effects. However, an increase in the frequency of migraine attacks and a decrease in the effectiveness of sumatriptan in relieving migraine headache have been reported in a patient receiving subcutaneous injections of sumatriptan intermittently while undergoing fluoxetine therapy.

Clinicians prescribing 5-HT_1 receptor agonists, SSRIs, and SNRIs should consider that triptans often are used intermittently and that either the 5-HT_1 receptor agonist, SSRI, or SNRI may be prescribed by a different clinician. Clinicians also should weigh the potential risk of serotonin syndrome or NMS-like reactions with the expected benefit of using a triptan concurrently with SSRI or SNRI therapy. If concomitant treatment with fluoxetine and a triptan is clinically warranted, the patient should be observed carefully, particularly during treatment initiation, dosage increases, and following the addition of other serotonergic agents. Patients receiving concomitant triptan and fluoxetine therapy should be informed of the possibility of serotonin syndrome or NMS-like reactions and advised to immediately seek medical attention if they experience symptoms of these syndromes.

Other Selective Serotonin-reuptake Inhibitors and Selective Serotonin- and Norepinephrine-reuptake Inhibitors Concomitant administration of fluoxetine with other SSRIs or SNRIs potentially may result in serotonin syndrome or NMS-like reactions and is therefore not recommended.

Antipsychotic Agents and Other Dopamine Antagonists Concomitant use of antipsychotic agents and other dopamine antagonists with fluoxetine potentially may result in serotonin syndrome or NMS-like reactions. If signs and symptoms of serotonin syndrome or NMS occur, treatment with fluoxetine and any concurrently administered antidopaminergic or serotonergic agents should be immediately discontinued and supportive and symptomatic treatment initiated. (See Drug Interactions: Antipsychotic Agents.)

Tramadol and Other Serotonergic Drugs Because of the potential risk of serotonin syndrome or NMS-like reactions, caution is advised whenever SSRIs, including fluoxetine, and SNRIs are concurrently administered with other drugs that may affect serotonergic neurotransmitter systems, including tramadol and St. John's wort (*Hypericum perforatum*).

Pentazocine, an opiate partial agonist analgesic, has been reported to cause transient symptoms of diaphoresis, ataxia, flushing, and tremor suggestive of the serotonin syndrome when used concurrently with fluoxetine.

Serotonin syndrome rarely may occur following concomitant use of fluoxetine and stimulants because stimulants can release serotonin, and amphetamine is metabolized by the cytochrome P-450 (CYP) 2D6 isoenzyme, which is inhibited by some SSRIs (e.g., fluoxetine, paroxetine).

■ **Drugs Undergoing Metabolism by Hepatic Microsomal Enzymes** ***Drugs Metabolized by Cytochrome P-450 (CYP) 2D6*** Fluoxetine, like many other antidepressants (e.g., other selective serotonin-

reuptake inhibitors, many tricyclic antidepressants), is metabolized by the drug-metabolizing cytochrome P-450 (CYP) 2D6 isoenzyme (debrisoquine hydroxylase). In addition, like many other drugs metabolized by CYP2D6, fluoxetine inhibits the activity of CYP2D6 and potentially may increase plasma concentrations of concomitantly administered drugs that also are metabolized by this enzyme. Fluoxetine may make normal CYP2D6 metabolizers resemble "poor metabolizers". Although similar interactions are possible with other selective serotonin-reuptake inhibitors, there is considerable variability among the drugs in the extent to which they inhibit CYP2D6; fluoxetine and paroxetine appear to be more potent in this regard than sertraline.

Concomitant use of fluoxetine with other drugs metabolized by CYP2D6 has not been systematically studied. The extent to which this potential interaction may become clinically important depends on the extent of inhibition of CYP2D6 by the antidepressant and the therapeutic index of the concomitantly administered drug. The drugs for which this potential interaction is of greatest concern are those that are metabolized principally by CYP2D6 and have a narrow therapeutic index, such as tricyclic antidepressants, class IC antiarrhythmics (e.g., propafenone, flecainide, encainide), vinblastine, and some phenothiazines (e.g., thioridazine).

Caution should be exercised whenever concurrent therapy with fluoxetine and other drugs metabolized by CYP2D6 is considered. If fluoxetine therapy is initiated in a patient already receiving a drug metabolized by CYP2D6, the need for decreased dosage of that drug should be considered. In addition, a low initial dosage should be used whenever a drug that is predominantly metabolized by CYP2D6 and has a relatively narrow therapeutic margin (e.g., tricyclic antidepressants, class IC antiarrhythmics) is initiated in a patients who is receiving or has received fluoxetine during the previous 5 weeks. Because of the risk of serious ventricular arrhythmias and sudden death potentially associated with increased plasma concentrations of thioridazine, thioridazine is contraindicated in any patient who is receiving or has received fluoxetine during the previous 5 weeks. (See Thioridazine under Drug Interactions: Antipsychotic Agents.)

Drugs Metabolized by Cytochrome P-450 (CYP) 3A4 Although fluoxetine can inhibit the cytochrome P-450 (CYP) 3A4 isoenzyme, results of in vitro and in vivo studies indicate that the drug is a much less potent inhibitor of this enzyme than many other drugs. In one in vivo drug interaction study, concomitant administration of single doses of the CYP3A4 substrate terfenadine (no longer commercially available in the US) and fluoxetine did not increase plasma concentrations of terfenadine. In addition, in vitro studies have shown that ketoconazole, a potent inhibitor of CYP3A4 activity, is at least 100 times more potent than fluoxetine or norfluoxetine as an inhibitor of several substrates of this enzyme (e.g., astemizole [no longer commercially available in the US], cisapride, midazolam). Some clinicians state that concomitant use of fluoxetine with astemizole or terfenadine is not recommended since substantially increased plasma concentrations of unchanged astemizole or terfenidine could occur, resulting in an increased risk of serious adverse cardiac effects. However, the manufacturer of fluoxetine states that the extent of fluoxetine's inhibition of CYP3A4 activity is unlikely to be of clinical importance.

■ **Tricyclic and Other Antidepressants** Concurrent administration of fluoxetine and a tricyclic antidepressant (e.g., nortriptyline, desipramine, imipramine) reportedly has resulted in adverse effects associated with tricyclic toxicity (including sedation, decreased energy, lightheadedness, psychomotor retardation, dry mouth, constipation, memory impairment). In patients receiving imipramine or desipramine, initiation of fluoxetine therapy reportedly resulted in plasma concentrations of these tricyclic antidepressants that were at least 2–10 times higher; this effect persisted for 3 weeks or longer after fluoxetine was discontinued. Elevated plasma trazodone concentrations and adverse effects possibly associated with trazodone toxicity (e.g., sedation, unstable gait) also have been reported during concomitant fluoxetine and trazodone therapy. Although the mechanism for this possible interaction has not been established, it has been suggested that fluoxetine may inhibit the hepatic metabolism of tricyclic antidepressants. (See Drugs Metabolized by Cytochrome P-450 (CYP) 2D6 under Drug Interactions: Drugs Undergoing Metabolism by Hepatic Microsomal Enzymes.) Further study of this potential interaction is needed, but current evidence suggests that patients receiving fluoxetine and a tricyclic antidepressant or trazodone concomitantly should be closely observed for adverse effects; monitoring of plasma tricyclic or trazodone concentrations also should be considered and their dosage reduced as necessary. Because fluoxetine may increase plasma concentrations and prolong the elimination half-life of tricyclic antidepressants, the need for more prolonged monitoring following combined tricyclic and fluoxetine overdose should be considered. In addition, because of the prolonged elimination of fluoxetine and norfluoxetine, the possibility that the drug may interact with tricyclic antidepressants after recent discontinuance of fluoxetine also should be considered.

■ **Antipsychotic Agents** Concomitant use of antipsychotic agents with fluoxetine potentially may result in serotonin syndrome or NMS-like reactions. If signs and symptoms of serotonin syndrome or NMS occur, treatment with fluoxetine and any concurrently administered antipsychotic agent should be immediately discontinued and supportive and symptomatic treatment initiated. (See Drug Interactions: Serotonergic Drugs.)

Some clinical data suggest a possible pharmacodynamic and/or pharmacokinetic interaction between SSRIs, including fluoxetine, and some antipsychotic agents.

Clozapine Concomitant use of fluoxetine and clozapine can increase plasma concentrations of clozapine and enhance clozapine's pharmacologic effects secondary to suspected inhibition of clozapine metabolism by fluoxetine. Increased plasma clozapine concentrations also have been reported in patients receiving other SSRIs (e.g., fluvoxamine, paroxetine). There has been at least one fatality related to clozapine toxicity following ingestion of clozapine, fluoxetine, and alcohol. The manufacturer of clozapine states that caution should be used and patients closely monitored if clozapine is used in patients receiving SSRIs, and a reduction in clozapine dosage should be considered.

Haloperidol Elevated plasma concentrations of haloperidol have been observed in patients receiving concomitant fluoxetine therapy. Severe extrapyramidal symptoms (e.g., tongue stiffness, parkinsonian symptoms, akathisia), which required hospitalization and were refractory to conventional therapy (including anticholinergic antiparkinsonian agents, diphenhydramine, and diazepam), reportedly occurred in a patient receiving fluoxetine and haloperidol concurrently; this patient previously had experienced only mild adverse extrapyramidal effects with haloperidol therapy alone. The extrapyramidal symptoms gradually abated following discontinuance of both drugs, and the patient subsequently tolerated haloperidol therapy with evidence of only a slight parkinsonian gait. The clinical importance of this possible interaction has not been established, and additional study is required to determine the safety of combined fluoxetine and antipsychotic therapy.

Olanzapine Concomitant administration of fluoxetine (60 mg as a single dose or 60 mg daily for 8 days) with a single 5-mg dose of oral olanzapine caused a small increase in peak plasma olanzapine concentrations (averaging 16%) and a small decrease (averaging 16%) in olanzapine clearance; the elimination half-life was not substantially affected. Fluoxetine is an inhibitor of CYP2D6, and thereby may affect a minor metabolic pathway for olanzapine. Although the changes in pharmacokinetics are statistically significant when olanzapine and fluoxetine are given concurrently, the changes are unlikely to be clinically important in comparison to the overall variability observed between individuals; therefore, routine dosage adjustment is not recommended.

When fluoxetine is used in fixed combination with olanzapine (Symbyax®), the drug interactions associated with olanzapine should also be considered. (See Drug Interactions in Olanzapine 28:16.08.04.)

Pimozide Clinical studies evaluating pimozide in combination with other antidepressants have demonstrated an increase in adverse drug interactions or QT_c prolongation during combined therapy. In addition, rare case reports have suggested possible additive cardiovascular effects of fluoxetine and pimozide, resulting in bradycardia. Marked changes in mental status (e.g., stupor, inability to think clearly) and hypersalivation also were reported in one woman who received both drugs concurrently. Although a specific study evaluating concurrent fluoxetine and pimozide therapy has not been performed to date, concurrent use of these drugs is contraindicated because of the potential for adverse drug interactions or QT_c prolongation.

Risperidone Extrapyramidal symptoms followed by persistent tardive dyskinesia (dyskinetic tongue movements) have occurred in one 18-year-old who received risperidone concomitantly with fluoxetine; however, a causal relationship has not been established. The AUC of risperidone increased during concomitant fluoxetine therapy in one study in psychotic patients, and the AUC of active drug (risperidone plus 9-hydroxyrisperidone) increased in poor and extensive metabolizers (determined by CYP2D6 genotyping); there was no evidence of increased severity or incidence of extrapyramidal symptoms in this 30-day study.

Thioridazine Although specific drug interaction studies evaluating concomitant use of fluoxetine and thioridazine are not available, concomitant use of other SSRIs (e.g., fluvoxamine) has resulted in increased plasma concentrations of the antipsychotic agent. Because of the risk of serious ventricular arrhythmia and sudden death associated with elevated plasma concentrations of thioridazine, thioridazine is contraindicated in any patient who is receiving or has received fluoxetine during the previous 5 weeks. (See Drugs Metabolized by Cytochrome P-450 (CYP) 2D6 under Drug Interactions: Drugs Undergoing Metabolism by Hepatic Microsomal Enzymes.)

■ **Benzodiazepines** Fluoxetine appears to inhibit the metabolism of diazepam, as evidenced by increases in the elimination half-life and plasma concentration of diazepam and decreases in diazepam clearance and the rate of formation of desmethyldiazepam (an active metabolite of diazepam) during concomitant use of the drugs. Although clinically important increase in psychomotor impairment has not been noted when fluoxetine and diazepam were administered concomitantly as compared with administration of diazepam alone, concomitant administration of alprazolam and fluoxetine has resulted in increased plasma concentrations of alprazolam and further psychomotor performance impairments. Pending further accumulation of data, the possibility that a clinically important interaction could occur in geriatric or other susceptible patients should be considered.

■ **Buspirone** Buspirone has serotonergic activity and may have been partially responsible for a case of serotonin syndrome that resulted in the death of a patient receiving fluoxetine, buspirone, and an MAO inhibitor (tranylcypromine) concomitantly. (See Drug Interactions: Serotonergic Drugs.)

In a patient with depression, generalized anxiety disorder, and panic attacks who was receiving concomitant buspirone and trazodone therapy, an increase in anxiety symptoms to a level comparable to that observed prior to buspirone

therapy occurred when fluoxetine was added to the regimen. Although the mechanism of this possible interaction has not been established, it was suggested that fluoxetine may have either directly antagonized the therapeutic activity of buspirone or may have precipitated the anxiety symptoms through a separate mechanism. However, combined use of the drugs also has been reported to potentiate therapeutic efficacy in patients with obsessive-compulsive disorder.

■ **Lithium** Fluoxetine and lithium have been used concurrently in a limited number of patients without apparent adverse effects. However, both increased and decreased serum lithium concentrations and adverse neuromuscular effects possibly associated with lithium toxicity and/or serotonin syndrome (e.g., ataxia, dizziness, dysarthria, stiffness of the extremities) have been reported during combined therapy with the drugs. Lithium appears to have some serotonergic activity, and serotonin syndrome has been reported following the initiation of lithium therapy in at least one patient receiving fluoxetine. (See Drug Interactions: Serotonergic Drugs.) The clinical importance of this potential interaction remains to be determined and further substantiation is required; however, caution should be exercised when fluoxetine and lithium are administered concurrently. It is recommended that serum lithium concentrations be monitored closely during concomitant fluoxetine therapy.

■ **Anticonvulsants** ***Carbamazepine*** Fluoxetine can increase plasma carbamazepine and carbamazepine 10,11-epoxide (CBZ-E, an active metabolite) concentrations, and carbamazepine toxicity (e.g., ocular changes, vertigo, tremor) has been reported in some patients maintained on carbamazepine following initiation of fluoxetine. It has been suggested that fluoxetine-induced inhibition of hepatic metabolism (e.g., inhibition of epoxide hydrolase) of carbamazepine and/or CBZ-E may be principally responsible for such increases; alteration in protein binding does not appear to be principally responsible for this interaction. The patient and plasma concentrations of carbamazepine and its metabolite should be monitored closely whenever fluoxetine therapy is initiated or discontinued; carbamazepine dosage should be adjusted accordingly.

Phenytoin Initiation of fluoxetine in patients stabilized on phenytoin has resulted in increased plasma phenytoin concentrations and clinical manifestations of phenytoin toxicity.

■ **β-Adrenergic Blocking Agents** Concomitant use of fluoxetine and a β-adrenergic blocking agent has resulted in increased plasma concentrations that have enhanced the β-adrenergic blocking effects of the drug, possibly resulting in cardiac toxicity. Metoprolol is metabolized by the CYP2D6 isoenzyme and fluoxetine is known to potently inhibit this enzyme. Although specific data are lacking, β-adrenergic blocking agents that are renally eliminated (e.g., atenolol) may be a safer choice. Patients who were previously stabilized on propranolol or metoprolol should be monitored for toxicity (e.g., bradycardia, conduction defects, hypotension, heart failure, central nervous system disturbances) following initiation of fluoxetine therapy.

■ **Protein-bound Drugs** Because fluoxetine is highly protein bound, the drug theoretically could be displaced from binding sites by, or it could displace from binding sites, other protein-bound drugs such as oral anticoagulants and digitoxin (no longer commercially available in the US). Pending further accumulation of data, patients receiving fluoxetine with any highly protein-bound drug should be observed for potential adverse effects associated with such therapy. (See Drug Interactions: Drugs Affecting Hemostasis.)

■ **Drugs Affecting Hemostasis** ***Warfarin*** Concomitant use of fluoxetine and warfarin has resulted in altered anticoagulant effects, including increased bleeding. Therefore, patients receiving warfarin should be carefully monitored whenever fluoxetine is initiated or discontinued.

Other Drugs that Interfere with Hemostasis Epidemiologic case-control and cohort design studies that have demonstrated an association between selective serotonin-reuptake inhibitor therapy and an increased risk of upper GI bleeding also have shown that concurrent use of aspirin or other nonsteroidal anti-inflammatory agents substantially increases the risk of GI bleeding. Although these studies focused on upper GI bleeding, there is some evidence suggesting that bleeding at other sites may be similarly potentiated. The precise mechanism for this increased risk remains to be clearly established; however, serotonin release by platelets is known to play an important role in homostasis, and selective serotonin-reuptake inhibitors decrease serotonin uptake from the blood by platelets, thereby decreasing the amount of serotonin in platelets. Patients receiving fluoxetine should be cautioned about the concomitant use of drugs that interfere with hemostasis, including aspirin and other nonsteroidal anti-inflammatory agents.

■ **Alcohol** Concurrent administration of single or multiple doses of fluoxetine and alcohol does not appear to alter blood or Breathalyzer® alcohol, plasma fluoxetine, or plasma norfluoxetine concentrations in healthy individuals, suggesting that there is no pharmacokinetic interaction between fluoxetine and alcohol. In addition, fluoxetine does not appear to potentiate the psychomotor and cognitive impairment or cardiovascular effects induced by alcohol. However, the drug's ability to reduce alcohol consumption in animals and humans suggests that there may be a serotonergically mediated, pharmacodynamic interaction between fluoxetine and alcohol within the CNS. (See Pharmacology: Effects on Alcohol Intake, and also see Uses: Alcohol Dependence.)

■ **Electroconvulsive Therapy** The effects of fluoxetine in conjunction with electroconvulsive therapy (ECT) for the management of depression have not been evaluated to date in clinical studies. Prolonged seizures reportedly have occurred rarely during concurrent use of fluoxetine and ECT.

■ **Antidiabetic Agents** Fluoxetine potentially may alter blood glucose concentrations in patients with diabetes mellitus. (See Cautions: Metabolic Effects.) Therefore, dosage adjustments of insulin and/or sulfonylurea antidiabetic agents may be necessary when fluoxetine therapy is initiated or discontinued in such patients.

Acute Toxicity

Limited information is available on the acute toxicity of fluoxetine.

■ **Pathogenesis** The acute lethal dose of fluoxetine in humans is not known. The median oral LD_{50} of fluoxetine has been reported to be approximately 452 and 248 mg/kg in rats and mice, respectively. In animals, oral administration of single large doses of the drug has resulted in hyperirritability and seizures. Tonic-clonic seizures occurred in 5 of 6 dogs given a toxic dose of fluoxetine orally; the seizures ceased immediately after IV administration of diazepam. In these dogs, the lowest plasma fluoxetine concentration at which seizures occurred reportedly was only twice the maximum plasma concentration reported in humans receiving 80 mg of the antidepressant daily during long-term therapy. Single large oral doses of fluoxetine reportedly do not cause QT- or PR-interval prolongation or widening of the QRS complex in dogs, although tachycardia and an increase in blood pressure have occurred.

The risk of fluoxetine overdosage may be increased in patients with a genetic deficiency in the cytochrome P-450 (CYP) isoenzyme 2D6.

■ **Manifestations** In general, overdosage of fluoxetine may be expected to produce effects that are extensions of the drug's pharmacologic and adverse effects. Animal studies and case reports in humans indicate that possible effects of overdosage include agitation, restlessness, hypomania, vertigo, insomnia, tremor, and other signs of CNS excitation; nausea and vomiting; and tachycardia and/or increased blood pressure. Seizures have been reported in at least one patient after overdosage of fluoxetine. Acute overdosage of fluoxetine alone reportedly has resulted in nystagmus, drowsiness, coma, urticaria, spontaneous emesis, and ST-segment depression. Nausea and vomiting appear to occur commonly following acute ingestion of relatively large single doses of the drug.

Several fatalities following fluoxetine overdosage have been reported to date. One of the deaths occurred in a patient who reportedly ingested 1.8 g of fluoxetine and an unknown quantity of maprotiline; plasma fluoxetine and maprotiline concentrations in this patient were approximately 4570 and 4180 ng/mL, respectively. Another patient died after concomitantly ingesting fluoxetine, codeine, and temazepam; plasma fluoxetine, norfluoxetine, codeine, and temazepam concentrations in this patient reportedly were 1930, 1110, 1800, and 3800 ng/mL, respectively. A fatal overdose also has been reported in a patient ingesting fluoxetine and alcohol concomitantly. There also are a few reported cases of overdose in which fatality was attributed to fluoxetine alone. In one such case, death was associated with extracted blood fluoxetine and norfluoxetine concentrations of 6000 and 5000 ng/mL, respectively, and biliary concentrations of 13,000 ng/mL each for the drug and metabolite. A patient enrolled in a clinical study of fluoxetine reportedly died following intentional ingestion of an unknown quantity of amitriptyline, clobazam, and pentazocine; however, it is not known whether this patient also ingested fluoxetine with the other drugs.

A patient with a history of seizures who reportedly ingested 3 g of fluoxetine and an unknown quantity of aspirin experienced 2 tonic-clonic seizures, tachycardia, dizziness, blurred vision, unsustained clonus, and ECG changes. The seizures occurred about 9 hours post-ingestion, lasted approximately 2–3 minutes, and remitted spontaneously without anticonvulsant therapy. Although the actual amount of fluoxetine absorbed by this patient may have been less than expected because of vomiting and gastric lavage, the plasma fluoxetine concentration reportedly was 2461 ng/mL when seizures occurred; the patient recovered with no apparent sequelae. Another patient reported that he experienced sleepiness and nausea that lasted for several days following the intentional ingestion of 840 mg of fluoxetine with alcohol; this patient did not seek medical treatment. Drowsiness, lethargy, and nausea occurred in a patient who reportedly ingested 1.4 g of fluoxetine and 15 mg of clonazepam. No ECG abnormalities were reported in 2 patients who intentionally ingested 200 mg and 1 g of fluoxetine.

A child with a genetic deficiency in the CYP2D6 isoenzyme died following prolonged therapy with fluoxetine, methylphenidate, and clonidine. Autopsy findings revealed blood, brain, and other tissue concentrations of fluoxetine and norfluoxetine that were several-fold higher than expected. Poor metabolism of fluoxetine via CYP2D6 was the likely cause of fluoxetine intoxication in this child.

■ **Treatment** Because fatalities and severe toxicity have been reported following overdosage of selective serotonin-reuptake inhibitors, particularly in large overdosage and when taken with other drugs or alcohol, some clinicians recommend that any overdosage involving these drugs be managed aggressively. Because suicidal ingestion often involves more than one drug, clinicians treating fluoxetine overdosage should be alert to possible toxic manifestations caused by drugs other than fluoxetine.

Clinicians also should consider the possibility of serotonin syndrome or NMS-like reactions in patients presenting with similar clinical features and a recent history of fluoxetine ingestion and/or ingestion of other serotonergic and/

or antipsychotic agents or other dopamine antagonists. (See Cautions: Precautions and Contraindications and see also Drug Interactions: Serotonergic Drugs.)

Management of fluoxetine overdosage generally involves symptomatic and supportive care. A patent airway should be established and maintained, and adequate oxygenation and ventilation should be assured. ECG and vital sign monitoring is recommended following acute overdosage with the drug, although the value of ECG monitoring in predicting the severity of fluoxetine-induced cardiotoxicity is not known. (See Acute Toxicity: Manifestations, in the Tricyclic Antidepressants General Statement.) There is no specific antidote for fluoxetine intoxication.

Following recent (i.e., within 4 hours) ingestion of a potentially toxic amount of fluoxetine and in the absence of signs and symptoms of cardiac toxicity, the stomach should be emptied immediately by inducing emesis or by gastric lavage. If the patient is comatose, having seizures, or lacks the gag reflex, gastric lavage may be performed if an endotracheal tube with cuff inflated is in place to prevent aspiration of gastric contents. Since administration of activated charcoal (which may be used in conjunction with sorbitol or a saline cathartic) may be as effective or more effective than induction of emesis or gastric lavage, its use has been recommended either in the initial management of fluoxetine overdosage or following induction of emesis or gastric lavage in patients who have ingested a potentially toxic quantity of the drug.

Based on data from animal studies, IV diazepam should be considered for the management of fluoxetine-induced seizures that do not remit spontaneously. If seizures are not controlled or recur following administration of diazepam, administration of phenytoin or phenobarbital has been recommended by some clinicians.

Fluoxetine and norfluoxetine are not substantially removed by hemodialysis. Because of the large volume of distribution and extensive protein binding of the drug and its principal metabolite, peritoneal dialysis, forced diuresis, hemoperfusion, and/or exchange transfusion probably are also ineffective in removing substantial amounts of fluoxetine and norfluoxetine from the body. Clinicians should consider consulting a poison control center for additional information on the management of fluoxetine overdosage.

Chronic Toxicity

Fluoxetine has not been studied systematically in animals or humans to determine whether therapy with the drug is associated with tolerance or psychologic and/or physical dependence. One patient receiving the drug for the management of obesity reportedly experienced nervousness 2 days following discontinuance of fluoxetine therapy. However, it is unclear whether this adverse effect represented a withdrawal reaction since both the parent drug and its principal metabolite have relatively long half-lives, and withdrawal reactions following discontinuance of fluoxetine therapy may therefore be more delayed. Although clinical experience to date has not revealed substantial evidence of drug-seeking behavior or a withdrawal syndrome associated with discontinuance of fluoxetine therapy, it is difficult to predict from the limited data currently available the extent to which a CNS-active drug like fluoxetine may be misused, diverted, and/or abused.

Despite the lack of substantial evidence for abuse potential or dependence liability, clinicians should carefully evaluate patients for a history of substance abuse prior to initiating fluoxetine therapy. If fluoxetine therapy is initiated in patients with a history of substance abuse, such patients should be monitored closely for signs of misuse or abuse of the drug (e.g., development of tolerance, use of increasing doses, drug-seeking behavior).

The potential for misuse of fluoxetine by depressed patients with concurrent eating disorders and/or those who may seek the drug for its appetite-suppressant effects also should be considered. One patient with an undisclosed history of anorexia nervosa and laxative abuse who was given fluoxetine for depression ingested larger-than-prescribed doses (e.g., 90–120 mg/day) and lost 9.1 kg within 2 months; this patient falsely claimed mood improvement in order to continue receiving the drug for its anorectic and weight-reducing effects.

Fluoxetine has produced phospholipidosis following long-term administration in animals; however, no evidence of phospholipidosis has been reported in humans receiving the drug to date. Additional study is needed to determine the clinical importance of these findings in patients receiving long-term fluoxetine therapy. (See Pharmacology: Effects on Phospholipids.)

Pharmacology

The pharmacology of fluoxetine is complex and in many ways resembles that of other antidepressant agents, particularly those agents (e.g., citalopram, clomipramine, escitalopram, fluvoxamine, paroxetine, sertraline, trazodone) that predominantly potentiate the pharmacologic effects of serotonin (5-HT). Like other selective serotonin-reuptake inhibitors (SSRIs), fluoxetine is a potent and highly selective reuptake inhibitor of serotonin and has little or no effect on other neurotransmitters.

■ **Nervous System Effects** The precise mechanism of antidepressant action of fluoxetine is unclear, but the drug has been shown to selectively inhibit the reuptake of serotonin at the presynaptic neuronal membrane. Fluoxetine-induced inhibition of serotonin reuptake causes increased synaptic concentrations of serotonin in the CNS, resulting in numerous functional changes associated with enhanced serotonergic neurotransmission. Like other selective serotonin-reuptake inhibitors (fluvoxamine, paroxetine, sertraline), fluoxetine appears to have minimal or no effect on the reuptake of norepinephrine or dopamine and does not exhibit clinically important anticholinergic, antihistaminic, or α_1-adrenergic blocking activity at usual therapeutic dosages.

Although the mechanism of antidepressant action of antidepressant agents may involve inhibition of the reuptake of various neurotransmitters (i.e., norepinephrine, serotonin) at the presynaptic neuronal membrane, it has been suggested that postsynaptic receptor modification is mainly responsible for the antidepressant action observed during long-term administration of antidepressant agents. During long-term therapy with most antidepressants (e.g., tricyclic antidepressants, monoamine oxidase [MAO] inhibitors), these adaptive changes generally consist of subsensitivity of the noradrenergic adenylate cyclase system in association with a decrease in the number of β-adrenergic receptors; such effects on noradrenergic receptor function commonly are referred to as "down-regulation." In addition, some antidepressants reportedly decrease the number of 5-HT binding sites following chronic administration. Fluoxetine may exert its antidepressant activity by somewhat different mechanisms than those usually associated with tricyclic and some other antidepressants. Although some evidence indicates that long-term administration of fluoxetine does not substantially decrease the number of β-adrenergic binding sites or reduce the sensitivity of β-adrenergic receptors, a decrease in the number of β-adrenergic binding sites in the brain has been reported in at least one study in animals. Data regarding the effects of fluoxetine on the number of serotonin (5-HT_1 and/or 5-HT_2) binding sites have been conflicting, with either no change or a reduction in the number of binding sites being reported during chronic administration of the drug. Increased postsynaptic receptor binding of GABA B also has been reported following prolonged administration of many antidepressants, including fluoxetine. The clinical importance of these findings for fluoxetine has not been fully elucidated to date, and further study is needed to determine the role, if any, of binding site alteration in the antidepressant action of fluoxetine and other antidepressants.

The precise mechanism of action responsible for the efficacy of fluoxetine in the treatment of obsessive-compulsive disorder is unclear. However, based on the efficacy of other selective serotonin-reuptake inhibitors (e.g., fluvoxamine, paroxetine, sertraline) and clomipramine in the treatment of obsessive-compulsive disorder and the potency of these drugs in inhibiting serotonin reuptake, a serotonergic hypothesis has been developed to explain the pathogenesis of the condition. The hypothesis postulates that a dysregulation of serotonin is responsible for obsessive-compulsive disorder and that fluoxetine and these other agents are effective because they correct this imbalance. Although the available evidence supports the serotonergic hypothesis of obsessive-compulsive disorder, additional studies are necessary to confirm this hypothesis.

Serotonergic Effects Fluoxetine is a highly selective inhibitor of serotonin reuptake at the presynaptic neuronal membrane. In addition, the potency and selectivity of serotonin-reuptake inhibition exhibited by fluoxetine's principal metabolite, norfluoxetine, appear to be similar to those of the parent drug. Fluoxetine- and norfluoxetine-induced inhibition of serotonin reuptake causes increased synaptic concentrations of serotonin, resulting in numerous functional changes associated with enhanced serotonergic neurotransmission.

Data from in vitro studies suggest that fluoxetine is approximately equivalent to or less potent than clomipramine as a serotonin-reuptake inhibitor; however, in vivo studies indicate that the serotonin-reuptake inhibiting effect of fluoxetine may be more potent than that of clomipramine on a weight as well as an equimolar basis. This apparent discrepancy may be explained at least in part by the relatively long elimination half-lives of fluoxetine and norfluoxetine. In addition, metabolism via *N*-demethylation decreases the potency and specificity of serotonin-reuptake inhibition of clomipramine but not fluoxetine. Data from both in vivo and in vitro studies indicate that fluoxetine also is a more potent serotonin-reuptake inhibitor than other currently available antidepressant agents, including imipramine and trazodone. Fluoxetine appears to have practically no affinity for serotonin (e.g., 5-HT_1 and 5-HT_2) receptors in vitro, although limited in vivo data suggest that the drug may bind to low-affinity sites on 5-HT receptors.

Fluoxetine appears to decrease the turnover of serotonin in the CNS, probably as a result of a decrease in the rate of serotonin synthesis. The drug reportedly decreases brain concentrations of 5-hydroxyindoleacetic acid (5-HIAA), the principal metabolite of serotonin; reduces the uptake of radiolabeled tryptophan by synaptosomes; and reduces the rate of conversion of tryptophan to serotonin. Fluoxetine also inhibits spontaneous firing of serotonergic neurons in the dorsal raphe nucleus.

Like other serotonin-reuptake inhibitors, administration of fluoxetine alone does not produce the serotonin behavioral syndrome (a characteristic behavioral pattern caused by central stimulation of serotonin activity) in animals. However, the drug potentiates the serotonin behavioral syndrome induced by oxitriptan (l-5-hydroxytryptophan, l-5HTP), MAO inhibitors, and MAO inhibitors combined with tryptophan.

Effects on Other Neurotransmitters Like other selective serotonin-reuptake inhibitors, fluoxetine appears to have little or no effect on the reuptake of other neurotransmitters such as norepinephrine or dopamine. In addition, the drug appears to have a substantially higher selectivity ratio of serotonin-to-norepinephrine reuptake inhibiting activity than tricyclic antidepressant agents, including clomipramine.

Unlike tricyclic and some other antidepressants, fluoxetine does not exhibit clinically important anticholinergic, α_1-adrenergic blocking, or antihistaminic activity at usual therapeutic dosages. As a result, the incidence of adverse effects commonly associated with blockade of muscarinic cholinergic receptors

(e.g., dry mouth, blurred vision, urinary retention, constipation, confusion), α_1-adrenergic receptors (e.g., orthostatic hypotension), and histamine H_1- and H_2-receptors (e.g., sedation) is lower in fluoxetine-treated patients. In vitro studies have demonstrated that the drug possesses only weak affinity for α_1- and α_2-adrenergic, β-adrenergic, H_1 and H_2, muscarinic, opiate, GABA-benzodiazepine, and dopamine receptors.

Effects on Sleep Like tricyclic and most other antidepressants, fluoxetine suppresses rapid eye movement (REM) sleep. Although not clearly established, there is some evidence that the REM-suppressing effects of antidepressant agents may contribute to the antidepressant activity of these drugs. In animal studies, fluoxetine produces a dose-related suppression of REM sleep; the drug generally appears to reduce the amount of REM sleep by increasing REM latency (the time to onset of REM sleep) and by decreasing the number rather than the duration of REM episodes. Limited data in animals suggest that REM rebound does not occur following discontinuance of fluoxetine. The precise mechanism has not been fully elucidated, but results of animal studies indicate that fluoxetine's effects on REM sleep are serotonergically mediated. Like other specific serotonin-reuptake inhibitors (e.g., zimeldine [previously zimelidine]), the effects of fluoxetine on non-REM sleep reported to date have been variable and do not appear to be as clearly defined as those of tricyclic antidepressants, which usually increase slow-wave sleep.

Effects on EEG Limited data currently are available regarding the effects of fluoxetine on the EEG. Substantial EEG changes did not occur following oral administration of single 30-mg doses of the drug in healthy individuals. An increase in alpha activity and a decrease in fast beta activity and slow activity were noted following single oral 60-mg doses in this study; such changes are characteristic of desipramine-type antidepressants and appear to indicate increased vigilance. Single 75-mg doses of fluoxetine produced an increase in slow and fast activity and a decrease in alpha activity; such EEG changes are similar to those observed with amitriptyline and imipramine and suggest possible sedative activity.

Effects on Psychomotor Function Fluoxetine does not appear to cause clinically important sedation and does not interfere with psychomotor performance. Controlled studies in healthy young adults 21–45 of years and in adults with major depression did not demonstrate any adverse effects on psychomotor performance in those receiving the drug. No adverse effects on psychomotor performance or cognitive function were observed in men with depression older than 60 years of age who received 20-mg doses of fluoxetine in a controlled study. Results of this study showed that overall cognition, as assessed by the critical flicker fusion thresholds test, generally was better in patients receiving fluoxetine than in those receiving amitriptyline (a tricyclic antidepressant); however, less sedating tricyclic antidepressants (e.g., desipramine) were not included in the study and it is possible that fluoxetine may not have such an advantage over these other agents. In a controlled study evaluating the effects of fluoxetine (20 mg daily for 22 days) on psychomotor performance and car driving in healthy adults, the drug did not affect the highway driving or the car following tests but slightly impaired performance in correctly detecting changes in visual signals was evident in the sustained attention test.

Analgesic Effects Like other serotonin-reuptake inhibitors (e.g., zimeldine), fluoxetine exhibits analgesic activity in some analgesic test systems when administered alone in animals, but the lack of such effects observed in other test systems suggests that demonstration of analgesic activity may be test-dependent. Fluoxetine has potentiated opiate agonist-induced analgesia in most but not all studies, possibly as a result of the drug's ability to enhance serotonergic neurotransmission. The clinical importance of these effects in the management of acute and chronic pain remains to be determined.

Effects on Respiration Usual therapeutic dosages of fluoxetine do not appear to affect respiration substantially in humans; however, the effect of higher dosages of the drug on respiratory function remains to be established. In animals, administration of single 20-mg/kg doses of fluoxetine reportedly increased blood Po_2 concentrations but did not alter blood Pco_2 concentrations. The drug also has been shown to attenuate morphine-induced respiratory depression, although the precise mechanism for this effect has not been established.

Effects on Thermoregulation Data are conflicting regarding the effect of fluoxetine on thermoregulation. In animals, fluoxetine has produced dose-dependent hypothermia in some studies, suggesting that serotonin may play a role in thermoregulation, but the drug has produced only slight or minimal hypothermia in other studies.

The drug has been used safely in at least one patient with established susceptibility to malignant hyperthermia; however, additional experience with the drug is needed to confirm the safety of fluoxetine in patients known to be susceptible to this condition.

■ **Cardiovascular Effects** The cardiovascular effects of fluoxetine have been studied in animals and to a limited extent in humans. Unlike some other antidepressant agents (e.g., tricyclic antidepressants, MAO inhibitors), fluoxetine has been associated with only minimal cardiovascular effects. The absence of substantial anticholinergic activity, α_1-adrenergic blocking activity, catecholamine-potentiating effects, and quinidine-like cardiotoxic effects appears to be the principal reason for the general lack of cardiovascular effects associated with fluoxetine.

Fluoxetine does not exhibit clinically important α_1-adrenergic blocking activity and does not inhibit catecholamine reuptake. Unlike tricyclic antidepressants, fluoxetine does not block the neuronal reuptake of norepinephrine and therefore does not potentiate the pressor response associated with administration of norepinephrine. In addition, the drug does not inhibit the reuptake of and has no effect on the pressor response to tyramine.

Fluoxetine does not appear to have substantial arrhythmogenic activity; however, safety of the drug in patients with a recent history of myocardial infarction or unstable cardiovascular disease has not been adequately evaluated to date. Fluoxetine generally does not appear to affect cardiac conduction, and clinically important ECG changes have not been reported in patients without preexisting heart disease receiving therapeutic dosages of the drug. Unlike tricyclic antidepressants, which commonly cause an increase in heart rate, fluoxetine reportedly reduces heart rate by an average of about 3 beats/minute in patients receiving usual therapeutic dosages of the antidepressant. (See Cautions: Cardiovascular Effects.) Unlike tricyclics, the drug does not appear to exhibit direct quinidine-like cardiotoxic activity, although the cardiovascular effects associated with fluoxetine overdosage have not been fully established to date. (See Acute Toxicity.)

■ **Effects on Appetite and Body Weight** Like some other serotonergic agents (e.g., fenfluramine [no longer commercially available in the US], zimeldine), fluoxetine possesses anorectic activity. Although the precise mechanism has not been clearly established, results of animal studies indicate that the drug's appetite-inhibiting action may result from serotonin-reuptake blockade and the resultant increase in serotonin availability at the neuronal synapse. Following administration of single and multiple doses of fluoxetine in both meal-fed and free-feeding animals, a reduction in food intake usually occurs, particularly at relatively high doses of the drug (i.e., 10 mg/kg). The anorectic effect of fluoxetine appears to be potentiated by oxitriptan. Tolerance to the anorectic effect of fluoxetine has not developed following short-term administration in humans and animals; however, long-term studies in humans are necessary to fully determine whether tolerance develops during chronic therapy with the drug.

In animal studies, fluoxetine has been shown to suppress palatability-induced food consumption (as determined by the volume of sweetened versus plain water ingested). Like fenfluramine, fluoxetine also appears to selectively suppress carbohydrate and overall food intake while maintaining protein intake. Such carbohydrate intake-suppressing and protein-sparing effects may be of potential clinical importance in the management of obesity; however, additional study is necessary. (See Uses: Obesity.) Fluoxetine therapy also has resulted in decreases in body weight in normal-weight and obese animals as well as in depressed, nondepressed, and obese individuals receiving the drug. (See Uses: Obesity and also see Cautions: Metabolic Effects.)

■ **Effects on Alcohol Intake** Like some other serotonergic agents, fluoxetine produces a dose-dependent decrease in voluntary alcohol intake in normal and alcohol-preferring animals. Like some other serotonin-reuptake inhibitors (e.g., citalopram, zimeldine), fluoxetine has been shown to reduce alcohol consumption in a limited number of heavy drinkers receiving 60 mg of the drug daily. Because serotonin appears to be involved in the regulation of alcohol intake, it has been suggested that fluoxetine may attenuate alcohol consumption via enhanced serotonergic neurotransmission. In addition, there is some evidence that such effects may be at least partially mediated by the renin-angiotensin-aldosterone system. (See Uses: Alcohol Dependence and see Drug Interactions: Alcohol.)

■ **Neuroendocrine Effects** Fluoxetine affects the endocrine system. Like other selective inhibitors of serotonin reuptake, the drug has produced a dose-related increase in serum corticosterone concentrations in animals. Fluoxetine also reportedly potentiates oxitriptan-induced elevation in serum corticosterone concentrations. Such effects appear to be serotonergically mediated. Following parenteral administration of fluoxetine in animals, the elevation in serum corticosterone concentration generally lasts only a few hours, although fluoxetine-induced inhibition of serotonin reuptake is known to persist for longer than 24 hours. Therefore, it has been suggested that other compensatory mechanisms, possibly including decreased firing of serotonergic neurons, may contribute to the restoration of normal hypothalamic-pituitary-adrenal (HPA) axis function despite prolonged blockade of serotonin reuptake by the drug. Fluoxetine also has increased corticotropin (ACTH) and vasopressin (antidiuretic hormone, ADH) concentrations in peripheral plasma and has increased corticotropin and corticotropin-releasing factor (CRF, corticoliberin) concentrations in hypophysial portal blood. These effects may represent the initial step in fluoxetine-induced elevation of plasma corticosterone concentrations.

The effects of fluoxetine on serum prolactin concentrations have not been clearly established. In some animal studies, fluoxetine potentiated tryptophan-induced increases in serum prolactin concentrations, although administration of the drug alone in animals and humans usually does not substantially alter prolactin concentrations. However, administration of fluoxetine alone reportedly increased serum prolactin concentrations in young but not old male rats in one study. Fluoxetine-induced effects on prolactin secretion appear to be serotonergically mediated.

■ **Effects on Phospholipids** Like many other cationic, amphiphilic drugs (e.g., amiodarone, fenfluramine, imipramine, ranitidine), fluoxetine reportedly increases tissue phospholipid concentrations following chronic ad-

ministration in animal studies; however, such effects have not been demonstrated in humans receiving fluoxetine to date. Histologic examination following long-term (i.e., 1–12 months) fluoxetine administration in animals has revealed the presence of characteristic concentric, lamellar inclusion bodies associated with phospholipidosis in alveolar macrophages of the lung, Kupffer cells of the liver, and adrenal cortical cells; an increase in phospholipid content of the lung also has been reported. Fluoxetine-induced phospholipid accumulation in these animals was reversible within 1–2 months following discontinuance of the drug.

Studies in humans receiving fluoxetine have not revealed biochemical or clinical evidence of drug-induced phospholipidosis to date. There was no evidence of increased phospholipid content or changes in lamellar inclusion bodies in peripheral blood lymphocytes of either healthy individuals receiving 1 month of fluoxetine therapy or depressed patients receiving long-term (0.9–2.6 years) therapy with the drug. In addition, ophthalmologic examination and chest radiographs in patients receiving fluoxetine during clinical studies have not revealed evidence of phospholipidosis induced by the drug. Although data from clinical studies suggest that fluoxetine-induced phospholipidosis is unlikely to occur in humans receiving long-term therapy with the drug, further study is needed to fully determine whether the phospholipidosis observed in animal studies is clinically important in humans receiving therapeutic dosages of the drug.

■ **Other Effects** Fluoxetine has demonstrated some antimyoclonic activity in animals and humans when used in combination with oxitriptan. Although the mechanism of fluoxetine's antimyoclonic activity has not been fully elucidated, some forms of myoclonus appear to be related to impaired serotonergic neurotransmission. Therefore, it has been suggested that fluoxetine-induced enhancement of serotonergic neurotransmission via serotonin-reuptake blockade potentially may contribute to oxitriptan-induced increases in CNS serotonin concentrations in the management of this condition. (See Uses: Myoclonus.)

Fluoxetine also has reduced cataplexy in both humans and animals. (See Uses: Cataplexy.)

Fluoxetine reportedly has produced a dose-related elevation in plasma β-endorphin and β-lipotropin concentrations in healthy individuals receiving single oral doses of the drug.

Pharmacokinetics

In all human studies described in the Pharmacokinetics section, fluoxetine was administered as the hydrochloride salt.

■ **Absorption** Fluoxetine hydrochloride appears to be well absorbed from the GI tract following oral administration. The oral bioavailability of fluoxetine in humans has not been fully elucidated to date, but at least 60–80% of an oral dose appears to be absorbed. However, the relative proportion of an oral dose reaching systemic circulation unchanged currently is not known. The oral conventional capsules and tablets, delayed-release capsules, and solution of fluoxetine hydrochloride reportedly are bioequivalent. However, onset of absorption of fluoxetine hydrochloride delayed-release capsules (Prozac® Weekly®) is delayed 1–2 hours relative to the onset of absorption when the drug is administered as a conventional preparation. Limited data from animals suggest that the drug may undergo first-pass metabolism and extraction in the liver and/or lung following oral administration. In these animals (beagles), approximately 72% of an oral dose reached systemic circulation unchanged. Food appears to cause a slight decrease in the rate, but not the extent, of absorption of fluoxetine in humans.

Peak plasma fluoxetine concentrations usually occur within 4–8 hours (range: 1.5–12 hours) after oral administration of conventional preparations. Following oral administration of a single 40-mg dose of the drug in healthy fasting adults, peak plasma concentrations of approximately 15–55 ng/mL are attained. Peak plasma fluoxetine concentrations following administration of single oral doses of 20–80 mg are approximately proportional and are linearly related to dose, although there appears to be considerable interindividual variation in plasma concentrations attained with a given dose. The manufacturer states that the peak plasma concentrations achieved following weekly administration of fluoxetine 90-mg delayed-release capsules are in the range of the average concentrations achieved following daily administration of 20-mg conventional preparations; however, average trough concentrations are reported to be lower following weekly administration of the delayed-release preparation. Peak-to-trough fluctuations in plasma concentrations of fluoxetine and norfluoxetine (the principal metabolite) reportedly are greater following weekly administration of the delayed-release capsules (164 and 43%, respectively) compared with daily administration of conventional preparations (24 and 17%, respectively).

Preliminary data suggest that fluoxetine may exhibit nonlinear accumulation following multiple dosing. (See Pharmacokinetics: Elimination.) The relatively slow elimination of fluoxetine and its active metabolite, norfluoxetine, leads to clinically important accumulation of these active species in chronic use and delayed attainment of steady state, even when a fixed dose is used. In healthy adults receiving 40 mg of fluoxetine daily for 30 days, plasma concentrations of 91–302 and 72–258 ng/mL of fluoxetine and norfluoxetine, respectively, were attained. These plasma concentrations of fluoxetine were higher than those predicted by single-dose studies because fluoxetine's metabolism is not proportional to dose. In addition, prolonged administration of the drug and/or patient's disease states did not appear to affect steady-state concentrations. In one study, steady-state plasma fluoxetine and norfluoxetine concentrations did not differ substantially among healthy individuals receiving 4 weeks of fluoxetine therapy, depressed patients receiving 5 weeks of fluoxetine therapy, or depressed patients receiving more than a year of fluoxetine therapy.

Average steady-state fluoxetine and norfluoxetine concentrations, however, were affected by patient age. In pediatric patients with major depressive disorder or obsessive-compulsive disorder (OCD) who received fluoxetine 20 mg daily for up to 62 days, average steady-state concentrations of fluoxetine and norfluoxetine in children 6–12 years of age were 2- and 1.5-fold higher, respectively, than in adolescents 13–17 years of age who received the same fluoxetine regimen. These results are consistent with those observed in another study in 94 pediatric patients 8–17 years of age diagnosed with major depressive disorder, and can be almost entirely explained by differences in children's weight. Higher average steady-state fluoxetine and norfluoxetine concentrations also were observed in children relative to adults; however, these concentrations were within the range of concentrations observed in the adult population. As in adults, fluoxetine and norfluoxetine accumulated extensively following multiple oral dosing. Following daily oral administration of the drug, steady-state plasma fluoxetine and norfluoxetine concentrations generally are achieved within about 2–4 weeks.

The manufacturer states that average steady-state plasma fluoxetine concentrations are approximately 50% lower with weekly administration of the 90-mg delayed-release capsules compared with daily administration of a 20-mg conventional preparation. In patients being switched from daily therapy with fluoxetine 20-mg conventional preparations to weekly therapy with fluoxetine 90-mg delayed-release capsules, peak plasma fluoxetine concentrations reportedly were 1.7 times higher with the weekly regimen than with the established daily regimen when there was no transition period (i.e., therapy with delayed-release fluoxetine was initiated the day after the last daily dose of fluoxetine 20 mg). When weekly therapy was initiated one week after the last daily dose of fluoxetine 20 mg, peak plasma fluoxetine concentrations for the 2 regimens were similar. (See Dosage and Administration: Dosage.)

The onset of antidepressant activity following oral administration of fluoxetine hydrochloride usually occurs within the first 1–3 weeks of therapy, but optimum therapeutic effect usually requires 4 weeks or more of therapy with the drug. Maximal EEG changes and behavioral changes on psychometric tests reportedly occur about 8–10 hours after single oral doses of the drug; the delay in maximal CNS effects compared with achievement of peak plasma fluoxetine concentrations may relate to formation of an active metabolite or to delayed distribution of the parent drug and its principal metabolite into the CNS.

The relationship between plasma fluoxetine and norfluoxetine concentrations and the therapeutic and/or toxic effects of the drug has not been clearly established. In a group of patients receiving fluoxetine for the management of major depressive disorder, there was no correlation between plasma fluoxetine, norfluoxetine, or total fluoxetine plus norfluoxetine concentrations and either the antidepressant response or the weight-reducing effect of the drug.

■ **Distribution** Distribution of fluoxetine and its metabolites into human body tissues and fluids has not been fully characterized. Limited pharmacokinetic data obtained during long-term administration of fluoxetine to animals suggest that the drug and some of its metabolites, including norfluoxetine, are widely distributed in body tissues, with highest concentrations occurring in the lungs and liver. The drug crosses the blood-brain barrier in humans and animals. In animals, fluoxetine:norfluoxetine ratios reportedly were similar in the cerebral cortex, corpus striatum, hippocampus, hypothalamus, brain stem, and cerebellum 1 hour after administration of a single dose of the drug.

The apparent volumes of distribution of fluoxetine and norfluoxetine in healthy adults each reportedly average 20–45 L/kg. Limited data suggest that the volume of distribution of fluoxetine is not altered substantially following multiple dosing. The apparent volume of distribution of norfluoxetine reportedly is higher in patients with cirrhosis than in healthy individuals, although this difference may reflect decreases in the rates of formation and elimination of the metabolite rather than changes in volume of distribution. The volumes of distribution of fluoxetine and norfluoxetine do not appear to be altered substantially in patients with renal impairment.

At in vitro plasma concentrations of 200–1000 ng/mL, fluoxetine is approximately 94.5% bound to plasma proteins, including albumin and α_1-acid glycoprotein (α_1-AGP); the extent of protein binding appears to be independent of plasma concentration. The extent of fluoxetine protein binding does not appear to be altered substantially in patients with hepatic cirrhosis or renal impairment, including those undergoing hemodialysis.

It is not known whether fluoxetine or its metabolites cross the placenta in humans, but fluoxetine and norfluoxetine reportedly cross the placenta in rats following oral administration. Fluoxetine and norfluoxetine are distributed into milk. Limited data indicate that concentrations of the drug and this metabolite in milk are about 20–30% of concurrent plasma concentrations.

■ **Elimination** Fluoxetine and norfluoxetine, the principal metabolite, are eliminated slowly. Following a single oral dose of fluoxetine in healthy adults, the elimination half-life of fluoxetine reportedly averages approximately 2–3 days (range: 1–9 days) and that of norfluoxetine averages about 7–9 days (range: 3–15 days). The plasma half-life of fluoxetine exhibits considerable interindividual variation, which may be related to genetic differences in the

rate of *N*-demethylation of the drug in the liver. The absence of either a bimodal or trimodal distribution of clearance values suggests that the rate of such metabolism may be under polygenic control. The half-life of fluoxetine reportedly is prolonged (to approximately 4–5 days) after administration of multiple versus single doses, suggesting a nonlinear pattern of drug accumulation during long-term administration. Norfluoxetine appears to exhibit dose-proportional pharmacokinetics following multiple dosing, although limited data indicate that the rate of formation of the metabolite is decreased slightly once steady-state plasma concentrations have been achieved.

Following oral administration of single doses of fluoxetine in healthy individuals, total apparent plasma clearances of fluoxetine and norfluoxetine average approximately 346 mL/minute (range: 94–703 mL/minute) and 145 mL/minute (range: 61–284 mL/minute), respectively. Limited data suggest that plasma clearance of fluoxetine decreases by approximately 75% following multiple oral doses of the drug once steady-state plasma fluoxetine concentrations have been achieved. Plasma clearances of fluoxetine and norfluoxetine also reportedly are decreased in patients with chronic liver disease (e.g., cirrhosis). Evidence from single-dose studies indicates that clearances of the drug and its principal metabolite are not altered substantially in patients with renal impairment.

The exact metabolic fate of fluoxetine has not been fully elucidated. The drug appears to be metabolized extensively, probably in the liver, to norfluoxetine and several other metabolites. Norfluoxetine (desmethylfluoxetine), the principal metabolite, is formed by *N*-demethylation of fluoxetine, which may be under polygenic control. The potency and selectivity of norfluoxetine's serotonin-reuptake inhibiting activity appear to be similar to those of the parent drug. Both fluoxetine and norfluoxetine undergo conjugation with glucuronic acid in the liver, and limited evidence from animals suggests that both the parent drug and its principal metabolite also undergo *O*-dealkylation to form *p*-trifluoromethylphenol, which subsequently appears to be metabolized to hippuric acid.

Following oral administration, fluoxetine and its metabolites are excreted principally in urine. In healthy individuals, approximately 60% of an orally administered, radiolabeled dose of fluoxetine is excreted in urine within 35 days, with approximately 72.8% of excreted drug as unidentified metabolites, 10% as norfluoxetine, 9.5% as norfluoxetine glucuronide, 5.2% as fluoxetine glucuronide, and 2.5% as unchanged drug. Approximately 12% of the dose was eliminated in feces within 28 days following oral administration, but the relative proportion of unabsorbed versus absorbed drug that is excreted in feces (e.g., via biliary elimination) is not known.

The effect of age on the elimination of fluoxetine has not been fully elucidated. Single-dose studies suggest that the pharmacokinetics of fluoxetine in healthy geriatric individuals do not differ substantially from those in younger adults. However, because the drug has a relatively long half-life and nonlinear disposition following multiple-dose administration, single-dose studies are not sufficient to exclude the possibility of altered pharmacokinetics in geriatric individuals, particularly those with systemic disease and/or in those receiving multiple medications concomitantly. The elimination half-lives of fluoxetine and norfluoxetine may be prolonged in patients with hepatic impairment. Following a single oral dose of the drug in patients with hepatic cirrhosis, the elimination half-lives of fluoxetine and norfluoxetine reportedly average approximately 7 and 12 days, respectively.

The elimination half-lives of fluoxetine and norfluoxetine do not appear to be altered substantially in patients with renal impairment following oral administration of single doses of the drug, although multiple-dose studies are needed to determine whether accumulation of the parent drug and/or its metabolites occurs during long-term therapy in such patients.

Fluoxetine and norfluoxetine are not removed substantially by hemodialysis. Because of the large volume of distribution and extensive protein binding of the drug and its principal metabolite, peritoneal dialysis, forced diuresis, hemoperfusion, and/or exchange transfusion also are likely to be ineffective in removing substantial amounts of fluoxetine and norfluoxetine from the body.

Chemistry and Stability

■ **Chemistry** Fluoxetine, a selective serotonin-reuptake inhibitor (SSRI) antidepressant, is a phenylpropylamine-derivative. The drug differs structurally from other selective serotonin-reuptake inhibitor antidepressants (e.g., citalopram, paroxetine, sertraline) and also differs structurally and pharmacologically from other currently available antidepressant agents (e.g., tricyclic antidepressants, monoamine oxidase inhibitors).

Fluoxetine contains a *p*-trifluoromethyl substituent that appears to contribute to the drug's high selectivity and potency for inhibiting serotonin reuptake, possibly as a result of its electron-withdrawing effect and lipophilicity. The commercially available drug is a racemic mixture of 2 optical isomers. Limited in vivo and in vitro data suggest that the pharmacologic activities of the optical isomers do not differ substantially, although the dextrorotatory isomer appears to have slightly greater serotonin-reuptake inhibiting activity and a longer duration of action than the levorotatory isomer.

Fluoxetine is commercially available as the hydrochloride salt, which occurs as a white to off-white crystalline solid and has a solubility of 14 mg/mL in water.

■ **Stability** Fluoxetine hydrochloride capsules and the oral solution should be stored in tight, light-resistant containers, both at 15–30°C. Fluoxetine tablets and delayed-release capsules should be stored at 15–30°C.

Preparations

Excipients in commercially available drug preparations may have clinically important effects in some individuals; consult specific product labeling for details.

Fluoxetine Hydrochloride

Oral		
Capsules	10 mg (of fluoxetine)*	**Fluoxetine Hydrochloride Capsules**
		Prozac®, Pulvules®, Dista
		Sarafem®, Pulvules®, Lilly
	20 mg (of fluoxetine)*	**Fluoxetine Hydrochloride Capsules**
		Prozac®, Pulvules®, Dista
		Sarafem®, Pulvules®, Lilly
	40 mg (of fluoxetine)*	**Fluoxetine Hydrochloride Capsules**
		Prozac®, Pulvules®, Dista
Capsules, delayed-release (containing enteric-coated pellets)	90 mg (of fluoxetine)	**Prozac®, Weekly, Dista**
Solution	20 mg (of fluoxetine) per 5 mL*	**Fluoxetine Hydrochloride Oral Solution**
		Prozac®, Dista
Tablets	10 mg (of fluoxetine)*	**Fluoxetine Hydrochloride Tablets** (scored)
		Sarafem®, Warner Chilcott
	15 mg (of fluoxetine)*	**Sarafem®, Warner Chilcott**
	20 mg (of fluoxetine)*	**Fluoxetine Hydrochloride Tablets**
		Sarafem®, Warner Chilcott

*available from one or more manufacturer, distributor, and/or repackager by generic (nonproprietary) name

Fluoxetine Hydrochloride Combinations

Oral		
Capsules	25 mg (of fluoxetine) with Olanzapine 6 mg	**Symbyax® (combination), Lilly**
	25 mg (of fluoxetine) with Olanzapine 12 mg	**Symbyax® (combination), Lilly**
	50 mg (of fluoxetine) with Olanzapine 6 mg	**Symbyax® (combination), Lilly**
	50 mg (of fluoxetine) with Olanzapine 12 mg	**Symbyax® (combination), Lilly**

†Use is not currently included in the labeling approved by the US Food and Drug Administration

Paroxetine

■ Paroxetine hydrochloride and paroxetine mesylate, selective serotonin-reuptake inhibitors (SSRIs), are antidepressant agents.

Uses

Paroxetine is commercially available in the US as paroxetine hydrochloride (e.g., Paxil®, Paxil CR®) and as paroxetine mesylate (i.e., Pexeva®). The US Food and Drug Administration (FDA) considers paroxetine mesylate (Pexeva®) conventional tablets to be a pharmaceutical *alternative* (as described in section 505[b][2] of the Federal Food, Drug, and Cosmetic Act) and not a pharmaceutical (generic) equivalent to paroxetine hydrochloride conventional tablets (e.g., Paxil®), since both contain the same active moiety (paroxetine) but have different salts. The clinical studies that established efficacy of paroxetine in various conditions have been conducted with paroxetine hydrochloride. Because paroxetine hydrochloride and paroxetine mesylate contain the same active moiety (paroxetine), clinical efficacy is expected to be similar between the 2 different salts.

Paroxetine hydrochloride conventional tablets and oral suspension are used in the treatment of major depressive disorder, obsessive-compulsive disorder, panic disorder with or without agoraphobia, social phobia (social anxiety disorder), generalized anxiety disorder, and posttraumatic stress disorder. Paroxetine hydrochloride extended-release tablets are used in the treatment of major depressive disorder, panic disorder with or without agoraphobia, social phobia, and premenstrual dysphoric disorder (PMDD). Paroxetine mesylate conventional tablets are used in the treatment of major depressive disorder, obsessive-compulsive disorder, and panic disorder with or without agoraphobia. In addition, paroxetine has been used in the treatment of premature ejaculation†,

of therapy or during periods of dosage adjustment. FDA recommends providing written patient information (medication guide) explaining risks of suicidality each time the drug is dispensed.

Risk of orthostatic hypotension, especially during initial dosage titration and at times of reinitiation of therapy or increases in dosage.

Risk of somnolence and impairment of judgment, thinking, or motor skills; avoid driving, operating machinery, or performing hazardous tasks until effects on the individual are known.

Importance of avoiding alcohol during quetiapine therapy.

Importance of informing clinicians of existing or contemplated concomitant therapy, including prescription and OTC drugs, as well as any concomitant illnesses (e.g., diabetes mellitus).

Importance of women informing clinicians if they are or plan to become pregnant or plan to breast-feed.

Importance of avoiding overheating or dehydration.

Importance of informing patients of other important precautionary information. (See Cautions.)

Overview (see Users Guide). **For additional information on this drug until a more detailed monograph is developed and published, the manufacturer's labeling should be consulted. It is *essential* that the manufacturer's labelling be consulted for more detailed information on usual cautions, precautions, contraindications, potential drug interactions, laboratory test interferences, and acute toxicity.**

Preparations

Excipients in commercially available drug preparations may have clinically important effects in some individuals; consult specific product labeling for details.

Quetiapine Fumarate

Oral		
Tablets, film-coated	25 mg (of quetiapine)	Seroquel®, AstraZeneca
	50 mg (of quetiapine)	Seroquel®, AstraZeneca
	100 mg (of quetiapine)	Seroquel®, AstraZeneca
	200 mg (of quetiapine)	Seroquel®, AstraZeneca
	300 mg (of quetiapine)	Seroquel®, AstraZeneca
	400 mg (of quetiapine)	Seroquel®, AstraZeneca

Risperidone

■ Risperidone has been described as an atypical or second-generation antipsychotic agent.

Uses

■ **Psychotic Disorders** Risperidone is used for the symptomatic management of psychotic disorders. Drug therapy is integral to the management of acute psychotic episodes and accompanying violent behavior in patients with schizophrenia and generally is required for long-term stabilization to sustain symptom remission or control and to minimize the risk of relapse. Antipsychotic agents are the principal class of drugs used for the management of all phases of schizophrenia. Patient response and tolerance to antipsychotic agents are variable, and patients who do not respond to or tolerate one drug may be successfully treated with an agent from a different class or with a different adverse effect profile.

Schizophrenia and Other Psychotic Disorders Efficacy of oral risperidone for the management of psychotic disorders has been established by controlled studies of 4–8 weeks' duration principally in patients with schizophrenic disorders in hospital settings. Schizophrenia is a major psychotic disorder that frequently has devastating effects on various aspects of the patient's life and carries a high risk of suicide and other life-threatening behaviors. Manifestations of schizophrenia involve multiple psychologic processes, including perception (e.g., hallucinations), ideation, reality testing (e.g., delusions), emotion (e.g., flatness, inappropriate affect), thought processes (e.g., loose associations), behavior (e.g., catatonia, disorganization), attention, concentration, motivation (e.g., avolition, impaired intention and planning), and judgment. The principal manifestations of this disorder usually are described in terms of positive and negative (deficit) symptoms, and more recently, disorganized symptoms. Positive symptoms include hallucinations, delusions, bizarre behavior, hostility, uncooperativeness, and paranoid ideation, while negative symptoms include restricted range and intensity of emotional expression (affective flattening), reduced thought and speech productivity (alogia), anhedonia, apathy, and decreased initiation of goal-directed behavior (avolition). Disorganized symptoms include disorganized speech (thought disorder) and behavior and poor attention. For additional information on the symptomatic management of schizophrenia, including treatment recommendations and results of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study, see Schizophrenia and Other Psychotic Disorders under Uses: Psychotic Disorders, in the Phenothiazines General Statement 28:16.08.24.

In clinical studies principally in patients with schizophrenia, oral risperidone was more effective than placebo and at least as effective as typical (e.g., haloperidol, perphenazine) and certain atypical (e.g., olanzapine) antipsychotics in the treatment of schizophrenia. Data from limited clinical studies indicate that risperidone improves both positive and negative manifestations of schizophrenia, but that such improvements may not be substantially greater than those achieved by haloperidol, a typical antipsychotic. Risperidone was more effective than haloperidol in preventing relapse in adult outpatients with clinically stable schizophrenia or schizoaffective disorders who were assigned to receive either drug for a minimum of 1 year. In this study, approximately 25% of patients who received usual dosages of risperidone had relapsed by the end of the study compared with approximately 40% of those receiving usual dosages of haloperidol. In these studies, improvement in manifestations of schizophrenia was based on the results of various psychiatric rating scales, including the Brief Psychiatric Rating Scale (BPRS) that assesses factors such as anergy, thought disturbances, activation, hostility/suspiciousness, and anxiety/depression; the BPRS psychosis cluster that assesses factors such as conceptual disorganization, hallucinatory behavior, suspiciousness, and unusual thought content in actively psychotic schizophrenic patients; the Scale for the Assessment of Negative Symptoms (SANS); the Positive and Negative Syndrome Scale (PANSS); and the Clinical Global Impression (CGI) scale.

Because of their safety and efficacy, some authorities consider conventional antipsychotic agents or risperidone to be reasonable first-line drugs for the management of the acute phase of schizophrenia. Risperidone may be particularly useful in patients who experience extrapyramidal reactions with typical antipsychotic agents since the drug appears to cause fewer extrapyramidal reactions at clinically effective dosages. Some authorities state that risperidone or newer atypical antipsychotic agents (such as olanzapine) also may be advantageous in patients who have not responded adequately to therapy with a conventional antipsychotic agent. However, the efficacy of atypical antipsychotics, other than clozapine, in treatment-resistant schizophrenia has yet to be established, and the possible clinical benefits of risperidone therapy should be weighed against the potential drawbacks, including its higher cost compared with standard agents and the lack of a parenteral preparation of the drug.

Geriatric Considerations. Although risperidone has been studied for use in the management of psychosis and aggression in institutionalized geriatric patients with moderate to severe dementia of the Alzheimer's† type (Alzheimer's disease, presenile or senile dementia), vascular dementia†, or a combination of the 2 types of dementia (i.e., mixed dementia†), there is evidence that use of the drug in geriatric patients with dementia may be associated with an increased risk of adverse cerebrovascular events. In randomized, placebo-controlled studies in nursing home residents with dementia, oral risperidone at a dosage of approximately 1 mg daily was more effective than placebo in decreasing psychotic and behavioral symptoms (e.g., aggression, agitation) of dementia, as assessed by the Behavioral Pathology in Alzheimer's Disease scale (BEHAVE-AD) and the Cohen-Mansfield Agitation Inventory (CMAI). However, evidence from these studies showed a significantly higher incidence of adverse cerebrovascular events such as stroke and transient ischemic attacks (TIAs) associated with risperidone therapy relative to placebo. In addition, geriatric patients with dementia-related psychosis treated with atypical antipsychotic agents appear to be at an increased risk of death compared with that among patients receiving placebo. (See Cautions: Geriatric Precautions.) Risperidone is not approved for the treatment with dementia-related psychosis.

■ **Bipolar Disorder** Risperidone is used alone or in conjunction with lithium or valproate for the management of manic and mixed episodes associated with bipolar I disorder. Efficacy of risperidone monotherapy in the treatment of acute manic and mixed episodes has been demonstrated in 2 placebo-controlled trials of 3 weeks' duration in patients who met the DSM-IV criteria for bipolar I disorder with acute manic or mixed episodes with or without psychotic features. The principal rating instrument used for assessing manic symptoms in these trials was the Young Mania Rating Scale (Y-MRS), an 11-item clinician-rated scale traditionally used to assess the degree of manic symptomatology in a range from 0 (no manic features) to 60 (maximum score). In the first 3-week, placebo-controlled trial, which was limited to patients with manic episodes, risperidone monotherapy was given at an initial dosage of 3 mg daily and subsequently in a flexible dosage ranging from 1–6 mg daily; the mean modal dosage was 4.1 mg daily. In the second 3-week, placebo-controlled trial, patients also were given an initial dosage of risperidone 3 mg daily and subsequently a flexible dosage ranging from 1–6 mg daily; the mean modal dosage was 5.6 mg daily. Risperidone was found to be superior to placebo in the reduction of the Y-MRS total score in both studies.

Efficacy of risperidone when used in conjunction with lithium or valproate in the treatment of acute manic or mixed episodes has been demonstrated in one placebo-controlled trial of 3 weeks' duration in patients who met the DSM-IV criteria for bipolar I disorder (with or without a rapid cycling course) and who met diagnostic criteria for an acute manic or mixed episode (with or without psychotic features). In this study, inpatients and outpatients with bipolar disorder experiencing manic or mixed episodes who had not adequately responded to lithium or valproate monotherapy were randomized to receive risperidone, haloperidol, or placebo in conjunction with their original therapy. Risperidone therapy was given in an initial dosage of 2 mg daily and subsequently given in a flexible dosage ranging from 1–6 mg daily; the mean modal dosage was 3.8 mg daily. Lithium and valproate were given in conjunction with risperidone and plasma drug concentrations were maintained within ther-

apeutic ranges of 0.6–1.4 mEq/L for lithium and 50–120 mcg/mL for valproate. Addition of risperidone to lithium or valproate was shown to be superior to continued monotherapy with lithium or valproate as assessed by reduction of Y-MRS total score.

In a second 3-week, placebo-controlled trial, inpatients and outpatients with bipolar mania receiving lithium, valproate (as divalproex), or carbamazepine therapy with inadequately controlled manic or mixed symptoms were randomized to receive risperidone or placebo in conjunction with their original therapy. Risperidone was given in a flexible dosage range of 1–6 mg daily, with an initial dosage of 2 mg daily; the mean modal dosage was 3.7 mg daily. Addition of risperidone to lithium, valproate, or carbamazepine therapy (with plasma drug concentrations maintained within therapeutic ranges of 0.6–1.4 mEq/L, 50–120 mcg/mL, or 4–12 mcg/mL, respectively) was not found to be superior to lithium, valproate, or carbamazepine given alone as assessed by reduction of the Y-MRS total score. A possible explanation for the failure of this trial was enzymatic induction of clearance of risperidone and its principal active metabolite, 9-hydroxyrisperidone, by carbamazepine in the subgroup of patients receiving combined therapy with these drugs, resulting in subtherapeutic plasma concentrations of risperidone and 9-hydroxyrisperidone.

For the initial management of less severe manic or mixed episodes in patients with bipolar disorder, current American Psychiatric Association (APA) recommendations state that monotherapy with lithium, valproate (e.g., valproate sodium, valproic acid, divalproex), or an antipsychotic such as olanzapine may be adequate. For more severe manic or mixed episodes, combined therapy with an antipsychotic and lithium or valproate is recommended as first-line therapy. For further information on the management of bipolar disorder, see Uses: Bipolar Disorder, in Lithium Salts 28:28.

The manufacturer states that efficacy of risperidone has not been systematically evaluated for long-term use (i.e., exceeding 3 weeks) in the treatment of acute manic episodes or for prophylactic use in patients with bipolar disorder.

■ **Autistic Disorder** Risperidone is used for the management of irritability associated with autistic disorder in children and adolescents, including symptoms of aggression towards others, deliberate self-injuriousness, temper tantrums, and quickly changing moods.

Short-term efficacy of risperidone in children and adolescents with autistic disorder has been demonstrated in 2 placebo-controlled trials of 8 weeks' duration in children and adolescents (aged 5–16 years) who met the DSM-IV criteria for autistic disorder. Over 90% of the patients in these 2 trials were under 12 years of age and the majority weighed over 20 kg (weight range: 16–104.3 kg). The principal rating instruments used for assessing efficacy in these trials were the Aberrant Behavior Checklist (ABC) and the Clinical Global Impression-Change (CGI-C) scale. The primary outcome measure in both trials was the change from baseline to endpoint in the Irritability subscale of the ABC (ABC-I), which measures the emotional and behavioral symptoms of autism, including aggression toward others, deliberate self-injuriousness, temper tantrums, and rapidly changing moods. The CGI-C rating at endpoint was a co-primary outcome measure in one of the studies.

In the first 8-week, placebo-controlled trial, children and adolescents with autistic disorder aged from 5 to 16 years received twice daily placebo or risperidone 0.5–3.5 mg daily on a weight-adjusted basis, starting at 0.25 mg daily or 0.5 mg daily if baseline weight was less than 20 kg or 20 kg or greater, respectively; dosage was then titrated according to clinical response. Risperidone (mean modal dosage of 1.9 mg/day; equivalent to 0.06 mg/kg daily) was found to substantially improve scores on the ABC-I subscale and the CGI-C scale compared with placebo in this study.

In the second 8-week, placebo-controlled trial, children and adolescents with autistic disorder aged from 5–12 years were given an initial risperidone dosage of 0.01 mg/kg daily, which was then titrated up to 0.02–0.06 mg/kg daily based on clinical response. Risperidone (mean modal dosage of 0.05 mg/kg daily; equivalent to 1.4 mg daily) improved scores on the ABC-I subscale compared with placebo.

The efficacy of risperidone for long-term use (i.e., longer than 8 weeks) in children and adolescents with autistic disorder has been demonstrated in an open-label extension of the first 8-week, placebo-controlled trial in which patients received risperidone for 4 or 6 months (depending on whether they received risperidone or placebo in the double-blind study). During the open-label treatment period, patients were maintained on a mean modal risperidone dosage of 1.8–2.1 mg daily (equivalent to 0.05–0.07 mg/kg daily).

Children and adolescents who maintained their positive response to risperidone (defined as at least a 25% improvement on the ABC-I subscale and a CGI-C rating of much improved or very much improved) during the 4–6 month open-label treatment period (average duration of therapy was 140 days) were randomized to receive either risperidone or placebo during an 8-week, double-blind withdrawal trial. A substantially lower relapse rate was observed in the risperidone group compared with the placebo group during the pre-planned interim analysis of data from this trial. Based on the interim analysis results, the study was terminated since a statistically significant effect on relapse prevention was demonstrated. Relapse was defined as at least a 25% worsening on the most recent assessment of the ABC-I subscale (in relation to baseline for the randomized withdrawal phase). The manufacturer states that clinicians who elect to use risperidone in children and adolescents with autistic disorder for extended periods should periodically re-evaluate the long-term risks and benefits of the drug for the individual patient.

Although not curative, pharmacologic agents, such as risperidone, generally are used in children and adolescents with autistic disorder to reduce behavioral disturbances associated with autism and to help facilitate the child's or adolescent's adjustment and engagement in intensive, targeted educational interventions. In clinical studies, risperidone was not found to improve certain core symptoms of autism (e.g., language deficits, impaired social relatedness). However, the drug was more effective than placebo for improving scores on subscales for sensory motor behaviors, affectual reactions, and sensory responses in a controlled study. The possible risks, including clinically important weight gain, tardive dyskinesia, withdrawal dyskinesia, and other extrapyramidal reactions associated with the drug, should be considered.

Risperidone also has been used for the treatment in a limited number of adults† with autistic disorder and other pervasive developmental disorders.

Dosage and Administration

■ **Administration** Risperidone is administered orally or by IM injection.

Oral Administration Risperidone is administered orally, either in a once-daily dose or in 2 equally divided doses daily. Because risperidone can cause orthostatic hypotension, twice-daily oral administration may be preferable during initiation of therapy and in patients who may be more susceptible to orthostatic hypotension, such as geriatric or debilitated patients. If once-daily dosing is being considered in geriatric or debilitated patients, it is recommended that the patient be titrated on a twice-daily regimen for 2–3 days at the target dose. Subsequent switching to the once-daily dosing regimen can be done thereafter. Some experts state that once-daily administration of risperidone may be sufficient in most patients receiving maintenance therapy because of the extended half-life of the drug's principal active metabolite (9-hydroxyrisperidone).

In children and adolescents receiving risperidone for the management of irritability associated with autistic disorder who experience persistent somnolence, administering the drug once daily at bedtime, twice-daily administration, or a reduction in dosage may be helpful.

Since food reportedly does not affect the rate or extent of GI absorption of risperidone, the drug can be administered without regard to meals. Compatibility tests show that risperidone oral solution is compatible in the following beverages: water, coffee, orange juice, and low-fat milk; such testing also indicates that risperidone oral solution is *not* compatible in cola or tea.

Patients receiving risperidone orally disintegrating tablets should be instructed not to remove a tablet from the blister until just prior to dosing. The tablet should not be pushed through the foil. With dry hands, the blister backing should be peeled completely off the blister. The tablet should then be gently removed and immediately placed on the tongue, where it rapidly disintegrates in saliva, and then subsequently swallowed with or without liquid. Risperidone orally disintegrating tablets should not be divided or chewed.

IM Administration The commercially available risperidone powder for injection containing the drug in extended-release microspheres must be reconstituted prior to administration using the components of the dose pack supplied by the manufacturer. The dose pack should be allowed to reach room temperature before reconstituting the injection. Risperidone extended-release microspheres should be reconstituted using only the diluent in the prefilled syringe supplied by the manufacturer. The entire contents of the prefilled syringe should be injected into the vial, and the vial should be shaken vigorously while the plunger rod is held down with the thumb for at least 10 seconds to ensure a homogeneous suspension; the reconstituted suspension should appear uniform, thick, and milky. The manufacturer's prescribing information should be consulted for additional details on use of the components of the dose pack to reconstitute and administer risperidone injection. The manufacturer states that different dosage strengths of IM risperidone should not be combined in a single administration.

Following reconstitution, immediate use is recommended because the suspension will settle over time. If more than 2 minutes pass before administration, the vial should again be vigorously shaken to resuspend the drug. The contents of the vial must be used within 6 hours of reconstitution and should not be exposed to temperatures exceeding 25°C.

The entire contents of the vial should be administered by deep IM injection into the upper outer quadrant of the gluteal area every 2 weeks, alternating buttocks. The injection should *not* be administered IV.

■ **Dosage** ***Schizophrenia*** Oral Dosage. Risperidone has a bell-shaped dose-response curve, with therapeutic efficacy of oral dosages of 12–16 mg daily lower than that of dosages of 4–8 mg daily in adults. Because dosage information contained in the manufacturer's labeling principally is derived from early clinical studies of the drug in patients not typical of the general population of patients treated in the community (i.e., in hospitalized, chronically-ill schizophrenic patients accustomed to high-dose antipsychotic therapies), dosage of risperidone should be individualized according to the patient's response and tolerance. Clinicians also may consider consulting published protocols for specific dosage information, particularly in geriatric or younger patients, and in those experiencing their first psychotic episode.

The manufacturer's labeling states that the initial oral dosage of risperidone in adults generally is 1 mg twice daily, with dosage increase in increments of 1 mg twice daily on the second and third day, as tolerated, to a target dosage of 6–8 mg daily (administered once daily or in 2 equally divided doses). However, more recent evidence from open labeled studies and clinical experience with the drug indicates that an initial dosage of 1–2 mg daily, with dosage

increases in increments of 0.5–1 mg daily titrated over 6–7 days, as tolerated, to a target dose of 4 mg daily may be more appropriate for the management of schizophrenia in most otherwise healthy adult patients. Because steady-state plasma concentrations of 9-hydroxyrisperidone (an active metabolite of risperidone) may not be attained for 7 days at a given dosage, subsequent dosage adjustments generally should be made at intervals of at least 7 days. Lower initial dosages (e.g., 1 mg daily) and slower dosage titrations to an initial target dosage of 2 mg daily may be appropriate for younger patients and in those being treated for their first psychotic episode; dosage may then be titrated up to 4 mg daily depending on clinical response at the lower dosage and adverse neurologic effects. Such patients appear to benefit optimally from risperidone dosage of 1–3 mg daily. A substantial number of patients being treated for their first psychotic episode start to develop extrapyramidal symptoms once dosages are increased above 2 mg daily. Dosage reductions should be considered in any patient who develops extrapyramidal symptoms.

While antipsychotic efficacy has been established in clinical trials at oral dosages ranging from 4–16 mg daily, maximum efficacy of the drug was observed in most patients at risperidone dosages of 4–8 mg daily. In addition, the manufacturer and some clinicians state that dosages exceeding 6 mg daily, when given in 2 divided doses, did not result in further improvement but were associated with increases in some adverse effects, including extrapyramidal manifestations. Therefore, the manufacturer states that dosages exceeding 6 mg (in 2 divided doses) daily generally are not recommended and those exceeding 16 mg daily have not been evaluated for safety. In a single study of once-daily dosing, efficacy results generally were stronger for 8 mg than for 4 mg.

The manufacturer states that there are no systematically collected data that specifically address switching from other antipsychotic agents to risperidone or concomitant administration with other antipsychotic agents. While immediate discontinuance of the previous antipsychotic treatment may be acceptable for some patients with schizophrenia, gradual discontinuance of the drug may be appropriate for most patients. In all cases, the period of overlapping antipsychotic administration should be minimized. The first risperidone dose should be administered in place of the next scheduled parenteral antipsychotic dose in schizophrenic patients being switched from long-acting (depot) parenteral antipsychotic therapy to oral risperidone therapy.

The optimum duration of oral risperidone therapy currently is not known, but maintenance therapy with risperidone 2–8 mg daily has been shown to be effective for up to 2 years. Patients should be reassessed periodically to determine the need for continued therapy with the drug. If risperidone therapy is reinitiated after a drug-free period, the manufacturer recommends that the appropriate recommended schedule of careful dosage titration be employed.

IM Dosage. For the management of schizophrenia, the recommended initial adult IM dosage of risperidone injection extended-release microspheres is 25 mg administered by deep IM injection in the gluteal area every 2 weeks. The manufacturer recommends that patients first receive oral risperidone to establish tolerability of the drug before the extended-release risperidone injection is used. To ensure that adequate plasma antipsychotic concentrations are maintained prior to the main release of risperidone from the injection site, therapy with oral risperidone or another oral antipsychotic agent (e.g., for patients being switched from other oral antipsychotic therapy to IM risperidone) should be given with the first IM injection of risperidone, and such oral therapy should be continued for 3 weeks, then discontinued. If risperidone injection is used in patients previously receiving other oral antipsychotic agents, the need for continuing any concomitant therapy for managing extrapyramidal manifestations should be periodically reevaluated.

Some patients not responding to the initial dosage of 25 mg every 2 weeks may benefit from increasing the IM dosage to 37.5 or 50 mg every 2 weeks. However, the dosage should not be increased more frequently than every 4 weeks, and clinical effects of the increased dosage should not be expected earlier than 3 weeks after the first injection of the higher dose. The maximum IM dosage should not exceed 50 mg every 2 weeks since higher dosages were associated with an increased incidence of adverse effects, but no additional clinical benefit was observed.

Although no controlled studies have been conducted to establish the optimum duration of IM risperidone therapy in patients with schizophrenia, oral risperidone has been shown to be effective in delaying time to relapse with longer term use. It is recommended that responding patients be continued on treatment with IM risperidone at the lowest dose needed. Patients should periodically be reassessed to determine the need for continued treatment.

If therapy with IM risperidone is reinitiated after a drug-free period, oral risperidone (or another oral antipsychotic agent) should again be administered for supplementation.

Bipolar Disorder For the management of acute manic and mixed episodes associated with bipolar disorder as monotherapy or as combined therapy in adults, an initial risperidone oral dosage of 2–3 mg given once daily was found to be effective in clinical trials. Dosage may be increased or decreased by 1 mg daily at intervals of not less than 24 hours, reflecting the procedures in the placebo-controlled trials. In these trials, the short-term (i.e., 3-week) antimanic efficacy of risperidone was demonstrated in a flexible dosage ranging from 1 to 6 mg daily. Safety of dosages exceeding 6 mg daily has not been established.

The optimum duration of risperidone therapy for bipolar disorder currently is not known. While it is generally agreed that pharmacologic treatment beyond an acute response in mania is desirable, both for maintenance of the initial response and for prevention of new manic episodes, there are no systematically obtained data to support the use of risperidone beyond 3 weeks. Therefore, the manufacturer states that clinicians who elect to use risperidone for extended periods should periodically reevaluate the long-term risks and benefits of the drug for the individual patient.

Autistic Disorder For the management of irritability associated with autistic disorder in children 5 years of age and older and adolescents, an initial risperidone oral dosage of 0.25 mg daily is recommended for patients weighing less than 20 kg and 0.5 mg daily is recommended for patients weighing 20 kg or more. The drug may be administered either once or twice daily.

Dosage should be individualized according to clinical response and tolerability of the patient. After a minimum of 4 days following initiation of therapy, the dosage may be increased to the recommended dosage of 0.5 mg daily for patients weighing less than 20 kg and 1 mg daily for patients weighing 20 kg or more; this dosage should then be maintained for a minimum of 14 days. In patients not responding adequately, increases in dosage may be considered at intervals of 2 weeks or longer in increments of 0.25 mg daily for patients weighing less than 20 kg or 0.5 mg daily for patients weighing 20 kg or more. Exercise caution with risperidone dosages in smaller children who weigh less than 15 kg. Safety and effectiveness in pediatric patients less than 5 years of age not established.

In clinical trials, 90% of patients who responded to risperidone therapy (based on at least 25% improvement in the Irritability subscale of the Aberrant Behavior Checklist [ABC-I]) received dosages from 0.5–2.5 mg daily. The maximum daily dosage in one of the pivotal trials, when the therapeutic effect reached a plateau, was 1 mg in patients weighing less than 20 kg, 2.5 mg in patients weighing 20 kg or more, and 3 mg in patients weighing more than 45 kg. Dosage data for children weighing less than 15 kg currently are lacking.

Once adequate clinical response has been achieved, consider a gradual reduction in dosage to achieve an optimal balance of efficacy and safety. Patients experiencing excessive somnolence may benefit from a once-daily dosage administered at bedtime or administering half the daily dosage twice daily, or a reduction in dosage.

The manufacturer states that clinicians who elect to use risperidone in children and adolescents with autistic disorder for extended periods should periodically reevaluate the long-term risks and benefits of the drug for the individual patient.

Geriatric Patients and Others at Risk of Orthostatic Hypotension Like other α-adrenergic blocking agents, risperidone can induce orthostatic hypotension (e.g., manifested as dizziness, tachycardia, and occasionally syncope), particularly during initiation of therapy with the drug. The manufacturer and some clinicians state that the risk of this effect can be minimized by limiting the initial oral dosage of risperidone to 1 mg twice daily in otherwise healthy adults and to 0.5 mg once or twice daily in geriatric or debilitated patients, in patients with renal or hepatic impairment, and in those predisposed to, or at risk from, hypotension. Dosages in such patients should then be increased gradually at increments of not more than 0.5 mg twice daily as necessary and tolerated. Increases beyond a dosage level of 1.5 mg twice daily generally should occur at intervals of at least 7 days. However, other clinicians recommend initiating risperidone therapy at a dosage of 0.25 mg daily in geriatric patients and gradually increasing the dosage as tolerated. (See Cautions: Geriatric Precautions.) Most geriatric patients should not be maintained at an oral dosage exceeding 3 mg daily.

For geriatric patients with schizophrenia, the recommended IM risperidone dosage of the extended-release injection is 25 mg every 2 weeks. Oral risperidone (or another oral antipsychotic agent) should be given with the first risperidone extended-release injection and should be continued for 3 weeks to ensure that adequate antipsychotic plasma concentrations are maintained prior to the main release phase of risperidone from the injection site.

Elderly patients and patients with a predisposition to hypotensive reactions or for whom such reactions would pose a particular risk should be instructed in nonpharmacologic interventions that help reduce the occurrence of orthostatic hypotension (e.g., sitting on the edge of the bed for several minutes before attempting to stand in the morning, slowly rising from a seated position). These patients should avoid sodium depletion or dehydration and circumstances that accentuate hypotension (e.g., alcohol intake, high ambient temperature). Monitoring of orthostatic vital signs should be considered.

Particular caution also is warranted in patients with known cardiovascular disease (e.g., history of myocardial infarction or ischemia, heart failure, conduction abnormalities), cerebrovascular disease, or conditions that would predispose to hypotension (e.g., dehydration, hypovolemia, concomitant antihypertensive therapy) and in those for whom such reactions would pose a risk, and cautious dosage titration and careful monitoring are necessary in such patients. Dosage reduction should be considered in any patient in whom hypotension develops.

■ **Dosage in Renal and Hepatic Impairment** Because elimination of risperidone may be reduced and the risk of adverse effects, particularly hypotension, increased in patients with renal impairment, oral risperidone therapy should be initiated at a reduced dosage of 0.5 mg twice daily in adults and increased as necessary and tolerated at increments of 0.5 mg twice daily; increases beyond a dosage level of 1.5 mg twice daily should be made at intervals of at least 7 days. Likewise, this reduced oral dosage should be employed in patients with hepatic impairment because of the risk of an increased free fraction of risperidone in such patients.

If IM risperidone is used for management of schizophrenia in adult patients

with renal or hepatic impairment, the patient should be treated with titrated doses of oral risperidone prior to initiating treatment with the extended-release injection. The recommended starting oral risperidone dosage is 0.5 mg twice daily during the first week, which can be increased to 1 mg twice daily or 2 mg once daily during the second week. If a dosage of at least 2 mg daily of oral risperidone is well tolerated, an IM dosage of 25 mg of the extended-release injection can be administered every 2 weeks. Oral supplementation should be continued for 3 weeks after the first injection until the main release of risperidone from the injection site has begun. In some patients, slower titration may be medically appropriate.

Cautions

Although risperidone differs chemically from the phenothiazines, the drug may be capable of producing many of the toxic manifestations of phenothiazine derivatives. Not all adverse effects of the phenothiazines have been reported with risperidone, but the possibility that they may occur should be considered. Adverse effects of risperidone and the phenothiazines are numerous and may involve nearly all organ systems. Although these effects usually are reversible when dosage is reduced or the drug is discontinued, some effects may be irreversible and, rarely, fatal. In some patients, unexpected death associated with antipsychotic therapy has been attributed to cardiac arrest or asphyxia resulting from failure of the gag reflex. (See Cautions: Cardiovascular Effects.) In other cases, the cause of death could not be determined or definitely attributed to antipsychotic drug therapy.

The most frequent adverse effects of oral risperidone reported in at least 5% of adult patients with schizophrenia who received the drug in 2 short-term (6–8 week) clinical studies and with an incidence of at least twice that of those who received placebo included nervous system (e.g., anxiety, dizziness, extrapyramidal symptoms, somnolence), GI (e.g., constipation, dyspepsia, nausea), dermatologic (e.g., rash), respiratory (e.g., rhinitis), and cardiovascular (e.g., tachycardia) effects. Approximately 9% of patients receiving risperidone in phase 2 or 3 studies discontinued treatment because of adverse effects compared with about 7% of those receiving placebo and 10% of those receiving an active control drug (haloperidol). Adverse effects commonly associated with discontinuance of therapy and considered to be possibly or probably related to risperidone include extrapyramidal symptoms, dizziness, hyperkinesia, somnolence, and nausea.

The most frequent adverse effects of oral risperidone reported in at least 5% of adult patients with bipolar mania who received the drug as monotherapy in the US placebo-controlled trial and with an incidence of at least twice that of those receiving placebo included nervous system (e.g., somnolence, dystonia, akathisia, parkinsonism, vision abnormalities) and GI (e.g., dyspepsia, nausea, increased salivation) effects. In the US placebo-controlled trial of risperidone in conjunction with mood stabilizers (lithium or valproate), the most common adverse effects associated with risperidone administration were somnolence, dizziness, parkinsonism, increased saliva, akathisia, abdominal pain, and urinary incontinence. In the US placebo-controlled trial of risperidone monotherapy, approximately 8% of patients receiving risperidone discontinued therapy because of adverse effects compared with about 6% of those receiving placebo. Adverse effects associated with discontinuance of therapy in this study and considered to be possibly, probably, or very likely related to risperidone included paroniria, somnolence, dizziness, extrapyramidal reaction, and involuntary muscle contractions; each of these occurred in 1 risperidone-treated patient (0.7%) but in none of those receiving placebo. In the US placebo-controlled trial of risperidone used in conjunction with mood stabilizers, there was no overall difference in the incidence of discontinuance because of adverse effects (4% for risperidone and 4% for placebo).

The most frequent adverse effects of oral risperidone reported in at least 5% of pediatric patients with autistic disorder who received the drug in 2 placebo-controlled trials and with an incidence of at least twice that of those receiving placebo included nervous system (e.g., somnolence, fatigue, tremor, dystonia, dizziness, parkinsonism, automatism, dyskinesia, confusion), GI (e.g., increased appetite, increased salivation, constipation, dry mouth), respiratory (e.g., upper respiratory tract infection), cardiovascular effects (e.g., tachycardia), and weight gain. Somnolence was the most frequent adverse effect in these trials, occurring in 67% of the risperidone-treated patients and in 23% of patients receiving placebo. Average weight gain over 8 weeks was 2.6 kg for the risperidone-treated patients compared with 0.9 kg for patients receiving placebo. Extrapyramidal symptoms occurred in approximately 28% of the risperidone-treated patients compared with 10% of those receiving placebo.

The most frequent adverse effects associated with use of risperidone extended-release IM injection reported in at least 5% of adult patients with schizophrenia in clinical trials and with an incidence of at least twice that of those receiving placebo included somnolence, akathisia, parkinsonism, dyspepsia, constipation, dry mouth, fatigue, and increased weight.

■ **Nervous System Effects** ***Tardive Dyskinesia*** Like other antipsychotic agents (e.g., phenothiazines), risperidone has been associated with tardive dyskinesias. Although it has been suggested that atypical antipsychotics appear to have a lower risk of tardive dyskinesia, whether antipsychotic drugs differ in their potential to cause tardive dyskinesia is as yet unknown. In one open-label study, an annual incidence of tardive dyskinesia of 0.3% was reported in patients with schizophrenia who received approximately 8–9 mg of oral risperidone daily for at least 1 year. The prevalence of this syndrome appears to be highest among geriatric patients (particularly females). The risk of developing tardive dyskinesia and the likelihood that it will become irreversible also appear to increase with the duration of therapy and cumulative dose of antipsychotic agents administered; however, the syndrome may occur, although much less frequently, after relatively short periods of treatment with low dosages. For additional information on tardive dyskinesia, see Tardive Dyskinesia under Cautions: Nervous System Effects, in the Phenothiazines General Statement 28:16.08.24.

Extrapyramidal Reactions Extrapyramidal reactions occurred in 17% of patients with schizophrenia receiving oral risperidone dosages of 10 mg daily or less and in 34% of patients receiving dosages of 16 mg daily in clinical studies. Although the incidence of extrapyramidal manifestations in patients receiving risperidone dosages of 10 mg daily or less was similar to that reported in patients receiving placebo, the incidence increased as the dosage of the drug increased, suggesting a dose-related effect. At recommended therapeutic dosages of risperidone (4–8 mg daily) for schizophrenia, the severity of extrapyramidal reactions appears to be comparable to placebo and clozapine 400 mg daily, and substantially less than that associated with haloperidol 10 or 20 mg daily. Similarly, the severity of parkinsonian symptoms, as assessed on the parkinsonism subscale of the Extrapyramidal Symptom Rating Scale (ESRS), is also linearly related to risperidone dosages of 2–16 mg daily, with the incidence of parkinsonian symptoms at risperidone dosages of 6 mg daily or less comparable to that of placebo and substantially less than that seen with haloperidol dosages of 20 mg daily.

Neuroleptic malignant syndrome (NMS), a potentially fatal symptom complex, has been reported in patients receiving antipsychotic agents. NMS requires immediate discontinuance of the drug and intensive symptomatic and supportive care. For additional information on NMS, see Neuroleptic Malignant Syndrome under Nervous System Effects: Extrapyramidal Reactions in Cautions, in the Phenothiazines General Statement 28:16.08.24.

Other Nervous System Effects Dose-related somnolence was a commonly reported adverse effect associated with risperidone treatment. Approximately 8% of adult patients with schizophrenia receiving 16 mg of oral risperidone daily and 1% of patients receiving placebo reported somnolence in studies utilizing direct questioning or a checklist to detect adverse events, respectively.

Insomnia, agitation, and anxiety have been reported in 20–26% of patients receiving risperidone. In addition, headache, dizziness, and aggressive reaction have been reported in 12–14, 4–7, and 1–3% of schizophrenia patients, respectively.

Adverse nervous system effects reported in 1% or more of patients with schizophrenia who received risperidone in clinical studies include increased sleep duration or dream activity, diminished sexual desire, fatigue, and nervousness. Impaired concentration, depression, apathy, catatonic reaction, euphoria, increased libido, amnesia, dysarthria, vertigo, stupor, paraesthesia,malaise, seizure, and confusion also have been reported in 0.1–1% of patients. In addition, aphasia, cholinergic syndrome, choreoathetosis, coma, delirium, emotional lability, hypoesthesia, hypotonia, hyperreflexia, leg cramps, migraine, nightmares, tongue paralysis, torticollis, withdrawal syndrome, and yawning have been reported in fewer than 0.1% of patients. Mania also has been reported during postmarketing surveillance; however, a causal relationship to the drug has not been established.

■ **Cardiovascular Effects** ***Orthostatic Hypotension*** Orthostatic hypotension associated with dizziness, tachycardia, and in some patients, syncope, especially during the initial dose-titration period has been reported in patients receiving risperidone, probably reflecting the drug's α-adrenergic antagonistic properties. The risk of orthostatic hypotension and syncope may be minimized by limiting initial doses in geriatric patients and patients with renal or hepatic impairment. (See Dosage and Administration.) Monitoring of orthostatic vital signs should be considered in patients for whom this is of concern. A dose reduction should be considered if hypotension occurs. Risperidone should be used with particular caution in patients with known cardiovascular disease (history of myocardial infarction or ischemia, heart failure, or conduction abnormalities), cerebrovascular disease, or conditions that would predispose to hypotension (e.g., dehydration, hypovolemia). Clinically important hypotension has been observed with concomitant use of risperidone and antihypertensive drug therapy.

Other Cardiovascular Effects Pooled analysis of results of placebo-controlled studies indicates that risperidone therapy is not associated with statistically significant changes in ECG parameters (e.g., PR, QT, or QT_c intervals, heart rate). In pivotal clinical studies, however, tachycardia, which may be dose dependent, occurred in 3 or 5% of patients with schizophrenia receiving daily oral dosages of risperidone of 10 mg or less or 16 mg, respectively. In addition, palpitation, hypertension, hypotension, AV block, and myocardial infarction have occurred in 1% or more of patients receiving risperidone. Ventricular tachycardia, angina pectoris, atrial premature complexes (APCs, PACs), T-wave inversions, ventricular extrasystoles, ST depression, and myocarditis have occurred in fewer than 0.1% of patients receiving the drug in clinical trials. Atrial fibrillation, pulmonary embolism, cerebrovascular disorders (including stroke and transient ischemic attack) (see Cautions: Geriatric Precautions), and rarely, sudden death and/or cardiopulmonary arrest also have been reported during postmarketing surveillance; however, a causal relationship to the drug has not been established.

■ **Endocrine and Metabolic Effects** Severe hyperglycemia, sometimes associated with ketoacidosis, hyperosmolar coma, or death, has been

reported in patients receiving certain atypical antipsychotic agents, including risperidone. While confounding factors such as an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population make it difficult to establish with certainty the relationship between use of agents in this drug class and glucose abnormalities, epidemiologic studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotic agents included in the studies (e.g., risperidone, clozapine, olanzapine, quetiapine).

Precise risk estimates for hyperglycemia-related adverse events in patients treated with atypical antipsychotics currently are not available. While some evidence suggests that the risk for diabetes may be greater with some atypical antipsychotics (e.g., clozapine, olanzapine) than with others (e.g., risperidone, quetiapine) in the class, available data are conflicting and insufficient to provide reliable estimates of relative risk associated with use of the various atypical antipsychotics.

Similar to other antipsychotic agents, risperidone causes elevated prolactin concentrations, which may persist during chronic use of the drug. Risperidone appears to be associated with a higher level of prolactin elevation than other currently available antipsychotic agents. The clinical importance of elevated serum prolactin concentrations is as yet unknown for most patients receiving these drugs. Gynecomastia and breast pain in men have been reported in fewer than 0.1% of patients. In addition, galactorrhea, amenorrhea, and impotence have been reported with agents that increase serum prolactin concentrations, including risperidone.

Hyponatremia, weight gain or loss, increased serum creatine kinase (CK, creatine phosphokinase, CPK) concentrations, thirst, and diabetes mellitus have been reported in 0.1–1% of schizophrenia patients receiving oral risperidone in clinical studies. In addition, decreased serum iron concentrations, cachexia, dehydration, disorders in antidiuretic hormone, hypokalemia, hypoproteinemia, hyperphosphatemia, hypertriglyceridemia, hyperuricemia, and hypoglycemia have been reported in fewer than 0.1% of patients. Precocious puberty and pituitary adenomas also have been reported during postmarketing surveillance; however, a causal relationship to the drug has not been established.

■ **GI Effects** Adverse GI effects that have been reported in 5–13% of patients with schizophrenia receiving oral risperidone in clinical studies include constipation, nausea, dyspepsia, and vomiting. Abdominal pain, increased salivation, and toothache also have been reported in 1–4% of patients receiving risperidone in clinical studies. In addition, anorexia and reduced salivation were reported in 1% or more of patients receiving risperidone in clinical trials. Flatulence, diarrhea, increased appetite, stomatitis, melena, dysphagia, hemorrhoids, and gastritis have also been reported in 0.1–1% of patients. In addition, fecal incontinence, eructation, gastroesophageal reflux, gastroenteritis, esophagitis, lingual discoloration, cholelithiasis, lingual edema, diverticulitis, gingivitis, discolored feces, GI hemorrhage, and hematemesis have been reported in fewer than 0.1% of patients receiving the drug in clinical trials. Although a causal relationship to risperidone has not been established, intestinal obstruction has been reported during postmarketing surveillance.

■ **Respiratory Effects** Rhinitis has been reported in 8–10% of patients with schizophrenia receiving oral risperidone and was the most common adverse respiratory effect reported during clinical studies. In addition, cough, sinusitis, pharyngitis, upper respiratory infections, and dyspnea have been reported in 1–3% of patients receiving risperidone in clinical studies. Hyperventilation, bronchospasm, pneumonia, and stridor also have been reported in 0.1–1% of patients receiving risperidone in clinical studies. Asthma, increased sputum, and aspiration have been rarely reported in fewer than 0.1% of patients. Although a causal relationship to the drug has not been established, apnea also has been reported during postmarketing surveillance.

■ **Dermatologic Effects and Sensitivity Reactions** Rash and dry skin have been reported in about 2–5% of patients with schizophrenia receiving oral risperidone in clinical studies. In addition, adverse dermatologic effects that have been reported in 1% or more of patients receiving risperidone include seborrhea and increased pigmentation. Increased or decreased sweating, acne, alopecia, hyperkeratosis, pruritus, and skin exfoliation were reported in 0.1–1% of patients in clinical trials. Bullous eruption, skin ulceration, aggravated psoriasis, furunculosis, verruca, dermatitis lichenoid, hypertrichosis, genital pruritus, and urticaria have been rarely reported.

Although a causal relationship has not been established, hypersensitivity reactions, including anaphylaxis, angioedema, and photosensitivity have been reported in patients receiving risperidone.

■ **Genitourinary Effects** Adverse genitourinary effects reported in 1% or more of patients with schizophrenia receiving oral risperidone include polyuria, polydipsia, menorrhagia, orgasmic dysfunction, and vaginal dryness. In addition, urinary incontinence, hematuria, dysuria, nonpuerperal lactation, amenorrhea, breast or perineal pain in females, leukorrhea, mastitis, dysmenorrhea, intermenstrual bleeding, and vaginal hemorrhage have been reported in 0.1–1% of patients receiving risperidone in clinical studies. Urinary retention, cystitis, and renal insufficiency also have been reported in fewer than 0.1% of patients.

In male patients, erectile dysfunction and ejaculation failure were reported in up to 1% of schizophrenia patients receiving oral risperidone in clinical studies. In addition, rare cases of priapism have been reported. While a causal relationship to risperidone use has not been established, other drugs with α-adrenergic blocking effects have been reported to cause priapism, and it is possible that risperidone may share this capacity. Severe priapism may require surgical intervention.

■ **Musculoskeletal Effects** Back or chest pain and arthralgia have been reported in 2–3% of patients with schizophrenia receiving oral risperidone in clinical studies. In addition, myalgia has been reported in 0.1–1% of patients. Arthrosis, synostosis, bursitis, arthritis, and skeletal pain also have occurred in fewer than 0.1% of patients.

■ **Hematologic Effects** Anemia, hypochromic anemia, epistaxis, and purpura have been reported in 0.1–1% of adult patients with schizophrenia and granulocytopenia has been reported in 0.1–1% of children and adolescents with autistic disorder receiving oral risperidone in clinical studies. Normocytic anemia, leukocytosis, lymphadenopathy, leukopenia, Pelger-Huet anomaly, hemorrhage, superficial phlebitis, thrombophlebitis, and thrombocytopenia also have been reported in fewer than 0.1% of patients. In addition, thrombotic thrombocytopenic purpura occurred in at least one patient (a 28 year-old female patient) receiving risperidone in a large, open-labeled study. This patient experienced jaundice, fever, and bruising but eventually recovered after receiving plasmapheresis. The relationship of this adverse event to risperidone therapy is unknown.

■ **Hepatic Effects** Increased SGOT and increased SGPT have been reported in 0.1–1% of patients with schizophrenia receiving oral risperidone in clinical studies. In addition, hepatic failure, cholestatic hepatitis, cholecystitis, cholelithiasis, hepatitis, and hepatocellular damage have been reported in fewer than 0.1% of patients. Although a causal relationship to the drug has not been established, jaundice also has been reported during postmarketing surveillance.

■ **Ocular and Otic Effects** Abnormal vision has been reported in 1–2% of patients with schizophrenia receiving oral risperidone in clinical studies. Abnormal accommodation and xerophthalmia also have been reported in 0.1–1% of patients receiving risperidone in clinical studies. In addition, diplopia, ocular pain, blepharitis, photopsia, photophobia, abnormal lacrimation, tinnitus, hyperacusis, and decreased hearing have been reported in fewer than 0.1% of patients.

■ **Other Adverse Effects** Chest pain and fever have been reported in 2–3% of patients with schizophrenia receiving oral risperidone in clinical studies. Although a causal relationship to the drug has not been established, pancreatitis and aggravated parkinsonian syndrome has been reported during postmarketing surveillance.

■ **Precautions and Contraindications** Risperidone shares many of the toxic potentials of other antipsychotic agents (e.g., phenothiazines), and the usual precautions associated with therapy with these agents should be observed. (See Cautions, in the Phenothiazines General Statement 28:16.08.24.)

Because severe hyperglycemia, sometimes associated with ketoacidosis, hyperosmolar coma, or death, has been reported in patients receiving certain atypical antipsychotic agents, including risperidone, the manufacturers of atypical antipsychotic agents state that patients with preexisting diabetes mellitus in whom therapy with an atypical antipsychotic is initiated should be closely monitored for worsening of glucose control; those with risk factors for diabetes (e.g., obesity, family history of diabetes) should undergo fasting blood glucose testing upon therapy initiation and periodically throughout treatment. (See Cautions: Endocrine and Metabolic Effects.) Any patient who develops manifestations of hyperglycemia during treatment with an atypical antipsychotic should undergo fasting blood glucose testing. In some cases, patients who developed hyperglycemia while receiving an atypical antipsychotic have required continuance of antidiabetic treatment despite discontinuance of the antipsychotic; in other cases hyperglycemia resolved with discontinuance of the suspect drug. For further information on the management of diabetes risks in patients receiving atypical antipsychotics, see Hyperglycemia and Diabetes Mellitus under Cautions: Precautions and Contraindications, in Clozapine 28:16.08.04.

Because of the possibility of orthostatic hypotension, caution should be observed in patients with known cardiovascular disease (e.g., history of myocardial infarction or ischemia, heart failure, conduction abnormalities), cerebrovascular disease (see Cautions: Geriatric Precautions), conditions that would predispose patients to hypotension (e.g., dehydration, hypovolemia), and patients receiving antihypertensive agents. Since patients with a recent history of myocardial infarction or unstable heart disease were excluded from clinical studies, clinicians should be aware that risperidone has not been evaluated or used to any appreciable extent in such patients. Patients receiving risperidone should be advised of the risk of orthostatic hypotension, especially during the period of initial dosage titration. (See Cautions: Cardiovascular Effects.)

Patients with parkinsonian syndrome or dementia with Lewy bodies who receive antipsychotics, including risperidone, reportedly have an increased sensitivity to antipsychotic agents. Clinical manifestations of this increased sensitivity have been reported to include confusion, obtundation, postural instability with more frequent falling, extrapyramidal adverse effects, and clinical features consistent with neuroleptic malignant syndrome. (For additional information on extrapyramidal adverse effects and neuroleptic malignant syndrome, see Cautions: Nervous System Effects, in the Phenothiazines General Statement 28:16.08.24.)

Plasma concentrations of risperidone and its principal active metabolite, 9-hydroxyrisperidone, are increased in patients with severe renal impairment (creatinine clearance less than 30 mL/minute per 1.73 m^2), and an increased free fraction of risperidone occurs in patients with severe hepatic impairment.

Therefore, lower initial dosages should be used in such patients. (See Dosage and Administration.)

Individuals with phenylketonuria (i.e., homozygous genetic deficiency of phenylalanine hydroxylase) and other individuals who must restrict their intake of phenylalanine should be warned that risperidone 0.5-, 1-, 2-, 3-, or 4-mg orally disintegrating tablets contain aspartame (e.g., NutraSweet®) which is metabolized in the GI tract to provide about 0.14, 0.28, or 0.42, 0.63, or 0.84 mg of phenylalanine, respectively, following oral administration.

Because seizures have occurred in 0.3% of patients receiving risperidone in clinical studies, the drug should be administered with caution to patients with a history of seizures.

Esophageal dysmotility and aspiration have been associated with the use of antipsychotic agents, including risperidone. Because aspiration pneumonia is a common cause of morbidity and mortality in patients with advanced dementia of the Alzheimer's type, risperidone and other antipsychotic drugs should be used with caution in patients at risk for aspiration pneumonia.

Because both hypothermia and hyperthermia have been associated with risperidone therapy, the drug should be administered with caution in patients who will be exposed to temperature extremes.

Because risperidone has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including driving automobiles, until they are reasonably certain that risperidone therapy does not adversely affect them.

Risperidone has an antiemetic effect in animals; this effect also may occur in humans, and may mask manifestations of overdosage with certain drugs or may obscure the cause of vomiting in various disorders such as intestinal obstruction, Reye's syndrome or brain tumor.

Patients should be advised to inform their clinician if they are taking, or plan to take, any prescription or nonprescription drugs, or have any concomitant illnesses (e.g., diabetes mellitus). Patients also should be advised to avoid alcohol while taking risperidone.

Risperidone is contraindicated in patients with known hypersensitivity to the drug.

■ **Pediatric Precautions** The manufacturer states that safety and effectiveness of risperidone in children with schizophrenia or acute mania associated with bipolar I disorder have not been established. However, efficacy and safety of the drug in the treatment of irritability associated with autistic disorder have been established in 2 placebo-controlled trials of 8 weeks' duration in 156 children and adolescents aged from 5–16 years. (See Uses: Autistic Disorder.) Additional safety information also was assessed from a long-term study in patients with autistic disorder and from short- and long-term studies in more than 1200 pediatric patients with other psychiatric disorders who were of similar age and weight and who received similar risperidone dosages as patients treated for irritability associated with autistic disorder. Safety and effectiveness of risperidone in pediatric patients with autistic disorder younger than 5 years of age have not been established.

In clinical trials in 1885 children and adolescents with autistic disorder or other psychiatric disorders treated with risperidone, 2 patients (0.1%) reportedly developed tardive dyskinesia, which resolved upon discontinuance of therapy. In addition, approximately 15% of children and adolescents receiving 0.5–2.5 mg daily dosages of risperidone developed withdrawal dyskinesia during the discontinuance phase of one long-term (6 month), open-label study.

In long-term, open-label trials in patients with autistic disorder or other psychiatric disorders, a mean body weight gain of 7.5 kg after 12 months of risperidone therapy was reported, which was higher than the normal expected weight gain (i.e., 3–3.5 kg per year adjusted for age, based on the Centers for Disease Control and Prevention normative data). The majority of the weight increase occurred within the first 6 months of drug exposure. Average percentiles at baseline and at 12 months were 49 and 60 for weight, 48 and 53 for height, and 50 and 62 for body mass index, respectively. When treating pediatric patients with risperidone, the manufacturer recommends that weight gain should be assessed against that expected with normal growth.

Somnolence frequently occurred in placebo-controlled trials in pediatric patients with autistic disorder. Most cases were mild to moderate in severity, occurred early during therapy (peak incidence during the first 2 weeks of therapy), and were transient (median duration of 16 days). Patients experiencing persistent somnolence may benefit from a change in dosage regimen.

Risperidone has been shown to elevate prolactin concentrations in children and adolescents as well as adults. In double-blind, placebo-controlled, 8-week trials in children and adolescents aged from 5–17 years, 49% of risperidone-treated patients had elevated prolactin concentrations compared with 2% of those receiving placebo.

In clinical trials conducted in 1885 children and adolescents with autistic disorder or other psychiatric disorders, galactorrhea and gynecomastia reportedly occurred in 0.8 and 2.3% of risperidone-treated patients, respectively.

The manufacturer states that the long-term effects of risperidone on growth and maturation have not been fully evaluated.

■ **Geriatric Precautions** Clinical studies of risperidone for the management of schizophrenia did not include sufficient numbers of patients 65 years of age and older to determine whether geriatric patients respond differently than younger patients. However, serious adverse effects, including an increased risk of death, have been reported in geriatric patients receiving risperidone or other atypical antipsychotic agents in clinical trials in patients with dementia-related psychosis. Risperidone is not approved for the treatment of dementia-related psychosis. (See Geriatric Considerations in Uses: Psychotic Disorders.)

Adverse cerebrovascular events (e.g., stroke, transient ischemic attack), some of which resulted in fatalities, have been reported in clinical studies of risperidone for the management of psychosis in geriatric patients (mean age 85 years; range 73–97) with dementia. Analysis of pooled data from 4 randomized, placebo-controlled studies indicates that adverse cerebrovascular events occurred in approximately 4% of geriatric patients with dementia of the Alzheimer's type, vascular dementia, or mixed dementia receiving risperidone compared with 2% of those receiving placebo. Although many of the patients who experienced adverse cerebrovascular events during the course of these studies had at least one risk factor for cerebrovascular events (e.g., arrhythmia, atherosclerosis, atrial fibrillation, diabetes, heart failure, hypertension, prior history of stroke or transient ischemic attack), the total number of such patients was too small to permit definitive conclusions about the relationship between known risk factors for cerebrovascular events and risperidone therapy. An increased risk of adverse cerebrovascular events has not been identified to date in clinical studies of risperidone for the management of schizophrenia.

An increased risk of death has been reported among geriatric patients with dementia-related psychosis treated with atypical antipsychotic drugs compared with that among patients receiving placebo. Analyses of 17 placebo-controlled trials (average duration of 10 weeks) revealed an approximate 1.6- to 1.7-fold increase in mortality among geriatric patients receiving atypical antipsychotic drugs (i.e., risperidone, aripiprazole, olanzapine, quetiapine) compared with that in patients receiving placebo. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5% compared with a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature.

A higher incidence of mortality also was observed in geriatric patients with dementia-related psychosis receiving risperidone and furosemide concurrently in placebo-controlled trials when compared with that in patients receiving risperidone alone or placebo and furosemide concurrently. The increase in mortality in patients receiving risperidone and furosemide concurrently was observed in 2 out of 4 clinical trials. The pathological mechanism for this finding remains to be established and no consistent pattern for the cause of death was observed. An increased incidence of mortality in geriatric patients with dementia-related psychosis was observed with risperidone regardless of concurrent furosemide administration.

Risperidone dosage generally should be titrated carefully in geriatric patients, usually initiating therapy at the low end of the dosage range. The greater frequency of decreased hepatic, renal, and/or cardiac function and of concomitant disease and drug therapy observed in the elderly also should be considered. Although geriatric patients exhibit a greater tendency to orthostatic hypotension, the manufacturer states that its risk may be minimized by limiting the initial oral dosage to 0.5 mg twice daily followed by careful titration and close monitoring of orthostatic vital signs in patients for whom this is of concern. More recent evidence however, indicates that even lower initial dosages and slower dosage titration are better tolerated in these patients. Therefore, some clinicians recommend initiating oral risperidone therapy at 0.25 mg daily, and gradually increasing dosages, as tolerated, to a dosage of 2 mg daily in these patients. Higher oral dosages (e.g., 3 or 4 mg daily) may be required in some patients, but are usually associated with greater incidence of extrapyramidal reactions. Most geriatric patients should *not* be maintained at an oral risperidone dosage exceeding 3 mg daily. (See Geriatric Patients and Others at Risk of Orthostatic Hypotension under Dosage and Administration: Dosage.)

■ **Mutagenicity and Carcinogenicity** Risperidone did not exhibit mutagenic potential in in vitro chromosomal aberration studies in human lymphocytes or Chinese hamster cells, mouse lymphoma assay, in vitro rat hepatocyte DNA-repair assay, in vivo micronucleus test in mice, the sex-linked recessive lethal test in Drosophila, or in microbial (Ames) test systems.

Statistically significant increases in pituitary gland adenomas and mammary gland adenocarcinomas were observed in female mice receiving risperidone dosages of 0.63, 2.5, and 10 mg/kg (equivalent to 2.4, 9.4, and 37.5 times the maximum recommended human dosage for schizophrenia on a mg/kg basis or 0.2, 0.75, and 3 times the maximum recommended human dosage on a mg/m^2 basis, respectively) for 18 months. In addition, statistically significant increases were observed in mammary gland adenocarcinomas in both male and female rats, and mammary gland neoplasms and endocrine pancreas adenomas in male rats receiving risperidone dosages of 0.63, 2.5, and 10 mg/kg (equivalent to 0.4, 1.5, and 6 times the maximum recommended human dosage for schizophrenia on a mg/kg basis or 0.2, 0.75, and 3 times the maximum recommended human dosage on a mg/m^2 basis, respectively) for 25 months.

Although an increase in mammary neoplasms has been found in rodents following long-term administration of prolactin-stimulating antipsychotic agents, no clinical or epidemiologic studies conducted to date have shown an association between long-term administration of prolactin-stimulating drugs and mammary tumorigenesis in humans. Current evidence is considered too limited to be conclusive, and further study is needed to determine the clinical importance in most patients of elevated serum prolactin concentrations associated with antipsychotic agents. Since in vitro tests indicate that approximately one-third of human breast cancers are prolactin-dependent, risperidone should be used with caution in patients with previously detected breast cancer.

■ **Pregnancy, Fertility, and Lactation** Reproductive studies in rats and rabbits using risperidone dosages of 0.4–6 times the maximum recom-

mended human dosage on a mg/m² basis have not revealed evidence of fetal malformation. However, risperidone has been shown to cross the placenta in rats, and an increased rate of stillborn rat pups occurred at dosages 1.5 times higher than the maximum recommended human dosage on a mg/m² basis. In 3 reproductive studies in rats, there was an increase in pup deaths during the first 4 days of lactation at dosages 0.1–3 times the human dosage on a mg/m² basis. It is not known whether these deaths resulted from a direct effect on the fetuses or pups or to effects on the dams. In a separate reproductive study in rats, an increased number of pup daths (at birth or by the day after birth) and a decrease in birth weight were observed in pups of dams treated with risperidone dosages that were 3 times the maximum recommended human dosage on a mg/m² basis. Risperidone also appeared to impair maternal behavior, as evidenced by reduced weight gain and decreased survival (from day 1–4 of lactation) in pups born to control dams but reared by risperidone-treated dams.

Although there are no adequate and controlled studies to date in humans, one case of agenesis of the corpus callosum has been reported in an infant exposed to risperidone in utero; however, a causal relationship to risperidone therapy is unknown. Reversible extrapyramidal adverse effects in the neonate also were observed following postmarketing use of risperidone during the third trimester of pregnancy. Risperidone should be used during pregnancy only when the potential benefits justify the possible risks to the fetus. The effect of risperidone on labor and delivery in humans is unknown.

Risperidone (0.16–5 mg/kg) has been shown to impair mating, but not fertility, in Wistar rats in 3 reproductive studies at dosages 0.1–3 times the maximum recommended human dosage on a mg/m² basis. The effect appeared to be in females since impaired mating behavior was not noted in the Segment I study in which males only were treated. Sperm motility and serum testosterone concentrations were decreased in beagles at dosages 0.6–10 times the human dose on a mg/m² basis. Serum testosterone and sperm parameters partially recovered but remained decreased after treatment was discontinued. A no-effect dosage was not found in these studies in either rats or dogs.

Risperidone and its principal active metabolite, 9-hydroxyrisperidone, are distributed into milk. The manufacturer states that women receiving risperidone should avoid nursing.

Description

Risperidone is a benzisoxazole-derivative antipsychotic agent and is chemically unrelated to other antipsychotic agents. While risperidone shares some of the pharmacologic actions of other antipsychotic agents, the drug has been described as an atypical or second-generation antipsychotic agent since many of its CNS effects differ from those of typical or first-generation agents (e.g., butyrophenones, phenothiazines). The exact mechanism of antipsychotic action of risperidone has not been fully elucidated but, like that of clozapine, appears to be more complex than that of most other antipsychotic agents and may involve antagonism of central type 2 serotonergic (5-HT_2) receptors and central dopamine D_2 receptors.

SumMon® (see Users Guide). For additional information on this drug until a more detailed monograph is developed and published, the manufacturer's labeling should be consulted. It is *essential* that the labeling be consulted for detailed information on the usual cautions, precautions, and contraindications concerning potential drug interactions and/or laboratory test interferences and for information on acute toxicity.

Preparations

Excipients in commercially available drug preparations may have clinically important effects in some individuals; consult specific product labeling for details.

Risperidone

Oral		
Solution	1 mg/mL	Risperdal®, Janssen
Tablets	0.25 mg	Risperdal® (scored), Janssen
	0.5 mg	Risperdal® (scored), Janssen
	1 mg	Risperdal® (scored), Janssen
	2 mg	Risperdal® (scored), Janssen
	3 mg	Risperdal® (scored), Janssen
	4 mg	Risperdal® (scored), Janssen
Tablets, orally disintegrating	0.5 mg	Risperdal® M-TAB®, Janssen
	1 mg	Risperdal® M-TAB®, Janssen
	2 mg	Risperdal® M-TAB®, Janssen
	3 mg	Risperdal® M-TAB®, Janssen
	4 mg	Risperdal® M-TAB®, Janssen
Parenteral		
For injectable suspension, extended-release, for IM use	25 mg	Risperdal® Consta® (available as dose pack containing a SmartSite® needle-free vial access device, a Needle-Pro® safety needle, and with 2-mL prefilled syringe diluent), Janssen
	37.5 mg	Risperdal® Consta® (available as dose pack containing a SmartSite® needle-free vial access device, a Needle-Pro® safety needle, and with 2-mL prefilled syringe diluent), Janssen
	50 mg	Risperdal® Consta® (available as dose pack containing a SmartSite® needle-free vial access device, a Needle-Pro® safety needle, and with 2-mL prefilled syringe diluent), Janssen

†Use is not currently included in the labeling approved by the US Food and Drug Administration

Ziprasidone

■ Ziprasidone has been referred to as an atypical or second-generation antipsychotic agent.

Uses

■ **Psychotic Disorders** *Schizophrenia* Ziprasidone is used for the symptomatic management of schizophrenia. Drug therapy is integral to the management of acute psychotic episodes and accompanying violent behavior in patients with schizophrenia and generally is required for long-term stabilization to sustain symptom remission or control and to minimize the risk of relapse. Antipsychotic agents are the principal class of drugs used for the management of all phases of schizophrenia. Patient response and tolerance to antipsychotic agents are variable, and patients who do not respond to or tolerate one drug may be successfully treated with an agent from a different class or with a different adverse effect profile.

Because of ziprasidone's greater capacity to prolong the QT/QT_c-interval compared with that of several other antipsychotic agents, use of ziprasidone may be reserved for patients whose disease fails to respond adequately to appropriate courses of other antipsychotic agents. (See Prolongation of QT interval under Warnings/Precautions: Warnings, in Cautions.) However, it should be noted that patients with a history of resistance to antipsychotic therapy (i.e., failed to respond to adequate courses of 2 or more antipsychotic agents) usually were excluded in clinical studies of ziprasidone.

Efficacy of oral ziprasidone was evaluated in 5 placebo-controlled studies of variable duration (4 short-term [4–6 weeks] and one long-term [52 weeks]), principally in patients with schizophrenic disorders in hospital settings. Ziprasidone appears to be superior to placebo in improving both positive and negative manifestations in acute exacerbations of schizophrenia and in reducing the rate of relapse for up to 52 weeks.

Although results of a limited comparative study suggest that oral ziprasidone hydrochloride dosages of 160 mg daily may be as effective as oral haloperidol 15 mg daily in reducing positive symptoms of schizophrenia, a reliable and valid comparison of ziprasidone and oral haloperidol cannot be made at this time based solely on this study due to its relatively small sample size (90 patients), high dropout rate (51.1%), and brief duration (4 weeks). Data from one unpublished comparative study also suggest that ziprasidone hydrochloride (mean dosage of 130 mg daily) may be as effective as olanzapine (mean dosage of 11 mg daily) in the treatment of schizophrenia.

Ziprasidone is used IM for the management of acute agitation in patients with schizophrenia for whom treatment with ziprasidone is appropriate and who require an IM antipsychotic agent for rapid control of behaviors that interfere with diagnosis and care (e.g., threatening behaviors, escalating or urgently distressing behavior, self-exhausting behavior). The efficacy of IM ziprasidone for the management of acute agitation in schizophrenia was established in single-day controlled trials in hospital settings. Because there is no experience regarding the safety of administering ziprasidone IM to schizophrenic patients already receiving oral ziprasidone, concomitant use of oral and IM formulations of ziprasidone is *not* recommended.

For additional information on the symptomatic management of schizophrenia, including treatment recommendations and results of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE), see Schizophrenia and Other Psychotic Disorders under Uses: Psychotic Disorders, in the Phenothiazines General Statement 28:16.08.24.

■ **Bipolar Disorder** Ziprasidone is used for the treatment of acute manic and mixed episodes (with or without psychotic features) associated with bipolar I disorder. According to DSM-IV criteria, manic episodes are distinct periods lasting 1 week or longer (or less than 1 week if hospitalization is required) of abnormally and persistently elevated, expansive, or irritable mood accompanied by at least 3 (or 4 if the mood is only irritability) of the following 7 symptoms: grandiosity, reduced need for sleep, pressure of speech, flight of ideas, distractibility, increased goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation, and engaging in high risk behavior (e.g., unrestrained buying sprees, sexual indiscretions, foolish business investments).

Efficacy of ziprasidone in the treatment of acute manic and mixed episodes has been demonstrated in 2 short-term (3 weeks' duration), double-blind, pla-

turer's labeling be consulted for more detailed information on usual cautions, precautions, contraindications, potential drug interactions, laboratory test interferences, and acute toxicity.

Preparations

Excipients in commercially available drug preparations may have clinically important effects in some individuals; consult specific product labeling for details.

Paliperidone

Oral		
Tablets, extended-release	3 mg	Invega®, Janssen
	6 mg	Invega®, Janssen
	9 mg	Invega®, Janssen

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Quetiapine Fumarate

■ Quetiapine is considered an atypical or second-generation antipsychotic agent.

Uses

■ **Psychotic Disorders** Quetiapine is used for the symptomatic management of psychotic disorders (e.g., schizophrenia). Drug therapy is integral to the management of acute psychotic episodes and accompanying violent behavior in patients with schizophrenia and generally is required for long-term stabilization to sustain symptom remission or control and to minimize the risk of relapse. Antipsychotic agents are the principal class of drugs used for the management of all phases of schizophrenia. Patient response and tolerance to antipsychotic agents are variable, and patients who do not respond to or tolerate one drug may be successfully treated with an agent from a different class or with a different adverse effect profile.

Schizophrenia Short-term efficacy of quetiapine for the management of schizophrenia has been established by placebo-controlled studies of 6 weeks' duration principally in hospitalized patients with schizophrenia. Schizophrenia is a major psychotic disorder that frequently has devastating effects on various aspects of the patient's life and carries a high risk of suicide and other life-threatening behaviors. Manifestations of schizophrenia involve multiple psychologic processes, including perception (e.g., hallucinations), ideation, reality testing (e.g., delusions), emotion (e.g., flatness, inappropriate affect), thought processes (e.g., loose associations), behavior (e.g., catatonia, disorganization), attention, concentration, motivation (e.g., avolition, impaired intention and planning), and judgment. The principal manifestations of this disorder usually are described in terms of positive and negative (deficit) symptoms, and more recently, disorganized symptoms. Positive symptoms include hallucinations, delusions, bizarre behavior, hostility, uncooperativeness, and paranoid ideation, while negative symptoms include restricted range and intensity of emotional expression (affective flattening), reduced thought and speech productivity (alogia), anhedonia, apathy, and decreased initiation of goal-directed behavior (avolition). Disorganized symptoms include disorganized speech (thought disorder) and behavior and poor attention.

In clinical studies in patients with schizophrenia, quetiapine was more effective than placebo in reducing the severity of symptoms associated with this disorder. Quetiapine appears to improve both positive and negative manifestations of schizophrenia. Results from comparative clinical studies and meta-analyses suggest that quetiapine is at least as effective as chlorpromazine or haloperidol in reducing positive and negative symptoms of schizophrenia.

The American Psychiatric Association (APA) considers certain atypical antipsychotic agents (i.e., quetiapine, aripiprazole, olanzapine, risperidone, ziprasidone) first-line drugs for the management of the acute phase of schizophrenia (including first psychotic episodes), principally because of the decreased risk of adverse extrapyramidal effects and tardive dyskinesia, with the understanding that the relative advantages, disadvantages, and cost-effectiveness of conventional and atypical antipsychotic agents remain controversial. The APA states that, with the possible exception of clozapine for the management of treatment-resistant symptoms, there currently is no definitive evidence that one atypical antipsychotic agent will have superior efficacy compared with another agent in the class, although meaningful differences in response may be observed in individual patients. Conventional antipsychotic agents may be considered first-line therapy in patients who have been treated successfully in the past with or who prefer conventional agents. The choice of an antipsychotic agent should be individualized, considering past response to therapy, adverse effect profile (including the patient's experience of subjective effects such as dysphoria), and the patient's preference for a specific drug, including route of administration.

Although the efficacy of quetiapine for long-term use has not been established in controlled studies, the manufacturer states that beneficial effects of the drug were maintained for up to 4 years in some patients during an open-label extension study in patients who achieved an initial response to treatment during double-blind clinical studies. If quetiapine is used for extended periods, the need for continued therapy should be reassessed periodically on an individualized basis. (See Dosage and Administration: Dosage.)

For additional information on the symptomatic management of schizophrenia, including treatment recommendations and results of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study, see Schizophrenia and Other Psychotic Disorders under Uses: Psychotic Disorders, in the Phenothiazines General Statement 28:16.08.24.

■ **Bipolar Disorder** Quetiapine is used alone or in conjunction with lithium or divalproex sodium for the management of acute manic episodes associated with bipolar I disorder. Efficacy of quetiapine monotherapy in the treatment of acute manic episodes has been demonstrated in 2 placebo-controlled studies of 12 weeks' duration in patients who met the DSM-IV criteria for bipolar disorder and who met diagnostic criteria for an acute manic episode (with or without psychotic features). Patients with rapid cycling and mixed episodes were excluded from these studies. The principal rating instrument used for assessing manic symptoms in these studies was the Young Mania Rating Scale (YMRS) score, an 11-item clinician rated scale traditionally used to assess the degree of manic symptomatology in a range from 0 (no manic features) to 60 (maximum score). In these studies, quetiapine was shown to be superior to placebo in reduction of the YMRS total score after 3 and 12 weeks of treatment.

Efficacy of quetiapine when used in combination with lithium or divalproex sodium in the management of acute manic episodes has been demonstrated in a placebo-controlled study of 3 weeks' duration in patients who met the DSM-IV criteria for bipolar I disorder with acute manic episodes (with or without psychotic features). Patients with rapid cycling and mixed episodes were excluded from enrollment and patients included in the study may or may not have received an adequate course of therapy with lithium or divalproex sodium prior to randomization. Quetiapine was shown to be superior to placebo when added to lithium or divalproex sodium alone in the reduction of YMRS total score. However, in a similarly designed study, quetiapine was associated with an improvement of YMRS scores but did not demonstrate superiority to placebo.

For the initial management of less severe manic or mixed episodes in patients with bipolar disorder, current APA recommendations state that monotherapy with lithium, valproate (e.g., valproate sodium, valproic acid, divalproex), or an antipsychotic (e.g., olanzapine) may be adequate. For more severe manic or mixed episodes, combination therapy with an antipsychotic and lithium or valproate is recommended as first-line therapy. For further information on the management of bipolar disorder, see Uses: Bipolar Disorder, in Lithium Salts 28:28.

Quetiapine also is used for the treatment of depressive episodes associated with bipolar disorder. Efficacy of quetiapine in the treatment of depressive episodes has been demonstrated in 2 randomized, double-blind, placebo-controlled studies of 8 weeks' duration in patients with bipolar I or II disorder (with or without a rapid-cycling course). Patients in these studies received fixed daily quetiapine dosages of 300 or 600 mg once daily. The principal rating instrument used for assessing depressive symptoms in these studies was the Montgomery-Asberg Depression Rating Scale (MADRS), a 10-item clinician-rated scale with scores ranging from 0 to 60. In both studies, quetiapine was found to be superior to placebo in reduction of MADRS scores at week 8, with improvements in scores evident within one week of treatment. In addition, patients receiving 300 mg of quetiapine daily demonstrated significant improvements compared to placebo recipients in overall quality of life and satisfaction related to various areas of functioning.

Dosage and Administration

■ **Administration** Quetiapine is administered orally. While food reportedly can marginally increase the peak concentration and oral bioavailability of quetiapine, the drug generally can be administered without regard to meals.

Dispensing and Administration Precautions Because of similarity in spelling between Seroquel® (the trade name for quetiapine fumarate) and Serzone® (the former trade name for nefazodone hydrochloride, an antidepressant agent; no longer commercially available in the US under this trade name), dispensing errors have been reported to the US Food and Drug Administration (FDA) and the manufacturer of Seroquel® (AstraZeneca). Accordiog to the medication error reports, the overlapping strengths (100 and 200 mg), dosage forms (tablets), and dosing intervals (twice daily) and the fact that these 2 drugs were stored closely together in pharmacies also were critical in causing these errors. Therefore, extra care should be exercised in ensuring the accuracy of both oral and written prescriptions for Seroquel® and Serzone®. Although the Serzone brand was discontinued in June 2004, clinicians may continue to refer to nefazodone by the former brand name in prescribing. Some experts recommend that pharmacists assess the measures of avoiding dispensing errors and implement them as appropriate (e.g., by verifying all orders for these agents by spelling both the trade and generic names to prescribers, using computerized name alerts, attaching reminders to drug containers and pharmacy shelves, separating the drugs on pharmacy shelves, counseling patients). (See Dispensing and Administration Precautions under Warnings/Precautions: General Precautions in Cautions.)

■ **Dosage** Dosage of quetiapine fumarate is expressed in terms of quetiapine and must be carefully adjusted according to individual requirements and response, using the lowest possible effective dosage.

Higher maintenance dosages of quetiapine may be required in patients receiving the antipsychotic drug concomitantly with phenytoin or other hepatic enzyme-inducing agents (e.g., carbamazepine, barbiturates, rifampin, glucocorticoids), and an increase in the maintenance dosage of quetiapine may be required to reestablish efficacy in patients receiving such concomitant therapy. (See Drug Interactions: Drugs Affecting Hepatic Microsomal Enzymes and also Phenytoin.)

Patients receiving quetiapine should be monitored for possible worsening of depression, suicidality, or unusual changes in behavior, especially at the beginning of therapy or during periods of dosage adjustments. (See Worsening of Depression and Suicidality Risk under Warnings/Precautions: Warnings, in Cautions.)

The manufacturer states that if quetiapine therapy is reinitiated after a drug-free period of less than 1 week, dosage titration is not necessary. However, if quetiapine therapy is reinitiated after a drug-free period exceeding 1 week, dosage generally should be titrated as with initial therapy.

Schizophrenia For the management of schizophrenia, the recommended initial dosage of quetiapine in adults is 25 mg twice daily. Dosage may be increased in increments of 25–50 mg 2 or 3 times daily on the second or third day, as tolerated, to a target dosage of 300–400 mg daily in 2 or 3 divided doses by the fourth day. Because steady-state plasma concentrations of quetiapine may not be attained for 1–2 days at a given dosage, subsequent dosage adjustments generally should be made at intervals of not less than 2 days, usually in increments or decrements of 25–50 mg twice daily. Effective dosages of quetiapine in clinical trials generally ranged from 150–750 mg daily. While the manufacturer states that increasing quetiapine dosages beyond 300 mg daily usually does not result in additional therapeutic effect, dosages of 400–500 mg daily apparently have been required in some patients, and a dosage range of 300–800 mg daily has been recommended. Safety of quetiapine in dosages exceeding 800 mg daily has not been established.

The optimum duration of quetiapine therapy currently is not known, but the efficacy of maintenance therapy with antipsychotic agents used in the treatment of schizophrenia is well established. Patients responding to quetiapine therapy should continue to receive the drug as long as clinically necessary and tolerated but at the lowest possible effective dosage, and the need for continued therapy with the drug should be reassessed periodically. The American Psychiatric Association (APA) states that prudent long-term treatment options in patients with remitted first- or multiple-episodes include either indefinite maintenance therapy or gradual discontinuance of the antipsychotic agent with close follow-up and a plan to reinstitute treatment upon symptom recurrence. Discontinuance of antipsychotic therapy should be considered only after a period of at least 1 year of symptom remission or optimal response while receiving the antipsychotic agent. In patients who have had multiple previous psychotic episodes or 2 psychotic episodes within 5 years, indefinite maintenance antipsychotic treatment is recommended.

If antipsychotic therapy is to be discontinued in patients with schizophrenia, precautions should include slow, gradual dose reduction over many months, more frequent clinician visits, and use of early intervention strategies. Patients and their family and caregivers should be advised about early signs of relapse, and clinicians should collaborate with them to develop plans for action should they emerge. The treatment program should be designed to respond quickly to evidence of prodromal symptoms or behaviors or exacerbations of schizophrenic symptoms.

Bipolar Disorder For the management of depressive episodes associated with bipolar I or II disorder, the recommended dosage of quetiapine in adults is 50 mg administered once daily at bedtime on the first day of therapy. The dosage of quetiapine should then be increased to 100 mg once daily on the second day of therapy, 200 mg once daily on the third day of therapy, and 300 mg once daily on the fourth day of therapy. In clinical trials demonstrating clinical efficacy, quetiapine was given in a dosing schedule of 50, 100, 200, and 300 mg once daily on days 1–4, respectively; patients who received 600 mg daily received 400 mg daily on day 5 and 600 mg daily on day 8. Although antidepressant efficacy was demonstrated with quetiapine at dosages of 300 mg daily and 600 mg daily, no additional benefit was seen in the 600-mg daily group.

For the management of acute mania associated with bipolar I disorder (alone or in conjunction with lithium or divalproex sodium), the recommended initial dosage of quetiapine in adults is 100 mg daily, administered in 2 divided doses. The dosage of quetiapine should be increased in increments of up to 100 mg daily in 2 divided doses to 400 mg daily on the fourth day of therapy. Subsequent dosage adjustments up to 800 mg daily by the sixth day of therapy should be made in increments not exceeding 200 mg daily. Data indicate that most patients respond to 400–800 mg daily. The safety of quetiapine dosages exceeding 800 mg daily has not been established.

The APA states that for patients treated with an antipsychotic agent during an acute episode in bipolar disorder, the need for ongoing antipsychotic treatment should be reassessed upon entering the maintenance phase. The APA recommends that antipsychotics be slowly tapered and discontinued unless they are required to control persistent psychosis or provide prophylaxis against recurrence. While maintenance therapy with atypical antipsychotics may be considered, there currently is limited evidence regarding their efficacy in the maintenance phase compared with that of agents such as lithium or valproate. The manufacturer of quetiapine states that efficacy of the drug has not been systematically evaluated for more than 12 weeks as monotherapy of acute manic episodes associated with bipolar I disorder or for more than 3 weeks as combined therapy with divalproex or lithium. In addition, the manufacturer of quetiapine states that efficacy of the drug has not been systematically evaluated for more than 8 weeks in the management of depressive episodes in patients with bipolar I or II disorder. If quetiapine is used for extended periods, the need for continued therapy should be reassessed periodically on an individualized basis.

Switching to or Concomitant Use with Other Antipsychotic Agents The manufacturer states that there are no systematically collected data that specifically address switching from other antipsychotic agents to quetiapine or concerning concomitant use of quetiapine with other antipsychotic agents. Although abrupt discontinuance of the previous antipsychotic agent may be acceptable for some patients with schizophrenia, gradual discontinuance may be most appropriate for others. In all cases, the period of overlapping antipsychotic administration should be minimized. In patients being switched from long-acting (depot) parenteral antipsychotic therapy to oral quetiapine therapy, the first oral dose of quetiapine should be administered in place of the next scheduled dose of the long-acting preparation. The need for continuing existing drugs used for the symptomatic relief of extrapyramidal manifestations should be reevaluated periodically.

■ **Special Populations** The manufacturer states that because quetiapine is substantially metabolized in the liver and because the pharmacokinetics of quetiapine appear to be altered in patients with hepatic impairment, an initial dosage of 25 mg daily should be used in adults with hepatic impairment. The dosage should be increased by 25–50 mg daily according to clinical response and tolerability until an effective dosage is reached.

Although elimination of quetiapine was reduced in patients with severe renal impairment (e.g., creatinine clearance of 10–30 mL/minute), the plasma quetiapine concentrations were similar to those in patients with normal renal function; therefore, the manufacturer states that dosage adjustment is not necessary in such patients.

Geriatric or debilitated patients and patients predisposed to hypotension or in whom hypotension would pose a risk (e.g., patients with dehydration or hypovolemia, those receiving antihypertensive drugs, patients with known cardiovascular or cerebrovascular disease) should have a slower rate of dosage titration and should receive lower target dosages of quetiapine. The risk of orthostatic hypotension can be minimized by limiting the initial dosage of quetiapine to 25 mg twice daily. If orthostatic hypotension occurs during titration to the target dosage, the manufacturer recommends a return to the previous dosage in the titration schedule.

Cautions

■ **Contraindications** Known hypersensitivity to quetiapine or any ingredient in the formulation.

■ **Warnings/Precautions** ***Warnings*** **Increased Mortality in Geriatric Patients with Dementia-related Psychosis.** Geriatric patients with dementia-related psychosis treated with atypical antipsychotic drugs appear to be at an increased risk of death compared with that among patients receiving placebo. Analyses of 17 placebo-controlled trials (average duration of 10 weeks) revealed an approximate 1.6- to 1.7-fold increase in mortality among geriatric patients receiving atypical antipsychotic drugs (i.e., quetiapine, aripiprazole, olanzapine, risperidone) compared with that in patients receiving placebo. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5% compared with a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. The manufacturer states that quetiapine is not approved for the treatment of dementia-related psychosis. (See Dosage and Administration: Special Populations and see also Geriatric Use under Warnings/Precautions: Specific Populations, in Cautions.)

Worsening of Depression and Suicidality Risk. Worsening of depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior may occur in both adult and pediatric (see Pediatric Use under Warnings/Precautions: Specific Populations, in Cautions) patients with major depressive disorder or other psychiatric disorders, whether or not they are taking antidepressants. This risk may persist until clinically important remission occurs with therapy. Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are the strongest predictors of suicide. However, there has been a long-standing concern that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients during the early phases of treatment. Pooled analyses of short-term, placebo-controlled studies of antidepressants (i.e., selective serotonin-reuptake inhibitors and other antidepressants) have shown an increased risk of suicidality in children, adolescents, and young adults (18–24 years of age) with major depressive disorder and other psychiatric disorders. An increased suicidality risk was not demonstrated with antidepressants compared to placebo in adults older than 24 years of age and a reduced risk was observed in adults 65 years of age or older.

The US Food and Drug Administration (FDA) recommends that all patients being treated with antidepressants for any indication be appropriately monitored and closely observed for clinical worsening, suicidality, and unusual changes in behavior, particularly during initiation of therapy (i.e., the first few months) and during periods of dosage adjustments. Families and caregivers of patients being treated with antidepressants for major depressive disorder or

other indications, both psychiatric and nonpsychiatric, also should be advised to monitor patients on a daily basis for the emergence of agitation, irritability, or unusual changes in behavior as well as the emergence of suicidality, and to report such symptoms immediately to a health-care provider.

Although a causal relationship between the emergence of symptoms such as anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia, hypomania, and/or mania and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality. Consequently, consideration should be given to changing the therapeutic regimen or discontinuing therapy in patients whose depression is persistently worse or in patients experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, particularly if such manifestations are severe, abrupt in onset, or were not part of the patient's presenting symptoms. FDA also recommends that the drugs be prescribed in the smallest quantity consistent with good patient management, in order to reduce the risk of overdosage.

Bipolar Disorder. It is generally believed (though not established in controlled trials) that treating a major depressive episode with an antidepressant alone may increase the likelihood of precipitating a mixed or manic episode in patients at risk for bipolar disorder. Therefore, patients should be adequately screened for bipolar disorder prior to initiating treatment with an antidepressant; such screening should include a detailed psychiatric history (e.g., family history of suicide, bipolar disorder, and depression). Quetiapine is approved for use in treating bipolar depression in adults. (See Bipolar Disorder under Uses.)

Neuroleptic Malignant Syndrome. Neuroleptic malignant syndrome (NMS), a potentially fatal syndrome requiring immediate discontinuance of the drug and intensive symptomatic treatment, has been reported in patients receiving antipsychotic agents, including quetiapine. For additional information on NMS, see Extrapyramidal Reactions under Cautions: Nervous System Effects, in the Phenothiazines General Statement 28:16.08.24.

Tardive Dyskinesia. Use of antipsychotic agents, including quetiapine, may be associated with tardive dyskinesias, a syndrome of potentially irreversible, involuntary, dyskinetic movements. For additional information on tardive dyskinesia, see Tardive Dyskinesia under Cautions: Nervous System Effects, in the Phenothiazines General Statement 28:16.08.24.

Hyperglycemia and Diabetes Mellitus. Severe hyperglycemia, sometimes associated with ketoacidosis, hyperosmolar coma, or death, has been reported in patients receiving all atypical antipsychotic agents, including quetiapine. While confounding factors such as an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population make it difficult to establish with certainty the relationship between use of agents in this drug class and glucose abnormalities, epidemiologic studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotic agents included in the studies (e.g., quetiapine, clozapine, olanzapine, risperidone).

Precise risk estimates for hyperglycemia-related adverse events in patients treated with atypical antipsychotics currently are not available. While some evidence suggests that the risk for diabetes may be greater with some atypical antipsychotics (e.g., clozapine, olanzapine) than with others in the class (e.g., quetiapine, risperidone), available data are conflicting and insufficient to provide reliable estimates of relative risk associated with use of the various atypical antipsychotics.

The manufacturers of atypical antipsychotic agents state that patients with preexisting diabetes mellitus in whom therapy with an atypical antipsychotic is initiated should be closely monitored for worsening of glucose control; those with risk factors for diabetes (e.g., obesity, family history of diabetes) should undergo fasting blood glucose testing upon therapy initiation and periodically throughout treatment. Any patient who develops manifestations of hyperglycemia (e.g., polydipsia, polyphagia, polyuria, weakness) during treatment with an atypical antipsychotic should undergo fasting blood glucose testing. In some cases, patients who developed hyperglycemia while receiving an atypical antipsychotic have required continuance of antidiabetic treatment despite discontinuance of the suspect drug; in other cases, hyperglycemia resolved with discontinuance of the antipsychotic.

For further information on the risk of hyperglycemia and diabetes mellitus associated with atypical antipsychotic agents, see Cautions: Endocrine and Metabolic Effects and see also Hyperglycemia and Diabetes Mellitus under Cautions: Precautions and Contraindications, in Clozapine 28:16.08.04.

Sensitivity Reactions Contact dermatitis, maculopapular rash, and photosensitivity reactions were reported infrequently during clinical trials. Anaphylaxis and Stevens-Johnson syndrome have been reported during postmarketing surveillance.

General Precautions **Cardiovascular Effects.** Orthostatic hypotension with associated dizziness, tachycardia, and/or syncope, particularly during the initial dosage titration period, has been reported. The risk of orthostatic hypotension and syncope may be minimized by limiting initial dosage. (See Dosage and Administration: Special Populations.) Use with caution in patients with known cardiovascular (e.g., history of myocardial infarction or ischemia, heart failure, conduction abnormalities) or cerebrovascular disease and/or conditions that would predispose patients to hypotension (e.g., dehydration, hypovolemia, concomitant antihypertensive therapy).

Ocular Effects. The development of cataracts in association with quetiapine was observed in animal studies. Lens changes also have been reported in some patients receiving long-term quetiapine therapy, although a causal relationship has not been established. Because the possibility of lens changes cannot be excluded, the manufacturer recommends ophthalmologic examination of the lens by methods adequate to detect cataract formation (e.g., slit lamp exam) be performed at the initiation of quetiapine therapy, or shortly thereafter, and at 6-month intervals during chronic quetiapine therapy.

Nervous System Effects. Seizures occurred in 0.6% of patients receiving quetiapine in controlled clinical trials. Use with caution in patients with a history of seizures or with conditions known to lower the seizure threshold (e.g., dementia of the Alzheimer's type, geriatric patients).

Somnolence occurred in 16–18 or 34% of patients receiving quetiapine as monotherapy (for the treatment of schizophrenia or bipolar disorder) or in conjunction with lithium or divalproex sodium (for the treatment of bipolar disorder), respectively, during clinical studies compared with 4–11% of those receiving placebo.

Endocrine Effects. Dose-related decreases in total and free thyroxine (T4) of approximately 20% were observed in patients receiving quetiapine dosages at the higher end of the therapeutic dosage range during clinical studies. These decreases were maximal during the first 2–4 weeks of therapy and were maintained without adaptation or progression during more chronic therapy. Generally, these changes were not considered clinically important and were reversible upon discontinuance of quetiapine, regardless of duration of therapy. Increases in TSH were observed in about 0.4 or 12% of patients receiving quetiapine alone or in conjunction with lithium or divalproex sodium, respectively. In patients receiving quetiapine monotherapy, thyroid replacement therapy was necessary in some patients who experienced increases in TSH.

Although not observed in patients receiving quetiapine during clinical trials, increases in prolactin concentrations and associated increases in mammary gland neoplasia were reported in animal studies.

Metabolic Effects. During clinical studies, 23 or 21% of patients with schizophrenia or acute mania receiving quetiapine gained at least 7% of their baseline weight compared with 6–7% of those receiving placebo. In patients receiving quetiapine as adjunctive therapy for acute mania, 13% gained at least 7% of their baseline weight compared with 4% of those receiving placebo.

Increases from baseline in cholesterol and triglyceride concentrations of 11 and 17%, respectively, were reported in patients receiving quetiapine compared with slight decreases in patients receiving placebo in clinical studies in patients with schizophrenia. These changes were weakly related to increases in weight observed in patients receiving quetiapine. For additional information on metabolic effects, see Hyperglycemia and Diabetes Mellitus under Warnings/Precautions, in Cautions.

Hepatic Effects. Asymptomatic, transient, and reversible increases in serum transaminases, principally ALT, have been reported in patients receiving quetiapine; these changes usually occurred within the first 3 weeks and resolved despite continued quetiapine therapy.

Sexual Dysfunction. One case of drug-induced priapism was reported in clinical studies of quetiapine.

Body Temperature Regulation. Although not reported in clinical studies with quetiapine, disruption of the body's ability to reduce core body temperature has been associated with use of antipsychotic agents. Use caution when quetiapine is administered in patients exposed to conditions that may contribute to an elevation in core body temperature (e.g., dehydration, extreme heat, strenuous exercise, concomitant use of anticholinergic agents).

GI Effects. Esophageal dysmotility and aspiration have been associated with the use of antipsychotic agents. Use with caution in patients at risk for aspiration pneumonia (e.g., geriatric patients, those with advanced Alzheimer's dementia).

Suicide. Attendant risk with bipolar disorder and psychotic illnesses; closely supervise high-risk patients. In clinical studies in patients with bipolar depression, the incidence of treatment-emergent suicidal ideation or suicide attempt in quetiapine-treated patients was low (1.7–2.6%) and similar to that observed with placebo (2%). Prescribe in the smallest quantity consistent with good patient management to reduce the risk of overdosage. (See Worsening of Depression and Suicidality Risk under Warnings/Precautions: Warnings, in Cautions.)

Dispensing and Administration Precautions. Because of similarity in spelling between Seroquel® (the trade name for quetiapine fumarate) and Serzone® (the former trade name for nefazodone hydrochloride, an antidepressant agent; no longer commercially available in the US under this trade name), dispensing errors have been reported to the US Food and Drug Administration (FDA) and the manufacturer of Seroquel® (AstraZeneca). According to the medication error reports, the overlapping strengths (100 and 200 mg), dosage forms (tablets), and dosing intervals (twice daily) and the fact that these 2 drugs were stored closely together in pharmacies also were critical in causing these errors. These medication errors may be associated with adverse CNS (e.g., mental status deterioration, hallucination, paranoia, muscle weakness, lethargy, dizziness) and GI effects (e.g., nausea, vomiting, diarrhea). As of November 2001, 4 patients had required emergency room visits and 3 patients reportedly had been hospitalized because of dispensing errors involving these 2 agents. One female patient 25 years of age experienced fever and respiratory arrest after mistakenly taking Seroquel® for 3 days instead of taking Serzone®, and even-

tually died, although a causal relationship has not been established. FDA also is concerned that several patients unintentionally ingested Serzone® or Seroquel® for a prolonged period of time before the error was discovered. Therefore, extra care should be exercised in ensuring the accuracy of both oral and written prescriptions for Seroquel® and Serzone®. Although the Serzone brand was discontinued in June 2004, clinicians may continue to refer to nefazodone by the former brand name in prescribing. Some experts recommend that pharmacists assess the measures of avoiding dispensing errors and implement them as appropriate (e.g., by verifying all orders for these agents by spelling both the trade and generic names to prescribers, using computerized name alerts, attaching reminders to drug containers and pharmacy shelves, separating the drugs on pharmacy shelves, counseling patients).

Patients should be advised to question the dispensing pharmacist regarding any changes in the appearance of their prescription in terms of shape, color, or size of the tablets. Dispensing errors involving Seroquel® (quetiapine) and Serzone® (nefazodone) should be reported to the manufacturers or directly to the FDA MedWatch program by phone (800-FDA-1088), by fax (800-FDA-0178), by the Internet (http://www.fda.gov/Safety/MedWatch/default.htm), or by mail (FDA Safety Information and Adverse Event Reporting Program, FDA, 5600 Fishers Lane, Rockville, MD 20852-9787).

Specific Populations **Pregnancy.** Category C. (See Users Guide.)

Lactation. Quetiapine is distributed into milk in animals. Not known whether quetiapine is distributed into milk in humans. The manufacturer states that women receiving quetiapine should not breast-feed.

Pediatric Use. Safety and efficacy not established in children younger than 18 years of age.

FDA warns that a greater risk of suicidal thinking or behavior (suicidality) occurred during first few months of antidepressant treatment (4%) compared with placebo (2%) in children and adolescents with major depressive disorder, obsessive-compulsive disorder (OCD), or other psychiatric disorders based on pooled analyses of 24 short-term, placebo-controlled trials of 9 antidepressant drugs (selective serotonin-reuptake inhibitors [SSRIs] and other antidepressants). However, a more recent meta-analysis of 27 placebo-controlled trials of 9 antidepressants (SSRIs and others) in patients younger than 19 years of age with major depressive disorder, OCD, or non-OCD anxiety disorders suggests that the benefits of antidepressant therapy in treating these conditions may outweigh the risks of suicidal behavior or suicidal ideation. No suicides occurred in these pediatric trials.

Carefully consider these findings when assessing potential benefits and risks of quetiapine in a child or adolescent for any clinical use. (See Worsening of Depression and Suicidality Risk under Warnings/Precautions: Warnings, in Cautions.)

Geriatric Use. In clinical studies, approximately 7% of 3400 patients were 65 years of age or older. While no substantial differences in safety relative to younger adults were observed, factors that decrease pharmacokinetic clearance, increase the pharmacodynamic response, or cause poorer tolerance (e.g., orthostasis) may be present in geriatric patients. (See Dosage and Administration: Special Populations and see also Increased Mortality in Geriatric Patients with Dementia-related Psychosis under Warnings/Precautions: Warnings, in Cautions.)

In pooled data analyses, a *reduced* risk of suicidality was observed in adults 65 years of age or older with antidepressant therapy compared with placebo. (See Worsening of Depression and Suicidality Risk under Warnings/Precautions: Warnings, in Cautions.)

Hepatic Impairment. Increased plasma concentrations expected in patients with hepatic impairment; dosage adjustment may be necessary. (See Dosage and Administration: Special Populations.)

Renal Impairment. Clearance may be decreased in patients with severe renal impairment, but dosage adjustment is not necessary.

■ **Common Adverse Effects** The most common adverse effects reported in 5% or more of patients receiving quetiapine therapy for schizophrenia or bipolar disorder and at a frequency twice that reported among patients receiving placebo in clinical trials include somnolence, sedation, asthenia, lethargy, dizziness, dry mouth, constipation, increased ALT, weight gain, dyspepsia, abdominal pain, postural hypotension, and pharyngitis.

Drug Interactions

■ **Drugs Affecting Hepatic Microsomal Enzymes** Inhibitors of cytochrome P-450 (CYP) isoenzyme 3A4 (e.g., erythromycin, fluconazole, itraconazole, ketoconazole): potential pharmacokinetic interaction (increased serum quetiapine concentrations). Use with caution.

Inducers of CYP3A4 (e.g., barbiturates, carbamazepine, glucocorticoids, phenytoin, rifampin): potential pharmacokinetic interaction (increased quetiapine metabolism and decreased serum quetiapine concentrations). Dosage adjustment may be necessary if these drugs are initiated or discontinued in patients receiving quetiapine. (See Drug Interactions: Phenytoin.)

■ **Drugs Metabolized by Hepatic Microsomal Enzymes** Substrates of CYP1A2, CYP3A4, CYP2C9, CYP2C19, or CYP2D6: pharmacokinetic interaction unlikely.

■ **Alcohol** Potential pharmacologic interaction (additive CNS effects). Avoid alcoholic beverages during quetiapine therapy.

■ **Cimetidine** Concomitant use of cimetidine (400 mg 3 times daily for 4 days) and quetiapine (150 mg 3 times daily) decreased mean clearance of quetiapine by 20%. However, dosage adjustment of quetiapine is not necessary.

■ **Divalproex** Potential pharmacokinetic interaction. Increased maximum plasma quetiapine concentrations, with no effect on extent of quetiapine absorption or mean clearance. Decreased maximum plasma valproic acid concentrations and extent of absorption (not clinically important).

■ **Fluoxetine, Haloperidol, Imipramine, Risperidone** No effect on steady-state pharmacokinetics of quetiapine observed.

■ **Hypotensive Agents** Potential pharmacologic interaction (additive hypotensive effects).

■ **Levodopa and Dopamine Agonists** Potential pharmacologic interaction (antagonistic effects).

■ **Lithium** No effect on steady-state lithium pharmacokinetics observed.

■ **Lorazepam** Potential pharmacokinetic interaction (decreased clearance of lorazepam). Concomitant use of quetiapine (250 mg 3 times daily) and lorazepam (single 2-mg dose) resulted in a 20% decrease in the mean clearance of lorazepam.

■ **Phenytoin** Concomitant use of quetiapine (250 mg 3 times daily) and phenytoin (100 mg 3 times daily) resulted in a fivefold increase in quetiapine clearance. An increase in quetiapine dosage may be required; caution advised if phenytoin is withdrawn and replaced with a noninducer of CYP3A4 (e.g., valproate).

■ **Thioridazine** Potential pharmacokinetic interaction (increased oral clearance of quetiapine).

■ **Other CNS Agents** Potential pharmacologic interaction (additive CNS effects). Use with caution.

Description

Quetiapine is a dibenzothiazepine-derivative antipsychotic agent. The drug is pharmacologically similar to clozapine, but differs pharmacologically from other currently available first-generation (typical) antipsychotic agents (e.g., phenothiazines, butyrophenones). Because of these pharmacologic differences, quetiapine is considered an atypical or second-generation antipsychotic agent.

The exact mechanism of quetiapine's antipsychotic action in schizophrenia and its mood stabilizing action in bipolar disorder has not been fully elucidated but may involve antagonism at serotonin type 1 (5-hydroxytryptamine [5-HT_{1A}]) and type 2 (5-HT_{2A}, 5-HT_{2C}) receptors, and at dopamine (D_1, D_2) receptors.

Current evidence suggests that the clinical potency and antipsychotic efficacy of both typical and atypical antipsychotic drugs generally are related to their affinity for and blockade of central dopamine D_2 receptors; however, antagonism at dopamine D_2 receptors does not appear to account fully for the antipsychotic effects of quetiapine. Results of in vivo and in vitro studies indicate that quetiapine is a comparatively weak antagonist at dopamine D_2 receptors. Receptor binding studies show quetiapine is a weak antagonist at D_1 receptors. Although their role in eliciting the pharmacologic effects of antipsychotic agents remains to be fully elucidated, dopamine D_3, D_4, and D_5 receptors also have been identified; quetiapine possesses no affinity for the dopamine D_4 receptor.

The therapeutic effects of antipsychotic drugs are thought to be mediated by dopaminergic blockade in the mesolimbic and mesocortical areas of the CNS, while antidopaminergic effects in the neostriatum appear to be associated with extrapyramidal effects. The apparently low incidence of extrapyramidal effects associated with quetiapine therapy suggests that the drug is more active in the mesolimbic than in the neostriatal dopaminergic system. In contrast to typical antipsychotic agents (e.g., chlorpromazine) but like other atypical antipsychotic drugs (e.g., clozapine), quetiapine does not cause sustained elevations in serum prolactin concentrations and therefore is unlikely to produce adverse effects such as amenorrhea, galactorrhea, and impotence.

Quetiapine exhibits α_1- and α_2-adrenergic blocking activity; blockade of α_1-adrenergic receptors may explain the occasional orthostatic hypotension associated with the drug. Quetiapine also blocks histamine H_1 receptors, which may explain the sedative effects associated with the drug. Quetiapine possesses little or no affinity for β-adrenergic, γ-aminobutyric acid (GABA), benzodiazepine, or muscarinic receptors.

Quetiapine is extensively metabolized in the liver principally via sulfoxidation and oxidation to inactive metabolites. In vitro studies suggest that the cytochrome P-450 (CYP) 3A4 isoenzyme is involved in the metabolism of quetiapine to the inactive sulfoxide metabolite, which is the principal metabolite. The mean terminal half-life of quetiapine is about 6 hours. Following oral administration of a single dose of quetiapine, approximately 73 and 20% of the dose is excreted in urine and feces, respectively; less than 1% of the dose is excreted unchanged. Based on in vitro studies, quetiapine and 9 of its metabolites do not appear likely to inhibit CYP isoenzymes 1A2, 3A4, 2C9, 2C19, or 2D6.

Advice to Patients

Risk of suicidality; importance of patients, family, and caregivers being alert to and immediately reporting emergence of suicidality, worsening depression, or unusual changes in behavior, especially during the first few months

of therapy or during periods of dosage adjustment. FDA recommends providing written patient information (medication guide) explaining risks of suicidality each time the drug is dispensed.

Risk of orthostatic hypotension, especially during initial dosage titration and at times of reinitiation of therapy or increases in dosage.

Risk of somnolence and impairment of judgment, thinking, or motor skills; avoid driving, operating machinery, or performing hazardous tasks until effects on the individual are known.

Importance of avoiding alcohol during quetiapine therapy.

Importance of informing clinicians of existing or contemplated concomitant therapy, including prescription and OTC drugs, as well as any concomitant illnesses (e.g., diabetes mellitus).

Importance of women informing clinicians if they are or plan to become pregnant or plan to breast-feed.

Importance of avoiding overheating or dehydration.

Importance of informing patients of other important precautionary information. (See Cautions.)

Overview (see Users Guide). **For additional information on this drug until a more detailed monograph is developed and published, the manufacturer's labeling should be consulted. It is *essential* that the manufacturer's labeling be consulted for more detailed information on usual cautions, precautions, contraindications, potential drug interactions, laboratory test interferences, and acute toxicity.**

Preparations

Excipients in commercially available drug preparations may have clinically important effects in some individuals; consult specific product labeling for details.

Quetiapine Fumarate

Oral

Tablets, film-coated	25 mg (of quetiapine)	Seroquel®, AstraZeneca
	50 mg (of quetiapine)	Seroquel®, AstraZeneca
	100 mg (of quetiapine)	Seroquel®, AstraZeneca
	200 mg (of quetiapine)	Seroquel®, AstraZeneca
	300 mg (of quetiapine)	Seroquel®, AstraZeneca
	400 mg (of quetiapine)	Seroquel®, AstraZeneca

Risperidone

■ Risperidone has been described as an atypical or second-generation antipsychotic agent.

Uses

■ **Psychotic Disorders** Risperidone is used for the symptomatic management of psychotic disorders. Drug therapy is integral to the management of acute psychotic episodes and accompanying violent behavior in patients with schizophrenia and generally is required for long-term stabilization to sustain symptom remission or control and to minimize the risk of relapse. Antipsychotic agents are the principal class of drugs used for the management of all phases of schizophrenia. Patient response and tolerance to antipsychotic agents are variable, and patients who do not respond to or tolerate one drug may be successfully treated with an agent from a different class or with a different adverse effect profile.

Schizophrenia and Other Psychotic Disorders Efficacy of oral risperidone for the management of psychotic disorders has been established by controlled studies of 4–8 weeks' duration principally in patients with schizophrenic disorders in hospital settings. Schizophrenia is a major psychotic disorder that frequently has devastating effects on various aspects of the patient's life and carries a high risk of suicide and other life-threatening behaviors. Manifestations of schizophrenia involve multiple psychologic processes, including perception (e.g., hallucinations), ideation, reality testing (e.g., delusions), emotion (e.g., flatness, inappropriate affect), thought processes (e.g., loose associations), behavior (e.g., catatonia, disorganization), attention, concentration, motivation (e.g., avolition, impaired intention and planning), and judgment. The principal manifestations of this disorder usually are described in terms of positive and negative (deficit) symptoms, and more recently, disorganized symptoms. Positive symptoms include hallucinations, delusions, bizarre behavior, hostility, uncooperativeness, and paranoid ideation, while negative symptoms include restricted range and intensity of emotional expression (affective flattening), reduced thought and speech productivity (alogia), anhedonia, apathy, and decreased initiation of goal-directed behavior (avolition). Disorganized symptoms include disorganized speech (thought disorder) and behavior and poor attention. For additional information on the symptomatic management of schizophrenia, including treatment recommendations and results of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study, see Schizophrenia and Other Psychotic Disorders under Uses: Psychotic Disorders, in the Phenothiazines General Statement 28:16.08.24.

In clinical studies principally in patients with schizophrenia, oral risperidone was more effective than placebo and at least as effective as typical (e.g., haloperidol, perphenazine) and certain atypical (e.g., olanzapine) antipsychotics in the treatment of schizophrenia. Data from limited clinical studies indicate that risperidone improves both positive and negative manifestations of schizophrenia, but that such improvements may not be substantially greater than those achieved by haloperidol, a typical antipsychotic. Risperidone was more effective than haloperidol in preventing relapse in adult outpatients with clinically stable schizophrenia or schizoaffective disorders who were assigned to receive either drug for a minimum of 1 year. In this study, approximately 25% of patients who received usual dosages of risperidone had relapsed by the end of the study compared with approximately 40% of those receiving usual dosages of haloperidol. In these studies, improvement in manifestations of schizophrenia was based on the results of various psychiatric rating scales, including the Brief Psychiatric Rating Scale (BPRS) that assesses factors such as anergy, thought disturbances, activation, hostility/suspiciousness, and anxiety/depression; the BPRS psychosis cluster that assesses factors such as conceptual disorganization, hallucinatory behavior, suspiciousness, and unusual thought content in actively psychotic schizophrenic patients; the Scale for the Assessment of Negative Symptoms (SANS); the Positive and Negative Syndrome Scale (PANSS); and the Clinical Global Impression (CGI) scale.

Because of their safety and efficacy, some authorities consider conventional antipsychotic agents or risperidone to be reasonable first-line drugs for the management of the acute phase of schizophrenia. Risperidone may be particularly useful in patients who experience extrapyramidal reactions with typical antipsychotic agents since the drug appears to cause fewer extrapyramidal reactions at clinically effective dosages. Some authorities state that risperidone or newer atypical antipsychotic agents (such as olanzapine) also may be advantageous in patients who have not responded adequately to therapy with a conventional antipsychotic agent. However, the efficacy of atypical antipsychotics, other than clozapine, in treatment-resistant schizophrenia has yet to be established, and the possible clinical benefits of risperidone therapy should be weighed against the potential drawbacks, including its higher cost compared with standard agents and the lack of a parenteral preparation of the drug.

Geriatric Considerations. Although risperidone has been studied for use in the management of psychosis and aggression in institutionalized geriatric patients with moderate to severe dementia of the Alzheimer's† type (Alzheimer's disease, presenile or senile dementia), vascular dementia†, or a combination of the 2 types of dementia (i.e., mixed dementia†), there is evidence that use of the drug in geriatric patients with dementia may be associated with an increased risk of adverse cerebrovascular events. In randomized, placebo-controlled studies in nursing home residents with dementia, oral risperidone at a dosage of approximately 1 mg daily was more effective than placebo in decreasing psychotic and behavioral symptoms (e.g., aggression, agitation) of dementia, as assessed by the Behavioral Pathology in Alzheimer's Disease scale (BEHAVE-AD) and the Cohen-Mansfield Agitation Inventory (CMAI). However, evidence from these studies showed a significantly higher incidence of adverse cerebrovascular events such as stroke and transient ischemic attacks (TIAs) associated with risperidone therapy relative to placebo. In addition, geriatric patients with dementia-related psychosis treated with atypical antipsychotic agents appear to be at an increased risk of death compared with that among patients receiving placebo. (See Cautions: Geriatric Precautions.) Risperidone is not approved for the treatment with dementia-related psychosis.

■ **Bipolar Disorder** Risperidone is used alone or in conjunction with lithium or valproate for the management of manic and mixed episodes associated with bipolar I disorder. Efficacy of risperidone monotherapy in the treatment of acute manic and mixed episodes has been demonstrated in 2 placebo-controlled trials of 3 weeks' duration in patients who met the DSM-IV criteria for bipolar I disorder with acute manic or mixed episodes with or without psychotic features. The principal rating instrument used for assessing manic symptoms in these trials was the Young Mania Rating Scale (Y-MRS), an 11-item clinician-rated scale traditionally used to assess the degree of manic symptomatology in a range from 0 (no manic features) to 60 (maximum score). In the first 3-week, placebo-controlled trial, which was limited to patients with manic episodes, risperidone monotherapy was given at an initial dosage of 3 mg daily and subsequently in a flexible dosage ranging from 1–6 mg daily; the mean modal dosage was 4.1 mg daily. In the second 3-week, placebo-controlled trial, patients also were given an initial dosage of risperidone 3 mg daily and subsequently a flexible dosage ranging from 1–6 mg daily; the mean modal dosage was 5.6 mg daily. Risperidone was found to be superior to placebo in the reduction of the Y-MRS total score in both studies.

Efficacy of risperidone when used in conjunction with lithium or valproate in the treatment of acute manic or mixed episodes has been demonstrated in one placebo-controlled trial of 3 weeks' duration in patients who met the DSM-IV criteria for bipolar I disorder (with or without a rapid cycling course) and who met diagnostic criteria for an acute manic or mixed episode (with or without psychotic features). In this study, inpatients and outpatients with bipolar disorder experiencing manic or mixed episodes who had not adequately responded to lithium or valproate monotherapy were randomized to receive risperidone, haloperidol, or placebo in conjunction with their original therapy. Risperidone therapy was given in an initial dosage of 2 mg daily and subsequently given in a flexible dosage ranging from 1–6 mg daily; the mean modal dosage was 3.8 mg daily. Lithium and valproate were given in conjunction with risperidone and plasma drug concentrations were maintained within ther-

desipramine recommends that the drug *not* be used in children. Although a causal relationship between the use of desipramine and the risk of sudden death has not been established, many clinicians recommend that desipramine *not* be used in children with this disorder when tricyclic antidepressant therapy is contemplated.

The US Food and Drug Administration (FDA) also has determined that antidepressants increase the risk of suicidal thinking and behavior (suicidality) in children and adolescents with major depressive disorder and other psychiatric disorders. However, FDA also states that depression and certain other psychiatric disorders are themselves associated with an increased risk of suicide. Anyone considering the use of desipramine in a child or adolescent for any clinical use must therefore balance the potential risk of therapy with the clinical need. (See Cautions: Precautions and Contraindications and Cautions: Pediatric Precautions, in the Tricyclic Antidepressants General Statement 28:16.04.28.)

■ **Geriatric Precautions** Geriatric patients may be at risk of drug-induced toxicity when treated with desipramine, a tricyclic antidepressant that is known to be eliminated mainly by the kidneys. In this patient population, the ratio of plasma concentrations of the principal metabolite, 2-hydroxydesipramine, to desipramine appears to be increased, most likely because of decreased renal elimination that occurs with aging. Therefore, particular attention should be paid to desipramine dosage and it may be useful to monitor renal function in these patients. Desipramine use in geriatric patients also has been associated with an increased risk of falling and mental confusion. (See Cautions: Geriatric Precautions, in the Tricyclic Antidepressants General Statement 28:16.04.28.)

Pharmacokinetics

■ **Absorption** Desipramine hydrochloride appears to be well absorbed from the GI tract. Peak plasma concentrations occur within 4–6 hours after oral administration.

■ **Distribution** Limited data indicate that desipramine is distributed into milk in concentrations similar to those present in maternal plasma.

■ **Elimination** The plasma half-life of desipramine ranges from 7 to longer than 60 hours. Desipramine is metabolized principally via oxidation to 2-hydroxydesipramine, which retains some of the parent compound's ability to block the uptake of amines and may have particularly prominent cardiac depressant activity.

Chemistry and Stability

■ **Chemistry** Desipramine is a dibenzazepine-derivative tricyclic antidepressant that is the active metabolite of imipramine. Desipramine hydrochloride occurs as a white to off-white crystalline powder and is soluble in water and in alcohol. The drug has pK_as of 1.5 and 10.2.

■ **Stability** Desipramine hydrochloride tablets should be stored in tight containers at room temperature, preferably less than 30°C, and protected from excessive heat. Commercially available desipramine hydrochloride tablets have expiration dates of 5 years following the date of manufacture.

For further information on chemistry, pharmacology, pharmacokinetics, uses, cautions, acute toxicity, drug interactions, and dosage and administration of desipramine, see the Tricyclic Antidepressants General Statement 28:16.04.28.

Preparations

Excipients in commercially available drug preparations may have clinically important effects in some individuals; consult specific product labeling for details.

Desipramine Hydrochloride

Oral		
Tablets	10 mg*	**Desipramine Hydrochloride Tablets**
	25 mg*	**Desipramine Hydrochloride Tablets**
	50 mg*	**Desipramine Hydrochloride Tablets**
	75 mg*	**Desipramine Hydrochloride Tablets**
	100 mg*	**Desipramine Hydrochloride Tablets**
	150 mg*	**Desipramine Hydrochloride Tablets**
Tablets, film-coated	10 mg	**Norpramin®, Sanofi-Aventis**
	25 mg	**Norpramin®, Sanofi-Aventis**
	50 mg	**Norpramin®, Sanofi-Aventis**
	75 mg	**Norpramin®, Sanofi-Aventis**
	100 mg	**Norpramin®, Sanofi-Aventis**
	150 mg	**Norpramin®, Sanofi-Aventis**

*available from one or more manufacturer, distributor, and/or repackager by generic (nonproprietary) name

Doxepin Hydrochloride

■ Doxepin hydrochloride is a dibenzoxepin-derivative tricyclic antidepressant.

Uses

■ **Depressive and Anxiety Disorders** Doxepin shares the pharmacologic actions of the other tricyclic antidepressants and is used principally in the treatment of depression and/or anxiety in psychoneurotic patients, depression and/or anxiety associated with alcoholism or organic disease, and psychotic depressive disorders with associated anxiety, including involutional depression and manic-depressive disorders. Symptoms of psychoneurosis that respond well to doxepin include anxiety, tension, depression, somatic symptoms and concerns, sleep disturbances, guilt, lack of energy, fear, apprehension, and worry.

For further information on treatment of major depression and considerations in choosing the most appropriate antidepressant for a particular patient, including considerations related to patient tolerance, patient age, and cardiovascular, sedative, and suicidality risks, see Considerations in Choosing Antidepressants under Uses: Major Depressive Disorder, in the Tricyclic Antidepressants General Statement 28:16.04.28.

■ **Chronic Idiopathic Urticaria** Doxepin also has been effective in the management of chronic idiopathic urticaria and may be used as an alternative to antihistamines, which generally are considered as first-line therapy in patients with this condition.

Dosage and Administration

■ **Administration** Doxepin hydrochloride is administered orally. Although doxepin has been administered in up to 3 divided doses throughout the day, it is long-acting and the entire daily dose may be administered at one time. Administration of the entire daily dose at bedtime may reduce daytime sedation.

Each dose of the oral concentrate should be diluted with approximately 120 mL of water, whole or skimmed milk, or orange, grapefruit, tomato, prune, or pineapple juice just prior to administration; the solution is physically incompatible with many carbonated beverages. For patients requiring doxepin therapy while on methadone maintenance, doxepin solution and methadone syrup can be mixed together with Gatorade®, lemonade, orange juice, sugar water, Tang®, or water, but not with grape juice. Bulk dilution and storage are not recommended by the manufacturers.

Doxepin is applied topically to the skin as an antipruritic. (See Doxepin Hydrochloride 84:08.)

■ **Dosage** Dosage of doxepin hydrochloride is expressed in terms of doxepin. There is a wide range of dosage requirements, and dosage must be carefully individualized. Initial dosages should be low and generally range from 30–150 mg daily, depending on the severity of the condition being treated. Dosage may be gradually adjusted to the level which produces maximal therapeutic effect with minimal toxicity and may range up to 300 mg daily. The manufacturers state that dosages exceeding 300 mg daily rarely produce additional therapeutic benefits. Hospitalized patients under close supervision may generally be given higher dosages than outpatients. Patients with very mild symptomatology or organic brain syndrome should usually be given lower than average dosages and may obtain satisfactory improvement with 25–50 mg of doxepin daily. The manufacturers state that appropriate dosage in geriatric patients should be selected with caution, usually initiating therapy at the low end of the dosage range since decreased hepatic, renal, or cardiac function occurs more frequently in these patients.

When doxepin is administered as a single daily dose, the maximum daily dose recommended by the manufacturers is 150 mg. Commercially available 150-mg capsules of doxepin are intended for maintenance therapy only and are not recommended for initial therapy. Maximum antidepressant effects may not occur for 2 or more weeks after therapy is begun, although anxiolytic effects may develop more rapidly.

After symptoms are controlled, dosage should be gradually reduced to the lowest level which will maintain relief of symptoms. To avoid the possibility of precipitating withdrawal symptoms, doxepin should not be terminated abruptly in patients who have received high dosages for prolonged periods.

Patients should be monitored for possible worsening of depression, suicidality, or unusual changes in behavior, especially at the beginning of therapy or during periods of dosage adjustment. (See Cautions: Precautions and Contraindications, in the Tricyclic Antidepressants General Statement 28:16.04.28.)

Cautions

Doxepin shares the pharmacologic actions and toxic potentials of the tricyclic antidepressants, and the usual precautions of tricyclic antidepressant administration should be observed. Patients should be fully advised about the risks, especially suicidal thinking and behavior (suicidality), associated with tricyclic antidepressant therapy. For a complete discussion, see Cautions: Precautions and Contraindications and Cautions: Pediatric Precautions, in the Tricyclic Antidepressants General Statement 28:16.04.28.

■ **Pediatric Precautions** Safety of doxepin in children younger than 12 years of age has not been established.

The US Food and Drug Administration (FDA) has determined that antidepressants increase the risk of suicidal thinking and behavior (suicidality) in children and adolescents with major depressive disorder and other psychiatric disorders. However, FDA also states that depression and certain other psychiatric disorders are themselves associated with an increased risk of suicide. Anyone considering the use of doxepin in a child or adolescent for any clinical use must therefore balance the potential risk of therapy with the clinical need. (See Cautions: Precautions and Contraindications and Cautions: Pediatric Precautions, in the Tricyclic Antidepressants General Statement 28:16.04.28.)

■ **Lactation** Limited data indicate that doxepin and its active *N*-demethylated metabolite are distributed into milk. Sedation and serious respiratory depression were reported in a nursing infant whose mother was receiving 75 mg of doxepin daily; substantial concentrations of the active metabolite of the drug were detected in the infant's serum and urine. In addition, poor sucking and swallowing while nursing, drowsiness, muscle hypotonia, and vomiting were reported in a nursing infant whose mother was receiving 35 mg of doxepin daily. Because of the potential for serious adverse reactions to doxepin and/or its active metabolite in nursing infants, a decision should be made whether to discontinue nursing or the drug, taking into account the importance of the drug to the woman.

Pharmacokinetics

■ **Absorption** The pharmacokinetics of doxepin have not been extensively studied, but the drug is well absorbed from the GI tract in animals. Peak plasma concentrations usually occur within 2 hours after oral administration of the drug.

■ **Distribution** Doxepin is highly bound to plasma proteins.

Limited data indicate that doxepin and its active *N*-demethylated metabolite are distributed into milk in concentrations reportedly ranging from about 30–140% and 10–115%, respectively, of those in maternal serum and that substantial concentrations of the active metabolite have been detected in the serum and urine of nursing infants whose mothers were receiving 75–150 mg of doxepin daily.

■ **Elimination** The plasma half-life of doxepin is 6–24.5 hours. The drug appears to be metabolized via the same pathways as are other tricyclic antidepressants; its *N*-demethylated metabolite is pharmacologically active.

Chemistry and Stability

■ **Chemistry** Doxepin hydrochloride is a dibenzoxepin-derivative tricyclic antidepressant. The drug occurs as a white powder, is freely soluble in water and in alcohol, and has a pK_a of 8. Doxepin hydrochloride oral concentrate has a pH of 4–7.

■ **Stability** Doxepin hydrochloride capsules should be stored in tight, light-resistant containers at a temperature between 15–30°C and the oral concentrate should be stored at a temperature between 20–25°C. Commercially available doxepin hydrochloride capsules have an expiration date of 36 months and the oral concentrate has an expiration date of 24 months following the date of manufacture.

Doxepin hydrochloride oral concentrate is physically incompatible with many carbonated beverages, but is compatible with some other beverages. (See Dosage and Administration: Administration.) Bulk preparation and storage of dilutions of the commercially available oral concentrate are not recommended by the manufacturers.

For further information on chemistry, pharmacology, pharmacokinetics, uses, cautions, acute toxicity, drug interactions, and dosage and administration of doxepin, see the Tricyclic Antidepressants General Statement 28:16.04.28.

Preparations

Excipients in commercially available drug preparations may have clinically important effects in some individuals; consult specific product labeling for details.

Doxepin Hydrochloride

Oral		
Capsules	10 mg (of doxepin)*	Doxepin Hydrochloride Capsules
		Sinequan®, Pfizer
	25 mg (of doxepin)*	Doxepin Hydrochloride Capsules
		Sinequan®, Pfizer
	50 mg (of doxepin)*	Doxepin Hydrochloride Capsules
		Sinequan®, Pfizer
	75 mg (of doxepin)*	Doxepin Hydrochloride Capsules
		Sinequan®, Pfizer
	100 mg (of doxepin)*	Doxepin Hydrochloride Capsules
		Sinequan®, Pfizer
	150 mg (of doxepin)*	Doxepin Hydrochloride Capsules
		Sinequan®, Pfizer
Solution, concentrate	10 mg (of doxepin) per mL*	Doxepin Hydrochloride Oral Solution (Concentrate)
		Sinequan® Oral Concentrate, Pfizer

*available from one or more manufacturer, distributor, and/or repackager by generic (nonproprietary) name

Imipramine Hydrochloride
Imipramine Pamoate

■ Imipramine is a dibenzazepine-derivative tricyclic antidepressant.

Dosage and Administration

■ **Administration** Imipramine hydrochloride and imipramine pamoate are administered orally. Although imipramine hydrochloride has been administered in up to 4 divided doses throughout the day, it is long-acting and the entire oral daily dose may be administered at one time. Imipramine pamoate may also be used to administer the daily oral dose of imipramine, but it has no advantages over the hydrochloride. Administration of the entire daily dose at bedtime may reduce daytime sedation; patients who experience insomnia and stimulation may be given the entire daily dose in the morning.

■ **Dosage** Dosage of imipramine salts is expressed in terms of imipramine hydrochloride.

Patients should be monitored for possible worsening of depression, suicidality, or unusual changes in behavior, especially at the beginning of therapy or during periods of dosage adjustment. (See Cautions: Precautions and Contraindications, in the Tricyclic Antidepressants General Statement 28:16.04.28.)

Major Depressive Disorder There is a wide range of oral dosage requirements, and dosage must be carefully individualized. Initial dosages of imipramine should be low and generally range from 75–100 mg daily, depending on the severity of the condition being treated. Dosage may be gradually adjusted to the level that produces maximal therapeutic effect with minimal toxicity and may range up to 300 mg daily. Hospitalized patients under close supervision may generally be given higher dosages than outpatients, and manufacturers state that dosages of greater than 200 mg daily are not recommended for outpatients. Geriatric patients should usually be given lower than average dosages. Manufacturers state that therapy should be initiated with 25–50 mg daily as imipramine hydrochloride (e.g., Tofranil®) in these patients and that optimal dosage rarely exceeds 100 mg daily. If the daily dosage is established at 75 mg or more, imipramine pamoate (e.g., Tofranil-PM®) may be administered. Maximum antidepressant effects may not occur for 2 or more weeks after therapy is begun.

After symptoms are controlled, dosage should be gradually reduced to the lowest level that will maintain relief of symptoms. If maintenance therapy is necessary, manufacturers recommend an adult dosage of 50–150 mg daily. To avoid the possibility of precipitating withdrawal symptoms, imipramine should not be terminated abruptly in patients who have received high dosage for prolonged periods.

Functional Enuresis in Children For the treatment of functional enuresis in children who are at least 6 years of age, the usual initial oral dosage of imipramine hydrochloride is 25 mg daily, administered 1 hour prior to bedtime. If a satisfactory response is not obtained within 1 week, dosage may be increased to 50 mg nightly for children younger than 12 years of age or 75 mg nightly for children 12 years of age and older. Dosages higher than 75 mg daily do not improve results and may increase the risk of adverse reactions. For children who are early-night bedwetters, better results may be obtained by administering 25 mg in midafternoon and again at bedtime. Dosage of imipramine hydrochloride for the treatment of functional enuresis in children should not exceed 2.5 mg/kg daily. Long-term effects of the drug in children have not been determined; therefore, after a satisfactory response has been maintained, imipramine hydrochloride should be gradually withdrawn. If dosage is gradually reduced after a favorable response of many weeks, relapses may be less frequent; children who relapse may not respond to subsequent treatment with imipramine. (See Cautions: Pediatric Precautions.)

Cautions

Imipramine shares the pharmacologic actions, uses, and toxic potentials of the tricyclic antidepressants, and the usual precautions of tricyclic antidepressant administration should be observed. Patients should be fully advised about the risks, especially suicidal thinking and behavior (suicidality), associated with tricyclic antidepressant therapy. For a complete discussion, see Cautions: Precautions and Contraindications and Cautions: Pediatric Precautions, in the Tricyclic Antidepressants General Statement 28:16.04.28.

Although the clinical importance is not known, ECG changes have been reported in pediatric patients receiving twice the recommended maximum daily dosage.

quently in patients receiving acamprosate than in those receiving placebo (2.4 versus 0.8%). Completed suicide occurred in 0.13% of patients receiving acamprosate in clinical studies and in 0.1% of those receiving placebo. While many of these events occurred in the context of alcohol relapse, a consistent pattern between recovery from alcoholism and the emergence of suicidality was not identified. These studies excluded patients with severe psychiatric impairment, and review of safety data did not show a difference in the incidence of adverse events designated as depression between those receiving acamprosate and those receiving placebo. The existence of a relationship between alcohol dependence, depression, and suicidality is well known.

Closely monitor patients for symptoms of depression and suicidal thinking.

Specific Populations **Pregnancy.** Category C. (See Users Guide.)

Lactation. Acamprosate is distributed into milk in rats; caution if used in nursing women.

Pediatric Use. Safety and efficacy not established in children younger than 18 years of age. Acamprosate has been evaluated in a limited number of adolescents 16–19 years of age.

Geriatric Use. Experience in those 65 years of age or older insufficient to determine whether they respond differently than younger adults.

Pharmacokinetics not evaluated in geriatric individuals. Because geriatric patients frequently have decreased renal function, plasma concentrations of acamprosate are expected to be higher in geriatric individuals than in younger adults. Select drug dosage carefully. Consider monitoring renal function.

Hepatic Impairment. Pharmacokinetics not altered in patients with mild or moderate hepatic impairment (Child-Pugh class A or B). Safety and pharmacokinetics not evaluated in patients with severe hepatic impairment.

Renal Impairment. Acamprosate is eliminated in urine as unchanged drug; clearance depends on renal function. Dosage adjustment recommended in patients with creatinine clearance of 30–50 mL/minute. (See Dosage and Administration: Special Populations.) Contraindicated in patients with creatinine clearance less than 30 mL/minute.

■ **Common Adverse Effects** Adverse effects reported in 5% or more of patients receiving acamprosate and more frequently than placebo include diarrhea and asthenia.

Drug Interactions

Safety profile in patients receiving acamprosate in conjunction with anxiolytics, hypnotics and sedatives (including benzodiazepines), or nonopiate analgesics in clinical studies was similar to that in patients receiving these drugs with placebo.

Alcohol. Pharmacokinetic interaction unlikely.

Antidepressants. Changes in weight (i.e., loss or gain) reported more frequently in patients receiving acamprosate concomitantly with an antidepressant than in patients receiving either agent alone.

No change in the pharmacokinetics of desipramine or imipramine.

Diazepam. Pharmacokinetic interaction unlikely.

Disulfiram. Pharmacokinetic interaction unlikely.

Naltrexone. Pharmacokinetic interaction (increased plasma concentrations of acamprosate; no change in plasma concentrations of naltrexone or its major metabolite, 6-β-naltrexol). No dosage adjustment recommended.

Description

Acamprosate calcium is a synthetic homotaurine derivative and is structurally related to γ-aminobutyric acid (GABA).

While the precise mechanism of action of acamprosate in the maintenance of abstinence from alcohol ingestion remains to be determined, the drug decreases glutamatergic transmission and modulates neuronal hyperexcitability during withdrawal from alcohol. Acamprosate reduces voluntary intake of alcohol in alcohol-dependent animals. Acamprosate did not exhibit anticonvulsant, antidepressant, or anxiolytic activity in animal studies. Administration of acamprosate was not associated with the development of tolerance or dependence in animal studies. Acamprosate is not known to cause alcohol aversion. Ingestion of alcohol by individuals receiving acamprosate therapy does not result in a disulfiram-like reaction.

Acamprosate is eliminated principally in urine as unchanged drug. The drug is not metabolized in the liver. Acamprosate does not induce cytochrome P-450 (CYP) isoenzymes 1A2 or 3A4, nor does it inhibit CYP isoenzymes 1A2, 2C9, 2C19, 2D6, 2E1, or 3A4.

Advice to Patients

Risk of psychomotor impairment; importance of exercising caution while driving or operating hazardous machinery until the effects of the drug on the individual are known.

Importance of continuing acamprosate as directed by their clinician, even in the event of a relapse. Importance of discussing any renewed use of alcohol with their clinician.

Advise patients that acamprosate helps maintain abstinence only when used as part of a treatment program that includes counseling and other supportive measures.

Risk of suicidality: importance of patients, families, and caregivers notifying clinicians of emergence of suicidality or symptoms of depression.

Importance of women informing clinicians if they are or plan to become pregnant or plan to breast-feed.

Importance of informing clinicians of existing or contemplated concomitant therapy, including prescription and OTC drugs, as well as any concomitant illnesses.

Importance of informing patients of other important precautionary information. (See Cautions.)

Overview[A] (see Users Guide). For additional information on this drug until a more detailed monograph is developed and published, the manufacturer's labeling should be consulted. It is *essential* that the manufacturer's labeling be consulted for more detailed information on usual cautions, precautions, contraindications, potential drug interactions, laboratory test interferences, and acute toxicity.

Preparations

Excipients in commercially available drug preparations may have clinically important effects in some individuals; consult specific product labeling for details.

Acamprosate Calcium

Oral		
Tablets, delayed-release (enteric-coated)	333 mg	Campral®, Forest

Atomoxetine Hydrochloride

■ Atomoxetine is a selective norepinephrine-reuptake inhibitor.

Uses

Atomoxetine hydrochloride is used as an adjunct to psychological, educational, social, and other remedial measures in the treatment of attention-deficit hyperactivity disorder (ADHD).

■ **Attention Deficit Hyperactivity Disorder** Atomoxetine hydrochloride is used as an adjunct to psychological, educational, social, and other remedial measures in the treatment of ADHD (hyperkinetic disorder, hyperkinetic syndrome of childhood, minimal brain dysfunction) in adults and children 6 years of age and older. Efficacy of the drug for this indication was established in short-term (6–9 weeks) controlled clinical studies in children and adolescents 6–18 years of age and also in 10-week controlled clinical studies in adults who met DSM-IV criteria for ADHD. Efficacy of atomoxetine in the treatment of ADHD also was established in one longer-term (12 months) controlled clinical study in children and adolescents 6–15 years of age.

In controlled clinical studies in children 7–13 years of age with ADHD, therapy with atomoxetine (mean final dosage of 1.6 mg/kg daily, administered in 2 divided doses in the morning and late afternoon for 9 weeks) was more effective than placebo in decreasing inattention and hyperactive/impulsive symptoms, as measured by the ADHD Rating Scale-IV-Parent Version (ADHDRS), Clinical Global Impressions-ADHD-Severity (CGI-ADHD-S), and Conners Parent Rating Scale-Revised: Short Form (CPRS-R:S). In another controlled clinical study in children and adolescents 6–16 years of age with ADHD, therapy with atomoxetine (mean final dosage of 1.3 mg/kg once daily in the morning for 6 weeks) was more effective than placebo in decreasing inattention and hyperactive/impulsive symptoms, as measured by the ADHDRS, Conners Parent Rating Scale, and Conners Teacher Rating Scale.

In a randomized, placebo-controlled, dose-response study with atomoxetine (0.5, 1.2, or 1.8 mg/kg daily, administered in 2 divided doses in the morning and late afternoon for 8 weeks) in children and adolescents 8–18 years of age with ADHD, therapy with atomoxetine 1.2 or 1.8 mg/kg daily was more effective than placebo in decreasing inattention and hyperactive/impulsive symptoms, as measured by the ADHDRS, and improving social and family functioning, as measured by the Child Health Questionnaire (CHQ). Patients receiving atomoxetine 0.5 mg/kg daily exhibited responses intermediate to those observed in patients receiving placebo or atomoxetine at higher dosages (1.2 or 1.8 mg/kg daily), but no differences in response were observed between patients receiving dosages of 1.2 versus 1.8 mg/kg daily.

In an open-label, multicenter study in boys 7–15 years of age and girls 7–9 years of age with ADHD, therapy with atomoxetine (up to 2 mg/kg daily, administered in 2 divided doses in the morning and late afternoon) or methylphenidate (up to 60 mg daily, administered once daily or in 2 or 3 divided doses) for 10 weeks produced similar results in the reduction of ADHD symptoms; however, double-blind clinical studies are needed to establish the comparative efficacy and tolerance of these therapies.

In a randomized, double-blind, placebo-controlled maintenance study, 604 children and adolescents 6–15 years of age with ADHD initially received open-label atomoxetine (1.2–1.8 mg/kg daily in 2 divided doses) for 10 weeks. Patients who responded to therapy during the open-label phase were randomized at week 12 to receive either atomoxetine (at the same dosage) or placebo for an additional 9 months. At study end point, relapse (defined as an increase in ADHDRS total score to 90% of baseline score *and* an increase of 2 or more

points on the CGI-S scale) occurred in fewer patients receiving atomoxetine compared with those receiving placebo (22 versus 38%). When the more-sensitive secondary definition of relapse (an increase in ADHDRS total score to 50% of baseline score *and* an increase of 2 or more points on the CGI-S scale) was used, the relapse rate also was substantially lower in atomoxetine-treated patients (28%) than in placebo-treated patients (48%). In addition, patients who continued receiving atomoxetine experienced a longer time to relapse and achieved superior psychosocial functioning compared to those receiving placebo.

In controlled clinical studies in adults with ADHD, therapy with atomoxetine (mean final dosage of 95 mg daily, administered in 2 equally divided doses in the morning and late afternoon/early evening for 10 weeks) was more effective than placebo in decreasing inattention and hyperactive/impulsive symptoms, as measured by the Conners Adult ADHD Rating Scale (CAARS).

Dosage and Administration

■ **Administration** Atomoxetine hydrochloride may be administered orally once daily in the morning or in 2 equally divided doses in the morning and late afternoon/early evening. The drug may be administered without regard to meals.

The manufacturer states that atomoxetine is an ocular irritant; therefore, the capsules should be swallowed whole and should not be broken or opened, nor should the capsule contents be sprinkled on food.

■ **Dosage** Dosage of atomoxetine hydrochloride is expressed in terms of atomoxetine.

The usual initial dosage of atomoxetine in adults or in children and adolescents weighing more than 70 kg is 40 mg daily; dosage may be increased after a minimum of 3 days to a target dosage of approximately 80 mg daily. If an optimum response has not been achieved after 2–4 additional weeks of therapy, dosage may be increased to a maximum of 100 mg daily; dosages exceeding 100 mg daily have not been shown in clinical trials to result in additional therapeutic benefit. In adults or in children and adolescents weighing more than 70 kg, if atomoxetine is used concomitantly with potent inhibitors of the cytochrome P-450 2D6 (CYP2D6) isoenzyme (e.g., paroxetine, fluoxetine, quinidine) or in patients with poor metabolizer phenotypes of the CYP2D6 isoenzyme, the initial atomoxetine dosage should be 40 mg daily and dosage should be increased to the usual target dosage of 80 mg daily only if ADHD symptoms fail to improve after 4 weeks of therapy and the initial dosage is well tolerated. The maximum recommended dosage of atomoxetine in adults or in children and adolescents weighing more than 70 kg is 100 mg daily. The safety of single doses exceeding 120 mg and total daily dosages exceeding 150 mg has not been established.

The usual initial dosage of atomoxetine in children and adolescents weighing 70 kg or less is approximately 0.5 mg/kg daily; dosage may be increased after a minimum of 3 days to a target dosage of approximately 1.2 mg/kg daily. In children and adolescents weighing 70 kg or less, if atomoxetine is used concomitantly with potent CYP2D6 inhibitors (e.g., paroxetine, fluoxetine, quinidine) or in patients with poor metabolizer phenotypes of the CYP2D6 isoenzyme, the initial atomoxetine dosage should be 0.5 mg/kg daily and dosage should be increased to the usual target dosage of 1.2 mg/kg daily only if ADHD symptoms fail to improve after 4 weeks of therapy and the initial dosage is well tolerated. Daily dosage of atomoxetine in children and adolescents weighing 70 kg or less should not exceed 100 mg or 1.4 mg/kg, whichever is less; dosages exceeding 1.2 mg/kg daily have not been shown in clinical trials to result in additional therapeutic benefit.

Because the effectiveness of atomoxetine for long-term use (i.e., more than 12 months in children and adolescents 6–15 years of age, more than 9 weeks in those 16–18 years of age, and more than 10 weeks in adults) has not been established, patients receiving atomoxetine for extended periods should be periodically reevaluated to assess the long-term usefulness of the drug.

Atomoxetine may be discontinued without tapering the dosage.

■ **Special Populations** The manufacturer recommends that usual initial and target dosages of atomoxetine be reduced by 50% in patients with moderate hepatic impairment (Child-Pugh class B) and by 75% in those with severe hepatic impairment (Child-Pugh class C).

Cautions

■ **Contraindications** Known hypersensitivity to atomoxetine or any ingredient in the formulation.

The manufacturer states that atomoxetine is contraindicated in patients currently receiving or having recently received (i.e., within 2 weeks) monoamine oxidase (MAO) inhibitor therapy. In addition, at least 2 weeks should elapse after discontinuing atomoxetine before initiating MAO inhibitor therapy. Severe, potentially fatal, reactions (including hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma) have been reported in patients receiving other drugs that affect brain monoamine concentrations concomitantly with MAO inhibitor therapy.

The manufacturer also states that atomoxetine should not be used in patients with angle-closure glaucoma, since the drug was associated with an increased risk of mydriasis in some patients during controlled clinical trials.

■ **Warnings/Precautions** ***Warnings*** **Suicidality Risk.** Atomoxetine may increase the risk of suicidal ideation in children and adolescents with attention deficit hyperactivity disorder (ADHD). (See Pediatric Use under Warnings/Precautions: Specific Populations, in Cautions.) Pediatric patients should be closely monitored for clinical worsening, suicidality (suicidal ideation or behaviors), or unusual changes in behavior, particularly during the first few months after initiation of therapy and during periods of dosage adjustments. Monitoring should include daily observation by family members and caregivers and frequent contact with the prescribing clinician, particularly if the patient's behavior changes or is a concern. The manufacturer recommends face-to-face contact between clinicians and patients or their family members or caregivers at least weekly during the first 4 weeks of therapy and then every other week for the next 4 weeks, with subsequent face-to-face contact at 12 weeks and as clinically indicated thereafter; additional contact via telephone may be appropriate between visits.

Discontinuance of therapy should be considered in patients with emergent suicidality or manifestations that may be precursors to emerging suicidality (e.g., anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia, hypomania, mania), particularly if such manifestations are severe or abrupt in onset or were not part of the patient's presenting symptoms.

Sensitivity Reactions Allergic reactions, including angioedema, urticaria, and rash, have been reported rarely in patients receiving atomoxetine.

Other Warnings and Precautions **Severe Hepatic Injury.** Severe hepatic injury was reported during postmarketing surveillance in 2 patients (an adolescent and an adult) who had received atomoxetine for several months. In one patient, hepatic injury was manifested by increased hepatic enzymes (up to 40 times the upper limit of normal [ULN]) and jaundice (bilirubin up to 12 times the ULN); manifestations recurred upon rechallenge with atomoxetine and resolved upon discontinuance of the drug, providing evidence that the hepatic injury was caused by atomoxetine. Both patients recovered and did not require liver transplantation. However, the manufacturer notes that severe drug-related hepatic injury may progress to acute hepatic failure resulting in death or requiring liver transplantation in a small percentage of patients. The actual incidence of hepatic injury in patients receiving atomoxetine is unknown because of possible underreporting of postmarketing adverse effects.

Adverse hepatic effects may occur several months after initiation of atomoxetine, and laboratory abnormalities may continue to worsen for several weeks after discontinuance of the drug. Hepatic enzyme concentrations should be determined after the first manifestation of hepatic dysfunction (e.g., pruritus, dark urine, jaundice, right upper quadrant tenderness, unexplained flu-like symptoms) in patients receiving atomoxetine. Atomoxetine should be discontinued in patients with jaundice or laboratory evidence of hepatic injury, and therapy with the drug should *not* be reinitiated in such patients.

Sudden Death and Serious Cardiovascular Events. Although a causal relationship to atomoxetine has not been established, sudden unexplained death, stroke, and myocardial infarction have been reported in adults receiving usual dosages of atomoxetine for the treatment of ADHD. Sudden unexplained death also has been reported in children and adolescents with structural cardiac abnormalities or other serious cardiac conditions receiving usual dosages of atomoxetine. Children, adolescents, and adults who are being considered for atomoxetine therapy should undergo a thorough medical history review (including evaluation for a family history of sudden death or ventricular arrhythmia) and physical examination to detect the presence of cardiac disease, and should receive further cardiac evaluation (e.g., ECG, echocardiogram) if initial findings suggest such disease. Although some serious cardiac conditions are independently associated with an increased risk of sudden death, atomoxetine generally should *not* be used in children, adolescents, or adults with known serious structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, coronary artery disease, or other serious cardiac conditions. Patients who develop exertional chest pain, unexplained syncope, or other manifestations suggestive of cardiac disease during atomoxetine therapy should undergo prompt cardiac evaluation.

For further information on screening for cardiac conditions, selecting appropriate candidates for stimulant therapy, and monitoring for treatment-emergent cardiac conditions, see Cardiovascular Precautions under Cautions: Precautions and Contraindications, in the Amphetamines General Statement 28:20.04.

Psychiatric Effects. Atomoxetine should be used with caution in the management of ADHD in patients with comorbid bipolar disorder because of the potential for precipitation of mixed or manic episodes in such patients. Prior to initiating atomoxetine therapy, patients with ADHD and comorbid depressive symptoms should be carefully screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history (e.g., family history of suicide, bipolar disorder, or depression).

Psychotic or manic symptoms (e.g., hallucinations, delusional thinking, mania) have been reported in children and adolescents without prior history of psychotic illness or mania who received usual dosages of atomoxetine. In a pooled analysis of multiple short-term, placebo-controlled studies, such symptoms occurred in about 0.2% of patients receiving usual dosages of atomoxetine compared with 0% of those receiving placebo. If psychotic or manic symptoms occur, a causal relationship to atomoxetine should be considered, and discontinuance of therapy may be appropriate.

Cardiovascular Effects. Increased blood pressure and heart rate were reported in children, adolescents, and adults receiving atomoxetine in controlled clinical studies. The drug should be used with caution in patients with hyper-

tension, tachycardia, or cardiovascular or cerebrovascular disease that might be affected by increases in blood pressure or heart rate. Blood pressure and pulse rate should be measured before initiation of atomoxetine, following any increase in dosage, and periodically during therapy.

Orthostatic hypotension and syncope also were reported in patients receiving atomoxetine in controlled clinical studies. The drug should be used with caution in patients with conditions that would predispose them to hypotension.

Peripheral Vascular Effects. Exacerbation or precipitation of Raynaud's phenomenon was reported during postmarketing surveillance in patients receiving atomoxetine.

Genitourinary Effects. Urinary retention and urinary hesitation were reported in adults receiving atomoxetine in controlled clinical studies.

Growth Effects. Temporary suppression of normal weight and height patterns has been observed in pediatric patients receiving atomoxetine therapy. Gains in weight and height generally lag behind predicted population values for about the first 9–12 months of therapy; however, weight and height gains rebound with continued treatment. Similar growth patterns have been observed regardless of metabolizer phenotype (poor or extensive metabolizer of the drug) or pubertal status upon initiation of treatment. The manufacturer states that growth should be monitored in patients receiving therapy with atomoxetine.

Children and adolescents 6–18 years of age receiving atomoxetine for up to 9 weeks in controlled clinical studies had an average weight loss of 0.4 kg compared with an average weight gain of 1.5 kg in those receiving placebo for the same time period; similar rates of weight loss have been reported in other controlled clinical studies with the drug. In one clinical trial, decreases in body weight of at least 3.5% occurred in 7–29% of patients receiving atomoxetine at various dosages, compared with 1.3% of patients receiving placebo. However, in patients receiving atomoxetine for 3 years, weight increased by an average of 17.9 kg (0.5 kg more than predicted by baseline data) and height increased by an average of 19.4 cm (0.4 cm less than predicted by baseline data) at 3 years. Gain in height stabilized at about 12 months.

Behavioral Effects. Aggressive behavior and hostility frequently are observed in pediatric patients with ADHD and have been reported in patients receiving drug therapy (including atomoxetine) for the disorder. In controlled clinical studies in pediatric patients, aggressive behavior or hostility was reported slightly (overall risk ratio of 1.33), but not significantly, more frequently in those receiving atomoxetine compared with those receiving placebo. Patients beginning treatment for ADHD should be monitored for the onset or worsening of aggressive behavior or hostility.

Priapism. Priapism was reported rarely during postmarketing surveillance in pediatric and adult patients receiving atomoxetine; if priapism is suspected, prompt medical attention is required. (See Advice to Patients.)

Tics. In a controlled study, atomoxetine did not worsen tics in patients with ADHD and comorbid Tourette's disorder.

Specific Populations **Pregnancy.** Category C. (See Users Guide.)

Lactation. Atomoxetine and/or its metabolites are distributed into milk in rats; it is not known whether the drug is distributed into milk in humans. Therefore, atomoxetine should be used with caution in nursing women.

Pediatric Use. Safety and efficacy of atomoxetine have not been established in children younger than 6 years of age.

Atomoxetine may increase the risk of suicidal ideation in children and adolescents with ADHD. In a pooled analysis of 12 short-term controlled clinical studies in pediatric patients with ADHD (11 studies) or enuresis (1 study), the risk of suicidal ideation was about 0.4% in those receiving atomoxetine versus 0% in those receiving placebo. One child receiving the drug attempted suicide; no completed suicides were reported. All events representing suicidal behavior or thinking occurred in children 12 years of age or younger and occurred during the first month of therapy. It is not known whether the risk of suicidal ideation in pediatric patients extends to long-term use of the drug. A similar analysis of data from adults with ADHD or major depressive disorder found no increased risk of suicidal ideation or behavior in those receiving atomoxetine. The potential risks of suicidality should be weighed against the clinical need for the drug prior to initiating atomoxetine therapy in children or adolescents. (See Suicidality Risk under Warnings/Precautions: Warnings, in Cautions.)

Sudden death has been reported in children and adolescents with structural cardiac abnormalities or other serious cardiac conditions receiving usual dosages of stimulants. (See Sudden Death and Serious Cardiovascular Events under Warnings/Precautions: Other Warnings and Precautions, in Cautions.)

Temporary suppression of normal weight and/or height patterns has been reported during the first 9–12 months of atomoxetine therapy; however, weight and height gains have rebounded with continued treatment. (See Growth Effects under Warnings/Precautions: Other Warnings and Precautions, in Cautions.) The growth of pediatric patients receiving atomoxetine should be monitored.

Geriatric Use. Safety and efficacy of atomoxetine have not been established in geriatric patients.

Hepatic Impairment. Systemic exposure to atomoxetine concentrations is increased twofold in patients with moderate hepatic impairment (Child-Pugh class B) and fourfold in those with severe hepatic impairment (Child-Pugh class C). (See Dosage and Administration: Special Populations.)

■ **Common Adverse Effects** Abdominal pain, decreased appetite, vomiting, somnolence, hubsea, fatigue, irritability, and dizziness each occurred in 5% or more of children and adolescents receiving atomoxetine in controlled clinical studies and were at least twice as frequent in patients receiving the drug as in those receiving placebo. Dry mouth, nausea, insomnia, decreased appetite, constipation, fatigue, erectile dysfunction, hot flush, urinary disorders (urinary hesitation, urinary retention), and dysmenorrhea each occurred in 5% or more of adults receiving atomoxetine in controlled clinical studies and were at least twice as frequent in patients receiving the drug as in those receiving placebo.

Drug Interactions

■ **Drugs Affecting Hepatic Microsomal Enzymes** Potential pharmacokinetic interaction (decreased metabolism of atomoxetine) when atomoxetine is used concomitantly with drugs that inhibit the activity of the cytochrome P-450 2D6 (CYP2D6) isoenzyme. Inhibitors of CYP2D6 may increase plasma concentrations of atomoxetine in patients with the extensive-metabolizer phenotype to such an extent that plasma concentrations of the drug are similar to those achieved in poor metabolizers. When atomoxetine is used concomitantly with potent CYP2D6 inhibitors (e.g., paroxetine, fluoxetine, quinidine), or in patients with poor-metabolizer phenotypes of the CYP2D6 isoenzyme, the manufacturer states that dosage adjustment of atomoxetine should be considered. (See Dosage and Administration: Dosage.) However, in vitro studies suggest that concomitant use of atomoxetine with CYP2D6 inhibitors will not increase plasma concentrations of atomoxetine in patients with the poor-metabolizer phenotype.

■ **Drugs Metabolized by Hepatic Microsomal Enzymes** Pharmacokinetic interaction unlikely; evidence to date suggests that atomoxetine does not cause clinically important inhibition or induction of cytochrome P-450 enzymes, including CYP1A2, CYP3A, CYP2D6, and CYP2C9.

■ **GI Drugs** No important pharmacokinetic interactions reported with drugs that increase gastric pH (e.g., antacids containing magnesium hydroxide and aluminum hydroxide, omeprazole).

■ **Protein-bound Drugs** Pharmacokinetic interaction unlikely. In vitro studies indicate that atomoxetine is not displaced from binding sites by, and does not displace from binding sites, other highly protein-bound drugs (e.g., warfarin, aspirin, phenytoin, diazepam) in therapeutic concentrations.

■ **Alcohol** No change in the intoxicating effects of alcohol when alcohol was ingested by individuals receiving atomoxetine.

■ **β-Adrenergic Agonists** Potential pharmacologic interaction (increased cardiovascular effects [e.g., increased heart rate and blood pressure]) when atomoxetine is used concomitantly with oral or parenteral β_2-adrenergic agonists (e.g., albuterol). Use with caution.

■ **Cardiovascular Agents** Potential pharmacologic interaction (increased hypertensive effects) with concomitant use of pressor agents (e.g., dopamine, dobutamine) and atomoxetine. Use with caution.

■ **Methylphenidate** No increase in cardiovascular effects with concomitant use of methylphenidate and atomoxetine relative to use of methylphenidate alone.

■ **Monoamine Oxidase Inhibitors** Potential pharmacologic interaction (inhibition of catecholamine metabolism). (See Cautions: Contraindications.)

Description

Atomoxetine is a selective norepinephrine-reuptake inhibitor. Atomoxetine is not considered a stimulant and also is structurally unrelated to other agents used for the treatment of attention deficit hyperactivity disorder (ADHD). The exact mechanism(s) of action of atomoxetine in the management of ADHD has not been fully elucidated but, based on in vitro studies, appears to be related to selective inhibition of the presynaptic norepinephrine transporter; the drug appears to have minimal affinity for other noradrenergic receptors or for other neurotransmitter transporters or receptors.

Atomoxetine is readily absorbed following oral administration. The drug is approximately 98% bound to plasma proteins, principally albumin, at therapeutic concentrations. Atomoxetine is metabolized principally via oxidation by the cytochrome P-450 2D6 (CYP2D6) isoenzyme and subsequent glucuronidation. Individuals who extensively metabolize atomoxetine via the CYP2D6 pathway exhibit the extensive-metabolizer phenotype, while those who have an impaired ability to metabolize the drug by this pathway exhibit the poor-metabolizer phenotype. In patients with the poor-metabolizer phenotype (about 7% of Caucasians and 2% of African-Americans), metabolic clearance of atomoxetine may be decreased; a fivefold increase in peak plasma concentrations of atomoxetine and a tenfold increase in area under the plasma concentration-time curve (AUC) have been reported in individuals with the poor-metabolizer phenotype relative to those with the extensive-metabolizer phenotype. The mean elimination half-life of atomoxetine is 5.2 or 21.6 hours in extensive or poor metabolizers, respectively. Atomoxetine does not inhibit or induce CYP2D6.

Advice to Patients

Importance of providing patient or caregiver with a copy of the manufacturer's patient information (medication guide); discuss and answer questions about its contents (e.g., benefits and risks of atomoxetine therapy, appropriate use) as needed. Importance of instructing the patient or caregiver to read and

understand the contents of the medication guide before initiating therapy and each time the prescription is refilled.

Risk of suicidal thinking. Importance of patients, caregivers, and family members immediately informing clinician if clinical worsening, anxiety, agitation, panic attacks, insomnia, irritability, aggressive behaviors, hostility, impulsivity, restlessness, mania, depression, suicidal ideation or behaviors, or unusual changes in behavior occur, particularly during the first few months after initiation of therapy or following dosage adjustments.

Patients and/or caregivers should be advised that hepatic dysfunction may develop rarely. Importance of informing clinician immediately if symptoms of hepatic injury occur (e.g., pruritus, jaundice, dark urine, upper right-sided abdominal tenderness, unexplained flu-like symptoms).

Importance of informing clinician immediately if adverse cardiovascular effects (e.g., chest pain, shortness of breath, fainting) occur.

Importance of informing clinician immediately if precipitation of psychotic (e.g., hallucinations, delusional thinking) or manic symptoms occurs.

Importance of exercising caution when driving or operating machinery until the effects of the drug on the individual are known.

Risk of priapism. Importance of seeking immediate medical attention if an erection persists for more than 4 hours.

Importance of taking atomoxetine exactly as prescribed. If a patient misses a dose of the drug, the missed dose should be taken as soon as it is remembered, but the amount of atomoxetine taken within a 24-hour period should not exceed the prescribed total daily dosage of the drug.

Importance of advising patient and/or caregivers that atomoxetine capsules should not be opened because the drug is an ocular irritant; if eye contact occurs, flush the affected eye(s) with water immediately, obtain medical advice, and wash hands and potentially contaminated surfaces as soon as possible.

Importance of informing clinician of any history of physical or mental disorders (e.g., cardiovascular disease, liver disease, depression).

Importance of women informing clinicians if they are or plan to become pregnant or plan to breast-feed.

Importance of informing clinicians of existing or contemplated concomitant therapy, including prescription and OTC drugs, dietary supplements, and herbal products, as well as any concomitant illnesses/conditions (e.g., glaucoma, suicidal ideation or behaviors, cardiac/cardiovascular disease, mental/psychiatric disorder, hepatic disease).

Importance of informing patients and/or caregivers of other important precautionary information. (See Cautions.)

Overview[a] (see Users Guide). For additional information on this drug until a more detailed monograph is developed and published, the manufacturer's labeling should be consulted. It is *essential* that the manufacturer's labeling be consulted for more detailed information on usual cautions, precautions, contraindications, potential drug interactions, laboratory test interferences, and acute toxicity.

Preparations

Excipients in commercially available drug preparations may have clinically important effects in some individuals; consult specific product labeling for details.

Atomoxetine Hydrochloride

Oral

Capsules	10 mg (of atomoxetine)	Strattera®, Lilly
	18 mg (of atomoxetine)	Strattera®, Lilly
	25 mg (of atomoxetine)	Strattera®, Lilly
	40 mg (of atomoxetine)	Strattera®, Lilly
	60 mg (of atomoxetine)	Strattera®, Lilly
	80 mg (of atomoxetine)	Strattera®, Lilly
	100 mg (of atomoxetine)	Strattera®, Lilly

Flumazenil

■ Flumazenil, a 1,4-imidazobenzodiazepine derivative, is a benzodiazepine antagonist.

Uses

Flumazenil is used in adults for the complete or partial reversal of benzodiazepine-induced sedation when benzodiazepines are used for induction or maintenance of general anesthesia or for diagnostic or therapeutic procedures (i.e., conscious sedation) and for the management of benzodiazepine intoxication. Flumazenil also is used in children 1–17 years of age for the reversal of benzodiazepine-induced sedation when benzodiazepines are used for diagnostic or therapeutic procedures. The manufacturer states that the safety and efficacy of flumazenil have *not* been established in pediatric patients for reversal of benzodiazepine-induced sedation when benzodiazepines are used for induction of general anesthesia, for the management of benzodiazepine intoxication, nor for the resuscitation of neonates. (See Special Populations: Pediatric Use.)

■ **Reversal of General Anesthesia** Flumazenil has been shown to be effective in reversing sedation and restoring psychomotor function in adults who received midazolam for induction or maintenance of general anesthesia. Efficacy was established in 4 clinical studies in adults who received 5–80 mg of midazolam alone or in conjunction with skeletal muscle relaxants, nitrous oxide, regional or local anesthetics, opiates, and/or inhalational anesthetics. A 0.2-mg dose of flumazenil was administered, followed by additional 0.2-mg doses as needed to reach a complete response (up to a maximum of 1 mg). In these studies, 81% of patients became completely alert or remained only slightly drowsy following total flumazenil doses of 0.4–0.6 mg (36%) or 0.8–1 mg (64%). However, resedation occurred in 10–15% of patients who responded to flumazenil. (See Warnings: Resedation.) Flumazenil failed to restore memory completely as tested by picture recall. In addition, flumazenil was not as effective in the reversal of sedation in patients who received multiple anesthetic agents in addition to benzodiazepines.

■ **Reversal of Conscious Sedation** Flumazenil has been shown to be effective in reversing the sedative and psychomotor effects of benzodiazepines when these drugs are used for diagnostic or therapeutic procedures but was less effective in completely and consistently reversing benzodiazepine-induced amnesia. Efficacy was established in 4 clinical studies in adults who received an average of 30 mg of diazepam or 10 mg of midazolam for sedation (with or without an opiate) for both inpatient and outpatient diagnostic or surgical procedures. Flumazenil was administered as an initial dose of 0.4 mg (2 doses of 0.2 mg each), with additional 0.2-mg doses administered as needed to achieve complete awakening, up to a maximum of 1 mg. In these studies, 78% of patients receiving flumazenil achieved complete consciousness, but approximately 50% of these patients required 2–3 additional doses of the drug in order to achieve this level of consciousness. In addition, while most patients remained alert throughout the 3-hour postprocedure observation period, resedation occurred in 3–9% of these patients.

Pediatric Considerations The safety and efficacy of flumazenil for the reversal of benzodiazepine-induced conscious sedation have been established in children 1 year of age and older. In one uncontrolled clinical trial involving 107 children 1–17 years of age who had received midazolam for conscious sedation, flumazenil was administered at doses of 0.01 mg/kg (maximum of 0.2 mg) up to a maximum of 5 doses or a total dose of 1 mg. In this study, 56% of the children achieved complete consciousness within 10 minutes of flumazenil administration, but 51% of them required the maximum number of doses of the drug allowed for initial treatment in order to achieve this level of consciousness. In addition, approximately 12% of the patients (all of whom were 1–5 years of age) who achieved complete consciousness following flumazenil administration experienced resedation within 19–50 minutes of initial administration of the drug. Episodes of resedation were reversed by additional doses of flumazenil. However, the manufacturer states that the safety and efficacy of repeated flumazenil administration in pediatric patients experiencing resedation have *not* been established.

■ **Benzodiazepine Overdosage** Flumazenil is used in adults for the management of benzodiazepine overdosage. The drug is an adjunct to, not a replacement for, appropriate supportive and symptomatic measures (e.g., ventilatory and circulatory support) in the management of benzodiazepine overdosage. Because patients admitted to hospitals for drug overdoses may have ingested multiple substances and/or are being treated for concomitant illnesses (e.g., depression, substance abuse), the presence of contraindications or precautions, which may limit the use of flumazenil therapy, should be considered. (See Contraindications under Warnings/Precautions, in Cautions.) Flumazenil has no known benefit other than reversal of benzodiazepine-induced sedation in seriously ill patients with multiple-drug overdosage, and the drug should *not* be used in cases where seizures (from any cause) are likely. In addition, the manufacturer warns that flumazenil should *not* be used in patients with serious cyclic depressant overdosage. (See Drug Interactions: Cyclic Antidepressants.) For information on the pathogenesis, manifestations, and treatment of benzodiazepine overdosage, see Acute Toxicity in the Benzodiazepines General Statement 28:24.08.

Efficacy of flumazenil has been established in 2 studies in patients who were presumed to have taken an overdose of a benzodiazepine, either alone or in combination with a variety of other agents. In these studies, of patients who were proven to have taken a benzodiazepine, 80% of those who received flumazenil responded with an improvement in level of consciousness. Of those who responded to flumazenil, 75% responded to a total dose of 1–3 mg. However, reversal of sedation was associated with an increased frequency of symptoms of CNS excitation, and 1–3% of patients who received flumazenil were treated for agitation or anxiety.

■ **Other Uses** The manufacturer states that the safety and efficacy of flumazenil for the treatment of benzodiazepine dependence or for the management of protracted benzodiazepine abstinence syndrome have not been established and therefore such use currently is not recommended.

Dosage and Administration

■ **General** Flumazenil is administered by rapid (over 15–30 seconds) IV injection through a freely flowing IV infusion into a large vein. Because of the risk of local irritation, the drug is recommended for IV use only, and extravasation into perivascular tissues should be avoided. Patients should have a secure airway and established IV access prior to administration of the drug.

Phenytoin appears to be distributed into milk in small amounts.

■ **Elimination** Following oral administration, the plasma half-life of phenytoin averages about 22 hours, although the half-life has ranged from 7–42 hours in individual patients. The plasma half-life of phenytoin in humans following IV administration ranges from 10–15 hours.

The major route of metabolism of phenytoin is oxidation by the liver to the inactive metabolite 5-(*p*-hydroxyphenyl)-5-phenylhydantoin (HPPH). Because this metabolism is a saturable process, small increases in dosage may produce substantial increases in plasma phenytoin concentrations; the steady-state plasma concentration may double or triple from a 10% or more increase in dosage, possibly resulting in toxicity. HPPH undergoes enterohepatic circulation and is excreted in urine via glomerular filtration and tubular secretion, mainly as the glucuronide. Approximately 60–75% of the daily dose of the drug is excreted in this form. Other minor metabolites also appear in urine. In therapeutic doses, approximately 1% is excreted unchanged in urine; in toxic doses, up to 10% of the ingested drug may be excreted unchanged by the kidneys.

Following equal doses of phenytoin, total plasma phenytoin concentrations are lower in chronic uremic patients than in non-uremic patients which suggests an altered metabolic disposition of the drug in patients with uremia.

Chemistry and Stability

■ **Chemistry** Phenytoin is a hydantoin-derivative anticonvulsant. Phenytoin occurs as a white powder and is practically insoluble in water, soluble in hot alcohol, and slightly soluble in cold alcohol. The drug has an apparent pK_a of 8.06–8.33. Phenytoin sodium occurs as a white, hygroscopic powder and is freely soluble in water, soluble in alcohol, and freely soluble in warm propylene glycol.

Aqueous solutions of phenytoin sodium gradually absorb carbon dioxide, and the drug undergoes partial hydrolysis to phenytoin, resulting in turbid solutions. The drug is more stable in propylene glycol. Commercially available phenytoin sodium injection is a sterile solution of the drug containing 40% propylene glycol and 10% alcohol in water for injection. Sodium hydroxide is added during manufacture of the injection to adjust the pH to 12. Each 100-mg phenytoin sodium capsule contains approximately 0.35 mEq of sodium, and phenytoin sodium injection contains about 0.2 mEq of sodium per mL.

Extended phenytoin sodium capsules are formulated so that they undergo slower dissolution with more prolonged absorption than prompt phenytoin sodium capsules.

■ **Stability** Commercially available phenytoin oral suspension and tablets, and extended and prompt phenytoin sodium capsules generally should be stored in tight containers at a room temperature less than 30°C, although one manufacturer recommends storage of their extended phenytoin sodium capsules (Phenytek®) at controlled room temperatures of 15–30°C; the extended capsules should be protected from light and moisture and the oral suspension should be protected from freezing and light. Phenytoin sodium injection should be stored at 15–30°C; freezing should be avoided. A precipitate may form if the injection is refrigerated or frozen; however, this will dissolve after warming to room temperature. Slight yellowish discoloration of the injection will not affect potency or efficacy, but the injection should not be used if the solution is not clear or if a precipitate is present. Precipitation of free phenytoin will occur at a pH of 11.5 or less.

Phenytoin sodium injection is physically and/or chemically incompatible with some drugs, but the compatibility depends on several factors (e.g., concentrations of the drugs, specific diluents used, resulting pH, temperature). Specialized references should be consulted for specific compatibility information.

For further information on chemistry and stability, pharmacology, pharmacokinetics, uses, cautions, acute toxicity, drug interactions, and dosage and administration of phenytoin, see the Anticonvulsants General Statement 28:12.

Preparations

Excipients in commercially available drug preparations may have clinically important effects in some individuals; consult specific product labeling for details.

Phenytoin

Oral		
Suspension	125 mg/5 mL*	Dilantin-125®, Pfizer
		Phenytoin Oral Suspension
Tablets, chewable	50 mg	Dilantin® Infatabs®, Pfizer

*available from one or more manufacturer, distributor, and/or repackager by generic (nonproprietary) name

Phenytoin Sodium

Parenteral		
Injection	50 mg/mL*	Phenytoin Sodium Injection

*available from one or more manufacturer, distributor, and/or repackager by generic (nonproprietary) name

Phenytoin Sodium, Extended

Oral		
Capsules	30 mg	Dilantin® Kapseals®, Pfizer
	100 mg*	Dilantin® Kapseals®, Pfizer
		Phenytoin Sodium Extended Capsules
	200 mg*	Phenytek®, Mylan
	300 mg*	Phenytek®, Mylan

*available from one or more manufacturer, distributor, and/or repackager by generic (nonproprietary) name

Phenytoin Sodium, Prompt

Oral		
Capsules	100 mg*	Phenytoin Sodium Prompt Capsules

*available from one or more manufacturer, distributor, and/or repackager by generic (nonproprietary) name
†Use is not currently included in the labeling approved by the US Food and Drug Administration

ANTICONVULSANTS, MISCELLANEOUS 28:12.92

Carbamazepine

■ Carbamazepine is an iminostilbene derivative that is used as both an anticonvulsant and for the relief of pain associated with trigeminal neuralgia (tic douloureux) as well as for various psychiatric disorders.

Uses

■ **Seizure Disorders** Carbamazepine is used in adults and children in the prophylactic management of partial seizures with complex symptomatology (psychomotor or temporal lobe seizures), generalized tonic-clonic (grand mal) seizures, and mixed seizure patterns that include partial seizures with complex symptomatology, generalized tonic-clonic seizures, or other partial or generalized seizures. Patients with partial seizures with complex symptomatology appear to show greater improvement during carbamazepine therapy than patients with other types of seizures. Although the drug is useful in the management of mixed seizures, the response in patients with mixed seizures may be variable. The drug is ineffective in the management of absence (petit mal) seizures or myoclonic and akinetic seizures.

Carbamazepine may be administered concomitantly with other anticonvulsants such as phenytoin, phenobarbital, or primidone. However, the drug should be administered with caution in conjunction with those anticonvulsants that produce toxic effects similar to carbamazepine such as phenacemide (no longer commercially available in the US), mephenytoin, or trimethadione or paramethadione (both no longer commercially available in the US).

■ **Neuropathic Pain** Carbamazepine is used in the symptomatic treatment of pain associated with true trigeminal neuralgia. *Carbamazepine is not a simple analgesic and should not be administered casually for relief of trivial facial pain.* Although some patients with glossopharyngeal neuralgia may respond to carbamazepine, the drug usually does not provide relief in facial pain from causes other than trigeminal neuralgia. Some patients with trigeminal neuralgia who did not respond to carbamazepine have been successfully treated with combined carbamazepine-phenytoin therapy.

Like certain other anticonvulsants, carbamazepine also has been used for the symptomatic treatment of chronic pain arising from other peripheral neuropathic syndromes†, including pain of diabetic neuropathy†. (See Uses: Neuropathic Pain, in the Anticonvulsants General Statement 28:12.)

■ **Schizophrenia** Carbamazepine has been used in the symptomatic management of the acute phase of schizophrenia† as an adjunct to therapy with an antipsychotic agent in patients who fail to respond to an adequate trial of the antipsychotic agent alone. For adjunctive therapy with an antipsychotic agent, carbamazepine generally is administered at the same range in dosage and therapeutic plasma concentrations as in the management of seizure disorders and bipolar disorder. The American Psychiatric Association (APA) states that, with the exception of schizophrenic patients whose illness has strong affective components, carbamazepine therapy *alone* (i.e., monotherapy rather than adjunctive therapy) has not been shown to be substantially effective in the long-term treatment of schizophrenia. For additional information on the management of schizophrenia, see Uses: Psychotic Disorders, in the Phenothiazines General Statement 28:16.08.24.

■ **Bipolar Disorder** Carbamazepine has been used alone or in combination with other drugs (e.g., antipsychotic agents) for the treatment and prevention of acute manic or mixed episodes in patients with bipolar disorder. However, results of clinical studies of the drug in the management of bipolar disorder have been inconsistent, and the APA currently recommends that carbamazepine be reserved for patients unable to tolerate or who had an inadequate therapeutic response to lithium and valproate (e.g., valproic acid, divalproex). For further information on the management of bipolar disorder, see Uses: Bipolar Disorder, in Lithium Salts 28:28.

■ **Other Uses** Carbamazepine has been used for the management of aggression (e.g., uncontrolled rage outbursts) and/or loss of control (dyscontrol) in patients with or without an underlying seizure disorder (e.g., as features of intermittent explosive disorder, conduct disorder, antisocial personality disorder, borderline personality disorder, dementia)†, alcohol withdrawal syndrome†, relief of neurogenic pain and/or control of seizures in a variety of conditions including "lightning" pains of tabes dorsalis†, pain and control of paroxysmal symptoms of multiple sclerosis†, paroxysmal kinesigenic choreoathetosis†, Klüver-Bucy syndrome†, post-hypoxic action myoclonus†, acute idiopathic polyneuritis (Landry-Guillain-Barré syndrome)†, pain of posttraumatic paresthesia†, and, in children, hemifacial spasm† and dystonia†. The drug also has been used for its antidiuretic effects in the management of neurohypophyseal diabetes insipidus†; however, other less toxic agents are available, and patients with primary polydipsia and polyuria have shown signs of water intoxication during carbamazepine therapy.

Dosage and Administration

■ **Administration** Carbamazepine conventional tablets and suspension are administered orally with meals. The oral suspension should be shaken well before administration. To minimize loss of carbamazepine oral suspension during oral administration via a nasogastric tube (secondary to adherence to PVC tubing), the suspension can be diluted with an equal volume of diluent (e.g., sterile water, 5% dextrose, 0.9% sodium chloride) prior to administration, combined with flushing of the tube with 100 mL of the diluent after administration.

Because a rubbery, orange substance was noticed in the stool of a patient who ingested chlorpromazine oral solution immediately after ingesting carbamazepine oral suspension and subsequent testing has shown that mixing carbamazepine oral suspension with chlorpromazine or thioridazine oral solution results in a rubbery, orange precipitate, the manufacturer recommends that carbamazepine oral suspension not be administered with other liquid preparations. In addition, it is not known whether the development of this precipitate results in decreased bioavailability of carbamazepine or the other drugs.

Extended-release tablets of carbamazepine (Tegretol®-XR) should be swallowed whole and not be broken or chewed. The manufacturer states that the extended-release tablets should be inspected visually for chips or cracks and that damaged tablets should not be used. Because the coating of the extended-release tablet is not absorbed, it may be noticeable in the stools. The extended-release tablet formulation of carbamazepine is administered twice daily. When patients are switched from conventional dosage forms to the extended-release tablets of carbamazepine, the same total daily dosage is then administered in 2 divided doses.

Extended-release capsules of carbamazepine (Carbatrol®) may be opened and the beads sprinkled over food (e.g., a teaspoonful of applesauce). Extended-release capsules of carbamazepine and their contents should not be chewed or crushed. In addition, the extended-release capsules of carbamazepine may be taken without regard to meals. Patients receiving total daily carbamazepine dosages of 400 mg or greater in other preparations may be switched to the extended-release capsules; the same total daily dosage is then administered in 2 divided doses.

Patients who are currently receiving or beginning therapy with carbamazepine and/or any other anticonvulsant for any indication should be closely monitored for the emergence or worsening of depression, suicidal thoughts or behavior (suicidality), and/or any unusual changes in mood or behavior. (See Cautions: Nervous System Effects and see Cautions: Precautions and Contraindications.)

Dispensing and Administration Precautions Because of similarity in spelling between Tegretol® or Tegretol®-XR (trade names for carbamazepine) and Toprol-XL® (a trade name for metoprolol succinate, a β-adrenergic blocking agent), the potential exists for dispensing errors involving these drugs. According to medication error reports, the overlapping tablet strengths (100 and 200 mg) between Tegretol® or Tegretol®-XR and Toprol-XL® and the fact that these drugs were stored closely together in pharmacies also may have been contributing factors in causing these errors. Therefore, extra care should be exercised to ensure the accuracy of both oral and written prescriptions for these drugs. The manufacturer of Toprol-XL® also recommends that pharmacists assess various measures of avoiding dispensing errors and implement them as appropriate (e.g., by verifying all orders for these drugs by citing both the trade and generic names to prescribers, attaching reminders to pharmacy shelves, separating the drugs on pharmacy shelves, counseling patients). (See Cautions: Precautions and Contraindications.)

■ **Dosage** Dosage of carbamazepine must be carefully and slowly adjusted according to individual requirements and response. It is important to begin therapy with a low dosage and to proceed slowly when increasing or decreasing the dosage of the drug. When carbamazepine is added to an anticonvulsant therapeutic regimen, the drug should usually be added gradually while the other anticonvulsant(s) is maintained or gradually decreased. Carbamazepine should be withdrawn slowly to avoid precipitating seizures or status epilepticus.

Because a given dose of carbamazepine administered as the oral suspension will produce higher peak concentrations of the drug than when administered as tablets, therapy with the oral suspension should be initiated with low, frequent doses (e.g., 50 mg 4 times daily for children 6–12 years of age) and increased slowly to reduce the risk of adverse effects (e.g., sedation). Alternatively, if rapid achievement of therapeutic plasma concentrations and control of seizures is necessary, an oral loading-dose regimen with carbamazepine oral suspension can be employed. When transferring patients from therapy with oral tablets to the oral suspension, the total daily dose administered as tablets should be divided into smaller, more frequent doses of the suspension (e.g., transfer from twice-daily divided dosing of tablets to thrice [3 times]-daily divided dosing of the suspension).

Seizure Disorders The usual initial dosage of carbamazepine for the management of seizure disorders in adults and children older than 12 years of age is 200 mg twice daily as tablets or 100 mg 4 times daily as the oral suspension. Dosage is increased by up to 200 mg daily at weekly intervals using a 3 or 4 times daily divided dosing regimen until the optimum response is obtained. Dosage generally should not exceed 1 g daily in children 12–15 years of age and 1.2 g daily in patients older than 15 years of age; however, some patients have required up to 1.6–2.4 g daily. When adequate seizure control is achieved, dosage should be adjusted to the minimum effective level, which is usually 800 mg to 1.2 g daily in adults and children older than 12 years of age.

In children 6–12 years of age, the usual initial dosage of carbamazepine is 100 mg twice daily as tablets or 50 mg 4 times daily as the oral suspension. Dosage is increased by up to 100 mg daily at weekly intervals using a 3 or 4 times daily divided dosing regimen until the optimum response is obtained. Dosage generally should not exceed 1 g daily in children 6–12 years of age. When adequate seizure control is achieved, dosage should be adjusted to the minimum effective level, which is usually 400–800 mg daily in children 6–12 years of age.

In children younger than 6 years of age, the initial daily dosage of carbamazepine given as conventional tablets or oral suspension is 10–20 mg/kg in 2 or 3 divided doses (as tablets) or 4 divided doses (as the oral suspension). Optimal clinical response in children younger than 6 years of age generally is achieved at daily maintenance dosages of less than 35 mg/kg. If satisfactory clinical response has not been achieved, plasma carbamazepine concentrations should be obtained to determine whether they are in the therapeutic range. The manufacturers state that safety of carbamazepine dosages exceeding 35 mg/kg in 24 hours in children younger than 6 years of age has not been established.

Therapeutic serum carbamazepine concentrations can be achieved more rapidly (in about 2 hours) by the use of an oral loading-dose regimen with the oral suspension, preferably in a clinic or hospital setting where plasma concentrations and the patient can be monitored closely. In this regimen, an initial oral loading dose (as the oral suspension) of 8 mg/kg in children 12 years of age and older or 10 mg/kg in children younger than 12 years of age is administered for the rapid control of seizures.

Neuropathic Pain For the symptomatic treatment of pain associated with trigeminal neuralgia, the usual initial adult dosage of carbamazepine on the first day of therapy is 100 mg twice daily as tablets or 50 mg 4 times daily as the oral suspension. Dosage may be increased gradually by up to 200 mg daily using 100-mg increments every 12 hours for tablets or by using 50-mg increments 4 times daily for the oral suspension until pain is relieved. The dosage necessary to relieve pain may range from 200 mg to 1.2 g daily; daily dosage should not exceed 1.2 g. After control of pain is achieved, maintenance dosages of 400–800 mg daily usually are adequate; however, some patients may require as little as 200 mg daily while others may require 1.2 g daily. At least once every 3 months throughout carbamazepine therapy for trigeminal neuralgia, an attempt should be made to decrease dosage to the minimum effective level or to discontinue the drug.

Bipolar Disorder Although dosage of carbamazepine for the management of bipolar disorder has not been established, experts generally recommend administering the drug at the same range in dosage and therapeutic plasma concentrations as in the management of seizure disorders. In patients older than 12 years of age, the usual initial dosage of carbamazepine for the management of bipolar disorder is 200–600 mg daily, given in 3 or 4 divided doses. Dosage may be titrated upward according to patient response and tolerability. In hospitalized patients with acute mania, dosages may be increased as tolerated in 200-mg daily increments up to 800 mg to 1 g daily, with slower increases thereafter as indicated. However, dosages should *not* exceed 1.6 g daily. In less acutely ill outpatients, dosage adjustments should be slower because rapid increases may cause patients to develop adverse GI (e.g., nausea, vomiting) or nervous system (e.g., drowsiness, dizziness, ataxia, clumsiness, diplopia) effects. If such adverse effects occur, temporary dosage reductions should be considered. Dosage may be increased again more slowly once these adverse effects have been resolved. Maintenance dosages of carbamazepine average about 1 g daily but may range from 200 mg to 1.6 g daily in routine clinical practice.

Cautions

■ **Hematologic Effects** Although transient or persistent, minor hematologic changes (e.g., decreased leukocyte counts) are not uncommon, the risk of serious carbamazepine-induced hematologic toxicity appears to be low. Deaths from aplastic anemia have occurred rarely following carbamazepine therapy. Other hematopoietic complications associated with the drug include leukopenia, agranulocytosis, eosinophilia, leukocytosis, thrombocytopenia, pancytopenia, bone marrow depression, and purpura. Although data from a population-based, case-control study indicate that the risk of developing aplastic anemia or agranulocytosis in patients receiving carbamazepine is 5–8 times greater than that in the general population, the overall risk of these reactions in the untreated general population is low (about 6 cases per million population per year for agranulocytosis and about 2 cases per million population per year for aplastic anemia). Transient or persistent decreases in platelet or leukocyte counts are not uncommonly associated with carbamazepine use, but currently available data do not permit accurate estimates of the incidence or outcome of

these effects; however, the vast majority of cases of leukopenia reportedly have not progressed to aplastic anemia or agranulocytosis. In addition, because the apparent frequency of minor hematologic changes progressing to agranulocytosis and aplastic anemia is very low, the vast majority of such changes observed during routine, periodic hematologic monitoring of carbamazepine-treated patients are unlikely to be signaling the impending development of either abnormality. Nonetheless, determination of baseline hematologic function should be performed prior to initiation of carbamazepine therapy, and patients exhibiting abnormalities during therapy with the drug should be monitored closely. (See Cautions: Precautions and Contraindications.)

■ **Dermatologic and Sensitivity Reactions** Serious and sometimes fatal dermatologic reactions, including toxic epidermal necrolysis and Stevens-Johnson syndrome, have been reported in patients receiving carbamazepine therapy. These reactions are estimated to occur in 1–6 per 10,000 new users of the drug in countries with mainly Caucasian populations; however, the risk in some Asian countries is estimated to be approximately 10 times higher. Retrospective, case-control studies in patients of Asian ancestry have demonstrated a strong association between the risk of developing Stevens-Johnson syndrome and toxic epidermal necrolysis with carbamazepine therapy and the presence of human leukocyte antigen (HLA)-B*1502, an inherited allelic variant of the HLA-B gene. The HLA-B*1502 allele is found almost exclusively in patients with ancestry across broad areas of Asia (including Han Chinese, Filipinos, Malaysians, South Asian Indians, and Thais), although marked variation exists in its prevalence among various Asian populations. Greater than 15% of the population is reportedly HLA-B*1502-positive in Hong Kong, Thailand, Malaysia, and parts of the Philippines compared with about 10% in Taiwan and 4% in North China. South Asians, including Indians, appear to have an intermediate prevalence of HLA-B*1502, which averages about 2–4% but may be higher in some groups. HLA-B*1502 is present in less than 1% of the population in Japan and Korea and is largely absent in individuals not of Asian origin (e.g., Caucasians, African-Americans, Hispanics, Native Americans).

The US Food and Drug Administration (FDA) and the manufacturers of carbamazepine recommend that patients with ancestry in genetically at-risk populations be screened for the presence of the HLA-B*1502 allele prior to initiating carbamazepine therapy. In deciding which patients to screen, the rates provided above for the prevalence of the HLA-B*1502 allele may provide a rough guide; however, clinicians should keep in mind the limitations of these figures because of the wide variability in rates even within ethnic groups, the difficulty in ascertaining ethnic ancestry, and the likelihood of mixed ancestry. High-resolution HLA-B*1502 typing is recommended in genetically at-risk patients; the test is considered positive if 1 or 2 HLA-B*1502 alleles are detected and negative if no HLA-B*1502 alleles are detected. Patients testing positive for this allele should not receive carbamazepine therapy unless the benefit clearly outweighs the risk. Patients who are found to be negative for the allele are thought to have a low risk of developing Stevens-Johnson syndrome and toxic epidermal necrolysis. In addition, over 90% of carbamazepine-treated patients who will experience Stevens-Johnson syndrome and toxic epidermal necrolysis develop these reactions within the first few months of therapy; this information may be considered in determining the need for screening genetically at-risk patients currently receiving the drug.

The HLA-B*1502 allele has not been found to predict risk of less severe adverse dermatologic reactions associated with carbamazepine (e.g., multiple-organ hypersensitivity reactions, non-serious rash such as maculopapular eruption). However, limited evidence suggests that HLA-B*1502 may be a risk factor for the development of Stevens-Johnson syndrome and toxic epidermal necrolysis in patients of Asian ancestry who are receiving other anticonvulsants associated with these reactions (e.g., lamotrigine, fosphenytoin, phenytoin). Avoidance of such drugs should therefore be considered in HLA-B*1502-positive patients when alternative therapies are otherwise equally acceptable.

FDA and the manufacturers caution that application of HLA-B*1502 genotyping as a screening tool has important limitations and must never substitute for appropriate clinical vigilance and patient management. Many HLA-B*1502-positive Asian patients treated with carbamazepine will never develop Stevens-Johnson syndrome and toxic epidermal necrolysis, and such reactions may develop infrequently in HLA-B*1502-negative patients of any ethnicity. The role of other possible factors, such as anticonvulsant drug dosage, compliance, concomitant medications and illnesses, in the development of, and morbidity from, these reactions and the level of dermatologic monitoring has not been adequately studied to date.

Other adverse dermatologic effects of carbamazepine include pruritic, erythematous, and maculopapular rashes (e.g., maculopapular eruption); urticaria; photosensitivity reactions; alterations in skin pigmentation; and exfoliative dermatitis. In addition, erythema multiforme and nodosum and development of a lupus erythematosus-like syndrome or aggravation of systemic lupus erythematosus have been reported. Alopecia also may occur. Although a causal relationship has not been established, hirsutism has been reported rarely in patients receiving carbamazepine.

Multiple-organ hypersensitivity reactions occurring days to weeks or months after initiation of carbamazepine therapy have been reported rarely. Manifestations may include (but are not limited to) fever, rashes, vasculitis, lymphadenopathy, disorders mimicking lymphoma, arthralgia, leukopenia, eosinophilia, hepatosplenomegaly, and abnormal liver function test results. These manifestations may initially be mild and may occur in various combinations and not necessarily concurrently. Various organs, including but not limited to, liver, skin, immune system, lungs, kidneys, pancreas, myocardium, and colon, may be affected.

Other hypersensitivity reactions, including fever, rash, peripheral eosinophilia, and reversible aseptic meningitis (manifested by confusion, myoclonus, and CSF pleocytosis), have been reported rarely in patients receiving carbamazepine.

■ **Cardiovascular Effects** Adverse cardiovascular effects (some of which may be fatal), including congestive heart failure, aggravation of hypertension, hypotension, syncope and collapse, edema, thrombophlebitis, thromboembolism, aggravation of coronary artery disease, arrhythmias, and AV block, have been reported. Myocardial infarction has been associated with tricyclic compounds.

■ **Hepatic Effects** Hepatic complications associated with the long-term administration of carbamazepine include abnormalities in liver function test results, cholestatic and hepatocellular jaundice, hepatitis, and very rare cases of hepatic failure.

■ **Genitourinary Effects** Genitourinary complications associated with carbamazepine include urinary frequency, acute urinary retention, oliguria with elevated blood pressure, azotemia, renal failure, and impotence. Albuminuria, glycosuria, elevated BUN concentrations, and microscopic deposits in the urine also have been reported.

■ **Nervous System Effects** Adverse neurologic and sensory effects of carbamazepine include dizziness, vertigo, drowsiness, fatigue, ataxia, disturbances of coordination, confusion, headache, nystagmus, blurred vision, transient diplopia, visual hallucinations, hyperacusis, oculomotor disturbances, speech disturbances, and abnormal involuntary movements. Rarely, peripheral neuritis and paresthesia, depression with agitation, talkativeness, and tinnitus may occur. Reports of associated paralysis and other symptoms of cerebral arterial insufficiency have been made, but the exact relationship of these reactions to the administration of carbamazepine has not been established.

The US Food and Drug Administration (FDA) has analyzed suicidality reports from placebo-controlled studies involving 11 anticonvulsants, including carbamazepine, and found that patients receiving anticonvulsants had approximately twice the risk of suicidal behavior or ideation (0.43%) compared with patients receiving placebo (0.24%). FDA's analysis included 199 randomized, placebo-controlled studies of 11 anticonvulsants (carbamazepine, felbamate, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, pregabalin, tiagabine, topiramate, valproate, and zonisamide) involving over 43,000 patients 5 years of age or older; the studies evaluated the effectiveness of the anticonvulsants in epilepsy, psychiatric disorders or (e.g., bipolar disorder, depression, anxiety), and other conditions (e.g., migraine, neuropathic pain). This increased suicidality risk was observed as early as one week after beginning therapy and continued through 24 weeks. The results were generally consistent among the 11 drugs studied. In addition, patients who were treated for epilepsy, psychiatric disorders, and other conditions were all found to be at increased risk for suicidality when compared with placebo; there did not appear to be a specific demographic subgroup of patients to which the increased risk could be attributed. However, the relative risk for suicidality was found to be higher in patients with epilepsy compared with patients who were given one of the drugs for psychiatric or other conditions. (See Cautions: Precautions and Contraindications.)

Initiation of carbamazepine for the management of complex partial seizures has been associated with exacerbation of seizures, principally atypical absence and/or generalized convulsive seizures, in some children with mixed seizure disorders. In one group of children, video-EEG monitoring revealed a generalized paroxysmal spike-and-wave discharge in all of the children in whom exacerbation of seizures occurred during carbamazepine therapy. Children who developed frequent generalized convulsive seizures had a pattern of spikes and slow waves with a frequency of 1–2 cycles/second, and those who developed more frequent and severe atypical absence seizures had a generalized spike-and-wave discharge of 2.5–3 cycles/second. Although the mechanism is not known, it was suggested that exacerbation of seizures in these children may result from carbamazepine-induced activation of epileptiform discharges. It has been suggested that carbamazepine be used with caution for the management of complex partial seizures in children with mixed seizure disorders; particularly those who have a generalized absence or atypical absence component, and that the drug be avoided when there is generalized, synchronous, spike-and-wave discharges of 2.5–3 cycles/second in association with clinical seizures regardless of their clinical manifestation. The possibility that a worsening of atypical absence and/or generalized convulsive seizures following initiation of carbamazepine therapy may be drug induced rather than the natural history of the child's epilepsy should be considered.

■ **GI Effects** Adverse GI effects of carbamazepine include nausea, vomiting, gastric distress, abdominal pain, diarrhea, constipation, anorexia, dryness of the mouth and pharynx, glossitis, and stomatitis.

■ **Other Adverse Effects** Other adverse effects reported during carbamazepine therapy include diaphoresis, fever and chills, adenopathy or lymphadenopathy, acute intermittent porphyria, aching joints and muscles, leg cramps, and conjunctivitis. Decreased plasma calcium concentrations and hyponatremia have been reported. Syndrome of inappropriate antidiuretic hormone secretion (SIADH) and cases of frank water intoxication, with hyponatremia and confusion, have also been reported. Pulmonary hypersensitivity, characterized by fever, dyspnea, pneumonitis, or pneumonia, also has occurred. Isolated cases of neuroleptic malignant syndrome have been reported with concomitant use of carbamazepine and psychotropic drugs.

Although scattered, punctate lens opacities have occurred only rarely in patients receiving carbamazepine, other drugs such as the phenothiazines have caused various ocular changes.

■ **Precautions and Contraindications** Carbamazepine may produce dangerous and alarming adverse effects, principally consisting of hematopoietic, dermatologic, cardiovascular, hepatic, and renal disturbances. The drug also shares the toxic potentials of the hydantoin-derivative anticonvulsants, and the usual precautions of anticonvulsant administration should be observed. When serious adverse effects occur requiring discontinuance of the drug, it is important to remember that abrupt withdrawal of any anticonvulsant drug in a responsive epileptic patient may precipitate seizures or status epilepticus. Carbamazepine therapy should be withdrawn gradually, whenever possible, to minimize the potential for increased seizure frequency. Patients must be carefully examined prior to initiation of carbamazepine therapy and should remain under close medical supervision throughout therapy with the drug. Carbamazepine should be prescribed only after careful benefit-to-risk evaluation in patients with a history of cardiac conduction disturbances; cardiac, hepatic, or renal damage; or adverse hematologic or hypersensitivity reaction to other drugs (e.g., other anticonvulsants) or who have had interrupted therapy with carbamazepine.

Serious and sometimes fatal dermatologic reactions, including toxic epidermal necrolysis and Stevens-Johnson syndrome, have been reported in patients receiving carbamazepine therapy. These reactions are estimated to occur in 1–6 per 10,000 new users of the drug in countries with mainly Caucasian populations; however, the risk in some Asian countries is estimated to be about 10 times higher. Carbamazepine should be discontinued at the first sign of a skin rash, unless the rash is clearly not drug-related. If signs or symptoms suggest Stevens-Johnson syndrome or toxic epidermal necrolysis, carbamazepine therapy should not be resumed and alternative therapy should be considered. Retrospective case-control studies in patients of Asian ancestry have demonstrated a strong association between the risk of developing Stevens-Johnson syndrome and toxic epidermal necrolysis and the presence of human leukocyte antigen (HLA)-B*1502, an inherited allelic variant of the HLA-B gene; this allele is found almost exclusively in patients with ancestry across broad areas of Asia. Therefore, the US Food and Drug Administration (FDA) and the manufacturers of carbamazepine recommend that patients with ancestry in genetically at-risk populations be screened for the presence of the HLA-B*1502 allele prior to initiating carbamazepine therapy. Patients testing positive for this allele should not receive carbamazepine therapy unless the benefit clearly outweighs the risk. (See Cautions: Dermatologic and Sensitivity Reactions.)

Multiple-organ hypersensitivity reactions occurring days to weeks or months following initiation of carbamazepine have been reported rarely. (See Cautions: Dermatologic and Sensitivity Reactions.) Discontinuance of carbamazepine should be considered if any evidence of hypersensitivity develops. Because hypersensitivity reactions to carbamazepine have been reported in patients with a history of hypersensitivity reactions to other anticonvulsants (e.g., phenytoin, phenobarbital), a detailed drug history should be obtained from patients and their immediate family members. Carbamazepine should be used with caution in patients with a history of hypersensitivity reactions to other anticonvulsants. Approximately 25–30% of patients who demonstrated hypersensitivity reactions to carbamazepine also may experience hypersensitivity reactions to oxcarbazepine.

Close attention by the patient and clinician to signs and symptoms of the possible development of adverse hematologic, dermatologic, or hypersensitivity reactions is important in patients receiving carbamazepine. Patients should be informed of the early signs and symptoms of these potential problems, such as fever, sore throat, infection, rash, mouth ulcers, easy bruising, lymphadenopathy, and petechial or purpuric hemorrhage, and should be instructed to report to their physician immediately if any such sign or symptom occurs. In addition, patients should be advised that these manifestations should be reported even if they are mild in severity or if they occur after extended use.

Although the manufacturers previously recommended initial frequent (possibly weekly during the first 3 months of therapy) and then less frequent, periodic (monthly for at least 2–3 years) testing of hematologic function in any patient receiving carbamazepine, they currently state that, because the frequency of minor hematologic changes progressing to aplastic anemia and agranulocytosis is very low, the vast majority of such changes observed during routine, periodic monitoring are unlikely to be signaling the impending development of either abnormality. Therefore, the manufacturers currently recommend that complete blood counts, including platelet and possibly reticulocyte counts and serum iron determinations, be performed prior to initiating carbamazepine therapy and that subsequent monitoring be individualized by the clinician. Guidelines for periodic monitoring of hematologic function have been suggested by some clinicians, and clinicians experienced in the use of carbamazepine and knowledgeable about the drug's potential toxicity can be consulted for more specific information. Patients exhibiting baseline abnormalities and those receiving other potentially myelotoxic drugs or with a history of adverse hematologic reactions to any drug should be considered at special risk, and carbamazepine therapy should be monitored closely or avoided in these patients. The manufacturers recommend that patients with a history of bone marrow depression *not* receive the drug. Patients who exhibit low or decreased leukocyte or platelet counts during the course of carbamazepine therapy should be monitored closely. Discontinuance of carbamazepine therapy should be considered if any evidence of significant bone marrow depression develops. In addition, if such evidence develops, particularly if it occurs as a result of overdosage, it has been suggested that complete blood counts, platelet counts, and reticulocyte counts be performed daily and bone marrow aspiration and trephine biopsy be done immediately and repeated as often as necessary to monitor recovery. Alternatively, one manufacturer suggests that the frequency of this monitoring in patients who develop evidence of significant bone marrow depression during the usual course of carbamazepine therapy (i.e., not resulting from overdosage) may be individualized by the clinician. Other special periodic hematologic studies may also be helpful in patients with evidence of significant bone marrow depression. Fully developed aplastic anemia requires appropriate, intensive monitoring and therapy for which specialized consultation should be sought. Some clinicians also advise hematologic consultation if neutropenia and depressed platelet and reticulocyte counts occur during therapy with the drug.

Adverse hepatic effects, ranging from slight elevations in hepatic enzymes to rare cases of hepatic failure, have been reported. In some cases, hepatic effects may progress despite discontinuance of the drug. Liver function tests should be performed prior to carbamazepine therapy, particularly in patients with a history of liver disease, and periodically thereafter. Carbamazepine should be immediately discontinued if evidence of liver dysfunction or active liver disease is observed. In addition, patients should be advised of the early manifestations of adverse hepatic effects (e.g., anorexia, nausea/vomiting, jaundice) and instructed to report such symptoms to their clinician immediately, even if the symptoms are mild or occur after extended use. Complete urinalysis and BUN determinations also should be performed prior to and periodically during carbamazepine therapy.

FDA has informed healthcare professionals about an increased risk of suicidality (suicidal behavior or ideation) observed in an analysis of studies using various anticonvulsants compared with placebo. (See Cautions: Nervous System Effects.) FDA recommends that all patients who are currently receiving or beginning therapy with any anticonvulsant for any indication be closely monitored for the emergence or worsening of depression, suicidal thoughts or behavior (suicidality), and/or unusual changes in mood or behavior. Symptoms such as anxiety, agitation, hostility, mania, and hypomania may be precursors to emerging suicidality. Clinicians should inform patients, their families, and caregivers of the potential for an increased risk of suicidality so that they are aware and able to notify their clinician of any unusual behavioral changes. Patients, family members, and caregivers also should be advised not to make any changes to the medication regimen without first consulting with the responsible clinician. They should pay close attention to any day-to-day changes in mood, behavior, and actions; since changes can happen very quickly, it is important to be alert to any sudden differences. In addition, patients, family members, and caregivers should be aware of common warning signs that may signal suicide risk (e.g., talking or thinking about wanting to hurt oneself or end one's life, withdrawing from friends and family, becoming depressed or experiencing worsening of existing depression, becoming preoccupied with death and dying, giving away prized possessions). If these or any new and worrisome behaviors occur, the responsible clinician should be contacted immediately. FDA also recommends that clinicians who prescribe carbamazepine or any other anticonvulsant balance the risk of suicidality with the risk of untreated illness. Epilepsy and many other illnesses for which anticonvulsants are prescribed are themselves associated with an increased risk of morbidity and mortality and an increased risk of suicidal thoughts and behavior. If suicidal thoughts and behavior emerge during anticonvulsant therapy, the clinician must consider whether the emergence of these symptoms in any given patient may be related to the illness being treated.

Carbamazepine may exacerbate seizures in some children with mixed seizure disorders. Some clinicians recommend that prolonged video-EEG monitoring be performed prior to initiating carbamazepine therapy in children with mixed seizure disorders in an attempt to identify those children who may be at risk for carbamazepine-induced exacerbation of seizures. (See Cautions: Nervous System Effects.)

Persons who perform hazardous tasks requiring mental alertness or physical coordination should be warned about the possible adverse neurologic and sensory effects of carbamazepine. Patients receiving carbamazepine also should be advised that there is a potential for additive CNS effects if alcohol is used concomitantly with carbamazepine. Because of the relationship of carbamazepine to other tricyclic compounds, the possibility of activation of a latent psychosis or, in geriatric patients, confusion or agitation should be kept in mind.

Baseline and periodic eye examinations including slit-lamp, funduscopy, and tonometry are recommended in patients receiving carbamazepine. Carbamazepine has shown mild anticholinergic activity; therefore, patients with increased intraocular pressure should be closely observed during carbamazepine therapy.

Because of similarity in spelling between Tegretol® or Tegretol®-XR (trade names for carbamazepine) and Toprol-XL® (metoprolol succinate, a β-adrenergic blocking agent), the potential exists for dispensing errors involving these drugs. These medication errors have been associated with serious adverse events sometimes requiring hospitalization as a result of either lack of the intended medication (e.g., seizure recurrence, return of hallucinations, suicide attempt, hypertension recurrence) or exposure to the wrong drug (e.g., bradycardia in a patient erroneously receiving metoprolol). Therefore, extra care should be exercised to ensure the accuracy of both oral and written prescriptions for these drugs. (See Dispensing and Administration Precautions under Dosage and Administration: Administration.) Dispensing errors involving Tegretol® or Tegretol®-XR (carbamazepine) and Toprol-XL® (metoprolol succinate) should be reported to the manufacturers, the USP/ISMP (Institute for Safe Medication Practices) Medication Errors Reporting Program by phone (800-233-7767), or directly to the FDA MedWatch program by phone (800-FDA-1088), fax (800-FDA-0178), or internet (http://www.fda.gov/Safety/MedWatch).

Carbamazepine is contraindicated in patients with a history of previous bone marrow depression, acute intermittent porphyria, and/or hypersensitivity to the drug or in patients who have demonstrated sensitivity to any of the tricyclic antidepressants (e.g., amitriptyline, desipramine, imipramine, nortriptyline, protriptyline). The drug also is contraindicated in patients currently re-

ceiving, or having recently received (i.e., within 2 weeks), monoamine oxidase (MAO) inhibitor therapy. (See Drug Interactions: Monoamine Oxidase Inhibitors.) Concomitant use of carbamazepine and nefazodone is contraindicated. (See Drug Interactions: Nefazodone.) In addition, the manufacturer of voriconazole states that concomitant use of carbamazepine and voriconazole is contraindicated. (See Drug Interactions: Azole Antifungal Agents.)

■ **Pediatric Precautions** Efficacy of carbamazepine for management of seizures in children is based on extrapolation of the demonstrated efficacy of carbamazepine in adults and also on in vitro studies that confirmed that the pathogenetic mechanisms associated with seizure propagation in adults are essentially the same as those in children; in addition, mechanism of action of carbamazepine in the treatment of seizures is the same in adults and children. The therapeutic range for plasma carbamazepine concentrations (i.e., 4–12 mcg/mL) is the same in children and adults. Safety of carbamazepine in children is based on clinical studies in which the drug was administered for up to 6 months. Data from long-term clinical studies in children are not available.

■ **Mutagenicity and Carcinogenicity** Bacterial and mammalian mutagenicity studies using carbamazepine have shown no evidence of mutagenicity. Carbamazepine has produced dose-related increases in the incidence of hepatocellular tumors in female rats and benign interstitial cell adenomas in male rats. The clinical importance of these findings is not known.

■ **Pregnancy and Lactation** Safe use of carbamazepine during pregnancy has not been established. Adverse fetal effects have been observed in reproduction studies in rats. Although several reports suggest an association between use of anticonvulsants in pregnant, epileptic women and an increased incidence of birth defects in children born to these women, a causal relationship to many of these drugs has not been established. However, epidemiologic data do suggest that an association between carbamazepine use during pregnancy and certain congenital abnormalities such as spina bifida may exist. Other congenital anomalies and developmental disorders (e.g., craniofacial defects, cardiovascular malformations, anomalies involving various body systems) also have been reported in association with carbamazepine use. Anticonvulsants should *not* be discontinued in pregnant women in whom the drugs are administered to prevent major seizures because of the strong possibility of precipitating status epilepticus with attendant hypoxia and threat to life. In individual cases, when the severity and frequency of the seizure disorder are such that discontinuance of therapy does not pose a serious threat to the patient, discontinuance of the drugs may be considered prior to and during pregnancy; however, it cannot be said with any certainty that even minor seizures do not pose some hazard to the fetus. Clinicians should carefully weigh these considerations in treating or counseling epileptic women of childbearing potential. Because carbamazepine can cause fetal harm when administered to pregnant women, the benefits of therapy must be weighed against the risks in women of childbearing potential. If carbamazepine is used during pregnancy, or if the patient becomes pregnant while receiving the drug, the patient should be apprised of the potential hazard to the fetus. Tests to detect fetal abnormalities using currently accepted procedures should be considered part of routine prenatal care in women of childbearing potential receiving carbamazepine.

There have been a few cases of seizures and/or respiratory depression in neonates born to women receiving carbamazepine concomitantly with other anticonvulsant agents. A few cases of vomiting, diarrhea, and/or decreased feeding also have been reported in neonates born to women receiving carbamazepine; these symptoms may represent a neonatal withdrawal syndrome.

To provide information regarding the effects of in utero exposure to carbamazepine, clinicians are advised to recommend that pregnant patients receiving carbamazepine enroll themselves in the North American Antiepileptic Drug (NAAED) Pregnancy Registry by calling 888-233-2334.

Carbamazepine and its epoxide metabolite (CBZ-E) are distributed into milk. Safe use of carbamazepine during lactation has not been established. Because of the potential for serious adverse reactions from carbamazepine in nursing infants, a decision should be made whether to discontinue nursing or the drug, taking into account the importance of the drug to the woman. Following daily oral administration of carbamazepine in nursing women, the milk-to-maternal plasma ratio of carbamazepine is about 0.4 and that of CBZ-E is about 0.5; it is estimated that neonates may receive about 2–5 and 1–2 mg of carbamazepine and CBZ-E, respectively, daily.

Drug Interactions

■ **Alcohol** Because of the risk of additive sedative effects, caution should be exercised if carbamazepine is used concomitantly with alcohol.

■ **Anticonvulsants** Because carbamazepine is an inducer of the cytochrome P-450 (CYP) 3A4 isoenzyme, concomitant use with certain other anticonvulsants (e.g., clonazepam, ethosuximide, lamotrigine, methsuximide, phensuximide [not commercially available in the US], phenytoin, tiagabine, topiramate, valproic acid, zonisamide) has been shown, or would be expected, to decrease plasma concentrations of the other anticonvulsant. It may be desirable to monitor serum concentrations of concomitantly administered anticonvulsants, making dosage adjustments as necessary.

Concomitant use of carbamazepine with other anticonvulsants that induce (e.g., methsuximide, phenobarbital, phenytoin, primidone) or inhibit (e.g., acetazolamide) CYP3A4 has been shown, or would be expected, to decrease or increase plasma carbamazepine concentrations, respectively. In addition, carbamazepine may decrease the half-life of phenytoin. Increased plasma concentrations of phenytoin and primidone have been reported following concomitant use with carbamazepine.

Felbamate and valproic acid apparently can affect both plasma carbamazepine and carbamazepine 10,11-epoxide (CBZ-E, an active metabolite) concentrations, but the interactions appear to be complex and resultant changes may be unpredictable. The effect of valproic acid on concentrations of the drug may depend principally on increases in plasma CBZ-E concentrations relative to parent drug (possibly secondary to inhibition of epoxide hydrolase activity), but other mechanisms (e.g., displacement of carbamazepine from protein binding sites) also have been suggested and may contribute to the overall effect. The importance of determining CBZ-E concentrations in patients exhibiting toxicity during concomitant carbamazepine and valproic acid therapy should be considered.

Recent evidence suggests that the human leukocyte antigen (HLA)-B *1502 allele, which is found almost exclusively in patients with ancestry across broad areas of Asia, may be a risk factor for the development of Stevens-Johnson syndrome and toxic epidermal necrolysis in patients of Asian ancestry who are receiving carbamazepine and some other anticonvulsants associated with these reactions (e.g., lamotrigine, fosphenytoin, phenytoin). Avoidance of such drugs should therefore be considered in HLA-B *1502-positive patients when alternative therapies are otherwise equally acceptable. The role of other possible factors, such as concomitant medications, anticonvulsant dosage, compliance, and illnesses, in the development of, and morbidity from, these reactions, and the level of dermatologic monitoring have not been adequately studied to date. (See Cautions: Dermatologic and Sensitivity Reactions and see Cautions: Precautions and Contraindications.)

Alterations of thyroid function have been reported with concomitant use of carbamazepine and other anticonvulsants.

■ **Lithium** Concomitant use of carbamazepine with lithium may increase the risk of adverse neurologic effects.

■ **Calcium-channel Blocking Agents** Concomitant use of carbamazepine and diltiazem or verapamil may result in increased plasma carbamazepine concentrations and subsequent toxicity. In several patients receiving 1–2 g of carbamazepine daily, initiation of 360 mg of verapamil hydrochloride daily resulted in development of neurologic manifestations (e.g., dizziness, ataxia, nystagmus) of carbamazepine toxicity within 36–96 hours. Plasma total and unbound carbamazepine concentrations increased by a mean of 46 and 33%, respectively, but returned to baseline values within 1 week after discontinuance of verapamil; manifestations of toxicity also resolved during this period. The ratio of plasma carbamazepine 10,11-epoxide to unchanged drug decreased during verapamil therapy but returned toward pretreatment levels following discontinuance of verapamil. Limited experience suggests that a similar interaction also may occur when diltiazem, but not nifedipine, is administered concomitantly with carbamazepine. It appears that verapamil and diltiazem inhibit hepatic metabolism of carbamazepine via the CYP3A4 isoenzyme.

If verapamil is initiated in patients receiving carbamazepine, a 40–50% reduction in carbamazepine dosage may be necessary during concomitant therapy. Patients should be monitored closely for manifestations of carbamazepine toxicity and for alterations in the pharmacokinetics of carbamazepine during concomitant therapy, adjusting carbamazepine dosage accordingly. If verapamil is discontinued, dosage of carbamazepine should be increased to avoid loss of seizure control.

Because carbamazepine is an inducer of the CYP3A4 isoenzyme, concomitant use with dihydropyridine calcium-channel blocking agents (e.g., felodipine) has been shown, or would be expected, to decrease plasma concentrations of the dihydropyridine calcium-channel blocking agent.

■ **Macrolides** Concomitant use of carbamazepine with certain macrolide antibiotics that inhibit CYP3A4 (e.g., clarithromycin, erythromycin, troleandomycin) has been shown, or would be expected, to increase plasma carbamazepine concentrations. Increased plasma concentrations of carbamazepine and subsequent signs of carbamazepine toxicity (e.g., ataxia, dizziness, drowsiness, vomiting) have occurred in adults or children following concomitant use of carbamazepine and erythromycin. Studies in adults indicate that erythromycin can substantially decrease serum clearance of carbamazepine, presumably by inhibiting hepatic metabolism of the drug. Patients receiving carbamazepine and erythromycin concomitantly should be monitored for evidence of carbamazepine toxicity; carbamazepine dosage should be reduced when necessary. Some clinicians suggest that use of an alternative anti-infective agent, instead of erythromycin, may be necessary in patients receiving carbamazepine.

■ **Doxycycline** Preliminary studies indicate that carbamazepine may decrease the half-life of doxycycline, probably by inducing hepatic microsomal enzymes that metabolize the antibiotic. Concomitant administration of doxycycline and carbamazepine should be avoided if possible. If concomitant therapy is necessary, doxycycline probably should be administered at 12-hour intervals and/or serum doxycycline concentrations should be closely monitored.

■ **Selective Serotonin-reuptake Inhibitors** Fluoxetine can increase plasma carbamazepine and carbamazepine 10,11-epoxide (CBZ-E, an active metabolite) concentrations, and carbamazepine toxicity (e.g., ocular changes, vertigo, tremor) has been reported in some patients maintained on carbamazepine following initiation of fluoxetine. It has been suggested that fluoxetine-induced inhibition of hepatic metabolism (e.g., inhibition of epoxide hydrolase) of carbamazepine and/or CBZ-E may be principally responsible for such increases; alteration in protein binding does not appear to be principally responsible for this interaction. The patient and plasma concentrations of carbamazepine and its metabolite should be monitored closely whenever fluoxetine therapy is initiated or discontinued; carbamazepine dosage should be adjusted accordingly.

Concomitant use of carbamazepine with fluvoxamine, an inhibitor of CYP3A4, has been shown, or would be expected, to increase plasma carbamazepine concentrations.

■ **Antipsychotic Agents** Because carbamazepine is an inducer of the CYP3A4 isoenzyme, concomitant use with some antipsychotic agents (e.g., aripiprazole, clozapine, haloperidol, risperidone, ziprasidone) has been shown, or would be expected, to decrease plasma concentrations of the antipsychotic agent. Reductions in antipsychotic efficacy with reemergence of symptoms has occurred in some, but not all, such patients. If carbamazepine therapy is added in patients receiving aripiprazole, the dosage of aripiprazole should be doubled and additional increases in aripiprazole dosage should be made based on clinical evaluation; if carbamazepine is withdrawn from combination therapy with aripiprazole, the dosage of aripiprazole should be reduced accordingly. Patients receiving carbamazepine and haloperidol concomitantly should be monitored carefully for loss of antipsychotic control and, if an interaction is suspected, haloperidol dosage adjusted accordingly. The possibility that haloperidol toxicity may occur following discontinuance of carbamazepine also should be considered.

Clozapine Concomitant use of carbamazepine and clozapine has been shown to decrease clozapine concentrations by about 40–50%. Both carbamazepine and clozapine also have the potential to cause adverse hematologic effects, including agranulocytosis. In addition, neuroleptic malignant syndrome (NMS) has been reported rarely during concomitant therapy with these drugs. Therefore, the manufacturers of clozapine and the American Psychiatric Association (APA) state that concomitant use of carbamazepine and clozapine generally is not recommended. However, if carbamazepine and clozapine are used concomitantly, it should be considered that discontinuance of carbamazepine may result in increased plasma concentrations of clozapine.

■ **Monoamine Oxidase Inhibitors** Combined therapy using carbamazepine and monoamine oxidase (MAO) inhibitors is contraindicated. A medication-free period of at least 14 days should be observed when transferring patients from MAO inhibitors to carbamazepine. Therapy with carbamazepine should then be initiated cautiously with gradual increases in dosage to obtain the desired response.

■ **Anticoagulants** Because carbamazepine is an inducer of the CYP3A4 isoenzyme, concomitant use with dicumarol or warfarin has been shown, or would be expected, to decrease plasma concentrations of the anticoagulant. In one study when carbamazepine was administered to patients being treated with warfarin, the serum concentration of warfarin decreased after about 10 days of carbamazepine therapy. Carbamazepine also shortened the half-life of warfarin in some patients. If warfarin and carbamazepine must be used together, the patient should be closely monitored and the dosage of both drugs adjusted as required.

■ **Theophylline** It has been suggested that concomitant administration of carbamazepine and theophylline may induce each other's metabolism, with resultant changes in elimination half-life and plasma concentrations. If carbamazepine and theophylline are used concomitantly, the patient and plasma concentrations of the drugs should be monitored and dosage adjusted accordingly.

■ **Hormonal Contraceptives** Concomitant use of carbamazepine and hormonal contraceptives (e.g., oral contraceptives, levonorgesterol subdermal implant contraceptives [no longer commercially available]) may cause increased metabolism of the contraceptive resulting from induction of hepatic microsomal enzymes. Breakthrough bleeding and unintended pregnancies have been reported in patients receiving carbamazepine and hormonal contraceptives. Because the reliability of hormonal contraceptive therapy may be adversely affected during concomitant administration of carbamazepine, a nonhormonal method of birth control should be considered.

■ **Antihistamines** Concomitant use of carbamazepine with antihistamines that inhibit CYP3A4 (e.g., loratadine, terfenadine [no longer commercially available]) has been shown, or would be expected, to increase plasma carbamazepine concentrations.

■ **Antituberculosis Agents** Concomitant use of carbamazepine with antituberculosis agents that inhibit CYP3A4 (e.g., isoniazid) has been shown, or would be expected, to increase plasma carbamazepine concentrations. Conversely, concomitant use of carbamazepine with antituberculosis agents that induce CYP3A4 (e.g., rifampin) has been shown, or would be expected, to decrease plasma carbamazepine concentrations.

■ **Antineoplastic Agents** Concomitant use of carbamazepine with antineoplastic agents that induce CYP3A4 (e.g., cisplatin, doxorubicin) has been shown, or would be expected, to decrease plasma carbamazepine concentrations.

■ **Azole Antifungal Agents** Concomitant use of carbamazepine with azole antifungal agents that inhibit CYP3A4 (e.g., fluconazole, itraconazole, ketoconazole, voriconazole) has been shown, or would be expected, to increase plasma carbamazepine concentrations.

Concomitant use of carbamazepine and fluconazole has resulted in increased carbamazepine concentrations and associated toxicity, presumably as the result of fluconazole inhibiting CYP isoenzymes involved in metabolism of the anticonvulsant. It has been suggested that carbamazepine concentrations be monitored in patients receiving fluconazole concomitantly.

Because carbamazepine also is an inducer of the CYP3A4 isoenzyme, concomitant use with itraconazole has been shown, or would be expected, to decrease plasma concentrations of itraconazole.

Although the interaction has not been specifically studied to date, carbamazepine would be expected to substantially decrease plasma voriconazole concentrations due to potent induction of CYP enzymes; therefore, the manufacturer of voriconazole states that concomitant use of carbamazepine and voriconazole is contraindicated.

■ **Corticosteroids** Because carbamazepine is an inducer of the CYP3A4 isoenzyme, concomitant use with corticosteroids metabolized by CYP3A4 (e.g., dexamethasone, prednisolone) has been shown, or would be expected, to decrease plasma concentrations of the corticosteroid.

■ **HIV Protease Inhibitors** Concomitant use of carbamazepine with HIV protease inhibitors that inhibit CYP3A4 has been shown, or would be expected, to increase plasma carbamazepine concentrations. Because carbamazepine is an inducer of CYP3A4, concomitant use with HIV protease inhibitors that are metabolized by CYP3A4 has been shown, or would be expected, to decrease plasma concentrations of the HIV protease inhibitor.

■ **Tricyclic Antidepressants** Because carbamazepine is an inducer of the CYP3A4 isoenzyme, concomitant use with tricyclic antidepressants metabolized by CYP3A4 (e.g., amitriptyline, imipramine, nortriptyline) has been shown, or would be expected, to decrease plasma concentrations of the tricyclic antidepressant.

■ **Nefazodone** Concomitant use of carbamazepine and nefazodone is contraindicated since this may reduce plasma concentrations of nefazodone and its active metabolite, hydroxynefazodone, by 95% resulting in levels insufficient to achieve an antidepressant effect.

■ **Trazodone** Because carbamazepine is an inducer of the CYP3A4 isoenzyme, concomitant use with trazodone has been shown to decrease plasma concentrations of trazodone. Concomitant use of carbamazepine (400 mg daily) with trazodone (100–300 mg daily) decreased plasma concentrations of trazodone and an active metabolite, *m*-chlorophenylpiperazine, by 76 and 60%, respectively. Patients receiving carbamazepine and trazodone concomitantly should be closely monitored and dosage of trazodone increased if necessary.

■ **Other Drugs** Concomitant use of carbamazepine with drugs or foods that inhibit CYP3A4 (e.g., cimetidine, danazol, grapefruit juice, niacinamide, propoxyphene) has been shown, or would be expected, to increase plasma carbamazepine concentrations. In addition, because carbamazepine is an inducer of the CYP3A4 isoenzyme, concomitant use with drugs metabolized by CYP3A4 (e.g., acetaminophen, alprazolam, cyclosporine, levothyroxine, methadone, midazolam, praziquantel, tramadol) has been shown, or would be expected, to decrease plasma concentrations of the other drug.

Laboratory Test Interferences

■ **Pregnancy Tests** Carbamazepine interferes with some pregnancy tests.

Acute Toxicity

■ **Pathogenesis** The lowest known lethal dose of carbamazepine is 3.2 and 1.6 g in adults and children, respectively.

■ **Manifestations** Carbamazepine overdosage produces dizziness, ataxia, drowsiness, stupor, nausea, vomiting, opisthotonos, restlessness, agitation, disorientation, tremor, involuntary movements, adiadochokinesis, abnormal reflexes (hypoactive or hyperactive), mydriasis, nystagmus, flushing, cyanosis, and urinary retention. Hypotension or hypertension may develop. Coma may follow. Laboratory findings in some cases of overdosage have included leukocytosis, reduced leukocyte count, glycosuria, and acetonuria. EEG may show dysrhythmias.

A 24-year-old woman who ingested 3.2 g of carbamazepine died of cardiac arrest, and a 24-year-old man died of pneumonia and hypoxic encephalopathy ingesting the same dose. A 14-year-old girl who ingested 4 g of carbamazepine died of cardiac arrest, and a 3-year-old girl who ingested 1.6 g of carbamazepine died of aspiration pneumonia.

■ **Treatment** Treatment of carbamazepine overdosage consists of inducing emesis or gastric lavage and general supportive therapy. Because of the relationship of carbamazepine to the tricyclic antidepressants, the ECG should be monitored, especially in children, to detect cardiac dysfunction.

Pharmacology

The pharmacologic actions of carbamazepine appear to be qualitatively similar to those of the hydantoin-derivative anticonvulsants. The anticonvulsant activity of carbamazepine, like phenytoin, principally involves limitation of seizure propagation by reduction of posttetanic potentiation (PTP) of synaptic transmission. Carbamazepine appears to provide relief of pain in trigeminal neuralgia by reducing synaptic transmission within the trigeminal nucleus. The drug has also demonstrated sedative, anticholinergic, antidepressant, muscle relaxant, antiarrhythmic, antidiuretic, and neuromuscular transmission-inhibitory actions. Carbamazepine has only slight analgesic properties.

Pharmacokinetics

The pharmacokinetic parameters of carbamazepine disposition are similar in children and in adults; however, there is a poor correlation between dosage and plasma concentrations of carbamazepine in children. The effects of race and gender on carbamazepine pharmacokinetics have not been systematically evaluated. However, retrospective, case-control studies in patients of Chinese ancestry have demonstrated a strong pharmacogenomic association between the risk of developing Stevens-Johnson syndrome and toxic epidermal necrolysis and the presence of HLA-B*1502, an inherited allelic variant of the HLA-B gene. (See Cautions: Dermatologic and Sensitivity Reactions.)

■ **Absorption** Carbamazepine is slowly absorbed from the GI tract. Following chronic oral administration of carbamazepine tablets, suspension, extended-release tablets, or extended-release capsules, peak plasma concentra-

tions are reached in 4.5, 1.5, 3–12, or 4.1–7.7 hours, respectively. The oral bioavailabilities of carbamazepine tablets and suspension reportedly are equivalent, although the rate of absorption is faster for the suspension. The bioavailability of the extended-release tablets is reportedly 89% of that of the suspension, and the absorption of the extended-release tablets is slightly slower than that of the conventional tablets. Peak plasma concentrations of the drug are higher and trough concentrations are lower for the suspension compared with tablets when the drug is administered once or twice daily, but steady-state concentrations reportedly are comparable when the suspension is administered in 3 divided doses daily and the tablets are administered in 2 divided doses daily. Following oral administration of carbamazepine extended-release capsules or tablets every 12 hours, steady-state plasma carbamazepine concentrations were comparable to those achieved with corresponding dosages of the conventional (immediate-release) tablets every 6 hours. Although one manufacturer states that peak plasma concentrations may be higher with chewable tablets than with conventional tablets, a crossover study employing this manufacturer's tablets in adults with seizure disorders showed no such difference. In this study, the oral pharmacokinetics, including bioavailability, and peak and trough plasma concentrations, were comparable for conventional and chewable tablets of the drug, although individual patients may have achieved somewhat higher concentrations for one or the other tablet formulation.

Two to 4 days of therapy may be required to achieve steady-state plasma concentrations. Although optimal therapeutic plasma concentrations suitable for all patients have not yet been determined, therapeutic plasma concentrations of carbamazepine (for both anticonvulsant effects and relief of pain of trigeminal neuralgia) are usually 3–14 mcg/mL. Some investigators have noted that nystagmus frequently occurs when plasma concentrations are greater than 4 mcg/mL and that ataxia, dizziness, and anorexia often occur when plasma concentrations are 10 mcg/mL or greater. There appears to be a wide variation in steady-state plasma concentrations produced by specific daily dosages of carbamazepine (e.g., daily dosages of 800 mg, 1.2 g, or 1.6 g may produce plasma concentrations of 2–10 mcg/mL).

In one study, when carbamazepine extended-release capsules (Carbatrol®) were administered as a single 400-mg dose with a high-fat meal, the rate, but not the extent, of carbamazepine absorption was increased when compared with administration of the capsules in the fasting state. Results of a multiple-dose study of the extended-release capsules indicate that when these capsules are administered after a meal, peak steady-state plasma concentrations are within the therapeutic range. When the extended-release capsules of carbamazepine (Carbatrol®) are broken and the beads sprinkled over applesauce prior to administration, the pharmacokinetic profile of the drug is similar to that following oral administration of the intact capsule to fasting individuals. The manufacturer of carbamazepine extended-release capsules states that the elimination half-life of the drug does not differ substantially between fasted and nonfasted conditions of administration.

■ **Distribution** Carbamazepine is widely distributed in the body; the drug has been detected in CSF (approximately 15–22% of serum concentrations), the brain (at autopsy), duodenal fluids, bile, and saliva. A major metabolite, carbamazepine 10,11-epoxide, has also been detected in CSF. Carbamazepine rapidly crosses the placenta (i.e., 30–60 minutes) and accumulates in fetal tissues, with higher concentrations in the liver and kidney than in brain and lungs. Carbamazepine and its epoxide metabolite are distributed in breast milk. The ratio of the concentration in breast milk to that in plasma is approximately 0.4 for the drug and 0.5 for the epoxide metabolite.

In vitro studies indicate that at plasma concentrations of 1–50 mcg/mL, 75–90% of the drug is bound to plasma proteins.

■ **Elimination** Carbamazepine has a relatively long plasma half-life, variously reported to be 8–72 hours. The variability results in part because carbamazepine can induce its own metabolism; autoinduction of metabolism usually is completed after 3–5 weeks of a fixed dosing regimen. The plasma half-life generally ranges from 25–65 hours initially and from 12–17 hours with multiple dosing.

The metabolic fate of carbamazepine has not been completely elucidated. A major metabolic pathway appears to be oxidation by microsomal enzymes in the liver (principally cytochrome P-450 isoform 3A4) to form carbamazepine 10,11-epoxide (CBZ-E), which is almost completely metabolized to *trans*-10,11-dihydroxy-10,11-dihydrocarbamazepine (*trans*-CBZ-diol) and excreted in urine mainly unconjugated. CBZ-E has anticonvulsant activity in animals and potent analgesic activity in patients with trigeminal neuralgia. CBZ-E also has been implicated as contributing to adverse neurologic effects of the drug. Carbamazepine is more rapidly metabolized to CBZ-E in children than in adults. In children younger than 15 years of age, there is an inverse relationship between the CBZ-E/CBZ ratio and increasing age; this ratio was reported to be 0.44 in children younger than 1 year old and 0.18 in children 10–15 years of age. Carbamazepine also undergoes aromatic hydroxylation to form 2-hydroxycarbamazepine and 3-hydroxycarbamazepine. The pathway is not clearly determined, but the drug also undergoes metabolism to form 9-hydroxymethyl-10-carbamoyl-acridan. Carbamazepine and its metabolites are excreted in urine. Only about 1–3% of the drug is excreted in urine unchanged. Carbamazepine induces liver microsomal enzymes and thus may accelerate its own metabolism and that of other concomitantly administered drugs that are metabolized by these enzymes. (See Drug Interactions.)

Chemistry and Stability

■ **Chemistry** Carbamazepine is an iminostilbene derivative that is used as both an anticonvulsant and for the relief of pain associated with trigeminal neuralgia (tic douloureux). Carbamazepine is structurally related to the tricyclic antidepressants such as amitriptyline and imipramine. Carbamazepine occurs as a white to off-white powder and is practically insoluble in water and soluble in alcohol and in acetone.

The multi-compartment, extended-release capsule formulation of carbamazepine (Carbatrol®) contains 3 different types of beads: immediate-, extended-, and enteric-release beads. The 3 bead types are combined in a specific ratio to allow for twice-daily dosing.

■ **Stability** Carbamazepine tablets, extended-release tablets, and chewable tablets should be stored in tight, light-resistant containers at temperatures not exceeding 30°C. Carbamazepine extended-release capsules should be stored in tight, light-resistant containers at 15–25°C. Because dissolution characteristics and associated oral bioavailability of carbamazepine tablets may be affected substantially by moisture, patients should be cautioned to keep containers of the tablets tightly closed and in a dry location; away from areas with excessive moisture (e.g., showers, bathrooms, humidifiers). Carbamazepine tablets may lose one-third or more of their oral bioavailability when exposed to excessive moisture. Tablets continuously exposed to 97% relative humidity at room temperature for 2 weeks become hardened and dissolve poorly.

Carbamazepine oral suspension should be stored in tight, light-resistant containers at temperatures not exceeding 30°C; freezing of the oral suspension should be avoided.

Testing has shown that mixing carbamazepine oral suspension either with chlorpromazine oral solution or with liquid thioridazine preparations results in a rubbery, orange precipitate. It is not known whether the development of this precipitate results in decreased bioavailability of either carbamazepine or the other drugs. The extent to which this interaction occurs with other liquid preparations also is not known. Therefore, the manufacturer recommends that carbamazepine oral suspension not be administered simultaneously with other liquid preparations.

For further information on pharmacology, cautions, and dosage and administration of carbamazepine, see the Anticonvulsants General Statement 28:12.

Preparations

Excipients in commercially available drug preparations may have clinically important effects in some individuals; consult specific product labeling for details.

Carbamazepine

Oral		
Capsules, extended-release	100 mg	**Carbatrol®, Shire**
	200 mg	**Carbatrol®, Shire**
	300 mg	**Carbatrol®, Shire**
Suspension	100 mg/5 mL*	**Carbamazepine Suspension**
		Tegretol®, Novartis
Tablets	200 mg*	**Carbamazepine Tablets**
		Epitol® (scored), Teva
		Tegretol® (scored), Novartis
Tablets, chewable	100 mg*	**Carbamazepine Chewable Tablets**
		Tegretol® (scored), Novartis
Tablets, extended-release	100 mg	**Tegretol®-XR, Novartis**
	200 mg	**Tegretol®-XR, Novartis**
	400 mg	**Tegretol®-XR, Novartis**

*Available from one or more manufacturer, distributor, and/or repackager by generic (nonproprietary) name
†Use is not currently included in the labeling approved by the US Food and Drug Administration

Felbamate

■ Felbamate, a dicarbamate, is an anticonvulsant.

Uses

In July 1993, felbamate (Felbatol®) originally was approved by the US Food and Drug Administration (FDA) for use as monotherapy or in combination with other anticonvulsant agents in the management of partial seizures with or without secondary generalization in adults. Felbamate also was approved by FDA at that time for use in combination with other anticonvulsant agents in the management of partial and generalized seizures associated with Lennox-Gastaut syndrome in children and has been designated an orphan drug by FDA for the treatment of this latter syndrome. However, because use of the drug has since been associated with marked increases in the incidences of **aplastic anemia** and **acute hepatic failure**, the manufacturer in conjunction with FDA warns that the drug should *only* be initiated or continued in the management

The US Food and Drug Administration (FDA) has determined that antidepressants increase the risk of suicidal thinking and behavior (suicidality) in children and adolescents with major depressive disorder and other psychiatric disorders. However, FDA also states that depression and certain other psychiatric disorders are themselves associated with an increased risk of suicide. Anyone considering the use of doxepin in a child or adolescent for any clinical use must therefore balance the potential risk of therapy with the clinical need. (See Cautions: Precautions and Contraindications and Cautions: Pediatric Precautions, in the Tricyclic Antidepressants General Statement 28:16.04.28.)

■ **Lactation** Limited data indicate that doxepin and its active *N*-demethylated metabolite are distributed into milk. Sedation and serious respiratory depression were reported in a nursing infant whose mother was receiving 75 mg of doxepin daily; substantial concentrations of the active metabolite of the drug were detected in the infant's serum and urine. In addition, poor sucking and swallowing while nursing, drowsiness, muscle hypotonia, and vomiting were reported in a nursing infant whose mother was receiving 35 mg of doxepin daily. Because of the potential for serious adverse reactions to doxepin and/or its active metabolite in nursing infants, a decision should be made whether to discontinue nursing or the drug, taking into account the importance of the drug to the woman.

Pharmacokinetics

■ **Absorption** The pharmacokinetics of doxepin have not been extensively studied, but the drug is well absorbed from the GI tract in animals. Peak plasma concentrations usually occur within 2 hours after oral administration of the drug.

■ **Distribution** Doxepin is highly bound to plasma proteins.

Limited data indicate that doxepin and its active *N*-demethylated metabolite are distributed into milk in concentrations reportedly ranging from about 30–140% and 10–115%, respectively, of those in maternal serum and that substantial concentrations of the active metabolite have been detected in the serum and urine of nursing infants whose mothers were receiving 75–150 mg of doxepin daily.

■ **Elimination** The plasma half-life of doxepin is 6–24.5 hours. The drug appears to be metabolized via the same pathways as are other tricyclic antidepressants; its *N*-demethylated metabolite is pharmacologically active.

Chemistry and Stability

■ **Chemistry** Doxepin hydrochloride is a dibenzoxepin-derivative tricyclic antidepressant. The drug occurs as a white powder, is freely soluble in water and in alcohol, and has a pK_a of 8. Doxepin hydrochloride oral concentrate has a pH of 4–7.

■ **Stability** Doxepin hydrochloride capsules should be stored in tight, light-resistant containers at a temperature between 15–30°C and the oral concentrate should be stored at a temperature between 20–25°C. Commercially available doxepin hydrochloride capsules have an expiration date of 36 months and the oral concentrate has an expiration date of 24 months following the date of manufacture.

Doxepin hydrochloride oral concentrate is physically incompatible with many carbonated beverages, but is compatible with some other beverages. (See Dosage and Administration: Administration.) Bulk preparation and storage of dilutions of the commercially available oral concentrate are not recommended by the manufacturers.

For further information on chemistry, pharmacology, pharmacokinetics, uses, cautions, acute toxicity, drug interactions, and dosage and administration of doxepin, see the Tricyclic Antidepressants General Statement 28:16.04.28.

Preparations

Excipients in commercially available drug preparations may have clinically important effects in some individuals; consult specific product labeling for details.

Doxepin Hydrochloride

Oral		
Capsules	10 mg (of doxepin)*	**Doxepin Hydrochloride Capsules**
		Sinequan*, Pfizer
	25 mg (of doxepin)*	**Doxepin Hydrochloride Capsules**
		Sinequan*, Pfizer
	50 mg (of doxepin)*	**Doxepin Hydrochloride Capsules**
		Sinequan*, Pfizer
	75 mg (of doxepin)*	**Doxepin Hydrochloride Capsules**
		Sinequan*, Pfizer
	100 mg (of doxepin)*	**Doxepin Hydrochloride Capsules**
		Sinequan*, Pfizer
	150 mg (of doxepin)*	**Doxepin Hydrochloride Capsules**
		Sinequan*, Pfizer
Solution, concentrate	10 mg (of doxepin) per mL*	**Doxepin Hydrochloride Oral Solution (Concentrate)**
		Sinequan* Oral Concentrate, Pfizer

*available from one or more manufacturer, distributor, and/or repackager by generic (nonproprietary) name

Imipramine Hydrochloride
Imipramine Pamoate

■ Imipramine is a dibenzazepine-derivative tricyclic antidepressant.

Dosage and Administration

■ **Administration** Imipramine hydrochloride and imipramine pamoate are administered orally. Although imipramine hydrochloride has been administered in up to 4 divided doses throughout the day, it is long-acting and the entire oral daily dose may be administered at one time. Imipramine pamoate may also be used to administer the daily oral dose of imipramine, but it has no advantages over the hydrochloride. Administration of the entire daily dose at bedtime may reduce daytime sedation; patients who experience insomnia and stimulation may be given the entire daily dose in the morning.

■ **Dosage** Dosage of imipramine salts is expressed in terms of imipramine hydrochloride.

Patients should be monitored for possible worsening of depression, suicidality, or unusual changes in behavior, especially at the beginning of therapy or during periods of dosage adjustment. (See Cautions: Precautions and Contraindications, in the Tricyclic Antidepressants General Statement 28:16.04.28.)

Major Depressive Disorder There is a wide range of oral dosage requirements, and dosage must be carefully individualized. Initial dosages of imipramine should be low and generally range from 75–100 mg daily, depending on the severity of the condition being treated. Dosage may be gradually adjusted to the level that produces maximal therapeutic effect with minimal toxicity and may range up to 300 mg daily. Hospitalized patients under close supervision may generally be given higher dosages than outpatients, and manufacturers state that dosages of greater than 200 mg daily are not recommended for outpatients. Geriatric patients should usually be given lower than average dosages. Manufacturers state that therapy should be initiated with 25–50 mg daily as imipramine hydrochloride (e.g., Tofranil®) in these patients and that optimal dosage rarely exceeds 100 mg daily. If the daily dosage is established at 75 mg or more, imipramine pamoate (e.g., Tofranil®-PM) may be administered. Maximum antidepressant effects may not occur for 2 or more weeks after therapy is begun.

After symptoms are controlled, dosage should be gradually reduced to the lowest level that will maintain relief of symptoms. If maintenance therapy is necessary, manufacturers recommend an adult dosage of 50–150 mg daily. To avoid the possibility of precipitating withdrawal symptoms, imipramine should not be terminated abruptly in patients who have received high dosage for prolonged periods.

Functional Enuresis in Children For the treatment of functional enuresis in children who are at least 6 years of age, the usual initial oral dosage of imipramine hydrochloride is 25 mg daily, administered 1 hour prior to bedtime. If a satisfactory response is not obtained within 1 week, dosage may be increased to 50 mg nightly for children younger than 12 years of age or 75 mg nightly for children 12 years of age and older. Dosages higher than 75 mg daily do not improve results and may increase the risk of adverse reactions. For children who are early-night bedwetters, better results may be obtained by administering 25 mg in midafternoon and again at bedtime. Dosage of imipramine hydrochloride for the treatment of functional enuresis in children should not exceed 2.5 mg/kg daily. Long-term effects of the drug in children have not been determined; therefore, after a satisfactory response has been maintained, imipramine hydrochloride should be gradually withdrawn. If dosage is gradually reduced after a favorable response of many weeks, relapses may be less frequent; children who relapse may not respond to subsequent treatment with imipramine. (See Cautions: Pediatric Precautions.)

Cautions

Imipramine shares the pharmacologic actions, uses, and toxic potentials of the tricyclic antidepressants, and the usual precautions of tricyclic antidepressant administration should be observed. Patients should be fully advised about the risks, especially suicidal thinking and behavior (suicidality), associated with tricyclic antidepressant therapy. For a complete discussion, see Cautions: Precautions and Contraindications and Cautions: Pediatric Precautions, in the Tricyclic Antidepressants General Statement 28:16.04.28.

Although the clinical importance is not known, ECG changes have been reported in pediatric patients receiving twice the recommended maximum daily dosage.

■ **Pediatric Precautions** Imipramine hydrochloride is used for the treatment of enuresis in children 6 years of age or older, but safety and efficacy of the drug for the treatment of this condition in younger children or for the treatment of any other condition in pediatric patients have not been established. The manufacturer of imipramine *pamoate* states that the drug should not be used in children of any age because of the high potency and risk of acute overdose.

The US Food and Drug Administration (FDA) has determined that antidepressants increase the risk of suicidal thinking and behavior (suicidality) in children and adolescents with major depressive disorder and other psychiatric disorders. However, FDA also states that depression and certain other psychiatric disorders are themselves associated with an increased risk of suicide. Anyone considering the use of imipramine in a child or adolescent for any clinical use must therefore balance the potential risk of therapy with the clinical need. (See Cautions: Precautions and Contraindications and Cautions: Pediatric Precautions, in the Tricyclic Antidepressants General Statement 28:16.04.28.)

Pharmacokinetics

■ **Absorption** In studies with radiolabeled imipramine, the drug was completely absorbed from the GI tract. Peak plasma concentrations of imipramine occur within 1–2 hours after oral administration and 30 minutes after IM administration (no longer commercially available in the US).

■ **Distribution** Limited data indicate that imipramine and its active metabolite, desipramine, are distributed into milk in concentrations similar to those present in maternal plasma.

■ **Elimination** The plasma half-life of imipramine ranges from 8–16 hours. Imipramine is metabolized via the same pathways as are other tricyclic antidepressants; desipramine, its *N*-monodemethylated metabolite, is pharmacologically active. Approximately 40% of a dose of imipramine is excreted in urine as inactive metabolites within 24 hours and 70% within 72 hours; small amounts are excreted in feces via biliary elimination.

Chemistry and Stability

■ **Chemistry** Imipramine is a dibenzazepine-derivative tricyclic antidepressant. The drug is commercially available as the hydrochloride and pamoate salts.

Imipramine hydrochloride occurs as a white to off-white, odorless or practically odorless, crystalline powder and is freely soluble in water and in alcohol. Imipramine pamoate occurs as a fine yellow powder and is insoluble in water and soluble in alcohol. Imipramine hydrochloride has a pK_a of 9.5.

■ **Stability** Imipramine hydrochloride turns yellowish or reddish on exposure to light; slight discoloration does not affect potency, but marked discoloration is associated with loss of potency. Solutions of imipramine hydrochloride are stable at pH 4–5. During storage, minute crystals may form in imipramine hydrochloride injection (no longer commercially available in the US); the efficacy of the preparation is unaltered if the crystals are redissolved by immersing the ampul in hot water for 1 minute.

Imipramine hydrochloride tablets and imipramine pamoate capsules should be stored in tight containers at a temperature between 15–30°C. Commercially available oral imipramine hydrochloride preparations have expiration dates of 3–5 years (depending on the manufacturer) following the date of manufacture. Commercially available imipramine pamoate capsules have an expiration date of 3 years following the date of manufacture.

For further information on chemistry, pharmacology, pharmacokinetics, uses, cautions, acute toxicity, drug interactions, and dosage and administration of imipramine, see the Tricyclic Antidepressants General Statement 28:16.04.28.

Preparations

Excipients in commercially available drug preparations may have clinically important effects in some individuals; consult specific product labeling for details.

Imipramine Hydrochloride

Oral		
Tablets	10 mg*	Imipramine Hydrochloride Tablets
		Tofranil®, Mallinckrodt
	25 mg*	Imipramine Hydrochloride Tablets
		Tofranil®, Mallinckrodt
	50 mg*	Imipramine Hydrochloride Tablets
		Tofranil®, Mallinckrodt
Tablets, film-coated	10 mg*	Imipramine Hydrochloride Film-coated Tablets
	25 mg*	Imipramine Hydrochloride Film-coated Tablets
	50 mg*	Imipramine Hydrochloride Film-coated Tablets

*available from one or more manufacturer, distributor, and/or repackager by generic (nonproprietary) name

Imipramine Pamoate

Oral		
Capsules	equivalent to Imipramine Hydrochloride 75 mg	Tofranil-PM®, Mallinckrodt
	equivalent to Imipramine Hydrochloride 100 mg	Tofranil-PM®, Mallinckrodt
	equivalent to Imipramine Hydrochloride 125 mg	Tofranil-PM®, Mallinckrodt
	equivalent to Imipramine Hydrochloride 150 mg	Tofranil-PM®, Mallinckrodt

Maprotiline Hydrochloride

■ Maprotiline hydrochloride is a tetracyclic antidepressant that is pharmacologically similar to the tricyclic antidepressants.

Uses

Maprotiline hydrochloride is used in the treatment of depressive affective (mood) disorders, including dysthymic disorder (depressive neurosis) and major depressive disorder. The drug has been used for the depressive phase of bipolar disorder; however, hypomanic or manic episodes may occur when the drug is given to patients with this disorder and other antidepressants (e.g., bupropion, selective serotonin-reuptake inhibitors) generally are preferred when an antidepressant is considered necessary in such patients. (See Considerations in Choosing Therapy for Depressive Episodes under Uses: Bipolar Disorder, in Lithium Salts 28:28.) Maprotiline is effective for the relief of anxiety associated with depression. Most studies comparing maprotiline with amitriptyline or imipramine in the treatment of patients with various types of depression have not demonstrated superiority of maprotiline over these tricyclic antidepressants. Although maprotiline has been reported to have a slightly more rapid onset of action than either amitriptyline or imipramine in some studies, this finding has not been adequately established.

For further information on treatment of major depressive disorder and considerations in choosing the most appropriate antidepressant for a particular patient, including considerations related to patient tolerance, patient age, and cardiovascular, sedative, and suicidal risks, see Considerations in Choosing Antidepressants under Uses: Major Depressive Disorder, in the Tricyclic Antidepressants General Statement 28:16.04.28.

Dosage and Administration

■ **Administration** Maprotiline hydrochloride is administered orally. Although maprotiline has been administered in 3 divided doses throughout the day, it is long-acting and the entire daily dose may be administered at one time.

Dispensing and Administration Precautions Dispensing errors have occurred because of the similarity in spelling between Ludiomil® (the former trade name for maprotiline hydrochloride; no longer commercially available under this trade name in the US) and Lamictal® (the trade name for lamotrigine, an anticonvulsant). Therefore, extra care should be exercised in ensuring the accuracy of both oral and written prescriptions for Ludiomil® and Lamictal®. The manufacturer of Lamictal® (GlaxoSmithKline) recommends that clinicians consider including the intended use of the particular drug on the prescription, in addition to alerting patients to carefully check the drug they receive and promptly bring any question or concern to the attention of the dispensing pharmacist. The manufacturer of Lamictal® also recommends that pharmacists assess various measures of avoiding dispensing errors and implement them as appropriate (e.g., by computerized filling and handling of prescriptions, patient counseling). (See Cautions.)

■ **Dosage** There is a wide range of dosage requirements, and dosage of maprotiline hydrochloride must be carefully individualized. The manufacturer suggests that the risk of seizures may be decreased by initiating therapy with low dosages of the drug. Initial dosages should be low, generally 75 mg daily in outpatients with mild to moderate depression, although a lower initial dosage may be used in some patients (e.g., geriatric patients). Because of the long elimination half-life of maprotiline, the initial dosage should be maintained for 2 weeks. Depending on tolerance and response, the daily dose may then be gradually increased in 25-mg increments. In most outpatients, a maximum dosage of 150 mg daily will be effective; it is recommended that this dosage be exceeded only in very severely depressed patients. Severely depressed hospitalized patients under close supervision may generally be given higher dosages than outpatients; such patients may be given an initial dosage of 100–150 mg daily which may be increased cautiously. Most hospitalized patients with moderate to severe depression will respond to a dosage of 150 mg daily, but dosages as high as 225 mg daily may be necessary in some patients; dosage should not exceed 225 mg daily. Geriatric patients (i.e., patients older than 60 years of age) should usually be given lower than average dosages; 50–75 mg daily is generally satisfactory for these patients. Antidepressant effects usually occur within 2–3 weeks in most patients who respond to maprotiline therapy and may occur within 3–7 days.

fate, dosage of these agents must be carefully adjusted because of the additive central depressant effects.

■ **Neuromuscular Blocking Agents** Excessive neuromuscular blockade has occurred in patients receiving parenteral magnesium sulfate and a neuromuscular blocking agent; these drugs should be administered concomitantly only with caution.

■ **Cardiac Glycosides** Magnesium salts should be administered with extreme caution in digitalized patients, because serious changes in cardiac conduction which can result in heart block may occur if administration of calcium is required to treat magnesium toxicity.

Pharmacology

Magnesium is the fourth most abundant cation in the body and is essential for the function of important enzymes, including those related to the transfer of phosphate groups, all reactions involving ATP, and every step related to the replication and transcription of DNA and the translation of mRNA. Magnesium also is required for cellular energy metabolism and is involved in membrane stabilization, nerve conduction, iron transport, and calcium-channel activity.

When administered parenterally in doses sufficient to produce hypermagnesemia (serum magnesium concentrations greater than 2.5 mEq/L), the drug may depress the CNS and block peripheral neuromuscular transmission, producing anticonvulsant effects. The exact mechanism of this depressant activity is not fully known; however, excess magnesium appears to decrease the amount of acetylcholine liberated by the motor nerve impulse. When serum concentrations of magnesium exceed 4 mEq/L, deep-tendon reflexes may be depressed. At serum concentrations of 10 mEq/L, deep-tendon reflexes may disappear and respiratory paralysis may occur. Serum magnesium concentrations in excess of 12 mEq/L may be fatal. Complete heart block can also occur at high serum concentrations of magnesium (approximately 10 mEq/L). Animal studies suggest that the effect of magnesium ions on cardiac muscle is to slow the rate of the sinoatrial node impulse formation and prolong conduction time. Limited data in patients with no evidence of heart disease indicate that IV infusion of magnesium prolongs PR interval, H(atria-His bundle) interval, antegrade AV nodal effective refractory period, and sinoatrial conduction time. Available data also suggest that magnesium produces systemic and coronary vasodilatation, possesses antiplatelet activity, suppresses automaticity in partially depolarized cells, and protects myocytes against calcium overload under conditions of ischemia by inhibiting calcium influx especially at the time of reperfusion. However, the clinical benefit of administering magnesium in patients with acute myocardial infarction has not been fully determined. (See Uses: Acute Myocardial Infarction.) Magnesium also acts peripherally, producing vasodilation. Moderate doses produce flushing and sweating; and higher doses lower blood pressure. Both the CNS depression and the peripheral neuromuscular transmission blockade produced by hypermagnesemia can be antagonized by administration of excess calcium.

Pharmacokinetics

When magnesium sulfate is administered IV, the onset of action is immediate and the duration of action is about 30 minutes. Following IM administration of the drug, the onset of action occurs in about 1 hour and the duration of action is 3–4 hours. As an anticonvulsant, effective serum concentrations of magnesium have been reported to range from 2.5–7.5 mEq/L.

Magnesium readily crosses the placenta and is distributed into milk following parenteral administration of magnesium sulfate. Milk concentrations of magnesium are increased for only about 24 hours after discontinuance of parenteral magnesium sulfate therapy; the amount of magnesium ingested by a nursing infant during this period is probably too small to be of clinical importance.

Magnesium sulfate is excreted by the kidneys at a rate that varies from one patient to another but that is directly proportional to the serum concentration and glomerular filtration.

Chemistry and Stability

■ **Chemistry** Parenteral magnesium sulfate exhibits anticonvulsant properties. Magnesium sulfate occurs as small, colorless crystals; usually needle-like, with a cooling, saline, bitter taste and is freely soluble in water and sparingly soluble in alcohol. The drug effloresces in warm, dry air. Each gram of magnesium sulfate heptahydrate contains 8.1 mEq of magnesium. The pHs of commercially available magnesium sulfate injection and magnesium sulfate in 5% dextrose injection are adjusted with sodium hydroxide and/or sulfuric acid; the injections have pHs of 3.5–7.

■ **Stability** Magnesium sulfate injection and magnesium sulfate in 5% dextrose injection should be stored at a temperature less than 40°C, preferably between 15–30°C; freezing should be avoided.

Magnesium sulfate is converted to the monohydrate when heated to 150–160°C. Magnesium sulfate is incompatible with alkali hydroxides (forming insoluble magnesium hydroxide), with alkali carbonates (forming basic carbonates), and with salicylates (forming basic salicylates). The drug reacts with arsenates, phosphates, and tartrates, precipitating the corresponding magnesium salts. Lead, barium, strontium, and calcium react with magnesium sulfate resulting in precipitation of the respective sulfates. Specialized references should be consulted for specific compatibility information. Following withdrawal of a dose from one of the solutions which do not contain preservatives, any unused portion should be discarded.

Preparations

Excipients in commercially available drug preparations may have clinically important effects in some individuals; consult specific product labeling for details.

Magnesium Sulfate

Crystals		
Parenteral		
Injection	50%*	Magnesium Sulfate Injection
Injection, for IV use only	4% (4, 20, and 40 g)*	Magnesium Sulfate Injection
	8% (4 g)*	Magnesium Sulfate Injection

*available from one or more manufacturer, distributor, and/or repackager by generic (nonproprietary) name

Magnesium Sulfate in Dextrose

Parenteral		
Injection, for IV use only	1% (1 g) in 5% Dextrose*	Magnesium Sulfate in 5% Dextrose Injection

*available from one or more manufacturer, distributor, and/or repackager by generic (nonproprietary) name
†Use is not currently included in the labeling approved by the US Food and Drug Administration

Oxcarbazepine

■ Oxcarbazepine is an anticonvulsant agent.

Uses

■ **Seizure Disorders** ***Partial Seizures*** Oxcarbazepine is used as monotherapy or in combination with other anticonvulsants in the management of partial seizures in adults and children 4 years of age and older.

Monotherapy. Efficacy of oxcarbazepine monotherapy in patients with partial seizures has been established in several multicenter, randomized, double-blind clinical trials. These studies have included adults and children 8 years of age or older. In one placebo-controlled, randomized clinical trial in patients with refractory partial seizures (undergoing evaluation for epilepsy surgery) who had been withdrawn from anticonvulsants prior to randomization, oxcarbazepine at dosages up to 2400 mg daily for 10 days was more effective than placebo. Results of another placebo-controlled clinical trial in patients with newly diagnosed or recent-onset partial seizures indicate that oxcarbazepine dosages up to 1200 mg daily for 84 days were more effective than placebo. In addition, therapy with oxcarbazepine 2400 mg daily for up to 126 days was substantially more effective than oxcarbazepine 300 mg daily in 2 other clinical trials in patients with partial seizures who had been withdrawn from therapy with 1 or 2 anticonvulsants because of inadequate control.

Results of several multicenter, randomized, double-blind monotherapy trials in patients with newly diagnosed or previously untreated partial or generalized seizures indicate that oxcarbazepine exhibits anticonvulsant activity similar to carbamazepine, phenytoin, or valproate sodium.

Combination Therapy Efficacy of oxcarbazepine as adjunctive therapy in patients with partial seizures was established in 2 multicenter, placebo-controlled, randomized, double-blind clinical trials in patients with partial seizures (one in adults and one in children 3–17 years of age). In both studies, patients initially were stabilized with optimum dosages of 1–3 anticonvulsants during an 8-week baseline period; those experiencing at least 8 (minimum 1–4 per month) partial seizures during this phase were randomized to receive oxcarbazepine or placebo during a dosage titration period of 2 weeks followed by a 14- or 24-week maintenance period in children or adults, respectively. Efficacy of oxcarbazepine in these studies was evaluated in terms of the change in seizure frequency (i.e., the median decrease [or increase] in average monthly [28-day] seizure rate). Adult patients receiving oxcarbazepine 600, 1200, or 2400 mg daily or placebo experienced a median decrease in seizure frequency of about 26, 40, 50, or 8%, respectively, while pediatric patients receiving oxcarbazepine maintenance dosages ranging from 30–46 mg/kg daily (depending on baseline body weight) or placebo experienced a median decrease in seizure frequency of about 35 or 9%, respectively.

■ **Bipolar Disorder** Oxcarbazepine has been used alone or in combination with other drugs (e.g., antipsychotic agents) for the treatment and prevention of acute manic or mixed episodes in patients with bipolar disorder†. Limited data suggest that oxcarbazepine may have equivalent efficacy and better tolerability than carbamazepine for this indication. However, the American Psychiatric Association (APA) currently recommends that oxcarbazepine be reserved for patients unable to tolerate or who had an inadequate therapeutic response to first-line agents such as lithium and valproate (e.g., valproic acid, divalproex). For further information on the management of bipolar disorder, see Uses: Bipolar Disorder, in Lithium Salts 28:28.

Dosage and Administration

■ **General** Oxcarbazepine tablets and suspension are administered orally twice daily without regard to meals.

Oxcarbazepine suspension should be shaken well prior to administration of each dose. The appropriate measured dose of the suspension should be administered using an oral dosing syringe. The oral suspension may be added to a small glass of water or swallowed directly from the syringe. After each use, the oral syringe should be rinsed with warm water and allowed to dry thoroughly.

The manufacturer of Trileptal® states that oral bioavailability of oxcarbazepine tablets appears to be similar to that of the suspension and, therefore, these preparations can be used interchangeably on a mg-for-mg basis.

Patients currently receiving or beginning therapy with oxcarbazepine and/or any other anticonvulsant for any indication should be closely monitored for the emergence or worsening of depression, suicidal thoughts or behavior (suicidality), and/or any unusual changes in mood or behavior. (See Suicidality Risk under Warnings/Precautions: Warnings, in Cautions.)

Partial Seizures **Monotherapy.** In adults and children older than 16 years of age with partial seizures being transferred from other anticonvulsant drug therapy to monotherapy with oxcarbazepine, the recommended initial dosage of oxcarbazepine is 600 mg daily given in 2 equally divided doses. Oxcarbazepine dosage may be increased by 600-mg daily increments at approximately weekly intervals to a recommended daily dosage of 2400 mg, usually within 2–4 weeks. As oxcarbazepine replaces the existing anticonvulsant therapeutic regimen, dosage of the other anticonvulsant(s) is simultaneously reduced and discontinued over 3–6 weeks. Patients should be observed during this transition phase.

In adults not receiving anticonvulsant drug therapy, the recommended initial daily dosage of oxcarbazepine as initial monotherapy is 600 mg daily administered in 2 equally divided doses. Dosage should be increased by 300-mg daily increments every third day to a maximum daily dosage of 1200 mg.

In children 4–16 years of age with partial seizures being transferred from other anticonvulsant drug therapy to monotherapy with oxcarbazepine, the recommended initial dosage of oxcarbazepine is 8–10 mg/kg daily given in 2 equally divided doses. Oxcarbazepine dosage may be increased in increments of up to 10 mg/kg daily at weekly intervals to achieve the recommended maintenance dosage. (See Table 1.) As oxcarbazepine replaces the existing anticonvulsant therapeutic regimen, dosage of the other anticonvulsant(s) is simultaneously reduced and discontinued over 3–6 weeks.

Children 4–16 years of age not receiving anticonvulsant drug therapy may initiate therapy with oxcarbazepine at a dosage of 8–10 mg/kg daily given in 2 equally divided doses. Dosage may be increased in increments of 5 mg/kg daily every third day until the recommended maintenance dosage is achieved. (See Table 1.)

Table 1. Recommended Range of Maintenance Dosages in Children Receiving Oxcarbazepine Monotherapy

Weight (kg)	Dosage Range (mg/day)
20	600–900
25	900–1200
30	900–1200
35	900–1500
40	900–1500
45	1200–1500
50	1200–1800
55	1200–1800
60	1200–2100
65	1200–2100
70	1500–2100

Combination Therapy. For adjunctive therapy in the management of partial seizures in adults and children older than 16 years of age, the initial dosage of oxcarbazepine is 600 mg daily administered in 2 equally divided doses. Oxcarbazepine dosage may be increased by 600-mg daily increments at approximately weekly intervals to a recommended daily dosage of 1200 mg. Although efficacy may be somewhat higher in patients receiving oxcarbazepine dosages exceeding 1200 mg daily, most patients cannot tolerate daily dosages of 2400 mg, mainly because of adverse CNS effects. The manufacturers recommend that patients be observed closely and that plasma concentrations of concomitantly administered anticonvulsants be monitored during dosage titration of oxcarbazepine since plasma concentrations of these drugs may be altered when dosage of oxcarbazepine exceeds 1200 mg daily.

For adjunctive therapy in the management of partial seizures in children 4–16 years of age, the recommended initial dosage of oxcarbazepine (administered in 2 equally divided doses) is 8–10 mg/kg daily, generally not exceeding 600 mg daily. The target daily maintenance dosage of 900–1800 mg depends on patient weight (900, 1200, or 1800 mg in children weighing 20–29, 29.1–39, or more than 39 kg, respectively) and should be reached within 2 weeks. Since clearance of the drug appears to be increased (by 30–40%) in children younger than 8 years of age compared with that in adults, such children received the highest maintenance dosage in controlled clinical trials.

■ **Special Populations** The manufacturers state that the initial dosage of oxcarbazepine should be 300 mg daily (one-half of the usual starting dosage) in patients with renal impairment (creatinine clearance less than 30 mL/minute); dosage should be increased slowly to achieve the desired clinical response.

In general, no dosage adjustments are necessary in patients with mild to moderate hepatic impairment.

Cautions

■ **Contraindications** Known hypersensitivity to oxcarbazepine or any ingredient in the formulation.

■ **Warnings/Precautions** ***Warnings*** **Hyponatremia.** Clinically important hyponatremia (serum sodium concentrations less than 125 mEq/L) has been reported in 2.5% of patients receiving oxcarbazepine in clinical studies, versus 0% in patients receiving placebo or active controls (i.e., carbamazepine, phenobarbital, phenytoin, valproic acid). Generally, hyponatremia occurred during the first 3 months of oxcarbazepine therapy, although this adverse effect was reported in some patients more than 1 year after initiation of such therapy. In clinical studies, most patients with hyponatremia were asymptomatic. However, it should be considered that these patients were monitored frequently, and in some patients dosage of oxcarbazepine was reduced or discontinued or the fluid intake restricted. It is not known whether these measures prevented development of hyponatremia. Symptomatic hyponatremia was reported in some patients during postmarketing surveillance. In clinical trials in patients developing hyponatremia, serum sodium concentrations returned to baseline values a few days after discontinuance of the drug. The manufacturers state that monitoring serum sodium concentrations should be considered during maintenance therapy with oxcarbazepine, particularly in patients concurrently receiving other drugs known to decrease serum sodium concentrations (e.g., drugs associated with inappropriate antidiuretic hormone secretion [SIADH]) or in those with symptoms of hyponatremia (e.g., nausea, malaise, headache, lethargy, confusion, obtundation, increase in seizure frequency or severity).

Suicidality Risk. The US Food and Drug Administration (FDA) has alerted healthcare professionals about an increased risk of suicidality (suicidal behavior or ideation) observed in an analysis of studies using various anticonvulsants, including oxcarbazepine, compared with placebo. The analysis of suicidality reports from placebo-controlled studies involving 11 anticonvulsants (i.e., carbamazepine, felbamate, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, pregabalin, tiagabine, topiramate, valproate, zonisamide) in patients with epilepsy, psychiatric disorders (e.g., bipolar disorder, depression, anxiety), and other conditions (e.g., migraine, neuropathic pain) found that patients receiving anticonvulsants had approximately twice the risk of suicidal behavior or ideation (0.43%) compared with patients receiving placebo (0.24%). This increased suicidality risk was observed as early as one week after beginning therapy and continued through 24 weeks. Although patients treated with an anticonvulsant for epilepsy, psychiatric disorders, and other conditions were all found to have an increased suicidality risk compared with those receiving placebo, the relative suicidality risk was higher for patients with epilepsy compared with those receiving anticonvulsants for other conditions.

Based on the current analysis of the available data, FDA recommends that clinicians inform patients, their families, and caregivers about the potential for an increase in the risk of suicidality with anticonvulsant therapy and that all patients currently receiving or beginning therapy with any anticonvulsant for any indication be closely monitored for the emergence or worsening of depression, suicidal thoughts or behavior (suicidality), and/or unusual changes in mood or behavior. Symptoms such as anxiety, agitation, hostility, hypomania, and mania may be precursors to emerging suicidality. Clinicians who prescribe oxcarbazepine or any other anticonvulsant should balance the risk of suicidality with the risk of untreated illness. Epilepsy and many other illnesses for which anticonvulsants are prescribed are themselves associated with an increased risk of morbidity and mortality and an increased risk of suicidal thoughts and behavior. If suicidal thoughts and behavior emerge during anticonvulsant therapy, the clinician should consider whether these symptoms may be related to the illness being treated. (See Advice to Patients.)

Discontinuance of Oxcarbazepine. Because of the possibility of increased seizure frequency, anticonvulsant drugs, including oxcarbazepine, should be withdrawn gradually. If a hypersensitivity reaction occurs, discontinue oxcarbazepine and initiate alternative therapy.

Sensitivity Reactions **History of Carbamazepine Hypersensitivity.** Approximately 25–30% of patients with a history of carbamazepine hypersensitivity will develop hypersensitivity to oxcarbazepine. Therefore, oxcarbazepine should only be used in patients with a history of such hypersensitivity if the potential benefits justify the potential risk to the patient. If a hypersensitivity reaction develops, oxcarbazepine should be discontinued immediately.

Dermatologic and Hypersensitivity Reactions. Serious dermatologic reactions, including Stevens-Johnson syndrome and toxic epidermal necrolysis, have been reported in adults and children receiving oxcarbazepine; reactions have been life-threatening, have required hospitalization, and rarely have been fatal. The incidence of Stevens-Johnson syndrome and toxic epidermal necrolysis reported in patients receiving oxcarbazepine exceeds the rate in the general population by threefold to tenfold. The median time to onset of these reactions was 19 days. Recurrence of serious dermatologic reactions following rechallenge with oxcarbazepine has occurred.

If a skin reaction develops in a patient receiving oxcarbazepine, consider discontinuance of the drug and initiation of therapy with another anticonvulsant agent.

Multiorgan hypersensitivity reactions occurring days to weeks or months (range 4–60 days) after initiation of oxcarbazepine therapy have been reported in adults and pediatric patients. Although these reactions have been reported rarely, many of these patients required hospitalization, and some reactions were considered life-threatening. Manifestations may include (but are not limited to) fever, rash, lymphadenopathy, hepatitis, abnormal liver function test results, eosinophilia, thrombocytopenia, neutropenia, pruritus, nephritis, oliguria, hepatorenal syndrome, arthralgia, and asthenia.

If a multiorgan hypersensitivity reaction is suspected, discontinue oxcarbazepine and initiate alternative therapy.

Possibility of cross-sensitivity with other drugs that produce multiorgan hypersensitivity reactions exists.

General Precautions **Nervous System Effects.** Neuropsychiatric effects reported during oxcarbazepine treatment are classified into 3 categories: impaired cognitive or psychomotor performance including difficulties in concentrating, language, and speech; somnolence or fatigue; and coordination difficulties (e.g., ataxia, gait disturbances). (See Suicidality Risk under Warnings/Precautions: Warnings, in Cautions.)

Specific Populations **Pregnancy.** Category C. (See Users Guide.) North American Antiepileptic Drug (NAAED) Pregnancy Registry at 888-233-2334 (for patients); registry information also available on the website http://www.aedpregnancyregistry.org.

The effect of oxcarbazepine on labor and delivery is unknown.

Lactation. Both oxcarbazepine and its active 10-monohydroxy metabolite (MHD) are distributed into milk in humans. Discontinue nursing or the drug, taking into account the importance of the drug to the woman.

Pediatric Use. Safety and efficacy of oxcarbazepine as monotherapy or adjunctive therapy for partial seizures in children younger than 4 years of age have not been established.

Efficacy of oxcarbazepine as adjunctive therapy for partial seizures in children 4–16 years of age established in clinical studies. Efficacy as monotherapy for partial seizures in children 4–16 years of age based on clinical studies and pharmacokinetic and pharmacodynamic considerations.

Oxcarbazepine has not been evaluated in clinical studies in children younger than 2 years of age.

Severe dermatologic and other sensitivity reactions have been reported in pediatric patients. (See Dermatologic and Hypersensitivity Reactions under Warnings/Precautions: Sensitivity Reactions, in Cautions.)

Geriatric Use. Although peak plasma concentrations of MHD and the area under the plasma concentration-time curve (AUC) may be 30–60% higher in adults 60 years of age or older than in younger adults (possibly related to decreases in renal function with age), the manufacturers do not make specific recommendations for dosage adjustment in such patients.

■ **Common Adverse Effects** Adverse effects occurring in 5% or more of patients and more frequently than placebo include dizziness, somnolence, diplopia, fatigue, nausea, vomiting, ataxia, abnormal vision, abdominal pain, tremor, dyspepsia, abnormal gait.

Drug Interactions

■ **Drugs Affecting Hepatic Microsomal Enzymes**

Anticonvulsants Oxcarbazepine may inhibit metabolism of other anticonvulsants (e.g., phenobarbital, phenytoin), possibly via inhibition of the cytochrome P-450 (CYP) isoenzyme 2C19, resulting in increased plasma concentrations of these drugs. Oxcarbazepine dosages exceeding 1200 mg daily may increase plasma phenytoin concentrations by 40% and, therefore, when such dosages of oxcarbazepine are used concomitantly with phenytoin, dosage reduction of phenytoin may be required.

Potent inducers of CYP isoenzymes (e.g., carbamazepine, phenytoin, phenobarbital) may decrease plasma concentrations of oxcarbazepine and its active 10-monohydroxy metabolite (MHD).

Oral Contraceptives Oxcarbazepine may induce metabolism of oral estrogen-progestin contraceptives, possibly via induction of CYP3A4 and CYP3A5, resulting in decreased area under the plasma concentration-time curve (AUC) and consequent decreased efficacy of the contraceptives.

Calcium-channel Blocking Agents Oxcarbazepine may induce metabolism of some calcium-channel blocking agents (e.g., felodipine, verapamil), possibly via induction of CYP3A4 and CYP3A5 isoenzymes, resulting in decreased AUC of the calcium-channel blocking agents.

Description

Oxcarbazepine is an anticonvulsant agent that is structurally and chemically related to carbamazepine. Although the exact mechanism of action of oxcarbazepine is unknown, in vitro electrophysiologic studies indicate that the drug may stabilize excitatory neuronal membranes, inhibit repetitive neuronal firing, and decrease propagation of synaptic impulses by blocking voltage-sensitive sodium channels, actions that may prevent spread of epileptic seizures. Increased potassium conductance and modulation of high-voltage activated calcium channels also may contribute to the anticonvulsant activity of oxcarbazepine. No substantial interactions between the drug and neurotransmitter receptors in the brain have been observed to date.

Oxcarbazepine and its active 10-monohydroxy metabolite (MHD) exhibit anticonvulsant activity in several animal seizure models. Oxcarbazepine protects against electrically induced tonic extension seizures and, to a lesser degree, chemically induced clonic seizures and may abolish or reduce frequency of chronically recurring focal seizures.

Following oral administration, oxcarbazepine is completely absorbed and extensively metabolized in the liver by cytosolic enzymes to MHD (10,11-dihydro-10-hydroxy-5*H*-dibenz[*b*, *f*]azepine-5-carboxamide), which is believed to be responsible for the pharmacologic activity of oxcarbazepine. The oral bioavailabilities of oxcarbazepine tablets and suspension appear to be similar. More than 95% of an oral dose of oxcarbazepine is excreted in urine, mainly as metabolites with less than 1% as unchanged drug; less than 4% is excreted in feces.

Advice to Patients

Importance of providing copy of written patient information (medication guide) each time oxcarbazepine is dispensed.

Risk of hypersensitivity reaction; patients who have had previous hypersensitivity reaction to carbamazepine at increased risk. Importance of immediately reporting hypersensitivity reactions, skin reactions, or fever accompanied by signs and/or symptoms of other organ system involvement (e.g., rash, lymphadenopathy).

Risk of dizziness and somnolence; avoid driving or operating machinery while taking oxcarbazepine until effects of the drug on the individual are known.

Risk of low sodium concentrations in the blood; manifestations may include nausea, extreme drowsiness and/or fatigue, discomfort, headache, confusion, increase in seizure frequency or severity, or dullness.

Importance of patients, family members, and caregivers being aware that anticonvulsants, including oxcarbazepine, may increase the risk of having suicidal thoughts or actions in a very small number of people (about 1 in 500). Advise patients, family members, and caregivers to pay close attention to any day-to-day changes in mood, behavior, and actions; these changes can happen very quickly. They should also be aware of common warning signs that may signal suicide risk (e.g., talking or thinking about wanting to hurt oneself or end one's life, withdrawing from friends and family, becoming depressed or experiencing worsening of existing depression, becoming preoccupied with death and dying, giving away prized possessions). Advise patients, family members, and caregivers to contact the responsible clinician immediately if these or any new and worrisome behaviors occur.

Caution if alcohol is used concomitantly because additive sedative effects may occur.

Importance of not abruptly discontinuing therapy.

Importance of women informing clinicians if they are or plan to become pregnant or plan to breast-feed. Importance of informing women of childbearing age that concomitant use of oxcarbazepine with oral contraceptives may result in decreased efficacy of the contraceptives.

Importance of informing clinicians of existing or contemplated concomitant therapy, including prescription and OTC drugs, as well as concomitant illnesses.

Importance of advising patients of other important precautionary information. (See Cautions.)

Overview* (see Users Guide). For additional information on this drug until a more detailed monograph is developed and published, the manufacturer's labeling be consulted. It is *essential* that the manufacturer's labeling be consulted for more detailed information on usual cautions, precautions, contraindications, potential drug interactions, laboratory test interferences, and acute toxicity.

Preparations

Excipients in commercially available drug preparations may have clinically important effects in some individuals; consult specific product labeling for details.

Oxcarbazepine

Oral		
Suspension	300 mg/5 mL	**Trileptal®**, Novartis
Tablets, film-coated	150 mg*	**Oxcarbazepine Tablets**
		Trileptal® (scored), Novartis
	300 mg*	**Oxcarbazepine Tablets**
		Trileptal® (scored), Novartis
	600 mg*	**Oxcarbazepine Tablets**
		Trileptal® (scored), Novartis

*available from one or more manufacturer, distributor, and/or repackager by generic (nonproprietary) name

†Use is not currently included in the labeling approved by the US Food and Drug Administration

Chemistry and Stability

■ **Chemistry** Dextroamphetamine is the dextrorotatory isomer of amphetamine. Dextroamphetamine sulfate occurs as a white, odorless, crystalline powder and has a bitter taste. Dextroamphetamine sulfate is freely soluble in water (about 1:10) and slightly soluble in alcohol (about 1:800). Dextroamphetamine sulfate also is commercially available as fixed-combination preparations with dextroamphetamine saccharate, amphetamine aspartate, and amphetamine sulfate.

■ **Stability** Preparations containing dextroamphetamine sulfate should be stored in tight, light-resistant containers at 15–30°C.

Preparations

Dextroamphetamine and dextroamphetamine sulfate preparations are subject to control under the Federal Controlled Substances Act of 1970 as schedule II (C-II) drugs.

Excipients in commercially available drug preparations may have clinically important effects in some individuals; consult specific product labeling for details.

Dextroamphetamine Sulfate

Oral

Capsules, extended-release	5 mg*	**Dexedrine* Spansule*** (C-II), GlaxoSmithKline
		Dextroamphetamine Sulfate Capsules SR (C-II)
	10 mg*	**Dexedrine* Spansule*** (C-II), GlaxoSmithKline
		Dextroamphetamine Sulfate Capsules SR (C-II)
	15 mg*	**Dexedrine* Spansule*** (C-II), GlaxoSmithKline
		Dextroamphetamine Sulfate Capsules SR (C-II)
Tablets	5 mg*	**Dexedrine*** (C-II; scored), GlaxoSmithKline
		Dextroamphetamine Sulfate Tablets (C-II; scored)
		DextroStat* (C-II; scored), Shire
	10 mg*	**Dextroamphetamine Sulfate Tablets** (C-II; scored)
		DextroStat* (C-II; double-scored), Shire

*available from one or more manufacturer, distributor, and/or repackager by generic (nonproprietary) name

Dextroamphetamine Sulfate Combinations

Oral

Capsules, extended-release	5 mg total amphetamine (as 1.25 mg with Amphetamine Sulfate 1.25 mg, Amphetamine Aspartate 1.25 mg, and Dextroamphetamine Saccharate 1.25 mg)	**Adderall XR*** (C-II), Shire
	10 mg total amphetamine (as 2.5 mg with Amphetamine Sulfate 2.5 mg, Amphetamine Aspartate 2.5 mg, and Dextroamphetamine Saccharate 2.5 mg)	**Adderall XR*** (C-II), Shire
	15 mg total amphetamine (as 3.75 mg with Amphetamine Sulfate 3.75 mg, Amphetamine Aspartate 3.75 mg, and Dextroamphetamine Saccharate 3.75 mg)	**Adderall XR*** (C-II), Shire
	20 mg total amphetamine (as 5 mg with Amphetamine Sulfate 5 mg, Amphetamine Aspartate 5 mg, and Dextroamphetamine Saccharate 5 mg)	**Adderall XR*** (C-II), Shire
	25 mg total amphetamine (as 6.25 mg with Amphetamine Sulfate 6.25 mg, Amphetamine Aspartate 6.25 mg, and Dextroamphetamine Saccharate 6.25 mg)	**Adderall XR*** (C-II), Shire
	30 mg total amphetamine (as 7.5 mg with Amphetamine Sulfate 7.5 mg, Amphetamine Aspartate 7.5 mg, and Dextroamphetamine Saccharate 7.5 mg)	**Adderall XR*** (C-II), Shire
Tablets	5 mg total amphetamine (as 1.25 mg with Amphetamine Aspartate 1.25 mg, Amphetamine Sulfate 1.25 mg, and Dextroamphetamine Saccharate 1.25 mg)*	**Adderall*** (C-II; double-scored), Shire
		Dextroamphetamine Saccharate, Amphetamine Aspartate, Dextroamphetamine Sulfate, and Amphetamine Sulfate Tablets (C-II; double-scored)
	7.5 mg total amphetamine (as 1.875 mg with Amphetamine Aspartate 1.875 mg, Amphetamine Sulfate 1.875 mg, and Dextroamphetamine Saccharate 1.875 mg)*	**Adderall*** (C-II; double-scored), Shire
		Dextroamphetamine Saccharate, Amphetamine Aspartate, Dextroamphetamine Sulfate, and Amphetamine Sulfate Tablets (C-II; double-scored)
	10 mg total amphetamine (as 2.5 mg with Amphetamine Aspartate 2.5 mg, Amphetamine Sulfate 2.5 mg, and Dextroamphetamine Saccharate 2.5 mg)*	**Adderall*** (C-II; double-scored), Shire
		Dextroamphetamine Saccharate, Amphetamine Aspartate, Dextroamphetamine Sulfate, and Amphetamine Sulfate Tablets (C-II; double-scored)
	12.5 mg total amphetamine (as 3.125 mg with Amphetamine Aspartate 3.125 mg, Amphetamine Sulfate 3.125 mg, and Dextroamphetamine Saccharate 3.125 mg)*	**Adderall*** (C-II; double-scored), Shire
		Dextroamphetamine Saccharate, Amphetamine Aspartate, Dextroamphetamine Sulfate, and Amphetamine Sulfate Tablets (C-II; double-scored)
	15 mg total amphetamine (as 3.75 mg with Amphetamine Aspartate 3.75 mg, Amphetamine Sulfate 3.75 mg, and Dextroamphetamine Saccharate 3.75 mg)*	**Adderall*** (C-II; double-scored), Shire
		Dextroamphetamine Saccharate, Amphetamine Aspartate, Dextroamphetamine Sulfate, and Amphetamine Sulfate Tablets (C-II; double-scored)
	20 mg total amphetamine (as 5 mg with Amphetamine Aspartate 5 mg, Amphetamine Sulfate 5 mg, and Dextroamphetamine Saccharate 5 mg)*	**Adderall*** (C-II; double-scored), Shire
		Dextroamphetamine Saccharate, Amphetamine Aspartate, Dextroamphetamine Sulfate, and Amphetamine Sulfate Tablets (C-II; double-scored)
	30 mg total amphetamine (as 7.5 mg with Amphetamine Aspartate 7.5 mg, Amphetamine Sulfate 7.5 mg, and Dextroamphetamine Saccharate 7.5 mg)*	**Adderall*** (C-II; double-scored), Shire
		Dextroamphetamine Saccharate, Amphetamine Aspartate, Dextroamphetamine Sulfate and Amphetamine Sulfate Tablets (C-II; double-scored)

*available from one or more manufacturer, distributor, and/or repackager by generic (nonproprietary) name

Lisdexamfetamine Dimesylate

■ Prodrug of dextroamphetamine; noncatechol, sympathomimetic amine with CNS-stimulating activity.

Uses

■ **Attention-Deficit Hyperactivity Disorder** Lisdexamfetamine dimesylate is used as an adjunct to psychological, educational, social, and other remedial measures in the treatment of attention deficit hyperactivity disorder (ADHD) (hyperkinetic disorder, hyperkinetic syndrome of childhood, minimal brain dysfunction). Safety and efficacy for this indication have been established in controlled clinical trials in children 6–12 years of age and in adults.

Safety and efficacy of lisdexamfetamine dimesylate in the treatment of ADHD in children 6–12 years of age who met DSM-IV-TR criteria for ADHD (combined type or predominantly hyperactive-impulsive type) have been evaluated in 2 randomized, double-blind, placebo-controlled clinical studies (one phase 2 and one phase 3). The phase 2 crossover study was conducted in an analog classroom environment. In this study, dosage of amphetamines was titrated over a 3-week period using an extended-release formulation of mixed amphetamine salts (Adderall XR®) to a final dosage of 10, 20, or 30 mg daily; the children then were assigned to receive, in randomly determined sequence, 1 week each of treatment with extended-release mixed amphetamine salts (continued at the same dosage), lisdexamfetamine dimesylate (30, 50, or 70 mg

daily, respectively, depending on the titrated amphetamines dosage), and placebo. The primary measure of efficacy was the Swanson, Kotkin, Agler, M-Flynn, and Pelham (SKAMP) deportment score. Assessments performed on day 7 of each treatment period (at various intervals from 2–12 hours after dosing) suggested that behavioral and symptomatic improvements observed with lisdexamfetamine were superior to those observed with placebo and not substantially different from those observed with mixed amphetamine salts. In the phase 3 parallel-group study, improvement in symptom scores, as measured using the ADHD Rating Scale version IV (ADHD-RS-IV), the revised Conners' Parent Rating Scale (CPRS-R), and the Cognitive Global Impression of Improvement (CGI-I) scale, from baseline to study end (4 weeks) was greater in children receiving lisdexamfetamine dimesylate titrated to a fixed, final dosage of 30, 50, or 70 mg daily than in those receiving placebo. Mean changes in symptom scores generally were similar for all 3 lisdexamfetamine dosage levels; however, changes in ADHD-RS-IV scores were numerically greater with the 70-mg dose than with the 30- and 50-mg doses. Symptom control in patients receiving the drug was maintained throughout the day up to 6 p.m.

Safety and efficacy of lisdexamfetamine in adults have been established in one phase 3 forced-titration, double-blind, randomized, placebo-controlled clinical study of 4 weeks' duration in 420 adults who met DSM-IV-TR criteria for ADHD. After a washout period, patients were randomized to receive 30, 50, or 70 mg of lisdexamfetamine dimesylate daily or placebo. All patients receiving lisdexamfetamine initially received 30 mg daily for the first week, with subsequent dosage titrations occurring in 20-mg increments at weekly intervals for those randomized to receive 50 or 70 mg of the drug daily. The primary measure of efficacy was the ADHD Rating Scale (ADHD-RS) score. At study end point (4 weeks), patients randomized to receive lisdexamfetamine demonstrated significant improvements in ADHD symptoms compared with placebo recipients. Significant improvements in ADHD symptoms were evident within the first week of treatment in all lisdexamfetamine groups. Patients randomized to receive lisdexamfetamine dimesylate 70 mg daily showed a greater reduction in ADHD-RS total score at weeks 3 and 4 compared with patients receiving lisdexamfetamine dimesylate 30 mg daily.

For further information on the management of ADHD, including the use of stimulants such as amphetamines, see Uses: Attention Deficit Hyperactivity Disorder in the Amphetamines General Statement 28:20.04, and also in Methylphenidate 28:20.92.

Dosage and Administration

■ **Administration** ***Oral Administration*** Administer once daily in the morning without regard to meals. Because of potential for insomnia, avoid administering in the afternoon.

Capsule may be swallowed whole or may be opened and the entire contents dissolved in water immediately prior to administration; resulting solution should *not* be stored for use at a later time.

Do *not* subdivide capsule contents; do *not* administer a dose less than the entire contents of one capsule.

■ **Dosage** Available as lisdexamfetamine dimesylate; dosage expressed in terms of the salt.

Adjust dosage according to individual response and tolerance; the smallest dose required to produce the desired response should always be used.

When possible, therapy should be interrupted occasionally to determine if there is a recurrence of behavioral symptoms sufficient to require continued treatment.

Pediatric Patients **Attention Deficit Hyperactivity Disorder.** *Oral*: Children 6–12 years of age: Initially, 30 mg once daily (as initial treatment for ADHD or in patients being switched to lisdexamfetamine from other drugs); dosage may be adjusted in 10- or 20-mg increments at weekly intervals up to a maximum dosage of 70 mg daily.

If the initial 30-mg daily dosage is not tolerated, dosage can be decreased to 20 mg daily.

Long-term use (i.e., exceeding 4 weeks) has not been studied systematically. If used for long-term therapy, periodically reevaluate the usefulness of the drug.

Adults **Attention Deficit Hyperactivity Disorder.** *Oral*: Initially, 30 mg once daily (as initial treatment for ADHD or in patients being switched to lisdexamfetamine from other drugs); dosage may be adjusted in 10- or 20-mg increments at weekly intervals up to a maximum dosage of 70 mg daily.

If the initial 30-mg daily dosage is not tolerated, dosage can be decreased to 20 mg daily.

Long-term use (i.e., exceeding 4 weeks) has not been studied systematically. If used for long-term therapy, periodically reevaluate the usefulness of the drug.

■ **Special Populations** No special population dosage recommendations at this time.

Cautions

■ **Contraindications** Contraindicated in patients with advanced arteriosclerosis, symptomatic cardiovascular disease, moderate to severe hypertension, hyperthyroidism, known hypersensitivity or idiosyncrasy to sympathomimetic amines, glaucoma, or a history of drug abuse; within 14 days of monoamine oxidase (MAO) inhibitor therapy; and in agitated patients.

Although amphetamines generally should not be used in patients with a history of drug abuse, some experts state that this is not an absolute contraindication, provided the patient can be monitored more carefully than would otherwise be indicated.

■ **Warnings/Precautions** ***Warnings*** **Abuse Potential.** Amphetamines have a high potential for abuse. Administration of amphetamines for prolonged periods of time may lead to drug dependence.

Particular attention should be paid to the possibility of individuals obtaining amphetamines for nontherapeutic use or distribution to others, and the drugs should be prescribed or dispensed sparingly. The possibility that family members may abuse the patient's medication should be considered.

Sudden Death and Serious Cardiovascular Events. Possible sudden death and serious cardiovascular events, particularly in individuals who abuse amphetamines.

Sudden unexplained death, stroke, and myocardial infarction have been reported in adults with ADHD receiving usual dosages of stimulants; sudden death also has been reported in children and adolescents with structural cardiac abnormalities or other serious cardiac conditions receiving usual dosages of the drugs. A small number of cases of sudden unexplained death also has been reported in children without structural cardiac abnormalities receiving amphetamine combinations; however, confounding factors were present in some of these incidents.

Results of one retrospective, case-control epidemiologic study showed a possible association between use of stimulant medications (amphetamine, dextroamphetamine, methamphetamine, methylphenidate, or their derivatives) and sudden unexplained death in healthy children and adolescents. (See Pediatric Use under Warnings/Precautions: Specific Populations, in Cautions.) Given the study limitations, the US Food and Drug Administration (FDA) is unable to conclude that these data affect the overall risk and benefit profile of stimulant medications used to treat ADHD in children and adolescents. Amphetamines or other stimulants should not be discontinued by parents of children or patients receiving these medications for ADHD before consulting with their clinician. Because of postmarketing reports and results of this and other epidemiologic studies, FDA is conducting an ongoing review of safety of amphetamines and other stimulants to evaluate a possible link between use of these agents and sudden death in children. To determine whether there is a direct causal relationship between use of stimulants and serious adverse cardiovascular events, the Agency for Healthcare Research and Quality (AHRQ) and FDA announced in 2007 that they are collaborating on a large study evaluating clinical data on approximately 500,000 adults and children who received these drugs for management of ADHD during a 7-year period ending in 2005; data collection for the study is expected to be completed in 2009.

Thoroughly review medical history (including evaluation for family history of sudden death or ventricular arrhythmia) *and* perform physical examination in all children, adolescents, and adults being considered for stimulant therapy; if initial findings suggest presence of cardiac disease, perform further cardiac evaluation (e.g., ECG, echocardiogram).

In general, *avoid* use of CNS stimulants in patients with known serious structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, coronary artery disease, or other serious cardiac conditions. (See Contraindications under Cautions.)

Patients who develop exertional chest pain, unexplained syncope, or other manifestations suggestive of cardiac disease during stimulant therapy should undergo prompt cardiac evaluation.

For further information on screening for cardiac conditions, selecting appropriate candidates for stimulant therapy, and monitoring for treatment-emergent cardiac conditions, see Cardiovascular Precautions under Cautions: Precautions and Contraindications, in the Amphetamines General Statement 28:20.04.

Other Warnings and Precautions Least amount of lisdexamfetamine feasible should be prescribed or dispensed at one time in order to minimize possible overdosage.

Effects on Blood Pressure and Heart Rate. Possible modest increases in average blood pressure (i.e., by about 2–4 mm Hg) and heart rate (i.e., by about 3–6 beats/minute); larger increases may occur. Modest increases not expected to have short-term sequelae; however, monitor all patients for *larger* changes in blood pressure and heart rate.

Caution advised in patients with underlying medical conditions that might be affected by increases in blood pressure or heart rate (e.g., hypertension, heart failure, recent myocardial infarction, ventricular arrhythmia).

Exacerbation or Precipitation of Psychotic Symptoms. May exacerbate symptoms of behavior disturbance and thought disorder in patients with preexisting psychotic disorder.

Psychotic symptoms (e.g., hallucinations, delusional thinking) may occur with usual dosages in children and adolescents without prior history of psychotic illness. If psychotic symptoms occur, consider causal relationship to stimulants, and discontinue therapy as appropriate.

Precipitation of Manic Symptoms. May precipitate mixed or manic episodes in ADHD patients with comorbid bipolar disorder; use with caution in these patients. Prior to initiating therapy, carefully screen patients with ADHD and comorbid depressive symptoms to identify risk for bipolar disorder; screening should include a detailed psychiatric history (e.g., family history of suicide, bipolar disorder, or depression).

Manic symptoms may occur with usual dosages in children and adolescents

without prior history of mania. If manic symptoms occur, consider causal relationship to stimulants, and discontinue therapy as appropriate.

Aggression. Aggressive behavior and hostility (frequently observed in children and adolescents with ADHD) reported in patients receiving drug therapy for ADHD. No systematic evidence that stimulants cause these adverse effects; however, monitor patients beginning treatment for ADHD for onset or worsening of aggressive behavior or hostility.

Growth Suppression. Long-term (i.e., exceeding 12 months) administration expected to cause at least a temporary suppression of normal weight and/or height patterns in some children and adolescents. Dose-related weight loss reported in children during 4 weeks of therapy with lisdexamfetamine.

Manufacturer recommends monitoring growth during treatment; patients not growing or gaining weight as expected may require temporary discontinuance of treatment. However, the American Academy of Pediatrics states that studies of stimulants in children found little or no decrease in expected height, with any decrease in growth early in treatment being compensated for later on.

Seizures. Possible lowering of seizure threshold in patients with history of seizures, in those with prior EEG abnormalities but no history of seizures, and, very rarely, in those without history of seizures and with no prior evidence of EEG abnormalities. If seizures occur, discontinue therapy.

Visual Effects. Visual disturbances (e.g., difficulty with accommodation, blurred vision) reported with stimulants.

Tics. Amphetamines reported to exacerbate motor and phonic tics and Tourette's syndrome. However, a history of tics or their development during therapy is *not* an absolute contraindication to continued use. Nevertheless, evaluate for presence of tics and Tourette's syndrome in children and their families prior to initiating stimulant therapy.

Other CNS Effects. Amphetamines may impair the ability to engage in potentially hazardous activities (e.g., operating machinery or vehicles).

Specific Populations **Pregnancy.** Category C.

Risk of prematurity, low birth weight, and withdrawal symptoms (e.g., dysphoria, lassitude, agitation) in infants born to dependent women.

Lactation. Distributed into milk; discontinue nursing or the drug.

Pediatric Use. Safety and efficacy of lisdexamfetamine not established in children 3–5 years of age. Amphetamines not recommended for ADHD in children younger than 3 years of age. Not studied to date in adolescents.

Aggressive behavior, hostility, and psychotic (e.g., hallucinations, delusional thinking) or manic symptoms reported in children and adolescents receiving stimulants for management of ADHD. (See Warnings under Cautions.)

Sudden death reported in children and adolescents with structural cardiac abnormalities or other serious cardiac conditions receiving usual dosages of stimulants. Sudden unexplained death also reported in a small number of children without structural cardiac abnormalities receiving amphetamine combinations. Results of one retrospective, case-control epidemiologic study suggested a possible association between use of stimulant medications and sudden unexplained death in healthy children and adolescents. (See Sudden Death and Serious Cardiovascular Events under Warnings/Precautions, in Cautions.)

Long-term administration expected to cause at least a temporary suppression of normal weight and/or height patterns in some children and adolescents. (See Growth Suppression under Cautions.)

Geriatric Use. Lisdexamfetamine has not been studied in this population.

Hepatic Impairment. Not specifically studied in hepatic impairment.

Renal Impairment. Not specifically studied in renal impairment.

■ **Common Adverse Effects** Children 6–12 years of age: Decreased appetite, insomnia, upper abdominal pain, irritability, vomiting, weight loss, nausea, dry mouth, dizziness, affect lability, rash, tic, pyrexia, somnolence.

Adults: Decreased appetite, insomnia, dry mouth, diarrhea, nausea, anxiety, anorexia, jitteriness, increased blood pressure, agitation, restlessness, hyperhidrosis, increased heart rate, tremor, dyspnea.

Drug Interactions

Active metabolite (dextroamphetamine) inhibits monoamine oxidase (MAO).

Lisdexamfetamine is not metabolized by cytochrome P-450 (CYP) isoenzymes. In vitro studies suggest only minor inhibition of CYP isoenzymes 1A2, 2D6, and 3A4 by amphetamine and/or its metabolites.

■ **Urinary Acidifying Agents** Increased urinary excretion and decreased serum concentrations and efficacy of amphetamines with concomitant use of urinary acidifying agents (ammonium chloride, sodium acid phosphate, cranberry juice).

■ **Adrenergic Blockers** Potential inhibition of adrenergic blockade.

■ **Alkalinizing Agents** Decreased urinary excretion of amphetamines with concomitant use of alkalinizing agents (carbonic anhydrase inhibitors, sodium bicarbonate).

■ **Tricyclic Antidepressants** Enhanced activity of tricyclic antidepressants; desipramine or protriptyline cause striking and sustained increases in the concentration of dextroamphetamine in the brain; cardiovascular effects can be potentiated.

■ **Antihistamines** Amphetamines may counteract the sedative effects of antihistamines.

■ **Antihypertensives** Amphetamines may antagonize the hypotensive effects of antihypertensives.

■ **Chlorpromazine** Chlorpromazine inhibits the central stimulant effects of amphetamines by blocking dopamine and norepinephrine receptors. Can be used to treat amphetamine poisoning.

■ **Ethosuximide** Intestinal absorption of ethosuximide may be delayed.

■ **Haloperidol** Haloperidol inhibits the central stimulant effects of amphetamines by blocking dopamine receptors.

■ **Lithium Carbonate** Lithium may inhibit the anorectic and stimulatory effects of amphetamine.

■ **MAO Inhibitors** MAO inhibitors slow the metabolism of amphetamines, increasing their effect on the release of norepinephrine and other monoamines leading to headaches and other signs of hypertensive crisis. Toxic neurologic effects, hypertensive crisis, and malignant hyperpyrexia can occur, sometimes with fatal results. Amphetamines contraindicated in patients currently or recently (within 14 days) receiving MAO inhibitor.

■ **Meperidine** Amphetamines potentiate the analgesic effect of meperidine.

■ **Methenamine** Acidifying agents used with methenamine increase urinary excretion and decrease efficacy of amphetamines.

■ **Norepinephrine** Amphetamines enhance the adrenergic effects of norepinephrine.

■ **Phenobarbital** Amphetamines may delay absorption of phenobarbital; concomitant use may produce a synergistic anticonvulsant action.

■ **Phenytoin** Amphetamines may delay absorption of phenytoin; concomitant use may produce a synergistic anticonvulsant action.

■ **Propoxyphene** In propoxyphene overdosage, amphetamine-induced CNS stimulation is potentiated and fatal convulsions can occur.

■ **Sympathomimetic Agents** Enhanced activity of sympathomimetic agents. Use with caution.

■ **Tests for Plasma Corticosteroids** Elevated plasma corticosteroid concentrations; this increase is greatest in the evening.

■ **Tests for Urinary Steroids** Possible interference with urinary steroid determinations.

■ **Veratrum Alkaloids** Amphetamines inhibit the hypotensive effect of veratrum.

Description

Lisdexamfetamine, a prodrug of dextroamphetamine, is a CNS stimulant. Lisdexamfetamine is inactive until hydrolyzed in vivo to *l*-lysine, a naturally occurring essential amino acid, and dextroamphetamine, which is responsible for the drug's activity. For information on the pharmacology of amphetamines, see Pharmacology in the Amphetamines General Statement 28:20.04.

Lisdexamfetamine is rapidly absorbed from the GI tract; following oral administration, the onset of action occurs within 2 hours. Conversion of lisdexamfetamine to *l*-lysine and dextroamphetamine is thought to occur by first-pass intestinal and/or hepatic metabolism. Lisdexamfetamine is not metabolized by the cytochrome P-450 (CYP) enzyme system, and the ability of dextroamphetamine to inhibit this enzyme pathway has not been fully elucidated. In vitro studies with human microsomes indicate minor inhibition of CYP isoenzymes 1A2, 2D6, and 3A4 by amphetamine and/or its metabolites. The plasma half-lives of lisdexamfetamine and dextroamphetamine are less than 1 hour and 9.4–9.7 hours, respectively. Approximately 96% of a radiolabeled dose of lisdexamfetamine is excreted in urine, with the parent drug accounting for only about 2% of the recovered radioactivity.

Advice to Patients

Provide patient or caregiver with a copy of the manufacturer's patient information (medication guide); discuss and answer questions about its contents as needed. Instruct patient or caregiver to read and understand contents of medication guide before initiating therapy and each time the prescription is refilled.

Advise parents with concerns about long-term effects (e.g., effects on weight) and the need for continued therapy that drug holidays can be considered in consultation with the patient's clinician. However, the benefits versus risks of such interruptions in therapy have not been established.

Question about possible substance abuse, including in other family members (since they may abuse the patient's medication supply).

Advise to take drug in the morning to minimize insomnia.

Advise that appetite suppression may occur. Giving the morning dose with a meal and providing a high-caloric drink or snack late in the evening when the stimulant effects have subsided may be helpful.

Advise to inform clinician immediately if adverse cardiovascular (e.g., chest pain, shortness of breath, fainting) or psychiatric effects (e.g., hallucinations, delusional thinking, mania) occur.

Instruct about the potential for amphetamines to impair patient's ability to perform potentially hazardous activities, such as driving or operating heavy machinery.

Importance of informing clinicians of existing or contemplated concomitant

therapy, including prescription and OTC drugs, dietary supplements, and herbal products, as well as any concomitant illnesses/conditions (e.g., cardiac/cardiovascular disease, thyroid disease, glaucoma, suicidal ideation or behaviors, mental/psychiatric disorder, seizures).

Importance of women informing clinicians if they are or plan to become pregnant or plan to breast-feed.

Importance of informing patients of other important precautionary information. (See Cautions.)

Overview* (see Users Guide). For additional information on this drug until a more detailed monograph is developed and published, the manufacturer's labeling should be consulted. It is *essential* that the manufacturer's labeling be consulted for more detailed information on usual cautions, precautions, contraindications, potential drug interactions, laboratory test interferences, and acute toxicity.

Preparations

Subject to control under the Federal Controlled Substances Act of 1970 as a schedule II (C-II) drug.

Excipients in commercially available drug preparations may have clinically important effects in some individuals; consult specific product labeling for details.

Lisdexamfetamine Dimesylate

Oral

Capsules	20 mg	Vyvanse® (C-II), Shire
	30 mg	Vyvanse® (C-II), Shire
	40 mg	Vyvanse® (C-II), Shire
	50 mg	Vyvanse® (C-II), Shire
	60 mg	Vyvanse® (C-II), Shire
	70 mg	Vyvanse® (C-II), Shire

Methamphetamine Hydrochloride

Desoxyephedrine Hydrochloride

■ Methamphetamine hydrochloride, the dextrorotatory isomer of phenylmethylamine, has pharmacologic actions that are qualitatively similar to those of amphetamine and ephedrine.

Uses

Methamphetamine has been used as an adjunct to caloric restriction in the short-term (i.e., a few weeks) treatment of exogenous obesity. However, short-term or intermittent therapy with methamphetamine is unlikely to maintain a long-term benefit, and prolonged administration of methamphetamine for the treatment of obesity is not indicated. Methamphetamine also is used as an adjunct to psychological, educational, social, and other remedial measures in the treatment of attention deficit hyperactivity disorder (ADHD). Methamphetamine also has been misused and abused for its CNS stimulatory effects.

■ **Exogenous Obesity** Methamphetamine has been used as an adjunct to caloric restriction in the short-term (i.e., a few weeks) treatment of exogenous obesity. The anorexigenic effect of sympathomimetic compounds used in the treatment of obesity is temporary, seldom lasting more than a few weeks, and tolerance may occur. However, obesity usually is a chronic disease, and short-term or intermittent therapy with these drugs is unlikely to maintain a long-term benefit; therefore, short-term use of anorexigenic agents, including methamphetamine, is not recommended. Furthermore, prolonged administration of methamphetamine in the treatment of obesity is not indicated. (See Cautions: Precautions and Contraindications.) To help bring about and maintain loss of weight, the patient must be taught to curtail overeating and to consume a suitable diet. For further information on the treatment of exogenous obesity, see Uses: Exogenous Obesity, in the Amphetamines General Statement 28:20.04.

■ **Attention Deficit Hyperactivity Disorder** Methamphetamine also is used as an adjunct to psychological, educational, social, and other remedial measures in the treatment of ADHD (hyperkinetic disorder, hyperkinetic syndrome of childhood, minimal brain dysfunction) in children older than 6 years of age.

Methamphetamine should not be used to combat fatigue or exhaustion or to replace sleep in normal persons.

ADHD usually is characterized by developmentally inappropriate symptoms (e.g., moderate to severe distractibility, short attention span, hyperactivity, emotional lability, impulsivity). The final diagnosis of this disorder should not be made if these symptoms are of only comparatively recent origin. Nonlocalizing (soft) neurologic signs, learning disability, and abnormal EEG may or may not be present, and a diagnosis of CNS dysfunction may or may not be warranted. Drug therapy is not indicated in all children with ADHD, and such therapy should be considered only after a complete evaluation including medical history has been performed. The decision to use amphetamines should depend on the age of the child and the physician's assessment of the severity and duration of symptoms and should not depend solely on one or more behavioral characteristics. When symptoms of ADHD are associated with acute stress reactions, use of amphetamines usually is not recommended. For a more detailed discussion on the management of ADHD, including the use of stimulants such as methamphetamine, see Uses: Attention Deficit Hyperactivity Disorder, in Methylphenidate 28:20.92.

■ **Misuse and Abuse** Misuse and abuse of amphetamines, especially methamphetamine, for CNS stimulatory effects have experienced a resurgence. In large part, this resurgence has resulted from the relative ease with which methamphetamine can be synthesized clandestinely from readily available chemicals such as ephedrine, phenylpropanolamine (no longer commercially available in the US), or pseudoephedrine. (See Chronic Toxicity, in the Amphetamines General Statement 28:20.04.) Legal restrictions, including enactment of the US Comprehensive Methamphetamine Control Act of 1996 and later the Methamphetamine Anti-Proliferation Act of 2000 and the Combat Methamphetamine Epidemic Act of 2005, on the availability of these compounds have been enacted in an effort to reverse this resurgence in misuse and abuse.

Dosage and Administration

■ **Administration** Methamphetamine hydrochloride is administered orally. Because of the potential for insomnia, administration of methamphetamine in the late evening should be avoided.

■ **Dosage** Dosage and potency of methamphetamine hydrochloride are expressed in terms of the hydrochloride. (See Chemistry and Stability: Chemistry.)

Dosage of methamphetamine hydrochloride should be adjusted according to individual response and tolerance; the smallest dose required to produce the desired response should always be used.

Exogenous Obesity As an adjunct in the treatment of exogenous obesity, the usual adult dosage of methamphetamine hydrochloride is 2.5–5 mg 2 or 3 times daily, given one-half hour before meals. Treatment should not exceed a duration of a few weeks.

Attention Deficit Hyperactivity Disorder As an adjunct in the treatment of attention deficit hyperactivity disorder (ADHD) in children 6 years of age and older, the usual initial dosage of methamphetamine hydrochloride is 5 mg once or twice daily. Daily dosage may be increased by 5 mg at weekly intervals until an optimum clinical response is achieved. The usual effective dosage is 20–25 mg daily. The total daily dose may be given as conventional tablets in 2 divided doses daily.

When possible, therapy should be interrupted occasionally to determine if there is a recurrence of behavioral symptoms sufficient to require continued treatment.

Cautions

Methamphetamine shares the toxic potentials of amphetamines, and the usual cautions, precautions, and contraindications of amphetamine therapy should be observed. (See Cautions, in the Amphetamines General Statement 28:20.04.)

■ **Cardiovascular Effects** Sudden death, stroke, myocardial infarction, hypertension or hypotension, tachycardia, palpitation, or cardiac arrhythmias may occur in patients receiving stimulants, including methamphetamine. (See Cardiovascular Precautions under Cautions: Precautions and Contraindications, in the Amphetamines General Statement 28:20.04.) Fatal cardiorespiratory arrest has been reported following abuse or misuse of methamphetamine.

■ **Nervous System Effects** Adverse nervous system effects of methamphetamine may include nervousness, insomnia, irritability, talkativeness, dizziness, headache, blurred vision, mydriasis, dizziness, dysphoria, euphoria, tremor, restlessness and hyperexcitability. Rarely, psychotic episodes have occurred in patients receiving recommended dosages. The drug may also exacerbate motor and vocal tics and Tourette's disorder. Seizures, aggressive behavior, and hostility also have been reported with stimulants. (See Psychiatric Precautions under Cautions: Precautions and Contraindications, in the Amphetamines General Statement 28:20.04.)

■ **GI Effects** GI disturbances of methamphetamine may include nausea, vomiting, abdominal cramps, diarrhea or constipation, dryness of the mouth, anorexia, and unpleasant taste.

■ **Other Adverse Effects** Urticaria, impotence, and changes in libido may occur in patients receiving methamphetamine. Visual disturbances (difficulty with accommodation, blurred vision) have been reported with stimulants.

■ **Precautions and Contraindications** The manufacturer's patient information (medication guide) should be provided to the patient or caregiver each time methamphetamine is dispensed, and the clinician should discuss and answer questions about its contents (e.g., benefits and risks of stimulant therapy, appropriate use) as needed. The patient or caregiver also should be instructed to read and understand the contents of the medication guide before initiating therapy and each time the prescription is refilled.

Patients should be warned that methamphetamine may impair their ability to perform hazardous activities requiring mental alertness or physical coordination (e.g., operating machinery, driving a motor vehicle).

Methamphetamine should be administered with caution, if at all, to patients with hyperexcitability states or to those receiving drugs that may produce this

Preparations

Excipients in commercially available drug preparations may have clinically important effects in some individuals; consult specific product labeling for details.

Paroxetine Hydrochloride

Oral		
Suspension	10 mg (of paroxetine) per 5 mL	**Paxil**®, GlaxoSmithKline
Tablets, extended-release, film-coated	12.5 mg (of paroxetine)	**Paxil CR**®, GlaxoSmithKline
	25 mg (of paroxetine)	**Paxil CR**®, GlaxoSmithKline
	37.5 mg (of paroxetine)	**Paxil CR**®, GlaxoSmithKline
Tablets, film-coated	10 mg (of paroxetine)*	**Paroxetine Hydrochloride Film-coated Tablets**
		Paxil® (scored), GlaxoSmithKline
	20 mg (of paroxetine)*	**Paroxetine Hydrochloride Film-coated Tablets**
		Paxil® (scored), GlaxoSmithKline
	30 mg (of paroxetine)*	**Paroxetine Hydrochloride Film-coated Tablets**
		Paxil®, GlaxoSmithKline
	40 mg (of paroxetine)*	**Paroxetine Hydrochloride Film-coated Tablets**
		Paxil®, GlaxoSmithKline

*available from one or more manufacturer, distributor, and/or repackager by generic (nonproprietary) name

Paroxetine Mesylate

Oral		
Tablets, film-coated	10 mg (of paroxetine)	**Pexeva**®, JDS Pharmaceuticals
	20 mg (of paroxetine)	**Pexeva**® (scored), JDS Pharmaceuticals
	30 mg (of paroxetine)	**Pexeva**®, JDS Pharmaceuticals
	40 mg (of paroxetine)	**Pexeva**®, JDS Pharmaceuticals

†Use is not currently included in the labeling approved by the US Food and Drug Administration

Sertraline Hydrochloride

■ Sertraline, a selective serotonin-reuptake inhibitor (SSRI), is an antidepressant agent.

Uses

■ **Major Depressive Disorder** Sertraline is used in the treatment of major depressive disorder. A major depressive episode implies a prominent and relatively persistent depressed or dysphoric mood that usually interferes with daily functioning (nearly every day for at least 2 weeks). According to DSM-IV criteria, a major depressive episode includes at least 5 of the following 9 symptoms (with at least one of the symptoms being either depressed mood or loss of interest or pleasure): depressed mood most of the day as indicated by subjective report (e.g., feels sad or empty) or observation made by others; markedly diminished interest or pleasure in all, or almost all, activities most of the day; significant weight loss (when not dieting) or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite; insomnia or hypersomnia; psychomotor agitation or retardation (observable by others, not merely subjective feelings of restlessness or being slowed down); fatigue or loss of energy; feelings of worthlessness or excessive or inappropriate guilt (not merely self-reproach or guilt about being sick); diminished ability to think or concentrate or indecisiveness (either by subjective account or as observed by others); and recurrent thoughts of death, recurrent suicidal ideation without a specific plan, or a suicide attempt or specific plan for committing suicide.

Treatment of major depressive disorder generally consists of an acute phase (to induce remission), a continuation phase (to preserve remission), and a maintenance phase (to prevent recurrence). Various interventions (e.g., psychotherapy, antidepressant drug therapy, electroconvulsive therapy [ECT]) are used alone or in combination to treat major depressive episodes. Treatment should be individualized and the most appropriate strategy for a particular patient is determined by clinical factors such as severity of depression (e.g., mild, moderate, severe), presence or absence of certain psychiatric features (e.g., suicide risk, catatonia, psychotic or atypical features, alcohol or substance abuse or dependence, panic or other anxiety disorder, cognitive dysfunction, dysthymia, personality disorder, seasonal affective disorder), and concurrent illness (e.g., asthma, cardiac disease, dementia, seizure disorder, glaucoma, hypertension). Demographic and psychosocial factors as well as patient preference also are used to determine the most effective treatment strategy.

While use of psychotherapy alone may be considered as an initial treatment strategy for patients with mild to moderate major depressive disorder (based on patient preference and presence of clinical features such as psychosocial stressors), combined use of antidepressant drug therapy and psychotherapy may be useful for initial treatment of patients with moderate to severe major depressive disorder with psychosocial issues, interpersonal problems, or a comorbid axis II disorder. In addition, combined use of antidepressant drug therapy and psychotherapy may be beneficial in patients who have a history of poor compliance or only partial response to adequate trials of either antidepressant drug therapy or psychotherapy alone.

Antidepressant drug therapy can be used alone for initial treatment of patients with mild major depressive disorder (if preferred by the patient) and usually is indicated alone or in combination with psychotherapy for initial treatment of patients with moderate to severe major depressive disorder (unless ECT is planned). ECT is not generally used for initial treatment of uncomplicated major depression, but is recommended as first-line treatment for severe major depressive disorder when it is coupled with psychotic features, catatonic stupor, severe suicidality, food refusal leading to nutritional compromise, or other situations when a rapid antidepressant response is required. ECT also is recommended for patients who have previously shown a positive response or a preference for this treatment modality and can be considered for patients with moderate or severe depression who have not responded to or cannot receive antidepressant drug therapy. In certain situations involving depressed patients unresponsive to adequate trials of several individual antidepressant agents, adjunctive therapy with another agent (e.g., buspirone, lithium) or concomitant use of a second antidepressant agent (e.g., bupropion) has been used; however, such combination therapy is associated with an increased risk of adverse reactions, may require dosage adjustments, and (if not contraindicated) should be undertaken only after careful consideration of the relative risks and benefits. (See Drug Interactions: Serotonergic Drugs, Drug Interactions: Tricyclic and Other Antidepressants, and Drug Interactions: Lithium.)

The efficacy of sertraline for the acute treatment of major depression has been established by 2 placebo-controlled studies in adult outpatients who met DSM-III criteria for major depression. In the first study of 8 weeks' duration, sertraline was administered with flexible dosing in a range of 50–200 mg daily; the mean daily dosage for patients completing the study was 145 mg daily. In the second study of 6 weeks' duration, sertraline was administered in fixed doses of 50, 100, and 200 mg daily. Overall, these 2 studies demonstrated that sertraline was superior to placebo in improving scores on the Hamilton Depression Rating Scale and the Clinical Global Impression Severity and Improvement Scales. However, the second study was not readily interpretable regarding whether there was a dose-response relationship for the drug's efficacy.

In a third study, depressed outpatients who had responded by the end of an initial 8-week open treatment phase to sertraline 50–200 mg daily were randomized to continue sertraline in the same dosage range or placebo for 44 weeks in a double-blind manner. The mean daily dosage of sertraline in those who completed this long-term study was 70 mg daily, and the relapse rate in the sertraline-treated patients was substantially lower than in those who received placebo.

An analysis of these 3 controlled studies for possible gender-related effects on treatment outcome did not suggest any difference in efficacy based on the gender of the patient.

While the optimum duration of sertraline therapy has not been established, many experts state that acute depressive episodes require several months or longer of sustained antidepressant therapy. In addition, some clinicians recommend that long-term antidepressant therapy be considered in certain patients at risk for recurrence of depressive episodes (such as those with highly recurrent unipolar depression). The efficacy of sertraline in maintaining an antidepressant response for up to 1 year without increased toxicity has been demonstrated in a controlled setting. The manufacturers state that the usefulness of the drug in patients receiving prolonged therapy should be reevaluated periodically. (See Dosage and Administration: Dosage.)

The manufacturers state that the drug's antidepressant efficacy in hospital settings has not been adequately studied to date.

As with certain other antidepressants, the possibility that sertraline may precipitate hypomanic or manic attacks in patients with bipolar or other major affective disorder should be considered. Sertraline is *not* approved for use in treating bipolar depression in adults.

Considerations in Choosing an Antidepressant A variety of antidepressant drugs is available for the treatment of major depressive disorder, including selective serotonin-reuptake inhibitors (SSRIs; e.g., citalopram, escitalopram, fluoxetine, paroxetine, sertraline), selective serotonin- and norepinephrine-reuptake inhibitors (SNRIs; e.g., desvenlafaxine, duloxetine, venlafaxine), tricyclic antidepressants (e.g., amitriptyline, amoxapine, desipramine, doxepin, imipramine, nortriptyline, protriptyline, trimipramine), monoamine oxidase (MAO) inhibitors (e.g., phenelzine, tranylcypromine), and other antidepressants (e.g., bupropion, maprotiline, nefazodone, trazodone). Most clinical studies have shown that the antidepressant effect of usual dosages of sertraline in patients with depression is greater than that of placebo and comparable to that of usual dosages of tricyclic antidepressants (e.g., amitriptyline), other SSRIs (e.g., fluoxetine), and other antidepressants (e.g., nefazodone). In geriatric patients with major depression, sertraline appears to be as effective as amitriptyline. The onset of action of sertraline appears to be comparable to that of tricyclic antidepressants.

In general, response rates in patients with major depression are similar for currently available antidepressants, and the choice of antidepressant agent for a given patient depends principally on other factors such as potential adverse effects, safety or tolerability of these adverse effects in the individual patient, psychiatric and medical history, patient or family history of response to specific therapies, patient preference, quantity and quality of available clinical data, cost, and relative acute overdose safety. No single antidepressant can be recommended as optimal for all patients because of substantial heterogeneity in individual responses and in the nature, likelihood, and severity of adverse effects. In addition, patients vary in the degree to which certain adverse effects and other inconveniences of drug therapy (e.g., cost, dietary restrictions) affect their preferences.

In the large-scale Sequenced Treatment Alternatives to Relieve Depression (STAR*D) effectiveness trial, patients with major depressive disorder who did not respond to or could not tolerate therapy with one SSRI (citalopram) were randomized to switch to extended-release ("sustained-release") bupropion, sertraline, or extended-release venlafaxine as a second step of treatment (level 2). Remission rates as assessed by the 17-item Hamilton Rating Scale for Depression (HRSD-17) and the Quick Inventory of Depressive Symptomatology—Self Report (QIDS-SR-16) were approximately 21 and 26% for extended-release bupropion, 18 and 27% for sertraline, and 25 and 25% for extended-release venlafaxine therapy, respectively; response rates as assessed by the QIDS-SR-16 were 26, 27, and 28% for extended-release bupropion, sertraline, and extended-release venlafaxine therapy, respectively. These results suggest that after unsuccessful initial treatment of depressed patients with an SSRI, approximately 25% of patients will achieve remission after therapy is switched to another antidepressant and that either another SSRI (e.g., sertraline) or an agent from another class (e.g., bupropion, venlafaxine) may be reasonable alternative antidepressants in patients not responding to initial SSRI therapy.

Patient Tolerance Considerations. Because of differences in the adverse effect profile between SSRIs and tricyclic antidepressants, particularly less frequent anticholinergic effects, cardiovascular effects, and weight gain with SSRIs, these drugs may be preferred in patients in whom such effects are not tolerated or are of potential concern. The decreased incidence of anticholinergic effects associated with sertraline and other SSRIs compared with tricyclic antidepressants is a potential advantage, since such effects may result in discontinuance of the drug early during therapy in unusually sensitive patients. In addition, some anticholinergic effects may become troublesome during long-term tricyclic antidepressant therapy (e.g., persistent dry mouth may result in tooth decay). Although SSRIs share the same overall tolerability profile, certain patients may tolerate one drug in this class better than another. In an open study, most patients who had discontinued fluoxetine therapy because of adverse effects subsequently tolerated sertraline therapy. Antidepressants other than SSRIs may be preferred in patients in whom certain adverse GI effects (e.g., nausea, anorexia), nervous system effects (e.g., anxiety, nervousness, insomnia), and/or weight loss are not tolerated or are of concern, since such effects appear to occur more frequently with this class of drugs.

Pediatric Considerations. The clinical presentation of depression in children and adolescents can differ from that in adults and generally varies with the age and developmental stages of the child. Younger children may exhibit behavioral problems such as social withdrawal, aggressive behavior, apathy, sleep disruption, and weight loss; adolescents may present with somatic complaints, self esteem problems, rebelliousness, poor performance in school, or a pattern of engaging in risky or aggressive behavior.

Only limited data are available to date from controlled clinical studies evaluating various antidepressant agents in children and adolescents, and many of these studies have methodologic limitations (e.g., nonrandomized or uncontrolled, small sample size, short duration, nonspecific inclusion criteria). However, there is some evidence that the response to antidepressants in pediatric patients may differ from that seen in adults, and caution should be used in extrapolating data from adult studies when making treatment decisions for pediatric patients. Results of several studies evaluating tricyclic antidepressants (e.g., amitriptyline, desipramine, imipramine, nortriptyline) in preadolescent and adolescent patients with major depression indicate a lack of overall efficacy in this age group. Based on the lack of efficacy data regarding use of tricyclic antidepressants and MAO inhibitors in pediatric patients and because of the potential for life-threatening adverse effects associated with the use of these drugs, many experts consider selective serotonin-reuptake inhibitors, including sertraline, the drugs of choice when antidepressant therapy is indicated for the treatment of major depressive disorder in children and adolescents. However, the US Food and Drug Administration (FDA) states that, while efficacy of fluoxetine has been established in pediatric patients, efficacy of other newer antidepressants (i.e., sertraline, citalopram, desvenlafaxine, duloxetine, escitalopram, fluvoxamine, mirtazapine, nefazodone, paroxetine, venlafaxine) was not conclusively established in clinical trials in pediatric patients with major depressive disorder. In addition, FDA now warns that antidepressants increase the risk of suicidal thinking and behavior (suicidality) in children and adolescents with major depressive disorder and other psychiatric disorders. (See Cautions: Pediatric Precautions.) FDA currently states that anyone considering using an antidepressant in a child or adolescent for any clinical use must balance the potential risk of therapy with the clinical need. (See Cautions: Precautions and Contraindications.)

Geriatric Considerations. The response to antidepressants in depressed geriatric patients without dementia is similar to that reported in younger adults, but depression in geriatric patients often is not recognized and is not treated. In geriatric patients with major depressive disorder, selective serotonin-reuptake inhibitors (SSRIs) appear to be as effective as tricyclic antidepressants (e.g., amitriptyline) but generally are associated with fewer overall adverse effects than these other agents. Geriatric patients appear to be especially sensitive to anticholinergic (e.g., dry mouth, constipation, vision disturbance), cardiovascular, orthostatic hypotensive, and sedative effects of tricyclic antidepressants. The low incidence of anticholinergic effects associated with sertraline and other SSRIs compared with tricyclic antidepressants also is a potential advantage in geriatric patients, since such effects (e.g., constipation, dry mouth, confusion, memory impairment) may be particularly troublesome in these patients. However, SSRI therapy may be associated with other troublesome adverse effects (e.g., nausea and vomiting, agitation and akathisia, parkinsonian adverse effects, sexual dysfunction, weight loss, hyponatremia). Some clinicians state that SSRIs such as sertraline may be preferred for treating depression in geriatric patients in whom the orthostatic hypotension associated with many antidepressants (e.g., tricyclics) potentially may result in injuries (such as severe falls). However, despite the fewer cardiovascular and anticholinergic effects associated with SSRIs, these drugs did not show any advantage over tricyclic antidepressants with regard to hip fracture in a case-control study. In addition, there was little difference in the rates of falls between nursing home residents receiving SSRIs and those receiving tricyclic antidepressants in a retrospective study. Therefore, all geriatric individuals receiving either type of antidepressant should be considered at increased risk of falls and appropriate measures should be taken. In addition, clinicians prescribing SSRIs in geriatric patients should be aware of the many possible drug interactions associated with these drugs, including those involving metabolism of the drugs through the cytochrome P-450 system. (See Drug Interactions.)

Patients with dementia of the Alzheimer's type (Alzheimer's disease, presenile or senile dementia) often present with depressive symptoms, such as depressed mood, appetite loss, insomnia, fatigue, irritability, and agitation. Most experts recommend that patients with dementia of the Alzheimer's type who present with clinically important and persistent depressive symptoms be considered as candidates for pharmacotherapy even if they fail to meet the criteria for a major depressive syndrome. The goals of such therapy are to improve mood, functional status (e.g., cognition), and quality of life. Treatment of depression also may reduce other neuropsychiatric symptoms associated with depression in patients with dementia, including aggression, anxiety, apathy, and psychosis. Although patients may present with depressed mood alone, the possibility of more extensive depressive symptomatology should be considered. Therefore, patients should be evaluated and monitored carefully for indices of major depression, suicidal ideation, and neurovegetative signs since safety measures (e.g., hospitalization for suicidality) and more vigorous and aggressive therapy (e.g., relatively high dosages, multiple drug trials) may be needed in some patients.

Although placebo-controlled trials of antidepressants in depressed patients with concurrent dementia have shown mixed results, the available evidence and experience with the use of antidepressants in patients with dementia of the Alzheimer's type and associated depressive manifestations indicate that depressive symptoms (including depressed mood alone and with neurovegetative changes) in such patients are responsive to antidepressant therapy. In some patients, cognitive deficits may partially or fully resolve during antidepressant therapy, but the extent of response will be limited to the degree of cognitive impairment that is directly related to depression. SSRIs such as sertraline, citalopram, escitalopram, fluoxetine, or paroxetine are generally considered as first-line agents in the treatment of depressed patients with dementia since they are better tolerated than some other antidepressants (e.g., tricyclic antidepressants, monoamine oxidase inhibitors). Some possible alternative agents to SSRIs include bupropion, mirtazapine, and venlafaxine. Some geriatric patients with dementia and depression may be unable to tolerate the antidepressant dosages needed to achieve full remission. When a rapid antidepressant response is not critical, some experts therefore recommend a very gradual dosage increase to increase the likelihood that a therapeutic dosage of the SSRI or other antidepressant will be reached and tolerated. In a randomized, placebo-controlled study in a limited number of patients with major depression and Alzheimer's disease, sertraline was found to be superior to placebo; depression reduction in this study was accompanied by lessened behavior disturbance and improved activities of daily living but not improved cognition.

Cardiovascular Considerations. The relatively low incidence of adverse cardiovascular effects, including orthostatic hypotension and conduction disturbances, associated with sertraline and other selective serotonin-reuptake inhibitors may be advantageous in patients in whom the cardiovascular effects associated with tricyclic antidepressants may be hazardous. Patients with a recent history of myocardial infarction or unstable cardiovascular disease were excluded from premarketing clinical studies with sertraline. However, the cardiovascular safety of sertraline (50–200 mg daily for 24 weeks; mean dosage of 89 mg daily) was evaluated in a postmarketing, double-blind, placebo-controlled study in adult outpatients with major depressive disorder and a recent history of myocardial infarction or unstable angina pectoris requiring hospitalization but who were otherwise free of life-threatening medical conditions. When therapy was initiated during the acute phase of recovery (within 30 days after a myocardial infarction or hospitalization for unstable angina), sertraline therapy did not differ from placebo on the following cardiovascular end points at week 16: left ventricular ejection fraction and total cardiovascular events (angina, chest pain, edema, palpitations, syncope, postural dizziness, chronic

heart failure, myocardial infarction, tachycardia, bradycardia, blood pressure changes). Although not statistically significant, approximately 20% fewer major cardiovascular events involving death or requiring hospitalization (e.g., for myocardial infarction, chronic heart failure, stroke, angina) occurred in the sertraline-treated patients compared with those receiving placebo. (See Cautions: Cardiovascular Effects and see also Cautions: Precautions and Contraindications.)

Sedative Considerations. Because sertraline and other SSRIs are generally less sedating than some other antidepressants (e.g., tricyclics), some clinicians state that these drugs may be preferable in patients who do not require the sedative effects associated with many antidepressant agents; however, an antidepressant with more prominent sedative effects (e.g., trazodone) may be preferable in certain patients (e.g., those with insomnia).

Suicidal Risk Considerations. Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are the strongest predictors of suicide. However, there has been a long-standing concern that antidepressants may have a role in inducing worsening of depression and the emergence of suicidal thinking and behavior (suicidality) in certain patients during the early phases of treatment. FDA states that antidepressants increased the risk of suicidality in short-term studies in children, adolescents, and young adults (18–24 years of age) with major depressive disorder and other psychiatric disorders. (See Cautions: Pediatric Precautions.) An increased suicidality risk was not demonstrated with antidepressants compared with placebo in adults older than 24 years of age and a reduced risk was observed in adults 65 years of age or older. It currently is unknown whether the suicidality risk extends to longer-term antidepressant use (i.e., beyond several months); however, there is substantial evidence from placebo-controlled maintenance trials in adults with major depressive disorder that antidepressants can delay the recurrence of depression. Because the risk of suicidality in depressed patients may persist until substantial remission of depression occurs, appropriate monitoring and close observation of all patients who are receiving antidepressant therapy is recommended. (See Cautions: Precautions and Contraindications.)

Other Considerations. Sertraline has been effective in patients with moderate to severe depression.

In the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) level 2 trial, patients with major depressive disorder who did not respond to or could not tolerate therapy with citalopram (another SSRI) were randomized to receive either extended-release ("sustained-release") bupropion or buspirone therapy in addition to citalopram. Although both extended-release bupropion and buspirone were found to produce similar remission rates, extended-release bupropion produced a greater reduction in the number and severity of symptoms and a lower rate of drug discontinuance than buspirone in this large-scale, effectiveness trial. These results suggest that augmentation of SSRI therapy with extended-release bupropion may be useful in some patients with refractory depression.

Sertraline has been effective in patients with depression and concurrent human immunodeficiency virus (HIV) infection and depression with anxiety.

In a double-blind, placebo-controlled study, both sertraline or imipramine were found to be more effective than placebo in reducing the depressive symptoms and improving psychosocial functioning in patients with dysthymia† without concurrent major depression; moreover, fewer patients treated with sertraline than those treated with imipramine or placebo discontinued therapy because of adverse effects. The results of several other studies, both controlled and uncontrolled, also suggest that sertraline may be effective in patients with dysthymia. Because dysthymia is a chronic condition and requires prolonged antidepressant therapy, the good tolerability demonstrated in clinical studies to date may be advantageous. Sertraline also has been used in the treatment of anger attacks associated with atypical depression and dysthymia† in a limited number of patients.

■ **Obsessive-Compulsive Disorder** Sertraline is used in the treatment of obsessive-compulsive disorder when the obsessions or compulsions cause marked distress, are time consuming (take longer than 1 hour daily), or interfere substantially with the patient's normal routine, occupational or academic functioning, or usual social activities or relationships. Obsessions are recurrent and persistent ideas, thoughts, impulses, or images that, at some time during the disturbance, are experienced as intrusive and inappropriate (i.e., "ego dystonic") and that cause marked anxiety or distress but that are not simply excessive worries about real-life problems. Compulsions are repetitive, intentional behaviors (e.g., hand washing, ordering, checking) or mental acts (e.g., praying, counting, repeating words silently) performed in response to an obsession or according to rules that must be applied rigidly (e.g., in a stereotyped fashion). Although the behaviors or acts are aimed at preventing or reducing distress or preventing some dreaded event or situation, they either are not connected in a realistic manner with what they are designed to neutralize or prevent or are clearly excessive. At some time during the course of the disturbance, the patient, if an adult, recognizes that the obsessions or compulsions are excessive or unreasonable; children may not make such a recognition.

The efficacy of sertraline for the management of obsessive-compulsive disorder has been established in several multicenter, placebo-controlled studies, including one study of 8 weeks' duration and 2 studies of 12 weeks' duration in adults and one study of 12 weeks' duration in children and adolescents 6–17 years of age. Patients in these studies had moderate to severe obsessive-compulsive disorder with mean baseline total scores on the Yale-Brown Obsessive-Compulsive Scale (YBOCS) of 23–25 in adults and 22 in children and adolescents (measured in the Children's Yale-Brown Obsessive-Compulsive Scale [CY-BOCS]). In the 8-week study with flexible dosing, adult patients received sertraline in dosages ranging from 50–200 mg daily; the mean dosage for those completing the study was 186 mg daily. Total scores on the YBOCS decreased by an average of approximately 4 points in sertraline-treated patients and 2 points in patients receiving placebo; this difference was statistically significant.

In a fixed-dose study of 12 weeks' duration involving sertraline dosages of 50, 100, and 200 mg daily, adult patients receiving 50 and 200 mg of the drug daily experienced substantially greater reductions in the YBOCS total score than those receiving placebo (approximately 6 to approximately 3 points, respectively). In a 12-week study with flexible dosing in the range of 50–200 mg daily, the mean sertraline dosage in adult patients completing the study was 185 mg daily. YBOCS total scores in the sertraline-treated patients were reduced by a mean of approximately 7 points, which was better than the mean reduction of approximately 4 points reported in the placebo-treated patients.

In a 12-week study with flexible dosing, sertraline therapy was initiated at dosages of 25 or 50 mg daily in children 6–12 years of age or adolescents 13–17 years of age, respectively. Subsequent dosage was titrated according to individual tolerance over the first 4 weeks to a maximum dosage of 200 mg daily; the mean dosage for those completing the study was 178 mg daily. The drug produced substantially greater reductions in scores in the Children's Yale-Brown Obsessive-Compulsive Scale (CY-BOCS), the National Institute of Mental Health Global Obsessive-Compulsive Scale (NIMH-OC), and the Clinical Global Impressions (CGI) Improvement Scale; total scores on the CY-BOCS decreased by an average of approximately 7 units in sertraline-treated patients and 3 units in patients receiving placebo. An analysis of these controlled studies for possible age- and gender-related effects on treatment outcome did not suggest any difference in efficacy based on either the age or gender of the patient.

In addition, in an uncontrolled 6-week study with flexible dosing (50–200 mg daily) in children or adolescents 6–17 years of age with obsessive-compulsive disorder or major depression†, those with a diagnosis of obsessive-compulsive disorder had mean baseline total scores on the CY-BOCS, NIMH-OC, and CGI of about 24.9, 10.2, and 5.2, respectively. Sertraline produced substantial reductions in all 3 of the scales; total scores on CY-BOCS, NIMH-OC, and CGI decreased to 12.9, 6.7, and 3.4, respectively. In another uncontrolled, 6-week study employing a sertraline dosage that was escalated from 25 to 200 mg daily over 3 weeks, the drug combined with behavioral therapy was effective in a limited number of adolescents 13–17 years of age with obsessive-compulsive disorder refractory to other therapies; total scores on the CY-BOCS at the end of the study decreased by 11 points (from 25.4 to 14.4).

Results from comparative studies to date suggest sertraline and other selective serotonin-reuptake inhibitors (SSRIs; e.g., fluoxetine, fluvoxamine, paroxetine) are as effective or somewhat less effective than clomipramine and more effective than tricyclic antidepressants (e.g., amitriptyline, desipramine, imipramine, nortriptyline) in the management of obsessive-compulsive disorder. In a pooled analysis of separate short-term (10–13 weeks) studies comparing clomipramine, fluoxetine, fluvoxamine, or sertraline with placebo, clomipramine was calculated as being more effective (as determined by measures on the YBOC scale) than SSRIs, although all drugs were superior to placebo. Like clomipramine, SSRIs reduce but do not completely eliminate obsessions and compulsions.

Many clinicians consider an SSRI (e.g., sertraline, fluoxetine, fluvoxamine, paroxetine) or clomipramine to be the drugs of choice for the pharmacologic treatment of obsessive-compulsive disorder. The decision whether to initiate therapy with an SSRI or clomipramine often is made based on the adverse effect profile of these drugs. For example, some clinicians prefer clomipramine in patients who may not tolerate the adverse effect profile of SSRIs (nausea, headache, overstimulation, sleep disturbances) while SSRIs may be useful alternatives in patients unable to tolerate the adverse effects (anticholinergic effects, cardiovascular effects, sedation) associated with clomipramine therapy. Consideration of individual patient characteristics (age, concurrent medical conditions), pharmacokinetics of the drug, potential drug interactions, and cost of therapy may also influence clinicians when selecting between SSRIs and clomipramine as first-line therapy in patients with obsessive-compulsive disorder. Although not clearly established, it has been suggested that the mechanism of action of sertraline and other potent serotonin-reuptake inhibitors (e.g., clomipramine, fluoxetine, fluvoxamine, paroxetine) used in the management of obsessive-compulsive disorder may be related to their serotonergic activity.

■ **Panic Disorder** Sertraline is used in the treatment of panic disorder with or without agoraphobia. Panic disorder is characterized by the occurrence of unexpected panic attacks and associated concern about having additional attacks, worry about the implications or consequences of the attacks, and/or a clinically important change in behavior related to the attacks.

According to DSM-IV, panic disorder is characterized by recurrent unexpected panic attacks, which consist of a discrete period of intense fear or discomfort in which 4 (or more) of the following symptoms develop abruptly and reach a peak within 10 minutes: palpitations, pounding heart, or accelerated heart rate; sweating; trembling or shaking; sensations of shortness of breath or smothering; feeling of choking; chest pain or discomfort; nausea or abdominal distress; feeling dizzy, unsteady, lightheaded, or faint; derealization (feelings of unreality) or depersonalization (being detached from oneself); fear of losing control; fear of dying; paresthesias (numbness or tingling sensations); and chills or hot flushes.

The efficacy of sertraline for the management of panic disorder has been established by 3 double-blind, placebo-controlled studies in adult outpatients who met DSM-III-R criteria for panic disorder with or without agoraphobia. The first 2 studies were of 10 weeks' duration and used a flexible dosing schedule. Sertraline therapy was initiated in a dosage of 25 mg daily for the first week and then dosage was escalated to 50–200 mg daily depending on clinical response and tolerability. The mean sertraline dosages for completers were 131 and 144 mg daily for the first 2 studies. Overall, these 2 studies demonstrated that sertraline was superior to placebo in decreasing the frequency of panic attacks and in improving scores on the Clinical Global Impression Severity of Illness and Global Improvement Scales. The difference between sertraline and placebo in reduction in the number of full panic attacks per week compared with baseline was approximately 2 in both studies.

The third study was a fixed-dose study of 12 weeks' duration. Sertraline was given in dosages of 50, 100, and 200 mg daily. The patients receiving sertraline demonstrated a substantially greater reduction in panic attack frequency than patients receiving placebo. However, the results of this study were not readily interpretable regarding a dose-response relationship for efficacy in this condition.

An analysis of these 3 controlled studies for possible age-, race-, or gender-related effects on treatment outcome did not suggest any difference in efficacy based on these patient characteristics.

Panic disorder can be treated with cognitive and behavioral psychotherapy and/or pharmacologic therapy. There are several classes of drugs that appear to be effective in the pharmacologic management of panic disorder, including tricyclic antidepressants, MAO inhibitors (e.g., phenelzine), selective serotonin-reuptake inhibitors (SSRIs; e.g., citalopram, fluoxetine, paroxetine, sertraline), and benzodiazepines (e.g., alprazolam, clonazepam). When choosing among the available drugs, clinicians should consider their acceptance and tolerability by patients; their ability to reduce or eliminate panic attacks, reduce clinically important anxiety and disability secondary to phobic avoidance, and ameliorate other common comorbid conditions (such as depression); and their ability to prevent relapse during long-term therapy. Because of their better tolerability when compared with other agents (such as the tricyclic antidepressants and benzodiazepines), the lack of physical dependence problems commonly associated with benzodiazepines, and efficacy in panic disorder with comorbid conditions (e.g., depression, other anxiety disorders such as obsessive-compulsive disorder, alcoholism), many clinicians prefer SSRIs as first-line therapy in the management of panic disorder. If SSRI therapy is ineffective or not tolerated, use of a tricyclic antidepressant or a benzodiazepine is recommended.

Sertraline has improved chronic idiopathic urticaria† associated with panic disorder in at least one patient, but further study is needed to determine whether serotonin is involved in the pathogenesis of urticaria and whether SSRIs are effective in this condition.

■ **Posttraumatic Stress Disorder** Sertraline is used in the treatment of posttraumatic stress disorder (PTSD). PTSD is an anxiety disorder that involves the development of certain characteristic symptoms following personal exposure to an extreme traumatic stressor. According to DSM-IV, PTSD requires exposure to a traumatic event(s) that involved actual or threatened death or serious injury, or threat to the physical integrity of self or others, and the response to the event must involve intense fear, helplessness, or horror (in children the response may be expressed by disorganized or agitated behavior). PTSD is characterized by persistent symptoms of *reexperiencing* the trauma (e.g., intrusive distressing recollections of the event; recurrent distressing dreams of the event; acting or feeling as if the event were recurring including illusions, hallucinations, or flashbacks; intense distress at exposure to internal or external cues that symbolize or resemble an aspect of the event; physiologic reactivity on exposure to internal or external cues that symbolize or resemble an aspect of the event), persistent *avoidance* of stimuli associated with the trauma and numbing of general responsiveness (e.g., efforts to avoid thoughts, feelings, or conversations related to the event; efforts to avoid activities, places, or people that arouse recollections of the event; inability to recall an important aspect of the event; markedly diminished interest or participation in significant activities; feeling of detachment or estrangement from others; restricted emotions and/or range of affect not present before the event; sense of a foreshortened future), and persistent symptoms of *increased arousal* (e.g., difficulty sleeping; irritability/outbursts of anger; difficulty concentrating; hypervigilance; exaggerated startle response). According to DSM-IV, a PTSD diagnosis requires the presence of 1 or more symptoms of *reexperiencing*, 3 or more symptoms of *avoidance*, and 2 or more symptoms of *increased arousal*, all of which must be present for at least one month and cause clinically important distress or impairment in social, occupational, or other important areas of functioning. PTSD, like other anxiety disorders, rarely occurs alone, and patients with PTSD often present with comorbid disorders (e.g., major depressive disorder, substance abuse disorders, panic disorder, generalized anxiety disorders, obsessive-compulsive disorder, social phobia); it is unknown whether these comorbid disorders precede or follow the onset of PTSD.

Psychotherapy alone or in combination with pharmacotherapy generally is considered the treatment of choice for PTSD. Pharmacologic therapy may be indicated in addition to psychotherapy for initial treatment of PTSD in patients who have comorbid disorders (e.g., major depressive disorder, bipolar disorder, other anxiety disorders) and also may be indicated in those who do not respond to initial treatment with psychotherapy alone. If pharmacotherapy is indicated in patients with PTSD, selective serotonin-reuptake inhibitors (SSRIs; e.g., sertraline, fluoxetine, paroxetine) usually are considered the drugs of choice (except in patients with bipolar disorder who require treatment with mood stabilizing agents).

The efficacy of sertraline for the management of PTSD has been established in 2 placebo-controlled studies of 12 weeks' duration in adult outpatients (76% women) who met DSM-III-R criteria for chronic PTSD (duration of symptoms 3 months or longer). The mean duration of PTSD for these patients was approximately 12 years and 44% of patients had secondary depressive disorders. Sertraline therapy was initiated at a dosage of 25 mg daily for the first week and then dosage was escalated (using a flexible dosage schedule) to 50–200 mg daily based on clinical response and tolerability. The mean sertraline dosage for patients who completed studies 1 and 2 was 146 mg and 151 mg daily, respectively. Overall, these 2 studies showed that sertraline was superior to placebo in improving scores on the Clinician-Administered PTSD Scale Part 2 total severity scale (a measure of the intensity and frequency of all 3 PTSD diagnostic symptom clusters [reexperiencing/intrusion, avoidance/numbing, and hyperarousal]), Impact of Event Scale (a patient rated measurement of the intrusion and avoidance symptoms), and the Clinical Global Impressions Severity of Illness and Global Improvement Scales.

However, in 2 additional placebo-controlled studies of similar design and duration, the difference in response to treatment on key assessment scales between patients receiving sertraline and those receiving placebo was not statistically significant. In one study of mostly female patients who met the DSM-III-R criteria for PTSD related to sexual/physical trauma, those receiving placebo experienced substantially greater improvement on the Impact of Event Scale than those receiving sertraline therapy. Although this study enrolled a higher proportion of patients with comorbid anxiety disorders and a higher proportion of patients receiving placebo with a successful response to previous psychotropic therapies than the studies demonstrating efficacy of the drug, it is unknown whether these factors alone account for the high placebo response in the study.

Efficacy of sertraline for the management of PTSD related to war or combat was evaluated in a study involving primarily white men in a VA medical center outpatient setting (mean duration of PTSD approximately 18 years). At the end of this study, patients receiving sertraline did not differ from those receiving placebo on any of the key efficacy assessment scales (e.g., Clinician-Administered PTSD scale, Davidson Self-Rating Trauma scale, Impact of Event Scale). In addition, the mean change from baseline for both treatment groups in this study was of a lesser magnitude than those of patients receiving placebo in the other reported studies. The lack of response to sertraline treatment in these combat veterans is consistent with controlled studies evaluating other selective serotonin-reuptake inhibitors (e.g., fluoxetine, brofaromine [not commercially available in the US]) in Vietnam veterans with PTSD. Some experts suggest that patients with combat- or war-related PTSD may be less responsive to treatment than patients with PTSD related to other traumatic events (e.g., sexual assault, accidents, natural disasters) because of some factor inherent in combat- or war-related trauma. However, other experts suggest that the poor treatment response in studies evaluating use in veterans may be the result of sampling error since veterans receiving treatment at VA hospitals may constitute a self-selected group of patients with chronic PTSD who have multiple impairments (comorbid disorders, substance abuse) that make them less responsive to treatment.

Since PTSD is a more common disorder in women than men, the majority (76%) of patients in reported studies were women. A retrospective analysis of pooled data has shown a substantial difference between sertraline and placebo on key efficacy assessment scales (e.g., Clinician-Administered PTSD scale, Impact of Event Scale, Clinical Global Impressions Severity of Illness Scale) in women (regardless of a baseline diagnosis of comorbid depression), but essentially no effect in the limited number of men studied. The clinical importance of this apparent gender effect is unknown; however, only limited data are available to date regarding use of SSRIs in men who have PTSD related to noncombat-related trauma (e.g., sexual assault, accidents, natural disasters). There are insufficient data to date to determine whether race or age has any effect on the efficacy of sertraline in the management of PTSD.

■ **Premenstrual Dysphoric Disorder** Sertraline is used in the treatment of premenstrual dysphoric disorder (previously late luteal phase dysphoric disorder). DSM-IV criteria for premenstrual dysphoric disorder (PMDD) requires that in most menstrual cycles of the previous year at least 5 of the following 11 symptoms must have been present for most of the time during the last week of the luteal phase (with at least one of the symptoms being one of the first 4 listed): marked depressed mood, feelings of hopelessness, or self-deprecating thoughts; marked anxiety, tension, feelings of being "keyed up" or on "edge"; marked affective lability (e.g., feeling suddenly sad or tearful or increased sensitivity to rejection); persistent and marked anger or irritability or increased interpersonal conflicts; decreased interest in usual activities (e.g., work, school, friends, hobbies); a subjective sense of difficulty in concentrating; lethargy, easy fatigability, or marked lack of energy; marked change in appetite, overeating, or specific food cravings; hypersomnia or insomnia; a subjective sense of being overwhelmed or out of control; and other physical symptoms, such as breast tenderness or swelling, headaches, joint or muscle pain, or a sensation of "bloating" or weight gain. Such symptoms should begin to remit within a few days of the onset of menses (follicular phase) and are always absent in the week following menses. The presence of this cyclical pattern of symptoms must be confirmed by at least 2 consecutive months of prospective daily symptom ratings. PMDD should be distinguished from the more common

premenstrual syndrome (PMS) by prospective daily ratings and the strict criteria listed above.

The efficacy of sertraline for the management of PMDD has been established in 2 randomized, placebo-controlled studies over 3 menstrual cycles in adult women who met DSM-III-R or DSM-IV criteria for PMDD. In these studies, flexible dosages (range: 50–150 mg daily) of sertraline administered continuously throughout the menstrual cycle or during the luteal phase only (i.e., for 2 weeks prior to the onset of menses) were shown to be substantially more effective than placebo in improving scores from baseline on the Daily Record of Severity of Problems (DRSP), the Clinical Global Impression of Severity of Illness (CGI-S) and Improvement (CGI-I), and/or the Hamilton Depression Rating Scales (HAMD-17). The mean dosage of sertraline in patients completing these trials was 102 or 74 mg daily for those receiving continuous or luteal-phase dosing of the drug, respectively.

When given in a flexible dosage of 50–150 mg daily in a separate double-blind, placebo-controlled study, sertraline was substantially better than placebo in improving symptoms (depressive symptoms, physical symptoms, anger/irritability) and functional impairment associated with this disorder. The beneficial effect of the drug was apparent by the first treatment cycle. In an open study comparing sertraline and desipramine in the treatment of premenstrual dysphoric disorder, sertraline and possibly desipramine were found to be effective; however, sertraline was better tolerated than desipramine. Additional controlled studies are needed to determine whether the efficacy of the drug is sustained during longer-term, maintenance therapy in women with this condition. In addition, efficacy of sertraline used in conjunction with oral contraceptives for the treatment of PMDD has not been determined since patients receiving oral contraceptives were excluded from most clinical studies to date.

■ **Social Phobia** Sertraline is used in the treatment of social phobia (social anxiety disorder). According to DSM-IV, social phobia is characterized by a marked and persistent fear of one or more social or performance situations in which the person is exposed to unfamiliar people or to possible scrutiny by others. Exposure to the feared situation almost invariably provokes anxiety, which may approach the intensity of a panic attack. The feared situations are avoided or endured with intense anxiety or distress. The avoidance, fear, or anxious anticipation of encountering the social or performance situation interferes significantly with the person's daily routine, occupational or academic functioning, or social activities or relationships, or there is marked distress about having the phobias. Lesser degrees of performance anxiety or shyness generally do not require psychotherapy or pharmacologic treatment.

The efficacy of sertraline in the treatment of social phobia has been established in 2 multicenter, placebo-controlled studies in adult outpatients who met DSM-IV criteria for social phobia. In one study of 12 weeks' duration, 47% of patients receiving flexible dosages of sertraline (50–200 mg daily; mean dosage of 144 mg daily) were characterized as responders (defined as a score of 1 or 2 on the Clinical Global Impressions [CGI] Global Improvement Scale) compared with 26% of those receiving placebo (intent-to-treat analysis). Sertraline also was found to be superior to placebo on the Liebowitz Social Anxiety Scale (LSAS), a 24-item clinician administered measure of fear, anxiety, and avoidance of social and performance situation, and on most secondary efficacy measures, including the Duke Brief Social Phobia Scale (BSPS) total score, fear and avoidance subscales of BSPS, and fear/anxiety and avoidance subscales of LSAS. These results were similar to those seen in a flexible-dose study of 20 weeks' duration, in which a score of 1 ("very much improved") or 2 ("much improved") on the CGI Global Improvement Scale was attained by the end of the treatment period by 53 or 29% of patients receiving sertraline (50–200 mg daily; mean dosage of 147 mg daily) or placebo, respectively (intent-to-treat analysis). Sixty-five patients in this study subsequently were enrolled in a separate controlled study, including 50 patients who had responded to sertraline in the initial study and then were randomized to receive either continued treatment with sertraline or placebo in the subsequent study and 15 patients who had responded to placebo in the initial study and continued to receive placebo in the subsequent study. Based on an intent-to-treat analysis, 4% of patients who continued treatment with sertraline, 36% of patients randomized to receive placebo, and 27% of those who continued treatment with placebo relapsed (defined as an increase of 2 or more points from baseline in the CGI Severity of Illness score or discontinuance of the study drug because of lack of efficacy) at the end of the 24-week treatment period. Similar to results of pivotal, short-term clinical studies, sertraline also was shown to be substantially more effective than placebo on the CGI Severity of Illness Scale, Marks Fear Questionnaire (MFQ) Social Phobia subscale, and BSPS total score.

Subgroup analysis of short-term, controlled studies in adult outpatients with social anxiety disorder did not reveal any evidence of gender-related differences in treatment outcome. There was insufficient information to determine the effect of race or age on treatment outcome. Safety and efficacy of sertraline for the treatment of social phobia in children or adolescents have not been established to date.

■ **Premature Ejaculation** Like some other serotonin-reuptake inhibitors, sertraline has been used with some success in the treatment of premature ejaculation†. In a placebo-controlled study, sertraline produced substantial improvements compared with placebo in time to ejaculation, number of successful attempts at intercourse, and incidence of ejaculation during foreplay, as well as overall clinical judgment of improvement. In addition, the drug was well tolerated in most patients. A trial with drug therapy may be particularly useful in patients who fail or refuse behavioral or psychotherapeutic treatment or when partners are unwilling to cooperate with such therapy.

■ **Other Uses** Sertraline has been used in a limited number of patients with various types of headache† with variable results; however, its use in this condition may be limited by frequent adverse effects.

Dosage and Administration

■ **Administration** Sertraline is administered orally. The drug usually is administered once daily in the morning or evening. The extent of GI absorption of sertraline reportedly may be increased slightly, the peak concentration increased by about 25%, and the time to peak concentration after a dose decreased from about 8 to 5.5 hours when the drug is administered with food, but such changes do not appear to be clinically important.

When sertraline hydrochloride concentrate for oral solution (Zoloft®) is used, doses of the drug should be measured carefully using the calibrated dropper provided by the manufacturer. The appropriate dose of the oral solution should be diluted in 120 mL of water, ginger ale, lemon/lime soda, lemonade, or orange juice before administration. The diluted solution containing sertraline hydrochloride should be mixed and administered immediately and should not be allowed to stand before administration. A slight haze may occasionally appear in the diluted oral solution, but the manufacturer states that this is normal.

■ **Dosage** Dosage of sertraline hydrochloride is expressed in terms of sertraline.

Patients receiving sertraline should be monitored for possible worsening of depression, suicidality, or unusual changes in behavior, especially at the beginning of therapy or during periods of dosage adjustment. (See Cautions: Precautions and Contraindications.)

Abrupt discontinuance of sertraline therapy should be avoided because of the potential for withdrawal reactions. (See Chronic Toxicity.) In addition, patients may experience a worsening of psychiatric status when the drug is discontinued abruptly. Therefore, it is recommended that dosage be tapered gradually (e.g., over a period of several weeks) and the patient monitored carefully when sertraline therapy is discontinued.

The manufacturers recommend that an interval of at least 2 weeks elapse when switching a patient from a monoamine oxidase (MAO) inhibitor to sertraline or when switching from sertraline to an MAO inhibitor. For additional information on potentially serious drug interactions that may occur between sertraline and MAO inhibitors or other serotonergic agents, see Cautions: Precautions and Contraindications and see also Drug Interactions: Serotonergic Drugs.

Clinical experience regarding the optimal timing of switching from other drugs used in the treatment of major depressive disorder, obsessive-compulsive disorder, panic disorder, posttraumatic stress disorder, premenstrual dysphoric disorder, and social anxiety disorder to sertraline therapy is limited. Therefore, the manufacturers recommend that care and prudent medical judgment be exercised when switching from other drugs to sertraline, particularly from long-acting agents (such as fluoxetine). Because some adverse reactions resembling serotonin syndrome have developed when fluoxetine therapy was discontinued abruptly and sertraline therapy was initiated immediately afterward, a washout period appears to be advisable when transferring a patient from fluoxetine to sertraline therapy. However, the appropriate duration of the washout period when switching from one selective serotonin-reuptake inhibitor to another has not been clearly established. Pending further experience in patients being transferred from therapy with another antidepressant to sertraline, it generally is recommended that the previous antidepressant be discontinued according to the recommended guidelines for the specific antidepressant prior to initiation of sertraline therapy. (See Drug Interactions: Serotonergic Drugs and see Drug Interactions: Tricyclic and Other Antidepressants.)

Major Depressive Disorder For the management of major depressive disorder in adults, the recommended initial dosage of sertraline is 50–100 mg once daily. If no clinical improvement is apparent, dosage may be increased at intervals of not less than 1 week up to a maximum of 200 mg daily. Clinical experience with the drug to date suggests that many patients will respond to 50–100 mg of the drug once daily. While a relationship between dose and antidepressant effect has not been established, efficacy of the drug was demonstrated in clinical trials employing 50–200 mg daily.

While the optimum duration of sertraline therapy has not been established, many experts state that acute depressive episodes require several months or longer of sustained antidepressant therapy. In addition, some clinicians recommend that long-term antidepressant therapy be considered in certain patients at risk for recurrence of depressive episodes (such as those with highly recurrent unipolar depression). Whether the dose of sertraline required to induce remission is identical to the dose needed to maintain and/or sustain euthymia is unknown. Systematic evaluation of sertraline has shown that its antidepressant efficacy is maintained for periods of up to 1 year in patients receiving 50–200 mg daily (mean dose of 70 mg daily). The usefulness of the drug in patients receiving prolonged therapy should be reevaluated periodically.

Obsessive-Compulsive Disorder For the management of obsessive-compulsive disorder in adults and adolescents 13–17 years of age, the recommended initial dosage of sertraline is 50 mg once daily. In children 6–12 years of age, the recommended initial dosage of sertraline is 25 mg once daily. If no clinical improvement is apparent, dosage may be increased at intervals of not less than 1 week up to a maximum of 200 mg daily. However, it should be considered that children usually have a lower body weight than adults and

particular care should be taken to avoid excessive dosage in children. While a relationship between dose and efficacy in obsessive-compulsive disorder has not been established, efficacy of the drug was demonstrated in clinical trials employing 50–200 mg daily in adults and 25–200 mg daily in children and adolescents.

While the optimum duration of sertraline therapy required to prevent recurrence of obsessive-compulsive symptoms has not been established to date, the manufacturer and many experts state that this disorder is chronic and requires several months or longer of sustained therapy. Whether the dose of sertraline required to induce remission is identical to the dose needed to maintain and/or sustain remission in patients with this disorder is unknown. Systematic evaluation of sertraline has shown that its efficacy in the management of obsessive-compulsive disorder is maintained for periods of up to 28 weeks in patients receiving 50–200 mg daily. The usefulness of the drug in patients receiving prolonged therapy should be reevaluated periodically.

Panic Disorder For the management of panic disorder in adults, the recommended initial dosage of sertraline is 25 mg once daily. After 1 week, the dosage should be increased to 50 mg once daily. If no clinical improvement is apparent, dosage may then be increased at intervals of not less than 1 week up to a maximum of 200 mg daily.

While the optimum duration of sertraline therapy required to prevent recurrence of panic disorder has not been established to date, the manufacturer and many experts state that this disorder is chronic and requires several months or longer of sustained therapy. Whether the dose of sertraline required to induce remission is identical to the dose needed to maintain and/or sustain remission in patients with this disorder is unknown. Systematic evaluation of sertraline has shown that its efficacy in the management of panic disorder is maintained for periods of up to 28 weeks in patients receiving 50–200 mg daily. The usefulness of the drug in patients receiving prolonged therapy should be reevaluated periodically.

Posttraumatic Stress Disorder For the management of posttraumatic stress disorder (PTSD) in adults, the recommended initial dosage of sertraline is 25 mg once daily. After 1 week, dosage should be increased to 50 mg once daily. If no clinical improvement is apparent, dosage may then be increased at intervals of not less than 1 week up to a maximum of 200 mg daily.

While the optimum duration of sertraline therapy required to prevent recurrence of PTSD has not been established to date, this disorder is chronic and it is reasonable to continue therapy in responding patients. Whether the dose of sertraline required to induce remission is identical to the dose needed to maintain and/or sustain remission in patients with this disorder is unknown. Systematic evaluation of sertraline has shown that its efficacy in the management of posttraumatic stress disorder is maintained for periods of up to 28 weeks in patients receiving 50–200 mg daily. The usefulness of the drug in patients receiving prolonged therapy should be reevaluated periodically.

Premenstrual Dysphoric Disorder For the treatment of premenstrual dysphoric disorder (previously late luteal-phase dysphoric disorder), the recommended initial dosage of sertraline is 50 mg daily given continuously throughout the menstrual cycle or given during the luteal-phase only (i.e., starting 2 weeks prior to the anticipated onset of menstruation and continuing through the first full day of menses). If no clinical improvement is apparent, dosage may be increased in 50-mg increments at the onset of each new menstrual cycle up to a maximum of 150 mg daily when administered continuously or 100 mg daily when administered during the luteal-phase only. If a dosage of 100 mg daily has been established with luteal phase dosing, dosages should be increased gradually over the first 3 days of each luteal phase dosing period. While a relationship between dose and effect in premenstrual dysphoric disorder (PMDD) has not been established, efficacy of the drug was demonstrated in clinical trials employing 50–150 mg daily.

The optimum duration of sertraline therapy required to treat PMDD has not been established to date. The manufacturer states that the efficacy of sertraline therapy beyond 3 menstrual cycles has not been demonstrated in controlled studies. However, because women commonly report that symptoms of PMDD worsen with age until relieved by the onset of menopause, the manufacturer recommends that long-term sertraline therapy be considered in responding women. Dosage adjustments, which may include transfers between dosing regimens (e.g., continuous versus luteal phase dosing), may be needed to maintain the patient on the lowest effective dosage, and patients should be periodically reassessed to determine the need for continued treatment.

Social Phobia For the management of social phobia in adults, the recommended initial dosage of sertraline is 25 mg once daily. After 1 week, the dosage should be increased to 50 mg once daily. If no clinical improvement is apparent, dosage may then be increased at intervals of not less than 1 week up to a maximum of 200 mg daily.

While the optimum duration of sertraline therapy required to prevent recurrence of social phobia symptoms has not been established to date, the manufacturer states that this disorder is chronic and requires several months or longer of sustained therapy. Whether the dose of sertraline required to induce remission is identical to the dose needed to maintain and/or sustain remission in patients with this disorder is unknown. Systematic evaluation of sertraline has shown that its efficacy in the management of social phobia is maintained for periods of up to 24 weeks following 20 weeks of therapy at dosages of 50–200 mg daily. Dosages should be adjusted so that the patient is maintained on the lowest effective dosage, and patients should be reassessed periodically to determine the need for continued therapy.

Premature Ejaculation For the management of premature ejaculation†, sertraline has been given in a dosage of 25–50 mg daily. Alternatively, patients have taken sertraline on an "as needed" basis using doses of 25–50 mg daily.

■ **Dosage in Geriatric Patients** *Major Depressive Disorder* For the management of depressive symptoms associated with dementia of the Alzheimer's type in geriatric patients, some experts recommend an initial sertraline dosage of 12.5–25 mg once daily. The dosage may then be gradually increased at intervals of 1–2 weeks up to a maximum dosage of 150–200 mg once daily.

■ **Dosage in Renal and Hepatic Impairment** The manufacturers state that, based on the pharmacokinetics of sertraline, there is no need for dosage adjustment in patients with renal impairment. Because sertraline does not appear to be removed substantially by dialysis, supplemental doses of the drug probably are unnecessary after dialysis.

Because sertraline is metabolized extensively by the liver, hepatic impairment can affect the elimination of the drug. (See Pharmacokinetics: Elimination.) Therefore, the manufacturers recommend that sertraline be administered with caution and in a reduced dosage or less frequently in patients with hepatic impairment.

■ **Treatment of Pregnant Women during the Third Trimester** Because some neonates exposed to sertraline and other SSRIs or selective serotonin- and norepinephrine-reuptake inhibitors (SNRIs) late in the third trimester of pregnancy have developed severe complications, consideration may be given to cautiously tapering sertraline therapy in the third trimester prior to delivery if the drug is administered during pregnancy. (See Pregnancy, under Cautions: Pregnancy, Fertility, and Lactation.)

Cautions

The adverse effect profile of sertraline is similar to that of other selective serotonin-reuptake inhibitors (SSRIs) (e.g., citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine). Because sertraline is a highly selective serotonin-reuptake inhibitor with little or no effect on other neurotransmitters, the incidence of some adverse effects commonly associated with tricyclic antidepressants, such as anticholinergic effects (dry mouth, constipation), adverse cardiovascular effects, drowsiness, and weight gain, is lower in patients receiving sertraline. However, certain adverse GI (e.g., nausea, diarrhea, anorexia) and nervous system (e.g., tremor, insomnia) effects appear to occur more frequently with sertraline and other SSRIs than with tricyclic antidepressants.

Overall, the adverse effect profile of sertraline in adults with depression, obsessive-compulsive disorder, or panic disorder appears to be similar. In controlled studies, the most common adverse effects occurring more frequently in adults receiving sertraline than in those receiving placebo included GI effects such as nausea, diarrhea or loose stools, dyspepsia, and dry mouth; nervous system effects such as somnolence, dizziness, insomnia, and tremor; sexual dysfunction in males (principally ejaculatory delay); and sweating. Discontinuance of sertraline therapy was required in about 15% of adults in clinical trials, principally because of adverse psychiatric (e.g., somnolence, insomnia, agitation, tremor), other nervous system (e.g., dizziness, headache), GI (e.g., nausea, diarrhea or loose stools, anorexia), or male sexual dysfunction (e.g., ejaculatory delay) effects or because of fatigue.

■ **Nervous System Effects** Headache is the most common adverse nervous system effect of sertraline, occurring in approximately 26% of patients receiving the drug in controlled clinical trials; headache occurred in 23% of those receiving placebo in these trials. Somnolence or drowsiness occurred in about 14% of patients receiving sertraline in controlled clinical trials. Headache or somnolence each required discontinuance of therapy in about 2% of patients. Fatigue has been reported in approximately 12% of patients receiving the drug in clinical trials and required discontinuance of therapy in about 1% of patients; this effect was reported in 8% of those receiving placebo in these trials.

Dizziness occurred in about 13% of patients receiving sertraline in controlled clinical trials and required discontinuance of therapy in less than 1% of patients. Insomnia occurred in about 22% of patients receiving the drug in controlled clinical trials. However, because insomnia is a symptom also associated with depression, relief of insomnia and improvement in sleep patterns may occur when clinical improvement in depression becomes apparent during antidepressant therapy. In clinical trials, about 2% of patients discontinued sertraline because of insomnia.

Tremor occurred in about 9%, nervousness in about 6%, anxiety (which occasionally may be severe [e.g., panic]) in about 4%, paresthesia in about 3%, and agitation in about 6% of patients receiving sertraline in controlled clinical trials. Tremor, agitation, and nervousness resulted in discontinuance of sertraline in about 1% of patients while anxiety resulted in discontinuance in less than 1% of patients in clinical trials. Agitation and anxiety may subside with continued therapy. Hypoesthesia, hypertonia, or malaise occurred in at least 1% of patients receiving sertraline in clinical trials. Impaired concentration, dystonia, or twitching occurred in approximately 0.1–1% of patients receiving sertraline, although these adverse effects have not been definitely attributed to the drug.

The incidence of seizures during sertraline therapy appears to be similar to or less than that observed during therapy with most other currently available antidepressants. Seizures occurred in less than 0.1% of patients receiving sertraline in clinical trials. (See Cautions: Precautions and Contraindications.)

Hypomania and mania have been reported in approximately 0.4% of patients receiving sertraline in controlled clinical trials, which is similar to the incidence reported in patients receiving active control agents (i.e., other antidepressants). In at least 2 patients, hypomanic symptoms occurred after they were receiving sertraline 200 mg daily for approximately 9 weeks. In both patients, the adverse reaction was obviated by a reduction in sertraline dosage. (See Cautions: Precautions and Contraindications.) Such reactions have occurred in patients receiving other antidepressant agents and may be caused by antidepressant-induced functional increases in catecholamine activity within the CNS, resulting in a "switch" from depressive to manic behavior. There is some evidence that patients with bipolar disorder may be more likely to experience antidepressant-induced hypomanic or manic reactions than patients without evidence of this disorder. In addition, limited evidence suggests that such reactions may occur more frequently in bipolar depressed patients receiving tricyclics and tetracyclics (e.g., maprotiline, mianserin [not commercially available in the US]) than in those receiving SSRIs (e.g., citalopram, escitalopram, fluoxetine, paroxetine, sertraline). However, further studies are needed to confirm these findings.

Asthenia has been reported in at least 1% of patients receiving sertraline; however, a causal relationship to the drug has not been established. Confusion, migraine, abnormal coordination, abnormal gait, hyperesthesia, ataxia, depersonalization, hallucinations, hyperkinesia, hypokinesia, nystagmus, vertigo, abnormal dreams, aggressive reaction, amnesia, apathy, paroniria, delusion, depression or aggravated depression, emotional lability, euphoria, abnormal thinking, or paranoid reaction have been reported in 0.1–1% of patients receiving the drug; although these adverse effects have not been definitely attributed to sertraline.

Adverse nervous system effects reported in less than 0.1% of patients receiving sertraline include dysphoria, choreoathetosis, dyskinesia, coma, dysphonia, hyporeflexia, hypotonia, ptosis, somnambulism, and illusion; these effects have not been definitely attributed to the drug. Although a causal relationship has not been established, psychosis, extrapyramidal symptoms, and oculogyric crisis have been reported during postmarketing surveillance. Serotonin syndrome and neuroleptic malignant syndrome (NMS)-like reactions also have been reported in patients receiving sertraline, other SSRIs, and selective serotonin- and norepinephrine-reuptake inhibitors. (See Cautions: Precautions and Contraindications, Drug Interactions: Serotonergic Drugs, and Acute Toxicity.)

A withdrawal syndrome, which also has not been definitely attributed to the drug, has been reported in less than 0.1% of sertraline-treated patients. Fatigue, severe abdominal cramping, memory impairment, and influenza-like symptoms were reported 2 days following the abrupt discontinuance of sertraline in one patient; when sertraline was restarted, the symptoms remitted. Electric shock-like sensations occurred in another patient 1 day after the last administered dose of sertraline; these sensations became less intense and eventually disappeared 13 weeks after sertraline therapy was discontinued. (See Chronic Toxicity.) Forgetfulness, panic attacks, and unspecified pain also have been reported rarely, although a causal relationship to sertraline has not been established. Sertraline also has been reported to precipitate or exacerbate "flashbacks" in patients who previously had used lysergic acid diethylamide (LSD).

Extrapyramidal reactions, including akathisia, stuttering (which may be a speech manifestation of akathisia), bilateral jaw stiffness, and torticollis, have been reported rarely with sertraline use, and such reactions appear to be a class effect of SSRIs and dose related. Reactions occurring *early* during therapy with these drugs may be secondary to preexisting parkinsonian syndrome and/or concomitant therapy.

Suicidality Suicidal ideation has been reported in less than 0.1% of adults receiving sertraline. The US Food and Drug Administration (FDA) has determined that antidepressants increase the risk of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults (18–24 years of age) with major depressive disorder and other psychiatric disorders. (See Suicidality, under Cautions: Nervous System Effects, in Paroxetine 28:16.04.20.) Patients, therefore, should be appropriately monitored and closely observed for clinical worsening, suicidality, and unusual changes in behavior, particularly during initiation of sertraline therapy (i.e., the first few months) and during periods of dosage adjustments. (See Cautions: Precautions and Contraindications and Cautions: Pediatric Precautions.)

■ **GI Effects** Like other selective serotonin-reuptake inhibitors (e.g., citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine), sertraline therapy is associated with a relatively high incidence of GI disturbances, principally nausea, dry mouth, and diarrhea/loose stools. The most frequent adverse effect associated with sertraline therapy is nausea, which occurred in about 28% of patients receiving the drug in controlled clinical trials. In clinical trials, nausea required discontinuance of sertraline in about 4% of patients. In general, the incidence of nausea associated with selective serotonin-reuptake inhibitors appears to be higher when therapy is initiated with high doses but decreases as therapy with these drugs is continued. While the mechanism(s) of sertraline-induced GI effects has not been fully elucidated, they appear to arise at least in part because of increased serotonergic activity in the GI tract (which may result in stimulation of small intestine motility and inhibition of gastric and large intestine motility) and possibly because of the drug's effect on central serotonergic type 3 (5-HT_3) receptors.

Diarrhea or loose stools occurred in about 20%, dry mouth in about 15%, constipation in about 7%, dyspepsia in about 8%, or anorexia in about 6% of patients receiving sertraline in controlled clinical trials. Other adverse GI effects associated with sertraline therapy include vomiting which occurred in about 4% and flatulence which occurred in about 3% of patients receiving the drug in controlled clinical trials. Abdominal pain was reported in approximately 2% and taste perversion in about 1% of patients receiving sertraline. In clinical trials, diarrhea or loose stools required discontinuance of sertraline in about 3% of patients and dry mouth required discontinuance of therapy in about 1% of patients.

Epidemiologic case-control and cohort design studies have suggested that selective serotonin-reuptake inhibitors may increase the risk of upper GI bleeding. Although the precise mechanism for this increased risk remains to be clearly established, serotonin release by platelets is known to play an important role in hemostasis, and selective serotonin-reuptake inhibitors decrease serotonin uptake from the blood by platelets thereby decreasing the amount of serotonin in platelets. In addition, concurrent use of aspirin or other nonsteroidal anti-inflammatory drugs was found to substantially increase the risk of GI bleeding in patients receiving selective serotonin-reuptake inhibitors in 2 of these studies. Although these studies focused on upper GI bleeding, there is some evidence suggesting that bleeding at other sites may be similarly potentiated. Further clinical studies are needed to determine the clinical importance of these findings. (See Cautions: Hematologic Effects, and see also Drug Interactions: Drugs Affecting Hemostasis.)

Although a causal relationship to sertraline has not been established, dysphagia, esophagitis, aggravation of dental caries, gastroenteritis, eructation, and increased salivation have been reported in 0.1–1% of patients receiving the drug. Aphthous stomatitis, ulcerative stomatitis, stomatitis, tongue ulceration or edema, glossitis, diverticulitis, gastritis, hemorrhagic peptic ulcer, rectal hemorrhage, colitis, proctitis, fecal incontinence, melena, or tenesmus has been reported in less than 0.1% of patients receiving sertraline; however, these adverse effects have not been definitely attributed to the drug. Pancreatitis also has been reported rarely in association with sertraline; however, a causal relationship to the drug has not been clearly established.

Although a causal relationship has not been established, nocturnal bruxism (clenching and/or grinding of the teeth during sleep) has developed within 2–4 weeks following initiation of sertraline or fluoxetine therapy in several patients. The bruxism remitted upon reduction in dosage of the serotonin-reuptake inhibitor and/or the addition of buspirone therapy.

Speech blockage also has been reported in at least one sertraline-treated patient.

■ **Dermatologic and Sensitivity Reactions** Sweating occurred in about 7% of patients receiving sertraline in controlled clinical trials.

Rash, which may be erythematous, follicular, maculopapular, or pustular, has been reported in about 3% of patients receiving sertraline in controlled clinical trials. Adverse dermatologic effects reported in 0.1–1% of patients receiving sertraline in controlled clinical trials include acne, alopecia, dry skin, urticaria, pruritus, and photosensitivity reaction (which may be severe); however, these adverse effects have not been definitely attributed to sertraline. Bullous eruption, eczema, contact dermatitis, skin discoloration, and hypertrichosis have been reported in less than 0.1% of patients receiving the drug, although a causal relationship to sertraline has not been established. Allergy, allergic reaction, and angioedema also have been reported rarely.

Other dermatologic and sensitivity events, which can be severe and potentially may be fatal, reported during the postmarketing surveillance of sertraline have included anaphylactoid reaction, angioedema, Stevens-Johnson syndrome, erythema multiforme, and vasculitis.

■ **Metabolic Effects** Thirst has been reported in 0.1–1% of patients receiving sertraline in controlled clinical trials.

Weight loss occurred in 0.1–1% of patients receiving sertraline. In controlled clinical trials, patients lost an average of about 0.45–0.9 kg while receiving sertraline. Rarely, weight loss has required discontinuance of therapy. Like fluoxetine, sertraline exhibits anorexigenic activity and can cause anorexia, which may be more pronounced in overweight patients and those with carbohydrate craving. Anorexia occurred in about 3% of patients receiving sertraline in controlled clinical trials and required discontinuance in at least 1% of patients. Increased appetite and weight gain have been reported in at least 1% of patients receiving sertraline in controlled clinical trials, although a causal relationship to the drug has not been established. (See Cautions: Pediatric Precautions.)

Sertraline use has been associated with small mean decreases (approximately 7%) in serum uric acid concentration as a result of a weak uricosuric effect; the clinical importance is not known and there have been no cases of acute renal failure associated with the drug. Small mean increases in serum total cholesterol (about 3%) and triglyceride (about 5%) concentrations also have been reported in patients receiving sertraline. Hypercholesterolemia has been reported in less than 0.1% of patients. Other adverse effects reported in less than 0.1% of patients receiving the drug include dehydration and hypoglycemia. These adverse effects have not been definitely attributed to sertraline.

■ **Ocular and Otic Effects** Abnormal vision (including blurred vision) occurred in about 4% of patients receiving sertraline in controlled clinical trials. Adverse ocular effects reported in 0.1–1% of patients receiving sertraline include abnormality of accommodation, conjunctivitis, mydriasis, and ocular pain. Although a causal relationship to sertraline has not been established, anisocoria, abnormal lacrimation, xerophthalmia, diplopia, scotoma, visual field defect, exophthalmos, hemorrhage of the anterior chamber of the eye,

glaucoma, or photophobia has been reported in less than 0.1% of patients receiving the drug. Other adverse ocular effects reported during postmarketing surveillance of sertraline have included blindness, optic neuritis, and cataract; however, a causal relationship to the drug has not been established.

Tinnitus occurred in at least 1% of patients receiving sertraline in controlled clinical trials. Earache has been reported in 0.1–1% of patients, and hyperacusis and labyrinthine disorder have been reported in less than 0.1% of patients.

■ **Cardiovascular Effects** Sertraline does not exhibit clinically important anticholinergic activity, and current evidence suggests that sertraline is less cardiotoxic than many antidepressant agents (e.g., tricyclic antidepressants, monoamine oxidase inhibitors). (See Cardiovascular Considerations in Uses: Major Depressive Disorder and see also Pharmacology: Cardiovascular Effects.) However, bradycardia, AV block, atrial arrhythmias, QT-interval prolongation, and ventricular tachycardia (including torsades de pointes-type arrhythmias) have been reported during postmarketing surveillance evaluations of the drug.

Hot flushes occurred in about 2% of patients receiving sertraline in controlled clinical trials. Palpitation and chest pain have been reported in at least 1% of patients receiving sertraline in controlled clinical trials. In one patient with underlying coronary artery disease, chest pain developed suddenly and was relieved with sublingual nitroglycerin but was not associated with ECG changes; the mechanism of this effect, particularly regarding any potential cardiovascular effect, is unclear and alternative mechanisms (e.g., GI) for the chest pain have been proposed.

Unlike tricyclic antidepressants, sertraline has been associated with hypotension (e.g., orthostatic) infrequently; in controlled clinical trials, postural effects (e.g., dizziness, hypotension [which can also be nonpostural]) occurred in 0.1–1% of patients receiving sertraline. Syncope also occurred in at least 0.1% of patients.

Hypertension, peripheral ischemia, and tachycardia have been reported in 0.1–1% of patients receiving the drug, although a definite causal relationship to sertraline has not been established. Precordial or substernal chest pain, aggravated hypertension, myocardial infarction, pallor, vasodilation, and cerebrovascular disorder have been reported in less than 0.1% of patients receiving sertraline; these adverse effects have not been definitely attributed to the drug.

Generalized, dependent, periorbital, or peripheral edema has been reported in at least 0.1% of patients receiving sertraline, and facial edema has been reported rarely. However, a causal relationship to the drug has not been established.

■ **Musculoskeletal Effects** Myalgia or back pain occurred in at least 1% of patients receiving sertraline in controlled clinical trials. Arthralgia, arthrosis, leg or other muscle cramps, or muscle weakness has been reported in 0.1–1% of patients receiving sertraline; these adverse effects have not been definitely attributed to the drug.

■ **Hematologic Effects** Purpura, aplastic anemia, pancytopenia, leukopenia, thrombocytopenia, and abnormal bleeding have been reported occasionally in patients receiving sertraline; however, these adverse effects have not been definitely attributed to the drug.

Altered platelet function and/or abnormal platelet laboratory results have been reported rarely, but a causal relationship to sertraline remains to be established. In addition, in at least one patient with idiopathic thrombocytopenic purpura, sertraline therapy was associated with an increase in platelet counts. Anemia has been reported in less than 0.1% of patients receiving sertraline, although a causal relationship to the drug has not been established. Neutropenia also has been reported rarely with sertraline use and has been a reason for drug discontinuance. Agranulocytosis and septic shock developed in a geriatric woman who had been receiving sertraline for about 1 month in addition to atenolol, bendroflumethiazide, and thioridazine; the patient responded to anti-infective and granulocyte colony-stimulating factor therapy and made a full recovery within 10 days.

Bleeding complications (e.g., ecchymosis, purpura, menorrhagia, rectal bleeding) have been reported infrequently in patients receiving selective serotonin-reuptake inhibitors. Although the precise mechanism for these reactions has not been established, it has been suggested that impaired platelet aggregation and prolonged bleeding time may be due at least in part to inhibition of serotonin reuptake into platelets and/or that increased capillary fragility and vascular tone may contribute to these cases. (See Cautions: GI Effects and see also Drug Interactions: Drugs Affecting Hemostasis.)

■ **Respiratory Effects** Rhinitis or yawning has been reported in at least 1% of patients receiving sertraline in controlled clinical trials. Adverse respiratory effects reported in 0.1–1% of patients receiving the drug include bronchospasm, dyspnea, epistaxis, upper respiratory tract infection, sinusitis, and coughing; however, a definite causal relationship to sertraline has not been established. Adverse respiratory effects reported in less than 0.1% of patients receiving sertraline include bradypnea, hypoventilation, hyperventilation, apnea, stridor, hiccups, hemoptysis, bronchitis, laryngismus, and laryngitis. Pulmonary hypertension also has been reported during postmarketing surveillance evaluations of the drug. However, these adverse effects have not been definitely attributed to the drug.

■ **Renal, Electrolyte, and Genitourinary Effects** ***Sexual Dysfunction*** Like other selective serotonin-reuptake inhibitors, adverse effects on sexual function have been reported in both men and women receiving sertraline. Although changes in sexual desire, sexual performance, and sexual satisfaction often occur as manifestations of a psychiatric disorder, they also may occur as the result of pharmacologic therapy. It is difficult to determine the true incidence and severity of adverse effects on sexual function during sertraline therapy, in part because patients and clinicians may be reluctant to discuss these effects. Therefore, incidence data reported in product labeling and earlier studies are most likely underestimates of the true incidence of adverse sexual effects. Recent reports indicate that up to 50% of patients receiving selective serotonin-reuptake inhibitors describe some form of sexual dysfunction during treatment and the actual incidence may be even higher.

Sexual dysfunction (principally ejaculatory delay) is the most common adverse urogenital effect of sertraline in males, occurring in about 14% of male patients receiving the drug in controlled clinical trials. In some cases, this effect has been used for therapeutic benefit in the treatment of premature ejaculation. (See Uses: Premature Ejaculation.) Impotence has occurred in at least 1% of male patients receiving sertraline in controlled trials, and priapism has been reported rarely. Female sexual dysfunction (e.g., anorgasmia) has been reported in at least 1% of female patients receiving the drug in controlled clinical trials. Decreased libido has been reported in males and females, occurring in 6% of patients in controlled clinical studies. Sexual dysfunction (principally ejaculatory delay) required discontinuance of therapy in at least 1% of patients in controlled clinical trials. Increased libido has been reported in less than 1% of patients receiving the drug.

Results of some (but not all) studies in men and women suggest that paroxetine may be associated with a higher incidence of sexual dysfunction than some other currently available selective serotonin-reuptake inhibitors, including sertraline and citalopram. Since it is difficult to know the precise risk of sexual dysfunction associated with serotonin-reuptake inhibitors, clinicians should routinely inquire about such possible adverse effects in patients receiving these drugs.

The long-term effects of selective serotonin-reuptake inhibitors on sexual function have not been fully determined to date. In a double-blind study evaluating 6 months of sertraline or citalopram therapy in depressed patients, sexual desire and overall sexual functioning (as mensured on the UKU Side Effect Scale) substantially improved in women and sexual desire improved in men. In men, no change in orgasmic dysfunction, erectile dysfunction, or overall sexual functioning was reported after 6 months of therapy with sertraline or citalopram, although there was a trend toward worsening of ejaculatory dysfunction. However, in the subgroups of women and men reporting no sexual problems at baseline, approximately 12% of women reported decreased sexual desire and 14% reported orgasmic dysfunction after 6 months of citalopram therapy; the corresponding figures in the same subgroup of men were approximately 17 and 19%, respectively, and as many as 25% experienced ejaculatory dysfunction after 6 months. No substantial differences between sertraline and citalopram were reported in this study.

Management of sexual dysfunction caused by selective serotonin-reuptake inhibitor therapy includes waiting for tolerance to develop; using a lower dosage of the drug; using drug holidays; delaying administration of the drug until after coitus; or changing to another antidepressant. Although further study is needed, there is some evidence that adverse sexual effects of the selective serotonin-reuptake inhibitors may be reversed by concomitant use of certain drugs, including buspirone, 5-hydroxytryptamine-2 (5-HT_2) receptor antagonists (e.g., nefazodone), 5-HT_3 receptor inhibitors (e.g., granisetron), or α_2-adrenergic receptor antagonists (e.g., yohimbine), selective phosphodiesterase (PDE) inhibitors (e.g., sildenafil), or dopamine receptor agonists (e.g., amantadine, dextroamphetamine, pemoline [no longer commercially available in the US], methylphenidate). In most patients, sexual dysfunction is fully reversed 1–3 days after discontinuance of the antidepressant.

Other Renal, Electrolyte, and Genitourinary Effects Although a definite causal relationship to sertraline has not been established, menstrual disorders, dysmenorrhea, intermenstrual bleeding, amenorrhea, vaginal hemorrhage, and leukorrhea have been reported in 0.1–1% of patients receiving sertraline. In addition, menorrhagia, breast enlargement, female breast pain or tenderness, acute mastitis in females, gynecomastia, and atrophic vaginitis have been reported in less than 0.1% of patients receiving sertraline; however, a causal relationship to the drug has not been clearly established.

Treatment with SSRIs, including sertraline, and selective serotonin- and norepinephrine-reuptake inhibitors (SNRIs) may result in hyponatremia. In many cases, this hyponatremia appears to be due to the syndrome of inappropriate antidiuretic hormone secretion (SIADH) and was reversible when the SSRI or SNRI was discontinued. Cases with serum sodium concentrations lower than 110 mEq/L have been reported. Hyponatremia and SIADH in patients receiving SSRIs usually develop an average of 2 weeks after initiating therapy (range: 3–120 days). Geriatric individuals and patients receiving diuretics or who are otherwise volume depleted may be at greater risk of developing hyponatremia during therapy with SSRIs or SNRIs. Discontinuance of sertraline should be considered in patients with symptomatic hyponatremia and appropriate medical intervention should be instituted. Because geriatric patients may be at increased risk for hyponatremia associated with these drugs, clinicians prescribing sertraline in such patients should be aware of the possibility that such reactions may occur. In addition, periodic monitoring of serum sodium concentrations (particularly during the first several months) in geriatric patients receiving SSRIs has been recommended by some clinicians.

A variety of urinary disorders, including urinary frequency, polyuria, urinary hesitancy and/or retention, dysuria, nocturia, and urinary incontinence, has been reported in 0.1–1% of patients receiving sertraline; however, these

effects have not been definitely attributed to the drug. In addition, cystitis, oliguria, pyelonephritis, hematuria, renal pain, strangury, and balanoposthitis have been reported in less than 0.1% of patients receiving sertraline, although a causal relationship to the drug has not been clearly established.

■ **Hepatic Effects** Impaired hepatic function has been reported in less than 1% of patients receiving sertraline in controlled clinical trials; in most cases, such reactions appeared to be reversible upon discontinuance of sertraline therapy. Asymptomatic elevations in serum AST (SGOT) and ALT (SGPT) concentrations have been reported in approximately 0.8% of patients receiving the drug and occasionally have been a reason for drug discontinuance. Elevations in aminotransferase concentrations usually occurred within the first 1–9 weeks of sertraline therapy and were rapidly reversible following discontinuance of the drug. In addition, in at least 2 patients, elevated liver enzymes returned to normal levels with continued therapy.

Increased serum alkaline phosphatase and bilirubin concentrations occurred rarely in patients receiving sertraline in clinical trials and required discontinuance of therapy in some cases. Other clinical features associated with adverse hepatic reactions that have been reported in at least one patient include hepatitis, hepatomegaly, jaundice, abdominal pain, vomiting, hepatic failure, and death. However, these effects have not been definitely attributed to the drug.

■ **Endocrine Effects** Low levels of total thyroxine developed in a depressed adolescent who had been receiving sertraline therapy; however, it appears that sertraline only displaced the bound fraction of total thyroxine but was not associated with true hypothyroidism. In a limited number of hypothyroid patients receiving thyroxine therapy, elevated serum thyrotropin and reduced serum thyroxine concentrations have been observed following the initiation of sertraline therapy. Hypothyroidism also has been reported. (See Cautions: Precautions and Contraindications.)

Hyperprolactinemia and galactorrhea also have been reported rarely; however, a causal relationship to the drug has not been established.

■ **Other Adverse Effects** Cold clammy skin, flushing, fever, or rigors has been reported in 0.1–1% of patients receiving the drug, although a causal relationship to sertraline has not been established. In addition, lupus-like syndrome and serum sickness have been reported during postmarketing surveillance evaluations of the drug; however, a causal relationship has not been definitively established.

■ **Precautions and Contraindications** Worsening of depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior may occur in both adult and pediatric (see Cautions: Pediatric Precautions) patients with major depressive disorder or other psychiatric disorders, whether or not they are taking antidepressants. This risk may persist until clinically important remission occurs. Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are the strongest predictors of suicide. However, there has been a long-standing concern that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients during the early phases of treatment. Pooled analyses of short-term, placebo-controlled studies of antidepressants (i.e., selective serotonin-reuptake inhibitors [SSRIs] and other antidepressants) have shown an increased risk of suicidality in children, adolescents, and young adults (18–24 years of age) with major depressive disorder and other psychiatric disorders. An increased suicidality risk was not demonstrated with antidepressants compared to placebo in adults older than 24 years of age and a reduced risk was observed in adults 65 years of age or older. It currently is unknown whether the suicidality risk extends to longer-term use (i.e., beyond several months); however, there is substantial evidence from placebo-controlled maintenance trials in adults with major depressive disorder that antidepressants can delay the recurrence of depression.

The US Food and Drug Administration (FDA) recommends that all patients being treated with antidepressants for any indication be appropriately monitored and closely observed for clinical worsening, suicidality, and unusual changes in behavior, particularly during initiation of therapy (i.e., the first few months) and during periods of dosage adjustments. Families and caregivers of patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and nonpsychiatric, also should be advised to monitor patients on a daily basis for the emergence of agitation, irritability, or unusual changes in behavior as well as the emergence of suicidality, and to report such symptoms immediately to a health-care provider. (See Suicidality under Cautions: Nervous System Effects, in Paroxetine 28:16.04.20.)

Although a causal relationship between the emergence of symptoms such as anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia, hypomania, and/or mania and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality. Consequently, consideration should be given to changing the therapeutic regimen, or discontinuing therapy in patients whose depression is persistently worse or in patients experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, particularly if such manifestations are severe, abrupt in onset, or were not part of the patient's presenting symptoms. If a decision is made to discontinue therapy, sertraline dosage should be tapered as rapidly as is feasible but with recognition of the risks of abrupt discontinuance. (See Dosage and Administration: Dosage.) FDA also recommends that the drugs be prescribed in the smallest quantity consistent with good patient management, in order to reduce the risk of overdosage.

It is generally believed (though not established in controlled trials) that treating a major depressive episode with an antidepressant alone may increase the likelihood of precipitating a mixed or manic episode in patients at risk for bipolar disorder. Therefore, patients should be adequately screened for bipolar disorder prior to initiating treatment with an antidepressant; such screening should include a detailed psychiatric history (e.g., family history of suicide, bipolar disorder, and depression).

Potentially life-threatening serotonin syndrome or neuroleptic malignant syndrome (NMS)-like reactions have been reported with SSRIs, including sertraline, and selective serotonin- and norepinephrine-reuptake inhibitors (SNRIs) alone, but particularly with concurrent administration of other serotonergic drugs (including serotonin [5-hydroxytryptamine; 5-HT] type 1 receptor agonists ["triptans"]), drugs that impair the metabolism of serotonin (e.g., monoamine oxidase [MAO] inhibitors), or antipsychotic agents or other dopamine antagonists. Symptoms of serotonin syndrome may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination), and/or GI symptoms (e.g., nausea, vomiting, diarrhea). In its most severe form, serotonin syndrome may resemble NMS, which is characterized by hyperthermia, muscle rigidity, autonomic instability with possible rapid fluctuation in vital signs, and mental status changes. Patients receiving sertraline should be monitored for the development of serotonin syndrome or NMS-like signs and symptoms.

Concurrent or recent (i.e., within 2 weeks) therapy with MAO inhibitors used for treatment of depression is contraindicated in patients receiving sertraline and vice versa. If concurrent therapy with sertraline and a 5-HT_1 receptor agonist (triptan) is clinically warranted, the patient should be observed carefully, particularly during initiation of therapy, when dosage is increased, or when another serotonergic agent is initiated. Concomitant use of sertraline and serotonin precursors (e.g., tryptophan) is not recommended. If signs and symptoms of serotonin syndrome or NMS develop during sertraline therapy, treatment with sertraline and any concurrently administered serotonergic or antidopaminergic agents, including antipsychotic agents, should be discontinued immediately and supportive and symptomatic treatment should be initiated. (See Drug Interactions: Serotonergic Drugs.)

The dropper dispenser provided with Zoloft® oral solution contains natural latex proteins in the form of dry natural rubber which may cause sensitivity reactions in susceptible individuals.

Because clinical experience with sertraline in patients with certain concurrent systemic disease, including cardiovascular disease and renal impairment, is limited, caution should be exercised when sertraline is administered to patients with any systemic disease or condition that may alter metabolism of the drug or adversely affect hemodynamic function. (See Dosage and Administration: Dosage.)

Sertraline should be used with caution in patients with hepatic impairment, since prolonged elimination of the drug has been reported to occur in patients with liver cirrhosis. (See Pharmacokinetics: Elimination and see Dosage and Administration: Dosage in Renal and Hepatic Impairment.)

The manufacturers recommend that patients receiving sertraline be advised to notify their clinician if they are taking or plan to take nonprescription (over-the-counter) or prescription medications or alcohol-containing beverages or preparations. Although no interactions with nonprescription medications have been reported to date, the potential for such adverse drug interactions exists. Therefore, the use of any nonprescription medication should be initiated cautiously according to the directions of use provided on the nonprescription medication. Although sertraline has not been shown to potentiate the impairment of mental and motor skills caused by alcohol, the manufacturers recommend that patients be advised to avoid alcohol while receiving the drug.

Sertraline generally is less sedating than most other currently available antidepressants and does not appear to produce substantial impairment of cognitive or psychomotor function. However, patients should be cautioned that sertraline may impair their ability to perform activities requiring mental alertness or physical coordination (e.g., operating machinery, driving a motor vehicle) and to avoid such activities until they experience how the drug affects them. Because the risk of using sertraline concomitantly with other CNS active drugs has not been evaluated systematically to date, the manufacturers recommend that such therapy be employed cautiously.

Seizures have been reported in patients receiving therapeutic dosages of sertraline. Because of limited experience with sertraline in patients with a history of seizures, the drug should be used with caution in such patients.

Activation of mania and hypomania has occurred in patients receiving therapeutic dosages of sertraline. The drug should be used with caution in patients with a history of mania or hypomania.

Treatment with SSRIs, including sertraline, and selective serotonin- and norepinephrine-reuptake inhibitors (SNRIs) may result in hyponatremia. In many cases, this hyponatremia appears to be due to the syndrome of inappropriate antidiuretic hormone secretion (SIADH) and was reversible when sertraline was discontinued. Cases with serum sodium concentrations lower than 110 mEq/L have been reported. Geriatric individuals and patients receiving diuretics or who are otherwise volume depleted may be at greater risk of developing hyponatremia during therapy with SSRIs or SNRIs. Signs and symptoms of hyponatremia include headache, difficulty concentrating, memory impairment, confusion, weakness, and unsteadiness, which may lead to falls; more severe and/or acute cases have been associated with hallucinations, syncope, seizures, coma, respiratory arrest, and death. Discontinuance of sertraline

should be considered in patients with symptomatic hyponatremia and appropriate medical intervention should be instituted. (See Cautions: Renal, Electrolyte, and Genitourinary Effects and see also Cautions: Geriatric Precautions.)

Altered platelet function has been reported rarely in patients receiving sertraline. In addition, use of the drug has been associated with several reports of abnormal bleeding or purpura. While a causal relationship to sertraline remains to be established, pending such establishment, the drug should be used with caution in patients with an underlying coagulation defect since the possible effects on hemostasis may be exaggerated in such patients. (See Cautions: Hematologic Effects.)

Sertraline has a weak uricosuric effect. (See Cautions: Metabolic Effects.) Pending further elucidation of the clinical importance, if any, of this effect, the drug should be used with caution in patients who may be adversely affected (e.g., those at risk for acute renal failure).

Because sertraline therapy has been associated with anorexia and weight loss (see Cautions: Metabolic Effects), the drug should be used with caution in patients who may be adversely affected by these effects (e.g., underweight patients).

Like many other antidepressant drugs, sertraline has been associated with hypothyroidism, elevated serum thyrotropin, and/or reduced serum thyroxine concentrations in a limited number of patients. Because of reports with other antidepressant agents and the complex interrelationship between the hypothalamic-pituitary-thyroid axis and affective (mood) disorders, at least one manufacturer recommends that thyroid function be reassessed periodically in patients with thyroid disease who are receiving sertraline.

Commercially available sertraline hydrochloride oral solution (Zoloft®) contains alcohol. Therefore, concomitant use of sertraline hydrochloride oral solution and disulfiram is contraindicated.

Sertraline is contraindicated in patients concurrently receiving pimozide. (See Drug Interactions: Pimozide.)

Sertraline also is contraindicated in patients who are hypersensitive to the drug or any ingredient in the formulation.

■ **Pediatric Precautions** Safety and efficacy of sertraline in children with obsessive-compulsive disorder (OCD) younger than 6 years of age have not been established. Safety and efficacy of sertraline in children with other disorders (e.g., major depressive disorder, panic disorder, posttraumatic stress disorder, premenstrual dysphoric disorder, social phobia) have not been established. The overall adverse effect profile of sertraline in over 600 pediatric patients who received sertraline in controlled clinical trials was generally similar to that seen in the adult clinical studies. However, adverse effects reported in at least 2% of the sertraline-treated pediatric patients in these trials and that occurred at least twice as frequently as in pediatric patients receiving placebo included fever, hyperkinesia, urinary incontinence, aggressive reaction, sinusitis, epistaxis, and purpura.

Efficacy of sertraline in pediatric patients with major depressive disorder was evaluated in 2 randomized, 10-week, double-blind, placebo-controlled, flexible-dose (50–200 mg daily) trials in 373 children and adolescents with major depressive disorder, but data from these studies were not sufficient to establish efficacy in pediatric patients. In a safety analysis of the pooled data from these 2 studies, a difference in weight change between the sertraline and placebo groups was noted of approximately 1 kg for both pediatric patients (6–11 years of age) and adolescents (12–17 years of age) representing a slight weight loss for those receiving sertraline and a slight weight gain for those receiving placebo. In addition, a larger difference was noted in children than in adolescents between the sertraline and placebo groups in the proportion of outliers for clinically important weight loss; about 7% of the children and about 2% of the adolescents receiving sertraline in these studies experienced a weight loss of more than 7% of their body weight compared with none of those receiving placebo.

A subset of patients who completed these controlled trials was continued into a 24-week, flexible-dose, open-label, extension study. A mean weight loss of approximately 0.5 kg was observed during the initial 8 weeks of treatment for those pediatric patients first exposed to sertraline during the extension study, which was similar to the weight loss observed among sertraline-treated patients during the first 8 weeks of the randomized controlled trials. The patients continuing in the extension study began gaining weight relative to their baseline weight by week 12 of sertraline therapy, and patients who completed the entire 34 weeks of therapy with the drug had a weight gain that was similar to that expected using data from age-adjusted peers. The manufacturers state that periodic monitoring of weight and growth is recommended in pediatric patients receiving long-term therapy with sertraline or other selective serotonin-reuptake inhibitors (SSRIs).

FDA warns that antidepressants increase the risk of suicidal thinking and behavior (suicidality) in children and adolescents with major depressive disorder and other psychiatric disorders. The risk of suicidality for these drugs was identified in a pooled analysis of data from a total of 24 short-term (4–16 weeks), placebo-controlled studies of 9 antidepressants (i.e., sertraline, bupropion, citalopram, fluoxetine, fluvoxamine, mirtazapine, nefazodone, paroxetine, venlafaxine) in over 4400 children and adolescents with major depressive disorder, OCD, or other psychiatric disorders. The analysis revealed a greater risk of adverse events representing suicidal behavior or thinking (suicidality) during the first few months of treatment in pediatric patients receiving antidepressants than in those receiving placebo. However, a more recent meta-analysis of 27 placebo-controlled trials of 9 antidepressants (SSRIs and others) in patients younger than 19 years of age with major depressive disorder, OCD, or non-OCD anxiety disorders suggests that the benefits of antidepressant therapy in treating these conditions may outweigh the risks of suicidal behavior or suicidal ideation. No suicides occurred in these pediatric trials.

The risk of suicidality in FDA's pooled analysis differed across the different psychiatric indications, with the highest incidence observed in the major depressive disorder studies. In addition, although there was considerable variation in risk among the antidepressants, a tendency toward an increase in suicidality risk in younger patients was found for almost all drugs studied. It is currently unknown whether the suicidality risk in pediatric patients extends to longer-term use (i.e., beyond several months). (See Suicidality, under Cautions: Nervous System Effects, in Paroxetine 28:16.04.20.)

As a result of this analysis and public discussion of the issue, FDA has directed manufacturers of all antidepressants to add a boxed warning to the labeling of their products to alert clinicians of this suicidality risk in children and adolescents and to recommend appropriate monitoring and close observation of patients receiving these agents. (See Cautions: Precautions and Contraindications.) The drugs that are the focus of the revised labeling are all drugs included in the general class of antidepressants, including those that have not been studied in controlled clinical trials in pediatric patients, since the available data are not adequate to exclude any single antidepressant from an increased risk. In addition to the boxed warning and other information in professional labeling on antidepressants, FDA currently recommends that a patient medication guide explaining the risks associated with the drugs be provided to the patient each time the drugs are dispensed. Caregivers of pediatric patients whose depression is persistently worse or who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality during antidepressant therapy should consult their clinician regarding the best course of action (e.g., whether the therapeutic regimen should be changed or the drugs discontinued). *Patients should not discontinue use of selective serotonin-reuptake inhibitors without first consulting their clinician; it is very important that the drugs not be abruptly discontinued (see Dosage and Administration: Dosage), as withdrawal effects may occur.*

Anyone considering the use of sertraline in a child or adolescent for any clinical use must balance the potential risk of therapy with the clinical need.

■ **Geriatric Precautions** In clinical studies in geriatric patients, 660 patients receiving sertraline for the treatment of depression were 65 years of age or older, and 180 were 75 years of age or older. No overall differences in efficacy or adverse effects were observed for geriatric patients in these studies relative to younger patients, and other clinical experience has revealed no evidence of age-related differences in safety. In addition, no adverse effects on psychomotor performance were observed in geriatric individuals who received the drug in one controlled study. However, the possibility that older patients may exhibit increased sensitivity to the drug cannot be excluded. (See Dosage in Geriatric Patients under Dosage and Administration.)

Limited evidence suggests that geriatric patients may be more likely than younger patients to develop sertraline-induced hyponatremia and transient syndrome of inappropriate secretion of antidiuretic hormone (SIADH). Therefore, clinicians prescribing sertraline in geriatric patients should be aware of the possibility that such reactions may occur. Periodic monitoring (especially during the first several months) of serum sodium concentrations in geriatric patients receiving the drug has been recommended by some clinicians. (See Cautions: Precautions and Contraindications.)

As with other psychotropic drugs, geriatric patients receiving antidepressants appear to have an increased risk of hip fracture. Despite the fewer cardiovascular and anticholinergic effects associated with selective serotonin-reuptake inhibitors (SSRIs), these drugs did not show any advantage over tricyclic antidepressants with regard to hip fracture in a case-control study. In addition, there was little difference in the rates of falls between nursing home residents receiving SSRIs and those receiving tricyclic antidepressants in a retrospective study. Therefore, all geriatric individuals receiving either type of antidepressant should be considered to be at increased risk of falls and appropriate measures should be taken.

In pooled data analyses, a *reduced* risk of suicidality was observed in adults 65 years of age or older with antidepressant therapy compared with placebo. (See Cautions: Precautions and Contraindications.)

Plasma clearance of sertraline may be decreased in geriatric patients; plasma clearance of the less active metabolite, *N*-desmethylsertraline, also may be decreased in older males.

■ **Mutagenicity and Carcinogenicity** Sertraline was not mutagenic, with or without metabolic activation, in several in vitro tests including the bacterial mutation assay and the mouse lymphoma mutation assay. Sertraline also was not mutagenic in tests for cytogenetic aberrations in vivo in mouse bone marrow and in vitro in human lymphocytes.

Lifetime studies to determine the carcinogenic potential of sertraline were performed in CD-1 mice and Long-Evans rats receiving dosages up to 40 mg/kg daily. This dosage corresponded to 1 and 2 times the maximum recommended human dose on a mg/m² basis in mice and rats, respectively. There was a dose-related increase in the incidence of hepatic adenomas in male mice receiving sertraline dosages of 10–40 mg/kg (0.25–1 times the maximum recommended human dose on a mg/m² basis). No increase was seen in female mice or in rats of either gender receiving the same dosages, nor was there an increase in hepatocellular carcinomas. Hepatic adenomas have a variable rate of spontaneous occurrence in this strain of mice, and the relevance of this finding to humans is not known. There was an increase in follicular adenomas

of the thyroid, not accompanied by thyroid hyperplasia, in female rats receiving a sertraline dosage of 40 mg/kg (2 times the maximum recommended human dose on a mg/m² basis). There also was an increase in uterine adenocarcinomas in rats receiving sertraline dosages of 10–40 mg/kg (0.5–2 times the maximum recommended human dose on a mg/m² basis); however, this effect could not be directly attributed to the drug.

■ **Pregnancy, Fertility, and Lactation** ***Pregnancy*** Some neonates exposed to sertraline and other SSRIs or SNRIs late in the third trimester of pregnancy have developed complications that have sometimes been severe and required prolonged hospitalization, respiratory support, enteral nutrition, and other forms of supportive care in special-care nurseries. Such complications can arise immediately upon delivery and usually last several days or up to 2–4 weeks. Clinical findings reported to date in the neonates have included respiratory distress, cyanosis, apnea, seizures, temperature instability or fever, feeding difficulty, dehydration, excessive weight loss, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, lethargy, reduced or lack of reaction to pain stimuli, and constant crying. These clinical features appear to be consistent with either a direct toxic effect of the SSRI or SNRI or, possibly, a drug withdrawal syndrome. It should be noted that in some cases the clinical picture was consistent with serotonin syndrome (see Drug Interactions: Serotonergic Drugs). When treating a pregnant woman with sertraline during the third trimester of pregnancy, the clinician should carefully consider the potential risks and benefits of such therapy. Consideration may be given to cautiously tapering sertraline therapy in the third trimester prior to delivery if the drug is administered during pregnancy. (See Treatment of Pregnant Women during the Third Trimester under Dosage and Administration: Dosage.)

FDA states that decisions about management of depression in pregnant women are challenging and that the patient and her clinician must carefully consider and discuss the potential benefits and risks of SSRI therapy during pregnancy for the individual woman. Two recent studies provide important information on risks associated with discontinuing or continuing antidepressant therapy during pregnancy.

The first study, which was prospective, naturalistic, and longitudinal in design, evaluated the potential risk of relapsed depression in pregnant women with a history of major depressive disorder who discontinued or attempted to discontinue antidepressant (SSRIs, tricyclic antidepressants, or others) therapy during pregnancy compared with that in women who continued antidepressant therapy throughout their pregnancy; all women were euthymic while receiving antidepressant therapy at the beginning of pregnancy. In this study, women who discontinued antidepressant therapy were found to be 5 times more likely to have a relapse of depression during their pregnancy than were women who continued to receive their antidepressant while pregnant, suggesting that pregnancy does not protect against a relapse of depression.

The second study suggests that infants exposed to SSRIs in late pregnancy may have an increased risk of persistent pulmonary hypertension of the newborn (PPHN), which is associated with substantial neonatal morbidity and mortality. PPHN occurs at a rate of 1–2 neonates per 1000 live births in the general population in the US. In this retrospective case-control study of 377 women whose infants were born with PPHN and 836 women whose infants were born healthy, the risk for developing persistent pulmonary hypertension of the newborn was approximately sixfold higher for infants exposed to SSRIs after the twentieth week of gestation compared with infants who had not been exposed to SSRIs during this period. The study was too small to compare the risk of PPHN associated with individual SSRIs, and the findings have not been confirmed. Although the risk of PPHN identified in this study still is low (6–12 cases per 1000) and further study is needed, the findings add to concerns from previous reports that infants exposed to SSRIs late in pregnancy may experience adverse effects.

Most epidemiologic studies of pregnancy outcome following first-trimester exposure to SSRIs, including sertraline, conducted to date have not revealed evidence of an increased risk of major congenital malformations. In a prospective, controlled, multicenter study, maternal use of several SSRIs (sertraline, fluvoxamine, paroxetine) in a limited number of pregnant women did not appear to increase the risk of congenital malformation, miscarriage, stillbirth, or premature delivery when used during pregnancy at recommended dosages. Birth weight and gestational age in neonates exposed to the drugs were similar to those in the control group. In another small study based on medical records review, the incidence of congenital anomalies reported in infants born to women who were treated with sertraline and other SSRIs during pregnancy was comparable to that observed in the general population. However, the results of epidemiologic studies indicate that exposure to paroxetine during the first trimester of pregnancy may increase the risk for congenital malformations, particularly cardiovascular malformations. (See Cautions: Pregnancy, Fertility, and Lactation, in Paroxetine 28:16.04.20.) Additional epidemiologic studies are needed to more thoroughly evaluate the relative safety of sertraline and other SSRIs during pregnancy, including their potential teratogenic risks and possible effects on neurobehavioral development.

The manufacturers state that there are no adequate and controlled studies to date using sertraline in pregnant women, and the drug should be used during pregnancy only when the potential benefits justify the possible risks to the fetus. Women should be advised to notify their physician if they become pregnant or plan to become pregnant during therapy with the drug. FDA states that women who are pregnant or thinking about becoming pregnant should not discontinue any antidepressant, including sertraline, without first consulting their clinician. The decision whether or not to continue antidepressant therapy should be made only after careful consideration of the potential benefits and risks of antidepressant therapy for each individual pregnant patient. If a decision is made to discontinue treatment with sertraline or other SSRIs before or during pregnancy, discontinuance of therapy should be done in consultation with the clinician in accordance with the prescribing information for the antidepressant and the patient should be closely monitored for possible relapse of depression.

Reproduction studies in rats using sertraline dosages up to 80 mg/kg daily and in rabbits using dosages up to 40 mg/kg daily have not revealed evidence of teratogenicity; these dosages correspond to approximately 4 times the maximum recommended human dosage on a mg/m² basis. No evidence of teratogenicity was observed at any dosage studied. When pregnant rats and rabbits were given sertraline during the period of organogenesis, delayed ossification was observed in fetuses at doses of 10 mg/kg (0.5 times the maximum recommended human dose on a mg/m² basis) in rats and 40 mg/kg (4 times the maximum recommended human dose on a mg/m² basis) in rabbits. When female rats received sertraline during the last third of gestation and throughout lactation, there was an increase in the number of stillborn pups and in the number of pups dying during the first 4 days after birth. The body weights of the pups also were decreased during the first 4 days after birth. These effects occurred at a dose of 20 mg/kg (approximately the same as the maximum recommended human dose on a mg/m² basis). At 10 mg/kg (0.5 times the maximum recommended human dose on a mg/m² basis), no effect on rat pup mortality was observed. The decrease in pup survival was shown to result from in utero exposure to the drug. The clinical importance of these effects is not known.

The effect of sertraline on labor and delivery is not known.

Fertility A decrease in fertility was observed in 1 of 2 reproduction studies in rats using sertraline dosages of 80 mg/kg (4 times the maximum recommended human dose on a mg/m² basis).

Lactation Sertraline and its principal metabolite, *N*-desmethylsertraline, are distributed into milk. Sertraline should be used with caution in nursing women, and women should be advised to notify their physician if they plan to breast-feed.

Drug Interactions

■ **Serotonergic Drugs** Use of selective serotonin-reuptake inhibitors (SSRIs) such as sertraline concurrently or in close succession with other drugs that affect serotonergic neurotransmission may result in serotonin syndrome or neuroleptic malignant syndrome (NMS)-like reactions. Symptoms of serotonin syndrome may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination), and/or GI symptoms (e.g., nausea, vomiting, diarrhea). Although the syndrome appears to be relatively uncommon and usually mild in severity, serious and potentially life-threatening complications, including seizures, disseminated intravascular coagulation, respiratory failure, and severe hyperthermia as well as death occasionally have been reported. In its most severe form, serotonin syndrome may resemble NMS, which is characterized by hyperthermia, muscle rigidity, autonomic instability with possible rapid fluctuation in vital signs, and mental status changes. The precise mechanism of these reactions is not fully understood; however, they appear to result from excessive serotonergic activity in the CNS, probably mediated by activation of serotonin 5-HT_{1A} receptors. The possible involvement of dopamine and 5-HT_2 receptors also has been suggested, although their roles remain unclear.

Serotonin syndrome most commonly occurs when 2 or more drugs that affect serotonergic neurotransmission are administered either concurrently or in close succession. Serotonergic agents include those that increase serotonin synthesis (e.g., the serotonin precursor tryptophan), stimulate synaptic serotonin release (e.g., some amphetamines, dexfenfluramine [no longer commercially available in the US], fenfluramine [no longer commercially available in the US]), inhibit the reuptake of serotonin after release (e.g., SSRIs, selective serotonin- and norepinephrine-reuptake inhibitors [SNRIs], tricyclic antidepressants, trazodone, dextromethorphan, meperidine, tramadol), decrease the metabolism of serotonin (e.g., MAO inhibitors), have direct serotonin postsynaptic receptor activity (e.g., buspirone), or nonspecifically induce increases in serotonergic neuronal activity (e.g., lithium salts). Selective agonists of serotonin (5-hydroxytryptamine; 5-HT) type 1 receptors ("triptans") and dihydroergotamine, agents with serotonergic activity used in the management of migraine headache, and St. John's wort (*Hypericum perforatum*) also have been implicated in serotonin syndrome.

The combination of SSRIs and MAO inhibitors may result in serotonin syndrome or NMS-like reactions. Such reactions have also been reported in patients receiving SSRIs concomitantly with tryptophan, lithium, dextromethorphan, sumatriptan, dihydroergotamine, or antipsychotics or other dopamine antagonists. In rare cases, serotonin syndrome reportedly has occurred in patients receiving the recommended dosage of a single serotonergic agent (e.g., clomipramine) or during accidental overdosage (e.g., sertraline intoxication in a child). Some other drugs that have been implicated in precipitating symptoms suggestive of serotonin syndrome or NMS-like reactions include buspirone, bromocriptine, dextropropoxyphene, linezolid, methylenedioxymethamphetamine (MDMA; "ecstasy"), selegiline (a selective MAO-B inhibitor), and sibutramine (an SNRI used for the management of obesity). Other drugs that

have been associated with the syndrome but for which less convincing data are available include carbamazepine, fentanyl, and pentazocine.

Clinicians should be aware of the potential for serious, possibly fatal reactions associated with serotonin syndrome or NMS-like reactions in patients receiving 2 or more drugs that affect serotonergic neurotransmission, even if no such interactions with the specific drugs have been reported to date in the medical literature. Pending further accumulation of data, serotonergic drugs should be used cautiously in combination and such combinations avoided whenever clinically possible. Serotonin syndrome may be more likely to occur when initiating therapy, increasing the dosage, or following the addition of another serotonergic drug. Some clinicians state that patients who have experienced serotonin syndrome may be at higher risk for recurrence of the syndrome upon reinitiation of serotonergic drugs. Pending further experience in such cases, some clinicians recommend that therapy with serotonergic agents be limited following recovery. In cases in which the potential benefit of the drug is thought to outweigh the risk of serotonin syndrome, lower potency agents and reduced dosages should be used, combination serotonergic therapy should be avoided, and patients should be monitored carefully for manifestations of serotonin syndrome. If signs and symptoms of serotonin syndrome or NMS develop during therapy, treatment with sertraline and any concurrently administered serotonergic or antidopaminergic agents, including antipsychotic agents, should be discontinued immediately and supportive and symptomatic treatment should be initiated.

For further information on serotonin syndrome, including manifestations and treatment, see Drug Interactions: Serotonergic Drugs, in Fluoxetine Hydrochloride 28:16.04.20.

Monoamine Oxidase Inhibitors Potentially serious, sometimes fatal serotonin syndrome or NMS-like reactions have been reported in patients receiving SSRIs, including sertraline, in combination with an MAO inhibitor. Severe serotonin syndrome reaction developed several hours after initiating sertraline in a woman already receiving phenelzine, lithium, thioridazine, and doxepin. Such reactions also have been reported in patients who recently have discontinued an SSRI and have been started on an MAO inhibitor.

Because of the potential risk of serotonin syndrome or NMS-like reactions, concomitant use of sertraline and MAO inhibitors is contraindicated. At least 2 weeks should elapse between discontinuance of MAO inhibitor therapy and initiation of sertraline therapy and vice versa.

Linezolid. Linezolid, an anti-infective agent that is a nonselective and reversible MAO inhibitor, has been associated with drug interactions resulting in serotonin syndrome, including some associated with SSRIs, and potentially may also cause NMS-like reactions. Therefore, some manufacturers of sertraline state that linezolid should be used with caution in patients receiving sertraline. The manufacturer of linezolid states that, unless patients are carefully observed for signs and/or symptoms of serotonin syndrome, the drug should not be used in patients receiving SSRIs. Some clinicians suggest that linezolid only be used with caution and close monitoring in patients concurrently receiving SSRIs, and some suggest that SSRI therapy should be discontinued before linezolid is initiated and not reinitiated until 2 weeks after linezolid therapy is completed.

Moclobemide. Moclobemide (not commercially available in the US), a selective and reversible MAO-A inhibitor, has been associated with serotonin syndrome, and such reactions have been fatal in several cases in which the drug was given in combination with the SSRI citalopram or with clomipramine. Pending further experience with such combinations, some clinicians recommend that concurrent therapy with moclobemide and SSRIs be used only with extreme caution and that SSRIs should have been discontinued for some time (depending on the elimination half-lives of the drug and its active metabolites) before initiating moclobemide therapy.

Selegiline. Selegiline, a selective MAO-B inhibitor used in the management of parkinsonian syndrome, has been reported to cause serotonin syndrome when given concurrently with SSRIs (e.g., fluoxetine, paroxetine, sertraline). Although selegiline is a selective MAO-B inhibitor at therapeutic dosages, the drug appears to lose its selectivity for the MAO-B enzyme at higher dosages (e.g., those exceeding 10 mg/kg), thereby increasing the risk of serotonin syndrome in patients receiving higher dosages of the drug either alone or in combination with other serotonergic agents. The manufacturer of selegiline recommends avoiding concurrent selegiline and SSRI therapy. In addition, the manufacturer of selegiline recommends that at least 2 weeks elapse between discontinuance of selegiline and initiation of SSRI therapy.

Isoniazid. Isoniazid, an antituberculosis agent, appears to have some MAO-inhibiting activity. In addition, iproniazid (not commercially available in the US), another antituberculosis agent structurally related to isoniazid that also possesses MAO-inhibiting activity, reportedly has resulted in serotonin syndrome in at least 2 patients when given in combination with meperidine. Pending further experience, clinicians should be aware of the potential for serotonin syndrome when isoniazid is given in combination with SSRI therapy (such as sertraline) or other serotonergic agents.

Tryptophan and Other Serotonin Precursors Because of the potential risk of serotonin syndrome or NMS-like reactions, concurrent use of tryptophan or other serotonin precursors should be avoided in patients receiving sertraline.

5-HT$_1$ Receptor Agonists ("Triptans") Weakness, hyperreflexia, and incoordination have been reported rarely during postmarketing surveillance in patients receiving sumatriptan concomitantly with an SSRI (e.g., citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline); these reactions resembled serotonin syndrome. Oral or subcutaneous sumatriptan and SSRIs were used concomitantly in some clinical studies without unusual adverse effects. However, an increase in the frequency of migraine attacks and a decrease in the effectiveness of sumatriptan in relieving migraine headache have been reported in a patient receiving subcutaneous injections of sumatriptan intermittently while undergoing fluoxetine therapy.

Clinicians prescribing 5-HT$_1$ receptor agonists, SSRIs, and SNRIs should consider that 5-HT$_1$ receptor agonists often are used intermittently and that either the 5-HT$_1$ receptor agonist, SSRI, or SNRI may be prescribed by a different clinician. Clinicians also should weigh the potential risk of serotonin syndrome or NMS-like reactions with the expected benefit of using a 5-HT$_1$ receptor agonist concurrently with SSRI or SNRI therapy. If concomitant treatment with sumatriptan or another 5-HT$_1$ receptor agonist and sertraline is clinically warranted, the patient should be observed carefully, particularly during treatment initiation, dosage increases, and following the addition of other serotonergic agents. Patients receiving concomitant 5-HT$_1$ receptor agonist and SSRI or SNRI therapy should be informed of the possibility of serotonin syndrome or NMS-like reactions and advised to immediately seek medical attention if they experience signs or symptoms of these syndromes.

Sibutramine Because of the possibility of developing potentially serious, sometimes fatal serotonin syndrome or NMS-like reactions, sibutramine should be used with caution in patients receiving sertraline.

Other Selective Serotonin-reuptake Inhibitors and Selective Serotonin- and Norepinephrine-reuptake Inhibitors Concomitant administration of sertraline with other SSRIs or SNRIs potentially may result in serotonin syndrome or NMS-like reactions and is therefore not recommended. (See Dosage and Administration: Dosage.)

Antipsychotic Agents and Other Dopamine Antagonists Concomitant use of antipsychotic agents and other dopamine antagonists with sertraline rarely may result in potentially serious, sometimes fatal serotonin syndrome or NMS-like reactions. If signs and symptoms of serotonin syndrome or NMS occur, treatment with sertraline and any concurrently administered antidopaminergic or serotonergic agents should be immediately discontinued and supportive and symptomatic treatment initiated. (See Drug Interactions: Clozapine and see also Drug Interactions: Pimozide.)

Tramadol and Other Serotonergic Drugs Because of the potential risk of serotonin syndrome or NMS-like reactions, caution is advised whenever SSRIs, including sertraline, and SNRIs are concurrently administered with other drugs that may affect serotonergic neurotransmitter systems, including tramadol and St. John's wort (*Hypericum perforatum*).

■ **Drugs Undergoing Hepatic Metabolism or Affecting Hepatic Microsomal Enzymes** Animal studies have demonstrated that sertraline induces hepatic microsomal enzymes. In humans, microsomal enzyme induction by sertraline was minimal as determined by a small (5%) but statistically significant decrease in antipyrine half-life following sertraline administration (200 mg daily) for 21 days. The manufacturers state that this small change in antipyrine half-life reflects a clinically unimportant change in hepatic metabolism. Nonetheless, caution should be exercised when sertraline is given to patients receiving drugs that are hepatically metabolized and that have a low therapeutic ratio, such as warfarin. (See Drug Interactions: Protein-bound Drugs and see also Anticoagulants under Drug Interactions: Drugs Affecting Hemostasis.)

Drugs Metabolized by Cytochrome P-450 (CYP) 2D6 Sertraline, like many other antidepressants (e.g., other SSRIs, many tricyclic antidepressants) is metabolized by the drug-metabolizing cytochrome P-450 (CYP) 2D6 isoenzyme (debrisoquine hydroxylase). In addition, like many other drugs metabolized by CYP2D6, sertraline inhibits the activity of CYP2D6 and potentially may increase plasma concentrations of concomitantly administered drugs that also are metabolized by this isoenzyme. Although similar interactions are possible with other SSRIs, there is considerable variability among the drugs in the extent to which they inhibit CYP2D6. At lower doses, sertraline has demonstrated a less prominent inhibitory effect on CYP2D6 than some other SSRIs. Nevertheless, even sertraline has the potential for clinically important CYP2D6 inhibition.

Concomitant use of sertraline with other drugs metabolized by CYP2D6 has not been systematically studied. The extent to which this potential interaction may become clinically important depends on the extent of inhibition of CYP2D6 by the antidepressant and the therapeutic index of the concomitantly administered drug. The drugs for which this potential interaction is of greatest concern are those that are metabolized principally by CYP2D6 and have a narrow therapeutic index, such as tricyclic antidepressants, class IC antiarrhythmics (e.g., propafenone, flecainide, encainide), and some phenothiazines (e.g., thioridazine).

Caution should be used whenever concurrent therapy with sertraline and other drugs metabolized by CYP2D6 is considered. Because concomitant use of sertraline and thioridazine may result in increased plasma concentrations of the phenothiazine and increase the risk of serious, potentially fatal, adverse cardiac effects (e.g., cardiac arrhythmias), the manufacturer of thioridazine states that the drug should not be used concomitantly with any drug that inhibits the CYP2D6 isozyme. The manufacturers of sertraline state that concurrent use of a drug metabolized by CYP2D6 may necessitate the administration of dos-

ages of the other drug that are lower than those usually prescribed. Furthermore, whenever sertraline therapy is discontinued (and plasma concentrations of sertraline are decreased) during concurrent therapy with another drug metabolized by CYP2D6, an increased dosage of the concurrently administered drug may be necessary.

Drugs Metabolized by Cytochrome P-450 (CYP) 3A4 Although sertraline can inhibit the cytochrome P-450 (CYP) 3A4 isoenzyme, results of in vitro and in vivo studies indicate that the drug is a much less potent inhibitor of this enzyme than many other drugs. In an in vivo drug interaction study, concomitant use of sertraline and the CYP3A4 substrate, carbamazepine, under steady-state conditions had no effect on plasma concentrations of carbamazepine. The manufacturers of sertraline state that these data suggest that the extent of sertraline's inhibition of CYP3A4 activity is unlikely to be of clinical importance. However, a marked increase in plasma concentrations (ranging from 80–250%) and bone marrow suppression developed within 1–2 months of initiating sertraline in a patient previously stabilized on carbamazepine and flecainide therapy. Although the precise mechanism for this possible interaction and the role of the cytochrome P-450 enzyme system are unclear, some clinicians recommend that carbamazepine concentrations be monitored during concomitant sertraline therapy.

Results of an in vivo drug interaction study with cisapride indicate that concomitant use of sertraline (200 mg daily) induces the metabolism of cisapride; peak plasma concentrations and area under the plasma concentration-time curve (AUC) of cisapride were decreased by about 35% in the study. However, the manufacturers of sertraline state that the extent of sertraline's inhibition of CYP3A4 activity is unlikely to be of clinical importance.

Results of another drug interaction study in which sertraline was used concomitantly with terfenadine (no longer commercially available in the US), a drug metabolized principally by the cytochrome P-450 microsomal enzyme system (mainly by the CYP3A4 isoenzyme), indicate that concurrent use of sertraline did not increase plasma concentrations of terfenadine and, therefore, the manufacturers state that these data suggest that the extent of sertraline's inhibition of CYP3A4 activity is unlikely to be of clinical importance. However, the manufacturer of astemizole (no longer commercially available in the US) and some clinicians state that until the clinical importance of these findings is established, concomitant use of sertraline with astemizole or terfenadine is not recommended since substantially increased plasma concentrations of unchanged astemizole or terfenadine could occur resulting in an increased risk of serious adverse cardiac effects.

■ **Tricyclic and Other Antidepressants** The extent to which SSRI interactions with tricyclic antidepressants may pose clinical problems depends on the degree of inhibition and the pharmacokinetics of the serotonin-reuptake inhibitor involved. In healthy individuals, sertraline has been shown to substantially reduce the clearance of two tricyclic antidepressants, desipramine and imipramine. This interaction appears to result from sertraline-induced inhibition of CYP2D6. Thus, the manufacturers and some clinicians recommend that caution be exercised during concurrent use of tricyclics with sertraline since sertraline may inhibit the metabolism of the tricyclic antidepressant. In addition, plasma tricyclic concentrations may need to be monitored and the dosage of the tricyclic reduced during concomitant administration. (See Dosage and Administration: Dosage and see also Drugs Metabolized by Cytochrome P-450 [CYP] 2D6 under Drug Interactions: Drugs Undergoing Hepatic Metabolism or Affecting Hepatic Microsomal Enzymes.)

Clinical experience regarding the optimal timing of switching from other antidepressants to sertraline therapy is limited. Therefore, the manufacturers recommend that care and prudent medical judgment be exercised when switching from other antidepressants to sertraline, particularly from long-acting agents (e.g., fluoxetine). Pending further experience in patients being transferred from therapy with another antidepressant to sertraline and as the clinical situation permits, it generally is recommended that the previous antidepressant be discontinued according to the recommended guidelines for the specific antidepressant prior to initiation of sertraline therapy. (See Drug Interactions: Serotonergic Drugs.)

■ **Protein-bound Drugs** Because sertraline is highly protein bound, the drug theoretically could be displaced from binding sites by, or it could displace from binding sites, other protein-bound drugs such as oral anticoagulants or digitoxin. In vitro studies to date have shown that sertraline has no effect on the protein binding of 2 other highly protein-bound drugs, propranolol or warfarin; these findings also have been confirmed in clinical studies. However, pending further accumulation of data, patients receiving sertraline concomitantly with any highly protein-bound drug should be observed for potential adverse effects associated with combined therapy. (See Anticoagulants under Drug Interactions: Drugs Affecting Hemostasis.)

■ **Drugs Affecting Hemostasis** *Anticoagulants* In a study comparing prothrombin time AUC (0–120 hour) following a dose of warfarin (0.75 mg/kg) or placebo prior to and after 21 days of either sertraline (50–200 mg daily) or placebo, prothrombin time increased by an average of 8% compared with baseline in the sertraline group and decreased by an average of 1% in those receiving placebo. In addition, the normalization of prothrombin time was slightly delayed in those receiving sertraline when compared with those receiving placebo. Because the clinical importance of these findings is not known, prothrombin time should be monitored carefully whenever sertraline therapy is initiated or discontinued in patients receiving anticoagulants. (See Drug Interactions: Protein-bound Drugs.)

Other Drugs That Interfere with Hemostasis Epidemiologic case-control and cohort design studies that have demonstrated an association between selective serotonin-reuptake inhibitor therapy and an increased risk of upper GI bleeding also have shown that concurrent use of aspirin or other nonsteroidal anti-inflammatory agents substantially increases the risk of GI bleeding. Although these studies focused on upper GI bleeding, there is some evidence suggesting that bleeding at other sites may be similarly potentiated. The precise mechanism for this increased risk remains to be clearly established; however, serotonin release by platelets is known to play an important role in hemostasis, and selective serotonin-reuptake inhibitors decrease serotonin uptake from the blood by platelets, thereby decreasing the amount of serotonin in platelets. Patients receiving sertraline should be cautioned about the concomitant use of drugs that interfere with hemostasis, including aspirin and other nonsteroidal anti-inflammatory agents.

■ **Alcohol** Sertraline administration did not potentiate the cognitive and psychomotor effects induced by alcohol in healthy individuals. In addition, no apparent additive CNS depressant effects were observed in geriatric patients receiving sertraline together with moderate amounts of alcohol. Nonetheless, the manufacturers state that concurrent use of sertraline and alcohol is not recommended.

■ **Electroconvulsive Therapy** The effects of sertraline in conjunction with electroconvulsive therapy (ECT) have not been evaluated to date in clinical studies.

■ **Cimetidine** In a study evaluating the effect of the addition of a single dose of sertraline (100 mg) on the second of 8 days of cimetidine administration (800 mg daily), the mean AUC, peak concentration, and elimination half-life of sertraline increased substantially (by 50, 24, and 26%, respectively) compared with the placebo group. The clinical importance of these changes is unknown.

■ **Benzodiazepines** In a study comparing the disposition of diazepam administered IV before and after 21 days of sertraline therapy (dosage titrated from 50–200 mg daily) or placebo, there was a 32% decrease in diazepam clearance in the sertraline recipients and a 19% decrease in those receiving placebo when compared with baseline. There was a 23% increase in the time to maximal plasma concentration for desmethyldiazepam in the sertraline group compared with a 20% decrease in the placebo group. The clinical importance of these findings is unknown; however, they suggest that sertraline and *N*-desmethylsertraline are not likely to substantially inhibit the CYP2C19 and CYP3A3/4 hepatic isoenzymes involved in the metabolism of diazepam.

■ **Clozapine** Concomitant use of SSRIs such as sertraline in patients receiving clozapine can increase plasma concentrations of the antipsychotic agent. In a study in schizophrenic patients receiving clozapine under steady-state conditions, initiation of paroxetine therapy resulted in only minor changes in plasma concentrations of clozapine and its metabolites; however, initiation of fluvoxamine therapy resulted in increases that were threefold compared with baseline. In other published reports, concomitant use of clozapine and SSRIs (fluvoxamine, paroxetine, sertraline) resulted in modest increases (less than twofold) in clozapine and metabolite concentrations. The manufacturer of clozapine states that caution should be exercised and patients closely monitored if clozapine is used in patients receiving SSRIs, and a reduction in clozapine dosage should be considered. (See Antipsychotic Agents and Other Dopamine Antagonists under Drug Interactions: Serotonergic Drugs.)

■ **Lithium** In a placebo-controlled trial, the administration of 2 doses of sertraline did not substantially alter steady-state plasma lithium concentrations or the renal clearance of lithium. Pending further accumulation of data, however, the manufacturers recommend that plasma lithium concentrations be monitored following initiation of sertraline in patients receiving lithium and that lithium dosage be adjusted accordingly. In addition, because of the potential risk of serotonin syndrome or NMS-like reactions, caution is advised during concurrent sertraline and lithium use. (See Drug Interactions: Serotonergic Drugs.)

■ **Hypoglycemic Drugs** In a placebo-controlled study in healthy male volunteers, sertraline administration for 22 days (including 200 mg daily for the final 13 days) caused a small but statistically significant decrease (16%) in the clearance of a 1-g IV dose of tolbutamide compared with baseline values and an increase in the terminal elimination half-life (from 6.9 to 8.6 hours). The decrease in clearance was not accompanied by any substantial changes in the plasma protein binding or the apparent volume of distribution of tolbutamide, which suggests that the change in tolbutamide clearance may be caused by a slight inhibition of the cytochrome P-450 isoenzyme CYP2C9/10 when sertraline is given in the maximum recommended dosage. The clinical importance of these findings remains to be determined.

■ **Digoxin** In a placebo-controlled trial in healthy volunteers, sertraline administration for 17 days (including 200 mg daily for the final 10 days) did not alter serum digoxin concentrations or renal clearance of digoxin. The results of this study suggest that dosage adjustment of digoxin may not be necessary in patients receiving concomitant sertraline.

■ **Atenolol** In a double-blind, placebo-controlled, randomized, crossover study, a single, 100-mg dose of sertraline had no effect on the β-adrenergic blocking activity of atenolol when administered to a limited number of healthy males.

■ **Amiodarone** A decrease in the plasma concentrations of amiodarone and its active metabolite, desmethylamiodarone, to 82 and 85% of the baseline values, respectively, occurred in one patient following the discontinuance of sertraline and carbamazepine therapy, suggesting that sertraline may have been inhibiting the metabolism of amiodarone by CYP3A4.

■ **Phenytoin** In a randomized, double-blind, placebo-controlled trial, chronic administration of high dosages of sertraline (200 mg daily) did not substantially affect the pharmacokinetics or pharmacodynamics of phenytoin when the 2 drugs were given concurrently in healthy volunteers. However, substantial reductions in plasma sertraline concentrations have been observed in sertraline-treated patients concurrently receiving phenytoin; it was suggested that induction of the cytochrome P-450 isoenzymes may be responsible. In addition, concurrent administration of sertraline and phenytoin reportedly resulted in elevated phenytoin concentrations in 2 geriatric patients. Pending further accumulation of data, the manufacturers and some clinicians recommend that plasma phenytoin concentrations be monitored following initiation of sertraline therapy and that phenytoin dosage should be adjusted as necessary, particularly in patients with multiple underlying medical conditions and/or those receiving multiple concomitant drugs.

■ **Pimozide** Concomitant use of sertraline and pimozide has resulted in substantial increases in peak plasma concentrations and area under the plasma concentration-time curve (AUC) of pimozide. In one controlled study, administration of a single 2-mg dose of pimozide in individuals receiving sertraline 200 mg daily resulted in a mean increase in pimozide AUC and peak plasma concentrations of about 40%, but was not associated with changes in ECG parameters. The effects on QT interval and pharmacokinetic parameters of pimozide administered in higher doses (i.e., doses exceeding 2 mg) in combination with sertraline are as yet unknown. Concomitant use of sertraline and pimozide is contraindicated because of the low therapeutic index of pimozide and because the reported interaction between the 2 drugs occurred at a low dose of pimozide. The mechanism of this interaction is as yet unknown. (See Antipsychotic Agents and Other Dopamine Antagonists under Drug Interactions: Serotonergic Drugs.)

■ **Valproic Acid** The effect of sertraline on plasma valproic acid concentrations remains to be evaluated in clinical studies. In the absence of such data, the manufacturers recommend monitoring plasma valproic acid concentrations following initiation of sertraline therapy and adjusting the dosage of valproic acid as necessary.

Acute Toxicity

■ **Pathogenesis** The acute lethal dose of sertraline in humans is not known. One patient who ingested 13.5 g of sertraline alone subsequently recovered. However, death occurred in another patient who ingested 2.5 g of the drug alone.

In general, overdosage of sertraline may be expected to produce effects that are extensions of the drug's pharmacologic and adverse effects. The most common signs and symptoms associated with nonfatal sertraline overdosage include somnolence, nausea, vomiting, tachycardia, dizziness, agitation, and tremor. Other adverse events observed in patients who received overdosages of sertraline (alone or in combination with other drugs) include bradycardia, bundle branch block, coma, seizures, delirium, hallucinations, hypertension, hypotension, manic reaction, pancreatitis, QT-interval prolongation, serotonin syndrome, stupor, and syncope. Prolonged tachycardia, hypertension, hallucinations, hyperthermia, tremors of the extremities, and skin flushing have occurred in a child after accidental sertraline ingestion; the reaction resembled serotonin syndrome. Flushing, anger, emotional lability, and distractability developed 1 hour after an adult female ingested 2 g of sertraline; recovery was uneventful apart from watery bowel movements.

■ **Treatment** Because fatalities and severe toxicity have been reported when sertraline was ingested alone or in combination with other drugs and/or alcohol, the manufacturers and some clinicians recommend that any overdosage involving sertraline be managed aggressively. Clinicians also should consider the possibility of serotonin syndrome or NMS-like reactions in patients presenting with similar clinical features and a recent history of sertraline and/or ingestion of other serotonergic agents and/or antipsychotic agents or other dopamine antagonists. (See Cautions: Precautions and Contraindications and see also Drug Interactions: Serotonergic Drugs.)

Management of sertraline overdosage generally involves symptomatic and supportive care. A patent airway should be established and maintained, and adequate oxygenation and ventilation should be ensured. ECG and vital sign monitoring is recommended following acute overdosage with the drug, although the value of ECG monitoring in predicting the severity of sertraline-induced cardiotoxicity is not known. (See Acute Toxicity: Manifestations, in the Tricyclic Antidepressants General Statement 28:16.04.28.) There is no specific antidote for sertraline intoxication. Because suicidal ingestion often involves more than one drug, clinicians treating sertraline overdosage should be alert to possible manifestations caused by drugs other than sertraline.

If the patient is comatose, having seizures, or lacks the gag reflex, gastric lavage may be performed if an endotracheal tube with cuff inflated is in place to prevent aspiration of gastric contents. Since administration of activated charcoal (which may be used in conjunction with sorbitol) may be as effective as or more effective than induction of emesis or gastric lavage, its use has been recommended either in the initial management of sertraline overdosage or following induction of emesis or gastric lavage in patients who have ingested a potentially toxic quantity of the drug.

Limited data indicate that sertraline is not appreciably removed by hemodialysis. Because of the large volume of distribution of sertraline and its principal metabolite, peritoneal dialysis, forced diuresis, hemoperfusion, and/or exchange transfusion also are likely to be ineffective in removing substantial amounts of sertraline and *N*-desmethylsertraline from the body.

Clinicians should consult a poison control center for additional information on the management of sertraline overdosage.

Chronic Toxicity

Sertraline has not been studied systematically in animals or humans to determine whether therapy with the drug is associated with abuse, tolerance, or physical dependence.

The premarketing clinical experience with sertraline did not reveal any tendency for a withdrawal syndrome or any drug-seeking behavior. However, fatigue, severe abdominal cramping, memory impairment, and influenza-like symptoms were reported 2 days following abrupt discontinuance of sertraline in one patient; when sertraline was restarted, the symptoms remitted. Electric shock-like sensations occurred in another patient 1 day after the last administered dose of sertraline; these sensations became less intense and eventually disappeared 13 weeks after sertraline therapy was discontinued. When evaluating these cases and those reported with other serotonin-reuptake inhibitors, it appears that a withdrawal syndrome may occur within several days following abrupt discontinuance of these drugs. The most commonly observed symptoms are those that resemble influenza, such as fatigue, stomach complaints (e.g., nausea), dizziness or lightheadedness, tremor, anxiety, chills, sweating, and incoordination. Other reported symptoms include memory impairment, insomnia, paresthesia, shock-like sensations, headache, palpitations, agitation, or aggression. Such reactions appear to be self-limiting and improve over 1 to several weeks. Pending further experience, sertraline therapy should be discontinued gradually to prevent the possible development of withdrawal reactions.

As with other CNS-active drugs, clinicians should carefully evaluate patients for a history of substance abuse prior to initiating sertraline therapy. If sertraline therapy is initiated in patients with a history of substance abuse, such patients should be monitored closely for signs of misuse or abuse of the drug (e.g., development of tolerance, use of increasing doses, drug-seeking behavior).

The potential for misuse of sertraline in patients with concurrent eating disorders and/or those who may seek the drug for its appetite-suppressant effects also may be considered.

Pharmacology

The pharmacology of sertraline is complex and in many ways resembles that of other antidepressant agents, particularly those agents (e.g., fluoxetine, fluvoxamine, paroxetine, clomipramine, trazodone) that predominantly potentiate the pharmacologic effects of serotonin (5-HT). Like other selective serotonin-reuptake inhibitors (SSRIs), sertraline is a potent and highly selective reuptake inhibitor of serotonin and has little or no effect on other neurotransmitters.

■ **Nervous System Effects** The precise mechanism of antidepressant action of sertraline is unclear, but the drug has been shown to selectively inhibit the reuptake of serotonin at the presynaptic neuronal membrane. Sertraline-induced inhibition of serotonin reuptake causes increased synaptic concentrations of serotonin in the CNS, resulting in numerous functional changes associated with enhanced serotonergic neurotransmission. Like other SSRIs (e.g., fluoxetine, fluvoxamine, paroxetine), sertraline appears to have only very weak effects on the reuptake of norepinephrine or dopamine and does not exhibit clinically important anticholinergic, antihistaminic, or adrenergic (α_1, α_2, β) blocking activity at usual therapeutic dosages.

Although the mechanism of antidepressant action of antidepressant agents may involve inhibition of the reuptake of various neurotransmitters (i.e., serotonin, norepinephrine) at the presynaptic neuronal membrane, it has been suggested that postsynaptic receptor modification is mainly responsible for the antidepressant action observed during long-term administration of antidepressant agents. During long-term therapy with most antidepressants (e.g., tricyclic antidepressants, monoamine oxidase [MAO] inhibitors), these adaptive changes mainly consist of subsensitivity of the noradrenergic adenylate cyclase system in association with a decrease in the number of β-adrenergic receptors; such effects on noradrenergic receptor function are commonly referred to as "down regulation." In animal studies, long-term administration of sertraline has been shown to downregulate noradrenergic receptors in the CNS as has been observed with many other clinically effective antidepressants. In addition, some antidepressants (e.g., amitriptyline) reportedly decrease the number of serotonergic (5-HT) binding sites following chronic administration. Although changes in the density of type 2 serotonergic (5-HT_2) binding sites were not observed during chronic administration of sertraline in animals in one study, the drug caused desensitization of the 5-HT_2 receptor transmembrane signaling system; the clinical importance of these findings requires further study.

The precise mechanism of action that is responsible for the efficacy of sertraline in the treatment of obsessive-compulsive disorder is unclear. However, because of the potency of clomipramine and other selective serotonin-reuptake inhibitors (e.g., fluoxetine, fluvoxamine, paroxetine) in inhibiting se-

rotonin reuptake and their efficacy in the treatment of obsessive-compulsive disorder, a serotonin hypothesis has been developed to explain the pathogenesis of the condition. The hypothesis postulates that a dysregulation of serotonin is responsible for obsessive-compulsive disorder and that sertraline and these other agents are effective because they correct this imbalance. Although the available evidence supports the serotonergic hypothesis of obsessive-compulsive disorder, additional studies are necessary to confirm this hypothesis.

Serotonergic mechanisms also appear to be involved at least in part in a number of other pharmacologic effects associated with selective serotonin-reuptake inhibitors, including sertraline, such as decreased food intake and altered food selection as well as decreased alcohol intake.

Serotonergic Effects Sertraline is a highly selective inhibitor of serotonin reuptake at the presynaptic neuronal membrane. Sertraline-induced inhibition of serotonin reuptake causes increased synaptic concentrations of the neurotransmitter, resulting in numerous functional changes associated with enhanced serotonergic neurotransmission.

Data from in vitro studies suggest that sertraline is more potent than fluvoxamine, fluoxetine, or clomipramine as a serotonin-reuptake inhibitor. Like some other serotonin-reuptake inhibitors, sertraline undergoes metabolism via *N*-demethylation to form *N*-desmethylsertraline, the principal metabolite. Data from in vivo and in vitro studies have shown that *N*-desmethylsertraline is approximately 5–10 times less potent as an inhibitor of serotonin reuptake than sertraline; however, the metabolite retains selectivity for serotonin reuptake compared with either norepinephrine or dopamine reuptake.

At therapeutic dosages (50–200 mg daily) in healthy individuals, sertraline has been shown to inhibit the reuptake of serotonin into platelets in a dose-dependent manner. Like other serotonin-reuptake inhibitors, sertraline inhibits the spontaneous firing of serotonergic neurons in the dorsal raphe nucleus. In vitro data have demonstrated that sertraline has substantial affinity for serotonergic (5-HT_{1A}, 5-HT_{1B}, 5-HT_2) receptors.

Effects on Other Neurotransmitters Like other serotonin-reuptake inhibitors, sertraline has been shown to have little or no activity in inhibiting the reuptake of norepinephrine. In addition, the drug has demonstrated a substantially higher selectivity ratio of serotonin-to-norepinephrine reuptake inhibiting activity than fluoxetine or tricyclic antidepressant agents, including clomipramine.

Although sertraline has only weak activity in inhibiting the reuptake of dopamine, the relative selectivity of sertraline for inhibiting serotonin reuptake relative to dopamine reuptake appears to be somewhat less than that of fluoxetine, fluvoxamine, zimelidine, or clomipramine. In addition, sertraline does not inhibit monoamine oxidase.

Unlike tricyclic and some other antidepressants, sertraline does not exhibit clinically important anticholinergic, α- or β-adrenergic blocking, or antihistaminic activity at usual therapeutic dosages. As a result, the incidence of adverse effects commonly associated with blockade of muscarinic cholinergic receptors (e.g., dry mouth, blurred vision, urinary retention, constipation, confusion), α-adrenergic receptors (e.g., orthostatic hypotension), and histamine H_1- and H_2-receptors (e.g., sedation) is lower in sertraline-treated patients. In vitro studies have demonstrated that sertraline does not possess clinically important affinity for α_1- or α_2-adrenergic, β-adrenergic, histaminergic, muscarinic, GABA, benzodiazepine, or dopamine receptors.

Effects on Sleep Like tricyclic and most other antidepressants, sertraline suppresses rapid eye movement (REM) sleep. Although not clearly established, there is some evidence that the REM-suppressing effects of antidepressant agents may contribute to the antidepressant activity of these drugs. In animal studies, sertraline suppressed REM sleep; the drug appears to reduce the amount of REM sleep by decreasing the number as well as the duration of REM episodes. Although the precise mechanism has not been fully elucidated, results of animal studies indicate that sertraline's effects on REM sleep are serotonergically mediated.

Effects on EEG Limited data currently are available regarding the effects of sertraline on the EEG. EEG changes in healthy individuals receiving single, 100-mg doses of sertraline resembled the EEG profiles of patients receiving desipramine-type antidepressants (increased alpha and decreased but accelerated delta activity) and suggest improved vigilance and psychometric performance. In individuals receiving higher single doses (200 and 400 mg) of the drug, sertraline produced EEG changes similar to imipramine-type antidepressants (reduced alpha and low beta activity and increased theta and fast beta activity), which reflect vigilance changes of the dissociative type and therefore possible sedative activity.

Effects on Psychomotor Function Sertraline does not appear to cause clinically important sedation and does not interfere with psychomotor performance. The drug did not appear to have any adverse effects on psychomotor performance when given to healthy women in single doses up to 100 mg. In healthy individuals over 50 years of age, single, 100-mg doses of sertraline increased the critical flicker fusion frequency slightly and the subjective perception of sedation; however, the drug had no depressant effect on objective tests of psychomotor performance. In addition, no adverse effects on psychomotor performance were observed in geriatric individuals who received the drug in a controlled study.

■ **Cardiovascular Effects** Sertraline appears to have little effect on the ECG. Data from controlled studies indicate sertraline does not produce clinically important changes in heart rate, cardiac conduction, or other ECG parameters in depressed patients.

■ **Effects on Appetite and Body Weight** Like some other serotonergic agents (e.g., fenfluramine [no longer commercially available in the US], fluoxetine, zimelidine), sertraline possesses anorexigenic activity. Limited data from animal studies suggest that fenfluramine has been the most effective inhibitor of food intake followed by fluoxetine and then sertraline. Although the precise mechanism has not been clearly established, results from animal studies indicate that sertraline's appetite-inhibiting action may result at least in part from serotonin-reuptake blockade and the resultant increase in serotonin availability at the neuronal synapse. Because sertraline's anorexigenic activity was not antagonized by prior administration of serotonergic antagonists, other mechanisms also may be involved but require further study. Following administration of single doses of sertraline in meal-fed animals, food intake was reduced in a dose-dependent manner. At a dose of 3 mg/kg, the reduction in food intake was substantially reduced and higher doses of 10 or 30 mg/kg reduced food intake by 45 or 74%, respectively.

Sertraline therapy has resulted in dose-dependent decreases in body weight in animals receiving the drug for 3 days; the weight loss was not accompanied by any overt signs of behavioral abnormality. Sertraline therapy also has resulted in decreases in body weight in individuals receiving the drug. However, weight loss is usually minimal and averaged about 0.45–0.9 kg in individuals treated with the drug in controlled clinical trials. (See Cautions: Metabolic Effects and see also Cautions: Pediatric Precautions.) Rarely, weight loss has required discontinuance of therapy.

■ **Effects on Alcohol Intake** Like some other serotonergic agents, sertraline produces a substantial decrease in voluntary alcohol intake in animals. Because serotonin appears to be involved in the regulation of alcohol intake, it has been suggested that selective serotonin-reuptake inhibitors may attenuate alcohol consumption via enhanced serotonergic neurotransmission. (See Cautions.)

■ **Neuroendocrine Effects** Limited data currently are available regarding the effects of sertraline on the endocrine system. In one animal study, sertraline did not demonstrate substantial neuroendocrine effects at a dose that substantially reduced gross activity.

Although a causal relationship has not been established, hypothyroidism, decreased serum thyroxine concentrations, and/or increased serum thyrotropin (thyroid-stimulating hormone, TSH) concentrations have been reported in a limited number of sertraline patients, some of whom were receiving thyroxine concurrently. (See Cautions: Other Adverse Effects and also see Precautions and Contraindications.)

■ **Other Effects** Sertraline appears to have a weak uricosuric effect; mean decreases in serum uric acid of approximately 7% have been reported in patients receiving the drug. The clinical importance of these findings is unknown, and there have been no reports of acute renal failure associated with the drug. (See Cautions: Precautions and Contraindications.)

Pharmacokinetics

In all human studies described in the Pharmacokinetics section, sertraline was administered as the hydrochloride salt; dosages and concentrations are expressed in terms of sertraline.

■ **Absorption** Sertraline appears to be slowly but well absorbed from the GI tract following oral administration. The oral bioavailability of sertraline in humans has not been fully elucidated to date because a preparation for IV administration is not available. However, the relative proportion of an oral dose that reaches systemic circulation unchanged appears to be relatively small because sertraline undergoes extensive first-pass metabolism. In animals, the oral bioavailability of sertraline ranges from 22–36%. The manufacturers state that the bioavailability of a single dose of sertraline hydrochloride tablets is approximately equal to that of an equivalent dose of sertraline hydrochloride oral solution. In a study in healthy adults who received a single 100-mg dose of sertraline as a tablet or oral solution, the solution to tablet ratios of the mean geometric AUC and peak plasma concentration were 114.8 and 120.6%, respectively.

The effect of food on the absorption of sertraline hydrochloride given as tablets or the oral solution has been studied in single-dose studies. Administration of a sertraline hydrochloride tablet with food slightly increased the area under the concentration-time curve (AUC) of sertraline, increased peak plasma concentrations by approximately 25%, and decreased the time to achieve peak plasma concentrations from about 8 to 5.5 hours. Administration of sertraline hydrochloride oral solution with food increased the time to achieve peak plasma concentrations from 5.9 to 7.0 hours.

Peak plasma sertraline concentrations usually occur within 4.5–8.4 hours following oral administration of 50–200 mg once daily for 14 days. Peak plasma sertraline concentrations following administration of single oral doses of 50–200 mg are proportional and linearly related to dose. Peak plasma concentrations and bioavailability are increased in geriatric individuals.

Following multiple dosing, steady-state plasma sertraline concentrations should be achieved after approximately 1 week of once-daily dosing. When compared with a single dose, there is an approximate twofold accumulation of sertraline after multiple daily dosing in dosages ranging from 50–200 mg daily.

N-Desmethylsertraline, sertraline's principal metabolite, exhibits time-related, dose-dependent increases in AUC (0–24 hour), peak plasma concentrations, and trough plasma concentrations with about a 5- to 9-fold increase in these parameters between day 1 and 14.

As with other serotonin-reuptake inhibitors, the relationship between plasma sertraline and *N*-desmethylsertraline concentrations and the therapeutic and/or toxic effects of the drug has not been clearly established.

■ **Distribution** Distribution of sertraline and its metabolites into human body tissues and fluids has not been fully characterized. However, limited pharmacokinetic data suggest that the drug and some of its metabolites are widely distributed in body tissues. Although the apparent volume of distribution of sertraline has not been determined in humans, values exceeding 20 L/kg have been reported in rats and dogs. The drug crosses the blood-brain barrier in humans and animals.

At in vitro plasma concentrations ranging from 20–500 ng/mL, sertraline is approximately 98% bound to plasma proteins, principally to albumin and α_1-acid glycoprotein. Protein binding is independent of plasma concentrations from 20–2000 mcg/mL. However, sertraline and *N*-desmethylsertraline did not alter the plasma protein binding of 2 other highly protein bound drugs, warfarin or propranolol, at concentrations of 300 and 200 ng/mL, respectively.

Sertraline and *N*-desmethylsertraline are distributed into milk. In a study involving 12 lactating women who received oral dosages of sertraline ranging from 25–200 mg daily, both sertraline and *N*-desmethylsertraline were present in all breast milk samples, with the highest concentrations observed in hind milk 7–10 hours after the maternal dose. Detectable concentrations of sertraline were found in 3 and *N*-desmethylsertraline in 6, respectively, out of 11 nursing infants.

■ **Elimination** The elimination half-life of sertraline averages approximately 25–26 hours and that of desmethylsertraline averages about 62–104 hours. In geriatric adults elimination half-life may be increased (e.g., to about 36 hours); however, such prolongation does not appear clinically important and does not warrant dosing alterations.

The exact metabolic fate of sertraline has not been fully elucidated. Sertraline appears to be extensively metabolized, probably in the liver, to *N*-desmethylsertraline and several other metabolites. Like some other serotonin-reuptake inhibitors, sertraline undergoes metabolism via *N*-demethylation to form *N*-desmethylsertraline, the principal metabolite. Unlike some other serotonin-reuptake inhibitors, the drug metabolizing isoenzyme CYP2D6 (a cytochrome P-450 isoenzyme implicated in the sparteine/debrisoquine polymorphism) does not appear to have a major role in the conversion of sertraline to *N*-desmethylsertraline. Nonetheless, sertraline has the potential for clinically important inhibition of this enzyme. (See Drug Interactions: Drugs Undergoing Hepatic Metabolism or Affecting Hepatic Microsomal Enzymes.) In vitro, the conversion of sertraline to *N*-desmethylsertraline correlates more with CYP3A3/4 activity than with CYP2D6 activity. Data from in vivo and in vitro studies have shown that *N*-desmethylsertraline is approximately 5–10 times less potent as an inhibitor of serotonin reuptake than sertraline; however, the metabolite retains selectivity for serotonin reuptake compared with either norepinephrine or dopamine reuptake. Both sertraline and desmethylsertraline undergo oxidative deamination and subsequent reduction, hydroxylation, and glucuronide conjugation. Desmethylsertraline has an elimination half-life approximately 2.5 times that of sertraline.

Following oral administration, sertraline and its metabolites are excreted in both urine and feces. Following oral administration of a single, radiolabeled dose in 2 healthy males, unchanged sertraline accounted for less than 5% of plasma radioactivity. Approximately 40–45% of the radiolabeled dose was excreted in urine within 9 days. Unchanged sertraline was not detectable in urine. During the same period, approximately 40–45% of the radiolabeled drug was eliminated in feces, including 12–14% of unchanged sertraline.

The effect of age on the elimination of sertraline has not been fully elucidated. Plasma clearance of sertraline was approximately 40% lower in a group of 16 geriatric patients (8 males and 8 females) who received 100 mg of the drug for 14 days than that reported in a similar study involving younger individuals (from 25–32 years of age). Based on these results, the manufacturers state that steady-state should be achieved in about 2–3 weeks in older individuals. In addition, decreased clearance of *N*-desmethylsertraline was noted in older males but not in older females. (See Dosage and Administration: Dosage in Geriatric Patients.)

Because sertraline is extensively metabolized by the liver, hepatic impairment can affect the elimination of the drug. In one study in patients with chronic mild hepatic impairment (Child-Pugh scores of 5–8) who received 50 mg of sertraline daily for 21 days, sertraline clearance was reduced resulting in a 2–3 times greater exposure to the drug and its metabolite (desmethylsertraline) than that reported for age-matched individuals without hepatic impairment. In a single-dose study in patients with mild, stable cirrhosis, the elimination half-life of sertraline was prolonged to a mean of 52 hours compared with 22 hours in individuals without hepatic disease. In addition, peak plasma concentrations and AUC values for sertraline were 1.7- and 4.4-fold higher, respectively, in patients with hepatic impairment when compared with healthy individuals without liver disease, reflecting decreased clearance of the drug. The pharmacokinetics of sertraline have not been studied to date in patients with moderate and severe hepatic impairment; therefore, the manufacturers recommend that sertraline be administered with caution and in reduced dosage or less frequently in patients with hepatic impairment. (See Cautions: Precautions and Contraindications and see Dosage and Administration: Dosage in Renal and Hepatic Impairment.)

Because sertraline is extensively metabolized in the liver and renal clearance of the drug is negligible, the manufacturers state that clinically important decreases in sertraline clearance are not anticipated if the drug is used in patients with renal impairment. Results of a multiple-dose study indicate that the pharmacokinetics of sertraline are not affected by renal impairment. In this study, individuals with mild to moderate renal impairment (creatinine clearance: 30–60 mL/minute), moderate to severe renal impairment (creatinine clearance: 10–29 mL/minute), or severe renal impairment (undergoing hemodialysis) received 200 mg of sertraline daily for 21 days; the pharmacokinetics and protein binding of the drug in these patients were similar to those reported for age-matched individuals without renal impairment. (See Cautions: Precautions and Contraindications and see Dosage and Administration: Dosage in Renal and Hepatic Impairment.)

Limited data indicate that sertraline is not appreciably removed by hemodialysis. Because of the large volume of distribution of sertraline and its principal metabolite, peritoneal dialysis, forced diuresis, hemoperfusion, and/or exchange transfusion also are likely to be ineffective in removing substantial amounts of sertraline and *N*-desmethylsertraline from the body.

Chemistry and Stability

■ **Chemistry** Sertraline, a selective serotonin-reuptake inhibitor antidepressant agent, is a naphthalenamine (naphthylamine)-derivative. Sertraline differs structurally from other selective serotonin-reuptake inhibitor antidepressants (e.g., citalopram, fluoxetine, paroxetine) and also differs structurally and pharmacologically from other currently available antidepressants (e.g., tricyclic antidepressants, monoamine oxidase inhibitors). Like most other serotonin-reuptake inhibitors, sertraline contains an asymmetric carbon; therefore, there are 2 existing optical isomers of the drug. However, only one of the optical isomers is present in the commercially available form of the drug.

Sertraline is commercially available as the hydrochloride salt, which occurs as a white, crystalline powder that is slightly soluble in water and isopropyl alcohol and sparingly soluble in ethanol. Commercially available sertraline hydrochloride oral solution is a clear, colorless solution with a menthol scent containing 20 mg of sertraline per mL and 12% alcohol.

■ **Stability** Commercially available sertraline hydrochloride tablets and oral solution should be stored at 25°C, but may be exposed to temperatures ranging from 15–30°C. Sertraline hydrochloride oral solution should be diluted only in the liquids specified by the manufacturer, and should be used immediately after dilution.

Preparations

Excipients in commercially available drug preparations may have clinically important effects in some individuals; consult specific product labeling for details.

Sertraline Hydrochloride

Oral		
For solution, concentrate	20 mg (of sertraline) per mL*	**Sertraline Hydrochloride Oral Solution** **Zoloft*** (with calibrated dropper dispenser containing latex rubber), Pfizer
Tablets, film-coated	25 mg (of sertraline)*	**Sertraline Hydrochloride Tablets** **Zoloft*** (scored), Pfizer
	50 mg (of sertraline)*	**Sertraline Hydrochloride Tablets** **Zoloft*** (scored), Pfizer
	100 mg (of sertraline)*	**Sertraline Hydrochloride Tablets** **Zoloft*** (scored), Pfizer
	150 mg (of sertraline)*	**Sertraline Hydrochloride Tablets,** Ranbaxy
	200 mg (of sertraline)*	**Sertraline Hydrochloride Tablets,** Ranbaxy

*available from one or more manufacturer, distributor, and/or repackager by generic (nonproprietary) name
†Use is not currently included in the labeling approved by the US Food and Drug Administration

Olanzapine

28:16.08.04 Atypical Antipsychotics (AHFS primary)

Special Alerts:

[Posted 01/29/2010] Lilly and FDA notified healthcare professionals of changes to the Prescribing Information for olanzapine (Zyprexa) related to its indication for use in adolescents (ages 13-17) for treatment of schizophrenia and bipolar I disorder [manic or mixed episodes]. The revised labeling states that:

- Section 1, Indications and Usage: When deciding among the alternative treatments available for adolescents, clinicians should consider the increased potential (in adolescents as compared with adults) for weight gain and hyperlipidemia. Clinicians should consider the potential long-term risks when prescribing to adolescents, and in many cases this may lead them to consider prescribing other drugs first in adolescents.
- Section 17.14, Need for comprehensive Treatment Program in Pediatric Patients: Olanzapine is indicated as an integral part of a total treatment program for pediatric patients with schizophrenia and bipolar disorder that may include other measures (psychological, educational, social) for patients with the disorder. Effectiveness and safety of olanzapine have not been established in pediatric patients less than 13 years of age.

For more information visit the FDA website at: http://www.fda.gov/Safety/MedWatch/SafetyInformation and http://www.fda.gov/Drugs/DrugSafety.

■ Olanzapine is considered an atypical or second-generation antipsychotic agent.

Uses

Pending revision, the material in this section should be considered in light of more recently available information in the MedWatch notification at the beginning of this monograph.

Olanzapine is used for the symptomatic management of psychotic disorders (e.g., schizophrenia). In addition, olanzapine is used alone or in conjunction with lithium or divalproex sodium for the management of acute mixed or manic episodes associated with bipolar I disorder; the drug also is used for longer-term maintenance monotherapy in patients with this disorder. Olanzapine also is used for the management of acute agitation in patients with bipolar disorder or schizophrenia.

■ Psychotic Disorders

Olanzapine is used for the symptomatic management of psychotic disorders (e.g., schizophrenia). Drug therapy is integral to the management of acute psychotic episodes and accompanying violent behavior in patients with schizophrenia and generally is required for long-term stabilization to sustain symptom remission or control and to minimize the risk of relapse. Antipsychotic agents are the principal class of drugs used for the management of all phases of schizophrenia. Patient response and tolerance to antipsychotic agents are variable, and patients who do not respond to or tolerate one drug may be successfully treated with an agent from a different class or with a different adverse effect profile.

Schizophrenia

Olanzapine is used orally for the management of schizophrenia. Schizophrenia is a major psychotic disorder that frequently has devastating effects on various aspects of the patient's life and carries a high risk of suicide and other life-threatening behaviors. Manifestations of schizophrenia involve multiple psychologic processes, including perception (e.g., hallucinations), ideation, reality testing (e.g., delusions), emotion (e.g., flatness, inappropriate affect), thought processes (e.g., loose associations), behavior (e.g., catatonia, disorganization), attention, concentration, motivation (e.g., avolition, impaired intention and planning), and judgment. The principal manifestations of this disorder usually are described in terms of positive and negative (deficit) symptoms, and more recently, disorganized symptoms. Positive symptoms include hallucinations, delusions, bizarre behavior, hostility, uncooperativeness, and paranoid ideation, while negative symptoms include restricted range and intensity of emotional expression (affective flattening), reduced thought and speech productivity (alogia), anhedonia, apathy, and decreased initiation of goal-directed behavior (avolition). Disorganized symptoms include disorganized speech (thought disorder) and behavior and poor attention.

The American Psychiatric Association (APA) considers certain atypical antipsychotic agents (i.e., olanzapine, aripiprazole, quetiapine, risperidone, ziprasidone) first-line drugs for the management of the acute phase of schizophrenia (including first psychotic episodes), principally because of the decreased risk of adverse extrapyramidal effects and tardive dyskinesia, with the understanding that the relative advantages, disadvantages, and cost-effectiveness of conventional (first-generation) and atypical antipsychotic agents remain controversial. The APA states that, with the possible exception of clozapine for the management of treatment-resistant symptoms, there currently is no definitive evidence that one atypical antipsychotic agent will have superior efficacy compared with another agent in the class, although meaningful differences in response may be observed in individual patients. Conventional antipsychotic agents may be considered first-line in patients who have been treated successfully in the past with or who prefer conventional agents. The choice of an antipsychotic agent should be individualized, considering past response to therapy, adverse effect profile (including the patient's experience of subjective effects such as dysphoria), and the patient's preference for a specific drug, including route of administration.

To compare the long-term effectiveness and tolerability of older, first-generation antipsychotic agents (i.e., perphenazine) with those of newer, atypical antipsychotic agents (i.e., olanzapine, quetiapine, risperidone, ziprasidone), a double-blind, multicenter study (the first phase of Clinical Antipsychotic Trials of Intervention Effectiveness [CATIE]) was sponsored by the National Institute of Mental Health. More than 1400 patients with schizophrenia received one of the drugs for up to 18 months or until therapy was discontinued for any reason. Patients with tardive dyskinesia could enroll in this trial; however, the randomization scheme prevented their assignment to the perphenazine group. The primary outcome measure in this study was the discontinuance of treatment for any cause; this measure was selected because discontinuing or switching an antipsychotic agent occurs frequently and is an important problem in the management of schizophrenia. In addition, this measure integrates the patient's and clinician's judgments concerning efficacy, safety, and tolerability into a more comprehensive measure of effectiveness reflecting therapeutic benefits in relation to adverse effects. Overall, 74% of patients in this study discontinued their medication before receiving the full 18 months of therapy because of inadequate efficacy, intolerable adverse effects, or for other reasons, suggesting substantial limitations in the long-term clinical effectiveness of currently available antipsychotic agents. Olanzapine appeared to be more effective than the other drugs evaluated in this study with a lower (64%) discontinuance rate and a lower rate of hospitalization for exacerbation of schizophrenia, while no significant differences between the effectiveness of the conventional agent, perphenazine, and the other second-generation agents studied were observed (discontinuance rates were 75, 82, 74, and 79% for perphenazine, quetiapine, risperidone, and ziprasidone, respectively). The time to discontinuance of therapy for any cause was found to be longer in the olanzapine group than in the quetiapine, risperidone, perphenazine, and ziprasidone groups in this study; however, the differences between the olanzapine and perphenazine groups and between the olanzapine and ziprasidone groups did not achieve statistical significance. Although there were no significant differences in the time until discontinuance of therapy because of drug intolerance among the drugs studied, the incidences of discontinuance for certain adverse effects differed among the drugs with olanzapine discontinued more frequently because of weight gain or metabolic effects (e.g., increases in glycosylated hemoglobin [hemoglobin A_{1c}; HbA_{1c}], cholesterol, and triglycerides) and perphenazine discontinued more frequently because of adverse extrapyramidal effects.

An open, multicenter, randomized, controlled trial comparing the relative long-term effectiveness (over a 1-year period) of a group of first-generation antipsychotic agents (e.g., chlorpromazine, flupentixol [not commercially available in the US], flupentixol decanoate [not commercially available in the US], fluphenazine decanoate, haloperidol, haloperidol decanoate, loxapine, methotrimeprazine (no longer commercially available in the US), pipothiazine palmitate [not commercially available in the US], sulpiride [not commercially available in the US], trifluoperazine, zuclopenthixol [not commercially available in the US], zuclopenthixol decanoate [not commercially available in the US]) with a group of second-generation antipsychotic agents other than clozapine (e.g., olanzapine, amisulpride [not commercially available in the US], quetiapine, risperidone, zotepine [not commercially available in the US]) in patients with schizophrenia was conducted throughout the United Kingdom by the National Health Service. In the Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CUtLASS 1), the primary outcome measure was the Quality of Life Scale score, and secondary outcome measures included symptom improvement, adverse effects, patient satisfaction, and costs of health care. Patients in the first-generation antipsychotic group demonstrated a trend toward greater improvements in the Quality of Life Scale and symptom improvements scores in this study. In addition, the patients studied did not report a clear preference for either group of drugs and costs of health care in the 2 groups were found to be similar.

Emerging data from the first phase of the pivotal CATIE trial and the CUtLASS 1 trial suggest that newer, atypical antipsychotics may not provide clinically important advantages over older, first-generation antipsychotics in patients with chronic schizophrenia and that several factors, including adequacy of symptom relief, tolerability of adverse effects, and cost of therapy, may influence a patient's ability and willingness to remain on long-term antipsychotic medication. In addition, these results suggest that it may often be necessary to try 2 or more different antipsychotic agents in an individual patient in order to provide optimal therapeutic benefit with an acceptable adverse effect profile.

In a randomized, double-blind, second phase trial, patients with schizophrenia who had discontinued an atypical antipsychotic agent during the first phase of the CATIE trial were reassigned to treatment with a different atypical antipsychotic agent (olanzapine, quetiapine, risperidone, or ziprasidone). Similarly to the first phase of the CATIE trial, efficacy and tolerability in this second phase study were principally measured by time until drug discontinuance for any reason. The time until antipsychotic treatment was discontinued was longer for patients receiving risperidone and olanzapine than for those receiving quetiapine and ziprasidone (median: 7, 6.3, 4, and 2.8 months, respectively). Among patients who discontinued their prior antipsychotic agent because of lack of efficacy, olanzapine was found to be more effective than quetiapine and ziprasidone, while risperidone was more effective than quetiapine.

In another study that was part of the second phase of the CATIE investigation, schizophrenic patients who had discontinued treatment with olanzapine, quetiapine,

risperidone, or ziprasidone during the first phase of the CATIE investigation, principally because of inadequate efficacy, were randomized to receive open-label clozapine therapy or blinded treatment with another atypical antipsychotic agent not previously received in the trial. Clozapine was found to be more effective in this study than switching to another atypical antipsychotic agent. Patients receiving clozapine also were found to be less likely to discontinue treatment for any reason than patients receiving quetiapine or risperidone. In addition, the clozapine-treated patients were less likely to discontinue therapy because of an inadequate clinical response than were patients receiving the other atypical antipsychotic agents.

Pending further data clarifying the relative effectiveness and tolerability of first- and second-generation antipsychotics in the treatment of schizophrenia, many clinicians recommend that the choice of an antipsychotic agent be carefully individualized taking into consideration the clinical efficacy and adverse effect profile (including the risk for extrapyramidal effects, weight gain, and adverse metabolic effects) of the antipsychotic agent as well as the individual patient's risk factors; the patient's previous experience of subjective effects such as dysphoria; the patient's preference for and willingness to take (i.e., compliance) a specific drug, including route of administration; and the relative cost of therapy. Olanzapine and clozapine may be reasonable alternatives in any patient with schizophrenia who has not achieved a full clinical remission with other antipsychotic agents; however, the risk of adverse metabolic effects with both drugs necessitates dietary and exercise counseling before therapy is initiated, monitoring during drug therapy, and possible discontinuance of therapy if these effects become troublesome during therapy. Additional analyses from data generated by the CATIE trial addressing other schizophrenia treatment-related issues such as quality of life and predictors of response are ongoing.

For additional information on the symptomatic management of schizophrenia, see Schizophrenia and Other Psychotic Disorders under Uses: Psychotic Disorders, in the Phenothiazines General Statement 28:16.08.24.

Atypical antipsychotic agents, including olanzapine, generally appear less likely to induce adverse extrapyramidal effects and tardive dyskinesia than conventional, first-generation antipsychotic agents. In addition, stabilization of or improvement in tardive dyskinesia associated with conventional antipsychotic agents has been reported in some patients when they have been switched to second-generation antipsychotic therapy, including olanzapine. Therefore, the APA and some clinicians recommend that atypical antipsychotic agents be considered in patients with schizophrenia who have experienced tardive dyskinesia associated with conventional antipsychotic agents.

The efficacy of oral olanzapine for the management of psychotic disorders has been established in hospital settings by 2 placebo-controlled studies of 6 weeks' duration in patients who met the DSM-III-R criteria for schizophrenia. In these and several other studies, improvement in manifestations of schizophrenia was based principally on the results of various psychiatric rating scales, including the Brief Psychiatric Rating Scale (BPRS) that assesses factors such as anergy, thought disturbances, activation, hostility/suspiciousness, and anxiety/depression; the Scale for the Assessment of Negative Symptoms (SANS); the Positive and Negative Symptoms Scale (PANSS); and the Clinical Global Impression (CGI).

In the first 6-week, placebo-controlled study, olanzapine was given in a fixed dosage of 1 or 10 mg once daily. Results indicated that the 10-mg, but not the 1-mg, once-daily dosage was more effective than placebo in improving the scores on the PANSS total (also on the extracted BPRS total), the BPRS psychosis cluster, the PANSS Negative subscale, and the CGI Severity assessments. Results of the second 6-week, placebo-controlled study, which evaluated 3 fixed dosage ranges (5 ± 2.5 mg once daily, 10 ± 2.5 mg once daily, and 15 ± 2.5 mg once daily), found that the 2 highest dosages (actual mean dosages were 12 and 16 mg once daily, respectively) were more effective than placebo in reducing the BPRS total score, BPRS psychosis cluster, and CGI severity score; the highest dosage also was superior to placebo on the SANS. There appeared to be no therapeutic advantage for the higher dosage of olanzapine compared with the medium dosage in this study. No race- or gender-related differences in outcome were noted in either of these studies.

The efficacy of oral olanzapine for long-term use (i.e., longer than 6 weeks) in schizophrenia has been established in one controlled study, and the drug has been used in some other patients for prolonged periods (e.g., reportedly up to 1 year) without apparent loss of clinical effect. In the long-term clinical trial, adult outpatients who predominantly met DSM-IV criteria for schizophrenia and who remained stable on olanzapine therapy during an open-label treatment phase lasting at least 8 weeks were randomized to continue receiving their current olanzapine dosage (ranging from 10–20 mg daily) or to receive placebo. Although the follow-up period to observe patients for relapse, which was defined in terms of increases in BPRS positive symptoms or hospitalization, initially was planned for 12 months, criteria were met for stopping the trial early because of an excess of placebo relapses compared with olanzapine relapses. In addition, olanzapine was found to be superior to placebo on prolonging time to relapse, which was the primary outcome measure in this study. Therefore, olanzapine was more effective than placebo at maintaining efficacy in schizophrenic patients stabilized for approximately 8 weeks and followed for an observation period of up to 8 months. If olanzapine is used for extended periods, the need for continued therapy should be reassessed periodically.

Olanzapine has been shown to be an effective, relatively rapid-acting, broad-spectrum antipsychotic agent in both controlled and uncontrolled studies of patients with schizophrenia. Like other second-generation antipsychotic agents, olanzapine appears to improve both positive (florid symptomatology such as hallucinations, conceptual disorganization, and suspiciousness) and negative ("deficit" symptomatology such as emotional withdrawal, motor retardation, blunted affect, and disorientation) manifestations of schizophrenia; conventional antipsychotic agents may have lesser effects on negative manifestations of the disorder. Some evidence also suggests that atypical antipsychotic agents may be more effective in treating cognitive and mood symptoms as well as global psychopathology than conventional antipsychotic agents, but this is controversial and remains to be fully established. In addition, some patients with schizophrenia who have been stabilized on long-term conventional antipsychotic therapy have demonstrated further improvement following a switch to an atypical antipsychotic agent.

Results from one comparative study suggest that oral olanzapine dosages of 7.5–17.5 mg daily may be as effective as oral haloperidol dosages of 10–20 mg daily in reducing positive symptoms of schizophrenia, while oral olanzapine dosages of 12.5–17.5 mg daily may be more effective than oral haloperidol dosages of 10–20 mg daily in reducing negative symptoms of schizophrenia. However, a randomized, controlled trial comparing the long-term (i.e., 1 year) effectiveness and cost of olanzapine and haloperidol therapy in patients with schizophrenia or schizoaffective disorder did not reveal any important advantage of olanzapine compared with haloperidol on measures of compliance, symptom improvement, adverse extrapyramidal effects, overall quality of life, and cost; olanzapine also was more frequently associated with weight gain. However, olanzapine therapy was associated with reduced akathisia, less tardive dyskinesia in a secondary analysis, and small but significant improvements in measures of memory and motor function compared with haloperidol. In other comparative studies, olanzapine usually was found to be at least as effective as or more effective than haloperidol and several other atypical antipsychotic agents, including quetiapine, risperidone, and ziprasidone. In a comparative, double-blind trial conducted in patients with schizophrenia or schizoaffective disorder, both olanzapine and risperidone were found to be effective and well tolerated, although greater reductions in the severity of positive and affective symptoms were noted in the risperidone-treated patients compared with those receiving olanzapine.

Olanzapine also has been studied in patients with treatment-refractory schizophrenia (i.e., patients who have demonstrated an inadequate response to prior antipsychotic therapy) in both open and comparative clinical trials. In an open trial of 6 weeks' duration, olanzapine (15–25 mg daily) was found to be effective and well tolerated in patients with treatment-refractory schizophrenia with 36% responding to the drug. In a double-blind trial of 8 weeks' duration, although olanzapine (25 mg daily) was found to be as effective as chlorpromazine (1.2 g daily with benztropine), the total amount of improvement with either drug was modest; olanzapine was better tolerated than chlorpromazine. In a double-blind trial of 14 weeks' duration comparing efficacy and safety of several atypical antipsychotics (olanzapine, clozapine, and risperidone) with each other and with haloperidol, olanzapine (mean dosage of approximately 30 mg daily) and clozapine produced greater clinical improvement in global psychopathology and negative symptoms than haloperidol (mean dosage of approximately 26 mg daily) in patients with chronic schizophrenia or schizoaffective disorder, but the effects of atypical antipsychotic agents were considered small and of limited clinical importance. In another study using the manufacturer's clinical trial database to retrospectively identify treatment-resistant schizophrenic patients, olanzapine (mean dosage of approximately 11 mg daily) was found to be more effective than haloperidol therapy (mean dosage of approximately 10 mg daily) in improving positive, negative, and mood symptoms and produced fewer extrapyramidal effects. The results of clinical trials to date suggest that olanzapine may be somewhat less effective than or similarly effective to clozapine in the management of resistant schizophrenia patients. Clozapine generally appears to be more effective in the management of treatment-refractory schizophrenia than most first-generation and other second-generation antipsychotic agents and may produce greater improvement in negative symptoms of schizophrenia than other antipsychotic agents; however, tolerability concerns (e.g., hematologic toxicity, hypotension, dizziness, sedation) limit its use in many patients. Although higher olanzapine dosages (i.e., up to 60 mg daily) have been used in some patients with treatment-resistant schizophrenia, it remains to be established whether higher dosages of the drug result in improved efficacy in such patients, and higher dosages may increase the risk of extrapyramidal and other adverse effects.

Like some other atypical antipsychotic agents (e.g., clozapine, risperidone), olanzapine therapy appears to reduce the risk of violent behavior in patients with schizophrenia. Although the precise mechanism(s) for the antiaggressive effects are not known, improved compliance with atypical antipsychotic agents may play a role.

Olanzapine also has been used with a variety of adjunctive agents, including other antipsychotic agents, antidepressants (including selective serotonin-reuptake inhibitors such as fluoxetine and fluvoxamine), valproate (e.g., divalproex sodium, valproic acid, valproate sodium), and topiramate, in some patients with treatment-refractory schizophrenia, inadequate response to antipsychotic therapy, or acute exacerbations of schizophrenia in both controlled and uncontrolled trials. Further controlled trials of olanzapine combined with these agents are necessary to more clearly determine the potential risks and benefits of such combined therapy.

Pediatric Considerations.

Pending revision, the material in this section should be considered in light of more recently available information in the MedWatch notification at the beginning of this monograph.

Although the manufacturer states that the safety and efficacy of olanzapine in children and adolescents with schizophrenia have not been established, the drug has

been successfully used for the management of childhood-onset schizophrenia in a limited number of children and adolescents†. In addition, a double-blind, placebo-controlled trial of 6 weeks' duration conducted in adolescents 13–17 years of age with schizophrenia has demonstrated that olanzapine is effective in the management of schizophrenia, but that the drug's adverse effects on weight and prolactin concentrations may be greater in adolescents.

Based on the observed efficacy and tolerability of atypical antipsychotics in adults and the available clinical experience in pediatric patients, the American Academy of Child and Adolescent Psychiatry (AACAP) currently states that the use of atypical antipsychotic agents in children and adolescents with schizophrenia is justified, and many clinicians consider atypical antipsychotic agents, with the exception of clozapine, the drugs of first choice in the management of childhood-onset schizophrenia . However, well-controlled studies are necessary to more clearly establish the efficacy and safety of atypical antipsychotics in pediatric patients, particularly during long-term therapy. For additional information on the symptomatic management of childhood-onset schizophrenia, see Pediatric Considerations under Psychotic Disorders: Schizophrenia, in Uses in the Phenothiazines General Statement 28:16.08.24.

Acute Agitation.

Olanzapine is used IM for the management of acute agitation in patients with schizophrenia for whom treatment with olanzapine is appropriate and who require an IM antipsychotic agent for rapid control of behaviors that interfere with diagnosis and care (e.g., threatening behaviors, escalating or urgently distressing behavior, self-exhausting behavior). According to DSM-IV, psychomotor agitation is excessive motor activity associated with a feeling of inner tension. The efficacy of IM olanzapine for the management of acute agitation in patients with schizophrenia was established in 2 short-term (single-day), placebo-controlled trials in hospital settings; an active comparator treatment arm using haloperidol injection was included in both studies. The patients in this study exhibited a level of agitation that met or exceeded a threshold score of 14 on the 5 items comprising the Positive and Negative Syndrome Scale (PANSS) Excited Component (i.e., poor impulse control, tension, hostility, uncooperativeness, and excitement items) with at least one individual item score of 4 ("moderate") or greater using a 1–7 scoring system, where scores of 1 or 7 indicate absent or extreme agitation, respectively. The primary measure used for assessing efficacy in managing agitation in these trials was the change from baseline in the PANSS Excited Component at 2 hours post-injection. Patients could receive up to 3 injections of IM olanzapine; however, patients could not receive the second injection until after the initial 2-hour period when the primary efficacy measure was assessed.

In the first placebo-controlled trial, IM olanzapine was given in fixed single doses of 2.5, 5, 7.5, or 10 mg in agitated hospitalized patients with schizophrenia. All 4 IM olanzapine doses were found to be statistically superior to placebo in reducing the PANSS Excited Component score at 2 hours following injection; however, the effect was larger and more consistent for the 3 highest doses studied. There were no significant differences in efficacy noted for the 7.5- and 10-mg doses compared with the 5-mg dose in this study. In the second placebo-controlled trial in agitated patients with schizophrenia, a fixed, 10-mg dose of IM olanzapine was evaluated and found to be superior to placebo on the PANSS Excited Component at 2 hours following injection. An analysis of these 2 controlled studies as well as an additional controlled study conducted in agitated patients with bipolar mania for possible age-, race-, or gender-related effects on treatment outcome did not suggest any difference in efficacy based on these patient characteristics.

■ Bipolar Disorder

Oral olanzapine is used alone or in conjunction with lithium or divalproex sodium for the management of acute mixed or manic episodes associated with bipolar I disorder; the drug also is used orally for longer-term maintenance monotherapy in patients with this disorder. According to DSM-IV criteria, manic episodes are distinct periods lasting 1 week or longer (or less than 1 week if hospitalization is required) of abnormally and persistently elevated, expansive, or irritable mood accompanied by at least 3 (or 4 if the mood is only irritability) of the following 7 symptoms: grandiosity, reduced need for sleep, pressure of speech, flight of ideas, distractibility, increased goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation, and engaging in high-risk behavior (e.g., unrestrained buying sprees, sexual indiscretions, foolish business investments).

For the initial management of less severe manic or mixed episodes in patients with bipolar disorder, current APA recommendations state that monotherapy with lithium, valproate (e.g., valproate sodium, valproic acid, divalproex), or an antipsychotic such as olanzapine may be adequate. For more severe manic or mixed episodes, combination therapy with an antipsychotic and lithium or valproate is recommended as first-line therapy. For further information on the management of bipolar disorder, see Uses: Bipolar Disorder, in Lithium Salts 28:28.

Acute Manic Episodes

Efficacy of oral olanzapine monotherapy in the treatment of acute manic episodes has been demonstrated in 2 short-term (i.e., 3 or 4 weeks' duration), randomized, double-blind, placebo-controlled, parallel-group trials in patients who met the DSM-IV criteria for bipolar I disorder (with or without a rapid-cycling course) and who met diagnostic criteria for an acute manic or mixed episode (with or without psychotic features). Olanzapine was given in an initial dosage of 10 mg once daily in the 3-week trial and 15 mg once daily in the 4-week trial; the dosage was subsequently adjusted within the range of 5–20 mg once daily in both of these trials. The principal rating instrument used for assessing manic symptoms in these trials was the Y-MRS score, an 11-item clinician-rated scale traditionally used to assess the degree of manic symptomatology (e.g., irritability, disruptive/aggressive behavior, sleep, elevated mood, speech, increased activity, sexual interest, language/thought disorder, thought content, appearance, insight) in a range from 0 (no manic features) to 60 (maximum score). All patients were hospitalized at the onset of these trials, but some patients were allowed to continue the studies on an outpatient basis after 1 week of hospitalization if their Clinical Global Impressions-Bipolar Version of severity of illness (CGI-BP) mania score was no greater than 3 (mild) and they had at least a 50% reduction in their Young Mania Rating Scale (Y-MRS) scores. In the 3- and 4-week placebo-controlled trials, approximately 49–65% of patients receiving 5–20 mg of olanzapine once daily achieved a 50% or greater improvement in Y-MRS total score from baseline compared with approximately 24–43% of those who received placebo. In addition, unlike therapy with typical antipsychotic agents, patients receiving olanzapine in these clinical studies did not experience a worsening in depressive symptoms (defined as an increase in the Hamilton Psychiatric Rating Scale for Depression-21 item [HAMD-21] score of at least 3 points) compared with those receiving placebo. In another 3-week, placebo-controlled trial that was designed identically to the first 3-week trial and was conducted simultaneously, olanzapine demonstrated a similar treatment difference in reduction of the Y-MRS total score but was not found to be superior to placebo on this outcome measure, possibly due to sample size and site variability.

Data from one limited comparative study suggest that oral olanzapine dosages of 10 mg daily may be as effective as lithium carbonate dosages of 400 mg twice daily in the treatment of manic episodes in patients with bipolar disorder. In a randomized, double-blind trial of 3 weeks' duration comparing olanzapine (5–20 mg daily) and divalproex sodium therapy in hospitalized patients with bipolar disorder experiencing acute manic or mixed episodes, olanzapine therapy was found to produce greater improvement in Y-MRS total scores, which was the primary efficacy measure in this trial. In addition, a significantly greater proportion of patients in the olanzapine group achieved remission compared with the divalproex group. In a randomized, double-blind study of 12 weeks' duration comparing olanzapine and divalproex sodium in patients with bipolar I disorder hospitalized for acute mania, the drugs were found to be equally effective although divalproex sodium was somewhat better tolerated than olanzapine.

Combined Therapy

Efficacy of oral olanzapine when used in combination with lithium or divalproex sodium in the short-term treatment of acute manic episodes has been demonstrated in 2 randomized, double-blind, placebo-controlled studies of 6 weeks' duration in patients who met the DSM-IV criteria for bipolar I disorder (with or without a rapid-cycling course) and who met diagnostic criteria for an acute manic or mixed episode (with or without psychotic features). In these studies, patients with bipolar disorder experiencing manic or mixed episodes (Y-MRS scores of 16 or greater) who had not responded to at least 2 weeks of lithium or divalproex sodium monotherapy despite adequate plasma drug concentrations (in a therapeutic range of 0.6–1.2 mEq/L for lithium or 50–125 mcg/mL of valproate for divalproex sodium) were randomized to receive either olanzapine (initial dosage of 10 mg once daily; range: 5–20 mg once daily) or placebo, in combination with their original therapy. Addition of olanzapine to lithium or divalproex sodium was shown to be superior to continued monotherapy with lithium or divalproex sodium in the reduction of Y-MRS total score in both of these studies.

Maintenance Monotherapy of Bipolar Disorder

Oral olanzapine also is used for maintenance monotherapy in patients with bipolar disorder. The long-term efficacy of oral olanzapine as maintenance monotherapy in bipolar disorder has been demonstrated in a double-blind, placebo-controlled trial and in double-blind comparative trials. In the placebo-controlled study, patients who met DSM-IV criteria for bipolar I disorder and experienced manic or mixed episodes and who had responded during an initial open-label treatment phase to oral olanzapine therapy (5–20 mg daily) for an average of about 2 weeks were randomized either to continue olanzapine at the same dosage or to receive placebo for up to 48 weeks and were observed for relapse. Response during the open-label phase was defined as a reduction in the Y-MRS total score of 12 or more and in the 21-item Hamilton Depression Rating Scale (HAM-D 21) of 8 or more; relapse during the double-blind phase of the study was defined as an increase in the Y-MRS or HAM-D 21 total score to 15 or more or being hospitalized for either mania or depression. Approximately 50% of the patients in the olanzapine group had discontinued therapy by day 59, and approximately 50% of the patients in the placebo group had discontinued placebo by day 23 of the double-blind phase. A longer time until relapse was observed in the patients receiving olanzapine compared with those receiving placebo (median of 174 and 22 days, respectively, for relapse into any mood episode) during the randomized phase of this study. The relapse rate also was significantly lower in the olanzapine group (approximately 47%) than in the placebo group (approximately 80%). If olanzapine is used for extended periods, the need for continued therapy should be reassessed periodically.

In a double-blind, 52-week trial comparing olanzapine and lithium maintenance therapy in patients with bipolar disorder, olanzapine was found to be significantly more effective than lithium in preventing relapses and recurrences of manic and mixed episodes following initial stabilization with combined olanzapine and lithium therapy. Olanzapine and lithium demonstrated comparable efficacy in preventing relapses and recurrences of depression in this study. In a retrospective analysis from this trial, patients were subcategorized into illness stage (early, intermediate, or later) based on the number of prior manic or mixed episodes they had experienced. The rates of relapse or recurrence of manic or mixed episodes were approximately 2 and 26%, 13 and 24%,

and 24 and 33% for olanzapine and lithium in the early, intermediate, and later stage groups of bipolar patients, respectively; no substantial treatment effect for treatment or illness stage for depressive relapse or recurrence was observed. Because olanzapine was associated with a lower rate of relapse or recurrence of manic and mixed episodes in early-stage patients, it was suggested that the drug may be particularly effective early in the course of bipolar disorder.

In a double-blind, 47-week trial comparing monotherapy with olanzapine or divalproex sodium in patients with bipolar disorder experiencing manic or mixed episodes, mean improvement in Y-MRS scores was greater for olanzapine-treated patients. In addition, the median time to symptomatic mania remission was shorter for patients receiving olanzapine compared with those receiving divalproex sodium (14 days vs. 62 days, respectively). However, no significant differences in the rates of symptomatic mania remission and symptomatic relapse into mania or depression between the olanzapine- and divalproex-treated patients were observed in this study. In a double-blind, 18-month, relapse prevention trial comparing the efficacy of combined olanzapine plus lithium or valproate therapy with lithium or valproate therapy alone in patients with bipolar disorder, more sustained symptomatic remission (163 days vs 42 days, respectively) occurred in the group receiving combined olanzapine plus lithium or valproate therapy than in the group receiving lithium or valproate therapy alone.

Rapid-Cycling Bipolar Disorder

In an analysis of pooled data from several trials comparing the clinical response to olanzapine therapy in rapid-cycling and non-rapid-cycling patients with bipolar disorder, relative clinical response to olanzapine was found to be similar in the 2 groups, although earlier responses were observed in the rapid-cycling group of patients, and long-term outcomes were more favorable in the non-rapid-cycling group. Rapid-cycling patients were found to be less likely to achieve an initial symptomatic remission, more likely to experience recurrences, especially of depression, and had more hospitalizations and suicide attempts than non-rapid-cycling patients in this study.

Acute Depressive Episodes in Bipolar Disorder

In a secondary analysis of data from dysphoric manic patients participating in a placebo-controlled trial evaluating olanzapine combined with lithium or valproate therapy in patients with bipolar I disorder, the addition of olanzapine was found to improve symptoms of depression, mania, and suicidality compared with lithium or valproate therapy alone.

Olanzapine also is used in combination with fluoxetine for the treatment of acute depressive episodes in patients with bipolar disorder. In 2 randomized, double-blind studies of 8 weeks' duration comparing a fixed combination of olanzapine and fluoxetine hydrochloride (Symbyax®) with olanzapine monotherapy and placebo, the fixed combination (flexible daily dosages of 6 mg olanzapine with 25 or 50 mg of fluoxetine or 12 mg of olanzapine with 50 mg of fluoxetine) was more effective than olanzapine monotherapy (5–20 mg daily) or placebo in improvement in depressive symptoms as assessed by the Montgomery-Asberg Depression Rating Scale (MADRS). Although the manufacturer states that efficacy beyond 8 weeks' duration remains to be established, patients have received the fixed combination for up to 24 weeks in clinical trials. Clinicians who elect to extend therapy beyond 8 weeks should reevaluate the risks and benefits of continued therapy periodically.

Pediatric Considerations

Although the manufacturer states that the safety and efficacy of olanzapine in children and adolescents with bipolar disorder have not been established, the drug has been successfully used for the management of bipolar disorder in a limited number of children and adolescents†. In a double-blind, placebo-controlled, 3-week study in adolescents 13–17 years of age with bipolar disorder, olanzapine was found to be effective in the treatment of acute manic or mixed episodes; however, weight gain and hyperprolactinemia occurred more often in patients receiving olanzapine compared with those receiving placebo.

Based on the observed efficacy and tolerability of mood stabilizers and atypical antipsychotic agents in clinical trials in adults and the available clinical experience in pediatric patients, the American Academy of Child and Adolescent Psychiatry (AACAP) currently states that the mood stabilizers lithium, divalproex sodium, and carbamazepine and the atypical antipsychotics olanzapine, quetiapine, and risperidone are drugs of first choice in the acute management of pediatric patients with bipolar I disorder experiencing manic or mixed episodes without psychosis. The AACAP also currently recommends that a mood stabilizer such as lithium, divalproex sodium, or carbamazepine combined with an atypical antipsychotic be used as first line therapy in pediatric patients with bipolar I disorder experiencing manic or mixed episodes accompanied by psychosis. Additional controlled studies are necessary to more clearly establish the efficacy and safety of atypical antipsychotics in pediatric patients with bipolar disorder, particularly during long-term therapy.

Acute Agitation

Olanzapine is used IM for the management of acute agitation in patients with bipolar I disorder for whom treatment with olanzapine is appropriate and who require an IM antipsychotic agent for rapid control of behaviors that interfere with their diagnosis and care (e.g., threatening behaviors, escalating or urgently distressing behavior, self-exhausting behavior). According to DSM-IV, psychomotor agitation is excessive motor activity associated with a feeling of inner tension.

The efficacy of IM olanzapine for the management of acute agitation in patients with bipolar mania was established in a short-term (single-day), double-blind, placebo-controlled trial in agitated, hospitalized patients who met the DSM-IV criteria for bipolar I disorder and who displayed an acute manic or mixed episode with or without psychotic features. The patients in this study exhibited a level of agitation that met or exceeded a threshold score of 14 on the 5 items comprising the Positive and Negative Syndrome Scale (PANSS) Excited Component (i.e., poor impulse control, tension, hostility, uncooperativeness, and excitement items) with at least one individual item score of 4 ("moderate") or greater using a 1–7 scoring system where scores of 1 or 7 indicate absent or extreme agitation, respectively. An active comparator treatment arm using IM lorazepam was included in this study. The primary measure used for assessing efficacy in managing agitation in this trial was the change from baseline in the PANSS Excited Component at 2 hours post-injection of a fixed, 10-mg IM dose of olanzapine. Patients in this study could receive up to 3 injections of IM olanzapine; however, patients could not receive the second injection until after the initial 2-hour period when the efficacy was assessed. IM olanzapine was found to be statistically superior to placebo in reducing the PANSS Excited Component score at 2 hours and at 24 hours following the initial injection. An analysis of this study as well as 2 additional controlled studies conducted in agitated patients with schizophrenia for possible age-, race-, or gender-related effects on treatment outcome did not suggest any difference in efficacy based on these patient characteristics.

Dosage and Administration

■ Reconstitution and Administration

Olanzapine is administered orally or by IM injection.

Oral Administration

Olanzapine conventional tablets and orally disintegrating tablets are administered orally. Since food does not appear to affect GI absorption of olanzapine, the drug generally can be administered as conventional tablets or orally disintegrating tablets without regard to meals. In patients who experience persistent or troublesome daytime sedation during oral olanzapine therapy, administration of the daily dosage in the evening at bedtime may be helpful.

Patients receiving olanzapine orally disintegrating tablets should be instructed not to remove a tablet from the blister until just prior to dosing. The tablet should not be pushed through the foil. With dry hands, the blister backing should be peeled completely off the blister. The tablet should then be gently removed and immediately placed on the tongue, where it rapidly disintegrates in saliva, and then subsequently swallowed with or without liquid.

The fixed combination capsules of olanzapine with fluoxetine hydrochloride are administered orally once daily in the evening. Although the manufacturer states that food has no appreciable effect on absorption of either drug when administered alone, absorption of the drugs when administered as the fixed combination has not been studied.

Dispensing and Administration Precautions

Because of similarities in spelling, dosage intervals (once daily), and tablet strengths (5 and 10 mg) of Zyprexa® (olanzapine) and Zyrtec® (cetirizine hydrochloride, an antihistamine), extra care should be exercised in ensuring the accuracy of prescriptions for these drugs. (See Cautions: Precautions and Contraindications.)

IM Administration

Commercially available olanzapine for injection must be reconstituted prior to administration by adding 2.1 mL of sterile water for injection to single-dose vials labeled as containing 10 mg of olanzapine to provide a solution containing approximately 5 mg/mL. Other solutions should not be used to reconstitute olanzapine for injection.

Following reconstitution, olanzapine for injection should be used immediately (within 1 hour). If necessary, the reconstituted solution may be stored for up to 1 hour at 20–25°C; after 1 hour, any unused portion should be discarded. Olanzapine for injection should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

Olanzapine for injection is administered only by IM injection and should *not* be administered IV or subcutaneously. The drug should be injected slowly, deep into the muscle mass.

■ Dosage

Pending revision, the material in this section should be considered in light of more recently available information in the MedWatch notification at the beginning of this monograph.

Conventional olanzapine tablets and orally disintegrating tablets of the drug are bioequivalent. However, IM administration of a 5-mg dose of the commercially available injection results in a maximum plasma olanzapine concentration that is about fivefold higher than that resulting from a 5-mg oral dose. Dosage of olanzapine must be adjusted carefully according to individual requirements and response, using the lowest possible effective dosage.

Oral Dosage

Schizophrenia.

For the management of schizophrenia, the recommended initial oral dosage of olanzapine is 5–10 mg daily, usually given as a single daily dose. Dosage may be increased by 5 mg daily within several days, to a target dosage of 10 mg daily. Because steady-state plasma concentrations of olanzapine may not be attained for 7 days at a given dosage, subsequent dosage adjustments generally should be made at intervals of not less than 7 days, usually in increments or decrements of 5 mg once daily. An initial

dosage of 5 mg daily is recommended in debilitated patients, in those predisposed to hypotension, in those who may be particularly sensitive to the effects of olanzapine, or in those who might metabolize olanzapine slowly (e.g., nonsmoking female patients who are 65 years of age or older).

While a relationship between dosage and antipsychotic effect has not been established, the effective oral dosage of olanzapine in clinical studies generally ranged from 10–15 mg daily. The manufacturer states that increasing olanzapine dosages beyond 10 mg daily usually does not result in additional therapeutic effect and recommends that such increases generally should occur only after the patient's clinical status has been assessed. In addition, the manufacturer states that safety of dosages exceeding 20 mg daily has not been established in clinical trials. However, olanzapine occasionally has been used in controlled and uncontrolled trials and in individual patients in dosages of up to 40 mg daily; dosages of up to 60 mg daily have been used in some patients with treatment-resistant schizophrenia. It remains to be established whether higher dosages of the drug are safe and result in improved efficacy in such patients. Some clinicians state that olanzapine dosages of up to 30 mg daily may produce further clinical improvement in schizophrenia patients who did not respond adequately to dosages of up to 20 mg daily; however, they recommend that caution be exercised when dosage of the drug exceeds 40 mg daily because of the potential for serious adverse effects (e.g., extrapyramidal reactions, excitement, metabolic changes, weight gain, cardiovascular complications).

Although clinical experience generally has not revealed age-related differences in tolerance of olanzapine in adults, dosage generally should be titrated carefully in geriatric patients 65 years of age or older, usually initiating therapy at the low end of the dosage range.

The optimum duration of olanzapine therapy currently is not known, but maintenance therapy with antipsychotic agents is well established. Patients responding to olanzapine therapy should continue to receive the drug as long as clinically necessary and tolerated, but at the lowest possible effective dosage, and the need for continued therapy with the drug should be reassessed periodically.

Bipolar Disorder.

As monotherapy for the management of acute mania associated with bipolar I disorder, the recommended initial oral dosage of olanzapine is 10 or 15 mg daily, usually given as a single dose. Dosage may be increased by 5 mg daily at intervals of not less than 24 hours, reflecting the procedures in the placebo-controlled trials. The effective dosage of olanzapine in clinical studies generally has ranged from 5–20 mg daily. Safety of dosages exceeding 20 mg daily has not been established.

When administered in conjunction with lithium or divalproex sodium for the management of acute manic episodes associated with bipolar I disorder, the recommended initial oral dosage of olanzapine is 10 mg once daily. The effective dosage of olanzapine as adjunctive therapy for up to 6 weeks in clinical studies generally ranged from 5–20 mg daily. Safety of dosages exceeding 20 mg daily has not been established.

When used in fixed combination with fluoxetine hydrochloride for acute depressive episodes in patients with bipolar disorder, olanzapine is administered once daily in the evening, usually initiating therapy with a dosage of 6 mg of olanzapine and 25 mg of fluoxetine (Symbyax® 6/25). This dosage generally should be used as initial and maintenance therapy in patients with a predisposition to hypotensive reactions, patients with hepatic impairment, or those with factors that may slow metabolism of the drugs(s) (e.g., female gender, geriatric age, nonsmoking status); when indicated, dosage should be escalated with caution. In other patients, dosage can be increased according to patient response and tolerance as indicated. In clinical trials, antidepressive efficacy was demonstrated at olanzapine dosages ranging from 6–12 mg daily and fluoxetine dosages ranging from 25–50 mg daily. Dosages exceeding 18 mg of olanzapine and 75 mg of fluoxetine have not been evaluated in clinical studies.

The long-term efficacy of oral olanzapine (dosage range: 5–20 mg daily) for maintenance monotherapy in patients with bipolar disorder has been demonstrated in a double-blind, placebo-controlled trial of 52 weeks' duration and in comparative studies of 47–52 weeks' duration. The mean modal dosage of olanzapine in the placebo-controlled study was 12.5 mg daily. The manufacturer states that patients receiving oral olanzapine for extended periods should be reassessed periodically to determine the need for continued therapy.

Although the manufacturer states that efficacy of the fixed-combination of olanzapine and fluoxetine beyond 8 weeks' duration remains to be established, patients have received the fixed combination for up to 24 weeks in clinical trials. Clinicians who elect to use the fixed combination for extended periods should periodically reevaluate the long-term risks and benefits of the drug for the individual patient.

IM Dosage for Acute Agitation in Schizophrenia or Bipolar Mania

For the prompt control of acute agitation in patients with schizophrenia or bipolar mania, the recommended initial adult IM dose is 10 mg given as a single dose. A lower initial IM dose (2.5, 5, or 7.5 mg) may be considered when clinically warranted. In clinical trials, the efficacy of IM olanzapine for controlling agitation in patients with schizophrenia or bipolar mania has been demonstrated in a dosage range of 2.5–10 mg.

If agitation necessitating additional IM doses of olanzapine persists following the initial dose, subsequent single doses of up to 10 mg may be given. However, the manufacturer states that the efficacy of repeated doses of IM olanzapine in agitated patients has not been systematically evaluated in controlled clinical trials. In addition, the safety of IM dosages exceeding 30 mg daily or of 10-mg IM doses given more frequently than 2 hours after the initial dose and 4 hours after the second dose has not been evaluated in clinical trials.

Maximal dosing of IM olanzapine (e.g., 3 doses of 10 mg administered 2–4 hours apart) may be associated with a substantial risk of clinically important orthostatic hypotension. Patients who experience drowsiness or dizziness after the IM injection should remain recumbent until an examination indicates that they are not experiencing orthostatic hypotension, bradycardia, and/or hypoventilation. (See Cardiovascular Effects under Precautions and Contraindications in Cautions.)

The manufacturer states that oral therapy should replace IM therapy as soon as possible. In one controlled study evaluating IM olanzapine in acutely agitated patients, patients initially received 1–3 IM injections of olanzapine 10 mg and were then switched to oral olanzapine therapy in dosages ranging from 5–20 mg daily for a period of 4 days.

A lower initial IM olanzapine dose of 5 mg may be considered for geriatric patients or when other clinical factors warrant. In addition, a lower IM dose of 2.5 mg per injection should be considered for patients who are debilitated, who may be predisposed to hypotensive reactions, or who may be more sensitive to the pharmacodynamic effects of olanzapine.

■ Dosage in Renal and Hepatic Impairment

The manufacturer states that because only minimal amounts of olanzapine (about 7%) are excreted in urine and because the pharmacokinetics of olanzapine appear not to be altered in patients with renal or hepatic impairment, dosage adjustment is not necessary in such patients.

Cautions

The adverse effect profile of olanzapine generally is similar to that of other atypical (second-generation) antipsychotic agents (e.g., aripiprazole, clozapine, quetiapine, risperidone, ziprasidone). Although olanzapine differs chemically from the phenothiazines, the drug also may be capable of producing many of the toxic manifestations of phenothiazine derivatives. (See Cautions in the Phenothiazines General Statement 28:16.08.24.) Not all adverse effects of the phenothiazines have been reported with olanzapine, but the possibility that they may occur should be considered. Adverse effects of olanzapine, other atypical antipsychotics, and the phenothiazines are numerous and may involve nearly all body organ systems.

In controlled studies, the most common adverse effects occurring more frequently in patients receiving oral olanzapine for schizophrenia or bipolar mania than in those receiving placebo included central and autonomic nervous system effects such as somnolence, asthenia, dry mouth, dizziness, tremor, personality disorder, and akathisia; cardiovascular system effects such as postural hypotension; GI effects such as constipation, dyspepsia, and increased appetite; and weight gain. There was no clear relationship between the incidence of adverse events and dosage in patients receiving oral olanzapine for schizophrenia in placebo-controlled trials except for certain extrapyramidal symptoms, asthenia, dry mouth, nausea, somnolence, and tremor. Discontinuance of olanzapine therapy was required in 5% of patients with schizophrenia compared with 6% for placebo in controlled trials; however, discontinuance because of increased serum ALT (SGPT) concentrations was required in 2% of the olanzapine-treated patients compared with none of those receiving placebo, and this adverse effect was considered to be drug related. Similar between olanzapine and placebo discontinuance rates were observed in the controlled trials for oral olanzapine for bipolar mania (2% for olanzapine and 2% for placebo) and IM olanzapine for acute agitation (0.4% for IM olanzapine and 0% for placebo).

Adverse effects occurring in 5% or more of patients with schizophrenia receiving oral olanzapine in short-term clinical studies and with an incidence of at least twice that of placebo included dizziness (11%), constipation (9%), personality disorder (i.e., nonaggressive objectionable behavior; 8%), weight gain (6%), postural hypotension (5%), and akathisia (5%).

Adverse effects occurring in 6% or more of patients with acute mania associated with bipolar disorder receiving oral olanzapine in clinical studies and with an incidence of at least twice that of placebo included somnolence (35%), dry mouth (22%), dizziness (18%), asthenia (15%), constipation (11%), dyspepsia (11%), increased appetite (6%), and tremor (6%).

When oral olanzapine was used in conjunction with lithium or divalproex sodium for treatment of acute mania associated with bipolar disorder, adverse effects occurring in 5% or more of patients in clinical studies and with an incidence of at least twice that of placebo included dry mouth (32%), weight gain (26%), increased appetite (24%), dizziness (14%), back pain (8%) constipation (8%), speech disorder (7%), increased salivation (6%), amnesia (5%), and paresthesia (5%).

When IM olanzapine was used for the management of acute agitation in short-term clinical studies, somnolence was the only adverse effect that occurred in 5% or more of patients with schizophrenia or bipolar mania and with an incidence at least twice that of placebo (6% and 3%, respectively).

Nervous System Effects Seizures

Seizures occurred in about 0.9% of patients receiving oral olanzapine in controlled clinical trials during premarketing testing. Confounding factors that may have contributed to the occurrence of seizures were present in many of these cases. Myoclonic status reportedly occurred shortly after initiation of olanzapine in one patient with probable dementia of the Alzheimer's type (Alzheimer's disease) who was concurrently receiving citalopram and donepezil; the myoclonic jerks in this patient

coincided with EEG changes indicative of seizure activity (spikes and polyspike/wave complexes), and the seizures subsided following discontinuance of olanzapine. A new-onset seizure also reportedly occurred in an adult female patient upon the addition of quetiapine to maintenance therapy with olanzapine and following discontinuance of clonazepam therapy. In addition, an apparent lowering of seizure threshold occurred in at least 2 epileptic patients who experienced increased seizure activity following initiation of olanzapine therapy that resolved upon discontinuance of the drug. Fatal status epilepticus also has been reported in a patient who had been receiving olanzapine therapy for 5 months.

Olanzapine should be administered with caution to patients with a history of seizures, with conditions known to lower the seizure threshold (e.g., Alzheimer's disease, geriatric patients), and during concurrent therapy with drugs that may lower seizure threshold.

Extrapyramidal Reactions

Like other atypical antipsychotic agents, olanzapine has a low potential for causing certain adverse extrapyramidal effects (e.g., dystonias). Results from controlled clinical trials suggest that extrapyramidal reactions associated with olanzapine therapy are dose related.

Tremor was reported in about 4% of patients receiving oral olanzapine and in about 1% of patients receiving IM olanzapine in controlled clinical trials; the incidence of tremor appears to be dose related. In addition, akathisia occurred in about 3% of patients receiving oral olanzapine and in less than 1% of patients receiving IM olanzapine; hypertonia occurred in about 3% of patients receiving oral olanzapine in short-term controlled clinical trials. Akinesia and cogwheel rigidity have been reported in less than 1% of patients; these adverse effects have not been definitely attributed to the drug. Oculogyric crisis also has been reported in a patient receiving olanzapine, lithium, and paroxetine concurrently. (See Drug Interactions: Other CNS-Active Agents and Alcohol.)

Neuroleptic Malignant Syndrome

Neuroleptic malignant syndrome (NMS), a potentially fatal symptom complex, has been reported in patients receiving antipsychotic agents, including olanzapine. Clinical manifestations of NMS generally include hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac arrhythmias). Additional signs of NMS may include increased serum creatine kinase (CK, creatine phosphokinase, CPK), myoglobinuria (rhabdomyolysis), and acute renal failure. NMS attributable to olanzapine therapy alone has been reported in some patients, and there also have been reports of NMS in olanzapine-treated patients concomitantly receiving other drugs, including antipsychotic agents, antidepressants, lithium, or valproate. Extrapyramidal reactions were present in approximately two-thirds of the olanzapine-treated patients diagnosed with NMS. Atypical presentations of NMS (e.g., absence of or lessened rigidity, presenting as fever of unknown origin) and less severe presentations of NMS also have been reported in some patients receiving olanzapine or other atypical antipsychotic agents.

The diagnostic evaluation of patients with NMS is complicated. In arriving at a diagnosis, serious medical illnesses (e.g., pneumonia, systemic infection) and untreated or inadequately treated extrapyramidal signs and symptoms must be excluded. In addition, clinical features of NMS and serotonin syndrome sometimes overlap, and it has been suggested that these 2 syndromes may share certain underlying pathophysiologic mechanisms. Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary CNS pathology.

The management of NMS should include immediate discontinuance of antipsychotic agents and other drugs not considered essential to concurrent therapy, intensive symptomatic treatment and medical monitoring, and treatment of any concomitant serious medical problems for which specific treatments are available. There currently is no specific drug therapy for NMS, although dantrolene, bromocriptine, amantadine, and benzodiazepines have been used in a limited number of patients. If a patient requires antipsychotic therapy following recovery from NMS, the potential reintroduction of drug therapy after several weeks should be carefully considered. If antipsychotic therapy is reintroduced, the dosage generally should be increased gradually and an antipsychotic agent other than the agent believed to have precipitated NMS generally is chosen. In addition, such patients should be carefully monitored since recurrences of NMS have been reported in some patients. For additional information on NMS, see Neuroleptic Malignant Syndrome under Cautions: Nervous System Effects, in the Phenothiazines General Statement 28:16.08.24.

Tardive Dyskinesia

Use of antipsychotic agents may be associated with tardive dyskinesia, a syndrome of potentially irreversible, involuntary, dyskinetic movements. Although the incidence of tardive dyskinesia appears to be highest among geriatric individuals, particularly geriatric females, it is not possible to reliably predict at the beginning of antipsychotic therapy which patients are likely to develop this syndrome. Tardive dyskinesia has been reported in less than 1% of patients receiving olanzapine therapy. Although the manufacturer states that it is not yet known whether antipsychotic agents differ in their potential to cause tardive dyskinesia, available evidence suggests that the risk appears to be substantially less with second-generation antipsychotic agents, including olanzapine, than with conventional, first-generation antipsychotic agents. Analyses from controlled, long-term trials have found an approximately 12-fold lower risk of tardive dyskinesia with olanzapine therapy compared with haloperidol therapy. In addition, stabilization of or improvement in tardive dyskinesia associated with conventional antipsychotic agents has been reported in some patients when they have been switched to second-generation antipsychotic therapy, including olanzapine. However, a transient increase in dyskinetic movements (sometimes referred to as withdrawal-emergent dyskinesia) occasionally may occur when a patient is switched from a first-generation to a second-generation antipsychotic agent or upon dosage reduction of an antipsychotic agent.

The risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, following relatively brief treatment periods at low dosages. There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic therapy is discontinued. However, antipsychotic therapy itself may suppress or partially suppress the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that such symptomatic suppression has upon the long-term course of tardive dyskinesia is unknown. There also is some evidence that vitamin E administration may reduce the risk of development of tardive dyskinesia; therefore, the American Psychiatric Association (APA) currently states that patients receiving antipsychotic agents may be advised to take 400-800 units of vitamin E daily for prophylaxis. (See Cautions in Vitamin E 88:20.)

Olanzapine should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment generally should be reserved for patients who suffer from a chronic illness that is known to respond to antipsychotic agents, and for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought, and the need for continued treatment should be reassessed periodically. The APA currently recommends that all patients receiving second-generation antipsychotic agents be assessed clinically for abnormal involuntary movements every 12 months and that patients considered to be at increased risk for tardive dyskinesia be assessed every 6 months. If signs and symptoms of tardive dyskinesia appear in a patient receiving olanzapine, drug discontinuance or a reduction in dosage should be considered. However, some patients may require treatment with olanzapine or another antipsychotic agent despite the presence of the syndrome. For additional information on tardive dyskinesia, see Tardive Dyskinesia under Cautions: Nervous System Effects, in the Phenothiazines General Statement 28:16.08.24.

Other Nervous System Effects

Somnolence or sedation, which usually appears to be moderate in severity compared with other antipsychotic agents and dose related, is among the most common adverse effects of olanzapine, occurring in approximately 29% of patients receiving oral olanzapine in controlled clinical trials. Somnolence associated with olanzapine and other antipsychotic agents generally is most pronounced during early therapy, since most patients develop some tolerance to the sedating effects with continued administration. Although sedation can have therapeutic benefits in some cases, persistent daytime drowsiness and increased sleep time can become troublesome in some patients and necessitate a lower dosage or evening administration of the drug. (See Administration under Dosage and Administration and see also Effects on Sleep under Pharmacology: Nervous System Effects.)

Insomnia occurred in about 12%, dizziness in about 11%, asthenia in about 10%, and abnormal gait in about 6% of patients receiving oral olanzapine in short-term controlled clinical trials. The incidence of asthenia appears to be dose related. In addition, articulation impairment was reported in about 2% of patients receiving oral olanzapine in short-term, controlled clinical trials.

Abnormal dreams, amnesia, delusions, emotional lability, euphoria, manic reaction, paresthesia, and schizophrenic reaction each has been reported in at least 1% of patients receiving oral olanzapine; however, a causal relationship to the drug has not been established. Alcohol misuse, antisocial reaction, ataxia, CNS stimulation, delirium, dementia, and depersonalization have been reported in less than 1% of patients; these adverse effects have not been definitely attributed to the drug.

Dysarthria, facial paralysis, hypesthesia, hypokinesia, hypotonia, incoordination, increased or decreased libido, migraine, obsessive-compulsive symptoms, phobias, somatization, and stimulant misuse have been reported in less than 1% of patients receiving oral olanzapine; these adverse effects have not been definitely attributed to the drug. Although a causal relationship has not been established, stupor, stuttering, vertigo, and withdrawal syndrome also have been reported in up to 1% of patients receiving oral olanzapine. Circumoral paresthesia, coma, encephalopathy, neuralgia, neuropathy, nystagmus, paralysis, suicide attempt, subarachnoid hemorrhage, and tobacco misuse have been reported in less than 0.1% of patients receiving oral olanzapine; however, a causal relationship to the drug has not been clearly established.

In short-term (i.e., 24-hour), controlled clinical trials of IM olanzapine for acute agitation, somnolence occurred in approximately 6%, dizziness in approximately 4%, and asthenia in about 2% of the patients. Abnormal gait, articulation impairment, confusion, and emotional lability have been reported in less than 1% of patients; these adverse effects have not been definitely attributed to the drug.

Cardiovascular Effects Hemodynamic Effects

Oral olanzapine may produce orthostatic hypotension that may be associated with dizziness, tachycardia, and, in some patients, syncope, particularly during the initial

period of dosage titration. In short-term, controlled clinical trials for oral olanzapine, postural hypotension and tachycardia occurred in approximately 3% and hypertension occurred in approximately 2% of patients. In addition, hypotension has been reported in at least 1% of patients receiving oral olanzapine in the short-term controlled clinical trials. Bradycardia, congestive heart failure, and vasodilatation have been reported in less than 1% of patients; these adverse effects have not been definitely attributed to the drug. These effects probably are due to the drug's α_1-adrenergic blocking activity.

Hypotension, bradycardia with or without hypotension, tachycardia, and syncope also were reported during the clinical trials with IM olanzapine. In an open trial in nonagitated patients with schizophrenia designed to evaluate the safety and tolerability of a dosage regimen of three 10-mg IM doses of olanzapine administered 4 hours apart, approximately one-third of the patients experienced a substantial orthostatic decrease in systolic blood pressure (i.e., decrease of 30 mm Hg or more).

Syncope was reported in 0.6% of olanzapine-treated patients in phase 2 and 3 clinical trials of oral olanzapine and in 0.3% of patients receiving IM olanzapine in the acute agitation clinical trials. In phase 1 trials of olanzapine, 3 healthy volunteers experienced hypotension, bradycardia, and sinus pauses of up to 6 seconds that spontaneously resolved; 2 of these cases occurred in association with IM olanzapine and one case involved oral olanzapine. In short-term, controlled clinical trials for IM olanzapine for acute agitation, hypotension occurred in approximately 2% and postural hypotension occurred in approximately 1% of the patients. Syncope has been reported in less than 1% of the patients receiving IM olanzapine in clinical trials. The manufacturer states that the risk for this sequence of hypotension, bradycardia, and sinus pause may be greater in nonpsychiatric patients compared with psychiatric patients, who may be more adapted to certain pharmacologic effects of psychotropic agents. (See Dosage and Administration and see also Cardiovascular Effects, under Cautions: Precautions and Contraindications.)

ECG Effects

Pooled analyses from controlled clinical trials did not reveal statistically significant differences in the proportions of olanzapine-treated patients experiencing potentially important ECG changes, including QT, QT_c, and PR intervals. Olanzapine was associated with a mean increase in heart rate of 2.4 beats per minute compared with no change among placebo patients in controlled trials. The manufacturer states that the slight tendency to cause tachycardia may be related to olanzapine's potential for inducing orthostatic changes in blood pressure. Like some other antipsychotic agents, olanzapine has been associated with prolongation of the QT_c interval in some patients and there is some evidence that higher dosages of the drug may increase the risk of QT_c interval prolongation; however, the clinical relevance of these findings remains to be established.

Other Cardiovascular Effects

In short-term, controlled clinical trials for oral olanzapine, chest pain occurred in approximately 3% of patients. Atrial fibrillation, cerebrovascular accident, cardiac arrest, hemorrhage, pallor, palpitation, and ventricular extrasystoles have been reported in less than 1% of patients; these adverse effects have not been definitely attributed to the drug.

Although a causal relationship has not been established, arteritis and heart failure have been reported in less than 0.1% of patients receiving oral olanzapine. In addition, venous thromboembolic effects, including pulmonary embolism and deep venous thrombosis, have been reported in patients receiving olanzapine during postmarketing surveillance.

In controlled clinical trials for IM olanzapine for acute agitation, AV block and heart block have been reported in less than 1% of the patients receiving IM olanzapine.

Hepatic Effects

During premarketing clinical trials, olanzapine therapy was associated with asymptomatic elevations in serum aminotransferase (transaminase) concentrations, including elevations in serum concentrations of ALT (SGPT), AST (SGOT), and γ-glutamyltransferase (GGT). Clinically important ALT elevations (3 or more times the upper limit of the normal range) were observed in 2% (6 of 243) of patients exposed to olanzapine in placebo-controlled clinical studies; none of these patients experienced jaundice. In 2 of these patients, the transaminases decreased toward normal values despite continued therapy, and in 2 other patients, the transaminases decreased upon discontinuance of olanzapine therapy. In the 2 remaining patients, one patient, who was seropositive for hepatitis C, had persistent transaminase elevations for 4 months after discontinuance of therapy, and the other patient had insufficient follow-up to determine whether the transaminase elevation normalized. Within the larger premarketing database of about 2400 patients with baseline ALT values of 90 IU/L or less, the incidence of SGPT elevation exceeding 200 IU/L was 2% (50 of 2381 patients). None of these patients experienced jaundice or other symptoms attributable to hepatic impairment, and most had transient changes that tended to normalize while olanzapine therapy was continued. Among 2500 patients receiving oral olanzapine in clinical trials, about 9% of the patients experienced transient elevations in serum transaminase levels, usually within 1–2 weeks following initiation of therapy, and the median time to maximal levels in these patients was about 4 weeks; olanzapine therapy was discontinued in about 1% (23 of 2500) of the patients because of transaminase elevations. (See Cautions: Precautions and Contraindications.)

Hepatitis has rarely been reported in postmarketing experience, as well as very rare cases of cholestatic or mixed hepatic injury. In addition, fatty deposit in the liver has been reported in less than 0.1% of patients receiving oral olanzapine in short-term clinical trials, although a causal relationship to the drug remains to be established.

Endocrine and Metabolic Effects Weight Gain

Like some conventional (first-generation) and atypical (second-generation) antipsychotic agents, olanzapine therapy may result in weight gain. In placebo-controlled studies of 6 weeks' duration, weight gain occurred in approximately 6% of patients receiving oral olanzapine, and increased appetite occurred in 3% of patients receiving oral olanzapine in short-term controlled trials. Patients receiving olanzapine in the 6-week, placebo-controlled studies gained an average of 2.8 kg compared with an average loss of 0.4 kg in those receiving placebo; 29% of the olanzapine-treated patients gained greater than 7% of their baseline weight compared with 3% of placebo recipients. Patients with a low body mass index (BMI) in these studies appeared to be more susceptible to olanzapine-induced weight gain than normal or overweight patients, although weight gain was substantially greater in all 3 groups compared with placebo. During long-term continuation therapy with olanzapine, 56% of olanzapine-treated patients gained greater than 7% of their baseline weight; the average weight gain observed during long-term therapy was 5.4 kg.

Although the precise mechanism(s) remains to be clearly established, weight gain may result at least in part from the drug's serotonergic-, histaminergic-, and adrenergic-blocking properties. Weight gain has been reported to be troublesome for some patients during long-term therapy with atypical antipsychotics, particularly olanzapine and clozapine, and may be an important cause of outpatient noncompliance. Some clinicians suggest regular physical exercise and nutritional counseling in the prevention and treatment of weight gain associated with these drugs. There currently are no well established pharmacologic treatments for antipsychotic agent-induced weight gain; however, a number of drugs, including amantadine, bupropion, histamine H_2-receptor antagonists (e.g., nizatidine) orlistat, metformin, sibutramine, and topiramate, have been used with limited success to date. Because the potential risk of adverse effects in patients receiving these drugs may outweigh their possible weight-reducing effects in some cases, routine use of pharmacologic therapy currently is not recommended by most clinicians, although individual patients may benefit. Additional controlled studies are needed to more clearly determine the optimum management of antipsychotic-associated weight gain during long-term therapy with these drugs.

Hyperglycemia and Diabetes Mellitus

Severe hyperglycemia, sometimes associated with ketoacidosis, hyperosmolar coma, or death, has been reported in patients receiving certain atypical antipsychotic agents, including olanzapine. While confounding factors such as an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population make it difficult to establish with certainty the relationship between use of agents in this drug class and glucose abnormalities, epidemiologic studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotic agents included in the studies (e.g., olanzapine, clozapine, quetiapine, risperidone). (See Cautions: Precautions and Contraindications.)

Precise risk estimates for hyperglycemia-related adverse events in patients treated with atypical antipsychotics currently are not available. While some evidence suggests that the risk for diabetes may be greater with some atypical antipsychotics (e.g., olanzapine, clozapine) than with others (e.g., quetiapine, risperidone) in the class, available data are conflicting and insufficient to provide reliable estimates of relative risk associated with use of the various atypical antipsychotics.

Diabetes mellitus has been reported in less than 1% of patients and diabetic acidosis has been reported in less than 0.1% of patients receiving oral olanzapine in short-term, controlled clinical trials.

Hyperlipidemia

Like some other antipsychotic agents, particularly clozapine, olanzapine therapy has been associated with hyperlipidemia, including elevations in serum triglyceride and cholesterol concentrations.

In clinical trials in olanzapine-treated patients with random triglyceride concentrations of less than 150 mg/dL at baseline, 0.5% of patients experi-enced elevated triglyceride concentrations of 500 mg/dL or higher at any time, and severely elevated triglyceride concentrations of 1000 mg/dL or more have been reported rarely during postmarketing surveillance. During the same trials, olanzapine-treated patients experienced a mean increase of 20 mg/dL in triglyceride concentrations from a mean baseline value of 175 mg/dL.

In placebo-controlled trials, olanzapine-treated patients who had random cholesterol concentrations of less than 200 mg/dL at baseline experienced elevated cholesterol concentrations of 240 mg/dL or higher at any time during the trials more frequently than those receiving placebo (approximately 4% and 2% of patients, respectively). In these trials, olanzapine-treated patients had a mean increase of 0.4 mg/dL in serum cholesterol concentrations while those receiving placebo had a mean decrease of 4.6 mg/dL, both from a mean baseline value of 203 mg/dL.

Hypercholesterolemia and hyperlipidemia have been reported in less than 1% of patients receiving oral olanzapine in short-term trials. In addition, cholesterol concentration of 240 mg/dL or higher have been reported rarely during postmarketing surveillance.

Although the manufacturer currently does not recommend routine monitoring of lipid parameters in patients receiving olanzapine, the APA recommends a baseline

lipid panel in all patients with schizophrenia and recommends that this be repeated at least every 5 years. In addition, some clinicians recommend that lipid profiles be monitored at baseline and periodically (e.g., every 3–6 months) in all patients receiving long-term therapy with atypical antipsychotic agents. There is some evidence from a study in individuals with developmental disabilities that the risk of hyperlipidemia in patients receiving atypical antipsychotic agents may be minimized or avoided by careful monitoring, dietary management, and suitable physical activity. In patients who develop persistent and clinically important hyperlipidemia during olanzapine therapy, nondrug therapies and measures (e.g., dietary management, weight control, an appropriate program of physical activity) and drug therapy (e.g., antilipemic agents) may be helpful. Consideration also may be given to switching to an alternative antipsychotic agent that is less frequently associated with hyperlipidemia (such as aripiprazole, risperidone, or ziprasidone).

Hyperprolactinemia

As with other drugs that antagonize dopamine D_2 receptors, olanzapine can elevate serum prolactin concentrations, and a modest elevation may persist during chronic administration of the drug. However, in contrast to conventional (first-generation) antipsychotic agents and similar to many other atypical antipsychotic agents, olanzapine therapy in usual dosages generally produces relatively modest and transient elevations in serum prolactin concentrations in humans. It has been suggested that the more transient effect of atypical antipsychotic agents on prolactin may be because these drugs appear to dissociate from dopamine receptors more rapidly than conventional antipsychotic agents.

Olanzapine is considered by many experts to be low in its potential for inducing hyperprolactinemia, and it has been recommended along with other prolactin-sparing atypical antipsychotics (e.g., aripiprazole, clozapine, quetiapine, ziprasidone) in patients with schizophrenia who are at risk of hyperprolactinemia. Although clinical disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been associated with prolactin-elevating drugs, the clinical importance of elevated prolactin concentrations is unknown for most patients.

Like other drugs that increase prolactin, an increase in mammary gland neoplasia was observed in olanzapine carcinogenicity studies conducted in mice and rats. However, neither clinical studies nor epidemiologic studies have demonstrated an association between chronic administration of dopamine antagonists and tumorigenesis in humans; the available evidence is considered too limited to be conclusive. (See Cautions: Precautions and Contraindications and see also Cautions: Mutagenicity and Carcinogenicity.) In patients who develop elevated prolactin concentrations during antipsychotic therapy, some clinicians recommend reducing the dosage of the current antipsychotic agent or switching to a prolactin-sparing antipsychotic agent. Dopamine receptor agonists (e.g., bromocriptine) also may be helpful, and estrogen replacement therapy may be considered in hypoestrogenic female patients.

Other Endocrine and Metabolic Effects

Peripheral edema has been reported in approximately 3% of patients receiving oral olanzapine in short-term clinical trials. Acidosis, increased serum alkaline phosphatase concentrations, bilirubinemia, dehydration, hypoglycemia, hypokalemia, hyponatremia, lower extremity edema, and upper extremity edema have been reported in less than 1% of patients receiving oral olanzapine in short-term trials; however, a causal relationship remains to be established. Goiter, gout, hyperkalemia, hypernatremia, hypoproteinemia, ketosis, and water intoxication have been reported in less than 0.1% of patients receiving oral olanzapine; these adverse effects have not been definitely attributed to the drug.

Adverse metabolic effects that have been reported in less than 1% of patients receiving IM olanzapine in short-term clinical trials include increased serum creatine phosphokinase concentrations, dehydration, and hyperkalemia; however, a causal relationship remains to be established.

GI Effects

Dryness of the mouth and constipation both occurred in about 9%, dyspepsia in about 7%, vomiting in about 4%, and increased appetite in about 3% of patients receiving oral olanzapine in short-term controlled clinical trials.

Flatulence, increased salivation, and thirst have been reported in at least 1% of patients receiving oral olanzapine in short-term clinical trials. Dysphagia, esophagitis, fecal impaction, fecal incontinence, gastritis, gastroenteritis, gingivitis, melena, mouth ulceration, nausea and vomiting, oral moniliasis, periodontal abscess, rectal hemorrhage, stomatitis, tongue edema, and tooth caries have been reported in less than 1% of olanzapine-treated patients; these adverse effects have not been definitely attributed to the drug.

Abdominal pain, diarrhea, and nausea have been reported in less than 1% of patients receiving IM olanzapine in clinical trials; these adverse effects have not been definitely attributed to the drug.

Aphthous stomatitis, enteritis, eructation, esophageal ulcer, glossitis, ileus, intestinal obstruction, and tongue discoloration have been reported in less than 0.1% of patients receiving oral olanzapine in short-term clinical trials, although a causal relationship to the drug remains to be established.

Respiratory Effects

Rhinitis occurred in about 7%, increased cough in about 6%, and pharyngitis in about 4% of patients receiving oral olanzapine in short-term controlled clinical trials. Dyspnea has been reported in at least 1% of patients receiving oral olanzapine in short-term clinical trials. Apnea, asthma, epistaxis, hemoptysis, hyperventilation, hypoxia, laryngitis, and voice alteration have been reported in less than 1% of olanzapine-treated patients; these adverse effects have not been definitely attributed to the drug. In addition, dyspnea and hyperventilation, which appeared to be dose related, have been reported together in a patient treated with oral olanzapine.

Atelectasis, hiccup, hypoventilation, lung edema, and stridor have been reported in less than 0.1% of patients receiving oral olanzapine; however, a causal relationship to the drug has not been clearly established. Respiratory failure developed in a geriatric individual with chronic lung disease who was receiving olanzapine therapy; although not clearly established, it was suggested that the respiratory failure was due at least in part to the sedative effect of the drug.

Dermatologic and Sensitivity Reactions

Sweating has been reported in at least 1% of patients receiving oral olanzapine and in less than 1% of patients receiving IM olanzapine in short-term clinical trials. Alopecia, contact dermatitis, dry skin, eczema, maculopapular rash, photosensitivity reaction, pruritus, seborrhea, skin discoloration (e.g., hyperpigmentation), skin ulcer, urticaria, and vesiculobullous rash have been reported in less than 1% of olanzapine-treated patients; these adverse effects have not been definitely attributed to the drug. Hirsutism and pustular rash have been reported in less than 0.1% of patients receiving oral olanzapine; however, a causal relationship to the drug has not been clearly established.

Allergic reactions (e.g., anaphylactoid reaction, angioedema, pruritus, urticaria) have been reported during postmarketing surveillance of olanzapine. In addition, a hypersensitivity syndrome consisting of a severe and generalized pruritic eruption, fever, eosinophilia, and toxic hepatitis has been reported in at least one olanzapine-treated patient; the manifestations improved following discontinuance of the drug, and skin and liver biopsy results suggested that the hypersensitivity syndrome was caused by olanzapine. Eruptive xanthomas, which are associated with hyperlipidemia, have occurred in several patients receiving olanzapine therapy. Leukocytoclastic vasculitis also has been reported in a geriatric patient receiving olanzapine and warfarin concurrently; the vasculitis improved following discontinuance of olanzapine in this patient but recurred when the drug was subsequently reintroduced.

Local Effects

Pain at the injection site also has been reported in at least 1% of patients receiving IM olanzapine in controlled clinical trials.

Genitourinary Effects

Urinary incontinence and urinary tract infection both have been reported in approximately 2% and vaginitis has been reported in at least 1% of patients receiving oral olanzapine in short-term controlled clinical trials, although a causal relationship to the drug remains to be established. Abnormal ejaculation, amenorrhea, breast pain, cystitis, decreased menstruation, dysuria, female lactation, glycosuria, gynecomastia, and hematuria have been reported in less than 1% of olanzapine-treated patients; these adverse effects have not been definitely attributed to the drug.

Impotence, increased menstruation, menorrhagia, metrorrhagia, polyuria, premenstrual syndrome, pyuria, urinary frequency, urinary retention, urinary urgency, impaired urination, enlarged uterine fibroids, and vaginal hemorrhage have been reported in less than 1% of patients receiving oral olanzapine in short-term clinical trials; however, a causal relationship to the drug remains to be established. Albuminuria, breast enlargement, mastitis, and oliguria have been reported in less than 0.1% of patients receiving oral olanzapine; however, these adverse effects have not been definitely attributed to the drug.

Priapism also has been reported in several male patients and at least one case of clitoral priapism has been reported in a female patient. The α-adrenergic blocking effect of olanzapine appears to be responsible for this rare but potentially serious adverse effect requiring immediate medical attention to prevent long-term consequences such as erectile dysfunction.

Musculoskeletal Effects

Joint pain, back pain, and extremity (other than joint) pain have been reported in 5% and joint stiffness and muscle twitching in more than 1% of patients receiving oral olanzapine; muscle twitching also has been reported in less than 1% of patients receiving IM olanzapine in short-term controlled clinical trials. Arthritis, arthrosis, leg cramps, and myasthenia have been reported in less than 1% of olanzapine-treated patients; these adverse effects have not been definitely attributed to the drug. Bone pain, bursitis, myopathy, osteoporosis, and rheumatoid arthritis have been reported in less than 0.1% of patients receiving oral olanzapine; however, a causal relationship to the drug has not been clearly established. Rhabdomyolysis also has been reported rarely in olanzapine-treated patients and may be seen as one of the clinical features of NMS. (See Neuroleptic Malignant Syndrome in Cautions: Nervous System Effects.)

Ocular and Otic Effects

Amblyopia has been reported in 3% of patients, and conjunctivitis has been reported in at least 1% of patients receiving oral olanzapine in short-term clinical trials; however, a causal relationship to the drug for these effects remains to be established. Accommodation abnormality, blepharitis, cataract, deafness, diplopia, dry eyes, ear pain, eye hemorrhage, eye inflammation, eye pain, ocular muscle abnormality, and tinnitus have been reported in less than 1% of olanzapine-treated patients; these adverse effects have not been definitely attributed to the drug. In addition, corneal lesion, glaucoma, keratoconjunctivitis, macular hyperpigmentation, miosis, mydriasis, and pigment

deposits in the eye lens have been reported in less than 0.1% of patients receiving oral olanzapine; however, a causal relationship to the drug has not been clearly established.

Hematologic Effects

Because of concern about neutropenia associated with other psychotropic agents (e.g., clozapine) and the finding of leukopenia associated with the administration of olanzapine in several animal models, hematologic parameters were carefully evaluated during premarketing clinical trials with olanzapine. There was no indication of a risk of clinically important neutropenia in olanzapine-treated patients in the premarketing database for the drug.

Ecchymosis has been reported in 5% of patients receiving oral olanzapine in short-term clinical trials; however, a causal relationship to the drug remains to be established. Anemia has been reported in less than 1% of patients receiving oral or IM olanzapine; this adverse effect has not been definitely attributed to the drug. Cyanosis, leukocytosis, leukopenia, lymphadenopathy, and thrombocytopenia have been reported in less than 1% of patients receiving oral olanzapine; however, a causal relationship to the drug remains to be established.

During premarketing clinical trials, asymptomatic elevation of the eosinophil count was reported in approximately 0.3% of patients receiving oral olanzapine. In addition, normocytic anemia and thrombocythemia have been reported in less than 0.1% of patients receiving oral olanzapine; however, a causal relationship to the drug has not been clearly established.

Other Adverse Effects

Accidental injury has been reported in approximately 12% of patients receiving oral olanzapine in short-term controlled trials. Fever has been reported in approximately 6% of patients receiving oral olanzapine and in less than 1% of patients receiving IM olanzapine in short-term clinical trials. Dental pain and flu syndrome have been reported in at least 1% of patients receiving oral olanzapine in short-term clinical trials; however, a causal relationship to the drug remains to be established. Enlarged abdomen, chills, facial edema, intentional injury, malaise, moniliasis, neck pain, neck rigidity, pelvic pain, and taste perversion have been reported in less than 1% of oral olanzapine-treated patients; these adverse effects have not been definitely attributed to the drug. In addition, chills accompanied by fever, hangover effect, and sudden death have been reported in less than 0.1% of patients receiving oral olanzapine; however, a causal relationship to the drug has not been clearly established.

Pancreatitis, which has been fatal in some cases, has occurred rarely in patients receiving atypical antipsychotic agents, including olanzapine, clozapine, and risperidone. In most of these cases, pancreatitis developed within 6 months of initiation of atypical antipsychotic therapy. Although the precise mechanism for this effect remains to be established, it has been suggested that it may be due at least in part to the adverse metabolic effects associated with these drugs.

■ Precautions and Contraindications

Pending revision, the material in this section should be considered in light of more recently available information in the MedWatch notification at the beginning of this monograph.

Olanzapine shares many of the toxic potentials of other antipsychotic agents (e.g., other atypical antipsychotic agents, phenothiazines), and the usual precautions associated with therapy with these agents should be observed. (See Cautions, in the Phenothiazines General Statement 28:16.08.24.)

When olanzapine is used in fixed combination with fluoxetine, the usual cautions, precautions, and contraindications associated with fluoxetine must be considered in addition to those associated with olanzapine.

Somnolence

Dose-related somnolence occurred in 26% of patients receiving oral olanzapine compared with 15% of those receiving placebo, and resulted in discontinuance of the drug in 0.4% of the patients in the premarketing database. Because of sedative effects of the drug and because it potentially may impair judgment, thinking, and motor skills, patients should be cautioned that olanzapine may impair their ability to perform activities requiring mental alertness or physical coordination (e.g., operating machinery, driving a motor vehicle) until they are reasonably certain that olanzapine does not adversely affect them.

Seizures

Although seizures occurred in about 0.9% of patients receiving oral olanzapine in controlled clinical trials during premarketing testing, it should be noted that confounding factors that may have contributed to the occurrence of seizures were present in many of these cases. Olanzapine should be administered with caution to patients with a history of seizures, patients with conditions known to lower the seizure threshold (e.g., Alzheimer's disease, geriatric patients), and during concurrent therapy with drugs that may lower the seizure threshold.

Body Temperature Regulation

Because disruption of the body's ability to reduce core body temperature has been associated with the use of antipsychotic agents, caution is advised when olanzapine is administered in patients exposed to conditions that may contribute to an elevation in core body temperature. Such conditions include strenuous exercise, exposure to extreme heat, concomitant use of drugs with anticholinergic activity, or dehydration. Patients receiving olanzapine should be advised to avoid overheating and dehydration.

Hepatic Effects

Because clinically important serum ALT elevations (3 or more times the upper limit of the normal range) were observed in about 2% of patients exposed to oral olanzapine in placebo-controlled clinical studies, the manufacturer states that olanzapine should be used with caution in patients with signs and symptoms of hepatic impairment, in patients with preexisting conditions associated with limited hepatic functional reserve, and in patients who are being treated concurrently with potentially hepatotoxic drugs. In addition, periodic assessment of transaminases is recommended in patients with clinically important hepatic disease.

Individuals with Phenylketonuria

Individuals with phenylketonuria (i.e., homozygous genetic deficiency of phenylalanine hydroxylase) and other individuals who must restrict their intake of phenylalanine should be warned that olanzapine 5, 10, 15, or 20 mg orally disintegrating tablets contain aspartame (e.g., NutraSweet®), which is metabolized in the GI tract to provide about 0.34, 0.45, 0.67, or 0.9 mg of phenylalanine, respectively, following oral administration.

Dysphagia

Because esophageal dysmotility and aspiration sometimes resulting in death have been associated with the use of antipsychotic agents, olanzapine and other antipsychotic agents should be used with caution in patients at risk for aspiration pneumonia. Aspiration pneumonia is a common cause of morbidity and mortality in patients with advanced Alzheimer's disease.

Suicide

Because the possibility of a suicide attempt is inherent in patients with schizophrenia and bipolar disorder, close supervision of high-risk patients is recommended during olanzapine therapy. The manufacturer recommends that the drug be prescribed in the smallest quantity consistent with good patient management to reduce the risk of overdosage.

Patients with Concomitant Illness

Clinical experience with olanzapine in patients with certain concurrent systemic diseases is limited. Olanzapine has demonstrated anticholinergic activity in vitro and constipation, dryness of the mouth, and tachycardia, possibly related to the drug's anticholinergic effects, have occurred in premarketing clinical trials. Although these adverse effects did not often result in drug discontinuance, the manufacturer states that olanzapine should be used with caution in patients with clinically important prostatic hypertrophy, angle-closure glaucoma, or a history of paralytic ileus.

Olanzapine has not been adequately evaluated in patients with a recent history of myocardial infarction or unstable cardiovascular disease to date and patients with these conditions were excluded from premarketing clinical trials. Because of the risk of orthostatic hypotension associated with olanzapine, the manufacturer states that the drug should be used with caution in patients with cardiovascular disease. (See Cautions: Cardiovascular Effects.)

Concomitant Medication or Alcohol Use

Because of the potential for adverse drug interactions, the manufacturer recommends that patients receiving olanzapine be advised to notify their clinician if they are taking or plan to take any prescription or nonprescription (over-the-counter) medications. The manufacturer also recommends that patients be advised to avoid alcohol while receiving the drug. (See Drug Interactions.)

Neuroleptic Malignant Syndrome

Neuroleptic malignant syndrome (NMS), a potentially fatal syndrome requiring immediate discontinuance of the drug and intensive symptomatic treatment, has been reported in patients receiving antipsychotic agents, including olanzapine. If a patient requires antipsychotic therapy following recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. If antipsychotic therapy is reintroduced, the dosage generally should be increased gradually, and an antipsychotic agent other than the agent believed to have precipitated NMS generally should be chosen. In addition, such patients should be carefully monitored since recurrences of NMS have been reported in some patients. (See Neuroleptic Malignant Syndrome in Cautions: Nervous System Effects.)

Tardive Dyskinesia

Because use of antipsychotic agents may be associated with tardive dyskinesia, a syndrome of potentially irreversible, involuntary, dyskinetic movements, olanzapine should be prescribed in a manner that is most likely to minimize the occurrence of this syndrome. Chronic antipsychotic treatment generally should be reserved for patients who suffer from a chronic illness that is known to respond to antipsychotic agents, and for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought, and the need for continued treatment should be reassessed periodically.

The APA currently recommends that patients receiving second-generation antipsychotic agents be assessed clinically for abnormal involuntary movements every 12 months and that patients considered to be at increased risk for tardive dyskinesia be assessed every 6 months. (See Tardive Dyskinesia in Cautions: Nervous System Effects.)

Dispensing and Administration Precautions

Because of similarities in spelling, dosage intervals (once daily), and tablet strengths (5 and 10 mg) of Zyprexa® (the trade name for olanzapine) and Zyrtec® (the trade name for cetirizine hydrochloride, an antihistamine), several dispensing or prescribing errors

have been reported to the manufacturer of Zyprexa®. These medication errors may result in unnecessary adverse events or a potential relapse in patients with schizophrenia or bipolar disorder. Therefore, the manufacturer of Zyprexa® cautions that extra care should be exercised in ensuring the accuracy of written prescriptions for Zyprexa® and Zyrtec® such as printing both the proprietary (brand) and nonproprietary (generic) names on all prescriptions for these drugs. The manufacturer also recommends that pharmacists assess various measures of avoiding dispensing errors and implement them as appropriate (e.g., placing drugs with similar names apart from one another on pharmacy shelves, patient counseling).

Cardiovascular Effects

Orthostatic hypotension associated with dizziness, tachycardia, and/or syncope, particularly during the initial dosage titration period, has been reported in patients receiving oral olanzapine therapy. The risk of orthostatic hypotension and syncope may be minimized by initiating therapy with a dosage of 5 mg orally once daily. A more gradual titration to the target dose should be considered if hypotension occurs. Patients should be cautioned about the risk of orthostatic hypotension, particularly during the initial dosage titration period and if the drug is given concurrently with drugs that may potentiate the orthostatic effect of olanzapine, including diazepam, or alcohol.

Hypotension, bradycardia with or without hypotension, tachycardia, and syncope have been reported in patients receiving IM olanzapine. The use of maximum recommended dosages of IM olanzapine (i.e., 3 doses of 10 mg each given IM 2–4 hours apart) may be associated with a substantial risk of clinically important orthostatic hypotension. Patients who experience drowsiness or dizziness after the IM injection should remain recumbent until an examination indicates that they are not experiencing orthostatic hypotension, bradycardia, and/or hypoventilation. Patients requiring additional IM injections of olanzapine should be assessed for orthostatic hypotension prior to administration of any subsequent doses. Administration of additional IM doses to patients with clinically important postural change in blood pressure is not recommended.

The manufacturer states that olanzapine should be used with caution in patients with known cardiovascular disease (e.g., history of myocardial infarction or ischemia, heart failure, conduction abnormalities), cerebrovascular disease, and/or other conditions that would predispose patients to hypotension (e.g., dehydration, hypovolemia, concomitant antihypertensive therapy) where the occurrence of syncope, hypotension, and/or bradycardia might put the patient at increased risk. The manufacturer also states that the drug should be used with caution in patients receiving other drugs that can induce hypotension, bradycardia, or respiratory and CNS depression. (See Drug Interactions.) Concurrent administration of IM olanzapine and parenteral benzodiazepines has not been well studied; therefore, combined use of these drugs is not recommended. If use of IM olanzapine in combination with parenteral benzodiazepine therapy is considered, careful evaluation of the patient's clinical status for excessive sedation and cardiorespiratory depression is recommended.

Hyperglycemia and Diabetes Mellitus

Because severe hyperglycemia, sometimes associated with ketoacidosis, hyperosmolar coma, or death, has been reported in patients receiving certain atypical antipsychotic agents, including olanzapine, the manufacturers state that patients with preexisting diabetes mellitus in whom therapy with an atypical antipsychotic is initiated should be closely monitored for worsening of glucose control; those with risk factors for diabetes (e.g., obesity, family history of diabetes) should undergo fasting blood glucose testing upon therapy initiation and periodically throughout treatment. Any patient who develops manifestations of hyperglycemia (e.g., polydipsia, polyphagia, polyuria, weakness) during treatment with an atypical antipsychotic should undergo fasting blood glucose testing. In some cases, patients who developed hyperglycemia while receiving an atypical antipsychotic have required continuance of antidiabetic treatment despite discontinuance of the suspect drug; in other cases, hyperglycemia resolved with discontinuance of the antipsychotic or with continuance of both the suspect drug and initiation of antidiabetic treatment.

Various experts have developed additional recommendations for the management of diabetes risks in patients receiving atypical antipsychotics; these include initial screening measures and regular monitoring (e.g., determination of diabetes risk factors; BMI determination using weight and height; waist circumference; blood pressure; fasting blood glucose; hemoglobin A_{1c} [HbA_{1c}]; fasting lipid profile), as well as provision of patient education and referral to clinicians experienced in the treatment of diabetes, when appropriate. Although some clinicians state that a switch from one atypical antipsychotic agent to another that has not been associated with substantial weight gain or diabetes should be considered in patients who experience weight gain (equal to or exceeding 5% of baseline body weight) or develop worsening glycemia or dyslipidemia at any time during therapy, such recommendations are controversial because differences in risk of developing diabetes associated with use of the different atypical antipsychotics remain to be fully established. Many clinicians consider antipsychotic efficacy the most important factor when making treatment decisions and suggest that detrimental effects of switching from a beneficial treatment regimen also should be considered in addition to any potential for exacerbation or development of medical conditions (e.g., diabetes). Decisions to alter drug therapy should be made on an individual basis, weighing the potential risks and benefits of the particular drug in each patient.

Contraindications

Olanzapine is contraindicated in patients with a known hypersensitivity to the drug. (See Cautions: Dermatologic and Sensitivity Reactions.)

■ Pediatric Precautions

Pending revision, the material in this section should be considered in light of more recently available information in the MedWatch notification at the beginning of this monograph.

The manufacturer states that safety and efficacy of olanzapine in children and adolescents younger than 18 years of age have not been established. However, the drug has been used in a limited number of children and adolescents with childhood-onset schizophrenia (see Pediatric Considerations under Psychotic Disorders: Schizophrenia, in Uses). In a double-blind, placebo-controlled trial of 6 weeks' duration conducted in 107 adolescents 13–17 years of age with schizophrenia, olanzapine was effective in the management of schizophrenia, but results indicated that the drug's effects on weight and prolactin concentrations may be greater in adolescents.

Olanzapine also has been effective and well tolerated in a limited number of children and adolescents with bipolar disorder (see Pediatric Considerations under Bipolar Disorder, in Uses) and pervasive developmental disorder, including autistic disorder. In a double-blind, placebo-controlled, 3-week study in 107 adolescents 13–17 years of age with bipolar disorder, olanzapine was found to be effective in the treatment of acute manic or mixed episodes; however, weight gain and hyperprolactinemia occurred more often in patients receiving olanzapine compared with those receiving placebo. Additional controlled and longer-term studies are needed to confirm these initial findings and to evaluate the relative benefits and risks of olanzapine therapy in pediatric patients.

As in adults, olanzapine therapy may be associated with weight gain in pediatric patients (see Cautions: Endocrine and Metabolic Effects). The American Academy of Child and Adolescent Psychiatry (AACAP) currently recommends that pediatric patients who experience weight gain associated with olanzapine or other agents be monitored closely for potential medical consequences associated with weight gain (e.g., diabetes mellitus, hyperlipidemia, elevations in serum transaminase concentrations) and be referred for exercise and nutritional counseling. (See Hyperglycemia and Diabetes Mellitus under Cautions: Precautions and Contraindications.)

■ Geriatric Precautions

Although clinical experience in patients with schizophrenia generally has not revealed age-related differences in safety of olanzapine, lower initial dosages and slower titration during the initial dosing period may be advisable in some geriatric patients.

The first phase of the large-scale Clinical Antipsychotic Trials of Intervention Effectiveness—Alzheimer's Disease (CATIE-AD) trial was designed to evaluate the overall effectiveness of atypical antipsychotic agents in the treatment of psychosis, aggression, and agitation associated with Alzheimer's disease. Patients in this multicenter, double-blind, placebo-controlled trial were randomized to receive either olanzapine, quetiapine, risperidone, or placebo for up to 36 weeks; the principal outcomes were the time from initial treatment until discontinuance of treatment for any reason and the number of patients with at least minimum improvement on the Clinical Global Impression of Change (CGIC) Scale at 12 weeks. No statistically significant differences were found among the 4 groups with regard to the time until discontinuation of treatment for any reason; patients remained on olanzapine, quetiapine, risperidone, and placebo for median times of approximately 8, 5, 7, and 8 weeks, respectively. In addition, no significant differences in CGIC Scale improvements were noted. However, patients receiving atypical antipsychotic therapy reportedly experienced more frequent adverse effects (e.g., drowsiness, weight gain, adverse extrapyramidal effects, confusion, and psychotic symptoms) compared with those receiving placebo. The authors stated that these results indicate that the overall therapeutic benefit of atypical antipsychotics in patients with Alzheimer's disease may be offset by the potential risk of adverse effects.

Studies in patients with dementia-related psychosis have suggested that there may be a different tolerability profile in patients 65 years of age or older with this condition compared with younger patients with schizophrenia. Geriatric patients with dementia-related psychosis receiving atypical antipsychotics including olanzapine appear to be at an increased risk of death compared with that among patients receiving placebo. Analyses of 17 placebo-controlled trials (average duration of 10 weeks) revealed an approximate 1.6- to 1.7-fold increase in mortality among geriatric patients receiving atypical antipsychotic drugs (i.e., olanzapine, aripiprazole, quetiapine, risperidone) compared with that in patients receiving placebo. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5% compared with a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature.

In placebo-controlled trials with olanzapine in geriatric individuals with dementia-related psychosis, an increased incidence of death also was observed; the incidence of death in olanzapine-treated patients was significantly higher than in patients receiving placebo (3.5% and 1.5%, respectively). In addition, a significantly higher incidence of adverse cerebrovascular effects (e.g., stroke, transient ischemic attack), including fatalities, was observed in patients receiving olanzapine compared with those receiving placebo in these trials. In 5 placebo-controlled studies of olanzapine in geriatric individuals with dementia-related psychosis, certain treatment-emergent adverse effects, including falls, somnolence, peripheral edema, abnormal gait, urinary incontinence, lethargy, increased weight, asthenia, pyrexia, pneumonia, dry mouth, and visual hallucinations, occurred in at least 2% of the patients and the incidence was significantly

higher than in patients receiving placebo. Discontinuance of therapy because of adverse effects occurred in a significantly higher number of olanzapine-treated patients than in those receiving placebo (13% and 7%, respectively) in these studies.

The manufacturer states that olanzapine is *not* approved for the treatment of patients with dementia-related psychosis. Some clinicians recommend that the potential risks, therapeutic benefits, and individual needs of patients be carefully considered prior to prescribing olanzapine and other atypical antipsychotic agents for the management of behavioral problems associated with Alzheimer's disease. If a clinician decides to treat geriatric patients with dementia-related psychosis with olanzapine, the manufacturer recommends that caution be exercised. For additional information on the use of antipsychotic agents in the management of dementia-related psychosis, see Geriatric Considerations under Uses: Psychotic Disorders, in the Phenothiazines General Statement 28:16.08.24.

■ Mutagenicity and Carcinogenicity

Olanzapine did not exhibit mutagenic potential in the Ames reverse mutation test, in vivo micronucleus mutation test in mice, the chromosomal aberration test in Chinese hamster ovary cells, unscheduled DNA synthesis test in rat hepatocytes, induction of forward mutation test in mouse lymphoma cells, or in vivo sister chromatid exchange test in bone marrow of Chinese hamsters.

In oral carcinogenicity studies conducted in mice, olanzapine was administered in 2 studies of 78-weeks' duration at dosages of 3, 10, and 30 mg/kg (later reduced to 20 mg/kg) initially then reduced to 20 mg/kg daily (equivalent to 0.8–5 times the maximum recommended human daily oral dosage on a mg/m^2 basis) and 0.25, 2, and 8 mg/kg daily (equivalent to 0.06–2 times the maximum recommended human daily oral dosage on a mg/m^2 basis). In oral carcinogenicity studies conducted in rats, olanzapine was administered for 2 years at dosages of 0.25, 1, 2.5, and 4 mg/kg daily in males (equivalent to 0.13–2 times the maximum recommended human daily oral dosage on a mg/m^2 basis) and 0.25, 1, 4, and 8 mg/kg daily in females (equivalent to 0.13–4 times the maximum recommended human daily oral dosage on a mg/m^2 basis). A is increased incidence of liver hemangiomas and hemangiosarcomas was observed in one mouse study in female mice receiving 8 mg/kg of the drug daily (equivalent to 2 times the maximum recommended human daily oral dosage on a mg/m^2 basis). The incidence of these tumors was not increased in another study in female mice receiving 10 or 30 mg/kg (later reduced to 20 mg/kg) of olanzapine daily (equivalent to 2–5 times the maximum recommended human daily oral dosage on a mg/m^2 basis); in this study, there was a high incidence of early mortalities in males in the 30 mg/kg (later reduced to 20 mg/kg) daily group. The incidence of mammary gland adenomas and adenocarcinomas was increased in female mice receiving 2 mg/kg or more of olanzapine daily and in female rats receiving 4 mg/kg or more of the drug daily (equivalent to 0.5 and 2 times the maximum recommended human daily oral dosage on a mg/m^2 basis, respectively).

Antipsychotic agents have been shown to chronically elevate prolactin concentrations in rodents. Serum prolactin concentrations were not measured during the olanzapine carcinogenicity studies; however, measurements during subchronic toxicity studies demonstrated that olanzapine administration produced up to a fourfold increase in serum prolactin concentrations in rats receiving the same dosages used in the carcinogenicity study. In addition, an increase in mammary gland neoplasms has been observed in rodents following chronic administration of other antipsychotic agents and generally is considered to be prolactin-mediated. However, the clinical importance in humans of this finding of prolactin-mediated endocrine tumors in rodents is unknown.

■ Pregnancy, Fertility, and Lactation

Pregnancy

Limited experience to date with olanzapine administration during pregnancy has been encouraging and has not revealed evidence of any obvious teratogenic risks; however, additional cases of olanzapine exposure during pregnancy need to be evaluated to more fully determine the relative safety of olanzapine and other antipsychotic agents when administered during pregnancy. The manufacturer states that there have been 7 pregnancies reported during clinical trials with olanzapine, including 2 resulting in normal births, one resulting in neonatal death due to a cardiovascular defect, 3 therapeutic abortions, and one spontaneous abortion. In a separate compilation of pregnancy exposures to olanzapine reported to the manufacturer during clinical trials and from spontaneous reports worldwide, outcomes were available from 23 prospectively-collected olanzapine-exposed pregnancies. Spontaneous abortion occurred in 13% of these pregnancies, stillbirth in 5%, major malformations in 0%, and prematurity in 5%; these rates were all within the range of normal historical control rates. In 11 retrospectively collected, olanzapine-exposed pregnancies, there was one case of dysplastic kidney, one case of Down's syndrome, and one case of heart murmur and sudden infant death syndrome at 2 months of age. In another study, the majority of women with schizophrenia receiving atypical antipsychotic agents were found to be overweight and to have reduced folate intake and low serum folate concentrations, which may increase the potential risk of neural tube defects. In a prospective, comparative trial assessing pregnancy outcome in women receiving atypical antipsychotic agents (olanzapine, clozapine, risperidone, and quetiapine) during pregnancy, atypical antipsychotics did not appear to be associated with an increased risk of major congenital malformations. In addition, several case reports have described healthy infants born to women without complications despite prenatal exposure to olanzapine.

The manufacturer and some clinicians state that there are no adequate and well-controlled studies to date using olanzapine in pregnant women, and the drug should be used during pregnancy only when the potential benefits justify the potential risks to the fetus. Women should be advised to notify their clinician if they become pregnant or plan to become pregnant during therapy with the drug.

Parturition in rats was not affected by olanzapine. The effect of olanzapine on labor and delivery is unknown.

In oral reproduction studies in rats receiving dosages of up to 18 mg/kg daily and in rabbits at dosages of up to 30 mg/kg daily (equivalent to 9 and 30 times the maximum recommended human daily oral dosage on a mg/m^2 basis, respectively), no evidence of teratogenicity was observed. In an oral rat teratology study, early resorptions and increased numbers of nonviable fetuses were observed at a dosage of 18 mg/kg daily (9 times the maximum recommended human daily oral dosage on a mg/m^2 basis), and gestation was prolonged at a dosage of 10 mg/kg daily (equivalent to 5 times the maximum recommended human daily oral dosage on a mg/m^2 basis). In an oral rabbit teratology study, fetal toxicity, which was manifested as increased resorptions and decreased fetal weight, occurred at a maternally toxic dosage of 30 mg/kg daily (equivalent to 30 times the maximum recommended human daily oral dosage on a mg/m^2 basis).

Fertility

In an oral fertility and reproductive performance study in rats, male mating performance, but not fertility, was impaired at an olanzapine dosage of 22.4 mg/kg daily, and female fertility was decreased at a dosage of 3 mg/kg daily (equivalent to 11 and 1.5 times the maximum recommended human daily oral dosage on a mg/m^2 basis, respectively). Discontinuance of olanzapine administration reversed the effects on male mating performance. In a female rat fertility study, the precoital period was increased, and the mating index reduced at a dosage of 5 mg/kg daily (equivalent to 2.5 times the maximum recommended human daily oral dosage on a mg/m^2 basis). Diestrus was prolonged and estrus was delayed at a dosage of 1.1 mg/kg daily (equivalent to 0.6 times the maximum recommended human daily oral dosage on a mg/m^2 basis).

Lactation

Olanzapine is distributed into milk. The mean dosage received by an infant at steady state is estimated to be about 1.8% of the maternal dosage. The manufacturer recommends that women receiving olanzapine not breast-feed.

Drug Interactions

■ Drugs Affecting Hepatic Microsomal Enzymes

Olanzapine is a substrate for cytochrome P-450 (CYP) isoenzyme 1A2 and concomitant administration of drugs that induce CYP1A2 or glucuronyl transferase enzymes (e.g., carbamazepine, omeprazole, rifampin) may cause an increase in olanzapine clearance. Inhibitors of CYP1A2 (e.g., fluvoxamine) could potentially inhibit olanzapine clearance. Although olanzapine is metabolized by multiple enzyme systems, induction or inhibition of a single enzyme may appreciably alter olanzapine clearance. Therefore, an increase or decrease in olanzapine dosage may be necessary during concomitant administration of olanzapine with specific drugs that induce or inhibit olanzapine metabolism, respectively.

Carbamazepine

Carbamazepine therapy (200 mg twice daily for 2 weeks) causes an approximately 50% increase in the clearance of a single, 10-mg dose of olanzapine. The manufacturer of olanzapine states that higher dosages of carbamazepine may cause an even greater increase in olanzapine clearance. Increased clearance of olanzapine probably is caused by carbamazepine-induced induction of CYP1A2 activity.

Selective Serotonin-reuptake Inhibitors

Concomitant administration of fluoxetine (60 mg as a single dose or 60 mg daily for 8 days) with a single 5-mg dose of oral olanzapine caused a small increase in peak plasma olanzapine concentrations (averaging 16%) and a small decrease (averaging 16%) in olanzapine clearance; the elimination half-life was not substantially affected. Fluoxetine is an inhibitor of CYP2D6, and thereby may affect a minor metabolic pathway for olanzapine. Although the changes in pharmacokinetics are statistically significant when olanzapine and fluoxetine are given concurrently, the changes are unlikely to be clinically important in comparison to the overall variability observed between individuals; therefore, routine dosage adjustment is not recommended.

Fluvoxamine, a CYP1A2 inhibitor, has been shown to decrease the clearance of olanzapine, which is metabolized by CYP1A2; there is some evidence that fluvoxamine-induced CYP1A2 inhibition is dose dependent. In one pharmacokinetic study, peak plasma olanzapine concentrations increased by an average of 54 and 77% and area under the plasma concentration-time curve (AUC) increased by an average of 52 and 108% in female nonsmokers and male smokers, respectively, when fluvoxamine and olanzapine were administered concomitantly. Symptoms of olanzapine toxicity also have been reported in at least one patient during combined therapy. The manufacturer and some clinicians state that a lower olanzapine dosage should therefore be considered in patients receiving concomitant treatment with fluvoxamine. Preliminary data indicate that concurrent fluvoxamine administration may potentially be used to therapeutic advantage by reducing the daily dosage of olanzapine and thereby the cost of therapy; further controlled studies are needed to more fully evaluate this approach. Although

combined therapy with olanzapine and fluvoxamine generally has been well tolerated and may be associated with clinical benefit, some clinicians recommend that caution be exercised and monitoring of plasma olanzapine concentrations be considered in patients receiving these drugs concurrently.

Preliminary results from a therapeutic drug monitoring service suggest that concurrent administration of sertraline and olanzapine does not substantially affect the pharmacokinetics of olanzapine.

Warfarin

Concomitant administration of a single 20-mg dose of warfarin (which has a potential CYP2C9 interaction) and a single oral 10-mg dose of olanzapine did not substantially alter the pharmacokinetics of olanzapine.

■ Drugs Metabolized by Hepatic Microsomal Enzymes

In vitro studies utilizing human liver microsomes suggest that olanzapine has little potential to inhibit metabolism of CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A substrates. Therefore, clinically important drug interactions between olanzapine and drugs metabolized by these isoenzymes are considered unlikely.

■ Levodopa and Dopamine Agonists

Olanzapine may antagonize the effects of levodopa and dopamine agonists.

■ Lamotrigine

In a multiple-dose study in healthy individuals, the pharmacokinetics of olanzapine and lamotrigine were not substantially affected when the drugs were administered concomitantly. In another multiple-dose study conducted in healthy volunteers, olanzapine did not substantially alter lamotrigine pharmacokinetics when the drugs were administered concurrently. However, the time to reach maximal plasma concentrations of lamotrigine was substantially prolonged in this study, possibly because of olanzapine's anticholinergic activity. The tolerability of this combination was found to be similar to that of olanzapine alone, with mild sedative effects reported in some patients receiving the drugs concurrently. Although routine dosage adjustment does not appear to be necessary when olanzapine and lamotrigine are given concurrently, adjustment in lamotrigine dosage may be necessary in some patients for therapeutic reasons when olanzapine therapy is initiated or discontinued. In addition, careful monitoring of patients receiving high dosages of olanzapine and lamotrigine has been recommended by some clinicians.

■ Other CNS-Active Agents and Alcohol

Because of the prominent CNS actions of olanzapine, the manufacturer states that caution should be exercised when olanzapine is administered concomitantly with other centrally acting drugs and alcohol. The manufacturer also states that concomitant use of olanzapine with CNS agents that are associated with hypotension (e.g., diazepam) may potentiate the orthostatic hypotension associated with olanzapine.

Benzodiazepines

Because of the prominent CNS actions of olanzapine, the manufacturer states that caution should be exercised when olanzapine is administered concomitantly with benzodiazepines. The manufacturer also states that concomitant use of olanzapine and diazepam or other benzodiazepines that are associated with hypotension may potentiate the orthostatic hypotension associated with olanzapine. However, administration of multiple doses of olanzapine did not substantially alter the pharmacokinetics of diazepam or its active metabolite *N*-desmethyldiazepam.

The pharmacokinetics of olanzapine, unconjugated lorazepam, and total lorazepam were not substantially affected when IM lorazepam (2 mg) was administered 1 hour after IM olanzapine (5 mg); however, increased somnolence was observed with this combination. Hypotension also has been reported when IM olanzapine and IM lorazepam have been administered concurrently. The manufacturer of olanzapine states that concurrent use of IM olanzapine in conjunction with parenteral benzodiazepines has not been adequately studied to date and therefore is not recommended. If therapy with IM olanzapine in conjunction with a parenteral benzodiazepine is considered, the clinical status of the patient should be carefully evaluated for excessive sedation and cardiorespiratory depression.

Tricyclic Antidepressants

Administration of single doses of olanzapine did not substantially affect the pharmacokinetics of imipramine or its active metabolite desipramine.

Lithium

Multiple doses of olanzapine (10 mg for 8 days) did not affect the pharmacokinetics of a single dose of lithium. Although combined olanzapine and lithium therapy generally has been well tolerated in controlled clinical studies, rare cases of apparent lithium toxicity and adverse extrapyramidal effects, including oculogyric crisis, have been reported in patients receiving these drugs concurrently; the mechanism(s) for this potential drug interaction remains to be established. The manufacturer of olanzapine states that lithium dosage adjustment is not necessary during concurrent olanzapine administration.

Valproic Acid

In vitro studies using human liver microsomes indicated that olanzapine has little potential to inhibit the major metabolic pathway (glucuronidation) of valproic acid. In addition, valproic acid has little potential effect on the metabolism of olanzapine in vitro. In a pharmacokinetic study, olanzapine administration (10 mg daily for 2 weeks) did not affect the steady-state plasma concentrations of valproic acid. However, substantially decreased plasma olanzapine concentrations have been reported in several patients following initiation of valproate in patients already receiving olanzapine; it was suggested that induction of the hepatic enzymes responsible for olanzapine's metabolism by valproate may have been responsible for these findings. Further studies are needed to determine whether a pharmacokinetic interaction exists between olanzapine and valproic acid since these drugs are frequently used in combination in clinical practice. The manufacturer of olanzapine currently states that routine dosage adjustment of valproic acid is not necessary during concurrent olanzapine administration.

Alcohol

In a pharmacokinetic study, concomitant administration of a single dose of alcohol did not substantially alter the steady-state pharmacokinetics of olanzapine (given in dosages of up to 10 mg daily). However, the manufacturer states that concomitant use of olanzapine with alcohol could potentiate the orthostatic hypotension associated with olanzapine and that alcohol should be avoided during olanzapine therapy.

■ Hypotensive Agents

Olanzapine therapy potentially may enhance the effects of certain hypotensive agents during concurrent use. In addition, the administration of dopamine, epinephrine, and/or other sympathomimetic agents with β-agonist activity should be avoided in the treatment of olanzapine-induced hypotension, since such stimulation may worsen hypotension in the presence of olanzapine-induced α-blockade. (See Acute Toxicity: Treatment.)

■ Antacids or Cimetidine

In pharmacokinetic studies, single doses of cimetidine (800 mg) or aluminum- and magnesium-containing antacids (30 mL) did not substantially affect the oral bioavailability of a single, 7.5-mg dose of olanzapine.

■ Activated Charcoal

Concurrent administration of activated charcoal (1 g) reduced peak plasma concentrations and the AUC of a single, 7.5-mg dose of olanzapine by approximately 60%. Since peak plasma concentrations are not usually obtained until about 6 hours after oral administration, activated charcoal may be useful in the management of olanzapine intoxication. (See Acute Toxicity: Treatment.)

■ Smoking

The manufacturer states that the clearance of olanzapine in smokers is approximately 40% higher than in nonsmokers. Therefore, plasma olanzapine concentrations generally are lower in smokers than in nonsmokers receiving the drug. Adverse extrapyramidal effects have been reported in one olanzapine-treated patient after a reduction in cigarette smoking, while worsened delusions, hostility, and aggressive behavior have been reported in another olanzapine-treated patient following a marked increase in smoking (i.e., an increase from 12 up to 80 cigarettes per day). Although the precise mechanism(s) for this interaction has not been clearly established, it has been suggested that induction of the CYP isoenzymes, particularly 1A2, by smoke constituents may be responsible at least in part for the reduced plasma olanzapine concentrations observed in smokers compared with nonsmokers.

Although the manufacturer states that routine dosage adjustment is not recommended in patients who smoke while receiving olanzapine, some clinicians recommend that patients treated with olanzapine should be monitored with regard to their smoking consumption and that dosage adjustment be considered in patients who have reduced or increased their smoking and/or who are not responding adequately or who are experiencing dose-related adverse reactions to the drug. In addition, monitoring of plasma olanzapine concentrations may be helpful in patients who smoke and have other factors associated with substantial alterations in metabolism of olanzapine (e.g., geriatric patients, women, concurrent fluvoxamine administration).

■ Other Drugs

Multiple doses of olanzapine did not substantially alter the pharmacokinetics of theophylline or its metabolites.

Multiple doses of olanzapine did not substantially affect the pharmacokinetics of biperiden.

Acute Toxicity

■ Pathogenesis

The acute lethal dose of olanzapine in humans remains to be established. However, the toxic and lethal doses of olanzapine and other atypical antipsychotic agents appear to be highly variable and depend on concurrent administration of other drugs or toxic substances, patient age and habituation, and the time from exposure until treatment is initiated; pediatric and/or nonhabituated patients appear to be more sensitive to the toxic effects of these drugs. During premarketing clinical trials involving more than 3100 patients and/or healthy individuals, accidental or intentional acute overdosage of olanzapine was identified in 67 patients. In one adult patient who took 300 mg of the drug, the only symptoms reported were drowsiness and slurred speech. In a limited number of patients who were evaluated in hospitals following olanzapine overdosage, no adverse changes in laboratory values or ECG findings were observed. In addition, vital signs usually were within normal limits following these overdosages.

Fatalities have been reported following overdosage of olanzapine alone. In one of these deaths, the amount of olanzapine acutely ingested was possibly as low as 450 mg, while it was estimated to be up to 600 mg in another case; however, in 2 other cases, patients reportedly survived acute ingestions of 1.1 and 1.5 g. The cases of olanzapine intoxication reported to date suggest that overdosages of less than 200 mg of the drug alone in adults generally result in moderate and self-limiting toxicity; however, olanzapine overdosages exceeding 200 mg and/or when taken in combination with

other psychoactive agents or alcohol often were associated with more severe toxicity, including profound CNS depression, mental status changes, and miotic pupils.

■ Manifestations

In postmarketing reports of overdosages with olanzapine alone, manifestations have been reported in the majority of cases. Following acute overdosage of olanzapine or other atypical antipsychotic agents, toxic effects usually begin within 1–2 hours and maximal toxic effects usually are seen 4–6 hours following acute ingestion. In general, overdosage of olanzapine may be expected to produce effects that are extensions of its pharmacologic and adverse effects. The most commonly reported manifestations of olanzapine overdosage and those that have occurred in 10% or more of symptomatic patients following postmarketing overdosage reports of olanzapine alone are agitation and/or aggressiveness, dysarthria, tachycardia, anticholinergic syndrome, miosis, various extrapyramidal symptoms, jerking and myoclonus, hypersalivation, and reduced level of consciousness ranging in severity from sedation to coma. Less commonly reported but potentially medically serious events included aspiration, cardiopulmonary arrest, cardiac arrhythmias (e.g., supraventricular tachycardia), delirium, possible neuroleptic malignant syndrome, respiratory depression and/or arrest, convulsions, hypertension, and hypotension (including orthostatic hypotension); one patient experienced sinus pause with spontaneous resumption of normal rhythm.

In some cases of acute olanzapine intoxication, rapid fluctuation in mental status (i.e., between sedation and agitation or agitation despite sedation) has been reported. In addition, olanzapine overdosage may resemble opiate overdosage because CNS depression and miosis sometimes are observed. Increased creatine kinase (CK, creatine phosphokinase, CPK) concentrations also have occurred following acute olanzapine overdosage. Cardiac arrhythmias, persistent choreoathetosis, nonconvulsive status epilepticus, hypersalivation, and coma occurred in an adult following an intentional ingestion estimated to be 750 mg of olanzapine; both coma and choreoathetosis persisted until the patient's death 8 weeks later.

The toxic effects of olanzapine and other atypical antipsychotic agents in children appear to be similar to those seen in adults. In young children, marked CNS depression and anticholinergic delirium have occurred following ingestion of 7.5–15 mg of olanzapine (equivalent to 0.5–1 mg/kg). In an adolescent who ingested 275 mg of olanzapine and had an extremely high serum olanzapine concentration (1503 ng/mL), somnolence, agitation, and extrapyramidal symptoms developed initially, but the patient recovered without complications. A 400-mg olanzapine overdosage in another adolescent reportedly produced severe respiratory depression requiring intubation and mechanical ventilation; the patient recovered after 3 days. In addition, polyuria and other signs suggesting possible diabetes insipidus, including hypo-osmolar urine, normo-osmolar plasma, and increased serum sodium concentrations, have been reported in one adolescent following an overdosage of olanzapine and prazepam (a benzodiazepine; not commercially available in the US).

■ Treatment

Management of olanzapine overdosage generally involves symptomatic and supportive care, including continuous cardiovascular and respiratory monitoring and ensuring IV access. Cardiovascular monitoring should be initiated immediately and should include continuous ECG monitoring to detect possible arrhythmias. There is no specific antidote for olanzapine intoxication. In managing olanzapine overdosage, the clinician should consider the possibility of multiple drug intoxication.

The manufacturer and many clinicians recommend establishing and maintaining an airway and ensuring adequate ventilation and oxygenation, which may include intubation. Gastric lavage (following intubation, if the patient is unconscious) and/or activated charcoal, which may be used with sorbitol, should be considered. (See Drug Interactions: Activated Charcoal.) The possibility that obtundation, seizures, or dystonic reaction of the head and neck following olanzapine overdosage may create a risk of aspiration with induction of emesis should be considered.

Hypotension and circulatory collapse, if present, should be treated with appropriate measures, such as Trendelenburg's position, IV fluids, and/or sympathomimetic agents (e.g., norepinephrine, phenylephrine). However, dopamine, epinephrine, and/or other sympathomimetic agents with β-adrenergic agonist activity should be avoided, since such stimulation may worsen hypotension in the presence of olanzapine-induced α-adrenergic blockade. Tachycardia associated with olanzapine intoxication usually does not require specific therapy. Atrial and ventricular arrhythmias and conduction disturbances should be treated with appropriate measures; sodium bicarbonate may be helpful if QRS interval prolongation is present. Seizures following olanzapine overdosage may be treated initially with a benzodiazepine followed by barbiturates, if necessary. Acute extrapyramidal reactions should be treated with anticholinergic agents (e.g., diphenhydramine, benztropine).

Physostigmine salicylate or benzodiazepine therapy may be useful in the management of severe agitation and delirium in patients with severe anticholinergic toxicity and a narrow QRS complex on their ECG. Physostigmine has been used successfully in the treatment of anticholinergic toxicity associated with overdosages of olanzapine or clozapine, another atypical antipsychotic agent. However, experience with physostigmine in the management of atypical antipsychotic overdosage is limited, and some clinicians recommend that the drug be used only by experienced clinicians and in cases in which the potential therapeutic benefit outweighs the potential risks.

Resolution of toxic effects following atypical antipsychotic intoxication generally occurs within 12–48 hours following acute overdosage, although it has taken up to 6 days. Patients should remain under close medical supervision and monitoring until fully recovered.

Hemodialysis has not been shown to be useful for enhancing elimination of olanzapine in acute overdosage. Clinical experience with other enhanced elimination techniques, including multiple-dose activated charcoal, hemoperfusion, forced diuresis, and urinary alkalinization, is lacking; however, these treatments also are unlikely to be beneficial following olanzapine overdosage because of the drug's large volume of distribution and extensive protein binding.

Chronic Toxicity

In animal studies prospectively designed to assess abuse and dependence potential, olanzapine was shown to produce acute CNS depressive effects but little or no potential for abuse or physical dependence in rats administered oral doses up to 15 times the maximum recommended human daily oral dosage (20 mg) and rhesus monkeys administered oral doses up to 8 times the maximum recommended human daily oral dosage on a mg/m^2 basis. Olanzapine has not been systematically evaluated in humans to date for its potential for abuse, tolerance, or physical dependence. While clinical trials did not reveal any tendency for drug-seeking behavior, these observations were not systematic, and it is not possible to predict on the basis of this limited experience the extent to which a CNS-active drug will be misused, diverted, and/or abused once marketed. Consequently, patients should be evaluated carefully for a history of drug abuse, and such patients should be observed closely for signs of misuse or abuse of olanzapine (e.g., development of tolerance, increases in dose, drug-seeking behavior).

Pharmacology

Olanzapine is a thienobenzodiazepine-derivative antipsychotic agent. The drug shares some of the pharmacologic actions of other antipsychotic agents and has been described as an atypical or second-generation antipsychotic agent. Like other atypical or second-generation antipsychotics (e.g., aripiprazole, clozapine, quetiapine, risperidone, ziprasidone), olanzapine produces minimal adverse extrapyramidal effects, is unlikely to cause tardive dyskinesia with chronic treatment, and is effective in the treatment of positive, negative, and depressive manifestations of schizophrenia.

■ Nervous System Effects

The exact mechanism of antipsychotic action of olanzapine and other atypical antipsychotic agents has not been fully elucidated but appears to be more complex than that of conventional, first-generation antipsychotic agents and may involve central antagonism at serotonin type 2 (5-hydroxytryptamine [$5\text{-}HT_{2A}$, $5\text{-}HT_{2C}$]), type 3 ($5\text{-}HT_3$), and type 6 ($5\text{-}HT_6$) and dopamine receptors.

The exact mechanism(s) of antimanic action of olanzapine is not fully known. However, it has been suggested that the ability of olanzapine to block and downregulate $5\text{-}HT_{2A}$ receptors may play a role in its antimanic activity. In addition, olanzapine's mood-stabilizing action may be caused at least in part by antagonism of D_2 receptors. Further studies are needed to more clearly elucidate the potential mechanism(s) of the drug's antimanic activity.

Although not clearly established, the efficacy of IM olanzapine in the treatment of acute agitation appears to be due at least in part to its distinct calming effects rather than solely to nonspecific sedation.

Antidopaminergic Effects

The therapeutic effects of antipsychotic drugs are thought to be mediated by dopaminergic blockade in the mesolimbic and mesocortical areas of the CNS, while antidopaminergic effects in the neostriatum appear to be associated with extrapyramidal effects. The relatively low incidence of extrapyramidal effects associated with olanzapine therapy suggests that the drug is more active in the mesolimbic than the neostriatal dopaminergic system.

Several (at least 5) different types or subtypes of dopamine receptors have been identified in animals or humans. The relative densities of these receptors and their distribution and function vary for different neuroanatomical regions, and olanzapine's effects may be secondary to regionally specific receptor interactions and/or other effects on dopaminergic neurons. Current evidence suggests that the clinical potency and antipsychotic efficacy of both typical and atypical antipsychotic drugs generally are related at least in part to their affinity for and blockade of central dopamine D_2 receptors. Some studies suggest that clinically effective dosages of most antipsychotic agents result in occupation of between 60 and 80% of central dopamine D_2 receptors. However, antagonism at D_2 receptors does not appear to account fully for the antipsychotic effects of olanzapine. In vivo and in vitro studies have demonstrated that olanzapine is a comparatively weak antagonist at D_2 receptors. Although their role in eliciting the pharmacologic effects of antipsychotic agents remains to be fully elucidated, dopamine D_3, D_4, and D_5 receptors also have been identified. Olanzapine may have a higher affinity for D_4 receptors than for D_2 or D_3 receptors. K_i values of olanzapine for dopamine $D_{1\text{-}4}$ receptors range from 11–31 nM.

Atypical antipsychotic agents generally have demonstrated relatively loose binding to dopamine D_2 receptors. Compared with typical antipsychotic agents, atypical antipsychotics appear to have faster dissociation rates from and lower affinity for dopamine D_2 receptors, which may result in fewer adverse extrapyramidal effects and less risk of elevated prolactin concentrations; however, further studies are needed to confirm these initial findings.

Serotonergic Effects

It has been suggested that schizophrenia may involve a dysregulation of serotonin- and/or dopamine-mediated neurotransmission, and olanzapine may at least partially restore a normal balance of neurotransmitter function, possibly through serotonergic modulation of dopaminergic tone. Olanzapine blocks serotonin type 2 (5-hydroxytryptamine [5-HT_{2A} and 5-HT_{2C}; K_i of 4 and 11 nM, respectively]), type 3 (5-HT_3; K_i of 57 nM), and type 6 (5-HT_6; K_i of 5 nM) receptors.

Anticholinergic Effects

Olanzapine blocks muscarinic cholinergic receptors and has demonstrated moderate affinity for all 5 muscarinic receptor subtypes (K_i values for M_{1-5} were 73, 96, 132, 32, and 48 nM, respectively). Anticholinergic activity in antipsychotic agents may contribute to certain adverse anticholinergic events associated with these drugs but also may help reduce the risk of adverse extrapyramidal reactions.

Effects on Other Central Neurotransmitters

Antagonism at receptors other than dopamine and 5-HT_2 receptors may produce some of the therapeutic and adverse effects associated with olanzapine. Olanzapine exhibits α_1-adrenergic blocking activity (K_i of 19 nM), which may explain the occasional orthostatic hypotension associated with the drug. In addition, olanzapine blocks histamine H_1 receptors (K_i of 7 nM), which may explain the sedative effects associated with the drug; affinity for H_2 and H_3 receptors appears to be low.

Olanzapine demonstrated weak binding affinity (K_i exceeding 10 μM) for β-adrenergic, γ-aminobutyric acid (GABA), and benzodiazepine receptors; the drug also has little or no affinity for opiate receptors.

Neurophysiologic Effects

In vivo electrophysiologic studies demonstrate different sensitivities of various brain areas to antipsychotic-mediated postsynaptic receptor blockade. While conventional antipsychotics generally reduce spontaneous firing activity in both the mesolimbic (A10) and nigrostriatal regions (A9), chronic administration of atypical antipsychotics generally reduces the number of spontaneously active dopaminergic neurons in the mesolimbic region but not in the nigrostriatal region. Although not clearly established, it has been suggested that the ability to decrease A10 but not A9 neurons is associated clinically with a low potential to cause adverse extrapyramidal reactions and tardive dyskinesia. Olanzapine has demonstrated such mesolimbic selectivity in the in vivo studies conducted to date.

Cognitive Effects in Humans

Clinical experience suggests that second-generation antipsychotics, including olanzapine, improve cognition in patients with schizophrenia and that there may be differences between these drugs in their effects on neurocognitive functioning. In an initial clinical trial evaluating the short-term effects of atypical antipsychotic agents on cognitive function, olanzapine-treated schizophrenic patients demonstrated improved learning and memory, verbal fluency, and executive function. In a controlled clinical trial evaluating the neurocognitive effects of olanzapine, clozapine, risperidone, and haloperidol in patients with treatment-resistant schizophrenia or schizoaffective disorder, global neurocognitive function improved with olanzapine and risperidone treatment, and these improvements were found to be superior to those seen with haloperidol. Patients treated with olanzapine exhibited improvement in the general and attention domains but not more than that observed with the other antipsychotic agents. In another controlled trial, patients with schizophrenia receiving long-term (1 year) therapy with olanzapine demonstrated improved results on a general cognition index compared with those receiving haloperidol and risperidone. Neurocognition also improved in olanzapine- and risperidone-treated schizophrenic and schizoaffective patients receiving the drug for 1 year in another controlled study; improvements in executive function, learning and memory, processing speed, attention and vigilance, verbal working memory, and motor function were reported. The clinical relevance of these cognitive findings in the management of schizophrenia remains to be determined and requires further study.

EEG Effects

Olanzapine may cause EEG changes. In one study, olanzapine-induced EEG slowing to a lesser extent than clozapine in patients with schizophrenia and did not appear to substantially alter epileptiform activity in most of the patients studied; further studies are needed to determine whether olanzapine can affect the seizure threshold. Similarly, a comparative study found that epileptiform activity did not increase during olanzapine therapy; however, EEG slowing and other nonspecific EEG changes did occur more frequently in olanzapine-treated patients than in those receiving certain other antipsychotic agents. In another study that was retrospective in design, EEG changes occurred more frequently in patients receiving olanzapine or clozapine than in those receiving typical antipsychotic agents, quetiapine, or risperidone. In a study in patients with schizophrenia, olanzapine therapy was associated with increased rates of slow waves, sharp waves, and paroxysmal slow wave discharges on EEG recordings in the patients evaluated; however, spike- and sharp-slow-wave complexes that indicate seizure risk were not observed in this study.

Seizures have been reported rarely (0.9% in premarketing clinical trials) in olanzapine-treated patients but confounding factors were present in most of these cases. Further studies and postmarketing surveillance are needed to determine whether olanzapine can affect the seizure threshold and to evaluate the clinical relevance of the observed EEG findings in patients receiving the drug.

Effects on Sleep

The available evidence suggests that atypical antipsychotics, including olanzapine, clozapine, and risperidone, substantially increase total sleep time and stage 2 sleep; both olanzapine and risperidone also have been shown to enhance slow-wave sleep. Olanzapine's beneficial effects on sleep quality are thought to be mediated principally via type 2 serotonergic (5-HT_2) receptors.

In a controlled study, administration of single evening doses of olanzapine (5 or 10 mg orally) in healthy individuals significantly increased slow-wave sleep in a dose-related manner; sleep continuity measures and subjective sleep quality also increased significantly. Single 10-mg doses of the drug also suppressed rapid eye movement (REM) sleep and increased REM sleep latency in this study. In another study in healthy males and females, single 10-mg oral doses of olanzapine also were found to increase slow-wave sleep but preserved the normal structure of sleep; these effects were more prominent in females than in males.

During subchronic administration of olanzapine (15–20 mg) in patients with schizophrenia with predominantly negative symptoms in an uncontrolled study, parameters of sleep efficiency improved and delta sleep and REM sleep increased. Acute olanzapine administration (10 mg orally) in schizophrenic patients improved sleep continuity variables and total sleep time in another study; the principal changes observed in sleep architecture were a reduction in stage 1 sleep, a significant enhancement in stage 2 and delta sleep, and an increase in REM density. In a study comparing the effect of aging on the improvement of subjective sleep quality in patients with schizophrenia receiving atypical antipsychotic agents, including olanzapine, the proportion of patients experiencing improved subjective sleep quality was significantly higher in geriatric patients than in middle-aged patients.

■ Neuroendocrine Effects

In contrast to conventional (first-generation) antipsychotic agents and similar to many other atypical antipsychotic agents, olanzapine therapy in usual dosages generally produces relatively modest and transient elevations in serum prolactin concentrations in humans. This prolactin-elevating effect appears to be mediated by dopamine blockade. The effect of atypical antipsychotic agents on prolactin generally appears to be transient, possibly because the drugs appear to dissociate from dopamine receptors more rapidly than conventional antipsychotic agents.

Pharmacokinetics

■ Absorption

Olanzapine is well absorbed following oral administration. However, because of extensive first-pass metabolism, only about 60% of an orally administered dose reaches systemic circulation unchanged. Olanzapine exhibits linear and dose-proportional pharmacokinetics when given orally within the clinical dosage range. Food does not appear to affect the rate or the extent of GI absorption of the drug. The relative oral bioavailability of olanzapine has been shown to be equivalent following administration of the conventional and orally disintegrating tablets of the drug. When olanzapine and fluoxetine hydrochloride are administered as the fixed-combination oral capsules, the pharmacokinetic characteristics of the drugs are expected to resemble those of the individual components; olanzapine pharmacokinetics are slightly altered when administered with fluoxetine, but the effects were not deemed to be clinically important. (See Selective Serotonin-reuptake Inhibitors under Drug Interactions: Drugs Affecting Hepatic Microsomal Enzymes.)

Following oral administration, peak plasma olanzapine concentrations occur in approximately 6 hours (range: 5–8 hours). Steady-state plasma concentrations of olanzapine are achieved after approximately 7 days of continuous dosing and are approximately twice those observed following single-dose administration.

Following IM administration, olanzapine is rapidly absorbed with peak plasma olanzapine concentrations occurring within 15–45 minutes. In one pharmacokinetic study performed in healthy individuals, a single 5-mg IM dose of olanzapine produced peak plasma concentrations that were an average of fivefold higher than the peak plasma concentrations produced following a single 5-mg oral dose of the drug. In this study, the areas under the plasma concentration-time curve (AUCs) achieved following IM and oral administration of the same dose of the drug were similar. Olanzapine exhibits linear pharmacokinetics when given IM within the clinical dosage range. Preliminary evidence suggests that the onset of antipsychotic action following IM administration of the drug is evident within 24 hours but may be observed as early as 2 hours after IM administration.

Plasma olanzapine concentrations may vary between individuals according to gender, smoking status, and age. There is limited evidence that gender may affect plasma olanzapine concentrations, with concentrations being somewhat higher, perhaps by as much as 30–40%, in females compared with males. Plasma concentrations of olanzapine also may be increased in geriatric individuals compared with younger individuals, possibly as a result of age-related decreases in hepatic elimination of the drug. Data from one limited study in children and adolescents 10–18 years of age with schizophrenia found that plasma olanzapine concentrations among adolescents were within the range reported in nonsmoking adult patients with schizophrenia. In vivo studies have shown that exposures to olanzapine are similar among Japanese, Chinese, and Caucasian individuals, particularly after normalization for body weight differences.

The therapeutic range for plasma olanzapine concentrations and the relationship of plasma concentration to clinical response and toxicity have not been clearly established; however, acutely ill schizophrenic patients with 24-hour post-dose plasma olanzapine concentrations of 9.3 ng/mL or higher in one study or 12-hour post-dose concentrations

of 23.2 ng/mL or higher in another study appeared to have a better clinical response to therapy than patients with lower plasma concentrations.

■ Distribution

Distribution of olanzapine, a highly lipophilic drug, into human body tissues is extensive.

The manufacturer states that the volume of distribution of olanzapine has been reported to be approximately 1000 L. In pharmacokinetic studies in healthy individuals, the apparent volume of distribution of the drug averaged 1150 L and ranged from 660 to 1790 L for the fifth to 95th percentiles. Olanzapine is 93% bound to plasma proteins over the concentration range of 7–1100 ng/mL, principally to albumin and α_1-acid glycoprotein.

Olanzapine and its glucuronide metabolite have been shown to cross the placenta in humans. Placental transfer of olanzapine also has been shown to occur in rat pups.

Olanzapine is distributed into milk. The manufacturer states that in a study in lactating, healthy women, the average infant dose of olanzapine at steady-state was estimated to be approximately 1.8% of the maternal olanzapine dose. In a separate study that evaluated the extent of infant exposure to olanzapine in 7 breastfeeding women who had been receiving 5–20 mg of olanzapine daily for periods ranging from 19–395 days, median and maximum relative infant doses of 1 and 1.2%, respectively, were observed. Olanzapine was not detected in the plasma of the breastfed infants, and adverse effects possibly related to olanzapine exposure were not reported in the infants in this study. In addition, peak milk concentrations were achieved a median of 5.2 hours later than the corresponding maximal maternal plasma concentrations. In a case report, a relative infant dose of approximately 4% was estimated in one woman after 4 and 10 days (estimated to be at steady state) of olanzapine therapy at a dosage of 20 mg daily based on measurements of drug concentration in serum and in expressed breast milk. (See Cautions: Pregnancy, Fertility, and Lactation.)

■ Elimination

Although the exact metabolic fate has not been clearly established, it appears that olanzapine is extensively metabolized. Following a single oral dose of radiolabeled olanzapine, 7% of the dose was recovered in urine as unchanged drug. Approximately 57 and 30% of the dose was recovered in the urine and feces, respectively. In plasma, olanzapine accounted for only 12% of the AUC for total radioactivity, suggesting substantial exposure to metabolites. After multiple doses of olanzapine, the principal circulating metabolites are the 10-*N*-glucoronide, which is present at steady state at 44% of the plasma concentration of the parent drug, and 4′-*N*-desmethyl olanzapine, which is present at steady state at 31% of the plasma concentration of olanzapine. Both of these metabolites lack pharmacologic activity at the concentrations observed.

Direct glucuronidation and cytochrome P-450 (CYP)-mediated oxidation are the principal pathways for olanzapine metabolism. In vitro studies suggest that the CYP isoenzymes 1A2 and 2D6 and the flavin-containing monooxygenase system are involved in the oxidation of olanzapine. However, CYP2D6-mediated oxidation appears to be a minor metabolic pathway for olanzapine in vivo since the clearance of the drug is not reduced in individuals deficient in this enzyme.

Following oral administration, olanzapine has an elimination half-life ranging from 21 to 54 hours for the fifth to 95th percentiles of individual values with a mean of 30 hours. Following IM administration, the half-life and metabolic profile of olanzapine were similar to those observed with oral administration. The apparent plasma clearance of olanzapine ranges from 12 to 47 L/hr (mean: 25 L/hour).

The clearance of olanzapine in smokers is approximately 40% higher than in nonsmokers. (See Drug Interactions: Smoking.)

The clearance of olanzapine in females may be reduced by approximately 30% compared with males.

In a single-dose pharmacokinetic study, the elimination half-life of olanzapine was 1.5 times longer in healthy geriatric individuals 65 years of age or older than in healthy younger adults. (See Dosage and Administration: Dosage and see also Cautions: Geriatric Precautions.)

In one pharmacokinetic study conducted in a limited number of children and adolescents 10–18 years of age with schizophrenia who were treated with oral olanzapine, the apparent plasma clearance at steady-state averaged 9.6 L/hr, which was approximately half of the clearance values reported in adult studies but similar to clearance values reported in nonsmoking male and female schizophrenic patients. The elimination half-life averaged 37.2 hours in this same study. (See Dosage and Administration: Dosage and see also Cautions: Pediatric Precautions.)

The combined effects of age, smoking, and gender could result in substantial pharmacokinetic differences in populations. The clearance in younger, smoking adult male patients may be 3 times higher than that in geriatric, nonsmoking females. Dosage adjustment may be necessary in patients who exhibit a combination of factors that may result in slower metabolism of olanzapine. (See Dosage and Administration: Dosage.)

Because olanzapine is extensively metabolized before excretion and only 7% of the drug is excreted unchanged, renal impairment alone is unlikely to substantially alter the pharmacokinetics of olanzapine. The pharmacokinetics of olanzapine were similar in patients with severe renal impairment and healthy individuals, suggesting that dosage adjustment based upon the degree of renal impairment is not necessary. The effect of renal impairment on the elimination of olanzapine's metabolites has not been evaluated to date.

Although the presence of hepatic impairment would be expected to reduce the clearance of olanzapine, a pharmacokinetic study evaluating the effect of impaired hepatic function in individuals with clinically important cirrhosis (Childs Pugh Classification A and B) revealed little effect on the pharmacokinetics of olanzapine.

Olanzapine is not appreciably removed by hemodialysis, probably due to its large volume of distribution and extensive protein binding. Clinical experience with other enhanced elimination techniques, including multiple-dose activated charcoal, hemoperfusion, forced diuresis, and urinary alkalinization, is lacking; however, these treatments are unlikely to be beneficial following olanzapine overdosage because of the drug's large volume of distribution and extensive protein binding.

Chemistry and Stability

■ Chemistry

Olanzapine is a thienobenzodiazepine-derivative antipsychotic agent. The drug is structurally similar to clozapine.

Olanzapine occurs as a yellow crystalline solid that is practically insoluble in water.

Olanzapine for injection contains lactose monohydrate and tartaric acid; hydrochloric acid and/or sodium hydroxide may have been added to adjust pH. When olanzapine for injection is reconstituted as directed, the resulting solution should appear clear and yellow.

■ Stability

Commercially available olanzapine conventional tablets, orally disintegrating tablets, and olanzapine for IM injection should be stored at a controlled room temperature of 20–25°C but may be exposed to temperatures ranging from 15–30°C. Olanzapine orally disintegrating tablets should be stored in their original sealed blister. The conventional and orally disintegrating tablets should be protected from light and moisture and olanzapine for injection should be protected from light and freezing.

Following reconstitution, olanzapine for injection may be stored at a controlled room temperature of 20–25°C for up to 1 hour if necessary, but immediate use is preferred. Lorazepam injection should not be used to reconstitute olanzapine for injection since this delays reconstitution time.

Olanzapine orally disintegrating tablets contain aspartame (e.g., NutraSweet®). (See Individuals with Phenylketonuria, under Cautions: Precautions and Contraindications.)

Olanzapine for IM injection should not be combined with diazepam injection in a syringe because precipitation occurs when these drugs are mixed. Olanzapine for injection should not be combined in a syringe with haloperidol injection because the resulting pH has been shown to degrade olanzapine over time. Specialized references should be consulted for additional specific compatibility information.

Preparations

Excipients in commercially available drug preparations may have clinically important effects in some individuals; consult specific product labeling for details.

Olanzapine

Oral

Tablets, film-coated

2.5 mg	**Zyprexa®**, Lilly
5 mg	**Zyprexa®**, Lilly
7.5 mg	**Zyprexa®**, Lilly
10 mg	**Zyprexa®**, Lilly
15 mg	**Zyprexa®**, Lilly
20 mg	**Zyprexa®**, Lilly

Tablets, orally disintegrating

5 mg	**Zyprexa® Zydis®**, Lilly
10 mg	**Zyprexa® Zydis®**, Lilly
15 mg	**Zyprexa® Zydis®**, Lilly
20 mg	**Zyprexa® Zydis®**, Lilly

Parenteral

For injection

10 mg	
	Zyprexa® IntraMuscular, Lilly

Olanzapine Combinations

Oral

Capsules

6 mg with Fluoxetine Hydrochloride 25 mg (of fluoxetine)	
	Symbyax®, Lilly
6 mg with Fluoxetine Hydrochloride 50 mg (of fluoxetine)	
	Symbyax®, Lilly
12 mg with Fluoxetine Hydrochloride 25 mg (of fluoxetine)	
	Symbyax®, Lilly
12 mg with Fluoxetine Hydrochloride 50 mg (of fluoxetine)	
	Symbyax®, Lilly

DRUGDEX® Evaluations

ARIPIPRAZOLE

0.0 Overview

1) Class
- **a)** This drug is a member of the following class(es):
  Antipsychotic

2) Dosing Information
- **a)** Adult
  - **1)** oral solution may be substituted for the tablet dosages on a mg-per-mg basis for up to a 25 mg dose; patients oral solution (Prod Info ABILIFY(R) oral tablets, solution, orally disintegrating tablets, IM injection, 2008)
    - **a)** Bipolar disorder - Psychomotor agitation
      - **1)** initial, 9.75 mg IM (dose range 5.25 mg to 15 mg); cumulative doses up to a total of 30 mg/day may b dose required, wait at least 2 h after initial dose; for ongoing therapy, oral aripiprazole in a range of 10 m injection as soon as possible (Prod Info ABILIFY(R) oral tablets, solution, orally disintegrating tablets, IM
    - **b)** Bipolar I disorder, Adjunctive therapy with lithium or valproate for acute manic or mixed episodes
      - **1)** initial and target dose, 15 mg ORALLY once a day; may increase to MAX dose of 30 mg ORALLY on solution, orally disintegrating tablets, IM injection, 2008)
    - **c)** Bipolar I disorder, Monotherapy, manic or mixed episodes
      - **1)** initial and target dose, 15 mg ORALLY once a day; may increase up to MAX dose of 30 mg ORALLY solution, orally disintegrating tablets, IM injection, 2008)
    - **d)** Major depressive disorder, Adjunctive treatment in patients also receiving antidepressants
      - **1)** initial, 2 mg to 5 mg ORALLY once daily; dose adjust in up to 5 mg/day increments at intervals of 1 w (Prod Info ABILIFY(R) oral tablets, solution, orally disintegrating tablets, IM injection, 2008)
    - **e)** Psychomotor agitation - Schizophrenia
      - **1)** initial, 9.75 mg IM (dose range 5.25 mg to 15 mg); cumulative doses up to a total of 30 mg/day may b dose required, wait at least 2 hr after initial dose; for ongoing therapy, oral aripiprazole in a range of 10 n injection as soon as possible (Prod Info ABILIFY(R) oral tablets, solution, orally disintegrating tablets, IM
    - **f)** Schizophrenia
      - **1)** initial, 10 to 15 mg ORALLY once daily (Prod Info ABILIFY(R) oral tablets, solution, orally disintegrati
      - **2)** maintenance, MAX daily dosage is 30 mg/day ORALLY; increase dose only after 2 weeks at each do greater with doses higher than 10 to 15 mg/day (Prod Info ABILIFY(R) oral tablets, solution, orally disinte
- **b)** Pediatric
  - **1)** safety and efficacy not established in pediatric patients with major depressive disorder or agitation associated less than 13 years of age with schizophrenia, or patients less than age 10 years with bipolar I disorder (Prod Info disintegrating tablets, IM injection, 2008)
  - **2)** oral solution may be substituted for the tablet dosages on a mg-per-mg basis for up to a 25 mg dose; patients oral solution (Prod Info ABILIFY(R) oral tablets, solution, orally disintegrating tablets, IM injection, 2008)
    - **a)** Bipolar I disorder, Monotherapy, manic or mixed episodes
      - **1)** 10 yr and older, oral tablets, initial, 2 mg ORALLY once a day for 2 days, then 5 mg ORALLY once a ORALLY once a day; MAX dose 30 mg ORALLY once a day, titrated in 5 mg per day increments (Prod I disintegrating tablets, IM injection, 2008)
    - **b)** Schizophrenia
      - **1)** initial, oral tablets, 2 mg ORALLY once daily; increase to 5 mg after 2 days and to 10 mg (target dose mg; efficacy not greater at 30 mg/day compared to 10 mg/day (Prod Info ABILIFY(R) oral tablets, solutio 2008)

3) Contraindications
- **a)** hypersensitivity to aripiprazole or any component of the product (Prod Info ABILIFY(R) oral tablets, oral solution, IM disintegrating tablets, 2008)

4) Serious Adverse Effects
- **a)** At risk for suicide
- **b)** Cerebrovascular accident
- **c)** Death
- **d)** Diabetic ketoacidosis
- **e)** Immune hypersensitivity reaction
- **f)** Leukopenia
- **g)** Neuroleptic malignant syndrome
- **h)** Prolonged QT interval
- **i)** Seizure
- **j)** Suicidal behavior
- **k)** Tardive dyskinesia
- **l)** Transient ischemic attack

5) Clinical Applications
- **a)** FDA Approved Indications

1) Bipolar disorder - Psychomotor agitation
2) Bipolar I disorder, Adjunctive therapy with lithium or valproate for acute manic or mixed episodes
3) Bipolar I disorder, Monotherapy, manic or mixed episodes
4) Major depressive disorder, Adjunctive treatment in patients also receiving antidepressants
5) Psychomotor agitation - Schizophrenia
6) Schizophrenia

1.0 Dosing Information

Drug Properties

Storage and Stability

Adult Dosage

Pediatric Dosage

1.1 Drug Properties

A) Information on specific products and dosage forms can be obtained by referring to the Tradename List (Product In
B) Synonyms
Aripiprazole
C) Physicochemical Properties
1) Molecular Weight
a) 448.38 (Prod Info Abilify™, 2002)

1.2 Storage and Stability

A) Preparation
1) Intramuscular route
a) Aripiprazole should not be injected by intravenous or subcutaneous injection. It should only be used intran
muscle mass. The required volumes of solution for a dose of 5.25 milligrams (mg), 9.75 mg, and 15 mg are 0
respectively. Discard any unused portion of the injection (Prod Info ABILIFY(R) oral tablets, solution, orally di
2) Oral route
a) Aripiprazole may be taken without regard to meals (Prod Info ABILIFY(R) oral tablets, solution, orally disin
B) Oral route
1) Solution
a) Aripiprazole oral solution should be stored at 25 degrees Celsius (77 degrees Fahrenheit) with excursions
Celsius (59 and 86 degrees Fahrenheit). The oral solution should be used within 6 months after opening, but
(Prod Info ABILIFY(R) oral tablets, disintegrating tablets, solution, 2006).
2) Tablet/Tablet, Disintegrating
a) Aripiprazole tablets should be stored at 25 degrees Celsius (77 degrees Fahrenheit) with excursions perm
to 86 degrees Fahrenheit) (Prod Info ABILIFY(R) oral tablets, disintegrating tablets, solution, 2006).

1.3 Adult Dosage

Normal Dosage

Dosage in Renal Failure

Dosage in Hepatic Insufficiency

Dosage in Geriatric Patients

1.3.1 Normal Dosage

Intramuscular route

Oral route

1.3.1.A Intramuscular route

Bipolar disorder - Psychomotor agitation

Psychomotor agitation - Schizophrenia

1.3.1.A.1 Bipolar disorder - Psychomotor agitation

a) The recommended dose to control agitation in patients with schizophrenia or bipolar mania is 9.75 mi
5.25 mg to 15 mg). No additional benefit was observed after a 15 mg dose compared to a 9.75 mg dose.
day may be administered if a second dose is required. However, the efficacy of repeated doses in agitat
evaluated in clinical trials. Additionally, the safety of total daily doses greater than 30 mg or injections ad
have not been adequately evaluated. For ongoing therapy, oral aripiprazole in a range of 10 mg to 30 m
as soon as possible (Prod Info ABILIFY(R) oral tablets, solution, orally disintegrating tablets, IM injection

b) Concomitant CYP3A4 Inhibitors

1) The dosage of aripiprazole should be reduced to one-half the usual dose when administered con
as ketoconazole or clarithromycin. When the CYP3A4 inhibitor is discontinued, the aripiprazole dose
oral tablets, solution, orally disintegrating tablets, IM injection, 2008).

c) Concomitant CYP3A4 Inducers

1) The dosage of aripiprazole should be doubled when administered concurrently with a potential C
dose may be further increased if needed based on clinical evaluation. When the CYP3A4 inducer is
reduced to 10 to 15 mg (Prod Info ABILIFY(R) oral tablets, solution, orally disintegrating tablets, IM i

d) Concomitant CYP2D6 Inhibitors

1) The dosage of aripiprazole should be reduced to at least one-half the usual dose when administe
inhibitors, such as quinidine, fluoxetine, or paroxetine. When the CYP2D6 inhibitor is discontinued fr
dose should be increased (Prod Info ABILIFY(R) oral tablets, solution, orally disintegrating tablets, Il

1.3.1.A.2 Psychomotor agitation - Schizophrenia

a) The recommended dose to control agitation in patients with schizophrenia is 9.75 milligrams (mg) intr
No additional benefit was observed after a 15 mg dose compared to a 9.75 mg dose. Cumulative doses
administered if a second dose is required. However, the efficacy of repeated doses in agitated patients h
clinical trials. Additionally, the safety of total daily doses greater than 30 mg or injections administered m
been adequately evaluated. For ongoing therapy, oral aripiprazole in a range of 10 mg to 30 mg/day sho
possible (Prod Info ABILIFY(R) oral tablets, solution, orally disintegrating tablets, IM injection, 2008).

b) Concomitant CYP3A4 Inhibitors

1) The dosage of aripiprazole should be reduced to one-half the usual dose when administered con
as ketoconazole or clarithromycin. When the CYP3A4 inhibitor is discontinued, the aripiprazole dose
oral tablets, solution, orally disintegrating tablets, IM injection, 2008).

c) Concomitant CYP3A4 Inducers

1) The dosage of aripiprazole should be doubled when administered concurrently with a potential C
dose may be further increased if needed based on clinical evaluation. When the CYP3A4 inducer is
reduced to 10 to 15 mg (Prod Info ABILIFY(R) oral tablets, solution, orally disintegrating tablets, IM i

d) Concomitant CYP2D6 Inhibitors

1) The dosage of aripiprazole should be reduced to at least one-half the usual dose when administe
inhibitors, such as quinidine, fluoxetine, or paroxetine. When the CYP2D6 inhibitor is discontinued fr
dose should be increased (Prod Info ABILIFY(R) oral tablets, solution, orally disintegrating tablets, Il

1.3.1.B Oral route

Bipolar I disorder, Adjunctive therapy with lithium or valproate for acute manic or mixed episodes

Bipolar I disorder, Monotherapy, manic or mixed episodes

Major depressive disorder, Adjunctive treatment in patients also receiving antidepressants

Schizophrenia

1.3.1.B.1 Bipolar I disorder, Adjunctive therapy with lithium or valproate for acute manic or mixed ep

a) As adjunctive therapy with lithium or valproate, the recommended initial and target dose is aripiprazol
Depending on clinical response, the dose may be increased to 30 mg orally once a day. There have bee
safety of daily doses greater than 30 mg (Prod Info ABILIFY(R) oral tablets, solution, orally disintegrating

b) Concomitant CYP3A4 Inhibitors

1) The dosage of aripiprazole should be reduced to one-half the usual dose when administered con
as ketoconazole or clarithromycin. When the CYP3A4 inhibitor is discontinued, the aripiprazole dose
oral tablets, solution, orally disintegrating tablets, IM injection, 2008).

c) Concomitant CYP3A4 Inducers

1) The dosage of aripiprazole should be doubled when administered concurrently with a potential C dose may be further increased if needed based on clinical evaluation. When the CYP3A4 inducer is reduced to 10 to 15 mg (Prod Info ABILIFY(R) oral tablets, solution, orally disintegrating tablets, IM i

d) Concomitant CYP2D6 Inhibitors

1) The dosage of aripiprazole should be reduced to at least one-half the usual dose when administe inhibitors, such as quinidine, fluoxetine, or paroxetine. When the CYP2D6 inhibitor is discontinued fr dose should be increased (Prod Info ABILIFY(R) oral tablets, solution, orally disintegrating tablets, IM

1.3.1.B.2 Bipolar I disorder, Monotherapy, manic or mixed episodes

a) The recommended starting and target dose is aripiprazole 15 milligrams (mg) orally once a day. Depe increased to 30 mg orally once a day. There have been no clinical trials performed evaluating the safety ABILIFY(R) oral tablets, solution, orally disintegrating tablets, IM injection, 2008).

b) Maintenance Therapy

1) Aripiprazole has been effective for stabilizing and maintaining patients with a recent manic or mix 2006). However, it is unclear how long a patient should remain on aripiprazole therapy. Patients who aripiprazole monotherapy for at least 6 weeks demonstrated a benefit from maintenance treatment. beyond 6 weeks should be reassessed at regular intervals to determine the need for ongoing treatm solution, orally disintegrating tablets, IM injection, 2008).

c) Concomitant CYP3A4 Inhibitors

1) The dosage of aripiprazole should be reduced to one-half the usual dose when administered con as ketoconazole or clarithromycin. When the CYP3A4 inhibitor is discontinued, the aripiprazole dose oral tablets, solution, orally disintegrating tablets, IM injection, 2008).

d) Concomitant CYP3A4 Inducers

1) The dosage of aripiprazole should be doubled when administered concurrently with a potential C dose may be further increased if needed based on clinical evaluation. When the CYP3A4 inducer is reduced to 10 to 15 mg (Prod Info ABILIFY(R) oral tablets, solution, orally disintegrating tablets, IM i

e) Concomitant CYP2D6 Inhibitors

1) The dosage of aripiprazole should be reduced to at least one-half the usual dose when administe inhibitors, such as quinidine, fluoxetine, or paroxetine. When the CYP2D6 inhibitor is discontinued fr dose should be increased (Prod Info ABILIFY(R) oral tablets, solution, orally disintegrating tablets, IM

1.3.1.B.3 Major depressive disorder, Adjunctive treatment in patients also receiving antidepressants

a) The recommended initial dose of aripiprazole as adjunctive treatment in patients with major depressiv 2 to 5 milligrams (mg) orally once daily. The aripiprazole dose may be gradually adjusted by 5 mg/day in patient tolerability and efficacy. In two 6-week, placebo-controlled trials, the aripiprazole dose ranged fro CYP2D6 inhibitors (eg, fluoxetine, paroxetine) and 2 to 20 mg/day in patients not on potential CYP2D6 in established; reassess periodically to evaluate the need for maintenance therapy (Prod Info ABILIFY(R) o tablets, IM injection, 2008).

1.3.1.B.4 Schizophrenia

a) The recommended initial and target oral dose of aripiprazole for the treatment of schizophrenia is 10 daily, with or without meals (Prod Info ABILIFY(R) oral tablets, solution, orally disintegrating tablets, IM in daily have been effective in patients with acutely relapsed schizophrenia or schizoaffective disorder (Kan Petrie et al, 1998a). However, in clinical trials efficacy has not been significantly greater with doses highe not should be made before 2 weeks at each dose strength (Prod Info ABILIFY(R) oral tablets, solution, o

b) Doses of 30 mg daily could be administered without dose titration in one study (Petrie et al, 1998a).

c) Maintenance Therapy

1) It is unclear how long a patient should remain on aripiprazole therapy; however, patients who had antipsychotic mediations for at least 3 months and were discontinued from those medication and giv weeks did demonstrate a benefit from maintenance treatment. Patients should be reassessed at reg ongoing treatment (Prod Info ABILIFY(R) oral tablets, solution, orally disintegrating tablets, IM inject

d) Switching from Other Antipsychotics

1) Data are not available to recommend guidelines for switching from other antipsychotics to aripipr other antipsychotics. The previous antipsychotic treatment may be immediately discontinued or mor individual patient. However, in all cases, duration of antipsychotic administration overlap should kep tablets, solution, orally disintegrating tablets, IM injection, 2008).

e) Concomitant CYP3A4 Inhibitors

1) The dosage of aripiprazole should be reduced to one-half the usual dose when administered con as ketoconazole or clarithromycin. When the CYP3A4 inhibitor is discontinued, the aripiprazole dose oral tablets, solution, orally disintegrating tablets, IM injection, 2008).

f) Concomitant CYP3A4 Inducers

1) The dosage of aripiprazole should be doubled when administered concurrently with a potential C dose may be further increased if needed based on clinical evaluation. When the CYP3A4 inducer is reduced to 10 to 15 mg (Prod Info ABILIFY(R) oral tablets, solution, orally disintegrating tablets, IM i

g) Concomitant CYP2D6 Inhibitors

1) The dosage of aripiprazole should be reduced to at least one-half the usual dose when administe inhibitors, such as quinidine, fluoxetine, or paroxetine. When the CYP2D6 inhibitor is discontinued fr dose should be increased (Prod Info ABILIFY(R) oral tablets, solution, orally disintegrating tablets, IM

1.3.1.B.5 Oral Solution

a) Doses of the aripiprazole oral solution may be substituted for the tablet dosages on a milligram (mg)-
receiving 30 mg tablets should receive 25 mg of the oral solution (Prod Info ABILIFY(R) oral tablets, solu
2008).

b) Patients using the oral solution should be advised that every milliliter of aripiprazole oral solution cont
200 mg (Prod Info ABILIFY(R) oral tablets, solution, orally disintegrating tablets, IM injection, 2008).

1.3.1.B.6 Orally Disintegrating Tablet

a) Dosing with orally disintegrating tablets is the same as for the oral tablets (Prod Info ABILIFY(R) oral
IM injection, 2008)

b) Abilify Discmelt(R) 10 milligram (mg) orally disintegrating tablets contain 1.12 mg of phenylalanine, a
phenylalanine (Prod Info ABILIFY(R) oral tablets, solution, orally disintegrating tablets, IM injection, 2008

1.3.2 Dosage in Renal Failure

A) Dosage adjustment is not necessary in patients with renal impairment (Prod Info ABILIFY(R) oral tablets, solu
2008).

1.3.3 Dosage in Hepatic Insufficiency

A) Dosage adjustment is not necessary in patients with hepatic impairment (Prod Info ABILIFY(R) oral tablets, so
injection, 2008).

1.3.4 Dosage in Geriatric Patients

A) Dosage adjustment is not necessary for elderly patients (Prod Info ABILIFY(R) oral tablets, solution, orally disi

1.4 Pediatric Dosage

Normal Dosage

Dosage in Renal Failure

Dosage in Hepatic Insufficiency

1.4.1 Normal Dosage

1.4.1.A Oral route

Bipolar I disorder, Adjunctive therapy with lithium or valproate for acute manic or mixed episodes

Bipolar I disorder, Monotherapy, manic or mixed episodes

Schizophrenia

1.4.1.A.1 Bipolar I disorder, Adjunctive therapy with lithium or valproate for acute manic or mixed ep

a) As adjunctive therapy with lithium or valproate, the recommended starting dose of oral tablets in pedi
aripiprazole 2 milligrams (mg) orally once a day for 2 days, then titrated to 5 mg orally once a day for 2 d
orally once a day. Depending on clinical response, the dose may be increased in 5 mg per day incremen
performed evaluating the safety of daily doses greater than 30 mg (Prod Info ABILIFY(R) oral tablets, so
2008).

b) Maintenance Therapy

1) The efficacy of aripiprazole for the maintenance treatment of bipolar I disorder in pediatric patien
maintenance therapy can be extrapolated from adult data. It is recommended that responding pedia
acute response, but at the lowest dose needed to maintain remission with periodic reassessments p
solution, orally disintegrating tablets, IM injection, 2008).

c) Concomitant CYP3A4 Inhibitors

1) The dosage of aripiprazole should be reduced to one-half the usual dose when administered con
as ketoconazole or clarithromycin. When the CYP3A4 inhibitor is discontinued, the aripiprazole dose
oral tablets, solution, orally disintegrating tablets, IM injection, 2008).

d) Concomitant CYP3A4 Inducers

1) The dosage of aripiprazole should be doubled when administered concurrently with a potential C
dose may be further increased if needed based on clinical evaluation. When the CYP3A4 inducer is
reduced to 10 to 15 mg (Prod Info ABILIFY(R) oral tablets, solution, orally disintegrating tablets, IM i

e) Concomitant CYP2D6 Inhibitors

1) The dosage of aripiprazole should be reduced to at least one-half the usual dose when administe

inhibitors, such as quinidine, fluoxetine, or paroxetine. When the CYP2D6 inhibitor is discontinued fr
dose should be increased (Prod Info ABILIFY(R) oral tablets, solution, orally disintegrating tablets, II

1.4.1.A.2 Bipolar I disorder, Monotherapy, manic or mixed episodes

a) The recommended starting dose of oral tablets in pediatric patients age 10 years and older is aripipra
days, then titrated to 5 mg orally once a day for 2 days, and titrated to the target dose of 10 mg orally on
dose may be titrated in 5 mg per day increments. There have been no clinical trials performed evaluating
(Prod Info ABILIFY(R) oral tablets, solution, orally disintegrating tablets, IM injection, 2008).

b) Maintenance Therapy

1) The efficacy of aripiprazole for the maintenance treatment of Bipolar I Disorder in pediatric patier
maintenance can be extrapolated from adult data. It is recommended that responding pediatric patie
response, but at the lowest dose needed to maintain remission with periodic reassessments perform
solution, orally disintegrating tablets, IM injection, 2008).

c) Concomitant CYP3A4 Inhibitors

1) The dosage of aripiprazole should be reduced to one-half the usual dose when administered con
as ketoconazole or clarithromycin. When the CYP3A4 inhibitor is discontinued, the aripiprazole dose
oral tablets, solution, orally disintegrating tablets, IM injection, 2008).

d) Concomitant CYP3A4 Inducers

1) The dosage of aripiprazole should be doubled when administered concurrently with a potential C
dose may be further increased if needed based on clinical evaluation. When the CYP3A4 inducer is
reduced to 10 to 15 mg (Prod Info ABILIFY(R) oral tablets, solution, orally disintegrating tablets, IM i

e) Concomitant CYP2D6 Inhibitors

1) The dosage of aripiprazole should be reduced to at least one-half the usual dose when administe
inhibitors, such as quinidine, fluoxetine, or paroxetine. When the CYP2D6 inhibitor is discontinued fr
dose should be increased (Prod Info ABILIFY(R) oral tablets, solution, orally disintegrating tablets, II

1.4.1.A.3 Schizophrenia

a) The recommended target dose for the treatment of schizophrenia in adolescents aged 13 to 17 years
tablets at 2 mg/day and increase the dose to 5 mg after 2 days and then to 10 mg after an additional 2 d
should be done in 5-mg increments. However, no additional benefit has been seen with the 30 mg dose
orally disintegrating tablets, IM injection, 2008).

b) Maintenance Therapy

1) The efficacy of aripiprazole for the maintenance treatment of schizophrenia in pediatric patients h
of maintenance can be extrapolated from adult data. It is recommended that responding pediatric pa
response, but at the lowest dose needed to maintain remission with periodic reassessments perform
solution, orally disintegrating tablets, IM injection, 2008).

c) Switching from Other Antipsychotics

1) Data are not available to recommend guidelines for switching from other antipsychotics to aripipr
other antipsychotics. The previous antipsychotic treatment may be immediately discontinued or mor
individual patient. However, in all cases, duration of antipsychotic administration overlap should kep
tablets, solution, orally disintegrating tablets, IM injection, 2008)

d) Concomitant CYP3A4 Inhibitors

1) The dosage of aripiprazole should be reduced to one-half the usual dose when administered con
as ketoconazole or clarithromycin. When the CYP3A4 inhibitor is discontinued, the aripiprazole dose
oral tablets, solution, orally disintegrating tablets, IM injection, 2008).

e) Concomitant CYP3A4 Inducers

1) The dosage of aripiprazole should be doubled when administered concurrently with a potential C
dose may be further increased if needed based on clinical evaluation. When the CYP3A4 inducer is
reduced to 10 to 15 mg (Prod Info ABILIFY(R) oral tablets, solution, orally disintegrating tablets, IM i

f) Concomitant CYP2D6 Inhibitors

1) The dosage of aripiprazole should be reduced to at least one-half the usual dose when administe
inhibitors, such as quinidine, fluoxetine, or paroxetine. When the CYP2D6 inhibitor is discontinued fr
dose should be increased (Prod Info ABILIFY(R) oral tablets, solution, orally disintegrating tablets, II

4) The safety and efficacy of aripiprazole have not been established in pediatric patients with major depressi
schizophrenia or bipolar mania, patients less than 13 years of age with schizophrenia, or patients less than a
ABILIFY(R) oral tablets, solution, orally disintegrating tablets, IM injection, 2008).

1.4.1.A.5 Oral Solution

a) Doses of the aripiprazole oral solution may be substituted for the tablet dosages on a milligram (mg)-
receiving 30 mg tablets should receive 25 mg of the oral solution (Prod Info ABILIFY(R) oral tablets, solu
2008).

b) Patients using the oral solution should be advised that every milliliter of aripiprazole oral solution con
200 mg (Prod Info ABILIFY(R) oral tablets, solution, orally disintegrating tablets, IM injection, 2008).

1.4.1.A.6 Orally Disintegrating Tablets

a) Dosing with orally disintegrating tablets is the same as for the oral tablets (Prod Info ABILIFY(R) oral
IM injection, 2008)

b) Abilify Discmelt(R) 10 milligram (mg) orally disintegrating tablets contains 1.12 mg of phenylalanine a
phenylalanine (Prod Info ABILIFY(R) oral tablets, solution, orally disintegrating tablets, IM injection, 2008

1.4.2 Dosage in Renal Failure

A) Dosage adjustment is not necessary in patients with renal impairment (Prod Info ABILIFY(R) oral tablets, solu 2008).

1.4.3 Dosage in Hepatic Insufficiency

A) Dosage adjustment is not necessary in patients with hepatic impairment (Prod Info ABILIFY(R) oral tablets, sc injection, 2008).

2.0 Pharmacokinetics

Onset and Duration

Drug Concentration Levels

ADME

2.1 Onset and Duration

A) Onset

1) Initial Response

a) SCHIZOPHRENIA, ORAL: 1 week (10 to 30 mg daily) (Petrie et al, 1998b; Anon, 2000b).

1) In phase II studies involving hospitalized schizophrenic patients, significant improvement (including n of therapy with aripiprazole 30 mg daily. With lower doses (2 or 10 mg daily), symptom improvement was less substantial (Petrie et al, 1998b).

2.2 Drug Concentration Levels

A) Therapeutic Drug Concentration

1) Not established.

B) Peak Concentration

1) Following an intramuscular dose, the geometric mean maximum concentration (Cmax) was on average 19% h administration (Prod Info ABILIFY(R) oral tablets, orally-disintegrating tablets, oral solution, IM injection, 2006).

C) Time to Peak Concentration

1) Oral: 3 to 5 hours (Anon, 2000b; Prod Info ABILIFY(R) oral tablets, orally-disintegrating tablets, oral solution, I

2) Intramuscular: 1 to 3 hours (Prod Info ABILIFY(R) oral tablets, orally-disintegrating tablets, oral solution, IM inj

a) In healthy subjects receiving once-daily doses of 5 and 20 mg, mean peak plasma levels on day 14 were in 3 to 5 hours (Anon, 2000b).

b) With a titrated dosing schedule of 10 mg daily for 2 days, then 20 mg daily for 2 days, and finally 30 mg da concentration on day 14 was 452 ng/mL (3 hours) (Anon, 2000b).

c) In 2 studies of healthy subjects, the median times to peak plasma concentrations following intramuscular a hours (Prod Info ABILIFY(R) oral tablets, orally-disintegrating tablets, oral solution, IM injection, 2006).

D) Area Under the Curve

1) The aripiprazole area under the curve (AUC) in the first 2 hours after an intramuscular injection was 90% great tablet; however, both routes had similar systemic exposure over 24 hours. When intramuscular aripiprazole doses schizophrenia or schizoaffective disorder, the pharmacokinetics of aripiprazole were linear over a dose range of 1 orally-disintegrating tablets, oral solution, IM injection, 2006).

2.3 ADME

Absorption

Distribution

Metabolism

Excretion

Elimination Half-life

2.3.1 Absorption

A) Bioavailability

1) Oral: tablet, 87%; solution, well-absorbed (Prod Info ABILIFY(R) oral tablets, orally-disintegrating tablets,

2) Intramuscular: 100% after a 5-mg intramuscular injection (Prod Info ABILIFY(R) oral tablets, orally-disinte

2006).

a) A comparative bioavailability study which compared the pharmacokinetics of a 30 milligram aripiprazo found that plasma concentrations of aripiprazole were higher with the solution than with the tablet. In hea concentration and area under the curve values were 22% and 14% higher with the solution as compared (R) oral tablets, orally-disintegrating tablets, oral solution, IM injection, 2006).

b) Pharmacokinetic studies with the orally disintegrating aripiprazole tablet indicate that they are bioequ ABILIFY(R) DISCMELT(TM) orally disintegrating tablets, 2006).

B) Effects of Food

1) Absorption unaffected (Prod Info ABILIFY(R) oral tablets, orally-disintegrating tablets, oral solution, IM inje

a) Peak serum levels and AUC of aripiprazole and dehydroaripiprazole are not significantly affected whe peak serum levels is delayed (by 3 hours for aripiprazole and by 12 hours for dehydroaripiprazole) (Prod disintegrating tablets, oral solution, IM injection, 2006).

2.3.2 Distribution

A) Distribution Sites

1) Protein Binding

a) greater than 99% (aripiprazole and dehydroaripiprazole) (Prod Info ABILIFY(R) oral tablets, orally-dis 2006).

B) Distribution Kinetics

1) Volume of Distribution

a) 404 L or 4.9 L/kg (intravenous) (Prod Info ABILIFY(R) oral tablets, orally-disintegrating tablets, oral so

2.3.3 Metabolism

A) Metabolism Sites and Kinetics

1) Liver, extent unknown (Lawler et al, 1999).

a) Metabolic pathways include dehydrogenation and hydroxylation (via cytochrome P450 (CYP)-3A4 an CYP-3A4 . Aripiprazole is the primary compound in plasma. Aripiprazole does not inhibit or induce the C tablets, orally-disintegrating tablets, oral solution, IM injection, 2006).

b) Poor metabolizers (CYP-2D6) have been identified (speculated as 8% of population); these patients l active compounds (aripiprazole and dehydroaripiprazole) . Inhibitors of CYP-2D6 are capable of increasi (Prod Info ABILIFY(R) oral tablets, orally-disintegrating tablets, oral solution, IM injection, 2006).

B) Metabolites

1) Dehydroaripiprazole (active) (Prod Info ABILIFY(R) oral tablets, orally-disintegrating tablets, oral solution,

a) Major metabolite, representing about 40% of aripiprazole AUC in plasma. This metabolite has affinitie compound and appears to contribute to pharmacologic activity (Prod Info ABILIFY(R) oral tablets, orally- injection, 2006).

2.3.4 Excretion

A) Kidney

1) Renal Excretion (%)

a) 25% of dose (less than 1% unchanged aripiprazole) (Prod Info ABILIFY(R) oral tablets, orally-disinteg 2006).

B) Feces

1) FECES, 55% of a dose (about 18% unchanged aripiprazole) (Prod Info ABILIFY(R) oral tablets, orally-disi 2006).

2.3.5 Elimination Half-life

A) Parent Compound

1) ELIMINATION HALF-LIFE

a) 75 hours (extensive metabolizers) (Prod Info ABILIFY(R) oral tablets, orally-disintegrating tablets, ora

1) An elimination half-life of 146 hours has been reported in poor metabolizers (Prod Info ABILIFY(R solution, IM injection, 2006).

B) Metabolites

1) Dehydroaripiprazole, 94 hours (Prod Info ABILIFY(R) oral tablets, orally-disintegrating tablets, oral solutio

3.0 Cautions

Contraindications

Precautions

Adverse Reactions

Teratogenicity/Effects in Pregnancy/Breastfeeding

Drug Interactions

3.0.A Black Box WARNING

1) Oral (Tablet; Tablet, Disintegrating; Solution)

Increased Mortality In Elderly Patients With Dementia-Related Psychosis

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of d controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed between 1.6 to 1.7 times the risk of death in placebo-treated patients. Over the course of a typical 10-week c patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of dea to be either cardiovascular (eg, heart failure, sudden death) or infectious (eg, pneumonia) in nature. Observa antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to wh observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the approved for the treatment of patients with dementia-related psychosis.

Suicidality and Antidepressant Drugs

Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in child term studies of Major Depressive Disorder (MDD) and other psychiatric disorders. Anyone considering the us antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk w adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with ages who are started on antidepressant therapy should be monitored appropriately and observed closely for changes in behavior. Families and caregivers should be advised of the need for close observation and comm not approved for use in pediatric patients with depression (Prod Info ABILIFY(R) oral tablets, oral solution, IM disintegrating tablets, 2008).

2) Intramuscular (Solution)

Increased Mortality In Elderly Patients With Dementia-Related Psychosis

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of d controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed between 1.6 to 1.7 times the risk of death in placebo-treated patients. Over the course of a typical 10-week c patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of dea to be either cardiovascular (eg, heart failure, sudden death) or infectious (eg, pneumonia) in nature. Observa antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to wh observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the approved for the treatment of patients with dementia-related psychosis.

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3.1 Contraindications

A) hypersensitivity to aripiprazole or any component of the product (Prod Info ABILIFY(R) oral tablets, oral solution, IM disintegrating tablets, 2008)

3.2 Precautions

A) elderly patients with dementia (unapproved use); increased risk of death mostly due to cardiovascular events (eg, (mostly pneumonia) reported when atypical antipsychotics were used off-label to treat behavorial disorders associated tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally disintegrating tablets, 2008)

B) first few months of therapy or following changes in dosage; increased risk of suicidal ideation and behavior or wors tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally disintegrating tablets, 2008)

C) suicidal ideation and behavior or worsening depression; increased risk, particularly in children, adolescents, and yo require therapy discontinuation (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) o

D) aspiration pneumonia, at-risk patients; esophageal dysmotility and aspiration have been reported, especially in the dementia (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally disintegrating tal

E) cardiovascular disease, preexisting (including history of myocardial infarction or ischemic heart disease, heart failu risk of orthostatic hypotension (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) or

F) cerebrovascular disease, preexisting; increased risk of orthostatic hypotension (Prod Info ABILIFY(R) oral tablets, (R) orally disintegrating tablets, 2008)

G) concomitant parenteral benzodiazepine therapy; monitor patient for orthostatic hypotension and for excessive seda solution, IM injection, ABILIFY DISCMELT(R) orally disintegrating tablets, 2008)

H) diabetes mellitus, preexisting or risk factors for (eg, obesity, family history of diabetes); may experience hyperglyce ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally disintegrating tablets, 2008)

I) elderly, increased risk of esophageal dysmotility, aspiration, and potentially-irreversible tardive dyskinesia (especial

oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally disintegrating tablets, 2008)
J) elevation in core body temperature; increased risk following strenuous exercise, exposure to extreme heat, concon
or dehydration (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally disintegrati
K) higher doses and longer treatment durations; increased risk of tardive dyskinesia, which may be irreversible (Prod
injection, ABILIFY DISCMELT(R) orally disintegrating tablets, 2008)
L) hyperglycemia, severe and associated with ketoacidosis, hyperosmolar coma, or death has been reported with aty
tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally disintegrating tablets, 2008)
M) hypotension, predisposition (such as dehydration, hypovolemia, and antihypertensive drug therapy); increased risk
(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally disintegrating tablets, 2008)
N) neuroleptic malignant syndrome has occurred; discontinue aripiprazole therapy and provide treatment as needed (
solution, IM injection, ABILIFY DISCMELT(R) orally disintegrating tablets, 2008)
O) seizures, history or condition that may lower the seizure threshold (eg, Alzheimer's dementia); increased risk of se
solution, IM injection, ABILIFY DISCMELT(R) orally disintegrating tablets, 2008)
P) tardive dyskinesia; has been reported and may be irreversible (Prod Info ABILIFY(R) oral tablets, oral solution, IM
disintegrating tablets, 2008)
Q) report suspected adverse reactions to Bristol-Myers Squibb at 1-800-721-5072 or to the US Food and Drug Admin
www.fda.gov/medwatch (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally di

3.3 Adverse Reactions

Cardiovascular Effects

Dermatologic Effects

Endocrine/Metabolic Effects

Gastrointestinal Effects

Hematologic Effects

Immunologic Effects

Musculoskeletal Effects

Neurologic Effects

Ophthalmic Effects

Psychiatric Effects

Respiratory Effects

Other

3.3.1 Cardiovascular Effects

Orthostatic hypotension

Prolonged QT interval

Summary

Tachycardia

3.3.1.A Orthostatic hypotension

1) Incidence: 0.6% to 4% (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(
2) Compared with placebo, aripiprazole therapy resulted in a higher incidence of orthostatic hypotension am
(1% vs 0.3%; n=2467), pediatric patients 10 to 17 years of age receiving oral aripiprazole (1% vs 0%; n=399)

(0.6% vs 0%; n=501) during short-term trials. Aripiprazole should be used cautiously in patients with preexisti
would predispose patients to hypotension (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILI
2008).
3) The frequency of a significant orthostatic change in blood pressure (ie, a decrease of at least 20 mmHg in
increase in heart rate of 25 or greater when changing from a supine to standing position) was not significantly
compared with those treated with placebo in the placebo controlled trials of adult patients (4% aripiprazole, 2
years (0%, 0.5%), or in aripiprazole injection-treated patients (3%, 2%) (Prod Info ABILIFY(R) oral tablets, ora
(R) orally disintegrating tablets, 2008).

3.3.1.B Prolonged QT interval

1) Incidence: 0.1% to 1% (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(
2) Prolongation of the QT-interval has been observed during clinical trials with a frequency between 1/1000 a
doses of aripiprazole at least 2 mg day. Aripiprazole should be used cautiously in patients with preexisting ca
abnormalities (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally dis

3.3.1.C Summary

1) Because orthostatic hypotension, prolonged QT interval, and tachycardia have been reported with aripipra
caution in patients with known cardiovascular disease or conduction abnormalities, or conditions which would
ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally disintegrating tablets, 2008)

3.3.1.D Tachycardia

1) Incidence: 2% (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally
2) In a pooled analysis of trials in which adult patients with agitation associated with schizophrenia or bipolar
intramuscularly 5.25 mg/day or greater (n=501) or placebo (n=220), tachycardia was reported in 2% of patien
than 1% of patients receiving placebo (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY
2008).

3.3.2 Dermatologic Effects

Acneiform drug eruption

Rash

3.3.2.A Acneiform drug eruption

1) Incidence: rare
2) A 23-year-old man developed acneiform drug eruptions 10 days after starting aripiprazole treatment for pa
year history of symptoms suggestive of paranoid schizophrenia. In the past had received an adequate trial of
treated with aripiprazole 20 mg/day with a good response. After 1 month of treatment with aripiprazole, the pa
remained symptomatic for 1 year. The patient was readmitted for aggravation of symptoms and upon admiss
hemogram, serum electrolytes, renal function and liver function. For acute control of his aggression, the patie
haloperidol 10 mg and promethazine 25 mg intramuscularly twice daily for 4 days. The patient was restarted
mg/day over 4 days. After 10 days of aripiprazole treatment, the patient developed papulopustular eruptions
worsened with sunlight exposure) The patient had no past history of the eruptions or aripiprazole exposure in
with aripiprazole-induced acneiform eruptions. Aripiprazole was discontinued and the patient was switched to
response. Consequently, the affected regions were treated with topical retinoic acid 0.25 mg ointment. Within
there was complete resolution of the acneiform eruptions with mild scarring. Because the patient was previou
rapid development of the acneiform lesions, the acneiform drug eruption may have been mediated through a
clinical signs of allergy were noted (Mishra et al, 2008).

3.3.2.B Rash

1) Incidence: 2% (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally
2) In a pooled analysis of trials in which pediatric patients age 10 to 17 years with schizophrenia or bipolar m
mg/day or greater) (n=399) or placebo (n=197), rash was reported in 2% of patients receiving aripiprazole co
(Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally disintegrating tab

3.3.3 Endocrine/Metabolic Effects

Blood glucose level - finding

Diabetes mellitus

Diabetic ketoacidosis

Hyperglycemia

Hyponatremia

Increased body temperature

Increased prolactin level

Metabolic syndrome

Summary

Triglyceride level - finding

Weight increased

3.3.3.A Blood glucose level - finding

1) Incidence: rare (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orall

2) Blood glucose fluctuation has been observed rarely in postmarketing surveillance of aripiprazole (Prod Inf injection, ABILIFY DISCMELT(R) orally disintegrating tablets, 2008).

3.3.3.B Diabetes mellitus

See Drug Consult reference: ATYPICAL ANTIPSYCHOTIC AGENTS - EFFECT ON GLUCOSE AND RISK C

3.3.3.C Diabetic ketoacidosis

1) A 44-year-old, obese, African-American man developed new-onset diabetes and diabetic ketoacidosis (DK treatment for schizoaffective disorder. The patient's medical history included a 16-year diagnosis of schizoaff upon admission was 43.3 kg/m(2)), and he had no personal or family history of diabetes and no current medi prior for schizoaffective disorder with a good clinical response to fluphenazine and valproic acid. Upon admis exacerbation of schizoaffective disorder symptoms (auditory hallucinations), treatment with fluphenazine 5 m fluphenazine was increased to 5 mg twice daily and valproic acid 1750 mg/day was added. By day 27, the pa hallucinations and aripiprazole 15 mg/day was initiated. Additionally, the patient was receiving fluphenazine, atorvastatin for hyperlipidemia. On day 28 the aripiprazole was increased to 30 mg/day. On day 43, after 16 d experienced a episode of urinary incontinence. On day 44, the patient refused to eat, experienced somnolenc ability to take his medication or drink fluids without assistance. The patient was treated with intravenous fluids sinus tachycardia. On day 45, the patient was lethargic, stopped communicating, had difficulty walking and ha hours. Laboratory analysis revealed hyperglycemia (glucose, 813 mg/dL), metabolic acidosis (bicarbonate, 9 gases pH, 7.2), moderate serum ketone levels, elevated serum creatinine (2.7 mg/dL), bilirubinemia (2.6 mg/ 14.9%. The patient was diagnosed with DKA, transferred to the medical intensive care unit where all psychiat patient was given intravenous insulin and fluids. The psychiatric team recommended fluphenazine, benztropi metabolic acidosis and azotemia resolved, and the intravenous insulin was changed to subQ long-acting insu back to the psychiatric service after the serum glucose had stabilized. The patient's discharge medications in aspart in addition to benztropine, fluphenazine, divalproex sodium, and escitalopram. Within 4 months after h insulin. According to the Naranjo scale (score of 5), aripiprazole was the probable catalyst triggering DKA. Th associated DKA may be attributed to preexisting glucose impairment (evidenced by the strong correlation bet (Makhzoumi et al, 2008).

2) A case of new-onset diabetes and diabetic ketoacidosis with elevated lipase was described in a 33-year-o following treatment with aripiprazole. Prior to current presentation, the patient had been on aripiprazole thera had a body mass index (BMI) was 32 kg/m(2) prior to taking aripiprazole. At the time of presentation, the pati epigastric abdominal pain. The patient had progressively gained weight since initiating aripiprazole treatment Laboratory tests indicated hyperglycemia (blood glucose of 1769 mg/dL), diabetic ketoacidosis (anion gap of milliosmoles/kg, CO2 of 6 mmol/L), and hyperlipasemia (lipase of 4068 International Units/L). An abdominal u pancreatitis and gallstones, and thyroid function tests were normal. The patient did not have a prior medical h Aripiprazole was discontinued and the patient was treated with intravenous fluids and insulin. A diagnosis of a lipase, secondary to diabetic ketoacidosis, was made and the patient was discharged home with haloperidol discontinuation of aripiprazole, the patient's BMI had decreased to 33 kg/m(2) and, while still diabetic, his insu proposed that patient's weight and blood glucose may need be monitored during aripiprazole therapy (Reddy

3.3.3.D Hyperglycemia

1) Hyperglycemia has been reported in patients treated with atypical antipsychotics; and in some instances, ketoacidosis, hyperosmolar coma, or death. There have been few reports of hyperglycemia in patients treate atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However risk of treatment-emergent hyperglycemia-related adverse events in patients treated with atypical antipsychot the time these studies were conducted, it is not known if aripiprazole is associated with this increased risk. Pa antipsychotics for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. If sy should undergo fasting blood glucose testing. Although hyperglycemia has resolved when the antipsychotic d

required continued antidiabetic treatment despite antipsychotic discontinuation (Prod Info ABILIFY(R) oral tab DISCMELT(R) orally disintegrating tablets, 2008).

3.3.3.E Hyponatremia

1) Hyponatremia was reported in a 69-year-old man when aripiprazole was added to sodium valproate maint His comorbid conditions included diabetes mellitus treated with metformin and glibenclamide, and hypothyroi While he was treated with a stable dose of sodium valproate 1000 mg/day, he experienced a relapse of mani mg/day was added. The patient developed persistent hiccoughs 2 days later, accompanied by a serum sodiu of 4.5 mEq/L, and urine specific gravity of 1.01; other laboratory and thyroid serology results were unremarka per day of water for the previous 3 weeks. When aripiprazole was withheld and water intake was restricted to mEq/L. However, sodium levels dropped again to 120 mEq/L one day following rechallenge with aripiprazole aripiprazole and was initiated on quetiapine (dose titrated to 400 mg/day over 2 weeks), his sodium levels gra later with spontaneous resolution of hiccoughs. Fluid restriction was then stopped. During the following 8 mor normal sodium levels (Behere et al, 2007).

3.3.3.F Increased body temperature

1) Disruption of the body's ability to reduce core body temperature has been associated with antipsychotic a appropriate care in patients who will be experiencing conditions that may contribute to an elevated core body exposure to extreme heat, or dehydration) (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABIL tablets, 2008).

3.3.3.G Increased prolactin level

1) Serum prolactin levels have been unaffected or increased only slightly by oral aripiprazole (2 to 30 mg dai Petrie et al, 1998; Kane et al, 2000b). Increases in prolactin levels were greater with haloperidol 10 mg daily i Saha et al, 1999a).

3.3.3.H Metabolic syndrome

See Drug Consult reference: ANTIPSYCHOTIC AGENTS - METABOLIC SYNDROME

3.3.3.I Summary

1) Blood glucose fluctuation, diabetic ketoacidosis, and hyperglycemia have been reported with aripiprazole factors for diabetes should be monitored for worsening glucose control and should undergo fasting blood gluc during aripiprazole treatment. Reports of weight gain, increased body temperature, a case report of hyponatr prolactin have been reported with aripiprazole use. Aripiprazole should be used cautiously in patients with the temperatures, dehydration, strenuous exercise, or other conditions which may increase core body temperatu solution, IM injection, ABILIFY DISCMELT(R) orally disintegrating tablets, 2008).

3.3.3.J Triglyceride level - finding

1) In pooled data of 2 placebo-controlled trials of adult patients with major depressive disorder receiving oral weeks in addition to continued antidepressant therapy (n=371) or antidepressant therapy alone (n=366), the triglycerides was 5% versus 0%, respectively (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, A tablets, 2008).

3.3.3.K Weight increased

1) Incidence: 2% to 30% (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(

2) In a short-term study of aripiprazole as adjunctive therapy for bipolar disorder, increased weight was repo mg/day or 30 mg/day orally (n=253) compared with 1% of patients receiving placebo (n=130). Patients receiv aripiprazole or placebo for up to 6 weeks (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILI 2008).

3) In pooled data of 2 placebo-controlled trials of adult patients with major depressive disorder receiving arip in addition to continued antidepressant therapy (n=371), compared with antidepressant therapy only (n=366), of patients, respectively. Comparing the aripiprazole adjunctive group with the adjunctive placebo group, the respectively, and the percentage of patients gaining 7% or greater of body weight was 5% vs 1%, respectivel solution, IM injection, ABILIFY DISCMELT(R) orally disintegrating tablets, 2008).

4) In 4- to 6-week trials in which adult patients with schizophrenia were treated with either aripiprazole 5 to 3 was observed among patients treated with aripiprazole compared with a weight loss of 0.05 kg observed amo greater gain in body weight from baseline was observed in 8% of the aripiprazole-treated patients compared Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally disintegrating tablets, 2

5) In 3-week trials in which adult patients with mania were treated with either aripiprazole or placebo, a weigl treated with aripiprazole compared with a weight loss of 0.2 kg observed among patients treated with placebo baseline was observed in 3% of the aripiprazole-treated patients compared with 2% of the placebo-treated pa solution, IM injection, ABILIFY DISCMELT(R) orally disintegrating tablets, 2008).

6) In a 6-week trial in which pediatric patients 13 to 17 years of age with schizophrenia were treated with eith 0.13 kg was observed among patients treated with aripiprazole compared with a weight loss of 0.83 kg obser 7% or greater gain in body weight from baseline was observed in 5% of the aripiprazole-treated patients com (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally disintegrating tab

7) In one large 4-week study, weight gain of more than 7% was observed in about 11% of patients treated w relationship) and 14% receiving haloperidol 10 mg daily (Saha et al, 1999a).

8) In a 26-week, placebo-controlled trial among patients treated with aripiprazole 15 mg daily for schizophrer greater body weight from baseline were as follows (Prod Info ABILIFY(R) oral tablets, oral solution, IM injecti disintegrating tablets, 2008):

Body-Mass Index (BMI)	Aripiprazole	Placebo
Less than 23	6.8%	3.7%
23 to 27	5.1%	4.2%
Greater than 27	5.7%	4.1%

p values not provided

9) In a 52-week, active-controlled trial with aripiprazole for schizophrenia, weight changes from baseline wer tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally disintegrating tablets, 2008):

Body-Mass Index (BMI)	Mean weight change from baseline (kg)	Weight gain
Less than 23	2.6	
23 to 27	1.4	
Greater than 27	-1.2	

p values not provided

3.3.4 Gastrointestinal Effects

Constipation

Diarrhea

Dysphagia

Excessive salivation

Increased appetite

Nausea

Summary

Vomiting

Xerostomia

3.3.4.A Constipation

1) Incidence: 5% to 11% (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(I
2) In pooled data of 2 placebo-controlled trials of adult patients with major depressive disorder receiving oral weeks in addition to continued antidepressant therapy (n=371) or antidepressant therapy only (n=366), const respectively (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally disin
3) In a pooled analysis of trials in which adult patients with schizophrenia or bipolar mania received either ari or placebo (n=1166), constipation was reported in 11% of patients receiving aripiprazole compared with 7% c ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally disintegrating tablets, 2008)

3.3.4.B Diarrhea

1) Incidence: 3% (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally
2) In a pooled analysis of trials in which pediatric patients age 10 to 17 years with schizophrenia or bipolar m mg/day or greater) (n=399) or placebo (n=197), diarrhea was reported in 3% of patients receiving aripiprazole placebo (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally disintegr

3.3.4.C Dysphagia

1) Esophageal dysmotility and aspiration have occurred with aripiprazole use. Dysphagia was reported infrec premarketing clinical trials. Nonetheless, like other antipsychotic drugs, aripiprazole should be used cautiousl (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally disintegrating tab

3.3.4.D Excessive salivation

1) Incidence: 3.1% to 8.1% (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMEL
2) In a short-term study of aripiprazole as adjunctive therapy for bipolar disorder, salivary hypersecretion wa aripiprazole 15 mg/day or 30 mg/day orally (n=253) compared with 2% of patients receiving placebo (n=130).

in addition to aripiprazole or placebo for up to 6 weeks (Prod Info ABILIFY(R) oral tablets, oral solution, IM inj disintegrating tablets, 2008).
3) In a short-term, placebo-controlled trial in which pediatric patients age 10 to 17 years with bipolar mania re orally or placebo, salivary hypersecretion was reported in 8.1% of the aripiprazole 30-mg group and 3.1% of t placebo group (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally dis
4) In a pooled analysis of trials in which pediatric patients age 10 to 17 years with schizophrenia or bipolar m mg/day or greater) (n=399) or placebo (n=197), salivary hypersecretion was reported in 4% of patients receiv receiving placebo (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally
5) A 27-year-old man with bipolar affective disorder and current-episode mania with mood-congruent psycho gram/day developed sialorrhea 3 months after the institution of aripiprazole 10 mg/day for persistent psychoti any associated sign suggestive of extrapyramidal syndrome. A significant reduction in sialorrhea was noted c mg/day (Praharaj et al, 2009).

3.3.4.E Increased appetite

1) Incidence: 3% to 4% (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R
2) In pooled data of 2 placebo-controlled trials of adult patients with major depressive disorder receiving oral weeks in addition to continued antidepressant therapy (n=371) or antidepressant therapy only (n=366), increa patients, respectively (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) o
3) In a pooled analysis of trials in which pediatric patients age 10 to 17 years with schizophrenia or bipolar m mg/day or greater) (n=399) or placebo (n=197), increased appetite was reported in 4% of patients receiving a receiving placebo (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally

3.3.4.F Nausea

1) Incidence: 8% to 15% (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(I
2) In a short-term study of aripiprazole as adjunctive therapy for bipolar disorder, nausea was reported in 8% or 30 mg/day orally (n=253) compared with 5% of patients receiving placebo (n=130). Patients received lithiu aripiprazole or placebo for up to 6 weeks (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIF 2008).
3) In a pooled analysis of trials in which adult patients with schizophrenia or bipolar mania received either ari or placebo (n=1166), nausea was reported in 15% of patients receiving aripiprazole compared with 11% of pa (R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally disintegrating tablets, 2008).
4) In a pooled analysis of trials in which adult patients with agitation associated with schizophrenia or bipolar mg/day or greater IM (n=501) or placebo (n=220), nausea was reported in 9% of patients receiving aripiprazo placebo (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally disintegr
5) In a short-term, placebo-controlled trial in which pediatric patients age 10 to 17 years with bipolar mania re orally or placebo, nausea was reported in 11% of the aripiprazole group (n=197) compared with 4% of the pla tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally disintegrating tablets, 2008).
6) In a pooled analysis of trials in which pediatric patients age 10 to 17 years with schizophrenia or bipolar m mg/day or greater) (n=399) or placebo (n=197), nausea was reported in 10% of patients receiving aripiprazol placebo (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally disintegr

3.3.4.G Summary

1) Nausea has been reported commonly in adult and pediatric patients treated with oral or injectable aripipra patients treated with oral or injectable aripiprazole. Constipation has been reported in adult patients treated w patients treated with oral aripiprazole have reported dry mouth and salivary hypersecretion. Diarrhea occurre aripiprazole. Although uncommon, dysphagia has been reported in patients treated with aripiprazole. Therefo patients at risk for aspiration pneumonia (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIF 2008).

3.3.4.H Vomiting

1) Incidence: 3% to 11% (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(I
2) In a short-term study of aripiprazole as adjunctive therapy for bipolar disorder, vomiting was reported in 4% or 30 mg/day orally (n=253) compared with 0% of patients receiving placebo (n=130). Patients received lithiu aripiprazole or placebo for up to 6 weeks (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIF 2008).
3) In a pooled analysis of trials in which adult patients with schizophrenia or bipolar mania received either ari or placebo (n=1166), vomiting was reported in 11% of patients receiving aripiprazole compared with 6% of pa (R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally disintegrating tablets, 2008).
4) In a pooled analysis of trials in which adult patients with agitation associated with schizophrenia or bipolar mg/day or greater IM (n=501) or placebo (n=220), vomiting was reported in 3% of patients receiving aripiprazo placebo (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally disintegr

3.3.4.I Xerostomia

1) Incidence: 2% to 5% (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R
2) In a short-term study of aripiprazole as adjunctive therapy for bipolar disorder, dry mouth was reported in mg/day or 30 mg/day orally (n=253) compared with 1% of patients receiving placebo (n=130). Patients receiv aripiprazole or placebo for up to 6 weeks (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIF 2008).

3) In a pooled analysis of trials in which adult patients with schizophrenia or bipolar mania received either ari
or placebo (n=1166), dry mouth was reported in 5% of patients receiving aripiprazole compared with 4% of pa
(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally disintegrating tablets, 2008).
4) In a pooled analysis of trials in which pediatric patients age 10 to 17 years with schizophrenia or bipolar m
mg/day or greater) (n=399) or placebo (n=197), dry mouth was reported in 2% of patients receiving aripiprazo
placebo (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally disintegr

3.3.5 Hematologic Effects

3.3.5.A Leukopenia

1) A case report described leukopenia in a 32-year-old man following treatment with risperidone and aripipra
paranoid schizophrenia, had been initiated on risperidone 2 mg/day a few years earlier. Although he reported
physical exam were normal, laboratory assessment showed a WBC and absolute neutrophil count (ANC) of 2
Risperidone-induced leukopenia was suspected and the patient agreed to reduce the risperidone dose to 1 m
showed WBC count and ANC at 2.7 x 10(9) and 1.22 x 10(9), respectively. Subsequently, risperidone was dis
aripiprazole 10 mg daily. He was evaluated every 4 weeks and reported no adverse effects. Six months later,
and 0.85 x 10(9), respectively, and aripiprazole was discontinued. Two weeks later, he experienced paranoid
hallucinations for which he was hospitalized. Upon admission, his WBC count and ANC were 6.4 x 10(9) and
after being reinitiated on aripiprazole 10 mg/day. At a follow-up appointment, his WBC count and ANC were a
respectively). It was decided to discontinue aripiprazole and treat the patient with paliperidone 6 mg and lithiu
change, his WBC count and ANC increased to 3.3 x 10(9) and 1.42 x 10(9). A full hematologic workup was p
& Rubin, 2008).

3.3.7 Immunologic Effects

3.3.7.A Immune hypersensitivity reaction

1) Incidence: rare (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orall
2) Allergic reactions (ie, anaphylactic reaction, angioedema, laryngospasm, pruritus/urticaria, or oropharynge
postmarketing surveillance of aripiprazole (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILI
2008).

3.3.8 Musculoskeletal Effects

Arthralgia

Myalgia

3.3.8.A Arthralgia

1) Incidence: 2% to 4% (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R
2) In pooled data of 2 placebo-controlled trials of adult patients with major depressive disorder receiving arip
in addition to continued antidepressant therapy (n=371) or antidepressant therapy alone (n=366), arthralgia o
respectively (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally disin
3) In a pooled analysis of trials in which pediatric patients age 10 to 17 years with schizophrenia or bipolar m
mg/day or greater) (n=399) or placebo (n=197), arthralgia was reported in 2% of patients receiving aripiprazo
placebo (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally disintegr

3.3.8.B Myalgia

1) Incidence: 3% (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally
2) In pooled data of 2 placebo-controlled trials of adult patients with major depressive disorder receiving arip
in addition to continued antidepressant therapy (n=371) or antidepressant therapy only (n=366), myalgia occu
(Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally disintegrating tab

3.3.9 Neurologic Effects

Akathisia

Cerebrovascular accident

Dizziness

Dystonia

Extrapyramidal disease

Headache

Insomnia

Sedated

Seizure

Somnolence

Summary

Tardive dyskinesia

Transient ischemic attack

Tremor

3.3.9.A Akathisia

1) Incidence: 2% to 25% (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(

2) In a short-term study of aripiprazole as adjunctive therapy for bipolar disorder, akathisia was reported in 1 mg/day or 30 mg/day orally (n=253) compared with 5% of patients receiving placebo (n=130). Patients receiv aripiprazole or placebo for up to 6 weeks (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILI 2008).

3) In pooled data of 2 placebo-controlled trials of adult patients with major depressive disorder receiving oral weeks in addition to continued antidepressant therapy (n=371) or antidepressant therapy only (n=366), akath respectively (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally disin

4) In a pooled analysis of 3-week, placebo-controlled trials in which adult patients with bipolar mania receive placebo (n=753), akathisia was reported in 13% of aripiprazole-treated patients compared with 4% of placeb tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally disintegrating tablets, 2008).

5) In a pooled analysis of trials in which adult patients with schizophrenia or bipolar mania received either ari or placebo (n=1166), akathisia was reported in 10% of patients receiving aripiprazole compared with 4% of p (R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally disintegrating tablets, 2008).

6) In a pooled analysis of trials in which adult patients with agitation associated with schizophrenia or bipolar mg/day or greater IM injection (n=501) or placebo (n=220), akathisia was reported in 2% of patients receiving receiving placebo (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orall

7) In a short-term, placebo-controlled trial in which pediatric patients age 10 to 17 years with bipolar mania re orally or placebo, akathisia was reported in 11.1% of the aripiprazole 30-mg group and 8.2% of the 10-mg gr (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally disintegrating tab

8) In a pooled analysis of trials in which pediatric patients age 10 to 17 years with schizophrenia or bipolar m mg/day or greater) (n=399) or placebo (n=197), akathisia was reported in 9% of patients receiving aripiprazol placebo (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally disintegr

9) A case series reported dose-dependent akathisia following initiation of aripiprazole therapy in 4 patients (a had a history of schizoaffective disorder. All patients were concurrently receiving SSRI therapy. The patients weeks following aripiprazole initiation. Dose adjustments and/or changes to the patient's psychiatric medicati akathisia subsequently improved or resolved with no further issues (Basu & Brar, 2006).

3.3.9.B Cerebrovascular accident

1) In three, 10-week, placebo-controlled clinical studies (two flexible dose and one fixed dose study) of deme patients (mean age of 84 years; range: 78 to 88 years) were treated with aripiprazole or placebo, cerebrovas ischemic attack), including fatalities, were reported with greater incidence in the aripiprazole-treated patients the fixed-dose study, there was a significant dose response relationship for cerebrovascular adverse events i not approved for the treatment of dementia-related psychosis (Prod Info ABILIFY(R) oral tablets, oral solution disintegrating tablets, 2008).

3.3.9.C Dizziness

1) Incidence: 4% to 10% (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(

2) In a short-term study of aripiprazole as adjunctive therapy for bipolar disorder, dizziness was reported in 4 or 30 mg/day orally (n=253) compared with 1% of patients receiving placebo (n=130). Patients received lithiu aripiprazole or placebo for up to 6 weeks (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILI 2008).

3) In pooled data of 2 placebo-controlled trials of adult patients with major depressive disorder receiving arip in addition to continued antidepressant therapy (n=371) or antidepressant therapy alone (n=366), dizziness o

respectively (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally disin
4) In a pooled analysis of trials in which adult patients with schizophrenia or bipolar mania received either ora
placebo (n=1166), dizziness was reported in 10% of patients receiving aripiprazole compared with 7% of pati
oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally disintegrating tablets, 2008).
5) In a pooled analysis of trials in which adult patients with agitation associated with schizophrenia or bipolar
injection of aripiprazole 5.25 mg/day or greater (n=501) or placebo (n=220), dizziness was reported in 8% of
5% of patients receiving placebo (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISC
6) In a short-term, placebo-controlled trial in which pediatric patients age 10 to 17 years with bipolar mania re
orally or placebo, dizziness was reported in 5% of the aripiprazole group (n=197) compared with 1% of the pl
oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally disintegrating tablets, 2008).
7) In a pooled analysis of trials in which pediatric patients age 10 to 17 years with schizophrenia or bipolar m
mg/day or greater) (n=399) or placebo (n=197), dizziness was reported in 5% of patients receiving aripiprazo
placebo (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally disintegr

3.3.9.D Dystonia

1) Incidence: 2% (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally
2) In a pooled analysis of trials in which pediatric patients age 10 to 17 years with schizophrenia or bipolar m
mg/day or greater) (n=399) or placebo (n=197), dystonia was reported in 2% of patients receiving aripiprazole
placebo (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally disintegr
3) A 25-year-old female with schizophrenia developed characteristics associated with tardive dystonia follow
diagnosed with schizoaffective disorder that included 2 previous psychotic episodes and 3 previous manic ep
changing to various antipsychotic medications due to adverse events which included skin rashes with carban
galactorrhea and severe extrapyramidal symptoms with risperidone , and tremors and drowsiness with valpro
mania with quetiapine, the patient switched to lithium. Lithium was reduced to 450 mg/day because of memo
lithium for 8 months with additional adverse effects. Aripiprazole 10 mg/day was added to lithium therapy due
treatment, aripiprazole was increased to 15 mg/day. After 2 months of lithium and aripiprazole therapy, she p
spasms over the latissimus dorsi, which worsened over time. The patient did not experience any other sympt
facial grimacing, or difficulty in breathing or chewing. However, the Extrapyramidal Symptom Rating Scale (E
from moderate to severe levels of extrapyramidal symptoms. The patient was started on trihexyphenidyl 6 mg
After 2 weeks, her dystonia improved and she had a ESRS score of zero. After 4 weeks, clozapine was adde
to 150 mg/day to treat her mood and psychotic symptoms. She remained symptom free 1 year after stopping
4) A 10-year-old boy with bipolar disorder developed dystonia following aripiprazole treatment. The child was
high energy and violent, impulsive behaviors with aggression toward his family and peers. His current medica
divided three times daily plus guanfacine 0.5 mg three times daily. Divalproex was discontinued and aripiprazo
was initiated the following day. Three days after initial aripiprazole therapy, the patient developed neck pain a
Upon examination, his symptoms were consistent with acute torticollis. His neck symptoms completely resolv
administration and aripiprazole discontinuation. The patient did not have any recurrence of dystonia after he w
times daily with bupropion SR 200 mg daily for mood disorder (Singh et al, 2007).

3.3.9.E Extrapyramidal disease

1) Incidence: 2% to 27.3% (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT
2) In a short-term study of aripiprazole as adjunctive therapy for bipolar disorder, extrapyramidal disorder wa
aripiprazole 15 mg/day or 30 mg/day orally (n=253) compared with 1% of patients receiving placebo (n=130).
in addition to aripiprazole or placebo for up to 6 weeks (Prod Info ABILIFY(R) oral tablets, oral solution, IM inj
disintegrating tablets, 2008).
3) In pooled data of 2 placebo-controlled trials of adult patients with major depressive disorder receiving arip
in addition to continued antidepressant therapy (n=371) or antidepressant therapy alone (n=366), extrapyram
patients, respectively (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) o
4) In a pooled analysis of 3-week, placebo-controlled trials in which adult patients with bipolar mania receive
placebo (n=753), extrapyramidal disorder was reported in 5% of aripiprazole-treated patients compared with
ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally disintegrating tablets, 2008)
5) In a pooled analysis of trials in which adult patients with schizophrenia or bipolar mania received either ari
or placebo (n=1166), extrapyramidal disorder was reported in 5% of patients receiving aripiprazole compared
Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally disintegrating tablets, 2
6) In a short-term, placebo-controlled trial in which pediatric patients age 13 to 17 years with schizophrenia r
extrapyramidal disorder was reported in 21.6% of the 30-mg aripiprazole group and 13% of the 10-mg aripipr
group (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally disintegrati
7) In a short-term, placebo-controlled trial in which pediatric patients age 10 to 17 years with bipolar mania re
mg/day or placebo, extrapyramidal disorder was reported in 27.3% of the aripiprazole 30-mg group and 12.2%
the placebo group (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orall
8) In a pooled analysis of trials in which pediatric patients age 10 to 17 years with schizophrenia or bipolar m
mg/day or greater) (n=399) or placebo (n=197), extrapyramidal disorder was reported in 19% of patients rece
patients receiving placebo (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT
9) A case report described the development of extrapyramidal symptoms (EPS) in a 56-year-old schizophrer
aripiprazole. The patient, who presented with psychiatric symptoms of paranoid and persecutory delusions, a
was started on aripiprazole 10 mg once daily. The dose was increased to 15 mg once daily the second week
Five weeks after the initiation of aripiprazole, including 3 weeks at the 30 mg dose, the patient developed stiff
mask-like facial expression, and hypersalivation. None of these symptoms had been documented in this patie

patient had not received treatment with any other antipsychotic agents previously. Akathisia was absent, and absence of opisthotonos, torticollis, oculogyric crisis, and the time of onset. Subsequently, the aripiprazole dc procyclidine 5 mg was added, which prompted resolution of the stiffness. However, the patient continued to h not improve. Aripiprazole treatment was stopped 7 days after the onset of EPS and nightly olanzapine therap followed by 5 mg thereafter. The hypersalivation resolved 10 days after discontinuation of aripiprazole and nc the exact mechanism for this adverse event was not elucidated, an idiosyncratic reaction to aripiprazole, rath as a possible cause for this effect (Salmoiraghi & Odiyoor, 2006).

10) Extrapyramidal symptoms have been minimal during oral aripiprazole therapy of schizophrenia in unpubl 1999a; Petrie et al, 1998; Inoue & Nakata, 2001a). In one 4-week study, the overall incidence of extrapyramic daily was similar to that in the placebo group; at least one dose of benztropine was required in 11 to 17% of p compared to 36% assigned to haloperidol 10 mg daily (Kane et al, 2000b). The frequency of extrapyramidal s than haloperidol in a phase II study (Saha et al, 1999a).

See Drug Consult reference: NEUROLEPTIC-INDUCED EXTRAPYRAMIDAL REACTIONS

3.3.9.F Headache

1) Incidence: 12% to 27% (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT

2) In a pooled analysis of trials in which adult patients with schizophrenia or bipolar mania received either ari or placebo (n=1166), headache was reported in 27% of patients receiving aripiprazole compared with 23% of (R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally disintegrating tablets, 2008).

3) In a pooled analysis of trials in which adult patients with agitation associated with schizophrenia or bipolar mg/day or greater IM (n=501) or placebo (n=220), headache was reported in 12% of patients receiving aripip placebo (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally disintegr

4) In a pooled analysis of trials in which pediatric patients age 10 to 17 years with schizophrenia or bipolar m mg/day or greater) (n=399) or placebo (n=197), headache was reported in 16% of patients receiving aripiprazole placebo (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally disintegr

3.3.9.G Insomnia

1) Incidence: 8% to 18% (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(

2) In a short-term study of aripiprazole as adjunctive therapy for bipolar disorder, insomnia was reported in 8 or 30 mg/day orally (n=253) compared with 4% of patients receiving placebo (n=130). Patients received lithiu aripiprazole or placebo for up to 6 weeks (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIF 2008).

3) In pooled data of 2 placebo-controlled trials of adult patients with major depressive disorder receiving oral weeks in addition to continued antidepressant therapy (n=371) or antidepressant therapy alone (n=366), inso respectively (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally disin

4) In a pooled analysis in which adult patients with schizophrenia or bipolar mania received either aripiprazol placebo (n=1166), insomnia was reported in 18% of patients receiving aripiprazole compared with 3% of patie oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally disintegrating tablets, 2008).

3.3.9.H Sedated

1) Incidence: 1% to 8% (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R

2) In a short-term study of aripiprazole as adjunctive therapy for bipolar disorder, sedation was reported in 4 or 30 mg/day orally (n=253) compared with 2% of patients receiving placebo (n=130). Patients received lithiu aripiprazole or placebo for up to 6 weeks (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIF 2008).

3) In pooled data of 2 placebo-controlled trials of adult patients with major depressive disorder receiving arip in addition to continued antidepressant therapy (n=371) or antidepressant therapy alone (n=366), sedation oc respectively (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally disin

4) In a pooled analysis of trials in which adult patients with schizophrenia or bipolar mania received either ari or placebo (n=1166), sedation was reported in 7% of patients receiving aripiprazole compared with 4% of pat oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally disintegrating tablets, 2008).

5) In a pooled analysis of 3-week, placebo-controlled trials in which adult patients with bipolar mania receive placebo (n=753), sedation was reported in 8% of aripiprazole-treated patients compared with 3% of placebo- tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally disintegrating tablets, 2008).

6) In a pooled analysis of trials in which adult patients with agitation associated with schizophrenia or bipolar mg/day or greater IM injection (n=501) or placebo (n=220), sedation was reported in 3% of patients receiving receiving placebo (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally

7) In a pooled analysis of trials in which pediatric patients age 10 to 17 years with schizophrenia or bipolar m mg/day or greater) (n=399) or placebo (n=197), sedation was reported in 1% of patients receiving aripiprazol placebo (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally disintegr

3.3.9.I Seizure

1) Incidence: 0.1% to 0.3% (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMEL

2) Seizures or convulsions have been reported with aripiprazole use. Use aripiprazole with caution in patient lower the seizure threshold (eg, Alzheimer's dementia) (Prod Info ABILIFY(R) oral tablets, oral solution, IM in disintegrating tablets, 2008).

3) In short-term, placebo-controlled trials, seizures or convulsions were reported in 0.1% (3 of 2467) of adult patients (ages 10 to 17 years) who received oral aripiprazole and 0.2% of adult patients (1 of 501) treated wit

oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally disintegrating tablets, 2008).

3.3.9.J Somnolence

1) Incidence: 5% to 26.3% (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT

2) In a short-term, placebo-controlled trial in which pediatric patients age 10 to 17 years with bipolar mania re orally or placebo, somnolence was reported in 23% of the aripiprazole group (n=197) compared with 3% of th oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally disintegrating tablets, 2008).

3) In pooled data of 2 placebo-controlled trials of adult patients with major depressive disorder receiving arip in addition to continued antidepressant therapy (n=371) or antidepressant therapy alone (n=366), somnolenc respectively (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally disin

4) In a pooled analysis of trials in which adult patients with schizophrenia or bipolar mania received either ari or placebo (n=1166), somnolence was reported in 5% of patients receiving aripiprazole compared with 3% of (R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally disintegrating tablets, 2008).

5) In a pooled analysis of trials in which adult patients with agitation associated with schizophrenia or bipolar mg/day or greater IM injection (n=501) or placebo (n=220), somnolence was reported in 7% of patients recei receiving placebo (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orall

6) In a short-term, placebo-controlled trial in which pediatric patients age 13 to 17 years with schizophrenia r somnolence was reported in 21.6% of the 30-mg aripiprazole group and 11% of the 10-mg aripiprazole group (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally disintegrating tab

7) In a short-term, placebo-controlled trial in which pediatric patients age 10 to 17 years with bipolar mania re mg/day or placebo, somnolence was reported in 26.3% of the 30-mg aripiprazole group and 19.4% of the 10- the placebo group (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orall

8) In a pooled analysis of trials in which pediatric patients age 10 to 17 years with schizophrenia or bipolar m mg/day or greater) (n=399) or placebo (n=197), somnolence was reported in 20% of patients receiving aripip placebo (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally disintegr

9) Excessive somnolence requiring hospitalization was observed in a 9-year-old girl weighing 25 kg within 3. 15 mg/day (0.6 mg/kg/day) for the treatment of oppositional defiant disorder. Although optimal dosing in pedia dose is up to three times higher than doses used in a clinical study including children of similar body weight t mg/day) (Davenport et al, 2004).

3.3.9.K Summary

1) Neuroleptic malignant syndrome (NMS), sometimes fatal, has been reported rarely in patients treated with aripiprazole is diagnosed with NMS, management should include immediate discontinuation of aripiprazole fo Cerebrovascular accident, lethargy, and tardive dyskinesia have been reported with aripiprazole use, particul for the treatment of dementia-related psychosis. Akathisia, dystonia, extrapyramidal disorder, insomnia and s should be used with caution in patients with a history of seizures or conditions that may lower the seizure thre somnolence, sedation, and tremor, there is the potential for cognitive and motor impairment. Patients who are use caution while operating machinery, including automobiles, until the effects of the drug are known (Prod In injection, ABILIFY DISCMELT(R) orally disintegrating tablets, 2008).

3.3.9.L Tardive dyskinesia

1) Tardive dyskinesia may develop in patients treated with antipsychotic drugs, with a higher prevalence in th of developing tardive dyskinesia and the likelihood of it becoming irreversible appear to increase as treatmen drug increase. Although less common, the condition can develop after relatively brief treatment periods at low discontinuation of the antipsychotic drug; however, the antipsychotic drug itself may mask the underlying proc lowest dose and the shortest duration of therapy to produce a satisfactory clinical response to minimize the o receiving aripiprazole therapy develops symptoms of tardive dyskinesia, consideration should be given to dis require aripiprazole treatment regardless of the presence of tardive dyskinesia (Prod Info ABILIFY(R) oral tab DISCMELT(R) orally disintegrating tablets, 2008).

2) Two case reports (involving Taiwanese women, ages 41 and 52 years) suggest a relationship between us first patient was maintained on amisulpiride 200 mg/day no adverse effects. However, she was concerned ov treatment. A combination of amisulpiride 200 mg/day and aripiprazole 10 mg/day was initiated and the patien remained stable. After 11 months of therapy, the patient presented with Parkinsonian symptoms including rab which persisted for 4 months. Amisulpiride was withdrawn and aripiprazole 15 mg/day was given. Dyskinetic amisulpiride discontinuation. However, the patient was reluctant to change medication since her psychotic sy dyskinetic symptoms improved and sustained after 21 months of aripiprazole therapy. The second patient, wh medications (sulpiride 50 to 200 mg/day for 6 years) was admitted due to reoccurring psychotic symptoms. U initiated titrating up to 10 mg/day in one week. She was discharged on this dose. After 2 months of aripiprazo dyskinesia (involuntary chewing and crunching movements). Diphenhydramine 150 mg/day was added to her eventually disappeared within 3 to 4 months (Wang et al, 2009).

3.3.9.M Transient ischemic attack

1) In three, 10-week, placebo-controlled clinical studies (two flexible dose and one fixed dose study) of deme patients (mean age of 84 years; range: 78 to 88 years) were treated with aripiprazole or placebo, cerebrovas ischemic attack), including fatalities, were reported with greater incidence in the aripiprazole-treated patients the fixed-dose study, there was a significant dose response relationship for cerebrovascular adverse events i not approved for the treatment of dementia-related psychosis (Prod Info ABILIFY(R) oral tablets, oral solution disintegrating tablets, 2008).

3.3.9.N Tremor

1) Incidence: 2% to 11.8% (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT

2) In a pooled analysis of 3-week, placebo-controlled trials in which adult patients with bipolar mania receive placebo (n=753), tremor was reported in 6% of aripiprazole-treated patients compared with 3% of placebo-tre tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally disintegrating tablets, 2008).

3) In a short-term study of aripiprazole as adjunctive therapy for bipolar disorder, tremor was reported in 9% 30 mg/day orally (n=253) compared with 6% of patients receiving placebo (n=130). Patients received lithium or placebo for up to 6 weeks (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMEL

4) In pooled data of 2 placebo-controlled trials in adult patients with major depressive disorder receiving aripi in addition to continued antidepressant therapy (n=371) or antidepressant therapy alone (n=366), tremor occu (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally disintegrating tab

5) In a pooled analysis of short-term trials in which adult patients with schizophrenia or bipolar mania receive (n=1843) or placebo (n=1166), tremor was reported in 5% of patients receiving aripiprazole compared with 3 ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally disintegrating tablets, 2008)

6) In a pooled analysis of trials in which pediatric patients age 10 to 17 years with schizophrenia or bipolar m mg/day or greater) (n=399) or placebo (n=197), tremor was reported in 5% of patients receiving aripiprazole placebo (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally disintegr

7) In a short-term, placebo-controlled trial in which pediatric patients age 13 to 17 years with schizophrenia r was reported in 11.8% of the 30-mg aripiprazole group and 2% of the 10-mg aripiprazole group compared wi (R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally disintegrating tablets, 2008).

3.3.10 Ophthalmic Effects

3.3.10.A Blurred vision

1) Incidence: 3% to 8% (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R

2) In a pooled analysis of trials in which adult patients with schizophrenia or bipolar mania received either ari or placebo (n=1166), blurred vision was reported in 3% of patients receiving aripiprazole compared with 1% ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally disintegrating tablets, 2008)

3) In pooled data of 2 placebo-controlled trials of adult patients with major depressive disorder receiving oral weeks in addition to continued antidepressant therapy (n=371) or antidepressant therapy alone (n=366), blur patients, respectively (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) o

4) In a short-term, placebo-controlled trial in which pediatric patients age 10 to 17 years with bipolar mania re orally or placebo, blurred vision was reported in 8% of the aripiprazole group (n=197) compared with 0% of th oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally disintegrating tablets, 2008).

5) In a pooled analysis of trials in which pediatric patients age 10 to 17 years with schizophrenia or bipolar m mg/day or greater) (n=399) or placebo (n=197), blurred vision was reported in 5% of patients receiving aripip placebo (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally disintegr

3.3.12 Psychiatric Effects

Agitation

Anxiety

At risk for suicide

Feeling nervous

Restlessness

Suicidal behavior

3.3.12.A Agitation

1) A case report described severe agitation in a 45-year-old woman after abrupt clozapine discontinuation ar woman, who had a history of psychosis (schizophrenia and chronic paranoid), substance abuse (cocaine and hospitalizations, was transferred to a state psychiatric hospital from a jail facility. Her medical history also incl normal glycemic control. Upon admission, risperidone and haloperidol were stopped due to lack of response included valproic acid and nortriptyline, as well as an albuterol inhaler and ibuprofen as needed. Her clozapin titrated upward. Although her glucose levels remained within normal range, she continued to experience psyc frustration tolerance. Subsequently, haloperidol 10 mg twice daily was reinitiated as adjunctive therapy. Two epigastric pain with emesis, dizziness and lethargy. Because her blood glucose levels were in the range of 4 the patient was sent to an ER at an outside hospital where she was diagnosed with new-onset diabetes with discontinued due to the potential for diabetogenic effects. Aripiprazole 15 mg was then initiated in its place, a

to the psychiatric hospital 7 days after clozapine discontinuation, she was stable with no signs of delusions or she experienced more restlessness, showed emotional distress (crying inconsolably and verbally threatening hallways. These symptoms persisted for several days, resulting in the discontinuation of aripiprazole. She wa titrated upward to 75 mg twice daily while haloperidol was continued. Over the next week, her condition impro and greater cooperation and alertness. The patient remained clinically stable over the next 12 weeks. The au agitation: 1) a withdrawal reaction due to abrupt clozapine withdrawn, and 2) the partial dopamine agonist eff 2009).

3.3.12.B Anxiety

1) Incidence: 4% to 17% (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R
2) In a short-term study of aripiprazole as adjunctive therapy for bipolar disorder, anxiety was reported in 4% or 30 mg/day orally (n=253) compared with 1% of patients receiving placebo (n=130). Patients received lithiu aripiprazole or placebo for up to 6 weeks (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIF 2008).
3) In a pooled analysis of short-term trials in which adult patients with schizophrenia or bipolar mania receive (n=1843) or placebo (n=1166), anxiety was reported in 17% of patients receiving aripiprazole compared with ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally disintegrating tablets, 2008)

3.3.12.C At risk for suicide

1) In pooled analysis of placebo-controlled trials of adult patients with major depressive disorder, or other psy antidepressant drugs in 77,000 patients, there was a tendency toward an increased risk of suicidality in the y and the absolute risk of suicidality was highest in patients with major depressive disorder. In patients less tha versus placebo, there were 14 additional cases per 1000 patients treated, and in patients age 18 to 24 years patients treated. Patients should be carefully monitored for clinical worsening of depression, suicidality, and u precursors to suicidality, especially if symptoms are severe, abrupt, or unusual. This is especially crucial duri therapy and during dose changes (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DIS
2) Because a suicide attempt is inherently possible in patients with a psychotic illness or bipolar disorder, hig receive close supervision (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R

3.3.12.D Feeling nervous

1) Incidence: 3% (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally
2) In pooled data of 2 placebo-controlled trials of adult patients with major depressive disorder receiving oral weeks in addition to continued antidepressant therapy (n=371) or antidepressant therapy only (n=366), feelin respectively (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally disin

3.3.12.E Restlessness

1) Incidence: 2% to 12% (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R
2) In a short-term study of aripiprazole as adjunctive therapy for bipolar disorder, restlessness was reported mg/day or 30 mg/day orally (n=253) compared with 1% of patients receiving placebo (n=130). Patients receiv aripiprazole or placebo for up to 6 weeks (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIF 2008).
3) In pooled data of 2 placebo-controlled trials of adult patients with major depressive disorder receiving arip in addition to continued antidepressant therapy (n=371) or antidepressant therapy alone (n=366), restlessnes respectively (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally disin
4) In a pooled analysis of 3-week, placebo-controlled trials in which adult patients with bipolar mania receive placebo (n=753), restlessness was reported in 6% of aripiprazole-treated patients compared with 3% of place tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally disintegrating tablets, 2008).
5) In a pooled analysis of trials in which adult patients with schizophrenia or bipolar mania received either ari or placebo (n=1166), restlessness was reported in 5% of patients receiving aripiprazole compared with 3% of ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally disintegrating tablets, 2008)

3.3.12.F Suicidal behavior

1) Adult and pediatric patients with major depressive disorder may experience unusual changes in behavior Antidepressant therapy may be associated with the emergence of suicidality and inducing worsening of depre treatment phase and in children, adolescents, and young adults ages 18 to 24 years. It is important that famil depressive disorder or other psychiatric and nonpsychiatric disorders be vigilant in monitoring (daily) signs of aggressiveness, impulsivity, akathisia, hypomania, mania, irritability, or any unusual changes in behavior. Ch discontinuing the antidepressant medication may be considered in patients with persistent worsening depress symptoms are abrupt in onset, severe, or were not part of the patient's initial presentation (Prod Info ABILIFY ABILIFY DISCMELT(R) orally disintegrating tablets, 2008).

3.3.15 Respiratory Effects

3.3.15.A Upper respiratory infection

1) Incidence: 6% (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally
2) In pooled data of 2 placebo-controlled trials of adult patients with major depressive disorder receiving arip in addition to continued antidepressant therapy (n=371), compared with antidepressant therapy only (n=366), 6% versus 4% of patients, respectively (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY

2008).

3.3.16 Other

Death

Extrapyramidal disease

Fatigue

Neuroleptic malignant syndrome

3.3.16.A Death

1) Elderly patients with dementia-related psychosis (unapproved use) treated with aripiprazole had a 1.6 to 1 placebo (4.5% vs 2.6%) in 17 placebo-controlled clinical studies (modal duration 10 weeks). The cause of de cardiovascular events including heart failure, or infectious events including pneumonia (Prod Info ABILIFY(R) ABILIFY DISCMELT(R) orally disintegrating tablets, 2008).

2) Results of a population-based, retrospective cohort study demonstrated that the use of conventional antip risk for death than atypical antipsychotics when administered to elderly patients (aged 66 years and older) wi use and conventional versus atypical antipsychotic use pair-wise comparisons were made. A total of 27,259 r dementia cohort was stratified based on place of residence (community versus long-term care facilities). In or status, propensity score matching was used. The primary outcome of the study was all-cause mortality. The r and 180 days after the antipsychotic medications were initially dispensed. There was a statistically significant associated with new use of atypical antipsychotic medications compared with nonuse in both the community- 1.31 (95% confidence interval (CI), 1.02 to 1.70); absolute risk difference, 0.2 percentage point) and long-ter 1.15 to 2.07); absolute risk difference, 1.2 percentage points). For both cohorts, the risk associated with atypi days. The risk for death associated with conventional antipsychotics was even greater than the risk identified adjusted HR for the community-dwelling cohort was 1.55 (95% CI, 1.19 to 2.02) and 1.26 (95% CI, 1.04 to 1.5 difference for both was 1.1 percentage points). The risk appeared to persist to 180 days for both groups. Son unknown or unmeasured confounders may influence the results and cause of death could not be examined (

3) Results of a population-based, retrospective cohort study demonstrated comparable to possibly greater ris conventional antipsychotic medications in the elderly (aged 65 years and older) compared with atypical antips patients with cancer and included only new users of antipsychotic medications. The primary study outcome w potential confounders was measured based on healthcare utilization data within 6 months before the initiatior elderly patients identified, 12,882 and 24,359 received conventional and atypical antipsychotic medications, r conventional drug group within the first 180 days was 14.1% compared with 9.6% in the atypical drug group (confidence interval (CI), 1.39 to 1.56). In the multi-variable analysis which controlled for potential confounders death within 180 days for conventional versus atypical drug therapy was 1.32 (95% CI, 1.23 to 1.42). When tl antipsychotic drugs were compared with risperidone, the mortality ratio associated with haloperidol was 2.14 (95% CI, 1.19 to 1.40), while there was no difference associated with olanzapine. The increased mortality risk was greatest when doses higher (above median) doses were used (mortality ratio 1.67; 95% CI, 1.5 to 1.86) (mortality ratio 1.6; 95% CI, 1.42 to 1.8). Confirmatory analyses consisting of multi-variable Cox regression, p estimation confirmed the results of the study (Schneeweiss et al, 2007).

4) The findings of one meta-analysis suggest that there may be a small increased risk of death associated w the treatment of dementia in elderly patients. The study analysis (n=5110), including 15 randomized, double-l of antipsychotic use (ie, aripiprazole (n=3), olanzapine (n=5), quetiapine (n=3), risperidone (n=5)) in elderly p dementia, found that death occurred more often in patients receiving atypical antipsychotic therapy as compa respectively). The overall odds ratio, as assessed by meta-analysis, for death in elderly patients receiving aty was 1.54 (95% CI, 1.06 to 2.23; p=0.02), and the risk difference was 0.01 (95% CI, 0.004 to 0.02; p=0.01). O antipsychotic use was 1.65 (95% CI, 1.19 to 2.29; p=0.003); however this increased risk was only identified w analyses of individual drugs did not show a statistically significant increased risk. A similar dropout rate was c treated patients (32.2% vs 31.4%, respectively), with no significant difference in dropouts found by meta-anal

5) The results of a retrospective cohort study indicate that conventional antipsychotic agents are at least as l increase the risk of death among elderly patients 65 years of age or older. The study included 9,142 new use years) and 13,748 new users of atypical agents (mean age, 83.5 years). A higher adjusted relative risk of dea conventional antipsychotics as compared with atypical antipsychotics at all time points studied after beginnin 1.27 to 1.49; less than 40 days: RR, 1.56; 95% CI, 1.37 to 1.78; 40 to 79 days: RR, 1.37; 95% CI, 1.19 to 1.5 1.41). In addition, the adjusted risks of death observed in patients with dementia (RR, 1.29; 95% CI, 1.15 to 1 1.30 to 1.63), in a nursing home (RR, 1.26; 95% CI, 1.08 to 1.47), or not in a nursing home (RR, 1.42; 95% C of conventional antipsychotic therapy as compared with atypical antipsychotic use. This risk appeared to be c higher dose (ie, greater than the median) conventional antipsychotics (RR, 1.73; 95% CI, 1.57 to 1.90). Addit optimum care of elderly patients requiring antipsychotic therapy are needed so that appropriate guidance reg provided (Wang et al, 2005).

3.3.16.B Extrapyramidal disease

See Drug Consult reference: NEUROLEPTIC-INDUCED EXTRAPYRAMIDAL REACTIONS

3.3.16.C Fatigue

1) Incidence: 2% to 11% (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(

2) In pooled data of 2 placebo-controlled trials of adult patients with major depressive disorder receiving oral weeks in addition to continued antidepressant therapy (n=371) or antidepressant therapy alone (n=366), fatig respectively (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally disin

3) In a pooled analysis of trials in which adult patients with schizophrenia or bipolar mania received either ari or placebo (n=1166), fatigue was reported in 6% of patients receiving aripiprazole compared with 4% of patie schizophrenia received acute therapy up to 6 weeks and patients with bipolar mania received treatment up to oral solution, IM injection, ABILIFY DISCMELT(R) orally disintegrating tablets, 2008).

4) In a pooled analysis of trials in which adult patients with agitation associated with schizophrenia or bipolar mg/day or greater IM injection (n=501) or placebo (n=220), fatigue was reported in 2% of patients receiving a receiving placebo (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally

5) In a short-term, placebo-controlled trial in which pediatric patients age 10 to 17 years with bipolar mania re orally or placebo, fatigue was reported in 11% of the aripiprazole group (n=197) compared with 4% of the pla tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally disintegrating tablets, 2008).

6) In a pooled analysis of trials in which pediatric patients age 10 to 17 years with schizophrenia or bipolar m mg/day or greater) (n=399) or placebo (n=197), fatigue was reported in 7% of patients receiving aripiprazole placebo (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally disintegr

3.3.16.D Neuroleptic malignant syndrome

1) Incidence: rare (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orall

2) Neuroleptic malignant syndrome (NMS) has been reported rarely in the worldwide clinical database in pat may include hyperpyrexia, muscle rigidity, altered mental status, evidence of autonomic instability, elevated c (rhabdomyolysis), and acute renal failure. The diagnosis of patients with NMS is complicated; differential diag serious illness and untreated extrapyramidal signs, as well as central anticholinergic toxicity, heat stroke, drug diagnosed, antipsychotic drugs and other concomitant drugs that are not essential should be immediately dis and receive intensive treatment for presenting symptoms and any concomitant serious medical problems. Fo require antipsychotic drug treatment and reintroduction of such therapy should be carefully considered and th recurrence of NMS (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) oral

3) Neuroleptic malignant syndrome (NMS) was reported in a 71-year-old female with pre-hypertension and p to an abrupt change in her baseline mental status, skin flushing, and worsening tardive dyskinesia including g upper extremity choreiform movements. In the previous 9 months, the patient was receiving aripiprazole 15 m buccal oral muscle movement and upper arm athetosis 4 weeks prior to admission. Despite aripiprazole dose hospitalization and a 1-week treatment of benztropine 1 mg/day for extrapyramidal reactions, her clinical con revealed a rectal temperature of 106.5 Fahrenheit, pulse of 137 beats per minute, respiratory rate of 22 breat ranging between 99/54 mmHg and 147/100 mmHg. The patient exhibited distress, marked muscle rigidity, ch worsening slurred speech that became muted. CPK rose from 78 units/L at admission to 103 units/L eight ho leukocytosis, unremarkable metabolic panel, urine analysis, and normal aged-consistent atrophic changes or with NMS and aripiprazole was discontinued. She was given intravenous hydration, supportive cooling therap benztropine 1 mg/day, and lorazepam 1 to 2 mg as needed. Five days later, the patient stabilized aside from to the care of her psychiatrist in a psychiatric hospital (Molina et al, 2007).

4) In a case report, a 14-year-old girl with psychotic depression and mental retardation developed partial neu aripiprazole treatment. The patient had no prior experience with any extrapyramidal symptoms with her past during previous hospitalizations. She did not experience any side effects from quetiapine 300 mg daily which aripiprazole 5 mg daily. Within 48 hours of aripiprazole initiation, the patient presented with tremors, drooling, incontinence, and agitation. The patient was disoriented and had slurred, incoherent speech with fluctuating (rpm) and a pulse of 131 beats per minute (bpm). The patient's serum creatine phosphokinase (CPK) increas myoglobinuria. However, her temperature and blood pressure were within normal parameters. Her white bloo (9300 per millimeter cubed (mm(3)) of blood) and urine toxicology screen was negative. Along with other sup sodium bicarbonate to alkalinize the urine. After 2 days, the patients CPK decreased to 6157 international un every 4 hours was administered to treat the tremors and agitation. The patient eventually recovered and retu

3.4 Teratogenicity/Effects in Pregnancy/Breastfeeding

A) Teratogenicity/Effects in Pregnancy

1) U.S. Food and Drug Administration's Pregnancy Category: Category C (Prod Info Abilify(TM), 2002) (All Trime

a) Either studies in animals have revealed adverse effects on the fetus (teratogenic or embryocidal or other) or studies in women and animals are not available. Drugs should be given only if the potential benefit justifies

See Drug Consult reference: PREGNANCY RISK CATEGORIES

2) Crosses Placenta: Unknown

3) Clinical Management

a) There is insufficient clinical experience with the use of aripiprazole in pregnancy to confirm its safety in tha a successful outcome in a 27-year-old, schizoaffective woman who was treated with aripiprazole during differ According to the manufacturer, aripiprazole was teratogenic and fetotoxic in animal studies (Prod Info Abilify(caution should be exercised with aripiprazole use pregnant women.

4) Literature Reports

a) In the case of a 27-year-old, medically healthy, schizoaffective woman, exposure to aripiprazole during dif
associated with fetal toxicity. The patient was being effectively treated with aripiprazole 15 mg/day when she
aripiprazole was withdrawn following a risk-to-benefit analysis. However, at week 20 of gestation, the patient
a revised risk-to-benefit analysis, aripiprazole was re-initiated at a 10 mg/day dose which was continued throu
weight gain at full term was 10 kg. Ultrasound scans and laboratory tests for serum glucose, thyroid function,
were normal. Although spontaneous labor occurred at term, development of unexplained fetal distress in the
section which resulted in the birth of a male infant weighing 3.25 kg. Failure to establish lactation led to the in
follow-up, the infant had achieved normal milestones (Mendhekar et al, 2006).

B) Breastfeeding

1) Thomson Lactation Rating: Infant risk cannot be ruled out.

a) Available evidence and/or expert consensus is inconclusive or is inadequate for determining infant risk wh
potential benefits of drug treatment against potential risks before prescribing this drug during breastfeeding.

2) Clinical Management

a) It is not known whether aripiprazole is excreted into human breast milk and the potential for adverse effec
drug are unknown. It is not known if aripiprazole affects the quantity or composition of breastmilk. According t
into the milk of lactating rats (Prod Info Abilify(TM), 2002a).

3) Literature Reports

a) No reports describing the use of aripiprazole during human lactation or measuring the amount, if any, of th

4) Drug Levels in Breastmilk

a) Active Metabolites

1) dehydro-aripiprazole (Prod Info ABILIFY(R) oral tablets, orally-disintegrating tablets, oral solution, IM

3.5 Drug Interactions

3.5.1 Drug-Drug Combinations

Carbamazepine

Fluoxetine

Itraconazole

Ketoconazole

Paroxetine

Quinidine

Ranolazine

3.5.1.A Carbamazepine

1) Interaction Effect: decreased aripiprazole concentrations

2) Summary: Coadministration of carbamazepine 200 milligrams (mg) twice daily with aripiprazole 30 mg on
concentration (Cmax) and the area under the concentration-time curve (AUC) values of both aripiprazole and
approximately 70%. Aripiprazole is partly metabolized by cytochrome P450 3A4 (CYP3A4) enzymes. Coadm
CYP3A4 inducer, could increase aripiprazole clearance causing decreased blood concentrations. The dose c
administered concurrently with carbamazepine. If therapy with carbamazepine is discontinued, the dose of ar
Info ABILIFY(R) oral tablets, oral solution, 2005).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Coadministration of aripiprazole and carbamazepine has resulted in decreased arip
aripiprazole should be doubled when it is administered concurrently with carbamazepine. If therapy with carb
aripiprazole should then be decreased.

7) Probable Mechanism: induction of CYP3A4-mediated aripiprazole metabolism

3.5.1.B Fluoxetine

1) Interaction Effect: increased aripiprazole levels

2) Summary: Aripiprazole is partly metabolized by cytochrome P450 2D6 (CYP2D6) enzymes. Coadministra
fluoxetine, may inhibit aripiprazole elimination causing increased blood concentrations. Consider a dosage re
coadministered. If therapy with fluoxetine is discontinued, the dose of aripiprazole should then be increased (
solution, 2005).

3) Severity: moderate

4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Increased aripiprazole plasma levels may result if used concomitantly with fluoxetin aripiprazole when these agents are coadministered. If therapy with fluoxetine is discontinued, the dose of arip
7) Probable Mechanism: inhibition of cytochrome P450 2D6-mediated metabolism of aripiprazole

3.5.1.C Itraconazole
1) Interaction Effect: increased aripiprazole concentrations
2) Summary: Coadministration of ketoconazole 200 milligrams (mg) per day for 14 days with a single 15 mg concentration-time curve (AUC) values of both aripiprazole and its active metabolite, dehydro-aripiprazole, by partly metabolized by cytochrome P450 3A4 (CYP3A4) enzymes. Ketoconazole, a potent CYP3A4 inhibitor, c in increased blood concentrations. Coadministration of aripiprazole with itraconazole, also a strong CYP3A4 i Consider reducing aripiprazole dose by one-half when these agents are coadministered. If therapy with itracc aripiprazole should then be increased (Prod Info ABILIFY(R) oral tablets, oral solution, 2005).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Increased aripiprazole plasma levels may result if used concomitantly with itraconaz approximately one-half when these agents are coadministered. If therapy with itraconazole is discontinued, th increased.
7) Probable Mechanism: inhibition of CYP3A4-mediated aripiprazole metabolism

3.5.1.D Ketoconazole
1) Interaction Effect: increased aripiprazole concentrations
2) Summary: Coadministration of ketoconazole 200 milligrams (mg) daily for 14 days with a single 15 mg arip under the concentration-time curve (AUC) values of both aripiprazole and its active metabolite, dehydro-aripip Aripiprazole is partly metabolized by cytochrome P450 3A4 (CYP3A4) enzymes. Coadministration with ketoc inhibit aripiprazole elimination resulting in increased blood concentrations. Reduce the aripiprazole dose to or are coadministered. If therapy with ketoconazole is discontinued, the dose of aripiprazole should then be incr solution, 2005).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Coadministration of aripiprazole and ketoconazole has resulted in increased aripipr dose to one-half of its normal dose when these agents are coadministered. If therapy with ketoconazole is dis then be increased.
7) Probable Mechanism: inhibition of CYP3A4-mediated aripiprazole metabolism

3.5.1.E Paroxetine
1) Interaction Effect: increased aripiprazole levels
2) Summary: Aripiprazole is partly metabolized by cytochrome P450 2D6 (CYP2D6) enzymes. Coadministra paroxetine, may inhibit aripiprazole elimination causing increased blood concentrations. Consider a dosage r are coadministered. If therapy with paroxetine is discontinued, the dose of aripiprazole should then be increas solution, 2005).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Increased aripiprazole plasma levels may result if used concomitantly with paroxeti aripiprazole when these agents are coadministered. If therapy with paroxetine is discontinued, the dose of ari
7) Probable Mechanism: inhibition of cytochrome P450 2D6-mediated metabolism of aripiprazole

3.5.1.F Quinidine
1) Interaction Effect: increased aripiprazole levels
2) Summary: Coadministration of quinidine 166 milligrams (mg) daily for 13 days with a single 10 mg dose of concentration-time curve (AUC) value of aripiprazole by 112% and decreased the AUC of its active metabolit is partly metabolized by cytochrome P450 2D6 (CYP2D6) enzymes. Coadministration with quinidine, a poten elimination resulting in increased blood concentrations. Reduce the aripiprazole dose to one-half of its norma If therapy with quinidine is discontinued, the dose of aripiprazole should then be increased (Prod Info ABILIF
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Coadministration of aripiprazole and quinidine has resulted in increased aripiprazol dose to one-half of its normal dose when these agents are coadministered. If therapy with quinidine is discon increased.
7) Probable Mechanism: inhibition of CYP2D6-mediated metabolism of aripiprazole

3.5.1.G Ranolazine
1) Interaction Effect: an increase in aripiprazole serum concentration

2) Summary: Ranolazine, and/or its metabolites, partially inhibit cytochrome P450-2D6-mediated aripiprazole aripiprazole exposure. Use caution when these agents are coadministered. Monitor patients for signs of incre aripiprazole doses as needed (Prod Info RANEXA(R) extended-release oral tablets, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concurrent administration of aripiprazole and ranolazine may increase aripiprazole these agents are coadministered. Monitor patients for signs of increased aripiprazole adverse effects and low RANEXA(R) extended-release oral tablets, 2008).
7) Probable Mechanism: ranolazine inhibition of cytochrome P450-2D6-mediated metabolism of aripiprazole

4.0 Clinical Applications

Monitoring Parameters

Patient Instructions

Place In Therapy

Mechanism of Action / Pharmacology

Therapeutic Uses

Comparative Efficacy / Evaluation With Other Therapies

4.1 Monitoring Parameters

A) Therapeutic
1) Physical Findings
a) Monitor patients for improvement of schizophrenic (positive and negative), bipolar, or depressive sympton

B) Toxic
1) Laboratory Parameters
a) Elevated creatine phosphokinase, myoglobinuria, and acute renal failure may be signs of neuroleptic mali experienced previous NMS, they should be closely monitored since NMS may reoccur (Prod Info ABILIFY(R) ABILIFY DISCMELT(R) orally disintegrating tablets, 2008).
b) Monitor patients with an established diagnosis of diabetes mellitus for worsening of glucose control during Patients with risk factors for diabetes mellitus (eg, obesity, family history of diabetes) who are beginning treat undergo fasting blood glucose testing at the beginning of treatment and periodically throughout treatment. Pa during atypical antipsychotic treatment should undergo fasting blood glucose testing (Prod Info ABILIFY(R) o DISCMELT(R) orally disintegrating tablets, 2008).
2) Physical Findings
a) Clinical worsening, suicidality, or unusual changes in behavior, should be monitored closely, particularly d times of dose changes and especially in children, adolescents, and young adults age 24 years and younger. emerging suicidality include anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, in hypomania, and mania. Instruct family members and caregivers to monitor daily for these symptoms and to re discontinuing treatment if symptoms are severe, abrupt in onset, were not part of the patient's presenting sym persistently worse, or where emergent suicidality or symptoms are precursors of worsening depression or sui solution, IM injection, ABILIFY DISCMELT(R) orally disintegrating tablets, 2008).
b) Elderly patients treated with aripiprazole for dementia-related psychosis (unapproved use) should be mon ischemic attack, and pneumonia; any cardiovascular, cerebrovascular, or infectious events.
c) Abnormal-movement detection (extrapyramidal symptoms) and early signs of tardive dyskinesia (eg, worm monitored, especially in the elderly and in elderly women. Longer duration of treatment and increased total cu tardive dyskinesia, but may also develop after brief treatment periods at low doses. Consider discontinuing tr dyskinesia appear following therapy (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DI 2008).
d) Blood pressure and heart rate determinations should be monitored, particularly in patients with preexisting conditions which predispose patients to hypotension (eg, dehydration, hypovolemia) or concomitant antihype
e) Body temperature regulation may be impaired especially in patients with conditions contributing to elevatio exercise, extreme heat exposure, dehydration) or concomitant drugs with anticholinergic effects.
f) ECG monitoring at baseline and periodically during therapy has been suggested (Pacher & Kecskemeti, 2
g) Esophageal dysmotility and aspiration should be monitored, especially elderly patients and in patient with use).
h) Excessive sedation and orthostatic hypotension should be monitoring in patients receiving concomitant pa (R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally disintegrating tablets, 2008).
i) Hyperpyrexia, muscle rigidity, altered mental status, irregular pulse or blood pressure, tachycardia, diapho

indicative of neuroleptic malignant syndrome (NMS). If patients have experienced previous NMS, they should
(Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally disintegrating tab
j) Polydipsia, polyuria, polyphagia, and weakness may be symptoms of hyperglycemia. Patients who exhibit
antipsychotic treatment should undergo fasting blood glucose testing. In some instances, hyperglycemia has
stopped; however, some patients required ongoing antidiabetic treatment despite discontinuation of the susp
tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally disintegrating tablets, 2008).
k) Seizures should be monitored in patients with a history of seizures, or with conditions that lower the seizu
tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally disintegrating tablets, 2008).

4.2 Patient Instructions

A) Aripiprazole (By mouth)

Aripiprazole

Treats mental illnesses, including schizophrenia and some symptoms of bipolar disorder (manic episodes). Also u
depression.

When This Medicine Should Not Be Used:
You should not use this medicine if you or your child have had an allergic reaction to aripiprazole.

How to Use This Medicine:
Liquid, Tablet, Dissolving Tablet

Your doctor will tell you how much of this medicine to use and how often. Your dose may need to be changed
best for you. Do not use more medicine or use it more often than your doctor tells you to.
You may take this medicine with or without food.
Measure the oral liquid medicine with a marked measuring spoon, oral syringe, or medicine cup.
If you are using the oral disintegrating tablet, make sure your hands are dry before you handle the tablet. Do
tablet until you are ready to take it. Remove the tablet from the blister pack by peeling back the foil, then takir
through the foil. Place the tablet on your tongue. It should melt quickly. If possible, take the tablet without any
Do not split the tablet.
This medicine should come with a Medication Guide. Read and follow these instructions carefully. Ask your d
Ask your pharmacist for the Medication Guide if you do not have one. Your doctor might ask you to sign som
information.

If a Dose is Missed:

If you miss a dose or forget to use your medicine, use it as soon as you can. If it is almost time for your next d
skip the missed dose. Do not use extra medicine to make up for a missed dose.

How to Store and Dispose of This Medicine:

Store the medicine in a closed container at room temperature, away from heat, moisture, and direct light. Ope
for up to 6 months after opening, but not beyond the expiration date on the bottle.
Ask your pharmacist, doctor, or health caregiver about the best way to dispose of any leftover medicine after
also need to throw away old medicine after the expiration date has passed.
Keep all medicine away from children and never share your medicine with anyone.

Drugs and Foods to Avoid:
Ask your doctor or pharmacist before using any other medicine, including over-the-counter medicines, vitamins, a

Make sure your doctor knows if you are also using medicine to lower blood pressure, such as hydrochlorothia
Accupril®, Cozaar®, Diovan®, Lotrel®, Norvasc®, Toprol®, Zestril®.
Tell your doctor if you are also using carbamazepine (Tegretol®), fluoxetine (Prozac®), ketoconazole (Nizora
Tell your doctor if you are using any medicines that make you sleepy. These include sleeping pills, cold and a
sedatives.
Do not drink alcohol while you are using this medicine.

Warnings While Using This Medicine:

Make sure your doctor knows if you or your child are pregnant or breastfeeding, or if you have heart disease
have a history of heart attack, stroke, seizures, drug abuse, alcohol abuse, or if you have ever experienced s
(NMS) in the past.
For some children, teenagers, and young adults, this medicine can increase thoughts of suicide. Tell your do
your child start to feel more depressed and have thoughts about hurting yourselves. Report any unusual thou
child, especially if they are new or are getting worse quickly. Make sure the doctor knows if you or your child
big increase in energy, or start to act reckless. Also tell the doctor if you or your child have sudden or strong f
restless, violent, or scared. Let the doctor know if you, your child, or anyone in your family has bipolar disorde
tried to commit suicide.
This medicine may raise your blood sugar. Tell your doctor if you or your child have diabetes. It may be nece
more often. The oral liquid form of this medicine also contains sugar.
Tardive dyskinesia (a movement disorder) may occur and may not go away after you stop using the medicine
your child have any of the following symptoms while taking this medicine: lip smacking or puckering, puffing c
of the tongue, uncontrolled chewing movements, or uncontrolled movements of the arms and legs.

Older adults may be more sensitive to the side effects of this medicine, including stroke. Make sure the docto
medicine has Alzheimer's disease. This medicine is not used to treat behavioral problems in older adults with
The oral disintegrating tablet form of this medicine contains phenylalanine. Make sure your doctor knows if yo
This medicine may make you or your child dizzy or drowsy. Avoid driving, using machines, or doing anything
alert. You may also feel lightheaded when getting up suddenly from a lying or sitting position, so get up slowly
You or your child may get overheated more easily while you are using this medicine. It might reduce how mu
you do not sweat enough. Be careful if you exercise often or are in high heat or humidity. If your body gets to
confused. You might vomit or have an upset stomach. Call your doctor if you are too hot and can not cool dow

Possible Side Effects While Using This Medicine:
Call your doctor right away if you notice any of these side effects:
Allergic reaction: Itching or hives, swelling in your face or hands, swelling or tingling in your mouth or throat, d
Anxiety, irritability, nervousness, restlessness, or trouble sleeping.
Change in how much or how often you urinate.
Chest pain, fast or slow heartbeat.
Confusion, unusual behavior, depressed mood, or thoughts of hurting yourself or others.
Excessive hunger or thirst, increased urination, and weakness.
Extreme sleepiness or weakness with nausea, vomiting, or diarrhea.
Fever, sweating, confusion, uneven heartbeat, or muscle stiffness.
Lightheadedness, dizziness, or fainting.
Problems with balance or walking.
Seizures or tremors.
Swelling in your hands, ankles, or feet.
Trouble swallowing.
Twitching or muscle movements you cannot control (often in your face, tongue, or jaw).
Unusual bleeding, bruising, or weakness.

If you notice these less serious side effects, talk with your doctor:
Blurred vision.
Change in appetite.
Dry mouth or drooling.
Headache or flu symptoms.
Muscle or joint pain.
Nausea, vomiting, constipation, or upset stomach.
Runny or stuffy nose.
Tiredness.
Unexpected weight gain or loss.

If you notice other side effects that you think are caused by this medicine, tell your doctor.

B) Aripiprazole (Injection)
Aripiprazole

Treats agitation associated with schizophrenia or bipolar disorder (manic or mixed).

When This Medicine Should Not Be Used:
You should not receive this medicine if you have had an allergic reaction to aripiprazole.

How to Use This Medicine:
Injectable
Your doctor will prescribe your exact dose and tell you how often it should be given. This medicine is given as
A nurse or other trained health professional will give you this medicine.

Drugs and Foods to Avoid:
Ask your doctor or pharmacist before using any other medicine, including over-the-counter medicines, vitamins, a
Make sure your doctor knows if you are also using medicine to lower blood pressure, such as hydrochlorothia
Accupril®, Cozaar®, Diovan®, Lotrel®, Norvasc®, Toprol®, Zestril®.
Tell your doctor if you are also using carbamazepine (Tegretol®), fluoxetine (Prozac®), ketoconazole (Nizora
Tell your doctor if you are using any medicines that make you sleepy. These include sleeping pills, cold and a
sedatives.
Do not drink alcohol while you are using this medicine.

Warnings While Using This Medicine:
Make sure your doctor knows if you are pregnant or breastfeeding, or if you have heart disease or low blood
of heart attack, stroke, seizures, drug abuse, alcohol abuse, or if you have ever experienced symptoms of ne
past.
For some children, teenagers, and young adults, this medicine can increase thoughts of suicide. Tell your do
your child start to feel more depressed and have thoughts about hurting yourselves. Report any unusual thou
child, especially if they are new or are getting worse quickly. Make sure the doctor knows if you or your child

big increase in energy, or start to act reckless. Also tell the doctor if you or your child have sudden or strong f
restless, violent, or scared. Let the doctor know if you, your child, or anyone in your family has bipolar disorde
tried to commit suicide.
Older adults may be more sensitive to the side effects of this medicine, including stroke. Make sure the docto
medicine has Alzheimer's disease. This medicine is not used to treat behavioral problems in older adults with
This medicine may raise your blood sugar. Tell your doctor if you have diabetes. It may be necessary to mea
Tardive dyskinesia (a movement disorder) may occur and may not go away after you stop using the medicine
your child have any of the following symptoms while taking this medicine: lip smacking or puckering, puffing c
of the tongue, uncontrolled chewing movements, or uncontrolled movements of the arms and legs.
This medicine may make you dizzy or drowsy. Avoid driving, using machines, or doing anything else that cou
also feel lightheaded when standing or sitting up straight, so stand up or sit up slowly.
You or your child may get overheated more easily while you are using this medicine. It might reduce how mu
you do not sweat enough. Be careful if you exercise often or are in high heat or humidity. If your body gets to
confused. You might vomit or have an upset stomach. Call your doctor if you are too hot and can not cool do

Possible Side Effects While Using This Medicine:
Call your doctor right away if you notice any of these side effects:
Allergic reaction: Itching or hives, swelling in your face or hands, swelling or tingling in your mouth or throat, c
Anxiety, irritability, nervousness, restlessness, or trouble sleeping.
Change in how much or how often you urinate.
Chest pain, fast or slow heartbeat.
Confusion, unusual behavior, depressed mood, or thoughts of hurting self or others.
Dry mouth, increased thirst or hunger, or muscle cramps.
Fever, sweating, confusion, uneven heartbeat, or muscle stiffness.
Lightheadedness, dizziness, or fainting.
Seizures or tremors.
Severe drowsiness or sleepiness.
Trouble swallowing.
Twitching or muscle movements you cannot control (often in your face, tongue, or jaw).
Unusual bleeding or bruising.
Unusual tiredness or weakness.

If you notice these less serious side effects, talk with your doctor:
Headache or flu symptoms.
Nausea, vomiting, or upset stomach.
Redness, pain, swelling, itching, blistering, or rash where the shot was given.
Weight gain or loss.

If you notice other side effects that you think are caused by this medicine, tell your doctor.

4.3 Place In Therapy

A) Current users of atypical antipsychotic drugs (including aripiprazole) and typical antipsychotic drugs had a similar c
according to a retrospective cohort of 93,300 adult users of antipsychotic drugs and 186,600 matched controls. The st
(mean 45.7 +/- 11.8 years) with similar cardiovascular risk at baseline who had at least one filled prescription and had
years. Sudden cardiac death was defined as occurring in the community and excluded deaths of patients admitted to t
extrinsic causes, or causes not related to ventricular tachyarrhythmia. Current use was defined as the interval betwee
end of the day's supply. Low and high doses was defined as comparable to less than 100 milligrams (mg) of chlorpron
chlorpromazine 300 mg or greater, respectively. The adjusted rate of sudden cardiac death (incidence-rate ratio) in cu
79,589 person-years was 2.26 (95% CI, 1.88 to 2.72, p less than 0.001) which was similar to the risk in current users c
years which was 1.99 (95% CI, 1.68 to 2.34, p less than 0.001). The risk of sudden cardiac death significantly increase
atypical antipsychotic drug groups. In atypical antipsychotic use, the incidence rate ratio increased from 1.59 (95% CI,
2.25 to 3.65) in high-dose use. To limit the effects of confounding of the study results, there was a secondary analysis
propensity score, which resulted in a similar risk of sudden death as the primary cohort analysis (Ray et al, 2009). In a
Medicine, it has been suggested that antipsychotic drugs continue to be used in patients with clear evidence of benefit
risk profiles (eg, elderly patients), there should be an age-dependent justification required prior to administration. It has
tested) that ECGs be performed before and shortly after initiation of antipsychotic therapy to screen for existing or eme
& Avorn, 2009).

B) Agitation Associated with Schizophrenia or Bipolar Mania

1) Aripiprazole as an intramuscular injection is approved for the treatment of agitation associated with schizophre
Info ABILIFY(R) oral tablets, oral solution, IM injection, DISCMELT(TM) orally disintegrating tablets, 2007).

2) Aripiprazole was more effective than placebo for the acute treatment of agitation in patients with schizophrenia
disorder in a dose-ranging, multicenter, randomized, double-blind clinical trial (Tran-Johnson et al, 2007).

3) A double-blind, placebo-controlled study demonstrated that intramuscular aripiprazole was noninferior to intrar
in voluntarily hospitalized agitated patients with schizophrenia or schizoaffective disorder (Andrezina et al, 2006).

4) In one short-term (24-hour), placebo-controlled trial (n=291), intramuscular aripiprazole was statistically superi
agitation in patients with Bipolar I Disorder (manic or mixed; using the Positive and Negative Syndrome Scale (PA
Clinical Global Impression of Improvement (CGI-I) scale scores) (Prod Info ABILIFY(R) oral tablets, oral solution,
disintegrating tablets, 2007).

C) Bipolar I Disorder, Mixed or Manic Episodes

1) Aripiprazole is indicated for the treatment of manic and mixed episodes associated with bipolar I disorder with and maintenance therapy) and pediatric patients age 10 to 17 years (acute therapy only) (Prod Info ABILIFY(R) o DISCMELT(TM) orally disintegrating tablets, 2007).

2) In a multicenter, randomized, double-blind, placebo-controlled study, aripiprazole was more effective than plac episodes in patients (n=262) with bipolar disorder (Keck et al, 2003).

3) In a randomized, double-blind, parallel-group trial (n=161), maintenance treatment with oral aripiprazole, at do to 26 weeks, resulted in a longer time to relapse compared to placebo in adults with a recent manic or mixed bipo aripiprazole (Keck et al, 2006).

D) Major Depressive Disorder, Adjunctive Treatment in Patients Receiving Antidepressants

1) Aripiprazole is indicated for use as an adjunctive treatment to antidepressants for major depressive disorder (F IM injection, DISCMELT(TM) orally disintegrating tablets, 2007).

2) In two 6-week, placebo-controlled trials (n=743), treatment with aripiprazole was superior to placebo in reducir depressive disorder (MDD) and an inadequate response to prior antidepressant therapies; additionally, one of the functioning with aripiprazole compared to placebo (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, D 2007).

E) Schizophrenia

1) Aripiprazole is indicated for the treatment of schizophrenia in adults and pediatric patients 13 to 17 years of ag solution, IM injection, DISCMELT(TM) orally disintegrating tablets, 2007).

2) Aripiprazole therapy was effective compared to placebo in the prevention of relapse in patients with chronic, st randomized, double-blind, placebo-controlled study (n=310) (Anon, 2003).

3) In a placebo-controlled, phase III study involving relapsed schizophrenic or schizoaffective patients (n=414), a 10 mg daily (fixed doses) were each statistically superior to placebo with regard to changes in Positive and Negat Psychiatric Rating Scale (BPRS) total scores; based on responder analysis (a 30% reduction in PANSS-total scor aripiprazole was significantly more effective than placebo, whereas haloperidol was not (Kane et al, 2000).

4) In a 6-week, placebo-controlled trial in adolescents 13 to 17 years of age, oral aripiprazole at doses of 10 or 3(placebo in the treatment of schizophrenia (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, DISCMEL

See Drug Consult reference: FIRST- VS SECOND-GENERATION ANTIPSYCHOTIC AGENTS FOR SCHIZOPHREN

4.4 Mechanism of Action / Pharmacology

A) MECHANISM OF ACTION

1) Aripiprazole is an atypical antipsychotic agent (quinolinone derivative). It exhibits relatively high affinity for dop HT1A and 5-HT2A receptors (Prod Info Abilify(TM), 2002b; Lawler et al, 1999; Inoue & Nakata, 2001). The efficac to partial agonist activity at D2 and 5-HT1A receptors (Lawler et al, 1999; Prod Info Abilify(TM), 2002b; Inoue & N antagonist activity at 5-HT2A receptors has also been speculated (Prod Info Abilify(TM), 2002b).

2) However, other actions may be involved. In vitro data have indicated D2- agonist activity of aripiprazole at pres at postsynaptic D2 receptors (regulating inhibition of cAMP synthesis) (Inoue et al, 2001; Inoue & Nakata, 2001; M Prioleau et al, 1998). These dual effects are seen at the same dose level (concentration) (Lawler et al, 1999), and drugs (typical and atypical). Preclinical and clinical data suggest that these actions minimize extrapyramidal and e (Inoue et al, 2001; Inoue & Nakata, 2001; Lawler et al, 1999).

3) Electrophysiological studies in animals suggest that aripiprazole acts as a dopamine-D2 agonist on dopaminer as a dopamine-D2 (and possibly D3) antagonist on striatal neurons and nucleus accumbens neurons (Matsubaya

4) In a small magnetoencephalographic study involving schizophrenic patients (n=5), treatment with aripiprazole decrease (normalizing effect) of abnormal delta and theta activity, loosely correlating with decreases in Positive a (Canive et al, 1998). The authors suggest evaluation of delta activity (near-normalization) as a predictor of respon accumulation in a larger number of patients is needed.

B) REVIEW ARTICLES

1) Pharmacologic basis for using partial agonists in schizophrenia (Inoue & Nakata, 2001).

4.5 Therapeutic Uses

Bipolar disorder - Psychomotor agitation

Bipolar I disorder, Adjunctive therapy with lithium or valproate for acute manic or mixed episodes

Bipolar I disorder, Monotherapy, manic or mixed episodes

Borderline personality disorder

Dementia

Major depressive disorder, Adjunctive treatment in patients also receiving antidepressants

Psychomotor agitation - Schizophrenia

Schizophrenia

4.5.A Bipolar disorder - Psychomotor agitation

FDA Labeled Indication

1) Overview

FDA Approval: Adult, yes (injectable only); Pediatric, no
Efficacy: Adult, Effective
Recommendation: Adult, Class IIa
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Aripiprazole injection is approved for the treatment of agitation associated with schizophrenia and bipolar
(R) oral tablets, oral solution, IM injection, DISCMELT(TM) orally disintegrating tablets, 2007a).
In one short-term (24-hour), placebo-controlled trial, intramuscular aripiprazole was statistically superior
in patients with Bipolar I Disorder (manic or mixed; using the Positive and Negative Syndrome Scale [PA
Clinical Global Impression of Improvement [CGI-I] scale scores) (Prod Info ABILIFY(R) oral tablets, oral s
disintegrating tablets, 2007a).

3) Adult:

a) In one short-term (24-hour), placebo-controlled trial (n=291), intramuscular aripiprazole (fixed doses of 9.7
statistically superior to placebo in improving symptoms of agitation in patients with Bipolar I Disorder (manic o
Syndrome Scale [PANSS] Excited Component scores and the Clinical Global Impression of Improvement [CG
active comparator treatment arm of lorazepam injection. Agitated patients predominantly meeting DSM-IV cri
received up to 3 injections during the 24-hour treatment period, with the second injection administered after th
efficacy measure was evaluated. All enrolled patients were judged by the clinical investigators as clinically ag
treatment with intramuscular medication. Additionally, all patients exhibited a level of agitation that met or exc
the five items comprising the PANSS Excited Component (eg; poor impulse control, tension, hostility, uncoop
least 2 individual item scores of 4 or greater using a 1 to 7 scoring system (1=absent, 4=moderate, 7=extrem
Component score ranged from 15 to 24 (out of a maximum score of 35) with the mean baseline score of 19; t
agitation with some patients experiencing mild or severe levels of agitation. The primary efficacy measure in t
Component from baseline to 2 hours post-injection. The CGI-I scale was a key secondary measure. After the
15 mg) were statistically superior to placebo in the PANSS Excited Component and on the CGI-I scale. There
the 15 mg dose when compared to the 9.75 mg dose (Prod Info ABILIFY(R) oral tablets, oral solution, IM inje
tablets, 2007a).

4.5.B Bipolar I disorder, Adjunctive therapy with lithium or valproate for acute manic or mixed episodes

FDA Labeled Indication

1) Overview

FDA Approval: Adult, yes; Pediatric, yes (age 10 years and older)
Efficacy: Adult, Evidence favors efficacy; Pediatric, Evidence favors efficacy
Recommendation: Adult, Class IIb; Pediatric, Class IIb
Strength of Evidence: Adult, Category B; Pediatric, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Aripiprazole is indicated for use in adults and children age 10 years or older as adjunctive therapy with lit
episodes of bipolar I disorder, with or without psychotic features (Prod Info ABILIFY(R) oral tablets, solut
2008).
Aripiprazole, added to either valproate or lithium, significantly improved symptoms of mania as early as o
who were partially nonresponsive to monotherapy during a randomized, placebo-controlled trial (Vieta et

3) Adult:

a) Aripiprazole, added to either valproate or lithium, significantly improved symptoms of mania as early as or
disorder (manic or mixed episodes) who were partially nonresponsive to monotherapy during a randomized, p
a 3 to 42 day screening phase to stabilize lithium (serum levels of 0.6 to 1 millimole/liter) or valproate (serum
therapy. Once stabilized, patients entered the baseline phase where they continued on valproate or lithium th
were allowed during week 1 (4 milligrams (mg) or less/day) and week 2 (3 mg or less/day) of this phase. Prop
daily) was also permitted during this time. If after 2 weeks there was an inadequate clinical response (Young
or greater during the screening phase and 25% or less improvement on the Y-MRS total score), patients were
with either placebo (n=131) or aripiprazole (n=253) 15 mg orally once a day for the 6 week double-blind phas
aripiprazole could be increased to 30 mg orally once a day after 7 days (mean aripiprazole dose at week 6 wa
treatment with benzodiazepines (2 mg or less of lorazepam or equivalents) were allowed for a maximum of 1
primary efficacy measure was the mean change from baseline to week 6 in Y-MRS total score (last observati
4 and weekly thereafter. A key secondary efficacy measure was the mean change from baseline to week 6 in
(CGI-BP) severity of illness (mania) score. At week 6, significantly greater improvements in Y-MRS total scor
treatment group compared with the placebo group (-13.3 (standard deviation (SD) 7.9) and -10.7 (SD 7.6), re
all subsequent endpoints, therapy with aripiprazole plus mood stabilizer resulted in significantly greater impro
than lithium/valproate monotherapy (p less than 0.05). Aripiprazole did not worsen manic symptoms and dem
elevated mood, sexual interest, irritability, speech, disruptive/aggressive behavior, and insight. Additionally, a

significant reductions in CGI-BP severity of illness mania score (-1.9 (SD 1.3)) compared with placebo (-1.6 (
depression was also significantly lower in patients receiving aripiprazole (7.7%) compared with patients recei
suggests that improvement in mania was not associated with a destabilization into depression. Tolerability ar
was similar to that demonstrated in previous aripiprazole monotherapy studies. The most frequently reported
occurred at a significantly greater rate with aripiprazole than with placebo (18.6% and 5.4%, respectively; p=(
adverse events occurred in 9% and 5% of patients receiving aripiprazole and placebo, respectively (Vieta et a

1) Maintenance Therapy

a) It is unclear how long a patient should remain on aripiprazole therapy for the treatment of bipolar
symptomatically stable on aripiprazole monotherapy for at least 6 weeks demonstrated a benefit fro
continued on treatment beyond 6 weeks should be reassessed at regular intervals to determine the
ABILIFY(R) oral tablets, solution, orally disintegrating tablets, IM injection, 2008).

4) Pediatric:

a) The efficacy of adjunctive aripiprazole therapy in pediatric patients 10 years of age and older with bipolar
additional pharmacokinetic comparisons in adults and pediatric patients (Prod Info ABILIFY(R) oral tablets, s
injection, 2008).

4.5.C Bipolar I disorder, Monotherapy, manic or mixed episodes

FDA Labeled Indication

1) Overview

FDA Approval: Adult, yes; Pediatric, yes (10 to 17 years old (acute therapy))
Efficacy: Adult, Effective; Pediatric, Evidence favors efficacy
Recommendation: Adult, Class IIb; Pediatric, Class IIb
Strength of Evidence: Adult, Category B; Pediatric, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Aripiprazole is indicated for the treatment of manic and mixed episodes associated with bipolar I disorde
(acute and maintenance therapy) and pediatric patients age 10 to 17 years (acute therapy only) (Prod In
disintegrating tablets, IV injection, 2008).
In a multicenter, randomized, double-blind, placebo-controlled study, aripiprazole was more effective tha
mixed episodes in patients (n=262) with bipolar disorder (Keck et al, 2003).
In a randomized, double-blind, parallel-group trial (n=161), maintenance treatment with oral aripiprazole,
for up to 26 weeks, resulted in a longer time to relapse compared to placebo in adults with a recent mani
stabilized on aripiprazole (Keck et al, 2006).
In a 4 week, double-blind, placebo-controlled study in pediatric patients with bipolar disorder (n=296), tre
symptomatology compared to placebo (Prod Info ABILIFY(R) oral tablets, solution, disintegrating tablets,

3) Adult:

a) Acute Therapy

1) Aripiprazole was more effective than placebo in the treatment of acute manic or mixed episodes in pa
randomized, double-blind, placebo-controlled study, patients (n=262) with bipolar disorder, mixed or mar
(Y-MRS) score of at least 20 received aripiprazole 30 milligrams (mg)/day (reduced to 15 mg/day if need
weeks. Patients were hospitalized for at least the first 2 weeks of treatment. Response was defined as a
50%. From baseline to endpoint, total Y-MRS scores of aripiprazole-treated patients were significantly m
received placebo (mean, -8.2 vs -3.4, respectively; p=0.002). This significant difference was present fron
also significantly higher in aripiprazole-treated patients as compared with placebo at all time points from
0.02) to endpoint (40% vs 19%, respectively; p less than or equal to 0.005). Adverse events were similar
constipation, somnolence, vomiting, akathisia, and accidental injury occurred more than twice as often in
placebo (Keck et al, 2003).

b) Maintenance Therapy

1) In a randomized, double-blind, parallel-group, placebo-controlled trial (n=161), oral aripiprazole, at do
more effective than placebo for preventing relapse in adults with a recent manic or mixed episode who w
double-blind phase, patients (n=567) with bipolar I disorder received open-label treatment with aripiprazo
stable. Stability was defined as a Young Mania Rating Scale (YMRS) total score of 10 or less and a Mon
(MADRS) total score of 13 or less during 4 consecutive visits over a minimum of 6 weeks. Mean YMRS s
and 2.6 +/- 0.3 for patients randomized to placebo and aripiprazole, respectively, at the start of double-bl
+/- 0.4 and 3.9 +/- 0.4, respectively. Following completion of the stabilization phase, 161 patients (mean
phase and were randomly assigned oral aripiprazole (n=78) or placebo (n=83) for up to 26 weeks. Aripip
during the open-label phase, with adjustments made to either 15 or 30 mg/day depending on clinical effe
medications were excluded, except for lorazepam (1 to 2 mg/day) and anticholinergic agents (up to benz
taken 12 hours before rating scale assessments). The primary efficacy measure, evaluated using Kaplar
mood episode, either manic, depressive, or mixed. Relapse was defined by study discontinuation due to
additional or increased doses of non-study medications for mood episode). Although 58% of study patier
n=55), mainly due to lack of efficacy (aripiprazole, n=19 ; placebo, n=36), patients receiving at least 1 do
primary outcome assessment were included in the analysis. The time to relapse was significantly longer
to the placebo-treated patients (p=0.02; hazard ratio (HR) 0.52, 95% confidence interval (CI), 0.3 to 0.91
lower in the aripiprazole group (25%; n=19/77) compared to the placebo group (43%; n=36/83; p=0.013)
the aripiprazole and placebo groups, respectively (p=0.009). Among key secondary efficacy endpoints, t
aripiprazole group vs placebo group (p=0.01; HR, 0.31; 95% CI, 0.12 to 0.77). The time to depressive rel
HR, 0.83; 95% CI, 0.35 to 2.01). However, the study was not powered to detect differences in secondary

episodes of manic (70%) or mixed (30%) symptoms at enrollment. Compared to placebo, the mean char
significantly in favor of aripiprazole during weeks 18 to 26 (p 0.01 to 0.05). There were no significant diffe
mean MADRS total scores. At week 26, the mean changes from baseline in the Clinical Global Impressic
score (aripiprazole, 0.7 vs placebo, 1.3; p=0.02) and mania score (aripiprazole, 0.4 vs placebo, 0.9; p=0.
events in the aripiprazole group included tremor (9.1%), akathisia (6.5%), vaginitis (6.4%) and pain in the
twice the incidence of placebo. Among aripiprazole-treated patients, 13% (n=7/56) experienced clinically
more) vs none of the placebo-treated patients (Keck et al, 2006).

4) Pediatric:

a) In a 4 week, double-blind, placebo-controlled study in pediatric patients with bipolar disorder (n=296), trea
symptomatology compared to placebo. Pediatric patients aged 10 to 17 years with manic and mixed episodes
without psychotic features and a Young Mania Rating Scale (Y-MRS) score of 20 or greater received a target
or 30 mg/day or placebo. Doses were initiated at 2 mg/day and increased to 5 mg after 2 days and then to a t
treatment arm) or 30 mg in 13 days (30 mg/day treatment arm). At week 4, both aripiprazole doses were supe
(Prod Info ABILIFY(R) oral tablets, solution, disintegrating tablets, IV injection, 2008).

4.5.D Borderline personality disorder

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Addition of aripiprazole may be beneficial for patients with borderline personality disorder who are resista
(Bellino et al, 2008).
Aripiprazole was superior to placebo for the treatment of multiple markers of borderline personality disor
Aripriprazole continued to demonstrate superior efficacy in the treatment of multiple markers of borderlin
follow up period (n=52) (Nickel et al, 2007).

3) Adult:

a) In a double-blind, placebo-controlled study, aripiprazole was superior to placebo for the treatment of multi
(n=52). Adult and adolescent patients, who met Diagnostic and Statistical Manual of Mental Disorders-IV (DS
disorder were randomized in a 1:1 fashion to receive either aripiprazole 15 milligrams (mg) tablets orally daily
women/4 men) for 8 weeks. The primary outcome was the mean change in score from baseline to week 8 in
D), the Hamilton Anxiety Rating Scale (HAM-A), the State-Trait Anger Expression Inventory (STAXI) and the
consisted of 9 symptoms: somatization, obsessive-compulsiveness, insecurity in social contact, depression, a
paranoid thinking and psychoticism. The intent-to-treat analysis revealed that aripiprazole was significantly su
and 8 of the 9 symptoms of SCL-90-R, excluding somatization as seen in the following table. The most comm
headache, insomnia, nausea, numbness, constipation and anxiety. Self injury occurred before and during stu
aripiprazole versus placebo during treatment, respectively. Limitations to this study include a small sample pc
(Nickel et al, 2006).

Change in scores over 8 weeks on 9 scales of the symptom check list, HAM-D, HAM-A and STAXI in pa
taking aripiprazole or placebo

Variable	Som SCL-90-R	OCD SCL-90-R	ISC SCL-90
Baseline	Mean/(SD)		
ARI-G	69.5 (9.1)	60.1 (6.4)	68.2 (6.9)
PL-G	68.8 (8.7)	58.3 (7.5)	67.3 (5.7)
Outcome	Mean/(SD)		
ARI-G	62.5 (7.3)	55.2 (4.3)	59.7 (5.3)
PL-G	65.4 (8.9)	58.6 (7.9)	64.2 (6.2)
difference in change in score between groups	95% CI -8.2 to 1	95% CI -8 to -2.4	95% CI -8 to -2.8
	p=0.15	p=0.01	p less than 0.001
KEY: Som = somatization; OCD = obsessiveness/compulsiveness; ISC = insecurity in social contacts; D AGG/HOS = aggression/hostility; PHOB/ANX = phobic anxiety; PAR = paranoid thinking; PSYCH = psy Rating Scale; HAM-D = Hamilton Depression Rating Scale; STAXI = State-Trait Anger Expression Inve placebo group; (SD) = standard deviation; CI = confidence interval.			

Change in scores over 8 weeks on 9 scales of the symptom check list, HAM-D, HAM-A and STAXI in pa
taking aripiprazole or placebo, continued

Variable	ANX SCL-90-R	AGG/HOS SCL-90-R	PHOB/ANX S
Baseline	Mean/(SD)		
ARI-G	72.3 (6.4)	78.6 (4.4)	72.1 (7.6)
PL-G	74.1 (5.9)	77.9 (3.9)	70.4 (8.3)
Outcome	Mean/(SD)		
ARI-G	61.1 (5.2)	64.6 (6.8)	61.4 (7.4)
PL-G	70.2 (7.3)	73.1 (7.8)	67.1 (9.5)
difference in change in score between groups	95% CI -9.9 to -4.7	95% CI -11.7 to -6.7	95% CI -10.9 to -3.9
	p less than 0.001	p less than 0.001	p less than 0.001

KEY: Som = somatization; OCD = obsessiveness/compulsiveness; ISC = insecurity in social contacts; D
= aggression/hostility; PHOB/ANX = phobic anxiety; PAR = paranoid thinking; PSYCH = psychoticism; I
HAM-D = Hamilton Depression Rating Scale; STAXI = State-Trait Anger Expression Inventory; ARI-G =
(SD) = standard deviation; CI = confidence interval.

Change in scores over 8 weeks on 9 scales of the symptom check list, HAM-D, HAM-A and STAXI in pa
taking aripiprazole or placebo, continued

Variable	PSYCH SCL-90-R	HAM-D	HAM-A
Baseline	Mean/(SD)		
ARI-G	60.5 (7.6)	20.3 (4.4)	23.3 (4.1)
PL-G	62.6 (7.9)	20.9 (3.9)	22.8 (5.3)
Outcome	Mean/(SD)		
ARI-G	54.3 (3.5)	13.9 (2.8)	16.3 (3.5)
PL-G	60.5 (6.2)	18.8 (4.7)	19.5 (5)
difference in change in score between groups	95% CI -6.9 to -1.3	95% CI -6.5 to -2.1	95% CI -6.2 to -1.2
	p=0.02	p=0.002	p=0.007

KEY: Som = somatization; OCD = obsessiveness/compulsiveness; ISC = insecurity in social contacts; D
= aggression/hostility; PHOB/ANX = phobic anxiety; PAR = paranoid thinking; PSYCH = psychoticism; I
HAM-D = Hamilton Depression Rating Scale; STAXI = State-Trait Anger Expression Inventory; ARI-G =
(SD) = standard deviation; CI = confidence interval.

change in scores over 8 weeks on 9 scales of the symptom check list, HAM-D, HAM-A and STAXI in pat
taking aripiprazole or placebo, continued

Variable	Trait Anger	Anger In	Anger Out
Baseline	Mean/(SD)		
ARI-G	30.5 (6.4)	24.5 (4.2)	25 (5.7)
PL-G	29.9 (5.8)	25.2 (4.8)	26.1 (5.5)
Outcome	Mean/(SD)		

ARI-G	18.1 (3)	16.3 (2.5)	14.3 (2.6)
PL-G	24 (4.7)	20.5 (3.3)	20.7 (4.1)
difference in change in score between groups	95% CI -9.3 to -3.7	95% CI -5.6 to -1.4	95% CI -7.8 to -2.8
	p less than 0.001	p=0.002	p less than 0.001
KEY: Som = somatization; OCD = obsessiveness/compulsiveness; ISC = insecurity in social contacts; D = aggression/hostility; PHOB/ANX = phobic anxiety; PAR = paranoid thinking; PSYCH = psychoticism; I HAM-D = Hamilton Depression Rating Scale; STAXI = State-Trait Anger Expression Inventory; ARI-G = (SD) = standard deviation; CI = confidence interval.			

1) Aripiprazole continued to demonstrate superior efficacy in the treatment of multiple markers of borde follow up, open-label, observational study (n=52). After final evaluation at 8 weeks in the previous study, discontinued (ex-placebo) and patients in the aripiprazole group continued 15 milligrams daily. The prima checklist (SCL-90-R), Hamilton Anxiety Rating Scale (HAM-A), Hamilton Depression Rating Scale (HAM at 18 months. Aripiprazole continued to demonstrate significantly superior efficacy compared with ex-pla HAM-A and HAM-D as indicated in the table. Self injury occurred in both groups during the 18 months of aripiprazole and ex-placebo, respectively. Two patients in the ex-placebo group attempted suicide. Both numbness, restlessness, constipation and anxiety (Nickel et al, 2007).

Changes in all scales of the symptom check list (SCL-90-R) HAM-D, HAM-A, and STAXI at 18 mont

Marker	ARI-G	
SCL-90-R, somatization	59 +/- 5.1	
SCL-90-R, obsessive/compulsiveness	53.1 +/- 6.9	
SCL-90-R, insecurity in social contact	57.2 +/- 7.3	
SCL-90-R, depression	45 +/-5.6	
SCL-90-R, anxiety	58 +/- 5.9	
SCL-90-R, hostility/aggression	61.7 +/- 3.4	
SCL-90-R, phobic anxiety	60 +/- 3.3	
SCL-90-R, paranoid thinking	58.8 +/- 3.6	
SCL-90-R, psychoticism	52.5 +/- 5.5	
HAM-A	13.9 +/- 3.1	
HAM-D	12 +/- 2.6	
STAXI	all scales	
KEY: < = less than; ARI-G = aripiprazole group; (SCL-90-R) = symptom checklist 90-R, (HAM-A) = Hamilton Depression Rating Scale; (STAXI) = State-Trait Anger Expression Inventory; p provided is		

2) An open-label study revealed addition of aripiprazole may be beneficial for patients with borderline pe sertraline treatment (n=21). Adult outpatients, (18 to 50 years of age) diagnosed with borderline persona respond to 12 weeks of sertraline 100 to 200 milligrams (mg) daily received aripiprazole 10 mg (initial do remained constant, for 12 weeks. Patients were considered responders if the Clinical Global Impression much improved or much improved) and a decrease of the Brief Psychiatric Rating Scale (BPRS) score w

to-treat analysis at week 12 revealed a statistically significant improvement in the responders (n=16) in n (p=0.018) and 34.63 +/- 3.89 (p=0.005), respectively. Statistically significant secondary outcomes that er Borderline Personality Disorder Severity Index (BPDSI) for impulsivity 5.66 +/- 1.18 (p=0.011), BPDSI fo 1.28 (p=0.036) and Barratt Impulsiveness Scale (BIS-11) 64.88 +/- 7.53 (p=0.017). However, no significa Rating Scale (HAM-D), the Hamilton Anxiety Rating Scale (HAM-A), Social Occupational Functioning As BPDSI. The most common adverse effects were headache (37.5%), insomnia and anxiety (25%). Limitat population size and short duration of treatment (Bellino et al, 2008).

4.5.E Dementia

See Drug Consult reference: BEHAVIORAL AND PSYCHOLOGICAL SYMPTOMS OF DEMENTIA

4.5.F Major depressive disorder, Adjunctive treatment in patients also receiving antidepressants

FDA Labeled Indication

1) Overview

FDA Approval: Adult, yes; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Aripiprazole is indicated for use as an adjunctive treatment to antidepressants for major depressive disor solution, IM injection, DISCMELT(TM) orally disintegrating tablets, 2007).
In two 6-week, placebo-controlled trials (n=743), treatment with aripiprazole was superior to placebo in re major depressive disorder (MDD) and an inadequate response to prior antidepressant therapies; addition patient functioning with aripiprazole compared to placebo (Prod Info ABILIFY(R) oral tablets, oral solutio disintegrating tablets, 2007).

3) Adult:

a) In two 6-week, placebo-controlled trials (n=381, n=362), treatment with aripiprazole was superior to placel patients with major depressive disorder (MDD) and an inadequate response to prior antidepressant therapy; improved patient functioning with aripiprazole compared to placebo. Patients with DSM-IV criteria for MDD, a 50% patient-perceived improvement after 6 weeks or greater of antidepressant therapy at or above the minim antidepressant therapies in the current depressive episode, and an inadequate response (defined as less tha the Hamilton Depression Rating Scale (HAMD17), a minimal HAMD17 score of 14, and a Clinical Global Imp minimal improvement) to 8 weeks of prospective antidepressant therapy were eligible. Prior therapies include extended-release, fluoxetine, escitalopram, or sertraline. Patients initially received oral aripiprazole 5 milligrar therapy. The aripiprazole dose was adjusted by 5 mg/day in 1-week intervals based on patient tolerability and (patients on potent CYP2D6 inhibitors (eg, fluoxetine, paroxetine)) or 2 to 20 mg/day (patients not on potent C aripiprazole doses were 10.7 and 11.4 mg/day in the two studies. Response to therapy was determined using Asberg Depression Rating Scale (MADRS), which assessed depressive symptoms and the 3-item, patient-ra assessed the impact of depression on work/school, social life, and family life functioning (0=not at all to 10=e aripiprazole was found to be superior in reducing mean MADRS total scores in both studies and in reducing r smaller mean reduction in total MADRS scores was observed in males compared to females; otherwise, resp prospective antidepressant choice, or race (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, DISC 2007).

4.5.G Psychomotor agitation - Schizophrenia

FDA Labeled Indication

1) Overview

FDA Approval: Adult, yes (injectable only); Pediatric, no
Efficacy: Adult, Effective
Recommendation: Adult, Class IIa
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Aripiprazole injection is approved for the treatment of agitation associated with schizophrenia and bipolar (R) oral tablets, oral solution, IM injection, DISCMELT(TM) orally disintegrating tablets, 2007a).
A double-blind, placebo-controlled study demonstrated that intramuscular aripiprazole was noninferior to placebo in voluntarily hospitalized agitated patients with schizophrenia or schizoaffective disorder (Andre In placebo-controlled trials, intramuscular aripiprazole was statistically superior to placebo in improving s schizophrenia (Tran-Johnson et al, 2007; Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, DI 2007a).

3) Adult:

a) Aripiprazole was more effective than placebo for the acute treatment of agitation in patients with schizoph schizophreniform disorder in a dose-ranging, multicenter, randomized, double-blind clinical trial. Patients who Positive and Negative Syndrome Scale (PANSS)-Excited Component (PEC) scores of 15 to 32, and a score 5 PEC items (excitement, hostility, tension, uncooperativeness, and poor impulse control; scores range from receive one of 4 aripiprazole doses (1 milligram (mg) (n=57), 5.25 mg (n=63), 9.75 mg (n=57), or 15 mg (n=5 (n=62). All doses were administered intramuscularly within 1 hour of baseline assessment and repeated up to

but no more than 20 hours could elapse between the first and third doses. In the placebo arm, aripiprazole 15
required. A rescue benzodiazepine, such as lorazepam, was permitted only at least 60 minutes after the seco
antipsychotic medications were discontinued prior to the study. The primary endpoint was the mean change f
one dose of aripiprazole compared to placebo, with a p-value of 0.0167 indicating a statistically significant dif
score at 2 hours was noted between each dose of aripiprazole, except the 1-mg group, and haloperidol comp
versus placebo). Significant differences were observed as early as 45 minutes in the aripiprazole 9.75-mg gro
The PEC response (defined as at least a 40% reduction in the mean PEC score from baseline to 2 hours) for
the haloperidol group ($p < 0.05$). The secondary endpoint of the Agitation-Calmness Evaluation Scale (ACES
compared to placebo for the 9.75-mg aripiprazole group ($p < 0.01$) and the haloperidol group ($p < 0.01$). Addi
Agitated Behavior Scale (CABS) score, the Clinical Global Impressions-Severity of Illness (CGI-S) score, the
(CGI-I) score, and the Brief Psychiatric Rating Scale (BPRS) total score were significantly improved at 2 hour
aripiprazole groups and the haloperidol group. Only the CGI-I score was significantly improved in the 1-mg ar
were observed for the mean change in BPRS-positive scores after 2 hours in any group compared to placebo
the placebo group compared to the aripiprazole 5.25-mg to 15-mg groups and the haloperidol group ($p < 0.05$
adverse events in the aripiprazole groups were headache (13%), dizziness (10%), somnolence (7%), and na
of patients in the aripiprazole groups, 10.5% of patients in the haloperidol group, and no patients in the placel
1.8% of the aripiprazole groups, 7% of the haloperidol group, and 0% of the placebo group (Tran-Johnson et

b) A double-blind, placebo-controlled study demonstrated that intramuscular aripiprazole was noninferior to i
placebo in voluntarily hospitalized, agitated patients with schizophrenia or schizoaffective disorder as measur
excited components from the Positive and Negative Syndrome Scale (PANSS)) to 2 hours after the first injec
cooperation, excitement, poor impulse control, and tension on a scale of 1 (absent) to 7 (extreme). Patients w
9.75 mg intramuscularly (IM) (n=175), haloperidol 6.5 mg IM (n=185), or placebo (n=88). The noninferiority m
score was 2.5. Patients could receive up to three IM injections spaced at least 2 hours apart. Analysis of the
improvement in PEC score at 2 hours from baseline of -7.27 aripiprazole group, -7.75 haloperidol group, and
after the first injection the percentage of patients achieving a clinical response (defined as a reduction in PEC
achieved by 55% aripiprazole group, 58% haloperidol group, and 36% in the placebo group (p less than 0.00
occurred in 41% aripiprazole patients (n=70), 34% haloperidol patients (n=62), and 57% in placebo (n=50), w
second dose of -5.92, -6.73 and -2.16 (p less than 0.001 vs placebo), respectively. The most frequently repor
(n=175) was headache (7.4%), dizziness (6.3%), nausea (5.7%) and insomnia (5.7%), and in the haloperidol
headache (8.2%), and extrapyramidal disorder (5.5%) (Andrezina et al, 2006).

c) In two short-term (24-hour), placebo-controlled trials, intramuscular aripiprazole was statistically superior t
in patients with schizophrenia (using the Positive and Negative Syndrome Scale [PANSS] Excited Componer
Improvement [CGI-I] scale scores). Both trials included a single active comparator treatment arm of haloperic
meeting DSM-IV criteria for schizophrenia received up to 3 injections during the 24-hour treatment period, wit
initial 2-hour period, when the primary efficacy measure was evaluated. All enrolled patients were judged by t
and clinically appropriate candidates for treatment with intramuscular medication. Additionally, all patients exl
exceeded a threshold score of 14 or greater on the five items comprising the PANSS Excited Component (eg
uncooperativeness and excitement items) with at least 2 individual item scores of 4 or greater using a 1 to 7 s
7=extreme). In both studies, the baseline PANSS Excited Component score ranged from 15 to 24 (out of a m
score of 19; this suggested mainly moderate levels of agitation with some patients experiencing mild or sever
measure in both trials was the change in the PANSS Excited Component from baseline to 2 hours post-inject
measure. In the first study (n=350), four fixed aripiprazole injection doses of 1 milligram (mg), 5.25 mg, 9.75 r
2-hour period, the 5.25 mg, 9.75 mg, and 15 mg doses were statistically superior to placebo in the PANSS Ex
the second study (n=445), one fixed aripiprazole injection dose of 9.75 mg was evaluated. After the initial 2-h
statistically superior to placebo in the PANSS Excited Component and on the CGI-I scale (Prod Info ABILIFY
DISCMELT(TM) orally disintegrating tablets, 2007a)

4.5.H Schizophrenia

FDA Labeled Indication

1) Overview

FDA Approval: Adult, yes; Pediatric, yes (13 to 17 years old)
Efficacy: Adult, Effective; Pediatric, Evidence favors efficacy
Recommendation: Adult, Class IIb; Pediatric, Class IIb
Strength of Evidence: Adult, Category B; Pediatric, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Aripiprazole is indicated for the treatment of schizophrenia in adults and pediatric patients 13 to 17 years
solution, IM injection, DISCMELT(TM) orally disintegrating tablets, 2007a).
Aripiprazole has been more effective than placebo in treating adult patients with acutely relapsed schizo
improve cognitive function in some patients (Petrie et al, 1998a; Saha et al, 1999b).
Longer time to relapse was seen in adult patients with schizophrenia treated with aripiprazole therapy (A
Treatment with oral aripiprazole, at doses of 10 or 30 milligrams per day for 6 weeks, was superior to pla
adolescents 13 to 17 years of age (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, DISCME

3) Adult:

a) General Information

1) Relatively large double-blind, placebo-controlled studies (unpublished) have indicated the efficacy of
in patients with acute relapse of schizophrenia or schizoaffective disorder (Petrie et al, 1998a; Kane et al
optimal dose appears to be 10 or 15 mg once daily; additional clinical benefit has not usually been obser

oral tablets, disintegrating tablets, solution, 2006). These studies indicated significant improvement relati
Syndrome Scale (PANSS)-total, PANSS-positive, PANSS-negative, Clinical Global Improvement (CGI)-s
(BPRS) scores. The drug demonstrated a low propensity for extrapyramidal symptoms. All studies have
extended open treatment phase was instituted in one study (Petrie et al, 1998a), although results were n

b) Clinical Trials

1) Aripiprazole therapy was effective in the prevention of relapse in patients with chronic, stable schizop
blind, placebo-controlled study, patients (n=310) with at least a 2-year history of schizophrenia and stabl
received oral aripiprazole (15 milligrams daily) or placebo for 26 weeks. Time to relapse after randomizat
treated patients as compared with patients who received placebo (p less than 0.001). Additionally, a high
relapsed as compared with those in the aripiprazole group (57% vs 33.8%, respectively). The relative ris
versus placebo was 0.59 (95% confidence interval, 0.45 to 0.75; p less than 0.001). Mean changes from
greater with aripiprazole therapy as compared with placebo for the Positive and Negative Syndrome Sca
subscale score, PANSS-derived Brief Psychiatric Rating Scale (BPRS) core score, Clinical Global Impre
or equal to 0.01, all values), and CGI-Severity score (p less than or equal to 0.05). Insomnia, tremor, aka
frequently reported adverse events with aripiprazole therapy (Pigott et al, 2003)(Anon, 2003).

2) In a placebo-controlled, phase III study involving relapsed schizophrenic or schizoaffective patients (r
haloperidol 10 mg daily (fixed doses) were each statistically superior to placebo with regard to changes i
on responder analysis (a 30% reduction in PANSS-total scores from baseline at last visit), each dose of a
than placebo, whereas haloperidol was not. There was evidence of better tolerability with aripiprazole co
requirements for extrapyramidal effects, prolactin increases, weight increase). Extrapyramidal symptoms
placebo, and fewer patients receiving aripiprazole discontinued treatment due to adverse events compar
2000). However, this study did not report statistical comparisons of aripiprazole and haloperidol for any p
effects); responder-analysis data revealed only a small difference between the two drugs. Overall, this st
aripiprazole is significantly more efficacious than haloperidol.

3) Some improvement in neurocognitive function (eg, verbal learning, executive functioning, vigilance) w
mg daily) in a randomized study (n=256); the drug tended to be superior to olanzapine (Kern et al, 2001a

4) Pediatric:

a) In a 6-week, placebo-controlled trial in adolescents 13 to 17 years of age, oral aripiprazole at doses of 10
placebo in the treatment of schizophrenia. Study patients (n=302) were outpatients who met the Diagnostic a
edition) criteria for schizophrenia and had a baseline Positive and Negative Syndrome Scale (PANSS) score
fixed daily doses of aripiprazole 10 mg, aripiprazole 30 mg, or placebo. Aripiprazole was initiated at 2 mg/day
and 11 days for the 10-mg and 30-mg groups, respectively. The mean improvement in PANSS total score fro
superior in both aripiprazole groups compared to placebo. The 30 mg/day dose was not found to be more effi
most common treatment-related adverse events with a possible dose-response relationship were extrapyram
21.6%; placebo, 5%); somnolence (incidence: 10 mg, 11%; 30 mg, 21.6%; placebo, 6%); and tremor (incider
(Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, DISCMELT(TM) orally disintegrating tablets, 20

4.6 Comparative Efficacy / Evaluation With Other Therapies

Chlorpromazine

Haloperidol

Olanzapine

Perphenazine

4.6.A Chlorpromazine

4.6.A.1 Schizophrenia

a) Based upon comparisons of minimum effective dosages identified in placebo- controlled, fixed-dose and f
minimum effective dose of aripiprazole was 15 milligrams/day (equivalent to chlorpromazine 200 milligrams/d

4.6.B Haloperidol

4.6.B.1 Schizophrenia

a) SUMMARY: Aripiprazole (up to 30 mg daily) and haloperidol (up to 20 mg daily) appear similarly effective
schizophrenia or schizoaffective disorder; adverse effects may be less with aripiprazole.

b) Haloperidol 5 to 20 mg daily, but not aripiprazole (5 to 30 mg daily), was superior to placebo with respect
study involving acutely relapsed inpatients with DSM-III/IV schizophrenia (n=103). Both haloperidol and aripip
responder analysis based on CGI-severity scores (Prod Info Abilify(TM), 2002).

c) In a placebo-controlled, phase III study involving relapsed schizophrenic or schizoaffective patients (n=41
haloperidol 10 mg daily (fixed doses) were each statistically superior to placebo with regard to changes in PA
responder analysis (a 30% reduction in PANSS-total scores from baseline at last visit), each dose of aripipraz

placebo, whereas haloperidol was not. There was evidence of better tolerability with aripiprazole compared to extrapyramidal effects, prolactin increases, weight increase). Extrapyramidal symptoms were reportedly simil patients receiving aripiprazole discontinued treatment due to adverse events compared to haloperidol and pla did not report statistical comparisons of aripiprazole and haloperidol for any parameter (efficacy versus basel data revealed only a small difference between the two drugs. Overall, this study does not provide evidence th than haloperidol.

d) Results of phase II studies also suggested fewer adverse effects with aripiprazole compared to haloperido studies, lower changes from baseline in Simpson-Angus Scale scores (parkinsonian symptoms) and less req all doses of aripiprazole (2, 10, or 30 mg daily) than with haloperidol 10 mg daily; prolactin levels were not inc significant increases with haloperidol, and significantly less weight gain was evident in the aripiprazole groups not presented.

4.6.C Olanzapine

4.6.C.1 Schizophrenia

a) A trend toward greater improvement in some areas of neurocognitive function (eg, verbal learning, workin mg daily compared to olanzapine 15 mg daily in a randomized study (n=256) (Kern et al, 2001). However, a p study are unavailable (unpublished).

4.6.D Perphenazine

4.6.D.1 Schizophrenia, Treatment resistant

a) Both aripiprazole and perphenazine improved symptoms associated with treatment-resistant schizophreni study. Patients (n=416) with treatment-resistant schizophrenia (ie, failure of at least 2 trials of antipsychotic th last 2 years) with a Positive and Negative Syndrome Scale (PANSS) total score of at least a 75, a score grea of conceptual disorganization, suspiciousness, hallucinatory behavior, or delusions, and a Clinical Global Imp or greater. After a 2-day washout period, patients entered a 4 to 6 week open-label treatment phase receiving or risperidone 2 to 8 mg/day to confirm treatment resistance. At the end of this open-label screening period, 3 washout period then were randomized to 6 weeks of treatment with aripiprazole 15 to 30 mg/day or perphena was mean change in PANSS score during the 6-week double-blind treatment period. In the aripiprazole group 9.8 points (95% confidence interval (CI), -13.2 to -6.3) from a mean total baseline score of 97.5 (95% CI, 95 t decrease in PANSS total score was 10.5 points (95% CI, -14 to -7) from a mean total baseline score of 99.5 (groups was not statistically significant (p-value not reported). At the end of 6 weeks, 27% (40/150) of patients of patients responded to perphenazine treatment, with response defined as at least a 30% decrease in PANS Extrapyramidal symptoms were reported in 13.7% (n=21) of patients in the aripiprazole group and 19.4% (n= Serious adverse events were reported in 21% (n=32) and 17% (n=24) of patients treated with aripiprazole an common being psychosis (9.8% and 6.3%, respectively) (Kane et al, 2007).

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Last Modified: June 23, 2009

DRUGDEX® Evaluations

AMPHETAMINE/DEXTROAMPHETAMINE

0.0 Overview

1) Class
- **a)** This drug is a member of the following class(es):
  Central Nervous System Agent
  CNS Stimulant

2) Dosing Information
- **a)** Adult
  - **1)** Attention deficit hyperactivity disorder
    - **a)** extended-release, 20 mg ORALLY daily (Prod Info ADDERALL XR(R) extended-release oral capsules, 20
  - **2)** Narcolepsy
    - **a)** immediate-release, 5 to 60 mg/day ORALLY in divided doses (Prod Info ADDERALL(R) oral tablets, 2006
- **b)** Pediatric
  - **1)** (immediate-release) not FDA approved in children under 3 years of age with attention deficit hyperactivity diso 2006)
  - **2)** (extended-release) not FDA approved in children under 6 years of age with attention deficit hyperactivity disor release oral capsules, 2006)
    - **a)** Attention deficit hyperactivity disorder
      - **1)** immediate release (age 3 to 5 yr), initial 2.5 mg ORALLY every morning; may increase daily dose in 2 optimal response (Prod Info ADDERALL(R) oral tablets, 2006)
      - **2)** immediate release (age 6 yr and older), initial 5 mg ORALLY once or twice daily; may increase daily d optimal response; give first dose in the morning and subsequent doses at 4 to 6 hour intervals; MAX 40 r 2006)
      - **3)** extended release (6 to 12 yr), initial 10 mg ORALLY every morning (alternatively, 5 mg/day if appropr increments at weekly intervals until optimal response; MAX 30 mg/day (Prod Info ADDERALL XR(R) ext
      - **4)** extended release (13 to 17 yr), initial 10 mg ORALLY every morning; may increase to 20 mg/day afte extended-release oral capsules, 2006)
    - **b)** Narcolepsy
      - **1)** immediate release (age 6 to 12 yr) initial, 5 mg ORALLY once daily; may increase daily dose in 5 mg response (Prod Info ADDERALL(R) oral tablets, 2006)
      - **2)** immediate release (age 12 yr and older) initial, 10 mg ORALLY once daily; may increase daily dose i optimal response (Prod Info ADDERALL(R) oral tablets, 2006)

3) Contraindications
- **a)** advanced arteriosclerosis (Prod Info ADDERALL(R) oral tablets, 2006)
- **b)** agitated states; may aggravate symptoms (Prod Info ADDERALL(R) oral tablets, 2006)
- **c)** cardiovascular disease, symptomatic (Prod Info ADDERALL(R) oral tablets, 2006)
- **d)** concomitant use of monoamine oxidase inhibitors (MAOI), or within 14 days of MAOI use; hypertensive crisis may 2006)
- **e)** drug dependence, history of; potential for abuse (Prod Info ADDERALL(R) oral tablets, 2006)
- **f)** glaucoma (Prod Info ADDERALL(R) oral tablets, 2006)
- **g)** hypersensitivity/idiosyncrasy to sympathomimetic amines (Prod Info ADDERALL(R) oral tablets, 2006)
- **h)** hypertension, moderate to severe (Prod Info ADDERALL(R) oral tablets, 2006)
- **i)** hyperthyroidism (Prod Info ADDERALL(R) oral tablets, 2006)

4) Serious Adverse Effects
- **a)** Cardiomyopathy
- **b)** Cerebrovascular accident
- **c)** Dead - sudden death
- **d)** Mania
- **e)** Myocardial infarction
- **f)** Psychotic disorder
- **g)** Seizure

5) Clinical Applications
- **a)** FDA Approved Indications
  - **1)** Attention deficit hyperactivity disorder
  - **2)** Narcolepsy

1.0 Dosing Information

Drug Properties

Storage and Stability

Adult Dosage

Pediatric Dosage

1.1 Drug Properties
A) Information on specific products and dosage forms can be obtained by referring to the Tradename List (Product In

1.2 Storage and Stability
A) Preparation
1) Oral
a) Give first dose (immediate-release) on awakening, and additional doses at 4 to 6-hour intervals. Avoid late
Info ADDERALL(R) oral tablets, 2006; Prod Info ADDERALL(R) XR extended release oral capsule, 2005).
b) Extended-release capsules may be swallowed whole with or without food. The entire capsule contents ma
immediately; the applesauce with sprinkled beads should be consumed in its entirety without chewing. Do no
ADDERALL(R) XR extended release oral capsule, 2005).

1.3 Adult Dosage

1.3.1 Normal Dosage

1.3.1.A Oral route

Attention deficit hyperactivity disorder

Narcolepsy

1.3.1.A.1 Attention deficit hyperactivity disorder
a) Extended-Release
1) The recommended initial dose for patients with attention deficit hyperactivity disorder is 20 milligr
extended-release oral capsules, 2006).

1.3.1.A.2 Narcolepsy
a) The recommended dose of immediate-release tablets is 5 to 60 milligrams/day ORALLY in divided do
2006).

1.4 Pediatric Dosage

1.4.1 Normal Dosage

1.4.1.A Oral route

Attention deficit hyperactivity disorder

Narcolepsy

1.4.1.A.1 Attention deficit hyperactivity disorder
a) Immediate-Release
1) For children aged 3 to 5 years, the recommended initial dose of immediate-release tablets is 2.5
be increased in 2.5-mg increments at weekly intervals until optimal response (Prod Info ADDERALL
2) For children aged 6 years and older, the recommended initial dose of immediate-release is 5 mill
increase in 5-mg increments at weekly intervals until optimal response, up to 40 mg/day. Give first d
to 6 hour intervals (Prod Info ADDERALL(R) oral tablets, 2006).
b) Extended-Release
1) For children 6 years of age and older, the starting dose of extended-release amphetamine/dextro
in the morning. Doses may be increased by 10 mg at weekly intervals to a MAXIMUM dose of 30 mg
XR(R) extended-release oral capsules, 2006).
2) For patients using immediate-release tablets, they should be switched to the same total daily dos
taken once daily in the morning (Prod Info Adderall XR(TM), 2001).

1.4.1.A.2 Narcolepsy
a) Immediate-Release

1) For children aged 6 to 12 years, the recommended initial dose of immediate-release tablets is 5 r
be increased in 5-mg increments at weekly intervals until optimal response (Prod Info ADDERALL(F
2) For children aged 12 years and older, the recommended initial dose of immediate-release tablet
dose increase in 10-mg increments at weekly intervals until optimal response. Take first dose on aw
intervals (Prod Info ADDERALL(R) oral tablets, 2006).

3.0 Cautions

Contraindications

Precautions

Adverse Reactions

Teratogenicity/Effects in Pregnancy/Breastfeeding

Drug Interactions

3.0.A Black Box WARNING

1) Oral (Tablet; Capsule, Extended Release)

a) Amphetamines have a high potential for abuse. Administration of amphetamines for prolonged periods of time
avoided. Particular attention should be paid to the possibility of subjects obtaining amphetamines for non-therape
should be prescribed or dispensed sparingly.

b) Misuse of amphetamine may cause sudden death and serious cardiovascular adverse events (Prod Info ADDI

3.1 Contraindications

A) advanced arteriosclerosis (Prod Info ADDERALL(R) oral tablets, 2006)
B) agitated states; may aggravate symptoms (Prod Info ADDERALL(R) oral tablets, 2006)
C) cardiovascular disease, symptomatic (Prod Info ADDERALL(R) oral tablets, 2006)
D) concomitant use of monoamine oxidase inhibitors (MAOI), or within 14 days of MAOI use; hypertensive crisis may
2006)
E) drug dependence, history of; potential for abuse (Prod Info ADDERALL(R) oral tablets, 2006)
F) glaucoma (Prod Info ADDERALL(R) oral tablets, 2006)
G) hypersensitivity/idiosyncrasy to sympathomimetic amines (Prod Info ADDERALL(R) oral tablets, 2006)
H) hypertension, moderate to severe (Prod Info ADDERALL(R) oral tablets, 2006)
I) hyperthyroidism (Prod Info ADDERALL(R) oral tablets, 2006)

3.2 Precautions

A) amphetamine misuse; may cause sudden death and serious cardiovascular events (Prod Info ADDERALL(R) oral
B) drug dependence, history of; potential for abuse (Prod Info ADDERALL(R) oral tablets, 2006)
C) bipolar disorder, comorbid; may precipitate a mixed/manic episode (Prod Info ADDERALL(R) oral tablets, 2006)
D) cardiovascular conditions which may be compromised by increases in blood pressure or heart rate (e.g., pre-existi
infarction, or ventricular arrhythmia) (Prod Info ADDERALL(R) oral tablets, 2006)
E) EEG abnormalities, especially with history of; may lower convulsive threshold (Prod Info ADDERALL(R) oral tablet
F) psychosis, pre-existing; may exacerbate symptoms of behavior disturbance and thought disorder (Prod Info ADDE
G) seizures, especially with a history of; may lower convulsive threshold (Prod Info ADDERALL(R) oral tablets, 2006)
H) structural cardiac abnormalities/conditions, serious, especially in children and adolescents; sudden death has beer
Info ADDERALL(R) oral tablets, 2006)
I) tics, motor and phonic, history of; risk of exacerbation (Prod Info ADDERALL(R) oral tablets, 2006)
J) Tourette's syndrome, history of; risk of exacerbation (Prod Info ADDERALL(R) oral tablets, 2006)

3.3 Adverse Reactions

Cardiovascular Effects

Endocrine/Metabolic Effects

Gastrointestinal Effects

Neurologic Effects

Psychiatric Effects

3.3.1 Cardiovascular Effects

Cardiomyopathy

Chest pain

Dead - sudden death

Hypertension

Myocardial infarction

Palpitations

Tachycardia

3.3.1.A Cardiomyopathy

1) Cardiomyopathy has been associated with chronic amphetamine use (Prod Info ADDERALL(R) oral capsı extended-release oral capsules, 2007).

3.3.1.B Chest pain

1) In a placebo controlled, 4-week, study of adults with ADHD, 0.5% of 191 patients discontinued Adderall XI symptoms such as exertional chest pain, unexplained syncope, or other symptoms suggestive of cardiac dise a prompt cardiac evaluation (Prod Info ADDERALL XR(R) extended-release oral capsules, 2007).

3.3.1.C Dead - sudden death

1) Incidence: rare

2) Children and Adolescents - With Preexisting Cardiac Risk

a) Sudden death has been reported in children and adolescents with structural cardiac abnormalities or medications at usual doses. Patients, including adults with serious structural or other cardiac abnormaliti abnormalities) should generally not be treated with stimulant medications. A cardiac evaluation (eg, elect performed in any patient experiencing exertional chest pain, unexplained syncope, or other symptoms in ADDERALL(R) oral capsules, 2007; Prod Info ADDERALL XR(R) extended-release oral capsules, 2007)

3) Children and Adolescents - Healthy

a) A retrospective, case-controlled study examines the association between stimulant medication, incluc combination drugs, and unexplained sudden death in healthy children and adolescents. In a collection of across the United States, 564 cases of sudden death in children and adolescents between the ages of 7 564 youngsters who died as passengers in motor vehicle accidents. The study determined that 1.8% (n= unexplained deaths were taking stimulant medication compared with only 0.4% (n=2) of youths in the mc 95% CI, 1.4 to 74.9; p=0.02). Limitations to this study included the time lag between the youths stimulant collected, family recall of information regarding clinical diagnoses, inconsistent postmortem inquiry, and t conditions. The authors stated that this finding should be considered when evaluating the overall risk and and adolescents (Gould et al, 2009). Given the limitations of this study, the U.S. Food and Drug Adminis benefits associated with stimulant medications (US Food and Drug Administration, 2009).

3.3.1.D Hypertension

1) Incidence: 7% to 22%, pediatric (Prod Info ADDERALL XR(R) extended-release oral capsules, 2007)

2) An average elevation of blood pressure of 2 to 4 mmHg has been reported following administration of Adc have larger increases. Larger increases in blood pressure should be monitored. Because stimulant medicatic with caution in patients with cardiac conditions which may be exacerbated by further blood pressure increase recent myocardial infarction, ventricular arrhythmia) (Prod Info ADDERALL(R) oral capsules, 2007; Prod Info capsules, 2007).

3) A 4-week controlled study was conducted in adolescents with ADHD. Isolated systolic blood pressure elev of patients in the Adderall XR treatment group compared to 11% of placebo-treated patients. Isolated diastoli were observed in 22% of patients in the Adderall XR treatment group compared to 25% of placebo-treated pa release oral capsules, 2007).

4) A single-dose study of 23 adolescents showed isolated increases in systolic blood pressure in patients tre patients treated with Adderall XR 20 mg (35%). All increases were transitory, appeared maximal at 2 to 4 hou (Prod Info ADDERALL XR(R) extended-release oral capsules, 2007).

3.3.1.E Myocardial infarction

1) Myocardial infarction has been reported in adults receiving amphetamine therapy at normal doses. Patien

other cardiac abnormalities (eg, cardiomyopathy, heart rhythm abnormalities) should generally not be treated (eg, electrocardiogram, echocardiogram) should be performed in any patient experiencing exertional chest pa indicative of cardiac disease (Prod Info ADDERALL(R) oral capsules, 2007; Prod Info ADDERALL XR(R) ext

3.3.1.F Palpitations

1) Palpitation has been associated with amphetamine use (Prod Info ADDERALL(R) oral capsules, 2007; Pr capsules, 2007).

3.3.1.G Tachycardia

1) Incidence: 6% (Prod Info ADDERALL XR(R) extended-release oral capsules, 2007)

2) Average heart rate increases of 3 to 6 bpm have been reported with stimulant medications. Patients shoul Because stimulant medications can cause increases in blood pressure, use with caution in patients with card further blood pressure increases (eg, preexisting hypertension, heart failure, recent myocardial infarction, ver (R) extended-release oral capsules, 2007).

3) Tachycardia has been reported in 6% of patients in the Adderall XR treatment group (n=191) compared to randomized, double-blind, placebo-controlled, parallel-group study conducted in adults with ADHD (Prod Info capsules, 2007). Tachycardia has been reported with Adderall also (Prod Info ADDERALL(R) oral capsules,

3.3.3 Endocrine/Metabolic Effects

3.3.3.A Weight loss

1) Incidence: 4% to 9%, pediatric; 11%, adults (Prod Info ADDERALL XR(R) extended-release oral capsules

2) Weight loss has occurred in 4% of pediatric patients in the Adderall XR treatment group (n=374) compare in a randomized, double-blind, placebo-controlled, parallel-group study conducted in children ages 6 to 12 wi extended-release oral capsules, 2007).

3) Weight loss has occurred in 9% of patients in the Adderall XR treatment group (n=233) compared to 0% c randomized, double-blind, placebo-controlled, multicenter, parallel-group study conducted in adolescents age XR(R) extended-release oral capsules, 2007).

4) Weight loss has occurred in 11% of patients in the Adderall XR treatment group (n=191) compared to 0% randomized, double-blind, placebo-controlled, parallel-group study conducted in adults with ADHD (Prod Info capsules, 2007).

3.3.4 Gastrointestinal Effects

Abdominal pain

Loss of appetite

Xerostomia

3.3.4.A Abdominal pain

1) Incidence: 11% to 14%, pediatrics (Prod Info ADDERALL XR(R) extended-release oral capsules, 2007)

2) Abdominal pain has occurred in 14% of pediatric patients in the Adderall XR treatment group (n=374) com (n=210) in a randomized, double-blind, placebo-controlled, parallel-group study conducted in children ages 6 extended-release oral capsules, 2007).

3) Abdominal pain has been reported in 11% of patients in the Adderall XR treatment group (n=233) compar in a randomized, double-blind, placebo-controlled, multicenter, parallel-group study conducted in adolescents ADDERALL XR(R) extended-release oral capsules, 2007).

3.3.4.B Loss of appetite

1) Incidence: 22% to 36% (Prod Info ADDERALL XR(R) extended-release oral capsules, 2007)

2) Loss of appetite has been reported in 22% (n=374) of pediatric patients in the Adderall XR treatment grou placebo group (n=210) in a randomized, double-blind, placebo-controlled, parallel-group study conducted in ADDERALL XR(R) extended-release oral capsules, 2007).

3) Loss of appetite has been reported in 36% of patients in the Adderall XR treatment group (n=233) compa in a randomized, double-blind, placebo-controlled, multicenter, parallel-group study conducted in adolescents ADDERALL XR(R) extended-release oral capsules, 2007).

4) Loss of appetite has been reported in 33% of patients in the Adderall XR treatment group (n=191) compa in a randomized, double-blind, placebo-controlled, parallel-group study conducted in adults with ADHD (Prod capsules, 2007).

3.3.4.C Xerostomia

1) Incidence: 35% (Prod Info ADDERALL XR(R) extended-release oral capsules, 2007)

2) Aptyalism has been reported in 35% of patients in the Adderall XR treatment group (n=191) compared to randomized, double-blind, placebo-controlled, parallel-group study conducted in adults with ADHD (Prod Info

capsules, 2007).

3.3.9 Neurologic Effects

Central nervous system stimulation, Overstimulation

Cerebrovascular accident

Gilles de la Tourette's syndrome

Headache

Insomnia

Seizure

Tic

Tremor

3.3.9.A Central nervous system stimulation, Overstimulation

1) Overstimulation has been associated with amphetamine use (Prod Info ADDERALL(R) oral capsules, 200 release oral capsules, 2007).

3.3.9.B Cerebrovascular accident

1) Cerebrovascular accident has been associated with amphetamine use (Prod Info ADDERALL(R) oral cap extended-release oral capsules, 2007).

3.3.9.C Gilles de la Tourette's syndrome

1) Summary

a) Exacerbation of Tourette's syndrome has been reported following administration of amphetamines (P Prod Info ADDERALL XR(R) extended-release oral capsules, 2007).

3.3.9.D Headache

1) Incidence: 26% (Prod Info ADDERALL XR(R) extended-release oral capsules, 2007)

2) Headache has been reported in 26% of patients in the Adderall XR treatment group (n=191) compared to randomized, double-blind, placebo-controlled, parallel-group study conducted in adults with ADHD (Prod Info capsules, 2007).

3.3.9.E Insomnia

1) Incidence: 12% to 17%, pediatric; 27%, adults (Prod Info ADDERALL XR(R) extended-release oral capsu

2) Insomnia occurred in 17% of pediatric patients in the Adderall XR treatment group (n=374) compared to 2 randomized, double-blind, placebo-controlled, parallel-group study conducted in children ages 6 to 12 with AI release oral capsules, 2007).

3) Insomnia occurred in 12% of patients in the Adderall XR treatment group (n=233) compared to 4% of pati randomized, double-blind, placebo-controlled, multicenter, parallel-group study conducted in adolescents age XR(R) extended-release oral capsules, 2007).

4) Insomnia was reported in 27% of patients in the Adderall XR treatment group (n=191) compared to 13% c randomized, double-blind, placebo-controlled, parallel-group study conducted in adults with ADHD (Prod Info capsules, 2007).

3.3.9.F Seizure

1) Some clinical evidence suggests patients with a history of seizures or EEG abnormalities may have a low XR should be discontinued if seizures are present (Prod Info ADDERALL(R) oral capsules, 2007; Prod Info A capsules, 2007).

3.3.9.G Tic

1) Exacerbation of motor and phonic tics has been reported following administration of amphetamines (Prod Info ADDERALL XR(R) extended-release oral capsules, 2007).

3.3.9.H Tremor

1) Tremors have been reported following administration of amphetamines (Prod Info ADDERALL(R) oral cap extended-release oral capsules, 2007).

3.3.12 Psychiatric Effects

Dysphoric mood

Euphoria

Feeling nervous

Mania

Psychotic disorder

Restlessness

3.3.12.A Dysphoric mood

1) Dysphoria has been associated with amphetamine use (Prod Info ADDERALL(R) oral capsules, 2007; Pro capsules, 2007).

3.3.12.B Euphoria

1) Euphoria has been associated with amphetamine use (Prod Info ADDERALL(R) oral capsules, 2007; Proc capsules, 2007).

3.3.12.C Feeling nervous

1) Incidence: 6% (Prod Info ADDERALL XR(R) extended-release oral capsules, 2007)

2) Nervousness has been reported in 6% of pediatric patients in the Adderall XR treatment group (n=374) co (n=210) in a randomized, double-blind, placebo-controlled, parallel-group study conducted in children ages 6 extended-release oral capsules, 2007).

3) Nervousness has been reported in 6% of patients in the Adderall XR treatment group (n=233) compared t a randomized, double-blind, placebo-controlled, multicenter, parallel-group study conducted in adolescents a XR(R) extended-release oral capsules, 2007).

3.3.12.D Mania

1) In a review of 49 randomized, controlled pediatric ADHD clinical trials involving pscyhostimulant medicatic hydrochloride, modafinil and dextromethylphenidate hydrochloride), the rate of psychosis/mania events in pe (95% CI, 0.74 to 2.65) per 100 person-years, with no comparable adverse events recorded in the placebo gro Administration to manufacturers of marketed ADHD drugs for submission of postmarketing case reports of ps 2005, yielded a total of 865 reports (pediatrics and adults) in which signs and/or symptoms of psychoses or n involved pediatric subjects, with almost half of the reports in children 10 years-old or younger, and approxima similar psychiatric conditions. Visual and/or tactile sensations of insects, snakes, or worms were commonly re each of the psychostimulant medications (methylphenidate hydrochloride, atomoxetine hydrochloride, and mi product) included in the analysis; and in many cases a strong temporal association was identified. The onset weeks, but in some cases it was months or years from the start of ADHD treatment and symptom onset (Mos

3.3.12.E Psychotic disorder

1) In a review of 49 randomized, controlled pediatric ADHD clinical trials involving pscyhostimulant medicatic hydrochloride, modafinil and dextromethylphenidate hydrochloride), the rate of psychosis/mania events in pe (95% CI, 0.74 to 2.65) per 100 person-years, with no comparable adverse events recorded in the placebo gro Administration to manufacturers of marketed ADHD drugs for submission of postmarketing case reports of ps 2005, yielded a total of 865 reports (pediatrics and adults) in which signs and/or symptoms of psychoses or n involved pediatric subjects, with almost half of the reports in children 10 years-old or younger, and approxima similar psychiatric conditions. Visual and/or tactile sensations of insects, snakes, or worms were commonly re each of the psychostimulant medications (methylphenidate hydrochloride, atomoxetine hydrochloride, and mi product) included in the analysis; and in many cases a strong temporal association was identified. The onset weeks, but in some cases it was months or years from the start of ADHD treatment and symptom onset (Mos

2) Psychotic or manic symptoms may occur among patients without prior history of psychosis, or may worse Chronic intoxication may result in severe psychosis, often similar to schizophrenia. Symptoms of psychosis o (4/3482) exposed to methylphenidate or amphetamine for several weeks at usual doses, in a pooled analysis studies (Prod Info ADDERALL XR(R) extended-release oral capsules, 2007).

3.3.12.F Restlessness

1) Restlessness has been associated with amphetamine use (Prod Info ADDERALL(R) oral capsules, 2007; oral capsules, 2007).

3.4 Teratogenicity/Effects in Pregnancy/Breastfeeding

A) Teratogenicity/Effects in Pregnancy

1) Amphetamine

a) U.S. Food and Drug Administration's Pregnancy Category: Category C (Prod Info ADDERALL XR(R) oral

1) Either studies in animals have revealed adverse effects on the fetus (teratogenic or embryocidal or ot women or studies in women and animals are not available. Drugs should be given only if the potential be

See Drug Consult reference: PREGNANCY RISK CATEGORIES

b) Crosses Placenta: Yes

c) Clinical Management

1) Because there is evidence of developmental and behavioral adverse effects in humans and animals f ADDERALL XR(R) oral capsules, 2007; Eriksson & Zetterstrom, 1994a; Levin, 1971a), amphetamines sl potential benefit to the mother outweighs the potential risk to the fetus (Prod Info ADDERALL XR(R) oral

d) Literature Reports

1) There are no adequate and well-controlled studies in pregnant women. There has been one report of esophageal fistula, and anal atresia (vater association) in a baby born following maternal exposure to de trimester of pregnancy. The risk of premature delivery and low birth weight is increased in infants born to infants may also experience symptoms of withdrawal as demonstrated by dysphoria, including agitation, XR(R) oral capsules, 2007). A statistically significant correlation between aggressive behavior and amph reported (Eriksson & Zetterstrom, 1994a).

2) Eleven infants were born with biliary atresia to mothers who had taken amphetamines in various dose development of a biliary tree). In a controlled group of 50 normal infants, it was noted that 3 of 50 mother

3) A large prospective, observational study of pregnancy and child development was undertaken relatec phenmetrazine) prescribed to gravid women during different stages of pregnancy and evaluated for their rate (SCA) per 100 live-born children at age 5 years did not differ from the SCA rate of the group of child There was, however, an excess of oral clefts in the infants of mothers who had amphetamines prescribe period. A rough test of efficacy of anorectic drugs was made by comparing mean weight gain in 4-week p showed only short-term and limited reduction of weight gain (Milkovich & Van Den Berg, 1977a).

4) In animal studies, there was no evidence of adverse effects on embryofetal morphological developme amphetamine/dextroamphetamine product (amphetamine d- to l-enantiomer ratio of 3:1) was orally admi up to 6 mg/kg/day (1.5 times the maximum recommended human dose (MRHD) of 30 mg/day on a body the MRHD), respectively, throughout the period of organogenesis. Fetal malformations and death and se mice following parenteral administration of d-amphetamine doses of 50 mg/kg/day (approximately 6 time term neurochemical and behavioral alterations (ie, learning and memory deficits, altered locomotor activi prenatal or early postnatal exposure to amphetamine (d- or d,l-), at doses similar to those used clinically 2007).

e) U.S. Food and Drug Administration's Pregnancy Category: Category C (Prod Info ADDERALL XR(R) oral

1) Either studies in animals have revealed adverse effects on the fetus (teratogenic or embryocidal or ot women or studies in women and animals are not available. Drugs should be given only if the potential be

See Drug Consult reference: PREGNANCY RISK CATEGORIES

f) Crosses Placenta: Yes

g) Clinical Management

1) Because there is evidence of developmental and behavioral adverse effects in humans and animals f ADDERALL XR(R) oral capsules, 2007; Eriksson & Zetterstrom, 1994a; Levin, 1971a), amphetamines sl potential benefit to the mother outweighs the potential risk to the fetus (Prod Info ADDERALL XR(R) oral

h) Literature Reports

1) There are no adequate and well-controlled studies in pregnant women. There has been one report of esophageal fistula, and anal atresia (vater association) in a baby born following maternal exposure to de trimester of pregnancy. The risk of premature delivery and low birth weight is increased in infants born to infants may also experience symptoms of withdrawal as demonstrated by dysphoria, including agitation, XR(R) oral capsules, 2007). A statistically significant correlation between aggressive behavior and amph reported (Eriksson & Zetterstrom, 1994a).

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2) Dextroamphetamine

a) U.S. Food and Drug Administration's Pregnancy Category: Category C (Prod Info Dexedrine(R), 2002) (A
1) Either studies in animals have revealed adverse effects on the fetus (teratogenic or embryocidal or ot
women or studies in women and animals are not available. Drugs should be given only if the potential be
See Drug Consult reference: PREGNANCY RISK CATEGORIES
b) Crosses Placenta: Unknown
c) Clinical Management
1) Amphetamines are not recommended for use during pregnancy except possibly in the case of narcol
which the drug is indicated and according to established regimens, amphetamines are not expected to c
However, maternal abuse of amphetamines does increase the potential risk of maternal, fetal, and neona
controversial, limited evidence suggests an increased incidence of cardiac defects and cleft palate in ne
during pregnancy (Berkowitz et al, 1981).
d) Literature Reports
1) Eleven infants were born with biliary atresia to mothers who had taken amphetamines in various dose
development of a biliary tree) (Levin, 1971). In a controlled group of 50 normal infants, it was noted that
2) A large prospective, observational study of pregnancy and child development was undertaken relatec
phenmetrazine) prescribed to gravid women during different stages of pregnancy and evaluated for their
1977). The severe congenital anomaly rate (SCA) per 100 live-born children at age 5 years did not differ
whose mothers did not use these drugs. There was, however, an excess of oral clefts in the offspring of
the first 55 days from the last menstrual period. A rough test of efficacy of anorectic drugs was made by
before and after the prescription; it showed only short-term and limited reduction of weight gain.
3) In a further report, clinicians evaluated the outcome of pregnancy in 52 women who had abused intra
throughout pregnancy, with results being compared to a control group of 52 nonabusing women (Little et
circumference was decreased significantly in neonates born to mothers abusing methamphetamine durir
congenital anomalies was not increased significantly compared to the control group.
4) A statistically significant correlation between aggressive behavior and amphetamine exposure during
Zetterstrom, 1994).
e) U.S. Food and Drug Administration's Pregnancy Category: Category C (Prod Info Dexedrine(R), 2002) (A
1) Either studies in animals have revealed adverse effects on the fetus (teratogenic or embryocidal or ot
women or studies in women and animals are not available. Drugs should be given only if the potential be
See Drug Consult reference: PREGNANCY RISK CATEGORIES
f) Crosses Placenta: Unknown
g) Clinical Management
1) Amphetamines are not recommended for use during pregnancy except possibly in the case of narcol
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the first 55 days from the last menstrual period. A rough test of efficacy of anorectic drugs was made by
before and after the prescription; it showed only short-term and limited reduction of weight gain.
3) In a further report, clinicians evaluated the outcome of pregnancy in 52 women who had abused intra
throughout pregnancy, with results being compared to a control group of 52 nonabusing women (Little et
circumference was decreased significantly in neonates born to mothers abusing methamphetamine durir
congenital anomalies was not increased significantly compared to the control group.
4) A statistically significant correlation between aggressive behavior and amphetamine exposure during
Zetterstrom, 1994).

B) Breastfeeding
1) Amphetamine
a) American Academy of Pediatrics Rating: Drugs of abuse for which adverse effects on the infant during bre
b) Thomson Lactation Rating: Infant risk has been demonstrated.
1) Evidence and/or expert consensus has demonstrated harmful infant effects when used during breastf
prescribed or patients should be advised to discontinue breastfeeding.
c) Clinical Management
1) Amphetamines have been shown to be excreted in human breast milk (Prod Info ADDERALL XR(R)
al, 1984). Adverse effects reported in exposed infants include irritability and poor sleeping patterns (Proc
Therefore, nursing mothers who are using amphetamines should be advised to avoid nursing (Prod Info
d) Literature Reports
1) Two case reports described methylamphetamine and amphetamine exposure in 4- and 2-month-old r
methylamphetamine by the 2 mothers ages 29 and 26 years, respectively, who were recruited from the i
HIT trial. The women self-injected a single methylamphetamine dose of unknown purity and quantity. Fo
collected. A 5- to 10-mL breast milk sample was collected just prior to drug use and then in 2 to 6 hour ir
methylamphetamine use. Methylamphetamine and amphetamine were estimated using high-performanc

detected in the urine and breast milk of both subjects was methylamphetamine with a small quantity of a methylamphetamine and amphetamine half-lives were 13.6 and 43 hours, respectively, in subject 1, and average concentration (Cavg) of methylamphetamine in the breast milk was 111 and 281 mcg/L for subje absolute infant dose of 16.7 and 42.2 mcg/kg/day. The Cavg of amphetamine in the breast milk was 4 ar resulting in an absolute infant dose of 0.8 and 2.5 mcg/kg/day (Bartu et al, 2009).

2) Concentrations of amphetamine were 3 and 7 times higher in breast milk than maternal plasma on th respectively, following administration of amphetamine 20 mg daily to a nursing mother with narcolepsy. A in the urine of the infant. Although only a small fraction of maternal dose is expected to be transferred to that patients abstain from long-term nursing during amphetamine treatment (Steiner et al, 1984).

e) American Academy of Pediatrics Rating: Drugs of abuse for which adverse effects on the infant during bre

f) Thomson Lactation Rating: Infant risk has been demonstrated.

1) Evidence and/or expert consensus has demonstrated harmful infant effects when used during breastf prescribed or patients should be advised to discontinue breastfeeding.

g) Clinical Management

1) Amphetamines have been shown to be excreted in human breast milk (Prod Info ADDERALL XR(R) al, 1984). Adverse effects reported in exposed infants include irritability and poor sleeping patterns (Proc Therefore, nursing mothers who are using amphetamines should be advised to avoid nursing (Prod Info

h) Literature Reports

1) Two case reports described methylamphetamine and amphetamine exposure in 4- and 2-month-old r methylamphetamine by the 2 mothers ages 29 and 26 years, respectively, who were recruited from the i HIT trial. The women self-injected a single methylamphetamine dose of unknown purity and quantity. Fo collected. A 5- to 10-mL breast milk sample was collected just prior to drug use and then in 2 to 6 hour ir methylamphetamine use. Methylamphetamine and amphetamine were estimated using high-performanc detected in the urine and breast milk of both subjects was methylamphetamine with a small quantity of a methylamphetamine and amphetamine half-lives were 13.6 and 43 hours, respectively, in subject 1, and average concentration (Cavg) of methylamphetamine in the breast milk was 111 and 281 mcg/L for subje absolute infant dose of 16.7 and 42.2 mcg/kg/day. The Cavg of amphetamine in the breast milk was 4 ar resulting in an absolute infant dose of 0.8 and 2.5 mcg/kg/day (Bartu et al, 2009).

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2) Dextroamphetamine

a) Thomson Lactation Rating: Infant risk has been demonstrated.

1) Evidence and/or expert consensus has demonstrated harmful infant effects when used during breastf prescribed or patients should be advised to discontinue breastfeeding.

b) Clinical Management

1) Amphetamines are concentrated in human breast milk. Adverse effects reported in exposed infants ir (Anon, 2001). The manufacturer of Adderal(R) suggests that breastfeeding women taking amphetamines Adderal(R), 2003).

c) Literature Reports

1) One study reported that concentrations of amphetamine were 3 and 7 times higher in breast milk thar delivery, respectively, following administration of dextroamphetamine 20 mg daily to a nursing mother wi effects occurred in the infant. Although only a small fraction of the maternal dose is expected to be transf suggest that patients abstain from long-term nursing during amphetamine treatment.

d) Thomson Lactation Rating: Infant risk has been demonstrated.

1) Evidence and/or expert consensus has demonstrated harmful infant effects when used during breastf prescribed or patients should be advised to discontinue breastfeeding.

e) Clinical Management

1) Amphetamines are concentrated in human breast milk. Adverse effects reported in exposed infants ir (Anon, 2001). The manufacturer of Adderal(R) suggests that breastfeeding women taking amphetamines Adderal(R), 2003).

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1) One study reported that concentrations of amphetamine were 3 and 7 times higher in breast milk thar delivery, respectively, following administration of dextroamphetamine 20 mg daily to a nursing mother wi effects occurred in the infant. Although only a small fraction of the maternal dose is expected to be transf suggest that patients abstain from long-term nursing during amphetamine treatment.

3.5 Drug Interactions

Drug-Drug Combinations

Drug-Food Combinations

3.5.1 Drug-Drug Combinations

Acetazolamide

Acetazolamide

Amitriptyline

Amoxapine

Calamus

Chlorpromazine

Citalopram

Clomipramine

Clorgyline

Clorgyline

Desipramine

Dothiepin

Doxepin

Furazolidone

Furazolidone

Guanethidine

Imipramine

Iproniazid

Iproniazid

Isocarboxazid

Isocarboxazid

Lofepramine

Moclobemide

Moclobemide

Nialamide

Nialamide

Nortriptyline

Opipramol

Pargyline

Pargyline

Phenelzine

Phenelzine

Procarbazine

Procarbazine

Protriptyline

Rasagiline

Selegiline

Selegiline

Sibutramine

Sodium Bicarbonate

Sodium Bicarbonate

Toloxatone

Toloxatone

Tranylcypromine

Tranylcypromine

Trimipramine

Venlafaxine

3.5.1.A Acetazolamide

1) Interaction Effect: amphetamine toxicity (hypertension, hyperpyrexia, seizures)
2) Summary: Concomitant acetazolamide and amphetamine therapy resulted in enhanced amphetamine effe
and the renal excretion of amphetamine is decreased due to increased reabsorption (Rowland, 1969; Anggar
3) Severity: moderate
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Lower doses of dextroamphetamine may be required with urinary alkalizers. Monito
7) Probable Mechanism: decreased renal clearance

3.5.1.B Acetazolamide

1) Interaction Effect: amphetamine toxicity (hypertension, hyperpyrexia, seizures)
2) Summary: Acetazolamide tends to alkalinize the urine, increasing the unionized amphetamine urine conce
tubular reabsorption. Enhanced effects of amphetamines may occur due to increased amphetamine concentr
3) Severity: minor
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Monitor for amphetamine toxicity and adjust the dose or discontinue the acetazolan
7) Probable Mechanism: decreased clearance

3.5.1.C Amitriptyline

1) Interaction Effect: hypertension, other cardiac effects, and CNS stimulation
2) Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been reporte from the release of norepinephrine (Beaumont, 1973; Raisfeld, 1972). A similar reaction might also occur wit Acute elevations in blood pressure have been noted (Flemenbaum, 1971a). Some amphetamine-like drugs m most combinations have not been studied. When amphetamine analogs are being used to treat obesity, it sh moderate weight gain (Russ & Ackerman, 1988). False positive urine tests for amphetamines have been rep & Browning, 1993). Caution is advised when concurrent administration of amphetamine-like agents and TCA monitored for increased cardiovascular effects (hypertension and dysrhythmias).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other sympatho increased cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Inf capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006; Flemenbaum, 1972). Use caution if closely for hypertension and dysrhythmias.
7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission
8) Literature Reports
a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agen amphetamine with TCAs such as desipramine or protriptyline results in sustained increases in d-amphet VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tab 2006).
b) Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transdermal system, 2006).
c) Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases i effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of comb methylphenidate usually results in the blood pressure returning to normotensive levels; reinstitution of th pressure elevation (Flemenbaum, 1971; Flemenbaum, 1972).
d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical doubled steady-state plasma levels of desipramine (Price et al, 1990).
e) There have been claims based on uncontrolled studies that a better antidepressant response may oc 1969). However, a systemic review of stimulants in the treatment of depression concluded that although ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated litt appear to be as effective as the conventional antidepressants in primary depression (Satel & Nelson, 19

3.5.1.D Amoxapine

1) Interaction Effect: hypertension, other cardiac effects, and CNS stimulation
2) Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been reporte from the release of norepinephrine (Beaumont, 1973; Raisfeld, 1972). A similar reaction might also occur wit Acute elevations in blood pressure have been noted (Flemenbaum, 1971a). Some amphetamine-like drugs m most combinations have not been studied. When amphetamine analogs are being used to treat obesity, it sh moderate weight gain (Russ & Ackerman, 1988). False positive urine tests for amphetamines have been rep & Browning, 1993). Caution is advised when concurrent administration of amphetamine-like agents and TCA monitored for increased cardiovascular effects (hypertension and dysrhythmias).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other sympatho increased cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Inf capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006; Flemenbaum, 1972). Use caution if closely for hypertension and dysrhythmias.
7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission
8) Literature Reports
a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agen amphetamine with TCAs such as desipramine or protriptyline results in sustained increases in d-amphet VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tab 2006).
b) Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transdermal system, 2006).
c) Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases i effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of comb methylphenidate usually results in the blood pressure returning to normotensive levels; reinstitution of th pressure elevation (Flemenbaum, 1971; Flemenbaum, 1972).
d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical doubled steady-state plasma levels of desipramine (Price et al, 1990).
e) There have been claims based on uncontrolled studies that a better antidepressant response may oc 1969). However, a systemic review of stimulants in the treatment of depression concluded that although

ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated litt
appear to be as effective as the conventional antidepressants in primary depression (Satel & Nelson, 19

3.5.1.E Calamus

1) Interaction Effect: reduced effect of amphetamines
2) Summary: Calamus antagonized spontaneous motor activity and amphetamine-induced hyperactivity in m
3) Severity: moderate
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Use caution with concomitant use of calamus and amphetamines.
7) Probable Mechanism: not specified
8) Literature Reports
a) Calamus antagonized spontaneous motor activity and amphetamine-induced hyperactivity in mice. C
(0.2 milliliters of 10, 25, 50 milligrams/kilogram (mg/kg)). One group of mice received 4 mg/kg chlorproma
spontaneous motor activity was compared to untreated mice. In another test, mice were injected IP with
calamus followed by amphetamine. Calamus significantly reduced spontaneous motor activity in a mann
and 25 mg/kg and significantly reduced amphetamine-induced hyperactivity at 25 mg/kg (Panchal et al,

3.5.1.F Chlorpromazine

1) Interaction Effect: decreased amphetamine and chlorpromazine effectiveness
2) Summary: Amphetamine may inhibit the antipsychotic effects of chlorpromazine (Casey, 1961) and chlorp
amphetamine (Modell & Hussar, 1965; Espelin & Done, 1968).
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Avoid combining amphetamines and chlorpromazine where possible.
7) Probable Mechanism: antagonism

3.5.1.G Citalopram

1) Interaction Effect: an increased risk of serotonin syndrome
2) Summary: Concurrent use of citalopram and dextroamphetamine resulted in symptoms of serotonin syndr
citalopram and dextroamphetamine are used concomitantly, monitor closely for symptoms of serotonin syndr
threatening. If serotonin syndrome develops, discontinue the offending agents and provide supportive care ar
Shannon, 2005).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: A case of serotonin syndrome was reported with coadministration of citalopram and
citalopram and dextroamphetamine are used concomitantly, monitor closely for symptoms of serotonin syndr
(including hyper-reflexia, tremor, muscle rigidity, clonus, peripheral hypertonicity, and shivering), autonomic h
diaphoresis, the presence of bowel sounds, and diarrhea), and mental status changes (including agitation an
threatening. If serotonin syndrome develops, discontinue the offending agents and provide supportive care ar
Shannon, 2005).
7) Probable Mechanism: additive pharmacologic effects
8) Literature Reports
a) A 32-year-old male on dextroamphetamine experienced serotonin syndrome approximately 1 week a
dextroamphetamine 5 mg three times daily for attention deficit hyperactivity disorder. He started 75 mg a
was increased to 150 mg daily. Approximately 2 weeks after starting venlafaxine he experienced markec
admission he was alert and oriented. He experienced diaphoresis, shivering, and fine motor tremor. His
pressure was 142/93 mmHg, and temperature was 37.3 degrees Celsius. No nystagmus or ocular clonus
reactive. He had generalized hypertonia, hyperreflexia, inducible ankle clonus, frequent myoclonic jerkin
oris muscle. No abnormality was shown on ECG, except sinus tachycardia with a baseline tremor. Dextr
discontinued and cyproheptadine (up to a total of 32 mg over 3 hours) was administered. Symptoms res
morning. Dextroamphetamine was restarted 3 days later. Four days later citalopram was started. Approx
symptoms as he did with dextroamphetamine and venlafaxine. Agitation, nausea, diarrhea, and teeth cle
was discontinued. Two doses of cyproheptadine were given and within 2 days he was asymptomatic (Pri

3.5.1.H Clomipramine

1) Interaction Effect: hypertension, other cardiac effects, and CNS stimulation
2) Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been reporte
from the release of norepinephrine (Beaumont, 1973; Raisfeld, 1972). A similar reaction might also occur wit
Acute elevations in blood pressure have been noted (Flemenbaum, 1971a). Some amphetamine-like drugs m
most combinations have not been studied. When amphetamine analogs are being used to treat obesity, it sh
moderate weight gain (Russ & Ackerman, 1988). False positive urine tests for amphetamines have been repo
& Browning, 1993). Caution is advised when concurrent administration of amphetamine-like agents and TCAs
monitored for increased cardiovascular effects (hypertension and dysrhythmias).
3) Severity: moderate
4) Onset: delayed

5) Substantiation: theoretical
6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other sympatho increased cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Inf capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006; Flemenbaum, 1972). Use caution if closely for hypertension and dysrhythmias.
7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission
8) Literature Reports
a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agen amphetamine with TCAs such as desipramine or protriptyline results in sustained increases in d-amphet VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tab 2006).
b) Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism c imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transdermal system, 2006).
c) Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases i effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of comb methylphenidate usually results in the blood pressure returning to normotensive levels; reinstitution of th pressure elevation (Flemenbaum, 1971; Flemenbaum, 1972).
d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine g fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical doubled steady-state plasma levels of desipramine (Price et al, 1990).
e) There have been claims based on uncontrolled studies that a better antidepressant response may oc 1969). However, a systemic review of stimulants in the treatment of depression concluded that although ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated litt appear to be as effective as the conventional antidepressants in primary depression (Satel & Nelson, 19

3.5.1.I Clorgyline
1) Interaction Effect: a hypertensive crisis (headache, hyperpyrexia, hypertension)
2) Summary: Use of dextroamphetamine concomitantly or within 14 days following the administration of a mo (Prod Info Dexedrine(R), 1995c). Amphetamines stimulate the release of norepinephrine, and the use of mon more norepinephrine being made available at nerve receptor sites through inhibition of catecholamine degrad of norepinephrine, which increases sympathetic activity (Gilman et al, 1990d). Coadministration of indirect-ac in severe hypertension and hyperpyrexia (Krisko et al, 1969d; Lloyd & Walker, 1965d; Mason, 1962d; Dally, 1 dextroamphetamine or pemoline in addition to a MAOI was observed during a study of patients with treatmen
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Dextroamphetamine use during or within 14 days following the administration of a m
7) Probable Mechanism: increased norepinephrine availability
8) Literature Reports
a) Severe headaches and hypertensive crises are well-documented in the literature as being associated include cardiac arrhythmias, chest pain, hyperpyrexia, and death (Goldberg, 1964b).
b) In a study of 32 patients with treatment-refractory depression, efficacy of combination therapy with a (pemoline or dextroamphetamine) with a monoamine oxidase inhibitor (MAOI) was studied. Some of the tricyclic antidepressants and lithium, in addition to the study medications. Most of the patients (78%) exp months during coadministration, and 31% of the patients continued treatment after the study. Four of the discontinued the medications due to impotence, orthostatic hypotension, elevated blood pressure, or sha dextroamphetamine and a MAOI discontinued the medications due to memory problems, parkinsonian s patients experienced mood cycling, five to hypomania and one to mania. No patients developed symptor (Fawcett et al, 1991h).

3.5.1.J Clorgyline
1) Interaction Effect: hypertensive crisis (headache, hyperpyrexia, hypertension)
2) Summary: The concurrent use of amphetamine and monoamine oxidase inhibitors (MAOIs) is contraindic the discontinuation of MAOIs before amphetamine therapy is instituted (Prod Info Biphetamine(R), 1995j). An norepinephrine, and the use of MAO inhibitors results in more norepinephrine being made available at nerve catecholamine degradation; concurrent use leads to greater amounts of norepinephrine which increases sym
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: established
6) Clinical Management: Amphetamine use is contraindicated during or within 14 days of administration of m
7) Probable Mechanism: increased norepinephrine availability
8) Literature Reports
a) Severe headaches and hypertensive crises are well-documented in the literature as being associated include cardiac arrhythmias, chest pain, hyperpyrexia, and death (Goldberg, 1964o).

3.5.1.K Desipramine
1) Interaction Effect: hypertension, other cardiac effects, and CNS stimulation
2) Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been reporte

from the release of norepinephrine (Beaumont, 1973; Raisfeld, 1972). A similar reaction might also occur with
Acute elevations in blood pressure have been noted (Flemenbaum, 1971a). Some amphetamine-like drugs m
most combinations have not been studied. When amphetamine analogs are being used to treat obesity, it sho
moderate weight gain (Russ & Ackerman, 1988). False positive urine tests for amphetamines have been repo
& Browning, 1993). Caution is advised when concurrent administration of amphetamine-like agents and TCAs
monitored for increased cardiovascular effects (hypertension and dysrhythmias).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other sympatho
increased cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Inf
capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006; Flemenbaum, 1972). Use caution if
closely for hypertension and dysrhythmias.
7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission
8) Literature Reports
a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agen
amphetamine with TCAs such as desipramine or protriptyline results in sustained increases in d-amphet
VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tab
2006).
b) Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism o
imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transdermal system, 2006).
c) Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases in
effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of comb
methylphenidate usually results in the blood pressure returning to normotensive levels; reinstitution of th
pressure elevation (Flemenbaum, 1971; Flemenbaum, 1972).
d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine g
fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical
doubled steady-state plasma levels of desipramine (Price et al, 1990).
e) There have been claims based on uncontrolled studies that a better antidepressant response may oc
1969). However, a systemic review of stimulants in the treatment of depression concluded that although
ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated litt
appear to be as effective as the conventional antidepressants in primary depression (Satel & Nelson, 19

3.5.1.L Dothiepin

1) Interaction Effect: hypertension, other cardiac effects, and CNS stimulation
2) Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been reported
from the release of norepinephrine (Beaumont, 1973; Raisfeld, 1972). A similar reaction might also occur with
Acute elevations in blood pressure have been noted (Flemenbaum, 1971a). Some amphetamine-like drugs m
most combinations have not been studied. When amphetamine analogs are being used to treat obesity, it sho
moderate weight gain (Russ & Ackerman, 1988). False positive urine tests for amphetamines have been repo
& Browning, 1993). Caution is advised when concurrent administration of amphetamine-like agents and TCAs
monitored for increased cardiovascular effects (hypertension and dysrhythmias).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other sympatho
increased cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Inf
capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006; Flemenbaum, 1972). Use caution if
closely for hypertension and dysrhythmias.
7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission
8) Literature Reports
a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agen
amphetamine with TCAs such as desipramine or protriptyline results in sustained increases in d-amphet
VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tab
2006).
b) Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism o
imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transdermal system, 2006).
c) Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases in
effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of comb
methylphenidate usually results in the blood pressure returning to normotensive levels; reinstitution of th
pressure elevation (Flemenbaum, 1971; Flemenbaum, 1972).
d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine g
fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical
doubled steady-state plasma levels of desipramine (Price et al, 1990).
e) There have been claims based on uncontrolled studies that a better antidepressant response may oc
1969). However, a systemic review of stimulants in the treatment of depression concluded that although
ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated litt
appear to be as effective as the conventional antidepressants in primary depression (Satel & Nelson, 19

3.5.1.M Doxepin

1) Interaction Effect: hypertension, other cardiac effects, and CNS stimulation

2) Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been reporte from the release of norepinephrine (Beaumont, 1973; Raisfeld, 1972). A similar reaction might also occur wit Acute elevations in blood pressure have been noted (Flemenbaum, 1971a). Some amphetamine-like drugs m most combinations have not been studied. When amphetamine analogs are being used to treat obesity, it sh moderate weight gain (Russ & Ackerman, 1988). False positive urine tests for amphetamines have been rep & Browning, 1993). Caution is advised when concurrent administration of amphetamine-like agents and TCA monitored for increased cardiovascular effects (hypertension and dysrhythmias).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other sympatho increased cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Inf capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006; Flemenbaum, 1972). Use caution if closely for hypertension and dysrhythmias.

7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission

8) Literature Reports

a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agen amphetamine with TCAs such as desipramine or protriptyline results in sustained increases in d-amphet VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tab 2006).

b) Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transdermal system, 2006).

c) Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases i effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of comb methylphenidate usually results in the blood pressure returning to normotensive levels; reinstitution of th pressure elevation (Flemenbaum, 1971; Flemenbaum, 1972).

d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical doubled steady-state plasma levels of desipramine (Price et al, 1990).

e) There have been claims based on uncontrolled studies that a better antidepressant response may oc 1969). However, a systemic review of stimulants in the treatment of depression concluded that although ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated litt appear to be as effective as the conventional antidepressants in primary depression (Satel & Nelson, 19

3.5.1.N Furazolidone

1) Interaction Effect: a hypertensive crisis (headache, hyperpyrexia, hypertension)

2) Summary: Furazolidone has significant MAOI activity (Pettinger et al, 1968; Pettinger et al, 1966). Use of days following the administration of a monoamine oxidase inhibitor is contraindicated (Prod Info Dexedrine(R activity such as dextroamphetamine cause the release of norepinephrine, and the use of MAOIs results in m nerve receptor sites through inhibition of catecholamine degradation; concurrent use leads to greater amount sympathetic activity (Gilman et al, 1990e). Coadministration of indirect-acting sympathomimetics and MAOIs & Bermudez, 1982; Cuthbert et al, 1969; Terry et al, 1975; Horler & Wynne, 1965).

3) Severity: contraindicated

4) Onset: rapid

5) Substantiation: theoretical

6) Clinical Management: Dextroamphetamine use during or within 14 days following the administration of a

7) Probable Mechanism: increased norepinephrine availability

3.5.1.O Furazolidone

1) Interaction Effect: hypertensive crisis (headache, hyperpyrexia, hypertension)

2) Summary: Furazolidone has significant MAOI activity (Pettinger et al, 1968a; Pettinger et al, 1966a) and s sympathomimetics. Sympathomimetics with indirect/mixed activity such as amphetamine cause the release results in more norepinephrine being made available at nerve receptor sites through inhibition of catecholami amounts of norepinephrine which increases sympathetic activity (Gilman et al, 1990p). Coadministration of in Inhibitors has resulted in serious hypertension (Smookler & Bermudez, 1982a; Cuthbert et al, 1969a; Terry e

3) Severity: major

4) Onset: rapid

5) Substantiation: theoretical

6) Clinical Management: Concurrent use of amphetamines and an MAO inhibitor, or medications with MAO I

7) Probable Mechanism: increased norepinephrine availability

3.5.1.P Guanethidine

1) Interaction Effect: decreased guanethidine effectiveness

2) Summary: Amphetamines displace guanethidine from the neuron and interfere with neuron uptake. If pos (Ober & Wang, 1973).

3) Severity: moderate
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Monitor patient for signs of decreased guanethidine effectiveness. Adjust the dosag
7) Probable Mechanism: antagonism
8) Literature Reports
a) Concomitant guanethidine and amphetamine administration has been reported to result in antagonisr appears that amphetamine displaces guanethidine from its site of action thereby reversing its hypotensiv 1971).
b) Available data indicate that amphetamine does not alter the orthostatic hypotension seen with guanet systolic blood pressure (Ober & Wang, 1970; Ober & Wang, 1971).

3.5.1.Q Imipramine
1) Interaction Effect: hypertension, other cardiac effects, and CNS stimulation
2) Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been reporte from the release of norepinephrine (Beaumont, 1973; Raisfeld, 1972). A similar reaction might also occur wit Acute elevations in blood pressure have been noted (Flemenbaum, 1971a). Some amphetamine-like drugs n most combinations have not been studied. When amphetamine analogs are being used to treat obesity, it sh moderate weight gain (Russ & Ackerman, 1988). False positive urine tests for amphetamines have been repo & Browning, 1993). Caution is advised when concurrent administration of amphetamine-like agents and TCA monitored for increased cardiovascular effects (hypertension and dysrhythmias).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other sympatho increased cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Inf capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006; Flemenbaum, 1972). Use caution if closely for hypertension and dysrhythmias.
7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission
8) Literature Reports
a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agen amphetamine with TCAs such as desipramine or protriptyline results in sustained increases in d-amphet VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tab 2006).
b) Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism c imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transdermal system, 2006).
c) Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases i effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of comb methylphenidate usually results in the blood pressure returning to normotensive levels; reinstitution of th pressure elevation (Flemenbaum, 1971; Flemenbaum, 1972).
d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine g fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical doubled steady-state plasma levels of desipramine (Price et al, 1990).
e) There have been claims based on uncontrolled studies that a better antidepressant response may oc 1969). However, a systemic review of stimulants in the treatment of depression concluded that although ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated litt appear to be as effective as the conventional antidepressants in primary depression (Satel & Nelson, 19

3.5.1.R Iproniazid
1) Interaction Effect: a hypertensive crisis (headache, hyperpyrexia, hypertension)
2) Summary: Use of dextroamphetamine concomitantly or within 14 days following the administration of a mo (Prod Info Dexedrine(R), 1995h). Amphetamines stimulate the release of norepinephrine, and the use of mor more norepinephrine being made available at nerve receptor sites through inhibition of catecholamine degrad of norepinephrine, which increases sympathetic activity (Gilman et al, 1990i). Coadministration of indirect-act in severe hypertension and hyperpyrexia (Krisko et al, 1969h; Lloyd & Walker, 1965h; Mason, 1962h; Dally, 1 dextroamphetamine or pemoline in addition to a MAOI was observed during a study of patients with treatmen
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Dextroamphetamine use during or within 14 days following the administration of a n
7) Probable Mechanism: increased norepinephrine availability
8) Literature Reports
a) In a study of 32 patients with treatment-refractory depression, efficacy of combination therapy with a c (pemoline or dextroamphetamine) with a monoamine oxidase inhibitor (MAOI) was studied. Some of the tricyclic antidepressants and lithium, in addition to the study medications. Most of the patients (78%) exp months during coadministration, and 31% of the patients continued treatment after the study. Four of the discontinued the medications due to impotence, orthostatic hypotension, elevated blood pressure, or sha dextroamphetamine and a MAOI discontinued the medications due to memory problems, parkinsonian s

patients experienced mood cycling, five to hypomania and one to mania. No patients developed symptor (Fawcett et al, 1991n).

3.5.1.S Iproniazid

1) Interaction Effect: a hypertensive crisis (headache, hyperpyrexia, hypertension)
2) Summary: The concurrent use of amphetamine and monoamine oxidase inhibitors (MAOIs) is contraindic the discontinuation of MAOIs before amphetamine therapy is instituted (Prod Info Biphetamine(R), 1995h). A norepinephrine, and the use of MAO inhibitors results in more norepinephrine being made available at nerve catecholamine degradation; concurrent use leads to greater amounts of norepinephrine which increases sym potential reactions include cardiac arrhythmias, chest pain, hyperpyrexia, and death (Goldberg, 1964m).
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Amphetamine use is contraindicated during or within 14 days of administration of m
7) Probable Mechanism: increased norepinephrine availability

3.5.1.T Isocarboxazid

1) Interaction Effect: a hypertensive crisis (headache, hyperpyrexia, hypertension)
2) Summary: Use of dextroamphetamine concomitantly or within 14 days following the administration of a m (Prod Info Dexedrine(R), 1995a; Prod Info Marplan(R), 1998). Amphetamines cause the release of norepinep norepinephrine being made available at nerve receptor sites through inhibition of catecholamine degradation. norepinephrine, which increases sympathetic activity (Gilman et al, 1990b). Coadministration of indirect-actin severe hypertension and hyperpyrexia (Krisko et al, 1969b; Lloyd & Walker, 1965b; Mason, 1962b; Dally, 196 dextroamphetamine or pemoline in addition to a MAOI was observed during a study of patients with treatmen
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Dextroamphetamine use during or within 14 days following the administration of a r
7) Probable Mechanism: increased norepinephrine availability
8) Literature Reports
a) Severe headaches and hypertensive crises are well-documented in the literature with this combinatio arrhythmias, chest pain, hyperpyrexia, and death (Goldberg, 1964a).
b) In a study of 32 patients with treatment-refractory depression, efficacy of combination therapy with a (pemoline or dextroamphetamine) with a monoamine oxidase inhibitor (MAOI) was studied. Some of the tricyclic antidepressants and lithium, in addition to the study medications. Most of the patients (78%) exp months during coadministration, and 31% of the patients continued treatment after the study. Four of the discontinued the medications due to impotence, orthostatic hypotension, elevated blood pressure, or sha dextroamphetamine and a MAOI discontinued the medications due to memory problems, parkinsonian s patients experienced mood cycling, five to hypomania and one to mania. No patients developed symptor (Fawcett et al, 1991d).

3.5.1.U Isocarboxazid

1) Interaction Effect: hypertensive crisis (headache, hyperpyrexia, hypertension)
2) Summary: The concurrent use of amphetamine and monoamine oxidase inhibitors (MAOIs) is contraindic days should elapse following the discontinuation of MAOIs before amphetamine therapy is instituted (Prod In cause the release of norepinephrine, and the use of MAO inhibitors results in more norepinephrine being ma inhibition of catecholamine degradation; concurrent use leads to greater amounts of norepinephrine which in Goldberg, 1964l).
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: established
6) Clinical Management: Amphetamine use is contraindicated during or within 14 days of administration of m
7) Probable Mechanism: increased norepinephrine availability
8) Literature Reports
a) Severe headaches and hypertensive crises are well-documented in the literature with this combinatio arrhythmias, chest pain, hyperpyrexia, and death (Goldberg, 1964k).
b) In a study of 32 patients with treatment-refractory depression, efficacy of combination therapy with a (pemoline or dextroamphetamine) with a monoamine oxidase inhibitor (MAOI) was studied. Some of the tricyclic antidepressants and lithium, in addition to the study medications. Most of the patients (78%) exp months during coadministration, and 31% of the patients continued treatment after the study. Four of the discontinued the medications due to impotence, orthostatic hypotension, elevated blood pressure, or sha dextroamphetamine and a MAOI discontinued the medications due to memory problems, parkinsonian s patients experienced mood cycling, five to hypomania and one to mania. No patients developed symptor (Fawcett et al, 1991r).

3.5.1.V Lofepramine

1) Interaction Effect: hypertension, other cardiac effects, and CNS stimulation
2) Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been reporte

from the release of norepinephrine (Beaumont, 1973; Raisfeld, 1972). A similar reaction might also occur with
Acute elevations in blood pressure have been noted (Flemenbaum, 1971a). Some amphetamine-like drugs m
most combinations have not been studied. When amphetamine analogs are being used to treat obesity, it sh
moderate weight gain (Russ & Ackerman, 1988). False positive urine tests for amphetamines have been repo
& Browning, 1993). Caution is advised when concurrent administration of amphetamine-like agents and TCAs
monitored for increased cardiovascular effects (hypertension and dysrhythmias).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other sympatho
increased cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Inf
capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006; Flemenbaum, 1972). Use caution if
closely for hypertension and dysrhythmias.
7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission
8) Literature Reports
a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agen
amphetamine with TCAs such as desipramine or protriptyline results in sustained increases in d-amphet
VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tab
2006).
b) Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism o
imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transdermal system, 2006).
c) Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases i
effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of comb
methylphenidate usually results in the blood pressure returning to normotensive levels; reinstitution of th
pressure elevation (Flemenbaum, 1971; Flemenbaum, 1972).
d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine g
fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical
doubled steady-state plasma levels of desipramine (Price et al, 1990).
e) There have been claims based on uncontrolled studies that a better antidepressant response may oc
1969). However, a systemic review of stimulants in the treatment of depression concluded that although
ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated litt
appear to be as effective as the conventional antidepressants in primary depression (Satel & Nelson, 19

3.5.1.W Moclobemide
1) Interaction Effect: a hypertensive crisis (headache, hyperpyrexia, hypertension)
2) Summary: Use of dextroamphetamine concomitantly or within 14 days following the administration of a mo
(Prod Info Dexedrine(R), 1995). Amphetamines stimulate the release of norepinephrine, and the use of monc
more norepinephrine being made available at nerve receptor sites through inhibition of catecholamine degrac
of norepinephrine, which increases sympathetic activity (Gilman et al, 1990). Coadministration of indirect-acti
in severe hypertension and hyperpyrexia (Krisko et al, 1969; Lloyd & Walker, 1965; Mason, 1962; Dally, 1962
dextroamphetamine or pemoline in addition to a MAOI was observed during a study of patients with treatmen
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Dextroamphetamine use during or within 14 days following the administration of a m
7) Probable Mechanism: increased norepinephrine availability
8) Literature Reports
a) In a study of 32 patients with treatment-refractory depression, efficacy of combination therapy with a c
(pemoline or dextroamphetamine) with a monoamine oxidase inhibitor (MAOI) was studied. Some of the
tricyclic antidepressants and lithium, in addition to the study medications. Most of the patients (78%) exp
months during coadministration, and 31% of the patients continued treatment after the study. Four of the
discontinued the medications due to impotence, orthostatic hypotension, elevated blood pressure, or sha
dextroamphetamine and a MAOI discontinued the medications due to memory problems, parkinsonian s
patients experienced mood cycling, five to hypomania and one to mania. No patients developed symptor
(Fawcett et al, 1991).

3.5.1.X Moclobemide
1) Interaction Effect: hypertensive crisis (headache, hyperpyrexia, hypertension)
2) Summary: The concurrent use of amphetamine and monoamine oxidase inhibitors (MAOIs) is contraindic
the discontinuation of MAOIs before amphetamine therapy is instituted (Prod Info Biphetamine(R), 1995). Am
norepinephrine, and the use of MAO inhibitors results in more norepinephrine being made available at nerve
catecholamine degradation; concurrent use leads to greater amounts of norepinephrine which increases sym
potential reactions include cardiac arrhythmias, chest pain, hyperpyrexia, and death (Goldberg, 1964e).
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Amphetamine use is contraindicated during or within 14 days of administration of m
7) Probable Mechanism: increased norepinephrine availability

3.5.1.Y Nialamide

1) Interaction Effect: a hypertensive crisis (headache, hyperpyrexia, hypertension)

2) Summary: Use of dextroamphetamine concomitantly or within 14 days following the administration of a mo (Prod Info Dexedrine(R), 1995j). Amphetamines stimulate the release of norepinephrine, and the use of mono more norepinephrine being made available at nerve receptor sites through inhibition of catecholamine degrad of norepinephrine, which increases sympathetic activity (Gilman et al, 1990k). Coadministration of indirect-ac in severe hypertension and hyperpyrexia (Krisko et al, 1969j; Lloyd & Walker, 1965j; Mason, 1962j; Dally, 19 dextroamphetamine or pemoline in addition to a MAOI was observed during a study of patients with treatmen

3) Severity: contraindicated

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: Dextroamphetamine use during or within 14 days following the administration of a n

7) Probable Mechanism: increased norepinephrine availability

8) Literature Reports

a) In a study of 32 patients with treatment-refractory depression, efficacy of combination therapy with a c (pemoline or dextroamphetamine) with a monoamine oxidase inhibitor (MAOI) was studied. Some of the tricyclic antidepressants and lithium, in addition to the study medications. Most of the patients (78%) exp months during coadministration, and 31% of the patients continued treatment after the study. Four of the discontinued the medications due to impotence, orthostatic hypotension, elevated blood pressure, or sha dextroamphetamine and a MAOI discontinued the medications due to memory problems, parkinsonian s patients experienced mood cycling, five to hypomania and one to mania. No patients developed symptor (Fawcett et al, 1991p).

3.5.1.Z Nialamide

1) Interaction Effect: a hypertensive crisis (headache, hyperpyrexia, hypertension)

2) Summary: The concurrent use of amphetamine and monoamine oxidase inhibitors (MAOIs) is contraindic the discontinuation of MAOIs before amphetamine therapy is instituted (Prod Info Biphetamine(R), 1995b). A norepinephrine, and the use of MAOIs results in more norepinephrine being made available at nerve recepto degradation; concurrent use leads to greater amounts of norepinephrine which increases sympathetic activity indirect-acting sympathomimetics and MAOIs has resulted in severe hypertension and hyperpyrexia (Krisko e 1962k; Dally, 1962k).

3) Severity: contraindicated

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: Amphetamine use is contraindicated during or within 14 days of administration of m

7) Probable Mechanism: increased norepinephrine availability

3.5.1.AA Nortriptyline

1) Interaction Effect: hypertension, other cardiac effects, and CNS stimulation

2) Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been reporte from the release of norepinephrine (Beaumont, 1973; Raisfeld, 1972). A similar reaction might also occur wit Acute elevations in blood pressure have been noted (Flemenbaum, 1971a). Some amphetamine-like drugs m most combinations have not been studied. When amphetamine analogs are being used to treat obesity, it sh moderate weight gain (Russ & Ackerman, 1988). False positive urine tests for amphetamines have been repo & Browning, 1993). Caution is advised when concurrent administration of amphetamine-like agents and TCA monitored for increased cardiovascular effects (hypertension and dysrhythmias).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other sympatho increased cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Inf capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006; Flemenbaum, 1972). Use caution if closely for hypertension and dysrhythmias.

7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission

8) Literature Reports

a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agen amphetamine with TCAs such as desipramine or protriptyline results in sustained increases in d-amphet VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tab 2006).

b) Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism c imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transdermal system, 2006).

c) Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases i effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of comb methylphenidate usually results in the blood pressure returning to normotensive levels; reinstitution of th pressure elevation (Flemenbaum, 1971; Flemenbaum, 1972).

d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine g fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical

doubled steady-state plasma levels of desipramine (Price et al, 1990).
e) There have been claims based on uncontrolled studies that a better antidepressant response may oc
1969). However, a systemic review of stimulants in the treatment of depression concluded that although
ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated litt
appear to be as effective as the conventional antidepressants in primary depression (Satel & Nelson, 19

3.5.1.AB Opipramol

1) Interaction Effect: hypertension, other cardiac effects, and CNS stimulation
2) Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been reporte
from the release of norepinephrine (Beaumont, 1973; Raisfeld, 1972). A similar reaction might also occur wit
Acute elevations in blood pressure have been noted (Flemenbaum, 1971a). Some amphetamine-like drugs m
most combinations have not been studied. When amphetamine analogs are being used to treat obesity, it sh
moderate weight gain (Russ & Ackerman, 1988). False positive urine tests for amphetamines have been repo
& Browning, 1993). Caution is advised when concurrent administration of amphetamine-like agents and TCAs
monitored for increased cardiovascular effects (hypertension and dysrhythmias).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other sympatho
increased cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Inf
capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006; Flemenbaum, 1972). Use caution if
closely for hypertension and dysrhythmias.
7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission
8) Literature Reports
a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agen
amphetamine with TCAs such as desipramine or protriptyline results in sustained increases in d-amphet
VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tab
2006).
b) Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism o
imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transdermal system, 2006).
c) Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases i
effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of comb
methylphenidate usually results in the blood pressure returning to normotensive levels; reinstitution of th
pressure elevation (Flemenbaum, 1971; Flemenbaum, 1972).
d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine g
fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical
doubled steady-state plasma levels of desipramine (Price et al, 1990).
e) There have been claims based on uncontrolled studies that a better antidepressant response may oc
1969). However, a systemic review of stimulants in the treatment of depression concluded that although
ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated litt
appear to be as effective as the conventional antidepressants in primary depression (Satel & Nelson, 19

3.5.1.AC Pargyline

1) Interaction Effect: a hypertensive crisis (headache, hyperpyrexia, hypertension)
2) Summary: Use of dextroamphetamine concomitantly or within 14 days following the administration of a mo
(Prod Info Dexedrine(R), 1995i). Amphetamines cause the release of norepinephrine, and the use of MAOIs
available at nerve receptor sites through inhibition of catecholamine degradation; concurrent use leads to gre
sympathetic activity (Gilman et al, 1990j). Coadministration of indirect-acting sympathomimetics and MAOIs h
hyperpyrexia (Krisko et al, 1969i; Lloyd & Walker, 1965i; Mason, 1962i; Dally, 1962i).
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Dextroamphetamine use during or within 14 days following the administration of a n
7) Probable Mechanism: increased norepinephrine availability

3.5.1.AD Pargyline

1) Interaction Effect: hypertensive crisis (headache, hyperpyrexia, hypertension)
2) Summary: The concurrent use of amphetamine and monoamine oxidase inhibitors (MAOIs) is contraindica
the discontinuation of MAOIs before amphetamine therapy is instituted (Prod Info Biphetamine(R), 1995e). A
norepinephrine, and the use of MAO inhibitors results in more norepinephrine being made available at nerve
catecholamine degradation; concurrent use leads to greater amounts of norepinephrine which increases sym
potential reactions include cardiac arrhythmias, chest pain, hyperpyrexia, and death (Goldberg, 1964i).
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Amphetamine use is contraindicated during or within 14 days of administration of m
7) Probable Mechanism: increased norepinephrine availability

3.5.1.AE Phenelzine

1) Interaction Effect: a hypertensive crisis (headache, hyperpyrexia, hypertension)

2) Summary: Amphetamines cause the release of norepinephrine, and the use of monoamine oxidase inhibit being made available at nerve receptor sites through inhibition of catecholamine degradation. Concurrent use which increases sympathetic activity (Gilman et al, 1990a). Coadministration of indirect-acting sympathomime hypertension and hyperpyrexia (Krisko et al, 1969a; Lloyd & Walker, 1965a; Mason, 1962a; Dally, 1962a). So dextroamphetamine or pemoline in addition to a MAOI was observed during a study of patients with treatmen However, the concurrent use of dextroamphetamine and phenelzine is contraindicated (Prod Info Nardil(R), 1

3) Severity: contraindicated

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: Dextroamphetamine use during or within 14 days following the administration of a n

7) Probable Mechanism: increased norepinephrine availability

8) Literature Reports

a) Severe headaches and hypertensive crises are well-documented in the literature with this combinatio arrhythmias, chest pain, hyperpyrexia, and death (Goldberg, 1964).

b) In a study of 32 patients with treatment-refractory depression, efficacy of combination therapy with a (pemoline or dextroamphetamine) with a monoamine oxidase inhibitor (MAOI) was studied. Some of the tricyclic antidepressants and lithium, in addition to the study medications. Most of the patients (78%) exp months during coadministration, and 31% of the patients continued treatment after the study. Four of the discontinued the medications due to impotence, orthostatic hypotension, elevated blood pressure, or sha dextroamphetamine and a MAOI discontinued the medications due to memory problems, parkinsonian s patients experienced mood cycling, five to hypomania and one to mania. No patients developed symptor (Fawcett et al, 1991b).

3.5.1.AF Phenelzine

1) Interaction Effect: hypertensive crisis (headache, hyperpyrexia, hypertension)

2) Summary: The concurrent use of amphetamine and monoamine oxidase inhibitors (MAOIs) is contraindic the discontinuation of MAOIs before amphetamine therapy is instituted (Prod Info Biphetamine(R), 1995c). An norepinephrine, and the use of MAO inhibitors results in more norepinephrine being made available at nerve catecholamine degradation; concurrent use leads to greater amounts of norepinephrine which increases sym potential reactions include cardiac arrhythmias, chest pain, hyperpyrexia, and death (Goldberg, 1964g).

3) Severity: contraindicated

4) Onset: rapid

5) Substantiation: established

6) Clinical Management: Amphetamine use is contraindicated during or within 14 days of administration of m

7) Probable Mechanism: increased norepinephrine availability

3.5.1.AG Procarbazine

1) Interaction Effect: a hypertensive crisis (headache, hyperpyrexia, hypertension)

2) Summary: Use of dextroamphetamine concomitantly or within 14 days following the administration of a mo (Prod Info Dexedrine(R), 1995f). Amphetamines stimulate the release of norepinephrine, and the use of mon more norepinephrine being made available at nerve receptor sites through inhibition of catecholamine degrad of norepinephrine, which increases sympathetic activity (Gilman et al, 1990g). Coadministration of indirect-ac in severe hypertension and hyperpyrexia (Krisko et al, 1969f; Lloyd & Walker, 1965f; Mason, 1962f; Dally, 19 dextroamphetamine or pemoline in addition to a MAOI was observed during a study of patients with treatmen

3) Severity: contraindicated

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: Dextroamphetamine use during or within 14 days following the administration of a n

7) Probable Mechanism: increased norepinephrine availability

8) Literature Reports

a) In a study of 32 patients with treatment-refractory depression, efficacy of combination therapy with a (pemoline or dextroamphetamine) with a monoamine oxidase inhibitor (MAOI) was studied. Some of the tricyclic antidepressants and lithium, in addition to the study medications. Most of the patients (78%) exp months during coadministration, and 31% of the patients continued treatment after the study. Four of the discontinued the medications due to impotence, orthostatic hypotension, elevated blood pressure, or sha dextroamphetamine and a MAOI discontinued the medications due to memory problems, parkinsonian s patients experienced mood cycling, five to hypomania and one to mania. No patients developed symptor (Fawcett et al, 1991l).

3.5.1.AH Procarbazine

1) Interaction Effect: a hypertensive crisis (headache, hyperpyrexia, hypertension)

2) Summary: The concurrent use of amphetamine and monoamine oxidase inhibitors (MAOIs) is contraindic the discontinuation of MAOIs before amphetamine therapy is instituted (Prod Info Biphetamine(R), 1995d). An norepinephrine, and the use of MAO inhibitors results in more norepinephrine being made available at nerve catecholamine degradation; concurrent use leads to greater amounts of norepinephrine which increases sym potential reactions include cardiac arrhythmias, chest pain, hyperpyrexia, and death (Goldberg, 1964h).

3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Amphetamine use is contraindicated during or within 14 days of administration of m
7) Probable Mechanism: increased norepinephrine availability

3.5.1.AI Protriptyline

1) Interaction Effect: hypertension, other cardiac effects, and CNS stimulation
2) Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been reporte from the release of norepinephrine (Beaumont, 1973; Raisfeld, 1972). A similar reaction might also occur wit Acute elevations in blood pressure have been noted (Flemenbaum, 1971a). Some amphetamine-like drugs m most combinations have not been studied. When amphetamine analogs are being used to treat obesity, it sh moderate weight gain (Russ & Ackerman, 1988). False positive urine tests for amphetamines have been repo & Browning, 1993). Caution is advised when concurrent administration of amphetamine-like agents and TCAs monitored for increased cardiovascular effects (hypertension and dysrhythmias).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other sympatho increased cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Inf capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006; Flemenbaum, 1972). Use caution if closely for hypertension and dysrhythmias.
7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission
8) Literature Reports

a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agen amphetamine with TCAs such as desipramine or protriptyline results in sustained increases in d-amphet VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tab 2006).

b) Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism o imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transdermal system, 2006).

c) Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases i effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of comb methylphenidate usually results in the blood pressure returning to normotensive levels; reinstitution of th pressure elevation (Flemenbaum, 1971; Flemenbaum, 1972).

d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine g fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical doubled steady-state plasma levels of desipramine (Price et al, 1990).

e) There have been claims based on uncontrolled studies that a better antidepressant response may oc 1969). However, a systemic review of stimulants in the treatment of depression concluded that although ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated litt appear to be as effective as the conventional antidepressants in primary depression (Satel & Nelson, 19

3.5.1.AJ Rasagiline

1) Interaction Effect: hypertensive crisis (headache, hyperpyrexia, hypertension) and serotonin syndrome (hy status changes)
2) Summary: Amphetamines cause the release of norepinephrine, and the use of MAO inhibitors results in m nerve receptor sites through inhibition of catecholamine degradation; concurrent use leads to greater amount sympathetic activity (Gilman et al, 1990o). Severe hypertensive reactions have been reported following the a and sympathomimetics. A minimum of 14 days should elapse after discontinuing rasagiline before initiating th oral tablets, 2006).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent use of amphetamine and rasagiline is contraindicated. Allow 14 day rasagiline and the initiation of therapy with amphetamine.
7) Probable Mechanism: increased norepinephrine availability

3.5.1.AK Selegiline

1) Interaction Effect: a hypertensive crisis (headache, hyperpyrexia, hypertension)
2) Summary: Use of dextroamphetamine concomitantly or within 14 days following the administration of a m (Prod Info Dexedrine(R), 1995g). Amphetamines cause the release of norepinephrine, and the use of MAOIs available at nerve receptor sites through inhibition of catecholamine degradation; concurrent use leads to gre sympathetic activity (Gilman et al, 1990h). Coadministration of indirect-acting sympathomimetics and MAOIs hyperpyrexia (Krisko et al, 1969g; Lloyd & Walker, 1965g; Mason, 1962g; Dally, 1962g).
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Dextroamphetamine use during or within 14 days following the administration of a r

7) Probable Mechanism: increased norepinephrine availability
8) Literature Reports
a) Severe headaches and hypertensive crises are well-documented in the literature as being associated include cardiac arrhythmias, chest pain, hyperpyrexia, and death (Goldberg, 1964d).

3.5.1.AL Selegiline
1) Interaction Effect: hypertensive crisis (headache, hyperpyrexia, hypertension) and serotonin syndrome (hy status changes)
2) Summary: The concurrent use of amphetamine and selegiline is contraindicated. At least 14 days should before amphetamine therapy is instituted and a minimum of 7 days should elapse after discontinuing propoxy (Prod Info EMSAM(R) transdermal patch, 2006; Prod Info Biphetamine(R), 1995f). Amphetamines cause the inhibitors results in more norepinephrine being made available at nerve receptor sites through inhibition of ca to greater amounts of norepinephrine which increases sympathetic activity (Gilman et al, 1990o).
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: established
6) Clinical Management: The concurrent use of amphetamine and selegiline is contraindicated. Allow 14 day selegiline and the initiation of therapy with amphetamine or allow a minimum of 7 days to elapse between the initiation of therapy with selegiline.
7) Probable Mechanism: increased norepinephrine availability
8) Literature Reports
a) Severe headaches and hypertensive crises are well-documented in the literature as being associated include cardiac arrhythmias, chest pain, circulatory failure, hyperpyrexia, and death (Goldberg, 1964j).

3.5.1.AM Sibutramine
1) Interaction Effect: an increased risk of hypertension and tachycardia
2) Summary: Sibutramine has been associated with substantial increases in blood pressure and heart rate ir administration of sibutramine and other centrally acting appetite suppressants has not been systematically ev and tachycardia may result. Therefore, the concurrent administration of sibutramine with another centrally act (Prod Info Meridia(R), 1997).
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concomitant administration of sibutramine with other centrally active appetite s
7) Probable Mechanism: additive pharmacologic effects

3.5.1.AN Sodium Bicarbonate
1) Interaction Effect: amphetamine toxicity (hypertension, hyperpyrexia, seizures)
2) Summary: Sodium bicarbonate (ie, greater than 2 grams daily) may alkalinize the urine, increasing the un allowing for increased renal tubular reabsorption. Enhanced effects of amphetamine may occur due to increa al, 1973a).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Lower doses of dextroamphetamine may be required with urinary alkalinizers. Moni
7) Probable Mechanism: decreased dextroamphetamine clearance

3.5.1.AO Sodium Bicarbonate
1) Interaction Effect: amphetamine toxicity (hypertension, hyperpyrexia, seizures)
2) Summary: Sodium bicarbonate (ie, greater than 2 grams daily) may alkalinize the urine, increasing the un allowing for increased renal tubular reabsorption. Enhanced effects of amphetamine may occur due to increa (Anggard et al, 1973b).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Monitor for possible amphetamine toxicity (eg, hypertension, hyperpyrexia, or seizu
7) Probable Mechanism: decreased renal clearance

3.5.1.AP Toloxatone
1) Interaction Effect: a hypertensive crisis (headache, hyperpyrexia, hypertension)
2) Summary: Use of dextroamphetamine concomitantly or within 14 days following the administration of a m (Prod Info Dexedrine(R), 1995b). Amphetamines stimulate the release of norepinephrine, and the use of mor more norepinephrine being made available at nerve receptor sites through inhibition of catecholamine degrad of norepinephrine, which increases sympathetic activity (Gilman et al, 1990c). Coadministration of indirect-ac in severe hypertension and hyperpyrexia (Krisko et al, 1969c; Lloyd & Walker, 1965c; Mason, 1962c; Dally, 1 dextroamphetamine or pemoline in addition to a MAOI was observed during a study of patients with treatmen
3) Severity: contraindicated
4) Onset: rapid

5) Substantiation: probable
6) Clinical Management: Dextroamphetamine use during or within 14 days following the administration of a r
7) Probable Mechanism: increased norepinephrine availability
8) Literature Reports
a) In a study of 32 patients with treatment-refractory depression, efficacy of combination therapy with a (pemoline or dextroamphetamine) with a monoamine oxidase inhibitor (MAOI) was studied. Some of the tricyclic antidepressants and lithium, in addition to the study medications. Most of the patients (78%) exp months during coadministration, and 31% of the patients continued treatment after the study. Four of the discontinued the medications due to impotence, orthostatic hypotension, elevated blood pressure, or sha dextroamphetamine and a MAOI discontinued the medications due to memory problems, parkinsonian s patients experienced mood cycling, five to hypomania and one to mania. No patients developed symptor (Fawcett et al, 1991f).

3.5.1.AQ Toloxatone
1) Interaction Effect: a hypertensive crisis (headache, hyperpyrexia, hypertension)
2) Summary: The concurrent use of amphetamine and monoamine oxidase inhibitors (MAOIs) is contraindic the discontinuation of MAOIs before amphetamine therapy is instituted (Prod Info Biphetamine(R), 1995a). A norepinephrine, and the use of MAO inhibitors results in more norepinephrine being made available at nerve catecholamine degradation; concurrent use leads to greater amounts of norepinephrine which increases sym potential reactions include cardiac arrhythmias, chest pain, hyperpyrexia, and death (Goldberg, 1964f). As a inhibitor, toloxatone may not potentiate the effects of amphetamine to the same frequency, extent, and durati further studies confirm the safety and efficacy of this combined therapy, concomitant use is contraindicated.
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Amphetamine use is contraindicated during or within 14 days of administration of m
7) Probable Mechanism: increased norepinephrine availability

3.5.1.AR Tranylcypromine
1) Interaction Effect: a hypertensive crisis (headache, hyperpyrexia, hypertension)
2) Summary: Use of dextroamphetamine concomitantly or within 14 days following the administration of a mo (Prod Info Dexedrine(R), 1995e). Amphetamines cause the release of norepinephrine, and the use of monoa norepinephrine being made available at nerve receptor sites through inhibition of catecholamine degradation. norepinephrine, which increases sympathetic activity (Gilman et al, 1990f). Coadministration of indirect-acting severe hypertension and hyperpyrexia (Krisko et al, 1969e; Lloyd & Walker, 1965e; Mason, 1962e; Dally, 196 dextroamphetamine or pemoline in addition to a MAOI was observed during a study of patients with treatmen
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Dextroamphetamine use during or within 14 days following the administration of a r
7) Probable Mechanism: increased norepinephrine availability
8) Literature Reports
a) Severe headaches and hypertensive crises are well-documented in the literature with this combinatio arrhythmias, chest pain, hyperpyrexia, and death (Goldberg, 1964c).
b) In a study of 32 patients with treatment-refractory depression, efficacy of combination therapy with a (pemoline or dextroamphetamine) with a monoamine oxidase inhibitor (MAOI) was studied. Some of the tricyclic antidepressants and lithium, in addition to the study medications. Most of the patients (78%) exp months during coadministration, and 31% of the patients continued treatment after the study. Four of the discontinued the medications due to impotence, orthostatic hypotension, elevated blood pressure, or sha dextroamphetamine and a MAOI discontinued the medications due to memory problems, parkinsonian s patients experienced mood cycling, five to hypomania and one to mania. No patients developed symptor (Fawcett et al, 1991j).

3.5.1.AS Tranylcypromine
1) Interaction Effect: hypertensive crisis (headache, hyperpyrexia, hypertension)
2) Summary: The concurrent use of amphetamine and monoamine oxidase inhibitors (MAOIs) is contraindic the discontinuation of MAOIs before amphetamine therapy is instituted (Prod Info Biphetamine(R), 1995i). An norepinephrine, and the use of MAO inhibitors results in more norepinephrine being made available at nerve catecholamine degradation; concurrent use leads to greater amounts of norepinephrine which increases sym potential reactions include cardiac arrhythmias, chest pain, hyperpyrexia, and death (Goldberg, 1964n).
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: established
6) Clinical Management: Amphetamine use is contraindicated during or within 14 days of administration of m
7) Probable Mechanism: increased norepinephrine availability

3.5.1.AT Trimipramine
1) Interaction Effect: hypertension, other cardiac effects, and CNS stimulation

2) Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been reporte from the release of norepinephrine (Beaumont, 1973; Raisfeld, 1972). A similar reaction might also occur wit Acute elevations in blood pressure have been noted (Flemenbaum, 1971a). Some amphetamine-like drugs n most combinations have not been studied. When amphetamine analogs are being used to treat obesity, it sh moderate weight gain (Russ & Ackerman, 1988). False positive urine tests for amphetamines have been repo & Browning, 1993). Caution is advised when concurrent administration of amphetamine-like agents and TCA monitored for increased cardiovascular effects (hypertension and dysrhythmias).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other sympatho increased cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Inf capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006; Flemenbaum, 1972). Use caution if closely for hypertension and dysrhythmias.
7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission
8) Literature Reports
a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agen amphetamine with TCAs such as desipramine or protriptyline results in sustained increases in d-amphet VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tab 2006).
b) Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism o imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transdermal system, 2006).
c) Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases i effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of comb methylphenidate usually results in the blood pressure returning to normotensive levels; reinstitution of th pressure elevation (Flemenbaum, 1971; Flemenbaum, 1972).
d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine g fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical doubled steady-state plasma levels of desipramine (Price et al, 1990).
e) There have been claims based on uncontrolled studies that a better antidepressant response may oc 1969). However, a systemic review of stimulants in the treatment of depression concluded that although ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated litt appear to be as effective as the conventional antidepressants in primary depression (Satel & Nelson, 19

3.5.1.AU Venlafaxine

1) Interaction Effect: an increased risk of serotonin syndrome
2) Summary: Two weeks of concurrent use of dextroamphetamine and venlafaxine resulted in symptoms of s et al, 2002). If dextroamphetamine and venlafaxine are used concomitantly, monitor closely for symptoms of life-threatening. If serotonin syndrome develops, discontinue the offending agents and provide supportive car Shannon, 2005).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: A case of serotonin syndrome was reported with coadministration of dextroamphet dextroamphetamine and venlafaxine are used concomitantly, monitor closely for symptoms of serotonin synd (including hyper-reflexia, tremor, muscle rigidity, clonus, peripheral hypertonicity, and shivering), autonomic h diaphoresis, the presence of bowel sounds, and diarrhea), and mental status changes (including agitation an threatening. If serotonin syndrome develops, discontinue the offending agents and provide supportive care a Shannon, 2005).
7) Probable Mechanism: additive pharmacologic effects
8) Literature Reports
a) A 32-year-old male on dextroamphetamine experienced serotonin syndrome approximately 2 weeks dextroamphetamine 5 mg three times daily for attention deficit hyperactivity disorder. He started 75 mg a was increased to 150 mg daily. Approximately 2 weeks after starting venlafaxine he experienced marked admission he was alert and oriented. He experienced diaphoresis, shivering, and fine motor tremor. His pressure was 142/93 mmHg, and temperature was 37.3 degrees Celsius. No nystagmus or ocular clonus reactive. He had generalized hypertonia, hyperreflexia, inducible ankle clonus, frequent myoclonic jerking oris muscle. No abnormality was shown on ECG, except sinus tachycardia with a baseline tremor. Dextr discontinued and cyproheptadine (up to a total of 32 mg over 3 hours) was administered. Symptoms res morning. Dextroamphetamine was restarted 3 days later. Four days later citalopram was started. Approx symptoms as he did with dextroamphetamine and venlafaxine. Agitation, nausea, diarrhea, and teeth cle was discontinued. Two doses of cyproheptadine were given and within 2 days he was asymptomatic (Pri

3.5.2 Drug-Food Combinations

3.5.2.A Acidic Food

1) Interaction Effect: altered serum concentrations
2) Summary: Maximal absorption of amphetamines occurs in the alkaline environment of the small intestine

taken with amphetamines may impair gastrointestinal absorption. Foods that increase urinary pH may decrea reabsorption of the amphetamine and increased serum levels. Foods that acidify urine increase renal clearan levels (Prod Info Dexedrine(R), 1998; Beckett & Rowland, 1965).
3) Severity: minor
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Dextroamphetamine should not be administered with acidic foods, such as citric fru
7) Probable Mechanism: pH-dependent absorption and clearance

4.0 Clinical Applications

Monitoring Parameters

Therapeutic Uses

4.1 Monitoring Parameters

A) Therapeutic
1) Physical Findings
a) Attention Deficit Hyperactivity Disorder (ADHD)
1) Improvement in mental and behavioral symptoms, including inappropriate inattention, impulsivity, hyp
b) Narcolepsy
1) Decreased frequency of narcoleptic attacks.
B) Toxic
1) Physical Findings
a) It is not conclusive whether chronic use of stimulants in children may be associated with suppression of gr during treatment (Prod Info Adderall (R) XR, 2005).
1) Attention Deficit Hyperactivity Disorder (ADHD)
a) The American Academy of Pediatrics (AAP) does not recommend the routine use of electrocardi cardiology evaluations (which were previously recommended by the American Heart Association (AH conditions that might place the child at risk for sudden cardiac death) before initiating stimulant thera ADHD in most children. The APA cited specific reasons for changing the recommendation including between stimulant drugs used to treat ADHD and sudden cardiac death (SCD), the frequency of suc stimulant drugs is not higher than that in the general population of children, and lack of cost-effective evaluation by pediatric cardiologist (Perrin et al, 2008).
b) Based on the American Academy of Pediatrics (AAP) and the American Heart Association (AHA monitoring recommendations have been established to assist clinicians in the evaluation of children amphetamine/dextroamphetamine combinations, for ADHD (Perrin et al, 2008; Vetter et al, 2008):
- Conduct a thorough examination prior to initiating amphetamine/dextroamphetamine combinat attention should be given to symptoms indicative of a cardiac condition, including palpitations, r
- Obtain a complete family and patient history for conditions associated with SCD, and determir the-counter medications.
- Conduct a complete physical evaluation of the patient for hypertension, cardiac murmurs, phys and signs of irregular cardiac rhythms.
- Perform further evaluation if family history, patient history or physical exam is suggestive of ca visits, and if indicated, consult pediatric cardiologist .
- Continue to assess the patient for cardiac symptoms and any changes in family history at follo
- Blood pressure and heart rate should be evaluated at baseline, during routine follow-up within 12 months. Increases in blood pressure and heart rate have been reported with stimulant use.

4.5 Therapeutic Uses

Attention deficit hyperactivity disorder

Narcolepsy

4.5.A Attention deficit hyperactivity disorder

FDA Labeled Indication
1) Overview
FDA Approval: Adult, yes; Pediatric, yes (immediate-release, age 3 years and older; extended-release, a
Efficacy: Adult, Evidence favors efficacy; Pediatric, Evidence favors efficacy
Recommendation: Adult, Class IIb; Pediatric, Class IIb
Strength of Evidence: Adult, Category B; Pediatric, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:
Amphetamine aspartate/amphetamine sulfate/dextroamphetamine saccharate/dextroamphetamine sulfa
treatment of attention deficit hyperactivity disorder (ADHD) (Prod Info ADDERALL XR(R) extended-relea

3) Adult:

a) Adderall(R), a mixture of L- and D-amphetamine, was effective in some cases of adult attention deficit hyp study (n=24). Dosing of Adderall was initiated at 5 milligrams (mg) twice daily orally and titrated according to a positive response was shown by 54% of patients (13 of 24) using the Clinical Global Impression scale to de much improved and 3 (12%) were much improved. Two patients (8%) were minimally improved. Among thes 10.33 mg or 0.14 mg/kg/day, and side effects were decreased appetite, insomnia, and sedation. Overall, 9 pa of 7 with comorbid anxiety experienced immediate acute anxiety (diaphoresis, tremor, shortness of breath, ar after day 1. Excluding those 4, mean score on the Copeland Symptom Checklist for adult ADD decreased fro ADD scales dropped from 76.75 to 50.85 (p less than 0.001 and 0.0001, respectively) (Horrigan and Barnhill,

4) Pediatric:

a) Extended-Release

1) In a double-blind, randomized, placebo-controlled, parallel-group study, extended release Adderall (A treatment of attention deficit hyperactivity disorder (ADHD) in children ages 6 to 12 years old. Patients (n Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria for hyperactive-impulsive or combined subt placebo (n=210), or 10 milligrams per day (mg/day; n=129), 20 mg/day (n=121), or 30 mg/day (n=124) A for a 1-week washout period. Once active treatment began, a dose escalation regimen was used for the 10 mg once daily was administered to all Adderall XR(TM) groups and increased each week by 10 mg p Efficacy was evaluated using the Conners Global Index Scale (teacher's version, CGIS-T or parent's ver Adderall XR (TM) groups showed significant improvement in CGIS scores compared to baseline and pla scores were 10.6, 11.5, 12.1, and 11.2 for the placebo, 10 mg/d, 20 mg/d, and 30 mg/day groups, respe study endpoint was -0.9, -5.3, -6.0, and -6.4, respectively. Adverse events that occurred more frequently group were anorexia (21.9% in Adderall XR(TM) groups versus 1.9% in placebo), insomnia (16.6% versu emotional lability (8.6% versus 1.9%), vomiting (7.2% versus 3.8%), and nervousness (5.6% versus 1.9% withdrawn from the study due to adverse events (Biederman et al, 2002).

b) Immediate-Release

1) Seven-day courses of oral Adderall(R) (a mixture of AMPHETAMINE AND DEXTROAMPHETAMINE (mg/kg) and 0.3 mg/kg, both twice daily, were found to be an efficacious treatment for attention-deficit/hy adolescents 5 to 18 years of age, based on a randomized, double-blind, crossover study. A 54% respons criteria requiring positive assessments seen by both parent and teacher, 81% were seen to respond as r to teachers. Overall, 137 of 154 subjects (89%) responded based on either parent or teacher positive ev by parent and teacher), 60% of children 5 to 7 years of age responded; 71% of those 8 to 9 years respor older. Side effects of Adderall(R) included decreased appetite, stomachache, insomnia, and headache; d prominent with the 0.3 mg/kg dose. According to the study design, subjects were randomized to start on 7-day treatment periods (Adderall(R), placebo, Adderall(R), placebo; or vice versa starting with placebo). hours, a washout period between the 7-day treatment periods was not thought to be necessary. The low dose, with a maximum Adderall(R) dose of 40 mg/day (Ahmann et al, 2001).

4.5.B Narcolepsy

FDA Labeled Indication

1) Overview

FDA Approval: Adult, yes (immediate release formulation only); Pediatric, yes ((6 years and older) imme
Efficacy: Adult, Evidence favors efficacy; Pediatric, Evidence favors efficacy
Recommendation: Adult, Class IIb; Pediatric, Class IIb
Strength of Evidence: Adult, Category B; Pediatric, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:
Amphetamine aspartate/amphetamine sulfate/dextroamphetamine saccharate/dextroamphetamine sulfa
treatment of narcolepsy (Prod Info ADDERALL XR(R) extended-release oral capsules, 2006)

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Last Modified: June 18, 2009

DRUGDEX® Evaluations

CLOMIPRAMINE

0.0 Overview

1) Class
- **a)** This drug is a member of the following class(es):
  Antidepressant
  Antidepressant, Tricyclic
  Central Nervous System Agent

2) Dosing Information
- **a)** Clomipramine Hydrochloride
  - **1)** Adult
    - **a)** Delusional disorder
      - **1)** initial, 25 mg/day ORALLY, may increase dosage to 100 mg/day during the first 2 weeks (MAX dose 250 mg/day, mean dose 140 mg/day)
    - **b)** Depression
      - **1)** initial, 75 mg/day ORALLY (3 divided doses); may increase dosage slowly as needed and tolerated to a range of 100-250 mg/day (3 divided doses)
    - **c)** Obsessive-compulsive disorder
      - **1)** initial, 25 mg/day ORALLY, may increase dosage to 100 mg per day during the first 2 weeks (MAX dose 250 mg/day outpatients, 300 mg/day inpatients)
    - **d)** Panic disorder
      - **1)** 25-75 mg/day ORALLY
  - **2)** Pediatric
    - **a)** safety and effectiveness in children up to 10 years of age have not been established
      - **1)** Depression
        - **a)** 20-30 mg/day ORALLY; may increase dosage by 10 mg/day at 4-5 day intervals as needed and tolerated
      - **2)** Obsessive-compulsive disorder
        - **a)** 10 yrs and older, initial, 25 mg/day ORALLY, may increase the dosage as needed and tolerated up to 100 mg/day; MAX dose 200 mg/day OR 3 mg/kg of body weight (whichever is less)

3) Contraindications
- **a)** Clomipramine Hydrochloride
  1) coadministration with an MAOI or use within 14 days of discontinuing an MAOI; may cause serious reactions (eg, hyperpyretic crisis, seizures, coma, death) (Prod Info ANAFRANIL(R) oral capsules, 2007)
  2) hypersensitivity to clomipramine hydrochloride or other tricyclic antidepressant (Prod Info ANAFRANIL(R) oral capsules, 2007)
  3) myocardial infarction, during the acute recovery period (Prod Info ANAFRANIL(R) oral capsules, 2007)

4) Serious Adverse Effects
- **a)** Clomipramine Hydrochloride
  1) Agranulocytosis
  2) Body temperature above normal
  3) Depression, worsening
  4) Hepatotoxicity
  5) Hyperglycemia
  6) Leukopenia
  7) Myocardial infarction
  8) Orthostatic hypotension
  9) Pancytopenia
  10) Seizure
  11) Suicidal thoughts
  12) Suicide
  13) Thrombocytopenia

5) Clinical Applications
- **a)** Clomipramine Hydrochloride
  - **1)** FDA Approved Indications
    - **a)** Obsessive-compulsive disorder
  - **2)** Non-FDA Approved Indications
    - **a)** Delusional disorder
    - **b)** Depression
    - **c)** Panic disorder

1.0 Dosing Information

Drug Properties

Adult Dosage

Pediatric Dosage

1.1 Drug Properties

A) Information on specific products and dosage forms can be obtained by referring to the Tradename List (Product Index)

B) Synonyms

Chlorimipramine
Chlorimipramine Hydrochloride
Clomipramine
Clomipramine HCl
Clomipramine Hydrochloride

C) Physicochemical Properties

1) Molecular Weight

a) Clomipramine hydrochloride: 351.3 (Prod Info Anafranil(R), 2001)

2) pH

a) Clomipramine hydrochloride: pH of a 10% solution in water is 3.5 to 5 (Sweetman, 2004)

3) Solubility

a) Clomipramine hydrochloride: Freely soluble in water, in methanol, and in methylene chloride; insoluble in ethyl ether and in hexane (Prod Info Anafranil(R), 2001)

1.3 Adult Dosage

1.3.1 Normal Dosage

Clomipramine

Clomipramine Hydrochloride

1.3.1.A Clomipramine

1.3.1.A.1 Cataplexy - Narcolepsy

See Drug Consult reference: NARCOLEPSY AND CATAPLEXY - DRUG THERAPY

1.3.1.B Clomipramine Hydrochloride

Intravenous route

Oral route

1.3.1.B.1 Intravenous route

a) In a study evaluating the effects of intravenous pulse loading of clomipramine in obsessive-compulsive disorder, 7 patients were given clomipramine 150 milligrams (mg) intravenously, over 90 minutes. The next day, clomipramine 200 mg intravenously, was given. The doses were preceded by trimethobenzamide hydrochloride 250 mg to reduce nausea. Oral clomipramine 150 mg was started 4.5 days after the second dose. This was increased by 25 mg every fourth day to 250 mg/day. Six out of 7 patients had responded before the oral dosing was started (Koran et al, 1997).

b) One worker has commented on his experience in treating over 60 patients with severe OCD with intravenous clomipramine (CMI) (Warneke, 1992). These patients had not responded to oral CMI and approximately 2/3 showed marked reduction in Y-BOCS scores. As much as 350 milligrams was used in a single infusion and induration and inflammation were the only reason (2 cases) that infusions had to be stopped. Duration of treatment was 14 days (one infusion each day). Patients were then changed to oral treatment.

c) A 62-year-old patient with a long history of obsessive compulsive disorder, whose symptoms were not adequately controlled with oral clomipramine (CMI) was treated with intravenous (IV) CMI. A daily dose of 25 milligrams in 500 milliliters of a dextrose-saline mixture (infused over 2 hours) was given followed by increases to 250 milligrams. Intravenous CMI was stopped after 10 days and replaced with oral CMI 250 milligrams. The patient took oral treatment for 18 months at which time the dose was

gradually decreased and the drug was eventually stopped.

1.3.1.B.2 Oral route

a) Treatment for obsessive-compulsive disorder with clomipramine should be initiated at a dosage of 25 milligrams daily and gradually increased, as tolerated, to approximately 100 milligrams during the first 2 weeks. During initial titration, clomipramine should be given in divided doses with meals to reduce gastrointestinal side effects. Thereafter, the dosage may be increased gradually over the next several weeks, up to a maximum of 250 milligrams daily. After titration, the total daily dose may be given once daily at bedtime to minimize daytime sedation (Prod Info Anafranil(R), 2001b).

b) When clomipramine is administered concomitantly with another drug that inhibits cytochrome P450 2D6, the dose of clomipramine or of the other drug may need to be lower than that usually prescribed. And, when either drug is withdrawn, the dose of the other may need to be increased (Prod Info Anafranil (R), 2001b).

c) During clinical trials for the treatment of OBSESSIVE-COMPULSIVE DISORDER, the usual therapeutic oral dose of clomipramine ranged from 75 to 300 milligrams/day in divided doses (Yaryura-Tobias et al, 1976; Marks et al, 1980a; Ananth et al, 1981a). Therapy usually starts at 25 milligrams at night with gradual increases over 4 weeks as tolerated.

d) The usual therapeutic oral dose of clomipramine for DEPRESSION ranges from 100 to 250 milligrams/day in 3 divided doses although daily doses as low as 50 or 75 milligrams have also been used (De Wilde et al, 1983a; Dimitriou et al, 1984a; Dunbar et al, 1985a; Larsen et al, 1984).

e) Clomipramine in low doses (25 to 75 milligrams orally per day) was reported effective in the treatment of panic ANXIETY and AGORAPHOBIA in outpatients in an uncontrolled clinical trial (Gloger et al, 1989). There was a trend towards the need for higher doses in agoraphobia (mean, 56 milligrams) as opposed to panic disorder (mean, 40 milligrams). Low-dose clomipramine 60 mg/day was as effective as high-dose clomipramine 150 mg/day in the treatment of phobias, anxiety, and panic attacks in a multi-center study (Caillard et al, 1999).

1.4 Pediatric Dosage

1.4.1 Normal Dosage

Clomipramine

Clomipramine Hydrochloride

1.4.1.A Clomipramine

1.4.1.A.1 Anorexia nervosa

See Drug Consult reference: ANOREXIA NERVOSA - DRUG THERAPY

1.4.1.B Clomipramine Hydrochloride

Intravenous route

Oral route

1.4.1.B.1 Intravenous route

a) A single pulse dose of clomipramine 200 milligrams intravenously has been administered to depressed adolescents (14-to 18-years-old), demonstrating dramatic and rapid reduction in depressive symptoms at day 6 post-clomipramine infusion as compared to placebo. The clomipramine effect may persist for up to 8 weeks in some patients (Sallee et al, 1997).

b) The use of intravenous clomipramine (CMI) in a 15-year-old female patient with obsessive compulsive disorder was reported (Warneke, 1985). After oral treatment with 200 milligrams of CMI plus 4 grams of L-tryptophan at bedtime for 3 weeks and no response, the patient was started on intravenous CMI. Doses ranged from 200 to 300 milligrams in 8 of 14 infusions. Dramatic response was seen, with marked reduction of obsessional thoughts and some reduction of compulsive rituals.

1.4.1.B.2 Oral route

a) As with adults, the starting dose for treating OBSESSIVE-COMPULSIVE DISORDER with clomipramine is 25 milligrams daily and should be gradually increased during the first 2 weeks, as tolerated, up to a daily maximum of 3 milligrams/kilogram or 100 milligrams, whichever is smaller. These initial doses should be divided and taken with meals to reduce gastrointestinal side effects. Thereafter, the dosage may be increased gradually over the next several weeks up to a daily maximum

of 3 milligrams/kilogram or 200 milligrams, whichever is smaller. After titration, the total daily dose may be given once daily at bedtime to minimize daytime sedation (Prod Info Anafranil(R), 2001b).
b) Oral clomipramine in the range of 100 to 200 milligrams/day in divided doses was successful in treating obsessive compulsive disorder in children aged 10 to 18 years (Flament et al, 1985a). The dose was started at 50 milligrams/day and was gradually increased to a maximum of 200 milligrams/day if tolerated.

2.0 Pharmacokinetics

Onset and Duration

Drug Concentration Levels

ADME

2.1 Onset and Duration

A) Onset
- **1)** Initial Response
  - **a)** Obsessive-compulsive disorder, oral: 4 to 10 weeks (Marks et al, 1980b).
  - **b)** Obsessive-compulsive disorder, intravenous: 5.5 days (Koran et al, 1997a).
  - **c)** Depression, oral: 2 weeks (Wolfersdorf et al, 1987a).

2.2 Drug Concentration Levels

A) Therapeutic Drug Concentration
- **1)** Obsessive-compulsive disorder, 100 to 250 ng/mL (clomipramine) plus 230 to 550 ng/mL (desmethylclomipramine) (Insel et al, 1983a; Stern et al, 1980a).
- **2)** Depression, greater than 160 to 200 ng/mL clomipramine plus desmethylclomipramine (Faravelli et al, 1984).
  - **a)** In a dose-effect study, there was a pronounced inter-patient variability in response. The authors attributed this to a variability in clomipramine steady state kinetics, clomipramine dose-dependent kinetics, and genetic polymorphism related to CYP2D6 (Anon, 1999).

B) Time to Peak Concentration
- **1)** Oral: 2 to 6 hours (mean, 4.7 hours) (Prod Info Anafranil(R), 2001a; Della Corte et al, 1993).

C) Area Under the Curve
- **1)** 600 ng/ml (0.7 mg/kg) (Della Corte et al, 1993).

2.3 ADME

Absorption

Distribution

Metabolism

Excretion

Elimination Half-life

2.3.1 Absorption

A) Bioavailability
- **1)** Oral: 20% to 78% (Kuss & Jungkunz, 1986; de Cuyper et al, 1981).

B) Effects of Food
- **1)** None (Prod Info Anafranil(R), 2001a).

2.3.2 Distribution

A) Distribution Sites
- **1)** Protein Binding
  - **a)** 97% (Prod Info Anafranil(R), 2001a; Reynolds, 1988).
    - **1)** Principally bound to albumin (Prod Info Anafranil(R), 2001a).
- **2)** OTHER DISTRIBUTION SITES
  - **a)** Cerebrospinal fluid (CSF), CSF:plasma ratio is 2.6 (Prod Info Anafranil(R), 2001a).

B) Distribution Kinetics

1) Volume of Distribution
a) 12 L/kg (range, 7 to 20 L/kg) (Nagy & Johansson, 1977).

2.3.3 Metabolism
A) Metabolism Sites and Kinetics
1) Liver (Nagy & Johansson, 1977).
a) Extensive first-pass effect (Nagy & Johansson, 1977).
b) The metabolism of CLOMIPRAMINE and desmethylclomipramine may be capacity limited (Prod Info Anafranil(R), 2001a).
B) Metabolites
1) Desmethylclomipramine, active (Nagy & Johansson, 1977).
a) Responders have a trend towards lower plasma CLOMIPRAMINE to desmethylclomipramine ratios (Mavissakalian et al, 1990).
2) 8-OH clomipramine and 8-OH desmethylclomipramine (Insel et al, 1983a).

2.3.4 Excretion
A) Kidney
1) Renal Excretion (%)
a) 51% to 60% recovered in the urine (Prod Info Anafranil(R), 2001a).
B) Total Body Clearance
1) 12.7 TO 56.5 L/hr (Shimoda et al, 1999).
a) In an interethnic study comparing the clearance of clomipramine between Japanese and Swedish patients, Japanese patients had a much lower clearance (12.7 L/hr) than the Swedish patients (62.7 L/hr) (Shimoda et al, 1999).
C) Other
1) OTHER EXCRETION
a) Feces, 24% to 32% recovered in the feces (Prod Info Anafranil(R), 2001a).

2.3.5 Elimination Half-life
A) Parent Compound
1) ELIMINATION HALF-LIFE
a) 19 hours to 37 hours (mean, 32 hours) (Prod Info Anafranil(R), 2001a; Dawling et al, 1980).
1) The half-life of CLOMIPRAMINE may be lengthened at higher doses (200 to 250 mg/day) (Prod Info Anafranil(R), 2001a).
B) Metabolites
1) Desmethylclomipramine, 54 to 77 hours (mean, 69 hours) (Prod Info Anafranil(R), 2001a).

3.0 Cautions

Contraindications

Precautions

Adverse Reactions

Teratogenicity/Effects in Pregnancy/Breastfeeding

Drug Interactions

3.0.A Black Box WARNING
1) Clomipramine Hydrochloride
a) Oral (Capsule)
Suicidality and Antidepressant Drugs
Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of clomipramine hydrochloride or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Clomipramine hydrochloride is not approved for use in pediatric patients except for patients with obsessive compulsive disorder (OCD) (Prod Info ANAFRANIL(R) oral capsules, 2007).

3.1 Contraindications

A) Clomipramine Hydrochloride

1) coadministration with an MAOI or use within 14 days of discontinuing an MAOI; may cause serious reactions (eg, hyperpyretic crisis, seizures, coma, death) (Prod Info ANAFRANIL(R) oral capsules, 2007)

2) hypersensitivity to clomipramine hydrochloride or other tricyclic antidepressant (Prod Info ANAFRANIL(R) oral capsules, 2007)

3) myocardial infarction, during the acute recovery period (Prod Info ANAFRANIL(R) oral capsules, 2007)

3.2 Precautions

A) Clomipramine Hydrochloride

1) suicidal ideation and behavior or worsening depression; increased risk, particularly in children, adolescents, and young adults during the first few months of therapy or following changes in dosage (Prod Info ANAFRANIL (R) oral capsules, 2007)

2) abrupt withdrawal; serious discontinuation symptoms have been reported (Prod Info ANAFRANIL(R) oral capsules, 2007)

3) adrenal medulla tumor (eg, pheochromocytoma, neuroblastoma); may cause hypertensive crisis (Prod Info ANAFRANIL(R) oral capsules, 2007)

4) bipolar disorder; increased risk of precipitation of a mixed/manic episode with only antidepressant treatment (Prod Info ANAFRANIL(R) oral capsules, 2007)

5) cardiovascular disease; may increase risk of ECG changes (Prod Info ANAFRANIL(R) oral capsules, 2007)

6) concurrent use with electroshock therapy; may increase hazards of electroshock therapy (Prod Info ANAFRANIL(R) oral capsules, 2007)

7) condition that may lower the seizure threshold (ie, alcoholism, brain damage, concomitant use of other drugs that lower seizure threshold); increased risk of seizure (Prod Info ANAFRANIL(R) oral capsules, 2007)

8) glaucoma, history of narrow-angle; exacerbation of condition due to cholinergic antagonism (Prod Info ANAFRANIL(R) oral capsules, 2007)

9) hyperthyroidism or concurrent use of thyroid medications; may cause cardiac toxicity (Prod Info ANAFRANIL (R) oral capsules, 2007)

10) intraocular pressure, increased; exacerbation of condition due to cholinergic antagonism (Prod Info ANAFRANIL(R) oral capsules, 2007)

11) liver disease; risk of hepatotoxicity (Prod Info ANAFRANIL(R) oral capsules, 2007)

12) mania/hypomania; risk of disease activation (Prod Info ANAFRANIL(R) oral capsules, 2007)

13) neuroleptic malignant syndrome; has been reported with clomipramine therapy (Prod Info ANAFRANIL(R) oral capsules, 2007)

14) renal function, significantly impaired (Prod Info ANAFRANIL(R) oral capsules, 2007)

15) schizophrenia, unrecognized; may precipitate psychosis (Prod Info ANAFRANIL(R) oral capsules, 2007)

16) seizures, history; may lower the convulsive threshold (Prod Info ANAFRANIL(R) oral capsules, 2007)

17) surgery, elective with general anesthetics (Prod Info ANAFRANIL(R) oral capsules, 2007)

18) urinary retention, history of; exacerbation of condition due to cholinergic antagonism (Prod Info ANAFRANIL (R) oral capsules, 2007)

3.3 Adverse Reactions

Cardiovascular Effects

Dermatologic Effects

Endocrine/Metabolic Effects

Gastrointestinal Effects

Hematologic Effects

Hepatic Effects

Musculoskeletal Effects

Neurologic Effects

Psychiatric Effects

Renal Effects

Reproductive Effects

Other

3.3.1 Cardiovascular Effects

3.3.1.A Clomipramine Hydrochloride

Cardiac arrest

Hypotension

3.3.1.A.1 Cardiac arrest

a) According to one study, the use of higher-dose tricyclic antidepressants (TCAs) was associated with an increased risk of SUDDEN CARDIAC DEATH, while lower doses did not increase this risk. In a cohort study including 481,744 persons and 1487 cases of sudden cardiac death occurring in a community setting, researchers found that compared to non-use, the current use of TCAs was associated with a dose-related increase in the risk of sudden cardiac death. For doses lower than 100 milligrams (mg) (amitriptyline or its equivalent), the rate ratio was 0.97 (95% CI, 0.72 to 1.29), however this increased to 2.53 (95% CI, 1.04 to 6.12) for doses of 300 mg or more (p=0.03, test for dose-response). In the entire cohort, users of TCAs in doses of 100 mg or higher (amitriptyline or its equivalent) had a 41% increased rate of sudden cardiac death (rate ratio, 1.41; 95% CI, 1.02 to 1.95). However, TCAs taken in doses of less than 100 mg (amitriptyline or its equivalent) were not associated with an increased risk of sudden cardiac death in the entire cohort or in any subgroups, including persons with treated cardiovascular disease. Use of selective serotonin reuptake inhibitors was not associated with an increased risk of sudden cardiac death (rate ratio, 0.95; 95% CI, 0.42 to 2.15) (Ray et al, 2004).

b) In a case report, a 31-year-old severely depressed woman developed severe epileptic convulsions followed by cardiac ARREST during a 300 mg infusion of parenteral clomipramine (Singh, 1972a). The patient had been started on parenteral clomipramine 25 mg/day which was slowly increased to 250 mg/day over 14 days. The cardiac arrest occurred on day 15 of treatment. She was resuscitated by external cardiac massage; EKG showed slight T wave flattening. One week later the patient restarted on oral clomipramine and was discharged 6 weeks later with no further cardiac problems.

3.3.1.A.2 Hypotension

a) Orthostatic hypotension worsened in both younger (less than 55 years of age, n=74) and older (55 to 70 years of age, n=28) people after taking clomipramine 150 milligrams per day for 2 weeks, but the fall in blood pressure was more severe in the older population (Stage et al, 2002).

b) A 57-year-old man who had been taking clomipramine 150 milligrams at bedtime for 2 years developed hypotension when he received general anesthesia in preparation for mitral valve repair. Anesthesia was induced with sodium thiopental and fentanyl and maintained with isoflurane. Forty-five minutes after induction of anesthesia, blood pressure and vascular resistance declined. Blood pressure was unresponsive to ephedrine, phenylephrine, and dopamine. After skin incision and sternotomy, systolic blood pressure decreased precipitously, to 55 millimeters of mercury. Despite multiple boluses of ephedrine and an infusion of norepinephrine, the patient developed third-degree atrioventricular block. Cardiopulmonary bypass was begun, and the surgery proceeded. The dosage of norepinephrine was increased before weaning from cardiopulmonary bypass. Prior to surgery, the patient had experienced postural hypotension, which was attributed to clomipramine. Therefore, a presumptive diagnosis of clomipramine-induced hypotension precipitated by anesthesia was made, and clomipramine was withheld. The patient was gradually weaned from norepinephrine (Malan et al, 2001).

c) Hypotension, TACHYCARDIA, and DIZZINESS have been reported at therapeutic doses of oral clomipramine (75 to 300 mg/day) (Dunbar et al, 1985a; De Wilde et al, 1983a; Pinder et al, 1980a). Most cases were mild and did not require any treatment.

3.3.2 Dermatologic Effects

3.3.2.A Clomipramine Hydrochloride

Diaphoresis

Discoloration of skin

3.3.2.A.1 Diaphoresis

a) Increased SWEATING was experienced by significantly more patients on clomipramine 50 to 300 mg/day than those on placebo during clinical trials of agoraphobic and obsessive compulsive patients (Johnston et al, 1988; Stern et al, 1980).

3.3.2.A.2 Discoloration of skin

a) A case of pseudocyanotic PIGMENTATION has occurred with clomipramine (Tunca et al, 1989).

3.3.3 Endocrine/Metabolic Effects

3.3.3.A Clomipramine Hydrochloride

Body temperature above normal

Galactorrhea

Hyperglycemia

Syndrome of inappropriate antidiuretic hormone secretion

Weight change finding

3.3.3.A.1 Body temperature above normal

a) More than 30 cases of hyperthemia have been associated with clomipramine. Most instances occurred when clomipramine was used in combination with other drugs. NEUROLEPTIC MALIGNANT SYNDROME has developed when clomipramine was administered concomitantly with a neuroleptic agent (Prod Info Anafranil(R), 2001b).

b) Sixteen of 38 inpatients with DSM-IIIR major depression treated with clomipramine alone developed at least one sympton of the serotonin syndrome in a prospective study (Lejoyeux et al, 1993). This syndrome includes confusion, agitation, myoclonus, diaphoresis, tremor, and diarrhea. In 14 cases, tremor and myoclonus occurred simultaneously and 10 patients presented tremor, myoclonus, diaphoresis, and shivering. With the exception of 2 patients, symptoms were transient, lasted less than 1 week, and resolved with treatment.

c) Two cases of clomipramine-moclobemide overdose resulted in fatal serotonin syndrome (Neuvonen et al, 1993j). A 23-year-old male and 19-year-old female ingested 1000-1500 mg moclobemide, an MAO-A selective inhibitor and 225 to 500 mg clomipramine in order to "get high". Two to 3 hours later they were euphoric, but developed extreme tremor within the next 2 hours followed by convulsions and loss of consciousness. Both patients died 9 to 10 hours after ingestion, one in status epilepticus and the other while in hyperthermia following generalized epileptiform convulsions. Blood levels of both drugs at autopsy were lower than expected, based on the estimated amount of drug ingested. This may reflect prolonged absorption or postmortem redistribution. There were no levels of desmethyl or hydroxy metabolites of clomipramine reported.

3.3.3.A.2 Galactorrhea

a) Summary

1) Clomipramine therapy has been associated with the development of galactorrhea, hyperprolactinemia, and amenorrhea.

b) Several cases of HYPERPROLACTINEMIA and galactorrhea have been reported with clomipramine therapy. A severely depressed woman in her late twenties was admitted to a psychiatric unit and started on oral clomipramine 75 mg twice daily and L-tryptophan 1 g 3 times daily. Two days later the patient developed profuse galactorrhea which was associated with AMENORRHEA. L-tryptophan was reduced and eventually stopped over a 3-week period with no change in breast secretion. Clomipramine was reduced to 25 mg twice daily and bromocriptine 2.5 mg twice daily was initiated. Galactorrhea gradually resolved after 6 weeks of this therapy and menstruation also returned at this time (Anand, 1985).

c) A woman who had been on oral clomipramine 10 mg twice daily for several years for anxiety developed galactorrhea, loss of libido, and uncomfortable breast engorgement 6 months after an increase of clomipramine to 50 mg at night (Fowlie & Burton, 1987). Her plasma prolactin levels were also above normal. Clomipramine was discontinued and within 2 weeks galactorrhea was reduced; within 3 months her breasts became normal and galactorrhea had resolved.

3.3.3.A.3 Hyperglycemia

a) Hyperglycemia, glucosuria and diabetes mellitus has been reported with the use of clomipramine (Prod Info ANAFRANIL(R) oral capsules, 2007a).

b) An 84-year-old woman developed severe hyperglycemia within 5 months following the initiation of clomipramine 25 mg/day. The patient had a medical history of well-controlled hypertension, atrial fibrillation and concomitant medications included aspirin and irbesartan. Her BMI was 23 kg/m(2) and she had a negative family history of diabetes or glucose intolerance. Upon physical examination the patient was dehydrated and neurological examination noted obtunded consciousness without other abnormalities. Laboratory analysis revealed severe hyperglycemia (serum glucose, 459 mg/dL (25.5 mmol/L)), ketonemia, metabolic acidosis, elevated HbA1C level (12%), serum sodium (158 mmol/L), SCr (1.8 mg/dL), glycosuria and ketonuria. Additional laboratory test results were within normal ranges (eg, CBC, serum lipase and serum amylase) and chest radiography and CT of the head and abdomen were unremarkable. Upon hospitalization, the clomipramine was discontinued and the patient was treated with IV insulin (30 units/day) and IV fluids. The patient's blood glucose level normalized with treatment and after 10 days, the insulin therapy was discontinued and the patient was discharged from the hospital. Three months after hospital discharge, laboratory analysis reported HbA1C level at 5% and the patient agreed to restart the clomipramine under medical surveillance. One week after restarting the clomipramine, the patient developed hyperglycemia (serum glucose, 250 mg/dL (13.88 mmol/L)), glycosuria, and ketonuria. Again, the clomipramine was discontinued and the blood glucose normalized after 2 days. A temporal relationship appears to exist between the administration of clomipramine and the development of hyperglycemia and with the resolution of the hyperglycemia upon withdrawal of clomipramine(Mumoli & Cei, 2008).

3.3.3.A.4 Syndrome of inappropriate antidiuretic hormone secretion

a) HYPONATREMIA secondary to the syndrome of inappropriate antidiuretic hormone secretion (SIADH) has been attributed to clomipramine (Pledger & Mathew, 1989). Hyponatremia developed in a 64-year-old woman 2 days following initiation of clomipramine 25 g three times daily. The patient was not receiving other medications. Clomipramine was discontinued and electrolyte levels a week later were normal.

3.3.3.A.5 Weight change finding

a) Weight gain was reported in 18% of patients in controlled studies receiving clomipramine compared to 1% of patients administered placebo. Twenty-eight percent of these patients had weight gain of at least 7% of their initial body weight and several patients had weight gains in excess of 25% of their initial body weight. Conversely, 5% of patients receiving clomipramine and 1% receiving placebo had weight losses of at least 7% of their body weight (Prod Info Anafranil(R), 2001b).

3.3.4 Gastrointestinal Effects

3.3.4.A Clomipramine Hydrochloride

3.3.4.A.1 Gastrointestinal tract finding

a) Mild to moderate CONSTIPATION has been reported as an adverse effect by patients on clomipramine therapy (75 to 300 mg/day) (Dick & Ferrero, 1983)(Stern et al, 1980; Langohr et al, 1985a).

b) DRY MOUTH has been reported to occur in over 50% of patients on clomipramine therapy (75 to 300 mg/day) (Dunbar et al, 1985a); (Dick & Ferrero, 1983)(Flament et al, 1985; Johnston et al, 1988; Stern et al, 1980).

3.3.5 Hematologic Effects

3.3.5.A Clomipramine Hydrochloride

Agranulocytosis

Hematology finding

Pancytopenia

3.3.5.A.1 Agranulocytosis

a) Incidence: rare

b) Agranulocytosis has been reported with tricyclic antidepressants (Miller, 1963; Bird, 1960; Crammer & Elkes, 1967) and clomipramine has been associated with this syndrome. A 37-year-old depressed woman received a total of 2.65 grams of both oral and parenteral clomipramine over a 26-day period (Souhami et al, 1976). She developed a sore throat and fever 3 weeks after stopping treatment. A white cell count revealed a complete absence of neutrophils. The patient developed a candida infection and was admitted to the hospital for antibiotic therapy. After 12 days of NEUTROPENIA, there was an increase in the lymphocyte count followed by a sudden reappearance of neutrophils. Clinical

improvement was noted with the reappearance of neutrophils and the patient was discharged 40 days after admission. In a second report, a 49-year-old postmenopausal caucasian female was treated with clomipramine 150 mg at bedtime for 38 days. Four days after stopping the drug, a routine hemogram revealed leukopenia: 1200/mm(3) from 4500/mm(3) one month earlier. One week later, the white blood cell count was 4200 and the agranulocytosis had resolved (Gravenor et al, 1986).
c) A 67-year-old man developed concurrent severe agranulocytosis with elevation of hepatic transaminases after treatment with clomipramine (CMI) for 1 month at 175 mg/day. The white count returned to normal 14 days after discontinuation of CMI (Alderman et al, 1993).

3.3.5.A.2 Hematology finding

a) Clomipramine has caused LEUKOPENIA, agranulocytosis, THROMBOCYTOPENIA, ANEMIA, and pancytopenia. Leukocyte and differential blood counts should be obtained in patients who develop fever and sore throat during treatment with clomipramine (Prod Info Anafranil(R), 2001b).

3.3.5.A.3 Pancytopenia

a) Incidence: rare
b) A 54-year-old man developed pancytopenia after being treated with oral clomipramine 50 mg/day for approximately 40 days and parenteral clomipramine 50 mg/day for several days before the onset of symptoms (Magni et al, 1987). Several days after admission the patient experienced increased fatigue, drowsiness, pallor and ecchymoses on the arms. A complete blood count revealed a progressive reduction of all cell lines, with platelets and white blood cells leading the way. On day 20 after admission clomipramine was discontinued and his blood count began to rise. The patient was discharged on day 49 with his blood count still below baseline, but continuing to rise.

3.3.6 Hepatic Effects

3.3.6.A Clomipramine Hydrochloride

Allergic hepatitis

Hepatotoxicity

3.3.6.A.1 Allergic hepatitis

a) A 41-year-old woman developed allergic hepatitis with extreme eosinophilia during the second month of treatment with clomipramine for suicidal depression. After 4 weeks of clomipramine treatment (dose incremented to 150 milligrams/day), she developed right-sided upper abdominal pain and had fever, which normalized after 2 days. Abdominal pain persisted. Liver enzymes were elevated, but there was no eosinophilia. By 6 weeks, eosinophils had increased to 65% of the differential white blood cell count. Allergic hepatitis was diagnosed and clomipramine was discontinued. Hematopoietic side-effects disappeared within 2 weeks. Liver function took longer to normalize. Her depression was then successfully treated with a chemically unrelated substance (moclobemide) (Wiersma et al, 2000).

3.3.6.A.2 Hepatotoxicity

a) Incidence: 1-3%
b) Clomipramine has induced elevated aspartate aminotransferase (AST or SGOT) and alanine aminotransferase (ALT or SGPT) in approximately 1% and 3% of patients, respectively, to levels 3 times the upper limit of normal (Prod Info Anafranil(R), 2001b). Caution is indicated in treating patients with known liver disease, and periodic monitoring of hepatic enzymes is recommended in such patients.
c) A 67-year-old man developed concurrent severe agranulocytosis with elevation of hepatic transaminases after treatment with clomipramine (CMI) for 1 month at 175 mg/day. The white count returned to normal 14 days after discontinuation of CMI (Alderman et al, 1993).

3.3.8 Musculoskeletal Effects

3.3.8.A Clomipramine Hydrochloride

Fracture of bone

Fracture of bone, Nonvertebral

3.3.8.A.1 Fracture of bone

a) In a case-control study including fracture cases (n=124,655) during the year 2000 and age- and gender-matched controls (n=373,962), there was an increased risk of any fracture in participants who

were using an average standard daily dose of clomipramine (adjusted odds ratio (OR), 1.49; 95% CI, 1.19 to 1.88) compared to those who were not exposed to clomipramine. Clomipramine use was associated with an increased risk of hip fracture (adjusted OR, 2.04; 95% CI, 1.11 to 3.75), but not forearm (adjusted OR, 1.61; 95% CI, 0.89 to 2.89) or spine fracture (adjusted OR, 2.79; CI, 0.88 to 8.8) (Vestergaard et al, 2008)

3.3.8.A.2 Fracture of bone, Nonvertebral

a) In a prospective, population-based, cohort study (n=7983) with a mean follow-up of 8.4 years, there was an increased risk of nonvertebral fracture in adult participants older than 55 years of age (mean age of 77.5 years) who were currently using an tricyclic antidepressant (TCA), including amitriptyline, clomipramine, dosulepine, doxepine, imipramine, maprotiline, nortriptyline, and opipramol, compared to those who were not exposed to antidepressants. Current TCA use was associated with an increased risk of nonvertebral fracture (hazard ratio (HR), 1.6; 95% confidence interval (CI), 1.08 to 2.38) compared with no antidepressant use. Current TCA use was also associated with an increased risk of nonvertebral fracture (HR, 1.6; 95% CI, 1.02 to 2.5) compared with past antidepressant use (n=1217). Duration of TCA use of greater than 6 months was not associated with an increased risk of fractures when compared with no antidepressant use and with past antidepressant use. Fractures of the hip (most frequent), wrist, humerus, and pelvis were reported (Ziere et al, 2008).

3.3.9 Neurologic Effects

Clomipramine

Clomipramine Hydrochloride

3.3.9.A Clomipramine

3.3.9.A.1 Seizure

See Drug Consult reference: COMPARATIVE INCIDENCE OF SEIZURES FROM ANTIDEPRESSANTS

3.3.9.B Clomipramine Hydrochloride

Central nervous system finding

Gilles de la Tourette's syndrome

Seizure

Serotonin syndrome

3.3.9.B.1 Central nervous system finding

a) Summary

1) Increased aggression, tremor and decreased cognitive function have been associated with clomipramine administration in obsessive-compulsive disorder (OCD) and depressed patients and in normal volunteers. It has also precipitated panic attacks in patients with panic disorder.

b) TREMOR is a commonly reported adverse effect with clomipramine 75 to 300 mg/day in both depressive and obsessive compulsive disorder patients (Flament et al, 1985; Stern et al, 1980; Larsen et al, 1984; Levin, 1982a). In one study, the tremor was rapid with low amplitude and was successfully treated within a few days with oral biperiden 6 mg/day (Klok et al, 1981a).

c) The effects of a 10-day regimen of clomipramine (CMI) 25 to 50 mg tid on psychomotor and cognitive function were assessed in 12 normal volunteer subjects. CMI had little effect on EEG but reaction speed was markedly slowed. Tolerance did not develop to acute MEMORY IMPAIRMENT on a verbal recall test and subjective ratings for mood and bodily symptoms were adversely affected by CMI (Allen et al, 1991).

d) Performance on tasks tapping automatic and voluntary aspects of memory, attention, and motor speed was examined in 14 patients with major depressive disorder, before and after 3 weeks of treatment with clomipramine 150 mg/day. Performance on tasks requiring frontal functions improved or did not change, whereas verbal learning and retention, where hippocampal functioning is critical, were impaired. The latter tasks were negatively related to cerebrospinal fluid (CSF) 5-HIAA levels and plasma concentration of clomipramine (Bartfai et al, 1991).

3.3.9.B.2 Gilles de la Tourette's syndrome

a) Vocal and motor tics (Tourettism) developed after administration of clomipramine to a young patient with obsessive compulsive disorder and schizoid personality disorder (Moshe et al, 1994).

3.3.9.B.3 Seizure

a) Summary

1) Seizures associated with clomipramine have been reported during therapy, upon withdrawal of therapy by patient or neonate, and with overdoses. The Medical Letter reports that 0.7% of approximately 3,000 patients in United States clinical trials with clomipramine have experienced seizures (Anon, 1988a).

b) Incidence: 0.7%

c) Several incidences of major motor SEIZURES and STATUS EPILEPTICUS have been reported during clinical trials. The patients had no history of epilepsy or seizures prior to clomipramine therapy. One patient who experienced 2 seizures while on oral clomipramine 150 mg/day had a slightly abnormal EEG before treatment began (Marshall, 1971). The other patient experiencing a seizure while on oral clomipramine 150 mg/day was withdrawn from the study (Anon, 1986). The patient who experienced status epilepticus was on oral clomipramine 50 mg 3 times a day. The seizures were controlled with anticonvulsants and he was withdrawn from the study (Klok et al, 1981a).

d) A 40-year-old man with no history of epileptic seizures or head trauma was admitted to an emergency room comatose with generalized tonic-clonic movements (Flechter et al, 1983). According to his wife, he had taken approximately 2.5 g (100 tablets each 25 mg) of clomipramine. Within 8 hours of admission he developed generalized myoclonic jerking. He was treated with diazepam, diuretics, and large volumes of intravenous fluids. Within 4 days the myoclonic attacks resolved and he became fully conscious.

e) Within 36 hours of stopping clomipramine 50 mg three times daily, a 67-year-old woman became unconscious and developed clonic contractions of her limbs (Robinson, 1978). Following her convulsion she was restarted on clomipramine and fully recovered in 6 weeks, at which time the drug was gradually reduced with no further problems. The patient had no history of epileptic seizures or head trauma.

f) Two cases of neonatal convulsions due to maternal withdrawal of clomipramine were reported (Cowe et al, 1982a). In the first case a 22-year-old mother had been receiving clomipramine at an unspecified dose for the last 7 weeks of pregnancy for depression. She delivered a normal term male infant which developed convulsions at 8 hours of age. Parenteral treatment with phenobarbital and paraldehyde did not control the convulsions, which occurred intermittently for 53 hours. In the second case a 38-year-old mother had been receiving clomipramine and flurazepam at unspecified doses throughout pregnancy. Convulsions in the infant began 7 hours after birth. Parenteral phenobarbital was started but the infant continued to have myoclonic jerks. After 24 hours parenteral clomipramine was started at 0.4 mg over 2 hours, which suppressed the convulsions for 11 hours. Twitching in all limbs returned at this time and the infant was started on a continuous infusion of clomipramine which was gradually decreased over 12 days. Oral clomipramine was started and also slowly decreased. The infant remained jittery but the convulsions were under control. The clomipramine was discontinued at day 17 with no ill effects.

g) During a 4-week comparative trial, 36 female patients received either oral clomipramine or oral fluvoxamine 50 mg 3 times daily. During the third treatment week, 1 patient on clomipramine developed status epilepticus that was controlled with anticonvulsants. The patient had no history of epilepsy and was withdrawn from the study (Klock et al, 1981).

h) Acute and chronic effects of clomipramine on the human EEG in patients treated for depression could not be differentiated (Ulrich et al, 1994).

3.3.9.B.4 Serotonin syndrome

a) A 60-year-old woman with depression and anxiety suffered a fatal case of serotonin syndrome secondary to her clomipramine treatment (Rosebush et al, 1999). The woman had been receiving clomipramine for 8 months and her dose had been increased to 250 mg daily. Other medication included lisinopril, glyburide, and clonazepam. She became ill over a period of hours and developed encephalopathy, myoclonus, hyperreflexia, tremulousness, diarrhea, and incoordination. Her creatine phosphokinase increased to 39,900 units/L. Liver function tests were elevated, platelet count was elevated, and her coagulation studies were consistent with disseminated intravascular coagulation. Her blood level of clomipramine plus the major metabolite was 2,230 nmol/L (normal range less than 1,900). She was treated with cooling blankets, intravenous fluids, lidocaine for ventricular tachycardia, and phenytoin for seizures. Rhabdomyolysis occurred resulting in acute renal failure and the need for dialysis. After 4 weeks, she developed opportunistic infections and died.

b) Sixteen of 38 inpatients with DSM-IIIR major depression treated with clomipramine alone developed at least one sympton of the serotonin syndrome in a prospective study (Lejoyeux et al, 1993). This syndrome includes confusion, agitation, myoclonus, diaphoresis, tremor, and diarrhea. In 14 cases, tremor and myoclonus occurred simultaneously and 10 patients presented tremor, myoclonus, diaphoresis, and shivering. With the exception of 2 patients, symptoms were transient, lasted less than 1 week, and resolved with treatment.

3.3.12 Psychiatric Effects

3.3.12.A Clomipramine Hydrochloride

Aggressive behavior

Delirium

Hallucinations

Mania

Panic attack

Suicidal thoughts

3.3.12.A.1 Aggressive behavior

a) Paranoid ideation and aggressive behavior developed in two adolescents with obsessive compulsive disorder during treatment with therapeutic doses of clomipramine. Possible pathogenetic factors involving serotonin and serotonin receptor abnormalities are discussed (Alarcon et al, 1991).

3.3.12.A.2 Delirium

a) Two women, 61 and 67 years old, whose DSM-IV major depression failed to respond to oral treatment with clomipramine 150 mg/day, developed delirium and HALLUCINATIONS when intravenous clomipramine 12.5 milligrams was added to the regimen. Delirium was diagnosed within 4 to 6 days after beginning intravenous administration. In both cases, discontinuation of intravenous administration resulted in gradual improvement, over days, of the delirious state. In both women, plasma levels of clomipramine and its metabolite, desmethylclomipramine, doubled with the introduction of intravenous dosing (Ueda et al, 2000).

3.3.12.A.3 Hallucinations

a) The onset of "music hallucinations" has been associated with the use of clomipramine 75 mg per day three weeks after it was initiated for the treatment of major depression in a 67-year-old widowed female patient (Valleda & Gentil, 1991).

3.3.12.A.4 Mania

a) MANIA developed in 6 of 25 patients being treated with clomipramine for unipolar depression (van Sheyen & van Kammen, 1979). The patients had been on oral clomipramine 150 to 225 mg/day in 3 divided doses for 6 to 13 weeks before the development of mania. Mania lasted from 15 to 49 days after clomipramine was stopped and perphenazine or haloperidol therapy was initiated. The duration of the mania strongly correlated with the duration of clomipramine therapy.

3.3.12.A.5 Panic attack

a) Low-dose (12.5 mg) intravenous clomipramine precipitated severe dysphoria/panic attacks in patients with diagnosed panic disorder (George et al, 1995).

3.3.12.A.6 Suicidal thoughts

a) Adult and pediatric patients being treated with antidepressants for major depressive disorder who experience symptoms of anxiety, agitation, panic attacks, insomnia, irritability, hostility (aggressiveness), impulsivity, akathisia (psychomotor restlessness), hypomania, or mania may be at risk of suicidal ideation and behavior (SUICIDALITY). This same concern applies to treating patients with other psychiatric and nonpsychiatric disorders. If these symptoms are observed, therapy should be reevaluated and it may be necessary to discontinue medications when symptoms are severe, sudden in onset, or were not part of the patient's initial symptoms. Patients and their caregivers should be provided with the Medication Guide that is available for this drug (Anon, 2004).

b) A causal role for antidepressants in inducing suicidality has been established in pediatric patients. Anyone considering the use of antidepressants in a child or adolescent must balance this risk with the clinical need. In pooled analyses of 24 short-term, placebo-controlled trials of nine antidepressants (citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, bupropion, mirtazapine, nefazodone, and venlafaxine extended-release) including over 4400 pediatric patients with major depressive disorder, obsessive compulsive disorder, or other psychiatric disorders, a greater risk of suicidal behavior or ideation during the first few months of therapy was demonstrated in patients receiving antidepressants as compared with placebo (4% vs 2%, respectively). The risk of suicidality was most consistently observed in the trials that included patients with major depressive disorder, but there were signs of risk emerging from trials in other psychiatric indications, such as obsessive compulsive disorder and social anxiety disorder. No suicides occurred in these trials. The risk of suicidality during longer-term use (ie,

beyond several months) in pediatric patients is not known. It is also unknown whether this risk extends to adult patients (Anon, 2004).

3.3.13 Renal Effects

3.3.13.A Clomipramine Hydrochloride

3.3.13.A.1 Urinary retention

a) A 15-year-old male experienced 2 episodes of urinary retention while on oral clomipramine therapy for obsessive-compulsive disorder (Hermesh et al, 1987). The patient was on clomipramine 50 mg 3 times a day and first experienced urinary adverse effects 3 weeks from the initiation of therapy. Subcutaneous bethanechol 5 mg and oral phenoxybenzamine 40 mg/day for 3 days failed to improve his symptoms. Improvement in his obsessive-compulsive behavior was noted throughout clomipramine therapy and was maximal when the dose was increased to 200 mg/day. However during week 20 of therapy the patient experienced urinary retention for 16 hours and required catheterization to remove 1200 mL of urine. Within 8 days of clomipramine discontinuation all urinary symptoms had resolved.

3.3.14 Reproductive Effects

Clomipramine

Clomipramine Hydrochloride

3.3.14.A Clomipramine

3.3.14.A.1 Sexual dysfunction

See Drug Consult reference: DRUG-INDUCED SEXUAL DYSFUNCTION

3.3.14.B Clomipramine Hydrochloride

Sexual dysfunction

Sperm finding

3.3.14.B.1 Sexual dysfunction

a) DELAYED EJACULATION has been reported during several studies of patients with obsessive compulsive disorder at clomipramine doses of 50 to 300 mg/day (Yaryura-Tobias et al, 1976; Insel et al, 1983; Volavka et al, 1985a).

b) Partial or total ANORGASMIA was experienced by 92% (n=24; 17 men and 7 women) of patients with obsessive compulsive disorder during a double-blind, placebo-controlled study to assess changes in sexual function (Monteiro et al, 1987). None of the 9 placebo patients experienced any sexual dysfunction. Patients received clomipramine 25 to 200 mg/day. Most patients still had interest in sex but noticed difficulty in achieving orgasm within the first few days of clomipramine therapy. Normal sexual function returned within 3 days of stopping clomipramine in all but 1 man who improved without treatment in 3 months.

c) Orgasmic inhibition was reported in 1 male and 2 female patients who were depressed with obsessive-compulsive features (Quirk & Einarson, 1982). Orgasmic dysfunction occurred shortly after beginning clomipramine, despite a return of libido as the depression improved. Two patients were switched to desipramine; this resulted in resolution of sexual dysfunction while maintaining depression control. The third patient manipulated the dosing interval and reduced the intensity of the anorgasmia. Strong anticholinergic/antiadrenergic activity is felt to be the cause of anorgasmia from clomipramine.

d) There have been several interesting cases of patients experiencing ORGASM when yawning while receiving clomipramine therapy. Upon discontinuation of clomipramine these symptoms resolved. These side effects were discovered during routine questioning, and no placebo-replacement or rechallenge with clomipramine have been tried (McLean et al, 1983).

e) Three cases of painful ejaculation associated with clomipramine during the first 3 weeks of treatment were reported. Dosage was 100 mg/d in one case and 150 mg/d in 2 cases. The adverse effect resolved within several days of dosage reduction or discontinuation of the medication (Aizenberg et al, 1991).

3.3.14.B.2 Sperm finding

a) All spermiograms of 9 patients treated with clomipramine 75 mg/day for 3 months were pathological in terms of volume, motility, and morphology compared with 37% of control patients (same as healthy

population). Hormone levels associated with the hypothalamic hypophyseal-gonadal axis were not affected in either group (Maier & Koinig, 1994).

3.3.16 Other

3.3.16.A Clomipramine Hydrochloride

Summary

Withdrawal sign or symptom

3.3.16.A.1 Summary

a) GENERAL

1) Other than orthostatic hypotension, side effects from clomipramine treatment (dry mouth, tremor, sweating, constipation, accommodation disturbances, sedation) were no more frequent or severe in an older population (55 to 70 years of age, n=28) than in a younger one (less than 55 years of age, n=74) (Stage et al, 2002).

3.3.16.A.2 Withdrawal sign or symptom

a) A variety of withdrawal symptoms have been reported in association with abrupt discontinuation of clomipramine, including dizziness, nausea, vomiting, headache, malaise, sleep disturbance, hyperthermia, and irritability. In addition, such patients may experience a worsening of psychiatric status. The dosage of clomipramine should be gradually tapered and the patient monitored carefully during discontinuation (Prod Info Anafranil(R), 2001b; Diamond et al, 1989).

3.4 Teratogenicity/Effects in Pregnancy/Breastfeeding

A) Teratogenicity/Effects in Pregnancy

1) U.S. Food and Drug Administration's Pregnancy Category: Category C (Prod Info Anafranil(R), 2001c) (All Trimesters)

a) Either studies in animals have revealed adverse effects on the fetus (teratogenic or embryocidal or other) and there are no controlled studies in women or studies in women and animals are not available. Drugs should be given only if the potential benefit justifies the potential risk to the fetus.

2) Australian Drug Evaluation Committee's (ADEC) Category: C (Batagol, 1996)

a) Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible. Accompanying texts should be consulted for further details.

See Drug Consult reference: PREGNANCY RISK CATEGORIES

3) Crosses Placenta: Yes

4) Clinical Management

a) Due to reported teratogenic effects with other tricyclic antidepressants, use of clomipramine during pregnancy should be avoided if possible, especially during the first trimester. The dangers of failure to treat major depression, however, are obvious, and in each case these dangers must be weighed against the potential for teratogenic effects.

5) Literature Reports

a) Clomipramine has not been associated with teratogenic effects in human case reports, however, other tricyclic antidepressants (imipramine, amitriptyline) have been associated with teratogenic effects. Neonatal withdrawal symptoms secondary to maternal use of clomipramine have been reported.

b) Two cases of neonatal convulsions due to maternal withdrawal of clomipramine have been reported (Cowe et al, 1982). In the first case a 22-year-old mother had been receiving clomipramine at an unspecified dose for the last 7 weeks of pregnancy for depression. She delivered a normal term male infant who developed convulsions at 8 hours of age. Parenteral treatment with phenobarbital and paraldehyde did not control the convulsions, which occurred intermittently for 53 hours. In the second case, a 38-year-old mother had been receiving clomipramine and flurazepam of unspecified doses throughout pregnancy. Convulsions in the infant began 7 hours after birth. Parenteral phenobarbital was started but the infant continued to have myoclonic jerks. After 24 hours parenteral clomipramine was started at 0.4 mg over 2 hours, which suppressed the convulsions for 11 hours. Twitching in all limbs returned at this time and the infant was started on a continuous infusion of clomipramine which was started and also slowly decreased. The infant remained jittery but the convulsions were under control. The clomipramine was discontinued at day 17 with no ill effects.

c) In a case report, a pregnant woman with endogenous depression had been taking oral clomipramine 200 mg daily throughout her pregnancy (Ostergaard & Pedersen, 1982). She delivered an infant who became cyanotic, lethargic, and tachypneic with moderate respiratory acidosis. Treatment with oxygen and incubation reversed these conditions. The infant developed twitches and tremors with an abnormal motor pattern within 24 hours of birth. Following treatment with phenobarbital, the symptoms gradually decreased and completely resolved in one week.

d) A mother treated with clomipramine during pregnancy delivered a normal infant at term (Schimmell et al, 1991). The newborn did show hypotonia and jitteriness at birth and both effects resolved spontaneously by 6 days of age. The infant was breast-fed while the mother took oral clomipramine in therapeutic dosage (150 mg/day), producing a clomipramine level in the infant of 0.4% of the material level. Four of five women who took clomipramine throughout their pregnancies delivered healthy babies with no evidence of congenital malformations. The fifth woman elected to terminate her pregnancy at 9 weeks. Thus, the authors concluded that clomipramine can be safely used in pregnant women and mothers who breast-feed their newborns without fear of clomipramine intoxication.

e) Based on data collected through the Motherisk Program, there appear to be no differences in cognitive function, temperament and general behavior in children exposed to clomipramine throughout gestation as compared to controls (Nulman et al, 2002). However, among infants who were exposed to either fluoxetine or tricyclic antidepressants thoughout gestation, those born to mothers with uncontrolled depressive symptoms showed lower cognitive and language achievements than those born to mothers who were well-controlled (Nulman et al, 2002).

B) Breastfeeding

1) American Academy of Pediatrics Rating: Drugs for which the effect on nursing infants is unknown but may be of concern. (Anon, 2001)

2) World Health Organization Rating: Compatible with breastfeeding. (Anon, 2002)

3) Thomson Lactation Rating: Infant risk cannot be ruled out.

a) Available evidence and/or expert consensus is inconclusive or is inadequate for determining infant risk when used during breastfeeding. Weigh the potential benefits of drug treatment against potential risks before prescribing this drug during breastfeeding.

4) Clinical Management

a) According to the American Academy of Pediatrics, clomipramine is among those agents that may be of concern when used while breastfeeding (Anon, 2001). Although clomipramine appears in breast milk, the concentration is low and may not be pharmacologically significant.

5) Literature Reports

a) Clomipramine is excreted in breast milk. A mother treated with clomipramine during pregnancy delivered a normal infant at term (Schimmell et al, 1991a). The newborn did show hypotonia and jitteriness at birth and both effects resolved spontaneously by 6 days of age. The milk:plasma ratios on the 4th and 6th days were 1.62 and 1.04, respectively. The infant was started on breastfeeding at the 7th day of age while the mother took oral clomipramine in therapeutic dosage (150 mg/day), producing a clomipramine level in the infant of 0.4% of the maternal level. The milk:plasma ratios on the 10th, 14th, and 35th days were 0.76, 0.84, and 1.22, respectively.The infant remained asymptomatic.

b) A report describing four women maintained on clomipramine 75 mg to 125 mg per day who breastfed their infants demonstrated that infant serum concentrations of clomipramine metabolites (N-desmethylclomipramine, 8-hydroxyclomipramine and 8-hydroxydesmethylclomipramine) were below the assay sensitivity of 10 ng/mL. The measurements were taken after approximately 3 weeks of consistent maternal dosing, and all infants were noted to be developing normally (Wisner et al, 1995).

6) Drug Levels in Breastmilk

a) Parent Drug

1) Milk to Maternal Plasma Ratio

a) 0.76-1.62 (Schimmell et al, 1991a)

b) Active Metabolites

1) DESMETHYLCLOMIPRAMINE (Nagy & Johansson, 1977a)

3.5 Drug Interactions

Drug-Drug Combinations

Drug-Food Combinations

3.5.1 Drug-Drug Combinations

Acenocoumarol

Amobarbital

Amphetamine

Amprenavir

Anisindione

Aprobarbital

Arbutamine

Arformoterol

Armodafinil

Atazanavir

Atomoxetine

Belladonna

Belladonna Alkaloids

Bepridil

Bethanidine

Butabarbital

Butalbital

Cannabis

Carbamazepine

Chlorotrianisene

Cimetidine

Cisapride

Clonidine

Clorgyline

Conjugated Estrogens

Dexfenfluramine

Dexmethylphenidate

Dextroamphetamine

Dicumarol

Dienestrol

Diethylpropion

Diethylstilbestrol

Diphenhydramine

Duloxetine

Enalaprilat

Enalapril Maleate

Epinephrine

Esterified Estrogens

Estradiol

Estriol

Estrone

Estropipate

Eterobarb

Ethinyl Estradiol

Etilefrine

Fenfluramine

Fluvoxamine

Formoterol

Fosamprenavir

Fosphenytoin

Gatifloxacin

Grepafloxacin

Guanadrel

Halofantrine

Heptabarbital

Hexobarbital

Iproniazid

Isocarboxazid

Linezolid

Lisdexamfetamine

Lumefantrine

Mazindol

Mephentermine

Mephobarbital

Mestranol

Methamphetamine

Methohexital

Methoxamine

Methylphenidate

Midodrine

Moclobemide

Modafinil

Moxifloxacin

Nefopam

Nialamide

Norepinephrine

Olanzapine

Oxilofrine

Oxybutynin

Pargyline

Paroxetine

Pemoline

Pentobarbital

Phendimetrazine

Phenelzine

Phenindione

Phenmetrazine

Phenobarbital

Phenprocoumon

Phentermine

Phenylephrine

Phenytoin

Primidone

Procarbazine

Propylhexedrine

Quinestrol

Quinidine

Rasagiline

S-Adenosylmethionine

Salmeterol

Secobarbital

Selegiline

Sertraline

St John's Wort

Tapentadol

Thiopental

Tibolone

Toloxatone

Tramadol

Tranylcypromine

Valproic Acid

Vasopressin

Venlafaxine

Warfarin

Yohimbine

3.5.1.A Acenocoumarol

1) Interaction Effect: increased risk of bleeding

2) Summary: Tricyclic antidepressants (TCAs) may increase the half-life and bioavailability of oral anticoagulants (Vesell et al, 1970k; Williams et al, 1976k). Considerable interindividual differences may be

found (Pond et al, 1975k).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: In patients receiving tricyclic antidepressants and oral anticoagulant therapy, the prothrombin time ratio or INR (international normalized ratio) should be closely monitored with the addition and withdrawal of the antidepressant, and should be periodically reassessed during concurrent therapy. Achieving a stable drug regimen which produces the desired level of anticoagulation may be difficult in patients on this combination, and frequent adjustments of the anticoagulant dose may be required.
7) Probable Mechanism: decreased acenocoumarol metabolism; increased acenocoumarol absorption
8) Literature Reports
a) In a study of healthy volunteers, the concurrent use of nortriptyline or amitriptyline resulted in an increase of dicumarol levels and an increase in the plasma half-life of dicumarol, although the effect was not consistent in all subjects (Pond et al, 1975j). This effect was not observed with warfarin.
b) A single oral dose of bishydroxycoumarin after 8 days of nortriptyline resulted in a significantly prolonged half-life and decreased volume of distribution of the coumarin anticoagulant in 6 healthy volunteers (Vesell et al, 1970j). The proposed mechanism of action was reduced bishydroxycoumarin metabolism and/or altered coumarin absorption.
c) Drug dosing was studied in 16 patients on long-term anticoagulant therapy who used concurrent TCAs (Williams et al, 1976j). TCAs affected the stability of anticoagulant control leading to frequent changes in the doses of anticoagulants. Inhibition of coumarin metabolism was the postulated mechanism.

3.5.1.B Amobarbital
1) Interaction Effect: possible decreased tricyclic antidepressant serum concentrations and possible additive adverse effects
2) Summary: Concomitant barbiturate and tricyclic antidepressant (TCA) therapy may result in increased metabolism of the TCA. There have been scattered reports of individuals with decreased serum levels of TCAs in the presence of a barbiturate (Moody et al, 1977a; Silverman & Braithwaite, 1972; Burrows & Davies, 1971). In addition, TCAs can worsen seizure control by reducing the seizure threshold (Brodie, 1992). These drugs also have additive CNS and respiratory depressant effects.
3) Severity: minor
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor for efficacy of antidepressant effect. Increases in tricyclic antidepressant dosages may be required. Additionally, monitor for toxicity when either drug is added to or withdrawn from therapy. Serum concentrations may be of value in determining appropriate dosage.
7) Probable Mechanism: increased tricyclic antidepressant metabolism
8) Literature Reports
a) The pharmacokinetics of a single oral dose of desipramine (100 mg) were studied in eight epileptic patients chronically treated with phenobarbital and in eight drug-free healthy controls (Spina et al, 1996). All subjects were extensive metabolizers with respect to the genetically determined CYP2D6-related metabolic polymorphism. Compared with controls, epileptic patients exhibited lower peak plasma desipramine concentrations (74 nmol/L vs. 107 nmol/L), smaller desipramine area under the concentration-time curve values (1943 nmol/L/h vs. 3234 nmol/L/h), and shorter desipramine elimination half-lives (15.1 h vs. 20.6 h). All barbiturates are believed to have similar effects leading to induction of hepatic enzymes and the 2D6 isozyme is believed to be important in the metabolism of most or all TCAs. Thus, similar effects should be expected with any combination of TCA and barbiturate.

3.5.1.C Amphetamine
1) Interaction Effect: hypertension, other cardiac effects, and CNS stimulation
2) Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been reported to result in enhanced amphetamine effects from the release of norepinephrine (Beaumont, 1973h; Raisfeld, 1972). A similar reaction might also occur with all drugs that have amphetamine-like effects. Acute elevations in blood pressure have been noted (Flemenbaum, 1971a). Some amphetamine-like drugs may inhibit the metabolism of TCAs, although most combinations have not been studied. When amphetamine analogs are being used to treat obesity, it should be noted that TCAs frequently lead to moderate weight gain (Russ & Ackerman, 1988). False positive urine tests for amphetamines have been reported during therapy with some TCAs (Merigian & Browning, 1993). Caution is advised when concurrent administration of amphetamine-like agents and TCAs is warranted. The patient should be closely monitored for increased cardiovascular effects (hypertension and dysrhythmias).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other sympathomimetic agents could lead to hypertension, increased cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006; Flemenbaum, 1972). Use caution if such

therapy is warranted. Monitor the patient closely for hypertension and dysrhythmias.
7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission
8) Literature Reports
a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agents. Additionally, coadministration of d-amphetamine with TCAs such as desipramine or protriptyline results in sustained increases in d-amphetamine concentration in the brain (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006).
b) Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism of some tricyclic antidepressants, such as imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transdermal system, 2006).
c) Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases in blood pressure such that the hypotensive effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of combined therapy. Discontinuation of the methylphenidate usually results in the blood pressure returning to normotensive levels; reinstitution of the methylphenidate resulted in further blood pressure elevation (Flemenbaum, 1971; Flemenbaum, 1972).
d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine given for at least four weeks, were given fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical improvement. However, fenfluramine more than doubled steady-state plasma levels of desipramine (Price et al, 1990).
e) There have been claims based on uncontrolled studies that a better antidepressant response may occur with combined therapy (Garrettson et al, 1969). However, a systemic review of stimulants in the treatment of depression concluded that although uncontrolled studies were generally positive, the ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated little advantage of drug over placebo and did not appear to be as effective as the conventional antidepressants in primary depression (Satel & Nelson, 1989).

3.5.1.D Amprenavir
1) Interaction Effect: increased tricyclic serum concentrations and potential toxicity (anticholinergic effects, sedation, confusion, cardiac arrhythmias)
2) Summary: Coadministered amprenavir may increase serum concentrations of tricyclic antidepressants, causing a potential risk of arrhythmias or other serious adverse effects. Currently no interaction study has been conducted. Amprenavir is metabolized by cytochrome P450 3A4 enzymes in addition to being a CYP3A4 inhibitor, and tricyclics may partially depend on this pathway for metabolism. Plasma concentrations of the tricyclic should be closely monitored and dose adjustments made accordingly in patients also receiving amprenavir (Prod Info Agenerase(R), 2000).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: If concomitant therapy with amprenavir and a tricyclic antidepressant is unavoidable, plasma concentrations of the tricyclic should be closely monitored and dose adjustments made accordingly. Also monitor patients for signs and symptoms of tricyclic toxicity (anticholinergic effects, sedation, confusion, cardiac arrhythmias).
7) Probable Mechanism: inhibition of cytochrome P450-mediated tricyclic metabolism

3.5.1.E Anisindione
1) Interaction Effect: increased risk of bleeding
2) Summary: Tricyclic antidepressants (TCAs) may increase the half-life and bioavailability of oral anticoagulants (Vesell et al, 1970e; Williams et al, 1976e). Considerable interindividual differences may be found (Pond et al, 1975e).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: In patients receiving tricyclic antidepressants and oral anticoagulant therapy, the prothrombin time ratio or INR (international normalized ratio) should be closely monitored with the addition and withdrawal of the antidepressant, and should be periodically reassessed during concurrent therapy. Achieving a stable drug regimen which produces the desired level of anticoagulation may be difficult in patients on this combination, and frequent adjustments of the anticoagulant dose may be required.
7) Probable Mechanism: decreased anisindione metabolism; increased anisindione absorption
8) Literature Reports
a) In a study of healthy volunteers, the concurrent use of nortriptyline or amitriptyline resulted in an increase of dicumarol levels and an increase in the plasma half-life of dicumarol, although the effect was not consistent in all subjects (Pond et al, 1975d). This effect was not observed with warfarin.
b) A single oral dose of bishydroxycoumarin after 8 days of nortriptyline resulted in a significantly prolonged half-life and decreased volume of distribution of the coumarin anticoagulant in 6 healthy volunteers (Vesell et al, 1970d). The mechanism of action was suggested to be reduced bishydroxycoumarin metabolism and/or altered coumarin absorption.
c) Drug dosing was studied in 16 patients on long-term anticoagulant therapy who used concurrent

TCAs (Williams et al, 1976d). TCAs affected the stability of anticoagulant control leading to frequent changes in the doses of anticoagulants. Inhibition of coumarin metabolism was the postulated mechanism.

3.5.1.F Aprobarbital

1) Interaction Effect: possible decreased tricyclic antidepressant serum concentrations and possible additive adverse effects
2) Summary: Concomitant barbiturate and tricyclic antidepressant (TCA) therapy may result in increased metabolism of the TCA. There have been scattered reports of individuals with decreased serum levels of TCAs in the presence of a barbiturate (Moody et al, 1977a; Silverman & Braithwaite, 1972; Burrows & Davies, 1971). In addition, TCAs can worsen seizure control by reducing the seizure threshold (Brodie, 1992). These drugs also have additive CNS and respiratory depressant effects.
3) Severity: minor
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor for efficacy of antidepressant effect. Increases in tricyclic antidepressant dosages may be required. Additionally, monitor for toxicity when either drug is added to or withdrawn from therapy. Serum concentrations may be of value in determining appropriate dosage.
7) Probable Mechanism: increased tricyclic antidepressant metabolism
8) Literature Reports
a) The pharmacokinetics of a single oral dose of desipramine (100 mg) were studied in eight epileptic patients chronically treated with phenobarbital and in eight drug-free healthy controls (Spina et al, 1996). All subjects were extensive metabolizers with respect to the genetically determined CYP2D6-related metabolic polymorphism. Compared with controls, epileptic patients exhibited lower peak plasma desipramine concentrations (74 nmol/L vs. 107 nmol/L), smaller desipramine area under the concentration-time curve values (1943 nmol/L/h vs. 3234 nmol/L/h), and shorter desipramine elimination half-lives (15.1 h vs. 20.6 h). All barbiturates are believed to have similar effects leading to induction of hepatic enzymes and the 2D6 isozyme is believed to be important in the metabolism of most or all TCAs. Thus, similar effects should be expected with any combination of TCA and barbiturate.

3.5.1.G Arbutamine

1) Interaction Effect: unreliable arbutamine test results
2) Summary: Because tricyclic antidepressants may affect heart rate, arbutamine should not be administered to a patient receiving a tricyclic antidepressant, since arbutamine test results may be unreliable (Prod Info GenESA(R), 1997).
3) Severity: moderate
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Arbutamine should not be administered to a patient receiving tricyclic antidepressant therapy.
7) Probable Mechanism: alteration of heart rate by the tricyclic antidepressant

3.5.1.H Arformoterol

1) Interaction Effect: an increased risk of cardiovascular excitation
2) Summary: Concurrent administration of arformoterol with a tricyclic antidepressant (TCA) may lead to potentiation of arformoterol's adrenergic effects on the cardiovascular system. Therefore, extreme caution is advised if arformoterol is administered to patients who are being treated with a TCA (Prod Info BROVANA (TM) inhalation solution, 2006). Monitor patients closely for adverse cardiovascular effects.
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Extreme caution and close observation for adverse cardiovascular effects are warranted when arformoterol is administered concurrently with a tricyclic antidepressant (TCA) as the cardiovascular effects of arformoterol can be potentiated by TCAs (Prod Info BROVANA(TM) inhalation solution, 2006).
7) Probable Mechanism: potentiation of cardiovascular effects

3.5.1.I Armodafinil

1) Interaction Effect: increased clomipramine exposure
2) Summary: Administration of armodafinil (R-enantiomer of modafinil) may cause moderate inhibition of CYP2C19 isozyme activity. Although not studied with clomipramine, a CYP2C19 substrate, concurrent administration of a single 400-mg dose of armodafinil with a 40-mg dose of omeprazole, also a CYP2C19 substrate, led to an approximately 40% increase in systemic exposure of omeprazole. Additionally, increased levels of clomipramine and its active metabolite, desmethylclomipramine, were reported in a narcoleptic patient receiving concomitant therapy with modafinil. Therefore, use caution when armodafinil and clomipramine are used concurrently. Dose reductions of clomipramine may be necessary (Prod Info NUVIGIL(TM) oral tablets, 2007). Also, monitor patients for increased clomipramine adverse events (dry mouth, sedation, urinary retention).

3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Use caution with the coadministration of armodafinil and clomipramine as this may result in increased clomipramine exposure. Dose reductions of clomipramine may be necessary (Prod Info NUVIGIL(TM) oral tablets, 2007). Monitor patients for increased clomipramine adverse events (dry mouth, sedation, urinary retention).
7) Probable Mechanism: inhibition of CYP2C19-mediated clomipramine metabolism

3.5.1.J Atazanavir
1) Interaction Effect: increased plasma concentrations of tricyclic antidepressants (drowsiness, hypotension, akathisia)
2) Summary: Coadministration of atazanavir and tricyclic antidepressants has not been studied. However, the coadministration of atazanavir and tricyclic antidepressants has the potential to produce serious and/or life-threatening adverse events (Prod Info Reyataz(TM), 2003).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: If atazanavir and tricyclic antidepressants are used concomitantly, monitor patient for clinical signs and symptoms of tricyclic antidepressant toxicity (hypotenstion, akathisia, anticholinergic effects, sedation, confusion, cardiac arrhythmias).
7) Probable Mechanism: unknown

3.5.1.K Atomoxetine
1) Interaction Effect: an increase in atomoxetine steady-state plasma concentrations
2) Summary: Atomoxetine is primarily metabolized by the cytochrome P450 2D6 (CYP 2D6) pathway to 4-hydroxyatomoxetine. In extensive metabolizers, atomoxetine steady-state plasma concentrations are increased with selective inhibitors of CYP2D6, such as clomipramine. The exposure is similar to that observed in poor metabolizers. In extensive metabolizers treated with clomipramine, the area under the concentration-time curve of atomoxetine is approximately 6- to 8-fold greater, and maximum plasma concentration at steady-state is about 3- to 4-fold greater than atomoxetine alone (Prod Info Strattera(TM), 2002).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Dosage adjustment of atomoxetine may be necessary when coadministered with clomipramine.
7) Probable Mechanism: inhibition of cytochrome P450 2D6-mediated metabolism of atomoxetine by clomipramine

3.5.1.L Belladonna
1) Interaction Effect: excessive anticholinergic activity (severe dry mouth, constipation, decreased urination, excessive sedation, blurred vision)
2) Summary: The anticholinergic activity of the active alkaloids present in belladonna may predispose the patient to excessive anticholinergic activity if taken with tricyclic antidepressants. Belladonna contains L-hyoscyamine, atropine, and scopolamine with a total alkaloid content of at least 0.3% in the leaves and 0.5% in the roots (Blumenthal et al, 1998). Because belladonna is typically available as a homeopathic preparation, the clinical severity of the interaction with tricyclic antidepressants is unknown. Caution is advised.
3) Severity: minor
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Excessive anticholinergic activity may be manifested by dry mouth, constipation, urinary retention, tachycardia, decreased sweating, mydriasis, blurred vision, elevated temperature, muscular weakness, and sedation. If such effects are noted, belladonna should be discontinued immediately. In severe cases, paralytic ileus, confusion, psychoses, agitation, delusions, delirium, and paranoia may be encountered as well as tachycardia, dysrhythmia, and hypertension. In severe cases, immediate medical attention should be obtained.
7) Probable Mechanism: additive anticholinergic effect

3.5.1.M Belladonna Alkaloids
1) Interaction Effect: excessive anticholinergic activity (severe dry mouth, constipation, decreased urination, excessive sedation, blurred vision)
2) Summary: The anticholinergic activity of the active alkaloids present in belladonna may predispose the patient to excessive anticholinergic activity if taken with tricyclic antidepressants. Belladonna contains L-hyoscyamine, atropine, and scopolamine with a total alkaloid content of at least 0.3% in the leaves and 0.5% in the roots (Blumenthal et al, 1998). Because belladonna is typically available as a homeopathic preparation, the clinical severity of the interaction with tricyclic antidepressants is unknown. Caution is

advised.
3) Severity: minor
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Excessive anticholinergic activity may be manifested by dry mouth, constipation, urinary retention, tachycardia, decreased sweating, mydriasis, blurred vision, elevated temperature, muscular weakness, and sedation. If such effects are noted, belladonna should be discontinued immediately. In severe cases, paralytic ileus, confusion, psychoses, agitation, delusions, delirium, and paranoia may be encountered as well as tachycardia, dysrhythmia, and hypertension. In severe cases, immediate medical attention should be obtained.
7) Probable Mechanism: additive anticholinergic effect

3.5.1.N Bepridil
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: In US clinical trials, the QT and QTc intervals were commonly prolonged by bepridil in a dose-related fashion (Prod Info Vascor(R), 2000). Tricyclic antidepressants (TCAs) have been shown to prolong the QTc interval at the recommended therapeutic dose (Marshall & Forker, 1982a).
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Concurrent use of bepridil and other drugs which may prolong the QTc interval, including tricyclic antidepressants, is contraindicated.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.O Bethanidine
1) Interaction Effect: decreased antihypertensive effectiveness
2) Summary: Antidepressants inhibit the uptake of bethanidine at its site of action in the adrenergic neuron. The antagonism may last for several days after discontinuation of the antidepressant (Skinner et al, 1969a; Avery, 1973a; Feagin et al, 1969).
3) Severity: moderate
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The combination of bethanidine and clomipramine, as well as other tricyclic antidepressant agents, should be avoided. An alternative antihypertensive agent should be considered.
7) Probable Mechanism: decreased uptake of bethanidine into adrenergic neurons
8) Literature Reports
a) Adequate control of hypertension was reported in only 2 of 8 adult hypertensive patients who received bethanidine or debrisoquine concurrently with a tricyclic antidepressant. In 24 control patients given the same drugs without antidepressants, blood pressure control was achieved in 18. Withdrawal of antidepressant therapy in several patients resulted in postural hypotension that necessitated a reduction in dosage of bethanidine or debrisoquine (Skinner et al, 1969).

3.5.1.P Butabarbital
1) Interaction Effect: possible decreased tricyclic antidepressant serum concentrations and possible additive adverse effects
2) Summary: Concomitant barbiturate and tricyclic antidepressant (TCA) therapy may result in increased metabolism of the TCA. There have been scattered reports of individuals with decreased serum levels of TCAs in the presence of a barbiturate (Moody et al, 1977a; Silverman & Braithwaite, 1972; Burrows & Davies, 1971). In addition, TCAs can worsen seizure control by reducing the seizure threshold (Brodie, 1992). These drugs also have additive CNS and respiratory depressant effects.
3) Severity: minor
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor for efficacy of antidepressant effect. Increases in tricyclic antidepressant dosages may be required. Additionally, monitor for toxicity when either drug is added to or withdrawn from therapy. Serum concentrations may be of value in determining appropriate dosage.
7) Probable Mechanism: increased tricyclic antidepressant metabolism
8) Literature Reports
a) The pharmacokinetics of a single oral dose of desipramine (100 mg) were studied in eight epileptic patients chronically treated with phenobarbital and in eight drug-free healthy controls (Spina et al, 1996). All subjects were extensive metabolizers with respect to the genetically determined CYP2D6-related metabolic polymorphism. Compared with controls, epileptic patients exhibited lower peak plasma desipramine concentrations (74 nmol/L vs. 107 nmol/L), smaller desipramine area under the concentration-time curve values (1943 nmol/L/h vs. 3234 nmol/L/h), and shorter desipramine elimination half-lives (15.1 h vs. 20.6 h). All barbiturates are believed to have similar effects leading to induction of hepatic enzymes and the 2D6 isozyme is believed to be important in the metabolism of most or all TCAs. Thus, similar effects should be expected with any combination of TCA and barbiturate.

3.5.1.Q Butalbital

1) Interaction Effect: possible decreased tricyclic antidepressant serum concentrations and possible additive adverse effects

2) Summary: Concomitant barbiturate and tricyclic antidepressant (TCA) therapy may result in increased metabolism of the TCA. There have been scattered reports of individuals with decreased serum levels of TCAs in the presence of a barbiturate (Moody et al, 1977a; Silverman & Braithwaite, 1972; Burrows & Davies, 1971). In addition, TCAs can worsen seizure control by reducing the seizure threshold (Brodie, 1992). These drugs also have additive CNS and respiratory depressant effects.

3) Severity: minor

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Monitor for efficacy of antidepressant effect. Increases in tricyclic antidepressant dosages may be required. Additionally, monitor for toxicity when either drug is added to or withdrawn from therapy. Serum concentrations may be of value in determining appropriate dosage.

7) Probable Mechanism: increased tricyclic antidepressant metabolism

8) Literature Reports

a) The pharmacokinetics of a single oral dose of desipramine (100 mg) were studied in eight epileptic patients chronically treated with phenobarbital and in eight drug-free healthy controls (Spina et al, 1996). All subjects were extensive metabolizers with respect to the genetically determined CYP2D6-related metabolic polymorphism. Compared with controls, epileptic patients exhibited lower peak plasma desipramine concentrations (74 nmol/L vs. 107 nmol/L), smaller desipramine area under the concentration-time curve values (1943 nmol/L/h vs. 3234 nmol/L/h), and shorter desipramine elimination half-lives (15.1 h vs. 20.6 h). All barbiturates are believed to have similar effects leading to induction of hepatic enzymes and the 2D6 isozyme is believed to be important in the metabolism of most or all TCAs. Thus, similar effects should be expected with any combination of TCA and barbiturate.

3.5.1.R Cannabis

1) Interaction Effect: tachycardia and delirium

2) Summary: Concomitant tetrahydrocannabinol and tricyclic antidepressant therapy has increased the heart rate and cause delirium beyond that expected with either drug alone (Wilens et al, 1997a; Hillard & Vieweg, 1983a).

3) Severity: moderate

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: Caution is advised if patients use cannabis with a tricyclic antidepressant. Monitor heart rate changes closely.

7) Probable Mechanism: possibly due to beta-adrenergic effect of cannabis coupled with the anticholinergic effect of tricyclic antidepressants

8) Literature Reports

a) A 21-year-old female receiving oral nortriptyline 30 milligrams at bedtime for 9 months developed marked sinus tachycardia (160 beats/minute) within 30 minutes of smoking a cannabis cigarette. The patient's heart rate was about 90 beats/minute before smoking the cannabis. She had used cannabis many times before starting the nortriptyline without ill effects (Hillard & Vieweg, 1983).

b) Four cases of tachycardia, cognitive changes, and delirium have been reported in adolescent males treated with tricyclic antidepressants who smoked marijuana. One of the four cases was evaluated by a physician, the others were later accounts of the event. The toxic effects were considered by the reporters to have resulted from a drug interaction because they occurred with lower doses of marijuana than are common in other reports of marijuana toxicity (usually greater than 20 mg). In case 1, a 16-year-old male taking nortriptyline 75 mg/day presented with tachycardia (130 beats/minute), delirium, confusion, and short-term memory loss 30 minutes after smoking one marijuana cigarette. Symptoms resolved spontaneously after 24 hours. In case 2, and 18-year-old male taking desipramine 200 mg/day presented 12 hours after smoking marijuana with symptoms of edginess, severe dry mouth, lightheadedness, confusion, short-term memory impairment, and tachycardia (110 beats/minute). Symptoms resolved within 48 hours. Case 3, a 15-year-old male taking desipramine 150 mg/day and sertraline 50 mg/day, reported mood lability, irritability, and a racing heart after smoking 2 marijuana cigarettes which resolved after 16 hours. Case 4, a 16-year-old male taking desipramine and clonidine reported hallucinations, confusion, mild shortness of breath, and elevated heart rate after smoking marijuana. This was different than the effect he experienced prior to taking desipramine (Wilens et al, 1997).

3.5.1.S Carbamazepine

1) Interaction Effect: decreased clomipramine effectiveness

2) Summary: The concomitant use of carbamazepine and antidepressants has been reported to decrease antidepressant levels (Leinonen et al, 1991; Brown et al, 1990). Although not reported for clomipramine, a similar interaction could occur.

3) Severity: moderate

4) Onset: delayed

5) Substantiation: theoretical
6) Clinical Management: Monitor for clinical efficacy of the clomipramine therapy and for any signs of toxicity of carbamazepine. Serum levels of both agents should be considered when either agent is added or discontinued, with appropriate dosage adjustments made accordingly.
7) Probable Mechanism: increased clomipramine metabolism
8) Literature Reports
a) Concomitant administration of imipramine and carbamazepine to children with attention deficit disorder (ADD) has been reported to result in a 50% decrease in the total plasma concentration of imipramine plus desipramine (Brown et al, 1988). Carbamazepine enhances the hepatic microsomal metabolism of imipramine and other tricyclic antidepressants by inducing hepatic enzymes (Moody et al, 1977). Although not reported specifically for clomipramine, be aware that the potential for a similar interaction exists. Patients on chronic carbamazepine therapy may require increased doses of tricyclic antidepressants.

3.5.1.T Chlorotrianisene
1) Interaction Effect: attenuation of antidepressant effectiveness; tricyclic toxicity (drowsiness, hypotension, akathisia)
2) Summary: In isolated cases, the pharmacologic effects of tricyclic antidepressants may be increased or decreased by estrogens (Somani & Khurana, 1973g), with paradoxical loss of antidepressant effect yet tricyclic toxicity being manifested simultaneously (Prange, 1972g). The effects of the interaction appear to be estrogen dose-related (Khurana, 1972g) and may be of clinical importance primarily in patients previously stabilized on tricyclic therapy who are being started on estrogen therapy (Krishnan et al, 1984g).
3) Severity: minor
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: If signs or symptoms of altered tricyclic response are noted, dose adjustment downward of either the estrogen or tricyclic component may be successful in restoring effectiveness or resolving toxicity. However, drug withdrawal may be required.
7) Probable Mechanism: possible estrogen-enhanced hepatic metabolism of the tricyclic
8) Literature Reports
a) The qualitative effects of concomitant administration of estrogen and TCAs was evaluated. In one trial, 30 depressed female prisoners were randomly assigned to 4 treatment groups. Ten patients received placebo, 10 received imipramine (150 milligrams/day) and placebo, 5 patients received imipramine (150 milligrams/day) and ethinyl estradiol (50 micrograms/day), while 5 patients received imipramine (150 milligrams/day) and ethinyl estradiol (25 micrograms/day). The 10 patients that received placebo did not improve over the 6 weeks of the study. The 10 patients taking estrogen and imipramine demonstrated a significantly greater improvement in symptoms than did the 10 patients taking imipramine alone. However, after 2 weeks, the 5 patients that received imipramine and high-dose estrogen had not improved as much as the patients receiving imipramine and low-dose estrogen. The only side-effect reported was drowsiness, which only affected the patients taking imipramine. Following the discontinuation of ethinyl estradiol, a time period of 2 weeks was required for the high-dose estrogen group to do as well as the low-dose group. This effect was attributed to the presence of residual estrogen in the high-dose group. In another group, 5 women received imipramine 150 milligrams and ethinyl estradiol 50 micrograms daily did not improve as much as 10 patients receiving only imipramine. Also, the patients on the combination had severe side-effects including lethargy, coarse tremor and systolic hypotension (Prange, 1972f).
b) A case reported demonstrated an interaction in a 32-year-old female taking conjugated estrogens 2.5 milligrams and imipramine 100 milligrams (Khurana, 1972f). The patient developed lethargy, tremors, and signs of depersonalization. After 2 years of therapy, the patient increased her estrogen dose to 5 milligrams and then 7.5 milligrams daily. The patient became nauseated, had constant headaches, and low normal blood pressure. All lab work was normal. Upon discontinuing the estrogen, the side-effects abated. Some investigators have proposed that the side effects resulted from enhanced TCA effects secondary to estrogen inhibition of hepatic microsomal enzymes (Somani & Khurana, 1973f).
c) A study in which women received clomipramine and oral contraceptives or clomipramine alone was reviewed. At the beginning of the study there were 30 women taking the combination, but 12 subsequently dropped out. The 18 patients on the combination were matched with 18 patients taking clomipramine alone. No significant difference was noted in the patients' responses to clomipramine. It was proposed that there was no significant difference in side-effects between the groups; however, the groups were matched after patients had dropped out of the study. Had the patients been matched prior to the study, different conclusions may have been drawn (Beaumont, 1973c).
d) The effects of oral contraceptives on clomipramine in 42 women between the ages of 18 and 40 was studied. Twenty-three women took clomipramine 25 milligrams at bedtime while 19 took clomipramine 25 milligrams at bedtime with oral contraceptives. Over the 4-week study, 3 control patients (2 due to side-effects) and 5 in the experimental group (2 due to side-effects) dropped out. Venous blood samples were drawn at weekly intervals for measurement of serum clomipramine concentrations. No difference in serum concentrations was noted between the groups. However, this result may be partially due to the low dose of clomipramine given (Luscombe & John, 1980c).

e) Akathisia in 3 patients receiving conjugated estrogens and tricyclic antidepressants concurrently was reported. A 24-year-old patient receiving clomipramine 120 milligrams/day for anorexia nervosa and conjugated estrogens 1.25 milligrams/day for amenorrhea developed restless legs and a constant desire to move continuously. Estrogen was discontinued and benztropine 2 milligrams was administered, resulting in marked reduction and resolution within 48 hours. Akathisia and disorientation developed in a 55-year-old patient on conjugated estrogens 1.25 milligrams/day who was prescribed amitriptyline 50 milligrams/day for depression. Within hours of amitriptyline, the patient was confused, restless, and possessed an inner desire to move continuously. Symptoms disappeared after discontinuing amitriptyline. Positive rechallenge at one week with doxepin 100 milligrams, with resolution following discontinuation of doxepin. A third case of akathisia was reported in a 35-year-old patient who received conjugated estrogens 1.25 milligrams/day and amitriptyline 50 milligrams/day. Akathisia developed within a few hours after taking the first dose of amitriptyline and resolved within 48 hours following discontinuation of the antidepressant (Krishnan et al, 1984f).
f) The absolute bioavailability of imipramine increased in women who received low-dose oral contraceptives (50 micrograms or less of ethinyl estradiol) from 27 to 44% (p less than 0.05) as evident by an increase in the area under the plasma concentration time curve (Abernethy et al, 1984c).
g) Estrogens may inhibit the oxidation of TCAs by affecting hepatic microsomal enzymes (John et al, 1980c). Many TCAs are metabolized via oxidation and conjugation pathways. Inhibition of the oxidation of TCAs could result in accumulation and toxicity due to decreased clearance. Estrogens are suspected of possessing other effects on the central nervous system resulting in an antidepressant effect (Oppenheim, 1983c).

3.5.1.U Cimetidine

1) Interaction Effect: clomipramine toxicity (dry mouth, blurred vision, urinary retention)
2) Summary: Cimetidine impairs the metabolism of tricyclic antidepressants (Miller et al, 1983; Sutherland et al, 1987; Steiner & Spina, 1987). Although not reported for clomipramine, it is likely that a similar interaction would occur because of the mechanism involved.
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Consider monitoring serum tricyclic antidepressant levels within the first few days of starting or discontinuing cimetidine. An H2 blocker that does not impair the metabolism of the tricyclic agents, such as ranitidine or famotidine, may be an alternative.
7) Probable Mechanism: decreased clomipramine metabolism

3.5.1.V Cisapride

1) Interaction Effect: cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Cisapride therapy has resulted in serious cardiac arrhythmias, including ventricular tachycardia, ventricular fibrillation, torsades de pointes, and QT prolongation. Because tricyclic antidepressant agents also may prolong the QT interval and increase the risk of arrhythmias, the concurrent administration of cisapride with a drug from this class is contraindicated (Prod Info Propulsid(R), 2000).
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent use of cisapride and tricyclic antidepressants is contraindicated.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.W Clonidine

1) Interaction Effect: decreased antihypertensive effectiveness
2) Summary: Concomitant clonidine and tricyclic antidepressant (TCA) therapy may impair the antihypertensive effects of clonidine (Prod Info Catapres(R), 1996). Tricyclic antidepressants increase the release of noradrenaline, presumably through re-uptake blockade. Clonidine reduces the release of noradrenaline by stimulating pre-synaptic alpha-2 adrenoreceptors, whose function is to inhibit noradrenaline release (Briant et al, 1973a; Hicks et al, 1981; Hui, 1983; Glass et al, 1982a). Mianserin, a tetracyclic antidepressant, was not shown to exhibit the impairment of clonidine's antihypertensive effects seen with tricyclic antidepressants (Elliott et al, 1981; Elliott et al, 1983).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Blood pressure should be monitored for an appropriate clinical response. Higher doses of clonidine may be required. An alternative class of antihypertensive agents or an alternative class of antidepressants might be considered.
7) Probable Mechanism: pharmacological antagonism at central alpha-2 receptors
8) Literature Reports

a) The interaction between clonidine and desipramine developed in five hypertensive patients. The results of this double-blind placebo controlled study showed that the introduction of the tricyclic antidepressant led to the loss of blood pressure control in four of the five subjects within two weeks. The rise in the arterial pressure was more prominent in the supine position than in the erect. The average

blood pressure increase in the desipramine period compared to the placebo period was 22/15 mm Hg in the lying position and 12/11 mm Hg standing (Briant et al, 1973).
b) Eleven drug-free patients who met the Research Diagnostic Criteria for Major Depressive Disorder enrolled in a study to determine the effects of desipramine on central adrenergic function. Patients were given a clonidine infusion after 0, 1 and 3 weeks of treatment with desipramine. Results showed that the sedative and hypotensive effects of clonidine were significantly inhibited after three weeks of treatment with desipramine. This interaction was also seen at one week, but did not reach clinical significance. The authors concluded that the effects that were observed during the study were due to an acute drug effect, rather than to a chronic adaptive change (Glass et al, 1982).
c) One case report describes a 65-year-old man who was experiencing perineal pain following the excision of a carcinoma. Pain management of amitriptyline 75 mg nightly and sodium valproate 500 mg three times daily was initiated after slow-release morphine only had a limited effect. A clonidine spinal intrathecal injection of 75 micrograms was given when it was felt that the patient had become tolerant to opioid treatment. Within five minutes, the patient was found to be in severe pain, which resolved within 30 minutes after diamorphine was given. Two mechanisms for this interaction were postulated. In the first, the pain could have been the result of a clonidine-cholinergic interaction. In the second, the tricyclic augmentation of serotoninergic transmission may have unmasked an effect of clonidine at central receptors to enhance nociception (Hardy & Wells, 1988).

3.5.1.X Clorgyline

1) Interaction Effect: neurotoxicity, seizures, or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)
2) Summary: Concomitant TCA and MAOI use has resulted in hyperpyrexia, convulsions, and death. Concurrent use of MAOIs and TCAs has also been reported to result in a condition termed serotonin syndrome (Insel et al, 1982r; Spigset et al, 1993q; Brodribb et al, 1994p; Neuvonen et al, 1993i). Serotonin syndrome is a rare but potentially fatal condition of serotonergic hyperstimulation characterized by hypertension, hyperthermia, myoclonus, and changes in mental status (Sternbach, 1991j). Consequently, coadministration of TCAs and MAOIs is contraindicated in most cases. If TCAs and MAOIs must be used concurrently, avoid large doses, use only oral TCAs, avoid imipramine, clomipramine, desipramine, and tranylcypromine, and monitor patients closely (Schuckit et al, 1971u; White & Simpson, 1984p).
3) Severity: contraindicated
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Concomitant use of clomipramine with a monoamine oxidase inhibitor (MAOI), such as clorgyline is contraindicated. If clomipramine is replacing treatment with clorgyline, a minimum of 14 days should elapse after clorgyline is discontinued before begin therapy with clomipramine. Similarly, if clomipramine is substituted by clorgyline, a minimum of 14 days should elapse after clomipramine is discontinued and begin therapy with clorgyline (Prod Info clomipramine hydrochloride oral capsule, 2002).
7) Probable Mechanism: altered catecholamine uptake and metabolism
8) Literature Reports
a) Concomitant administration of monoamine oxidase inhibitors (MAOIs) with tricyclic antidepressants (TCAs) has been considered an absolute contraindication in the past and still is listed as such by the manufacturers (Prod Info clomipramine hydrochloride oral capsule, 2002). Reports of excitation, hyperpyrexia, convulsions, and possible death have been attributed to the combination (Lockett & Milner, 1965j; Brachfeld et al, 1963f; Winston, 1971j; Schuckit et al, 1971t; Sargent, 1965f; Spiker & Pugh, 1976j). The mechanism may relate to the combined inhibition of catecholamine reuptake into the central nervous system and inhibition of catecholamine metabolism (Sjoqvist, 1965j).
b) Administration of a TCA after MAOI therapy may result in the development of serotonin syndrome. In a double-blind, crossover study examining the effects of clorgyline and clomipramine for the treatment of obsessive-compulsive disorder, two subjects developed severe reactions characteristic of serotonin syndrome. During the study, patients had received clorgyline therapy, followed by a washout period of approximately four weeks and subsequent clomipramine therapy. After taking the first 100 mg dose of clomipramine, one patient developed coarse myoclonic jerking in both legs, hyperreflexia, diaphoresis, and arrhythmia. Another patient developed a similar reaction after the first dose, with upper motor neuron symptoms, myoclonic movements, and cardiac irritability. Both patient's symptoms resolved several hours later, and both patients were later treated successfully with clomipramine without adverse effects (Insel et al, 1982q).
c) A drug interaction was reported in a 76-year old woman who had been taking clomipramine 50 mg daily for several months prior to switching to moclobemide 300 mg daily. The patient experienced somnolence, confusion, and fever which then progressed to further mental impairment, muscle stiffness, myoclonus, and convulsive attacks. The patient's symptoms were described as fulfilling the diagnostic criteria for serotonin syndrome and were resolved a few days later after discontinuing all antidepressant medications (Spigset et al, 1993p).
d) A 39-year old woman with bipolar disorder developed serotonin syndrome after imipramine was added to moclobemide. The patient was taking moclobemide 300 mg twice daily when imipramine was started at 50 mg daily, followed by two dosage increases of imipramine to 200 mg and a reduction of moclobemide dosage to 150 mg twice daily. Five days after the increase in imipramine to 200 mg per day, the patient developed symptoms of serotonin syndrome, including sweating, shivering, confusion,

fever, and spasms in the extremities. The patient was treated with chlorpromazine and symptoms resolved over the next few days without further complications (Brodribb et al, 1994o).
e) Three patients with bipolar disorder developed manic symptoms while undergoing concurrent therapy with isocarboxazid and amitriptyline. In all three cases the patients had been given MAOIs and TCAs alone without complications. It was only when the drugs were used in combination that symptoms of mania emerged, suggesting a synergistic effect (de la Fuente et al, 1986d).
f) In one case, clomipramine 10 mg twice daily was added to a stable regimen of tranylcypromine in a physically healthy 34-year old man. After taking several doses, the patients developed symptoms of nausea and profuse sweating, followed by pyrexia, dyspnea, and agitation. The hyperpyrexical state led to disseminated intravascular coagulation and eventual death (Tackley & Tregaskis, 1987i).
g) There is evidence that MAOIs and TCAs can be given concomitantly in patients previously unresponsive to the MAOI or TCA alone. A few precautions must be followed including: a) avoidance of large doses (no more than 150 mg amitriptyline or its equivalent, 45 mg phenelzine, or 60 mg isocarboxazid) b) oral administration c) avoidance of clomipramine, imipramine, desipramine, and tranylcypromine in any combination, and d) close monitoring of patients (Kline, 1974e; Winston, 1971j; Schuckit et al, 1971t; White & Simpson, 1984o; Rom & Benner, 1972e). The combination may be utilized in one of two ways. Most frequently, the recommendation is to stop all previous antidepressants (five to ten days for TCAs and 14 days for MAOIs); the combination is then simultaneously started (Perry et al, 1991i). Alternatively, in a patient previously receiving a TCA, small doses of the MAOI may be slowly added (Schoonover, 1983). Some sources suggest that the combination of amitriptyline and isocarboxazid is preferred (Perry et al, 1991i). Numerous studies in patients with refractory depression or phobic anxiety states have successfully used the combination of MAOIs and TCAs (Ponto et al, 1977j; Schuckit et al, 1971t; Ashcroft, 1975i).

3.5.1.Y Conjugated Estrogens

1) Interaction Effect: possible attenuation of antidepressant effectiveness; tricyclic toxicity (drowsiness, hypotension, akathisia)
2) Summary: In isolated cases, the pharmacologic effects of tricyclic antidepressants may be increased or decreased by estrogens (Somani & Khurana, 1973i), with paradoxical loss of antidepressant effect yet tricyclic toxicity being manifested simultaneously (Prange, 1972i). The effects of the interaction appear to be estrogen dose-related (Khurana, 1972i) and may be of clinical importance primarily in patients previously stabilized on tricyclic therapy who are being started on estrogen therapy (Krishnan et al, 1984i).
3) Severity: minor
4) Onset: delayed
5) Substantiation: established
6) Clinical Management: If signs or symptoms of altered tricyclic response are noted, dose adjustment downward of either the estrogen or tricyclic component may be successful in restoring effectiveness or resolving toxicity. However, drug withdrawal may be required.
7) Probable Mechanism: possible inhibition of hepatic metabolism of the tricyclic antidepressant
8) Literature Reports
a) Some studies evaluated the qualitative effects of concomitant administration of estrogen and TCAs. In one trial, 30 depressed female prisoners were randomly assigned to four treatment groups. Ten patients received placebo, 10 received imipramine (150 mg daily) and placebo, five patients received imipramine (150 mg daily) and ethinyl estradiol (50 mcg daily), while five patients received imipramine (150 mg daily) and ethinyl estradiol (25 mcg daily). The 10 patients that received placebo did not improve over the six weeks of the study. The 10 patients taking estrogen and imipramine demonstrated a significantly greater improvement in symptoms than did the 10 patients taking imipramine alone. However, after two weeks, the five patients that received imipramine and high-dose estrogen had not improved as much as the patients receiving imipramine and low-dose estrogen. The only side-effect reported was drowsiness, which only affected the patients taking imipramine. Following the discontinuation of ethinyl estradiol, a time period of two weeks was required for the high-dose estrogen group to do as well as the low-dose group. This effect was attributed to the presence of residual estrogen in the high-dose group. In another group, five women received imipramine 150 mg and ethinyl estradiol 50 mrg daily did not improve as much as 10 patients receiving only imipramine. Also, the patients on the combination had severe side-effects including lethargy, coarse tremor and systolic hypotension (Prange, 1972h).
b) A 32-year-old female taking conjugated estrogens 2.5 mg and imipramine 100 mg developed lethargy, tremors, and signs of depersonalization. After two years of therapy, the patient increased her estrogen dose to 5 mg and then 7.5 mg daily. The patient became nauseated, had constant headaches, and low normal blood pressure. All lab work was normal. Upon discontinuing the estrogen, the side effects abated. Some investigators have proposed that the side effects resulted from enhanced TCA effects secondary to estrogen inhibition of hepatic microsomal enzymes (Somani & Khurana, 1973h; Khurana, 1972h).
c) In a study women received clomipramine and oral contraceptives or clomipramine alone. At the beginning of the study there were 30 women taking the combination, but 12 subsequently dropped out. The 18 patients on the combination were matched with 18 patients taking clomipramine alone. No significant difference was noted in the patients' responses to clomipramine. It was proposed that there was no significant difference in side-effects between the groups; however, the groups were matched

after patients had dropped out of the study. Had the patients been matched prior to the study, different conclusions may have been drawn (Beaumont, 1973d).
d) The effects of oral contraceptives on clomipramine was studied in 42 women between the ages of 18 and 40. Twenty-three women took clomipramine 25 mg at bedtime while 19 took clomipramine 25 mg at bedtime with oral contraceptives. Over the four-week study, three control patients (two due to side-effects) and five in the experimental group (two due to side-effects) dropped out. Venous blood samples were drawn at weekly intervals for measurement of serum clomipramine concentrations. No difference in serum concentrations was noted between the groups. However, this result may be partially due to the low dose of clomipramine given (Luscombe & John, 1980d).
e) The onset of akathisia was reported in 3 patients receiving conjugated estrogens and tricyclic antidepressants concurrently. A 24-year-old patient receiving clomipramine 120 mg daily for anorexia nervosa and conjugated estrogens 1.25 mg daily for amenorrhea developed restless legs and a constant desire to move continuously. Estrogen was discontinued and benztropine 2 mg was administered, resulting in marked reduction and resolution within 48 hours. Akathisia and disorientation developed in a 55-year-old patient on conjugated estrogen 1.25 mg daily who was prescribed amitriptyline 50 mg daily for depression. Within hours of amitriptyline, the patient was confused, restless, and possessed an inner desire to move continuously. Symptoms disappeared after discontinuing amitriptyline. A third case of akathisia was reported in a 35-year-old patient who received conjugated estrogen 1.25 mg daily and amitriptyline 50 mg daily. Akathisia developed within a few hours after taking the first dose of amitriptyline and resolved within 48 hours following discontinuation of the antidepressant (Krishnan et al, 1984h).
f) The absolute bioavailability of imipramine increased in women who received low-dose oral contraceptives (50 mcg or less of ethinyl estradiol) from 27% to 44% (p less than 0.05) as evident by an increase in the area under the plasma concentration time curve (Abernethy et al, 1984d).
g) Estrogens may inhibit the oxidation of TCAs by affecting hepatic microsomal enzymes (John et al, 1980d). Many TCAs are metabolized via oxidation and conjugation pathways. Inhibition of the oxidation of TCAs could result in accumulation and toxicity due to decreased clearance. Estrogens are suspected of possessing other effects on the central nervous system resulting in an antidepressant effect (Oppenheim, 1983d).

3.5.1.Z Dexfenfluramine

1) Interaction Effect: hypertension, other cardiac effects, and CNS stimulation
2) Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been reported to result in enhanced amphetamine effects from the release of norepinephrine (Beaumont, 1973h; Raisfeld, 1972). A similar reaction might also occur with all drugs that have amphetamine-like effects. Acute elevations in blood pressure have been noted (Flemenbaum, 1971a). Some amphetamine-like drugs may inhibit the metabolism of TCAs, although most combinations have not been studied. When amphetamine analogs are being used to treat obesity, it should be noted that TCAs frequently lead to moderate weight gain (Russ & Ackerman, 1988). False positive urine tests for amphetamines have been reported during therapy with some TCAs (Merigian & Browning, 1993). Caution is advised when concurrent administration of amphetamine-like agents and TCAs is warranted. The patient should be closely monitored for increased cardiovascular effects (hypertension and dysrhythmias).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other sympathomimetic agents could lead to hypertension, increased cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006; Flemenbaum, 1972). Use caution if such therapy is warranted. Monitor the patient closely for hypertension and dysrhythmias.
7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission
8) Literature Reports
a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agents. Additionally, coadministration of d-amphetamine with TCAs such as desipramine or protriptyline results in sustained increases in d-amphetamine concentration in the brain (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006).
b) Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism of some tricyclic antidepressants, such as imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transdermal system, 2006).
c) Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases in blood pressure such that the hypotensive effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of combined therapy. Discontinuation of the methylphenidate usually results in the blood pressure returning to normotensive levels; reinstitution of the methylphenidate resulted in further blood pressure elevation (Flemenbaum, 1971; Flemenbaum, 1972).
d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine given for at least four weeks, were given fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical improvement. However, fenfluramine more than doubled

steady-state plasma levels of desipramine (Price et al, 1990).
e) There have been claims based on uncontrolled studies that a better antidepressant response may occur with combined therapy (Garrettson et al, 1969). However, a systemic review of stimulants in the treatment of depression concluded that although uncontrolled studies were generally positive, the ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated little advantage of drug over placebo and did not appear to be as effective as the conventional antidepressants in primary depression (Satel & Nelson, 1989).

3.5.1.AA Dexmethylphenidate

1) Interaction Effect: hypertension, other cardiac effects, and CNS stimulation
2) Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been reported to result in enhanced amphetamine effects from the release of norepinephrine (Beaumont, 1973h; Raisfeld, 1972). A similar reaction might also occur with all drugs that have amphetamine-like effects. Acute elevations in blood pressure have been noted (Flemenbaum, 1971a). Some amphetamine-like drugs may inhibit the metabolism of TCAs, although most combinations have not been studied. When amphetamine analogs are being used to treat obesity, it should be noted that TCAs frequently lead to moderate weight gain (Russ & Ackerman, 1988). False positive urine tests for amphetamines have been reported during therapy with some TCAs (Merigian & Browning, 1993). Caution is advised when concurrent administration of amphetamine-like agents and TCAs is warranted. The patient should be closely monitored for increased cardiovascular effects (hypertension and dysrhythmias).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other sympathomimetic agents could lead to hypertension, increased cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006; Flemenbaum, 1972). Use caution if such therapy is warranted. Monitor the patient closely for hypertension and dysrhythmias.
7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission
8) Literature Reports
a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agents. Additionally, coadministration of d-amphetamine with TCAs such as desipramine or protriptyline results in sustained increases in d-amphetamine concentration in the brain (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006).
b) Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism of some tricyclic antidepressants, such as imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transdermal system, 2006).
c) Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases in blood pressure such that the hypotensive effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of combined therapy. Discontinuation of the methylphenidate usually results in the blood pressure returning to normotensive levels; reinstitution of the methylphenidate resulted in further blood pressure elevation (Flemenbaum, 1971; Flemenbaum, 1972).
d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine given for at least four weeks, were given fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical improvement. However, fenfluramine more than doubled steady-state plasma levels of desipramine (Price et al, 1990).
e) There have been claims based on uncontrolled studies that a better antidepressant response may occur with combined therapy (Garrettson et al, 1969). However, a systemic review of stimulants in the treatment of depression concluded that although uncontrolled studies were generally positive, the ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated little advantage of drug over placebo and did not appear to be as effective as the conventional antidepressants in primary depression (Satel & Nelson, 1989).

3.5.1.AB Dextroamphetamine

1) Interaction Effect: hypertension, other cardiac effects, and CNS stimulation
2) Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been reported to result in enhanced amphetamine effects from the release of norepinephrine (Beaumont, 1973h; Raisfeld, 1972). A similar reaction might also occur with all drugs that have amphetamine-like effects. Acute elevations in blood pressure have been noted (Flemenbaum, 1971a). Some amphetamine-like drugs may inhibit the metabolism of TCAs, although most combinations have not been studied. When amphetamine analogs are being used to treat obesity, it should be noted that TCAs frequently lead to moderate weight gain (Russ & Ackerman, 1988). False positive urine tests for amphetamines have been reported during therapy with some TCAs (Merigian & Browning, 1993). Caution is advised when concurrent administration of amphetamine-like agents and TCAs is warranted. The patient should be closely monitored for increased cardiovascular effects (hypertension and dysrhythmias).
3) Severity: moderate
4) Onset: delayed

5) Substantiation: theoretical
6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other sympathomimetic agents could lead to hypertension, increased cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006; Flemenbaum, 1972). Use caution if such therapy is warranted. Monitor the patient closely for hypertension and dysrhythmias.
7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission
8) Literature Reports
a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agents. Additionally, coadministration of d-amphetamine with TCAs such as desipramine or protriptyline results in sustained increases in d-amphetamine concentration in the brain (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006).
b) Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism of some tricyclic antidepressants, such as imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transdermal system, 2006).
c) Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases in blood pressure such that the hypotensive effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of combined therapy. Discontinuation of the methylphenidate usually results in the blood pressure returning to normotensive levels; reinstitution of the methylphenidate resulted in further blood pressure elevation (Flemenbaum, 1971; Flemenbaum, 1972).
d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine given for at least four weeks, were given fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical improvement. However, fenfluramine more than doubled steady-state plasma levels of desipramine (Price et al, 1990).
e) There have been claims based on uncontrolled studies that a better antidepressant response may occur with combined therapy (Garrettson et al, 1969). However, a systemic review of stimulants in the treatment of depression concluded that although uncontrolled studies were generally positive, the ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated little advantage of drug over placebo and did not appear to be as effective as the conventional antidepressants in primary depression (Satel & Nelson, 1989).

3.5.1.AC Dicumarol
1) Interaction Effect: increased risk of bleeding
2) Summary: Tricyclic antidepressants (TCAs) may increase the half-life and bioavailability of oral anticoagulants (Vesell et al, 1970g; Williams et al, 1976g). Considerable interindividual differences may be found (Pond et al, 1975g).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: In patients receiving tricyclic antidepressants and oral anticoagulant therapy, the prothrombin time ratio or INR (international normalized ratio) should be closely monitored with the addition and withdrawal of the antidepressant, and should be periodically reassessed during concurrent therapy. Achieving a stable drug regimen which produces the desired level of anticoagulation may be difficult in patients on this combination, and frequent adjustments of the anticoagulant dose may be required.
7) Probable Mechanism: decreased dicumarol metabolism; increased dicumarol absorption
8) Literature Reports
a) In a study of healthy volunteers, the concurrent use of nortriptyline or amitriptyline resulted in an increase of dicumarol levels and an increase in the plasma half-life of dicumarol, although the effect was not consistent in all subjects (Pond et al, 1975f). This effect was not observed with warfarin.
b) A single oral dose of bishydroxycoumarin after 8 days of nortriptyline resulted in a significantly prolonged half-life and decreased volume of distribution of the coumarin anticoagulant in 6 healthy volunteers (Vesell et al, 1970f). The mechanism of action was suggested to be reduced bishydroxycoumarin metabolism and/or altered coumarin absorption.
c) Drug dosing was studied in 16 patients on long-term anticoagulant therapy who used concurrent TCAs (Williams et al, 1976f). TCAs affected the stability of anticoagulant control leading to frequent changes in the doses of anticoagulants. Inhibition of coumarin metabolism was the postulated mechanism.

3.5.1.AD Dienestrol
1) Interaction Effect: attenuation of antidepressant effectiveness; tricyclic toxicity (drowsiness, hypotension, akathisia)
2) Summary: In isolated cases, the pharmacologic effects of tricyclic antidepressants may be increased or decreased by estrogens (Somani & Khurana, 1973a), with paradoxical loss of antidepressant effect yet tricyclic toxicity being manifested simultaneously (Prange, 1972a). The effects of the interaction appear to be estrogen dose-related (Khurana, 1972a) and may be of clinical importance primarily in patients previously stabilized on tricyclic therapy who are being started on estrogen therapy (Krishnan et al, 1984a).
3) Severity: minor

4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: If signs or symptoms of altered tricyclic response are noted, dose adjustment downward of either the estrogen or tricyclic component may be successful in restoring effectiveness or resolving toxicity. However, drug withdrawal may be required.
7) Probable Mechanism: possible estrogen-enhanced hepatic metabolism of the tricyclic
8) Literature Reports

a) Some studies evaluated the qualitative effects of concomitant administration of estrogen and TCAs. In one trial, 30 depressed female prisoners were randomly assigned to 4 treatment groups. Ten patients received placebo, 10 received imipramine (150 milligrams/day) and placebo, 5 patients received imipramine (150 milligrams/day) and ethinyl estradiol (50 micrograms/day), while 5 patients received imipramine (150 milligrams/day) and ethinyl estradiol (25 micrograms/day). The 10 patients that received placebo did not improve over the 6 weeks of the study. The 10 patients taking estrogen and imipramine demonstrated a significantly greater improvement in symptoms than did the 10 patients taking imipramine alone. However, after 2 weeks, the 5 patients that received imipramine and high-dose estrogen had not improved as much as the patients receiving imipramine and low-dose estrogen. The only side-effect reported was drowsiness, which only affected the patients taking imipramine. Following the discontinuation of ethinyl estradiol, a time period of 2 weeks was required for the high-dose estrogen group to do as well as the low-dose group. This effect was attributed to the presence of residual estrogen in the high-dose group. In another group, 5 women received imipramine 150 milligrams and ethinyl estradiol 50 micrograms daily did not improve as much as 10 patients receiving only imipramine. Also, the patients on the combination had severe side-effects including lethargy, coarse tremor and systolic hypotension (Prange, 1972).

b) A case report demonstrated an interaction in a 32-year-old female taking conjugated estrogens 2.5 milligrams and imipramine 100 milligrams. The patient developed lethargy, tremors, and signs of depersonalization. After 2 years of therapy, the patient increased her estrogen dose to 5 milligrams and then 7.5 milligrams daily. The patient became nauseated, had constant headaches, and low normal blood pressure. All lab work was normal. Upon discontinuing the estrogen, the side-effects abated (Khurana, 1972). Some investigators have proposed that the side effects resulted from enhanced TCA effects secondary to estrogen inhibition of hepatic microsomal enzymes (Somani & Khurana, 1973).

c) In a study women received clomipramine and oral contraceptives or clomipramine alone. At the beginning of the study there were 30 women taking the combination, but 12 subsequently dropped out. The 18 patients on the combination were matched with 18 patients taking clomipramine alone. No significant difference was noted in the patients' responses to clomipramine. It was proposed that there was no significant difference in side-effects between the groups; however, the groups were matched after patients had dropped out of the study. Had the patients been matched prior to the study, different conclusions may have been drawn (Beaumont, 1973).

d) The effects of oral contraceptives on clomipramine were studied in 42 women between the ages of 18 and 40. Twenty-three women took clomipramine 25 milligrams at bedtime while 19 took clomipramine 25 milligrams at bedtime with oral contraceptives. Over the 4-week study, 3 control patients (2 due to side-effects) and 5 in the experimental group (2 due to side-effects) dropped out. Venous blood samples were drawn at weekly intervals for measurement of serum clomipramine concentrations. No difference in serum concentrations was noted between the groups. However, this result may be partially due to the low dose of clomipramine given (Luscombe & John, 1980).

e) Akathisia was reported in 3 patients receiving conjugated estrogens and tricyclic antidepressants concurrently. A 24-year-old patient receiving clomipramine 120 milligrams/day for anorexia nervosa and conjugated estrogens 1.25 milligrams/day for amenorrhea developed restless legs and a constant desire to move continuously. Estrogen was discontinued and benztropine 2 milligrams was administered, resulting in marked reduction and resolution within 48 hours. Akathisia and disorientation developed in a 55-year-old patient on conjugated estrogens 1.25 milligrams/day who was prescribed amitriptyline 50 milligrams/day for depression. Within hours of amitriptyline, the patient was confused, restless, and possessed an inner desire to move continuously. Symptoms disappeared after discontinuing amitriptyline. Positive rechallenge at one week with doxepin 100 milligrams, with resolution following discontinuation of doxepin. A third case of akathisia was reported in a 35-year-old patient who received conjugated estrogens 1.25 milligrams/day and amitriptyline 50 milligrams/day. Akathisia developed within a few hours after taking the first dose of amitriptyline and resolved within 48 hours following discontinuation of the antidepressant (Krishnan et al, 1984).

f) The absolute bioavailability of imipramine increased in women who received low-dose oral contraceptives (50 micrograms or less of ethinyl estradiol) from 27 to 44% (p less than 0.05) as evident by an increase in the area under the plasma concentration time curve (Abernethy et al, 1984).

g) Estrogens may inhibit the oxidation of TCAs by affecting hepatic microsomal enzymes (John et al, 1980). Many TCAs are metabolized via oxidation and conjugation pathways. Inhibition of the oxidation of TCAs could result in accumulation and toxicity due to decreased clearance. Estrogens are suspected of possessing other effects on the central nervous system resulting in an antidepressant effect (Oppenheim, 1983).

3.5.1.AE Diethylpropion

1) Interaction Effect: hypertension, other cardiac effects, and CNS stimulation

2) Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been reported to result in enhanced amphetamine effects from the release of norepinephrine (Beaumont, 1973h; Raisfeld, 1972). A similar reaction might also occur with all drugs that have amphetamine-like effects. Acute elevations in blood pressure have been noted (Flemenbaum, 1971a). Some amphetamine-like drugs may inhibit the metabolism of TCAs, although most combinations have not been studied. When amphetamine analogs are being used to treat obesity, it should be noted that TCAs frequently lead to moderate weight gain (Russ & Ackerman, 1988). False positive urine tests for amphetamines have been reported during therapy with some TCAs (Merigian & Browning, 1993). Caution is advised when concurrent administration of amphetamine-like agents and TCAs is warranted. The patient should be closely monitored for increased cardiovascular effects (hypertension and dysrhythmias).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other sympathomimetic agents could lead to hypertension, increased cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006; Flemenbaum, 1972). Use caution if such therapy is warranted. Monitor the patient closely for hypertension and dysrhythmias.
7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission
8) Literature Reports
a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agents. Additionally, coadministration of d-amphetamine with TCAs such as desipramine or protriptyline results in sustained increases in d-amphetamine concentration in the brain (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006).
b) Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism of some tricyclic antidepressants, such as imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transdermal system, 2006).
c) Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases in blood pressure such that the hypotensive effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of combined therapy. Discontinuation of the methylphenidate usually results in the blood pressure returning to normotensive levels; reinstitution of the methylphenidate resulted in further blood pressure elevation (Flemenbaum, 1971; Flemenbaum, 1972).
d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine given for at least four weeks, were given fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical improvement. However, fenfluramine more than doubled steady-state plasma levels of desipramine (Price et al, 1990).
e) There have been claims based on uncontrolled studies that a better antidepressant response may occur with combined therapy (Garrettson et al, 1969). However, a systemic review of stimulants in the treatment of depression concluded that although uncontrolled studies were generally positive, the ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated little advantage of drug over placebo and did not appear to be as effective as the conventional antidepressants in primary depression (Satel & Nelson, 1989).

3.5.1.AF Diethylstilbestrol
1) Interaction Effect: attenuation of antidepressant effectiveness; tricyclic toxicity (drowsiness, hypotension, akathisia)
2) Summary: In isolated cases, the pharmacologic effects of tricyclic antidepressants may be increased or decreased by estrogens (Somani & Khurana, 1973m), with paradoxical loss of antidepressant effect yet tricyclic toxicity being manifested simultaneously (Prange, 1972l). The effects of the interaction appear to be estrogen dose-related (Khurana, 1972m) and may be of clinical importance primarily in patients previously stabilized on tricyclic therapy who are being started on estrogen therapy (Krishnan et al, 1984l).
3) Severity: minor
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: If signs or symptoms of altered tricyclic response are noted, dose adjustment downward of either the estrogen or tricyclic component may be successful in restoring effectiveness or resolving toxicity. However, drug withdrawal may be required.
7) Probable Mechanism: possible estrogen-enhanced hepatic metabolism of the tricyclic
8) Literature Reports
a) Some studies evaluated the qualitative effects of concomitant administration of estrogen and TCAs. In one trial, 30 depressed female prisoners were randomly assigned to 4 treatment groups. Ten patients received placebo, 10 received imipramine (150 milligrams/day) and placebo, 5 patients received imipramine (150 milligrams/day) and ethinyl estradiol (50 micrograms/day), while 5 patients received imipramine (150 milligrams/day) and ethinyl estradiol (25 micrograms/day). The 10 patients that received placebo did not improve over the 6 weeks of the study. The 10 patients taking estrogen and imipramine demonstrated a significantly greater improvement in symptoms than did the 10 patients taking imipramine alone. However, after 2 weeks, the 5 patients that received imipramine and high-dose

estrogen had not improved as much as the patients receiving imipramine and low-dose estrogen. The only side-effect reported was drowsiness, which only affected the patients taking imipramine. Following the discontinuation of ethinyl estradiol, a time period of 2 weeks was required for the high-dose estrogen group to do as well as the low-dose group. This effect was attributed to the presence of residual estrogen in the high-dose group. In another group, 5 women received imipramine 150 milligrams and ethinyl estradiol 50 micrograms daily did not improve as much as 10 patients receiving only imipramine. Also, the patients on the combination had severe side-effects including lethargy, coarse tremor and systolic hypotension (Prange, 1972k).

b) A case report demonstrated an interaction in a 32-year-old female taking conjugated estrogens 2.5 milligrams and imipramine 100 milligrams. The patient developed lethargy, tremors, and signs of depersonalization. After 2 years of therapy, the patient increased her estrogen dose to 5 milligrams and then 7.5 milligrams daily. The patient became nauseated, had constant headaches, and low normal blood pressure. All lab work was normal. Upon discontinuing the estrogen, the side-effects abated (Khurana, 1972l). Some investigators have proposed that the side effects resulted from enhanced TCA effects secondary to estrogen inhibition of hepatic microsomal enzymes (Somani & Khurana, 1973l).

c) In a study women received clomipramine and oral contraceptives or clomipramine alone. At the beginning of the study there were 30 women taking the combination, but 12 subsequently dropped out. The 18 patients on the combination were matched with 18 patients taking clomipramine alone. No significant difference was noted in the patients' responses to clomipramine. It was proposed that there was no significant difference in side-effects between the groups; however, the groups were matched after patients had dropped out of the study. Had the patients been matched prior to the study, different conclusions may have been drawn (Beaumont, 1973g).

d) The effects of oral contraceptives on clomipramine were studied in 42 women between the ages of 18 and 40. Twenty-three women took clomipramine 25 milligrams at bedtime while 19 took clomipramine 25 milligrams at bedtime with oral contraceptives. Over the 4-week study, 3 control patients (2 due to side-effects) and 5 in the experimental group (2 due to side-effects) dropped out. Venous blood samples were drawn at weekly intervals for measurement of serum clomipramine concentrations. No difference in serum concentrations was noted between the groups. However, this result may be partially due to the low dose of clomipramine given (Luscombe & John, 1980e).

e) Akathisia was reported in 3 patients receiving conjugated estrogens and tricyclic antidepressants concurrently. A 24-year-old patient receiving clomipramine 120 milligrams/day for anorexia nervosa and conjugated estrogens 1.25 milligrams/day for amenorrhea developed restless legs and a constant desire to move continuously. Estrogen was discontinued and benztropine 2 milligrams was administered, resulting in marked reduction and resolution within 48 hours. Akathisia and disorientation developed in a 55-year-old patient on conjugated estrogens 1.25 milligrams/day who was prescribed amitriptyline 50 milligrams/day for depression. Within hours of amitriptyline, the patient was confused, restless, and possessed an inner desire to move continuously. Symptoms disappeared after discontinuing amitriptyline. Positive rechallenge at one week with doxepin 100 milligrams, with resolution following discontinuation of doxepin. A third case of akathisia was reported in a 35-year-old patient who received conjugated estrogens 1.25 milligrams/day and amitriptyline 50 milligrams/day. Akathisia developed within a few hours after taking the first dose of amitriptyline and resolved within 48 hours following discontinuation of the antidepressant (Krishnan et al, 1984k).

f) The absolute bioavailability of imipramine increased in women who received low-dose oral contraceptives (50 micrograms or less of ethinyl estradiol) from 27 to 44% (p less than 0.05) as evident by an increase in the area under the plasma concentration time curve (Abernethy et al, 1984f).

g) Estrogens may inhibit the oxidation of TCAs by affecting hepatic microsomal enzymes (John et al, 1980f). Many TCAs are metabolized via oxidation and conjugation pathways. Inhibition of the oxidation of TCAs could result in accumulation and toxicity due to decreased clearance. Estrogens are suspected of possessing other effects on the central nervous system resulting in an antidepressant effect (Oppenheim, 1983f).

3.5.1.AG Diphenhydramine

1) Interaction Effect: increased anticholinergic effects (dry mouth, urinary retention)

2) Summary: Concomitant antidepressants with strong anticholinergic effects (e.g., amitriptyline, amoxapine, clomipramine) and antihistamines may increase the possibility of adynamic ileus, urinary retention, or chronic glaucoma. This interaction may be more prominent in elderly patients (Blazer et al, 1983; Arnold et al, 1981).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: Patients should be warned that taking antihistamines, including over-the-counter sleeping pills and cold and allergy preparations, may increase the side effects of clomipramine. Patients should be monitored for dry mouth, drowsiness, and problems with urination. Lower dose of diphenhydramine might be considered, particularly in elderly individuals.

7) Probable Mechanism: additive anticholinergic effects

3.5.1.AH Duloxetine

1) Interaction Effect: increased tricyclic antidepressant serum concentrations and potential toxicity

(anticholinergic effects, sedation, confusion, cardiac arrhythmias)
2) Summary: The coadministration of duloxetine with a tricyclic antidepressant is likely to increase bioavailability of the tricyclic agent, increasing the risk of adverse events. Duloxetine is a moderately potent inhibitor of CYP2D6. When a single dose of the CYP2D6 substrate desipramine 50 mg and duloxetine 60 mg twice daily were coadministered, the desipramine AUC increased 3-fold over baseline (Prod Info CYMBALTA(R) delayed-release oral capsules, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Use caution with the combined use of duloxetine with tricyclic antidepressants (TCAs). If concomitant therapy with duloxetine and a TCA is unavoidable, plasma concentrations of the tricyclic should be closely monitored and dose adjustments made accordingly (Prod Info CYMBALTA(R) delayed-release oral capsules, 2008). Also, monitor patients for signs and symptoms of TCA toxicity (anticholinergic effects, sedation, confusion, and cardiac arrhythmias).
7) Probable Mechanism: duloxetine inhibition of CYP2D6-mediated tricyclic agent metabolism

3.5.1.AI Enalaprilat
1) Interaction Effect: clomipramine toxicity (confusion, insomnia, irritability)
2) Summary: The addition of clomipramine to long-standing enalapril therapy resulted in high blood levels of clomipramine and signs of toxicity (confusion, insomnia, irritability, and mood changes) in 2 cases. Reduction of the clomipramine dose resulted in lower blood levels (Toutoungi, 1992).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor for signs of clomipramine toxicity; lower doses may be required with concurrent therapy with enalapril.
7) Probable Mechanism: unknown

3.5.1.AJ Enalapril Maleate
1) Interaction Effect: clomipramine toxicity (confusion, insomnia, irritability)
2) Summary: The addition of clomipramine to long-standing enalapril therapy resulted in high blood levels of clomipramine and signs of toxicity (confusion, insomnia, irritability, and mood changes) in 2 cases. Reduction of the clomipramine dose resulted in lower blood levels (Toutoungi, 1992).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor for signs of clomipramine toxicity; lower doses may be required with concurrent therapy with enalapril.
7) Probable Mechanism: unknown

3.5.1.AK Epinephrine
1) Interaction Effect: hypertension, cardiac arrhythmias, and tachycardia
2) Summary: Clinical trials have demonstrated a 2- to 8-fold increase in the effects of intravenous infusions of alpha adrenergic drugs to volunteers on tricyclic antidepressants. Arrhythmias and other severe adverse effects have also been reported (Ghose, 1980; Avery, 1973; Boakes et al, 1973a; Boakes, 1973; Mitchell et al, 1970; Stone et al, 1964). Local use (e.g., dental anesthesia) of epinephrine in concentrations of 1:100,000 or less is less likely to precipitate clinically significant hemodynamic changes (Steinberg & Block, 1971).
3) Severity: major
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: The vasoconstriction and other alpha-adrenergic effects of sympathomimetic drugs are substantially enhanced in the presence of tricyclic antidepressants (TCAs). Concomitant use should be avoided. If these drugs are given together, careful monitoring and a dose reduction of the sympathomimetic is required. Patients should be instructed to inform their doctor or dentist that they are taking a tricyclic antidepressant prior to any surgery or procedure.
7) Probable Mechanism: inhibition of norepinephrine reuptake
8) Literature Reports
a) Four healthy volunteers received intravenous infusions of various sympathomimetic amines (epinephrine, norepinephrine, phenylephrine, and isoproterenol) before and after imipramine (25 mg three times daily for five days). They showed an increased pressor response to epinephrine (2- to 4-fold), norepinephrine (4- to 8-fold), and phenylephrine (2- to 3-fold) after imipramine, but no difference was observed in the response to isoproterenol. Thus, the increased pressor response appeared to occur only for alpha adrenergic effects. All four subjects demonstrated changes in cardiac rhythm with epinephrine and imipramine consisting of sinus arrhythmia in three subjects and multiple ectopic beats and a nodal rhythm in the fourth subject (Boakes et al, 1973).
b) A review of spontaneous reports of adverse reactions to vasoconstrictors in local anesthetics found that 15 patients receiving a local anesthetic with norepinephrine (1:25,000) had severe reactions

(severe headaches, chest tightness, subarachnoid hemorrhage). The drug history was incomplete, but at least three had been taking a tricyclic antidepressant at the time (Anon, 1972).

3.5.1.AL Esterified Estrogens

1) Interaction Effect: possible attenuation of antidepressant effectiveness; tricyclic toxicity (drowsiness, hypotension, akathisia)

2) Summary: In isolated cases, the pharmacologic effects of tricyclic antidepressants may be increased or decreased by estrogens (Somani & Khurana, 1973i), with paradoxical loss of antidepressant effect yet tricyclic toxicity being manifested simultaneously (Prange, 1972i). The effects of the interaction appear to be estrogen dose-related (Khurana, 1972i) and may be of clinical importance primarily in patients previously stabilized on tricyclic therapy who are being started on estrogen therapy (Krishnan et al, 1984i).

3) Severity: minor

4) Onset: delayed

5) Substantiation: established

6) Clinical Management: If signs or symptoms of altered tricyclic response are noted, dose adjustment downward of either the estrogen or tricyclic component may be successful in restoring effectiveness or resolving toxicity. However, drug withdrawal may be required.

7) Probable Mechanism: possible inhibition of hepatic metabolism of the tricyclic antidepressant

8) Literature Reports

a) Some studies evaluated the qualitative effects of concomitant administration of estrogen and TCAs. In one trial, 30 depressed female prisoners were randomly assigned to four treatment groups. Ten patients received placebo, 10 received imipramine (150 mg daily) and placebo, five patients received imipramine (150 mg daily) and ethinyl estradiol (50 mcg daily), while five patients received imipramine (150 mg daily) and ethinyl estradiol (25 mcg daily). The 10 patients that received placebo did not improve over the six weeks of the study. The 10 patients taking estrogen and imipramine demonstrated a significantly greater improvement in symptoms than did the 10 patients taking imipramine alone. However, after two weeks, the five patients that received imipramine and high-dose estrogen had not improved as much as the patients receiving imipramine and low-dose estrogen. The only side-effect reported was drowsiness, which only affected the patients taking imipramine. Following the discontinuation of ethinyl estradiol, a time period of two weeks was required for the high-dose estrogen group to do as well as the low-dose group. This effect was attributed to the presence of residual estrogen in the high-dose group. In another group, five women received imipramine 150 mg and ethinyl estradiol 50 mrg daily did not improve as much as 10 patients receiving only imipramine. Also, the patients on the combination had severe side-effects including lethargy, coarse tremor and systolic hypotension (Prange, 1972h).

b) A 32-year-old female taking conjugated estrogens 2.5 mg and imipramine 100 mg developed lethargy, tremors, and signs of depersonalization. After two years of therapy, the patient increased her estrogen dose to 5 mg and then 7.5 mg daily. The patient became nauseated, had constant headaches, and low normal blood pressure. All lab work was normal. Upon discontinuing the estrogen, the side effects abated. Some investigators have proposed that the side effects resulted from enhanced TCA effects secondary to estrogen inhibition of hepatic microsomal enzymes (Somani & Khurana, 1973h; Khurana, 1972h).

c) In a study women received clomipramine and oral contraceptives or clomipramine alone. At the beginning of the study there were 30 women taking the combination, but 12 subsequently dropped out. The 18 patients on the combination were matched with 18 patients taking clomipramine alone. No significant difference was noted in the patients' responses to clomipramine. It was proposed that there was no significant difference in side-effects between the groups; however, the groups were matched after patients had dropped out of the study. Had the patients been matched prior to the study, different conclusions may have been drawn (Beaumont, 1973d).

d) The effects of oral contraceptives on clomipramine was studied in 42 women between the ages of 18 and 40. Twenty-three women took clomipramine 25 mg at bedtime while 19 took clomipramine 25 mg at bedtime with oral contraceptives. Over the four-week study, three control patients (two due to side-effects) and five in the experimental group (two due to side-effects) dropped out. Venous blood samples were drawn at weekly intervals for measurement of serum clomipramine concentrations. No difference in serum concentrations was noted between the groups. However, this result may be partially due to the low dose of clomipramine given (Luscombe & John, 1980d).

e) The onset of akathisia was reported in 3 patients receiving conjugated estrogens and tricyclic antidepressants concurrently. A 24-year-old patient receiving clomipramine 120 mg daily for anorexia nervosa and conjugated estrogens 1.25 mg daily for amenorrhea developed restless legs and a constant desire to move continuously. Estrogen was discontinued and benztropine 2 mg was administered, resulting in marked reduction and resolution within 48 hours. Akathisia and disorientation developed in a 55-year-old patient on conjugated estrogen 1.25 mg daily who was prescribed amitriptyline 50 mg daily for depression. Within hours of amitriptyline, the patient was confused, restless, and possessed an inner desire to move continuously. Symptoms disappeared after discontinuing amitriptyline. A third case of akathisia was reported in a 35-year-old patient who received conjugated estrogen 1.25 mg daily and amitriptyline 50 mg daily. Akathisia developed within a few hours after taking the first dose of amitriptyline and resolved within 48 hours following discontinuation of the antidepressant (Krishnan et al, 1984h).

f) The absolute bioavailability of imipramine increased in women who received low-dose oral contraceptives (50 mcg or less of ethinyl estradiol) from 27% to 44% (p less than 0.05) as evident by an increase in the area under the plasma concentration time curve (Abernethy et al, 1984d).
g) Estrogens may inhibit the oxidation of TCAs by affecting hepatic microsomal enzymes (John et al, 1980d). Many TCAs are metabolized via oxidation and conjugation pathways. Inhibition of the oxidation of TCAs could result in accumulation and toxicity due to decreased clearance. Estrogens are suspected of possessing other effects on the central nervous system resulting in an antidepressant effect (Oppenheim, 1983d).

3.5.1.AM Estradiol

1) Interaction Effect: possible attenuation of antidepressant effectiveness; tricyclic toxicity (drowsiness, hypotension, akathisia)
2) Summary: In isolated cases, the pharmacologic effects of tricyclic antidepressants may be increased or decreased by estrogens (Somani & Khurana, 1973i), with paradoxical loss of antidepressant effect yet tricyclic toxicity being manifested simultaneously (Prange, 1972i). The effects of the interaction appear to be estrogen dose-related (Khurana, 1972i) and may be of clinical importance primarily in patients previously stabilized on tricyclic therapy who are being started on estrogen therapy (Krishnan et al, 1984i).
3) Severity: minor
4) Onset: delayed
5) Substantiation: established
6) Clinical Management: If signs or symptoms of altered tricyclic response are noted, dose adjustment downward of either the estrogen or tricyclic component may be successful in restoring effectiveness or resolving toxicity. However, drug withdrawal may be required.
7) Probable Mechanism: possible inhibition of hepatic metabolism of the tricyclic antidepressant
8) Literature Reports

a) Some studies evaluated the qualitative effects of concomitant administration of estrogen and TCAs. In one trial, 30 depressed female prisoners were randomly assigned to four treatment groups. Ten patients received placebo, 10 received imipramine (150 mg daily) and placebo, five patients received imipramine (150 mg daily) and ethinyl estradiol (50 mcg daily), while five patients received imipramine (150 mg daily) and ethinyl estradiol (25 mcg daily). The 10 patients that received placebo did not improve over the six weeks of the study. The 10 patients taking estrogen and imipramine demonstrated a significantly greater improvement in symptoms than did the 10 patients taking imipramine alone. However, after two weeks, the five patients that received imipramine and high-dose estrogen had not improved as much as the patients receiving imipramine and low-dose estrogen. The only side-effect reported was drowsiness, which only affected the patients taking imipramine. Following the discontinuation of ethinyl estradiol, a time period of two weeks was required for the high-dose estrogen group to do as well as the low-dose group. This effect was attributed to the presence of residual estrogen in the high-dose group. In another group, five women received imipramine 150 mg and ethinyl estradiol 50 mrg daily did not improve as much as 10 patients receiving only imipramine. Also, the patients on the combination had severe side-effects including lethargy, coarse tremor and systolic hypotension (Prange, 1972h).
b) A 32-year-old female taking conjugated estrogens 2.5 mg and imipramine 100 mg developed lethargy, tremors, and signs of depersonalization. After two years of therapy, the patient increased her estrogen dose to 5 mg and then 7.5 mg daily. The patient became nauseated, had constant headaches, and low normal blood pressure. All lab work was normal. Upon discontinuing the estrogen, the side effects abated. Some investigators have proposed that the side effects resulted from enhanced TCA effects secondary to estrogen inhibition of hepatic microsomal enzymes (Somani & Khurana, 1973h; Khurana, 1972h).
c) In a study women received clomipramine and oral contraceptives or clomipramine alone. At the beginning of the study there were 30 women taking the combination, but 12 subsequently dropped out. The 18 patients on the combination were matched with 18 patients taking clomipramine alone. No significant difference was noted in the patients' responses to clomipramine. It was proposed that there was no significant difference in side-effects between the groups; however, the groups were matched after patients had dropped out of the study. Had the patients been matched prior to the study, different conclusions may have been drawn (Beaumont, 1973d).
d) The effects of oral contraceptives on clomipramine was studied in 42 women between the ages of 18 and 40. Twenty-three women took clomipramine 25 mg at bedtime while 19 took clomipramine 25 mg at bedtime with oral contraceptives. Over the four-week study, three control patients (two due to side-effects) and five in the experimental group (two due to side-effects) dropped out. Venous blood samples were drawn at weekly intervals for measurement of serum clomipramine concentrations. No difference in serum concentrations was noted between the groups. However, this result may be partially due to the low dose of clomipramine given (Luscombe & John, 1980d).
e) The onset of akathisia was reported in 3 patients receiving conjugated estrogens and tricyclic antidepressants concurrently. A 24-year-old patient receiving clomipramine 120 mg daily for anorexia nervosa and conjugated estrogens 1.25 mg daily for amenorrhea developed restless legs and a constant desire to move continuously. Estrogen was discontinued and benztropine 2 mg was administered, resulting in marked reduction and resolution within 48 hours. Akathisia and disorientation developed in a 55-year-old patient on conjugated estrogen 1.25 mg daily who was prescribed

amitriptyline 50 mg daily for depression. Within hours of amitriptyline, the patient was confused, restless, and possessed an inner desire to move continuously. Symptoms disappeared after discontinuing amitriptyline. A third case of akathisia was reported in a 35-year-old patient who received conjugated estrogen 1.25 mg daily and amitriptyline 50 mg daily. Akathisia developed within a few hours after taking the first dose of amitriptyline and resolved within 48 hours following discontinuation of the antidepressant (Krishnan et al, 1984h).

f) The absolute bioavailability of imipramine increased in women who received low-dose oral contraceptives (50 mcg or less of ethinyl estradiol) from 27% to 44% (p less than 0.05) as evident by an increase in the area under the plasma concentration time curve (Abernethy et al, 1984d).

g) Estrogens may inhibit the oxidation of TCAs by affecting hepatic microsomal enzymes (John et al, 1980d). Many TCAs are metabolized via oxidation and conjugation pathways. Inhibition of the oxidation of TCAs could result in accumulation and toxicity due to decreased clearance. Estrogens are suspected of possessing other effects on the central nervous system resulting in an antidepressant effect (Oppenheim, 1983d).

3.5.1.AN Estriol

1) Interaction Effect: possible attenuation of antidepressant effectiveness; tricyclic toxicity (drowsiness, hypotension, akathisia)

2) Summary: In isolated cases, the pharmacologic effects of tricyclic antidepressants may be increased or decreased by estrogens (Somani & Khurana, 1973i), with paradoxical loss of antidepressant effect yet tricyclic toxicity being manifested simultaneously (Prange, 1972i). The effects of the interaction appear to be estrogen dose-related (Khurana, 1972i) and may be of clinical importance primarily in patients previously stabilized on tricyclic therapy who are being started on estrogen therapy (Krishnan et al, 1984i).

3) Severity: minor

4) Onset: delayed

5) Substantiation: established

6) Clinical Management: If signs or symptoms of altered tricyclic response are noted, dose adjustment downward of either the estrogen or tricyclic component may be successful in restoring effectiveness or resolving toxicity. However, drug withdrawal may be required.

7) Probable Mechanism: possible inhibition of hepatic metabolism of the tricyclic antidepressant

8) Literature Reports

a) Some studies evaluated the qualitative effects of concomitant administration of estrogen and TCAs. In one trial, 30 depressed female prisoners were randomly assigned to four treatment groups. Ten patients received placebo, 10 received imipramine (150 mg daily) and placebo, five patients received imipramine (150 mg daily) and ethinyl estradiol (50 mcg daily), while five patients received imipramine (150 mg daily) and ethinyl estradiol (25 mcg daily). The 10 patients that received placebo did not improve over the six weeks of the study. The 10 patients taking estrogen and imipramine demonstrated a significantly greater improvement in symptoms than did the 10 patients taking imipramine alone. However, after two weeks, the five patients that received imipramine and high-dose estrogen had not improved as much as the patients receiving imipramine and low-dose estrogen. The only side-effect reported was drowsiness, which only affected the patients taking imipramine. Following the discontinuation of ethinyl estradiol, a time period of two weeks was required for the high-dose estrogen group to do as well as the low-dose group. This effect was attributed to the presence of residual estrogen in the high-dose group. In another group, five women received imipramine 150 mg and ethinyl estradiol 50 mrg daily did not improve as much as 10 patients receiving only imipramine. Also, the patients on the combination had severe side-effects including lethargy, coarse tremor and systolic hypotension (Prange, 1972h).

b) A 32-year-old female taking conjugated estrogens 2.5 mg and imipramine 100 mg developed lethargy, tremors, and signs of depersonalization. After two years of therapy, the patient increased her estrogen dose to 5 mg and then 7.5 mg daily. The patient became nauseated, had constant headaches, and low normal blood pressure. All lab work was normal. Upon discontinuing the estrogen, the side effects abated. Some investigators have proposed that the side effects resulted from enhanced TCA effects secondary to estrogen inhibition of hepatic microsomal enzymes (Somani & Khurana, 1973h; Khurana, 1972h).

c) In a study women received clomipramine and oral contraceptives or clomipramine alone. At the beginning of the study there were 30 women taking the combination, but 12 subsequently dropped out. The 18 patients on the combination were matched with 18 patients taking clomipramine alone. No significant difference was noted in the patients' responses to clomipramine. It was proposed that there was no significant difference in side-effects between the groups; however, the groups were matched after patients had dropped out of the study. Had the patients been matched prior to the study, different conclusions may have been drawn (Beaumont, 1973d).

d) The effects of oral contraceptives on clomipramine was studied in 42 women between the ages of 18 and 40. Twenty-three women took clomipramine 25 mg at bedtime while 19 took clomipramine 25 mg at bedtime with oral contraceptives. Over the four-week study, three control patients (two due to side-effects) and five in the experimental group (two due to side-effects) dropped out. Venous blood samples were drawn at weekly intervals for measurement of serum clomipramine concentrations. No difference in serum concentrations was noted between the groups. However, this result may be partially due to the low dose of clomipramine given (Luscombe & John, 1980d).

e) The onset of akathisia was reported in 3 patients receiving conjugated estrogens and tricyclic antidepressants concurrently. A 24-year-old patient receiving clomipramine 120 mg daily for anorexia nervosa and conjugated estrogens 1.25 mg daily for amenorrhea developed restless legs and a constant desire to move continuously. Estrogen was discontinued and benztropine 2 mg was administered, resulting in marked reduction and resolution within 48 hours. Akathisia and disorientation developed in a 55-year-old patient on conjugated estrogen 1.25 mg daily who was prescribed amitriptyline 50 mg daily for depression. Within hours of amitriptyline, the patient was confused, restless, and possessed an inner desire to move continuously. Symptoms disappeared after discontinuing amitriptyline. A third case of akathisia was reported in a 35-year-old patient who received conjugated estrogen 1.25 mg daily and amitriptyline 50 mg daily. Akathisia developed within a few hours after taking the first dose of amitriptyline and resolved within 48 hours following discontinuation of the antidepressant (Krishnan et al, 1984h).
f) The absolute bioavailability of imipramine increased in women who received low-dose oral contraceptives (50 mcg or less of ethinyl estradiol) from 27% to 44% (p less than 0.05) as evident by an increase in the area under the plasma concentration time curve (Abernethy et al, 1984d).
g) Estrogens may inhibit the oxidation of TCAs by affecting hepatic microsomal enzymes (John et al, 1980d). Many TCAs are metabolized via oxidation and conjugation pathways. Inhibition of the oxidation of TCAs could result in accumulation and toxicity due to decreased clearance. Estrogens are suspected of possessing other effects on the central nervous system resulting in an antidepressant effect (Oppenheim, 1983d).

3.5.1.AO Estrone

1) Interaction Effect: possible attenuation of antidepressant effectiveness; tricyclic toxicity (drowsiness, hypotension, akathisia)
2) Summary: In isolated cases, the pharmacologic effects of tricyclic antidepressants may be increased or decreased by estrogens (Somani & Khurana, 1973i), with paradoxical loss of antidepressant effect yet tricyclic toxicity being manifested simultaneously (Prange, 1972i). The effects of the interaction appear to be estrogen dose-related (Khurana, 1972i) and may be of clinical importance primarily in patients previously stabilized on tricyclic therapy who are being started on estrogen therapy (Krishnan et al, 1984i).
3) Severity: minor
4) Onset: delayed
5) Substantiation: established
6) Clinical Management: If signs or symptoms of altered tricyclic response are noted, dose adjustment downward of either the estrogen or tricyclic component may be successful in restoring effectiveness or resolving toxicity. However, drug withdrawal may be required.
7) Probable Mechanism: possible inhibition of hepatic metabolism of the tricyclic antidepressant
8) Literature Reports

a) Some studies evaluated the qualitative effects of concomitant administration of estrogen and TCAs. In one trial, 30 depressed female prisoners were randomly assigned to four treatment groups. Ten patients received placebo, 10 received imipramine (150 mg daily) and placebo, five patients received imipramine (150 mg daily) and ethinyl estradiol (50 mcg daily), while five patients received imipramine (150 mg daily) and ethinyl estradiol (25 mcg daily). The 10 patients that received placebo did not improve over the six weeks of the study. The 10 patients taking estrogen and imipramine demonstrated a significantly greater improvement in symptoms than did the 10 patients taking imipramine alone. However, after two weeks, the five patients that received imipramine and high-dose estrogen had not improved as much as the patients receiving imipramine and low-dose estrogen. The only side-effect reported was drowsiness, which only affected the patients taking imipramine. Following the discontinuation of ethinyl estradiol, a time period of two weeks was required for the high-dose estrogen group to do as well as the low-dose group. This effect was attributed to the presence of residual estrogen in the high-dose group. In another group, five women received imipramine 150 mg and ethinyl estradiol 50 mrg daily did not improve as much as 10 patients receiving only imipramine. Also, the patients on the combination had severe side-effects including lethargy, coarse tremor and systolic hypotension (Prange, 1972h).
b) A 32-year-old female taking conjugated estrogens 2.5 mg and imipramine 100 mg developed lethargy, tremors, and signs of depersonalization. After two years of therapy, the patient increased her estrogen dose to 5 mg and then 7.5 mg daily. The patient became nauseated, had constant headaches, and low normal blood pressure. All lab work was normal. Upon discontinuing the estrogen, the side effects abated. Some investigators have proposed that the side effects resulted from enhanced TCA effects secondary to estrogen inhibition of hepatic microsomal enzymes (Somani & Khurana, 1973h; Khurana, 1972h).
c) In a study women received clomipramine and oral contraceptives or clomipramine alone. At the beginning of the study there were 30 women taking the combination, but 12 subsequently dropped out. The 18 patients on the combination were matched with 18 patients taking clomipramine alone. No significant difference was noted in the patients' responses to clomipramine. It was proposed that there was no significant difference in side-effects between the groups; however, the groups were matched after patients had dropped out of the study. Had the patients been matched prior to the study, different conclusions may have been drawn (Beaumont, 1973d).
d) The effects of oral contraceptives on clomipramine was studied in 42 women between the ages of

18 and 40. Twenty-three women took clomipramine 25 mg at bedtime while 19 took clomipramine 25 mg at bedtime with oral contraceptives. Over the four-week study, three control patients (two due to side-effects) and five in the experimental group (two due to side-effects) dropped out. Venous blood samples were drawn at weekly intervals for measurement of serum clomipramine concentrations. No difference in serum concentrations was noted between the groups. However, this result may be partially due to the low dose of clomipramine given (Luscombe & John, 1980d).

e) The onset of akathisia was reported in 3 patients receiving conjugated estrogens and tricyclic antidepressants concurrently. A 24-year-old patient receiving clomipramine 120 mg daily for anorexia nervosa and conjugated estrogens 1.25 mg daily for amenorrhea developed restless legs and a constant desire to move continuously. Estrogen was discontinued and benztropine 2 mg was administered, resulting in marked reduction and resolution within 48 hours. Akathisia and disorientation developed in a 55-year-old patient on conjugated estrogen 1.25 mg daily who was prescribed amitriptyline 50 mg daily for depression. Within hours of amitriptyline, the patient was confused, restless, and possessed an inner desire to move continuously. Symptoms disappeared after discontinuing amitriptyline. A third case of akathisia was reported in a 35-year-old patient who received conjugated estrogen 1.25 mg daily and amitriptyline 50 mg daily. Akathisia developed within a few hours after taking the first dose of amitriptyline and resolved within 48 hours following discontinuation of the antidepressant (Krishnan et al, 1984h).

f) The absolute bioavailability of imipramine increased in women who received low-dose oral contraceptives (50 mcg or less of ethinyl estradiol) from 27% to 44% (p less than 0.05) as evident by an increase in the area under the plasma concentration time curve (Abernethy et al, 1984d).

g) Estrogens may inhibit the oxidation of TCAs by affecting hepatic microsomal enzymes (John et al, 1980d). Many TCAs are metabolized via oxidation and conjugation pathways. Inhibition of the oxidation of TCAs could result in accumulation and toxicity due to decreased clearance. Estrogens are suspected of possessing other effects on the central nervous system resulting in an antidepressant effect (Oppenheim, 1983d).

3.5.1.AP Estropipate

1) Interaction Effect: possible attenuation of antidepressant effectiveness; tricyclic toxicity (drowsiness, hypotension, akathisia)

2) Summary: In isolated cases, the pharmacologic effects of tricyclic antidepressants may be increased or decreased by estrogens (Somani & Khurana, 1973i), with paradoxical loss of antidepressant effect yet tricyclic toxicity being manifested simultaneously (Prange, 1972i). The effects of the interaction appear to be estrogen dose-related (Khurana, 1972i) and may be of clinical importance primarily in patients previously stabilized on tricyclic therapy who are being started on estrogen therapy (Krishnan et al, 1984i).

3) Severity: minor

4) Onset: delayed

5) Substantiation: established

6) Clinical Management: If signs or symptoms of altered tricyclic response are noted, dose adjustment downward of either the estrogen or tricyclic component may be successful in restoring effectiveness or resolving toxicity. However, drug withdrawal may be required.

7) Probable Mechanism: possible inhibition of hepatic metabolism of the tricyclic antidepressant

8) Literature Reports

a) Some studies evaluated the qualitative effects of concomitant administration of estrogen and TCAs. In one trial, 30 depressed female prisoners were randomly assigned to four treatment groups. Ten patients received placebo, 10 received imipramine (150 mg daily) and placebo, five patients received imipramine (150 mg daily) and ethinyl estradiol (50 mcg daily), while five patients received imipramine (150 mg daily) and ethinyl estradiol (25 mcg daily). The 10 patients that received placebo did not improve over the six weeks of the study. The 10 patients taking estrogen and imipramine demonstrated a significantly greater improvement in symptoms than did the 10 patients taking imipramine alone. However, after two weeks, the five patients that received imipramine and high-dose estrogen had not improved as much as the patients receiving imipramine and low-dose estrogen. The only side-effect reported was drowsiness, which only affected the patients taking imipramine. Following the discontinuation of ethinyl estradiol, a time period of two weeks was required for the high-dose estrogen group to do as well as the low-dose group. This effect was attributed to the presence of residual estrogen in the high-dose group. In another group, five women received imipramine 150 mg and ethinyl estradiol 50 mrg daily did not improve as much as 10 patients receiving only imipramine. Also, the patients on the combination had severe side-effects including lethargy, coarse tremor and systolic hypotension (Prange, 1972h).

b) A 32-year-old female taking conjugated estrogens 2.5 mg and imipramine 100 mg developed lethargy, tremors, and signs of depersonalization. After two years of therapy, the patient increased her estrogen dose to 5 mg and then 7.5 mg daily. The patient became nauseated, had constant headaches, and low normal blood pressure. All lab work was normal. Upon discontinuing the estrogen, the side effects abated. Some investigators have proposed that the side effects resulted from enhanced TCA effects secondary to estrogen inhibition of hepatic microsomal enzymes (Somani & Khurana, 1973h; Khurana, 1972h).

c) In a study women received clomipramine and oral contraceptives or clomipramine alone. At the beginning of the study there were 30 women taking the combination, but 12 subsequently dropped out.

The 18 patients on the combination were matched with 18 patients taking clomipramine alone. No significant difference was noted in the patients' responses to clomipramine. It was proposed that there was no significant difference in side-effects between the groups; however, the groups were matched after patients had dropped out of the study. Had the patients been matched prior to the study, different conclusions may have been drawn (Beaumont, 1973d).

d) The effects of oral contraceptives on clomipramine was studied in 42 women between the ages of 18 and 40. Twenty-three women took clomipramine 25 mg at bedtime while 19 took clomipramine 25 mg at bedtime with oral contraceptives. Over the four-week study, three control patients (two due to side-effects) and five in the experimental group (two due to side-effects) dropped out. Venous blood samples were drawn at weekly intervals for measurement of serum clomipramine concentrations. No difference in serum concentrations was noted between the groups. However, this result may be partially due to the low dose of clomipramine given (Luscombe & John, 1980d).

e) The onset of akathisia was reported in 3 patients receiving conjugated estrogens and tricyclic antidepressants concurrently. A 24-year-old patient receiving clomipramine 120 mg daily for anorexia nervosa and conjugated estrogens 1.25 mg daily for amenorrhea developed restless legs and a constant desire to move continuously. Estrogen was discontinued and benztropine 2 mg was administered, resulting in marked reduction and resolution within 48 hours. Akathisia and disorientation developed in a 55-year-old patient on conjugated estrogen 1.25 mg daily who was prescribed amitriptyline 50 mg daily for depression. Within hours of amitriptyline, the patient was confused, restless, and possessed an inner desire to move continuously. Symptoms disappeared after discontinuing amitriptyline. A third case of akathisia was reported in a 35-year-old patient who received conjugated estrogen 1.25 mg daily and amitriptyline 50 mg daily. Akathisia developed within a few hours after taking the first dose of amitriptyline and resolved within 48 hours following discontinuation of the antidepressant (Krishnan et al, 1984h).

f) The absolute bioavailability of imipramine increased in women who received low-dose oral contraceptives (50 mcg or less of ethinyl estradiol) from 27% to 44% (p less than 0.05) as evident by an increase in the area under the plasma concentration time curve (Abernethy et al, 1984d).

g) Estrogens may inhibit the oxidation of TCAs by affecting hepatic microsomal enzymes (John et al, 1980d). Many TCAs are metabolized via oxidation and conjugation pathways. Inhibition of the oxidation of TCAs could result in accumulation and toxicity due to decreased clearance. Estrogens are suspected of possessing other effects on the central nervous system resulting in an antidepressant effect (Oppenheim, 1983d).

3.5.1.AQ Eterobarb

1) Interaction Effect: possible decreased tricyclic antidepressant serum concentrations and possible additive adverse effects

2) Summary: Concomitant barbiturate and tricyclic antidepressant (TCA) therapy may result in increased metabolism of the TCA. There have been scattered reports of individuals with decreased serum levels of TCAs in the presence of a barbiturate (Moody et al, 1977a; Silverman & Braithwaite, 1972; Burrows & Davies, 1971). In addition, TCAs can worsen seizure control by reducing the seizure threshold (Brodie, 1992). These drugs also have additive CNS and respiratory depressant effects.

3) Severity: minor

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Monitor for efficacy of antidepressant effect. Increases in tricyclic antidepressant dosages may be required. Additionally, monitor for toxicity when either drug is added to or withdrawn from therapy. Serum concentrations may be of value in determining appropriate dosage.

7) Probable Mechanism: increased tricyclic antidepressant metabolism

8) Literature Reports

a) The pharmacokinetics of a single oral dose of desipramine (100 mg) were studied in eight epileptic patients chronically treated with phenobarbital and in eight drug-free healthy controls (Spina et al, 1996). All subjects were extensive metabolizers with respect to the genetically determined CYP2D6-related metabolic polymorphism. Compared with controls, epileptic patients exhibited lower peak plasma desipramine concentrations (74 nmol/L vs. 107 nmol/L), smaller desipramine area under the concentration-time curve values (1943 nmol/L/h vs. 3234 nmol/L/h), and shorter desipramine elimination half-lives (15.1 h vs. 20.6 h). All barbiturates are believed to have similar effects leading to induction of hepatic enzymes and the 2D6 isozyme is believed to be important in the metabolism of most or all TCAs. Thus, similar effects should be expected with any combination of TCA and barbiturate.

3.5.1.AR Ethinyl Estradiol

1) Interaction Effect: attenuation of antidepressant effectiveness; tricyclic toxicity (drowsiness, hypotension, akathisia)

2) Summary: In isolated cases, the pharmacologic effects of tricyclic antidepressants may be increased or decreased by estrogens (Somani & Khurana, 1973c), with paradoxical loss of antidepressant effect yet tricyclic toxicity being manifested simultaneously (Prange, 1972c). The effects of the interaction appear to be estrogen dose-related (Khurana, 1972c) and may be of clinical importance primarily in patients previously stabilized on tricyclic therapy who are being started on estrogen therapy (Krishnan et al, 1984c).

3) Severity: minor

4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: If signs or symptoms of altered tricyclic response are noted, dose adjustment downward of either the estrogen or tricyclic component may be successful in restoring effectiveness or resolving toxicity. However, drug withdrawal may be required.
7) Probable Mechanism: possible estrogen-enhanced hepatic metabolism of the tricyclic
8) Literature Reports

a) Some studies evaluated the qualitative effects of concomitant administration of estrogen and TCAs. In one trial, 30 depressed female prisoners were randomly assigned to 4 treatment groups. Ten patients received placebo, 10 received imipramine (150 milligrams/day) and placebo, 5 patients received imipramine (150 milligrams/day) and ethinyl estradiol (50 micrograms/day), while 5 patients received imipramine (150 milligrams/day) and ethinyl estradiol (25 micrograms/day). The 10 patients that received placebo did not improve over the 6 weeks of the study. The 10 patients taking estrogen and imipramine demonstrated a significantly greater improvement in symptoms than did the 10 patients taking imipramine alone. However, after 2 weeks, the 5 patients that received imipramine and high-dose estrogen had not improved as much as the patients receiving imipramine and low-dose estrogen. The only side-effect reported was drowsiness, which only affected the patients taking imipramine. Following the discontinuation of ethinyl estradiol, a time period of 2 weeks was required for the high-dose estrogen group to do as well as the low-dose group. This effect was attributed to the presence of residual estrogen in the high-dose group. In another group, 5 women received imipramine 150 milligrams and ethinyl estradiol 50 micrograms daily did not improve as much as 10 patients receiving only imipramine. Also, the patients on the combination had severe side-effects including lethargy, coarse tremor and systolic hypotension (Prange, 1972b).

b) A case report demonstrated an interaction in a 32-year-old female taking conjugated estrogens 2.5 milligrams and imipramine 100 milligrams. The patient developed lethargy, tremors, and signs of depersonalization. After 2 years of therapy, the patient increased her estrogen dose to 5 milligrams and then 7.5 milligrams daily. The patient became nauseated, had constant headaches, and low normal blood pressure. All lab work was normal. Upon discontinuing the estrogen, the side-effects abated (Khurana, 1972b). Some investigators have proposed that the side effects resulted from enhanced TCA effects secondary to estrogen inhibition of hepatic microsomal enzymes (Somani & Khurana, 1973b).

c) In a study women received clomipramine and oral contraceptives or clomipramine alone. At the beginning of the study there were 30 women taking the combination, but 12 subsequently dropped out. The 18 patients on the combination were matched with 18 patients taking clomipramine alone. No significant difference was noted in the patients' responses to clomipramine. It was proposed that there was no significant difference in side-effects between the groups; however, the groups were matched after patients had dropped out of the study. Had the patients been matched prior to the study, different conclusions may have been drawn (Beaumont, 1973a).

d) The effects of oral contraceptives on clomipramine were studied in 42 women between the ages of 18 and 40. Twenty-three women took clomipramine 25 milligrams at bedtime while 19 took clomipramine 25 milligrams at bedtime with oral contraceptives. Over the 4-week study, 3 control patients (2 due to side-effects) and 5 in the experimental group (2 due to side-effects) dropped out. Venous blood samples were drawn at weekly intervals for measurement of serum clomipramine concentrations. No difference in serum concentrations was noted between the groups. However, this result may be partially due to the low dose of clomipramine given (Luscombe & John, 1980a).

e) Akathisia was reported in 3 patients receiving conjugated estrogens and tricyclic antidepressants concurrently. A 24-year-old patient receiving clomipramine 120 milligrams/day for anorexia nervosa and conjugated estrogens 1.25 milligrams/day for amenorrhea developed restless legs and a constant desire to move continuously. Estrogen was discontinued and benztropine 2 milligrams was administered, resulting in marked reduction and resolution within 48 hours. Akathisia and disorientation developed in a 55-year-old patient on conjugated estrogens 1.25 milligrams/day who was prescribed amitriptyline 50 milligrams/day for depression. Within hours of amitriptyline, the patient was confused, restless, and possessed an inner desire to move continuously. Symptoms disappeared after discontinuing amitriptyline. Positive rechallenge at one week with doxepin 100 milligrams, with resolution following discontinuation of doxepin. A third case of akathisia was reported in a 35-year-old patient who received conjugated estrogens 1.25 milligrams/day and amitriptyline 50 milligrams/day. Akathisia developed within a few hours after taking the first dose of amitriptyline and resolved within 48 hours following discontinuation of the antidepressant (Krishnan et al, 1984b).

f) The absolute bioavailability of imipramine increased in women who received low-dose oral contraceptives (50 micrograms or less of ethinyl estradiol) from 27 to 44% (p less than 0.05) as evident by an increase in the area under the plasma concentration time curve (Abernethy et al, 1984a).

g) Estrogens may inhibit the oxidation of TCAs by affecting hepatic microsomal enzymes (John et al, 1980a). Many TCAs are metabolized via oxidation and conjugation pathways. Inhibition of the oxidation of TCAs could result in accumulation and toxicity due to decreased clearance. Estrogens are suspected of possessing other effects on the central nervous system resulting in an antidepressant effect (Oppenheim, 1983a).

3.5.1.AS Etilefrine

1) Interaction Effect: hypertension, cardiac arrhythmias, and tachycardia

2) Summary: Clinical trials have demonstrated a 2- to 8-fold increase in the effects of intravenous infusions of alpha adrenergic drugs to volunteers on tricyclic antidepressants. Arrhythmias and other severe adverse effects have also been reported (Ghose, 1980; Avery, 1973; Boakes et al, 1973a; Boakes, 1973; Mitchell et al, 1970; Stone et al, 1964). Local use (e.g., dental anesthesia) of epinephrine in concentrations of 1:100,000 or less is less likely to precipitate clinically significant hemodynamic changes (Steinberg & Block, 1971).
3) Severity: major
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: The vasoconstriction and other alpha-adrenergic effects of sympathomimetic drugs are substantially enhanced in the presence of tricyclic antidepressants (TCAs). Concomitant use should be avoided. If these drugs are given together, careful monitoring and a dose reduction of the sympathomimetic is required. Patients should be instructed to inform their doctor or dentist that they are taking a tricyclic antidepressant prior to any surgery or procedure.
7) Probable Mechanism: inhibition of norepinephrine reuptake
8) Literature Reports
a) Four healthy volunteers received intravenous infusions of various sympathomimetic amines (epinephrine, norepinephrine, phenylephrine, and isoproterenol) before and after imipramine (25 mg three times daily for five days). They showed an increased pressor response to epinephrine (2- to 4-fold), norepinephrine (4- to 8-fold), and phenylephrine (2- to 3-fold) after imipramine, but no difference was observed in the response to isoproterenol. Thus, the increased pressor response appeared to occur only for alpha adrenergic effects. All four subjects demonstrated changes in cardiac rhythm with epinephrine and imipramine consisting of sinus arrhythmia in three subjects and multiple ectopic beats and a nodal rhythm in the fourth subject (Boakes et al, 1973).
b) A review of spontaneous reports of adverse reactions to vasoconstrictors in local anesthetics found that 15 patients receiving a local anesthetic with norepinephrine (1:25,000) had severe reactions (severe headaches, chest tightness, subarachnoid hemorrhage). The drug history was incomplete, but at least three had been taking a tricyclic antidepressant at the time (Anon, 1972).

3.5.1.AT Fenfluramine

1) Interaction Effect: hypertension, other cardiac effects, and CNS stimulation
2) Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been reported to result in enhanced amphetamine effects from the release of norepinephrine (Beaumont, 1973h; Raisfeld, 1972). A similar reaction might also occur with all drugs that have amphetamine-like effects. Acute elevations in blood pressure have been noted (Flemenbaum, 1971a). Some amphetamine-like drugs may inhibit the metabolism of TCAs, although most combinations have not been studied. When amphetamine analogs are being used to treat obesity, it should be noted that TCAs frequently lead to moderate weight gain (Russ & Ackerman, 1988). False positive urine tests for amphetamines have been reported during therapy with some TCAs (Merigian & Browning, 1993). Caution is advised when concurrent administration of amphetamine-like agents and TCAs is warranted. The patient should be closely monitored for increased cardiovascular effects (hypertension and dysrhythmias).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other sympathomimetic agents could lead to hypertension, increased cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006; Flemenbaum, 1972). Use caution if such therapy is warranted. Monitor the patient closely for hypertension and dysrhythmias.
7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission
8) Literature Reports
a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agents. Additionally, coadministration of d-amphetamine with TCAs such as desipramine or protriptyline results in sustained increases in d-amphetamine concentration in the brain (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006).
b) Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism of some tricyclic antidepressants, such as imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transdermal system, 2006).
c) Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases in blood pressure such that the hypotensive effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of combined therapy. Discontinuation of the methylphenidate usually results in the blood pressure returning to normotensive levels; reinstitution of the methylphenidate resulted in further blood pressure elevation (Flemenbaum, 1971; Flemenbaum, 1972).
d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine given for at least four weeks, were given fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical improvement. However, fenfluramine more than doubled steady-state plasma levels of desipramine (Price et al, 1990).

e) There have been claims based on uncontrolled studies that a better antidepressant response may occur with combined therapy (Garrettson et al, 1969). However, a systemic review of stimulants in the treatment of depression concluded that although uncontrolled studies were generally positive, the ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated little advantage of drug over placebo and did not appear to be as effective as the conventional antidepressants in primary depression (Satel & Nelson, 1989).

3.5.1.AU Fluvoxamine

1) Interaction Effect: clomipramine toxicity (dry mouth, urinary retention, sedation)
2) Summary: Coadministration of fluvoxamine and clomipramine was found to significantly increase plasma levels of clomipramine (Bertschy et al, 1991a). A bidirectional effect was suggested in which fluvoxamine increased clomipramine concentrations (by interfering with N-demethylation) and clomipramine increased fluvoxamine levels (Hartter et al, 1993a).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor patients for signs of clomipramine and fluvoxamine toxicity; lower doses of one or both agents may be required with concomitant therapy.
7) Probable Mechanism: decreased clomipramine metabolism
8) Literature Reports
a) Fluvoxamine has been shown to significantly increase plasma levels of amitriptyline and clomipramine and to mildly increase levels of their metabolites nortriptyline and desmethylclomipramine, respectively. This may be due to competitive inhibition of oxidative metabolism in the liver (Bertschy et al, 1991).
b) Metabolism of tricyclic antidepressants coadministered with fluvoxamine was studied in eight depressed patients (four patients received clomipramine). Fluvoxamine was found to interfere with N-demethylation and 8-hydroxylation of clomipramine. The combination of fluvoxamine and clomipramine led to increased plasma levels of clomipramine and decreased concentrations of clomipramine's N-demethylated metabolite, desmethylclomipramine. In addition, plasma levels of fluvoxamine were increased (Hartter et al, 1993).

3.5.1.AV Formoterol

1) Interaction Effect: an increased risk of cardiovascular excitation
2) Summary: Concurrent administration of formoterol with a tricyclic antidepressant (TCA) may lead to potentiation of formoterol's adrenergic effects on the cardiovascular system. Therefore, extreme caution is advised if formoterol is administered to patients who are being treated with a TCA (Prod Info FORADIL(R) AEROLIZER(R) inhalation powder, 2006). Monitor patients closely for adverse cardiovascular effects.
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Extreme caution and close observation for adverse cardiovascular effects are warranted when formoterol is administered concurrently with a tricyclic antidepressant (TCA) as the cardiovascular effects of formoterol can be potentiated by TCAs (Prod Info FORADIL(R) AEROLIZER(R) inhalation powder, 2006).
7) Probable Mechanism: potentiation of cardiovascular effects

3.5.1.AW Fosamprenavir

1) Interaction Effect: increased tricyclic agent serum concentrations and potential toxicity (anticholinergic effects, sedation, confusion, cardiac arrhythmias)
2) Summary: Coadministration of fosamprenavir with a tricyclic antidepressant may provoke increased serum concentrations of the tricyclic antidepressant, causing a potential risk of arrhythmias or other serious adverse effects. Fosamprenavir is a prodrug of amprenavir, an inhibitor of the CYP3A4 isoenzyme in addition to being a CYP3A4 substrate. Tricyclic agents may partially depend on the CYP3A4 pathway for metabolism. Plasma concentrations of the tricyclic agent should be closely monitored in patients also receiving fosamprenavir (Prod Info LEXIVA(R) oral solution, oral tablets, 2009).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: If concomitant therapy with fosamprenavir and a tricyclic antidepressant is unavoidable, plasma concentrations of the tricyclic agent should be closely monitored. Also monitor patients for signs and symptoms of tricyclic toxicity (anticholinergic effects, sedation, confusion, cardiac arrhythmias) (Prod Info LEXIVA(R) oral solution, oral tablets, 2009).
7) Probable Mechanism: inhibition of CYP3A4-mediated tricyclic agent metabolism

3.5.1.AX Fosphenytoin

1) Interaction Effect: an increased risk of phenytoin toxicity (ataxia, hyperreflexia, nystagmus, tremor)
2) Summary: Fosphenytoin is a prodrug of phenytoin and the same interactions that occur with phenytoin are expected to occur with fosphenytoin (Prod Info Cerebyx(R), 1999). A few case reports have indicated

that imipramine inhibits phenytoin metabolism resulting in increased serum phenytoin concentration (Petti & Campbell, 1975; Perucca & Richens, 1977). Tricyclic antidepressants (TCAs) may lower the seizure threshold in epileptic patients stabilized on anticonvulsants. Theoretically, because phenytoin is an enzyme inducer, the metabolism of antidepressants may be increased resulting in reduced TCA serum levels.
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Consider monitoring phenytoin serum levels if a tricyclic antidepressant is added to therapy or if the patient begins to exhibit signs of toxicity (tremor, nystagmus, ataxia, hyperreflexia); lower doses of phenytoin may be required. If phenytoin is added to tricyclic antidepressant therapy, monitor for clinical efficacy of the tricyclic agent.
7) Probable Mechanism: inhibition of phenytoin metabolism

3.5.1.AY Gatifloxacin
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Gatifloxacin may prolong the QT interval in some patients, which may result in ventricular tachycardia, ventricular fibrillation, and torsades de pointes. Although pharmacokinetic studies between gatifloxacin and other drugs which prolong the QT interval have not been performed, an additive effect cannot be excluded. Therefore, the concurrent administration of gatifloxacin and a tricyclic antidepressant is not recommended (Prod Info Tequin(TM), 1999).
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of gatifloxacin and a tricyclic antidepressant is not recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.AZ Grepafloxacin
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Healthy volunteers who received grepafloxacin during a Phase I study experienced prolongation of the QTc interval. On an outpatient basis, grepafloxacin is contraindicated with other drugs that are known to also prolong the QTc interval or cause torsades de pointes, including tricyclic antidepressants. When appropriate cardiac monitoring can be assured, such as in the hospitalized patient, these two agents should be coadministered with caution (Prod Info Raxar(R), 1999).
3) Severity: contraindicated
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: The concurrent use of grepafloxacin and tricyclic antidepressants is contraindicated unless appropriate cardiac monitoring can be assured, such as in the hospitalized patient.
7) Probable Mechanism: additive cardiac effects

3.5.1.BA Guanadrel
1) Interaction Effect: decreased antihypertensive effectiveness
2) Summary: Tricyclic antidepressants inhibit the uptake of guanethidine, and possibly guanadrel, into the adrenergic neuron, resulting in an inhibition of its antihypertensive effect (Mitchell et al, 1967; Ober & Wang, 1973). When a patient is on concomitant tricyclic antidepressant and guanadrel therapy, caution should be exercised when the tricyclic antidepressant is discontinued, since an exaggerated effect of guanadrel may be seen (Prod Info Hylorel(R), 1995).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Blood pressure should be monitored for an appropriate clinical response; higher doses of guanadrel may be required. An alternative class of antihypertensive agents, such as an angiotensin-converting enzyme inhibitor, might be considered.
7) Probable Mechanism: decreased uptake of guanadrel into adrenergic neurons

3.5.1.BB Halofantrine
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Halofantrine can prolong the QT interval in some patients, which may result in ventricular tachycardia, ventricular fibrillation, and torsades de pointes. Because tricyclic antidepressants may also prolong the QT interval and increase the risk of arrhythmias, the concurrent administration of halofantrine and tricyclic antidepressants is not recommended (Prod Info Halfan(R), 1998; Marshall & Forker, 1982b).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable

6) Clinical Management: The concurrent administration of halofantrine and a tricyclic antidepressant is not recommended.
7) Probable Mechanism: additive cardiac effects

3.5.1.BC Heptabarbital
1) Interaction Effect: possible decreased tricyclic antidepressant serum concentrations and possible additive adverse effects
2) Summary: Concomitant barbiturate and tricyclic antidepressant (TCA) therapy may result in increased metabolism of the TCA. There have been scattered reports of individuals with decreased serum levels of TCAs in the presence of a barbiturate (Moody et al, 1977a; Silverman & Braithwaite, 1972; Burrows & Davies, 1971). In addition, TCAs can worsen seizure control by reducing the seizure threshold (Brodie, 1992). These drugs also have additive CNS and respiratory depressant effects.
3) Severity: minor
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor for efficacy of antidepressant effect. Increases in tricyclic antidepressant dosages may be required. Additionally, monitor for toxicity when either drug is added to or withdrawn from therapy. Serum concentrations may be of value in determining appropriate dosage.
7) Probable Mechanism: increased tricyclic antidepressant metabolism
8) Literature Reports
a) The pharmacokinetics of a single oral dose of desipramine (100 mg) were studied in eight epileptic patients chronically treated with phenobarbital and in eight drug-free healthy controls (Spina et al, 1996). All subjects were extensive metabolizers with respect to the genetically determined CYP2D6-related metabolic polymorphism. Compared with controls, epileptic patients exhibited lower peak plasma desipramine concentrations (74 nmol/L vs. 107 nmol/L), smaller desipramine area under the concentration-time curve values (1943 nmol/L/h vs. 3234 nmol/L/h), and shorter desipramine elimination half-lives (15.1 h vs. 20.6 h). All barbiturates are believed to have similar effects leading to induction of hepatic enzymes and the 2D6 isozyme is believed to be important in the metabolism of most or all TCAs. Thus, similar effects should be expected with any combination of TCA and barbiturate.

3.5.1.BD Hexobarbital
1) Interaction Effect: possible decreased tricyclic antidepressant serum concentrations and possible additive adverse effects
2) Summary: Concomitant barbiturate and tricyclic antidepressant (TCA) therapy may result in increased metabolism of the TCA. There have been scattered reports of individuals with decreased serum levels of TCAs in the presence of a barbiturate (Moody et al, 1977a; Silverman & Braithwaite, 1972; Burrows & Davies, 1971). In addition, TCAs can worsen seizure control by reducing the seizure threshold (Brodie, 1992). These drugs also have additive CNS and respiratory depressant effects.
3) Severity: minor
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor for efficacy of antidepressant effect. Increases in tricyclic antidepressant dosages may be required. Additionally, monitor for toxicity when either drug is added to or withdrawn from therapy. Serum concentrations may be of value in determining appropriate dosage.
7) Probable Mechanism: increased tricyclic antidepressant metabolism
8) Literature Reports
a) The pharmacokinetics of a single oral dose of desipramine (100 mg) were studied in eight epileptic patients chronically treated with phenobarbital and in eight drug-free healthy controls (Spina et al, 1996). All subjects were extensive metabolizers with respect to the genetically determined CYP2D6-related metabolic polymorphism. Compared with controls, epileptic patients exhibited lower peak plasma desipramine concentrations (74 nmol/L vs. 107 nmol/L), smaller desipramine area under the concentration-time curve values (1943 nmol/L/h vs. 3234 nmol/L/h), and shorter desipramine elimination half-lives (15.1 h vs. 20.6 h). All barbiturates are believed to have similar effects leading to induction of hepatic enzymes and the 2D6 isozyme is believed to be important in the metabolism of most or all TCAs. Thus, similar effects should be expected with any combination of TCA and barbiturate.

3.5.1.BE Iproniazid
1) Interaction Effect: neurotoxicity, seizures, or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)
2) Summary: Concomitant TCA and MAOI use has resulted in hyperpyrexia, convulsions, and death. Concurrent use of MAOIs and TCAs has also been reported to result in a condition termed serotonin syndrome (Insel et al, 1982k; Spigset et al, 1993j; Brodribb et al, 1994h; Neuvonen et al, 1993e). Serotonin syndrome is a rare but potentially fatal condition of serotonergic hyperstimulation characterized by hypertension, hyperthermia, myoclonus, and changes in mental status (Sternbach, 1991f). If TCAs and MAOIs must be used concurrently, avoid large doses, use only oral TCAs, avoid imipramine, clomipramine, desipramine, and tranylcypromine, and monitor patients closely (Schuckit et al, 1971m; White & Simpson, 1984i).
3) Severity: major

4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Concomitant use of a tricyclic antidepressant (TCA) and a monoamine oxidase inhibitor (MAOI) should be done only with close monitoring and where the clinical benefit outweighs the potential risk. Other antidepressant therapy should first be considered. Consider using a 14 day washout period between treatment with both medicines. If deemed clinically necessary, avoid large doses and use agents other than imipramine, clomipramine, desipramine, and tranylcypromine.
7) Probable Mechanism: altered catecholamine uptake and metabolism
8) Literature Reports

a) Concomitant administration of monoamine oxidase inhibitors (MAOIs) with tricyclic antidepressants (TCAs) has been considered an absolute contraindication in the past. Reports of excitation, hyperpyrexia, convulsions, and possible death have been attributed to the combination (Lockett & Milner, 1965f; Winston, 1971f; Schuckit et al, 1971l; Spiker & Pugh, 1976f). The mechanism may relate to the combined inhibition of catecholamine reuptake into the central nervous system and inhibition of catecholamine metabolism (Sjoqvist, 1965f).

b) Administration of a TCA after MAOI therapy may result in the development of serotonin syndrome. In a double-blind, crossover study examining the effects of clorgyline and clomipramine for the treatment of obsessive-compulsive disorder, two subjects developed severe reactions characteristic of serotonin syndrome. During the study, patients had received clorgyline therapy, followed by a washout period of approximately four weeks and subsequent clomipramine therapy. After taking the first 100 mg dose of clomipramine, one patient developed coarse myoclonic jerking in both legs, hyperreflexia, diaphoresis, and arrhythmia. Another patient developed a similar reaction after the first dose, with upper motor neuron symptoms, myoclonic movements, and cardiac irritability. Both patient's symptoms resolved several hours later, and both patients were later treated successfully with clomipramine without adverse effects (Insel et al, 1982j).

c) A drug interaction occurred in a 76-year old woman who had been taking clomipramine 50 mg daily for several months prior to switching to moclobemide 300 mg daily. The patient experienced somnolescence, confusion, and fever which then progressed to further mental impairment, muscle stiffness, myoclonus, and convulsive attacks. The patient's symptoms were described as fulfilling the diagnostic criteria for serotonin syndrome and were resolved a few days later after discontinuing all antidepressant medications (Spigset et al, 1993i).

d) In one case, clomipramine 10 mg twice daily was added to a stable regimen of tranylcypromine in a physically healthy 34-year old man. After taking several doses, the patients developed symptoms of nausea and profuse sweating, followed by pyrexia, dyspnea, and agitation. The hyperpyrexical state led to disseminated intravascular coagulation and eventual death (Tackley & Tregaskis, 1987f).

e) There is evidence that MAOIs and TCAs can be given concomitantly in patients previously unresponsive to the MAOI or TCA alone. The combination may be utilized in one of two ways. Most frequently, the recommendation is to stop all previous antidepressants (five to ten days for TCAs and 14 days for MAOIs); the combination is then simultaneously started (Perry et al, 1991e). Alternatively, in a patient previously receiving a TCA, small doses of the MAOI may be slowly added (Schoonover, 1983). Numerous studies in patients with refractory depression or phobic anxiety states have successfully used the combination of MAOIs and TCAs (Ponto et al, 1977f; Schuckit et al, 1971l; Ashcroft, 1975e).

3.5.1.BF Isocarboxazid

1) Interaction Effect: neurotoxicity, seizures, or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)
2) Summary: The concurrent administration of isocarboxazid and clomipramine is contraindicated (Prod Info Marplan(R), 1998). Concomitant TCA and MAOI use has resulted in hyperpyrexia, convulsions, and death. Concurrent use of MAOIs and TCAs has also been reported to result in a condition termed serotonin syndrome (Insel et al, 1982g; Spigset et al, 1993h; Brodribb et al, 1994f; Neuvonen et al, 1993c). Serotonin syndrome is a rare but potentially fatal condition of serotonergic hyperstimulation characterized by hypertension, hyperthermia, myoclonus, and changes in mental status (Sternbach, 1991d). If TCAs and MAOIs must be used concurrently, avoid large doses, use only oral TCAs, avoid imipramine, clomipramine, desipramine, and tranylcypromine, and monitor patients closely (Schuckit et al, 1971i; White & Simpson, 1984f).
3) Severity: contraindicated
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: The concurrent use of clomipramine and isocarboxazid is contraindicated. In patients being transferred to isocarboxazid therapy from a dibenzazepine-related entity, allow at least a one-week medication-free interval and then initiate isocarboxazid at one-half of the normal dose for at least the first week of therapy. Also allow one week to elapse between the discontinuation of isocarboxazid and the administration of another MAO inhibitor or dibenzazepine-related entity.
7) Probable Mechanism: altered catecholamine uptake and metabolism
8) Literature Reports

a) Concomitant administration of monoamine oxidase inhibitors (MAOI) with tricyclic antidepressants (TCAs) has been considered an absolute contraindication in the past and still is listed as such by the manufacturers. Reports of excitation, hyperpyrexia, convulsions, and possible death have been

attributed to the combination (Lockett & Milner, 1965d; Brachfeld et al, 1963b; Winston, 1971d; Schuckit et al, 1971h; Sargent, 1965b; Spiker & Pugh, 1976d). The mechanism may relate to the combined inhibition of catecholamine reuptake into the central nervous system and inhibition of catecholamine metabolism (Sjoqvist, 1965d).

b) The development of serotonin syndrome was reported due to administration of a TCA after MAOI therapy. In a double-blind, crossover study examining the effects of clorgyline and clomipramine for the treatment of obsessive-compulsive disorder, two subjects developed severe reactions characteristic of serotonin syndrome. During the study, patients had received clorgyline therapy, followed by a washout period of approximately four weeks and subsequent clomipramine therapy. After taking the first 100 mg dose of clomipramine, one patient developed coarse myoclonic jerking in both legs, hyperreflexia, diaphoresis, and arrhythmia. Another patient developed a similar reaction after the first dose, with upper motor neuron symptoms, myoclonic movements, and cardiac irritability. Both patient's symptoms resolved several hours later, and both patients were later treated successfully with clomipramine without adverse effects (Insel et al, 1982f).

c) A drug interaction was reported when a 76-year old woman who had been taking clomipramine 50 mg daily for several months was switched to moclobemide 300 mg daily. The patient experienced somnolescence, confusion, and fever which then progressed to further mental impairment, muscle stiffness, myoclonus, and convulsive attacks. The patient's symptoms were described as fulfilling the diagnostic criteria for serotonin syndrome and were resolved a few days later after discontinuing all antidepressant medications (Spigset et al, 1993g).

d) A 39-year old woman with bipolar disorder developed serotonin syndrome after imipramine was added to moclobemide. The patient was taking moclobemide 300 mg twice daily when imipramine was started at 50 mg daily, followed by two dosage increases of imipramine to 200 mg and a reduction of moclobemide dosage to 150 mg twice daily. Five days after the increase in imipramine to 200 mg per day, the patient developed symptoms of serotonin syndrome, including sweating, shivering, confusion, fever, and spasms in the extremities. The patient was treated with chlorpromazine and symptoms resolved over the next few days without further complications (Brodribb et al, 1994e).

e) Three patients with bipolar disorder developed manic symptoms while undergoing concurrent therapy with isocarboxazid and amitriptyline. In all three cases the patients had been given MAOIs and TCAs alone without complications. It was only when the drugs were used in combination that symptoms of mania emerged, suggesting a synergistic effect (de la Fuente et al, 1986a).

f) In one case, clomipramine 10 mg twice daily was added to a stable regimen of tranylcypromine in a physically healthy 34-year old man. After taking several doses, the patients developed symptoms of nausea and profuse sweating, followed by pyrexia, dyspnea, and agitation. The hyperpyrexical state led to disseminated intravascular coagulation and eventual death (Tackley & Tregaskis, 1987d).

g) There is evidence that MAOIs and TCAs can be given concomitantly in patients previously unresponsive to the MAOI or TCA alone. A few precautions must be followed including: a) avoidance of large doses (no more than 150 mg amitriptyline or its equivalent, 45 mg phenelzine, or 60 mg isocarboxazid) b) oral administration c) avoidance of clomipramine, imipramine, desipramine, and tranylcypromine in any combination, and d) close monitoring of patients (Kline, 1974a; Winston, 1971d; Schuckit et al, 1971h; White & Simpson, 1984e; Rom & Benner, 1972a). The combination may be utilized in one of two ways. Most frequently, the recommendation is to stop all previous antidepressants (five to ten days for TCAs and 14 days for MAOIs); the combination is then simultaneously started (Perry et al, 1991c). Alternatively, in a patient previously receiving a TCA, small doses of the MAOI may be slowly added (Schoonover, 1983). Some sources suggest that the combination of amitriptyline and isocarboxazid is preferred (Perry et al, 1991c). Numerous studies in patients with refractory depression or phobic anxiety states have successfully used the combination of MAOIs and TCAs (Ponto et al, 1977d; Schuckit et al, 1971h; Ashcroft, 1975c).

3.5.1.BG Linezolid

1) Interaction Effect: increased risk of serotonin syndrome (hyperthermia, hyperreflexia, myoclonus, mental status changes)

2) Summary: Concomitant use of linezolid and a tricyclic antidepressant, such as clomipramine, is contraindicated in the absence of monitoring for serotonin syndrome. If symptoms occur, consider discontinuation of either one or both of the drugs. Linezolid is a reversible, nonselective inhibitor of monoamine oxidase and may therefore interact with tricyclic antidepressants. Spontaneous reports of serotonin syndrome associated with the co-administration of linezolid and serotonergic agents have been reported (Prod Info ZYVOX(R) IV injection, oral tablets, oral suspension, 2008).

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concurrent use of linezolid and tricyclic antidepressants, such as clomipramine, is contraindicated unless patient is closely observed for signs and/or symptoms of serotonin syndrome. If concomitant use is clinically warranted, monitor for signs and symptoms of serotonin syndrome, such as neuromuscular abnormalities (including hyper-reflexia, tremor, muscle rigidity, clonus, peripheral hypertonicity, and shivering), autonomic hyperactivity (including tachycardia, mydriasis, diaphoresis, the presence of bowel sounds, and diarrhea), and mental status changes (including agitation and delirium). Serotonin syndrome can be life-threatening. If serotonin syndrome develops, discontinue the offending

agents and provide supportive care and other therapy as necessary (Boyer & Shannon, 2005; Prod Info ZYVOX(R) IV injection, oral tablets, oral suspension, 2008).
7) Probable Mechanism: linezolid inhibition of monoamine oxidase resulting in an increased concentration of serotonin

3.5.1.BH Lisdexamfetamine

1) Interaction Effect: hypertension, other cardiac effects, and CNS stimulation
2) Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been reported to result in enhanced amphetamine effects from the release of norepinephrine (Beaumont, 1973h; Raisfeld, 1972). A similar reaction might also occur with all drugs that have amphetamine-like effects. Acute elevations in blood pressure have been noted (Flemenbaum, 1971a). Some amphetamine-like drugs may inhibit the metabolism of TCAs, although most combinations have not been studied. When amphetamine analogs are being used to treat obesity, it should be noted that TCAs frequently lead to moderate weight gain (Russ & Ackerman, 1988). False positive urine tests for amphetamines have been reported during therapy with some TCAs (Merigian & Browning, 1993). Caution is advised when concurrent administration of amphetamine-like agents and TCAs is warranted. The patient should be closely monitored for increased cardiovascular effects (hypertension and dysrhythmias).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other sympathomimetic agents could lead to hypertension, increased cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006; Flemenbaum, 1972). Use caution if such therapy is warranted. Monitor the patient closely for hypertension and dysrhythmias.
7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission
8) Literature Reports

a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agents. Additionally, coadministration of d-amphetamine with TCAs such as desipramine or protriptyline results in sustained increases in d-amphetamine concentration in the brain (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006).

b) Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism of some tricyclic antidepressants, such as imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transdermal system, 2006).

c) Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases in blood pressure such that the hypotensive effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of combined therapy. Discontinuation of the methylphenidate usually results in the blood pressure returning to normotensive levels; reinstitution of the methylphenidate resulted in further blood pressure elevation (Flemenbaum, 1971; Flemenbaum, 1972).

d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine given for at least four weeks, were given fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical improvement. However, fenfluramine more than doubled steady-state plasma levels of desipramine (Price et al, 1990).

e) There have been claims based on uncontrolled studies that a better antidepressant response may occur with combined therapy (Garrettson et al, 1969). However, a systemic review of stimulants in the treatment of depression concluded that although uncontrolled studies were generally positive, the ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated little advantage of drug over placebo and did not appear to be as effective as the conventional antidepressants in primary depression (Satel & Nelson, 1989).

3.5.1.BI Lumefantrine

1) Interaction Effect: an increased risk of QT interval prolongation
2) Summary: Lumefantrine is a CYP2D6 inhibitor and may cause QT interval prolongation. Concomitant use of artemether/lumefantrine and a CYP2D6 substrate (eg, amitriptyline, clomipramine, flecainide, and imipramine) can lead to elevated drug levels of the CYP2D6 substrate. As some CYP2D6 substrates can also prolong the QT interval, there is potential for additive QT prolongation. Therefore, artemether/lumefantrine should not be coadministered with CYP2D6 substrates that possess cardiac effects (Prod Info COARTEM(R) oral tablets, 2009).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Artemether/lumefantrine should not be administered concomitantly with CYP2D6 substrates, such as amitriptyline, clomipramine, flecainide, and imipramine, due to the potential additive effect on QT interval prolongation (Prod Info COARTEM(R) oral tablets, 2009).
7) Probable Mechanism: additive effects on QT interval prolongation

3.5.1.BJ Mazindol

1) Interaction Effect: hypertension, other cardiac effects, and CNS stimulation
2) Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been reported to result in enhanced amphetamine effects from the release of norepinephrine (Beaumont, 1973h; Raisfeld, 1972). A similar reaction might also occur with all drugs that have amphetamine-like effects. Acute elevations in blood pressure have been noted (Flemenbaum, 1971a). Some amphetamine-like drugs may inhibit the metabolism of TCAs, although most combinations have not been studied. When amphetamine analogs are being used to treat obesity, it should be noted that TCAs frequently lead to moderate weight gain (Russ & Ackerman, 1988). False positive urine tests for amphetamines have been reported during therapy with some TCAs (Merigian & Browning, 1993). Caution is advised when concurrent administration of amphetamine-like agents and TCAs is warranted. The patient should be closely monitored for increased cardiovascular effects (hypertension and dysrhythmias).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other sympathomimetic agents could lead to hypertension, increased cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006; Flemenbaum, 1972). Use caution if such therapy is warranted. Monitor the patient closely for hypertension and dysrhythmias.
7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission
8) Literature Reports
a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agents. Additionally, coadministration of d-amphetamine with TCAs such as desipramine or protriptyline results in sustained increases in d-amphetamine concentration in the brain (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006).
b) Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism of some tricyclic antidepressants, such as imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transdermal system, 2006).
c) Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases in blood pressure such that the hypotensive effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of combined therapy. Discontinuation of the methylphenidate usually results in the blood pressure returning to normotensive levels; reinstitution of the methylphenidate resulted in further blood pressure elevation (Flemenbaum, 1971; Flemenbaum, 1972).
d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine given for at least four weeks, were given fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical improvement. However, fenfluramine more than doubled steady-state plasma levels of desipramine (Price et al, 1990).
e) There have been claims based on uncontrolled studies that a better antidepressant response may occur with combined therapy (Garrettson et al, 1969). However, a systemic review of stimulants in the treatment of depression concluded that although uncontrolled studies were generally positive, the ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated little advantage of drug over placebo and did not appear to be as effective as the conventional antidepressants in primary depression (Satel & Nelson, 1989).

3.5.1.BK Mephentermine

1) Interaction Effect: hypertension, other cardiac effects, and CNS stimulation
2) Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been reported to result in enhanced amphetamine effects from the release of norepinephrine (Beaumont, 1973h; Raisfeld, 1972). A similar reaction might also occur with all drugs that have amphetamine-like effects. Acute elevations in blood pressure have been noted (Flemenbaum, 1971a). Some amphetamine-like drugs may inhibit the metabolism of TCAs, although most combinations have not been studied. When amphetamine analogs are being used to treat obesity, it should be noted that TCAs frequently lead to moderate weight gain (Russ & Ackerman, 1988). False positive urine tests for amphetamines have been reported during therapy with some TCAs (Merigian & Browning, 1993). Caution is advised when concurrent administration of amphetamine-like agents and TCAs is warranted. The patient should be closely monitored for increased cardiovascular effects (hypertension and dysrhythmias).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other sympathomimetic agents could lead to hypertension, increased cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006; Flemenbaum, 1972). Use caution if such therapy is warranted. Monitor the patient closely for hypertension and dysrhythmias.
7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission
8) Literature Reports
a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic

agents. Additionally, coadministration of d-amphetamine with TCAs such as desipramine or protriptyline results in sustained increases in d-amphetamine concentration in the brain (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006).
b) Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism of some tricyclic antidepressants, such as imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transdermal system, 2006).
c) Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases in blood pressure such that the hypotensive effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of combined therapy. Discontinuation of the methylphenidate usually results in the blood pressure returning to normotensive levels; reinstitution of the methylphenidate resulted in further blood pressure elevation (Flemenbaum, 1971; Flemenbaum, 1972).
d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine given for at least four weeks, were given fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical improvement. However, fenfluramine more than doubled steady-state plasma levels of desipramine (Price et al, 1990).
e) There have been claims based on uncontrolled studies that a better antidepressant response may occur with combined therapy (Garrettson et al, 1969). However, a systemic review of stimulants in the treatment of depression concluded that although uncontrolled studies were generally positive, the ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated little advantage of drug over placebo and did not appear to be as effective as the conventional antidepressants in primary depression (Satel & Nelson, 1989).

3.5.1.BL Mephobarbital

1) Interaction Effect: possible decreased tricyclic antidepressant serum concentrations and possible additive adverse effects
2) Summary: Concomitant barbiturate and tricyclic antidepressant (TCA) therapy may result in increased metabolism of the TCA. There have been scattered reports of individuals with decreased serum levels of TCAs in the presence of a barbiturate (Moody et al, 1977a; Silverman & Braithwaite, 1972; Burrows & Davies, 1971). In addition, TCAs can worsen seizure control by reducing the seizure threshold (Brodie, 1992). These drugs also have additive CNS and respiratory depressant effects.
3) Severity: minor
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor for efficacy of antidepressant effect. Increases in tricyclic antidepressant dosages may be required. Additionally, monitor for toxicity when either drug is added to or withdrawn from therapy. Serum concentrations may be of value in determining appropriate dosage.
7) Probable Mechanism: increased tricyclic antidepressant metabolism
8) Literature Reports
a) The pharmacokinetics of a single oral dose of desipramine (100 mg) were studied in eight epileptic patients chronically treated with phenobarbital and in eight drug-free healthy controls (Spina et al, 1996). All subjects were extensive metabolizers with respect to the genetically determined CYP2D6-related metabolic polymorphism. Compared with controls, epileptic patients exhibited lower peak plasma desipramine concentrations (74 nmol/L vs. 107 nmol/L), smaller desipramine area under the concentration-time curve values (1943 nmol/L/h vs. 3234 nmol/L/h), and shorter desipramine elimination half-lives (15.1 h vs. 20.6 h). All barbiturates are believed to have similar effects leading to induction of hepatic enzymes and the 2D6 isozyme is believed to be important in the metabolism of most or all TCAs. Thus, similar effects should be expected with any combination of TCA and barbiturate.

3.5.1.BM Mestranol

1) Interaction Effect: attenuation of antidepressant effectiveness; tricyclic toxicity (drowsiness, hypotension, akathisia)
2) Summary: In isolated cases, the pharmacologic effects of tricyclic antidepressants may be increased or decreased by estrogens (Somani & Khurana, 1973c), with paradoxical loss of antidepressant effect yet tricyclic toxicity being manifested simultaneously (Prange, 1972c). The effects of the interaction appear to be estrogen dose-related (Khurana, 1972c) and may be of clinical importance primarily in patients previously stabilized on tricyclic therapy who are being started on estrogen therapy (Krishnan et al, 1984c).
3) Severity: minor
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: If signs or symptoms of altered tricyclic response are noted, dose adjustment downward of either the estrogen or tricyclic component may be successful in restoring effectiveness or resolving toxicity. However, drug withdrawal may be required.
7) Probable Mechanism: possible estrogen-enhanced hepatic metabolism of the tricyclic
8) Literature Reports
a) Some studies evaluated the qualitative effects of concomitant administration of estrogen and TCAs. In one trial, 30 depressed female prisoners were randomly assigned to 4 treatment groups. Ten patients received placebo, 10 received imipramine (150 milligrams/day) and placebo, 5 patients received

imipramine (150 milligrams/day) and ethinyl estradiol (50 micrograms/day), while 5 patients received imipramine (150 milligrams/day) and ethinyl estradiol (25 micrograms/day). The 10 patients that received placebo did not improve over the 6 weeks of the study. The 10 patients taking estrogen and imipramine demonstrated a significantly greater improvement in symptoms than did the 10 patients taking imipramine alone. However, after 2 weeks, the 5 patients that received imipramine and high-dose estrogen had not improved as much as the patients receiving imipramine and low-dose estrogen. The only side-effect reported was drowsiness, which only affected the patients taking imipramine. Following the discontinuation of ethinyl estradiol, a time period of 2 weeks was required for the high-dose estrogen group to do as well as the low-dose group. This effect was attributed to the presence of residual estrogen in the high-dose group. In another group, 5 women received imipramine 150 milligrams and ethinyl estradiol 50 micrograms daily did not improve as much as 10 patients receiving only imipramine. Also, the patients on the combination had severe side-effects including lethargy, coarse tremor and systolic hypotension (Prange, 1972b).

b) A case report demonstrated an interaction in a 32-year-old female taking conjugated estrogens 2.5 milligrams and imipramine 100 milligrams. The patient developed lethargy, tremors, and signs of depersonalization. After 2 years of therapy, the patient increased her estrogen dose to 5 milligrams and then 7.5 milligrams daily. The patient became nauseated, had constant headaches, and low normal blood pressure. All lab work was normal. Upon discontinuing the estrogen, the side-effects abated (Khurana, 1972b). Some investigators have proposed that the side effects resulted from enhanced TCA effects secondary to estrogen inhibition of hepatic microsomal enzymes (Somani & Khurana, 1973b).

c) In a study women received clomipramine and oral contraceptives or clomipramine alone. At the beginning of the study there were 30 women taking the combination, but 12 subsequently dropped out. The 18 patients on the combination were matched with 18 patients taking clomipramine alone. No significant difference was noted in the patients' responses to clomipramine. It was proposed that there was no significant difference in side-effects between the groups; however, the groups were matched after patients had dropped out of the study. Had the patients been matched prior to the study, different conclusions may have been drawn (Beaumont, 1973a).

d) The effects of oral contraceptives on clomipramine were studied in 42 women between the ages of 18 and 40. Twenty-three women took clomipramine 25 milligrams at bedtime while 19 took clomipramine 25 milligrams at bedtime with oral contraceptives. Over the 4-week study, 3 control patients (2 due to side-effects) and 5 in the experimental group (2 due to side-effects) dropped out. Venous blood samples were drawn at weekly intervals for measurement of serum clomipramine concentrations. No difference in serum concentrations was noted between the groups. However, this result may be partially due to the low dose of clomipramine given (Luscombe & John, 1980a).

e) Akathisia was reported in 3 patients receiving conjugated estrogens and tricyclic antidepressants concurrently. A 24-year-old patient receiving clomipramine 120 milligrams/day for anorexia nervosa and conjugated estrogens 1.25 milligrams/day for amenorrhea developed restless legs and a constant desire to move continuously. Estrogen was discontinued and benztropine 2 milligrams was administered, resulting in marked reduction and resolution within 48 hours. Akathisia and disorientation developed in a 55-year-old patient on conjugated estrogens 1.25 milligrams/day who was prescribed amitriptyline 50 milligrams/day for depression. Within hours of amitriptyline, the patient was confused, restless, and possessed an inner desire to move continuously. Symptoms disappeared after discontinuing amitriptyline. Positive rechallenge at one week with doxepin 100 milligrams, with resolution following discontinuation of doxepin. A third case of akathisia was reported in a 35-year-old patient who received conjugated estrogens 1.25 milligrams/day and amitriptyline 50 milligrams/day. Akathisia developed within a few hours after taking the first dose of amitriptyline and resolved within 48 hours following discontinuation of the antidepressant (Krishnan et al, 1984b).

f) The absolute bioavailability of imipramine increased in women who received low-dose oral contraceptives (50 micrograms or less of ethinyl estradiol) from 27 to 44% (p less than 0.05) as evident by an increase in the area under the plasma concentration time curve (Abernethy et al, 1984a).

g) Estrogens may inhibit the oxidation of TCAs by affecting hepatic microsomal enzymes (John et al, 1980a). Many TCAs are metabolized via oxidation and conjugation pathways. Inhibition of the oxidation of TCAs could result in accumulation and toxicity due to decreased clearance. Estrogens are suspected of possessing other effects on the central nervous system resulting in an antidepressant effect (Oppenheim, 1983a).

3.5.1.BN Methamphetamine

1) Interaction Effect: hypertension, other cardiac effects, and CNS stimulation

2) Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been reported to result in enhanced amphetamine effects from the release of norepinephrine (Beaumont, 1973h; Raisfeld, 1972). A similar reaction might also occur with all drugs that have amphetamine-like effects. Acute elevations in blood pressure have been noted (Flemenbaum, 1971a). Some amphetamine-like drugs may inhibit the metabolism of TCAs, although most combinations have not been studied. When amphetamine analogs are being used to treat obesity, it should be noted that TCAs frequently lead to moderate weight gain (Russ & Ackerman, 1988). False positive urine tests for amphetamines have been reported during therapy with some TCAs (Merigian & Browning, 1993). Caution is advised when concurrent administration of amphetamine-like agents and TCAs is warranted. The patient should be closely monitored for increased cardiovascular effects (hypertension and dysrhythmias).

3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other sympathomimetic agents could lead to hypertension, increased cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006; Flemenbaum, 1972). Use caution if such therapy is warranted. Monitor the patient closely for hypertension and dysrhythmias.
7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission
8) Literature Reports

a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agents. Additionally, coadministration of d-amphetamine with TCAs such as desipramine or protriptyline results in sustained increases in d-amphetamine concentration in the brain (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006).

b) Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism of some tricyclic antidepressants, such as imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transdermal system, 2006).

c) Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases in blood pressure such that the hypotensive effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of combined therapy. Discontinuation of the methylphenidate usually results in the blood pressure returning to normotensive levels; reinstitution of the methylphenidate resulted in further blood pressure elevation (Flemenbaum, 1971; Flemenbaum, 1972).

d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine given for at least four weeks, were given fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical improvement. However, fenfluramine more than doubled steady-state plasma levels of desipramine (Price et al, 1990).

e) There have been claims based on uncontrolled studies that a better antidepressant response may occur with combined therapy (Garrettson et al, 1969). However, a systemic review of stimulants in the treatment of depression concluded that although uncontrolled studies were generally positive, the ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated little advantage of drug over placebo and did not appear to be as effective as the conventional antidepressants in primary depression (Satel & Nelson, 1989).

3.5.1.BO Methohexital

1) Interaction Effect: possible decreased tricyclic antidepressant serum concentrations and possible additive adverse effects
2) Summary: Concomitant barbiturate and tricyclic antidepressant (TCA) therapy may result in increased metabolism of the TCA. There have been scattered reports of individuals with decreased serum levels of TCAs in the presence of a barbiturate (Moody et al, 1977a; Silverman & Braithwaite, 1972; Burrows & Davies, 1971). In addition, TCAs can worsen seizure control by reducing the seizure threshold (Brodie, 1992). These drugs also have additive CNS and respiratory depressant effects.
3) Severity: minor
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor for efficacy of antidepressant effect. Increases in tricyclic antidepressant dosages may be required. Additionally, monitor for toxicity when either drug is added to or withdrawn from therapy. Serum concentrations may be of value in determining appropriate dosage.
7) Probable Mechanism: increased tricyclic antidepressant metabolism
8) Literature Reports

a) The pharmacokinetics of a single oral dose of desipramine (100 mg) were studied in eight epileptic patients chronically treated with phenobarbital and in eight drug-free healthy controls (Spina et al, 1996). All subjects were extensive metabolizers with respect to the genetically determined CYP2D6-related metabolic polymorphism. Compared with controls, epileptic patients exhibited lower peak plasma desipramine concentrations (74 nmol/L vs. 107 nmol/L), smaller desipramine area under the concentration-time curve values (1943 nmol/L/h vs. 3234 nmol/L/h), and shorter desipramine elimination half-lives (15.1 h vs. 20.6 h). All barbiturates are believed to have similar effects leading to induction of hepatic enzymes and the 2D6 isozyme is believed to be important in the metabolism of most or all TCAs. Thus, similar effects should be expected with any combination of TCA and barbiturate.

3.5.1.BP Methoxamine

1) Interaction Effect: hypertension, cardiac arrhythmias, and tachycardia
2) Summary: Clinical trials have demonstrated a 2- to 8-fold increase in the effects of intravenous infusions of alpha adrenergic drugs to volunteers on tricyclic antidepressants. Arrhythmias and other severe adverse effects have also been reported (Ghose, 1980; Avery, 1973; Boakes et al, 1973a; Boakes, 1973; Mitchell et al, 1970; Stone et al, 1964). Local use (e.g., dental anesthesia) of epinephrine in concentrations of 1:100,000 or less is less likely to precipitate clinically significant hemodynamic changes (Steinberg & Block, 1971).

3) Severity: major
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: The vasoconstriction and other alpha-adrenergic effects of sympathomimetic drugs are substantially enhanced in the presence of tricyclic antidepressants (TCAs). Concomitant use should be avoided. If these drugs are given together, careful monitoring and a dose reduction of the sympathomimetic is required. Patients should be instructed to inform their doctor or dentist that they are taking a tricyclic antidepressant prior to any surgery or procedure.
7) Probable Mechanism: inhibition of norepinephrine reuptake
8) Literature Reports
a) Four healthy volunteers received intravenous infusions of various sympathomimetic amines (epinephrine, norepinephrine, phenylephrine, and isoproterenol) before and after imipramine (25 mg three times daily for five days). They showed an increased pressor response to epinephrine (2- to 4-fold), norepinephrine (4- to 8-fold), and phenylephrine (2- to 3-fold) after imipramine, but no difference was observed in the response to isoproterenol. Thus, the increased pressor response appeared to occur only for alpha adrenergic effects. All four subjects demonstrated changes in cardiac rhythm with epinephrine and imipramine consisting of sinus arrhythmia in three subjects and multiple ectopic beats and a nodal rhythm in the fourth subject (Boakes et al, 1973).
b) A review of spontaneous reports of adverse reactions to vasoconstrictors in local anesthetics found that 15 patients receiving a local anesthetic with norepinephrine (1:25,000) had severe reactions (severe headaches, chest tightness, subarachnoid hemorrhage). The drug history was incomplete, but at least three had been taking a tricyclic antidepressant at the time (Anon, 1972).

3.5.1.BQ Methylphenidate
1) Interaction Effect: hypertension, other cardiac effects, and CNS stimulation
2) Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been reported to result in enhanced amphetamine effects from the release of norepinephrine (Beaumont, 1973h; Raisfeld, 1972). A similar reaction might also occur with all drugs that have amphetamine-like effects. Acute elevations in blood pressure have been noted (Flemenbaum, 1971a). Some amphetamine-like drugs may inhibit the metabolism of TCAs, although most combinations have not been studied. When amphetamine analogs are being used to treat obesity, it should be noted that TCAs frequently lead to moderate weight gain (Russ & Ackerman, 1988). False positive urine tests for amphetamines have been reported during therapy with some TCAs (Merigian & Browning, 1993). Caution is advised when concurrent administration of amphetamine-like agents and TCAs is warranted. The patient should be closely monitored for increased cardiovascular effects (hypertension and dysrhythmias).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other sympathomimetic agents could lead to hypertension, increased cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006; Flemenbaum, 1972). Use caution if such therapy is warranted. Monitor the patient closely for hypertension and dysrhythmias.
7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission
8) Literature Reports
a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agents. Additionally, coadministration of d-amphetamine with TCAs such as desipramine or protriptyline results in sustained increases in d-amphetamine concentration in the brain (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006).
b) Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism of some tricyclic antidepressants, such as imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transdermal system, 2006).
c) Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases in blood pressure such that the hypotensive effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of combined therapy. Discontinuation of the methylphenidate usually results in the blood pressure returning to normotensive levels; reinstitution of the methylphenidate resulted in further blood pressure elevation (Flemenbaum, 1971; Flemenbaum, 1972).
d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine given for at least four weeks, were given fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical improvement. However, fenfluramine more than doubled steady-state plasma levels of desipramine (Price et al, 1990).
e) There have been claims based on uncontrolled studies that a better antidepressant response may occur with combined therapy (Garrettson et al, 1969). However, a systemic review of stimulants in the treatment of depression concluded that although uncontrolled studies were generally positive, the ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated little advantage of drug over placebo and did not appear to be as effective as the conventional antidepressants in primary depression (Satel & Nelson, 1989).

3.5.1.BR Midodrine

1) Interaction Effect: hypertension, cardiac arrhythmias, and tachycardia

2) Summary: Clinical trials have demonstrated a 2- to 8-fold increase in the effects of intravenous infusions of alpha adrenergic drugs to volunteers on tricyclic antidepressants. Arrhythmias and other severe adverse effects have also been reported (Ghose, 1980; Avery, 1973; Boakes et al, 1973a; Boakes, 1973; Mitchell et al, 1970; Stone et al, 1964). Local use (e.g., dental anesthesia) of epinephrine in concentrations of 1:100,000 or less is less likely to precipitate clinically significant hemodynamic changes (Steinberg & Block, 1971).

3) Severity: major

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: The vasoconstriction and other alpha-adrenergic effects of sympathomimetic drugs are substantially enhanced in the presence of tricyclic antidepressants (TCAs). Concomitant use should be avoided. If these drugs are given together, careful monitoring and a dose reduction of the sympathomimetic is required. Patients should be instructed to inform their doctor or dentist that they are taking a tricyclic antidepressant prior to any surgery or procedure.

7) Probable Mechanism: inhibition of norepinephrine reuptake

8) Literature Reports

a) Four healthy volunteers received intravenous infusions of various sympathomimetic amines (epinephrine, norepinephrine, phenylephrine, and isoproterenol) before and after imipramine (25 mg three times daily for five days). They showed an increased pressor response to epinephrine (2- to 4-fold), norepinephrine (4- to 8-fold), and phenylephrine (2- to 3-fold) after imipramine, but no difference was observed in the response to isoproterenol. Thus, the increased pressor response appeared to occur only for alpha adrenergic effects. All four subjects demonstrated changes in cardiac rhythm with epinephrine and imipramine consisting of sinus arrhythmia in three subjects and multiple ectopic beats and a nodal rhythm in the fourth subject (Boakes et al, 1973).

b) A review of spontaneous reports of adverse reactions to vasoconstrictors in local anesthetics found that 15 patients receiving a local anesthetic with norepinephrine (1:25,000) had severe reactions (severe headaches, chest tightness, subarachnoid hemorrhage). The drug history was incomplete, but at least three had been taking a tricyclic antidepressant at the time (Anon, 1972).

3.5.1.BS Moclobemide

1) Interaction Effect: neurotoxicity, seizures, or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)

2) Summary: Concomitant TCA and MAOI use has resulted in hyperpyrexia, convulsions, and death. Concurrent use of MAOIs and TCAs has also been reported to result in a condition termed serotonin syndrome (Insel et al, 1982i; Spigset & Mjorndal, 1993a; Brodribb et al, 1994g; Neuvonen et al, 1993d). Serotonin syndrome is a rare but potentially fatal condition of serotonergic hyperstimulation characterized by hypertension, hyperthermia, myoclonus, and changes in mental status (Sternbach, 1991e). Consequently, coadministration of TCAs and MAOIs is contraindicated in most cases. If TCAs and MAOIs must be used concurrently, avoid large doses, use only oral TCAs, avoid imipramine, clomipramine, desipramine, and tranylcypromine, and monitor patients closely (Schuckit et al, 1971k; White & Simpson, 1984h). An 18-year-old woman suffered irritability, twitching, agitation, myoclonus, and hypertonicity after changing from clomipramine to moclobemide with no washout period (Chan et al, 1998).

3) Severity: contraindicated

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Concomitant use of moclobemide and a tricyclic antidepressant, such as clomipramine, is contraindicated. If clomipramine is replacing treatment with moclobemide, a minimum of two days should elapse after moclobemide is discontinued and clomipramine therapy is begun (Prod Info Manerix(R), 2001). However, the manufacturer of clomipramine recommends that the monoamine oxidase inhibitor (MAOI) be discontinued for at least 14 days before treatment with doxepin is initiated. If moclobemide is replacing treatment with clomipramine, a minimum of 14 days should elapse after clomipramine is discontinued and moclobemide therapy is begun (Prod Info clomipramine hydrochloride oral capsule, 2002).

7) Probable Mechanism: altered catecholamine uptake and metabolism

8) Literature Reports

a) Concomitant administration of monoamine oxidase inhibitors (MAOIs) with tricyclic antidepressants (TCAs) has been considered an absolute contraindication in the past and still is listed as such by the manufacturers. Reports of excitation, hyperpyrexia, convulsions, and possible death have been attributed to the combination (Lockett & Milner, 1965e; Brachfeld et al, 1963c; Winston, 1971e; Schuckit et al, 1971j; Sargent, 1965c; Spiker & Pugh, 1976e). The mechanism may relate to the combined inhibition of catecholamine reuptake into the central nervous system and inhibition of catecholamine metabolism (Sjoqvist, 1965e).

b) A clinical study designed to detect an interaction between moclobemide and a tricyclic antidepressant (clomipramine) resulted in severe adverse effects, and the study was terminated. Information about interactions with moclobemide and other tricyclic antidepressants is limited (Prod Info

Manerix(R), 2001).
c) A drug interaction occurred in which a 76-year old woman who had been taking clomipramine 50 mg daily for several months prior to switching to moclobemide 300 mg daily. The patient experienced somnolence, confusion, and fever which then progressed to further mental impairment, muscle stiffness, myoclonus, and convulsive attacks. The patient's symptoms were described as fulfilling the diagnostic criteria for serotonin syndrome and were resolved a few days later after discontinuing all antidepressant medications (Spigset & Mjorndal, 1993).
d) Administration of a TCA after MAOI therapy may result in the development of serotonin syndrome. In a double-blind, crossover study examining the effects of clorgyline and clomipramine for the treatment of obsessive-compulsive disorder, two subjects developed severe reactions characteristic of serotonin syndrome. During the study, patients had received clorgyline therapy, followed by a washout period of approximately four weeks and subsequent clomipramine therapy. After taking the first 100 mg dose of clomipramine, one patient developed coarse myoclonic jerking in both legs, hyperreflexia, diaphoresis, and arrhythmia. Another patient developed a similar reaction after the first dose, with upper motor neuron symptoms, myoclonic movements, and cardiac irritability. Both patient's symptoms resolved several hours later, and both patients were later treated successfully with clomipramine without adverse effects (Insel et al, 1982h).
e) In one case, clomipramine 10 mg twice daily was added to a stable regimen of tranylcypromine in a physically healthy 34-year old man. After taking several doses, the patients developed symptoms of nausea and profuse sweating, followed by pyrexia, dyspnea, and agitation. The hyperpyrexical state led to disseminated intravascular coagulation and eventual death (Tackley & Tregaskis, 1987e).
f) There is evidence that MAOIs and TCAs can be given concomitantly in patients previously unresponsive to the MAOI or TCA alone. A few precautions must be followed including: a) avoidance of large doses (no more than 150 mg amitriptyline or its equivalent, 45 mg phenelzine, or 60 mg isocarboxazid) b) oral administration c) avoidance of clomipramine, imipramine, desipramine, and tranylcypromine in any combination, and d) close monitoring of patients (Kline, 1974b; Winston, 1971e; Schuckit et al, 1971j; White & Simpson, 1984g; Rom & Benner, 1972b). The combination may be utilized in one of two ways. Most frequently, the recommendation is to stop all previous antidepressants (five to ten days for TCAs and 14 days for MAOIs); the combination is then simultaneously started (Perry et al, 1991d). Alternatively, in a patient previously receiving a TCA, small doses of the MAOI may be slowly added (Schoonover, 1983). Some sources suggest that the combination of amitriptyline and isocarboxazid is preferred (Perry et al, 1991d). Numerous studies in patients with refractory depression or phobic anxiety states have successfully used the combination of MAOIs and TCAs (Ponto et al, 1977e; Schuckit et al, 1971j; Ashcroft, 1975d).
g) A 29-year-old male presented to the emergency department of a hospital one hour after ingesting moclobemide 7.5 g, clomipramine 1 g, and clorazepate 450 mg. He was treated with gastric lavage, charcoal 30 g, and flumazenil, and was admitted to the hospital for observation. One hour later, he began to experience severe tremor, increased body temperature, and tonic-clonic seizures. He died of a cardiorespiratory arrest approximately 145 minutes after his arrival to the hospital. Moclobemide overdoses of 7 g to 8 g produce fatigue, agitation, increased blood pressure, and tachycardia with few other complications. However, in this case, the addition of clomipramine produced a fatal serotonin syndrome (Ferrer-Dufol et al, 1998).
h) A 25-year-old female with recurrent depressive disorder was stabilized on clomipramine 150 mg daily and alprazolam 1.5 to 3 mg daily for seven months when her depressive disorder again reappeared. Clomipramine therapy was discontinued, and moclobemide 300 mg daily was initiated 24 hours later. Moclobemide was rapidly increased to 600 mg daily, and the alprazolam dose remained the same. One week after the start of moclobemide, the patient presented with confusion, mild euphoria, and disinhibition. She reported that within a few hours of starting moclobemide therapy, she experienced an elevation of her mood, nausea, shivering, and flushing. Moclobemide was discontinued, with complete recovery from the drug interaction-induced symptoms eight days later. Because clomipramine has a half-life of 22 to 84 hours, significant amounts of the drug may still have been present when moclobemide therapy was instituted, causing serotonin syndrome (Dardennes et al, 1998).

3.5.1.BT Modafinil
1) Interaction Effect: increased plasma levels of clomipramine and desmethylclomipramine
2) Summary: A narcoleptic patient experienced an increase in her clomipramine levels when modafinil was added to her therapeutic regimen. Hepatic enzymes also increased from 2- to 7-fold, requiring that clomipramine be discontinued (Grozinger et al, 1998a). However, in healthy volunteers, the coadministration of a single dose of clomipramine 50 mg during the first day of a 3-day regimen of modafinil 200 mg daily did not result in an alteration in the pharmacokinetics of either drug (Prod Info Provigil(R), 1998).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor patients receiving modafinil and clomipramine concurrently for signs and symptoms of tricyclic intoxication. Liver enzymes should also be closely followed for marked increases.
7) Probable Mechanism: unknown
8) Literature Reports

a) A 60-year-old narcoleptic female was being treated with clomipramine without complete resolve of her symptoms. At a clomipramine dose of 75 mg under steady-state conditions, her clomipramine (CI) and desmethylclomipramine (DMCI) blood levels were 109 ng/mL and 212 ng/mL, respectively. These levels increased to 129 ng/mL and 208 ng/mL, respectively, when the clomipramine dose was increased to 100 mg. When modafinil 200 mg was instituted, the clomipramine dose was decreased to 75 mg, and the CI/DMCI levels increased to 158/238 ng/mL. With modafinil 400 mg and clomipramine 75 mg, the CI/DMCI levels further rose to 210/449 ng/mL. Hepatic enzymes (GOT, GLDH, GGT, GPT) increased from 2- to 7-fold, necessitating the discontinuation of clomipramine. Three weeks later, the DMCI level was 63 ng/mL, while clomipramine was no longer detectable. Hepatic enzymes also returned to baseline. The patient was determined to be a poor metabolizer with regard to cytochrome P450 2D6 (CYP2D6) isoenzymes, indicating that CYP2D6 was not a factor in this drug interaction (Grozinger et al, 1998).

3.5.1.BU Moxifloxacin

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Moxifloxacin has been shown to prolong the QT interval in some patients and should be avoided in those patients receiving agents that also prolong the QT interval, such as tricyclic antidepressants. Although pharmacokinetic studies between moxifloxacin and other drugs which prolong the QT interval have not been performed, an additive effect cannot be excluded. Therefore, moxifloxacin should be used with caution when given concurrently with a tricyclic antidepressant (Prod Info Avelox(TM), 2000).
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Moxifloxacin should be used with caution when given concurrently with a tricyclic antidepressant.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.BV Nefopam

1) Interaction Effect: an increased risk of seizures
2) Summary: Nefopam inhibits the neuronal uptake of norepinephrine and serotonin and increases the risk of seizures, especially in patients with a history of a convulsive disorder. Tricyclic antidepressants also lower the seizure threshold. Therefore, the manufacturer of nefopam advises caution in patients on concurrent tricyclic antidepressant therapy (Pillans & Woods, 1995).
3) Severity: major
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Because of the increased risk of seizures, extreme caution should be exercised in patients receiving nefopam and a tricyclic antidepressant. An alternative analgesic may be considered.
7) Probable Mechanism: additive lowering of seizure threshold

3.5.1.BW Nialamide

1) Interaction Effect: neurotoxicity, seizures, or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)
2) Summary: Concomitant TCA and MAOI use has resulted in hyperpyrexia, convulsions, and death. Concurrent use of MAOIs and TCAs has also been reported to result in a condition termed serotonin syndrome (Insel et al, 1982c; Spigset et al, 1993d; Brodribb et al, 1994b; Neuvonen et al, 1993a). Serotonin syndrome is a rare but potentially fatal condition of serotonergic hyperstimulation characterized by hypertension, hyperthermia, myoclonus, and changes in mental status (Sternbach, 1991b). If TCAs and MAOIs must be used concurrently, avoid large doses, use only oral TCAs, avoid imipramine, clomipramine, desipramine, and tranylcypromine, and monitor patients closely (Schuckit et al, 1971c; White & Simpson, 1984a).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Concomitant use of a tricyclic antidepressant (TCA) and a monoamine oxidase inhibitor (MAOI) should be done only with close monitoring and where the clinical benefit outweighs the potential risk. Other antidepressant therapy should first be considered. If deemed clinically necessary, avoid large doses and use agents other than imipramine, clomipramine, desipramine, and tranylcypromine.
7) Probable Mechanism: altered catecholamine uptake and metabolism
8) Literature Reports
a) Concomitant administration of monoamine oxidase inhibitors (MAOIs) with tricyclic antidepressants (TCAs) has been considered an absolute contraindication in the past. Reports of excitation, hyperpyrexia, convulsions, and possible death have been attributed to the combination (Lockett & Milner, 1965a; Winston, 1971a; Schuckit et al, 1971b; Spiker & Pugh, 1976a). The mechanism may relate to the combined inhibition of catecholamine reuptake into the central nervous system and inhibition of catecholamine metabolism (Sjoqvist, 1965a).
b) In a double-blind, crossover study examining the effects of clorgyline and clomipramine for the

treatment of obsessive-compulsive disorder, two subjects developed severe reactions characteristic of serotonin syndrome. During the study, patients had received clorgyline therapy, followed by a washout period of approximately four weeks and subsequent clomipramine therapy. After taking the first 100 mg dose of clomipramine, one patient developed coarse myoclonic jerking in both legs, hyperreflexia, diaphoresis, and arrhythmia. Another patient developed a similar reaction after the first dose, with upper motor neuron symptoms, myoclonic movements, and cardiac irritability. Both patient's symptoms resolved several hours later, and both patients were later treated successfully with clomipramine without adverse effects (Insel et al, 1982b).

c) A drug interaction occurred in a 76-year old woman who had been taking clomipramine 50 mg daily for several months prior to switching to moclobemide 300 mg daily. The patient experienced somnolescence, confusion, and fever which then progressed to further mental impairment, muscle stiffness, myoclonus, and convulsive attacks. The patient's symptoms were described as fulfilling the diagnostic criteria for serotonin syndrome and were resolved a few days later after discontinuing all antidepressant medications (Spigset et al, 1993c).

d) In one case, clomipramine 10 mg twice daily was added to a stable regimen of tranylcypromine in a physically healthy 34-year old man. After taking several doses, the patients developed symptoms of nausea and profuse sweating, followed by pyrexia, dyspnea, and agitation. The hyperpyrexical state led to disseminated intravascular coagulation and eventual death (Tackley & Tregaskis, 1987b).

e) There is evidence that MAOIs and TCAs can be given concomitantly in patients previously unresponsive to the MAOI or TCA alone. The combination may be utilized in one of two ways. Most frequently, the recommendation is to stop all previous antidepressants (five to ten days for TCAs and 14 days for MAOIs); the combination is then simultaneously started (Perry et al, 1991a). Alternatively, in a patient previously receiving a TCA, small doses of the MAOI may be slowly added (Schoonover, 1983). Numerous studies in patients with refractory depression or phobic anxiety states have successfully used the combination of MAOIs and TCAs (Ponto et al, 1977a; Schuckit et al, 1971b; Ashcroft, 1975a).

3.5.1.BX Norepinephrine

1) Interaction Effect: hypertension, cardiac arrhythmias, and tachycardia

2) Summary: Clinical trials have demonstrated a 2- to 8-fold increase in the effects of intravenous infusions of alpha adrenergic drugs to volunteers on tricyclic antidepressants. Arrhythmias and other severe adverse effects have also been reported (Ghose, 1980; Avery, 1973; Boakes et al, 1973a; Boakes, 1973; Mitchell et al, 1970; Stone et al, 1964). Local use (e.g., dental anesthesia) of epinephrine in concentrations of 1:100,000 or less is less likely to precipitate clinically significant hemodynamic changes (Steinberg & Block, 1971).

3) Severity: major

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: The vasoconstriction and other alpha-adrenergic effects of sympathomimetic drugs are substantially enhanced in the presence of tricyclic antidepressants (TCAs). Concomitant use should be avoided. If these drugs are given together, careful monitoring and a dose reduction of the sympathomimetic is required. Patients should be instructed to inform their doctor or dentist that they are taking a tricyclic antidepressant prior to any surgery or procedure.

7) Probable Mechanism: inhibition of norepinephrine reuptake

8) Literature Reports

a) Four healthy volunteers received intravenous infusions of various sympathomimetic amines (epinephrine, norepinephrine, phenylephrine, and isoproterenol) before and after imipramine (25 mg three times daily for five days). They showed an increased pressor response to epinephrine (2- to 4-fold), norepinephrine (4- to 8-fold), and phenylephrine (2- to 3-fold) after imipramine, but no difference was observed in the response to isoproterenol. Thus, the increased pressor response appeared to occur only for alpha adrenergic effects. All four subjects demonstrated changes in cardiac rhythm with epinephrine and imipramine consisting of sinus arrhythmia in three subjects and multiple ectopic beats and a nodal rhythm in the fourth subject (Boakes et al, 1973).

b) A review of spontaneous reports of adverse reactions to vasoconstrictors in local anesthetics found that 15 patients receiving a local anesthetic with norepinephrine (1:25,000) had severe reactions (severe headaches, chest tightness, subarachnoid hemorrhage). The drug history was incomplete, but at least three had been taking a tricyclic antidepressant at the time (Anon, 1972).

3.5.1.BY Olanzapine

1) Interaction Effect: an increased risk of seizures

2) Summary: Psychotropic drugs have been shown to reduce the seizure threshold. A case report describes a patient without an underlying seizure disorder who received treatment with olanzapine and clomipramine concomitantly. This combination resulted in seizures which were repeated upon rechallenge with olanzapine and clomipramine. It is advised to use caution when administering olanzapine concomitantly with clomipramine, or any agent known to reduce seizure threshold (Deshauer et al, 2000a).

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: It is advised to use caution when administering olanzapine concomitantly with

clomipramine, or other agents known to lower the seizure threshold.
7) Probable Mechanism: unknown
8) Literature Reports
a) A 34-year-old male with schizophrenia and obsessive-compulsive disorder (OCD) without any underlying seizure disorder, presented for treatment following long-term noncompliance. Inpatient olanzapine treatment (20 mg/day) was initiated and positive psychotic symptoms subsequently resolved. Patient was discharged and readmitted because of inability to control symptoms. Clomipramine 250 mg per day was initiated. Within a week, dizziness and myoclonic jerks were reported which quickly progressed to general motor seizures and postictal somnolence (without incontinence). Spike waves and paroxysmal slowing on the EEG was consistent with seizure activity. Clomipramine and olanzapine were subsequently withheld, and the seizures were controlled with diazepam 30 mg per day for three days. This pattern repeated upon re-challenge with the combination of olanzapine and clomipramine. Presumably from the temporal relationship between clomipramine and olanzapine administration and seizure manifestation, it can be suspected that this adverse event is due to an interaction between these two drugs. Clomipramine and olanzapine are both metabolized by the cytochrome P450 isoenzymes 1A2 and 2D6. One theory is that coadministration may result in elevated levels of both compounds. Although the mechanism by which this interaction occurs is not yet known, it is advised to use caution when administering olanzapine concomitantly with clomipramine, or other agents known to lower the seizure threshold (Deshauer et al, 2000).

3.5.1.BZ Oxilofrine
1) Interaction Effect: hypertension, cardiac arrhythmias, and tachycardia
2) Summary: Clinical trials have demonstrated a 2- to 8-fold increase in the effects of intravenous infusions of alpha adrenergic drugs to volunteers on tricyclic antidepressants. Arrhythmias and other severe adverse effects have also been reported (Ghose, 1980; Avery, 1973; Boakes et al, 1973a; Boakes, 1973; Mitchell et al, 1970; Stone et al, 1964). Local use (e.g., dental anesthesia) of epinephrine in concentrations of 1:100,000 or less is less likely to precipitate clinically significant hemodynamic changes (Steinberg & Block, 1971).
3) Severity: major
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: The vasoconstriction and other alpha-adrenergic effects of sympathomimetic drugs are substantially enhanced in the presence of tricyclic antidepressants (TCAs). Concomitant use should be avoided. If these drugs are given together, careful monitoring and a dose reduction of the sympathomimetic is required. Patients should be instructed to inform their doctor or dentist that they are taking a tricyclic antidepressant prior to any surgery or procedure.
7) Probable Mechanism: inhibition of norepinephrine reuptake
8) Literature Reports
a) Four healthy volunteers received intravenous infusions of various sympathomimetic amines (epinephrine, norepinephrine, phenylephrine, and isoproterenol) before and after imipramine (25 mg three times daily for five days). They showed an increased pressor response to epinephrine (2- to 4-fold), norepinephrine (4- to 8-fold), and phenylephrine (2- to 3-fold) after imipramine, but no difference was observed in the response to isoproterenol. Thus, the increased pressor response appeared to occur only for alpha adrenergic effects. All four subjects demonstrated changes in cardiac rhythm with epinephrine and imipramine consisting of sinus arrhythmia in three subjects and multiple ectopic beats and a nodal rhythm in the fourth subject (Boakes et al, 1973).
b) A review of spontaneous reports of adverse reactions to vasoconstrictors in local anesthetics found that 15 patients receiving a local anesthetic with norepinephrine (1:25,000) had severe reactions (severe headaches, chest tightness, subarachnoid hemorrhage). The drug history was incomplete, but at least three had been taking a tricyclic antidepressant at the time (Anon, 1972).

3.5.1.CA Oxybutynin
1) Interaction Effect: decreased clomipramine efficacy
2) Summary: Oxybutynin was suspected of inducing the metabolism of clomipramine in an elderly female patient. Subsequent dextromethorphan testing of the patient showed that she was an extensive metabolizer (EM) of cytochrome P450 2D6 (CYP2D6). A pilot study exploring the long- and short-term effects of oxybutynin on the activity of CYP2D6 and another isoenzyme, probably of the CYP3A family, showed that oxybutynin caused a disproportionate increase of hydroxymorphinan compared with dextrorphan. Because the formation of hydroxymorphinan is mainly dependent on the activity of CYP2D6 and CYP3A4, but only the latter is known to be inducible, the authors suggest that oxybutynin is an inducer of a CYP3A subfamily (Grozinger et al, 1999a).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Patients receiving concurrent therapy with clomipramine and oxybutynin should be monitored for loss of clomipramine efficacy, including worsening of symptoms. Plasma levels of clomipramine may be helpful in determining if efficacy is being compromised.
7) Probable Mechanism: induction by oxybutynin of cytochrome P450 3A-mediated clomipramine

metabolism
8) Literature Reports
a) A 72-year-old female was receiving clomipramine 150 mg daily for depression with a clomipramine and desmethylclomipramine blood level of 230 ng/mL and 348 ng/mL, respectively. Clomipramine was decreased to 25 mg daily, and fluvoxamine 100 mg daily was added to therapy. Eighteen days later, her clomipramine and desmethylclomipramine levels were 405 ng/mL and 50 ng/mL, respectively. Oxybutynin 5 mg daily was initiated for urinary incontinence, and within one week the clomipramine and desmethylclomipramine levels had decreased to 133 ng/mL and less than 25 ng/mL. They remained low one week later. The patient refused to discontinue oxybutynin to determine if her clomipramine blood levels would again increase (Grozinger et al, 1999).

3.5.1.CB Pargyline
1) Interaction Effect: neurotoxicity, seizures, or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)
2) Summary: Concomitant TCA and MAOI use has resulted in hyperpyrexia, convulsions, and death. Concurrent use of MAOIs and TCAs has also been reported to result in a condition termed serotonin syndrome (Insel et al, 1982a; Spigset et al, 1993a; Brodribb et al, 1994; Neuvonen et al, 1993). Serotonin syndrome is a rare but potentially fatal condition of serotonergic hyperstimulation characterized by hypertension, hyperthermia, myoclonus, and changes in mental status (Sternbach, 1991a). If TCAs and MAOIs must be used concurrently, avoid large doses, use only oral TCAs, avoid imipramine, clomipramine, desipramine, and tranylcypromine, and monitor patients closely (Schuckit et al, 1971a; White & Simpson, 1984).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Concomitant use of a tricyclic antidepressant (TCA) and a monoamine oxidase inhibitor (MAOI) should be done only with close monitoring and where the clinical benefit outweighs the potential risk. Other antidepressant therapy should first be considered. If deemed clinically necessary, avoid large doses and use agents other than imipramine, clomipramine, desipramine, and tranylcypromine.
7) Probable Mechanism: altered catecholamine uptake and metabolism
8) Literature Reports
a) Concomitant administration of monoamine oxidase inhibitors (MAOIs) with tricyclic antidepressants (TCAs) has been considered an absolute contraindication in the past. Reports of excitation, hyperpyrexia, convulsions, and possible death have been attributed to the combination (Lockett & Milner, 1965; Winston, 1971; Schuckit et al, 1971; Spiker & Pugh, 1976). The mechanism may relate to the combined inhibition of catecholamine reuptake into the central nervous system and inhibition of catecholamine metabolism (Sjoqvist, 1965).
b) Administration of a TCA after MAOI therapy may result in the development of serotonin syndrome. In a double-blind, crossover study examining the effects of clorgyline and clomipramine for the treatment of obsessive-compulsive disorder, two subjects developed severe reactions characteristic of serotonin syndrome. During the study, patients had received clorgyline therapy, followed by a washout period of approximately four weeks and subsequent clomipramine therapy. After taking the first 100 mg dose of clomipramine, one patient developed coarse myoclonic jerking in both legs, hyperreflexia, diaphoresis, and arrhythmia. Another patient developed a similar reaction after the first dose, with upper motor neuron symptoms, myoclonic movements, and cardiac irritability. Both patient's symptoms resolved several hours later, and both patients were later treated successfully with clomipramine without adverse effects (Insel et al, 1982).
c) A drug interaction occurred in a 76-year old woman who had been taking clomipramine 50 mg daily for several months prior to switching to moclobemide 300 mg daily. The patient experienced somnolescence, confusion, and fever which then progressed to further mental impairment, muscle stiffness, myoclonus, and convulsive attacks. The patient's symptoms were described as fulfilling the diagnostic criteria for serotonin syndrome and were resolved a few days later after discontinuing all antidepressant medications (Spigset et al, 1993).
d) In one case, clomipramine 10 mg twice daily was added to a stable regimen of tranylcypromine in a physically healthy 34-year old man. After taking several doses, the patients developed symptoms of nausea and profuse sweating, followed by pyrexia, dyspnea, and agitation. The hyperpyrexical state led to disseminated intravascular coagulation and eventual death (Tackley & Tregaskis, 1987).
e) There is evidence that MAOIs and TCAs can be given concomitantly in patients previously unresponsive to the MAOI or TCA alone. The combination may be utilized in one of two ways. Most frequently, the recommendation is to stop all previous antidepressants (five to ten days for TCAs and 14 days for MAOIs); the combination is then simultaneously started (Perry et al, 1991). Alternatively, in a patient previously receiving a TCA, small doses of the MAOI may be slowly added (Schoonover, 1983). Numerous studies in patients with refractory depression or phobic anxiety states have successfully used the combination of MAOIs and TCAs (Ponto et al, 1977; Schuckit et al, 1971; Ashcroft, 1975).

3.5.1.CC Paroxetine
1) Interaction Effect: clomipramine toxicity (dry mouth, sedation, urinary retention)
2) Summary: Concurrent use of paroxetine with drugs that are metabolized by cytochrome P450 2D6, such

as clomipramine, should be approached with caution (Prod Info Paxil(R), 2003).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When paroxetine is coadministered with clomipramine, monitor patients for signs and symptoms of clomipramine toxicity (dry mouth, sedation, urinary retention, blurred vision). Clomipramine doses may need to be reduced.
7) Probable Mechanism: decreased cytochrome P450 2D6-mediated clomipramine metabolism

3.5.1.CD Pemoline
1) Interaction Effect: hypertension, other cardiac effects, and CNS stimulation
2) Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been reported to result in enhanced amphetamine effects from the release of norepinephrine (Beaumont, 1973h; Raisfeld, 1972). A similar reaction might also occur with all drugs that have amphetamine-like effects. Acute elevations in blood pressure have been noted (Flemenbaum, 1971a). Some amphetamine-like drugs may inhibit the metabolism of TCAs, although most combinations have not been studied. When amphetamine analogs are being used to treat obesity, it should be noted that TCAs frequently lead to moderate weight gain (Russ & Ackerman, 1988). False positive urine tests for amphetamines have been reported during therapy with some TCAs (Merigian & Browning, 1993). Caution is advised when concurrent administration of amphetamine-like agents and TCAs is warranted. The patient should be closely monitored for increased cardiovascular effects (hypertension and dysrhythmias).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other sympathomimetic agents could lead to hypertension, increased cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006; Flemenbaum, 1972). Use caution if such therapy is warranted. Monitor the patient closely for hypertension and dysrhythmias.
7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission
8) Literature Reports
a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agents. Additionally, coadministration of d-amphetamine with TCAs such as desipramine or protriptyline results in sustained increases in d-amphetamine concentration in the brain (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006).
b) Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism of some tricyclic antidepressants, such as imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transdermal system, 2006).
c) Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases in blood pressure such that the hypotensive effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of combined therapy. Discontinuation of the methylphenidate usually results in the blood pressure returning to normotensive levels; reinstitution of the methylphenidate resulted in further blood pressure elevation (Flemenbaum, 1971; Flemenbaum, 1972).
d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine given for at least four weeks, were given fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical improvement. However, fenfluramine more than doubled steady-state plasma levels of desipramine (Price et al, 1990).
e) There have been claims based on uncontrolled studies that a better antidepressant response may occur with combined therapy (Garrettson et al, 1969). However, a systemic review of stimulants in the treatment of depression concluded that although uncontrolled studies were generally positive, the ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated little advantage of drug over placebo and did not appear to be as effective as the conventional antidepressants in primary depression (Satel & Nelson, 1989).

3.5.1.CE Pentobarbital
1) Interaction Effect: possible decreased tricyclic antidepressant serum concentrations and possible additive adverse effects
2) Summary: Concomitant barbiturate and tricyclic antidepressant (TCA) therapy may result in increased metabolism of the TCA. There have been scattered reports of individuals with decreased serum levels of TCAs in the presence of a barbiturate (Moody et al, 1977a; Silverman & Braithwaite, 1972; Burrows & Davies, 1971). In addition, TCAs can worsen seizure control by reducing the seizure threshold (Brodie, 1992). These drugs also have additive CNS and respiratory depressant effects.
3) Severity: minor
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor for efficacy of antidepressant effect. Increases in tricyclic antidepressant dosages may be required. Additionally, monitor for toxicity when either drug is added to or withdrawn from

therapy. Serum concentrations may be of value in determining appropriate dosage.
7) Probable Mechanism: increased tricyclic antidepressant metabolism
8) Literature Reports
a) The pharmacokinetics of a single oral dose of desipramine (100 mg) were studied in eight epileptic patients chronically treated with phenobarbital and in eight drug-free healthy controls (Spina et al, 1996). All subjects were extensive metabolizers with respect to the genetically determined CYP2D6-related metabolic polymorphism. Compared with controls, epileptic patients exhibited lower peak plasma desipramine concentrations (74 nmol/L vs. 107 nmol/L), smaller desipramine area under the concentration-time curve values (1943 nmol/L/h vs. 3234 nmol/L/h), and shorter desipramine elimination half-lives (15.1 h vs. 20.6 h). All barbiturates are believed to have similar effects leading to induction of hepatic enzymes and the 2D6 isozyme is believed to be important in the metabolism of most or all TCAs. Thus, similar effects should be expected with any combination of TCA and barbiturate.

3.5.1.CF Phendimetrazine
1) Interaction Effect: hypertension, other cardiac effects, and CNS stimulation
2) Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been reported to result in enhanced amphetamine effects from the release of norepinephrine (Beaumont, 1973h; Raisfeld, 1972). A similar reaction might also occur with all drugs that have amphetamine-like effects. Acute elevations in blood pressure have been noted (Flemenbaum, 1971a). Some amphetamine-like drugs may inhibit the metabolism of TCAs, although most combinations have not been studied. When amphetamine analogs are being used to treat obesity, it should be noted that TCAs frequently lead to moderate weight gain (Russ & Ackerman, 1988). False positive urine tests for amphetamines have been reported during therapy with some TCAs (Merigian & Browning, 1993). Caution is advised when concurrent administration of amphetamine-like agents and TCAs is warranted. The patient should be closely monitored for increased cardiovascular effects (hypertension and dysrhythmias).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other sympathomimetic agents could lead to hypertension, increased cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006; Flemenbaum, 1972). Use caution if such therapy is warranted. Monitor the patient closely for hypertension and dysrhythmias.
7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission
8) Literature Reports
a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agents. Additionally, coadministration of d-amphetamine with TCAs such as desipramine or protriptyline results in sustained increases in d-amphetamine concentration in the brain (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006).
b) Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism of some tricyclic antidepressants, such as imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transdermal system, 2006).
c) Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases in blood pressure such that the hypotensive effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of combined therapy. Discontinuation of the methylphenidate usually results in the blood pressure returning to normotensive levels; reinstitution of the methylphenidate resulted in further blood pressure elevation (Flemenbaum, 1971; Flemenbaum, 1972).
d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine given for at least four weeks, were given fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical improvement. However, fenfluramine more than doubled steady-state plasma levels of desipramine (Price et al, 1990).
e) There have been claims based on uncontrolled studies that a better antidepressant response may occur with combined therapy (Garrettson et al, 1969). However, a systemic review of stimulants in the treatment of depression concluded that although uncontrolled studies were generally positive, the ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated little advantage of drug over placebo and did not appear to be as effective as the conventional antidepressants in primary depression (Satel & Nelson, 1989).

3.5.1.CG Phenelzine
1) Interaction Effect: neurotoxicity, seizures, or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)
2) Summary: Concomitant TCA and MAOI use has resulted in hyperpyrexia, convulsions, and death. Concurrent use of MAOIs and TCAs has also been reported to result in a condition termed serotonin syndrome (Insel et al, 1982e; Spigset et al, 1993f; Brodribb et al, 1994d; Neuvonen et al, 1993b). Serotonin syndrome is a rare but potentially fatal condition of serotonergic hyperstimulation characterized by hypertension, hyperthermia, myoclonus, and changes in mental status (Sternbach, 1991c). Consequently, coadministration of TCAs and MAOIs is contraindicated in most cases. If TCAs and MAOIs must be used

concurrently, avoid large doses, use only oral TCAs, avoid imipramine, clomipramine, desipramine, and tranylcypromine, and monitor patients closely (Schuckit et al, 1971e; White & Simpson, 1984c).
3) Severity: contraindicated
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of clomipramine with a monoamine oxidase inhibitor (MAOI), such as phenelzine, is contraindicated. If clomipramine is replacing treatment with phenelzine, a minimum of 14 days should elapse after phenelzine is discontinued before begin therapy with clomipramine. If clomipramine is substituted by phenelzine, a minimum of 14 days should elapse after clomipramine is discontinued and before phenelzine therapy begins (Prod Info clomipramine hydrochloride oral capsule, 2002). However, the manufacturer of phenelzine recommends that at least 10 days should elapse after clomipramine therapy is discontinued before starting phenelzine (Prod Info NARDIL(R) Tablets, USP, 2005).
7) Probable Mechanism: altered catecholamine uptake and metabolism
8) Literature Reports
a) Concomitant administration of monoamine oxidase inhibitors (MAOIs) with tricyclic antidepressants (TCAs) has been considered an absolute contraindication in the past and still is listed as such by the manufacturers (Prod Info clomipramine hydrochloride oral capsule, 2002). Reports of excitation, hyperpyrexia, convulsions, and possible death have been attributed to the combination (Lockett & Milner, 1965b; Brachfeld et al, 1963; Winston, 1971b; Schuckit et al, 1971d; Sargent, 1965; Spiker & Pugh, 1976b). The mechanism may relate to the combined inhibition of catecholamine reuptake into the central nervous system and inhibition of catecholamine metabolism (Sjoqvist, 1965b).
b) Administration of a TCA after MAOI therapy may result in the development of serotonin syndrome. In a double-blind, crossover study examining the effects of clorgyline and clomipramine for the treatment of obsessive-compulsive disorder, two subjects developed severe reactions characteristic of serotonin syndrome. During the study, patients had received clorgyline therapy, followed by a washout period of approximately four weeks and subsequent clomipramine therapy. After taking the first 100 mg dose of clomipramine, one patient developed coarse myoclonic jerking in both legs, hyperreflexia, diaphoresis, and arrhythmia. Another patient developed a similar reaction after the first dose, with upper motor neuron symptoms, myoclonic movements, and cardiac irritability. Both patient's symptoms resolved several hours later, and both patients were later treated successfully with clomipramine without adverse effects (Insel et al, 1982d).
c) A drug interaction was reported in a 76-year old woman who had been taking clomipramine 50 mg daily for several months prior to switching to moclobemide 300 mg daily. The patient experienced somnolence, confusion, and fever which then progressed to further mental impairment, muscle stiffness, myoclonus, and convulsive attacks. The patient's symptoms were described as fulfilling the diagnostic criteria for serotonin syndrome and were resolved a few days later after discontinuing all antidepressant medications (Spigset et al, 1993e).
d) A 39-year old woman with bipolar disorder developed serotonin syndrome after imipramine was added to moclobemide. The patient was taking moclobemide 300 mg twice daily when imipramine was started at 50 mg daily, followed by two dosage increases of imipramine to 200 mg and a reduction of moclobemide dosage to 150 mg twice daily. Five days after the increase in imipramine to 200 mg per day, the patient developed symptoms of serotonin syndrome, including sweating, shivering, confusion, fever, and spasms in the extremities. The patient was treated with chlorpromazine and symptoms resolved over the next few days without further complications (Brodribb et al, 1994c).
e) Three patients with bipolar disorder developed manic symptoms while undergoing concurrent therapy with isocarboxazid and amitriptyline. In all three cases the patients had been given MAOIs and TCAs alone without complications. It was only when the drugs were used in combination that symptoms of mania emerged, suggesting a synergistic effect (de la Fuente et al, 1986).
f) In one case, clomipramine 10 mg twice daily was added to a stable regimen of tranylcypromine in a physically healthy 34-year old man. After taking several doses, the patient developed symptoms of nausea and profuse sweating, followed by pyrexia, dyspnea, and agitation. The hyperpyrexical state led to disseminated intravascular coagulation and eventual death (Tackley & Tregaskis, 1987c).
g) There is evidence that MAOIs and TCAs can be given concomitantly in patients previously unresponsive to the MAOI or TCA alone. A few precautions must be followed including: a) avoidance of large doses (no more than 150 mg amitriptyline or its equivalent, 45 mg phenelzine, or 60 mg isocarboxazid) b) oral administration c) avoidance of clomipramine, imipramine, desipramine, and tranylcypromine in any combination, and d) close monitoring of patients (Kline, 1974; Winston, 1971b; Schuckit et al, 1971d; White & Simpson, 1984b; Rom & Benner, 1972). The combination may be utilized in one of two ways. Most frequently, the recommendation is to stop all previous antidepressants (five to ten days for TCAs and 14 days for MAOIs); the combination is then simultaneously started (Perry et al, 1991b). Alternatively, in a patient previously receiving a TCA, small doses of the MAOI may be slowly added (Schoonover, 1983). Some sources suggest that the combination of amitriptyline and isocarboxazid is preferred (Perry et al, 1991b). Numerous studies in patients with refractory depression or phobic anxiety states have successfully used the combination of MAOIs and TCAs (Ponto et al, 1977b; Schuckit et al, 1971d; Ashcroft, 1975b).

3.5.1.CH Phenindione
1) Interaction Effect: increased risk of bleeding

2) Summary: Tricyclic antidepressants (TCAs) may increase the half-life and bioavailability of oral anticoagulants (Vesell et al, 1970c; Williams et al, 1976c). Considerable interindividual differences may be found (Pond et al, 1975c).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: In patients receiving tricyclic antidepressants and oral anticoagulant therapy, the prothrombin time ratio or INR (international normalized ration) should be closely monitored with the addition and withdrawal of the antidepressant, and should be periodically reassessed during concurrent therapy. Achieving a stable drug regimen which produces the desired level of anticoagulation may be difficult in patients on this combination, and frequent adjustments of the anticoagulant dose may be required.
7) Probable Mechanism: decreased phenindione metabolism; increased phenindione absorption
8) Literature Reports
a) In a study of healthy volunteers, the concurrent use of nortriptyline or amitriptyline resulted in an increase of dicumarol levels and an increase in the plasma half-life of dicumarol, although the effect was not consistent in all subjects (Pond et al, 1975b). This effect was not observed with warfarin.
b) A single oral dose of bishydroxycoumarin after 8 days of nortriptyline resulted in a significantly prolonged half-life and decreased volume of distribution of the coumarin anticoagulant in 6 healthy volunteers (Vesell et al, 1970b). The mechanism of action was suggested to be reduced bishydroxycoumarin metabolism and/or altered coumarin absorption.
c) Drug dosing was studied in 16 patients on long-term anticoagulant therapy who used concurrent TCAs (Williams et al, 1976b). TCAs affected the stability of anticoagulant control leading to frequent changes in the doses of anticoagulants. Inhibition of coumarin metabolism was the postulated mechanism.

3.5.1.CI Phenmetrazine
1) Interaction Effect: hypertension, other cardiac effects, and CNS stimulation
2) Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been reported to result in enhanced amphetamine effects from the release of norepinephrine (Beaumont, 1973h; Raisfeld, 1972). A similar reaction might also occur with all drugs that have amphetamine-like effects. Acute elevations in blood pressure have been noted (Flemenbaum, 1971a). Some amphetamine-like drugs may inhibit the metabolism of TCAs, although most combinations have not been studied. When amphetamine analogs are being used to treat obesity, it should be noted that TCAs frequently lead to moderate weight gain (Russ & Ackerman, 1988). False positive urine tests for amphetamines have been reported during therapy with some TCAs (Merigian & Browning, 1993). Caution is advised when concurrent administration of amphetamine-like agents and TCAs is warranted. The patient should be closely monitored for increased cardiovascular effects (hypertension and dysrhythmias).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other sympathomimetic agents could lead to hypertension, increased cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006; Flemenbaum, 1972). Use caution if such therapy is warranted. Monitor the patient closely for hypertension and dysrhythmias.
7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission
8) Literature Reports
a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agents. Additionally, coadministration of d-amphetamine with TCAs such as desipramine or protriptyline results in sustained increases in d-amphetamine concentration in the brain (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006).
b) Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism of some tricyclic antidepressants, such as imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transdermal system, 2006).
c) Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases in blood pressure such that the hypotensive effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of combined therapy. Discontinuation of the methylphenidate usually results in the blood pressure returning to normotensive levels; reinstitution of the methylphenidate resulted in further blood pressure elevation (Flemenbaum, 1971; Flemenbaum, 1972).
d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine given for at least four weeks, were given fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical improvement. However, fenfluramine more than doubled steady-state plasma levels of desipramine (Price et al, 1990).
e) There have been claims based on uncontrolled studies that a better antidepressant response may occur with combined therapy (Garrettson et al, 1969). However, a systemic review of stimulants in the treatment of depression concluded that although uncontrolled studies were generally positive, the ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated little

advantage of drug over placebo and did not appear to be as effective as the conventional antidepressants in primary depression (Satel & Nelson, 1989).

3.5.1.CJ Phenobarbital

1) Interaction Effect: possible decreased tricyclic antidepressant serum concentrations and possible additive adverse effects

2) Summary: Concomitant barbiturate and tricyclic antidepressant (TCA) therapy may result in increased metabolism of the TCA. There have been scattered reports of individuals with decreased serum levels of TCAs in the presence of a barbiturate (Moody et al, 1977a; Silverman & Braithwaite, 1972; Burrows & Davies, 1971). In addition, TCAs can worsen seizure control by reducing the seizure threshold (Brodie, 1992). These drugs also have additive CNS and respiratory depressant effects.

3) Severity: minor

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Monitor for efficacy of antidepressant effect. Increases in tricyclic antidepressant dosages may be required. Additionally, monitor for toxicity when either drug is added to or withdrawn from therapy. Serum concentrations may be of value in determining appropriate dosage.

7) Probable Mechanism: increased tricyclic antidepressant metabolism

8) Literature Reports

a) The pharmacokinetics of a single oral dose of desipramine (100 mg) were studied in eight epileptic patients chronically treated with phenobarbital and in eight drug-free healthy controls (Spina et al, 1996). All subjects were extensive metabolizers with respect to the genetically determined CYP2D6-related metabolic polymorphism. Compared with controls, epileptic patients exhibited lower peak plasma desipramine concentrations (74 nmol/L vs. 107 nmol/L), smaller desipramine area under the concentration-time curve values (1943 nmol/L/h vs. 3234 nmol/L/h), and shorter desipramine elimination half-lives (15.1 h vs. 20.6 h). All barbiturates are believed to have similar effects leading to induction of hepatic enzymes and the 2D6 isozyme is believed to be important in the metabolism of most or all TCAs. Thus, similar effects should be expected with any combination of TCA and barbiturate.

3.5.1.CK Phenprocoumon

1) Interaction Effect: increased risk of bleeding

2) Summary: Tricyclic antidepressants (TCAs) may increase the half-life and bioavailability of oral anticoagulants (Vesell et al, 1970a; Williams et al, 1976a). Considerable interindividual differences may be found (Pond et al, 1975a).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: In patients receiving tricyclic antidepressants and oral anticoagulant therapy, the prothrombin time ratio or INR (international normalized ratio) should be closely monitored with the addition and withdrawal of the antidepressant, and should be periodically reassessed during concurrent therapy. Achieving a stable drug regimen which produces the desired level of anticoagulation may be difficult in patients on this combination, and frequent adjustments of the anticoagulant dose may be required.

7) Probable Mechanism: decreased phenprocoumon metabolism; increased phenprocoumon absorption

8) Literature Reports

a) In a study of healthy volunteers, the concurrent use of nortriptyline or amitriptyline resulted in an increase of dicumarol levels and an increase in the plasma half-life of dicumarol, although the effect was not consistent in all subjects (Pond et al, 1975). This effect was not observed with warfarin.

b) A single oral dose of bishydroxycoumarin after 8 days of nortriptyline resulted in a significantly prolonged half-life and decreased volume of distribution of the coumarin anticoagulant in 6 healthy volunteers (Vesell et al, 1970). The mechanism of action was suggested to be reduced bishydroxycoumarin metabolism and/or altered coumarin absorption.

c) Drug dosing was studied in 16 patients on long-term anticoagulant therapy who used concurrent TCAs (Williams et al, 1976). TCAs affected the stability of anticoagulant control leading to frequent changes in the doses of anticoagulants. Inhibition of coumarin metabolism was the postulated mechanism.

3.5.1.CL Phentermine

1) Interaction Effect: hypertension, other cardiac effects, and CNS stimulation

2) Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been reported to result in enhanced amphetamine effects from the release of norepinephrine (Beaumont, 1973h; Raisfeld, 1972). A similar reaction might also occur with all drugs that have amphetamine-like effects. Acute elevations in blood pressure have been noted (Flemenbaum, 1971a). Some amphetamine-like drugs may inhibit the metabolism of TCAs, although most combinations have not been studied. When amphetamine analogs are being used to treat obesity, it should be noted that TCAs frequently lead to moderate weight gain (Russ & Ackerman, 1988). False positive urine tests for amphetamines have been reported during therapy with some TCAs (Merigian & Browning, 1993). Caution is advised when concurrent administration of amphetamine-like agents and TCAs is warranted. The patient should be closely monitored for increased cardiovascular effects (hypertension and dysrhythmias).

3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other sympathomimetic agents could lead to hypertension, increased cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006; Flemenbaum, 1972). Use caution if such therapy is warranted. Monitor the patient closely for hypertension and dysrhythmias.
7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission
8) Literature Reports
a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agents. Additionally, coadministration of d-amphetamine with TCAs such as desipramine or protriptyline results in sustained increases in d-amphetamine concentration in the brain (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006).
b) Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism of some tricyclic antidepressants, such as imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transdermal system, 2006).
c) Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases in blood pressure such that the hypotensive effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of combined therapy. Discontinuation of the methylphenidate usually results in the blood pressure returning to normotensive levels; reinstitution of the methylphenidate resulted in further blood pressure elevation (Flemenbaum, 1971; Flemenbaum, 1972).
d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine given for at least four weeks, were given fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical improvement. However, fenfluramine more than doubled steady-state plasma levels of desipramine (Price et al, 1990).
e) There have been claims based on uncontrolled studies that a better antidepressant response may occur with combined therapy (Garrettson et al, 1969). However, a systemic review of stimulants in the treatment of depression concluded that although uncontrolled studies were generally positive, the ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated little advantage of drug over placebo and did not appear to be as effective as the conventional antidepressants in primary depression (Satel & Nelson, 1989).

3.5.1.CM Phenylephrine
1) Interaction Effect: hypertension, cardiac arrhythmias, and tachycardia
2) Summary: Clinical trials have demonstrated a 2- to 8-fold increase in the effects of intravenous infusions of alpha adrenergic drugs to volunteers on tricyclic antidepressants. Arrhythmias and other severe adverse effects have also been reported (Ghose, 1980; Avery, 1973; Boakes et al, 1973a; Boakes, 1973; Mitchell et al, 1970; Stone et al, 1964). Local use (e.g., dental anesthesia) of epinephrine in concentrations of 1:100,000 or less is less likely to precipitate clinically significant hemodynamic changes (Steinberg & Block, 1971).
3) Severity: major
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: The vasoconstriction and other alpha-adrenergic effects of sympathomimetic drugs are substantially enhanced in the presence of tricyclic antidepressants (TCAs). Concomitant use should be avoided. If these drugs are given together, careful monitoring and a dose reduction of the sympathomimetic is required. Patients should be instructed to inform their doctor or dentist that they are taking a tricyclic antidepressant prior to any surgery or procedure.
7) Probable Mechanism: inhibition of norepinephrine reuptake
8) Literature Reports
a) Four healthy volunteers received intravenous infusions of various sympathomimetic amines (epinephrine, norepinephrine, phenylephrine, and isoproterenol) before and after imipramine (25 mg three times daily for five days). They showed an increased pressor response to epinephrine (2- to 4-fold), norepinephrine (4- to 8-fold), and phenylephrine (2- to 3-fold) after imipramine, but no difference was observed in the response to isoproterenol. Thus, the increased pressor response appeared to occur only for alpha adrenergic effects. All four subjects demonstrated changes in cardiac rhythm with epinephrine and imipramine consisting of sinus arrhythmia in three subjects and multiple ectopic beats and a nodal rhythm in the fourth subject (Boakes et al, 1973).
b) A review of spontaneous reports of adverse reactions to vasoconstrictors in local anesthetics found that 15 patients receiving a local anesthetic with norepinephrine (1:25,000) had severe reactions (severe headaches, chest tightness, subarachnoid hemorrhage). The drug history was incomplete, but at least three had been taking a tricyclic antidepressant at the time (Anon, 1972).

3.5.1.CN Phenytoin
1) Interaction Effect: an increased risk of phenytoin toxicity (ataxia, hyperreflexia, nystagmus, tremors)
2) Summary: A few case reports have indicated that imipramine inhibits phenytoin metabolism resulting in

increased serum phenytoin concentration (Petti & Campbell, 1975a; Perucca & Richens, 1977a). Tricyclic antidepressants (TCAs) may lower the seizure threshold in epileptic patients stabilized on anticonvulsants. Theoretically, because phenytoin is an enzyme inducer, the metabolism of antidepressants may be increased resulting in reduced TCA serum levels.
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Consider phenytoin serum levels if a tricyclic antidepressant is added to therapy or if the patient begins to exhibit signs of toxicity; lower doses of phenytoin may be required. If phenytoin is added to tricyclic antidepressant therapy, monitor for clinical efficacy of the tricyclic agent.
7) Probable Mechanism: inhibition of phenytoin metabolism

3.5.1.CO Primidone
1) Interaction Effect: possible decreased tricyclic antidepressant serum concentrations and possible additive adverse effects
2) Summary: Concomitant barbiturate and tricyclic antidepressant (TCA) therapy may result in increased metabolism of the TCA. There have been scattered reports of individuals with decreased serum levels of TCAs in the presence of a barbiturate (Moody et al, 1977a; Silverman & Braithwaite, 1972; Burrows & Davies, 1971). In addition, TCAs can worsen seizure control by reducing the seizure threshold (Brodie, 1992). These drugs also have additive CNS and respiratory depressant effects.
3) Severity: minor
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor for efficacy of antidepressant effect. Increases in tricyclic antidepressant dosages may be required. Additionally, monitor for toxicity when either drug is added to or withdrawn from therapy. Serum concentrations may be of value in determining appropriate dosage.
7) Probable Mechanism: increased tricyclic antidepressant metabolism
8) Literature Reports
a) The pharmacokinetics of a single oral dose of desipramine (100 mg) were studied in eight epileptic patients chronically treated with phenobarbital and in eight drug-free healthy controls (Spina et al, 1996). All subjects were extensive metabolizers with respect to the genetically determined CYP2D6-related metabolic polymorphism. Compared with controls, epileptic patients exhibited lower peak plasma desipramine concentrations (74 nmol/L vs. 107 nmol/L), smaller desipramine area under the concentration-time curve values (1943 nmol/L/h vs. 3234 nmol/L/h), and shorter desipramine elimination half-lives (15.1 h vs. 20.6 h). All barbiturates are believed to have similar effects leading to induction of hepatic enzymes and the 2D6 isozyme is believed to be important in the metabolism of most or all TCAs. Thus, similar effects should be expected with any combination of TCA and barbiturate.

3.5.1.CP Procarbazine
1) Interaction Effect: neurotoxicity, seizures
2) Summary: Concomitant tricyclic antidepressant and more potent MAOI use has resulted in hyperpyrexia, convulsions, and death. Procarbazine has relatively weak MAOI actions, so while the potential for drug interactions between tricyclic antidepressants and procarbazine exists, clinical data are lacking at this time (Schuckit et al, 1971g; White & Simpson, 1984d). Concurrent use is not recommended (Prod Info Matulane (R), 1997).
3) Severity: major
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Concomitant use is not recommended and should probably be initiated only under close medical supervision, and then only if other antidepressant class agents have proven unsuccessful. With more potent MAOIs, recommendations for concurrent use of TCAs have included avoiding large doses of the TCA, using only oral tricyclics, and avoiding imipramine, clomipramine, and desipramine. Procarbazine therapy should not begin until seven days following discontinuation of tricyclic antidepressants and 14 days following the discontinuation of other MAO inhibitors.
7) Probable Mechanism: altered catecholamine uptake and metabolism
8) Literature Reports
a) Procarbazine is primarily used as an antineoplastic agent, but was originally investigated as a monoamine oxidase inhibitor (Gilman et al, 1985). Animal studies have indicated that procarbazine is a monoamine oxidase inhibitor (MAOI) (DeVita et al, 1965) but appears to be a relatively weak MAOI in man (Gilman et al, 1985). Hypertensive reactions may still result from concomitant administration of tricyclic antidepressants, sympathomimetics, and tyramine-containing foods (Gilman et al, 1985; Ponto et al, 1977c). Concomitant administration of monoamine oxidase (MAO) inhibitors with tricyclic antidepressants has been considered an absolute contraindication in the past and still is listed as such by the manufacturers. Reports of excitation, hyperpyrexia, convulsions, and possible death have been attributed to the combination (Lockett & Milner, 1965c; Brachfeld et al, 1963a; Winston, 1971c; Schuckit et al, 1971f; Sargent, 1965a; Spiker & Pugh, 1976c). Careful examination of such reports indicate unusual circumstances in most cases such as parenteral administration of a tricyclic. The mechanism may relate to the combined inhibition of catecholamine reuptake into the central nervous system and

inhibition of catecholamine metabolism (Sjoqvist, 1965c).
b) Procarbazine therapy should not begin until 7 days following discontinuation of tricyclic antidepressants and 14 days following the discontinuation of other MAO inhibitors (AMA Department of Drugs, 1992; Gilman et al, 1985).

3.5.1.CQ Propylhexedrine

1) Interaction Effect: hypertension, other cardiac effects, and CNS stimulation
2) Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been reported to result in enhanced amphetamine effects from the release of norepinephrine (Beaumont, 1973h; Raisfeld, 1972). A similar reaction might also occur with all drugs that have amphetamine-like effects. Acute elevations in blood pressure have been noted (Flemenbaum, 1971a). Some amphetamine-like drugs may inhibit the metabolism of TCAs, although most combinations have not been studied. When amphetamine analogs are being used to treat obesity, it should be noted that TCAs frequently lead to moderate weight gain (Russ & Ackerman, 1988). False positive urine tests for amphetamines have been reported during therapy with some TCAs (Merigian & Browning, 1993). Caution is advised when concurrent administration of amphetamine-like agents and TCAs is warranted. The patient should be closely monitored for increased cardiovascular effects (hypertension and dysrhythmias).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other sympathomimetic agents could lead to hypertension, increased cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006; Flemenbaum, 1972). Use caution if such therapy is warranted. Monitor the patient closely for hypertension and dysrhythmias.
7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission
8) Literature Reports
a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agents. Additionally, coadministration of d-amphetamine with TCAs such as desipramine or protriptyline results in sustained increases in d-amphetamine concentration in the brain (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006).
b) Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism of some tricyclic antidepressants, such as imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transdermal system, 2006).
c) Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases in blood pressure such that the hypotensive effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of combined therapy. Discontinuation of the methylphenidate usually results in the blood pressure returning to normotensive levels; reinstitution of the methylphenidate resulted in further blood pressure elevation (Flemenbaum, 1971; Flemenbaum, 1972).
d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine given for at least four weeks, were given fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical improvement. However, fenfluramine more than doubled steady-state plasma levels of desipramine (Price et al, 1990).
e) There have been claims based on uncontrolled studies that a better antidepressant response may occur with combined therapy (Garrettson et al, 1969). However, a systemic review of stimulants in the treatment of depression concluded that although uncontrolled studies were generally positive, the ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated little advantage of drug over placebo and did not appear to be as effective as the conventional antidepressants in primary depression (Satel & Nelson, 1989).

3.5.1.CR Quinestrol

1) Interaction Effect: attenuation of antidepressant effectiveness; tricyclic toxicity (drowsiness, hypotension, akathisia)
2) Summary: In isolated cases, the pharmacologic effects of tricyclic antidepressants may be increased or decreased by estrogens (Somani & Khurana, 1973k), with paradoxical loss of antidepressant effect yet tricyclic toxicity being manifested simultaneously (Prange, 1972j). The effects of the interaction appear to be estrogen dose-related (Khurana, 1972k) and may be of clinical importance primarily in patients previously stabilized on tricyclic therapy who are being started on estrogen therapy (Krishnan et al, 1984j).
3) Severity: minor
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: If signs or symptoms of altered tricyclic response are noted, dose adjustment downward of either the estrogen or tricyclic component may be successful in restoring effectiveness or resolving toxicity. However, drug withdrawal may be required.
7) Probable Mechanism: possible estrogen-enhanced hepatic metabolism of the tricyclic
8) Literature Reports
a) Some studies evaluated the qualitative effects of concomitant administration of estrogen and TCAs.

In one trial, 30 depressed female prisoners were randomly assigned to 4 treatment groups. Ten patients received placebo, 10 received imipramine (150 milligrams/day) and placebo, 5 patients received imipramine (150 milligrams/day) and ethinyl estradiol (50 micrograms/day), while 5 patients received imipramine (150 milligrams/day) and ethinyl estradiol (25 micrograms/day). The 10 patients that received placebo did not improve over the 6 weeks of the study. The 10 patients taking estrogen and imipramine demonstrated a significantly greater improvement in symptoms than did the 10 patients taking imipramine alone. However, after 2 weeks, the 5 patients that received imipramine and high-dose estrogen had not improved as much as the patients receiving imipramine and low-dose estrogen. The only side-effect reported was drowsiness, which only affected the patients taking imipramine. Following the discontinuation of ethinyl estradiol, a time period of 2 weeks was required for the high-dose estrogen group to do as well as the low-dose group. This effect was attributed to the presence of residual estrogen in the high-dose group. In another group, 5 women received imipramine 150 milligrams and ethinyl estradiol 50 micrograms daily did not improve as much as 10 patients receiving only imipramine. Also, the patients on the combination had severe side-effects including lethargy, coarse tremor and systolic hypotension (Prange, 1972d).

b) A case report demonstrated an interaction in a 32-year-old female taking conjugated estrogens 2.5 milligrams and imipramine 100 milligrams. The patient developed lethargy, tremors, and signs of depersonalization. After 2 years of therapy, the patient increased her estrogen dose to 5 milligrams and then 7.5 milligrams daily. The patient became nauseated, had constant headaches, and low normal blood pressure. All lab work was normal. Upon discontinuing the estrogen, the side-effects abated (Khurana, 1972j). Some investigators have proposed that the side effects resulted from enhanced TCA effects secondary to estrogen inhibition of hepatic microsomal enzymes (Somani & Khurana, 1973j).

c) In one study, women received clomipramine and oral contraceptives or clomipramine alone. At the beginning of the study there were 30 women taking the combination, but 12 subsequently dropped out. The 18 patients on the combination were matched with 18 patients taking clomipramine alone. No significant difference was noted in the patients' responses to clomipramine. It was proposed that there was no significant difference in side-effects between the groups; however, the groups were matched after patients had dropped out of the study. Had the patients been matched prior to the study, different conclusions may have been drawn (Beaumont, 1973e).

d) In a study women received clomipramine and oral contraceptives or clomipramine alone. At the beginning of the study there were 30 women taking the combination, but 12 subsequently dropped out. The 18 patients on the combination were matched with 18 patients taking clomipramine alone. No significant difference was noted in the patients' responses to clomipramine. It was proposed that there was no significant difference in side-effects between the groups; however, the groups were matched after patients had dropped out of the study. Had the patients been matched prior to the study, different conclusions may have been drawn (Beaumont, 1973f).

e) Akathisia was reported in 3 patients receiving conjugated estrogens and tricyclic antidepressants concurrently. A 24-year-old patient receiving clomipramine 120 milligrams/day for anorexia nervosa and conjugated estrogens 1.25 milligrams/day for amenorrhea developed restless legs and a constant desire to move continuously. Estrogen was discontinued and benztropine 2 milligrams was administered, resulting in marked reduction and resolution within 48 hours. Akathisia and disorientation developed in a 55-year-old patient on conjugated estrogen 1.25 milligrams/day who was prescribed amitriptyline 50 milligrams/day for depression. Within hours of amitriptyline, the patient was confused, restless, and possessed an inner desire to move continuously. Symptoms disappeared after discontinuing amitriptyline. Positive rechallenge at one week with doxepin 100 milligrams, with resolution following discontinuation of doxepin. A third case of akathisia was reported in a 35-year-old patient who received conjugated estrogen 1.25 milligrams/day and amitriptyline 50 milligrams/day. Akathisia developed within a few hours after taking the first dose of amitriptyline and resolved within 48 hours following discontinuation of the antidepressant (Krishnan et al, 1984d).

f) The absolute bioavailability of imipramine increased in women who received low-dose oral contraceptives (50 micrograms or less of ethinyl estradiol) from 27 to 44% (p less than 0.05) as evident by an increase in the area under the plasma concentration time curve (Abernethy et al, 1984e).

g) Estrogens may inhibit the oxidation of TCAs by affecting hepatic microsomal enzymes (John et al, 1980e). Many TCAs are metabolized via oxidation and conjugation pathways. Inhibition of the oxidation of TCAs could result in accumulation and toxicity due to decreased clearance. Estrogens are suspected of possessing other effects on the central nervous system resulting in an antidepressant effect (Oppenheim, 1983e).

3.5.1.CS Quinidine

1) Interaction Effect: clomipramine toxicity (dry mouth, sedation)

2) Summary: The concomitant use of quinidine and clomipramine is not recommended. Two studies have demonstrated that concomitant use of quinidine and imipramine or desipramine results in increased serum concentrations of these antidepressants (Brosen & Gram, 1989a; Steiner et al, 1987). A similar interaction may occur with other tricyclic antidepressants including clomipramine.

3) Severity: major

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: Monitor for increased antidepressant side effects with concomitant therapy with

quinidine; lower doses of the tricyclic agent may be required. Conversely, if quinidine is discontinued from therapy, monitor for antidepressant efficacy. Tricyclic antidepressant serum levels might be considered in some clinical situations.
7) Probable Mechanism: decreased clomipramine metabolism
8) Literature Reports
a) Quinidine is an inhibitor of the cytochrome P450 2D6 isoenzyme responsible for the 2-hydroxylation of imipramine and desipramine (Brosen & Gram, 1989). Inhibition of this enzyme system can result in a 35% decrease in imipramine clearance and 85% decrease in desipramine clearance. Demethylation of imipramine by the cytochrome P450 3A3/4 isoenzyme is unaffected by this interaction. Until more information is available all patients having quinidine added to drug regimen containing imipramine or desipramine should be monitored for increased antidepressant serum concentrations and potential toxicity.
b) In a placebo controlled study, imipramine 3.5 mg/kg was administered daily for seven patients with severe depression and doses were titrated to obtain therapeutic plasma concentrations. Two patients displayed premature atrial depolarizations and premature ventricular depolarizations before therapy. On patient had 33 premature atrial depolarizations (PAD) and 30 premature ventricular depolarizations (PVD) per hour, which decreased to 0.4 PAC and zero PVC per hour on imipramine. The other patient had 12 PAD and 169 PVD per hour before treatment and 1.8 PAD and 28.1 PVD per hour on imipramine. The authors also cautioned that the incidence of cardiotoxicity may increase if tricyclic antidepressants are administered with Type I antiarrhythmics. It was also recommended that quinidine and procainamide not be used to treat the arrhythmias of a tricyclic overdose. The similarities between these agents may exacerbate the cardiotoxicity (Kantor et al, 1978).

3.5.1.CT Rasagiline
1) Interaction Effect: severe CNS toxicity
2) Summary: Concomitant use of rasagiline and tricyclic antidepressants should be avoided. Concurrent administration or overlapping therapy with tricyclic antidepressants and non-selective MAOIs has been reported to cause serious, sometimes fatal, reactions; the mechanisms of these reactions are not fully understood. Signs and symptoms include severe CNS toxicity (behavioral and mental status changes, diaphoresis, muscular rigidity, hypertension, and syncope) associated with hyperpyrexia and death. Data from clinical studies, where rasagiline-treated patients (n=115) were concomitantly exposed to tricyclic antidepressants, are insufficient to rule out an interaction. At least 14 days should elapse after discontinuing rasagiline before initiating therapy with a tricyclic antidepressant (Prod Info AZILECT(R) oral tablets, 2006).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concurrent use of rasagiline and a tricyclic antidepressant is not recommended. Wait at least 14 days after discontinuing rasagiline before initiating therapy with a tricyclic antidepressant (Prod Info AZILECT(R) oral tablets, 2006).
7) Probable Mechanism: unknown

3.5.1.CU S-Adenosylmethionine
1) Interaction Effect: an increased risk of serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)
2) Summary: A single case has been reported of serotonin syndrome likely resulting from the combination of S-adenosylmethionine (SAMe) and clomipramine (Iruela et al, 1993a). SAMe was shown to hasten the onset of therapeutic response of imipramine in a clinical trial involving 40 patients, without serotonergic side effects (Berlanga et al, 1992). If therapy is initiated with SAMe and a tricyclic antidepressant, the patient should be monitored closely for early signs of serotonin syndrome. Serotonin syndrome is a condition of serotonergic hyperstimulation and manifests as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. If the syndrome is not recognized and correctly treated, death can result (Sternbach, 1991).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: S-adenosylmethionine (SAMe) used concomitantly with imipramine was found to decrease depressive symptoms sooner than imipramine alone (Berlanga et al, 1992). One case has been reported of serotonin syndrome likely resulting from concomitant use of SAMe and clomipramine (Iruela et al, 1993). If SAMe and a tricyclic antidepressant are used together, use low doses of each and titrate upward slowly, while monitoring closely for early signs of serotonin syndrome such as increasing anxiety, confusion, and disorientation.
7) Probable Mechanism: additive pharmacologic effects resulting in excessive serotonergic stimulation
8) Literature Reports
a) A 71 year-old female was hospitalized with anxiety, agitation, confusion, and symptoms of serotonin syndrome. She had been taking S-adenosylmethionine 100 milligrams (mg) intramuscularly daily and clomipramine 25 mg daily for 10 days, which was then increased to 75 mg/day. Within 48-72 hours of the increased clomipramine dosage, she became progressively anxious, agitated, and confused. On admission she was verbally unresponsive and stuporous, with heart rate 130 beats/minute, respiratory

rate 30 breaths/minute, temperature 40.5 degrees Celsius, diarrhea, myoclonus, generalized tremors, rigidity, hyperreflexia, shivering, diaphoresis, and dehydration. Temperature increased to 43 degrees Celsius during her hospital stay, with no documented infection. White blood cell count (WBC) was 13,040 mm3, lactic dehydrogenase was 662 units/liter (U/L), creatine phosphokinase was 8920 U/L, serum potassium 2.7 milliequivalents/liter (mEq/L), creatinine 1.1 mg/100 milliliter (mL) (laboratory reference values were not provided). A cranial computed tomography (CT) scan was normal. The patient was not taking neuroleptics. Serum benzodiazepine and tricyclic antidepressant levels were normal. Symptoms resolved gradually with 4 days of hydration and supportive care. The interaction was proposed to be a result of synergistic activity of S-adenosylmethionine and clomipramine (Iruela et al, 1993).

3.5.1.CV Salmeterol

1) Interaction Effect: an increased risk of cardiovascular excitation
2) Summary: Salmeterol should be administered with extreme caution to patients who are being treated with a tricyclic antidepressant, or within two weeks of the discontinuation of a tricyclic antidepressant (Prod Info SEREVENT(R) DISKUS(R) inhalation powder, 2006). Clinically significant changes in systolic and diastolic blood pressure, pulse rate, and electrocardiograms have been seen with the use of salmeterol, and these changes may be exacerbated by the use of a tricyclic antidepressant.
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Close observation for adverse cardiovascular effects is warranted when these agents are administered concurrently or if salmeterol is given within two weeks of discontinuation of a tricyclic antidepressant.
7) Probable Mechanism: potentiation of vascular effects

3.5.1.CW Secobarbital

1) Interaction Effect: possible decreased tricyclic antidepressant serum concentrations and possible additive adverse effects
2) Summary: Concomitant barbiturate and tricyclic antidepressant (TCA) therapy may result in increased metabolism of the TCA. There have been scattered reports of individuals with decreased serum levels of TCAs in the presence of a barbiturate (Moody et al, 1977a; Silverman & Braithwaite, 1972; Burrows & Davies, 1971). In addition, TCAs can worsen seizure control by reducing the seizure threshold (Brodie, 1992). These drugs also have additive CNS and respiratory depressant effects.
3) Severity: minor
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor for efficacy of antidepressant effect. Increases in tricyclic antidepressant dosages may be required. Additionally, monitor for toxicity when either drug is added to or withdrawn from therapy. Serum concentrations may be of value in determining appropriate dosage.
7) Probable Mechanism: increased tricyclic antidepressant metabolism
8) Literature Reports
a) The pharmacokinetics of a single oral dose of desipramine (100 mg) were studied in eight epileptic patients chronically treated with phenobarbital and in eight drug-free healthy controls (Spina et al, 1996). All subjects were extensive metabolizers with respect to the genetically determined CYP2D6-related metabolic polymorphism. Compared with controls, epileptic patients exhibited lower peak plasma desipramine concentrations (74 nmol/L vs. 107 nmol/L), smaller desipramine area under the concentration-time curve values (1943 nmol/L/h vs. 3234 nmol/L/h), and shorter desipramine elimination half-lives (15.1 h vs. 20.6 h). All barbiturates are believed to have similar effects leading to induction of hepatic enzymes and the 2D6 isozyme is believed to be important in the metabolism of most or all TCAs. Thus, similar effects should be expected with any combination of TCA and barbiturate.

3.5.1.CX Selegiline

1) Interaction Effect: neurotoxicity, seizures, or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)
2) Summary: Concomitant TCA and MAOI use has resulted in hyperpyrexia, convulsions, and death. Concurrent use of MAOIs and TCAs has also been reported to result in a condition termed serotonin syndrome (Insel et al, 1982n; Spigset et al, 1993m; Brodribb et al, 1994l; Neuvonen et al, 1993g). Serotonin syndrome is a rare but potentially fatal condition of serotonergic hyperstimulation characterized by hypertension, hyperthermia, myoclonus, and changes in mental status (Sternbach, 1991h). Consequently, coadministration of TCAs and MAOIs is contraindicated in most cases. If TCAs and MAOIs must be used concurrently, avoid large doses, use only oral TCAs, avoid imipramine, clomipramine, desipramine, and tranylcypromine, and monitor patients closely (Schuckit et al, 1971q; White & Simpson, 1984l).
3) Severity: contraindicated
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of clomipramine with a monoamine oxidase inhibitor (MAOI), such as selegiline is contraindicated. A minimum of 14 days should elapse after selegiline is discontinued

before therapy with clomipramine is begun. Similarly, a minimum of 14 days should elapse after clomipramine is discontinued and therapy with selegiline is begun (Prod Info clomipramine hydrochloride oral capsule, 2002).

7) Probable Mechanism: altered catecholamine uptake and metabolism

8) Literature Reports

a) Concomitant administration of monoamine oxidase inhibitors (MAOIs) with tricyclic antidepressants (TCAs) has been considered an absolute contraindication in the past and still is listed as such by the manufacturers (Prod Info clomipramine hydrochloride oral capsule, 2002). Reports of excitation, hyperpyrexia, convulsions, and possible death have been attributed to the combination (Lockett & Milner, 1965h; Brachfeld et al, 1963d; Winston, 1971h; Schuckit et al, 1971p; Sargent, 1965d; Spiker & Pugh, 1976h). The mechanism may relate to the combined inhibition of catecholamine reuptake into the central nervous system and inhibition of catecholamine metabolism (Sjoqvist, 1965h).

b) Administration of a TCA after MAOI therapy may result in the development of serotonin syndrome. In a double-blind, crossover study examining the effects of clorgyline and clomipramine for the treatment of obsessive-compulsive disorder, two subjects developed severe reactions characteristic of serotonin syndrome. During the study, patients had received clorgyline therapy, followed by a washout period of approximately four weeks and subsequent clomipramine therapy. After taking the first 100 mg dose of clomipramine, one patient developed coarse myoclonic jerking in both legs, hyperreflexia, diaphoresis, and arrhythmia. Another patient developed a similar reaction after the first dose, with upper motor neuron symptoms, myoclonic movements, and cardiac irritability. Both patient's symptoms resolved several hours later, and both patients were later treated successfully with clomipramine without adverse effects (Insel et al, 1982m).

c) A drug interaction was reported in a 76-year old woman who had been taking clomipramine 50 mg daily for several months prior to switching to moclobemide 300 mg daily. The patient experienced somnolence, confusion, and fever which then progressed to further mental impairment, muscle stiffness, myoclonus, and convulsive attacks. The patient's symptoms were described as fulfilling the diagnostic criteria for serotonin syndrome and were resolved a few days later after discontinuing all antidepressant medications (Spigset et al, 1993l).

d) A 39-year old woman with bipolar disorder developed serotonin syndrome after imipramine was added to moclobemide. The patient was taking moclobemide 300 mg twice daily when imipramine was started at 50 mg daily, followed by two dosage increases of imipramine to 200 mg and a reduction of moclobemide dosage to 150 mg twice daily. Five days after the increase in imipramine to 200 mg per day, the patient developed symptoms of serotonin syndrome, including sweating, shivering, confusion, fever, and spasms in the extremities. The patient was treated with chlorpromazine and symptoms resolved over the next few days without further complications (Brodribb et al, 1994k).

e) Three patients with bipolar disorder developed manic symptoms while undergoing concurrent therapy with isocarboxazid and amitriptyline. In all three cases the patients had been given MAOIs and TCAs alone without complications. It was only when the drugs were used in combination that symptoms of mania emerged, suggesting a synergistic effect (de la Fuente et al, 1986b).

f) In one case, clomipramine 10 mg twice daily was added to a stable regimen of tranylcypromine in a physically healthy 34-year old man. After taking several doses, the patient developed symptoms of nausea and profuse sweating, followed by pyrexia, dyspnea, and agitation. The hyperpyrexical state led to disseminated intravascular coagulation and eventual death (Tackley & Tregaskis, 1987g).

g) There is evidence that MAOIs and TCAs can be given concomitantly in patients previously unresponsive to the MAOI or TCA alone. A few precautions must be followed including: a) avoidance of large doses (no more than 150 mg amitriptyline or its equivalent, 45 mg phenelzine, or 60 mg isocarboxazid) b) oral administration c) avoidance of clomipramine, imipramine, desipramine, and tranylcypromine in any combination, and d) close monitoring of patients (Kline, 1974c; Winston, 1971h; Schuckit et al, 1971p; White & Simpson, 1984k; Rom & Benner, 1972c). The combination may be utilized in one of two ways. Most frequently, the recommendation is to stop all previous antidepressants (five to ten days for TCAs and 14 days for MAOIs); the combination is then simultaneously started (Perry et al, 1991g). Alternatively, in a patient previously receiving a TCA, small doses of the MAOI may be slowly added (Schoonover, 1983). Some sources suggest that the combination of amitriptyline and isocarboxazid is preferred (Perry et al, 1991g). Numerous studies in patients with refractory depression or phobic anxiety states have successfully used the combination of MAOIs and TCAs (Ponto et al, 1977h; Schuckit et al, 1971p; Ashcroft, 1975g).

3.5.1.CY Sertraline

1) Interaction Effect: modest elevations of clomipramine serum levels or possible serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)

2) Summary: There is limited evidence suggesting that sertraline may inhibit tricyclic antidepressant (TCA) metabolism resulting in higher TCA serum concentrations. Sertraline inhibits cytochrome P450 2D6 enzyme activity and may increase the plasma concentrations of coadministered drugs that are metabolized by this pathway, including the tricyclic antidepressants (Prod Info Zoloft(R), 2002; Preskorn et al, 1994a; Lydiard et al, 1993). Effects of the interaction may have little or no clinical impact, however. Increases in TCA serum levels associated with sertraline coadministration were modest compared with those found when fluoxetine (another selective serotonin reuptake inhibitor) was combined with desipramine (von Moltke et al, 1994). Monitor patients on clomipramine-sertraline therapy for TCA toxicity (dry mouth, urinary retention, CNS

depression). Clomipramine doses may need to be reduced.
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: The combined use of tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs) may result in the inhibition of the TCA metabolism. A few cases of serotonin syndrome have also been reported with concurrent TCA and SSRI therapy. Caution should be observed when drugs in these two classes are used together.
7) Probable Mechanism: inhibition of clomipramine metabolism
8) Literature Reports
a) The pharmacokinetics of desipramine were studied in 18 healthy male volunteers. Study subjects received only desipramine (50 mg daily) for seven days followed by desipramine with sertraline (50 mg daily) for 21 days. When sertraline was added to desipramine therapy, the mean maximum concentration of desipramine increased by 34% and the area under the concentration-time curve increased by 26%. Trough concentrations of desipramine were close to baseline one week after sertraline was discontinued. The changes in desipramine concentrations were modest and the interaction may not be clinically significant (Preskorn et al, 1994).

3.5.1.CZ St John's Wort
1) Interaction Effect: an increased risk of serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)
2) Summary: Theoretically, since St. John's Wort is thought to inhibit serotonin reuptake and may have mild monoamine oxidase inhibitory activity (Singer et al, 1999; Thiede & Walper, 1994), serotonin syndrome could result when St. John's Wort is taken along with a tricyclic antidepressant. This theoretical risk of serotonin syndrome is also based on case reports of serotonin syndrome resulting from concomitant use of selective serotonin reuptake inhibitors with tricyclic antidepressants (Alderman & Lee, 1996), as well as concomitant use of monoamine oxidase inhibitors with tricyclic antidepressants (Brodribb et al, 1994a; Spigset et al, 1993b; Tackley & Tregaskis, 1987a). Coadministration of amitriptyline and St. John's Wort decreased the area under the concentration-time curve of amitriptyline and its metabolite nortriptyline (Roots et al, 2000); if other tricyclic antidepressants are similarly affected by St. John's Wort, the risk of serotonin syndrome may be reduced, yet effectiveness of the tricyclic antidepressant may also be reduced. To maintain maximal effectiveness of the tricyclic antidepressant, as well as avoid any potential risk of serotonin syndrome, avoid concomitant use of St. John's Wort and tricyclic antidepressants.
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Avoid concomitant use of St. John's Wort with tricyclic antidepressants.
7) Probable Mechanism: additive pharmacologic effects resulting in excessive serotonergic stimulation

3.5.1.DA Tapentadol
1) Interaction Effect: increased risk of serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)
2) Summary: Concurrent use of tapentadol and a tricyclic antidepressant may result in serotonin syndrome, which may be life-threatening. Symptoms of serotonin syndrome may include restlessness, hallucinations, loss of coordination, fast heart beat, rapid changes in blood pressure, increased body temperature, overreactive reflexes, nausea, vomiting, and diarrhea (Prod Info tapentadol immediate release oral tablets, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of tapentadol and a tricyclic antidepressant may result in a life-threatening condition called serotonin syndrome. If these agents are used together, monitor the patient closely for symptoms of serotonin syndrome (restlessness, hyperthermia, hyperreflexia, incoordination), especially during treatment initiation and dose increases (Prod Info tapentadol immediate release oral tablets, 2008).
7) Probable Mechanism: additive serotonergic effect

3.5.1.DB Thiopental
1) Interaction Effect: possible decreased tricyclic antidepressant serum concentrations and possible additive adverse effects
2) Summary: Concomitant barbiturate and tricyclic antidepressant (TCA) therapy may result in increased metabolism of the TCA. There have been scattered reports of individuals with decreased serum levels of TCAs in the presence of a barbiturate (Moody et al, 1977a; Silverman & Braithwaite, 1972; Burrows & Davies, 1971). In addition, TCAs can worsen seizure control by reducing the seizure threshold (Brodie, 1992). These drugs also have additive CNS and respiratory depressant effects.
3) Severity: minor
4) Onset: delayed
5) Substantiation: probable

6) Clinical Management: Monitor for efficacy of antidepressant effect. Increases in tricyclic antidepressant dosages may be required. Additionally, monitor for toxicity when either drug is added to or withdrawn from therapy. Serum concentrations may be of value in determining appropriate dosage.
7) Probable Mechanism: increased tricyclic antidepressant metabolism
8) Literature Reports
a) The pharmacokinetics of a single oral dose of desipramine (100 mg) were studied in eight epileptic patients chronically treated with phenobarbital and in eight drug-free healthy controls (Spina et al, 1996). All subjects were extensive metabolizers with respect to the genetically determined CYP2D6-related metabolic polymorphism. Compared with controls, epileptic patients exhibited lower peak plasma desipramine concentrations (74 nmol/L vs. 107 nmol/L), smaller desipramine area under the concentration-time curve values (1943 nmol/L/h vs. 3234 nmol/L/h), and shorter desipramine elimination half-lives (15.1 h vs. 20.6 h). All barbiturates are believed to have similar effects leading to induction of hepatic enzymes and the 2D6 isozyme is believed to be important in the metabolism of most or all TCAs. Thus, similar effects should be expected with any combination of TCA and barbiturate.

3.5.1.DC Tibolone
1) Interaction Effect: attenuation of antidepressant effectiveness; tricyclic toxicity (drowsiness, hypotension, akathisia)
2) Summary: In isolated cases, the pharmacologic effects of tricyclic antidepressants may be increased or decreased by estrogens (Somani & Khurana, 1973e), with paradoxical loss of antidepressant effect yet tricyclic toxicity being manifested simultaneously (Prange, 1972e). The effects of the interaction appear to be estrogen dose-related (Khurana, 1972e) and may be of clinical importance primarily in patients previously stabilized on tricyclic therapy who are being started on estrogen therapy (Krishnan et al, 1984e).
3) Severity: minor
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: If signs or symptoms of altered tricyclic response are noted, dose adjustment downward of either the estrogen or tricyclic component may be successful in restoring effectiveness or resolving toxicity. However, drug withdrawal may be required.
7) Probable Mechanism: possible estrogen-enhanced hepatic metabolism of the tricyclic
8) Literature Reports
a) Some studies evaluated the qualitative effects of concomitant administration of estrogen and TCAs. In one trial, 30 depressed female prisoners were randomly assigned to 4 treatment groups. Ten patients received placebo, 10 received imipramine (150 milligrams/day) and placebo, 5 patients received imipramine (150 milligrams/day) and ethinyl estradiol (50 micrograms/day), while 5 patients received imipramine (150 milligrams/day) and ethinyl estradiol (25 micrograms/day). The 10 patients that received placebo did not improve over the 6 weeks of the study. The 10 patients taking estrogen and imipramine demonstrated a significantly greater improvement in symptoms than did the 10 patients taking imipramine alone. However, after 2 weeks, the 5 patients that received imipramine and high-dose estrogen had not improved as much as the patients receiving imipramine and low-dose estrogen. The only side-effect reported was drowsiness, which only affected the patients taking imipramine. Following the discontinuation of ethinyl estradiol, a time period of 2 weeks was required for the high-dose estrogen group to do as well as the low-dose group. This effect was attributed to the presence of residual estrogen in the high-dose group. In another group, 5 women received imipramine 150 milligrams and ethinyl estradiol 50 micrograms daily did not improve as much as 10 patients receiving only imipramine. Also, the patients on the combination had severe side-effects including lethargy, coarse tremor and systolic hypotension (Prange, 1972d).
b) A case report demonstrated an interaction in a 32-year-old female taking conjugated estrogens 2.5 milligrams and imipramine 100 milligrams. The patient developed lethargy, tremors, and signs of depersonalization. After 2 years of therapy, the patient increased her estrogen dose to 5 milligrams and then 7.5 milligrams daily. The patient became nauseated, had constant headaches, and low normal blood pressure. All lab work was normal. Upon discontinuing the estrogen, the side-effects abated (Khurana, 1972d). Some investigators have proposed that the side effects resulted from enhanced TCA effects secondary to estrogen inhibition of hepatic microsomal enzymes (Somani & Khurana, 1973d).
c) A study in which women received clomipramine and oral contraceptives or clomipramine alone was reviewed (Beaumont, 1973b). At the beginning of the study there were 30 women taking the combination, but 12 subsequently dropped out. The 18 patients on the combination were matched with 18 patients taking clomipramine alone. No significant difference was noted in the patients' responses to clomipramine. It was proposed that there was no significant difference in side-effects between the groups; however, the groups were matched after patients had dropped out of the study. Had the patients been matched prior to the study, different conclusions may have been drawn.
d) The effects of oral contraceptives on clomipramine were studied in 42 women between the ages of 18 and 40. Twenty-three women took clomipramine 25 milligrams at bedtime while 19 took clomipramine 25 milligrams at bedtime with oral contraceptives. Over the 4-week study, 3 control patients (2 due to side-effects) and 5 in the experimental group (2 due to side-effects) dropped out. Venous blood samples were drawn at weekly intervals for measurement of serum clomipramine concentrations. No difference in serum concentrations was noted between the groups. However, this result may be partially due to the low dose of clomipramine given (Luscombe & John, 1980b).

e) Akathisia was reported in 3 patients receiving conjugated estrogens and tricyclic antidepressants concurrently. A 24-year-old patient receiving clomipramine 120 milligrams/day for anorexia nervosa and conjugated estrogens 1.25 milligrams/day for amenorrhea developed restless legs and a constant desire to move continuously. Estrogen was discontinued and benztropine 2 milligrams was administered, resulting in marked reduction and resolution within 48 hours. Akathisia and disorientation developed in a 55-year-old patient on conjugated estrogen 1.25 milligrams/day who was prescribed amitriptyline 50 milligrams/day for depression. Within hours of amitriptyline, the patient was confused, restless, and possessed an inner desire to move continuously. Symptoms disappeared after discontinuing amitriptyline. Positive rechallenge at one week with doxepin 100 milligrams, with resolution following discontinuation of doxepin. A third case of akathisia was reported in a 35-year-old patient who received conjugated estrogen 1.25 milligrams/day and amitriptyline 50 milligrams/day. Akathisia developed within a few hours after taking the first dose of amitriptyline and resolved within 48 hours following discontinuation of the antidepressant (Krishnan et al, 1984d).
f) The absolute bioavailability of imipramine increased in women who received low-dose oral contraceptives (50 micrograms or less of ethinyl estradiol) from 27 to 44% (p less than 0.05) as evident by an increase in the area under the plasma concentration time curve (Abernethy et al, 1984b).
g) Estrogens may inhibit the oxidation of TCAs by affecting hepatic microsomal enzymes (John et al, 1980b). Many TCAs are metabolized via oxidation and conjugation pathways. Inhibition of the oxidation of TCAs could result in accumulation and toxicity due to decreased clearance. Estrogens are suspected of possessing other effects on the central nervous system resulting in an antidepressant effect (Oppenheim, 1983b).

3.5.1.DD Toloxatone

1) Interaction Effect: neurotoxicity, seizures, or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)
2) Summary: Concomitant TCA and MAOI use has resulted in hyperpyrexia, convulsions, and death. Concurrent use of MAOIs and TCAs has also been reported to result in a condition termed serotonin syndrome (Insel et al, 1982l; Spigset et al, 1993k; Brodribb et al, 1994j; Neuvonen et al, 1993f). Serotonin syndrome is a rare but potentially fatal condition of serotonergic hyperstimulation characterized by hypertension, hyperthermia, myoclonus, and changes in mental status (Sternbach, 1991g). If TCAs and MAOIs must be used concurrently, avoid large doses, use only oral TCAs, avoid imipramine, clomipramine, desipramine, and tranylcypromine, and monitor patients closely (Schuckit et al, 1971o; White & Simpson, 1984j).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Concomitant use of a tricyclic antidepressant (TCA) and a monoamine oxidase inhibitor (MAOI) should be done only with close monitoring and where the clinical benefit outweighs the potential risk. Other antidepressant therapy should first be considered. If deemed clinically necessary, avoid large doses and use agents other than imipramine, clomipramine, desipramine, and tranylcypromine.
7) Probable Mechanism: altered catecholamine uptake and metabolism
8) Literature Reports

a) Concomitant administration of monoamine oxidase inhibitors (MAOIs) with tricyclic antidepressants (TCAs) has been considered an absolute contraindication in the past. Reports of excitation, hyperpyrexia, convulsions, and possible death have been attributed to the combination (Lockett & Milner, 1965g; Winston, 1971g; Schuckit et al, 1971n; Spiker & Pugh, 1976g). The mechanism may relate to the combined inhibition of catecholamine reuptake into the central nervous system and inhibition of catecholamine metabolism (Sjoqvist, 1965g).
b) There is minimal risk of a clinically significant pharmacokinetic interaction between amitriptyline and toloxatone, a MAOI-A (Vandel et al, 1993). Seventeen inpatients being treated for major depressive illness were administered amitriptyline 125 mg once daily for two weeks, and the following two weeks they received amitriptyline 125 mg daily and toloxatone 600 mg daily. With combined therapy there was a small, nonsignificant increase in amitriptyline plasma levels. The availability and urinary excretion of amitriptyline and its metabolites were not significantly affected.
c) There is evidence that MAOIs and TCAs can be given concomitantly in patients previously unresponsive to the MAOI or TCA alone. The combination may be utilized in one of two ways. Most frequently, the recommendation is to stop all previous antidepressants (five to ten days for TCAs and 14 days for MAOIs); the combination is then simultaneously started (Perry et al, 1991f). Alternatively, in a patient previously receiving a TCA, small doses of the MAOI may be slowly added (Schoonover, 1983). Numerous studies in patients with refractory depression or phobic anxiety states have successfully used the combination of MAOIs and TCAs (Ponto et al, 1977g; Schuckit et al, 1971n; Ashcroft, 1975f).
d) Serotonin syndrome has been reported with the use of moclobemide, a reversible inhibitor of monoamine oxidase, and a TCA. A 39-year old woman with bipolar disorder developed serotonin syndrome after imipramine was added to moclobemide. The patient was taking moclobemide 300 mg twice daily when imipramine was started at 50 mg daily, followed by two dosage increases of imipramine to 200 mg and a reduction of moclobemide dosage to 150 mg twice daily. Five days after the increase in imipramine to 200 mg per day, the patient developed symptoms of serotonin syndrome, including sweating, shivering, confusion, fever, and spasms in the extremities. The patient was treated

with chlorpromazine and symptoms resolved over the next few days without further complications (Brodribb et al, 1994i).

3.5.1.DE Tramadol

1) Interaction Effect: an increased risk of seizures
2) Summary: Seizures have been reported in patients using tramadol. Some medications, including tricyclic antidepressants (TCAs), are known to reduce the seizure threshold. The risk of seizures may be enhanced when clomipramine and tramadol therapy are combined (Prod Info Ultram(R), 1998).
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Caution should be used if tramadol is to be administered to patients receiving concomitant TCA therapy. If possible, avoid this combination, especially in patients with underlying conditions that might predispose to seizures.
7) Probable Mechanism: unknown

3.5.1.DF Tranylcypromine

1) Interaction Effect: neurotoxicity, seizures, or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)
2) Summary: Concomitant TCA and MAOI use has resulted in hyperpyrexia, convulsions, and death. Concurrent use of MAOIs and TCAs has also been reported to result in a condition termed serotonin syndrome (Insel et al, 1982p; Spigset et al, 1993o; Brodribb et al, 1994n; Neuvonen et al, 1993h). Serotonin syndrome is a rare but potentially fatal condition of serotonergic hyperstimulation characterized by hypertension, hyperthermia, myoclonus, and changes in mental status (Sternbach, 1991i). Consequently, coadministration of TCAs and MAOIs is contraindicated in most cases. If TCAs and MAOIs must be used concurrently, avoid large doses, use only oral TCAs, avoid imipramine, clomipramine, desipramine, and tranylcypromine, and monitor patients closely (Schuckit et al, 1971s; White & Simpson, 1984n).
3) Severity: contraindicated
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Concomitant use of clomipramine with a monoamine oxidase inhibitor (MAOI), such as tranylcypromine is contraindicated. If clomipramine is replacing treatment with tranylcypromine, a minimum of 14 days should elapse after tranylcypromine is discontinued and therapy with clomipramine begins. If clomipramine is substituted by tranylcypromine, a minimum of 14 days should elapse after clomipramine is discontinued and tranylcypromine treatment begins (Prod Info clomipramine hydrochloride oral capsule, 2002). However, the manufacturer of tranylcypromine recommends that at least 7 days should elapse before tranylcypromine therapy is replaced by clomipramine. Similarly, if clomipramine therapy is substituted by tranylcypromine, there should be a 7 day washout period. Tranylcypromine should then be given using half the normal starting dosage for, minimally, the first week of therapy (Prod Info Parnate(R), 2001).
7) Probable Mechanism: altered catecholamine uptake and metabolism
8) Literature Reports

a) Concomitant administration of monoamine oxidase inhibitors (MAOIs) with tricyclic antidepressants (TCAs) has been considered an absolute contraindication in the past and still is listed as such by the manufacturers (Prod Info clomipramine hydrochloride oral capsule, 2002). Reports of excitation, hyperpyrexia, convulsions, and possible death have been attributed to the combination (Lockett & Milner, 1965i; Brachfeld et al, 1963e; Winston, 1971i; Schuckit et al, 1971r; Sargent, 1965e; Spiker & Pugh, 1976i). The mechanism may relate to the combined inhibition of catecholamine reuptake into the central nervous system and inhibition of catecholamine metabolism (Sjoqvist, 1965i).

b) Administration of a TCA after MAOI therapy may result in the development of serotonin syndrome. In a double-blind, crossover study examining the effects of clorgyline and clomipramine for the treatment of obsessive-compulsive disorder, two subjects developed severe reactions characteristic of serotonin syndrome. During the study, patients had received clorgyline therapy, followed by a washout period of approximately four weeks and subsequent clomipramine therapy. After taking the first 100 mg dose of clomipramine, one patient developed coarse myoclonic jerking in both legs, hyperreflexia, diaphoresis, and arrhythmia. Another patient developed a similar reaction after the first dose, with upper motor neuron symptoms, myoclonic movements, and cardiac irritability. Both patient's symptoms resolved several hours later, and both patients were later treated successfully with clomipramine without adverse effects (Insel et al, 1982o).

c) A drug interaction was reported in which a 76-year old woman who had been taking clomipramine 50 mg daily for several months prior to switching to moclobemide 300 mg daily. The patient experienced somnolence, confusion, and fever which then progressed to further mental impairment, muscle stiffness, myoclonus, and convulsive attacks. The patient's symptoms were described as fulfilling the diagnostic criteria for serotonin syndrome and were resolved a few days later after discontinuing all antidepressant medications (Spigset et al, 1993n).

d) A 39-year old woman with bipolar disorder developed serotonin syndrome after imipramine was added to moclobemide. The patient was taking moclobemide 300 mg twice daily when imipramine was started at 50 mg daily, followed by two dosage increases of imipramine to 200 mg and a reduction of

moclobemide dosage to 150 mg twice daily. Five days after the increase in imipramine to 200 mg per day, the patient developed symptoms of serotonin syndrome, including sweating, shivering, confusion, fever, and spasms in the extremities. The patient was treated with chlorpromazine and symptoms resolved over the next few days without further complications (Brodribb et al, 1994m).
e) Three patients with bipolar disorder developed manic symptoms while undergoing concurrent therapy with isocarboxazid and amitriptyline. In all three cases the patients had been given MAOIs and TCAs alone without complications. It was only when the drugs were used in combination that symptoms of mania emerged, suggesting a synergistic effect (de la Fuente et al, 1986c).
f) In one case, clomipramine 10 mg twice daily was added to a stable regimen of tranylcypromine in a physically healthy 34-year old man. After taking several doses, the patient developed symptoms of nausea and profuse sweating, followed by pyrexia, dyspnea, and agitation. The hyperpyrexical state led to disseminated intravascular coagulation and eventual death (Tackley & Tregaskis, 1987h).
g) There is evidence that MAOIs and TCAs can be given concomitantly in patients previously unresponsive to the MAOI or TCA alone. A few precautions must be followed including: a) avoidance of large doses (no more than 150 mg amitriptyline or its equivalent, 45 mg phenelzine, or 60 mg isocarboxazid) b) oral administration c) avoidance of clomipramine, imipramine, desipramine, and tranylcypromine in any combination, and d) close monitoring of patients (Kline, 1974d; Winston, 1971i; Schuckit et al, 1971r; White & Simpson, 1984m; Rom & Benner, 1972d). The combination may be utilized in one of two ways. Most frequently, the recommendation is to stop all previous antidepressants (five to ten days for TCAs and 14 days for MAOIs); the combination is then simultaneously started (Perry et al, 1991h). Alternatively, in a patient previously receiving a TCA, small doses of the MAOI may be slowly added (Schoonover, 1983). Some sources suggest that the combination of amitriptyline and isocarboxazid is preferred (Perry et al, 1991h). Numerous studies in patients with refractory depression or phobic anxiety states have successfully used the combination of MAOIs and TCAs (Ponto et al, 1977i; Schuckit et al, 1971r; Ashcroft, 1975h).

3.5.1.DG Valproic Acid

1) Interaction Effect: an increased risk of clomipramine toxicity (agitation, confusion, hallucinations, urinary retention, tachycardia, seizures, coma)
2) Summary: Comedication with clomipramine and valproic acid may increase serum levels of clomipramine resulting in increased side effects. Clomipramine toxicity developed in a patient twelve days after valproic acid therapy was initiated. Metabolism of clomipramine is mediated through N-demethylation, hydroxylation, and glucuronidation, and valproic acid appears to inhibit the enzymes responsible for this mode of metabolism (Fehr et al, 2000a).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor serum clomipramine levels to avoid overdosing as a result of elevated concentrations of clomipramine when comedicating with valproic acid. The clomipramine dose may need to be reduced when valproic acid is added to therapy.
7) Probable Mechanism: inhibition of cytochrome P450 2C-mediated metabolism of clomipramine
8) Literature Reports
a) A case report describes a 46-year-old female with personality disorder whose serum clomipramine concentrations became elevated after she began concomitant therapy with valproic acid. Antidepressant therapy with clomipramine and lorazepam was initiated while being hospitalized for treatment of her psychiatric disorder. These two agents were chosen to reduce the frequency of panic attacks and to improve symptoms of suicidal and self-destructive behavior. A target dose of clomipramine 150 mg/day resulted in serum clomipramine levels in the normal range. Lorazepam was initiated at a dose of 2 mg/day After two weeks of therapy valproate was initiated at 1000 mg/day because emotional instability and self-destructive behavior remained unimproved. After five days of therapy the serum levels of clomipramine and desmethylclomipramine increased to 447 ng/mL and 85 ng/mL, respectively. Valproate serum concentration was 63.2 mcg/mL. The valproate dose was subsequently adjusted to 1400 mg/day. Seven days after the increase in valproate dose, clomipramine and desmethylclomipramine serum concentrations were 479 ng/mL and 269 ng/mL respectively. Conversely, the valproate serum level was 55 mcg/mL. The patient noted a feeling of numbness and exaggerated sleep disturbances. After the clomipramine dose was reduced to 75 mg/day, these symptoms resolved. The author concludes that the increase in serum clomipramine concentrations was primarily due to comedication with valproate (Fehr et al, 2000).

3.5.1.DH Vasopressin

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Tricyclic antidepressants and vasopressin have been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Vivactil(R), 1999; McCue et al, 1989; Munger & Effron, 1988; Mauro et al, 1988; Marshall & Forker, 1982c; Goldstein & Claghorn, 1980; Buckhardt et al, 1978; Pinder et al, 1977; Thorstrand, 1976; Singh, 1972). Even though no formal drug interaction studies have been done, the coadministration of drugs known to prolong the QTc interval is not recommended.
3) Severity: major

4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of drugs that prolong the QT interval, such as tricyclic antidepressants and vasopressin, is not recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.DI Venlafaxine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest) and adverse effects of both drugs
2) Summary: Tricyclic antidepressants (TCAs) and venlafaxine have been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Effexor(R) XR, 2003; Marshall & Forker, 1982). Even though no formal drug interaction studies have been done, the coadministration of tricyclic antidepressants and other drugs known to prolong the QTc interval, such as venlafaxine, is not recommended (Prod Info Elavil(R), 1999). In addition, venlafaxine and tricyclic antidepressants (TCAs) may competitively inhibit each other's metabolism which may increase side effects of both drugs (Perry, 2000; Prod Info Effexor(R) XR, 2003; Ellingrod & Perry, 1994). Venlafaxine increased the AUC, Cmax, and Cmin of desipramine by approximately 35%. The AUCs of 2-OH-desipramine increased by 2.5 and 4.5 fold when administered with venlafaxine 37.5 mg and 75 mg every 12 hours, respectively. The pharmacokinetics of imipramine and the 2-hydroxy metabolite were not affected (Prod Info venlafaxine extended release oral tablets, 2008).
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Due to the potential for additive effects on the QT interval, the concurrent administration of venlafaxine and tricyclic antidepressants is not recommended.
7) Probable Mechanism: decreased TCA and venlafaxine metabolism; additive effects on QT prolongation
8) Literature Reports
a) When administered with imipramine, the pharmacokinetics of imipramine and the 2-hydroxy metabolite were not affected. Venlafaxine increased the area under the concentration-time curve (AUC), maximum concentration (Cmax), and minimum concentration (Cmin) of desipramine by approximately 35%. The 2-OH-desipramine AUCs increased by 2.5-fold (venlafaxine 37.5 mg every 12 hours) and by 4.5-fold (venlafaxine 75 mg every 12 hours). The clinical significance of this finding is unknown (Prod Info venlafaxine extended release oral tablets, 2008).

3.5.1.DJ Warfarin

1) Interaction Effect: an increased risk of bleeding
2) Summary: Tricyclic antidepressants (TCAs) may increase the half-life and bioavailability of oral anticoagulants (Vesell et al, 1970i; Williams et al, 1976i). Considerable interindividual differences may be found (Pond et al, 1975i).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: In patients being treated concurrently with warfarin and clomipramine, the prothrombin time ratio or international normalized ratio (INR) should be closely monitored to assess the stability of the anticoagulant response. Warfarin dosage adjustments may be required.
7) Probable Mechanism: decreased warfarin metabolism; increased warfarin absorption
8) Literature Reports
a) In a study of healthy volunteers, the concurrent use of nortriptyline or amitriptyline resulted in an increase of dicumarol levels and an increase in the plasma half-life of dicumarol, although the effect was not consistent in all subjects (Pond et al, 1975h). This effect was not observed with warfarin.
b) A single oral dose of bishydroxycoumarin after eight days of nortriptyline resulted in a significantly prolonged half-life and decreased volume of distribution of the coumarin anticoagulant in six healthy volunteers (Vesell et al, 1970h). The mechanism of action was suggested to be reduced bishydroxycoumarin metabolism and/or altered coumarin absorption.
c) Drug dosing was studied in 16 patients on long-term anticoagulant therapy who used concurrent TCAs (Williams et al, 1976h). TCAs affected the stability of anticoagulant control leading to frequent changes in the doses of anticoagulants. Inhibition of coumarin metabolism was the postulated mechanism.

3.5.1.DK Yohimbine

1) Interaction Effect: increased risk of hypertension
2) Summary: Yohimbine increased blood pressure and decreased orthostatic hypotension experienced by depressed patients treated with clomipramine on a short-term basis (less than 2 weeks of clomipramine treatment, with 4 days of concomitant yohimbine treatment) (Lacomblez et al, 1989a). The effect of yohimbine on orthostatic hypotension induced by clomipramine beyond this time frame is unknown. Levels of yohimbine may continue to increase during the period when clomipramine is accumulating (i.e. at the start of therapy and following any dosage changes). Demethylclomipramine may decrease first pass hepatic metabolism of yohimbine, increasing yohimbine levels and thereby increasing the hypertensive effect of

yohimbine. It was also proposed that patients with depression may have increased sensitivity to the effect of yohimbine on alpha2-receptors (Lacomblez et al, 1989a).
3) Severity: moderate
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Monitor orthostatic and sitting blood pressure in patients taking clomipramine who initiate therapy with yohimbine, as yohimbine may increase blood pressure.
7) Probable Mechanism: inhibition of hepatic metabolism of yohimbine
8) Literature Reports
a) Yohimbine 12 milligrams daily significantly increased blood pressure in a randomized, double-blind, placebo-controlled, crossover study of 12 patients with depression. Patients had been treated with clomipramine 150 mg for a minimum of 48 hours to 1 week maximum and experienced a fall in systolic blood pressure of at least 20 mmHg after 2 and 5 minutes of standing up. Patients received yohimbine 4 mg three times daily for 3 days, and 4 mg once on day 4. Supine blood pressure was significantly increased on day 1 (p between 0.001 and 0.05) and on day 4 (p between 0.01 and 0.05). Standing blood pressure was significantly increased on day 1 (p between 0.01 and 0.05), and on day 4 (p between 0.001 and 0.05). Hypertensive effects lasted 17 to 24 hours after yohimbine administration and were accompanied by an increase in heart rate (Lacomblez et al, 1989).
b) Since yohimbine concentrations are undetectable after 17 to 24 hours, the interaction with clomipramine was suggested to involve more than pharmacokinetic alterations. The hypertensive effect of yohimbine was significantly correlated with plasma yohimbine levels (p equals 0.0025). Plasma levels of yohimbine were significantly correlated with plasma levels of demethylclomipramine, the main metabolite of clomipramine (p less than 0.006), but not with clomipramine levels. The low dose of yohimbine used in this study had no effect on blood pressure in healthy (non-depressed, normotensive) subjects. Demethylclomipramine may decrease first pass hepatic metabolism of yohimbine, increasing yohimbine levels and thereby increasing the hypertensive effect of yohimbine. It was proposed that patients with depression may have increased sensitivity to the effect of yohimbine on alpha2-receptors (Lacomblez et al, 1989).

3.5.2 Drug-Food Combinations

Ethanol

Grapefruit Juice

3.5.2.A Ethanol
1) Interaction Effect: enhanced drowsiness; impairment of motor skills
2) Summary: Ethanol in combination with antidepressants may alter behavior, with the predominant effect being enhanced impairment in psychomotor performance. Almost all studies to date have evaluated the effects of the combination on motor skills, driving behavior and psychomotor skills (Landauer et al, 1969; Patman et al, 1969; Milner & Landauer, 1973a; Seppala et al, 1975; Seppala, 1977). There are no studies evaluating respiratory response with the combination.
3) Severity: moderate
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Encourage abstention from alcohol during at least the first few weeks of tricyclic administration to allow patient accommodation to potential CNS depressant effects of the tricyclic.
7) Probable Mechanism: additive CNS depressant activity; impaired hepatic metabolism of the tricyclic antidepressant
8) Literature Reports
a) The studies available indicate that the interaction between amitriptyline (and other antidepressants) in combination with ethanol is unpredictable. They indicate that antidepressants may enhance, prevent, or not affect the CNS depressant actions of ethanol. The most significant effect reported is enhanced CNS depression. However, there are reports that tricyclic antidepressants may actually antagonize the sedative effects of ethanol (Milner & Landauer, 1973).
b) The propensity for interaction may be related to the inherent CNS depressant action of the tricyclic antidepressant, listed in one series in descending order as amitriptyline, doxepin, imipramine, nortriptyline, desipramine, and protriptyline (Marco & Randels, 1981).
c) Imipramine and amitriptyline are the best documented examples of disruptions of metabolism. Clearance of imipramine was 3-fold higher in alcoholics compared with healthy volunteers (Ciraulo et al, 1988).
d) Individual case reports have documented "blackouts" following modest amounts of alcohol in combination with either amitriptyline or imipramine (Hudson, 1981), and reversible extrapyramidal effects (parkinsonian effects, akathisia) with amoxapine (Shen, 1984).

3.5.2.B Grapefruit Juice

1) Interaction Effect: an increased risk of clomipramine toxicity

2) Summary: Clomipramine is metabolized by several different cytochrome P450 pathways, including CYP1A2, 3A4, and 2D6. Grapefruit juice has been shown to inhibit CYP3A4, causing an increase in the concentrations of drugs which require CYP3A4 for metabolism. Two case reports demonstrated that the addition of grapefruit juice to a clomipramine regimen increased the trough plasma concentrations of clomipramine. Whether the inhibition of clomipramine metabolism by grapefruit juice would be sustained over time is not known (Oesterheld & Kallepalli, 1997a).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Monitor clomipramine and desmethylclomipramine trough levels in patients receiving grapefruit juice. Also monitor the patient for signs of clomipramine toxicity.

7) Probable Mechanism: inhibition of clomipramine metabolism by grapefruit juice

8) Literature Reports

a) An 8-year-old male patient was being treated with clomipramine 25 mg three times daily for obsessive-compulsive disorder. Trough plasma levels of clomipramine (CMI) and desmethylclomipramine (DMCI) were 73 ng/mL and 144 ng/mL, respectively. When 250 mL of grapefruit juice was administered with each dose of clomipramine, the trough levels of CMI and DMCI increased to 198 ng/mL and 233 ng/mL, respectively, after three days. In another case, a 13-year-old female being treated with clomipramine 125 mg daily had a CMI trough blood level of 48 ng/mL and a DMCI trough blood level of 195 ng/mL. Grapefruit juice 250 mL was administered with each clomipramine dose for three days, and the CMI trough level increased to 69 ng/mL while the DMCI trough level decreased to 170 ng/mL (Oesterheld & Kallepalli, 1997).

4.0 Clinical Applications

Monitoring Parameters

Patient Instructions

Place In Therapy

Mechanism of Action / Pharmacology

Therapeutic Uses

Comparative Efficacy / Evaluation With Other Therapies

4.1 Monitoring Parameters

A) Clomipramine Hydrochloride

1) Therapeutic

a) Physical Findings

1) DEPRESSION

a) Improvement in mood, affect, and behavior.

b) Improvement in vegetative signs including appetite, sleep pattern, interest in work/recreation, and improvement in weight (if abnormal).

2) OBSESSIVE COMPULSIVE DISORDER (OCD)

a) Reduction in frequency and severity of obsessions and compulsions characteristic of the patient.

b) Improvement in work function, and reduction in amount of time spent with obsessions/compulsions.

2) Toxic

a) Laboratory Parameters

1) Liver function tests

b) Physical Findings

1) Signs of central and peripheral hyperactivity: tremor, seizures, manic- like behavior, increased aggression.

2) Constipation, urinary retention, dry mouth, or blurred vision.

3) Orthostatic hypotension, tachycardia.

4) Sexual dysfunction of both genders: impotence, ejaculation problems, anorgasmia.

5) Monitor patients receiving antidepressants for worsening of depression, suicidality, or unusual changes in behavior, especially at the initiation of therapy or when the dose increases or decreases. Such monitoring should include at least weekly face-to-face contact with patients or their family

members or caregivers during the initial 4 weeks of treatment, then visits every other week for the next 4 weeks, then at 12 weeks, and then as clinically indicated beyond 12 weeks. Families and caregivers should be advised of the need for close observation (ie, daily observation) of patients and communication with the prescriber (Anon, 2004).

6) Patients who experience symptoms of anxiety, agitation, panic attacks, insomnia, irritability, hostility, impulsivity, akathisia, hypomania, or mania may be at an increased risk for worsening depression or suicidality. If these symptoms are observed, therapy should be re-evaluated and it may be necessary to discontinue medications when symptoms are severe, sudden in onset, or were not part of the patient's initial symptoms (Anon, 2004).

4.2 Patient Instructions

A) Clomipramine (By mouth)

Clomipramine

Treats obsessive-compulsive disorder, depression, chronic pain, bulimia, sleep disorders, and panic disorder. This medicine is a tricyclic antidepressant (TCA).

When This Medicine Should Not Be Used:
You should not use this medicine if you have had an allergic reaction to clomipramine or to related medicine such as Elavil® or nortriptyline. You should not use this medicine if you have had a recent heart attack or have used an MAO inhibitor (MAOI) such as Eldepryl®, Marplan®, Nardil®, or Parnate® within the past 14 days.

How to Use This Medicine:
Capsule, Tablet

Your doctor will tell you how much of this medicine to use and how often. Your dose may need to be changed several times in order to find out what works best for you. Do not use more medicine or use it more often than your doctor tells you to.
Your doctor may tell you to take the medicine at bedtime, because clomipramine can make you sleepy.
You may take the tablet with or without food. It is best to take the oral capsules with food to decrease stomach upset.
Do not break or chew the capsules. You may open the capsule and mix the medicine beads with soft food (applesauce, pudding). Swallow the mixture without chewing.
It may be 2 to 3 weeks after you start clomipramine before you notice an improvement in your symptoms.
Do not stop taking clomipramine suddenly without asking your doctor.
This medicine should come with a Medication Guide. Read and follow these instructions carefully. Ask your doctor or pharmacist if you have any questions. Ask your pharmacist for the Medication Guide if you do not have one. Your doctor might ask you to sign some forms to show that you understand this information.

If a Dose is Missed:

If you miss a dose or forget to use your medicine, use it as soon as you can. If it is almost time for your next dose, wait until then to use the medicine and skip the missed dose. Do not use extra medicine to make up for a missed dose.
If you take one dose a day at bedtime, you should not use the missed dose the next morning without asking your doctor.

How to Store and Dispose of This Medicine:

Store the medicine in a closed container at room temperature, away from heat, moisture, and direct light.
Ask your pharmacist, doctor, or health caregiver about the best way to dispose of any leftover medicine after you have finished your treatment. You will also need to throw away old medicine after the expiration date has passed.
Keep all medicine away from children and never share your medicine with anyone.

Drugs and Foods to Avoid:
Ask your doctor or pharmacist before using any other medicine, including over-the-counter medicines, vitamins, and herbal products.

Make sure your doctor knows if you are using cimetidine (Tagamet®), clonidine (Catapres®), digoxin (Lanoxin®), guanethidine (Ismelin®), haloperidol (Haldol®), methylphenidate (Ritalin®), or phenothiazine medicine (such as prochlorperazine, Compazine®, Mellaril®, Phenergan®, Thorazine®, or Trilafon®). Tell your doctor if you are also using other medicines to treat depression (such as fluoxetine, sertraline, paroxetine, fluvoxamine, Prozac®, Zoloft®, Paxil®, or Luvox®), medicine to treat seizures (such as phenytoin, phenobarbital, Dilantin®, or Luminal®), certain medicine for heart rhythm problem (such as quinidine, flecainide, propafenone, Quinaglute®, Tambocor®, or Rythmol®), or a blood thinner (such as warfarin or Coumadin®).
Tell your doctor if you are using any medicines that make you sleepy. These include sleeping pills, cold and allergy medicine, narcotic pain relievers, and sedatives.
Do not drink alcohol while you are using this medicine.

Warnings While Using This Medicine:

Make sure your doctor knows if you are pregnant or breastfeeding, or if you have kidney disease, liver disease, thyroid problems, glaucoma, high blood pressure, heart problems, trouble going to the bathroom (urinating), adrenal gland tumor (such as pheochromocytoma or neuroblastoma), or a history of seizure disorder.
For some children, teenagers, and young adults, this medicine can increase thoughts of suicide. Tell your doctor or your child's doctor right away if you or your child start to feel more depressed and have thoughts about hurting yourselves. Report any unusual thoughts or behaviors that trouble you or your child, especially if they are new or are getting worse quickly. Make sure the doctor knows if you or your child have trouble sleeping, get upset easily, have a big increase in energy, or start to act reckless. Also tell the doctor if you or your child have sudden or strong feelings, such as feeling nervous, angry, restless, violent, or scared. Let the doctor know if you, your child, or anyone in your family has bipolar disorder (manic-depressive) or has tried to commit suicide.
This medicine may make you dizzy or drowsy. Avoid driving, using machines, or doing anything else that could be dangerous if you are not alert.
Make sure any doctor or dentist who treats you knows that you are using this medicine. You may need to stop using this medicine several days before having surgery or medical tests.
This medicine may make your skin more sensitive to sunlight. Use a sunscreen when you are outdoors. Avoid sunlamps and tanning beds.
Your doctor will need to check your progress at regular visits while you are using this medicine. Be sure to keep all appointments.

Possible Side Effects While Using This Medicine:
Call your doctor right away if you notice any of these side effects:
Allergic reaction: Itching or hives, swelling in your face or hands, swelling or tingling in your mouth or throat, chest tightness, trouble breathing.
Change in how much or how often you urinate, or painful or difficult urination.
Changes in behavior, or thoughts of hurting yourself or others.
Chest pain.
Ear pain or discharge, or ringing in the ears.
Fast, pounding heartbeat.
Fever, chills, cough, sore throat, runny or stuffy nose, and body aches.
Lightheadedness or dizziness when getting up suddenly from a lying or sitting position.
Memory problems, confusion, or depression.
Nervousness, anxiety, agitation, or irritability.
Numbness, tingling, or burning pain in your hands, arms, legs, or feet.
Tremors, or muscle twitching or stiffness.
Trouble sleeping, unusual dreams.
Trouble swallowing.
Unusual bleeding, bruising, or weakness.

If you notice these less serious side effects, talk with your doctor:
Changes in appetite.
Changes in taste.
Changes in vision.
Dry mouth or tooth problems.
Headache or drowsiness.
Menstrual cramps or change in monthly periods.
Muscle, joint, or back pain.
Nausea, vomiting, diarrhea, constipation, or stomach pain or upset.
Problems with sex.
Skin rash or itching.
Sweating.
Tiredness.
Warmth or redness in your face, neck, arms, or upper chest.
Weight changes.

If you notice other side effects that you think are caused by this medicine, tell your doctor.

4.3 Place In Therapy

A) Clomipramine is indicated for the treatment of obsessive compulsive disorder. It is recommended as first-line therapy along with behavioral therapy (Park et al, 1997). Other first-line agents include fluvoxamine, fluoxetine, sertraline, and paroxetine. However, clomipramine may be selected for patients with concomitant insomnia, akathisia, or nausea/diarrhea (Anon, 1997).

B) Clomipramine is not superior to tricyclic antidepressants, including imipramine and amitriptyline, for treating major depression. The drug has been effective for obsessive compulsive behavior associated with depression, although imipramine seems to be equally suited for treating this disorder. Clomipramine appears to be more effective than amitriptyline for relieving chronic pain caused by trigeminal neuralgia and tension headaches, but not post-herpetic neuralgia.

C) Clomipramine should be considered for hospital formulary inclusion for the treatment of obsessive compulsive disorder, with or without major depression (Kelly & Myers, 1990). Clomipramine cannot be recommended for first-line treatment of chronic pain induced by trigeminal neuralgia or tension headaches until additional controlled studies are conducted, but may be considered for those patients refractory to amitriptyline.

4.4 Mechanism of Action / Pharmacology

A) MECHANISM OF ACTION

1) The exact mechanism of action of clomipramine is not known. The drug is classified as a tertiary amine tricyclic antidepressant with very potent inhibition of serotonin uptake (Bertilsson et al, 1974; Asberg et al, 1977). The active metabolite, desmethylclomipramine, is a potent norepinephrine uptake inhibitor and may retain some serotonin uptake inhibition (Benfield et al, 1980; Ross & Renyi, 1975). Several researchers feel that the effect of clomipramine's serotonin uptake may be essential to the anti-obsessive compulsive activity observed (Flament et al, 1987); (Thoren et al, 1980)(Zohar et al, 1988). Obsessive-compulsive patients with initially high cerebrospinal fluid levels of the serotonin metabolite, 5-hydroxyindole-acetic acid (5-HIAA), demonstrated a positive correlation with the improvement of obsessive-compulsive behavior and the reduction of the cerebrospinal fluid levels of 5-HIAA during clomipramine therapy (Thoren et al, 1980). High pretreatment levels of platelet serotonin were a strong predictor of clomipramine treatment response (Flament et al, 1987). During clomipramine therapy clinical improvement in obsessive-compulsive symptoms was positively correlated with a reduction in platelet serotonin levels.

2) The therapeutic effects of clomipramine in obsessive compulsive disorder are mediated via serotonergic mechanisms (Benkelfat et al, 1989). The plasma ratio of tryptophan (TRP) to other large neutral amino acids (LNAA) were studied in 44 patients with major depression (Moller et al, 1990). The LNAA selected were thought to reflect brain serotonin formation. The patients were subsequently treated with paroxetine (N=27) or clomipramine (N=17) in double-blind fashion on fixed dosage schedules for 4 weeks. Endogenous and nonendogenous patients were comparable with respect to the ratio of TRP/LNAA. The clomipramine group showed a significant inverse correlation between the TRP/LNAA ratio and clinical improvement. Patients with a TRP/LNAA ratio below the mean showed a trend towards greater improvement than patients with a higher ratio, but with comparable serum drug levels. These findings suggest that it may be possible to increase the efficacy of antidepressant treatment in populations of depressed patients by prior selection based on plasma amino acid patterns. The published evidence that supports a link between depression and obsessive-compulsive disorder from a biochemical basis was reviewed (Asberg et al, 1982).

3) The effect of clomipramine (CMI) treatment on serum prolactin (PRL) levels was studied in 18 children and adolescents with obsessive compulsive disorder. PRL was measured at baseline and after 4 and 8 weeks of CMI treatment. Baseline PRL was higher in patients with tics and OCD than in patients with OCD alone. CMI administration significantly increased basal PRL levels. A slight decline in PRL during the last 4 weeks of CMI treatment was positively correlated with a favorable response and negatively correlated with duration of illness. If these PRL changes are related to changes in serotonergic neurotransmission, the results suggest that CMI treatment of OCD produces an adaptive decrease in the responsiveness of serotonergic receptors (Hanna et al, 1991).

4) Cytokine production by peripheral blood mononuclear cells (PBMC) was assessed in 10 patients with major depression (5 male, 5 female) before and after 4 weeks of clomipramine (CMI) treatment and in age- and gender-matched controls (Weizman et al, 1994). A significant reduction in interleukin-1B (IL-1B), interleukin-2 (IL-2) and interleukin-3-like activity (IL-3-LA) was observed in untreated depressed patients when compared to controls. IL-1B and IL-3-LA synthesis was significantly increased after treatment with CMI. The suppression of cytokine production by PBMC in depressed patients may be associated with the depression per se, or may be related to depression-related hyperactivity of the hypothalamic-pituitary-adrenal axis. The authors did not discuss the role of serotonergic drugs (clomipramine) in possible reversal of cytokine suppression.

B) REVIEW ARTICLES

1) Treatment guidelines for obsessive compulsive disorders including the use of clomipramine have been published (Goodman, 1999; Ellingrod, 1998; Anon, 1997a; Park et al, 1997a; Flament & Bisserbe, 1997; Rasmussen & Eisen, 1997; Jackson et al, 1994; Jenike, 1992).

2) Comprehensive review articles on CLOMIPRAMINE have been prepared (Peters et al, 1990; McTavish & Benfield, 1990).

3) The worldwide use of CLOMIPRAMINE was summarized (Trimble, 1990).

4) The pharmacokinetics of CLOMIPRAMINE are summarized in a review (Balant-Gorgia et al, 1991).

5) Drug-interactions of antidepressants are reviewed in German language (Zapotoczky & Simhandl, 1995).

4.5 Therapeutic Uses

Clomipramine

Clomipramine Hydrochloride

4.5.A Clomipramine

Anorexia nervosa

Cataplexy - Narcolepsy

4.5.A.1 Anorexia nervosa

See Drug Consult reference: ANOREXIA NERVOSA - DRUG THERAPY

4.5.A.2 Cataplexy - Narcolepsy

See Drug Consult reference: NARCOLEPSY AND CATAPLEXY - DRUG THERAPY

4.5.B Clomipramine Hydrochloride

Anorexia nervosa

Autistic disorder

Chronic pain

Delusional disorder

Depression

Disorder of ejaculation

Obsessive-compulsive disorder

Obsessive-compulsive disorder, Intravenous therapy

Panic disorder

Pervasive developmental disorder

Premenstrual syndrome

Self-injurious behavior

Steinert myotonic dystrophy syndrome

Trichotillomania

4.5.B.1 Anorexia nervosa

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Ineffective
Recommendation: Adult, Class III
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Found to be no more effective than placebo in producing weight gain in patients with anorexia nervosa

c) Adult:

1) In a double-blind, placebo-controlled trial of 16 female ANOREXIA NERVOSA patients, CLOMIPRAMINE 50 milligrams/day was found no more effective than placebo in producing weight gain (Lacey & Crisp, 1980). Placebo or oral CLOMIPRAMINE 50 milligrams was administered once daily to anorexic patients until their predetermined target weight was attained. Patients on CLOMIPRAMINE had increased appetite, hunger and calorie consumption during the early part of the study; however, this had no impact on the final outcome. Patients on placebo took a mean of 72 days to attain their target weight, while those on CLOMIPRAMINE took a mean of 76 days. Two patients on CLOMIPRAMINE and 1 patient on placebo did not complete the study. At a 4-year follow-up, measurement outcomes of

nutritional status, sexual adjustment, socioeconomic adjustment and mental state showed no significant differences between the 2 groups (Crisp et al, 1987a). Patients treated with CLOMIPRAMINE and placebo- treated patients were at a mean of 94% and 93% of target weight, respectively.

4.5.B.2 Autistic disorder

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Effective in one study

c) Adult:

1) CLOMIPRAMINE (CMI) was superior to placebo and desipramine (DMI) on ratings of autistic symptoms such as anger, and compulsive, ritualized behaviors in a 10-week, double-blind crossover comparison of CMI and placebo and CMI and DMI (Gordon et al, 1993a).

4.5.B.3 Chronic pain

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Possibly effective for chronic low back pain in selected patients

c) Adult:

1) In an open study, 23 out of 30 patients with chronic low back pain responded to clomipramine treatment. Clomipramine 25 milligrams (mg) was increased to 150 mg/day intravenously during a 10-day hospital stay. After discharge, clomipramine 150 mg/day orally was used for 20 days. Patients with lower initial mean scores on the Minnesota Multiphasic Personality Inventory (MMPI) for hypochondria, depression, and hysteria were more likely to respond to treatment (p less than 0.02, p less than 0.05, p less than 0.02, respectively). These study findings may assist in proper patient selection for beneficial clomipramine therapy, however further placebo-controlled studies are recommended (Fouquet et al, 1997).

2) In 2 case reports, patients with schizophrenia and obsessive-compulsive symptoms had their chronic back pain alleviated by clomipramine (Kurokawa & Tanino, 1997). Doses used ranged from 30 to 75 milligrams. The authors believe that the back pain was related to serotonin dysfunction.

4.5.B.4 Delusional disorder

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Appears effective in the treatment of some types of delusional disorders including DELUSIONAL DISORDER, SOMATIC TYPE and BODY DYSMORPHIC DISORDER

c) Adult:

1) In a double-blind, cross-over trial clomipramine was more effective than desipramine in patients with body dysmorphic disorder (BDD)(Hollander et al, 1999). Patients (n=29) with distress or impairment in functioning due to BDD were randomized to receive first either clomipramine, a selective serotonin reuptake inhibitor, or desipramine, a selective norepinephrine reuptake inhibitor (specifically an active placebo), for 8 weeks each. Patients initially received 25 milligrams (mg)/day and were increased to a maximum of 250 mg/day or the highest tolerated dose. Mean dosages attained were 138 mg/day for clomipramine and 147 mg/day for desipramine. Assessments were done using a BDD modified version of the Yale-Brown Obsessive Compulsive Scale (BDD-YBOCS), a modified National Institute of Mental Health Global Obsessive-Compulsive Scale (BDD-NIMH), and the Clinical Global Impression Scale specific to BDD symptoms (BDD-CGI). Clomipramine was superior to desipramine on all 3 of the outcome measures. On the BDD-YBOCS there was a 65% improvement rate with clomipramine and a 35% rate with desipramine (p=0.09). On the BDD-NIMH the response rate was 70% with clomipramine and 30% with desipramine (p=0.02). For the BDD-CGI, clomipramine was also significantly better than desipramine (p=0.01). Also of significance was that patients who were more delusional appeared to improve more with clomipramine therapy (BDD-CGI, p=0.007). Adverse effects were similar for both drugs. This is the first study demonstrating the effectiveness of clomipramine for BDD.

2) Four patients with delusional disorder of the somatic type showed clinical improvement with

clomipramine therapy (Wada et al, 1999). All patients persistently complained that something was moving inside their bodies although nothing was found after extensive evaluations. All repeatedly visited physicians complaining of symptoms with 1 patient receiving a possibly unnecessary surgery. Another patient was unresponsive to multiple therapies including sulpiride, nemonapride, mosapramine, levomepromazine, risperidone, fluphenazine, pimozide, and clocapramine. The dosage of clomipramine ranged from 60 to 120 milligrams daily and the time to improvement ranged from 27 to 52 days. Further studies including comparisons with pimozide are needed.

4.5.B.5 Depression

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy; Pediatric, Evidence favors efficacy
Recommendation: Adult, Class IIb; Pediatric, Class IIb
Strength of Evidence: Adult, Category B; Pediatric, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Oral and intravenous clomipramine have been successfully used to treat dysthymia and major depression (Faravelli & Pallanti, 1987)
Intravenous therapy has had no advantage over oral therapy (Faravelli & Pallanti, 1987)
Early improvement in severe depressive symptoms may be achieved by using loading doses of oral or intravenous CLOMIPRAMINE

c) Adult:

1) Five days after pulse-therapy with oral or intravenous clomipramine, symptoms of depression significantly improved in 22 inpatients. Patients were given either an evening infusion of 150 milligrams of clomipramine and placebo tablets or 150 milligrams of oral clomipramine and an isotonic saline infusion. Twenty-four hours later, this was repeated using 200 milligrams of clomipramine. Pulse-therapy with oral and intravenous clomipramine showed no difference in efficacy or side effects in treating depression. In this double-blind randomized trial results were based on the Hamilton Depression, Raskin, and Beck scales (Pollock et al, 1989).

2) Clomipramine was significantly (p equals 0.02) more effective than placebo in improving mood in 21 depressed patients with probable Alzheimer's disease. Results were based on the Hamilton Depression scores. Clomipramine- treated patients showed a significantly (p less than 0.01) lower Mini-Mental State score than placebo; no significant drug effects were seen on the Independence measure scores. Patients received 6 weeks of clomipramine or placebo in a double-blind crossover design. During the first 6 week period, 9 of 11 clomipramine-treated patients experienced a complete remission while the same effect occurred in only 3 of 10 placebo-treated patients. Clomipramine was administered at 25 mg for 1 week, 50 mg for week 2, 75 mg for week 3, and 100 mg for weeks 4 to 6 (Petracca et al, 1996).

d) Pediatric:

1) A single pulse dose of clomipramine 200 milligrams intravenously was administered in a double-blind, placebo-controlled trial of 16 depressed adolescents, (14-to 18-years-old), demonstrating dramatic and rapid reduction in depressive symptoms at day 6 post-clomipramine infusion, based upon decreases in Hamilton Depression Rating Scale score ($p = 0.04$) and Clinical Global Impression severity score ($p = 0.003$). The clomipramine effect (88% study response rate) may persist for up to 8 weeks in some patients. The authors suggest that gradually administered clomipramine is less effective than pulse intravenous clomipramine due to the pulse regimen's rapid enhancement of serotonergic transmission (Sallee et al, 1997).

4.5.B.6 Disorder of ejaculation

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Useful in the treatment of ejaculatory disorders

c) Adult:

1) Daily dosing with clomipramine was successful in treating premature ejaculation in men who were unresponsive to clomipramine 25 milligrams (mg) on an "as needed" basis. Four men who, in an earlier study, were nonresponders to clomipramine 25 mg "as needed" participated in a 12 week study in which they took clomipramine 0, 10, 20, and 30 mg daily, each dose for 3 weeks. Latencies were significantly longer with the 30-mg per day dose than with the previous 25-mg regimen. Ejaculatory control, sexual arousal, and penile rigidity were not significantly affected by treatment. All subjects reported satisfaction with the treatment. Side-effects were mild and generally transient. Of the 3 men who opted to continue clomipramine treatment, 1 chose 30 mg as needed, and 2 chose 20 mg daily (Rowland et al, 2001).

2) Clomipramine 25 milligrams, as needed, effectively increased ejaculatory latency in men with primary premature ejaculation. In a prospective, double-blind, placebo controlled, crossover study,

patients with primary premature ejaculation (n=8), premature ejaculation and erectile dysfunction (n=6), and controls (n=8) were randomly given clomipramine for a 3 week period and placebo for 3 a week period. Each was to be used 12 to 24 hours before sexual activity. Patients with ejaculatory latency increased their time to ejaculation from approximately 2 to 8 minutes (p=0.035). No significant effects occurred in controls and men with premature ejaculation and erectile dysfunction (Haensel et al, 1996).
3) CLOMIPRAMINE (CMI) was useful in the treatment of PREMATURE EJACULATION (Segraves et al, 1993). Twenty patients with premature ejaculation were randomly allocated to treatment with CLOMIPRAMINE or placebo in a double-blind study. Mean estimated time to ejaculation after vaginal penetration increased to 6.1 minutes on CMI 25 mg and to 8.4 minutes on CMI 50 mg. These estimated times were significantly different from estimated time to ejaculation while on placebo. The results suggest that low-dose CMI may be useful in the treatment of premature ejaculation.
4) Two of 3 cases of RETROGRADE EJACULATION were successfully treated with oral CLOMIPRAMINE 25 milligrams twice a day. Two of the 3 patients responded with normal ejaculation within 5 days and subsequent conception, while the third patient only partially improved (Eppel & Berzin, 1984).

4.5.B.7 Obsessive-compulsive disorder

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes; Pediatric, yes (10 years and older)
Efficacy: Adult, Effective; Pediatric, Effective
Recommendation: Adult, Class IIa; Pediatric, Class IIa
Strength of Evidence: Adult, Category B; Pediatric, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Indicated for the treatment of obsessions and compulsions associated with obsessive compulsive disorder

c) Adult:

1) Double-blind, placebo-controlled trials have demonstrated the efficacy of CLOMIPRAMINE in relieving some obsessive compulsive symptoms (Greist et al, 1990; DeVeaugh-Geiss et al, 1989; Pato et al, 1988; Flament et al, 1985a; Marks et al, 1980a). Some researchers feel that patients with a depressive component will do better with CLOMIPRAMINE. Other researchers believe that behavioral therapy is also required to alleviate ritualistic behavior. Large long-term studies have been difficult to conduct because of the apparent low incidence of this disorder. In a meta-analysis, it was concluded that the most common treatments for obsessive-compulsive disorder include CLOMIPRAMINE, FLUOXETINE, and exposure-based behavior therapy (Cox et al, 1993). Results from 25 appropriate treatment studies from 1975 to 1991 revealed that all three treatments were significantly effective for most of the outcome variables (overall severity, anxiety, depression). Exposure was not significantly effective for reducing depressed mood.
2) A 24-year-old female with a 3-year history of obsessive compulsive disorder (OCD) experienced a 90% resolution of symptoms in 4 weeks following inpatient behavior therapy and treatment with clomipramine 50 milligrams (mg) gradually increased to 150 mg daily. Patient symptoms included fear of contamination from touching various items she considered dirty and excessive hand washing (30-50 times per contact with a dirty object). The symptoms began to adversely affect her social and academic life, and depression developed. She failed an outpatient behavior program and treatment with fluoxetine 40 mg to 60 mg daily prior to being admitted to an inpatient behavior program. Clomipramine therapy was started at 50 mg daily and was gradually increased to 150 mg daily; therapy was well tolerated with the exception of periodic sedation. Upon discharge, her compulsive rituals were 90% improved and she was maintained on clomipramine 25 mg daily. No relapses of OCD or severe depression occurred during a 5-year follow-up period (Al-Sughayir, 2000).
3) A 93-year-old woman with a long-standing history of obsessive-compulsive disorder that worsened after developing Alzheimer's disease was helped by clomipramine therapy (Trappler, 1999). Her obsessions consisted of needing to know and remember trivial events with a compulsion of making excessive lists of these events. She had previously failed trials of fluoxetine and buspirone. She began clomipramine 25 milligrams (mg) daily and was increased over 10 days to 50 mg. After 9 weeks her score on the Yale-Brown Obsessive-Compulsive Scale dropped from 29 to 3. The author notes that clomipramine was effective and well-tolerated in this very old patient.
4) A combination of CLOMIPRAMINE and FLUOXETINE was effective in 4 cases of OCD where either drug used alone was ineffective. No increased side effects resulted (Browne et al, 1993).
5) There was no significant difference in treatment outcome with CLOMIPRAMINE between those patients with at least one personality disorder and those with no personality disorders. The effect of Axis II diagnosis on the outcome of treatment with CLOMIPRAMINE was determined in 55 patients with obsessive-compulsive disorder (Baer et al, 1992). Patients with paranoid, schizoid, or schizotypal personality disorders (DSM-III) had significantly higher obsessive-compulsive disorder severity scores at baseline, and the number of personality disorders was strongly related to baseline severity of obsessive compulsive symptoms. At the conclusion of this 12-week study, the presence of schizotypal, borderline, and avoidant personality disorders, along with the total number of personality disorders, did predict poorer treatment outcome.

6) Using standard OCD assessment tools, it was shown that CLOMIPRAMINE (CMI) was significantly more effective than placebo (38 to 44% response vs 3 to 5% response). Two double-blind studies at 21 centers evaluated the efficacy and safety of up to 300 mg/d of CMI vs placebo in 520 patients with OCD. TCA-like side effects were reported for CMI. Although uncommon, seizures and elevated aminotransferase values are potentially serious side effects of CMI (Anon, 1991).
7) Ten patients with DSM-III-R obsessive compulsive disorder (OCD) who were being treated chronically with CLOMIPRAMINE (CMI) in a mean dosage of 270 milligrams/day, were studied to determine the minimum dose of CMI needed to maintain therapeutic benefit. Gradual, open dosage reduction resulted in a mean dosage of 165 milligrams/day, a reduction of 105 milligrams/day (approximately 40%). This decrease in dosage was accompanied by no significant change in three OC measures, as determined by the paired t-test. These results suggest that even though OCD patients were not able to discontinue medication completely, they were able to do well at lower doses than those used initially in the treatment of the disorder (Pato et al, 1990).

d) Pediatric:
1) Continued CLOMIPRAMINE (CMI) treatment seems necessary for children and adolescents. The need for continued CLOMIPRAMINE (CMI) treatment in children and adolescents with obsessive compulsive disorder (OCD) was evaluated in a double-blind DESIPRAMINE substitution study. Twenty-six children and adolescents with severe primary OCD receiving long-term CMI maintenance treatment (mean 17 months) entered an 8-month study. All patients received CMI for the first 3 months, then half received CMI and half were given DESIPRAMINE (DMI) for the next 2 months, then all subjects were given CMI for the last 3 months. Eighty-nine percent of the substituted versus 18% of the non-substituted group relapsed during the 2-month comparison period. However, even subjects who continued uninterrupted CMI treatment experienced OC symptoms which varied in severity over time (Leonard et al, 1991a).
2) In a case series, 7 children and adolescents (9-to 23-years-old) with obsessive compulsive disorder, benefited from combination therapy of clomipramine and a selective, serotonin reuptake inhibitor (Figueroa et al, 1998). The combination therapy appeared to augment the effectiveness of monotherapy. Clomipramine was used in doses of 25 to 100 milligrams. The serotonin reuptake inhibitors used included: fluoxetine, sertraline, paroxetine, and fluvoxamine. In 2 cases, once the combination was effective, one of the drugs was successfully discontinued. Two cases of QTc interval prolongation occurred.

4.5.B.8 Obsessive-compulsive disorder, Intravenous therapy

a) Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:
Appears effective in the treatment of obsessive-compulsive disorder even in some patients refractory to oral clomipramine
Intravenous clomipramine is not FDA approved

c) Adult:
1) Intravenous clomipramine was more effective than placebo in the treatment of obsessive-compulsive disorder (OCD) in patients refractory to oral clomipramine (Fallon et al, 1998). In a double-blind 4-week study, OCD patients refractory to oral clomipramine were randomized to receive 1-hour infusions of 500 milliliters of 0.9% isotonic sodium chloride solution containing either clomipramine (n=28) or placebo (n=23). Clomipramine was titrated over 14 infusions from 25 milligrams (mg) daily to 250 mg daily. Oral clomipramine was started in all patients after the infusions. Patients were evaluated using the Clinical Global Impression (CGI) scale. After the seventh infusion, no patients showed improvement. After infusion 14, 6 (20.7%) clomipramine patients were responders on the CGI versus none in the placebo group (p less than 0.02). At 1 week after the infusions, 9 out of 21 (43%) clomipramine patients were responders according to the CGI (not all patients were evaluated at this time point). Again there were no responders in the placebo group. At 1 month after the infusion, 9 out of 16 patients were rated as overall intravenous clomipramine responders. Further study is needed comparing the intravenous route to the oral route of therapy.
2) Intravenous pulse loading of clomipramine was beneficial in 6 out of 7 patients with obsessive compulsive disorder. Patients were randomized to receive either oral loading of clomipramine (n=8) or intravenous loading (n=7). The intravenous loading consisted of clomipramine 150 milligrams (mg) given intravenously over 90 minutes, followed by clomipramine 200 mg intravenously, 24 hours later. Trimethobenzamide hydrochloride 250 mg was given before each dose to reduce nausea. The oral loading consisted of clomipramine 150 mg on day 1 and 200 mg given on day 2. Oral clomipramine 150 mg was started in all patients 4.5 days after the second dose and increased by 25 mg every fourth day to 250 mg/day. Using the Yale-Brown scale, 6 out of 7 patients in the intravenous group had responded before the oral dosing was started while only 1 in the oral dose group had responded (p=0.009). After 8 weeks, there was no difference in the 2 groups, both had 4 responders (p=0.38). Pulse intravenous loading may be an effective method for quickly testing patient responsiveness to clomipramine therapy

(Koran et al, 1997).
3) A 25-year-old woman with schizophrenia and ego-dystonic checking and cleaning rituals benefited from intravenous clomipramine (Poyurovsky & Weizman, 1998). Her schizophrenia was stabilized with perphenazine 8 milligrams (mg) daily. She had failed trials of fluvoxamine and fluoxetine for her obsessive-compulsive disorder (OCD). Further deterioration of her OCD led to hospitalization where a course of intravenous clomipramine 75 mg was added to her perphenazine. The infusion was repeated the next day. Five days later her Yale-Brown Obsessive Compulsive score had dropped from 19 to 4. She was maintained on clomipramine 150 mg daily and has had no recurrence of her OCD symptoms over the last 6 months.

4.5.B.9 Panic disorder

a) Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:
Reported to be effective in the treatment of panic attacks and AGORAPHOBIA

c) Adult:
1) Low-dose clomipramine 60 mg/day was as effective as high-dose clomipramine 150 mg/day in the treatment of phobias, anxiety, and panic attacks in a multi-center study (Caillard et al, 1999). In an 8-week study, patients were randomized to clomipramine 150 milligrams (mg)/day (n=56), clomipramine 60 mg/day (n=51), or placebo (n=51). Doses were titrated over 2 weeks. At the end of 8 weeks, phobias as evaluated on the Cottraux Scale were significantly improved in both clomipramine groups as compared to placebo (p=0.002). For anxiety, both clomipramine groups were significantly better than the placebo group as measured on the anxiety subscale of the Cottraux Anxiety Scale (p=0.002). For panic attacks, the average number of attacks during the previous week was not significantly different in either of the clomipramine groups or for placebo. However, the number of DSM-III-R symptoms of panic attacks was decreased in both clomipramine groups but not in the placebo group (p=0.03). There was no difference seen between the 2 clomipramine therapies in these 3 areas. The author notes that differences may have become evident if a longer treatment period had been used.
2) In a randomized, placebo-controlled, 10-week study, exercise was found to be effective for the treatment of panic disorder, however, clomipramine was even more effective. Forty-six patients with panic disorder were assigned to either regular aerobic exercise (running), clomipramine (increasing doses over three weeks up to 112.5 milligrams/day), or placebo capsules. The dropout rate was 31% for the exercise group, 27% for the placebo group, and 0% for the clomipramine group. On the Bandelow Panic and Agoraphobia Scale, Observer-Rated, clomipramine and exercise improved anxiety symptoms more effectively than placebo (p less than 0.001, p less than 0.05, respectively). Improvements in the clomipramine group were seen as early as 4 weeks while exercise improvements were not seen until the 8th week. Patients receiving clomipramine or placebo experienced more side effects (dry mouth, sweating, mild tremor, dizziness, tachycardia, nausea, constipation, diarrhea) than those in the exercise group. Additional studies are warranted to investigate exercise in the treatment of anxiety disorders, perhaps in combination with drug treatment (Broocks et al, 1998).
3) Despite lowering the initial starting dose of clomipramine to 10 milligrams (mg)/day to maximize compliance, a study involving 58 patients with panic disorder (with or without agoraphobia) resulted in a 45% dropout rate due to adverse reactions occurring mostly during the first two weeks of treatment. Of those completing the study, 84% were markedly or moderately improved. The initial dose was clomipramine 10 mg at bedtime and increased slowly to 20 mg/day after 4 days, then by 10 mg at 1-to 2-week intervals up to 80 mg after 8 weeks. Patients could receive up to 250 mg daily if the drug was tolerated, with the mean daily dosage being 96.9 mg after 13 weeks of treatment. The primary adverse reactions reported were increased nervousness and agitation (Papp et al, 1997).
4) Clomipramine (10 milligrams (mg) for three days and 20 mg for four days) and fluvoxamine (50 mg/day for seven days) were both effective in decreasing the hypersensitivity to 35% carbon dioxide, supporting the serotonergic effect of these drugs to decrease panic attacks through modification of carbon dioxide sensitivity. Thirty-nine panic disorder patients were enrolled in a double-blind, randomized, placebo-controlled study, where each patient was given the 35% carbon dioxide challenge on days 0, 3, and 7. Patients on clomipramine and fluvoxamine showed significant reduction in sensitivity over placebo after seven days as seen by the percent change on a visual analogue for anxiety scale (p=0.027) (Perna et al, 1997a).
5) Clinical improvement was modest on agoraphobia in panic disorder patients who failed to respond to exposure-based behavioral treatment and were treated then with CLOMIPRAMINE (CMI) (Hoffart et al, 1993). Eighteen patients with panic disorder with agoraphobia who had not responded to previous inpatient behavioral treatment entered a 12-week, placebo- controlled, double-blind crossover study of CLOMIPRAMINE at maximum doses of 150 milligrams/kilogram for 3 weeks. Patient outcome was assessed on measures of phobic avoidance, agoraphobic cognitions, panic, state and trait anxiety, subjective anxiety, and depression. Seventeen of 18 patients completed the study. One patient (placebo group) dropped out after 6 weeks after developing acute gastric pain. On most outcome measures,

patients had significantly lower symptom scores at posttest in the active drug period than at posttest in the placebo period. However, while this study showed short-term efficacy of CLOMIPRAMINE for agoraphobic patients who did not respond to behavioral treatment, its ability to produce lasting benefits remains to be proven.
6) CLOMIPRAMINE in low doses (25 to 75 milligrams daily) was reported effective in the treatment of panic ANXIETY and agoraphobia in outpatients in an uncontrolled 8-week clinical trial (Gloger et al, 1989). Of 17 patients treated, panic attacks were abolished completely in 13, and markedly decreased in 4 others. In 7 agoraphobic patients, avoidance behavior disappeared in 5. Overall mean doses were 45 milligrams daily, with 8 patients (6 panic and 2 agoraphobic) receiving 25 milligrams daily or less (mean, 18.76 milligrams). There was a trend towards the need for higher doses in agoraphobia (mean, 56 milligrams) as opposed to panic disorder (mean, 40 milligrams). Well-controlled clinical trials are required to confirm these findings and determine the optimal dose of CLOMIPRAMINE in panic disorder and agoraphobia.
7) Oral CLOMIPRAMINE was significantly superior to placebo on measures of DEPRESSION, DYSPHORIA, and on several indexes of PHOBIC SYMPTOMS in an 8-week double-blind, placebo-controlled study of 94 agoraphobic women as diagnosed by DSM-III guidelines (Johnston et al, 1988a). CLOMIPRAMINE was started at 25 milligrams/day which was slowly increased up to a maximum of 300 milligrams/day as tolerated. At the end of the study the mean daily dose of CLOMIPRAMINE was 83 milligrams. Adverse effects associated with CLOMIPRAMINE use included dry mouth, high energy levels, constipation, and increased sweating.

4.5.B.10 Pervasive developmental disorder

a) Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:
May be effective in adults with pervasive developmental disorders (PDDs)

c) Adult:
1) Clomipramine was found to be effective in 18 of 35 adult patients (55%) with pervasive developmental disorders (PDDs) (18 patients with autistic disorder, 6 with Asperger's disorder, 11 with PDD not otherwise specified). In an open-label study, clomipramine was started at 50 milligrams (mg) at bedtime and increased by 50 mg every 3 or 4 days to a maximum dosage of 250 mg daily within 3 weeks and continued for a minimum of 9 additional weeks. Based on the Clinical Global Impression scale, 18 patients were "much" or "very much" improved (p less than 0.001). In those 18 patients, clomipramine significantly reduced total repetitive thoughts and behavior (p less than 0.001), aggression (p less than 0.001), and some aspects of social relatedness such as eye contact and verbal responsiveness (p less than 0.001). Improvements were not related to a specific subtype of PDD. Three patients had seizures during treatment (two having a prior seizure history), prompting the authors to recommend a selective serotonin uptake inhibitor in these patients (Brodkin et al, 1997).

4.5.B.11 Premenstrual syndrome

a) Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class III
Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:
Effective in reducing the symptoms of Premenstrual Syndrome in small studies

c) Adult:
1) Intermittent administration of low-dose CLOMIPRAMINE (25 to 75 milligrams/day) during the luteal phase only for the treatment of premenstrual syndrome was effective (N=29), and the onset of clinical effect was shorter than when clomipramine was used to treat depression, panic disorder, or obsessive-compulsive disorder (Sunblad et al, 1993).
2) CLOMIPRAMINE (CMI) was effective in reducing symptoms of Premenstrual Syndrome (PMS) in a placebo-controlled trial. Forty non-depressed women with severe premenstrual irritability and/or dysphoria and fulfilling DSM-IIIR diagnostic criteria for late luteal phase dysphoric disorder were treated daily for 3 menstrual cycles with either CMI (25 to 75 milligrams/d) or placebo. Both groups had 20 patients. The response rate in the placebo group was 40% compared with 80% for the CMI group. The possible role of serotonin in the pathophysiology of PMS is discussed (Sundblad et al, 1992).
3) Subjects reported a dramatic reduction in premenstrual complaints with clomipramine therapy. CLOMIPRAMINE was administered orally as 25 to 50 milligrams/day for 5 consecutive menstrual cycles to 5 non-depressed women with severe premenstrual irritability and sadness (Eriksson et al, 1990).

4.5.B.12 Self-injurious behavior

a) Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category C
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:
Useful in certain types of self-injurious behaviors such as severe NAIL BITING

c) Adult:
1) In an open clinical trial, CLOMIPRAMINE was useful for chronic stereotypic and self-injurious behaviors in 11 consecutive patients with concomitant development disorders (Garber et al, 1992). Patients received CLOMIPRAMINE in a mean dosage of 70 milligrams/d (range 25 to 125 mg/d). Ten patients (91%) had marked decreases in rates of target behaviors as early as 2 days after starting treatment and as late as 1 month. No seizures occurred despite the inclusion of six patients with previous histories of epileptic events, and improvement was evident regardless of level of mental retardation. These findings support the use of serotonergic medications in this population and the need for further research.
2) CLOMIPRAMINE has been helpful in reducing SELF-MUTILATING BEHAVIOR in a 25-year-old female patient with obsessive compulsive disorder. Excessive nail-biting and arm-burning with cigarettes was successfully curtailed after 4 months of treatment with CMI at doses of 250 milligrams per day (Lipinski, 1991).
3) CLOMIPRAMINE (CMI) was significantly more effective than DESIPRAMINE (DMI) in decreasing severe nail-biting in 25 adult subjects with severe morbid ONYCHOPHAGIA. During a 10-week double-blind, crossover trial CMI at 120 milligrams/day was superior to DMI at 135 mg/d as determined by nail-biting rating scale assessments. It is hypothesized that similar biological systems mediate a spectrum of "grooming" behaviors, including onychophagia, trichotillomania, and obsessive compulsive disorder (Leonard et al, 1991a).

4.5.B.13 Steinert myotonic dystrophy syndrome

a) Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:
Has improved some symptoms associated with myotonic dystrophy

c) Adult:
1) CLOMIPRAMINE (CMI) has improved grip myotonia in patients with myotonic dystrophy in a placebo-controlled double-blind, crossover study. Fifteen of 17 patients completed the two 33-day treatment periods separated by a 30-day washout period. Grip myotonia was determined by a standardized test and was video-taped for later analysis. Results showed that mean relaxation time after CLOMIPRAMINE was significantly shorter than after placebo (Antonini et al, 1990).

4.5.B.14 Trichotillomania

a) Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Ineffective
Recommendation: Adult, Class III
Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:
Effective for short-term treatment of trichotillomania

c) Adult:
1) In a 9-week study comparing cognitive-behavioral therapy (CBT), clomipramine, and placebo in the treatment of trichotillomania, CBT significantly reduced symptoms from pretreatment to posttreatment, whereas clomipramine and placebo did not. Twenty-three patients were randomized to receive either CBT, clomipramine (50 mg at bedtime titrated as tolerated to 250 mg at bedtime), or placebo and were evaluated on a weekly basis by either a psychiatrist (clomipramine and placebo patients) or a behavioral psychologist (CBT patients). Of the 16 patients that completed the trial, severity and impairment of trichotillomania were significantly reduced ($p=0.002$ and $p=0.006$, respectively) in the CBT group (n=5); however, significant differences were not noted in the clomipramine (n=6) or the placebo (n=5) groups. Clomipramine did produce more changes in pretreatment and posttreatment evaluations ($p=0.061$) than placebo; however, given the low power of the study conventional levels of significance were not achieved. Documented side effects of moderate or severe intensity included tremor, sedation, dry mouth, constipation, memory difficulty, and nausea (Ninan, 2000).
2) Four consecutive patients treated for trichotillomania (hair-pulling) with CLOMIPRAMINE reported initial dramatic reductions in symptoms. However, three of the four patients had relapsed completely at

3-month follow-up, although all four were taking previously effective dosages of the drug. The fourth patient relapsed for about 2 weeks but regained initial treatment benefits. Daily dosage used was 150 milligrams (1), 100 milligrams (2), and 50 milligrams (1) (Pollard et al, 1991).

4.6 Comparative Efficacy / Evaluation With Other Therapies

Albuterol

Amineptine

Amitriptyline

Buspirone

Citalopram

Desipramine

Diazepam

Dixyrazine

Dothiepin

Doxepin

Fluoxetine

Fluvoxamine

Haloperidol

Imipramine

Lithium

Lofepramine

Maprotiline

Metoprolol

Mianserin

Milnacipran

Moclobemide

Nortriptyline

Oxaprotiline

Paroxetine

Pentazocine

Phenelzine

Sildenafil

Venlafaxine

4.6.A Albuterol

4.6.A.1 Depression

a) In depression, albuterol 6 milligram/day was superior to clomipramine 150 milligram/day, both given by intravenous infusion. Ten patients received each drug; symptoms were evaluated by 2 blind observers at days 0, 5, and 15, using the Hamilton rating scale. With albuterol, global improvement on day 5 was significantly superior to clomipramine. This improvement included mood retardation, anxiety, and insomnia. On day 15, the improvement in the albuterol group was only slightly increased over the clomipramine group. Eight of 10 patients in the albuterol group, and 5 of 10 patients in the clomipramine group demonstrated a clear improvement. An additional 2 patients responded to clomipramine 1 week later (Lecrubier et al, 1980).

4.6.B Amineptine

4.6.B.1 Depression

a) Amineptine and clomipramine were found to have similar antidepressant activity in 62 depressed patients during a 6-week, randomized, double-blind study (Lemoine et al, 1981). Patients were diagnosed with psychotic, non-psychotic, or melancholic depression by the investigators; however, the diagnostic criteria were not described. The Hamilton Rating Scale for Depression was used to evaluate therapeutic effects. Oral daily doses of amineptine 100 to 300 milligrams (mean 180 mg) or clomipramine 50 to 150 milligrams (mean 84 mg) were administered during the trial. Improvement in depression symptoms were seen in both groups and no apparent differences in antidepressant activity could be determined. Fifteen patients did not complete the study: 4 on amineptine and 11 on clomipramine.

4.6.C Amitriptyline

Chronic pain

Obsessive-compulsive disorder

4.6.C.1 Chronic pain

a) Clomipramine appeared to be better than amitriptyline in treating chronic trigeminal neuralgia and tension headache pain; however, amitriptyline was more effective in treating postherpetic neuralgia during a 3-month, randomized, single-blind study with 67 chronic pain sufferers (Carasso et al, 1979). Oral clomipramine was dosed between 20 and 75 milligrams daily in 3 divided doses, while oral amitriptyline was dosed between 30 and 110 milligrams daily in 3 divided doses. Severe sedation was the most commonly reported adverse effect with amitriptyline. The most severe adverse effect with clomipramine was motor agitation, which was experienced by 4 of 35 (10%) patients. Anticholinergic effects were experienced with both drugs.

4.6.C.2 Obsessive-compulsive disorder

a) Oral clomipramine produced a statistically significant reduction in the number or severity of obsessive-compulsive symptoms over amitriptyline on the Psychiatric Questionnaire for Obsessive-Compulsive Disorder (Ananth et al, 1981). Twenty patients with chronic obsessive-compulsive disorder were randomized to receive either clomipramine or amitriptyline in a 4-week, double-blind study. Both drugs were started at 75 milligrams/day and increased up to 300 mg/day as tolerated. The clomipramine-treated group demonstrated improvement over amitriptyline on depression and anxiety scales. The most common adverse effects experienced by both groups included dizziness, drowsiness, and dry mouth. Three patients failed to complete the study: 1 from each group due to syncope and 1 from amitriptyline due to an inadequate response.

4.6.D Buspirone

4.6.D.1 Obsessive-compulsive disorder

a) A double-blind study comparing buspirone and clomipramine in the tretment of obsessive-compulsive disorder (OCD) was performed (Pato et al, 1991). Eighteen of 20 study entrants completed the trial, which included an initial 2-week placebo washout period, a 2-week titration phase (in which doses were increased as tolerated to a daily maximum of 60 mg buspirone or 250 mg clomipramine), and a 4-week dose maintenance phase; subjects then received half the maximum tolerated dose for 4 days, followed by 3-1/2 weeks of placebo. Although the study was conducted in a crossover fashion, with the alternate treatment

given after the 3-1/2 week placebo washout, the trial results were analyzed as a parallel design because subjects did not return to baseline status by the beginning of the second active treatment period. The authors reported similar efficacy of the 2 active treatments, with at least half of the patients in each group evidencing a minimum of 20% improvement in several measures of OCD and one of depression. However, the small sample size may have obscured differences in efficacy. The authors noted that response was not correlated with dose of clomipramine (mean 225 +/- 49 mg/day) or of buspirone (mean 58 +/- 7 mg/day), or with previous use of benzodiazepines. Buspirone warrants further study as a possible treatment for OCD.

4.6.E Citalopram

4.6.E.1 Depression

a) Clomipramine (a tricyclic antidepressant with potent 5-HT reuptake inhibiting properties) 150 milligrams once daily was statistically superior to citalopram 40 milligrams once daily in the treatment of endogenously depressed patients in a 5-week double-blind study (n=75). Clomipramine appeared to have a faster onset and was particularly more effective in improving sleep disturbances, although other depressive symptoms were also improved to a greater degree with this agent compared to citalopram. In the subgroup of patients with nonendogenous depression in this study (n=27), a similar trend was observed in favor of clomipramine; however, the number of patients treated was too small to enable an effective comparison. Orthostatic symptoms, dry mouth, and perspiration were seen only with clomipramine, whereas nausea, vomiting, and headache were more common with citalopram (Anon, 1986). Flaws in this study were that fixed doses of each agent were employed and the duration of 5 weeks may have been too short. The onset of full antidepressant effects of citalopram may take 5 to 6 weeks. Titrating the dose of each agent based on clinical response would enable a more effective comparison in that optimal doses for specific patients could be achieved. A further comparison of these agents with flexible dosing regimens is warranted.

4.6.E.2 Efficacy

a) A small, 5-week, double-blind study reported significant orthostatic hypotensive effects (systolic pressure) in depressed patients treated with clomipramine 150 milligrams once daily but not citalopram 40 milligrams once daily. Diastolic blood pressure was also significantly reduced, although to a lesser extent, with clomipramine, whereas this change did not occur in citalopram-treated patients (Christensen et al, 1985).

b) Similar findings were reported in a clinical efficacy comparison of clomipramine and citalopram (Anon, 1986), and these results are consistent with other clinical data suggesting the lower propensity of citalopram to induce cardiovascular effects compared to tricyclic antidepressants (Milne & Goa, 1991).

4.6.F Desipramine

Autistic disorder

Diabetic neuropathy

Nail biting

Obsessive-compulsive disorder

Paraphilia

Trichotillomania

4.6.F.1 Autistic disorder

a) Clomipramine was superior to both desipramine and placebo for treatment of autistic behavior such as stereotypies, anger, and compulsive, ritualized behavior. Clomipramine and desipramine were both superior to placebo, and had equivalent effects in reducing hyperactivity of patients with autistic disorder (Gordon et al, 1993).

4.6.F.2 Diabetic neuropathy

a) Clomipramine and desipramine both significantly reduced symptoms of diabetic neuropathy as determined by investigators and self-rating compared to placebo (Sindrup et al, 1990). In this double-blind, placebo-controlled, 3-way crossover study, 19 patients were randomized to 2 weeks of treatment with oral desipramine 50 or 200 milligrams/day, clomipramine 50 or 75 milligrams/day, or placebo. Washout between treatment periods was not mentioned. Both agents significantly reduced neuropathy symptoms (pain, paresthesia, dysesthesia, numbness, nightly deterioration, and sleep disturbances) compared to placebo. No significant difference between active treatments was observed. The most common adverse events, which occurred with equal frequency in each active treatment group, included dry mouth, sweating, orthostatic dizziness, and fatigue.

4.6.F.3 Nail biting

a) Clomipramine was superior to desipramine in the treatment of onychophagia in a 10-week, double-blind, crosover study. Of the 25 patients enrolled, only 14 complete the study perhaps due to lack of other psychiatric disturbance (Leonard et al, 1991a).

4.6.F.4 Obsessive-compulsive disorder

a) Clomipramine was significantly more effective than desipramine for treating obsessive compulsive disorder. In a 10-week, double-blind, crossover study forty-eight children and adolescents (ages 6 to 18 years) received clomipramine (mean dose 150 milligrams/day) then desipramine (153 milligrams/day). Sixty-four percent of the patients who received clomipramine for the first time demonstrated a relapse during desipramine therapy. None of the subjects studied exhibited a greater than 20% improvement as measured by the Global OCD Scale during a 2-week, single-blind trial before receiving active treatment. Unlike desipramine, clomipramine decreased obsessive compulsive ratings and depression ratings measured on the Hamilton and NIMH Depression scales (Leonard et al, 1989).
b) Oral clomipramine was superior to desipramine in a comparative, crossover, double-blind study in childhood obsessive-compulsive disorder (Leonard et al, 1989). Twenty-one adolescents were treated for 5 weeks with each drug in increasing doses to a maximum of 3 mg/kg. The results showed a striking superiority of clomipramine over desipramine and the clinical effects were not attributed to a nonspecific antidepressant effect. In a group of 26 obsessive compulsive patients on clomipramine who entered a double-blind drug substitution study using desipramine, clomipramine was superior to desipramine (Leonard et al, 1991).

4.6.F.5 Paraphilia

a) Clomipramine and desipramine had similar efficacy in the treatment of paraphilias in a small, double-blind, crossover study. Eight of 15 patients completed the study in which each patient received a mean maximal daily dose of clomipramine 162.5 milligrams (range 75 to 250 mg) and desipramine 212.5 milligrams (range 100 to 250 mg) for 5 weeks after a 2-week placebo phase. Four of the 8 were also clinically depressed, and there was a great deal of variety in the paraphilias demonstrated by this patient population. As measured by the Schedule for Affective Disorders and Schizophrenia, Lifetime Version, severity of paraphilic symptoms were significantly decreased by both clomipramine (p less than or = 0.005) and desipramine (p less than or = 0.002) as compared with placebo (Kruesi et al, 1992).

4.6.F.6 Trichotillomania

a) Clomipramine was superior to desipramine in the treatment of trichotillomania (hair pulling) during a 10-week, double-blind, crossover study involving 13 women (Swedo et al, 1989). In this study, capsules containing 50 mg of either clomipramine or desipramine were administered; initial doses were 50 milligrams daily, increasing over 3 weeks to a maximum dose of 3 milligrams/kilogram/day (250 mg daily). Mean maximal doses were 180 mg daily for clomipramine and 173 mg daily for desipramine. Clomipramine was superior to desipramine by a physician's rating scale and a trichotillomania-impairment scale. Symptom severity was reduced more with clomipramine as compared to desipramine and clomipramine patients were better able to resist the urge to pull hair as opposed to desipramine patients. Clomipramine appears to be a specific antitrichotillomanic agent; this disorder may be related to an obsessive-compulsive disorder.

4.6.G Diazepam

4.6.G.1 Agoraphobia

a) Clomipramine was significantly superior to diazepam in the treatment of 33 agoraphobic patients during a 12-week, multicentered, randomized, double-blind study (Allsopp et al, 1984). The patients were diagnosed with agoraphobia or social phobia of at least a 1-month duration. Both drugs were administered orally in low doses initially; the doses were then increased to 25 to 150 milligrams in 3 divided daily doses for clomipramine and to 10 to 30 milligrams in 3 divided daily doses of diazepam. Headaches were experienced more in the diazepam group, while dry mouth and drowsiness were more prevalent in the clomipramine group. By the end of the study, clomipramine demonstrated significant improvement over diazepam in total scores for situational anxiety, interference in life-style, and accompanied travel distance on an agoraphobia inventory.

4.6.H Dixyrazine

4.6.H.1 Panic disorder

a) Dixyrazine plus clomipramine was more effective than clomipramine alone in reducing the number of panic attacks. In a 12-week study, 45 patients with panic attacks (with or without agoraphobia) were treated with clomipramine titrated up to 250 milligrams (mg) per day plus either dixyrazine 50 mg per day or placebo. Patients treated with dixyrazine plus clomipramine showed a larger reduction in the Hamilton Anxiety Rating Scale (HARS-P) scores for panic attacks from week 6 to week 12 than the patients in the placebo group (p less than 0.05). The reduction of the number of panic attacks and the increase in patients daily functioning were also significantly greater in the dixyrazine- clomipramine group (p less than 0.05) (Feet & Gotestam, 1994).

4.6.I Dothiepin

4.6.I.1 Depression

a) Although dothiepin and clomipramine were equally capable of diminishing depressive symptoms in a randomized, double-blind, parallel-group comparison of the two tricyclic antidepressants over 6 weeks, adverse events affected 50% more patients in the clomipramine group (n=45) than in the dothiepin group (n=47), and overall more than one-quarter of patients in the clomipramine group withdrew because of such adverse effects as dry mouth, dizziness, and somnolence (Welch et al, 1997).

4.6.J Doxepin

4.6.J.1 Dysthymia

a) Results were equivocal in a study that compared clomipramine and doxepin (75 milligrams/day of either) in a group of 66 patients with neurotic depression. Patient-rated measures did not show a superior agent. Clomipramine was rated better by physician-rated measures. There were no significant differences in side effects (Kornhaber & Horwitz, 1984).

b) Doxepin (25 milligrams three times a day) and clomipramine (25 milligrams three times a day), were more effective than L-tryptophan (500 mg three times a day) in 42 neurotically-depressed patients. The findings of the study were that doxepin and clomipramine resulted in more responses than L-tryptophan, therapeutic blood levels of clomipramine and doxepin were much smaller than those found in endogenously depressed patients, that responders had a significantly higher blood level of the two than non-responders at 21 days, and that the response to clomipramine, but not doxepin, parallelled its accumulation in the blood. (Linnoila et al, 1980).

4.6.K Fluoxetine

4.6.K.1 Obsessive-compulsive disorder

a) Treatment with fluoxetine (FLX) was compared with treatment with clomipramine (CMI) in two groups of patients with obsessive compulsive disorder (OCD) using two different experimental designs. In the first group of 11 patients with OCD studied using a randomized, double-blind, crossover design, treatment with FLX (20 to 80 milligrams/d) for 10 weeks was found to produce therapeutic effects similar to that obtained with CMI (50 to 250 milligrams/d) for 10 weeks. There were significantly fewer total side effects reported during FLX than CMI treatment. Drug tapering and placebo substitution in the 4-week crossover interval phase led to substantial relapses in OCD symptoms and depression. In addition, response to the second drug took as long as response to the first drug, despite a putative common mechanism of action of serotonin uptake inhibition. A second group of 21 patients with OCD that had been previously stabilized on CMI with at least partial benefit were crossed over to FLX in double blind fashion. After 10 weeks of FLX, most patients manifested behavioral rating scores of OCD and depressive symptoms that were comparable with pre-crossover ratings completed during CMI treatment. A significant exacerbation in OCD and depression ratings as well as a similar lag in therapeutic efficacy were also noted in this second cohort of patients with OCD. Platelet serotonin concentrations were reduced 95% during both CMI and FLX treatment periods. These results suggest that FLX may represent a viable alternative to CMI in the treatment of OCD, although more studies with larger sample sizes are needed (Pigott et al, 1990).

b) Clomipramine (CMI) and fluoxetine (FLX) were shown to be equally effective in the treatment of 120 patients with DSM-III major unipolar depressive disorder over a 6-week period. Adverse effects were more frequent with CMI. Those that did occur with FLX tended to disappear during the course of the study (Noguera et al, 1991).

4.6.L Fluvoxamine

Anxiety

Cataplexy

Depression

Obsessive-compulsive disorder

Panic disorder

4.6.L.1 Anxiety

a) Fluvoxamine and clomipramine were comparable in reducing anxiety symptoms in patients with agoraphobia with panic attacks (APA), generalized anxiety disorders (GAD), and obsessive-compulsive

disorders (OCD) as classified by DSM-III during a randomized, double-blind study (Westenberg et al, 1987). Of the 50 patients in this study, 39 diagnosed with APA, 5 with GAD, and 6 with OCD. Patients were randomly assigned to receive either clomipramine, up to 150 milligrams/day, or fluvoxamine, up to 100 milligrams/day, for the 6-week study. Both drugs demonstrated significant improvement in anxiety symptoms after drug therapy when compared to pretreatment.

4.6.L.2 Cataplexy

a) Both fluvoxamine and clomipramine improved cataplexy, but not narcolepsy, in 18 patients with these diseases during a cross-over study (Schachter & Parkes, 1980). It was not revealed if either the patients or researchers were blinded to drug therapy. It should be noted that 15 of the 18 patients were receiving clomipramine 25 to 100 milligrams/daily at the start of the trial, and may have been accustomed to the adverse effects of clomipramine. Also, if the patients were not blinded to drug therapy, some patients may have associated more adverse effects with a new drug, fluvoxamine. Patients were randomly allocated to receive fluvoxamine or clomipramine for a 3-week interval. After a 1-week drug-free period, the patients crossed over to the other drug. The daily dosing range for both drugs ranged from 25 to 200 milligrams/day. All patients were clinically assessed by observers on 5 occasions. The observers' impression was that fluvoxamine caused a moderate reduction in the frequency of attacks of cataplexy and sleep paralysis in most subjects. Fluvoxamine abolished cataplexy in 4 patients and sleep paralysis in 2 patients; only 12 of the 18 patients completed the fluvoxamine-treatment period. The observers felt that clomipramine was more effective than fluvoxamine in preventing both cataplexy and sleep paralysis. Clomipramine abolished cataplexy in 4 patients and sleep paralysis in 5 patients.

4.6.L.3 Depression

a) SUMMARY: Several double-blind, short-term studies have demonstrated fluvoxamine to be as effective as clomipramine in the treatment of depression (De Wilde et al, 1983; Klok et al, 1981). Anticholinergic adverse effects appear to be less common with fluvoxamine therapy.

b) Fluvoxamine and clomipramine were compared for antidepressant activity in a 6-week, randomized, double-blind study of 43 outpatients with major depression (De Wilde et al, 1983). Oral fluvoxamine 100 to 300 milligrams or oral clomipramine 50 to 150 milligrams was administered once daily in the evening. Assessments of the HAM-D (Hamilton Rating Scale for Depression) during the study and at the end failed to demonstrate any significant differences in antidepressant activity between the 2 drugs. The incidence of anticholinergic adverse effects were slightly more significant in the clomipramine-treated group.

c) Clomipramine and fluvoxamine appeared to be equally effective in the treatment of depression for 36 female inpatients during a 4-week, randomized, double-blind study (Klok et al, 1981). Patients were randomized to receive either oral clomipramine or oral fluvoxamine 50 milligrams 3 times daily. Diazepam 10 to 30 mg/day for severe agitation and/or anxiety was the only other psychotropic agent administered. Significant improvements in the Hamilton Rating Scale for Depression, the Clinical Global Impression, and the Zung Self-Rating Depression scale were seen in both treatment groups. Anticholinergic adverse effects appeared more frequently in the clomipramine-treated patients, while gastrointestinal effects were more prevalent in the fluvoxamine group.

d) Fluvoxamine and clomipramine appeared to have similar clinical efficacy in the treatment of endogenous depression for 30 unipolar and bipolar inpatients during a 4-week, randomized, double-blind study (De Wilde et al, 1983). Both drugs were administered orally in doses of 150 to 300 milligrams/day in 3 divided doses. At the end of the study, the fluvoxamine-treated patients demonstrated a 73% improvement on the Hamilton Rating Scale for Depression, while the clomipramine-treated patients had a 62% improvement. In the bipolar patients, 3 of 4 on fluvoxamine responded, while only 1 of 5 on clomipramine demonstrated a good response on the CGI Global Change Scale. Overall, the differences in efficacy between the 2 drugs were not statistically significant. Adverse anticholinergic effects were significantly more prevalent in the clomipramine-treated group.

e) Both clomipramine and fluvoxamine produced significant improvements on the Hamilton Rating Scale for Depression (HAM-D) in 32 patients with mixed depression during a 4-week, randomized, double-blind study (Dick & Ferrero, 1983). The average daily dosage was 130 milligrams and 132.8 milligrams for fluvoxamine and clomipramine, respectively. The mean percentage improvement on the HAM-D for the fluvoxamine-treated patients was 63.8%, and for the clomipramine-treated patients it was 66.3%.

4.6.L.4 Obsessive-compulsive disorder

a) Fluvoxamine (150 to 125 milligrams/day) and clomipramine (100 to 250 milligrams/day were equally effective in the treatment (10 weeks) of 66 outpatients with obsessive compulsive disorder. Both treatments were well-tolerated. Fluvoxamine produced fewer anticholinergic adverse effects and caused less sexual dysfunction than clomipramine, but caused more headache and insomnia (Freeman et al, 1994). under OBSESSIVE COMPULSIVE DISORDER add:

b) In a randomized, double-blind study of 26 patients with obsessive compulsive disorder without comorbid diseases, fluvoxamine and clomipramine, each titrated from an initial dose of 50 milligrams (mg) in the evening up to a maximum of 300 mg daily within two weeks, were equally effective (38% improvement over baseline with fluvoxamine versus 40% for clomipramine). Efficacy was assessed according to the Yale-Brown Obsessive Compulsive Scale and Clinical Global Impression Scale. Fluvoxamine was better tolerated, with less anticholinergic adverse effects while clomipramine had a quicker onset of action. Further studies are needed to demonstrate a time-related effect that might differentiate these drugs (Milanfranchi et

al, 1997).

4.6.L.5 Panic disorder

a) Clomipramine (10 milligrams (mg) for three days and 20 mg for four days) and fluvoxamine (50 mg/day for seven days) were both effective in decreasing the hypersensitivity to 35% carbon dioxide, supporting the serotonergic effect of these drugs to decrease panic attacks through modification of carbon dioxide sensitivity. Thirty-nine panic disorder patients were enrolled in a double-blind, randomized, placebo-controlled study, where each patient was given the 35% carbon dioxide challenge on days 0, 3, and 7. Patients on clomipramine and fluvoxamine showed significant reduction in sensitivity over placebo after seven days as seen by the percent change on a visual analogue for anxiety scale (p=0.027) (Perna et al, 1997).

4.6.M Haloperidol

4.6.M.1 Autistic disorder

a) Among subjects who completed full therapeutic trials of haloperidol and clomipramine for treatment of autistic disorder, the two drugs were comparable; however, haloperidol was superior to clomipramine on an intent-to-treat basis, because of the large proportion of patients who were unable to complete clomipramine treatment due to side effects and behavior problems. In a double- blind, placebo-controlled crossover study, 36 subjects with a DSM- IV diagnosis of autism were given placebo, haloperidol, and clomipramine for periods of 7 weeks each. Clomipramine was begun at 25 milligrams (mg) at bedtime for 2 days and increased to 25 mg twice a day for 2 days, 25 mg 3 times a day for 2 days, and finally 50 mg twice a day. Haloperidol was begun at 0.25 mg at bedtime for 2 days and increased to 0.25 mg twice a day for 2 days, 0.25 mg 3 times a day for 2 days, and finally 0.5 mg twice a day. For both drugs, adjustments of the final dose could be made as clinically indicated. During week 7 of each period, drug dosages were tapered in preparation for the next treatment. Percentages of subjects completing each trial were 70% for haloperidol, 38% for clomipramine, and 66% for placebo. In the haloperidol trials, 7 of 10 discontinuations were for side effects (fatigue or lethargy, dystonia, depression) and the remainder for behavior problems. With clomipramine, 12 of 20 discontinuations were for side effects (fatigue or lethargy, tremors, tachycardia, insomnia, diaphoresis, nausea or vomiting, and decreased appetite) and the remainder for behavior problems. In the placebo trials, 10 of 11 discontinuations were for behavior problems. On an intent-to-treat basis, significant improvement in irritability (p less than 0.05) and hyperactivity (p less than 0.05) was seen with haloperidol only (versus baseline). No differences among treatments were observed for stereotypic behavior, lethargy, or inappropriate speech. When data only from patients completing full therapeutic trials were assessed, both haloperidol and clomipramine were superior to baseline with regard to irritability and stereotypy (Remington et al, 2001).

4.6.N Imipramine

Depression

Obsessive-compulsive disorder

4.6.N.1 Depression

a) Clomipramine was as effective as imipramine in treating depression in 24 patients during a 44-day, randomized, double-blind study (McClure et al, 1973). The patients were diagnosed with psychotic depression independently by 2 psychiatrists. Oral imipramine or oral clomipramine was administered 3 times daily in 50 milligrams doses. Throughout the study periodic assessments using the Hamilton Depression Rating Scale and the Beck Depression Inventory demonstrated a significant reduction in depression from baseline for both drugs; however, a significant difference in antidepressant effects between drugs could not be seen. Minor and transient anticholinergic adverse effects were noted in all patients and included blurred vision, dry mouth, increased sweating, hand tremor, and dizziness. Three patients dropped out of the study, but none of these was due to adverse effects.

4.6.N.2 Obsessive-compulsive disorder

a) SUMMARY: Clomipramine is superior to imipramine in the treatment of obsessive-compulsive disorder.
b) Oral clomipramine was slightly superior to oral imipramine in improving symptoms of obsessive-compulsive disorder (Volavka et al, 1985). A 12-week, double-blind study of 23 patients according to DSM-III with secondary depression diagnosed was conducted to compare the 2 drugs. Both drugs were started at 50 milligrams/day; this was gradually increased to 300 mg/day as tolerated. Seven patients did not complete the study: 4 because of adverse effects (2 from each group), 2 because of unsatisfactory therapeutic response with imipramine, and 1 for no apparent reason. Both drugs produced improvement in depressive symptoms; however, only clomipramine demonstrated improvement in obsessive symptoms when compared to baseline. Typical anticholinergic adverse effects were experienced by both treatment groups with no significant differences between the two. It is difficult to accurately evaluate the clinical response in this study

because of the small number of patients and the methods used for statistical analysis.
c) Both oral clomipramine and oral imipramine were effective in improving symptoms in obsessive-compulsive disorder patients who met DSM-III criteria (Mavissakalian et al, 1985). The study was a 12-week, double-blind trial that compared the efficacy of clomipramine and imipramine in treating obsessive-compulsive disorders. Both drugs were begun at 25 to 50 milligrams/day; this was increased to 300 mg/day as tolerated. At the end of the trial, the mean daily dose of both drugs was 220 mg. Two of 3 clomipramine-treated patients and 2 of 5 imipramine-treated patients were classified as responders. For both drugs, maximal improvement in depression was evident at 4 weeks, while maximal improvement in obsessive-compulsive symptoms was not seen until 8 weeks. The responders also had higher pretreatment depression scores than did nonresponders, which corresponded with the results of another study (Marks et al, 1980). Because of the small sample size, differences (n=8) in efficacy between clomipramine and imipramine could not be determined.
d) The relationship between the antiobsessional and antidepressant effects of tricyclic drugs was studied in primary obsessive-compulsive disorder. Study 1 consisted of a controlled 12-week trial with clomipramine (n=7) and placebo (n=5); study 2 analyzed the pooled data from 15 uniformly selected patients who were treated with either clomipramine or imipramine. Although the antiobsessional and antidepressant effects of the drugs covaried, antidepressant action was not a prerequisite for antiobsessional effects. Clomipramine, and probably imipramine, possess specific antiobsessive effects that are at least partially independent of the antidepressant effects (Mavissakalian et al, 1985).

4.6.O Lithium

4.6.O.1 Depression
a) The effects of lithium and clomipramine (CMI) on signs and symptoms were compared in 22 patients with major depression (Linder et al, 1989). They also compared effects of the two drugs on serum calcium and magnesium. Evaluation of response using the Comprehensive Psychopathological Rating Scale (CPRS) and side effects was made after a 5 to 7 day placebo period, at 2 weeks and at 4 weeks of treatment. After 2 weeks of treatment, the rated scores dropped for more than half of the CPRS items. After 4 weeks, the scores for all but one item were reduced in both groups and after 4 weeks global scores were also reduced. There was no significant difference between lithium patients and CMI patients in response at 2 and 4 weeks. Lithium treatment was associated with fluctuations in calcium and magnesium levels in plasma but there were no changes in CMI patients. Serum prolactin increased during CMI treatment but was unaffected by lithium treatment. There was no correlation between rating scores and drug blood levels, serum prolactin, calcium or magnesium.

4.6.P Lofepramine

4.6.P.1 Depression
a) A meta-analysis of 4 studies comparing lofepramine (n=79) with clomipramine (n=79) concluded that lofepramine was superior to clomipramine in efficacy and tolerance (Kerihuel & Dreyfus, 1991). Overall, there was a significant difference between the number of lofepramine-treated patients (62%) and clomipramine-treated patients (37%) who improved during the 6-week trials. Fewer patients reported side effects with lofepramine than clomipramine (54% vs 65%; p less than 0.15). Lofepramine doses ranged from 70 to 210 milligrams/d, and clomipramine doses ranged from 50 to 150 milligrams/d.
b) Oral lofepramine 70 milligrams twice daily was slightly superior to oral clomipramine 50 milligrams twice daily in a 6-week, randomized, double-blind study involving 60 depressed patients. Lofepramine-treated patients demonstrated a significantly greater improvement on the Hamilton Depression Scale than clomipramine by the end of the study. Statistical significance between the 2 drugs could not be determined in the Self-Rating Depression Scale. Typical mild anticholinergic effects were experienced by both groups, with no significant differences between the drugs (Dimitriou et al, 1984).

4.6.Q Maprotiline

Depression

Pain, Idiopathic

4.6.Q.1 Depression
a) Maprotiline and clomipramine were equally effective in a 4-week, randomized, double-blind study in 12 depressed patients (Ridges, 1977). All patients were endogenously depressed; however, diagnosis criteria was not discussed. Both drugs were started orally at 75 milligrams/day; this was increased to 225 mg/day after 2 weeks if 150 mg/day was inadequate. The Hamilton Depression Rating Scale was used to assess therapeutic efficacy. At the end of the study, both drugs improved depression symptoms to a similar degree and no difference in efficacy could be distinguished. The clomipramine-treated patients appeared to improve sooner than the maprotiline-treated patients. Adverse effects were generally mild and similar for both drugs:

dry mouth, constipation, and tremor. Because of the small number of patients and short duration of the study, further studies are required to adequately compare the 2 drugs in the treatment of depression.

4.6.Q.2 Pain, Idiopathic

a) Oral clomipramine (mean 97 milligrams/day) was more effective in reducing the overall idiopathic pain syndrome symptoms than oral maprotiline (mean 100 milligrams/day) during a 6-week, randomized, double-blind study of 52 patients (Eberhard et al, 1988). An overall improvement was seen in 63% of the clomipramine-treated patients and in only 36% of the maprotiline-treated patients. Clomipramine produced improvements in pain, memory disturbances, concentration difficulties, inner tension, sadness, and bodily discomfort. The most common adverse effect for both drugs was dry mouth, while sweating was more prevalent with clomipramine. Eight clomipramine patients withdrew from the study because of adverse effects compared to only 1 maprotiline-treated patient.

4.6.R Metoprolol

4.6.R.1 Migraine

a) Metoprolol, in oral doses up to 100 milligrams/day, was superior to oral clomipramine (up to 100 milligrams/day) and placebo in 63 migraine headache sufferers during a 16-week, randomized, double-blind, crossover study (Langohr et al, 1985). All patients were diagnosed with common or classic migraines according to the Ad Hoc Committee on Classification of Headache. The drugs were administered at 4-week intervals, with 4-week washout periods before crossover. Metoprolol was the only agent that significantly reduced both the frequency and duration of migraine attacks. When compared to placebo, clomipramine had no influence on migraine attacks. Adverse effects from clomipramine caused 18 patients to discontinue treatment. The most commonly reported adverse effects with clomipramine included insomnia, sweating, tiredness, and constipation.

4.6.S Mianserin

Depression

Headache

Pain

4.6.S.1 Depression

a) SUMMARY: Comparative clinical trials with mianserin and clomipramine fail to demonstrate any significant differences in antidepressant activity. Clomipramine may produce more adverse effects than mianserin.

b) Oral mianserin 60 mg daily and oral clomipramine 150 mg daily were compared for antidepressant activity during a 4-week, multicenter, randomized, double-blind study of 145 depressed patients (Pinder et al, 1980). At the end of the trial, both drugs produced significant but indistinguishable improvement in depression. The clomipramine patients demonstrated a slightly significant increase in adverse effects that were mild and included dry mouth, hypotension, and tremor. Ten patients, 4 on mianserin and 6 on clomipramine, did not complete the study because of drug-related problems; these included adverse effects, clinical deterioration, and increased suicidal risk.

c) A 5-week, randomized, double-blind study compared the safety and efficacy of mianserin and clomipramine in 42 patients with primary unipolar depression according to the International Classification of Diseases (Anon, 1968; Levin, 1982). Patients were started on either oral mianserin 30 milligrams or oral clomipramine 75 milligrams once daily; both doses were doubled beginning in the second week. Both groups demonstrated significant improvement in depression symptoms; however, the mianserin group demonstrated slightly more improvement after 5 weeks of therapy. Adverse effects were similar in both groups, but more prevalent in the clomipramine group, and included dry mouth, tremor, tachycardia, dizziness, excitement, and nasal congestion. Tachycardia and excitement were only present in the clomipramine group. One mianserin patient and 5 clomipramine patients withdrew from the study because of adverse effects.

d) The antidepressant activity of oral mianserin 30 to 60 milligrams daily and oral clomipramine 75 to 150 milligrams daily was compared in 62 mildly depressed patients during a 4-week, randomized, double-blind study (Dunbar et al, 1985). No significant difference in antidepressant activity could be demonstrated between the 2 drugs. Similar anticholinergic adverse effects were experienced by both groups; however, clomipramine patients reported more tremor, dry mouth, tachycardia, and dizziness and 2 withdrew from the study because of adverse effects.

4.6.S.2 Headache

a) Mianserin, clomipramine, and placebo were studied in a double-blind, parallel group comparison involving 82 patients with chronic tension headaches. Both mianserin and clomipramine produced

improvements in pain scores in light of a significant placebo response after 6 weeks of therapy with either oral clomipramine 75 to 150 milligrams/day or mianserin 30 to 60 milligrams/day (Langemark et al, 1990).

4.6.S.3 Pain

a) No significant difference was found among oral clomipramine (75 to 150 milligrams/day), mianserin (30 to 60 milligrams/day), and placebo in a study of 253 patients with chronic idiopathic pain syndrome. Improvement rate was about 40% after 6 weeks when using a 50% or better reduction in pain level. In patients who fulfilled checklist criteria for minor-to-major depression (30% of patients), clomipramine was superior to mianserin and placebo, with an improvement rate of 75% after 7 weeks. Both mianserin and clomipramine were superior to placebo in patients with low back pain. No difference among the 3 treatments was found in patients with burning mouth syndrome or abdominal pain (Loldrup et al, 1989).

4.6.T Milnacipran

4.6.T.1 Depression

a) Milnacipran offers no efficacy advantage over tricyclic antidepressants. Milnacipran 50 to 100 mg twice daily has been comparable to or less effective than imipramine 100 to 150 mg daily, amitriptyline 150 mg daily, and clomipramine 75 to 150 mg daily in the treatment of major depressive disorders; primary endpoints were improvements on the Hamilton and Montgomery-Asberg scales (Tignol et al, 1998; Leinonen et al, 1997; Kasper et al, 1996; Anon, 1997b; Von Frenckell et al, 1990; Ansseau et al, 1989). A more rapid onset of action has been observed with clomipramine and amitriptyline (Leinonen et al, 1997; Ansseau et al, 1989).

b) Greater improvement of CGI-3 scores (therapeutic index, incorporating efficacy and tolerance) was reported with milnacipran in a manufacturer-prepared meta analysis of tricyclic antidepressant comparative trials (Anon, 1997b; Kasper et al, 1996), and this appears in manufacturer product information. However, statistical significance between treatments was not demonstrated (Anon, 1997b).

4.6.U Moclobemide

4.6.U.1 Depression

a) SUMMARY: Clomipramine and moclobemide have been similarly effective in the treatment of depression; a faster onset of action and lower incidence of adverse effects have been reported with moclobemide in some studies. Drop-out rates due to clinical worsening and suicidality were more likely with moclobemide than clomipramine in one study.

b) Clomipramine in doses of 75 to 200 milligrams daily has been as effective as moclobemide 300 to 600 milligrams daily in treating endogenous and non-endogenous depression in most controlled studies (Dierick et al, 1990; Civeira et al, 1990; Lecrubier & Guelfi, 1990). One study (Larsen et al, 1989) reported that moclobemide, imipramine, and placebo were all associated with similar clinical improvement in patients with non-endogenous depression. Lack of statistical superiority of these agents over placebo in this report may have been a reflection of the small number of patients treated (20 in each group). In a larger controlled trial (n=191), moclobemide and clomipramine produced similar and significant improvement in non-endogenously depressed patients; however, placebo was not incorporated into this study (Stabl et al, 1989).

c) An advantage for moclobemide with regard to tolerability (particularly its lesser anticholinergic effects) was reported in some of these studies. However, a similar adverse effect profile for moclobemide and clomipramine emerged in others (Civeira et al, 1990).

d) The onset of antidepressant effect was quicker with moclobemide (10 days) as compared to clomipramine (13 days) in some studies (Lecrubier & Guelfi, 1990).

e) Antidepressant and adverse effects of moclobemide (MCB) (400 milligrams/day) and clomipramine (CMI) (150 milligrams/day) were compared in a double-blind, randomized, inpatient, fixed-dose study with weekly ratings and drug level measurements. After 1 week on single-blind treatment, 115 patients with major depression who met inclusion criteria were begun on active treatment for 6 weeks. MCB drop-outs (N=20) were primarily due to clinical worsening and suicidality (N=9) whereas CMI drop-outs were related primarily to adverse effects (N=6) with none due to clinical worsening. End-point analysis using the Hamilton Depression Scale showed a significant difference favoring CMI over MCB (Anon, 1993).

4.6.V Nortriptyline

4.6.V.1 Pain

a) Twenty-four patients with central pain completed a randomized, crossover, placebo-controlled study of the efficacy and tolerability of clomipramine and nortriptyline. Results showed strong predominance of active drugs over placebo and a significantly more effective analgesic effect of clomipramine over nortriptyline. The analgesic effect of both tricyclic compounds is independent of any antidepressant effect (Panerai et al, 1990).

4.6.W Oxaprotiline

4.6.W.1 Depression

a) Oral oxaprotiline 150 milligrams/day and oral clomipramine 150 milligrams/day were compared for

efficacy in the treatment of 38 depressed patients during a 4-week, randomized, double-blind study (Wolfersdorf et al, 1987). All patients were diagnosed as having either endogenous or psychogenous (psychotic) depression according to ICD (International Classification of Diseases) criteria and were divided equally between the 2 drug therapy groups. After 2 weeks of therapy, both drugs demonstrated equal improvement in depression as assessed by a trained therapist; however, after 4 weeks, the clomipramine group was slightly more improved as determined by the Hamilton Depression Rating Scale and the Self-Rating Scale of Depression. Adverse effects were generally mild and similar for both drugs; they included tremor, sweating, agitation, headaches, and dizziness. Three patients withdrew from the study: 1 from each group due to perceived lack of efficacy and the third due to a venous thrombosis that was not felt to be drug-related.

4.6.X Paroxetine

Depression

Obsessive-compulsive disorder

4.6.X.1 Depression

a) In a large (n=1002) clinical trial, treatment with paroxetine or clomipramine produced similar decreases in anxiety and depression scores; however, adverse effects occurred in significantly (p=0.025) more patients treated with clomipramine than paroxetine (Ravindran et al, 1997). Statistically significant differences between treatments were NOT found on the Montgomery-Asberg Depresssion Rating Scale (MADRS) or Clinical Anxiety Scale (CAS), but a trend in favor of paroxetine was observed for the Clinical Global Impressions (CGI) score at 6 and 12 weeks (p=0.015). Patients entered into this trial had depression with anxiety which was treated in a primary care setting. Paroxetine 20 milligrams (mg) daily was used initially but the protocol permitted an increase to 40 mg daily, if needed, after 4 weeks. Clomipramine titration proceeded as follows: (1) 25 mg in the evening for 3 days; (2) 50 mg in the evening for 4 days; (3) 75 mg daily (25 mg in the morning and 50 mg in the evening); and (4) after 4 weeks, the dose could be increased to 150 mg/day. Based on this study, paroxetine and clomipramine have comparable efficacy but the incidence of adverse effects (AE) including serious AE is lower in patients treated with paroxetine.
b) Paroxetine 30 milligrams once daily was as effective as clomipramine 25 milligrams three times daily in the treatment of major depressive disorder in a 6-week, double-blind study involving 79 elderly patients (60 years of age or older) (Guillibert et al, 1989). Anticholinergic effects and somnolence occurred to a greater degree with clomipramine, whereas nausea and vomiting were observed more frequently with paroxetine.
c) Clomipramine demonstrated a significantly better therapeutic effect than paroxetine using categorical response measures and group averages of rating scores during a double-blind, randomized, inpatient study of 120 depressed patients (Anon, 1990). Patients were randomized to receive either paroxetine 30 milligrams/day or clomipramine 150 milligrams/day for this 6-week study. At the end of week 4, 27 patients were rated as nonresponders and were terminated from the study. Of thses 27 patients, 23 were in the paroxetine group.

4.6.X.2 Obsessive-compulsive disorder

a) In a 12-week, comparative study, paroxetine was as effective as clomipramine for treating obsessive compulsive disorder. Patients were randomly assigned to receive placebo (n=99), paroxetine 10 milligrams (mg) (n=201), or clomipramine 25 mg daily (n=99); the dose of active treatments was titrated to a maximum of 60 mg and 250 mg for paroxetine and clomipramine, respectively. No statistically significant differences were found in the primary efficacy measures, the Yale-Brown Obsessive-Compulsive Scale or the National Institute of Mental Health Obsessive-Compulsive Scale, between paroxetine or clomipramine; however, both drugs were significantly better than placebo. Adverse effects requiring treatment withdrawal occurred in fewer patients treated with paroxetine (9%; p=0.033) than clomipramine (17%). Limitations of the study are the relatively short duration, and the potential loss of blinding due to differences in adverse effects (Zohar et al, 1996).

4.6.Y Pentazocine

4.6.Y.1 Postoperative pain

a) Clomipramine was as effective as pentazocine for relieving postoperative pain. Forty patients (30 to 50 years old) received either intramuscular clomipramine 50 mg or pentazocine 30 mg a half an hour after the end of anesthesia for hysterectomies or laparotomies. No significant difference was observed between either agent for analgesia (Tiengo et al, 1987).

4.6.Z Phenelzine

4.6.Z.1 Obsessive-compulsive disorder

a) Clomipramine and phenelzine had similar efficacy in a double-blind clinical trial conducted in 30 patients

suffering from DSM-III obsessive-compulsive disorder. The study period was 12 weeks and the maximum doses used (from the fifth week on) were 225 milligrams/d for clomipramine (14 patients) and 75 milligrams/d for phenelzine (12 patients); four patients dropped out. Obsessive symptoms improved significantly in both drug groups, but there was no significant difference between groups. Depressive symptoms responded faster than obsessive symptoms (Vallejo et al, 1992).

4.6.AA Sildenafil

4.6.AA.1 Premature ejaculation

a) According to a double-blind, randomized, cross-over study (n=31), as-needed SILDENAFIL was superior in the treatment of premature ejaculation compared with CLOMIPRAMINE, PAROXETINE, SERTRALINE, and PAUSE-SQUEEZE technique. Clomipramine, paroxetine, and sertraline had generally similar efficacy and safety. Paroxetine exhibited improved efficacy and satisfaction over pause-squeeze, while efficacy and satisfaction were similar to pause-squeeze for clomipramine and sertraline. Median intravaginal ejaculation latency time (IVELT) increased significantly to 4 minutes (min), 4 min, 3 min, 15 min, and 3 min from baseline 1 min for clomipramine, paroxetine, sertraline, sildenafil, and pause-squeeze, respectively (all p less than 0.0001). Paroxetine was superior to pause-squeeze with respect to IVELT (p=0.04) and sexual satisfaction (p=0.025). A significant positive correlation occurred between ejaculation latency and sexual satisfaction. No significant differences in adverse effects were found among the 4 drugs. Three patients dropped out due to side effects, including sildenafil (2) and clomipramine (1; also lack of efficacy in this patient). Three additional patients dropped out due to lack of efficacy related to clomipramine, paroxetine, sertraline, and/or pause-squeeze. Medications were administered as needed 3 to 5 hours before planned intercourse and not more than twice a week. Doses were clomipramine 25 milligrams (mg), paroxetine 20 mg, sertraline 50 mg, and sildenafil 50 mg (Abdel-Hamid et al, 2001).

4.6.AB Venlafaxine

4.6.AB.1 Depression

a) Venlafaxine 105 milligrams/day (average dose) tended to be more effective than clomipramine 105 milligrams/day (average dose) for the treatment of depression in a 6-week study with 102 patients; however, the difference was not statistically significant (Holliday & Benfield, 1995). Patients were assessed using the Hamilton Depression Rating Scale, Montgomery-Asberg Depression Rating Scale, and the Clinical Global Impressions scale. Venlafaxine was associated with fewer anticholinergic side effects and a greater incidence of headache/nausea than clomipramine.

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Last Modified: June 02, 2009

DRUGDEX® Evaluations

CLOZAPINE

0.0 Overview

1) Class
- **a)** This drug is a member of the following class(es):
  Antipsychotic
  Dibenzodiazepine

2) Dosing Information
- **a)** Adult
  - **1)** Schizoaffective disorder - Suicidal behavior, Recurrent
    - **a)** initial, 12.5 mg ORALLY 1-2 times a day, then continued with daily dosage increments of 25-50 mg/day, if well-tolerated, to achieve a target dose of 300-450 mg/day (in 2-3 divided doses) by the end of 2 weeks
    - **b)** maintenance: dosage adjustments should be made no more than 1-2 times per week, in increments not to exceed 100 mg; MAX daily dosage is 900 mg/day
  - **2)** Schizophrenia, Treatment-resistant
    - **a)** initial, 12.5 mg ORALLY 1-2 times a day, then continued with daily dosage increments of 25-50 mg/day, if well-tolerated, to achieve a target dose of 300-450 mg/day (in 2-3 divided doses) by the end of 2 weeks
    - **b)** maintenance: dosage adjustments should be made no more than 1-2 times per week, in increments not to exceed 100 mg; MAX daily dosage is 900 mg/day
  - **3)** Schizophrenia - Suicidal behavior, Recurrent
    - **a)** initial, 12.5 mg ORALLY 1-2 times a day, then continued with daily dosage increments of 25-50 mg/day, if well-tolerated, to achieve a target dose of 300-450 mg/day (in 2-3 divided doses) by the end of 2 weeks
    - **b)** maintenance: dosage adjustments should be made no more than 1-2 times per week, in increments not to exceed 100 mg; MAX daily dosage is 900 mg/day
- **b)** Pediatric
  - **1)** safety and effectiveness in pediatric patients have not been established

3) Contraindications

a) agranulocytosis or severe granulocytopenia, clozapine-induced, history; increased risk of subsequent episodes (Prod Info CLOZARIL(R) oral tablets, 2008; Prod Info FAZACLO(R) orally disintegrating tablets, 2008)

b) concomitant use with other drugs having a known potential to cause agranulocytosis or suppress bone marrow function (Prod Info CLOZARIL(R) oral tablets, 2008; Prod Info FAZACLO(R) orally disintegrating tablets, 2008)

c) hypersensitivity to clozapine or any other component of this drug (Prod Info CLOZARIL(R) oral tablets, 2008; Prod Info FAZACLO(R) orally disintegrating tablets, 2008)

d) myeloproliferative disorders, preexisting (Prod Info CLOZARIL(R) oral tablets, 2008; Prod Info FAZACLO(R) orally disintegrating tablets, 2008)

e) paralytic ileus, preexisting (Prod Info CLOZARIL(R) oral tablets, 2008; Prod Info FAZACLO(R) orally disintegrating tablets, 2008)

f) severe central nervous system depression or comatose states from any cause; preexisting (Prod Info CLOZARIL (R) oral tablets, 2008; Prod Info FAZACLO(R) orally disintegrating tablets, 2008)

g) uncontrolled epilepsy or other predisposing factors, preexisting; may increase risk of seizure (Prod Info CLOZARIL(R) Tablets, 2005)

4) Serious Adverse Effects

a) Agranulocytosis
b) Bowel obstruction
c) Cardiac arrest
d) Colitis, Necrotizing
e) Death
f) Drug-induced eosinophilia
g) Fecal impaction
h) Gastrointestinal hypomotility
i) Hepatitis
j) Hyperglycemia
k) Ischemic bowel disease
l) Leukopenia
m) Myocarditis, 5 cases/100,000 patient years
n) Neuroleptic malignant syndrome
o) Neutropenia
p) Orthostatic hypotension
q) Pancreatitis
r) Paralytic ileus
s) Perforation of intestine
t) Pericardial effusion
u) Pulmonary embolism

v) Respiratory arrest
w) Seizure
x) Sudden cardiac death
y) Syncope
z) Tardive dyskinesia
aa) Thrombocytopenia
ab) White blood cell finding, Decreased

5) Clinical Applications
a) FDA Approved Indications
1) Schizoaffective disorder - Suicidal behavior, Recurrent
2) Schizophrenia, Treatment-resistant
3) Schizophrenia - Suicidal behavior, Recurrent

1.0 Dosing Information

Drug Properties

Storage and Stability

Adult Dosage

Pediatric Dosage

1.1 Drug Properties

A) Information on specific products and dosage forms can be obtained by referring to the Tradename List (Product Index)
B) Synonyms
Clozapine
C) Physicochemical Properties
1) Molecular Weight
a) 326.83 (Canada, 1997)
2) Solubility
a) Systemic: Very slightly soluble in water (Prod Info Clozapine, 98).

1.2 Storage and Stability

A) Oral route
1) Storage temperatures for clozapine tablets should not exceed 86 degrees F (30 degrees C) (Prod Info Clozaril(R), 2002).
2) Store clozapine oral disintegrating tablets at 25 degrees Celsius (77 degrees Fahrenheit) with excursions permitted to 15 to 30 degrees Celsius (59 to 86 degrees Fahrenheit) (Prod Info Fazaclo(TM), 2003).
B) Extemporaneous Formulation - Oral route
1) A 20-milligram per milliliter (mg/mL) suspension prepared from crushed tablets in a pediatric mixture base (containing syrup, carboxymethylcellulose, methylhydroxybenzoate and propylhydroxybenzoate) was found to be chemically stable for 18 days at room temperature. However, an expiration date of 7 days was recommended due to lack of microbial testing (Ramuth et al, 1996).

1.3 Adult Dosage

Normal Dosage

Dosage in Geriatric Patients

1.3.1 Normal Dosage

Intramuscular route

Oral route

Parkinson's disease - Psychotic disorder

Tardive dyskinesia

1.3.1.A Intramuscular route

1) Short-term intramuscular administration of clozapine effectively managed 59 treatment-resistant schizophrenic patients whose refusal to take oral medications precipitated an acute exacerbation. Patients had previously received oral clozapine at a mean dose of 307 milligrams/day. The average parenteral dose was 202 milligrams/day for a duration of 3 to 8 days. All patients improved and 90% became compliant with oral clozapine. In addition to the desired sedative effect, parenteral clozapine was associated with constipation (12%), headache (10%), dry mouth (7%) and injection site reactions (5%) (Lokshin et al, 1999).
2) In clinical trials, patients have been treated with clozapine intramuscularly in daily doses of up to 600 milligrams/day. The usual range is 150 to 300 milligrams daily (Ayd, 1974c).

1.3.1.B Oral route

1) The recommended initial dose of clozapine for treatment-resistant schizophrenia and recurrent suicidal behavior is 12.5 milligrams (mg) (one-half 25 mg tablet) once or twice daily (Prod Info Clozaril(R), 2002; Prod Info Fazaclo(TM), 2003). If tolerated, daily dosage increments of 25 to 50 mg may be added to achieve a target dose of 300 to 450 mg/day by the end of 2 weeks. Subsequent increases should be made no more than 1 to 2 times weekly in increments not exceeding 100 mg. For maintenance therapy, the lowest dose of clozapine to maintain remission should be used.
In schizophrenia, initial doses of oral clozapine have been suggested (Taniguchi & Icaza, 1996):

day 1	12.5 milligrams twice daily
day 2	25 milligrams in the AM
day 3	25 milligrams twice daily
day 4	25 milligrams in the AM, 50 milligrams at bedtime
day 5	50 milligrams twice daily
day 6	50 milligrams in the AM, 75 milligrams at bedtime
day 7 and 8	50 milligrams in the AM, 100 milligrams at bedtime
days 9 and 10	100 milligrams twice daily
days 11 and 12	50 milligrams in the AM, 200 milligrams at bedtime
days 13 and 14	100 milligrams in the AM, 200 milligrams at bedtime

Target doses of 300 to 450 milligrams/day are usually achieved by the end of 2 weeks. Cautious titration and a divided dosage schedule are necessary to minimize the risks of hypotension, seizures, and sedation.
2) If therapy is interrupted for two days or more, clozapine should be reinitiated at a dose of 12.5 milligrams once or twice daily. If well-tolerated, titration to the therapeutic dose may proceed more rapidly than recommended for initial therapy. Patients previously experiencing untoward reactions with initial therapy should be retitrated with caution even following 24 hours off of the drug (Prod Info Clozaril(R), 2002; Prod Info Fazaclo(TM), 2003).
3) In a double-blind trial conducted at a state psychiatric hospital (n=50), daily doses of 300 to 600 milligrams were generally superior to 100 milligrams/day. The study sample was severely and chronically ill with refractory schizophrenia or schizoaffective disorder (mean age: 45 years, mean illness duration: 25 years, mean length of current hospitalization: 8.6 years). Subjects were slowly titrated to one of three target doses (100, 300 or 600 milligrams/day) and treated for 16 weeks. Nonresponders at the target dose were crossed over to a different target dose for an additional 16-week period, with a third 16-week trial at the remaining target dose for continuing nonresponders. Only 10% (n=2 on 300 milligrams/day, n=3 on 600 milligrams/day) of this sample met response criteria. At the 16-week timepoint, the 600 milligrams/day dose was statistically superior to the lower doses (p less than 0.05). After 48 weeks, both 300 milligrams/day and 600 milligrams/day were statistically equivalent, with 100 milligrams/day being inferior to both (p less than 0.0001). In an open-label extension, four additional subjects responded to higher doses (800 to 900 milligrams/day) (Simpson et al, 1999).
4) To minimize the overall risk of adverse effects with clozapine, investigators recommend using the lowest possible effective dose with very gradual dose titration (Miller, 2000a; Naber, 1999a).
5) One author reports that therapeutic doses of clozapine range from 50 to 800 milligrams daily. Most patients appear to respond to doses of 200 to 400 milligrams daily. In most patients 3 divided doses at intervals of 4 to 6 hours appear to be effective; however, because of the sedating effects of clozapine, it may be advantageous to either give low doses in the morning and at midday with the bulk of the total daily dose in the evening, or to give the entire daily dose in the evening (Ayd, 1974c).

1.3.1.C Parkinson's disease - Psychotic disorder

See Drug Consult reference: THERAPY OF PSYCHOTIC DISTURBANCES IN PARKINSONIAN PATIENTS

1.3.1.D Tardive dyskinesia

See Drug Consult reference: TARDIVE DYSKINESIA - DRUG THERAPY

1.3.1.E IMPORTANT NOTE

1) Clozapine should NOT be dispensed without appropriate white blood cell count monitoring (Prod Info Clozaril(R), 2002).

2) A 1-week supply of clozapine tablets may be supplied to the patient at the initiation of therapy for emergency use such as weather or holidays (Prod Info Clozaril(R), 2002).

1.3.1.F DISCONTINUATION OF TREATMENT

1) Gradually reduce the dose over a 1- to 2-week period. If abrupt discontinuation is required, carefully monitor the patient for recurrence of psychotic and cholinergic rebound symptoms such as diarrhea, nausea, vomiting, and headache (Prod Info Clozaril(R), 2002; Prod Info Fazaclo(TM), 2003).

1.3.1.G MAXIMUM DOSE

1) Many patients with schizophrenia will respond to clozapine doses between 300 and 600 milligrams/day, but if necessary, the dose can be increased to 600 to 900 milligrams/day. Due to an enhanced risk of adverse effects, the dose should not exceed 900 milligrams/day and patients should be periodically re-evaluated to assess whether continued therapy is appropriate or whether a reduction in dose is possible (Prod Info Clozaril(R), 2002; Prod Info Fazaclo(TM), 2003).

1.3.1.H ORAL DISINTEGRATING TABLETS - PATIENT INSTRUCTIONS

1) Oral disintegrating tablets are supplied as blister packs and should not be opened until ready for use. Peel back foil to expose tablet; do NOT push the tablet through the foil. Just prior to use, remove the tablet from the blister unit and immediately place the entire tablet in the mouth; allow the tablet to disintegrate and then swallow with saliva. Water is not needed to take clozapine oral disintegrating tablets (Prod Info Fazaclo (TM), 2003).

1.3.4 Dosage in Geriatric Patients

A) Clinical studies of clozapine did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. However, elderly patients may have an increased risk for agranulocytosis and should be carefully monitored during therapy (Prod Info Clozaril(R), 2002).

B) Elderly patients may be particularly susceptible to the anticholinergic effects of Clozaril (clozapine), such as urinary retention and constipation (Prod Info Clozaril(R), 2002).

C) Many elderly patients with Parkinson's disease cannot tolerate an initial clozapine dose of 25 milligrams because of side effects including sedation and orthostasis. An initial dose of 6.25 or 12.5 milligrams should be considered in elderly psychotic patients with Parkinson's disease (Wolk & Douglas, 1994).

D) Low-dose initial treatment for geriatric patients is recommended (12.5 milligrams given once on the first day) with subsequent increases not exceeding 25 mg daily (Prod Info Clozaril(R) Australia, 1996).

1.4 Pediatric Dosage

Normal Dosage

Dosage in Other Disease States

1.4.1 Normal Dosage

1.4.1.A Oral route

1) Safety and effectiveness for use in children has not been established (Prod Info Clozaril(R), 2002); (Prod Info Clozaril(R) Australia, 1996).

2) In an open trial of 11 adolescents (ages 12 to 17 years) with childhood-onset schizophrenia refractory to other neuroleptic agents, clozapine was given as an initial dose of 12.5 to 25 milligrams/day and increased every 4 days by one or two times the starting dose (Frazier et al, 1994). The dose was advanced based on clinical response and the emergence of adverse effects to a maximal possible dose of 900 milligrams/day. The mean dose at week 6 of the trial was 370.5 milligrams/day.

1.4.5 Dosage in Other Disease States

A) INFECTIOUS/INFLAMMATORY/HYPERSENSITIVITY PROCESSES

1) If an infectious, hypersensitivity, or inflammatory process is suspected, clozapine plasma levels should be closely monitored and the clozapine dose may need to be reduced by up to 50% (de Leon & Diaz, 2003; Haack et al, 2003).

2.0 Pharmacokinetics

Onset and Duration

Drug Concentration Levels

ADME

2.1 Onset and Duration

A) Onset

1) Initial Response

a) Schizophrenia, Oral: 3 months (Wilson, 1996).

1) In a small number of patients, clinical improvement may be delayed up to 12 months (Wilson, 1996).

2.2 Drug Concentration Levels

A) Time to Peak Concentration

1) ORAL: 2.3 to 3 hours (range, 1 to 6 hours) (Prod Info Fazaclo(TM), 2003; Guitton et al, 1998; Prod Info Clozaril(R), 2002p; Cheng et al, 1988).

B) Schizophrenia, 350 to 420 micrograms/Liter (not clearly defined) (Olesen, 1998); (Freeman & Oyewumi, 1997).

1) Plasma levels show a significant degree of variation (Kurz et al, 1998). Levels are higher in women and increase with age in all patients (Lane et al, 1999).

2) Clozapine and norclozapine levels should only be quantified in plasma since serum levels underestimate blood levels (Kaladjian et al, 1999). Plasma and saliva levels of clozapine do not correlate (r=0.56) (Dumortier et al, 1998).

2.3 ADME

Absorption

Distribution

Metabolism

Excretion

Elimination Half-life

2.3.1 Absorption

A) Effects of Food

1) No effect (Prod Info Clozaril(R), 2002p; Prod Info Fazaclo(TM), 2003).

B) Clozapine tablets and solution are equally bioavailable (Prod Info Clozaril(R), 2002p).

C) Clozapine orally disintegrating tablets (Fazaclo (TM)) are bioequivalent to clozapine tablets (Clozaril (R)) (Prod Info Fazaclo(TM), 2003).

2.3.2 Distribution

A) Distribution Sites

1) Protein Binding

a) 97% (Prod Info Clozaril(R), 2000; Prod Info Fazaclo(TM), 2003).

2) OTHER DISTRIBUTION SITES

a) Red blood cells

B) Distribution Kinetics

1) Volume of Distribution

a) 6 L/kg (Guitton et al, 1998).

2.3.3 Metabolism

A) Metabolism Sites and Kinetics

1) Extrahepatic presystemic routes (Cheng et al, 1988), extensive (Prod Info Clozaril(R), 2002p; Ayd, 1974b; Stock et al, 1977).

a) Metabolites are eliminated in the urine, principally in unconjugated form (Prod Info Clozaril(R), 2002p; Ayd, 1974b; Stock et al, 1977).

b) The average hepatic extraction ratio is 0.2 (Cheng et al, 1988).

c) The cytochrome P-450 enzyme system is involved in the metabolism of the parent compound to the major metabolites desmethylclozapine (both CYP1A2 and CYP3A4) and clozapine N-oxide (CYP3A4) (Eiermann et al, 1997; Jerling et al, 1997).

B) Metabolites

1) N-desmethylclozapine, active (Guitton et al, 1998; Gerson et al, 1994a).

a) N-desmethylclozapine, the major metabolite of clozapine, is a potent 5-HT(1C) receptor antagonist and has affinity for the D(2) and 5-HT(2) receptors. It is further metabolized to an unstable compound that is toxic to hemopoietic precursors of both myeloid and erythroid lineages (Guitton et al, 1998; Gerson et al, 1994a).

2) Hydroxylated and n-oxide derivatives, inactive (Guitton et al, 1998; Prod Info Clozaril(R), 2002p).

2.3.4 Excretion

A) Kidney

1) Renal Excretion (%)

a) 50% (Prod Info Clozaril(R), 2002p; Prod Info Fazaclo(TM), 2003).

1) Excreted in urine as the demethylated, hydroxylated, and n-oxide derivatives, only trace amounts of unchanged drug are detected in urine (Prod Info Clozaril(R), 2002p; Prod Info Fazaclo (TM), 2003).

2) Feces, 30% (Prod Info Clozaril(R), 2002p; Prod Info Fazaclo(TM), 2003).

a) Approximately 30% of a dose is excreted in the feces as the demethylated, hydroxylated, and n-oxide derivatives; only trace amounts of unchanged drug are detected in the feces (Prod Info Clozaril (R), 2002p; Prod Info Fazaclo(TM), 2003).

B) Total Body Clearance

1) 38 to 41 L/hr (Olesen, 1998; Guitton et al, 1998)

C) Other

1) OTHER EXCRETION

a) Blood clearance, 250 mL/min (Cheng et al, 1988).

2.3.5 Elimination Half-life

A) Parent Compound

1) ELIMINATION HALF-LIFE, 8 hours (range 4 to 12 hours), with single dose (Prod Info Clozaril(R), 2002p; Guitton et al, 1998; Prod Info Fazaclo(TM), 2003).

a) Elimination half-life is 12 hours (range, 4 to 66 hours) with multiple dosing (Prod Info Fazaclo(TM), 2003).

B) Metabolites

1) N-desmethylclozapine, 13.2 hours (Guitton et al, 1998)

2) N-oxide metabolite, 7 hours (Guitton et al, 1998)

3.0 Cautions

Contraindications

Precautions

Adverse Reactions

Teratogenicity/Effects in Pregnancy/Breastfeeding

Drug Interactions

3.0.A Black Box WARNING

1) Oral (Tablet; Tablet, Disintegrating)

Agranulocytosis

Because of a significant risk of agranulocytosis, a potentially life-threatening adverse event, clozapine should be reserved for use in (1) the treatment of severely ill patients with schizophrenia who fail to show an acceptable response to adequate courses of standard antipsychotic drug treatment, or (2) for reducing the risk of recurrent suicidal behavior in patients with schizophrenia or schizoaffective disorder who are judged to be at risk of reexperiencing suicidal behavior.

Patients being treated with clozapine must have a baseline white blood cell (WBC) count and absolute neutrophil count (ANC) before initiation of treatment as well as regular WBC counts and ANCs during treatment and for at least 4 weeks after discontinuation of treatment.

Clozapine is available only through a distribution system that ensures monitoring of WBC counts and ANCs according to the schedule described below prior to delivery of the next supply of medication.

Seizures

Seizures have been associated with the use of clozapine. Dose appears to be an important predictor of seizure, with a greater likelihood at higher clozapine doses. Caution should be used when administering clozapine to patients having a history of seizures or other predisposing factors. Patients should be advised not to engage in any activity where sudden loss of consciousness could cause serious risk to themselves or others.

Myocarditis

Analyses of postmarketing safety databases suggest that clozapine is associated with an increased risk of fatal myocarditis, especially during, but not limited to, the first month of therapy. In patients in whom myocarditis is suspected, clozapine treatment should be promptly discontinued.

Other Adverse Cardiovascular and Respiratory Effects

Orthostatic hypotension, with or without syncope, can occur with clozapine treatment. Rarely, collapse can

be profound and be accompanied by respiratory and/or cardiac arrest. Orthostatic hypotension is more likely to occur during initial titration in association with rapid dose escalation. In patients who have had even a brief interval off clozapine (ie, 2 or more days since the last dose) treatment should be started with 12.5 mg once or twice daily.

Since collapse, respiratory arrest and cardiac arrest during initial treatment has occurred in patients who were being administered benzodiazepines or other psychotropic drugs, caution is advised when clozapine is initiated in patients taking a benzodiazepine or any other psychotropic drug.

Increased Mortality in Elderly Patients with Dementia-Related Psychosis

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analysis of seventeen placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of between 1.6 to 1.7 times the risk of death in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (eg, heart failure, sudden death) or infectious (eg, pneumonia) in nature. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear. Clozapine is not approved for the treatment of patients with dementia-related psychosis (Prod Info FAZACLO(R) orally disintegrating tablets, 2008; Prod Info CLOZARIL(R) oral tablets, 2008; Novartis Pharmaceuticals,Corporation, 2008).

3.1 Contraindications

A) agranulocytosis or severe granulocytopenia, clozapine-induced, history; increased risk of subsequent episodes (Prod Info CLOZARIL(R) oral tablets, 2008; Prod Info FAZACLO(R) orally disintegrating tablets, 2008)

B) concomitant use with other drugs having a known potential to cause agranulocytosis or suppress bone marrow function (Prod Info CLOZARIL(R) oral tablets, 2008; Prod Info FAZACLO(R) orally disintegrating tablets, 2008)

C) hypersensitivity to clozapine or any other component of this drug (Prod Info CLOZARIL(R) oral tablets, 2008; Prod Info FAZACLO(R) orally disintegrating tablets, 2008)

D) myeloproliferative disorders, preexisting (Prod Info CLOZARIL(R) oral tablets, 2008; Prod Info FAZACLO(R) orally disintegrating tablets, 2008)

E) paralytic ileus, preexisting (Prod Info CLOZARIL(R) oral tablets, 2008; Prod Info FAZACLO(R) orally disintegrating tablets, 2008)

F) severe central nervous system depression or comatose states from any cause; preexisting (Prod Info CLOZARIL (R) oral tablets, 2008; Prod Info FAZACLO(R) orally disintegrating tablets, 2008)

G) uncontrolled epilepsy or other predisposing factors, preexisting; may increase risk of seizure (Prod Info CLOZARIL(R) Tablets, 2005)

3.2 Precautions

A) agranulocytosis may occur; monitoring recommended (Prod Info CLOZARIL(R) oral tablets, 2008; Prod Info FAZACLO(R) orally disintegrating tablets, 2008)

B) cardiovascular and/or pulmonary disease; possible increased risk for adverse cardiovascular and/or respiratory events (Prod Info CLOZARIL(R) oral tablets, 2008; Prod Info FAZACLO(R) orally disintegrating tablets, 2008)

C) concurrent use of benzodiazepines or other psychotropic medications (Prod Info CLOZARIL(R) oral tablets, 2008; Prod Info FAZACLO(R) orally disintegrating tablets, 2008)

D) elderly patients with dementia-related psychosis (unapproved use); increased risk of death; most deaths were attributed to cardiovascular events (eg, heart failure or sudden death) or infections (eg, pneumonia (Prod Info CLOZARIL(R) oral tablets, 2008; Prod Info FAZACLO(R) orally disintegrating tablets, 2008)

E) myocarditis, including fatalities, has been reported; consider discontinuing therapy; rechallenge not recommended (Prod Info CLOZARIL(R) oral tablets, 2008; Prod Info FAZACLO(R) orally disintegrating tablets, 2008)

F) orthostatic hypotension, with or without syncope may occur (Prod Info CLOZARIL(R) Tablets, 2005)

G) seizures, history or predisposing factors ; dose-related risk of seizures associated with clozapine therapy (Prod Info CLOZARIL(R) oral tablets, 2008; Prod Info FAZACLO(R) orally disintegrating tablets, 2008)

H) cardiomyopathy may occur (Prod Info CLOZARIL(R) oral tablets, 2008; Prod Info FAZACLO(R) orally disintegrating tablets, 2008)

I) concurrent general anesthesia administration (Prod Info CLOZARIL(R) oral tablets, 2008; Prod Info FAZACLO(R) orally disintegrating tablets, 2008)

J) deep vein thrombosis or respiratory symptomatology may occur; consider presence of pulmonary embolism (Prod Info CLOZARIL(R) oral tablets, 2008; Prod Info FAZACLO(R) orally disintegrating tablets, 2008)

K) diabetes mellitus or at risk of diabetes mellitus; increased risk for severe hyperglycemia (Prod Info CLOZARIL(R) oral tablets, 2008; Prod Info FAZACLO(R) orally disintegrating tablets, 2008)

L) eosinophilia has been rarely reported; therapy interruption may be necessary (Prod Info CLOZARIL(R) oral tablets, 2008; Prod Info FAZACLO(R) orally disintegrating tablets, 2008)

M) fever, possibly benign, may occur; evaluate to rule out sign of infection, sign of agranulocytosis, or neuroleptic malignant syndrome (Prod Info CLOZARIL(R) oral tablets, 2008; Prod Info FAZACLO(R) orally disintegrating tablets, 2008)

N) glaucoma, narrow angle; condition may be exacerbated due to anticholinergic properties (Prod Info CLOZARIL(R) oral tablets, 2008; Prod Info FAZACLO(R) orally disintegrating tablets, 2008)

O) hepatic disease; increased risk of hepatitis (Prod Info CLOZARIL(R) oral tablets, 2008; Prod Info FAZACLO(R) orally disintegrating tablets, 2008)
P) hyperglycemia (some extreme cases associated with ketoacidosis or hyperosmolar coma or death) has been reported (Prod Info CLOZARIL(R) oral tablets, 2008; Prod Info FAZACLO(R) orally disintegrating tablets, 2008)
Q) increased duration of treatment and/or higher cumulative doses; increased risk of tardive dyskinesia (Prod Info CLOZARIL(R) oral tablets, 2008; Prod Info FAZACLO(R) orally disintegrating tablets, 2008)
R) intestinal peristalsis impairment, ranging from constipation to intestinal obstruction, fecal impaction and paralytic ileus, including fatal cases, have been reported during postmarketing use (Prod Info CLOZARIL(R) oral tablets, 2008; Prod Info FAZACLO(R) orally disintegrating tablets, 2008)
S) Jewish background; associated with more cases of agranulocytosis than general US population (Prod Info CLOZARIL(R) oral tablets, 2008; Prod Info FAZACLO(R) orally disintegrating tablets, 2008)
T) leukopenia, moderate, initial episode; increased risk for subsequent episodes of agranulocytosis (Prod Info CLOZARIL(R) oral tablets, 2008; Prod Info FAZACLO(R) orally disintegrating tablets, 2008)
U) neuroleptic malignant syndrome, potentially fatal, has been reported in association with antipsychotic therapy; immediately discontinue drug has occurred (Prod Info CLOZARIL(R) oral tablets, 2008; Prod Info FAZACLO(R) orally disintegrating tablets, 2008)
V) phenylketonurics; Fazaclo(R) 12.5-mg, 25-mg, and 100-mg orally disintegrating tablets contain 0.87 mg, 1.74 mg, and 6.96 mg phenylalanine per tablet, respectively (Prod Info FAZACLO(R) orally disintegrating tablets, 2008)
W) prostatic enlargement; condition may be exacerbated due to anticholinergic properties (Prod Info CLOZARIL(R) oral tablets, 2008; Prod Info FAZACLO(R) orally disintegrating tablets, 2008)
X) suicide risk (Prod Info CLOZARIL(R) oral tablets, 2008; Prod Info FAZACLO(R) orally disintegrating tablets, 2008)
Y) tardive dyskinesia, potentially irreversible, may occur (Prod Info CLOZARIL(R) oral tablets, 2008; Prod Info FAZACLO(R) orally disintegrating tablets, 2008)

3.3 Adverse Reactions

Cardiovascular Effects

Dermatologic Effects

Endocrine/Metabolic Effects

Gastrointestinal Effects

Hematologic Effects

Hepatic Effects

Immunologic Effects

Musculoskeletal Effects

Neurologic Effects

Ophthalmic Effects

Otic Effects

Psychiatric Effects

Renal Effects

Respiratory Effects

Other

3.3.1 Cardiovascular Effects

Abnormal ECG

Cardiac complication

Cardiac dysrhythmia

Cardiomyopathy

Edema

Hypertension

Hypotension

Orthostatic hypotension

Phlebitis

Sudden cardiac death

Tachyarrhythmia

3.3.1.A Abnormal ECG

1) Premature ventricular contractions are temporally associated with clozapine and occur with patients at a frequency less than 1%. A minority of patients experience ECG repolarization changes including ST segment depression and flattening of T-waves or inversion of T-waves; clinical significance is unclear. All of these effects normalize after clozapine is discontinued (Prod Info Clozaril(R), 2002).

3.3.1.B Cardiac complication

1) In clinical trials, several patient cases have experienced ischemic changes, myocardial infarction, and sudden death with clozapine therapy. Additionally, postmarketing evaluation revealed cases of myocarditis, pericarditis and/or pericardial effusions; causality was complicated because of serious preexisting cardiac disease (Prod Info Clozaril(R), 2002).

2) Pancreatitis followed by pericardial effusion occurred in a 17-year-old, male, patient who was receiving clozapine for the treatment of paranoid schizophrenia. Following 23 days of treatment during which time the clozapine dose was titrated from 25 mg/day to 175 mg/day, the patient experienced mild epigastric pain and had elevated levels of pancreas amylase and lipase. A diagnosis of pancreatitis was made and the clozapine was discontinued. One day later, the clozapine was resumed at 100 mg/day and the epigastric pain disappeared within 3 days. Amylase and lipase levels returned to normal after 19 days. Four days after decreasing the dose, the patient experienced inspiratory chest pain, increasing pain in both shoulders, and had a heart rate of 120 beats/min. A CT scan of the chest revealed a pericardial effusion. The clozapine was again discontinued and the patient recovered following cardiocentesis that removed 250 mL of slightly hemorrhagic fluid (Wehmeier et al, 2003).

3.3.1.C Cardiac dysrhythmia

1) Adverse effects temporally associated with clozapine and occurring at a frequency less than 1% include bradycardia. Other effects reported from postmarketing experience and a case report include atrial fibrillation and ventricular fibrillation; a causal relationship with clozapine could not be determined (Prod Info Clozaril (R), 2002; Low et al, 1998).

2) A 69-year-old male with chronic paranoid schizophrenia developed atrial fibrillation and possible congestive heart failure after having his clozapine titrated to 325 mg/day over 3 weeks. This was confirmed upon rechallenge (Low et al, 1998).

3.3.1.D Cardiomyopathy

1) In the US, the reported rate of cardiomyopathy in clozapine-treated patients is 8.9 per 100,000 person-years compared to a rate of 9.7 per 100,000 person-years in the general US population (1999 National Hospital Discharge Survey data). Eighty percent of the patients with cardiomyopathy treated with clozapine were less than 50 years of age. The duration of clozapine treatment prior to the diagnosis of cardiomyopathy was greater than 6 months in 65% of the patients. Dilated cardiomyopathy was the most frequently reported type. Signs and symptoms suggestive of cardiomyopathy include: exertional dyspnea, fatigue, orthopnea, paroxysmal nocturnal dyspnea and peripheral edema. If cardiomyopathy is confirmed, clozapine should be discontinued unless the benefit to the patient clearly outweighs the risk (Prod Info Clozaril(R), 2002).

2) A total of 82 reports of myocarditis associated with clozapine use have been received from the USA, Canada, UK, and Australia. The incidence of myocarditis was 5, 16.3, 43.2, and 96.6 cases per 100,000

patient years, respectively. This is 17 to 322 times higher than the rate of myocarditis in the general population. In 51 (62%) of these cases, myocarditis occurred during the first month of treatment. There were 31 (38%) fatalities in this group with 25 of the 31 patients showing evidence of myocarditis at autopsy (Prod Info Clozaril(R), 2002).
3) Twenty-eight cases of myocarditis, including 18 deaths, and 41 cases of cardiomyopathy, including 10 deaths, were reported to the Food and Drug Administration in clozapine recipients over a 10-year period (La Grenade et al, 2001). Additionally, postmarketing evaluation revealed cases of congestive heart failure; causality was complicated because of serious preexisting cardiac disease (Prod Info Clozaril(R), 2002).
4) Plasma and red-cell selenium concentrations were significantly (p less than 0.01) lower in schizophrenic patients treated with clozapine (n=54) compared to patients with mood disorders (n=36), schizophrenic patients not treated with clozapine (n=41) and a healthy control group (n=56). The plasma and red-cell selenium concentrations (micromoles/L) were 1.28 +/- 0.33, 1.47 +/- 0.57; 1.39 +/- 0.29, 1.70 +/- 0.4; 1.47 +/- 0.41, 1.7 +/- 0.48; and 1.49 +/- 0.3, 1.8 +/- 0.58 for the four groups, respectively. Selenium deficiency has been associated with cardiomyopathy and with myocarditis and these same adverse effects are also known to occur with clozapine treatment. Although it could not be determined by this study whether clozapine causes selenium deficiency or if treatment-resistant schizophrenic patients (who are often treated with clozapine) are selenium deficient prior to treatment, the authors suggested that it may prove beneficial to provide selenium supplementation to schizophrenic patients receiving clozapine (Vaddadi et al, 2003).
5) Based on reports to the Food and Drug Administration, those who developed myocarditis and survived were generally treated for a shorter time (median 2 weeks vs 4 weeks) and took a lower daily dose (median 225 mg vs 450 mg) than those who died. However in patients with cardiomyopathy, the median dose (450 mg vs 500 mg) and the duration of therapy (8 months vs 10 months) were similar in those who survived and those who died (La Grenade et al, 2001).
6) Voluntary postmarketing reports to the Adverse Drug Reactions Advisory Committee of Australia over 6 years included 15 cases of myocarditis and 8 cases of cardiomyopathy among 8000 registered clozapine recipients (0.29%). Objective evidence confirmed the diagnosis in all 23 cases (87% male, mean age 36 years, clozapine dose range 100 to 725 mg/day). The median onset of myocarditis was 15 days, with subsequent early death in 5 cases in which autopsy revealed florid myocardial inflammatory infiltrates (eosinophilic in 3, lymphocytic in 1, mixed in 1). Recovery was documented in 5 patients, while the outcome of the remaining 5 was unknown. Five of 8 cardiomyopathy cases manifested during months 2 to 6 of therapy, while the remaining 3 cases occurred much later (30 to 36 months after initiation). One case was fatal after 2 years; 2 patients were stable to improved; the final outcome was unknown in 5 cases. The investigators discovered no confounding factors to account for these cardiac complications (Kilian et al, 1999).
7) A case of cardiomyopathy, possibly related to clozapine, occurred in a 26-year-old woman with no prior cardiac history. Following a total of 5 months of therapy with clozapine 700 mg/day, the patient developed malaise, dyspnea, and edema. Echocardiography demonstrated cardiomyopathy with a low ventricular ejection fraction. The patient improved following discontinuation of clozapine and institution of digoxin therapy. Because baseline echocardiography studies were not performed, it is difficult to determine a causal relationship, or if therapy with clozapine aggravated a previously undiagnosed cardiac problem (Leo et al, 1996).

3.3.1.E Edema

1) Edema and periorbital edema temporally associated with clozapine has been reported and occurs at a frequency 1% or less (Prod Info Clozaril(R), 2002). In a case report, a 24-year-old woman treated with clozapine 400 mg daily for 6 weeks, developed pedal edema and peri-orbital puffiness. After the dosage was reduced to 200 mg over 10 days the edema gradually disappeared (Durst et al, 2000).

3.3.1.F Hypertension

1) Hypertension and chest pain/angina have been reported in 1% to 4% of patients(Prod Info Clozaril(R), 2002).
2) Four obese patients developed a pseudopheochromocytoma syndrome while being treated with clozapine for serious refractory psychiatric disturbances. All patients manifested hypertension and profuse sweating. Urinary catecholamine concentrations were elevated in all 4 patients. Pheochromocytoma was excluded. In 2 cases, catecholamine concentrations normalized and clinical features improved or resolved with withdrawal of the drug. Clozapine dose was reduced in one patient, and treatment was continued unchanged in one patient because of spontaneous lowering of his blood pressure. The author suggested that concurrent sulpiride may have contributed to clinical symptoms in 2 patients (Krentz, 2001).
3) A 34-year-old male with paranoid schizophrenia developed moderate hypertension, tachycardia, pallor, and irritability after the initiation of clozapine (confirmed upon re-challenge). Propranolol 180 mg/day in divided doses was used successfully to control his blood pressure while clozapine was increased to 350 mg/day (George & Winther, 1996). In a similar case, a 19-year-old man developed tachycardia and hypertension and was successfully treated with atenolol (Ennis & Parker, 1997).
4) A 27-year-old man with catatonic schizophrenia treated with clozapine 300 mg developed hypertension. Blood pressure increased to 146/106 (previously 110/70 to 120/80). Amlodipine 5 mg daily controlled the high blood pressure. Upon further testing, it was noted that urinary adrenaline and noradrenaline were also elevated mimicking a pheochromocytoma-type reaction. Clozapine was eventually withdrawn over 10 weeks (Li et al, 1997).

3.3.1.G Hypotension

1) Hypotension and syncope were reported with an incidence greater than 5% of patients, usually after the first dose or during dosage escalation. Rarely, the collapse can be profound and may be accompanied by respiratory arrest and/or cardiac arrest (Prod Info Clozaril(R), 2002).

2) A 51-year-old male maintained on clozapine 600 mg/day suffered from refractory hypotension following coronary artery bypass graft surgery. The initial postoperative systolic blood pressure reading was 50 mL of mercury (mmHg), necessitating vasoconstrictor (methoxamine and metaraminol) and inotropic (dopamine) support. Even with the addition of epinephrine, systolic pressure was only 60 mmHg. A 3-day norepinephrine infusion was required to maintain blood pressure. The alpha-1 blockade and resultant vasodilatation induced by clozapine was the likely etiology (Donnelly & MacLeod, 1999).

3.3.1.H Orthostatic hypotension

1) Orthostatic hypotension with or without syncope can occur during clozapine therapy; usually occurring during initial titration in association with rapid dose escalation. In rare cases (approximately 1 case per 3000 patients), collapse can be profound and may be seen with respiratory arrest and/or cardiac arrest. Collapse and respiratory arrest have occurred with initial doses as low as 12.5 mg. If patients have been off clozapine therapy for 2 days or more, reinitiate with 12.5 mg once or twice daily. Some patients experiencing collapse, respiratory arrest, or cardiac arrest also received benzodiazepines or other psychotropic drugs. Elderly patients, particularly those with compromised cardiac functioning, may be more susceptible to these effects (Prod Info Clozaril(R), 2002; Kane, 1996a).

2) In clinical trials (n=842), greater than 5% of patients experienced syncope (Prod Info Clozaril(R), 2002).

3.3.1.I Phlebitis

1) Adverse effects temporally associated with clozapine and occurring at a frequency less than 1% include phlebitis, thrombophlebitis, cyanosis, and epistaxis (Prod Info Clozaril(R), 2002).

3.3.1.J Sudden cardiac death

1) In a large, retrospective, cohort study that included a primary cohort of 93,300 users of antipsychotic drugs and 186,600 non-users of antipsychotic drugs, there was an increased risk of sudden cardiac death in adult participants 30 to 74 years of age (mean age of 45.7 years) who were using clozapine compared to those who were not using antipsychotic drugs (incidence-rate ratio, 3.67; 95% confidence interval (CI), 1.94 to 6.94; p less than 0.001). In participants being treated with atypical antidepressants (clozapine, olanzapine, quetiapine, risperidone), the incidence-rate ratio for sudden cardiac death increased from 1.59 (95% CI, 1.03 to 2.46) for those using low doses to 2.86 (95% CI, 2.25 to 3.65) for those using high doses (p=0.01) (Ray et al, 2009).

3.3.1.K Tachyarrhythmia

1) Incidence: 25%

2) Tachycardia has been observed in approximately 25% of patients receiving clozapine and may be sustained. The sustained tachycardia is present in all positions monitored; the average increase in pulse is 10 to 15 beats per minute. Adverse effects temporally associated with clozapine and occurring at a frequency less than 1% include palpitations (Prod Info Clozaril(R), 2002; Wolf & Otten, 1991).

3) A 44-year-old man with chronic schizophrenia developed ventricular tachycardia after 2 weeks of clozapine therapy. He presented with a fever (38.5 degrees Celsius), pallor, and lethargy. Macular rashes appeared on his forearms and feet. Electrocardiogram showed ST elevation in leads V2 and V3. He was treated with lidocaine and amiodarone via a central line. Atrial fibrillation also developed lasting for 24 hours (Varma & Achan, 1999).

3.3.2 Dermatologic Effects

Cellulitis

Dermatological finding

Rash

Sweating symptom

3.3.2.A Cellulitis

1) Summary

a) A 37-year-old male developed right arm cellulitis and progressively increasing eosinophil count after 5 days of clozapine therapy and a left-sided pleural effusion after 12 days. Clozapine was discontinued and he improved with antibiotics. A later trial of clozapine 25 milligrams daily resulted in recurrence of

symptoms (Chatterjee & Safferman, 1997).

3.3.2.B Dermatological finding

1) Summary

a) Adverse effects temporally associated with clozapine and occurring at a frequency less than 1% include PRURITUS, PALLOR, ECZEMA, ERYTHEMA, BRUISE, DERMATITIS, PETECHIAE, and URTICARIA. Voluntary postmarketing reports included STEVENS-JOHNSON SYNDROME, ERYTHEMA MULTIFORME, PHOTOSENSITIVITY, and VASCULITIS. However, a causal relationship could not be determined (Prod Info Clozaril(R), 2002).

2) Rash has occurred with some frequency in patients during clozapine therapy. Adverse effects temporally associated with clozapine and occurring at a lower frequency include pruritus, pallor, eczema, erythema, sweating, bruising, dermatitis, petechiae, and urticaria. Reports of other rare adverse effects include Stevens-Johnson syndrome, erythema multiforme, photosensitivity, and vasculitis.

3.3.2.C Rash

1) Summary

a) In clinical trials, rash occurred in 2% of patients (n=842) during clozapine therapy (Prod Info Clozaril (R), 2002).

2) Incidence: 2%

3) LITERATURE REPORTS

a) A well-circumscribed, erythematous, papular pruritic rash spread over the torso and extremities of a 37-year-old female approximately 9 days after clozapine initiation and titration to 150 milligrams/day. An initial skin biopsy revealed possible furunculosis, but a later biopsy was consistent with a drug hypersensitivity reaction. The rash was preceded by fever to 39.9 degrees Celsius, headache, neck stiffness and chest pain, evolving into bilateral pleural effusions. All signs and symptoms began to subside shortly after clozapine's discontinuation (Stanislav & Gonzalez-Blanco, 1999).

3.3.2.D Sweating symptom

1) Summary

a) A 31-year-old male developed increased sweating with clozapine therapy. Biperiden, titrated to 6 milligrams per day, resulted in prompt cessation of generalized sweating (Richardson et al, 2001).

2) Incidence: 6%

3.3.3 Endocrine/Metabolic Effects

Acid-base balance - finding

Body temperature finding

Diabetes mellitus

Diabetic ketoacidosis

Disorder of fluid AND/OR electrolyte

Excessive salivation

Hyperlipidemia

Hyperprolactinemia

Lactic acidosis

Metabolic syndrome

Selenium deficiency

Sweating

Weight gain

3.3.3.A Acid-base balance - finding

1) Refractory lactic acidosis and diabetic ketoacidosis have been reported with clozapine use.

3.3.3.B Body temperature finding

1) Adverse effects temporally associated with clozapine and occurring at a frequency of less than 1% include chills, hot flashes, and hypothermia (Prod Info Clozaril(R), 2002).

3.3.3.C Diabetes mellitus

1) Summary

a) Hyperglycemia, glucose intolerance, and new-onset diabetes have been reported with clozapine therapy. Clozapine therapy may modify glucose-insulin homeostasis by increasing insulin secretion, either by a direct effect on the pancreatic beta cells or via induction of peripheral insulin resistance, and impairing growth hormone secretion (Rigalleau et al, 2000; Melkersson et al, 1999; Popli et al (1997). One study found patients receiving clozapine tended to have diabetes type 2 or impaired glucose tolerance more often than a control group of patients receiving depot neuroleptics (Hagg et al, 1998). The manufacturer reports that severe hyperglycemia, sometimes leading to ketoacidosis, hyperosmolar coma, or death, has been reported in patients with no prior history of hyperglycemia, but that a causal relationship could not be definitively established (Prod Info Clozaril(R), 2004). A case-control study investigated the possible association between clozapine use and development of diabetes mellitus; it found no significant relationship (Wang et al, 2002).

2) Literature Reports

a) A case-control study found no significant association between clozapine use and development of diabetes mellitus. Using data from the New Jersey (NJ) Medicaid program (covering the period January 1, 1990 to June 30, 1995), NJ Medicare, and NJ Pharmaceutical Assistance to the Aged and Disabled program, 7227 cases of newly treated diabetes were compared to 6780 controls. Both groups represented patients having psychiatric diagnoses recorded in the previous 6 months. In the group with newly diagnosed diabetes, 1.3% were using clozapine. In the control group (ie, patients with psychiatric diagnoses but not newly diagnosed with diabetes), 1.7% were using clozapine (p=0.073). The adjusted odds ratio (OR) of developing diabetes with clozapine use was 0.98. There was no increased risk associated with higher clozapine doses or longer duration of clozapine therapy. By comparison, persons in the control group using non-clozapine antipsychotic medication had a modest but significantly increased risk of developing diabetes (OR 1.13). The antipsychotic agents particularly associated with an increased risk for diabetes were chlorpromazine (adjusted OR 1.31) and perphenazine (adjusted OR 1.34). The data also showed that there was an increased risk of developing diabetes among those using prochlorperazine (adjusted OR 1.21) and an oral corticosteroid (Wang et al, 2002).

b) A Chinese male schizophrenia patient developed hyperglycemia, hyperlipemia, and periodic paralysis while taking clozapine. Symptoms resolved when clozapine was withdrawn and recurred when clozapine treatment was reestablished. Symptoms appeared at clozapine doses as low as 37.5 milligrams (mg) per day. Other drugs were not as effective as clozapine for treating his mental state. His mental state was finally stabilized with a combination of clozapine 25 mg/day and haldol 20 mg/day, without elevations of blood glucose or lipids (Wu et al, 2000).

c) Three cases of new-onset diabetes were reported in Caucasian men who were on clozapine for 3 to 6 months. They had a distinct presentation including weight loss, ketosis (one ketoacidosis), severe hyperglycemia requiring insulin therapy, and relative insulin deficiency. In all cases, insulin was discontinued one month after the clozapine was stopped (Rigalleau et al, 2000).

d) Clozapine therapy may modify glucose-insulin homeostasis by increasing insulin secretion, either by a direct effect on the pancreatic beta cells or via induction of peripheral insulin resistance, and impairing growth hormone secretion. In a study of 28 patients (median age: 42) on classical antipsychotics and 13 patients (median age: 35) on clozapine for schizophrenia and related psychotic disorders, body mass index (BMI), fasting serum glucose, fasting serum insulin, and insulin-like growth factor binding protein-1 (IGFBP-1) did not differ statistically between groups. Age-correlated insulin-like growth factor-1 (IGF-1) was significantly lower in clozapine recipients, which investigators speculated may be due to decreased growth hormone secretion. A higher percentage of clozapine users (46% versus 21%, p=NS) had above normal insulin levels, but only one subject had abnormal glucose levels. BMI was elevated in 54% and 46% of the classical and clozapine groups, respectively. Findings unique to clozapine users were lack of correlations between IGFBP-1 and insulin and between IGFBP-1 and BMI; a negative correlation between IGF-1 and IGFBP-1; and a positive correlation between serum drug concentration and insulin. These data, and their relationship to the risk of developing or exacerbating diabetes mellitus, require further confirmation (Melkersson et al, 1999).

e) Patients receiving clozapine tended to have diabetes type 2 or impaired glucose tolerance more often than a control group of patients receiving depot neuroleptics (Hagg et al, 1998). Patients at a psychiatric clinic receiving either clozapine or depot neuroleptics were recruited for a diabetes screening. None of the patients had a previous diagnosis or evidence of diabetes mellitus. After screening, 13 out of 60 patients (22%) treated with clozapine were diagnosed with type 2 diabetes or impaired glucose tolerance while only 6 out of 63 (10%) in the depot neuroleptic group received these diagnoses. The difference did not reach statistical significance (p=0.06).

f) Severe hyperglycemia (blood glucose 585 milligrams/deciliter) was reported in a 37-year-old Jewish male after 11 weeks of clozapine therapy. This was accompanied with refractory lactic acidosis,

agranulocytosis, fever, candidiasis and fatal myocardial failure (Koren et al, 1997).

g) Four adults developed increasing glucose intolerance following the initiation of clozapine therapy (Popli et al, 1997). Two of the patients developed severe diabetic ketoacidosis. The other 2 patients developed an exacerbation of their preexisting, well-controlled, diabetes mellitus within 2 weeks of initiation of clozapine therapy. The authors, in their limited experience (treated 147 patients over 10 years), noted a 2.7% incidence of clinically significant changes in glucose tolerance during clozapine therapy.

h) Two cases of patients developing diabetes mellitus and 2 cases of exacerbation of preexisting, but well controlled diabetes mellitus, in patients starting clozapine therapy were reported (Popli et al, 1997).

See Drug Consult reference: ATYPICAL ANTIPSYCHOTIC AGENTS - EFFECT ON GLUCOSE AND RISK OF DIABETES

3.3.3.D Diabetic ketoacidosis

1) Summary

a) Four case reports have noted the development of ketoacidosis with therapeutic use of clozapine therapy (Avram et al, 2001; Colli et al, 1999; Ai et al, 1998; Pierides, 1997).

2) Literature Reports

a) A 33-year-old male, without past or family history of diabetes mellitus, developed diabetic ketoacidosis after taking clozapine 50 milligrams twice a day for 8 months (Avram et al, 2001).

b) A 31-year-old Caucasian man developed ketoacidosis 3 months after beginning clozapine 200 milligrams daily (Colli et al, 1999). His blood sugars rapidly normalized after the discontinuation of clozapine. A repeat trial of clozapine resulted in increased blood sugars within 72 hours.

c) A 30-year-old Afro-Caribbean man treated with clozapine 150 milligrams twice daily for 5 months developed ketoacidosis (Ai et al, 1998). Initially he was treated with insulin until clozapine was discontinued. He was then switched to an oral hypoglycemic agent. Eight months after discontinuing the clozapine, the patient still required an oral agent.

d) Hyperglycemia, hyperkalemia and ketoacidosis (pH 7.09) developed after 1 week of initiating and titrating clozapine from 25 milligrams/day (mg/day) to 300 mg/day in a 50-year-old male with chronic refractory schizophrenia. Presenting symptoms included lethargy, thirst, chest pain, and dyspnea. The patient improved with clozapine withdrawal and insulin therapy (Pierides, 1997).

3.3.3.E Disorder of fluid AND/OR electrolyte

1) In voluntary postmarketing reports adverse effects of hyperuricemia and hyponatremia occurred during clozapine therapy. A causal relationship could not be determined (Prod Info Clozaril(R), 2002).

3.3.3.F Excessive salivation

1) Incidence: 31% (Prod Info Clozaril(R), 2002)

2) In clinical trials, increased salivation was reported in 31% of patients (n=842). Salivation may be profuse particularly during sleep but may be diminished with a dosage reduction (Prod Info Clozaril(R), 2002). .

3.3.3.G Hyperlipidemia

1) Summary

a) There have been case reports of significant hyperlipidemia associated with clozapine use (Ball et al, 2005; Wu et al, 2000), in one case precipitating acute pancreatitis (Ahmed et al, 2009).

2) Literature Reports

a) In a case report, a 47 year old male treated for 2 years with clozapine for treatment-resistant schizophrenia developed xanthomas associated with significant dyslipidemia which developed into acute pancreatitis. Following discontinuation of clozapine therapy, his metabolic parameters normalized. When rechallenged with clozapine, significant dyslipidemia reoccurred within 10 weeks. The patient had no personal or family history of abnormal lipids or elevated blood glucose prior to clozapine initiation. He was maintained on clozapine 450 mg daily with an average plasma level of 490 ng/mL and presented with xanthomas, fasting cholesterol 772.2 mg/dL, fasting triglyceride 4886.1 mg/dL, and a normal fasting glucose. Clozapine therapy was continued with the addition of statin therapy for the next 11 years. The patient was admitted with acute pancreatitis, cholesterol 1404 mg/dL, triglyceride 14,418 mg/dL, and fasting glucose of 147.6 mg/dL. Discontinuation of clozapine resulted in normalization of metabolic parameters within 3 weeks. When psychotic symptoms deteriorated, clozapine was reintroduced and titrated up to 400 mg daily. Within 10 weeks, the cholesterol level increased to 417.3 mg/dL, triglyceride 3008.2 mg/dL, and fasting glucose 167.4 mg/dL. Clozapine discontinuation normalized levels within 10 days (Ahmed et al, 2009).

b) New-onset hyperlipidemia was reported in the case of a 42-year-old schizophrenic patient treated with clozapine. At a dose of 300 mg/day, corresponding total cholesterol (TC) was increased at 256 mg/dL and triglycerides (TG) at 285 mg/dL. At clozapine doses of 500 mg/day, TG increased to greater than 400 mg/day. Lipid-lowering drug therapy did not adequately improve the lipid profile. The highest levels measured were TC 477 mg/dL and TG 4758 mg/dL. With sporadic clozapine compliance, TC measured 213 mg/dL, TG 298 mg/dL and low density lipoprotein cholesterol (LDL-C) 146 mg/dL. Clozapine was discontinued, and aripiprazole initiated and titrated to 45 mg/day. After 3 weeks, TC measured 107 mg/dL, TG 49 mg/dL and LDL-C 47 mg/dL (Ball et al, 2005).

c) A Chinese male schizophrenia patient developed hyperglycemia, hyperlipidemia, and periodic

paralysis while taking clozapine. Symptoms resolved when clozapine was withdrawn and recurred when clozapine treatment was reestablished. Symptoms appeared at clozapine doses as low as 37.5 milligrams (mg) per day. Other drugs were not as effective as clozapine for treating his mental state. His mental state was finally stabilized with a combination of clozapine 25 mg/day and haloperidol 20 mg/day, without elevations of blood glucose or lipids (Wu et al, 2000).

3.3.3.H Hyperprolactinemia

1) Summary

a) With clozapine therapy, resolution of chronic hyperprolactinemia was observed in 2 female patients (Dickson et al, 2000). Clozapine does not cause sustained increases in serum prolactin levels as the traditional neuroleptics do. One author theorized that due to both the resolution of impaired sexual functioning secondary to hyperprolactinemia and improved social interactions secondary to clozapine treatment, higher birth rates may occur with clozapine therapy(Dickson & Edwards, 1997).

2) Literature Reports

a) Clozapine does not cause sustained increases in serum prolactin levels as the traditional neuroleptics do. One author theorized that due to both the resolution of impaired sexual functioning secondary to hyperprolactinemia and improved social interactions secondary to clozapine treatment, higher birth rates may occur with clozapine therapy. At the Calgary General Day Hospital clinic, 235 patients were treated primarily for schizophrenia with 12% taking clozapine. In this small group taking clozapine, 4 babies were born (to 3 patients), while the other 88% of the patients not taking clozapine produced only 5 children (to 4 patients). Further studies are needed to elicit the effects of clozapine on fertility (Dickson & Edwards, 1997).

3.3.3.I Lactic acidosis

1) Refractory lactic acidosis (blood pH 6.97, bicarbonate 8 mEq/liter, and lactate 92.3 milligrams/deciliter), with hyperglycemia and heart failure, agranulocytosis and candidiasis, has been reported following several weeks of clozapine therapy (Koren et al, 1997).

3.3.3.J Metabolic syndrome

See Drug Consult reference: ANTIPSYCHOTIC AGENTS - METABOLIC SYNDROME

3.3.3.K Selenium deficiency

1) Summary

a) Clozapine was associated with decreased plasma and red-cell selenium concentrations in one study. Selenium deficiency has been associated with cardiomyopathy and with myocarditis and these same adverse effects are also known to occur with clozapine treatment (Vaddadi et al, 2003).

2) Literature Reports

a) Plasma and red-cell selenium concentrations were significantly (p less than 0.01) lower in schizophrenic patients treated with clozapine (n=54) compared to patients with mood disorders (n=36), schizophrenic patients not treated with clozapine (n=41) and a healthy control group (n=56). The plasma and red-cell selenium concentrations (micromoles/liter) were 1.28 +/- 0.33, 1.47 +/- 0.57; 1.39 +/- 0.29, 1.70 +/- 0.40; 1.47 +/- 0.41, 1.70 +/- 0.48; and 1.49 +/- 0.30, 1.80 +/- 0.58 for the four groups respectively. Selenium deficiency has been associated with cardiomyopathy and with myocarditis and these same adverse effects are also known to occur with clozapine treatment. Although it could not be determined by this study whether clozapine causes selenium deficiency or if treatment-resistant schizophrenic patients (who are often treated with clozapine) are selenium deficient prior to treatment, the authors suggested that it may prove beneficial to provide selenium supplementation to schizophrenic patients receiving clozapine (Vaddadi et al, 2003).

3.3.3.L Sweating

1) Incidence: 4% to 6% (Prod Info Clozaril(R), 2002)

2) In clinical trials (n=842) with therapeutic use of clozapine increased sweating was reported in 4% to 6% of patients (Prod Info Clozaril(R), 2002).

3.3.3.M Weight gain

1) Summary

a) In clinical trials (n=842) weight gain was reported in 4% to 6% of patients with therapeutic use of clozapine. One percent of patients experienced an appetite increase (Prod Info Clozaril(R), 2000). In other studies the report of weight gain and increased appetite was as high as 50% to 75%(Briffa & Meehan, 1998; Cohen et al, 1990; Norris & Israelstam, 1975). Two proposed mechanisms of clozapine-induced weight gain include increased insulin secretion, either by a direct effect on the pancreatic beta cells or via induction of peripheral insulin resistance, and impaired growth hormone secretion (Melkersson et al, 1999).

2) Incidence: 4%

3) Literature Reports

a) The weight plateau achieved with clozapine apparently depends on genotype. Male monozygotic twins developed paranoid type schizophrenia at ages 17.4 years and 17.6 years. The first one was treated with risperidone and gained 17 kilograms (kg) over 11 months. The other was treated with

classic antipsychotics for 2 months and gained 2 kg. Because of insufficient clinical response, both were switched to clozapine (500 mg/day and 450 mg/day). Both gained weight. Both twins developed binge eating episodes (2 to 3 per week) after starting clozapine. At the time of this report, weight gains since the initiation of antipsychotic treatment had totaled 38 and 40 kg (Theisen et al, 2001).
b) Two proposed mechanisms of clozapine-induced weight gain include increased insulin secretion, either by a direct effect on the pancreatic beta cells or via induction of peripheral insulin resistance, and impaired growth hormone secretion. In a study of 28 patients (median age: 42) on classical antipsychotics and 13 patients (median age: 35) on clozapine for schizophrenia and related psychotic disorders, body mass index (BMI), fasting serum glucose, fasting serum insulin, and insulin-like growth factor binding protein-1 (IGFBP-1) did not differ statistically between groups. Age-correlated insulin-like growth factor-1 (IGF-1) was significantly lower in clozapine recipients, which investigators speculated may be due to decreased growth hormone secretion. A higher percentage of clozapine users (46% versus 21%, p=NS) had above-normal insulin levels, but only one subject had abnormal glucose levels. BMI was elevated in 54% and 46% of the classical and clozapine groups, respectively. Findings unique to clozapine users were lack of correlations between IGFBP-1 and insulin and between IGFBP-1 and BMI; a negative correlation between IGF-1 and IGFBP-1; and a positive correlation between serum drug concentration and insulin. These data require further confirmation (Melkersson et al, 1999).
c) In four case reports (males with schizophrenia or other psychotic disorders, aged 32 to 42), clozapine therapy (500 to 900 milligrams (mg)/day) was associated with increased serum triglyceride levels, which declined after clozapine discontinuation. Individual changes in triglyceride levels after substitution of risperidone for clozapine included: 229 to 104 mg/deciliter (dL); 140 to 60 mg/dL; 309 to 164 mg/dL; and 194 to 150 mg/dL. Total cholesterol levels showed similar reductions in two cases, but remained stable in two cases; all values were below 200 mg/dL. Two individuals stopped risperidone and restarted clozapine, with accompanying increases in triglyceride levels of 164 to 270 mg/dL and 150 to 262 mg/dL, respectively (Ghaeli & Dufresne, 1999).
d) Significant weight gain occurred in patients prescribed clozapine (Briffa & Meehan, 1998). In a group of 48 patients, a mean absolute weight gain of 3.6 kilograms (kg) occurred over the first 3 months of therapy. An average of 4.95 kg was gained by 36 patients while 12 patients lost an average of 0.4 kg. Weight increase was most notable in men. After 1 year, 36 patients were available for follow-up and they gained an average of 3.35 kg. An average of 7.48 kg was gained by 25 patients while 11 patients lost an average of 4.7 kg.
e) Nine of 13 patients receiving clozapine (10 for the treatment of behavior disorder and 3 for schizophrenia) had an enormous and persistent increase in appetite resulting in day-long compulsive eating. Four patients gained between 10 and 20 kg within a 2-month period. After discontinuation of clozapine in 2 patients, their weight gain was rapidly lost (Norris & Israelstam, 1975).
f) Significant weight gain occurs during both short- and long-term treatment with clozapine. A group of 82 patients were studied for a period of 90 months; the cumulative incidence of patients becoming 20% or more overweight was 54%. Monitoring and dietary counseling are necessary to minimize this long-term health risk (Umbricht et al, 1994). Six of 7 patients gained between 6 and 69 pounds with clozapine therapy (Cohen et al, 1990).

3.3.4 Gastrointestinal Effects

Abdominal discomfort

Bowel obstruction

Colitis, Necrotizing

Constipation

Diarrhea

Excessive salivation

Fecal impaction

Gastrointestinal hypomotility

Heartburn

Ischemic bowel disease

Nausea

Nausea and vomiting

Pancreatitis

Paralytic ileus

Parotitis

Perforation of intestine

Summary

Swelling of salivary gland

Vomiting

Xerostomia

3.3.4.A Abdominal discomfort

1) Incidence: 4% (Prod Info FAZACLO(R) orally disintegrating tablets, 2007)

2) Abdominal discomfort/heartburn occurred in 4% of patients treated with clozapine in clinical trials (n=842) (Prod Info FAZACLO(R) orally disintegrating tablets, 2007).

3.3.4.B Bowel obstruction

1) In postmarketing reports, intestinal obstruction/paralytic ileus has occurred in patients receiving clozapine with some cases resulting in death. Treat constipation with adequate hydration and ancillary medications (eg, bulk laxatives) and consider consulting with a gastroenterologist for serious cases (Prod Info FAZACLO (R) orally disintegrating tablets, 2007).

2) Intestinal obstruction necessitating hospitalization occurred in a 51-year-old male and a 35-year-old female with resistant schizophrenia receiving clozapine 275 milligrams (mg)/day for 2 months and 500 mg/day for 4 months, respectively. No other predisposing factors were identified. The patients recovered with conservative management and continued on clozapine therapy with adjunctive dietary measures and stool softeners (Tang & Ungvari, 1999).

3.3.4.C Colitis, Necrotizing

1) A 36-year-old male developed fatal necrotizing colitis 4 months after beginning clozapine (Shammi & Remington, 1997).

3.3.4.D Constipation

1) Incidence: 14% (Prod Info FAZACLO(R) orally disintegrating tablets, 2007)

2) Constipation occurred in 14% of patients treated with clozapine in clinical trials (n=842). Elderly patients may be particularly susceptible to the anticholinergic effects of clozapine, such as constipation. Intestinal peristalsis leading to fecal impaction, paralytic ileus, and intestinal obstruction has also been reported with some cases resulting in death. Treat constipation with adequate hydration and ancillary medications (eg, bulk laxatives) and consider consulting with a gastroenterologist for serious cases (Prod Info FAZACLO(R) orally disintegrating tablets, 2007).

3) Constipation occurs when the daily dose exceeds 150 milligrams. These adverse effects may disappear with continued administration of the same dose. However, if not, they are managed easily by dose reduction or temporary discontinuation of clozapine (Ayd, 1974a).

3.3.4.E Diarrhea

1) Incidence: 2% (Prod Info FAZACLO(R) orally disintegrating tablets, 2007)

2) Diarrhea occurred in 2% of patients treated with clozapine in clinical trials (n=842) (Prod Info FAZACLO (R) orally disintegrating tablets, 2007).

3) Diarrhea, associated with decreasing lymphocyte counts, was reported in 3 patients between 13 days and 9 months following initiation of clozapine therapy. Re-challenge in 2 cases did not cause further diarrhea. The mechanism for this is unclear (Harvey et al, 1992).

3.3.4.F Excessive salivation

1) Incidence: 31% (Prod Info FAZACLO(R) orally disintegrating tablets, 2007)

2) Salivation occurred in 31% of patients treated with clozapine in clinical trials (n=842). Salivation may be profuse, particularly during sleep, but may be diminished with a dosage reduction (Prod Info FAZACLO(R) orally disintegrating tablets, 2007).
3) Ipratropium nasal spray given sublingually provided relief of sialorrhea in 8 patients receiving daily clozapine. A retrospective analysis of patients receiving daily clozapine (150 to 600 milligrams (mg)) for schizophrenia or bipolar disorder who complained about excessive drooling was conducted. Nine patients received an intranasal formulation of ipratropium (0.03% or 0.06%) to be used sublingually (2 sprays) up to 3 times daily, if needed, for excessive drooling. After several weeks of use, full response was reported by 2 patients, partial response (symptoms controlled for 2 to 8 hours) by 5 patients, and no response by 1 patient. One patient rated the spray not effective and discontinued drug after a few days. Sublingual ipratropium nasal spray may be useful for situations in which drooling would be socially undesirable (Freudenreich et al, 2004).
4) An overview of clozapine-induced hypersalivation explores possible mechanisms involved as well as management options. Potential contributing factors are clozapine's muscarinic M4 receptor stimulation, alpha-2 antagonism and/or interference with the normal swallowing reflex. Published data have not documented any increase in daytime salivary flow rate with clozapine; however, nighttime flow rates have not been studied. Management strategies include clozapine dosage reduction if clinically feasible, sleeping with a towel over the pillow to absorb excess saliva, chewing gum to stimulate swallowing, and as a last resort, an anticholinergic agent or alpha-2 agonist. Because supportive studies are lacking, treatment decisions must be individualized (Davydov & Botts, 2000).
5) In a 50-year-old schizophrenic woman, hypersalivation and sedation developed after several days on clozapine. By day 10, she developed aspiration pneumonia. This prompted the authors to warn that aspiration precautions may be necessary with hypersalivation due to clozapine (Hinkes et al, 1996).
6) Hypersalivation was reported in 16 of 19 patients receiving clozapine therapy. Doses ranged from 75 to 800 milligrams (mg)/day (Lapierre et al, 1980). Nocturnal hypersalivation occurred at a dosage range of 225 to 800 mg/day (Kirkegaard et al, 1982).

3.3.4.G Fecal impaction

1) In postmarketing reports, fecal impaction has occurred in patients receiving clozapine with some cases resulting in death. Treat constipation with adequate hydration and ancillary medications (eg, bulk laxatives) and consider consulting with a gastroenterologist for serious cases (Prod Info FAZACLO(R) orally disintegrating tablets, 2007).
2) A 20-year-old otherwise healthy male receiving clozapine for schizophrenia had fecal impaction and experienced fatal bowel ischemia and infarction following complaints of constipation. During a 1-year period, the patient was titrated up to a clozapine dose of 900 milligrams (mg)/day; additionally, amisulpiride 400 mg twice daily had been added for persistent negative symptoms with good results after one month. He presented to his physician with severe abdominal pain following a 2-day history of constipation and was prescribed medication and returned home. The patient collapsed and died a few hours later before reaching a hospital; subsequently, a postmortem examination discovered the patient had impacted feces leading to bowel-wall ischemia and infarction (Townsend & Curtis, 2006).

3.3.4.H Gastrointestinal hypomotility

1) A review of pharmacovigilance data from the Australian Adverse Drug Reactions Advisory Committee (ADRAC) and New Zealand's Intensive Medicines Monitoring Program (IMMP) identified 74 cases of serious clozapine-induced gastrointestinal hypomotility (CIGH). A total of 102 cases of suspected life-threatening CIGH were compiled using data from ADRAC and IMMP. Cases of CIGH were further identified as serious in the database if they were recorded as: 1) serious or life-threatening constipation or constipation resulting in hospitalization, surgery, or a fatal outcome; 2) fecal impaction; 3) ileus; 4) bowel obstruction, ischemia, necrosis, or perforation; or 5) megacolon. Only cases identified by pharmacovigilance staff as having possible or probable association with clozapine were included from the ADRAC data while 2 authors identified and excluded cases with confounding pathology from the IMMP data. Additionally, multiple reports of the same or similar adverse events for 1 patient were treated as single cases to avoid duplication. There were 57 and 17 cases, respectively, from ADRAC and IMMP data that met the criteria for being cases of serious CIGH. Of these cases, the mortality rate was 27.5% and incidence was higher in males (66.7%) than in females (30.4%). Of the patients who developed serious CIGH, 20% developed it within the first month of treatment, 36.3% within the first 4 months, and 50% within the first year of treatment. The risk seemed to be greater at higher doses of clozapine (535 milligrams/day in fatal cases) (Palmer et al, 2008).

3.3.4.I Heartburn

1) Incidence: 4% (Prod Info FAZACLO(R) orally disintegrating tablets, 2007)
2) Abdominal discomfort/heartburn occurred in 4% of patients treated with clozapine in clinical trials (n=842) (Prod Info FAZACLO(R) orally disintegrating tablets, 2007).

3.3.4.J Ischemic bowel disease

1) A 20-year-old otherwise healthy male receiving clozapine for schizophrenia experienced fatal bowel ischemia following complaints of constipation. During a 1-year period, the patient was titrated up to a clozapine dose of 900 milligrams (mg)/day; additionally, amisulpiride 400 mg twice daily had been added for persistent negative symptoms with good results after one month. He presented to his physician with severe

abdominal pain following a 2-day history of constipation and was prescribed medication and returned home. The patient collapsed and died a few hours later before reaching a hospital; subsequently, a postmortem examination discovered the patient had impacted feces leading to bowel-wall ischemia and infarction (Townsend & Curtis, 2006).

3.3.4.K Nausea

1) Incidence: 5% (Prod Info FAZACLO(R) orally disintegrating tablets, 2007)

2) Nausea occurred in 5% of patients treated with clozapine in clinical trials (n=842) (Prod Info FAZACLO (R) orally disintegrating tablets, 2007).

3) Nausea occurs when the daily dose exceeds 150 milligrams. These adverse effects may disappear with continued administration of the same dose; however, if not, they are managed easily by dose reduction or temporary discontinuation of clozapine (Ayd, 1974a).

3.3.4.L Nausea and vomiting

1) Incidence: 3% (Prod Info FAZACLO(R) orally disintegrating tablets, 2007)

2) Nausea/vomiting occurred in 3% of patients treated with clozapine in clinical trials (n=842) (Prod Info FAZACLO(R) orally disintegrating tablets, 2007).

3) Nausea occurs when the daily dose exceeds 150 milligrams. These adverse effects may disappear with continued administration of the same dose; however, if not, they are managed easily by dose reduction or temporary discontinuation of clozapine (Ayd, 1974a).

3.3.4.M Pancreatitis

1) In postmarketing reports, pancreatitis has occurred in patients receiving clozapine (Prod Info FAZACLO (R) orally disintegrating tablets, 2007).

2) Pancreatitis followed by pericardial effusion occurred in a 17-year-old male patient who was receiving clozapine for the treatment of paranoid schizophrenia. Following 23 days of treatment, during which time the clozapine dose was titrated from 25 milligrams (mg) per day to 175 mg/day, the patient experienced mild epigastric pain and had elevated levels of pancreas amylase and lipase. A diagnosis of pancreatitis was made and the clozapine was discontinued. One day later, the clozapine was resumed at 100 mg/day and the epigastric pain disappeared within 3 days. Amylase and lipase levels returned to normal after 19 days. Four days after decreasing the dose, the patient experienced inspiratory chest pain, increasing pain in both shoulders, and had a heart rate of 120 beats per minute. A CT scan of the chest revealed a pericardial effusion. The clozapine was again discontinued and the patient recovered following cardiocentesis that removed 250 milliliters of slightly hemorrhagic fluid (Wehmeier et al, 2003).

3) In one study of reported cases (n=192) of antipsychotic-induced pancreatitis, 40% of the cases were associated with the use of clozapine at a mean daily dose of 306.7 milligrams. In most patients, time to onset of pancreatitis was within 6 months after initiation of treatment (Koller et al, 2003c).

3.3.4.N Paralytic ileus

1) Patients with paralytic ileus should not receive clozapine. In postmarketing reports, intestinal obstruction/paralytic ileus has occurred in patients receiving clozapine with some cases resulting in death. Treat constipation with adequate hydration and ancillary medications (eg, bulk laxatives) and consider consulting with a gastroenterologist for serious cases (Prod Info FAZACLO(R) orally disintegrating tablets, 2007).

2) Intestinal obstruction necessitating hospitalization occurred in a 51-year-old male and a 35-year-old female with resistant schizophrenia receiving clozapine 275 milligrams (mg)/day for 2 months and 500 mg/day for 4 months, respectively. No other predisposing factors were identified. The patients recovered with conservative management and continued on clozapine therapy with adjunctive dietary measures and stool softeners (Tang & Ungvari, 1999).

3.3.4.O Parotitis

1) A 49-year-old woman receiving clozapine 300 milligrams (mg) daily developed parotitis. She was first noted to have swelling on the right side of her face and pain in her right parotid gland. She received a 7-day course of penicillin and benztropine 2 mg. Her symptoms improved after 1 week (Southall & Fernando, 1999).

3.3.4.P Perforation of intestine

1) Colon perforation with peritonitis and sepsis occurred in a 49-year-old patient receiving clozapine 200 milligrams twice daily for 6 weeks. Clozapine was discontinued and after emergency hemicolectomy and colostomy, the patient was successfully treated with risperidone (Freudenreich & Goff, 2000).

3.3.4.Q Summary

1) Common gastrointestinal effects associated with clozapine therapy include constipation (14%) and nausea (5%). Elderly patients may be particularly susceptible to the anticholinergic effects of clozapine, such as constipation. Intestinal peristalsis leading to fecal impaction, paralytic ileus, and intestinal obstruction has also been reported with some cases resulting in death. Treat constipation with adequate hydration and ancillary medications (eg, bulk laxatives) and consider consulting with a gastroenterologist for serious cases (Prod Info FAZACLO(R) orally disintegrating tablets, 2007).

3.3.4.R Swelling of salivary gland

1) In postmarketing reports, salivary gland swelling has occurred in patients receiving clozapine (Prod Info FAZACLO(R) orally disintegrating tablets, 2007).

2) A 49-year-old woman receiving clozapine 300 milligrams (mg) daily developed parotitis. She was first noted to have swelling on the right side of her face and pain in her right parotid gland. She received a 7-day course of penicillin and benztropine 2 mg. Her symptoms improved after 1 week (Southall & Fernando, 1999).

3) Salivary gland swelling has been reported with clozapine. One case describes transient swelling of the left submandibular salivary gland in a patient on stable clozapine treatment for 13 months (Troia et al, 1996). Another case describes painless, bilateral swelling in the parotid region associated with hypersalivation after only 14 days of therapy (Patkar & Alexander, 1996).

3.3.4.S Vomiting

1) Incidence: 3% (Prod Info FAZACLO(R) orally disintegrating tablets, 2007)

2) Vomiting occurred in 3% of patients treated with clozapine in clinical trials (n=842) (Prod Info FAZACLO (R) orally disintegrating tablets, 2007).

3.3.4.T Xerostomia

1) Incidence: 6% (Prod Info FAZACLO(R) orally disintegrating tablets, 2007)

2) Dry mouth occurred in 6% of patients treated with clozapine in clinical trials (n=842) (Prod Info FAZACLO (R) orally disintegrating tablets, 2007).

3.3.5 Hematologic Effects

Agranulocytosis

Blood coagulation disorder

Disorder of hematopoietic structure

Drug-induced eosinophilia

Hematology finding

Neutropenia

Thromboembolic disorder

3.3.5.A Agranulocytosis

1) Summary

a) In pre-marketing evaluation, the cumulative incidence of agranulocytosis at 1 year was 1.3% (15 of 1743 patients). Agranulocytosis was defined as a neutrophil count of less than 500 cells/millimeters cubed. In the US there have been 585 cases (n=150,409) of agranulocytosis as of August 21, 1997; 19 of which were fatal. Few deaths have been reported since 1977 due to increased knowledge of clozapine-induced agranulocytosis and the importance of white blood cell monitoring (Prod Info Clozaril (R), 2002). One reference reports that the incidence of agranulocytosis following clozapine treatment is 10 to 20 times higher than that of phenothiazines (Oren et al, 1993).

b) Asymptomatic agranulocytosis developing in a patient several months after start of treatment with clozapine for treatment- resistant schizophrenia was initially attributed to clozapine treatment but later was found to be a result of a large B-cell lymphoma. Replacement of clozapine with chlorpromazine and quetiapine resulted in deterioration of the patient's mental state, resulting in hospitalization. During hospitalization, the lymphoma was discovered and was treated with chemotherapy. Clozapine was later reintroduced for better antipsychotic control and was continued with good effect, despite significant neutropenia secondary to the chemotherapy (Hundertmark & Campbell, 2001).

c) In data evaluating 11,555 patients, the majority of agranulocytosis occurred within the first three months of drug therapy; older patients and women appeared to be at an increased risk. Recent studies suggest people of Jewish and Asian origin may also be at higher risk (Meged et al, 1999; Munro et al, 1999). The hazard can be reduced by weekly monitoring of the white blood cell count (Alvir et al, 1993). Some cases of clozapine-induced agranulocytosis have been successfully treated with filgrastim or sargramostim (Gullion & Yeh, 1994). The mechanisms of clozapine-induced agranulocytosis have been reviewed (Pirmohamed & Park, 1997a)

2) Incidence: 1.3%

3) LITERATURE REPORTS

a) Two 18-year-old, female monozygotic twins developed schizophrenia within 2 weeks of one another and both developed agranulocytosis after 9 weeks of treatment with clozapine. Twin A responded poorly to initial treatment with haloperidol (prominent extrapyramidal symptoms) and was switched to sulpiride 400 milligrams (mg) per day and clozapine 6 mg/day. Her condition worsened and she was given 4 electroconvulsive (ECT) treatments. She was discharged, fully remitted, at 6 weeks after the start of clozapine treatment, with a maintenance dose of clozapine 150 mg/day. At discharge her leucocyte count was 13,700/milliliter (mL). At 10 weeks after start of clozapine treatment, her leukocyte count was 1400/mL. Clozapine was discontinued. Her leukocyte level normalized within 3 weeks, but psychotic symptoms recurred. Complete remission was obtained with risperidone 5 mg/day. Because of her sister's experience with haloperidol, twin B was treated immediately with clozapine, up to a dose of 300 mg/day. Because of insufficient response, she was given 8 ECT treatments. After 8 weeks of treatment, she was discharged, fully remitted. Her leukocyte count at discharge was 6100/mL. By 9 weeks after start of clozapine treatment, her leukocyte count was 1800/mL. Clozapine was discontinued, resulting in a recurrence of psychotic symptoms. Leukocytopenia persisted for 11 weeks. After control of her psychotic symptoms, her leukocyte level normalized. Her psychotic symptoms disappeared only after addition of oxazepam 15 mg/day to her regimen of risperidone 4 mg/day. This case report suggests that genetic factors play a role in the timing of onset of schizophrenia and also on the timing of agranulocytosis in response to clozapine treatment (Horacek et al, 2001).

b) In a study of 50 Jewish clozapine recipients, a 20-year-old female of Ashkenazi origin with the human leukocyte antigens (HLA) B38 and DR4 developed agranulocytosis with sepsis 12 weeks after initiation of clozapine (last dose: 300 milligrams (mg)/day). She recovered with antibiotic treatment and colony stimulating factor support. Two other females, a 20-year-old of Ashkenazi origin with HLA-B38 and a 33-year-old of non-Ashkenazi origin without suspected HLA haplotypes, experienced neutropenia. Overall, 38% of the study sample were of Ashkenazi origin, yet they represented two-thirds of those with resultant neutropenia/agranulocytosis. An additional 7 individuals manifested abnormalities in white blood cell count such as reduction that did not meet criteria for neutropenia (n=4); eosinophilia (n=2); and leukocytosis (n=1). Five of 7 (71%) in this group were of Ashkenazi origin. Because of the small numbers involved, none of the comparisons reached statistical significance. The authors note that the HLA susceptibility antigens are B38 and DR4 in Jews, and B7 and DR2 in non-Jews. Investigation is continuing as to whether a rare allele of these HLA haplotypes is responsible for agranulocytosis in the presence of clozapine and whether other non-major histocompatibility complex genes might be involved (Meged et al, 1999).

c) The cumulative incidence of clozapine-induced agranulocytosis was 0.73%, based on the Clozaril Patient Monitoring System (1990 to 1997, n=12,760) in the United Kingdom and Ireland. The peak onset was during weeks 6 to 18 of therapy. Only 2 of 93 cases were fatal. In this registry, the average and mean maximum clozapine doses were 388 and 462 milligrams/day, respectively. Cox proportional hazards regression analysis revealed a 53% increased risk with each 10-year increase in age at clozapine initiation (p=0.0001) and a 2.4 times higher risk among Asians compared to Caucasians (p=0.03). The authors categorized "Asian" and "Oriental" races separately without explanation. Maximum dose was inversely associated with risk (Munro et al, 1999).

d) Toxicity, inborn errors of metabolism, and/or immunological reactions may be involved in clozapine-induced agranulocytosis (Claas, 1989; Hasegawa et al, 1994). Other authors have suggested that genetic factors marked by major histocompatibility complex haplotypes may be associated with the susceptibility to agranulocytosis (Lieberman et al, 1990; Joseph et al, 1992). There is a 20% incidence in a Jewish group of patients strongly correlating with the presence of the haplotype HLA-B38, DR4, or DQW3. In addition, clozapine-induced agranulocytosis was reported in two non-Jewish patients, both of whom expressed HLA-B38 but did not express DR4 or DQW3 (Joseph et al, 1992).

e) A 37-year-old, Ashkenazic Jewish man developed fatal agranulocytosis and FEVER 11 weeks after starting clozapine therapy. At 10 weeks, the patient's white blood cell count fell to 3900 cells/cubic millimeter (mm(3)) with a neutrophil count of 1400 cells/mm(3) and lymphocyte count of 2000 cells/mm (3). The clozapine was discontinued. Four days later the patient was admitted with fever and severe agranulocytosis (neutrophil count 120 cells/mm(3), lymphocyte count 810 cell/mm(3)). Filgrastim, piperacillin and gentamicin were initiated. However, 6 hours later the patient collapsed and was found to have severe HYPERGLYCEMIA (blood glucose 1000 milligrams/dl) and LACTIC ACIDOSIS (pH 7.13; bicarbonate 10 mEq/liter, and lactate 79.3 milligrams/deciliter). Despite intensive treatment the patient developed intractable HYPOTENSION, ANURIA and CARDIAC ARREST. He died 36 hours after admission (Koren et al, 1997).

f) Clozapine-induced agranulocytosis was prolonged in 3 patients with the initiation of olanzapine therapy. The granulocyte recovery time was 21 days, as compared to an average 3 days in a group of patients not receiving olanzapine. The authors recommend avoiding olanzapine in this setting until hematologic indices have returned to normal (Flynn et al, 1997).

g) Five cases of clozapine-induced agranulocytosis were reported as being successfully treated with rG-CSF (filgrastim) (Gullion & Yeh, 1994). The patients were treated with at least 300 micrograms/day of filgrastim administered subcutaneously with the onset of agranulocytosis, increasing by 300 micrograms/day for the first 3 days to a total of 900 micrograms/day until resolution of agranulocytosis. Time from onset until resolution was a mean of 8.2 days, as compared to a historical control group of 15.7 days. One patient was successfully treated with sargramostim 3 micrograms/kilogram/day for 4

days (Oren et al, 1993).

h) Clozapine has been associated with a significant risk for granulocytopenia during clinical trials at therapeutic dosages and onset of symptoms occur between the 6th and 18th week of therapy(Bablenis et al, 1989); (Povlsen et al, 1985).

3.3.5.B Blood coagulation disorder

1) Summary

a) An increased aPPT of 34.2 sec (control 27 sec) was reported as a result of a positive lupus anticoagulant in a 39 year-old male after therapy with clozapine (225 milligrams/day), Klonopin, Cogentin, and Lopid. Normal laboratory tests included PT (14 sec), CBC, TT (21 sec), and a negative ANA titer (Kanjolia et al, 1997).

3.3.5.C Disorder of hematopoietic structure

1) Summary

a) Adverse effects that were temporally associated with clozapine and occurred in less than 1% of patients include ANEMIA and LEUKOCYTOSIS. Other adverse effects voluntarily reported by the manufacturer include ELEVATED HEMOGLOBIN, ELEVATED HEMATOCRIT, INCREASED ERYTHROCYTE SEDIMENTATION RATE, THROMBOCYTOPENIA, and SEPSIS; a causal relationship could not be determined (Prod Info Clozaril(R), 2002).

2) LITERATURE REPORTS

a) Aplastic anemia developed in a 53-year-old man with Parkinson's disease following the administration of clozapine. The patient developed aplastic anemia after taking clozapine 50 milligrams daily for the treatment of dopamine-induced psychosis with hallucinations. The man developed a fever one week after beginning therapy. Blood tests exposed a severe form of drug-induced aplastic anemia. Clozapine was discontinued and the patient received treatment including blood transfusions, hematopoietic growth factors and antibiotics. The aplastic anemia resolved within 14 days and the patient's hallucinations and delusions were successfully treated with quetiapine (Ziegenbein et al, 2003).

b) N-DESMETHYLCLOZAPINE, the major metabolite of clozapine, is toxic. N-desmethylclozapine is further metabolized to an unstable compound that is toxic to hemopoietic precursors of both myeloid and erythroid lineages (Gerson et al, 1994).

3.3.5.D Drug-induced eosinophilia

1) Summary

a) In clinical studies, 1% of patients developed eosinophilia; rarely were cases substantial. If a differential count indicates a total eosinophil count above 4000 cell/cubic millimeter (mm(3)), interrupt therapy until the count falls below 3000 cells/mm(3) (Prod Info Clozaril(R), 2002). The onset of eosinophilia usually occurs after 3 to 5 weeks of treatment (Meged et al, 1999; Chatterton, 1997; Pirmohamed & Park, 1997a).

2) Incidence: 1%

3) LITERATURE REPORTS

a) A In a study of 50 Jewish clozapine recipients, two males aged 34 and 46 years developed eosinophilia 4 and 6 weeks after clozapine initiation, respectively. Their most recent clozapine doses were 150 and 300 milligrams/day, respectively. Their eosinophil counts peaked at 1365 and 984 per cubic millimeter, respectively (Meged et al, 1999).

b) In a study comparing the incidences of eosinophilia and neutropenia for patients on clozapine (n=41) versus haldol (n=29), no significant differences were found. During a 6 month period, patients were monitored weekly for blood dyscrasias. Eosinophilia was defined as an absolute eosinophil level in excess of 500 cells/cubic millimeter (mm(3)) and neutropenia was defined as an absolute neutrophil count below 2000 cells/mm(3). In the clozapine group, eosinophilia and neutropenia occurred in 32% and 7% of the patients, while the occurrence in the haloperidol group was 31% and 7%, respectively. Most patients developed eosinophilia in the first 6 weeks. No significant differences were found between men and women, ethnic groups, or age groups. Also, eosinophilia did not predict neutropenia (Ames et al, 1996). In a retrospective review, the rate of eosinophilia reported at an Australian hospital was 13% (Chatterton, 1997).

c) A 30-year-old woman receiving clozapine 200 milligrams/day developed eosinophilia with a peak of 1320/microliter on treatment day 26 (Lucht & Riestschel, 1998). Clozapine was discontinued and the eosinophil count decreased to 220/microliter on day 45. Also of note is that neutropenia developed with a low of 1800/microliter on day 32 and IgE increased to 254 IU/deciliter (reference value less than 120 IU/deciliter).

d) A 37-year-old man developed eosinophilia (700 cells/cubic millimeter) 2 weeks after beginning clozapine therapy (Amital et al, 1997). The eosinophil count remained stable for 7 weeks until he developed severe agranulocytosis, necessitating clozapine discontinuation. After 3 weeks the granulocyte count returned to normal. It has been theorized that eosinophilia predicts later agranulocytosis.

e) Eosinophilia developed in a 38-year-old schizophrenic patient following 5 weeks of clozapine therapy (eosinophil count of 1500 cells/cubic millimeter). Within 4 days of clozapine discontinuation, leukocyte and differential counts returned to normal and clozapine was restarted with no further abnormalities

(Tihonen & Paanila, 1992). Another case of eosinophilia has been reported when treated therapeutically with clozapine; anecdotal knowledge of several more cases exists (Stricker & Tielens, 1991).

3.3.5.E Hematology finding

1) N-desmethylclozapine, the major metabolite of clozapine, is toxic. N- desmethylclozapine is further metabolized to an unstable compound that is toxic to hemopoietic precursors of both myeloid and erythroid lineages. Therapeutic use of clozapine has been associated with neutropenia, agranulocytosis, neutrophilia, and rare eosinophilia. A few recent studies suggest patients of Jewish and Asian origin may be at higher risk for agranulocytosis. Adverse effects that were temporally associated with clozapine and occurred in patients are anemia and leukocytosis. Other effects voluntarily reported by the manufacturer include sepsis, thrombocytopenia, thrombocytosis, pulmonary embolism, deep vein thrombosis, elevated hemoglobin, elevated hematocrit, and increased erythrocyte sedimentation rate and a causal relationships that could not be determined.

2) Plasma and red-cell selenium concentrations were significantly (p less than 0.01) lower in schizophrenic patients treated with clozapine (n=54) compared to patients with mood disorders (n=36), schizophrenic patients not treated with clozapine (n=41) and a healthy control group (n=56). The plasma and red-cell selenium concentrations (micromoles/liter) were 1.28 +/- 0.33, 1.47 +/- 0.57; 1.39 +/- 0.29, 1.70 +/- 0.40; 1.47 +/- 0.41, 1.70 +/- 0.48; and 1.49 +/- 0.30, 1.80 +/- 0.58 for the four groups respectively. Selenium deficiency has been associated with cardiomyopathy and with myocarditis and these same adverse effects are also known to occur with clozapine treatment. Although it could not be determined by this study whether clozapine causes selenium deficiency or if treatment-resistant schizophrenic patients (who are often treated with clozapine) are selenium deficient prior to treatment, the authors suggested that it may prove beneficial to provide selenium supplementation to schizophrenic patients receiving clozapine (Vaddadi et al, 2003).

3.3.5.F Neutropenia

1) Summary

a) In clinical studies, neutropenia occurred in 2.7 to 22% of patients The peak onset was during weeks 6 to 18 of therapy. Cox proportional hazards regression analysis revealed a 17% decreased risk with each 10-year increase in age at clozapine initiation and a 77% greater risk in African-Caribbean subjects compared to Caucasians. The racial difference may be partially explained by significantly lower baseline white blood cell counts (an independent predictor of neutropenia) among African-Caribbeans. Maximum dose was inversely associated with risk (Prod Info Clozaril(R), 2002; Munro et al, 1999; Atkin et al, 1996; Hummer et al, 1997a).

2) Incidence: 3%

3) LITERATURE REPORTS

a) Although recommended by the manufacturer, the emergence of neutropenia in clozapine-treated patients has not required discontinuation of clozapine therapy in several cases. In a retrospective chart review, researchers assessed outcome over 600 days in patients (n=5) who continued clozapine therapy despite the development of neutropenia in the "red alert zone" (ie, white blood cell count below 3000 per cubic millimeter (mm(3)) or absolute neutrophil count (ANC) below 1500 per mm(3)). All five patients were maintained on clozapine after initial onset and recovery of neutropenia with no recurrence of neutropenia during the observation period. In three patients, the neutrophil counts remained at or just above the "amber zone" (ie, ANC 1500 to 2000 per mm(3)) throughout long-term follow-up while no hematological abnormalities were observed in the other two patients. Favorable response to clozapine treatment was observed in four of the five patients as assessed by Clinical Global Impression-Severity scores. The authors suggest the need for methods to differentiate between benign neutropenia and neutropenia progressing to agranulocytosis (Ahn et al, 2004).

b) TRANSIENT NEUTROPENIA developed in a 44-year-old Caucasian man after taking clozapine (200 to 400 milligrams (mg)/day) for the treatment of paranoid schizophrenia. Twenty-seven weeks after initiation of clozapine therapy, the patient's morning neutrophil count had declined to 1300/cubic millimeter (mm(3)), while the total white blood cell (WBC) count was within a normal range (4100/mm (3)). However, the blood sample taken the same afternoon at 2 p.m. showed that the neutrophil count had returned to normal (2200/mm(3)) and the total WBC count had risen to 5500/mm(3). Blood tests were continued twice a week and whenever the morning neutrophil counts fell between 1200 and 1900/mm(3) (WBC counts: 4100 to 4700/mm(3)), they were between 2200 and 2700/mm(3) in the afternoon (WBC counts: 5400 to 5800/mm(3)). Because the neutrophil counts were normal in the afternoon, the risk of the patient developing agranulocytosis was considered to be low and clozapine was continued at a dose of 200 mg daily. Decreased neutrophil counts were no longer observed after 30 weeks of clozapine therapy (Esposito et al, 2003).

c) After 20 months of clozapine treatment, the white blood cell (WBC) count declined over a four-month period and resulted in neutropenia in a 36-year-old chronic, paranoid schizophrenic man. During the prior 20 months of clozapine therapy (400 milligrams per day), the patient's WBC count was stable and ranged between 6000 and 10000 cubic millimeters (mm(3)). On the 21st and 22nd months of treatment, his WBC count decreased to an average of 4500 with an absolute neutrophil count (ANC) of 2300. By the fourth week of the 25th month of treatment, his WBC count continued its steady decline and was 2400 with an ANC of 1100. At that time the patient developed a high fever and the diagnosis of neutropenia was made and the clozapine was discontinued (Taman et al, 2001).

d) The cumulative incidence of clozapine-induced neutropenia was 2.7%, based on the Clozaril Patient

Monitoring System (1990 to 1997, n=12,760) in the United Kingdom and Ireland. The peak onset was during weeks 6 to 18 of therapy. In this registry, the average and mean maximum clozapine doses were 388 and 462 milligrams/day, respectively. Cox proportional hazards regression analysis revealed a 17% decreased risk with each 10-year increase in age at clozapine initiation (p=0.0003) and a 77% greater risk in African-Caribbean subjects compared to Caucasians (p=0.003). The age association is opposite that observed for agranulocytosis risk. The racial difference may be partially explained by significantly lower baseline white blood cell counts (an independent predictor of neutropenia) among African-Caribbeans. Maximum dose was inversely associated with risk (Munro et al, 1999).

e) Neutropenia has been reported in up to 22% of patients therapeutically treated with clozapine (Hummer et al, 1997a).

f) A 17-year-old boy with severe schizophrenic disorder was able to continue clozapine treatment (50 milligrams) despite decreased leukocytes (2480 cells/cubic millimeter (mm(3)), decreased neutrophil granulocytes (800 cells/mm(3)) and an acute febrile respiratory infection. He received G-CSF 300 micrograms with an increase in leukocytes and neutrophils 6 hours later (2680/mm(3) and 1250/mm(3), respectively), and normal body temperature the next morning. Over the next 2 days he received 2 more G-CSF injections. He continued clozapine for an additional 38 weeks until he experienced another decrease in granulocytes and clozapine was discontinued. One year later, the patient again required clozapine and after 20 weeks of therapy required G-CSF. After 2 doses of G-CSF 300 mcg, he was again maintained on clozapine for an additional 8 months (Sperner-Unterweger et al, 1998).

g) A 29-year-old male with schizophrenia was able to reinitiate clozapine therapy despite previous neutropenia after receiving pretreatment with lithium. Clozapine was previously discontinued after a decrease in granulocytes to 1400 cells/cubic millimeter. After failing other antipsychotics, lithium was initiated and increased to 0.8 to 1.1 millimoles/liter. Clozapine was introduced 2 weeks later at 12.5 milligrams (mg) and increased to 200 mg/day. Over the next 9 months white blood cell counts remained stable. The rational for lithium use was to increase granulopoiesis by enhancement of the production of granulocyte-macrophage colony-stimulating factor (Silverstone, 1998).

3.3.5.G Thromboembolic disorder

1) Summary

a) Six cases of PULMONARY EMBOLISM and 6 cases of VENOUS THROMBOSIS were reported during clozapine therapy. The adverse reaction was fatal in 5 cases with the affected patients being 3 women and 9 men aged 25-59 years. Complications that included VENOUS THROMBOEMBOLISM developed within the first 3 months of clozapine therapy in 8 of the patients (Hagg & Soderstrom, 2000). Adverse effects voluntarily reported by the manufacturer are THROMBOCYTOSIS and DEEP VEIN THROMBOSIS; a causal relationship could not be determined (Prod Info Clozaril(R), 2002).

2) LITERATURE REPORTS

a) Between April 1989 and March 2000, 6 cases of pulmonary embolism and 6 cases of venous thrombosis were reported during clozapine therapy. The adverse reaction was fatal in 5 cases. The affected patients were 3 women and 9 men. Venous thromboembolism (VTE) complications developed within the first 3 months of clozapine therapy in 8 of the patients. The mean clozapine dose was 277 milligrams per day (Hagg & Soderstrom, 2000). After reviewing the available literature on case reports of VTE from the Swedish Adverse Reactions Advisory Committee, the authors suggest that VTE may not be clozapine associated after all and that other risk factors, such as reduced motor activity, should be taken into account. The authors concluded that an increased risk of VTE seems to be a general property of the antipsychotic drugs (Thomassen et al, 2000).

3.3.6 Hepatic Effects

Hepatotoxicity

Increased liver enzymes

Liver finding

3.3.6.A Hepatotoxicity

1) Summary

a) In clinical trials of clozapine, LIVER FUNCTION ABNORMALITIES occurred; in patients with clinically relevant elevations or with jaundice, clozapine should be discontinued. CHOLESTASIS, HEPATITIS, and JAUNDICE were voluntarily reported in postmarketing experience (Prod Info Clozaril (R), 2002). A 39-year-old male also developed fatal acute fulminant LIVER FAILURE with encephalopathy and coagulopathy after 8 weeks of clozapine therapy (Macfarlane et al, 1997).

3.3.6.B Increased liver enzymes

1) Summary

a) Clozapine, in therapeutic dosages, has been associated with a rise in liver enzymes in 37. 3% to

61% of patients (Hummer et al, 1997a; Gaertner et al, 2001). A case report also notes this adverse effect (Panagiotis, 1999).

2) LITERATURE REPORTS

a) In a prospective study, the incidence of alanine aminotransferase (ALT) elevation to more than twice the upper normal limit was statistically greater with clozapine (37%, n=167) than with haloperidol (17%, n=71). Among those receiving clozapine, the rates of elevations in aspartate aminotransferase (AST) and gamma-glutamyl transpeptidase (GGT) to more than twice the upper normal limit were 12% and 15%, respectively. No such increases in bilirubin or alkaline phosphatase occurred in clozapine-treated patients. These effects were transient in the majority of patients (disappearing by week 13) with no clinical manifestations reported (Hummer et al, 1997a).

b) A 30-year-old man developed abnormal liver enzymes and a grand mal seizure while receiving clozapine 400 milligrams (Panagiotis, 1999). Liver enzymes and electroencephalogram (EEG) were normal before therapy. After 4 weeks, he presented with a grand mal seizure and clozapine was reduced to 300 milligrams. Liver enzymes were evaluated 5 days after the seizure. The aspartate aminotransferase and gamma-glutamyl transferase were 3 times the upper limits of normal and the alanine aminotransferase was 5 times the upper limits of normal. Clozapine was discontinued.

3.3.6.C Liver finding

1) Liver function abnormalities have occurred with clozapine therapy that include elevated liver enzymes, liver failure, jaundice, hepatitis and cholestasis.

3.3.7 Immunologic Effects

Drug-induced lupus erythematosus, Systemic

Immune hypersensitivity reaction

Immunology finding

Systemic lupus erythematosus

3.3.7.A Drug-induced lupus erythematosus, Systemic

1) Summary

a) Two cases of lupus-like reactions have been reported with clozapine therapy (Kanjolia et al, 1997; Wickert et al, 1994).

2) LITERATURE REPORTS

a) A positive lupus anticoagulant, with resultant increased aPTT, was reported in an adult male taking clozapine (225 milligrams/day), Klonopin, Cogentin and Lopid. The etiologic relationship of clozapine to the lupus anticoagulant is probable (Kanjolia et al, 1997).

b) A case of systemic lupus erythematosus-like reaction was reported in a 39-year-old man taking 300 milligrams per day of clozapine for paranoid schizophrenia. The patient rapidly improved over 5 days following discontinuation of the clozapine. The symptom complex included: fever, fatigue, cough, chest pain, arthralgia, elevated activated partial thromboplastin time, and other hematological abnormalities (Wickert et al, 1994).

3.3.7.B Immune hypersensitivity reaction

1) Summary

a) Hypersensitivity reactions have been noted in a few case reports during clozapine therapy. Monitor plasma levels if a hypersensitivity reaction is suspected (Haack et al, 2003; Stanislav & Gonzalez-Blanco, 1999; Jaunkalns et al, 1992; Stoppe et al, 1992).

2) LITERATURE REPORTS

a) A hypersensitivity reaction to clozapine manifested as fever, bilateral pleural effusions and rapidly spreading papular rash in a 37-year-old woman 9 days after initiation and titration to 150 milligrams/day. Other etiologies were ruled out. Signs and symptoms began to resolve within a week of discontinuing clozapine (Stanislav & Gonzalez-Blanco, 1999).

b) A 33-year-old woman with chronic paranoid schizophrenia refractory to numerous neuroleptics started clozapine at 25 milligrams daily increments. On day 15, fever myalgia, arthralgia, and urticarial plaques on elbows and knees developed. Clozapine was stopped and symptoms abated. All tests including rechallenge with clozapine indicated that the extremely high titers of antimyeloperoxidase antibodies may have contributed to the pathogenesis of the syndrome. The relationship between idiosyncratic drug reactions, especially agranulocytosis, and myeloperoxidase system was described (Jaunkalns et al, 1992).

c) A 69-year-old woman suffering from chronic paranoid schizophrenia received clozapine for three weeks with no complications. For unknown reasons clozapine was discontinued. Two years later and 1

day after the first dose of clozapine, this patient developed an alarming, life-threatening allergic asthmatic reaction requiring intensive care treatment. When clozapine was restarted, the patient had a similar asthma-like attack. This reaction could be a delayed hypersensitivity or pseudoallergic reaction to the drug. This reaction is not due to its weak binding to D, and D2 dopamine receptors, or the blockage of S2 serotonergic, alpha, adrenergic, muscarinic, and H1 histamine receptors (Stoppe et al, 1992).

3.3.7.C Immunology finding

1) Malaise and hypersensitivity reactions occurred with clozapine therapy.

3.3.7.D Systemic lupus erythematosus

See Drug Consult reference: DRUG-INDUCED SYSTEMIC LUPUS ERYTHEMATOSUS

3.3.8 Musculoskeletal Effects

Musculoskeletal finding

Pain

Polyserositis

Rhabdomyolysis

Serum creatinine raised

3.3.8.A Musculoskeletal finding

1) Summary

a) In clinical trials (n=842), during clozapine therapy adverse effects temporally associated with clozapine and occurring at a frequency less than 1% included TWITCHING. A voluntary postmarketing report noted MYASTHENIC SYNDROME however a causal relationship could not be determined (Prod Info Clozaril(R), 2002).

2) Muscle weakness, muscle spasms, muscle pain, back pain, neck pain, and leg pain occurred in patients with clozapine therapy. Adverse effects temporally associated with clozapine and occurring at a lower frequency include twitching and joint pain. Other less common effects include rhabdomyolysis, lupus-like findings, cpk elevations, and myasthenic syndrome.

3.3.8.B Pain

1) Summary

a) In clinical trials, MUSCLE WEAKNESS, MUSCLE SPASMS, MUSCLE PAIN, BACK PAIN, NECK PAIN, and LEG PAIN occurred in 1% of patients (n=842) during clozapine therapy. JOINT PAIN was temporally associated with clozapine and occurring at a frequency less than 1% (Prod Info Clozaril(R), 2002).

3.3.8.C Polyserositis

1) Summary

a) Polyserositis developed in a 74-year-old man after receiving clozapine (initial, 25 milligrams (mg) daily, then increased by 12.5 mg increments at weekly intervals) for the treatment of schizoaffective disorder. Initial symptoms, including dry cough, chills, and fever, developed twenty days after the initiation of therapy. He was treated for an assumed chest infection; however, respiratory symptoms worsened and the patient developed a PERICARDIAL EFFUSION and BILATERAL PLEURAL EFFUSION. Clozapine was withdrawn and systematic symptoms resolved within a week (Lim et al, 2003).

3.3.8.D Rhabdomyolysis

1) Summary

a) A 42-year-old man receiving clozapine and being treated for polydipsia developed rhabdomyolysis during the correction of the hyponatremia. After correction of his hyponatremia, his creatine kinase (CK) level was 8184 units/L and then 6186 units/L; however at 68 hours after admission, his CK peaked at 62,730 units/L. He had no muscle aches. To prevent acute renal insufficiency, high-volume alkaline diuresis was initiated. The CK concentration fell and returned to normal after 14 days. The authors feel that the rhabdomyolysis may have been enhanced by the use of clozapine (Wicki et al, 1998).

3.3.8.E Serum creatinine raised

1) Summary

a) Clozapine may be associated with increases in creatine kinase (CK), without features of neuroleptic malignant syndrome, and mild MYOPATHY. In 37 consecutive clozapine-treated outpatients, weekly CK levels were evaluated. Extreme CK elevations (greater than 20,000 International Units/Liter(IU/L)) without myoglobinuria occurred in 3 patients, and moderate CK elevation (between 725 and 20,000 IU/L) in 10 patients. Six patients in the moderately elevated CK group also had MUSCLE WEAKNESS. Five patients had mild myopathic dysfunction by electromyography. The CK elevations were not dependent upon clozapine dose (Scelsa et al, 1996).

3.3.9 Neurologic Effects

Dizziness

Dystonia

EEG finding

Headache

Movement disorder

Myoclonus

Neuroleptic malignant syndrome

Neurological finding

Paralysis

Seizure

Somnolence

Stuttering

3.3.9.A Dizziness

1) Summary

a) In clinical trials (n=842), dizziness and VERTIGO occurred in 19% of patients during therapeutic use of clozapine (Prod Info Clozaril(R), 2002).

2) Incidence: 19%

3.3.9.B Dystonia

1) Summary

a) During the first few days after initiating treatment with an antipsychotic medication, symptoms of dystonia may occur in susceptible individuals. Symptoms may include spasm of neck muscles, which may progress to tightening of the throat, swallowing difficulty, breathing difficulty, and/or protrusion of the tongue. These symptoms can occur at low doses but most often occur (and occur with a greater severity) with high potency and at higher doses of first generation antipsychotic medications. Males and younger age groups appear to be at greater risk for developing acute dystonia (Prod Info CLOZARIL(R) oral tablets, 2008).

b) Several case reports note dystonic reactions in patients during therapeutic use of clozapine (Mendhekar & Duggal, 2006)(Elliott et al, 2000)(Molho & Factor, 1999; Poersch et al, 1996; Kastrup et al, 1994). In the manufacturer's clinical trials (n=842), a few cases of tardive dyskinesia have also been reported in patients receiving clozapine; however, a causal relationship could not be established(Prod Info Clozaril(R), 2002). Atypical antipsychotics such as clozapine are associated with a lower risk of extrapyramidal symptoms (EPS) than conventional antipsychotics because of higher (ie, more balanced) serotonin-to-dopamine blockade ratios. This may also partially explain the decreased incidence of tardive dyskinesia with atypical agents, as one proposed mechanism of tardive dyskinesia involves "supersensitivity" to chronic, unopposed dopamine blockade (Glazer, 2000; Reynolds, 2000).

2) A case of clozapine induced tardive dyskinesia occurred in a 47-year-old woman with a history of with schizophrenia and hypothyroidism. Significant past medical history include extrapyramidal side effects from haloperidol. The patient's concurrent medications included levothyroxine (100 mg/day) and clozapine (150

mg/day). She presented with dyskinetic movements of the tongue and horizontal grinding movements of the lower jaw 7-months after starting clozapine. She was initially and unsuccessfully treated by discontinuing her levothyroxine for 8 weeks; her dyskinetic movements persisted and her thyroid stimulating hormone level increased. Diagnostic testing, which included computed tomography scan and electroencephalogram, were unremarkable. She was restarted on levothyroxine and also given a sequential trial of propranolol (80 mg/day) and tetrabenazine (125 mg/day) with improvement only in her thyroid profile. She subsequently was diagnosed with tardive dyskinesia and an attempt to reduce her clozapine dose to 125 mg/day failed. The dose reduction worsened her psychotic symptoms requiring an even higher dose of clozapine (200 mg/day) to manage her schizophrenia. Neither reduction nor increase of her clozapine dose improved the dyskinetic movements, which she continued to exhibit (Mendhekar & Duggal, 2006).

3) An acute dystonic reaction involving the tongue and neck developed in a 44-year-old male inpatient the day after a 50-milligram (mg) clozapine dosage increase to 450 mg/day. Despite a 20-year history of schizophrenia, extrapyramidal symptoms and tardive dyskinesia had not been previously documented. However, a pseudoparkinsonian tremor and orofacial movements consistent with tardive dyskinesia were noted on admission. His outpatient medication regimen had included clozapine and haloperidol. At the time of the dystonic reaction, the only concomitant medications were vitamin E and aspirin. The dystonia abated following a dose of intramuscular diphenhydramine (Elliott et al, 2000).

4) Tardive dystonia characterized by left rotational torticollis with intermittent spasms was attributed to clozapine 825 milligrams/day in a 37-year-old male with a 21-year history of schizophrenia. The dystonia first appeared 2 years after initiation of clozapine monotherapy and continued to worsen despite daily trihexyphenidyl. Other concomitant medications included metformin and glyburide. The torticollis continued unabated 4 years later, as the patient was intolerant to increased dosages of trihexyphenidyl (Molho & Factor, 1999).

5) 58-year-old patient treated for psychosis with clozapine 600 milligrams and benperidol 30 milligrams daily experienced episodes of ASTERIXIS, tachycardia and sweating, exacerbated by hypoglycemia (blood sugar 65 to 75 milligrams/deciliter). The symptoms disappeared upon reduction in an oral hypoglycemic agent that the patient was taking concurrently (Poersch et al, 1996).

6) A case of acute DYSTONIA manifested as retrocollic torsion and dystonic cramps of the tongue and mouth was reported after six weeks of therapy with clozapine at a dose of 400 milligrams/day. The dystonia was successfully treated with biperiden and the clozapine tapered to 250 milligrams/day. Biperiden was then discontinued without further incidences of dystonia (Kastrup et al, 1994).

3.3.9.C EEG finding

1) Summary

a) EEG changes have been noted in patients with clozapine use. There is some disagreement on whether these changes are dose-related occurrences or normal baselines within the patient population being treated with clozapine (Silvestri et al, 1998; Welch et al, 1994; Tihonen et al, 1991; Spatz et al, 1978).

2) LITERATURE REPORTS

a) One author states that most patients receiving clozapine treatment have abnormal EEGs. However, they believed that abnormal EEGs should not contraindicate increase of the clozapine dose beyond 600 milligrams/day if no signs of clinical adverse effects are observed (Tihonen et al, 1991). However, another author advocates lowering the clozapine dose by 25 to 50 milligrams per day and adjusting the dose weekly until the EEG returns to baseline (Welch et al, 1994).

b) In a group of 35 patients, 26 (74%) were found to have evidence of EEG abnormalities (slowing, dysrhythmia, or paroxysmal discharges) during clozapine treatment (Welch et al, 1994). EEGs were measured as a means of detecting clinical toxicity and reducing the incidence of seizures.

c) Eight out of 12 psychiatric patients receiving clozapine were found to have interictal epileptiform abnormalities on EEG. Six of the 8 had seizures while receiving clozapine. The abnormalities were focal or multifocal with a predominance of left temporal foci (Silvestri et al, 1998).

d) Changes in the EEG pattern similar to those caused by other neuroleptics has been seen in patients receiving clozapine. Monthly EEGs were evaluated in 34 schizophrenic patients treated with clozapine 100 to 700 milligrams daily. After 2 to 6 months of treatment, the EEG in 6 patients showed dysrhythmias and other changes similar to those caused by other neuroleptics. In 2 months after discontinuation of clozapine, the EEG had reverted to the pretreatment pattern (Gross & Langner, 1966). Similar results have been reported by other authors (Spatz et al, 1978).

3.3.9.D Headache

1) Summary

a) In clinical trials (n=842) 7% of patients experienced headache with clozapine therapy (Prod Info Clozaril(R), 2002).

2) Incidence: 7%

3.3.9.E Movement disorder

1) Summary

a) In clinical trials (n=842) 6% of patients experienced TREMOR. The following adverse effects were also reported in 1% to 4% of patients: HYPOKINESIA, AKINESIA, RIGIDITY, AKATHISIA, HYPERKINESIA, WEAKNESS, and ATAXIA. Adverse effects that were temporally associated with

clozapine and occurred in less than 1% of patients include TICS, POOR COORDINATION, INVOLUNTARY MOVEMENTS, DYSARTHRIA, HISTRIONIC MOVEMENTS, SHAKINESS, PARKINSONISM, and NUMBNESS (Prod Info Clozaril(R), 2002). One case of asterixis has been reported (Poersch et al, 1996).

3.3.9.F Myoclonus

1) Summary

a) Myoclonic jerking and EPILEPTIFORM MOVEMENTS have developed in patients taking therapeutic doses of clozapine (Prod Info Clozaril(R), 2002); (Antelo et al, 1994). A case report noted that 40-year-old man developed OROLARYNGEAL MYOCLONUS after 1 month of clozapine therapy. The myoclonus resolved with a reduction in clozapine dose (Knoll, 1997).

3.3.9.G Neuroleptic malignant syndrome

1) Summary

a) The estimated overall incidence of neuroleptic malignant syndrome (NMS) is 1% in patients receiving neuroleptics. Although the incidence is thought to be less with clozapine than with other neuroleptics, there are reports in the literature describing this syndrome following therapy with clozapine, some in conjunction with other neuroleptics or lithium. The syndrome generally occurs within the first two weeks of treatment and is associated with elevated creatine phosphokinase (CPK) and white blood cell count (WBC); symptoms usually persist 5 to 10 days after medications are discontinued. Without prompt treatment, patients may experience crippling effects of muscle destruction, renal impairment, encephalopathy, and even death (Prod Info Clozaril(R), 2002); (Kontaxkis et al, 2001)(Karagianis et al, 1999; Dalkilic & Grosch, 1997; Campellone et al, 1995; Viner & Escobar, 1994; Keshavan et al, 1994; DasGupta & Young, 1991); (Miller et al, 1991)(Anderson & Powers, 1991); (Muller et al, 1988).

b) Clozapine-induced neuroleptic malignant syndrome (NMS) developed in a 52-year-old man with a concomitant underlying brain injury. The patient was admitted to the hospital for exacerbation of psychotic and affective symptoms, including self-injurious behavior, after having been treated effectively for bipolar disorder for the previous ten years with clozapine at a daily dose of 400 milligrams (mg). Clozapine was increased to 500 mg daily on the first day of hospitalization. On day 4, altered mental status, moderate rigidity, urinary retention, and fever were observed; and laboratory findings revealed leucocytosis, elevated levels of creatine phosphokinase (CPK), alanine aminotransferase (ALT), and aspartate aminotransferase (AST). Clozapine was discontinued after magnetic resonance imaging showed a subacute bilateral frontal hematoma. The CPK peaked on day 5 at 18,000 international units/liter and then started to decrease, returning to normal on day 9 along with resolution of fever, rigidity, and altered mental status. The author attributes the development of NMS in this patient to concurrent clozapine administration and an underlying brain injury, which may have been caused by the patient's self-injurious behavior (Duggal, 2004).

2) LITERATURE REPORTS

a) Two patients presented with neuroleptic malignant syndrome associated with clozapine which was not similar to the presentation with classical neuroleptic agents. One man presented after 16 days of clozapine therapy with a temperature of 38.4 degrees Celsius (C) and increased heart rate. There was no rigidity noted. Five days later his white blood cell (WBC) count peaked at 15,000/mm(3) and his creatine kinase at 1501 units(U)/liter(L). Marked neck rigidity was noted. Medications were discontinued and he recovered; however, intubation was required. In the other case, a woman treated with clozapine for 2 years developed diaphoresis, pallor and vomiting. Her temperature was 37.7 C. Two weeks later, she was found to be disoriented. Finally, 1 week later she was admitted and found to have a mild neck stiffness. Her temperature peaked at 38.3 C. Her WBC count was 10,600/mm(3). Her creatine kinase peaked at 189 units/L (normal 20 to 184). Clozapine was discontinued and she improved after 1 week (Karagianis et al, 1999).

b) In a review of clozapine and cases of presumed neuroleptic malignant syndrome, approximately 9 of the 19 cases were designated as having high probability of actually being neuroleptic malignant syndrome. Alternative diagnoses in low probability cases included benzodiazepine withdrawal, infection, drug-drug interaction, or serotonin syndrome (Hasan & Buckley, 1998).

c) The Australian Adverse Drug Reactions Advisory Committee has received 11 reports of Neuroleptic Malignant Syndrome associated with clozapine therapy (1 case questionable). The patients were all male (median age 40 years) and onset occurred primarily in the first two weeks after initiating treatment but ranged from 6 days to 9 months. Clozapine doses ranged from 75 to 600 milligrams (mg) daily (median 400 mg). Clinical symptomology included fever, confusion, disorientation, profuse sweating, tachycardia, and delirium. Laboratory tests revealed leukocytosis in 7 cases and elevated creatinine kinase levels in 10 cases (230 to 12,800 units/liter); all but 1 patient recovered (Anon, 1997a).

d) A patient with a history of neuroleptic malignant syndrome (NMS) following neuroleptic therapy also developed NMS after initiation of clozapine. After 4 days of clozapine treatment (12.5 milligrams daily), the patient experienced marked changes in mental status, weakness, and dizziness; creatine phosphokinase (CPK) was significantly elevated. Following discontinuation of the drug, the patient completely recovered after several days (Illing & Ancill, 1996).

e) A 71-year-old man with chronic paranoid schizophrenia presented with fever, rigidity, and altered mental status. Medications were therapeutic doses of clozapine and 1500 milligrams of valproic acid

used for prophylaxis for clozapine-induced seizures. His creatine phosphokinase level was 2536 U/liter, his urine contained myoglobin, and he had evidence of acute renal insufficiency. Despite discontinuation of clozapine, intravenous hydration, bromocriptine, diazepam, dantrolene, etc, the patient developed pulmonary and renal infection, multiorgan failure, gastrointestinal hemorrhage and subsequently died (Campellone et al, 1995).

3.3.9.H Neurological finding

1) Summary

a) In clinical trials (n=842), the following adverse effects were reported in 1% to 4% of patients were CONFUSION, FATIGUE, LETHARGY, and SLURRED SPEECH. Adverse effects that were temporally associated with clozapine and occurred in less than 1% of patients include LOSS OF SPEECH, AMENTIA, STUTTERING, DYSARTHRIA, NYSTAGMUS, AMNESIA/MEMORY LOSS and PARESTHESIA. (Prod Info Clozaril(R), 2002).

2) Drowsiness and sedation are very common dose-dependent adverse effects with therapeutic use of clozapine and are likely to subside with continued therapy or dose reduction. Dizziness and vertigo also commonly occur. Tremor, headache and seizures occur with some frequency. The following adverse effects that were less frequently reported and include hypokinesia, akinesia, agitation, rigidity, akathisia, confusion, fatigue, hyperkinesia, weakness, lethargy, ataxia, delirium, EEG changes, asterixis, paresthesia, slurred speech, and epileptiform movements/myoclonic jerks. Adverse effects that were temporally associated with clozapine therapy include loss of speech, tics, poor coordination, involuntary movements, stuttering, dysarthria, histrionic movements, shakiness, parkinsonism and numbness. Several cases of dystonic reactions have been reported but a causal relationship could not be established.

3.3.9.I Paralysis

1) A Chinese male schizophrenia patient developed hyperglycemia, hyperlipemia, and PERIODIC PARALYSIS while taking clozapine. The episodes of paralysis often lasted 30 to 40 minutes and then spontaneously stopped. Symptoms resolved when clozapine was withdrawn and recurred when clozapine treatment was reestablished. Symptoms appeared at clozapine doses as low as 37.5 milligrams (mg) per day. Other drugs were not as effective as clozapine for treating his mental state. His mental state was finally stabilized with a combination of clozapine 25 mg/day and haldol 20 mg/day, without elevations of blood glucose or lipids (Wu et al, 2000).

3.3.9.J Seizure

1) Summary

a) In the manufacturer's clinical trials (n=842) one or more seizures occurred in 5% (61 of 1743) of patients. During earlier clinical trials, the reported prevalence of seizures was also 5% of patients treated with 600 to 900 milligrams daily. Therapeutic use of clozapine has been reported to lower the seizure threshold, especially in epileptic patients and patients with organic brain disease. Seizures appear to be dose-related. Patients with a history of seizures or predisposing factors should be closely monitored during clozapine therapy. These patients should not be engaged in any activities where the sudden loss of consciousness could cause serious risk to themselves or others. STATUS EPILEPTICUS was reported, however a causal relationship with clozapine could not be determined. (Prod Info Clozaril(R), 2002; Supprian et al, 1999; Panagiotis, 1999; Devinsky & Pacia, 1994; Haller & Binder, 1990a).

2) Incidence: 5%

3) LITERATURE REPORTS

a) In one case, a 30-year-old man developed a grand mal seizure and liver toxicity after 3 weeks of clozapine therapy which had been increased to 400 milligrams per day (Panagiotis, 1999).

b) A 49-year-old female on maintenance clozapine therapy for refractory schizophrenia experienced a generalized epileptic seizure after a self-imposed dose increase to 750 milligrams (mg)/day. Myoclonic jerks continued for 2 hours, necessitating intravenous phenytoin. Electroencephalographic abnormalities (initial diffuse slowing progressing to triphasic sharp waves) had previously coincided with dosage increases from 450 to 650 mg/day. Preceding the seizure was new-onset stuttering at 700 mg/day, with dose-related fluctuations in severity. After the seizure, the patient was stabilized on valproate 900 mg/day and clozapine 600 mg/day, with no further stuttering or seizures during 6 months of follow-up. The authors speculated that clozapine-induced stuttering might be an indicator of epileptic brain activity (Supprian et al, 1999).

c) Seizures occur in approximately 1% of patients treated with antipsychotic drugs, but the reported prevalence of seizures is higher with clozapine and appears to be dose-dependent: 1% with less than 300 milligrams/day, 3% with 300 to 599 milligrams/day, and 5% with 600 to 900 milligrams/day. Clinical management of the seizures including the use of anticonvulsants or the discontinuation of clozapine has been outlined (Haller & Binder, 1990a). Another author reported similar results (Devinsky et al, 1991).

d) Some data do not clearly confirm the dose-dependent effect (Devinsky & Pacia, 1994). A 28-year-old woman with schizophrenia experienced a grand mal seizure while receiving clozapine at a low dose of 200 milligrams (Ravasia & Dickson, 1998). This occurred after 6 months of clozapine that included a 5-month initial taper. Her clozapine level was, however, 3290 nmol/liter (suggested range: 153 to 1836 nmol/liter).

See Drug Consult reference: PREVENTION OF CLOZAPINE-INDUCED SEIZURES

3.3.9.K Somnolence

1) Summary

a) In the manufacturer's clinical trials with clozapine therapy, drowsiness and SEDATION were reported in 39% of patients (n=842) and was reported likely to subside with continued therapy or dose reduction (Prod Info Clozaril(R), 2002). Earlier studies have also noted that drowsiness was a common dose-dependent adverse effect of clozapine (Bablenis et al, 1989; Haller & Binder, 1990a; Kirkegaard et al, 1982; Ayd, 1974a; Battegay et al, 1977).

2) Incidence: 39%

3.3.9.L Stuttering

1) Summary

a) Stuttering was noted to occur with clozapine use.

2) LITERATURE REPORTS

a) A 28-year-old, paranoid schizophrenic, man began stuttering when his clozapine dose reached 300 milligrams (mg) per day. An earlier EEG taken when he was receiving 150 mg/day showed bilateral frontotemporal slowing (left more than right), a photic convulsive response, and generalized nonparoxysmal sharp and slow waves. As he had a good response to clozapine his dose was increased to 300 mg/day and he began to stutter. At 425 mg/day he had a generalized tonic-clonic seizure. His clozapine dose was reduced to 200 mg/day and valproate 800 mg/day was added. There was no recurrence of stuttering when his clozapine dose was again increased to 300 mg/day. The authors speculate that stuttering accompanied by left-sided slowing or other EEG abnormalities may be a forerunner to seizures (Duggal et al, 2002).

3.3.10 Ophthalmic Effects

3.3.10.A Eye / vision finding

1) Summary

a) In clinical manufacturer trials, VISUAL DISTURBANCES occurred in 5% of patients (n=842) during clozapine therapy. MYDRIASIS, EYELID DISORDER, and BLOODSHOT EYES occurred in less than 1% of patients; a causal relationship with clozapine could not be determined (Prod Info Clozaril(R), 2002). ACCOMMODATION DIFFICULTIES may also be noted (Reynolds, 2000). No pathological pigmentation in the refractive media or retina were observed in 11 patients treated with clozapine for 6 months to 2 years (Gross & Langner, 1970).

2) Visual disturbances have occurred in patients during clozapine therapy that include mydriasis, eyelid disorder, accommodation difficulties and bloodshot eyes.

3.3.11 Otic Effects

Disorder of ear

Ear and auditory finding

3.3.11.A Disorder of ear

1) Summary

a) Ear disorder was temporally associated with clozapine therapy and occurred at a frequency less than 1% (Prod Info Clozaril(R), 2002).

3.3.11.B Ear and auditory finding

1) Ear disorder was temporally associated with clozapine therapy.

3.3.12 Psychiatric Effects

Delirium

Obsessive-compulsive disorder

Psychiatric sign or symptom

3.3.12.A Delirium

1) Summary

a) Delirium may occur, secondary to antimuscarinic side-effects, following therapeutic dosages (Reynolds, 2000; Burke et al, 1998); (Wilkins-Ho & Hollarder, 1997). An incidence of 8% was reported

in a case series of 391 treatments in 315 inpatients (Gaetner et al, 1989). Some authors recommended a low starting dose and gradual titration in retreatment with clozapine (Szymanski et al, 1991b)

2) LITERATURE REPORTS

a) Two cases of NEUROLEPTIC-SENSITIVITY were reported with clozapine therapy in patients with Lewy body dementia. Both received low doses of clozapine (6.25 or 12.5 milligrams) and experienced increased confusion, hallucinations, and behavioral symptoms. These symptoms persisted despite discontinuation of clozapine. Both families noted that the patients never returned to their pre-clozapine level of mental function (Burke et al, 1998).

b) A 48-year-old woman with a past history of alcohol dependency developed delirium after 3 days of clozapine therapy. Clozapine was discontinued and a slower upward titration resulted in no recurrence of her schizoaffective symptoms or her delirium (Wilkins-Ho & Hollander, 1997).

c) A 22-year-old man with chronic schizophrenia experienced acute symptoms of an ANTICHOLINERGIC SYNDROME (delirium, DECREASED GASTROINTESTINAL MOTILITY, TACHYCARDIA, and urinary hesitancy), antiadrenergic symptoms (orthostatic hypotension), and drug-induced HYPERBILIRUBINEMIA and HYPERAMYLASEMIA, after reintroduction of clozapine at a moderate and previously well-tolerated dosage. The authors recommended a low starting dose and gradual titration in retreatment with clozapine (Szymanski et al, 1991b).

3.3.12.B Obsessive-compulsive disorder

1) Summary

a) Adverse effects that have been reported during clozapine therapy are unmasked obsessive compulsive disorder, PSYCHOTIC EXACERBATIONS and CATAPLEXY (Prod Info Clozaril(R), 2002; Biondi et al, 1999; de Haan et al, 1999; Suppes & Rush, 1996; Baker et al, 1992).

2) LITERATURE REPORTS

a) In a retrospective cohort study of recent-onset schizophrenia or other psychotic disorders (n=121, mean age 21 years, 79% male), significantly more clozapine recipients (7 of 34, 21%) reported emergent or worsened obsessions compared to recipients of other antipsychotics (1 of 76, 1.3%, p less than 0.01). Clozapine-associated obsessions were new-onset in 5 of 7 (71%) cases. Discontinuation of clozapine produced complete remission of obsessive symptoms in one case. Three were successfully managed with clozapine dosage reduction plus adjunctive selective serotonin reuptake inhibitor (SSRI) therapy. Obsessions were refractory to SSRI therapy in the remaining patients (de Haan et al, 1999).

b) A 27-year-old man experienced obsessive-compulsive symptoms while receiving clozapine 150 milligrams/day for his schizophrenia (Biondi et al, 1999). Symptoms emerged after 5 weeks of clozapine. He had no previous history of obsessive-compulsive disorder. His score on the Yale-Brown Obsessive Compulsive Scale was 30. This decreased to 10 after clomipramine 110 milligrams/day was added.

c) Clozapine has produced or unmasked obsessive compulsive symptoms in 6 patients. In a review of 49 patients treated with clozapine for at least 3 months, five patients experienced de novo obsessive compulsive symptoms or a worsening of previous obsessive compulsive symptoms with improvement of psychosis (Baker et al, 1992). A similar case has been reported (Suppes & Rush, 1996).

3.3.12.C Psychiatric sign or symptom

1) Summary

a) In clinical trials (n=842), the following adverse effects were reported in 1% to 4% of patients; DISTURBED SLEEP/NIGHTMARES, RESTLESSNESS, AGITATION, PANIC, INSOMNIA, DEPRESSION, and ANXIETY. Adverse effects that were temporally associated with clozapine and occurred in less than 1% of patients include AMENTIA, DELUSIONS/HALLUCINATIONS, AMNESIA/MEMORY LOSS, PARANOIA, and IRRITABILITY. (Prod Info Clozaril(R), 2002; Bressan et al, 2000).

2) The following adverse effects that were less frequently reported in include disturbed sleep/nightmares, depression, restlessness, insomnia, and anxiety disorders. Adverse effects that were temporally associated with clozapine therapy include amentia, delusions/hallucinations, amnesia/memory loss, paranoia and irritability. Other adverse effects that have been reported are unmasked obsessive compulsive disorder, psychotic exacerbation and cataplexy.

3) LITERATURE REPORTS

a) A 34-year-old woman treated with clozapine 400 milligrams (mg) daily, developed daily PANIC and agoraphobic symptoms after 20 weeks that confined her to the house. Even with a reduction of clozapine to 250 mg daily, the patient only showed modest improvement. Clozapine was discontinued and changed to olanzapine without further recurrence of anxiety symptoms (Bressan et al, 2000).

3.3.13 Renal Effects

Interstitial nephritis

Nocturnal enuresis

Urinary incontinence

Urinary retention

Urogenital finding

3.3.13.A Interstitial nephritis

1) Summary

a) Voluntary postmarketing reports from the manufacturer include the adverse effect of acute interstitial nephritis during clozapine therapy, however a causal relationship could not be determined (Prod Info Clozaril(R), 2002). There have also been a few case reports of interstitial nephritis (Fraser and Jibani, 2000)(Elias et al, 1999).

2) LITERATURE REPORTS

a) In one report, a 49-year-old man developed ACUTE RENAL FAILURE due to interstitial nephritis during treatment with clozapine. He received no other medication except diazepam as needed. On clozapine day 42, blood draw showed marked renal impairment. He was dehydrated and pyrexial on day 45 with no abnormality on physical exam or chest x-ray. Blood and urine cultures were negative, clozapine was stopped, and he was started on intravenous cefotaxime. Despite hydration, dopamine, and furosemide infusions his plasma urea and creatinine continued to rise. On day 47 he started peritoneal dialysis. A percutaneous renal biopsy on day 50 showed a florid interstitial nephritis. He was treated with intravenous methylprednisolone 1 gram on each of days 51 to 53 then switched to oral prednisolone. He was switched to hemodialysis on day 52 and by day 61, his biochemistry improved and was taken off dialysis. Discontinuation of the drug often leads to resolution in those with mild to moderate renal failure but unless the offending agent is discontinued, the renal failure may be irreversible. Also included were details of 7 additional cases of acute renal failure associated with clozapine therapy reported to the Committee On Safety Of Medicines in the UK (Fraser and Jibani, 2000).

b) Investigators reported a case of acute interstitial nephritis, diagnosed by renal biopsy in a 38-year-old female, which they attributed to a hypersensitivity reaction to clozapine. Eleven days after initiation of clozapine 125 milligrams twice daily, the patient developed anuric renal failure necessitating hemodialysis and the discontinuation of all medications. Other possible etiologies were ruled out. The patient began improving after 1 week with renal function values normalizing by day 15 (Elias et al, 1999).

3.3.13.B Nocturnal enuresis

1) Summary

a) Bladder urgency and/or enuresis occurred in a series of 10 patients during treatment with clozapine (Frankenburg et al, 1996). In another study it occurred in 11 of 25 patients (Lin et al, 1999). The incidence of nocturnal enuresis was at least 0.23% to as high as 41% of patients treated with clozapine (Lin et al, 1999; Steingard, 1994). URINARY URGENCY and URINARY FREQUENCY, occurred in 1% of patients (n=842) with therapeutic use of clozapine (Prod Info Clozaril(R), 2002).

2) LITERATURE REPORTS

a) The incidence of NOCTURNAL ENURESIS was 41% in a sample of 61 Chinese inpatients with chronic schizophrenia treated with clozapine for at least 3 months. Daytime urinary incontinence accompanied nocturnal enuresis in 11 of 25 cases (Lin et al, 1999).

b) Bladder urgency and/or enuresis occurred in a series of 10 patients during treatment with clozapine. Eight of the patients experienced these symptoms during medication initiation, and two of the patients had preexistent enuresis that worsened with clozapine therapy. Oxybutynin (5 to 15 milligrams/day) was effective in relieving the symptoms of enuresis and urgency in five patients; intranasal desmopressin was effective in another four. The authors also report a cumulative incidence of enuresis in two previous studies of 28% and suggest that all clozapine-treated patients be questioned about changes in bladder habits (Frankenburg et al, 1996).

c) Nocturnal enuresis has been reported to occur in at least 0.23% of patients treated with clozapine. Desmopressin acetate administered intranasally at a dose of one puff (10 micrograms) in each nostril at bedtime was reported as successfully treating this side effect in one case report (Steingard, 1994).

3.3.13.C Urinary incontinence

1) Summary

a) In clinical manufacturer trials, incontinence has occurred in 1% of patients (n=842) with therapeutic use of clozapine (Prod Info Clozaril(R), 2002). Two other studies reported incontinence in patients ranging from 29% to 44% (Lin et al, 1999; Fuller et al, 1996).

2) LITERATURE REPORTS

a) In a retrospective review of 61 Chinese inpatients with chronic schizophrenia treated with clozapine for at least 3 months, the incidence of urinary incontinence (UI) was 44%. Investigators compared age, gender, clozapine dose and duration, length of hospitalization, duration of illness and age at onset of

illness and found no significant difference between those who did and did not experience UI. The same characteristics were also statistically equivalent between subjects with persistent versus self-limiting UI. Of the 27 patients with UI, 15 (56%) had persistent and 12 (44%) had self-limiting UI; 25 (93%) had nocturnal enuresis with (n=11) or without (n=14) daytime symptoms; 2 (7%) had daytime UI only. Concomitant medications were not associated with UI in this sample (Lin et al, 1999).

b) In one report, urinary incontinence developed in 17 of 57 inpatients after initiation of clozapine therapy. Patients who developed incontinence were significantly more likely to be receiving a typical antipsychotic agent in addition to clozapine, receiving a higher dose of the agent, and to be female. Sixteen of the incontinent patients were treated with ephedrine (25 to 150 milligrams/day) with 12 patients having a complete response to treatment (Fuller et al, 1996).

3.3.13.D Urinary retention

1) Summary

a) Urinary retention occurred in 1% of patients (n=842) during clozapine therapy. Elderly patients may be particularly susceptible to the anticholinergic effects of clozapine, such as urinary retention (Prod Info Clozaril(R), 2002).

3.3.13.E Urogenital finding

1) Summary

a) In clinical trials, ABNORMAL EJACULATION occurred in 1% of patients (n=842) with clozapine therapy. Adverse effects temporally associated with clozapine and occurring at a frequency less than 1% include DYSMENORRHEA, IMPOTENCE, DECREASE LIBIDO, INCREASED LIBIDO, BREAST PAIN, VAGINAL ITCHING, and POLYDIPSIA. Voluntary postmarketing reports also noted PRIAPISM, however a causal relationship could not be determined (Prod Info Clozaril(R), 2002).

2) In clinical trials, incontinence, urinary urgency/urinary frequency, urinary retention, and abnormal ejaculation have occurred in patients with clozapine therapy. Elderly patients may be particularly susceptible to the anticholinergic effects of Clozaril (clozapine), such as urinary retention Adverse effects temporally associated with clozapine and occurring less frequently include dysmenorrhea, impotence, decrease libido, increased libido, breast pain, vaginal itching, and polydipsia. Reports also include acute interstitial nephritis and priapism but a causal relationship could not be determined.

3.3.15 Respiratory Effects

Lung finding

Pleural effusion

Pulmonary embolism

Respiratory finding

3.3.15.A Lung finding

1) Summary

a) Clozapine has induced orthostatic hypotension severe enough to cause collapse and respiratory arrest. This adverse effect usually occurs following the initial titration or during rapid escalation of the dose. In clinical trials, DYSPNEA, NASAL CONGESTION, and THROAT DISCOMFORT occurred in 1% of patients (n=842). Adverse effects temporally associated with clozapine and occurring at a frequency less than 1% include COUGHING, PNEUMONIA, RHINORRHEA, HYPERVENTILATION, WHEEZING, BRONCHITIS, LARYNGITIS, and SNEEZING. Voluntary postmarketing reports include ASPIRATION and PLEURAL EFFUSIONS; a causal relationship could not be determined (Prod Info Clozaril(R), 2002).

3.3.15.B Pleural effusion

1) Summary

a) Two cases of pulmonary effusion were reported with clozapine therapy (Stanislav & Gonzalez-Blanco, 1999; Chatterjee & Safferman, 1997).

2) LITERATURE REPORTS

a) Bilateral pleural effusion, accompanied by a fever and papular rash, appeared in a 37-year-old female 9 days after clozapine initiation and titration to 150 milligrams/day. Diagnostic findings were consistent with a drug hypersensitivity reaction, as no infectious or cardiopulmonary etiology was identified. The remainder of her medication regimen had been stable with no recent dose changes. Within a week of clozapine discontinuation, signs and symptoms resolved (Stanislav & Gonzalez-Blanco, 1999).

b) A 37-year-old male developed right arm cellulitis after 5 days of clozapine therapy and a left-sided

pleural effusion after 12 days. Eosinophilia was also present (white blood cell count of 17,100 cells/cubic millimeter, 23.6% eosinophils). Clozapine was discontinued and he improved with antibiotics. The patient was re-challenged with clozapine. After 8 days, he again experienced right arm swelling and chest x-ray showed reemergence of left-sided pleural effusion (Chatterjee & Safferman, 1997).

3.3.15.C Pulmonary embolism

1) Summary

a) (Hagg et al, 2000f) identified 12 cases of thromboembolism associated with clozapine treatment (mean dose of 277 milligrams per day). Six cases of venous thrombosis and 6 cases of pulmonary embolism were reported; five patients died. No confounding illness was found in any of the patients that would have contributed to thromboembolic disease. One other case of pulmonary embolism was noted and the patient recovered (Maynes, 2000).

2) Incidence: rare

3) LITERATURE REPORTS

a) A case of bilateral pulmonary embolism was reported in a 30-year-old man, five months after starting clozapine. He had a sudden onset of shortness of breath and dizziness while walking. He then collapsed on the street and taken to the emergency room. Upon examination he was found to be diaphoretic and tachycardic, with a pulse of 115 beats per minute. Further investigation included a ventilation-perfusion scan, and he was diagnosed with a bilateral pulmonary embolism. The patient was anticoagulated with heparin then warfarin and he made a gradual recovery (Maynes, 2000).

3.3.15.D Respiratory finding

1) Pulmonary effusion and embolisms have occurred with therapeutic clozapine use. Clozapine has induced orthostatic hypotension severe enough to cause collapse and respiratory arrest. This adverse effect usually occurs following the initial titration or during rapid escalation of the dose. Dyspnea and nasal congestion occurred in patients. Adverse effects temporally associated with clozapine and occurring at a low frequency include coughing, pneumonia, rhinorrhea, hyperventilation, wheezing, bronchitis, laryngitis, aspiration and sneezing.

3.3.16 Other

Summary

Dead - sudden death

Death

Extrapyramidal disease

Fever

Malaise

Seizure

Withdrawal sign or symptom

3.3.16.A Summary

1) OTHER EFFECTS

a) Withdrawal and sudden death has been associated with clozapine therapy.

3.3.16.B Dead - sudden death

1) Summary

a) In a retrospective review of inpatient mental health records (1991 to 1997, n=5479) and national death registry data, investigators discovered a higher incidence of sudden death among clozapine users compared to nonusers. Of 561 clozapine recipients, there were 6 sudden deaths (1.07%), 2 suicides (0.35%), and 2 disease-related deaths (0.35%). The 6 sudden deaths occurred in 4 current and 2 former (2 weeks and 5 years posttreatment) users of clozapine, respectively. Of 4918 not exposed to clozapine, there were 14 sudden deaths (0.28%), 5 suicides (0.1%) and 86 disease-related deaths (1.75%). Sudden deaths were significantly more frequent in the clozapine group (p less than 0.01), while disease-related deaths were significantly more common in the non-clozapine group (p less than 0.05). The average age at sudden death was lower in clozapine users (41 versus 51 years, p less than 0.04). However, the validity of attributing a sudden death to clozapine 5 years after its discontinuation is

doubtful. These data should be interpreted with caution because of the small numbers of sudden deaths and lack of autopsies (Modai et al, 2000).

3.3.16.C Death

1) Results of a population-based, retrospective cohort study demonstrated that the use of conventional antipsychotics was associated with an even greater risk for death than atypical antipsychotics when administered to elderly patients (aged 66 years and older) with dementia. Atypical versus no antipsychotic use and conventional versus atypical antipsychotic use pair-wise comparisons were made. A total of 27,259 matched pairs were identified and the dementia cohort was stratified based on place of residence (community versus long-term care facilities). In order to adjust for difference in baseline health status, propensity score matching was used. The primary outcome of the study was all-cause mortality. The risk for death was evaluated at 30, 60, 120, and 180 days after the antipsychotic medications were initially dispensed. There was a statistically significant increase in the risk for death at 30 days associated with new use of atypical antipsychotic medications compared with nonuse in both the community-dwelling cohort (adjusted hazard ratio (HR), 1.31 (95% confidence interval (CI), 1.02 to 1.70); absolute risk difference, 0.2 percentage point) and long-term care cohort (adjusted HR, 1.55 (95% CI, 1.15 to 2.07); absolute risk difference, 1.2 percentage points). For both cohorts, the risk associated with atypical antipsychotics appeared to persist to 180 days. The risk for death associated with conventional antipsychotics was even greater than the risk identified with atypical antipsychotics. At 30 days, the adjusted HR for the community-dwelling cohort was 1.55 (95% CI, 1.19 to 2.02) and 1.26 (95% CI, 1.04 to 1.53) for the long-term care cohort (adjusted risk difference for both was 1.1 percentage points). The risk appeared to persist to 180 days for both groups. Some important limitations to the study include unknown or unmeasured confounders may influence the results and cause of death could not be examined (Gill et al, 2007).

2) Results of a population-based, retrospective cohort study demonstrated comparable to possibly greater risk of death associated with the use of conventional antipsychotic medications in the elderly (aged 65 years and older) compared with atypical antipsychotic medications. The analysis excluded patients with cancer and included only new users of antipsychotic medications. The primary study outcome was 180-day all-cause mortality. A set of potential confounders was measured based on healthcare utilization data within 6 months before the initiation of antipsychotic medications. Of the 37,241 elderly patients identified, 12,882 and 24,359 received conventional and atypical antipsychotic medications, respectively. The risk of death in the conventional drug group within the first 180 days was 14.1% compared with 9.6% in the atypical drug group (unadjusted mortality ratio, 1.47; 95% confidence interval (CI), 1.39 to 1.56). In the multi-variable analysis which controlled for potential confounders, the adjusted mortality ratio for the risk of death within 180 days for conventional versus atypical drug therapy was 1.32 (95% CI, 1.23 to 1.42). When the most frequently prescribed conventional antipsychotic drugs were compared with risperidone, the mortality ratio associated with haloperidol was 2.14 (95% CI, 1.86 to 2.45) and loxapine was 1.29 (95% CI, 1.19 to 1.40), while there was no difference associated with olanzapine. The increased mortality risk for conventional versus atypical drug therapy was greatest when doses higher (above median) doses were used (mortality ratio 1.67; 95% CI, 1.5 to 1.86) and also during the first 40 days of therapy (mortality ratio 1.6; 95% CI, 1.42 to 1.8). Confirmatory analyses consisting of multi-variable Cox regression, propensity score, and instrumental variable estimation confirmed the results of the study (Schneeweiss et al, 2007).

3) The results of a retrospective cohort study indicate that conventional antipsychotic agents are at least as likely as atypical antipsychotic agents to increase the risk of death among elderly patients 65 years of age or older. The study included 9,142 new users of conventional agents (mean age, 83.2 years) and 13,748 new users of atypical agents (mean age, 83.5 years). A higher adjusted relative risk of death was associated with the use of conventional antipsychotics as compared with atypical antipsychotics at all timepoints studied after beginning therapy (within 180 days: relative risk) RR, 1.37; 95% confidence interval (CI), 1.27 to 1.49; less than 40 days: RR, 1.56; 95% CI, 1.37 to 1.78; 40 to 79 days: RR, 1.37; 95% CI, 1.19 to 1.59; 80 to 180 days: RR, 1.27; 95% CI, 1.14 to 1.41). In addition, the adjusted risks of death observed in patients with dementia (RR, 1.29; 95% CI, 1.15 to 1.45), without dementia (RR, 1.45; 95% CI, 1.30 to 1.63), in a nursing home (RR, 1.26; 95% CI, 1.08 to 1.47), or not in a nursing home (RR, 1.42; 95% CI, 1.29 to 1.56) were also higher with the use of conventional antipsychotic therapy as compared with atypical antipsychotic use. This risk appeared to be dose-related and was greater with the use of higher dose (ie, greater than the median) conventional antipsychotics (RR, 1.73; 95% CI, 1.57 to 1.90). Additional studies which specifically investigate the optimum care of elderly patients requiring antipsychotic therapy are needed so that appropriate guidance regarding therapeutic intervention can be provided (Wang et al, 2005).

3.3.16.D Extrapyramidal disease

See Drug Consult reference: NEUROLEPTIC-INDUCED EXTRAPYRAMIDAL REACTIONS

3.3.16.E Fever

1) Summary

a) Fever was associated in 4% to 6% of patients (sometimes along with flu-like symptoms) following therapeutic dosages of clozapine. It (100.4 degrees Farenheit (38 degrees Centigrade)) is usually transient with a peak occurring within the first 3 weeks of therapy. The fever is generally benign and self-limiting. Temperature elevation appeared to be independent of dose (Prod Info Clozaril(R), 2002); (Blum, 1990).

2) Incidence: 5%

3.3.16.F Malaise

1) Summary

a) Malaise was temporally associated with clozapine therapy and occurred at a frequency less than 1% (Prod Info Clozaril(R), 2002).

3.3.16.G Seizure

See Drug Consult reference: PREVENTION OF CLOZAPINE-INDUCED SEIZURES

3.3.16.H Withdrawal sign or symptom

1) Summary

a) Several different kinds of withdrawal symptoms including cholinergic rebound, dystonias, dyskinesias and worsening psychotic symptoms have occurred with clozapine therapy (Tollefson et al, 1999; Delassus-Guenault et al, 1999; Stanilla et al, 1997)

2) LITERATURE REPORTS

a) In a double-blind, placebo-controlled study of 106 patients undergoing elective discontinuation of clozapine, the immediate substitution of olanzapine 10 milligrams (mg)/day attenuated some withdrawal symptoms. Clozapine doses were gradually tapered to 300 mg/day or less prior to abrupt discontinuation, followed by randomization to either placebo or olanzapine for a 3- to 5-day study period. During this time, 24.5% and 7.5% of placebo- and olanzapine-treated patients, respectively, experienced a worsening of at least one psychotic sign or symptom (p=0.02). This was reflected by significant between-group differences in the Positive and Negative Syndrome Scale total score (p=0.04) and general psychopathology subscale (p=0.03) as well as the Montgomery-Asberg Depression Rating Scale total score (p less than 0.001). However, the primary efficacy variable, the Clinical Global Impression Scale-Severity, was statistically similar in both groups. All subjects then entered a 9-week open-label olanzapine period, with equivalent outcomes. Investigators stress the importance of a gradual taper of clozapine with possible overlap and/or substitution with olanzapine to minimize the risk of withdrawal symptoms. Olanzapine may be preferred over risperidone or typical antipsychotics because its receptor affinities are similar to those of clozapine (Tollefson et al, 1999).

b) In two case reports, rapid clozapine tapering from high doses resulted in severe cholinergic rebound symptoms despite substitution with olanzapine. Maintenance clozapine doses of 700 to 800 milligrams (mg)/day were tapered over only 4 to 7 days, discontinued and replaced by olanzapine 5 to 10 mg/day. Withdrawal symptoms included severe anxiety, agitation, aggression, nausea, vomiting, diaphoresis, confusion and disorientation, necessitating medical hospitalization in one case. The authors recommend a 2- to 3-week taper period for clozapine with concomitant anticholinergic therapy (Delassus-Guenault et al, 1999).

c) Severe dystonias and dyskinesias were experienced by 4 patients withdrawn from clozapine therapy (Ahmed et al, 1998). Patients were 18 to 60 years old and had a history of extrapyramidal symptoms while receiving high potency and older neuroleptics. In 3 patients clozapine was discontinued abruptly. Cholinergic rebound was experienced by 2 subjects. Severe limb-axial and neck dystonias, and dyskinesias were experienced by 3 patients for 5 to 14 days. The dystonias were so severe in 2 patients that they were unable to ambulate. Significant improvement was seen after 2 restarted clozapine, 1 started risperidone, and 1 started olanzapine.

d) Three cases of acute delirium and psychosis occurred upon withdrawal of clozapine. The patients involved were male, ages 38, 46, and 63, whose schizophrenia had been controlled on 250 to 600 milligrams/day for 12 to 18 months. In two patients, clozapine was abruptly stopped, while the other was weaned off clozapine over 2 weeks. Withdrawal symptoms (hallucinations, diaphoresis, agitation, disorientation, choreoathetoid movements) appeared within 24 to 48 hours of the last clozapine dose and resolved upon reinstitution of clozapine. When a prolonged taper of clozapine is not possible, the authors recommend the temporary use of thioridazine when transitioning to another antipsychotic agent to counteract cholinergic hyperactivity (Stanilla et al, 1997).

e) A withdrawal syndrome occurred in 9 of 13 patients after sudden discontinuation of long-term clozapine therapy at doses ranging from 50 to 200 milligrams/day. After sudden discontinuation, patients experienced a severe relapse requiring hospitalization within 24 to 48 hours. Five patients reported vomiting, sleeplessness, depression, stupor, fatigue, and dizziness. Withdrawal akathisia was reported by 4 patients. These symptoms regressed when the patient was given clozapine or disappeared gradually when patients began to receive other neuroleptics (Zapletalek et al, 1980).

f) Difficulty in switching patients from other neuroleptics to clozapine has been reported. In 7 patients, unspecific restlessness, psychotic symptoms, and extrapyramidal symptoms which required hospitalization were seen for an average of 4 weeks after withdrawal of neuroleptics and starting clozapine (Mauthe et al, 1980).

3.4 Teratogenicity/Effects in Pregnancy/Breastfeeding

A) Teratogenicity/Effects in Pregnancy

1) U.S. Food and Drug Administration's Pregnancy Category: Category B (Prod Info CLOZARIL(R) oral tablets, 2008) (All Trimesters)

a) Either animal-reproduction studies have not demonstrated a fetal risk but there are no controlled studies in pregnant women or animal-reproduction studies have shown adverse effect (other than a decrease in

fertility) that was not confirmed in controlled studies in women in the first trimester (and there is no evidence of a risk in later trimesters).

2) Australian Drug Evaluation Committee's (ADEC) Category: C(Australian Drug Evaluation Committee, 1999)

a) Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible. Accompanying texts should be consulted for further details.

See Drug Consult reference: PREGNANCY RISK CATEGORIES

3) Crosses Placenta: Unknown

4) Clinical Management

a) Limited human data from case reports indicate no complications during pregnancy or delivery and no adverse effects on the infant when clozapine is administered during pregnancy. Animal studies have also not demonstrated adverse effects due to clozapine use during gestation in rats and rabbits. Therefore, in consideration of maintaining the lowest effective dose of any drug during pregnancy and because animal studies are not always predictive of human response, clozapine should be used during pregnancy only if clearly needed (Prod Info CLOZARIL(R) oral tablets, 2008).

5) Literature Reports

a) Two case reports described uncomplicated pregnancies and vaginal term deliveries resulting in healthy infants when clozapine 200 mg/day was used during the pregnancies of 2 women with schizophrenia. In both cases, breast feeding was not recommended. In the first case, the patient was taking clozapine 400 mg/day. One year later, the patient wanted to conceive. Subsequently, clozapine was tapered off to the point of psychotic symptoms to determine the lowest effective dose. Prior to pregnancy, her BMI was 23.6 and serum folate level was 8.2 nanograms/mL. No psychotic symptoms occurred during gestation. The newborn's height of 52 cm and weight of 2900 g were normal . APGAR scores were 9 and 10 in minute 1 and 5, respectively. WBC count was normal with no neonatal history of seizures. In a subsequent pregnancy 1.5 years later, the patient was still taking clozapine 200 mg/day. Routine follow-up during pregnancy revealed no gestational diabetes, orthostatic hypotension, agranulocytosis, or psychotic symptoms. The second child was 50 cm and 3000 g with APGAR scores of 10 in minutes 1 and 5. In the second case, a woman had been experiencing auditory hallucinations for which she was initiated on clozapine 400 mg/day while tapering off of other drugs that were not working. She improved significantly and wanted a second child. Her BMI was 24.1. Birth control or clozapine dose reduction in the event of pregnancy was recommended. The patient presented to an outpatient clinic reporting that she had delivered healthy twins who were 51 and 49 cm and 3100 and 2940 g with APGAR scores in minute 1 and 5 of 9 and 10, respectively, for one twin and 10 for the other. WBC count was not monitored during pregnancy. No seizures or agranulocytosis were recorded (Duran et al, 2008).

b) A case report described an uncomplicated pregnancy and delivery resulting in a healthy infant who exhibited normal development, except for speech, when clozapine was used during pregnancy in a 30-year-old woman with schizophrenia. The mother had been maintained on clozapine 100 mg/day for 6 months when she became pregnant. Laboratory tests for blood glucose, hemoglobin, and WBC count were within normal limits. The 100-mg daily clozapine dose was maintained throughout her pregnancy. Weight gain was normal and no psychotic exacerbations occurred during gestation. A term delivery (9 months and 2 days) resulted in a healthy baby girl with a normal weight of 2.95 kg and no perinatal complications. The patient was maintained on the same clozapine dose while breast-feeding her infant until 1 year of age The infant achieved normal developmental milestones, with the exception of speech. At the age of 1 year, she began using consonants and began using combined syllables at the age of 18 months. She spoke only 6 to 8 words at 2 years of age and would speak only 12 to 15 words until 3 years of age. She was also stuttering. At 4 years of age, she developed speaking skills with small sentences of 2 or 3 words and she could repeat small sentences. She was able to speak fluently by the end of 5 years. Local pathology was ruled out and audiometric assessment was within normal limits. The mother-child relationship was not impaired and there was no evidence of familial phonological disorder or a bilingual environment (Mendhekar, 2007).

c) Cases of clozapine use during pregnancy (150 to 625 mg/day) have not resulted in fetal abnormalities (Dickson & Hogg, 1998; Stoner et al, 1997). A case report described a 30-year-old female who was treated with clozapine throughout her pregnancy. The patient delivered a female infant at 39 weeks gestation with abnormal findings including a cephalhematoma, hyperpigmentation folds, and a coccygeal dimple, all of which were resolving within 2 days of delivery. At 8 days old, the infant was reported to have a seizure and developed gastroenteritis, both of which resolved. At 2 years of age, the child was reported to be healthy with no physical problems (Stoner et al, 1997). Another case report described a 32-year-old female who was treated with clozapine throughout her pregnancy. She delivered a female at 40 weeks gestational age with no reported abnormalities except a low-grade fever which resolved prior to hospital discharge (Stoner et al, 1997).

d) A case report described an infant born to a mother treated with clozapine 100 mg per day until the last nine weeks of pregnancy at which time the dose was decreased to 50 mg/day. The infant girl weighed 3600 g at birth and had Apgar scores of 5 at one minute and 8 at five minutes. The infant had normal l psychomotor development up to 6 months of age. Maternal clozapine plasma levels were measured monthly during pregnancy, the day of delivery, one day after delivery when the mother began lactating, and one week after delivery. While taking 100 mg/day, the mother's clozapine plasma levels were 38 to 55 nanograms (ng)/mL; at 50 mg/day, the level was 15.4 ng/mL. When the infant was delivered, the maternal, amniotic, and fetal plasma levels were 14.1 ng/mL, 11.6 ng/mL, 27 ng/mL, respectively. The accumulation of drug in the fetal plasma can be explained by the higher concentration of albumin in fetal blood which binds

clozapine, an acidic, lipophilic drug, and by ion trapping in the fetal compartment which results in a pH gradient in the fetus (Barnas et al, 1994).

e) There are no adequate and well-controlled studies in pregnant women. In animal studies, there was no evidence of impaired fertility or harm to the fetus when rat and rabbits were exposed to disease approximately 2 to 4 times the human dose (Prod Info CLOZARIL(R) oral tablets, 2008).

B) Breastfeeding

1) American Academy of Pediatrics Rating: Drugs for which the effect on nursing infants is unknown but may be of concern. (Anon, 2001)

2) Thomson Lactation Rating: Infant risk cannot be ruled out.

a) Available evidence and/or expert consensus is inconclusive or is inadequate for determining infant risk when used during breastfeeding. Weigh the potential benefits of drug treatment against potential risks before prescribing this drug during breastfeeding.

3) Clinical Management

a) Human data showing the effects, if any, of clozapine on the nursing infant are limited. A case report demonstrated a milk/plasma ratio of greater than 2.5 in a woman taking clozapine 100 mg/day. The high milk/plasma ratio was attributed to the high lipid solubility and lipophilic properties of clozapine (Barnas et al, 1994a). Another case report described a problem with speech development in an infant who had been breast-fed for 1 year while her mother was maintained on a daily 100-mg dose of clozapine. However, it is not possible to determine whether the speech difficulty is a result of postnatal exposure to clozapine (Mendhekar, 2007). Animal studies have indicated that clozapine may be excreted in breast milk. Therefore, breast-feeding should be avoided during clozapine treatment (Prod Info CLOZARIL(R) oral tablets, 2008).

4) Literature Reports

a) A case report described an uncomplicated pregnancy and delivery resulting in a healthy infant who exhibited normal development, except for speech, when clozapine was used during pregnancy and lactation in a 30-year-old woman with schizophrenia. The mother had been maintained on clozapine 100 mg/day for 6 months when she became pregnant. Laboratory tests for blood glucose, hemoglobin, and WBC count were within normal limits. The 100-mg daily clozapine dose was maintained throughout her pregnancy. Weight gain was normal and no psychotic exacerbations occurred during gestation. A term delivery (9 months and 2 days) resulted in a healthy baby girl with a normal weight of 2.95 kg and no perinatal complications. The patient was maintained on the same clozapine dose while breast-feeding her infant until 1 year of age The infant achieved normal developmental milestones, with the exception of speech. At the age of 1 year, she began using consonants. At 18 months, she began using combined syllables. She spoke only 6 to 8 words at 2 years of age and would speak only 12 to 15 words until 3 years of age. She was also stuttering. At 4 years of age, she developed speaking skills with small sentences of 2 or 3 words and she could repeat small sentences. She was able to speak fluently by the end of 5 years. Local pathology was ruled out and audiometric assessment was within normal limits. The mother-child relationship was not impaired and there was no evidence of familial phonological disorder or a bilingual environment (Mendhekar, 2007).

b) A case report described a healthy infant born to a mother treated with clozapine 100 mg/day until the last 9 weeks of pregnancy at which time, the dose was decreased to 50 mg/day. The infant girl weighed 3600 g at birth and had Apgar scores of 5 at one minute and 8 at five minutes. She had normal psychomotor development up to 6 months of age. Maternal clozapine plasma levels were measured monthly during pregnancy, the day of delivery, one day after delivery when the mother began lactating, and one week after delivery. While taking 100 mg/day, the mother's clozapine plasma level was 38 to 55 nanograms (ng)/mL; at 50 mg/day, her level was 15.4 ng/mL. When the infant was delivered, the maternal, amniotic, and fetal plasma levels were 14.1 ng/mL, 11.6 ng/mL, 27 ng/mL, respectively. The day after delivery, the concentration of clozapine in the maternal plasma was 14.7 ng/mL and the first portion of the breast milk contained 63.5 ng/mL. At one week postdelivery, the mother was taking clozapine 100 mg/day; the breast milk concentration of drug measured 115.6 ng/mL, and plasma level measured 41.4 ng/mL. The authors postulated that clozapine accumulates in the breast milk because of the high lipid concentration of breast milk (Barnas et al, 1994a).

5) Drug Levels in Breastmilk

a) Parent Drug

1) Milk to Maternal Plasma Ratio

a) 2.8 to 4.3 (Barnas et al, 1994a)

3.5 Drug Interactions

Drug-Drug Combinations

Drug-Food Combinations

3.5.1 Drug-Drug Combinations

Aprindine

Belladonna

Belladonna Alkaloids

Benztropine

Buspirone

Carbamazepine

Cimetidine

Ciprofloxacin

Citalopram

Dehydroepiandrosterone

Droperidol

Encainide

Erythromycin

Flecainide

Fluoxetine

Fluvoxamine

Fosphenytoin

Guarana

Lithium

Lorazepam

Lorcainide

Mate

Nefazodone

Nicotine

Norfloxacin

Paroxetine

Perphenazine

Phenobarbital

Phenylalanine

Phenytoin

Propafenone

Quinidine

Rifampin

Risperidone

Ritonavir

Sertraline

St John's Wort

Thioridazine

Tramadol

Venlafaxine

Zotepine

3.5.1.A Aprindine

1) Interaction Effect: increased plasma concentrations of clozapine and or class I antiarrhythmic agents
2) Summary: Coadministration of clozapine with other drugs that are metabolized by cytochrome P450 2D6, such as class I antiarrhythmics, should be approached with caution (Prod Info Clozaril(R), 2002j).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Concomitant use of clozapine with other drugs metabolized by cytochrome P450 2D6, such as class I antiarrhythmic agents, may require lower doses than usually prescribed for either clozapine or the class I antiarrhythmic.
7) Probable Mechanism: competitive substrate inhibition

3.5.1.B Belladonna

1) Interaction Effect: excessive anticholinergic activity (severe dry mouth, constipation, decreased urination, excessive sedation, blurred vision)
2) Summary: The anticholinergic activity of the active alkaloids present in belladonna may predispose the patient to excessive anticholinergic activity if taken with clozapine. Belladonna contains L-hyoscyamine, atropine, and scopolamine with a total alkaloid content of at least 0.3% in the leaves and 0.5% in the roots (Blumenthal et al, 1998). Because belladonna is typically available as a homeopathic preparation, the clinical severity of the interaction with clozapine is unknown. Caution is advised.
3) Severity: minor
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Excessive anticholinergic activity may be manifested by dry mouth, constipation, urinary retention, tachycardia, decreased sweating, mydriasis, blurred vision, elevated temperature, muscular weakness, and sedation. If such effects are noted, belladonna should be discontinued immediately. In severe cases, paralytic ileus, confusion, psychoses, agitation, delusions, delirium, and paranoia may be encountered as well as tachycardia, dysrhythmia, and hypertension. In severe cases, immediate medical attention should be obtained.
7) Probable Mechanism: additive anticholinergic effect

3.5.1.C Belladonna Alkaloids

1) Interaction Effect: excessive anticholinergic activity (severe dry mouth, constipation, decreased urination, excessive sedation, blurred vision)
2) Summary: The anticholinergic activity of the active alkaloids present in belladonna may predispose the patient to excessive anticholinergic activity if taken with clozapine. Belladonna contains L-hyoscyamine, atropine, and scopolamine with a total alkaloid content of at least 0.3% in the leaves and 0.5% in the roots (Blumenthal et al, 1998). Because belladonna is typically available as a homeopathic preparation, the

clinical severity of the interaction with clozapine is unknown. Caution is advised.
3) Severity: minor
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Excessive anticholinergic activity may be manifested by dry mouth, constipation, urinary retention, tachycardia, decreased sweating, mydriasis, blurred vision, elevated temperature, muscular weakness, and sedation. If such effects are noted, belladonna should be discontinued immediately. In severe cases, paralytic ileus, confusion, psychoses, agitation, delusions, delirium, and paranoia may be encountered as well as tachycardia, dysrhythmia, and hypertension. In severe cases, immediate medical attention should be obtained.
7) Probable Mechanism: additive anticholinergic effect

3.5.1.D Benztropine
1) Interaction Effect: excessive anticholinergic effects (sedation, constipation, dry mouth)
2) Summary: The use of antipsychotics and anticholinergics may increase the incidence of ileus, hyperpyrexia, or neurologic deficits. In addition, the concurrent use of these drugs may decrease the gastrointestinal absorption of selected antipsychotics. Anticholinergic drugs that pass into the central nervous system may antagonize antipsychotic effects (Linnoila et al, 1980; Mann & Boger, 1978).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Use this combination only when clearly indicated. Monitor for excessive anticholinergic effects. Dosage adjustments may be required.
7) Probable Mechanism: additive anticholinergic effects

3.5.1.E Buspirone
1) Interaction Effect: an increased risk of gastrointestinal bleeding and hyperglycemia
2) Summary: A 33-year old male who was taking clozapine for more than a year without adverse effects, but developed gastrointestinal bleeding and severe hyperglycemia when buspirone therapy was also instituted, has been reported (Good, 1997). Since clozapine can cause gastric ulcer and hyperglycemia by itself, it is possible that buspirone augmented the serum level of clozapine, either by enzyme inhibition or by displacing clozapine from its binding sites.
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Caution should be observed when clozapine and buspirone are coadministered. Monitor blood glucose levels and watch for signs and symptoms of bleeding, especially from the gastrointestinal tract.
7) Probable Mechanism: unknown
8) Literature Reports
a) A 33-year old institutionalized paranoid schizophrenic male was placed on clozapine 600 mg daily for hallucinations and serious assaultiveness. A series of other medications failed to control his feelings of anxiety, so buspirone therapy was initiated at a dose of 5 mg three times daily. His clozapine serum level was 390 ng/mL (range 100-700 ng/mL) prior to buspirone therapy. One month after buspirone was started, the dose was increased to 20 mg daily, and the patient began to complain of nausea and epigastric pain. After an episode of coffee-grounds emesis, he was transferred to the intensive care unit, where he was found to have severe acidosis. His blood glucose level was over 1300 mg/dL, and hematocrit had dropped to 31 mL/dL. Both the clozapine and buspirone were discontinued. An upper gastrointestinal series did not reveal a source of the bleeding, and the patient required insulin therapy until his blood glucose level eventually returned to normal. Clozapine was reinitiated because of his assaultiveness, and he had no recurrence of adverse effects (Good, 1997).

3.5.1.F Carbamazepine
1) Interaction Effect: an increased risk of bone marrow suppression, asterixis, or decreased serum clozapine levels
2) Summary: Clozapine and carbamazepine both have the potential to cause bone marrow suppression, including agranulocytosis (Prod Info Clozaril(R), 2002n). Asterixis (flapping tremor) has also been reported in patients undergoing concurrent therapy with carbamazepine and clozapine (Rittmannsberger, 1996a). In addition, a therapeutic drug monitoring study revealed significantly lower clozapine concentrations when carbamazepine was added to therapy (Jerling et al, 1994c). The mechanism may be due to carbamazepine induction of clozapine metabolism through cytochrome P450 3A4. Controlled studies are needed to further evaluate the pharmacokinetic and clinical effects of combining these agents.
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Avoid concurrent use; an alternative anticonvulsant agent should be considered. If coadministration of these agents is necessary, monitor patients for decreased response to clozapine and agranulocytosis. Lower doses of either clozapine or carbamazepine may be required.

7) Probable Mechanism: additive bone marrow-suppressive effects and neurotoxicity; induction of clozapine metabolism

8) Literature Reports

a) One agranulocytosis fatality has been reported in association with the use of a multi-drug regimen which included clozapine, carbamazepine, clonazepam, benztropine, and lithium (Gerson & Lieberman JA Friedenberg, 1991). This case exhibited pancytopenia which is not characteristic of clozapine-induced agranulocytosis.

b) Over a three-year period, some drug combinations caused a greater risk of asterixis (flapping tremor) in patients on a regimen of multiple psychopharmacologic agents (Rittmannsberger, 1996). With regard to the agents carbamazepine, clozapine, and lithium, incidence of asterixis was greatest in those patients that were on at least two of these three agents. Out of ten patients developing asterixis, five patients received carbamazepine and clozapine as part of multi-drug therapy, and in two cases carbamazepine and clozapine were the sole psychopharmacologic agents. In all cases serum levels of all the drugs were within normal therapeutic ranges, suggesting an additive effect of combination therapy rather than the effect of a single agent.

c) Therapeutic drug monitoring data showed a 50% lower clozapine concentration/dose (C/D) ratio when concurrent carbamazepine was taken compared to clozapine alone. The clozapine C/D ratio was inversely correlated with the dose of carbamazepine. An additional analysis of eight patients confirmed that upon addition of carbamazepine to the drug regimen, clozapine concentrations decreased significantly. The mean C/D ratio during monotherapy was 1.21 and during cotherapy with carbamazepine fell to 0.30. The change in clozapine metabolism was suggested to be due to carbamazepine induction of cytochrome P450 3A4 (Jerling et al, 1994b).

3.5.1.G Cimetidine

1) Interaction Effect: an increased risk of clozapine side effects (dizziness, vomiting, hypotension, bone marrow suppression)

2) Summary: Concomitant administration of drugs known to inhibit the activity of cytochrome P450 isozymes may increase the plasma levels of clozapine, potentially resulting in adverse effects (Prod Info Clozaril(R), 2002a). In a case report the concomitant use of clozapine and cimetidine resulted in elevated serum levels of clozapine and subsequent side effects (Szymanski et al, 1991a).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: With concurrent use, monitor patients for clozapine toxicity. Consider selecting another H2 antagonist (eg, ranitidine or famotidine) that has less potential to alter drug metabolism or switching to another anti-ulcer medication such as sucralfate.

7) Probable Mechanism: cimetidine inhibits cytochrome P450-mediated clozapine metabolism

8) Literature Reports

a) An elevation in the serum level of clozapine and subsequent side effects developed following the administration of cimetidine in a patient receiving clozapine 900 mg/day. The patient did not experience any side effects with the concomitant administration of cimetidine 800 mg/day. However, within 3 days following an increase to cimetidine 1200 mg/day, marked diaphoresis, dizziness, vomiting, severe orthostatic hypotension, and generalized weakness developed. Cimetidine was discontinued and the clozapine dose was reduced to 200 mg/day; symptoms gradually resolved over 5 days. Clozapine was reinitiated over 1 week to 900 mg/day. The patient continued to experience epigastric distress; therefore, ranitidine 150 mg twice daily was instituted and no interaction has been identified over a 3-month follow-up (Szymanski et al, 1991).

3.5.1.H Ciprofloxacin

1) Interaction Effect: increased clozapine serum concentrations and increased risk of side effects (sedation, incoordination, slurred speech, seizures, hematologic abnormalities)

2) Summary: Concomitant administration of drugs known to inhibit the activity of cytochrome P450 isozymes, such as ciprofloxacin, may increase the plasma levels of clozapine, potentially resulting in adverse effects (Brouwers et al, 2009; Prod Info CLOZARIL(R) tablets, 2005a).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: Monitor patients for signs and symptoms of clozapine intoxication (sedation, incoordination, slurred speech, seizures, hematologic abnormalities). Doses of clozapine may need to be reduced when ciprofloxacin is added to therapy.

7) Probable Mechanism: inhibition of cytochrome P450 3A4 by ciprofloxacin resulting in delayed clozapine metabolism

8) Literature Reports

a) Coadministration of ciprofloxacin and clozapine led to elevated clozapine plasma level in a 46-year-old male presented with urosepsis. History included smoking, caffeine use, and treatment at a psychiatric facility with citalopram, lorazepam, valproic acid, and clozapine. He was treated with a 5-day course of IV ciprofloxacin 400 mg twice daily and amoxicillin while on maintenance therapy of clozapine 900 mg daily for paranoid schizophrenia, and was discharged after 4 days in good condition. He

returned 3 days later with suspected rhabdomyolysis, but did not report any pain. Lab results indicated creatine phosphokinase (CPK) levels of 195,000 units per liter, lactic dehydrogenase (LDH) of 6687 units per liter, aspartate aminotransferase (AST) 845 units per liter, alanine aminotransferase (ALT) of 93 units per liter, and a urine test positive for myoglobin. Clozapine treatment was stopped and high-volume alkaline diuresis started. Three days after the end of ciprofloxacin treatment and one day after stopping clozapine, the patient's clozapine plasma concentration was 890 nanograms/mL, higher than the recommended therapeutic concentration of 350 to 600 ng/mL. Five days after stopping clozapine, the clozapine plasma concentration was undetectable. LDH, AST, and ALT concentrations returned to normal by day 18, and CPK levels returned to normal by day 28. The patient did not show signs of worsening psychotic symptoms after the cessation of clozapine; however, clozapine was restarted 2 weeks after discharge. The Drug Interaction Probability Scale (DIPS) score was 5, indicating a probable reaction between the clozapine and the ciprofloxacin (Brouwers et al, 2009).

b) Coadministration of ciprofloxacin and clozapine led to elevated clozapine plasma level in a 58-year-old male presented with delirium and suspected urinary tract infection or pneumonia. History included smoking, caffeine use, and treatment at a psychiatric facility with valproic acid, hydrochlorothiazide, clonazepam, and clozapine 300 mg per day. Lab results before the addition of ciprofloxacin indicated normal aspartate aminotransferase (AST; 10 units/L) and alanine aminotransferase (ALT; 13 units/L) levels, and his clozapine plasma concentration was 850 nanograms/mL. He was treated with IV ciprofloxacin 200 mg twice daily. AST and ALT levels slightly increased (46 and 74 units/liter, respectively), and ciprofloxacin was stopped after 2 days due to the suspected drug-drug interaction between ciprofloxacin and clozapine. Three days after the start of ciprofloxacin treatment, the patient's clozapine plasma concentration was 1720 ng/mL although he did not show signs of rhabdomyolysis or other clozapine-induced adverse effects. He was discharged after 5 days. The Drug Interaction Probability Scale (DIPS) score was 6, indicating a probable reaction between the clozapine and the ciprofloxacin (Brouwers et al, 2009).

3.5.1.I Citalopram

1) Interaction Effect: an increased risk of clozapine toxicity (sedation, seizures, hypotension)

2) Summary: Coadministration of clozapine with other drugs that are metabolized by cytochrome P450 2D6, such as antidepressants, should be approached with caution (Prod Info Clozaril(R), 2002f). Five hospitalized patients who had been receiving a constant dose of clozapine for at least two weeks were started on citalopram 20 mg daily. Plasma clozapine levels were closely monitored for 14 days after the start of citalopram. Out of the five participants, one patient experienced an increase in their clozapine level from 0.70 mg/L to 1.16 mg/L. Plasma clozapine levels did not change in one patient, but the other three patients experienced a slight decline. Overall, clozapine mean serum levels were 1.13 mg/L prior to citalopram, 1.07 mg/L following one week of coadministration, and 0.93 mg/L following two weeks of concurrent administration. The ratio of clozapine to norclozapine remained much the same during the study. These results suggest that citalopram use is safe in patients receiving clozapine, although further studies are needed to verify this hypothesis (Taylor et al, 1998).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Monitor the therapeutic efficacy of clozapine and for any evidence of toxicity, particularly when the daily clozapine dose exceeds 300 mg or 3.5 mg/kg. Lower clozapine dosage may be required in some clinical situations.

7) Probable Mechanism: inhibition by citalopram of N-dealkylation and N-oxidation of clozapine via the cytochrome P450 2D6 enzymatic pathway

8) Literature Reports

a) In a case report, Borba and Henderson describe a 39-year-old white male with a 20-year history of DSM-IV schizoaffective disorder, depressive type, who was referred for a trial of clozapine after failing various antipsychotic and antidepressant medications. Prior to switching to clozapine 400 mg/day, the patient's medications included lithium 900 mg/day, risperidone 3 mg/day, and bupropion 300 mg/day. Improvement in positive and negative symptoms occurred with clozapine. Citalopram dosage was 20 mg/day for two weeks then 40 mg/day. The patient experienced worsening sedation, new onset fatigue, enuresis, hypersalivation and mild confusion. The citalopram dose was reduced to 20 mg/day which resulted in complete resolution of symptoms within two weeks. The patient has continued with the combination of clozapine 400 mg/day and citalopram 20 mg/day with good results. The authors conclude that this case report suggests higher serum concentrations of clozapine may result when given with citalopram 40 mg/day. Inhibition of metabolism of clozapine occurs with citalopram 40 mg/day, resulting in higher serum concentrations compared with citalopram 20 mg/day. It has been documented that other selective serotonin reuptake inhibitors (SSRIs) elevate serum clozapine levels by inhibiting CYP1A2 and CYP3A3/4. Presumably, inhibition of CYP1A2 or CYP3A3/4 enzymes with citalopram may be dose related (Borba & Henderson, 2000).

3.5.1.J Dehydroepiandrosterone

1) Interaction Effect: reduced effectiveness of clozapine

2) Summary: Dehydroepiandrosterone (DHEA) levels within the normal range of 100 to 400 microgram/deciliter (mcg/dL) are conducive to optimal treatment of patients with psychosis (Howard, 1992a).

In case reports, patients have been resistant to antipsychotics when DHEA levels were elevated (Howard, 1992a). Patients being treated with clozapine should avoid DHEA supplementation.
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Avoid concomitant use of dehydroepiandrosterone (DHEA) and clozapine. If DHEA is elevated, treatment with dexamethasone 1 mg orally per day may be used to normalize DHEA levels.
7) Probable Mechanism: elevated dehydroepiandrosterone (DHEA) blood levels may reduce responsiveness to clozapine
8) Literature Reports
a) A 24-year-old female diagnosed with schizophrenia was resistant to daily doses of haloperidol 20 milligrams (mg), fluphenazine 40 mg, lithium carbonate 1200 mg, and lithium carbonate 900 mg plus thioridazine 300 mg. The patient appeared Cushinoid with moon face, acne, facial hair, abdominal hair, and a 40 pound weight gain in the previous 8 months. Dehydroepiandrosterone (DHEA) measured as part of an endocrine panel was 725 micrograms/deciliter (mcg/dL) (normal: 100 to 400 mcg/dL). Dexamethasone 1 mg orally at bedtime resulted in substantial improvement within one week. The patient appeared calmer, more alert with improved psychotic symptoms and ability to concentrate. At two weeks, a repeated DHEA level was within normal range (328 mcg/dL). The author concluded that elevated DHEA levels were associated with severe psychosis resistant to conventional antipsychotic therapy (Howard, 1992).
b) A 13-year-old male decompensated with a subsequent two-year period of emotional problems accompanied by heavy use of LSD, hashish, barbiturates, and alcohol. His mental status included bizarre, disorganized, delusional thinking, auditory and visual hallucinations, paranoia, lack of attention to personal hygiene, agitation, and combativeness. He was diagnosed with chronic paranoid schizophrenia; schizophrenia, chronic undifferentiated type, and schizoaffective disorder, excited type. He was resistant to daily doses of trifluoperazine 40 mg, chlorpromazine 400 mg, and imipramine 100 mg. He was also resistant to combination therapy with chlorpromazine 400 mg with thiothixene 80 mg, thioridazine 1000 mg, perphenazine 48 mg with lithium carbonate 1200 mg, clonazepam 4 mg, and carbamazepine 1200 mg daily. Baseline DHEA level exceeded 900 mcg/dL. A seven-day suppression test with dexamethasone 1 mg orally at bedtime resulted in a normal DHEA level of 200 mcg/dL. By day 5, psychosis improved and the patient was well-oriented, conversational, and was making good eye contact. Once dexamethasone was discontinued, rapid decompensation and florid psychosis ensued despite "substantial amounts of psychotropic medications." DHEA increased to 536 mcg/dL. The author concluded that elevated DHEA levels were associated with florid psychosis resistant to conventional antipsychotic therapy (Howard, 1992).

3.5.1.K Droperidol
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Any drug known to have the potential to prolong the QT interval should not be used together with droperidol. Possible pharmacodynamic interactions can occur between droperidol and potentially arrhythmogenic agents such as neuroleptics that prolong the QT interval (Prod Info Inapsine(R), 2001).
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of droperidol and agents that prolong the QT interval, such as neuroleptics, is contraindicated.
7) Probable Mechanism: additive cardiac effects

3.5.1.L Encainide
1) Interaction Effect: increased plasma concentrations of clozapine and or class I antiarrhythmic agents
2) Summary: Coadministration of clozapine with other drugs that are metabolized by cytochrome P450 2D6, such as class I antiarrhythmics, should be approached with caution (Prod Info Clozaril(R), 2002j).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Concomitant use of clozapine with other drugs metabolized by cytochrome P450 2D6, such as class I antiarrhythmic agents, may require lower doses than usually prescribed for either clozapine or the class I antiarrhythmic.
7) Probable Mechanism: competitive substrate inhibition

3.5.1.M Erythromycin
1) Interaction Effect: increased clozapine serum concentrations and risk of side effects (sedation, incoordination, slurred speech, seizures, hematologic abnormalities)
2) Summary: Coadministered erythromycin may inhibit clozapine metabolism, resulting in increased clozapine serum concentrations and clozapine toxicity (Prod Info Clozaril(R), 2002g; Cohen et al, 1996a; Funderburg et al, 1994a). Elevated levels of clozapine have been associated with somnolence, disorientation, dizziness, nausea, seizures, and leukocytosis. It is not known if similar effects will occur when

other macrolide antibiotics are given concomitantly with clozapine.
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor patients for signs and symptoms of clozapine intoxication (sedation, incoordination, slurred speech, seizures, hematologic abnormalities). Doses of clozapine may need to be reduced when erythromycin is added to therapy. Alternatively, consider using azithromycin, which is less likely to interfere with clozapine metabolism, or a non-macrolide antibiotic.
7) Probable Mechanism: inhibition by erythromycin of hepatic cytochrome P450 3A4 metabolism of clozapine
8) Literature Reports
a) A 32-year-old male was being treated with clozapine 800 mg daily for schizophrenia. A week after beginning erythromycin 250 mg four times a day for pharyngitis, he experienced a tonic-clonic seizure followed by a period of postictal confusion. Shortly after the seizure, his clozapine serum concentration was 1300 mcg/mL. Both erythromycin and clozapine were discontinued. Two days later, low-dose clozapine therapy was initiated and gradually increased to the former dose. With a daily clozapine dose of 800 mg, his serum concentration was 700 mcg/mL (Funderburg et al, 1994).
b) A 34-year-old male with schizophrenia was stabilized for three months on a regimen of clozapine 600 mg daily, thiothixene 10 mg three times daily, divalproex sodium 1000 mg three times daily, and propranolol 20 mg three times daily. Three days before admission, he had started erythromycin 333 mg three times a day for a lower respiratory infection. The day after beginning erythromycin, the patient experienced increased somnolence, incoordination, and difficulty walking. Two days later, he had slurred speech, increasing disorientation, and incontinence of urine and stool. On admission, his white blood cell count was 31 X 10(9)/L and his clozapine serum concentration was 1150 mcg/L. Clozapine and erythromycin were discontinued, and intravenous acyclovir, ampicillin, and ceftriaxone were administered for suspected CNS infection. Four days later, treatment with clozapine was resumed, with the dose gradually increased to 600 mg daily. His clozapine serum concentration was 385 mcg/mL and his leukocyte count was normal. The authors postulated that the mechanism of this interaction was inhibition by erythromycin of P450 isoenzymes (including CYP2D6 and CYP3A) responsible for clozapine metabolism (Cohen et al, 1996).
c) Erythromycin was not found to inhibit the metabolism of a single dose of clozapine in twelve healthy male volunteers. Each participant received a single dose of clozapine 12.5 mg alone or in combination with erythromycin 1500 mg daily in a randomized, crossover manner. No significant differences were observed in the clozapine area under the concentration-time curve (AUC), half-life, maximum concentration (Cmax), time to Cmax (tmax), or apparent oral clearance. The authors suggest that cytochrome P450 3A4 (CYP3A4) only plays a minor role in clozapine metabolism (Hagg et al, 1999). However, erythromycin steady-state was not reached in this study, and doses of clozapine used are typically much higher than the starting dose of 12.5 mg.

3.5.1.N Flecainide
1) Interaction Effect: increased plasma concentrations of clozapine and or class I antiarrhythmic agents
2) Summary: Coadministration of clozapine with other drugs that are metabolized by cytochrome P450 2D6, such as class I antiarrhythmics, should be approached with caution (Prod Info Clozaril(R), 2002j).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Concomitant use of clozapine with other drugs metabolized by cytochrome P450 2D6, such as class I antiarrhythmic agents, may require lower doses than usually prescribed for either clozapine or the class I antiarrhythmic.
7) Probable Mechanism: competitive substrate inhibition

3.5.1.O Fluoxetine
1) Interaction Effect: an increased risk of clozapine toxicity (sedation, seizures, hypotension)
2) Summary: With concurrent administration of fluoxetine, increased serum clozapine concentrations have been reported (Prod Info Clozaril(R), 2002m; Centorrino et al, 1994a; Centorrino et al, 1996e; Spina et al, 1998a). Certain adverse effects associated with clozapine are dose-dependent, including sedation (Ayd, 1974) and seizures (Haller & Binder, 1990), and might be expected to occur with concurrent use of these medications.
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor the therapeutic efficacy of clozapine and for any evidence of toxicity, particularly when the daily clozapine dose exceeds 300 mg or 3.5 mg/kg. Lower clozapine dosage may be required in some clinical situations.
7) Probable Mechanism: inhibition by fluoxetine of N-dealkylation and N-oxidation of clozapine via the cytochrome P450 2D6 enzymatic pathway
8) Literature Reports
a) Subjects receiving concurrent clozapine and fluoxetine had 76% higher serum clozapine

concentrations and 61% higher metabolite concentrations on average compared with controls receiving only clozapine. The mean ratio of total drug level (clozapine plus metabolites) to dose was 60% higher and the mean ratio of concentrations to dose was 75% higher in patients receiving clozapine and fluoxetine compared with concentrations in patients receiving clozapine alone (Centorrino et al, 1994).
b) A study evaluated the serum concentrations of clozapine and norclozapine, the major metabolite, when given in combination with the selective serotonin reuptake inhibitors (SSRIs) fluoxetine, paroxetine, and sertraline. Eighty outpatients receiving clozapine all had been diagnosed with schizophrenia or major affective disorder, and 40 of these patients were receiving an SSRI in combination with clozapine. Of these 40 patients, 14 were receiving fluoxetine, 10 were receiving sertraline, and 16 were receiving paroxetine therapy. Among the patients on SSRI therapy, serum concentrations of clozapine and norclozapine were 41.1% and 44.8% higher, respectively, than in matched patients who were not receiving an SSRI. The ratio of clozapine plus norclozapine concentration to dose was also 37.7% higher in patients receiving SSRIs, indicating clozapine impaired clearance. The differences between the three SSRIs were minor, and the study groups were too limited for an accurate statistical comparison between the individual SSRIs (Centorrino et al, 1996d).
c) A 44-year-old male receiving fluoxetine and clozapine was found dead in his yard. The dates of the prescriptions and the number of tablets which remained indicated that he had been taking his medications as prescribed. Autopsy results showed a high therapeutic fluoxetine concentration (0.7 mcg/mL) and also a high therapeutic norfluoxetine concentration (0.6 mcg/mL). Fluoxetine found in his gastric contents also indicated that the medication was being taken as directed. The clozapine blood concentration was in the lethal concentration range (4.9 mcg/mL), but the clozapine in the gastric contents suggested that the clozapine was being taken as prescribed and that the patient had not consumed a large overdose amount prior to his death. Other pathological findings included pulmonary edema, visceral vascular congestion, paralytic ileus, gastroenteritis, and eosinophilia, which are all consistent with clozapine toxicity. The combined central nervous system, respiratory, and cardiovascular depression caused by these two drugs was sufficient to result in the death of this patient, and his death was ruled to be a clozapine overdose due to a fatal drug interaction (Ferslew et al, 1998).
d) Ten institutionalized schizophrenic patients stabilized on clozapine therapy for at least one month participated in a prospective study to evaluate the effect of fluoxetine on clozapine pharmacokinetics. Fluoxetine 20 mg once daily was administered for eight consecutive weeks. Mean plasma clozapine concentrations increased from 348 ng/mL to 550 ng/mL (58%) at week 8. Plasma levels of norclozapine were also increased by 36% (from 280 ng/mL to 381 ng/mL). Clozapine N-oxide levels rose from 89 ng/mL at baseline to 128 ng/mL, representing a 38% increase. However, these increases in clozapine and metabolite plasma concentrations were not associated with significant changes in efficacy or safety (Spina et al, 1998).

3.5.1.P Fluvoxamine

1) Interaction Effect: increased serum clozapine concentrations
2) Summary: Coadministration of clozapine with fluvoxamine has been reported to result in increased clozapine levels and worsening of psychotic symptoms (Prod Info Clozaril(R), 2002c; Chong et al, 1997a; Jerling et al, 1994a). Extrapyramidal symptoms have also been reported with this drug combination (Kuo et al, 1998a). Fluvoxamine, a potent inhibitor of CYP1A2, may decrease metabolism of clozapine, resulting in increased serum concentrations (Chong et al, 1997a; Wetzel et al, 1998a).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Clinicians should be aware of a potential interaction between clozapine and fluvoxamine. If these drugs are given concurrently, monitor patients for increased serum clozapine concentrations, worsening of psychosis, and the development of extrapyramidal symptoms. Downward dosage adjustments of clozapine may be necessary.
7) Probable Mechanism: inhibition of cytochrome P450 1A2-mediated clozapine metabolism
8) Literature Reports
a) Therapeutic drug monitoring data showed higher clozapine concentration/dose ratios in three of four patients when concurrent fluvoxamine was used compared with clozapine alone. In two of these patients, clozapine concentrations were 5 to 10 times higher when fluvoxamine was coadministered. One patient experienced adverse effects, including sedation and urinary incontinence. Inhibition of the CYP1A2 enzyme by fluvoxamine was thought to be the mechanism in this drug interaction (Jerling et al, 1994).
b) One study presented two case reports in which addition of a selective serotonin reuptake inhibitor (SSRI) to clozapine therapy resulted in exacerbation of psychotic symptoms. The first patient, a 26-year old woman with schizophrenia, had been taking clozapine 175 mg per day. Other medications included propranolol for tachycardia and trihexyphenidyl for hypersalivation. After marked improvement in psychotic symptoms but continued compulsive behavior, sertraline 50 mg per day was added. Within four weeks, the patient's obsessive-compulsive symptoms and psychotic symptoms worsened. Plasma clozapine concentrations increased from 325 ng/mL before sertraline therapy to 695 ng/mL after sertraline therapy. Patient 2, a 24-year old woman with schizophrenia, was placed on a regimen of clozapine 500 mg per day which was later increased to 600 mg per day. After fluvoxamine 50 mg per day was started as adjunctive treatment, the patient's clozapine level rose from 1146 ng/mL before

fluvoxamine treatment to 2750 ng/mL after 28 days of fluvoxamine treatment. During this time the patient's compulsive symptoms remained unchanged, but psychotic symptoms worsened. The authors postulated that the worsening of psychotic symptoms could be due to SSRI inhibition of clozapine metabolism by cytochrome P450 isozymes, or an imbalance of the serotonergic and dopaminergic blockade caused by coadministration the two drugs (Chong et al, 1997).
c) Fluvoxamine significantly increased serum levels of clozapine in 16 patients with schizophrenia. Clozapine 2.5 to 3 mg/kg/day was given for 14 days, then fluvoxamine 50 mg daily was added for 14 days. Serum concentrations of clozapine and two metabolites were measured on days 1, 7, and 14. The increase in clozapine serum concentration was approximately 3-fold when given with fluvoxamine compared to clozapine alone (Wetzel et al, 1998).
d) Two patients experienced the onset of extrapyramidal symptoms (EPS) when fluvoxamine was added to an existing regimen that included clozapine. The first patient, a 46-year-old male, was stabilized on clozapine 400 mg daily for more than a year when fluvoxamine 25 mg daily was started. No signs of EPS were present before fluvoxamine therapy, and the clozapine plasma level was 686.2 ng/mL. Four days after fluvoxamine was initiated, the patient experienced rigidity and an Extrapyramidal Symptom Rating Scale (ESRS) score of 6. Three weeks later, the ESRS had increased to 8 and the clozapine level was 817.9 ng/mL. Fluvoxamine was discontinued, and the ESRS score and clozapine level decreased to 1 and 686.8 ng/mL, respectively, three weeks later. The second patient, a 46-year-old female, was maintained on clozapine 600 mg daily for more than two years with a plasma level of 1292.5 ng/mL and no signs of EPS. Fluvoxamine was started at 25 mg daily and six days later she developed moderate akathisia and tremors (ESRS of 7). Three weeks and six weeks into combination therapy, her clozapine plasma levels were 1438.2 ng/mL and 1548.9 ng/mL, respectively. The ESRS increased to 9, but the patient preferred the combination therapy due to the efficacy in alleviating psychotic symptoms (Kuo et al, 1998).

3.5.1.Q Fosphenytoin

1) Interaction Effect: decreased clozapine plasma levels associated with marked worsening of psychosis
2) Summary: Fosphenytoin is a prodrug of phenytoin and the same interactions that occur with phenytoin are expected to occur with fosphenytoin (Prod Info Cerebyx(R), 1999). Two case reports (Miller, 1991a) demonstrate that the addition of phenytoin to clozapine therapy can reduce steady-state plasma concentrations of clozapine by 65% to 85%, resulting in increased psychotic symptoms. Subsequent increases in clozapine dosage may be necessary.
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: When adding fosphenytoin therapy to patients stabilized on clozapine, monitor patient closely for worsening of psychotic symptoms. If needed, increase the clozapine dose cautiously on basis of psychotic symptoms.
7) Probable Mechanism: increased metabolism of clozapine due to induction of cytochrome P-450 enzymes by fosphenytoin
8) Literature Reports
a) Two 29-year-old schizophrenic patients were stabilized on clozapine therapy. Their clozapine plasma concentrations decreased and psychotic symptoms markedly worsened after the addition of phenytoin for seizure activity. Phenytoin reduced clozapine plasma concentrations by 65% to 85% and necessitated an increase in clozapine dosage. The author's possible explanations for the decrease in clozapine plasma concentrations were a) induction of cytochrome P-450 enzymes by phenytoin, causing increased clozapine metabolism, b) decreased clozapine absorption due to phenytoin, and/or c) decreased protein binding of clozapine making more free drug available for metabolism. If the deterioration in clinical status was not related to the decrease in clozapine plasma levels, Miller's possible explanations were rebound psychosis after abruptly decreasing clozapine at the time of seizure activity, spontaneous fluctuation in illness, postictal exacerbation of preexisting psychosis, or postictal psychosis. The author recommends that clinicians closely monitor clozapine patients for worsening of psychotic symptoms when phenytoin is added to therapy (Miller, 1991).

3.5.1.R Guarana

1) Interaction Effect: increased clozapine levels, (leukopenia, agranulocytosis, and seizures) or increased guarana levels, (headache, insomnia, restlessness, diuresis, tachycardia)
2) Summary: The primary ingredient of guarana is caffeine. Caffeine inhibits CYP1A2, a major metabolic pathway for clozapine, thereby decreasing clozapine metabolism with resultant increased clozapine levels (Hagg et al, 2000c; Carrillo et al, 1998c). Patients who consume caffeine, especially acutely, may be at increased risk for clozapine toxicity. A case report has described an acute psychotic exacerbation in a patient taking clozapine who ingested caffeine acutely (Vainer & Chouinard, 1994c). Patients taking clozapine should take caffeine-containing products with caution to maintain a consistent intake.
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Ideally, patients should avoid caffeine-containing products such as guarana as well as coffee, tea, and cola during clozapine treatment. Patients who are unwilling to discontinue caffeine intake

should be instructed to maintain consistent intake, and advised of the consequences of abrupt discontinuation (i.e., decreased clozapine levels and decreased effectiveness). Conversely, if a patient has been stabilized on clozapine and initiates a significant intake of caffeine, clozapine metabolism will likely be decreased, resulting in increased clozapine blood levels. Such patients will then be at increased risk for clozapine toxicity that may manifest as leukopenia, agranulocytosis, and seizures.

7) Probable Mechanism: caffeine component of guarana may inhibit metabolism of clozapine or clozapine may also inhibit the metabolism of caffeine

8) Literature Reports

a) In 12 healthy, nonsmoking subjects, caffeine intake increased clozapine area under the curve (AUC) following a single dose of clozapine in a randomized, crossover trial. Subjects refrained from other medication use during and 2 weeks prior to the study. Clozapine was administered as a 12.5 milligram (mg) dose. Dietary caffeine intake was allowed during the caffeine phase but not during the clozapine control phase, and was registered and estimated. Total caffeine intake during the caffeine phase ranged from 500-700 mg on day 1, and 400-1000 mg on day 2 (mean 550 mg/day). In one subject, clozapine AUC was doubled with concomitant caffeine intake, indicating individual variation. Overall, clozapine AUC was increased 19% as a result of caffeine intake (p equal to 0.05), with a range from -14% to +97%. Clozapine clearance was decreased 14% as a result of caffeine intake (p equal to 0.05), with a range from -49% to +7% (Hagg et al, 2000b).

b) In a study of 7 hospitalized patients (six men and one woman) averaging 31.0 +/- 5.5 years (range: 25-41 years) with a DSM-IV diagnosis of schizophrenia, clozapine levels decreased when caffeine was removed from the diet. All patients received monotherapy with clozapine at 271 +/- 102 milligrams/day (mg/day). Clozapine, norclozapine, and clozapine-N-oxide were assayed in plasma by high-performance liquid chromatography. Assays were conducted at three time points: with concomitant intake of caffeine, 5 days after caffeine withdrawal, and 2 weeks after rechallenge with habitual caffeine intake (mean caffeine intake: 296.4 +/- 354.8 mg; range: 150-1100 mg daily). Clozapine levels decreased from 486 nanograms/milliliter (ng/mL) during initial concomitant intake to 306 ng/mL (-47%) (p less than 0.02) 5 days after a caffeine-free diet. Clozapine-N-oxide levels decreased from 66 to 49 ng/mL (-31%) (p less than 0.03). All parameters returned to initial values after 2 weeks of resumption of caffeine intake (Carrillo et al, 1998b).

c) In a study of 14 healthy volunteers, clozapine metabolism was found to co-vary with CYP1A2 activity as determined by concomitant caffeine metabolism. Subjects were administered caffeine 150 mg as an oral tablet with clozapine 10 mg orally. N1- and N7-demethylation indices of caffeine correlated with clozapine clearance (r (s) equal to 0.89 and 0.85; p equal to 0.0013 and 0.0023, respectively). The authors conclude that 70% of the variance of clozapine clearance was accounted for by caffeine N3-demethylation reflecting CYP1A2 activity. There was no correlation between the area under the curve (AUC) for clozapine and the caffeine indices of xanthine oxidase (r(s) equal to -0.32) or N-acetyl transferase (rs equal to -0.33) activity (Bertilsson et al, 1994a).

d) Supraventricular tachycardia (SVT) was reported in a 66-year-old woman administered clozapine and caffeine while receiving electroconvulsive therapy (ECT). The patient suffered from severe, recurrent, affect psychosis necessitating ECT. During her first course of ECT, the duration of seizures decreased, requiring caffeine sodium benzoate 1000 mg (titrated from an initial dose of 125 mg). Although arrhythmias are a known side effect of ECT, none occurred, including none during augmentation with caffeine. Despite an initial response, the patient relapsed and was started on clozapine, titrated to a dosage of 300 mg daily. After one week, ECT was re-instituted with caffeine sodium benzoate titrated to 500 mg by the ninth treatment. The patient developed SVT with a heart rate of 180 beats/minute. The patient responded to verapamil 5 mg intravenously, converting to sinus tachycardia at 102 beats/minute and recovered uneventfully. Interestingly, 1000 mg intravenous caffeine augmentation was tolerated during the first course of therapy but 500 mg was not tolerated during the course of therapy accompanied by clozapine administration. This is suggestive of a caffeine-clozapine interaction (Beale et al, 1994a).

e) A 39-year-old man with paranoid schizophrenia with long-standing refractoriness to neuroleptics was treated with clozapine titrated up to 150 mg daily within 6 months of initiation. Clozapine was taken with two cups of coffee and the patient experienced a short-lasting acute psychotic exacerbation characterized by marked anxiety, agitation, insomnia, weakness, headaches, generalized stiffness, and intense paranoid ideation. These acute reactions were completely prevented when water replaced coffee. The acute episodes resumed when he took 200 mg/day clozapine with a caffeinated cola (40-50mg caffeine in each 12-ounce bottle). When taken with a decaffeinated cola beverage, the patient had no acute psychotic episodes (Vainer & Chouinard, 1994b).

3.5.1.S Lithium

1) Interaction Effect: weakness, dyskinesias, increased extrapyramidal symptoms, encephalopathy, and brain damage

2) Summary: An encephalopathic syndrome followed by irreversible brain damage has occurred in a few patients treated with lithium plus a dopamine-2 antagonist, particularly haloperidol. A causal relationship between these events and the concomitant administration of a dopamine-2 antagonist and lithium has not been established (Prod Info LITHOBID(R) slow-release oral tablets, 2005). Coadministration of lithium and a number of antipsychotic drugs has caused a wide variety of encephalopathic symptoms, brain damage, extrapyramidal symptoms, and dyskinesias in isolated case reports. In most cases, these effects have

occurred with therapeutic lithium levels (Amdisen, 1982; Prakash, 1982; Addonizio et al, 1988a). However, many series and trials have reported using such combinations with no severe adverse consequences (Goldney & Spence, 1986). The mechanism is not fully understood, but chronic lithium treatment decreases neostriatal dopaminergic activity, probably through a direct action on the G protein and the capacity of the G proteins, once activated, to stimulate adenyl cyclase (Carli et al, 1994). Hyperglycemic reactions have also occurred during combined phenothiazine and lithium use (Zall et al, 1968).

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Monitor patients closely for any signs of toxicity or extrapyramidal symptoms, especially if high doses of dopamine-2 antagonists, particularly haloperidol, and lithium are used. Serum lithium levels should be monitored periodically. Some clinicians advocate maintaining levels in the low therapeutic range.

7) Probable Mechanism: unknown

8) Literature Reports

a) Concomitant haloperidol and lithium therapy has resulted in symptoms of encephalopathy, confusion, extrapyramidal symptoms, and fever in several patients with mania (Cohen & Cohen, 1974; Loudon & Waring, 1976; Thomas, 1979). Irreversible neurological injuries have been reported (Sandyk & Hurwitz, 1983; Keitner & Rahman, 1984).

b) Seizures, encephalopathy, delirium, and abnormal EEG occurred in four patients during combined lithium and thioridazine therapy (Spring, 1979). Serum lithium levels were below 1 mEq/L at the time of the toxic reaction in all cases. All patients had previously tolerated lithium in combination with another phenothiazine. Three of these patients developed symptoms within eight days of initiating combination therapy.

c) The addition of lithium to neuroleptic therapy exacerbated extrapyramidal symptoms (EPS) in a small study (Addonizio et al, 1988). The patients had received at least five days of treatment with either oral thiothixene, haloperidol, or fluphenazine in mean doses of 607.5 chlorpromazine equivalents prior to initiation of the lithium and were experiencing drug-induced extrapyramidal symptoms. Oral lithium was added when clinically indicated in sufficient doses to achieve a therapeutic serum concentration. The maximum levels attained were 0.65 to 1.27 mEq/L. The EPS ratings increased in all ten patients following the addition of lithium. However, only three patients developed marked symptoms and no patient developed lithium toxicity. Significantly increased symptoms included gait, shoulder shaking, elbow rigidity, and tremor.

d) Ten patients treated with clozapine and lithium were studied (Blake et al, 1992). Of the ten patients, four experienced significant neurologic effects, including jerking of limbs, facial spasms and tics, tremor of hands and arms, tongue twitching, and stumbling gait. One of these also experienced delirium. These effects reversed when lithium was discontinued or given at a lower dose. On rechallenge, one of two patients suffered recurrence of symptoms. By keeping serum lithium no greater than 0.5 mEq/L, clozapine could be safely coadministered.

e) Chlorpromazine serum levels can be significantly reduced in the presence of lithium treatment. If used concurrently, abrupt cessation of lithium may result in rebound elevation of chlorpromazine levels, resulting in chlorpromazine toxicity. In patients on a lithium-chlorpromazine combination, abrupt withdrawal of the lithium may precipitate chlorpromazine cardiotoxicity. In this report, such toxicity was manifested as sudden ventricular fibrillation associated with prolongation of the QTc interval. Hypotension and EPS are also possible in this situation (Stevenson et al, 1989).

f) However, other data do not support that such adverse events are frequent or indeed causally related to combination therapy. Combination of dopamine antagonist antipsychotic drugs and lithium have been used successfully in many patients with manic-depressive illness. It has been proposed that the interaction may only become significant with very high doses of one or both drugs or with failure to discontinue dosing in the presence of toxic symptoms (Miller & Menninger, 1987).

g) A 69-year-old patient with oxygen-dependent chronic obstructive pulmonary disorder and a 25-year history of bipolar disorder was started on risperidone 3 mg for the treatment of new-onset auditory and visual hallucinations. She had also been maintained on a regimen of lithium (450 mg daily) for more than 10 years. In addition, she was given amantadine (100 mg twice daily) for tremor. Three weeks after the start of risperidone, the patient experienced a decline in mental status in addition to dizziness, worsening tremors, nausea and vomiting, polyuria, depression, and visual and auditory hallucinations. She was then admitted to the hospital for delirium. Her lithium serum level was 1.36 mEq/L at the time of the admission. All medications were discontinued. Although her lithium level decreased to 0.41 mEq/L, she continued to experience profound delirium, tremors, lethargy, and hallucinations for almost one week. After she started to respond to commands, she was restarted on lithium (300 mg at bedtime) because of the onset of mild hypomania. Five days later, she was discharged with a regimen of lithium and low-dose lorazepam for treatment of insomnia. It is suggested that delirium could have been caused by the concurrent use of lithium and risperidone. Other factors could also have caused delirium, such as the patient's serum lithium level and the underlying pulmonary pathology. In addition, amantadine, which facilitates the release of presynaptic dopamine and has a mild anticholinergic effect, may have contributed (Chen & Cardasis, 1996).

3.5.1.T Lorazepam

1) Interaction Effect: CNS depression
2) Summary: Two cases have been reported in which concomitant use of clozapine and lorazepam resulted in marked sedation, excessive salivation, and ataxia (Cobb et al, 1991). The manufacturer advises caution when giving clozapine with a benzodiazepine (Prod Info Clozaril(R), 1997).
3) Severity: minor
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Monitor for signs of intoxication (eg, marked sedation, dizziness, ataxia, weakness, decreased cognition or motor performance, excessive salivation). If symptoms are present, reduce lorazepam dose.
7) Probable Mechanism: additive

3.5.1.U Lorcainide

1) Interaction Effect: increased plasma concentrations of clozapine and or class I antiarrhythmic agents
2) Summary: Coadministration of clozapine with other drugs that are metabolized by cytochrome P450 2D6, such as class I antiarrhythmics, should be approached with caution (Prod Info Clozaril(R), 2002j).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Concomitant use of clozapine with other drugs metabolized by cytochrome P450 2D6, such as class I antiarrhythmic agents, may require lower doses than usually prescribed for either clozapine or the class I antiarrhythmic.
7) Probable Mechanism: competitive substrate inhibition

3.5.1.V Mate

1) Interaction Effect: inhibition of clozapine metabolism (increasing the risk for leukopenia, agranulocytosis, and seizures) or inhibition of mate metabolism (headache, insomnia, restlessness, diuresis, tachycardia)
2) Summary: One of the primary ingredients of mate is caffeine. Caffeine inhibits CYP1A2, a major metabolic pathway for clozapine, thereby decreasing clozapine metabolism with resultant increased clozapine levels (Hagg et al, 2000a; Carrillo et al, 1998a). Patients who consume caffeine, especially acutely, may be at increased risk for clozapine toxicity. A case report has described an acute psychotic exacerbation in a patient taking clozapine who ingested caffeine acutely (Vainer & Chouinard, 1994a). Patients taking clozapine should take caffeine-containing products with caution to maintain a consistent intake.
3) Severity: major
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Ideally, patients should avoid caffeine-containing products such as mate as well as coffee, tea, and cola during clozapine treatment. Patients who are unwilling to discontinue caffeine intake should be instructed to maintain consistent intake, advising them of the consequences of abrupt discontinuation (i.e., decreased clozapine levels and decreased effectiveness). Conversely, if a patient has been stabilized on clozapine and initiates a significant intake of caffeine, clozapine metabolism will likely be decreased, resulting in increased clozapine blood levels. Such patients will then be at increased risk for clozapine toxicity that may manifest as leukopenia, agranulocytosis, and seizures.
7) Probable Mechanism: caffeine inhibits CYP1A2 activity and can increase clozapine levels; caffeine was also found to inhibit clozapine clearance
8) Literature Reports

a) In 12 healthy, nonsmoking subjects, caffeine intake increased clozapine area under the curve (AUC) following a single dose of clozapine in a randomized, crossover trial. Subjects refrained from other medication use during and 2 weeks prior to the study. Clozapine was administered as a 12.5 milligram (mg) dose. Dietary caffeine intake was allowed during the caffeine phase but not during the clozapine control phase, and was registered and estimated. Total caffeine intake during the caffeine phase ranged from 500-700 mg on day 1, and 400-1000 mg on day 2 (mean 550 mg/day). In one subject, clozapine AUC was doubled with concomitant caffeine intake, indicating individual variation. Overall, clozapine AUC was increased 19% as a result of caffeine intake (p equal to 0.05), with a range from -14% to +97%. Clozapine clearance was decreased 14% as a result of caffeine intake (p equal to 0.05), with a range from -49% to +7% (Hagg et al, 2000).

b) In a study of 7 hospitalized patients (six men and one woman) averaging 31.0 +/- 5.5 years (range: 25-41 years) with a DSM-IV diagnosis of schizophrenia, clozapine levels decreased when caffeine was removed from the diet. All patients received monotherapy with clozapine at 271 +/- 102 milligrams/day (mg/day). Clozapine, norclozapine, and clozapine-N-oxide were assayed in plasma by high-performance liquid chromatography. Assays were conducted at three time points: with concomitant intake of caffeine, 5 days after caffeine withdrawal, and 2 weeks after rechallenge with habitual caffeine intake (mean caffeine intake: 296.4 +/- 354.8 mg; range: 150-1100 mg daily). Clozapine levels decreased from 486 nanograms/milliliter (ng/mL) during initial concomitant intake to 306 ng/mL (-47%) (p less than 0.02) 5 days after a caffeine-free diet. In a similar fashion, clozapine-N-oxide levels decreased from 66 to 49 ng/mL (-31%) (p less than 0.03). All parameters returned to initial values after 2 weeks of resumption of caffeine intake (Carrillo et al, 1998).

c) In a study of 14 healthy volunteers, clozapine metabolism was found to co-vary with CYP1A2 activity as determined by concomitant caffeine metabolism. Subjects were administered caffeine 150 mg as an oral tablet with clozapine 10 mg orally. N1- and N7-demethylation indices of caffeine correlated with clozapine clearance (rs equal to 0.89 and 0.85; p equal to 0.0013 and 0.0023, respectively). The authors conclude that 70% of the variance of clozapine clearance was accounted for by caffeine N3-demethylation reflecting CYP1A2 activity. There was no correlation between the area under the curve (AUC) for clozapine and the caffeine indices of xanthine oxidase (rs equal to -0.32) or N-acetyl transferase (rs equal to -0.33) activity (Bertilsson et al, 1994).
d) Supraventricular tachycardia (SVT) was reported in a 66-year-old woman administered clozapine and caffeine while receiving electroconvulsive therapy (ECT). The patient suffered from severe, recurrent, affect psychosis necessitating ECT. During her first course of ECT, the duration of seizures decreased, requiring caffeine sodium benzoate 1000 mg (titrated from an initial dose of 125 mg). Although arrhythmias are a known side effect of ECT, none occurred, including none during augmentation with caffeine. Despite an initial response, the patient relapsed and was started on clozapine, titrated to a dosage of 300 mg daily. After one week, ECT was re-instituted with caffeine sodium benzoate titrated to 500 mg by the ninth treatment. The patient developed SVT with a heart rate of 180 beats/minute. The patient responded to verapamil 5 mg intravenously, converting to sinus tachycardia at 102 beats/minute and recovered uneventfully. Interestingly, 1000 mg intravenous caffeine augmentation was tolerated during the first course of therapy but 500 mg was not tolerated during the course of therapy accompanied by clozapine administration. This is suggestive of a caffeine-clozapine interaction (Beale et al, 1994).
e) A 39-year-old man with paranoid schizophrenia with long-standing refractoriness to neuroleptics was treated with clozapine titrated up to 150 mg daily within 6 months of initiation. Clozapine was taken with two cups of coffee and the patient experienced a short-lasting acute psychotic exacerbation characterized by marked anxiety, agitation, insomnia, weakness, headaches, generalized stiffness, and intense paranoid ideation. These acute reactions were completely prevented when water replaced coffee. The acute episodes resumed when he took 200 mg/day clozapine with a caffeinated cola (40-50mg caffeine in each 12-ounce bottle). When taken with a decaffeinated cola beverage, the patient had no acute psychotic episodes (Vainer & Chouinard, 1994).
f) Caffeine-induced reinforcement of dopaminergic enhancement may predispose some patients to exacerbations of psychosis. Caffeine elimination does not appear to improve or worsen schizophrenia. Chronic use of caffeine may lead to tolerance of adverse effects (Hughes et al, 1998).

3.5.1.W Nefazodone

1) Interaction Effect: increased clozapine plasma concentrations and clozapine toxicity (sedation, seizures, hypotension)
2) Summary: A study reported clozapine concentrations increased by an average of 19 mcg/L (4% of baseline) and norclozapine concentrations increased by 46 mcg/L (16% of baseline) (Taylor et al, 1999a). Concomitant administration of nefazodone resulted in decreased clearance resulting in elevated plasma concentrations of clozapine and norclozapine in a 40-year-old male. Seven days after initiation of treatment with nefazodone, the patient was increasingly anxious, increasingly dizzy and had mild hypotension. Nefazodone dose reduction resolved the patient's hypotension and other symptoms. Nefazodone may cause a modest, dose-dependent reduction in the clearance of both clozapine and norclozapine, with resultant increases in serum concentrations. The author suggests that this effect may be due to nefazodone inhibition of the cytochrome P450 3A4 isoenzyme. Caution is suggested when prescribing nefazodone concomitantly with clozapine (Khan & Preskorn, 2001a).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor the therapeutic efficacy of clozapine and for any evidence of toxicity, particularly when the daily clozapine dose exceeds 300 mg or 3.5 mg/kg. Lower clozapine dosage may be required in some clinical situations.
7) Probable Mechanism: inhibition of cytochrome P450-mediated clozapine metabolism by nefazodone
8) Literature Reports
a) Concomitant administration of nefazodone may result in decreased clearance resulting in elevated plasma concentrations of clozapine and norclozapine. A 40-year-old male with a history of schizophrenia was successfully treated with clozapine and risperidone for several years. After experiencing persistent negative symptoms, nefazodone was initiated at 200 mg/day for seven days and then increased to 300 mg/day. Seven days later, the patient reported increased anxiety and dizziness. Physical exam revealed mild hypotension. An increase in plasma concentrations and decrease in clearance of both clozapine and norclozapine was documented. Nefazodone dose was reduced to 200 mg/day and, within one week, the patient's symptoms and hypotension resolved. Nefazodone may cause a modest, dose-dependent reduction in the clearance of both clozapine and norclozapine, with resultant increases in serum concentrations. The author suggests that this effect may be due to nefazodone inhibition of the cytochrome P450 3A4 isoenzyme. Caution is suggested when prescribing nefazodone concomitantly with clozapine (Khan & Preskorn, 2001).
b) Six patients receiving a stable dose of clozapine for at least two weeks were selected to begin nefazodone therapy at 100 mg twice daily for one week and then 200 mg daily for two more weeks. The

overall changes in clozapine pharmacokinetics were minimal when nefazodone was coadministered. Clozapine concentrations increased by an average of 19 mcg/L (4% of baseline) and norclozapine concentrations increased by 46 mcg/L (16% of baseline). Cytochrome P450 3A4 (CYP3A4) has been postulated to play a significant role in the metabolism of clozapine. Nefazodone is an inhibitor of CYP3A4. Because this study failed to show a significant interaction between these two drugs, CYP3A4 may play only an insignificant role in the metabolism of clozapine, or alternative routes of metabolism may be activated when CYP3A4 is inhibited (Taylor et al, 1999).

3.5.1.X Nicotine

1) Interaction Effect: decreased plasma clozapine levels
2) Summary: Concomitant administration of agents known to induce cytochrome P450 enzymes such as nicotine, may decrease the plasma levels of clozapine. This may result in a decrease in effectiveness of a previously effective clozapine dose (Prod Info Clozaril(R), 2002b).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Observe patients for signs and symptoms of decreased clozapine efficacy when nicotine is added to clozapine.
7) Probable Mechanism: induction of cytochrome P450-mediated clozapine metabolism by nicotine

3.5.1.Y Norfloxacin

1) Interaction Effect: increased clozapine serum concentrations
2) Summary: In vitro studies have shown that quinolones, including norfloxacin, are CYP1A2 inhibitors. Concomitant use with clozapine, a CYP1A2 substrate, may result in increased clozapine serum levels when given in usual doses. Caution is advised if these agents are used together. Monitor patients closely for signs and symptoms of clozapine intoxication (Prod Info NOROXIN(R) oral tablets, 2006).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of clozapine and norfloxacin may result in increased clozapine serum levels when given in usual doses. Use caution if these agents are used together and monitor patients closely (Prod Info NOROXIN(R) oral tablets, 2006). Signs and symptoms of clozapine intoxication may include sedation, incoordination, slurred speech, seizures, hematologic abnormalities.
7) Probable Mechanism: inhibition of CYP1A2-mediated clozapine metabolism

3.5.1.Z Paroxetine

1) Interaction Effect: an increased risk of clozapine toxicity (sedation, seizures, hypotension)
2) Summary: Increased serum concentrations of clozapine and its metabolites have been observed when it is given with serotonin reuptake inhibitors; however, other published reports describe paroxetine having no effect on serum concentrations of clozapine or its metabolites (Prod Info Clozaril(R), 2002l; Centorrino et al, 1996c; Wetzel et al, 1998c).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor for signs of clozapine toxicity or serum concentrations when paroxetine is given concomitantly.
7) Probable Mechanism: decreased clozapine metabolism
8) Literature Reports

a) Paroxetine had no significant effect on serum levels of clozapine in 14 patients with schizophrenia. Clozapine 2.5 to 3 mg/kg/day was given for 14 days, then paroxetine 20 mg daily was added for 14 days. Serum concentrations of clozapine and two metabolites were measured on days 1, 7, and 14. Over the course of this study there was no significant difference in serum concentrations of clozapine or its metabolites (Wetzel et al, 1998b).

b) Serum concentrations of clozapine and norclozapine, the major metabolite, were evaluated when given in combination with the selective serotonin reuptake inhibitors (SSRIs) fluoxetine, paroxetine, and sertraline. Eighty outpatients receiving clozapine all had been diagnosed with schizophrenia or major affective disorder, and 40 of these patients were receiving an SSRI in combination with clozapine. Of these 40 patients, 14 were receiving fluoxetine, 10 were receiving sertraline, and 16 were receiving paroxetine therapy. Among the patients on SSRI therapy, serum concentrations of clozapine and norclozapine were 41.1% and 44.8% higher, respectively, than in matched patients who were not receiving an SSRI. The ratio of clozapine plus norclozapine concentration to dose was also 37.7% higher in patients receiving SSRIs, indicating clozapine impaired clearance. The differences between the three SSRIs were minor, and the study groups were too limited for an accurate statistical comparison between the individual SSRIs (Centorrino et al, 1996b).

3.5.1.AA Perphenazine

1) Interaction Effect: increased plasma concentrations of clozapine and or the phenothiazine
2) Summary: Coadministration of clozapine with other drugs that are metabolized by cytochrome P450 2D6,

such as phenothiazines, should be approached with caution (Prod Info Clozaril(R), 2002h).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Concomitant use of clozapine with other drugs metabolized by cytochrome P450 2D6, such as phenothiazines, may require lower doses than usually prescribed for either clozapine or the phenothiazine.
7) Probable Mechanism: competitive substrate inhibition

3.5.1.AB Phenobarbital
1) Interaction Effect: decreased clozapine plasma levels associated with marked worsening of psychosis
2) Summary: Clozapine levels have been reported to be markedly elevated when phenobarbital therapy was discontinued (Lane et al, 1998a). Two case reports (Miller, 1991b) demonstrate that the addition of phenytoin, another enzyme inducer, to clozapine therapy can reduce steady-state plasma concentrations of clozapine by 65% to 85%, resulting in increased psychotic symptoms. Phenobarbital is capable of inducing multiple cytochrome P450 enzyme systems, including CYP1A2 and CYP3A4. Because clozapine is metabolized primarily by CYP1A2, a significant interaction with phenobarbital is possible (Lane et al, 1998a). A study conducted with 22 schizophrenic patients revealed 35% lower clozapine concentrations when given concurrently with phenobarbital, versus clozapine administration alone. In addition, the clozapine N-oxide metabolite concentrations were 64% higher, supporting the theory that phenobarbital induces clozapine metabolism (Facciola et al, 1998a).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When adding phenobarbital therapy to patients stabilized on clozapine, monitor patient closely for worsening of psychotic symptoms. If needed, increase the clozapine dose cautiously on the basis of psychotic symptoms. Conversely, when discontinuing phenobarbital, levels of clozapine may increase significantly.
7) Probable Mechanism: increased metabolism of clozapine due to induction of cytochrome P450 enzymes by phenobarbital
8) Literature Reports
a) A 26-year-old male schizophrenic patient was stabilized on clozapine 300 mg twice daily when he experienced a seizure. Phenobarbital 60 mg daily was initiated, and the clozapine dose was decreased to 400 mg daily over a period of two months because of the patient's stable mental status. One month after the clozapine dose was at 400 mg daily, the plasma levels for clozapine and its major metabolites, desmethylclozapine and clozapine-N-oxide were 346 ng/mL, 241 ng/mL, and 65 ng/mL, respectively. Phenobarbital therapy was tapered off over one month. Two and four weeks after the discontinuation of phenobarbital, the clozapine, desmethylclozapine, and clozapine-N-oxide levels were 608 ng/mL and 602 ng/mL, 253 ng/mL and 280 ng/mL, and 87 ng/mL and 96 ng/mL, respectively. The increase in the plasma levels of clozapine and its metabolites may be due to the fact that phenobarbital is an inducer of cytochrome P450 1A2 enzymes, and discontinuing phenobarbital slowed the metabolism of clozapine (Lane et al, 1998).
b) Steady-state plasma concentrations of clozapine and its two major metabolites were compared in 22 schizophrenic patients. Patients were distributed into two groups, either receiving clozapine monotherapy, or clozapine plus phenobarbital. The two groups were matched for age, sex, body weight, and daily dosage of clozapine. The group receiving combined therapy demonstrated mean plasma concentrations of clozapine which were 35% lower than the monotherapy group. In addition, the mean clozapine N-oxide metabolite concentrations were 64% higher in the combined therapy group. The authors concluded that these findings support the theory that phenobarbital induces metabolism of clozapine, and recommended careful monitoring of clozapine plasma concentrations when combined with phenobarbital (Facciola et al, 1998).

3.5.1.AC Phenylalanine
1) Interaction Effect: increased incidence of tardive dyskinesia
2) Summary: Taking phenylalanine concomitantly with certain neuroleptic drugs may exacerbate tardive dyskinesia (Gardos et al, 1992a). Abnormal phenylalanine metabolism in certain patients may lead to phenylalanine accumulation in the brain and in turn, reduced brain availability of other large neutral amino acids. This may interfere with the synthesis of catecholamines (Gardos et al, 1992a).
3) Severity: moderate
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Caution is advised if phenylalanine is administered with a neuroleptic agent. Monitor the patient closely for signs of tardive dyskinesia.
7) Probable Mechanism: reduced brain availability of other large neutral amino acids and interference with catecholamine synthesis
8) Literature Reports
a) Phenylalanine tended to increase the incidence of tardive dyskinesia in patients taking neuroleptics in an open study. Three groups of patients were studied: (1) patients with unipolar depression with

tardive dyskinesia (n=11), (2) patients with no tardive dyskinesia with current or past exposure to greater than or equal to 100 milligrams (mg) of a chlorpromazine equivalent for at least 3 months (n=10), and (3) patients with no tardive dyskinesia not previously exposed to a neuroleptic drug (n=10). Neuroleptic agents were taken during the study by 6 patients in group 1, and 5 patients in group 2. Patients received powdered phenylalanine 100 mg/kilogram dissolved in orange juice after an overnight fast. Blood samples were obtained just prior to phenylalanine administration and 2 hours after administration. Three patients in group 1 (with tardive dyskinesia) had the highest postloading phenylalanine plasma levels, this group as a whole had higher (though nonsignificant) mean phenylalanine levels than the other groups. Tardive dyskinesia score (measured using the Abnormal Involuntary Movements Scale (AIMS)) nonsignificantly increased in group 1. Postloading phenylalanine level and postloading AIMS scores were significantly positively correlated in group 1 (rs=0.347, p less than 0.05; Spearman correlation coefficient 0.543, p less than 0.05). Postloading phenylalanine level and baseline AIMS scores demonstrated a trend toward correlation (rs=0.246, p=0.092; Spearman correlation coefficient 0.679, p less than 0.05). In all patients, phenylalanine loading increased plasma phenylalanine levels approximately eight-fold, and plasma tyrosine increased 2.5 times as a result of conversion of phenylalanine to tyrosine. Plasma levels of competing large neutral amino acids such as tryptophan decreased slightly (Gardos et al, 1992).

3.5.1.AD Phenytoin

1) Interaction Effect: decreased clozapine plasma levels associated with marked worsening of psychosis
2) Summary: Concomitant administration of drugs known to induce cytochrome P450 enzymes may decrease the clozapine plasma levels, resulting in a decrease in effectiveness of a previously effective clozapine dose (Prod Info Clozaril(R), 2002e). Two case reports (Miller, 1991d) demonstrate that the addition of phenytoin to clozapine therapy can reduce steady-state plasma concentrations of clozapine by 65% to 85%, resulting in increased psychotic symptoms. Subsequent increases in clozapine dosage may be necessary.
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When adding phenytoin therapy to patients stabilized on clozapine, monitor patient closely for worsening of psychotic symptoms. If needed, increase the clozapine dose cautiously on basis of psychotic symptoms. Conversely, when phenytoin is discontinued, levels of clozapine may significantly increase.
7) Probable Mechanism: increased metabolism of clozapine due to induction of cytochrome P-450 enzymes by phenytoin
8) Literature Reports

a) Two 29-year-old schizophrenic patients were stabilized on clozapine therapy. Their clozapine plasma concentrations decreased and psychotic symptoms markedly worsened after the addition of phenytoin for seizure activity. Phenytoin reduced clozapine plasma concentrations by 65% to 85% and necessitated an increase in clozapine dosage. The author's possible explanations for the decrease in clozapine plasma concentrations were a) induction of cytochrome P-450 enzymes by phenytoin, causing increased clozapine metabolism, b) decreased clozapine absorption due to phenytoin, and/or c) decreased protein binding of clozapine making more free drug available for metabolism. If the deterioration in clinical status was not related to the decrease in clozapine plasma levels, Miller's possible explanations were rebound psychosis after abruptly decreasing clozapine at the time of seizure activity, spontaneous fluctuation in illness, postictal exacerbation of preexisting psychosis, or postictal psychosis. The author recommends that clinicians closely monitor clozapine patients for worsening of psychotic symptoms when phenytoin is added to therapy (Miller, 1991c).

3.5.1.AE Propafenone

1) Interaction Effect: increased plasma concentrations of clozapine and or class I antiarrhythmic agents
2) Summary: Coadministration of clozapine with other drugs that are metabolized by cytochrome P450 2D6, such as class I antiarrhythmics, should be approached with caution (Prod Info Clozaril(R), 2002j).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Concomitant use of clozapine with other drugs metabolized by cytochrome P450 2D6, such as class I antiarrhythmic agents, may require lower doses than usually prescribed for either clozapine or the class I antiarrhythmic.
7) Probable Mechanism: competitive substrate inhibition

3.5.1.AF Quinidine

1) Interaction Effect: increased plasma concentrations of clozapine
2) Summary: Coadministration of clozapine and quinidine should be approached with caution. Quinidine inhibits cytochrome P450 2D6, the isozyme that also metabolizes clozapine (Prod Info Clozaril(R), 2002k).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable

6) Clinical Management: Concomitant use of clozapine with drugs that inhibit cytochrome P450 2D6, such as quinidine, should be approached with caution.
7) Probable Mechanism: inhibition of cytochrome P450 2D6-mediated metabolism of clozapine by quinidine.

3.5.1.AG Rifampin
1) Interaction Effect: subtherapeutic concentrations of clozapine and decreased clozapine efficacy
2) Summary: Concomitant administration of drugs known to induce cytochrome P450 enzymes may decrease the clozapine plasma levels, resulting in a decrease in effectiveness of a previously effective clozapine dose (Prod Info CLOZARIL(R) oral tablets, 2005). Case reports have shown subtherapeutic clozapine concentrations, with decreased clozapine efficacy during concomitant administration with rifampin (Joos et al, 1998; Peritogiannis et al, 2007).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Use caution when prescribing rifampin to patients who take clozapine as there have been reports of decreased clozapine levels and efficacy with concomitant use (Joos et al, 1998; Peritogiannis et al, 2007). Monitor clozapine levels when rifampin therapy is added, changed, or discontinued.
7) Probable Mechanism: induction of CYP450-mediated clozapine metabolism by rifampin
8) Literature Reports
a) A 33-year-old male schizophrenic patient was controlled on clozapine therapy for a few years when a chest X-ray revealed an opacity in the right lower quadrant. Rifampin, isoniazid, and pyrazinamide therapy was instituted for suspected tuberculosis. Within three and a half weeks, the patient became restless and sleepless, and clozapine serum concentrations were found to have significantly decreased to a subtherapeutic range. The dose of clozapine was increased from 400 mg daily to 600 mg daily without clinical improvement of the patient's psychosis. Rifampin therapy was substituted with ciprofloxacin when the opportunistic infection was found to be mycobacterium xenopi, and within three days the clozapine serum concentration increased back to a therapeutic level (Joos et al, 1998).
b) A case report described loss of clozapine efficacy following concomitant rifampin administration in a 30-year-old male schizophrenic. The patient had been initiated on clozapine for paranoid schizophrenia. Following problems with clozapine's adverse events (sedation, hypersalivation) at therapeutically successful doses, he had been controlled on clozapine therapy for 3 months at 300 mg daily when he was diagnosed with pulmonary tuberculosis. The patient was started on rifampin monotherapy at 600 mg daily. Two weeks later, the patient no longer complained of sedation and hypersalivation, but his psychotic symptoms worsened. At the end of the month, his psychopathology was as severe as when clozapine was first initiated. The dose of clozapine was increased to 550 mg daily with only mild improvement. However, the patient complained of no adverse events and was compliant with therapy. Following discontinuation of rifampin after 6 months of therapy, sedation and hypersalivation reappeared within 1 week. The dose of clozapine was not decreased to below 500 mg daily due to the marked improvement in the patient's psychotic symptoms. Induction of the CYP450-mediated clozapine metabolism was postulated as a probable mechanism. However, clozapine plasma levels were not available for confirmation due to laboratory difficulties (Peritogiannis et al, 2007).

3.5.1.AH Risperidone
1) Interaction Effect: decreased risperidone clearance
2) Summary: The manufacturer reports that clozapine may decrease risperidone clearance with chronic combined use (Prod Info Risperdal(R) Consta(TM), 2003).
3) Severity: minor
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Monitor patients for increased adverse effects of risperidone when these drugs are given concurrently.
7) Probable Mechanism: unknown

3.5.1.AI Ritonavir
1) Interaction Effect: increased clozapine plasma concentrations and clozapine toxicity (sedation, seizures, hypotension)
2) Summary: When coadministering ritonavir with clozapine, a cytochrome P450 3A4 substrate, substantial increases in concentrations of clozapine may occur, possibly requiring a dosage reduction of clozapine (less than 50%) (Prod Info Norvir(R), 2000).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor the therapeutic efficacy of clozapine and for any evidence of toxicity, particularly when the daily clozapine dose exceeds 300 mg or 3.5 mg/kg. Lower clozapine dosage may be required in some clinical situations.
7) Probable Mechanism: inhibition of cytochrome P450 3A4-mediated clozapine metabolism by ritonavir

3.5.1.AJ Sertraline

1) Interaction Effect: an increased risk of clozapine toxicity (sedation, seizures, hypotension)

2) Summary: Coadministration of clozapine with sertraline has been reported to result in increased clozapine concentrations and worsening of psychotic symptoms (Prod Info Clozaril(R), 2002d; Chong et al, 1997c; Centorrino et al, 1996a). Clozapine is metabolized by the cytochrome P450 2D6 isoenzyme (CYP2D6). Sertraline is considered a moderate to weak inhibitor of this isoenzyme, in addition to being metabolized by CYP2D6 itself (Prod Info Zoloft(R), 1999; DeVane, 1994). Cytochrome P450 3A4 may also be involved with clozapine metabolism, and sertraline also inhibits CYP3A4 (Chong & Remington, 1998).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Monitor the therapeutic efficacy of clozapine and for any evidence of toxicity, particularly when the daily clozapine dose exceeds 300 mg or 3.5 mg/kg. Lower clozapine dosage may be required in some clinical situations.

7) Probable Mechanism: decreased clozapine metabolism

8) Literature Reports

a) Two case reports revealed the exacerbation of psychotic symptoms with the addition of a selective serotonin reuptake inhibitor (SSRI) to clozapine. The first patient, a 26-year old woman with schizophrenia, had been taking clozapine 175 mg per day. Other medications included propranolol for tachycardia and trihexyphenidyl for hypersalivation. After marked improvement in psychotic symptoms but continued compulsive behavior, sertraline 50 mg per day was added. Within four weeks, the patient's obsessive-compulsive symptoms and psychotic symptoms worsened. Plasma clozapine concentrations increased from 325 ng/mL before sertraline therapy to 695 ng/mL after sertraline therapy. Patient 2, a 24-year old woman with schizophrenia, was placed on a regimen of clozapine 500 mg per day which was later increased to 600 mg per day. After fluvoxamine 50 mg per day was started as adjunctive treatment, the patient's clozapine level rose from 1146 ng/mL before fluvoxamine treatment to 2750 ng/mL after 28 days of fluvoxamine treatment. During this time the patient's compulsive symptoms remained unchanged, but psychotic symptoms worsened. The authors postulated that the worsening of psychotic symptoms could be due to SSRI inhibition of clozapine metabolism by cytochrome P450 isozymes, or an imbalance of the serotonergic and dopaminergic blockade caused by coadministration of the two drugs (Chong et al, 1997b).

b) A study evaluated the serum concentrations of clozapine and norclozapine, the major metabolite, when given in combination with the selective serotonin reuptake inhibitors (SSRI) fluoxetine, paroxetine, and sertraline. Eighty outpatients receiving clozapine all had been diagnosed with schizophrenia or major affective disorder, and 40 of these patients were receiving an SSRI in combination with clozapine. Of these 40 patients, 14 were receiving fluoxetine, 10 were receiving sertraline, and 16 were receiving paroxetine therapy. Among the patients on SSRI therapy, serum concentrations of clozapine and norclozapine were 41.1% and 44.8% higher, respectively, than in matched patients who were not receiving an SSRI. The ratio of clozapine plus norclozapine concentration to dose was also 37.7% higher in patients receiving SSRIs, indicating clozapine impaired clearance. The differences between the three SSRIs were minor, and the study groups were too limited for an accurate statistical comparison between the individual SSRIs (Centorrino et al, 1996).

3.5.1.AK St John's Wort

1) Interaction Effect: reduced clozapine efficacy

2) Summary: This interaction is based on in vitro information that St. John's Wort induced CYP1A2 enzymes, and a case report of a patient experiencing reduced blood theophylline concentrations and loss of efficacy (Nebel et al, 1999). Since clozapine is metabolized by CYP1A2 enzymes, like theophylline, clozapine may be similarly affected. If St. John's Wort and clozapine are taken together, their dosages should be consistently administered, recognizing that increased dosages of clozapine may be required. Discontinuation of St. John's Wort should be done carefully as side effects of clozapine may increase and dose reduction may be required.

3) Severity: moderate

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: Avoid concomitant use of clozapine with St. John's Wort. If patients elect to remain on St. John's Wort, they should maintain consistent dosing. Clozapine dosage may need to be increased. Patients should not discontinue St. John's Wort without first consulting their clinician as downward adjustments in clozapine dose may be necessary as well as monitoring for increased side effects of clozapine (e.g. decreased white blood cell count, increased salivation, orthostatic hypotension, tachycardia, sedation, seizures).

7) Probable Mechanism: induction of cytochrome P450 1A2 enzymes by St. John's Wort

3.5.1.AL Thioridazine

1) Interaction Effect: increased plasma concentrations of clozapine and or the phenothiazine

2) Summary: Coadministration of clozapine with other drugs that are metabolized by cytochrome P450 2D6, such as phenothiazines, should be approached with caution (Prod Info Clozaril(R), 2002h).

3) Severity: moderate

4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Concomitant use of clozapine with other drugs metabolized by cytochrome P450 2D6, such as phenothiazines, may require lower doses than usually prescribed for either clozapine or the phenothiazine.
7) Probable Mechanism: competitive substrate inhibition

3.5.1.AM Tramadol
1) Interaction Effect: an increased risk of seizures
2) Summary: Seizures have been reported in patients using tramadol. The manufacturer of tramadol states that combining neuroleptic medications with tramadol may enhance the risk of seizures (Prod Info Ultram(R), 1998).
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Caution should be used if tramadol is to be administered to patients receiving neuroleptic therapy. If possible, avoid this combination, especially in patients with underlying conditions that might predispose to seizures.
7) Probable Mechanism: unknown

3.5.1.AN Venlafaxine
1) Interaction Effect: increased serum concentrations of clozapine and venlafaxine
2) Summary: Coadministration of clozapine with other drugs that are metabolized by cytochrome P450 2D6, such as antidepressants, should be approached with caution (Prod Info Clozaril(R), 2002i). The hepatic P450IID6 isoenzyme is apparently involved with clozapine metabolism. Venlafaxine is a weak inhibitor of this isoenzyme, in addition to being metabolized by cytochrome P450IID6 itself (Prod Info Effexor(R) XR, 1999; Ellingrod & Perry, 1994). With clozapine-venlafaxine coadministration, both agents may competitively inhibit the other's metabolism resulting in enhanced serum concentrations of both. Controlled studies are needed to validate these expectations and to document the clinical impact.
3) Severity: moderate
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Monitor patients receiving concurrent clozapine and venlafaxine for signs of clozapine toxicity (dizziness, sedation, vomiting, hypotension, hematologic abnormalities) and venlafaxine toxicity (somnolence). Doses of either or both medications may need to be reduced.
7) Probable Mechanism: decreased clozapine and venlafaxine metabolism

3.5.1.AO Zotepine
1) Interaction Effect: increased risk of seizures
2) Summary: Zotepine used concurrently with neuroleptics may increase the risk of seizures (Prod Info Nipolept(R), 1994; Hori et al, 1992).
3) Severity: major
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Monitoring for seizures is particularly important in those patients who: (1) are taking large doses of zotepine; (2) have a history of seizure disorders; (3) are of young age; or (4) have a past history of brain injury.
7) Probable Mechanism: unknown

3.5.2 Drug-Food Combinations

3.5.2.A Caffeine
1) Interaction Effect: an increased risk of clozapine toxicity (sedation, seizures, hypotension)
2) Summary: Caffeine may significantly inhibit the metabolism of clozapine when ingested in quantities ranging from 400 mg to 1000 mg daily. Caffeine is metabolized by cytochrome P450 1A2 (CYP1A2) enzymes, which are also responsible for the metabolism of clozapine. Because of dose-dependent caffeine pharmacokinetics, clozapine clearance is reduced when caffeine is ingested in moderate to high quantities (Prod Info Clozaril(R), 2002o; Hagg et al, 2000e).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Patients receiving clozapine therapy should be advised to avoid changes in habitual caffeine intake. Variations in caffeine ingestion should be considered when clozapine concentrations fluctuate.
7) Probable Mechanism: inhibition of cytochrome P450 1A2-mediated clozapine metabolism
8) Literature Reports
a) Twelve healthy nonsmoking male volunteers took part in an investigation to determine whether caffeine affects the pharmacokinetics of clozapine. In both phases of the randomized cross-over study,

single doses of clozapine 12.5 mg were administered after an overnight fast. During the caffeine phase, subjects received caffeine 100 mg as an oral tablet in addition to dietary caffeine intake. The mean caffeine ingestion was 550 mg daily. The clozapine area under the concentration-time curve (AUC) increased by 19% while the oral clearance decreased by 14% during the caffeine phase. However, in one subject, the AUC was nearly doubled, indicating that certain individuals may be more predisposed to this interaction than others (Hagg et al, 2000d).

4.0 Clinical Applications

Monitoring Parameters

Patient Instructions

Place In Therapy

Mechanism of Action / Pharmacology

Therapeutic Uses

Comparative Efficacy / Evaluation With Other Therapies

4.1 Monitoring Parameters

A) Therapeutic

1) Physical Findings

a) Decrease in signs and symptoms of psychoses

b) One small study (n=15) suggests that weight gain is a predictor of long-term (21 months) clozapine efficacy in treatment-resistant schizophrenic patients. Further studies are needed (Jalenques et al, 1996).

2) SERUM LEVEL

a) A decrease of 40% or more in the plasma level of clozapine from baseline values (baseline value determined when patient was free from positive symptoms for at least 4 months) for an extended period may be a predictor of relapse of schizophrenic psychosis. Eight of 12 patients who exhibited such "at-risk" plasma clozapine levels for more than 8.6 months during the study period (12% of the study interval) had relapses, while 2 of 11 patients who exhibited "at-risk" plasma levels for less than 8.6 months relapsed. Relapse rates were the same for the 2 groups for the first 2 years but after that increased rapidly in the group with the longer exposure to "at risk" plasma clozapine levels (Gaertner et al, 2001).

B) Toxic

1) Laboratory Parameters

a) AGRANULOCYTOSIS

1) A white blood cell (WBC) count and an absolute neutrophil count (ANC) should be obtained before beginning therapy. Do not start therapy if the WBC count is less than 3500 cells/cubic millimeter (mm (3)), if the ANC is less than 2000 cells/mm(3), or if the patient has a history of a myeloproliferative disorder or previous clozapine-induced granulocytopenia or agranulocytosis (Prod Info CLOZARIL(R) Tablets, 2005)). Sandoz Australia guidelines prohibit initiation of clozapine treatment in patients with a WBC count less than 3 x 10(9) cells/L and/or a neutrophil count less than 1.5 x 10(9) cells/L (Prod Info Clozaril(R) Australia, 1996).

2) Repeat WBC counts and ANC should be obtained weekly during the first 6 months of clozapine therapy . If the WBC count remains greater than or equal to 3500cells/mm(3) and the ANC remains greater than or equal to 2000cells/mm(3), then WBC and ANC may be monitored every 2 weeks for the next 6 months. Thereafter, if acceptable WBC counts and ANC have been maintained during the second 6 months of continuous therapy, WBC count and ANC can be monitored every 4 weeks. Weekly WBC counts and ANC should be continued for at least 4 weeks after the discontinuation of clozapine or until WBC count is greater than or equal to 3500/mm(3) and ANC is greater than or equal to 2000/mm (3) (Prod Info CLOZARIL(R) Tablets, 2005).

3) For interruptions in therapy, the following guidelines should be used for reinitiation of monitoring white blood cell counts (see below for guidelines on restarting therapy with specific abnormal blood counts) (Prod Info Clozaril(R), 2002):

Length of Therapy	Length of Break	History of Abnormal Blood Event (WBC less than 3500 cells/mm(3) or ANC less than 2000 cells/mm(3)	Recommended Monitoring (*reduced monitoring permitted only if all WBC counts are greater than or equal to 3500 and ANC is greater than or equal to 2000)
Less than 6 months	Less than 1 month	No	Continue 6 months of weekly testing
	Greater		

Less than 6 months	than 1 month	No	Restart 6 months of weekly testing
6 to 12 months	Less than 1 month	No	Weekly testing for 6 weeks, then return to every 2 weeks for 6 months*
6 to 12 months	Greater than 1 month	No	Weekly testing for 6 months, then return to every 2 weeks for 6 months*
Greater than 12 months	Less than 1 month	No	Weekly testing for 6 weeks, then return to every 4 weeks*
Greater than 12 months	Greater than 1 month	No	Weekly testing for 6 months, then every 2 weeks for 6 months, then return to every 4 weeks*

* Transition to reduced monitoring frequency only if all WBC >= 3500 AND >= 2000

4) If there is a substantial drop in WBC or ANC after starting therapy, a repeat WBC count and ANC should be done. A substantial drop is considered to be a single drop or cumulative drop within a 3-week period of 3000 more in the WBC count or 1500 or more of ANC. If the repeat WBC count and ANC reveal a total WBC count between 3000 and 3500 cells/mm(3) and an ANC above 2000 cells/mm(3), WBC counts and ANC should be monitored twice weekly (Prod Info CLOZARIL(R) Tablets, 2005); (Prod Info Clozaril(R) Australia, 1996).

5) If mild leukopenia (WBC count is 3000/mm(3) or greater but less than 3500/mm(3)) and/or mild granulocytopenia (ANC is 1000/mm(3) or greater but less than 1500/mm(3)) develop, monitoring should be twice-weekly until WBC count is greater than 3500/mm(3) and ANC is greater than 2000/mm(3). At this point, return to previous monitoring (Prod Info CLOZARIL(R) Tablets, 2005).

6) If moderate leukopenia (WBC count is 2000/mm(3) or greater but less than 3000/mm(3)) and/or moderate granulocytopenia (ANC is 1000/mm(3) or greater but less than 1500/mm(3)) develop, therapy should be interrupted. Monitor daily until WBC are greater than 3000/mm(3) and ANC is greater than 1500/mm(3), then twice-weekly until WBC is greater than 3500/mm(3) and ANC is greater than 2000/mm(3). Rechallenge may occur when WBC are greater than 3500/mm(3) and ANC is greater than 2000/mm(3). If rechallenged, monitor weekly for 1 year before returning to the usual monitoring schedule of every 2 weeks for 6 months and then every 4 weeks indefinitely (Prod Info CLOZARIL(R) Tablets, 2005).

7) If the total WBC count falls below 2000 cells/mm(3) and/or the ANC falls below 1000 cells/mm(3), clozapine therapy should be discontinued and patient should not be rechallenged. WBC counts and ANC should be monitored daily until WBC are greater than 3000 cells/mm(3) and the ANC returns to levels above 1500 cells/mm(3). Twice-weekly WBC counts and ANC should be taken until the total WBC counts return to levels above 3500 cells/mm(3) and ANC return to levels above 2000/mm(3). After WBC are greater than 3500/mm(3), monitor weekly (Prod Info CLOZARIL(R) Tablets, 2005).

b) PLASMA LEVEL

1) If an infectious, hypersensitivity, or inflammatory process is suspected, clozapine plasma levels should be closely monitored and the clozapine dose may need to be reduced by up to 50%. Toxic clozapine levels of 1100 to 2400 micrograms/liter (mcg/L) have been reported in several cases. However, toxic effects are possible at plasma levels of 1000 mcg/L and higher; and adverse effects are twice as likely at concentrations above 350 mcg/L (de Leon & Diaz, 2003; Haack et al, 2003).

2) Physical Findings

a) AGRANULOCYTOSIS

1) Monitor for any signs of infection including lethargy, weakness, fever, or sore throat (Prod Info CLOZARIL(R) Tablets, 2005).

b) CARDIOMYOPATHY

1) Signs and symptoms suggestive of cardiomyopathy include: exertional dyspnea, fatigue, orthopnea, paroxysmal nocturnal dyspnea and peripheral edema. If the diagnosis of cardiomyopathy is confirmed, discontinue clozapine unless the benefit to the patient clearly outweighs the risk (Prod Info CLOZARIL (R) Tablets, 2005).

c) DIABETES MELLITUS

1) Monitor patients with an established diagnosis of diabetes mellitus for worsening of glucose control during treatment with an atypical antipsychotic. Patients with risk factors for diabetes mellitus (ie, obesity, family history of diabetes) who are beginning treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically throughout treatment (Prod Info CLOZARIL(R) Tablets, 2005).

d) HYPERGLYCEMIA

1) Monitor patients for signs and symptoms of hyperglycemia (ie, polydipsia, polyuria, polyphagia, and weakness). Patients who exhibit symptoms of hyperglycemia during atypical antipsychotic treatment should undergo fasting blood glucose testing. In some instances, hyperglycemia has resolved when the atypical antipsychotic was stopped; however, some patients required ongoing antidiabetic treatment despite discontinuation of the suspect medication (Prod Info CLOZARIL(R) Tablets, 2005).

e) MYOCARDITIS

1) If tachycardia develops, particularly during the first month of treatment, monitor closely for signs of

myocarditis. Patients who present with unexplained fatigue, dyspnea, tachypnea, fever, chest pain, palpitations, ST-T wave abnormalities, arrhythmias, or other signs or symptoms of heart failure should also be evaluated for myocarditis (Prod Info CLOZARIL(R) Tablets, 2005).

f) SEIZURE ACTIVITY

1) Patients who receive clozapine should be monitored for seizure activity, especially if there is a history of seizures or predisposing factors (Prod Info CLOZARIL(R) Tablets, 2005).

3) IMPORTANT NOTE

a) In the United States, the Clozaril(R) Patient Management System was phased out in May 1991 (Anon, 1991). Information on monitoring for agranulocytosis is available from the manufacturer (Prod Info CLOZARIL(R) Tablets, 2005).

4.2 Patient Instructions

A) Clozapine (By mouth)

Clozapine

Treats schizophrenia.

When This Medicine Should Not Be Used:
You should not use this medicine if you have had an allergic reaction to clozapine. You should not use this medicine if you have certain blood problems, a bone marrow disorder, uncontrolled seizures, bowel blockage, certain nervous system problems, or certain heart problems.

How to Use This Medicine:
Tablet, Dissolving Tablet

Your doctor will tell you how much of this medicine to use and how often. Your dose may need to be changed several times in order to find out what works best for you. Do not use more medicine or use it more often than your doctor tells you to.
You may take this medicine with or without food.
Drink extra fluids so you will pass more urine while you are using this medicine. This will keep your kidneys working well and help prevent kidney problems.

If a Dose is Missed:

If you miss a dose or forget to use your medicine, use it as soon as you can. If it is almost time for your next dose, wait until then to use the medicine and skip the missed dose. Do not use extra medicine to make up for a missed dose.
If for any reason you stop taking clozapine for longer than 2 days, do not start back on the same dose. Ask your doctor what dose you should take.

How to Store and Dispose of This Medicine:

Store the medicine in a closed container at room temperature, away from heat, moisture, and direct light.
Ask your pharmacist, doctor, or health caregiver about the best way to dispose of any leftover medicine after you have finished your treatment. You will also need to throw away old medicine after the expiration date has passed.
Keep all medicine away from children and never share your medicine with anyone.

Drugs and Foods to Avoid:
Ask your doctor or pharmacist before using any other medicine, including over-the-counter medicines, vitamins, and herbal products.

There are many other drugs that can interact with clozapine. Make sure your doctor knows about all other medicines you are using.
Make sure your doctor knows if you are using fluvoxamine (Luvox®), paroxetine (Paxil®), cimetidine (Tagamet®), carbamazepine (Tegretol®), ciprofloxacin (Cipro®), erythromycin (Ery-tab®), phenytoin (Dilantin®), quinidine, or rifampin (Rifadin®, Rimactane®). Tell your doctor if you are using atropine, dicyclomine (Bentyl®), glycopyrrolate (Robinul®), hyoscyamine (Cystospaz®), propantheline (Pro-Banthine®), or scopolamine (Transderm Scop®).
Make sure your doctor knows if you are also using medicine to lower blood pressure (such as atenolol, hydrochlorothiazide [HCTZ], lisinopril, metoprolol, quinapril, Accupril®, Cozaar®, Diovan®, Lotrel®, Norvasc®, Toprol®, Zestril®) or medicine for heart rhythm problems (such as flecainide, encainide, propafenone, Rythmol®, Tambocor®).
Tell your doctor if you are also using other medicine to treat mental illness (such as chlorpromazine, haloperidol, risperidone, thioridazine, Haldol®, Mellaril®, Risperdal®, Thorazine®), medicine to treat anxiety (such as alprazolam, clonazepam, Ativan®, Valium®, Xanax®), medicine for nausea or vomiting (such as prochlorperazine, promethazine, Compazine®, Phenergan®), or medicine to treat depression (such as citalopram, venlafaxine, Celexa®, Effexor®).
Tell your doctor if you are using any medicines that make you sleepy. These include sleeping pills, cold and allergy medicine, narcotic pain relievers, and sedatives.
Do not drink alcohol while you are using this medicine.

Warnings While Using This Medicine:

Make sure your doctor knows if you are pregnant or breastfeeding, or if you ever had neuroleptic malignant syndrome (NMS). Tell your doctor if you have heart disease, liver disease, kidney disease, lung disease, an enlarged prostate, or a problem with your intestines. Tell your doctor if you have glaucoma, if you have ever had a head injury, or if you have a history of seizures.

Tell your doctor if you have diabetes, because this medicine may raise your blood sugar.

This medicine lowers the number of some types of blood cells in your body. Because of this, you may bleed or get infections more easily. To help with these problems, avoid being near people who are sick or have infections. Wash your hands often. Stay away from rough sports or other situations where you could be bruised, cut, or injured. Brush and floss your teeth gently. Be careful when using sharp objects, including razors and fingernail clippers.

This medicine can cause drowsiness or seizures. Avoid driving, swimming, climbing, using machines, or doing anything else that could be dangerous if you are not alert. You may also feel lightheaded when getting up suddenly from a lying or sitting position, so stand up slowly.

Your doctor will need to check your blood at regular visits while you are using this medicine. Be sure to keep all appointments.If you do not have your scheduled blood test, you may not be given your next week's supply of this medicine.

This medicine is not approved to treat behavior disorders in older people who have dementia. Using this medicine to treat this problem could increase the risk of death. This risk has not been shown for the approved uses of this medicine.

Tardive dyskinesia (a movement disorder) may occur and may not go away after you stop using the medicine. Check with your doctor right away if you have any of the following symptoms while taking this medicine: lip smacking or puckering, puffing of the cheeks, rapid or worm-like movements of the tongue, uncontrolled chewing movements, or uncontrolled movements of the arms and legs.

Make sure any doctor or dentist who treats you knows that you are using this medicine. You may need to stop using this medicine several days before having surgery or medical tests.

Do not stop using this medicine suddenly without asking your doctor. You may need to slowly decrease your dose before stopping it completely.

Possible Side Effects While Using This Medicine:

Call your doctor right away if you notice any of these side effects:

Blistering, red, or peeling skin rash.

Constant muscle movement that you cannot control, often in your face, lips, tongue, jaw, arms, or legs.

Dark-colored urine or pale stools.

Fever with chills, cough, sore throat, and body aches.

Fever with sweating, confusion, uneven heartbeat, or muscle stiffness.

Lightheadedness or fainting.

Nausea, vomiting, loss of appetite, or pain in your upper stomach.

Pain in your lower leg (calf).

Seizures.

Swelling in your hands, ankles, or feet.

Weak and rapid heartbeat, tiredness, chest pain, fever, trouble breathing.

Yellowing of your skin or the whites of your eyes.

If you notice these less serious side effects, talk with your doctor:

Blurred vision or vision problems.

Constipation.

Dry mouth, increased sweating.

Excess saliva or drooling.

If you notice other side effects that you think are caused by this medicine, tell your doctor.

4.3 Place In Therapy

A) Current users of atypical antipsychotic drugs (including clozapine) and typical antipsychotic drugs had a similar dose-dependent risk of sudden cardiac death, according to a retrospective cohort of 93,300 adult users of antipsychotic drugs and 186,600 matched controls. The study included patients age 30 to 74 years (mean 45.7 +/- 11.8 years) with similar cardiovascular risk at baseline who had at least one filled prescription and had 1 outpatient visit in each of the 2 preceding years. Sudden cardiac death was defined as occurring in the community and excluded deaths of patients admitted to the hospital, non-sudden deaths, deaths due to extrinsic causes, or causes not related to ventricular tachyarrhythmia. Current use was defined as the interval between the time the prescription was filled and the end of the day's supply. Low and high doses was defined as comparable to less than 100 milligrams (mg) of chlorpromazine, and doses comparable to chlorpromazine 300 mg or greater, respectively. The adjusted rate of sudden cardiac death (incidence-rate ratio) in current users of atypical antipsychotic drugs in 79,589 person-years was 2.26 (95% CI, 1.88 to 2.72, p less than 0.001) which was similar to the risk in current users of typical antipsychotic drugs in 86,735 person-years which was 1.99 (95% CI, 1.68 to 2.34, p less than 0.001). The risk of sudden cardiac death in current clozapine users in 4654 person-years was 3.67 (95% CI, 1.94 to 6.94, p less than 0.001). The risk of sudden cardiac death significantly increased with increasing dose in both the typical and atypical antipsychotic drug groups. In atypical antipsychotic use, the incidence rate ratio increased from 1.59 (95% CI, 1.03 to

2.46) in low-dose use to 2.86 (95% CI, 2.25 to 3.65) in high-dose use. To limit the effects of confounding of the study results, there was a secondary analysis performed in a cohort of patients matched by propensity score, which resulted in a similar risk of sudden death as the primary cohort analysis (Ray et al, 2009). In an editorial in The New England Journal of Medicine, it has been suggested that antipsychotic drugs continue to be used in patients with clear evidence of benefit, but in vulnerable populations with cardiac risk profiles (eg, elderly patients), there should be an age-dependent justification required prior to administration. It has also been suggested (although not formally tested) that ECGs be performed before and shortly after initiation of antipsychotic therapy to screen for existing or emergent QT interval prolongation (Schneeweiss & Avorn, 2009).
B) Clozapine is considered to be an atypical antipsychotic agent because of its limited propensity to cause extrapyramidal adverse effects often associated with other antipsychotic agents. The drug has demonstrated efficacy in the therapy of treatment-resistant schizophrenic patients (Conley, 1998; Bablenis et al, 1989).
C) Because of the higher risk of agranulocytosis, clozapine should be reserved for those treatment-resistant patients who have not responded to adequate trials of other antipsychotic agents (Prod Info Clozaril(R), 2002). Prior to the initiation of clozapine treatment, patients should be given at least two trials, each with a different standard drug product for schizophrenia at an adequate dose and for an adequate duration to insure safety and efficacy (Prod Info CLOZARIL(R) tablets, 2005). Clozapine may also be useful in patients who cannot tolerate other antipsychotics because of their associated extrapyramidal symptoms or in patients with tardive dyskinesia (Conley, 1998).
D) A number of studies by different investigators (Kane et al, 1988; Conley et al, 1988; Mattes, 1989) showed that treatment resistant schizophrenic patients responded to clozapine. Clozapine is a useful addition to therapy for long-term treatment of schizophrenia despite the risks and the need for frequent blood tests. Clozapine improves both positive and negative symptoms, and may improve organization of thoughts, and certain aspects of cognitive function (Conley, 1998).
See Drug Consult reference: FIRST- VS SECOND-GENERATION ANTIPSYCHOTIC AGENTS FOR SCHIZOPHRENIA

4.4 Mechanism of Action / Pharmacology

A) MECHANISM OF ACTION

1) Clozapine is a neuroleptic agent with a tricyclic structure that is similar to the antidepressant dibenzepine.
2) Clozapine exhibits relatively potent serotonergic S2-, serotonergic S3-, alpha-1-adrenergic, histamine H1-, and muscarinic antagonism activity, and appears to induce preferential blockade of dopamine D1- (versus dopamine D2-) and Dy receptors in vivo (Kumar & Brecher, 1999; Shaikh et al, 1993; Fitton & Heel, 1990). Although the exact mechanism of action of clozapine has not been established, it has been suggested that the antipsychotic effects of clozapine might be related to central dopamine D1- or a combination of dopamine D1- and D2- receptor blockade with serotonergic, S2-receptor antagonism possibly playing a supplementary role. It has been postulated that the therapeutic effects of neuroleptics are mediated by mesolimbic and mesocortical dopaminergic pathways, while the neostriatum is associated with extrapyramidal side effects of these drugs. The low incidence of extrapyramidal side effects of clozapine might be attributable to a selective action on mesolimbic dopaminergic receptors (Fitton & Heel, 1990; Gudelsky et al, 1989).
3) A positive correlation was seen for the overall score on the Scale for the Assessment of Positive Symptoms (p=0.02) (and for the subscores for hallucination (p=0.02), and delusion (p=0.001)), and prolactin release as evoked by d-fenfluramine. The prolactin response to d-fenfluramine is a highly specific test of 5-HT function. The authors hypothesize that this 5-HT antagonism is therefore relevant to clozapine's efficacy in alleviating hallucinations and to the positive symptoms of schizophrenia (Jones et al, 1998).
4) A high degree of D2 dopamine receptor blockade by antipsychotic drugs is usually necessary for clinical response. However, about 30% of schizophrenic patients do not respond. To test this assumption, one author compared clinical response with central D2 dopamine receptor availability measured by I-123 iodobenzamide single photon emission tomography in two groups of schizophrenic patients. Six patients on typical antipsychotics showed poor therapeutic response despite D2 receptor blockade. Significant clinical improvement occurred in all 10 patients on the antipsychotic clozapine, but at a lower level of D2 blockade by the drug. These findings suggest a more complex relation between D2 blockade and clinical efficacy than was previously thought (Pilowsky et al, 1992).
5) Positron emission tomography (PET) has been used for quantification of D2 receptor occupancy induced by antipsychotic drugs in the basal ganglia. The classical neuroleptics have their antipsychotic effects mediated by a blockade of D2 receptors. In clozapine-treated patients, the D2 receptor occupancy was low, thus classifying it as an "atypical" antipsychotic. PET and the radioligand (11-C)N-methylspiperone were used to determine cortical 5-HT2 receptor occupancy in three psychotic patients treated with 125, 175, and 200 milligrams of clozapine daily (Nordstrom et al, 1993). The results show that clinical treatment with clozapine induces a high 5-HT2 receptor occupancy in psychotic patients at a low clozapine dosage. In another study, a very high degree of serotonin 5-HT(2a) receptor blockade was found with both clozapine and high doses of chlorpromazine. This lead the authors to hypothesize that it is actually the difference in the dopamine D(2) receptor occupancy that accounts for the differences in clinical properties between clozapine and the typical antipsychotic drugs (Trichard et al, 1998).
6) Dopamine D4 receptors have greater affinity for clozapine than for any other antipsychotic. The D4 receptor occurs in at least 7 polymorphic forms and can be rapidly identified. These polymorphic forms may influence the receptor to clozapine. It is concluded that response to clozapine is not pharmacogenetically dichoromous (Shaikh et al, 1993).
7) Results on assessing clozapine's effect on dopamine and serotonin metabolites have been inconsistent. The dopamine-serotonin relationship was reappraised in a group of 19 neuroleptic refractory and intolerant

schizophrenic patients treated with clozapine (Szymanski et al, 1993). Only a small change in cerebrospinal fluid and plasma homovanillic acid (HVA) and 5-hydroxyindoacetic acid (5-HIAA) levels was found. The modest relationship between HVA and 5-HIAA and treatment response suggests the involvement of both neurotransmitters in the pathophysiology of schizophrenia.
8) The plasma levels of dopamine, norepinephrine, and their metabolites homovanillic acid (HVA) and 3-methoxy-4-hydroxyphenylglycol (MHPG) were measured in eight schizophrenic patients treated with clozapine for 12 weeks. They found the plasma levels of HVA and MHPG decreased during the initial weeks of treatment in responders, but not in nonresponders; and plasma levels of dopamine and norepinephrine increased in both responders and nonresponders to clozapine treatment (Green et al, 1993).
9) It has been well established with other clinically active neuroleptics that elevations in serum prolactin occur (Langer et al, 1977; Meltzer et al, 1978). This is believed to result from the blockade of dopamine receptors in the pituitary. One study reported that the degree of acute prolactin elevation in man following the parenteral administration of a neuroleptic drug appeared to be highly correlated with the milligram for milligram antipsychotic potency (Langer et al, 1977). However, various reports (Sachar et al, 1976; Nair et al, 1979; Meltzer et al, 1979) have shown that clozapine may cause no increase or only a minimal increase of prolactin secretion in man. They observed a 17% elevation in basal serum prolactin levels but also saw a marked inhibition of growth hormone response to 0.75 mg apomorphine which was administered subcutaneously in 6 of 7 subjects. In one study, data suggest that clozapine can block dopamine receptors responsible for apomorphine growth hormone effect without effecting the pituitary dopamine receptors involved in prolactin response. Ten schizophrenic male patients received a maximum clozapine dose of 100 mg/day and a total of 200 mg during the 3-day study (Nair et al, 1979). Based on this, one author has suggested that this may indicate a difference between the hypothalamic and pituitary dopamine receptors (Meltzer et al, 1979).
10) Clozapine differed from haloperidol, chlorpromazine, and fluphenazine in that clozapine produced only a brief elevation of serum prolactin but a marked increase of corticosterone and ACTH. Moreover, it increased the activity of tuberoinfundibular dopamine neurons. In view of the lack of propensity of clozapine to induce extrapyramidal symptoms, it has been hypothesized that clozapine selectively affects mesocorticolimbic dopamine function (Owen et al, 1993; Gudelsky et al, 1989). It has been proposed that schizophrenia may involve a dysregulation of 5-HT-2 and D-2-mediated neurotransmission and that a more normal balance in serotonergic and dopaminergic eurotransmission is at least partially restored by clozapine (Meltzer, 1989).
11) Clozapine is highly anticholinergic and stimulates higher human brain anticholinergic activity than risperidone (Tracy et al, 1998). However, it may still be less than other traditional neuroleptics such as haloperidol.

B) REVIEW ARTICLES
1) Optimization of clozapine therapy has been reviewed (Naber, 1999; Conley, 1998a).
2) The pharmacokinetics and pharmacodynamics of clozapine have been reviewed in patients with schizophrenia (Jann et al, 1993).
3) Clozapine and agranulocytosis has been reviewed (Pirmohamed & Park, 1997; Feldman, 1996).
4) Clozapine for the treatment of psychosis in Parkinson's disease has been reviewed (Auzou et al, 1996).
5) A comprehensive review of clozapine's use in treating movement disorders, including Parkinson's disease, essential tremor, Huntington's disease and tardive dyskinesia is available (Factor & Friedman, 1997).
6) Evaluations of the clinical studies on new drug therapies for treatment-resistant schizophrenia (Kane, 1996) and schizoaffective disorder have been reviewed (Keck et al, 1996).
7) The use of atypical antipsychotic medications in adults (Markowitz et al, 1999; Brown et al, 1999), older adults (Chan et al, 1999), and children (Lewis, 1998; Toren et al, 1998) has been reviewed.
8) A review on clozapine use in schizophrenia has been included in the American Psychiatric Association's Practice Guideline for the Treatment of Patients with Schizophrenia (Anon, 1997).
9) Review articles evaluating the adverse effect profiles of clozapine (Miller, 2000) along with other antipsychotic agents in the elderly (Masand, 2000) and in bipolar disorder (Zarate, 2000) are available.
10) A review of published, comparative data of clozapine versus other atypical antipsychotic agents is available (Fleischhacker, 1999).

4.5 Therapeutic Uses

Aggressive behavior

Anorexia nervosa

Bipolar disorder

Borderline personality disorder

Catatonia

Cognitive function finding

Dementia

Depression

Excessive thirst

Extrapyramidal disease

Gilles de la Tourette's syndrome

HIV infection - Psychotic disorder

Movement disorder, Involuntary

Multiple sclerosis - Psychotic disorder

Parkinson's disease

Parkinson's disease - Psychotic disorder

Postpartum psychosis

Schizoaffective disorder, Refractory

Schizoaffective disorder - Suicidal behavior, Recurrent

Schizophrenia, Treatment-resistant

Schizophrenia - Suicidal behavior, Recurrent

Tardive dyskinesia

4.5.A Aggressive behavior

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class III
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Appears beneficial for the treatment of aggressive behavior
Sedative effects may contribute to the beneficial results

3) Adult:

a) Clozapine was effective in lessening frequency and intensity of aggressive and SELF-DESTRUCTIVE BEHAVIOR in 80% of 42 non-psychotic hospitalized patients. Patients received clozapine 15 to 75 milligrams daily (Balassa et al, 1971).

4.5.B Anorexia nervosa

See Drug Consult reference: ANOREXIA NERVOSA - DRUG THERAPY

4.5.C Bipolar disorder

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy; Pediatric, Evidence is inconclusive
Recommendation: Adult, Class IIb; Pediatric, Class IIb
Strength of Evidence: Adult, Category B; Pediatric, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Effective in patients with bipolar or schizoaffective disorder with refractory MANIA in uncontrolled trials
Effective in patients with psychotic bipolar disorder in a small prospective cohort study

3) Adult:

a) Clozapine was effective and relatively well tolerated in acute and long-term treatment of patients with psychotic bipolar disorder who have not responded to conventional pharmacotherapies. A small cohort prospective study included 34 bipolar disorder patients with psychotic features who were treated with clozapine at flexible doses (25 mg to 600 mg per day) over a 24-month period. All patients showed significant improvement 24 months from intake as assessed by the Brief Psychiatric Rating Scale and the Clinical Global Impressions-Severity of Illness scale (p less than 0.001). Such improvement was significantly greater among patients with bipolar disorder than with schizophrenia (p less than 0.05). For patients with bipolar disorder with psychotic features who are resistant to or intolerant of usual treatment options, clozapine may be an effective alternative (Ciapparelli et al, 2000).

b) Clozapine was more effective in a group of schizophrenic patients with bipolar features (n=41) than those without bipolar features (n=19) (Cassano et al, 1997). In an open, follow-up study, both groups received clozapine 75 to 600 milligrams (mg) and other drugs necessary for the relief of their symptoms. The average dose after 1 year for the bipolar group was 261 mg versus 298 mg for the group without bipolar features. After 12 months of treatment, according to the Brief Psychiatric Rating Scale scores, patients with bipolar features tended to respond significantly better (p less than 0.001 versus baseline) than those without bipolar features (p less than 0.05 versus baseline).

c) An open-label trial demonstrated the effectiveness of add-on clozapine for up to 1 year in treatment-resistant patients with a history of mania. Subjects had diagnoses of schizoaffective disorder, bipolar type (n=12) or bipolar I disorder (n=26) and were randomized to add-on clozapine or optimization of standard therapy for 1 year. The average daily dose of clozapine differed by diagnosis: 623 milligrams (mg)/day for schizoaffective and 234 mg/day for bipolar I (p=0.008). The dropout rates due to intolerance were 16% for clozapine and 47% for standard therapy (who were then crossed over to clozapine). Five of six psychiatric rating scales showed significantly greater improvement with add-on clozapine versus standard therapy alone. The Brief Psychiatric Rating scale score improved at least 30% from baseline to 6 months in 82% and 57% of clozapine recipients and the comparator group, respectively. Clozapine's additive efficacy permitted significant decreases in the concurrent medication regimen. Individuals without psychotic features benefited from clozapine to a similar degree as those with psychotic features. As evaluated via somatic complaint questionnaire, the incidence and severity of adverse effects did not differ between groups. Lack of blinding may have introduced bias into the study; further research is warranted (Suppes et al, 1999).

d) Clozapine has been shown to be an effective therapy for treatment of mania in resistant bipolar disorder patients (N=10) and schizoaffective disorder patients (N=15). In a prospective, open trial of clozapine, patients who had either a poor response or were intolerant of lithium, failed at least 2 neuroleptics, and failed either valproate or carbamazepine were treated with clozapine. Marked improvement (defined as a 50% improvement in score) was noted in 72% of the patients on the Young Mania Rating Scale and 32% exhibited marked improvement on the Brief Psychiatric Rating Scale (Calabrese et al, 1996).

e) In a non-controlled study, clozapine was used in the treatment of 17 bipolar disorder patients who had either failed or were intolerant to trials of lithium, valproate, carbamazepine, or neuroleptics. The study suggests that clozapine monotherapy is an effective mood stabilizer that reduces the number of affective episodes and rehospitalizations in patients with severe refractory bipolar illness. A controlled study is needed (Zarate et al, 1995).

f) Another author reported marked improvement in seven patients treated with clozapine for bipolar disorder, characterized by dysphonic mania with psychotic features and chronic disability refractory to standard treatments and anticonvulsants. During the subsequent follow up (3 to 5 years) most of the patients sustained gains in psychosocial function, and 6 of the 7 patients remaining on clozapine required no further hospitalization (Suppes et al, 1992).

4) Pediatric:

a) A 15-year-old male adolescent with severe treatment refractory bipolar disorder with psychotic features experienced a dramatic improvement in mood and psychotic symptoms when clozapine 300 milligrams (mg) per day was added to lithium 1350 mg per day. He had previously been treated with combinations of lithium, carbamazepine, and typical neuroleptics. Ten days after starting clozapine in combination with lithium, clinical improvement in restlessness, insomnia, and speech became apparent. Three weeks after beginning clozapine, Brief Psychiatric Rating Scale decreased from 74 to 37, Children Global Assessment Scale changed from 25 to 72, and Clinical Global Impression Severity of Illness subscale decreased from 7 to 3. Side effects included mild sedation and an increase in body weight. The patient continued to do well after nine months of therapy with lithium and clozapine 200 mg daily (Masi & Milone, 1998).

4.5.D Borderline personality disorder

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Lead to improvements in symptomatology in a small sample of patients with borderline personality disorder

3) Adult:

a) Clozapine treatment greatly reduced the need for hospitalization in 7 patients with borderline personality

disorder (BPD), whether or not they had comorbid psychosis. Retrospective analysis of the records of patients who had been hospitalized for BPD and treated with clozapine revealed that, for the 7 patients who were initially discharged on clozapine treatment (average dose 334 milligrams/day; range 175 to 550 milligrams/day), state hospital use was reduced from an average of 110 days per year to 6.3 days per year (Brickman et al, 2002).

b) Preliminary data from a case series (n=7) of severe borderline personality disorder suggest that clozapine (mean dose: 421 milligrams/day) may decrease self- mutilation and aggressive behavior. The subjects were Caucasian females (mean age: 37 years) at state psychiatric facilities who were refractory to various combinations of psychotropic medications. Investigators reviewed patients' medical records to compare outcomes during 1 year before versus 1 year after the index date of clozapine initiation. Average Global Assessment of Functioning scores improved 48%; hospital privileges increased 60%; concurrent anxiolytic and antipsychotic medication use decreased 67% and 89%, respectively; and injuries to staff and peers dropped 93%. Both the number and duration of seclusion and restraint incidents (as proxy measures for self-mutilation) were reduced by 91% to 98% (Chengappa et al, 1999).

c) In a 4-month, open-label trial, low-dose clozapine improved symptomatology in patients (n=12) with severe borderline personality disorder (BPD) (Benedetti et al, 1998). BPD patients with severe psychotic-like symptoms who had failed a previous therapeutic program received clozapine starting at 12.5 milligrams (mg) and titrated to the lowest effective dose. Clozapine doses ranged from 25 to 100 mg/day (mean 43.8 mg/day). Since no available rating scale is specifically structured to assess changes in symptomatology of BPD patients, outcomes were difficult to measure. Utilizing the 5 items from the Brief Psychiatric Rating Scale relating to psychotic-like symptoms (items 4, 8, 11, 12, 15), 6 of 12 patients showed a 50% reduction in score after 1 month and 8 of 12 patients showed a 50% reduction after 4 months.

4.5.E Catatonia

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Effective in 1 case report

3) Adult:

a) A 56-year-old woman with organic catatonia following frontal lobe injury responded to clozapine therapy (Rommel et al, 1998). Her catatonia manifested as restlessness, and rhythmic repetitive movements of her arms with rocking motion of her trunk. She did not respond to phenothiazines or haloperidol decanoate. Clozapine 350 milligrams made her symptoms slowly resolve. After 2 months, clozapine was withdrawn and symptoms reappeared 2 days later. Clozapine was successfully restarted and then gradually withdrawn after 1 year without relapse.

4.5.F Cognitive function finding

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

May improve cognitive function in schizophrenic patients

3) Adult:

a) Data from 12 published trials suggest that clozapine may improve some aspects of cognitive functioning in schizophrenia. The author of a review article reported positive results with clozapine for the following parameters: verbal fluency (6 of 7 studies); attention/ psychomotor speed (7 of 10 studies); verbal learning and memory (5 of 8 studies). The latter component is important in terms of employment potential. Mixed or equivocal results were noted for executive functioning, verbal working memory, and visual learning and memory. Two trials showed no cognitive improvements with clozapine (McGurk, 1999).

b) One study reported improved cognitive function, especially attention and verbal fluency in both treatment-resistant and non-treatment-resistant schizophrenia after clozapine therapy, for at least six weeks, with major improvement noted at six months. The data also suggest that clozapine treatment was superior to typical neuroleptics in improving cognitive function in schizophrenia (Lee et al, 1994).

4.5.G Dementia

See Drug Consult reference: BEHAVIORAL AND PSYCHOLOGICAL SYMPTOMS OF DEMENTIA

4.5.H Depression

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive

Recommendation: Adult, Class III
Strength of Evidence: Adult, Category C
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:
Conflicting data regarding the efficacy of clozapine in patients with depression (Ayd, 1974; Nahunek et al, 1973)

3) Adult:
a) A case of recurrent psychotic depression, unresponsive to multiple drug therapies and electroconvulsive therapy, responded to clozapine treatment (Dassa et al, 1993).
b) A 45-year-old woman with psychotic depression responded to a trial of clozapine instituted because of concomitant parkinsonian syndrome. The patient was resistant to conventional therapy (Parsa et al, 1991).

4.5.I Excessive thirst

1) Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:
May be of value in reducing the severity of psychogenic polydipsia in patients with chronic schizophrenia
Unknown mechanism of action (Lee et al, 1991)

3) Adult:
a) Patients with polydipsia-hyponatremia syndrome improved after switching to clozapine therapy from their previous conventional neuroleptic agent (Canuso & Goldman, 1999). In an open study, 10 patients with polydipsia and hyponatremia (plasma sodium less than 125 milliequivalents/liter (mEq/L) were switched to clozapine therapy at 300, 600, and 900 milligrams (mg). Two patients were unable to tolerate the clozapine 900-mg dose. However, plasma osmolality normalized with clozapine 300 mg/day and the 2 higher doses were found to have no further effect. Plasma osmolality rose an average of 15.2 milliosmoles/kilogram above the patients' mean values. No fluid restrictions were required during the 18 weeks of clozapine therapy.

4.5.J Extrapyramidal disease

1) Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:
May ameliorate classic neuroleptic-induced extrapyramidal syndrome consisting of concurrent chronic akathisia, parkinsonism, TARDIVE DYSKINESIA and dystonia.

3) Adult:
a) Drug-induced LARYNGEAL DYSTONIA resolved after clozapine was substituted for other drugs being used to treat schizophrenia in a 26-year-old woman. The woman presented in a florid psychotic state and with acute laryngeal dysfunction, including dysphonia and dysphagia. She showed no other extrapyramidal side effects. Her current medications (thioridazine, haloperidol, and zuclopentixol) were tapered and discontinued. She was given 2 other regimens (chlorpromazine and biperiden; promethazine, gabapentin, and biperiden), which were discontinued because of persistence of dysphonia and psychosis. Six days after admission she had an episode of food asphyxiation. Clozapine was prescribed, with the dose increased to 550 milligrams/day over 3 weeks. Improvement of laryngeal dysfunction was evident in the first week. Vocalization problems eventually resolved. There was also improvement of her psychotic state. The authors attributed the improvement in dystonia to a direct action of clozapine as an antidystonic agent (Lanzaro et al, 2001).
b) Clozapine successfully managed severe, disabling neuroleptic-induced blepharospasm, a rare form of tardive dystonia, in a case series (n=4). With slow titration to doses ranging from 100 to 200 milligrams (mg)/day, clozapine completely suppressed the symptoms of blepharospasm within 3 to 4 months with no psychotic exacerbations. In one instance, discontinuation of clozapine "unmasked" blepharospasm, which disappeared again with the reinstitution of clozapine. Clozapine continued to control blepharospasm for up to 5 years of follow-up (Levin & Reddy, 2000).
c) In an 18-week open, prospective trial, clozapine demonstrated efficacy in the treatment of all 3 co-existing aspects of neuroleptic-induced extrapyramidal syndrome in 20 patients with refractory schizophrenia. By the end of the study, clozapine (average dose 209 milligrams/day) significantly improved akathisia, parkinsonism and tardive dyskinesia by 78%, 69% and 74%, respectively, as assessed by standard rating scales (p less than 0.0001). Subjects also experienced statistical improvement in scores for psychosis, depression and anxiety (Spivak et al, 1997a).
d) Cases of disabling tardive dystonia and psychosis not responding well to antipsychotics, but

progressively improving with clozapine treatment were presented (Bassitt & Neto, 1998a; Raja et al, 1996a; Friedman, 1994a).
e) Case studies have shown that low doses of clozapine (mean dose 26.4 milligrams at bedtime) were found effective for the relief of nocturnal akathisia in nine patients with Parkinson's disease (Linazasoro et al, 1993). Three patients also experienced a marked improvement in resting tremor and five patients experienced a resolution of the confused state accompanying the akathisia.
f) Tardive dyskinesia response to clozapine was variable in 37 patients treated over a 4-year period. It was thought that those with the dystonic subtype may be effectively treated with clozapine (Lieberman et al, 1989). A review of 8 published studies reported similar findings (Lieberman et al, 1991).

4.5.K Gilles de la Tourette's syndrome

1) Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category C
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:
Effective in 1 case report of TICS

3) Adult:
a) A 30-year-old man with acute paranoid syndrome and a long history of tics achieved total remission of his tics with clozapine therapy (Schmider, 1998). He was considered to have a nongenetic form of tics with multiple simple motor tics of the limbs and face, and simple and complex vocal tics. Clozapine was increased to 350 milligrams/day with a stable remission reported 1 month later.

4.5.L HIV infection - Psychotic disorder

1) Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class III
Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:
Pilot data suggest possible benefit with clozapine

3) Adult:
a) Clozapine was efficacious in relieving both psychotic and neuroleptic-induced parkinsonian symptoms in an open-label pilot study of 6 patients with acquired immunodeficiency syndrome. After a one-week neuroleptic washout, subjects received clozapine 12.5 milligrams (mg)/day with upward titration. Psychotic symptoms decreased significantly from baseline to month 3 of treatment at a mean dose of 27 mg/day, as evidenced by changes in average Brief Psychiatric Rating Scale scores (54 to 24 points, p less than 0.001) and Clinical Global Impression scores (2 to 8 points, p less than 0.001). The mean Unified Parkinson's Disease Rating scale also improved significantly over the same time period (14.5 to 3.4 points, p less than 0.001). The only adverse effect was leukopenia necessitating clozapine discontinuation and colony stimulating factor support (n=1) (Lera & Zirulnik, 1999).

4.5.M Movement disorder, Involuntary

1) Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:
May reduce involuntary movements in patients with Huntington's disease or Parkinson's disease
Also effective in 1 case of paroxysmal hemidystonia, 4 cases of generalized dystonia and 1 case of Meige syndrome, although adverse effects were often treatment-limiting

3) Adult:
a) A case series of generalized dystonia (n=4) and Meige syndrome (n=1) refractory to multiple prior medications revealed beneficial effects with clozapine. The patients ranged in age from 23 to 65 years with illness durations of 2 to 20 years. The Burke-Fahn-Marsden Evaluation Scale for Dystonia showed average 32% and 38% improvements on movement score and disability score, respectively. Patients' visual analog scale ratings of subjective feelings of normalcy increased from a mean of 10% to 37% on clozapine. Three of five patients reported some degree of pain relief with clozapine. Efficacy was not found to be dose-related. Despite gradual dose titration, clozapine-induced adverse effects were problematic, necessitating dose reductions in all patients and discontinuation in one patient (Karp et al, 1999).
b) In a small number of patients (n=18) with Huntington's disease or Parkinson's disease, clozapine reduced or suppressed involuntary movements. Doses received were between 12.5 and 500 milligrams/day. Patients with Huntington's disease experienced improvement in 3 to 5 weeks; patients with Parkinson's

experienced improvement in 1 to 2 days (Bonuccelli et al, 1994; Bennett et al, 1994; Friedman & Lannon, 1990; Caine et al, 1979). Patients with Gilles de la Tourette's syndrome and atypical persistent DYSKINESIAS failed to improve.

c) In an open-label study of 10 patients with idiopathic Parkinson's disease and LEVODOPA-INDUCED DYSKINESIAS, clozapine in a mean daily dose of 30 milligrams (mg) significantly reduced dyskinesias as rated by the Abnormal Involuntary Movements Scale (AIMS). Patients had a mean duration of Parkinson's symptoms of 11 years, a Hoehn & Yahr score of three, and had taken levodopa for 10 years. Improvement in the AIMS began 1 week after initiation of therapy and continued for 4 months of observation. Beginning in the third week of clozapine therapy, significant improvements in AIMS score was seen at 30, 60, 90, 120, and 150 minutes following levodopa dose, when compared to baseline conditions (p less than 0.05). Six patients experienced optimal response to clozapine (decrease in AIMS score by more than 60%). No significant differences were noted over the four months in the United Parkinson's Disease Rating Scale III. One patient experienced orthostatic hypotension and was taken off clozapine and four other patients experienced sedation and were not titrated above a clozapine 25-mg dose. No patients experienced neutropenia (Pierelli et al, 1998).

d) A 54-year-old woman with delayed-onset PAROXYSMAL HEMIDYSTONIA improved with clozapine therapy (Maurer et al, 1998). She also had fixed dystonia of the foot in combination with symptomatic epilepsy and secondary generalized seizures. Her paroxysmal involuntary movements had begun at the age of 15 years and occurred intermittently every other day for less than 1 minute. She was wheelchair-bound and treated with anticonvulsants. There was no response to tiapride or levodopa. After clozapine 75 milligrams (mg) was initiated, there were no paroxysmal movements for the next 10 days. Clozapine had no effect on the fixed dystonia. She was maintained on clozapine 125 mg daily.

e) Clozapine effectively reduced mixed tremor (both resting and postural) associated with Parkinson's disease in a prospective trial (n=17). A single 12.5 milligram (mg) clozapine dose resulted in moderate to marked tremor improvement in 88% of subjects. Chronic use over 15.5 months at an average dose of 45 mg/day revealed sustained efficacy without adverse effects. Initial sedation disappeared with continued use of clozapine. The authors recommend a trial of clozapine for the treatment of mixed tremor in Parkinson's disease before resorting to neurosurgery (Bonuccelli et al, 1997).

f) Clozapine was administered in increasing doses of 25, 50, and 150 milligrams/day for three weeks to a group of five patients with abnormal involuntary movements of Huntington's chorea (Bonuccelli et al, 1994). They reported reduction of chorea, with moderate to marked reduction of abnormal involuntary movements and improvement of activities of daily living. No significant side effects were noted. In another case report, gradual and modest improvement in depression and psychotic symptoms were noted but there was no effect on abnormal movements (Sajatovic et al, 1991).

g) The effect of clozapine on resting tremor in five parkinsonian patients who previously failed to respond to standard parkinsonian drugs was studied. One patient had dramatic improvement of severe resting tremors and four others had significant improvement. The clozapine dose ranged between 12.5 to 25 milligrams daily. The tremor controlling effects of clozapine were observed within 1 to 2 days. The most common adverse effects were weight gain and sedation. One patient had worsening of his shuffling gait (Friedman & Lannon, 1990). Another author reported that the addition of clozapine therapy (100 to 200 milligrams/day) to six patients with advanced Parkinson's disease suppressed the L-DOPA-induced dyskinesias without altering relief of Parkinsonism. (Bennett et al, 1994).

4.5.N Multiple sclerosis - Psychotic disorder

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Effective in treating psychosis associated with multiple sclerosis in 1 case

3) Adult:

a) The successful use of clozapine to treat psychosis (paranoid delusions, thought disorder, and deterioration of self-care) in a 43-year-old woman with multiple sclerosis (MS) was described (Chong & Ko, 1997). Similar to other MS patients, this woman had a poor response to typical neuroleptics and easily developed extrapyramidal symptoms. Over 1 year on clozapine 125 milligrams/day, she improved her Brief Psychiatric Rating Scale score from 71 to 34. However, she did have 3 attacks of weakness in her lower limbs that lasted 1 to 2 days each time.

4.5.O Parkinson's disease

See Drug Consult reference: PARKINSON'S DISEASE - DRUG OVERVIEW

4.5.P Parkinson's disease - Psychotic disorder

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:
Clozapine therapy has been effective in treating psychosis associated with Parkinson's disease
Clozapine did not worsen Parkinson's symptoms
See Drug Consult reference: THERAPY OF PSYCHOTIC DISTURBANCES IN PARKINSONIAN PATIENTS

3) Adult:

a) The authors of a review article recommend clozapine as the second-line antipsychotic for patients with Parkinson's-associated psychosis. Two controlled trials plus numerous open studies and case reports attest to the efficacy and safety of clozapine for this indication. Daily clozapine doses are much lower (6.25 to 50 milligrams) than required for schizophrenia. The major advantage of clozapine in this setting is its lack of parkinsonian adverse effects. However, the risk of agranulocytosis coupled with the expense and inconvenience of weekly blood monitoring prompted the authors to consider quetiapine as the first-line antipsychotic despite relatively limited efficacy data (Friedman & Factor, 2000).

b) In a double-blind, placebo-controlled trial (n=60), clozapine improved drug-induced psychosis in patients with Parkinson's disease, even though the patients continued to take antiparkinsonian drugs. Clozapine did not worsen the symptoms of Parkinson's disease and actually decreased motor tremor. Subjects (mean age: 71 years, disease duration: 10 years) were randomized to 4 weeks of therapy with either placebo or clozapine, titrated from 6.25 milligrams (mg)/day to a maximum of 50 mg/day. At a mean dose of 25 mg/day, clozapine produced significant improvements in the Clinical Global Impression (CGI) scale (in comparison to placebo ,p less than 0.001) and the Brief Psychiatric Rating Scale (BPRS) (in comparison to placebo, p=0.02) Changes (from baseline) in total score and motor score on the Unified Parkinson's Disease Rating Scale (UPDRS) were not statistically different for clozapine and placebo, but the improvement in tremor score was significantly better with clozapine than with placebo (p=0.02). Three patients withdrew from the clozapine group: one because of leukopenia, one because of myocardial infarction, and one because of sedation. Three patients in the placebo group discontinued the study (Anon, 1999a). In a 12-week, open label extension of this trial, 52 patients were all given clozapine, starting with 6.25 mg per day, with no ceiling dose. Those patients who had received placebo in the double-blind portion of the trial improved to a degree similar to that of the patients originally randomized to clozapine. Improvement was maintained in both groups through week 16. Clozapine did not worsen motor scores. The average dose of clozapine was 28.8 mg/day, similar to that in the double-blind portion of the study, when there was a 50 mg ceiling. Of the original 60 patients, 6 patients died and another 12 were hospitalized. The most common cause was pulmonary (usually pneumonia). The relation of the high morbidity and mortality to clozapine treatment is uncertain (Factor et al, 2001).

c) In a retrospective chart review, 172 patients with Parkinson's disease at 4 centers benefited from clozapine (mean dose 31.4 milligrams; mean duration 16.7 months) (Trosch et al, 1998a). Visual hallucinations that were present in 114 of the patients improved in 89.5% with clozapine therapy. Auditory hallucinations, present in 9 patients had an 89% improvement rate. Delusions in 64 patients showed an improvement rate of 91%. Clozapine was discontinued in 40 patients (23%) due to adverse affects. Agranulocytosis was not seen at any site.

d) Patients with Parkinson's disease (n=49) received clozapine (16 to 31 milligrams/day) with 3 of 49 patients (6%) having complete relief of their psychotic symptoms. Improvement was seen in 76% of patients at 3 months, in 70% at 6 months, in 84% at 12 months, and in 70% at 18 months. Similar results were reported in 18 additional patients with Parkinson's disease and psychosis (Wagner et al, 1996; Lew & Waters, 1993; Wolk & Douglas, 1992; Friedman & Lannon, 1989).

e) An 81-year-old man with zoophilia, intermittent hypersexuality, and impulsivity due to his dopaminergic medication for Parkinson's disease benefited from clozapine therapy (Fernandex & Durso, 1998). He was receiving carbidopa/levodopa with pergolide with good control of his parkinsonian symptoms when the hypersexuality began. Clozapine 12.5 milligrams was begun and titrated up to 50 mg with no recurrence of the hypersexuality or impulsivity and a decrease in hallucinations.

f) In an open-label study, it was concluded that clozapine can improve hallucinations and psychosis without compromising motor function in patients with advanced Parkinson's disease (PD). Eleven patients with PD complicated by psychosis received clozapine long term (Kahn et al, 1991).

g) Mixed results on the efficacy and side effects of clozapine were reported in five parkinsonian patients with levodopa-induced hallucinations (Pfeiffer et al, 1990a).

4.5.Q Postpartum psychosis

1) Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category C
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:
Postpartum psychosis has been successfully treated in one case report

3) Adult:

a) Postpartum psychosis was managed successfully in a lactating 28-year-old patient with mastitis. The psychosis was treated initially with zuclopenthixol 600 milligram (mg) that produced severe extrapyramidal

side effects, and the mastitis was treated with bromocriptine 7.5 mg. Bromocriptine was discontinued and zuclopenthixol was gradually replaced with clozapine at a final dose of 200 milligrams. Both the psychosis and mastitis resolved within a few days. Because clozapine does not cause long-term increases in serum prolactin, the authors recommend it as the drug of choice in postpartum psychosis in lactating patients with mastitis (Kornhuber & Weller, 1991). However, breast-feeding during clozapine treatment is not recommended by the manufacturer; clozapine has been detected in breast milk in animal studies (Prod Info Clozaril(R) Australia, 1996).

4.5.R Schizoaffective disorder, Refractory

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Combination therapy with lithium and clozapine was beneficial for patients with schizoaffective disorder but not for schizophrenic patients

Effective in patients with schizoaffective disorder in a small, prospective cohort study

3) Adult:

a) The addition of lithium to maintenance clozapine therapy was beneficial for patients with treatment-resistant schizoaffective disorder but not for schizophrenic patients. In a randomized, placebo-controlled, double-crossover study, hospitalized patients with treatment-resistant schizoaffective disorder (n=10) or schizophrenia (n=10) and on a stable clozapine regimen (range, 100 to 800 milligrams (mg)/day) received alternating augmentation therapy with lithium (initial, 300 mg every 12 hours; target plasma level, 0.5 mmol/L) or placebo for four 4-week phases. At the end of the first crossover, lithium treatment was associated with significantly better improvements on the Clinical Global Improvement (CGI) scale and the Positive and Negative Symptom Scale (PANSS) total score in schizoaffective patients (p less than or equal to 0.01 and p less than or equal to 0.02, respectively). The PANSS Negative score was significantly more improved with lithium therapy in the schizoaffective patients at the end of both crossover periods (p less than or equal to 0.01). Significant improvements in CGI and PANSS scores were not found with clozapine and lithium combination therapy in patients with schizophrenia, however, two (20%) of the patients in this group developed transient neurological impairments, typical of lithium toxicity, during the first week of lithium administration. Overall, safety data showed significant increases in absolute neutrophil counts and total white blood cell counts with each phase of lithium treatment. Commonly reported adverse effects included hypersalivation, sedation, tremor, and polyuria (Small et al, 2003).

b) Clozapine was effective and relatively well tolerated in acute and long-term treatment of patients with schizoaffective disorder who have not responded to conventional pharmacotherapies. A small cohort prospective study included 26 schizoaffective disorder patients who were treated with clozapine at flexible doses (25 mg to 600 mg per day) over a 24-month period. All patients showed significant improvement 24 months from intake as assessed by the Brief Psychiatric Rating Scale and the Clinical Global Impressions-Severity of Illness scale (p less than 0.001). Such improvement was significantly greater among patients with schizoaffective disorder than with schizophrenia (p less than 0.05). For patients with schizoaffective disorder who are resistant to or intolerant of usual treatment options, clozapine is an effective alternative (Ciapparelli et al, 2000).

4.5.S Schizoaffective disorder - Suicidal behavior, Recurrent

FDA Labeled Indication

1) Overview

FDA Approval: Adult, yes; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIa
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Shown to be effective in decreasing the number of suicide attempts in patients with schizophrenia and schizoaffective disorder at high risk for suicide

3) Adult:

a) In the International Suicide Prevention Trial (InterSePT), clozapine was shown to be more effective than olanzapine in reducing suicidal behavior in high-risk, adult, patients with schizophrenia or schizoaffective disorder. Men and women between the ages of 18 to 65 years, at high risk of committing suicide, were recruited to participate in this 2-year, prospective, randomized, international, parallel group, study. The endpoints in this study included significant suicide attempts (including completed suicides) or hospitalization due to imminent suicide risk (type 1 events) or ratings of "much worse" or "very much worse" on the Clinical Global Impression of Suicide Severity (CGI-SS) scale (type 2 events). Of the total sample of 980 patients enrolled in the study, 62% (609) were diagnosed as having schizophrenia and 38% (371) were diagnosed with schizoaffective disorder. Twenty-seven percent (263) of these patients were considered treatment resistant. The patients were divided into two treatment groups (clozapine or olanzapine) and did not differ

significantly in terms of age, sex, race, diagnosis, treatment resistance, number of previous suicide attempts, or baseline concomitant medications. Both groups had weekly or biweekly clinical contact. Dropout rates for the two groups were similar with 192 discontinuing treatment with clozapine and 187 with olanzapine. Clozapine showed a hazard ratio of 0.76 (95% CI, 0.58-0.97) for type 1 events (p=.03) and 0.78 (95% CI, 0.61-0.99) for type 2 events (p=.04) compared to olanzapine. The most frequently reported adverse events for the olanzapine group were weight gain, somnolence, dry mouth, and dizziness, while salivary hypersecretion, somnolence, weight gain, and dizziness were the most frequently reported adverse events reported for the clozapine group. The overall number of adverse events did not differ significantly between the two groups. Decreased white blood cell counts occurred in 5.8% of clozapine-treated patients and in 0.8% of olanzapine-treated patients, but there were no reports of agranulocytosis or deaths due to granulocytopenia in either group. There was a total of 8 suicide deaths in the two groups (5 clozapine and 3 olanzapine). The mean daily olanzapine dosage was 16.6 +/- 6.4 mg and the mean daily clozapine dosage was 274.2 +/- 155.0 mg (Meltzer et al, 2003a).

b) It has been reported that clozapine reduces the risk of suicide by 75% to 80%. The International Suicide Prevention Trial (InterSePT) is a prospective study investigating the effect of clozapine (300 mg to 900 mg daily) versus olanzapine (10 mg to 20mg daily) on suicidal rates of patients with schizophrenia (Meltzer et al, 2000).

4.5.T Schizophrenia, Treatment-resistant

FDA Labeled Indication

1) Overview

FDA Approval: Adult, yes; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIa
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Indicated for the management of severely ill schizophrenic patients who fail to respond adequately to standard antipsychotic drug treatment

3) Adult:

a) GENERAL INFORMATION

1) Clozapine was effective and relatively well tolerated in acute and long-term treatment of patients with refractory schizophrenia who have not responded to conventional pharmacotherapies. A small cohort prospective study included 31 refractory schizophrenia patients who were treated with clozapine at flexible doses (25 mg to 600 mg per day) over a 24-month period. All patients showed significant improvement 24 months from intake as assessed by the Brief Psychiatric Rating Scale and the Clinical Global Impressions-Severity of Illness scale (p less than 0.001). For patients with refractory schizophrenia who are resistant to or intolerant of usual treatment options, clozapine is an effective alternative (Ciapparelli et al, 2000).

2) Results from short- and long-term retrospective, noncomparative studies indicate that 30% to 60% of patients with treatment-resistant schizophrenia show a marked improvement with clozapine as compared to previous standard antipsychotic agents (Alvarez et al, 1997; Fitton & Heel, 1990a). Positive schizophrenic symptoms, mainly hallucinations, delusions, unusual thought content, psychomotor hyperactivity, hostility and aggression appear to be significantly alleviated by clozapine (Keck et al, 2000; Volavka, 1999; Lindstrom, 1988) possibly even better than with haloperidol (Buchanan et al, 1998). Some evidence suggests that clozapine may decrease comorbid depressive symptoms, substance abuse and SUICIDAL BEHAVIOR (Keck et al, 2000; Zimmet et al, 2000; Volavka, 1999; Meltzer, 1999). In comparative studies of patients refractory to classic antipsychotics, clozapine (less than or equal to 900 milligrams/day) had significant superior overall antipsychotic efficacy (in terms of Brief Psychiatric Rating Scale score) to chlorpromazine (less than or equal to 1800 milligrams/day) over a 6-week treatment period (Conley et al, 1988a; Herrera et al, 1988; Kane et al, 1988b). Results from various studies in treatment-resistant schizophrenia indicate that patients intolerant to classic neuroleptics and presenting tardive dyskinesia/extrapyramidal side effects have improved response to clozapine therapy (greater than or equal to 3 months' duration) when compared to previous antipsychotic therapy (Lieberman et al, 1994; Kane et al, 1994; Maier, 1992; Davies et al, 1991; Meltzer et al, 1990; Meltzer et al, 1989). Patients have continued to improve even after 5 to 10 years of therapy with clozapine (Lindstrom & Lundberg, 1997).

3) A meta-analysis of 30 randomized trials comparing clozapine to conventional neuroleptics determined that clozapine was generally superior in terms of clinical outcome (rating scale scores) and relapse rates in short-term treatment of hospitalized adults. Adverse effects such as blood dyscrasias, hypersalivation, fever and sedation were generally more frequent with clozapine, while extrapyramidal symptoms and dry mouth were more common with traditional agents. The authors noted that more long-term, community-based studies are needed with evaluation of global and social functioning, ability to work, patient satisfaction and family burden. More controlled data are also required to assess clozapine therapy in special patient populations (ie, children, adolescents, various comorbidities) (Wahlbeck et al, 1999).

4) Combination therapies of clozapine and fluoxetine, and clozapine, risperidone, and paroxetine have been used successfully in refractory schizophrenia (Patel et al, 1997; Cassady & Thaker, 1992). The

combination of clozapine and paroxetine was effective in schizophrenia with comorbid obsessive-compulsive symptoms in a case report (Strous et al, 1999). Combination clozapine and electroconvulsive therapy has also been used (James & Gray, 1999).

5) In a comparison of responders and non-responders, characteristics which were associated with response to CLOZAPINE included (1) lower severity of illness at baseline according to the Clinical Global Impressions-Severity of Illness (CGI-S) scale, (2) lower baseline level of negative symptoms as assessed on the Scale for the Assessment of Negative Symptoms (SANS), and (3) lower level of acute extrapyramidal symptoms at baseline. After controlling for the foregoing characteristics, a higher total score on the Brief Psychiatric Rating Scale (BPRS) was predictive of a positive response to clozapine. Patient history did not influence response to clozapine. Subjects in this study (n=37) were partially treatment-refractory outpatients diagnosed with schizophrenia or schizoaffective disorder (DSM-III-R), of which 22 (59%) responded to clozapine given for 29 weeks (ie, showed a 20% decrease in BPRS psychosis factor scores). Targeted clozapine dose titration was to reach 500 milligrams (mg)/day by the end of week 5 (minimum 250 mg/day; maximum 850 mg/day) (Umbricht et al, 1994a).

b) SINGLE DRUG THERAPY

1) A reduction in left caudate nucleus volume (CNV) was correlated with improvement in positive symptoms and general symptoms of schizophrenia, though not in negative symptoms, in patients who had been unresponsive to conventional antipsychotropic drugs but who responded to clozapine. Treatment with conventional antipsychotropic drugs was associated with an increase in left CNV in this population of 28 patients. Treatment was switched to clozapine (mean dose 346 milligrams/day) and CNV was assessed again at 24 weeks and 52 weeks of treatment. In responders to clozapine, but not in nonresponders, left (but not right) CNV was significantly reduced by 24 weeks (p less than 0.005). The change in CNV between weeks 24 and 52 was not significant. Scores on the Positive and Negative Syndrome scale showed significant improvement at 24 weeks compared to baseline scores (p less than 0.001) and continued to improve through week 52 (p less than 0.01 for comparison to 24-week scores). These results suggest that the caudate nucleus may play a role in the positive and general symptoms of schizophrenia (Scheepers et al, 2001).

2) In an open-label 12-week study of treatment-refractory schizophrenic patients, clozapine (n=21) and risperidone (n=14) significantly improved psychopathology as rated by the Positive and Negative Syndrome Scale (PANSS), p less than 0.003. Patients were included if they met DSM-IV criteria for schizophrenia, had poor response to two prior neuroleptic treatments, had a minimum baseline Brief Psychiatric Rating Scale score of 46, and persistently poor functioning for at least 2 years. Patients had a mean age of 39 years and a mean duration of illness of 18 years. Improvements in the Clinical Global Impressions scale were seen with both treatments (p less than 0.011). Neurocognitive measures did not improve greatly over the 12-week treatment period. Patients receiving risperidone (mean dose 9 milligrams per day) experienced improvements within the first 2 weeks of therapy and remained stable over the treatment period; however, patients receiving clozapine (mean dose 363 milligrams per day) continued to improve over the 12-week treatment period. Extrapyramidal symptoms improved significantly in the clozapine group (p less than 0.01), but not the risperidone group. Tardive dyskinesia symptoms did not change significantly with either group (Lindenmayer et al, 1998).

3) In a prospective, 12-month study, clozapine elicited therapeutic responses in 68% of 50 inpatients with schizophrenia. Subjects were refractory to at least 2 adequate trials of antipsychotic drug therapy, in addition to a 6-week trial of haloperidol or perphenazine just prior to study entry. Clozapine was initiated at 25 milligrams (mg)/day, then titrated slowly to 400 to 450 mg/day within 3 weeks. Doses were advanced as necessary every 6 weeks thereafter to a maximum of 900 mg/day. The average onset and dose for therapeutic response were 82 days and 468 mg/day, respectively. Investigators concluded that an 8-week trial is sufficient to assess response after a dose change (Conley et al, 1997).

4) Fifty percent of treatment-refractory patients and 76% of treatment-intolerant patients had a favorable response to clozapine. The clinical responses of 84 schizophrenic patients who were either intolerant or refractory to other neuroleptic agents were evaluated for a period of up to 52 weeks (Lieberman et al, 1994). The authors suggested that predictors of a good response to clozapine include the presence of extrapyramidal side effects during previous treatment with classic neuroleptics and a diagnosis of paranoid schizophrenia.

5) Data from a retrospective review (n=33) support the efficacy and tolerability of clozapine in patients with mental retardation and comorbid treatment-resistant psychotic illness. All had failed three or more traditional antipsychotics with or without mood stabilizers and required hospitalization for acute exacerbation. Patients categorized as having mild (58%), moderate (39%) or severe (3%) mental retardation were initiated on clozapine 25 milligrams (mg)/day and titrated to a median dose of 400 mg/day. After a mean inpatient stay of 40 days, the average Clinical Global Impression (CGI)-Improvement score indicated much improvement, while the mean CGI-Efficacy Index score indicated decided improvement, partial symptom remission and no or minimal adverse effects. The clinical benefits were sustained for a mean follow-up of 25 months (Antonacci & de Groot, 2000). Four out of five MENTALLY RETARDED patients responded to clozapine therapy with progressive improvement in psychopathology, social functioning and ability to participate in daily activities. Clozapine was studied in a group of five patients with treatment-resistant schizophrenia or schizoaffective disorder and borderline intellectual function or mental retardation (Sajatovic et al, 1994).

c) COMBINATION THERAPY

1) The addition of lithium to maintenance clozapine therapy was beneficial for patients with treatment-

resistant schizoaffective disorder but not for schizophrenic patients. In a randomized, placebo-controlled, double-crossover study, hospitalized patients with treatment-resistant schizoaffective disorder (n=10) or schizophrenia (n=10) and on a stable clozapine regimen (range, 100 to 800 milligrams (mg)/day) received alternating augmentation therapy with lithium (initial, 300 mg every 12 hours; target plasma level, 0.5 mmol/L) or placebo for four 4-week phases. At the end of the first crossover, lithium treatment was associated with significantly better improvements on the Clinical Global Improvement (CGI) scale and the Positive and Negative Symptom Scale (PANSS) total score in schizoaffective patients (p less than or equal to 0.01 and p less than or equal to 0.02, respectively). The PANSS Negative score was significantly more improved with lithium therapy in the schizoaffective patients at the end of both crossover periods (p less than or equal to 0.01). Significant improvements in CGI and PANSS scores were not found with clozapine and lithium combination therapy in patients with schizophrenia, however, two (20%) of the patients in this group developed transient neurological impairments, typical of lithium toxicity, during the first week of lithium administration. Overall, safety data showed significant increases in absolute neutrophil counts and total white blood cell counts with each phase of lithium treatment. Commonly reported adverse effects included hypersalivation, sedation, tremor, and polyuria (Small et al, 2003).

2) Treatment-resistant schizophrenic patients refusing to give blood or swallow tablets benefited from combined electroconvulsive therapy (ECT) and clozapine (James & Gray, 1999). Six patients received ECT (2 treatments) before beginning clozapine therapy on day 6. Clozapine was then titrated to 300 mg daily by the end of ECT (10 more treatments) at week 6. At the end of the ECT, all patients consented voluntarily to weekly blood testing. Scores on the Brief Psychiatric Rating Scale had increased by 32%. Improvement persisted for 4 to 8 weeks post-ECT. After 6 months, all patients were still receiving clozapine with 3 freely compliant, 2 compliant with difficulty, and 1 threatening to refuse medication.

3) Two SEVERELY PSYCHOTIC patients, both of whom had a diagnosis of schizoaffective disorder, were successfully treated with electroconvulsive therapy (ECT) which facilitated clozapine administration and clinical stability (Green et al, 1994). The authors concluded that ECT may be useful in patients whose behavior is so disruptive that they cannot or will not take oral medication, and in cases where rapid control of behavior is necessary for the safety of themselves and others. In the two reported cases, following pretreatment with ECT, both patients have been successfully maintained on clozapine therapy for up to three years. Similar cases have been reported (Poyurovsky & Weizman, 1996).

4) Pediatric:

a) Clozapine has been reported to be effective in the treatment of young adolescents (ages 12 to 17 years) with severe symptoms of schizophrenia refractory to other neuroleptics (Turpeinen, 1996; Frazier et al, 1994; Jacobsen et al, 1994; Towbin et al, 1994). Usual side effects were observed, with precautionary measures taken to avoid seizures and agranulocytosis.

b) Clozapine has been successful in treating 4 children (ages 10 to 12) with schizophrenia. Early onset schizophrenic patients generally do not respond well to treatment with other conventional neuroleptics (Mozes et al, 1994).

4.5.U Schizophrenia - Suicidal behavior, Recurrent

FDA Labeled Indication

1) Overview

FDA Approval: Adult, yes; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIa
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Shown to be effective in decreasing the number of suicide attempts in patients with schizophrenia and schizoaffective disorder at high risk for suicide

3) Adult:

a) In the International Suicide Prevention Trial (InterSePT), clozapine was shown to be more effective than olanzapine in reducing suicidal behavior in high-risk, adult, patients with schizophrenia or schizoaffective disorder. Men and women between the ages of 18 to 65 years, at high risk of committing suicide, were recruited to participate in this 2-year, prospective, randomized, international, parallel group, study. The endpoints in this study included significant suicide attempts (including completed suicides) or hospitalization due to imminent suicide risk (type 1 events) or ratings of "much worse" or "very much worse" on the Clinical Global Impression of Suicide Severity (CGI-SS) scale (type 2 events). Of the total sample of 980 patients enrolled in the study, 62% (609) were diagnosed as having schizophrenia and 38% (371) were diagnosed with schizoaffective disorder. Twenty-seven percent (263) of these patients were considered treatment resistant. The patients were divided into two treatment groups (clozapine or olanzapine) and did not differ significantly in terms of age, sex, race, diagnosis, treatment resistance, number of previous suicide attempts, or baseline concomitant medications. Both groups had weekly or biweekly clinical contact. Dropout rates for the two groups were similar with 192 discontinuing treatment with clozapine and 187 with olanzapine. Clozapine showed a hazard ratio of 0.76 (95% CI, 0.58-0.97) for type 1 events (p=.03) and 0.78 (95% CI, 0.61-0.99) for type 2 events (p=.04) compared to olanzapine. The most frequently reported adverse events for the olanzapine group were weight gain, somnolence, dry mouth, and dizziness, while salivary

hypersecretion, somnolence, weight gain, and dizziness were the most frequently reported adverse events reported for the clozapine group. The overall number of adverse events did not differ significantly between the two groups. Decreased white blood cell counts occurred in 5.8% of clozapine-treated patients and in 0.8% of olanzapine-treated patients, but there were no reports of agranulocytosis or deaths due to granulocytopenia in either group. There was a total of 8 suicide deaths in the two groups (5 clozapine and 3 olanzapine). The mean daily olanzapine dosage was 16.6 +/- 6.4 mg and the mean daily clozapine dosage was 274.2 +/- 155.0 mg (Meltzer et al, 2003a).
b) It has been reported that clozapine reduces the risk of suicide by 75% to 80%. The International Suicide Prevention Trial (InterSePT) is a prospective study investigating the effect of clozapine (300 mg to 900 mg daily) versus olanzapine (10 mg to 20mg daily) on suicidal rates of patients with schizophrenia (Meltzer et al, 2000).

4.5.V Tardive dyskinesia
See Drug Consult reference: TARDIVE DYSKINESIA - DRUG THERAPY

4.6 Comparative Efficacy / Evaluation With Other Therapies

Chlorpromazine

Haloperidol

Olanzapine

Risperidone

4.6.A Chlorpromazine

4.6.A.1 Schizophrenia
a) Clozapine was more effective and induced fewer adverse effects than chlorpromazine for the treatment of schizophrenia (Claghorn et al, 1987). One hundred fifty-one schizophrenic patients were enrolled in a double-blind, randomized, placebo-controlled multicenter study. Each patient received either clozapine 150 to 900 milligrams/day or chlorpromazine 300 to 1800 milligrams/day over a 28-day period. Eleven chlorpromazine patients compared with one clozapine patient were dropped from the study due to extrapyramidal side effects. As measured by the Brief Psychiatric Rating and Clinical Global Impression scales, clozapine was superior to chlorpromazine (Claghorn et al, 1987).
b) In a double-blind follow-up for a year following the initiation of a clinical trial comparing chlorpromazine and clozapine, a higher percentage of clozapine patients were evaluated as clinically recovered as compared with chlorpromazine patients. Patients receiving clozapine received a mean dose of 600 milligrams/day as compared with 600 milligrams of chlorpromazine per day. During the initial 6-week study, 92% clozapine and 60% of chlorpromazine patients were evaluated as clinically recovered. At both the 3-year and the 4-year follow-up evaluation, the difference in clozapine and chlorpromazine continued. The results of this study must be viewed with caution, however, since both chlorpromazine and clozapine were dosed in equal doses and other investigators (Meltzer et al, 1979a) have found that the mean clinical antipsychotic dose of clozapine was 241 +/- 162 mg/day in contrast with the mean clinical antipsychotic dose of chlorpromazine of 691 +/- 411 mg/day. In the study by Leon, more equivalent results may have been obtained if equivalent antipsychotic doses had been used (Leon, 1979).
c) Clozapine was found to be more effective than chlorpromazine in the treatment of acutely psychotic schizophrenic individuals. Unlike chlorpromazine, no extrapyramidal reactions occurred in those patients taking clozapine. Characteristic clinical side effects of clozapine included sedation, hypotension, and increased salivation (Shopsin et al, 1979). Similar results have also been reported from investigators in Canada (Guirguis et al, 1977).

4.6.B Haloperidol

Hostile behavior

Schizophrenia, Refractory

4.6.B.1 Hostile behavior
a) Clozapine reduced hostility in patients with schizophrenia and was superior to haloperidol and risperidone in that regard. One hundred fifty seven patients with a diagnosis of schizophrenia or schizoaffective disorder and a history of poor response to drug treatment were randomly assigned to receive

clozapine, olanzapine, risperidone, or haloperidol in cross-titration with the antipsychotic drug used prior to the start of the study. Concomitant mood stabilizers and antidepressants had been phased out earlier. Daily doses of olanzapine, risperidone, and haloperidol were escalated within the first week to the target doses of 20, 8, and 20 milligrams (mg), respectively. Patients receiving clozapine were scheduled to achieve the target daily dose of 500 mg on day 24. Doses remained fixed for the remainder of the initial 8-week period. In a second (6-week) period, doses were allowed to vary: 200 to 800 mg for clozapine, 10 to 40 mg for olanzapine, 4 to 16 mg for risperidone, and 10 to 30 mg for haloperidol. Hostility, measured by the hostility item of the Positive and Negative Syndrome Scale (PANSS), improved significantly (in comparison to baseline) in the clozapine group only (p=0.019). This effect was independent of effects on psychotic symptoms (delusional thinking, hallucinations) or on sedation. The effect of clozapine on hostility was superior to that of haloperidol (p=0.021) or risperidone (p=0.012) but not to that of olanzapine (Citrome et al, 2001).

4.6.B.2 Schizophrenia, Refractory

a) Olanzapine and risperidone improved neurocognitive deficits more than did haloperidol or clozapine in patients with schizophrenia or schizoaffective disorder that was refractory to treatment with typical antipsychotics. In a randomized, double-blind study, inpatients were given clozapine (n=24) 200 to 800 milligrams (mg) per day, olanzapine (n=26) 10 to 40 mg/day, risperidone (n=26) 4 to 16 mg day, or haloperidol (n=25) 10 to 30 mg/day. Dose escalation and fixed-dose treatment (target doses: olanzapine 20 mg/day, risperidone 8 mg/day, haloperidol 20 mg/day, clozapine 500 mg/day) occurred during the first 8 weeks of the 14-week study; during the last 6 weeks, dosages were adjusted individually (generally increased if response was insufficient, but sometimes reduced because of adverse effects). Improvement over time in global neurocognitive score was seen for olanzapine and risperidone. In general executive and perceptual organization and in processing speed and attention, improvement was seen with olanzapine. In simple motor function, there was improvement with clozapine. Changes in global neurocognitive performance with olanzapine and risperidone were of medium magnitude (approximately 8 to 9 "IQ equivalents") but large enough to be clinically significant. Beneficial changes with clozapine were modest. Despite cognitive gains, patients still had significant impairments of cognitive ability and social/vocational functioning. Improvements in neurocognitive deficits were associated with improvements in negative symptoms (Bilder et al, 2002).

b) Schizophrenic patients treated with clozapine were more likely to be rated as improved and less likely to discontinue treatment due to lack of efficacy than a matched group treated with haloperidol. Seventy-one patients between the ages of 20 to 55 years with a diagnosis of schizophrenic or schizoaffective disorder were enrolled in this 6-month, double-blind, prospective, randomized trial. These outpatients, were documented as poor or partial responders to antipsychotic therapy and had a rating of at least moderate on 1 of 4 Brief Psychiatric Rating Scale (BSRS) items (conceptual disorganization, suspiciousness, hallucinatory behavior, or unusual thought content). The two major outcome measures for this study were time to discontinuation of study medication due to lack of clinical response and 20% improvement in the 4 item BPRS cluster during two consecutive rating periods. The haloperidol group (n=34) was targeted to receive 10 milligrams (mg)/day, along with 2 mg/day of benztropine, while the clozapine group was to receive 500 mg/day (n=37). Doses could be adjusted in either group to a range of 4 to 16 mg/day for the haloperidol group and 200 to 800 mg/day for the clozapine group depending upon the patient's clinical course. At the end of 29 weeks, 50.5% of the haloperidol-treated group (mean dose 18.9 mg/day) and 11.6% of the clozapine group (mean dose 523 mg/day) had discontinued treatment due to lack of efficacy (p=0.02). The mean BPRS ratings at the end of the study were 3.2 and 4.2 for the clozapine and haloperidol groups respectively (p less than 0.001). There was no difference found between the groups as measured by the Schedule for Assessment of Negative Symptoms (SANS) score using the sum of the 4 global ratings. Haloperidol-treated patients experienced more dry mouth and decreased appetite, while the clozapine-treated group reported more salivation, sweating, and dizziness. Three haloperidol and 2 clozapine-treated patients dropped-out of the study due to adverse drug effects (Kane et al, 2001).

c) Clozapine exhibited improved efficacy with fewer adverse effects as compared to haloperidol in a randomized, double-blind, 12-month study conducted at Veterans Affairs medical centers (n=423 with refractory schizophrenia). Using intention-to-treat analysis, schizophrenia symptom scores were significantly improved with clozapine over haloperidol at 6 weeks (p equals 0.008) and 6 months (p equals 0.001), with no statistical difference in quality of life measures. When crossover cases were excluded, quality of life measures were significantly better in the clozapine group at 3 months and 1 year (p equals 0.02). Clozapine also reduced scores for tardive dyskinesia, akathisia and extrapyramidal syndrome. Clozapine's higher costs for drug acquisition and laboratory monitoring were offset by decreased inpatient hospital stays (Rosenheck et al, 1997).

d) These investigators later evaluated compliance with clozapine versus haloperidol. The results confirmed that clozapine established better medication continuation and regimen compliance. Patients taking clozapine continued taking the study drug for a mean of 35.5 weeks as compared with on 27.2 weeks among haloperidol patients (p=0.0001). No differences were found between the groups in the proportion of prescribed pills that were returned at any time point. Continuation with medication is greater with clozapine than haloperidol and is partly explained by greater symptom improvement and reduced side effects. No differences were discovered in regimen compliance (Rosenheck et al, 2000).

4.6.B.3 Adverse Effects

a) The results of one study suggest that patients receiving atypical antipsychotics have a higher incidence

of PANCREATITIS than patients receiving a conventional antipsychotic medication. In a retrospective, pharmacovigilance study, 192 cases of pancreatitis were identified in patients taking clozapine (mean dose, 306.7 milligrams (mg)/day), olanzapine (mean dose, 15 mg/day), risperidone, (mean dose, 4 mg/day) or haloperidol (mean dose, 8.2 mg/day). Of the identified cases, 40%, 33%, and 16% were related to treatment with the atypical antipsychotic medications clozapine, olanzapine, or risperidone, respectively, as compared with 12% of the cases which were related to the conventional neuroleptic, haloperidol. In most patients, time to onset of pancreatitis was within 6 months after initiation of treatment (Koller et al, 2003).
b) No significant difference was found in sexual disturbances occurring in clozapine-treated versus haloperidol-treated patients (Hummer et al, 1999). Inpatients receiving either clozapine (n=100) or haloperidol (n=53) were screened. The most common adverse event in both groups was diminished sexual desire occurring in 4 (33.3%) of the haloperidol-treated women, 26 (63.4%) of the haloperidol-treated men, 7 (28%) of the clozapine-treated women, and 43 (57.3%) of the clozapine-treated men. Among women treated, amenorrhea occurred in 4 (33.3%) of the haloperidol patients and in 3 (12%) of the clozapine patients. Larger studies may be needed to show differences.
c) In a prospective study, the incidence of alanine aminotransferase (ALT) elevation to more than twice the upper normal limit was statistically greater with clozapine (37%, n=167) than with haloperidol (17%, n=71). Among those receiving clozapine, the rates of elevations in aspartate aminotransferase (AST) and gamma-glutamyl transpeptidase (GGT) to more than twice the upper normal limit were 12% and 15%, respectively. No such increases in bilirubin or alkaline phosphatase occurred in clozapine-treated patients. These effects were transient in the majority of patients (disappearing by week 13) with no clinical manifestations reported (Hummer et al, 1997).

4.6.C Olanzapine

Bipolar disorder

Drug-induced psychosis

Hostile behavior

Schizophrenia

Schizophrenia - Suicidal intent

4.6.C.1 Bipolar disorder

a) In a retrospective study of 50 consecutive patients treated for bipolar disorder with atypical antipsychotic medications, clozapine (n=5), olanzapine (n=20), and risperidone (n=25), along with standard mood stabilizers, showed similar efficacy. Overall, 68% of patients showed improvement of at least 1 point in their Clinical Global Impressions assessment over the 12-week study. Mean dosages were 210 milligrams (mg) per day for clozapine, 11.7 mg/day for olanzapine, and 1.7 mg day for risperidone. The only serious adverse event to occur during the study was a seizure in a patient taking clozapine. Extrapyramidal symptoms (EPS) were reported in 12 of 42 subjects (28.6%). Parkinsonism occurred in 4 of 25 patients taking risperidone, 1 of 20 taking olanzapine, and 1 of 5 taking clozapine. Weight gain was more extreme in patients taking clozapine and olanzapine than in those taking risperidone. Weight gain, which was greater than reported in other studies, may have been affected by concurrent mood enhancing medications (Guille et al, 2000).

4.6.C.2 Drug-induced psychosis

a) In a small (n=18), open study, clozapine and olanzapine were both effective in reducing symptoms of dopaminergic drug-induced psychosis in patients with Parkinson's disease. However, olanzapine and not clozapine caused worsening of Parkinsonian symptoms. The starting dose of clozapine was 6.25 to 25 milligrams (mg) per day and was increased at weekly intervals as necessary to optimize clinical status. The final mean dose of clozapine at the end of the 8-week study was 16.9 mg /day (range: 6.25 to 37.5 mg/day). Olanzapine was started at 2.5 to 5 mg/day. The final mean dose of olanzapine for the 6 patients completing the study was 4.7 mg/day (range: 2.5 to 10 mg/day). Three patients dropped out of the study after receiving the starting dose of olanzapine (2.5 mg for 2 patients, 5 mg for 1 patient) because of worsening of parkinsonism. All patients in the clozapine group completed the study, despite side effects of somnolence, falls, orthostatic hypotension, and syncope. Neuropsychiatric symptoms markedly improved with both medications (72% and 65% reduction in Neuropsychiatric Inventory global scores for clozapine and olanzapine, respectively). Parkinsonian motor scores (raw scores) improved by 20% in the clozapine group and worsened by 25% in the olanzapine group. It is possible that the differences observed were due to non-equivalence of the doses and that the dosage of olanzapine was excessive (Gimenez-Roldan & Mateo D Navarro, 2001).

4.6.C.3 Hostile behavior

a) Clozapine reduced hostility in patients with schizophrenia and was superior to haloperidol and risperidone in that regard. One hundred fifty seven patients with a diagnosis of schizophrenia or schizoaffective disorder and a history of poor response to drug treatment were randomly assigned to receive clozapine, olanzapine, risperidone, or haloperidol in cross-titration with the antipsychotic drug used prior to the start of the study. Concomitant mood stabilizers and antidepressants had been phased out earlier. Daily doses of olanzapine, risperidone, and haloperidol were escalated within the first week to the target doses of 20, 8, and 20 milligrams (mg), respectively. Patients receiving clozapine were scheduled to achieve the target daily dose of 500 mg on day 24. Doses remained fixed for the remainder of the initial 8-week period. In a second (6-week) period, doses were allowed to vary: 200 to 800 mg for clozapine, 10 to 40 mg for olanzapine, 4 to 16 mg for risperidone, and 10 to 30 mg for haloperidol. Hostility, measured by the hostility item of the Positive and Negative Syndrome Scale (PANSS), improved significantly (in comparison to baseline) in the clozapine group only (p=0.019). This effect was independent of effects on psychotic symptoms (delusional thinking, hallucinations) or on sedation. The effect of clozapine on hostility was superior to that of haloperidol (p=0.021) or risperidone (p=0.012) but not to that of olanzapine (Citrome et al, 2001a).

4.6.C.4 Schizophrenia

a) Olanzapine and risperidone improved neurocognitive deficits more than did haloperidol or clozapine in patients with schizophrenia or schizoaffective disorder that was refractory to treatment with typical antipsychotics. In a randomized, double-blind study, inpatients were given clozapine (n=24) 200 to 800 milligrams (mg) per day, olanzapine (n=26) 10 to 40 mg/day, risperidone (n=26) 4 to 16 mg day, or haloperidol (n=25) 10 to 30 mg/day. Dose escalation and fixed-dose treatment (target doses: olanzapine 20 mg/day, risperidone 8 mg/day, haloperidol 20 mg/day, clozapine 500 mg/day) occurred during the first 8 weeks of the 14-week study; during the last 6 weeks, dosages were adjusted individually (generally increased if response was insufficient, but sometimes reduced because of adverse effects). Improvement over time in global neurocognitive score was seen for olanzapine and risperidone. In general executive and perceptual organization and in processing speed and attention, improvement was seen with olanzapine. In simple motor function, there was improvement with clozapine. Changes in global neurocognitive performance with olanzapine and risperidone were of medium magnitude (approximately 8 to 9 "IQ equivalents") but large enough to be clinically significant. Beneficial changes with clozapine were modest. Despite cognitive gains, patients still had significant impairments of cognitive ability and social/vocational functioning. Improvements in neurocognitive deficits were associated with improvements in negative symptoms (Bilder et al, 2002a).

4.6.C.5 Schizophrenia - Suicidal intent

a) In the International Suicide Prevention Trial (InterSePT), clozapine was shown to be more effective than olanzapine in reducing suicidal behavior in high-risk, adult, patients with schizophrenia or schizoaffective disorder. Men and women between the ages of 18 to 65 years, at high risk of committing suicide, were recruited to participate in this 2-year, prospective, randomized, international, parallel group, study. The endpoints in this study included significant suicide attempts (including completed suicides) or hospitalization due to imminent suicide risk (type 1 events) or ratings of "much worse" or "very much worse" on the Clinical Global Impression of Suicide Severity (CGI-SS) scale (type 2 events). Of the total sample of 980 patients enrolled in the study, 62% (609) were diagnosed as having schizophrenia and 38% (371) were diagnosed with schizoaffective disorder. Twenty-seven percent (263) of these patients were considered treatment resistant. The patients were divided into two treatment groups (clozapine or olanzapine) and did not differ significantly in terms of age, sex, race, diagnosis, treatment resistance, number of previous suicide attempts, or baseline concomitant medications. Both groups had weekly or biweekly clinical contact. Dropout rates for the two groups were similar with 192 discontinuing treatment with clozapine and 187 with olanzapine. Clozapine showed a hazard ratio of 0.76 (95% CI, 0.58-0.97) for type 1 events (p=.03) and 0.78 (95% CI, 0.61-0.99) for type 2 events (p=.04) compared to olanzapine. The most frequently reported adverse events for the olanzapine group were weight gain, somnolence, dry mouth, and dizziness, while salivary hypersecretion, somnolence, weight gain, and dizziness were the most frequently reported adverse events reported for the clozapine group. The overall number of adverse events did not differ significantly between the two groups. Decreased white blood cell counts occurred in 5.8% of clozapine-treated patients and in 0.8% of olanzapine-treated patients, but there were no reports of agranulocytosis or deaths due to granulocytopenia in either group. There was a total of 8 suicide deaths in the two groups (5 clozapine and 3 olanzapine). The mean daily olanzapine dosage was 16.6 +/- 6.4 mg and the mean daily clozapine dosage was 274.2 +/- 155.0 mg (Meltzer et al, 2003).

4.6.C.6 Adverse Effects

a) The results of one study suggest that patients receiving atypical antipsychotics have a higher incidence of PANCREATITIS than patients receiving a conventional antipsychotic medication. In a retrospective, pharmacovigilance study, 192 cases of pancreatitis were identified in patients taking clozapine (mean dose, 306.7 milligrams (mg)/day), olanzapine (mean dose, 15 mg/day), risperidone, (mean dose, 4 mg/day) or haloperidol (mean dose, 8.2 mg/day). Of the identified cases, 40%, 33%, and 16% were related to treatment with the atypical antipsychotic medications clozapine, olanzapine, or risperidone, respectively, as compared with 12% of the cases which were related to the conventional neuroleptic, haloperidol. In most patients, time to onset of pancreatitis was within 6 months after initiation of treatment (Koller et al, 2003a).

b) Results of a retrospective analysis showed that olanzapine treatment was associated with a lower rate of

extrapyramidal symptoms (EPS) than haloperidol, but was similar to rates occurring with risperidone and clozapine therapy. In a pooled analysis of 23 randomized, controlled clinical trials in 4611 patients with schizophrenia, frequency and severity of EPS associated with olanzapine therapy (2.5 to 20 milligrams (mg)/day) was compared with that of haloperidol (1 to 20 mg/day), risperidone (4 to 12 mg/day), clozapine (25 to 625 mg/day), and placebo. Dystonic events (ie, dystonia, oculogyric crisis, opisthotonos, torticollis) occurred in significantly fewer patients during olanzapine treatment as compared with haloperidol (0.5% vs 5.6%, respectively; p less than 0.001) or risperidone (1% vs 3.2%, respectively; p=0.047) treatment, while no significant difference was found between olanzapine- and clozapine-treated patients. As compared with olanzapine-treated patients, a significantly higher percentage of haloperidol-treated patients experienced parkinsonian events (ie, akinesia, cogwheel rigidity, extrapyramidal syndrome, hypertonia, hypokinesia, masked facies, and tremor) (9.3% vs 28.3%, respectively; p less than 0.001) or akathisia events (ie, akathisia, hyperkinesia) (6.7% vs 20.4%, respectively; p less than 0.001) during therapy. However, no significant difference was observed between the olanzapine group as compared with the placebo, risperidone, or clozapine groups in regard to the occurrence of parkinsonian or akathisia events. Overall, EPS occurred in significantly more patients treated with haloperidol as compared with olanzapine (44.4% vs 16.2%, respectively; p less than 0.001) and in fewer patients treated with clozapine as compared with olanzapine (2.6% vs 6.8%, respectively; p=0.047). The overall rate of EPS was similar between the placebo and risperidone groups as compared with olanzapine. Significantly fewer patients received anticholinergic medications in the olanzapine group as compared with the haloperidol (p less than 0.001) or risperidone (p=0.018) groups. No difference was found between olanzapine-treated patients as compared with placebo or clozapine in regard to percentage of patients given anticholinergic drugs during therapy (Carlson et al, 2003).

c) In an open-label trial (n=24), olanzapine-treated patients had significantly lower levels of serum anticholinergic activity than clozapine-treated patients. Prior to enrollment, subjects were stabilized on therapeutic doses, averaging 15 milligrams (mg)/day and 444 mg/day for olanzapine and clozapine, respectively. The mean serum anticholinergic levels were 0.96 and 5.47 picomoles/atropine equivalents in the olanzapine and clozapine groups, respectively (p less than 0.001). Scores assessing clinical anticholinergic effects were significantly higher for salivation, constipation, micturition disturbances and palpitations/tachycardia in clozapine versus olanzapine recipients (p less than 0.05). Dry mouth was more problematic with olanzapine therapy (p less than 0.0008). The groups did not differ cognitively with respect to Mini Mental State Exam scores. Although efficacy was not a primary endpoint, the Brief Psychiatric Rating Scale scores favored clozapine (p=0.002), with no statistical difference in Clinical Global Impression Scale, Severity subscale scores. No patients in either group discontinued therapy due to adverse effects (Chengappa et al, 2000).

4.6.D Risperidone

Bipolar disorder

Hostile behavior

Parkinson's disease - Psychotic disorder

Schizophrenia

4.6.D.1 Bipolar disorder

a) In a retrospective study of 50 consecutive patients treated for bipolar disorder with atypical antipsychotic medications, clozapine (n=5), olanzapine (n=20), and risperidone (n=25), along with standard mood stabilizers, showed similar efficacy. Overall, 68% of patients showed improvement of at least 1 point in their Clinical Global Impressions assessment over the 12-week study. Mean dosages were 210 milligrams (mg) per day for clozapine, 11.7 mg/day for olanzapine, and 1.7 mg day for risperidone. The only serious adverse event to occur during the study was a seizure in a patient taking clozapine. Extrapyramidal symptoms (EPS) were reported in 12 of 42 subjects (28.6%). Parkinsonism occurred in 4 of 25 patients taking risperidone, 1 of 20 taking olanzapine, and 1 of 5 taking clozapine. Weight gain was more extreme in patients taking clozapine and olanzapine than in those taking risperidone. Weight gain, which was greater than reported in other studies, may have been affected by concurrent mood enhancing medications (Guille et al, 2000a).

4.6.D.2 Hostile behavior

a) Clozapine reduced hostility in patients with schizophrenia and was superior to haloperidol and risperidone in that regard. One hundred fifty seven patients with a diagnosis of schizophrenia or schizoaffective disorder and a history of poor response to drug treatment were randomly assigned to receive clozapine, olanzapine, risperidone, or haloperidol in cross-titration with the antipsychotic drug used prior to the start of the study. Concomitant mood stabilizers and antidepressants had been phased out earlier. Daily doses of olanzapine, risperidone, and haloperidol were escalated within the first week to the target doses of

20, 8, and 20 milligrams (mg), respectively. Patients receiving clozapine were scheduled to achieve the target daily dose of 500 mg on day 24. Doses remained fixed for the remainder of the initial 8-week period. In a second (6-week) period, doses were allowed to vary: 200 to 800 mg for clozapine, 10 to 40 mg for olanzapine, 4 to 16 mg for risperidone, and 10 to 30 mg for haloperidol. Hostility, measured by the hostility item of the Positive and Negative Syndrome Scale (PANSS), improved significantly (in comparison to baseline) in the clozapine group only (p=0.019). This effect was independent of effects on psychotic symptoms (delusional thinking, hallucinations) or on sedation. The effect of clozapine on hostility was superior to that of haloperidol (p=0.021) or risperidone (p=0.012) but not to that of olanzapine (Citrome et al, 2001b).

4.6.D.3 Parkinson's disease - Psychotic disorder

a) In subjects with Parkinson's Disease (PD), risperidone may be considered as an alternative to clozapine however, risperidone may worsen extrapyramidal symptoms more than clozapine and therefore must be used with caution. A small (n=10) double-blind trial compared the efficacy and safety of risperidone and clozapine for the treatment of psychosis in patients with PD. Five patients were randomized to receive clozapine and five patients received risperidone. Clozapine was started at 12.5 mg at bedtime and risperidone was started at 0.5 mg per day and both were titrated to symptomatic improvement was achieved or intolerable side effects emerged. Each subject received drug for 3 months and was assessed prior to initiation of treatment and after 2, 4, 8, and 12 weeks of treatment. Assessment was based on scores from the Brief Psychiatric Rating Scale and the Unified Parkinson's Disease Rating Scale. Mean improvement in the Brief Psychiatric Rating Scale psychosis score was similar in the clozapine and the risperidone groups (p=0.23). Although the mean motor Unified Parkinson's Disease Rating Scale scores worsened in the risperidone group and improved in the clozapine group, this difference did not reach statistical significance. Risperidone may be a reasonable alternative to clozapine in the treatment of psychosis in patients with PD however, it must be used with caution since it may worsen extrapyramidal side effects (Ellis et al, 2000).

4.6.D.4 Schizophrenia

a) Olanzapine and risperidone improved neurocognitive deficits more than did haloperidol or clozapine in patients with schizophrenia or schizoaffective disorder that was refractory to treatment with typical antipsychotics. In a randomized, double-blind study, inpatients were given clozapine (n=24) 200 to 800 milligrams (mg) per day, olanzapine (n=26) 10 to 40 mg/day, risperidone (n=26) 4 to 16 mg day, or haloperidol (n=25) 10 to 30 mg/day. Dose escalation and fixed-dose treatment (target doses: olanzapine 20 mg/day, risperidone 8 mg/day, haloperidol 20 mg/day, clozapine 500 mg/day) occurred during the first 8 weeks of the 14-week study; during the last 6 weeks, dosages were adjusted individually (generally increased if response was insufficient, but sometimes reduced because of adverse effects). Improvement over time in global neurocognitive score was seen for olanzapine and risperidone. In general executive and perceptual organization and in processing speed and attention, improvement was seen with olanzapine. In simple motor function, there was improvement with clozapine. Changes in global neurocognitive performance with olanzapine and risperidone were of medium magnitude (approximately 8 to 9 "IQ equivalents") but large enough to be clinically significant. Beneficial changes with clozapine were modest. Despite cognitive gains, patients still had significant impairments of cognitive ability and social/vocational functioning. Improvements in neurocognitive deficits were associated with improvements in negative symptoms (Bilder et al, 2002b).

b) Clozapine was superior to risperidone for improving positive and negative symptoms of schizophrenia in patients with poor previous response to treatment. In a prospective, double-blind study, patients meeting DSM-IV criteria for schizophrenia and having had poor response to previous treatment underwent a single-blind placebo run-in period when all psychotropic and anticholinergic medications were withdrawn. They were then randomly assigned to treatment with clozapine (n=138) or risperidone (n=135). Starting with daily doses of clozapine 12.5 milligrams (mg) and risperidone 1 mg, dosages were titrated over a period of 4 weeks to a minimum of 300 mg/day and 4 mg/day, respectively, and possibly to 600 mg/day and 6 mg/day. Patients unable to tolerate the minimum dose were withdrawn from the study. During the next 8 weeks, doses were adjusted at 2-week intervals within the range of 200 to 900 mg/day for clozapine and 2 to 15 mg/day for risperidone. For patients who completed the 12-week study (n=201), median final daily doses were 600 mg for clozapine and 9 mg for risperidone. Changes in the Positive and Negative Syndrome Scale of the BPRS (Brief Psychiatric Rating Scale) and in the Clinical Global Impression (CBI) scale were significantly greater in the clozapine group than in the risperidone group for the intent-to-treat population (those who received at least one dose of treatment medication and had one post-dose BPRS evaluation) and in the per- protocol population (those who completed the 28-day dose-setting period) (p less than 0.008 for all comparisons). Eighty-six percent of patients in the clozapine per-protocol population and 70% in the risperidone per-protocol population showed 20% or more improvement in the BPRS score (for difference between groups, p less than 0.01). By the end of the study, 94 (76%) patients in the clozapine group and 81 (64%) in the risperidone group no longer met the severity of psychopathology inclusion criteria (p less than 0.05). Extrapyramidal symptoms occurred significantly less frequently in the clozapine group than in the risperidone group (13% vs 28%, p=0.008). However, convulsions, dizziness, sialorrhea, tachycardia, and somnolence occurred significantly more frequently among those receiving clozapine. No case of agranulocytosis was observed during the study. Granulocytopenia occurred with low incidence in both groups (1% clozapine, 2% risperidone). Low neutrophil count was significantly more frequent among risperidone-treated patients (3% vs 11%, p less than 0.01). Hypotension occurred more frequently among

risperidone-treated patients (p less than 0.01). Weight gain was significantly greater for the clozapine group (2.4 kilograms vs 0.2 kilograms; p less than 0.002) (Azorin et al, 2001).

c) In the treatment of refractory schizophrenia, giving a risperidone trial before clozapine was more beneficial given its better side effect profile. A retrospective review study compared the relative efficacy profiles of clozapine and risperidone in a group of the most refractory, chronically institutionalized patients. The specific goal was to identify superiority (or lack thereof) of either agent on global clinical outcome as well as on specific symptom domains, including positive symptoms, negative symptoms, and aggressive behavior, compared with a baseline of conventional antipsychotic treatment in a total of 24 patients. Information obtained from systematic retrospective chart review was blindly rated by 2 psychiatrists using the 7-point Clinical Global Impressions Improvement (CGI-I) scale on overall clinical state and along specific symptom domains as above. The mean dose was 520 +/- 94 mg daily for clozapine and 7.5 +/- 2.2 mg daily for risperidone. Fourteen patients (58%) were classified as responders to clozapine, while 6 (25%) responded to risperidone. On specific symptom domains, response rates to clozapine were 38% (9/24) on positive symptoms, 29% (7/24) on negative symptoms, and 71% (12/17) on aggressive behavior. For risperidone, response rates were 17% (4/24) on positive symptoms, 8% (2/24) on negative symptoms, and 41% (7/17) on aggressive behavior. The results of this study would support the utility of first giving a risperidone trial in patients with treatment-refractory schizophrenia because of its better side effect profile compared with clozapine (Sharif et al, 2000).

d) Risperidone and clozapine had similar antipsychotic effects in 59 patients with paranoid schizophrenia. In a double-blind randomized study, patients were divided in three groups receiving either 4 milligrams risperidone, 8 milligrams risperidone, or 400 milligrams clozapine daily for 28 days. The antipsychotic effect was highly significant for both risperidone and clozapine. Patients on 4 milligrams of risperidone better tolerated therapy than those patients receiving clozapine. Withdrawals from clozapine treatment were mostly due to side effects, whereas withdrawals from risperidone treatment occurred from lack of therapeutic response (Heinrich et al, 1994).

e) Similar effectiveness of risperidone and clozapine was also observed in an 8-week, double-blind trial that allowed dose adjustment based on response in 86 patients with treatment-resistant chronic schizophrenia. The mean effective dose was 6.4 milligrams (mg) for risperidone and 291 mg for clozapine. The larger proportion of patients with clinical improvement after 7 and 14 days' treatment with risperidone suggested earlier onset of effect compared to clozapine treatment (Bondolfi et al, 1998)

f) In a prospective, open-label, 12-week trial, risperidone was found to be a poor substitute for clozapine in the treatment of chronic refractory schizophrenia. Six patients with schizophrenia and 4 with schizoaffective disorder were switched from a mean clozapine dose of 565 milligrams(mg)/day to a mean dose of risperidone 8 mg/day at 12 weeks. No subjects improved after being switched. Overall, patients who were switched from clozapine tended to worsen when taking risperidone. Statistically significant increases over baseline in the mean total of the Positive and Negative Syndrome Scale occurred at 9 and 12 weeks (P less than 0.05). The Brief Psychiatric Rating Scale scores also increased significantly over baseline at weeks 6, 9, and 12 (P less than 0.05). Five subjects failed to complete the entire 12 weeks. Of the 5 patients that completed the 12 weeks, the Clinical Global Impressions Scale indicated that 2 patients were unchanged, one was minimally worse, and 2 were much worse. The authors concluded that this study does not support replacing clozapine with risperidone for patients with treatment-resistant schizophrenia (Still et al, 1996).

4.6.D.5 Adverse Effects

a) Adverse effects and death were more commonly reported as the reasons for the discontinuation of clozapine while ineffectiveness was more often reported as the reason for discontinuation of risperidone (long-acting injection) in a retrospective, phase 3 study (n=322). Patients with a diagnosis of schizophrenia, schizoaffective disorder, bipolar disorder or other psychotic disorders who received clozapine (n=161), and had mean duration of therapy of 12.3 +/- 18.6 months (range, 0.25 to 100 months; median, 3 months) were matched by age (mean age, 40 +/- 12.6 years (yr); range, 18 to 83 yr) and gender at discontinuation to patients who discontinued risperidone long-acting injection (n=161). The risperidone patients (mean age, 39.9 +/- 13.1 yr , range 18 to 83 yr) were matched without knowledge of the reason for discontinuation of therapy (mean duration of therapy of 5.9 +/- 8.7 months; range, 0.5 to 46 months; median, 3 months). The reasons for discontinuation differed significantly between clozapine and risperidone injection; additionally, death as reason for discontinuation was significantly more common with clozapine (13%) vs risperidone injection (1.9%) (Taylor et al, 2009).

Reasons for Discontinuation: Clozapine vs Risperidone

Reason	Clozapine (n=161) n (%)	Risperidone (n=161) n (%)	OR (95% CI)	p value
Patient's decision	77 (47.8)	64 (39.7)	1.41 (0.89 to 2.21)	0.139
Adverse effects	57 (35.4)	32 (19.9)	2.19 (1.31 to 3.67)	0.0023
Ineffectiveness	3 (1.9)	59 (36.6)	0.034 (0.01 to 0.14)	less than 0.0001
Death	21 (13)	3 (1.9)	7 (2.09 to 23.5)	0.0003

Other	3 (1.9)	3 (1.9)	-	-

The cause of death reported in clozapine patients (mean age, 49.2 +/- 14.5 yr, range 30 to 83 yr) included: pneumonia (n=5), lung carcinoma (n=3), other carcinoma (n=2), myocardial infarction (n=2), cerebrovascular accident (n=2), clozapine overdose (n=2), gastrointestinal hemorrhage (n=1), cardiac arrest (n=1), left ventricular failure (n=1), asphyxia during restraint (n=1) and sepsis (n=1). There was no incidence of neutropenia or agranulocytosis at the time of death in any of the patients. The cause of death in the risperidone patients included: myocardial infarction (n=1), left ventricular failure (n=1) and sudden unexplained death (n=1). The mortality rate for clozapine patients was 8.5 per 1000 patient-years (95% CI, 5.53 to 13.07) vs 5.3 per 1000 patient-years (95% CI, 1.7 to 16.61) (Taylor et al, 2009).

b) The results of one study suggest that patients receiving atypical antipsychotics have a higher incidence of pancreatitis than patients receiving a conventional antipsychotic medication. In a retrospective, pharmacovigilance study, 192 cases of pancreatitis were identified in patients taking clozapine (mean dose, 306.7 milligrams (mg)/day), olanzapine (mean dose, 15 mg/day), risperidone, (mean dose, 4 mg/day) or haloperidol (mean dose, 8.2 mg/day). Of the identified cases, 40%, 33%, and 16% were related to treatment with the atypical antipsychotic medications clozapine, olanzapine, or risperidone, respectively, as compared with 12% of the cases which were related to the conventional neuroleptic, haloperidol. In most patients, time to onset of pancreatitis was within 6 months after initiation of treatment (Koller et al, 2003b).

c) Clozapine was associated with fewer extrapyramidal side effects (EPS) than was risperidone (Miller et al, 1998). Outpatients receiving stable doses of clozapine (n=41), risperidone (n=23), or conventional antipsychotics (n=42) were screened for EPS. Utilizing the Barnes Akathisia Scale, akathisia was noted in 7.3% of clozapine patients, 13% of risperidone patients, and 23.8% of conventional antipsychotic users. From the Simpson-Angus scale, rigidity and cogwheeling were noted in 4.9% and 2.4% of clozapine patients, 17.4% and 17.4% of risperidone patients, and 35.7% and 26.2% of conventional antipsychotic users, respectively. However, salivation was noted in 36.6% of clozapine patients, 8.7% of risperidone patients, and 4.8% of conventional antipsychotic users.

d) Insomnia and extrapyramidal side effects were more common with risperidone, and sedation and weight gain were more common with clozapine in a single-blind, crossover pilot study of the side effect profiles of the 2 drugs (Daniel et al, 1996). Twenty outpatients with schizophrenia or schizoaffective disorder were randomized to each drug for 6 weeks separated by a 1-week tapering-off period before crossover. The mean doses at week 6 were 6.1 milligrams/day (range 1 to 10 mg/d) of risperidone and 375 milligrams/day (range 75 to 800 mg/d) of clozapine. Three patients dropped out of the study; there was no significant difference in therapeutic effect between the 2 treatment groups. Mean body weight was greater (p less than 0.005) and sleepiness and lack of alertness were reported more often after the clozapine treatment phase. Restlessness and insomnia were more frequent complaints after the risperidone phase. A longer, double-blind study with a large sample of patients is needed to further elucidate the therapeutic differences and side effect profiles of these 2 drugs.

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Last Modified: June 23, 2009

DRUGDEX® Evaluations

METHYLPHENIDATE

0.0 Overview

1) Class

a) This drug is a member of the following class(es):
Amphetamine Related
Central Nervous System Agent
CNS Stimulant

2) Dosing Information

a) Methylphenidate

1) Pediatric

a) safety and effectiveness not established in pediatric patients under 6 years of age (Prod Info DAYTRANA

1) Attention deficit hyperactivity disorder

a) apply TOPICALLY 2 hours before needed effect and remove 9 hours after application; week-1, 1 (2)); week-3, 20 mg (25 cm(2)); week-4, 30 mg (37.5 cm(2)); titrate dose to effect (Prod Info DAYTR

b) Methylphenidate Hydrochloride

1) Adult

a) individualize dosage according to need and response of patient (Prod Info CONCERTA(R) extended-relea

1) Attention deficit hyperactivity disorder

a) immediate-release (IR), 10 to 60 mg/day ORALLY divided 2 to 3 times daily, preferably 30 to 45

b) extended-release (Concerta(R)), (age up to 65 yr), no prior methylphenidate therapy, initial, 18 o adjust dosage at weekly intervals in 18 mg increments; MAX 72 mg/day (Prod Info CONCERTA(R)

c) extended-release (Concerta(R)), (age up to 65 yr) conversion from prior methylphenidate therapy to 15 mg/day), 18 mg ORALLY in morning; (prior therapy of 20 to 30 mg/day); 36 mg in morning; (pr morning; (prior therapy of 40 to 60 mg/day), 72 mg in morning (Prod Info CONCERTA(R) extended-

d) extended-release (Metadate(R) CD), 20 mg ORALLY once daily in the morning; may adjust dosa MAX 60 mg/day

e) extended-release (Ritalin LA(R), no prior methylphenidate therapy), 20 mg ORALLY once daily i intervals in 10 mg increments; MAX 60 mg/day

f) extended-release (Ritalin LA(R), prior methylphenidate therapy), once daily (taken in the morning total daily oral dose of prior methylphenidate therapy; may adjust dosage at weekly intervals in 10 m

2) Fatigue

a) immediate release, 7.5 mg ORALLY twice daily, titrate up to MAX 60 mg/day

3) Narcolepsy

a) immediate release, 10- to 60 mg/day ORALLY divided 2 to 3 times daily, preferably 30 to 45 min

2) Pediatric

a) safety and effectiveness not established in pediatric patients under 6 years of age (Prod Info CONCERTA

b) individualize dosage according to need and response of patient (Prod Info CONCERTA(R) extended-relea

1) Attention deficit hyperactivity disorder

a) immediate-release, (age 6 yr and older) 5 mg ORALLY twice daily (before breakfast and lunch); intervals; MAX 60 mg/day

b) extended-release (Concerta(R)), (age 6 to 12 yr) no prior methylphenidate therapy, initial, 18 mg dosage at weekly intervals in 18 mg increments; MAX 54 mg/day (Prod Info CONCERTA(R) extend

c) extended-release (Concerta(R)), (age 13 to 17 yr) no prior methylphenidate therapy, initial, 18 m dosage at weekly intervals in 18 mg increments; MAX 72 mg/day or 2 mg/kg/day (Prod Info CONCE

d) extended-release (Concerta(R)), (age 6 to 17 yr) conversion from prior methylphenidate therapy 15 mg/day), 18 mg ORALLY in morning; (prior therapy of 20 to 30 mg/day), 36 mg in morning; (prior (Prod Info CONCERTA(R) extended-release oral tablets, 2008)

e) extended-release (Concerta(R)), (age 13 to 17 yr) conversion from prior methylphenidate therapy 60 mg/day), 72 mg ORALLY in the morning (Prod Info CONCERTA(R) extended-release oral tablets

f) extended-release (Metadate(R) CD), (age 6 y and older) 20 mg ORALLY once daily in the mornir mg increments; MAX 60 mg/day

g) extended-release (Ritalin LA(R), (no prior methylphenidate therapy), 20 mg ORALLY once daily intervals in 10 mg increments; MAX 60 mg/day

h) extended-release (Ritalin LA(R), (prior methylphenidate therapy), once daily (taken in the mornin total daily oral dose of prior methylphenidate therapy; may adjust dosage at weekly intervals in 10 m

2) Narcolepsy

a) (age 6 y and older) immediate-release, 5 mg ORALLY twice daily (before breakfast and lunch); d intervals; MAX 60 mg/day

3) Contraindications

a) Methylphenidate

1) marked agitation, anxiety, and tension; may aggravate symptoms (Prod Info DAYTRANA(TM) transdermal sys

2) glaucoma (Prod Info DAYTRANA(TM) transdermal system, 2006)

3) hypersensitivity to methylphenidate or other components of the product (Prod Info DAYTRANA(TM) transderm
4) monoamine oxidase inhibitors, such as isocarboxazid, phenelzine, selegiline, tranylcypromine, within 14 days (Prod Info DAYTRANA(TM) transdermal system, 2006)
5) tics, motor (Prod Info DAYTRANA(TM) transdermal system, 2006)
6) Tourette's syndrome, family history or diagnosis (Prod Info DAYTRANA(TM) transdermal system, 2006)

b) Methylphenidate Hydrochloride
1) angina pectoris; may increase blood pressure or heart rate (Prod Info METADATE CD(TM) extended release (TM) extended release oral capsules, 2008)
2) cardiac arrhythmias; may increase blood pressure or heart rate (Prod Info METADATE CD(TM) extended relea CD(TM) extended release oral capsules, 2008)
3) fructose intolerance, glucose-galactose malabsorption, or sucrase-isomaltase insufficiency; contains sucrose ((TM) extended release oral capsules, 2008)
4) glaucoma (Prod Info METADATE CD(TM) extended release oral capsules, 2008; Prod Info RITALIN(R) oral ta tablets, 2006)
5) halogenated anesthetics; risk of sudden blood pressure increase during surgery, do not take on day of surgery (TM) extended release oral capsules, 2008)
6) heart failure; may increase blood pressure or heart rate (Prod Info METADATE CD(TM) extended release oral
7) hypersensitivity to methylphenidate or other components of the product (Prod Info METADATE CD(TM) extend RITALIN(R) oral tablets, RITALIN-SR(R) sustained-release oral tablets, 2006)
8) hypertension, severe; may increase blood pressure (Prod Info METADATE CD(TM) extended release oral cap extended release oral capsules, 2008)
9) hyperthyroidism or thyrotoxicosis; may increase blood pressure or heart rate (Prod Info METADATE CD(TM) e METADATE CD(TM) extended release oral capsules, 2008)
10) marked agitation, anxiety, and tension; may aggravate symptoms (Prod Info METADATE CD(TM) extended r (R) oral tablets, RITALIN-SR(R) sustained-release oral tablets, 2006)
11) monoamine oxidase inhibitors, such as isocarboxazid, phenelzine, selegiline, tranylcypromine, within 14 days crisis (Prod Info METADATE CD(TM) extended release oral capsules, 2008; Prod Info RITALIN(R) oral tablets, R 2006)
12) myocardial infarction, recent; may increase blood pressure or heart rate (Prod Info METADATE CD(TM) exte METADATE CD(TM) extended release oral capsules, 2008)
13) tics, motor (Prod Info METADATE CD(TM) extended release oral capsules, 2008; Prod Info RITALIN(R) oral tablets, 2006)
14) Tourette's syndrome, family history or diagnosis (Prod Info METADATE CD(TM) extended release oral capsu RITALIN-SR(R) sustained-release oral tablets, 2006)

4) Serious Adverse Effects
a) Methylphenidate
1) Contact dermatitis
2) Decreased body growth
3) Drug dependence
4) Lowered convulsive threshold
5) Mania
6) Psychotic disorder
7) Tic

b) Methylphenidate Hydrochloride
1) Aggressive behavior
2) Cerebrovascular accident
3) Dead - sudden death
4) Decreased body growth
5) Drug dependence
6) Gastrointestinal obstruction
7) Mania
8) Myocardial infarction
9) Psychotic disorder
10) Seizure
11) Visual disturbance

5) Clinical Applications
a) Methylphenidate
1) FDA Approved Indications
a) Attention deficit hyperactivity disorder

b) Methylphenidate Hydrochloride
1) FDA Approved Indications
a) Attention deficit hyperactivity disorder
b) Narcolepsy

2) Non-FDA Approved Indications
a) Fatigue

1.0 Dosing Information

Drug Properties

Storage and Stability

Adult Dosage

Pediatric Dosage

1.1 Drug Properties

A) Information on specific products and dosage forms can be obtained by referring to the Tradename List (Product In

B) Synonyms

Methylphenidate
Methylphenidate HCl
Methylphenidate Hydrochloride
Methylphenidylacetate

C) Physicochemical Properties

1) Molecular Weight

a) 269.77 (Fleeger, 1994)

1.2 Storage and Stability

A) Methylphenidate

1) Preparation

a) Topical application route

1) APPLICATION

a) Apply the patch to a clean, dry area of the hip area 2 hours before an effect is needed. Avoid wa
When applying the patch the next morning, place on the opposite hip at a new site if possible (Prod
2006).

b) Apply patch immediately after opening the pouch and removing the protective liner. Do not use if
press firmly in place with palm of the hand for approximately 30 seconds. Make sure there is good c
around the edges. Once the patch has been properly placed, bathing, swimming, or showering will r
that a patch should fall off, a new patch may be applied at a different site, but the total recommende
Do not expose the patch application site to direct external heat sources, such as heating pads, elect
wearing the patch. Temperature-dependent increases in methylphenidate exposure of greater than
DAYTRANA(TM) transdermal system, 2006).

2) DISPOSAL OF PATCH

a) After patch removal, fold patch so the patch adheres to itself. The folded patch may be flushed d
lidded container. If the patient discontinues the prescription, each unused patch should be removed
liner, folded onto itself, and flushed down the toilet or disposed of in an appropriate lidded container
system, 2006).

B) Methylphenidate Hydrochloride

1) Preparation

a) Oral route

1) For extended-release tablets, the dose should be given once daily in the morning, with or without foo
liquids and must not be chewed, divided, or crushed (Prod Info CONCERTA(R) extended-release oral ta

2) For extended-release capsules, the dose should be given once daily in the morning. Capsules may b
over a spoonful of applesauce; the applesauce should not be warm, and the drug/applesauce mixture sh
(Prod Info RITALIN LA(R) oral extended-release capsule, 2004). Capsule contents of Ritalin(R) LA shou
RITALIN LA(R) oral extended-release capsule, 2004).

C) Transdermal route

1) Patch, Extended Release

a) Store at 25 degrees Celsius (77 degrees Fahrenheit); excursions permitted between 15 and 30 degrees C
store patches unpouched. Use within 2 months after opening tray (Prod Info DAYTRANA(TM) transdermal sy

1.3 Adult Dosage

Normal Dosage

Dosage in Renal Failure

Dosage in Hepatic Insufficiency

Dosage in Other Disease States

1.3.1 Normal Dosage

1.3.1.A Methylphenidate Hydrochloride

1.3.1.A.1 Oral route

Attention deficit hyperactivity disorder

Cancer; Adjunct

Dementia

Depression, Monotherapy

Narcolepsy

Shivering, Postanesthesia; Treatment and Prophylaxis

Syncope

Traumatic brain injury

1.3.1.A.1.a Attention deficit hyperactivity disorder

1) Extended-Release

a) The recommended starting dose of Concerta(R) extended-release tablet for new patients is morning. Dosage may be adjusted weekly in 18 mg increments to a maximum of 72 mg per day methylphenidate regimens may follow the dosage conversion recommendation below (Prod Info 2008):

Previous Methylphenidate Daily Dose	Recommended Concerta Dose
5 mg twice or 3 times daily	18 mg in the mor
10 mg twice or 3 times daily	36 mg in the mor
15 mg twice or 3 times daily	54 mg in the mor
20 mg twice or 3 times daily	72 mg in the mor

b) Pharmacologic treatment of attention deficit hyperactivity disorder may be needed for extend indicate how long the patient should be treated. The physician should periodically reevaluate th off medication to assess the patient's functioning without pharmacotherapy. Improvement may b temporarily or permanently discontinued. The dosage should be reduced or discontinued if para adverse events occur. If improvement is not observed after appropriate dosage adjustments ov drug should occur (Prod Info CONCERTA(R) extended-release oral tablets, 2008).

c) For methylphenidate extended release capsules (Metadate(R) CD), the starting dose is 20 n breakfast. Doses may be increased by 20 mg at weekly intervals to a MAXIMUM dose of 60 mg dosages above 60 mg are not recommended (Prod Info Metadate(R) CD, 2002).

2) Immediate-Release

a) Recommended dosage is from 10 to 60 milligrams daily. Average dose is 20 to 30 milligram times daily preferably 30 to 45 minutes before meals (Prod Info RITALIN(R) oral tablet, RITALIN

b) Methylphenidate in doses of 10 to 90 milligrams orally daily was reported more effective tha disorder, residual type, in adults in a double-blind crossover trial (Wender et al, 1985).

1.3.1.A.1.b Cancer; Adjunct

1) The combination of oral methylphenidate 15 milligrams (mg) daily (10 mg at breakfast and 5 mg to enhance the analgesic efficacy of the narcotic agents and decrease sedation in patients with chro et al, 1987a).

1.3.1.A.1.c Dementia

1) Some of the negative symptoms associated with vascular dementia and dementia of Alzheimer's milligrams/day in an open-label, non-blinded preliminary study. Results were similar among the 12 A (Galynker et al, 1997a).

1.3.1.A.1.d Depression, Monotherapy

1) Methylphenidate 5 to 40 milligrams per day appears to be safe and effective for the treatment of lacking contraindications for use (Frye, 1997a; Emptage & Semla, 1996a).
2) Methylphenidate 10 to 20 milligrams per day produced a positive response in 7 of 8 post-liver tra symptoms (Plutchik et al, 1998a).
3) Acute stroke patients (n=21) receiving methylphenidate 30 milligrams per day demonstrated grea activities of daily living, and motor function than patients receiving placebo in a prospective, random (Grade et al, 1998a).
4) A report of the efficacy of methylphenidate in the treatment of depression in cancer patients has Methylphenidate was given in doses of 10 milligrams orally three times daily initially, with subsequer period of 2 to 3 days; increases to a maximum of 80 milligrams daily were permitted by week 2 of tre marked improvement, with 13 showing moderate improvement; maximum improvement was genera

1.3.1.A.1.e Narcolepsy
1) Recommended dosage is from 10 to 60 milligrams daily. Average dose is 20 to 30 milligrams dai SR(R) oral tablet, 2004).
2) Doses should be administered 2 to 3 times daily preferably 30 to 45 minutes before meals (Prod tablet, 2004).

1.3.1.A.1.f Shivering, Postanesthesia; Treatment and Prophylaxis
1) Methylphenidate 20 mg suppressed postoperative shivering in 17 of 42 post-anesthetic patients received halothane anesthesia (Imray & White, 1968).

1.3.1.A.1.g Syncope
1) Six of 7 patients with recurrent NEUROCARDIOGENIC SYNCOPE became clinically asymptoma milligrams 3 times daily for 7 months. The patients were previously unresponsive to or poorly tolerar

1.3.1.A.1.h Traumatic brain injury
1) Methylphenidate 0.25 milligrams/kilogram twice daily improved speed of mental processing in pa injury, but orienting to distractions, sustained attention, and motor speed were unaffected (Whyte et

1.3.2 Dosage in Renal Failure
A) Methylphenidate Hydrochloride
1) Due to minimal excretion as unchanged drug (Faraj et al, 1974a; Prod Info RITALIN LA(R) oral extended- methylphenidate are unlikely to be altered significantly in renal impairment, suggesting no need for dose adju

1.3.3 Dosage in Hepatic Insufficiency
A) Methylphenidate Hydrochloride
1) As methylphenidate is metabolized primarily to ritalinic acid (essentially inactive) via non-microsomal este are unlikely to be altered significantly in liver disease (Prod Info RITALIN LA(R) oral extended-release capsul adjustment. However, adequate studies in this setting are lacking.

1.3.6 Dosage in Other Disease States
A) Methylphenidate Hydrochloride
1) GLAUCOMA
a) Use of methylphenidate in patients with glaucoma is contraindicated (Prod Info RITALIN(R) oral table has been suggested that when used cautiously in conjunction with glaucoma medications and regular op pressure measurements, methylphenidate may be safe in patients with well-controlled, open-angle glauc

1.4 Pediatric Dosage

Normal Dosage

Dosage in Renal Failure

Dosage in Hepatic Insufficiency

Dosage in Other Disease States

1.4.1 Normal Dosage

Methylphenidate

Methylphenidate Hydrochloride

1.4.1.A Methylphenidate

1.4.1.A.1 Transdermal route

1.4.1.A.1.a Attention deficit hyperactivity disorder

1) The recommended dose titration schedule for children 6 to 12 years of age for the treatment of a the table below (Prod Info DAYTRANA(TM) transdermal system, 2006):

	Upward Titration, if Response is Not Maximiz	
	Week 1	Week 2
Patch size	12.5 cm(2)	18.75 cm(2)
Nominal Delivered Dose *	10 mg/9 hrs	15 mg/9 hrs
Delivery rate *	1.1 mg/hr	1.6 mg/hr
Key: * = nominal in vivo delivery rate in pediatric subjects aged 6 to 12 when applied to the hip, centimeters squared mg = milligrams, hrs = hours		

Individualize titration, final dosage, and wear time for each patient according to the needs and r before desired effect and remove patch 9 hours after application. The patch may be removed e is preferred or late day side effects occur. The dose titration schedule applies to methylphenida children (Prod Info DAYTRANA(TM) transdermal system, 2006).

2) Although the design of a double-blind, placebo-controlled, randomized trial did not allow for evalu not appear to be improved efficacy with a dose increase from 20 mg over 9 hours to 30 mg over 9 h system, 2006).

2) Safety and effectiveness not established in pediatric patients under 6 years of age (Prod Info DAYTRANA

1.4.1.B Methylphenidate Hydrochloride

1.4.1.B.1 Oral route

1.4.1.B.1.a Attention deficit hyperactivity disorder

1) Extended Release

a) For Ritalin(R) LA extended-release capsules, the starting dose recommended by the manufa gradual upward titration based on efficacy and tolerability; weekly 10-mg increments to a maxim RITALIN LA(R) oral extended-release capsule, 2004). When a lower initial dose is desired, low may given; following titration to 10 mg twice daily of the immediate-release formulation, patients Ritalin(R) LA dose guidelines are for these latter patients, and those currently receiving immedi methylphenidate who are to be switched to Ritalin(R) LA (Prod Info RITALIN LA(R) oral extende

1) Patients currently receiving methylphenidate 10 mg twice daily or 20-mg methylphenida daily

2) Patients currently receiving methylphenidate 15 mg twice daily should be given Ritalin(R

3) Patients currently receiving methylphenidate 20 mg twice daily or 40-mg methylphenida daily

4) Patients currently receiving methylphenidate 30 mg twice daily or 60-mg methylphenida daily

The recommended starting dose of Concerta(R) extended-release tablet for new patients a day in the morning. Dosage may be adjusted weekly in 18 mg increments to a maximum of and to a maximum of 72 mg per day (not to exceed 2 mg/kg/day) in adolescents 13 to 17 y thrice daily regimens of methylphenidate may follow the dosage conversion recommendati release oral tablets, 2008):

Previous Methylphenidate Daily Dose	Recommended Concerta(R) Starting Dose
5 mg twice or 3 times daily	18 mg in the morning
10 mg twice or 3 times daily	36 mg in the morning
15 mg twice or 3 times daily	54 mg in the morning
20 mg twice or 3 times daily	72 mg in the morning (age 13 to 17 years only)

Initial conversion dosage should not exceed 54 milligrams (mg) daily in children 6 to 12 yea 17 years of age. Following conversion, doses may be adjusted if needed up to the maximu generally occur at weekly intervals (Prod Info CONCERTA(R) extended-release oral tablets Pharmacologic treatment of attention deficit hyperactivity disorder may be needed for exter that indicate how long the patient should be treated. The physician should periodically reev with trials off medication to assess the patient's functioning without pharmacotherapy. Impr either temporarily or permanently discontinued. The dosage should be reduced or discontir other adverse events occur. If improvement is not observed after appropriate dosage adjus of the drug should occur (Prod Info CONCERTA(R) extended-release oral tablets, 2008).

b) CHILDREN 6 YEARS & OLDER: For methylphenidate extended release capsules (Metadate once daily in the morning before breakfast. Doses may be increased by 20 mg at weekly interva

once daily in the morning. Daily dosages above 60 mg are not recommended. Metadate CD ext whole or the content of the capsule may be sprinkled onto a tablespoonful of applesauce and ta capsule or its content (Prod Info Metadate(R) CD, 2002).
c) Average total daily dose was 34.3 mg/day for EXTENDED-RELEASE METHYLPHENIDATE mg/day for IMMEDIATE-RELEASE METHYLPHENIDATE (n=94) among children 6 to 12 years comparing the efficacy of the 2 formulations of the drug. Immediate-release (given 3 times daily methylphenidate had comparable efficacy, and both were significantly superior to placebo (p les

2) Immediate Release
a) In children over 6 years of age, usual dose is 5 milligrams twice daily increased at weekly int to administer 5 milligrams before breakfast and lunch (Prod Info RITALIN(R) oral tablet, RITALI
b) The maximum recommended dose is 60 milligrams. Drug should be discontinued if there is (Prod Info RITALIN(R) oral tablet, RITALIN-SR(R) oral tablet, 2004).
c) According to the results of one triple-blind, placebo controlled, crossover study involving 25 (ADHD), three times a day dosing produces the most reliable improvements in the treatment of on weight, ranged from 5 to 20 milligrams (mean dose = 8.8 milligrams; 0.30 milligram/kilogram dosing schedule was associated with a greater improvement in behavioral measures compared were no significant differences between the two dosing schedules in the incidence of adverse e
d) In 11 hyperkinetic children aged 7 to 12, 0.3 milligram/kilogram/day markedly improved impu milligram/kilogram/day produced results similar to placebo in a double blind study (Brown & Sle to be no more efficacious and more toxic than lower (0.3 milligram/kilogram/day) doses (Holliste
e) Isolated studies have raised the possibility that a small group of children may develop some al, 1980; Eichlseder, 1985; Winsberg et al, 1974). Other non-controlled studies have observed medications in children with attention deficit disorders (Riddle & Rapoport, 1976; Charles et al, determined whether some hyperactive children who initially respond to methylphenidate develo is probably a rare occurrence. In patients who become less responsive to methylphenidate ther dosing or noncompliance should also be considered.
f) Methylphenidate 0.3 milligram/kilogram twice daily at 8 am and 12 noon for 14 days improve children (n=14) with acquired attention disorder secondary to brain injury in a double-blind, plac 1998).

1.4.2 Dosage in Renal Failure

A) Methylphenidate
1) Transdermal methylphenidate has not been studied in patients with renal insufficiency (Prod Info DAYTRA

B) Methylphenidate Hydrochloride
1) Due to minimal excretion as unchanged drug (Faraj et al, 1974a; Prod Info RITALIN LA(R) oral extended- methylphenidate are unlikely to be altered significantly in renal impairment, suggesting no need for dose adju

1.4.3 Dosage in Hepatic Insufficiency

A) Methylphenidate
1) Transdermal methylphenidate has not been studied in patients with hepatic insufficiency (Prod Info DAYT

B) Methylphenidate Hydrochloride
1) As methylphenidate is metabolized primarily to ritalinic acid (essentially inactive) via non-microsomal este are unlikely to be altered significantly in liver disease (Prod Info RITALIN LA(R) oral extended-release capsul adjustment. However, adequate studies in this setting are lacking.

1.4.5 Dosage in Other Disease States

A) Methylphenidate Hydrochloride
1) EPILEPSY
a) Use of methylphenidate (0.3 milligram/kilogram once daily) appears to be safe and effective to treat a children with epilepsy who are seizure free, while receiving antiepileptic drugs, before starting methylphe for those children still having seizures while receiving antiepileptic drugs (Gross-Tsur et al, 1997a).

2) TOURETTE'S SYNDROME
a) In a 2-year non-blinded, prospective, follow-up study of 32 children (aged 6.1 to 11.9 years) receiving from a previous trial (mean 16.5 milligrams (mg), range 5 to 40 mg), long-term methylphenidate therapy with attention deficit hyperactivity disorder (ADHD) and chronic multiple tic disorder or Tourette's syndror not worsen tics in patients with ADHD and Tourette's syndrome, the possibility of individual exacerbation 1999a).

2.0 Pharmacokinetics

Onset and Duration

Drug Concentration Levels

ADME

2.1 Onset and Duration

A) Onset

1) Initial Response

a) ATTENTION-DEFICIT/HYPERACTIVITY DISORDER, ORAL: within 2 weeks (Prod Info Ritalin(R) LA, 200

1) Represents time to significant improvement in symptoms scores in children treated with 10 to 40 mg

2.2 Drug Concentration Levels

A) Peak Concentration

1) TRANSDERMAL: 39 ng/mL (Prod Info DAYTRANA(TM) transdermal system, 2006).

a) The mean peak d-methylphenidate plasma concentration was 39 ng/mL (0 to 114 ng/mL) in pediatric child wear times of transdermal methylphenidate. These mean peak concentrations varied inversely by age rangin to 53 ng/mL (18 to 83 ng/mL) in 6 year olds (Prod Info DAYTRANA(TM) transdermal system, 2006).

b) The mean peak d-methylphenidate concentrations were 1.9 times higher for transdermal methylphenidate over a period of 7.5 to 10.5 hours, when Tmax usually occurs. These higher concentrations were consistent a and 4 days of multiple dosing the Cmaxs were higher with chronic dosing of transdermal methylphenidate. Si produced similar Cmaxs as single doses of the once daily oral methylphenidate (Prod Info DAYTRANA(TM) t

2) ORAL (Ritalin and Ritalin-SR at 0.3 mg/kg): Children-10.8 ng/mL(Gillis & editor, 2000); Adults-7.8 nanograms 3.7 ng/mL (Prod Info Concerta™, 2000a).

a) Ritalin and Ritalin-SR brands of methylphenidate- Following administration of 0.3 mg of methylphenidate p nanograms per mL(Gillis & editor, 2000); Adults-7.8 nanograms per mL(Gillis & editor, 2000)

b) Peak plasma concentrations showed marked variability between subjects (Gillis & editor, 2000).

c) Concerta brand of methylphenidate-Following administration of 18 mg of methylphenidate: 3.7 nanograms

d) Metadate(R) CD brand of methylphenidate-Following administration of 20 mg of Metadate(R) CD: an early ml due to the immediate release component, and a later maximum concentration of 10.9 nanograms per mL component (Prod Info Metadate CD(R), 2001).

e) The peak plasma concentration was increased by 30% when Metadate(R) CD 40 mg was administered fo

f) Dose-proportionality was demonstrated in peak plasma concentrations and area under the concentration-t methylphenidate.

B) Time to Peak Concentration

1) ORAL: 1 to 3 hours (Dayton et al, 1970); 6 to 8 hours (extended- release tablets or capsules) (Prod Info Conce

a) In 35 healthy adults, the PEAK PLASMA CONCENTRATION of methylphenidate after a single dose of OR immediate-release 5 mg every 4 hours, and a single dose of slow-release 20 mg was 3.75 ng/mL, 4.17 ng/ml PEAK PLASMA CONCENTRATION was 6.7 hours, 6.5 hours, and 3.7 hours, respectively (Modi et al, 2000).

b) The peak plasma concentration of a SINGLE and MULTIPLE doses of methylphenidate OROS(R) formula respectively and the time to peak concentration was 7.4 hours and 6.6 hours, respectively in 32 healthy adult

c) Following 20 to 100 milligrams (mg) doses of methylphenidate, plasma levels of 0.02 mg/liter (L) were rep levels reported to range from 1 to 3 hours after a single oral dose (Dayton et al, 1970).

d) Plasma levels varied from 7.7 to 22.5 nanograms/milliliter (ng/mL) in 4 children with attention deficit disorc orally twice daily (Hungund et al, 1979).

e) Following a single oral dose of methylphenidate extended-release capsules (Ritalin(R) LA) in children or a approximately 4 hours apart, with the second peak usually somewhat higher than the first. Compared to imm 4 hours apart, a lower second peak level, higher interpeak minimum level, and less peak/trough fluctuations a Ritalin(R) LA, 2002a).

f) With a 20-mg dose of Ritalin(R) LA in children, the first peak plasma level (mean) occurred in 2 hours (10 ng/mL) in an unpublished study; the mean interpeak minimum plasma level was 6 ng/mL (4.5 hours) (Prod In

2) TRANSDERMAL: average lag time was 3.1 hours (Prod Info DAYTRANA(TM) transdermal system, 2006)

a) The average lag time (time to any d-methylphenidate is detectable in the circulation) was 3.1 hours (range transdermal system, 2006).

C) Area Under the Curve

1) ORAL (20 mg, long acting): 45.8 ng x h/mL (Modi et al, 2000)

a) With a single 20-mg dose of Ritalin(R) LA, the mean AUC(0-infinity) in adult was 45.8 ng x h/mL and in ch LA, 2002a).

b) The AUC of methylphenidate is 2 times higher when heat is applied to transdermal methylphenidate after when the patch is applied to inflamed skin (Prod Info DAYTRANA(TM) transdermal system, 2006).

c) In 35 healthy adults, the AUC of methylphenidate after a single dose of OROS(R) formulation 18 mg, 3 do and a single dose of slow-release 20 mg was 42 ng x h/mL, 38 ng x h/mL, and 47 ng x h/mL, respectively (M

d) The AUC of a single and multiple doses of methylphenidate OROS(R) formulation 18 mg was 32.9 ng x h healthy adults (Modi et al, 2000).

2.3 ADME

Absorption

Distribution

Metabolism

Excretion

Elimination Half-life

2.3.1 Absorption

A) Bioavailability

1) ORAL: 10 to 52% (immediate-release, children) (Prod Info Ritalin(R) LA, 2002a).

B) Effects of Food

1) None (Prod Info DAYTRANA(TM) transdermal system, 2006; Prod Info Concerta(TM), 2001).

a) Food does not affect the pharmacokinetics or the pharmacodynamics of extended-release oral methy methylphenidate (Prod Info DAYTRANA(TM) transdermal system, 2006; Prod Info Concerta(TM), 2001).

b) Cmax and AUC of methylphenidate after a single dose in 26 healthy adults were unaffected by taking compared to taking the whole capsule (Prod Info Metadate(R) CD, 2002a).

C) DOSAGE FORM ABSORPTION

1) Extended-release Capsules

a) Ritalin(R) LA extended-release capsules have a bimodal release profile, using the SODAS(R) (Spher dose is in immediate-release beads, with the remainder in enteric-coated, delayed-release beads (enabli 2002b). Single daily doses of Ritalin(R) LA extended-release capsules 20, 30, and 40 milligrams (mg) pr twice-daily administration of immediate release Ritalin(R) tablets 10, 15, or 20 mg, respectively (Prod Inf

2) Extended-release Tablets

a) Concerta(R) extended-release tablet uses osmotic pressure to deliver methylphenidate at a constant tri-layer core surrounded by a semipermeable membrane with an immediate-release overcoat, which dis (such as the gastrointestinal tract) providing the initial dose. As water permeates through a laser-drilled o through the orifice by the osmotic pressure created by the polymer excipients in the core. The membrane rate at which water enters the tablet core. The tablet must be swallowed whole with the aid of liquids, an Info Concerta(TM), 2001).

3) Sustained-release Tablets

a) Ritalin SR(R) tablets are formulated with a wax matrix core in which the medication is placed into cha in half would disrupt the medication channels in the tablet core and thereby alter the sustained release c Ritalin SR(R) tablets in half is not recommended (Pers Comm, 1987).

2.3.2 Distribution

A) Distribution Sites

1) Protein Binding

a) 10% to 33% (Prod Info RITALIN LA(R) oral extended-release capsule, 2004; Hungund et al, 1979).

B) Distribution Kinetics

1) Volume of Distribution

a) 1.1 to 6 liters/kilogram (L/kg) (Prod Info Ritalin(R) LA, 2002a; Hungund et al, 1979).

1) Vd in children (Hungund et al, 1979).

2.3.3 Metabolism

A) Metabolism Sites and Kinetics

1) TISSUES, extensive (Prod Info Ritalin(R) LA, 2002a; Faraj et al, 1974).

a) Methylphenidate is rapidly and extensively metabolized by nonmicrosomal hydrolytic esterases in live (Prod Info Ritalin(R) LA, 2002a).

B) Metabolites

1) Ritalinic acid (essentially inactive) (Prod Info DAYTRANA(TM) transdermal system, 2006)(Foraj et al, 197 LA, 2002a; Dayton et al, 1970).

a) Ritalinic acid (alpha-phenyl-piperidine acetic acid) possess minimal-to-no pharmacologic activity (Pro 2006; Prod Info Ritalin(R) LA, 2002a). Clinical efficacy is mainly due to the parent compound.

b) Compared to oral administration on a mg/kg basis, transdermal methylphenidate results in higher exp pass effect. Minimal to no l-methylphenidate is systemically available after oral administration. In contras high as d-methylphenidate after transdermal methylphenidate administration (Prod Info DAYTRANA(TM)

2) Hydroxymethylphenidate and hydroxyritalinic acid (only small amounts of each in plasma) (Prod Info Rital

a) 6-oxo-alpha-phenyl-2-piperidine acetic acid (Foraj et al, 1974)(Bartlett & Egger, 1972; Dayton et al, 1

2.3.4 Excretion

A) Kidney

1) Renal Excretion (%)

a) Immediate release: 78% to 97%, less than 1% unchanged (Prod Info RITALIN LA(R) oral extended-re Faraj et al, 1974; Dayton et al, 1970); sustained release, children: 67% (Prod Info RITALIN(R) oral tablet release, adults: 86% (Prod Info RITALIN(R) oral tablet, RITALIN-SR(R) oral tablet, 2004).

1) About 90% of radiolabeled methylphenidate was recovered in the urine after oral dosing. Ritalinic

dose (Prod Info Concerta(TM), 2001).

B) Feces

1) Immediate-release: 1% to 3% (Prod Info RITALIN LA(R) oral extended-release capsule, 2004)

C) Other

1) PLASMA CLEARANCE, 3.1 to 8.5 L/kg/hr in children (Shader et al, 1999; Hungund et al, 1979).

2.3.5 Elimination Half-life

A) Parent Compound

1) (Oral) 2 to 7 hours (average, 3 hours) (Shader et al, 1999; Faraj et al, 1974); (Intravenous) 1 to 2 hours (F

a) In children aged 6 to 12 years, the mean elimination half-life for transdermal methylphenidate applied removal of the patch and 1.4 to 2.9 hours for d-methylphenidate and l-methylphenidate, respectively (Pro 2006).

b) In 36 healthy adults, the plasma half-life of methylphenidate after a single dose of methylphenidate O immediate-release 5 mg every 4 hours, and a single dose of slow-release 20 mg was 3.5 hours, 3.0 hou

c) The elimination half-life of a single dose and multiple doses (once a day on day 3 through day 6) of m was 3.9 hours (Modi et al, 2000).

B) Metabolites

1) Ritalinic acid, 3 to 4 hours (Prod Info Ritalin(R) LA, 2002a).

3.0 Cautions

Contraindications

Precautions

Adverse Reactions

Teratogenicity/Effects in Pregnancy/Breastfeeding

Drug Interactions

3.0.A Black Box WARNING

1) Methylphenidate

a) Transdermal (Patch, Extended Release)

1) Methylphenidate patch should be given cautiously to patients with a history of drug dependence or alcoho tolerance and psychological dependence with varying degrees of abnormal behavior. Frank psychotic episod Careful supervision is required during withdrawal from abusive use, since severe depression may occur. Wit unmask symptoms of the underlying disorder that may require follow-up (Prod Info DAYTRANA(TM) transde

2) Methylphenidate Hydrochloride

a) Oral (Tablet; Tablet, Extended Release; Tablet, Chewable; Capsule, Extended Release; Solution)

1) Methylphenidate hydrochloride should be given cautiously to emotionally unstable patients, such as those alcoholism, because such patients may increase dosage on their own initiative.

2) Chronically abusive use can lead to marked tolerance and psychic dependence with varying degrees of a occur, especially with parenteral abuse. Careful supervision is required during drug withdrawal, since severe overactivity can be unmasked. Long term follow-up may be required because of the patient's basic personalit tablet, RITALIN-SR(R) oral sustained-release tablet, 2004; Prod Info METHYLIN(R) oral solution, 2004; Prod Prod Info RITALIN LA(R) oral extended-release capsule, 2004).

3.1 Contraindications

A) Methylphenidate

1) marked agitation, anxiety, and tension; may aggravate symptoms (Prod Info DAYTRANA(TM) transdermal sys

2) glaucoma (Prod Info DAYTRANA(TM) transdermal system, 2006)

3) hypersensitivity to methylphenidate or other components of the product (Prod Info DAYTRANA(TM) transderm

4) monoamine oxidase inhibitors, such as isocarboxazid, phenelzine, selegiline, tranylcypromine, within 14 days (Prod Info DAYTRANA(TM) transdermal system, 2006)

5) tics, motor (Prod Info DAYTRANA(TM) transdermal system, 2006)

6) Tourette's syndrome, family history or diagnosis (Prod Info DAYTRANA(TM) transdermal system, 2006)

B) Methylphenidate Hydrochloride

1) angina pectoris; may increase blood pressure or heart rate (Prod Info METADATE CD(TM) extended release (TM) extended release oral capsules, 2008)

2) cardiac arrhythmias; may increase blood pressure or heart rate (Prod Info METADATE CD(TM) extended relea CD(TM) extended release oral capsules, 2008)

3) fructose intolerance, glucose-galactose malabsorption, or sucrase-isomaltase insufficiency; contains sucrose ((TM) extended release oral capsules, 2008)

4) glaucoma (Prod Info METADATE CD(TM) extended release oral capsules, 2008; Prod Info RITALIN(R) oral ta

tablets, 2006)
5) halogenated anesthetics; risk of sudden blood pressure increase during surgery, do not take on day of surgery
(TM) extended release oral capsules, 2008)
6) heart failure; may increase blood pressure or heart rate (Prod Info METADATE CD(TM) extended release oral
7) hypersensitivity to methylphenidate or other components of the product (Prod Info METADATE CD(TM) extend
RITALIN(R) oral tablets, RITALIN-SR(R) sustained-release oral tablets, 2006)
8) hypertension, severe; may increase blood pressure (Prod Info METADATE CD(TM) extended release oral cap
extended release oral capsules, 2008)
9) hyperthyroidism or thyrotoxicosis; may increase blood pressure or heart rate (Prod Info METADATE CD(TM) e
METADATE CD(TM) extended release oral capsules, 2008)
10) marked agitation, anxiety, and tension; may aggravate symptoms (Prod Info METADATE CD(TM) extended r
(R) oral tablets, RITALIN-SR(R) sustained-release oral tablets, 2006)
11) monoamine oxidase inhibitors, such as isocarboxazid, phenelzine, selegiline, tranylcypromine, within 14 days
crisis (Prod Info METADATE CD(TM) extended release oral capsules, 2008; Prod Info RITALIN(R) oral tablets, R
2006)
12) myocardial infarction, recent; may increase blood pressure or heart rate (Prod Info METADATE CD(TM) exte
METADATE CD(TM) extended release oral capsules, 2008)
13) tics, motor (Prod Info METADATE CD(TM) extended release oral capsules, 2008; Prod Info RITALIN(R) oral
tablets, 2006)
14) Tourette's syndrome, family history or diagnosis (Prod Info METADATE CD(TM) extended release oral capsu
RITALIN-SR(R) sustained-release oral tablets, 2006)

3.2 Precautions

A) Methylphenidate
1) history of drug dependence or alcoholism; abuse potential (Prod Info DAYTRANA(TM) transdermal system, 20
2) cardiac abnormalities, structural; sudden death has been reported with CNS stimulant treatment (Prod Info DA
3) contact sensitization; may lead to future systemic sensitization or other systemic reactions when methylphenid
DAYTRANA(TM) transdermal system, 2006)
4) depression, severe; should not be used to treat (Prod Info DAYTRANA(TM) transdermal system, 2006)
5) EEG abnormalities; may lower convulsive threshold (Prod Info DAYTRANA(TM) transdermal system, 2006)
6) external heat source exposure; increase release of drug from patch (Prod Info DAYTRANA(TM) transdermal s
7) fatigue states, normal; should not be used to prevent or treat (Prod Info DAYTRANA(TM) transdermal system,
8) psychosis; may exacerbate symptoms of behavior disturbance and thought disorder (Prod Info DAYTRANA(TI
9) seizures, history of; may lower convulsive threshold (Prod Info DAYTRANA(TM) transdermal system, 2006)
10) underlying medical conditions that may be compromised by increases in blood pressure or heart rate such as
myocardial infarction, or hyperthyroidism (Prod Info DAYTRANA(TM) transdermal system, 2006)
B) Methylphenidate Hydrochloride
1) history of drug dependence or alcoholism; abuse potential (Prod Info RITALIN(R) oral tablets, RITALIN-SR(R)
2) bipolar disorder; risk of induction of a mixed/manic episode (Prod Info METADATE CD(TM) extended release
3) cardiac abnormalities, structural or other heart problems; sudden death has been reported with CNS stimulant
RITALIN-SR(R) sustained-release oral tablets, 2006)
4) depression, severe; should not be used to treat (Prod Info RITALIN(R) oral tablets, RITALIN-SR(R) sustained-
5) EEG abnormalities; may lower convulsive threshold (Prod Info RITALIN(R) oral tablets, RITALIN-SR(R) sustai
6) fatigue states, normal; should not be used to prevent or treat (Prod Info RITALIN(R) oral tablets, RITALIN-SR(
7) psychosis; may exacerbate symptoms of behavior disturbance and thought disorder (Prod Info RITALIN(R) ora
tablets, 2006)
8) seizures, history of; may lower convulsive threshold (Prod Info RITALIN(R) oral tablets, RITALIN-SR(R) sustai
9) underlying medical conditions that may be compromised by increases in blood pressure or heart rate such as
myocardial infarction, or hyperthyroidism (Prod Info RITALIN(R) oral tablets, RITALIN-SR(R) sustained-release or

3.3 Adverse Reactions

Cardiovascular Effects

Dermatologic Effects

Endocrine/Metabolic Effects

Gastrointestinal Effects

Hematologic Effects

Hepatic Effects

Immunologic Effects

Musculoskeletal Effects

Neurologic Effects

Ophthalmic Effects

Psychiatric Effects

Renal Effects

Reproductive Effects

Respiratory Effects

Other

3.3.1 Cardiovascular Effects

Methylphenidate

Methylphenidate Hydrochloride

3.3.1.A Methylphenidate

Increased blood pressure

Increased heart rate

3.3.1.A.1 Increased blood pressure

a) Modest increases in systolic and diastolic blood pressure have been reported in studies. Use methylp underlying medical conditions (such as preexisting hypertension, heart failure, recent myocardial infarctic with increases in blood pressure (Prod Info DAYTRANA(TM) transdermal system, 2006).

3.3.1.A.2 Increased heart rate

a) Modest increases in heart rate have been reported in studies. Use methylphenidate cautiously in pati as preexisting hypertension, heart failure, recent myocardial infarction, or hyperthyroidism) may be comp DAYTRANA(TM) transdermal system, 2006).

3.3.1.B Methylphenidate Hydrochloride

Angina

Bradyarrhythmia

Cardiorespiratory arrest

Cerebral vasculitis

Dead - sudden death

Hypertension

Myocardial infarction

Premature beats

Raynaud's phenomenon

Supraventricular tachycardia

Tachyarrhythmia

Ventricular premature beats

3.3.1.B.1 Angina

a) Angina pectoris was reported during postmarketing experience with methylphenidate hydrochloride e extended-release oral tablets, 2008).

3.3.1.B.2 Bradyarrhythmia

a) Bradycardia was reported during postmarketing experience with methylphenidate hydrochloride exter extended-release oral tablets, 2008).

3.3.1.B.3 Cardiorespiratory arrest

a) Adults

1) A 19-year-old male suffered full cardiopulmonary arrest after inhaling crushed methylphenidate ta damage and subsequently developed fever, tachycardia, and elevated CK-MB concentrations. Echo hypokinesis with low ejection fraction, consistent with a congestive cardiomyopathy or global myoca revealed cardiac lesions that were similar to catecholamine cardiomyopathy without the contraction principal metabolite of methylphenidate) were 2 to 3 times the therapeutic concentrations upon adm methylphenidate may be fatal (Massello & Carpenter, 1999).

3.3.1.B.4 Cerebral vasculitis

a) Children

1) A case of cerebral vasculitis was reported in an 8-year-old boy who was taking methylphenidate behavioral problems. A year and a half after he started the methylphenidate treatment, he suddenly intensity over a 4-month period. At the third episode, the paresthesias resulted in ataxia, dysmetria i the left upper limb. Cerebral angiogram revealed bilateral complete occlusion of the posterior cerebr arteries, indicating localized vasculitis. After discontinuing the methylphenidate treatment, he was fre

3.3.1.B.5 Dead - sudden death

a) Incidence: rare

b) Adults

1) Sudden death, stroke, and myocardial infarction have occurred in adults taking usual doses of st cases is unknown, however, adults have a greater likelihood than children of having serious structur serious heart rhythm abnormalities, coronary artery disease, or other serious cardiac problems. Adu treated with stimulant drugs. Perform a thorough history to determine if there is a family history of su physical exam to assess the existence of cardiac disease prior to prescribing these drugs to patients oral tablets, 2008).

c) Children and Adolescents - With Preexisting Cardiac Risk

1) Taking usual doses of stimulant drugs may cause sudden death in children and adolescents with problems. Children or adolescents with known serious cardiac problems should not be treated with s determine if there is a family history of sudden death or ventricular arrhythmia and a physical exam t to prescribing these drugs to patients (Prod Info CONCERTA(R) extended-release oral tablets, 2008

d) Children and Adolescents - Healthy

1) A retrospective, case-controlled study examines the association between stimulant medication, in sudden death in healthy children and adolescents. In a collection of data from state vital statistics ar of sudden death in children and adolescents between the ages of 7 to 19 years were matched and c passengers in motor vehicle accidents. The study determined that 1.8% (n=10) of youths who exper stimulant medication compared with only 0.4% (n=2) of youths in the motor vehicle accident group (p=0.02). Limitations to this study included the time lag between the youths stimulant medication use of information regarding clinical diagnoses, inconsistent postmortem inquiry, and the exclusion of de stated that this finding should be considered when evaluating the overall risk and benefit of stimulan (Gould et al, 2009). Given the limitations of this study, the U.S. Food and Drug Administration is una associated with stimulant medication (US Food and Drug Administration, 2009).

3.3.1.B.6 Hypertension

a) Incidence: less than 1% (Prod Info CONCERTA(R) extended-release oral tablets, 2008)

b) Hypertension occurred in less than 1% of patients on methylphenidate hydrochloride extended-releas trials (Prod Info CONCERTA(R) extended-release oral tablets, 2008).

c) Modest increases in average blood pressure (about 2 to 4 mmHg) have been caused by the use of st changes in blood pressure. Medical conditions that place patients at risk when blood pressure increases

heart failure, recent myocardial infarction, or ventricular arrhythmia (Prod Info CONCERTA(R) extended-

d) Adults

1) During a placebo-controlled, 7-week dose-titration study (n=401), adults taking methylphenidate mg/day) had mean changes from baseline in standing blood pressure that ranged from 0.1 to 2.2 mı compared with 1.1 mmHg and -1.8 mmHg, respectively, for placebo treated patients. At the end of d controlled, 5-week fixed-dose study (n=226), adults taking methylphenidate hydrochloride extended- mean changes from baseline blood pressure of -1.2 mmHg systolic and 1.1 diastolic, compared with placebo treated patients (Prod Info CONCERTA(R) extended-release oral tablets, 2008).

2) Since methylphenidate is not used as frequently in adults, there is little literature regarding the ca hypertensive adults. Methylphenidate has been shown to increase blood pressure in patients who a (Flemenbaum, 1972a).

e) Children

1) Compared to placebo, systolic and diastolic blood pressure increased approximately 1 to 4 mmH times a day methylphenidate. In a randomized, placebo-controlled trial of 177 adolescent subjects, r mmHg diastolic above baseline blood pressures for subjects taking methylphenidate hydrochloride (experienced compared to 0.7 mmHg systolic and 1.4 mmHg diastolic for patients receiving the place oral tablets, 2008).

3.3.1.B.7 Myocardial infarction

a) Adults

1) Myocardial infarction, sudden deaths, and stroke have occurred in adults taking usual doses of s cases is unknown, however, adults have a greater likelihood than children of having serious structur serious heart rhythm abnormalities, coronary artery disease, or other serious cardiac problems. Adu treated with stimulant drugs. Perform a thorough history to determine if there is a family history of su physical exam to assess the existence of cardiac disease prior to prescribing these drugs to patients oral tablets, 2008).

3.3.1.B.8 Premature beats

a) Extrasystoles were reported during postmarketing experience with methylphenidate hydrochloride ex extended-release oral tablets, 2008).

3.3.1.B.9 Raynaud's phenomenon

a) Raynaud's phenomenon was reported during postmarketing experience with methylphenidate hydroc CONCERTA(R) extended-release oral tablets, 2008).

3.3.1.B.10 Supraventricular tachycardia

a) Supraventricular tachycardia was reported during postmarketing experience with methylphenidate hy CONCERTA(R) extended-release oral tablets, 2008).

3.3.1.B.11 Tachyarrhythmia

a) Summary

1) Compared to placebo, resting pulses increased approximately 2 to 6 beats per minute (bpm) dur day methylphenidate. In a randomized, placebo-controlled trial of 177 adolescent subjects, mean inc rate for subjects taking methylphenidate hydrochloride extended-release (up to 72 mg/day (1.4 mg/k for patients receiving the placebo. During a placebo-controlled, 7-week dose-titration study (n=401), extended-release (36 to 108 mg/day) experienced dose-dependent mean increases of 3.9 to 9.8 bp with 2.7 bpm in the placebo group. In a second placebo-controlled, 5-week fixed-dose study (n=226 extended-release (18, 36, and 72 mg/day) experienced mean changes from baseline in resting puls bpm in the placebo group. Monitor patients for larger changes in heart rate. Medical conditions that include those with preexisting hypertension, heart failure, recent myocardial infarction, or ventricular extended-release oral tablets, 2008).

b) Incidence: 4.8% (Prod Info CONCERTA(R) extended-release oral tablets, 2008)

c) Adults

1) Tachycardia occurred in 4.8% of adult patients on methylphenidate hydrochloride extended-relea placebo (n=212), in 2 double-blind, placebo-controlled clinical trials (Prod Info CONCERTA(R) exter

3.3.1.B.12 Ventricular premature beats

a) Ventricular extrasystoles were reported during postmarketing experience with methylphenidate hydro CONCERTA(R) extended-release oral tablets, 2008).

3.3.2 Dermatologic Effects

Methylphenidate

Methylphenidate Hydrochloride

3.3.2.A Methylphenidate

Contact dermatitis

Erythema

3.3.2.A.1 Contact dermatitis

a) Although, no cases of contact sensitization has occurred when transdermal methylphenidate is used
than 9 hours and alternating application sites on the hip); contact sensitization may occur. However, con
in clinical effectiveness studies. Contact sensitization is characterized by erythema with intense local rea
significantly improve within 2 days or spreads beyond the patch site. Diagnosis should be confirmed by a
not indicative of contact sensitization. Once a patient is sensitized to transdermal methylphenidate, admi
sensitization or other systemic reactions. Systemic reactions include flare-up of previous dermatitis or of
eruptions in previously unaffected skin; headache; fever; malaise; arthralgia; diarrhea; or vomiting. Patie
transdermal methylphenidate might not be able to take methylphenidate in any form (Prod Info DAYTRA

1) A study designed to provoke skin sensitization demonstrated transdermal methylphenidate to be
were exposed continuously for 3 weeks, followed by a 2 week rest period, and the challenge/rechall
irritating than both the placebo control and the saline control. At least 18 (13.5%) of subjects (n=133
methylphenidate based on the results of the challenge and/or rechallenge phases of the study (Proc
2006).

3.3.2.A.2 Erythema

a) Erythema of no or minimal discomfort is a common adverse effect with the use of transdermal methyl
efficacy studies, the majority of subjects experienced minimal to definite erythema. In general, the erythe
therapy or discontinuation from treatment. If erythema is accompanied by intense local reaction (edema,
improve within 2 days or spreads beyond the patch site, then contact sensitization should be suspected.
papules do not resolve or significantly reduce within 24 hours after patch removal (Prod Info DAYTRANA

3.3.2.B Methylphenidate Hydrochloride

Alopecia

Erythema

Erythroderma

Generalized hyperhidrosis

Rash

3.3.2.B.1 Alopecia

a) Alopecia has been reported in postmarketing experience with methylphenidate hydrochloride extende
release oral tablets, 2008).

3.3.2.B.2 Erythema

a) Erythema has been reported in postmarketing experience with methylphenidate hydrochloride extend
release oral tablets, 2008).

3.3.2.B.3 Erythroderma

a) A case of a 73-year-old white female treated with 10 milligrams (mg) twice daily of methylphenidate fo
has been reported (Weil, 1968). Two days after initiating therapy, the patient developed an itching RASH
fever. Discontinuation of the drug and treatment with antihistamines and prednisone resulted in resolutio
reinstitution of the methylphenidate, the dermatitis reappeared and was again abolished upon discontinu

3.3.2.B.4 Generalized hyperhidrosis

a) Incidence: 5.1% (Prod Info CONCERTA(R) extended-release oral tablets, 2008)
b) Adults

1) Hyperhidrosis has occurred in 5.1% of adult patients on methylphenidate hydrochloride extended
patients on placebo (n=212), in 2 double-blind, placebo-controlled clinical trials (Prod Info CONCER

3.3.2.B.5 Rash

a) Incidence: less than 1% (Prod Info CONCERTA(R) extended-release oral tablets, 2008)
b) Rash and rash-macular have occurred in less than 1% of patients on methylphenidate hydrochloride (Prod Info CONCERTA(R) extended-release oral tablets, 2008).

3.3.3 Endocrine/Metabolic Effects

Methylphenidate

Methylphenidate Hydrochloride

3.3.3.A Methylphenidate

Decreased body growth

Weight decreased

3.3.3.A.1 Decreased body growth

a) It is unknown if chronic use of stimulants, including methylphenidate, in children may cause suppress transdermal system, 2006). However, multiple studies identified growth suppression with oral methylphe 1980; Croche et al, 1979; Satterfield et al, 1979; Oettinger et al, 1977; McNutt et al, 1977; Gross, 1976; M Millichap, 1975; Safer et al, 1975; Safer & Allen, 1975; Safer et al, 1972; Eisenberg, 1972; Satterfield et

1) Long-term treatment with oral methylphenidate, especially with doses greater than 20 milligrams of growth in some hyperactive children; however, the growth retarding effects appear transient, and reduced with prolonged therapy in most children. The duration of growth suppression and the doses weight deficits after the first year of treatment may be offset by growth spurts in the second year of t pertaining to the effects of stimulants on growth is complicated since methods of measuring growth have had a follow-up period ranging from 1 to 16 years have generally failed to demonstrate a signif with CNS stimulants (Mattes & Gittelman, 1983; Hollister, 1980; Croche et al, 1979; Satterfield et al, Gross, 1976; McNutt et al, 1976; Gross, 1976; Millichap & Millichap, 1975; Safer et al, 1975; Safer & 1972). Investigators supporting the observation that methylphenidate can induce some growth supp result from some disorder in growth hormone secretion. However, data evaluating this hypothesis ha al, 1979; Barter & Kammer, 1978; Brown, 1977; Brown & Williams, 1976). It has also been suggeste stimulants, the temporary deficit in height gain that occurs is related to ADHD-associated delayed m is associated with dysregulation of several neurotransmitter systems that may alter neuroendocrine al, 1998).

2) In 1 study, use of methylphenidate was shown to slightly diminish the response to growth hormo deficiency (IGHD), but not those with idiopathic short stature (ISS). Methylphenidate therapy had a r magnitude of the effect was small and the magnitude of the difference in the change in height betwe methylphenidate and children with IGHD not treated with methylphenidate decreased with time (Rac

3) One study compared the growth of 63 hyperactive children, 29 received dextroamphetamine (me methylphenidate (median, 20 mg/day) and 14 received no medication. Height measurements were r years from student health records. Long-term administration of dextroamphetamine and methylphen inhibition of growth when compared to the control group; however, when the mean percentile loss w centimeters (cm), GROWTH SUPPRESSION was only minimal, 1.5 and 1 cm/year, respectively. Gr greater than 20 mg/day of methylphenidate (Safer & Allen, 1973). A follow-up study demonstrated th the CNS stimulant during the summer months (Safer et al, 1975).

4) One study involving 72 hyperactive children found a statistically significant decrease in height aft 1.03 centimeters (cm)), but the initial first year height deficits were made up the second year by a gr suggested the development of tolerance to growth suppression with prolonged treatment (Satterfield growth with continued treatment was eluded to by another study (Gross, 1976). In this study of 60 cl dose, 34 milligrams (mg)/day), no significant decrease in height was noticed during the first year and duration 5.1 years), the height was statistically greater than the predicted norms.

3.3.3.A.2 Weight decreased

a) Incidence: 9% (Prod Info DAYTRANA(TM) transdermal system, 2006)
b) A decreased weight occurred in 9% of patients on transdermal methylphenidate compared with 0% o (n=183) (Prod Info DAYTRANA(TM) transdermal system, 2006).

3.3.3.B Methylphenidate Hydrochloride

3.3.3.B.1 Decreased body growth

a) Children

1) Studies of children ages 7 to 10 years who were randomized to either methylphenidate or non-m

frame, and children ages 10 to 13 years in naturalistic subgroups of newly treated and non-medicati indicate that children who are treated 7 days per week throughout the year experience slowing grow growth in height and 2.7 kg less growth in weight over 3 years) without growth rebound during this d treatment with stimulants (Prod Info CONCERTA(R) extended-release oral tablets, 2008).
2) Long-term treatment with methylphenidate, especially with doses greater than 20 milligrams (mg growth in some hyperactive children; however, the growth retarding effects appear transient, and ov reduced with prolonged therapy in most children. The duration of growth suppression and the doses weight deficits after the first year of treatment may be offset by growth spurts in the second year of t pertaining to the effects of stimulants on growth is complicated since methods of measuring growth have had a follow-up period ranging from 1 to 16 years have generally failed to demonstrate a signif with CNS stimulants (Mattes & Gittelman, 1983; Hollister, 1980; Croche et al, 1979; Satterfield et al, Gross, 1976; McNutt et al, 1976; Gross, 1976; Millichap & Millichap, 1975; Safer et al, 1975; Safer & 1972). Investigators supporting the observation that methylphenidate can induce some growth supp result from some disorder in growth hormone secretion. However, data evaluating this hypothesis ha al, 1979; Barter & Kammer, 1978; Brown, 1977; Brown & Williams, 1976). It has also been suggeste stimulants, the temporary deficit in height gain that occurs is related to ADHD-associated delayed m is associated with dysregulation of several neurotransmitter systems that may alter neuroendocrine al, 1998).
3) In 1 study, use of methylphenidate was shown to slightly diminish the response to growth hormo deficiency (IGHD), but not those with idiopathic short stature (ISS). Methylphenidate therapy had a r magnitude of the effect was small and the magnitude of the difference in the change in height betwe methylphenidate and children with IGHD not treated with methylphenidate decreased with time (Rac
4) One study compared the growth of 63 hyperactive children, 29 received dextroamphetamine (me methylphenidate (median, 20 mg/day) and 14 received no medication. Height measurements were r years from student health records. Long-term administration of dextroamphetamine and methylphen inhibition of growth when compared to the control group; however, when the mean percentile loss w centimeters (cm), GROWTH SUPPRESSION was only minimal, 1.5 and 1 cm/year, respectively. Gr greater than 20 mg/day of methylphenidate (Safer & Allen, 1973). A follow-up study demonstrated th the CNS stimulant during the summer months (Safer et al, 1975).
5) One study involving 72 hyperactive children found a statistically significant decrease in height aft 1.03 centimeters (cm)), but the initial first year height deficits were made up the second year by a gr suggested the development of tolerance to growth suppression with prolonged treatment (Satterfield growth with continued treatment was eluded to by another study (Gross, 1976). In this study of 60 cl dose, 34 milligrams (mg)/day), no significant decrease in height was noticed during the first year and duration 5.1 years), the height was statistically greater than the predicted norms.

3.3.4 Gastrointestinal Effects

Methylphenidate

Methylphenidate Hydrochloride

3.3.4.A Methylphenidate

Decrease in appetite

Loss of appetite

Nausea

Vomiting

3.3.4.A.1 Decrease in appetite

a) Incidence: 26% (Prod Info DAYTRANA(TM) transdermal system, 2006)
b) Decreased appetite occurred in 26% of patients on transdermal methylphenidate compared with 5% study (n=183) (Prod Info DAYTRANA(TM) transdermal system, 2006).

3.3.4.A.2 Loss of appetite

a) Incidence: 5% (Prod Info DAYTRANA(TM) transdermal system, 2006)
b) Anorexia occurred in 5% of patients on transdermal methylphenidate compared with 1% of placebo t (Prod Info DAYTRANA(TM) transdermal system, 2006). During an open-label study (n=191) of 40-month worn for 12 hours daily, anorexia occurred in 46% of subjects leading to a 4% discontinuation rate (Prod

2006).

3.3.4.A.3 Nausea

a) Incidence: 12% (Prod Info DAYTRANA(TM) transdermal system, 2006)

b) Nausea occurred in 12% of patients on transdermal methylphenidate compared with 2% of placebo t (Prod Info DAYTRANA(TM) transdermal system, 2006).

3.3.4.A.4 Vomiting

a) Incidence: 10% (Prod Info DAYTRANA(TM) transdermal system, 2006)

b) Vomiting occurred in 10% of patients on transdermal methylphenidate compared with 5% of placebo (Prod Info DAYTRANA(TM) transdermal system, 2006).

3.3.4.B Methylphenidate Hydrochloride

Constipation

Decrease in appetite

Gastrointestinal obstruction

Indigestion

Loss of appetite

Nausea

Stomach ache

Upper abdominal pain

Vomiting

Xerostomia

3.3.4.B.1 Constipation

a) Incidence: 1.4% (Prod Info CONCERTA(R) extended-release oral tablets, 2008)

b) Adults

1) Constipation has been reported in 1.4% of adult patients on methylphenidate hydrochloride exter patients on placebo (n=212), in 2 double-blind, placebo-controlled clinical trials (Prod Info CONCER

3.3.4.B.2 Decrease in appetite

a) Incidence: 25.3% (Prod Info CONCERTA(R) extended-release oral tablets, 2008)

b) Adults

1) Decreased appetite has been reported in 25.3% of adult patients on methylphenidate hydrochlor 6.6% of patients on placebo (n=212), in 2 double-blind, placebo-controlled clinical trials (Prod Info C 2008).

c) In a direct, double-blind, crossover comparison of adverse effect profiles, both dextroamphetamine 0. methylphenidate 0.3 mg/kg twice daily were well-tolerated in 125 children with attention deficit disorder (reported more frequently during drug therapy than at baseline were appetite suppression (both drugs) ar mean severity of adverse effects was significantly higher in the dextroamphetamine group. However, onl discontinue therapy because of adverse effects (Efron et al, 1997).

3.3.4.B.3 Gastrointestinal obstruction

a) Rare cases of obstructive symptoms have been reported in patients with known gastrointestinal narro the ingestion of drugs in nondeformable controlled-release formulations. This drug should only be used i whole (Prod Info CONCERTA(R) extended-release oral tablets, 2008).

3.3.4.B.4 Indigestion

a) Incidence: 2.2% (Prod Info CONCERTA(R) extended-release oral tablets, 2008)

b) Adults

1) Indigestion has been reported in 2.2% of adult patients on methylphenidate hydrochloride extenc patients on placebo (n=212), in 2 double-blind, placebo-controlled clinical trials (Prod Info CONCER

3.3.4.B.5 Loss of appetite

a) Incidence: 1.7% (Prod Info CONCERTA(R) extended-release oral tablets, 2008)

b) Anorexia has been reported in 1.7% of adult patients on methylphenidate hydrochloride extended-rel placebo (n=212), in 2 double-blind, placebo-controlled clinical trials (Prod Info CONCERTA(R) extended-

3.3.4.B.6 Nausea

a) Incidence: 12.8% (Prod Info CONCERTA(R) extended-release oral tablets, 2008)

b) Adults

1) Nausea has been reported in 12.8% of adult patients on methylphenidate hydrochloride extende patients on placebo (n=212), in 2 double-blind, placebo-controlled clinical trials (Prod Info CONCER

3.3.4.B.7 Stomach ache

a) Incidence: less than 1% (Prod Info CONCERTA(R) extended-release oral tablets, 2008)

b) Stomach discomfort occurred in less than 1% of patients on methylphenidate hydrochloride extended clinical trials (Prod Info CONCERTA(R) extended-release oral tablets, 2008).

3.3.4.B.8 Upper abdominal pain

a) Incidence: 5.9% (Prod Info CONCERTA(R) extended-release oral tablets, 2008)

b) Children

1) Upper abdominal pain has been reported in 5.9% of children and adolescent patients on methylp (n=321) compared with 3.8% of patients on placebo (n=318), in 4 double-blind, placebo-controlled c release oral tablets, 2008).

3.3.4.B.9 Vomiting

a) Incidence: 1.7%, adults; 2.8%, children (Prod Info CONCERTA(R) extended-release oral tablets, 200

b) Adults

1) Vomiting has been reported in 1.7% of adult patients on methylphenidate hydrochloride extende patients on placebo (n=212), in 2 double-blind, placebo-controlled clinical trials (Prod Info CONCER

c) Children

1) Vomiting has been reported in 2.8% of children and adolescent patients on methylphenidate hyd with 1.6% of patients on placebo (n=318), in 4 double-blind, placebo-controlled clinical trials (Prod In tablets, 2008).

3.3.4.B.10 Xerostomia

a) Incidence: 14% (Prod Info CONCERTA(R) extended-release oral tablets, 2008)

b) Adults

1) Dry mouth has been reported in 14% of adult patients on methylphenidate hydrochloride extende patients on placebo (n=212), in 2 double-blind, placebo-controlled clinical trials (Prod Info CONCER

3.3.5 Hematologic Effects

3.3.5.A Methylphenidate Hydrochloride

Eosinophil count raised

Leukopenia

Pancytopenia

Thrombocytopenia

Thrombocytopenic purpura

3.3.5.A.1 Eosinophil count raised

a) Methylphenidate abuse by the intravenous route can cause an eosinophilia (Hayashi et al, 1980). Abs 30,338.

3.3.5.A.2 Leukopenia

a) Incidence: less than 1% (Prod Info CONCERTA(R) extended-release oral tablets, 2008)

b) Leukopenia occurred in less than 1% of patients on methylphenidate hydrochloride extended-release Leukopenia was also reported during open-label studies. Periodically monitor CBC, differential, and plate CONCERTA(R) extended-release oral tablets, 2008).

3.3.5.A.3 Pancytopenia

a) Pancytopenia was reported during postmarketing experience with methylphenidate hydrochloride ext extended-release oral tablets, 2008).

3.3.5.A.4 Thrombocytopenia

a) Thrombocytopenia was reported during postmarketing experience with methylphenidate hydrochlorid extended-release oral tablets, 2008).

1) Children

a) Thrombocytopenia was reported in a 10-year-old boy who received methylphenidate for atte had been treated with methylphenidate for 10 months when a routine blood count revealed thro within 2 weeks of drug discontinuation (Kuperman et al, 2003).

3.3.5.A.5 Thrombocytopenic purpura

a) Thrombocytopenic purpura was reported during postmarketing experience with methylphenidate hydr CONCERTA(R) extended-release oral tablets, 2008).

3.3.6 Hepatic Effects

3.3.6.A Methylphenidate Hydrochloride

Autoimmune hepatitis

Hepatotoxicity

3.3.6.A.1 Autoimmune hepatitis

a) Autoimmune hepatitis occurred in a 57-year-old, asymptomatic Caucasian male 1 month following ini a history of orthotopic liver transplantation secondary to chronic hepatitis C infection 4 years prior, was fo chemistries during a routine scheduled follow-up. Baseline liver chemistries had been stable in the montl AST, ALT, and total bilirubin were 572 units/L, 338 units/L, and 2.7 mg/dL, respectively. Medications take venlafaxine, omeprazole, hydrochlorothiazide, fosinopril, and a multivitamin. Long-acting methylphenidat presentation for impaired concentration and depressive symptoms. The patient denied alcohol abuse an and did not have any fever, chills, abdominal pain, or urine discoloration. Physical examination revealed hepatosplenomegaly evident. No change in mental status or asterixis was found on neurological examin anti-smooth muscle antibody (1:40) and antinuclear antibody (1:80), with a nucleolar pattern, and an elev normal at baseline. A liver biopsy showed severe lobular and periportal necroinflammatory infiltrate with eosinophils, but lacking endothelialitis and bile duct damage. Subsequently, methylphenidate therapy wa normalize. Besides methylphenidate, other prior medications were continued and prednisone 10 mg/day chemistries returned to patient's approximate baseline values over the next few months, and a liver biop improvement. Later, the patient was started on combination amphetamine/dextroamphetamine with no fu 2007).

3.3.6.A.2 Hepatotoxicity

a) Liver dysfunction is a rare side effect of methylphenidate. Intravenous abuse of methylphenidate was marked elevations in bilirubin, SGOT and SGPT in a 19-year-old black woman. Hepatic biopsy revealed cells and eosinophils. Focal collections of mononuclear cells with Kupffer cell hyperplasia was observed rechallenge with 20 milligrams (mg) intravenously (IV) methylphenidate (Ritalin(R)) twice daily for 2 days hepatotoxicity (Mehta et al, 1984). These data suggest the hepatotoxic potential of the drug when given

3.3.7 Immunologic Effects

3.3.7.A Methylphenidate Hydrochloride

Anaphylaxis

Angioedema

Auricular dilatation

Bullous eruption

Generalized exfoliative dermatitis

Generalized pruritus

Immune hypersensitivity reaction

Nasopharyngitis

3.3.7.A.1 Anaphylaxis

a) Hypersensitivity reactions such as anaphylactic reactions have been reported in postmarketing exper extended-release (Prod Info CONCERTA(R) extended-release oral tablets, 2008).

3.3.7.A.2 Angioedema

a) Hypersensitivity reactions such as angioedema has been reported in postmarketing experience with r (Prod Info CONCERTA(R) extended-release oral tablets, 2008).

3.3.7.A.3 Auricular dilatation

a) Hypersensitivity reactions such as auricular swelling has been reported in postmarketing experience release (Prod Info CONCERTA(R) extended-release oral tablets, 2008).

3.3.7.A.4 Bullous eruption

a) Hypersensitivity reactions such as bullous conditions have been reported in postmarketing experienc release (Prod Info CONCERTA(R) extended-release oral tablets, 2008).

3.3.7.A.5 Generalized exfoliative dermatitis

a) Hypersensitivity reactions such as exfoliative conditions have been reported in postmarketing experie extended-release (Prod Info CONCERTA(R) extended-release oral tablets, 2008).

3.3.7.A.6 Generalized pruritus

a) Hypersensitivity reactions such as pruritus have been reported in postmarketing experience with metl (Prod Info CONCERTA(R) extended-release oral tablets, 2008).

3.3.7.A.7 Immune hypersensitivity reaction

a) Hypersensitivity reactions to methylphenidate are rare in occurrence. However, 2 cases have been re and in the other case erythema multiforme was described (Rothschild, 1972); (Weil, 1968).

3.3.7.A.8 Nasopharyngitis

a) Incidence: 2.8% (Prod Info CONCERTA(R) extended-release oral tablets, 2008)

b) Children

1) Nasopharyngitis has occurred in 2.8% of child and adolescent patients (n=321) on methylphenid compared with 2.2% of patients on placebo (n=318), in 4 double-blind, placebo-controlled clinical tri oral tablets, 2008).

3.3.8 Musculoskeletal Effects

Methylphenidate

Methylphenidate Hydrochloride

3.3.8.A Methylphenidate

3.3.8.A.1 Bone finding

a) Oral methylphenidate did not significantly affect BONE MINERAL DENSITY and BONE TURNOVER from 3 to 10 years), who were treated with a mean dose of methylphenidate 10 milligrams for an average disorder (ADHD), their bone mineral density (as measured by using dual photon absorptiometry), serum for BONE MINERALIZATION), urinary deoxypyridinoline excretion (an indicator of BONE RESORPTION significantly different from boys of the control group (n=9). All the children in the treatment group were wi period (Lahat et al, 2000).

b) In a retrospective cohort study of 42 male and female children (between 7 and 16 years old), dental r dose of 30 milligrams (mg) of oral methylphenidate (MH) for a mean duration of 54 months. Inclusion crit MH for a minimum of 2 years at the time of panoramic radiograph. The gender-and age-matched control had not ingested any long-term medication. An oral, written, and radiographic review of gender- and age outcome of the study was the dental age difference score, which was defined as dental age score for MH The mean dental age score for MH subjects was approximately 6 months behind matched control subjec compared, MH and control subjects were similar (p =0.27). Multiple regression demonstrated there were length of drug use were considered (Batterson et al, 2005).

3.3.8.B Methylphenidate Hydrochloride

Arthralgia

Bone finding

Muscle rigidity

Muscle twitch

Myalgia

3.3.8.B.1 Arthralgia

a) Arthralgia has been reported in postmarketing experience with methylphenidate extended-release (Pr tablets, 2008).

3.3.8.B.2 Bone finding

a) Children

1) Methylphenidate did not significantly affect bone mineral density and bone turnover in children. In years), who were treated with a mean dose of methylphenidate 10 milligrams for an average of 13 m (ADHD), their bone mineral density (as measured by using dual photon absorptiometry), serum bon bone mineralization), urinary deoxypyridinoline excretion (an indicator of bone resorption), and seru different from boys of the control group (n=9). All the children in the treatment group were within the (Lahat et al, 2000).

2) In a retrospective cohort study of 42 male and female children (between 7 and 16 years old), der average dose of 30 milligrams (mg) of methylphenidate (MH) for a mean duration of 54 months. Incl mg/day of MH for a minimum of 2 years at the time of panoramic radiograph. The gender-and age-m were healthy and had not ingested any long-term medication. An oral, written, and radiographic revi compared. The main outcome of the study was the dental age difference score, which was defined a score for control subjects. The mean dental age score for MH subjects was approximately 6 months when the median differences were compared, MH and control subjects were similar (p =0.27). Multip difference in scores when gender, age, or length of drug use were considered (Batterson et al, 2005

3.3.8.B.3 Muscle rigidity

a) Incidence: 1.9% (Prod Info CONCERTA(R) extended-release oral tablets, 2008)

b) Adults

1) Muscle tightness has occurred in 1.9% of adult patients on methylphenidate hydrochloride exten patients on placebo (n=212), in 2 double-blind, placebo-controlled clinical trials (Prod Info CONCER

3.3.8.B.4 Muscle twitch

a) Muscle twitching has been reported in postmarketing experience with methylphenidate extended-rele oral tablets, 2008).

3.3.8.B.5 Myalgia

a) Myalgia has been reported in postmarketing experience with methylphenidate extended-release (Pro tablets, 2008).

3.3.9 Neurologic Effects

Methylphenidate

Methylphenidate Hydrochloride

3.3.9.A Methylphenidate

Headache

Insomnia

Lowered convulsive threshold

Tic

3.3.9.A.1 Headache

a) During an open-label study (n=191) of 40-month duration with transdermal methylphenidate worn for subjects(Prod Info DAYTRANA(TM) transdermal system, 2006)

3.3.9.A.2 Insomnia

a) Incidence: 13% (Prod Info DAYTRANA(TM) transdermal system, 2006)

b) Insomnia occurred in 13% of patients on transdermal methylphenidate compared with 5% of placebo (Prod Info DAYTRANA(TM) transdermal system, 2006). During an open-label study (n=191) of 40-month worn for 12 hours daily, insomnia occurred in 30% of subjects leading to a 4% discontinuation rate (Prod 2006).

3.3.9.A.3 Lowered convulsive threshold

a) There is some clinical evidence that methylphenidate may lower convulsive threshold in patients with prior electroencephalogram (EEG) abnormalities in the absence of a history of seizures, and, very rarely prior EEG evidence of seizures. Discontinue methylphenidate if seizures develop (Prod Info DAYTRANA

1) Children with attention deficit hyperactive disorder (ADHD) who have normal electroencephalogr they receive stimulant therapy for ADHD (methylphenidate, dextroamphetamine, or combination am (R)). However, children with epileptiform EEGs may have considerable risk for eventual seizure, alth be attributable to use of the stimulant. These conclusions were based on a study of 234 children wit ADHD. All had EEGs prior to parental choosing of stimulant treatment or foregoing stimulant treatme children (15.4%) demonstrated epileptiform abnormalities compared with 198 with normal EEGs. Of treatment for ADHD. Three of the 30 who received stimulant therapy experienced seizures (p less th year-old male, and a 6-year-old male. The girl was treated uneventfully with methylphenidate for 12 methylphenidate experienced a 4-minute generalized tonic-clonic seizure. Her EEG had revealed a boys, the first experienced a 2-minute generalized tonic clonic seizure with focal onset 3 years after an episode at 10 months after initiation of methylphenidate; he was heard to fall and was unrespons EEGs of both boys had shown rolandic spikes, a focal epileptiform abnormality. One child who had a beginning methylphenidate (Hemmer et al, 2001).

3.3.9.A.4 Tic

a) Incidence: 7% (Prod Info DAYTRANA(TM) transdermal system, 2006)

b) Tic occurred in 7% of patients on transdermal methylphenidate compared with 0% of placebo treated Transdermal methylphenidate is contraindicated in patients with motor tics or with a family history or diag DAYTRANA(TM) transdermal system, 2006).

1) The incidence of TICS emergence was 7.8% in children treated with stimulant medication (methy for attention deficit hyperactivity disorder, based on a retrospective chart review (n=555). These stim if they were free of tics and without a history of tics according to the practice of the settings in which 8.3% of subjects treated with methylphenidate, 6.3% treated with dextroamphetamine, and 7.7% tre to dose or duration of stimulant therapy. Mean age of subjects was 11 years. A significant correlatio development of tics. As the authors noted, these children may have developed tics, regardless of tre et al, 2001).

2) Although stimulant therapy was suspected to exacerbate tics, long-term methylphenidate treatme effective in children with attention-deficit hyperactivity disorder (ADHD) and chronic multiple tic disor blinded, prospective, follow-up study, 32 children (age ranging from 6.1 and 11.9 years) received mi previous trial (mean 16.5 milligrams (mg), range=5 to 40 mg). The children were evaluated in a simu their on-task, fidgeting, worksheet behaviors, and vocal and motor tic frequency. In almost every me than placebo (p ranging from less than 0.001 to 0.03). There was no difference in tic condition betwe behaviors were not significantly different between baseline and placebo, whereas children spent sig medication conditions than placebo (p less than 0.001). There was no significant difference betweer growth table values. Systolic blood pressure and heart rate were significantly increased (p=0.02 and clinically insignificant. Although this study showed methylphenidate did not worsen tics in patients w possibility of individual exacerbation of tic cannot be ruled out (Gadow et al, 1999). In another study syndrome, abrupt withdrawal of methylphenidate and dextroamphetamine in long-term therapy DID frequency (Nolan et al, 1999).

3) Tourette's syndrome may be exacerbated or precipitated by the use of stimulant medications for children. Early signs of Tourette's syndrome or tics are difficult to distinguish from hyperactive and a therefore mistakenly be treated with stimulant medications (dextroamphetamine, methylphenidate, p the severe motor and phonic tics requiring discontinuation of the stimulants and possible institution o having an attention deficit disorder, clinical evaluation for Tics and Tourette's Syndrome in the childr stimulant medication. In children with no symptoms of Tourette's syndrome but with a familial history use of stimulants is contraindicated in children with Tourette's Syndrome. If tics occur during stimula discontinued (Lowe et al, 1982).

4) Numerous case reports have demonstrated tics either starting or worsening after methylphenidat is no correlation between stimulant dosages (high or low) or duration of treatment, and tic developm

days, months, even years. Many of the patients who developed tics years later were within the age r
so it is unknown if disease onset was independent of stimulant use. The highest risk for tic exacerba
are treated with stimulant medication early in life and/or for a long duration. Investigators have noted
tics, discontinuing the stimulant decreased tic severity but did not necessarily completely resolve the
1985; Lowe et al, 1982); (Balhman, 1981)(Mitchell & Matthews, 1980; Bremness & Surerd, 1979; Pc
1974); (Myerhoff & Synder, 1973).
5) One group of investigators evaluated 1500 children who received methylphenidate in the treatme
incidence of tics following the drugs administration. The authors found that the incidence of tics deve
The types of tics described included eyelid, facial muscle, head, jaw, neck, limb and trunk tics. The a
relation to dose or duration of therapy and that in most patients discontinuing the drug resulted in re
contrast, another study (Erenberg et al, 1985) found that stimulant medications aggravated existing

3.3.9.B Methylphenidate Hydrochloride

Akathisia

Central nervous system finding

Cerebrovascular accident

Chorea

Confusion

Dizziness

Dyskinesia

Gilles de la Tourette's syndrome

Headache

Insomnia

Lethargy

Paresthesia

Seizure

Sleep disorder

Somnolence

Tension-type headache

Tremor

Vertigo

3.3.9.B.1 Akathisia

a) Adults

1) Symptoms of akathisia occurred in a 46-year-old Caucasian female following initiation of methylp
recurrent type major depressive disorder, alcohol dependence in full sustained remission, nicotine d
multiple pulmonary eosinophilic granulomas, was prescribed oral methylphenidate 10 mg twice daily
additionally receiving a complex regimen of medications, which included quetiapine. Although she e
of methylphenidate, she continued treatment. By the fifth day, she was restless, pacing, and felt like
clonazepam and diazepam (part of her regular regimen of medications) did not resolve the symptom
began experiencing tremors in her left arm. She presented to the emergency room where she was a

led to a prompt relief of symptoms. She was advised to discontinue methylphenidate and following c benztropine, her symptoms did not recur. It was proposed that the addition of methylphenidate may symptoms, a potential side effect of quetiapine (Almeida et al, 2006).

3.3.9.B.2 Central nervous system finding

a) Following administration of usual therapeutic doses in the treatment of minimal brain dysfunction/hyp have been reported with the use of methylphenidate. Symptoms have included restlessness, behavior di hallucinations, slurred speech, ataxia, vertigo, and uncontrollable facial and tongue movements (Lucas & the drug usually results in subsiding of these reactions within a few days.

3.3.9.B.3 Cerebrovascular accident

a) Adults

1) Stroke, sudden death, and myocardial infarction have occurred in adults taking usual doses of st cases is unknown, however, adults have a greater likelihood than children of having serious structur serious heart rhythm abnormalities, coronary artery disease, or other serious cardiac problems. Adu treated with stimulant drugs (Prod Info CONCERTA(R) extended-release oral tablets, 2008).

3.3.9.B.4 Chorea

a) Children

1) A case of chorea induced by methylphenidate in a 5-year-old boy receiving the drug for hyperact 1978). The choreic disorder disappeared 2 months after methylphenidate was discontinued.

3.3.9.B.5 Confusion

a) Incidence: 1.2% (Prod Info CONCERTA(R) extended-release oral tablets, 2008)

b) Adults

1) Confusional state has occurred in 1.2% of adult patients on methylphenidate hydrochloride exter patients on placebo (n=212), in 2 double-blind, placebo-controlled clinical trials (Prod Info CONCER

3.3.9.B.6 Dizziness

a) Incidence: 6.7%, adults; 1.9%, children (Prod Info CONCERTA(R) extended-release oral tablets, 200

b) Adults

1) Dizziness occurred in 6.7% of adult patients on methylphenidate hydrochloride compared with 5. placebo-controlled clinical trials (n=627) (Prod Info CONCERTA(R) extended-release oral tablets, 2(

c) Children

1) Dizziness occurred in 1.9% of children and adolescent patients on methylphenidate hydrochlorid of patients on placebo (n=318), in 4 double-blind, placebo-controlled clinical trials (Prod Info CONCE

3.3.9.B.7 Dyskinesia

a) Dyskinesia was reported during postmarketing experience with methylphenidate hydrochloride extend extended-release oral tablets, 2008).

3.3.9.B.8 Gilles de la Tourette's syndrome

a) Incidence: 1 to 9% (Prod Info CONCERTA(R) extended-release oral tablets, 2008; Varley et al, 2001

b) Children

1) The cumulative incidence of onset of new tics was 9% in children after 27 months of treatment w release in a long-term uncontrolled study (n=432) . The cumulative incidence of onset of new tics wa methylphenidate hydrochloride extended-release for up to 9 months, in a uncontrolled study (n=682 oral tablets, 2008).

2) The incidence of tics emergence was 7.8% in children treated with stimulant medication (methylp attention deficit hyperactivity disorder, based on a retrospective chart review (n=555). These stimula they were free of tics and without a history of tics according to the practice of the settings in which th of subjects treated with methylphenidate, 6.3% treated with dextroamphetamine, and 7.7% treated w dose or duration of stimulant therapy. Mean age of subjects was 11 years. A significant correlation c of tics. As the authors noted, these children may have developed tics, regardless of treatment with th

3) Although stimulant therapy was suspected to exacerbate tics, long-term methylphenidate treatme effective in children with attention-deficit hyperactivity disorder (ADHD) and chronic multiple tic disor blinded, prospective, follow-up study, 32 children (age ranging from 6.1 and 11.9 years) received mi previous trial (mean 16.5 milligrams (mg), range=5 to 40 mg). The children were evaluated in a simu their on-task, fidgeting, worksheet behaviors, and vocal and motor tic frequency. In almost every me than placebo (p ranging from less than 0.001 to 0.03). There was no difference in tic condition betwe behaviors were not significantly different between baseline and placebo, whereas children spent sig medication conditions than placebo (p less than 0.001). There was no significant difference between growth table values. Systolic blood pressure and heart rate were significantly increased (p=0.02 and clinically insignificant. Although this study showed methylphenidate did not worsen tics in patients w possibility of individual exacerbation of tic cannot be ruled out (Gadow et al, 1999). In another study syndrome, abrupt withdrawal of methylphenidate and dextroamphetamine in long-term therapy DID frequency (Nolan et al, 1999).

4) One group of investigators evaluated 1500 children who received methylphenidate in the treatme

incidence of tics following the drugs administration. The authors found that the incidence of tics deve
The types of tics described included eyelid, facial muscle, head, jaw, neck, limb and trunk tics. The a
relation to dose or duration of therapy and that in most patients discontinuing the drug resulted in re
contrast, another study (Erenberg et al, 1985) found that stimulant medications aggravated existing
5) Tourette's syndrome may be exacerbated or precipitated by the use of stimulant medications for
children. Early signs of Tourette's syndrome or tics are difficult to distinguish from hyperactive and a
therefore mistakenly be treated with stimulant medications (dextroamphetamine, methylphenidate, p
the severe motor and phonic tics requiring discontinuation of the stimulants and possible institution
having an attention deficit disorder, clinical evaluation for Tics and Tourette's Syndrome in the childr
stimulant medication. In children with no symptoms of Tourette's syndrome but with a familial history
use of stimulants is contraindicated in children with Tourette's Syndrome. If tics occur during stimula
discontinued (Lowe et al, 1982).

c) Numerous case reports have demonstrated tics either starting or worsening after methylphenidate, pe
correlation between stimulant dosages (high or low) or duration of treatment, and tic development. Tics h
even years. Many of the patients who developed tics years later were within the age range where tics fre
disease onset was independent of stimulant use. The highest risk for tic exacerbation appears to be in su
stimulant medication early in life and/or for a long duration. Investigators have noted that in those patient
stimulant decreased tic severity but did not necessarily completely resolve the condition (Price et al, 198
(Balhman, 1981)(Mitchell & Matthews, 1980; Bremness & Surerd, 1979; Pollack et al, 1977; Denckla et a
1973).

3.3.9.B.9 Headache

a) Incidence: 22.2%, adults (Prod Info CONCERTA(R) extended-release oral tablets, 2008); greater tha

b) Adults

1) Headache occurred in 22.2% of adult patients on methylphenidate hydrochloride extended-releas
placebo (n=212), in 2 double-blind, placebo-controlled clinical trials (Prod Info CONCERTA(R) exter

c) Children

1) In unpublished study data provided by the manufacturer involving children 6 to 12 years of age tr
(R) LA) for up to 4 weeks, insomnia and headache reportedly occurred in greater than 5% of patient

3.3.9.B.10 Insomnia

a) Incidence: 4.3% to 12.3%, adults; (Prod Info CONCERTA(R) extended-release oral tablets, 2008)2.8
release oral tablets, 2008)

b) Adults

1) Insomnia has occurred in 12.3% of adult patients on methylphenidate hydrochloride extended-re
on placebo (n=212), in 2 double-blind, placebo-controlled clinical trials (Prod Info CONCERTA(R) ex
2) Initial insomnia has occurred in 4.3% of adult patients on methylphenidate hydrochloride extende
patients on placebo (n=212), in 2 double-blind, placebo-controlled clinical trials (Prod Info CONCER

c) Children

1) Insomnia has occurred in 2.8% of child and adolescent patients extended-release (n=321) comp
in 4 double-blind, placebo-controlled clinical trials(Prod Info CONCERTA(R) extended-release oral t

3.3.9.B.11 Lethargy

a) Incidence: less than 1% (Prod Info CONCERTA(R) extended-release oral tablets, 2008)

b) Adults

1) Lethargy occurred in less than 1% of patients on methylphenidate hydrochloride extended-releas
trials (Prod Info CONCERTA(R) extended-release oral tablets, 2008).

3.3.9.B.12 Paresthesia

a) Incidence: 1.2% (Prod Info CONCERTA(R) extended-release oral tablets, 2008)

b) Adults

1) Paresthesia occurred in 1.2% of adult patients on methylphenidate hydrochloride extended-relea
patients, in 2 double-blind, placebo-controlled clinical trials (n=627) (Prod Info CONCERTA(R) exter

3.3.9.B.13 Seizure

a) For patients with a prior history of seizures, prior EEG abnormalities without seizures, and patients wi
evidence of seizures, stimulants may lower the convulsive threshold. Discontinue methylphenidate hydro
Info CONCERTA(R) extended-release oral tablets, 2008).

b) Convulsions and grand mal convulsions were reported during postmarketing experience (Prod Info C
2008).

c) Children

1) Children with attention deficit hyperactive disorder (ADHD) who have normal electroencephalogr
they receive stimulant therapy for ADHD (methylphenidate, dextroamphetamine, or combination am
(R)). However, children with epileptiform EEGs may have considerable risk for eventual seizure, alth
be attributable to use of the stimulant. These conclusions were based on a study of 234 children wit
ADHD. All had EEGs prior to parental choosing of stimulant treatment or foregoing stimulant treatme
children (15.4%) demonstrated epileptiform abnormalities compared with 198 with normal EEGs. Of
treatment for ADHD. Three of the 30 who received stimulant therapy experienced seizures (p less th

year-old male, and a 6-year-old male. The girl was treated uneventfully with methylphenidate for 12
methylphenidate experienced a 4-minute generalized tonic-clonic seizure. Her EEG had revealed a
the first experienced a 2-minute generalized tonic clonic seizure with focal onset 3 years after startir
episode at 10 months after initiation of methylphenidate; he was heard to fall and was unresponsive
of both boys had shown rolandic spikes, a focal epileptiform abnormality. One child who had a norm
methylphenidate (Hemmer et al, 2001).
2) Use of methylphenidate appears to be safe and effective to treat attention deficit hyperactivity dis
seizure free, while receiving antiepileptic drugs, before starting methylphenidate therapy. However,
having seizures while receiving antiepileptic drugs (Gross-Tsur et al, 1997).

3.3.9.B.14 Sleep disorder
a) Incidence: less than 1% (Prod Info CONCERTA(R) extended-release oral tablets, 2008)
b) Sleep disorders have occurred in less than 1% of patients on methylphenidate hydrochloride extende
clinical trials (Prod Info CONCERTA(R) extended-release oral tablets, 2008).

3.3.9.B.15 Somnolence
a) Incidence: less than 1% (Prod Info CONCERTA(R) extended-release oral tablets, 2008)
b) Adults
1) Somnolence occurred in less than 1% of patients on methylphenidate hydrochloride extended-re
trials (Prod Info CONCERTA(R) extended-release oral tablets, 2008).

3.3.9.B.16 Tension-type headache
a) Incidence: 1.2% (Prod Info CONCERTA(R) extended-release oral tablets, 2008)
b) Adults
1) Tension headache occurred in 1.2% of adult patients on methylphenidate hydrochloride extende
treated patients, in 2 double-blind, placebo-controlled clinical trials (n=627) (Prod Info CONCERTA(I

3.3.9.B.17 Tremor
a) Incidence: 2.7% (Prod Info CONCERTA(R) extended-release oral tablets, 2008)
b) Adults
1) Tremor occurred in 2.7% of adult patients on methylphenidate hydrochloride extended-release (r
placebo (n=212), in 2 double-blind, placebo-controlled clinical trials (Prod Info CONCERTA(R) exter

3.3.9.B.18 Vertigo
a) Incidence: 1.7% (Prod Info CONCERTA(R) extended-release oral tablets, 2008)
b) Adults
1) Vertigo has occurred in 1.7% of adult patients on methylphenidate hydrochloride extended-releas
placebo (n=212), in 2 double-blind, placebo-controlled clinical trials (Prod Info CONCERTA(R) exter

3.3.10 Ophthalmic Effects

Methylphenidate

Methylphenidate Hydrochloride

3.3.10.A Methylphenidate

Blurred vision

Disorder of accommodation

Visual disturbance

3.3.10.A.1 Blurred vision
a) Blurring of vision has been reported (Prod Info DAYTRANA(TM) transdermal system, 2006).

3.3.10.A.2 Disorder of accommodation
a) Difficulties with accommodation have been reported (Prod Info DAYTRANA(TM) transdermal system,

3.3.10.A.3 Visual disturbance
a) Incidence: rare (Prod Info DAYTRANA(TM) transdermal system, 2006)
b) Rarely, symptoms of visual disturbances have been experienced (Prod Info DAYTRANA(TM) transde

3.3.10.B Methylphenidate Hydrochloride

Diplopia

Dry eye

Glaucoma

Mydriasis

Retinopathy

Visual disturbance

3.3.10.B.1 Diplopia

a) Diplopia was reported during postmarketing experience with methylphenidate hydrochloride extended release oral tablets, 2008).

3.3.10.B.2 Dry eye

a) Incidence: less than 1% (Prod Info CONCERTA(R) extended-release oral tablets, 2008)

b) Dry eyes have occurred in less than 1% of patients on methylphenidate hydrochloride extended-relea clinical trials (Prod Info CONCERTA(R) extended-release oral tablets, 2008).

3.3.10.B.3 Glaucoma

a) Use of methylphenidate in patients with glaucoma is contraindicated (Prod Info Ritalin (R), 2001a). H cautiously in conjunction with glaucoma medications and regular ophthalmologic monitoring, particularly methylphenidate may be safe in patients with well-controlled, open-angle glaucoma (Bartlik & Harmon, 1

3.3.10.B.4 Mydriasis

a) Mydriasis was reported during postmarketing experience with methylphenidate hydrochloride extende release oral tablets, 2008).

3.3.10.B.5 Retinopathy

a) Intravenous abuse of methylphenidate can result in the development of retinopathy which is believed cornstarch, filtering materials, and other contaminants acting as microemboli (Tse, 1980; Kresca, 1979).

3.3.10.B.6 Visual disturbance

a) Incidence: 1.7% (Prod Info CONCERTA(R) extended-release oral tablets, 2008)

b) Adults

1) Blurred vision has occurred in 1.7% of adult patients on methylphenidate hydrochloride extended patients on placebo (n=212), in 2 double-blind, placebo-controlled clinical trials (Prod Info CONCER

c) Stimulant treatment may cause blurred vision and difficulties with accommodation. Visual disturbance experience (Prod Info CONCERTA(R) extended-release oral tablets, 2008).

3.3.12 Psychiatric Effects

Methylphenidate

Methylphenidate Hydrochloride

3.3.12.A Methylphenidate

Labile affect, Mild

Mania

Psychotic disorder

3.3.12.A.1 Labile affect, Mild

a) Incidence: 6% (Prod Info DAYTRANA(TM) transdermal system, 2006)
b) Mild affect lability occurred in 6% of patients on transdermal methylphenidate compared with 0% of p
Of the 6 patients who experienced affect lability, symptoms were characterized as increased emotionally
emotional lability, and intermittent emotional lability (Prod Info DAYTRANA(TM) transdermal system, 200

3.3.12.A.2 Mania

a) In a review of 49 randomized, controlled pediatric ADHD clinical trials involving pscyhostimulant medi
methylphenidate hydrochloride, modafinil and dextromethylphenidate hydrochloride), the rate of psychos
active drug was 1.48 (95% CI, 0.74 to 2.65) per 100 person-years, with no comparable adverse events r
the US Food and Drug Administration to manufacturers of marketed ADHD drugs for submission of postr
events between 2000 and 2005, yielded a total of 865 reports (pediatrics and adults) in which signs and/
reported. The majority of reports involved pediatric subjects, with almost half of the reports in children 10
of cases involving no prior history of similar psychiatric conditions. Visual and/or tactile sensations of inse
reported. Positive rechallenge was reported for each of the psychostimulant medications (methylphenida
and mixed salts of a single entity amphetamine product) included in the analysis; and in many cases a st
onset of psychiatric symptoms ranged from days to weeks, but in some cases it was months or years fro
onset (Mosholder et al, 2009).

3.3.12.A.3 Psychotic disorder

a) In a review of 49 randomized, controlled pediatric ADHD clinical trials involving pscyhostimulant medi
methylphenidate hydrochloride, modafinil and dextromethylphenidate hydrochloride), the rate of psychos
active drug was 1.48 (95% CI, 0.74 to 2.65) per 100 person-years, with no comparable adverse events r
the US Food and Drug Administration to manufacturers of marketed ADHD drugs for submission of postr
events between 2000 and 2005, yielded a total of 865 reports (pediatrics and adults) in which signs and/
reported. The majority of reports involved pediatric subjects, with almost half of the reports in children 10
of cases involving no prior history of similar psychiatric conditions. Visual and/or tactile sensations of inse
reported. Positive rechallenge was reported for each of the psychostimulant medications (methylphenida
and mixed salts of a single entity amphetamine product) included in the analysis; and in many cases a st
onset of psychiatric symptoms ranged from days to weeks, but in some cases it was months or years fro
onset (Mosholder et al, 2009).
b) Exacerbation of psychosis (behavior disturbance and thought disorder) has occurred during clinical e
DAYTRANA(TM) transdermal system, 2006).

3.3.12.B Methylphenidate Hydrochloride

Aggressive behavior

Agitation

Anxiety

Bruxism

Crying associated with mood

Depression

Disorientated

Feeling angry

Feeling nervous

Irritability

Mania

Mood swings

O/E - hypervigilance

Obsessive-compulsive disorder

Psychotic disorder

Reduced libido

Restlessness

Stuttering

Tension

3.3.12.B.1 Aggressive behavior

a) Incidence: 1.7% (Prod Info CONCERTA(R) extended-release oral tablets, 2008)

b) Adults

1) Aggression has occurred in 1.7% of adult patients on methylphenidate hydrochloride extended-re on placebo (n=212), in 2 double-blind, placebo-controlled clinical trials (Prod Info CONCERTA(R) ex

3.3.12.B.2 Agitation

a) Incidence: 2.2% (Prod Info CONCERTA(R) extended-release oral tablets, 2008)

b) Adults

1) Agitation has occurred in 2.2% of adult patients on methylphenidate hydrochloride extended-rele placebo (n=212), in 2 double-blind, placebo-controlled clinical trials (Prod Info CONCERTA(R) exter

3.3.12.B.3 Anxiety

a) Incidence: 8.2% (Prod Info CONCERTA(R) extended-release oral tablets, 2008)

b) Adults

1) Anxiety has occurred in 8.2% of adult patients on methylphenidate hydrochloride extended-relea placebo (n=212), in 2 double-blind, placebo-controlled clinical trials (Prod Info CONCERTA(R) exter

3.3.12.B.4 Bruxism

a) Incidence: 1.7% (Prod Info CONCERTA(R) extended-release oral tablets, 2008)

b) Adults

1) Bruxism has occurred in 1.7% of adult patients on methylphenidate hydrochloride extended-relea placebo (n=212), in 2 double-blind, placebo-controlled clinical trials (Prod Info CONCERTA(R) exter

3.3.12.B.5 Crying associated with mood

a) Incidence: less than 1% (Prod Info CONCERTA(R) extended-release oral tablets, 2008)

b) Tearfulness has occurred in less than 1% of patients on methylphenidate hydrochloride extended-rel trials (Prod Info CONCERTA(R) extended-release oral tablets, 2008).

3.3.12.B.6 Depression

a) Incidence: 1.7% to 3.9% (Prod Info CONCERTA(R) extended-release oral tablets, 2008)

b) Adults

1) Depression has occurred in 1.7% of adult patients on methylphenidate hydrochloride extended-re on placebo (n=212), in 2 double-blind, placebo-controlled clinical trials (Prod Info CONCERTA(R) ex

2) Depressed mood has occurred in 3.9% of adult patients on methylphenidate hydrochloride exten patients on placebo (n=212), in 2 double-blind, placebo-controlled clinical trials (Prod Info CONCER

3.3.12.B.7 Disorientated

a) Disorientation has been reported during postmarketing experience with methylphenidate hydrochlorid extended-release oral tablets, 2008).

3.3.12.B.8 Feeling angry

a) Incidence: less than 1% (Prod Info CONCERTA(R) extended-release oral tablets, 2008)

b) Anger has occurred in less than 1% of patients on methylphenidate hydrochloride extended-release i (Prod Info CONCERTA(R) extended-release oral tablets, 2008).

3.3.12.B.9 Feeling nervous

a) Incidence: 3.1% (Prod Info CONCERTA(R) extended-release oral tablets, 2008)

b) Adults

1) Nervousness has occurred in 8.2% of adult patients on methylphenidate hydrochloride extended on placebo (n=212), in 2 double-blind, placebo-controlled clinical trials (Prod Info CONCERTA(R) ex

3.3.12.B.10 Irritability

a) Incidence: 5.8% (Prod Info CONCERTA(R) extended-release oral tablets, 2008)

b) Adults

1) Irritability has occurred in 5.8% of adult patients on methylphenidate hydrochloride extended-rele placebo (n=212), in 2 double-blind, placebo-controlled clinical trials .

3.3.12.B.11 Mania

a) In a review of 49 randomized, controlled pediatric ADHD clinical trials involving pscyhostimulant medi methylphenidate hydrochloride, modafinil and dextromethylphenidate hydrochloride), the rate of psychos active drug was 1.48 (95% CI, 0.74 to 2.65) per 100 person-years, with no comparable adverse events r the US Food and Drug Administration to manufacturers of marketed ADHD drugs for submission of postı events between 2000 and 2005, yielded a total of 865 reports (pediatrics and adults) in which signs and/ reported. The majority of reports involved pediatric subjects, with almost half of the reports in children 10 of cases involving no prior history of similar psychiatric conditions. Visual and/or tactile sensations of inse reported. Positive rechallenge was reported for each of the psychostimulant medications (methylphenida and mixed salts of a single entity amphetamine product) included in the analysis; and in many cases a st onset of psychiatric symptoms ranged from days to weeks, but in some cases it was months or years fro onset (Mosholder et al, 2009).

b) Stimulants may induce mixed/manic episodes in patients with comorbid bipolar disorders. Exercise ca (Prod Info CONCERTA(R) extended-release oral tablets, 2008).

c) Stimulants may cause treatment-emergent psychotic or manic symptoms (eg, hallucinations, delusion of mania or psychotic illness. In a pooled analysis of multiple short-term, placebo-controlled studies, thes 0.1% of patients treated with stimulants (n=3482) compared with 0% in placebo treated patients (Prod In tablets, 2008).

d) Methylphenidate was associated with mania in a 10-year-old boy who was treated for severe hyperac received increasing doses up to 45 milligrams (mg) daily, which resulted in manic episodes during the th resulted in improvement over 2 days and lithium carbonate therapy was initiated. This patient had a posi

3.3.12.B.12 Mood swings

a) Incidence: less than 1% (Prod Info CONCERTA(R) extended-release oral tablets, 2008)

b) Mood swings have occurred in less than 1% of patients on methylphenidate hydrochloride extended- clinical trials (Prod Info CONCERTA(R) extended-release oral tablets, 2008).

3.3.12.B.13 O/E - hypervigilance

a) Incidence: less than 1% (Prod Info CONCERTA(R) extended-release oral tablets, 2008)

b) Hypervigilance has occurred in less than 1% of patients on methylphenidate hydrochloride extended- clinical trials (Prod Info CONCERTA(R) extended-release oral tablets, 2008).

3.3.12.B.14 Obsessive-compulsive disorder

a) High-dose methylphenidate was associated with obsessive-compulsive symptoms in a 10-year-old gi hyperactive disorder (ADHD), for which she was receiving methylphenidate (doses increased gradually t clonidine (0.025 mg nightly). For 2 years, the child was uncontrollably stealing from peers, teachers, neig was unable to control her urge to steal. The dose of methylphenidate was tapered to 30 mg/day. Her ste occasional basis. She was hospitalized so methylphenidate could be withdrawn under observation; sertr ADHD were observed after methylphenidate withdrawal; stealing episodes were further reduced. At 1-ye (Kotsopoulos & Spivak, 2001).

3.3.12.B.15 Psychotic disorder

a) In a review of 49 randomized, controlled pediatric ADHD clinical trials involving pscyhostimulant medi methylphenidate hydrochloride, modafinil and dextromethylphenidate hydrochloride), the rate of psychos active drug was 1.48 (95% CI, 0.74 to 2.65) per 100 person-years, with no comparable adverse events r the US Food and Drug Administration to manufacturers of marketed ADHD drugs for submission of postı events between 2000 and 2005, yielded a total of 865 reports (pediatrics and adults) in which signs and/ reported. The majority of reports involved pediatric subjects, with almost half of the reports in children 10 of cases involving no prior history of similar psychiatric conditions. Visual and/or tactile sensations of inse reported. Positive rechallenge was reported for each of the psychostimulant medications (methylphenida and mixed salts of a single entity amphetamine product) included in the analysis; and in many cases a st onset of psychiatric symptoms ranged from days to weeks, but in some cases it was months or years fro onset (Mosholder et al, 2009).

b) Hallucinations have been reported during postmarketing experience with methylphenidate hydrochlor extended-release oral tablets, 2008).

3.3.12.B.16 Reduced libido

a) Incidence: 1.7% (Prod Info CONCERTA(R) extended-release oral tablets, 2008)

b) Adults

1) Decreased libido has occurred in 1.7% of adult patients on methylphenidate hydrochloride exten patients on placebo (n=212), in 2 double-blind, placebo-controlled clinical trials (Prod Info CONCER

3.3.12.B.17 Restlessness

a) Incidence: 3.1% (Prod Info CONCERTA(R) extended-release oral tablets, 2008)

b) Adults
1) Restlessness has occurred in 3.1% of adult patients on methylphenidate hydrochloride extended on placebo (n=212), in 2 double-blind, placebo-controlled clinical trials (Prod Info CONCERTA(R) ex

3.3.12.B.18 Stuttering
a) Stuttering has been temporally associated with the use of pemoline (9.375 milligrams(mg)/day) and n in a 3-year-old girl. The stuttering stopped with the discontinuation of each drug (Burd & Kerbeshian, 19

3.3.12.B.19 Tension
a) Incidence: 1.2% (Prod Info CONCERTA(R) extended-release oral tablets, 2008)
b) Adults
1) Tension has occurred in 1.2% of adult patients on methylphenidate hydrochloride extended-relea placebo (n=212), in 2 double-blind, placebo-controlled clinical trials (Prod Info CONCERTA(R) exter

3.3.13 Renal Effects

3.3.13.A Methylphenidate Hydrochloride

3.3.13.A.1 Urogenital finding
a) Methylphenidate has been shown to increase urinary catecholamines.
b) Intravenous abuse of methylphenidate can result in the development of a foreign body granuloma in t cornstarch) contained in the tablets (Hahn, 1969).

3.3.14 Reproductive Effects

3.3.14.A Methylphenidate Hydrochloride

3.3.14.A.1 Erectile dysfunction
a) Incidence: less than 1% (Prod Info CONCERTA(R) extended-release oral tablets, 2008)
b) Erectile dysfunction has occurred in less than 1% of patients on methylphenidate hydrochloride in pla Info CONCERTA(R) extended-release oral tablets, 2008).

3.3.15 Respiratory Effects

Methylphenidate

Methylphenidate Hydrochloride

3.3.15.A Methylphenidate

Nasal congestion

Nasopharyngitis

3.3.15.A.1 Nasal congestion
a) Incidence: 6% (Prod Info DAYTRANA(TM) transdermal system, 2006)
b) Nasal congestion occurred in 6% of patients on transdermal methylphenidate compared with 1% of p (n=183) (Prod Info DAYTRANA(TM) transdermal system, 2006).

3.3.15.A.2 Nasopharyngitis
a) Incidence: 5% (Prod Info DAYTRANA(TM) transdermal system, 2006)
b) Nasopharyngitis occurred in 5% of patients on transdermal methylphenidate compared with 2% of pla (n=183) (Prod Info DAYTRANA(TM) transdermal system, 2006).

3.3.15.B Methylphenidate Hydrochloride

Cough

Dyspnea

Respiratory finding

Upper respiratory infection

3.3.15.B.1 Cough

a) Incidence: 1.9% (Prod Info CONCERTA(R) extended-release oral tablets, 2008)

b) Children

1) Cough has occurred in 1.9% of children and adolescent patients on methylphenidate hydrochlori 0.3% of patients on placebo (n=318), in 4 double-blind, placebo-controlled clinical trials (Prod Info C 2008).

3.3.15.B.2 Dyspnea

a) Incidence: less than 1% (Prod Info CONCERTA(R) extended-release oral tablets, 2008)

b) Dyspnea has occurred in less than 1% of patients on methylphenidate hydrochloride extended-releas trials (Prod Info CONCERTA(R) extended-release oral tablets, 2008).

3.3.15.B.3 Respiratory finding

a) Pulmonary dysfunction associated with methylphenidate use is related to inappropriate parenteral adı abusers dissolve methylphenidate tablets, which contain fillers such as talc, in water and then inject the ı potential to embolize in the lung and produce pulmonary dysfunction (Hahn et al, 1969). Also with intrave arterial hypertension and medial hypertrophy of muscular pulmonary arteries, including fibrous intimal pr (Arnett, 1976).

3.3.15.B.4 Upper respiratory infection

a) Incidence: 2.2% (Prod Info CONCERTA(R) extended-release oral tablets, 2008)

b) Adults

1) Upper respiratory infections have occurred in 2.2% of adult patients on methylphenidate hydroch 0.9% of patients on placebo (n=212), in 2 double-blind, placebo-controlled clinical trials (Prod Info C 2008).

3.3.16 Other

Methylphenidate

Methylphenidate Hydrochloride

3.3.16.A Methylphenidate

Drug dependence

Viral disease

3.3.16.A.1 Drug dependence

a) Marked tolerance and psychological dependence with varying degrees of abnormal behavior have be abused methylphenidate. Frank psychotic episodes can occur, particularly with parenteral abuse. Risk fa alcoholism. Withdrawing methylphenidate in a patient who has abused it may lead to severe depression. may unmask symptoms of the underlying disorder that may require follow-up (Prod Info DAYTRANA(TM

1) Among children with attention deficit disorder treated with methylphenidate, no strong conclusive methylphenidate with the occurrence of adult drug abuse.

2) Ingestion of high doses (doses above those normally recommended) of methylphenidate for exte the euphoric effect and psychological dependence. Dependence on methylphenidate may be charac degrees of abnormal behavior. Intravenous administration of methylphenidate has been reported to of 30 to 100 milligrams (mg)/day for 14 days. Severe depression and amphetamine-like withdrawal s belligerence, anxiety, muscular aches, chills, tremors, sleep disturbances, lethargy, exhaustion, and methylphenidate withdrawal. Withdrawal therapy usually consists of adjunctive neuroleptic and/or ar gradual methylphenidate withdrawal. The gradual tapering of methylphenidate doses in dependent i duration of withdrawal symptoms. Further studies are needed to justify any advantage of gradual ov this drug may result in toxic psychosis. Multiple organ failure including hepatic, renal, pancreatic, an intravenous or intra-arterial injection of crushed methylphenidate tablets (Keeley & Licht, 1985; Stec Gunby, 1979; Extein, 1978; Spensley, 1972; Spensley & Rockwell, 1972; AtLee, 1972; Lindell et al, 1970).

3.3.16.A.2 Viral disease

a) During an open-label study (n=191) of 40 months duration with transdermal methylphenidate worn fo

of subjects (Prod Info DAYTRANA(TM) transdermal system, 2006).

3.3.16.B Methylphenidate Hydrochloride

Drug dependence

Drug tolerance - finding

Fatigue

Fever

3.3.16.B.1 Drug dependence

a) Methylphenidate hydrochloride should be given cautiously to patients with a history of drug depender to marked tolerance and psychological dependence, with varying degrees of abnormal behavior (Prod In tablets, 2008).

b) Among children with attention deficit disorder treated with methylphenidate, no strong conclusive evic methylphenidate with the occurrence of adult drug abuse.

c) Ingestion of high doses (doses above those normally recommended) of methylphenidate for extende euphoric effect and psychological dependence. Dependence on methylphenidate may be characterized abnormal behavior. Intravenous administration of methylphenidate has been reported to produce depend milligrams (mg)/day for 14 days. Severe depression and amphetamine-like withdrawal symptoms includi anxiety, muscular aches, chills, tremors, sleep disturbances, lethargy, exhaustion, and suicidal ideations Withdrawal therapy usually consists of adjunctive neuroleptic and/or antidepressant therapy along with a The gradual tapering of methylphenidate doses in dependent individuals may not altered the severity or studies are needed to justify any advantage of gradual over abrupt drug withdrawal. Chronic ingestion of organ failure including hepatic, renal, pancreatic, and pulmonary toxicity may occur following intravenous methylphenidate tablets (Keeley & Licht, 1985; Stecyk, 1985; Anon, 1985; Hodding et al, 1980; Gunby, 1 Rockwell, 1972; AtLee, 1972; Lindell et al, 1972; Sugar et al, 1971; Hopkins & Taylor, 1970).

3.3.16.B.2 Drug tolerance - finding

a) Two double-blind, randomized, crossover trials evaluating the effectiveness of various drug delivery p tolerance to methylphenidate may exist in the treatment of children with attention deficit hyperactivity dis methylphenidate delivery patterns (twice-daily, flat, and ascending) and placebo were compared. The tw methylphenidate was designed to produce typical school day peak and trough concentrations. The flat re followed by a uniform methylphenidate concentration throughout the day. The ascending regimen produc low-drug concentration early in the morning to a high-drug concentration by the end of the day. The flat c for measures of efficacy than the twice daily regimen in the afternoon, which suggests that acute tolerar may be emerging throughout the day. In Study II, 32 children were assigned three treatments profiles (th the timing of the middle bolus of the three-times daily regimen was either 9:30 am (tid-am) or 1:30 pm (ti increases in efficacy were measured in the tid-am regimen after the second dose compared with large in following the second dose. Following the administration of the third bolus dose in each regimen, a larger regimen compared with small increases in efficacy for the tid-pm regimen. The interpretation of these pa hypothesis. The results of Study I and Study II support the hypothesis that acute tolerance may contribut drug delivery compared with immediate-release drug delivery of methylphenidate (Swanson et al, 1999).

3.3.16.B.3 Fatigue

a) Incidence: less than 1% (Prod Info CONCERTA(R) extended-release oral tablets, 2008)

b) Fatigue has occurred in less than 1% of patients on methylphenidate hydrochloride extended-release (Prod Info CONCERTA(R) extended-release oral tablets, 2008).

3.3.16.B.4 Fever

a) Incidence: 2.2% (Prod Info CONCERTA(R) extended-release oral tablets, 2008)

b) Children

1) Pyrexia has occurred in 2.2% of child and adolescent patients on methylphenidate hydrochloride of patients on placebo (n=318), in 4 double-blind, placebo-controlled clinical trials in placebo-control CONCERTA(R) extended-release oral tablets, 2008).

3.4 Teratogenicity/Effects in Pregnancy/Breastfeeding

A) Teratogenicity/Effects in Pregnancy

1) U.S. Food and Drug Administration's Pregnancy Category: Category C (Prod Info Concerta(R), 2001) (All Trim

a) Either studies in animals have revealed adverse effects on the fetus (teratogenic or embryocidal or other) studies in women and animals are not available. Drugs should be given only if the potential benefit justifies th

2) Australian Drug Evaluation Committee's (ADEC) Category: B2 (Batagol, 1999)

a) Drugs which have been taken by only a limited number of pregnant women and women of childbearing ag malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in available data show no evidence of an increased occurrence of fetal damage.

See Drug Consult reference: PREGNANCY RISK CATEGORIES

3) Crosses Placenta: Unknown

4) Clinical Management

a) Although a causal relationship between methylphenidate and teratogenic effects has not been found, the has yet to be confirmed. Until additional data are available, caution should be exercised with the use of methy

5) Literature Reports

a) No human studies of pregnancy outcomes after exposure to methylphenidate have been published and th inadvertent exposure during pregnancy. Adequate studies to establish safe use of methylphenidate during pr Concerta(R), 2001). One source describes a series of women (n=11) who used methylphenidate (dose unspe no birth defects or other abnormalities were reported in any of the infants and all 11 were considered normal al, 1993) discussed the outcomes of another 38 women who used methylphenidate during pregnancy. Althou be premature, growth retarded, and to show signs of neonatal withdrawal, no increase in congenital abnorma small that no pattern or estimate of risk can be determined at this time.

B) Breastfeeding

1) Thomson Lactation Rating: Infant risk cannot be ruled out.

a) Available evidence and/or expert consensus is inconclusive or is inadequate for determining infant risk wh potential benefits of drug treatment against potential risks before prescribing this drug during breastfeeding.

2) Clinical Management

a) It is not known whether methylpheidate is excreted into human breast milk and the potential for adverse e drug are unknown. Given the drug's low molecular weight of approximately 270, transfer into milk would be e

3) Literature Reports

a) No reports describing the use of methylphenidate during human lactation or measuring the amount, if any

3.5 Drug Interactions

Drug-Drug Combinations

Intravenous Admixtures

3.5.1 Drug-Drug Combinations

Amitriptyline

Amoxapine

Brofaromine

Carbamazepine

Citalopram

Clomipramine

Clorgyline

Clovoxamine

Desipramine

Dicumarol

Dothiepin

Doxepin

Escitalopram

Femoxetine

Fluoxetine

Fluvoxamine

Furazolidone

Imipramine

Iproniazid

Isocarboxazid

Lazabemide

Linezolid

Lofepramine

Moclobemide

Nefazodone

Nialamide

Nortriptyline

Opipramol

Pargyline

Paroxetine

Phenelzine

Phenobarbital

Phenytoin

Primidone

Procarbazine

Protriptyline

Rasagiline

Selegiline

Sertraline

Toloxatone

Tranylcypromine

Trimipramine

Tyrosine

Warfarin

Zimeldine

3.5.1.A Amitriptyline

1) Interaction Effect: hypertension, other cardiac effects, and CNS stimulation

2) Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been reporte from the release of norepinephrine (Beaumont, 1973; Raisfeld, 1972). A similar reaction might also occur wit Acute elevations in blood pressure have been noted (Flemenbaum, 1971a). Some amphetamine-like drugs m most combinations have not been studied. When amphetamine analogs are being used to treat obesity, it sh moderate weight gain (Russ & Ackerman, 1988). False positive urine tests for amphetamines have been repo & Browning, 1993). Caution is advised when concurrent administration of amphetamine-like agents and TCA monitored for increased cardiovascular effects (hypertension and dysrhythmias).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other sympatho increased cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Inf capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006; Flemenbaum, 1972). Use caution if closely for hypertension and dysrhythmias.

7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission

8) Literature Reports

a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agen amphetamine with TCAs such as desipramine or protriptyline results in sustained increases in d-amphet VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tab 2006).

b) Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism o imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transdermal system, 2006).

c) Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases i effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of comb methylphenidate usually results in the blood pressure returning to normotensive levels; reinstitution of th pressure elevation (Flemenbaum, 1971; Flemenbaum, 1972).

d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine g fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical doubled steady-state plasma levels of desipramine (Price et al, 1990).

e) There have been claims based on uncontrolled studies that a better antidepressant response may oc 1969). However, a systemic review of stimulants in the treatment of depression concluded that although ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated litt appear to be as effective as the conventional antidepressants in primary depression (Satel & Nelson, 19

3.5.1.B Amoxapine

1) Interaction Effect: hypertension, other cardiac effects, and CNS stimulation

2) Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been reporte from the release of norepinephrine (Beaumont, 1973; Raisfeld, 1972). A similar reaction might also occur wit Acute elevations in blood pressure have been noted (Flemenbaum, 1971a). Some amphetamine-like drugs m most combinations have not been studied. When amphetamine analogs are being used to treat obesity, it sh moderate weight gain (Russ & Ackerman, 1988). False positive urine tests for amphetamines have been repo & Browning, 1993). Caution is advised when concurrent administration of amphetamine-like agents and TCA monitored for increased cardiovascular effects (hypertension and dysrhythmias).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other sympatho increased cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Inf capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006; Flemenbaum, 1972). Use caution if closely for hypertension and dysrhythmias.

7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission

8) Literature Reports

a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agen amphetamine with TCAs such as desipramine or protriptyline results in sustained increases in d-amphet VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tab

2006).
b) Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism c
imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transdermal system, 2006).
c) Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases i
effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of comb
methylphenidate usually results in the blood pressure returning to normotensive levels; reinstitution of th
pressure elevation (Flemenbaum, 1971; Flemenbaum, 1972).
d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine g
fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical
doubled steady-state plasma levels of desipramine (Price et al, 1990).
e) There have been claims based on uncontrolled studies that a better antidepressant response may oc
1969). However, a systemic review of stimulants in the treatment of depression concluded that although
ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated litt
appear to be as effective as the conventional antidepressants in primary depression (Satel & Nelson, 19

3.5.1.C Brofaromine

1) Interaction Effect: hypertensive crisis (headache, palpitation, and neck stiffness)
2) Summary: Coadministration of methylphenidate and a monoamine oxidase inhibitor may result in hyperte
such as headache, palpitation, neck stiffness, nausea, and vomiting. Hypertensive crisis associated with mor
Info Concerta(TM), 2000). The concomitant administration of methylphenidate with monoamine oxidase inhib
be initiated, the monoamine oxidase inhibitor must be discontinued for a minimum of 14 days (Prod Info DAY
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent use of monoamine oxidase inhibitors and methylphenidate is contra
the monoamine oxidase inhibitor must be discontinued for a minimum of 14 days.
7) Probable Mechanism: unknown

3.5.1.D Carbamazepine

1) Interaction Effect: loss of methylphenidate efficacy
2) Summary: Two case reports describe the loss of methylphenidate efficacy after carbamazepine therapy w
cytochrome P450 enzymes, a pathway involved in methylphenidate metabolism. Although methylphenidate p
measured, they may be helpful in patients receiving carbamazepine who are showing no benefits or side effe
Schaller & Behar, 1999a).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Clinicians should monitor patient response to methylphenidate therapy when carba
methylphenidate levels may also be helpful. Doses of methylphenidate may need to be increased to maintain
7) Probable Mechanism: induction by carbamazepine of cytochrome P450 3A4-mediated methylphenidate m
8) Literature Reports
a) A 7-year-old male with severe mental retardation and attention deficit disorder was failing to respond
thiothixene 10 mg daily. Other drug therapy included carbamazepine 1000 mg daily to control grand mal
medication compliance, plasma levels of methylphenidate were measured two hours after the morning d
their metabolites could be found. Doses were increased to methylphenidate 30 mg every four hours and
efficacy or side effects. Both agents were then discontinued (Behar et al, 1998).
b) Attention deficit/hyperactivity disorder (ADHD) was being treated with methylphenidate 20 mg three ti
mood lability and significant impulsivity, carbamazepine was introduced at 200 mg daily. The strict two-h
serum level was 5.3 ng/mL (normal range 5 to 20 ng/mL) at this time. ADHD symptoms began to worsen
800 mg daily. Six weeks after the start of combination therapy, the patient's methylphenidate and ritalinic
decreased to 4.2 ng/mL. A month later, the carbamazepine dose was increased to 1000 mg daily with a
an increase in her methylphenidate dose to 35 mg three times daily, her methylphenidate and ritalinic ac
ng/mL. After another two months, her carbamazepine dose was 1200 mg daily with a steady-state blood
increased to 60 mg three times daily to regain the benefit from the drug that she had experienced before
Behar, 1999).

3.5.1.E Citalopram

1) Interaction Effect: increased selective serotonin reuptake inhibitor plasma concentrations
2) Summary: Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metab
(SSRIs). Downward dose adjustments of the SSRI may be necessary when it is used concurrently with methy
discontinuing methylphenidate, the SSRI dose may need to be adjusted as needed (Prod Info METADATE C
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Use caution when prescribing methylphenidate to patients who take an selective se
use of methylphenidate and an SSRI may cause elevated SSRI plasma concentrations. Consider a decrease
coadministered. Additionally, consider adjusting the SSRI dose if necessary when initiating or discontinuing m
CD(R) extended-release oral capsules, 2007).

7) Probable Mechanism: inhibition of selective serotonin reuptake inhibitor metabolism by methylphenidate

3.5.1.F Clomipramine

1) Interaction Effect: hypertension, other cardiac effects, and CNS stimulation

2) Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been reporte from the release of norepinephrine (Beaumont, 1973; Raisfeld, 1972). A similar reaction might also occur wit Acute elevations in blood pressure have been noted (Flemenbaum, 1971a). Some amphetamine-like drugs m most combinations have not been studied. When amphetamine analogs are being used to treat obesity, it sh moderate weight gain (Russ & Ackerman, 1988). False positive urine tests for amphetamines have been repo & Browning, 1993). Caution is advised when concurrent administration of amphetamine-like agents and TCAs monitored for increased cardiovascular effects (hypertension and dysrhythmias).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other sympatho increased cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Inf capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006; Flemenbaum, 1972). Use caution if closely for hypertension and dysrhythmias.

7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission

8) Literature Reports

a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agen amphetamine with TCAs such as desipramine or protriptyline results in sustained increases in d-amphet VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tab 2006).

b) Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism o imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transdermal system, 2006).

c) Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases i effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of comb methylphenidate usually results in the blood pressure returning to normotensive levels; reinstitution of th pressure elevation (Flemenbaum, 1971; Flemenbaum, 1972).

d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine g fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical doubled steady-state plasma levels of desipramine (Price et al, 1990).

e) There have been claims based on uncontrolled studies that a better antidepressant response may oc 1969). However, a systemic review of stimulants in the treatment of depression concluded that although ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated litt appear to be as effective as the conventional antidepressants in primary depression (Satel & Nelson, 19

3.5.1.G Clorgyline

1) Interaction Effect: hypertensive crisis (headache, palpitation, and neck stiffness)

2) Summary: Coadministration of methylphenidate and a monoamine oxidase inhibitor may result in hyperte such as headache, palpitation, neck stiffness, nausea, and vomiting. Hypertensive crisis associated with mor Info Concerta(TM), 2000). The concomitant administration of methylphenidate with monoamine oxidase inhib be initiated, the monoamine oxidase inhibitor must be discontinued for a minimum of 14 days (Prod Info DAY

3) Severity: contraindicated

4) Onset: rapid

5) Substantiation: theoretical

6) Clinical Management: The concurrent use of monoamine oxidase inhibitors and methylphenidate is contra the monoamine oxidase inhibitor must be discontinued for a minimum of 14 days.

7) Probable Mechanism: unknown

3.5.1.H Clovoxamine

1) Interaction Effect: increased selective serotonin reuptake inhibitor plasma concentrations

2) Summary: Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metab (SSRIs). Downward dose adjustments of the SSRI may be necessary when it is used concurrently with meth discontinuing methylphenidate, the SSRI dose may need to be adjusted as needed (Prod Info METADATE C

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Use caution when prescribing methylphenidate to patients who take an selective se use of methylphenidate and an SSRI may cause elevated SSRI plasma concentrations. Consider a decrease coadministered. Additionally, consider adjusting the SSRI dose if necessary when initiating or discontinuing m CD(R) extended-release oral capsules, 2007).

7) Probable Mechanism: inhibition of selective serotonin reuptake inhibitor metabolism by methylphenidate

3.5.1.I Desipramine

1) Interaction Effect: hypertension, other cardiac effects, and CNS stimulation

2) Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been reporte

from the release of norepinephrine (Beaumont, 1973; Raisfeld, 1972). A similar reaction might also occur with
Acute elevations in blood pressure have been noted (Flemenbaum, 1971a). Some amphetamine-like drugs m
most combinations have not been studied. When amphetamine analogs are being used to treat obesity, it sh
moderate weight gain (Russ & Ackerman, 1988). False positive urine tests for amphetamines have been repo
& Browning, 1993). Caution is advised when concurrent administration of amphetamine-like agents and TCAs
monitored for increased cardiovascular effects (hypertension and dysrhythmias).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other sympatho
increased cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Inf
capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006; Flemenbaum, 1972). Use caution if
closely for hypertension and dysrhythmias.
7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission
8) Literature Reports
a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agen
amphetamine with TCAs such as desipramine or protriptyline results in sustained increases in d-amphet
VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tab
2006).
b) Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism o
imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transdermal system, 2006).
c) Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases i
effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of comb
methylphenidate usually results in the blood pressure returning to normotensive levels; reinstitution of th
pressure elevation (Flemenbaum, 1971; Flemenbaum, 1972).
d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine g
fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical
doubled steady-state plasma levels of desipramine (Price et al, 1990).
e) There have been claims based on uncontrolled studies that a better antidepressant response may oc
1969). However, a systemic review of stimulants in the treatment of depression concluded that although
ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated litt
appear to be as effective as the conventional antidepressants in primary depression (Satel & Nelson, 19

3.5.1.J Dicumarol
1) Interaction Effect: an increased risk of bleeding
2) Summary: Methylphenidate may increase the hypoprothrombinemic effect of dicumarol (Prod Info Dicuma
demonstrated that methylphenidate may inhibit the metabolism of coumarin anticoagulants, such as dicumar
may be necessary when it is used concurrently with methylphenidate. Additionally, coagulation times should
discontinuing methylphenidate, and should be reassessed periodically during concurrent therapy. Dicumarol
order to maintain the desired level of anticoagulation (Prod Info DAYTRANA(TM) transdermal system, 2006).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of methylphenidate and dicumarol may increase dicumarol levels
methylphenidate. In patients receiving oral anticoagulant therapy, the prothrombin time ratio or international r
monitored with the addition and withdrawal of treatment with methylphenidate, and should be reassessed per
of the dicumarol dose may be necessary in order to maintain the desired level of anticoagulation.
7) Probable Mechanism: inhibition of dicumarol metabolism

3.5.1.K Dothiepin
1) Interaction Effect: hypertension, other cardiac effects, and CNS stimulation
2) Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been reporte
from the release of norepinephrine (Beaumont, 1973; Raisfeld, 1972). A similar reaction might also occur with
Acute elevations in blood pressure have been noted (Flemenbaum, 1971a). Some amphetamine-like drugs m
most combinations have not been studied. When amphetamine analogs are being used to treat obesity, it sh
moderate weight gain (Russ & Ackerman, 1988). False positive urine tests for amphetamines have been repo
& Browning, 1993). Caution is advised when concurrent administration of amphetamine-like agents and TCAs
monitored for increased cardiovascular effects (hypertension and dysrhythmias).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other sympatho
increased cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Inf
capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006; Flemenbaum, 1972). Use caution if
closely for hypertension and dysrhythmias.
7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission
8) Literature Reports
a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agen

amphetamine with TCAs such as desipramine or protriptyline results in sustained increases in d-amphet
VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tab
2006).
b) Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism c
imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transdermal system, 2006).
c) Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases i
effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of comb
methylphenidate usually results in the blood pressure returning to normotensive levels; reinstitution of th
pressure elevation (Flemenbaum, 1971; Flemenbaum, 1972).
d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine g
fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical
doubled steady-state plasma levels of desipramine (Price et al, 1990).
e) There have been claims based on uncontrolled studies that a better antidepressant response may oc
1969). However, a systemic review of stimulants in the treatment of depression concluded that although
ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated litt
appear to be as effective as the conventional antidepressants in primary depression (Satel & Nelson, 19

3.5.1.L Doxepin

1) Interaction Effect: hypertension, other cardiac effects, and CNS stimulation
2) Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been reporte
from the release of norepinephrine (Beaumont, 1973; Raisfeld, 1972). A similar reaction might also occur wit
Acute elevations in blood pressure have been noted (Flemenbaum, 1971a). Some amphetamine-like drugs m
most combinations have not been studied. When amphetamine analogs are being used to treat obesity, it sh
moderate weight gain (Russ & Ackerman, 1988). False positive urine tests for amphetamines have been repo
& Browning, 1993). Caution is advised when concurrent administration of amphetamine-like agents and TCAs
monitored for increased cardiovascular effects (hypertension and dysrhythmias).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other sympatho
increased cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Inf
capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006; Flemenbaum, 1972). Use caution if
closely for hypertension and dysrhythmias.
7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission
8) Literature Reports
a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agen
amphetamine with TCAs such as desipramine or protriptyline results in sustained increases in d-amphet
VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tab
2006).
b) Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism c
imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transdermal system, 2006).
c) Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases i
effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of comb
methylphenidate usually results in the blood pressure returning to normotensive levels; reinstitution of th
pressure elevation (Flemenbaum, 1971; Flemenbaum, 1972).
d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine g
fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical
doubled steady-state plasma levels of desipramine (Price et al, 1990).
e) There have been claims based on uncontrolled studies that a better antidepressant response may oc
1969). However, a systemic review of stimulants in the treatment of depression concluded that although
ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated litt
appear to be as effective as the conventional antidepressants in primary depression (Satel & Nelson, 19

3.5.1.M Escitalopram

1) Interaction Effect: increased selective serotonin reuptake inhibitor plasma concentrations
2) Summary: Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metab
(SSRIs). Downward dose adjustments of the SSRI may be necessary when it is used concurrently with meth
discontinuing methylphenidate, the SSRI dose may need to be adjusted as needed (Prod Info METADATE C
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Use caution when prescribing methylphenidate to patients who take an selective se
use of methylphenidate and an SSRI may cause elevated SSRI plasma concentrations. Consider a decrease
coadministered. Additionally, consider adjusting the SSRI dose if necessary when initiating or discontinuing m
CD(R) extended-release oral capsules, 2007).
7) Probable Mechanism: inhibition of selective serotonin reuptake inhibitor metabolism by methylphenidate

3.5.1.N Femoxetine

1) Interaction Effect: increased selective serotonin reuptake inhibitor plasma concentrations
2) Summary: Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metab
(SSRIs). Downward dose adjustments of the SSRI may be necessary when it is used concurrently with methy
discontinuing methylphenidate, the SSRI dose may need to be adjusted as needed (Prod Info METADATE C
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Use caution when prescribing methylphenidate to patients who take an selective se
use of methylphenidate and an SSRI may cause elevated SSRI plasma concentrations. Consider a decrease
coadministered. Additionally, consider adjusting the SSRI dose if necessary when initiating or discontinuing n
CD(R) extended-release oral capsules, 2007).
7) Probable Mechanism: inhibition of selective serotonin reuptake inhibitor metabolism by methylphenidate

3.5.1.O Fluoxetine
1) Interaction Effect: increased selective serotonin reuptake inhibitor plasma concentrations
2) Summary: Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metab
(SSRIs). Downward dose adjustments of the SSRI may be necessary when it is used concurrently with methy
discontinuing methylphenidate, the SSRI dose may need to be adjusted as needed (Prod Info METADATE C
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Use caution when prescribing methylphenidate to patients who take an selective se
use of methylphenidate and an SSRI may cause elevated SSRI plasma concentrations. Consider a decrease
coadministered. Additionally, consider adjusting the SSRI dose if necessary when initiating or discontinuing n
CD(R) extended-release oral capsules, 2007).
7) Probable Mechanism: inhibition of selective serotonin reuptake inhibitor metabolism by methylphenidate

3.5.1.P Fluvoxamine
1) Interaction Effect: increased selective serotonin reuptake inhibitor plasma concentrations
2) Summary: Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metab
(SSRIs). Downward dose adjustments of the SSRI may be necessary when it is used concurrently with methy
discontinuing methylphenidate, the SSRI dose may need to be adjusted as needed (Prod Info METADATE C
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Use caution when prescribing methylphenidate to patients who take an selective se
use of methylphenidate and an SSRI may cause elevated SSRI plasma concentrations. Consider a decrease
coadministered. Additionally, consider adjusting the SSRI dose if necessary when initiating or discontinuing n
CD(R) extended-release oral capsules, 2007).
7) Probable Mechanism: inhibition of selective serotonin reuptake inhibitor metabolism by methylphenidate

3.5.1.Q Furazolidone
1) Interaction Effect: hypertensive crisis (headache, palpitation, and neck stiffness)
2) Summary: Coadministration of methylphenidate and a monoamine oxidase inhibitor may result in hyperte
such as headache, palpitation, neck stiffness, nausea, and vomiting. Hypertensive crisis associated with mor
Info Concerta(TM), 2000). The concomitant administration of methylphenidate with monoamine oxidase inhib
be initiated, the monoamine oxidase inhibitor must be discontinued for a minimum of 14 days (Prod Info DAY
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent use of monoamine oxidase inhibitors and methylphenidate is contra
the monoamine oxidase inhibitor must be discontinued for a minimum of 14 days.
7) Probable Mechanism: unknown

3.5.1.R Imipramine
1) Interaction Effect: hypertension, other cardiac effects, and CNS stimulation
2) Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been reporte
from the release of norepinephrine (Beaumont, 1973; Raisfeld, 1972). A similar reaction might also occur with
Acute elevations in blood pressure have been noted (Flemenbaum, 1971a). Some amphetamine-like drugs m
most combinations have not been studied. When amphetamine analogs are being used to treat obesity, it sh
moderate weight gain (Russ & Ackerman, 1988). False positive urine tests for amphetamines have been repo
& Browning, 1993). Caution is advised when concurrent administration of amphetamine-like agents and TCAs
monitored for increased cardiovascular effects (hypertension and dysrhythmias).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other sympatho
increased cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Inf

capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006; Flemenbaum, 1972). Use caution if closely for hypertension and dysrhythmias.
7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission
8) Literature Reports
a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agen amphetamine with TCAs such as desipramine or protriptyline results in sustained increases in d-amphet VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tab 2006).
b) Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism c imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transdermal system, 2006).
c) Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases i effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of comb methylphenidate usually results in the blood pressure returning to normotensive levels; reinstitution of th pressure elevation (Flemenbaum, 1971; Flemenbaum, 1972).
d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine g fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical doubled steady-state plasma levels of desipramine (Price et al, 1990).
e) There have been claims based on uncontrolled studies that a better antidepressant response may oc 1969). However, a systemic review of stimulants in the treatment of depression concluded that although ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated litt appear to be as effective as the conventional antidepressants in primary depression (Satel & Nelson, 19

3.5.1.S Iproniazid
1) Interaction Effect: hypertensive crisis (headache, palpitation, and neck stiffness)
2) Summary: Coadministration of methylphenidate and a monoamine oxidase inhibitor may result in hyperte such as headache, palpitation, neck stiffness, nausea, and vomiting. Hypertensive crisis associated with mor Info Concerta(TM), 2000). The concomitant administration of methylphenidate with monoamine oxidase inhib be initiated, the monoamine oxidase inhibitor must be discontinued for a minimum of 14 days (Prod Info DAY
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent use of monoamine oxidase inhibitors and methylphenidate is contra the monoamine oxidase inhibitor must be discontinued for a minimum of 14 days.
7) Probable Mechanism: unknown

3.5.1.T Isocarboxazid
1) Interaction Effect: hypertensive crisis (headache, palpitation, and neck stiffness)
2) Summary: Coadministration of methylphenidate and a monoamine oxidase inhibitor may result in hyperte such as headache, palpitation, neck stiffness, nausea, and vomiting. Hypertensive crisis associated with mor Info Concerta(TM), 2000). The concomitant administration of methylphenidate with monoamine oxidase inhib be initiated, the monoamine oxidase inhibitor must be discontinued for a minimum of 14 days (Prod Info DAY
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent use of monoamine oxidase inhibitors and methylphenidate is contra the monoamine oxidase inhibitor must be discontinued for a minimum of 14 days.
7) Probable Mechanism: unknown

3.5.1.U Lazabemide
1) Interaction Effect: hypertensive crisis (headache, palpitation, and neck stiffness)
2) Summary: Coadministration of methylphenidate and a monoamine oxidase inhibitor may result in hyperte such as headache, palpitation, neck stiffness, nausea, and vomiting. Hypertensive crisis associated with mor Info Concerta(TM), 2000). The concomitant administration of methylphenidate with monoamine oxidase inhib be initiated, the monoamine oxidase inhibitor must be discontinued for a minimum of 14 days (Prod Info DAY
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent use of monoamine oxidase inhibitors and methylphenidate is contra the monoamine oxidase inhibitor must be discontinued for a minimum of 14 days.
7) Probable Mechanism: unknown

3.5.1.V Linezolid
1) Interaction Effect: hypertensive crisis (headache, palpitation, and neck stiffness)
2) Summary: Coadministration of methylphenidate and a monoamine oxidase inhibitor may result in hyperte such as headache, palpitation, neck stiffness, nausea, and vomiting. Hypertensive crisis associated with mor Info Concerta(TM), 2000). The concomitant administration of methylphenidate with monoamine oxidase inhib be initiated, the monoamine oxidase inhibitor must be discontinued for a minimum of 14 days (Prod Info DAY
3) Severity: contraindicated

4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent use of monoamine oxidase inhibitors and methylphenidate is contra
the monoamine oxidase inhibitor must be discontinued for a minimum of 14 days.
7) Probable Mechanism: unknown

3.5.1.W Lofepramine

1) Interaction Effect: hypertension, other cardiac effects, and CNS stimulation
2) Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been reporte
from the release of norepinephrine (Beaumont, 1973; Raisfeld, 1972). A similar reaction might also occur wit
Acute elevations in blood pressure have been noted (Flemenbaum, 1971a). Some amphetamine-like drugs n
most combinations have not been studied. When amphetamine analogs are being used to treat obesity, it sh
moderate weight gain (Russ & Ackerman, 1988). False positive urine tests for amphetamines have been repo
& Browning, 1993). Caution is advised when concurrent administration of amphetamine-like agents and TCAs
monitored for increased cardiovascular effects (hypertension and dysrhythmias).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other sympatho
increased cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Inf
capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006; Flemenbaum, 1972). Use caution if
closely for hypertension and dysrhythmias.
7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission
8) Literature Reports
a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agen
amphetamine with TCAs such as desipramine or protriptyline results in sustained increases in d-amphet
VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tab
2006).
b) Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism o
imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transdermal system, 2006).
c) Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases i
effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of comb
methylphenidate usually results in the blood pressure returning to normotensive levels; reinstitution of th
pressure elevation (Flemenbaum, 1971; Flemenbaum, 1972).
d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine g
fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical
doubled steady-state plasma levels of desipramine (Price et al, 1990).
e) There have been claims based on uncontrolled studies that a better antidepressant response may oc
1969). However, a systemic review of stimulants in the treatment of depression concluded that although
ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated litt
appear to be as effective as the conventional antidepressants in primary depression (Satel & Nelson, 19

3.5.1.X Moclobemide

1) Interaction Effect: hypertensive crisis (headache, palpitation, and neck stiffness)
2) Summary: Coadministration of methylphenidate and a monoamine oxidase inhibitor may result in hyperte
such as headache, palpitation, neck stiffness, nausea, and vomiting. Hypertensive crisis associated with mor
Info Concerta(TM), 2000). The concomitant administration of methylphenidate with monoamine oxidase inhib
be initiated, the monoamine oxidase inhibitor must be discontinued for a minimum of 14 days (Prod Info DAY
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent use of monoamine oxidase inhibitors and methylphenidate is contra
the monoamine oxidase inhibitor must be discontinued for a minimum of 14 days.
7) Probable Mechanism: unknown

3.5.1.Y Nefazodone

1) Interaction Effect: increased selective serotonin reuptake inhibitor plasma concentrations
2) Summary: Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metab
(SSRIs). Downward dose adjustments of the SSRI may be necessary when it is used concurrently with meth
discontinuing methylphenidate, the SSRI dose may need to be adjusted as needed (Prod Info METADATE C
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Use caution when prescribing methylphenidate to patients who take an selective se
use of methylphenidate and an SSRI may cause elevated SSRI plasma concentrations. Consider a decrease
coadministered. Additionally, consider adjusting the SSRI dose if necessary when initiating or discontinuing n
CD(R) extended-release oral capsules, 2007).
7) Probable Mechanism: inhibition of selective serotonin reuptake inhibitor metabolism by methylphenidate

3.5.1.Z Nialamide

1) Interaction Effect: hypertensive crisis (headache, palpitation, and neck stiffness)
2) Summary: Coadministration of methylphenidate and a monoamine oxidase inhibitor may result in hyperte
such as headache, palpitation, neck stiffness, nausea, and vomiting. Hypertensive crisis associated with mor
Info Concerta(TM), 2000). The concomitant administration of methylphenidate with monoamine oxidase inhib
be initiated, the monoamine oxidase inhibitor must be discontinued for a minimum of 14 days (Prod Info DAY
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent use of monoamine oxidase inhibitors and methylphenidate is contra
the monoamine oxidase inhibitor must be discontinued for a minimum of 14 days.
7) Probable Mechanism: unknown

3.5.1.AA Nortriptyline

1) Interaction Effect: hypertension, other cardiac effects, and CNS stimulation
2) Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been reporte
from the release of norepinephrine (Beaumont, 1973; Raisfeld, 1972). A similar reaction might also occur wit
Acute elevations in blood pressure have been noted (Flemenbaum, 1971a). Some amphetamine-like drugs m
most combinations have not been studied. When amphetamine analogs are being used to treat obesity, it sh
moderate weight gain (Russ & Ackerman, 1988). False positive urine tests for amphetamines have been repo
& Browning, 1993). Caution is advised when concurrent administration of amphetamine-like agents and TCA
monitored for increased cardiovascular effects (hypertension and dysrhythmias).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other sympatho
increased cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Inf
capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006; Flemenbaum, 1972). Use caution if
closely for hypertension and dysrhythmias.
7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission
8) Literature Reports

a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agen
amphetamine with TCAs such as desipramine or protriptyline results in sustained increases in d-amphet
VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tab
2006).

b) Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism o
imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transdermal system, 2006).

c) Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases i
effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of comb
methylphenidate usually results in the blood pressure returning to normotensive levels; reinstitution of th
pressure elevation (Flemenbaum, 1971; Flemenbaum, 1972).

d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine g
fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical
doubled steady-state plasma levels of desipramine (Price et al, 1990).

e) There have been claims based on uncontrolled studies that a better antidepressant response may oc
1969). However, a systemic review of stimulants in the treatment of depression concluded that although
ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated litt
appear to be as effective as the conventional antidepressants in primary depression (Satel & Nelson, 19

3.5.1.AB Opipramol

1) Interaction Effect: hypertension, other cardiac effects, and CNS stimulation
2) Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been reporte
from the release of norepinephrine (Beaumont, 1973; Raisfeld, 1972). A similar reaction might also occur wit
Acute elevations in blood pressure have been noted (Flemenbaum, 1971a). Some amphetamine-like drugs m
most combinations have not been studied. When amphetamine analogs are being used to treat obesity, it sh
moderate weight gain (Russ & Ackerman, 1988). False positive urine tests for amphetamines have been repo
& Browning, 1993). Caution is advised when concurrent administration of amphetamine-like agents and TCA
monitored for increased cardiovascular effects (hypertension and dysrhythmias).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other sympatho
increased cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Inf
capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006; Flemenbaum, 1972). Use caution if
closely for hypertension and dysrhythmias.
7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission
8) Literature Reports

a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agen amphetamine with TCAs such as desipramine or protriptyline results in sustained increases in d-amphet VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tab 2006).
b) Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism c imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transdermal system, 2006).
c) Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases i effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of comb methylphenidate usually results in the blood pressure returning to normotensive levels; reinstitution of th pressure elevation (Flemenbaum, 1971; Flemenbaum, 1972).
d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine g fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical doubled steady-state plasma levels of desipramine (Price et al, 1990).
e) There have been claims based on uncontrolled studies that a better antidepressant response may oc 1969). However, a systemic review of stimulants in the treatment of depression concluded that although ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated litt appear to be as effective as the conventional antidepressants in primary depression (Satel & Nelson, 19

3.5.1.AC Pargyline

1) Interaction Effect: hypertensive crisis (headache, palpitation, and neck stiffness)
2) Summary: Coadministration of methylphenidate and a monoamine oxidase inhibitor may result in hyperte such as headache, palpitation, neck stiffness, nausea, and vomiting. Hypertensive crisis associated with mor Info Concerta(TM), 2000). The concomitant administration of methylphenidate with monoamine oxidase inhib be initiated, the monoamine oxidase inhibitor must be discontinued for a minimum of 14 days (Prod Info DAY
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent use of monoamine oxidase inhibitors and methylphenidate is contra the monoamine oxidase inhibitor must be discontinued for a minimum of 14 days.
7) Probable Mechanism: unknown

3.5.1.AD Paroxetine

1) Interaction Effect: increased selective serotonin reuptake inhibitor plasma concentrations
2) Summary: Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metab (SSRIs). Downward dose adjustments of the SSRI may be necessary when it is used concurrently with meth discontinuing methylphenidate, the SSRI dose may need to be adjusted as needed (Prod Info METADATE C
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Use caution when prescribing methylphenidate to patients who take an selective se use of methylphenidate and an SSRI may cause elevated SSRI plasma concentrations. Consider a decrease coadministered. Additionally, consider adjusting the SSRI dose if necessary when initiating or discontinuing m CD(R) extended-release oral capsules, 2007).
7) Probable Mechanism: inhibition of selective serotonin reuptake inhibitor metabolism by methylphenidate

3.5.1.AE Phenelzine

1) Interaction Effect: hypertensive crisis (headache, palpitation, and neck stiffness)
2) Summary: Coadministration of methylphenidate and a monoamine oxidase inhibitor may result in hyperte such as headache, palpitation, neck stiffness, nausea, and vomiting. Hypertensive crisis associated with mor Info Concerta(TM), 2000). The concomitant administration of methylphenidate with monoamine oxidase inhib be initiated, the monoamine oxidase inhibitor must be discontinued for a minimum of 14 days (Prod Info DAY
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent use of monoamine oxidase inhibitors and methylphenidate is contra the monoamine oxidase inhibitor must be discontinued for a minimum of 14 days.
7) Probable Mechanism: unknown

3.5.1.AF Phenobarbital

1) Interaction Effect: increased phenobarbital plasma concentrations
2) Summary: Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metab Downward dose adjustments of phenobarbital may be necessary when it is used concurrently with methylphe may need to be monitored when initiating or discontinuing methylphenidate and phenobarbital dose adjusted transdermal system, 2006).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of methylphenidate and phenobarbital may increase phenobarbita

metabolism by methylphenidate. Consider a decrease in phenobarbital dose when these agents are coadmin
phenobarbital concentrations when initiating or discontinuing methylphenidate and adjust phenobarbital dose
7) Probable Mechanism: inhibition of phenobarbital metabolism by methylphenidate

3.5.1.AG Phenytoin

1) Interaction Effect: increased phenytoin plasma concentrations
2) Summary: Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metab
Downward dose adjustments of phenytoin may be necessary when it is used concurrently with methylphenida
need to be monitored when initiating or discontinuing methylphenidate and phenytoin dose adjusted as neces
system, 2006).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of methylphenidate and phenytoin may increase phenytoin levels
methylphenidate. Consider a decrease in phenytoin dose when these agents are coadministered. Additionally
concentrations when initiating or discontinuing methylphenidate and adjust phenytoin dose if necessary.
7) Probable Mechanism: inhibition of phenytoin metabolism by methylphenidate

3.5.1.AH Primidone

1) Interaction Effect: increased primidone plasma concentrations
2) Summary: Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metab
Downward dose adjustments of primidone may be necessary when it is used concurrently with methylphenida
need to be monitored when initiating or discontinuing methylphenidate and primidone dose adjusted as neces
system, 2006).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of methylphenidate and primidone may increase primidone levels
methylphenidate. Consider a decrease in primidone dose when these agents are coadministered. Additionally
concentrations when initiating or discontinuing methylphenidate and adjust primidone dose if necessary.
7) Probable Mechanism: inhibition of primidone metabolism by methylphenidate

3.5.1.AI Procarbazine

1) Interaction Effect: hypertensive crisis (headache, palpitation, and neck stiffness)
2) Summary: Coadministration of methylphenidate and a monoamine oxidase inhibitor may result in hyperte
such as headache, palpitation, neck stiffness, nausea, and vomiting. Hypertensive crisis associated with mor
Info Concerta(TM), 2000). The concomitant administration of methylphenidate with monoamine oxidase inhib
be initiated, the monoamine oxidase inhibitor must be discontinued for a minimum of 14 days (Prod Info DAY
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent use of monoamine oxidase inhibitors and methylphenidate is contra
the monoamine oxidase inhibitor must be discontinued for a minimum of 14 days.
7) Probable Mechanism: unknown

3.5.1.AJ Protriptyline

1) Interaction Effect: hypertension, other cardiac effects, and CNS stimulation
2) Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been reporte
from the release of norepinephrine (Beaumont, 1973; Raisfeld, 1972). A similar reaction might also occur with
Acute elevations in blood pressure have been noted (Flemenbaum, 1971a). Some amphetamine-like drugs m
most combinations have not been studied. When amphetamine analogs are being used to treat obesity, it sh
moderate weight gain (Russ & Ackerman, 1988). False positive urine tests for amphetamines have been repo
& Browning, 1993). Caution is advised when concurrent administration of amphetamine-like agents and TCAs
monitored for increased cardiovascular effects (hypertension and dysrhythmias).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other sympatho
increased cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Inf
capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006; Flemenbaum, 1972). Use caution if
closely for hypertension and dysrhythmias.
7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission
8) Literature Reports
a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agen
amphetamine with TCAs such as desipramine or protriptyline results in sustained increases in d-amphet
VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tab
2006).
b) Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism c

imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transdermal system, 2006).
c) Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases i
effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of comb
methylphenidate usually results in the blood pressure returning to normotensive levels; reinstitution of th
pressure elevation (Flemenbaum, 1971; Flemenbaum, 1972).
d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine g
fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical
doubled steady-state plasma levels of desipramine (Price et al, 1990).
e) There have been claims based on uncontrolled studies that a better antidepressant response may oc
1969). However, a systemic review of stimulants in the treatment of depression concluded that although
ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated litt
appear to be as effective as the conventional antidepressants in primary depression (Satel & Nelson, 19

3.5.1.AK Rasagiline

1) Interaction Effect: hypertensive crisis (headache, palpitation, and neck stiffness)
2) Summary: Coadministration of methylphenidate and a monoamine oxidase inhibitor may result in hyperte
such as headache, palpitation, neck stiffness, nausea, and vomiting. Hypertensive crisis associated with mor
Info Concerta(TM), 2000). The concomitant administration of methylphenidate with monoamine oxidase inhib
be initiated, the monoamine oxidase inhibitor must be discontinued for a minimum of 14 days (Prod Info DAY
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent use of monoamine oxidase inhibitors and methylphenidate is contra
the monoamine oxidase inhibitor must be discontinued for a minimum of 14 days.
7) Probable Mechanism: unknown

3.5.1.AL Selegiline

1) Interaction Effect: hypertensive crisis (headache, palpitation, and neck stiffness)
2) Summary: Coadministration of methylphenidate and a monoamine oxidase inhibitor may result in hyperte
such as headache, palpitation, neck stiffness, nausea, and vomiting. Hypertensive crisis associated with mor
Info Concerta(TM), 2000). The concomitant administration of methylphenidate with monoamine oxidase inhib
be initiated, the monoamine oxidase inhibitor must be discontinued for a minimum of 14 days (Prod Info DAY
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent use of monoamine oxidase inhibitors and methylphenidate is contra
the monoamine oxidase inhibitor must be discontinued for a minimum of 14 days.
7) Probable Mechanism: unknown

3.5.1.AM Sertraline

1) Interaction Effect: increased selective serotonin reuptake inhibitor plasma concentrations
2) Summary: Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metab
(SSRIs). Downward dose adjustments of the SSRI may be necessary when it is used concurrently with methy
discontinuing methylphenidate, the SSRI dose may need to be adjusted as needed (Prod Info METADATE C
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Use caution when prescribing methylphenidate to patients who take an selective se
use of methylphenidate and an SSRI may cause elevated SSRI plasma concentrations. Consider a decrease
coadministered. Additionally, consider adjusting the SSRI dose if necessary when initiating or discontinuing m
CD(R) extended-release oral capsules, 2007).
7) Probable Mechanism: inhibition of selective serotonin reuptake inhibitor metabolism by methylphenidate

3.5.1.AN Toloxatone

1) Interaction Effect: hypertensive crisis (headache, palpitation, and neck stiffness)
2) Summary: Coadministration of methylphenidate and a monoamine oxidase inhibitor may result in hyperte
such as headache, palpitation, neck stiffness, nausea, and vomiting. Hypertensive crisis associated with mor
Info Concerta(TM), 2000). The concomitant administration of methylphenidate with monoamine oxidase inhib
be initiated, the monoamine oxidase inhibitor must be discontinued for a minimum of 14 days (Prod Info DAY
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent use of monoamine oxidase inhibitors and methylphenidate is contra
the monoamine oxidase inhibitor must be discontinued for a minimum of 14 days.
7) Probable Mechanism: unknown

3.5.1.AO Tranylcypromine

1) Interaction Effect: hypertensive crisis (headache, palpitation, and neck stiffness)

2) Summary: Coadministration of methylphenidate and a monoamine oxidase inhibitor may result in hyperte such as headache, palpitation, neck stiffness, nausea, and vomiting. Hypertensive crisis associated with mor Info Concerta(TM), 2000). The concomitant administration of methylphenidate with monoamine oxidase inhib be initiated, the monoamine oxidase inhibitor must be discontinued for a minimum of 14 days (Prod Info DAY
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent use of monoamine oxidase inhibitors and methylphenidate is contra the monoamine oxidase inhibitor must be discontinued for a minimum of 14 days.
7) Probable Mechanism: unknown

3.5.1.AP Trimipramine

1) Interaction Effect: hypertension, other cardiac effects, and CNS stimulation
2) Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been reporte from the release of norepinephrine (Beaumont, 1973; Raisfeld, 1972). A similar reaction might also occur wit Acute elevations in blood pressure have been noted (Flemenbaum, 1971a). Some amphetamine-like drugs m most combinations have not been studied. When amphetamine analogs are being used to treat obesity, it sh moderate weight gain (Russ & Ackerman, 1988). False positive urine tests for amphetamines have been repo & Browning, 1993). Caution is advised when concurrent administration of amphetamine-like agents and TCAs monitored for increased cardiovascular effects (hypertension and dysrhythmias).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other sympatho increased cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Inf capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006; Flemenbaum, 1972). Use caution if closely for hypertension and dysrhythmias.
7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission
8) Literature Reports

a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agen amphetamine with TCAs such as desipramine or protriptyline results in sustained increases in d-amphet VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tab 2006).

b) Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism o imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transdermal system, 2006).

c) Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases i effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of comb methylphenidate usually results in the blood pressure returning to normotensive levels; reinstitution of th pressure elevation (Flemenbaum, 1971; Flemenbaum, 1972).

d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine g fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical doubled steady-state plasma levels of desipramine (Price et al, 1990).

e) There have been claims based on uncontrolled studies that a better antidepressant response may oc 1969). However, a systemic review of stimulants in the treatment of depression concluded that although ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated litt appear to be as effective as the conventional antidepressants in primary depression (Satel & Nelson, 19

3.5.1.AQ Tyrosine

1) Interaction Effect: increased adverse effects
2) Summary: Tyrosine prolonged the effect of methylphenidate in rats (Woods & Meyer, 1991a).
3) Severity: moderate
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Caution is advised if tyrosine and methylphenidate are used together. Monitor the p methylphenidate.
7) Probable Mechanism: not specified
8) Literature Reports

a) Exogenous tyrosine supplementation prolonged the effect of methylphenidate (MPD) in rats. Simultar MPD into the nucleus accumbens of Sprague-Dawley rats resulted in potentiation and prolongation of th final 20 minutes of infusion when dopamine concentrations already declined during the MPD-alone expe maximum MPD effect was observed (Woods & Meyer, 1991).

3.5.1.AR Warfarin

1) Interaction Effect: increased warfarin plasma concentrations and an increased risk of bleeding
2) Summary: Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metab warfarin. Downward dose adjustments of warfarin may be necessary when it is used concurrently with methy should be closely monitored, when initiating or discontinuing methylphenidate, and should be reassessed per dose adjustments may be made as necessary in order to maintain the desired level of anticoagulation (Prod I

2006).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of methylphenidate and warfarin may increase warfarin levels due methylphenidate. Consider a decrease in warfarin dose when these agents are coadministered. Additionally, discontinuing methylphenidate and adjust warfarin dose if necessary.
7) Probable Mechanism: inhibition of warfarin metabolism by methylphenidate

3.5.1.AS Zimeldine
1) Interaction Effect: increased selective serotonin reuptake inhibitor plasma concentrations
2) Summary: Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metab (SSRIs). Downward dose adjustments of the SSRI may be necessary when it is used concurrently with methy discontinuing methylphenidate, the SSRI dose may need to be adjusted as needed (Prod Info METADATE C
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Use caution when prescribing methylphenidate to patients who take an selective se use of methylphenidate and an SSRI may cause elevated SSRI plasma concentrations. Consider a decrease coadministered. Additionally, consider adjusting the SSRI dose if necessary when initiating or discontinuing n CD(R) extended-release oral capsules, 2007).
7) Probable Mechanism: inhibition of selective serotonin reuptake inhibitor metabolism by methylphenidate

3.5.5 Intravenous Admixtures

Drugs

Solutions

3.5.5.1 Drugs

Amobarbital

Dextran

Methohexital

Pentobarbital

Phenobarbital

Procainamide

Procaine

Secobarbital

Thiopental

3.5.5.1.A Amobarbital
1) Incompatible
a) Methylphenidate (incompatible with amobarbital; conditions not specified) (Kramer et al, 1971)

3.5.5.1.B Dextran
1) Compatible
a) Dextran 70 6% in Dextrose 5% in water with methylphenidate 30 mg/L, physically compatible for al, 1961b; Smith, 1965)
b) Dextran 70 6% in Sodium chloride 0.9% with methylphenidate 30 mg/L, physically compatible fo al, 1961b; Smith, 1965)

3.5.5.1.C Methohexital
1) Incompatible
a) Methohexital (barbiturates physically incompatible with methylphenidate; drug concentrations an

3.5.5.1.D Pentobarbital
1) Incompatible
a) Pentobarbital (barbiturates physically incompatible with methylphenidate; drug concentrations an

3.5.5.1.E Phenobarbital
1) Incompatible
a) Methylphenidate 1 mL, reconstituted, with phenobarbital 1 mL, reconstituted, both added to Steri was reported within 2 hours; exact drug concentrations not specified (Misgen, 1965a)
b) Phenobarbital barbiturates physically incompatible with methylphenidate; drug concentrations an

3.5.5.1.F Procainamide
1) Compatible
a) Methylphenidate 1 mL, reconstituted, with procainamide 1 mL, reconstituted, both added to Steri for 2 hours (Misgen, 1965).

3.5.5.1.G Procaine
1) Compatible
a) Procaine (0.1% in Sodium chloride 0.9% with methylphenidate 30 mg/L physically compatible; cc
b) Methylphenidate (30 mg/L with procaine 1 g/L physically compatible in Sodium chloride 0.9%; cc

3.5.5.1.H Secobarbital
1) Incompatible
a) Secobarbital (barbiturates physically incompatible with methylphenidate; drug concentrations anc

3.5.5.1.I Thiopental
1) Incompatible
a) Thiopental (barbiturates physically incompatible with methylphenidate; drug concentrations and c
b) Methylphenidate (incompatible with barbiturates; conditions not specified) (Kramer et al, 1971a)

3.5.5.2 Solutions

ALKALINE SOLUTIONS

Dextrose 10% in lactated Ringer's injection

Dextrose 10% in Ringer's injection

Dextrose 10% in Sodium chloride 0.9%

DEXTROSE 10% in water

Dextrose 2.5% in half-strength lactated Ringer's injection

Dextrose 2.5% in half-strength Ringer's injection

Dextrose 2.5% in Sodium chloride 0.45%

Dextrose 2.5% in Sodium chloride 0.9%

DEXTROSE 2.5% in water

DEXTROSE 20% in water

Dextrose 5% in lactated Ringer's injection

Dextrose 5% in Ringer's injection

Dextrose 5% in sodium chloride 0.225%

Dextrose 5% in Sodium chloride 0.45%

Dextrose 5% in Sodium chloride 0.9%

DEXTROSE 5% in water

DEXTROSE 50% in water

FRUCTOSE 10%

FRUCTOSE 10% IN SODIUM CHLORIDE 0.9%

Invert sugar 10%

Invert sugar 10% in sodium chloride 0.9%

Invert sugar 5%

Invert sugar 5% in sodium chloride 0.9%

IONOSOL(R) B IN DEXTROSE 5%

Ionosol(R) D, modified in invert sugar 10%

IONOSOL(R) DCM

IONOSOL(R) DCM IN DEXTROSE 5%

IONOSOL(R) D IN DEXTROSE 10%

Ionosol(R) D in invert sugar 10%

IONOSOL(R) G IN DEXTROSE 10%

IONOSOL(R) G IN INVERT SUGAR 10%

IONOSOL(R) K IN INVERT SUGAR 10%

IONOSOL(R) MB IN DEXTROSE 5%

IONOSOL(R) PSL

Ionosol(R) T in dextrose 5%

LACTATED RINGER'S INJECTION

RINGER'S INJECTION

SODIUM CHLORIDE 0.45%

SODIUM CHLORIDE 0.9%

SODIUM CHLORIDE 3%

SODIUM CHLORIDE 5%

SODIUM LACTATE 1/6 M

3.5.5.2.A ALKALINE SOLUTIONS
1) Incompatible
a) Alkaline solutions (physically incompatible with methylphenidate; conditions not specified) (Kram

3.5.5.2.B Dextrose 10% in lactated Ringer's injection
1) Compatible
a) Methylphenidate 30 mg/L is physically compatible with Dextrose 10% in lactated Ringer's injectio

3.5.5.2.C Dextrose 10% in Ringer's injection
1) Compatible
a) Methylphenidate 30 mg/L is physically compatible with Dextrose 10% in Ringer's injection; condit

3.5.5.2.D Dextrose 10% in Sodium chloride 0.9%
1) Compatible
a) Methylphenidate 30 mg/L is physically compatible with Dextrose 10% in Sodium chloride 0.9%; c

3.5.5.2.E DEXTROSE 10% in water
1) Compatible
a) Methylphenidate 30 mg/L is physically compatible with Dextrose 10% in water; conditions not spe

3.5.5.2.F Dextrose 2.5% in half-strength lactated Ringer's injection
1) Compatible
a) Methylphenidate 30 mg/L is physically compatible with Dextrose 2.5% in half-strength lactated R (Kirkland et al, 1961c)

3.5.5.2.G Dextrose 2.5% in half-strength Ringer's injection
1) Compatible
a) Methylphenidate 30 mg/L is physically compatible with Dextrose 2.5% in half-strength Ringer's in 1961c)

3.5.5.2.H Dextrose 2.5% in Sodium chloride 0.45%
1) Compatible
a) Methylphenidate 30 mg/L is physically compatible with Dextrose 2.5% in Sodium chloride 0.45%

3.5.5.2.I Dextrose 2.5% in Sodium chloride 0.9%
1) Compatible
a) Methylphenidate 30 mg/L is physically compatible with Dextrose 2.5% in Sodium chloride 0.9%;

3.5.5.2.J DEXTROSE 2.5% in water
1) Compatible
a) Methylphenidate 30 mg/L is physically compatible with Dextrose 2.5% in water; conditions not sp

3.5.5.2.K DEXTROSE 20% in water
1) Compatible
a) Methylphenidate 30 mg/L is physically compatible with Dextrose 20% in water; conditions not spe

3.5.5.2.L Dextrose 5% in lactated Ringer's injection
1) Compatible
a) Methylphenidate 30 mg/L is physically compatible with Dextrose 5% in lactated Ringer's injection

3.5.5.2.M Dextrose 5% in Ringer's injection
1) Compatible
a) Methylphenidate 30 mg/L is physically compatible with Dextrose 5% in Ringer's injection; conditi

3.5.5.2.N Dextrose 5% in sodium chloride 0.225%
1) Compatible
a) Methylphenidate 30 mg/L is physically compatible with Dextrose 5% in sodium chloride 0.225%;

3.5.5.2.O Dextrose 5% in Sodium chloride 0.45%
1) Compatible
a) Methylphenidate 30 mg/L is physically compatible with Dextrose 5% in Sodium chloride 0.45%; c

3.5.5.2.P Dextrose 5% in Sodium chloride 0.9%
1) Compatible

a) Methylphenidate 30 mg/L is physically compatible with Dextrose 5% in Sodium chloride 0.9%; co

3.5.5.2.Q DEXTROSE 5% in water

1) Compatible

a) Methylphenidate 30 mg/L is physically compatible with Dextrose 5% in water; conditions not spe

3.5.5.2.R DEXTROSE 50% in water

1) Compatible

a) Methylphenidate 30 mg/L is physically compatible with Dextrose 50% in water; conditions not sp

3.5.5.2.S FRUCTOSE 10%

1) Compatible

a) Fructose 10% (with methylphenidate 30 mg/L physically compatible; conditions not specified) (Ki

b) Methylphenidate (30 mg/L in FRUCTOSE 10% or FRUCTOSE 10% IN SODIUM CHLORIDE 0.9 specified) (Kirkland et al, 1961d)

3.5.5.2.T FRUCTOSE 10% IN SODIUM CHLORIDE 0.9%

1) Compatible

a) Fructose 10% in sodium chloride 0.9% (with methylphenidate 30 mg/L physically compatible; cor

b) Methylphenidate (30 mg/L in FRUCTOSE 10% or FRUCTOSE 10% IN SODIUM CHLORIDE 0.9 specified) (Kirkland et al, 1961d)

3.5.5.2.U Invert sugar 10%

1) Compatible

a) Invert sugar 10% (with methylphenidate 30 mg/L physically compatible; conditions not specified)

b) Methylphenidate (30 mg/L in Invert sugar 10% physically compatible; conditions not specified) (K

3.5.5.2.V Invert sugar 10% in sodium chloride 0.9%

1) Compatible

a) Invert sugar 10% in sodium chloride 0.9% (with methylphenidate 30 mg/L physically compatible;

b) Methylphenidate (30 mg/L in Invert sugar 10% in sodium chloride 0.9% physically compatible; co

3.5.5.2.W Invert sugar 5%

1) Compatible

a) Invert sugar 5% (with methylphenidate 30 mg/L physically compatible; conditions not specified) (

b) Methylphenidate (30 mg/L in Invert sugar 5% physically compatible; conditions not specified) (Ki

3.5.5.2.X Invert sugar 5% in sodium chloride 0.9%

1) Compatible

a) Invert sugar 5% in sodium chloride 0.9% (with methylphenidate 30 mg/L physically compatible; c

b) Methylphenidate (30 mg/L in Invert sugar 5% in sodium chloride 0.9% physically compatible; cor

3.5.5.2.Y IONOSOL(R) B IN DEXTROSE 5%

1) Compatible

a) Ionosol(R) B in dextrose 5% (with methylphenidate 30 mg/L physically compatible; conditions no

3.5.5.2.Z Ionosol(R) D, modified in invert sugar 10%

1) Compatible

a) Ionosol(R) D, modified in invert sugar 10% (with methylphenidate 30 mg/L physically compatible;

3.5.5.2.AA IONOSOL(R) DCM

1) Compatible

a) Ionosol(R) DCM (with methylphenidate 30 mg/L physically compatible; conditions not specified) (

3.5.5.2.AB IONOSOL(R) DCM IN DEXTROSE 5%

1) Compatible

a) Ionosol(R) DCM in dextrose 5% (with methylphenidate 30 mg/L physically compatible; conditions

3.5.5.2.AC IONOSOL(R) D IN DEXTROSE 10%

1) Compatible

a) Ionosol(R) D in dextrose 10% (with methylphenidate 30 mg/L physically compatible; conditions n

3.5.5.2.AD Ionosol(R) D in invert sugar 10%

1) Compatible

a) Ionosol(R) D in invert sugar 10% (with methylphenidate 30 mg/L physically compatible; condition

3.5.5.2.AE IONOSOL(R) G IN DEXTROSE 10%

1) Compatible

a) Ionosol(R) G in dextrose 10% (with methylphenidate 30 mg/L physically compatible; conditions n

3.5.5.2.AF IONOSOL(R) G IN INVERT SUGAR 10%
1) Compatible
a) Ionosol(R) G in invert sugar 10% (with methylphenidate 30 mg/L physically compatible; condition

3.5.5.2.AG IONOSOL(R) K IN INVERT SUGAR 10%
1) Compatible
a) Ionosol(R) K in invert sugar 10% (with methylphenidate 30 mg/L physically compatible; condition

3.5.5.2.AH IONOSOL(R) MB IN DEXTROSE 5%
1) Compatible
a) Ionosol(R) MB in dextrose 5% (with methylphenidate 30 mg/L physically compatible; conditions r

3.5.5.2.AI IONOSOL(R) PSL
1) Compatible
a) Ionosol(R) PSL (with methylphenidate 30 mg/L physically compatible; conditions not specified) (I

3.5.5.2.AJ Ionosol(R) T in dextrose 5%
1) Compatible
a) Ionosol(R) T in dextrose 5% (with methylphenidate 30 mg/L physically compatible; conditions not

3.5.5.2.AK LACTATED RINGER'S INJECTION
1) Compatible
a) Lactated Ringer's injection (with methylphenidate 30 mg/L physically compatible; conditions not s

3.5.5.2.AL RINGER'S INJECTION
1) Compatible
a) Ringer's injection (with methylphenidate 30 mg/L physically compatible; conditions not specified)

3.5.5.2.AM SODIUM CHLORIDE 0.45%
1) Compatible
a) SODIUM CHLORIDE 0.45% (with methylphenidate 30 mg/L physically compatible; conditions no

3.5.5.2.AN SODIUM CHLORIDE 0.9%
1) Compatible
a) SODIUM CHLORIDE 0.9% (with methylphenidate 30 mg/L physically compatible; conditions not

3.5.5.2.AO SODIUM CHLORIDE 3%
1) Compatible
a) SODIUM CHLORIDE 3% (with methylphenidate 30 mg/L physically compatible; conditions not sp

3.5.5.2.AP SODIUM CHLORIDE 5%
1) Compatible
a) SODIUM CHLORIDE 5% (with methylphenidate 30 mg/L physically compatible; conditions not sp

3.5.5.2.AQ SODIUM LACTATE 1/6 M
1) Compatible
a) Sodium lactate 1/6 M (with methylphenidate 30 mg/L physically compatible; conditions not specif
b) Methylphenidate (30 mg/L in Sodium lactate 1/6 M physically compatible; conditions not specifie

4.0 Clinical Applications

Monitoring Parameters

Patient Instructions

Place In Therapy

Mechanism of Action / Pharmacology

Therapeutic Uses

Comparative Efficacy / Evaluation With Other Therapies

4.1 Monitoring Parameters

A) Methylphenidate

1) Therapeutic

a) Physical Findings

1) Improvement in the mental and behavioral symptoms of attention deficit hyperactivity disorder (ADHD hyperactivity, and cognitive performance.

2) Periodic reassessment of the need for continued methylphenidate treatment (by temporarily withdraw behavioral symptoms and their severity; slow dose-tapering may be indicated to prevent withdrawal sym system, 2006).

2) Toxic

a) Laboratory Parameters

1) Monitor CBC, differential, and platelet counts periodically during prolonged therapy (Prod Info DAYTR

b) Physical Findings

1) The American Academy of Pediatrics (AAP) does not recommend the routine use of electrocardiogra evaluations (which were previously recommended by the American Heart Association (AHA) scientific st place the child at risk for sudden cardiac death) before initiating stimulant therapy to treat attention-defici The APA cited specific reasons for changing the recommendation including: lack of evidence establishin treat ADHD and sudden cardiac death (SCD), the frequency of sudden unexpected deaths among patier in the general population of children, and lack of cost-effective analysis to support ECG screening or spe al, 2008).

2) Based on the American Academy of Pediatrics (AAP) and the American Heart Association (AHA) con monitoring recommendations have been established to assist clinicians in the evaluation of children treat methylphenidate, for ADHD (Perrin et al, 2008; Vetter et al, 2008):

- Conduct a thorough examination prior to initiating methylphenidate therapy for a diagnosis of ADH symptoms indicative of a cardiac condition, including palpitations, near syncope, or syncope.
- Obtain a complete family and patient history for conditions associated with SCD, and determine cu counter medications.
- Conduct a complete physical evaluation of the patient for hypertension, cardiac murmurs, physical signs of irregular cardiac rhythms.
- Perform further evaluation if family history, patient history or physical exam is suggestive of cardiac and if indicated, consult pediatric cardiologist .
- Continue to assess the patient for cardiac symptoms and any changes in family history at follow up
- Blood pressure and heart rate should be evaluated at baseline, during routine follow-up within 1 to months. Increases in blood pressure and heart rate have been reported with stimulant use.

3) Assess growth determinations (body weight and height) periodically (Prod Info DAYTRANA(TM) trans

B) Methylphenidate Hydrochloride

1) Therapeutic

a) Attention Deficit Hyperactivity Disorder (ADHD)

1) Improvement in the mental and behavioral symptoms of attention deficit hyperactivity disorder (ADHD hyperactivity, and cognitive performance.

2) Periodic reassessment of the need for continued methylphenidate treatment (by temporarily withdraw behavioral symptoms and their severity; slow dose-tapering may be indicated to prevent withdrawal sym release oral tablets, 2007; Prod Info CONCERTA(R) extended-release oral tablets, 2007).

b) Narcolepsy

1) Decreased frequency of narcoleptic attacks.

2) Toxic

a) Laboratory Parameters

1) Monitor CBC, differential, and platelet counts periodically during prolonged therapy (Prod Info RITALI release tablet, 2004; Prod Info RITALIN LA(R) oral extended-release capsule, 2004; Prod Info METHYLI METHYLIN(R) oral solution, 2004; Prod Info CONCERTA(R) extended-release tablets , 2004; Prod Info 2002).

b) Physical Findings

1) The American Academy of Pediatrics (AAP) does not recommend the routine use of electrocardiogra evaluations (which were previously recommended by the American Heart Association (AHA) scientific st place the child at risk for sudden cardiac death) before initiating stimulant therapy to treat attention-defici The APA cited specific reasons for changing the recommendation including: lack of evidence establishin treat ADHD and sudden cardiac death (SCD), the frequency of sudden unexpected deaths among patier in the general population of children, and lack of cost-effective analysis to support ECG screening or spe al, 2008).

2) Based on the American Academy of Pediatrics (AAP) and the American Heart Association (AHA) con monitoring recommendations have been established to assist clinicians in the evaluation of children treat methylphenidate, for ADHD (Perrin et al, 2008; Vetter et al, 2008):

- Conduct a thorough examination prior to initiating methylphenidate therapy for a diagnosis of ADH symptoms indicative of a cardiac condition, including palpitations, near syncope, or syncope.
- Obtain a complete family and patient history for conditions associated with SCD, and determine cu counter medications.
- Conduct a complete physical evaluation of the patient for hypertension, cardiac murmurs, physical

signs of irregular cardiac rhythms.
- Perform further evaluation if family history, patient history or physical exam is suggestive of cardiac
and if indicated, consult pediatric cardiologist .
- Continue to assess the patient for cardiac symptoms and any changes in family history at follow up
- Blood pressure and heart rate should be evaluated at baseline, during routine follow-up within 1 to
months. Increases in blood pressure and heart rate have been reported with stimulant use.

3) Assess growth determinations (body weight and height) periodically (Prod Info RITALIN(R) oral tablet
2004; Prod Info RITALIN LA(R) oral extended-release capsule, 2004; Prod Info METHYLIN(R) chewable
solution, 2004; Prod Info CONCERTA(R) extended-release tablets , 2004; Prod Info METADATE(R) ER

4.2 Patient Instructions

A) Methylphenidate (Absorbed through the skin)

Methylphenidate

Treats attention deficit hyperactivity disorder (ADHD). This medicine is a stimulant.

When This Medicine Should Not Be Used:
You should not apply this medicine if you or your child have had an allergic reaction to methylphenidate. You shou
or if you are anxious, tense, or agitated most of the time. You should not use this medicine if you have muscle tics
that causes you to have muscle twitches or to make sounds you are not able to control. Do not use this medicine
called an MAO inhibitor (MAOI), such as Eldepryl®, Marplan®, Nardil®, or Parnate®, in the past 14 days. This me
than 6 years of age unless your doctor tells you otherwise.

How to Use This Medicine:
Patch

Your doctor will tell you how many patches to use, where to apply them, and how often to apply them. Do not
than your doctor tells you to.
This medicine should come with a Medication Guide. Read and follow these instructions carefully. Ask your d
Ask your pharmacist for the Medication Guide if you do not have one. Your doctor might ask you to sign some
information.
The Medication Guide will show the body areas where you or your child can wear the patch. When putting on
these areas. Do not put the new patch on the same place you or your child wore the last one. Be sure to rem
Wash your hands with soap and water before and after applying a patch. Make sure the skin area is clean (fr
powder, oil, or lotion before you apply the patch.
Leave the patch in its sealed wrapper until you are ready to put it on. Tear the wrapper open carefully. NEVE
Do not use any patch that has been cut by accident.
Apply the patch right away after removing it from the pouch or sealed wrapper.
Do not put the patch over burns, cuts, or irritated skin.
Put on a new patch if the old one has fallen off and cannot be reapplied. Remove the new patch 9 hours after

If a Dose is Missed:

If you forget to wear or change a patch, put one on as soon as you can. If it is almost time to put on your next
skip the one you missed. Do not apply extra patches to make up for a missed dose.

How to Store and Dispose of This Medicine:

Store the patches at room temperature in a closed container, away from heat, moisture, and direct light.
Throw any used patch away so that children or pets cannot get to it. There is still enough medicine in a used
throwing away a patch, fold it in half with the sticky sides together and flush it down the toilet, and then wash
When you stop treatment with this medicine, take all of the leftover patches out of the pouches and flush ther
the protective liners down the toilet. Put them in a trash can with a cover. You will also need to throw away ol
Keep all medicine away from children and never share your medicine with anyone.

Drugs and Foods to Avoid:
Ask your doctor or pharmacist before using any other medicine, including over-the-counter medicines, vitamins, a

Make sure your doctor knows if you or your child are also using cold or allergy medicines, clonidine (Catapres
(such as captopril, metoprolol, Capoten®, or Lopressor®), a blood thinner (such as warfarin or Coumadin®),
phenytoin, primidone, Dilantin®, or Mysoline®), or medicines to treat depression (such as clomipramine, desi
Anafranil®, Celexa®, Effexor®, Lexapro™, Norpramin®, Paxil®, Tofranil®, or Zoloft®).

Warnings While Using This Medicine:

Make sure your doctor knows if you or your child are pregnant, planning to become pregnant, or breastfeedin
of seizures, heart disease, high blood pressure, depression or mental illness, thyroid problems, skin problems
alcohol problems.
This medicine may be habit-forming. If you feel that the medicine is not working as well, do not use more than
instructions.
Tell your doctor right away if you or your family notices any unusual changes in behavior, such as an increas
suicidal thinking or behaviors. Also tell your doctor if you have hallucinations or any unusual thoughts, especi
This medicine may make you dizzy or drowsy. It may also cause blurred vision or other vision problems. If an

do anything else that could be dangerous if you are not alert or not able to see well.
This medicine may cause slow growth. If your child is using this medicine, the doctor will need to keep track c
that your child is growing properly.
This medicine may cause skin irritation. Tell your doctor about any skin rash that occurs where this medicine
Avoid putting this medicine near external sources of direct heat, such as hair dryers, heating pads, electric bl
Your doctor will need to check your blood at regular visits while you are using this medicine. Be sure to keep

Possible Side Effects While Using This Medicine:
Call your doctor right away if you notice any of these side effects:
Allergic reaction: Itching or hives, swelling in your face or hands, swelling or tingling in your mouth or throat, c
Changes in vision.
Chest pain or shortness of breath.
Convulsions or tremors.
Fast, pounding, or irregular heartbeat.
Fever, chills, runny or stuffy nose, cough, sore throat, and body aches.
Lightheadedness, dizziness, or fainting.
Mood or mental changes, confusion, or unusual behavior.
Seeing, hearing, or feeling things that are not there.
Severe redness, swelling, itching, or blistering of the skin where the patch is worn.
Uncontrollable muscle movements or twitching.

If you notice these less serious side effects, talk with your doctor:
Decreased appetite.
Feeling restless or nervous.
Headache.
Nausea or vomiting.
Trouble sleeping.
Warmth or redness in your child's face, neck, arms, or upper chest.
Weight loss.

If you notice other side effects that you think are caused by this medicine, tell your doctor.

B) Methylphenidate (By mouth)
Methylphenidate

Treats attention deficit hyperactivity disorder (ADHD) and narcolepsy (sudden attacks of uncontrollable sleepines

When This Medicine Should Not Be Used:
You should not use this medicine if you or your child have had an allergic reaction to methylphenidate. You shoul
if you are anxious, tense, or agitated most of the time. You should not use this medicine if you have muscle tics o
that causes you to have muscle twitches or to make sounds you are not able to control. Do not use this medicine
called an MAO inhibitor (MAOI), such as Eldepryl®, Marplan®, Nardil®, or Parnate®, in the past 14 days. This me
years of age unless your doctor tells you otherwise.

How to Use This Medicine:
Long Acting Capsule, Liquid, Tablet, Chewable Tablet, Long Acting Tablet
Your doctor will tell you how much of this medicine to use and how often. Your dose may need to be changed
best for you. Do not use more medicine or use it more often than your doctor tells you to.
This medicine should come with a Medication Guide. Read and follow these instructions carefully. Ask your d
Ask your pharmacist for the Medication Guide if you do not have one. Your doctor might ask you to sign som
information.
You may take this medicine with or without food.
It is best to take the immediate-release tablets 30 to 45 minutes before meals. If you or your child have proble
before 6 p.m.
The extended-release form of this medicine is taken once a day, usually just before the morning meal. Swallo
chew, or crush it. If you or your child cannot swallow the extended-release capsule whole, carefully open the
tablespoon of applesauce. Swallow this mixture right away and drink some water. Do not save the mixture fo
Tell your doctor if you or your child cannot swallow the sustained-release tablet whole. A different medicine m

If a Dose is Missed:
If you miss a dose or forget to use your medicine, use it as soon as you can. If it is almost time for your next c
the missed dose. Do not use extra medicine to make up for a missed dose.

How to Store and Dispose of This Medicine:
Store the medicine in a closed container at room temperature, away from heat, moisture, and direct light.
Ask your pharmacist, doctor, or health caregiver about the best way to dispose of any leftover medicine after
need to throw away old medicine after the expiration date has passed.
Keep all medicine away from children and never share your medicine with anyone.

Drugs and Foods to Avoid:
Ask your doctor or pharmacist before using any other medicine, including over-the-counter medicines, vitamins, a
Make sure your doctor knows if you or your child are also using antacids, certain blood pressure medicines (s
Clorpres®, Combipres®, or Ismelin®), blood thinners (such as warfarin or Coumadin®), cold or allergy medic
(such as amitriptyline, clomipramine, desipramine, imipramine, trazodone, Anafranil®, Celexa®, Effexor®, Lu
Tofranil®, Vivactil®, or Zoloft®), or medicine for seizures (such as phenobarbital, phenytoin, primidone, Dilan

Warnings While Using This Medicine:
Make sure your doctor knows if you or your child are pregnant, planning to become pregnant, or breastfeedin
of seizures, thyroid problems, stomach problems, heart disease, high blood pressure, depression or mental il
doctor if you or anyone in your family has tried to commit suicide or talked about suicide.
This medicine may be habit-forming. If you feel that the medicine is not working as well, do not use more thar
instructions.
This medicine may make you dizzy or drowsy. It may also cause blurred vision or other vision problems. If an
do anything else that could be dangerous if you are not alert or not able to see well.
This medicine may cause slow growth. If your child is using this medicine, the doctor will need to keep track c
that your child is growing properly.
Your doctor will need to check your progress at regular visits while you are using this medicine. Be sure to ke

Possible Side Effects While Using This Medicine:
Call your doctor right away if you notice any of these side effects:
Allergic reaction: Itching or hives, swelling in your face or hands, swelling or tingling in your mouth or throat, c
Chest pain or shortness of breath.
Convulsions or tremors.
Fast, slow, pounding, or irregular heartbeat.
Lightheadedness, dizziness, drowsiness, or fainting.
Mood and mental changes, or unusual behavior.
Seeing, hearing, or feeling things that are not there.
Trouble seeing or blurred vision.
Uncontrollable muscle movements or twitching.
Vomiting, agitation, confusion, sweating, fever, or tremors.

If you notice these less serious side effects, talk with your doctor:
Feeling restless or nervous.
Headache.
Nausea, loss of appetite, or stomach pain.
Runny or stuffy nose, cough, or sore throat.
Trouble sleeping.
Weight loss.

If you notice other side effects that you think are caused by this medicine, tell your doctor.

4.3 Place In Therapy

A) Oral and transdermal methylphenidate are primarily used as an adjunct to the treatment of attention deficit disorde
6 years of age (oral) and 6 to 12 years (transdermal) (Prod Info DAYTRANA(TM) transdermal system, 2006; Prod Info
METHYLIN(R) chewable tablets, 2004; Prod Info RITALIN(R) oral tablet, RITALIN-SR(R) oral tablet, 2004; Prod Info M
2002). Children who exhibit ADHD-like symptoms that are secondary to environmental factors and/or other primary ps
be candidates for use of stimulants such as methylphenidate (Prod Info DAYTRANA(TM) transdermal system, 2006).
Advisory Committee recommends that transdermal methylphenidate be used after oral forms have been considered. T
risks of sensitization of the topical form (FDAAdvisoryCommittee.com, 2005). Patients who develop a contact sensitiza
be able to take methylphenidate in any form (Prod Info DAYTRANA(TM) transdermal system, 2006). Methylphenidate
narcolepsy.
B) Sustained-release methylphenidate (MSR) therapy for cognitive impairment in HIV-1-infected substance abusers r
neuropsychological test performance when compared to placebo treatment in a pilot study. However, when used as a
confirm superiority over placebo (van Dyck et al, 1997).
C) Other potential therapeutic uses of methylphenidate include treatment of depression, chronic pain, brain tumors, sy
cocaine abuse (Frye, 1997; Emptage & Semla, 1996; Plutchik et al, 1998; Grade et al, 1998; Meyers et al, 1998; Levin
1987; Grubb et al, 1996; Whyte et al, 1997).

4.4 Mechanism of Action / Pharmacology

A) MECHANISM OF ACTION
1) Methylphenidate is a mild central nervous system stimulant; the drug has similar pharmacological properties a
activity and minimal effects on the cardiovascular system. Although its exact mechanism of action is not known, m
brainstem arousal system, cortex, and subcortical structures including the thalamus to produce its stimulant effect
exerts its behavioral effects in children has not been determined (Prod Info DAYTRANA(TM) transdermal system,
B) REVIEW ARTICLES
1) A review of the efficacy and safety of methylphenidate treatment in children with attention deficit disorder acco
cancer, epilepsy, traumatic brain injury, encephalitis, and mental retardation has been provided (Weber & Lutschg

2) The OROS(R) extended-release formulation of methylphenidate is reviewed, including pharmacodynamics, ph
al, 2001).

4.5 Therapeutic Uses

Methylphenidate

Methylphenidate Hydrochloride

4.5.A Methylphenidate

4.5.A.1 Attention deficit hyperactivity disorder

FDA Labeled Indication

a) Overview

FDA Approval: Adult, no; Pediatric, yes (6 to 12 years)
Efficacy: Pediatric, Effective
Recommendation: Pediatric, Class IIb
Strength of Evidence: Pediatric, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Transdermal methylphenidate, in a 9-hour of delivery once daily dose, is an effective treatment of at
providing symptom reduction (McGough et al, 2006)
Transdermal methylphenidate is indicated for the treatment of attention deficit hyperactivity disorder
DAYTRANA(TM) transdermal system, 2006)
Transdermal methylphenidate improves behavior measures when compared to placebo (Pelham et
Long-term effects (greater than 7 weeks) in children have not been well established (Prod Info DAY

c) Pediatric:

1) In pediatric patients age 6 to 12 years with attention deficit hyperactivity disorder (ADHD), the use of
wear time of 9 hours resulted in optimal treatment results when compared with placebo (PTS), according
Patients with a mean age 9.1 years, 72% male, and a total score of 26 or higher on the ADHD rating sca
who were known to be responsive to stimulants, or naive to stimulants (37%) were included in the intent
optimization phase, patients were randomized to receive one of 4 optimized daily doses of MTS (n=41) c
optimized to the MTS patch delivering 16 or 20 mg dose over 9 hours. After one week of treatment, patie
following week. All patients attended 2 days of simulated classroom, which provided 12 to 14 hours of ob
performance data. Patients in the MTS group performed significantly better compared with the PTS grou
(Swanson, Kotkin, Agler, M-Flynn and Pellham Teacher Rating Scale). The least square (LS) mean of th
significantly lower (improved) (3.2 +/- 0.58) compared with the PTS group (8 +/- 0.58, p less than 0.0001
post-dose assessment at 2 hours, continuing through the final 12 hour postdose assessment. Comparing
number of math problems attempted was 113.8 versus 86.2 (difference of 27.5, 95% CI, 19.48 - 35.59, p
math problems correct was 109.4 versus 80.7 (difference of 28.7, 95% CI, 21.09 - 35.34, p less than 0.0
Global Impressions) the MTS group was more likely rated as improved compared with the PTS group (79
on the parent rated CGI-I scores of 71.1% versus 15.8% (p less than 0.0001). In the safety assessment
emergent adverse events in 24 patients recorded in the MTS group compared with 25 events in 18 patie
occurring 2% or more, comparing the MTS with the PTS group, the incidence of any adverse effect was
nausea (3% vs 0%) (McGough et al, 2006).

2) Transdermal methylphenidate (MTS) was effective for the treatment of attention deficit hyperactivity d
double-blind, placebo-controlled, randomized trial. All patients received MTS in an open-label phase to d
15 mg, 20 mg, and 30 mg for 5 weeks). Then patients were randomized to placebo or MTS patch (at the
for 9 hours every day, then removed. The primary efficacy outcome was the mean differences in change
Agler, M-Flynn, and Pelham) Deportment Scores between MTS and placebo. Children were evaluated b
setting. From 2 hours after patch application through 12 hours after application, SKAMP Scores improve
Info DAYTRANA(TM) transdermal system, 2006).

3) Transdermal methylphenidate (MTS) was effective for the treatment of attention deficit hyperactivity d
double-blind, placebo-controlled, randomized trial. Children were randomized to placebo or MTS patch in
milligrams (mg), 15 mg, 20 mg, and 30 mg for 5 weeks. Then the patients were followed for 2 weeks dur
dose. The patch was worn for 9 hours every day, then removed. The primary efficacy outcome was the r
ADHD-Rating Scale-IV between MTS and placebo. ADHD-Rating Scale-IV improved statistically more w
the study did not allow for evaluation of a dose-response, in general, there did not appear to be improved
9 hours to 30 mg over 9 hours (Prod Info DAYTRANA(TM) transdermal system, 2006).

4) In a multicenter, double-blind, randomized, dose-ranging study of transdermal methylphenidate (MTS
MTS were superior to placebo in behavioral measures. Enrolled in the study were 33 boys and 3 girls, ag
the summer treatment program. Patients were randomized to receive placebo, MTS 6.25 centimeters sq
(2), worn for at least 12 hours daily. The time of application was also studied along with the dose and pat
patch either 60 or 120 minutes before the start of the summer treatment program day. Therefore, there w
administered one time to each patient. Patients were instructed to continue their usual medication regime

a placebo practice day. During the day patients participated in both academic and nonacademic activities system that assessed point systems, time outs, and daily report cards. After the 8 study days, the point s noncompliance, interruption, complaining, conduct problems, and negative verbalizations) were all signif placebo in pairwise comparisons (p less than 0.05). The classroom measures for following rules and the significantly improved at all MTS doses compared to placebo in pairwise comparisons (p less than 0.05). among the groups for the amount of classroom work completed correctly. The daily report cards also sho groups and the placebo group in pairwise comparisons (p less than 0.05). The most common side effects across doses) and trouble sleeping (47% of the children across doses), with incidence increasing with hi in 40% to 50% of the patients, more incidence on active MTS than placebo days (Pelham et al, 2005).
5) Transdermal methylphenidate (MTS) combined with behavioral modification produced significant imp hyperactivity disorder (ADHD) compared to either treatment alone. The study enrolled 25 boys and 2 girl in a summer treatment program. Patients were randomly assigned to receive placebo, MTS 12.5 centime cm(2) on Monday through Thursday for 24 days. The drug conditions were double-blind and varied on a drug condition once each week. All of the MTS doses were applied at 7 a.m. and removed at 3:30 p.m. E basis, so each patient had 2 days in each medication condition without behavioral treatment and 4 days treatment. The children spent 2 hours each day in an academic setting and the remainder of their day co behavior was assessed using a point system (following activity rules, rule violations, noncompliance, inte negative verbalizations), classroom measures (rule violations, completed work and accuracy of complete tests showed significant improvement at all three doses of MTS compared to placebo in point system crit daily report cards (all doses of MTS compared to placebo in pairwise tests, p less than 0.05). Exceptions not statistically significant at any dose of MTS regardless of behavior modification, interruption was not s modification and completion of classroom work was not significant at MTS 12.5 cm(2) with no behavior m adverse effect that increased as the dose increased was loss of appetite (Pelham et al, 2005).

4.5.B Methylphenidate Hydrochloride

Attention deficit hyperactivity disorder

Autistic disorder

Bipolar disorder; Adjunct

Bulimia nervosa

Cancer; Adjunct

Cataplexy - Narcolepsy

Cerebral palsy - Spasticity; Adjunct

Cocaine dependence

Dementia

Depression, Combination therapy

Depression, Monotherapy

Epilepsy

Fatigue

Finding related to coordination / incoordination - Impaired cognition

Hiccoughs, Intractable

Indifference

Narcolepsy

Paraphilia; Adjunct

Schizophrenia

Selective serotonin re-uptake inhibitor adverse reaction - Sexual dysfunction

Shivering, Postanesthesia; Treatment and Prophylaxis

Syncope

Traumatic brain injury

4.5.B.1 Attention deficit hyperactivity disorder

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes (Concerta(R), age up to 65 yr); Pediatric, yes (age 6 yr and older)
Efficacy: Adult, Effective; Pediatric, Effective
Recommendation: Adult, Class IIa; Pediatric, Class IIa
Strength of Evidence: Adult, Category B; Pediatric, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

The efficacy of methylphenidate extended-release (ER) tablets (Concerta(R)) for the treatment of AI
double-blind, placebo-controlled, randomized trials involving a total of 627 patients aged 18 to 65 ye
oral tablets, 2008).
Extended-release methylphenidate maintained effectiveness in children aged 6 to 13 years with ADI
(n=407) (Wilens et al, 2005).
Extended-release methylphenidate has been well tolerated and clinically superior to placebo during
involving children with ADHD and who were 6 years of age and older (Greenhill et al, 2002; Pelham
Extended-release methylphenidate demonstrated equivalent efficacy to immediate-release methylph
controlled trials involving children aged 6 and older with a diagnosis of ADHD (Pelham et al, 2001; W
The racemic mixture of L- and D-amphetamine was equivalent to methylphenidate in the treatment o
placebo-controlled trial (n=25) and was still effective 4 to 5 hours post-administration (Pelham et al,
Oral methylphenidate appears to be safe and effective in children with epilepsy who are seizure free
starting methylphenidate therapy (Gross-Tsur et al, 1997a).
Both methylphenidate and clonidine are beneficial in ADHD with tics; however, the combination app
agent alone (Anon, 2002a).

c) Adult:

1) The efficacy of methylphenidate extended-release (ER) tablets (Concerta(R)) was demonstrated in tw
randomized trials involving a total of 627 patients aged 18 to 65 years who had been diagnosed with atte
first study was a 7-week dose-titration study which randomized 226 patients to treatment with methylphe
per day or placebo. Incremental increases of 18 mg/day in the methylphenidate ER dose were allowed b
108 mg/day. The primary outcome measure was change from baseline on the Adult ADHD Investigator R
mean change scores for the investigator rating on the AISRS demonstrated a statistically significant impr
compared with placebo. The second study was a 5-week, fixed dose study which randomized 401 patien
or placebo. Primary outcome measure was improvement in the Conners' Adult ADHD Rating Scale (CAA
all doses of methylphenidate ER was statistically significant compared with placebo (Prod Info CONCER
2) Methylphenidate in doses of 10 to 90 milligrams (mg) orally daily was reported more effective than pla
disorder, residual type, in adults in a double-blind crossover trial (Wender et al, 1985). A moderate-to-ma
patients (57%), as compared to only 4 patients (11%) receiving placebo. Improvement was observed in a
lability and impulsivity.

d) Pediatric:

1) Monotherapy - Extended Release

a) In a multisite, open-label study once daily OROS methylphenidate (Concerta(R)) was found to m
deficit/hyperactivity disorder (ADHD) for up to 2 years. A total of 407 children between the ages of 6
229 children completed the 24-month trial. Patients were initially assigned to receive one of three do
milligrams (mg) once daily) which was based on their dose in a previous efficacy or pharmacokinetic
downward in 18 mg increments throughout the 24 month trial depending on clinical response and ad
medication reduced or stopped for weekends or non-school days and to take medication holidays. E
parents/caregivers, teachers and researchers by using the Global Assessment of Effectiveness ratir
all groups throughout the study period. Values for parent/caregiver global assessment ranged from 8
Investigator assessment for the second year of treatment ranged from 91% to 95%. Parent treatmer
pleased, very pleased, or extremely pleased with OROS methylphenidate at the time of their last ob
dose increased 26% from baseline (35.2 mg (baseline) to 44.2 mg (month 21/24)). The majority of r
the 407 children treated in the study, 363 (89.2%) reported at least one adverse event, and 282 (69.

investigators deemed to be possibly related to OROS methylphenidate (headache, insomnia, decrea were no significant differences found in patients expected height and weight for their age at the end slight changes in blood pressure and heart rate throughout the study with the only significant increas +/- 8.1 mmHg at baseline to 108.1 +/- 8.7 mmHg at end of study; p less than 0.0001). No clinically s liver function tests were found throughout the trial (Wilens et al, 2005).

b) In a 2-week, unpublished double-blind study involving 134 children with ADHD (6 to 12 years), m (Ritalin(R) LA) 10 to 40 milligrams (mg) daily were statistically superior to placebo in improving symp Scale for Teachers (CADS-T) during the second week (first-week data not provided). The dose rang a previous dose-titration phase (Prod Info RITALIN LA(R) oral extended-release capsule, 2004).

c) Compared with placebo, a 3-week course of once daily methylphenidate (Metadate CD(R)) (give significantly improved symptoms of attention-deficit hyperactivity disorder over the course of the mo double-blind, multi-center trial (n=321 children, 6 to 16 years of age). The form of methylphenidate u formulation (also called 'modified-release'), which released approximately 30% of its dose on an imn release. Subjects (n=158) randomized to methylphenidate (MPH) initiated therapy as 20 milligrams titrated to effect (maximum 60 mg/day), with the mean dose reaching 40.7 mg/day (1.28 mg/kilogran teacher-rated Conners' Global Index dropped from 12.7 to 4.9 in the MPH group after 3 weeks, whe placebo group (p less than 0.001, MPH versus control (least squares mean)). For MPH-treated chilc 4.8 and the mean afternoon score to 5.4, showing that MPH had a sustained effect throughout the s parents demonstrated a similar pattern to that of teachers (a drop of 6.2 versus 2.8 points for MPH a Clinical Global Impression ratings by investigators classified 64% of the MPH group as responders (with 27% of the placebo group. Most common adverse effects were headache, anorexia, abdominal occurring significantly more often in the MPH group than in controls (9.7% vs 2.5%; p=0.007). Two M adverse events. No serious side effects were reported in either group (Greenhill et al, 2002).

d) In a double-blind, cross-over study (n=68), 7-day courses of EXTENDED-RELEASE METHYLPH demonstrated equivalent efficacy to IMMEDIATE-RELEASE METHYLPHENIDATE given 3 times a were significantly superior to PLACEBO for treatment of attention- deficit/hyperactive disorder (ADH who met diagnostic criteria for ADHD (DSM-IV) and who had received a stable dose of MPH for at le the 3 established MPH dose levels. The dose levels were: (1) Concerta(R) 18 milligrams (mg) once Concerta(R) 36 mg once daily or IR MPH 10 mg 3 times a day; or (3) Concerta(R) 54 mg once daily dosing in the study was 35 mg of Concerta(R) and 29 mg of immediate release (IR) MPH. Teachers card which was sent home to the child's parents (who provided rewards for a positive report card). T Inattention/Overactivity (I/O) with Aggression (IOWA) Conners Rating Scale. Parents also completec Scales each week. Children attended 3 Saturday Laboratory Sessions, with ratings made on acader On all domain ratings by all reviewers in all settings, Concerta(R) and IR MPH provided significantly than 0.001). The only differences between the 2 MPH formulations was in 2 parent ratings (I/O and (R) significantly better than IR MPH ratings (p less than 0.05). In the laboratory sessions, rule violati observed disruptive behaviors were significantly different for MPH (both forms) compared with place withdrawals due to adverse events occurred. Most common adverse effects of MPH were headache of motor tics, all during IR MPH therapy. Poor sleep was reported in 16%, 7%, and 10% of recipients dosing, respectively. Usual appetite was reported for 77%, 66%, and 59% during the same 3 treatm diastolic blood pressure were significantly higher in both MPH groups (p less than 0.05), as was mea (Pelham et al, 2001).

e) In a multi-center, double-blind trial (n=277), a 4-week course of Concerta(R) (EXTENDED-RELE demonstrated to be significantly more effective than placebo (p less than 0.001), and to have similar (IR MPH) in children 6 to 12 years of age with attention-deficit/hyperactive disorder. Enrollees were OROS 18 milligrams (mg) once daily or IR MPH 5 mg 3 times a day; (2) OROS 36 mg once daily or mg once daily or IR MPH 15 mg 3 times a day. Children who had not received MPH previously parti determine their MPH dose; those who had previously used MPH were converted to one of the estab OROS, IR MPH, or placebo. Average total daily dose was 29.5 mg/day for those taking the immedia extended-release form-OROS (n=94). The primary efficacy measure was the IOWA Conners Rating and Oppositional/Defiance subscales completed by both teachers and parents. Ratings on the IOW efficacy for extended-release and immediate-release methylphenidate. Fifty- nine subjects discontin placebo group, 11 (16%) from the extended-release group, and 10 (14%) from the immediate-releas during the study. No significant difference between groups was observed in sleep quality; more chilc as eating less than usual compared with the control group. Five patients had tics reported as advers (Wolraich et al, 2001)

2) Monotherapy - Immediate Release

a) General Information

1) Controlled, blinded studies have shown methylphenidate to be effective in increasing attentic hyperkinetic children (Barkley & Cunningham, 1979)(Charles et al, 1979a; Klorman et al, 1979). occur in restrictive environments, and not in "free play" settings (Barkley & Cunningham, 1979). drug improves the behavioral style, not learning efficiency (Whalen et al, 1979) and has adverse Cunningham, 1979b) and judgmental behavior. Other studies have found that methylphenidate function, motor performance, social behavior, and right hemisphere functioning, but has little eff 1996; Famularo & Fenton, 1987; Werry et al, 1980). Tachyphylaxis may occur (Charles et al, 19 effective in children with epilepsy who are seizure free, while receiving antiepileptic drugs, befor et al, 1997a).

b) The racemic mixture of L and D-amphetamine (Adderall(R)) was as least as effective as methylp

attention deficit hyperactivity disorder (ADHD), and was more effective at 4 to 5 hours post-administ duration of action). In this within-subject, double-blind, placebo-controlled, crossover study, 25 childı methylphenidate 10 milligram (mg), 17.5 mg, Adderall(R) 7.5 mg, 12.5 mg, and placebo twice a day manner every day for 24 days. Teachers and counselors rated their behavior throughout the day an duration of action (noon and 5 p.m.). Parents rated them at the end of the day and in the evening fo placebo, Adderall(R) and methylphenidate significantly improved in-school behaviors (p less than 0. measures (p less than 0.0001), recess violations (p less than 0.0001), and after-school behaviors (p significantly affected by time (p less than 0.01). Adderall(R) consistently resulted in higher effect size consistently resulted in higher ES than lower doses. Adderall(R) was also significantly more effectiv day (p less than 0.05). The ES of both drugs dropped at midday and steadily increased in the aftern afternoon dose. Side effects were reported more frequently with Adderall(R) but did not preclude the eliminated from the study due to exacerbation of his motor tic condition. Further studies are needed Adderall(R), and to compare the efficacy of methylphenidate to D-amphetamine (Pelham et al, 1999

c) Two double-blind, randomized, cross-over trials evaluating the effectiveness of various drug deliv acute tolerance to methylphenidate may exist in the treatment of children with attention deficit hyper methylphenidate delivery patterns (twice-daily, flat, and ascending) and placebo were compared. Th methylphenidate was designed to produce typical school day peak and trough concentrations. The f peak followed by a uniform methylphenidate concentration throughout the day. The ascending regim level from a low drug concentration early in the morning to a high drug concentration by the end of t less efficacious for measures of efficacy than the twice daily regimen in the afternoon, which sugges methylphenidate concentrations may be emerging throughout the day. In Study II, 32 children were daily, ascending, and placebo) where the timing of the middle bolus of the three-times daily regimen after the 7:30 am dose. Only small increases in efficacy were measured in the tid-am regimen after in efficacy in the tid-pm regimen following the second dose. Following the administration of the third efficacy was observed in the tid-am regimen compared with small increases in efficacy for the tid-pm suggests a consistency with the tolerance hypothesis. The results of Study I and Study II support th to the reduced efficacy of sustained-release drug delivery compared with immediate-release drug de 1999a).

d) Methylphenidate 0.4 to 1.2 milligrams/kilogram (mg/kg)/day, in two divided doses, was reported children with attention deficit disorder without hyperactivity (ages, 7 to 12 years). During one acaden resulted in an improvement in school grades, when compared to a preceding grading period and the that methylphenidate may be useful in this type of attention deficit disorder and controlled studies ar

3) Use In Patients With Epilepsy

a) Use of methylphenidate (0.3 milligram/kilogram once daily) appears to be safe and effective to tr (ADHD) in children with EPILEPSY who are seizure free, while receiving antiepileptic drugs, before month study involving 30 children with epilepsy and ADHD, none of the 25 children who were seizur seizures while taking methylphenidate. Of the 5 children continuing to have seizures despite antiepil showed no change or a reduction in seizures while receiving methylphenidate. In this study methylp However, the authors advise that caution is warranted for those children still having seizures while r 1997a).

4) Use In Patients With Neurofibromatosis

a) Use of methylphenidate can improve cognitive, academic, and social behavior in children with at neurofibromatosis type 1 (NF1). This study involved children with ADHD and NF1 (n=20), those with normally developing children (n=14). Methylphenidate was given to each child in the ADHD-NF1 gro of methylphenidate (5 to 15 milligrams (mg) daily; average 7.5 mg) to children with ADHD and NF1 of Variables of Attention (TOVA) scores and the Child Behavior Checklist (CBCL) scores. In additior behavior improved and aggressive behavior declined in children with ADHD and NF1. Children in th significant improvement in measured variables (Mautner et al, 2002).

5) Use In Patients With Tourette's Syndrome Or Tics

a) In children with attention deficit hyperactive disorder (ADHD) and TICS (both by DSM-IV criteria) (MPH) alone, or combination CLONIDINE/MPH provided symptomatic improvement in ADHD withou CLONIDINE/MPH combination therapy provided the greatest benefit. This finding emanated from a years of age (n=136). Subjects were randomized to placebo (n=32), clonidine alone starting at 0.1 m 5 mg/day (n=37), or combination clonidine/MPH (n=33). Average daily doses were 0.25 mg for cloni MPH, 25.7 mg for MPH alone, and 26.1 mg for MPH given with clonidine. Based on the primary end Teacher), a significant treatment effect was observed for clonidine (compared to no clonidine; p=0.0 p=0.003), and either clonidine or MPH was more effective than placebo (both p=0.02). However, the was seen with combination clonidine/MPH (p less than 0.0001 compared to placebo). Worsening of 8 receiving MPH alone, 6 on combination clonidine/MPH, and 7 receiving placebo. Compared with p treatment groups according to the Yale Global Tic Severity Scale, the Global Tic Rating Scale, and were well tolerated except for sedation caused by clonidine; 48% of those receiving clonidine report clonidine seemed to be most helpful for impulsivity and hyperactivity, while MPH appeared most hel

b) Tourette's syndrome may be exacerbated or precipitated by the use of stimulant medications for children. Early signs of Tourette's Syndrome or TICS are difficult to distinguish from hyperactive and therefore mistakenly be treated with stimulant medications (dextroamphetamine, methylphenidate, p the severe motor and phonic tics requiring discontinuation of the stimulants and possible institution having an attention deficit disorder, clinical evaluation for Tics and Tourette's Syndrome in the childr stimulant medication. In children with no symptoms of Tourette's Syndrome but with a familial histor

The use of stimulants is contraindicated in children with Tourette's Syndrome. If tics occur during sti
discontinued (Lowe et al, 1982a).
c) Although stimulant therapy was suspected to exacerbate tics, LONG-TERM methylphenidate tre
effective in children with attention-deficit hyperactivity disorder (ADHD) AND CHRONIC MULTIPLE
In this 2-year non-blinded, prospective, follow-up study, 32 children (age ranging from 6.1 and 11.9
methylphenidate from a previous trial (mean 16.5 milligrams (mg), range=5 to 40 mg). The children
months for 2 years for their on-task, fidgeting, worksheet behaviors, and vocal and motor tic frequen
significantly worse at baseline than placebo (p ranging from less than 0.001 to 0.03). There was no
methylphenidate. ADHD behaviors were not significantly different between baseline and placebo, wl
task during the medication conditions than placebo (p less than 0.001). There was no significant diff
when compared to growth table values. Systolic blood pressure and heart rate were significantly inc
considered clinically insignificant. Although this study showed methylphenidate did not worsen tics ir
the possibility of individual exacerbation of tic cannot be ruled out (Gadow et al, 1999a). In another s
syndrome, abrupt withdrawal of methylphenidate and dextroamphetamine in long-term therapy DID
frequency (Nolan et al, 1999a).

4.5.B.2 Autistic disorder

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Pediatric, Evidence is inconclusive
Recommendation: Pediatric, Class IIb
Strength of Evidence: Pediatric, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Methylphenidate may be useful in the treatment of autism
Methylphenidate may improve concentration, hyperactivity, constructive behavior, and stereotyped r
sadness and exacerbate temper tantrums

c) Pediatric:

1) One group of investigators reported the efficacy of methylphenidate 10 to 50 milligrams daily (mean,
an open study involving 9 children (4 to 16 years of age). All children improved significantly during treatm
movements or significant toxicity. The authors suggest that a placebo-controlled, two month study of hyp
evaluate the efficacy of methylphenidate in this patient population (Birmaher et al, 1988).
2) Methylphenidate 10 milligrams orally twice daily was reported beneficial in a 6-year-old boy with autis
randomly administered methylphenidate or placebo daily, under double-blind conditions. Methylphenidat
and hyperactivity, as well as constructive behavior and stereotyped movements; negative effects were ol
exacerbation of temper tantrums); however, beneficial effects were considered to outweigh these negati
suggests that methylphenidate may not be contraindicated in autistic children. More studies are required
in autism.

4.5.B.3 Bipolar disorder; Adjunct

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class III
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Some DEPRESSED patients with bipolar disorder experienced symptomatic improvement with methylph

c) Adult:

1) In a small 12-week, open-label pilot study (n=14), the addition of METHYLPHENIDATE to mood stab
symptoms to some depressed patients with bipolar disorder. Ten patients had bipolar type I illness (DSM
had a manic episode secondary to controlled hydrocephalus or antidepressant therapy. All had a score
Depression (HAM-D). Methylphenidate was started at 5 milligrams (mg) twice daily and titrated based or
completing the study (9) and 10 mg in those who discontinued (5). Terminations were secondary to deve
agitation (1), anxiety (1), alcohol abuse (1), and lost to follow-up (1). HAM-D scores dropped from baseli
Psychiatric Symptom Assessment Scale (PSAS) scores dropped from 17.9 to 4.8 (p=0.016) (El-Mallakh,

4.5.B.4 Bulimia nervosa

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class III
Strength of Evidence: Adult, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Possibly effective in the treatment of bulimia nervosa with cluster B personality disorder

c) Adult:

1) Methylphenidate (MPH) was effective in the treatment of 2 patients with bulimia nervosa associated v

Bulimics with cluster B personality disorder responded poorly to psychotherapy and antidepressant treat
these treatments and were put on MPH therapy. Patient 1, a 20-year-old woman with 5-year history of bu
disorders, had symptoms of attention deficient hyperactivity disorder (ADHD) since age 7. She was put c
noon, and 5 mg at 5 p.m. At 10 months after discharge, her urges to binge and induce vomiting had sign
scale, ranging from 0 to 36, improved from an average 12.6 to 2.6 on the first 3 days of MPH 20 mg/day
improved from an average of 28.9 to 16.3. Patient 2, a 38-year-old woman with 20-year history of bulimia
generalized anxiety disorder, and major depressive disorder, improved her anxiety and depression with p
did not improve on her binging and purging. She was treated with MPH 5 mg 3 times per day for 1 month
purging, and decreased impulsivity. Her Conner score improved from 34 to 13. A trial of PEMOLINE was
Her symptoms of bulimia nervosa and irritability returned. She was put on long-acting MPH with reduced
MPH may be useful in the treatment of bulimics with cluster B personality disorder. Further studies are n
drug abuse potential in this population, MPH treatment was not recommended by the authors at this time

4.5.B.5 Cancer; Adjunct

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Methylphenidate may improve neurobehavioral functioning in patients with malignant brain tumors
Effective for depression associated with cancer
Methylphenidate may be effective for alleviating fatigue in patients with advanced cancer
Methylphenidate may enhance the analgesic efficacy of narcotic analgesics and decrease sedation
advanced cancer

c) Adult:

1) BRAIN TUMORS

a) Methylphenidate may improve neurobehavioral functioning in patients with malignant brain tumo
result of their disease and/or treatment (i.e., radiation and chemotherapy). In this study, patients (n=
methylphenidate 10 to 30 milligrams twice daily. Methylphenidate treatment was associated with sub
and daily functioning. Results of neuropsychologic tests indicate improvements in psychomotor spee
motor speed, executive function, and fine-motor coordination. Subjective functional improvements ir
concentration, brighter mood, improved motivation, and increased stamina. In addition, the majority
to decrease their dose. Adverse effects were minimal, no patient experienced an increase in seizure
(Meyers et al, 1998a).

2) DEPRESSION

a) A report of the efficacy of methylphenidate in the treatment of depression in cancer patients has
Methylphenidate was given in doses of 10 milligrams orally three times daily initially, with subsequer
period of 2 to 3 days; increases to a maximum of 80 milligrams daily were permitted by week 2 of tre
marked improvement, with 13 showing moderate improvement; maximum improvement was genera

3) FATIGUE

a) Methylphenidate may be effective for alleviating fatigue in patients with advanced cancer. In this
years) with advanced cancer were given methylphenidate 5 to 30 milligrams daily for a mean evalua
considered responders (at least 30% improvement). Mean visual analogue scale (VAS) scores for fa
54, respectively (p=0.01). According to log-rank test, there was a significant difference in survival tim
vs 36 days, respectively; p=0.01). Adverse effects were relatively mild and reversible (Sugawara et a

4) PAIN

a) Methylphenidate doses of 15 milligrams (mg) orally daily (10 mg orally at breakfast; 5 mg orally a
was reported to enhance the analgesic efficacy of the narcotic agents and decrease sedation in pati
advanced cancer (Bruera et al, 1987a). Patients were receiving either morphine, hydromorphone, le

4.5.B.6 Cataplexy - Narcolepsy

See Drug Consult reference: NARCOLEPSY AND CATAPLEXY - DRUG THERAPY

4.5.B.7 Cerebral palsy - Spasticity; Adjunct

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class III
Strength of Evidence: Adult, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Effective in relieving spasticity and dystonia in one patient with cerebral palsy

c) Adult:

1) Methylphenidate was effective in alleviating SPASTICITY and DYSTONIA in a 44-year-old woman wi
in a wheelchair due to marked spasticity of the legs and choreoathetosis of the face, trunk, and upper ex
clonazepam, biperiden, trihexyphenidyl, diazepam, tizanidine, and baclofen had little benefit. Botuline to

successful. Methylphenidate 10 milligrams (mg) twice a day markedly improved her spasticity and chore returned during an interruption of the treatment. The patient's neurologic condition continued to be stable 1 year. No side effects were noted (Boogerd & Beijnen, 2000).

4.5.B.8 Cocaine dependence

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class III
Strength of Evidence: Adult, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Methylphenidate may be effective in the treatment of adults with attention deficit hyperactivity disord
Limited data indicate that methylphenidate is ineffective in the treatment of cocaine abusers without

c) Adult:

1) Results of a 12-week open trial suggest that methylphenidate combined with relapse prevention thera hyperactivity disorder (ADHD), cocaine craving, and cocaine use in adults with ADHD and cocaine depe sustained-release methylphenidate 40 to 80 milligrams/day in 2 divided doses along with weekly relapse indicated significant reductions in attention difficulties, hyperactivity, impulsivity, cocaine use, and craving urinalysis (Levin et al, 1998a).

2) Methylphenidate therapy (5 to 20 milligrams (mg) four times daily) was reported ineffective in the mar involving 5 cocaine abusers (without attention deficit disorders). Clinical improvement or cocaine abstine al, 1985).

4.5.B.9 Dementia

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class III
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Efficacy in the treatment of senile dementia is questionable; available data are anecdotal
Some of the negative symptoms associated with vascular dementia or dementia of Alzheimer's type
Withdrawn, non-agitated patients with moderate dementia are most likely to respond to methylpheni

c) Adult:

1) Results of an open-label, non-blinded preliminary study indicate that the negative symptoms associat Alzheimer's type respond to methylphenidate (10 to 20 milligrams/day). Results were similar for Alzheim patients. Depressive symptoms in this population did not respond to methylphenidate. Some cognitive im dementia, but not in those with dementia of Alzheimer's type. It appears that withdrawn, non-agitated pat to respond to methylphenidate (Galynker et al, 1997a).

2) Methylphenidate has been used to treat senile dementia and is possibly effective; however, there are stems from clinical experience and anecdotes. Most references to the use of methylphenidate (or amphe (Rossman, 1979; Anon, 1978; Yesavage & Hollister, 1978; Borowitz, 1976; Steinberg, 1976).

4.5.B.10 Depression, Combination therapy

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class III
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

A 4-week, randomized, double-blind, placebo-controlled study of patients with treatment-resistant de demonstrated no statistically significant benefit with the addition of extended-release methylphenida antidepressant therapy (n=60) (Patkar et al, 2006)

The results of a small case series involving 5 patients appear to indicate that methylphenidate (10 to augmenting the therapeutic effects of serotonin selective reuptake inhibitors (SSRIs) (eg, fluoxetine, depression (Stoll et al, 1996)

The combination of MAO inhibitors (tranylcypromine, isocarboxazid, phenelzine) and stimulants (am as therapy of severe treatment-resistant depression (Feighner et al, 1985)

The combination of MAO inhibitors and stimulants plus tricyclic antidepressants (amitriptyline, protrip effective and safe in this type of intractable depression (Feighner et al, 1985)

c) Adult:

1) A 4-week, randomized, double-blind, placebo-controlled study of patients with treatment-resistant dep demonstrated no statistically significant benefit with the addition of extended-release methylphenidate hy antidepressant therapy. Patients (n=60; mean age, 48.5 years) with major depressive disorder who had therapy were randomized to either methylphenidate (n=30) or placebo (n=30), with methylphenidate dos

in 18-mg/day increments each week to a maximum dose of 54 mg/day. Subjects maintained their preexis
period. The primary efficacy measurement was the change in the 21-item Hamilton Depression Rating S
treatment), with a response defined as at least 50% reduction and remission defined as a score of 7 or le
were included changes in the Clinical Global Impression-Improvement and Severity (CGI-I and CGI-S, re
Depression Inventory-Second Edition (BDI-II) scores. There were no statistically significant differences b
primary or secondary efficacy measurements. Changes in the mean HAM-D-21 scores were -6.9 for the
group (p=0.22). Patients receiving methylphenidate achieved response and remission (40% and 13.3%,
receiving placebo (23.3% and 3.3%, respectively), but the differences were not statistically significant (p=
statistically significant differences for changes in CGI-I (p=0.34), changes in CGI-S (p=0.18), or BDI-II (p=
moderate in severity and the dropout rates were similar between groups (Patkar et al, 2006).
2) The results of a small case series involving 5 patients appear to indicate that methylphenidate (10 to
augmenting the therapeutic effects of serotonin selective reuptake inhibitors (SSRIs) (eg, fluoxetine, paro
depression. In this series, methylphenidate added to ineffective or only partially effective SSRI treatment
symptoms, without side effects, significant tolerance, or abuse of methylphenidate (Stoll et al, 1996).
3) The combination of MAO inhibitors (tranylcypromine, isocarboxazid, phenelzine) and stimulants (amp
as therapy of severe treatment-resistant depression. In addition, the combination of MAO inhibitors and s
(amitriptyline, protriptyline, amoxapine, nortriptyline) has also been effective and safe in this type of intra
suggested that the following regimen be utilized when combining these agents: (1) the individual drugs a
has had a prior partial response; (2) with combined MAO inhibitor and stimulant therapy, the MAO inhibit
dextroamphetamine or methylphenidate in 2.5 milligrams (mg) increments to stabilize blood pressure an
administering the combination of MAO inhibitors, stimulants, and antidepressants, the tricyclic antidepres
days, adding the MAO inhibitor during the daytime for 4 to 5 days, then adding low doses of the stimulan
response is positive. The most frequent complication of this therapy is orthostatic hypotension; other pati
and agitation. However, no serious side effects or life-threatening reactions were reported.

4.5.B.11 Depression, Monotherapy

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class III
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Improves selected types of depression (Ayd, 1985; Janowsky et al, 1973); (Rickels et al, 1970 & 197
Effective for depression in medically ill elderly patients (Frye, 1997a; Emptage & Semla, 1996a)
Effective for depression associated with cancer and cardiac surgery (Macleod, 1998; Fernandez et a
May be effective for depressive and/or cognitive symptoms in post liver transplant and post-stroke p
1998a)

c) Adult:

1) GENERAL INFORMATION

a) Studies have shown that methylphenidate (10 to 30 milligrams (mg)/day) can improve selected c
et al, 1973); (Rickels et al, 1970 & 1972). However, 1 study found methylphenidate ineffective for de
methylphenidate may exacerbate pre-existing agitation, anxiety, mania, psychosis, or depression. M
safe and effective for the treatment of depression in medically ill elderly patients lacking contraindica
action, usually within 2 to 5 days, is a potential advantage over other antidepressants in this patient
1996a). Methylphenidate has been effective in the treatment of depression associated with cancer a
et al, 1987); (Kaufmann et al, 1984). Methylphenidate may be useful for the treatment of depressive
transplant and post-stroke patients (Grade et al, 1998a; Plutchik et al, 1998a).

2) Results of a small, uncontrolled, preliminary study indicate that methylphenidate may be useful for the
symptoms in post liver transplant patients. In this study, a positive response was reported in 7 of 8 patier
milligrams/day. Methylphenidate was noted to improve cognition, mood, motivation, appetite, and alertne
3) Results of a prospective, randomized, double-blind, placebo- controlled study indicate that methylphe
stroke depression. In this study, acute stroke patients (n=21) receiving methylphenidate (30 milligrams/d
mood, ability to conduct activities of daily living, and motor function than patients receiving placebo. Trea
with an increased number of adverse effects (Grade et al, 1998a).
4) Methylphenidate has been demonstrated to be useful in the treatment of depression following cardiac
milligrams (mg) orally twice daily produced improvement in depressive symptoms following cardiovascul
considered a viable alternative in patients with contradictions to tricyclic antidepressants.
5) A report of the efficacy of methylphenidate in the treatment of depression in cancer patients has beer
Methylphenidate was given in doses of 10 milligrams orally three times daily initially, with subsequent do
2 to 3 days; increases to a maximum of 80 milligrams daily were permitted by week 2 of treatment. Of 30
improvement, with 13 showing moderate improvement; maximum improvement was generally seen by th
6) Methylphenidate in doses of 5 milligrams (mg) orally twice daily, increasing by 5 mg twice daily every
ineffective as an antidepressant in a controlled study involving 20 mildly depressed patients (Hamilton D
1985).

4.5.B.12 Epilepsy

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class III
Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:
Methylphenidate may reduce sedation and fatigue and improve cognition and quality of life in patients wi

c) Adult:
1) Methylphenidate appears to reduce sedation and fatigue and improve cognition and quality of life in p adversely affecting seizure activity. In this open-label, non-randomized, pilot study involving 8 epilepsy p years) on multiple antiepileptic drugs (AEDs), methylphenidate (dosage range 7.5 to 25 milligrams (mg)/ patients' current AED regimens for 3 months. Six of 8 patients were seizure free at baseline, 5 remained experienced an increase, 1 a decrease, and 1 no change in seizure activity. Overall, all quality of life indi scores, and emotional well-being scores showed significant improvement from baseline after methylpher analogue scale fatigue scores decreased 63.3% from baseline (p=0.015). Methylphenidate did not signif serum concentrations of AEDs changed less than 10% from baseline to the end of the study. No serious 2002).

4.5.B.13 Fatigue

a) Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:
May reduce fatigue in some HIV-positive patients
Methylphenidate may be effective for alleviating fatigue in patients with advanced cancer

c) Adult:
1) Methylphenidate may be effective for alleviating fatigue in patients with advanced cancer. In this preli with advanced cancer were given methylphenidate 5 to 30 milligrams daily for a mean evaluation period responders (at least 30% improvement). Mean visual analogue scale (VAS) scores for fatigue before and (p=0.01). According to log-rank test, there was a significant difference in survival time between responde respectively; p=0.01). Adverse effects were relatively mild and reversible (Sugawara et al, 2002).
2) A 6-week course of an oral psychostimulant medication, METHYLPHENIDATE or PEMOLINE, reduc quality of life also tended to improve with methylphenidate and pemoline therapy, and drug-induced side least 5 on a 10-point scale for persistent fatigue. Methylphenidate (n=53) was initiated at 7.5 milligrams (mg/day (mean end-of-study dose 51 mg/day); pemoline (n=45) was started at 18.75 mg twice daily with study dose 96 mg/day). At 6 weeks, total scores on the Piper Fatigue Scale (patient-rated) were significa pemoline-treated subjects compared with placebo (p=0.04). Also, on the patient-rated visual analog scal significantly higher for those receiving methylphenidate or pemoline (p=0.02). No significant differences comparing methylphenidate and pemoline. Significant correlations were found between improvement in f dropped out due to side effects (methylphenidate (2), pemoline (2), control (1)). Only jitteriness and hype often by those on methylphenidate or pemoline than those on placebo (Breitbart et al, 2001a).

4.5.B.14 Finding related to coordination / incoordination - Impaired cognition

a) Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Pediatric, Evidence favors efficacy
Recommendation: Pediatric, Class IIb
Strength of Evidence: Pediatric, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:
Methylphenidate may improve cognitive and motor performance in intellectually subaverage children
May improve attention span in children with neurocognitive impairment related to childhood cancer

c) Pediatric:
1) A double-blind, randomized trial (n=32) provided preliminary evidence that METHYLPHENIDATE ma survived childhood malignant brain tumors (n=25) or acute lymphoblastic leukemia (n=7) but who exhibit for the study included estimated intelligence quotient greater than 50; academic achievement in the sixte math, or spelling; and ability to sustain attention on a computerized performance test in the sixteenth per study protocol, enrollees completed a battery of tests on day 1. On day 2, subjects were randomized to p milligram/kilogram (maximum 20 milligrams) (n=15). Approximately 90 minutes after ingestion of methylp selected portions of the battery of tests. Compared with placebo, methylphenidate-treated subjects had a Conners' Continuous Performance Test (CPT) for sustained attention (p=0.015) and overall index of atte not improved by methylphenidate included errors of commission (indicative of impulsiveness) or reaction scores were not significantly different between methylphenidate-treated patients and controls, and, on a greater improvement in the methylphenidate group but it did not reach statistical significance (Thompson
2) One group of investigators reported a controlled study of methylphenidate and thioridazine in improvi

intellectually subaverage children. Twenty-seven children with subaverage intelligence quotas (IQs) parti
cross-over study comparing methylphenidate (0.4 milligrams/kilogram/day and thioridazine (1.75 milligra
performance, breadth of attention, and performance on a series of electronically-controlled cognitive-mot
a memory task, reduced omission errors on an attention task, and reduced seat movements on two tasks
improving cognitive-motor performance. It did not produce deleterious effects on IQ performance when s
Thioridazine at the given dose did not adversely effect performance on any of the cognitive-motor perfor

4.5.B.15 Hiccoughs, Intractable

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class III
Strength of Evidence: Adult, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Stopped intractable hiccups in one patient in a case report

c) Adult:

1) A 56-year-old man with refractory hiccup was treated with a regimen that included methylphenidate 5
noon as well as haloperidol 4 mg every 8 hours and metoclopramide 10 mg four times a day. The patien
lung cancer and was diagnosed with peptic esophagitis and gastroparesis. Oral haloperidol did not stop
which point the hiccups stopped for 2 days and then restarted. Methylphenidate administration resulted i
free of hiccups until his death 6 weeks later (Marechal et al, 2003).

4.5.B.16 Indifference

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Methylphenidate may improve apathy (Padala et al, 2005)

c) Adult:

1) A case report involving a 47-year-old woman found that treatment with methylphenidate significantly i
improvement in depression. The patient had a 20 year history of recurrent major depression and was dia
initiative and motivation. She had been treated with several antidepressants in the past and was currentl
morning for the past 4 months. Her other current medications included vitamin B12 1000 micrograms (m
0.25 mg at bedtime as needed, and montelukast sodium 10 mg in the evening as needed. Methylphenid
and was increased after one week to 20 mg twice daily due to lack of response. After 4 weeks of treatme
in apathy and scored 31 on the Apathy Evaluation Scale (AES), a 46% reduction from baseline. Her subj
interests with a desire to resume previous employment. She was also able to awaken earlier and felt less
treatment with methylphenidate. Her depression was assessed by the 21-item Hamilton Rating Scale for
unchanged from baseline with a HAM-D of 33. The patient denied experiencing any adverse effects from

4.5.B.17 Narcolepsy

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes (immediate release formulations and Ritalin(R)-SR only); Pediatric, yes (a
and Ritalin(R)-SR only)
Efficacy: Adult, Effective; Pediatric, Effective
Recommendation: Adult, Class IIa; Pediatric, Class IIa
Strength of Evidence: Adult, Category B; Pediatric, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Methylphenidate is effective for the treatment of narcolepsy in adults and children 6 years and over
Methylphenidate improves performance and ability to stay awake
Methylphenidate has been used for various diseases which exhibit hypersomnia as a prominent clin

c) Adult:

1) Methylphenidate (10 to 60 milligrams/day) is indicated for the treatment of narcolepsy in adults and cl
performance and ability to stay awake (Prod Info RITALIN(R) oral tablet, RITALIN-SR(R) oral tablet, 200
1987a; Mitler et al, 1986c; Honda et al, 1979a).

2) Methylphenidate has been shown to be effective in the treatment of post-traumatic narcolepsy. In 1 c
twice daily was successfully used to treat narcolepsy resulting from moderate brain injury. Following the
tetrad of narcolepsy: cataplexy, excessive daytime sleepiness, sleep paralysis, and hypnagogic hallucina
methylphenidate, the patient was completely asymptomatic (Francisco & Ivanhoe, 1996).

3) Methylphenidate has been used for various diseases such as Kleine-Levin syndrome, myotonic dystr
exhibit hypersomnia as a prominent clinical feature. The treatment of HYPERSOMNOLENCE follows the
that the response to CNS stimulants including pemoline, methylphenidate, and dextroamphetamine is les

hypersomnolence, pemoline is usually inadequate so methylphenidate, dextroamphetamine, phenmetraz prescribed (Culebrar, 1996; Guilleminault, 1994; Guilleminault, 1994a; Aoyama et al, 1994; Jozefowicz &

a) In hypersomnolence associated with myotonic dystrophy of a central origin rather than due to sle 40 milligrams/day) has resulted in sustained benefit in some patients for several years (2 to 6 years) al, 1986).

b) KLEINE-LEVIN SYNDROME, a periodic hypersomnia, is a rare primary condition featuring episo hyperphagia and hypersexuality. Episodes typically appear in adolescent males and last from sever remission. In 1 case report, Kleine-Levin syndrome was successfully treated with methylphenidate (1976). In another case report, methylphenidate therapy (40 mg/day) was only partially successful in 1978).

4.5.B.18 Paraphilia; Adjunct

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Effective adjunctive treatment for some cases of paraphilia

c) Adult:

1) An 8-week course of sustained release METHYLPHENIDATE added to selective serotonin reuptake i produced additional improvement in some patients with paraphilia (n=14) or paraphilia-related behavior (study (n=26). Indications for addition of methylphenidate to SSRI therapy included retrospective diagnos residual sexual target symptoms despite SSRI, residual depressive symptoms, relapse of sex/depressive effects such as fatigue. The mean dose of methylphenidate was 40 milligrams (mg)/day (range 20 to 100 outlets per week and minutes per day related to paraphilia decreased significantly during SSRI treatmen methylphenidate AND SSRI treatment, further reductions occurred in total sexual outlets per week (p=0.((p=0.04). With methylphenidate plus an SSRI, total sexual outlet measure decreased by 39% (p=0.003), behavior decreased by 44% (p=0.04). Side effects of methylphenidate therapy (usually managed by dos (1), increased sex drive (1), shallow sleep (2), distractibility (2), and mild anxiety (2) (Kafka & Hennen, 20

4.5.B.19 Schizophrenia

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive; Pediatric, Evidence is inconclusive
Recommendation: Adult, Class III; Pediatric, Class III
Strength of Evidence: Adult, Category C; Pediatric, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Methylphenidate has had some success in the treatment of schizophrenia in adults and children
Methylphenidate may provoke schizophrenic symptoms with intensification of preexisting psychotic s

c) Adult:

1) Methylphenidate 40 milligrams intravenously (over 90 seconds) was reported effective in eliminating l schizophrenic patient who had been unresponsive to intravenous phenobarbital (Frost, 1989).

2) When administered intravenously in a dose of 0.5 milligram/kilogram methylphenidate has provoked s preexisting psychotic symptoms in actively ill patients. It was noted that symptom activation occurred wit minutes and persisted 2 to 6 hours. It was also noted that antipsychotic agents did not appear to effect p (Janowsky et al, 1973).

d) Pediatric:

1) Methylphenidate in doses of 10 milligrams (mg) twice daily in combination with chlorpromazine has b 11-year-old boy. Prior neuroleptic therapy was ineffective (Rogeness & Macedo, 1983).

4.5.B.20 Selective serotonin re-uptake inhibitor adverse reaction - Sexual dysfunction

See Drug Consult reference: SELECTIVE SEROTONIN REUPTAKE INHIBITOR-INDUCED SEXUAL DYSFU

4.5.B.21 Shivering, Postanesthesia; Treatment and Prophylaxis

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Methylphenidate appears to be effective in suppressing post-anesthetic shivering

c) Adult:

1) In a triple-blind study of 153 patients investigators (Liem & Aldrete, 1974) compared the effectiveness methylphenidate (20 mg), calcium chloride (200 mg) and a placebo (normal saline) in the treatment of pc

patients (60.4%) who received magnesium after the injection, whereas 17 of the 42 patients (40.4%) wh
Calcium chloride only stopped shivering in 8 of the 23 patients (34.6%). Seven of 40 patients treated wit
minutes after the injection was given.
2) One study reported that methylphenidate is effective in suppressing shivering after the use of halotha
34 patients who developed shivering following halothane anesthesia. In all 34 cases the methylphenidate
is no indication of any controls used in this report (Imray & White, 1968).

4.5.B.22 Syncope

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class III
Strength of Evidence: Adult, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Methylphenidate may be effective in the treatment of recurrent neurocardiogenic syncope in patients tha
forms of therapy

c) Adult:

1) Methylphenidate may be effective in the treatment of recurrent NEUROCARDIOGENIC SYNCOPE in
tolerant of others forms of therapy. Six of 7 patients with recurrent syncope and positive head upright tilt
to other therapy) became both tilt negative and clinically asymptomatic after receiving methylphenidate 1
(Grubb et al, 1996a).

4.5.B.23 Traumatic brain injury

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy; Pediatric, Evidence favors efficacy
Recommendation: Adult, Class IIb; Pediatric, Class IIb
Strength of Evidence: Adult, Category B; Pediatric, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

May enhance the rate, but not the ultimate level of overall recovery
Improves speed of mental processing

c) Adult:

1) In patients with nonpenetrating traumatic brain injury, methylphenidate significantly improves the spe
placebo-controlled, crossover study, patients (n=19) received methylphenidate 0.25 milligram/kilogram t
attributable to slowed mental processing, but orienting to distractions, sustained attention, and motor spe
speed of mental processing did not generally occur at the expense of accuracy (Whyte et al, 1997a).
2) One group of investigators report that subacute administration of methylphenidate for the treatment o
enhance the rate but not the ultimate level of overall recovery. In this double-blind, placebo-controlled tri
milligram/kilogram (mg/kg) or placebo was administered the day following baseline cognitive assessmen
evaluation at 90 days. Although the methylphenidate group was significantly better on attention tests at 3
patients. No significant difference in cognitive function was seen between the groups at 90 days; howeve
patients (Plenger et al, 1996).

d) Pediatric:

1) Methylphenidate significantly improved the attention and concentration behaviors of children with acq
INJURY. This double blind, placebo-controlled, cross-over study included 14 children with varying degre
or methylphenidate 0.3 milligram/kilogram twice a day at 8 AM and 12 noon for 14 days. Following a 12-
to the other group. The performance of attention and concentration tasks was significantly improved with
placebo (P values ranged from less than 0.04 to less than 0.005). There were not any significant differen
and the placebo. More studies will be needed to determine the long-term benefits of methylphenidate (M

4.6 Comparative Efficacy / Evaluation With Other Therapies

Amphetamine

Clonidine

Dexmethylphenidate

Dextroamphetamine

Lithium

Pemoline

Protriptyline

Thioridazine

4.6.A Amphetamine

4.6.A.1 Attention deficit hyperactivity disorder

a) SUMMARY: In comparative studies, Adderall(R) (combination AMPHETAMINE/DEXTROAMPHETAMINE efficacy in the treatment of attention deficit hyperactive disorder in children. METHYLPHENIDATE requires tv daily doses.

b) The racemic mixture of L- and D-amphetamine (ADDERALL(R)) was at least as effective as methylphenic deficit hyperactivity disorder (ADHD), and was more effective at 4 to 5 hours post-administration (beyond me this within-subject, double-blind, placebo-controlled, crossover study, 25 children with ADHD (mean age 9.6 (mg), 17.5 mg, Adderall(R) 7.5 mg, 12.5 mg, and placebo twice a day (at 7:45 a.m. and 12:15 p.m.) in a rand and counselors rated their behavior throughout the day and at times beyond methylphenidate's expected dur them at the end of the day and in the evening for possible rebound effects. When compared to placebo, Adde improved in-school behaviors (p less than 0.0001 and 0.001, respectively), classroom measures (p less than and after-school behaviors (p less than 0.0001). Drug effects were significantly affected by time (p less than effect size (ES) than methylphenidate and higher doses consistently resulted in higher ES than lower doses. than methylphenidate at midday and end of day (p less than 0.05). The ES of both drugs dropped at midday implicating the possibility of reducing the afternoon dose. Side effects were reported more frequently with Ad medications. Only 1 patient was eliminated from the study due to exacerbation of his motor tic condition. Furt possibility of once daily dosing of Adderall(R), and to compare the efficacy of methylphenidate to D-amphetar

c) Once-daily Adderall(R) (combination AMPHETAMINE/DEXTROAMPHETAMINE) appeared to be as effec treatment of attention deficit hyperactive disorder in children aged 6 to 12 years, according to a double-blind, Also, a mid-afternoon dose of either Adderall or methylphenidate (MPH) produced better evening behavior th although either active treatment tended to induce loss of appetite and sleep difficulties. In a randomized mani received each day 1 of 7 treatment protocols: (1)MPH 0.3 milligram/kilogram (mg/kg) at 7:30, 11:30, and 15:3 MPH 0.15 mg/kg at 15:30; (3)MPH 0.3 mg/kg at 7:30; (4)Adderall 0.3 mg/kg at 7:30 and 15:30; (5)Adderall 0. 15:30; (6)Adderall 0.3 mg/kg at 7:30; or (7)placebo. While twice-daily MPH 0.3 mg/kg did not differ significant single morning-dose MPH 0.3 mg/kg produced less significant effects than either once-daily Adderall 0.3 mg/ MPH began to lose its effectiveness approximately 6.5 hours later. Evening behavior was rated better after M no evening differences were seen after mid-afternoon doses of either 0.3 or 0.15 mg/kg. Children showed dif responded more positively to MPH, 37% responded more positively to Adderall, and 38% responded equally responding more positively to MPH, one dose of MPH was sufficient to carry them all day and into the evenin positively to Adderall needed only once-daily dosing of the drug (Pelham et al, 1999aa).

4.6.B Clonidine

4.6.B.1 Attention deficit hyperactivity disorder

a) In children with attention deficit hyperactive disorder (ADHD) and TICS (both by DSM-IV criteria), CLONID or combination CLONIDINE/MPH provided symptomatic improvement in ADHD without causing worsening of therapy provided the greatest benefit. This finding emanated from a double-blind, multi-center trial in children randomized to placebo (n=32), clonidine alone starting at 0.1 milligram (mg)/day (n=34), MPH alone starting clonidine/MPH (n=33). Average daily doses were 0.25 mg for clonidine alone, 0.28 mg for clonidine given wit MPH given with clonidine. Based on the primary endpoint (Conners Abbreviated Questionnaire-Teacher), a s clonidine (compared to no clonidine; p=0.002), and for MPH (compared to no MPH; p=0.003), and either clon (both p=0.02). However, the greatest improvement on symptomatic ratings was seen with combination clonid placebo). Worsening of tics was reported in 9 receiving clonidine alone, 8 receiving MPH alone, 6 on combin Compared with placebo, severity of tics decreased in all active treatment groups according to the Yale Globa and the Tic Symptom Self-Report. Study medications were well tolerated except for sedation caused by cloni this side effect. The authors observed that clonidine seemed to be most helpful for impulsivity and hyperactiv inattentiveness (Anon, 2002).

b) An open pilot study compared oral and transdermal clonidine to methylphenidate in attention deficit disorc equivalent to methylphenidate (MPH). Both were more effective than placebo. In another study, MPH acted p deficit and moderate hyperactivity. In ADHD children with symptoms of hyperarousal, hyperactivity, and aggr

4.6.C Dexmethylphenidate

4.6.C.1 Attention deficit hyperactivity disorder

a) No comparisons with methylphenidate have been published, and data released by the manufacturer have this data is available. In a completed 4- week, placebo-controlled study described in the package insert (Prod to 20 milligrams (mg) daily was compared to methylphenidate 10 to 40 mg daily (each in two divided doses) i age). Patients included had all subtypes of ADHD (combined type, inattentive type, hyperactive-impulsive typ significantly greater improvement of symptom scores from baseline on the Swanson, Noland, and Pelham (S (mean change, -0.7 versus -0.2). Although methylphenidate was the comparator, no results for methylphenid

b) In manufacturer releases, apparently referring to the same package insert trial described above, the effica reported similar to methylphenidate (Anon, 2001)(Anon, 2001a). Earlier releases also did not indicate a signif drugs (Anon, 1999; Anon, 1999a), although they were carefully prepared to avoid this conclusion.
c) One manufacturer release suggested a longer duration of action of dexmethylphenidate in ADHD; in this s dexmethylphenidate was reportedly seen at all time points, but there was failure of methylphenidate to contro hours postdose) (Anon, 1999). However, the duration of action of methylphenidate was not given, precluding relative to dexmethylphenidate. The duration of dexmethylphenidate in this trial was similar to that of methylp suggesting this difference is small. No study has provided comparative improvements in symptom scores fror points.
d) Available studies have not indicated a more favorable adverse- effect profile for dexmethylphenidate com 2001).

4.6.D Dextroamphetamine

4.6.D.1 Attention deficit hyperactivity disorder

a) SUMMARY: In comparative studies, Adderall(R) (combination AMPHETAMINE/DEXTROAMPHETAMINE efficacy in the treatment of attention deficit hyperactive disorder in children. METHYLPHENIDATE requires tw daily doses.
b) The racemic mixture of L- and D-amphetamine (ADDERALL (R)) was at least as effective as methylpheni deficit hyperactivity disorder (ADHD), and was more effective at 4 to 5 hours post-administration (beyond met this within-subject, double-blind, placebo-controlled, crossover study, 25 children with ADHD (mean age 9.6 y (mg), 17.5 mg, Adderall (R) 7.5 mg, 12.5 mg, and placebo twice a day (at 7:45 a.m. and 12:15 p.m.) in a ranc Teachers and counselors rated their behavior throughout the day and at times beyond methylphenidate's exp Parents rated them at the end of the day and in the evening for possible rebound effects. When compared to significantly improved in-school behaviors (p less than 0.0001 and 0.001, respectively), classroom measures than 0.0001), and after-school behaviors (p less than 0.0001). Drug effects were significantly affected by time resulted in higher effect size (ES) than methylphenidate and higher doses consistently resulted in higher ES t significantly more effective than methylphenidate at midday and end of day (p less than 0.05). The ES of both increased in the afternoon, implicating the possibility of reducing the afternoon dose. Side effects were report preclude the use of both medications. Only 1 patient was eliminated from the study due to exacerbation of his to evaluate the possibility of once daily dosing of Adderall(R), and to compare the efficacy of methylphenidate
c) Once-daily Adderall(R) (combination AMPHETAMINE/DEXTROAMPHETAMINE) appeared to be as effec treatment of attention deficit hyperactive disorder in children aged 6 to 12 years, according to a double-blind, Also, a mid-afternoon dose of either Adderall or methylphenidate (MPH) produced better evening behavior th although either active treatment tended to induce loss of appetite and sleep difficulties. In a randomized mani received each day 1 of 7 treatment protocols: (1)MPH 0.3 milligram/kilogram (mg/kg) at 7:30, 11:30, and 15:3 MPH 0.15 mg/kg at 15:30; (3)MPH 0.3 mg/kg at 7:30; (4)Adderall 0.3 mg/kg at 7:30 and 15:30; (5)Adderall 0. 15:30; (6)Adderall 0.3 mg/kg at 7:30; or (7)placebo. While twice-daily MPH 0.3 mg/kg did not differ significant single morning-dose MPH 0.3 mg/kg produced less significant effects than either once-daily Adderall 0.3 mg/ MPH began to lose its effectiveness approximately 6.5 hours later. Evening behavior was rated better after M no evening differences were seen after mid-afternoon doses of either 0.3 or 0.15 mg/kg. Children showed dif responded more positively to MPH, 37% responded more positively to Adderall, and 38% responded equally responding more positively to MPH, one dose of MPH was sufficient to carry them all day and into the evenin positively to Adderall needed only once-daily dosing of the drug (Pelham et al, 1999a).
d) In a direct, double-blind, cross-over comparison of adverse effect profiles, both DEXTROAMPHETAMINE METHYLPHENIDATE 0.3 mg/kg twice daily were well-tolerated in 125 children with attention deficit disorder reported more frequently during drug therapy than at baseline were appetite suppression (both drugs) and ins severity of adverse effects was significantly higher in the dextroamphetamine group. However, only 1.6% of c because of adverse effects (Efron et al, 1997).

4.6.E Lithium

4.6.E.1 Attention deficit hyperactivity disorder

a) In a preliminary randomized, double-blind, crossover study, lithium and methylphenidate had comparable attention-deficit/hyperactivity disorder (ADHD). Adult patients (n=32) met the Diagnostic and Statistical Manu criteria for ADHD at age 7 years and at the time of the study. Patients were randomly assigned to receive eith 8 weeks of the study, and then switch to the other 8-week treatment arm after a 2-week washout period. For dose of 10 milligrams (mg) once daily for the first 2 weeks; the daily dose was increased by 10 mg every 2 we study arm. For the lithium arm, the initial oral dose was 300 mg once daily for 2 weeks; the daily dose was inc for the 8 week duration of the study arm. After the first 2 weeks of the study arm, lithium and MPH administra study arm, the average daily doses of MPH and lithium carbonate were 38.9 mg and 1173 mg, respectively. the study; 9 patients dropped out due to side effects (4 of 9), lack of perceived benefit (4 of 9), or relocation to improvement of ADHD, as assessed by a 30% or more reduction in the Conners' Adult ADHD Rating Scale s and Impulsivity, was 48% for the MPH arm and 37% for the lithium arm. When evaluating only the patients th improvement rate was 47% and 43% for the MPH and lithium arms, respectively. Side effects included heada orthostatic hypertension. A limitation of the study was the presence of a substantial arm effect, in which the ir maintained during the second arm. In addition, the study had small number of patients and lacked a placebo sequence by arm interaction, suggesting that MPH and lithium had comparable efficacy (Dorrego et al, 2002)

4.6.F Pemoline

Attention deficit hyperactivity disorder

Fatigue

Narcolepsy

4.6.F.1 Attention deficit hyperactivity disorder

a) In a retrospective chart review (n=485), METHYLPHENIDATE (MPD) and PEMOLINE (PEM) were both e hyperactive disorder (ADHD) and attention deficit disorder (ADD) (DSM- IV) in children 4 to 18 years of age; l treatment were shown by more PEM-treated than MPD-treated patients (PEM 225 of 245 (92%); MPD 168 of scale for treatment efficacy ranged from 1 to 4; 1-poor or no response; 2-initially good but not sustained; 3-go efficacy ratings for the MPD and PEM groups were 2.7 and 3.5, respectively. Most frequent adverse effects w and insomnia and irritability for the PEM group. The rates of drug discontinuation for lack of efficacy were 32% Discontinuations due to adverse effects were higher in the PEM group (22% compared with 5% for MPD). No either group. Standard doses were 1.44 milligrams/kilogram (mg/kg) for PEM given once daily and 0.4 mg/kg release form and in 2 or 3 divided doses daily for the immediate-release form. The sustained-release form of the immediate-release form (Andriola, 2000).

4.6.F.2 Fatigue

a) A 6-week course of an oral psychostimulant medication, METHYLPHENIDATE or PEMOLINE, reduced th quality of life also tended to improve with methylphenidate (MPH) and PEMOLINE (PEM) therapy, and drug-i score of at least 5 on a 10-point scale for persistent fatigue. MPH (n=53) was initiated at 7.5 milligrams (mg) t (mean end-of-study dose 51 mg/day); PEM (n=45) was started at 18.75 mg twice daily with maximum titration mg/day). At 6 weeks, total scores on the Piper Fatigue Scale (patient- rated) were significantly improved amo with placebo (p=0.04). Also, on the patient-rated visual analog scale for fatigue (VAS-F), the energy subscore MPH or PEM (p=0.02). No significant differences were found on any outcome measurement comparing MPH between improvement in fatigue and better quality of life. Five patients dropped out due to side effects (MPH hyperactivity were experienced significantly more often by those on MPH or PEM than those on placebo (Bre

4.6.F.3 Narcolepsy

a) One group of investigators studied the efficacy of methylphenidate, pemoline, and protriptyline in the treat data. Six subjects received methylphenidate at dosages of 10 milligrams (mg), 30 mg, and 60 mg/day (1 wee pemoline at dosages of 18.75 mg, 56.25 mg, and 112.5 mg/day (1 week at each dosage). Two subjects recei and 60 mg/day and two subjects received protriptyline dosages of 10 mg, 20 mg, and 40 mg/day (1 week at e randomized from patient to patient. Nine healthy subjects with no sleep disorder received placebos and serve methylphenidate significantly improves the ability of the narcoleptic to stay awake, pemoline seems to improv significantly alter the ability to stay awake or perform. More data are needed to confirm these findings, and fu

4.6.G Protriptyline

4.6.G.1 Narcolepsy

a) Protriptyline did not improve either the ability to stay awake or perform tasks in a double-blind, parallel (by 1986). Three dose levels of 3 drugs were compared in the treatment of narcolepsy in 17 patients. The drugs milligrams (mg)/day), methylphenidate (10, 30, or 60 mg/day) and protriptyline (10, 30, and 60 mg/day). Meth and perform tasks. Pemoline improved the ability to perform tasks, but not to stay awake.

4.6.H Thioridazine

1) Adverse Effects

a) One group of investigators reported a controlled study of methylphenidate and thioridazine in improving co subaverage children. Twenty-seven children with subaverage IQs participated in a double-blind, placebo-con methylphenidate (0.4 milligrams/kilogram/day and thioridazine (1.75 milligrams/kilogram/day. The children we attention, and performance on a series of electronically-controlled cognitive-motor tests. Methylphenidate imp omission errors on an attentional task, and reduced seat movements on two tasks. Thioridazine had no signif performance. It did not produce deleterious effects on IQ performance when subjects received reinforcers for did not adversely effect performance on any of the cognitive-motor performance tests (Aman et al, 1991).

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Last Modified: June 18, 2009

To content

DRUGDEX® Evaluations

DULOXETINE

0.0 Overview

1) Class
- **a)** This drug is a member of the following class(es):
  - Antidepressant
  - Central Nervous System Agent
  - Neuropathic Pain Agent
  - Serotonin/Norepinephrine Reuptake Inhibitor

2) Dosing Information
- **a)** Duloxetine Hydrochloride
  - **1)** Adult
    - **a)** Diabetic peripheral neuropathy - Pain
      - **1)** 60 mg ORALLY once daily (Prod Info CYMBALTA(R) delayed-rele
    - **b)** Fibromyalgia
      - **1)** initial, 30 mg ORALLY once daily for 1 week; increase to recomm CYMBALTA(R) delayed-release oral capsules, 2008)
    - **c)** Generalized anxiety disorder
      - **1)** 60 mg ORALLY once daily, may start at 30 mg ORALLY once dai depending on tolerability (Prod Info CYMBALTA(R) delayed-release
      - **2)** may increase by increments of 30 mg once daily to a MAX of 120 additional benefit in clinical trials (Prod Info CYMBALTA(R) delayed-r
    - **d)** Major depressive disorder
      - **1)** initial (acute), 20 mg ORALLY twice daily up to 60 mg/day (once d release oral capsules, 2008)
      - **2)** maintenance, 60 mg ORALLY once daily (Prod Info CYMBALTA(
    - **e)** Urinary incontinence
      - **1)** 40 mg ORALLY twice daily (clinical trial dosing) (Weinstein et al, 2
  - **2)** Pediatric
    - **a)** safety and efficacy in pediatric patients have not been established (Pro

3) Contraindications
- **a)** Duloxetine Hydrochloride
  - **1)** concomitant use of MAOIs (Prod Info Cymbalta(R) Delayed-release oral ca
  - **2)** narrow-angle glaucoma, uncontrolled; increased risk of mydriasis (Prod Inf

4) Serious Adverse Effects
- **a)** Duloxetine Hydrochloride
  - **1)** Bleeding, Abnormal
  - **2)** Depression, worsening
  - **3)** Hepatotoxicity
  - **4)** Serotonin syndrome
  - **5)** Suicidal thoughts
  - **6)** Withdrawal sign or symptom

5) Clinical Applications
- **a)** Duloxetine Hydrochloride
  - **1)** FDA Approved Indications
    - **a)** Diabetic peripheral neuropathy - Pain
    - **b)** Fibromyalgia
    - **c)** Generalized anxiety disorder
    - **d)** Major depressive disorder
  - **2)** Non-FDA Approved Indications
    - **a)** Urinary incontinence

1.0 Dosing Information

Drug Properties

Storage and Stability

Adult Dosage

Pediatric Dosage

1.1 Drug Properties

A) Information on specific products and dosage forms can be obtained by referring

B) Synonyms

Duloxetine
Duloxetine HCl
Duloxetine Hydrochloride

C) Physicochemical Properties

1) Duloxetine Hydrochloride

a) Molecular Weight

1) 333.88 (Prod Info CYMBALTA(R) delayed-release oral capsules,

b) Solubility

1) Slightly soluble in water (Prod Info CYMBALTA(R) delayed-releas

1.2 Storage and Stability

A) Duloxetine Hydrochloride

1) Preparation

a) Oral route

1) Duloxetine hydrochloride (HCl) capsules should be swallowed wh
food or mixed with liquids. Duloxetine HCl may be given with food or
release oral capsules, 2008).

B) Duloxetine Hydrochloride

1) Oral route

a) Capsule, Delayed Release

1) Store at controlled room temperature, 25 degrees Celsius (77 deg
degrees Celsius (59 and 86 degrees Fahrenheit) (Prod Info CYMBAL

1.3 Adult Dosage

Normal Dosage

Dosage in Renal Failure

Dosage in Hepatic Insufficiency

Dosage in Geriatric Patients

1.3.1 Normal Dosage

1.3.1.A Duloxetine Hydrochloride

1.3.1.A.1 Oral route

Diabetic peripheral neuropathy - Pain

Fibromyalgia

Generalized anxiety disorder

Major depressive disorder

Urinary incontinence

1.3.1.A.1.a Diabetic peripheral neuropathy - Pain

1) The recommended dose of duloxetine for the treatment of ne 60 milligrams (mg) once daily. There is no evidence that doses h lower starting dose may be considered for patients in whom tole oral capsules, 2008).

2) Therapy Withdrawal

a) Abrupt discontinuation of duloxetine has lead to sympton irritability, and nightmare. Gradual reduction of the dose, rat symptoms occur following a decrease in dose, resuming the smaller decreases (Prod Info CYMBALTA(R) delayed-releas

1.3.1.A.1.b Fibromyalgia

1) The recommended dose for the management of fibromyalgia mg once daily for 1 week and increase to 60 mg/day based on tc The duration of maintenance therapy should be based on clinica clinical trials (Prod Info CYMBALTA(R) delayed-release oral cap maintained at 6 months of therapy (Russell et al, 2008). Howeve in clinical trials, even among those who did not respond to the 6(adverse events (Prod Info CYMBALTA(R) delayed-release oral c

2) Therapy Withdrawal

a) Abrupt discontinuation of duloxetine has lead to sympton irritability, and nightmare. Gradual reduction of the dose, rat symptoms occur following a decrease in dose, resuming the smaller decreases (Prod Info CYMBALTA(R) delayed-releas

1.3.1.A.1.c Generalized anxiety disorder

1) The recommended dose of duloxetine for the treatment of ge without regard to meals. If tolerability is a concern, patients may mg once daily. There is no evidence that doses greater than 60 r my be increased by increments of 30 mg once daily to a maximu delayed-release oral capsules, 2008).

2) Therapy Withdrawal

a) Abrupt discontinuation of duloxetine has lead to sympton irritability, and nightmare. Gradual reduction of the dose, rat symptoms occur following a decrease in dose, resuming the smaller decreases (Prod Info CYMBALTA(R) delayed-releas

1.3.1.A.1.d Major depressive disorder

1) Initial (acute) Therapy

a) The recommended initial dose of duloxetine hydrochlorid milligrams (mg) orally twice daily. The dose may be increase tolerability is a concern, patients may be started at 30 mg or is no evidence that doses greater than 60 mg/day confer an oral capsules, 2008).

2) Maintenance Therapy

a) The recommended maintenance dose of duloxetine hydr is 60 milligrams orally once daily. Maintenance treatment wi Reassess the dose and the need for maintenance therapy ir release oral capsules, 2008).

3) Therapy Withdrawal

a) Abrupt discontinuation of duloxetine has lead to sympton irritability, and nightmare. Gradual reduction of the dose, rat symptoms occur following a decrease in dose, resuming the smaller decreases (Prod Info CYMBALTA(R) delayed-releas

1.3.1.A.1.e Urinary incontinence

1) In clinical trials, duloxetine 40 milligrams orally twice daily wa incontinence episodes in clinical trials among women with stress Dmochowski et al, 2003) and mixed urinary incontinence (Bent e

1.3.2 Dosage in Renal Failure

A) Duloxetine Hydrochloride

1) In renally impaired patients, duloxetine should be initiated at a lower d recommended for patients with end-stage renal disease (requiring dialysis

milliliters/minute) (Prod Info CYMBALTA(R) delayed-release oral capsules

1.3.3 Dosage in Hepatic Insufficiency

A) Duloxetine Hydrochloride

1) Duloxetine is not recommended for use in patients with any hepatic ins capsules, 2008).

1.3.4 Dosage in Geriatric Patients

A) Duloxetine Hydrochloride

1) No dosage adjustment is recommended for elderly patients. Caution is CYMBALTA(R) delayed-release oral capsules, 2008).

1.4 Pediatric Dosage

1.4.1 Normal Dosage

1.4.1.A Duloxetine Hydrochloride

1) The safety and efficacy in pediatric patients have not been established 2008).

2.0 Pharmacokinetics

Onset and Duration

Drug Concentration Levels

ADME

2.1 Onset and Duration

A) Onset

1) Duloxetine Hydrochloride

a) Initial Response

1) Depression, oral: within 2 weeks (Hirschfeld et al, 2005).

a) Patients treated with duloxetine experienced significant impro (HAMD-17) compared to placebo-treated patients by the second week trials, which compared duloxetine 60 mg orally once daily (depressive disorder, rapid improvements in the individual sympto and psychic anxiety were demonstrated by the end of the first we

b) Peak Response

1) Platelet serotonin uptake inhibition, oral: 4 to 6 hours (Kasahara e

a) Represents time to maximal or near-maximal inhibition in plat pharmacodynamic parameter may correlate with CNS activity (Is for clinical monitoring has not been determined.

B) Duration

1) Duloxetine Hydrochloride

a) Multiple Dose

1) Platelet serotonin uptake inhibition, oral: at least 7 days (Kasahara

a) Represents duration of inhibition after the last dose of a regim levels of duloxetine were no longer detectable.

2.2 Drug Concentration Levels

A) Duloxetine Hydrochloride

1) Therapeutic Drug Concentration

a) DEPRESSION, not established.

1) Studies attempting to define plasma levels that are associated wit

2) Significant inhibition of serotonin uptake in platelets from healthy s concentrations exceeding 5 ng/mL (Ishigooka, 1997). This pharmaco 1997; Kasahara et al, 1996), although its usefulness for clinical monit

2) Peak Concentration

a) Oral: 13 ng/mL (20-mg dose) (Johnson et al, 1995).

1) Following single oral doses of 20 mg, a mean peak duloxetine pla desmethyl metabolite (active) were less than 2 ng/mL (Johnson et al,

3) Time to Peak Concentration

a) Oral: 6 to 10 hours (Prod Info CYMBALTA(R) delayed-release oral cap

1) Maximal plasma concentrations (Cmax) of duloxetine occur 6 hou
presence of food (Prod Info CYMBALTA(R) delayed-release oral cap
2) Values represent times to peak levels over the range of 10 to 40 r
higher doses. Duloxetine exhibits linear pharmacokinetics (Sharma e
3) Steady-State: Steady-state has been reached in 3 to 5 days with 2
in healthy subjects; with the latter regimen, the mean peak plasma le
1995).
4) During oral administration of 20 and 30 mg twice daily in healthy s
approximately 15 ng/mL and 20 ng/mL, respectively, in one study (Sh

4) Area Under the Curve
a) After a single 60-milligram dose of duloxetine, patients with end stage
Cmax and AUC values approximately 100% greater than those of patients
glucuronide and 5-hydroxy, 6-methoxy duloxetine sulfate, the major circul
approximately 7- to 9-fold higher and would be expected to increase furth
release oral capsules, 2008).
b) After a single 20-milligram dose of duloxetine, 6 cirrhotic patients with
fold increase in AUC compared to non-cirrhotic patients (Prod Info CYMB

2.3 ADME

Absorption

Distribution

Metabolism

Excretion

Elimination Half-life

2.3.1 Absorption

A) Duloxetine Hydrochloride
1) Bioavailability
a) Oral: 30% to 80% (Bymaster et al, 2005).
1) The absolute oral bioavailability of a 60-mg dose averaged 5(
b) There is a median 2-hour lag until absorption begins (Prod Info C
c) With an evening dose, there is a 3-hour delay in absorption and a
dose (Prod Info CYMBALTA(R) delayed-release oral capsules, 2008)
2) Effects of Food
a) slows absorption
b) Food does not affect Cmax but delays time to peak concentration
(Prod Info CYMBALTA(R) delayed-release oral capsules, 2008).

2.3.2 Distribution

A) Distribution Sites
1) Duloxetine Hydrochloride
a) Protein Binding
1) greater than 90%, primarily to albumin and alpha-1-acid glyco
capsules, 2008).
b) Other Distribution Sites
1) Saliva, 0% (Johnson et al, 1995).
B) Distribution Kinetics
1) Duloxetine Hydrochloride
a) Volume of Distribution
1) 1640 L (Prod Info CYMBALTA(R) delayed-release oral capsu

2.3.3 Metabolism

A) Metabolism Sites and Kinetics
1) Duloxetine Hydrochloride
a) LIVER, extensive (Sharma et al, 2000; Artigas, 1995).
1) The major metabolic pathways involve oxidation of the naphtl
cytochrome P450 (CYP) isozymes, CYP1A2 and CYP2D6 (Prod
B) Metabolites
1) Duloxetine Hydrochloride

a) 4-hydroxy duloxetine glucuronide (inactive) (Prod Info CYMBALTA Lantz et al, 2003).
1) Approximately 47% of a given dose is conjugated to 4-hydrox since the inhibition constant (Ki) values for serotonin and norepir compound duloxetine (Bymaster et al, 2005).
b) 5-hydroxy-6-methoxy duloxetine sulfate (inactive) (Prod Info CYM 2005; Lantz et al, 2003).
1) Approximately 22% of a given dose is conjugated to 5-hydrox activity since the inhibition constant (Ki) values for serotonin and parent compound duloxetine (Bymaster et al, 2005).

2.3.4 Excretion

A) Kidney
1) Duloxetine Hydrochloride
a) Renal Excretion (%)
1) 70% (Prod Info CYMBALTA(R) delayed-release oral capsules
a) Excreted mainly as metabolites; only trace amounts (less CYMBALTA(R) delayed-release oral capsules, 2008).
B) Feces
1) Duloxetine Hydrochloride
a) 20% (Prod Info CYMBALTA(R) delayed-release oral capsules, 20
1) Approximately 20% of duloxetine is excreted in the feces (Pro is unclear from available data if this represents unabsorbed drug
C) Total Body Clearance
1) Duloxetine Hydrochloride
a) 114 L/hr (Sharma et al, 2000).
1) Value after oral doses in healthy subjects.
2) Cirrhotic (Child-Pugh Class B) patients (n=6) had a clearance a 20-milligram dose of duloxetine (Prod Info CYMBALTA(R) dela

2.3.5 Elimination Half-life

A) Parent Compound
1) Duloxetine Hydrochloride
a) Elimination Half-Life
1) 12 hours (range: 8 to 17 hours) (Prod Info CYMBALTA(R) del
a) Duloxetine pharmacokinetics are dose proportional over release oral capsules, 2008).
b) The elimination half-life of duloxetine in 6 cirrhotic patien a significantly longer half-life (47.8 hours vs 13.5 hours, p <

3.0 Cautions

Contraindications

Precautions

Adverse Reactions

Teratogenicity/Effects in Pregnancy/Breastfeeding

Drug Interactions

3.0.A Black Box WARNING
1) Duloxetine Hydrochloride
a) Oral (Capsule, Delayed Release)
Suicidality and Antidepressant Drugs
Antidepressants increased the risk compared to placebo of suicidal th young adults in short-term studies of major depressive disorder (MDD of duloxetine hydrochloride or any other antidepressant in a child, ad need. Short-term studies did not show an increase in the risk of suici beyond age 24; there was a reduction in risk with antidepressants co certain other psychiatric disorders are themselves associated with inc started on antidepressant therapy should be monitored appropriately unusual changes in behavior. Families and caregivers should be adv the prescriber. Duloxetine hydrochloride is not approved for use in pe

capsules, 2009).

3.1 Contraindications

A) Duloxetine Hydrochloride

1) concomitant use of MAOIs (Prod Info Cymbalta(R) Delayed-release oral ca
2) narrow-angle glaucoma, uncontrolled; increased risk of mydriasis (Prod Inf

3.2 Precautions

A) Duloxetine Hydrochloride

1) suicidal ideation and behavior or worsening depression; increased risk, par
first few months of therapy or following changes in dosage (Prod Info Cymbalt
2) abnormal bleeding has been reported, including life-threatening hemorrhag
2009)
3) abrupt withdrawal; serious discontinuation symptoms have been reported (
4) alcohol, substantial use; increased risk of liver injury (Prod Info Cymbalta(F
5) bipolar disorder; increased risk of precipitation of a mixed/manic episode (F
6) concomitant use of thioridazine or serotonergic drugs (serotonin precursors
inhibitors); use is not recommended (Prod Info Cymbalta(R) Delayed-release c
7) concomitant use of potent CYP1A2 inhibitors (fluvoxamine, cimetidine, quin
be avoided (Prod Info Cymbalta(R) Delayed-release oral capsules, 2009)
8) concomitant use of CNS-acting drugs, 5-hydroxytryptamine receptor agonis
warfarin), tricyclic antidepressants (nortriptyline, amitriptyline, imipramine), phe
flecainide); use cautiously (Prod Info Cymbalta(R) Delayed-release oral capsu
9) conditions that slow gastric emptying, such as diabetes; may affect stability
capsules, 2009)
10) diabetes; may worsen glycemic control (Prod Info Cymbalta(R) Delayed-r
11) hepatic impairment; use is not recommended (Prod Info Cymbalta(R) Dela
12) hepatotoxicity, including hepatitis, jaundice, and elevated transaminase le
release oral capsules, 2009)
13) liver disease, chronic; may aggravate condition (Prod Info Cymbalta(R) D
14) mania, history; risk of activation of mania/hypomania (Prod Info Cymbalta
15) narrow-angle glaucoma, controlled; increased risk of mydriasis (Prod Info
16) renal impairment, severe and end stage renal disease (creatinine clearan
Cymbalta(R) Delayed-release oral capsules, 2009)
17) seizures, history (Prod Info CYMBALTA(R) delayed-release oral capsules
18) serotonin syndrome has been reported, including cases that are life-threa
monitoring recommended (Prod Info CYMBALTA(R) delayed-release oral caps
19) use of duloxetine within 14 days of MAOI discontinuation (Prod Info CYMB
20) use of an MAOI within 5 days after duloxetine discontinuation (Prod Info C
21) urinary retention requiring hospitalization and/or catheterization has been
capsules, 2008)
22) volume-depleted, elderly, or concurrent diuretic therapy; hyponatremia, sy
(SIADH) has occurred with duloxetine; discontinue if symptoms develop (Prod
23) report suspected adverse reaction to Eli Lilly and Company at 1-800-LillyR
(Prod Info CYMBALTA(R) delayed-release oral capsules, 2008)

3.3 Adverse Reactions

Cardiovascular Effects

Dermatologic Effects

Endocrine/Metabolic Effects

Gastrointestinal Effects

Hematologic Effects

Hepatic Effects

Musculoskeletal Effects

Neurologic Effects

3.3.1 Cardiovascular Effects

3.3.1.A Duloxetine Hydrochloride

3.3.1.A.1 Increased blood pressure

a) In clinical trials of all indications, duloxetine hydrochloride treatme
systolic and up to 2.3 mmHg in diastolic blood pressures compared w
therapy initiation and periodically during treatment (Prod Info CYMBA
b) Small increases in systolic/diastolic blood pressure and decrease
twice-daily dosing in recumbent healthy subjects; no significant effect
position (Sharma et al, 2000a).

3.3.1.A.2 Orthostatic hypotension

a) Orthostatic hypotension and syncope have been associated with t
first week of therapy, but can occur at any time and is especially seer
who are on concomitant medications that induce orthostatic hypotens
(fluvoxamine, cimetidine, quinolone antimicrobials (ciprofloxacin, eno
capsules, 2008).

3.3.1.A.3 Palpitations

a) Incidence: 1% to 2% (Prod Info CYMBALTA(R) delayed-release o
b) In pooled clinical trials of major depressive disorder and generaliz
of patients receiving duloxetine hydrochloride (n=2995) compared wit
also reported in 1% or greater of patients receiving duloxetine hydroc
indications of duloxetine (Prod Info CYMBALTA(R) delayed-release c
c) In placebo-controlled trials, palpitations were reported in 2% of fib
compared with 2% of patients receiving placebo (n=535) (Prod Info C

3.3.1.A.4 Syncope

a) Orthostatic hypotension and syncope have been associated with t
first week of therapy, but can occur at any time and is especially seer
who are on concomitant medications that induce orthostatic hypotens
(fluvoxamine, cimetidine, quinolone antimicrobials (ciprofloxacin, eno
capsules, 2008).

3.3.2 Dermatologic Effects

3.3.2.A Duloxetine Hydrochloride

Flushing

Pruritus

Rash

3.3.2.A.1 Diaphoresis

a) Incidence: 6% to 8% (Prod Info CYMBALTA(R) delayed-release o
b) In major depressive disorder and generalized anxiety disorder pla
patients receiving duloxetine hydrochloride compared with 2% of the
delayed-release oral capsules, 2008).
c) In diabetic peripheral neuropathy placebo-controlled trials, hyperh
receiving duloxetine hydrochloride at 60 mg twice daily, 6% of the 22
daily, compared 2% of the 223 subjects receiving placebo (Prod Info
d) In fibromyalgia placebo-controlled trials, hyperhidrosis was report
compared with 1% of patients receiving placebo (n=535) (Prod Info C
e) In clinical trials of all approved indications, hyperhidrosis was repo
with 2% of patients receiving placebo (n=3048), and was one of the r
CYMBALTA(R) delayed-release oral capsules, 2008).

3.3.2.A.2 Flushing

a) Incidence: 2% to 3% (Prod Info CYMBALTA(R) delayed-release o
b) In major depressive disorder and generalized anxiety disorder pla
patients receiving duloxetine hydrochloride compared with less than
CYMBALTA(R) delayed-release oral capsules, 2008).
c) In fibromyalgia placebo-controlled trials, hot flush was reported in
compared with 2% of patients receiving placebo (n=535) (Prod Info C

3.3.2.A.3 Pruritus

a) Incidence: 3% (Prod Info CYMBALTA(R) delayed-release oral cap
b) In fibromyalgia placebo-controlled trials, pruritus was reported in 3
compared with 2% of patients receiving placebo (n=535) (Prod Info C

3.3.2.A.4 Rash

a) Incidence: 4% (Prod Info CYMBALTA(R) delayed-release oral cap
b) In fibromyalgia placebo-controlled trials, rash was reported in 4%
compared with 2% of patients receiving placebo (n=535) (Prod Info C

3.3.3 Endocrine/Metabolic Effects

3.3.3.A Duloxetine Hydrochloride

Blood glucose abnormal

Hyponatremia

Syndrome of inappropriate antidiuretic hormone secretion

Weight loss

3.3.3.A.1 Blood glucose abnormal

a) Based on pooled data from three 12-week, double-blind, randomiz
week, open-label extension phase (n=867), duloxetine therapy was a
(FPG) among patients treated for diabetic peripheral neuropathy (DP
randomized to receive placebo (n=339) or duloxetine 60 mg once or
patients were then re-randomized in a 2:1 ratio during the extension p
investigator-driven routine care (n=287), such as gabapentin, venlafa
history of DPN, and more than 88% had type 2 diabetes mellitus. The
(mg/dL) (10.1 millimoles/liter (mmol/L)) and 7.8%, respectively. Dulox
with placebo during the acute phase (9 mg/dL (0.5 mmol/L) vs -2 mg/
routine care during the extension phase (12 mg/dL (0.67 mmol/L) vs
changes in HbA1C associated with duloxetine was significantly differ

vs 0.19%; p less than 0.001) (Hardy et al, 2007).

3.3.3.A.2 Hyponatremia

a) Summary

1) Hyponatremia has been associated with duloxetine therapy. S reported and were reversible upon duloxetine discontinuation. In syndrome of inappropriate antidiuretic hormone secretion (SIADI patients are at greater risk of hyponatremia. Discontinuation of d symptomatic hyponatremia (Prod Info CYMBALTA(R) delayed-re

b) Hyponatremia developed in 5 depressed patients after approxima duloxetine. The 5 patients (35 to 70 years old) had a history of recurr severe acute episode. Duloxetine was initiated at 30 mg/day followec was subsequently increased to 90 mg/day or 120 mg/day, after 3 to 4 medications were lorazepam and zopiclone. Serum osmolality, and s week after the dose increase, patients developed fatigue, lethargy, ar in all patients. Duloxetine was discontinued in 4 patients and the dose on water restriction (less than 1200 mL/day), and the intake of sodiur salt tablets in 2 patients. Symptoms of hyponatremia and serum sodi hyponatremia such as advanced age, thiazide diuretics, polypharmac insufficiency, hypothyroidism, tumors, respiratory disease, or acute c Lindstaedt, 2007).

c) In a case report, a 48-year-old woman developed syndrome of ina hyponatremia and seizures when administered duloxetine. The patier upon psychiatric evaluation was diagnosed with minor depression an days later, she developed 2 generalized seizures, was afebrile, coma analysis revealed serum sodium level of 103 mEq/L, and a BUN of 6 diagnosed with SIADH (urinary sodium 118 mEq/L, serum osmolality The patient was inadvertently rechallenged with duloxetine on days 3 levels 120 mEq/L on day 3, and 98 mEq/L on day 4) and she had 1 a 2 days the patient regained consciousness and was uneventfully disc

3.3.3.A.3 Syndrome of inappropriate antidiuretic hormone secretion

a) Hyponatremia has been associated with duloxetine therapy. Seru and were reversible upon duloxetine discontinuation. In many cases inappropriate antidiuretic hormone secretion (SIADH). The elderly, pa greater risk of hyponatremia. Discontinuation of duloxetine therapy sh hyponatremia (Prod Info CYMBALTA(R) delayed-release oral capsul

b) In a case report, a 48-year-old woman developed syndrome of ina hyponatremia and seizures when administered duloxetine. The patier upon psychiatric evaluation was diagnosed with minor depression an she developed 2 generalized seizures, was afebrile, comatose, and h revealed serum sodium level of 103 mEq/L, and a BUN of 6 mg/dL. D SIADH (urinary sodium 118 mEq/L, serum osmolality 215 mOsm/kg H inadvertently rechallenged with duloxetine on days 3 and 4, which rep on day 3, and 98 mEq/L on day 4) and she had 1 additional seizure. patient regained consciousness and was uneventfully discharged 7 d

3.3.3.A.4 Weight loss

a) Incidence: 2% (Prod Info CYMBALTA(R) delayed-release oral cap

b) In major depressive disorder and generalized anxiety disorder pla patients receiving duloxetine hydrochloride compared with less than with duloxetine hydrochloride for up to 10 weeks in clinical trials show placebo-treated patients showed a weight gain of approximately 0.2 k 2008).

c) In diabetic peripheral neuropathy placebo-controlled clinical trials, weeks experienced a mean weight loss of approximately 1.1 kg, com placebo-treated patients (Prod Info CYMBALTA(R) delayed-release c

d) In fibromyalgia placebo-controlled trials, patients receiving duloxe weight loss of approximately 0.4 kg compared with a mean weight ga Info CYMBALTA(R) delayed-release oral capsules, 2008).

3.3.4 Gastrointestinal Effects

3.3.4.A Duloxetine Hydrochloride

Constipation

Decrease in appetite

Diarrhea

Indigestion

Loose stool

Nausea

Taste sense altered

Vomiting

Xerostomia

3.3.4.A.1 Constipation

a) Incidence: 5% to 15% (Prod Info CYMBALTA(R) delayed-release
b) In major depressive disorder and generalized anxiety disorder pla
patients receiving duloxetine hydrochloride compared with 4% of the
delayed-release oral capsules, 2008).
c) In diabetic peripheral neuropathy placebo-controlled trials, constip
hydrochloride at 60 mg twice daily, 11% of the 228 patients at 60 mg
with 3% of the 223 subjects receiving placebo (Prod Info CYMBALTA
d) In fibromyalgia placebo-controlled trials, constipation was reporte
compared with 4% of patients receiving placebo (n=535) (Prod Info C
e) In clinical trials of all approved indications, constipation was repor
with 4% of patients receiving placebo (n=3048), and was one of the r
CYMBALTA(R) delayed-release oral capsules, 2008).

3.3.4.A.2 Decrease in appetite

a) In major depressive disorder and generalized anxiety disorder pla
occurred in 7% of the 2995 patients receiving duloxetine hydrochloric
(Prod Info CYMBALTA(R) delayed-release oral capsules, 2008).
b) In diabetic peripheral neuropathy placebo-controlled trials, decrea
patients receiving duloxetine hydrochloride at 60 mg twice daily, 7% c
20 mg daily, compared with less than 2% of the 223 subjects receivin
capsules, 2008).
c) In fibromyalgia placebo-controlled trials, decreased appetite (inclu
duloxetine hydrochloride (n=876) compared with 2% of patients recei
release oral capsules, 2008).
d) In clinical trials of all approved indications, decreased appetite (in
duloxetine (n=4843) compared with 2% of patients receiving placebo
adverse reactions (Prod Info CYMBALTA(R) delayed-release oral cap

3.3.4.A.3 Diarrhea

a) Incidence: 7% to 13% (Prod Info CYMBALTA(R) delayed-release
b) In major depressive disorder and generalized anxiety disorder pla
patients receiving duloxetine hydrochloride compared with 7% of the
delayed-release oral capsules, 2008).
c) In diabetic peripheral neuropathy placebo-controlled trials, diarrhe
hydrochloride at 60 mg twice daily, 11% of the 228 patients at 60 mg
with 6% of the 223 subjects receiving placebo (Prod Info CYMBALTA
d) In fibromyalgia placebo-controlled trials, diarrhea was reported in
compared with 8% of patients receiving placebo (n=535) (Prod Info C
e) In clinical trials of all approved indications, diarrhea was reported
7% of patients receiving placebo (n=3048) (Prod Info CYMBALTA(R)

3.3.4.A.4 Indigestion

a) Incidence: 4% to 5% (Prod Info CYMBALTA(R) delayed-release o
b) In diabetic peripheral neuropathy placebo-controlled trials, dyspep
hydrochloride at 60 mg twice daily, 4% of the 228 patients at 60 mg c
less than 3% of the 223 subjects receiving placebo (Prod Info CYMB

c) In fibromyalgia placebo-controlled trials, dyspepsia was reported i
compared with 3% of patients receiving placebo (n=535) (Prod Info C

3.3.4.A.5 Loose stool

a) Incidence: 2% to 3% (Prod Info CYMBALTA(R) delayed-release o
b) In diabetic peripheral neuropathy placebo-controlled trials, loose s
hydrochloride at 60 mg twice daily, 3% of the 228 patients at 60 mg c
1% of the 223 subjects receiving placebo (Prod Info CYMBALTA(R) c

3.3.4.A.6 Nausea

a) Incidence: 14% to 30% (Prod Info CYMBALTA(R) delayed-release
b) In major depressive disorder and generalized anxiety disorder pla
patients receiving duloxetine hydrochloride compared with 9% of the
delayed-release oral capsules, 2008).
c) In diabetic peripheral neuropathy placebo-controlled trials, nausea
hydrochloride at 60 mg twice daily, 22% of the 228 patients at 60 mg
with 9% of the 223 subjects receiving placebo. Nausea led to discont
0.4% placebo-treated individuals (Prod Info CYMBALTA(R) delayed-r
d) In placebo-controlled trials, nausea was reported in 29% of fibrom
compared with 11% of patients receiving placebo (n=535) (Prod Info
e) In clinical trials of all approved indications, nausea was reported ir
9% of patients receiving placebo (n=3048), and was one of the most
(R) delayed-release oral capsules, 2008).

3.3.4.A.7 Taste sense altered

a) Incidence: 3% (Prod Info CYMBALTA(R) delayed-release oral cap
b) In fibromyalgia placebo-controlled trials, dysgeusia was reported i
compared with 1% of patients receiving placebo (n=535) (Prod Info C

3.3.4.A.8 Vomiting

a) Incidence: 5% to 6% (Prod Info CYMBALTA(R) delayed-release o
b) In major depressive disorder and generalized anxiety disorder pla
patients receiving duloxetine hydrochloride compared with 2% of the
delayed-release oral capsules, 2008).
c) In diabetic peripheral neuropathy placebo-controlled trials, vomitin
hydrochloride at 60 mg twice daily, 5% of the 228 patients at 60 mg c
4% of the 223 subjects receiving placebo (Prod Info CYMBALTA(R) c

3.3.4.A.9 Xerostomia

a) Incidence: 5% to 18% (Prod Info CYMBALTA(R) delayed-release
b) In major depressive disorder and generalized anxiety disorder pla
patients receiving duloxetine hydrochloride compared with 6% of the
delayed-release oral capsules, 2008).
c) In diabetic peripheral neuropathy placebo-controlled trials, dry mo
hydrochloride at 60 mg twice daily, 7% of the 228 patients at 60 mg c
4% of the 223 subjects receiving placebo (Prod Info CYMBALTA(R) c
d) In fibromyalgia placebo-controlled trials, dry mouth was reported i
compared with 5% of patients receiving placebo (n=535) (Prod Info C
e) In clinical trials of all approved indications, dry mouth was reporte
with 6% of patients receiving placebo (n=3048), and was one of the n
CYMBALTA(R) delayed-release oral capsules, 2008).

3.3.5 Hematologic Effects

3.3.5.A Duloxetine Hydrochloride

3.3.5.A.1 Bleeding, Abnormal

a) In case reports and epidemiological studies, drugs which interfere
reuptake inhibitors (SNRIs)) have been associated with an increased
including ecchymoses, hematomas, epistaxes, petechiae, gastrointes
reported with SSRI and SNRI use. Because the risk of bleeding may
coagulation (eg, NSAIDs, aspirin, warfarin), use caution when these a
Additionally, patients receiving concurrent warfarin therapy should be
Info CYMBALTA(R) delayed-release oral capsules, 2008).

3.3.6 Hepatic Effects

3.3.6.A Duloxetine Hydrochloride

3.3.6.A.1 Hepatotoxicity

a) The risk for elevated serum transaminase levels increases with th
transaminase levels has been approximately 2 months and has resul
of patients. In the cohort of controlled trials in any indication, alanine
limit of normal were observed in 1.1% (85/7632) of patients receiving
placebo group. During placebo-controlled, fixed-dose trials, dose resp
elevations greater than 5 times the upper limit of normal and ALT ele
observed (Prod Info CYMBALTA(R) delayed-release oral capsules, 2
b) During the postmarketing use of duloxetine, hepatomegaly and tra
limit of normal with or without jaundice have been reported. Additiona
occurred. Patients with chronic liver disease or cirrhosis have experie
Due to the potential for aggravation of preexisting liver disease or the
concurrently, duloxetine should not be given to patients consuming s
chronic liver disease (Prod Info CYMBALTA(R) delayed-release oral

3.3.8 Musculoskeletal Effects

3.3.8.A Duloxetine Hydrochloride

Asthenia

Cramp

Musculoskeletal pain

Myalgia

Spasm

3.3.8.A.1 Asthenia

a) Incidence: 2% to 8% (Prod Info CYMBALTA(R) delayed-release o
b) In diabetic peripheral neuropathy placebo-controlled trials, asthen
hydrochloride at 60 mg twice daily, 4% of the 228 patients at 60 mg c
1% of the 223 subjects receiving placebo (Prod Info CYMBALTA(R) c

3.3.8.A.2 Cramp

a) Incidence: 4% to 5% (Prod Info CYMBALTA(R) delayed-release o
b) In diabetic peripheral neuropathy placebo-controlled trials, muscle
hydrochloride at 60 mg twice daily, 4% of the 228 patients at 60 mg c
3% of the 223 subjects receiving placebo (Prod Info CYMBALTA(R) c

3.3.8.A.3 Musculoskeletal pain

a) Incidence: 5% (Prod Info CYMBALTA(R) delayed-release oral cap
b) In fibromyalgia placebo-controlled trials, musculoskeletal pain was
(n=876) compared with 4% of patients receiving placebo (n=535) (Pr

3.3.8.A.4 Myalgia

a) Incidence: 1% to 4% (Prod Info CYMBALTA(R) delayed-release o
b) In diabetic peripheral neuropathy placebo-controlled trials, myalgi
hydrochloride at 60 mg twice daily, 1% of the 228 patients at 60 mg c
less than 1% of the 223 subjects receiving placebo (Prod Info CYMB

3.3.8.A.5 Spasm

a) Incidence: 4% (Prod Info CYMBALTA(R) delayed-release oral cap
b) In fibromyalgia placebo-controlled trials, muscle spasm was repor
(n=876) compared with 3% of patients receiving placebo (n=535) (Pr

3.3.9 Neurologic Effects

3.3.9.A Duloxetine Hydrochloride

Dizziness

Headache

Insomnia

Restless legs syndrome

Seizure

Somnolence

Tremor

Vertigo

3.3.9.A.1 Dizziness

a) Incidence: 6% to 17% (Prod Info CYMBALTA(R) delayed-release
b) In major depressive disorder and generalized anxiety disorder pla
patients receiving duloxetine hydrochloride compared with 6% of the
delayed-release oral capsules, 2008).
c) In diabetic peripheral neuropathy placebo-controlled trials, dizzine
hydrochloride at 60 mg twice daily, 14% of the 228 patients at 60 mg
with 6% of the 223 subjects receiving placebo. Dizziness led to disco
and 0.4% placebo-treated patients (Prod Info CYMBALTA(R) delayed
d) In fibromyalgia placebo-controlled trials, dizziness was reported ir
compared with 7% of patients receiving placebo (n=535) (Prod Info C
e) In clinical trials of all approved indications, dizziness was reported
with 6% of patients receiving placebo (n=3048) (Prod Info CYMBALT

3.3.9.A.2 Headache

a) Incidence: 13% to 20% (Prod Info CYMBALTA(R) delayed-release
b) In diabetic peripheral neuropathy placebo-controlled trials, headac
hydrochloride at 60 mg twice daily, 13% of the 228 patients at 60 mg
with 10% of the 223 subjects receiving placebo (Prod Info CYMBALT
c) In fibromyalgia placebo-controlled trials, headache was reported i
compared with 12% of patients receiving placebo (n=535) (Prod Info
d) In clinical trials of all approved indications, headache was reported
with 15% of patients receiving placebo (n=3048) (Prod Info CYMBAL

3.3.9.A.3 Insomnia

a) Incidence: 8% to 16% (Prod Info CYMBALTA(R) delayed-release
b) In major depressive disorder and generalized anxiety disorder pla
early morning awakening, and initial insomnia) occurred in 10% of the
with 6% of the 1955 subjects receiving placebo (Prod Info CYMBALT
c) In diabetic peripheral neuropathy placebo-controlled trials, insomn
hydrochloride at 60 mg twice daily, 8% of the 228 patients at 60 mg c
7% of the 223 subjects receiving placebo (Prod Info CYMBALTA(R) c
d) In fibromyalgia placebo-controlled trials, insomnia (including midd
reported in 16% of patients receiving duloxetine hydrochloride (n=876
(Prod Info CYMBALTA(R) delayed-release oral capsules, 2008).
e) In clinical trials of all approved indications, insomnia was reported
with 7% of patients receiving placebo (n=3048) (Prod Info CYMBALT

3.3.9.A.4 Restless legs syndrome

a) In a prospective, naturalistic study of patients (median age, 46 yea
271 (9%) subjects experienced new-onset restless leg syndrome (RL
treatment. Antidepressants included fluoxetine, paroxetine, citaloprar
and mirtazapine. Mirtazapine led to a marked decline of RLS in 28%
other antidepressants showed RLS symptoms (newly occurred or det
occurred early in treatment (median of 2.5 days, range 1 to 23 days)

3.3.9.A.5 Seizure

a) Incidence: 0.03% (Prod Info CYMBALTA(R) delayed-release oral
b) In placebo-controlled clinical trials, seizures occurred in 0.03% (3/
hydrochloride compared with 0.01% (1/6770) of patients receiving pla
surveillance reports (Prod Info CYMBALTA(R) delayed-release oral c
c) In a case report, a 48-year-old woman developed syndrome of ina
hyponatremia and seizures when administered duloxetine. The patier
upon psychiatric evaluation was diagnosed with minor depression an
she developed 2 generalized seizures, was afebrile, comatose, and h
revealed serum sodium level of 103 mEq/L, and a BUN of 6 mg/dL. D
SIADH (urinary sodium 118 mEq/L, serum osmolality 215 mOsm/kg h
inadvertently rechallenged with duloxetine on days 3 and 4, which rep
on day 3, and 98 mEq/L on day 4) and she had one additional seizur
patient regained consciousness and was uneventfully discharged 7 d

3.3.9.A.6 Somnolence

a) Incidence: 7% to 21% (Prod Info CYMBALTA(R) delayed-release
b) In major depressive disorder and generalized anxiety disorder pla
sedation) occurred in 10% of the 2995 patients receiving duloxetine h
placebo (Prod Info CYMBALTA(R) delayed-release oral capsules, 20
c) In diabetic peripheral neuropathy placebo-controlled trials, somno
hydrochloride at 60 mg twice daily, 15% of the 228 patients at 60 mg
with 5% of the 223 subjects receiving placebo. Somnolence led to dis
patients and none in the placebo-treated group (Prod Info CYMBALT
d) In fibromyalgia placebo-controlled trials, somnolence (including hy
receiving duloxetine hydrochloride (n=876) compared with 3% of pati
delayed-release oral capsules, 2008).
e) In clinical trials of all approved indications, somnolence (including
receiving duloxetine (n=4843) compared with 3% of patients receiving
reported adverse reactions (Prod Info CYMBALTA(R) delayed-releas

3.3.9.A.7 Tremor

a) Incidence: up to 5% (Prod Info CYMBALTA(R) delayed-release or
b) In major depressive disorder and generalized anxiety disorder pla
patients receiving duloxetine hydrochloride compared with less than
CYMBALTA(R) delayed-release oral capsules, 2008).
c) In diabetic peripheral neuropathy placebo-controlled trials, tremor
hydrochloride at 60 mg twice daily, 1% of the 228 patients at 60 mg c
0% of the 223 subjects receiving placebo (Prod Info CYMBALTA(R) c
d) In fibromyalgia placebo-controlled trials, tremor was reported in 4
compared with 1% of patients receiving placebo (n=535) (Prod Info C

3.3.9.A.8 Vertigo

a) Incidence: 1% or greater (Prod Info CYMBALTA(R) delayed-relea
b) Vertigo has been reported in 1% or greater of patients receiving d
indications (n=27,229) (Prod Info CYMBALTA(R) delayed-release ora

3.3.10 Ophthalmic Effects

3.3.10.A Duloxetine Hydrochloride

Blurred vision

Mydriasis

3.3.10.A.1 Blurred vision

a) Incidence: 1% or greater (Prod Info CYMBALTA(R) delayed-relea
b) In major depressive disorder and generalized anxiety disorder pla
patients receiving duloxetine hydrochloride compared with 2% of the
delayed-release oral capsules, 2008).
c) In placebo-controlled trials, blurred vision was reported in 2% of fi
compared with 1% of patients receiving placebo (n=535) (Prod Info C
d) Blurred vision has been reported in 1% or greater of patients (n=2
all indications (Prod Info CYMBALTA(R) delayed-release oral capsule

3.3.10.A.2 Mydriasis

a) In clinical trials, duloxetine hydrochloride has been associated witl uncontrolled narrow-angle glaucoma and should be used cautiously i delayed-release oral capsules, 2008).

3.3.12 Psychiatric Effects

3.3.12.A Duloxetine Hydrochloride

Agitation

Anxiety

Bipolar disorder, Rapid cycling induction

Depression, worsening

Dream disorder

Posttraumatic stress disorder, exacerbation of symptoms

Suicidal thoughts

3.3.12.A.1 Agitation

a) Incidence: 5% to 6% (Prod Info CYMBALTA(R) delayed-release o
b) In major depressive disorder and generalized anxiety disorder pla nervousness, restlessness, tension, and psychomotor agitation) occu hydrochloride compared with 3% of the 1955 subjects receiving place 2009).
c) In placebo-controlled trials, agitation (including feeling jittery, nerv was reported in 6% of fibromyalgia patients receiving duloxetine hydr placebo (n=535) (Prod Info CYMBALTA(R) delayed-release oral caps

3.3.12.A.2 Anxiety

a) Incidence: 3% (Prod Info CYMBALTA(R) delayed-release oral cap
b) In major depressive disorder and generalized anxiety disorder pla patients receiving duloxetine hydrochloride compared with 2% of the delayed-release oral capsules, 2009).

3.3.12.A.3 Bipolar disorder, Rapid cycling induction

a) A 17-year-old female (weight 45 kg) with bipolar disorder experier starting duloxetine. Significant medical history included a depressive medications were oral sodium valproate 400 mg/day and oral olanzap became depressed without reason, with signs of sadness, frequent c and would not do any work. She was started on oral duloxetine 20 m excessively, was euphoric, had assertions of high intelligence and ab aggressive and abusive behavior. It was subsequently noticed that ab euphoria and depression. Duloxetine was stopped, the dose of sodiu olanzapine was maintained at 10 mg/day. At week 4 follow-up, her m depressive symptoms (Desarkar et al, 2007).

3.3.12.A.4 Depression, worsening

a) Clinical worsening of depression has been reported in patients rec months of treatment and during dose adjustments. It may persist unti antidepressants for any indication should be monitored for signs of cl capsules, 2009).

3.3.12.A.5 Dream disorder

a) Incidence: 2% to 3% (Prod Info CYMBALTA(R) delayed-release o
b) In major depressive disorder and generalized anxiety disorder pla occurred in 2% of the 2995 patients receiving duloxetine hydrochloric (Prod Info CYMBALTA(R) delayed-release oral capsules, 2009).
c) In placebo-controlled trials, abnormal dreams (including nightmare duloxetine hydrochloride (n=876) compared with 1% of patients recei

release oral capsules, 2009).

3.3.12.A.6 Posttraumatic stress disorder, exacerbation of symptom

a) In a case report, a 53-year-old Vietnam veteran with post- traumat depression experienced severe exacerbation of PTSD symptoms. Th propranolol, and risperidone. Within 1 week of beginning duloxetine 6 Vietnam, nightmares, emotional numbing, increased startle response Decreasing his duloxetine dose to 30 mg per day lessened the PTSD did the symptoms return to baseline (Deneys & Ahearn, 2006).

3.3.12.A.7 Suicidal thoughts

a) Adult and pediatric patients being treated with antidepressants for anxiety, agitation, panic attacks, insomnia, irritability, hostility (aggres hypomania, or mania may be at risk of suicidal ideation and behavior with other psychiatric and nonpsychiatric disorders. If these symptom necessary to discontinue medications when symptoms are severe, su symptoms. Patients and their caregivers should be provided with the patients especially during the initial few months of therapy or at times oral capsules, 2009).

b) A causal role for antidepressants in inducing suicidality has been antidepressants in a child or adolescent must balance this risk with th controlled trials of nine antidepressants (citalopram, fluoxetine, fluvox nefazodone, and venlafaxine extended-release) including over 4400 obsessive compulsive disorder (OCD), or other psychiatric disorders, few months of therapy was demonstrated in patients receiving antide suicidality was most consistently observed in the trials that included p trials in other psychiatric indications, such as obsessive compulsive d

1) In a pooled analyses of placebo-controlled trials in adults with trials (median duration of 2 months) of 11 antidepressant drugs i among the drugs studied. However, for almost all drugs studied, patients. The risk difference (drug versus placebo in the number additional cases in patients less than 18 years of age, 5 addition to 64 years, and 6 fewer cases in patients 65 years and older. No the adult trials; however, the number of suicides was insufficient use (ie, beyond several months) in pediatric patients is not know maintenance trials in adults with depression to substantiate a del (Prod Info LEXAPRO(R) Oral solution, Oral tablets, 2009; Anon,

3.3.13 Renal Effects

3.3.13.A Duloxetine Hydrochloride

Delay when starting to pass urine

Increased frequency of urination

Urinary retention

3.3.13.A.1 Delay when starting to pass urine

a) Urinary hesitation has been associated with the use of selective s Info CYMBALTA(R) delayed-release oral capsules, 2008).

3.3.13.A.2 Increased frequency of urination

a) Incidence: 1% to 5% (Prod Info CYMBALTA(R) delayed-release o

b) In diabetic peripheral neuropathy placebo-controlled trials, pollaki hydrochloride at 60 mg twice daily, 1% of the 228 patients at 60 mg d of the 223 subjects receiving placebo (Prod Info CYMBALTA(R) dela

3.3.13.A.3 Urinary retention

a) Urethral retention has been associated with the use of selective s During postmarketing surveillance of duloxetine, cases of urinary rete reported (Prod Info CYMBALTA(R) delayed-release oral capsules, 20

3.3.14 Reproductive Effects

3.3.14.A Duloxetine Hydrochloride

Abnormal ejaculation

Erectile dysfunction

Late ejaculation

Orgasm disorder

Reduced libido

3.3.14.A.1 Abnormal ejaculation

a) Incidence: 2% to 4% (Prod Info CYMBALTA(R) delayed-release o
b) In major depressive disorder and generalized anxiety disorder pla
failure and ejaculation dysfunction) occurred in 2% of the male patien
1% of the male patients receiving placebo (Prod Info CYMBALTA(R)
c) In fibromyalgia placebo-controlled trials, ejaculation disorder (inclu
reported in 4% of male patients receiving duloxetine hydrochloride (n
(n=26) (Prod Info CYMBALTA(R) delayed-release oral capsules, 200

3.3.14.A.2 Erectile dysfunction

a) Incidence: 1% to 5% (Prod Info CYMBALTA(R) delayed-release o
b) In major depressive disorder and generalized anxiety disorder pla
male patients receiving duloxetine hydrochloride compared with 1% o
(R) delayed-release oral capsules, 2008).
c) In diabetic peripheral neuropathy placebo-controlled trials, erectile
duloxetine hydrochloride at 60 mg twice daily, 1% of the 228 patients
compared with 0% of the 223 subjects receiving placebo (Prod Info C

3.3.14.A.3 Late ejaculation

a) Incidence: 3% (Prod Info CYMBALTA(R) delayed-release oral cap
b) In major depressive disorder and generalized anxiety disorder pla
male patients receiving duloxetine hydrochloride compared with less
CYMBALTA(R) delayed-release oral capsules, 2008).

3.3.14.A.4 Orgasm disorder

a) Incidence: 3% (Prod Info CYMBALTA(R) delayed-release oral cap
b) In major depressive disorder and generalized anxiety disorder pla
occurred in 3% of the 2995 patients receiving duloxetine hydrochloric
placebo (Prod Info CYMBALTA(R) delayed-release oral capsules, 20
c) In fibromyalgia placebo-controlled trials, abnormal orgasm (includi
duloxetine hydrochloride (n=876) compared with less than 1% of pati
delayed-release oral capsules, 2008).

3.3.14.A.5 Reduced libido

a) Incidence: 2% to 4% (Prod Info CYMBALTA(R) delayed-release o
b) In major depressive disorder and generalized anxiety disorder pla
occurred in 4% of the 2995 patients receiving duloxetine hydrochloric
(Prod Info CYMBALTA(R) delayed-release oral capsules, 2008).
c) In fibromyalgia placebo-controlled trials, decreased libido (includir
duloxetine hydrochloride (n=876) compared with less than 1% of pati
delayed-release oral capsules, 2008).

3.3.15 Respiratory Effects

3.3.15.A Duloxetine Hydrochloride

Cough

Nasopharyngitis

Pain in throat

Upper respiratory infection

3.3.15.A.1 Cough

a) Incidence: 3% to 6% (Prod Info CYMBALTA(R) delayed-release o
b) In diabetic peripheral neuropathy placebo-controlled trials, cough
hydrochloride at 60 mg twice daily, 3% of the 228 patients at 60 mg c
of the 223 subjects receiving placebo (Prod Info CYMBALTA(R) dela
c) In fibromyalgia placebo-controlled trials, cough was reported in 4%
compared with 3% of patients receiving placebo (n=535) (Prod Info C

3.3.15.A.2 Nasopharyngitis

a) Incidence: 7% to 9% (Prod Info CYMBALTA(R) delayed-release o
b) In diabetic peripheral neuropathy placebo-controlled trials, nasopl
duloxetine hydrochloride at 60 mg twice daily, 7% of the 228 patients
compared with 5% of the 223 subjects receiving placebo (Prod Info C

3.3.15.A.3 Pain in throat

a) Incidence: 1% to 6% (Prod Info CYMBALTA(R) delayed-release o
b) In diabetic peripheral neuropathy placebo-controlled trials, pharyn
duloxetine hydrochloride at 60 mg twice daily, 1% of the 228 patients
compared 1% of the 223 subjects receiving placebo (Prod Info CYME
c) In fibromyalgia placebo-controlled trials, pharyngolaryngeal pain w
hydrochloride (n=876) compared with 3% of patients receiving placeb
capsules, 2008).

3.3.15.A.4 Upper respiratory infection

a) Incidence: 7% (Prod Info CYMBALTA(R) delayed-release oral cap
b) In fibromyalgia placebo-controlled trials, upper respiratory tract inf
hydrochloride (n=876) compared with 6% of patients receiving placeb
capsules, 2008).

3.3.16 Other

3.3.16.A Duloxetine Hydrochloride

Fatigue

Fever

Serotonin syndrome

Withdrawal sign or symptom

3.3.16.A.1 Fatigue

a) Incidence: 2% to 15% (Prod Info CYMBALTA(R) delayed-release
b) In major depressive disorder and generalized anxiety disorder pla
10% of the 2995 patients receiving duloxetine hydrochloride compare
CYMBALTA(R) delayed-release oral capsules, 2008).
c) In diabetic peripheral neuropathy placebo-controlled trials, fatigue
hydrochloride at 60 mg twice daily, 10% of the 228 patients at 60 mg
with 5% of the 223 subjects receiving placebo. Fatigue led to disconti
none in the placebo-treated group (Prod Info CYMBALTA(R) delayed
d) In fibromyalgia placebo-controlled trials, fatigue (including astheni
hydrochloride (n=876) compared with 8% of patients receiving placeb
capsules, 2008).
e) In clinical trials of all approved indications, fatigue was reported in
6% of patients receiving placebo (n=3048) (Prod Info CYMBALTA(R)

3.3.16.A.2 Fever

a) Incidence: 1% to 3% (Prod Info CYMBALTA(R) delayed-release o

b) In diabetic peripheral neuropathy placebo-controlled trials, pyrexia hydrochloride at 60 mg twice daily, 1% of the 228 patients at 60 mg c 1% of the 223 subjects receiving placebo (Prod Info CYMBALTA(R) c

3.3.16.A.3 Serotonin syndrome

a) Serotonin syndrome, including life-threatening cases, or neurolept reported with the use of duloxetine alone. Signs and symptoms of ser hallucination, coma), autonomic instability (eg, tachycardia, labile blo hyperreflexia, incoordination) and/or gastrointestinal symptoms (eg, r resemble NMS with symptoms including hyperthermia, muscle rigidity signs, and mental status changes. Serotonin syndrome occurs most c including triptans, with drugs that impair metabolism of serotonin, incl antagonists (Prod Info Cymbalta(R) Delayed-release oral capsules, 2

3.3.16.A.4 Withdrawal sign or symptom

a) Incidence: 1% or greater (Prod Info CYMBALTA(R) delayed-relea

b) In clinical trials, abrupt discontinuation of duloxetine resulted in 1% dizziness, nausea, headache, fatigue, paresthesia, vomiting, irritabilit vertigo compared with patients discontinuing placebo. During marketi (SNRIs), reports of dysphoric mood, irritability, agitation, dizziness, se headache, lethargy, emotional lability, insomnia, hypomania, tinnitus, limiting, however some have been severe. All patients should be mor should be gradually tapered. If intolerable symptoms occur, treatmen instituting a more gradual decrease in dose (Prod Info CYMBALTA(R

c) In a pooled analysis of 9 clinical trials divided into three categories duloxetine n=490, placebo n=380), 2 long-term placebo-controlled (3 open-label study (52 weeks; duloxetine n=553), discontinuation-emer therapy was abruptly stopped. Patients experiencing at least one DE 22.9% placebo), 9.1% (versus 2% placebo) and 50% (open-label), re common DEAE was dizziness reported in 12.4% (vs. 0.8% placebo), respectively, followed by nausea (5.9% (vs 0.3% placebo), 0.8% (vs 0.8% placebo), 0.8% (vs 0% placebo), and 7.2% (open-label)). Patier moderate in severity, and incidence and severity was not affected by DEAEs resolved by study end with 68.2%, 47.1% and 63.7% resolvin placebo-controlled, and long-term open-label studies, respectively. Th less than 2 weeks prior to discontinuation of duloxetine therapy (Pera

d) Small increases in heart rate and sleep disturbances (insomnia, a discontinuation of multiple-dose administration in healthy subjects (SI relatively high (20 to 40 mg twice daily). Withdrawal data following on patients are unavailable.

3.4 Teratogenicity/Effects in Pregnancy/Breastfeeding

A) Teratogenicity/Effects in Pregnancy

1) U.S. Food and Drug Administration's Pregnancy Category: Category C (Pro (All Trimesters)

a) Either studies in animals have revealed adverse effects on the fetus (te studies in women or studies in women and animals are not available. Dru potential risk to the fetus.

See Drug Consult reference: PREGNANCY RISK CATEGORIES

2) Crosses Placenta: Unknown

3) Clinical Management

a) Due to the lack of adequate, well-controlled studies in pregnant women only if the potential benefit outweighs the potential risk to the fetus. Becau SSRI- and SNRI-exposed neonates late in the third trimester, the potentia should be taken into account. Tapering duloxetine may be considered in p CYMBALTA(R) delayed-release oral capsules, 2008).

4) Literature Reports

a) Neonates exposed to serotonin and norepinephrine reuptake inhibitors complications necessitating extended hospitalization, respiratory support, upon delivery. Respiratory distress, cyanosis, apnea, seizures, temperatu hypotonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying of a toxic effect of the drug or a drug discontinuation syndrome. In some c syndrome (Prod Info CYMBALTA(R) delayed-release oral capsules, 2008

b) There are no adequate and well-controlled studies with duloxetine in p studies of rats and rabbits treated with oral duloxetine up to 45 mg/kg/day recommended human dose [MRHD; 60 mg/day] on a mg/m(2) basis for ra decreased. When pregnant rats were treated with duloxetine 30 mg/kg/da

weights decreased, and the incidence of stillborn pups and pup mortality i
mg/kg/day (2 times the MRHD). Maternal exposure to 30 mg/kg/day also
and decreased habituation of locomotor activity) (Prod Info CYMBALTA(F

B) Breastfeeding

1) Thomson Lactation Rating: Infant risk cannot be ruled out.

a) Available evidence and/or expert consensus is inconclusive or is inade
breastfeeding. Weigh the potential benefits of drug treatment against pote

2) Clinical Management

a) Duloxetine is excreted in human breast milk at approximately 0.14% o
adverse effects in the nursing infant from exposure to the drug are unkno
(Prod Info CYMBALTA(R) delayed-release oral capsules, 2008; Lobo et a
outweigh the potential risk to the infant and duloxetine is administered to
closely for adverse effects (Lobo et al, 2008)

3) Literature Reports

a) Duloxetine was found in human breast milk during a study of 6 lactatin
weeks postpartum), who received duloxetine 40 mg twice daily for 3.5 da
mcg/day (range, 4 to 15 mcg/day). The estimated daily infant dose was 2
approximately 0.14% (maximum 0.25%) of the maternal dose. The mean
0.25 (95% CI, 0.18 to 0.35). Excretion of duloxetine metabolites into brea

3.5 Drug Interactions

3.5.1 Drug-Drug Combinations

Abciximab

Aceclofenac

Acemetacin

Acenocoumarol

Acetophenazine

Alclofenac

Almotriptan

Amineptine

Amitriptyline

Amitriptylinoxide

Amoxapine

Anagrelide

Ancrod

Anisindione

Antithrombin III Human

Ardeparin

Aspirin

Benoxaprofen

Bivalirudin

Bromfenac

Bufexamac

Carprofen

Celecoxib

Certoparin

Chlorpromazine

Cifenline

Cilostazol

Ciprofloxacin

Citalopram

Clomipramine

Clonixin

Clopidogrel

Cyclobenzaprine

Dalteparin

Danaparoid

Defibrotide

Dermatan Sulfate

Desipramine

Desirudin

Desvenlafaxine

Dexketoprofen

Dibenzepin

Diclofenac

Dicumarol

Diflunisal

Dipyridamole

Dipyrone

Dixyrazine

Dothiepin

Doxepin

Droxicam

Eletriptan

Encainide

Enoxacin

Enoxaparin

Epoprostenol

Eptifibatide

Escitalopram

Ethopropazine

Etodolac

Etofenamate

Etoricoxib

Felbinac

Fenbufen

Fenoprofen

Fentiazac

Flecainide

Floctafenine

Flufenamic Acid

Fluoxetine

Fluphenazine

Flurbiprofen

Fluvoxamine

Fondaparinux

Frovatriptan

Heparin

Ibuprofen

Iloprost

Imipramine

Indecainide

Indomethacin

Indoprofen

Isocarboxazid

Isoxicam

Ketoprofen

Ketorolac

Lamifiban

Lexipafant

Linezolid

Lithium

Lofepramine

Lorcainide

Lornoxicam

Meclofenamate

Mefenamic Acid

Melitracen

Meloxicam

Mesoridazine

Methdilazine

Methotrimeprazine

Metopimazine

Milnacipran

Morniflumate

Nabumetone

Nadroparin

Naproxen

Naratriptan

Niflumic Acid

Nimesulide

Nortriptyline

Opipramol

Oxaprozin

Parecoxib

Parnaparin

Paroxetine

Pentosan Polysulfate Sodium

Perazine

Periciazine

Perphenazine

Phenindione

Phenprocoumon

Phenylbutazone

Pipotiazine

Pirazolac

Piroxicam

Pirprofen

Procarbazine

Prochlorperazine

Promazine

Promethazine

Propafenone

Propiomazine

Propyphenazone

Proquazone

Protriptyline

Quinidine

Rasagiline

Rasagiline

Recainam

Reviparin

Rizatriptan

Rofecoxib

Selegiline

Sertraline

Sibrafiban

St John's Wort

Sulfinpyrazone

Sulindac

Sulodexide

Sumatriptan

Suprofen

Tamoxifen

Tapentadol

Tenidap

Tenoxicam

Thiethylperazine

Thiopropazate

Thioproperazine

Thioridazine

Tianeptine

Tiaprofenic Acid

Ticlopidine

Tinzaparin

Tirofiban

Tolmetin

Tramadol

Tranylcypromine

Trifluoperazine

Triflupromazine

Trimeprazine

Trimipramine

Tryptophan

Valdecoxib

Venlafaxine

Warfarin

Xemilofiban

Zolmitriptan

Zomepirac

3.5.1.A Abciximab

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta
that the combined use of selective serotonin and norepinephrine reuptake
been associated with an increased risk of bleeding. Bleeding events repo
petechiae, and life-threatening hemorrhages (Prod Info CYMBALTA(R) de
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When duloxetine and an antiplatelet agent are g
bleeding (Prod Info CYMBALTA(R) delayed-release oral capsules, 2008).
7) Probable Mechanism: unknown

3.5.1.B Aceclofenac

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta
that the combined use of selective serotonin and norepinephrine reuptake
associated with an increased risk of bleeding. Bleeding events have inclu

threatening hemorrhages (Prod Info CYMBALTA(R) oral delayed-release
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When duloxetine and a nonsteroidal antiinflamm
increased bleeding (Prod Info CYMBALTA(R) oral delayed-release capsu
7) Probable Mechanism: unknown

3.5.1.C Acemetacin

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta
that the combined use of selective serotonin and norepinephrine reuptake
associated with an increased risk of bleeding. Bleeding events have inclu
threatening hemorrhages (Prod Info CYMBALTA(R) oral delayed-release
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When duloxetine and a nonsteroidal antiinflamm
increased bleeding (Prod Info CYMBALTA(R) oral delayed-release capsu
7) Probable Mechanism: unknown

3.5.1.D Acenocoumarol

1) Interaction Effect: increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta
that the combined use of selective serotonin and norepinephrine reuptake
associated with an increased risk of bleeding. Bleeding events reported h
life-threatening hemorrhages. A population-based, case-controlled study
with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted
bleeding (Schalekamp et al, 2008). Altered anticoagulant effects (includin
coadministration of serotonin and norepinephrine reuptake inhibitors with
release oral capsules, 2008). Conversely, one case report described a pe
dose in a patient maintained on acenocoumarol (Monastero et al, 2007).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When duloxetine and an anticoagulant are giver
Patients who are taking warfarin should be monitored closely for altered a
duloxetine therapy is initiated or discontinued (Prod Info CYMBALTA(R) d
7) Probable Mechanism: unknown
8) Literature Reports
a) A population-based, case-controlled study of new coumarin users
selective serotonin reuptake inhibitors (SSRIs) resulted in an increas
Using national pharmacy and hospitalization records, Netherlands re
abnormal bleeding and compared them with 5818 control subjects al
was 220 days (range, 1 to 4690 days). Patients on SSRIs showed gr
(adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.
0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et
b) A case report describes a 44-year-old female patient maintained
after 55 days of concomitant duloxetine treatment. Warfarin was initia
medication regimen included atorvastatin 10 mg, warfarin 7.5 mg to 1
mg, and albuterol extended-release 4 mg twice a day. Duloxetine 30
day 58, only the warfarin was discontinued, and by day 85 the patien
mcg/mL (therapeutic range 2 to 8 mcg/mL). Intravenous vitamin K 10
the INR was again elevated at 6.4, vitamin K-dependent clotting facto
normal. Duloxetine was then discontinued, and 4 days later the INR
to 54%. INR was 0.9 by day 105, and warfarin was restarted on day
maintained on 7.5 to 10 mg/day. According to the Naranjo algorithm,
probable. The authors suggest that duloxetine may have an effect on
warfarin from its protein-binding sites, or may have unique metabolic
c) A 63-year-old woman successfully maintained on acenocoumarol
mechanical, prosthetic mitral-valve substitution experienced a persist
mg/day. Ten hours after taking duloxetine, the patient was taken to th
blood pressure had increased to 190/110 mmHg and her INR had dra
administered intravenously for the headache and hypertension, dulox
titrated to 12 mg/wk. Twenty-one days later, the INR returned to base
Follow-up examinations on days 28, 56, 84, 168, and 252 revealed st
family interviews discounted the possibility of acenocoumarol self-into

measured and the patient was not genotyped for CYP2D6 or CYP1A2 duloxetine was deemed as probable based on the Naranjo Adverse D

3.5.1.E Acetophenazine

1) Interaction Effect: increased phenothiazine serum concentrations and orthostatic hypotension, hyperthermia, extrapyramidal effects)
2) Summary: Duloxetine is a moderately potent inhibitor of CYP2D6; ther likely to increase bioavailability of the phenothiazine agent, increasing the delayed-release oral capsules, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Use caution when prescribing duloxetine to pati elevated phenothiazine plasma concentrations. Monitor for increased phe release oral capsules, 2008).
7) Probable Mechanism: duloxetine inhibition of CYP2D6-mediated phen

3.5.1.F Alclofenac

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta that the combined use of selective serotonin and norepinephrine reuptake associated with an increased risk of bleeding. Bleeding events have inclu threatening hemorrhages (Prod Info CYMBALTA(R) oral delayed-release
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When duloxetine and a nonsteroidal antiinflamm increased bleeding (Prod Info CYMBALTA(R) oral delayed-release capsu
7) Probable Mechanism: unknown

3.5.1.G Almotriptan

1) Interaction Effect: increased risk of serotonin syndrome
2) Summary: A life-threatening condition known as serotonin syndrome m combination with a serotonin and norepinephrine reuptake inhibitor (SNRI include restlessness, hallucinations, loss of coordination, fast heart beat, overreactive reflexes, nausea, vomiting, and diarrhea. Clinicians should b that either the triptan or the SNRI may be prescribed by a different physic are prescribed this combination and monitor them closely for symptoms o dose increases (Prod Info CYMBALTA(R) delayed-release oral capsules,
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of a triptan, such as almotripta (SNRI), such as duloxetine, may result in a life-threatening condition calle commonly used intermittently and that either the triptan or the SNRI may b together, discuss the risks of serotonin syndrome with the patient and mo hyperthermia, hyperreflexia, incoordination), especially during treatment i release oral capsules, 2008).
7) Probable Mechanism: additive pharmacologic effects resulting in exce

3.5.1.H Amineptine

1) Interaction Effect: increased tricyclic antidepressant serum concentrati confusion, cardiac arrhythmias)
2) Summary: The coadministration of duloxetine with a tricyclic antidepre increasing the risk of adverse events. Duloxetine is a moderately potent i substrate desipramine 50 mg and duloxetine 60 mg twice daily were coad baseline (Prod Info CYMBALTA(R) delayed-release oral capsules, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Use caution with the combined use of duloxetin with duloxetine and a TCA is unavoidable, plasma concentrations of the t made accordingly (Prod Info CYMBALTA(R) delayed-release oral capsule TCA toxicity (anticholinergic effects, sedation, confusion, and cardiac arrh
7) Probable Mechanism: duloxetine inhibition of CYP2D6-mediated tricyc

3.5.1.I Amitriptyline

1) Interaction Effect: increased tricyclic antidepressant serum concentrati
confusion, cardiac arrhythmias)
2) Summary: The coadministration of duloxetine with a tricyclic antidepre
increasing the risk of adverse events. Duloxetine is a moderately potent ir
substrate desipramine 50 mg and duloxetine 60 mg twice daily were coad
baseline (Prod Info CYMBALTA(R) delayed-release oral capsules, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Use caution with the combined use of duloxetine
with duloxetine and a TCA is unavoidable, plasma concentrations of the tr
made accordingly (Prod Info CYMBALTA(R) delayed-release oral capsule
TCA toxicity (anticholinergic effects, sedation, confusion, and cardiac arrh
7) Probable Mechanism: duloxetine inhibition of CYP2D6-mediated tricyc

3.5.1.J Amitriptylinoxide
1) Interaction Effect: increased tricyclic antidepressant serum concentrati
confusion, cardiac arrhythmias)
2) Summary: The coadministration of duloxetine with a tricyclic antidepre
increasing the risk of adverse events. Duloxetine is a moderately potent ir
substrate desipramine 50 mg and duloxetine 60 mg twice daily were coad
baseline (Prod Info CYMBALTA(R) delayed-release oral capsules, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Use caution with the combined use of duloxetine
with duloxetine and a TCA is unavoidable, plasma concentrations of the tr
made accordingly (Prod Info CYMBALTA(R) delayed-release oral capsule
TCA toxicity (anticholinergic effects, sedation, confusion, and cardiac arrh
7) Probable Mechanism: duloxetine inhibition of CYP2D6-mediated tricyc

3.5.1.K Amoxapine
1) Interaction Effect: increased tricyclic antidepressant serum concentrati
confusion, cardiac arrhythmias)
2) Summary: The coadministration of duloxetine with a tricyclic antidepre
increasing the risk of adverse events. Duloxetine is a moderately potent ir
substrate desipramine 50 mg and duloxetine 60 mg twice daily were coad
baseline (Prod Info CYMBALTA(R) delayed-release oral capsules, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Use caution with the combined use of duloxetine
with duloxetine and a TCA is unavoidable, plasma concentrations of the tr
made accordingly (Prod Info CYMBALTA(R) delayed-release oral capsule
TCA toxicity (anticholinergic effects, sedation, confusion, and cardiac arrh
7) Probable Mechanism: duloxetine inhibition of CYP2D6-mediated tricyc

3.5.1.L Anagrelide
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta
that the combined use of selective serotonin and norepinephrine reuptake
been associated with an increased risk of bleeding. Bleeding events repor
petechiae, and life-threatening hemorrhages (Prod Info CYMBALTA(R) de
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When duloxetine and an antiplatelet agent are g
bleeding (Prod Info CYMBALTA(R) delayed-release oral capsules, 2008).
7) Probable Mechanism: unknown

3.5.1.M Ancrod
1) Interaction Effect: increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta
that the combined use of selective serotonin and norepinephrine reuptake
associated with an increased risk of bleeding. Bleeding events reported h
life-threatening hemorrhages. A population-based, case-controlled study
with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted i

bleeding (Schalekamp et al, 2008). Altered anticoagulant effects (includin
coadministration of serotonin and norepinephrine reuptake inhibitors with
release oral capsules, 2008). Conversely, one case report described a pe
dose in a patient maintained on acenocoumarol (Monastero et al, 2007).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When duloxetine and an anticoagulant are giver
Patients who are taking warfarin should be monitored closely for altered a
duloxetine therapy is initiated or discontinued (Prod Info CYMBALTA(R) d
7) Probable Mechanism: unknown
8) Literature Reports
a) A population-based, case-controlled study of new coumarin users
selective serotonin reuptake inhibitors (SSRIs) resulted in an increas
Using national pharmacy and hospitalization records, Netherlands re
abnormal bleeding and compared them with 5818 control subjects al
was 220 days (range, 1 to 4690 days). Patients on SSRIs showed gr
(adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.
0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et
b) A case report describes a 44-year-old female patient maintained
after 55 days of concomitant duloxetine treatment. Warfarin was initia
medication regimen included atorvastatin 10 mg, warfarin 7.5 mg to 1
mg, and albuterol extended-release 4 mg twice a day. Duloxetine 30
day 58, only the warfarin was discontinued, and by day 85 the patien
mcg/mL (therapeutic range 2 to 8 mcg/mL). Intravenous vitamin K 10
the INR was again elevated at 6.4, vitamin K-dependent clotting facto
normal. Duloxetine was then discontinued, and 4 days later the INR r
to 54%. INR was 0.9 by day 105, and warfarin was restarted on day
maintained on 7.5 to 10 mg/day. According to the Naranjo algorithm,
probable. The authors suggest that duloxetine may have an effect on
warfarin from its protein-binding sites, or may have unique metabolic
c) A 63-year-old woman successfully maintained on acenocoumarol
mechanical, prosthetic mitral-valve substitution experienced a persist
mg/day. Ten hours after taking duloxetine, the patient was taken to th
blood pressure had increased to 190/110 mmHg and her INR had dra
administered intravenously for the headache and hypertension, dulox
titrated to 12 mg/wk. Twenty-one days later, the INR returned to base
Follow-up examinations on days 28, 56, 84, 168, and 252 revealed st
family interviews discounted the possibility of acenocoumarol self-into
measured and the patient was not genotyped for CYP2D6 or CYP1A2
duloxetine was deemed as probable based on the Naranjo Adverse D

3.5.1.N Anisindione

1) Interaction Effect: increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta
that the combined use of selective serotonin and norepinephrine reuptake
associated with an increased risk of bleeding. Bleeding events reported h
life-threatening hemorrhages. A population-based, case-controlled study o
with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted i
bleeding (Schalekamp et al, 2008). Altered anticoagulant effects (includin
coadministration of serotonin and norepinephrine reuptake inhibitors with
release oral capsules, 2008). Conversely, one case report described a pe
dose in a patient maintained on acenocoumarol (Monastero et al, 2007).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When duloxetine and an anticoagulant are giver
Patients who are taking warfarin should be monitored closely for altered a
duloxetine therapy is initiated or discontinued (Prod Info CYMBALTA(R) d
7) Probable Mechanism: unknown
8) Literature Reports
a) A population-based, case-controlled study of new coumarin users
selective serotonin reuptake inhibitors (SSRIs) resulted in an increas
Using national pharmacy and hospitalization records, Netherlands re
abnormal bleeding and compared them with 5818 control subjects al
was 220 days (range, 1 to 4690 days). Patients on SSRIs showed gr
(adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.

0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et
b) A case report describes a 44-year-old female patient maintained o
after 55 days of concomitant duloxetine treatment. Warfarin was initia
medication regimen included atorvastatin 10 mg, warfarin 7.5 mg to 1
mg, and albuterol extended-release 4 mg twice a day. Duloxetine 30
day 58, only the warfarin was discontinued, and by day 85 the patient
mcg/mL (therapeutic range 2 to 8 mcg/mL). Intravenous vitamin K 10
the INR was again elevated at 6.4, vitamin K-dependent clotting factc
normal. Duloxetine was then discontinued, and 4 days later the INR r
to 54%. INR was 0.9 by day 105, and warfarin was restarted on day
maintained on 7.5 to 10 mg/day. According to the Naranjo algorithm,
probable. The authors suggest that duloxetine may have an effect on
warfarin from its protein-binding sites, or may have unique metabolic
c) A 63-year-old woman successfully maintained on acenocoumarol
mechanical, prosthetic mitral-valve substitution experienced a persist
mg/day. Ten hours after taking duloxetine, the patient was taken to th
blood pressure had increased to 190/110 mmHg and her INR had dra
administered intravenously for the headache and hypertension, dulox
titrated to 12 mg/wk. Twenty-one days later, the INR returned to base
Follow-up examinations on days 28, 56, 84, 168, and 252 revealed st
family interviews discounted the possibility of acenocoumarol self-intc
measured and the patient was not genotyped for CYP2D6 or CYP1A2
duloxetine was deemed as probable based on the Naranjo Adverse D

3.5.1.O Antithrombin III Human

1) Interaction Effect: increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintа
that the combined use of selective serotonin and norepinephrine reuptake
associated with an increased risk of bleeding. Bleeding events reported h
life-threatening hemorrhages. A population-based, case-controlled study c
with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted i
bleeding (Schalekamp et al, 2008). Altered anticoagulant effects (includin
coadministration of serotonin and norepinephrine reuptake inhibitors with
release oral capsules, 2008). Conversely, one case report described a pe
dose in a patient maintained on acenocoumarol (Monastero et al, 2007).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When duloxetine and an anticoagulant are given
Patients who are taking warfarin should be monitored closely for altered a
duloxetine therapy is initiated or discontinued (Prod Info CYMBALTA(R) d
7) Probable Mechanism: unknown
8) Literature Reports
a) A population-based, case-controlled study of new coumarin users
selective serotonin reuptake inhibitors (SSRIs) resulted in an increase
Using national pharmacy and hospitalization records, Netherlands res
abnormal bleeding and compared them with 5818 control subjects als
was 220 days (range, 1 to 4690 days). Patients on SSRIs showed gr
(adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5
0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et
b) A case report describes a 44-year-old female patient maintained o
after 55 days of concomitant duloxetine treatment. Warfarin was initia
medication regimen included atorvastatin 10 mg, warfarin 7.5 mg to 1
mg, and albuterol extended-release 4 mg twice a day. Duloxetine 30
day 58, only the warfarin was discontinued, and by day 85 the patient
mcg/mL (therapeutic range 2 to 8 mcg/mL). Intravenous vitamin K 10
the INR was again elevated at 6.4, vitamin K-dependent clotting factc
normal. Duloxetine was then discontinued, and 4 days later the INR r
to 54%. INR was 0.9 by day 105, and warfarin was restarted on day
maintained on 7.5 to 10 mg/day. According to the Naranjo algorithm,
probable. The authors suggest that duloxetine may have an effect on
warfarin from its protein-binding sites, or may have unique metabolic
c) A 63-year-old woman successfully maintained on acenocoumarol
mechanical, prosthetic mitral-valve substitution experienced a persist
mg/day. Ten hours after taking duloxetine, the patient was taken to th
blood pressure had increased to 190/110 mmHg and her INR had dra
administered intravenously for the headache and hypertension, dulox

titrated to 12 mg/wk. Twenty-one days later, the INR returned to base
Follow-up examinations on days 28, 56, 84, 168, and 252 revealed st
family interviews discounted the possibility of acenocoumarol self-intc
measured and the patient was not genotyped for CYP2D6 or CYP1A2
duloxetine was deemed as probable based on the Naranjo Adverse D

3.5.1.P Ardeparin

1) Interaction Effect: increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for mainta
that the combined use of selective serotonin and norepinephrine reuptake
associated with an increased risk of bleeding. Bleeding events reported h
life-threatening hemorrhages. A population-based, case-controlled study c
with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted i
bleeding (Schalekamp et al, 2008). Altered anticoagulant effects (includin
coadministration of serotonin and norepinephrine reuptake inhibitors with
release oral capsules, 2008). Conversely, one case report described a pe
dose in a patient maintained on acenocoumarol (Monastero et al, 2007).

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: When duloxetine and an anticoagulant are giver
Patients who are taking warfarin should be monitored closely for altered a
duloxetine therapy is initiated or discontinued (Prod Info CYMBALTA(R) d

7) Probable Mechanism: unknown

8) Literature Reports

a) A population-based, case-controlled study of new coumarin users
selective serotonin reuptake inhibitors (SSRIs) resulted in an increas
Using national pharmacy and hospitalization records, Netherlands re
abnormal bleeding and compared them with 5818 control subjects als
was 220 days (range, 1 to 4690 days). Patients on SSRIs showed gr
(adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5
0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et

b) A case report describes a 44-year-old female patient maintained c
after 55 days of concomitant duloxetine treatment. Warfarin was initia
medication regimen included atorvastatin 10 mg, warfarin 7.5 mg to 1
mg, and albuterol extended-release 4 mg twice a day. Duloxetine 30
day 58, only the warfarin was discontinued, and by day 85 the patien
mcg/mL (therapeutic range 2 to 8 mcg/mL). Intravenous vitamin K 10
the INR was again elevated at 6.4, vitamin K-dependent clotting factc
normal. Duloxetine was then discontinued, and 4 days later the INR r
to 54%. INR was 0.9 by day 105, and warfarin was restarted on day 1
maintained on 7.5 to 10 mg/day. According to the Naranjo algorithm,
probable. The authors suggest that duloxetine may have an effect on
warfarin from its protein-binding sites, or may have unique metabolic

c) A 63-year-old woman successfully maintained on acenocoumarol
mechanical, prosthetic mitral-valve substitution experienced a persist
mg/day. Ten hours after taking duloxetine, the patient was taken to th
blood pressure had increased to 190/110 mmHg and her INR had dra
administered intravenously for the headache and hypertension, dulox
titrated to 12 mg/wk. Twenty-one days later, the INR returned to base
Follow-up examinations on days 28, 56, 84, 168, and 252 revealed st
family interviews discounted the possibility of acenocoumarol self-intc
measured and the patient was not genotyped for CYP2D6 or CYP1A2
duloxetine was deemed as probable based on the Naranjo Adverse D

3.5.1.Q Aspirin

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for mainta
that the combined use of selective serotonin and norepinephrine reuptake
been associated with an increased risk of bleeding. Bleeding events repor
petechiae, and life-threatening hemorrhages (Prod Info CYMBALTA(R) de

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When duloxetine and an antiplatelet agent are g
bleeding (Prod Info CYMBALTA(R) delayed-release oral capsules, 2008).

7) Probable Mechanism: unknown

3.5.1.R Benoxaprofen

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for mainta
that the combined use of selective serotonin and norepinephrine reuptake
associated with an increased risk of bleeding. Bleeding events have inclu
threatening hemorrhages (Prod Info CYMBALTA(R) oral delayed-release

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When duloxetine and a nonsteroidal antiinflamm
increased bleeding (Prod Info CYMBALTA(R) oral delayed-release capsu

7) Probable Mechanism: unknown

3.5.1.S Bivalirudin

1) Interaction Effect: increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for mainta
that the combined use of selective serotonin and norepinephrine reuptake
associated with an increased risk of bleeding. Bleeding events reported h
life-threatening hemorrhages. A population-based, case-controlled study
with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted
bleeding (Schalekamp et al, 2008). Altered anticoagulant effects (includin
coadministration of serotonin and norepinephrine reuptake inhibitors with
release oral capsules, 2008). Conversely, one case report described a pe
dose in a patient maintained on acenocoumarol (Monastero et al, 2007).

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: When duloxetine and an anticoagulant are giver
Patients who are taking warfarin should be monitored closely for altered a
duloxetine therapy is initiated or discontinued (Prod Info CYMBALTA(R) d

7) Probable Mechanism: unknown

8) Literature Reports

a) A population-based, case-controlled study of new coumarin users
selective serotonin reuptake inhibitors (SSRIs) resulted in an increas
Using national pharmacy and hospitalization records, Netherlands re
abnormal bleeding and compared them with 5818 control subjects al
was 220 days (range, 1 to 4690 days). Patients on SSRIs showed gr
(adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5
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after 55 days of concomitant duloxetine treatment. Warfarin was initia
medication regimen included atorvastatin 10 mg, warfarin 7.5 mg to 1
mg, and albuterol extended-release 4 mg twice a day. Duloxetine 30
day 58, only the warfarin was discontinued, and by day 85 the patien
mcg/mL (therapeutic range 2 to 8 mcg/mL). Intravenous vitamin K 10
the INR was again elevated at 6.4, vitamin K-dependent clotting facto
normal. Duloxetine was then discontinued, and 4 days later the INR r
to 54%. INR was 0.9 by day 105, and warfarin was restarted on day
maintained on 7.5 to 10 mg/day. According to the Naranjo algorithm,
probable. The authors suggest that duloxetine may have an effect on
warfarin from its protein-binding sites, or may have unique metabolic

c) A 63-year-old woman successfully maintained on acenocoumarol
mechanical, prosthetic mitral-valve substitution experienced a persist
mg/day. Ten hours after taking duloxetine, the patient was taken to th
blood pressure had increased to 190/110 mmHg and her INR had dra
administered intravenously for the headache and hypertension, dulox
titrated to 12 mg/wk. Twenty-one days later, the INR returned to base
Follow-up examinations on days 28, 56, 84, 168, and 252 revealed st
family interviews discounted the possibility of acenocoumarol self-into
measured and the patient was not genotyped for CYP2D6 or CYP1A2
duloxetine was deemed as probable based on the Naranjo Adverse D

3.5.1.T Bromfenac

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for mainta
that the combined use of selective serotonin and norepinephrine reuptake

associated with an increased risk of bleeding. Bleeding events have inclu
threatening hemorrhages (Prod Info CYMBALTA(R) oral delayed-release
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When duloxetine and a nonsteroidal antiinflamm
increased bleeding (Prod Info CYMBALTA(R) oral delayed-release capsu
7) Probable Mechanism: unknown

3.5.1.U Bufexamac
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta
that the combined use of selective serotonin and norepinephrine reuptake
associated with an increased risk of bleeding. Bleeding events have inclu
threatening hemorrhages (Prod Info CYMBALTA(R) oral delayed-release
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When duloxetine and a nonsteroidal antiinflamm
increased bleeding (Prod Info CYMBALTA(R) oral delayed-release capsu
7) Probable Mechanism: unknown

3.5.1.V Carprofen
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta
that the combined use of selective serotonin and norepinephrine reuptake
associated with an increased risk of bleeding. Bleeding events have inclu
threatening hemorrhages (Prod Info CYMBALTA(R) oral delayed-release
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When duloxetine and a nonsteroidal antiinflamm
increased bleeding (Prod Info CYMBALTA(R) oral delayed-release capsu
7) Probable Mechanism: unknown

3.5.1.W Celecoxib
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta
that the combined use of selective serotonin and norepinephrine reuptake
associated with an increased risk of bleeding. Bleeding events have inclu
threatening hemorrhages (Prod Info CYMBALTA(R) oral delayed-release
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When duloxetine and a nonsteroidal antiinflamm
increased bleeding (Prod Info CYMBALTA(R) oral delayed-release capsu
7) Probable Mechanism: unknown

3.5.1.X Certoparin
1) Interaction Effect: increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta
that the combined use of selective serotonin and norepinephrine reuptake
associated with an increased risk of bleeding. Bleeding events reported h
life-threatening hemorrhages. A population-based, case-controlled study
with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted
bleeding (Schalekamp et al, 2008). Altered anticoagulant effects (includin
coadministration of serotonin and norepinephrine reuptake inhibitors with
release oral capsules, 2008). Conversely, one case report described a pe
dose in a patient maintained on acenocoumarol (Monastero et al, 2007).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When duloxetine and an anticoagulant are giver
Patients who are taking warfarin should be monitored closely for altered a
duloxetine therapy is initiated or discontinued (Prod Info CYMBALTA(R) d
7) Probable Mechanism: unknown
8) Literature Reports

a) A population-based, case-controlled study of new coumarin users selective serotonin reuptake inhibitors (SSRIs) resulted in an increas Using national pharmacy and hospitalization records, Netherlands re abnormal bleeding and compared them with 5818 control subjects al was 220 days (range, 1 to 4690 days). Patients on SSRIs showed gr (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et
b) A case report describes a 44-year-old female patient maintained c after 55 days of concomitant duloxetine treatment. Warfarin was initia medication regimen included atorvastatin 10 mg, warfarin 7.5 mg to 1 mg, and albuterol extended-release 4 mg twice a day. Duloxetine 30 day 58, only the warfarin was discontinued, and by day 85 the patien mcg/mL (therapeutic range 2 to 8 mcg/mL). Intravenous vitamin K 10 the INR was again elevated at 6.4, vitamin K-dependent clotting facto normal. Duloxetine was then discontinued, and 4 days later the INR r to 54%. INR was 0.9 by day 105, and warfarin was restarted on day maintained on 7.5 to 10 mg/day. According to the Naranjo algorithm, probable. The authors suggest that duloxetine may have an effect on warfarin from its protein-binding sites, or may have unique metabolic
c) A 63-year-old woman successfully maintained on acenocoumarol mechanical, prosthetic mitral-valve substitution experienced a persist mg/day. Ten hours after taking duloxetine, the patient was taken to th blood pressure had increased to 190/110 mmHg and her INR had dra administered intravenously for the headache and hypertension, dulox titrated to 12 mg/wk. Twenty-one days later, the INR returned to base Follow-up examinations on days 28, 56, 84, 168, and 252 revealed st family interviews discounted the possibility of acenocoumarol self-into measured and the patient was not genotyped for CYP2D6 or CYP1A2 duloxetine was deemed as probable based on the Naranjo Adverse D

3.5.1.Y Chlorpromazine

1) Interaction Effect: increased phenothiazine serum concentrations and orthostatic hypotension, hyperthermia, extrapyramidal effects)
2) Summary: Duloxetine is a moderately potent inhibitor of CYP2D6; ther likely to increase bioavailability of the phenothiazine agent, increasing the delayed-release oral capsules, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Use caution when prescribing duloxetine to pati elevated phenothiazine plasma concentrations. Monitor for increased phe release oral capsules, 2008).
7) Probable Mechanism: duloxetine inhibition of CYP2D6-mediated phen

3.5.1.Z Cifenline

1) Interaction Effect: increased class IC antiarrhythmic serum concentrati torsades de pointes, cardiac arrest)
2) Summary: Duloxetine is a moderately potent inhibitor of CYP2D6. Give antiarrhythmic agents as well as considering that they are CYP2D6 substr whenever duloxetine is coadministered with this class of antiarrhythmic ag 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Use caution when prescribing duloxetine to pati cause elevated plasma concentrations of the antiarrhythmic (Prod Info CY class IC antiarrhythmic serum concentrations and ECG for signs of potent hypotension); adjust dose accordingly. Alternatively, consider selecting an pharmacokinetics of class IC antiarrhythmic agents.
7) Probable Mechanism: inhibition of CYP2D6-mediated metabolism of cl

3.5.1.AA Cilostazol

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta that the combined use of selective serotonin and norepinephrine reuptake been associated with an increased risk of bleeding. Bleeding events repor petechiae, and life-threatening hemorrhages (Prod Info CYMBALTA(R) de

3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When duloxetine and an antiplatelet agent are g
bleeding (Prod Info CYMBALTA(R) delayed-release oral capsules, 2008).
7) Probable Mechanism: unknown

3.5.1.AB Ciprofloxacin
1) Interaction Effect: increased duloxetine bioavailability and risk of adver
2) Summary: Since duloxetine is a substrate for cytochrome P450 isoforn
expected to occur in the presence of coadministration with ciprofloxacin, a
and about 2.5-fold, respectively, when duloxetine was administered with fl
(R) delayed-release oral capsules, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Use caution with the concomitant use of ciproflo
exposure and serum levels (Prod Info CYMBALTA(R) delayed-release ora
events and adjust duloxetine dose as necessary.
7) Probable Mechanism: inhibition of CYP1A2-mediated duloxetine metal

3.5.1.AC Citalopram
1) Interaction Effect: an increased risk of serotonin syndrome
2) Summary: Duloxetine is a selective serotonin and norepinephrine reup
citalopram, a selective serotonin reuptake inhibitor, is not recommended c
CYMBALTA(R) delayed-release oral capsules, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concomitant use of citalopram and duloxetir
serotonin syndrome (Prod Info CYMBALTA(R) delayed-release oral capsu
7) Probable Mechanism: potentiation of serotonergic activity in the CNS b

3.5.1.AD Clomipramine
1) Interaction Effect: increased tricyclic antidepressant serum concentrati
confusion, cardiac arrhythmias)
2) Summary: The coadministration of duloxetine with a tricyclic antidepre
increasing the risk of adverse events. Duloxetine is a moderately potent ir
substrate desipramine 50 mg and duloxetine 60 mg twice daily were coad
baseline (Prod Info CYMBALTA(R) delayed-release oral capsules, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Use caution with the combined use of duloxetine
with duloxetine and a TCA is unavoidable, plasma concentrations of the tr
made accordingly (Prod Info CYMBALTA(R) delayed-release oral capsule
TCA toxicity (anticholinergic effects, sedation, confusion, and cardiac arrh
7) Probable Mechanism: duloxetine inhibition of CYP2D6-mediated tricyc

3.5.1.AE Clonixin
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta
that the combined use of selective serotonin and norepinephrine reuptake
associated with an increased risk of bleeding. Bleeding events have inclu
threatening hemorrhages (Prod Info CYMBALTA(R) oral delayed-release
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When duloxetine and a nonsteroidal antiinflamm
increased bleeding (Prod Info CYMBALTA(R) oral delayed-release capsu
7) Probable Mechanism: unknown

3.5.1.AF Clopidogrel
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta
that the combined use of selective serotonin and norepinephrine reuptake
been associated with an increased risk of bleeding. Bleeding events repor

petechiae, and life-threatening hemorrhages (Prod Info CYMBALTA(R) de
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When duloxetine and an antiplatelet agent are g
bleeding (Prod Info CYMBALTA(R) delayed-release oral capsules, 2008).
7) Probable Mechanism: unknown

3.5.1.AG Cyclobenzaprine

1) Interaction Effect: an increased risk of serotonin syndrome
2) Summary: Concomitant use of cyclobenzaprine and duloxetine resulte
Other possibly contributing drugs in this case were bupropion and opiates
concomitant use of cyclobenzaprine and duloxetine is warranted, monitor
abnormalities (including hyper-reflexia, tremor, muscle rigidity, clonus, pe
(including tachycardia, mydriasis, diaphoresis, and the presence of bowel
agitation and delirium). Discuss the risks and symptoms of serotonin syn
serotonin syndrome develops, discontinue the offending drugs, and provi
necessary (Boyer & Shannon, 2005).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: A case of serotonin syndrome was reported wit
therefore, concomitant use is discouraged. Other possibly contributing dr
hydromorphone) (Keegan et al, 2006). If cyclobenzaprine and duloxetine
syndrome such as neuromuscular abnormalities (including hyper-reflexia,
shivering), autonomic hyperactivity (including tachycardia, mydriasis, diap
mental status changes (including agitation and delirium). Serotonin syndr
discontinue the offending agents and provide supportive care, correction
Shannon, 2005).
7) Probable Mechanism: additive serotonergic effects
8) Literature Reports
a) A 53-year-old male on duloxetine experienced serotonin syndrom
patient had a history of chronic pain and depression. His previous me
oxycodone for several weeks, bupropion 300 mg/day for more than 6
for an unstated time. On the second day after an uneventful surgical
hallucinations shortly after starting cyclobenzaprine 10 mg 3 times da
tachycardia, marked agitation, pronounced tremors, spontaneous sus
Laboratory analysis revealed hypernatremia (154 mEq/L), lactic acido
(peaked at 265 units/L). Severe agitation required administration of p
treated with hydration, a beta-blocker, and cyproheptadine 8 mg via r
and duloxetine were discontinued. Improvement occurred over the fo
without any complications. Other possibly contributing drugs towards
or hydromorphone) (Keegan et al, 2006).

3.5.1.AH Dalteparin

1) Interaction Effect: increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta
that the combined use of selective serotonin and norepinephrine reuptake
associated with an increased risk of bleeding. Bleeding events reported h
life-threatening hemorrhages. A population-based, case-controlled study
with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted
bleeding (Schalekamp et al, 2008). Altered anticoagulant effects (includin
coadministration of serotonin and norepinephrine reuptake inhibitors with
release oral capsules, 2008). Conversely, one case report described a pe
dose in a patient maintained on acenocoumarol (Monastero et al, 2007).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When duloxetine and an anticoagulant are giver
Patients who are taking warfarin should be monitored closely for altered a
duloxetine therapy is initiated or discontinued (Prod Info CYMBALTA(R) d
7) Probable Mechanism: unknown
8) Literature Reports
a) A population-based, case-controlled study of new coumarin users
selective serotonin reuptake inhibitors (SSRIs) resulted in an increas
Using national pharmacy and hospitalization records, Netherlands re
abnormal bleeding and compared them with 5818 control subjects al

was 220 days (range, 1 to 4690 days). Patients on SSRIs showed gr
(adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5
0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et
b) A case report describes a 44-year-old female patient maintained
after 55 days of concomitant duloxetine treatment. Warfarin was initia
medication regimen included atorvastatin 10 mg, warfarin 7.5 mg to 1
mg, and albuterol extended-release 4 mg twice a day. Duloxetine 30
day 58, only the warfarin was discontinued, and by day 85 the patien
mcg/mL (therapeutic range 2 to 8 mcg/mL). Intravenous vitamin K 10
the INR was again elevated at 6.4, vitamin K-dependent clotting facto
normal. Duloxetine was then discontinued, and 4 days later the INR r
to 54%. INR was 0.9 by day 105, and warfarin was restarted on day
maintained on 7.5 to 10 mg/day. According to the Naranjo algorithm,
probable. The authors suggest that duloxetine may have an effect on
warfarin from its protein-binding sites, or may have unique metabolic
c) A 63-year-old woman successfully maintained on acenocoumarol
mechanical, prosthetic mitral-valve substitution experienced a persist
mg/day. Ten hours after taking duloxetine, the patient was taken to th
blood pressure had increased to 190/110 mmHg and her INR had dra
administered intravenously for the headache and hypertension, dulox
titrated to 12 mg/wk. Twenty-one days later, the INR returned to base
Follow-up examinations on days 28, 56, 84, 168, and 252 revealed st
family interviews discounted the possibility of acenocoumarol self-into
measured and the patient was not genotyped for CYP2D6 or CYP1A2
duloxetine was deemed as probable based on the Naranjo Adverse D

3.5.1.AI Danaparoid

1) Interaction Effect: increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for mainta
that the combined use of selective serotonin and norepinephrine reuptake
associated with an increased risk of bleeding. Bleeding events reported h
life-threatening hemorrhages. A population-based, case-controlled study
with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted i
bleeding (Schalekamp et al, 2008). Altered anticoagulant effects (includin
coadministration of serotonin and norepinephrine reuptake inhibitors with
release oral capsules, 2008). Conversely, one case report described a pe
dose in a patient maintained on acenocoumarol (Monastero et al, 2007).

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: When duloxetine and an anticoagulant are giver
Patients who are taking warfarin should be monitored closely for altered a
duloxetine therapy is initiated or discontinued (Prod Info CYMBALTA(R) d

7) Probable Mechanism: unknown

8) Literature Reports

a) A population-based, case-controlled study of new coumarin users
selective serotonin reuptake inhibitors (SSRIs) resulted in an increas
Using national pharmacy and hospitalization records, Netherlands re
abnormal bleeding and compared them with 5818 control subjects al
was 220 days (range, 1 to 4690 days). Patients on SSRIs showed gr
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0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et
b) A case report describes a 44-year-old female patient maintained
after 55 days of concomitant duloxetine treatment. Warfarin was initia
medication regimen included atorvastatin 10 mg, warfarin 7.5 mg to 1
mg, and albuterol extended-release 4 mg twice a day. Duloxetine 30
day 58, only the warfarin was discontinued, and by day 85 the patien
mcg/mL (therapeutic range 2 to 8 mcg/mL). Intravenous vitamin K 10
the INR was again elevated at 6.4, vitamin K-dependent clotting facto
normal. Duloxetine was then discontinued, and 4 days later the INR r
to 54%. INR was 0.9 by day 105, and warfarin was restarted on day
maintained on 7.5 to 10 mg/day. According to the Naranjo algorithm,
probable. The authors suggest that duloxetine may have an effect on
warfarin from its protein-binding sites, or may have unique metabolic
c) A 63-year-old woman successfully maintained on acenocoumarol
mechanical, prosthetic mitral-valve substitution experienced a persist
mg/day. Ten hours after taking duloxetine, the patient was taken to th

blood pressure had increased to 190/110 mmHg and her INR had dra
administered intravenously for the headache and hypertension, dulox
titrated to 12 mg/wk. Twenty-one days later, the INR returned to base
Follow-up examinations on days 28, 56, 84, 168, and 252 revealed st
family interviews discounted the possibility of acenocoumarol self-into
measured and the patient was not genotyped for CYP2D6 or CYP1A2
duloxetine was deemed as probable based on the Naranjo Adverse D

3.5.1.AJ Defibrotide

1) Interaction Effect: increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for mainta
that the combined use of selective serotonin and norepinephrine reuptake
associated with an increased risk of bleeding. Bleeding events reported h
life-threatening hemorrhages. A population-based, case-controlled study o
with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted i
bleeding (Schalekamp et al, 2008). Altered anticoagulant effects (includin
coadministration of serotonin and norepinephrine reuptake inhibitors with
release oral capsules, 2008). Conversely, one case report described a pe
dose in a patient maintained on acenocoumarol (Monastero et al, 2007).

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: When duloxetine and an anticoagulant are giver
Patients who are taking warfarin should be monitored closely for altered a
duloxetine therapy is initiated or discontinued (Prod Info CYMBALTA(R) d

7) Probable Mechanism: unknown

8) Literature Reports

a) A population-based, case-controlled study of new coumarin users
selective serotonin reuptake inhibitors (SSRIs) resulted in an increas
Using national pharmacy and hospitalization records, Netherlands res
abnormal bleeding and compared them with 5818 control subjects als
was 220 days (range, 1 to 4690 days). Patients on SSRIs showed gr
(adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5
0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et

b) A case report describes a 44-year-old female patient maintained o
after 55 days of concomitant duloxetine treatment. Warfarin was initia
medication regimen included atorvastatin 10 mg, warfarin 7.5 mg to 1
mg, and albuterol extended-release 4 mg twice a day. Duloxetine 30
day 58, only the warfarin was discontinued, and by day 85 the patien
mcg/mL (therapeutic range 2 to 8 mcg/mL). Intravenous vitamin K 10
the INR was again elevated at 6.4, vitamin K-dependent clotting facto
normal. Duloxetine was then discontinued, and 4 days later the INR r
to 54%. INR was 0.9 by day 105, and warfarin was restarted on day
maintained on 7.5 to 10 mg/day. According to the Naranjo algorithm,
probable. The authors suggest that duloxetine may have an effect on
warfarin from its protein-binding sites, or may have unique metabolic

c) A 63-year-old woman successfully maintained on acenocoumarol
mechanical, prosthetic mitral-valve substitution experienced a persist
mg/day. Ten hours after taking duloxetine, the patient was taken to th
blood pressure had increased to 190/110 mmHg and her INR had dra
administered intravenously for the headache and hypertension, dulox
titrated to 12 mg/wk. Twenty-one days later, the INR returned to base
Follow-up examinations on days 28, 56, 84, 168, and 252 revealed st
family interviews discounted the possibility of acenocoumarol self-into
measured and the patient was not genotyped for CYP2D6 or CYP1A2
duloxetine was deemed as probable based on the Naranjo Adverse D

3.5.1.AK Dermatan Sulfate

1) Interaction Effect: increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for mainta
that the combined use of selective serotonin and norepinephrine reuptake
associated with an increased risk of bleeding. Bleeding events reported h
life-threatening hemorrhages. A population-based, case-controlled study o
with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted i
bleeding (Schalekamp et al, 2008). Altered anticoagulant effects (includin
coadministration of serotonin and norepinephrine reuptake inhibitors with
release oral capsules, 2008). Conversely, one case report described a pe

dose in a patient maintained on acenocoumarol (Monastero et al, 2007).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When duloxetine and an anticoagulant are giver
Patients who are taking warfarin should be monitored closely for altered a
duloxetine therapy is initiated or discontinued (Prod Info CYMBALTA(R) d
7) Probable Mechanism: unknown
8) Literature Reports
a) A population-based, case-controlled study of new coumarin users
selective serotonin reuptake inhibitors (SSRIs) resulted in an increas
Using national pharmacy and hospitalization records, Netherlands re
abnormal bleeding and compared them with 5818 control subjects al
was 220 days (range, 1 to 4690 days). Patients on SSRIs showed gr
(adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5
0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et
b) A case report describes a 44-year-old female patient maintained
after 55 days of concomitant duloxetine treatment. Warfarin was initia
medication regimen included atorvastatin 10 mg, warfarin 7.5 mg to 1
mg, and albuterol extended-release 4 mg twice a day. Duloxetine 30
day 58, only the warfarin was discontinued, and by day 85 the patien
mcg/mL (therapeutic range 2 to 8 mcg/mL). Intravenous vitamin K 10
the INR was again elevated at 6.4, vitamin K-dependent clotting facto
normal. Duloxetine was then discontinued, and 4 days later the INR r
to 54%. INR was 0.9 by day 105, and warfarin was restarted on day
maintained on 7.5 to 10 mg/day. According to the Naranjo algorithm,
probable. The authors suggest that duloxetine may have an effect on
warfarin from its protein-binding sites, or may have unique metabolic
c) A 63-year-old woman successfully maintained on acenocoumarol
mechanical, prosthetic mitral-valve substitution experienced a persist
mg/day. Ten hours after taking duloxetine, the patient was taken to th
blood pressure had increased to 190/110 mmHg and her INR had dra
administered intravenously for the headache and hypertension, dulox
titrated to 12 mg/wk. Twenty-one days later, the INR returned to base
Follow-up examinations on days 28, 56, 84, 168, and 252 revealed st
family interviews discounted the possibility of acenocoumarol self-into
measured and the patient was not genotyped for CYP2D6 or CYP1A2
duloxetine was deemed as probable based on the Naranjo Adverse D

3.5.1.AL Desipramine
1) Interaction Effect: increased tricyclic antidepressant serum concentrati
confusion, cardiac arrhythmias)
2) Summary: The coadministration of duloxetine with a tricyclic antidepre
increasing the risk of adverse events. Duloxetine is a moderately potent in
substrate desipramine 50 mg and duloxetine 60 mg twice daily were coad
baseline (Prod Info CYMBALTA(R) delayed-release oral capsules, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Use caution with the combined use of duloxetine
with duloxetine and a TCA is unavoidable, plasma concentrations of the tr
made accordingly (Prod Info CYMBALTA(R) delayed-release oral capsule
TCA toxicity (anticholinergic effects, sedation, confusion, and cardiac arrh
7) Probable Mechanism: duloxetine inhibition of CYP2D6-mediated tricyc

3.5.1.AM Desirudin
1) Interaction Effect: increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta
that the combined use of selective serotonin and norepinephrine reuptake
associated with an increased risk of bleeding. Bleeding events reported h
life-threatening hemorrhages. A population-based, case-controlled study o
with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted i
bleeding (Schalekamp et al, 2008). Altered anticoagulant effects (includin
coadministration of serotonin and norepinephrine reuptake inhibitors with
release oral capsules, 2008). Conversely, one case report described a pe
dose in a patient maintained on acenocoumarol (Monastero et al, 2007).
3) Severity: major

4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When duloxetine and an anticoagulant are giver
Patients who are taking warfarin should be monitored closely for altered a
duloxetine therapy is initiated or discontinued (Prod Info CYMBALTA(R) d
7) Probable Mechanism: unknown
8) Literature Reports
a) A population-based, case-controlled study of new coumarin users
selective serotonin reuptake inhibitors (SSRIs) resulted in an increas
Using national pharmacy and hospitalization records, Netherlands re
abnormal bleeding and compared them with 5818 control subjects al
was 220 days (range, 1 to 4690 days). Patients on SSRIs showed gr
(adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5
0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et
b) A case report describes a 44-year-old female patient maintained
after 55 days of concomitant duloxetine treatment. Warfarin was initia
medication regimen included atorvastatin 10 mg, warfarin 7.5 mg to 1
mg, and albuterol extended-release 4 mg twice a day. Duloxetine 30
day 58, only the warfarin was discontinued, and by day 85 the patien
mcg/mL (therapeutic range 2 to 8 mcg/mL). Intravenous vitamin K 10
the INR was again elevated at 6.4, vitamin K-dependent clotting facto
normal. Duloxetine was then discontinued, and 4 days later the INR r
to 54%. INR was 0.9 by day 105, and warfarin was restarted on day
maintained on 7.5 to 10 mg/day. According to the Naranjo algorithm,
probable. The authors suggest that duloxetine may have an effect on
warfarin from its protein-binding sites, or may have unique metabolic
c) A 63-year-old woman successfully maintained on acenocoumarol
mechanical, prosthetic mitral-valve substitution experienced a persist
mg/day. Ten hours after taking duloxetine, the patient was taken to th
blood pressure had increased to 190/110 mmHg and her INR had dra
administered intravenously for the headache and hypertension, dulox
titrated to 12 mg/wk. Twenty-one days later, the INR returned to base
Follow-up examinations on days 28, 56, 84, 168, and 252 revealed st
family interviews discounted the possibility of acenocoumarol self-into
measured and the patient was not genotyped for CYP2D6 or CYP1A2
duloxetine was deemed as probable based on the Naranjo Adverse D

3.5.1.AN Desvenlafaxine
1) Interaction Effect: increased risk of serotonin syndrome (hypertension,
2) Summary: Both desvenlafaxine and duloxetine are selective serotonin
of desvenlafaxine and duloxetine is not recommended as it may result in s
CYMBALTA(R) delayed-release oral capsules, 2008). Symptoms of serot
coordination, fast heart beat, rapid changes in blood pressure, increased
diarrhea. Discuss the risks of serotonin syndrome with patients who are p
closely for symptoms of serotonin syndrome, especially during therapy ini
extended-release tablets, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concomitant use of desvenlafaxine and dulo
recommended (Prod Info CYMBALTA(R) delayed-release oral capsules, 2
serotonin syndrome with the patient and monitor closely for symptoms of
incoordination), especially during treatment initiation and dose increases
7) Probable Mechanism: additive serotonergic effect

3.5.1.AO Dexketoprofen
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta
that the combined use of selective serotonin and norepinephrine reuptake
associated with an increased risk of bleeding. Bleeding events have inclu
threatening hemorrhages (Prod Info CYMBALTA(R) oral delayed-release
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When duloxetine and a nonsteroidal antiinflamm
increased bleeding (Prod Info CYMBALTA(R) oral delayed-release capsu
7) Probable Mechanism: unknown

3.5.1.AP Dibenzepin

1) Interaction Effect: increased tricyclic antidepressant serum concentrati
confusion, cardiac arrhythmias)
2) Summary: The coadministration of duloxetine with a tricyclic antidepre
increasing the risk of adverse events. Duloxetine is a moderately potent ir
substrate desipramine 50 mg and duloxetine 60 mg twice daily were coad
baseline (Prod Info CYMBALTA(R) delayed-release oral capsules, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Use caution with the combined use of duloxetine
with duloxetine and a TCA is unavoidable, plasma concentrations of the tr
made accordingly (Prod Info CYMBALTA(R) delayed-release oral capsule
TCA toxicity (anticholinergic effects, sedation, confusion, and cardiac arrh
7) Probable Mechanism: duloxetine inhibition of CYP2D6-mediated tricyc

3.5.1.AQ Diclofenac

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta
that the combined use of selective serotonin and norepinephrine reuptake
associated with an increased risk of bleeding. Bleeding events have inclu
threatening hemorrhages (Prod Info CYMBALTA(R) oral delayed-release
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When duloxetine and a nonsteroidal antiinflamm
increased bleeding (Prod Info CYMBALTA(R) oral delayed-release capsu
7) Probable Mechanism: unknown

3.5.1.AR Dicumarol

1) Interaction Effect: increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta
that the combined use of selective serotonin and norepinephrine reuptake
associated with an increased risk of bleeding. Bleeding events reported h
life-threatening hemorrhages. A population-based, case-controlled study c
with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted i
bleeding (Schalekamp et al, 2008). Altered anticoagulant effects (includin
coadministration of serotonin and norepinephrine reuptake inhibitors with
release oral capsules, 2008). Conversely, one case report described a pe
dose in a patient maintained on acenocoumarol (Monastero et al, 2007).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When duloxetine and an anticoagulant are giver
Patients who are taking warfarin should be monitored closely for altered a
duloxetine therapy is initiated or discontinued (Prod Info CYMBALTA(R) d
7) Probable Mechanism: unknown
8) Literature Reports
a) A population-based, case-controlled study of new coumarin users
selective serotonin reuptake inhibitors (SSRIs) resulted in an increas
Using national pharmacy and hospitalization records, Netherlands re
abnormal bleeding and compared them with 5818 control subjects al
was 220 days (range, 1 to 4690 days). Patients on SSRIs showed gr
(adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5
0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et
b) A case report describes a 44-year-old female patient maintained c
after 55 days of concomitant duloxetine treatment. Warfarin was initia
medication regimen included atorvastatin 10 mg, warfarin 7.5 mg to 1
mg, and albuterol extended-release 4 mg twice a day. Duloxetine 30
day 58, only the warfarin was discontinued, and by day 85 the patien
mcg/mL (therapeutic range 2 to 8 mcg/mL). Intravenous vitamin K 10
the INR was again elevated at 6.4, vitamin K-dependent clotting factc
normal. Duloxetine was then discontinued, and 4 days later the INR r
to 54%. INR was 0.9 by day 105, and warfarin was restarted on day
maintained on 7.5 to 10 mg/day. According to the Naranjo algorithm,
probable. The authors suggest that duloxetine may have an effect on

warfarin from its protein-binding sites, or may have unique metabolic
c) A 63-year-old woman successfully maintained on acenocoumarol
mechanical, prosthetic mitral-valve substitution experienced a persist
mg/day. Ten hours after taking duloxetine, the patient was taken to th
blood pressure had increased to 190/110 mmHg and her INR had dra
administered intravenously for the headache and hypertension, dulox
titrated to 12 mg/wk. Twenty-one days later, the INR returned to base
Follow-up examinations on days 28, 56, 84, 168, and 252 revealed st
family interviews discounted the possibility of acenocoumarol self-into
measured and the patient was not genotyped for CYP2D6 or CYP1A2
duloxetine was deemed as probable based on the Naranjo Adverse D

3.5.1.AS Diflunisal

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta
that the combined use of selective serotonin and norepinephrine reuptake
associated with an increased risk of bleeding. Bleeding events have inclu
threatening hemorrhages (Prod Info CYMBALTA(R) oral delayed-release
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When duloxetine and a nonsteroidal antiinflamm
increased bleeding (Prod Info CYMBALTA(R) oral delayed-release capsu
7) Probable Mechanism: unknown

3.5.1.AT Dipyridamole

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta
that the combined use of selective serotonin and norepinephrine reuptake
been associated with an increased risk of bleeding. Bleeding events repo
petechiae, and life-threatening hemorrhages (Prod Info CYMBALTA(R) de
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When duloxetine and an antiplatelet agent are g
bleeding (Prod Info CYMBALTA(R) delayed-release oral capsules, 2008).
7) Probable Mechanism: unknown

3.5.1.AU Dipyrone

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta
that the combined use of selective serotonin and norepinephrine reuptake
associated with an increased risk of bleeding. Bleeding events have inclu
threatening hemorrhages (Prod Info CYMBALTA(R) oral delayed-release
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When duloxetine and a nonsteroidal antiinflamm
increased bleeding (Prod Info CYMBALTA(R) oral delayed-release capsu
7) Probable Mechanism: unknown

3.5.1.AV Dixyrazine

1) Interaction Effect: increased phenothiazine serum concentrations and
orthostatic hypotension, hyperthermia, extrapyramidal effects)
2) Summary: Duloxetine is a moderately potent inhibitor of CYP2D6; ther
likely to increase bioavailability of the phenothiazine agent, increasing the
delayed-release oral capsules, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Use caution when prescribing duloxetine to pati
elevated phenothiazine plasma concentrations. Monitor for increased phe
release oral capsules, 2008).
7) Probable Mechanism: duloxetine inhibition of CYP2D6-mediated phen

3.5.1.AW Dothiepin

1) Interaction Effect: increased tricyclic antidepressant serum concentrati

confusion, cardiac arrhythmias)
2) Summary: The coadministration of duloxetine with a tricyclic antidepre
increasing the risk of adverse events. Duloxetine is a moderately potent ir
substrate desipramine 50 mg and duloxetine 60 mg twice daily were coad
baseline (Prod Info CYMBALTA(R) delayed-release oral capsules, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Use caution with the combined use of duloxetine
with duloxetine and a TCA is unavoidable, plasma concentrations of the tr
made accordingly (Prod Info CYMBALTA(R) delayed-release oral capsule
TCA toxicity (anticholinergic effects, sedation, confusion, and cardiac arrh
7) Probable Mechanism: duloxetine inhibition of CYP2D6-mediated tricyc

3.5.1.AX Doxepin
1) Interaction Effect: increased tricyclic antidepressant serum concentrati
confusion, cardiac arrhythmias)
2) Summary: The coadministration of duloxetine with a tricyclic antidepre
increasing the risk of adverse events. Duloxetine is a moderately potent ir
substrate desipramine 50 mg and duloxetine 60 mg twice daily were coad
baseline (Prod Info CYMBALTA(R) delayed-release oral capsules, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Use caution with the combined use of duloxetine
with duloxetine and a TCA is unavoidable, plasma concentrations of the tr
made accordingly (Prod Info CYMBALTA(R) delayed-release oral capsule
TCA toxicity (anticholinergic effects, sedation, confusion, and cardiac arrh
7) Probable Mechanism: duloxetine inhibition of CYP2D6-mediated tricyc

3.5.1.AY Droxicam
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta
that the combined use of selective serotonin and norepinephrine reuptake
associated with an increased risk of bleeding. Bleeding events have inclu
threatening hemorrhages (Prod Info CYMBALTA(R) oral delayed-release
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When duloxetine and a nonsteroidal antiinflamm
increased bleeding (Prod Info CYMBALTA(R) oral delayed-release capsu
7) Probable Mechanism: unknown

3.5.1.AZ Eletriptan
1) Interaction Effect: increased risk of serotonin syndrome
2) Summary: A life-threatening condition known as serotonin syndrome m
combination with a serotonin and norepinephrine reuptake inhibitor (SNRI
include restlessness, hallucinations, loss of coordination, fast heart beat, r
overreactive reflexes, nausea, vomiting, and diarrhea. Clinicians should b
that either the triptan or the SNRI may be prescribed by a different physici
are prescribed this combination and monitor them closely for symptoms o
dose increases (Prod Info CYMBALTA(R) delayed-release oral capsules,
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of a triptan, such as eletriptan,
such as duloxetine, may result in a life-threatening condition called seroto
intermittently and that either the triptan or the SNRI may be prescribed by
discuss the risks of serotonin syndrome with the patient and monitor close
hyperthermia, hyperreflexia, incoordination), especially during treatment in
release oral capsules, 2008).
7) Probable Mechanism: additive pharmacologic effects resulting in exces

3.5.1.BA Encainide
1) Interaction Effect: increased class IC antiarrhythmic serum concentrati
torsades de pointes, cardiac arrest)
2) Summary: Duloxetine is a moderately potent inhibitor of CYP2D6. Give

antiarrhythmic agents as well as considering that they are CYP2D6 substr
whenever duloxetine is coadministered with this class of antiarrhythmic ag
2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Use caution when prescribing duloxetine to pati
cause elevated plasma concentrations of the antiarrhythmic (Prod Info CY
class IC antiarrhythmic serum concentrations and ECG for signs of potent
hypotension); adjust dose accordingly. Alternatively, consider selecting ar
pharmacokinetics of class IC antiarrhythmic agents.
7) Probable Mechanism: inhibition of CYP2D6-mediated metabolism of cl

3.5.1.BB Enoxacin
1) Interaction Effect: increased duloxetine bioavailability and risk of adver
2) Summary: Since duloxetine is a substrate for cytochrome P450 isoforr
expected to occur in the presence of coadministration with enoxacin, a CY
and about 2.5-fold, respectively, when duloxetine was administered with fl
(R) delayed-release oral capsules, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Use caution with the concomitant use of duloxet
exposure and serum levels (Prod Info CYMBALTA(R) delayed-release ora
events and adjust duloxetine dose as necessary.
7) Probable Mechanism: inhibition of CYP1A2-mediated duloxetine metal

3.5.1.BC Enoxaparin
1) Interaction Effect: increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta
that the combined use of selective serotonin and norepinephrine reuptake
associated with an increased risk of bleeding. Bleeding events reported h
life-threatening hemorrhages. A population-based, case-controlled study c
with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted i
bleeding (Schalekamp et al, 2008). Altered anticoagulant effects (includin
coadministration of serotonin and norepinephrine reuptake inhibitors with
release oral capsules, 2008). Conversely, one case report described a pe
dose in a patient maintained on acenocoumarol (Monastero et al, 2007).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When duloxetine and an anticoagulant are giver
Patients who are taking warfarin should be monitored closely for altered a
duloxetine therapy is initiated or discontinued (Prod Info CYMBALTA(R) d
7) Probable Mechanism: unknown
8) Literature Reports
a) A population-based, case-controlled study of new coumarin users
selective serotonin reuptake inhibitors (SSRIs) resulted in an increas
Using national pharmacy and hospitalization records, Netherlands re
abnormal bleeding and compared them with 5818 control subjects als
was 220 days (range, 1 to 4690 days). Patients on SSRIs showed gr
(adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5
0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et
b) A case report describes a 44-year-old female patient maintained c
after 55 days of concomitant duloxetine treatment. Warfarin was initia
medication regimen included atorvastatin 10 mg, warfarin 7.5 mg to 1
mg, and albuterol extended-release 4 mg twice a day. Duloxetine 30
day 58, only the warfarin was discontinued, and by day 85 the patient
mcg/mL (therapeutic range 2 to 8 mcg/mL). Intravenous vitamin K 10
the INR was again elevated at 6.4, vitamin K-dependent clotting factc
normal. Duloxetine was then discontinued, and 4 days later the INR r
to 54%. INR was 0.9 by day 105, and warfarin was restarted on day 1
maintained on 7.5 to 10 mg/day. According to the Naranjo algorithm,
probable. The authors suggest that duloxetine may have an effect on
warfarin from its protein-binding sites, or may have unique metabolic
c) A 63-year-old woman successfully maintained on acenocoumarol
mechanical, prosthetic mitral-valve substitution experienced a persist

mg/day. Ten hours after taking duloxetine, the patient was taken to th
blood pressure had increased to 190/110 mmHg and her INR had dra
administered intravenously for the headache and hypertension, dulox
titrated to 12 mg/wk. Twenty-one days later, the INR returned to base
Follow-up examinations on days 28, 56, 84, 168, and 252 revealed st
family interviews discounted the possibility of acenocoumarol self-into
measured and the patient was not genotyped for CYP2D6 or CYP1A2
duloxetine was deemed as probable based on the Naranjo Adverse D

3.5.1.BD Epoprostenol

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta
that the combined use of selective serotonin and norepinephrine reuptake
been associated with an increased risk of bleeding. Bleeding events repor
petechiae, and life-threatening hemorrhages (Prod Info CYMBALTA(R) de
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When duloxetine and an antiplatelet agent are g
bleeding (Prod Info CYMBALTA(R) delayed-release oral capsules, 2008).
7) Probable Mechanism: unknown

3.5.1.BE Eptifibatide

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta
that the combined use of selective serotonin and norepinephrine reuptake
been associated with an increased risk of bleeding. Bleeding events repor
petechiae, and life-threatening hemorrhages (Prod Info CYMBALTA(R) de
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When duloxetine and an antiplatelet agent are g
bleeding (Prod Info CYMBALTA(R) delayed-release oral capsules, 2008).
7) Probable Mechanism: unknown

3.5.1.BF Escitalopram

1) Interaction Effect: an increased risk of serotonin syndrome
2) Summary: Duloxetine is a selective serotonin and norepinephrine reup
escitalopram, a selective serotonin reuptake inhibitor, is not recommende
CYMBALTA(R) delayed-release oral capsules, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concomitant use of duloxetine and escitalop
of serotonin syndrome (Prod Info CYMBALTA(R) delayed-release oral cap
7) Probable Mechanism: additive serotonergic effects

3.5.1.BG Ethopropazine

1) Interaction Effect: increased phenothiazine serum concentrations and
orthostatic hypotension, hyperthermia, extrapyramidal effects)
2) Summary: Duloxetine is a moderately potent inhibitor of CYP2D6; ther
likely to increase bioavailability of the phenothiazine agent, increasing the
delayed-release oral capsules, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Use caution when prescribing duloxetine to pati
elevated phenothiazine plasma concentrations. Monitor for increased phe
release oral capsules, 2008).
7) Probable Mechanism: duloxetine inhibition of CYP2D6-mediated phen

3.5.1.BH Etodolac

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta
that the combined use of selective serotonin and norepinephrine reuptake
associated with an increased risk of bleeding. Bleeding events have inclu
threatening hemorrhages (Prod Info CYMBALTA(R) oral delayed-release

3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When duloxetine and a nonsteroidal antiinflamm
increased bleeding (Prod Info CYMBALTA(R) oral delayed-release capsu
7) Probable Mechanism: unknown

3.5.1.BI Etofenamate
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta
that the combined use of selective serotonin and norepinephrine reuptake
associated with an increased risk of bleeding. Bleeding events have inclu
threatening hemorrhages (Prod Info CYMBALTA(R) oral delayed-release
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When duloxetine and a nonsteroidal antiinflamm
increased bleeding (Prod Info CYMBALTA(R) oral delayed-release capsu
7) Probable Mechanism: unknown

3.5.1.BJ Etoricoxib
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta
that the combined use of selective serotonin and norepinephrine reuptake
associated with an increased risk of bleeding. Bleeding events have inclu
threatening hemorrhages (Prod Info CYMBALTA(R) oral delayed-release
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When duloxetine and a nonsteroidal antiinflamm
increased bleeding (Prod Info CYMBALTA(R) oral delayed-release capsu
7) Probable Mechanism: unknown

3.5.1.BK Felbinac
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta
that the combined use of selective serotonin and norepinephrine reuptake
associated with an increased risk of bleeding. Bleeding events have inclu
threatening hemorrhages (Prod Info CYMBALTA(R) oral delayed-release
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When duloxetine and a nonsteroidal antiinflamm
increased bleeding (Prod Info CYMBALTA(R) oral delayed-release capsu
7) Probable Mechanism: unknown

3.5.1.BL Fenbufen
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta
that the combined use of selective serotonin and norepinephrine reuptake
associated with an increased risk of bleeding. Bleeding events have inclu
threatening hemorrhages (Prod Info CYMBALTA(R) oral delayed-release
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When duloxetine and a nonsteroidal antiinflamm
increased bleeding (Prod Info CYMBALTA(R) oral delayed-release capsu
7) Probable Mechanism: unknown

3.5.1.BM Fenoprofen
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta
that the combined use of selective serotonin and norepinephrine reuptake
associated with an increased risk of bleeding. Bleeding events have inclu
threatening hemorrhages (Prod Info CYMBALTA(R) oral delayed-release
3) Severity: moderate
4) Onset: unspecified

5) Substantiation: probable
6) Clinical Management: When duloxetine and a nonsteroidal antiinflamm
increased bleeding (Prod Info CYMBALTA(R) oral delayed-release capsu
7) Probable Mechanism: unknown

3.5.1.BN Fentiazac
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta
that the combined use of selective serotonin and norepinephrine reuptake
associated with an increased risk of bleeding. Bleeding events have inclu
threatening hemorrhages (Prod Info CYMBALTA(R) oral delayed-release
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When duloxetine and a nonsteroidal antiinflamm
increased bleeding (Prod Info CYMBALTA(R) oral delayed-release capsu
7) Probable Mechanism: unknown

3.5.1.BO Flecainide
1) Interaction Effect: increased class IC antiarrhythmic serum concentrati
torsades de pointes, cardiac arrest)
2) Summary: Duloxetine is a moderately potent inhibitor of CYP2D6. Give
antiarrhythmic agents as well as considering that they are CYP2D6 substr
whenever duloxetine is coadministered with this class of antiarrhythmic ag
2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Use caution when prescribing duloxetine to pati
cause elevated plasma concentrations of the antiarrhythmic (Prod Info CY
class IC antiarrhythmic serum concentrations and ECG for signs of potent
hypotension); adjust dose accordingly. Alternatively, consider selecting ar
pharmacokinetics of class IC antiarrhythmic agents.
7) Probable Mechanism: inhibition of CYP2D6-mediated metabolism of cl

3.5.1.BP Floctafenine
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta
that the combined use of selective serotonin and norepinephrine reuptake
associated with an increased risk of bleeding. Bleeding events have inclu
threatening hemorrhages (Prod Info CYMBALTA(R) oral delayed-release
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When duloxetine and a nonsteroidal antiinflamm
increased bleeding (Prod Info CYMBALTA(R) oral delayed-release capsu
7) Probable Mechanism: unknown

3.5.1.BQ Flufenamic Acid
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta
that the combined use of selective serotonin and norepinephrine reuptake
associated with an increased risk of bleeding. Bleeding events have inclu
threatening hemorrhages (Prod Info CYMBALTA(R) oral delayed-release
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When duloxetine and a nonsteroidal antiinflamm
increased bleeding (Prod Info CYMBALTA(R) oral delayed-release capsu
7) Probable Mechanism: unknown

3.5.1.BR Fluoxetine
1) Interaction Effect: increased duloxetine and fluoxetine serum concentr
2) Summary: Duloxetine is a selective serotonin and norepinephrine reup
fluoxetine, an SSRI, is not recommended due to the potential for serotonir
fluoxetine is likely to increase the bioavailability of either drug, increasing
are both substrates for, and moderately potent inhibitors of CYP2D6. Coa

(the potent CYP2D6 inhibitor paroxetine 20 mg once daily) resulted in a 6
Info CYMBALTA(R) delayed-release oral capsules, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: The concomitant use of duloxetine and fluoxetin
serotonin syndrome. Additionally, concomitant use has resulted in increas
CYMBALTA(R) delayed-release oral capsules, 2008).
7) Probable Mechanism: fluoxetine inhibition of CYP2D6-mediated dulox

3.5.1.BS Fluphenazine
1) Interaction Effect: increased phenothiazine serum concentrations and
orthostatic hypotension, hyperthermia, extrapyramidal effects)
2) Summary: Duloxetine is a moderately potent inhibitor of CYP2D6; ther
likely to increase bioavailability of the phenothiazine agent, increasing the
delayed-release oral capsules, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Use caution when prescribing duloxetine to pati
elevated phenothiazine plasma concentrations. Monitor for increased phe
release oral capsules, 2008).
7) Probable Mechanism: duloxetine inhibition of CYP2D6-mediated phen

3.5.1.BT Flurbiprofen
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta
that the combined use of selective serotonin and norepinephrine reuptake
associated with an increased risk of bleeding. Bleeding events have inclu
threatening hemorrhages (Prod Info CYMBALTA(R) oral delayed-release
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When duloxetine and a nonsteroidal antiinflamm
increased bleeding (Prod Info CYMBALTA(R) oral delayed-release capsu
7) Probable Mechanism: unknown

3.5.1.BU Fluvoxamine
1) Interaction Effect: increased duloxetine bioavailability and an increase
2) Summary: Duloxetine is a selective serotonin and norepinephrine reup
CYP1A2 and CYP2D6 isozymes. The concomitant use of duloxetine with
for serotonin syndrome. In addition, coadministration of fluvoxamine 100 r
14 CYP2D6 poor metabolizer subjects resulted in a 6-fold increase in dul
given duloxetine 60 mg together with fluvoxamine 100 mg, duloxetine AU
3-fold, respectively (Prod Info CYMBALTA(R) delayed-release oral capsul
3) Severity: major
4) Onset: unspecified
5) Substantiation: established
6) Clinical Management: The concomitant use of duloxetine and fluvoxam
of serotonin syndrome. Additionally, concomitant use has resulted in signi
Info CYMBALTA(R) delayed-release oral capsules, 2008).
7) Probable Mechanism: inhibition of CYP1A2-mediated duloxetine metal

3.5.1.BV Fondaparinux
1) Interaction Effect: increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta
that the combined use of selective serotonin and norepinephrine reuptake
associated with an increased risk of bleeding. Bleeding events reported h
life-threatening hemorrhages. A population-based, case-controlled study
with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted
bleeding (Schalekamp et al, 2008). Altered anticoagulant effects (includin
coadministration of serotonin and norepinephrine reuptake inhibitors with
release oral capsules, 2008). Conversely, one case report described a pe
dose in a patient maintained on acenocoumarol (Monastero et al, 2007).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable

6) Clinical Management: When duloxetine and an anticoagulant are giver
Patients who are taking warfarin should be monitored closely for altered a
duloxetine therapy is initiated or discontinued (Prod Info CYMBALTA(R) d
7) Probable Mechanism: unknown
8) Literature Reports
a) A population-based, case-controlled study of new coumarin users
selective serotonin reuptake inhibitors (SSRIs) resulted in an increas
Using national pharmacy and hospitalization records, Netherlands re
abnormal bleeding and compared them with 5818 control subjects al
was 220 days (range, 1 to 4690 days). Patients on SSRIs showed gr
(adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.
0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et
b) A case report describes a 44-year-old female patient maintained
after 55 days of concomitant duloxetine treatment. Warfarin was initia
medication regimen included atorvastatin 10 mg, warfarin 7.5 mg to 1
mg, and albuterol extended-release 4 mg twice a day. Duloxetine 30
day 58, only the warfarin was discontinued, and by day 85 the patien
mcg/mL (therapeutic range 2 to 8 mcg/mL). Intravenous vitamin K 10
the INR was again elevated at 6.4, vitamin K-dependent clotting facto
normal. Duloxetine was then discontinued, and 4 days later the INR r
to 54%. INR was 0.9 by day 105, and warfarin was restarted on day
maintained on 7.5 to 10 mg/day. According to the Naranjo algorithm,
probable. The authors suggest that duloxetine may have an effect on
warfarin from its protein-binding sites, or may have unique metabolic
c) A 63-year-old woman successfully maintained on acenocoumarol
mechanical, prosthetic mitral-valve substitution experienced a persist
mg/day. Ten hours after taking duloxetine, the patient was taken to th
blood pressure had increased to 190/110 mmHg and her INR had dra
administered intravenously for the headache and hypertension, dulox
titrated to 12 mg/wk. Twenty-one days later, the INR returned to base
Follow-up examinations on days 28, 56, 84, 168, and 252 revealed st
family interviews discounted the possibility of acenocoumarol self-into
measured and the patient was not genotyped for CYP2D6 or CYP1A2
duloxetine was deemed as probable based on the Naranjo Adverse D

3.5.1.BW Frovatriptan
1) Interaction Effect: increased risk of serotonin syndrome
2) Summary: A life-threatening condition known as serotonin syndrome m
combination with a serotonin and norepinephrine reuptake inhibitor (SNRI
include restlessness, hallucinations, loss of coordination, fast heart beat, r
overreactive reflexes, nausea, vomiting, and diarrhea. Clinicians should b
that either the triptan or the SNRI may be prescribed by a different physici
are prescribed this combination and monitor them closely for symptoms o
dose increases (Prod Info CYMBALTA(R) delayed-release oral capsules,
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of a triptan, such as frovatripta
(SNRI), such as duloxetine, may result in a life-threatening condition calle
commonly used intermittently and that either the triptan or the SNRI may l
together, discuss the risks of serotonin syndrome with the patient and mo
hyperthermia, hyperreflexia, incoordination), especially during treatment in
release oral capsules, 2008).
7) Probable Mechanism: additive pharmacologic effects resulting in exce

3.5.1.BX Heparin
1) Interaction Effect: increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta
that the combined use of selective serotonin and norepinephrine reuptake
associated with an increased risk of bleeding. Bleeding events reported h
life-threatening hemorrhages. A population-based, case-controlled study o
with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted i
bleeding (Schalekamp et al, 2008). Altered anticoagulant effects (includin
coadministration of serotonin and norepinephrine reuptake inhibitors with
release oral capsules, 2008). Conversely, one case report described a pe
dose in a patient maintained on acenocoumarol (Monastero et al, 2007).
3) Severity: major

4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When duloxetine and an anticoagulant are giver
Patients who are taking warfarin should be monitored closely for altered a
duloxetine therapy is initiated or discontinued (Prod Info CYMBALTA(R) d
7) Probable Mechanism: unknown
8) Literature Reports
a) A population-based, case-controlled study of new coumarin users
selective serotonin reuptake inhibitors (SSRIs) resulted in an increas
Using national pharmacy and hospitalization records, Netherlands re
abnormal bleeding and compared them with 5818 control subjects al
was 220 days (range, 1 to 4690 days). Patients on SSRIs showed gr
(adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.
0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et
b) A case report describes a 44-year-old female patient maintained
after 55 days of concomitant duloxetine treatment. Warfarin was initia
medication regimen included atorvastatin 10 mg, warfarin 7.5 mg to 1
mg, and albuterol extended-release 4 mg twice a day. Duloxetine 30
day 58, only the warfarin was discontinued, and by day 85 the patien
mcg/mL (therapeutic range 2 to 8 mcg/mL). Intravenous vitamin K 10
the INR was again elevated at 6.4, vitamin K-dependent clotting facto
normal. Duloxetine was then discontinued, and 4 days later the INR r
to 54%. INR was 0.9 by day 105, and warfarin was restarted on day
maintained on 7.5 to 10 mg/day. According to the Naranjo algorithm,
probable. The authors suggest that duloxetine may have an effect on
warfarin from its protein-binding sites, or may have unique metabolic
c) A 63-year-old woman successfully maintained on acenocoumarol
mechanical, prosthetic mitral-valve substitution experienced a persist
mg/day. Ten hours after taking duloxetine, the patient was taken to th
blood pressure had increased to 190/110 mmHg and her INR had dra
administered intravenously for the headache and hypertension, dulox
titrated to 12 mg/wk. Twenty-one days later, the INR returned to base
Follow-up examinations on days 28, 56, 84, 168, and 252 revealed st
family interviews discounted the possibility of acenocoumarol self-into
measured and the patient was not genotyped for CYP2D6 or CYP1A2
duloxetine was deemed as probable based on the Naranjo Adverse D

3.5.1.BY Ibuprofen
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta
that the combined use of selective serotonin and norepinephrine reuptake
associated with an increased risk of bleeding. Bleeding events have inclu
threatening hemorrhages (Prod Info CYMBALTA(R) oral delayed-release
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When duloxetine and a nonsteroidal antiinflamm
increased bleeding (Prod Info CYMBALTA(R) oral delayed-release capsu
7) Probable Mechanism: unknown

3.5.1.BZ Iloprost
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta
that the combined use of selective serotonin and norepinephrine reuptake
been associated with an increased risk of bleeding. Bleeding events repo
petechiae, and life-threatening hemorrhages (Prod Info CYMBALTA(R) de
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When duloxetine and an antiplatelet agent are g
bleeding (Prod Info CYMBALTA(R) delayed-release oral capsules, 2008).
7) Probable Mechanism: unknown

3.5.1.CA Imipramine
1) Interaction Effect: increased tricyclic antidepressant serum concentrati
confusion, cardiac arrhythmias)
2) Summary: The coadministration of duloxetine with a tricyclic antidepre

increasing the risk of adverse events. Duloxetine is a moderately potent ir
substrate desipramine 50 mg and duloxetine 60 mg twice daily were coad
baseline (Prod Info CYMBALTA(R) delayed-release oral capsules, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Use caution with the combined use of duloxetine
with duloxetine and a TCA is unavoidable, plasma concentrations of the tr
made accordingly (Prod Info CYMBALTA(R) delayed-release oral capsule
TCA toxicity (anticholinergic effects, sedation, confusion, and cardiac arrh
7) Probable Mechanism: duloxetine inhibition of CYP2D6-mediated tricyc

3.5.1.CB Indecainide
1) Interaction Effect: increased class IC antiarrhythmic serum concentrati
torsades de pointes, cardiac arrest)
2) Summary: Duloxetine is a moderately potent inhibitor of CYP2D6. Give
antiarrhythmic agents as well as considering that they are CYP2D6 substr
whenever duloxetine is coadministered with this class of antiarrhythmic ag
2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Use caution when prescribing duloxetine to patie
cause elevated plasma concentrations of the antiarrhythmic (Prod Info CY
class IC antiarrhythmic serum concentrations and ECG for signs of potent
hypotension); adjust dose accordingly. Alternatively, consider selecting ar
pharmacokinetics of class IC antiarrhythmic agents.
7) Probable Mechanism: inhibition of CYP2D6-mediated metabolism of cl

3.5.1.CC Indomethacin
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta
that the combined use of selective serotonin and norepinephrine reuptake
associated with an increased risk of bleeding. Bleeding events have inclu
threatening hemorrhages (Prod Info CYMBALTA(R) oral delayed-release
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When duloxetine and a nonsteroidal antiinflamm
increased bleeding (Prod Info CYMBALTA(R) oral delayed-release capsu
7) Probable Mechanism: unknown

3.5.1.CD Indoprofen
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta
that the combined use of selective serotonin and norepinephrine reuptake
associated with an increased risk of bleeding. Bleeding events have inclu
threatening hemorrhages (Prod Info CYMBALTA(R) oral delayed-release
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When duloxetine and a nonsteroidal antiinflamm
increased bleeding (Prod Info CYMBALTA(R) oral delayed-release capsu
7) Probable Mechanism: unknown

3.5.1.CE Isocarboxazid
1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, h
2) Summary: Duloxetine exerts inhibitory effects on both norepinephrine
overlapping therapy with duloxetine and an MAOI, such as isocarboxazid,
serotonergic state characterized by symptoms such as agitation and restl
diaphoresis, shivering, and tremor. Serious, even fatal, reactions have be
inhibitors and MAOIs. Concomitant administration of duloxetine and isoca
elapse after discontinuing isocarboxazid before initiating therapy with dulo
discontinuing duloxetine before initiating therapy with isocarboxazid (Prod
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical

6) Clinical Management: Concurrent use of duloxetine and isocarboxazid isocarboxazid before initiating duloxetine. Wait at least 5 days after discor (Prod Info Cymbalta(R) Delayed-release oral capsules, 2009).
7) Probable Mechanism: additive serotonergic effects

3.5.1.CF Isoxicam
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta that the combined use of selective serotonin and norepinephrine reuptake associated with an increased risk of bleeding. Bleeding events have inclu threatening hemorrhages (Prod Info CYMBALTA(R) oral delayed-release
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When duloxetine and a nonsteroidal antiinflamm increased bleeding (Prod Info CYMBALTA(R) oral delayed-release capsu
7) Probable Mechanism: unknown

3.5.1.CG Ketoprofen
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta that the combined use of selective serotonin and norepinephrine reuptake associated with an increased risk of bleeding. Bleeding events have inclu threatening hemorrhages (Prod Info CYMBALTA(R) oral delayed-release
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When duloxetine and a nonsteroidal antiinflamm increased bleeding (Prod Info CYMBALTA(R) oral delayed-release capsu
7) Probable Mechanism: unknown

3.5.1.CH Ketorolac
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta that the combined use of selective serotonin and norepinephrine reuptake associated with an increased risk of bleeding. Bleeding events have inclu threatening hemorrhages (Prod Info CYMBALTA(R) oral delayed-release
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When duloxetine and a nonsteroidal antiinflamm increased bleeding (Prod Info CYMBALTA(R) oral delayed-release capsu
7) Probable Mechanism: unknown

3.5.1.CI Lamifiban
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta that the combined use of selective serotonin and norepinephrine reuptake been associated with an increased risk of bleeding. Bleeding events repo petechiae, and life-threatening hemorrhages (Prod Info CYMBALTA(R) de
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When duloxetine and an antiplatelet agent are g bleeding (Prod Info CYMBALTA(R) delayed-release oral capsules, 2008).
7) Probable Mechanism: unknown

3.5.1.CJ Lexipafant
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta that the combined use of selective serotonin and norepinephrine reuptake been associated with an increased risk of bleeding. Bleeding events repo petechiae, and life-threatening hemorrhages (Prod Info CYMBALTA(R) de
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When duloxetine and an antiplatelet agent are g

bleeding (Prod Info CYMBALTA(R) delayed-release oral capsules, 2008).
7) Probable Mechanism: unknown

3.5.1.CK Linezolid
1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, h
2) Summary: Linezolid is a reversible, nonselective inhibitor of monoamir tablets, oral suspension, 2008). Concurrent administration or overlapping toxicity or serotonin syndrome, a hyperserotonergic state characterized by mental status, hyperreflexia, diaphoresis, shivering, and tremor. There ha with concomitant use of linezolid and serotonergic agents, including one c concomitant therapy with linezolid and serotonergic agents be clinically ne serotonin syndrome (hyperreflexia, incoordination, hyperpyrexia, or impair oral suspension, 2008). Serotonin syndrome can be life-threatening. If ser and provide supportive care and other therapy as necessary (Boyer & Sha
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Unless carefully monitored for serotonin syndror duloxetine (Prod Info ZYVOX(R) IV injection, oral tablets, oral suspension monitor closely for symptoms of serotonin syndrome such as neuromuscu rigidity, clonus, peripheral hypertonicity, and shivering), autonomic hypera diarrhea), and mental status changes (including agitation and delirium). S syndrome develops, discontinue the offending agents and provide suppor 2005).
7) Probable Mechanism: inhibition of monoamine oxidase-mediated sero
8) Literature Reports
a) Serotonin syndrome was induced in a 55-year-old woman maintai following the addition of intravenous linezolid 600 mg every 12 hours an inpatient oncology center for pain management and treatment of a vancomycin-resistant enterococcus in wound cultures, linezolid was a first dose of linezolid, the patient demonstrated mental status change movements. Additional symptoms occurring over the following hours nonsensical speech, involuntary movements of the extremities, contir were noncontributory; a low-grade fever (38 degrees Celsius) was pr throughout the day, returning to baseline mental and physical status l later the patient chose to resume duloxetine at a 30-mg/day dose. Du hospital stay. A week later, the patient died from malignancy-associat

3.5.1.CL Lithium
1) Interaction Effect: an increased risk of serotonin syndrome
2) Summary: Duloxetine is a selective serotonin and norepinephrine reup concurrently with agents affecting the serotonergic neurotransmitter syste serotonin syndrome (Prod Info CYMBALTA(R) delayed-release oral capsu symptoms of serotonin syndrome such as neuromuscular abnormalities (i peripheral hypertonicity, and shivering), autonomic hyperactivity (including bowel sounds and diarrhea), and mental status changes (including agitati syndrome with patients who are prescribed this combination. If serotonin s provide supportive care, correction of vital signs, or other therapy, as nece
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Use caution if duloxetine is coadministered with syndrome (Prod Info CYMBALTA(R) delayed-release oral capsules, 2008 symptoms of serotonin syndrome such as neuromuscular abnormalities (i peripheral hypertonicity, and shivering), autonomic hyperactivity (including sounds, and diarrhea), and mental status changes (including agitation and serotonin syndrome develops, discontinue the offending agents and provi as necessary (Boyer & Shannon, 2005).
7) Probable Mechanism: additive serotonergic effects

3.5.1.CM Lofepramine
1) Interaction Effect: increased tricyclic antidepressant serum concentrati confusion, cardiac arrhythmias)
2) Summary: The coadministration of duloxetine with a tricyclic antidepre increasing the risk of adverse events. Duloxetine is a moderately potent ir substrate desipramine 50 mg and duloxetine 60 mg twice daily were coad baseline (Prod Info CYMBALTA(R) delayed-release oral capsules, 2008).

3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Use caution with the combined use of duloxetine with duloxetine and a TCA is unavoidable, plasma concentrations of the tr made accordingly (Prod Info CYMBALTA(R) delayed-release oral capsule TCA toxicity (anticholinergic effects, sedation, confusion, and cardiac arrh
7) Probable Mechanism: duloxetine inhibition of CYP2D6-mediated tricyc

3.5.1.CN Lorcainide
1) Interaction Effect: increased class IC antiarrhythmic serum concentrati torsades de pointes, cardiac arrest)
2) Summary: Duloxetine is a moderately potent inhibitor of CYP2D6. Give antiarrhythmic agents as well as considering that they are CYP2D6 substr whenever duloxetine is coadministered with this class of antiarrhythmic ag 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Use caution when prescribing duloxetine to pati cause elevated plasma concentrations of the antiarrhythmic (Prod Info CY class IC antiarrhythmic serum concentrations and ECG for signs of potent hypotension); adjust dose accordingly. Alternatively, consider selecting ar pharmacokinetics of class IC antiarrhythmic agents.
7) Probable Mechanism: inhibition of CYP2D6-mediated metabolism of cl

3.5.1.CO Lornoxicam
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta that the combined use of selective serotonin and norepinephrine reuptake associated with an increased risk of bleeding. Bleeding events have inclu threatening hemorrhages (Prod Info CYMBALTA(R) oral delayed-release
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When duloxetine and a nonsteroidal antiinflamm increased bleeding (Prod Info CYMBALTA(R) oral delayed-release capsu
7) Probable Mechanism: unknown

3.5.1.CP Meclofenamate
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta that the combined use of selective serotonin and norepinephrine reuptake associated with an increased risk of bleeding. Bleeding events have inclu threatening hemorrhages (Prod Info CYMBALTA(R) oral delayed-release
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When duloxetine and a nonsteroidal antiinflamm increased bleeding (Prod Info CYMBALTA(R) oral delayed-release capsu
7) Probable Mechanism: unknown

3.5.1.CQ Mefenamic Acid
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta that the combined use of selective serotonin and norepinephrine reuptake associated with an increased risk of bleeding. Bleeding events have inclu threatening hemorrhages (Prod Info CYMBALTA(R) oral delayed-release
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When duloxetine and a nonsteroidal antiinflamm increased bleeding (Prod Info CYMBALTA(R) oral delayed-release capsu
7) Probable Mechanism: unknown

3.5.1.CR Melitracen
1) Interaction Effect: increased tricyclic antidepressant serum concentrati

confusion, cardiac arrhythmias)
2) Summary: The coadministration of duloxetine with a tricyclic antidepre increasing the risk of adverse events. Duloxetine is a moderately potent ir substrate desipramine 50 mg and duloxetine 60 mg twice daily were coad baseline (Prod Info CYMBALTA(R) delayed-release oral capsules, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Use caution with the combined use of duloxetine with duloxetine and a TCA is unavoidable, plasma concentrations of the t made accordingly (Prod Info CYMBALTA(R) delayed-release oral capsule TCA toxicity (anticholinergic effects, sedation, confusion, and cardiac arrh
7) Probable Mechanism: duloxetine inhibition of CYP2D6-mediated tricyc

3.5.1.CS Meloxicam
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta that the combined use of selective serotonin and norepinephrine reuptake associated with an increased risk of bleeding. Bleeding events have inclu threatening hemorrhages (Prod Info CYMBALTA(R) oral delayed-release
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When duloxetine and a nonsteroidal antiinflamm increased bleeding (Prod Info CYMBALTA(R) oral delayed-release capsu
7) Probable Mechanism: unknown

3.5.1.CT Mesoridazine
1) Interaction Effect: increased phenothiazine serum concentrations and orthostatic hypotension, hyperthermia, extrapyramidal effects)
2) Summary: Duloxetine is a moderately potent inhibitor of CYP2D6; ther likely to increase bioavailability of the phenothiazine agent, increasing the delayed-release oral capsules, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Use caution when prescribing duloxetine to pati elevated phenothiazine plasma concentrations. Monitor for increased phe release oral capsules, 2008).
7) Probable Mechanism: duloxetine inhibition of CYP2D6-mediated phen

3.5.1.CU Methdilazine
1) Interaction Effect: increased phenothiazine serum concentrations and orthostatic hypotension, hyperthermia, extrapyramidal effects)
2) Summary: Duloxetine is a moderately potent inhibitor of CYP2D6; ther likely to increase bioavailability of the phenothiazine agent, increasing the delayed-release oral capsules, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Use caution when prescribing duloxetine to pati elevated phenothiazine plasma concentrations. Monitor for increased phe release oral capsules, 2008).
7) Probable Mechanism: duloxetine inhibition of CYP2D6-mediated phen

3.5.1.CV Methotrimeprazine
1) Interaction Effect: increased phenothiazine serum concentrations and orthostatic hypotension, hyperthermia, extrapyramidal effects)
2) Summary: Duloxetine is a moderately potent inhibitor of CYP2D6; ther likely to increase bioavailability of the phenothiazine agent, increasing the delayed-release oral capsules, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Use caution when prescribing duloxetine to pati elevated phenothiazine plasma concentrations. Monitor for increased phe release oral capsules, 2008).

7) Probable Mechanism: duloxetine inhibition of CYP2D6-mediated phen

3.5.1.CW Metopimazine

1) Interaction Effect: increased phenothiazine serum concentrations and orthostatic hypotension, hyperthermia, extrapyramidal effects)
2) Summary: Duloxetine is a moderately potent inhibitor of CYP2D6; ther likely to increase bioavailability of the phenothiazine agent, increasing the delayed-release oral capsules, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Use caution when prescribing duloxetine to pati elevated phenothiazine plasma concentrations. Monitor for increased phe release oral capsules, 2008).
7) Probable Mechanism: duloxetine inhibition of CYP2D6-mediated phen

3.5.1.CX Milnacipran

1) Interaction Effect: increased risk of serotonin syndrome (hypertension,
2) Summary: Concurrent use of milnacipran and an SSRI or a serotonin r hypertension, coronary artery vasoconstriction or serotonin syndrome, wh may include restlessness, hallucinations, loss of coordination, fast heart b temperature, overreactive reflexes, nausea, vomiting, and diarrhea (Prod
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of milnacipran and an SSRI or result in hypertension and coronary artery vasoconstriction through the ac discuss the risks of serotonin syndrome with the patient and monitor close hyperthermia, hyperreflexia, incoordination), especially during treatment ir tablets, 2009).
7) Probable Mechanism: additive serotonergic effect

3.5.1.CY Morniflumate

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta that the combined use of selective serotonin and norepinephrine reuptake associated with an increased risk of bleeding. Bleeding events have inclu threatening hemorrhages (Prod Info CYMBALTA(R) oral delayed-release
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When duloxetine and a nonsteroidal antiinflamm increased bleeding (Prod Info CYMBALTA(R) oral delayed-release capsu
7) Probable Mechanism: unknown

3.5.1.CZ Nabumetone

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta that the combined use of selective serotonin and norepinephrine reuptake associated with an increased risk of bleeding. Bleeding events have inclu threatening hemorrhages (Prod Info CYMBALTA(R) oral delayed-release
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When duloxetine and a nonsteroidal antiinflamm increased bleeding (Prod Info CYMBALTA(R) oral delayed-release capsu
7) Probable Mechanism: unknown

3.5.1.DA Nadroparin

1) Interaction Effect: increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta that the combined use of selective serotonin and norepinephrine reuptake associated with an increased risk of bleeding. Bleeding events reported h life-threatening hemorrhages. A population-based, case-controlled study with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted bleeding (Schalekamp et al, 2008). Altered anticoagulant effects (includin coadministration of serotonin and norepinephrine reuptake inhibitors with

release oral capsules, 2008). Conversely, one case report described a pe
dose in a patient maintained on acenocoumarol (Monastero et al, 2007).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When duloxetine and an anticoagulant are giver
Patients who are taking warfarin should be monitored closely for altered a
duloxetine therapy is initiated or discontinued (Prod Info CYMBALTA(R) d
7) Probable Mechanism: unknown
8) Literature Reports
a) A population-based, case-controlled study of new coumarin users
selective serotonin reuptake inhibitors (SSRIs) resulted in an increas
Using national pharmacy and hospitalization records, Netherlands re
abnormal bleeding and compared them with 5818 control subjects al
was 220 days (range, 1 to 4690 days). Patients on SSRIs showed gr
(adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5
0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et
b) A case report describes a 44-year-old female patient maintained
after 55 days of concomitant duloxetine treatment. Warfarin was initia
medication regimen included atorvastatin 10 mg, warfarin 7.5 mg to 1
mg, and albuterol extended-release 4 mg twice a day. Duloxetine 30
day 58, only the warfarin was discontinued, and by day 85 the patien
mcg/mL (therapeutic range 2 to 8 mcg/mL). Intravenous vitamin K 10
the INR was again elevated at 6.4, vitamin K-dependent clotting facto
normal. Duloxetine was then discontinued, and 4 days later the INR r
to 54%. INR was 0.9 by day 105, and warfarin was restarted on day
maintained on 7.5 to 10 mg/day. According to the Naranjo algorithm,
probable. The authors suggest that duloxetine may have an effect on
warfarin from its protein-binding sites, or may have unique metabolic
c) A 63-year-old woman successfully maintained on acenocoumarol
mechanical, prosthetic mitral-valve substitution experienced a persist
mg/day. Ten hours after taking duloxetine, the patient was taken to th
blood pressure had increased to 190/110 mmHg and her INR had dra
administered intravenously for the headache and hypertension, dulox
titrated to 12 mg/wk. Twenty-one days later, the INR returned to base
Follow-up examinations on days 28, 56, 84, 168, and 252 revealed st
family interviews discounted the possibility of acenocoumarol self-into
measured and the patient was not genotyped for CYP2D6 or CYP1A2
duloxetine was deemed as probable based on the Naranjo Adverse D

3.5.1.DB Naproxen
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta
that the combined use of selective serotonin and norepinephrine reuptake
associated with an increased risk of bleeding. Bleeding events have inclu
threatening hemorrhages (Prod Info CYMBALTA(R) oral delayed-release
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When duloxetine and a nonsteroidal antiinflamm
increased bleeding (Prod Info CYMBALTA(R) oral delayed-release capsu
7) Probable Mechanism: unknown

3.5.1.DC Naratriptan
1) Interaction Effect: increased risk of serotonin syndrome
2) Summary: A life-threatening condition known as serotonin syndrome m
combination with a serotonin and norepinephrine reuptake inhibitor (SNRI
include restlessness, hallucinations, loss of coordination, fast heart beat,
overreactive reflexes, nausea, vomiting, and diarrhea. Clinicians should b
that either the triptan or the SNRI may be prescribed by a different physici
are prescribed this combination and monitor them closely for symptoms o
dose increases (Prod Info CYMBALTA(R) delayed-release oral capsules,
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of a triptan, such as naratripta
(SNRI), such as duloxetine, may result in a life-threatening condition calle

commonly used intermittently and that either the triptan or the SNRI may l
together, discuss the risks of serotonin syndrome with the patient and mo
hyperthermia, hyperreflexia, incoordination), especially during treatment i
release oral capsules, 2008).
7) Probable Mechanism: additive pharmacologic effects resulting in exce

3.5.1.DD Niflumic Acid
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta
that the combined use of selective serotonin and norepinephrine reuptake
associated with an increased risk of bleeding. Bleeding events have inclu
threatening hemorrhages (Prod Info CYMBALTA(R) oral delayed-release
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When duloxetine and a nonsteroidal antiinflamm
increased bleeding (Prod Info CYMBALTA(R) oral delayed-release capsu
7) Probable Mechanism: unknown

3.5.1.DE Nimesulide
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta
that the combined use of selective serotonin and norepinephrine reuptake
associated with an increased risk of bleeding. Bleeding events have inclu
threatening hemorrhages (Prod Info CYMBALTA(R) oral delayed-release
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When duloxetine and a nonsteroidal antiinflamm
increased bleeding (Prod Info CYMBALTA(R) oral delayed-release capsu
7) Probable Mechanism: unknown

3.5.1.DF Nortriptyline
1) Interaction Effect: increased tricyclic antidepressant serum concentrati
confusion, cardiac arrhythmias)
2) Summary: The coadministration of duloxetine with a tricyclic antidepre
increasing the risk of adverse events. Duloxetine is a moderately potent ir
substrate desipramine 50 mg and duloxetine 60 mg twice daily were coad
baseline (Prod Info CYMBALTA(R) delayed-release oral capsules, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Use caution with the combined use of duloxetine
with duloxetine and a TCA is unavoidable, plasma concentrations of the t
made accordingly (Prod Info CYMBALTA(R) delayed-release oral capsule
TCA toxicity (anticholinergic effects, sedation, confusion, and cardiac arrh
7) Probable Mechanism: duloxetine inhibition of CYP2D6-mediated tricyc

3.5.1.DG Opipramol
1) Interaction Effect: increased tricyclic antidepressant serum concentrati
confusion, cardiac arrhythmias)
2) Summary: The coadministration of duloxetine with a tricyclic antidepre
increasing the risk of adverse events. Duloxetine is a moderately potent ir
substrate desipramine 50 mg and duloxetine 60 mg twice daily were coad
baseline (Prod Info CYMBALTA(R) delayed-release oral capsules, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Use caution with the combined use of duloxetine
with duloxetine and a TCA is unavoidable, plasma concentrations of the t
made accordingly (Prod Info CYMBALTA(R) delayed-release oral capsule
TCA toxicity (anticholinergic effects, sedation, confusion, and cardiac arrh
7) Probable Mechanism: duloxetine inhibition of CYP2D6-mediated tricyc

3.5.1.DH Oxaprozin
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta

that the combined use of selective serotonin and norepinephrine reuptake
associated with an increased risk of bleeding. Bleeding events have inclu
threatening hemorrhages (Prod Info CYMBALTA(R) oral delayed-release
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When duloxetine and a nonsteroidal antiinflamm
increased bleeding (Prod Info CYMBALTA(R) oral delayed-release capsu
7) Probable Mechanism: unknown

3.5.1.DI Parecoxib

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta
that the combined use of selective serotonin and norepinephrine reuptake
associated with an increased risk of bleeding. Bleeding events have inclu
threatening hemorrhages (Prod Info CYMBALTA(R) oral delayed-release
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When duloxetine and a nonsteroidal antiinflamm
increased bleeding (Prod Info CYMBALTA(R) oral delayed-release capsu
7) Probable Mechanism: unknown

3.5.1.DJ Parnaparin

1) Interaction Effect: increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta
that the combined use of selective serotonin and norepinephrine reuptake
associated with an increased risk of bleeding. Bleeding events reported h
life-threatening hemorrhages. A population-based, case-controlled study
with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted
bleeding (Schalekamp et al, 2008). Altered anticoagulant effects (includin
coadministration of serotonin and norepinephrine reuptake inhibitors with
release oral capsules, 2008). Conversely, one case report described a pe
dose in a patient maintained on acenocoumarol (Monastero et al, 2007).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When duloxetine and an anticoagulant are giver
Patients who are taking warfarin should be monitored closely for altered a
duloxetine therapy is initiated or discontinued (Prod Info CYMBALTA(R) d
7) Probable Mechanism: unknown
8) Literature Reports
a) A population-based, case-controlled study of new coumarin users
selective serotonin reuptake inhibitors (SSRIs) resulted in an increas
Using national pharmacy and hospitalization records, Netherlands re
abnormal bleeding and compared them with 5818 control subjects al
was 220 days (range, 1 to 4690 days). Patients on SSRIs showed gr
(adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.
0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et
b) A case report describes a 44-year-old female patient maintained
after 55 days of concomitant duloxetine treatment. Warfarin was initia
medication regimen included atorvastatin 10 mg, warfarin 7.5 mg to 1
mg, and albuterol extended-release 4 mg twice a day. Duloxetine 30
day 58, only the warfarin was discontinued, and by day 85 the patien
mcg/mL (therapeutic range 2 to 8 mcg/mL). Intravenous vitamin K 10
the INR was again elevated at 6.4, vitamin K-dependent clotting facto
normal. Duloxetine was then discontinued, and 4 days later the INR r
to 54%. INR was 0.9 by day 105, and warfarin was restarted on day
maintained on 7.5 to 10 mg/day. According to the Naranjo algorithm,
probable. The authors suggest that duloxetine may have an effect on
warfarin from its protein-binding sites, or may have unique metabolic
c) A 63-year-old woman successfully maintained on acenocoumarol
mechanical, prosthetic mitral-valve substitution experienced a persist
mg/day. Ten hours after taking duloxetine, the patient was taken to th
blood pressure had increased to 190/110 mmHg and her INR had dra
administered intravenously for the headache and hypertension, dulox
titrated to 12 mg/wk. Twenty-one days later, the INR returned to base

Follow-up examinations on days 28, 56, 84, 168, and 252 revealed st
family interviews discounted the possibility of acenocoumarol self-into
measured and the patient was not genotyped for CYP2D6 or CYP1A2
duloxetine was deemed as probable based on the Naranjo Adverse D

3.5.1.DK Paroxetine

1) Interaction Effect: increased duloxetine serum concentrations and an i
2) Summary: Duloxetine is a selective serotonin and norepinephrine reup
paroxetine, an SSRI, is not recommended due to the potential for seroton
potent CYP2D6 inhibitor, at a dose of 20 mg once daily with duloxetine 40
concentration (Prod Info CYMBALTA(R) delayed-release oral capsules, 2
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: The concomitant use of duloxetine and paroxeti
serotonin syndrome. Additionally, concomitant use has resulted in signific
(R) delayed-release oral capsules, 2008).
7) Probable Mechanism: paroxetine inhibition of CYP2D6-mediated dulox

3.5.1.DL Pentosan Polysulfate Sodium

1) Interaction Effect: increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta
that the combined use of selective serotonin and norepinephrine reuptake
associated with an increased risk of bleeding. Bleeding events reported h
life-threatening hemorrhages. A population-based, case-controlled study
with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted i
bleeding (Schalekamp et al, 2008). Altered anticoagulant effects (includin
coadministration of serotonin and norepinephrine reuptake inhibitors with
release oral capsules, 2008). Conversely, one case report described a pe
dose in a patient maintained on acenocoumarol (Monastero et al, 2007).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When duloxetine and an anticoagulant are giver
Patients who are taking warfarin should be monitored closely for altered a
duloxetine therapy is initiated or discontinued (Prod Info CYMBALTA(R) d
7) Probable Mechanism: unknown
8) Literature Reports

a) A population-based, case-controlled study of new coumarin users
selective serotonin reuptake inhibitors (SSRIs) resulted in an increas
Using national pharmacy and hospitalization records, Netherlands re
abnormal bleeding and compared them with 5818 control subjects als
was 220 days (range, 1 to 4690 days). Patients on SSRIs showed gr
(adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5
0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et
b) A case report describes a 44-year-old female patient maintained
after 55 days of concomitant duloxetine treatment. Warfarin was initia
medication regimen included atorvastatin 10 mg, warfarin 7.5 mg to 1
mg, and albuterol extended-release 4 mg twice a day. Duloxetine 30
day 58, only the warfarin was discontinued, and by day 85 the patien
mcg/mL (therapeutic range 2 to 8 mcg/mL). Intravenous vitamin K 10
the INR was again elevated at 6.4, vitamin K-dependent clotting facto
normal. Duloxetine was then discontinued, and 4 days later the INR r
to 54%. INR was 0.9 by day 105, and warfarin was restarted on day
maintained on 7.5 to 10 mg/day. According to the Naranjo algorithm,
probable. The authors suggest that duloxetine may have an effect on
warfarin from its protein-binding sites, or may have unique metabolic
c) A 63-year-old woman successfully maintained on acenocoumarol
mechanical, prosthetic mitral-valve substitution experienced a persist
mg/day. Ten hours after taking duloxetine, the patient was taken to th
blood pressure had increased to 190/110 mmHg and her INR had dra
administered intravenously for the headache and hypertension, dulox
titrated to 12 mg/wk. Twenty-one days later, the INR returned to base
Follow-up examinations on days 28, 56, 84, 168, and 252 revealed st
family interviews discounted the possibility of acenocoumarol self-into
measured and the patient was not genotyped for CYP2D6 or CYP1A2
duloxetine was deemed as probable based on the Naranjo Adverse D

3.5.1.DM Perazine

1) Interaction Effect: increased phenothiazine serum concentrations and orthostatic hypotension, hyperthermia, extrapyramidal effects)
2) Summary: Duloxetine is a moderately potent inhibitor of CYP2D6; ther likely to increase bioavailability of the phenothiazine agent, increasing the delayed-release oral capsules, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Use caution when prescribing duloxetine to pati elevated phenothiazine plasma concentrations. Monitor for increased phe release oral capsules, 2008).
7) Probable Mechanism: duloxetine inhibition of CYP2D6-mediated phen

3.5.1.DN Periciazine

1) Interaction Effect: increased phenothiazine serum concentrations and orthostatic hypotension, hyperthermia, extrapyramidal effects)
2) Summary: Duloxetine is a moderately potent inhibitor of CYP2D6; ther likely to increase bioavailability of the phenothiazine agent, increasing the delayed-release oral capsules, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Use caution when prescribing duloxetine to pati elevated phenothiazine plasma concentrations. Monitor for increased phe release oral capsules, 2008).
7) Probable Mechanism: duloxetine inhibition of CYP2D6-mediated phen

3.5.1.DO Perphenazine

1) Interaction Effect: increased phenothiazine serum concentrations and orthostatic hypotension, hyperthermia, extrapyramidal effects)
2) Summary: Duloxetine is a moderately potent inhibitor of CYP2D6; ther likely to increase bioavailability of the phenothiazine agent, increasing the delayed-release oral capsules, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Use caution when prescribing duloxetine to pati elevated phenothiazine plasma concentrations. Monitor for increased phe release oral capsules, 2008).
7) Probable Mechanism: duloxetine inhibition of CYP2D6-mediated phen

3.5.1.DP Phenindione

1) Interaction Effect: increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta that the combined use of selective serotonin and norepinephrine reuptake associated with an increased risk of bleeding. Bleeding events reported h life-threatening hemorrhages. A population-based, case-controlled study with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted bleeding (Schalekamp et al, 2008). Altered anticoagulant effects (includin coadministration of serotonin and norepinephrine reuptake inhibitors with release oral capsules, 2008). Conversely, one case report described a pe dose in a patient maintained on acenocoumarol (Monastero et al, 2007).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When duloxetine and an anticoagulant are giver Patients who are taking warfarin should be monitored closely for altered a duloxetine therapy is initiated or discontinued (Prod Info CYMBALTA(R) d
7) Probable Mechanism: unknown
8) Literature Reports
a) A population-based, case-controlled study of new coumarin users selective serotonin reuptake inhibitors (SSRIs) resulted in an increas Using national pharmacy and hospitalization records, Netherlands re abnormal bleeding and compared them with 5818 control subjects als was 220 days (range, 1 to 4690 days). Patients on SSRIs showed gr

(adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5
0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et
b) A case report describes a 44-year-old female patient maintained o
after 55 days of concomitant duloxetine treatment. Warfarin was initia
medication regimen included atorvastatin 10 mg, warfarin 7.5 mg to 1
mg, and albuterol extended-release 4 mg twice a day. Duloxetine 30
day 58, only the warfarin was discontinued, and by day 85 the patient
mcg/mL (therapeutic range 2 to 8 mcg/mL). Intravenous vitamin K 10
the INR was again elevated at 6.4, vitamin K-dependent clotting factc
normal. Duloxetine was then discontinued, and 4 days later the INR r
to 54%. INR was 0.9 by day 105, and warfarin was restarted on day
maintained on 7.5 to 10 mg/day. According to the Naranjo algorithm,
probable. The authors suggest that duloxetine may have an effect on
warfarin from its protein-binding sites, or may have unique metabolic
c) A 63-year-old woman successfully maintained on acenocoumarol
mechanical, prosthetic mitral-valve substitution experienced a persist
mg/day. Ten hours after taking duloxetine, the patient was taken to th
blood pressure had increased to 190/110 mmHg and her INR had dra
administered intravenously for the headache and hypertension, dulox
titrated to 12 mg/wk. Twenty-one days later, the INR returned to base
Follow-up examinations on days 28, 56, 84, 168, and 252 revealed st
family interviews discounted the possibility of acenocoumarol self-intc
measured and the patient was not genotyped for CYP2D6 or CYP1A2
duloxetine was deemed as probable based on the Naranjo Adverse D

3.5.1.DQ Phenprocoumon

1) Interaction Effect: increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintа
that the combined use of selective serotonin and norepinephrine reuptake
associated with an increased risk of bleeding. Bleeding events reported h
life-threatening hemorrhages. A population-based, case-controlled study c
with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted i
bleeding (Schalekamp et al, 2008). Altered anticoagulant effects (includin
coadministration of serotonin and norepinephrine reuptake inhibitors with
release oral capsules, 2008). Conversely, one case report described a pe
dose in a patient maintained on acenocoumarol (Monastero et al, 2007).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When duloxetine and an anticoagulant are giver
Patients who are taking warfarin should be monitored closely for altered a
duloxetine therapy is initiated or discontinued (Prod Info CYMBALTA(R) d
7) Probable Mechanism: unknown
8) Literature Reports
a) A population-based, case-controlled study of new coumarin users
selective serotonin reuptake inhibitors (SSRIs) resulted in an increas
Using national pharmacy and hospitalization records, Netherlands res
abnormal bleeding and compared them with 5818 control subjects als
was 220 days (range, 1 to 4690 days). Patients on SSRIs showed gr
(adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5
0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et
b) A case report describes a 44-year-old female patient maintained o
after 55 days of concomitant duloxetine treatment. Warfarin was initia
medication regimen included atorvastatin 10 mg, warfarin 7.5 mg to 1
mg, and albuterol extended-release 4 mg twice a day. Duloxetine 30
day 58, only the warfarin was discontinued, and by day 85 the patient
mcg/mL (therapeutic range 2 to 8 mcg/mL). Intravenous vitamin K 10
the INR was again elevated at 6.4, vitamin K-dependent clotting factc
normal. Duloxetine was then discontinued, and 4 days later the INR r
to 54%. INR was 0.9 by day 105, and warfarin was restarted on day
maintained on 7.5 to 10 mg/day. According to the Naranjo algorithm,
probable. The authors suggest that duloxetine may have an effect on
warfarin from its protein-binding sites, or may have unique metabolic
c) A 63-year-old woman successfully maintained on acenocoumarol
mechanical, prosthetic mitral-valve substitution experienced a persist
mg/day. Ten hours after taking duloxetine, the patient was taken to th
blood pressure had increased to 190/110 mmHg and her INR had dra

administered intravenously for the headache and hypertension, dulox
titrated to 12 mg/wk. Twenty-one days later, the INR returned to base
Follow-up examinations on days 28, 56, 84, 168, and 252 revealed st
family interviews discounted the possibility of acenocoumarol self-intc
measured and the patient was not genotyped for CYP2D6 or CYP1A2
duloxetine was deemed as probable based on the Naranjo Adverse D

3.5.1.DR Phenylbutazone

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta
that the combined use of selective serotonin and norepinephrine reuptake
associated with an increased risk of bleeding. Bleeding events have inclu
threatening hemorrhages (Prod Info CYMBALTA(R) oral delayed-release
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When duloxetine and a nonsteroidal antiinflamm
increased bleeding (Prod Info CYMBALTA(R) oral delayed-release capsu
7) Probable Mechanism: unknown

3.5.1.DS Pipotiazine

1) Interaction Effect: increased phenothiazine serum concentrations and
orthostatic hypotension, hyperthermia, extrapyramidal effects)
2) Summary: Duloxetine is a moderately potent inhibitor of CYP2D6; ther
likely to increase bioavailability of the phenothiazine agent, increasing the
delayed-release oral capsules, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Use caution when prescribing duloxetine to pati
elevated phenothiazine plasma concentrations. Monitor for increased phe
release oral capsules, 2008).
7) Probable Mechanism: duloxetine inhibition of CYP2D6-mediated phen

3.5.1.DT Pirazolac

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta
that the combined use of selective serotonin and norepinephrine reuptake
associated with an increased risk of bleeding. Bleeding events have inclu
threatening hemorrhages (Prod Info CYMBALTA(R) oral delayed-release
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When duloxetine and a nonsteroidal antiinflamm
increased bleeding (Prod Info CYMBALTA(R) oral delayed-release capsu
7) Probable Mechanism: unknown

3.5.1.DU Piroxicam

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta
that the combined use of selective serotonin and norepinephrine reuptake
associated with an increased risk of bleeding. Bleeding events have inclu
threatening hemorrhages (Prod Info CYMBALTA(R) oral delayed-release
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When duloxetine and a nonsteroidal antiinflamm
increased bleeding (Prod Info CYMBALTA(R) oral delayed-release capsu
7) Probable Mechanism: unknown

3.5.1.DV Pirprofen

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta
that the combined use of selective serotonin and norepinephrine reuptake
associated with an increased risk of bleeding. Bleeding events have inclu
threatening hemorrhages (Prod Info CYMBALTA(R) oral delayed-release
3) Severity: moderate

4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When duloxetine and a nonsteroidal antiinflamm
increased bleeding (Prod Info CYMBALTA(R) oral delayed-release capsu
7) Probable Mechanism: unknown

3.5.1.DW Procarbazine
1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, h
2) Summary: Duloxetine exerts inhibitory effects on both norepinephrine
overlapping therapy with duloxetine and an MAOI, such as procarbazine,
serotonergic state characterized by symptoms such as agitation and restl
diaphoresis, shivering, and tremor. Serious, even fatal, reactions have be
inhibitors and MAOIs. Concomitant administration of duloxetine and proca
elapse after discontinuing procarbazine before initiating therapy with dulo
discontinuing duloxetine before initiating therapy with procarbazine (Prod
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concurrent use of duloxetine and procarbazine
procarbazine before initiating duloxetine. Wait at least 5 days after discon
(Prod Info Cymbalta(R) Delayed-release oral capsules, 2009).
7) Probable Mechanism: additive serotonergic effects

3.5.1.DX Prochlorperazine
1) Interaction Effect: increased phenothiazine serum concentrations and
orthostatic hypotension, hyperthermia, extrapyramidal effects)
2) Summary: Duloxetine is a moderately potent inhibitor of CYP2D6; ther
likely to increase bioavailability of the phenothiazine agent, increasing the
delayed-release oral capsules, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Use caution when prescribing duloxetine to pati
elevated phenothiazine plasma concentrations. Monitor for increased phe
release oral capsules, 2008).
7) Probable Mechanism: duloxetine inhibition of CYP2D6-mediated phen

3.5.1.DY Promazine
1) Interaction Effect: increased phenothiazine serum concentrations and
orthostatic hypotension, hyperthermia, extrapyramidal effects)
2) Summary: Duloxetine is a moderately potent inhibitor of CYP2D6; ther
likely to increase bioavailability of the phenothiazine agent, increasing the
delayed-release oral capsules, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Use caution when prescribing duloxetine to pati
elevated phenothiazine plasma concentrations. Monitor for increased phe
release oral capsules, 2008).
7) Probable Mechanism: duloxetine inhibition of CYP2D6-mediated phen

3.5.1.DZ Promethazine
1) Interaction Effect: increased phenothiazine serum concentrations and
orthostatic hypotension, hyperthermia, extrapyramidal effects)
2) Summary: Duloxetine is a moderately potent inhibitor of CYP2D6; ther
likely to increase bioavailability of the phenothiazine agent, increasing the
delayed-release oral capsules, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Use caution when prescribing duloxetine to pati
elevated phenothiazine plasma concentrations. Monitor for increased phe
release oral capsules, 2008).
7) Probable Mechanism: duloxetine inhibition of CYP2D6-mediated phen

3.5.1.EA Propafenone
1) Interaction Effect: increased class IC antiarrhythmic serum concentrati

torsades de pointes, cardiac arrest)
2) Summary: Duloxetine is a moderately potent inhibitor of CYP2D6. Give antiarrhythmic agents as well as considering that they are CYP2D6 substr whenever duloxetine is coadministered with this class of antiarrhythmic ag 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Use caution when prescribing duloxetine to pati cause elevated plasma concentrations of the antiarrhythmic (Prod Info CY class IC antiarrhythmic serum concentrations and ECG for signs of potent hypotension); adjust dose accordingly. Alternatively, consider selecting ar pharmacokinetics of class IC antiarrhythmic agents.
7) Probable Mechanism: inhibition of CYP2D6-mediated metabolism of cl

3.5.1.EB Propiomazine
1) Interaction Effect: increased phenothiazine serum concentrations and orthostatic hypotension, hyperthermia, extrapyramidal effects)
2) Summary: Duloxetine is a moderately potent inhibitor of CYP2D6; ther likely to increase bioavailability of the phenothiazine agent, increasing the delayed-release oral capsules, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Use caution when prescribing duloxetine to pati elevated phenothiazine plasma concentrations. Monitor for increased phe release oral capsules, 2008).
7) Probable Mechanism: duloxetine inhibition of CYP2D6-mediated phen

3.5.1.EC Propyphenazone
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta that the combined use of selective serotonin and norepinephrine reuptake associated with an increased risk of bleeding. Bleeding events have inclu threatening hemorrhages (Prod Info CYMBALTA(R) oral delayed-release
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When duloxetine and a nonsteroidal antiinflamm increased bleeding (Prod Info CYMBALTA(R) oral delayed-release capsu
7) Probable Mechanism: unknown

3.5.1.ED Proquazone
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta that the combined use of selective serotonin and norepinephrine reuptake associated with an increased risk of bleeding. Bleeding events have inclu threatening hemorrhages (Prod Info CYMBALTA(R) oral delayed-release
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When duloxetine and a nonsteroidal antiinflamm increased bleeding (Prod Info CYMBALTA(R) oral delayed-release capsu
7) Probable Mechanism: unknown

3.5.1.EE Protriptyline
1) Interaction Effect: increased tricyclic antidepressant serum concentrati confusion, cardiac arrhythmias)
2) Summary: The coadministration of duloxetine with a tricyclic antidepre increasing the risk of adverse events. Duloxetine is a moderately potent ir substrate desipramine 50 mg and duloxetine 60 mg twice daily were coad baseline (Prod Info CYMBALTA(R) delayed-release oral capsules, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Use caution with the combined use of duloxetine with duloxetine and a TCA is unavoidable, plasma concentrations of the tr

made accordingly (Prod Info CYMBALTA(R) delayed-release oral capsule
TCA toxicity (anticholinergic effects, sedation, confusion, and cardiac arrh
7) Probable Mechanism: duloxetine inhibition of CYP2D6-mediated tricyc

3.5.1.EF Quinidine

1) Interaction Effect: increased duloxetine serum concentrations and risk
2) Summary: The coadministration of duloxetine (a substrate of CYP2D6
increase the bioavailability of duloxetine, increasing the risk of serious adv
with another potent CYP2D6 inhibitor (paroxetine 20 mg once daily) resul
(Prod Info CYMBALTA(R) delayed-release oral capsules, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Use caution when prescribing duloxetine to pati
quinidine may cause elevated duloxetine plasma concentrations (Prod Inf
7) Probable Mechanism: quinidine inhibition of CYP2D6-mediated duloxe

3.5.1.EG Rasagiline

1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, h
2) Summary: Duloxetine exerts inhibitory effects on both norepinephrine
overlapping therapy with duloxetine and an MAOI, such as rasagiline, ma
serotonergic state characterized by symptoms such as agitation and restl
diaphoresis, shivering, and tremor. Serious, even fatal, reactions have be
inhibitors and MAOIs. Concomitant administration of duloxetine and rasag
elapse after discontinuing rasagiline before initiating therapy with duloxeti
duloxetine before initiating therapy with rasagiline (Prod Info Cymbalta(R)
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concurrent use of duloxetine and rasagiline is c
rasagiline before initiating duloxetine. Wait at least 5 days after discontinu
Info Cymbalta(R) Delayed-release oral capsules, 2009).
7) Probable Mechanism: additive serotonergic effects

3.5.1.EH Rasagiline

1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, h
2) Summary: Concomitant use of rasagiline and duloxetine, a selective s
avoided. Concurrent administration or overlapping therapy with SSRIs an
sometimes fatal reactions. Signs and symptoms included hyperthermia, ri
fluctuations, and mental status changes progressing to extreme agitation,
SNRIs and non-selective MAOIs. At least 14 days should elapse after dis
Info AZILECT(R) oral tablets, 2006). Similarly, at least 5 days should elap
rasagiline (Prod Info CYMBALTA(R) delayed-release oral capsules, 2008
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concurrent use of duloxetine and rasagiline is n
rasagiline before initiating therapy with duloxetine, or wait at least 5 days
rasagiline (Prod Info AZILECT(R) oral tablets, 2006; Prod Info CYMBALT
7) Probable Mechanism: inhibition of monamine oxidase-mediated seroto

3.5.1.EI Recainam

1) Interaction Effect: increased class IC antiarrhythmic serum concentrati
torsades de pointes, cardiac arrest)
2) Summary: Duloxetine is a moderately potent inhibitor of CYP2D6. Give
antiarrhythmic agents as well as considering that they are CYP2D6 substr
whenever duloxetine is coadministered with this class of antiarrhythmic ag
2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Use caution when prescribing duloxetine to pati
cause elevated plasma concentrations of the antiarrhythmic (Prod Info CY
class IC antiarrhythmic serum concentrations and ECG for signs of potent
hypotension); adjust dose accordingly. Alternatively, consider selecting ar
pharmacokinetics of class IC antiarrhythmic agents.
7) Probable Mechanism: inhibition of CYP2D6-mediated metabolism of c

3.5.1.EJ Reviparin

1) Interaction Effect: increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for mainta that the combined use of selective serotonin and norepinephrine reuptake associated with an increased risk of bleeding. Bleeding events reported h life-threatening hemorrhages. A population-based, case-controlled study with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted bleeding (Schalekamp et al, 2008). Altered anticoagulant effects (includin coadministration of serotonin and norepinephrine reuptake inhibitors with release oral capsules, 2008). Conversely, one case report described a pe dose in a patient maintained on acenocoumarol (Monastero et al, 2007).

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: When duloxetine and an anticoagulant are giver Patients who are taking warfarin should be monitored closely for altered a duloxetine therapy is initiated or discontinued (Prod Info CYMBALTA(R) d

7) Probable Mechanism: unknown

8) Literature Reports

a) A population-based, case-controlled study of new coumarin users selective serotonin reuptake inhibitors (SSRIs) resulted in an increas Using national pharmacy and hospitalization records, Netherlands re abnormal bleeding and compared them with 5818 control subjects al was 220 days (range, 1 to 4690 days). Patients on SSRIs showed gr (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et

b) A case report describes a 44-year-old female patient maintained after 55 days of concomitant duloxetine treatment. Warfarin was initia medication regimen included atorvastatin 10 mg, warfarin 7.5 mg to 1 mg, and albuterol extended-release 4 mg twice a day. Duloxetine 30 day 58, only the warfarin was discontinued, and by day 85 the patien mcg/mL (therapeutic range 2 to 8 mcg/mL). Intravenous vitamin K 10 the INR was again elevated at 6.4, vitamin K-dependent clotting facto normal. Duloxetine was then discontinued, and 4 days later the INR r to 54%. INR was 0.9 by day 105, and warfarin was restarted on day maintained on 7.5 to 10 mg/day. According to the Naranjo algorithm, probable. The authors suggest that duloxetine may have an effect on warfarin from its protein-binding sites, or may have unique metabolic

c) A 63-year-old woman successfully maintained on acenocoumarol mechanical, prosthetic mitral-valve substitution experienced a persist mg/day. Ten hours after taking duloxetine, the patient was taken to th blood pressure had increased to 190/110 mmHg and her INR had dra administered intravenously for the headache and hypertension, dulox titrated to 12 mg/wk. Twenty-one days later, the INR returned to base Follow-up examinations on days 28, 56, 84, 168, and 252 revealed st family interviews discounted the possibility of acenocoumarol self-into measured and the patient was not genotyped for CYP2D6 or CYP1A duloxetine was deemed as probable based on the Naranjo Adverse D

3.5.1.EK Rizatriptan

1) Interaction Effect: increased risk of serotonin syndrome

2) Summary: A life-threatening condition known as serotonin syndrome m combination with a serotonin and norepinephrine reuptake inhibitor (SNRI include restlessness, hallucinations, loss of coordination, fast heart beat, overreactive reflexes, nausea, vomiting, and diarrhea. Clinicians should b that either the triptan or the SNRI may be prescribed by a different physici are prescribed this combination and monitor them closely for symptoms o dose increases (Prod Info CYMBALTA(R) delayed-release oral capsules,

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Coadministration of a triptan, such as rizatriptan such as duloxetine, may result in a life-threatening condition called seroto intermittently and that either the triptan or the SNRI may be prescribed by discuss the risks of serotonin syndrome with the patient and monitor close hyperthermia, hyperreflexia, incoordination), especially during treatment i

release oral capsules, 2008).
7) Probable Mechanism: additive pharmacologic effects resulting in exce

3.5.1.EL Rofecoxib
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta that the combined use of selective serotonin and norepinephrine reuptake associated with an increased risk of bleeding. Bleeding events have inclu threatening hemorrhages (Prod Info CYMBALTA(R) oral delayed-release
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When duloxetine and a nonsteroidal antiinflamm increased bleeding (Prod Info CYMBALTA(R) oral delayed-release capsu
7) Probable Mechanism: unknown

3.5.1.EM Selegiline
1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, h
2) Summary: Duloxetine exerts inhibitory effects on both norepinephrine overlapping therapy with duloxetine and an MAOI, such as selegiline, may serotonergic state characterized by symptoms such as agitation and restl diaphoresis, shivering, and tremor. Serious, even fatal, reactions have be inhibitors and MAOIs. Concomitant administration of duloxetine and seleg elapse after discontinuing selegiline before initiating therapy with duloxeti duloxetine before initiating therapy with selegiline (Prod Info Cymbalta(R)
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concurrent use of duloxetine and selegiline is c selegiline before initiating duloxetine. Wait at least 5 days after discontinu Cymbalta(R) Delayed-release oral capsules, 2009).
7) Probable Mechanism: additive serotonergic effects

3.5.1.EN Sertraline
1) Interaction Effect: an increased risk of serotonin syndrome
2) Summary: Duloxetine is a selective serotonin and norepinephrine reup sertraline, a selective serotonin reuptake inhibitor, is not recommended du CYMBALTA(R) delayed-release oral capsules, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concomitant use of duloxetine and sertralin serotonin syndrome (Prod Info CYMBALTA(R) delayed-release oral capsu
7) Probable Mechanism: additive serotonergic effects

3.5.1.EO Sibrafiban
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta that the combined use of selective serotonin and norepinephrine reuptake been associated with an increased risk of bleeding. Bleeding events repo petechiae, and life-threatening hemorrhages (Prod Info CYMBALTA(R) de
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When duloxetine and an antiplatelet agent are g bleeding (Prod Info CYMBALTA(R) delayed-release oral capsules, 2008).
7) Probable Mechanism: unknown

3.5.1.EP St John's Wort
1) Interaction Effect: an increased risk of serotonin syndrome
2) Summary: Duloxetine is a selective serotonin and norepinephrine reup affect the serotonergic neurotransmitter systems, may result in an increas delayed-release oral capsules, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Use caution if duloxetine is coadministered with

serotonin syndrome (Prod Info CYMBALTA(R) delayed-release oral capsu
7) Probable Mechanism: additive serotonergic effects

3.5.1.EQ Sulfinpyrazone
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta that the combined use of selective serotonin and norepinephrine reuptake been associated with an increased risk of bleeding. Bleeding events repo petechiae, and life-threatening hemorrhages (Prod Info CYMBALTA(R) de
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When duloxetine and an antiplatelet agent are g bleeding (Prod Info CYMBALTA(R) delayed-release oral capsules, 2008).
7) Probable Mechanism: unknown

3.5.1.ER Sulindac
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta that the combined use of selective serotonin and norepinephrine reuptake associated with an increased risk of bleeding. Bleeding events have inclu threatening hemorrhages (Prod Info CYMBALTA(R) oral delayed-release
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When duloxetine and a nonsteroidal antiinflamm increased bleeding (Prod Info CYMBALTA(R) oral delayed-release capsu
7) Probable Mechanism: unknown

3.5.1.ES Sulodexide
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta that the combined use of selective serotonin and norepinephrine reuptake been associated with an increased risk of bleeding. Bleeding events repo petechiae, and life-threatening hemorrhages (Prod Info CYMBALTA(R) de
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When duloxetine and an antiplatelet agent are g bleeding (Prod Info CYMBALTA(R) delayed-release oral capsules, 2008).
7) Probable Mechanism: unknown

3.5.1.ET Sumatriptan
1) Interaction Effect: increased risk of serotonin syndrome
2) Summary: A life-threatening condition known as serotonin syndrome m combination with a serotonin and norepinephrine reuptake inhibitor (SNRI include restlessness, hallucinations, loss of coordination, fast heart beat, overreactive reflexes, nausea, vomiting, and diarrhea. Clinicians should b that either the triptan or the SNRI may be prescribed by a different physic are prescribed this combination and monitor them closely for symptoms o dose increases (Prod Info CYMBALTA(R) delayed-release oral capsules,
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of a triptan, such as sumatripta (SNRI), such as duloxetine, may result in a life-threatening condition calle commonly used intermittently and that either the triptan or the SNRI may b together, discuss the risks of serotonin syndrome with the patient and mo hyperthermia, hyperreflexia, incoordination), especially during treatment i release oral capsules, 2008).
7) Probable Mechanism: additive pharmacologic effects resulting in exce

3.5.1.EU Suprofen
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta that the combined use of selective serotonin and norepinephrine reuptake associated with an increased risk of bleeding. Bleeding events have inclu

threatening hemorrhages (Prod Info CYMBALTA(R) oral delayed-release
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When duloxetine and a nonsteroidal antiinflamm
increased bleeding (Prod Info CYMBALTA(R) oral delayed-release capsu
7) Probable Mechanism: unknown

3.5.1.EV Tamoxifen

1) Interaction Effect: decreased plasma concentrations of the active meta
2) Summary: Duloxetine is a moderate CYP2D6 inhibitor (Prod Info CYM
is a prodrug metabolized to active metabolites by CYP450 enzymes. Con
tamoxifen efficacy by inhibiting the formation of endoxifen, an active meta
interactions may result in variations in endoxifen concentrations, which ma
efficacy (Desta et al, 2004). Tamoxifen use in the presence of CYP2D6 in
may substantially reduce the plasma concentrations of endoxifen and may
However, one small case control study found that pharmacokinetic alterat
tumor recurrence in breast cancer patients (Lehmann et al, 2004).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of tamoxifen and paroxetine, a
concentrations of 4-hydroxy-N-desmethyl tamoxifen, an active metabolite
moderate CYP2D6 inhibitor (Prod Info CYMBALTA(R) delayed-release or
with coadministration may be necessary.
7) Probable Mechanism: inhibition of CYP2D6-mediated tamoxifen metab
8) Literature Reports
a) The use of CYP2D6 inhibitors should be avoided in breast cancer
reduced plasma concentrations of the antiestrogenic tamoxifen metal
postmenopausal breast cancer patients receiving tamoxifen were ger
medication history. Adjusted analysis showed that decreased metabo
(hazard ratio 1.74; 95% confidence interval (CI), 1.1 to 2.74; p=0.017
p=0.027), and shorter time to recurrence (hazard ratio 1.91; 95% CI,
(n=115). The greatest risk of breast cancer relapse was found in the
7.55; p=0.007) (Goetz et al, 2007). Decreased metabolizers had eithe
inhibitor together with tamoxifen (regardless of genotype), and extens
receiving a CYP2D6 inhibitor (Goetz et al, 2008).
b) Plasma concentrations of 4-hydroxy-N-desmethyl tamoxifen (endo
CYP2D6 metabolic pathway. Studies have shown that concomitant u
resulted in reduced plasma concentrations of endoxifen (Johnson et
CYP2D6 inhibitor (Prod Info CYMBALTA(R) delayed-release oral cap
c) Concomitant use of paroxetine, a potent inhibitor of CYP2D6, and
the antiestrogenic metabolite (endoxifen), results in substantially redu
diagnosed breast cancer patients taking tamoxifen 20 mg/day were g
CYP3A5, and sulfotransferase (SULT) 1A1 genes. After 1 and 4 mon
and endoxifen were measured. After 4 months of tamoxifen, plasma
those with a CYP2D6 homozygous variant genotype (20 nM; 95% CI
33.3 to 52.9) than those with a homozygous wild-type genotype (78 n
endoxifen concentration for subjects with a homozygous wild-type ge
than those not taking such inhibitors (38.6 nM versus 91.4 nM, 95% C
venlafaxine, a weak inhibitor of CYP2D6, resulted in slightly reduced
paroxetine, a potent inhibitor of CYP2D6, resulted in substantial redu
tamoxifen and metabolites were not altered significantly by genetic va
d) A case control study (n=28) designed to evaluate the effect of CY
tamoxifen for estrogen receptor-positive breast cancer found no signi
exposure (3 months or greater) to CYP2D6, 2C9, or 3A4 inhibitors or
(patients without recurrent breast cancer) were matched by cancer st
exposure. Selective serotonin reuptake inhibitors, including paroxetin
for the metabolism of tamoxifen to the potent antiestrogen 4-hydroxy
norepinephrine reuptake inhibitors are also inhibitors of CYP2D6, sim

3.5.1.EW Tapentadol

1) Interaction Effect: increased risk of serotonin syndrome (hypertension,
2) Summary: Concurrent use of duloxetine and tapentadol may result in s
of serotonin syndrome may include restlessness, hallucinations, loss of co
increased body temperature, overreactive reflexes, nausea, vomiting, and
2008).

3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of duloxetine and tapentadol n
syndrome. If these agents are used together, monitor the patient closely f
hyperthermia, hyperreflexia, incoordination), especially during treatment i
release oral tablets, 2008).
7) Probable Mechanism: additive serotonergic effect

3.5.1.EX Tenidap
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta
that the combined use of selective serotonin and norepinephrine reuptake
associated with an increased risk of bleeding. Bleeding events have inclu
threatening hemorrhages (Prod Info CYMBALTA(R) oral delayed-release
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When duloxetine and a nonsteroidal antiinflamm
increased bleeding (Prod Info CYMBALTA(R) oral delayed-release capsu
7) Probable Mechanism: unknown

3.5.1.EY Tenoxicam
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta
that the combined use of selective serotonin and norepinephrine reuptake
associated with an increased risk of bleeding. Bleeding events have inclu
threatening hemorrhages (Prod Info CYMBALTA(R) oral delayed-release
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When duloxetine and a nonsteroidal antiinflamm
increased bleeding (Prod Info CYMBALTA(R) oral delayed-release capsu
7) Probable Mechanism: unknown

3.5.1.EZ Thiethylperazine
1) Interaction Effect: increased phenothiazine serum concentrations and
orthostatic hypotension, hyperthermia, extrapyramidal effects)
2) Summary: Duloxetine is a moderately potent inhibitor of CYP2D6; ther
likely to increase bioavailability of the phenothiazine agent, increasing the
delayed-release oral capsules, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Use caution when prescribing duloxetine to pati
elevated phenothiazine plasma concentrations. Monitor for increased phe
release oral capsules, 2008).
7) Probable Mechanism: duloxetine inhibition of CYP2D6-mediated phen

3.5.1.FA Thiopropazate
1) Interaction Effect: increased phenothiazine serum concentrations and
orthostatic hypotension, hyperthermia, extrapyramidal effects)
2) Summary: Duloxetine is a moderately potent inhibitor of CYP2D6; ther
likely to increase bioavailability of the phenothiazine agent, increasing the
delayed-release oral capsules, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Use caution when prescribing duloxetine to pati
elevated phenothiazine plasma concentrations. Monitor for increased phe
release oral capsules, 2008).
7) Probable Mechanism: duloxetine inhibition of CYP2D6-mediated phen

3.5.1.FB Thioproperazine
1) Interaction Effect: increased phenothiazine serum concentrations and
orthostatic hypotension, hyperthermia, extrapyramidal effects)
2) Summary: Duloxetine is a moderately potent inhibitor of CYP2D6; ther

likely to increase bioavailability of the phenothiazine agent, increasing the
delayed-release oral capsules, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Use caution when prescribing duloxetine to pati
elevated phenothiazine plasma concentrations. Monitor for increased phe
release oral capsules, 2008).
7) Probable Mechanism: duloxetine inhibition of CYP2D6-mediated phen

3.5.1.FC Thioridazine
1) Interaction Effect: increased thioridazine serum concentrations and ris
2) Summary: Given thioridazine's tendency to prolong the QTc-interval in
serious or fatal ventricular arrhythmias precludes the safe concomitant us
potent inhibitor of CYP2D6 (for which thioridazine is a substrate) and ther
likely to produce elevated thioridazine plasma concentrations with attenda
CYMBALTA(R) delayed-release oral capsules, 2008).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of duloxetine and thioridazine
7) Probable Mechanism: duloxetine inhibition of CYP2D6-mediated thiori

3.5.1.FD Tianeptine
1) Interaction Effect: increased tricyclic antidepressant serum concentrati
confusion, cardiac arrhythmias)
2) Summary: The coadministration of duloxetine with a tricyclic antidepre
increasing the risk of adverse events. Duloxetine is a moderately potent ir
substrate desipramine 50 mg and duloxetine 60 mg twice daily were coad
baseline (Prod Info CYMBALTA(R) delayed-release oral capsules, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Use caution with the combined use of duloxetine
with duloxetine and a TCA is unavoidable, plasma concentrations of the tr
made accordingly (Prod Info CYMBALTA(R) delayed-release oral capsule
TCA toxicity (anticholinergic effects, sedation, confusion, and cardiac arrh
7) Probable Mechanism: duloxetine inhibition of CYP2D6-mediated tricyc

3.5.1.FE Tiaprofenic Acid
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta
that the combined use of selective serotonin and norepinephrine reuptake
associated with an increased risk of bleeding. Bleeding events have inclu
threatening hemorrhages (Prod Info CYMBALTA(R) oral delayed-release
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When duloxetine and a nonsteroidal antiinflamm
increased bleeding (Prod Info CYMBALTA(R) oral delayed-release capsu
7) Probable Mechanism: unknown

3.5.1.FF Ticlopidine
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta
that the combined use of selective serotonin and norepinephrine reuptake
been associated with an increased risk of bleeding. Bleeding events repor
petechiae, and life-threatening hemorrhages (Prod Info CYMBALTA(R) de
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When duloxetine and an antiplatelet agent are g
bleeding (Prod Info CYMBALTA(R) delayed-release oral capsules, 2008).
7) Probable Mechanism: unknown

3.5.1.FG Tinzaparin
1) Interaction Effect: increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for mainta
that the combined use of selective serotonin and norepinephrine reuptake
associated with an increased risk of bleeding. Bleeding events reported h
life-threatening hemorrhages. A population-based, case-controlled study
with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted
bleeding (Schalekamp et al, 2008). Altered anticoagulant effects (includin
coadministration of serotonin and norepinephrine reuptake inhibitors with
release oral capsules, 2008). Conversely, one case report described a pe
dose in a patient maintained on acenocoumarol (Monastero et al, 2007).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When duloxetine and an anticoagulant are giver
Patients who are taking warfarin should be monitored closely for altered a
duloxetine therapy is initiated or discontinued (Prod Info CYMBALTA(R) d
7) Probable Mechanism: unknown
8) Literature Reports
a) A population-based, case-controlled study of new coumarin users
selective serotonin reuptake inhibitors (SSRIs) resulted in an increas
Using national pharmacy and hospitalization records, Netherlands re
abnormal bleeding and compared them with 5818 control subjects al
was 220 days (range, 1 to 4690 days). Patients on SSRIs showed gr
(adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.
0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et
b) A case report describes a 44-year-old female patient maintained
after 55 days of concomitant duloxetine treatment. Warfarin was initia
medication regimen included atorvastatin 10 mg, warfarin 7.5 mg to 1
mg, and albuterol extended-release 4 mg twice a day. Duloxetine 30
day 58, only the warfarin was discontinued, and by day 85 the patien
mcg/mL (therapeutic range 2 to 8 mcg/mL). Intravenous vitamin K 10
the INR was again elevated at 6.4, vitamin K-dependent clotting facto
normal. Duloxetine was then discontinued, and 4 days later the INR r
to 54%. INR was 0.9 by day 105, and warfarin was restarted on day
maintained on 7.5 to 10 mg/day. According to the Naranjo algorithm,
probable. The authors suggest that duloxetine may have an effect on
warfarin from its protein-binding sites, or may have unique metabolic
c) A 63-year-old woman successfully maintained on acenocoumarol
mechanical, prosthetic mitral-valve substitution experienced a persist
mg/day. Ten hours after taking duloxetine, the patient was taken to th
blood pressure had increased to 190/110 mmHg and her INR had dra
administered intravenously for the headache and hypertension, dulox
titrated to 12 mg/wk. Twenty-one days later, the INR returned to base
Follow-up examinations on days 28, 56, 84, 168, and 252 revealed st
family interviews discounted the possibility of acenocoumarol self-into
measured and the patient was not genotyped for CYP2D6 or CYP1A2
duloxetine was deemed as probable based on the Naranjo Adverse D

3.5.1.FH Tirofiban

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta
that the combined use of selective serotonin and norepinephrine reuptake
been associated with an increased risk of bleeding. Bleeding events repo
petechiae, and life-threatening hemorrhages (Prod Info CYMBALTA(R) de
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When duloxetine and an antiplatelet agent are g
bleeding (Prod Info CYMBALTA(R) delayed-release oral capsules, 2008).
7) Probable Mechanism: unknown

3.5.1.FI Tolmetin

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta
that the combined use of selective serotonin and norepinephrine reuptake
associated with an increased risk of bleeding. Bleeding events have inclu
threatening hemorrhages (Prod Info CYMBALTA(R) oral delayed-release
3) Severity: moderate

4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When duloxetine and a nonsteroidal antiinflamm
increased bleeding (Prod Info CYMBALTA(R) oral delayed-release capsu
7) Probable Mechanism: unknown

3.5.1.FJ Tramadol
1) Interaction Effect: an increased risk of serotonin syndrome
2) Summary: Duloxetine is a selective serotonin and norepinephrine reup
concurrently with agents affecting the serotonergic neurotransmitter syste
serotonin syndrome (Prod Info CYMBALTA(R) delayed-release oral capsu
symptoms of serotonin syndrome such as neuromuscular abnormalities (i
peripheral hypertonicity, and shivering), autonomic hyperactivity (including
bowel sounds and diarrhea), and mental status changes (including agitati
syndrome with patients who are prescribed this combination. If serotonin s
provide supportive care, correction of vital signs, or other therapy, as nece
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Use caution if duloxetine is coadministered with
syndrome (Prod Info CYMBALTA(R) delayed-release oral capsules, 2008
symptoms of serotonin syndrome such as neuromuscular abnormalities (i
peripheral hypertonicity, and shivering), autonomic hyperactivity (including
sounds, and diarrhea), and mental status changes (including agitation and
serotonin syndrome develops, discontinue the offending agents and provi
as necessary (Boyer & Shannon, 2005).
7) Probable Mechanism: additive serotonergic effects

3.5.1.FK Tranylcypromine
1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, h
2) Summary: Duloxetine exerts inhibitory effects on both norepinephrine
overlapping therapy with duloxetine and an MAOI, such as tranylcypromin
serotonergic state characterized by symptoms such as agitation and restl
diaphoresis, shivering, and tremor. Serious, even fatal, reactions have be
inhibitors and MAOIs. Concomitant administration of duloxetine and tranyl
should elapse after discontinuing tranylcypromine before initiating therapy
discontinuing duloxetine before initiating therapy with tranylcypromine (Pr
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concurrent use of duloxetine and tranylcypromi
tranylcypromine before initiating duloxetine. Wait at least 5 days after disc
tranylcypromine (Prod Info Cymbalta(R) Delayed-release oral capsules, 2
7) Probable Mechanism: additive serotonergic effects

3.5.1.FL Trifluoperazine
1) Interaction Effect: increased phenothiazine serum concentrations and
orthostatic hypotension, hyperthermia, extrapyramidal effects)
2) Summary: Duloxetine is a moderately potent inhibitor of CYP2D6; ther
likely to increase bioavailability of the phenothiazine agent, increasing the
delayed-release oral capsules, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Use caution when prescribing duloxetine to pati
elevated phenothiazine plasma concentrations. Monitor for increased phe
release oral capsules, 2008).
7) Probable Mechanism: duloxetine inhibition of CYP2D6-mediated phen

3.5.1.FM Triflupromazine
1) Interaction Effect: increased phenothiazine serum concentrations and
orthostatic hypotension, hyperthermia, extrapyramidal effects)
2) Summary: Duloxetine is a moderately potent inhibitor of CYP2D6; ther
likely to increase bioavailability of the phenothiazine agent, increasing the
delayed-release oral capsules, 2008).
3) Severity: moderate
4) Onset: unspecified

5) Substantiation: theoretical
6) Clinical Management: Use caution when prescribing duloxetine to pati elevated phenothiazine plasma concentrations. Monitor for increased phe release oral capsules, 2008).
7) Probable Mechanism: duloxetine inhibition of CYP2D6-mediated phen

3.5.1.FN Trimeprazine
1) Interaction Effect: increased phenothiazine serum concentrations and orthostatic hypotension, hyperthermia, extrapyramidal effects)
2) Summary: Duloxetine is a moderately potent inhibitor of CYP2D6; ther likely to increase bioavailability of the phenothiazine agent, increasing the delayed-release oral capsules, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Use caution when prescribing duloxetine to pati elevated phenothiazine plasma concentrations. Monitor for increased phe release oral capsules, 2008).
7) Probable Mechanism: duloxetine inhibition of CYP2D6-mediated phen

3.5.1.FO Trimipramine
1) Interaction Effect: increased tricyclic antidepressant serum concentrati confusion, cardiac arrhythmias)
2) Summary: The coadministration of duloxetine with a tricyclic antidepre increasing the risk of adverse events. Duloxetine is a moderately potent ir substrate desipramine 50 mg and duloxetine 60 mg twice daily were coad baseline (Prod Info CYMBALTA(R) delayed-release oral capsules, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Use caution with the combined use of duloxetine with duloxetine and a TCA is unavoidable, plasma concentrations of the tr made accordingly (Prod Info CYMBALTA(R) delayed-release oral capsule TCA toxicity (anticholinergic effects, sedation, confusion, and cardiac arrh
7) Probable Mechanism: duloxetine inhibition of CYP2D6-mediated tricyc

3.5.1.FP Tryptophan
1) Interaction Effect: an increased risk of serotonin syndrome
2) Summary: Duloxetine is a selective serotonin and norepinephrine reup serotonergic agents such as tryptophan (serotonin precursor) is not recon CYMBALTA(R) delayed-release oral capsules, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concomitant use of duloxetine and tryptoph serotonin syndrome (Prod Info CYMBALTA(R) delayed-release oral capsu
7) Probable Mechanism: potentiation of serotonergic activity in the CNS b

3.5.1.FQ Valdecoxib
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta that the combined use of selective serotonin and norepinephrine reuptake associated with an increased risk of bleeding. Bleeding events have inclu threatening hemorrhages (Prod Info CYMBALTA(R) oral delayed-release
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When duloxetine and a nonsteroidal antiinflamm increased bleeding (Prod Info CYMBALTA(R) oral delayed-release capsu
7) Probable Mechanism: unknown

3.5.1.FR Venlafaxine
1) Interaction Effect: an increased risk of serotonin syndrome
2) Summary: Duloxetine is a selective serotonin and norepinephrine reup venlafaxine, also a selective serotonin and norepinephrine reuptake inhibi syndrome (Prod Info CYMBALTA(R) delayed-release oral capsules, 2008
3) Severity: major

4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concomitant use of duloxetine and venlafax
serotonin syndrome (Prod Info CYMBALTA(R) delayed-release oral capsu
7) Probable Mechanism: additive serotonergic effects

3.5.1.FS Warfarin

1) Interaction Effect: increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta
that the combined use of selective serotonin and norepinephrine reuptake
associated with an increased risk of bleeding. Bleeding events reported h
life-threatening hemorrhages. A population-based, case-controlled study
with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted
bleeding (Schalekamp et al, 2008). Altered anticoagulant effects (includin
coadministration of serotonin and norepinephrine reuptake inhibitors with
release oral capsules, 2008). Conversely, one case report described a pe
dose in a patient maintained on acenocoumarol (Monastero et al, 2007).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When duloxetine and an anticoagulant are giver
Patients who are taking warfarin should be monitored closely for altered a
duloxetine therapy is initiated or discontinued (Prod Info CYMBALTA(R) d
7) Probable Mechanism: unknown
8) Literature Reports
a) A population-based, case-controlled study of new coumarin users
selective serotonin reuptake inhibitors (SSRIs) resulted in an increas
Using national pharmacy and hospitalization records, Netherlands re
abnormal bleeding and compared them with 5818 control subjects al
was 220 days (range, 1 to 4690 days). Patients on SSRIs showed gr
(adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.
0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et
b) A case report describes a 44-year-old female patient maintained
after 55 days of concomitant duloxetine treatment. Warfarin was initia
medication regimen included atorvastatin 10 mg, warfarin 7.5 mg to 1
mg, and albuterol extended-release 4 mg twice a day. Duloxetine 30
day 58, only the warfarin was discontinued, and by day 85 the patien
mcg/mL (therapeutic range 2 to 8 mcg/mL). Intravenous vitamin K 10
the INR was again elevated at 6.4, vitamin K-dependent clotting facto
normal. Duloxetine was then discontinued, and 4 days later the INR
to 54%. INR was 0.9 by day 105, and warfarin was restarted on day
maintained on 7.5 to 10 mg/day. According to the Naranjo algorithm,
probable. The authors suggest that duloxetine may have an effect on
warfarin from its protein-binding sites, or may have unique metabolic
c) A 63-year-old woman successfully maintained on acenocoumarol
mechanical, prosthetic mitral-valve substitution experienced a persist
mg/day. Ten hours after taking duloxetine, the patient was taken to th
blood pressure had increased to 190/110 mmHg and her INR had dra
administered intravenously for the headache and hypertension, dulox
titrated to 12 mg/wk. Twenty-one days later, the INR returned to base
Follow-up examinations on days 28, 56, 84, 168, and 252 revealed st
family interviews discounted the possibility of acenocoumarol self-into
measured and the patient was not genotyped for CYP2D6 or CYP1A
duloxetine was deemed as probable based on the Naranjo Adverse D

3.5.1.FT Xemilofiban

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta
that the combined use of selective serotonin and norepinephrine reuptake
been associated with an increased risk of bleeding. Bleeding events repo
petechiae, and life-threatening hemorrhages (Prod Info CYMBALTA(R) de
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When duloxetine and an antiplatelet agent are g
bleeding (Prod Info CYMBALTA(R) delayed-release oral capsules, 2008).
7) Probable Mechanism: unknown

3.5.1.FU Zolmitriptan

1) Interaction Effect: increased risk of serotonin syndrome

2) Summary: A life-threatening condition known as serotonin syndrome n combination with a serotonin and norepinephrine reuptake inhibitor (SNRI include restlessness, hallucinations, loss of coordination, fast heart beat, overreactive reflexes, nausea, vomiting, and diarrhea. Clinicians should b that either the triptan or the SNRI may be prescribed by a different physic are prescribed this combination and monitor them closely for symptoms o dose increases (Prod Info CYMBALTA(R) delayed-release oral capsules,

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Coadministration of a triptan, such as zolmiptrta (SNRI), such as duloxetine, may result in a life-threatening condition calle commonly used intermittently and that either the triptan or the SNRI may l together, discuss the risks of serotonin syndrome with the patient and mo hyperthermia, hyperreflexia, incoordination), especially during treatment i release oral capsules, 2008).

7) Probable Mechanism: additive pharmacologic effects resulting in exce

3.5.1.FV Zomepirac

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for mainta that the combined use of selective serotonin and norepinephrine reuptake associated with an increased risk of bleeding. Bleeding events have inclu threatening hemorrhages (Prod Info CYMBALTA(R) oral delayed-release

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When duloxetine and a nonsteroidal antiinflamm increased bleeding (Prod Info CYMBALTA(R) oral delayed-release capsu

7) Probable Mechanism: unknown

4.0 Clinical Applications

4.1 Monitoring Parameters

A) Duloxetine Hydrochloride

1) Therapeutic

a) Physical Findings

1) In patients with diabetic peripheral neuropathic pain, assess pain

2) Monitor fibromyalgia patients for reduction or improvement in pain

3) In patients with generalized anxiety disorder, monitor for improver

4) In patients with major depressive disorder, monitor reduction or im

2) Toxic

a) Laboratory Parameters

1) Consider monitor liver function prior to initiating therapy and perio fatal, has been reported in patients receiving duloxetine. Case preser abdominal pain, hepatomegaly, and elevation of transaminases to m jaundice). Discontinue duloxetine therapy in patients who develop jau dysfunction. Do not resume duloxetine therapy unless causal associa

CYMBALTA(R) delayed-release oral capsules, 2008).
2) Consider monitoring for signs of hyponatremia. There have been r
110 micromoles/liter; however, levels reversed following duloxetine th
diuretics, or volume-depleted patients may be at greater risk. Conside
symptomatic hyponatremia (Prod Info CYMBALTA(R) delayed-releas

b) Physical Findings
1) Monitor blood pressure and pulse in patients prior to initiating trea
delayed-release oral capsules, 2008).
2) Consider monitoring ocular pressure in patients with controlled na
3) Monitor patients for withdrawal symptoms (e.g. dysphoric mood, ir
abrupt discontinuation of therapy (Prod Info CYMBALTA(R) delayed-
4) Monitor for worsening of depression, suicidality, or unusual chang
dose increases or decreases. Such monitoring should include at leas
members or caregivers during the initial 4 weeks of treatment, then vi
and then as clinically indicated beyond 12 weeks. Families and careg
daily observation) of patients and communication with the prescriber
Anon, 2004).
5) Consider monitoring for signs and symptoms of hyponatremia (he
confusion, weakness, and unsteadiness). There have been reports o
micromoles/liter; however, levels reversed following duloxetine therap
diuretics, or volume-depleted patients may be at greater risk. Conside
symptomatic hyponatremia (Prod Info CYMBALTA(R) delayed-releas

4.2 Patient Instructions

A) Duloxetine (By mouth)

Duloxetine

Treats depression, generalized anxiety disorder, nerve pain caused by diabete
a selective serotonin and norepinephrine reuptake inhibitor (SSNRI).

When This Medicine Should Not Be Used:
You should not use this medicine if you have had an allergic reaction to duloxe
Eldepryl®, Marplan®, Nardil®, or Parnate® within the past 14 days. You shoul
glaucoma, liver disease, or severe kidney disease.

How to Use This Medicine:
Delayed Release Capsule
Your doctor will tell you how much of this medicine to use and how often.
find out what works best for you. Do not use more medicine or use it more
You may take this medicine with or without food.
Swallow the delayed-release capsule whole. Do not sprinkle contents of th
not crush, break, open, or chew the capsule.
You may need to use this medicine for several weeks before you begin to
not improving, and talk to your doctor.
This medicine should come with a Medication Guide. Read and follow the
have any questions. Ask your pharmacist for the Medication Guide if you
to show that you understand this information.

If a Dose is Missed:
If you miss a dose or forget to use your medicine, use it as soon as you ca
the medicine and skip the missed dose. Do not use extra medicine to mak

How to Store and Dispose of This Medicine:
Store the medicine in a closed container at room temperature, away from
Ask your pharmacist, doctor, or health caregiver about the best way to dis
treatment. You will also need to throw away old medicine after the expirat
Keep all medicine away from children and never share your medicine with

Drugs and Foods to Avoid:
Ask your doctor or pharmacist before using any other medicine, including over
Do not take cimetidine (Tagamet®), thioridazine (Mellaril®), or medicine t
Cipro®, Penetrex®) while you are being treated with this medicine, unless
Make sure your doctor knows if you are using St. John's Wort, lithium (Litl
medicines to treat depression (such as amitriptyline, desipramine, fluoxeti
Effexor®, Lexapro™, Luvox®, Norpramin®, Paxil®, Zoloft®), medicine to
Relpax®), medicine to treat an infection (such as linezolid, Levaquin®, Te
prochlorperazine, Compazine®, Phenergan®, Thorazine®, Trilafon®), me

propafenone, quinidine, Rythmol®, Tambocor®), pain or arthritis medicine
Celebrex®, Vioxx®), or a blood thinner (such as warfarin, Coumadin®).
Tell your doctor if you are using any medicines that make you sleepy. The
pain relievers, and sedatives.
Do not drink alcohol while you are using this medicine. Drinking alcohol w
If you regularly drink 3 or more alcoholic drinks every day, tell your doctor

Warnings While Using This Medicine:

Make sure your doctor knows if you are pregnant, trying to become pregn
disease, high blood pressure, narrow-angle glaucoma, diabetes, any dige
the blood). Also tell your doctor if you have a history of seizures or mania.
For some children, teenagers, and young adults, this medicine can increa
right away if you or your child start to feel more depressed and have thou
behaviors that trouble you or your child, especially if they are new or get v
have trouble sleeping, get upset easily, have a big increase in energy, or
sudden or strong feelings, such as feeling nervous, angry, restless, violen
your family has bipolar disorder (manic-depressive) or has tried to commit
Make sure your doctor knows if you have ever abused drugs or alcohol.
This medicine may make you dizzy or drowsy. Avoid driving, using machi
not alert. You may also feel lightheaded when getting up from a lying or si
bothering you or keeping you from doing your daily activities, tell your doc
Your doctor will need to check your progress at regular visits while you ar
Do not stop using this medicine suddenly without asking your doctor. You
completely.
After you stop using the medicine, call your doctor if you have mood or be
seizures, tingling pain, or ringing in your ears.

Possible Side Effects While Using This Medicine:

Call your doctor right away if you notice any of these side effects:

Allergic reaction: Itching or hives, swelling in your face or hands, swelling
breathing.
Aggression, anxiety, anger, or hostility.
Dark-colored urine or pale stools.
Extreme sleepiness or drowsiness.
Fast or uneven heartbeat, or dizziness.
Feeling confused, nervous, restless, or clumsy.
Lightheadedness or fainting.
Muscle spasms, twitching, or stiffness.
Nausea, vomiting, loss of appetite, or pain in your stomach.
Panic attacks, tremors, or feeling irritable.
Severe nausea or diarrhea.
Unexplained fever, sweating, or shivering.
Unusual behavior, or thoughts about hurting yourself.
Unusual bleeding or bruising.
Unusual tiredness or weakness.
Yellowing of your skin or the whites of your eyes.

If you notice these less serious side effects, talk with your doctor:

Blurred vision.
Cough, sore throat, or runny or stuffy nose.
Dry mouth, constipation, upset stomach, or mild nausea or diarrhea.
Feeling tired, or having trouble sleeping.
Headache.
Increased sweating.
Problems with sex, or loss of interest in sex.
Problems with urination.
Skin rash.
Weight loss.

If you notice other side effects that you think are caused by this medicine, tell

4.3 Place In Therapy

A) Duloxetine Hydrochloride

1) Depression

a) Duloxetine hydrochloride is indicated for the acute and maintenance tr
and venlafaxine, duloxetine is a serotonin/norepinephrine reuptake inhibit
capsules, 2008). These agents are claimed to be at least as effective as t

selective serotonin reuptake inhibitors (SSRIs). The primary role of SNRIs who have responded poorly to other agents (eg, tricyclics or SSRIs).

b) At present, duloxetine is not recommended over other available SNRIs

2) Diabetic Peripheral Neuropathic Pain

a) Duloxetine is indicated for the treatment of neuropathic pain associate release oral capsules, 2008). At doses of either 60 milligrams (mg) once c neuropathic pain compared to placebo in randomized, double-blind, phas between the once-daily and twice-daily dose, the once-daily dose was bet al, 2005; Raskin et al, 2005).

3) Generalized Anxiety Disorder

a) Duloxetine is effective for the treatment of generalized anxiety disorde Info CYMBALTA(R) delayed-release oral capsules, 2008). If duloxetine tre should periodically monitor their patients for long-term effectiveness (Proc multicenter, randomized, double-blind trial (n=487), monotherapy with dul comparable efficacy to extended-release venlafaxine 77 to 225 mg/day ar generalized anxiety disorder (Hartford et al, 2007).

4) Fibromyalgia

a) Duloxetine is indicated for the management of fibromyalgia (Prod Info was established in several randomized, placebo-controlled, double-blind t or women alone. In a 12-week, randomized, double-blind, placebo-contro was effective and safe in the treatment of fibromyalgia in female patients 2005). In another randomized, double- blind trial (n=207) trial, a 12-week fibromyalgia compared with placebo, and women were affected to signific reduction in pain severity seen at 3 months following treatment with oral d another multicenter, randomized, double-blind, placebo-controlled trial (n=

4.4 Mechanism of Action / Pharmacology

A) Duloxetine Hydrochloride

1) Mechanism of Action

a) Duloxetine is a dual-selective serotonin (5HT) and norepinephrine reup unrelated, the mechanism and pharmacodynamic characteristics of duloxe (Artigas, 1995; Pinder, 1997; Sharma et al, 2000). Duloxetine is the (+)-is structural similarity to fluoxetine and tomoxetine.

b) Duloxetine is a secondary amine, whereas venlafaxine and milnacipra to inhibit norepinephrine and 5HT uptake in preclinical studies; both dulox norepinephrine reuptake, whereas milnacipran was a more potent inhibito Duloxetine has exhibited higher potency at both reuptake sites than milna Goodnick, 1999). In vitro, duloxetine has not shown significant affinity for 5HT-1A, 5HT-1B, 5HT-1D, 5HT-2A, 5HT-2C, or opioid receptors (Artigas,

c) The in vitro activity of antidepressants has not always been predictive duloxetine compared to venlafaxine may not imply greater clinical efficacy duloxetine in inhibiting 5HT and norepinephrine reuptake (Wong et al, 19 serotonin/norepinephrine reuptake inhibitors (SNRIs) are essential to dete

d) Duloxetine has increased neural sphincter activity and bladder capacit has been investigated in urinary incontinence.

2) Review Articles

a) A review of the pharmacology, pharmacokinetic profile, and clinical eff al, 2005).

b) Advances in the treatment of depression, including duloxetine (Leonar

c) Mechanisms, pharmacology, pharmacokinetics, and clinical efficacy of

4.5 Therapeutic Uses

4.5.A Duloxetine Hydrochloride

Cancer pain

Diabetic peripheral neuropathy - Pain

Fibromyalgia

Generalized anxiety disorder

Major depressive disorder

Urinary incontinence

4.5.A.1 Cancer pain

See Drug Consult reference: MANAGEMENT OF CANCER-RELATED PA

4.5.A.2 Diabetic peripheral neuropathy - Pain

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIa
Strength of Evidence: Adult, Category A

See Drug Consult reference: RECOMMENDATION AND EVIDENCE

b) Summary:

Duloxetine is indicated for the treatment of neuropathic pain asso
delayed-release oral capsules, 2008).
Duloxetine, when given at doses of either 60 milligrams daily or t
compared to placebo in randomized, double-blind, placebo-contr
al, 2005; Raskin et al, 2005).
No differences in pain relief between duloxetine 60 milligrams (m
trials, but the 60-mg once-daily dose was better tolerated than th
2005; Raskin et al, 2005).

c) Adult:

1) Duloxetine significantly improved diabetic peripheral neuropathic p
blind, phase 3 clinical trial. Patients (n=344; mean age, 60.7 +/- 10.6
peripheral neuropathic pain, which began in the feet with symmetric c
have baseline scores of at least 3 (mean, 5.6 +/- 1.5) on the Michigar
average pain severity mean score of 4 or more assessed with an 11-
randomization. Patients had to have stable glycemic control and glyc
depression, generalized anxiety disorder, or other specified psychiatr
duloxetine 60 mg once daily for 12 weeks followed by a dose reductio
mg twice daily (initiated at 60 mg daily for 3 days) for 12 weeks follow
(n=112), or placebo for 13 weeks (n=108). At baseline, mean duratio
diabetic neuropathy was 3.8 +/- 4.4 years for all patients, while a sign
groups in the mean Brief Pain Inventory (BPI) score: 60-mg once-dail
placebo group, 4.2 +/- 2.2. The change at 12 weeks from baseline in
in patient diaries, assessed with the same 11-point Likert scale used
improved ($p < 0.001$) in each of the duloxetine treatment groups (onc
group, -2.84 +/- 0.23 SE) compared to placebo (-1.39 +/- 0.23 SE). A
score, defined as a reduction of at least 2 points (30%), occurred in 6
placebo), 69% of the duloxetine twice-daily group ($p < 0.001$ versus p
in the weekly mean of the 24-hour worst pain score was significantly
groups (once-daily group, -3.21 +/- 0.25 SE; twice-daily group, -3.39
the change in the weekly mean of the night pain score (once-daily gro
< 0.001; placebo group, -1.83 +/- 0.24 SE). The median average daily
duloxetine twice-daily group (23.81 mg) compared to both the once-d
mg; $p < 0.001$). Significant improvements were also found in each du
Severity score, the Clinical Global Impression of Severity (CGI-Sever
Improvement score, the Sensory Portion of the Short Form McGill Pa
(EQ-5D) score, and various domains of the Short Form 36 (SF-36). T
(duloxetine once-daily, 28.1%; duloxetine twice-daily, 32.1%, and pla
more frequently in the duloxetine once-daily group compared to place
erectile dysfunction, and tremor occurred significantly more often in th
Significantly more patients discontinued treatment due to adverse ev
compared to the placebo group (7.4%) (Wernicke et al, 2006).

2) Duloxetine significantly improved diabetic peripheral neuropathy c
phase 3 clinical trial. Patients (n=348; mean age, 58.8 +/- 10.1 years)
bilateral peripheral neuropathy, which began in the feet with symmetr
to have baseline scores of at least 3 on the Michigan Neuropathy Scr
mean score of 4 or more assessed with an 11-point Likert scale (0, n
Patients with depression, generalized anxiety disorder, or other speci
randomized to duloxetine 60 mg once daily for 12 weeks followed by
(n=116), duloxetine 60 mg twice daily (initiated at 60 mg daily for 3 da
daily for the 13th week (n=116), or placebo for 13 weeks (n=116). At
and mean duration of diabetic neuropathy was 4.3 +/- 4.2 years for al
between treatment groups in the mean MNSI score: 60-mg once-daily

placebo group, 5.2 +/- 1.6. The change at 12 weeks from baseline in
in patient diaries, assessed with the same 11-point Likert scale used
improved (p < 0.001) in each of the duloxetine treatment groups (onc
group, -2.47 +/- 0.18 SE) compared to placebo (-1.6 +/- 0.18 SE). A c
score, defined as a reduction of at least 30%, occurred in 68.14% of t
64.04% of the duloxetine twice-daily group (p=0.002 versus placebo)
the weekly mean of the 24-hour worst pain score was significantly im
group, -2.97 +/- 0.2 SE, p < 0.001; twice-daily group, -2.84 +/- 0.2 SE
change in the weekly mean of the night pain score (once-daily group,
0.001; placebo group, -1.87 +/- 0.19 SE). The mean average daily do
group (202.52 mg) compared to the duloxetine twice-daily group (121
Significant improvements were also found in each duloxetine treatme
(BPI)-Severity score, the Clinical Global Impression of Severity (CGI-
Improvement score, the Sensory Portion of the Short Form McGill Pa
the BPI-Interference scale. No significant differences were found betv
Rating Scale, or between the 2 duloxetine groups for any endpoint. V
in the duloxetine twice-daily group compared to placebo, while nause
significantly more often in each duloxetine group compared to placeb
adverse events in the duloxetine twice-daily group (12.1%; p=0.01) c
the duloxetine once-daily group was 4.3%) (Raskin et al, 2005).

4.5.A.3 Fibromyalgia

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes; Pediatric, no
Efficacy: Adult, Effective
Recommendation: Adult, Class IIa
Strength of Evidence: Adult, Category A

See Drug Consult reference: RECOMMENDATION AND EVIDENCE

b) Summary:

Duloxetine is indicated for the management of fibromyalgia (Proc
Treatment with oral duloxetine 60 or 120 milligrams (mg) per day
fibromyalgia patients with or without current major depressive dis
blind, placebo-controlled trial (n=520) (Russell et al, 2008).
In a 12-week, randomized, double-blind, placebo-controlled trial
effective and safe in the treatment of fibromyalgia in female patie
2005).
A 12-week course of duloxetine was safe and improved some sy
were affected to significantly greater extent than men, based on

c) Adult:

In a multicenter, randomized, double-blind, placebo-controlled trial (n
per day for 3 months was safe and effective in reducing pain severity
depressive disorder; furthermore, efficacy was maintained at 6 month
female) meeting the American College of Rheumatology criteria for fi
higher on the average pain severity item (in the past 24 hours) of the
any current primary psychiatric diagnosis other than MDD were exclu
randomized to receive either duloxetine 20 mg/day (n=79), 60 mg/day
weeks (total, 3 months). In the 60 and 120 mg/day groups, duloxetine
weekly intervals to achieve target doses. The co-primary outcome me
pain to 10=worst pain) and the Patient Global Impression of Improver
much worse). Following assessment of the primary outcomes at 3 mo
fashion for up to 6 months; however, the duloxetine dose in the 20 m
mean BPI average pain severity score ranged from 6.4 to 6.8, and ap
current MDD diagnosis. An intention-to-treat analysis (included patier
revealed significant improvements in baseline BPI average pain seve
but not the 20 mg/day group, compared to placebo. For the co-primar
occurred with all 3 duloxetine doses compared to placebo. Improvem
therapy initiation in the 60 mg/day and 120 mg/day groups, and were
rates (defined as 50% or greater improvement from baseline in avera
in the duloxetine group, they were statistically significant only in the 1
(95% confidence interval, 3.7 to 18.1)) and not in the 20 mg/day (32.5
secondary outcomes at 3 months, both the duloxetine 60 mg/day and
placebo in the Clinical Global Impression-Severity scale scores, the F
Short Form Health Survey (mental component). However, the mean t
duloxetine groups versus placebo. At the 6-month endpoint, while sig
severity score were maintained in all 3 duloxetine groups compared t
the duloxetine 20/60 mg/day and 120 mg/day groups but not the 60 m

placebo (21.6%) in all 3 duloxetine groups (20/60 mg/day, 36.4%, p=
p=0.009). Notably, path analyses revealed that the direct analgesic e
greater proportion of the total treatment effect at 3 and 6 months thar
depressive symptoms. During 6 months of therapy, treatment-emerge
frequency than placebo included nausea (22.8% to 31.3% vs 13.2%)
20.4% vs 4.2%), somnolence (8% to 17% vs 4.2%), and fatigue (8.2%
outcomes at 3 and 6 months are presented in the table (Russell et al.

Outcome	Duloxetine 20 mg/day n=79 LS mean +/- SE	Duloxetine 60 n=150 LS mean +/- S
3-month results		
BPI average pain severity score	-1.92 +/- 0.27	-1.99 +/- 0.2*
PGI-I score	2.85 +/- 0.17**	3.04 +/- 0.13*
CGI-S score	-0.96 +/- 0.12	-1.06 +/- 0.1**
FIQ total score	-14.6 +/- 1.83*	-15.41 +/- 1.4*
6-month results		
BPI average pain severity score	-2.22 +/- 0.28*	-1.98 +/- 0.21*
PGI-I	2.79 +/- 0.17**	3.08 +/- 0.13

Key: mg=milligrams; LS=least squares; SE=standard error; BPI=Brie
Improvement; CGI-S=Clinical Global Impression-Severity; FIQ=Fibro
*p less than or equal to 0.05
**p less than or equal to 0.01
***p less than or equal to 0.001

1) In a 12-week, randomized, double-blind, placebo-controlled trial (r
was effective and safe in the treatment of fibromyalgia in female patie
age 49.6 years; 26% with current major depressive disorder) were ra
(n=118) or duloxetine 60 mg twice daily (n=116), or placebo (n=120).
was the primary outcome measure. Response to treatment was desc
endpoint. Overall, 39% (n=138) of subjects did not complete the stud
improved significantly more on the Brief Pain Inventory average pain
0.001). Significantly more patients treated with duloxetine had a decr
daily (55%; p less than 0.001); duloxetine 60 mg twice daily (54%; p=
symptoms were independent of the effect on mood and the presence
groups had significantly greater improvement compared with those in
interference scores, Fibromyalgia Impact Questionnaire, Clinical Glob
Improvement, and several quality-of-life measures. Overall, duloxetin
2) A 12-week course of duloxetine was safe and improved some syn
were affected to significantly greater extent than men, based on a rar
fibromyalgia symptoms were independent of whether or not subjects
met the criteria for fibromyalgia of the American College of Rheumato
disorder (DSM-IV). Randomization was to duloxetine 60 milligrams tw
subjects did not complete the study. After 12 months, total scores on
improved) by a significantly greater extent among duloxetine-treated
reductions of 13.46 and 7.93 points in the duloxetine and placebo gro
0.63 points lower in the duloxetine group, which was not significantly
27.7% and 16.7% for the duloxetine and placebo groups, respectively
(p=0.06). In secondary efficacy outcomes, those in the duloxetine gro
Inventory average pain severity score (p=0.008), in the Brief Pain Inv
of tender points (p=0.002), and FIQ stiffness score (p=0.048). These
status with respect to major depressive disorder. While female subjec
outcome measures, male subjects treated with duloxetine did not res
efficacy criteria. Significantly more subjects in the duloxetine group re
were generally mild or moderate in severity (most commonly insomni

4.5.A.4 Generalized anxiety disorder

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes; Pediatric, no
Efficacy: Adult, Effective
Recommendation: Adult, Class IIa

Strength of Evidence: Adult, Category A
See Drug Consult reference: RECOMMENDATION AND EVIDENCE

b) Summary:

Duloxetine is indicated for the treatment of generalized anxiety d
capsules, 2008).
Monotherapy with duloxetine demonstrated comparable efficacy
placebo in the treatment of adult generalized anxiety disorder in
et al, 2007).
Patients with generalized anxiety disorder randomized to duloxet
symptoms and functioning compared to placebo in three random
2007; Prod Info CYMBALTA(R) delayed-release oral capsules, 2

c) Adult:

1) In a multicenter, randomized, double-blind trial (n=487), monother
more effective than placebo in the treatment of adult generalized anx
years; 62.6% female) had GAD illness of moderate severity at baseli
Depression Scale (HADS) anxiety subscale score of 10 or higher, an
Severity (CGI-S) scale. Additionally, all study patients were required f
or lower on all items in the Raskin Depression Scale, and the Covi An
score. Patients with any other primary DSM-IV Axis I diagnosis within
randomized to receive either duloxetine (n=162; mean age, 40.4 yea
years), or placebo (n=161; mean age, 41.9 years) orally once daily fo
initiated at 30 milligrams (mg)/day, increased to 60 mg/day after 1 we
maximum dose of 120 mg/day. Venlafaxine ER was initiated at 37.5 r
mg/day. Dosage adjustments were permitted based on the investigat
be increased if the CGI-Improvement (CGI-I) scale score was 3 or hig
duloxetine and venlafaxine study doses at 10 weeks were 107.73 mg
mg/day), respectively. At baseline, the mean Hamilton Anxiety Rating
duloxetine, venlafaxine ER, and placebo groups, respectively. An inte
postbaseline assessment) revealed significantly greater improvement
venlafaxine ER-treated patients compared to placebo. At 10 weeks, t
baseline in HAMA total score (primary endpoint) was -11.8 +/- 0.69 (p
equal to 0.001) for the duloxetine and venlafaxine ER groups, respec
Response rates when defined as a 50% or greater reduction from ba
placebo in the venlafaxine ER group (54% vs 37%; p less than or equ
between-group differences were evident as early as week 1 for the du
were maintained throughout the 10-week study. Among secondary ou
greater improvements over placebo in HAMA psychic anxiety factor s
and the HADS anxiety and depression subscales as well as on the C
Sheehan Disability Scale global improvement scores (p less than or e
significant between-group differences for mean change from baseline
treatment due to adverse events in both the duloxetine (14.2%) and v
or equal to 0.0001 for both). Nausea (31.5%), constipation (14.2%), s
commonly reported in the duloxetine group (Hartford et al, 2007).

2) Treatment with oral duloxetine effectively reduced generalized anx
in adults in a multicenter, randomized, double-blind, placebo-controlle
(mean, 43.8 years; 67.8% female) meeting the DSM-IV criteria for ge
were included. Following a 1-week, single-blind, placebo run-in, study
milligrams (mg) (n=168), duloxetine 120 mg (n=170), or placebo (n=1
tapering-off phase. Duloxetine was initiated at 60 mg/day; however, it
to titrate down to 30 mg/day before increasing gradually to 60 mg/day
HAMA total scores were 25, 25.2, and 25.8 in the duloxetine 60 mg/d
An intention-to-treat analysis (included patients with at least 1 postba
in anxiety symptom severity in the duloxetine-treated patients compa
change from baseline in HAMA total score (primary endpoint) was -1
equal to 0.001) for the duloxetine 60 mg/day and 120 mg/day groups
there was a 49% improvement from baseline in HAMA total scores fo
differences were evident as early as week 2 and were maintained thr
patients in the duloxetine groups had significantly greater improveme
somatic anxiety factor score, HAMA anxious mood (item 1), HAMA te
(HADS) (p less than or equal to 0.01 to 0.001 for all vs placebo). Add
greater improvement ratings over placebo at endpoint on the Clinical
Impressions Improvement scales (p less than or equal to 0.001 for all
demonstrated in the Sheehan Disability Scale global and specific dor
rates, defined as a 50% or greater reduction from baseline HAMA tot
(58%) and duloxetine 120 mg/day (56%) groups compared to placebo
significantly more patients in the duloxetine groups met remission crit
placebo (duloxetine 60 mg/day, 31% (p less than or equal to 0.01); du

placebo, 19%). Among study dropouts (24.2%), rates of discontinuati
duloxetine groups (60 mg/day, 11.3%; 120 mg/day, 15.3%; placebo,
commonly reported adverse event in the duloxetine groups (mild, 13.
7.1%). Dizziness was the most frequently reported discontinuation-er
were discontinued abruptly (60 mg/day, 9.9%; 120 mg/day, 8.6% vs p
2007).

3) Duloxetine treatment effectively reduced generalized anxiety com
controlled, flexible-dose studies. The studies included patients betwe
generalized anxiety disorder. The study protocol called for titrating du
mg (n=168 and n=162) once daily for 10 weeks compared to placebo
was initially started at 30 mg once daily for 1 week before increasing
hydrochloride was initiated at 60 mg once daily; however, if patients c
30 mg before increasing to 60 mg once daily. The mean dose at stud
104.75 mg/day. Duloxetine hydrochloride significantly improved gene
Hamilton Anxiety Scale (HAMA) total scores and the Sheehan Disabi
includes three main functioning life domains including work/school, sc
Although duloxetine hydrochloride 120 mg once daily was shown to b
mg/day provided any additional benefit. Fifteen percent of patients re
increasing to 60 mg once daily. The most common adverse events w
insomnia, decreased appetite, and hyperhidrosis (Prod Info CYMBAL

4.5.A.5 Major depressive disorder

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes; Pediatric, no
Efficacy: Adult, Effective
Recommendation: Adult, Class IIa
Strength of Evidence: Adult, Category A

See Drug Consult reference: RECOMMENDATION AND EVIDENCE

b) Summary:

Duloxetine hydrochloride is indicated for the acute and maintena
CYMBALTA(R) delayed-release oral capsules, 2008).
Duloxetine was effective in treating major depression in several c
Brannan et al, 2005; Nelson et al, 2005) and demonstrated non-i
physical symptoms of depression in one randomized, double-blir
Patients with major depressive disorder treated with duloxetine c
overall relapse during the continuation phase following successfu
double-blind, placebo-controlled trial with an active treatment lea

c) Adult:

1) In a randomized, double-blind, placebo-controlled trial with an acti
of re-emergence of depressive symptoms and relapse following succ
beyond 12 weeks with continued treatment. In the active phase of the
at least moderate MDD (Hamilton Rating Scale for Depression (HRSI
Severity (CGI-S) score of 4 or greater) received open-label duloxetine
of the trial included patients with a HRSD17 score of 9 or less and a C
either duloxetine 60 mg daily (n=136), or placebo (n=142) for 26 wee
placebo who relapsed (CGI-S score increase of 2 or more points and
reinitiate with duloxetine 60 mg daily, and duloxetine patients who rel
After the 26 week continuation phase, and a dose reduction of 50% fo
drug for 1 week when the efficacy and safety data was collected. Ana
relapse during the continuation phase was longer in the duloxetine gr
duloxetine separating from placebo one month after randomization an
continuation phase comparing duloxetine (n=132), with placebo (n=13
the study's conclusion, the estimated probability of relapse was 19.7%
transient worsening of depressive illness indicated by an increase in
weeks after randomization in the continuation phase. Adverse effects
included nausea (2.1%), somnolence (0.8%), suicide attempt (0.6%),
significant mean changes in blood pressure or heart rate in the duloxe
phase included increases in serum aspartate aminotransferase or ala
during the course of the study (Perahia et al, 2006).

2) In two multicenter, double-blind studies of patients age 55 years a
significantly decreased scores for depression. Patients from 2 identic
(Hamilton Rating Score for Depression (HAMD17) of 15 or greater (m
Impression of Severity (CGI-S) score of 4 or greater (mean 4.37 plac
milligrams/day (mg/day) (n=47, 59.6% female), or placebo (n=43, 60.
Scales (VAS) overall pain score was 26 (on a 100 point scale). Presc
Analysis at week 9 revealed the mean total HAMD17 change from ba

placebo groups, respectively. Analyzing secondary endpoints reveale
placebo groups for CGI-S (-1.85 vs -1.21, p=0.016), overall painful ph
decreases in 4 of 5 subscales of the HAMD17 (significant in all, excep
(p=0.08), defined as a HAMD17 total score of 7 or less, after 9 weeks
patients, compared with 16.1% and 14.3% in placebo, respectively. F
greater, who received duloxetine 40 mg -120 mg/day (n=119, mean a
63.9 years, 58.9% female) revealed discontinuation due to adverse e
groups, respectively. The main reasons for discontinuation of duloxet
somnolence, and syncope. Treatment emergent adverse effects with
constipation, decreased appetite, insomnia, fatigue and decreased lib
experiencing syncope compared with 0% placebo (p=0.136) (Nelson
3) In a multicenter, double-blind, placebo controlled trial of patients w
physical symptoms, duloxetine therapy led to significant improvemen
placebo. Patients (mean age 40 years) with MDD (Hamilton Rating S
randomized to receive either duloxetine 60 milligrams daily (n=141) o
out phase. All patients were permitted to use nonnarcotic prescription
were not significantly different between the 2 groups, except for the H
p=0.022). In intent-to-treat analysis, the difference in mean BPI avera
(p=0.066), duloxetine -2.32 (n=132) and placebo -1.8 (n=136). In ana
2 of 7 mean changes in BPI pain interference measures (walking abil
placebo, was the nonsignificant mean change in depressive symptom
(-1.54 vs -1.58, p=0.829). There was one case of nephrolithiasis in th
discontinuation due to adverse effects was 14.2% vs 2.1% (p less tha
Main reasons for duloxetine discontinuation was nausea, fatigue, and
4) Duloxetine therapy was more effective than placebo and non-infer
physical symptoms of depression. In a randomized, double-blind, pla
depressive disorder, a Hamilton Depression Rating Scale (HAM-D) to
Impression (CGI) Severity rating (score of at least 4) received oral du
40 mg daily (in divided doses), paroxetine 20 mg daily, or placebo for
from baseline in the HAM-D total score and remission was defined as
dosing regimens of duloxetine produced significantly greater reductio
(mean difference, 3.62 points, 95% CI 1.38, 5.86; p=0.002 and 2.34 p
greater reduction in HAM-D total scores was also observed with dulo
(mean difference, 2.39 points, 95% CI 0.14, 4.65; p=0.037). Paroxeti
8, however at weeks 2, 4, and 6; paroxetine treatment was superior t
higher in patients treated with duloxetine 80 mg as compared with pla
remission rate in the duloxetine 80 mg group (50%) was significantly
patients in the duloxetine 40 mg group (35%; p=0.045) and the place
the paroxetine group (37%; p=ns). Significant reductions from baselir
treated with duloxetine 80 mg (reduction from baseline, 47%; -7.5 poi
placebo, however significant reductions were not seen with paroxetin
duloxetine and paroxetine were generally well tolerated and only insc
treated (80 mg) patients as compared with paroxetine-treated patient

4.5.A.6 Urinary incontinence

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE

b) Summary:

Duloxetine 40 milligrams orally twice daily decreased the frequer
(n=271) and Hispanic (n=368) women in the DESIRE (Duloxetin
populations) study (Weinstein et al, 2006).
Two 12-week, phase 3, randomized, double-blind, placebo-contr
conducted in study centers in four continents (n=458) showed sig
in women receiving duloxetine for stress urinary incontinence (M
Duloxetine 80 milligrams/day was more effective than placebo at
mixed urinary incontinence in an 8-week, randomized, double-bli
Patient discontinuation rates due to adverse events, nausea beir
2006; Dmochowski et al, 2003; Millard et al, 2004).

c) Adult:

1) Mixed Urinary Incontinence

a) In an 8-week, multicenter, randomized, double-blind trial (n=5
than placebo at reducing incontinence episode frequency (IEF) i
aged between 19 to 85 years (mean, 53 years) with a history of e

MUI (UPMUI), or balanced MUI for 3 or more of the previous cor
week were randomized to receive either duloxetine 40 mg twice
15.5 IEF/week). The validated Stress/Urge Incontinence Questio
SPMUI, UPMUI, or balanced MUI. While antimuscarinic agents v
19.4% of duloxetine and placebo subjects, respectively, used an
norepinephrine) concurrently during the study. Patients recorded
throughout the study by documenting voids, stress urinary incont
episodes. In the intent-to-treat analysis (n=588), duloxetine subje
(primary endpoint) compared to placebo subjects (mean change
between groups, -3.5 to -0.17; p=0.049). This difference persiste
(SUI mean change, -3.76 vs -2.87; 95% CI for difference betwee
2.33; 95% CI for difference between groups, -1.59 to -0.22; p=0.
duloxetine vs placebo regardless of whether the subtype was as
results (p=0.0013 and p less than 0.001, respectively), results fo
process (p=0.0183 and p=0.176, respectively). Balanced MUI su
regardless of assignment method (p=1 and p=0.777, respectively
in time between voids (secondary endpoint) compared with place
minutes; p=0.002). Quality of life, as measured on a scale of 0 (l
Quality of Life Questionnaire, increased more in duloxetine patie
95% CI of difference between groups, 1.36 to 6.31; p=0.002), an
much better" or "much better" according to the Patient Global Im
subjects (p=0.001). A significantly greater number of placebo pat
patients (78%), with adverse effects being the most common rea
(TEAEs) occurred in 61.3% of duloxetine subjects vs 44.8% of pl
common complaint in both groups (18% vs 4.5%, respectively; p
duloxetine patients and at a rate greater than 5% included dry m
(6.7%) (Bent et al, 2008).

2) Stress Urinary Incontinence

a) The Duloxetine Efficacy and Safety for Incontinence in Racial
label, multicenter study, demonstrated non-inferiority efficacy in A
receiving duloxetine for stress urinary incontinence compared to
and Hispanic women with characteristics similar to Caucasian w
older, at least 7 incontinence episodes per week at baseline, and
included in the study. Baseline characteristics of patients in the A
and Hispanic (mean age, 47.4 years; range, 20-86 years) subgro
years; range, 18-97 years) were significantly different ($p < 0.05$)
Incontinence Quality of Life (I-QOL) and Patient Global Impressi
number of pads used per week. All patients received duloxetine
week lead-in period. Non-inferiority efficacy was determined by c
episode frequency in the African-American and Hispanic subgrou
treatment. All three subgroups had significant improvement ($p <$
baseline (African-American group, 7 versus (vs) 21 episodes/we
Caucasian group, 5 vs 19.25 episodes/week (-75%)). Additionall
less than 0.001) in quality of life questionnaire scores after treatr
scale (African-American group, 71.5 vs 51.7 points; Hispanic gro
and the Patient Global Impression of Improvement (African-Ame
Caucasian group, 66.6% improved); however, significantly less (
reduction in incontinence episode frequency compared with Cau
of patients completed the study, and the most common reason fo
common adverse event occurring in 21.8 to 28% of patients and
(African-American group, 6.6%; Hispanic group, 5.7%; Caucasia
(p less than 0.05) in Hispanic patients compared to Caucasian p
7.4%), and somnolence (12.2% vs 7%) (Weinstein et al, 2006).

b) Incontinence episode frequency (IEF) was reduced following
urinary incontinence in a randomized, double-blind, placebo-con
urinary incontinence of at least 3 months duration and experienc
duloxetine 40 milligrams twice daily or placebo for 12 weeks. The
than half of patients averaged two or more episodes daily. From
in the duloxetine group as compared with the placebo group (per
this effect was even stronger in patients with a baseline IEF of 14
respectively; p=0.022). In addition, the average voiding interval i
compared with those who received placebo (20.4 vs 8.5 minutes
patients in the duloxetine group also showed greater improveme
questionnaire as compared with patients in the placebo group (m
were significantly more frequent with duloxetine treatment than v
and resulted in significantly higher discontinuation rates in the du
respectively; p less than 0.001). In duloxetine-treated patients, th

headache (14.5%), insomnia (13.7%), constipation (12.8%), dry
(8.4%), anorexia (6.6%), vomiting (6.2%), and increased sweatin
c) Duloxetine was effective in the treatment of stress urinary inc
blind, placebo-controlled, multicenter trial. Women (n=683) 22 to
experiencing 7 or more episodes weekly received duloxetine 80
Incontinence episode frequency decreased by 50% to 100% in 5
placebo-treated patients (p less than 0.001). Mean improvement
score was also significantly better for patients in the duloxetine g
respectively; p less than 0.001). Adverse events occurred more f
24.1% vs 4.1%; p less than 0.001) and included nausea (22.7%)
constipation (9.6%), somnolence (8.7%), dizziness (7.6%), head

4.6 Comparative Efficacy / Evaluation With Other Therapies

Escitalopram

Paroxetine

Venlafaxine

4.6.A Escitalopram

4.6.A.1 Major depressive disorder

a) In an 8-week randomized, double-blind, placebo- and active-comparat
(n=684) with major depressive disorder (MDD), onset of efficacy for dulox
escitalopram 10 mg daily, and patients in both active treatment groups we
Patients aged 18 years or older (range, 18 to 79 years), meeting the DSM
Depression Rating Scale (MADRS) total score of 22 or greater and a Clini
greater were included. Patients were randomized to receive either duloxe
Hamilton Rating Scale for Depression (HAMD) Maier subscale score, 17.6
mean baseline HAMD score, 17.8), or placebo (n=137; mean age, 42.5 ye
acute treatment period. Onset of efficacy (primary endpoint) was defined a
week 2 that was sustained for the remainder of the acute treatment period
efficacy onset criteria was similar in the duloxetine and escitalopram grou
confidence interval (CI), -1.3% to 16.2%; p=0.097), and patients in both gr
placebo patients (21.5%; duloxetine vs placebo, p less than 0.001; escital
escitalopram was maintained following a per-protocol analysis. In an anal
were pooled, a significantly greater proportion of duloxetine patients achie
greater proportion of patients in both active treatment groups achieved eff
0.018 for both). The median time to onset was significantly shorter among
placebo-treated patients (23 days vs 41 days vs 55 days, respectively; du
less than 0.001), and median time to onset did not differ between escitalo
achieving a treatment response (secondary endpoint) by week 8, defined
similar among the duloxetine (48.7%), escitalopram (45.3%), and placebo
score of 7 or less) also did not differ between the groups (40.1% vs 33% v
complete the study were evenly distributed among the groups, and a simil
effects. Nausea more commonly caused discontinuation among duloxetin
respectively; p=0.02). Both nausea and dry mouth occurred more often in
patients and at a rate greater than 10% (nausea, 23.8% vs 12% vs 8.8%;
Although this study focused on the acute 8-week treatment period, subjec
for an additional 6 months (Nierenberg et al, 2007). During the 6-month ex
mg/day and the escitalopram dose ranged from 10 to 20 mg/day; placebo
assigned in a double-blind fashion to active treatment. Among the 431 pa
no significant differences in antidepressant efficacy between the duloxetin
probability of remission was 70% and 75% among the duloxetine and esc
significant difference between the groups was on the HAMD sleep subsca
improvement in insomnia than duloxetine-treated patients (mean change
discontinuation rates over the 8-month study were higher in the duloxetine
discontinuation due to adverse events were similar (12.8% vs 12%, respe
b) In a randomized, double-blind, fixed-dose, noninferiority trial (n=294), a
for the long term treatment of major depressive disorder (MDD), escitalop
outpatients aged 18 to 73 years old with MDD according to the DSM-IV (T
Rating Scale (MADRS) total score of 26 or greater, and with a Clinical Glo
were included. With the exception of obsessive-compulsive disorder, post

secondary, current, comorbid anxiety disorder were included. Study patie
(n=151) or escitalopram 20 mg (initial dose, 10 mg/day; increased after 2
MADRS scores were 32.1 +/- 4.4 and 32.5 +/- 4.3 in the duloxetine and es
study, the mean change from baseline in MADRS score in the intent-to-tre
duloxetine were -23.4 and -21.7, respectively (p=0.055). Based on a per-p
(escitalopram minus duloxetine) in MADRS scores at 24 weeks was 0.67
which met the prespecified noninferiority criteria (ie, upper limit of the one
escitalopram was evident (ie, upper limit of the one-sided CI did not inclu
treatment differences of 2.54 (95% CI, p=0.011) and 2.21 (p=0.027), resp
81.6% (n=115) of escitalopram-treated patients were considered to be res
total score) compared with 73% (n=112) of duloxetine-treated patients. An
effective than duloxetine in CGI-I (p=0.039) score reduction from baseline
duloxetine in the Sheehan Disability Scale (SDS) work score reduction at
less than 0.05 for all). Significantly more patients on duloxetine reported in
compared to escitalopram, with almost twice the withdrawal rate due to ad
0.05) (Wade et al, 2007).

4.6.B Paroxetine

4.6.B.1 Major depressive disorder

a) Duloxetine therapy was more effective than placebo and non-inferior to
physical symptoms of depression. In a randomized, double-blind, placebo
depressive disorder, a Hamilton Depression Rating Scale (HAM-D) total s
(CGI) Severity rating (score of at least 4) received oral duloxetine 80 millig
divided doses), paroxetine 20 mg daily, or placebo for 8 weeks. Response
HAM-D total score and remission was defined as a HAM-D score of 7 or l
duloxetine produced significantly greater reductions in HAM-D scores fror
points, 95% CI 1.38, 5.86; p=0.002 and 2.34 points, 95% CI 0.19, 4.66; p=
D total scores was also observed with duloxetine 80 mg therapy as compa
95% CI 0.14, 4.65; p=0.037). Paroxetine therapy was not significantly diffe
paroxetine treatment was superior to placebo. The response rate at endpo
80 mg as compared with placebo (51% vs 31%, p=0.009, respectively). A
(50%) was significantly higher at endpoint as compared with remission rat
and the placebo group (30%; p=0.008), but was not superior to patients in
baseline to endpoint in overall pain severity were observed in patients trea
points on VAS scale, 95%CI -25, 1; p=0.005), as compared with placebo,
or duloxetine 40 mg therapy as compared with placebo. Both duloxetine a
was reported significantly more often in duloxetine-treated (80 mg) patient
respectively; p=0.031) (Goldstein et al, 2004).

4.6.C Venlafaxine

4.6.C.1 Major depressive disorder

a) A meta-analysis of published, peer-reviewed, randomized, placebo-co
venlafaxine extended-release (XR) are significantly superior compared to
disorder and although there was a trend in favor of venlafaxine XR the dif
to duloxetine. A systematic literature search of Cochrane, EMBASE, and
independent reviewers. Data was obtained from 8 trials to evaluate efficac
a one week placebo lead-in period followed by either duloxetine 40 to 120
day for a minimum of 8 weeks. The primary outcomes were remission and
the Hamilton Rating Scale for Depression (HAM-D) score to less than or e
(MADRS) score of less than or equal to 10. Response was defined as an
MADRS scores. The secondary outcomes evaluated were dropout rates a
improved for duloxetine and venlafaxine XR and were statistically significa
difference was found for remission and response rates when duloxetine a
had a higher dropout rate due to lack of efficacy compared to those patien
0.001). More patients in the active drug treatment groups dropped out due
venlafaxine XR p less than 0.001). Again, when duloxetine and venlafaxin
were found for dropout rates due to lack of efficacy or adverse drug reacti
drugs. A sensitivity analysis was also performed and included 2 additional
with comorbid anxiety and one study for duloxetine dealing with patients v
results with both drugs having a statistically significant difference from pla

Outcome	Active Drug	Active Dr	
		Difference(a)	
Remission	duloxetine	0.142	0.0
	venlafaxine XR	0.178	0.0

Response	duloxetine	0.186	0.1
	venlafaxine XR	0.244	0.1
Dropout rate due to ADRs	duloxetine	0.057	0.
	venlafaxine XR	0.061	0.0
Dropout rate due to lack of efficacy	duloxetine	-0.111 (c)	-0.1
	venlafaxine XR	-0.107	-0.1
ADRs = adverse drug reactions; XR = extended release; CI = confide			
(a) The rate when meta-analytic rate of placebo is subtracted from th			
(b) Corresponding p value of the difference rate calculated with a Z-t			
(c) Negative difference rates indicate a larger effect for placebo.			

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Last Modified: July 24, 2009

DRUGDEX® Evaluations

VALPROIC ACID

0.0 Overview

1) Class

a) This drug is a member of the following class(es):

Anticonvulsant
Antimanic
Antimigraine
Valproic Acid (class)

2) Dosing Information

a) Valproic Acid

1) Adult

a) Absence seizure, Simple and complex

1) initial, 15 mg/kg/day ORALLY (give in 2 to 3 divided doses if total daily dose exceeds 250 mg) (Prod I (R) oral capsules, oral syrup, 2006; Prod Info STAVZOR(R) delayed release oral capsules, 2008)

2) maintenance, may increase dosage 5 to 10 mg/kg/day ORALLY at one week intervals until seizures a side effects preclude further increases (give in 2 to 3 divided doses if total daily dose exceeds 250 mg)(M or less with a therapeutic serum range of 50 to 100 mcg/mL) (Prod Info DEPAKENE(R) oral capsules, or Prod Info STAVZOR(R) delayed release oral capsules, 2008)

b) Complex partial epileptic seizure

1) monotherapy, initial 10 to 15 mg/kg/day ORALLY (give in 2 to 3 divided doses if total daily dose exce increase dosage 5 to 10 mg/kg/week to achieve optimal clinical response (MAX 60 mg/kg/day or less wit serum range of 50 to 100 mcg/mL) (Prod Info DEPAKENE(R) oral capsules, oral syrup, 2006; Prod Info delayed release oral capsules, 2008)

2) conversion to monotherapy, 10 to 15 mg/kg/day ORALLY (give in 2 to 3 divided doses if total daily do mg), may increase dosage 5 to 10 mg/kg/week to achieve optimal clinical response (MAX 60 mg/kg/day therapeutic serum range of 50 to 100 mcg/mL); reduce concomitant antiepilepsy drug dosage by approxi 2 weeks (reduction may be started at initiation of therapy or delayed by 1 to 2 weeks if there is a concern likely to occur with a reduction) (Prod Info DEPAKENE(R) oral capsules, oral syrup, 2006; Prod Info STA release oral capsules, 2008)

3) adjunct, may be added to the patient's regimen at an initial dosage of 10 to 15 mg/kg/day ORALLY (g divided doses if total daily dose exceeds 250 mg), may increase dosage 5 to 10 mg/kg/week to achieve response (MAX 60 mg/kg/day or less with a therapeutic serum range of 50 to 100 mcg/mL) (Prod Info DE capsules, oral syrup, 2006; Prod Info STAVZOR(R) delayed release oral capsules, 2008)

c) Manic bipolar I disorder

1) initial, delayed-release 750 mg ORALLY daily, in divided doses; may increase dose to achieve desire or desired range of plasma concentrations (MAX 60 mg/kg/day or less with a therapeutic serum range of mcg/mL) (Prod Info STAVZOR(R) delayed release oral capsules, 2008)

d) Migraine; Prophylaxis

1) delayed-release 250 mg ORALLY twice daily; MAX dose 1000 mg/day (Prod Info STAVZOR(R) delay capsules, 2008)

e) Seizure, Multiple seizure types; Adjunct

1) 10 to 15 mg/kg/day ORALLY (give in 2 to 3 divided doses if total daily dose exceeds 250 mg), may in to 10 mg/kg/week to achieve optimal clinical response (MAX 60 mg/kg/day or less with a therapeutic ser 100 mcg/mL) (Prod Info DEPAKENE(R) oral capsules, oral syrup, 2006; Prod Info STAVZOR(R) delayed capsules, 2008)

2) Pediatric

a) increased risk of fatal hepatotoxicity in patients under the age of 2 years (Prod Info DEPAKENE(R) oral ca 2006; Prod Info STAVZOR(R) delayed release oral capsules, 2008)

b) safety and efficacy of delayed-release valproic acid (Stavzor(R)) for the treatment of acute mania associat disorder and for migraine prophylaxis have not been established in pediatric patients (Prod Info STAVZOR(R oral capsules, 2008)

1) Absence seizure, Simple and complex

a) (10 yr and older) initial, 15 mg/kg/day ORALLY (give in 2 to 3 divided doses if total daily dose exc (Prod Info DEPAKENE(R) oral capsules, oral syrup, 2006; Prod Info STAVZOR(R) delayed release 2008)

b) (10 yr and older) maintenance, may increase dosage 5 to 10 mg/kg/day ORALLY at one week in seizures are controlled or side effects preclude further increases (give in 2 to 3 divided doses if total exceeds 250 mg)(MAX 60 mg/kg/day or less with a therapeutic serum range of 50 to 100 mcg/mL) (DEPAKENE(R) oral capsules, oral syrup, 2006; Prod Info STAVZOR(R) delayed release oral capsu

2) Complex partial epileptic seizure

a) (10 yr and older) monotherapy, initial 10 to 15 mg/kg/day ORALLY (give in 2 to 3 divided doses i exceeds 250 mg), may increase dosage 5 to 10 mg/kg/week to achieve optimal clinical response (M

or less with a therapeutic serum range of 50 to 100 mcg/mL) (Prod Info DEPAKENE(R) oral capsule 2006; Prod Info STAVZOR(R) delayed release oral capsules, 2008)

b) (10 yr and older) conversion to monotherapy, 10 to 15 mg/kg/day ORALLY (give in 2 to 3 divided dose exceeds 250 mg), may increase dosage 5 to 10 mg/kg/week to achieve optimal clinical respon mg/kg/day or less with a therapeutic serum range of 50 to 100 mcg/mL); reduce concomitant antiepi by approximately 25% every 2 weeks (reduction may be started at initiation of therapy or delayed by there is a concern that seizures are likely to occur with a reduction) (Prod Info DEPAKENE(R) oral c syrup, 2006; Prod Info STAVZOR(R) delayed release oral capsules, 2008)

c) (10 yr and older) adjunct, may be added to the patient's regimen at an initial dosage of 10 to 15 r ORALLY (give in 2 to 3 divided doses if total daily dose exceeds 250 mg), may increase dosage 5 to achieve optimal clinical response (MAX 60 mg/kg/day or less with a therapeutic serum range of 50 t (Prod Info DEPAKENE(R) oral capsules, oral syrup, 2006; Prod Info STAVZOR(R) delayed release 2008)

3) Seizure, Multiple seizure types; Adjunct

a) (10 yr and older) 10 to 15 mg/kg/day ORALLY (give in 2 to 3 divided doses if total daily dose exc may increase dosage 5 to 10 mg/kg/week to achieve optimal clinical response (MAX 60 mg/kg/day therapeutic serum range of 50 to 100 mcg/mL) (Prod Info DEPAKENE(R) oral capsules, oral syrup, STAVZOR(R) delayed release oral capsules, 2008)

b) Divalproex Sodium

1) Adult

a) converting from valproic acid: initiate divalproex sodium sprinkle capsules at the same daily dose and dos stabilized, divalproex sodium given 2 or 3 times a day may be instituted (Prod Info DEPAKOTE(R) sprinkle o 2008).

b) converting delayed-release to extended-release: administer extended-release tablets (Depakote(R) ER) o 8% to 20% higher than the total daily dose of divalproex sodium delayed-release tablets (Prod Info DEPAKO extended-release oral tablets, 2008)

1) Absence seizure, Simple and complex

a) initial, 15 mg/kg/day ORALLY, may increase dosage by 5 to 10 mg/kg/day at 1-week intervals un controlled or side effects preclude further increases (MAX 60 mg/kg/day; usual therapeutic range, 5(total daily doses greater than 250 mg should be given in divided doses for delayed-release and spri DEPAKOTE(R) ER extended-release oral tablets, 2008; Prod Info DEPAKOTE(R) sprinkle oral caps Info DEPAKOTE(R) delayed-release oral tablets, 2006)

2) Complex partial epileptic seizure

a) monotherapy, initial, 10 to 15 mg/kg/day ORALLY, may increase dosage 5 to 10 mg/kg/week to a clinical response (MAX 60 mg/kg/day; therapeutic range, 50 to 100 mcg/mL) (Prod Info DEPAKOTE release oral tablets, 2008; Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008; Prod Info DEPAK release oral tablets, 2006)

b) adjunct, initial, 10 to 15 mg/kg/day ORALLY, may increase dosage 5 to 10 mg/kg/week to achiev response (MAX 60 mg/kg/day; therapeutic range, 50 to 100 mcg/mL) (Prod Info DEPAKOTE(R) ER oral tablets, 2008; Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008; Prod Info DEPAKOTE(R) oral tablets, 2006)

c) conversion to monotherapy, initial, 10 to 15 mg/kg/day ORALLY, may increase dosage 5 to 10 m achieve optimal clinical response (MAX 60 mg/kg/day; therapeutic range, 50 to 100 mcg/mL); reduc antiepileptic dosage by approximately 25% every 2 weeks (reduction may be started at initiation of t by 1 to 2 weeks if there is a concern that seizures are likely to occur with a reduction) (Prod Info DE extended-release oral tablets, 2008; Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008; Prod Inf delayed-release oral tablets, 2006)

3) Manic bipolar I disorder

a) (Depakote (R) ER, extended-release) initial, 25 mg/kg/day ORALLY once daily; increase dose as possible to clinical effect; usual trough plasma level, 85 to 125 mcg/mL; MAX 60 mg/kg/day (Prod In ER extended-release oral tablets, 2008)

b) (Depakote (R), delayed-release) initial, 750 mg ORALLY daily in divided doses; increase dose as possible to clinical effect; usual trough plasma level, 50 to 125 mcg/mL; MAX 60 mg/kg/day (Prod In delayed-release oral tablets, 2006)

4) Migraine; Prophylaxis

a) (Depakote (R) ER, extended-release) initial, 500 mg ORALLY once daily for 1 week, thereafter ir mg once daily (Prod Info DEPAKOTE(R) ER extended-release oral tablets, 2008)

b) (Depakote (R) delayed-release) initial, 250 mg ORALLY twice daily; may increase to a MAX 100 Info DEPAKOTE(R) delayed-release oral tablets, 2006)

2) Pediatric

a) safety and efficacy for the treatment of epilepsy in children less than 10 years of age have not been estab DEPAKOTE(R) ER extended-release oral tablets, 2008; Prod Info DEPAKOTE(R) sprinkle oral capsules, 200

b) efficacy for use in pediatric population for the treatment of mania or migraine prophylaxis has not been es Info DEPAKOTE(R) ER extended-release oral tablets, 2008).

c) converting from valproic acid: initiate divalproex sodium sprinkle capsules at the same daily dose and dos stabilized, divalproex sodium given 2 or 3 times a day may be instituted (Prod Info DEPAKOTE(R) sprinkle o 2008).

d) converting delayed-release to extended-release: administer extended-release tablets (Depakote(R) ER) o

8% to 20% higher than the total daily dose of divalproex sodium delayed-release tablets (Prod Info DEPAKO capsules, 2008)

1) Absence seizure, Simple and complex

a) 10 years and older, initial, 15 mg/kg/day ORALLY, may increase dosage 5 to 10 mg/kg/day at 1- seizures are controlled or side effects preclude further increases (MAX 60 mg/kg/day; usual therape 100 mcg/mL; total daily doses greater than 250 mg should be given in divided doses for delayed-rel (Prod Info DEPAKOTE(R) ER extended-release oral tablets, 2008; Prod Info DEPAKOTE(R) sprinkl 2008; Prod Info DEPAKOTE(R) delayed-release oral tablets, 2006)

2) Complex partial epileptic seizure

a) 10 yr and older, monotherapy, initial, 10 to 15 mg/kg/day ORALLY, may increase dosage 5 to 10 achieve optimal clinical response (MAX 60 mg/kg/day; therapeutic range, 50 to 100 mcg/mL) (Prod (R) ER extended-release oral tablets, 2008; Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008; DEPAKOTE(R) delayed-release oral tablets, 2006)

b) 10 yr and older, adjunct, initial, 10 to 15 mg/kg/day ORALLY, may increase dosage 5 to 10 mg/k optimal clinical response (MAX 60 mg/kg/day; therapeutic range, 50 to 100 mcg/mL) (Prod Info DEP extended-release oral tablets, 2008; Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008; Prod Inf delayed-release oral tablets, 2006)

c) 10 yr and older, conversion to monotherapy, initial, 10 to 15 mg/kg/day ORALLY, may increase c mg/kg/week to achieve optimal clinical response (MAX 60 mg/kg/day; therapeutic range, 50 to 100 r concomitant antiepileptic dosage by approximately 25% every 2 weeks (reduction may be started at therapy or delayed by 1 to 2 weeks if there is a concern that seizures are likely to occur with a reduc DEPAKOTE(R) ER extended-release oral tablets, 2008; Prod Info DEPAKOTE(R) sprinkle oral caps Info DEPAKOTE(R) delayed-release oral tablets, 2006)

c) Valproate Sodium

1) Adult

a) Absence seizure, Simple and complex

1) 15 mg/kg/day IV, may increase dosage 5 to 10 mg/kg/day at one week intervals until seizures are cor effects preclude further increases (MAX 60 mg/kg/day or less with a therapeutic range of 50 to 100 mcg/ DEPACON(R) IV injection, 2006)

b) Complex partial epileptic seizure

1) monotherapy, 10 to 15 mg/kg/day IV, may increase dosage 5 to 10 mg/kg/week to achieve optimal cli (MAX 60 mg/kg/day or less with a therapeutic range of 50 to 100 mcg/mL) (Prod Info DEPACON(R) IV ir

2) conversion to monotherapy, 10 to 15 mg/kg/day IV, may increase dosage 5 to 10 mg/kg/week to achi response (MAX 60 mg/kg/day or less with a therapeutic range of 50 to 100 mcg/mL); reduce concomitan dosage by approximately 25% every 2 weeks (reduction may be started at initiation of therapy or delaye there is a concern that seizures are likely to occur with a reduction) (Prod Info DEPACON(R) IV injection

3) adjunct, may be added to the patient's regimen at an initial dosage of 10 to 15 mg/kg/day IV, may inc 10 mg/kg/week to achieve optimal clinical response (MAX 60 mg/kg/day or less with a therapeutic range mcg/mL) (Prod Info DEPACON(R) IV injection, 2006)

c) Seizure, Multiple seizure types; Adjunct

1) 10 to 15 mg/kg/day IV, may increase 5 to 10 mg/kg/week to achieve optimal clinical response (MAX 6 less with a therapeutic range of 50 to 100 mcg/mL) (Prod Info DEPACON(R) IV injection, 2006)

2) Pediatric

a) safety and effectiveness in pediatric patients under age 10 have not been established

1) Complex partial epileptic seizure

a) (10 yr and older) monotherapy, 10 to 15 mg/kg/day IV, may increase dosage 5 to 10 mg/kg/week optimal clinical response (MAX 60 mg/kg/day or less with a therapeutic range of 50 to 100 mcg/mL) DEPACON(R) IV injection, 2006)

b) (10 yr and older) conversion to monotherapy, 10 to 15 mg/kg/day IV, may increase dosage 5 to 1 achieve optimal clinical response (MAX 60 mg/kg/day or less with a therapeutic range of 50 to 100 r concomitant antiepilepsy drug dosage by approximately 25% every 2 weeks (reduction may be start therapy or delayed by 1 to 2 weeks if there is a concern that seizures are likely to occur with a reduc DEPACON(R) IV injection, 2006)

c) (10 yr and older) adjunct, may be added to the patient's regimen at an initial dosage of 10 to 15 r increase dosage 5 to 10 mg/kg/week to achieve optimal clinical response (MAX 60 mg/kg/day or les therapeutic range of 50 to 100 mcg/mL) (Prod Info DEPACON(R) IV injection, 2006)

2) Seizure, Multiple seizure types; Adjunct

a) 10 yr and older, 10 to 15 mg/kg/day IV, may increase 5 to 10 mg/kg/week to achieve optimal clin (MAX 60 mg/kg/day or less with a therapeutic range of 50 to 100 mcg/mL) (Prod Info DEPACON(R)

3) Contraindications

a) Valproic Acid

1) hepatic disease or significant hepatic dysfunction (Prod Info STAVZOR(R) delayed release oral capsules, 200 DEPACON(R) IV injection, 2006; Prod Info DEPAKENE(R) oral capsules, syrup, 2006; Prod Info DEPAKOTE(R) oral tablets, 2006; Prod Info DEPAKOTE(R) ER extended-release tablet, 2006; Prod Info DEPAKOTE(R) sprinkle 2003)

2) hypersensitivity to sodium valproate, divalproex sodium, or valproic acid (Prod Info STAVZOR(R) delayed rele 2008; Prod Info DEPACON(R) IV injection, 2006; Prod Info DEPAKENE(R) oral capsules, syrup, 2006; Prod Info delayed-release oral tablets, 2006; Prod Info DEPAKOTE(R) ER extended-release tablet, 2006; Prod Info DEPAK

oral capsules, 2003)
3) urea cycle disorders, known; hyperammonemic encephalopathy, including fatalities, has occurred (Prod Info S delayed release oral capsules, 2008; Prod Info DEPACON(R) IV injection, 2006; Prod Info DEPAKENE(R) oral ca 2006; Prod Info DEPAKOTE(R) delayed-release oral tablets, 2006; Prod Info DEPAKOTE(R) ER extended-releas Prod Info DEPAKOTE(R) sprinkle oral capsules, 2003)

b) Divalproex Sodium
1) hepatic disease or significant hepatic dysfunction (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008; Proc (R) ER extended-release oral tablets, 2008)
2) hypersensitivity to divalproex sodium (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008; Prod Info DEPAI extended-release oral tablets, 2008)
3) urea cycle disorders (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008; Prod Info DEPAKOTE(R) ER ext tablets, 2008)

c) Valproate Sodium
1) hepatic disease or significant hepatic dysfunction (Prod Info DEPACON(R) IV injection, 2006)
2) hypersensitivity to valproate sodium, valproic acid, or divalproex sodium (Prod Info DEPACON(R) IV injection,
3) known urea cycle disorders; hyperammonemic encephalopathy, including fatalities, has occurred (Prod Info DI injection, 2006)

4) Serious Adverse Effects

a) Valproic Acid
1) Coma, Hyperammonemia-induced
2) Hematemesis
3) Hyperammonemia
4) Hyperammonemic encephalopathy
5) Immune hypersensitivity reaction
6) Ototoxicity - deafness
7) Palpitations
8) Pleural effusion
9) Pulmonary hemorrhage
10) Tachycardia
11) Thrombocytopenia, Dose-related

b) Divalproex Sodium
1) Hyperammonemia
2) Hyperammonemic encephalopathy
3) Immune hypersensitivity reaction
4) Liver failure
5) Ototoxicity - deafness
6) Palpitations
7) Pancreatitis
8) Tachycardia
9) Thrombocytopenia, Dose-related

c) Valproate Sodium
1) Liver failure, Children under the age of two years are at increased risk
2) Pancreatitis, Life-threatening
3) Thrombocytopenia, Dose-related

5) Clinical Applications

a) Valproic Acid
1) FDA Approved Indications
a) Absence seizure, Simple and complex
b) Complex partial epileptic seizure
c) Manic bipolar I disorder
d) Migraine; Prophylaxis
e) Seizure, Multiple seizure types; Adjunct

b) Divalproex Sodium
1) FDA Approved Indications
a) Absence seizure, Simple and complex
b) Complex partial epileptic seizure
c) Manic bipolar I disorder
d) Migraine; Prophylaxis

c) Valproate Sodium
1) FDA Approved Indications
a) Absence seizure, Simple and complex
b) Complex partial epileptic seizure
c) Seizure, Multiple seizure types; Adjunct

1.0 Dosing Information

Drug Properties

Storage and Stability

Adult Dosage

Pediatric Dosage

1.1 Drug Properties

A) Information on specific products and dosage forms can be obtained by referring to the Tradename List (Product In

B) Synonyms

Divalproex Na
Divalproex Sodium
Sodium Valproate
Valproate Na
Valproate Sodium
Valproic Acid

1.2 Storage and Stability

A) Valproic Acid

1) Preparation

a) Oral route

1) Valproic acid capsules should be swallowed whole without chewing to avoid local irritation of the mou Divided doses should be given if the total daily dose exceeds 250 milligrams. A slow titration from the ini giving with food may help to decrease gastrointestinal irritation in patients who experience it (Prod Info D capsules, oral syrup, 2006; Prod Info STAVZOR(R) delayed release oral capsules, 2008).

B) Divalproex Sodium

1) Preparation

a) Oral route

1) Extended-Release

a) Extended-release formulations are for once daily dosing and should be swallowed whole and not chewed. Patients who experience gastrointestinal irritation should take divalproex sodium with food titration from the initial dose (Prod Info DEPAKOTE(R) ER extended-release oral tablets, 2008).

2) Delayed-Release

a) The delayed-release formulation may be taken with or without food. Patients who experience gas irritation should take divalproex sodium with food or utilize slow dose titration from the initial dose (P DEPAKOTE(R) delayed-release oral tablets, 2006).

3) Sprinkle-Capsules

a) The sprinkle-capsules may be swallowed whole, or opened and contents sprinkled on a small an teaspoonful) of soft food such as applesauce or pudding. The drug/food mixture should not be store but should be swallowed immediately without chewing. Patients who experience gastrointestinal irrit divalproex sodium with food or utilize slow dose titration from the initial dose (Prod Info DEPAKOTE capsules, 2008).

C) Valproic Acid

1) Oral route

a) Capsule, Delayed Release

1) Store delayed-release capsules at controlled room temperature, 25 degrees Celsius (77 degrees Fah excursions permitted between 15 and 30 degrees Celsius (59 and 86 degrees Fahrenheit) (Prod Info ST delayed release oral capsules, 2008).

b) Capsule, Liquid Filled

1) Store liquid-filled capsules between 15 and 25 degrees Celsius (59 and 77 degrees Fahrenheit) (Proc (R) capsules and syrup, 2003).

c) Syrup

1) Store syrup below 30 degrees Celsius (86 degrees Fahrenheit) (Prod Info DEPAKENE(R) capsules a

D) Divalproex Sodium

1) Oral route

a) Capsule

1) Divalproex sodium sprinkle capsules should be stored below 77 degrees Fahrenheit (25 degrees Cel DEPAKOTE(R) oral sprinkle capsule, 2003).

b) Tablet, Delayed Release

1) Divalproex sodium delayed-release tablets should be stored below 86 degrees Fahrenheit (30 degree Info Depakote(R) Tablets, 2002).

c) Tablet, Extended Release

1) Divalproex sodium extended-release tablets should be stored at 77 degrees Fahrenheit (25 degrees excursions permitted between 59 and 86 degrees Fahrenheit (15 and 30 degrees Celsius) (Prod Info DE Tablets, 2005).

E) Valproate Sodium

1) Injection route
a) Solution
1) Valproate sodium injection should be stored at room temperature, 15 to 30 degrees Celsius (59 to 86 Fahrenheit) (Prod Info Depacon(R), , 2003).
2) Valproate sodium injection is stable in 5% dextrose injection, 0.9% sodium chloride injection and lacta injection for at least 24 hours in glass or polyvinyl chloride chloride (PVC) bags at 15 to 30 degrees Celsi degrees Fahrenheit) (Prod Info Depacon(R), , 2003).

1.3 Adult Dosage

Normal Dosage

Dosage in Renal Failure

Dosage in Hepatic Insufficiency

Dosage in Geriatric Patients

Dosage Adjustment During Dialysis

1.3.1 Normal Dosage

Divalproex Sodium

Valproate Sodium

Valproic Acid

1.3.1.A Divalproex Sodium

Oral route

Alcohol withdrawal syndrome

1.3.1.A.1 Oral route

Absence seizure, Simple and complex

Complex partial epileptic seizure

Manic bipolar I disorder

Migraine; Prophylaxis

1.3.1.A.1.a Absence seizure, Simple and complex
1) The recommended initial dose is 15 milligrams/kilogram/day (mg/kg/day), increasing at 1-week ir mg/kg/day until the desired therapeutic effect is reached or adverse effects occur. The maximum rec is 60 mg/kg/day. The usual therapeutic serum concentration ranges from 50 to 100 micrograms/milli there is no good correlation between daily dose, serum concentrations, and therapeutic effect. Some experience seizure control with higher or lower serum levels. For the delayed-release tablets and sp total daily doses exceeding 250 mg should be given in divided doses. As divalproex sodium doses a upwards, the blood levels of phenobarbital and/or phenytoin may be affected (Prod Info DEPAKOTE release oral tablets, 2008; Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008; Prod Info DEPAK release oral tablets, 2006).

1.3.1.A.1.b Complex partial epileptic seizure

1) Initial Monotherapy

a) The recommended initial oral dosage for monotherapy is 10 to 15 milligrams/kilogram/day (r increasing by 5 to 10 mg/kg/week until the desired therapeutic effect is reached or adverse effe clinical response is typically achieved at daily doses below 60 mg/kg/day. If a satisfactory respo obtained, plasma levels should be measured to determine whether or not they are in the accept range (50 to 100 mcg/mL). Doses above 60 mg/kg/day are not recommended (Prod Info DEPAI extended-release oral tablets, 2008; Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008; Prc (R) delayed-release oral tablets, 2006).

2) Adjunctive Therapy

a) The recommended oral dosage when adding valproic acid to a patient's regimen is 10 to 15 milligrams/kilogram/day (mg/kg/day) increasing by 5 to 10 mg/kg/week until the desired therape reached or adverse effects occur. Optimal clinical response is typically achieved at daily doses mg/kg/day. If a satisfactory response has not been obtained, plasma levels should be measure whether or not they are in the accepted therapeutic range (50 to 100 mcg/mL). Doses above 60 recommended (Prod Info DEPAKOTE(R) ER extended-release oral tablets, 2008; Prod Info DE sprinkle oral capsules, 2008; Prod Info DEPAKOTE(R) delayed-release oral tablets, 2006).

3) Conversion to Monotherapy

a) When converting to monotherapy, the recommended initial oral dosage is 10 to 15 milligram (mg/kg/day) increasing by 5 to 10 mg/kg/week until the desired therapeutic effect is reached or occur. Optimal clinical response is typically achieved at daily doses below 60 mg/kg/day. If a sa has not been obtained, plasma levels should be measured to determine whether or not they are therapeutic range (50 to 100 mcg/mL). The concomitant antiepileptic dosage may be reduced a valproic acid therapy or after 1 to 2 weeks of therapy. The dosage of the concomitant antiepilep reduced by approximately 25% every 2 weeks. Valproic acid doses above 60 mg/kg/day are no (Prod Info DEPAKOTE(R) ER extended-release oral tablets, 2008; Prod Info DEPAKOTE(R) sp capsules, 2008; Prod Info DEPAKOTE(R) delayed-release oral tablets, 2006).

1.3.1.A.1.c Manic bipolar I disorder

1) Depakote (R) ER, extended-release: The initial dose is 25 milligrams/kilogram/day (mg/kg/day) a once daily with increases in dose done as quickly as possible to achieve the desired clinical effect. I the target trough plasma level range was 85 to 125 micrograms/milliliter. The maximum recommend mg/kg/day (Prod Info DEPAKOTE(R) ER extended-release oral tablets, 2008).

2) Depakote (R), delayed-release: The initial dose is 750 mg orally per day in divided doses with inc done as quickly as possible to achieve the desired clinical effect. In clinical studies, the target trough 50 to 125 micrograms/milliliter. The maximum recommended dose is 60 mg/kg/day (Prod Info DEPA release oral tablets, 2006)

3) A divalproex loading dose of 20 milligrams/kilogram/day (mg/kg/day) has been given to achieve s concentrations of 80 milligrams/liter. This dosage strategy has been used to rapidly achieve therape patients with acute psychotic manic symptoms (McElroy et al, 1996).

4) Another accelerated loading regimen used divalproex 30 milligrams per kilogram per day (mg/kg and 2 followed by 20 mg/kg/day for days 3 through 10, which resulted in 16 of 19 (84%) of patients a therapeutic serum valproate levels of 50 micrograms/milliliter by day 3 of the study (Hirschfeld, 1999

1.3.1.A.1.d Migraine; Prophylaxis

1) The recommended initial dose of extended-release tablets is 500 milligrams (mg) orally once a d followed by an increase to 1000 mg orally once daily (Prod Info DEPAKOTE(R) ER extended-releas 2008).

2) The recommended initial dose of delayed-release tablets is 250 milligrams (mg) twice daily. In sc up to 1000 mg/day are beneficial (Prod Info DEPAKOTE(R) delayed-release oral tablets, 2006).

1.3.1.A.1.e Conversion From Valproic Acid

1) When converting patients from valproic acid, initiate divalproex sodium sprinkle capsules at the s and dosing schedule. Once stabilized, a schedule of divalproex sodium 2 or 3 times a day may be ir DEPAKOTE(R) sprinkle oral capsules, 2008; Prod Info DEPAKOTE(R) delayed-release oral tablets,

1.3.1.A.1.f Conversion From Delayed-Release To Extended-Release Formulations

1) When converting from divalproex sodium delayed-release tablets (Depakote(R) Tablets), adminis sodium extended-release tablets (Depakote(R) ER) once daily in doses 8% to 20% higher than the t divalproex sodium delayed-release tablets (Depakote(R) Tablets). Due to pharmacokinetic variation patients, monitor plasma levels if satisfactory clinical response has not been achieved.

Divalproex Sodium Dose Conversion	
Delayed-release (Depakote(R)) total daily dose (mg)	Extended-release (Depakote(R) ER) (mg)
500* - 625	750
750* - 875	1000
1000* - 1125	1250
1250 - 1375	1500

1500 - 1625	1750
1750	2000
1875 - 2000	2250
2125 - 2250	2500
2375	2750
2500 - 2750	3000
2875	3250
3000 - 3125	3500
* these total daily doses cannot be directly converted to extended-release since the required dosing strengths are not available	

In cases where the total daily dose of delayed-release product cannot be directly converted to a release product because the required dosing strengths are not available, consider increasing th the next higher dosage before converting to the appropriate total daily dose of the extended-rele (Prod Info DEPAKOTE(R) ER extended-release oral tablets, 2008).

1.3.1.A.1.g Withdrawal Schedule

1) The risk factors associated with withdrawal of anticonvulsants in 92 patients who had been free o years with single agent therapy were evaluated. The dose of each anticonvulsant was reduced by 1 2 weeks (1 unit equivalent to 200 milligrams of carbamazepine or valproic acid or 100 milligrams of mean follow-up period of 26 months (range, 6 to 62 months). Relapse occurred in 31 patients, with 6 remaining free of seizures (relapse rate 33.7%) (Callaghan et al, 1988).

1.3.1.A.2 Alcohol withdrawal syndrome

See Drug Consult reference: DRUG THERAPY OF ETHANOL WITHDRAWAL

1.3.1.B Valproate Sodium

Intravenous route

Rectal route

1.3.1.B.1 Intravenous route

Absence seizure, Simple and complex

Complex partial epileptic seizure

Seizure, Multiple seizure types; Adjunct

1.3.1.B.1.a Absence seizure, Simple and complex

1) The initial dosage is 15 milligrams/kilogram/day (mg/kg/day), increasing at 1-week intervals by 5 until the desired therapeutic effect is reached or adverse effects occur. Total daily doses exceeding given in divided doses, and the maximum recommended dosage is 60 mg/kg/day (Prod Info DEPAC injection, 2006).

1.3.1.B.1.b Complex partial epileptic seizure

1) Initial Monotherapy

a) The usual recommended initial intravenous dosage for monotherapy is 10 to 15 milligrams/k (mg/kg/day), increasing at 1-week intervals by 5 to 10 mg/kg/day until the desired therapeutic e adverse effects occur. Total daily doses exceeding 250 milligrams should be given in divided do maximum recommended dose is 60 mg/kg/day (Prod Info DEPACON(R) IV injection, 2006).

2) Adjunctive Therapy

a) The usual recommended intravenous dosage when adding valproic acid to a patient's regim milligrams/kilogram/day (mg/kg/day), increasing at 1-week intervals by 5 to 10 mg/kg/day until t therapeutic effect is reached or adverse effects occur. Total daily doses exceeding 250 milligrar in divided doses, and the maximum recommended dose is 60 mg/kg/day (Prod Info DEPACON 2006).

3) Conversion to Monotherapy

a) Concomitant antiepilepsy drug dosage may be reduced by approximately 25% every 2 week of valproic acid therapy or after 1 to 2 weeks of therapy (Prod Info DEPACON(R) IV injection, 2

1.3.1.B.1.c Seizure, Multiple seizure types; Adjunct

1) Administer 10 to 15 milligrams per kilograms (mg/kg) per day intravenously. The dose may be in
mg/kg/week to achieve optimal clinical response, which is typically seen at a therapeutic range of 5(
The maximum recommended dose is 60 mg/kg/day (Prod Info DEPACON(R) IV injection, 2006).

1.3.1.B.1.d Important Note

1) Valproate sodium injection is for intravenous use only and should be used in patients who are te
use the oral form of valproic acid. Use of valproate sodium injection for periods of more than 14 day
studied. As soon as it is clinically feasible, patients should be switched back to oral valproic acid. Va
injection should be administered as a 60 minute infusion and not faster than 20 milligrams/minute. It
with at least 50 milliliters of a compatible diluent. The same frequency of administration should be us
products. Plasma concentrations should be monitored (Prod Info Depacon(R), 2003).

2) There have been reports of hyperammonemic encephalopathy (including fatalities) in patients wi
disorders (UCD) who have received valproate therapy. UCD is a genetic disorder with an estimated
1:8000 to 1:30,000 births. Patients suspected of having UCD should not receive valproic acid, divalp
valproate sodium (Prod Info Depakote(R), 2003; Prod Info Depakote ER(R), 2003; Prod Info Depako
2003; Prod Info Depakene(R), 2003; Prod Info Depacon(R), 2003).

a) To achieve high therapeutic levels of valproic acid, RAPID INTRAVENOUS INFUSION at 3
milligrams/kilogram (mg/kg)/minute for a duration of 4.17 or 8.34 minutes, respectively, has bee
21 to 28 mg/kg (mean dose 24.2 mg/kg) were given to 21 patients (2 to 54 years old). Peak ser
concentrations measured 20 minutes post-infusion were 105 to 204 micrograms/milliliter. The ir
tolerated and no cardiac or central nervous system adverse effects were reported (Venkataram
1999).

b) Intravenous valproic acid was used in 4 patients (3 children and 1 adult) for the treatment of
WAVE STATUS EPILEPTICUS. Loading doses of 30 milligrams/kilogram were given over an h
dosages required in the 3 pediatric patients ranged from 120 to 160 mg/kg/day divided every 6
1999).

3) Valproate sodium injection should be administered as a 60 minute infusion and not faster than 2(
milligrams/minute. It should be diluted with at least 50 milliliters of a compatible diluent. The same fr
administration should be used as the oral products. Plasma concentrations should be monitored (Pr
(R), 2003).

e) The total daily dose of valproate sodium injection should be equivalent to the total daily dose of the o
product and should be administered as a 60 minute infusion with the same frequency as the oral product
concentration monitoring and dosage adjustments may be necessary. Infusions should not exceed 20 m
(mg)/minute. If the total daily dose exceeds 250 mg, it should be given in divided doses (Prod Info Depac

f) The manufacturer states that the equivalence shown between valproate sodium injection and oral valp
at steady state was only evaluated in an every 6 hour dosing regimen. If valproate sodium injection is giv
trough levels may fall below those measured using the oral route. Close monitoring of trough plasma lev
if valproate sodium injection is given only 2 or 3 times daily (Prod Info Depacon(TM), 1999).

1.3.1.B.2 Rectal route

a) In one patient, a 65-year-old male, status epilepticus did not respond to commonly used anticonvulsa
completely controlled by SODIUM VALPROATE syrup given rectally (250 to 500 milligrams every 6 to 8
was mixed with 30 milliliters of water and given as a retention enema. It was well-absorbed rectally and c
respiratory depression than other agents (Thorpy, 1980).

1.3.1.B.3 Withdrawal Schedule

a) The risk factors associated with withdrawal of anticonvulsants in 92 patients who had been free of sei
with single agent therapy were evaluated. The dose of each anticonvulsant was reduced by 1 unit at inte
unit equivalent to 200 milligrams of CARBAMAZEPINE or VALPROIC ACID, or 100 milligrams of PHEN
mean follow-up period of 26 months (range, 6 to 62 months). Relapse occurred in 31 patients, with 61 pa
free of seizures (relapse rate 33.7%) (Callaghan et al, 1988).

1.3.1.C Valproic Acid

Oral route

Hiccoughs

1.3.1.C.1 Oral route

Absence seizure, Simple and complex

Complex partial epileptic seizure

Manic bipolar I disorder

Migraine; Prophylaxis

Myoclonic seizure

Seizure, Multiple seizure types; Adjunct

1.3.1.C.1.a Absence seizure, Simple and complex

1) The usual recommended dosage is 15 milligrams/kilogram/day (mg/kg/day) orally, increasing at
5 to 10 mg/kg/day until the desired therapeutic effect is reached or adverse effects occur. The maxi
recommended dosage is 60 mg/kg/day . Total daily doses of valproic acid exceeding 250 mg should
divided doses. Therapeutic valproate serum concentrations for most patients with absence seizures
range from 50 to 100 micrograms/milliliter (Prod Info DEPAKENE(R) oral capsules, oral syrup, 2006
STAVZOR(R) delayed release oral capsules, 2008).

2) The initial dose should be determined by weight and not age. The manufacturer of (Depakene(R)
following dosage schedule based on body weight (Prod Info DEPAKENE(R) oral capsules, oral syru

Pounds (lbs)	Kilograms (kg)	Daily dose
22 to 54.9 lbs	10 to 24.9 kg	250 mg
55 to 87.9 lbs	25 to 39.9 kg	500 mg
88 to 131.9 lbs	40 to 59.9 kg	750 mg
132 to 164.9 lbs	60 to 74.9 kg	1000 mg
165 to 197.9 lbs	75 to 89.9 kg	1250 mg

1.3.1.C.1.b Complex partial epileptic seizure

1) Initial Monotherapy

a) The usual recommended initial oral dosage for monotherapy is 10 to 15 milligrams/kilogram/
increasing at 1 week intervals by 5 to 10 mg/kg/week until the desired therapeutic effect is reac
optimal clinical response is achieved at daily doses below 60 mg/kg/day. If a satisfactory respor
obtained, plasma levels should be measured to determine whether or not they are in the accept
serum range (50 to 100 mcg/mL). Doses above 60 mg/kg/day are not recommended. Total dail
acid exceeding 250 milligrams should be given in 2 to 3 divided doses (Prod Info DEPAKENE(F
oral syrup, 2006; Prod Info STAVZOR(R) delayed release oral capsules, 2008) .

2) Conversion to Monotherapy

a) When converting to monotherapy, the usual recommended initial oral dosage is 10 to 15
milligrams/kilogram/day (mg/kg/day) increasing at 1 week intervals by 5 to 10 mg/kg/week until
therapeutic effect is reached. Usually, optimal clinical response is achieved at daily doses belov
a satisfactory response has not been obtained, plasma levels should be measured to determine
they are in the accepted therapeutic serum range (50 to 100 mcg/mL). Concomitant antiepileps
be reduced at the initiation of valproic acid therapy or after 1 to 2 weeks of therapy. The dosage
concomitant antiepilepsy drug can be reduced by approximately 25% every 2 weeks. Valproic a
60 mg/kg/day are not recommended. Total daily doses of valproic acid exceeding 250 milligram
in 2 to 3 divided doses (Prod Info DEPAKENE(R) oral capsules, oral syrup, 2006; Prod Info STA
release oral capsules, 2008).

3) Adjunctive Therapy

a) The usual recommended oral dosage when adding valproic acid to a patient's regimen is 10
milligrams/kilogram/day (mg/kg/day), increasing at 1 week intervals by 5 to 10 mg/kg/week until
therapeutic effect is reached. Usually, optimal clinical response is achieved at daily doses belov
a satisfactory response has not been obtained, plasma levels should be measured to determine
they are in the accepted therapeutic serum range (50 to 100 mcg/mL). Doses above 60 mg/kg/d
recommended. Total daily doses of valproic acid exceeding 250 milligrams should be given in 2
(Prod Info DEPAKENE(R) oral capsules, oral syrup, 2006; Prod Info STAVZOR(R) delayed rele
2008).

1.3.1.C.1.c Manic bipolar I disorder

1) The recommended initial dose of delayed-release valproic acid is 750 milligrams (mg) orally daily
The dose should be increased as quickly as possible to achieve the lowest therapeutic dose that wil
desired clinical response or desired range of plasma concentrations. The maximum recommended d
mg/kilogram/day or less with a therapeutic serum range of 50 to 125 micrograms/milliliter (Prod Info
delayed release oral capsules, 2008).

1.3.1.C.1.d Migraine; Prophylaxis

1) For the prophylaxis of migraine, the recommended initial dose of delayed-release valproic acid (S
milligrams (mg) orally twice daily. Some patients may benefit from doses up to 1000 mg/day. Higher
to greater efficacy in clinical trials (Prod Info STAVZOR(R) delayed release oral capsules, 2008).

1.3.1.C.1.e Myoclonic seizure

1) A starting dose of 15 milligrams/kilogram/day (mg/kg/day) provided seizure control for 63% of 76 juvenile myoclonic epilepsy. Twenty-five percent of patients were controlled at 20 mg/kg/day, 4% at 8% required addition of a second drug. After a 2-year seizure-free period, 22% of patients could be 5 mg/kg/day, 33% on 6 to 8 mg/kg/day, and 42% required more than 9 mg/kg/day (Panagariya et al,

1.3.1.C.1.f Seizure, Multiple seizure types; Adjunct

1) The recommended initial dose is 10 to 15 milligrams/kilogram/day (mg/kg) orally. The dose may to 10 mg/kg/week to achieve optimal clinical response. If total daily dose exceeds 250 mg, give in 2 Maximum daily dose is 60 mg/kg/day or less with a therapeutic serum range of 50 to 100 microgram Info DEPAKENE(R) oral capsules, oral syrup, 2006; Prod Info STAVZOR(R) delayed release oral ca

1.3.1.C.1.g Withdrawal Schedule

1) The risk factors associated with withdrawal of anticonvulsants in 92 patients who had been free o years with single agent therapy were evaluated. The dose of each anticonvulsant was reduced by 1 2 weeks (1 unit equivalent to 200 milligrams of carbamazepine or valproic acid, or 100 milligrams of mean follow-up period of 26 months (range, 6 to 62 months). Relapse occurred in 31 patients, with 6 remaining free of seizures (relapse rate 33.7%) (Callaghan et al, 1988).

1.3.1.C.2 Hiccoughs

See Drug Consult reference: HICCUPS - ETIOLOGY AND TREATMENT

1.3.2 Dosage in Renal Failure

A) Valproic Acid

1) Renal excretion of sodium valproate as the unchanged drug is 1.8% (Hardman et al, 1996a). A 27% reduc unbound clearance of valproate has been reported in patients with a creatinine clearance of less than 10 milli however, hemodialysis typically decreases valproate concentrations by about 20%. Therefore, dosage adjust unnecessary in patients with renal failure. Monitoring total concentrations of valproic acid may be misleading renal failure because protein binding in these patients is significantly reduced (Prod Info DEPAKENE(R) oral syrup, 2006; Prod Info STAVZOR(R) delayed release oral capsules, 2008).

B) Divalproex Sodium

1) Dose adjustments are not required in renal failure (Prod Info DEPAKOTE(R) ER extended-release oral tal Bennett et al, 1994). However, increased free levels of valproic acid have been reported, and monitoring of to may be misleading (Lapierre et al, 1999). Renal excretion of sodium valproate as the unchanged drug is 1.8% 1996a). A 27% reduction in the unbound clearance of valproate has been reported in patients with a creatinir less than 10 milliliters/minute (Prod Info DEPAKOTE(R) ER extended-release oral tablets, 2008).

C) Valproate Sodium

1) Dosage adjustments are not required in renal failure (Prod Info Depakote(R) Tablets, 2002a; Bennett et al increased free levels of valproic acid have been reported and monitoring of total concentrations may be misle al, 1999). Renal excretion of SODIUM VALPROATE as the unchanged drug is 1.8% (Hardman et al, 1996a). in the unbound clearance of valproate has been reported in patients with a creatinine clearance of less than 1 milliliters/minute.

1.3.3 Dosage in Hepatic Insufficiency

A) Valproic Acid

1) Valproic acid should not be administered to patients with hepatic disease or significant hepatic insufficienc impairs the capacity to eliminate valproate. In one study, the clearance of free valproate was decreased by 5(cirrhosis and by 16% in patients with acute hepatitis. Patients with liver disease have decreased albumin con larger unbound fractions by a 2 to 2.6 fold increase. Monitoring of total concentrations may be misleading sin concentrations may be significantly elevated in patients with hepatic disease, with total concentrations appea (Prod Info DEPAKENE(R) oral capsules, oral syrup, 2006; Prod Info STAVZOR(R) delayed release oral caps

2) Mean serum half-life of valproic acid was shown to increase in 7 patients with alcoholic cirrhosis or recove hepatitis. Single doses of 450 milligrams orally (solution) were administered (Klotz et al, 1978).

B) Divalproex Sodium

1) Divalproex sodium should not be administered to patients with hepatic disease or significant hepatic insuf disease impairs the capacity to eliminate valproate. In one study, the clearance of free valproate was decreas patients with cirrhosis and by 16% in patients with acute hepatitis. Patients with liver disease have decreased concentrations and larger unbound fractions by a 2- to 2.6-fold increase. Monitoring of total concentrations m (Prod Info DEPAKOTE(R) ER extended-release oral tablets, 2008; Prod Info DEPAKOTE(R) sprinkle oral cap Info DEPAKOTE(R) delayed-release oral tablets, 2006).

2) Mean serum half-life of valproic acid was shown to increase in 7 patients with alcoholic cirrhosis or recove hepatitis (Klotz et al, 1978). Single doses of 450 milligrams orally (solution) were administered.

C) Valproate Sodium

1) VALPROIC ACID or DIVALPROEX should not be administered to patients with hepatic disease or signific insufficiency (Prod Info Depakene(R), 1999)(Prod Info Depakote(R) Tablets, 2002a). Liver disease impairs th eliminate valproate. In one study, the clearance of free valproate was decreased by 50% in patients with cirrh in patients with acute hepatitis. Patients with liver disease have decreased albumin concentrations and larger by a 2 to 2.6 fold increase. Monitoring of total concentrations may be misleading.

2) Mean serum half-life of VALPROIC ACID was shown to increase in 7 patients with alcoholic cirrhosis or re acute hepatitis (Klotz et al, 1978). Single doses of 450 milligrams orally (solution) were administered.

1.3.4 Dosage in Geriatric Patients

A) Valproic Acid

1) The manufacturer recommends that the starting dose be reduced due to a decrease in unbound clearanc a potential increase in sensitivity to somnolence in the elderly. Slow dosage titration and close monitoring of f intake, dehydration and adverse effects are also recommended. In patients with decreased food or fluid intak with excessive somnolence, dose reductions or discontinuation of therapy should be considered. Maintenanc based on clinical response (Prod Info DEPAKENE(R) oral capsules, oral syrup, 2006; Prod Info STAVZOR(R oral capsules, 2008).

B) Divalproex Sodium

1) Due to a 39% decrease in intrinsic clearance and a 44% increase in free fraction, decrease the initial dose patients. Slow dosage titration and close monitoring of fluid and nutritional intake, dehydration, and adverse e recommended. Maintenance doses should be based on clinical response (Prod Info DEPAKOTE(R) ER exte tablets, 2008; Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008; Prod Info DEPAKOTE(R) delayed-relea 2006).

C) Valproate Sodium

1) The manufacturer recommends that the starting dose be reduced due to a decrease in unbound clearanc a potential increase in sensitivity to somnolence in the elderly. Slow dosage titration and close monitoring of f intake, dehydration and adverse effects are also recommended. Maintenance doses should be based on clin (Prod Info Depakote(R) Tablets, 2002a).

1.3.5 Dosage Adjustment During Dialysis

A) Valproic Acid

1) Hemodialysis typically reduces valproate concentrations by about 20%, but a 27% reduction in the unbou valproate has been reported in patients with a creatinine clearance of less than 10 milliliters/minute. Therefor supplementation is required in patients following hemodialysis, peritoneal dialysis, or continuous arteriovenou Monitoring total concentrations of valproic acid may be misleading in patients with renal failure because prote patients is significantly reduced (Prod Info DEPAKENE(R) oral capsules, oral syrup, 2006; Prod Info STAVZO release oral capsules, 2008).

B) Divalproex Sodium

1) No dosage supplementation is required in patients following hemodialysis, peritoneal dialysis, or continuo hemofiltration (Bennett et al, 1994). Hemodialysis typically reduces valproate concentrations by about 20% a is substantially reduced. Monitoring total concentrations may be misleading (Prod Info DEPAKOTE(R) ER ex oral tablets, 2008).

C) Valproate Sodium

1) No dosage supplementation is required in patients following hemodialysis, peritoneal dialysis, or continuo hemofiltration (Prod Info Depakote(R) Tablets, 2002a; Bennett et al, 1994). Hemodialysis typically reduces va concentrations by about 20% and protein binding is substantially reduced. Monitoring total concentrations ma (Prod Info Depakote(R) Tablets, 2002a).

1.4 Pediatric Dosage

Normal Dosage

Dosage in Renal Failure

Dosage in Hepatic Insufficiency

Dosage Adjustment During Dialysis

1.4.1 Normal Dosage

Divalproex Sodium

Valproate Sodium

Valproic Acid

1.4.1.A Divalproex Sodium

1.4.1.A.1 Oral route

Absence seizure, Simple and complex

Complex partial epileptic seizure

1.4.1.A.1.a Absence seizure, Simple and complex

1) The recommended initial dose is 15 milligrams/kilogram/day (mg/kg/day), increasing at 1-week ir mg/kg/day until the desired therapeutic effect is reached or adverse effects occur. The maximum rec dosage is 60 mg/kg/day. The usual therapeutic serum concentration ranges from 50 to 100 microgra however, there is no good correlation between daily dose, serum concentrations, and therapeutic ef patients may experience seizure control with higher or lower serum levels. For the delayed-release t capsules, total daily doses exceeding 250 mg should be given in divided doses. As divalproex sodiu titrated upwards, the blood levels of phenobarbital and/or phenytoin may be affected (Prod Info DEP extended-release oral tablets, 2008; Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008; Prod Inf delayed-release oral tablets, 2006).

1.4.1.A.1.b Complex partial epileptic seizure

1) Initial Monotherapy

a) Initial monotherapy (children 10 years of age or older): The recommended initial oral dosage is 10 to 15 milligrams/kilogram/day (mg/kg/day), increasing by 5 to 10 mg/kg/week until the des effect is reached or adverse effects occur. Optimal clinical response is typically achieved at dail mg/kg/day. If a satisfactory response has not been obtained, plasma levels should be measure whether or not they are in the accepted therapeutic range (50 to 100 mcg/mL). Doses above 60 recommended (Prod Info DEPAKOTE(R) ER extended-release oral tablets, 2008; Prod Info DE sprinkle oral capsules, 2008; Prod Info DEPAKOTE(R) delayed-release oral tablets, 2006).

2) Adjunctive Therapy

a) Adjunctive therapy (children 10 years of age or older): The recommended initial oral dosage valproic acid to a patient's current regimen is 10 to 15 milligrams/kilogram/day (mg/kg/day), incr mg/kg/week until the desired therapeutic effect is reached or adverse effects occur. Optimal clir typically achieved at daily doses below 60 mg/kg/day. If a satisfactory response has not been o levels should be measured to determine whether or not they are in the accepted therapeutic rar mcg/mL). Doses above 60 mg/kg/day are not recommended (Prod Info DEPAKOTE(R) ER exte tablets, 2008; Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008; Prod Info DEPAKOTE(R) oral tablets, 2006).

3) Conversion To Monotherapy

a) Conversion to monotherapy (children 10 years of age or older): The recommended initial ora monotherapy is 10 to 15 milligrams/kilogram/day (mg/kg/day), increasing by 5 to 10 mg/kg/wee therapeutic effect is reached or adverse effects occur. Optimal clinical response is typically achi doses below 60 mg/kg/day. If a satisfactory response has not been obtained, plasma levels sho to determine whether or not they are in the accepted therapeutic range (50 to 100 mcg/mL). Do mg/kg/day are not recommended. The concomitant antiepileptic drug dosage may be reduced a valproic acid therapy or after 1 to 2 weeks of therapy and can be reduced by approximately 25% (Prod Info DEPAKOTE(R) ER extended-release oral tablets, 2008; Prod Info DEPAKOTE(R) sp capsules, 2008; Prod Info DEPAKOTE(R) delayed-release oral tablets, 2006).

1.4.1.A.1.c Safety and Efficacy

1) The safety and efficacy for the treatment of epilepsy in children less than 10 years of age have n established (Prod Info DEPAKOTE(R) ER extended-release oral tablets, 2008; Prod Info DEPAKOT capsules, 2008).

2) The efficacy for use in the pediatric population for the treatment of mania or migraine prophylaxis established (Prod Info DEPAKOTE(R) ER extended-release oral tablets, 2008).

1.4.1.A.1.d Conversion From Valproic Acid

1) When converting patients from valproic acid, initiate divalproex sodium sprinkle capsules at the s and dosing schedule. Once stabilized, a schedule of divalproex sodium 2 or 3 times a day may be ir DEPAKOTE(R) sprinkle oral capsules, 2008; Prod Info DEPAKOTE(R) delayed-release oral tablets,

1.4.1.A.1.e Conversion From Delayed-Release To Extended-Release Formulations

1) When converting from divalproex sodium delayed-release tablets (Depakote(R) Tablets), adminis sodium extended-release tablets (Depakote(R) ER) once daily in doses 8% to 20% higher than the t divalproex sodium delayed-release tablets (Depakote(R) Tablets). Due to pharmacokinetic variation patients, monitor plasma levels if satisfactory clinical response has not been achieved.

Divalproex Sodium Dose Conversion	
Delayed-release (Depakote(R)) total daily dose (mg)	Extended-release (Depakote(R) ER) (mg)
500* - 625	750

750* - 875	1000
1000* - 1125	1250
1250 - 1375	1500
1500 - 1625	1750
1750	2000
1875 - 2000	2250
2125 - 2250	2500
2375	2750
2500 - 2750	3000
2875	3250
3000 - 3125	3500
* these total daily doses cannot be directly converted to extended-release since the required dosing strengths are not available	

In cases where the total daily dose of delayed-release product cannot be directly converted to a release product because the required dosing strengths are not available, consider increasing th the next higher dosage before converting to the appropriate total daily dose of the extended-rel (Prod Info DEPAKOTE(R) ER extended-release oral tablets, 2008).

1.4.1.A.1.f Withdrawal Schedule

1) The risk factors associated with withdrawal of anticonvulsants in 92 patients who had been free o years with single agent therapy were evaluated. The dose of each anticonvulsant was reduced by 1 2 weeks (1 unit equivalent to 200 milligrams of carbamazepine or valproic acid, or 100 milligrams of mean follow-up period of 26 months (range, 6 to 62 months). Relapse occurred in 31 patients, with 6 remaining free of seizures (relapse rate 33.7%) (Callaghan et al, 1988).

1.4.1.B Valproate Sodium

Intravenous route

Oral route

1.4.1.B.1 Intravenous route

Absence seizure, Simple and complex

Complex partial epileptic seizure

Seizure, Multiple seizure types; Adjunct

1.4.1.B.1.a Absence seizure, Simple and complex

1) For children 10 years of age and older, the initial dosage is 15 milligrams/kilogram/day (mg/kg/da week intervals by 5 to 10 mg/kg/day until the desired therapeutic effect is reached or adverse effects doses exceeding 250 mg should be given in divided doses, and the maximum recommended dosag (Prod Info DEPACON(R) IV injection, 2006).

1.4.1.B.1.b Complex partial epileptic seizure

1) Initial Monotherapy (children 10 years of age or older)

a) The usual recommended initial dosage for monotherapy is 10 to 15 milligrams/kilogram/day increasing at 1 week intervals by 5 to 10 mg/kg/day until the desired therapeutic effect is reache effects occur. Total daily doses exceeding 250 milligrams should be given in divided doses, and recommended dose is 60 mg/kg/day (Prod Info DEPACON(R) IV injection, 2006).

2) Adjunctive Therapy (children 10 years of age or older)

a) The usual recommended dosage when adding valproic acid to a patient's regimen is 10 to 1 milligrams/kilogram/day (mg/kg/day), increasing at 1 week intervals by 5 to 10 mg/kg/day until t therapeutic effect is reached or adverse effects occur. Total daily doses exceeding 250 milligra in divided doses, and the maximum recommended dose is 60 mg/kg/day (Prod Info DEPACON 2006).

3) Conversion to Monotherapy

a) Concomitant antiepilepsy drug dosage may be reduced by approximately 25% every 2 week of valproic acid therapy or after 1 to 2 weeks of therapy (Prod Info DEPACON(R) IV injection, 2

1.4.1.B.1.c Seizure, Multiple seizure types; Adjunct

1) For children 10 years and older, administer 10 to 15 milligrams per kilograms (mg/kg) per day int dose may be increased by 5 to 10 mg/kg/week to achieve optimal clinical response, which is typicall therapeutic range of 50 to 100 mcg/mL. The maximum recommended dose is 60 mg/kg/day (Prod Ir IV injection, 2006).

1.4.1.B.1.d Important Note

1) Valproate sodium injection is for intravenous use only and should be used in patients who are ter use the oral form of valproic acid. Use of valproate sodium injection for periods of more than 14 days studied. As soon as it is clinically feasible, patients should be switched back to oral valproic acid. Va injection should be administered as a 60 minute infusion and not faster than 20 milligrams/minute. It with at least 50 milliliters of a compatible diluent. The same frequency of administration should be us products. Plasma concentrations should be monitored (Prod Info Depacon(R), 2003).

2) There have been reports of hyperammonemic encephalopathy (including fatalities) in patients wi disorders (UCD) who have received valproate therapy. UCD is a genetic disorder with an estimated 1:8000 to 1:30,000 births. Patients suspected of having UCD should not receive valproic acid, divalp valproate sodium (Prod Info Depakote(R), 2003; Prod Info Depakote ER(R), 2003; Prod Info Depako 2003; Prod Info Depakene(R), 2003; Prod Info Depacon(R), 2003).

e) Two patients (ages 10 years and 34 months) receiving multiple antiepileptic inducing agents including coma required a loading dose of valproate 20 milligrams/kilogram (mg/kg). A maintenance infusion of 4 r required to maintain a level of approximately 75 mg/Liter (Hovinga et al, 1999).

f) To achieve high therapeutic levels of valproic acid, RAPID INTRAVENOUS INFUSION at 3 or 6 millig (mg/kg)/minute for a duration of 4.17 or 8.34 minutes, respectively, has been used. Doses of 21 to 28 mg 24.2 mg/kg) were given to 21 patients (2 to 54-years-old). Peak serum valproate concentrations measure post-infusion were 105 to 204 micrograms/milliliter. The infusions were well-tolerated and no cardiac or c system adverse effects were reported (Venkataraman & Wheless, 1999).

1.4.1.B.1.g Intravenous valproic acid was used in 4 patients (3 children and 1 adult) for the treatment o WAVE STATUS EPILEPTICUS. Loading doses of 30 milligrams/kilogram were given over an hour. Main required in the 3 pediatric patients ranged from 120 to 160 mg/kg/day divided every 6 hours (Chez et al,

1) Equivalent Doses

a) The total daily dose of valproate sodium injection should be equivalent to the total daily dose valproic acid product and should be administered as a 60 minute infusion with the same freque products. Plasma concentration monitoring and dosage adjustments may be necessary. Infusio exceed 20 milligrams(mg)/minute. If the total daily dose exceeds 250 mg, it should be given in c (Prod Info Depacon(TM), 1999).

b) The manufacturer states that the equivalence shown between valproate sodium injection an products at steady state was only evaluated in an every 6 hour dosing regimen. If valproate soc given less frequently, trough levels may fall below those measured using the oral route. Close m trough plasma levels may be needed if valproate sodium injection is given only 2 or 3 times dail Depacon(TM), 1999).

2) Intravenous Rate of Administration

a) Valproate sodium injection should be administered as a 60 minute infusion and not faster tha milligrams/minute. It should be diluted with at least 50 milliliters of a compatible diluent. The sar administration should be used as the oral products. Plasma concentrations should be monitored Depacon(R), 2003).

b) In a prospective pilot study involving 4 hospitalized and acutely ill children, intravenous sodi safely administered at an infusion rate of 1 milligram/kilogram/minute. The patients ranged from age and weighed between 17.2 to 60 kilograms. Before and during the infusion, vital signs and were recorded every 5 minutes. Blood samples were also collected pre-infusion, at 0.5 hours ar hours post-infusion. Doses ranged between 8.3 to 15.4 milligrams/kilogram (mg/kg) and the dur infusions ranged from 8 to 15 minutes. Intravenous sodium valproate was diluted 1:1 (v/v) with 5 sterile water. The investigators found no clinically significant changes in blood pressure, heart ra rate (values not reported). The only reported adverse reaction was local inflammation at the inje in 1 patient. Unbound valproate acid concentrations were greater at 0.5 hours post-infusion than infusion (median percent of unbound valproate acid 22% vs 15%, respectively). Study investiga being cautious when using rapid infusions to acutely ill patients as higher unbound drug levels r excessive toxicity although total drug levels are within the target range (Birnbaum et al, 2003).

c) To achieve high therapeutic levels of valproic acid, RAPID INTRAVENOUS INFUSION at 3 milligrams/kilogram (mg/kg)/minute for a duration of 4.17 or 8.34 minutes, respectively, has bee 21 to 28 mg/kg (mean dose 24.2 mg/kg) were given to 21 patients (2 to 54-years-old). Peak ser concentrations measured 20 minutes post-infusion were 105 to 204 micrograms/milliliter. The in tolerated and no cardiac or central nervous system adverse effects were reported (Venkataram 1999).

d) Two patients (ages 10 years and 34 months) receiving multiple antiepileptic inducing agents phenobarbital, required a loading dose of valproate 20 milligrams/kilogram (mg/kg). A maintena 6 mg/kg/hour was required to maintain a level of approximately 75 mg/Liter (Hovinga et al, 199

1.4.1.B.2 Oral route

1.4.1.B.2.a West syndrome

1) Monotherapy with VALPROIC ACID was effective in the treatment of INFANTILE SPASMS in a p involving 22 children aged 4 to 11 months (Siemes et al, 1988). VALPROIC ACID (as SODIUM VAL given initially in oral doses of 15 milligrams/kilogram/day; this was increased every second day by 1(milligrams/kilogram until seizures ceased or a maximum dose of 100 milligrams/kilogram/day was a(were not controlled or reduced after 4 to 6 weeks of treatment, oral DEXAMETHASONE 0.4 to 0.5 m added to the regimen. The doses of SODIUM VALPROATE ranged from 40 to 100 milligrams/kilogra 74).

1.4.1.C Valproic Acid

Oral route

Rectal route

1.4.1.C.1 Oral route

Absence seizure, Simple and complex

Complex partial epileptic seizure

Migraine; Prophylaxis

Seizure, Multiple seizure types; Adjunct

1.4.1.C.1.a Absence seizure, Simple and complex

1) In children, 10 years and older, the usual recommended dosage is 15 milligrams/kilogram/day (m increasing at 1 week intervals by 5 to 10 mg/kg/day until the desired therapeutic effect is reached or occur. The maximum recommended dosage is 60 mg/kg/day. Total daily doses of valproic acid exce should be given in 2 to 3 divided doses. Therapeutic valproate serum concentrations for most patien seizures is considered to range from 50 to 100 micrograms/milliliter (Prod Info DEPAKENE(R) oral c syrup, 2006; Prod Info STAVZOR(R) delayed release oral capsules, 2008).

2) The initial dose should be determined by weight and not age. The manufacturer of (Depakene(R) following dosage schedule based on body weight (Prod Info DEPAKENE(R) oral capsules, oral syru

Pounds (lbs)	Kilograms (kg)	Daily dose
22 to 54.9 lbs	10 to 24.9 kg	250 mg
55 to 87.9 lbs	25 to 39.9 kg	500 mg
88 to 131.9 lbs	40 to 59.9 kg	750 mg
132 to 164.9 lbs	60 to 74.9 kg	1000 mg
165 to 197.9 lbs	75 to 89.9 kg	1250 mg

1.4.1.C.1.b Complex partial epileptic seizure

1) Initial Monotherapy

a) In children 10 years and older, the usual recommended initial oral dosage for monotherapy i milligrams/kilogram/day (mg/kg/day) increasing at 1 week intervals by 5 to 10 mg/kg/week until therapeutic effect is reached. Usually, optimal clinical response is achieved at daily doses belov a satisfactory response has not been obtained, plasma levels should be measured to determine they are in the accepted therapeutic serum range (50 to 100 mcg/mL). Doses above 60 mg/kg/d recommended. Total daily doses of valproic acid exceeding 250 milligrams should be given in 2 (Prod Info DEPAKENE(R) oral capsules, oral syrup, 2006; Prod Info STAVZOR(R) delayed rele 2008) .

2) Conversion to Monotherapy

a) When converting to monotherapy in children 10 years and older, the usual recommended ini 10 to 15 milligrams/kilogram/day (mg/kg/day) increasing at 1 week intervals by 5 to 10 mg/kg/w desired therapeutic effect is reached or adverse effects occur. Usually, optimal clinical response daily doses below 60 mg/kg/day. If a satisfactory response has not been obtained, plasma level measured to determine whether or not they are in the accepted therapeutic serum range (50 to Concomitant antiepilepsy drug dosage may be reduced at the initiation of valproic acid therapy weeks of therapy. The dosage of the concomitant antiepilepsy drug can be reduced by approxi 2 weeks. Valproic acid doses above 60 mg/kg/day are not recommended. Total daily doses of v

exceeding 250 milligrams should be given in 2 to 3 divided doses (Prod Info DEPAKENE(R) ora syrup, 2006; Prod Info STAVZOR(R) delayed release oral capsules, 2008).

3) Adjunctive Therapy

a) In children 10 years and older, the usual recommended oral dosage when adding valproic a regimen is 10 to 15 milligrams/kilogram/day (mg/kg/day), increasing at 1 week intervals by 5 to until the desired therapeutic effect is reached. Usually, optimal clinical response is achieved at 60 mg/kg/day. If a satisfactory response has not been obtained, plasma levels should be measu whether or not they are in the accepted therapeutic serum range (50 to 100 mcg/mL). Doses ab are not recommended. Total daily doses of valproic acid exceeding 250 milligrams should be gi divided doses (Prod Info DEPAKENE(R) oral capsules, oral syrup, 2006; Prod Info STAVZOR(R oral capsules, 2008).

1.4.1.C.1.c Migraine; Prophylaxis

1) Valproic acid 15 to 30 milligrams/kilogram/day divided into 2 doses has been used for the prophy children (Hamalainen, 1998). However, the efficacy has not been confirmed in clinical trials (Prod In delayed release oral capsules, 2008; Prod Info DEPAKOTE(R) ER extended-release oral tablets, 20

1.4.1.C.1.d Seizure, Multiple seizure types; Adjunct

1) In children, 10 years and older, the recommended initial dose is 10 to 15 milligrams/kilogram/day The dose may be increased by 5 to 10 mg/kg/week to achieve optimal clinical response. If total daily 250 mg, give in 2 to 3 divided doses. Maximum daily dose is 60 mg/kg/day or less with a therapeutic 50 to 100 micrograms/milliliter (Prod Info DEPAKENE(R) oral capsules, oral syrup, 2006; Prod Info S delayed release oral capsules, 2008).

e) There is an increased risk of fatal hepatotoxicity in patients under 2 years of age (Prod Info DEPAKEI capsules, oral syrup, 2006; Prod Info STAVZOR(R) delayed release oral capsules, 2008). The safety an delayed-release valproic acid (Stavzor(R)) in patients under 18 years of age for the treatment of acute m with bipolar disorder and for the prophylaxis of migraines have not been established (Prod Info STAVZO release oral capsules, 2008).

1.4.1.C.1.f Withdrawal Schedule

1) The risk factors associated with withdrawal of anticonvulsants in 92 patients who had been free o years with single agent therapy were evaluated. The dose of each anticonvulsant was reduced by 1 2 weeks (1 unit equivalent to 200 milligrams of carbamazepine or valproic acid, or 100 milligrams of mean follow-up period of 26 months (range, 6 to 62 months). Relapse occurred in 31 patients, with 6 remaining free of seizures (relapse rate 33.7%) (Callaghan et al, 1988).

1.4.1.C.2 Rectal route

a) The bioavailability of diluted valproic acid syrup given rectally is comparable to that following oral adm are, therefore, the same for rectal or oral administration. Rectal administration of valproic acid syrup app alternative to oral administration when the oral route is not available (Cloyd & Kriel, 1981).

b) Rectal administration of valproic acid has been successful in the treatment of intractable status epilep Commercially available valproic acid syrup (Depakene(R) 250 mg/5 mL) was diluted 1:1 with tap water a retention enema in a loading dose of 10 to 20 milligrams/kilogram. Maintenance doses were started 8 ho initial loading dose (10 to 15 milligrams/kilogram every 8 hours. Five of 7 children (mean age, 7.7 years) seizures within 24 hours after starting rectal therapy. Duration of therapy ranged from 1 to 8 days (mean authors suggest that loading doses of 20 milligrams/kilogram be administered which will attain plasma le approximately 50 mcg/mL. Marked increases in aspartate aminotransferase activity occurred in 3 of the requiring cessation of valproic acid therapy (Snead & Miles, 1985).

c) The successful use of rectal anticonvulsants was described as an alternative route to oral drug therap seizures undergoing gastrointestinal surgery. Perioperative rectal therapy was employed for clonazepam valproate (retention enema in tap water or saline), and given until the patients could again receive oral m duration of use was generally 48 to 72 hours. All patients maintained excellent seizure control without to rectally administered preparations (Woody et al, 1989).

1.4.2 Dosage in Renal Failure

A) Valproic Acid

1) Renal excretion of sodium valproate as the unchanged drug is 1.8% (Hardman et al, 1996a). A 27% reduc unbound clearance of valproate has been reported in patients with a creatinine clearance of less than 10 milli however, hemodialysis typically decreases valproate concentrations by about 20%. Therefore, dosage adjust unnecessary in patients with renal failure. Monitoring total concentrations of valproic acid may be misleading renal failure because protein binding in these patients is significantly reduced (Prod Info DEPAKENE(R) oral syrup, 2006; Prod Info STAVZOR(R) delayed release oral capsules, 2008).

B) Divalproex Sodium

1) Dose adjustments are not required in renal failure (Prod Info DEPAKOTE(R) ER extended-release oral tal Bennett et al, 1994). However, increased free levels of valproic acid have been reported and monitoring of to may be misleading (Lapierre et al, 1999). Renal excretion of sodium valproate as the unchanged drug is 1.8% 1996a). A 27% reduction in the unbound clearance of valproate has been reported in patients with a creatinir less than 10 milliliters/minute (Prod Info DEPAKOTE(R) ER extended-release oral tablets, 2008).

C) Valproate Sodium

1) Renal excretion of SODIUM VALPROATE as the unchanged drug is 1.8% (Hardman et al, 1996a). A 27% unbound clearance of valproate has been reported in patients with a creatinine clearance of less than 10 milli Dosage adjustments are not required in renal failure (Prod Info Depakote(R) Tablets, 2002a; Bennett et al, 19 increased free levels of valproic acid have been reported and monitoring of total concentrations may be misle al, 1999).

1.4.3 Dosage in Hepatic Insufficiency

A) Valproic Acid

1) Valproic acid should not be administered to patients with hepatic disease or significant hepatic insufficienc impairs the capacity to eliminate valproate. In one study, the clearance of free valproate was decreased by 5(cirrhosis and by 16% in patients with acute hepatitis. Patients with liver disease have decreased albumin con larger unbound fractions by a 2 to 2.6 fold increase. Monitoring of total concentrations may be misleading sin concentrations may be significantly elevated in patients with hepatic disease, with total concentrations appea (Prod Info DEPAKENE(R) oral capsules, oral syrup, 2006; Prod Info STAVZOR(R) delayed release oral caps

B) Divalproex Sodium

1) Divalproex sodium should not be administered to patients with hepatic disease or significant hepatic insuf disease impairs the capacity to eliminate valproate. In one study, the clearance of free valproate was decreas patients with cirrhosis and by 16% in patients with acute hepatitis. Patients with liver disease have decreased concentrations and larger unbound fractions by a 2- to 2.6-fold increase. Monitoring of total concentrations m (Prod Info DEPAKOTE(R) ER extended-release oral tablets, 2008; Prod Info DEPAKOTE(R) sprinkle oral ca Info DEPAKOTE(R) delayed-release oral tablets, 2006).

C) Valproate Sodium

1) VALPROIC ACID or DIVALPROEX should not be administered to patients with hepatic disease or signific insufficiency (Prod Info Depakene(R), 1999; Prod Info Depakote(R), 1999). Liver disease impairs the capacity valproate. In one study, the clearance of free valproate was decreased by 50% in patients with cirrhosis and with acute hepatitis. Patients with liver disease have decreased albumin concentrations and larger unbound f 2.6 fold increase. Monitoring of total concentrations may be misleading.

1.4.4 Dosage Adjustment During Dialysis

A) Valproic Acid

1) Hemodialysis typically reduces valproate concentrations by about 20%, but a 27% reduction in the unbou valproate has been reported in patients with a creatinine clearance of less than 10 milliliters/minute. Therefor supplementation is required in patients following hemodialysis, peritoneal dialysis, or continuous arteriovenou Monitoring total concentrations of valproic acid may be misleading in patients with renal failure because prote patients is significantly reduced (Prod Info DEPAKENE(R) oral capsules, oral syrup, 2006; Prod Info STAVZO release oral capsules, 2008).

B) Divalproex Sodium

1) No dosage supplementation is required in patients following hemodialysis, peritoneal dialysis, or continuo hemofiltration (Bennett et al, 1994). Hemodialysis typically reduces valproate concentrations by about 20% a is substantially reduced. Monitoring total concentrations may be misleading (Prod Info DEPAKOTE(R) ER ex oral tablets, 2008).

C) Valproate Sodium

1) No dosage supplementation is required in patients following hemodialysis, peritoneal dialysis, or continuo hemofiltration (Prod Info Depakote(R) Tablets, 2002a; Bennett et al, 1994). Hemodialysis typically reduces va concentrations by about 20% and protein binding is substantially reduced. Monitoring total concentrations ma (Prod Info Depakote(R) Tablets, 2002a).

2.0 Pharmacokinetics

Onset and Duration

Drug Concentration Levels

ADME

2.1 Onset and Duration

A) Onset

1) Peak Response

a) Epilepsy, oral: 2 weeks (Lance & Anthony, 1977a; Lance & Anthony, 1977b).

2.2 Drug Concentration Levels

A) Therapeutic Drug Concentration

1) Epilepsy, 50 to 100 mcg/mL (Prod Info STAVZOR(R) delayed release oral capsules, 2008)(Prod Info Depaken Info Depakote(R), Tablets 2003; Prod Info Depacon(R), 1999)(Turnbull et al, 1983a; Rimmer & Richens, 1985d).

a) A free concentration therapeutic range has not been established (Prod Info Depakene(R), 1999).

b) High concentration valproic acid (80 to 150 mcg/mL) may be needed to reduce seizure frequency of some seizures and secondarily generalized tonic-clonic seizures (Beydoun et al, 1997d).

c) Plasma concentrations fluctuate between doses, varying between 100% and 140% of the steady state co (Schobben et al, 1975a; Loiseau et al, 1975).

d) Comparable plasma levels occur when switching from oral valproate to intravenous valproate sodium (Pro (R), 1999).

2) Acute mania, 50 to 125 mcg/mL (Prod Info STAVZOR(R) delayed release oral capsules, 2008)(Prod Info Depa 2003).

B) Peak Concentration

1) When a single dose of valproic acid delayed release 500 milligram (mg) oral capsules was compared to a sing divalproex sodium delayed release 500 mg oral tablets under fasted conditions, similar plasma concentration-time noted with the exception of median Tmax, which occurred earlier with the delayed release capsules (2 hours vers When valproic acid delayed release capsules were administered with food, there was a 23% decrease in Cmax o median Tmax was increased to 4.8 hours (Prod Info STAVZOR(R) delayed release oral capsules, 2008).

C) Time to Peak Concentration

1) Oral, valproic acid delayed-release capsules, single 500-mg dose, fasted: 2 hr (Prod Info STAVZOR(R) delaye capsules, 2008)

a) When a single dose of valproic acid delayed release 500 milligram (mg) oral capsules was compared to a divalproex sodium delayed release 500 mg oral tablets under fasted conditions, similar plasma concentration noted with the exception of median Tmax, which occurred earlier with the delayed release capsules (2 hours (Prod Info STAVZOR(R) delayed release oral capsules, 2008).

2) Oral, valproic acid delayed-release capsules, single 500-mg dose, with food: 4.8 hr (Prod Info STAVZOR(R) d capsules, 2008)

a) When a single dose of valproic acid delayed release 500 milligram capsules was administered with food, t decrease in Cmax of valproic acid and median Tmax was increased to 4.8 hours compared with administratio state (Prod Info STAVZOR(R) delayed release oral capsules, 2008).

3) Oral, valproic acid capsules (Depakene(R)): 1 to 4 hours (Prod Info Depakene(R), 1999)(Hardman et al, 1996)

4) Oral, divalproex tablet: 4 to 8 hours (Prod Info Depakote(R) Tablets, 2002; Oelkers et al, 1977).

5) Oral, divalproex sprinkle capsule: 3.3 to 4.8 (Prod Info Depakote(R) Sprinkle Capsules, 1999).

6) Oral, divalproex sodium extended-release tablet: 4 - 17 hours (Prod Info Depakote(R) ER, 2003m)

a) When a single dose of valproic acid delayed release 500 milligram (mg) oral capsules was compared to a divalproex sodium delayed release 500 mg oral tablets under fasted conditions, similar plasma concentration noted with the exception of median Tmax, which occurred earlier with the delayed release capsules (2 hours (Prod Info STAVZOR(R) delayed release oral capsules, 2008).

b) Maximum valproate plasma concentration (Cmax) of divalproex sodium extended-release tablets at stead relative to divalproex sodium delayed-release tablets given twice a day (Prod Info Depakote(R) ER, 2003m).

7) Oral, sodium valproate solution: 1.2 hours (Klotz & Antonin, 1977).

8) Intravenous, Depacon(R): At the end of a 1 hour infusion (Prod Info Depacon(R), 1999).

9) Rectal, diluted valproic acid syrup: 3.1 hours (Holmes et al, 1989).

D) Area Under the Curve

1) When a single dose of valproic acid delayed release 500 milligram (mg) oral capsules was compared to a sing divalproex sodium delayed release 500 mg oral tablets under fasted conditions, the plasma concentration-time pr in terms of valproic acid. Coadministration with food did not alter systemic exposure of valproic acid (Prod Info ST delayed release oral capsules, 2008).

2) Equivalent areas under the curve were achieved at steady state, when divalproex sodium tablets and valproat given as a one hour infusion, were administered at 250 mg every 6 hours for 4 days (Prod Info Depacon(R), 1999

3) The area under the curve and the maximum concentration resulting from a valproate sodium injection 500 mg and a 500 mg dose of valproic acid syrup were equivalent (Prod Info Depacon(R), 1999).

4) When extended release divalproex sodium tablets (Depakote(R) ER) are administered once daily in doses 8 t the total daily dose of delayed release divalproex sodium tablets (Depakote(R) Tablets), equivalent areas under t achieved (Prod Info Depakote(R) ER, 2003m).

2.3 ADME

Absorption

Distribution

Metabolism

Excretion

Elimination Half-life

Extracorporeal Elimination

2.3.1 Absorption

A) Bioavailability

1) Oral, extended-release tablets: 90% (Prod Info Depakote(R) ER, 2003m)

a) The absolute bioavailability of divalproex sodium extended- release tablet administered as a single do was approximately 90% relative to intravenous infusion (Prod Info Depakote(R) ER, 2003m).

b) Divalproex sodium extended-release tablets given on an empty stomach produced an average bioava 89% relative to divalproex sodium delayed-release tablets given twice a day (Prod Info Depakote(R) ER,

B) Effects of Food

1) No significant effect on systemic availability (Prod Info STAVZOR(R) delayed release oral capsules, 2008)

a) When a single dose of valproic acid delayed release 500 milligram capsules was administered with fo 23% decrease in Cmax of valproic acid and median Tmax was increased from 2 to 4.8 hours compared v under a fasted state but there was no change in systemic exposure (Prod Info STAVZOR(R) delayed rel capsules, 2008).

b) Coadministration of oral valproate products with food is not expected to have any significant clinical e management of patients with epilepsy (Prod Info STAVZOR(R) delayed release oral capsules, 2008).

2.3.2 Distribution

A) Distribution Sites

1) Protein Binding

a) 90% (primarily to albumin) (Prod Info Depakene(R), 1999) (Prod Info STAVZOR(R) delayed release o 2008; Prod Info Depakote(R) Tablets, 2002; Hardman et al, 1996; Klotz & Antonin, 1977).

1) Protein binding is concentration-dependent and decreases at high valproate concentrations (Pro (R), 1999). Free fraction plasm protein concentration increases from approximately 10% at 40 mcg/m mcg/mL (Prod Info STAVZOR(R) delayed release oral capsules, 2008; Prod Info Depakote(R) ER, 2

2) Plasma protein binding decreased in the elderly resulting in an increase in the free fraction by 44 Depakote(R) ER Tablets, 2003)(Rimmer & Richens, 1985d). Liver disease is associated with 2 to 2.5 unbound valproate (Prod Info STAVZOR(R) delayed release oral capsules, 2008)(Prod Info Depako 2003)(Klotz et al, 1978a). Plasma protein binding is also decreased in patients with renal disease (L (Marbury et al, 1980; Gugler & Mueller, 1978), in hyperlipidemic patients (Prod Info Depakote(R) ER and in the presence of other drugs such as aspirin (Prod Info STAVZOR(R) delayed release oral cap Conversely, valproate may displace other protein-bound medications such as phenytoin, carbamaze tolbutamide (Prod Info STAVZOR(R) delayed release oral capsules, 2008).

3) A 108% increase in free valproic acid was observed in the sera of patients with HIV (Dasgupta &

2) Tissues and Fluids

a) CEREBROSPINAL FLUID, 10% (Prod Info STAVZOR(R) delayed release oral capsules, 2008; Pinde

1) Valproate concentration in cerebrospinal fluid is approximately 10% of the total concentration (Pr (R) delayed release oral capsules, 2008).

B) Distribution Kinetics

1) Volume of Distribution

a) 0.14 to 0.23 L/kg (Puentas et al, 1999)(Bennett et al, 1994a).

1) Differences in volume of distribution occur between young and elderly (0.13 and 0.19 L/kg, respe et al, 1984; Bryson et al, 1983).

2) The volume of distribution for total valproate is 11 L/1.73 m(2), free valproate is 92 L/1.73 m(2) (F STAVZOR(R) delayed release oral capsules, 2008; Prod Info Depakote(R) ER, 2003m).

2.3.3 Metabolism

A) Metabolism Sites and Kinetics

1) Liver, rapidly and extensively (Prod Info STAVZOR(R) delayed release oral capsules, 2008)(Prod Info De (Prod Info Depakote(R) Tablets, 2002).

a) Valproate undergoes conjugation (30% to 50%), mitochondrial beta oxidation (40%), and microsomal numerous metabolites (15% to 20%). Less than 3% of an administered dose is excreted unchanged in th STAVZOR(R) delayed release oral capsules, 2008; Prod Info Depakote(R) ER, 2003m); (Prod Info Depa (Prod Info Depakote(R) Tablets, 2002).

b) A cytochrome P450 microsomal enzyme appears to metabolize valproic acid (Zaccara et al, 1988).

B) Metabolites

1) 2-propyl-3-keto-pentanoic acid, activity unknown (Prod Info Depakene(R), 1999)(Prod Info Depakote(R) T

2) 2-propyl-hydroxypentanoic acids, activity unknown (Prod Info Depakene(R), 1999)(Prod Info Depakote(R)

a) Approximately 70% of a dose is excreted as the glucuronide (Nau & Loscher, 1984; Loscher, 1981; B 1979).

2.3.4 Excretion

A) Kidney

1) Renal Clearance (rate)

a) Total valproate, adults: 0.56 L/hr/1.73 square meter (Prod Info STAVZOR(R) delayed release oral cap

b) Free valproate, adults: 4.6 L/hr/1.73 square meter (Prod Info STAVZOR(R) delayed release oral caps

2) Renal Excretion (%)

a) 70% to 80% (Bruni & Wilder, 1979; Schobben et al, 1975a).

b) In adult patients on monotherapy, 30% to 50% of an administered dose appears in the urine as glucu (Prod Info STAVZOR(R) delayed release oral capsules, 2008).

c) Less than 3% of an administered dose of valproate is excreted unchanged in the liver total valproate, square meter (Prod Info STAVZOR(R) delayed release oral capsules, 2008).

B) Bile

1) Bile, 7% (Pinder et al, 1977d).

C) Other

1) TOTAL PLASMA CLEARANCE

a) 0.9 L/hr (Puentes et al, 1999).

1) Clearance decreases with increasing age (Snachez-Alcaraz et al, 1998). Clearances in specific a found to be: 24.5 ml/kg/hr for less than 2 years old, 19.9 ml/kg/hr for 2 to 4 years old, 12.7 ml/kg/hr f years old.

2) Children between 3 months and 10 years have 50% higher clearance rates when compared to a the age of 10, pharmacokinetic parameters of children are similar to those of adults (Prod Info STAV release oral capsules, 2008).

3) Intrinsic clearance in the elderly (age ranged from 68 to 89 years) is reduced by 39% and free fra by 44% when compared with young adults (age ranged from 22 to 26 years) (Prod Info STAVZOR(R oral capsules, 2008; Prod Info Depakote(R) ER, 2003m).

4) Clearance is increased by 10% with coadministration of phenobarbital (Yukawa et al, 1997a).

5) Clearance is increased by coadministration of carbamazepine (dose-related) (Yukawa et al, 199

6) There are no differences in the body surface area adjusted unbound clearance between male an L/hr/1.73 m(2) and 4.7 L/hr/1.73 m(2), respectively) (Prod Info Depakote(R) ER, 2003m). However, clearance in female patients is 10% less than in male patients (Yukawa et al, 1997a).

7) Clearance of free valproate is decreased in patients with liver disease. One study demonstrated clearance in 7 patients with cirrhosis and a 16% decrease in clearance in 4 patients with acute hepa 6 healthy subjects (Prod Info STAVZOR(R) delayed release oral capsules, 2008; Prod Info Depakot 2002).

8) There is a 27% decrease in the unbound clearance of valproate in patients with a creatinine clea mL/minute (Prod Info STAVZOR(R) delayed release oral capsules, 2008)(Prod Info Depakote(R) EF

2) OTHER EXCRETION

a) Lung, 2 to 18% (Pinder et al, 1977d).

1) Excreted in expired air as carbon dioxide (Pinder et al, 1977d).

2.3.5 Elimination Half-life

A) Parent Compound

1) Adults: 6 to 17 hours (Prod Info STAVZOR(R) delayed release oral capsules, 2008)(Prod Info Depakene(R et al, 1996; Rimmer & Richens, 1985d; Perucca et al, 1984; Bryson et al, 1983).

a) The mean terminal half-life for valproate monotherapy ranged from 9 to 16 hours following oral dosing to 1000 milligrams (Prod Info STAVZOR(R) delayed release oral capsules, 2008).

b) In one study, the half life of valproate was increased from 12 to 18 hours in patients with liver disease Depakote(R) Tablets, 2002).

2) Adults, liver disease: 18 hours (Prod Info STAVZOR(R) delayed release oral capsules, 2008)

a) Compared with 6 healthy subjects, the half-life of valproate in patients with liver disease increased fro in one study involving 7 patients with cirrhosis and 4 patients with acute hepatitis (Prod Info STAVZOR(R oral capsules, 2008; Prod Info Depakote(R) Tablets, 2002).

3) Neonates less than 10 days old: 10 to 67 hours (Prod Info STAVZOR(R) delayed release oral capsules, 2

a) Children within the first 2 months of life have decreased ability to eliminate valproate compared to old adults. This is due to reduced clearance and increased volume of distribution (Prod Info STAVZOR(R) de capsules, 2008).

4) Neonates greater than 2 months old: 7 to 13 hours (Prod Info STAVZOR(R) delayed release oral capsules

a) Children within the first 2 months of life have decreased ability to eliminate valproate compared to old adults. This is due to reduced clearance and increased volume of distribution (Prod Info STAVZOR(R) de capsules, 2008).

2.3.6 Extracorporeal Elimination

A) Hemodialysis

1) Dialyzable: Yes (Prod Info STAVZOR(R) delayed release oral capsules, 2008; Johnson et al, 1999); (Frar (Marbury et al, 1980).

a) Hemodialysis of 4 hours duration removed 15% to 22% of valproic acid in chronic renal failure patient 1980).

b) Acute valproic acid overdose (serum concentration greater than 1200 mcg/mL) in a 25-year-old woma suicide attempts was successfully treated with high-flux hemodialysis using a highly permeable polysulfo membrane. High- flux hemodialysis was performed for 4 hours and lowered the valproic acid half-life to 2 increased the calculated elimination rate constant to 0.2522 h(-1). The authors concluded that high-flux h as effective as combination hemodialysis and charcoal hemoperfusion and avoided the attendant risks o hemoperfusion (Kane et al, 2000).

c) A 43-year-old woman who ingested approximately 19 grams of valproic acid had 15.5 grams removed hemodialysis (high-flux polysulfone hemodialysis membrane) (Johnson et al, 1999). Her valproic acid se

decreased from 940 to 164 micrograms/milliliter. The half-life of valproic acid was reduced from 7.2 to 2.

B) Peritoneal

1) Dialyzable: Yes (Orr et al, 1983).

a) In a 9-year-old boy receiving chronic peritoneal dialysis, only an average of 4.5% of the valproic acid over 12- or 24-hour dialysis periods (Orr et al, 1983).

C) Hemoperfusion

1) Dialyzable: Yes (Franssen et al, 1999).

a) A 27-year-old male was successfully treated with serial hemodialysis, and hemoperfusion with resin a following a valproic acid overdose (Franssen et al, 1999). The patient was dialyzed during two 3-hour se highly permeable polysulfone hemodialysis membrane. A charcoal hemoperfusion column was added dc first session and a resin column for the second. The hemodialysis was effective while the hemofiltration v in the first hour. This was due to rapid saturation of the column. The resin column appeared to be more e charcoal.

3.0 Cautions

Contraindications

Precautions

Adverse Reactions

Teratogenicity/Effects in Pregnancy/Breastfeeding

Drug Interactions

3.0.A Black Box WARNING

1) Valproic Acid

a) Oral (Syrup; Capsule, Liquid Filled)

Hepatotoxicity

Hepatic failure resulting in fatalities has occurred in patients receiving valproic acid and its derivatives. E indicated that children under the age of two years are at a considerably increased risk of developing fata especially those on multiple anticonvulsants, those with congenital metabolic disorders, those with sever accompanied by mental retardation, and those with organic brain disease. When valproic acid is used in they should be used with extreme caution and as a sole agent. The benefits of therapy should be weighe risks. Above this age group, experience in epilepsy has indicated that the incidence of fatal hepatotoxicit considerably in progressively older patient groups.

These incidents usually have occurred during the first six months of treatment. Serious or fatal hepatoto preceded by non-specific symptoms such as malaise, weakness, lethargy, facial edema, anorexia, and v patients with epilepsy, a loss of seizure control may also occur. Patients should be monitored closely for these symptoms. Liver function tests should be performed prior to therapy and at frequent intervals there during the first six months.

Pancreatitis

Cases of life-threatening pancreatitis have been reported in both children and adults receiving valproate. cases have been described as hemorrhagic with a rapid progression from initial symptoms to death. Cas reported shortly after initial use as well as after several years of use. Patients and guardians should be w abdominal pain, nausea, vomiting, and/or anorexia can be symptoms of pancreatitis that require prompt evaluation. If pancreatitis is diagnosed, valproate should ordinarily be discontinued. Alternative treatmen medical condition should be initiated as clinically indicated.

Teratogenicity

Valproate can produce teratogenic effects such as neural tube defects (eg, spina bifida). Accordingly, the products in women of childbearing potential requires that the benefits of its use be weighed against the r fetus. This is especially important when the treatment of a spontaneously reversible condition not ordinar permanent injury or risk of death (eg, migraine) is contemplated (Prod Info DEPACON(R) IV injection, 20 DEPAKENE(R) oral capsules, syrup, 2006; Prod Info DEPAKOTE(R) delayed-release oral tablets, 2006; DEPAKOTE(R) ER extended-release tablet, 2006; Prod Info DEPAKOTE(R) sprinkle oral capsules, 200

b) Oral (Capsule, Delayed Release)

Hepatotoxicity

Hepatic failure resulting in fatalities has occurred in patients receiving valproic acid and its derivatives. C age of two years are at a considerably increased risk of developing fatal hepatotoxicity, especially those anticonvulsants, those with congenital metabolic disorders, those with severe seizure disorders accompa retardation, and those with organic brain disease. When valproic acid is used in this patient group, it sho extreme caution and as a sole agent. The benefits of therapy should be weighed against the risks. The ir hepatotoxicity decreases considerably in progressively older patient groups.

These incidents usually have occurred during the first six months of treatment. Serious or fatal hepatoto

preceded by non-specific symptoms such as malaise, weakness, lethargy, facial edema, anorexia, and v
patients with epilepsy, a loss of seizure control may also occur. Patients should be monitored closely for
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reported shortly after initial use as well as after several years of use. Patients and guardians should be w
abdominal pain, nausea, vomiting and/or anorexia can be symptoms of pancreatitis that require prompt r
If pancreatitis is diagnosed, valproate should ordinarily be discontinued. Alternative treatment for the unc
condition should be initiated as clinically indicated (Prod Info STAVZOR(R) delayed release oral capsule

2) Divalproex Sodium

a) Oral (Tablet, Enteric Coated; Tablet, Extended Release; Capsule, Delayed Release)

Hepatotoxicity

Hepatic failure resulting in fatalities has occurred in patients receiving valproic acid and its derivatives. C
age of two years are at a considerably increased risk of developing fatal hepatotoxicity, especially those
anticonvulsants, those with congenital metabolic disorders, those with severe seizure disorders accompa
retardation, and those with organic brain disease. When divalproex sodium is used in this patient group,
with extreme caution and as a sole agent. The benefits of therapy should be weighed against the risks. T
fatal hepatotoxicity decreases considerably in progressively older patient groups.

These incidents usually have occurred during the first six months of treatment. Serious or fatal hepatotox
preceded by non-specific symptoms such as malaise, weakness, lethargy, facial edema, anorexia, and v
patients with epilepsy, a loss of seizure control may also occur. Patients should be monitored closely for
these symptoms. Liver function tests should be performed prior to therapy and at frequent intervals there
during the first six months.

Teratogenicity

Valproate can produce teratogenic effects such as neural tube defects (eg, spina bifida). Accordingly, the
sodium in women of childbearing potential requires that the benefits of its use be weighed against the ris
fetus. This is especially important when the treatment of a spontaneously reversible condition not ordinar
permanent injury or risk of death (eg, migraine) is contemplated.

An information sheet describing the teratogenic potential of valproate is available for patients.

Pancreatitis

Cases of life-threatening pancreatitis have been reported in both children and adults receiving valproate.
cases have been described as hemorrhagic with a rapid progression from initial symptoms to death. Cas
reported shortly after initial use as well as after several years of use. Patients and guardians should be w
abdominal pain, nausea, vomiting, and/or anorexia can be symptoms of pancreatitis that require prompt
evaluation. If pancreatitis is diagnosed, valproate should ordinarily be discontinued. Alternative treatmen
medical condition should be initiated as clinically indicated (Prod Info DEPAKOTE(R) sprinkle oral capsu
Info DEPAKOTE(R) ER extended-release oral tablets, 2008).

3) Valproate Sodium

a) Intravenous (Solution)

HEPATOTOXICITY

Hepatic failure resulting in fatalities has occurred in patients receiving valproic acid and its derivatives. E
indicated that children under the age of two years are at a considerably increased risk of developing fata
especially those on multiple anticonvulsants, those with congenital metabolic disorders, those with sever
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These incidents usually have occurred during the first six months of treatment. Serious or fatal hepatotox
preceded by non-specific symptoms such as malaise, weakness, lethargy, facial edema, anorexia, and v
patients with epilepsy, a loss of seizure control may also occur. Patients should be monitored closely for
these symptoms. Liver function tests should be performed prior to therapy and at frequent intervals there
during the first six months(Prod Info DEPACON(R) IV injection, 2006).

PANCREATITIS

Cases of life-threatening pancreatitis have been reported in both children and adults receiving valproate.
cases have been described as hemorrhagic with a rapid progression from initial symptoms to death. Cas
reported shortly after initial use as well as after several years of use. Patients and guardians should be w
abdominal pain, nausea, vomiting, and/or anorexia can be symptoms of pancreatitis that require prompt
evaluation. If pancreatitis is diagnosed, valproate should ordinarily be discontinued. Alternative treatmen
medical condition should be initiated as clinically indicated (Prod Info DEPACON(R) IV injection, 2006).

TERATOGENICITY

Valproate can produce teratogenic effects such as neural tube defects (eg, spina bifida). Accordingly, the

products in women of childbearing potential requires that the benefits of its use be weighed against the r
fetus. This is especially important when the treatment of a spontaneously reversible condition not ordinar
permanent injury or risk of death (eg, migraine) is contemplated (Prod Info DEPACON(R) IV injection, 20

3.1 Contraindications

A) Valproic Acid

1) hepatic disease or significant hepatic dysfunction (Prod Info STAVZOR(R) delayed release oral capsules, 200
DEPACON(R) IV injection, 2006; Prod Info DEPAKENE(R) oral capsules, syrup, 2006; Prod Info DEPAKOTE(R)
oral tablets, 2006; Prod Info DEPAKOTE(R) ER extended-release tablet, 2006; Prod Info DEPAKOTE(R) sprinkle
2003)

2) hypersensitivity to sodium valproate, divalproex sodium, or valproic acid (Prod Info STAVZOR(R) delayed rele
2008; Prod Info DEPACON(R) IV injection, 2006; Prod Info DEPAKENE(R) oral capsules, syrup, 2006; Prod Info
delayed-release oral tablets, 2006; Prod Info DEPAKOTE(R) ER extended-release tablet, 2006; Prod Info DEPAK
oral capsules, 2003)

3) urea cycle disorders, known; hyperammonemic encephalopathy, including fatalities, has occurred (Prod Info S
delayed release oral capsules, 2008; Prod Info DEPACON(R) IV injection, 2006; Prod Info DEPAKENE(R) oral ca
2006; Prod Info DEPAKOTE(R) delayed-release oral tablets, 2006; Prod Info DEPAKOTE(R) ER extended-releas
Prod Info DEPAKOTE(R) sprinkle oral capsules, 2003)

B) Divalproex Sodium

1) hepatic disease or significant hepatic dysfunction (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008; Proc
(R) ER extended-release oral tablets, 2008)

2) hypersensitivity to divalproex sodium (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008; Prod Info DEPAK
extended-release oral tablets, 2008)

3) urea cycle disorders (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008; Prod Info DEPAKOTE(R) ER exte
tablets, 2008)

C) Valproate Sodium

1) hepatic disease or significant hepatic dysfunction (Prod Info DEPACON(R) IV injection, 2006)

2) hypersensitivity to valproate sodium, valproic acid, or divalproex sodium (Prod Info DEPACON(R) IV injection,

3) known urea cycle disorders; hyperammonemic encephalopathy, including fatalities, has occurred (Prod Info DI
injection, 2006)

3.2 Precautions

A) Valproic Acid

1) children, especially under the age of 2 years; increased risk of hepatotoxicity; discontinue immediately if signifi
dysfunction occurs (Prod Info STAVZOR(R) delayed release oral capsules, 2008; Prod Info DEPACON(R) IV inje
Info DEPAKENE(R) oral capsules, syrup, 2006; Prod Info DEPAKOTE(R) delayed-release oral tablets, 2006; Proc
(R) ER extended-release tablet, 2006; Prod Info DEPAKOTE(R) sprinkle oral capsules, 2003)

2) concurrent use of multiple anticonvulsants; increased risk of hepatotoxicity; discontinue immediately if significa
dysfunction occurs (Prod Info STAVZOR(R) delayed release oral capsules, 2008; Prod Info DEPACON(R) IV inje
Info DEPAKENE(R) oral capsules, syrup, 2006; Prod Info DEPAKOTE(R) delayed-release oral tablets, 2006; Proc
(R) ER extended-release tablet, 2006; Prod Info DEPAKOTE(R) sprinkle oral capsules, 2003)

3) hepatic disease, prior history of; increased risk of hepatotoxicity; discontinue immediately if significant hepatic
(Prod Info STAVZOR(R) delayed release oral capsules, 2008; Prod Info DEPACON(R) IV injection, 2006; Prod In
oral capsules, syrup, 2006; Prod Info DEPAKOTE(R) delayed-release oral tablets, 2006; Prod Info DEPAKOTE(R
release tablet, 2006; Prod Info DEPAKOTE(R) sprinkle oral capsules, 2003)

4) metabolic disorders, congenital; increased risk of hepatotoxicity; discontinue immediately if significant hepatic
(Prod Info STAVZOR(R) delayed release oral capsules, 2008; Prod Info DEPACON(R) IV injection, 2006; Prod In
oral capsules, syrup, 2006; Prod Info DEPAKOTE(R) delayed-release oral tablets, 2006; Prod Info DEPAKOTE(R
release tablet, 2006; Prod Info DEPAKOTE(R) sprinkle oral capsules, 2003)

5) organic brain disease; increased risk of hepatotoxicity; discontinue immediately if significant hepatic dysfunctio
Info STAVZOR(R) delayed release oral capsules, 2008; Prod Info DEPACON(R) IV injection, 2006; Prod Info DEP
capsules, syrup, 2006; Prod Info DEPAKOTE(R) delayed-release oral tablets, 2006; Prod Info DEPAKOTE(R) ER
tablet, 2006; Prod Info DEPAKOTE(R) sprinkle oral capsules, 2003)

6) pancreatitis, sometimes life-threatening, may occur; discontinuation is recommended (Prod Info STAVZOR(R)
oral capsules, 2008; Prod Info DEPACON(R) IV injection, 2006; Prod Info DEPAKENE(R) oral capsules, syrup, 20
DEPAKOTE(R) delayed-release oral tablets, 2006; Prod Info DEPAKOTE(R) ER extended-release tablet, 2006; P
DEPAKOTE(R) sprinkle oral capsules, 2003)

7) pregnancy; increased risk of birth defects (Prod Info STAVZOR(R) delayed release oral capsules, 2008; Prod
IV injection, 2006; Prod Info DEPAKENE(R) oral capsules, syrup, 2006; Prod Info DEPAKOTE(R) delayed-releas
2006; Prod Info DEPAKOTE(R) ER extended-release tablet, 2006; Prod Info DEPAKOTE(R) sprinkle oral capsule

8) seizure disorders, severe and accompanied by mental retardation; increased risk of hepatotoxicity; discontinue
significant hepatic dysfunction occurs (Prod Info STAVZOR(R) delayed release oral capsules, 2008; Prod Info DE
injection, 2006; Prod Info DEPAKENE(R) oral capsules, syrup, 2006; Prod Info DEPAKOTE(R) delayed-release o
Prod Info DEPAKOTE(R) ER extended-release tablet, 2006; Prod Info DEPAKOTE(R) sprinkle oral capsules, 200

9) abrupt discontinuation in epileptic patients; may precipitate status epilepticus (Prod Info STAVZOR(R) delayed
capsules, 2008; Prod Info DEPACON(R) IV injection, 2006; Prod Info DEPAKENE(R) oral capsules, syrup, 2006;
DEPAKOTE(R) delayed-release oral tablets, 2006; Prod Info DEPAKOTE(R) ER extended-release tablet, 2006; P
DEPAKOTE(R) sprinkle oral capsules, 2003)

10) acute head trauma; IV use is not recommended for prophylaxis of post-traumatic seizures (Prod Info DEPAC 2006)
11) ataxia; possible undiagnosed urea cycle disorder, which is a contraindication (Prod Info STAVZOR(R) delaye capsules, 2008; Prod Info DEPACON(R) IV injection, 2006; Prod Info DEPAKENE(R) oral capsules, syrup, 2006; DEPAKOTE(R) delayed-release oral tablets, 2006; Prod Info DEPAKOTE(R) ER extended-release tablet, 2006; F DEPAKOTE(R) sprinkle oral capsules, 2003)
12) cyclical vomiting and lethargy; possible undiagnosed urea cycle disorder, which is a contraindication (Prod In delayed release oral capsules, 2008; Prod Info DEPACON(R) IV injection, 2006; Prod Info DEPAKENE(R) oral ca 2006; Prod Info DEPAKOTE(R) delayed-release oral tablets, 2006; Prod Info DEPAKOTE(R) ER extended-releas Prod Info DEPAKOTE(R) sprinkle oral capsules, 2003)
13) elderly; increased incidence of somnolence, especially in the presence of reduced nutritional intake and weig STAVZOR(R) delayed release oral capsules, 2008; Prod Info DEPACON(R) IV injection, 2006; Prod Info DEPAKI capsules, syrup, 2006; Prod Info DEPAKOTE(R) delayed-release oral tablets, 2006; Prod Info DEPAKOTE(R) ER tablet, 2006; Prod Info DEPAKOTE(R) sprinkle oral capsules, 2003)
14) elevated plasma ammonia or glutamine, history of; possible undiagnosed urea cycle disorder, which is a cont Info STAVZOR(R) delayed release oral capsules, 2008; Prod Info DEPACON(R) IV injection, 2006; Prod Info DEI capsules, syrup, 2006; Prod Info DEPAKOTE(R) delayed-release oral tablets, 2006; Prod Info DEPAKOTE(R) ER tablet, 2006; Prod Info DEPAKOTE(R) sprinkle oral capsules, 2003)
15) encephalopathy, history of unexplained encephalopathy or coma, encephalopathy associated with a protein l related or postpartum encephalopathy; possible undiagnosed urea cycle disorder, which is a contraindication (Pro (R) delayed release oral capsules, 2008; Prod Info DEPACON(R) IV injection, 2006; Prod Info DEPAKENE(R) ora 2006; Prod Info DEPAKOTE(R) delayed-release oral tablets, 2006; Prod Info DEPAKOTE(R) ER extended-releas Prod Info DEPAKOTE(R) sprinkle oral capsules, 2003)
16) family history of urea cycle disorders; possible undiagnosed urea cycle disorder, which is a contraindication (STAVZOR(R) delayed release oral capsules, 2008; Prod Info DEPACON(R) IV injection, 2006; Prod Info DEPAKI capsules, syrup, 2006; Prod Info DEPAKOTE(R) delayed-release oral tablets, 2006; Prod Info DEPAKOTE(R) ER tablet, 2006; Prod Info DEPAKOTE(R) sprinkle oral capsules, 2003)
17) higher doses (ie, approximately 50 mg/kg/day); increased risk for dose-related thrombocytopenia and elevate (Prod Info DEPACON(R) IV injection, 2006; Prod Info DEPAKENE(R) oral capsules, syrup, 2006; Prod Info DEPA release oral tablets, 2006; Prod Info DEPAKOTE(R) ER extended-release tablet, 2006; Prod Info DEPAKOTE(R) capsules, 2003)
18) hyperammonemia; may be present despite normal liver function tests; possible undiagnosed urea cycle disor contraindication; discontinue if hyperammonemia develops (Prod Info STAVZOR(R) delayed release oral capsule DEPACON(R) IV injection, 2006; Prod Info DEPAKENE(R) oral capsules, syrup, 2006; Prod Info DEPAKOTE(R) oral tablets, 2006; Prod Info DEPAKOTE(R) ER extended-release tablet, 2006; Prod Info DEPAKOTE(R) sprinkle 2003)
19) hypersensitivity reactions, multi-organ; have been reported within first 40 days of therapy and may be life-thre discontinue treatment (Prod Info STAVZOR(R) delayed release oral capsules, 2008; Prod Info DEPACON(R) IV i Prod Info DEPAKENE(R) oral capsules, syrup, 2006; Prod Info DEPAKOTE(R) delayed-release oral tablets, 2006 DEPAKOTE(R) ER extended-release tablet, 2006; Prod Info DEPAKOTE(R) sprinkle oral capsules, 2003)
20) irritability, episodic and extreme; possible undiagnosed urea cycle disorder, which is a contraindication (Prod delayed release oral capsules, 2008; Prod Info DEPACON(R) IV injection, 2006; Prod Info DEPAKENE(R) oral ca 2006; Prod Info DEPAKOTE(R) delayed-release oral tablets, 2006; Prod Info DEPAKOTE(R) ER extended-releas Prod Info DEPAKOTE(R) sprinkle oral capsules, 2003)
21) low BUN or protein avoidance; possible undiagnosed urea cycle disorder, which is a contraindication (Prod Ir delayed release oral capsules, 2008; Prod Info DEPACON(R) IV injection, 2006; Prod Info DEPAKENE(R) oral ca 2006; Prod Info DEPAKOTE(R) delayed-release oral tablets, 2006; Prod Info DEPAKOTE(R) ER extended-releas Prod Info DEPAKOTE(R) sprinkle oral capsules, 2003)
22) mental retardation, unexplained; possible undiagnosed urea cycle disorder, which is a contraindication (Prod delayed release oral capsules, 2008; Prod Info DEPACON(R) IV injection, 2006; Prod Info DEPAKENE(R) oral ca 2006; Prod Info DEPAKOTE(R) delayed-release oral tablets, 2006; Prod Info DEPAKOTE(R) ER extended-releas Prod Info DEPAKOTE(R) sprinkle oral capsules, 2003)
23) signs and symptoms of urea cycle disorders; possible undiagnosed urea cycle disorder, which is a contraindi STAVZOR(R) delayed release oral capsules, 2008; Prod Info DEPACON(R) IV injection, 2006; Prod Info DEPAKI capsules, syrup, 2006; Prod Info DEPAKOTE(R) delayed-release oral tablets, 2006; Prod Info DEPAKOTE(R) ER tablet, 2006; Prod Info DEPAKOTE(R) sprinkle oral capsules, 2003)
24) suicidality, increased risk of; based on data analysis of 199 placebo-controlled studies of 11 antiepileptic drug risk occurred as early as 1 week after starting therapy and continued to at least 24 weeks (US Food and Drug Adı
25) total valproate concentrations of 110 mcg/mL or higher in females, or 135 mcg/mL or higher in males; increas thrombocytopenia (delayed-release capsules) (Prod Info STAVZOR(R) delayed release oral capsules, 2008)
26) unexplained infant deaths (especially males), family history of; possible undiagnosed urea cycle disorder, wh contraindication (Prod Info STAVZOR(R) delayed release oral capsules, 2008; Prod Info DEPACON(R) IV injectio DEPAKENE(R) oral capsules, syrup, 2006; Prod Info DEPAKOTE(R) delayed-release oral tablets, 2006; Prod Inf ER extended-release tablet, 2006; Prod Info DEPAKOTE(R) sprinkle oral capsules, 2003)

B) Divalproex Sodium

1) hepatic failure, some cases fatal, has occurred; increased risk in patients with a history of hepatic disease, on anticonvulsant, with congenital metabolic disorders, severe seizure disorder accompanied by developmental disal disease and in children (especially under the age of 2 years); LFT monitoring is recommended (Prod Info DEPAK

oral capsules, 2008; Prod Info DEPAKOTE(R) ER extended-release oral tablets, 2008)
2) pancreatitis, sometimes life-threatening, has been reported (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2
DEPAKOTE(R) ER extended-release oral tablets, 2008)
3) pregnant women; increased risk of birth defects (eg, neural tube defects) (Prod Info DEPAKOTE(R) sprinkle o
Prod Info DEPAKOTE(R) ER extended-release oral tablets, 2008)
4) abrupt discontinuation in epileptic patients; may precipitate status epilepticus (Prod Info DEPAKOTE(R) sprink
2008; Prod Info DEPAKOTE(R) ER extended-release oral tablets, 2008)
5) elderly patients; increased incidence of adverse effects (ie, somnolence, dehydration); slow dosage titration ar
recommended (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008; Prod Info DEPAKOTE(R) ER extended-rel
2008)
6) hypothermia has occurred (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008; Prod Info DEPAKOTE(R) E
release oral tablets, 2008)
7) hyperammonemia has been reported (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008; Prod Info DEPA
extended-release oral tablets, 2008)
8) multiorgan hypersensitivity reactions have occurred (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008; Pr
DEPAKOTE(R) ER extended-release oral tablets, 2008)
9) signs and symptoms (eg, encephalopathy; unexplained mental retardation, infant deaths (particularly males), c
elevated plasma ammonia or glutamine; history of cyclical vomiting and lethargy, ataxia, low BUN, or protein avoi
history of urea cycle disorders; may indicate an undiagnosed urea cycle disorder which is a contraindication (Proc
(R) sprinkle oral capsules, 2008; Prod Info DEPAKOTE(R) ER extended-release oral tablets, 2008)
10) suicidality, increased risk of; based on data analysis of 199 placebo-controlled studies of 11 antiepileptic drug
risk occurred as early as 1 week after starting therapy and continued to at least 24 weeks (US Food and Drug Adı
11) thrombocytopenia has occurred; higher doses (ie, approximately 50 mg/kg/day or higher) may increase risk;
coagulation test monitoring is recommended; dose reduction or withdrawal of therapy may be warranted if bleedir
occur (eg, hemorrhage, bruising, hemostasis/coagulation disorder) (Prod Info DEPAKOTE(R) sprinkle oral capsul
DEPAKOTE(R) ER extended-release oral tablets, 2008)

C) Valproate Sodium
1) children, especially under the age of 2 years; increased risk of hepatotoxicity (Prod Info DEPACON(R) IV injec
2) concurrent use of multiple anticonvulsants; increased risk of hepatotoxicity (Prod Info DEPACON(R) IV injectio
3) metabolic disorders, congenital; increased risk of hepatotoxicity (Prod Info DEPACON(R) IV injection, 2006)
4) organic brain disease; increased risk of hepatotoxicity (Prod Info DEPACON(R) IV injection, 2006)
5) pancreatitis, sometimes life-threatening, may occur (Prod Info DEPACON(R) IV injection, 2006)
6) pregnancy; increased risk of birth defects (Prod Info DEPACON(R) IV injection, 2006)
7) seizure disorders, severe, accompanied by mental retardation; increased risk of hepatotoxicity (Prod Info DEP
injection, 2006)
8) abrupt discontinuation in epileptic patients; may precipitate status epilepticus (Prod Info DEPACON(R) IV injec
9) acute head trauma; not recommended for prophylaxis of post-traumatic seizures (Prod Info DEPACON(R) IV i
10) ataxia; possible undiagnosed urea cycle disorder, which is a contraindication (Prod Info DEPACON(R) IV inje
11) cyclical vomiting and lethargy; possible undiagnosed urea cycle disorder, which is a contraindication (Prod In
IV injection, 2006)
12) elderly; increased incidence of adverse effects (ie, somnolence, dehydration), sometimes with reduced nutriti
weight loss (Prod Info DEPACON(R) IV injection, 2006)
13) elevated plasma ammonia or glutamine, history of; possible undiagnosed urea cycle disorder, which is a cont
Info DEPACON(R) IV injection, 2006)
14) encephalopathy, history of unexplained encephalopathy or coma, encephalopathy associated with a protein l
related or postpartum encephalopathy; possible undiagnosed urea cycle disorder, which is a contraindication (Prc
(R) IV injection, 2006)
15) family history of urea cycle disorders; possible undiagnosed urea cycle disorder, which is a contraindication (
DEPACON(R) IV injection, 2006)
16) hepatic disease; prior history of; increased risk of hepatotoxicity (Prod Info DEPACON(R) IV injection, 2006)
17) higher doses (ie, approximately 50 mg/kg/day); increased risk for dose-related thrombocytopenia and elevate
(Prod Info DEPACON(R) IV injection, 2006)
18) hyperammonemia; may be present despite normal liver function tests; possible undiagnosed urea cycle disor
contraindication (Prod Info DEPACON(R) IV injection, 2006)
19) hypersensitivity reactions, multi-organ; have been reported within first 40 days of therapy and may be life-thre
DEPACON(R) IV injection, 2006)
20) irritability, episodic and extreme; possible undiagnosed urea cycle disorder, which is a contraindication (Prod
IV injection, 2006)
21) low blood urea nitrogen or protein avoidance; possible undiagnosed urea cycle disorder, which is a contraind
DEPACON(R) IV injection, 2006)
22) mental retardation, unexplained; possible undiagnosed urea cycle disorder, which is a contraindication (Prod
IV injection, 2006)
23) signs and symptoms of urea cycle disorders; possible undiagnosed urea cycle disorder, which is a contraindi
DEPACON(R) IV injection, 2006)
24) suicidality, increased risk of; based on data analysis of 199 placebo-controlled studies of 11 antiepileptic drug
risk occurred as early as 1 week after starting therapy and continued to at least 24 weeks (US Food and Drug Adı
25) unexplained infant deaths (especially males), history of; possible undiagnosed urea cycle disorder, which is a
(Prod Info DEPACON(R) IV injection, 2006)

3.3 Adverse Reactions

Cardiovascular Effects

Dermatologic Effects

Endocrine/Metabolic Effects

Gastrointestinal Effects

Hematologic Effects

Hepatic Effects

Immunologic Effects

Musculoskeletal Effects

Neurologic Effects

Ophthalmic Effects

Otic Effects

Psychiatric Effects

Renal Effects

Reproductive Effects

Respiratory Effects

Other

3.3.1 Cardiovascular Effects

Valproic Acid

Divalproex Sodium

3.3.1.A Valproic Acid

Chest pain

Hypertension

Hypotension

Palpitations

Peripheral edema

Tachycardia

3.3.1.A.1 Chest pain

a) Incidence: 1% to less than 5% (Prod Info STAVZOR(R) delayed release oral capsules, 2008)

b) Chest pain was reported in more than 1% but less than 5% of patients receiving valproate during plac clinical trials of migraine and acute mania and during monotherapy treatment of complex partial seizures causality could not be attributed to valproate alone in the complex partial seizures trial, as patients were another antiepilepsy drug during the first part of the study (Prod Info STAVZOR(R) delayed release oral

3.3.1.A.2 Hypertension

a) Incidence: 1% to less than 5% (Prod Info STAVZOR(R) delayed release oral capsules, 2008)

b) Hypertension was reported in more than 1% but less than 5% of patients receiving valproate during p clinical trials of acute mania and during monotherapy treatment of complex partial seizures. In many cas not be attributed to valproate alone in the complex partial seizures trial, as patients were titrated off of an drug during the first part of the study (Prod Info STAVZOR(R) delayed release oral capsules, 2008).

3.3.1.A.3 Hypotension

a) Incidence: 1% to less than 5% (Prod Info STAVZOR(R) delayed release oral capsules, 2008)

b) Hypotension and postural hypotension was reported in more than 1% but less than 5% of 89 patients valproate during two clinical trials of valproate treatment of manic episodes associated with bipolar disor STAVZOR(R) delayed release oral capsules, 2008).

c) A mentally retarded 11-year-old girl experienced profound hypotension during an IV valproate infusio given to treat status epilepticus. Upon arrival in the emergency department, the girl was given IV diazepa the seizure temporarily. When the seizures began again, the girl was given IV lorazepam and started on mg. Her blood pressure 5 minutes prior to the start of the valproate infusion was 130/80 mmHg, but decr mmHg 39 minutes after the start of the infusion. She was given IV fluids and her blood pressure ranged mmHg and 60/30 mmHg. She was intubated and given dopamine and recovered 10 days later without fu (White & Santos, 1999)

3.3.1.A.4 Palpitations

a) Incidence: 1% to less than 5% (Prod Info STAVZOR(R) delayed release oral capsules, 2008)

b) Palpitations were reported in more than 1% but less than 5% of patients receiving valproate during pl clinical trials of acute mania and during monotherapy treatment of complex partial seizures. In many cas not be attributed to valproate alone in the complex partial seizures trial, as patients were titrated off of an drug during the first part of the study (Prod Info STAVZOR(R) delayed release oral capsules, 2008).

3.3.1.A.5 Peripheral edema

a) Incidence: 3% to 8% (Prod Info STAVZOR(R) delayed release oral capsules, 2008)

b) During a clinical trial of valproate monotherapy for complex partial seizures, peripheral edema was re patients receiving high-dose valproate (n=131) compared with 3% of patients receiving low-dose valproa many cases, causality could not be determined as patients were being titrated off another antiepilepsy dr part of the trial (Prod Info STAVZOR(R) delayed release oral capsules, 2008).

3.3.1.A.6 Tachycardia

a) Incidence: 1% to less than 5% (Prod Info STAVZOR(R) delayed release oral capsules, 2008)

b) Tachycardia was reported in more than 1% but less than 5% of patients receiving valproate during pl clinical trials of acute mania and during monotherapy treatment of complex partial seizures. In many cas not be attributed to valproate alone in the complex partial seizures trial, as patients were titrated off of an drug during the first part of the study (Prod Info STAVZOR(R) delayed release oral capsules, 2008).

3.3.1.B Divalproex Sodium

Chest pain

Hypertension

Palpitations

Peripheral edema

Tachycardia

3.3.1.B.1 Chest pain

a) Incidence: 1% to less than 5% (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008)

b) Chest pain was reported in more than 1% but less than 5% of patients receiving divalproex sodium (r

monotherapy treatment of complex partial seizures. In many cases, causality could not be attributed to d patients were titrated off of another antiepilepsy drug during the first part of the trial (Prod Info DEPAKOT capsules, 2008).

3.3.1.B.2 Hypertension

a) Incidence: 1% to less than 5% (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008)

b) Hypertension was reported in more than 1% but less than 5% of patients receiving divalproex sodium monotherapy treatment of complex partial seizures. In many cases, causality could not be attributed to d patients were titrated off of another antiepilepsy drug during the first part of the trial (Prod Info DEPAKOT capsules, 2008).

3.3.1.B.3 Palpitations

a) Incidence: 1% to less than 5% (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008)

b) Palpitations were reported in more than 1% but less than 5% of patients receiving divalproex sodium monotherapy treatment of complex partial seizures. In many cases, causality could not be attributed to d patients were titrated off of another antiepilepsy drug during the first part of the trial (Prod Info DEPAKOT capsules, 2008).

3.3.1.B.4 Peripheral edema

a) Incidence: 3% to 8% (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008)

b) Peripheral edema was reported in 8% of patients receiving high-dose divalproex sodium (n=131) com patients receiving low-dose divalproex sodium (n=134) for monotherapy treatment of complex partial sei cases, causality could not be attributed to divalproex alone, as patients were titrated off of another antiep the first part of the trial (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008).

3.3.1.B.5 Tachycardia

a) Incidence: 1% to less than 5% (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008)

b) Tachycardia was reported in more than 1% but less than 5% of patients receiving divalproex sodium monotherapy treatment of complex partial seizures. In many cases, causality could not be attributed to d patients were titrated off of another antiepilepsy drug during the first part of the trial (Prod Info DEPAKOT capsules, 2008).

3.3.2 Dermatologic Effects

Valproic Acid

Divalproex Sodium

3.3.2.A Valproic Acid

Alopecia

Cutaneous pseudolymphoma

Injection site disorder

Rash

Stevens-Johnson syndrome

3.3.2.A.1 Alopecia

a) Incidence: 6% to 24% (Prod Info STAVZOR(R) delayed release oral capsules, 2008)

b) During a clinical trial where valproate was given as adjunctive therapy for treatment of complex partia alopecia was reported in 6% of patients receiving valproate (n=77) compared with 1% of patients receivi In most cases, causality could not be determined as patients also received other antiepilepsy drugs conc valproate (Prod Info STAVZOR(R) delayed release oral capsules, 2008).

c) During a clinical trial of valproate monotherapy for complex partial seizures, alopecia was reported in receiving high-dose valproate (n=131) compared with 13% of patients receiving low-dose valproate (n=1 cases, causality could not be determined as patients were being titrated off another antiepilepsy drug du the trial (Prod Info STAVZOR(R) delayed release oral capsules, 2008).

d) Alopecia was reported in 7% of migraine patients receiving valproate (n=202) compared with 1% of p placebo (n=81) during two clinical trials and their long-term extension (Prod Info STAVZOR(R) delayed r

capsules, 2008).
e) In a double-blind, concentration-response clinical trial using valproic acid as monotherapy, high conce
acid (n=96, target level 80 to 150 mcg/mL) caused alopecia in 27 patients (28%) versus 2 patients (4%)
to low concentration valproic acid (n=47, target range of 25 to 50 mcg/mL) (Beydoun et al, 1997c).

3.3.2.A.2 Cutaneous pseudolymphoma

a) Cutaneous pseudolymphoma erupted on the left shoulder of a 41-year-old man after sodium valproat
recurred when the patient was switched to carbamazepine. Valproate 500 mg twice daily was ordered af
experienced an extradural hematoma secondary to cranial trauma. His lesion was an itchy infiltrated eryt
histologically mimicking a non-epidermotropic T-cell lymphoma. Applying polymerase chain reaction to th
produced monoclonal rearrangement of the T-cell gamma gene. Valproate was discontinued and replace
carbamazepine 400 mg twice daily (the patient was using no other medications). The lesion became pro
infiltrated, but did not totally disappear. Approximately 6 months later, two additional papules appeared in
Cutaneous biopsy showed a pattern histologically identical to the original papule. Carbamazepine was w
other antiepileptic drugs were prescribed. All 3 skin lesions disappeared after 3 months; no relapse occu
of follow-up (Cogrel et al, 2001).

3.3.2.A.3 Injection site disorder

a) The manufacturer reports that injection site reactions including inflammation and pain have been repo
acid intravenous therapy (Prod Info Depacon(TM), 1999).

3.3.2.A.4 Rash

a) Incidence: 6% (Prod Info STAVZOR(R) delayed release oral capsules, 2008)
b) During two clinical trials of valproate treatment of manic episodes associated with bipolar disorder, ra
6% of patients receiving valproate (n=89) compared with 3% of patients receiving placebo (n=97) (Prod I
delayed release oral capsules, 2008).

3.3.2.A.5 Stevens-Johnson syndrome

a) After 45 days of valproate 400 mg 3 times daily, a 20-year-old man developed lip ulcerations and targ
on the trunk. Liver function tests were elevated with an aspartate aminotransferase level of 3550 units/L,
aminotransferase 5770 units/L and alkaline phosphatase level of 421 units/L. Stevens-Johnson syndrom
and with 2 weeks of prednisolone therapy his skin lesions cleared. After 30 days, liver function tests retu
(Tsai & Chen, 1998). Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have beer
occasionally during the early stages of valproic acid therapy. In a case-control study of patients taking va
agents, 73 cases of SJS or TEN were identified; of these, 13 were due to valproic acid ingestion. SJS/TE
occurred during the first 8 weeks of valproic acid therapy (Rzany et al, 1999).

3.3.2.B Divalproex Sodium

Alopecia

Petechiae

Rash

3.3.2.B.1 Alopecia

a) Incidence: 6% to 24% (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008)
b) In a clinical trial of adjunctive therapy for complex partial seizures, alopecia was reported in 6% of pat
divalproex sodium (n=77) compared with 1% of patients receiving placebo (n=70) (Prod Info DEPAKOTE
capsules, 2008).
c) Alopecia was reported in 24% of patients receiving high-dose divalproex sodium (n=131) compared w
patients receiving low-dose divalproex sodium (n=134) for monotherapy treatment of complex partial sei
cases, causality could not be attributed to divalproex alone, as patients were titrated off of another antiep
the first part of the trial (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008).

3.3.2.B.2 Petechiae

a) Incidence: 1% to less than 5% (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008)
b) Petechia was reported in more than 1% but less than 5% of patients receiving divalproex sodium (n=
monotherapy treatment of complex partial seizures. In many cases, causality could not be attributed to d
patients were titrated off of another antiepilepsy drug during the first part of the trial (Prod Info DEPAKOT
capsules, 2008).

3.3.2.B.3 Rash

a) Incidence: 1% to less than 5% (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008)
b) Rash was reported in more than 1% but less than 5% of patients receiving divalproex sodium (n=358

treatment of complex partial seizures. In many cases, causality could not be attributed to divalproex alon titrated off of another antiepilepsy drug during the first part of the trial (Prod Info DEPAKOTE(R) sprinkle 2008).

3.3.3 Endocrine/Metabolic Effects

Valproic Acid

Divalproex Sodium

3.3.3.A Valproic Acid

Acute intermittent porphyria

Carnitine nutritional deficiency

Finding of thyroid function

Hormone level - finding, Sex

Hyperammonemia

Hyperglycinemia

Hyperhomocysteinemia

Hyperprolactinemia

Increased appetite

Lipids abnormal

Syndrome of inappropriate antidiuretic hormone secretion

Weight gain

Weight loss

3.3.3.A.1 Acute intermittent porphyria

See Drug Consult reference: DRUGS CONSIDERED UNSAFE- ACUTE PORPHYRIAS

3.3.3.A.2 Carnitine nutritional deficiency

a) A case of carnitine deficiency associated with hyperammonemia (venous ammonia level of 377 mcm (Glasgow Coma Scale score 8) without hepatic dysfunction, and with a therapeutic serum valproic acid c reported in a 41-year-old male on chronic valproic acid therapy. His venous ammonia level dropped to 4 after the administration of 10 g of L-carnitine IV over 1 hour. The patient was alert, with a normal physica within 24 hours (Barrueto & Hack, 2001).

b) Chronic therapeutic use of valproic acid in young children may cause a carnitine deficiency resulting i symptoms of lethargy, weakness or hypotonia, hepatotoxicity, and hyperammonemia. An incidence of fa children under the age of two years of 1/800 has been reported (Raskind & El-Chaar, 2000).

c) Decreased plasma carnitine was reported in 14 children. Thirteen children were symptomless, yet on signs of valproic acid hepatotoxicity (appearing as a Reye's-like syndrome). After withdrawal of valproic a symptomatic patient recovered. The mechanism is believed to be increased excretion of carnitine in the and valproyl metabolites (Murphy et al, 1985).

d) A 3-year-old girl developed acute liver disease along with the typical features of Reye's syndrome aft valproate for 6 months. Serum free carnitine was decreased as well as 3-keto-valproic acid, the main me oxidation of valproate. The possible importance of carnitine in the pathogenesis of liver disease induced (Bohles et al, 1982).

e) An inverse relationship was found between plasma carnitine concentrations and the dosage of valpro between plasma carnitine and blood ammonia values (Ohtani et al, 1982).

3.3.3.A.3 Finding of thyroid function

a) One study found valproic acid slightly increased serum thyrotropin hormone (TSH) levels in girls with effects were reversible upon discontinuation of therapy. Patients, between the ages of 8 and 18 years, w 54 age-matched controls. Mean TSH levels in were 3.3 milliunits/L compared to 2.5 milli-units/L in the co than 0.01). Thyroxine (T4), free thyroxine (FT4), and free triiodothyronine (FT3) levels were not significar between the groups. Patients had been on therapy for a mean of 3 years (range 0.8 to 10.3 years). A se taken a mean of 5.8 years later was performed. Thyroid hormone levels in patients who had discontinue did not significantly differ from the controls. Patients had been off therapy for a mean of 7 years (Vainion

3.3.3.A.4 Hormone level - finding, Sex

a) Antiepileptic agents have been associated with changes in serum concentrations of male reproductiv compared to healthy controls (n=41), carbamazepine-treated men with partial epilepsy (n=15) had lower dehydroepiandrosterone sulfate concentrations (3068 nanogram/mL for controls versus 1952 nanograms carbamazepine; p less than 0.001). No statistically significant differences in dehydroepiandrosterone lev between controls and oxcarbazepine treated (n=18) or valproic acid treated (n=27) men with generalized also found that men in the valproic acid group had higher androstenedione levels (5.9 nanograms/mL) w the control group (2.2 nanograms/mL; p less than 0.001) whereas the other arms did not. Serum testoste hormone binding globulin, free androgen index, luteinizing hormone, follicle stimulating hormone, prolact measurements were not statistically significantly different between all 4 groups. Whether the differences hormones are epilepsy-induced changes or antiepileptic agent-induced changes remains to be determin 2004).

b) Carbamazepine and (to a lesser extent) valproic acid were found to alter serum concentrations of sex young male epileptic patients (aged 15 to 18 years; n=48) treated at least 2 years with these drugs; how were not permanently changed and soon after the drugs were withdrawn, hormone levels normalized (Ve Compared with concentrations in normal healthy male controls, subjects treated with carbamazepine mo had decreased levels of free testosterone (FT) (p less than 0.05) and dehydro- epiandrosterone sulphate than 0.001); concentrations of sex hormone-binding globulin were significantly increased (p less than 0.0 treated with valproic acid monotherapy (n=18) had insignificantly decreased levels of FT and DHEAS. Su combination carbamazepine and valproic acid (n=10) had the same significant alterations as those on ca monotherapy. At least four months after withdrawal of these drugs, all values had returned to normal. Le testosterone, luteinizing hormone, follicle stimulating hormone, and prolactin were normal throughout the ovaries, hyperandrogenism, and menstrual disorders were more common among women being treated f valproate (n=37) than among women being treated for epilepsy with carbamazepine (n=35) or among co (n=52). Seventy-nine percent of obese valproate-treated women and 65% of lean valproate- treated wom ovaries or hyperandrogenism or both, compared to 20% of carbamazepine-treated women and 19% of c Seventy-nine percent of obese and 48% of lean valproate- treated women had menstrual disorders, whe and 17% of lean control women had menstrual disorders (p less than 0.001) (Isojarvi et al, 2001).

c) Reproductive hormone levels in men with epilepsy may be affected by use of valproic acid or carbam some effect shown by oxcarbazepine at high doses. In valproate-treated men (n=21), androstenedione le significantly increased compared with controls (n=25) (p less than 0.001), and more than half of the coho (57%) had serum concentrations of testosterone, androstenedione, or dehydroepiandrosterone (DHEA) reference range (p less than 0.001). Follicle stimulating hormone levels were abnormally low in valproate less than 0.05). Among carbamazepine-treated men (n=40), serum concentrations of DHEA were low (p and sex hormone-binding globulin (SHBG) levels were high (p less than 0.05). In men taking high doses (900 milligrams/day or more), serum concentrations of testosterone, luteinizing hormone, and SHBG wer p=0.02, p=0.005, respectively). The authors noted that serum insulin levels were high across all groups (2001).

d) Hyperandrogenism has been reported in girls taking valproic acid. Evaluation of testosterone levels ir years old, taking valproic acid revealed significantly higher serum testosterone levels compared to contro same pubertal stage. Of girls receiving valproic acid, 38% of prepubertal girls, 36% of pubertal girls, and postpubertal girls were hyper-androgenic (Vainionpaa et al, 1999).

e) Evidence is strongly suggestive of a causative link between reproductive endocrine disorders and val treatment in women with epilepsy. In a study of 238 adult epileptic women, 27% of those who received v 20 or later, and 80% of those who received valproic acid before the age of 20, demonstrated polycystic o serum testosterone levels. In both age groups, the incidence of hyper-androgenic effects was significantl valproic acid than for other antiepileptic medications (p less than 0.01) (Isojarvi et al, 1993).

3.3.3.A.5 Hyperammonemia

a) Hyperammonemia, sometimes present despite normal liver function tests, has been reported with val Patients who develop symptoms of hyperammonemia (hypothermia, unexplained lethargy and vomiting, changes) while receiving valproate therapy should receive prompt treatment (including discontinuation of therapy) and be evaluated for underlying urea cyclic disorder (Prod Info STAVZOR(R) delayed release o 2008).

b) An 88-year-old man developed hyperammonemia and worsening confusion two months after starting four times a day for a presumed seizure disorder. His liver function tests were within normal limits except

concentration of 836 mcg/dL (reference range 19 to 60 mcg/dL). His trough valproate serum concentratio
His medication was changed to phenytoin 150 mg twice day and his confusion resolved. One week later
was 63 mcmol/L (reference range 11 to 35 mcmol/L) and his phenytoin and valproate concentrations we
and less than 10 mcg/mL, respectively. He was inadvertently started on valproate again at the former do
days his ammonia concentration increased to 130 mcmol/L. He became confused and lethargic and his l
bilateral 5 to 7 hertz (Hz) slowing and abnormal, irregular 2-Hz to 3-Hz activity on the right. Valproate wa
his ammonia concentration decreased to 60 mcmol/L after one day and on the second day his confusion
baseline (Feil et al, 2002).

c) A 37-year-old man with previously unknown ornithine transcarbamylase deficiency developed plasma
of up to 800 mcmol/L (normal less than 40 mcmol/L) after beginning sodium valproate therapy. He had b
with spinocerebellar degeneration and was having severe pain in the region of a sural-nerve biopsy whe
prescribed valproate 200 mg 3 times daily. After 9 days he appeared drowsy and confused with a 3-day
and vomiting. It was noted that plasma ammonia levels were increased and valproate was discontinued.
hospital however, he died. It was not established until after his death that he had ornithine transcarbamy
(Ellaway et al, 1999).

d) One study reported significantly higher postprandial plasma ammonia levels in children who received
other anticonvulsant(s) as compared to the control group (average 34 versus 20 mcg/dL, respectively). T
did find a positive correlation between serum valproic acid and plasma ammonia levels. Oral L-carnitine
reduced ammonia levels to normal within 15 to 45 days of therapy (Altunbasak et al, 1997).

e) The frequency of hyperammonemia in asymptomatic children receiving valproic acid was evaluated. V
concentrations were evaluated in three groups of children (receiving valproic acid only, receiving valproic
anticonvulsants, and control patients receiving other anticonvulsants). Hyperammonemia was reported ir
receiving valproic acid alone or in combination with anticonvulsants (ammonia levels exceeding 45 micro
(mcg%)), as compared to 28% of the controlled group. Valproic acid serum concentrations ranged from 2
and there was no correlation with ammonia levels and drug serum concentrations. The authors suggest t
mild elevations in ammonia levels in adults can result in subtle neurologic dysfunction, that monitoring of
concentrations in valproic acid treated patients is desirable (Wyllie et al, 1983).

f) A case of a Reye-like syndrome was reported in a 13-year-old female who had received valproic acid
Hyperammonemia and severe hepatic damage, as well as diffuse small droplets in liver biopsy material,
demonstrated. It is suggested that valproic acid or its metabolites may decrease the activity on N-acetylg
can decrease the activity of carbamyl phosphate synthetase I, inducing hyperammonemia (Sugimoto et a

3.3.3.A.6 Hyperglycinemia

a) In a patient with preexistent nonketotic hyperglycinemia, hyperglycinemia occurred with valproic acid
associated with a fatal outcome (Prod Info STAVZOR(R) delayed release oral capsules, 2008).

3.3.3.A.7 Hyperhomocysteinemia

a) In a study of 60 adolescent epileptic patients (aged 14 to 18 years), a one-year course of carbamazep
therapy was found to produce significantly higher plasma concentrations of homocysteine compared with
prior to therapy and compared with levels in a healthy age- and sex-matched control group (p less than 0
comparisons). The finding of hyperhomocystinemia held true with both fasting and post-methionine homo
measurements. For the patients taking carbamazepine or valproate, serum concentrations of folate and p
5-phosphate (PLP) were significantly decreased with respect to pretreatment values and to values in the
less than 0.01, folate; p less than 0.001, PLP). Levels of vitamin B12 and erythrocyte folate remained in t
(Verrotti et al, 2000a).

3.3.3.A.8 Hyperprolactinemia

a) Sodium valproate was given to 20 normal and 15 hyperprolactinemic patients. Prolactin levels were s
lowered in both groups following valproate administration; however, prolactin levels in the hyperprolactin
decreased in those patients without evidence of prolactinoma. This study suggests that enhancement of
is followed by inhibition of prolactin secretion (Melis et al, 1982).

3.3.3.A.9 Increased appetite

a) Incidence: 6% (Prod Info STAVZOR(R) delayed release oral capsules, 2008)

b) Increased appetite was reported in 6% of migraine patients receiving valproate (n=202) compared wit
receiving placebo (n=81) during two clinical trials and their long-term extension (Prod Info STAVZOR(R)
oral capsules, 2008).

3.3.3.A.10 Lipids abnormal

a) In a study evaluating lipids in children and adolescents receiving carbamazepine (n=14), valproic acid
phenobarbital (n=20), serum lipid and lipoprotein levels returned completely to normal at 1 to 1.5 years a
discontinued. During therapy patients receiving carbamazepine demonstrated increased levels of total ch
triglycerides, LDL cholesterol, and HDL as compared to a control group (n=110)(all p less than 0.01). Ch
valproic acid had low triglycerides (p less than 0.05) and LDL (p less than 0.05) and high levels of HDL (p
as compared to the control group. Children receiving phenobarbital had high concentrations of total chole
cholesterol and low concentrations of triglycerides as compared to the control group (all p less than 0.01
1998).

b) Serum lipids and lipoproteins in 33 epileptic children were measured. All of the children were being cl

with phenobarbital, valproate and carbamazepine. HDL cholesterol was significantly higher in the epilept 2 control groups (healthy nonepileptic children and epileptic children before starting anticonvulsant thera indicate that anticonvulsant drugs should be added to the list of substances that affect serum HDL (Held 1983).

3.3.3.A.11 Syndrome of inappropriate antidiuretic hormone secretion

a) Syndrome of inappropriate secretion of antidiuretic hormone (SIADH) in a 62-year-old man was attrib long-term use of sodium valproate. At age 56, the man had his first generalized tonic-clonic seizure, and mg/day was initiated. Symptoms such as hyponatremia, elevated serum concentrations of antidiuretic ho cloudiness of consciousness, disorientation, psychomotor excitement, and a tonic-clonic seizure occurre year. These episodes were different from his original tonic-clonic convulsion, as originally hyponatremia, and cloudiness of consciousness were not present. Laboratory findings included serum sodium of 127 m picograms (pg)/mL, an increase in urinary sodium excretion, and slight elevation of urinary osmosity. Se concentrations were 10.5 mcg/mL. SIADH was diagnosed. The patient was switched from valproate to z 18 months, his serum ADH had normalized (0.8 pg/mL); he had no symptoms of SIADH and he no longe type of seizures. The authors concluded that SIADH in this case was due to long-term administration of v weakness in the CNS (bilateral hippocampal atrophy) (Miyaoka et al, 2001).

b) A 50-year-old male with Henoch-Schonlein nephritis was discovered to have hyponatremia (serum so mEq/L) during a routine follow-up. His only medication was valproate 2000 mg/day. He had no complaint volume depletion, hypothyroidism, or renal or adrenal insufficiency. His plasma osmolality was low at 26 Repeated water loading at different valproate doses confirmed the ability to excrete water was reduced i dependent manner. The authors concluded that the valproate caused syndrome of inappropriate secretio hormone (SIADH). Water restriction corrected the hyponatremia (Branten et al, 1998).

3.3.3.A.12 Weight gain

a) Incidence: 4% to 9% (Prod Info STAVZOR(R) delayed release oral capsules, 2008)

b) Weight gain was reported in 8% of migraine patients receiving valproate (n=202) compared with 2% o receiving placebo (n=81) during two clinical trials and their long-term extension (Prod Info STAVZOR(R) oral capsules, 2008).

c) During a clinical trial of valproate monotherapy for complex partial seizures, weight gain was reported receiving high-dose valproate (n=131) compared with 4% of patients receiving low-dose valproate (n=13 causality could not be determined as patients were being titrated off another antiepilepsy drug during the trial (Prod Info STAVZOR(R) delayed release oral capsules, 2008).

d) A retrospective, longitudinal study revealed that epileptic children between the ages of 2 and 8 years 0.8 yr; 53% male) experienced a significant increase in BMI z-scores following valproic acid treatment. H percentage of patients who were overweight or obese at the end of 3.1 yr follow-up was not statistically s BMI z-score of 0.1 was calculated at initiation of treatment, which increased to 0.8 (p=0.001) at 3.1 years therapy, 6.9% of the patients were overweight, which increased to 16% (p=0.081) following 3.1 yr of valp treatment. A total of 3.5% of patients were obese at baseline, which increased to 5.7% following 3.1 yr of however this increase in weight was also not statistically significant (p=0.8). This study data suggests tha occurred during the first 16 months of treatment but leveled off with continued treatment. Over the cours significant increases in serum triglyceride levels, total serum cholesterol levels, or fasting blood glucose l reported (Grosso et al, 2009).

e) Obesity in children treated with valproate was common in a study of 55 children. Body mass index wa 90th percentile-for-age in 14 patients at baseline which increased to 20 patients at follow-up. The risk of gain with valproate was significant as seen in changes in weight Z-score and in body mass index (p=0.0 respectively). Also seen was impaired growth in girls as measured by height Z-score (p=0.001) (Novak e et al, 1977c).

f) In a retrospective study of 70 epileptic patients treated with long-term valproic acid (mean 27 months) weight gain in excess of 10% over their baseline measurement, and another 24% gained an additional 5 control group of patients treated with carbamazepine monotherapy, 14% of patients had weight gain grea 28% had weight gain between 5% and 10% (Corman et al, 1997). In another study of patients treated lon valproic acid for epilepsy (female patients only), 11 of 22 (50%) experienced marked weight gain (mean indisputable despite preexisting obesity. Weight gain was frequently associated with hyperinsulinemia ar growth factor-binding protein 1 (Isojarvi et al, 1996).

3.3.3.A.13 Weight loss

a) Incidence: 6% (Prod Info STAVZOR(R) delayed release oral capsules, 2008)

b) During a clinical trial where valproate was given as adjunctive therapy for treatment of complex partia loss was reported in 6% of patients receiving valproate (n=77) compared with 0% of patients receiving pl most cases, causality could not be determined as patients also received other antiepilepsy drugs concur valproate (Prod Info STAVZOR(R) delayed release oral capsules, 2008).

3.3.3.B Divalproex Sodium

Hyperammonemia

Increased appetite

Weight gain

Weight loss

3.3.3.B.1 Hyperammonemia

a) Hyperammonemia, sometimes present despite normal liver function tests, has been reported with val
Patients who develop symptoms of hyperammonemia (hypothermia, unexplained lethargy and vomiting,
changes) while receiving valproate therapy should receive prompt treatment (including discontinuation o
therapy) and be evaluated for underlying urea cyclic disorder (Prod Info DEPAKOTE(R) sprinkle oral cap

3.3.3.B.2 Increased appetite

a) Incidence: 1% to less than 5% (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008)

b) Increased appetite was reported in more than 1% but less than 5% of patients receiving divalproex so
monotherapy treatment of complex partial seizures. In many cases, causality could not be attributed to d
patients were titrated off of another antiepilepsy drug during the first part of the trial (Prod Info DEPAKOT
capsules, 2008).

3.3.3.B.3 Weight gain

a) Incidence: 4% to 9% (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008)

b) Weight gain was reported in 9% of patients receiving high-dose divalproex sodium (n=131) compared
patients receiving low-dose divalproex sodium (n=134) for monotherapy treatment of complex partial sei
cases, causality could not be attributed to divalproex alone, as patients were titrated off of another antiep
the first part of the trial (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008).

3.3.3.B.4 Weight loss

a) Incidence: 6% (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008)

b) In a clinical trial of adjunctive therapy for complex partial seizures, weight loss was reported in 6% of
divalproex sodium (n=77) compared with 0% of patients receiving placebo (n=70) (Prod Info DEPAKOTE
capsules, 2008).

3.3.4 Gastrointestinal Effects

Valproic Acid

Divalproex Sodium

3.3.4.A Valproic Acid

Abdominal pain

Constipation

Diarrhea

Hematemesis

Indigestion

Loss of appetite

Nausea

Pancreatitis

Vomiting

3.3.4.A.1 Abdominal pain

a) Incidence: 9% to 23% (Prod Info STAVZOR(R) delayed release oral capsules, 2008)

b) During two clinical trials of valproate treatment of manic episodes associated with bipolar disorder, ab reported in 9% of patients receiving valproate (n=89) compared with 8% of patients receiving placebo (n= STAVZOR(R) delayed release oral capsules, 2008).

c) Abdominal pain was reported in 9% of migraine patients receiving valproate (n=202) compared with 4 receiving placebo (n=81) during two clinical trials and their long-term extension (Prod Info STAVZOR(R) oral capsules, 2008).

d) During a clinical trial where valproate was given as adjunctive therapy for treatment of complex partia abdominal pain was reported in 23% of patients receiving valproate (n=77) compared with 6% of patients (n=70). In most cases, causality could not be determined as patients also received other antiepilepsy dru with valproate (Prod Info STAVZOR(R) delayed release oral capsules, 2008).

e) During a clinical trial of valproate monotherapy for complex partial seizures, abdominal pain was repo patients receiving high-dose valproate (n=131) compared with 9% of patients receiving low-dose valproa many cases, causality could not be determined as patients were being titrated off another antiepilepsy dr part of the trial (Prod Info STAVZOR(R) delayed release oral capsules, 2008).

3.3.4.A.2 Constipation

a) Incidence: 5% (Prod Info STAVZOR(R) delayed release oral capsules, 2008)

b) During a clinical trial where valproate was given as adjunctive therapy for treatment of complex partia constipation was reported in 5% of patients receiving valproate (n=77) compared with 1% of patients rec (n=70). In most cases, causality could not be determined as patients also received other antiepilepsy dru with valproate (Prod Info STAVZOR(R) delayed release oral capsules, 2008).

3.3.4.A.3 Diarrhea

a) Incidence: 12% to 23% (Prod Info STAVZOR(R) delayed release oral capsules, 2008)

b) Diarrhea was reported in 12% of migraine patients receiving valproate (n=202) compared with 7% of placebo (n=81) during two clinical trials and their long-term extension (Prod Info STAVZOR(R) delayed r capsules, 2008).

c) During a clinical trial where valproate was given as adjunctive therapy for treatment of complex partia diarrhea was reported in 13% of patients receiving valproate (n=77) compared with 6% of patients receiv (n=70). In most cases, causality could not be determined as patients also received other antiepilepsy dru with valproate (Prod Info STAVZOR(R) delayed release oral capsules, 2008).

d) During a clinical trial of valproate monotherapy for complex partial seizures, diarrhea was reported in receiving high-dose valproate (n=131) compared with 19% of patients receiving low-dose valproate (n=1 cases, causality could not be determined as patients were being titrated off another antiepilepsy drug du the trial (Prod Info STAVZOR(R) delayed release oral capsules, 2008).

3.3.4.A.4 Hematemesis

a) Incidence: 1% to less than 5% (Prod Info STAVZOR(R) delayed release oral capsules, 2008)

b) Hematemesis was reported in more than 1% but less than 5% of patients receiving valproate (n=265) treatment of complex partial seizures. In many cases, causality could not be attributed to valproate alone titrated off of another antiepilepsy drug during the first part of the trial (Prod Info STAVZOR(R) delayed re capsules, 2008).

3.3.4.A.5 Indigestion

a) Incidence: 8% to 13% (Prod Info STAVZOR(R) delayed release oral capsules, 2008)

b) During two clinical trials of valproate treatment of manic episodes associated with bipolar disorder, dy reported in 9% of patients receiving valproate (n=89) compared with 8% of patients receiving placebo (n= STAVZOR(R) delayed release oral capsules, 2008).

c) Dyspepsia was reported in 13% of migraine patients receiving valproate (n=202) compared with 9% o receiving placebo (n=81) during two clinical trials and their long-term extension (Prod Info STAVZOR(R) oral capsules, 2008).

d) During a clinical trial of valproate monotherapy for complex partial seizures, dyspepsia was reported i receiving high-dose valproate (n=131) compared with 10% of patients receiving low-dose valproate (n=1 cases, causality could not be determined as patients were being titrated off another antiepilepsy drug du the trial (Prod Info STAVZOR(R) delayed release oral capsules, 2008).

e) During a clinical trial where valproate was given as adjunctive therapy for treatment of complex partia dyspepsia was reported in 8% of patients receiving valproate (n=77) compared with 4% of patients receiv (n=70). In most cases, causality could not be determined as patients also received other antiepilepsy dru with valproate (Prod Info STAVZOR(R) delayed release oral capsules, 2008).

3.3.4.A.6 Loss of appetite

a) Incidence: 4% to 12% (Prod Info STAVZOR(R) delayed release oral capsules, 2008)

b) During a clinical trial where valproate was given as adjunctive therapy for treatment of complex partia anorexia was reported in 12% of patients receiving valproate (n=77) compared with 0% of patients receiv (n=70). In most cases, causality could not be determined as patients also received other antiepilepsy dru with valproate (Prod Info STAVZOR(R) delayed release oral capsules, 2008).

c) During a clinical trial of valproate monotherapy for complex partial seizures, anorexia was reported in receiving high-dose valproate (n=131) compared with 4% of patients receiving low-dose valproate (n=13 causality could not be determined as patients were being titrated off another antiepilepsy drug during the trial (Prod Info STAVZOR(R) delayed release oral capsules, 2008).

3.3.4.A.7 Nausea

a) Incidence: 22% to 48% (Prod Info STAVZOR(R) delayed release oral capsules, 2008)

b) During two clinical trials of valproate treatment of manic episodes associated with bipolar disorder, na in 22% of patients receiving valproate (n=89) compared with 15% of patients receiving placebo (n=97) (P STAVZOR(R) delayed release oral capsules, 2008).

c) Nausea was reported in 31% of migraine patients receiving valproate (n=202) compared with 10% of placebo (n=81) during two clinical trials and their long-term extension (Prod Info STAVZOR(R) delayed r capsules, 2008).

d) During a clinical trial where valproate was given as adjunctive therapy for treatment of complex partia was reported in 48% of patients receiving valproate (n=77) compared with 14% of patients receiving plac most cases, causality could not be determined as patients also received other antiepilepsy drugs concur valproate (Prod Info STAVZOR(R) delayed release oral capsules, 2008).

e) During a clinical trial of valproate monotherapy for complex partial seizures, nausea was reported in 3 receiving high-dose valproate (n=131) compared with 26% of patients receiving low-dose valproate (n=1 cases, causality could not be determined as patients were being titrated off another antiepilepsy drug du the trial (Prod Info STAVZOR(R) delayed release oral capsules, 2008).

3.3.4.A.8 Pancreatitis

a) Incidence: 1% to less than 5% (Prod Info STAVZOR(R) delayed release oral capsules, 2008)

b) Life-threatening pancreatitis has been reported with valproate use in both children and adults shortly after several years of therapy. Some cases of hemorrhagic pancreatitis with rapid progression from initia death have been described. Symptoms of pancreatitis requiring prompt medical evaluation include abdo nausea, vomiting, and anorexia. There were 2 cases of pancreatitis reported among 2416 patients receiv during clinical trials, representing 1044 patient-years of experience. Pancreatitis has recurred upon recha valproate (Prod Info STAVZOR(R) delayed release oral capsules, 2008).

c) Pancreatitis was reported in more than 1% but less than 5% of patients receiving valproate (n=265) fo treatment of complex partial seizures. In many cases, causality could not be attributed to valproate alone titrated off of another antiepilepsy drug during the first part of the trial (Prod Info STAVZOR(R) delayed re capsules, 2008).

d) Of 45 published cases of valproic acid-induced pancreatitis, 3 cases were found to be definite (by the drug reaction probability scale), 32 probable, and 10 possible. There was no correlation between valproic plasma concentration and development of pancreatitis. Thirty percent of patients developed symptoms w starting valproic acid, 58% within 12 months, and 30% 2 years or more after starting valproic acid. Many with discontinuation of valproic acid. However, 13 (29%) died (Chapman et al, 2001).

e) A 22-year-old woman who been taking valproic acid for 19 years for epiloia developed an acute exac pancreatitis. At the time, her valproic acid dosage was 25 mg/kg/day. She also took other medications fo She was treated conservatively, with discontinuation of valproic acid and increased doses of other agent seizures. Serum markers of pancreatitis normalized by 4 days and she was discharged on day 22. A day readmitted because of recurrent pancreatitis, which required surgical resection of the pancreatic head ar preservation of the stomach and pyloric ring. The resected specimens were notable for a large volume o in the pancreatic head and fibrosis around the main pancreatic duct. Findings suggested that the cause was flow disturbance of pancreatic juice due to calculi in the main pancreatic duct. There had been no re pancreatitis at 2 years postsurgery (Taira et al, 2001).

f) A 35-year-old man demonstrated signs and symptoms of pancreatitis 17 months after beginning valpr and again upon rechallenge. Signs and symptoms included abdominal pain, increased enzymes, and ult computed tomographic scan showing thickening of the body and tail of the pancreas. Rechallenge was c after valproic acid discontinuance due to increased seizure frequency and irritability. Pancreatitis develop restarting valproic acid (Fecik et al, 1999).

g) A 23-year-old male, on hemodialysis for endstage renal disease secondary to hemolytic uremic syndr pancreatitis following a 3 month course of valproic acid (2500 mg/day) and phenobarbital (200 mg/day). valproic acid and administering symptomatic therapy, the pancreatitis resolved. Phenobarbital was contin further pancreatic symptoms (Plaza et al, 1999).

h) Two pediatric cases of valproic acid-associated pancreatitis occurred in the presence of endstage ren amylase levels were 232 units/L and 465 units/L, respectively, in a 14-year-old female on peritoneal dialy figures were 880 units/L and 530 units/L in a 12-year-old male on hemodialysis. Both had received valpr for seizure disorder (doses not given). The 14-year-old also developed hepatotoxicity and subsequently old recovered with valproic acid discontinuation (Levin et al, 1997).

i) Development of VPA (valproic acid)-associated pancreatitis is a relative contraindication to further trea routine monitoring of serum amylase is not necessary in asymptomatic patients. Other cases of fatal and induced pancreatitis have been described (Evans et al, 1995)(Pinkston & Walker, 1997).

j) Four cases of pancreatitis secondary to valproic acid were described. Doses of valproic acid were ran mg/kg/day for 7 months to 4.5 years (age of patients, 3, 7, 18, and 27 years). Complications of pancreati pseudocyst, pericardial effusion, laparotomy wound infection, and coagulopathy occurred in one patient;

one other patient. Withdrawal of valproic acid resulted in recovery (Wyllie et al, 1984).
k) Fourteen cases of valproate-associated pancreatitis are reviewed. None of the cases experienced oth effects and pancreatitis was not dose-related. It developed as early as one week and as late as 4.5 years treatment. Two of 14 patients died. Of 7 rechallenged with valproic acid, 6 had recurrence of pancreatitis 1984).
l) Attacks of pancreatitis were described in an 11-year-old girl receiving valproic acid 15 mg/kg/day. Trai discomfort occurred at this dosage (exact duration of therapy unspecified), and 2 days after beginning 45 daily) the patient developed severe abdominal pain. Laparotomy for suspected appendicitis was institute mesenteric fat necrosis. Postoperative serum amylase was 225 units/dL (normal less than 160). The pat after a period of 2 weeks. Valproic acid was initiated again after a period of 4 weeks and was again asso abdominal pain and elevated serum amylase (696 units/dL) after the dosage was increased from 20 to 2 patient recovered fully upon discontinuation of valproic acid. The second case, a 1-year-old boy, develop abdominal pain following meals at doses of 55 mg/kg/day (900 mg daily) with serum amylase increasing units/dL. The patient recovered 2 weeks after discontinuation of valproic acid. It is not possible to attribut pancreatitis in these children to the use of valproic acid. However, signs of unusual abdominal discomfor followed by serum amylase examination in order to rule out the possibility of acute pancreatitis (Camfield

3.3.4.A.9 Vomiting

a) Incidence: 11% to 27% (Prod Info STAVZOR(R) delayed release oral capsules, 2008)
b) During two clinical trials of valproate treatment of manic episodes associated with bipolar disorder, vo reported in 12% of patients receiving valproate (n=89) compared with 3% of patients receiving placebo (r STAVZOR(R) delayed release oral capsules, 2008).
c) Vomiting was reported in 11% of migraine patients receiving valproate (n=202) compared with 1% of placebo (n=81) during two clinical trials and their long-term extension (Prod Info STAVZOR(R) delayed r capsules, 2008).
d) During a clinical trial where valproate was given as adjunctive therapy for treatment of complex partia vomiting was reported in 27% of patients receiving valproate (n=77) compared with 7% of patients receiv (n=70). In most cases, causality could not be determined as patients also received other antiepilepsy dru with valproate (Prod Info STAVZOR(R) delayed release oral capsules, 2008).
e) During a clinical trial of valproate monotherapy for complex partial seizures, vomiting was reported in receiving high-dose valproate (n=131) compared with 15% of patients receiving low-dose valproate (n=1 cases, causality could not be determined as patients were being titrated off another antiepilepsy drug du the trial (Prod Info STAVZOR(R) delayed release oral capsules, 2008).

3.3.4.B Divalproex Sodium

Abdominal pain

Constipation

Diarrhea

Hematemesis

Indigestion

Loss of appetite

Nausea

Pancreatitis

Vomiting

3.3.4.B.1 Abdominal pain

a) Incidence: 9% to 23% (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008)
b) In a clinical trial of adjunctive therapy for complex partial seizures, abdominal pain was reported in 23 receiving divalproex sodium (n=77) compared with 6% of patients receiving placebo (n=70) (Prod Info DI sprinkle oral capsules, 2008).
c) Abdominal pain was reported in 12% of patients receiving high-dose divalproex sodium (n=131) comp patients receiving low-dose divalproex sodium (n=134) for monotherapy treatment of complex partial sei cases, causality could not be attributed to divalproex alone, as patients were titrated off of another antiep

the first part of the trial (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008).

3.3.4.B.2 Constipation

a) Incidence: 5% (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008)

b) In a clinical trial of adjunctive therapy for complex partial seizures, constipation was reported in 5% of divalproex sodium (n=77) compared with 1% of patients receiving placebo (n=70) (Prod Info DEPAKOTE capsules, 2008).

3.3.4.B.3 Diarrhea

a) Incidence: 13% to 23% (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008)

b) In a clinical trial of adjunctive therapy for complex partial seizures, diarrhea was reported in 13% of pa divalproex sodium (n=77) compared with 6% of patients receiving placebo (n=70) (Prod Info DEPAKOTE capsules, 2008).

c) Diarrhea was reported in 23% of patients receiving high-dose divalproex sodium (n=131) compared w patients receiving low-dose divalproex sodium (n=134) for monotherapy treatment of complex partial sei cases, causality could not be attributed to divalproex alone, as patients were titrated off of another antiep the first part of the trial (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008).

3.3.4.B.4 Hematemesis

a) Incidence: 1% to less than 5% (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008)

b) Hematemesis was reported in more than 1% but less than 5% of patients receiving divalproex sodium monotherapy treatment of complex partial seizures. In many cases, causality could not be attributed to d patients were titrated off of another antiepilepsy drug during the first part of the trial (Prod Info DEPAKOT capsules, 2008).

3.3.4.B.5 Indigestion

a) Incidence: 8% to 11% (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008)

b) In a clinical trial of adjunctive therapy for complex partial seizures, dyspepsia was reported in 8% of p divalproex sodium (n=77) compared with 4% of patients receiving placebo (n=70) (Prod Info DEPAKOTE capsules, 2008).

c) Dyspepsia was reported in 11% of patients receiving high-dose divalproex sodium (n=131) compared patients receiving low-dose divalproex sodium (n=134) for monotherapy treatment of complex partial sei cases, causality could not be attributed to divalproex alone, as patients were titrated off of another antiep the first part of the trial (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008).

3.3.4.B.6 Loss of appetite

a) Incidence: 4% to 12% (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008)

b) In a clinical trial of adjunctive therapy for complex partial seizures, anorexia was reported in 12% of p divalproex sodium (n=77) compared with 0% of patients receiving placebo (n=70) (Prod Info DEPAKOTE capsules, 2008).

c) Anorexia was reported in 11% of patients receiving high-dose divalproex sodium (n=131) compared w receiving low-dose divalproex sodium (n=134) for monotherapy treatment of complex partial seizures. In causality could not be attributed to divalproex alone, as patients were titrated off of another antiepilepsy first part of the trial (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008).

3.3.4.B.7 Nausea

a) Incidence: 26% to 48% (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008)

b) In a clinical trial of adjunctive therapy for complex partial seizures, nausea was reported in 48% of pa divalproex sodium (n=77) compared with 14% of patients receiving placebo (n=70) (Prod Info DEPAKOT capsules, 2008).

c) Nausea was reported in 34% of patients receiving high-dose divalproex sodium (n=131) compared wi receiving low-dose divalproex sodium (n=134) for monotherapy treatment of complex partial seizures. In causality could not be attributed to divalproex alone, as patients were titrated off of another antiepilepsy first part of the trial (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008).

3.3.4.B.8 Pancreatitis

a) Incidence: 1% to less than 5% (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008)

b) Life-threatening pancreatitis has been reported with valproate use in both children and adults shortly after several years of therapy. Some cases of hemorrhagic pancreatitis with rapid progression from initia death have been described. Symptoms of pancreatitis requiring prompt medical evaluation include abdo nausea, vomiting, and anorexia. There were 2 cases of pancreatitis reported among 2416 patients receiv during clinical trials, representing 1044 patient-years of experience. Pancreatitis may recur upon rechalle (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008).

c) Pancreatitis was reported in more than 1% but less than 5% of patients receiving divalproex sodium (monotherapy treatment of complex partial seizures. In many cases, causality could not be attributed to d patients were titrated off of another antiepilepsy drug during the first part of the trial (Prod Info DEPAKOT capsules, 2008).

3.3.4.B.9 Vomiting

a) Incidence: 15% to 27% (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008)

b) In a clinical trial of adjunctive therapy for complex partial seizures, vomiting was reported in 27% of pa divalproex sodium (n=77) compared with 7% of patients receiving placebo (n=70) (Prod Info DEPAKOTE capsules, 2008).

c) Vomiting was reported in 23% of patients receiving high-dose divalproex sodium (n=131) compared w patients receiving low-dose divalproex sodium (n=134) for monotherapy treatment of complex partial sei cases, causality could not be attributed to divalproex alone, as patients were titrated off of another antiep the first part of the trial (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008).

3.3.5 Hematologic Effects

Valproic Acid

Divalproex Sodium

3.3.5.A Valproic Acid

Acute promyelocytic leukemia, FAB M3

Blood coagulation disorder

Ecchymosis

Factor VII deficiency

Hematology finding

Myelosuppression

Neutropenia

Pancytopenia

Protein C deficiency disease

Pure red cell aplasia

Thrombocytopenia

Thrombocytopenia, Dose-related

von Willebrand factor inhibitor disorder

3.3.5.A.1 Acute promyelocytic leukemia, FAB M3

a) Valproic acid therapy produced hematopoietic changes consistent with acute promyelocytic leukemia year-old Native American female. The patient had received 65 mg/kg/day for seizure disorder for 1 year presentation with anemia, thrombocytopenia, leukocytosis, and coagulopathy. The valproic acid serum le normal range (82 mcg/mL). Abnormal/immature myeloid precursor cells appeared in the bone marrow ar Although the diagnosis of APML was considered, the patient gradually recovered after valproic acid disc (Bottom et al, 1997).

3.3.5.A.2 Blood coagulation disorder

a) Summary

1) Sodium valproate has been shown to inhibit the secondary phase of platelet aggregation. This ca increased bleeding times and hemorrhage (Prod Info STAVZOR(R) delayed release oral capsules, 2 Bruni & Wilder, 1979a; Gerber et al, 1979; Addison & Gordon, 1980; Hintze et al, 1987; Gidal et al, 1 inhibition of platelet aggregation is usually of no clinical significance unless patients are receiving otl

affect hemostasis (aspirin, warfarin) or undergoing surgery. Children appear to be particularly susce
1977c).

b) Hemostatic disturbances occurred in a 9-year-old female receiving oral valproate sodium 600 mg dail
3 years for grand mal epilepsy. During valproate therapy, the patient developed an acute pulmonary infe
resulted in severe nasal bleeding, hemoptysis, thrombocytopenia and abnormal clotting tests. Partial thro
74.8 seconds (normal 50), fibrinogen was 420 mg% (normal 160 to 400) and hemoglobin was 6 gram%.
and antibiotics were administered resulting in complete recovery (Klose et al, 1977).

c) The effects of sodium valproate on platelet function in 20 children with seizures was evaluated. Clinic
hemorrhagic disease including petechiae, epistaxis, otorrhagia, and prolonged bleeding after surgery we
several patients. Bleeding time was increased in 6 patients and platelet adhesiveness was found to be d
patients (von Voss et al, 1976).

3.3.5.A.3 Ecchymosis

a) Incidence: 4% to 5% (Prod Info STAVZOR(R) delayed release oral capsules, 2008)

b) During a clinical trial of valproate monotherapy for complex partial seizures, ecchymosis was reporte
receiving high-dose valproate (n=131) compared with 4% of patients receiving low-dose valproate (n=13
causality could not be determined as patients were being titrated off another antiepilepsy drug during the
trial (Prod Info STAVZOR(R) delayed release oral capsules, 2008).

3.3.5.A.4 Factor VII deficiency

a) A 3-year-old boy with a history of afebrile convulsions developed acquired factor VII deficiency while
with valproate 20 mg/kg for 7 months. There was no reported personal or family history of hematologic d
other drug treatments, toxic compound exposure, infection, or immunization. The child had experienced
bruising over his body 1 month after beginning valproate treatment. Neurological examination revealed h
tendon reflexes in both lower extremities and positive Babinski sign and clonus. The patient's laboratory
normal with the exception of prolonged prothrombin time (PT, 15.6 sec) and reduced factor VII concentra
the parents had factor VII levels within normal range. Twelve months following discontinuation of valproa
institution of phenobarbital), bruising resolved and factor VII concentrations and PT intervals returned to
range (50% and 13 sec, respectively) (Unalp et al, 2008).

3.3.5.A.5 Hematology finding

a) Valproic acid therapy resulted in myelodysplastic hematologic changes including macrocytosis, throm
pelger-huet neutrophils in two case reports. Neither had folate or vitamin B12 deficiencies. The patients i
48-year-old female on valproic acid 6000 mg/day for 3 years for refractory bipolar disorder, with a serum
of 95.4 mcg/mL, and a 2-year-old female with congenital anomalies and seizure disorder on valproic acid
(duration unknown), with a serum level of 125 mcg/mL. Hematology profiles improved in both cases with
(Fawcett, 1997; Hongeng et al, 1997).

b) In a cohort study involving 29,357 recipients of anticonvulsive therapy (receiving 684,706 prescription
drugs, one being valproate), serious blood dyscrasias were rarely found in these patients. Among the 4 c
appear different. An overall rate of blood dyscrasias was reported to be 3 to 4 per 100,000 prescriptions
(Blackburn et al, 1998).

3.3.5.A.6 Myelosuppression

a) Valproate-associated dysmyelopoiesis was reported in a 62-year-old man and in a 62-year-old woma
received valproate 200 mg twice a day for seizure control. Two weeks later he developed a mild pancyto
bone marrow aspirate showed mild dysmyelopoiesis. His blood cell counts normalized 12 days after disc
valproate. The woman had received valproate 1500 mg/day for 10 years and developed a mild, persister
thrombocytopenia. Following an increase in dosage to 1500 mg twice a day her valproate concentration
therapeutic level to 1447 mcmol/L (therapeutic range, 347 to 693 mcmol/L). Severe pancytopenia occurr
and a diagnosis of dysmyelopoiesis was made following examination of her bone marrow aspirate. She v
carbamazepine and her blood counts normalized in 6 weeks (So & Wong, 2002).

b) Valproic acid therapy resulted in myelodysplastic hematologic changes including macrocytosis, throm
Pelger-Huet neutrophils in two case reports. Neither had folate or B12 deficiencies. The patients involve
old female on valproic acid 6000 mg/day for 3 years for refractory bipolar disorder, with a serum valproic
mcg/mL; and a 2-year-old female with congenital anomalies and seizure disorder on valproic acid 90 mg
unknown), with a serum level of 125 mcg/mL. Hematology profiles improved in both cases with valproic a
reduction (Fawcett, 1997; Hongeng et al, 1997).

c) In a study of 1,251 hospitalized patients receiving valproate therapy, 6 developed moderate to severe
less than 4000/mm(3)); 2 of these patients were also taking carbamazepine (Tohen et al, 1995).

3.3.5.A.7 Neutropenia

a) In a case report, valproic acid use was associated with severe neutropenia that resolved after drug di
56-year-old female was hospitalized for seizure activity secondary to a superior frontoparietal cortex abs
initially treated with phenytoin, however it was replaced with valproic acid due to an adverse reaction. Va
titrated to a dose of 500 mg 3 times daily. Concomitant medications included ceftriaxone and metronidaz
absolute neutrophil count (ANC) prior to the administration of valproic acid was 2064 cells/mm(3). Two d
patient's ANC decreased to 735 cells/mm(3). The following day the ceftriaxone was discontinued and lev
started. On day 4 of valproic acid use the ANC dropped to 56 cells/mm(3) despite a dose of filgrastim. Th

was then discontinued. The next day, the ANC dropped to its nadir of 47 cells/mm(3) and the patient rec
of filgrastim. From that point forward the ANC continued to rise and the neutropenia resolved (Vesta & M

3.3.5.A.8 Pancytopenia

a) Pancytopenia occurred in a 65-year-old man taking valproate 1000 mg daily for bipolar mood disorde
of therapy his WBC count was 6.8, RBC count was 4.52 and platelets (PLT) were 160. He then started ta
750 mg daily. At 10 weeks of treatment his hematological values were: WBC 4.7, RBC 4.21, PLT 137. H
increased to 1000 mg daily and at 14 weeks the hematologic values were: WBC 3.5, RBC 4.18, PLT 132
valproate was discontinued, the indices were: WBC 3.2, RBC 3.83, and PLT 106. The pancytopenia app
related and reversible, disappearing on the valproate was stopped (Oluboka et al, 2000).

b) Fatal pancytopenia developed in a 3-year-old child administered high-dose valproate therapy (Rajant

3.3.5.A.9 Protein C deficiency disease

a) Protein C deficiency may be associated with use of valproic acid, based on a comparison of children
(n=20) and those using other anticonvulsants (n=20), such as carbamazepine, phenytoin, and lamotrigin
group, 19 of 20 children had normal values for coagulation proteins (protein C antigen, protein C functior
protein S free, antithrombin). In the valproic acid group, 45% (9 of 20) had abnormally low values for prot
(p=0.001 compared with other anticonvulsant group), and 40% (8 of 20) had abnormally low values for p
(p=0.002). The authors decided to investigate a potential relationship between valproic acid and protein
a stroke occurred in an 18-month-old child being treated with valproic acid for a seizure disorder. Ruling
which might have caused the child's stroke (a stroke seemingly consistent with ischemic injury) led to a f
abnormally low protein C and related low anticoagulation activity seemed to be the most plausible cause
(Gruppo et al, 2000).

3.3.5.A.10 Pure red cell aplasia

a) Pure red cell aplasia has been associated with sodium valproate therapy. A case of pure red cell apla
9-year-old girl following sodium valproate therapy with 200 mg three times a day for a period of 6 months
previously, the girl had an attack of measles followed immediately by severe chicken pox. It has been su
infective episodes may have sensitized the patient to a potentially hematotoxic drug (valproic acid) that h
been well tolerated. Within one month of drug withdrawal regeneration of bone marrow erythroid precurs
The patient was rechallenged with sodium valproate 200 mg 3 times daily. Within 6 weeks there was evi
aplasia, and the drug was withdrawn. Over the next 6 weeks, the child improved, and red cell aplasia res
(MacDougall, 1982).

3.3.5.A.11 Thrombocytopenia

a) Summary

1) The most common hematologic abnormality with valproic acid is thrombocytopenia, possibly rela
autoimmune mechanism (Rimmer & Richens, 1985f; Covanis et al, 1982; Barr et al, 1982). The inci
induced thrombocytopenia has been reported to vary from 1% to 30% (Allarakhia et al, 1996a; Hoffr
al, 1982; Morris et al, 1981; Smith & Boots, 1980). The rate of occurrence of thrombocytopenia amo
was nearly double that among younger patients (Conley et al, 2001). The risk of thrombocytopenia i
increasing doses of valproic acid and with coadministration of aspirin (Conley et al, 2001). The risk i
total valproate plasma trough levels above 110 mcg/mL in females and 135 mcg/mL in males (Prod
Tablets, 2002a). Nadir platelet counts after valproate administration ranged from 15,000/mm(3) to 8
the time course was variable. A thrombocytopenia rate of 1.6 per 100,000 valproic acid prescriptions
reported by the United Kingdom Department of Health's General Practice Research Database with 5
6465 valproic acid recipients (Blackburn et al, 1998). Valproate-induced thrombocytopenia may be t
related. Platelet aggregation inhibition has also been described (Rimmer & Richens, 1985f; Prod Inf
Tablets, 2002a).

b) In a double-blind, concentration-response clinical trial using valproic acid as monotherapy, high conc
acid (n=96, target level 80 to 150 mcg/mL) caused thrombocytopenia (platelet count of less than 75,000
patients (31%) versus 0 patients in those assigned to low concentration valproic acid (n=47, target range
mcg/mL). Although none of the patients were symptomatic, 12 patients were withdrawn for this adverse
al, 1997c).

c) The effects of valproate in 30 patients ranging in age from 26 years to 76 years were studied. Patient
valproate doses of 1200 mg to 3000 mg. No other anticonvulsants were administered. Following valproa
significant reductions in platelet counts of 49,000/mm(3) from baseline was reported with moderate dose
1700 mg) and a reduction of 69,000/mm(3) was reported with high doses (2100 mg to 3000 mg). Platele
reduced to the lower limit of normal in 10 patients. All patients were asymptomatic. After discontinuation
platelet counts returned to baseline within 4 to 12 days (Neophytides et al, 1979).

d) Children receiving valproic acid had lower platelet counts as compared to control subjects. Patients r
acid mean dose of 20 mg/kg and mean level of 60 mcg/mL. After 6 months of therapy, children receiving
(n=20) had significantly lower platelet counts than age-matched controls (n=15) (194,000/mcL versus 29
than 0.01). Platelet counts were significantly correlated with dose (r=-0.49, p less than 0.05) and plasma
0.52, p less than 0.01). Decreased platelet aggregation and ATP release impairment was also noted in t
group. Discontinuation of valproic acid was not necessary since the decreases were not clinically importa
1999).

e) The incidence of thrombocytopenia (defined as a platelet count of less than 200,000/mm(3)) in childre

Serum valproic acid concentrations of greater than 90 mcg/mL and older adolescent age (16 to 21 years predictive of thrombocytopenia. The degree of thrombocytopenia was mild; the authors concluded that th thrombocytopenia with valproic acid therapy is low and that drug discontinuation is not necessary in the (Allarakhia et al, 1996).

f) A one-year prospective study of 45 children (median age of 6 years) was conducted in which the incid induced thrombocytopenia was evaluated. Twelve patients also received treatment with other anticonvul cases of thrombocytopenia (defined as a platelet count less than 150,000/mm(3) occurring 3 to 8 months of valproate) were noted that were reported to be transient and self-limited. In 82% of cases, thrombocyt associated with an increase in platelet-associated IgG antibodies. There was an inverse relationship in t and the serum concentration of platelet-associated IgG antibody. There was not a significant difference b serum concentrations in patients with or without thrombocytopenia. It was concluded that immune-media thrombocytopenia may be common, but appears to be transient and self-limited despite continuations of (Barr et al, 1982).

g) A case of thrombocytopenia-induced fatal pulmonary hemorrhage was reported in a 30-year-old fema valproate monotherapy. Its been suggested that viral infections may be associated with thrombocytopeni receiving valproate therapy (Sleiman et al, 2000).

3.3.5.A.12 Thrombocytopenia, Dose-related

a) Incidence: 1% to 27% (Prod Info STAVZOR(R) delayed release oral capsules, 2008)

b) During clinical trials of patients with epilepsy, thrombocytopenia (at least 1 platelet value of 75 x 10(9) reported in 27% (34/126) of patients receiving valproate monotherapy at approximately 50 mg/kg/day. Pl returned to normal in all patients regardless of whether the drug was withdrawn or continued. Higher tota concentrations (110 mcg/mL or greater in females and 135 mcg/mL or greater in males) were significantl thrombocytopenia occurrence. Monitoring of platelet counts and coagulation is recommended prior to va and at periodic intervals during therapy (Prod Info STAVZOR(R) delayed release oral capsules, 2008).

c) During a clinical trial of valproate monotherapy for complex partial seizures, thrombocytopenia was re patients receiving high-dose valproate (n=131) compared with 1% of patients receiving low-dose valproa many cases, causality could not be determined as patients were being titrated off another antiepilepsy dr part of the trial (Prod Info STAVZOR(R) delayed release oral capsules, 2008).

3.3.5.A.13 von Willebrand factor inhibitor disorder

a) Below-normal levels of von Willebrand factor activity was observed in 6 of 29 (21%) children who had valproic acid for at least 6 months for treatment of epilepsy. The 6 children were regarded as having "acc Willebrand's Disease." No correlation was found between von Willebrand factor activity and dose or bloo acid or duration of therapy. The authors cautioned that when surgery is necessary, factor VIII von Willebr concentrations should be supplemented (Serdaroglu et al, 2002).

3.3.5.B Divalproex Sodium

Ecchymosis

Thrombocytopenia, Dose-related

3.3.5.B.1 Ecchymosis

a) Incidence: 4% to 5% (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008)

b) Ecchymosis was reported in 5% of patients receiving high-dose divalproex sodium (n=131) compared patients receiving low-dose divalproex sodium (n=134) for monotherapy treatment of complex partial sei cases, causality could not be attributed to divalproex alone, as patients were titrated off of another antiep the first part of the trial (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008).

3.3.5.B.2 Thrombocytopenia, Dose-related

a) Incidence: 1% to 27% (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008)

b) During clinical trials of patients with epilepsy, thrombocytopenia (at least 1 platelet value of 75 x 10(9) reported in 27% (34/126) of patients receiving divalproex sodium monotherapy at approximately 50 mg/k counts returned to normal in all patients regardless of whether the drug was withdrawn or continued. Hig concentrations (110 mcg/mL or greater in females and 135 mcg/mL or greater in males) were significantl thrombocytopenia occurrence. Monitoring of platelet counts and coagulation is recommended prior to div initiation and at periodic intervals during therapy, especially prior to planned surgery. Drug discontinuatio reduction is recommended if patient experiences hemorrhage, bruising, or a hemostasis/coagulation disc divalproex sodium therapy (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008).

c) Thrombocytopenia was reported in 24% of patients receiving high-dose divalproex sodium (n=131) co of patients receiving low-dose divalproex sodium (n=134) for monotherapy treatment of complex partial s cases, causality could not be attributed to divalproex alone, as patients were titrated off of another antiep the first part of the trial (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008).

3.3.6 Hepatic Effects

Valproic Acid

Divalproex Sodium

3.3.6.A Valproic Acid

ALT (SGPT) level raised

AST/SGOT level raised

Hepatitis

Hepatotoxicity

Increased liver function test

Liver failure

3.3.6.A.1 ALT (SGPT) level raised

a) Incidence: 1% to less than 5% (Prod Info STAVZOR(R) delayed release oral capsules, 2008)

b) Increased SGPT was reported in more than 1% but less than 5% of patients receiving valproate durir (n=202) and during monotherapy treatment of complex partial seizures (n=265). In many cases, causalit attributed to valproate alone, as patients were titrated off of another antiepilepsy drug during the first par monotherapy trial (Prod Info STAVZOR(R) delayed release oral capsules, 2008).

3.3.6.A.2 AST/SGOT level raised

a) Incidence: 1% to less than 5% (Prod Info STAVZOR(R) delayed release oral capsules, 2008)

b) Increased SGOT was reported in more than 1% but less than 5% of patients receiving valproate durir (n=202) and during monotherapy treatment of complex partial seizures (n=265). In many cases, causalit attributed to valproate alone, as patients were titrated off of another antiepilepsy drug during the first par monotherapy trial (Prod Info STAVZOR(R) delayed release oral capsules, 2008).

3.3.6.A.3 Hepatitis

a) An 8-year-old boy taking valproate 40 mg/kg daily for epilepsy died from a normally benign viral hepa acquired from his sister. The boy presented with jaundice, decreased consciousness, lethargy, hyperam increased valproate level. Despite aggressive medical treatment and discontinuation of the valproate the liver enzymes decreased while his bilirubin level and bleeding time increased and the patient died 12 da to the hospital. The authors postulate that the additive hepatotoxicity associated with the increased valpr have contributed to the development of fulminant liver failure and death in this patient (Fayad et al, 2000)

3.3.6.A.4 Hepatotoxicity

a) Fatal hepatotoxicity is reported in 1/800 children under the age of 2 years following antiepileptic thera acid. It is suggested that valproic acid may induce a carnitine deficiency in young children and result in n symptoms of deficiency, hepatotoxicity, and hyperammonemia. Carnitine supplementation may help prev hepatotoxicity (Raskind & El-Chaar, 2000).

b) A 52-year-old male with no known risk factors developed fulminant hepatotoxicity that progressed to while taking valproic acid 500 mg twice daily for migraine prophylaxis. He presented with altered mental jaundice and anuria. An exhaustive diagnostic work-up failed to reveal an etiology. The patient had asso as well as acute tubular necrosis with renal failure and rhabdomyolysis. He fully recovered after 16 days and supportive care (Pinkston & Walker, 1997).

c) One study indicated that the greatest risk of fatal hepatotoxicity occurred in children between the age who were receiving multiple anticonvulsant therapy. The incidence of fatal hepatotoxicity in this group wa greater than the overall incidence of fatal hepatotoxicity of 1/10,000). The incidence of fatal hepatotoxicit age group was 1/7000. No hepatic fatalities were described in patients over the age of 10 years who rec as monotherapy. The risk of fatal hepatotoxic reactions in children over the age of 2 years receiving poly considerably lower (1/12,000), with the risk of fatal hepatic dysfunction in patients above 2 years of age r acid as monotherapy being 1/45,000. Thus, the risk of fatal hepatic reactions appears to be greatest in v (0 to 2 years of age) and declines significantly with age (Dreifuss et al, 1987).

3.3.6.A.5 Increased liver function test

a) Summary

1) Elevated liver enzymes have been reported following chronic administration of valproate (Lewis, Wilder, 1979a; Gerber et al, 1979; Addison & Gordon, 1980; Coulter & Allen, 1981; Rawat et al, 198 elevations in transaminases (aspartate aminotransferase (AST; SGOT) and alanine aminotransferas and lactate dehydrogenase are frequently seen and are dose-related. Increased serum bilirubin and function tests may also be seen. These may reflect a more serious problem. It is speculated that val normally toxic substance, but in the presence of metabolic abnormalities such as an inborn error of r administration with other drugs, it may become toxic (Rimmer & Richens, 1985f).

3.3.6.A.6 Liver failure

a) Serious hepatotoxicity and hepatic failure have been reported in patients receiving valproic acid and i usually in the first 6 months of treatment. Serious or fatal hepatic toxicity may be preceded by symptoms lethargy, anorexia, malaise, facial edema, weakness, or loss of seizure control (in epileptic patients). Mo function tests should be initiated prior to therapy and at frequent intervals during treatment, mainly during months. However, abnormal serum biochemistry may not be present in all cases. Children under the age increased risk of developing hepatotoxicity, especially if they are taking multiple anticonvulsants, have co disorders, have severe seizure disorders accompanied by mental retardation, or have organic brain dise dysfunction has progressed in some cases, even with the discontinuation of drug (Prod Info STAVZOR(R oral capsules, 2008).

b) A case of fulminant liver failure induced by valproate therapy was reported in a 39-year-old woman w bilateral ptosis and chronic progressive external ophthalmoplegia (CPEO). The patient developed fulmina months after she was treated with valproate for status epilepticus and died due to multiorgan failure and syndrome. The patient's 2 siblings also had congenital bilateral ptosis and CPEO, a typical sign of mitoch cytopathies, but none of them had any previous signs of liver disease. This report suggested that mitoch should be considered a risk factor for valproate-induced liver failure and should be excluded before valpr (Krahenbuhl et al, 2000).

c) It is speculated that valproic acid is not a normally toxic substance, but in the presence of metabolic a as an inborn error of metabolism or administration with other drugs, it may become toxic (Rimmer & Rich one case, medium chain acyl-CoA dehydrogenase deficiency, resulting in abnormal fatty acid beta-oxida in a 10-year-old male who died of liver failure 3 months after valproic acid initiation (Njolstad et al, 1997).

d) In one report, hepatic failure occurred in a 15-year-old boy following approximately 5 years of valproic epilepsy. The patient had also been receiving phenytoin and phenobarbital. The patient developed cereb in a 24-hour period. These data suggest that hepatic failure secondary to valproic acid can also occur aft therapy (van Egmond et al, 1987).

e) Acute hepatic failure resulting in fatality in 2 children (5 years and 11.5 years) following 650 mg daily months and 250 mg to 1000 mg daily over approximately 7 weeks (with other anticonvulsants), respectiv described. Autopsy revealed mixed toxic cholestatic hepatitis with diffuse hepatocellular injury which tern centrolobular microvesicular fatty changes and submassive necrosis. The site of injury appeared to be bi apparatus, canaliculi and ducts of Hering (Suchy et al, 1979).

3.3.6.B Divalproex Sodium

ALT (SGPT) level raised

AST/SGOT level raised

Liver failure

3.3.6.B.1 ALT (SGPT) level raised

a) Incidence: 1% to less than 5% (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008)

b) Increased SGPT was reported in more than 1% but less than 5% of patients receiving divalproex sod monotherapy treatment of complex partial seizures. In many cases, causality could not be attributed to d patients were titrated off of another antiepilepsy drug during the first part of the trial (Prod Info DEPAKOT capsules, 2008).

3.3.6.B.2 AST/SGOT level raised

a) Incidence: 1% to less than 5% (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008)

b) Increased SGOT was reported in more than 1% but less than 5% of patients receiving divalproex soc monotherapy treatment of complex partial seizures. In many cases, causality could not be attributed to d patients were titrated off of another antiepilepsy drug during the first part of the trial (Prod Info DEPAKOT capsules, 2008).

3.3.6.B.3 Liver failure

a) Serious hepatotoxicity and hepatic failure have been reported in patients receiving valproic acid and i

usually in the first 6 months of treatment. Serious or fatal hepatic toxicity may be preceded by symptoms lethargy, anorexia, malaise, facial edema, weakness, or loss of seizure control (in epileptic patients). Mo function tests should be initiated prior to therapy and at frequent intervals during treatment, mainly during months. However, abnormal serum biochemistry may not be present in all cases. Children under the age increased risk of developing hepatotoxicity, especially if they are taking multiple anticonvulsants, have co disorders, have severe seizure disorders accompanied by mental retardation, or have organic brain dise dysfunction has progressed in some cases, even with the discontinuation of drug (Prod Info DEPAKOTE capsules, 2008).

3.3.7 Immunologic Effects

Valproic Acid

Divalproex Sodium

3.3.7.A Valproic Acid

HIV infection, Progression

Immune hypersensitivity reaction

Immunology finding

Systemic lupus erythematosus

3.3.7.A.1 HIV infection, Progression

a) Valproate therapy may reduce intracellular levels of glutathione and inhibit activity of glutathione redu red blood cells. There may be a link between intracellular levels of glutathione and the progression of hu immunodeficiency virus (HIV) disease. Decreased glutathione levels may activate the replication of HIV. with cell lines infected with HIV showed the addition of valproate increased viral expression and replicati drug concentrations (Hardy & Nardacci, 1999).

3.3.7.A.2 Immune hypersensitivity reaction

a) Incidence: rare (Prod Info STAVZOR(R) delayed release oral capsules, 2008)

b) Multiorgan hypersensitivity reactions (eg, fever and rash associate with other organ system involvem rarely reported between 1 and 40 days following initiation of valproate therapy in both adult and pediatric reactions have led to hospitalization and at least one death. If a hypersensitivity reaction occurs, disconti therapy and begin an alternative treatment (Prod Info STAVZOR(R) delayed release oral capsules, 2008

c) A 6-year-old boy developed hypersensitivity syndrome after receiving valproic acid for about 1.5 mon ethosuximide for 1 month. Both drugs were in the therapeutic range. He developed a diffuse morbilliform edema of the face, high fever, and enlarged lymph nodes. He also had a leukocytosis, eosinophilia, lymp monocytosis, and stimulated lymphocytes. Liver enzymes were also slightly elevated. Since the authors infections may contribute to the pathogenesis of hypersensitivity, the child was tested for reactivation of l 6. Titers were significantly increased within 15 days. Patch testing revealed hypersensitivity to both valpr ethosuximide (Conilleau et al, 1999).

3.3.7.A.3 Immunology finding

a) IgA deficiency was reported in 29% of 41 epileptic patients receiving 1 or more anticonvulsants (valpr phenytoin, phenobarbital, carbamazepine) was reported. Patients receiving valproate sodium exhibited s mean IgA levels than nonusers of valproate sodium (Joubert et al, 1977).

3.3.7.A.4 Systemic lupus erythematosus

a) A case of systemic lupus erythematosus, marked by increased antihistone antibody level, arthralgias, weakness, fatigue and fever, was reported in a 30-year-old female epileptic patient after 1 year of treatm acid. The laboratory and clinical symptoms disappeared after discontinuation of valproic acid (Gigli et al, See Drug Consult reference: DRUG-INDUCED SYSTEMIC LUPUS ERYTHEMATOSUS

3.3.7.B Divalproex Sodium

3.3.7.B.1 Immune hypersensitivity reaction

a) Incidence: rare (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008)

b) Multi-organ hypersensitivity reactions (eg, fever and rash associate with other organ system involvem

rarely reported between 1 and 40 days following initiation of valproate therapy in both adult and pediatric reactions have led to hospitalization and at least one death. If a hypersensitivity reaction occurs, disconti therapy and begin an alternative treatment (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008).

3.3.8 Musculoskeletal Effects

Valproic Acid

Divalproex Sodium

3.3.8.A Valproic Acid

Asthenia

Backache

Osteomalacia

Secondary myopathy

3.3.8.A.1 Asthenia

a) Incidence: 10% to 27% (Prod Info STAVZOR(R) delayed release oral capsules, 2008)

b) During two clinical trials of valproate treatment of manic episodes associated with bipolar disorder, as reported in 10% of patients receiving valproate (n=89) compared with 7% of patients receiving placebo (n STAVZOR(R) delayed release oral capsules, 2008).

c) Asthenia was reported in 20% of migraine patients receiving valproate (n=202) compared with 9% of placebo (n=81) during two clinical trials and their long-term extension (Prod Info STAVZOR(R) delayed re capsules, 2008).

d) During a clinical trial where valproate was given as adjunctive therapy for treatment of complex partia asthenia was reported in 27% of patients receiving valproate (n=77) compared with 7% of patients receiv (n=70). In most cases, causality could not be determined as patients also received other antiepilepsy dru with valproate (Prod Info STAVZOR(R) delayed release oral capsules, 2008).

e) During a clinical trial of valproate monotherapy for complex partial seizures, asthenia was reported in receiving high-dose valproate (n=131) compared with 10% of patients receiving low-dose valproate (n=1 cases, causality could not be determined as patients were being titrated off another antiepilepsy drug du the trial (Prod Info STAVZOR(R) delayed release oral capsules, 2008).

3.3.8.A.2 Backache

a) Incidence: 8% (Prod Info STAVZOR(R) delayed release oral capsules, 2008)

b) Back pain was reported in 8% of migraine patients receiving valproate (n=202) compared with 6% of placebo (n=81) during two clinical trials and their long-term extension (Prod Info STAVZOR(R) delayed re capsules, 2008).

3.3.8.A.3 Osteomalacia

a) A 2-year cross-sectional and retrospective study concluded that lumbar spine bone mineral density va significantly reduced in prepubertal children treated with valproic acid and carbamazepine compared to c children treated with antiepileptics (valproic acid: 17 boys, 16 girls; mean age 8.8 +/- 2 years; carbamaze girls; mean age 9.7 +/-1.6 years) were compared to age- and sex-matched controls (13 boys, 9 girls; me years). Patients were ambulatory with normal activity and had adequate nutritional intake, which exclude could reduce BMD or biochemical markers of bone turnover. Mean length of treatment was 33.72 +/- 15 acid and 35.52 +/- 12.84 months for carbamazepine. Mean BMD z-scores at lumbar spine were -1.28 +/- acid, -1.69 +/- 0.85 for carbamazepine, and -0.23 +/- 0.87 for the control group. Differences in serum insu factor (IGF)-I and IGF binding protein (IGFBP)-3 levels, which affect bone metabolism and BMD, betwee receiving antiepileptics compared to controls were not significant (Kumandas et al, 2006).

3.3.8.A.4 Secondary myopathy

a) A 4-year-old male child developed myopathy with symptoms of progressive weakness in all limbs 16 starting valproate sodium for epilepsy. Over 1 year the valproate sodium dose was gradually increased fr 40 mg/kg. Four months after starting on 40 mg/kg, he developed lower limb weakness resulting in difficu jumping, climbing up stairs, and standing from a sitting position. Examination revealed weakness in prox muscles of all four limbs (more pronounced in the lower limbs), lordosis, a waddling gait, and normal sen tendon reflexes. No hypertrophy or atrophy was noted. Serum valproate and creatinine phosphokinase c

were within normal limits. The findings on electromyogram (EMG) were suggestive of myopathy. Plasma was below normal at 16 mcmol/L (normal, 20 to 43 mcmol/L). Valproate-induced-myopathy secondary to deficiency was suspected. Carbamazepine replaced valproate and L-carnitine 100 mg/kg/day was initiate there was improvement and within 2 months complete recovery. Complete recovery was further demons months later (Kasturi & Sawant, 2005).
b) Chronic therapeutic use of valproic acid in young children may cause a carnitine deficiency resulting i symptoms of lethargy, weakness or hypotonia, hepatotoxicity, and hyperammonemia. An incidence of fa children under the age of two years of 1/800 has been reported (Raskind & El-Chaar, 2000). An inverse found between plasma carnitine concentrations and the dosage of valproic acid, and between plasma ca ammonia values (Ohtani et al, 1982).
c) The syndrome known as MELAS, including mitochondrial myopathy, encephalopathy, lactic acidosis episodes, was precipitated by valproic acid therapy in a 12-year-old male. Signs and symptoms included exacerbation, hemiparesis, hypotonia, elevated deproteinized blood lactate and pyruvate, and brain infar was found to have a point mutation in mitochondrial DNA. He stabilized upon valproic acid withdrawal (L

3.3.8.B Divalproex Sodium

Arthralgia

Backache

Generalized myasthenia

Myalgia

3.3.8.B.1 Arthralgia
a) Incidence: 1% to 5% (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008)
b) Arthralgia was reported in more than 1% but less than 5% of patients receiving divalproex sodium (n= monotherapy treatment of complex partial seizures. In many cases, causality could not be attributed to d patients were titrated off of another antiepilepsy drug during the first part of the trial (Prod Info DEPAKOT capsules, 2008).

3.3.8.B.2 Backache
a) Incidence: 1% to less than 5% (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008)
b) Back pain was reported in more than 1% but less than 5% of patients receiving divalproex sodium (n= monotherapy treatment of complex partial seizures. In many cases, causality could not be attributed to d patients were titrated off of another antiepilepsy drug during the first part of the trial (Prod Info DEPAKOT capsules, 2008).

3.3.8.B.3 Generalized myasthenia
a) Incidence: 1% to 5% (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008)
b) Myasthenia was reported in more than 1% but less than 5% of patients receiving divalproex sodium (monotherapy treatment of complex partial seizures. In many cases, causality could not be attributed to d patients were titrated off of another antiepilepsy drug during the first part of the trial (Prod Info DEPAKOT capsules, 2008).

3.3.8.B.4 Myalgia
a) Incidence: 1% to less than 5% (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008)
b) Myalgia was reported in more than 1% but less than 5% of patients receiving divalproex sodium (n=3 monotherapy treatment of complex partial seizures. In many cases, causality could not be attributed to d patients were titrated off of another antiepilepsy drug during the first part of the trial (Prod Info DEPAKOT capsules, 2008).

3.3.9 Neurologic Effects

Valproic Acid

Divalproex Sodium

3.3.9.A Valproic Acid

Abnormal behavior

Amnesia

Ataxia

Cerebral atrophy

Coma, Hyperammonemia-induced

Dementia

Demyelinating disease of central nervous system

Dizziness

Extrapyramidal disease

Feeling nervous

Headache

Hyperammonemic encephalopathy

Insomnia

Paresthesia

Seizure

Somnolence

Tremor

3.3.9.A.1 Abnormal behavior

a) Behavioral changes were seen in 56 out of 88 pediatric patients receiving sodium valproate monothe included irritability, longer and deeper sleep, superficial sleep, hyperactivity, increased alertness, lassitu increased sociability, calmness, increased sadness, happiness, and aggression. It was emphasized that reactions with valproic acid were as frequent as depressive effects (Herranz et al, 1984b).

3.3.9.A.2 Amnesia

a) Incidence: 4% to 7% (Prod Info STAVZOR(R) delayed release oral capsules, 2008)

b) During a clinical trial of valproate monotherapy for complex partial seizures, amnesia was reported in receiving high-dose valproate (n=131) compared with 4% of patients receiving low-dose valproate (n=13 causality could not be determined as patients were being titrated off another antiepilepsy drug during the trial (Prod Info STAVZOR(R) delayed release oral capsules, 2008).

3.3.9.A.3 Ataxia

a) Incidence: 8% (Prod Info STAVZOR(R) delayed release oral capsules, 2008)

b) During a clinical trial where valproate was given as adjunctive therapy for treatment of complex partia was reported in 8% of patients receiving valproate (n=77) compared with 1% of patients receiving placeb cases, causality could not be determined as patients also received other antiepilepsy drugs concurrently (Prod Info STAVZOR(R) delayed release oral capsules, 2008).

3.3.9.A.4 Cerebral atrophy

a) In a series of 16 patients treated with valproate in whom cranial computer tomography (CT) were perf demonstrated new or progressive cerebral atrophy. The atrophy improved in the two patients in whom cr repeated after valproate was discontinued (Armon et al, 1996).

3.3.9.A.5 Coma, Hyperammonemia-induced

a) A 56-year-old woman experienced life-threatening hyperammonemic coma following a moderate dos divalproex sodium. The patient had been poorly controlled while receiving divalproex sodium for 6 years

phenobarbital, phenytoin, carbamazepine, and gabapentin. The divalproex sodium dose was increased f to 2500 mg/day, and the phenobarbital, phenytoin, carbamazepine and gabapentin were slowly discontir initially presented with a 3-hour period of unresponsiveness on divalproex sodium monotherapy. Her am mcg/dL (reference range 22 to 78). The divalproex sodium dose was increased to 3000 mg/day. The pat after 10 hours of the dose escalation. Her venous ammonia level was 921 mcg/dL, and the arterial amm mcg/dL (reference range 22 to 78). Possible causes of hyperammonemia and coma were excluded by e gastrointestinal bleeding or portosystemic shunt and other metabolic, toxic, and structural factors respec divalproex sodium was discontinued and within 48 hours, the ammonia level normalized to 69 mcg/dL ar regained consciousness. A possible urea enzyme deficiency may have contributed to the development o hyperammonemic coma. The Naranjo probability scale conducted stated that the causal relationship bet and hyperammonemic coma was probable (Cuturic, 2005).

3.3.9.A.6 Dementia

a) Long-term therapy with valproic acid was associated with the occurrence of a reversible dementia in a with epilepsy. Withdrawal of the drug resulted in dramatic improvement in memory and other tasks of int It is suggested that valproic acid may induce a dementia-like syndrome via either a direct toxic central ne (CNS) effect, a paradoxical epileptogenic effect, or an indirect CNS effect via production of hyperammon Cohen, 1986).

3.3.9.A.7 Demyelinating disease of central nervous system

a) A 23-year-old male with fulminant demyelinating disease experienced an acute progression after an e valproate-induced hyperammonemic encephalopathy. He had been experiencing uncontrolled seizures v phenytoin and phenobarbital when valproic acid 500 mg twice daily was added to his regimen. After 3 da progressively lethargic and was eventually unresponsive. His venous ammonia level was 524 mcmol/L (r mcmol/L) with normal liver enzymes. Serum carnitine levels were also low. After 15 days, a repeat crania extensive progression of his demyelinating disease. He expired 3 weeks thereafter. The authors specula hyperammonemia may have exacerbated his disease. They conclude that valproic acid should be avoide of seizures in patients with demyelinating disease (Blindauer et al, 1998).

3.3.9.A.8 Dizziness

a) Incidence: 12% to 25% (Prod Info STAVZOR(R) delayed release oral capsules, 2008)

b) During a clinical trial of valproate monotherapy for complex partial seizures, dizziness was reported ir receiving high-dose valproate (n=131) compared with 13% of patients receiving low-dose valproate (n=1 cases, causality could not be determined as patients were being titrated off another antiepilepsy drug du the trial (Prod Info STAVZOR(R) delayed release oral capsules, 2008).

c) During two clinical trials of valproate treatment of manic episodes associated with bipolar disorder, diz reported in 12% of patients receiving valproate (n=89) compared with 4% of patients receiving placebo (r STAVZOR(R) delayed release oral capsules, 2008).

d) Dizziness was reported in 12% of migraine patients receiving valproate (n=202) compared with 6% o placebo (n=81) during two clinical trials and their long-term extension (Prod Info STAVZOR(R) delayed r capsules, 2008).

e) During a clinical trial where valproate was given as adjunctive therapy for treatment of complex partia dizziness was reported in 25% of patients receiving valproate (n=77) compared with 13% of patients rec (n=70). In most cases, causality could not be determined as patients also received other antiepilepsy dru with valproate (Prod Info STAVZOR(R) delayed release oral capsules, 2008).

3.3.9.A.9 Extrapyramidal disease

a) Summary

1) A 77-year-old man, with a diagnosis of dementia of the Alzheimer's type, developed an acute Pa movement disorder 1 week after starting valproate therapy. This man, who had no prior history of m was started on valproate due to an increase in aggressive and violent behaviors. The valproate dos increased to 300 mg per day over one week and resulted in a serum level of 11 mcg/mL. At this time experienced resting tremors, rigidity, gait disturbance, and bradykinesis and his Unified Parkinson's Scale (UPDRS) score increased from 18 to 59. Valproate was discontinued 2 weeks later when ther lessening in the Parkinsonian symptoms. Movement disorder signs gradually resolved following disc valproate (Iijima, 2002).

2) Parkinson's syndrome has been associated with chronic valproate therapy. In a series of 36 patie valproate, 27 (75%) had clinical evidence of Parkinsonism (Armon et al, 1996). Of these patients 19 of instability, 16 (44%) reported tremor, 30 (80%) demonstrated cognitive impairment, 22 (62%) had (55%) had abulia and 16 (44%) had upper motor neuron signs (Armon et al, 1996). Most patients im valproate was discontinued. An extrapyramidal syndrome, unresponsive to antiparkinson medicatior developed in a 52-year-old man with schizophrenia who was given sodium valproate 1 to 2 g/day (L

3.3.9.A.10 Feeling nervous

a) Incidence: 7% to 11% (Prod Info STAVZOR(R) delayed release oral capsules, 2008)

b) During a clinical trial of valproate monotherapy for complex partial seizures, nervousness was reporte patients receiving high-dose valproate (n=131) compared with 7% of patients receiving low-dose valproa many cases, causality could not be determined as patients were being titrated off another antiepilepsy dr

part of the trial (Prod Info STAVZOR(R) delayed release oral capsules, 2008).

3.3.9.A.11 Headache

a) Incidence: 5% to 31% (Prod Info STAVZOR(R) delayed release oral capsules, 2008)

b) During a clinical trial where valproate was given as adjunctive therapy for treatment of complex partia headache was reported in 31% of patients receiving valproate (n=77) compared with 21% of patients rec (n=70). In most cases, causality could not be determined as patients also received other antiepilepsy dru with valproate (Prod Info STAVZOR(R) delayed release oral capsules, 2008).

c) During a clinical trial of valproate monotherapy for complex partial seizures, headache was the only a reported in at least 5% of patients receiving high-dose (n=131) valproate and occurring at an equal or gr patients receiving low-dose valproate (n=134). In many cases, causality could not be determined as pati titrated off another antiepilepsy drug during the first part of the trial (Prod Info STAVZOR(R) delayed rele 2008).

3.3.9.A.12 Hyperammonemic encephalopathy

a) Hyperammonemic encephalopathy, sometimes fatal, has been reported with valproic acid use in pati cycle disorders (particularly ornithine transcarbamylase deficiency) and in patients receiving concomitant Patients who develop symptoms of hyperammonemic encephalopathy (unexplained lethargy and vomitin changes) while receiving valproate therapy should receive prompt treatment (including discontinuation of therapy) and be evaluated for underlying urea cyclic disorder. Most patients receiving concomitant topira resolution of hyperammonemia upon discontinuation of either drug (Prod Info STAVZOR(R) delayed rele 2008).

b) An 88-year-old man developed hyperammonemia and worsening confusion two months after starting four times a day for a presumed seizure disorder. His liver function tests were within normal limits except concentration of 836 mcg/dL (reference range 19 to 60 mcg/dL). His trough valproate serum concentratio His medication was changed to phenytoin 150 mg twice day and his confusion resolved. One week later was 63 mcmol/L (reference range 11 to 35 mcmol/L) and his phenytoin and valproate concentrations we and less than 10 mcg/mL, respectively. He was inadvertently started on valproate again at the former do days his ammonia concentration increased to 130 mcmol/L. He became confused and lethargic and his E bilateral 5 to 7 hertz (Hz) slowing and abnormal, irregular 2-Hz to 3-Hz activity on the right. Valproate wa his ammonia concentration decreased to 60 mcmol/L after 1 day and on the second day his confusion de baseline (Feil et al, 2002).

c) Clinicians reported two adult cases of valproate-induced hyperammonemic encephalopathy, which oc combination therapy including valproate and topiramate. The patients were a 32-year-old man who had l epilepsy with complex partial and secondarily generalized seizures and a 37-year-old woman with focal e right parietal angioma. Among the patient's symptoms were sudden somnolence, slurred speech, ataxia, horizontal nystagmus, and nausea. One day after admission, the man was reacting only to strong stimuli experienced 2 secondarily generalized tonic-clonic seizures (the first time in 10 years for the woman). EE revealed continuous generalized slowing for both. The patients had previously tolerated valproate in com medications (phenobarbital, carbamazepine, lamotrigine). The encephalopathy occurred in both instance and topiramate were given concurrently in a combination regimen. Both had serum levels of valproate be therapeutic range (ie, 38 and 47 mcg/mL, respectively; therapeutic range, 50 to 100 mcg/mL) and elevat ammonia concentrations (116 and 88 mcmol/L, respectively; normal range 11 to 60 mcmol/L). One patie by discontinuation of valproate and the other, by withdrawal of topiramate. The authors suggested that to increase ammonia levels by its inhibition of carbonic anhydrase and cerebral glutamine synthetase (Ham

d) Ten days following initiation of valproic acid (10 mg/kg/day), a 51-year-old female presented with a ra level of consciousness (Glasgow coma score 5/15). EEG showed triphasic waves consistent with hepatic Serum valproic acid and liver enzyme levels were normal; blood arterial ammonia concentration was sign (234 mcmol/L) 10 hours after presentation. Following discontinuation of valproic acid and administration her neurological condition improved within 18 hours (Borbath et al, 2000).

e) A 16-year-old girl with undiagnosed heterozygous ornithine transcarbamylase deficiency (OTC) devel hyperammonemic encephalopathy after valproic acid therapy. OTC deficiency is an X-linked disorder wh common inherited cause of hyperammonemia. The child was experiencing frequent seizures and had va to her carbamazepine therapy. After 7 days, she became deeply somnolent. Her plasma ammonia level (normal less than 50 mcmol) with normal serum transaminases and fibrinogen. Valproic acid was discon deficiency diagnosis was based on non-detectable serum citrulline and high urinary excretion of orotic ac treated with a low-protein diet, sodium benzoate, sodium phenylbutyrate, and substitution of L-arginine. A ammonia levels fell to 55 mcmol (Ochsner et al, 1998).

f) A 23-year-old male with fulminant demyelinating disease experienced an acute progression after an e valproate-induced hyperammonemic encephalopathy. He had been experiencing uncontrolled seizures v phenytoin and phenobarbital when valproic acid 500 mg twice daily was added to his regimen. After 3 da progressively lethargic and was eventually unresponsive. His venous ammonia level was 524 mcmol/L (n mcmol/L) with normal liver enzymes. Serum carnitine levels were also low. After 15 days, a repeat crania extensive progression of his demyelinating disease. He expired 3 weeks thereafter. The authors specula hyperammonemia may have exacerbated his disease. They conclude that valproic acid should be avoide of seizures in patients with demyelinating disease (Blindauer et al, 1998).

g) A 31-year-old woman with systemic lupus erythematous and a seizure disorder treated with valproic a developed fatal hyperammonemia. The woman had also been receiving aspirin 81 mg and cimetidine 40

elevation in anti-cardiolipin-beta2-glycoprotein-1Ab. After 15 months of valproic acid therapy, she was di
nephritis and treated with repeated steroid pulse therapy. This was ineffective and hemodialysis was inst
and finally coma developed and she was found to have a serum ammonia level of 500 mcmol/L. Despite
her ammonia level continued to rise and she died of hyperammonemic encephalopathy (Ichikawa et al, 1

3.3.9.A.13 Insomnia

a) Incidence: 9% to 15% (Prod Info STAVZOR(R) delayed release oral capsules, 2008)

b) During a clinical trial of valproate monotherapy for complex partial seizures, insomnia was reported ir
receiving high-dose valproate (n=131) compared with 9% of patients receiving low-dose valproate (n=13
causality could not be determined as patients were being titrated off another antiepilepsy drug during the
trial (Prod Info STAVZOR(R) delayed release oral capsules, 2008).

3.3.9.A.14 Paresthesia

a) Incidence: 1% to less than 5% (Prod Info STAVZOR(R) delayed release oral capsules, 2008)

b) Paresthesia was reported in more than 1% but less than 5% of patients receiving valproate during pla
clinical trials of migraine and acute mania and during monotherapy treatment of complex partial seizures
causality could not be attributed to valproate alone in the complex partial seizures trial, as patients were
another antiepilepsy drug during the first part of the study (Prod Info STAVZOR(R) delayed release oral

3.3.9.A.15 Seizure

a) In 2 children, ages 5 and 10 years old, valproic acid therapy for infrequent absence seizures resulted
deterioration to absence status with atonic generalized seizures, along with drop attacks in the younger
experienced an increase in the frequency and duration of absences and progressive disorientation. The
effects of valproic acid occurred at doses of 80 to 120 mg twice per day for the 5-year-old patient and 50
for the 10-year-old patient. After valproic acid administration was stopped, both patients experienced a d
absence frequency and duration (to pretreatment levels) along with a clearing of disorientation (Shahar e

b) A 14-year-old boy receiving phenobarbital for tonic-clonic seizures presented with status epilepticus a
valproic acid added. Initially, tonic seizures occurred which increased after 13 days to status. Serum plas
of both valproic acid and phenobarbital were within the therapeutic range. Valproic acid was discontinue
a later date with similar results (Capocchi et al, 1998).

c) Increasing generalized spike and wave activity with increasing somnolence to the point of absence st
25-year-old woman after beginning valproic acid therapy. The woman suffered from multiple seizure type
generalized tonic-clonic, gelastic, absence, and drop attacks. She was being treated with carbamazepine
and fluphenazine. Valproic acid (maximum dose 2500 mg after 4 days) was added for hallucinations ass
frequent seizures. Spike and wave activity during wakefulness was noted to increase as the blood conce
acid increased. Her ammonia level also increased to 104 mcmol/L. Valproic acid was discontinued and la
started (Stecker & Kita, 1998).

d) A breakthrough seizure occurred in a 19-year-old epileptic girl following substitution of Depakene(R)
generic form of valproic acid capsules. Re-initiation of Depakene(R) therapy resulted in no recurrence of
months of follow-up (MacDonald, 1987).

3.3.9.A.16 Somnolence

a) Incidence: 17% to 30% (Prod Info STAVZOR(R) delayed release oral capsules, 2008)

b) In a double-blinded study involving elderly patients with dementia (mean age of 83 years), the occurr
somnolence was significantly higher in the valproate arm (target dose of 20 mg/kg/day) compared with p
approximately half of the affected patients, somnolence was associated with reduced nutritional intake, v
baseline albumin concentration, lower valproate clearance, and higher BUN. When dosing elderly patien
recommended to increase doses more slowly and to monitor fluid and nutritional intake, dehydration, and
adverse reactions (including somnolence) on a regular basis. Consider dose reductions or discontinuatio
excessive somnolence or in patients with reduced fluid or nutritional intake (Prod Info STAVZOR(R) dela
capsules, 2008).

c) During a clinical trial of valproate monotherapy for complex partial seizures, somnolence was reporte
patients receiving high-dose valproate (n=131) compared with 18% of patients receiving low-dose valpro
many cases, causality could not be determined as patients were being titrated off another antiepilepsy dr
part of the trial (Prod Info STAVZOR(R) delayed release oral capsules, 2008).

d) During two clinical trials of valproate treatment of manic episodes associated with bipolar disorder, so
reported in 19% of patients receiving valproate (n=89) compared with 12% of patients receiving placebo
STAVZOR(R) delayed release oral capsules, 2008).

e) Somnolence was reported in 17% of migraine patients receiving valproate (n=202) compared with 5%
receiving placebo (n=81) during two clinical trials and their long-term extension (Prod Info STAVZOR(R)
oral capsules, 2008).

f) During a clinical trial where valproate was given as adjunctive therapy for treatment of complex partial
somnolence was reported in 27% of patients receiving valproate (n=77) compared with 11% of patients r
(n=70). In most cases, causality could not be determined as patients also received other antiepilepsy dru
with valproate (Prod Info STAVZOR(R) delayed release oral capsules, 2008).

g) Due to a higher risk of somnolence among the elderly, the valproate starting dose should be reduced
adjustment should be conservative (Prod Info STAVZOR(R) delayed release oral capsules, 2008).

3.3.9.A.17 Tremor

a) Incidence: 9% to 57% (Prod Info STAVZOR(R) delayed release oral capsules, 2008)

b) During a clinical trial of valproate monotherapy for complex partial seizures, tremor was reported in 5 receiving high-dose valproate (n=131) compared with 19% of patients receiving low-dose valproate (n=1 cases, causality could not be determined as patients were being titrated off another antiepilepsy drug du the trial (Prod Info STAVZOR(R) delayed release oral capsules, 2008).

c) During a clinical trial where valproate was given as adjunctive therapy for treatment of complex partia was reported in 25% of patients receiving valproate (n=77) compared with 6% of patients receiving place cases, causality could not be determined as patients also received other antiepilepsy drugs concurrently (Prod Info STAVZOR(R) delayed release oral capsules, 2008).

d) Tremor was reported in 9% of migraine patients receiving valproate (n=202) compared with 0% of pa placebo (n=81) during two clinical trials and their long-term extension (Prod Info STAVZOR(R) delayed r capsules, 2008).

e) In 28 consecutive valproic acid-treated patients (mean duration: 3.8 years, mean dose: 1259 mg), 3 h parkinsonism, 15 had intentional tremor, and 16 had postural tremor. None of the patients with parkinsor levodopa (Nouzeilles et al, 1999).

f) In a double-blind, concentration-response clinical trial using valproic acid as monotherapy, high conce acid (n=96, target level 80 to 150 mcg/mL) caused tremor in 61 patients (64%) versus 3 patients (6%) in low concentration valproic acid (n=47, target range of 25 to 50 mcg/mL) (Beydoun et al, 1997c).

g) The effects of propranolol, amantadine, diphenhydramine, benztropine, and cyproheptadine on valpro patients were studied. Propranolol was clearly the most therapeutic. Amantadine was moderately effecti cyproheptadine, diphenhydramine and benztropine gave little or no relief (Karas et al, 1983).

3.3.9.B Divalproex Sodium

Amnesia

Asthenia

Ataxia

Dizziness

Feeling nervous

Headache

Hyperammonemic encephalopathy

Insomnia

Nystagmus

Paresthesia

Somnolence

Tremor

3.3.9.B.1 Amnesia

a) Incidence: 4% to 7% (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008)

b) In a clinical trial of adjunctive therapy for complex partial seizures, amnesia was reported in 5% of pa divalproex sodium (n=77) compared with 1% of patients receiving placebo (n=70) (Prod Info DEPAKOTE capsules, 2008).

c) Amnesia was reported in 7% of patients receiving high-dose divalproex sodium (n=131) compared wi receiving low-dose divalproex sodium (n=134) for monotherapy treatment of complex partial seizures. In causality could not be attributed to divalproex alone, as patients were titrated off of another antiepilepsy first part of the trial (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008).

3.3.9.B.2 Asthenia

a) Incidence: 10% to 27% (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008)

b) In a clinical trial of adjunctive therapy for complex partial seizures, asthenia was reported in 27% of p divalproex sodium (n=77) compared with 7% of patients receiving placebo (n=70) (Prod Info DEPAKOTE capsules, 2008).
c) Asthenia was reported in 21% of patients receiving high-dose divalproex sodium (n=131) compared v patients receiving low-dose divalproex sodium (n=134) for monotherapy treatment of complex partial sei cases, causality could not be attributed to divalproex alone, as patients were titrated off of another antiep the first part of the trial (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008).

3.3.9.B.3 Ataxia
a) Incidence: 8% (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008)
b) In a clinical trial of adjunctive therapy for complex partial seizures, ataxia was reported in 8% of patie divalproex sodium (n=77) compared with 1% of patients receiving placebo (n=70) (Prod Info DEPAKOTE capsules, 2008).

3.3.9.B.4 Dizziness
a) Incidence: 13% to 25% (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008)
b) In a clinical trial of adjunctive therapy for complex partial seizures, dizziness was reported in 25% of p divalproex sodium (n=77) compared with 13% of patients receiving placebo (n=70) (Prod Info DEPAKOT capsules, 2008).
c) Dizziness was reported in 18% of patients receiving high-dose divalproex sodium (n=131) compared patients receiving low-dose divalproex sodium (n=134) for monotherapy treatment of complex partial sei cases, causality could not be attributed to divalproex alone, as patients were titrated off of another antiep the first part of the trial (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008).

3.3.9.B.5 Feeling nervous
a) Incidence: 7% to 11% (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008)
b) Nervousness was reported in 11% of patients receiving high-dose divalproex sodium (n=131) compa patients receiving low-dose divalproex sodium (n=134) for monotherapy treatment of complex partial sei cases, causality could not be attributed to divalproex alone, as patients were titrated off of another antiep the first part of the trial (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008).

3.3.9.B.6 Headache
a) Incidence: 31% (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008)
b) In a clinical trial of adjunctive therapy for complex partial seizures, headache was reported in 31% of divalproex sodium (n=77) compared with 21% of patients receiving placebo (n=70) (Prod Info DEPAKOT capsules, 2008).

3.3.9.B.7 Hyperammonemic encephalopathy
a) Hyperammonemic encephalopathy, sometimes fatal, has been reported with valproic acid use in patie cycle disorders (particularly ornithine transcarbamylase deficiency) and in patients receiving concomitant Patients who develop symptoms of unexplained hyperammonemic encephalopathy (unexplained letharg mental status changes) while receiving valproate therapy should receive prompt treatment (including dis valproate therapy) and be evaluated for underlying urea cyclic disorder. Most patients receiving concomi experienced resolution of hyperammonemia upon discontinuation of either drug (Prod Info DEPAKOTE(R capsules, 2008).

3.3.9.B.8 Insomnia
a) Incidence: 9% to 15% (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008)
b) Insomnia was reported in 15% of patients receiving high-dose divalproex sodium (n=131) compared v receiving low-dose divalproex sodium (n=134) for monotherapy treatment of complex partial seizures. In causality could not be attributed to divalproex alone, as patients were titrated off of another antiepilepsy first part of the trial (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008).

3.3.9.B.9 Nystagmus
a) Incidence: 1% to 8% (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008)
b) In a clinical trial of adjunctive therapy for complex partial seizures, nystagmus was reported in 8% of divalproex sodium (n=77) compared with 1% of patients receiving placebo (n=70) (Prod Info DEPAKOTE capsules, 2008).
c) Nystagmus was reported in 7% of patients receiving high-dose divalproex sodium (n=131) compared patients receiving low-dose divalproex sodium (n=134) for monotherapy treatment of complex partial sei cases, causality could not be attributed to divalproex alone, as patients were titrated off of another antiep the first part of the trial (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008).

3.3.9.B.10 Paresthesia
a) Incidence: 1% to less than 5% (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008)
b) Paresthesia was reported in more than 1% but less than 5% of patients receiving divalproex sodium monotherapy treatment of complex partial seizures. In many cases, causality could not be attributed to d patients were titrated off of another antiepilepsy drug during the first part of the trial (Prod Info DEPAKOT

capsules, 2008).

3.3.9.B.11 Somnolence

a) Incidence: 18% to 30% (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008)

b) In a clinical trial of adjunctive therapy for complex partial seizures, somnolence was reported in 27% receiving divalproex sodium (n=77) compared with 11% of patients receiving placebo (n=70) (Prod Info D sprinkle oral capsules, 2008).

c) Somnolence was reported in 30% of patients receiving high-dose divalproex sodium (n=131) compar patients receiving low-dose divalproex sodium (n=134) for monotherapy treatment of complex partial sei cases, causality could not be attributed to divalproex alone, as patients were titrated off of another antiep the first part of the trial (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008).

d) Due to a higher risk of somnolence among the elderly, the starting dose should be reduced and dose be conservative (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008).

3.3.9.B.12 Tremor

a) Incidence: 19% to 57% (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008)

b) In a clinical trial of adjunctive therapy for complex partial seizures, tremor was reported in 25% of pati divalproex sodium (n=77) compared with 6% of patients receiving placebo (n=70) (Prod Info DEPAKOTE capsules, 2008).

c) Tremor was reported in 57% of patients receiving high-dose divalproex sodium (n=131) compared wi receiving low-dose divalproex sodium (n=134) for monotherapy treatment of complex partial seizures. In causality could not be attributed to divalproex alone, as patients were titrated off of another antiepilepsy first part of the trial (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008).

3.3.10 Ophthalmic Effects

Valproic Acid

Divalproex Sodium

3.3.10.A Valproic Acid

Amblyopia

Blurred vision

Diplopia

Nystagmus

3.3.10.A.1 Amblyopia

a) During a clinical trial of valproate monotherapy for complex partial seizures, amblyopia/blurred vision 8% of patients receiving high-dose valproate (n=131) compared with 4% of patients receiving low-dose v In many cases, causality could not be determined as patients were being titrated off another antiepilepsy first part of the trial (Prod Info STAVZOR(R) delayed release oral capsules, 2008).

b) During a clinical trial where valproate was given as adjunctive therapy for treatment of complex partia amblyopia/blurred vision was reported in 12% of patients receiving valproate (n=77) compared with 9% receiving placebo (n=70). In most cases, causality could not be determined as patients also received oth drugs concurrently with valproate (Prod Info STAVZOR(R) delayed release oral capsules, 2008).

3.3.10.A.2 Blurred vision

a) During a clinical trial of valproate monotherapy for complex partial seizures, amblyopia/blurred vision 8% of patients receiving high-dose valproate (n=131) compared with 4% of patients receiving low-dose v In many cases, causality could not be determined as patients were being titrated off another antiepilepsy first part of the trial (Prod Info STAVZOR(R) delayed release oral capsules, 2008).

b) During a clinical trial where valproate was given as adjunctive therapy for treatment of complex partia amblyopia/blurred vision was reported in 12% of patients receiving valproate (n=77) compared with 9% receiving placebo (n=70). In most cases, causality could not be determined as patients also received oth drugs concurrently with valproate (Prod Info STAVZOR(R) delayed release oral capsules, 2008).

3.3.10.A.3 Diplopia

a) Incidence: 16% (Prod Info STAVZOR(R) delayed release oral capsules, 2008)

b) During a clinical trial where valproate was given as adjunctive therapy for treatment of complex partia was reported in 16% of patients receiving valproate (n=77) compared with 9% of patients receiving place cases, causality could not be determined as patients also received other antiepilepsy drugs concurrently (Prod Info STAVZOR(R) delayed release oral capsules, 2008).

3.3.10.A.4 Nystagmus

a) Incidence: 1% to 8% (Prod Info STAVZOR(R) delayed release oral capsules, 2008)

b) During a clinical trial of valproate monotherapy for complex partial seizures, nystagmus was reported receiving high-dose valproate (n=131) compared with 1% of patients receiving low-dose valproate (n=13 causality could not be determined as patients were being titrated off another antiepilepsy drug during the trial (Prod Info STAVZOR(R) delayed release oral capsules, 2008).

c) During a clinical trial where valproate was given as adjunctive therapy for treatment of complex partia nystagmus was reported in 8% of patients receiving valproate (n=77) compared with 1% of patients rece (n=70). In most cases, causality could not be determined as patients also received other antiepilepsy dru with valproate (Prod Info STAVZOR(R) delayed release oral capsules, 2008).

3.3.10.B Divalproex Sodium

Abnormal vision

Amblyopia

Blurred vision

Diplopia

3.3.10.B.1 Abnormal vision

a) Incidence: 1% to less than 5% (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008)

b) Abnormal vision was reported in more than 1% but less than 5% of patients receiving divalproex sodi monotherapy treatment of complex partial seizures. In many cases, causality could not be attributed to d patients were titrated off of another antiepilepsy drug during the first part of the trial (Prod Info DEPAKOT capsules, 2008).

3.3.10.B.2 Amblyopia

a) In a clinical trial of adjunctive therapy for complex partial seizures, amblyopia/blurred vision was repo patients receiving divalproex sodium (n=77) compared with 9% of patients receiving placebo (n=70) (Pro (R) sprinkle oral capsules, 2008).

b) Amblyopia/blurred vision was reported in 8% of patients receiving high-dose divalproex sodium (n=13 4% of patients receiving low-dose divalproex sodium (n=134) for monotherapy treatment of complex part many cases, causality could not be attributed to divalproex alone, as patients were titrated off of another during the first part of the trial (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008).

3.3.10.B.3 Blurred vision

a) In a clinical trial of adjunctive therapy for complex partial seizures, amblyopia/blurred vision was repo patients receiving divalproex sodium (n=77) compared with 9% of patients receiving placebo (n=70) (Pro (R) sprinkle oral capsules, 2008).

b) Amblyopia/blurred vision was reported in 8% of patients receiving high-dose divalproex sodium (n=13 4% of patients receiving low-dose divalproex sodium (n=134) for monotherapy treatment of complex part many cases, causality could not be attributed to divalproex alone, as patients were titrated off of another during the first part of the trial (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008).

3.3.10.B.4 Diplopia

a) Incidence: 16% (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008)

b) In a clinical trial of adjunctive therapy for complex partial seizures, diplopia was reported in 16% of pa divalproex sodium (n=77) compared with 9% of patients receiving placebo (n=70) (Prod Info DEPAKOTE capsules, 2008).

3.3.11 Otic Effects

Valproic Acid

Divalproex Sodium

3.3.11.A Valproic Acid

Ototoxicity - deafness

Tinnitus

3.3.11.A.1 Ototoxicity - deafness

a) Incidence: 1% to less than 5% (Prod Info STAVZOR(R) delayed release oral capsules, 2008)

b) Deafness was reported in more than 1% but less than 5% of patients receiving valproate during acute (n=89) and during monotherapy treatment of complex partial seizures (n=265). In many cases, causality attributed to valproate alone, as patients were titrated off of another antiepilepsy drug during the first part monotherapy trial (Prod Info STAVZOR(R) delayed release oral capsules, 2008).

3.3.11.A.2 Tinnitus

a) Incidence: 1% to 7% (Prod Info STAVZOR(R) delayed release oral capsules, 2008)

b) During a clinical trial of valproate monotherapy for complex partial seizures, tinnitus was reported in 7 receiving high-dose valproate (n=131) compared with 1% of patients receiving low-dose valproate (n=13 causality could not be determined as patients were being titrated off another antiepilepsy drug during the trial (Prod Info STAVZOR(R) delayed release oral capsules, 2008).

c) A 52-year-old man experienced tinnitus after receiving valproic acid for treatment of bipolar disorder. admitted to a psychiatric unit for bipolar disorder; symptoms included agitation, loudness, pressured spe grandiose delusions, and paranoia. His treatment included olanzapine 10 mg and divalproex sodium 500 day, and lorazepam as needed. Two days later, he complained of noises in his head. This complaint was worsening of his psychotic symptoms. By day 8, he was calm and coherent but continued to report increa ears. At that time, his serum valproic acid level was 67.5 mcg/mL (within the therapeutic range). The pati that he had experienced the same problem when he had taken valproate several years earlier. Valproate and his tinnitus resolved over a period of 10 days (Reeves et al, 2000).

3.3.11.B Divalproex Sodium

Otitis media

Ototoxicity - deafness

Tinnitus

3.3.11.B.1 Otitis media

a) Incidence: 1% to less than 5% (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008)

b) Otitis media was reported in more than 1% but less than 5% of patients receiving divalproex sodium (monotherapy treatment of complex partial seizures. In many cases, causality could not be attributed to d patients were titrated off of another antiepilepsy drug during the first part of the trial (Prod Info DEPAKOT capsules, 2008).

3.3.11.B.2 Ototoxicity - deafness

a) Incidence: 1% to less than 5% (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008)

b) Deafness was reported in more than 1% but less than 5% of patients receiving divalproex sodium (n= monotherapy treatment of complex partial seizures. In many cases, causality could not be attributed to d patients were titrated off of another antiepilepsy drug during the first part of the trial (Prod Info DEPAKOT capsules, 2008).

3.3.11.B.3 Tinnitus

a) Incidence: 1% to 7% (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008)

b) Tinnitus was reported in 7% of patients receiving high-dose divalproex sodium (n=131) compared wit receiving low-dose divalproex sodium (n=134) for monotherapy treatment of complex partial seizures. In causality could not be attributed to divalproex alone, as patients were titrated off of another antiepilepsy first part of the trial (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008).

3.3.12 Psychiatric Effects

Valproic Acid

Divalproex Sodium

Valproate Sodium

3.3.12.A Valproic Acid

Depression

Disturbance in thinking

Mood swings

Psychiatric sign or symptom

Suicidal thoughts

3.3.12.A.1 Depression

a) Incidence: 4% to 5% (Prod Info STAVZOR(R) delayed release oral capsules, 2008)

b) Depression was reported in 5% of patients receiving high-dose valproate (n=131) compared with 4% receiving low-dose valproate (n=134) for monotherapy treatment of complex partial seizures. In many ca could not be attributed to valproate alone, as patients were titrated off of another antiepilepsy drug during the trial (Prod Info STAVZOR(R) delayed release oral capsules, 2008).

3.3.12.A.2 Disturbance in thinking

a) Incidence: 6% (Prod Info STAVZOR(R) delayed release oral capsules, 2008)

b) During a clinical trial where valproate was given as adjunctive therapy for treatment of complex partia abnormal thinking was reported in 6% of patients receiving valproate (n=77) compared with 0% of patien placebo (n=70). In most cases, causality could not be determined as patients also received other antiepil concurrently with valproate (Prod Info STAVZOR(R) delayed release oral capsules, 2008).

3.3.12.A.3 Mood swings

a) Incidence: 6% (Prod Info STAVZOR(R) delayed release oral capsules, 2008)

b) In a clinical trial of adjunctive therapy for complex partial seizures, emotional lability was reported in 6 receiving valproate (n=77) compared with 4% of patients receiving placebo (n=70). In most cases, causa determined as patients also received other antiepilepsy drugs concurrently with valproate (Prod Info STA release oral capsules, 2008).

3.3.12.A.4 Psychiatric sign or symptom

a) Behavioral changes were reported 1 week after starting therapy in a 34-year-old male who was receiv valproic acid per day as part of a controlled study. The valproic acid was discontinued and 5 days later th recovered (Alvarez et al, 1982).

b) A psychotic reaction in a 14-year-old male who received valproate sodium 1600 mg daily for 14 days described. The patient at this time was seizure-free but experienced confusion, bizarre behavior, and hal Plasma levels of valproate at the time were 13 mcg/mL. The drug was discontinued and restarted at 800 patient remained seizure-free with no further psychotic episodes (Bellman & Ross, 1977).

3.3.12.A.5 Suicidal thoughts

a) Data reviewed by the US Food and Drug Administration suggest an increased risk of suicidal behavio exist in patients receiving therapy with antiepileptic drugs (AEDs). The analysis included 199 placebo-co studies covering 11 different AEDs used for several different indications such as epilepsy, selected psych and other conditions, including migraine and neuropathic pain syndromes. The analysis included 27,863 with AEDs and 16,029 patients who received placebo, and patients were aged 5 years and older. There suicides among patients in the AED treatment groups versus (vs) none in the placebo groups. Suicidal b occurred in 0.43% of patients in the AED treatment groups compared to 0.22% of patients in the placebo corresponded to an estimated 2.1 per 1000 (95% confidence interval, 0.7 to 4.2) more patients in the AE groups having suicidal behavior or ideation than the placebo groups. The increased risk of suicidality wa after starting an AED and continued to at least 24 weeks. When compared to placebo, results were gene among the drugs and were seen in all demographic subgroups. Patients treated for epilepsy, psychiatric conditions were all at an increased risk for suicidality compared to placebo. Closely monitor patients trea emergence or worsening of depression, suicidality and other unusual changes in behavior, which may in such as anxiety, agitation, hostility, mania, and hypomania (US Food and Drug Administration, 2008).

3.3.12.B Divalproex Sodium

Anxiety

Confusion

Depression

Disturbance in thinking

Mood swings

Suicidal thoughts

3.3.12.B.1 Anxiety

a) Incidence: 1% to less than 5% (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008)

b) Anxiety was reported in more than 1% but less than 5% of patients receiving divalproex sodium (n=3
monotherapy treatment of complex partial seizures. In many cases, causality could not be attributed to d
patients were titrated off of another antiepilepsy drug during the first part of the trial (Prod Info DEPAKOT
capsules, 2008).

3.3.12.B.2 Confusion

a) Incidence: 1% to less than 5% (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008)

b) Confusion was reported in more than 1% but less than 5% of patients receiving divalproex sodium (n
monotherapy treatment of complex partial seizures. In many cases, causality could not be attributed to d
patients were titrated off of another antiepilepsy drug during the first part of the trial (Prod Info DEPAKOT
capsules, 2008).

3.3.12.B.3 Depression

a) Incidence: 4% to 5% (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008)

b) Depression was reported in 5% of patients receiving high-dose divalproex sodium (n=131) compared
patients receiving low-dose divalproex sodium (n=134) for monotherapy treatment of complex partial sei
cases, causality could not be attributed to divalproex alone, as patients were titrated off of another antiep
the first part of the trial (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008).

3.3.12.B.4 Disturbance in thinking

a) Incidence: 6% (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008)

b) In a clinical trial of adjunctive therapy for complex partial seizures, abnormal thinking was reported in
receiving divalproex sodium (n=77) compared with 0% of patients receiving placebo (n=70) (Prod Info DI
sprinkle oral capsules, 2008).

3.3.12.B.5 Mood swings

a) Incidence: 6% (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008)

b) In a clinical trial of adjunctive therapy for complex partial seizures, emotional lability was reported in 6
receiving divalproex sodium (n=77) compared with 4% of patients receiving placebo (n=70) (Prod Info DI
sprinkle oral capsules, 2008).

3.3.12.B.6 Suicidal thoughts

a) Data reviewed by the US Food and Drug Administration suggest an increased risk of suicidal behavio
exist in patients receiving therapy with antiepileptic drugs (AEDs). The analysis included 199 placebo-co
studies covering 11 different AEDs used for several different indications such as epilepsy, selected psyc
and other conditions, including migraine and neuropathic pain syndromes. The analysis included 27,863
with AEDs and 16,029 patients who received placebo, and patients were aged 5 years and older. There
suicides among patients in the AED treatment groups versus (vs) none in the placebo groups. Suicidal b
occurred in 0.43% of patients in the AED treatment groups compared to 0.22% of patients in the placebo
corresponded to an estimated 2.1 per 1000 (95% confidence interval, 0.7 to 4.2) more patients in the AE
groups having suicidal behavior or ideation than the placebo groups. The increased risk of suicidality wa
after starting an AED and continued to at least 24 weeks. When compared to placebo, results were gene
among the drugs and were seen in all demographic subgroups. Patients treated for epilepsy, psychiatric
conditions were all at an increased risk for suicidality compared to placebo. Closely monitor patients trea
emergence or worsening of depression, suicidality and other unusual changes in behavior, which may in
such as anxiety, agitation, hostility, mania, and hypomania (US Food and Drug Administration, 2008).

3.3.12.C Valproate Sodium

3.3.12.C.1 Suicidal thoughts

a) Data reviewed by the US Food and Drug Administration suggest an increased risk of suicidal behavic exist in patients receiving therapy with antiepileptic drugs (AEDs). The analysis included 199 placebo-co studies covering 11 different AEDs used for several different indications such as epilepsy, selected psyc and other conditions, including migraine and neuropathic pain syndromes. The analysis included 27,863 with AEDs and 16,029 patients who received placebo, and patients were aged 5 years and older. There suicides among patients in the AED treatment groups versus (vs) none in the placebo groups. Suicidal b occurred in 0.43% of patients in the AED treatment groups compared to 0.22% of patients in the placebc corresponded to an estimated 2.1 per 1000 (95% confidence interval, 0.7 to 4.2) more patients in the AE groups having suicidal behavior or ideation than the placebo groups. The increased risk of suicidality wa after starting an AED and continued to at least 24 weeks. When compared to placebo, results were gene among the drugs and were seen in all demographic subgroups. Patients treated for epilepsy, psychiatric conditions were all at an increased risk for suicidality compared to placebo. Closely monitor patients trea emergence or worsening of depression, suicidality and other unusual changes in behavior, which may in such as anxiety, agitation, hostility, mania, and hypomania (US Food and Drug Administration, 2008).

3.3.13 Renal Effects

Fanconi syndrome

Nocturnal enuresis

3.3.13.A Fanconi syndrome

1) The manufacturer reports that rare reports of Fanconi's syndrome have occurred mainly in children (Prod delayed release oral capsules, 2008). A case of Fanconi's syndrome occurred in a young girl following 18 an therapy of valproic acid and clobazam, respectively. The patient presented with hypophosphatemia, phospha glycosuria, mild metabolic acidosis, aminoaciduria, and evidence of rickets. Symptoms slowly improved follov discontinuation of both drugs. It is difficult to determine from this report whether this adverse reaction occurre therapy with one of the drugs, or possibly, a combination of both agents (Smith et al, 1995).

3.3.13.B Nocturnal enuresis

1) Summary

a) Enuresis has occurred with valproic acid therapy (Prod Info STAVZOR(R) delayed release oral capsu et al, 1979; Suchy et al, 1979). Nocturnal enuresis was described as a side effect of valproic acid in 2 Gr treated for seizures. Enuresis developed within 2 to 3 days after initiation of valproic acid treatment and c seizure-free period; enuresis remitted upon reduction of the dose or withdrawal of valproic acid (Panayio

3.3.14 Reproductive Effects

Semen finding

Testicular hypofunction

3.3.14.A Semen finding

1) Antiepileptic agents have been associated with changes in sperm morphology and motility. A lower freque morphologically normal sperm was found in carbamazepine treated men with partial epilepsy (n=15), in valpr men with generalized epilepsy and in oxcarbazepine treated men with partial epilepsy (n=18) (p less than 0.0 carbamazepine and valproic acid and p less than 0.05 for oxcarbazepine) compared to healthy controls (n=4 significant decrease in the frequency of motile sperm was also found with all treatment groups combined whe healthy controls (p less than 0.05). Within the various treatment groups, valproic acid treated patients had a s significant decrease in the frequency of motile sperm than in the control group (p less than 0.05). Carbamaze had high frequencies of abnormally low sperm concentration (p less than 0.001) and poorly motile sperm (p l when compared to controls (Isojarvi et al, 2004).

3.3.14.B Testicular hypofunction

1) When compared to healthy controls (n=41), valproic acid treated men with generalized epilepsy (n=27) ha volumes (p=0.01). Within the same study however, the testicular volumes of carbamazepine treated men with (n=15) or oxcarbazepine treated men with generalized epilepsy (n=18) did not differ from controls. When furth valproic acid treated men with abnormal sperm morphology had smaller testicular volumes than control wher volumes of valproic acid treated men with normal sperm were similar to controls (Isojarvi et al, 2004).

3.3.15 Respiratory Effects

Valproic Acid

Divalproex Sodium

3.3.15.A Valproic Acid

Bronchitis

Dyspnea

Pharyngitis

Pleural effusion

Pulmonary hemorrhage

Respiratory tract infection

Rhinitis

3.3.15.A.1 Bronchitis

a) Incidence: 5% (Prod Info STAVZOR(R) delayed release oral capsules, 2008)

b) During a clinical trial where valproate was given as adjunctive therapy for treatment of complex partia bronchitis was reported in 5% of patients receiving valproate (n=77) compared with 1% of patients receiv (n=70). In most cases, causality could not be determined as patients also received other antiepilepsy dru with valproate (Prod Info STAVZOR(R) delayed release oral capsules, 2008).

3.3.15.A.2 Dyspnea

a) Incidence: 5% (Prod Info STAVZOR(R) delayed release oral capsules, 2008)

b) During a clinical trial of valproate monotherapy for complex partial seizures, dyspnea was reported in receiving high-dose valproate (n=131) compared with 1% of patients receiving low-dose valproate (n=13 causality could not be determined as patients were being titrated off another antiepilepsy drug during the trial (Prod Info STAVZOR(R) delayed release oral capsules, 2008).

3.3.15.A.3 Pharyngitis

a) Incidence: 8% (Prod Info STAVZOR(R) delayed release oral capsules, 2008)

b) During a clinical trial of valproate monotherapy for complex partial seizures, pharyngitis was reported receiving high-dose valproate (n=131) compared with 2% of patients receiving low-dose valproate (n=13 causality could not be determined as patients were being titrated off another antiepilepsy drug during the trial (Prod Info STAVZOR(R) delayed release oral capsules, 2008).

3.3.15.A.4 Pleural effusion

a) Incidence: rare

b) Recurrent transudative pleural effusion associated with sodium valproate therapy was diagnosed in a with a history of smoking, atrial fibrillation (treated with digoxin), and posttraumatic epilepsy (treated with 500 mg/day for one year). The patient had his first occurrence 8 months earlier when he was diagnosed pleural effusion containing 700 mL of neutrophilic transudate. Current symptoms included a 5-day fever dry cough, and dyspnea and laboratory examination revealed mild anemia and slightly increased erythro rate and C-reactive protein. Chest X-ray and thoracentesis revealed a right-sided pleural effusion with 12 neutrophilic transudative. One day after the fluid was drained, a CT showed pleural fluid in both pleural c was switched from sodium valproate to gabapentin 300 mg/day and the patient had no recurrence of ple months follow-up. After 7 months, an epileptic episode caused the patient to resume sodium valproate th month later the patient experienced a recurrence of right-sided pleural effusion with transudative effusion relapse, gabapentin was increased to 400 mg twice daily and no pleural fluid recurrence was observed u (Tryfon et al, 2009).

c) Eosinophilic pleural effusion developed in a 34-year-old male treated with valproic acid 1500 mg/day. months after the initiation of therapy, the patient presented with fever and nonproductive cough. Upon ho medications were discontinued and a full medical workup was conducted. There was no evidence of pne hemothorax, pulmonary infiltrates, lymphadenopathy or infection. The symptoms resolved and the patien Rechallenge with valproic acid resulted in the reappearance of symptoms (Kravetz & Federman, 2003).

3.3.15.A.5 Pulmonary hemorrhage

a) Incidence: rare

b) A case of thrombocytopenia-induced fatal pulmonary hemorrhage was reported in a 30-year-old fema valproate monotherapy, with a history of a viral illness 3 weeks earlier. Initial serum valproate level was 1 (normal 50 to 100 mcg/mL). The authors suggested that viral infections may be associated with thrombo patients on valproate therapy (Sleiman et al, 2000).

3.3.15.A.6 Respiratory tract infection

a) Incidence: 12% to 20% (Prod Info STAVZOR(R) delayed release oral capsules, 2008)

b) During a clinical trial where valproate was given as adjunctive therapy for treatment of complex partia respiratory tract infection was reported in 12% of patients receiving valproate (n=77) compared with 6% receiving placebo (n=70). In most cases, causality could not be determined as patients also received oth drugs concurrently with valproate (Prod Info STAVZOR(R) delayed release oral capsules, 2008).

c) During a clinical trial of valproate monotherapy for complex partial seizures, respiratory tract infection 20% of patients receiving high-dose valproate (n=131) compared with 13% of patients receiving low-dos (n=134). In many cases, causality could not be determined as patients were being titrated off another an during the first part of the trial (Prod Info STAVZOR(R) delayed release oral capsules, 2008).

3.3.15.A.7 Rhinitis

a) Incidence: 5% (Prod Info STAVZOR(R) delayed release oral capsules, 2008)

b) In a clinical trial of adjunctive therapy for complex partial seizures, rhinitis was reported in 5% of patie valproate (n=77) compared with 4% of patients receiving placebo (n=70) (Prod Info STAVZOR(R) delaye capsules, 2008).

3.3.15.B Divalproex Sodium

Bronchitis

Dyspnea

Epistaxis

Pharyngitis

Pneumonia

Rhinitis

Sinusitis

3.3.15.B.1 Bronchitis

a) Incidence: 5% (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008)

b) In a clinical trial of adjunctive therapy for complex partial seizures, bronchitis was reported in 5% of p divalproex sodium (n=77) compared with 1% of patients receiving placebo (n=70) (Prod Info DEPAKOTE capsules, 2008).

3.3.15.B.2 Dyspnea

a) Incidence: 1% to 5% (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008)

b) Dyspnea was reported in 1% of patients receiving high-dose divalproex sodium (n=131) compared wi receiving low-dose divalproex sodium (n=134) for monotherapy treatment of complex partial seizures. In causality could not be attributed to divalproex alone, as patients were titrated off of another antiepilepsy first part of the trial (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008).

3.3.15.B.3 Epistaxis

a) Incidence: 1% to less than 5% (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008)

b) Epistaxis was reported in more than 1% but less than 5% of patients receiving divalproex sodium (n= monotherapy treatment of complex partial seizures. In many cases, causality could not be attributed to d patients were titrated off of another antiepilepsy drug during the first part of the trial (Prod Info DEPAKOT capsules, 2008).

3.3.15.B.4 Pharyngitis

a) Incidence: 2% to 8% (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008)

b) Pharyngitis was reported in 8% of patients receiving high-dose divalproex sodium (n=131) compared

patients receiving low-dose divalproex sodium (n=134) for monotherapy treatment of complex partial sei
cases, causality could not be attributed to divalproex alone, as patients were titrated off of another antiep
the first part of the trial (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008).

3.3.15.B.5 Pneumonia

a) Incidence: 1% to less than 5% (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008)

b) Pneumonia was reported in more than 1% but less than 5% of patients receiving divalproex sodium (
monotherapy treatment of complex partial seizures. In many cases, causality could not be attributed to d
patients were titrated off of another antiepilepsy drug during the first part of the trial (Prod Info DEPAKOT
capsules, 2008).

3.3.15.B.6 Rhinitis

a) Incidence: 5% (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008)

b) In a clinical trial of adjunctive therapy for complex partial seizures, rhinitis was reported in 5% of patie
divalproex sodium (n=77) compared with 4% of patients receiving placebo (n=70) (Prod Info DEPAKOTE
capsules, 2008).

3.3.15.B.7 Sinusitis

a) Incidence: 1% to less than 5% (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008)

b) Sinusitis was reported in more than 1% but less than 5% of patients receiving divalproex sodium (n=3
monotherapy treatment of complex partial seizures. In many cases, causality could not be attributed to d
patients were titrated off of another antiepilepsy drug during the first part of the trial (Prod Info DEPAKOT
capsules, 2008).

3.3.16 Other

Valproic Acid

Divalproex Sodium

3.3.16.A Valproic Acid

Fever

Influenza

Reye's syndrome

3.3.16.A.1 Fever

a) Incidence: 2% (Prod Info STAVZOR(R) delayed release oral capsules, 2008)

b) In a clinical trial of adjunctive therapy for complex partial seizures, fever was reported in 6% of patien
valproate (n=77) compared with 4% of patients receiving placebo (n=70). In many cases, causality could
to valproate alone, as patients were titrated off of another antiepilepsy drug during the first part of the tria
STAVZOR(R) delayed release oral capsules, 2008).

3.3.16.A.2 Influenza

a) Incidence: 12% (Prod Info STAVZOR(R) delayed release oral capsules, 2008)

b) In a clinical trial of adjunctive therapy for complex partial seizures, flu syndrome was reported in 12%
receiving valproate (n=77) compared with 9% of patients receiving placebo (n=70). In many cases, causa
attributed to valproate alone, as patients were titrated off of another antiepilepsy drug during the first part
Info STAVZOR(R) delayed release oral capsules, 2008).

3.3.16.A.3 Reye's syndrome

a) Summary

1) Valproic acid has been associated with a Reye-like syndrome (RLS). In some reports, there was
decreased serum carnitine levels. Clinical signs and symptoms were similar among patients with rev
fatal outcomes. Most patients presented with nausea, vomiting and apathy. Increase in seizure frequ
concurrent febrile illness also occur. Patients developing any signs of RLS should have valproic acid
immediately (Sugimoto et al, 1983; Gerber et al, 1979).

b) A case of Reye-like syndrome (RLS) was reported in a 6-month-old infant who received valproic acid
This infant became unresponsive to therapy for seizure control and developed signs of valproic acid-indu
hepatotoxicity. Laboratory values revealed increased plasma ammonia levels, increased liver enzymes a
plasma carnitine. Valproic acid was discontinued and the patient recovered. This report supported the vi

acid-associated RLS may be mediated by carnitine depletion (Murphy et al, 1985).
c) A case of a Reye-like syndrome was reported in a 13-year-old female who had received valproic acid
Hyperammonemia and severe hepatic damage, as well as diffuse small droplets in liver biopsy material,
demonstrated. It was suggested that valproic acid or its metabolites may decrease the activity on N-acet
can decrease the activity of carbamyl phosphate synthetase I, inducing hyperammonemia (Sugimoto et a
d) Features of Reye's syndrome were reported in a 3-year-old girl receiving valproic acid 600 mg daily.
attack, which caused unconsciousness and subsequent recovery, the patient became increasingly drows
Blood ammonia levels and bilirubin were elevated, but liver enzymes were within a normal to slightly elev
serum carnitine was decreased. Postmortem liver biopsy revealed microvesicular steatosis of hepatocyte
suggested that valproic acid and its metabolites needed to be investigated for their influence on carnitine
the resultant storage of free fatty acids as lipid particles (Bohles et al, 1982).
e) Reye-like syndrome (RLS) associated with valproic acid was reported in a 40-month-old mentally reta
severe refractory multifocal seizure disorder. The patient was receiving phenytoin and ethosuximide in a
acid. Increased liver enzymes were noted 2 weeks prior to admission. A low-grade fever and loose, foul
were noted shortly before onset of generalized seizure activity. Blood ammonia levels were increased. Li
widespread disorganization of the parenchyma with swelling of the hepatocytes and compression of the
diffuse fatty infiltration, including macrovacuoles and microvacuoles was also identified (Keene et al, 198
f) A fatal case of Reye-like syndrome was reported in an 8-year-old boy receiving valproic acid 375 mg t
seizure episode, the boy became febrile and tachypneic; liver enzymes and blood ammonia levels were
Postmortem examination revealed panlobular microvesicular fatty changes in the liver and renal tubules.
appeared swollen, but did not have other gross or microscopic pathological changes (Young et al, 1980)
g) Reye-like syndrome (RLS) associated with valproic acid was reported in a 12-year-old girl. The patien
multiple medications including valproic acid 250 mg three times daily, phenobarbital 60 mg daily, phenyto
and acetazolamide 125 mg twice daily. The patient developed a viral respiratory infection and steadily de
increasing temperature and loss of consciousness. Liver enzymes and blood ammonia levels were eleva
examination revealed a bronchopneumonia and an enlarged, yellow, greasy liver with a mottled appeara
of venous congestion. Biopsy showed marked fatty changes in the liver with fat formed vacuoles which fi
in most of the cells; kidney biopsy revealed numerous small lipid vacuoles in most proximal tubular cells
1979).

3.3.16.B Divalproex Sodium

Fever

Infectious disease

Influenza

Malaise

3.3.16.B.1 Fever
a) Incidence: 6% (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008)
b) In a clinical trial of adjunctive therapy for complex partial seizures, fever was reported in 6% of patien
divalproex sodium (n=77) compared with 4% of patients receiving placebo (n=70) (Prod Info DEPAKOTE
capsules, 2008).

3.3.16.B.2 Infectious disease
a) Incidence: 12% to 20% (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008)
b) In a clinical trial of adjunctive therapy for complex partial seizures, infection was reported in 12% of pa
divalproex sodium (n=77) compared with 6% of patients receiving placebo (n=70) (Prod Info DEPAKOTE
capsules, 2008).
c) Infection was reported in 20% of patients receiving high-dose divalproex sodium (n=131) compared w
patients receiving low-dose divalproex sodium (n=134) for monotherapy treatment of complex partial sei
cases, causality could not be attributed to divalproex alone, as patients were titrated off of another antiep
the first part of the trial (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008).

3.3.16.B.3 Influenza
a) Incidence: 12% (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008)
b) In a clinical trial of adjunctive therapy for complex partial seizures, flu syndrome was reported in 12%
receiving divalproex sodium (n=77) compared with 9% of patients receiving placebo (n=70) (Prod Info DI
sprinkle oral capsules, 2008).

3.3.16.B.4 Malaise
a) Incidence: 1% to less than 5% (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008)

b) Malaise was reported in more than 1% but less than 5% of patients receiving divalproex sodium (n=3 monotherapy treatment of complex partial seizures. In many cases, causality could not be attributed to d patients were titrated off of another antiepilepsy drug during the first part of the trial (Prod Info DEPAKOT capsules, 2008).

3.4 Teratogenicity/Effects in Pregnancy/Breastfeeding

A) Teratogenicity/Effects in Pregnancy

1) U.S. Food and Drug Administration's Pregnancy Category: Category D (Prod Info DEPAKOTE(R) ER extende tablets, 2006) (All Trimesters)

a) There is positive evidence of human fetal risk, but the benefits from use in pregnant women may be accep risk (e.g., if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs car ineffective).

2) Australian Drug Evaluation Committee's (ADEC) Category: D (Batagol, 1999)

a) Drugs which have caused, are suspected to have caused, or may be expected to cause an increased inci fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Acc should be consulted for further details.

See Drug Consult reference: PREGNANCY RISK CATEGORIES

3) Crosses Placenta: Yes

4) Clinical Management

a) As valproic acid can be teratogenic and cause congenital malformations such as neural tube defects, cons valproic acid or its salt form, sodium divalproex in women of childbearing potential only after the risks have be discussed with the patient and the potential benefits outweigh the risk of injury to the fetus. This is particularly treating a spontaneously reversible condition which does not bear a risk of permanent injury or risk of death (cases where the severity and frequency of the seizure disorder may permit removal of the drug without posin therapy to the patient, clinicians may consider discontinuation of the drug prior to or during pregnancy. Where unavoidable or unanticipated, the pregnant mother should be advised of possible consequences to the fetus. neural tube defects is recommended and clotting parameters should be routinely monitored. Although it is un folic acid supplementation in pregnant women receiving valproate can reduce risk of neural tube defects in th should be routinely recommended in patients contemplating pregnancy, both prior to and during pregnancy (P DEPAKOTE(R) ER extended-release oral tablets, 2006; Prod Info DEPAKOTE(R) oral sprinkle capsules, 200 DEPAKOTE(R) delayed-release oral tablets, 2006a; Prod Info DEPACON(R) IV injection, 2006; Prod Info DE capsules, oral syrup, 2006). Infants born to mothers treated with valproate during pregnancy should have blo monitored during the first several hours of life (Ebbesen et al, 2000).

5) Literature Reports

a) Data collected from the Antiepileptic Drug (AED) Pregnancy Registry revealed 16 cases of congenital mal infants born of pregnant women (n=149) exposed valproate monotherapy (doses of approximately 1,000 mg/ first trimester. The prevalence rate of birth defects was 10.7% (95% confidence interval (CI), 6.3% to 16.9%). defects occurred in 2% of the infants (n=3/149) while 4% of the infants (n=6/149) had less severe malformatic (n=1,048) exposed to other AED monotherapies, the malformation rate was 2.9% (95% CI, 2% to 4.1%). Con malformations in valproic acid-exposed mothers was 4-fold higher compared to those treated with other AED a group (odds ratio, 4.0; 95% CI, 2.1% to 7.4%) (Prod Info DEPAKOTE(R) ER extended-release oral tablets, DEPAKOTE(R) oral sprinkle capsules, 2006; Prod Info DEPAKOTE(R) delayed-release oral tablets, 2006a; P DEPACON(R) IV injection, 2006; Prod Info DEPAKENE(R) oral capsules, oral syrup, 2006).

b) Data collected from the Antiepileptic Drug (AED) Pregnancy Registry for over 3,000 pregnant women exp included 123 completed pregnancies exposed to valproate monotherapy (Holmes et al, 2003). The prevalenc was 8.9% in this subset compared to 2.8% (RR 3.5; 95% CI 2.0 to 6.2) of women exposed to monotherapy w to 1.6% (RR 6.0; 95% CI 3.5 to 10.2) of an external comparison group. Anomalies reported in order of freque neural tube, hypospadias, polydactyly, bilateral inguinal hernia, dysplastic kidneys, and club foot. Similarly, a retrospective cohort study (n=1411) showed an increased risk of major congenital abnormalities in the offspri treated with either carbamazepine (relative risk (RR) 2.6) or valproate (RR 4.1) monotherapy during the first t pregnancy (Samren et al, 1999). Risk associated with valproate was dose-dependent. Valproate alone and in other AEDs were associated with an increased risk of neural tube defects (RR 4.0, p=0.03; RR 5.4, p=0.004, risk of hypospadia was similarly higher in the monotherapy and combination therapy groups (RR 4.8, p=0.05; respectively).

c) Numerous cases have been reported of fetal neural tube defects, primarily spina bifida, and/or cardiac def of Fallot, patent ductus arteriosus, valvular aortic stenosis, and ventricular septal defect). There is an increas neural tube defects with exposure during the first trimester of pregnancy. Risk of spina bifida in children of wo valproic acid during pregnancy is estimated to be 1% to 2% by the CDC. While the American College of Obst Gynecologists estimates the general risk for congenital neural tube defects to be 0.14% to 0.2%, data from th Drug (AED) Pregnancy Registry showed that neural tube defects occurred at a rate of 2% (n=3/149) (Prod In ER extended-release oral tablets, 2006; Prod Info DEPAKOTE(R) oral sprinkle capsules, 2006; Prod Info DE delayed-release oral tablets, 2006a; Prod Info DEPACON(R) IV injection, 2006; Prod Info DEPAKENE(R) ora syrup, 2006; Ardinger et al, 1988; Bertollini et al, 1987; Jager-Roman et al, 1986; Bailey et al, 1983; Jeavons Guibaud, 1982; Thomas & Buchanan, 1981; Clay et al, 1981; Dalens et al, 1980).

d) Various other reports of fetal abnormalities resemble those seen in fetal hydantoin syndrome, including cr skeletal or limb defects (Prod Info DEPAKOTE(R) ER extended-release oral tablets, 2006; Prod Info DEPAK sprinkle capsules, 2006; Prod Info DEPAKOTE(R) delayed-release oral tablets, 2006a; Prod Info DEPACON 2006; Prod Info DEPAKENE(R) oral capsules, oral syrup, 2006; DiLiberti et al, 1984; Jager-Roman et al, 198

1988). It is not clearly established, however, whether these anomalies constitute a fetal valproic acid syndrom of other factors such as genetic or environmental factors, combination therapy with other anticonvulsants, an episodes during gestation. A case-control study in which 57 of 22,294 malformed infants and 10 of 21,937 co exposed to valproic acid estimated a risk for limb deficiencies to be about 0.42% (Rodriguez-Pinilla et al, 200 analysis calculated an odds ratio of 6.17 (confidence interval 1.28-29.66, p = 0.023) for limb deficiencies afte prenatal exposure to valproic acid. The types of limb deficiencies reported included overlapping digits, talipes clinodactyly, arachnodactyly, hip dislocation, and others.

e) The relationship of first-trimester plasma antiepileptic drug (AED) concentrations and pregnancy outcome women was assessed, including 44 women on valproic acid monotherapy (Canger et al, 1999). Valproic acid significantly higher rate of malformations (p less than 0.02) compared to monotherapy with other AEDs such carbamazepine, phenobarbital, phenytoin, and clonazepam. In addition, the mothers of malformed fetuses us valproic acid during their first trimester than did mother of nonmalformed fetuses.

f) Twenty-two infants with in utero exposure to a median daily dose of 1 g valproate in the first trimester and third trimester were described by (Ebbesen et al, 2000). In 13 of the 22 infants, blood glucose dropped below the first hypoglycemic episode occurring within one hour of birth in seven infants and within 2 hours in three i infants exhibited withdrawal symptoms within 12 to 24 hours including irritability, jitteriness, hypertonia, seizu problems.

g) Other reported fetotoxic effects include a case of an infant with afibrinogenemia who died of hemorrhage, hepatic failure that resulted in death of a newborn infant (Prod Info DEPAKOTE(R) ER extended-release oral Prod Info DEPAKOTE(R) oral sprinkle capsules, 2006; Prod Info DEPAKOTE(R) delayed-release oral tablets DEPACON(R) IV injection, 2006; Prod Info DEPAKENE(R) oral capsules, oral syrup, 2006).

h) If phenytoin or carbamazepine (or any prodrugs) is used in pregnant women, there is a substantially incre teratogenicity with many combinations of other anticonvulsants. The teratogenicity of these drugs is largely o the levels of the reactive epoxide metabolites (Buehler et al, 1990c; Van Dyke et al, 1991c; Finnell et al, 1992 epoxide/parent drug ratio is generally increased when phenytoin or carbamazepine is combined with each otl drugs that induce cytochrome P450 enzymes (3A4, 2C9, 2C19), or drugs which inhibit epoxide hydrolase, su acid, progabide, and lamotrigine (Bianchetti et al, 1987c; Ramsay et al, 1990c; Spina et al, 1996c). Such com the risk of major birth defects 3- to 4-fold over monotherapy and about 10-fold over background rates.

B) Breastfeeding

1) American Academy of Pediatrics Rating: Maternal medication usually compatible with breastfeeding. (Anon, 2

2) World Health Organization Rating: Compatible with breastfeeding. Monitor infant for side effects. (Anon, 2002)

3) Thomson Lactation Rating: Infant risk cannot be ruled out.

a) Available evidence and/or expert consensus is inconclusive or is inadequate for determining infant risk wh breastfeeding. Weigh the potential benefits of drug treatment against potential risks before prescribing this dr breastfeeding.

4) Clinical Management

a) Valproate is excreted into breast milk, with levels reported to be 1% to 10% of maternal serum levels. The recommends to consider discontinuing nursing when valproic acid is administered to a nursing woman (Prod (R) ER extended-release oral tablets, 2006; Prod Info DEPAKOTE(R) oral sprinkle capsules, 2006; Prod Info delayed-release oral tablets, 2006a; Prod Info DEPACON(R) IV injection, 2006; Prod Info DEPAKENE(R) ora syrup, 2006).However, valproic acid is considered to be compatible with breastfeeding by the American Acad (Anon, 2001). Children younger than two years of age who use valproic acid may, however, be at risk of fatal (Zimmerman, 1993). Additionally, a case report described thrombocytopenia and anemia in a 3-month-old inf mother received sodium valproate (Stahl et al, 1997). Therefore, nursing mothers should monitor their infants toxicity such as drowsiness, petechiae, vomiting, and/or diarrhea (Iqbal et al, 2001).

5) Literature Reports

a) Early data indicated that valproic acid was excreted in breast milk in significant levels (approximately 10% levels) (Pinder et al, 1977a), but the number of women studied was low (16 in the largest study) (Chaudron & Data from other studies have supported the findings that the drug is not contraindicated during the breastfeed (Rimmer & Richens, 1985c; Von Uhruh et al, 1984; Dickinson et al, 1979).

b) One report describes a 3-month-old infant presenting with thrombocytopenia and anemia caused by sodiu administration to the nursing mother. The infant's serum valproate level was 6.6 mcg/mL. Breastfeeding was hematologic abnormalities resolved within 35 days(Stahl et al, 1997).

6) Drug Levels in Breastmilk

a) Parent Drug

1) Milk to Maternal Plasma Ratio

a) 0.1-0.42 (Lawrence & Lawrence, 1999)

3.5 Drug Interactions

Drug-Drug Combinations

Drug-Lab Modifications

Intravenous Admixtures

3.5.1 Drug-Drug Combinations

Acyclovir

Amitriptyline

Aspirin

Betamipron

Carbamazepine

Cholestyramine

Clarithromycin

Clomipramine

Dehydroepiandrosterone

Doripenem

Ertapenem

Erythromycin

Ethosuximide

Evening Primrose

Felbamate

Fosphenytoin

Ginkgo

Imipenem

Isoniazid

Lamotrigine

L-Methylfolate

Lopinavir

Lorazepam

Mefloquine

Meropenem

Nifedipine

Nimodipine

Nortriptyline

Oxcarbazepine

Panipenem

Phenobarbital

Phenytoin

Primidone

Rifampin

Rifapentine

Risperidone

Ritonavir

Rufinamide

Tipranavir

Topiramate

Vorinostat

Zidovudine

3.5.1.A Acyclovir

1) Interaction Effect: decreased valproic acid plasma concentrations and potential increased seizure activity

2) Summary: A case report from the University of Bologna in Italy documents a reduction in plasma levels of and valproic acid when combined with acyclovir treatment. This reduction resulted in increased seizure activi approximately one per month to 25 in one day. Phenytoin dosage was increased and plasma levels returned ranges after 10 days (Parmeggiani et al, 1995a).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Monitor patients for reduction in antiepileptic plasma levels. Consider alternative an

7) Probable Mechanism: increased gastrointestinal transit or change in gastrointestinal fluid pH

8) Literature Reports

a) According to a case report from the University of Bologna in Italy, a seven-year-old child with a histor experienced increased seizure activity after being treated with acyclovir in addition to his antiepileptic me patient's trough plasma levels of phenytoin and valproic acid were 17 and 32 mcg/mL, respectively, 10 d acyclovir treatment for viral throat and mouth lesions. Four days after initiation of acyclovir treatment, the were 5.0 and 22 mcg/mL, respectively. Acyclovir treatment was discontinued after six days. Three and si acyclovir withdrawal, phenytoin and valproic acid plasma levels were still low, and the patient experience seizures five days after discontinuation. Phenytoin dosage was increased to reach therapeutic plasma le frequency of seizures was reduced to two or three per week. The authors suggest that further study of th interaction is warranted (Parmeggiani et al, 1995).

3.5.1.B Amitriptyline

1) Interaction Effect: increased serum concentrations of amitriptyline and its metabolite nortriptyline

2) Summary: A controlled study observed increases in the area under the concentration-time curve (AUC) ar concentration (Cmax) for amitriptyline and its active metabolite, nortriptyline, when given concurrently with div (Wong et al, 1996a). Monitor amitriptyline levels in patients taking valproate concomitantly. Consideration sho lowering the dose of amitriptyline in the presence of valproate (Prod Info Depakote(R) ER, 2003).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: theoretical
6) Clinical Management: Monitor amitriptyline levels and nortripyline concentrations in patients taking valproa with amitriptyline. A lower dose of amitriptyline may be necessary if given concurrently with valproate.
7) Probable Mechanism: decreased amitriptyline plasma clearance
8) Literature Reports
a) In an open-label study of 15 healthy volunteers, the pharmacokinetic interactions between divalproex amitriptyline were studied. Subjects were given amitriptyline 50 mg alone and two hours after receiving n divalproex sodium 500 mg, which was given every 12 hours. Coadministration of amitriptyline with divalp resulted in a 17% increase in amitriptyline maximum concentration (Cmax) and a 31% increase in the an under the concentration-time curve (AUC). Time to maximum concentration (Tmax) for amitriptyline was coadministration with divalproex sodium. For nortriptyline, the metabolite of amitriptyline, AUC was incre Cmax was increased by 28%, and Tmax was unaffected. The authors postulated that divalproex sodium amitriptyline and nortriptyline disposition, possibly through inhibition of hepatic metabolism (Wong et al, 1
b) The addition of valpromide to a stable amitriptyline regimen may result in an increase of antidepressa concentrations. Twenty patients with major depressive illness (DSM - III criteria) were divided into two gr with amitriptyline alone and one treated with both amitriptyline and valpromide. All patients received oral mg once daily in the evening for 20 days. Only benzodiazepines (diazepam, lorazepam, bromazepam, cl dipotassique), 5-30 mg/day, were also administered. Ten patients also received 600 mg valpromide daily amitriptyline to avoid relapses and/or to decrease irritability and agitation. No statistically significant differ amitriptyline and nortriptyline plasma levels were determined on days 10 and 20, respectively in ten patie amitriptyline 125 mg daily. In the ten patients who received valpromide 600 mg, amitriptyline and nortript increased. The mean amitriptyline level increased from 70.5 +/- 35.9 nanograms/milliliter (ng/mL) to 105. (p less than 0.0003, paired Student's t test), and the mean nortriptyline level rose from 61.0 +/- 34.3 to 1(less than 0.01). No significant relationship was seen between the percentage increase of amitriptyline lev plasma level of valproic acid, the main valpromide metabolite. There was a significant linear relationship plasma levels of amitriptyline before and after valpromide (r equal to 0.94, p less than 0.001) and betwee plasma levels before and after valpromide (r equal to 0.87, p less than 0.001). Tricyclic antidepressant pl increase above the therapeutic window after addition of valpromide. Monitoring of plasma levels of tricyc is advisable to control this interaction (Vandel et al, 1988).

3.5.1.C Aspirin

1) Interaction Effect: increased free valproic acid concentrations
2) Summary: Salicylates have been shown to alter both the metabolism and protein binding of valproic acid. in increased free valproate free fractions (Prod Info Depakote(R) ER, 2003j) by 30% to 65% (Abbott et al, 198 1987).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: An occasional single dose of aspirin would not likely present a problem; however, w doses, monitoring of valproic acid concentrations might be considered. An alternative analgesic such as acet be considered if appropriate.
7) Probable Mechanism: altered binding and metabolism
8) Literature Reports
a) Six epileptic children who were taking valproic acid received antipyretic doses of aspirin. The steady-s of valproate rose from 12% to 43% in the presence of salicylate in five of these patients. Half-life of valpr total and free valproate concentrations, increased. Renal excretion of unchanged valproate decreased w Salicylates appear to displace valproate from serum protein binding sites and alter valproate metabolism Farrell et al, 1982).

3.5.1.D Betamipron

1) Interaction Effect: decreased valproic acid efficacy
2) Summary: Three case reports describe a decrease in valproic acid serum concentrations when panipener therapy was instituted, resulting in the recurrence of seizures in two patients. Although the exact mechanism is not known, panipenem/betamipron should be avoided in patients treated with valproic acid (Yamagata et a
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Patients receiving valproic acid anticonvulsant therapy should not be treated with panipenem/betamipron. An alternative antibiotic which does not affect valproic acid serum levels should be c
7) Probable Mechanism: unknown
8) Literature Reports
a) A 4-year-old female with spastic quadriplegia, epilepsy, and mental retardation was receiving valproic mg/kg/day and phenobarbital 5 mg/kg/day with serum levels of 55.1 mg/dL and 28.4 mg/dL, respectively admitted to the hospital for pneumonia, and her valproic acid dose was increased to 30 mg/kg/day while was decreased to 4.5 mg/kg/day. Panipenem/betamipron therapy was initiated at 60 mg/kg/day in three daily, and the serum valproic acid level decreased to 22.9 mg/mL by day 6. Although no seizures develo this decrease, panipenem/betamipron was discontinued, and the valproic acid serum concentration incre mg/dL (Yamagata et al, 1998).

b) A 3-year-old girl with quadriplegia, epilepsy, and mental retardation was receiving valproic acid 35 mg carbamazepine 11 mg/kg/day, and phenytoin 10 mg/kg/day for two months before a hospital admission f pneumonia. Valproic acid serum concentration was 88.7 mg/mL prior to the start of panipenem/betamipr and amikacin 5 mg/kg/day. Three days later, generalized tonic-clonic seizures began to occur once or tw valproic acid level had decreased to 30.9 mg/mL and further dropped to 26.8 mg/mL two days later. Des the valproic acid dose to 42 mg/kg/day, the serum concentration continued to decrease to 15.3 mg/mL o treatment with panipenem/betamipron. The valproic acid level started to increase within 24 hours of disc panipenem/betamipron. The phenytoin serum level was undetectable on day 3 of panipenem/betamipror carbamazepine level was not significantly altered (Yamagata et al, 1998).

c) Panipenem/betamipron 30 mg/kg/day resulted in intense, generalized seizures and frequent myoclon year-old male who had previously been stabilized on valproic acid 32 mg/kg/day, clonazepam 0.9 mg/kg phenytoin 5 mg/kg/day. Prior to panipenem/betamipron therapy, his valproic acid serum level ranged fro 108.9 mg/mL. However, by day 5 of panipenem/betamipron treatment, the valproic acid level was 26.7 m the valproic acid dose was increased to 34 mg/kg/day, serum levels were undetectable by day 25 of panipenem/betamipron therapy. After the antibiotic was discontinued, the serum valproic acid concentrat 55 mg/mL and the frequency of the seizures was decreased. Incidentally, in this patient, the phenytoin a levels were not significantly altered by the presence of panipenem/betamipron (Yamagata et al, 1998).

3.5.1.E Carbamazepine

1) Interaction Effect: carbamazepine toxicity (ataxia, nystagmus, diplopia, headache, vomiting, apnea, seizur decreased valproic acid effectiveness

2) Summary: The literature contains conflicting data regarding the effects of combined carbamazepine and v Carbamazepine may decrease valproic acid levels by 15% to 25% while increasing clearance by up to 30% (1979a; Rimmer & Richens, 1985b; Mahaly et al, 1979a; Jann et al, 1988a). Furthermore, the conversion of va ene-VPA (thought to be the most toxic metabolite with potential for hepatotoxicity and teratogenicity) is signifi with coadministration of carbamazepine (Kondo et al, 1990a). Valproic acid may increase, decrease, or caus carbamazepine concentrations (Mattson et al, 1982a; Levy et al, 1984a; Pisani et al, 1990a; Anderson et al, 1

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Monitor patients for signs of carbamazepine toxicity such as nausea, vomiting, drow when valproic acid is added. Serum carbamazepine concentrations should also be measured, though clinicia aware of the increase in the concentration of the active metabolite, carbamazepine-epoxide, which is not rout but does contribute to the efficacy and toxicity of the drug. If carbamazepine is added to valproic acid therapy acid levels; increased valproic acid dosage may be required.

7) Probable Mechanism: increased valproic acid clearance; variable effects on carbamazepine metabolism

8) Literature Reports

a) Significant increases (59%) in valproic acid serum concentrations have been reported following the w carbamazepine in six epileptic patients. A new plateau for the valproic acid serum level was observed at weeks after withdrawal of the carbamazepine (Jann et al, 1988).

b) Several reports have indicated conflicting effects of valproic acid on carbamazepine serum levels (Ri 1985a; Flachs et al, 1979; Adams et al, 1978). In an in vitro study of protein binding, valproic acid compe carbamazepine plasma protein binding sites, resulting in significant increases in free carbamazepine (Ma Concurrent therapy of valproic acid and carbamazepine in seven patients was found to decrease levels o by 3% to 59% and protein binding decreased. The plasma concentration ratio of carbamazepine-10,11-e carbamazepine increased in all patients by 11% to 500% (Levy et al, 1984; Pisani et al, 1990) probably d epoxide hydroxylase by valproic acid (Robbins et al, 1990). In addition, carbamazepine may cause a red valproic acid half-life with increased clearance secondary to enzyme induction and increased hepatic me et al, 1979; Rimmer & Richens, 1985a; Mahaly et al, 1979). Infrequent reports have indicated symptoms nausea, or confusion when valproic acid was added to carbamazepine therapy (Lhermitte et al, 1978; Ha A single case of psychosis following the addition of carbamazepine to valproic acid has been reported in refractory epilepsy (McKee et al, 1989).

c) Select patients with suspected genetic deficiencies may tolerate poorly the effects of valproic acid on certain amino and fatty acids, which may impact anticonvulsant therapy based on carbamazepine-valpro these individuals (Anderson et al, 1994a).

d) The pharmacokinetics of valproic acid and its metabolites when coadministered with carbamazepine epileptic patients. The ratio of valproic acid concentration to dose was significantly lower in those patient acid with carbamazepine compared with those receiving only valproic acid. Additionally, the ratio of 4-en concentration to valproic acid concentration was significantly higher in those receiving combined carbam acid compared with those on valproic acid monotherapy. 4-ene-VPA, reported to be the most toxic of val metabolites, may manifest as hepatotoxicity and teratogenicity (Kondo et al, 1990).

e) If phenytoin or carbamazepine (or any prodrug) is used in pregnant women, there is a substantially in teratogenicity with many combinations of other anticonvulsants. The teratogenicity of these drugs is large related to the levels of the reactive epoxide metabolites (Buehler et al, 1990a; Van Dyke et al, 1991a; Fir The epoxide/parent drug ratio is generally increased when phenytoin or carbamazepine is combined with other drugs that induce cytochrome P450 enzymes (3A4, 2C9, 2C19), or drugs which inhibit epoxide hyc valproic acid, progabide, and lamotrigine (Bianchetti et al, 1987a; Ramsay et al, 1990a; Spina et al, 1996 combinations increase the risk of major birth defects 3- to 4-fold over monotherapy and about 10-fold ov

rates.

3.5.1.F Cholestyramine

1) Interaction Effect: decreased serum valproic acid concentrations

2) Summary: A controlled study observed that the concurrent administration of valproic acid and cholestyram significantly reduced valproic acid area under the concentration-time curve (AUC) and maximum concentratic However, administration of valproic acid three hours before taking cholestyramine resulted in no significant pl changes (Malloy et al, 1996a).

3) Severity: moderate

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: Clinicians should be aware that valproic acid taken concurrently with cholestyramin serum valproic acid concentrations. If these drugs are to be given together, administer cholestyramine at leas valproic acid, and monitor patients for valproic acid therapeutic efficacy.

7) Probable Mechanism: decreased absorption of valproic acid

8) Literature Reports

a) In an open-label, three-way crossover study, the effects of cholestyramine on the plasma concentrati were investigated in six healthy volunteers. Subjects participated in three treatment phases, with a minim washout period between phases. During phase 1, the subjects received a single dose of valproic acid 25 phase 2, subjects received cholestyramine 4 g twice daily for one day, followed by valproic acid 250 mg dose of cholestyramine. Phase 3 was identical to phase 2 except that the valproic acid 250 mg was take before the morning dose of cholestyramine. When valproic acid was given concurrently with cholestyram acid area under the concentration-time curve (AUC) decreased by 21% and the valproic acid maximum c (Cmax) decreased by 15% compared to valproic acid alone. When valproic acid was given three hours b cholestyramine, no significant changes in AUC or Cmax were observed. Based on this data, decreases i concentrations can be partially avoided by taking the cholestyramine three hours after valproic acid (Mall

3.5.1.G Clarithromycin

1) Interaction Effect: increased serum levels of valproate

2) Summary: There have been reports of interactions of clarithromycin with drugs not thought to be metaboli P450 3A4, such as valproate (Prod Info Biaxin(R), 2002).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: Monitor plasma concentrations of valproate closely in patients receiving concomitar therapy.

7) Probable Mechanism: unknown

3.5.1.H Clomipramine

1) Interaction Effect: an increased risk of clomipramine toxicity (agitation, confusion, hallucinations, urinary re tachycardia, seizures, coma)

2) Summary: Comedication with clomipramine and valproic acid may increase serum levels of clomipramine increased side effects. Clomipramine toxicity developed in a patient twelve days after valproic acid therapy w Metabolism of clomipramine is mediated through N-demethylation, hydroxylation, and glucuronidation, and va appears to inhibit the enzymes responsible for this mode of metabolism (Fehr et al, 2000a).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Monitor serum clomipramine levels to avoid overdosing as a result of elevated conc clomipramine when comedicating with valproic acid. The clomipramine dose may need to be reduced when v added to therapy.

7) Probable Mechanism: inhibition of cytochrome P450 2C-mediated metabolism of clomipramine

8) Literature Reports

a) A case report describes a 46-year-old female with personality disorder whose serum clomipramine cc became elevated after she began concomitant therapy with valproic acid. Antidepressant therapy with cl lorazepam was initiated while being hospitalized for treatment of her psychiatric disorder. These two age reduce the frequency of panic attacks and to improve symptoms of suicidal and self-destructive behavior clomipramine 150 mg/day resulted in serum clomipramine levels in the normal range. Lorazepam was in 2 mg/day After two weeks of therapy valproate was initiated at 1000 mg/day because emotional instabilit destructive behavior remained unimproved. After five days of therapy the serum levels of clomipramine a desmethylclomipramine increased to 447 ng/mL and 85 ng/mL, respectively. Valproate serum concentra mcg/mL. The valproate dose was subsequently adjusted to 1400 mg/day. Seven days after the increase clomipramine and desmethylclomipramine serum concentrations were 479 ng/mL and 269 ng/mL respec the valproate serum level was 55 mcg/mL. The patient noted a feeling of numbness and exaggerated sle After the clomipramine dose was reduced to 75 mg/day, these symptoms resolved. The author conclude in serum clomipramine concentrations was primarily due to comedication with valproate (Fehr et al, 200

3.5.1.I Dehydroepiandrosterone

1) Interaction Effect: reduced effectiveness of valproic acid
2) Summary: Dehydroepiandrosterone (DHEA) in a single case report was noted to cause mania in a patient personal or family history of bipolar disorder (Markowitz et al, 1999a). Elevated DHEA levels have been found mental disorders; DHEA suppression has lead to improvement in psychotic symptoms (Howard, 1992). Patie medication for bipolar disorder or patients with a personal and/or family history of bipolar disorder should not further data is available to characterize this drug-herb interaction.
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: If valproic acid is being used for manic symptoms, concomitant use of dehydroepian (DHEA) may cause a return of symptoms. Patients with a personal or family history of bipolar disorder should avoid DHEA use.
7) Probable Mechanism: proserotonergic activity of dehydroepiandrosterone may predispose patients to mar dehydroepiandrosterone is a precursor to androgenic steroids, which in high doses may precipitate mania
8) Literature Reports
a) A 68-year-old male with no documented psychiatric history initiated dehydroepiandrosterone (DHEA) (mg) daily and increased the dose to 200 to 300 mg daily for 6 months. Within 3 months, family members of odd behavior with prominent symptoms of agitation, delusional thinking, decreased sleep and appetite sprees. The patient was not taking any prescribed medication but did ingest alcohol in amounts up to 1 c Another 3 months elapsed, leading to involuntary inpatient admission secondary to rapid, loud, pressured grandiose thoughts. At admission, the patient reported that he had decreased alcohol intake to 2 beers c concerns about his behavior changes. There was no family history of bipolar disorder. Urinary drug scree Over the seven-day hospital stay, with the institution of valproic acid 500 mg twice daily, the patient's beh patterns improved, and the patient believed DHEA led to his symptoms. There were no ethanol withdraw patient was discharged with follow-up care from his primary care physician with a diagnosis of substance disorder (Markowitz et al, 1999).

3.5.1.J Doripenem

1) Interaction Effect: reduced valproic acid serum concentrations
2) Summary: Frequently monitor valproic acid concentrations after starting doripenem as coadministration re valproic acid concentrations and may result in loss of seizure control. If valproic acid concentrations cannot b within the therapeutic range or a seizure occurs, alternative antibiotic or anticonvulsant therapy should be con DORIBAX(R) IV injection, 2009).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Frequently monitor valproic acid concentrations after starting doripenem as coadmi result in reduced valproic acid concentrations and possibly a loss of seizure control. If valproic acid concentra maintained within the therapeutic range or a seizure occurs, alternative antibiotic or anticonvulsant therapy sh considered (Prod Info DORIBAX(R) IV injection, 2009).
7) Probable Mechanism: unknown
8) Literature Reports
a) Valproic acid AUC was reduced by 63% in healthy volunteers following coadministration of doripenem DORIBAX(R) IV injection, 2009).

3.5.1.K Ertapenem

1) Interaction Effect: decreased valproic acid plasma concentrations and loss of anticonvulsant effect
2) Summary: Clinically significant reductions in serum valproic acid levels have been reported in patients rec carbapenem antibiotics concomitantly. Two case reports describe significant decreases in serum valproic aci with coadministration of ertapenem, leading to seizures in one (Lunde et al, 2007; CabanesMariscal et al, 20 exact mechanism is not understood, in vitro and animal data suggest that carbapenems may inhibit valproic a hydrolysis. If ertapenem is initiated in patients receiving valproic acid, frequent monitoring of valproic acid lev recommended. Use alternative antibacterial or anticonvulsant therapy if valproic acid blood levels drop below or if a seizure occurs (Prod Info INVANZ(R) IV, IM injection, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: If concomitant administration of valproic acid and ertapenem is required, monitor va concentration frequently. Consider alternative antibiotic or anticonvulsant therapy if serum valproic acid levels therapeutic range or if a seizure occurs (Prod Info INVANZ(R) IV, IM injection, 2008).
7) Probable Mechanism: unknown
8) Literature Reports
a) A 41-year-old man maintained on divalproex sodium for seizure prophylaxis experienced recurrent to on day 7 of concomitant ertapenem (1000 mg) every 24 hours) therapy. His medical history was significa hypertension controlled with metoprolol, seizure disorder secondary to traumatic brain injury, and chronic osteomyelitis. Approximately 3 months prior to starting ertapenem, the patient's serum valproic acid conc therapeutic at 130 mcg/mL while taking divalproex sodium 2000 mg/day. He was admitted to the emerge 3 seizure episodes, the last of which was a witnessed tonic-clonic seizure lasting longer than one minute

valproic acid concentration was 70 mcg/mL. The dose of divalproex sodium was increased to 2750 mg/d was discharged. He returned 4 days later with recurrent seizures and a serum valproic acid concentratio Intravenous valproic acid 1000 mg was administered along with one oral dose of divalproex sodium 100 was discontinued, and intravenous ampicillin-sulbactam 3 grams every 6 hours was begun. The followin serum valproic acid concentration increased to 55 mcg/mL. Oral divalproex sodium was again increased and 2 days later his level was 88.1 mcg/mL. Five days after ertapenem was discontinued his serum valp concentration reached 146 mcg/mL, necessitating a decrease in divalproex sodium dose. He subsequen seizure-free (Lunde et al, 2007; Personal Communication, 04/28/2008).

b) An 80-year-old woman, chronically treated with valproic acid solution 1100 mg/day for complex partia secondary to severe cerebrovascular disease, experienced significantly reduced serum valproic acid cor beginning 4 days after the initiation of ertapenem 1000 mg every 24 hours. Approximately, 1.5 months p exposure, her total serum valproic acid concentration was 72 mcg/mL. Admitted to the hospital for aspira the patient was treated with ertapenem. Four days later serum valproic acid concentration was reported mcg/mL, and her valproic acid dose was increased to 1600 mg/day. Two days later serum valproic acid mcg/mL and the drug dose increased to 2000 mg/day. A level of 1.04 mcg/mL was measured 4 days afte increase. Ertapenem was discontinued. With intravenous administration of valproic acid (800 mg loading 400 mg every 6 hours), the patient's serum concentration gradually returned to therapeutic range over th She was subsequently maintained on oral valproic acid 1400 mg/day (CabanesMariscal et al, 2006).

3.5.1.L Erythromycin

1) Interaction Effect: valproic acid toxicity (CNS depression, seizures)

2) Summary: One case report described the concurrent use of erythromycin and valproic acid resulting in inc acid concentration and symptoms of valproate toxicity. Discontinuation of erythromycin led to lowered valproa resolution of the symptoms (Redington et al, 1992a).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: If erythromycin and valproic acid are used concurrently, monitor patient for signs of (CNS depression, seizures). Monitor valproic acid serum concentrations during and after erythromycin therap

7) Probable Mechanism: decreased valproic acid metabolism

8) Literature Reports

a) One study describes a 38-year-old female outpatient receiving valproate 3500 mg daily, clorazepate mg four times daily, and lithium carbonate 300 mg twice daily; her valproate level was 88.8 mg/L (therap 100 mg/L). Erythromycin 250 mg four times daily was prescribed for a respiratory infection; within a weel difficulty in walking, confusion, lethargy, slurred speech, and poor concentration. Her valproate level was admission; at that time both erythromycin and valproate were discontinued. Fifteen hours later the valpro mg/L, and valproate was restarted at the original dosage. All signs of adverse reaction resolved (Redingt

3.5.1.M Ethosuximide

1) Interaction Effect: an increased risk of ethosuximide toxicity

2) Summary: Concomitant valproic acid and ethosuximide therapy does not appear to influence the pharmac parameters of ethosuximide. This was demonstrated in an evaluation in which valproic acid was added to a c ethosuximide regimen. There was no apparent change in total or nonrenal clearance of ethosuximide (Bauer However, the above combination did result in elevated ethosuximide levels (Mattson & Cramer, 1980). Admir ethosuximide in patients receiving valproic acid therapy was reported to result in significant increases in etho (from 44 to 54 hours) and a significant decrease in total body clearance (11.2 to 9.5 mL/minute) (Pisani et al, suggest that valproic acid is capable of inhibiting the metabolism of ethosuximide.

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Monitor patients receiving valproate and ethosuximide concomitantly for alterations concentrations of both drugs.

7) Probable Mechanism: inhibition of ethosuximide metabolism

8) Literature Reports

a) Valproate inhibits the metabolism of ethosuximide. Administration of a single ethosuximide 500 mg d (800 to 1600 mg/day) to six healthy volunteers resulted in a 25% increase in elimination half-life of ethos 15% decrease in valproate total clearance compared to ethosuximide alone. Patients on concomitant val ethosuximide should be monitored for alterations in serum concentrations of both drugs (Prod Info Depal 2003k).

3.5.1.N Evening Primrose

1) Interaction Effect: reduced anticonvulsant effectiveness

2) Summary: Theoretically, evening primrose oil may reduce the effectiveness of anticonvulsants by lowering threshold. Evening primrose oil is contraindicated in patients with epilepsy (Barber, 1998; Newall et al, 1996).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: Avoid concomitant use of evening primrose oil with anticonvulsants.

7) Probable Mechanism: evening primrose oil may reduce the seizure threshold

3.5.1.O Felbamate

1) Interaction Effect: increased valproic acid concentrations

2) Summary: Coadministration of felbamate (1200 mg to 2400 mg daily) and valproic acid resulted in an incr valproic acid AUC (28% and 54%), peak concentrations (34% and 55%), and average steady-state concentra 54%) (Wagner et al, 1992; Prod Info Felbatol(R), 2000). A decrease in valproate dosage may be necessary v therapy is initiated (Prod Info Depakote(R) ER, 2003e).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Monitor valproic acid levels when initiating or discontinuing felbamate. Tremor, irrita and restlessness are more common when valproic acid serum levels exceed 100 mcg/mL. A decrease in the acid may be necessary.

7) Probable Mechanism: decreased valproic acid clearance

3.5.1.P Fosphenytoin

1) Interaction Effect: altered valproate levels or altered phenytoin levels

2) Summary: Fosphenytoin is a prodrug of phenytoin and the same interactions that occur with phenytoin are occur with fosphenytoin (Prod Info Cerebyx(R), 1999). Valproic acid may initially cause a decrease in total ph displacement of phenytoin from protein binding sites (Levy & Koch, 1982; Bruni et al, 1980; Monks et al, 1978 decrease in the bound fraction of phenytoin; the phenytoin which is displaced by valproic acid re-equilibrates capacity of the tissue compartment such that the unbound plasma concentration remains unchanged (Winter al, 1978). The degree of displacement appears to be valproic acid dose related (Monks & Richens, 1980). Va also inhibit phenytoin metabolism (Levy & Koch, 1982; Bruni et al, 1980; Patel et al, 1980; Winter, 1988; de W

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Due to the complex situation involving displacement of protein-bound phenytoin and phenytoin metabolism, as well as the potential for decreased valproic acid concentrations, patients should be phenytoin toxicity and therapeutic efficacy. Free plasma phenytoin levels should be measured if possible to p accurate assessment of phenytoin activity early in therapy. At steady-state free phenytoin concentrations and concentrations should be normalized.

7) Probable Mechanism: altered clearance and protein binding of both drugs

8) Literature Reports

a) If phenytoin or carbamazepine (or any prodrugs) is used in pregnant women, there is a substantially i teratogenicity with many combinations of other anticonvulsants. The teratogenicity of these drugs is large related to the levels of the reactive epoxide metabolites (Buehler et al, 1990; Van Dyke et al, 1991; Finne epoxide/parent drug ratio is generally increased when phenytoin or carbamazepine is combined with eac drugs that induce cytochrome P450 enzymes (3A4, 2C9, 2C19), or drugs which inhibit epoxide hydrolase acid, progabide, and lamotrigine (Bianchetti et al, 1987; Ramsay et al, 1990; Spina et al, 1996). Such co increase the risk of major birth defects 3- to 4-fold over monotherapy and about 10-fold over background

3.5.1.Q Ginkgo

1) Interaction Effect: decreased anticonvulsant effectiveness

2) Summary: In a case report, 2 patients with epilepsy previously well controlled by valproate sodium develo of seizures after ingesting ginkgo extract. Seizure control was regained after ginkgo was withdrawn (Granger developed seizures after exposure to 4'-O-methylpyridoxine arising from ingestion of ginkgo seeds (Yagi et a compound 4'-O-methylpyridoxine, a neurotoxin, is found in ginkgo seeds (used as food in Japan) as well as i ginkgo component from which commercially available extracts are derived (Arenz et al, 1996a). The majority products should not contain sufficient amounts of 4'-O-methylpyridoxine to cause seizures. However, ginkgo commonly assayed to assure that 4'-O-methylpyridixone is not contained in the commercial product. Of conc instances where, depending on the harvest season and the potential introduction of contamination, 4'-O-meth be present in sufficient amounts to be problematic in vulnerable populations (eg, infants or those with known

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Avoid concomitant use of ginkgo and anticonvulsants in patients with epilepsy. If se the first time or recur in patients previously controlled by anticonvulsant medication, inquire about the use of g extract. If possible, an assay should be conducted on the specific product to ascertain if 4'-O-methylpyridoxin

7) Probable Mechanism: neurotoxin 4'-O-methylpyridoxine (found in leaves and seeds of ginkgo biloba) may

8) Literature Reports

a) The serum of a 21-month-old patient with gin-nan food poisoning was assayed for 4'-O-methylpyridox serum concentration was 0.9 micrograms/milliliter (mcg/mL) at 8.5 hours after ingesting ginkgo seeds, de mcg/mL at 15.5 hours. The authors concluded that the 4'-O-methylpyridoxine content was responsible fo convulsions and loss of consciousness observed. They further observed that infants are particularly vuln 1993).

b) Four to six milligrams of the neurotoxin 4'-O-methylpyridoxine have been isolated from 2 kilograms of

leaves which is the source of commercially-available products. Highest amounts were found in seeds (85 (mcg)/seed) and leaves (5 mcg/leaf) derived from the tree at the end of July and beginning of August. Th seed can contain 105.15 mcg/gram dry weight, but this is reduced to 0.75-1.32 mcg/gram dry weight whe unprocessed seed coats contain from 5.44-7.15 mcg/gram dry weight. The neurotoxin in ginkgo leaf was medications and it was even detectable in homeopathic preparations. Specifically, 8.13 mcg/mL of 4'-O-m was found in Tebonin Forte(R), 9.77 mcg/mL in Rokan(R), 3.80 mcg/mL in Kaveri Forte(R), and 7.18 mc (R). Based on recommended daily intake, this translates into a maximum daily intake of 4'-O-methylpyrid mcg, 58.62 mcg, 11.40 mcg, and 43.08 mcg for Tebonin Forte(R), Rokan(R), Kaveri Forte(R), and Gingi respectively. Among the homeopathic products, Ginkgo biloba Urtinktur Hanosan(R) and Ginkgo biloba U contained 0.301 mcg/mL and 0.589 mcg/mL of 4'-O-methylpyridoxine, respectively. However, the author amount contained in medicinal extracts of ginkgo leaves may be too low to be of clinical significance. Co the variance in 4'-O-methylpyridoxine content depending on the season during which the ginkgo was har al, 1996).

c) Seizures recurred in 2 patients, both with epilepsy that was well controlled prior to ingesting ginkgo bi patients (an 84-year-old woman and a 78-year-old man) had been free of seizures for at least 18 months therapy with Gb 120 milligrams daily to treat cognitive decline. Both patients developed seizures within 2 beginning Gb therapy, and both remained seizure-free (without changing anticonvulsant therapy) after di (Granger, 2001).

3.5.1.R Imipenem

1) Interaction Effect: decreased valproic acid plasma concentrations and loss of anticonvulsant effect

2) Summary: Clinically significant reductions in serum valproic acid levels have been reported in patients rec carbapenem antibiotics concomitantly. If imipenem is initiated in patients receiving valproic acid, frequent mo acid levels is recommended. Use alternative antibacterial or anticonvulsant therapy if valproic acid blood leve therapeutic range or if a seizure occurs (Prod Info DEPAKOTE(R) ER extended-release oral tablets, 2008).

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: If concomitant administration of valproic acid and imipenem is required, monitor val concentration frequently. Consider alternative antibiotic or anticonvulsant therapy if serum valproic acid levels therapeutic range or if a seizure occurs (Prod Info DEPAKOTE(R) ER extended-release oral tablets, 2008).

7) Probable Mechanism: unknown

3.5.1.S Isoniazid

1) Interaction Effect: valproic acid or isoniazid toxicity

2) Summary: In a case report, the concurrent use of valproic acid and isoniazid resulted in increased SGPT l and a higher incidence of tonic-clonic seizures. Isoniazid may inhibit the metabolism of valproic acid, or valpr increase the risk of isoniazid toxicity (Dockweiler, 1987).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: Consider monitoring liver function tests periodically with therapy, as well as continu therapeutic efficacy of valproic acid. Monitor serum valproic acid trough concentrations as indicated. If toxicity alternative anticonvulsant may be appropriate.

7) Probable Mechanism: altered metabolism

3.5.1.T Lamotrigine

1) Interaction Effect: increased elimination half-life of lamotrigine leading to lamotrigine toxicity (fatigue, drow an increased risk of life-threatening rashes

2) Summary: Valproic acid interferes with the metabolic clearance of lamotrigine. The normal elimination half is approximately 24 hours; in patients receiving concomitant valproic acid therapy, the half-life increases to ap 60 hours. The mechanism of this interaction is thought to be competition of the two drugs for hepatic metabol 1986; Peck, 1991; Eriksson et al, 1996; Sallustio & Morris, 1997). Fever, rash, multiorgan dysfunction, dissem intravascular coagulation, and fatal toxic necrolysis have been reported with this combination in adults and pe (Chattergoon et al, 1997a; Page II et al, 1998a). Given the increased risk of rash in pediatric patients, careful lamotrigine serum concentrations may be advisable for children younger than 16 years of age, for whom the i lamotrigine is restricted to those who have been diagnosed with either partial seizures or Lennox-Gastaut syn of lamotrigine should be reduced when coadministered with valproate (Prod Info Depakote(R) ER, 2003c; Pro oral tablets, 2006).

3) Severity: major

4) Onset: delayed

5) Substantiation: established

6) Clinical Management: Dosage reductions of lamotrigine are necessary with concurrent valproic acid thera in conjunction with other enzyme-inducing medications. The manufacturer recommends a lamotrigine dose o other day for the first two weeks, increasing to 25 mg once daily for the next two weeks, advancing to a maint 100 mg to 400 mg daily in increments of 25 mg to 50 mg daily every one to two weeks. If valproic acid is the antiepileptic medication, the usual maintenance dose of lamotrigine is 100 to 200 mg daily. Discontinue use o first sign of a rash unless the rash is clearly not drug related (Prod Info lamotrigine oral tablets, 2006).

7) Probable Mechanism: decreased lamotrigine metabolism
8) Literature Reports
a) A 23-year-old woman presented to the emergency room with generalized rash, redness and swelling lips, fever, weakness, blisters, and a sore throat 3 weeks after lamotrigine was added to her anti-epilepsy initial regimen consisted of carbamazepine 400 mg twice a day. Valproic acid 500 mg twice daily was ad lamotrigine 50 mg twice daily was added 3 weeks prior to current presentation. The patient had an eleva sedimentation rate and C-reactive protein. However, serum carbamazepine and valproic acid levels were range. Serum lamotrigine concentrations were not measured. She was diagnosed with lamotrigine-induc Johnson syndrome (SJS), with a Naranjo Adverse Drug Reactions Probability Scale score of 6 (probably Lamotrigine was discontinued and treatment was initiated for the SJS. She was discharged on day 18 or carbamazepine 400 mg twice daily and oral valproic acid 1500 mg/day. At the one month follow-up, she significant improvement in oromucosal and skin lesions, with areas of hyperpigmentation. The patient's i developing SJS may have potentially been a result of either the combination of lamotrigine and valproic a decreased metabolism of lamotrigine, or due to initiation of lamotrigine at a dose higher than the manufa recommended starting dose of 25 mg per day (Kocak et al, 2007).
b) Fever, rash, multiorgan dysfunction, and disseminated intravascular coagulation were reported in two with valproic acid and lamotrigine. Both children were receiving valproic acid for treatment of seizures. La added because of poor control. Symptoms developed within nine days of starting lamotrigine, but did not lamotrigine was discontinued (Chattergoon et al, 1997).
c) A 54-year-old male presented to the hospital with a five-day history of facial swelling, intermittent feve and pruritic rash on the chest, upper extremities, neck, and back. He had been taking allopurinol 100 mg 50 mg daily for four years prior to admission. Because of a glioblastoma multiforme brain tumor, valproic lamotrigine therapy was begun and the doses were titrated to valproic acid 500 mg three times daily and twice daily approximately four weeks prior to his hospital admission. By hospital day 7, the patient was e extensive sloughing of his skin along his back, face, and trunk, accounting for more than 60% of his total area. He continued to deteriorate and was withdrawn from life support on hospital day 12. His death was epidermal necrolysis probably due to lamotrigine therapy and possibly enhanced by valproic acid (Page
d) A study including 28 patients with intractable epilepsy was conducted to determine whether the dose serum concentrations (Css) of valproic acid were inversely related to lamotrigine clearance. Valproic acid 500 mg/day for 3 days and increased to 750 mg/day on day 4, depending on tolerance and response. Th dose was increased 125 to 250 mg every 3 weeks, until patients became seizure-free or developed adve initiation of valproic acid, the dose of lamotrigine was decreased by 50%, so as to maintain lamotrigine C levels to those reached during monotherapy. A 50% reduction in lamotrigine clearance was reported in th dose of lamotrigine needs to be decreased by 50% at the start of valproic acid therapy to maintain comp Css. However, additional increases in valproic acid dose would not require further reductions of lamotrigi stable lamotrigine Css. Seizure-free periods were significantly longer during treatment with both lamotrig acid than during lamotrigine monotherapy, an indication that therapeutic synergism exists between lamot acid (Kanner & Frey, 2000).
e) A study involving eight patients with epilepsy found a significant increase in lamotrigine area under th time curve (AUC) and longer half-life with concomitant valproic acid administration. Dosages of valproic a mg/day resulted in mean increases in lamotrigine AUC of more than 2.5-fold. Even low doses of valproic resulted in significant increases in lamotrigine AUC (mean 84%). Significant increases in plasma lamotrig by inhibiting lamotrigine metabolism and increased half-life has been achieved with the use of low to mod valproic acid (Morris et al, 2000).
f) Lamotrigine decreased valproic acid steady-state concentrations by 25% in 18 healthy volunteers ove and then stabilized. Adding lamotrigine to the existing therapy did not cause a change in plasma valproat in adult or pediatric patients in controlled clinical trials. The addition of valproate increased lamotrigine st concentrations in normal volunteers by more than 2-fold (Prod Info Lamictal(R), 2004).
g) In a black box warning from the manufacturer, the incidence of severe rash may be higher in patients administered valproic acid and lamotrigine (Prod Info Lamictal(R), 2003).

3.5.1.U L-Methylfolate

1) Interaction Effect: decreased valproic acid serum levels
2) Summary: Concomitant administration of first-generation anticonvulsants, including valproic acid, with high may lead to decreased serum levels of the anticonvulsant, thereby decreasing valproic acid efficacy and incre seizures. Although there have been no such reports with the use of l-methylfolate and valproic acid, caution is agents are used concomitantly (Prod Info DEPLIN(R) oral tablets, 2006; Prod Info Zervalx(R) oral tablets, 20 patients for loss of valproic acid efficacy.
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Caution is advised if l-methylfolate is prescribed to patients receiving valproic acid a folate may theoretically result in decreased serum valproic acid levels, thereby reducing valproic acid efficacy the frequency of seizures (Prod Info DEPLIN(R) oral tablets, 2006; Prod Info Zervalx(R) oral tablets, 2008). If used concomitantly, monitor patients for loss of valproic acid efficacy.
7) Probable Mechanism: unknown

3.5.1.V Lopinavir

1) Interaction Effect: decreased valproic acid serum concentrations
2) Summary: Coadministering lopinavir/ritonavir with valproic acid may decrease the plasma concentration o
case report suggests the mechanism may be due to ritonavir induction of VPA metabolism via glucuronidatio
2006). Monitoring of valproic acid plasma concentrations is recommended (Prod Info NORVIR(R), 2005).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor therapeutic concentrations of valproic acid when coadministering with lopin
valproic acid dose increase may be needed.
7) Probable Mechanism: ritonavir-induced metabolism of valproic acid
8) Literature Reports
a) A case report describes a 30-year-old man with bipolar disorder and HIV who became increasingly m
addition of lamivudine 150 mg/zidovudine 300 mg twice a day and lopinavir 133 mg/ritonavir 33 mg (3 ca
day) to his drug regimen. The patient had been maintained on valproic acid (VPA) 250 mg 3 times a day
concentration of 495 mcmol/L, when the antiretrovirals were prescribed during a hospital admission for m
Paroxetine 10 mg/day was simultaneously given for the depressive episode. The patient became hypom
and the paroxetine was switched to sertraline 50 mg/day. Twenty-one days after the initiation of antiretro
became increasingly manic and was again admitted. He had continued all medications except sertraline
including the same VPA dose. Serum VPA concentration 6 to 10 hours post-dose was subtherapeutic at
decrease of 48% from the previous documented concentration. Olanzapine and an increase in VPA to 1
effectively managed the manic episode. The patient adhered to this new drug regimen, including the pre
antiretrovirals, and 10 days later a 14-hour post-dose VPA level measured in the therapeutic range at 39
the patient was not taking concomitant medications known to affect VPA metabolism, it was hypothesize
decrease in VPA concentrations was due to ritonavir induction of VPA metabolism (via glucuronidation)
2006).

3.5.1.W Lorazepam

1) Interaction Effect: increased lorazepam concentrations
2) Summary: In a small study of healthy subjects (n=8), valproic acid was found to decrease lorazepam clea
compared to controls (Anderson et al, 1994). When lorazepam and valproic acid are coadministered, the dos
should be reduced by 50% (Prod Info Ativan(R), 1997a).
3) Severity: moderate
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: When lorazepam and valproic acid are coadministered, the dose of lorazepam shou
50%. The patient should then still be monitored for evidence of lorazepam toxicity, including excessive sedati
depression.
7) Probable Mechanism: decreased lorazepam metabolism
8) Literature Reports
a) In a study involving six healthy male subjects, the coadministration of intravenous lorazepam 2 mg wi
acid 250 twice daily for three days resulted in a decrease of 40% in the total clearance of lorazepam. The
glucuronide formation rate was also decreased by 55%. Plasma concentrations of lorazepam were appro
times higher for at least 12 hours following concurrent administration. The manufacturer of lorazepam re
reducing the dose of lorazepam by 50% during valproic acid coadministration (Prod Info Ativan(R), 1997

3.5.1.X Mefloquine

1) Interaction Effect: loss of seizure control
2) Summary: The concomitant use of mefloquine in patients taking an anticonvulsant may cause reduced se
lowering plasma levels of the anticonvulsant (Prod Info Lariam(R), 2003). One case report describes a male v
an increase in the frequency of his seizures after he was prescribed mefloquine for malaria prophylaxis. His a
medication included carbamazepine and sodium valproate. Pharmacokinetic studies determined that the half
valproate was significantly reduced by the administration of mefloquine, while carbamazepine was not affecte
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: If mefloquine and valproic acid must be administered concurrently, monitor the leve
Adjustments of the valproic acid dose may be required. Also monitor the patient for seizure control.
7) Probable Mechanism: unknown
8) Literature Reports
a) A 38-year old male epileptic controlled by carbamazepine 1200 mg daily and sodium valproate 1 grar
mefloquine 250 mg weekly. The patient began to experience multiple partial seizures. The pharmacokine
antiepileptic drugs were studied to determine the cause of this patient's seizures. A reduction in the half-
valproate (from 8-20 hours to 5.6 hours) was observed, although that of carbamazepine was unchanged
mefloquine accelerated the metabolism of sodium valproate, since they both share the same hepatic me
(Jallon, 1988).

3.5.1.Y Meropenem

1) Interaction Effect: decreased valproic acid plasma concentrations and loss of anticonvulsant effect

2) Summary: As described in a case report, the coadministration of meropenem with valproic acid produced in valproic acid (VPA) plasma concentrations, causing recurrent seizure activity (Coves-Orts et al, 2005) . Sin VPA serum concentrations were reported in several other patients receiving concomitant treatment with VPA No patient developed seizures (Nacarkucuk et al, 2004; De Turck et al, 1998). A single retrospective study of confirms that the concurrent use of valproic acid with meropenem results in subtherapeutic VPA plasma conc corresponding increases in seizure activity and electroencephalogram changes (Spriet et al, 2007).
3) Severity: major
4) Onset: rapid
5) Substantiation: established
6) Clinical Management: Patients receiving valproic acid anticonvulsant therapy should avoid being treated v Consider an alternative antibiotic which does not affect valproic acid serum levels. If concomitant administrati and meropenem is unavoidable, monitor valproic acid serum concentration closely (Spriet et al, 2007).
7) Probable Mechanism: unknown
8) Literature Reports

a) A retrospective study of 39 patients with concurrent treatment with valproic acid (VPA) and meropene an average decrease of valproic acid levels of 66% within 24 hours. In patients receiving meropenem aft the mean plasma concentrations of VPA decreased from 64.3 milligrams/liter (mg/L) to 22.5 mg/L. Thera plasma concentrations range from 50 to 100 (mg/L). Patients receiving VPA after meropenem did not ac plasma levels of VPA, with mean levels of 11.8 mg/L. Despite additional loading doses and increased ma only one patient achieved therapeutic plasma levels after the maintenance dose was increased to 12 gra adverse patient outcomes or incomplete data, 20 patients were evaluated for causality and clinical releva interaction. The interaction was rated probable in 16 and possible in 4 of the 20 patients. Eleven of these experienced an increase in seizures, electroencephalogram changes, or both. VPA concentrations achie range approximately 8 days after concurrent use of the two medications ceased, and seizure activity was et al, 2007).

b) The coadministration of meropenem with valproic acid produced a pronounced decline in valproic aci concentrations. In a case report, a 21-year-old woman was administered valproic acid (VPA) 1920 milligı continuous intravenous (I.V.) infusion over 24 hours in an attempt to control recurrent tonic-clonic seizure concentration of 52.5 micrograms/milliliter (mcg/mL) was attained on treatment day 6, with therapeutic se concentrations maintained on days 8, 10, and 12. On day 13, the patient developed a fever for which intı meropenem 1 gram 3 times daily was started. Two days later, numerous myoclonic events were observe arms and face; VPA serum concentration was measured at 42 mcg/mL. VPA dose was increased to 288 I.V. infusion over 24 hours), yet tonic-clonic seizures recurred on day 17 in conjunction with a further dec concentration to 7 mcg/mL. VPA dose was increased the following day to 3600 mg; however, VPA serun did not exceed 10 mcg/mL. Intravenous ceftazidime and ciprofloxacin were substituted for meropenem o which serum concentration of VPA increased over the next several days, eventually attaining therapeutic cessation of seizure activity (Coves-Orts et al, 2005).

c) As described in a series of case reports, serum concentration levels of valproic acid were substantiall the concurrent administration of meropenem. In the first case, a 14-year-old boy with epilepsy had been with valproic acid (VPA) 50 milligrams/kilogram (mg/kg)/day, prior to receiving meropenem and tobramyc unspecified) for treatment of Acinetobacter pneumonia. VPA serum concentrations subsequently decline therapeutic levels (nadir of 15 micrograms/milliliter (mcg/mL)) despite an increase in VPA dose to 200 m after completing meropenem therapy, VPA serum concentrations returned to therapeutic levels (114 mcg patient was a 7-month-old girl with West syndrome, receiving anticonvulsant treatment with VPA 75 mg/k VPA plasma concentrations were within therapeutic range (69 to 90 mcg/mL) prior to receiving concomit meropenem and vancomycin to treat an Acinetobacter nosocomial pneumonia. VPA was increased to 13 plasma VPA declined to as low as 18 mcg/mL. The patient continued to receive meropenem for 14 days, activity, and sustained an increase in plasma VPA concentrations to 81 mcg/mL on the third day after co meropenem therapy. The third patient, a 14-month-old girl, was receiving VPA 75 mg/kg/day for anticonv West syndrome symptoms. Baseline VPA serum concentrations were 85 mcg/mL. The patient received ı therapy for treatment of an Acinetobacter urinary tract infection; within 3 days of beginning meropenem t plasma concentrations decreased to a nadir of 10 mcg/mL, yet returned to within therapeutic range 3 day the course of meropenem treatment (Nacarkucuk et al, 2004).

d) In 2 patients, substantial reductions occurred in valproic acid (VPA) plasma concentrations when mer added to previously stable dose regimens of VPA. The first patient, a 65-year-old woman, received an in intravenous VPA 1200 milligrams (mg) over 24 hours following shunt placement for management of a su hemorrhage. Therapeutic VPA concentration levels were maintained with a dose range of 1200 mg to 16 approximately 23 days, intravenous meropenem 1 gram 3 times daily was administered with amikacin to negative bacillus infection. On the day following initiation of meropenem, the VPA serum concentration d approximately 55 mg/mL to 25 mg/L (per graphic analysis), despite supplementation of VPA dose. In the report, a 57-year-old woman was given a prophylactic infusion of intravenous VPA (dose unspecified) alc 100 mg 3 times daily administered on postop days 9-15. Due to development of a lung infection with Klel Pseudomonas organisms, intravenous meropenem and amikacin were administered at an indeterminate during the postoperative course, accompanied by an unspecified supplementation of VPA dose. Despite augmentation, serum concentration of VPA declined from 44 mg/L to 5 mg/L within 24 hours of beginning this second patient, the plasma elimination half life of VPA was found to have declined from an expected to only 4 hours (De Turck et al, 1998).

3.5.1.Z Nifedipine

1) Interaction Effect: increased plasma concentration of nifedipine

2) Summary: Nifedipine plasma concentrations may be increased by the presence of valproic acid. Clinical n nifedipine toxicity is recommended (Prod Info Adalat(R) CC Extended Release Tablets, 2004).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: Concomitant administration of nifedipine and valproic acid may increase exposure t Monitor for clinical signs of nifedipine toxicity, including hypotension, peripheral edema, and bradycardia. Cor reduction of nifedipine.

7) Probable Mechanism: unknown

3.5.1.AA Nimodipine

1) Interaction Effect: nimodipine toxicity (dizziness, headache, flushing, peripheral edema)

2) Summary: A single dose study has shown that concurrent use of valproic acid with nimodipine results in ir nimodipine AUC with no change in half-life (Tartara et al, 1991a).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Monitor for clinical or toxic effects of nimodipine (hypotension is most likely). Downv adjustment may be necessary to maintain desired cardiovascular response.

7) Probable Mechanism: decreased nimodipine metabolism

8) Literature Reports

a) Three groups of eight subjects were studied (Tartara et al, 1991). Group 1 was comprised of healthy had epileptic patients treated at least four months with carbamazepine, phenobarbital, phenytoin (all enz a combination, and group 3 included epileptic patients treated for at least four months with sodium valpro the control group, nimodipine AUCs averaged a 7-fold decrease in the enzyme inducer group, probably d first-pass metabolism. The nimodipine AUCs were increased by 50% in the valproate-treated group.

3.5.1.AB Nortriptyline

1) Interaction Effect: increased serum nortriptyline levels

2) Summary: The manufacturer reports a 34% decrease in plasma clearance of nortriptyline and a 21% decr clearance of amitriptyline following the administration of amitriptyline 50 mg (single dose) and valproate 500 r 15 healthy volunteers. However, concurrent use of valproate and amitriptyline (nortriptyline precursor) has ra associated with overt toxicity (Prod Info Depacon(R), 2002). Monitor nortriptyline levels in patients taking valp concomitantly. Consider lowering the dose of nortriptyline in the presence of valproate (Prod Info Depakote(R

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Monitor nortriptyline levels in patients taking valproate concomitantly. Consider lowe nortriptyline in the presence of valproate.

7) Probable Mechanism: inhibition of nortriptyline metabolism

8) Literature Reports

a) In an open-label study of 15 healthy volunteers, the pharmacokinetic interactions between divalproex amitriptyline were studied. Subjects were given amitriptyline 50 mg alone and two hours after receiving n divalproex sodium 500 mg, which was given every 12 hours. Coadministration of amitriptyline with divalp resulted in a 17% increase in amitriptyline maximum concentration (Cmax) and a 31% increase in the an under the concentration-time curve (AUC). Time to maximum concentration (Tmax) for amitriptyline was coadministration with divalproex sodium. For nortriptyline, the metabolite of amitriptyline, AUC was increa Cmax was increased by 28%, and Tmax was unaffected. The authors postulated that divalproex sodium amitriptyline and nortriptyline disposition, possibly through inhibition of hepatic metabolism (Wong et al, 1

b) The combination of valproic acid and nortriptyline has resulted in toxic levels of nortriptyline. A 33-yea bipolar disorder had elected to discontinue her lithium treatment which she had been maintained on for 8 developed severe depression two months later. Nortriptyline 25 mg at bedtime was initiated on day 1 of l day 10, the dosage was increased to nortriptyline 100 mg at bedtime. Valproate 250 mg three times daily day 7 and increased to 500 mg twice daily on day 10. On day 13 of the patient noticed marked tremulous and fingers, which worsened over the next 3 days. After 15 days of nortriptyline treatment the nortriptylin ng/nL (range, 40 to 130 ng/mL). The valproate level was 105 mg/liter (range, 50 to 100 mg/liter). Both me discontinued and the patient's tremulousness decreased over the next 2 days (Fu et al, 1994).

c) A 36-year old male with bipolar disorder was treated initially with lithium but had terminated his lithium of suspected lithium-induced hypothyroidism. His current regimen consisted of thioridazine 75 mg/day ar mg/day. His nortriptyline level at that time was 146 ng/mL. His thioridazine dose was tapered over a 20-d then discontinued due to difficulties with sexual dysfunction. One month later his mood became dysphori presentation to the emergency room, he was restarted on thioridazine 75 mg/day and nortriptyline was ir mg/day. His nortriptyline level was 218 ng/mL, and his nortriptyline was decreased to 75 mg/day. Valproa times daily was subsequently added to the patient's regimen to provide mood stabilization. Valproate wa 1250 mg/day within a few weeks. The patient then stopped thioridazine and started loxapine 10 mg/day. level of nortriptyline was 345 ng/mL. Nortriptyline was titrated down to 25 mg/day and a subsequent drug

ng/mL. This was within the therapeutic range (Fu et al, 1994).
d) The addition of valpromide to a stable amitriptyline regimen may result in an increase of antidepressa
Twenty patients with major depressive illness (DSM - III criteria) were divided into two groups, one treate
alone and one treated with both amitriptyline and valpromide. All patients received oral amitriptyline 125
the evening for 20 days. Only benzodiazepines (diazepam, lorazepam, bromazepam, clorazepate dipota
mg/day, were also administered. Ten patients also received 600 mg valpromide daily after 10 days on ar
relapses and/or to decrease irritability and agitation. No statistically significant difference between amitrip
nortriptyline plasma levels were determined on days 10 and 20, respectively in ten patients treated with a
mg daily. In the ten patients who received valpromide 600 mg, amitriptyline and nortriptyline plasma leve
mean amitriptyline level increased from 70.5 +/- 35.9 nanograms/milliliter (ng/mL) to 105.5 +/- 49.4 ng/m
0.0003, paired Student's t test), and the mean nortriptyline level rose from 61.0 +/- 34.3 to 100.5 +/- 65.1
No significant relationship was seen between the percentage increase of amitriptyline levels and the plas
valproic acid, the main valpromide metabolite. There was a significant linear relationship between the pla
amitriptyline before and after valpromide (r equal to 0.94, p less than 0.001) and between the nortriptylin
before and after valpromide (r equal to 0.87, p less than 0.001). Tricyclic antidepressant plasma levels m
the therapeutic window after addition of valpromide. Monitoring of plasma levels of tricyclic antidepressa
control this interaction (Vandel et al, 1988a).

3.5.1.AC Oxcarbazepine

1) Interaction Effect: decreased plasma concentration of the active 10-monohydroxy metabolite of oxcarbaze
2) Summary: Concurrent administration of oxcarbazepine (600 to 1,800 milligrams (mg)/day) in patients rece
with valproic acid (400 to 2,800 mg/day) resulted in a 18% decrease (90% confidence interval, 13% decrease
in the plasma concentration of oxcarbazepine's 10-monohydroxy derivative (MHD) and a less than 10% chan
acid concentration (Prod Info TRILEPTAL(R) oral tablets, oral suspension, 2005). Although, the clinical signif
interaction is unknown, decreased plasma MHD concentrations may result in a potential loss of oxcarbazepin
oxcarbazepine and valproic acid are administered concurrently, clinical response to oxcarbazepine may need
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Coadministration of oxcarbazepine and valproic acid may result in a decreased con
active 10-monohydroxy metabolite of oxcarbazepine. Monitor patients for clinical response to oxcarbazepine.
7) Probable Mechanism: unknown

3.5.1.AD Panipenem

1) Interaction Effect: decreased valproic acid efficacy
2) Summary: Three case reports describe a decrease in valproic acid serum concentrations when panipener
therapy was instituted, resulting in the recurrence of seizures in two patients. Although the exact mechanism
is not known, panipenem/betamipron should be avoided in patients treated with valproic acid (Yamagata et a
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Patients receiving valproic acid anticonvulsant therapy should not be treated with
panipenem/betamipron. An alternative antibiotic which does not affect valproic acid serum levels should be c
7) Probable Mechanism: unknown
8) Literature Reports
a) A 4-year-old female with spastic quadriplegia, epilepsy, and mental retardation was receiving valproic
mg/kg/day and phenobarbital 5 mg/kg/day with serum levels of 55.1 mg/dL and 28.4 mg/dL, respectively
admitted to the hospital for pneumonia, and her valproic acid dose was increased to 30 mg/kg/day while
was decreased to 4.5 mg/kg/day. Panipenem/betamipron therapy was initiated at 60 mg/kg/day in three
daily, and the serum valproic acid level decreased to 22.9 mg/mL by day 6. Although no seizures develo
this decrease, panipenem/betamipron was discontinued, and the valproic acid serum concentration incre
mg/dL (Yamagata et al, 1998).
b) A 3-year-old girl with quadriplegia, epilepsy, and mental retardation was receiving valproic acid 35 mg
carbamazepine 11 mg/kg/day, and phenytoin 10 mg/kg/day for two months before a hospital admission f
pneumonia. Valproic acid serum concentration was 88.7 mg/mL prior to the start of panipenem/betamipr
and amikacin 5 mg/kg/day. Three days later, generalized tonic-clonic seizures began to occur once or tw
valproic acid level had decreased to 30.9 mg/mL and further dropped to 26.8 mg/mL two days later. Des
the valproic acid dose to 42 mg/kg/day, the serum concentration continued to decrease to 15.3 mg/mL o
treatment with panipenem/betamipron. The valproic acid level started to increase within 24 hours of disc
panipenem/betamipron. The phenytoin serum level was undetectable on day 3 of panipenem/betamipror
carbamazepine level was not significantly altered (Yamagata et al, 1998).
c) Panipenem/betamipron 30 mg/kg/day resulted in intense, generalized seizures and frequent myoclon
year-old male who had previously been stabilized on valproic acid 32 mg/kg/day, clonazepam 0.9 mg/kg/
phenytoin 5 mg/kg/day. Prior to panipenem/betamipron therapy, his valproic acid serum level ranged fro
108.9 mg/mL. However, by day 5 of panipenem/betamipron treatment, the valproic acid level was 26.7 m
the valproic acid dose was increased to 34 mg/kg/day, serum levels were undetectable by day 25 of
panipenem/betamipron therapy. After the antibiotic was discontinued, the serum valproic acid concentrat
55 mg/mL and the frequency of the seizures was decreased. Incidentally, in this patient, the phenytoin a

levels were not significantly altered by the presence of panipenem/betamipron (Yamagata et al, 1998).

3.5.1.AE Phenobarbital

1) Interaction Effect: phenobarbital toxicity or decreased valproic acid effectiveness

2) Summary: Concurrent administration of valproic acid and phenobarbital results in decreased phenobarbita increased serum concentrations (Prod Info Depakote(R) ER, 2003g; Bourgeois, 1988; Fernandez de Gatta et al, 1980a). It may be necessary to decrease the phenobarbital dosage with concomitant use. Conversely, val may decrease significantly with concurrent use (May & Rambeck, 1985).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: With the addition of valproic acid therapy in a patient stabilized on phenobarbital, th be monitored for signs of phenobarbital toxicity and a serum phenobarbital level obtained. Phenobarbital dos be decreased in some cases. Due to increased valproic acid metabolism, periodic determinations of valproic barbiturate concentrations should be considered.

7) Probable Mechanism: decreased phenobarbital metabolism or increased valproic acid metabolism

8) Literature Reports

a) Elevations in serum phenobarbital levels have occurred with concurrent sodium valproate administrat secondary to inhibition of phenobarbital metabolism (Schobben et al, 1975; Johannessen, 1977; Richens Suganuma et al, 1981; Kapetanovic et al, 1981; Bruni et al, 1980a; Anon, 1978). Conversely, phenobarb the serum half-life of sodium valproate due to the induction of liver enzymes (Pinder et al, 1977; Rimmer Furlanut et al, 1982). A 10% increase in clearance of valproic acid has been observed in patients taking (Yukawa et al, 1997).

b) Phenobarbital metabolism is inhibited by valproate. Six subjects received valproate 250 mg twice dail phenobarbital which resulted in a 50% increase in half-life and a 30% decrease in plasma clearance of p mg single dose). The fraction of phenobarbital dose excreted unchanged increased by 50% in presence Info Depakote(R) ER, 2003f).

3.5.1.AF Phenytoin

1) Interaction Effect: altered valproate levels or altered phenytoin levels

2) Summary: Valproic acid may initially cause a decrease in total phenytoin level by displacement of phenytc binding sites (Prod Info Depakote(R) ER, 2003l; Levy & Koch, 1982a; Bruni et al, 1980a; Monks et al, 1978a) decrease in the bound fraction of phenytoin; the phenytoin which is displaced by valproic acid re-equilibrates capacity of the tissue compartment such that the unbound plasma concentration remains unchanged (Winter et al, 1978a). The degree of displacement appears to be valproic acid dose related (Monks & Richens, 1980a may also inhibit phenytoin metabolism (Levy & Koch, 1982a; Bruni et al, 1980a; Patel et al, 1980b; Winter, 19 al, 1982a).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Due to the complex situation involving displacement of protein-bound phenytoin and phenytoin metabolism, as well as the potential for decreased valproic acid concentrations, patients should be phenytoin toxicity and therapeutic efficacy. Free plasma phenytoin levels should be measured if possible to p accurate assessment of phenytoin activity early in therapy. At steady-state free phenytoin concentrations and concentrations should be normalized.

7) Probable Mechanism: altered clearance and protein binding of both drugs

8) Literature Reports

a) If phenytoin or carbamazepine (or any prodrugs) is used in pregnant women, there is a substantially i teratogenicity with many combinations of other anticonvulsants. The teratogenicity of these drugs is large related to the levels of the reactive epoxide metabolites (Buehler et al, 1990b; Van Dyke et al, 1991b; Fir The epoxide/parent drug ratio is generally increased when phenytoin or carbamazepine is combined with other drugs that induce cytochrome P450 enzymes (3A4, 2C9, 2C19), or drugs which inhibit epoxide hyc valproic acid, progabide, and lamotrigine (Spina et al, 1996b; Bianchetti et al, 1987b; Ramsay et al, 1990 combinations increase the risk of major birth defects 3- to 4-fold over monotherapy and about 10-fold ove rates.

3.5.1.AG Primidone

1) Interaction Effect: severe central nervous system depression

2) Summary: The concurrent use of valproic acid and phenobarbital may result in severe central nervous sys possibly due to the impairment of non-renal phenobarbital clearance. Serum concentrations of phenobarbital significantly increased. Since primidone is metabolized to phenobarbital, the same interaction may be possibl Depakote(R) ER, 2003b; Prod Info Depakene(R), 1998).

3) Severity: major

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: All patients receiving concurrent primidone and valproic acid therapy should be mor excessive central nervous system depression and neurological toxicity. Serum primidone and derived phenob should be monitored and the dosage of primidone decreased, if necessary.

7) Probable Mechanism: impairment of phenobarbital clearance
8) Literature Reports
a) One hundred epileptic patients taking primidone alone or in combination with other anticonvulsants w studied (Yukawa et al, 1989). Primidone doses ranged from 1.45 mg per kg to 27.03 mg per kg. All patie taking the same dosage for at least three weeks prior to blood sampling. Results showed no significant c primidone serum level when given concomitantly with valproate sodium, but there was a significant incre phenobarbital serum level.

3.5.1.AH Rifampin
1) Interaction Effect: reduced valproate levels
2) Summary: A 40% increase in the oral clearance of valproate was observed in a study involving the admini dose of valproate (7 mg per kg) 36 hours after five nights of daily dosing with rifampin (600 mg) (Prod Info De When coadministered with rifampin, valproate dosage adjustment may be required (Prod Info Depakote(R) E
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor valproate levels and the patient for seizure control. An adjustment in the do may be necessary when coadministered with rifampin.
7) Probable Mechanism: increased valproate oral clearance

3.5.1.AI Rifapentine
1) Interaction Effect: decreased anticonvulsant effectiveness
2) Summary: The efficacy of anticonvulsants may be impaired with concomitant use of rifapentine. Rifapentir the metabolism of other coadministered drugs that are metabolized by cytochrome P450 3A4 or 2C8/9. Dosa anticonvulsants may be necessary if given concurrently with rifapentine (Prod Info Priftin(R), 2000).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor serum anticonvulsant levels and with concomitant use and adjust doses ac
7) Probable Mechanism: increased hepatic metabolism

3.5.1.AJ Risperidone
1) Interaction Effect: increased plasma valproic acid concentrations
2) Summary: The addition of risperidone to valproic acid produces a significant increase in the peak plasma (Cmax) of valproic acid (Prod Info Risperdal(R) Consta(TM), 2003a) as well as marked increases in ammonia al, 2007). The high protein capacity of risperidone could lead to a competition for protein-binding with the high capacity of valproic acid, leading to displacement of valproic acid from plasma protein-binding sites (van Wat However, Valproic acid can be added safely to a treatment regimen consisting of risperidone (Spina et al, 20(ammonia levels may be warranted in patients who exhibited new or increased manic behavior when taking va risperidone, especially in patients vulnerable to valproic acid-induced hyperammonemia, including the young, polytherapy, severely handicapped, or suffering from malnutrition, protein load, and decreased free serum ca al, 2007). In patients prescribed this combination of drugs, monitoring of plasma risperidone or 9-OH-risperid does not appear to be warranted.
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Monitor for increased ammonia levels and plasma valproic acid concentrations with risperidone to drug therapy or changes in risperidone dose.
7) Probable Mechanism: unknown
8) Literature Reports
a) In 2 case reports of 11 year-old boys, there were marked exacerbations in manic behavior and a 2 to serum ammonia levels when risperidone and valproic acid were concomitantly administered. The first pa history of Asperger's disorder, attention-deficit/hyperactivity disorder (ADHD), psychosis, and manic sym admitted for increasing aggressive behavior. Chlorpromazine was added as needed and risperidone was his aripiprazole. Following the initiation of valproic acid 250 mg twice daily, the patient experienced a qua exacerbation of manic behavior. The risperidone dosage was eventually adjusted to 2 mg/day and valpro mg/day. The patient's valproate level ranged from 87 to 90 and ammonia level was 213. When valproic a discontinued, and the ammonia level fell to 55, his manic behavior stopped. The second patient, with a h epilepsy and ADHD, was on stable doses of valproic acid. Because of his psychotic symptoms, risperido and increased to 1.125 mg/day over 5 weeks. The patients exhibited markedly pronounced manic behav serum ammonia level of 113, despite a normal valproic acid level of 71. Upon discontinuation of risperid acid, the ammonia level normalized to 55 and the manic behavior resolved. One month later when the pa rechallenged with risperidone (in the absence of valproic acid), there was no return of either mania or hy (Carlson et al, 2007).
b) A study was performed to evaluate the pharmacokinetic interaction between risperidone and valproic plasma concentrations of risperidone and 9-hydroxyrisperidone (9-OH risperidone) were compared in pa risperidone alone or in patients comedicated with valproic acid. Thirty-three patients with a DSM-IV diagr schizophrenia, schizoaffective disorder or bipolar disorder, were stabilized with risperidone alone or in co

valproic acid. The results demonstrate that valproic acid given at doses up to 1200-1500 mg/day had clir effects on plasma concentrations of risperidone and its active metabolite. Valproic acid can be added sat regimen consisting of risperidone. In patients prescribed this combination of drugs, monitoring of plasma OH-risperidone concentrations does not appear to be warranted (Spina et al, 2000).

c) The combination of valproic acid and risperidone led to significantly increased levels of valproic acid i year-old male suffered from mood swings and increasingly aggressive behavior. Valproic acid treatment titrated up to 1750 mg/day. Valproate serum levels were in the therapeutic range. After 10 days of treatm mg/day was added, which was increased to 3 mg/day on day 4. On day 5 after risperidone was started, t symptoms improved but valproic acid levels were above the therapeutic range at 191 mg/L. Valproic acic 1000 mg/day and the level normalized to 108 mg/L within 3 days and subsequently stabilized. The autho the high-protein-binding capacity of risperidone could lead to a competition for protein-binding with the hi capacity of valproic acid, leading to displacement of valproic acid from plasma protein-binding sites (Van

d) In 21 patients, repeated oral doses of risperidone 4 mg daily did not affect the pre-dose or average pl concentrations or exposure (area under the concentration-time curve) of valproate 1000 mg daily compa There was, however, a 20% increase in valproate maximum plasma concentration (Cmax) after risperidc coadministration (Prod Info Risperdal(R) Consta(TM), 2003).

3.5.1.AK Ritonavir

1) Interaction Effect: decreased valproic acid serum concentrations

2) Summary: Coadministering ritonavir with valproic acid may decrease the plasma concentration of valproic report suggests the mechanism may be due to ritonavir induction of VPA metabolism via glucuronidation (Sh Monitoring of valproic acid plasma concentrations is recommended (Prod Info NORVIR(R), 2005).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Monitor therapeutic concentrations of valproic acid when coadministering with ritona acid dose increase may be needed.

7) Probable Mechanism: ritonavir-induced metabolism of valproic acid

8) Literature Reports

a) A case report describes a 30-year-old man with bipolar disorder and HIV who became increasingly m addition of lamivudine 150 mg/zidovudine 300 mg twice a day and lopinavir 133 mg/ritonavir 33 mg (3 ca day) to his drug regimen. The patient had been maintained on valproic acid (VPA) 250 mg 3 times a day concentration of 495 mcmol/L, when the antiretrovirals were prescribed during a hospital admission for m Paroxetine 10 mg/day was simultaneously given for the depressive episode. The patient became hypom and the paroxetine was switched to sertraline 50 mg/day. Twenty-one days after the initiation of antiretro became increasingly manic and was again admitted. He had continued all medications except sertraline including the same VPA dose. Serum VPA concentration 6 to 10 hours post-dose was subtherapeutic at decrease of 48% from the previous documented concentration. Olanzapine and an increase in VPA to 1! effectively managed the manic episode. The patient adhered to this new drug regimen, including the pre antiretrovirals, and 10 days later a 14-hour post-dose VPA level measured in the therapeutic range at 39 the patient was not taking concomitant medications known to affect VPA metabolism, it was hypothesize decrease in VPA concentrations was due to ritonvavir induction of VPA metabolism (via glucuronidation) 2006).

3.5.1.AL Rufinamide

1) Interaction Effect: increased rufinamide plasma concentrations

2) Summary: Concomitant administration of rufinamide and valproate may result in rufinamide concentration 70%. Larger increases in rufinamide plasma concentrations were observed in children with higher valproate doses/concentrations (Prod Info BANZEL(TM) oral tablets, 2008).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: Caution is advised if rufinamide and valproate are coadministered as this may resul rufinamide plasma concentrations. Risk is increased in children with higher valproate doses/concentrations (F (TM) oral tablets, 2008).

7) Probable Mechanism: unknown

3.5.1.AM Tipranavir

1) Interaction Effect: decreased valproic acid plasma concentrations and potential for decreased efficacy

2) Summary: Coadministration of tipranavir and valproic acid may result in decreased valproic acid concentra decrease the efficacy of valproic acid (Prod Info APTIVUS(R) oral capsules, 2007). Valproic acid doses may adjusted and frequent monitoring of valproic acid levels for efficacy may be required.

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Use caution when prescribing valproic acid to patients who are taking tipranavir. Va less effective due to decreased valproic acid concentrations in patients taking concomitant tipranavir (Prod In oral capsules, 2007). Monitor patients for loss of valproic acid efficacy and adjust doses as necessary.

7) Probable Mechanism: unknown

3.5.1.AN Topiramate

1) Interaction Effect: decreased topiramate or valproic acid concentrations, and increased risk of hyperammo encephalopathy

2) Summary: Controlled, clinical pharmacokinetic studies in patients with epilepsy showed an 11% decrease concentration of valproic acid when topiramate was added. However, when topiramate was given alone, the topiramate decreased by 14% when valproic acid was added (Prod Info TOPAMAX(R) oral tablets, oral sprin 2008). In two controlled studies involving a total of seven epileptic patients already receiving valproic acid, the topiramate did not significantly change the serum concentration of valproic acid or valproic acid trough conce et al, 1996; Floren et al, 1989a). The coadministration of valproic acid and topiramate has also been implicate development of hyperammonemic encephalopathy (Hamer et al, 2000a). As described in a series of case rep encephalopathy developed in 5 patients with drug-resistant epilepsy, shortly after beginning a combination ar regimen comprising topiramate and valproic acid. Symptoms largely resolved after either drug was reduced i completely withdrawn (Latour et al, 2004). Although not studied, concomitant use of topiramate and valproic a exacerbate existing defects or unmask deficiencies in susceptible patients. Patients with inborn errors of met hepatic mitochondrial activity may be at an increased risk for hyperammonemia with or without encephalopat TOPAMAX(R) oral tablets, oral sprinkle capsules, 2008).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Concomitant use of topiramate and valproic acid may result in hyperammonemia a encephalopathy. It may also result in decreased plasma concentrations of one or both drugs (Prod Info TOPA tablets, oral sprinkle capsules, 2008). Upon the coadministration of topiramate and valproic acid, dosing adju required for either or both drugs. Consider monitoring patients for seizure control and excessive adverse effe

7) Probable Mechanism: unknown

8) Literature Reports

a) In a controlled study, interactions with topiramate were assessed in six epileptic patients already takir three epileptic patients already taking valproic acid. The patients were given topiramate 100 mg every m increased to the maximum tolerated dose (no greater than 1200 mg per day). Plasma concentration-time observed over the next eight weeks. No apparent changes were observed in either phenytoin or valproic the concentration-time curve (AUC) profiles or trough plasma concentrations (Floren et al, 1989).

b) Stuporous encephalopathy developed in 5 patients with drug-resistant epilepsy, shortly after beginnir anticonvulsant regimens comprising topiramate (TPM) and valproic acid (VPA). Hyperammonemia was the patients (age ranging from 29 to 41 years). Blood ammonia levels ranged from 62 to 146 mcmol/L. A dose or withdrawal of TPM or VPA, blood ammonia levels returned to normal. In the 5th case report, a 1 developed impaired consciousness, 10 days after VPA 1500 mg/day was added to a stable dose regime 300 mg/day, phenytoin (PHT) 300 mg/day, and carbamazepine 6 mg/day. Blood ammonia concentration normal limits; however, elevations were observed in plasma concentrations of gamma glutamyl-transfera phosphatase. The patient's cognitive status returned to baseline after TPM was tapered and withdrawn, a reduction of PHT dose (Latour et al, 2004).

c) A 32-year-old male with centro-temporal epilepsy was controlled on phenobarbital 200 mg daily and t daily when valproic acid was added to his regimen. Two days prior to hospital admission, valproic acid w 1500 mg daily and the patient became drowsy with nausea and slurred speech. The phenobarbital conce mcg/mL (therapeutic range 15 mcg/mL to 40 mcg/mL) and the valproic acid level was 38 mcg/mL (therap mcg/mL to 100 mcg/mL) at hospital admission. The ammonia concentration was elevated at 116 mcmol/ mcmol/L to 60 mcmol/L), as was the gamma glutamyl transpeptidase (GGT) level. Acute valproic acid er suspected, and valproic acid was discontinued. The patient recovered within the next three days and the concentration decreased to within normal limits (Hamer et al, 2000).

d) A 37-year-old female with focal epilepsy was receiving topiramate 400 mg daily, carbamazepine 1000 lamotrigine 150 mg daily with little effect on her seizure frequency. Valproic acid 1200 mg daily was slow lamotrigine, and the patient became somnolent and dysarthric within three weeks. Laboratory results sho acid level of 47 mcg/mL (therapeutic range 50 mcg/mL to 100 mcg/mL) and a carbamazepine level of 5.2 (therapeutic range 8 mcg/mL to 12 mcg/mL). The ammonia level was increased to 88 mmol/L and valpro hyperammonemic encephalopathy was suspected. Topiramate was slowly discontinued over a seven-da patient completely recovered, although the ammonia level remained elevated. Valproic acid was then als and the ammonia concentration returned to a normal range (Hamer et al, 2000).

3.5.1.AO Vorinostat

1) Interaction Effect: severe thrombocytopenia and gastrointestinal bleeding

2) Summary: Severe thrombocytopenia and gastrointestinal bleeding have occurred with the concomitant us other histone deacetylase inhibitors, such as valproic acid. Caution is advised if these agents are coadministe platelet count every 2 weeks for the first 2 months of therapy (Prod Info ZOLINZA(TM) oral capsules, 2006).

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: Concomitant use of vorinostat with other histone deacetylase inhibitors, such as val resulted in severe thrombocytopenia and gastrointestinal bleeding. Use caution if these agents are coadminis

platelet count every 2 weeks for the first 2 months of therapy (Prod Info ZOLINZA(TM) oral capsules, 2006).
7) Probable Mechanism: unknown

3.5.1.AP Zidovudine
1) Interaction Effect: increased zidovudine plasma concentrations and potential zidovudine toxicity (asthenia hematologic abnormalities)
2) Summary: Coadministered valproic acid increases the bioavailability of zidovudine and may lead to zidovu (Lertora et al, 1994a; Prod Info Retrovir(R), 2003). In six patients who were seropositive for HIV, the clearanc (100 mg q8h) was decreased by 38% after administration of valproate (250 or 500 mg q8h) (Prod Info Depak
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor patients for signs and symptoms of zidovudine toxicity (asthenia, fatigue, na hematologic abnormalities). It may be necessary to reduce zidovudine doses when valproic acid is added to t increase doses when valproic acid is discontinued.
7) Probable Mechanism: inhibition by valproic acid of zidovudine metabolism
8) Literature Reports
a) Zidovudine pharmacokinetics were studied in six HIV-infected volunteers administered four days of zi and four days of zidovudine combined with valproic acid. Study subjects received zidovudine 100 mg ora hours and valproic acid 250 mg orally every eight hours (one patient was given 500 mg of valproic acid e The area under the concentration-time curve of zidovudine increased by 80%, from 0.65 to 1.17 mcg/hr/l concomitant valproic acid was given. Zidovudine oral clearance decreased 38% from 2351 to 1449 mL/m life of zidovudine was not significantly altered during coadministration. In this short-term study, no chang hematologic parameters or renal and hepatic function tests. The clinical impact of long-term use of this c date unknown. Effects on valproic acid concentrations were not studied. The mechanism of the interactio be inhibition by valproic acid of first-pass glucuronidation of zidovudine (Prod Info Depakote(R) ER, 2003 1994).

3.5.3 Drug-Lab Modifications

Plasma free fatty acid measurement

Urinalysis, acetone or ketone bodies measurement

3.5.3.A Plasma free fatty acid measurement
1) Interaction Effect: falsely elevated plasma free fatty acid levels
2) Summary: In a plasma mixing experiment, free fatty acids falsely increased when measured by a colorime therapeutic concentrations of valproic acid were added (Albani et al, 1982). Consider using a more specific m determine FFA concentration in patients receiving valproic acid.
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Consider avoiding calorimetric methods to determine plasma free fatty acid levels in valproic acid. More specific methods for free fatty acid determination should be used.
7) Probable Mechanism: assay interference
8) Literature Reports
a) When free fatty acids (FFA) are measured by colorimetric methods, false elevations may occur due to valproic acid, a short branched-chain organic acid. In a controlled plasma mixing experiment, the additio micrograms/milliliter valproic acid increased the apparent FFA by an average 246 micromole/liter in 10 re to 705 micromole/liter). Using more specific methods to determine FFA concentrations in patients receivi should avoid this interference (Albani et al, 1982). The concentration of valproic acid used in the experim within the approved therapeutic ranges used for epilepsy (50 to 100 micrograms/milliliter) and acute mar micrograms/milliliter trough concentration), respectively (Prod Info Depakote(R), valproic acid, 2000).

3.5.3.B Urinalysis, acetone or ketone bodies measurement
1) Interaction Effect: a false-positive urine ketone test
2) Summary: In patients receiving valproic acid, false-positive reactions for ketones in the urine may occur b acid is partially eliminated in the urine as a keto-metabolite (Prod Info DEPAKOTE(R) ER extended-release c Use caution when interpreting urine ketone test results in patients receiving concurrent therapy with valproic a
3) Severity: minor
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Valproic acid is partially eliminated in the urine as a keto-metabolite, which may res reactions for ketones in the urine (Prod Info DEPAKOTE(R) ER extended-release oral tablets, 2008). Interpre results with caution in patients receiving valproic acid therapy.

7) Probable Mechanism: valproic acid being partially eliminated in the urine as a keto-metabolite

3.5.5 Intravenous Admixtures

3.5.5.2 Solutions

3.5.5.2.A Valproate Sodium

DEXTROSE 5%

Lactated Ringer's Injection

SODIUM CHLORIDE 0.9%

3.5.5.2.A.1 DEXTROSE 5%

a) Compatible

1) Valproate sodium injection was found to be physically compatible and chemically stable in d
least 24 hours when stored in glass or polyvinyl chloride bags at controlled room temperature, 1
Celsius (Prod Info Depacon(R), 1999).

3.5.5.2.A.2 Lactated Ringer's Injection

a) Compatible

1) Valproate sodium injection was found to be physically compatible and chemically stable in la
injection for at least 24 hours when stored in glass or polyvinyl chloride bags at controlled room
30 degrees Celsius (Prod Info Depacon(R), 1999).

3.5.5.2.A.3 SODIUM CHLORIDE 0.9%

a) Compatible

1) Valproate sodium injection was found to be physically compatible and chemically stable in s
0.9% for at least 24 hours when stored in glass or polyvinyl chloride bags at controlled room ter
degrees Celsius (Prod Info Depacon(R), 1999).

4.0 Clinical Applications

Monitoring Parameters

Patient Instructions

Place In Therapy

Mechanism of Action / Pharmacology

Therapeutic Uses

Comparative Efficacy / Evaluation With Other Therapies

4.1 Monitoring Parameters

A) Therapeutic

1) Monitor the reduction in the incidence and severity of seizures.

a) SERUM LEVELS

1) The therapeutic range in epilepsy is 50 to 100 mcg/mL of total valproate (Prod Info Depakene(R), 19
Depakote(R) Tablets, 2002a); (Prod Info Depacon(R), 1999)(Turnbull et al, 1983aa; Rimmer & Richens,

a) A free concentration therapeutic range has not been established (Prod Info Depakene(R), 1999).

b) High concentration valproic acid (80 to 150 mcg/mL) may be needed to reduce seizure frequency
partial seizures and secondarily generalized tonic-clonic seizures (Beydoun et al, 1997c).

2) Studies with valproate in acute mania utilized the following therapeutic range: 50 to 125 mcg/mL (Pro
Tablets, 2002a).

B) Toxic

1) Laboratory Parameters

a) Liver function tests should be monitored prior to the initiation of therapy and at frequent intervals. Liver tox
mainly during the first 6 months of therapy.

1) Ammonia concentrations should be monitored in cases of mental confusion

b) Complete Blood Count

1) Platelet counts and coagulation tests should be undertaken before and during therapy at periodic inte planned surgeries.

c) Amylase levels (serum)

d) Monitor concentrations; increase frequency of monitoring when concomitant antiepileptics are introduced

e) Some healthcare providers recommend against routine monitoring of serum for pancreatic enzymes beca induced pancreatitis has low occurrence, there is wide variability in time to onset, and mild, asymptomatic ele pancreatic enzyme markers occurs frequently without progression to pancreatitis. Those healthcare providers counseling of patients to recognize the signs and symptoms of pancreatitis and advising them to seek immed assistance if those symptoms occur (Chapman et al, 2001).

2) Physical Findings

a) Data reviewed by the US Food and Drug Administration suggest an increased risk of suicidal behavior or in patients receiving therapy with antiepileptic drugs (AEDs). The increased risk of suicidality was noted at 1 w an AED and continued to at least 24 weeks. Patients treated for epilepsy, psychiatric disorders, or other cond an increased risk for suicidality compared to placebo. Closely monitor patients treated with AEDs for emergen of depression, suicidality, and other unusual changes in behavior, which may include symptoms such as anxi hostility, mania, and hypomania (US Food and Drug Administration, 2008).

4.2 Patient Instructions

A) Divalproex (By mouth)

Divalproex Sodium

Treats seizures (epilepsy). Also used to treat the manic phase of bipolar disorder (manic-depressive illness) and t headaches. Belongs to a class of drugs called anticonvulsants.

When This Medicine Should Not Be Used:

You or your child should not use this medicine if you have had an allergic reaction to valproic acid or divalproex, c severe liver disease, a urea cycle disorder (a disease that causes too much ammonia in the blood), or are pregna get pregnant.

How to Use This Medicine:

Long Acting Tablet, Delayed Release Tablet, Coated Tablet, Delayed Release Capsule

Your doctor will tell you how much of this medicine to use and how often. Your dose may need to be changed order to find out what works best for you. Do not use more medicine or use it more often than your doctor tells May be taken with food to decrease stomach upset.

Swallow the capsule or tablet whole. Do not crush, break or chew it.

You may open the sprinkle capsule and mix the medicine beads with a small amount (about a spoonful) of so applesauce or pudding. Swallow the mixture whole. Do not chew.

If a Dose is Missed:

If you miss a dose or forget to use your medicine, use it as soon as you can. If it is almost time for your next d then to use the medicine and skip the missed dose. Do not use extra medicine to make up for a missed dose If you miss two or more doses, call your doctor.

How to Store and Dispose of This Medicine:

Store the medicine in a closed container at room temperature, away from heat, moisture, and direct light.

Ask your pharmacist, doctor, or health caregiver about the best way to dispose of any leftover medicine after your treatment. You will also need to throw away old medicine after the expiration date has passed.

Keep all medicine away from children and never share your medicine with anyone.

Drugs and Foods to Avoid:

Ask your doctor or pharmacist before using any other medicine, including over-the-counter medicines, vitamins, a products.

Make sure your doctor knows if you or your child are taking a blood thinner (such as aspirin, warfarin, or Cou medicines that could make you sleepy, such as sleeping pills (such as alprazolam, lorazepam, Ativan®, Xana medicines (Lorcet®, Percocet®, Tylenol® with Codeine, Vicodin®, Vicoprofen®), or cold medicines. Tell your your child are using any other medicine for seizures.

Tell your doctor if you or your child are taking meropenem (Merrem®), rifampin (Rifadin®, Rimactane®), amit Vanatrip®), topiramate (Topamax®), or zidovudine (Retrovir®).

Do not drink alcohol while you are using this medicine.

Warnings While Using This Medicine:

Using this medicine while you are pregnant can harm your unborn baby. Use an effective form of birth contro getting pregnant. If you think you have become pregnant while using the medicine, tell your doctor right away

Make sure your doctor knows if you are breastfeeding, or if you or your child have liver disease, pancreas dis disorders. Tell your doctor if you have a family history of urea cycle disorders or unexplained infant deaths.

Because of the risk of increased seizures, do not stop using this medicine suddenly without asking your docto

to slowly decrease your dose before stopping it completely.
If you or your child are taking this medicine in the form of sprinkle capsules, you may see small amounts of th stool. This is normal.
This medicine may make you dizzy or drowsy. Avoid driving, using machines, or doing anything else that cou you are not alert.
Make sure any doctor or dentist who treats you knows that you are using this medicine. This medicine may a certain medical tests.
Your doctor will need to check your blood at regular visits while you are using this medicine. Be sure to keep

Possible Side Effects While Using This Medicine:
Call your doctor right away if you notice any of these side effects:
Allergic reaction: Itching or hives, swelling in your face or hands, swelling or tingling in your mouth or throat, c trouble breathing.
Changes in vision.
Chest pain.
Dark-colored urine or pale stools.
Fast, pounding heartbeat.
Fever, chills, cough, sore throat, runny or stuffy nose, and body aches.
Lightheadedness, dizziness, drowsiness, or fainting.
Sudden and severe stomach pain, nausea, vomiting, loss of appetite.
Swelling on your face, hands, ankles, or feet.
Tremors or loss of seizure control.
Trouble breathing.
Unusual bleeding or bruising.
Yellowing of your skin or the whites of your eyes.

If you notice these less serious side effects, talk with your doctor:
Back pain.
Diarrhea, constipation, or upset stomach.
Hair loss.
Headache.
Increase in appetite.
Mood changes, unusual thoughts, or memory loss.
Nervousness or depression.
Rash or hives with itching.
Restlessness or irritability.
Ringing in the ears.
Trouble sleeping.
Weight gain or weight loss.

If you notice other side effects that you think are caused by this medicine, tell your doctor.

B) Valproate Sodium (Injection)
Valproate Sodium

Treats different types of seizures (epilepsy). This medicine is an anticonvulsant.

When This Medicine Should Not Be Used:
You should not receive this medicine if you have had an allergic reaction to valproate, or if you have certain liver p should not receive this medicine if you have a genetic (inherited) urea cycle disorder, which causes the body to ha rid of ammonia (a waste product in the blood).

How to Use This Medicine:
Injectable
A nurse or other trained health professional will give you this medicine.Your doctor will prescribe your exact d how often it should be given. This medicine is given through a needle placed in one of your veins.

Drugs and Foods to Avoid:
Ask your doctor or pharmacist before using any other medicine, including over-the-counter medicines, vitamins, a products.
Do not use aspirin without your doctor's OK.
There are many other drugs that can interact with valproate. Make sure your doctor knows about all other me using, especially blood thinners, and medicine to treat seizures, depression, or mood problems.
Do not drink alcohol while you are using this medicine.

Warnings While Using This Medicine:
Tell your doctor if you are pregnant or breast feeding, or if you have had a recent head injury. Make sure you you have a history of coma, unexplained mental or behavior problems, frequent vomiting, a family history of u disorders, or a family history of unexplained infant deaths. Tell your doctor if you have HIV or AIDS, or if you

caused by cytomegalovirus (CMV).
If this medicine is to be given to your child, make sure the doctor knows if your child is under the age of two y
using other medicine to treat seizures. Tell the doctor if your child was born with a disease that affects his me
making process of the body). Make sure the doctor knows if your child has mental retardation or a brain disea
Using this medicine while you are pregnant can harm your unborn baby. Use an effective form of birth contro
getting pregnant. If you think you have become pregnant while using the medicine, tell your doctor right away
Make sure any doctor or dentist who treats you knows that you are using this medicine. This medicine may a
certain medical tests.
Your doctor will need to check your blood at regular visits while you are using this medicine. Be sure to keep
This medicine may make you drowsy or less alert. Avoid driving, using machines, or doing anything else that
dangerous if you are not alert.

Possible Side Effects While Using This Medicine:
Call your doctor right away if you notice any of these side effects:
Allergic reaction: Itching or hives, swelling in your face or hands, swelling or tingling in your mouth or throat, c
trouble breathing.
Chest pain or slow heartbeat.
Confusion or hallucinations (sensing things that are not there).
Fever or new coughing.
Lightheadedness, dizziness, severe tiredness, or fainting.
Nausea, vomiting, or sudden and severe stomach pain.
Poor seizure control.
Redness, pain, or swelling at the injection site.
Swelling in your arms or legs, skin rash, or blistering, peeling skin.
Tremors (shaking), or problems with coordination (movement) or posture (remaining upright).
Unusual bleeding or bruising.
Vision changes.
Weakness, loss of appetite, unexplained weight loss, or rapid weight gain.

If you notice these less serious side effects, talk with your doctor:
Dark or bloody urine, pain or burning with urination, or a change in how much or how often you urinate.
Heartburn, diarrhea, or constipation.
Headache.
Hair loss.
Mood changes.
Menstrual (period) changes.
Tiredness or feeling generally unwell.

If you notice other side effects that you think are caused by this medicine, tell your doctor.

C) Valproic Acid (By mouth)
Valproic Acid

Treats seizures (epilepsy). Also used to treat mood disorders and prevent migraine headaches. Belongs to a clas
anticonvulsants.

When This Medicine Should Not Be Used:
You should not use this medicine if you have had an allergic reaction to valproic acid or divalproex, if you have se
or if you are pregnant.

How to Use This Medicine:
Liquid, Liquid Filled Capsule, Delayed Release Capsule
Your doctor will tell you how much of this medicine to use and how often. Do not use more medicine or use it
your doctor tells you to.
May be taken with food to lessen stomach upset.
Swallow the capsule whole. Do not crush, break or chew.
Measure the oral liquid medicine with a marked measuring spoon, oral syringe, or medicine cup.

If a Dose is Missed:
If you miss a dose or forget to use your medicine, use it as soon as you can. If it is almost time for your next c
then to use the medicine and skip the missed dose. Do not use extra medicine to make up for a missed dose
If you miss two or more doses, call your doctor.

How to Store and Dispose of This Medicine:
Keep this medicine in the original tightly closed container. Store at room temperature, away from heat and m
Ask your pharmacist, doctor, or health caregiver about the best way to dispose of any outdated medicine or n
needed.
Keep all medicine away from children and never share your medicine with anyone.

Drugs and Foods to Avoid:
Ask your doctor or pharmacist before using any other medicine, including over-the-counter medicines, vitamins, a products.
Avoid drinking alcohol.
Make sure your doctor knows if you are taking "blood thinners" (medicines such as aspirin or Coumadin®) or other medicines that could make you sleepy such as sleeping pills, cold medicine, or sedatives.

Warnings While Using This Medicine:
Check with your doctor before taking this medicine if you are breastfeeding, or if you have liver disease, kidn blood disorder.
Talk to your doctor before taking this medicine if you are pregnant. If you become pregnant while being treate medicine, tell your doctor right away. This medicine may be harmful to your unborn baby.
Because of the risk of increased seizures, do not suddenly stop taking this medicine without first checking wit
This medicine may cause drowsiness. Be careful when driving or using machinery.

Possible Side Effects While Using This Medicine:
Call your doctor right away if you notice any of these side effects:
Loss of seizure control
Severe weakness or dizziness
Severe vomiting that doesn't go away
Unusual bleeding or bruising
Yellowing of the skin or eyes
Rash or hives with itching

If you notice these less serious side effects, talk with your doctor:
Nausea, vomiting, or stomach cramps
Drowsiness or dizziness
Restlessness or irritability
Diarrhea or constipation
Trembling of hands or arms
Hair loss

If you notice other side effects that you think are caused by this medicine, tell your doctor.

4.3 Place In Therapy

A) Valproic Acid

1) Seizures

a) Valproic acid is indicated as monotherapy and adjunctive therapy for complex partial seizures occurring in association with other types of seizures in patients 10 years and older. Valproic acid is also indicated for use and adjunctive therapy in the treatment of complex absence seizures, and adjunctively in patients with multip that include absence seizures (Prod Info STAVZOR(R) delayed release oral capsules, 2008; Prod Info DEPA capsules, oral syrup, 2006).

b) Although valproic acid is considered a first-line therapy for treating generalized tonic-clonic seizures, simp and complex partial seizures, carbamazepine is generally preferred due to its lesser toxicity. Valproic acid is agent for the treatment of absence seizures; ethosuximide is generally preferred, however (Young & Koda-Ki 1989).

c) Valproic acid and carbamazepine appear to have less of an effect on cognitive function and behavioral dis comparison with phenobarbital, phenytoin, and primidone. For this reason, both valproic acid and carbamaze preferred over these other agents for treating seizure disorders in children (Trimble, 1988; Anon, 1985).

2) Bipolar disorder

a) Valproic acid (Stavzor(R)) is indicated for the treatment of the manic episodes associated with bipolar disc week, placebo-controlled, parallel-group studies, valproate had significantly superior results on all measures outcomes for acute mania compared with placebo (Prod Info STAVZOR(R) delayed release oral capsules, 20

b) Valproic acid has been effective in treating mania associated with bipolar disorder in clinical studies (Faw 1989; Post, 1989; McElroy et al, 1989; Calabrese & Delucchi, 1989; Pope et al, 1988; Grunze et al, 1999; Pra

c) Valproic acid has been shown to be effective for the treatment of acute mania. Response has been seen i unresponsive to lithium therapy and to those with mixed mania and rapid cycling (Keck et al, 1998). A greater reduction is seen in approximately 50% of patients. The therapeutic onset correlates with therapeutic plasma Controlled studies are needed to assess valproic acid in the treatment of acute bipolar depression and maint of bipolar disorder.

3) Migraine prophylaxis

a) Valproic acid (Stavzor(R)) is indicated for prophylaxis of migraine in adults and children 16 years and olde randomized, placebo-controlled clinical trials established the efficacy of valproate for prophylaxis of migraine Info STAVZOR(R) delayed release oral capsules, 2008).

B) Divalproex Sodium

1) BIPOLAR DISORDER

a) In a decision analysis model, divalproex was found to be less costly than lithium for the acute and prophyl patients with bipolar disorder over a one-year time period. Four attributes of overall patient management were

model: the response rate to initial therapy; the mean length of hospital stay; the rates of adverse effects; and treatment costs. In the overall analysis, initial therapy with divalproex resulted in costs that were 9% lower tha treatment with lithium, most likely due to a more rapid response with divalproex and shorter length of hospital were most significant in patients with mixed mania and rapid cycling; however, cost savings with lithium thera recognized in patients with classic mania (Keck et al, 1996).

C) Valproate Sodium

1) SEIZURES

a) Valproate sodium injection should be used in patients who temporarily cannot use the oral form of valproic it is clinically feasible, patients should be switched back to oral valproic acid (Prod Info valproate sodium injec

4.4 Mechanism of Action / Pharmacology

A) MECHANISM OF ACTION

1) Although the mechanism of action is presently unknown, it is postulated that the drug's effects are mediated th the function of brain gamma-aminobutyric acid (GABA), specifically by increasing brain concentrations of this inhil (Prod Info STAVZOR(R) delayed release oral capsules, 2008; Beckner, 1979; Godin et al, 1969; Simler et al, 197

2) The drug has been shown to be an inhibitor of GABA-aminotransferase and succinic semialdehyde dehydroge involved in the synthesis and degradation of GABA (Simler et al, 1973; Loscher, 1980; Sawaya et al, 1975), and s of GABA have been reported to occur in synaptosomes, primarily in areas of high GABA activity (Iadarola & Gale, Richens, 1985d). However, this proposed mechanism of action has been disputed (Rimmer & Richens, 1985d; Hc Concentrations of the drug are reportedly too low for enzyme effects to occur with therapeutic doses, and increas GABA are reportedly too small to account for anticonvulsant effects (Rimmer & Richens, 1985d). Alternately, it ha that valproic acid may selectively enhance postsynaptic GABA responses (Rimmer & Richens, 1985d; MacDonalc Other hypotheses which have been advanced are: (1) direct effect of the drug on neuronal membranes and (2) re excitatory transmission by aspartate (Rimmer & Richens, 1985d; Slater & Johnston, 1978). However, no mechani adequately supported by experimental data (Rimmer & Richens, 1985d).

3) There is some evidence that valproic acid may inhibit the re-uptake of GABA into the glia and nerve endings (E

B) REVIEW ARTICLES

1) Basic reviews of the treatment of seizures have been written; these include treatment of first seizure and statu (Willmore, 1998), treatment of the elderly (Rowan, 1998), and management of epilepsy in adults (Feely, 1999; Ma Pediatric seizure management has also been reviewed (Wolf et al, 1998; Pellock, 1995).

2) A comprehensive review concerning the use of valproate in psychiatric conditions is available (Davis et al, 200

3) The association between valproate therapy and the development of polycystic ovarian syndrome is discussed 1999).

4) A review of clinical trial data on valproic acid's efficacy in migraine prophylaxis is available (Rothrock, 1997).

5) With the addition of the newer antiepileptic drugs, polypharmacy in epilepsy is being revisited (Schneiderman, 1998).

6) The clinical pharmacology, pharmacokinetics, and kinetics of valproic acid in disease states have been extens (Bruni & Albright, 1984).

7) An extensive study of first-dose and steady-state pharmacokinetics with valproic acid in children with seizures al, 1983). A detailed case review of the kinetics of valproic acid in neonates is provided (Irvine-Meek et al, 1982).

8) Pharmacokinetics of valproic acid has been reviewed (Zaccara et al, 1988).

9) The treatment of pediatric malignant glioma with valproic acid has been reviewed (Driever et al, 1999).

10) The clinical studies evaluating the efficacy of valproic acid in bipolar disorder have been reviewed (Guay, 19

4.5 Therapeutic Uses

Valproic Acid

Divalproex Sodium

Valproate Sodium

4.5.A Valproic Acid

Absence seizure, Simple and complex

Alcohol hallucinosis

Behavioral syndrome - Dementia

Bipolar disorder

Brain injury; Prophylaxis - Seizure

Chorea

Cluster headache

Complex partial epileptic seizure

Dementia

Febrile seizure

Hiccoughs

Hiccoughs, Intractable

Mania

Manic bipolar I disorder

Mental disorder - Mood disorder

Migraine; Prophylaxis

Myelodysplastic syndrome

Myoclonic seizure

Myoclonus

Nelson syndrome

Obsessive-compulsive disorder

Panic disorder

Periodic limb movement disorder

Sedative withdrawal delirium

Seizure, Multiple seizure types; Adjunct

Social phobia

Stiff-man syndrome

Tinnitus

Visual hallucinations

4.5.A.1 Absence seizure, Simple and complex

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes; Pediatric, yes (10 years and older)
Efficacy: Adult, Effective; Pediatric, Effective
Recommendation: Adult, Class IIa; Pediatric, Class IIa
Strength of Evidence: Adult, Category B; Pediatric, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Valproic acid is indicated as adjunct or monotherapy for patients with simple and complex absence s
DEPAKENE(R) oral capsules, oral syrup, 2006; Prod Info STAVZOR(R) delayed release oral capsu

c) Adult:

1) Valproic acid is indicated for use as sole and adjunctive therapy in the treatment of simple and compl seizures. Results of several clinical studies have shown that sodium valproate is effective in patients with seizures (petit mal seizures) with response rates approaching 100% (Rimmer & Richens, 1985g). Result involving 354 patients indicate there is at least a 75% reduction in seizure frequency in about 66% of pat 45 (13%) patients failed to show any significant improvement in this review (Pinder et al, 1977e). Ethosu preferred over valproic acid for treatment of absence seizures as it is equally effective and better tolerate Kimble, 1995a). Combination therapy with valproic acid and ethosuximide was successful in treating abs patients who were refractory to either drug alone (Rowan et al, 1983).

d) Pediatric:

1) Valproic acid monotherapy was reported effective in the treatment of absence epilepsy in 6 of 7 childr patient also responded when clonazepam was added to valproic acid. Prior to therapy, 3 patients had be unsatisfactorily with ethosuximide, alone or in combination with carbamazepine. Valproic acid was given 15 milligrams/kilogram/day for 7 days, followed by 20 to 25 milligrams/kilogram/day for a further 14 days subsequently adjusted based upon seizure response (maximum plasma levels of 700 micromoles/liter). I responding to monotherapy, the EEG normalized completely in 4, with a 95% reduction in epileptic disch remaining two. In these patients, a valproic acid serum level of 440 to 660 micromoles/liter was required 50% reduction of seizures (Braathen et al, 1988). It is suggested that valproic acid is a reasonable altern seizures in children when ethosuximide has failed.

4.5.A.2 Alcohol hallucinosis

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Valproate was effective for the treatment of acute alcohol hallucinosis in a randomized, double-blind conducted in 40 patients (Aliyev & Aliyev, 2008).

c) Adult:

1) Valproate, in the form divalproex sodium, was effective and well-tolerated for the treatment of acute a in a randomized, double-blind, placebo-controlled study of 40 men. Within 24 hours of hospital admissior initiated with valproate or placebo, increasing over 3 days from 1000 mg to 3000 mg in 3 divided doses. evaluated using the Positive and Negative Syndrome Scale (PANSS) subscale for verbal hallucinosis (sc 7 being the most severe), with response defined as at least 50% improvement from baseline after 10 day Study subjects consumed an average of 200 to 300 grams of ethanol per day, and had a history of 10 +/ abuse. At baseline, the mean PANSS verbal hallucinosis subscale scores were 6 +/- 2.3 and 5.9 +/- 0.6 and placebo group, respectively. Based on an intent-to-treat analysis, the mean PANSS score for valpro patients at the end of 10 days improved to 2 +/- 0.9 and 5 +/-1.4 for the placebo group (p=0.001). Secon of response based on the Clinical Global Impression (CGI) determined that 73.68% of valproate-treated "much" or "very much" improved compared to 26.31% of placebo-treated patients (p less than 0.001) (Al 2008).

4.5.A.3 Behavioral syndrome - Dementia

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

In an open study, valproic acid therapy provided some improvement in 50% of dementia patients wit (Herrmann, 1998).

Valproic acid decreased behavioral disturbances in 5 of 10 elderly subjects with dementia in an oper (Kasckow et al, 1997).

Benefit was shown in a retrospective chart review of 25 elderly patients with dementia who received alone or in addition to a neuroleptic for behavioral disturbances (Narayan & Nelson, 1997).

c) Adult:

1) In an open study, valproic acid therapy provided some improvement in 50% of dementia patients with Agitated patients (n=16, 68 to 95 years old) with Alzheimer's disease, vascular dementia, or Lewy body d valproic acid 125 milligrams (mg) twice daily. Doses were increased to target serum levels of 350 to 700 Average daily doses were 1438 mg over the average trial length of 9 weeks. Benefits were seen within 4 the Clinical Global Impression Scale, 1 patient was rated as very much improved, 3 patients were much minimally improved and 8 were unchanged (Herrmann, 1998).

2) Valproic acid, initiated at 250 milligrams daily and titrated upward for a 2- to 5-week treatment duratio

behavioral disturbances in 5 of 10 elderly subjects with dementia in an open-label pilot study. The remai
either no change (n=3) or worsened behavior (n=2) (Kasckow et al, 1997).
3) According to a retrospective chart review of 25 elderly patients with dementia who received valproic a
addition to a neuroleptic for behavioral disturbances, 56% showed much or very much improvement on t
Impressions (CGI) scale. The average valproic acid dose and serum level was 1650 milligrams/day and
micrograms/milliliter, respectively (Narayan & Nelson, 1997).

4.5.A.4 Bipolar disorder

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

A randomized, partially blinded trial reported improved efficacy with the combination of valproic acid
serum level of 50 to 125 micrograms/milliliter) and lithium as compared to lithium alone in 12 subject
disorder (Solomon et al, 1997).
A retrospective review of 36 patients with documented bipolar disorders refractory to lithium, neurole
antidepressants, and electroconvulsive treatments who had received valproic acid demonstrated tha
showed a marked response after the addition of valproic acid (McElroy et al, 1987).
Valproic acid was effective in bipolar disorder in mentally retarded adults (Sovner, 1989).
Twelve lithium non-responders suffering from bipolar disorder improved with the addition of valproic
1985).

c) Adult:

1) A randomized, partially blinded trial reported improved efficacy with the combination of valproic acid (
level of 50 to 125 micrograms/milliliter) and lithium as compared to lithium alone in 12 subjects with bipol
the time of enrollment, 50% had depression and 50% had mania. After at least 40 weeks average follow-
combination therapy were significantly less likely to experience a relapse or recurrence, but more likely t
to severe adverse effect(s) than patients on lithium monotherapy (Solomon et al, 1997).
2) Valproic acid was useful in 5 cases of bipolar disorder in mentally retarded adults (1 patient with Frag
with autistic disorder, two with rapidly cycling illness). Valproic acid was used in doses of 1000 to 2000 m
maintain blood levels in the usual therapeutic serum range of 50 to 100 mcg/mL. In 4 of these cases, the
antipsychotic medications was continued. Four of the 5 patients showed a significant response to valproi
improvements in sleep cycle, maladaptive behaviors, distractibility and assaultiveness; the other patient
a moderate response. Antipsychotic medications were successfully tapered or discontinued in all of the p
1989).
3) A retrospective review of 36 patients with documented bipolar disorders refractory to lithium, neurolep
antidepressants, and electroconvulsive treatments who had received valproic acid demonstrated that 44
showed a marked response after the addition of valproic acid . A therapeutic response was generally see
after attaining therapeutic levels (50 to 100 milligrams/liter) (McElroy et al, 1987).
4) Twelve lithium non-responders suffering from bipolar disorder improved with the addition of valproic a
received valproic acid alone as he did not tolerate lithium) . Initial Inpatient Multidimensional Psychiatric S
scores were reduced by an average of 49.6%, and the average improvement ratio comparing the course
valproic acid treatment with prior lithium prophylaxis was 5.3; ratios greater than 1 reflect improvement (E

4.5.A.5 Brain injury; Prophylaxis - Seizure

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class III
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Valproic acid was as effective as phenytoin for the prophylaxis of short- and long-term seizures follo
brain injury in a randomized study (n=379); however, there was a trend towards increased mortality
groups (Temkin et al, 1999).

c) Adult:

1) Valproic acid was as effective as phenytoin for the prophylaxis of short- and long-term seizures follow
injury in a randomized study (n=379); however, there was a trend towards increased mortality in the valp
Within 24 hours of injury, patients (ages 14 years and older) were randomized to receive either phenytoi
(n=132), valproic acid for 1 month (n=120), or valproic acid for 6 months (n=127). A phenytoin loading do
administered at 20 milligrams/kilogram (mg/kg) intravenously (IV) followed by maintenance dosing at 5 m
into 2 doses. A valproic acid loading dose was given at 20 mg/kg intravenously followed by a maintenan
mg/kg/day divided into 4 doses. Plasma concentrations of each drug were followed and adjusted to thera
Early seizures occurred in 1.5% of the phenytoin treated patients and in 4.5% of the combined valproic a
significant). There was also no significant difference in the occurrence of late seizures. The death rate af
13.4% for the combined valproic acid groups and 7.2% for the phenytoin group (p=0.07). The authors co

lack of any additional benefit from valproic acid over phenytoin, and the possibly higher mortality rate, su
acid should not be routinely used for prevention of posttraumatic seizures (Temkin et al, 1999).

4.5.A.6 Chorea

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive; Pediatric, Evidence favors efficacy
Recommendation: Adult, Class IIb; Pediatric, Class IIb
Strength of Evidence: Adult, Category C; Pediatric, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Valproic acid was reported effective in the treatment of 5 patients with Sydenham's chorea (Dhanara
Valproic acid was found to be safe and effective in the treatment of choreic movements in 7 pediatri
Sydenham's chorea in an open-label trial (Genel et al, 2002).

c) Adult:

1) Valproic acid in doses of 15 to 25 milligrams/kilogram/day was reported effective in the treatment of 5
Sydenham's chorea, resulting in disappearance of choreic movements within 10 days (Dhanaraj et al, 19
1500 milligrams/day successfully treated a recurrence of Sydenham's chorea in a 74-year-old male with
(Black et al, 1997).

d) Pediatric:

1) Valproic acid was found to be safe and effective in the treatment of choreic movements in 7 pediatric
female; 12.4 +/- 1.5 years old) with Sydenham's chorea in an open-label trial. The children received 20 t
kilogram per day of sodium valproate. Onset of clinical improvement was 8 +/- 4 days; time to complete r
choreic movements was 10.1 +/- 8.5 weeks; and the duration of treatment was 4.3 +/- 2.8 months. There
rate of 14.3% and no adverse drug events were reported during the trial (Genel et al, 2002).

4.5.A.7 Cluster headache

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Valproic acid was effective in 2 case reports of patients with cluster headaches with migraine-like fe
1998).

c) Adult:

1) Two patients with cluster headache and prominent migraine-like features had their headaches remit v
use. Both patients had been unresponsive to multiple medications and one to surgical interventions. The
man with a 15-year history of cluster headaches with an atypical visual aura, received divalproex 500 mi
daily. Headache remission occurred within 2 months. Divalproex was tapered after 9 months and he rem
The second, a 55-year-old man with a 16-year history of cluster headaches along with migraine without a
divalproex 250 mg 3 times daily with 750 mg nightly. Headache remission occurred within 2 months. He
tapered down to 375 mg daily (Wheeler, 1998).

2) Sodium valproate (600 to 1200 milligrams/day in divided doses) has also been effective in a small se
the treatment of cluster headache (Kuritzky & Hering, 1987).

4.5.A.8 Complex partial epileptic seizure

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes; Pediatric, yes (10 years and older)
Efficacy: Adult, Effective; Pediatric, Effective
Recommendation: Adult, Class IIa; Pediatric, Class IIa
Strength of Evidence: Adult, Category B; Pediatric, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Valproic acid is indicated as monotherapy and adjunctive therapy for complex partial seizures occur
in association with other types of seizures (Prod Info DEPAKENE(R) oral capsules, oral syrup, 2006
STAVZOR(R) delayed release oral capsules, 2008).

In a dose-comparison study of valproate monotherapy in 265 patients converted from other antiepile
either no change or a reduction in complex partial seizure rates in 54% and 64% of patients on low-
dose valproate monotherapy, respectively (Prod Info STAVZOR(R) delayed release oral capsules, 2
DEPAKENE(R) oral capsules, oral syrup, 2006).

In a double-blind, concentration-response clinical trial using valproic acid as monotherapy, high con
acid (target level 80 to 150 micrograms/milliliter) reduced seizure frequency of complex partial seizu
secondarily generalized tonic-clonic seizures (p=0.018) better than those assigned to low concentra
(target range of 25 to 50 micrograms/milliliter)(Beydoun et al, 1997e).

In a 16 week, placebo-controlled study of 144 patients with complex partial seizures (CPS), the use

adjunctive therapy was more effective in reducing the incidence of seizure compared with placebo (I
STAVZOR(R) delayed release oral capsules, 2008; Prod Info DEPAKENE(R) oral capsules, oral syr

c) Adult:

1) Monotherapy

a) In a dose-comparison study of valproate monotherapy in 265 patients converted from other antie
was either no change or a reduction in complex partial seizure rates in 54% and 64% of patients on
high-dose valproate monotherapy, respectively. Patients who experienced 2 or more CPS per 4 wee
adequate doses of carbamazepine, phenobarbital, primidone, or phenytoin monotherapy were rando
valproate with either low-dose (mean concentration, 71 micrograms/milliliter (mcg/mL); n=134) or hig
concentration, 123 mcg/mL; n=131) monotherapy. Following a 2-week transition period of conversio
results at 8 weeks demonstrated a greater reduction in seizures in the high-dose group (13.2 seizure
10.7) compared to the low-dose group (14.2 seizures at baseline to 13.8) (p less than 0.05). It shoul
there was no control group in this study, and less than 50% of the patients randomized completed th
STAVZOR(R) delayed release oral capsules, 2008; Prod Info DEPAKENE(R) oral capsules, oral syr

b) In a double-blind, concentration-response clinical trial using valproic acid as monotherapy, high c
valproic acid (target level 80 to 150 micrograms/milliliter) reduced seizure frequency of complex part
(p=0.001) and secondarily generalized tonic-clonic seizures (p=0.018) better than those assigned to
valproic acid (target range of 25 to 50 micrograms/milliliter). Participating patients had partial epileps
at least 2 complex partial seizures per month with or without secondarily generalized tonic-clonic sei
maintained on a therapeutic level of another antiepileptic drug. They were randomly assigned to high
valproic acid (n=96) or low concentration valproic acid (n=47) with an 8 week dosage adjustment pe
was started and the other drug was tapered off) followed by a 16-week dosage maintenance period.
baseline, there was a 30% median reduction in complex partial seizures for patients in the high grou
increase for those in the low group. The median reduction for secondarily generalized tonic-clonic se
for patients in the high group compared with a 22% increase in the low group. The authors conclude
is efficacious as monotherapy for partial-onset seizures and that it should be considered as first-line
et al, 1997e).

2) Adjunctive Therapy

a) In a 16 week, placebo-controlled study of 144 patients with complex partial seizures (CPS), the u
adjunctive therapy was more effective in reducing the incidence of seizure compared with placebo. P
experienced 8 or more CPS per 8 weeks despite therapeutic levels of carbamazepine or phenytoin r
randomized to add-on therapy with either valproate (n=75) or placebo (n=69). The results at 16 wee
reduction from baseline of 16 seizures to 8.9 for valproate, compared with 14.5 seizures at baseline
than or equal to 0.05) for placebo. Comparing valproate to placebo, there were 45% vs 23% of patie
least a 50% reduction in CPS rate, respectively (Prod Info STAVZOR(R) delayed release oral capsu
Info DEPAKENE(R) oral capsules, oral syrup, 2006).

4.5.A.9 Dementia

See Drug Consult reference: BEHAVIORAL AND PSYCHOLOGICAL SYMPTOMS OF DEMENTIA

4.5.A.10 Febrile seizure

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Pediatric, Evidence is inconclusive
Recommendation: Pediatric, Class IIb
Strength of Evidence: Pediatric, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

The American Academy of Pediatrics (AAP) Clinical Practice Guideline does not recommend long-te
both daily use of phenobarbital, primidone, or valproic acid and intermittent therapy with oral diazepa
6 months to 5 years with 1 or more simple febrile seizures even though there is evidence that both a
reducing the risk of recurrence (Steering Committee on Quality Improvement and Management,Sub
Febrile Seizures American Academy of Pediatrics, 2008).

Valproic acid has been as effective as phenobarbital for prophylaxis of febrile seizures, with a lower
(Herranz et al, 1984c; Lee & Melchior, 1981a; Wallace & Aldridge-Smith, 1980).

c) Pediatric:

1) The American Academy of Pediatrics (AAP) Clinical Practice Guideline does not recommend long-ter
both daily use of phenobarbital, primidone, or valproic acid and intermittent therapy with oral diazepam ir
months to 5 years with 1 or more simple febrile seizures even though there is evidence that both are effe
the risk of recurrence. The rationale behind the lack of recommendation is because the number of childre
seizures in the first few years of life is extremely high but the associated risks are benign, and there are r
term effects in these children identified up to date. With the exception of the high rate of recurrence, febr
harmful, they do not cause a decline in IQ nor behavioral abnormalities, and do not significantly increase
development of future epilepsy. The use of anticonvulsants has high potential for adverse effects and the
demonstrated improvement in children's long-term outcomes. Adverse effects of anticonvulsant therapy
hepatotoxicity, especially children less than 2 years of age who are also at greater risk of febrile seizures
thrombocytopenia, weight loss, weight gain, gastrointestinal disturbances, and pancreatitis with valproic
irritability, lethargy, and sleep disturbances with phenobarbital and primidone; lethargy, drowsiness and a

intermittent diazepam as well as the risk of masking an evolving central nervous system infection, such a
Therefore, the AAP does not recommend either continuous or intermittent anticonvulsant therapy due to
toxicities associated with these agents outweigh the low risks associated with simple febrile seizures (St
on Quality Improvement and Management,Subcommittee on Febrile Seizures American Academy of Ped
2) Valproic acid has been as effective as phenobarbital for prophylaxis of febrile seizures, with a lower o
(Herranz et al, 1984c; Lee & Melchior, 1981a; Wallace & Aldridge-Smith, 1980). However, phenobarbital
of choice (despite its propensity to cause behavioral abnormalities) due to the hepatotoxic potential of va
Richens, 1985g; Addy, 1981). In general, use of anticonvulsant agents for febrile seizures remains contr

4.5.A.11 Hiccoughs

See Drug Consult reference: HICCUPS - ETIOLOGY AND TREATMENT

4.5.A.12 Hiccoughs, Intractable

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Five patients with incapacitating, intractable hiccups were successfully treated with valproic acid, aft
had failed (Jacobson et al, 1981a).

c) Adult:

1) Five patients with incapacitating, intractable hiccups were successfully treated with valproic acid, afte
granulated sugar, carbamazepine, chlorpromazine, and nasopharyngeal stimulation had failed. Valproic
initiated with 15 milligrams/kilogram/day in divided doses. The dose was gradually increased by 250 mg
until hiccups ceased or side effects occurred. Symptoms were eliminated in 4 patients and markedly imp
patient; however, therapy was discontinued after 6 weeks in the fifth patient due to mild gastrointestinal b
patient, hiccups returned to pretreatment levels following withdrawal of valproic acid. Two patients were
off valproic acid; however, 2 patients required continued therapy. Effective peak valproic acid plasma lev
to 96 mcg/mL. It appears that some patients may be successfully treated with valproic acid therapy and
this agent (Jacobson et al, 1981a).

4.5.A.13 Mania

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive; Pediatric, Evidence is inconclusive
Recommendation: Adult, Class IIb; Pediatric, Class III
Strength of Evidence: Adult, Category B; Pediatric, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Valproic acid was successful in treating AIDS-related mania in 2 cases (RachBeisel & Weintraub, 19
Valproic acid may reduce the frequency, number, and severity of manic episodes in patients with sc
disorders (Puzynski & Klosiewicz, 1984).
Valproic acid was effective in the treatment of severe kleptomania and mixed mania refractory to flu
report (Kmetz et al, 1997).

c) Adult:

1) During the 26 to 51 months of valproic acid treatment of 15 patients with affective and schizoaffective
authors observed reduction in the number, length and severity of affective episodes especially mania. In
fragmentation of long and severe relapses into short and mild mania or depression occurred. The numbe
hospital admissions dropped in all patients (Puzynski & Klosiewicz, 1984).
2) Valproic acid, titrated to a serum level of 94 to 110 micrograms/milliliter, successfully treated AIDS-re
case reports (RachBeisel & Weintraub, 1997).
3) Valproic acid 2000 milligrams/day was effective in the treatment of severe kleptomania and mixed ma
fluoxetine in a 36-year-old female (Kmetz et al, 1997).

4.5.A.14 Manic bipolar I disorder

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes (Stavzor(R) only); Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIa
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Valproic acid, delayed-release ((Stavzor(R)) is indicated for the treatment of the manic episodes ass
bipolar disorder in adults (Prod Info STAVZOR(R) delayed release oral capsules, 2008).
In two 3-week, placebo-controlled, parallel-group studies, valproate had significantly superior results

of assessed outcomes for acute mania compared with placebo (Prod Info STAVZOR(R) delayed rel capsules, 2008).
Valproic acid has been effective in treating mania associated with bipolar disorder in clinical studies Brown, 1989; Post, 1989; McElroy et al, 1989; Calabrese & Delucchi, 1989; Pope et al, 1988; Grunz Prasad, 1984).
Efficacy of valproate for the treatment of children with pediatric bipolar disorder was not established outpatient, double-blind, placebo controlled trial (n=150; 76 on valproate) (Prod Info STAVZOR(R) d oral capsules, 2008; Prod Info DEPAKOTE(R) ER extended-release oral tablets, 2008).

c) Adult:

1) In two 3-week, placebo-controlled, parallel-group studies, valproate had significantly superior results assessed outcomes for acute mania compared with placebo. In both studies, patients were initiated with milligrams (mg) orally three times a day and adjusted to achieve serum valproate levels in the range of 5 micrograms/milliliter (mcg/mL) in study 1, and 40 to 150 mcg/mL in study 2. At the completion of the stuc receiving a mean dose of 2402 mg/day in study 1 and a mean dose of 2006 mg/day in study 2. The perc who achieved a 30% or greater reduction from baseline in symptom scores in the valproate group compa was 60% vs 26% in study 1, and 58% vs 29% in study 2 (p less than 0.05 for each valproate group comp (Prod Info STAVZOR(R) delayed release oral capsules, 2008).

2) Valproic acid, delayed-release is indicated for the treatment of the manic episodes associated with bi adults (Prod Info STAVZOR(R) delayed release oral capsules, 2008). Valproic acid is effective in the trea suffering from bipolar disorder, even in those who have failed conventional therapy (Fawcett, 1989; Brow 1989; McElroy et al, 1989; Calabrese & Delucchi, 1989), and in bipolar disorder secondary to head injury 1988).

3) Four out of 5 acutely manic patients responded to intravenous valproate loading in an open study. Fiv received valproate 1200 or 1800 milligrams on day 1 followed by dosage individualization based on side mean baseline Bech-Rafaelson Mania Rating Scale score was 30.2 which improved to 8 by day 5. One p been unresponsive to oral valproate. On day 5 most were switched to oral dosing. The authors believe th intravenous loading a quick saturation of plasma-binding proteins occurred which could have contributed action (Grunze et al, 1999).

4) One uncontrolled study reported improvement in 5 of 7 patients with mania given valproic acid (up to daily) for 6 weeks. All patients had not responded to previous therapy with lithium and neuroleptics (Pras

d) Pediatric:

1) Efficacy of valproate for the treatment of children with pediatric bipolar disorder was not established in outpatient, double-blind, placebo controlled trial (n=150; 76 on valproate). Children 10 to 17 years of age bipolar disorder received an initial daily dose of valproate of 15 milligrams/kilogram (mg/kg)(max 750 mg dosing used to achieve a clinical response and/or target serum valproate level of 80 to 125 mcg/mL with of 35 mg/kg. Change from baseline on the YMRS scale at final evaluation was the primary efficacy endp maximum daily dose of 1457 mg (27.1 mg/kg) and mean final serum valproate concentration of 80 mcg/m during the study (Prod Info STAVZOR(R) delayed release oral capsules, 2008; Prod Info DEPAKOTE(R) release oral tablets, 2008).

4.5.A.15 Mental disorder - Mood disorder

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive; Pediatric, Evidence is inconclusive
Recommendation: Adult, Class IIb; Pediatric, Class IIb
Strength of Evidence: Adult, Category C; Pediatric, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Although data is limited, valproic acid appears useful in the management of affective disorders in me children and adults (Kastner et al, 1990; Sovner, 1989).

c) Adult:

1) Although data is limited, valproic acid appears useful in the management of affective disorders in mer children and adults. Valproic acid was noted in studies to have advantages over carbamazepine, lithium, antipsychotics for use in mentally retarded patients since it does not carry the same risks of tremor, incor impairment, worsening of mood, and increased seizures associated with other classes of medication (Ka Sovner, 1989).

2) Valproic acid was useful in 5 cases of bipolar disorder in mentally deficient adults (1 patient with Frag with autistic disorder, two with rapidly cycling illness) . Valproic acid was used in doses of 1000 to 2000 r maintain blood levels in the usual therapeutic serum range of 50 to 100 mcg/mL. In 4 of these cases, the antipsychotic medications was continued. Four of the 5 patients showed a significant response to valproi improvements in sleep cycle, maladaptive behaviors, distractibility and assaultiveness; the other patient a moderate response. Antipsychotic medications were successfully tapered or discontinued in all of the p 1989).

d) Pediatric:

1) Significant improvement was seen with valproic acid in 3 mentally deficient children and adolescents disorders characterized by irritability, aggressiveness, self-injurious behavior, hyperactivity and sleep dis symptoms had been unresponsive to previous therapy or the patient had been unable to tolerate side eff with previous medications. Valproic acid 1500 to 3000 milligrams daily, at blood levels of 78 to 111 mcg/

significant improvement in all 3 patients (Kastner et al, 1990).

4.5.A.16 Migraine; Prophylaxis

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes (Stavzor(R) only); Pediatric, no
Efficacy: Adult, Effective; Pediatric, Evidence favors efficacy
Recommendation: Adult, Class IIb; Pediatric, Class IIb
Strength of Evidence: Adult, Category B; Pediatric, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Valproic acid, delayed-release (Stavzor(R)) is indicated for prophylaxis of migraine in adults (Prod Ir
delayed release oral capsules, 2008).
Two multicenter, randomized, placebo-controlled clinical trials established the efficacy of valproate f
migraine headache (Prod Info STAVZOR(R) delayed release oral capsules, 2008).
Valproic acid in doses adjusted to produce trough valproate concentrations of 70 to 120 milligrams/li
effective in the prophylaxis of migraine headache in a double-blind trial (n=107) (Mathew et al, 1995
A 12-week controlled study (n=176) demonstrated that 44% of valproic acid-treated patients had at l
reduction in migraine frequency, as compared to 21% of placebo-treated patients (Mathew, 1997).
Valproic acid has been effective as prophylaxis against migraine headache (common and classic) (S
Efficacy of valproate was not established for migraine prophylaxis in a single, double-blind, placebo-
parallel-group, four equal armed (placebo, 250 milligrams (mg), 500 mg, and 1000 mg) study (n=304
valproate) in pediatric patients ages 12 to 17 years old (Prod Info STAVZOR(R) delayed release ora
Valproic acid 15 to 30 milligrams/kilogram/day divided into 2 doses has been used for the prophylax
children (Hamalainen, 1998).

See Drug Consult reference: MIGRAINE - RECOMMENDATIONS FOR TREATMENT IN CHILDREN AN
ADOLESCENTS

c) Adult:

1) Two multicenter, randomized, placebo-controlled clinical trials established the efficacy of valproate fo
migraine headache. In both trials, patients with a history of migraine with or without aura (of at least 6 mo
who were experiencing at least 2 migraine headaches a month during the previous 3 months were recrui
following a 4-week single-blind placebo baseline period, patients were randomized to valproate or placeb
treatment phase, comprised of a 4-week dose titration followed by an 8-week maintenance period. In the
aged 26 to 73 years), 90 patients completed the 8-week maintenance period. Patients in the valproate gr
with doses ranging from 500 to 2500 milligrams (mg) with a mean treatment dose of 1087 mg/day resulti
trough total valproate level of 72.5 micrograms/milliliter (mcg/mL)(range, 31 to 133 mcg/mL). During the t
the mean 4-week migraine headache rate was 5.7 in the placebo group compared to 3.5 in the valproate
significantly different). In the second study (n=176; aged 17 to 76 years), 137 patients completed the 8-w
period. Patients were randomized equally to one of 3 valproate groups (500, 1000, or 1500 mg/day) or p
were initialized with 250 mg and titrated up every 4 to 8 days to the randomized target dose. The mean t
valproate levels during the treatment period were 39.6, 62.5, and 72.5 mcg/mL in the valproate 500, 100
mg/day groups, respectively. During the treatment phase, the mean 4-week migraine headache rates adj
differences in baseline rates, were 4.5 in the placebo group compared to 3.3, 3, and 3.3 in the valproate
1500 mg/day groups, respectively, based on intent-to-treat results. Migraine headache rates in the comb
1000/1500 mg group were significantly lower than in the placebo group (Prod Info STAVZOR(R) delayed
capsules, 2008).

2) Valproic acid in doses adjusted to produce trough valproate concentrations of 70 to 120 milligrams/lite
effective in the prophylaxis of migraine headache. In a double-blind trial, 107 patients were randomized t
either divalproex or placebo for a period of 12 weeks. Forty-eight percent of divalproex-treated patients e
or greater reduction in the frequency of migraine headaches compared to 14% of placebo-treated patien
common side effects noted in patients treated with divalproex were weakness, fatigue, nausea, and vom
only 13% of patients required discontinuation of therapy (Mathew et al, 1995). Another 12-week controlle
demonstrated that 44% of valproic acid-treated patients had at least a 50% reduction in migraine frequer
to 21% of placebo-treated patients. This dose-ranging trial also found no significant difference between t
(mg), 1000 mg, or 1500 mg daily dose in preventing migraine (Klapper et al, 1997). An accompanying ed
that valproic acid be considered for migraine prophylaxis in patients with coexisting epilepsy or mania, or
(s) to beta-blockers (Mathew, 1997).

3) Valproic acid has been effective as prophylaxis against migraine headache (common and classic) . T
in open fashion to 22 patients. Initial doses were 600 milligrams orally twice daily, followed by dosing adj
achieve serum levels of 700 micromol/liter in the morning before the first daily dose. Eleven patients wer
attacks during the duration of follow-up (mean, 6.5 months; range, from 3 to 12 months). Six patients had
headache frequency, and no effect was observed in 1 patient. Four patients were withdrawn from the stu
cooperation. Adverse effects consisted of hepatotoxicity (1 patient), weight gain (3 patients), drowsiness
paresthesias (2 patients who had also used ergotamine suppositories chronically prior to valproic acid) (S

d) Pediatric:

1) Efficacy of valproate was not established for migraine prophylaxis in a single, double-blind, placebo-c
group, four equal armed (placebo, 250 milligrams (mg), 500 mg, and 1000 mg) study (n=304; 231 on val
patients ages 12 to 17 years old. The study consisted of a 4 week baseline period followed by a 12 week

period (including an initial 2 week titration period) with placebo compared to each dose. Reduction from l
week migraine headache rate was the primary efficacy endpoint (Prod Info STAVZOR(R) delayed releas
2008; Prod Info DEPAKOTE(R) ER extended-release oral tablets, 2008).
2) Valproic acid 15 to 30 milligrams/kilogram/day divided into 2 doses has been used for the prophylaxis
children . Monitor valproic acid concentrations after 2 to 3 weeks of therapy and after dosage increases.
follow-up should be done with height and weight observations (Hamalainen, 1998).

4.5.A.17 Myelodysplastic syndrome

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Valproic acid monotherapy resulted in a response rate of 44% in 23 patients with myelodysplastic sy
(Kuendgen et al, 2004).

c) Adult:

1) A 44% response rate was achieved with valproic acid (VPA) monotherapy in 23 patients with myelody
syndromes (MDS) and acute myelogenous leukemia secondary to MDS (sAML/MDS). In an open-label,
patients, aged 35 to 78 years, with MDS for 3 to 122 months, received daily VPA monotherapy (n=18) or
combination with all trans retinoic acid (ATRA) 80 milligrams/meter squared (mg/m(2)) daily (in two divid
1 through 7 every other week (n=5). VPA dose was titrated to maintain serum levels between 50 and 10
micrograms/milliliter (mcg/mL). Patients who failed monotherapy or relapsed were switched to combinati
Response was rated according to the International Working Group (IWG) criteria. A response was obser
(44%) patients receiving VPA monotherapy. The median time to response was 30 days (range, 14 to 38
median VPA dose of 1250 mg (range, 900 to 2550 mg) and median duration of 6 months (range, 2 to 23
Hematologic improvement was observed in 7 patients and a partial response in 1 patient. Relapse occur
a median of 4 months, of which, 4 patients were switched to combination therapy. Two of these 4 patient
therapy for another 11 and 16 months. Stable disease was seen in 4 patients at a median duration of 5 r
patients had progressive disease and were switched to combination therapy without success. None of th
receiving combination therapy initially responded to therapy. Of note, all 3 patients considered low-risk a
international prognostic scoring system showed a major response, while only 1 patient considered high-r
minor response. Furthermore, 3 of 9 patients with an elevated blast count achieved a significant reductio
marrow blasts. Therapy was well tolerated as only one patient discontinued VPA because of vertigo and
and thrombocytopenia were attributed to study medication in 2 patients (Kuendgen et al, 2004).

4.5.A.18 Myoclonic seizure

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Patients with juvenile myoclonic epilepsy (JME) (n=76) were successfully treated with lower than us
valproic acid, and after a period of 2 years free from seizures, could be maintained on still lower dos
al, 2001).
Combination therapy with valproic acid (1500 to 1800 mg daily), clonazepam (6 to 10 mg daily) and
to 100 mg daily) was effective in improving severe progressive myoclonus epilepsy in adults in a lon
clinical study (Iivanainen & Himberg, 1982).

c) Adult:

1) Patients with juvenile myoclonic epilepsy (JME) were successfully treated with lower than usual dose
and after a period of 2 years free from seizures, could be maintained on still lower doses. Seventy-six pa
diagnosed with JME, were initially treated with sodium valproate 15 milligrams/kilogram/day (mg/kg/day)
controlled at that dose continued with the same dose. Doses were increased to 20 to 40 mg/kg/day in th
controlled. In those who were not controlled at 40 mg/kg/day, a second drug was added. Sixty-three perc
were controlled at the 15 mg/kg/day dose, 25% at 20 mg/kg/day, 4% at 40 mg/kg/day, and 8% required a
second drug. After a seizure-free period of 2 years, 22% could be maintained on 3 to 5 mg/kg/day, 33%
mg/kg/day, and 42% required more than 9 mg/kg/day (Panagariya et al, 2001).
2) Combination therapy with valproic acid (1500 to 1800 milligrams (mg) daily), clonazepam (6 to 10 mg
phenobarbital (50 to 100 mg daily) was effective in improving severe progressive myoclonus epilepsy in
term prospective clinical study. All previous medications (phenytoin and other antiepileptic agents) were
to initiation of combination therapy. After 6 years of continuous follow-up, improvement was still observe
not benefited from previous anticonvulsant therapy at optimal doses. Effective plasma levels evaluated i
28 milligrams/liter (mg/L) for valproic acid, 0.05 mg/L for clonazepam, and 19 mg/L for phenobarbital (Iiva
Himberg, 1982).

4.5.A.19 Myoclonus

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Valproic acid was reported effective in 3 patients with nonepileptic myoclonus (Sotaniemi, 1982).

c) Adult:

1) Valproic acid 900 to 1200 milligrams daily was reported effective in 3 patients with nonepileptic myocl with post-anoxic myoclonus and 2 with nocturnal myoclonus). These patients had no epileptic manifestat seizure activity and no other medications were given. Valproic acid may have a role in the treatment of m however further studies are warranted. The mechanism of action in the condition is unclear (Sotaniemi, 1

4.5.A.20 Nelson syndrome

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Clinical outcomes have varied in studies on the efficacy of valproic acid in the treatment of Nelson's et al, 1984; Buckingham, 1983; Jones et al, 1981; Mercado-Asis et al, 1997a; Loli et al, 1988; Loli et

c) Adult:

1) Numerous studies have documented the efficacy of valproic acid in the treatment of Nelson's syndror Cushing's disease. Decreases in circulating ACTH levels have been documented in patients receiving va or in combination with diazepam, cyproheptadine, or metyrapone (Glaser et al, 1984; Buckingham, 1983 1981). Other studies have failed to find any effects with valproic acid.

2) Valproic acid alone or in combination with cyproheptadine failed to suppress plasma adrenocorticotro (ACTH) secretion in Nelson's Syndrome. Six women with Nelson's Syndrome had their ACTH measured placebo, cyproheptadine, valproic acid, bromocriptine; and the combination of cyproheptadine and valpro combination of bromocriptine, cyproheptadine and valproic acid. Only bromocriptine caused a significant plasma ACTH (P less than 0.05), as did the combination of the 3 drugs (P less than 0.05). However, the the 3 drugs did not significantly exceed the effect of bromocriptine alone (Mercado-Asis et al, 1997a).

3) Chronic valproate acid therapy with 600 milligrams/day was effective in reducing the size of an adren hormone (ACTH)-secreting pituitary macroadenoma in a patient with Nelson's syndrome (Loli et al, 1988 1.5 years, the patient received 2 courses of therapy with valproic acid lasting 4 months each; both treatm tumor reduction that was documented by computed tomography. More studies are required to evaluate t valproic acid in this clinical setting.

4) Another study failed to show the effectiveness of valproic acid in 8 patients with Nelson's syndrome. A unaffected by valproic acid administration. They concluded that the GABAergic system plays a role in the ACTH hypersecretion in Nelson's syndrome (Loli et al, 1984).

4.5.A.21 Obsessive-compulsive disorder

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Valproate was effective for obsessive compulsive disorder in 1 case report (Cora-Locatelli et al, 199

c) Adult:

1) Valproate was effective for obsessive compulsive disorder in a 35-year-old man who stopped working obsessed with touching his parents 70 to 80 times per day. He had previously discontinued fluoxetine du agitation. Fluoxetine 5 mg was restarted along with valproate 250 milligrams (mg) in the morning and 50 evening to alleviate side effects. After 2 weeks he was able to resume work and felt less anxious and mo control" (Cora-Locatelli et al, 1998).

4.5.A.22 Panic disorder

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Valproic acid was effective in a case report of a patient with panic disorder associated with multiple s & Cassano, 1996).

c) Adult:

1) Valproic acid was effective in a case report of panic disorder associated with multiple sclerosis. After with alprazolam, imipramine, and clonazepam was ineffective, valproic acid titrated to a dose of 1500 mil caused a complete disappearance of symptoms after two months. The patient remained symptom-free a (Marazziti & Cassano, 1996).

4.5.A.23 Periodic limb movement disorder

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Sleep quality and duration were improved in 6 outpatients given long-term valproate for periodic limb disorder (Ehrenberg et al, 2000).

c) Adult:

1) Sleep quality and duration were improved in 6 outpatients (aged 28 to 62 years, mean 41.5 years) giv valproate for periodic limb movement disorder. After a mean 6 months of therapy, dosages of valproate r 600 milligrams taken at bedtime. Polysomnographic findings included a significant increase in sleep effic significant decrease in stage 1 (light) sleep (p=0.04), significant increases in stages 3 and 4 (deep) sleep change in stage 2 (rapid eye movement-REM) sleep. Mean total sleep time increased from 5.8 to 6.4 hou trend toward a reduction in the number of periodic limb movements per hour of sleep and in the number arousals (p=0.062). Daytime alertness was subjectively reported to be improved. No subject discontinue the end of the study; subsequently 2 patients terminated the drug, 1 due to weight gain and the other du side effects (Ehrenberg et al, 2000).

4.5.A.24 Sedative withdrawal delirium

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class III
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Four controlled studies and several case reports and case series suggest that valproate may be effe and benzodiazepine withdrawal (Harris et al, 2000).

c) Adult:

1) Four controlled studies and several case reports and case series suggest that valproate may be effec and benzodiazepine withdrawal. In contrast, one double-blind, controlled trial failed to support the use of benzodiazepine withdrawal. In an open-label study, there were no significant differences in subjective alc symptoms between valproate- and phenobarbital-treated patients, nor were there differences in blood pr rate responses associated with the 2 agents. In another comparative study, valproate and chlormethiazo have similar efficacy in ethanol withdrawal, but physiological effects were poorly documented. A double-l trial might have supported this use of valproate, but dismissed the treatment drug (valproate) because of association with GI distress (probably related to use of the valproic acid form of the drug). In a study com and lorazepam, valproate was found to be effective and well-tolerated in the treatment of ethanol withdra report, two manic schizoaffective patients had successful withdrawal from ethanol when valproate 20 milligrams/kilogram/day was combined with low-dose lorazepam. A patient with panic disorder failed to b clonazepam until valproate was added to therapy. Another report describes 4 cases of protracted withdra during tapering of benzodiazepines; the symptoms were notably eased after the addition of valproate. Tw reported in which valproate prevented alcohol or benzodiazepine relapse (Harris et al, 2000).

4.5.A.25 Seizure, Multiple seizure types; Adjunct

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes; Pediatric, yes (10 years and older)
Efficacy: Adult, Effective; Pediatric, Effective
Recommendation: Adult, Class IIa; Pediatric, Class IIa
Strength of Evidence: Adult, Category B; Pediatric, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Valproic acid is indicated as adjunctive therapy for multiple seizure types (Prod Info DEPAKENE(R) syrup, 2006; Prod Info STAVZOR(R) delayed release oral capsules, 2008).

Valproic acid, orally or rectally, was reported effective in preventing generalized tonic-clonic seizures

withdrawal of anticonvulsant agents in seizure patients undergoing intensive monitoring for diagnost purposes (Rosenfeld et al, 1987).
Valproic acid has been demonstrated effective in a variety of seizure types which include absence s seizures, and tonic-clonic seizures (grand mal), including patients who have been unresponsive to o anticonvulsants (Rimmer & Richens, 1985g; Sato et al, 1982a; Jeavons et al, 1977).

c) Adult:

1) General Information

a) Valproic acid is indicated as adjunctive therapy in patients with multiple seizure types such as ge Valproic acid has been effective in generalized epilepsy (Rimmer & Richens, 1985g; AMA Departme Sato et al, 1982a; Jeavons et al, 1977); however, carbamazepine is generally preferred because of (Young & Koda-Kimble, 1995a).

2) Clinical Trials

a) Valproic acid in loading doses of approximately 12.5 milligrams/kilogram (mg/kg), orally or rectall 15.9 mg/kg) was reported effective in preventing generalized tonic-clonic seizures following withdrav anticonvulsant agents in seizure patients undergoing intensive monitoring for diagnostic and therape Seizure activity was prevented in 23 of 35 patients (66%) following a single loading dose. Serum co ranging from 284 to 458 micromole/L were observed 1.5 hours following administration in 6 of 8 pati These data suggest the benefits of valproic acid given orally or rectally in patients undergoing anticc withdrawal. The rectal route appears to have a place in the treatment of patients unable to take oral to GI disorders, surgery or coma (Rosenfeld et al, 1987).

b) Valproic acid is indicated as adjunctive therapy in patients with multiple seizure types. Valproic a demonstrated effective in a variety of seizure types which include absence seizures, partial seizures seizures (grand mal), including patients who have been unresponsive to other anticonvulsants. The more effective in generalized epilepsy than partial seizures, and appears most useful for the treatme absence seizures (petit mal) and photosensitive epilepsy (Rimmer & Richens, 1985g; Sato et al, 198 1977). Although valproic acid is considered a first-line therapy for treating generalized tonic-clonic s or complex partial seizures, carbamazepine is generally preferred because of its lesser toxicity. Etho generally preferred over valproic acid for treatment of absence seizures because it is equally effectiv tolerated (Young & Koda-Kimble, 1995a). Oral and rectal valproic acid have been effective in refract epilepticus (Vajda et al, 1977; Manhire & Espir, 1974). The drug is usually combined with other antic producing seizure reduction in 75 to 100% in greater than 40% of patients with intractable epilepsy, improvement being seen in myoclonic seizures, absence seizures and grand mal seizures (Simon & However, single-agent therapy has also been effective (Rimmer & Richens, 1985g; Turnbull et al, 19 1983; Covanis et al, 1982a; Callaghan et al, 1982a; Shakir et al, 1981).

c) In 52 severely brain damaged (mental retardation) patients with intractable seizures, valproic aci their drug regimens. Sixty-one percent improved clinically. Valproic acid significantly reduced the fre generalized tonic-clonic seizures, generalized myoclonus, absence and atonic seizures. There was correlation between clinical improvement and reduction of EEG paroxysmal activity (Chayasirisobho 1983).

4.5.A.26 Social phobia

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class III
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Valproic acid improved Liebowitz Social Anxiety Scale (LSAS) scores in 17 patients with social anxie open-label, 12-week study (Kinrys et al, 2003).

c) Adult:

1) Valproic acid improved Liebowitz Social Anxiety Scale (LSAS) scores in 17 patients with social anxiet open-label, 12-week study. Valproic acid therapy was initially dosed at 250 milligrams (mg) twice daily, w tolerated, doses were increased to 1000 mg daily. Doses were adjusted according to tolerability and ther however doses were kept between 500 mg daily and 2500 mg daily. Intent to treat analysis demonstrate decrease in the total LSAS score of 19.1 (p less than 0.0001). Individual LSAS scores also showed a sig improvement in fear and avoidance symptoms (p less than 0.0001). Mild cases of nausea, headache, so dizziness, and fatigue were reported with the use of valproic acid in this study group. The authors ackno sample size, and the lack of placebo control and blinding were limitations in study design (Kinrys et al, 2(

4.5.A.27 Stiff-man syndrome

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Sodium valproate showed efficacy for stiff man syndrome in one case report (Spehlmann et al, 1981

c) Adult:

1) Stiff man syndrome was described in a 55-year-old male which was poorly treated by diazepam 130 r clonazepam 18 mg, and baclofen 60 mg in divided doses each day. Valproate was gradually added to th increased to a dose of 2 grams daily. The patient showed marked improvement and was able to walk wit and without his cane. Although the effectiveness of sodium valproate is only cited in one case report, it d trials for this indication (Spehlmann et al, 1981).

4.5.A.28 Tinnitus

See Drug Consult reference: DRUG THERAPY OF TINNITUS

4.5.A.29 Visual hallucinations

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class III
Strength of Evidence: Adult, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Valproic acid was efficacious in controlling visual hallucinations associated with Charles Bonnet syn reports (Hori et al, 2000).

c) Adult:

1) Two psychologically normal elderly women (ages 73 and 77) experiencing complex visual hallucinatic sensory deprivation (decreased visual acuity) and mild cerebral dysfunction were successfully treated wi 400 milligrams (mg) to 800 mg daily. The 73-year-old had partial resolution of symptoms at 400 mg daily disappearance of all hallucinations with 800 mg daily. The 77-year-old woman was started on 200 mg da increased to 400 mg daily, at which point she was able to sleep and experienced no more hallucinations. experienced adverse effects (Hori et al, 2000).

4.5.B Divalproex Sodium

Absence seizure, Simple and complex

Alcohol withdrawal syndrome

Behavioral syndrome - Dementia

Bipolar I disorder, Maintenance

Bipolar II disorder, Maintenance

Borderline personality disorder

Brain injury - Seizure; Prophylaxis

Cluster headache

Complex partial epileptic seizure

Headache disorder, chronic

Manic bipolar I disorder

Migraine; Prophylaxis

Panic disorder

Periodic limb movement disorder

Pervasive developmental disorder

Posttraumatic headache

Schizoaffective disorder, bipolar type

Sedative withdrawal delirium

4.5.B.1 Absence seizure, Simple and complex

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes; Pediatric, yes (10 years and older)
Efficacy: Adult, Effective; Pediatric, Effective
Recommendation: Adult, Class IIa; Pediatric, Class IIa
Strength of Evidence: Adult, Category B; Pediatric, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Indicated in adults and children age 10 years and older as monotherapy or adjunctive therapy for sir absence seizures occurring in isolation and as adjunctive therapy for simple and complex absence s in association with other types of seizures (Prod Info DEPAKOTE(R) ER extended-release oral table DEPAKOTE(R) sprinkle oral capsules, 2008; Prod Info DEPAKOTE(R) delayed-release oral tablets,

4.5.B.2 Alcohol withdrawal syndrome

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

May be effective for treatment of alcohol withdrawal and prevention of relapse (Reoux et al, 2001a;

See Drug Consult reference: DRUG THERAPY OF ETHANOL WITHDRAWAL

c) Adult:

1) Divalproex sodium was more effective than placebo in decreasing the need for oxazepam during moc withdrawal. Thirty-six subjects (75% white, 97% male) with a score of at least 10 on the Clinical Institute Assessment-Alcohol revised instrument (CIWA-Ar) completed this 7-day, randomized, double-blind, plac study. All patients received an initial 30 milligram (mg) dose of oxazepam; additional 30 mg doses of oxa every hour if the subject's CIWA-Ar score was 10 or higher. The divalproex group received 500 mg of div (sprinkle formulation) three times a day in addition to the oxazepam. The divalproex group required signi (p=0.033) oxazepam than the placebo group (85 +/- 63.64 mg vs. 111.7 +/- 119.5 mg, respectively) to m withdrawal symptoms. Six percent (1 of 18) of subjects in the divalproex group and 40% (7 of 18) of the p had an increase in withdrawal symptoms (1 point and 3 points respectively) compared to baseline. Adver similar between groups with somnolence reported significantly more frequently (p less than 0.05) in the d (Reoux et al, 2001a).

2) A 51-year-old man with a 30-year history of heavy drinking was successfully withdrawn from alcohol u sodium. On admission, he was found to meet diagnostic criteria for alcohol dependency (DSM-IV), and e liver enzymes and an increased mean corpuscular volume. He had no other mental or physical co-morbi the Clinical Institute Withdrawal Assessment-Alcohol revised instrument (CIWA-Ar) increased from an ini at 8 hours post-admission. He began divalproex detoxification with a loading dose of 750 milligrams (mg) mg/kilogram body weight; the second half of his loading dose 750 mg was given 6 hours later. During the his CIWA-Ar score decreased to below 6, where it remained for the duration of his hospital stay. He was 4 (divalproex level 83 mg/milliliter), and maintained on a dose of divalproex 750 mg twice daily for 6 wee abstinence during the 6 weeks of follow-up. His laboratory results improved. Divalproex was tapered and patient remained abstinent. According to the author, advantages of divalproex over benzodiazepines for include its lack of abuse potential and absence of synergistic reaction with alcohol, and, in contrast to oth anticonvulsants, divalproex can be initiated with an oral loading dose to effect a rapid onset of action (Lo

4.5.B.3 Behavioral syndrome - Dementia

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Benefit was shown in a retrospective review (Showalter & Kimmel, 2000).

c) Adult:

1) In a retrospective chart review (n=29), divalproex was found to improve symptoms of agitation in patie
48.2 years; range, 13 to 89 years) who had suffered acute brain injury and were recovering in a brain inju
unit. All subjects had agitation unsuccessfully controlled on prior benzodiazepine therapy, with or without
Overall, 18 of 29 (62%) were recorded as having significantly improved or decreased agitation symptoms
resolution of symptoms within 7 days after reaching a mean daily divalproex dose of 1257 milligrams (mg
doses in this group showed a wide range: 250 (n=1), 750 (n=1), 1000 (n=5), 1125 (n=1), 1250 (n=2), 150
mg (n=2). In another subgroup (n=8, 28%), rapid resolution of agitation to near total recovery occurred w
dose of 714 mg divalproex and no other psychotropic medications. Divalproex was soon discontinued in
recurrence of agitation. Most patients (93%) were discharged to their home or community sites. One pati
response to divalproex and in 2 cases, lethargy was worsened and the drug was withdrawn (Showalter &

4.5.B.4 Bipolar I disorder, Maintenance

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Pediatric, Evidence favors efficacy
Recommendation: Pediatric, Class IIb
Strength of Evidence: Pediatric, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Divalproex may be effective for mania or mixed episodes associated with bipolar I disorder in childre
2005)

c) Pediatric:

1) Divalproex sodium may be effective for mixed manic episodes associated with bipolar I disorder, as e
open-label, time-series study. Patients (n=35; mean age 12.3 +/-3.7 years) with a diagnosis of mixed epi
disorder and greater than 20 on the Young Mania Rating Scale (YMRS) were offered divalproex treatme
up to 6 months. The treatment protocol consisted of divalproex sodium at an initial dose of 250 to 500 m
to achieve target doses of 15 to 20 mg/kg/day and serum concentrations of 50 to 120 micrograms/millilite
Risperidone, benztropine, and trazodone were allowed for limited treatment of breakthrough symptoms a
Patients with attention-deficit/hyperactivity disorder were allowed to continue prescribed stimulants at a s
Response was defined as at least a 50% change from baseline on YMRS and no more than 40 on the C
Rating Scale-Revised (CDRS-R). Remission was defined as at least a 50% change from baseline on YM
40 on CDRS-R, no more than 2 on the Clinical Global Impression Scale for Bipolar Disorder (CGI-BP; 1
improved, 2 = much improved) and at least 51 on the Children's Global Assessment of Functioning Scale
subject dropped out of the study due to worsening of symptoms prior to follow-up; therefore, the final sar
34 patients. The mean YMRS score decreased from approximately 30 at baseline to approximately 12 at
treatment ($p < 0.001$). The mean CDRS-R score decreased from approximately 55 at baseline to approx
months of treatment ($p < 0.001$). The response rate was 73.5% and the remission rate was 52.9%. An ov
size of 2.9 was calculated by Cohen's d, with 0.8 generally considered to be large in magnitude. Seventee
required risperidone (mean length, 7 +/- 1 day), 5 patients received trazodone (mean length, 5 +/- 2 days
continued to receive methylphenidate. Common adverse events encountered were: weight gain (58.8%),
increased appetite (47.1%), cognitive dulling (41.2%), nausea (26.5%), stomach pain (23.5%), agitation (
tremor (14.7%). Six patients had elevated alanine transferase levels that normalized after 2 months of tre
et al, 2005).

2) No difference in efficacy was found between divalproex sodium and lithium sodium for the maintenan
pediatric bipolar I or II disorder in a double-blind, randomized study. Patients (n=139; mean age 10.8 +/-
enrolled if they had a primary diagnosis of bipolar I or II disorder and had experienced at least one manic
episode within the past 3 months. In phase I (stabilization phase), all patients received open-label combi
immediate release lithium sodium and divalproex sodium for up to 20 weeks. Lithium was titrated to a tar
mg/kg/day and adjusted to maintain serum levels of 0.6 to 1.2 millimoles/liter (mmol/L). Divalproex was ti
dose of 20 mg/kg/day and adjusted to maintain serum levels of 50 to 100 micrograms/milliliter (mcg/mL).
remission criteria (40 or less on the Children's Depression Rating Scale-Revised (CDRS-R), 12.5 or less
Mania Rating Scale (YMRS), and at least 51 on the Children's Global Assessment Scale (CGAS)) for 4 c
and were able to tolerate the minimum serum concentration levels of lithium or divalproex while receiving
stabilizers, antipsychotics, or antidepressants were eligible for enrollment in phase II (double-blind maint
phase II, patients were randomized to receive either lithium or divalproex, maintaining desired serum lev
weeks. Patients with attention-deficit/hyperactivity disorder were allowed to continue prescribed stimulan
(maximum dosage 6 micrograms/kg/day) at stable doses 4 weeks prior to phase II. One hundred thirty-n
treated in phase I, with 60 continuing into phase II (lithium, n=30; divalproex, n=30). Sixty-three percent (
discontinued the study due to mood-related reasons. Median time to mood relapse was 114 days (standa
57.4 days) for patients treated with lithium and 112 days (SE +/- 56 days) for patients treated with divalpr
Median time to discontinuation for any reason was 91 days (SE +/- 30.1 days) for patients treated with lit
(SE +/- 19.9 days) for patients treated with divalproex (p=0.72). Statistically significant differences were r
frequency of reported emesis (30% lithium versus 10% divalproex; p=0.05), enuresis (30% lithium versus
p=0.02), and increased thirst (16.7% lithium versus 0% divalproex). Differences in frequency of headach
versus 23.3% divalproex) and stomach pain (10% lithium versus 23.3% divalproex) were also noted, but
significant. Other adverse events reported in over 5% of patients in phase II were tremor, nausea, diarrh
appetite, upper respiratory congestion, fever and sore throat. Five patients withdrew from the study due t
(alopecia, one from each; abnormal thyrotropin blood level, one on divalproex; thrombocytopenia, one or

enuresis, one on lithium) (Findling et al, 2005).

4.5.B.5 Bipolar II disorder, Maintenance

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Pediatric, Evidence favors efficacy
Recommendation: Pediatric, Class IIb
Strength of Evidence: Pediatric, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

No difference in efficacy was found between divalproex sodium and lithium sodium for the maintena pediatric bipolar I or II disorder (Findling et al, 2005).

c) Pediatric:

1) No difference in efficacy was found between divalproex sodium and lithium sodium for the maintenan pediatric bipolar I or II disorder in a double-blind, randomized study. Patients (n=139; mean age 10.8 +/- enrolled if they had a primary diagnosis of bipolar I or II disorder and had experienced at least one manic episode within the past 3 months. In phase I (stabilization phase), all patients received open-label combi immediate release lithium sodium and divalproex sodium for up to 20 weeks. Lithium was titrated to a tar mg/kg/day and adjusted to maintain serum levels of 0.6 to 1.2 millimoles/liter (mmol/L). Divalproex was ti dose of 20 mg/kg/day and adjusted to maintain serum levels of 50 to 100 micrograms/milliliter (mcg/mL). remission criteria (40 or less on the Children's Depression Rating Scale-Revised (CDRS-R), 12.5 or less Mania Rating Scale (YMRS), and at least 51 on the Children's Global Assessment Scale (CGAS)) for 4 c and were able to tolerate the minimum serum concentration levels of lithium or divalproex while receiving stabilizers, antipsychotics, or antidepressants were eligible for enrollment in phase II (double-blind maint phase II, patients were randomized to receive either lithium or divalproex, maintaining desired serum lev weeks. Patients with attention-deficit/hyperactivity disorder were allowed to continue prescribed stimulan (maximum dosage 6 micrograms/kg/day) at stable doses 4 weeks prior to phase II. One hundred thirty-n treated in phase I, with 60 continuing into phase II (lithium, n=30; divalproex, n=30). Sixty-three percent (discontinued the study due to mood-related reasons. Median time to mood relapse was 114 days (stand 57.4 days) for patients treated with lithium and 112 days (SE +/- 56 days) for patients treated with divalpr Median time to discontinuation for any reason was 91 days (SE +/- 30.1 days) for patients treated with lit (SE +/- 19.9 days) for patients treated with divalproex (p=0.72). Statistically significant differences were r frequency of reported emesis (30% lithium versus 10% divalproex; p=0.05), enuresis (30% lithium versus p=0.02), and increased thirst (16.7% lithium versus 0% divalproex). Differences in frequency of headach versus 23.3% divalproex) and stomach pain (10% lithium versus 23.3% divalproex) were also noted, but significant. Other adverse events reported in over 5% of patients in phase II were tremor, nausea, diarrh appetite, upper respiratory congestion, fever and sore throat. Five patients withdrew from the study due t (alopecia, one from each; abnormal thyrotropin blood level, one on divalproex; thrombocytopenia, one or enuresis, one on lithium) (Findling et al, 2005).

4.5.B.6 Borderline personality disorder

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Preliminary results suggest possible efficacy; more studies in larger trials needed (Townsend et al, 2

c) Adult:

1) In a small, prospective, open-label case series, some patients with borderline personality disorder an (DSM-IV) showed improvement during a course of divalproex sodium therapy. Of the 10 patients enrolle 8-week study; one each completed weeks 3, 4, 5, and 6; one dropped out after the initial visit. Divalproex initiated at 250 milligrams (mg) twice daily, and could be increased by 250 to 500 mg at weekly visits if in not seen. At their last visit (whenever it occurred), mean dose of responders was 1125 mg/day compared for non-responders. Six of nine evaluable subjects were rated as "much improved" or better on the Clinic Impression Scale (CGI) at their last weekly visit. Scores on the Mania Rating Scale (MRS) declined, but extent. In 3 responders, serum valproic acid concentrations ranged from 51 to 113 nanograms/milliliter. F studies were suggested by the investigators (Townsend et al, 2001).

2) A pilot study suggests that a 10-week course of divalproex sodium may provide symptomatic improve with borderline personality disorders (DSM-IV axis II); however, the validity of these results are limited du out rate and small sample size. In a double- blind, randomized (2:1 ratio) manner, 16 patients were assig sodium or placebo. Six patients completed the study and 10 dropped out. Overall, 100% of those assigne withdrew, while 50% allocated to divalproex sodium withdrew. No one withdrew due to side effects. Com baseline, divalproex sodium-treated patients had significantly improved scores on the Clinical Global Imp Improvement scale (CGI-I) (p=0.006). Of the 6 patients, 5 were considered to be responders, ie, were m very much improved, based on the CGI-I. On the Global Assessment Scale (assessment of overall funct treated with divalproex sodium had significantly improved scores compared with baseline (p=0.003). Son

among those in the divalproex sodium group was shown on the Beck Depression Inventory (BDI) and sli
occurred on the Aggression Questionnaire (AQ), related to aggressive feelings and actions. Divalproex s
as 250 milligrams at bedtime and gradually titrated to doses sufficient to maintain serum levels of 80 mic
the highest tolerated dose. The authors concluded that more study of divalproex sodium in this patient p
warranted (Hollander et al, 2001).

4.5.B.7 Brain injury - Seizure; Prophylaxis

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class III
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Not effective prophylaxis (Glantz et al, 1996)

c) Adult:

1) Divalproex is not effective for the prophylaxis of seizures in patients with brain tumors. In a study of 7
newly-diagnosed brain tumors, divalproex or placebo was given within 14 days of diagnosis. Divalproex
adjusted to achieve trough levels in the range of 50 to 100 mcg/mL; the median duration of follow-up wa
five percent of patients treated with divalproex suffered seizures compared to 24% of patients treated wi
authors conclude that anticonvulsant therapy is not indicated in patients with brain tumors unless they su
(Glantz et al, 1996).

4.5.B.8 Cluster headache

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Effective in 2 cases of cluster headaches with migraine-like features (Wheeler, 1998)

c) Adult:

1) Two patients with cluster headache and prominent migraine-like features had their headaches remit v
use (Wheeler, 1998). Both patients had been unresponsive to multiple medications and one to surgical i
first, a 37-year-old man with a 15-year history of cluster headaches with an atypical visual aura, received
milligrams (mg) twice daily. Headache remission occurred within 2 months. Divalproex was tapered after
remained in remission. The second, a 55-year-old man with a 16-year history of cluster headaches alon
without aura, was given divalproex 250 mg 3 times daily with 750 mg nightly. Headache remission occur
months. He was then slowly tapered down to 375 mg daily.

4.5.B.9 Complex partial epileptic seizure

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes; Pediatric, yes (10 years and older)
Efficacy: Adult, Effective; Pediatric, Effective
Recommendation: Adult, Class IIa; Pediatric, Class IIa
Strength of Evidence: Adult, Category B; Pediatric, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Indicated in adults and children age 10 years and older as monotherapy or adjunctive therapy for co
seizures occurring in isolation or in association with other types of seizures (Prod Info DEPAKOTE(R
release oral tablets, 2008; Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008; Prod Info DEPAK
release oral tablets, 2006)

c) Adult:

1) Monotherapy

a) In a dose-comparison study of divalproex sodium monotherapy in 265 patients converted from ot
there was either no change or a reduction in complex partial seizure rates in 54% and 64% of patien
and high-dose divalproex sodium monotherapy, respectively. Patients who experienced 2 or more C
despite adequate doses of carbamazepine, phenobarbital, primidone, or phenytoin monotherapy we
receive divalproex sodium with either low-dose (mean concentration, 71 micrograms/milliliter (mcg/m
high-dose (mean concentration, 123 mcg/mL; n=131) monotherapy. Following a 2-week transition p
to divalproex sodium, the results at 8 weeks demonstrated a greater reduction in seizures in the high
seizures at baseline to 10.7) compared to the low-dose group (14.2 seizures at baseline to 13.8) (p
should be noted that there was no control group in this study, and less than 50% of the patients ran
the study (Prod Info DEPAKOTE(R) ER extended-release oral tablets, 2008; Prod Info DEPAKOTE(
capsules, 2008; Prod Info DEPAKOTE(R) delayed-release oral tablets, 2006).

2) Adjunctive Therapy

a) In a 16 week, placebo-controlled study of 144 patients with complex partial seizures (CPS), the u sodium as adjunctive therapy was more effective in reducing the incidence of seizure compared with who experienced 8 or more CPS per 8 weeks despite therapeutic levels of carbamazepine or pheny were randomized to add-on therapy with either divalproex sodium (n=75) or placebo (n=69). The res demonstrated a reduction from baseline of 16 seizures to 8.9 for divalproex sodium, compared with seizures at baseline to 11.5 (p less than or equal to 0.05). Comparing divalproex sodium to placebo, vs 23% of patients who had at least a 50% reduction in CPS rate, respectively (Prod Info DEPAKOT extended-release oral tablets, 2008; Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008; Prod Inf delayed-release oral tablets, 2006).

b) Add-on therapy with divalproex was effective in reducing seizure frequency in a group of 137 pat partial seizures. Patients taking either carbamazepine or phenytoin, whose seizures were inadequat monotherapy, were randomized to either divalproex sodium or placebo after optimization of their mo regimen. The dose of divalproex was slowly adjusted to a maximum of 90 milligrams/kilogram/day. T divalproex resulted in a median seizure reduction of 7.9 seizures in eight weeks compared to 2.5 in treated with placebo. Six of the divalproex-treated patients became seizure-free during the study pe al, 1996).

4.5.B.10 Headache disorder, chronic

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Divalproex sodium demonstrated effectiveness in the treatment of adult patients with chronic daily h retrospective study (Freitag et al, 2001).

c) Adult:

1) Results from a retrospective study (n=138) indicated that divalproex sodium was effective in the treat patients with chronic daily headache. In this study, 67% (93 of 138) of the patients had at least a 50% re headache frequency (Freitag et al, 2001).

4.5.B.11 Manic bipolar I disorder

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes (tablets, delayed-release tablets, extended-release tablets); Pediatric, no
Efficacy: Adult, Evidence favors efficacy; Pediatric, Evidence is inconclusive
Recommendation: Adult, Class IIb; Pediatric, Class IIb
Strength of Evidence: Adult, Category B; Pediatric, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Indicated for the treatment of acute manic or mixed episodes associated with bipolar disorder (with psychotic features) (Prod Info DEPAKOTE(R) ER extended-release oral tablets, 2008; Prod Info DE delayed-release oral tablets, 2006)

Ineffective in the treatment of manic symptoms in elderly patients with dementia (Tariot et al, 2001)

Efficacy of divalproex sodium extended-release tablets was not established in a single 4-week outpa placebo controlled trial (n=150; 76 on divalproex sodium) for the treatment of pediatric bipolar disorc DEPAKOTE(R) ER extended-release oral tablets, 2008).

c) Adult:

1) In two 3-week, placebo-controlled, parallel-group studies, divalproex sodium had significantly superio measures of assessed outcomes for acute mania compared with placebo. In both studies, patients were divalproex sodium delayed-release 250 milligrams (mg) orally three times a day and adjusted to achieve levels in the range of 50 to 100 micrograms/milliliter (mcg/mL) in study 1, and 40 to 150 mcg/mL in study completion of the study, patients were receiving a mean dose of 2402 mg/day in study 1 and a mean dos in study 2. The percentage of patients who achieved a 30% or greater reduction from baseline in sympto divalproex sodium group compared with placebo was 60% vs 26% in study 1, and 58% vs 29% in study for each divalproex group compared to placebo) (Prod Info DEPAKOTE(R) delayed-release oral tablets,

2) In a 3-week, randomized, double-blind, parallel-group study, adult patients diagnosed with bipolar I di mixed type, hospitalized with acute mania treated with divalproex sodium extended-release had significa Mania Rating Scale (MRS) scores compared with placebo. Patients received an initial dose of divalproex release 25 milligrams/kilogram (mg/dg) orally once a day, increased by 500 mg/day on day 3, and then a a plasma valproate level of 85 to 125 microgram/milliliter (mcg/mL). At the end of the study, the mean da mg (range, 1500 to 5500 mg), and mean valproate plasma levels were 89.5 mcg/mL (Prod Info DEPAKC extended-release oral tablets, 2008).

3) Divalproex sodium (target dosage of 20 milligrams/kilogram/day) did not improve signs and symptom associated with dementia in elderly patients during a double-blind, placebo-controlled study (n=172), but symptoms of agitation. In this 6-week trial, there was no significant difference between drug and placebo from the Brief Psychiatric Rating Scale (BPRS), but scores on the Cohen-Mansfield Agitation (CMAI) Inv

significant improvement in the divalproex sodium-treated group. Twenty-two percent of divalproex sodiur and 4% of patients who received placebo withdrew from the study because of adverse effects, primarily s et al, 2001).

d) Pediatric:

1) Efficacy of divalproex sodium extended-release tablets was not established in a single 4-week outpat placebo controlled trial (n=150; 76 on divalproex sodium) for the treatment of pediatric bipolar disorder. C years of age, with pediatric bipolar disorder received an initial daily dose of divalproex sodium of 15 milli (mg/kg)(max 750 mg) with flexible dosing used to achieve a clinical response and/or target serum valpro 125 mcg/mL with a maximum dose of 35 mg/kg. Change from baseline on the YMRS scale at final evalu primary efficacy endpoint. A mean maximum daily dose of 1457 mg (27.1 mg/kg) and mean final serum v concentration of 80 mcg/mL were attained during the study (Prod Info DEPAKOTE(R) ER extended-relea 2008).

2) Oral loading doses of divalproex sodium 15 milligrams/kilogram/day (in divided doses) produced troug concentrations in the therapeutic range by day 5 of dosing in male pediatric psychiatry inpatients (n=16; years). All subjects in this retrospective study received concomitant atypical neuroleptics. Divalproex the defined as 50 to 120 micrograms/milliliter (mcg/mL). These doses were well tolerated by the normal-weig more side effects seen at plasma concentrations above 90 mcg/mL. Overweight subjects benefited from the formula: ideal body weight (IBW) plus 40% multiplied by actual weight minus IBW (Good et al, 2001).

4.5.B.12 Migraine; Prophylaxis

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes (tablets, delayed-release tablets, extended-release tablets); Pediatric, no
Efficacy: Adult, Evidence favors efficacy; Pediatric, Evidence is inconclusive
Recommendation: Adult, Class IIb; Pediatric, Class IIb
Strength of Evidence: Adult, Category B; Pediatric, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Divalproex sodium is indicated for the prophylaxis of migraine headache in adults (Prod Info DEPAK extended-release oral tablets, 2008; Prod Info DEPAKOTE(R) delayed-release oral tablets, 2006).
Efficacy of divalproex sodium extended-release tablets for migraine prophylaxis was not established double-blind, placebo-controlled, parallel-group, four equal armed (placebo, 250 milligrams (mg), 50 mg) study (n=304; 231 on divalproex sodium) in pediatric patients ages 12 to 17 years old (Prod Info ER extended-release oral tablets, 2008).
In an open-label, retrospective study in 42 adolescents and children, divalproex sodium provided a 5 reduction in migraine frequency (Caruso et al, 2000).

c) Adult:

1) The average incidence of migraine headache attacks was reduced following once-daily prophylactic t divalproex sodium extended-release (ER) tablets. In a randomized, controlled, double- blind, multicenter at least a 6-month history of migraine headache attacks and experiencing an average of 2 or more migra the previous 3 months entered a 4-week baseline phase during which they maintained a headache diary reported at least 2 migraine attacks during the baseline period received either divalproex sodium-ER (n= milligrams (mg)/day for 1 week titrated to 1000 mg/day; mean dose, 871 mg/day) or placebo (n=115) for Following 12 weeks of treatment, a significantly greater reduction in the mean baseline migraine headacl in patients who took divalproex sodium-ER as compared with placebo (mean reduction, 1.2 vs 0.6, respe This reduction from baseline reached significance during the first 4 weeks of treatment (p=0.035) and rer throughout the second and third 4-week periods (p=0.006 and p=0.045, respectively). Adverse events w between treatment groups (Freitag et al, 2002).

2) A case report describes how divalproex brought dramatic relief of migraine headaches induced by se serotonin reuptake inhibitor (SSRI), in a 44-year-old woman with a history of refractory major depression 2000). Divalproex 750 milligrams (mg)/day immediately reduced the frequency, severity, and duration of (valproate serum level was 240 micromoles/liter). After 3 months, the patient was headache-free most of months, the dose of divalproex was increased to 1500 mg/day as the migraines had become more frequ patient was successfully maintained on a daily regimen of sertraline 100 mg, divalproex 1500 mg, and ox needed. The authors suggest that valproate be considered for patients who have a history of migraine or experience migraine while being treated with a selective serotonin reuptake inhibitor.

d) Pediatric:

1) Efficacy of divalproex sodium extended-release tablets for migraine prophylaxis was not established i blind, placebo-controlled, parallel-group, four equal armed (placebo, 250 milligrams (mg), 500 mg, and 1 (n=304; 231 on divalproex sodium) in pediatric patients ages 12 to 17 years old. The study consisted of a period followed by a 12 week experimental period (including an initial 2 week titration period) with placeb each dose. Reduction from baseline in the 4 week migraine headache rate was the primary efficacy endp DEPAKOTE(R) ER extended-release oral tablets, 2008).

2) In an open-label, retrospective study (n=42), divalproex sodium was shown to be safe and effective fo treatment of migraine headache in adolescents and children (aged 7 to 16 years, mean 11.3 years) (Car Study subjects had a history of 1 to 4 headaches per month. After a 4-month course of divalproex treatm in headache frequency occurred in 33 (78.5%), 75% reduction in headache frequency in 6 (14.2%), and were virtually headache-free (p less than 0.05). Initial doses of divalproex were 15 milligrams/kilogram (n

(divided into 2 doses) with titration upward over 6 weeks based on response. Daily doses over the 4-mor
period included 15 mg/kg (n=9), 25 mg/kg (n=16), 35 mg/kg (n=10), and 45 mg/kg (n=7). Most common
were gastrointestinal upset, weight gain, somnolence, dizziness, and tremor; mild transient elevation of li
occurred in 4 patients. Doses were decreased but no one discontinued divalproex due to side effects.

4.5.B.13 Panic disorder

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Efficacy in small, open-label studies only (Baetz & Bowen, 1998)

c) Adult:

1) In an 8-week, open-label study, divalproex was shown to be effective in patients with previously unres
disorder and mood instability (Baetz & Bowen, 1998). Patients (18 to 65 years old) received divalproex 2
twice daily and increased by 250-mg increments to a target level of 300 to 600 micromoles/L (45 to 90 m
patients completed the study and 2 dropped out due to side effects. Panic attacks decreased significantly
2.6/week (p=0.0318). Also decreased were the Hamilton Anxiety Rating Scale (p=0.0001) and the Beck
(p=0.003).

4.5.B.14 Periodic limb movement disorder

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Improvement in sleep occurred in a small study cohort receiving valproate (Ehrenberg et al, 2000)

c) Adult:

1) Sleep quality and duration were improved in 6 outpatients (aged 28 to 62 years, mean 41.5 years) giv
valproate for periodic limb movement disorder. After a mean 6 months of therapy, dosages of valproate r
600 milligrams taken at bedtime. Polysomnographic findings included a significant increase in sleep effic
significant decrease in stage 1 (light) sleep (p=0.04), significant increases in stages 3 and 4 (deep) sleep
change in stage 2 (rapid eye movement-REM) sleep. Mean total sleep time increased from 5.8 to 6.4 ho
trend toward a reduction in the number of periodic limb movements per hour of sleep and in the number
arousals (p=0.062). Daytime alertness was subjectively reported to be improved. No subject discontinue
the end of the study; subsequently 2 patients terminated the drug, 1 due to weight gain and the other du
side effects (Ehrenberg et al, 2000).

4.5.B.15 Pervasive developmental disorder

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

A small cohort of patients with autism disorders showed some improvement with valproate treatmen
2001).

c) Adult:

1) Divalproex sodium therapy was associated with some improvement of social interaction skills, repetiti
impulsivity, and other traits related to autism in an open-label, retrospective study (n=14). Included in the
consecutive patients with autism (10; DSM-IV), Asperger's disorder (2), and pervasive developmental dis
otherwise specified (2). Ten were children/adolescents and 4 were adults (age range 5 to 40 years, mea
scores ranged from 20 to 105, mean 69.1). Three subjects had a history of seizures. Divalproex sodium
doses and adjusted to maintain concentrations within the therapeutic range (between 50 and 100 milligra
Mean final dose was 768 mg/day (range 125 to 2500 mg/day) and mean duration of valproate treatment
Concomitant medications were taken by 10 patients, and included antidepressants, atypical neuroleptics
and alpha-1 agonists. Based on the Clinical Global Impressions-Improvement scale (CGI-I), 10 of 14 sub
sustained responders, with ratings of much or very much improved. Four patients showed improvement i
interactions. Four showed improvement related to repetitive behavior (ie, reduced obsessive-compulsive
subject improved in language and communication skills. Five became less impulsive, and 4 were less ag
patients were discontinued in the first 2 weeks due to severe behavioral activation. Other adverse effects
(5), digestive disturbances (3), weight gain (3), hair loss (2), mood lability (1), and elevated liver enzymes
recommend that controlled studies be undertaken (Hollander et al, 2001).

4.5.B.16 Posttraumatic headache

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Effective in some patients based on a retrospective study (Packard, 2000)

c) Adult:

1) Of 100 patients with chronic daily posttraumatic headache, 60% showed mild (n=44) to moderate (n= (patient-rated) after at least 1 month of divalproex sodium, based on a retrospective chart review; the dru well tolerated, with no serious side effects. Mild improvement was defined as 25% to 50% better, and mo than 50% improvement. In all subjects, headache was the result of mild head injury and had persisted fo months. Six patients became headache-free for 1 month or more, and 35 patients reported that their dail became episodic, with headache-free days between episodes. Twenty-six patients had no improvement, discontinued therapy due to side effects (nausea, weight gain, hair loss, tremor). Divalproex dosing was generally started as 250 milligrams (mg) daily (sometimes as 125 mg twice daily), increased by 250 mg response, and peaked at a maximum of 500 mg 3 times a day (Packard, 2000).

4.5.B.17 Schizoaffective disorder, bipolar type

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Adjunctive use may produce improvements in bipolar type schizoaffective disorder (Bogan et al, 200 Standard preparations and extended-release formulations of divalproex sodium are equally efficacio schizoaffective disorders; however, higher daily doses of extended-release formulations are require 2003).

c) Adult:

1) In a retrospective study (n=20), add-on divalproex therapy appeared to be well-tolerated and efficacic with schizoaffective disorder, bipolar type (aged 23 to 52 years, mean 38 years). Improvement in the Clir Impression (CGI) Scale scores occurred in 15 of 20 (75%) patients (p=0.0001); no change in CGI scores patients. None of the cohort showed worsening of their disorder; and no one discontinued divalproex due effects. Most common side effects were anxiety (n=2) and agitation (n=2); 1 person experienced extrapy symptoms/tremors. Other concurrent medications were most frequently antipsychotics (n=19), antidepre lithium (n=6). Mean daily dose of divalproex was 986 milligrams (mg) (range, 375 to 1750 mg); mean pe 61 micrograms/milliliter. Mean follow-up was 24 weeks (Bogan et al, 2000).

2) In a 6-week, open-label pilot study, dose-adjusted extended-release divalproex was equally efficaciou the standard preparation in bipolar and schizoaffective disorders. Twelve euthymic and clinically stable p enrolled into the study. Eight of these patients had been diagnosed with bipolar I or II disorder and 4 wer bipolar-type schizoaffective disorder. Each patient had received regular divalproex sodium twice daily for weeks and were maintained at serum valproic acid concentrations between 50 to 120 micrograms/millilit dose. Patients were switched to extended-release divalproex at doses rounded to the nearest 500 milligr Extended-release divalproex doses were administered once daily at bedtime. Doses were adjusted to at valproic acid levels achieved with the standard preparation. Average daily doses of the extended-release 20.7% higher than those of the standard preparation (1.19 grams versus 1.5 grams, p=0.0009). Clinical s evaluated using the Young Mania Rating Scale, the Hamilton Depression Rating Scale, Clinical Global Ir severity and improvement, the Global Assessment of Functioning Scale and the Brief Psychiatric Rating no significant differences between the baseline and endpoint ratings. Reported adverse effects were also an increase in polyuria-polydipsia (p=0.03) (Centorrino et al, 2003).

4.5.B.18 Sedative withdrawal delirium

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class III
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

May reduce symptoms associated with sedative-hypnotic withdrawal (Harris et al, 2000)

c) Adult:

1) Four controlled studies and several case reports and case series suggest that valproate may be effec withdrawal and benzodiazepine withdrawal. In contrast, one double-blind, controlled trial failed to suppor

valproate for benzodiazepine withdrawal. In an open-label study, there were no significant differences in withdrawal symptoms between valproate- and phenobarbital-treated patients, nor were there differences or pulse rate responses associated with the 2 agents. In another comparative study, valproate and chlor reported to have similar efficacy in ethanol withdrawal, but physiological effects were poorly documented controlled trial might have supported this use of valproate, but dismissed the treatment drug (valproate) b frequent association with GI distress (probably related to use of the valproic acid form of the drug). In a s valproate and lorazepam, valproate was found to be effective and well-tolerated in the treatment of ethar another report, two manic schizoaffective patients had successful withdrawal from ethanol when valproat milligrams/kilogram/day was combined with low-dose lorazepam. A patient with panic disorder failed to b clonazepam until valproate was added to therapy. Another report describes 4 cases of protracted withdra during tapering of benzodiazepines; the symptoms were notably eased after the addition of valproate. Tw reported in which valproate prevented alcohol or benzodiazepine relapse (Harris et al, 2000).

4.5.C Valproate Sodium

Absence seizure, Simple and complex

Behavioral syndrome - Dementia

Brain injury; Prophylaxis - Seizure

Catatonia

Complex partial epileptic seizure

Febrile seizure

Manic bipolar I disorder

Migraine

Myoclonus

Neuropathic pain

Seizure, Multiple seizure types; Adjunct

Status epilepticus

Tardive dyskinesia

Trigeminal neuralgia

West syndrome

4.5.C.1 Absence seizure, Simple and complex

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes; Pediatric, yes (10 years and older)
Efficacy: Adult, Effective; Pediatric, Evidence is inconclusive
Recommendation: Adult, Class IIa; Pediatric, Class IIb
Strength of Evidence: Adult, Category B; Pediatric, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Intravenous sodium valproate is indicated for simple and complex absence seizures when administr valproate products is not possible (Prod Info DEPACON(R) IV injection, 2006)

4.5.C.2 Behavioral syndrome - Dementia

a) Overview

FDA Approval: Adult, no; Pediatric, no

Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:
Conflicting results reported regarding the effectiveness of valproic acid in the treatment of dementia-
AGITATION (Sival et al, 2003) (Sival et al, 2002)

c) Adult:
1) Sodium valproate treatment offered no advantage over placebo in the treatment of dementia-related a
behavior in forty-two patients. In a randomized, double-blind, placebo-controlled, cross- over trial, patient
behavior and senile dementia received oral doses of either placebo or sodium valproate suspension 480
divided doses) for three weeks and then crossed over to the other treatment arm following a one-week w
Sodium valproate was no more effective than placebo in the treatment of aggression in this group of pati
2003).
2) In a randomized, placebo-controlled, double-blind study of 42 elderly patients (mean age=80.4 years)
had no effect versus placebo in the treatment of aggressive behavior in dementia. Sodium valproate was
three weeks at a fixed dose of 6 milliliters (mL) of a 40 milligram per milliliter (mg/mL) oral suspension tw
daily dose was 480 mg. Significant improvements in other measures, such as restlessness, melancholic,
behaviors, suggest that treatment duration was sufficient to produce therapeutic effects (Sival et al, 2002

4.5.C.3 Brain injury; Prophylaxis - Seizure

a) Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class III
Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:
Not effective prophylaxis

c) Adult:
1) Valproate sodium injection should not be used in patients with acute head trauma for the prophylaxis
seizures. In a study evaluating the effect of valproate sodium injection in the prevention of post-traumatic
patients with acute head injuries, patients were assigned to receive either valproate sodium injection for
by oral valproate for either one or six months, or phenytoin intravenous given for one week followed by p
incidence of death was found to be higher in the 2 groups assigned to the valproic acid treatment compa
those assigned to the phenytoin treatment group (13% versus 8.5%). Evaluation of the cause of death di
specific drug-related causation. Furthermore, without a placebo group it is difficult to determine the actua
these head trauma patients. Until further information is available, the manufacturer recommends not usir
sodium injection in patients with acute head trauma for the prophylaxis of post-traumatic seizures (Prod I
1999).

4.5.C.4 Catatonia

a) Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category C
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:
Several cases of catatonia were improved with intravenous VALPROIC ACID

c) Adult:
1) A 38-year-old man with severe catatonic schizophrenia was markedly improved after receiving intrave
VALPROIC ACID (Kruger & Braunig, 2001). The patient required an average of 10 hospital admissions p
acute phases of his illness. In the acute phases, he would exhibit motor excitement, impulsive aggressio
iterations, screaming, negativism, gegenhalten, and impulsive behavior (such as binge eating, pica, and
masturbation). Between acute phases, he had severe negative symptoms, along with bizarre behaviors.
unsuccessfully treated with typical and atypical neuroleptics. On the index admission, he could not be giv
because he was unable to open his mouth due to extreme rigidity. He was started on high-dose IV valpro
milligrams (mg)/day, followed on the succeeding days by 3000 mg, 2500 mg, and 1800 mg. Each day his
symptoms were reduced from the previous day (90% symptom reduction over 4 days). After day 4, he w
valproate orally (900 mg/day for a plasma level of 60 micrograms/liter maintenance dosing). He required
admissions for the following 6 months. The authors noted that since this case, they have treated 3 more
successfully with a similar regimen.

4.5.C.5 Complex partial epileptic seizure

FDA Labeled Indication

a) Overview
FDA Approval: Adult, yes; Pediatric, yes (10 years and older)

Efficacy: Adult, Effective; Pediatric, Effective
Recommendation: Adult, Class IIa; Pediatric, Class IIa
Strength of Evidence: Adult, Category B; Pediatric, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Intravenous sodium valproate is indicated as monotherapy and adjunctive therapy for complex partia occurring in isolation or in association with other types of seizures when administration of oral valpro possible (Prod Info DEPACON(R) IV injection, 2006)
Carbamazepine is generally the first line agent for complex partial seizures

4.5.C.6 Febrile seizure

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Pediatric, Evidence is inconclusive
Recommendation: Pediatric, Class IIb
Strength of Evidence: Pediatric, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

As effective as PHENOBARBITAL

c) Pediatric:

1) Recurrence rates of febrile convulsions during one year were not statistically different among 196 chil convulsions treated with either PHENOBARBITAL, PRIMIDONE or SODIUM VALPROATE (Minagawa & The children on SODIUM VALPROATE received either 20 to 25 milligrams/kilogram/day (mg/kg/day) twi mg/kg/day three times daily, or 30 mg/kg/day twice daily. However, the dosage regimen of VALPROATE mg/kg/day twice daily was relatively inferior to the other regimens of VALPROATE in the prophylactic eff regimens were of equal efficacy in the long-term prophylaxis of febrile convulsions in children.

4.5.C.7 Manic bipolar I disorder

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Valproate has been used for mania secondary to bipolar disorder

c) Adult:

1) Four out of 5 acutely manic patients responded to intravenous valproate loading in an open study (Gr Five bipolar I patients received valproate 1200 or 1800 milligrams on day 1 followed by dosage individua side effects. Their mean baseline Bech-Rafaelson Mania Rating Scale score was 30.2 which improved t patient had actually been unresponsive to oral valproate. On day 5 most were switched to oral dosing. T that with the intravenous loading a quick saturation of plasma-binding proteins occurred which could hav beneficial action.

2) One uncontrolled study reported improvement in 5 of 7 patients with MANIA given VALPROIC ACID (milligrams daily) for 6 weeks. All patients had not responded to previous therapy with LITHIUM and neur 1984).

4.5.C.8 Migraine

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Valproate sodium has been used with mixed results for acute treatment of migraine headache (Math (Tanen, 2003)

c) Adult:

1) Results from an open-label, prospective study (n=61) indicate that intravenous valproate sodium (300 effective for the acute treatment of migraine headache. In this preliminary report, significant improvemen 0.001) (decreased headache severity) occurred in 73% of the migraine sufferers. Mean time to onset of r complete relief were 8 minutes and 25 minutes, respectively (Mathew et al, 2000).

2) In a randomized, double-blinded trial, intravenous prochlorperazine was more effective than intraven treating acute migraine headaches. Forty patients presented to emergency with a migraine headache wi and were recruited into the trial. Patients received either 500 milligrams (mg) of sodium valproate or 10 m prochlorperazine diluted to 10 milliliters in normal saline. After the 2 minute infusion, patients used visual grade their pain, nausea and sedation every 15 minutes for 60 minutes. Median pain scores improved 64 (mm) in the prochlorperazine group and 9 mm in the valproate group (p less than 0.001). Median nausea

35.5 mm in prochlorperazine patients and 2 mm in valproate patients (p less than 0.001). Median sedatic
4 mm in prochlorperazine patients and 0 mm in valproate patients (p=0.603). Over time, prochlorperazin
improvement in patient pain 30 minutes post dose (p less than 0.001) and in patient nausea 15 minutes
(p=0.002). Sodium valproate did not show significant improvement in symptoms over time. At the conclu
minute follow-up period, 79% of valproate patients and 25% of prochlorperazine patients required rescue
insufficient symptom relief (p=0.001). Extrapyramidal reactions were reported in 2 prochlorperazine patie

4.5.C.9 Myoclonus

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

In case reports, valproic acid was useful for myoclonus

c) Adult:

1) Sodium valproate diminished MYOCLONIC ASTATIC ATTACKS and sudden falls in 18 parkinsonian
(Henneberg et al, 1998). These patients also had polyspikes or polyspike-wave complexes on electroenc
(EEG). Sodium valproate 600 to 1800 milligrams/day was administered to achieve a level of at least 60 u
and EEG readings improved in 16 patients. The authors suspect that a generalized epilepsy may have c
myoclonus and falls.

4.5.C.10 Neuropathic pain

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Some pain reduction in patients with cancer-related neuropathic pain in a pilot study

c) Adult:

1) According to an open-label phase II study, a 2-week course of sodium valproate brought some pain r
with cancer-related neuropathic pain. Valproate was initiated at 200 milligrams (mg) twice a day with titra
not controlled and toxicity was not present) of 200 mg at intervals of 2 to 3 days to a maximum of 600 mg
Nineteen of 25 patients completed the study and the median valproate dose at day 15 was 600 mg twice
55.6% of those completing the study had a reduction in average pain by at least one category (eg, from s
moderate, or from moderate to mild), and 66.7% also had a decline in pain category for their worst pain.
timeframe, 66.7% had a decline in their absolute pain score (scale of 1 to 10 based on the Brief Pain Inv
average and worst pain. The proportion reporting a 50% reduction in pain score was 27.8% for both aver
pain. Most common side effects were drowsiness, unsteadiness, nausea, and decreased appetite; one p
due to toxicity. It was noted that after the study period ended, 89% of subjects continued on valproate as
the patient or doctor to be of benefit (Hardy et al, 2001).

4.5.C.11 Seizure, Multiple seizure types; Adjunct

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes; Pediatric, yes (10 years and older)
Efficacy: Adult, Effective; Pediatric, Effective
Recommendation: Adult, Class IIa; Pediatric, Class IIa
Strength of Evidence: Adult, Category B; Pediatric, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Intravenous sodium valproate is indicated as adjunctive therapy for multiple seizure types when adm
valproate products is not possible (Prod Info DEPACON(R) IV injection, 2006)

c) Adult:

1) General Information

a) Results of several clinical trials indicate that SODIUM VALPROATE alone or in combination with
anticonvulsants is effective in GRAND MAL SEIZURES (Covanis et al, 1982a; Pinder et al, 1977e; F
1975a; Simon & Penry, 1975). Of 519 patients who received SODIUM VALPROATE, mostly as an a
anticonvulsant agents, 239 (46%) experienced a 75% or more reduction in seizure frequency. Howe
ineffective in about 33% of these patients (Pinder et al, 1977e). Other studies have reported respons
100% when used as single-agent therapy (Rimmer & Richens, 1985g; Fuerstein, 1983; Covanis et a

2) The efficacy of VALPROATE SODIUM in 10 patients (21 to 50 years of age) with INTRACTABLE SE
DISORDERS was evaluated (Adams et al, 1978a). VALPROATE was administered initially in doses of 3
every 8 hours and increased weekly over a period of 12 weeks. All patients received concomitant anticor
responses were observed in general seizure disorders including tonic, tonic-clonic, atonic-akinetic and si

types. The most impressive results were observed in ATONIC-AKINETIC SPELLS. Considerable variatic
partial seizures, with 0% to 75% decrease in seizure frequency. EEG reading revealed the degree of epi
roughly correlated with the decrease in seizure frequency. Plasma levels of VALPROATE SODIUM of ap
mcg/mL in 5 patients was associated with a 50% decrease in seizure frequency.

d) Pediatric:

1) Successful results were reported in 22 of 27 children with grand mal seizures given SODIUM VALPR
600 and 2000 milligrams daily (dose depended upon age), for 4 to 5 weeks (Forster, 1972).

2) Good results were reported in one 17-year-old female with status epilepticus administered initial dose
milligrams 4 times daily followed by an increase to 600 mg 4 times daily for greater than 6 weeks (Manhi
The patient responded well to gradually increasing doses of sodium valproate and made a rapid recover
discharged and a follow-up 6 weeks later revealed the patient was much improved with relatively few sei

4.5.C.12 Status epilepticus

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy; Pediatric, Evidence favors efficacy
Recommendation: Adult, Class IIb; Pediatric, Class IIb
Strength of Evidence: Adult, Category C; Pediatric, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Oral, rectal and intravenous VALPROIC ACID have been effective treating status epilepticus refract
anticonvulsants

c) Adult:

1) Two female patients were successfully treated with 500 milligrams of intravenous valproate for myocl
epilepticus. Each girl presented with a history of epilepsy treatment and chief complaints of 24 hours or r
spells, jerking, shuddering, and confusion. Mental status returned to normal and jerking and shuddering s
approximately 5 minutes after the infusion was completed in each girl (Sheth et al, 2000).

2) A 25-year-old woman with generalized nonconvulsive status epilepticus was successfully treated with
valproate (Kaplan, 1999). She had been receiving oral valproate and required levels greater than 125 mi
(mg)/milliliter to control her seizures. During a previous episode, she had been treated with intravenous l
lethargy had led to a hospital admission. Intravenous valproate 500 mg was administered at 20 mg/minu
minutes. There were no adverse effects locally or on pulse or blood pressure. The patient was able to re
afterwards.

3) Two mentally retarded patients with intractable status epilepticus were treated with SODIUM VALPRO
1977). The first patient was given SODIUM VALPROATE via nasogastric tube and then 400 mg by recta
days. The second patient was given 600 mg every 6 hours as a rectal suppository for 5 days. Prior to ad
patients were receiving DIAZEPAM, PHENYTOIN, SODIUM AMOBARBITAL, and 1 patient was also rec
clonazepam. Seizures were controlled in both patients and AMOBARBITAL was subsequently withdrawn
in seizure activity. The authors suggest that rectal administration may be a practical and effective metho
epilepticus when the oral route is not available.

4) One adult patient in focal spike-and-wave status epilepticus responded to valproic acid 30 milligrams/
intravenously (Chez et al, 1999).

d) Pediatric:

1) Three pediatric patients in slow spike-and-wave status epilepticus responded to valproic acid 30 milli
intravenously (Chez et al, 1999).

2) Good results were reported in one 17-year-old female with status epilepticus administered initial dose
milligrams 4 times daily by an increase to 600 mg 4 times daily for greater than 6 weeks. (Manhire & Esp
patients responded well to gradually increasing doses of SODIUM VALPROATE and made a rapid recov
was discharged and a follow-up 6 weeks later revealed the patients was much improved with relatively fe

4.5.C.13 Tardive dyskinesia

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class III
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Mixed results have occurred

c) Adult:

1) Tardive dyskinesia improved in some patients receiving VALPROATE SODIUM at 300 milligrams 3 ti
over a period of 2 weeks in a controlled study. All patients received concomitant neuroleptic therapy. Res
VALPROATE SODIUM produced improvement in 14 of 32 patients with oro-facial dyskinesia, with impro
in akinesia, rigidity, akathisia and dystonic spasms (Linnoila & Viukari, 1979). Further data are required t
efficacy of VALPROATE in tardive dyskinesia.

4.5.C.14 Trigeminal neuralgia

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class III
Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:
Produces mixed results

c) Adult:
1) Mixed outcomes occurred when SODIUM VALPROATE was tried in 20 patients with trigeminal neura patients had no attacks for 6 to 18 months, while in 3 patients the frequency and severity of attacks were least 50%. Four patients responded well when SODIUM VALPROATE was used in combination with oth patients showed little or no response while one patient showed poor tolerance to SODIUM VALPROATE 1980).

4.5.C.15 West syndrome

a) Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Pediatric, Evidence favors efficacy
Recommendation: Pediatric, Class IIb
Strength of Evidence: Pediatric, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:
Effective in INFANTILE SPASMS (40% of patients) (Siemes et al, 1988a)

c) Pediatric:
1) Monotherapy with VALPROIC ACID was effective in the treatment of infantile spasms in a prospectiv 22 children aged 4 to 11 months (Siemes et al, 1988a). VALPROIC ACID (as SODIUM VALPROATE) w oral doses of 15 milligrams/kilogram/day; this was increased every second day by 10 milligrams/kilogram ceased or a maximum dose of 100 milligrams/kilogram/day was achieved. If seizures were not controlled to 6 weeks of treatment, oral DEXAMETHASONE 0.4 to 0.5 mg/kg/day was added to the regimen. The d VALPROATE ranged from 40 to 100 milligrams/kilogram/day (mean, 74). Total seizure control was achie patients within 3 months of starting VALPROATE; after 6 to 12 months, 73% of patients were free of seiz monotherapy, and at 18 to 24 months, 88% of children remained seizure free. Developmental status afte treatment demonstrated severe and very severe retardation in approximately 40% of children, with mode 25% and no or slight retardation in approximately 35%.

4.6 Comparative Efficacy / Evaluation With Other Therapies

Biperiden

Bromocriptine

Carbamazepine

Cyproheptadine

Ethosuximide

Haloperidol

Lithium

Olanzapine

Phenobarbital

Phenytoin

Primidone

Prochlorperazine

Progabide

Propranolol

Topiramate

4.6.A Biperiden

4.6.A.1 Extrapyramidal disease

a) A double-blind crossover comparison of valproic acid, biperiden, and placebo was conducted in 15 psychi neuroleptic-induced extrapyramidal symptoms (Friis et al, 1983). Biperiden therapy was superior to valproic a decreasing symptoms. Valproic acid had no significant effects on akathisia, a slight beneficial effect on hyper movements, and aggravated parkinsonism-like symptoms.

4.6.B Bromocriptine

4.6.B.1 Nelson syndrome

a) Bromocriptine significantly suppressed plasma adrenocorticotropin hormone (ACTH) secretion in 6 wome Syndrome. ACTH was measured after receiving therapy with each of the following: placebo, cyproheptadine, bromocriptine. Also they received each of the following combinations: cyproheptadine and valproic acid; and cyproheptadine and valproic acid. Only bromocriptine caused a significant decrease in plasma ACTH (P less the combination of the 3 drugs (P less than 0.05). However, the combined effect of the 3 drugs did not signifi effect of bromocriptine alone (Mercado-Asis et al, 1997a).

4.6.C Carbamazepine

Epilepsy

Epilepsy, Children

Rheumatic chorea

4.6.C.1 Epilepsy

a) One hundred eighty-one patients with previously untreated epilepsy were randomized to valproic acid, phe carbamazepine as monotherapy and followed for 14 to 24 months. All 3 drugs were highly effective in the cor seizures but less effective for partial seizures. There was no significant difference between the overall incider between the 3 drugs (Callaghan et al, 1985a).

b) Carbamazepine and sodium valproate were shown to be equally effective in controlling seizures in patient diagnosed primary generalized or partial seizures (Richens et al, 1994). In this large multicenter study patient randomized to either carbamazepine or valproate and followed for a period of three years. Although long-term similar in the two groups, significantly more patients in the carbamazepine group (15% vs 5%) discontinued t first six months due to adverse reactions (predominantly rash). Headache and dizziness were also reported n the carbamazepine group; weight gain was reported more often in patients receiving sodium valproate.

c) Results from a large multicenter trial comparing valproate with carbamazepine in the treatment of complex secondarily generalized tonic-clonic seizures indicate similar effectiveness of both drugs for control of seconc tonic-clonic seizures. However, for complex partial seizures, carbamazepine was more effective and was ass adverse reactions (Mattson et al, 1992). Long-term side effects associated with valproate therapy included w loss or change in texture, and tremor. Hypersensitivity, characterized by rash, occurred more frequently in tho carbamazepine.

d) Patients switched to high dose valproic acid (target serum level 80 to 150 micrograms/milliliter) demonstra improved seizure control versus treatment with their baseline antiepileptic drug. Participating patients had pa history of at least 2 complex partial seizures per month with or without secondarily generalized tonic-clonic se maintained on therapeutic levels of either carbamazepine, phenytoin, phenobarbital or primidone. A 30% me complex partial seizures and a 70% median reduction for secondarily generalized tonic-clonic seizures over p occurred. The authors conclude that valproic acid is efficacious as monotherapy for partial-onset seizures an considered as first-line therapy (Beydoun et al, 1997).

e) In a double-blinded, randomized study, topiramate, carbamazepine and valproate monotherapy demonstr to study exit, times to first seizure and proportions of patients who were seizure-free during the final 6 months Newly diagnosed epilepsy patients were randomized to receive topiramate 100 milligrams (mg) daily (n=210) mg daily (n=199), or traditional therapy (n=204). Patients in the traditional therapy arm were prescribed either 600 mg/day or valproate 1250 mg/day depending on the prescribing physician's treatment choice. Patients w months after the final patient was enrolled. Of the total 285 patients, 46% completed the study. Adverse even 19% and 23% of discontinuations in the topiramate and traditional therapy arms, respectively. Ineffective trea for 11% and 12% of discontinuations in the topiramate and traditional therapy arms, respectively. The time to to first seizure between the arms did not differ (p=0.53 and 0.35, respectively). The proportion of patients who

experience a seizure during the last 6 months of the study was 49% of topiramate-100 mg patients and 44% other arms. Dose related paresthesia (25 to 33%), difficulty with concentration or attention (4 to 11%), langua 7%), confusion (3 to 6%), nausea (7 to 14%) and abdominal pain (3 to 7%) were reported with topiramate. Ca valproate were associated with concentration and attention difficulty (4% and 1%), and language problems (6 Carbamazepine was also associated with confusion (3%) (Privitera et al, 2003a).

4.6.C.2 Epilepsy, Children

a) The efficacy and tolerability of phenobarbital, phenytoin, carbamazepine, and sodium valproate in the trea epilepsy were compared in a long-term, prospective, randomized trial (de Silva et al, 1996a). Children aged 3 (n=167) with at least two previously untreated tonic-clonic or partial seizures were eligible for participation in t drugs were equally efficacious with 20% of the patients remaining seizure free and 73% achieving 1-year rem However, randomization to phenobarbital was discontinued early in the study period due to unacceptable sid Carbamazepine and sodium valproate were the best tolerated with only 4% of children discontinuing treatmer 9% of children treated with phenytoin.

4.6.C.3 Rheumatic chorea

a) Carbamazepine and valproic acid were found to be safe and equally effective in the treatment of choreic r of clinical improvement, time to complete remission, duration of treatment, and recurrence rates in a group of patients with Sydenham's chorea. In this open-label trial, 7 children received 20 to 25 milligrams per kilogram sodium valproate and a matched group of 17 children received 15 mg/kg/day of carbamazepine. No adverse reported by either group.

Demographics and Response to Treatment			
	Sodium valproate	Carbamazepine	P
Female sex (%)	71.4	58.8	0.56
Age (years)	12.4 +/- 1.5	10.9 +/- 2.4	0.13
Onset of improvement (days)	8.0 +/- 4.0	7.4 +/- 8.2	0.88
Time to remission (weeks)	10.1 +/- 8.5	6.7 +/- 6.3	0.36
Duration of treatment (months)	4.3 +/- 2.8	5.0 +/- 2.4	0.56
Recurrences (%)	14.3	17.6	0.84
Generalized chorea (%)	71.4	64.7	0.75
(Genel et al, 2002)			

4.6.D Cyproheptadine

4.6.D.1 Nelson syndrome

a) Bromocriptine significantly suppressed plasma adrenocorticotropin hormone (ACTH) secretion in Nelson's women with Nelson's Syndrome had their ACTH measured after receiving therapy with each of the following: cyproheptadine, valproic acid, and bromocriptine. Also they received each of the following combinations: cypr valproic acid; and bromocriptine, cyproheptadine and valproic acid. Only bromocriptine caused a significant d ACTH (P less than 0.05), as did the combination of the 3 drugs (P less than 0.05). However, the combined ef did not significantly exceed the effect of bromocriptine alone (Mercado-Asis et al, 1997).

4.6.E Ethosuximide

4.6.E.1 Absence seizure

a) SUMMARY: Sodium valproate has been as effective as ethosuximide in children with petit mal seizures (P Suzuki et al, 1972; Sato et al, 1982; Callaghan et al, 1982). Sodium valproate 500 to 2400 mg daily (mean, 8 been as effective as ethosuximide 200 to 1200 mg daily (mean, 438 mg daily) (Pinder et al, 1977b).

b) Valproic acid and ethosuximide were compared in a double-blind, response-conditional crossover study o in 16 previously untreated patients and 29 refractory patients (18 male and 27 female; 4 to 18 years of age) (In the previously untreated patients, valproic acid was as effective as ethosuximide in reducing generalized s discharges on the telemetered EEG. Adverse reactions to valproic acid or ethosuximide were generally mild a

withdrawal or dosage reduction.

4.6.F Haloperidol

4.6.F.1 Mania

a) Divalproex and haloperidol were found to be equally efficacious in the management of acute psychotic ma bipolar disorder. In this study, patients (n=36) were randomized to therapy with divalproex (20 mg/kg/day) or mg/kg/day) for a period of six days. Divalproex was given at a dosage considered to be a loading dose to pro concentrations of approximately 80 mg/L after one day of treatment. Improvement was greatest during the fir treatment; extrapyramidal side effects were observed much more often in patients treated with haloperidol (M 1996).

4.6.G Lithium

4.6.G.1 Bipolar disorder - Mania

a) SUMMARY: Valproic acid may be superior to lithium in managing patients with higher numbers of depress episodes; therapeutic serum levels of either drug may help predict clinical response and outcome. Limited ev that suicide risk may be lower with lithium than with divalproex.

b) A review of 3 randomized, double-blinded, placebo-controlled studies concluded that a more rapid antima achieved with olanzapine or oral loading of divalproex than with standard titration divalproex, lithium or placel term studies, oral-loaded divalproex (n=80) was either initiated at 30 milligrams/kilogram/day (mg/kg/day) for and maintained at 20 mg/kg/day or it was initiated at 20 mg/kg/day for the first 2 days and gradually increase 20 mg/kg/day plus 1000 mg by day 6. This regimen was compared to divalproex (n=87) initiated at 250 mg 3 titrated to serum levels of 40 to 150 micrograms/milliliter (mcg/mL), lithium (n=54) initiated at 300 mg 3 times to 0.4 to 1.5 milliequivalents per liter, and olanzapine (n=55) initiated at 10 mg/day and titrated to a maximum placebo (n=72). Patients were followed for 10 days and efficacy was assessed using the change from baselir the Mania Rating Scale (MRS), the Manic Syndrome Scale (MSS) and the Behavior and Ideation Scale (BIS) analyses showed that MRS measurements from oral-loaded divalproex patients were not significantly differer patients. However, it showed significant differences from standard titration divalproex and placebo by day 5 a days 7 to 8 (p less than 0.02). Similar results were found for MSS and BIS measurements. Dry mouth and inc was more commonly reported with divalproex load compared to standard titration (p less than 0.05). Howeve divalproex was associated with an increased incidence of dizziness, general pain and back pain (p less than overall was associated with greater decreases in platelet counts than other groups (p less than 0.05). Lithium with greater reports of headache and fever (p less than 0.05) and olanzapine was associated with greater ad as dry mouth, weight gain, edema, speech disorder, rhinitis, increases in total cholesterol and increases in se aminotransferase) overall (p less than 0.05) (Hirschfeld et al, 2003a).

c) In a large-scale retrospective review of claims data, lithium treatment was associated with a lower risk of s death compared to the same risks while on divalproex. Health plan data from two managed care organizatior identify 20638 health plan members with type 1 or type 2 bipolar disorder, who had received 1 or more presc divalproex, or carbamazepine. Over an 8-year follow-up period and using lithium as a referent, patients on di hazard ratios of 2.7 for suicide death (event rate per 1000 person-years 1.7, versus 0.7 for lithium); 1.7 for att hospitalization (event rate per 1000 person-years 10.5, versus 4.2 for lithium); and 1.8 for attempts ascertaine emergency department (event rates not reported for both study sites). Comparisons of lithium to carbamazep drug therapy, or no drug treatment were less consistent or stable (Goodwin et al, 2003). Confounding factors interpretation of these results include underrepresentation of certain patient populations in managed care mo diagnoses that might influence drug choice, and reliance on diagnostic coding rather than evaluative researcl outcomes.

d) Response to lithium, but not to valproic acid, worsened with increased numbers of depressive or manic ep hospitalized for the treatment of manic episodes had their records reviewed for their illness histories. Using a fitting equation for change in Manic Syndrome Score of the Schedule of Affective Disorders and Schizophren conducted of the relationship between treatment response and the number of previous episodes. It was note episodes, the response to lithium dropped for subjects having at least 11 or more episodes. For subjects with manic episodes, response to lithium and divalproex was identical. However, in subjects with more than 11 ma response to lithium decreased and differed significantly from that to divalproex (p=0.007). Similarly, in patient depressive episodes, patients were less likely to respond to lithium as compared to divalproex (p=0.004)(Swa

e) In a retrospective review, lithium appeared to be more effective than valproic acid in the treatment of mani however, when only patients with therapeutic levels were reviewed, results were similar (Chen et al, 1999). C patients (55-years-old or older) were reviewed to assess the efficacy of lithium (n=30) and valproic acid (n=2 Global Impression rating scale was used to assess outcomes on day 5 and at discharge. Overall more patien with lithium than valproic acid at day 5 (p=0.033) and at discharge (p=0.011). However, patients with a lithium millimoles/liter or greater, or with valproic acid levels of 65 to 90 micrograms/milliliter had similar outcomes. T suggest that there may be no difference in outcome if appropriate drug serum levels are achieved in elderly p

f) In a 3-week parallel, double-blind study, a history of multiple (greater than 10) pervious episodes of mania with a poor response to lithium but not to valproic acid (Swann et al, 1999). Patients with acute mania (n=154 to lithium, valproic acid or placebo. The primary efficacy measure was the manic syndrome score from the Sc Disorder and Schizophrenia scale. A relationship between response to medication and number of previous m apparent at approximately greater than or less than 10 episodes. For a low number of previous episodes (les lithium and valproic acid were significantly more effective than placebo (p less than 0.005 for both). For patie

episodes (greater than 10) only the response to valproic acid was significantly better than placebo (p less tha
g) Pretreatment depression-related symptoms were a strong predictor of a better response to valproic acid tl
179 patients hospitalized with an acute manic episode, patients were randomized to receive a 3 week treatm
valproic acid, lithium, or placebo. Patients had comprehensive evaluations of behavior and symptoms with th
measure being the change in mania factor scores on the Schedule for Affective Disorders and Schizophrenia
This study also noted that: lithium was substantially more effective in classic mania than in depressive mania
valproic acid did not differ between classic and depressive mania; and lithium resistance in depressive mania
gender, age, substance abuse, or overall severity of illness (Swann et al, 1997).
h) The efficacy of lithium carbonate was compared with that of valproate in 27 patients with DSM-III-R acute
(Freeman et al, 1992). The study was a 3-week, randomized, double-blind, parallel groups design in which se
symptoms was measured with the Schedule for Affective Disorders and Schizophrenia, change version (SAD
Assessment Scale (GAS), and the Brief Psychiatric Rating Scale (BPRS). Nine of 14 patients treated with val
13 treated with lithium responded favorably at the end of the study. Elevated pre-treatment SADS-C depressi
associated with good response to valproate but not to lithium. Lithium and valproate were both effective in im
symptoms, and lithium was slightly more efficacious overall. Treatment with valproate alone may be particula
manic patients with mixed affective states.
i) In a decision analysis model, divalproex was found to be less costly than lithium for the acute and prophyla
patients with bipolar disorder over a one-year time period. Four attributes of overall patient management were
model: the response rate to initial therapy; the mean length of hospital stay; the rates of adverse effects; and
treatment costs. In the overall analysis, initial therapy with divalproex resulted in costs that were 9% lower tha
treatment with lithium, most likely due to a more rapid response with divalproex and shorter length of hospital
were most significant in patients with mixed mania and rapid cycling; however, cost savings with lithium thera
recognized in patients with classic mania (Keck et al, 1996a).

4.6.H Olanzapine

4.6.H.1 Mania

a) A review of 3 randomized, double-blinded, placebo-controlled studies concluded that a more rapid antima
achieved with olanzapine and oral loading of divalproex than with standard titration divalproex, lithium or plac
short-term studies, oral-loaded divalproex (n=80) was either initiated at 30 milligrams/kilogram/day (mg/kg/da
days and maintained at 20 mg/kg/day or it was initiated at 20 mg/kg/day for the first 2 days and gradually incr
maximum of 20 mg/kg/day plus 1000 mg by day 6. This regimen was compared to divalproex (n=87) initiated
daily and titrated to serum levels of 40 to 150 micrograms/milliliter (mcg/mL), lithium (n=54) initiated at 300 m
and titrated to 0.4 to 1.5 milliequivalents per liter, and olanzapine (n=55) initiated at 10 mg/day and titrated to
mg/day and placebo (n=72). Patients were followed for 10 days and efficacy was assessed using the change
measurement of the Mania Rating Scale (MRS), the Manic Syndrome Scale (MSS) and the Behavior and Ide
Intent-to-treat analyses showed that MRS measurements from oral-loaded divalproex patients were not signi
from olanzapine patients. However, it showed significant differences from standard titration divalproex and pl
and from lithium by days 7 to 8 (p less than 0.02). Similar results were found for MSS and BIS measurements
increased appetite was more commonly reported with divalproex load compared to standard titration (p less t
However, standard titration divalproex was associated with an increased incidence of dizziness, general pain
less than 0.05). Divalproex overall was associated with greater decreases in platelet counts than other groups
0.05). Lithium was associated with greater reports of headache and fever (p less than 0.05) and olanzapine v
with greater adverse events (such as dry mouth, weight gain, edema, speech disorder, rhinitis, increases in t
and increases in serum alanine aminotransferase) overall (p less than 0.05) (Hirschfeld et al, 2003).
b) Olanzapine was superior to divalproex for the treatment of acute mania in a 3-week, randomized, double-
hundred fifty one patients with bipolar I disorder, manic or mixed episode, and with or without psychotic featu
flexibly dosed olanzapine (5 to 20 milligrams (mg) per day) or divalproex (500 to 2500 mg/day). Modal doses
for olanzapine and 1401 mg/day for divalproex. A divalproex blood level of 50 microgram/liter (mcg/L) or grea
therapeutic range) was attained by approximately 87% of divalproex-treated patients. The mean improvemen
Mania Rating Scale total score was 13.4 points for the olanzapine group and 10.4 points for the divalproex gr
0.03). In subgroup analysis, the difference was significant (in favor of olanzapine) among patients without psy
(p=0.06), but there was no difference between treatments among patients with psychotic features. Clinical res
greater improvement in they Young Mania Rating Scale score) was achieved by 54% of olanzapine-treated p
divalproex-treated patients (p=0.058). Time-to- remission was significantly shorter with olanzapine (3 days vs
than 0.04). There were more adverse events with olanzapine, mainly somnolence, dry mouth, and weight gai
occurred more frequently in the divalproex group (Tohen et al, 2002).

4.6.I Phenobarbital

Epilepsy

Febrile seizure

4.6.I.1 Epilepsy

a) The efficacy and tolerability of phenobarbital, phenytoin, carbamazepine, and sodium valproate in the trea epilepsy were compared in a long-term, prospective, randomized trial (de Silva et al, 1996b). Children aged 3 (n=167) with at least two previously untreated tonic-clonic or partial seizures were eligible for participation in t drugs were equally efficacious with 20% of the patients remaining seizure free and 73% achieving 1-year rem
b) Patients switched to high concentration valproic acid (target level 80 to 150 micrograms/mililiter) demonst or improved seizure control versus treatment with their baseline antiepileptic drug. Participating patients had and a history of at least 2 complex partial seizures per month with or without secondarily generalized tonic-cl while being maintained on therapeutic levels of either carbamazepine, phenytoin, phenobarbital or primidone reduction in complex partial seizures and a 70% median reduction for secondarily generalized tonic-clonic se baseline therapy occurred. The authors conclude that valproic acid is efficacious as monotherapy for partial-c that it should be considered as first-line therapy (Beydoun et al, 1997a).

4.6.I.2 Febrile seizure

a) Phenobarbital in doses of 3 to 5 milligrams/kilogram/day was reported as effective as valproic acid 20 to 3 milligrams/kilogram/day in preventing febrile seizures (Wallas et al, 1980; Cavazzuti, 1975), whereas a more indicated that, in these doses, valproic acid was superior to phenobarbital with a lower order of toxicity (Lee &
b) Phenobarbital in doses of approximately 5 milligrams/kilogram/day was as effective as valproic acid in dos approximately 35 milligrams/kilogram/day in prevention of febrile convulsions (Herranz et al, 1984). These do plasma levels of approximately 16 mcg/mL for phenobarbital and 57 mcg/mL for valproic acid, resulting in effi 91% of children, respectively. Side effects occurred in 77% of phenobarbital-treated children as opposed to 4 acid-treated children; phenobarbital toxicity was primarily irritability, hyperactivity and sleep disorders, wherea produced gastrointestinal symptoms. In this study, primidone in doses of approximately 18 mg/kg/day (serum phenobarbital, 14 mcg/mL) was effective in 88% of patients. These data suggest that both valproic acid and p effective as phenobarbital in the prophylaxis of febrile convulsions. Although side effects were higher with phe therapy, valproic acid required dosage change and withdrawal of treatment in 10% and 4% of patients, respe no withdrawal of therapy was required in phenobarbital-treated patients. Changes in dose were required in 1 phenobarbital-treated patients.
c) Although valproic acid may be as effective as phenobarbital in prevention of febrile convulsions, the poten of the drug would preclude its routine initial use (Lott, 1982).

4.6.J Phenytoin

Epilepsy

Epilepsy, Children

Seizure; Prophylaxis

4.6.J.1 Epilepsy

a) SUMMARY: Valproic acid is as effective as phenytoin in the treatment of newly diagnosed generalized tor (Rimmer & Richens, 1985e; Wilder et al, 1983; Turnbull et al, 1983).
b) One hundred eighty-one patients with previously untreated epilepsy were randomized to valproic acid, phe carbamazepine as monotherapy and followed for 14 to 24 months (Callaghan et al, 1985). The oral drug dose phenytoin 300 mg/day (adults) and 5 to 10 mg/kg/day (children), carbamazepine 600 mg/day (adults) and 5 t (children), and valproic acid 600 mg/day (adults) and 5 to 10 mg/kg/day (children). All 3 drugs were highly eff control of generalized seizures but less effective for partial seizures. There was no significant difference betw incidence of side effects between the 3 drugs.
c) No difference was reported in efficacy between valproic acid and phenytoin therapy in previously untreate or partial seizures (Turnbull et al, 1985).
d) One study reported the similar efficacy of phenytoin and valproate in newly diagnosed complex partial sei al, 1983).
e) Patients switched to high concentration valproic acid (target level 80 to 150 micrograms/milliliter) demonst or improved seizure control versus treatment with their baseline antiepileptic drug. Participating patients had and a history of at least 2 complex partial seizures per month with or without secondarily generalized tonic-cl while being maintained on therapeutic levels of either carbamazepine, phenytoin, phenobarbital or primidone reduction in complex partial seizures and a 70% median reduction for secondarily generalized tonic-clonic se baseline therapy occurred. The authors conclude that valproic acid is efficacious as monotherapy for partial-c that it should be considered as first-line therapy (Beydoun et al, 1997).

4.6.J.2 Epilepsy, Children

a) The efficacy and tolerability of phenobarbital, phenytoin, carbamazepine, and sodium valproate in the trea epilepsy were compared in a long-term, prospective, randomized trial (de Silva et al, 1996). Children aged 3 t (n=167) with at least two previously untreated tonic-clonic or partial seizures were eligible for participation in t drugs were equally efficacious with 20% of the patients remaining seizure free and 73% achieving 1-year rem

4.6.J.3 Seizure; Prophylaxis

a) In a double-blind, 1-year study, phenytoin and valproate were equally effective in preventing seizures afte (Beenen, 1999). Patients undergoing surgery for brain tumor, trauma, or vascular lesions were randomized p receive either phenytoin 100 milligrams (mg) 3 times daily (n=50) or valproate 500 mg 3 times daily (n=50). A started intravenously after surgery and switched to oral dosing (or via nasogastric tube) as soon as possible. each group experienced a seizure. There was no difference found in the 2 groups in time to first seizure or se There was also no significant difference in the number of patients having to discontinue therapy due to adver phenytoin group, 2 in the valproate group). Neuropsychological testing also showed no significant differences phenytoin and valproate groups on cognitive functioning. This study verifies that either drug may be used for prophylaxis. Since 4 patients experienced their first seizure on the day of surgery, the authors recommend st the week before surgery or giving a loading dose after surgery.

b) Valproic acid was as effective as phenytoin for the prophylaxis of short- and long-term seizures following t injury, however there was a trend seen towards increased mortality in the valproic acid groups (Temkin et al, hours of injury, patients (ages 14-years and older) were randomized to receive either phenytoin for 1 week (n acid for 1 month (n=120), or valproic acid for 6 months (n=127). A phenytoin loading dose was administered a milligrams/kilogram (mg/kg) intravenously (IV) followed by maintenance dosing at 5 mg/kg/day divided into 2 acid loading dose was given at 20 mg/kg intravenously followed by a maintenance dose of 15 mg/kg/day divi Plasma concentrations of each drug were followed and adjusted to therapeutic levels. Early seizures occurre phenytoin treated patients and in 4.5% of the combined valproic acid groups (p not significant). There was als difference in the occurrence of late seizures. The death rate after 2 years was 13.4% for the combined valpro 7.2% for the phenytoin group (p=0.07). The authors conclude that the lack of any additional benefit from valp phenytoin, and the possibly higher mortality rate, suggest that valproic acid should not be routinely used for p posttraumatic seizures.

c) The incidence of death was higher in patients receiving valproate sodium injection followed by oral valproa receiving phenytoin intravenous followed by placebo for the prophylaxis of post-traumatic seizures in patients trauma. In a study evaluating the effect of valproate sodium injection in the prevention of post- traumatic seizu assigned to receive either valproate sodium injection for one week followed by oral valproate for either one or phenytoin intravenous given for one week followed by placebo. The incidence of death was found to be highe assigned to the valproate treatment compared to the rate in those assigned to the phenytoin treatment group 8.5%). Evaluation of the cause of death did not reveal any specific drug-related causation. Furthermore, witho group, it is difficult to determine the actual mortality rate of these head trauma patients. Until further informatio manufacturer recommends not using valproate sodium injection in patients with acute head trauma for the pr traumatic seizures (Prod Info Depacon(R), 1999).

4.6.K Primidone

Epilepsy

Febrile seizure

4.6.K.1 Epilepsy

a) Patients switched to high concentration valproic acid (target level 80 to 150 micrograms/milliliter) demonst or improved seizure control versus treatment with their baseline antiepileptic drug. Participating patients had and a history of at least 2 complex partial seizures per month with or without secondarily generalized tonic-cl while being maintained on therapeutic levels of either carbamazepine, phenytoin, phenobarbital or primidone reduction in complex partial seizures and a 70% median reduction for secondarily generalized tonic-clonic se baseline therapy occurred. The authors conclude that valproic acid is efficacious as monotherapy for partial-o that it should be considered as first-line therapy (Beydoun et al, 1997b).

4.6.K.2 Febrile seizure

a) Primidone, phenobarbital and valproic acid were equally effective over a 1-year period in the prophylaxis o convulsions in 95 children (Herranz et al, 1984a). Inclusion criteria included complicated febrile convulsions (than 15 minutes, focal or followed by transient or permanent neurological changes) or simple febrile convulsi factors (convulsions before 12-months-old, 3 or more seizures, history of neurological disorder, delay in move deficiency, microcephaly, or a history of febrile convulsions in parents or siblings). Patients were not randomi disclosed if therapy was blinded. All groups of patients presented with similar clinical characteristics and risk significantly difference between the groups was that the primidone group contained patients who all had expe seizure attacks while the other 2 groups only had approximately 70% of patients experience that many attack distribution was also uneven with 30 phenobarbital patients, 17 primidone patients and 48 valproic acid patie phenobarbital were dosed to achieve phenobarbital levels of 15 mcg/mL and valproic acid was dosed to achi plasma levels of 50 mcg/mL. Successful therapy was determined if there was no recurrence of febrile convul first year. The percentages of patients without recurrence of febrile convulsions were 80%, 88%, and 92% of with phenobarbital, primidone, and valproic acid, respectively. The differences between the groups were not s Adverse effects were experienced by 77%, 53%, and 45% of the patients treated with phenobarbital, primido acid, respectively. The adverse effects experienced with primidone were relatively less severe than with pher

valproic acid. None of the children on primidone had to change doses or withdraw from the study because of while 10% and 4% of the children on valproic acid and phenobarbital, respectively, did so. The most common with primidone and phenobarbital included hyperactivity, irritability, and disturbances of sleep, while with valp gastrointestinal effects (nausea, vomiting, and anorexia) were most common.

b) The recurrence rate of febrile convulsions over a one year period in 196 children under 3-years-old were r different between phenobarbital, primidone, or valproic acid prophylaxis therapy (Minagawa & Miura, 1981). F 5 mg/kg/day in 2 doses, primidone 15 to 20 mg/kg/day in 2 doses, valproic acid 20 to 25 mg/kg/day in 2 or 3 acid 30 mg/kg/day in 2 doses were administered to 196 children who had experienced at least 2 febrile convu method for dividing the patients into the drug therapy groups and any differences between them were not dis dosage regimen of valproic acid 20 to25 mg/kg/day in 2 doses was noted to be relatively inferior to the other dosing regimens for prophylactic effect. The remaining regimens appeared to be of equal efficacy in the long- of febrile convulsions.

4.6.L Prochlorperazine

4.6.L.1 Migraine, acute

a) In a randomized, double-blinded trial, intravenous prochlorperazine was more effective than intravenous v acute migraine headaches. Forty patients presented to emergency with a migraine headache with or without recruited into the trial. Patients received either 500 milligrams (mg) of sodium valproate or 10 mg of prochlorp 10 milliliters in normal saline. After the 2 minute infusion, patients used visual analog scales to grade their pa sedation every 15 minutes for 60 minutes. Median pain scores improved 64.5 millimeters (mm) in the prochlo and 9 mm in the valproate group (p less than 0.001). Median nausea scores improved 35.5 mm in prochlorpe and 2 mm in valproate patients (p less than 0.001). Median sedation scores improved 4 mm in prochlorperaz mm in valproate patients (p=0.603). Over time, prochlorperazine led to marked improvement in patient pain 3 dose (p less than 0.001) and in patient nausea 15 minutes post dose (p=0.002). Sodium valproate did not sh improvement in symptoms over time. At the conclusion of the 60 minute follow-up period, 79% of valproate p prochlorperazine patients required rescue therapy due to insufficient symptom relief (p=0.001). Extrapyramid reported in 2 prochlorperazine patients (Tanen et al, 2003).

4.6.M Progabide

4.6.M.1 Epilepsy

a) In a single-blind, cross-over study, progabide (median maximal dose of 2.4 grams (g) daily) was reported acid (median maximal dose of 1.8 g daily) as add-on therapy in patients with refractory epilepsy. In addition, associated with increases in serum glutamic-oxaloacetic transaminase (SGOT) levels (more than twice the u 62 patients treated; an adverse interaction with phenytoin and progabide resulted in phenytoin intoxication ar phenytoin dosage in 9 patients (Crawford & Chadwick, 1986).

4.6.N Propranolol

4.6.N.1 Migraine; Prophylaxis

a) Valproic acid exhibited equivalent efficacy to propranolol in the prophylaxis of migraine without aura in a s crossover study (n=37). Each 12-week treatment phase, separated by a 4-week placebo washout, consisted divalproex sodium 125 milligrams (mg) twice daily titrated to a goal 1500 mg/day, or propranolol sustained-re titrated to a goal 180 mg/day. Significant (at least 50%) reductions in migraine frequency occurred in 19%, 63 placebo, valproic acid and propranolol groups, respectively. Active treatments were well-tolerated and signific efficacious than placebo, but did not differ statistically from each other (Kaniecki, 1997).

4.6.O Topiramate

4.6.O.1 Epilepsy

a) In a double-blinded, randomized study, topiramate, carbamazepine and valproate monotherapy demonstr to study exit, times to first seizure and proportions of patients who were seizure-free during the final 6 months Newly diagnosed epilepsy patients were randomized to receive topiramate 100 milligrams (mg) daily (n=210) mg daily (n=199), or traditional therapy (n=204). Patients in the traditional therapy arm were prescribed either 600 mg/day or valproate 1250 mg/day depending on the prescribing physician's treatment choice. Patients w months after the final patient was enrolled. Of the total 285 patients, 46% completed the study. Adverse even 19% and 23% of discontinuations in the topiramate and traditional therapy arms, respectively. Ineffective trea for 11% and 12% of discontinuations in the topiramate and traditional therapy arms, respectively. The time to to first seizure between the arms did not differ (p=0.53 and 0.35, respectively). The proportion of patients who experience a seizure during the last 6 months of the study was 49% of topiramate-100 mg patients and 44% other arms. Dose related paresthesia (25 to 33%), difficulty with concentration or attention (4 to 11%), langua 7%), confusion (3 to 6%), nausea (7 to 14%) and abdominal pain (3 to 7%) were reported with topiramate. Ca valproate were associated with concentration and attention difficulty (4% and 1%), and language problems (6 Carbamazepine was also associated with confusion (3%) (Privitera et al, 2003).

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Last Modified: June 23, 2009

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DRUGDEX® Evaluations

TRAZODONE

0.0 Overview

1) Class
- **a)** This drug is a member of the following class(es):
  - Antidepressant
  - Triazolopyridine

2) Dosing Information
- **a)** Trazodone Hydrochloride
  - **1)** Adult
    - **a)** Depression
      - **1)** outpatients, 150 mg/day ORALLY in divided doses; may increase
      days; MAX dosage 400 mg/day (Prod Info trazodone hcl tablets, 200
      - **2)** inpatients, 150 mg/day ORALLY in divided doses; may increase d
      days; MAX dosage 600 mg/day (Prod Info trazodone hcl tablets, 200
  - **2)** Pediatric
    - **a)** Safety and effectiveness in pediatric patients have not been establishe

3) Contraindications
- **a)** Trazodone Hydrochloride
  - **1)** Hypersensitivity to trazodone

4) Serious Adverse Effects
- **a)** Trazodone Hydrochloride
  - **1)** Cardiac dysrhythmia
  - **2)** Depression, worsening
  - **3)** Hemolytic anemia
  - **4)** Hypertension
  - **5)** Hypotension
  - **6)** Leukocytosis
  - **7)** Methemoglobinemia
  - **8)** Priapism
  - **9)** Seizure
  - **10)** Suicidal thoughts
  - **11)** Suicide

5) Clinical Applications
- **a)** Trazodone Hydrochloride
  - **1)** FDA Approved Indications
    - **a)** Depression

1.0 Dosing Information

Drug Properties

Adult Dosage

1.1 Drug Properties

A) Information on specific products and dosage forms can be obtained by referring Index)

B) Synonyms
Trazodone
Trazodone HCl

Trazodone Hydrochloride
C) Physicochemical Properties
1) Molecular Weight
a) 408.33
2) Systemic: Trazodone is not chemically related to tricyclic, tetracyclic, or oth
Info Desyrel, 88) (Prod Info Trazodone Hydrochloride (generic), 88) (Prod Info
(generic), 86) (Prod Info Trazodone Hydrochloride (generic), 86a).

1.3 Adult Dosage

Normal Dosage

Dosage in Renal Failure

Dosage in Geriatric Patients

1.3.1 Normal Dosage

Trazodone

Trazodone Hydrochloride

1.3.1.A Trazodone

1.3.1.A.1 Electroconvulsive therapy
See Drug Consult reference: DRUGS FOR SEIZURE PROLONGATI

1.3.1.B Trazodone Hydrochloride

1.3.1.B.1 Oral route
a) The therapeutic dose ranges from 50 to 600 milligrams daily. Mos
100 to 300 milligrams/day in single or divided daily doses (Anon, 197
200 milligrams/day have been well tolerated (Rawls, 1982c).
b) The manufacturer recommends that therapy be initiated with 150
and increased gradually, as needed, every 3 to 4 days in increments
doses should not exceed 400 milligrams/day in divided doses. Inpatie
milligrams/day in divided doses, but this dose should not be exceede
on the lowest effective dose (Prod Info Desyrel(R), 1998c).
c) Gradual increases in dosage by 25 to 50 milligrams every 2 week
reduce drowsiness and dizziness with large doses on initiation of ther

1.3.1.B.2 DEPENDENCE
a) After a 60-day study of 50 patients, no drug dependence was obs
25 milligrams three times daily therapy (Piccione & Laguardia, 1975).

1.3.1.B.3 OBESITY
a) The clearance of trazodone appeared unchanged in obese individ
kilograms). It was suggested that the dose of the drug during chronic
rather than total body weight in this patient population (Greenblatt et

1.3.2 Dosage in Renal Failure
A) Trazodone Hydrochloride
1) Dosage adjustments are not required in renal insufficiency (Catanese

1.3.4 Dosage in Geriatric Patients
A) Trazodone Hydrochloride
1) Geriatric patients may not tolerate a single daily dose of trazodone and
considered (Anon, 1979). In one controlled study involving 20 geriatric inp
optimal dose of trazodone was reported to be 150 milligrams daily, in divi
1986).
2) A reduction in clearance and an increase in the half-life of trazodone w
following single intravenous and oral doses (25 and 50 milligrams, respec
The clearance of the drug in elderly females was not significantly affected
patients. Based upon these data, it is suggested that dose reductions of t

chronic therapy in elderly males.

2.0 Pharmacokinetics

Onset and Duration

Drug Concentration Levels

ADME

2.1 Onset and Duration

A) Onset

1) Initial Response

a) 1 week (Prod Info Desyrel(R), 1998b).

1) Symptomatic relief may be seen during the first week, with optima evident within 2 weeks. Twenty-five percent of those who respond to weeks (up to 4 weeks) of drug administration (Prod Info Desyrel(R), 1

2.2 Drug Concentration Levels

A) Time to Peak Concentration

1) 0.5 to 2 hours (Rawls, 1982a; Georgotas et al, 1982a).

2.3 ADME

Absorption

Distribution

Metabolism

Excretion

Elimination Half-life

2.3.1 Absorption

A) Bioavailability

1) 65% (Nilsen & Dale, 1992a).

B) Effects of Food

1) increased absorption (Prod Info Desyrel(R), 1998b).

a) Total drug absorption may be up to 20% higher when the drug is t empty stomach; hence, trazodone should be given shortly after a me side effects may increase under fasting conditions (Prod Info Desyrel

2.3.2 Distribution

A) Distribution Sites

1) Protein Binding

a) 89% to 95% (Rawls, 1982a; Georgotas et al, 1982a).

2) OTHER DISTRIBUTION SITES

a) PLASMA

1) Trazodone does not appear to selectively localize in any one in the plasma (Prod Info Desyrel(R), 1998b).

B) Distribution Kinetics

1) Volume of Distribution

a) 0.47 to 0.84 L/kg (Nilsen et al, 1993; Nilsen & Dale, 1992a).

1) The volume of distribution following a single 100-mg oral traz following multiple oral trazodone doses, the Vd ranges from 0.47 (Nilsen et al, 1993; Nilsen & Dale, 1992a).

2.3.3 Metabolism

A) Metabolism Sites and Kinetics

1) Liver, extensive (Rawls, 1982a; Georgotas et al, 1982a).

a) Trazodone is extensively metabolized in the liver by oxidation and
Georgotas et al, 1982a). Cytochrome P450 3A4 metabolizes trazodo
chlorophenylpiperazine (Prod Info Desyrel(R), 2003b). It appears tha
involved in its metabolism (Otani et al, 1998). Only 0.13% of a dose i
unchanged trazodone (Brogden et al, 1981).

B) Metabolites
1) meta-Chlorophenylpiperazine, active (Otani et al, 1998).
2) Conjugated compounds, inactive (Baiocchi et al, 1974).
3) Diol derivative, inactive (Baiocchi et al, 1974).
4) Hydroxy derivative, inactive (Baiocchi et al, 1974).
5) N-oxide, inactive (Baiocchi et al, 1974).

2.3.4 Excretion
A) Kidney
1) Renal Clearance (rate)
a) 3 to 5.3 L/hr (Nilsen & Dale, 1992a; Nilsen et al, 1993).
2) Renal Excretion (%)
a) 70% to 75% (Al-Yassiri et al, 1981; Brogden et al, 1981).
B) Other
1) OTHER EXCRETION
a) FECES
1) 21% (Jauch et al, 1976).

2.3.5 Elimination Half-life
A) Parent Compound
1) ELIMINATION HALF-LIFE
a) 7.1 hours (Nilsen & Dale, 1992a; Nilsen et al, 1993).
1) The manufacturer reports a biphasic elimination pattern with
followed by a slower phase half-life of 5 to 9 hours (Prod Info De

3.0 Cautions

Contraindications

Precautions

Adverse Reactions

Teratogenicity/Effects in Pregnancy/Breastfeeding

Drug Interactions

3.0.A Black Box WARNING
1) Trazodone Hydrochloride
a) Oral (Tablet)
1) Antidepressants increased the risk of suicidal thinking and behavior (s
children and adolescents with Major Depressive Disorder (MDD) and othe
considering the use of trazodone hydrochloride or any other antidepressa
balance this risk with the clinical need. Patients who are started on therap
clinical worsening, suicidality, or unusual changes in behavior. Families a
of the need for close observation and communication with the prescriber.
approved for use in pediatric patients.
2) Pooled analyses of short-term (4 weeks to 16 weeks) placebo-controll
(SSRIs and others) in children and adolescents with major depressive dis
compulsive disorder (OCD), or other psychiatric disorders (a total of 24 tri
have revealed a greater risk of adverse events representing suicidal think
the first few months of treatment in those receiving antidepressants. The
patients receiving antidepressants was 4%, twice the placebo risk of 2%.
trials (Prod Info trazodone hydrochloride oral tablet, 2005).

3.1 Contraindications
A) Trazodone Hydrochloride
1) Hypersensitivity to trazodone

3.2 Precautions

A) Trazodone Hydrochloride
1) Suicidal ideation and behavior or worsening depression; increased risk, pa
adolescents, during the first few months of therapy (Anon, 2004)
2) Bipolar disorder; the possibility that a major depressive episode may be the
disorder should be ruled out prior to initiating antidepressant therapy (Anon, 2
3) Cardiac disease; trazodone is potentially arrhythmogenic
4) Concomitant administration of antihypertensive drugs may require decreas
antihypertensive drug
5) Concomitant treatment with electroconvulsive therapy
6) Discontinue use of trazodone for as long as clinically feasible prior to electi
7) During the acute recovery period after myocardial infarction
8) In suicidal or seriously depressed patients, prescribe in limited quantities u
9) May increase or decrease prothrombin time (PT) in patients taking warfari
10) Pregnancy or lactation
11) Priapism may occur, possibly requiring surgical intervention

3.3 Adverse Reactions

Cardiovascular Effects

Dermatologic Effects

Endocrine/Metabolic Effects

Gastrointestinal Effects

Hematologic Effects

Hepatic Effects

Musculoskeletal Effects

Neurologic Effects

Ophthalmic Effects

Psychiatric Effects

Renal Effects

Reproductive Effects

Respiratory Effects

Other

3.3.1 Cardiovascular Effects

3.3.1.A Trazodone Hydrochloride

Bradyarrhythmia

Cardiac dysrhythmia

Cardiovascular finding

Edema

Heart block

Hypotension

Prolonged QT interval

Tachyarrhythmia

3.3.1.A.1 Bradyarrhythmia

a) Summary

1) Occasional sinus BRADYCARDIA has occurred in long-term
1998a).

3.3.1.A.2 Cardiac dysrhythmia

a) Summary

1) Recent clinical studies in patients with pre-existing cardiac dis
may be arrhythmogenic in some patients in that population. Arrh
premature ventricular contractions, ventricular couplets, and in tv
beats) of ventricular tachycardia. There have also been several p
arrhythmias in trazodone- treated patients who had pre-existing
of prospective studies are available, patients with pre- existing ca
monitored, particularly for cardiac arrhythmias (Prod Info Desyre
Janowsky et al, 1983a; Aronson & Hafez, 1986; Pellettier & Bart
1983).

b) Incidence: rare

c) LITERATURE REPORTS

1) Trazodone administration has been associated with aggravat
patients with pre-existing cardiac disease (Janowsky et al, 1983;
patient had a mitral valve prolapse and the other had hypertensio
atherosclerosis. Administration of trazodone 50 to 300 milligrams
the frequency of ventricular arrhythmias within 1 to 2 weeks. The
with cardiac arrhythmias and/or mitral valve prolapse should be
trazodone administration. Although trazodone presumably lacks
manufacturer warns that close monitoring is recommended for pa
(Prod Info Desyrel(R), 1998a).

2) Trazodone was associated with the occurrence of premature
angina in a 45-year-old male when the dose of the drug was incr
daily, following an approximate one month course of 50 to 150 m
After withdrawal from trazodone, the chest pain and arrhythmias
previous history of cardiovascular disease.

3) In a hospitalized patient who developed ventricular fibrillation
of trazodone 75 milligrams for three days was associated with si
bradycardia and sinus arrest, hypotension, and premature ventri
Bartolucci, 1984).

4) In three patients, aged 26, 61 and 41 years with preexisting c
trazodone appears to have exacerbated premature ventricular co
ventricular tachycardia in one case (Janowsky et al, 1983; Vlay &

3.3.1.A.3 Cardiovascular finding

a) Summary

1) In clinical trials, cardiovascular effects of trazodone reported i
HYPERTENSION, hypotension, SYNCOPE, tachycardia or PALI
breath (Prod Info Desyrel(R), 1998a). Additional cardiovascular e
voluntarily reported to the manufacturer include CARDIOSPASM
ACCIDENT OR STROKE, CONGESTIVE HEART FAILURE, ede
CONDUCTION BLOCK, ATRIAL FIBRILLATION, MYOCARDIAL
ARREST, arrhythmia, and ventricular ectopic activity, including v
Desyrel(R), 1998a).

b) Arrhythmia, bradycardia, edema, heart block, hypotension, tachyc
have been reported with the administration of trazodone.

3.3.1.A.4 Edema

a) Summary

1) Peripheral edema was described in 10 of 100 patients admini

to 600 milligrams (mg) daily for depression (Barrnett et al, 1985). was 56 years, with 9 being women. The mean dose of the drug t daily and was associated with a weight gain of 4.5 kilogram (kg) authors failed to provide information on the time of onset of eden Withdrawal of the drug or reduction in dose resulted in edema re edema, with an onset within 24 hours of initiation of trazodone th allergic response in one case, but no immunologic evidence was 1987).

3.3.1.A.5 Heart block

a) Summary

1) Trazodone has been reported to produce minimal to no effect not produced the cardiotoxicity observed with tricyclic antidepres 1981). However, other data have described ventricular arrhythmi in heart patients (Janowsky et al, 1983; Rausch et al, 1984), sug pre-existing cardiac disease (Prod Info Desyrel(R), 1998a; Raus

b) LITERATURE REPORTS

1) Complete heart block occurred in 77-year-old alcoholic with d single dose of trazodone (50 milligrams). The patient had a histo cardiovascular disease, hypertension and mitral regurgitation; a attacks was also present (Rausch et al, 1984). These data sugge trazodone may produce cardiac conduction defects in patients at

3.3.1.A.6 Hypotension

a) Summary

1) The most frequent cardiovascular side effect during therapy is may be accompanied by syncope, especially in patients taking c therapy (Rakel, 1984)(Spivak et al, 1987). The mild hypotension trazodone therapy is usually transient and not requiring discontin 1980a; Rawls, 1982b; Georgotas et al, 1982b). However, adjustr medication may be necessary if administered concurrently (Prod

b) Incidence: rare

3.3.1.A.7 Prolonged QT interval

a) Summary

1) Trazodone 150 milligrams, administered in a single dose to e to significantly prolong the QTc interval and decrease T wave he (Burgess et al, 1982).

3.3.1.A.8 Tachyarrhythmia

a) Summary

1) Trazodone may be associated with the exacerbation of ventri 1990; Himmelhoch et al, 1984; Vlay & Friedling, 1983).

b) LITERATURE REPORTS

1) Exercise-induced nonsustained ventricular tachycardia was d with no underlying heart disease receiving trazodone 50 milligrar trazodone was confirmed by treadmill testing initially, following di rechallenge with trazodone (Vitullo et al, 1990).

2) Trazodone does not appear to produce tachycardia, even in p consistently lowers baseline heart rate in therapeutic doses (Him

3) Exacerbation of ventricular tachycardia was associated with a 41-year-old female patient. The patient had a history of complex symptomatic only with palpitations. On one occasion, while not r started on trazodone 50 milligrams daily for depression. Two wee patient experienced dizzy spells and a Holter recording demonst rate of 160 beats per minute. Trazodone was discontinued and v returned to baseline. Due to potential hazards, the patient was n 1983). Administration of trazodone to patients with ventricular ec cardiac monitoring.

3.3.2 Dermatologic Effects

3.3.2.A Trazodone Hydrochloride

Dermatological finding

Diaphoresis

Erythema multiforme

Rash

3.3.2.A.1 Dermatological finding

a) Summary

1) Dermatologic effects of trazodone therapy voluntarily reporte ALOPECIA, LEUKONYCHIA or white patches under the nails, P URTICARIA (Prod Info Desyrel(R), 1998a).

b) Trazodone has been reported to cause alopecia, pruritus, diaphor rash.

3.3.2.A.2 Diaphoresis

a) Summary

1) Allergic and edematous skin reactions and SWEATING or CL of patients or more treated with trazodone in clinical trials (Prod I

3.3.2.A.3 Erythema multiforme

a) Summary

1) Erythema multiforme was described in a 63-year-old woman days of oral trazodone 300 to 400 milligrams. The patient presen papular eruption and erythematous scaly plaques on both the ha carbonate had also been prescribed and both drugs were discon symptomatic treatment with betamethasone ointment. The patie heel and erosions on the tongue and buccal mucosa two days af foot soaks and Chloraseptic(R) mouthwash were begun. The pat sequelae. Lithium has not been associated with erythema multif patient for two weeks without incident. The first symptoms of a ra trazodone was begun; this led the authors to suggest that trazod (Ford & Jenike, 1985).

3.3.2.A.4 Rash

a) Summary

1) Skin rashes, which respond to drug withdrawal and/or antihis during trazodone therapy (Trapp et al, 1979); (Al- Yassiri & Bridg

3.3.3 Endocrine/Metabolic Effects

3.3.3.A Trazodone Hydrochloride

Body temperature finding

Endocrine finding

Isolated prolactin deficiency

Metabolic finding

Shivering

Weight change finding

3.3.3.A.1 Body temperature finding

a) Trazodone has been reported to cause chills.

3.3.3.A.2 Endocrine finding

a) Summary

1) Endocrine effects of trazodone therapy voluntarily reported to HYPERAMYLASEMIA and syndrome of inappropriate antidiureti

(Prod Info Desyrel(R), 1998a). Additional endocrine effects of tra
reported to the manufacturer include BREAST ENLARGEMENT
HIRSUTISM (Prod Info Desyrel(R), 1998a).

b) Hyperamylasemia, syndrome of inappropriate antidiuretic hormon
prolactin levels have been reported with the administration of trazodo

3.3.3.A.3 Isolated prolactin deficiency

a) Summary

1) Several studies have demonstrated no change (Nair, 1979) o
prolactin levels (Roccatagliata et al, 1979; Rolandi et al, 1981a)
reports of BREAST TENDERNESS were found in the literature (
manufacturer received 8 incident reports, although none had sub
Comm, 1985).

3.3.3.A.4 Metabolic finding

a) Trazodone has been reported to cause both weight gain and weig

3.3.3.A.5 Shivering

a) Summary

1) Chills has been reported voluntarily to the manufacturer as ar
therapy (Prod Info Desyrel(R), 1998a).

3.3.3.A.6 Weight change finding

a) Summary

1) WEIGHT GAIN and WEIGHT LOSS were both reported in ov
(Prod Info Desyrel(R), 1998a).

3.3.4 Gastrointestinal Effects

3.3.4.A Trazodone Hydrochloride

Constipation

Gastrointestinal tract finding

Loss of appetite

Nausea and vomiting

Xerostomia

3.3.4.A.1 Constipation

a) Summary

1) Constipation has been reported as an adverse effect of trazo
study with imipramine, the incidence of constipation was less in t
imipramine treated patients (20%) (Gershon & Newton, 1980a).

3.3.4.A.2 Gastrointestinal tract finding

a) Summary

1) Other gastrointestinal effects reported in 1% of patients or mo
abdominal or GASTRIC DISORDERS, TASTE DISORDERS, DI
reduced appetite. Increased SALIVATION has also been reporte
Desyrel(R), 1998a).

b) Anorexia, constipation, dry mouth, nausea, vomiting, and diarrhea
administration of trazodone.

3.3.4.A.3 Loss of appetite

a) Summary

1) CASE REPORT - Anorexia and hypomania were reported in
(mg) trazodone and 500 mg of tryptophan three times a week. A
was discontinued (Patterson & Srisopark, 1989).

3.3.4.A.4 Nausea and vomiting

a) Summary

1) Nausea and vomiting are the most frequently reported advers
1998a).

3.3.4.A.5 Xerostomia

a) Summary

1) XEROSTOMIA has been reported with trazodone therapy, bu
than in imipramine-treated patients (45%) (Gershon & Newton, 1

3.3.5 Hematologic Effects

3.3.5.A Trazodone Hydrochloride

Agranulocytosis

Hematology finding

3.3.5.A.1 Agranulocytosis

a) Summary

1) CASE REPORT - A 40-year-old male had been using trazodo
admission, with no history of any other concurrent drug or chemi
perianal furuncles. Hematology laboratory values were normal w
erythrocyte sedimentation rate (ESR) and decreased leukocyte c
of 4.0 - 10.0 x 10(9)). Differential cell count was reported to be 7
and 1% eosinophils (absolute neutrophil count 0). Pus from his f
aureus. Treatment was begun with flucloxacillin. Trazodone thera
later, his leukocyte count had increased and ESR had decreased
laboratory values had returned to normal (Van der Klauw et al, 1

3.3.5.A.2 Hematology finding

a) Summary

1) Hematologic effects of trazodone therapy voluntarily reported
HEMOLYTIC ANEMIA, LEUKOCYTOSIS, and METHEMOGLOE
1998a).

b) Agranulocytosis, hemolytic anemia, leukocytosis, and methemogl
trazodone therapy.

3.3.6 Hepatic Effects

3.3.6.A Trazodone Hydrochloride

Cholestasis

Hepatitis

Increased liver enzymes

Liver finding

3.3.6.A.1 Cholestasis

a) Summary

1) Cholestasis has resulted from the use of trazodone (Rettman
Nies, 1983).

b) LITERATURE REPORTS

1) A 46-year-old Hispanic man developed acute hepatitis and ch
trazodone as part of standard protocol for cocaine withdrawal. Th
Ab positive, and hepatitis C virus positive. The detoxification trea
milligrams (mg) per day, clonidine 0.1 mg twice daily, and trazod
symptoms of depression, listlessness, fatigue, and poor sleep ov
to cocaine withdrawal. However, laboratory tests on day 5 showe
(alanine amino transferase) and a 50-fold increase in AST (aspa
Clonidine and trazodone were discontinued. Ten days later, hepa
Six months later, laboratory results were completely normal and

Since trazodone has been previously associated with hepatotoxi
since the timing and extent of response were not characteristic o
was presumed that trazodone was responsible for the hepatotox
2001).

2) Intrahepatic cholestasis was reported in a 71-year-old womar
milligrams daily for two weeks. The patient presented with increa
transaminase (AST), and alkaline phosphatase levels (ALP). Tes
negative. Upon discontinuation of trazodone, bilirubin levels cont
and ALP levels both decreased. Eight weeks after trazodone wa
bilirubin returned to normal (Sheikh & Nies, 1983). It is suggeste
enzymes and bilirubin be undertaken during the first four weeks
patients.

3.3.6.A.2 Hepatitis

a) Summary

1) Hepatitis has resulted from use of trazodone (Rettman & McC

b) LITERATURE REPORTS

1) A 46-year-old Hispanic man developed acute hepatitis and ch
trazodone as part of standard protocol for cocaine withdrawal. Th
Ab positive, and hepatitis C virus positive. The detoxification trea
milligrams (mg) per day, clonidine 0.1 mg twice daily, and trazod
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Clonidine and trazodone were discontinued. Ten days later, hepa
Six months later, laboratory results were completely normal and
Since trazodone has been previously associated with hepatotoxi
since the timing and extent of response were not characteristic o
was presumed that trazodone was responsible for the hepatotox
2001).

2) A 75-year-old Asian woman, who had experienced chronic na
trazodone, presented with dark urine, pale stools, and jaundice f
months of trazodone treatment, 150 milligrams/day, for depressi
elevated prothrombin time (PT), partial thromboplastin time (PTT
Negative immunostains on liver biopsy and serologic tests for he
remote past exposure to hepatitis B but not of ongoing viral infec
discontinuing trazodone, the nausea and anorexia resolved. Ami
and PPT normalized within 2 weeks, while bilirubin and gamma g
gradually returned to normal in 6 months (Beck et al, 1993).

3.3.6.A.3 Increased liver enzymes

a) Summary

1) Trazodone has been reported to cause elevated liver enzyme
normalize after discontinuing the drug (Fernandes et al, 2000; Cl

b) LITERATURE REPORTS

1) Jaundice and elevated liver function tests occurred in a 38-ye
taking trazodone for 18 months and while she was also using lov
arthritis. She presented with itching, nausea, and an episode of v
withdrawn, and her liver tests started to improve. Approximately
own took trazodone for two days. Her bilirubin, aspartate aminotr
transaminase levels promptly rose. Normalization occurred with
(Fernandes et al, 2000).

2) Hepatotoxicity was reported in a 63-year-old male treated for
disorder with trazodone, following three weeks of therapy (doses
that time, liver function tests were mildly elevated. Eight days lat
elevated and biopsy revealed mild portal expansion with modera
several mononuclear and polymorphonuclear leukocytes, scatter
acidophil bodies. Hepatic enzymes returned to normal four week
(Chu et al, 1983). A cause and effect relationship is difficult to es
enzymes did not peak until eight days after discontinuing the dru

3.3.6.A.4 Liver finding

a) Summary

1) Hepatic effects of trazodone therapy voluntarily reported to th
cholestasis, HYPERBILIRUBINEMIA, JAUNDICE, and LIVER EN
Info Desyrel(R), 1998a).

b) Cholestasis, elevated liver enzymes, and hepatitis have been rep

trazodone.

3.3.8 Musculoskeletal Effects

3.3.8.A Trazodone Hydrochloride

Musculoskeletal finding

Myalgia

3.3.8.A.1 Musculoskeletal finding

a) Muscle aches and pains have been reported in some patients with

3.3.8.A.2 Myalgia

a) Summary

1) Musculoskeletal aches and pains were reported in approxima trazodone in clinical trials (Prod Info Desyrel(R), 1998a).

3.3.9 Neurologic Effects

Trazodone

Trazodone Hydrochloride

3.3.9.A Trazodone

3.3.9.A.1 Seizure

See Drug Consult reference: COMPARATIVE INCIDENCE OF SEIZU ANTIDEPRESSANTS

3.3.9.B Trazodone Hydrochloride

Dystonia

Myoclonus

Neurological finding

Parkinsonism

Seizure

Somnolence

3.3.9.B.1 Dystonia

a) Summary

1) Dystonic reactions have been reported only in case reports. A effect is impairment of nigrostriatal dopamine activity by serotoni 1997).

b) LITERATURE REPORTS

1) In one case report, a 14-year-old boy was initially treated with (mg)/day (given in the morning) with gradual increases to 150 mg mg/day (given at night) was added to the regimen on day seven. treatment), the boy developed acute DYSTONIA, manifested as which was controlled with three intramuscular doses of 2 mg ber Trazodone was discontinued and the symptoms did not recur (Te

2) In a case report, dystonia was reported in a 24-year-old man disorder. The patient started on trazodone 25 milligrams (mg) at this dose was increased to 50 mg. Three days after starting the h

the emergency department with his mouth immobile in an open p stiffness and feeling as if his face was "frozen." The symptoms w a single 50 mg dose of intravenous diphenhydramine. Because t noted over a year later in the patient's treatment after he began t authors hypothesized that the mechanism causing the dystonia v possibly associated with enhancement of serotonergic neurotran dopamine activity (Lewis et al, 1997).

3.3.9.B.2 Myoclonus

a) Summary

1) Myoclonus has been reported in patients receiving trazodone upon withdrawal of trazodone (Patel et al, 1988; Garvey & Tollef

b) LITERATURE REPORTS

1) Myoclonus was reported in a 38-year-old woman receiving 30 1988). This may be related to serotonergic activity.

2) A high incidence of myoclonus was reported with cyclic antide imipramine, desipramine, amitriptyline, doxepin, trazodone, nortr Tollefson, 1987). Ninety-eight patients (93%) with major depress with these agents in initial doses of 50 milligrams (mg) daily of im increasing to a maximum of 300 mg daily after several weeks. O developed myoclonus after initiation of therapy, with the myoclor nine (9%) and resulting in withdrawal of the antidepressant or a r occurred within one month of therapy in 81% of the 39 patients, v myoclonus within two weeks; the mean dose of antidepressant b myoclonus was 169 mg daily in imipramine equivalents, which w utilized by the patients not developing myoclonus (164 mg daily) withdrawal of the antidepressant but persisted if medication char spontaneous remission of myoclonus was observed in nine patie development of myoclonus were observed.

3.3.9.B.3 Neurological finding

a) Summary

1) Central nervous system effects reported in over 1% of patient DISORIENTATION, HEADACHE, INSOMNIA, MEMORY IMPAIR COORDINATION, PARESTHESIA, and TREMORS (Prod Info D effects of trazodone therapy voluntarily reported to the manufact EXTRAPYRAMIDAL SYMPTOMS, GRAND MAL SEIZURES, IN DYSKINESIA, VERTIGO, and WEAKNESS (Prod Info Desyrel(F FATIGUE have also been reported in relatively high incidence.

b) Delirium, drowsiness, dystonia, myoclonus, headache, ataxia, sei dizziness, and fatigue have been reported with administration of trazo

3.3.9.B.4 Parkinsonism

a) Summary

1) CASE REPORT: A 57-year-old man who had undergone hem stage renal disease was given oral trazodone 100 milligrams/day depressive symptoms disappeared, but over 18 months he gradu symptoms, including cogwheel rigidity, akinesia, and gait disturb within 1 week of discontinuing trazodone. No serum concentratio were obtained, but the clinical course strongly suggested that the induced by trazodone (Fukunishi et al, 2002).

3.3.9.B.5 Seizure

a) Summary

1) Based on reports to the manufacturer, over 30 cases of seizu administration. Sixteen reported cases had previous documente al, 1985; Pers Comm, 1983; Tasini, 1986).

b) Incidence: rare

c) LITERATURE REPORTS

1) Another report described a 47-year-old man who developed c treatment with trazodone 150 mg/day for three weeks. Electroen abnormal after discontinuation of trazodone and it was speculate underlying seizure disorder (Tasini, 1986).

2) Multiple tonic-clonic seizures occurred in a 50-year-old woma following 18 days of trazodone therapy (50 milligrams daily) (Lefl also had fever on admission; it was unclear if this contributed to

3.3.9.B.6 Somnolence

a) Summary

1) The most commonly reported adverse effects of trazodone th LETHARGY. In a study of nine patients who received trazodone days, three were lethargic and two were drowsy (Kellams et al, 1 1982b).

b) LITERATURE REPORTS

1) Twelve of 50 patients who were receiving 200 to 600 milligrar dizzy during a four week treatment period (Feighner, 1980a). Dr patients in another report (Rawls, 1982b).

3.3.10 Ophthalmic Effects

3.3.10.A Trazodone Hydrochloride

Blurred vision

Eye / vision finding

Intraocular pressure finding

3.3.10.A.1 Blurred vision

a) Summary

1) Blurred vision has been reported as an adverse effect of traz patients in clinical trials (Prod Info Desyrel(R), 1998a). However, imipramine, the incidence of blurred vision was less in trazodone patients (20%) (Gershon & Newton, 1980a).

3.3.10.A.2 Eye / vision finding

a) Summary

1) Tired, red, or ITCHING EYES were reported in approximately trazodone in clinical trials. DIPLOPIA, in association with trazodc reported to the manufacturer (Prod Info Desyrel(R), 1998a).

2) The reappearance or persistence of an image has been asso patients receiving trazodone therapeutically (Hughes & Lessell,

b) Trazodone has been reported to cause blurred vision, intraocular and itchy eyes, and vision changes.

3.3.10.A.3 Intraocular pressure finding

a) Summary

1) Trazodone produces a slight decrease in intraocular pressure glaucoma by increasing outflow and decreasing production of aq reduction occurs in 180 minutes. However, after three hours intra level slightly below pretreatment values (Daniel & Fiore, 1972). T beneficial in patients with open-angle glaucoma and concomitan associated trazodone use with increased IOP (Pae et al, 2003).

b) LITERATURE REPORTS

1) A 61-year-old woman, with a 6-year history of angle-closure g increase in intraocular pressure (IOP) following the administratio maintained an IOP of 13 to 19 millimeters of mercury (mmHg) in regimen of daily drops of timolol 0.5% and pilocarpine 5%. Three milligrams (mg) per day for depressive symptoms, she develope eye pain and intermittent headache. Her IOP, 6 days after startin left eye and 40 mmHg in the right eye. Trazodone was discontinu acetazolamide 500 mg/day. Two days later her IOP returned to b

3.3.12 Psychiatric Effects

3.3.12.A Trazodone Hydrochloride

Delirium

Mania

Panic attack

Psychiatric sign or symptom

Suicidal thoughts

3.3.12.A.1 Delirium

a) Summary

1) Trazodone has been reported to cause delirium in patients. T
usually hallucinations, psychomotor agitation, and cognitive char
Damlouji & Ferguson, 1984).

b) LITERATURE REPORTS

1) Trazodone-induced delirium was reported in three patients, tv
organic cerebral lesions and one of whom had thyroid dysfunctio
hallucinations, psychomotor agitation, and cognitive changes, wa
shortly after initiation of trazodone therapy (with aggravation of th
dosage in one patient). Shortly after discontinuation of the trazoc
and, in one patient, symptoms recurred after reinstitution of trazo
that the delirium might be caused by a heightened sensitivity to t
meta- chlorphenylpiperazine, which has specific 5-HT agonist pr
2) Three cases of delirium occurred in patients with bulimia and
following short-term trazodone administration (Damlouji & Fergus
developed within two to three hours of the first dose. In the third
dosing adjustment from 150 to 200 milligrams daily. The authors
be more susceptible to delirium secondary to trazodone, possibly
neuroregulatory system.

3.3.12.A.2 Mania

a) Summary

1) Nine cases of mania following initiation of trazodone therapy
Bick, 1984; Arana & Kaplan, 1985; Lennhoff, 1987; Knobler et al

3.3.12.A.3 Panic attack

a) Summary

1) Panic attacks were reported at doses of 0.26 to 0.5 milligrams
chlorophenylpiperazine (MCPP), a trazodone metabolite and dire
al, 1990).

3.3.12.A.4 Psychiatric sign or symptom

a) Summary

1) Central nervous system effects reported in over 1% of patient
or HOSTILITY, CONFUSION, DREAM DISTURBANCES, EXCIT
general feeling of MALAISE or of a "heavy" or "full" head (Prod In
effects of trazodone therapy voluntarily reported to the manufact
ANXIETY, HALLUCINATIONS, INSOMNIA, PARANOID REACT
and VERTIGO (Prod Info Desyrel(R), 1998a).

b) Mania, panic attacks, hallucinations, agitation, hostility, and psych
result of trazodone use.

3.3.12.A.5 Suicidal thoughts

a) Incidence: rare

b) Adult and pediatric patients being treated with antidepressants for
experience symptoms of anxiety, agitation, panic attacks, insomnia, i
(aggressiveness), impulsivity, akathisia (psychomotor restlessness),
risk of suicidal ideation and behavior (SUICIDALITY). This same con
with other psychiatric and nonpsychiatric disorders. If these symptom
be re-evaluated and it may be necessary to discontinue medications
sudden in onset, or were not part of the patient's initial symptoms. Pa
be provided with the Medication Guide that is available for this drug (

c) A causal role for antidepressants in inducing suicidality has been
Anyone considering the use of antidepressants in a child or adolesce
clinical need. In pooled analyses of 24 short-term, placebo-controlled
(citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, bupropion
venlafaxine extended-release) including over 4400 pediatric patients
obsessive compulsive disorder, or other psychiatric disorders, a grea

ideation during the first few months of therapy was demonstrated in p
as compared with placebo (4% vs 2%, respectively). The risk of suici
observed in the trials that included patients with major depressive dis
emerging from trials in other psychiatric indications, such as obsessiv
anxiety disorder. No suicides occurred in these trials. The risk of suic
beyond several months) in pediatric patients is not known. It is also u
to adult patients (Anon, 2004).

3.3.13 Renal Effects

3.3.13.A Trazodone Hydrochloride

Urinary retention

Urogenital finding

3.3.13.A.1 Urinary retention

a) Summary

1) URINARY HESITANCY has been reported as an adverse eff
comparative study with imipramine, the incidence of urinary hesi
patients (1%) than imipramine patients (4%) (Gershon & Newton

3.3.13.A.2 Urogenital finding

a) Trazodone has been reported to cause both an increase and decr
ejaculatory dysfunction, and urinary retention.

3.3.14 Reproductive Effects

Trazodone

Trazodone Hydrochloride

3.3.14.A Trazodone

3.3.14.A.1 Sexual dysfunction

See Drug Consult reference: DRUG-INDUCED SEXUAL DYSFUNCT

3.3.14.B Trazodone Hydrochloride

Abnormal ejaculation

Increased libido

Priapism

Reduced libido

3.3.14.B.1 Abnormal ejaculation

a) Summary

1) INHIBITION OF EJACULATION was reported in a 51-year-ol
50 milligrams (mg) at bedtime for 3 days, then 100 mg at bedtim
trazodone and substitution with doxepin 50 mg at bedtime result
EJACULATORY INHIBITION (Jones, 1984).

3.3.14.B.2 Increased libido

a) Summary

1) Trazodone administration produced an increase in libido in th
cases, trazodone was given in gradually increasing doses up to
sexual drive were observed when this dose was achieved. Two p

drug due to this effect (Gartrell, 1986).

3.3.14.B.3 Priapism

a) Summary

1) Trazodone therapy has been associated with the occurrence surgical intervention (Prod Info Desyrel(R), 1998a; Pecknold & L Pescatori et al, 1993); (Scher et al, 1983)(Hanno et al, 1988); (C

b) Incidence: rare

c) LITERATURE REPORTS

1) In a case report, a patient treated first with nefazodone and th priapism after beginning trazodone therapy. A 51- year-old man, depressive disorder, participated in a trial of nefazodone at a dos day for a period of 6 weeks. After completion of the experimental therapy with trazodone 300 mg/day. After 17 days of therapy witl allopurinol for gout contracted during this period) the patient repo was discontinued. The patient subsequently was treated with net of priapism were reported (Pecknold & Langer, 1996).

2) A 34-year-old woman who had received fluoxetine 40 milligra treatment of depression was started on trazodone to combat fluo fluoxetine was decreased to 20 mg per day and trazodone 25 mg 50 mg at bedtime was added. Five days after starting trazodone onset irritation in the clitoral region that four days later developed PRIAPISM. Both drugs were discontinued and she received oral hydrochloride/guaifenesin twice daily for 2 days. The clitoral disc within 24 hours and there was no further clitoral dysfunction repo

3) Priapism has been seen as an adverse effect from therapeuti (Hanno et al, 1988); (Carson & Mino, 1988). Surgery was require the manufacturer and permanent impotence has been a sequela

4) In 57 cases reported to the United States Food and Drug Adr be mostly likely to occur during the first 28 days of therapy, with (mg) daily (median, 150 mg daily) (Warner et al, 1987). The med developed priapism was 40 years; however, all age groups appe adverse effect. It is suggested that patients be well informed of th given trazodone and to discontinue the drug if any unusual erect

3.3.14.B.4 Reduced libido

a) Summary

1) Decreased libido was reported in 1% of patients in clinical tria trazodone therapy voluntarily reported to the manufacturer incluc incontinence and urinary retention (Prod Info Desyrel(R), 1998a)

3.3.15 Respiratory Effects

3.3.15.A Trazodone Hydrochloride

3.3.15.A.1 Respiratory finding

a) Summary

1) Sinus or NASAL CONGESTION was reported in approximate trials. APNEA, in association with trazodone therapy, was volunt (Prod Info Desyrel(R), 1998a).

b) Nasal congestion and apnea have been reported with the adminis

3.3.16 Other

3.3.16.A Trazodone Hydrochloride

Summary

Anticholinergic adverse reaction

Died without sign of disease

Drug withdrawal

3.3.16.A.1 Summary

a) OTHER EFFECTS

1) Although trazodone produces fewer anticholinergic effects tha these effects have been reported with trazodone use. Unexplain with the administration of trazodone.

3.3.16.A.2 Anticholinergic adverse reaction

a) Summary

1) Trazodone produces significantly fewer anticholinergic effects (Taylor et al, 1980; Georgotas et al, 1982b; Gershon & Newton, one study, the incidence of anticholinergic effects with trazodone similar to placebo, but imipramine, in comparison, produced sign (Gershon & Newton, 1980a). Trazodone's lower degree of antich drug useful in glaucoma patients with depression (Rawls, 1982b) of increased intraocular pressure associated with trazodone use

3.3.16.A.3 Died without sign of disease

a) Summary

1) Unexplained death has been reported voluntarily to the manu trazodone therapy (Prod Info Desyrel(R), 1998a).

3.3.16.A.4 Drug withdrawal

a) Summary

1) Although uncommon, a withdrawal syndrome has been repor discontinuation of trazodone.

b) LITERATURE REPORTS

1) A trazodone withdrawal syndrome has been reported followin therapeutic doses of traxodone. It has been suggested that deve due to serotonergic effects and short half-lives of trazodone and chlorophenylpiperazine, which may result in noradrenergic rebou Withdrawal signs/symptoms have consisted of insomnia, vivid dr abdominal pain. anxiety, palpitations, hypomania, headache. my formication (Otani et al, 1994; Peabody, 1987; Menza, 1986); (TI Rapid withdrawal has been reported to result in predominantly ga respond to administration of atropine. It has been suggested that following rapid withdrawal (Montalbetti & Zis, 1988).

3.4 Teratogenicity/Effects in Pregnancy/Breastfeeding

A) Teratogenicity/Effects in Pregnancy

1) U.S. Food and Drug Administration's Pregnancy Category: Category C (Pro Trimesters)

a) Either studies in animals have revealed adverse effects on the fetus (te other) and there are no controlled studies in women or studies in women a Drugs should be given only if the potential benefit justifies the potential ris

See Drug Consult reference: PREGNANCY RISK CATEGORIES

2) Crosses Placenta: Unknown

3) Clinical Management

a) There is insufficient clinical experience with trazodone to confirm its sa data are available, caution should be exercised with the use of trazodone

4) Literature Reports

a) One report describes the outcomes of 12 pregnancies exposed to traz electively terminated, and the remaining ten resulted in children without m 1996). One hundred newborns (out of 229,101 births in a surveillance stu recipients) had been exposed to trazodone during the first trimester of pre exposures, one major birth defect was observed; no details are available (Rosa & Baum, 1995).

b) Animal studies indicate that high doses in rats and rabbits (15 to 50 tin contributed to increased fetal resorption and congenital anomalies. Early a lower birth weights for offspring in animals receiving high doses (Rivett & These studies were designed with trazodone dosing of 10 to 300 mg/kg d to and during mating, throughout pregnancy and lactation, and in a separa days of pregnancy and throughout lactation. Additionally, rats and rabbits during the middle portion of pregnancy developed no anomalies in offsprin Suzuki, 1973).

B) Breastfeeding

1) American Academy of Pediatrics Rating: Drugs for which the effect on nurs be of concern. (Anon, 2001)

2) Thomson Lactation Rating: Infant risk cannot be ruled out.
a) Available evidence and/or expert consensus is inconclusive or is inade when used during breastfeeding. Weigh the potential benefits of drug trea before prescribing this drug during breastfeeding.
3) Clinical Management
a) Trazodone is excreted into human milk in small amounts. Despite the effects in breast-fed infants, the American Academy of Pediatrics classifie effect on nursing infants is unknown, but may be of concern (Anon, 2001)
4) Literature Reports
a) Trazodone is excreted in low concentrations in breast milk following si were administered single oral doses of 50 mg, with a resultant milk-plasm that newborn infants would ingest less than 0.005 mg/kg of trazodone foll mother and subsequent breast feeding for a 12-hour period (Verbeeck et
5) Drug Levels in Breastmilk
a) Parent Drug
1) Milk to Maternal Plasma Ratio
a) 0.142 (Bennett, 1996)
b) Active Metabolites
1) meta-Chlorophenylpiperazine (Otani et al, 1998a)

3.5 Drug Interactions

Drug-Drug Combinations

Drug-Food Combinations

3.5.1 Drug-Drug Combinations

Acetophenazine

Amiodarone

Amprenavir

Atazanavir

Carbamazepine

Chlorpromazine

Clarithromycin

Darunavir

Delavirdine

Digoxin

Droperidol

Ethopropazine

Fluoxetine

Fluphenazine

Fosamprenavir

Foxglove

Ginkgo

Indinavir

Itraconazole

Ketoconazole

Linezolid

Mesoridazine

Methotrimeprazine

Nefazodone

Nelfinavir

Paroxetine

Perphenazine

Phenytoin

Pipotiazine

Prochlorperazine

Promazine

Promethazine

Propiomazine

Ritonavir

St John's Wort

Thiethylperazine

Thioridazine

Tipranavir

Trifluoperazine

Triflupromazine

Venlafaxine

3.5.1.A Acetophenazine

1) Interaction Effect: hypotension

2) Summary: Concomitant administration of trazodone with chlorpromazi

additive hypotensive effects in two case reports. Withdrawal of trazodone hypotension (Asayesh, 1986f).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Monitor blood pressure, particularly in patients v effect. Advise patient to rise slowly from laying or sitting position.
7) Probable Mechanism: additive hypotensive effects

3.5.1.B Amiodarone
1) Interaction Effect: increased risk of QT interval prolongation and torsac
2) Summary: Both amiodarone and trazodone are metabolized by CYP3A amiodarone is also a CYP3A4 inhibitor (Prod Info CORDARONE(R) oral t prolongation and torsades de pointes has been reported with the coadmir trazodone in 2 cases (Antonelli et al, 2005; Mazur et al, 1995). Caution is coadministered. Cardiac function may need to be closely monitored.
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: QT interval prolongation and torsades de pointe amiodarone and trazodone has been reported (Prod Info CORDARONE(R al, 2005; Mazur et al, 1995). Use caution if these agents are coadminister be monitored.
7) Probable Mechanism: unknown
8) Literature Reports
a) A case report described QT interval prolongation and polymorpho (torsades de pointes) in a 74-year-old woman receiving amiodarone a woman, who had a history of hypertension, stable angina, diastolic he pacemaker for sick sinus syndrome, and depression, presented with medications included nifedipine, furosemide, and aspirin. Amiodarone mg/day, and was later reduced to 100 mg/day 6 months prior to curre been initiated 2 months prior to current presentation at an initial dose increased over 2 weeks to 150 mg/day. While neurological exam and normal, cardiac examination revealed a II/VI systolic ejection murmur prolonged QT, QTc, and JTc intervals (0.72, 0.777, and 0.561 second to an ECG obtained prior to initiation of trazodone (baseline). Subsec trazodone were discontinued. However, recurrent episodes of polymo developed. Although treatment with intravenous lidocaine and magne episodes were managed by increasing the ventricular pacing rate to 9 episodes did not recur following gradual reduction of the ventricular p minutes over 48 hours, and the ECG pattern was similar to baseline, shortening to 0.52, 0.561, and 0.324 seconds, respectively (Mazur et
b) A chart review of 6 patients revealed a case of syncope and TdP i addition of amiodarone (50 mg/day) for paroxysmal atrial fibrillation to mg/day). The patient, who had a history of coronary artery disease, d hyperlipidemia, presented with syncope 2 months following the initiat proposed that in addition to the amiodarone-trazodone combination, p have contributed to the occurrence of torsades in this patient (Antone

3.5.1.C Amprenavir
1) Interaction Effect: an increase in trazodone plasma levels and may inc
2) Summary: Concomitant use of amprenavir and trazodone may result in concentrations due to amprenavir inhibition of CYP3A4-mediated trazodo when using these medications together and consider a reduction of trazoc trazodone side effects such as nausea, dizziness, hypotension, and syncc Capsules, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Consider a lower dose of trazodone if it is used amprenavir. Monitor patients receiving trazodone and amprenavir for adve nausea, dizziness, hypotension, and syncope.
7) Probable Mechanism: inhibition of CYP3A4-mediated trazodone metab
8) Literature Reports
a) Coadministration of trazodone with ritonavir, a potent CYP3A4 inh amprenavir, resulted in significant trazodone pharmacokinetic change concurrent administration of a total of 4 doses ritonavir 200 mg twice

trazodone increased the peak plasma trazodone concentration (Cma
the concentration-time curve (AUC) 2.4-fold, increased the half-life 2.
clearance 52%. During concomitant use of trazodone and ritonavir, a
nausea, hypotension, and syncope (Prod Info Desyrel(R) Oral Tablet

3.5.1.D Atazanavir

1) Interaction Effect: an increase in trazodone plasma levels and increase (nausea, dizziness, hypotension)

2) Summary: Atazanavir may inhibit the CYPA-mediated metabolism of tr atazanavir (with or without ritonavir) and trazodone may elevate plasma le should be monitored for increased trazodone side effects including nause hypotension. A reduction in trazodone dosing may be warranted (Prod Inf 2005).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: Caution is advised for the concomitant use of at and trazodone. Patients receiving atazanavir and trazodone should be mo effects and hypotension. Consider a reduction in trazodone dosing (Prod 2005).

7) Probable Mechanism: inhibition of CYP3A4-mediated trazodone metab

3.5.1.E Carbamazepine

1) Interaction Effect: decreased trazodone plasma concentrations

2) Summary: An increase in carbamazepine concentration/dose ratio was added to therapy, although the patient did not exhibit any signs of carbam 1999a). Trazodone serum concentrations have been decreased during co carbamazepine. Patients should be closely monitored to see if there is a r trazodone when taking both drugs (Prod Info Desyrel(R), 2003a).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: When given concurrently with carbamazepine, t should be closely monitored and trazodone dose adjustments made as ne

7) Probable Mechanism: induction of trazodone CYP3A4-mediated metal

8) Literature Reports

a) A 53-year-old male diagnosed with generalized partial epilepsy wa mg daily with a corresponding serum concentration of 7.9 mg/L. The calculated by dividing the serum concentration (mg/L) by the dose (m therapy was initiated for depression, and two months later the carban had increased to 10.0 mg/L with a corresponding concentration/dose concentration of the main pharmacologically active metabolite of carb 10,11-epoxide, was not measured. Although this patient did not show carbamazepine toxicity, this drug interaction may be clinically signific higher carbamazepine steady-state concentration (Romero et al, 199

3.5.1.F Chlorpromazine

1) Interaction Effect: hypotension

2) Summary: Concomitant administration of trazodone with chlorpromazi additive hypotensive effects in two case reports. Withdrawal of trazodone hypotension (Asayesh, 1986o).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Monitor blood pressure, particularly in patients v effect. Advise patient to rise slowly from laying or sitting position.

7) Probable Mechanism: additive hypotensive effects

3.5.1.G Clarithromycin

1) Interaction Effect: an increase in trazodone plasma levels

2) Summary: Patients receiving trazodone therapy concurrently with clari exposure to trazodone due to clarithromycin-mediated inhibition of CYP3A 2009).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: established

6) Clinical Management: Consider a lower dose of trazodone if it is used

clarithromycin. Monitor patients receiving trazodone and clarithromycin fo
sedation, memory impairment, or impaired psychomotor performance.
7) Probable Mechanism: inhibition of CYP3A-mediated trazodone metabo
8) Literature Reports
a) Increased plasma concentrations and pharmacodynamic effects c
with clarithromycin was demonstrated in a randomized, double-blind,
healthy volunteers. The study involved five treatment protocols: (a) pl
(5 mg) plus placebo, (c) zolpidem (5 mg) plus clarithromycin (500 mg
placebo, and (e) trazodone (50 mg) plus clarithromycin (500 mg). Blo
intermittently throughout the study to determine plasma concentratior
clarithromycin. Coadministration of trazodone with clarithromycin con
increase in trazodone Cmax (922 +/- 161 nanogram/mL versus 681 +
trazodone AUC (9,275 +/- 3,216 nanogram/mL per hour versus 4,668
Trazodone elimination half-life increased with coadministration of clar
(13.9 +/- 8.1 hr versus 7.1 +/- 1.6 hr), and oral clearance was reduce
+/- 27 mL/min). The sedative effects of trazodone were also enhance
no significant changes in pharmacokinetics or pharmacodynamics of
clarithromycin treatment groups (Farkas et al, 2009).

3.5.1.H Darunavir
1) Interaction Effect: increased trazodone plasma concentrations
2) Summary: Coadministration of ritonavir-boosted darunavir and trazodo
plasma concentrations of trazodone, possibly due to inhibition of CYP3A-
by darunavir/ritonavir. As this may result in trazodone adverse effects (na
syncope), caution is advised when darunavir/ritonavir and trazodone are a
lower dose of trazodone should be considered (Prod Info PREZISTA(R) fi
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concurrent administration of ritonavir-boosted d
increase trazodone plasma concentrations. Use caution when these agen
patients for signs of increased trazodone adverse effects (nausea, dizzine
consider using a lower trazodone dose (Prod Info PREZISTA(R) film coat
7) Probable Mechanism: inhibition of CYP3A-mediated trazodone metabo

3.5.1.I Delavirdine
1) Interaction Effect: increased plasma concentrations of trazodone and i
adverse effects (nausea, dizziness, hypotension, syncope)
2) Summary: Trazodone is metabolized in the liver by CYP3A4 enzymes.
inhibitors, such as delavirdine, may decrease the metabolism of trazodon
plasma concentrations. Although, the drug interaction between delavirdine
studied, adverse effects such as nausea, dizziness, hypotension and sync
coadministration of trazodone and ritonavir. Therefore, caution is advised
are administered concomitantly and a reduction in trazodone dosage shou
RESCRIPTOR(R) oral tablets, 2006).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Use caution with the coadministration of delavirc
patients for signs of increased trazodone adverse effects (nausea, dizzine
Consider reducing trazodone dosage when administering concomitantly w
7) Probable Mechanism: inhibition of cytochrome P450 3A4-mediated tra

3.5.1.J Digoxin
1) Interaction Effect: increased digoxin serum concentrations and an incr
(nausea, vomiting, arrhythmias)
2) Summary: Digoxin maximum serum concentrations were increased ne
after nefazodone (an antidepressant structurally related to trazodone) wa
randomized, crossover interaction study (Dockens et al, 1996a). Digoxin t
woman after trazodone was added to a stable treatment regimen that incl
had remained within a stable therapeutic range for many months prior to t
(Rauch & Jenike, 1984c). Increased serum digoxin serum concentrations
patients treated concurrently with trazodone and digoxin (Prod Info Desyr
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor digoxin concentrations when trazodone

discontinued from concomitant treatment with digoxin. Also, monitor patie
digoxin toxicity. Adjust digoxin dose accordingly.
7) Probable Mechanism: unknown
8) Literature Reports
a) Digoxin serum concentrations were increased nearly 30% compar
(a phenylpiperazine antidepressant structurally related to trazodone)
digoxin. In an open, randomized, triple-crossover interaction study, h
an 8-day oral regimen of digoxin 0.2 milligrams (mg) daily, nefazodor
drugs administered concomitantly during each 8-day trial period; all s
alternate study regimen after a 10-day wash-out period. Steady-state
time curve (AUC) and peak (Cmax) and trough (Cmin) serum concen
by 15%, 29% and 27%, respectively (p less than 0.05, each paramet
observed in vital signs, heart rate, or PR, QRS, and QT intervals. The
adverse events did not differ between treatment groups (Dockens et
b) Digoxin toxicity occurred in a 68-year-old woman after trazodone
regimen that included digoxin. Prior to beginning trazodone therapy,
remained within therapeutic range for many months (at a dose of digo
and on admission was 0.8 nanograms/milliliter (ng/mL). She was hos
trazodone was initiated at a dose of 50 milligrams (mg) on day 1, and
by day 11. On treatment day 14, the patient complained of nausea ar
measured at 2.8 ng/mL. Trazodone 300 mg daily was continued and
therapeutic digoxin serum levels were restored. The patient's digoxin
therapeutic range after conversion to an every-other-day regimen of
continued to receive trazodone 300 mg daily (Rauch & Jenike, 1984b
c) Increased serum concentrations of digoxin have been observed ir
treatment with trazodone (Prod Info Desyrel(R), 2003b).

3.5.1.K Droperidol
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation,
arrest)
2) Summary: Any drug known to have the potential to prolong the QT inte
with droperidol. Possible pharmacodynamic interactions can occur betwee
arrhythmogenic agents such as antidepressants that prolong the QT inter
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Droperidol should be administered with extreme
factors for development of prolonged QT syndrome, such as treatment wi
7) Probable Mechanism: additive cardiac effects

3.5.1.L Ethopropazine
1) Interaction Effect: hypotension
2) Summary: Concomitant administration of trazodone with chlorpromazi
additive hypotensive effects in two case reports. Withdrawal of trazodone
hypotension (Asayesh, 1986a).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Monitor blood pressure, particularly in patients v
effect. Advise patient to rise slowly from laying or sitting position.
7) Probable Mechanism: additive hypotensive effects

3.5.1.M Fluoxetine
1) Interaction Effect: trazodone toxicity (sedation, dry mouth, urinary rete
(hypertension, hyperthermia, myoclonus, mental status changes)
2) Summary: When given concurrently, trazodone and fluoxetine have be
effective with and without side effects (Metz & Shader, 1990; Swerdlow &
1992; Maes et al, 1997a). Coadministration of trazodone and fluoxetine ha
speech dysfunction in a 43-year old man following traumatic brain injury (
have also been several reports of serotonin syndrome due to interactions
reuptake inhibitors and antidepressants (George & Godleski, 1996a; Reev
Lee, 1996). Serotonin syndrome is a rare but potentially fatal condition of
characterized by hypertension, hyperthermia, myoclonus and changes in
Further clinical studies are necessary to determine the incidence and impl
associated with this drug combination.
3) Severity: major
4) Onset: delayed

5) Substantiation: probable
6) Clinical Management: Due to the potential for impairment in trazodone monitored for any signs of trazodone toxicity. Occasional dosage reductio Serotonin syndrome, characterized by hypertension, hyperthermia, myocl may also occur during concomitant therapy.
7) Probable Mechanism: decreased trazodone clearance
8) Literature Reports
a) Five cases of elevated antidepressant levels, four involving tricycli imipramine, desipramine) and one involving trazodone, have been re fluoxetine, the ratio of antidepressant level to dose increased by 109 tricyclics and by 31% in the patient on trazodone. The trazodone-trea and unstable gait (Aranow et al, 1989).
b) A 44-year-old man developed symptoms characteristic of serotoni interaction between fluoxetine and trazodone. The patient had been t trazodone 100 mg daily for approximately two months before sympto experienced disorientation, tremor, diaphoresis, and anxiety, followec loss of consciousness. After the patient was treated with cyproheptac resolved over the next 30 minutes. Trazodone was discontinued and fluoxetine 40 mg daily without further complications (George & Godle
c) Serotonin syndrome was also reported in a 29-year-old woman ta The patient was treated with trazodone 200 mg daily at bedtime for a depression and insomnia. The patient's depressive symptoms were u trazodone was subsequently decreased to 50 mg daily at bedtime for mg every morning was added. Within 24 hours after the first dose of agitated, confused, shaky, and diaphoretic. Upon examination, the pa intermittent myoclonus in all extremities, hyperreflexia, tremor, and di antidepressant medications, the patient's symptoms resolved (Reeve
d) A 43-year-old male with traumatic brain injury developed speech fluoxetine and trazodone. The patient was being treated with trazodo pain as a result of a fall. After undergoing a comprehensive psychiatr rehabilitation, fluoxetine 20 mg every morning was added to the patie symptoms of depression. Within one week of starting therapy with flu his speech and later exhibited a slow rate of speech, increased paus phonemes, and word-finding difficulties. After discontinuation of fluox therapy, the patient had marked improvement in speech difficulty and week (Patterson et al, 1997).
e) The pharmacokinetic effect of trazodone and fluoxetine cotherapy a major depressive episode. All were treated with trazodone 100 mg the addition of fluoxetine 20 mg daily, pindolol 7.5 mg daily, or placeb placebo had no significant effect on the plasma concentrations of traz meta-chlorophenylpiperazine (mCPP). However, when fluoxetine was of mCPP increased from a mean baseline value of 11.3 ng/mL to 38. increase was also associated with an improvement in the clinical resp (Maes et al, 1997).

3.5.1.N Fluphenazine

1) Interaction Effect: hypotension
2) Summary: Concomitant administration of trazodone with chlorpromazi additive hypotensive effects in two case reports. Withdrawal of trazodone hypotension (Asayesh, 1986n).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Monitor blood pressure, particularly in patients v effect. Advise patient to rise slowly from laying or sitting position.
7) Probable Mechanism: additive hypotensive effects

3.5.1.O Fosamprenavir

1) Interaction Effect: an increase in trazodone plasma levels
2) Summary: Concomitant use of amprenavir, the active metabolite of fos result in increased trazodone plasma concentrations due to amprenavir in trazodone metabolism. Exercise caution when using these medications to of trazodone dosing. Monitor for trazodone side effects such as nausea, d syncope (Prod Info LEXIVA(R) oral solution, oral tablets, 2009; Prod Info 2005).
3) Severity: moderate
4) Onset: unspecified

5) Substantiation: theoretical
6) Clinical Management: Concomitant use of fosamprenavir (with or witho
cause increased trazodone plasma concentrations, and should be used w
dose of trazodone if it is used with a CYP3A4 inhibitor such as fosampren
fosamprenavir and trazodone for adverse effects, including sedation, naus
syncope (Prod Info LEXIVA(R) oral solution, oral tablets, 2009).
7) Probable Mechanism: inhibition of CYP3A4-mediated trazodone metal
metabolite of fosamprenavir
8) Literature Reports
a) Coadministration of trazodone with ritonavir, a potent CYP3A4 inh
fosamprenavir, resulted in significant trazodone pharmacokinetic cha
concurrent administration of a total of 4 doses ritonavir 200 mg twice
trazodone increased the peak plasma trazodone concentration (Cma
fold, increased the half-life 2.2-fold, and decreased trazodone clearar
of trazodone and ritonavir, adverse effects reported included nausea,
Info Desyrel(R) Oral Tablet, 2005).

3.5.1.P Foxglove

1) Interaction Effect: increased risk of digitalis toxicity
2) Summary: A single case report documents digoxin toxicity resulting fro
(Rauch & Jenike, 1984a). Theoretically, foxglove may be similarly affected
to digoxin.
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Avoid concomitant use of foxglove and trazodor
intermittent trazodone doses will affect foxglove clearance (i.e., delayed e
to digitalis toxicity). Patients who choose to combine foxglove with trazodo
closely for signs and symptoms of toxicity (e.g., nausea, vomiting, drowsir
muscle weakness, hallucinations).
7) Probable Mechanism: not specified
8) Literature Reports
a) Trazodone added to a previously stable dose of digoxin resulted i
days. A 68-year-old woman with a 30-year history of unipolar affectiv
inpatient psychiatric service. Medical history was significant for conge
atrial tachyarrhythmias, and impaired renal function presumed secon
She was stabilized on digoxin (125 mcg/day) and quinidine with achie
levels for each drug. Digoxin level on admission was 0.8 ng/mL (thera
and quinidine level was 4.0 mcg/mL (therapeutic range 1.5 to 5.0 mcg
bedtime was begun and increased in 50 mg increments every other d
on Day 11. On Day 14 she complained of nausea and vomiting. A dig
The quinidine level remained within therapeutic limits at 1.6 mcg/mL.
nausea and vomiting resolved within 3 days. She continued trazodon
resumed at 125 mcg every other day resulting in therapeutic levels (F

3.5.1.Q Ginkgo

1) Interaction Effect: excessive sedation and potential coma
2) Summary: A single case report has described a semicomatose state fo
trazodone. Since no rechallenge of either agent alone or together was per
reaction was due to the combination or an unusual reaction to either agen
agonist activity at GABA receptors (Sasaki et al, 1999; Cott, 1995), as we
cytochrome P450 3A4 (CYP3A4) activity, producing more of the active me
which further enhances the release of GABA (Galluzzi et al, 2000a). In co
in vitro (Budzinski et al, 2000a). However, in vitro findings may not transla
therefore the clinical significance of this in vitro finding is unknown.
3) Severity: major
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: A single case report has described a semicomat
with trazodone. Since no rechallenge of either agent alone or together wa
the reaction was due to the combination or an unusual adverse reaction to
known about this potential interaction, avoid concomitant use of ginkgo ar
cannot be avoided, use a low dose of trazodone and monitor the patient c
sedation.
7) Probable Mechanism: induction of cytochrome P450 3A4 by ginkgo to
metabolite mCPP of trazodone
8) Literature Reports

a) An 80-year-old female diagnosed with probable Alzheimer's disea
80 mg twice daily and trazodone 20 mg twice daily following treatmer
bromazepam 3.5 mg daily, donepizil 5 mg at bedtime, and vitamin E
donepezil, and vitamin E were discontinued. On the third day of treat
the patient developed gait instability and drowsiness, fell asleep one
awakened. Blood pressure was 120/55, Glasgow coma scale was 6/
and the patient woke immediately. Trazodone and ginkgo were disco
bromazepam. At evaluation 2 months later, cognitive function and be
mechanism of the interaction between gingko and trazodone was hyp
combination of weak GABA agonist activity of ginkgo, and induction
increased production of the active metabolite of trazodone, mCPP wh
release (Galluzzi et al, 2000).
b) Ginkgo biloba inhibited CYP3A4 in vitro with an IC50 of 4.75 mmo
CYP3A4 inhibitor, was compared with ginkgo and other phytochemic
mmol, making it 23.3 times more inhibitory than the most inhibitory pl
with an IC50 of 0.03 mmol. Ginkgo was a much weaker inhibitor of C
significant drug interactions may occur with the inhibitory phytochemi
metabolized by CYP3A4 (Budzinski et al, 2000).

3.5.1.R Indinavir
1) Interaction Effect: an increase in trazodone plasma levels
2) Summary: Coadministration of trazodone with ritonavir (an indinavir-re
potent CYP3A4 inhibition) produced increases in peak plasma trazodone
elimination half-life, increased area under the concentration-time curve, a
clearance. During concomitant use of trazodone and ritonavir, adverse eff
hypotension, and syncope. Other signs and symptoms associated with ex
included priapism, respiratory arrest, seizures, and EKG changes (Prod Ir
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Consider a lower dose of trazodone if it is used
indinavir. Monitor patients receiving trazodone and indinavir for adverse e
hypotension, syncope, and/or priapism.
7) Probable Mechanism: inhibition of CYP3A-mediated trazodone metabo

3.5.1.S Itraconazole
1) Interaction Effect: increased trazodone serum concentrations
2) Summary: Substantial elevations are expected in trazodone serum co
concomitantly with itraconazole, a potent CYP3A4 inhibitor (Prod Info Des
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Consider a lower dose of trazodone if it is used
CYP3A4 inhibitor such as itraconazole. Monitor patients receiving trazodo
effects, including sedation, nausea, hypotension, syncope, and/or priapis
7) Probable Mechanism: inhibition of CYP3A4-mediated trazodone metal

3.5.1.T Ketoconazole
1) Interaction Effect: an increase in trazodone plasma levels
2) Summary: Patients receiving trazodone therapy concurrently with keto
exposure to trazodone due to ketoconazole-mediated inhibition of CYP3A
of trazodone with ritonavir (another potent CYP3A4 inhibitor) produced in
concentration, prolongation of elimination half-life, increases in area unde
and decreased trazodone clearance. During concomitant use of trazodon
reported included nausea, hypotension, and syncope. Other signs and sy
trazodone exposure have included priapism, respiratory arrest, seizures,
Desyrel(R), 2003).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Consider a lower dose of trazodone if it is used
ketoconazole. Monitor patients receiving trazodone and ketoconazole for
sedation, nausea, hypotension, syncope, and/or priapism.
7) Probable Mechanism: inhibition of CYP3A-mediated trazodone metabo

3.5.1.U Linezolid
1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, h

status changes)
2) Summary: Linezolid is a reversible, nonselective inhibitor of monoamir interactions reported with the concomitant administration of selective sero and monoamine oxidase inhibitors (MAOIs), concurrent administration or trazodone and linezolid may result in CNS toxicity or serotonin syndrome HCl, 1993). Serotonin syndrome is a hyperserotonergic state characterize restlessness, myoclonus, changes in mental status, hyperreflexia, diapho There have been spontaneous reports of serotonin syndrome associated and serotonergic agents (Prod Info ZYVOX(R) IV injection, oral tablets, or and trazodone are used concomitantly, monitor closely for symptoms of s syndrome can be life-threatening. If serotonin syndrome develops, discon provide supportive care and other therapy as necessary (Boyer & Shanno
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: If linezolid and trazodone are used concomitantl of serotonin syndrome such as neuromuscular abnormalities (including hy rigidity, clonus, peripheral hypertonicity, and shivering), autonomic hypera mydriasis, diaphoresis, and diarrhea), and mental status changes (includi Serotonin syndrome can be life-threatening. If serotonin syndrome develo agents and provide supportive care and other therapy as necessary (Boye
7) Probable Mechanism: inhibition of serotonin metabolism by monoamin
8) Literature Reports
a) In one case report, a 37-year-old male experienced symptoms of s concomitant treatment with citalopram and linezolid. He was admitted right leg. His medical history consisted of hypertension, multiple myel passive-aggressive behavior, and adaptation trouble. The patient was resistant staphylococcus aureus (MRSA) with intravenous vancomyci was receiving oral citalopram 40 mg daily, olanzapine 2.5 mg daily, tr clonazepam 2 mg three times daily, hydromorphone 125 mg subcuta medications. On day five, the patient's infection improved and vancor discharged two days later on a regimen of oral linezolid 600 mg twice days of linezolid therapy, the patient reported having panic attacks ar linezolid, he was readmitted to the hospital for these symptoms, when tremors, excessive sweating, palpitations, and peribuccal numbness. mmHg) and heart rate (112 bpm) were elevated. On day two, his bloc he was still anxious and experiencing multiple panic attacks. Methotri bisoprolol 5 mg daily, and ondansetron 8 mg as needed were introdu increased to 12.5 mg/day. One day four, linezolid was suspected as a syndrome and was discontinued. Only one dose of linezolid remained five, the patient's level of anxiety decreased and blood pressure varie his symptoms subsided and blood pressure (140/80 mmHg) and hea normal (Bergeron et al, 2005).

3.5.1.V Mesoridazine
1) Interaction Effect: hypotension
2) Summary: Concomitant administration of trazodone with chlorpromazi additive hypotensive effects in two case reports. Withdrawal of trazodone hypotension (Asayesh, 1986h).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Monitor blood pressure, particularly in patients v effect. Advise patient to rise slowly from laying or sitting position.
7) Probable Mechanism: additive hypotensive effects

3.5.1.W Methotrimeprazine
1) Interaction Effect: hypotension
2) Summary: Concomitant administration of trazodone with chlorpromazi additive hypotensive effects in two case reports. Withdrawal of trazodone hypotension (Asayesh, 1986d).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Monitor blood pressure, particularly in patients v effect. Advise patient to rise slowly from laying or sitting position.
7) Probable Mechanism: additive hypotensive effects

3.5.1.X Nefazodone

1) Interaction Effect: increased trazodone serum concentrations
2) Summary: Substantial elevations are expected in trazodone serum cor concomitantly with nefazodone, a CYP3A4 inhibitor (Prod Info Desyrel(R)
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Consider a lower dose of trazodone if it is used inhibitor such as nefazodone. Monitor patients receiving trazodone and ne including sedation, nausea, hypotension, syncope, and/or priapism.
7) Probable Mechanism: inhibition of CYP3A4-mediated trazodone metal

3.5.1.Y Nelfinavir

1) Interaction Effect: increased plasma concentrations of trazodone and i adverse effects (nausea, dizziness, hypotension, syncope)
2) Summary: Trazodone is metabolized by cytochrome P450 3A4 (CYP3 nelfinavir, which are cytochrome P450 3A substrates and inhibitors, may c trazodone, causing increased trazodone plasma concentrations. Although nelfinavir and trazodone has not been studied, adverse effects such as na syncope have occurred following coadministration of trazodone and ritona when nelfinavir and trazodone are administered concomitantly. Reduction considered (Prod Info VIRACEPT(R) oral tablets, oral powder, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Use caution with the coadministration of nelfinav patients for signs of increased trazodone adverse effects (nausea, dizzine Consider reducing trazodone dosage when administering concomitantly w VIRACEPT(R) oral tablets, oral powder, 2005).
7) Probable Mechanism: inhibition of cytochrome P450 3A4-mediated tra

3.5.1.Z Paroxetine

1) Interaction Effect: serotonin syndrome (hypertension, hyperthermia, m
2) Summary: There have been several reports of serotonin syndrome du selective serotonin reuptake inhibitors and antidepressants, including one and trazodone coadministration (George & Godleski, 1996c; Reeves & Bu 1996a). Serotonin syndrome is a rare but potentially fatal condition of sero characterized by hypertension, hyperthermia, myoclonus and changes in Further clinical studies or case reports are necessary to determine the inc serotonin syndrome associated with this drug combination.
3) Severity: major
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Concurrent use of paroxetine and trazodone sho Monitor patients for signs and symptoms of serotonin syndrome (hyperter mental status changes).
7) Probable Mechanism: additive serotonergic effects
8) Literature Reports
a) Serotonin syndrome was reported in a 29-year old woman taking patient was treated with trazodone 200 mg daily at bedtime for appro depression and insomnia. The patient's depressive symptoms were u trazodone was subsequently decreased to 50 mg daily at bedtime for mg every morning was added. Within 24 hours after the first dose of p agitated, confused, shaky, and diaphoretic. Upon examination, the pa intermittent myoclonus in all extremities, hyperreflexia, tremor, and di antidepressant medications, the patient's symptoms resolved (Reeve
b) A 44-year old man developed symptoms characteristic of serotoni interaction between fluoxetine and trazodone. The patient had been t trazodone 100 mg daily for approximately two months before sympto experienced disorientation, tremor, diaphoresis, and anxiety, followed loss of consciousness. After the patient was treated with cyproheptac resolved over the next 30 minutes. Trazodone was discontinued and fluoxetine 40 mg daily without further complications (George & Godle

3.5.1.AA Perphenazine

1) Interaction Effect: hypotension

2) Summary: Concomitant administration of trazodone with chlorpromazi additive hypotensive effects in two case reports. Withdrawal of trazodone hypotension (Asayesh, 1986l).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Monitor blood pressure, particularly in patients v effect. Advise patient to rise slowly from laying or sitting position.
7) Probable Mechanism: additive hypotensive effects

3.5.1.AB Phenytoin
1) Interaction Effect: increased phenytoin serum concentrations and an ir (ataxia, hyperreflexia, nystagmus, tremor)
2) Summary: Increased phenytoin serum concentrations have occurred i treatment with trazodone and phenytoin (Prod Info Desyrel(R), 2003d). Ph patient receiving concurrent treatment with the 2 drugs (Dorn, 1986).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Measure serum levels of phenytoin after initiatio discontinuation of trazodone; adjust dosage accordingly.
7) Probable Mechanism: unknown
8) Literature Reports
a) In 1 case concomitant administration of phenytoin and trazodone increases in phenytoin serum concentrations and phenytoin toxicity. I may competitively inhibit the metabolism of phenytoin, binding of phe phenytoin excretion. It may be prudent to monitor phenytoin serum cc the combination until further data is available (Dorn, 1986).

3.5.1.AC Pipotiazine
1) Interaction Effect: hypotension
2) Summary: Concomitant administration of trazodone with chlorpromazi additive hypotensive effects in two case reports. Withdrawal of trazodone hypotension (Asayesh, 1986).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Monitor blood pressure, particularly in patients v effect. Advise patient to rise slowly from laying or sitting position.
7) Probable Mechanism: additive hypotensive effects

3.5.1.AD Prochlorperazine
1) Interaction Effect: hypotension
2) Summary: Concomitant administration of trazodone with chlorpromazi additive hypotensive effects in two case reports. Withdrawal of trazodone hypotension (Asayesh, 1986e).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Monitor blood pressure, particularly in patients v effect. Advise patient to rise slowly from laying or sitting position.
7) Probable Mechanism: additive hypotensive effects

3.5.1.AE Promazine
1) Interaction Effect: hypotension
2) Summary: Concomitant administration of trazodone with chlorpromazi additive hypotensive effects in two case reports. Withdrawal of trazodone hypotension (Asayesh, 1986b).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Monitor blood pressure, particularly in patients v effect. Advise patient to rise slowly from laying or sitting position.
7) Probable Mechanism: additive hypotensive effects

3.5.1.AF Promethazine
1) Interaction Effect: hypotension

2) Summary: Concomitant administration of trazodone with chlorpromazi additive hypotensive effects in two case reports. Withdrawal of trazodone hypotension (Asayesh, 1986j).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Monitor blood pressure, particularly in patients v effect. Advise patient to rise slowly from laying or sitting position.
7) Probable Mechanism: additive hypotensive effects

3.5.1.AG Propiomazine
1) Interaction Effect: hypotension
2) Summary: Concomitant administration of trazodone with chlorpromazi additive hypotensive effects in two case reports. Withdrawal of trazodone hypotension (Asayesh, 1986i).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Monitor blood pressure, particularly in patients v effect. Advise patient to rise slowly from laying or sitting position.
7) Probable Mechanism: additive hypotensive effects

3.5.1.AH Ritonavir
1) Interaction Effect: an increase in trazodone plasma levels and increase
2) Summary: Ritonavir inhibits the CYPA-mediated metabolism of trazod with trazodone produced a 34% (95% CI) increase in peak plasma trazod (95%CI) increase in total area under the concentration-time curve, and a life. Patients should be monitored for increased trazodone side effects inc syncope and hypotension. A reduction in trazodone dosing may be warra liquid-filled capsule, oral solution, 2005; Greenblatt et al, 2003a).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Patients receiving trazodone and ritonavir shoul sedative effects and hypotension. Consider a reduction in trazodone dosi
7) Probable Mechanism: inhibition of CYP3A-mediated trazodone metab
8) Literature Reports
a) Coadministration of ritonavir and trazodone produces a significant trazodone concentration (Cmax), prolongation of elimination half-life, reduction in oral clearance. Ten subjects participated in a randomize study with 7 days elapsing between treatments. The four treatment c placebo to match trazodone, plus placebo to match ritonavir; Treatme ritonavir placebo; Treatment C: placebo to match trazodone plus ritor Treatment D: trazodone 50 mg plus ritonavir 200 mg X 4 doses. Rito coadministration produced a significant increase in trazodone Cmax 842 +/- 64 ng/mL (treatment B) and 1125 +/- 111 ng/mL (treatment D SE elimination half-life in treatment B was 6.7 +/- 0.7 h and in treatme 0.05). The mean +/- SE total AUC for treatment B was 5.86 +/- 0.83 r was 13.88 +/- 2.89 (p less than 0.01). The mean +/- SE apparent ora B was 155 +/- 23 and for treatment D was 75 +/- 12 (p less than 0.00 psychomotor performance (the DSST), and a quantitatively small incr EEG caused by trazodone were all enhanced by coadministration of

3.5.1.AI St John's Wort
1) Interaction Effect: an increased risk of serotonin syndrome (hypertensi mental status changes)
2) Summary: One pooly defined case of a patient developing serotonin s therapy with St. John's Wort has been reported (DeMott, 1998a). Four ca serotonin syndrome-like symptoms following the addition of St. John's Wo case with nefazodone therapy (Lantz et al, 1999). A patient exhibited a s sedative/hypnotic intoxication after adding St. John's Wort to paroxetine t Wort is thought to inhibit serotonin reuptake and may have mild monoami (Singer et al, 1999; Thiede & Walper, 1994), which when added to selecti may result in serotonin syndrome. This interaction may be extended to tra SSRI, inhibits serotonin uptake. Serotonin syndrome is a condition of ser manifests as restlessness, myoclonus, changes in mental status, hyperre tremor. If the syndrome is not recognized and correctly treated, death can

3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Avoid concomitant use of St. John's Wort and tr
trazodone of up to 15 hours, St. John's Wort should be avoided for at leas
trazodone discontinuation.
7) Probable Mechanism: additive pharmacologic effects resulting in exce
8) Literature Reports
a) A patient discontinued trazodone treatment, replacing it with St. Jo
patient then experienced mental confusion, muscle twitching, sweatir
authors characterized as serotonin syndrome. Dosage for neither of t
the exact time frame of the reaction (DeMott, 1998).

3.5.1.AJ Thiethylperazine
1) Interaction Effect: hypotension
2) Summary: Concomitant administration of trazodone with chlorpromazi
additive hypotensive effects in two case reports. Withdrawal of trazodone
hypotension (Asayesh, 1986g).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Monitor blood pressure, particularly in patients v
effect. Advise patient to rise slowly from laying or sitting position.
7) Probable Mechanism: additive hypotensive effects

3.5.1.AK Thioridazine
1) Interaction Effect: hypotension
2) Summary: Concomitant administration of trazodone with chlorpromazi
additive hypotensive effects in two case reports. Withdrawal of trazodone
hypotension (Asayesh, 1986m).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor blood pressure, particularly in patients v
effect. Advise patient to rise slowly from laying or sitting position.
7) Probable Mechanism: additive hypotensive effects
8) Literature Reports
a) In one study, 11 depressed patients received trazodone 150 mg o
weeks. In addition, thioridazine 40 mg daily was given for one week,
obtained prior to and after the coadministration. Thioridazine significa
concentrations of both trazodone and m-chlorophenylpiperazine, the
These results suggest the involvement of cytochrome P4502D6 (CYP
trazodone, since thioridazine is a known inhibitor of this isozyme (Yas

3.5.1.AL Tipranavir
1) Interaction Effect: increased plasma concentrations of trazodone and i
adverse effects (nausea, dizziness, hypotension, syncope)
2) Summary: Coadministration of tipranavir/ritonavir with trazodone may i
trazodone metabolism, causing increased trazodone plasma concentratio
between tipranavir and trazodone has not been studied, adverse effects s
hypotension and syncope have occurred following coadministration of traz
caution is advised when tipranavir/ritonavir and trazodone are administere
a lower dose of trazodone (Prod Info APTIVUS(R) oral capsules, 2006).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Concurrent administration of tipranavir/ritonavir
trazodone plasma concentrations. Use caution when these agents are co
a lower trazodone dose (Prod Info APTIVUS(R) oral capsules, 2006). Mor
increased trazodone adverse effects (nausea, dizziness, hypotension, syr
7) Probable Mechanism: inhibition of CYP3A4-mediated trazodone metab
8) Literature Reports
a) Coadministration of ritonavir and trazodone produces a significant
trazodone concentration (Cmax), prolongation of elimination half-life,
reduction in oral clearance. Ten subjects participated in a randomized
study with 7 days elapsing between treatments. The four treatment co
placebo to match trazodone, plus placebo to match ritonavir; Treatme

ritonavir placebo; Treatment C: placebo to match trazodone plus ritor
Treatment D: trazodone 50 mg plus ritonavir 200 mg X 4 doses. Ritor
coadministration produced a significant increase in trazodone Cmax
842 +/- 64 ng/mL (treatment B) and 1125 +/- 111 ng/mL (treatment D
SE elimination half-life in treatment B was 6.7 +/- 0.7 h and in treatme
0.05). The mean +/- SE total AUC for treatment B was 5.86 +/- 0.83 r
was 13.88 +/- 2.89 (p less than 0.01). The mean +/- SE apparent oral
B was 155 +/- 23 and for treatment D was 75 +/- 12 (p less than 0.00
psychomotor performance (the DSST), and a quantitatively small incr
EEG caused by trazodone were all enhanced by coadministration of

3.5.1.AM Trifluoperazine

1) Interaction Effect: hypotension
2) Summary: Concomitant administration of trazodone with chlorpromazi
additive hypotensive effects in two case reports. Withdrawal of trazodone
hypotension (Asayesh, 1986c).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor blood pressure, particularly in patients v
effect. Advise patient to rise slowly from laying or sitting position.
7) Probable Mechanism: additive hypotensive effects

3.5.1.AN Triflupromazine

1) Interaction Effect: hypotension
2) Summary: Concomitant administration of trazodone with chlorpromazi
additive hypotensive effects in two case reports. Withdrawal of trazodone
hypotension (Asayesh, 1986k).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Monitor blood pressure, particularly in patients v
effect. Advise patient to rise slowly from laying or sitting position.
7) Probable Mechanism: additive hypotensive effects

3.5.1.AO Venlafaxine

1) Interaction Effect: an increased risk of serotonin syndrome
2) Summary: Concurrent use of trazodone and venlafaxine resulted in sy
a 50-year-old male who was also taking methadone (McCue & Joseph, 2
are used concomitantly, monitor closely for symptoms of serotonin syndro
life-threatening. If serotonin syndrome develops, discontinue the offendin
care and other therapy as necessary (Boyer & Shannon, 2005).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: A case of serotonin syndrome was reported with
and venlafaxine (McCue & Joseph, 2001). If trazodone and venlafaxine a
closely for symptoms of serotonin syndrome such as neuromuscular abno
tremor, muscle rigidity, clonus, peripheral hypertonicity, and shivering), au
tachycardia, mydriasis, diaphoresis, the presence of bowel sounds, and d
changes (including agitation and delirium). Serotonin syndrome can be life
syndrome develops, discontinue the offending agents and provide suppor
necessary (Boyer & Shannon, 2005).
7) Probable Mechanism: additive pharmacologic effects
8) Literature Reports

a) A 50-year-old male experienced serotonin syndrome 18 days afte
trazodone. Venlafaxine extended release for depression, trazodone f
dependence, and docusate were started after he was admitted to the
anhedonia, hopelessness, insomnia, and suicidal ideation. The dose
over 7 days to 225 mg/day. Eighteen days after hospitalization, he be
experienced myoclonic jerking, gross tremulousness, and diaphoresis
signs were unremarkable. All his drugs were discontinued because h
worsened. Intravenous hydration was initiated. He significantly impro
and docusate were restarted and mirtazapine was started. He experi
Significant past medical history includes selective serotonin reuptake
methadone, without any similar symptoms (McCue & Joseph, 2001).

3.5.2 Drug-Food Combinations

3.5.2.A Food

1) Interaction Effect: increased time to peak levels

2) Summary: Although the rate of absorption of trazodone is reduced whe
may be a slight increase in the total amount of drug absorbed. The maxim
up to 30%, and the time to reach peak levels is prolonged (Nilsen & Dale,
Rawls, 1982). Trazodone should be taken shortly after a meal or light sna

3) Severity: minor

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: Trazodone should be taken shortly after a meal

7) Probable Mechanism: delayed absorption

4.0 Clinical Applications

4.1 Monitoring Parameters

A) Trazodone Hydrochloride

1) Toxic

a) Laboratory Parameters

1) blood pressure (Prod Info Desyrel(R) Oral Tablet, 2005)

2) ECG in patients with cardiac disease (Prod Info Desyrel(R) Oral T

3) white blood cell and differential count; in patients with signs of infe
Tablet, 2005)

b) Physical Findings

1) Monitor patients receiving antidepressants for worsening of depre
changes in behavior, especially at the initiation of therapy or when th
Such monitoring should include at least weekly face-to-face contact v
members or caregivers during the initial 4 weeks of treatment, then vi
4 weeks, then at 12 weeks, and then as clinically indicated beyond 1
should be advised of the need for close observation (i.e., daily obser
communication with the prescriber (Anon, 2004).

2) Patients who experience symptoms of anxiety, agitation, panic att
hostility, impulsivity, akathisia, hypomania, or mania may be at an inc
depression or suicidality. If these symptoms are observed, therapy sh
be necessary to discontinue medications when symptoms are severe
part of the patient's initial symptoms (Anon, 2004).

4.2 Patient Instructions

A) Trazodone (By mouth)

Trazodone

Treats depression, and depression with anxiety.

When This Medicine Should Not Be Used:
You should not use this medicine if you have had an allergic reaction to trazoc

How to Use This Medicine:
Tablet

Your doctor will tell you how much of this medicine to use and how often.
changed several times in order to find out what works best for you. Do no

more often than your doctor tells you to.
It is best to take this medicine with food or milk.
This medicine should come with a Medication Guide. Read and follow the
doctor or pharmacist if you have any questions. Ask your pharmacist for t
have one. Your doctor might ask you to sign some forms to show that you

If a Dose is Missed:
If you miss a dose or forget to use your medicine, use it as soon as you c
dose, wait until then to use the medicine and skip the missed dose. Do nc
for a missed dose.

How to Store and Dispose of This Medicine:
Store the medicine in a closed container at room temperature, away from
Ask your pharmacist, doctor, or health caregiver about the best way to dis
after you have finished your treatment. You will also need to throw away c
date has passed.
Keep all medicine away from children and never share your medicine with

Drugs and Foods to Avoid:
Ask your doctor or pharmacist before using any other medicine, including over
and herbal products.
Make sure your doctor knows if you are taking digoxin, phenytoin (Dilantir
you drowsy such as sleeping pills, tranquilizers, other medicine for depres
narcotic pain killers.
Tell your doctor if you are using carbamazepine (Tegretol®), an antiviral c
Crixivan®, Norvir®), or a medicine to treat fungal infections (such as fluco
ketoconazole, Diflucan®, Nizoral®, Sporanox®).
Make sure your doctor knows if you are also using medicine to decrease y
pressure medicines are atenolol, hydrochlorothiazide (HCTZ), lisinopril, m
Diovan®, Lotrel®, Norvasc®, Prinivil®, Toprol®, and Zestril®.

Warnings While Using This Medicine:
Make sure your doctor knows if you are pregnant or breast feeding, or if y
For some children and teenagers, this medicine can increase thoughts of
leaflet are true for a child or teenager who is using this medicine.Tell your
feel more depressed. Also tell your doctor right away if you have thoughts
any unusual thoughts or behaviors that trouble you, especially if they are
sure your caregiver knows if you have trouble sleeping, get upset easily, h
start to act reckless. Also tell your doctor if you have sudden or strong fee
angry, restless, violent, or scared.Let your doctor know if you or anyone ir
(manic-depressive) or has tried to commit suicide.
Do not stop using this medicine suddenly without asking your doctor. You
your dose before stopping it completely.
You may need to take trazodone for 2 to 4 weeks before you start to feel l
Get up slowly from a lying or sitting position to decrease dizziness caused
This medicine may make you dizzy or drowsy. Avoid driving, using machi
could be dangerous if you are not alert.
Make sure any doctor or dentist who treats you knows that you are using
stop using this medicine several days before having surgery or medical te
Your doctor will need to check your progress at regular visits while you ar
keep all appointments.

Possible Side Effects While Using This Medicine:
Call your doctor right away if you notice any of these side effects:
Allergic reaction: Itching or hives, swelling in your face or hands, swelling
chest tightness, trouble breathing.
Painful, prolonged erection of your penis.
Skin rash.
Unexplained fever or sore throat.

If you notice these less serious side effects, talk with your doctor:
Changes in vision, such as trouble focusing.
Constipation or diarrhea.
Drowsiness or dizziness.
Dry mouth.
Headache.
Nausea, vomiting, upset stomach.

Nervousness, trouble sleeping.

If you notice other side effects that you think are caused by this medicine, tell y

4.3 Place In Therapy

A) Depression is a complicated disorder and consequently this disease's treatmer most prevalent diagnostic syndromes among affective disorders are major depress tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), ar inhibitors (MAOIs) are considered the most effective agents for treating major depr disorders, lithium is the preferred therapy; carbamazepine and valproic acid are co

B) Trazodone is equally effective for treating mild typical or endogenous depressic questions remain as to the effectiveness of trazodone for treating moderate-to-sev patients seem to have difficulty tolerating adequate doses. Trazodone possesses t without anticholinergic effects. Other advantageous characteristics of this agent inc anxiety disorders, agitation, obsessive compulsive behavior, and a comparatively s following overdoses. Trazodone may also be safely combined with MAOIs for refra of trazodone include a high incidence of priapism, orthostatic hypotension, and indi and ventricular arrhythmias. However, compared with the TCAs, trazodone is still c

C) Trazodone does have a place in therapy for treating endogenous or typical dep secondary to the TCAs, the SSRIs, and the MAOIs in most circumstances. Trazod without anticholinergic effects may be useful in elderly patients refractory to standa patients with an unusually high potential for suicide, trazodone may be considered that commonly treat elderly depressed patients, refractory depressed patients, or o threatening suicide should consider trazodone for formulary inclusion.

4.4 Mechanism of Action / Pharmacology

A) MECHANISM OF ACTION

1) Trazodone, which was first synthesized in 1966, represents a different clas triazolopyridines. Structurally, it does not bear any similarity to tricyclic antidep antidepressants, or MAO inhibitors. The antidepressant activity of trazodone a selectively inhibit serotonin reuptake. At low doses, trazodone appears to act a higher doses as an agonist (Maj et al, 1979; Stefanini et al, 1976).

2) Unlike other antidepressants, trazodone does not potentiate catecholamine It does appear to have a sedative effect and slight muscle relaxant properties, (Silvestrini et al, 1968). Trazodone does not have any significant effect on prol 1979)(Rolandi et al, 1981).

3) Trazodone appears to be equally effective in bipolar and unipolar depressic antidepressant therapy is its short onset of action and low incidence of anticho effects. However, some studies have indicated the onset of action of trazodon (Rawls, 1982a; Brogden et al, 1981; Rickels, 1981). Some data has suggested which may be less than or equal to other benzodiazepines; however, sufficient determine that these effects are related directly to properties of the drug or sec existing depression.

B) REVIEW ARTICLES

1) A comprehensive review of the second-generation antidepressant agents (trazodone, nomifensine) has been presented (Caccaro & Siever, 1985).

2) Other uses of antidepressant agents, including enuresis, bulimia, anorexia pain, migraine headache, and peptic ulcer disease have been reviewed (Orsul

3) A review of clinical guidelines for utilizing antidepressants in the treatment is available (Salzman, 1985).

4) Drug-interactions of antidepressants are reviewed in German language (Za

4.5 Therapeutic Uses

Trazodone

Trazodone Hydrochloride

4.5.A Trazodone

Dementia

Electroconvulsive therapy

4.5.A.1 Dementia
See Drug Consult reference: BEHAVIORAL AND PSYCHOLOGICAL SY

4.5.A.2 Electroconvulsive therapy
See Drug Consult reference: DRUGS FOR SEIZURE PROLONGATION I

4.5.B Trazodone Hydrochloride

Adverse reaction to drug - Insomnia

Agoraphobia

Alcohol withdrawal syndrome

Benzodiazepine withdrawal

Chronic pain

Dementia

Depression

Diabetic neuropathy

Erectile dysfunction; Diagnosis

Essential tremor

Insomnia

Migraine, Pediatric; Prophylaxis

Neuroleptic-induced acute akathisia

Schizophrenia

4.5.B.1 Adverse reaction to drug - Insomnia

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE

b) Summary:

Effective for treatment of INSOMNIA induced by monoamine oxidase

c) Adult:

1) In a small double-blind, placebo-controlled, crossover trial (n=7), a TRAZODONE 50 milligrams each evening improved sleep disturbanc who had responded to brofaromine, but who had experienced insomr oxidase inhibitor (MAO-I). Mean number of nightly awakenings and n lower after trazodone therapy compared with baseline (p=0.019 and Subjectively, some patients felt they had better and deeper sleep with mild. Larger controlled trials are needed (Haffmans & Vos, 1999).

2) The benefits of trazodone in the treatment of insomnia secondary (MAOI) therapy were demonstrated in a small, open study (Nierenbe patients with depression were treated with either tranylcypromine, ph developed insomnia after receiving MAOI therapy for 5 to 60 days. Tr 200 milligrams daily (mean, 85 milligrams daily) was reported to prod 12 patients (92%) within 1 week of treatment; 9 of the 13 patients we

inhibitors with trazodone without the occurrence of intolerable advers
are required to further evaluate the efficacy of trazodone in this clinic

4.5.B.2 Agoraphobia

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE

b) Summary:

Effective for symptomatic improvement

c) Adult:

1) Trazodone 300 milligrams daily was effective in reducing anxiety,
symptoms in outpatients with PANIC DISORDER or agoraphobia wit
study involving 11 patients (Mavissakalian et al, 1987).

4.5.B.3 Alcohol withdrawal syndrome

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE

b) Summary:

Appears to be beneficial in the treatment of acute alcohol withdrawal

c) Adult:

1) Total abstinence was reported after 90 days of trazodone treatme
patient open study. After completing acute detoxification (mean perio
(50 to 100 milligrams (mg) per day) and tiapride (300 to 600 mg/day),
detoxification program and began trazodone therapy with daily doses
(mean 135 mg). Baseline and 90-day Discan scale scores for anxiety
exhibited a significant reduction in mean score at the end of the trial (
abstinence combined with the rate of controlled drinking patterns was
drugs used in this indication, as was the recidivism rate (Janiri et al, 1
2) Seventeen chronic alcoholics abruptly stopped drinking ethanol a
trazodone 100 milligrams/day. Based on the Hamilton anxiety rating s
significant global improvements and regression of pre-treatment clinic
depression, fear, and insomnia. After 3 to 5 days of trazodone therap
completely. It is thought that trazodone is beneficial due to the dopam
activity (Roccatogliata et al, 1980).

4.5.B.4 Benzodiazepine withdrawal

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE

b) Summary:

Effective as an aid to discontinuing benzodiazepine in a small study

c) Adult:

1) Ten patients experienced generally mild and transitory benzodiaz
receiving trazodone (100 mg three times a day) during a 2- to 4-week
benzodiazepine dependence. After their benzodiazepines were progr
discontinued, the patients were discharged on trazodone 300 milligra
benzodiazepine-free during a 1-year follow-up and showed significan
(300 to 185 milligrams/day) and in Hamilton Rating Scales scores for
screens were not performed; benzodiazepine abstinence was determ
general practitioner assessments (Ansseau & De Roeck, 1993).

4.5.B.5 Chronic pain

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Ineffective
Recommendation: Adult, Class III
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE

b) Summary:
NOT effective for relief of BURNING MOUTH SYNDROME in a small

c) Adult:
1) An 8-week course of oral TRAZODONE 200 milligrams every eve analgesic efficacy for CHRONIC MOUTH PAIN than did placebo in a weeks, patient-rated visual analog pain scores dropped by 13.9 and trazodone and control groups (NS). Overall, 8 of 11 (73%) trazodone (76%) placebo-treated patients rated themselves as 'improved' (NS). more dizziness (p less than 0.001) and drowsiness (p less than 0.05) 1999).

4.5.B.6 Dementia

a) Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE

b) Summary:
May offer some benefit to patients with aggressive behavior or repetit dementia

c) Adult:
1) A pilot open-label study found that oral TRAZODONE produced s behavior of 14 consecutive patients (mean age 70.5 years) with FRO diagnosed according to criteria of the Lund and Manchester Groups (received trazodone 50 milligrams (mg) 3 times a day, followed by a 2 day. Ratings on the Neuropsychiatric Inventory (NPI) showed signific aggression, anxiety, and irritability, comparing scores after 4 weeks c than 0.05). After completion of the 300-mg dosing period, significant disinhibition, and aberrant motor behavior were also noted (p less tha 1999).
2) Trazodone was effective in the treatment of PALILALIA, a conditic involuntary repetition (two or more times) of a phrase or word, in an 8 dementia. Within three weeks of treatment, an oral dose level of 300 and the palilalia was no longer evident. The patient had also exhibite and aggressiveness. These conditions disappeared as well and the p sedation. The patient died 9 months later but had no further episodes that time (Serra-Mestres et al, 1996).
3) Trazodone, gradually increased to 300 milligrams/day, effectively SCREAMING (10 to 12 hours per day) of a 84-year-old psychiatric pa episodes stopped 2 weeks after receiving trazodone, and no serious Her repetitive screaming was previously unaltered by trials of either h hydroxyzine (Pasion & Kirby, 1993).
4) Combined therapy with trazodone and tryptophan was effective in dementia (Wilcock et al, 1987). Trazodone 50 milligrams two times a milligrams two times a day, with dosing adjustments to achieve thera effects, was reported effective in improving aggressiveness in 4 of 6 dementia.
5) One case report described benefits of a combination of trazodone L-tryptophan (up to 2.5 grams daily) in the treatment of disordered be in an 82-year-old woman with moderately advanced dementia (Greer

4.5.B.7 Depression

FDA Labeled Indication

a) Overview
FDA Approval: Adult, yes; Pediatric, no
Efficacy: Adult, Effective
Recommendation: Adult, Class IIa
Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE

b) Summary:
Effective for depression with or without prominent anxiety (Prod Info I

c) Adult:
1) In a randomized trial of 379 patients from 16 centers, patients rec milligrams/day, imipramine 100 to 300 milligrams/day, or placebo for Hamilton scores were reduced by 25% in the placebo-treated patient

imipramine-treated patients. Anticholinergic effects were much more
imipramine than in patients treated with trazodone or placebo. Fifteer
44% of the imipramine patients had dry mouth. Blurred vision occurre
imipramine-treated patients. Bowel disturbances occurred in 8% and
urine flow in 1% and 4%, respectively (Gershon & Newton, 1980b).
2) A year-long study was conducted in 79 subjects to evaluate the lo
trazodone compared to imipramine in the treatment of primary depres
(36%) and 7 (24%) patients remained on either trazodone or imipram
found to be more effective in HAM-D illness rating and clinical global
statistical significance not presented). Anticholinergic side effects wer
imipramine group but drowsiness was more frequent in the trazodone
3) In a double-blind study of 60 geriatric patients receiving trazodone
milligrams/day) or imipramine (average dose 145 milligrams/day) for
treatment of unipolar depression, both trazodone and imipramine sho
significant improvement in the Hamilton depression scale for both dru
difference in the Beck depression scale between trazodone and imipr
efffects seen with the trazodone-treated patients (Gerner et al, 1980b
4) Several reports have suggested efficacy of trazodone in the treatr
suggesting the drug has anxiolytic effects separate from its antidepre
One study has reported that trazodone 75 mg daily and diazepam 15
effective than placebo in the treatment of anxiety. In the treatment of
was reported superior to diazepam. Another report indicated that traz
daily had definite anxiolytic properties, but it was not superior to chlor
(Rawls, 1982c).
5) Many clinical trials have compared the effectiveness of trazodone
studies found trazodone to be as effective as imipramine in treating d
than placebo, with trazodone causing more sedation but fewer antich
(Davis & Vogel, 1981; Mann et al, 1980; Gershon et al, 1981; Kellam
Feighner, 1980b; Escobar et al, 1980a).

4.5.B.8 Diabetic neuropathy

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE

b) Summary:

61.3% rate of symptomatic improvement; 22.6% complete relief
Controlled studies needed
Trazodone has been used to treat painful diabetic neuropathy (P
of chronic pain (Manufacturer comment., 5/88.; Panel comment.,

c) Adult:

1) In a prospective, open-label study, 19 of 31 adult patients (61.3%)
diabetic neuropathy with use of oral TRAZODONE 50 or 100 milligra
patients (22.6%) obtained complete relief. Therapeutic failures includ
no relief (100-mg doses) and 8 patients (25.8%) who discontinued th
doses), which included dizziness (5), headache (2), and insomnia (1)
50 mg/day at bedtime; after 2 weeks, doses were raised to 100 mg/d
and had not experienced complete relief (Wilson, 1999).

4.5.B.9 Erectile dysfunction; Diagnosis

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Ineffective
Recommendation: Adult, Class III
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE

b) Summary:

No efficacy shown in the treatment of ERECTILE DYSFUNCTION

c) Adult:

1) Oral trazodone in a total daily dose of 150 milligrams (mg) was no
the treatment of erectile dysfunction in a double-blind, placebo-contro
run-in period, patients randomized to the trazodone treatment group t
morning and two 50-mg capsules in the evening for 4 weeks; patients
identical capsules on the same schedule. To avoid selection bias, the
impotence was not identified until after completion of the treatment re

results demonstrated no significant difference (p=0.98) between the t group treated with placebo. Patients with psychogenic impotence res other patients, 23% versus 15%, respectively, but the difference was (p=0.45) (Meinhardt et al, 1997a).
2) A 3-month course of TRAZODONE 50 milligrams orally at bedtime placebo for treatment of erectile dysfunction, according to a randomiz the group receiving trazodone, 19% reported improved erections com placebo (p less than 0.5) (Costabile & Spevak, 1999).

4.5.B.10 Essential tremor

a) Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category C
See Drug Consult reference: RECOMMENDATION AND EVIDENCE

b) Summary:
Efficacy suggested in early case report, but not supported in subsequ

c) Adult:
1) Trazodone 150 milligrams orally per day was ineffective in the trea in a small, controlled study (Koller, 1989). This study suggests that al neurotransmission are most likely not involved in the pathophysiology
2) Trazodone 100 to 150 milligrams daily, in divided doses, appeared of essential tremor in 2 patients (McLeod & White, 1986). Improveme after 3 weeks of treatment; both patients had not responded to propra milligrams daily).

4.5.B.11 Insomnia

a) Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class III
Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE

b) Summary:
Improved sleep latency and duration in primary insomnia, although d placebo diminished over time

c) Adult:
1) Single-dose TRAZODONE orally at bedtime improved insomnia ir accompanied by a depressive state (concomitant hypnotics were pro study). Patients received bedtime trazodone 50 milligrams (mg)/day f of either 50-mg (n=16), 75-mg (n=6), or 100-mg doses (n=11). Score (HAS) (related to sleep disorders) and the Hamilton Rating Scale for morning awakening, lack of sound sleep, difficulty in initiating sleep) v weeks of trazodone therapy (p values not reported) and showed furth (p=0.01, HAS scores for 50- and 100-mg groups). After 6 weeks, tota prolonged for patients receiving 50-mg (p less than 0.05) or 100-mg c Depressive state symptoms also improved. No one dropped out due considered the 100-mg nightly dose to be the most effective (Mashiko
2) Trazodone 50 milligrams (mg) before bedtime was somewhat effe insomnia in a parallel-group, double-blind, 2-week randomized study zolpidem 10 mg and placebo (n=278). At the end of the first week, th lower in trazodone-treated patients (p=0.01), relative to placebo. How week, sleep latency in trazodone-treated patients (54.5 minutes) did patients treated with placebo (64.7 minutes). Sleep duration was sign with trazodone therapy (366.4 minutes) than with placebo (344.6 min difference in these 2 treatment groups was no longer significant at th clinical significance in both parameters was primarily due to improver over time while the level of improvement with both drugs was essenti week of treatment. Zolpidem was slightly superior to both trazodone a (Walsh et al, 1998a).

4.5.B.12 Migraine, Pediatric; Prophylaxis

a) Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Pediatric, Evidence is inconclusive
Recommendation: Pediatric, Class III

Strength of Evidence: Pediatric, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE

b) Summary:
May be effective in decreasing frequency and duration of headaches
See Drug Consult reference: MIGRAINE - RECOMMENDATIONS FO AND ADOLESCENTS

c) Pediatric:
1) The effectiveness of trazodone in the prophylaxis of PEDIATRIC M measured in a double-blind, placebo-controlled study. Thirty-five pedi subjects received either trazodone (1 milligram/kilogram/day) or place week washout period, the groups were switched to the opposite treat There was no difference in frequency or duration of migraine attacks either the first 12 weeks or during the 4-week washout period. During the trazodone group was significantly improved in relation to both freq compared to the placebo group. The strong placebo effect demonstra not unusual in migraine studies, and the authors concluded that trazo antidepressants in the prophylaxis of pediatric migraine headaches (E

4.5.B.13 Neuroleptic-induced acute akathisia

a) Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE

b) Summary:
Improved symptoms of neuroleptic-induced akathisia in pilot study

c) Adult:
1) Symptoms of neuroleptic-induced akathisia improved following tra schizophrenia. In an open-label, pilot study, schizophrenic patients (n received trazodone (50 milligrams (mg)/day for 1 day, then increased addition to their current, stable, neuroleptic medication for 5 days. Me scores improved significantly from baseline to endpoint (p less than 0 anxiety, and psychosis were also improved from baseline to endpoint of insomnia during treatment. All patients withdrawn from treatment a reemergence of neuroleptic-induced akathisia within 1 day after the n when therapy was re- initiated in one patient, relief was reported with (Stryjer et al, 2003).

4.5.B.14 Schizophrenia

a) Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class III
Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE

b) Summary:
Appears to have no effect on psychotic episodes, but may improve so depression

c) Adult:
1) Trazodone has been evaluated in the treatment of schizophrenia, drug has any effect on psychotic episodes (Deutsch et al, 1977; Sing reports trazodone did appear to improve depression associated with s prove useful in these types of patients. Trazodone apparently does n as opposed to other tricyclic antidepressants (Rawls, 1982c).

4.6 Comparative Efficacy / Evaluation With Other Therapies

Amitriptyline

Chlordiazepoxide

Clorazepate

Desipramine

Dothiepin

Doxepin

Fluoxetine

Imipramine

Mianserin

Triazolam

Venlafaxine

Zolpidem

4.6.A Amitriptyline

Depression

Impaired cognition

Rheumatoid arthritis

4.6.A.1 Depression

a) SUMMARY: Many comparative studies have reported that trazodone i
the treatment of endogenous depression (Rickels & Case, 1982; Goldberg
Finnerty, 1980; Goldberg et al, 1981).

b) In a study of 40 depressed patients (20 agitated, 20 retarded), patients
milligrams (mg) three times a day or trazodone 50 mg three times a day a
washout period (LaPierre et al, 1980). The agitated, depressed patients w
and the retarded, depressed patients who were treated with trazodone we
than the agitated, depressed patients on trazodone and the retarded, dep
Based on multivarient analysis of the clinical global impression, amitriptyli
agitated depressed patients and trazodone was more effective in retarded

c) The efficacy of trazodone was compared with amitriptyline and placebo
depression in 202 outpatients (Rickels & Case, 1982). Patients were rand
milligrams (mg), amitriptyline 25 mg, or lactose placebo. Initial dose of all
for 7 days followed by adjustment to the maximum of eight capsules daily
effective than placebo with clinical efficacy of each agent being similar. Th
toxicity was lower in trazodone-treated patients. This study suggests that
as effective as amitriptyline 75 to 200 mg in treating depression in outpati
less anticholinergic toxicity.

d) No significant difference between trazodone 150 to 300 milligrams (mg
150 mg/day in antidepressant effect or onset was seen in a study of 50 pa
depression (Carney et al, 1984). Trazodone demonstrated an early superi
caused dry mouth more commonly; other side effects were comparable.

4.6.A.2 Impaired cognition

a) The effects of trazodone 100 milligrams (mg), amitriptyline 50 mg, and
healthy, geriatric patients in a double-blind, cross-over study (Burns et al,
tracking multiple stimuli to perform simultaneous tasks (DA), rapidly coord
output (CTT), processing information gathered in short-term memory (VBI
task (vigilance). Amitriptyline impaired DA, CTT, and vigilance, while trazo
authors concluded that trazodone caused less impairment of the central n
amitriptyline.

4.6.A.3 Rheumatoid arthritis

a) Amitriptyline 1 milligram/kilogram (mg/kg) per day for 3 days, followed
reported superior to both desipramine 1 mg/kg/day for 3 days, followed by

trazodone 1.5 mg/kg/day for 3 days, followed by 3 mg/kg/day thereafter, i
depressed and nondepressed patients with rheumatoid arthritis (Frank et
regimens produced significant decreases in pain relative to baseline, only
better than placebo; amitriptyline was associated with a significant reducti
tender joints.

4.6.B Chlordiazepoxide

4.6.B.1 Anxiety

a) No significant difference in improvement of anxiety in patients treated
chlordiazepoxide has been reported (Wheatley, 1976). A double-blind stu
mg/day and chlordiazepoxide for a 4-week period using the Hamilton Anx
from each treatment group were very much improved. Ten trazodone and
were much improved and 10 trazodone and 11 chlordiazepoxide patients
worse. Three patients were not evaluable. For both treatment groups drov
adverse effect with 22 patients experiencing the effect.

4.6.C Clorazepate

Adjustment disorder - Cancer

Adjustment disorder - HIV infection

4.6.C.1 Adjustment disorder - Cancer

a) SUMMARY: TRAZODONE may have equal or greater efficacy compa
treatment of adjustment disorders in breast-cancer patients; trazodone an
and tolerability.

b) A small, double-blind pilot study (n=23; efficacy analysis=18) found tha
TRAZODONE had equal or greater benefit compared with CLORAZEPAT
adjustment disorders (DSM-III-R) accompanied by anxiety or depressed r
emotion and conduct (Razavi et al, 1999). Included were women with a 1
Hospital Anxiety and Depression Scale (HADS). Enrollees were randomiz
milligrams (mg)/day (n=13) or oral clorazepate 10 mg/day (n=10), with up
days. Trazodone mean daily dose was 111.5 mg, and clorazepate, mean
investigator ratings on the Clinical Global Impression (CGI) scale showed
group (10 of 11) and 57.1% of the clorazepate group (4 of 7) were 'very m
'minimally improved' (p=0.14). Improvement on the Global Severity Index
trazodone-treated patients (-0.68) compared with clorazepate-treated pati
adverse events rated as severe occurred in the trazodone and 5 severe a
clorazepate group. One patient receiving trazodone withdrew due to adve

4.6.C.2 Adjustment disorder - HIV infection

a) SUMMARY: TRAZODONE may be more efficacious than CLORAZEP
adjustment disorders in patients with HIV; trazodone appeared to have gr

b) A small, double-blind trial (n=21) found a 28-day course of TRAZODO
treatment than CLORAZEPATE for HIV-positive patients with adjustment
accompanied by anxiety or depressed mood and/or mixed disturbance of
were patients with a 14 or greater score on the French Hospital Anxiety a
Enrollees were randomized to oral trazodone 50 milligrams/day (mg/day)
mg/day (n=11), with upward titration of both drugs over 5 days. After 28 d
Clinical Global Impression (CGI) scale showed that 80% of the trazodone
clorazepate group were 'very much improved', 'improved', or 'minimally im
appeared to be more marked in the trazodone group for depressive symp
slightly more pronounced in the clorazepate group for anxiety symptoms (
adverse event occurred in 8 clorazepate-treated patients and 6 trazodone
treatment, doses were reduced in 1 patient treated with trazodone and 2 t
adverse effects. More adverse events and a higher number of severe adv
clorazepate treatment. One patient in each group withdrew due to adverse
to lack of efficacy (De Wit et al, 1999).

4.6.D Desipramine

4.6.D.1 Depression

a) A double-blind study of 30 patients with endogenous, endoreactive, re
compared the effects of trazodone 200 to 400 mg/day to desipramine. Aft

similar results for both drugs for the parameters of depression, suicide, ins agitation as measured by the Hamilton Rating scale. Trazodone-treated p anxiety than did desipramine treated patients (Piccione et al, 1975).

4.6.E Dothiepin

4.6.E.1 Depression

a) No significant differences in efficacy or type of adverse effects were se with trazodone in 196 patients with mixed anxiety/depression (Moon et al, preferable to dothiepin because of lesser severity of side effects. In a 6-w study, either trazodone 150 mg (n=97) or dothiepin 75 mg (n=99) were ac included the 17- item and 21-item Hamilton Depression Rating Scales (HI Scale (HARS), and the investigator's judgement of global severity and imp improvement in depression scores (P=0.0001) and anxiety scores (P=0.0 Global severity significantly improved in both groups; at week 6, improven improved for 54 patients (71%) in the trazodone group and 52 patients (69 Although types of adverse effects were similar for both groups, the trazod proportion of mild symptoms compared with the dothiepin group; at weeks reported a lower percentage of symptoms as severe.

b) Dothiepin (75 to 150 mg/d) and trazodone (150 to 300 mg/d) were equ depression in a single-blind, 24-week study of 35 depressed patients (Pie were not matched for severity of depression which varied greatly among t completed the 6-month trial. Both treatment groups showed significant rec ratings from 4 weeks onward, and there was significant improvement in th first week onward. There were no significant differences between the 2 gr Drowsiness was the most frequent side effect in the trazodone-treated gro were more common in the dothiepin-treated group.

c) In a 6-week, double-blind study, lofepramine and dothiepin had similar depression in elderly patients (range 65 to 88 years); lofepramine had an incidence of dry mouth, blurred vision, and drowsiness (Fairbairn et al, 19 dothiepin-treated group and 6 in the lofepramine-treated group did not co patients in each group. Many of the participants were receiving other med phenothiazines, benzodiazepines, and chlormethiazole, throughout the tri lofepramine 70 mg/d were given for 1 week, then doses were doubled for measured on the Montgomery-Asberg Depression Scale (MADRS) at wee improvement occurred in both treatment groups. There were not significar Compared with dothiepin-treated patients, the lofepramine-treated patient and day-time drowsiness; only 1 patient in each group withdrew from the

4.6.F Doxepin

4.6.F.1 Depression

a) No significant difference in safety or efficacy was seen in a comparison during weeks 1, 3, and 6 was 125 milligrams (mg), 221 mg, and 246 mg) during weeks 1, 3, and 6 was 58 mg, 105 mg, and 127 mg) in 30 outpatie in a 6-week, double-blind, parallel study (Himmelhoch, 1986).

b) No significant difference was reported in a double-blind study of 101 p trazodone and doxepin in the treatment of depression (Murphy & Ankier,

4.6.G Fluoxetine

Depression

Mania

4.6.G.1 Depression

a) Fluoxetine was as effective as trazodone in the treatment of major dep outpatient study involving 43 patients (Debus et al, 1988). The mean final fluoxetine in the responding patients were 284 and 29 mg daily, respectiv corresponding doses were 327 and 33 mg, respectively. HAM-D scores w fluoxetine when compared to trazodone and sleep was improved to a grea Adverse effects occurred to a similar degree with each agent with the exc frequent with fluoxetine) and dizziness (more frequent with trazodone).

b) A six-week, double-blind trial compared fluoxetine (21 patients) with tra treatment of major depression (Perry et al, 1989). Although trazodone app

greater improvement in HAM-D and Clinical Global Impressions scores at
not statistically significant at 4, 5, and 6 weeks. The authors surmise that
been due to: an insufficient fluoxetine dose early in the trial (mean daily d
during week 3 were 21 mg and 241 mg, respectively), which was mitigate
in fluoxetine doses compared to trazodone doses; a slower onset of antid
compared to trazodone; or a higher incidence of depressive illness lasting
fluoxetine group (67%) than in the trazodone group (37%, reported incorre
authors cite the statistically significant fluoxetine-associated weight loss s
lb/patient) as a clinically significant advantage for this agent, trazodone wa
loss in this study (mean 0.13 lb/patient), and the weight losses exhibited b
significantly different.

4.6.G.2 Mania

a) In literature reports of drug-induced mania caused by fluoxetine or traz
manifested symptoms of mania more slowly than trazodone-treated patien
onset of mania in fluoxetine-treated patients was significantly longer than
days (range = 10 to 154 days) versus 16 days (range =4 to 70 days) resp

4.6.H Imipramine

4.6.H.1 Depression

a) Trazodone is not therapeutically superior to imipramine, but its side eff
et al, 1979; Feighner, 1980; Gerner et al, 1980; Escobar et al, 1980; Work
1984). Anticholinergic side effects occurred more frequently in patients tre
treated with trazodone in a multi-centre trial (Gershon & Newton, 1980).

b) A multicenter trial involving 379 patients treated with trazodone 200 to
imipramine 100 to 300 mg/day or placebo for 21 to 24 days demonstrated
of equal efficacy (Gershon & Newton, 1980). Another study involving 28 p
depression receiving an average trazodone dose of 287 mg/day or an ave
mg/day for 28 days also demonstrated equal effectiveness between the 2
results of a double-blind study involving 45 patients suggested that trazod
a more rapid and prolonged improvement than did imipramine 100 to 300
double-blind controlled study of 40 patients with endogenous depression,
300 mg) produced more improvement of Hamilton depression scale score
trazodone (maximum daily dose 600 mg) (Escobar et al, 1980).

c) Seventy-four patients were enrolled in a nonrandomized study with pla
evaluate the efficacy of imipramine, alprazolam, and trazodone in the trea
al, 1986). Twenty-nine patients were assigned to imipramine, 28 to trazod
treatment. All patients were treated with placebo for 3 weeks and then blir
for clinical response and side effects. Both imipramine and alprazolam we
agoraphobia, however, alprazolam had a faster onset of action. Clinical re
one week with alprazolam therapy and were generally not observed in imi
third or fourth week of therapy. Trazodone therapy was considered not eff
agoraphobia.

d) In a double-blind controlled study, imipramine and placebo were comp
treatment of 45 hostile patients with primary depression. The mean doses
6.26 capsules/day of 50 milligrams (mg) trazodone, 6.37 capsules/day of
capsules/day of placebo. Three of 17 patients in the trazodone groups ex
Hamilton total score on or before day 7 of therapy. On day 14, 8 patients
achieved this level of improvement. Of the imipramine- treated patients, n
improvement at day 7. However, by day 14, eight patients in the group ha
reduction in total Hamilton differences in the subjects tested through the s
Clinical global impressions showed a highly significant difference betweer
proportion of improved patients at the end of 28 days of treatment. Global
trazodone was significantly (p less than 0.01) better than placebo for tens
behavior and difficulty in sleeping. It was significantly (p less than 0.05) be
lacking energy behavior and anxious, worried, afraid behavior and concer
was slightly better (p less than 0.10) for irritable, annoyed, impatient or an
most frequent side effect experienced by trazodone treated patients. Antic
common effects in the imipramine group (Feighner, 1980).

e) Ten institutions participated in a multi-center, double-blind, placebo-co
trazodone or imipramine in 263 in-patients. Inclusion criteria included prim
endogenous type, minimum score of 18 on the Hamilton Rating Scale for
7 of 21 symptoms in 3 of 5 categories of the symptom profile for depressic
100 mg daily for trazodone or imipramine. At the end of 28 days, 113 patic
efficacy or side effects. Drop out rates were 37% each for imipramine and
Both drugs were statistically superior to placebo in improvement of HAM-

There was no significant difference between trazodone and imipramine. B
caused statistically significantly fewer anticholinergic side effects, 19% an
imipramine 52% (Gershon, 1981).

4.6.I Mianserin

Depression

Erectile dysfunction

4.6.I.1 Depression

a) SUMMARY: Several clinical trials have shown mianserin to be equally
treatment of depression (Altamura et al, 1989; Bucknall et al, 1988; Beaur
double-blind trial, 100 to 200 milligrams (mg) trazodone was compared wi
(Beaumont et al, 1984) . Although there were significant dropouts in the m
equally effective. Due to side-effects associated with mianserin, trazodone
(30 to 80 mg) was compared with trazodone (150 to 400 mg) and placebo
study involving 16 cardiac patients (Bucknall et al, 1988) . Both drugs wer
significant cardiovascular effects detected. A trend toward hypotension wa
b) Oral mianserin 30 to 120 milligrams (mg) daily was reported as effectiv
mg daily in the treatment of mild-to-moderate depression (endogenous or
(Bennie et al, 1984).
c) Trazodone in doses of 100 to 200 milligrams (mg) daily was reported s
(60 to 120 mg daily) and diazepam (15 to 30 mg daily) in reducing sympto
study over 3 to 6 weeks compared the antidepressant and anxiolytic effec
diazepam in patients with mild to moderate depression (with or without an
superior to diazepam in improving the patients ability to concentrate and r
Significantly more patients developed side effects with mianserin than eith
(Richards et al, 1982).
d) Clinical outcomes were equal in all 3 groups of patients in a double-bli
trazodone, mianserin, and amitriptyline in the treatment of 106 elderly dep
associated with fewer overall side effects (Altamura et al, 1989).

4.6.I.2 Erectile dysfunction

a) Trazodone was more effective than mianserin, ketanserin, or placebo i
double-blind, randomized, placebo-controlled trial. One hundred patients v
trazodone 50 milligrams (mg) three times a day, ketanserin 20 mg twice a
times a day, or placebo. Patients were evaluated after 30 days. Positive re
of trazodone-treated patients, 19.1% of ketanserin-treated patients, 31.6%
and 13.6% with placebo. Response to trazodone was significantly greater

4.6.J Triazolam

1) Adverse Effects
a) In a comparison of adverse effects of triazolam in doses of 0.125, 0.25
trazodone in doses of 50, 100, and 200 mg and placebo, trazodone did no
of study tasks. Triazolam, in the highest dose, significantly impaired learni
Subjective ratings of drug effect and sedation demonstrated comparable d
drugs, indicating some equivalence on a behavioral basis. Test subjects v
0.5, 1, 1.5, 2, 2.5, 3, 4, 5, and 6 hours after drug administration. Testing o
rated by subjects and/or observers, including: Profile of Mood States (POI
Inventory (ARCI); drug effect questionnaire; end-of-day questionnaire; obs
learning, recall, and performance measures; repeated acquisition procedu
Symbol-Substitution Test (DSST); circular lights test; balance task; and pi
did not investigate the relative abuse potential of the drugs, but the author
in this area would be useful because of the high incidence of anxiety and
histories of drug abuse (Rush et al, 1997).

4.6.K Venlafaxine

4.6.K.1 Depression

a) Venlafaxine produced antidepressant efficacy comparable to trazodon
controlled trial. In this outpatient study, 225 patients were randomized to v
(mg) per day, trazodone (mean = 300 mg/day) or placebo. Response rate
respectively. Venlafaxine appeared to be more effective than trazodone ir
disturbance and retardation factor as evidenced on the Hamilton Rating S

was noted that this effect may have been due to the sedating nature of tra common in the venlafaxine group compared to dizziness and somnolence (Cunningham et al, 1994).

4.6.L Zolpidem

4.6.L.1 Insomnia

a) Zolpidem 10 milligrams (mg) was slightly superior to trazodone 50 mg increasing sleep duration in a 2-week, randomized, parallel-group, double The periods of sleep latency at the end of week 1 were 48.2 minutes and treated with zolpidem or trazodone, respectively (p less than 0.037), but d end of week 2 (64.7 minutes versus 54.5 minutes, respectively). The slee in both groups compared to the group treated with placebo (p=0.001). Pat reported longer sleep durations at week 1 than those treated with trazodo minutes, respectively) with a trend toward significance (p less than 0.060) between drugs at week 2. The reduction in clinical significance in both pa compared with placebo, was primarily due to improvement in the placebo level of improvement with both drugs was essentially unchanged in the se of the slightly shorter period of sleep latency, zolpidem may have some ac treatment of primary insomnia (Walsh et al, 1998).

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Last Modified: July 02, 2009

DRUGDEX® Evaluations

DEXTROAMPHETAMINE

0.0 Overview

1) Class
- **a)** This drug is a member of the following class(es):
  Amphetamine (class)
  CNS Stimulant

2) Dosing Information
- **a)** Dextroamphetamine Sulfate
  - **1)** Adult
    - **a)** Narcolepsy
      - **1)** immediate-release, 5 to 60 mg ORALLY in 2 to 3 divided doses daily (Prod Info dextroamphetamine s
      - **2)** sustained-release, 5 to 60 mg ORALLY as single daily dose (Prod Info DEXEDRINE(R) oral tablets, s
  - **2)** Pediatric
    - **a)** (immediate-release) not FDA approved for children under 3 yr of age with attention deficit hyperactivity dis
    - **b)** (sustained-release) not FDA approved for children under 6 yr of age with attention deficit hyperactivity dis
    sustained-release oral capsules, 2007)
      - **1)** Attention deficit hyperactivity disorder
        - **a)** (immediate-release, age 3 to 5 yr) initial, 2.5 mg ORALLY once daily, increase by 2.5 mg/day at
        mg/day (Prod Info dextroamphetamine sulfate oral tablets, 2007)
        - **b)** (immediate-release, age 6 yr and older) initial, 5 mg ORALLY once or twice daily, increase by 5 r
        40 mg/day (Prod Info dextroamphetamine sulfate oral tablets, 2007)
        - **c)** (sustained-release, age 6 yr and older) initial, 5 mg ORALLY once or twice daily, increase by 5-m
        response; MAX 40 mg/day (Prod Info DEXEDRINE(R) oral tablets, sustained-release oral capsules,
      - **2)** Narcolepsy
        - **a)** (age 6 to 12 yr) 5 mg/day ORALLY, increase by 5 mg/day at 1 wk intervals to optimum response
        should be dosed once daily, immediate-release doses may be given at intervals of 4 to 6 hours (Pro
        2007; Prod Info DEXEDRINE(R) oral tablets, sustained-release oral capsules, 2007)
        - **b)** (age 12 yr and older) 10 mg/day ORALLY, increase by 10 mg/day at 1 wk intervals to optimum re
        tablets should be dosed once daily, immediate-release doses may be given at intervals of 4 to 6 hou
        tablets, 2007; Prod Info DEXEDRINE(R) oral tablets, sustained-release oral capsules, 2007)

3) Contraindications
- **a)** Dextroamphetamine Sulfate
  - **1)** advanced arteriosclerosis (Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006)
  - **2)** agitated states; may aggravate symptoms (Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tab
  - **3)** cardiovascular disease, symptomatic (Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets,
  - **4)** concomitant use of monoamine oxidase inhibitors (MAOI), or within 14 days of MAOI use; hypertensive crisis r
  release oral capsules, oral tablets, 2006)
  - **5)** drug dependence, history of; potential for abuse (Prod Info DEXEDRINE(R) sustained-release oral capsules, c
  - **6)** glaucoma (Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006)
  - **7)** hypersensitivity/idiosyncrasy to sympathomimetic amines (Prod Info DEXEDRINE(R) sustained-release oral ca
  - **8)** hypertension, moderate to severe (Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 20
  - **9)** hyperthyroidism (Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006)

4) Serious Adverse Effects
- **a)** Dextroamphetamine Sulfate
  - **1)** Body temperature above normal
  - **2)** Central nervous system stimulation (Severe)
  - **3)** Dead - sudden death
  - **4)** Hypersensitivity disorder
  - **5)** Psychotic disorder
  - **6)** Tachyarrhythmia

5) Clinical Applications
- **a)** Dextroamphetamine Sulfate
  - **1)** FDA Approved Indications
    - **a)** Attention deficit hyperactivity disorder
    - **b)** Narcolepsy

1.0 Dosing Information

Drug Properties

Storage and Stability

Adult Dosage

Pediatric Dosage

1.1 Drug Properties

A) Information on specific products and dosage forms can be obtained by referring to the Tradename List (Product In

B) Synonyms

D-Amphetamine
Dexamfetamine
Dexamphetamine
Dextroamphetamine
Dextroamphetamine Sulf
Dextroamphetamine Sulfate

1.2 Storage and Stability

A) Dextroamphetamine Sulfate

1) Preparation

a) Oral route

1) Avoid late evening doses due to resulting insomnia (Prod Info DEXEDRINE(R) oral tablets, sustained Dexedrine(R), 2002)

2) Give first dose of immediate-release tablet on awakening, and additional doses at intervals of 4 to 6 h

B) Oral route

1) Dextroamphetamine tablets should be stored in well-closed containers, and the elixir in tight, light-resistant cor degrees Centigrade, preferably at 15 to 30 degrees Centigrade (59 to 86 degrees F); freezing of the elixir should should be stored at temperature, between 20 and 25 degrees C (68 and 77 degrees F) (Prod Info Dexedrine(R), (R) capsules, 1999; Prod Info Dextrostat(R), 1998).

1.3 Adult Dosage

1.3.1 Normal Dosage

1.3.1.A Cataplexy - Narcolepsy

See Drug Consult reference: NARCOLEPSY AND CATAPLEXY - DRUG THERAPY

1.4 Pediatric Dosage

1.4.1 Normal Dosage

1.4.1.A Dextroamphetamine Sulfate

1.4.1.A.1 Oral route

Attention deficit hyperactivity disorder

Narcolepsy

1.4.1.A.1.a Attention deficit hyperactivity disorder

1) Immediate-Release

a) For children 3 to 5 years of age with attention deficit disorder, the recommended initial oral d milligrams/day. The daily dosage is increased by 2.5 milligrams at weekly intervals until the opti should rarely exceed 40 milligrams. The first dose should be given on awakening if tablets or lic intervals of 4 to 6 hours (Prod Info dextroamphetamine sulfate oral tablets, 2007).

b) For children 6 years of age and older with attention deficit disorder, the recommended initial once or twice daily. The daily dosage is increased by 5 milligrams at weekly intervals until the o total daily dose exceed 40 milligrams . The first dose should be given on awakening, with subse (Prod Info dextroamphetamine sulfate oral tablets, 2007).

2) Extended-Release

a) For children aged 6 years and older with attention deficit disorder, the recommended initial d release is 5 milligrams (mg) once or twice daily, with 5-mg increases at weekly intervals until the daily dose of 40 mg is rarely necessary (Prod Info DEXEDRINE(R) oral tablets, sustained-relea

1.4.1.A.1.b Narcolepsy

1) Immediate-release

a) For children 6 to 12 years of age with narcolepsy, the recommended initial dose of oral dextı milligrams (mg) daily, with 5-mg increases at weekly intervals until the optimum dose is attainec tablets, 2007).
b) For children 12 years of age and older with narcolepsy, the initial dose of oral dextroamphet 10-mg increases at weekly intervals until the optimum dose is attained. The first dose should be or 2) spaced at intervals of 4 to 6 hours. Exceeding a total dose of 40 mg/day is rarely necessai recommended to determine if there is a recurrence of behavioral symptoms sufficient to require dextroamphetamine sulfate oral tablets, 2007).

2) Sustained-release
a) For children 6 to 12 years of age with narcolepsy, the recommended initial dose of oral dextı (mg) once daily, with 5-mg increases at weekly intervals until the optimum dose is attained (Pro release oral capsules, 2007).
b) For children 12 years of age and older with narcolepsy, the recommended initial dose of ora once daily, with 10-mg increases at weekly intervals until the optimum dose is attained (Prod In release oral capsules, 2007).
c) Dosage should be reduced if adverse reactions become intolerable (Prod Info DEXEDRINE(2007).

2.0 Pharmacokinetics

Onset and Duration

Drug Concentration Levels

ADME

2.1 Onset and Duration

A) Onset
1) Initial Response
a) 2 to 3 hours (Angrist et al, 1987).
B) Duration
1) Single Dose
a) 4 to 24 hours (Johnson et al, 1971).
1) The duration of the effects may be prolonged by alkalinization or shortened by acidification of the urin
2) Each dextroamphetamine sustained-release capsule is prepared such that an initial dose is promptly released gradually over a prolonged period of time. Dextroamphetamine's therapeutic effects may persis

2.2 Drug Concentration Levels

A) Time to Peak Concentration
1) Oral, tablets: 60 to 180 minutes (Prod Info Dexedrine(R), dextroamphetamine sulfate tablets and Spansule(R) 1998a).
2) Oral, extended-release capsules: approximately 8 hours (Prod Info Dexedrine(R), dextroamphetamine sulfate
3) Oral, extended-release capsules: approximately 7 hours (Prod Info Adderall XR(TM), 2002);(Tulloch et al, 200
B) URINE ASSAY
1) A semiquantitative EMIT(R) homogenous enzyme immunoassay is available for measurement of the commonl limit (sensitivity) is 2 mcg/mL for amphetamine or methamphetamine. The assay also detects phenylethylamines a to eliminate interference from over-the-counter cold medications that contain ephedrine, pseudoephedrine, or phe assay is also available that detects as little as 0.7 mcg/mL of amphetamine; this method correlated well with GLC studies (Prod Info EMIT(R) urine amphetamine assay, 1983).

2.3 ADME

Absorption

Distribution

Metabolism

Excretion

Elimination Half-life

Extracorporeal Elimination

2.3.1 Absorption
A) Bioavailability
1) well-absorbed (Becket & Tucker, 1968; Becket et al, 1968).
a) The bioavailability of the extended-release capsule is similar to that of the immediate-release tablet (F sulfate tablets and Spansule(R) capsules, 1999a).
B) Effects of Food
1) none (Angrist et al, 1987).
a) Absorption of the extended-release capsule is similar in either the fed or fasted state (Prod Info Dexe Spansule(R) capsules, 1999a).
b) Food does not affect absorption, but it prolongs time to reach maximal plasma concentration by 2.5 h high-fat meal) (Prod Info Adderall XR(TM), 2002);(Tulloch et al, 2002).

2.3.2 Distribution
A) Distribution Sites
1) Tissues and Fluids
a) CEREBROSPINAL FLUID
1) Cerebrospinal fluid levels of dextroamphetamine are approximately 80% of plasma levels (Angga
B) Distribution Kinetics
1) Volume of Distribution
a) 6.11 L/kg (Anggard, 1970a).

2.3.3 Metabolism
A) Metabolism Sites and Kinetics
1) Liver, extensive
a) Amphetamine is hepatically metabolized to both acidic and basic metabolites primarily by deaminatio et al, 1972; Anggard et al, 1973b; Beckett & Shenoy, 1973). Dextroamphetamine is the dextrorotatory isc behave in a similar fashion.
B) Metabolites
1) Hippuric acid (Davies et al, 1971)(Caldwell et al, 1972; Anggard et al, 1973b; Sever et al, 1973).
2) Benzoic acid (Davies et al, 1971)(Caldwell et al, 1972; Anggard et al, 1973b; Sever et al, 1973).
3) Norephedrine (Davies et al, 1971)(Caldwell et al, 1972; Anggard et al, 1973b; Sever et al, 1973).
4) 4-hydroxynorephedrine (Davies et al, 1971)(Caldwell et al, 1972; Anggard et al, 1973b; Sever et al, 1973)
5) Benzyl methyl ketone (Davies et al, 1971)(Caldwell et al, 1972; Anggard et al, 1973b; Sever et al, 1973).

2.3.4 Excretion
A) Kidney
1) Renal Excretion (%)
a) 17% to 73% (Anggard et al, 1973b).
1) The urinary excretion of dextroamphetamine is dependent on pH; at a pH of less than 6.6, 67% t urine (Olin, 1990; Anggard et al, 1973b; Caldwell et al, 1972; Beckett & Shenoy, 1973). At a urine pH unchanged in the urine (Anggard et al, 1973b).

2.3.5 Elimination Half-life
A) Parent Compound
1) ELIMINATION HALF-LIFE
a) 7 to 34 hours (Prod Info Dextrostat(R), 1998a; Anggard et al, 1973b).
1) The half-life of dextroamphetamine is dependent on urine pH. In patients with a urine pH of less t in patients with a urine pH of greater than 6.7, the half-life ranges from 17 to 34 hours (Anggard et a
2) Average half-life of dextroamphetamine tablets is 10 to 12 hours (Prod Info Dexedrine(R), dextro capsules, 1999a; Prod Info Dextrostat(R), 1998a). Half-life of the extended-release capsules is appr

2.3.6 Extracorporeal Elimination
A) Hemodialysis
1) Dialyzable: Yes (Zalis & Parmley, 1963).
a) Hemodialysis has been demonstrated to enhance the elimination of amphetamine in animals (Zalis & procedure in human overdoses has not been proven. Dextroamphetamine is the dextrorotatory isomer o behave in a similar fashion.
B) Peritoneal
1) Dialyzable: Yes (Zalis & Parmley, 1963).
a) Peritoneal dialysis has been demonstrated to enhance the elimination of amphetamine is animals (Za procedure in human overdoses has not been proven. Dextroamphetamine is the dextrorotatory isomer o behave in a similar fashion.

3.0 Cautions

Contraindications

Precautions

Adverse Reactions

Teratogenicity/Effects in Pregnancy/Breastfeeding

Drug Interactions

3.0.A Black Box WARNING
1) Dextroamphetamine Sulfate
a) Oral (Tablet; Capsule, Extended Release)
1) Amphetamines have a high potential for abuse. Administration of amphetamines for prolonged periods of avoided. Particular attention should be paid to the possibility of subjects obtaining amphetamines for non-the drugs should be prescribed or dispensed sparingly. Misuse of amphetamines may cause sudden death and s DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006).

3.1 Contraindications
A) Dextroamphetamine Sulfate
1) advanced arteriosclerosis (Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006)
2) agitated states; may aggravate symptoms (Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tab
3) cardiovascular disease, symptomatic (Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets,
4) concomitant use of monoamine oxidase inhibitors (MAOI), or within 14 days of MAOI use; hypertensive crisis r release oral capsules, oral tablets, 2006)
5) drug dependence, history of; potential for abuse (Prod Info DEXEDRINE(R) sustained-release oral capsules, c
6) glaucoma (Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006)
7) hypersensitivity/idiosyncrasy to sympathomimetic amines (Prod Info DEXEDRINE(R) sustained-release oral ca
8) hypertension, moderate to severe (Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 20
9) hyperthyroidism (Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006)

3.2 Precautions
A) Dextroamphetamine Sulfate
1) amphetamine misuse; may cause sudden death and serious cardiovascular events (Prod Info DEXEDRINE(R) 2006)
2) bipolar disorder, comorbid; may precipitate a mixed/manic episode (Prod Info DEXEDRINE(R) sustained-relea
3) cardiovascular conditions which may be compromised by increases in blood pressure or heart rate (eg, pre-ex myocardial infarction, or ventricular arrhythmia) (Prod Info DEXEDRINE(R) sustained-release oral capsules, oral t
4) EEG abnormalities, especially with history of; may lower convulsive threshold (Prod Info DEXEDRINE(R) susta
5) psychosis, pre-existing; may exacerbate symptoms of behavior disturbance and thought disorder (Prod Info DI oral tablets, 2006)
6) seizures, especially with a history of; may lower convulsive threshold (Prod Info DEXEDRINE(R) sustained-rel
7) structural cardiac abnormalities/conditions, serious, especially in children and adolescents; sudden death has (Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006)
8) tartrazine (FD&C Yellow No. 5) sensitivity, especially with aspirin sensitivity; may cause allergic-type reaction (release oral capsules, oral tablets, 2006)
9) tics, motor and phonic, history of; risk of exacerbation (Prod Info DEXEDRINE(R) sustained-release oral capsu
10) Tourette's syndrome, history of; risk of exacerbation (Prod Info DEXEDRINE(R) sustained-release oral capsu

3.3 Adverse Reactions

Cardiovascular Effects

Dermatologic Effects

Endocrine/Metabolic Effects

Gastrointestinal Effects

Hematologic Effects

Immunologic Effects

Neurologic Effects

Psychiatric Effects

Reproductive Effects

Other

3.3.1 Cardiovascular Effects

3.3.1.A Dextroamphetamine Sulfate

Dead - sudden death

Increased blood pressure

Palpitations

Tachyarrhythmia

3.3.1.A.1 Dead - sudden death

a) Incidence: rare

b) Children and Adolescents - With Preexisting Cardiac Risk

1) Over the 5-year period (1999 to 2003), the US Food and Drug Administration (FDA) received 12 among pediatric patients using Adderall(R) for ADHD. Five of the 12 cases were found to have card (1), idiopathic hypertrophic subaortic stenosis (1), bicuspid aortic valve (1), and cardiac hypertrophy increase or toxic amphetamine level (2), family history of ventricular arrhythmia (1), extreme exercis who were all male, ranged from 7 to 16 years (mean 12 years); duration of therapy ranged from 1 da (1), 20 mg (5), 30 mg (1), 40 mg (1), and 50 mg (1), with dose not reported in 3 cases. With respect mentioned in 9 cases and 1 other medication noted in 3 cases. Eleven of the 12 were autopsied. Th Canada (the Canadian agency which regulates drugs) to suspend marketing of Adderall XR(R) in th professionals that Adderall(R) products should not be used in adults or children with structural cardia

2) In children with structural cardiac abnormalities, sudden death has been reported in association v (Prod Info Adderall XR(R), 2004).

c) Children and Adolescents - Healthy

1) A retrospective, case-controlled study examines the association between stimulant medication, i unexplained sudden death in healthy children and adolescents. In a collection of data from state vita States, 564 cases of sudden death in children and adolescents between the ages of 7 to 19 years w who died as passengers in motor vehicle accidents. The study determined that 1.8% (n=10) of youth were taking stimulant medication compared with only 0.4% (n=2) of youths in the motor vehicle acci 74.9; p=0.02). Limitations to this study included the time lag between the youths stimulant medicatio recall of information regarding clinical diagnoses, inconsistent postmortem inquiry, and the exclusion authors stated that this finding should be considered when evaluating the overall risk and benefit of adolescents (Gould et al, 2009). Given the limitations of this study, the U.S. Food and Drug Adminis and benefits associated with stimulant medications (US Food and Drug Administration, 2009).

3.3.1.A.2 Increased blood pressure

a) Cardiovascular toxicities, including elevations of blood pressure, have been reported during dextroam 1988). One clinician reports a case of acute myocardial infarction that was complicated by chronic amph

3.3.1.A.3 Palpitations

a) Cardiovascular toxicities, including palpitations, have been reported during dextroamphetamine thera reports a case of acute myocardial infarction that was complicated by chronic amphetamine abuse (Orze

3.3.1.A.4 Tachyarrhythmia

a) Cardiovascular toxicities, including tachycardia, have been reported during dextroamphetamine thera reports a case of acute myocardial infarction that was complicated by chronic amphetamine abuse (Orze

b) In children with structural cardiac abnormalities, sudden death has been reported in association with Info Adderall XR(R), 2004).

c) Increases in heart rate and blood pressure were reported with use of dextroamphetamine. In a placeb effects, dextroamphetamine 30 mg in 3 divided doses (midnight, 0400 hours, and 0800 hours) was admi pilots during sleep-deprivation periods (Caldwell, 1996). Heart rates were elevated from 2 hours after the

third dose. In females, average heart rates associated with dextroamphetamine and placebo were 84 an
males, these rates were 70 and 63 bpm, respectively. Systolic blood pressure (SBP) in males was eleva
hours after the third dose; SBP in females was increased 1 hour after the third 10-mg dose and remaine
pressure (DBP) was elevated from 2 hours after the second dose and continued for 6 hours after the las
dextroamphetamine and placebo was 128 and 120 mmHg, respectively, and DBP was 72 and 69 mmHg
respectively.

3.3.2 Dermatologic Effects

3.3.2.A Dextroamphetamine Sulfate

Rash

Urticaria

3.3.2.A.1 Rash

a) Rash has been associated with amphetamine use (Prod Info ADDERALL XR(R) extended-release or

3.3.2.A.2 Urticaria

a) Urticaria has been associated with amphetamine use (Prod Info ADDERALL XR(R) extended-release

3.3.3 Endocrine/Metabolic Effects

3.3.3.A Dextroamphetamine Sulfate

3.3.3.A.1 Hyperthyroidism

a) One group of clinicians reports 4 cases of amphetamine abuse that resulted in an elevated free thyro
and symptoms of hyperthyroidism (Morely et al, 1980). The levels of T4 appeared to be inappropriately e
HYPERTHYROXINEMIA appeared to be secondary to an increase in circulating TSH. All levels returned
amphetamine in 2 of the 4 cases; the remaining 2 patients refused further follow-up after the initial levels
dextrorotatory isomer of amphetamine and would be expected to behave in a similar fashion.

b) The signs and symptoms of amphetamine abuse are similar to those of THYROTOXICOSIS; it is unc
secondary to hyperthyroxinemia (Morely et al, 1980).

3.3.4 Gastrointestinal Effects

3.3.4.A Dextroamphetamine Sulfate

3.3.4.A.1 Gastrointestinal tract finding

a) A variety of gastrointestinal effects including DRY MOUTH, UNPLEASANT TASTE, DIARRHEA, CON
have been reported during dextroamphetamine therapy (Prod Info Dexedrine(R), dextroamphetamine su
Prod Info Dextrostat(R), 1998).

3.3.5 Hematologic Effects

3.3.5.A Dextroamphetamine Sulfate

3.3.5.A.1 Leukemia

a) One report describes a case of a 24-year-old white male who ingested 8 to 16 tablets/day of amphet
myeloblastic leukemia that was heralded by weakness, sweating, calf pain, and fever (Berry, 1966). Des
rapidly deteriorated into coma, apnea, and death. A possible cause and effect relationship with chronic a
drug possesses a benzene ring that has been known to cause hematologic effects. Dextroamphetamine
and would be expected to behave in a similar fashion.

3.3.7 Immunologic Effects

3.3.7.A Dextroamphetamine Sulfate

3.3.7.A.1 Hypersensitivity disorder

a) Hypersensitivity reactions, including angioedema and anaphylaxis, have been associated with amphe
extended-release oral capsules, 2006).

3.3.9 Neurologic Effects

3.3.9.A Dextroamphetamine Sulfate

Central nervous system finding

Cerebrovascular disease

Disturbance in speech

Extrapyramidal sign

Gilles de la Tourette's syndrome

3.3.9.A.1 Central nervous system finding

a) Children with attention deficit hyperactive disorder (ADHD) who have normal electroencephalograms they receive stimulant therapy for ADHD (METHYLPHENIDATE, DEXTROAMPHETAMINE, or combinat DEXTROAMPHETAMINE (Adderall(R)). However, children with epileptiform EEGs may have considerab occurrence of seizure may or may not be attributable to use of the stimulant. These conclusions were ba epilepsy who were diagnosed with ADHD. All had EEGs prior to parental choosing of stimulant treatmen children's ADHD. Overall, 36 children (15.4%) demonstrated epileptiform abnormalities compared with 1 abnormalities, 30 received stimulant treatment for ADHD. Three of the 30 who received stimulant therap including a 9-year-old female, a 7-year-old male, and a 6-year- old male. The girl was treated uneventful months after withdrawal of methylphenidate experienced a 4-minute generalized tonic-clonic seizure. He abnormality. Of the 2 boys, the first experienced a 2-minute generalized tonic clonic seizure with focal or second boy had an episode at 10 months after initiation of methylphenidate; he was heard to fall and wa minutes. EEGs of both boys had shown rolandic spikes, a focal epileptiform abnormality. One child who beginning methylphenidate (Hemmer et al, 2001).

b) Dextroamphetamine 0.15 mg/kg intravenously induced a dysphoric reaction, with DROWSINESS, an postmenopausal women (Halbreich et al, 1981). Young healthy men, who received the same dose, expe patients were screened to rule out physical and mental disorders.

c) One author reports 3 cases of OBSESSIVE-COMPULSIVE BEHAVIOR as a result of dextroampheta diagnosed as suffering from attention deficit disorder. The duration of stimulant therapy before the devel and 7 years, and the duration of symptoms was 4 to 7 months. A case of amphetamine-induced COMPU responsive to pyridoxine (B6) therapy (Frye & Arnold, 1981).

d) Due to its mechanism of action, dextroamphetamine may cause central nervous system (CNS) stimu DIZZINESS, INSOMNIA, EUPHORIA, dysphoria, TREMOR, and HEADACHE (Prod Info Dexedrine(R),

3.3.9.A.2 Cerebrovascular disease

a) Investigators reported 4 cases of INTRACRANIAL HEMORRHAGE following oral or nasal use of amp al, 1983). Two of these patients had abnormal appearing cerebral blood vessels on angiography. Availab hemorrhage may also occur in patients who use these drugs for the first time and nonrecreationally.

b) One article reports a case of intracranial hemorrhage that occurred 3 hours after the ingestion of amp (D'Souza & Shraberg, 1981). The admitting blood pressure was 210/120 (systolic/diastolic). No evidence was found on CT Scan. Others report INTRACRANIAL HYPERTENSION in a chronic amphetamine abu prednisone without a residual neurologic deficit. Dextroamphetamine is the dextrorotatory isomer of amp similar fashion (Delaney & Estes, 1981).

c) Four cases of STROKE were reported in patients (29 to 45 years of age) thought to have abused me hemorrhaging and 2 had cerebral ischemic infarctions (Perez et al, 1999).

3.3.9.A.3 Disturbance in speech

a) Central nervous system (CNS) stimulants can increase the rate of speech and reduce the fine coordi DYSPHONIA and VOICE TREMORS (Damste, 1978).

3.3.9.A.4 Extrapyramidal sign

a) Chronic amphetamine abuse may induce extrapyramidal effects such as choreiform or ATHETOID M that resemble the gait seen in Huntington's chorea. The syndrome generally develops during amphetami abstinence; however, the symptoms may persist for long periods of time. Dopamine receptor-blocking ag (Lundh & Lunving, 1981)(Rundell et al, 1988). Dextroamphetamine is the dextrorotatory isomer of amphe similar fashion.

3.3.9.A.5 Gilles de la Tourette's syndrome

a) The incidence of TICS emergence was 7.8% in children treated with stimulant medication (METHYLF PEMOLINE) for attention deficit hyperactivity disorder, based on a retrospective chart review (n=555). Th children if they were free of tics and without a history of tics according to the practice of the settings in wh 8.3% of subjects treated with methylphenidate, 6.3% treated with dextroamphetamine, and 7.7% treated dose or duration of stimulant therapy. Mean age of subjects was 11 years. A significant correlation occur tics. As the authors noted, these children may have developed tics, regardless of treatment with the med

b) Tourette's syndrome may be precipitated with the use of stimulant medications in the treatment of att
TOURETTE'S syndrome are difficult to distinguish from the attention deficit disorder symptoms. Children
additional stimulant medications. Stimulants may exacerbate severe motor and PHONIC TICS; discontin
initiation of haloperidol therapy is often required. In patients diagnosed as having an attention deficit disc
Tourette's syndrome in children and their families should precede the use of stimulant medication. The u
children with Tourette's syndrome or tics. In children with no symptoms of Tourette's syndrome or tics bu
very cautiously. If tics emerge during dextroamphetamine therapy, the drug should be discontinued (Low
c) These authors present several cases of children with attention deficit disorders who experienced hyp
cases, MOTOR TIC symptoms (Lowe et al, 1982a). The patients were placed on stimulant therapy and e
or Tourette's syndrome. Stimulant withdrawal and haloperidol therapy controlled the motor and phonic sy
d) Researchers reviewed the medication histories of 200 children with Tourette's syndrome (Erenberg e
stimulant drugs: 42 methylphenidate, 5 dextroamphetamine, 13 pemoline. Thirty-nine of the 48 (81%) pa
of the tics. Of these, the stimulant drugs increased tics in 8 patients, caused no change in 22, and decrea
therapy resulted in no difference in the incidence or frequency of tics in 8 patients. The patients who dev
decrease in the incidence and frequency after discontinuation of the stimulant.
e) Another report describes 2 cases of hyperactive boys who developed motor and phonic tics during de
Patterson, 1986). The tics disappeared in both cases after the discontinuation of dextroamphetamine an
suggest that neuroleptic-induced tics may be the result of presynaptic dopamine blockade.

3.3.12 Psychiatric Effects

3.3.12.A Dextroamphetamine Sulfate

3.3.12.A.1 Psychotic disorder

a) Incidence: rare
b) Amphetamine psychosis can present with visual, tactile, auditory and/or olfactory HALLUCINATIONS
AGGRESSIVENESS, SUSPICION, PARANOIA, increased motor activity, and CONCENTRATION DIFFI
treatment with benzodiazepines have been useful in resolving the symptoms (Bell, 1965; Ladewig et al,
1970; Hasse et al, 1973; Dow & Silver, 1973). The administration of amphetamines to patients with schiz
PSYCHOTIC BEHAVIOR (West, 1974; Alverno et al, 1975). Healthy persons who ingest dextroampheta
clinically indistinguishable from paranoid SCHIZOPHRENIA (Morley et al, 1980).
c) It was reported that patients whose urine is acidified with ammonium chloride have a shorter duration
days) than patients with amphetamine psychosis who have alkaline urine (approximately 4.5 days) (Angg
behavior was the first symptom to clear; this occurred within 1 day.
d) Others report a case of PARANOID PSYCHOSIS from intoxication with dextroamphetamine; the drug
(DeVeaugh-Geiss & Pandurangi, 1982). Use of amphetamines may exacerbate symptoms of BEHAVIOR
psychotic pediatric patients (Prod Info Dexedrine(R), dextroamphetamine sulfate tablets and Spansule(R
1998).

3.3.14 Reproductive Effects

3.3.14.A Dextroamphetamine Sulfate

3.3.14.A.1 Sexual dysfunction

a) IMPOTENCE and LIBIDO CHANGES have been reported during dextroamphetamine therapy (Prod I
tablets and Spansule(R) capsules, 1999).

3.3.16 Other

3.3.16.A Dextroamphetamine Sulfate

3.3.16.A.1 Drug withdrawal

a) The cessation of, or reduction in, amphetamine use that has been heavy and prolonged can result in
DYSPHORIC MOOD, FATIGUE, VIVID and UNPLEASANT DREAMS, INSOMNIA or HYPERSOMNIA, I
RETARDATION or AGITATION, ANHEDONIA, and DRUG CRAVING. Withdrawal symptoms may devel
cessation of or reduction in amphetamine use (Prod Info Adderall XR(TM), 2002; American Psychiatric A
b) Marked withdrawal symptoms can occur following intense, high dose amphetamine use. Characterist
feelings of LASSITUDE and DEPRESSION, and a marked INCREASE IN APPETITE with rapid WEIGH
days and may be accompanied by SUICIDAL IDEATION (American Psychiatric Association, 1994).

3.4 Teratogenicity/Effects in Pregnancy/Breastfeeding

A) Teratogenicity/Effects in Pregnancy
1) U.S. Food and Drug Administration's Pregnancy Category: Category C (Prod Info Dexedrine(R), 2002) (All Tri
a) Either studies in animals have revealed adverse effects on the fetus (teratogenic or embryocidal or other)
studies in women and animals are not available. Drugs should be given only if the potential benefit justifies th
See Drug Consult reference: PREGNANCY RISK CATEGORIES
2) Crosses Placenta: Unknown
3) Clinical Management

a) Amphetamines are not recommended for use during pregnancy except possibly in the case of narcolepsy drug is indicated and according to established regimens, amphetamines are not expected to create a significa abuse of amphetamines does increase the potential risk of maternal, fetal, and neonatal morbidity. Although evidence suggests an increased incidence of cardiac defects and cleft palate in neonates born to mothers tak et al, 1981).

4) Literature Reports

a) Eleven infants were born with biliary atresia to mothers who had taken amphetamines in various doses du development of a biliary tree) (Levin, 1971). In a controlled group of 50 normal infants, it was noted that 3 of 5

b) A large prospective, observational study of pregnancy and child development was undertaken related to a phenmetrazine) prescribed to gravid women during different stages of pregnancy and evaluated for their tera The severe congenital anomaly rate (SCA) per 100 live-born children at age 5 years did not differ from the SC did not use these drugs. There was, however, an excess of oral clefts in the offspring of mothers who had am the last menstrual period. A rough test of efficacy of anorectic drugs was made by comparing mean weight ga prescription; it showed only short-term and limited reduction of weight gain.

c) In a further report, clinicians evaluated the outcome of pregnancy in 52 women who had abused intravenc pregnancy, with results being compared to a control group of 52 nonabusing women (Little et al, 1988). Body was decreased significantly in neonates born to mothers abusing methamphetamine during pregnancy. Howe not increased significantly compared to the control group.

d) A statistically significant correlation between aggressive behavior and amphetamine exposure during fetal 1994).

B) Breastfeeding

1) Thomson Lactation Rating: Infant risk has been demonstrated.

a) Evidence and/or expert consensus has demonstrated harmful infant effects when used during breastfeedi prescribed or patients should be advised to discontinue breastfeeding.

2) Clinical Management

a) Amphetamines are concentrated in human breast milk. Adverse effects reported in exposed infants includ 2001). The manufacturer of Adderal(R) suggests that breastfeeding women taking amphetamines be counse 2003).

3) Literature Reports

a) One study reported that concentrations of amphetamine were 3 and 7 times higher in breast milk than pla respectively, following administration of dextroamphetamine 20 mg daily to a nursing mother with narcolepsy occurred in the infant. Although only a small fraction of the maternal dose is expected to be transferred to the patients abstain from long-term nursing during amphetamine treatment.

4) Drug Levels in Breastmilk

a) Parent Drug

1) Milk to Maternal Plasma Ratio

a) One study reported that concentrations of amphetamine were 3 and 7 times higher in breast milk delivery, respectively, following administration of dextroamphetamine 20 mg daily to a nursing moth untoward effects occurred in the infant. Although only a small fraction of the maternal dose is expect the authors suggest that patients abstain from long-term nursing during amphetamine treatment.

3.5 Drug Interactions

Drug-Drug Combinations

Drug-Food Combinations

3.5.1 Drug-Drug Combinations

Acetazolamide

Amitriptyline

Amoxapine

Calamus

Citalopram

Clomipramine

Clorgyline

Desipramine

Dothiepin

Doxepin

Furazolidone

Imipramine

Iproniazid

Isocarboxazid

Lofepramine

Moclobemide

Nialamide

Nortriptyline

Opipramol

Pargyline

Phenelzine

Procarbazine

Protriptyline

Selegiline

Sibutramine

Sodium Bicarbonate

Toloxatone

Tranylcypromine

Trimipramine

Venlafaxine

3.5.1.A Acetazolamide

1) Interaction Effect: amphetamine toxicity (hypertension, hyperpyrexia, seizures)
2) Summary: Concomitant acetazolamide and amphetamine therapy resulted in enhanced amphetamine effe
and the renal excretion of amphetamine is decreased due to increased reabsorption (Rowland, 1969; Anggar
3) Severity: moderate
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Lower doses of dextroamphetamine may be required with urinary alkalizers. Monitc
7) Probable Mechanism: decreased renal clearance

3.5.1.B Amitriptyline

1) Interaction Effect: hypertension, other cardiac effects, and CNS stimulation
2) Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been reporte
from the release of norepinephrine (Beaumont, 1973; Raisfeld, 1972). A similar reaction might also occur wit
Acute elevations in blood pressure have been noted (Flemenbaum, 1971a). Some amphetamine-like drugs m
most combinations have not been studied. When amphetamine analogs are being used to treat obesity, it sh
moderate weight gain (Russ & Ackerman, 1988). False positive urine tests for amphetamines have been rep
& Browning, 1993). Caution is advised when concurrent administration of amphetamine-like agents and TCA
monitored for increased cardiovascular effects (hypertension and dysrhythmias).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other sympatho
increased cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Inf
capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006; Flemenbaum, 1972). Use caution if
closely for hypertension and dysrhythmias.
7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission
8) Literature Reports
a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agen
amphetamine with TCAs such as desipramine or protriptyline results in sustained increases in d-amphet
VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tab
2006).
b) Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism o
imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transdermal system, 2006).
c) Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases i
effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of comb
methylphenidate usually results in the blood pressure returning to normotensive levels; reinstitution of th
pressure elevation (Flemenbaum, 1971; Flemenbaum, 1972).
d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine g
fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical
doubled steady-state plasma levels of desipramine (Price et al, 1990).
e) There have been claims based on uncontrolled studies that a better antidepressant response may oc
1969). However, a systemic review of stimulants in the treatment of depression concluded that although
ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated litt
appear to be as effective as the conventional antidepressants in primary depression (Satel & Nelson, 19

3.5.1.C Amoxapine

1) Interaction Effect: hypertension, other cardiac effects, and CNS stimulation
2) Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been reporte
from the release of norepinephrine (Beaumont, 1973; Raisfeld, 1972). A similar reaction might also occur wit
Acute elevations in blood pressure have been noted (Flemenbaum, 1971a). Some amphetamine-like drugs m
most combinations have not been studied. When amphetamine analogs are being used to treat obesity, it sh
moderate weight gain (Russ & Ackerman, 1988). False positive urine tests for amphetamines have been rep
& Browning, 1993). Caution is advised when concurrent administration of amphetamine-like agents and TCA
monitored for increased cardiovascular effects (hypertension and dysrhythmias).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other sympatho
increased cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Inf
capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006; Flemenbaum, 1972). Use caution if
closely for hypertension and dysrhythmias.
7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission
8) Literature Reports
a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agen
amphetamine with TCAs such as desipramine or protriptyline results in sustained increases in d-amphet
VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tab
2006).
b) Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism o
imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transdermal system, 2006).
c) Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases i
effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of comb
methylphenidate usually results in the blood pressure returning to normotensive levels; reinstitution of th
pressure elevation (Flemenbaum, 1971; Flemenbaum, 1972).
d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine g
fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical
doubled steady-state plasma levels of desipramine (Price et al, 1990).
e) There have been claims based on uncontrolled studies that a better antidepressant response may oc
1969). However, a systemic review of stimulants in the treatment of depression concluded that although

ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated litt
appear to be as effective as the conventional antidepressants in primary depression (Satel & Nelson, 19

3.5.1.D Calamus

1) Interaction Effect: reduced effect of amphetamines
2) Summary: Calamus antagonized spontaneous motor activity and amphetamine-induced hyperactivity in m
3) Severity: moderate
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Use caution with concomitant use of calamus and amphetamines.
7) Probable Mechanism: not specified
8) Literature Reports

a) Calamus antagonized spontaneous motor activity and amphetamine-induced hyperactivity in mice. C
(0.2 milliliters of 10, 25, 50 milligrams/kilogram (mg/kg)). One group of mice received 4 mg/kg chlorproma
spontaneous motor activity was compared to untreated mice. In another test, mice were injected IP with
calamus followed by amphetamine. Calamus significantly reduced spontaneous motor activity in a mann
and 25 mg/kg and significantly reduced amphetamine-induced hyperactivity at 25 mg/kg (Panchal et al,

3.5.1.E Citalopram

1) Interaction Effect: an increased risk of serotonin syndrome
2) Summary: Concurrent use of citalopram and dextroamphetamine resulted in symptoms of serotonin syndr
citalopram and dextroamphetamine are used concomitantly, monitor closely for symptoms of serotonin syndr
threatening. If serotonin syndrome develops, discontinue the offending agents and provide supportive care ar
Shannon, 2005).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: A case of serotonin syndrome was reported with coadministration of citalopram and
citalopram and dextroamphetamine are used concomitantly, monitor closely for symptoms of serotonin syndr
(including hyper-reflexia, tremor, muscle rigidity, clonus, peripheral hypertonicity, and shivering), autonomic h
diaphoresis, the presence of bowel sounds, and diarrhea), and mental status changes (including agitation an
threatening. If serotonin syndrome develops, discontinue the offending agents and provide supportive care ar
Shannon, 2005).
7) Probable Mechanism: additive pharmacologic effects
8) Literature Reports

a) A 32-year-old male on dextroamphetamine experienced serotonin syndrome approximately 1 week a
dextroamphetamine 5 mg three times daily for attention deficit hyperactivity disorder. He started 75 mg a
was increased to 150 mg daily. Approximately 2 weeks after starting venlafaxine he experienced markec
admission he was alert and oriented. He experienced diaphoresis, shivering, and fine motor tremor. His
pressure was 142/93 mmHg, and temperature was 37.3 degrees Celsius. No nystagmus or ocular clonus
reactive. He had generalized hypertonia, hyperreflexia, inducible ankle clonus, frequent myoclonic jerking
oris muscle. No abnormality was shown on ECG, except sinus tachycardia with a baseline tremor. Dextr
discontinued and cyproheptadine (up to a total of 32 mg over 3 hours) was administered. Symptoms reso
morning. Dextroamphetamine was restarted 3 days later. Four days later citalopram was started. Approx
symptoms as he did with dextroamphetamine and venlafaxine. Agitation, nausea, diarrhea, and teeth cle
was discontinued. Two doses of cyproheptadine were given and within 2 days he was asymptomatic (Pri

3.5.1.F Clomipramine

1) Interaction Effect: hypertension, other cardiac effects, and CNS stimulation
2) Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been reporte
from the release of norepinephrine (Beaumont, 1973; Raisfeld, 1972). A similar reaction might also occur with
Acute elevations in blood pressure have been noted (Flemenbaum, 1971a). Some amphetamine-like drugs m
most combinations have not been studied. When amphetamine analogs are being used to treat obesity, it sh
moderate weight gain (Russ & Ackerman, 1988). False positive urine tests for amphetamines have been repo
& Browning, 1993). Caution is advised when concurrent administration of amphetamine-like agents and TCAs
monitored for increased cardiovascular effects (hypertension and dysrhythmias).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other sympatho
increased cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Inf
capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006; Flemenbaum, 1972). Use caution if
closely for hypertension and dysrhythmias.
7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission
8) Literature Reports

a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agen
amphetamine with TCAs such as desipramine or protriptyline results in sustained increases in d-amphet
VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tab

2006).
b) Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism c
imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transdermal system, 2006).
c) Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases i
effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of comb
methylphenidate usually results in the blood pressure returning to normotensive levels; reinstitution of th
pressure elevation (Flemenbaum, 1971; Flemenbaum, 1972).
d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine g
fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical
doubled steady-state plasma levels of desipramine (Price et al, 1990).
e) There have been claims based on uncontrolled studies that a better antidepressant response may oc
1969). However, a systemic review of stimulants in the treatment of depression concluded that although
ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated litt
appear to be as effective as the conventional antidepressants in primary depression (Satel & Nelson, 19

3.5.1.G Clorgyline

1) Interaction Effect: a hypertensive crisis (headache, hyperpyrexia, hypertension)
2) Summary: Use of dextroamphetamine concomitantly or within 14 days following the administration of a mo
(Prod Info Dexedrine(R), 1995c). Amphetamines stimulate the release of norepinephrine, and the use of mon
more norepinephrine being made available at nerve receptor sites through inhibition of catecholamine degrad
of norepinephrine, which increases sympathetic activity (Gilman et al, 1990d). Coadministration of indirect-ac
in severe hypertension and hyperpyrexia (Krisko et al, 1969d; Lloyd & Walker, 1965d; Mason, 1962d; Dally, 1
dextroamphetamine or pemoline in addition to a MAOI was observed during a study of patients with treatmen
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Dextroamphetamine use during or within 14 days following the administration of a m
7) Probable Mechanism: increased norepinephrine availability
8) Literature Reports
a) Severe headaches and hypertensive crises are well-documented in the literature as being associated
include cardiac arrhythmias, chest pain, hyperpyrexia, and death (Goldberg, 1964b).
b) In a study of 32 patients with treatment-refractory depression, efficacy of combination therapy with a c
(pemoline or dextroamphetamine) with a monoamine oxidase inhibitor (MAOI) was studied. Some of the
tricyclic antidepressants and lithium, in addition to the study medications. Most of the patients (78%) exp
months during coadministration, and 31% of the patients continued treatment after the study. Four of the
discontinued the medications due to impotence, orthostatic hypotension, elevated blood pressure, or sha
dextroamphetamine and a MAOI discontinued the medications due to memory problems, parkinsonian s
patients experienced mood cycling, five to hypomania and one to mania. No patients developed symptor
(Fawcett et al, 1991h).

3.5.1.H Desipramine

1) Interaction Effect: hypertension, other cardiac effects, and CNS stimulation
2) Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been reporte
from the release of norepinephrine (Beaumont, 1973; Raisfeld, 1972). A similar reaction might also occur with
Acute elevations in blood pressure have been noted (Flemenbaum, 1971a). Some amphetamine-like drugs m
most combinations have not been studied. When amphetamine analogs are being used to treat obesity, it sh
moderate weight gain (Russ & Ackerman, 1988). False positive urine tests for amphetamines have been repo
& Browning, 1993). Caution is advised when concurrent administration of amphetamine-like agents and TCAs
monitored for increased cardiovascular effects (hypertension and dysrhythmias).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other sympatho
increased cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Inf
capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006; Flemenbaum, 1972). Use caution if
closely for hypertension and dysrhythmias.
7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission
8) Literature Reports
a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agen
amphetamine with TCAs such as desipramine or protriptyline results in sustained increases in d-amphet
VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tab
2006).
b) Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism c
imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transdermal system, 2006).
c) Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases i
effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of comb
methylphenidate usually results in the blood pressure returning to normotensive levels; reinstitution of th
pressure elevation (Flemenbaum, 1971; Flemenbaum, 1972).

d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine g fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical doubled steady-state plasma levels of desipramine (Price et al, 1990).
e) There have been claims based on uncontrolled studies that a better antidepressant response may oc 1969). However, a systemic review of stimulants in the treatment of depression concluded that although ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated litt appear to be as effective as the conventional antidepressants in primary depression (Satel & Nelson, 19

3.5.1.I Dothiepin

1) Interaction Effect: hypertension, other cardiac effects, and CNS stimulation
2) Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been reporte from the release of norepinephrine (Beaumont, 1973; Raisfeld, 1972). A similar reaction might also occur wit Acute elevations in blood pressure have been noted (Flemenbaum, 1971a). Some amphetamine-like drugs m most combinations have not been studied. When amphetamine analogs are being used to treat obesity, it sh moderate weight gain (Russ & Ackerman, 1988). False positive urine tests for amphetamines have been repo & Browning, 1993). Caution is advised when concurrent administration of amphetamine-like agents and TCAs monitored for increased cardiovascular effects (hypertension and dysrhythmias).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other sympatho increased cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Inf capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006; Flemenbaum, 1972). Use caution if closely for hypertension and dysrhythmias.
7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission
8) Literature Reports

a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agen amphetamine with TCAs such as desipramine or protriptyline results in sustained increases in d-amphet VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tab 2006).
b) Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism o imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transdermal system, 2006).
c) Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases i effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of comb methylphenidate usually results in the blood pressure returning to normotensive levels; reinstitution of th pressure elevation (Flemenbaum, 1971; Flemenbaum, 1972).
d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine g fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical doubled steady-state plasma levels of desipramine (Price et al, 1990).
e) There have been claims based on uncontrolled studies that a better antidepressant response may oc 1969). However, a systemic review of stimulants in the treatment of depression concluded that although ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated litt appear to be as effective as the conventional antidepressants in primary depression (Satel & Nelson, 19

3.5.1.J Doxepin

1) Interaction Effect: hypertension, other cardiac effects, and CNS stimulation
2) Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been reporte from the release of norepinephrine (Beaumont, 1973; Raisfeld, 1972). A similar reaction might also occur wit Acute elevations in blood pressure have been noted (Flemenbaum, 1971a). Some amphetamine-like drugs m most combinations have not been studied. When amphetamine analogs are being used to treat obesity, it sh moderate weight gain (Russ & Ackerman, 1988). False positive urine tests for amphetamines have been repo & Browning, 1993). Caution is advised when concurrent administration of amphetamine-like agents and TCAs monitored for increased cardiovascular effects (hypertension and dysrhythmias).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other sympatho increased cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Inf capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006; Flemenbaum, 1972). Use caution if closely for hypertension and dysrhythmias.
7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission
8) Literature Reports

a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agen amphetamine with TCAs such as desipramine or protriptyline results in sustained increases in d-amphet VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tab 2006).
b) Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism o imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transdermal system, 2006).

c) Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases i
effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of comb
methylphenidate usually results in the blood pressure returning to normotensive levels; reinstitution of th
pressure elevation (Flemenbaum, 1971; Flemenbaum, 1972).
d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine g
fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical
doubled steady-state plasma levels of desipramine (Price et al, 1990).
e) There have been claims based on uncontrolled studies that a better antidepressant response may oc
1969). However, a systemic review of stimulants in the treatment of depression concluded that although
ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated litt
appear to be as effective as the conventional antidepressants in primary depression (Satel & Nelson, 19

3.5.1.K Furazolidone

1) Interaction Effect: a hypertensive crisis (headache, hyperpyrexia, hypertension)
2) Summary: Furazolidone has significant MAOI activity (Pettinger et al, 1968; Pettinger et al, 1966). Use of
days following the administration of a monoamine oxidase inhibitor is contraindicated (Prod Info Dexedrine(R
activity such as dextroamphetamine cause the release of norepinephrine, and the use of MAOIs results in mo
nerve receptor sites through inhibition of catecholamine degradation; concurrent use leads to greater amount
sympathetic activity (Gilman et al, 1990e). Coadministration of indirect-acting sympathomimetics and MAOIs
& Bermudez, 1982; Cuthbert et al, 1969; Terry et al, 1975; Horler & Wynne, 1965).
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Dextroamphetamine use during or within 14 days following the administration of a n
7) Probable Mechanism: increased norepinephrine availability

3.5.1.L Imipramine

1) Interaction Effect: hypertension, other cardiac effects, and CNS stimulation
2) Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been reporte
from the release of norepinephrine (Beaumont, 1973; Raisfeld, 1972). A similar reaction might also occur with
Acute elevations in blood pressure have been noted (Flemenbaum, 1971a). Some amphetamine-like drugs m
most combinations have not been studied. When amphetamine analogs are being used to treat obesity, it sh
moderate weight gain (Russ & Ackerman, 1988). False positive urine tests for amphetamines have been repo
& Browning, 1993). Caution is advised when concurrent administration of amphetamine-like agents and TCAs
monitored for increased cardiovascular effects (hypertension and dysrhythmias).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other sympatho
increased cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Inf
capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006; Flemenbaum, 1972). Use caution if
closely for hypertension and dysrhythmias.
7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission
8) Literature Reports
a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agen
amphetamine with TCAs such as desipramine or protriptyline results in sustained increases in d-amphet
VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tab
2006).
b) Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism o
imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transdermal system, 2006).
c) Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases i
effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of comb
methylphenidate usually results in the blood pressure returning to normotensive levels; reinstitution of th
pressure elevation (Flemenbaum, 1971; Flemenbaum, 1972).
d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine g
fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical
doubled steady-state plasma levels of desipramine (Price et al, 1990).
e) There have been claims based on uncontrolled studies that a better antidepressant response may oc
1969). However, a systemic review of stimulants in the treatment of depression concluded that although
ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated litt
appear to be as effective as the conventional antidepressants in primary depression (Satel & Nelson, 19

3.5.1.M Iproniazid

1) Interaction Effect: a hypertensive crisis (headache, hyperpyrexia, hypertension)
2) Summary: Use of dextroamphetamine concomitantly or within 14 days following the administration of a mo
(Prod Info Dexedrine(R), 1995h). Amphetamines stimulate the release of norepinephrine, and the use of mor
more norepinephrine being made available at nerve receptor sites through inhibition of catecholamine degrad
of norepinephrine, which increases sympathetic activity (Gilman et al, 1990i). Coadministration of indirect-act

in severe hypertension and hyperpyrexia (Krisko et al, 1969h; Lloyd & Walker, 1965h; Mason, 1962h; Dally, 1
dextroamphetamine or pemoline in addition to a MAOI was observed during a study of patients with treatmen
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Dextroamphetamine use during or within 14 days following the administration of a n
7) Probable Mechanism: increased norepinephrine availability
8) Literature Reports
a) In a study of 32 patients with treatment-refractory depression, efficacy of combination therapy with a d
(pemoline or dextroamphetamine) with a monoamine oxidase inhibitor (MAOI) was studied. Some of the
tricyclic antidepressants and lithium, in addition to the study medications. Most of the patients (78%) exp
months during coadministration, and 31% of the patients continued treatment after the study. Four of the
discontinued the medications due to impotence, orthostatic hypotension, elevated blood pressure, or sha
dextroamphetamine and a MAOI discontinued the medications due to memory problems, parkinsonian s
patients experienced mood cycling, five to hypomania and one to mania. No patients developed symptor
(Fawcett et al, 1991n).

3.5.1.N Isocarboxazid

1) Interaction Effect: a hypertensive crisis (headache, hyperpyrexia, hypertension)
2) Summary: Use of dextroamphetamine concomitantly or within 14 days following the administration of a mo
(Prod Info Dexedrine(R), 1995a; Prod Info Marplan(R), 1998). Amphetamines cause the release of norepinep
norepinephrine being made available at nerve receptor sites through inhibition of catecholamine degradation.
norepinephrine, which increases sympathetic activity (Gilman et al, 1990b). Coadministration of indirect-actin
severe hypertension and hyperpyrexia (Krisko et al, 1969b; Lloyd & Walker, 1965b; Mason, 1962b; Dally, 196
dextroamphetamine or pemoline in addition to a MAOI was observed during a study of patients with treatmen
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Dextroamphetamine use during or within 14 days following the administration of a n
7) Probable Mechanism: increased norepinephrine availability
8) Literature Reports
a) Severe headaches and hypertensive crises are well-documented in the literature with this combinatio
arrhythmias, chest pain, hyperpyrexia, and death (Goldberg, 1964a).
b) In a study of 32 patients with treatment-refractory depression, efficacy of combination therapy with a d
(pemoline or dextroamphetamine) with a monoamine oxidase inhibitor (MAOI) was studied. Some of the
tricyclic antidepressants and lithium, in addition to the study medications. Most of the patients (78%) exp
months during coadministration, and 31% of the patients continued treatment after the study. Four of the
discontinued the medications due to impotence, orthostatic hypotension, elevated blood pressure, or sha
dextroamphetamine and a MAOI discontinued the medications due to memory problems, parkinsonian s
patients experienced mood cycling, five to hypomania and one to mania. No patients developed symptor
(Fawcett et al, 1991d).

3.5.1.O Lofepramine

1) Interaction Effect: hypertension, other cardiac effects, and CNS stimulation
2) Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been reported
from the release of norepinephrine (Beaumont, 1973; Raisfeld, 1972). A similar reaction might also occur with
Acute elevations in blood pressure have been noted (Flemenbaum, 1971a). Some amphetamine-like drugs m
most combinations have not been studied. When amphetamine analogs are being used to treat obesity, it sho
moderate weight gain (Russ & Ackerman, 1988). False positive urine tests for amphetamines have been repo
& Browning, 1993). Caution is advised when concurrent administration of amphetamine-like agents and TCAs
monitored for increased cardiovascular effects (hypertension and dysrhythmias).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other sympatho
increased cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Inf
capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006; Flemenbaum, 1972). Use caution if
closely for hypertension and dysrhythmias.
7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission
8) Literature Reports
a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agen
amphetamine with TCAs such as desipramine or protriptyline results in sustained increases in d-amphet
VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tab
2006).
b) Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism o
imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transdermal system, 2006).
c) Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases in
effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of comb

methylphenidate usually results in the blood pressure returning to normotensive levels; reinstitution of th pressure elevation (Flemenbaum, 1971; Flemenbaum, 1972).

d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine g fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical doubled steady-state plasma levels of desipramine (Price et al, 1990).

e) There have been claims based on uncontrolled studies that a better antidepressant response may oc 1969). However, a systemic review of stimulants in the treatment of depression concluded that although ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated litt appear to be as effective as the conventional antidepressants in primary depression (Satel & Nelson, 19

3.5.1.P Moclobemide

1) Interaction Effect: a hypertensive crisis (headache, hyperpyrexia, hypertension)

2) Summary: Use of dextroamphetamine concomitantly or within 14 days following the administration of a mo (Prod Info Dexedrine(R), 1995). Amphetamines stimulate the release of norepinephrine, and the use of monc more norepinephrine being made available at nerve receptor sites through inhibition of catecholamine degrac of norepinephrine, which increases sympathetic activity (Gilman et al, 1990). Coadministration of indirect-acti in severe hypertension and hyperpyrexia (Krisko et al, 1969; Lloyd & Walker, 1965; Mason, 1962; Dally, 1962 dextroamphetamine or pemoline in addition to a MAOI was observed during a study of patients with treatmen

3) Severity: contraindicated

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: Dextroamphetamine use during or within 14 days following the administration of a r

7) Probable Mechanism: increased norepinephrine availability

8) Literature Reports

a) In a study of 32 patients with treatment-refractory depression, efficacy of combination therapy with a ((pemoline or dextroamphetamine) with a monoamine oxidase inhibitor (MAOI) was studied. Some of the tricyclic antidepressants and lithium, in addition to the study medications. Most of the patients (78%) exp months during coadministration, and 31% of the patients continued treatment after the study. Four of the discontinued the medications due to impotence, orthostatic hypotension, elevated blood pressure, or sha dextroamphetamine and a MAOI discontinued the medications due to memory problems, parkinsonian s patients experienced mood cycling, five to hypomania and one to mania. No patients developed symptor (Fawcett et al, 1991).

3.5.1.Q Nialamide

1) Interaction Effect: a hypertensive crisis (headache, hyperpyrexia, hypertension)

2) Summary: Use of dextroamphetamine concomitantly or within 14 days following the administration of a mo (Prod Info Dexedrine(R), 1995j). Amphetamines stimulate the release of norepinephrine, and the use of monc more norepinephrine being made available at nerve receptor sites through inhibition of catecholamine degrac of norepinephrine, which increases sympathetic activity (Gilman et al, 1990k). Coadministration of indirect-ac in severe hypertension and hyperpyrexia (Krisko et al, 1969j; Lloyd & Walker, 1965j; Mason, 1962j; Dally, 19(dextroamphetamine or pemoline in addition to a MAOI was observed during a study of patients with treatmen

3) Severity: contraindicated

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: Dextroamphetamine use during or within 14 days following the administration of a r

7) Probable Mechanism: increased norepinephrine availability

8) Literature Reports

a) In a study of 32 patients with treatment-refractory depression, efficacy of combination therapy with a ((pemoline or dextroamphetamine) with a monoamine oxidase inhibitor (MAOI) was studied. Some of the tricyclic antidepressants and lithium, in addition to the study medications. Most of the patients (78%) exp months during coadministration, and 31% of the patients continued treatment after the study. Four of the discontinued the medications due to impotence, orthostatic hypotension, elevated blood pressure, or sha dextroamphetamine and a MAOI discontinued the medications due to memory problems, parkinsonian s patients experienced mood cycling, five to hypomania and one to mania. No patients developed symptor (Fawcett et al, 1991p).

3.5.1.R Nortriptyline

1) Interaction Effect: hypertension, other cardiac effects, and CNS stimulation

2) Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been reporte from the release of norepinephrine (Beaumont, 1973; Raisfeld, 1972). A similar reaction might also occur wit Acute elevations in blood pressure have been noted (Flemenbaum, 1971a). Some amphetamine-like drugs m most combinations have not been studied. When amphetamine analogs are being used to treat obesity, it sh moderate weight gain (Russ & Ackerman, 1988). False positive urine tests for amphetamines have been repo & Browning, 1993). Caution is advised when concurrent administration of amphetamine-like agents and TCAs monitored for increased cardiovascular effects (hypertension and dysrhythmias).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other sympatho increased cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Inf capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006; Flemenbaum, 1972). Use caution if closely for hypertension and dysrhythmias.
7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission
8) Literature Reports
a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agen amphetamine with TCAs such as desipramine or protriptyline results in sustained increases in d-amphet VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tab 2006).
b) Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism c imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transdermal system, 2006).
c) Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases i effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of comb methylphenidate usually results in the blood pressure returning to normotensive levels; reinstitution of th pressure elevation (Flemenbaum, 1971; Flemenbaum, 1972).
d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine g fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical doubled steady-state plasma levels of desipramine (Price et al, 1990).
e) There have been claims based on uncontrolled studies that a better antidepressant response may oc 1969). However, a systemic review of stimulants in the treatment of depression concluded that although ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated litt appear to be as effective as the conventional antidepressants in primary depression (Satel & Nelson, 19

3.5.1.S Opipramol

1) Interaction Effect: hypertension, other cardiac effects, and CNS stimulation
2) Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been reporte from the release of norepinephrine (Beaumont, 1973; Raisfeld, 1972). A similar reaction might also occur wit Acute elevations in blood pressure have been noted (Flemenbaum, 1971a). Some amphetamine-like drugs m most combinations have not been studied. When amphetamine analogs are being used to treat obesity, it sh moderate weight gain (Russ & Ackerman, 1988). False positive urine tests for amphetamines have been repo & Browning, 1993). Caution is advised when concurrent administration of amphetamine-like agents and TCA monitored for increased cardiovascular effects (hypertension and dysrhythmias).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other sympatho increased cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Inf capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006; Flemenbaum, 1972). Use caution if closely for hypertension and dysrhythmias.
7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission
8) Literature Reports
a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agen amphetamine with TCAs such as desipramine or protriptyline results in sustained increases in d-amphet VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tab 2006).
b) Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism c imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transdermal system, 2006).
c) Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases i effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of comb methylphenidate usually results in the blood pressure returning to normotensive levels; reinstitution of th pressure elevation (Flemenbaum, 1971; Flemenbaum, 1972).
d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine g fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical doubled steady-state plasma levels of desipramine (Price et al, 1990).
e) There have been claims based on uncontrolled studies that a better antidepressant response may oc 1969). However, a systemic review of stimulants in the treatment of depression concluded that although ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated litt appear to be as effective as the conventional antidepressants in primary depression (Satel & Nelson, 19

3.5.1.T Pargyline

1) Interaction Effect: a hypertensive crisis (headache, hyperpyrexia, hypertension)
2) Summary: Use of dextroamphetamine concomitantly or within 14 days following the administration of a m (Prod Info Dexedrine(R), 1995i). Amphetamines cause the release of norepinephrine, and the use of MAOIs available at nerve receptor sites through inhibition of catecholamine degradation; concurrent use leads to gre sympathetic activity (Gilman et al, 1990j). Coadministration of indirect-acting sympathomimetics and MAOIs h hyperpyrexia (Krisko et al, 1969i; Lloyd & Walker, 1965i; Mason, 1962i; Dally, 1962i).
3) Severity: contraindicated

4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Dextroamphetamine use during or within 14 days following the administration of a r
7) Probable Mechanism: increased norepinephrine availability

3.5.1.U Phenelzine

1) Interaction Effect: a hypertensive crisis (headache, hyperpyrexia, hypertension)
2) Summary: Amphetamines cause the release of norepinephrine, and the use of monoamine oxidase inhibit being made available at nerve receptor sites through inhibition of catecholamine degradation. Concurrent use which increases sympathetic activity (Gilman et al, 1990a). Coadministration of indirect-acting sympathomime hypertension and hyperpyrexia (Krisko et al, 1969a; Lloyd & Walker, 1965a; Mason, 1962a; Dally, 1962a). So dextroamphetamine or pemoline in addition to a MAOI was observed during a study of patients with treatmen However, the concurrent use of dextroamphetamine and phenelzine is contraindicated (Prod Info Nardil(R), 1
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Dextroamphetamine use during or within 14 days following the administration of a r
7) Probable Mechanism: increased norepinephrine availability
8) Literature Reports
a) Severe headaches and hypertensive crises are well-documented in the literature with this combinatio arrhythmias, chest pain, hyperpyrexia, and death (Goldberg, 1964).
b) In a study of 32 patients with treatment-refractory depression, efficacy of combination therapy with a (pemoline or dextroamphetamine) with a monoamine oxidase inhibitor (MAOI) was studied. Some of the tricyclic antidepressants and lithium, in addition to the study medications. Most of the patients (78%) exp months during coadministration, and 31% of the patients continued treatment after the study. Four of the discontinued the medications due to impotence, orthostatic hypotension, elevated blood pressure, or sha dextroamphetamine and a MAOI discontinued the medications due to memory problems, parkinsonian s patients experienced mood cycling, five to hypomania and one to mania. No patients developed symptor (Fawcett et al, 1991b).

3.5.1.V Procarbazine

1) Interaction Effect: a hypertensive crisis (headache, hyperpyrexia, hypertension)
2) Summary: Use of dextroamphetamine concomitantly or within 14 days following the administration of a mo (Prod Info Dexedrine(R), 1995f). Amphetamines stimulate the release of norepinephrine, and the use of mon more norepinephrine being made available at nerve receptor sites through inhibition of catecholamine degrad of norepinephrine, which increases sympathetic activity (Gilman et al, 1990g). Coadministration of indirect-ac in severe hypertension and hyperpyrexia (Krisko et al, 1969f; Lloyd & Walker, 1965f; Mason, 1962f; Dally, 19 dextroamphetamine or pemoline in addition to a MAOI was observed during a study of patients with treatmen
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Dextroamphetamine use during or within 14 days following the administration of a r
7) Probable Mechanism: increased norepinephrine availability
8) Literature Reports
a) In a study of 32 patients with treatment-refractory depression, efficacy of combination therapy with a (pemoline or dextroamphetamine) with a monoamine oxidase inhibitor (MAOI) was studied. Some of the tricyclic antidepressants and lithium, in addition to the study medications. Most of the patients (78%) exp months during coadministration, and 31% of the patients continued treatment after the study. Four of the discontinued the medications due to impotence, orthostatic hypotension, elevated blood pressure, or sha dextroamphetamine and a MAOI discontinued the medications due to memory problems, parkinsonian s patients experienced mood cycling, five to hypomania and one to mania. No patients developed symptor (Fawcett et al, 1991l).

3.5.1.W Protriptyline

1) Interaction Effect: hypertension, other cardiac effects, and CNS stimulation
2) Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been reporte from the release of norepinephrine (Beaumont, 1973; Raisfeld, 1972). A similar reaction might also occur wit Acute elevations in blood pressure have been noted (Flemenbaum, 1971a). Some amphetamine-like drugs m most combinations have not been studied. When amphetamine analogs are being used to treat obesity, it sh moderate weight gain (Russ & Ackerman, 1988). False positive urine tests for amphetamines have been repo & Browning, 1993). Caution is advised when concurrent administration of amphetamine-like agents and TCAs monitored for increased cardiovascular effects (hypertension and dysrhythmias).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other sympatho increased cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Inf capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006; Flemenbaum, 1972). Use caution if

closely for hypertension and dysrhythmias.
7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission
8) Literature Reports
a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agen amphetamine with TCAs such as desipramine or protriptyline results in sustained increases in d-amphet VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tab 2006).
b) Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism c imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transdermal system, 2006).
c) Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases i effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of comb methylphenidate usually results in the blood pressure returning to normotensive levels; reinstitution of th pressure elevation (Flemenbaum, 1971; Flemenbaum, 1972).
d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine g fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical doubled steady-state plasma levels of desipramine (Price et al, 1990).
e) There have been claims based on uncontrolled studies that a better antidepressant response may oc 1969). However, a systemic review of stimulants in the treatment of depression concluded that although ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated litt appear to be as effective as the conventional antidepressants in primary depression (Satel & Nelson, 19

3.5.1.X Selegiline
1) Interaction Effect: a hypertensive crisis (headache, hyperpyrexia, hypertension)
2) Summary: Use of dextroamphetamine concomitantly or within 14 days following the administration of a m (Prod Info Dexedrine(R), 1995g). Amphetamines cause the release of norepinephrine, and the use of MAOIs available at nerve receptor sites through inhibition of catecholamine degradation; concurrent use leads to gre sympathetic activity (Gilman et al, 1990h). Coadministration of indirect-acting sympathomimetics and MAOIs hyperpyrexia (Krisko et al, 1969g; Lloyd & Walker, 1965g; Mason, 1962g; Dally, 1962g).
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Dextroamphetamine use during or within 14 days following the administration of a r
7) Probable Mechanism: increased norepinephrine availability
8) Literature Reports
a) Severe headaches and hypertensive crises are well-documented in the literature as being associated include cardiac arrhythmias, chest pain, hyperpyrexia, and death (Goldberg, 1964d).

3.5.1.Y Sibutramine
1) Interaction Effect: an increased risk of hypertension and tachycardia
2) Summary: Sibutramine has been associated with substantial increases in blood pressure and heart rate ir administration of sibutramine and other centrally acting appetite suppressants has not been systematically ev and tachycardia may result. Therefore, the concurrent administration of sibutramine with another centrally act (Prod Info Meridia(R), 1997).
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concomitant administration of sibutramine with other centrally active appetite s
7) Probable Mechanism: additive pharmacologic effects

3.5.1.Z Sodium Bicarbonate
1) Interaction Effect: amphetamine toxicity (hypertension, hyperpyrexia, seizures)
2) Summary: Sodium bicarbonate (ie, greater than 2 grams daily) may alkalinize the urine, increasing the un allowing for increased renal tubular reabsorption. Enhanced effects of amphetamine may occur due to increa al, 1973a).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Lower doses of dextroamphetamine may be required with urinary alkalinizers. Moni
7) Probable Mechanism: decreased dextroamphetamine clearance

3.5.1.AA Toloxatone
1) Interaction Effect: a hypertensive crisis (headache, hyperpyrexia, hypertension)
2) Summary: Use of dextroamphetamine concomitantly or within 14 days following the administration of a m (Prod Info Dexedrine(R), 1995b). Amphetamines stimulate the release of norepinephrine, and the use of mor more norepinephrine being made available at nerve receptor sites through inhibition of catecholamine degrac of norepinephrine, which increases sympathetic activity (Gilman et al, 1990c). Coadministration of indirect-ac in severe hypertension and hyperpyrexia (Krisko et al, 1969c; Lloyd & Walker, 1965c; Mason, 1962c; Dally, 1 dextroamphetamine or pemoline in addition to a MAOI was observed during a study of patients with treatmen

3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Dextroamphetamine use during or within 14 days following the administration of a n
7) Probable Mechanism: increased norepinephrine availability
8) Literature Reports
a) In a study of 32 patients with treatment-refractory depression, efficacy of combination therapy with a c (pemoline or dextroamphetamine) with a monoamine oxidase inhibitor (MAOI) was studied. Some of the tricyclic antidepressants and lithium, in addition to the study medications. Most of the patients (78%) exp months during coadministration, and 31% of the patients continued treatment after the study. Four of the discontinued the medications due to impotence, orthostatic hypotension, elevated blood pressure, or sha dextroamphetamine and a MAOI discontinued the medications due to memory problems, parkinsonian s patients experienced mood cycling, five to hypomania and one to mania. No patients developed symptor (Fawcett et al, 1991f).

3.5.1.AB Tranylcypromine

1) Interaction Effect: a hypertensive crisis (headache, hyperpyrexia, hypertension)
2) Summary: Use of dextroamphetamine concomitantly or within 14 days following the administration of a mo (Prod Info Dexedrine(R), 1995e). Amphetamines cause the release of norepinephrine, and the use of monoa norepinephrine being made available at nerve receptor sites through inhibition of catecholamine degradation. norepinephrine, which increases sympathetic activity (Gilman et al, 1990f). Coadministration of indirect-acting severe hypertension and hyperpyrexia (Krisko et al, 1969e; Lloyd & Walker, 1965e; Mason, 1962e; Dally, 196 dextroamphetamine or pemoline in addition to a MAOI was observed during a study of patients with treatmen
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Dextroamphetamine use during or within 14 days following the administration of a n
7) Probable Mechanism: increased norepinephrine availability
8) Literature Reports
a) Severe headaches and hypertensive crises are well-documented in the literature with this combinatio arrhythmias, chest pain, hyperpyrexia, and death (Goldberg, 1964c).
b) In a study of 32 patients with treatment-refractory depression, efficacy of combination therapy with a c (pemoline or dextroamphetamine) with a monoamine oxidase inhibitor (MAOI) was studied. Some of the tricyclic antidepressants and lithium, in addition to the study medications. Most of the patients (78%) exp months during coadministration, and 31% of the patients continued treatment after the study. Four of the discontinued the medications due to impotence, orthostatic hypotension, elevated blood pressure, or sha dextroamphetamine and a MAOI discontinued the medications due to memory problems, parkinsonian s patients experienced mood cycling, five to hypomania and one to mania. No patients developed symptor (Fawcett et al, 1991j).

3.5.1.AC Trimipramine

1) Interaction Effect: hypertension, other cardiac effects, and CNS stimulation
2) Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been reported from the release of norepinephrine (Beaumont, 1973; Raisfeld, 1972). A similar reaction might also occur with Acute elevations in blood pressure have been noted (Flemenbaum, 1971a). Some amphetamine-like drugs m most combinations have not been studied. When amphetamine analogs are being used to treat obesity, it sho moderate weight gain (Russ & Ackerman, 1988). False positive urine tests for amphetamines have been repo & Browning, 1993). Caution is advised when concurrent administration of amphetamine-like agents and TCAs monitored for increased cardiovascular effects (hypertension and dysrhythmias).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other sympatho increased cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Inf capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006; Flemenbaum, 1972). Use caution if closely for hypertension and dysrhythmias.
7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission
8) Literature Reports
a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agen amphetamine with TCAs such as desipramine or protriptyline results in sustained increases in d-amphet VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tab 2006).
b) Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism o imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transdermal system, 2006).
c) Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases in effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of comb methylphenidate usually results in the blood pressure returning to normotensive levels; reinstitution of th pressure elevation (Flemenbaum, 1971; Flemenbaum, 1972).

d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine g fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical doubled steady-state plasma levels of desipramine (Price et al, 1990).
e) There have been claims based on uncontrolled studies that a better antidepressant response may oc 1969). However, a systemic review of stimulants in the treatment of depression concluded that although ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated litt appear to be as effective as the conventional antidepressants in primary depression (Satel & Nelson, 19

3.5.1.AD Venlafaxine

1) Interaction Effect: an increased risk of serotonin syndrome
2) Summary: Two weeks of concurrent use of dextroamphetamine and venlafaxine resulted in symptoms of s et al, 2002). If dextroamphetamine and venlafaxine are used concomitantly, monitor closely for symptoms of life-threatening. If serotonin syndrome develops, discontinue the offending agents and provide supportive car Shannon, 2005).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: A case of serotonin syndrome was reported with coadministration of dextroampheta dextroamphetamine and venlafaxine are used concomitantly, monitor closely for symptoms of serotonin synd (including hyper-reflexia, tremor, muscle rigidity, clonus, peripheral hypertonicity, and shivering), autonomic h diaphoresis, the presence of bowel sounds, and diarrhea), and mental status changes (including agitation an threatening. If serotonin syndrome develops, discontinue the offending agents and provide supportive care a Shannon, 2005).
7) Probable Mechanism: additive pharmacologic effects
8) Literature Reports
a) A 32-year-old male on dextroamphetamine experienced serotonin syndrome approximately 2 weeks dextroamphetamine 5 mg three times daily for attention deficit hyperactivity disorder. He started 75 mg a was increased to 150 mg daily. Approximately 2 weeks after starting venlafaxine he experienced markec admission he was alert and oriented. He experienced diaphoresis, shivering, and fine motor tremor. His pressure was 142/93 mmHg, and temperature was 37.3 degrees Celsius. No nystagmus or ocular clonus reactive. He had generalized hypertonia, hyperreflexia, inducible ankle clonus, frequent myoclonic jerkin oris muscle. No abnormality was shown on ECG, except sinus tachycardia with a baseline tremor. Dextr discontinued and cyproheptadine (up to a total of 32 mg over 3 hours) was administered. Symptoms res morning. Dextroamphetamine was restarted 3 days later. Four days later citalopram was started. Approx symptoms as he did with dextroamphetamine and venlafaxine. Agitation, nausea, diarrhea, and teeth cle was discontinued. Two doses of cyproheptadine were given and within 2 days he was asymptomatic (Pri

3.5.2 Drug-Food Combinations

3.5.2.A Acidic Food

1) Interaction Effect: altered serum concentrations
2) Summary: Maximal absorption of amphetamines occurs in the alkaline environment of the small intestine taken with amphetamines may impair gastrointestinal absorption. Foods that increase urinary pH may decrea reabsorption of the amphetamine and increased serum levels. Foods that acidify urine increase renal clearan levels (Prod Info Dexedrine(R), 1998; Beckett & Rowland, 1965).
3) Severity: minor
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Dextroamphetamine should not be administered with acidic foods, such as citric fru
7) Probable Mechanism: pH-dependent absorption and clearance

4.0 Clinical Applications

Monitoring Parameters

Patient Instructions

Place In Therapy

Mechanism of Action / Pharmacology

Therapeutic Uses

Comparative Efficacy / Evaluation With Other Therapies

4.1 Monitoring Parameters

A) Dextroamphetamine Sulfate

1) Therapeutic

a) Physical Findings

1) Attention Deficit Hyperactivity Disorder (ADHD)

a) Improvement in mental and behavioral symptoms of ADHD, including inappropriate inattention, i performance.

2) Narcolepsy

a) Decreased frequency of narcoleptic attacks.

2) Toxic

a) Physical Findings

1) Attention Deficit Hyperactivity Disorder (ADHD)

a) The American Academy of Pediatrics (AAP) does not recommend the routine use of electrocardi cardiology evaluations (which were previously recommended by the American Heart Association (AI conditions that might place the child at risk for sudden cardiac death) before initiating stimulant thera ADHD in most children. The APA cited specific reasons for changing the recommendation including between stimulant drugs used to treat ADHD and sudden cardiac death (SCD), the frequency of suc stimulant drugs is not higher than that in the general population of children, and lack of cost-effective evaluation by pediatric cardiologist (Perrin et al, 2008).

b) Based on the American Academy of Pediatrics (AAP) and the American Heart Association (AHA monitoring recommendations have been established to assist clinicians in the evaluation of children dextroamphetamine, for ADHD (Perrin et al, 2008; Vetter et al, 2008):

- Conduct a thorough examination prior to initiating dextroamphetamine therapy for a diagnosis symptoms indicative of a cardiac condition, including palpitations, near syncope, or syncope.
- Obtain a complete family and patient history for conditions associated with SCD, and determir the-counter medications.
- Conduct a complete physical evaluation of the patient for hypertension, cardiac murmurs, phys and signs of irregular cardiac rhythms.
- Perform further evaluation if family history, patient history or physical exam is suggestive of ca visits, and if indicated, consult pediatric cardiologist (Perrin et al, 2008).
- Continue to assess the patient for cardiac symptoms and any changes in family history at follo
- Blood pressure and heart rate should be evaluated at baseline, during routine follow-up within 12 months. Increases in blood pressure and heart rate have been reported with stimulant use.

c) It is not conclusive whether chronic use of stimulants in children may be associated with suppres monitored during treatment (Prod Info DEXEDRINE(R) oral tablets, sustained-release oral capsules

4.2 Patient Instructions

A) Dextroamphetamine (By mouth)

Dextroamphetamine

Treats attention deficit hyperactivity disorder (ADHD). Also treats narcolepsy (a sleep problem). This medicine is a

When This Medicine Should Not Be Used:
You should not use this medicine if you or your child have had an allergic reaction to dextroamphetamine. You sh glaucoma, heart disease, blood vessel problems, an overactive thyroid, or high blood pressure. Do not use this m you are very nervous, tense, or agitated most of the time. You should not use this medicine if you have used a dru (MAOI), such as Eldepryl®, Marplan®, Nardil®, or Parnate®, in the past 14 days. Do not give the tablet and oral s the extended-release capsule to a child younger than 6 years old.

How to Use This Medicine:
Tablet, Liquid, Long Acting Capsule

Your doctor will tell you how much of this medicine to use and how often. Your dose may need to be changed best for you. Do not use more medicine or use it more often than your doctor tells you to.
This medicine should come with a Medication Guide. Read and follow these instructions carefully. Ask your d Ask your pharmacist for the Medication Guide if you do not have one. Your doctor might ask you to sign some information.
It is best to take the extended-release capsule form in the morning. Taking this medicine in the afternoon or e asleep.
If you use the short-acting tablet form of this medicine, take your last dose for the day about 6 hours before b instructions.
Swallow the extended-release capsule whole. Do not crush, break, or chew it.
This medicine is part of an ADHD treatment program that may also include counseling or special education. C all treatment measures.

If a Dose is Missed:

If you miss a dose or forget to use your medicine, use it as soon as you can. If it is almost time for your next d the missed dose. Do not use extra medicine to make up for a missed dose.

How to Store and Dispose of This Medicine:
Store the medicine in a closed container at room temperature, away from heat, moisture, and direct light.
Ask your pharmacist, doctor, or health caregiver about the best way to dispose of any leftover medicine after need to throw away old medicine after the expiration date has passed.
Keep all medicine away from children and never share your medicine with anyone.

Drugs and Foods to Avoid:
Ask your doctor or pharmacist before using any other medicine, including over-the-counter medicines, vitamins, a
Make sure your doctor knows if you are using ammonium chloride, sodium acid phosphate, acetazolamide (D furazolidone (Furoxone®), glutamic acid, guanethidine (Ismelin®), norepinephrine (Levophed®), reserpine (H blood pressure medicines (such as atenolol, lisinopril, metoprolol, Cozaar®, or Diovan®), or certain pain mec Demerol®, or Darvon®).
Tell your doctor if you are also using cold or allergy medicines, ethosuximide (Zarontin®), haloperidol (Haldol medicines for depression (such as amitriptyline, doxepin, nortriptyline, Pamelor®, or Sinequan®), methenami or phenytoin (Dilantin®).
Do not eat citrus fruits (oranges, lemons, limes, grapefruit) or drink citrus juice when you take this medicine. D medicine.

Warnings While Using This Medicine:
Make sure your doctor knows if you are pregnant or breastfeeding, or if you or your child have heart problems
Tell your doctor if you or your child have muscle tics or Tourette's syndrome, a condition that causes you to h not able to control.
Your doctor should know if you or your child have epilepsy, or a history of seizures, depression, or mental illn problems. Also tell your doctor if you or anyone in your family has tried to commit suicide.
This medicine may be habit-forming. If you feel that the medicine is not working as well, do not use more thar instructions.
Do not stop using this medicine suddenly without asking your doctor. You may need to slowly decrease your
This medicine may cause blurred vision or make you dizzy or drowsy. If any of these occur, do not drive, use dangerous if you are not alert or not able to see well.
This medicine may cause slow growth. If your child is using this medicine, the doctor will need to keep track o that your child is growing properly.
Your doctor will need to check your progress at regular visits while you are using this medicine. Be sure to ke

Possible Side Effects While Using This Medicine:
Call your doctor right away if you notice any of these side effects:
Allergic reaction: Itching or hives, swelling in your face or hands, swelling or tingling in your mouth or throat, o
Blurred vision.
Changes in your mood or behavior.
Chest pain, shortness of breath, or fainting.
Fast, pounding, or uneven heartbeat.
Feeling very excited, fearless, restless, or happy.
Seeing, hearing, or feeling things that are not there.
Seizures.
Tremors or shaking.
Uncontrollable muscle movements or twitching.

If you notice these less serious side effects, talk with your doctor:
Constipation, diarrhea, or upset stomach.
Dry mouth or bad taste in your mouth.
Feeling restless or nervous.
Headache or dizziness.
Loss of appetite or weight loss.
Mild skin rash or itching.
Problems having sex.
Trouble sleeping.

If you notice other side effects that you think are caused by this medicine, tell your doctor.

4.3 Place In Therapy

A) The primary indication for the use of amphetamines is the clinical condition of narcolepsy which relies on the centra stimulant properties of the drugs. In children with hyperkinesia and other abnormal behavioral problems, the amphetar remedial measures to reduce observed motor activity from baseline levels (Green & Warshauer, 1981). This reduced o hyperactive children given dextroamphetamine) accompanied by improved behavior and improved attention seems to (classroom situations) but also physically active tasks (structured sports situations).

4.4 Mechanism of Action / Pharmacology

A) MECHANISM OF ACTION

1) Dextroamphetamine is a non-catechol sympathetic amine with pharmacologic actions that are similar to ephec
Dextroamphetamine produces central nervous system (CNS) and respiratory stimulation, a pressor response, my
urinary sphincter. The drug is felt to have a direct effect on both alpha- and beta-receptor sites in the peripheral sy
nerve terminals. The central nervous system action is thought to occur in the cerebral cortex and reticular activati
dextroamphetamine is probably secondary to the CNS stimulating effect in the hypothalamic feeding center (Weir
2) Dextroamphetamine sulfate is used to treat narcolepsy because of its CNS and respiratory stimulant properties
abnormal behavioral problems, dextroamphetamine appears to be of value in combination with other remedial me
baseline levels (Green & Warshauer, 1981a). This reduced observed motor activity from baseline values (in hyper
accompanied by improved behavior and improved attention seems to occur not only in physically inactive tasks (c
tasks (structured sports situations) (Rapoport et al, 1980).

4.5 Therapeutic Uses

Dextroamphetamine

Dextroamphetamine Sulfate

4.5.A Dextroamphetamine

4.5.A.1 Cataplexy - Narcolepsy

See Drug Consult reference: NARCOLEPSY AND CATAPLEXY - DRUG THERAPY

4.5.B Dextroamphetamine Sulfate

Attention deficit hyperactivity disorder

Cocaine dependence

Depression

Mania

Narcolepsy

Personality disorder

Schizophrenia

Sleep deprivation

4.5.B.1 Attention deficit hyperactivity disorder

FDA Labeled Indication

a) Overview

FDA Approval: Adult, no; Pediatric, yes (immediate-release, age 3 to 16 years ; sustained-release, a
Efficacy: Adult, Effective; Pediatric, Effective
Recommendation: Adult, Class IIa; Pediatric, Class IIa
Strength of Evidence: Adult, Category B; Pediatric, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Indicated for the treatment of attention deficit disorder with hyperactivity (ADHD) as an integral part
psychological, educational and social measures (Prod Info dextroamphetamine sulfate oral tablets,
sustained-release oral capsules, 2007)
May cause anxiety in susceptible individuals

c) Adult:

1) Some adult patients with a diagnosis of hyperactivity have also responded well to dextroamphetamin
paradoxical response to stimulant medication is exhibited only in prepubertal children (Woods et al, 1986
1980). One report describes a 20-year-old male with hyperkinetic syndrome who responded to dextroam
activity, increased concentration, depression of mood, drowsiness, reduction in aggression, and disappe
Joseph, 1980). The patient also showed typical amphetamine responses of tachycardia, hypertension, a

d) Pediatric:

1) Investigators examined 29 children (ages 6 to 13 years) who were referred for evaluation of hyperacti

dextroamphetamine, levoamphetamine, or placebo in a random, double-blind fashion. Medication was c
week, the procedure was repeated for each drug. While off medication, the hyperactive responders to ar
frequency (EEG) and shorter latencies of selected EP (evoked potential; visual or auditory) waves than c
electrophysiologic parameters may be of practical use in the selection of potential nonresponders. It was
found in the clinical efficacy between d-amphetamine and l-amphetamine as reported by the parents anc
2) One study found that once an effective dose of dextroamphetamine sulfate is determined, tolerance t
collected from neurophysiologic tests were used to assess tolerance to dextroamphetamine in 6 hyperac
The lack of tolerance displayed in this study is encouraging from many points of view, but the small popu
generalizations difficult (Golinko et al, 1981).
3) Others studied the urinary and plasma monoamines and metabolites within the same clinical sample
hyperactivity treated with dextroamphetamine (up to 1.5 milligrams/kg/day), methylphenidate (up to 3 mil
double-blind, crossover trial. Both drugs showed striking clinical efficacy. Dextroamphetamine, but not m
methoxy-4-hydroxyphenyl glycol and whole body norepinephrine turnover. Either drug did not alter the u
acid. Methylphenidate but not dextroamphetamine increased plasma norephinephrine. Urinary epinephri
drugs (Elia et al, 1990).
4) Ten boys diagnosed as having attention deficit disorder with hyperactivity and conduct problems were
crossover trial to determine the aggression lowering effect of dextroamphetamine. Drug dosages ranged
milligram/kilogram) divided over a 2-week period. The authors concluded that dextroamphetamine reduc
playroom observation of overt aggressive behavior (Amery et al, 1984).
5) Dextroamphetamine in doses ranging from 2.5 to 15 milligrams/day has been found to improve symp
MINIMAL BRAIN DYSFUNCTION in certain selected pediatric patients as measured by increase in atter
(Green & Warshauer, 1981b; Gross, 1976; Burks, 1964).

4.5.B.2 Cocaine dependence

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class III
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Dextroamphetamine may diminish cocaine responsiveness (Grabowski et al, 2001)

c) Adult:

1) DEXTROAMPHETAMINE sustained-release (DEX) appears to warrant further study as agonist treatr
double-blind, placebo-controlled trial (n=128). At entry, subjects were randomized to 1 of 3 regimens: pla
mg, or DEX 30 mg later raised to 60 mg. Study drugs were administered twice daily, within 2 hours of aw
period was 10 days in length, followed by a 4-week study period. Then doses were doubled and the seco
followed by 8-week study period. Participants attended the clinic twice a week for obtaining medication, p
behavioral therapy session. Study completion/retention rates were 22.9%, 40.4%, and 8.7% for the place
group, respectively (p=0.0012 for the rate differences). Amphetamine-positive urine screens indicated th
ranged from 81% to 82%. Urine screens were considered positive for cocaine if benzoylecgonine levels
subjects had no positive urine screens from intake through study completion; these subjects were remov
the study, the proportion of cocaine urine screens that were positive approximated 80% for the placebo g
32% to 33% for the 30/60-mg group. The difference between the placebo and 30/60-mg group almost re
month (p=0.061). Scores on the Beck Depression Inventory declined for the 30/60-mg group, increased
the placebo group. Six subjects dropped out due to side effects of study medication (Grabowski et al, 20

4.5.B.3 Depression

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class III
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Dextroamphetamine has been used successfully to treat depression, including AIDS patients with lo
Placebo-controlled studies are lacking

c) Adult:

1) Dextroamphetamine was found to be effective for treatment of post-stroke depression. Researchers r
stroke depression treated with either DEXTROAMPHETAMINE or METHYLPHENIDATE during a 5-year
of patients improved on psychostimulants; 47% of patients demonstrated a marked or moderate improve
difference in efficacy existed between the 2 agents. Patients improved quickly within the first 2 days. Onl
treatment due to side effects.
2) A positive therapeutic response to DEXTROAMPHETAMINE therapy in 3 medically-ill and depressed
1982). The patients were diagnosed as having a secondary depression that met DSM-III criteria for majc
with, a medical illness. In a pilot open-label study, DEXTROAMPHETAMINE was used successfully to in
patients (Wagner et al, 1997).
3) Arousal, mood, and anorexic effects improved in a dose-related manner with DEXTROAMPHETAMIN

evaluated for the effect of DEXTROAMPHETAMINE on visual analogue scale (VAS) ratings of hunger, a
Subjects were given placebo, dextroamphetamine 10 milligrams, and dextroamphetamine 20 milligrams
effect of the 2 dextroamphetamine doses were statistically significant. Subjective ratings of arousal and r
compared to placebo.
4) One study examined the effect of intravenous DEXTROAMPHETAMINE in 21 depressed patients (Pc
as having unipolar disease and 10 as having bipolar disease. All patients received piribedil (a direct-actir
(100 to 240 milligrams/dose) and dextroamphetamine 20 milligrams. Results showed consistent psychor
following dextroamphetamine administration, although a range of effects on mood (from euphoria to dysp

a) Combination Therapy

1) The combination of monoamine oxidase (MAO) inhibitors (tranylcypromine, isocarboxazid, p
methylphenidate) has been effective therapy in severe treatment-resistant depression. In additi
stimulants plus tricyclic antidepressants (amitriptyline, protriptyline, amoxapine, nortriptyline) ha
intractable depression (Sovner, 1990)(Feighner et al, 1985). Although no serious side-effects w
an overdose situation could be fatal. With the advent of newer and safer agents such as the ser
MAO Inhibitors, stimulants, and cyclic antidepressants should have a limited role in the treatme

4.5.B.4 Mania

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class III
Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Case reports have suggested that amphetamines may be of benefit in the treatment of acute mania

c) Adult:

1) One group of investigators conducted a study to evaluate the effect of dextroamphetamine on mania
dextroamphetamine 15 milligrams every 6 hours (total daily dose, 60 milligrams) for 72 hours (Garvey et
of the 6 (83%) patients experienced a 50% or greater reduction in their Raskin Severity of Mania scores,
therapy: 2 refused participation, 1 was lethargic and nauseated, 1 complained of "skipped" heart beats, a
severe manic symptoms. No patient demonstrated a worsening of manic or other psychiatric symptoms v

4.5.B.5 Narcolepsy

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes; Pediatric, yes (age 6 years and older)
Efficacy: Adult, Effective; Pediatric, Effective
Recommendation: Adult, Class IIa; Pediatric, Class IIa
Strength of Evidence: Adult, Category B; Pediatric, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Dextroamphetamine is indicated for the treatment of narcolepsy, and dosage should be individualize
dextroamphetamine sulfate oral tablets, 2007; Prod Info dextroamphetamine sulfate oral tablets, 200
Dextroamphetamine is effective in reducing the frequency and duration of narcoleptic attacks (Schin

4.5.B.6 Personality disorder

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class III
Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Dextroamphetamine, administered to patients with borderline personality disorder, may lead to symp
al, 1985)

c) Adult:

1) Dextroamphetamine 30 milligrams was administered to 8 BORDERLINE PERSONALITY DISORDEF
study. The results were compared to the responses of healthy patients under identical conditions. All pat
Dextroamphetamine led to symptoms of psychosis in 50% of the borderline patients, while none of the h
procedure. Global feelings of well-being were significantly elevated in the borderline group as compared
reduced response to growth hormone after dextroamphetamine compared to healthy patients, but this w
borderline personality disorder patients respond differently to dextroamphetamine than healthy patients (
2) Researchers studied 16 patients in whom borderline personality disorder was suspected to determine
following ingestion of a dopamine-agonist. In this double-blind study, none of the patients had been rece
Patients were randomly assigned to receive placebo or 30 milligrams dextroamphetamine and then cros
received only dextroamphetamine because they became transiently psychotic during testing and were gi
Psychiatric Rating Scale (BPRS) scores significantly increased from baseline after dextroamphetamine a
disturbance were the symptoms that significantly changed. Those patients with borderline personality dis

more psychotic symptoms after receiving amphetamine than did the patients with borderline personality
p=0.06). The authors conclude that not only do borderline patients change significantly following dextroa
response to dextroamphetamine in borderline patients is not heterogeneous as some patients have a wo
(Schulz et al, 1988).

4.5.B.7 Schizophrenia

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class III
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Amphetamine improves symptoms in some patients with schizophrenia.
Dopaminergic functions are reduced in the frontal cortex in schizophrenia; the use of a dopamine ag
cortical function in patients with schizophrenia.
However, because amphetamines are not selective, it would also increase dopamine release and bl
systems, possibly exacerbating psychotic symptoms.

c) Adult:

1) One report briefly describes 2 patients diagnosed with schizophrenia and nonresponsive to neurolept
in disease after the initiation of dextroamphetamine 5 to 10 milligrams/day (Desai et al, 1984).

2) One study demonstrated that intravenous dextroamphetamine (20 milligrams) induced an acute chan
Of the 45 drug-free SCHIZOPHRENIC PATIENTS studied, 18 patients worsened, 13 improved, and 14 h
Placebo produced no change in 14 patients. The 18 patients who worsened after dextroamphetamine ha
for the main metabolite of norepinephrine, 3-methoxy-4-hydroxyphenylglycol, as compared to those patie
who worsened were also significantly more psychotic at baseline than those patients who indicated no cl
schizophrenia is state-dependent and not trait-dependent (van Kammen et al, 1982).

3) Investigators administered dextroamphetamine 0.25 milligram/kilogram orally to 21 patients with chro
controlled, crossover study. All patients were receiving haloperidol 0.4 milligram/kilogram day. The result
more active and performed psychomotor tests more quickly while receiving amphetamine. Six patients w
terms of affect, cooperation, and engagement with the environment. However, the authors do not advoca
of schizophrenia (Goldberg et al, 1991).

4.5.B.8 Sleep deprivation

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class III
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Dextroamphetamine enhanced aviator performance during periods of forced wakefulness and sleep
placebo (Caldwell et al, 2000)

c) Adult:

1) Oral dextroamphetamine (DXT) maintained helicopter pilots (n=6; 5 men, 1 woman) in simulator flight
cycles, based on a double-blind, placebo-controlled trial. The greatest difference in the effects of DXT ar
periods (from approximately 0300 to 1200) on the second and third days without sleep (sleep deprivatior
Dextroamphetamine 10 milligrams or placebo was given at midnight, 0400, and 0800 on sleep deprivatic
deprivation cycles, with a 2-day interval between cycles. Performance on the flight simulator was worse
and 1300 on the first deprivation day, and on all flight-simulation times during the second deprivation day
monitoring showed higher delta and theta brain activity (normally predominant during sleep) under place
DXT, self-perceptions of vigor were maintained, while perceptions of fatigue and confusion were reduced
placebo than DXT. Recovery sleep was lighter after DXT, with disturbed REM sleep. No clinically signific
(Caldwell et al, 2000).

4.6 Comparative Efficacy / Evaluation With Other Therapies

Diethylpropion

Fenfluramine

Mazindol

Methylphenidate

Modafinil

Pemoline

Phentermine

4.6.A Diethylpropion

4.6.A.1 Obesity

a) The amphetamines (amphetamine sulfate, dextroamphetamine sulfate, methamphetamine HCl) are no lor
their high incidence of cardiovascular side effects and high abuse potential (Douglas & Munro, 1981; AMA De
effective as amphetamines in suppressing appetite (Scoville, 1973) but produces minimal cardiovascular effe

4.6.B Fenfluramine

Attention deficit hyperactivity disorder

Obesity

4.6.B.1 Attention deficit hyperactivity disorder

a) Dextroamphetamine was better than fenfluramine and placebo in reducing motor activity and in improving
diagnoses of attention deficit disorder with hyperactivity during a randomized, double-blind, crossover trial (D
b) Dextroamphetamine sulfate (0.5 milligram/kilogram/day, given in 2 divided doses) was reported effective i
hyperactivity (ADD) in a double-blind comparison with placebo and fenfluramine (Donnelly et al, 1989). Dextr
improvement in disruptive, overactive behavior. However, fenfluramine (in doses of 0.6 milligram/kilogram/da
milligrams/kilogram/day) produced no effect on any behavioral measure. Both drugs reportedly decreased lev
hydroxyphenylglycol (MHPG) and vanillylmandelic acid; however, fenfluramine also produced decreases in p
urinary norepinephrine. Urinary epinephrine levels were increased with dextroamphetamine but decreased si
decreased significantly with both agents. The results of this double-blind, crossover study suggest that fenflu
or other behaviors in children with ADD who are responsive to dextroamphetamine therapy. Differences in ef
similarity of the 2 agents, as well as some common overall effects on catecholamine metabolism and similar

4.6.B.2 Obesity

a) Dextroamphetamine was superior to fenfluramine and placebo in terms of weight loss, behavioral treatme
habit change in 59 overweight female volunteers during a 5-week, randomized, double-blind study (Bigelow e
no significant differences in mean weight between the 3 treatment groups. Also, none of the groups differed s
Patients in the fenfluramine group reported the most gastrointestinal upset, while the dextroamphetamine gro
stimulation.
b) Fenfluramine and dextroamphetamine were comparable in the treatment of obesity. In a study with fenflu
were randomly assigned to 1 of 3 groups: fenfluramine 20 mg, dextroamphetamine 5 mg, or placebo. Patient
three times a day at least one hour before meals. The patients who tolerated the drugs were allowed to incre
and were given advice on eating habits, but no specific diet was prescribed. Fenfluramine was clearly more e
dextroamphetamine in producing weight loss. At 7 weeks, fenfluramine patients lost 6.6 pounds compared to
The frequency of adverse effects with fenfluramine was significantly higher than with dextroamphetamine (St

4.6.C Mazindol

Narcolepsy

Obesity

4.6.C.1 Narcolepsy

a) Mazindol and dextroamphetamine were comparable for narcolepsy therapy. Mazindol was retrospectively
treatment of narcolepsy in 34 patients (Parkes & Schachter, 1979). Thirty-two patients had previously receive
daily (mean dose 47 milligrams). Oral mazindol was given as an initial dose of 2 milligrams twice a day 7 day
The dose of mazindol was adjusted by clinical response. After 1 year of treatment, the daily mazindol doses r
mazindol, 25 patients received clomipramine and 6 received clonazepam for cataplexy. Mazindol produced s
day-sleep attacks by 50%. This response was similar to that seen with dextroamphetamine, and both treatme
some patients responded to one drug and not the other. Mazindol had no effect on cataplexy or sleep paralys
with mazindol compared to dextroamphetamine. Mazindol produced less euphoria, sweating, and palpitations
considered as effective as dextroamphetamine 50 milligrams/day in preventing narcolepsy.

4.6.C.2 Obesity

a) Mazindol is as effective or more effective than dextroamphetamine in the treatment of exogenous obesity 1980a). Comparable doses are mazindol 1 milligram three times a day and dextroamphetamine 5 milligrams 1980a). Mazindol is indicated over dextroamphetamine and all amphetamines for the treatment of obesity. In treatment of obesity due to the high probability for dependence and the lack of significant advantages over ot

b) Mazindol is chemically unrelated to amphetamine derivatives; however, the anorectic effects are mediatec not serotoninergic mechanisms) (Garratini et al, 1974). Mazindol has some advantages over amphetamine d dependence potential (Craddock, 1976). Mazindol does produce stimulation to the central nervous system, b less severe than with amphetamines (Craddock, 1976). In addition, mazindol appears to be relatively safe for diabetes mellitus, mild-to-moderate hypertension, and rheumatoid arthritis are present (Weintraub & Lasagna used in patients with hypertension or diabetes.

4.6.D Methylphenidate

4.6.D.1 Attention deficit hyperactivity disorder

a) SUMMARY: In comparative studies, Adderall(R) (combination AMPHETAMINE/DEXTROAMPHETAMINE efficacy in the treatment of attention deficit hyperactive disorder in children. METHYLPHENIDATE requires tv daily doses.

b) The racemic mixture of L- and D-amphetamine (ADDERALL (R)) was at least as effective as methylpheni deficit hyperactivity disorder (ADHD), and was more effective at 4 to 5 hours post-administration (beyond met this within-subject, double-blind, placebo-controlled, crossover study, 25 children with ADHD (mean age 9.6 y (mg), 17.5 mg, Adderall (R) 7.5 mg, 12.5 mg, and placebo twice a day (at 7:45 a.m. and 12:15 p.m.) in a ranc Teachers and counselors rated their behavior throughout the day and at times beyond methylphenidate's exp Parents rated them at the end of the day and in the evening for possible rebound effects. When compared to significantly improved in-school behaviors (p less than 0.0001 and 0.001, respectively), classroom measures than 0.0001), and after-school behaviors (p less than 0.0001). Drug effects were significantly affected by time resulted in higher effect size (ES) than methylphenidate and higher doses consistently resulted in higher ES t significantly more effective than methylphenidate at midday and end of day (p less than 0.05). The ES of both increased in the afternoon, implicating the possibility of reducing the afternoon dose. Side effects were report preclude the use of both medications. Only 1 patient was eliminated from the study due to exacerbation of his to evaluate the possibility of once daily dosing of Adderall(R), and to compare the efficacy of methylphenidate

c) Once-daily Adderall(R) (combination AMPHETAMINE/DEXTROAMPHETAMINE) appeared to be as effec treatment of attention deficit hyperactive disorder in children aged 6 to 12 years, according to a double-blind, Also, a mid-afternoon dose of either Adderall or methylphenidate (MPH) produced better evening behavior th although either active treatment tended to induce loss of appetite and sleep difficulties. In a randomized mani received each day 1 of 7 treatment protocols: (1)MPH 0.3 milligram/kilogram (mg/kg) at 7:30, 11:30, and 15:3 MPH 0.15 mg/kg at 15:30; (3)MPH 0.3 mg/kg at 7:30; (4)Adderall 0.3 mg/kg at 7:30 and 15:30; (5)Adderall 0. 15:30; (6)Adderall 0.3 mg/kg at 7:30; or (7)placebo. While twice-daily MPH 0.3 mg/kg did not differ significant single morning-dose MPH 0.3 mg/kg produced less significant effects than either once-daily Adderall 0.3 mg/ MPH began to lose its effectiveness approximately 6.5 hours later. Evening behavior was rated better after M no evening differences were seen after mid-afternoon doses of either 0.3 or 0.15 mg/kg. Children showed dif responded more positively to MPH, 37% responded more positively to Adderall, and 38% responded equally responding more positively to MPH, one dose of MPH was sufficient to carry them all day and into the evenin positively to Adderall needed only once-daily dosing of the drug (Pelham et al, 1999a).

d) In a direct, double-blind, cross-over comparison of adverse effect profiles, both DEXTROAMPHETAMINE METHYLPHENIDATE 0.3 mg/kg twice daily were well-tolerated in 125 children with attention deficit disorder reported more frequently during drug therapy than at baseline were appetite suppression (both drugs) and ins severity of adverse effects was significantly higher in the dextroamphetamine group. However, only 1.6% of c because of adverse effects (Efron et al, 1997).

4.6.E Modafinil

Attention deficit hyperactivity disorder, Adult

Sleep disorder

4.6.E.1 Attention deficit hyperactivity disorder, Adult

a) Both modafinil and dextroamphetamine demonstrated efficacy and were well tolerated in the treatment of adults. During a double-blind, three-phase crossover study, 22 adults (mean age 40.8 years) who met DSM-I modafinil, dextroamphetamine, and placebo. The study design included three, 2-week drug treatment phases periods. At the beginning of each drug phase, patients received one capsule twice daily containing 50 milligra lactose. The dose was increased by an additional capsule twice daily every 1 to 2 days as tolerated up to a m dextroamphetamine, or 8 capsules of lactose. The mean optimum doses of modafinil and dextroamphetamin respectively. Rating scales and cognitive testing were completed at baseline and on the last day of each drug

When compared to placebo, modafinil and dextroamphetamine were associated with a significant reduction c (p less than 0.001). Although not statistically significant, less severe ADHD symptoms were associated with r Cognitive performance as measured by the Controlled Oral Word Association Test (COWAT) reached trend l compared to placebo (p less than 0.05). Both modafinil and dextroamphetamine were well-tolerated with insc suppression being the most commonly reported adverse effects (Taylor & Russo, 2000).

4.6.E.2 Sleep disorder

a) In studies involving healthy young and elderly subjects, oral modafinil 100 to 200 milligrams (mg) modafin of normal sleep than with dextroamphetamine 10 to 20 mg. Specifically, dextroamphetamine produced greate architecture, and deterioration of subjective sleep quality. The authors suggest the importance of differentiatir from "vigilance-increasing" properties of amphetamines (Saletu et al, 1989a; Saletu et al, 1989). However, dif significant in these studies. Total sleep time and sleep efficiency were also reduced significantly by modafinil with dextroamphetamine.

4.6.F Pemoline

4.6.F.1 Attention deficit hyperactivity disorder

a) Dextroamphetamine and pemoline are comparable for the treatment of attention deficit disorder. Magnesi dextroamphetamine in a double-blind, randomized, placebo-controlled study of 81 children with minimal brair received a maximum dose of 125 milligrams magnesium pemoline (mean 82 milligrams) and 40 milligrams of psychological tests were administered at baseline and at 8 weeks. At both 4 and 8 weeks, both drugs were s dextroamphetamine patients, 77% of the pemoline patients, and 30% of the placebo patients were improved. significant (p less than 0.003) changes for defiance, inattentiveness, and hyperactivity factors with both drugs showed a significant effect at 2 weeks (p=0.057) and at 4 weeks (p=0.022) compared to pemoline. Only after from placebo. After 8 weeks, however, the 2 treatments were indistinguishable for these factors. Anxiety and either drug. On the eight-factor parent symptom list, conduct disturbance, impulsivity, immaturity, and antisoc than 0.04). Factors not affected were anxiety, somatic complaints, obsessional traits, and hyperactivity. A res weeks and no difference between the 2 drugs was demonstrated at 8 weeks. The psychological test battery s placebo (p less than 0.004) in spelling, reading, Porteus Mazes, Frostig perceptual quotient, eye-motor coord drug-drug differences were noted. The major side effects with both drugs were insomnia and anorexia; insom therapy. Less than 5% of patients on dextroamphetamine experienced moderate or severe insomnia by the e psychological heterogenicity exists among children with minimal brain dysfunction. A child should receive dru probability that he will respond has been determined.

4.6.G Phentermine

4.6.G.1 Obesity

a) Despite differences in the pharmacologic effects and toxicity of the available anorexiant agents, all of the and no drug has been found superior to dextroamphetamine (AMA Department of Drugs, 1983). In addition, t of Drugs has indicated that amphetamines have no advantages over other anorectic agents that have a lowe Diethylpropion, mazindol, and phentermine are the preferred drugs for the management of obesity, based up central nervous system or cardiovascular toxicity (AMA Department of Drugs, 1983).

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214. Product Information: Dexedrine(R), dextroamphetamine. SmithKline Beecham Pharmaceuticals, Philadelphia, PA,
215. Product Information: Dexedrine(R), dextroamphetamine. SmithKline Beecham Pharmaceuticals, Philadelphia, PA,
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Last Modified: June 18, 2009

DRUGDEX® Evaluations

VENLAFAXINE

0.0 Overview

1) Class
- **a)** This drug is a member of the following class(es):
  - Antidepressant
  - Antidepressant, Bicyclic
  - Phenethylamine (class)
  - Serotonin/Norepinephrine Reuptake Inhibitor

2) Dosing Information
- **a)** Venlafaxine Hydrochloride
  - **1)** Adult
    - **a)** may convert to extended-release capsules or tablets based on nearest equivalent dose (mg/day) of stable
    2008; Prod Info venlafaxine extended release oral tablets, 2008)
    - **b)** taper dose prior to discontinuation to minimize risk of withdrawal symptoms (Prod Info EFFEXOR(R) oral
    venlafaxine extended release oral tablets, 2008)
      - **1)** Generalized anxiety disorder
        - **a)** (extended-release capsule) initial, 37.5 to 75 mg/day ORALLY (single dose); may increase dosa
        extended-release oral capsules, 2008)
      - **2)** Major depressive disorder
        - **a)** (immediate-release tablets) outpatients, 75 mg/day ORALLY (2-3 divided doses); may increase d
        oral tablets, 2008)
        - **b)** (immediate-release tablets) inpatients, 75 mg/day ORALLY (2-3 divided doses); may increase do
        Info EFFEXOR(R) oral tablets, 2008)
        - **c)** (extended-release capsules and tablets) 37.5 to 75 mg/day ORALLY (single dose); may increase
        XR(R) extended-release oral capsules, 2008; Prod Info venlafaxine extended release oral tablets, 2
      - **3)** Panic disorder, With or without agoraphobia
        - **a)** (extended-release capsule) starting dose, 37.5 mg/day ORALLY for 7 days; increase dose after
        intervals to a MAX dose of 225 mg/day (Prod Info EFFEXOR XR(R) extended-release oral capsules
      - **4)** Social phobia
        - **a)** (extended-release capsules and tablets) 75 mg/day ORALLY (single-dose) (Prod Info EFFEXOR
        tablets, 2008)
  - **2)** Pediatric
    - **a)** safety and efficacy not established in children (Prod Info EFFEXOR(R) oral tablets, 2008; Prod Info EFFE
    release oral tablets, 2008)

3) Contraindications
- **a)** Venlafaxine Hydrochloride
  - **1)** concomitant use of monoamine oxidase inhibitors (MAOI) (Prod Info Effexor(R) oral tablets, 2009; Prod Info Ef
  release oral tablets, 2009)

4) Serious Adverse Effects
- **a)** Venlafaxine Hydrochloride
  - **1)** Bleeding, Abnormal
  - **2)** Depression, exacerbation
  - **3)** Gastrointestinal hemorrhage
  - **4)** Hepatitis
  - **5)** Hypomania
  - **6)** Hyponatremia
  - **7)** Mania
  - **8)** Neuroleptic malignant syndrome
  - **9)** Seizure
  - **10)** Serotonin syndrome
  - **11)** Suicidal thoughts

5) Clinical Applications
- **a)** Venlafaxine Hydrochloride
  - **1)** FDA Approved Indications
    - **a)** Generalized anxiety disorder
    - **b)** Major depressive disorder
    - **c)** Panic disorder, With or without agoraphobia
    - **d)** Social phobia

1.0 Dosing Information

Drug Properties

Storage and Stability

Adult Dosage

Pediatric Dosage

1.1 Drug Properties

A) Information on specific products and dosage forms can be obtained by referring to the Tradename List (Product In

B) Synonyms

Venlafaxine
Venlafaxine HCl
Venlafaxine Hydrochloride

C) Physicochemical Properties

1) Venlafaxine Hydrochloride

a) Molecular Weight

1) O-desmethylvenlafaxine (ODV): 263 (Howell et al, 1993); Venlafaxine: 277 (Howell et al, 1993); Venla EFFEXOR XR(R) extended-release oral capsules, 2008; Canada, 1997)

b) Partition Coefficient

1) Octanol/water: 0.43 (Prod Info EFFEXOR(R) oral tablets, 2008; Prod Info EFFEXOR XR(R) extendec

c) pKa

1) 9.4 (Ellingrod & Perry, 1994)

d) Solubility

1) Venlafaxine hydrochloride has a solubility of 572 milligrams/milliliter in water adjusted to ionic strengtl Info EFFEXOR XR(R) extended-release oral capsules, 2008).

1.2 Storage and Stability

A) Venlafaxine Hydrochloride

1) Preparation

a) Oral route

1) Venlafaxine and venlafaxine extended-release should not be administered concurrently with a monoa and initiation of venlafaxine hydrochloride or at least 7 days between discontinuation of venlafaxine hydr EFFEXOR XR(R) extended-release oral capsules, 2008; Prod Info venlafaxine extended release oral tab

2) Administer venlafaxine and venlafaxine extended-release with food at approximately the same time e release oral capsules, 2008; Prod Info venlafaxine extended release oral tablets, 2008).

3) Swallow venlafaxine extended-release (XR) capsules and tablets whole with fluid. Do not divide, crus XR capsules may be administered by opening the capsule and sprinkling the contents on a spoonful of a (Prod Info EFFEXOR XR(R) extended-release oral capsules, 2008; Prod Info venlafaxine extended relea

B) Venlafaxine Hydrochloride

1) Oral route

a) Capsule, Extended Release/Tablet

1) Store at controlled room temperature, 20 to 25 degrees Celsius (68 to 77 degrees Fahrenheit) (Prod capsules, 2008).

1.3 Adult Dosage

Normal Dosage

Dosage in Renal Failure

Dosage in Hepatic Insufficiency

Dosage in Geriatric Patients

Dosage Adjustment During Dialysis

Dosage in Other Disease States

1.3.1 Normal Dosage

1.3.1.A Venlafaxine Hydrochloride

1.3.1.A.1 Oral route

Generalized anxiety disorder

Major depressive disorder

Panic disorder, With or without agoraphobia

Social phobia

1.3.1.A.1.a Generalized anxiety disorder

1) The initial recommended dosage for venlafaxine extended-release (XR) is 75 milligrams (mg)/da should be taken consistently at the same time each day. To allow new patients to adjust to therapy, made at intervals of at least 4 days. The maximum recommended dose is 225 mg/day. Although ver the need for continuing medication in patients with generalized anxiety disorder who improve with ve extended-release oral capsules, 2008).

1.3.1.A.1.b Major depressive disorder

1) The initial recommended dosage of regular-release venlafaxine is 75 milligrams (mg)/day, admin mg/day at intervals of at least 4 days. In the outpatient setting, doses above 225 mg/day demonstra inpatients responded to a mean dose of 350 mg/day. Therefore, the maximum recommended dose generally recommended that acute episodes of major depressive disorder be treated with sustained unknown whether the dose of venlafaxine required for maintenance treatment is the same as the do recommended in order to determine need for maintenance treatment and the appropriate maintenar
2) The initial recommended dosage for venlafaxine extended-release capsules and tablets is 75 mil may be taken in the morning or evening but should be taken consistently at the same time each day for 4 to 7 days. Dosage increases of 75 mg/day should be made at intervals of at least 4 days. The episodes of major depressive disorder be treated with sustained pharmacological therapy for severa required for maintenance treatment is the same as the dose needed to achieve an initial response. maintenance treatment and the appropriate maintenance dose (Prod Info EFFEXOR XR(R) extende
3) Administration of immediate-release venlafaxine once daily versus twice daily produced similar ir produced more rapid improvement (at 2 weeks) than once daily administration, but dose escalation once daily dosing, dose escalation proceeded as follows: (1) week 1 - 37.5 milligrams daily, (2) wee The twice daily regimen was similar except for the initial week where patients received 37.5 mg on c

1.3.1.A.1.c Panic disorder, With or without agoraphobia

1) The recommended starting dose of venlafaxine hydrochloride extended-release (XR) capsules fo day orally for 7 days. The dose may be increased to 75 mg per day after 1 week. For patients not re made at intervals of not less than 7 days. The maximum recommended dose is 225 mg per day (Pro
2) Patients may need to be evaluated periodically to determine the need for continuing medication. treatment with venlafaxine XR, patients who continued on venlafaxine XR experienced a significantl extended-release oral capsules, 2008).

1.3.1.A.1.d Social phobia

1) The initial recommended dosage for venlafaxine extended-release capsules and tablets is 75 mil evening but should be taken consistently at the same time each day. There is no evidence that high and efficacy in clinical trials lasting up to 6 months, the need for continuing medication in patients wi periodically reassessed (Prod Info EFFEXOR XR(R) extended-release oral capsules, 2008; Prod Inf

1.3.1.A.1.e Conversion To Venlafaxine XR

1) Depressed patients who are stabilized on immediate-release venlafaxine may be switched to the tablets. Further, individual dosage adjustments may be necessary (Prod Info EFFEXOR XR(R) exte 2008).

1.3.1.A.1.f Withdrawal Schedule

1) To minimize the risk of withdrawal symptoms, a gradual reduction in the dose rather than abrupt recommended. During clinical trials, the dose of venlafaxine XR was reduced by 75 milligrams per d EFFEXOR(R) oral tablets, 2008; Prod Info EFFEXOR XR(R) extended-release oral capsules, 2008;

1.3.2 Dosage in Renal Failure

A) Venlafaxine Hydrochloride

1) During clinical trials, clearance was decreased while the elimination half-life was increased for venlafaxine filtration rate between 10 and 70 milliliters/minute). Therefore, the total daily dose should be reduced by 25% tablets, 2008; Prod Info EFFEXOR XR(R) extended-release oral capsules, 2008; Prod Info venlafaxine exten

1.3.3 Dosage in Hepatic Insufficiency

A) Venlafaxine Hydrochloride
1) During clinical trials, clearance of venlafaxine was decreased while the elimination half-life was increased and mild to moderate hepatic impairment. Therefore, the total daily dose should be reduced by 50% in patien dose even more than 50%, and further individualization of dose may be necessary in some patients with cirrh EFFEXOR(R) oral tablets, 2008; Prod Info EFFEXOR XR(R) extended-release oral capsules, 2008; Prod Info

1.3.4 Dosage in Geriatric Patients
A) Venlafaxine Hydrochloride
1) Clearance of venlafaxine is reduced by approximately 15% in the elderly, presumably because of the sligh adjustment based upon age of the patient is generally unnecessary. However, caution should be taken when EFFEXOR XR(R) extended-release oral capsules, 2008; Prod Info venlafaxine extended release oral tablets,

1.3.5 Dosage Adjustment During Dialysis
A) Venlafaxine Hydrochloride
1) Total daily dose should be reduced by 50% in hemodialysis patients (Prod Info EFFEXOR(R) oral tablets, venlafaxine extended release oral tablets, 2008).

1.3.6 Dosage in Other Disease States
A) Venlafaxine Hydrochloride
1) Pregnancy
a) Neonatal complications requiring prolonged hospitalization, respiratory support, and tube feeding hav reuptake inhibitors, and selective serotonin reuptake inhibitors late in the third trimester. The physician m tablets, 2008; Prod Info EFFEXOR XR(R) extended-release oral capsules, 2008; Prod Info venlafaxine e

1.4 Pediatric Dosage

1.4.1 Normal Dosage

1.4.1.A Venlafaxine Hydrochloride

1.4.1.A.1 Oral route
a) The safety and efficacy have not been established in children (Prod Info EFFEXOR(R) oral tablets, 2(venlafaxine extended release oral tablets, 2008).

2.0 Pharmacokinetics

Onset and Duration

Drug Concentration Levels

ADME

2.1 Onset and Duration
A) Onset
1) Venlafaxine Hydrochloride
a) Initial Response
1) Depression, oral: 2 weeks to several months (Cantu et al, 1994; Montgomery, 1993; Prod Info EFFE) 2008)
a) Although some symptoms of major depression may improve within about 2 weeks (Cantu et al, 1 longer (Prod Info EFFEXOR(R) oral tablets, 2008; Prod Info EFFEXOR XR(R) extended-release ora

2.2 Drug Concentration Levels
A) Venlafaxine Hydrochloride
1) Peak Concentration
a) Venlafaxine hydrochloride, oral, regular-release tablets: 53 ng/mL (25-mg dose); 167 to 225 ng/mL (75-mg
1) Mean Cmax for venlafaxine regular-release when 75 milligrams was administered every 12 hours wa 2008)
2) Mean Cmax values following administration of 25, 75, or 150 mg of the regular-release dosage form c 167, and 393 nanograms/mL (0.19, 0.603, and 1.42 micromoles/L), respectively (Klamerus et al, 1992a). venlafaxine per day (Prod Info EFFEXOR(R) oral tablets, 2008; Schweizer et al, 1994).
b) Venlafaxine hydrochloride, oral, extended-release capsules: 150 ng/mL (Prod Info EFFEXOR XR(R) exte
1) The mean Cmax value of venlafaxine following administration of 150 milligrams extended-release cap between the regular- and extended-release formulations when equal daily doses were administered. The capsules. Venlafaxine exhibits linear pharmacokinetics over the dose range of 75 to 450 mg of venlafaxi
2) Time to Peak Concentration

a) Venlafaxine hydrochloride, oral, regular-release tablets: 1 to 2 hours (Prod Info EFFEXOR XR(R) extende
1) Mean Tmax for venlafaxine regular-release when 75 milligrams was administered every 12 hours was maximum concentration was not significantly different when venlafaxine was administered as a tablet or
b) Venlafaxine hydrochloride, oral, extended-release capsules: 5.5 hours (Prod Info EFFEXOR XR(R) exten
1) The mean Tmax value of venlafaxine following administration of 150 milligrams extended-release cap regular- and extended-release formulations when equal daily doses were administered. The fluctuation i Venlafaxine exhibits linear pharmacokinetics over the dose range of 75 to 450 mg of venlafaxine per day

2.3 ADME

Absorption

Distribution

Metabolism

Excretion

Elimination Half-life

Extracorporeal Elimination

2.3.1 Absorption

A) Venlafaxine Hydrochloride
1) Bioavailability
a) Oral, regular-release: 12.6% (Ellingrod & Perry, 1994d).
1) About 92% of an oral dose is absorbed. Due to extensive first pass metabolism, only 12.6% is av Perry, 1994d).
2) The relative bioavailability was 100% in tablet form when compared to an oral solution (Prod Info
3) Compared to healthy subjects, venlafaxine oral bioavailability increased 2- to 3-fold when admini Info EFFEXOR(R) oral tablets, 2008).
b) Oral, extended release: 45% (Prod Info EFFEXOR XR(R) extended-release oral capsules, 2008).
1) At least 92% of a single oral dose of venlafaxine is absorbed. The absolute bioavailability of venl capsules, 2008).
2) Compared to healthy subjects, venlafaxine oral bioavailability increased 2- to 3-fold when admini Info EFFEXOR XR(R) extended-release oral capsules, 2008).
2) Effects of Food
a) No effect on systemic bioavailability (Prod Info EFFEXOR(R) oral tablets, 2008; Prod Info EFFEXOR
1) Food had no effect on the absorption or bioavailability of venlafaxine or its active metabolite, O-d EFFEXOR XR(R) extended-release oral capsules, 2008).

2.3.2 Distribution

A) Distribution Sites
1) Venlafaxine Hydrochloride
a) Protein Binding
1) 27% to 30% (Prod Info EFFEXOR(R) oral tablets, 2008; Prod Info EFFEXOR XR(R) extended-re
a) Venlafaxine and O-desmethylvenlafaxine, the major active metabolite, are approximately 27 Info EFFEXOR XR(R) extended-release oral capsules, 2008; Klamerus et al, 1992).
B) Distribution Kinetics
1) Venlafaxine Hydrochloride
a) Volume of Distribution
1) 7.5 L/kg (Prod Info EFFEXOR(R) oral tablets, 2008; Prod Info EFFEXOR XR(R) extended-releas
a) The steady state volume of distribution is 7.5 and 5.7 L/kg for venlafaxine and O-desmethyl XR(R) extended-release oral capsules, 2008).

2.3.3 Metabolism

A) Metabolism Sites and Kinetics
1) Venlafaxine Hydrochloride
a) Liver, extensive (Prod Info EFFEXOR(R) oral tablets, 2008; Prod Info EFFEXOR XR(R) extended-rel
1) Venlafaxine is metabolized via the CYP2D6 isoenzyme (Prod Info EFFEXOR XR(R) extended-re
2) Following absorption, venlafaxine undergoes extensive first-pass metabolism in the liver, primaril desmethylvenlafaxine, N,O-didesmethylvenlafaxine, and other minor metabolites. The formation of release oral capsules, 2008; Troy et al, 1997b; Klamerus et al, 1992).
B) Metabolites

1) Venlafaxine Hydrochloride
a) O-desmethylvenlafaxine, active (Prod Info EFFEXOR(R) oral tablets, 2008; Prod Info EFFEXOR XR(
1) O-desmethylvenlafaxine is the only major active metabolite of venlafaxine hydrochloride (Prod In capsules, 2008).
b) N-desmethylvenlafaxine, active (Prod Info EFFEXOR XR(R) extended-release oral capsules, 2008; K
1) This metabolite is less active than O-desmethylvenlafaxine (Prod Info EFFEXOR XR(R) extende
c) N,O-didesmethylvenlafaxine, active (Prod Info EFFEXOR XR(R) extended-release oral capsules, 200
1) This metabolite is less active than O-desmethylvenlafaxine (Prod Info EFFEXOR XR(R) extende

2.3.4 Excretion

A) Kidney
1) Venlafaxine Hydrochloride
a) Renal Clearance (rate)
1) 0.074 to 0.079 L/hr/kg (Troy et al, 1997b).
b) Renal Excretion (%)
1) 87% (Prod Info EFFEXOR(R) oral tablets, 2008; Prod Info EFFEXOR XR(R) extended-release o
a) Within 48 hours, approximately 87% of a venlafaxine dose is recovered in the urine as eithe conjugated ODV (26%), or other minor inactive metabolites (27%). Renal elimination of venlafa tablets, 2008; Prod Info EFFEXOR XR(R) extended-release oral capsules, 2008).
b) After single oral doses of venlafaxine 80 to 100 mg, approximately 1 to 10% is excreted in th desmethylvenlafaxine, the active metabolite. Another 6% to 19% and 1%, respectively, is excre al, 1992).

B) Feces
1) Venlafaxine Hydrochloride
a) 2% (Troy et al, 1994; Howell et al, 1993; Klamerus et al, 1992a)
1) Within 35 days, approximately 2% of a venlafaxine dose is excreted in the feces (Troy et al, 199

C) Total Body Clearance
1) Venlafaxine Hydrochloride
a) 1.3 L/hr/kg (Prod Info EFFEXOR(R) oral tablets, 2008; Prod Info EFFEXOR XR(R) extended-release
1) Mean steady-state plasma clearance of venlafaxine and its major metabolite, O-desmethylvenlaf 2008; Prod Info EFFEXOR XR(R) extended-release oral capsules, 2008).
2) After oral administration of venlafaxine to renally impaired patients (GFR of 10 to 70 milliliters/mi subjects. Clearance of O-desmethylvenlafaxine remained unchanged in patients with renal impairme EFFEXOR XR(R) extended-release oral capsules, 2008).
3) After oral administration of venlafaxine to patients requiring dialysis, the clearance of venlafaxine compared to normal subjects (Prod Info EFFEXOR(R) oral tablets, 2008; Prod Info EFFEXOR XR(R
4) After oral administration of venlafaxine to 9 patients with hepatic cirrhosis, clearance of venlafaxi respectively. Three patients with more severe cirrhosis had an approximate 90% decrease in venlaf Prod Info EFFEXOR XR(R) extended-release oral capsules, 2008).
5) After oral and intravenous administration of venlafaxine to Child-Pugh A (n=8) and Child-Pugh B more than 50% when compared to normal subjects (n=21). Clearance of O-desmethylvenlafaxine w EFFEXOR XR(R) extended-release oral capsules, 2008).

2.3.5 Elimination Half-life

A) Parent Compound
1) Venlafaxine Hydrochloride
a) ELIMINATION HALF-LIFE
1) 5 hours (Prod Info EFFEXOR(R) oral tablets, 2008; Prod Info EFFEXOR XR(R) extended-releas
a) The mean steady state elimination half-life of venlafaxine is 5 hours (Prod Info EFFEXOR(R The elimination half-life is independent of the dose (Klamerus et al, 1992).
b) After oral administration of venlafaxine to 9 patients with hepatic cirrhosis, elimination half-lif tablets, 2008; Prod Info EFFEXOR XR(R) extended-release oral capsules, 2008).
c) After oral and intravenous administration of venlafaxine to Child-Pugh A (n=8) and Child-Pug approximately twice as long as compared to normal subjects (n=21) (Prod Info EFFEXOR(R) or
d) After oral administration of venlafaxine to renally impaired patients (GFR of 10 to 70 milliliter compared to normal subjects (Prod Info EFFEXOR(R) oral tablets, 2008; Prod Info EFFEXOR X
e) After oral administration of venlafaxine to patients requiring dialysis, the elimination half-life (Prod Info EFFEXOR(R) oral tablets, 2008; Prod Info EFFEXOR XR(R) extended-release oral c

B) Metabolites
1) Venlafaxine Hydrochloride
a) O-desmethylvenlafaxine, 11 hours (Prod Info EFFEXOR(R) oral tablets, 2008; Prod Info EFFEXOR X
b) After oral administration of venlafaxine to 9 patients with hepatic cirrhosis, elimination half-life of O-de 2008; Prod Info EFFEXOR XR(R) extended-release oral capsules, 2008).
c) After oral and intravenous administration of venlafaxine to Child-Pugh A (n=8) and Child-Pugh B (n=1 prolonged by approximately 40% as compared to normal subjects (n=21) (Prod Info EFFEXOR(R) oral ta
d) After oral administration of venlafaxine to renally impaired patients (GFR of 10 to 70 milliliters/minute compared to normal subjects (Prod Info EFFEXOR(R) oral tablets, 2008; Prod Info EFFEXOR XR(R) ext
e) After oral administration of venlafaxine to patients requiring dialysis, the elimination half-life of O-desv

(Prod Info EFFEXOR(R) oral tablets, 2008; Prod Info EFFEXOR XR(R) extended-release oral capsules,

2.3.6 Extracorporeal Elimination

A) Hemodialysis

1) Venlafaxine Hydrochloride

a) Dialyzable: No (Troy et al, 1994a).

3.0 Cautions

Contraindications

Precautions

Adverse Reactions

Teratogenicity/Effects in Pregnancy/Breastfeeding

Drug Interactions

3.0.A Black Box WARNING

1) Venlafaxine Hydrochloride

a) Oral (Tablet; Capsule, Extended Release; Tablet, Extended Release)

Suicidality and Antidepressant Drugs

Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in child
(MDD) and other psychiatric disorders. Anyone considering the use of venlafaxine hydrochloride or any other
clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants comp
antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric c
ages who are started on antidepressant therapy should be monitored appropriately and observed closely for
should be advised of the need for close observation and communication with the prescriber. Venlafaxine hyd
2009; Prod Info Effexor XR(R) extended-release oral capsules, 2009; Prod Info venlafaxine extended release

3.1 Contraindications

A) Venlafaxine Hydrochloride

1) concomitant use of monoamine oxidase inhibitors (MAOI) (Prod Info Effexor(R) oral tablets, 2009; Prod Info Ef
release oral tablets, 2009)

3.2 Precautions

A) Venlafaxine Hydrochloride

1) suicidal ideation and behavior or worsening depression has been reported, particularly in children, adolescents
monitoring recommended (Prod Info Effexor(R) oral tablets, 2009; Prod Info Effexor XR(R) extended-release oral

2) abnormal bleeding has been reported, including life-threatening hemorrhages (Prod Info Effexor(R) oral tablets
venlafaxine extended release oral tablets, 2009)

3) abrupt withdrawal; serious discontinuation symptoms have been reported; monitoring recommended; reduce d
extended-release oral capsules, 2009; Prod Info venlafaxine extended release oral tablets, 2009)

4) bipolar disorder; increased risk of precipitation of a mixed/manic episode; rule out disorder prior to initiating the
oral capsules, 2009; Prod Info venlafaxine extended release oral tablets, 2009)

5) concomitant use of NSAIDs, aspirin, warfarin, or other drugs that affect coagulation (Prod Info Effexor(R) oral t
venlafaxine extended release oral tablets, 2009)

6) concomitant use of serotonergic drugs (SSRIs, serotonin-norepinephrine reuptake inhibitors, triptans); use is n
extended-release oral capsules, 2009; Prod Info venlafaxine extended release oral tablets, 2009)

7) concomitant use with serotonin precursors, (eg, tryptophan supplements); use is not recommended (Prod Info
2009; Prod Info venlafaxine extended release oral tablets, 2009)

8) concomitant use with weight loss agents (eg, phentermine); use is not recommended (Prod Info Effexor(R) ora
venlafaxine extended release oral tablets, 2009)

9) glaucoma, narrow-angle (angle-closure glaucoma) or raised intraocular pressure, history or at risk for; increase
extended-release oral capsules, 2009; Prod Info venlafaxine extended release oral tablets, 2009)

10) hypertension, uncontrolled; may exacerbate condition (Prod Info Effexor(R) oral tablets, 2009; Prod Info Effe
oral tablets, 2009)

11) hypertension (sustained) has occurred; may require dose reduction or discontinuation (Prod Info Effexor(R) o
venlafaxine extended release oral tablets, 2009)

12) increased heart rate has been reported; underlying medical conditions associated with increased heart rate (e
(Prod Info Effexor(R) oral tablets, 2009; Prod Info Effexor XR(R) extended-release oral capsules, 2009; Prod Info

13) hepatic impairment, including cirrhosis; decreased venlafaxine clearance; lower dose may be required (Prod
2009; Prod Info venlafaxine extended release oral tablets, 2009)

14) interstitial lung disease and eosinophilic pneumonia have been rarely reported (Prod Info Effexor(R) oral tabl

venlafaxine extended release oral tablets, 2009)
15) mania, history; risk of activation of mania/hypomania (Prod Info Effexor(R) oral tablets, 2009; Prod Info Effex oral tablets, 2009)
16) medical diseases or conditions that could affect metabolism or hemodynamic responses (eg, myocardial infa XR(R) extended-release oral capsules, 2009)
17) renal impairment (glomerular filtration rate, 10 to 70 mL/min); decreased venlafaxine clearance; lower dose r release oral capsules, 2009; Prod Info venlafaxine extended release oral tablets, 2008)
18) seizures, history (Prod Info Effexor(R) oral tablets, 2009; Prod Info Effexor XR(R) extended-release oral caps
19) serotonin syndrome has been reported, including cases that are life-threatening or that resemble neuroleptic Prod Info Effexor XR(R) extended-release oral capsules, 2009)
20) use of venlafaxine within 14 days of MAOI discontinuation (Prod Info Effexor(R) oral tablets, 2009; Prod Info release oral tablets, 2009)
21) use of MAOIs within 7 days after venlafaxine discontinuation (Prod Info Effexor(R) oral tablets, 2009; Prod In release oral tablets, 2009)
22) volume-depleted, elderly, or concurrent diuretic therapy; hyponatremia, syndrome of inappropriate antidiureti Effexor(R) oral tablets, 2009; Prod Info Effexor XR(R) extended-release oral capsules, 2009; Prod Info venlafaxin

3.3 Adverse Reactions

Cardiovascular Effects

Dermatologic Effects

Endocrine/Metabolic Effects

Gastrointestinal Effects

Hematologic Effects

Hepatic Effects

Musculoskeletal Effects

Neurologic Effects

Ophthalmic Effects

Psychiatric Effects

Renal Effects

Reproductive Effects

Respiratory Effects

Other

3.3.1 Cardiovascular Effects

3.3.1.A Venlafaxine Hydrochloride

Heart failure

Hypertension

Increased heart rate

Palpitations

Prolonged QT interval

Summary

Vasodilatation

3.3.1.A.1 Heart failure

a) Two cases of interstitial pneumonia with heart failure have been reported following the use of venlafa month) in combination with steroid treatment led to a complete recovery in a 21- year-old woman. Howev multiple-organ failure and died despite attempts at treatment (Drent et al, 2003).

3.3.1.A.2 Hypertension

a) Incidence: 3% to 13%(Prod Info EFFEXOR(R) oral tablets, 2008; Prod Info EFFEXOR XR(R) extende

b) Immediate-release

1) In a dose comparison study of venlafaxine, a mean increase in supine diastolic blood pressure (S venlafaxine daily. There were essentially no changes observed in patients receiving 75 and 225 mg (Prod Info EFFEXOR(R) oral tablets, 2008).

2) Sustained increases in blood pressure have been reported in patients receiving therapeutic dose sustained increased supine diastolic blood pressure of 3% for venlafaxine doses less than 100 mg/c mg/day, and 13% for doses greater than 300 mg/day. Most of the blood pressure increases were be consequences. There have also been cases of elevated blood pressure during postmarketing use th controlled before treatment with venlafaxine and that blood pressure is routinely monitored during tr patients who experience a sustained increase in blood pressure while receiving venlafaxine (Prod In capsules, 2008).

3) Meta-analysis of controlled clinical studies revealed a crude incidence of sustained elevation in s imipramine, and 2.1% for placebo; this information was obtained during controlled clinical trials. Duri (p=0.0503) (Thase, 1998).

c) Extended-release

1) In premarketing studies, sustained hypertension occurred with the following frequency in patients capsules, 2008):

Studies #	Dose Range	Percent of patients with sustained HTN
Major depressive disorder	75 to 375 mg/day	3% (19/705)
Generalized anxiety disorder	37.5 to 225 mg/day	0.5% (5/101)
Social anxiety disorder	75 to 225 mg/day	0.6% (5/771)
Panic disorder	75 to 225 mg/day	0.9% (9/973)

Key: # = patients were on extended-release venlafaxine; * sustained hypertension (HTN) = defi mmHg or greater above baseline for 3 consecutive on-therapy visits; mg/day = milligrams/day; respectively; ** = up to 12 weeks and up to 6 months, respectively

Studies #	Discontinuation Rate due to sustained HTN ##	Range of SDBP increase
Major depressive disorder	0.7% (5/705)	12 to 16 mmHg
Generalized anxiety disorder	0.7% (10/1381) *	12 to 25 mmHg *
	1.3% (7/535) **	8 to 28 mmHg **
Social anxiety disorder	0.6% (5/771) ***	1 to 24 mmHg ***
Panic disorder	0.5% (5/1001) ***	7 to 19 mmHg ***

Key: # = patients were on extended-release venlafaxine; ## sustained hypertension (HTN) = defined as treatment-emergent supine diastolic blood pressure 90 mmHg or greater and 10 mmHg or greater above baseline for 3 consecutive on-therapy visits; * = up to 8 weeks; ** = up to 6 months;
*** = up to 12 weeks

Across all clinical trials in major depressive disorder, generalized anxiety disorder, social anxiet experienced an increase in supine diastolic blood pressure of 15 mmHg or more compared to 0 release venlafaxine experienced an increase in supine diastolic blood pressure of 20 mmHg or extended-release oral capsules, 2008).

3.3.1.A.3 Increased heart rate

a) Immediate-release

1) During clinical trials, venlafaxine hydrochloride treatment (averaged over all dose groups) was as no change for placebo. In a study with venlafaxine doses ranging from 200 to 375 milligrams (mg)/d approximately 2 beats per minute compared with a mean decrease of approximately 1 beat per minu

2) When electrocardiograms from 769 patients treated with venlafaxine and 450 patients with place baseline was 4 beats per minute in the venlafaxine group. In a flexible-dose study, the mean heart r

from 200 to 375 mg/day (mean dose greater than 300 mg/day) compared with 1.7 beats per minute heart rate include hyperthyroidism, heart failure, or recent myocardial infarction, particularly with dos

b) Extended-release

1) Treatment with extended-release venlafaxine was associated with a mean increase in pulse rate disorder, and panic disorder clinical trials (Prod Info EFFEXOR XR(R) extended-release oral capsul

Trial	Duration	Mean Change In Pulse Venlafaxine Extended-Release	Mean Char Plac
Major Depressive Disorder	up to 12 weeks	+ 2 beats/minute	+ 1 bea
Generalized Anxiety Disorder	up to 8 weeks	+ 2 beats/minute	+ less than 1
Social Anxiety Disorder	up to 12 weeks	+ 3 beats/minute	+ 1 bea
Panic Disorder	up to 12 weeks	+ 1 beat/minute	decrease of less t

2) When electrocardiograms were analyzed, extended-release venlafaxine was associated with an oral capsules, 2008). Results are summarized below:

Trial	Number of Patients With Analyzed Electrocardiograms (venlafaxine extended-release/placebo)	Mean Change In Hear Venlafaxine Exte
Major Depressive Disorder	495 (275/220)	+ 4 beats
Generalized Anxiety Disorder	908 (610/298)	+ 3 beats
Social Anxiety Disorder	1127 (593/534)	+ 5 beats
Panic Disorder	1056 (661/395)	+ 3 beat

3.3.1.A.4 Palpitations

a) Incidence: 3% (Prod Info EFFEXOR XR(R) extended-release oral capsules, 2008)

b) Palpitations have been reported in 3% of venlafaxine extended-release treated patients (n=819) com trials involving patients with social anxiety disorder (Prod Info EFFEXOR XR(R) extended-release oral ca

c) Palpitations were reported in 3 of 66 patients receiving venlafaxine 75 to 375 milligrams/day in one st

3.3.1.A.5 Prolonged QT interval

a) The corrected QT interval increased from baseline for venlafaxine extended-release treated patients recent history of myocardial infarction or unstable heart disease. The duration of the studies range from interval in venlafaxine extended-release relative to placebo treated patients (Prod Info EFFEXOR XR(R)

Studies	Mean change from baseline in QTc interval	
	Venlafaxine ER	Placebo
Major depressive disorder (n=495)	+ 4.7 msec	- 1.9 msec
Generalized anxiety disorder (n=908)	no difference from placebo	---
Social anxiety disorder (n=1127)	+ 3.4 msec	- 1.6 msec
Panic disorder (n=1056)	+ 1.5 msec	- 0.7 msec
Key: ER = extended-release; msec = millisecond		

b) A 60-year-old woman receiving 150 mg of venlafaxine daily for depression developed QT interval pro mmHg in both arms and mild dyspnea. An ECG showed sinus rhythm and a corrected QT (QTc) interval venlafaxine administration was stopped, and she was hospitalized for further evaluation. Her CBC, electr was not on any other medications besides venlafaxine and she denied consumption of grapefruit juice or death. A 24-hour ECG recorded multifocal premature ventricular complexes and couplets and a transtho the next several days, the QTc interval gradually decreased before stabilizing at 430 milliseconds (Letsa

3.3.1.A.6 Summary

a) Hypertension, palpitations, and vasodilation, primarily hot flashes have been experienced in patients EFFEXOR XR(R) extended-release oral capsules, 2008). The corrected QT interval increased from base placebo-treated patients. The mean heart rate increase was 8.5 beats per minute in patients receiving ve compared with 1.7 beats per minute for placebo (Prod Info EFFEXOR(R) oral tablets, 2008; Prod Info EF prolongation has been reported in a 60-year-old woman receiving venlafaxine for depression (Letsas et a following the use of venlafaxine (Drent et al, 2003).

3.3.1.A.7 Vasodilatation

a) Incidence: 2% to 5.6% (Prod Info EFFEXOR(R) oral tablets, 2008; Prod Info EFFEXOR(R) XR oral ex

b) During a dose comparison trial involving 358 patients, the incidence of vasodilatation was 0% for plac 375 milligrams/day, respectively (Prod Info EFFEXOR(R) oral tablets, 2008).

c) Vasodilation, primarily hot flashes, occurred in 3% to 4% of patients on extended-release venlafaxine extended-release oral capsules, 2008).

3.3.2 Dermatologic Effects

3.3.2.A Venlafaxine Hydrochloride

Acquired keratoderma palmaris et plantaris

Alopecia

Subungual hyperkeratosis

Sweating symptom

3.3.2.A.1 Acquired keratoderma palmaris et plantaris

a) A 57-year-old male smoker acquired palmoplantar keratoderma (psoriasiform) and subungual hyperk soles showed evidence of severe hyperkeratosis with an inflammatory red border. The epidermis had ps infiltrate on histopathological specimens. Massive subungual hyperkeratosis with paronychia was noted was noted after topical treatment with 10% urea, salicylic acid, caryolysin and oral retinoids. Within 4 to 5 improvement of the nails occurred (Dalle et al, 2006).

3.3.2.A.2 Alopecia

a) A 50-year-old woman experienced hair loss while being treated for depression with venlafaxine. The of 75 milligrams (mg) per day was raised to 150 mg/day after two weeks. Two weeks later she began to venlafaxine after three months, and her hair loss stopped completely one month later. In another episode days after achieving the dose of 150 mg/day. She discontinued venlafaxine and attained complete remis

3.3.2.A.3 Subungual hyperkeratosis

a) A 57-year-old male smoker acquired palmoplantar keratoderma (psoriasiform) and subungual hyperk soles showed evidence of severe hyperkeratosis with an inflammatory red border. The epidermis had ps infiltrate on histopathological specimens. Massive subungual hyperkeratosis with paronychia was noted was noted after topical treatment with 10% urea, salicylic acid, caryolysin and oral retinoids. Within 4 to 5 improvement of the nails occurred (Dalle et al, 2006).

3.3.2.A.4 Sweating symptom

a) Incidence: 6.7% to 25% (Prod Info EFFEXOR(R) oral tablets, 2008; Prod Info EFFEXOR XR(R) exter
b) During 4- to 8-week placebo-controlled trials of venlafaxine hydrochloride (dose ranging from 75 to 37 was 12% compared to 3% in patients receiving placebo (n=609) (Prod Info EFFEXOR(R) oral tablets, 20
c) During a dose comparison trial involving 358 patients, the incidence of sweating was 5.4% for placeb 375 milligrams/day, respectively (Prod Info EFFEXOR(R) oral tablets, 2008).
d) During clinical trials, sweating occurred in 10% to 14% of patients on extended-release venlafaxine c release capsules, 2006).

The table below provides the incidence rates of anorexia during clinical trials of extended-release ve

Studies	Incidence of Sweating	
	Venlafaxine ER	Placebo
Major depressive disorder (n=642)	14%	3%
Generalized anxiety disorder (n=1936)	10%	3%
Social anxiety disorder (n=1514)	13%	4%
Panic disorder (n=1663)	10%	2%
Key: ER = extended-release		

e) At 9 and 14 weeks, diaphoresis and pruritus occurred in 2 elderly women who were receiving venlafa (mg)/day and noted profuse night sweats, increased daytime sweating, and generalized itching without r without addition of allergy medications. The second patient noted profuse, generalized sweating and itch venlafaxine XR was effective in resolving her symptoms. The medication history, physical examination, a symptoms (Schwartz, 1999).
f) Profuse sweating has been reported in two patients following oral venlafaxine therapy for the treatmer (Adesanya & Varma, 1997; Garber & Gregory, 1997). The patient was restarted on venlafaxine therapy, diaphoresis did not recur, and the venlafaxine was increased to 75 mg three times daily with no subsequ
g) A study reported a 25% incidence of increased sweating in patients receiving venlafaxine 75 to 375 n (Schweizer et al, 1991).

3.3.3 Endocrine/Metabolic Effects

3.3.3.A Venlafaxine Hydrochloride

Height / growth finding

Hot sweats

Hyponatremia

Serum cholesterol raised

Serum triglycerides raised

Syndrome of inappropriate antidiuretic hormone secretion

Weight loss

3.3.3.A.1 Height / growth finding

a) Pediatric patients, especially patients younger than 12 years of age, on venlafaxine grew less than pe extended-release (n=122), on average, grew 0.3 centimeters (cm) compared with 1 cm for placebo treat disorder study. Pediatric patients on venlafaxine extended-release (n=146), on average, grew 0.8 centim major depressive disorder study. Height increases were less than expected based on data from age-and extended-release capsules, 2006).

3.3.3.A.2 Hot sweats

a) A 52-year-old menopausal woman experienced hot flashes while being treated for depression with ve total hysterectomy and bilateral salpingo-oophorectomy. Although she experienced hot flashes immediat After two weeks of therapy with extended- release venlafaxine 75 mg per day, the woman reported trans flashes were occurring daily and were rated moderate to severe. After seven weeks, the severity and fre was then increased to 150 mg/day to increase the antidepressant response. The woman had five days o Venlafaxine has been used to treat hot flashes (Grady-Weliky & Hartmann, 2001).

3.3.3.A.3 Hyponatremia

a) Summary

1) Hyponatremia has been reported with the use of selective serotonin reuptake inhibitors (SSRIs) a the syndrome of inappropriate antidiuretic hormone secretion (SIADH). Serum sodium levels lower t hyponatremia with SSRIs and SNRIs include the elderly and patients receiving diuretics or who are memory impairment, confusion, weakness, and unsteadiness which may or may not lead to falls. Sig respiratory arrest, and death. Discontinuation of venlafaxine therapy should be considered and appr (Prod Info EFFEXOR(R) oral tablets, 2008; Prod Info EFFEXOR XR(R) extended-release oral capsu

b) LITERATURE REPORTS

1) Hyponatremia was reported in 15 patients following therapeutic use of venlafaxine. The average sodium concentrations ranged from 116 to 130 milliequivalents/liter (mEq/L) (normal 135 to 145 mE

2) A 70-year-old woman developed hyponatremia (125 millimoles per liter (mmol/L)) while taking ve She had previously developed SIADH while taking mirtazapine (Blass & Pearson, 2000).

3) A 76-year-old female developed hyponatremia (serum sodium level of 118 milliequivalents/liter) f and the patient's serum sodium level returned to baseline three days later following fluid restriction,

3.3.3.A.4 Serum cholesterol raised

a) Incidence: 5.3% (Prod Info EFFEXOR(R) oral tablets, 2008; Prod Info EFFEXOR XR(R) extended-rel

b) Clinically relevant increases in serum cholesterol occur in 5.3% of venlafaxine immediate-release trea Clinically relevant was defined as a final or an average on-therapy increase in serum cholesterol of 50 m greater. Significant increases in mean serum cholesterol have been reported in patients receiving venlaf capsules (1 to 11.4 mg/dL) during multiple clinical trials. Periodic monitoring is recommended during long extended-release oral capsules, 2008; Anon, 1993).

c) Treatment with extended-release venlafaxine was associated with increases in serum cholesterol cor extended-release oral capsules, 2008). Results are summarized below:

Trial	Duration	Mean Change in Serum Cholesterol Venlafaxine Extended-Release	Mean Change
Major Depressive Disorder	up to 12 weeks	+ 1.5 mg/dL	-
Generalized Anxiety Disorder	up to 8 weeks up to 6 months	+1.0 mg/dL + 2.3 mg/dL	- -
Social Anxiety Disorder	up to 12 weeks up to 6 months	+ 7.9 mg/dL + 5.6 mg/dL	- -

Panic Disorder	up to 12 weeks	+ 5.8 mg/dL	- 3
mg/dL = milligrams/deciliter			

3.3.3.A.5 Serum triglycerides raised

a) Treatment with extended-release venlafaxine was associated with increases in fasting serum triglyce
(R) extended-release oral capsules, 2008). Results are summarized below:

Trials	Duration	Mean Change in Serum Triglycerides Venlafaxine Extended-Release	Mean Change in S Place
Social Anxiety Disorder	up to 12 weeks up to 6 months	+ 8.2 mg/dL + 11.8 mg/dL	+ 0.4 n + 1.8 n
Panic Disorder	up to 12 weeks up to 6 months	+ 5.9 mg/dL + 9.3 mg/dL	+ 0.9 n - 0.3 n
mg/dL = milligrams/deciliter			

3.3.3.A.6 Syndrome of inappropriate antidiuretic hormone secretion

a) Summary

1) Syndrome of inappropriate secretion of antidiuretic hormone has occurred in patients on venlafax
Info EFFEXOR(R) oral tablets, 2008; Prod Info EFFEXOR XR(R) extended-release oral capsules, 2

b) LITERATURE REPORTS

1) About 8 months after starting venlafaxine, a 92-year-old woman developed the syndrome of inap
the serum sodium gradually fell from 133 to 124 milliequivalents/liter; the antidiuretic hormone conce
milliosmole/kilogram (mOsm/kg) was high compared to a low serum osmolality of 255 mOsm/kg. Ve
month. Due to the temporal relationship and similar reports to other selective serotonin reuptake inh

2) A 65-year-old man developed the syndrome of inappropriate antidiuretic hormone (SIADH) possi
he complained of dizziness; abnormal laboratory values included a serum sodium of 114 millimole/li
239 millimole/24 hours, and urine osmolality of 640 mOsm/L. Venlafaxine was stopped, and the pati
restriction was stopped, the serum sodium concentration and osmolality remained normal. Medical c
is recommended that patients treated with a selective serotonin reuptake inhibitor who develop sym
have a serum sodium measured (Meynaar et al, 1997).

3.3.3.A.7 Weight loss

a) Incidence: 3% to 47% (Prod Info EFFEXOR(R) oral tablets, 2008; Prod Info EFFEXOR XR(R) extend

b) Adults

1) Treatment with immediate-release venlafaxine for several weeks in adults was associated with a
3% and 1% in patients receiving another antidepressant or placebo, respectively. The weight loss a
Info EFFEXOR(R) oral tablets, 2008).

2) During short-term placebo-controlled major depressive disorder trials, weight loss of 5% or more
release and placebo, respectively, and the discontinuation rate due to weight loss was 0.1%. During
7% or more occurred in 3% of venlafaxine extended-release treated patients compared with 1% in p
duration of up to 8 weeks was 0.3% for patients receiving venlafaxine extended-release. During 6-m
occurred in 4% of venlafaxine extended-release treated patients compared with 1% in placebo patie
placebo, respectively, sustained a loss of 7% or more of body weight during up to 12 weeks of treatr
weight loss in either the social anxiety disorder or panic disorder trials (Prod Info EFFEXOR XR(R) e

c) Pediatrics

1) Results of a pooled analysis of four 8-week, double-blind, placebo-controlled, flexible dose trials
(ages 6 to 17 years) indicate that a weight loss of at least 3.5% occurred in 18% of venlafaxine exte
0.001) . On average, 0.45 kilograms (kg) (n=333) was lost in the venlafaxine extended-release grou
less than 12 years old were at a greater risk than adolescents older than 12 years for weight loss, w
open-label study was evaluated (Prod Info EFFEXOR(R) XR oral extended-release capsules, 2006)

2) Pediatric patients enrolled in a 16-week, double-blind, placebo-controlled trial for social anxiety d
(kg) compared to an average gain of 0.76 kg in patients receiving placebo. A weight loss of at least
release compared with 14% of patients receiving placebo (p less than 0.001) (Prod Info EFFEXOR(

3) Children less than 12 years old were at a greater risk than adolescents older than 12 years for w
gain) from an open-label major depressive disorder study was evaluated (Prod Info EFFEXOR(R) X

3.3.4 Gastrointestinal Effects

3.3.4.A Venlafaxine Hydrochloride

Constipation

Diarrhea

Gastrointestinal hemorrhage

Grinding teeth

Loss of appetite

Nausea

Summary

Vomiting

Xerostomia

3.3.4.A.1 Constipation

a) Incidence: 8% to 15% (Prod Info EFFEXOR(R) oral tablets, 2008; Prod Info EFFEXOR XR(R) extend
b) During 4- to 8-week placebo-controlled trials of venlafaxine hydrochloride (dose ranging from 75 to 3
was 15% compared to 7% in patients receiving placebo (n=609) (Prod Info EFFEXOR(R) oral tablets, 20
c) Constipation occurred in 8% to 10% of patients on extended-release venlafaxine compared with 3% t
extended-release capsules, 2006).

The table below provides the incidence rates of constipation during clinical trials of extended-release

Studies	Percent of patients with constipation	
	Venlafaxine ER	Placebo
Major depressive disorder (n=642)	8%	5%
Generalized anxiety disorder (n=1936)	10%	4%
Social anxiety disorder (n=1514)	9%	3%
Panic disorder (n=1663)	9%	3%
Key: ER = extended-release		

3.3.4.A.2 Diarrhea

a) Incidence: 8% (Prod Info EFFEXOR(R) oral tablets, 2008; Prod Info EFFEXOR XR(R) extended-relea
b) During 4- to 8-week placebo-controlled trials of venlafaxine hydrochloride (dose ranging from 75 to 3
was 8% compared to 7% in patients receiving placebo (n=609) (Prod Info EFFEXOR(R) oral tablets, 200
c) Diarrhea occurred in 8% of patients on extended-release venlafaxine (n=819) compared with 6% of p
EFFEXOR XR(R) extended-release oral capsules, 2008).

3.3.4.A.3 Gastrointestinal hemorrhage

a) Incidence: rare (Prod Info EFFEXOR(R) oral tablets, 2008; Prod Info EFFEXOR(R) XR oral extended
b) In case reports and epidemiological studies, drugs which interfere with serotonin reuptake (e.g., selec
(SNRIs)) have been associated with an increased incidence of gastrointestinal hemorrhage. Gastrointest
patients) in the premarketing evaluation of patients receiving venlafaxine hydrochloride (HCl). Additionall
venlafaxine HCl in postmarketing reports, although a causal relationship has not been definitively establi
affect coagulation (e.g., NSAIDs, aspirin, warfarin), use caution when these agents are co-administered
therapy should be monitored when venlafaxine is started or discontinued (Prod Info EFFEXOR(R) oral ta

3.3.4.A.4 Grinding teeth

a) A 50-year-old man was prescribed 37.5 mg of oral venlafaxine (a serotonin and norepinephrine reupt
the patient reported anxiety, tremor, insomnia, and clenching and grinding of teeth day and night . After
five weeks of treatment, the patient reported anxiety, tremor, insomnia, and clenching and grinding of tee
two days after the initiation of oral gabapentin 300 mg at night, bruxism ceased (Brown & Hong, 1999).

3.3.4.A.5 Loss of appetite

a) Incidence: 8% to 22% (Prod Info EFFEXOR(R) oral tablets, 2008; Prod Info EFFEXOR XR(R) extend
b) During 4- to 8-week placebo-controlled trials of venlafaxine hydrochloride (dose ranging from 75 to 3
was 11% compared to 2% in patients receiving placebo (n=609) (Prod Info EFFEXOR(R) oral tablets, 20
c) During a dose comparison trial involving 358 patients, the incidence of anorexia was 2.2% for placeb
375 milligrams/day, respectively (Prod Info EFFEXOR(R) oral tablets, 2008).

The table below provides the incidence rates of anorexia during clinical trials of extended-release ve

Studies	Percent of patients with anorexia	
	Venlafaxine ER	Placebo

Major depressive disorder (n=642)	8%	4%
Generalized anxiety disorder (n=1936)	8%	2%
Social anxiety disorder (n=1514)	17%*	2%
Panic disorder (n=1663)	8%*	3%
Key: ER = extended-release; * mostly described as decreased appetite and loss of appetite		

The discontinuation rate for venlafaxine extended-release due to anorexia was 1% in major depress in social anxiety disorder studies of up to 12 weeks, and 0.4% in panic disorder studies of up 10 12

d) Pediatrics

1) The incidence of anorexia in pediatric patients (aged 6 to 17 years) during clinical trials for gener were treated with venlafaxine extended-release and placebo, respectively. None of the patients in th disorder trials in patients aged 8 to 17 years, the incidence of anorexia was 22% and 3% in patients discontinuation rates of venlafaxine extended-release and placebo due to anorexia were 0.7% and venlafaxine extended-release and placebo (Prod Info EFFEXOR XR(R) extended-release oral capsu

3.3.4.A.6 Nausea

a) Incidence: 21% to 58% (Prod Info EFFEXOR(R) oral tablets, 2008; Prod Info EFFEXOR XR(R) exten

b) During 4- to 8-week placebo-controlled trials of venlafaxine hydrochloride (dose ranging from 75 to 3 37% compared to 11% in patients receiving placebo (n=609) (Prod Info EFFEXOR(R) oral tablets, 2008)

c) During a dose comparison trial involving 358 patients, the incidence of nausea was 14.1% for placeb 375 milligrams/day, respectively. Over a 6-week period, there was evidence of adaptation to nausea with

The table below provides the incidence rates of nausea during clinical trials of extended-release ver

Studies	Percent of patients with nausea	
	Venlafaxine ER	Placebo
Major depressive disorder (n=642)	31%	12%
Generalized anxiety disorder (n=1936)	35%	12%
Social anxiety disorder (n=1514)	31%	9%
Panic disorder (n=1663)	21%	14%
Key: ER = extended-release		

d) The discontinuation rate due to nausea for venlafaxine extended-release was 2% to 8% compared wi release oral capsules, 2008).

e) Although venlafaxine is a highly effective antidepressant, up to one- third of patients develop nausea. However, in others, reduction of the dose or discontinuation of the drug is required. For this group, cisap treatment with venlafaxine. Other alternatives to reduce nausea include: (1) administration of venlafaxine (3) counseling patients about possible nausea with reassurance that it will decrease over time (Amchin & induced nausea and vomiting is increased serotonin levels within the chemoreceptor trigger zone and ar and vomiting (McManis & Talley, 1997).

3.3.4.A.7 Summary

a) Adverse effects which commonly occurred during clinical trials of venlafaxine and venlafaxine extend Rare cases of gastrointestinal hemorrhage have been reported rarely (defined as occurring in fewer thar hydrochloride (HCl). Additionally, hemorrhage, including gastrointestinal bleeding, has been associated definitively established (Prod Info EFFEXOR(R) oral tablets, 2008; Prod Info EFFEXOR XR(R) extended

3.3.4.A.8 Vomiting

a) Incidence: 3% to 7.9% (Prod Info EFFEXOR(R) oral tablets, 2008; Prod Info EFFEXOR XR(R) exten

b) During 4- to 8-week placebo-controlled trials of venlafaxine hydrochloride (dose ranging from 75 to 3 was 6% compared to 2% in patients receiving placebo (n=609) (Prod Info EFFEXOR(R) oral tablets, 200

c) During a dose comparison trial involving 358 patients, the incidence of vomiting was 1.1% for placeb milligrams/day, respectively (Prod Info EFFEXOR(R) oral tablets, 2008).

The table below provides the incidence rates of vomiting during clinical trials of extended-release ve

Studies	Percent of patients with vomiting	
	Venlafaxine ER	Placebo
Major depressive disorder (n=642)	4%	2%
Generalized anxiety disorder (n=1936)	5%	3%
Social anxiety disorder (n=1514)	3%	2%
Key: ER = extended-release		

d) The proposed mechanism for selective serotonin reuptake inhibitor-induced nausea and vomiting is i brainstem, the primary areas within the brain associated with nausea and vomiting (McManis & Talley, 1 (Klamerus et al, 1992b; Saletu et al, 1992b; Schweizer et al, 1988; Schweizer et al, 1991).

3.3.4.A.9 Xerostomia

a) Incidence: 12% to 22% (Prod Info EFFEXOR(R) oral tablets, 2008; Prod Info EFFEXOR XR(R) exten

b) During 4- to 8-week placebo-controlled trials of venlafaxine hydrochloride (dose ranging from 75 to 3

was 22% compared to 11% in patients receiving placebo (n=609) (Prod Info EFFEXOR(R) oral tablets, 2
c) Dry mouth occurred in 12% to 17% of patients on extended-release venlafaxine compared with 4% to
extended-release capsules, 2006).

The table below provides the incidence rates of dry mouth during clinical trials of extended-release v

Studies	Percent of patients with dry mouth	
	Venlafaxine ER	Placebo
Major depressive disorder (n=642)	12%	6%
Generalized anxiety disorder (n=1936)	16%	6%
Social anxiety disorder (n=1514)	17%	4%
Panic disorder (n=1663)	12%	6%
Key: ER = extended-release		

3.3.5 Hematologic Effects

3.3.5.A Venlafaxine Hydrochloride

Agranulocytosis

Bleeding, Abnormal

Ecchymosis

3.3.5.A.1 Agranulocytosis

a) Approximately 3 weeks after discontinuing mianserin therapy and 5 days after beginning venlafaxine
58/microliter; total WBC count, 2,900). The patient completely recovered following the discontinuation of
(Lucht et al, 2000).

3.3.5.A.2 Bleeding, Abnormal

a) In case reports and epidemiological studies, drugs which interfere with serotonin reuptake (e.g., selec
(SNRIs)) have been associated with an increased incidence of gastrointestinal hemorrhage. Bleeding ev
gastrointestinal bleeding, and life-threatening hemorrhages have been reported with SSRI and SNRI use
affect coagulation (e.g., NSAIDs, aspirin, warfarin), use caution when these agents are co-administered
therapy should be monitored when venlafaxine is started or discontinued (Prod Info EFFEXOR(R) oral ta
b) A 19-year-old woman developed easy and spontaneous bruising on her arms one week after beginni
studies were within normal limits; bleeding time was not evaluated. Ten days after stopping venlafaxine,
possible. She was initially treated with sertraline 50 mg daily, but due to intolerable diarrhea, it was stopp
are an interaction between venlafaxine and sertraline or a change in platelet serotonin transporter which

3.3.5.A.3 Ecchymosis

a) Incidence: 1% or greater (Prod Info EFFEXOR(R) oral tablets, 2008; Prod Info EFFEXOR XR(R) exte
b) Ecchymosis has been reported frequently (defined as occurring on one or more occasions in at least
hydrochloride (HCl). Because the risk of bleeding may be increased by the concomitant use of drugs tha
administered with venlafaxine HCl. Additionally, patients receiving concurrent warfarin therapy should be
tablets, 2008; Prod Info EFFEXOR XR(R) extended-release oral capsules, 2008).

3.3.6 Hepatic Effects

3.3.6.A Venlafaxine Hydrochloride

3.3.6.A.1 Hepatitis

a) Incidence: rare (Horsmans et al, 1999; Cardona et al, 2000)
b) LITERATURE REPORTS
1) Venlafaxine 150 milligrams/day for six months was associated with acute hepatitis in a 44-year-o
venlafaxine was started. Due to severe asthenia, LFTs were repeated with the following results: alar
tests for hepatitis were negative, and abdominal ultrasonography was normal; however, a liver biops
stopped, LFTs returned to normal. This patient received lormetazepam and trazodone before venlaf
2) A 78-year-old man with a past history of Parkinson disease and a major depression episode dev
returned to normal after venlafaxine therapy was progressively discontinued (Cardona et al, 2000).

3.3.8 Musculoskeletal Effects

3.3.8.A Venlafaxine Hydrochloride

3.3.8.A.1 Rhabdomyolysis

a) A 38-year-old male developed rhabdomyolysis after ingesting venlafaxine and lamotrigine (Peano et

3.3.9 Neurologic Effects

3.3.9.A Venlafaxine Hydrochloride

Asthenia

Dizziness

Dream disorder

Headache

Insomnia

Restless legs syndrome

Seizure

Somnolence

Summary

Tremor

3.3.9.A.1 Asthenia

a) Incidence: 8% to 19% (Prod Info EFFEXOR(R) oral tablets, 2008; Prod Info EFFEXOR XR(R) extend

b) Immediate-release

1) During 4- to 8-week placebo-controlled trials of venlafaxine hydrochloride (dose ranging from 75 (n=1033) was 12% compared to 6% in patients receiving placebo (n=609) (Prod Info EFFEXOR(R)

2) During a dose comparison trial involving 358 patients, the incidence of asthenia was 3.3% for pla and 375 milligrams/day, respectively (Prod Info EFFEXOR(R) oral tablets, 2008).

c) Extended-release

1) Asthenia led to discontinuation in 1% to 3% of patients on extended release venlafaxine and 0% incidence rates of asthenia during clinical trials of extended-release venlafaxine (Prod Info EFFEXO

Studies	Percent of patients with asthenia	
	Venlafaxine ER	Placebo
Major depressive disorder (n=642)	8%	7%
Generalized anxiety disorder (n=1936)	12%	8%
Social anxiety disorder (n=1514)	19%	9%
Panic disorder (n=1663)	10%	8%
Key: ER = extended-release		

3.3.9.A.2 Dizziness

a) Incidence: 11% to 23.9% (Prod Info EFFEXOR(R) oral tablets, 2008; Prod Info EFFEXOR XR(R) exte

b) Immediate-release

1) Dizziness is a relatively common side effect with venlafaxine, usually occurring at higher doses. EFFEXOR(R) oral tablets, 2008; Klamerus et al, 1992b; Saletu et al, 1992b).

2) During 4- to 8-week placebo-controlled trials of venlafaxine hydrochloride (dose ranging from 75 (n=1033) was 19% compared to 7% in patients receiving placebo (n=609) (Prod Info EFFEXOR(R)

3) During a dose comparison trial involving 358 patients, the incidence of dizziness was 4.3% for pl and 375 milligrams/day, respectively (Prod Info EFFEXOR(R) oral tablets, 2008).

c) Extended-release

1) The table below provides the incidence rates of dizziness associated with extended-release venl release oral capsules, 2008):

Studies	Percent of patients with dizziness	
	Venlafaxine ER	Placebo
Major depressive disorder (n=642)	20%	9%

Generalized anxiety disorder (n=1936)	16%	11%
Social anxiety disorder (n=1514)	16%	8%
Panic disorder (n=1663)	11%	10%
Key: ER = extended-release		

3.3.9.A.3 Dream disorder

a) Incidence: 3% to 7% (Prod Info EFFEXOR(R) oral tablets, 2008; Prod Info EFFEXOR XR(R) extende

b) During 4- to 8-week placebo-controlled trials of venlafaxine hydrochloride (dose ranging from 75 to 37 (n=1033) was 4% compared to 3% in patients receiving placebo (n=609) (Prod Info EFFEXOR(R) oral ta

c) The table below provides the incidence rates of abnormal dreams, primarily described as "vivid dream venlafaxine (Prod Info EFFEXOR XR(R) extended-release oral capsules, 2008):

Studies	Percent of patients with abnormal dreams	
	Venlafaxine ER	Placebo
Major depressive disorder (n=642)	7%	2%
Generalized anxiety disorder (n=1936)	3%	2%
Social anxiety disorder (n=1514)	3%	less than 1%
Key: ER = extended-release		

3.3.9.A.4 Headache

a) Incidence: 25% to 38% (Prod Info EFFEXOR(R) oral tablets, 2008; Prod Info EFFEXOR XR(R) exten

b) During 4- to 8-week placebo-controlled trials of venlafaxine hydrochloride (dose ranging from 75 to 37 was 25% compared to 24% in patients receiving placebo (n=609) (Prod Info EFFEXOR(R) oral tablets, 2

c) In short-term, placebo-controlled clinical trials involving patients with social anxiety disorder (n=1514) patients experienced headache (Prod Info EFFEXOR XR(R) extended-release oral capsules, 2008)

d) Headache and fatigue are frequently reported side effects and have occurred with higher single dose 1992b; Saletu et al, 1992b).

3.3.9.A.5 Insomnia

a) Incidence: 14% to 24% (Prod Info EFFEXOR(R) oral tablets, 2008; Prod Info EFFEXOR(R) XR oral e

b) Immediate-release

1) During 4- to 8-week placebo-controlled trials of venlafaxine hydrochloride (dose ranging from 75 (n=1033) was 18% compared to 10% in patients receiving placebo (n=609). Insomnia led to drug dis depression studies (Prod Info EFFEXOR(R) oral tablets, 2008).

2) During a dose comparison trial involving 358 patients, the incidence of insomnia was 9.8% for pla and 375 milligrams/day, respectively (Prod Info EFFEXOR(R) oral tablets, 2008).

c) Extended-release

1) The table below provides the incidence rates of insomnia during clinical trials of extended-releas

Studies	Percent of patients with insomnia	
	Venlafaxine ER	Placebo
Major depressive disorder (n=642)	17%	11%
Generalized anxiety disorder (n=1936)	15%	10%
Social anxiety disorder (n=1514)	24%	8%
Panic disorder (n=1663)	17%	9%
Key: ER = extended-release		

The discontinuation rates due to insomnia were 1% to 3% of patients on extended-release venl EFFEXOR XR(R) extended-release oral capsules, 2008).

3.3.9.A.6 Restless legs syndrome

a) In a prospective, naturalistic study of patients (median age, 46 years; range, 18 to 87 years) treated w syndrome (RLS) or worsening of preexisting RLS as a side effect related to treatment. Antidepressants i duloxetine, reboxetine, and mirtazapine. Mirtazapine led to a marked decline of RLS in 28% of subjects symptoms (newly occurred or deteriorated) at the rate of 5% to 10%. Subjects stated symptoms occurre

3.3.9.A.7 Seizure

a) Incidence: 0.3% (Prod Info EFFEXOR(R) oral tablets, 2008; Prod Info EFFEXOR XR(R) extended-rel

b) During premarketing studies of immediate-release venlafaxine, seizures occurred in 8 out of 3082 (0. 5 occurred in patients receiving doses of 150 milligrams daily or less. During premarketing studies of ext extended-release venlafaxine. Venlafaxine should be cautiously used in patients with a history of seizure when venlafaxine and monamine oxidase inhibitor (MAOI) therapy were started or stopped within close p venlafaxine started after a recent discontinuation of an MAOI) (Prod Info EFFEXOR(R) oral tablets, 2008

3.3.9.A.8 Somnolence

a) Incidence: 14% to 26% (Prod Info EFFEXOR(R) oral tablets, 2008; Prod Info EFFEXOR XR(R) exten

b) During 4- to 8-week placebo-controlled trials of venlafaxine hydrochloride (dose ranging from 75 to 37
was 23% compared to 9% in patients receiving placebo (n=609) (Prod Info EFFEXOR(R) oral tablets, 20
c) During a dose comparison trial involving 358 patients, the incidence of somnolence was 4.3% for plac
375 milligrams/day, respectively (Prod Info EFFEXOR(R) oral tablets, 2008).
d) The table below provides the incidence rates of somnolence during clinical trials of extended-release

Studies	Percent of patients with somnolence	
	Venlafaxine ER	Placebo
Major depressive disorder (n=642)	17%	8%
Generalized anxiety disorder (n=1936)	14%	8%
Social anxiety disorder (n=1514)	20%	8%
Panic disorder (n=1663)	12%	6%
Key: ER = extended-release		

e) The discontinuation rates due to somnolence were 0% to 3% in patients on extended-release venlafa
Info EFFEXOR XR(R) extended-release oral capsules, 2008).

3.3.9.A.9 Summary

a) Asthenia, dizziness, headache), insomnia, drowsiness, tremor , and abnormal dreams have common
(R) oral tablets, 2008; Prod Info EFFEXOR XR(R) extended-release oral capsules, 2008). Serious side e
syndrome. Features resembling neuroleptic malignant syndrome have occurred when venlafaxine and m
of each other (MAOI started after a recent discontinuation of venlafaxine or venlafaxine started after a re
EFFEXOR XR(R) extended-release oral capsules, 2008).

3.3.9.A.10 Tremor

a) Incidence: 1.1% to 10.2% (Prod Info EFFEXOR(R) oral tablets, 2008; Prod Info EFFEXOR(R) XR ora
b) During 4- to 8-week placebo-controlled trials of venlafaxine hydrochloride (dose ranging from 75 to 37
5% compared to 1% in patients receiving placebo (n=609) (Prod Info EFFEXOR(R) oral tablets, 2008).
c) During a dose comparison trial involving 358 patients, the incidence of tremor was 0% for placebo co
milligrams/day, respectively (Prod Info EFFEXOR(R) oral tablets, 2008).
d) The table below provides the incidence rates of tremor during clinical trials of extended-release venla

Studies	Percent of patients with tremor	
	Venlafaxine ER	Placebo
Major depressive disorder (n=642)	5%	2%
Generalized anxiety disorder (n=1936)	4%	less than 1%
Social anxiety disorder (n=1514)	2%	2%
Panic disorder (n=1663)	5%	2%
Key: ER = extended-release		

3.3.10 Ophthalmic Effects

3.3.10.A Venlafaxine Hydrochloride

Blurred vision

Disorder of accommodation

Glaucoma

Mydriasis

3.3.10.A.1 Blurred vision

a) Incidence: 4% to 6% (Prod Info EFFEXOR XR(R) extended-release oral capsules, 2008; Prod Info EF
b) During 4- to 8-week placebo-controlled trials of venlafaxine hydrochloride (dose ranging from 75 to 37
(n=1033) was 6% compared to 2% in patients receiving placebo (n=609) (Prod Info EFFEXOR(R) oral ta
c) The table below provides the incidence rates of abnormal vision during clinical trials of extended-relea

Studies	Venlafaxine ER	Placebo
Major depressive disorder (n=642)	4%*	less than 1%
Generalized anxiety disorder (n=1936)	5%*	less than 1%
Social anxiety disorder (n=1514)	4%**	2%
Key: ER = extended-release; * mostly described as blurred vision and difficulty focusing eyes; **		

mostly described as blurred vision

3.3.10.A.2 Disorder of accommodation

a) Incidence: 5.6% to 9.1% (Prod Info EFFEXOR(R) oral tablets, 2008)

b) During a dose comparison trial involving 358 patients, the incidence of abnormality of accommodatio venlafaxine 75, 225, and 375 milligrams/day, respectively (Prod Info EFFEXOR(R) oral tablets, 2008).

3.3.10.A.3 Glaucoma

a) A 45-year-old woman with bipolar disorder developed bilateral acute angle closure glaucoma when sl 150 mg daily). At admission, she was taking sodium valproate 1500 mg per day and slow-release lithium nausea and vomiting, and subsequent swelling and drooping of the left upper eyelid and a dilated and fix intraocular pressure was elevated (50 mmHg). Treatment with intravenous mannitol, topical apraclonidin to 35 mmHg. Laser iridotomy was done repeatedly until successful. Eight days after starting venlafaxine, Venlafaxine was discontinued and successful laser iridotomy was performed. After 8 weeks, her intraocu

3.3.10.A.4 Mydriasis

a) Incidence: 2% (Prod Info EFFEXOR(R) oral tablets, 2008)

b) During 4- to 8-week placebo-controlled trials of venlafaxine hydrochloride (dose ranging from 75 to 3 was 2% compared to less than 1% in patients receiving placebo (n=609). As mydriasis has been reporte angle glaucoma require monitoring during therapy (Prod Info EFFEXOR(R) oral tablets, 2008).

3.3.12 Psychiatric Effects

3.3.12.A Venlafaxine Hydrochloride

Anxiety

Depression, exacerbation

Feeling nervous

Hallucinations

Hypomania

Mania

Paranoid delusion

Suicidal thoughts

Summary

3.3.12.A.1 Anxiety

a) Incidence: 5% to 11.2% (Prod Info EFFEXOR(R) oral tablets, 2008; Prod Info EFFEXOR XR(R) exter

b) During 4- to 8-week placebo-controlled trials of venlafaxine hydrochloride (dose ranging from 75 to 3 6% compared to 3% in patients receiving placebo (n=609). Anxiety led to drug discontinuation in 2% of p EFFEXOR(R) oral tablets, 2008).

c) During a dose comparison trial involving 358 patients, the incidence of anxiety was 4.3% for placebo milligrams/day, respectively (Prod Info EFFEXOR(R) oral tablets, 2008).

d) Anxiety was experienced in 5% of extended-release venlafaxine treated patients and 4% of placebo-t Info EFFEXOR XR(R) extended-release oral capsules, 2008).

3.3.12.A.2 Depression, exacerbation

a) Incidence: rare (Prod Info EFFEXOR(R) oral tablets, 2008; Prod Info EFFEXOR XR(R) extended-rele

b) Adult and pediatric patients being treated with antidepressants for major depressive disorder who exp aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, mania, or other unusual l antidepressant treatment and when the dose is adjusted. Symptoms such as these indicate the need for to treating patients with other psychiatric and nonpsychiatric disorders. If these symptoms are observed, symptoms are severe, sudden in onset, or were not part of the patient's initial symptoms. Patients and th (Prod Info EFFEXOR(R) oral tablets, 2008; Prod Info EFFEXOR XR(R) extended-release oral capsules,

3.3.12.A.3 Feeling nervous

a) Incidence: 4% to 21.3% (Prod Info EFFEXOR(R) oral tablets, 2008; Prod Info EFFEXOR XR(R) exter

b) During 4- to 8-week placebo-controlled trials of venlafaxine hydrochloride (dose ranging from 75 to 37 (n=1033) was 13% compared to 6% in patients receiving placebo (n=609). Nervousness led to drug disc depression studies (Prod Info EFFEXOR(R) oral tablets, 2008).

c) During a dose comparison trial involving 358 patients, the incidence of anxiety was 4.3% for placebo 375 milligrams/day, respectively (Prod Info EFFEXOR(R) oral tablets, 2008).

d) The table below provides the incidence rates of nervousness during clinical trials of extended-release

Studies	Percent of patients with nervousness	
	Venlafaxine ER	Placebo
Major depressive disorder (n=642)	10%	5%
Generalized anxiety disorder (n=1936)	6%	4%
Social anxiety disorder (n=1514)	10%	5%
Panic Disorder (n=1663)	4%	6%
Key: ER = extended-release		

The discontinuation rates due to nervousness were 0.1% to 3% of patients on extended-release ver 2008).

3.3.12.A.4 Hallucinations

a) In a case report, a 17-year-old male exhibited visual and tactile hallucinations following a dose increa headaches. The patient had a family history of anxiety (maternal) and a personal history of DSM-IV mod disorder. He also had a history of drug reactions which included delirium following anesthesia, and visua psychiatric systems were normal. Upon presentation, he had a 6- to 7-month escalation of depression ar anxiety. Concomitant drugs included lamotrigine, eletriptan (once a week), hydrocodone/acetaminophen treatment with venlafaxine immediate release 37.5 mg once daily, the patient's symptoms persisted and dose he experienced visual and tactile hallucinations of crawling bugs and became disoriented 1 hour la delirium. Venlafaxine treatment was suspended until the next morning. On the second day, the patient w morning dose, the patient again experienced visual and tactile hallucinations and within 30 to 60 minutes to the emergency department the patient's symptoms resolved overnight 16 to 20 hours following his las and his anxiety has begun to improve with cognitive-behavioral therapy (Jacob & Ash, 2009).

3.3.12.A.5 Hypomania

a) During Phase 2 and Phase 3 trials with immediate-release venlafaxine, mania or hypomania occurred hypomania occurred in 0.3% of patients receiving venlafaxine extended-release compared with 0% of pla anxiety disorder studies was 0% and 0.2% for venlafaxine extended-release and placebo, respectively, v respectively. During panic disorder trials, the incidence of mania or hypomania was 0.1% and 0% in patie be used cautiously in patients with a history of mania (Prod Info EFFEXOR(R) oral tablets, 2008; Prod In

b) Two women with bipolar affective disorder developed hypomania after starting venlafaxine (Wilson & antidepressants during a two year period of depression. Venlafaxine 75 mg titrated to 225 mg daily resul of venlafaxine. After beginning venlafaxine 75 mg titrated to 150 mg, the second patient became hypoma 5 cases of mania associated with venlafaxine were reported to the United Kingdom's Committee on Safe venlafaxine in patients with bipolar disorder (Wilson & Jenkins, 1997).

3.3.12.A.6 Mania

a) During Phase 2 and Phase 3 trials with immediate-release venlafaxine, mania or hypomania occurred hypomania occurred in 0.3% of patients receiving venlafaxine extended-release compared with 0% of pla anxiety disorder studies was 0% and 0.2% for venlafaxine extended-release and placebo, respectively, v respectively. During panic disorder trials, the incidence of mania or hypomania was 0.1% and 0% in patie be used cautiously in patients with a history of mania (Prod Info EFFEXOR(R) oral tablets, 2008; Prod In

b) A 17-year-old female diagnosed with severe major depressive disorder per DSM-IV criteria experienc She started venlafaxine 37.5 mg/day, which was then gradually increased to 150 mg/day over a 2-week elated moods, increased energy levels, increased speech output, decreased need for sleep, increased g behavior which warranted hospital admission; and she met DSM-IV criteria for mania. Venlafaxine was d and valproate 750 mg/day (subsequently increased to 1500 mg/day) were initiated. The patient reached weeks and the patient remained euthymic during the last 6 month of valproate treatment. Since the patie venlafaxine treatment, the authors suspected venlafaxine-induced mania (Raman et al, 2007).

c) Three patients with no history of mania or hypomania developed mania when they were treated for de months (Shulman et al, 2001)

d) A 63-year-old man with bipolar disorder developed mania six days after venlafaxine was increased to daily and nefazodone but depressive symptoms had not improved after eight months of treatment with n Behavioral symptoms included verbal agitation, hyperactivity, grandiose ideas, thoughts of persecution, i fluphenazine 10 mg at bedtime and an increase in the divalproex sodium dose. Two weeks after stoppin weeks. This patient had been hospitalized several times for manic behavior, and this episode may have temporal relationship to initiation and discontinuation of venlafaxine suggests that venlafaxine may have

3.3.12.A.7 Paranoid delusion

a) Paranoid delusion developed in an 85-year-old Caucasian man following administration of venlafaxin dose from 75 milligrams (mg) daily to 150 mg daily for increasing depression, he began having paranoid the dose to 75 mg/day. Venlafaxine was withdrawn and symptoms resolved within 48 hours. Treatment v symptoms resolved again with the withdrawal of the drug. Sertraline therapy was initiated and no further

3.3.12.A.8 Suicidal thoughts

a) Incidence: rare (Prod Info EFFEXOR(R) oral tablets, 2008; Prod Info EFFEXOR XR(R) extended-rele
b) Adult and pediatric patients being treated with antidepressants for major depressive disorder who exp aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, mania, or other unusual during early antidepressant treatment and when the dose is adjusted. Symptoms such as these indicate concern applies to treating patients with other psychiatric and nonpsychiatric disorders. If these symptom medications when symptoms are severe, sudden in onset, or were not part of the patient's initial symptor available for this drug (Prod Info EFFEXOR(R) oral tablets, 2008; Prod Info EFFEXOR XR(R) extended-
c) A causal role for antidepressants in inducing suicidality has been established in pediatric patients. An with the clinical need. In pooled analyses of 24 short-term, placebo-controlled trials of nine antidepressar nefazodone, and venlafaxine extended-release) including over 4400 pediatric patients with major depres greater risk of suicidal behavior or ideation during the first few months of therapy was demonstrated in pa risk of suicidality was most consistently observed in the trials that included patients with major depressiv such as obsessive compulsive disorder and social anxiety disorder. No suicides occurred in these trials. patients is not known. It is also unknown whether this risk extends to adult patients (Anon, 2004). :
d) Pooled analyses of short-term placebo-controlled trials of antidepressants indicated that treatment wi adolescents and young adults with major depressive disorder and other psychiatric disorders. The poole (citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, bupropion, mirtazapine, nefazodone, and ver disorder (MDD), obsessive compulsive disorder, or other psychiatric disorders, as well as 295 trials (with MDD or other psychiatric disorders. There was a tendency toward an increase in the risk of suicidality in was highest in patients with MDD. The risk differences between drug versus placebo are provided below oral capsules, 2008):

Age Range	Drug-Placebo Difference in Number of Cases of Suicidality per 100 Patients Treated
Less than 18 years	14 Additional Cases
18 to 24 years	5 Additional Cases
25 to 64 years	1 Fewer Case
65 years and older	6 Fewer Cases

3.3.12.A.9 Summary

a) Anxiety, mania/hypomania, nervousness, and suicidal ideation/worsening of depression (rare) have b discontinuation of venlafaxine during clinical trials. Adult and pediatric patients being treated with antidep panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restless of their depression and/or suicidality, especially during early antidepressant treatment and when the dos possible changes in the medication (Prod Info EFFEXOR(R) oral tablets, 2008). Two women with bipolar 1997).

3.3.13 Renal Effects

3.3.13.A Venlafaxine Hydrochloride

Difficulty passing urine

Finding of frequency of urination

3.3.13.A.1 Difficulty passing urine

a) Incidence: 2% (Prod Info EFFEXOR(R) oral tablets, 2008)
b) During 4- to 8-week placebo-controlled trials of venlafaxine hydrochloride (dose ranging from 75 to 37 (n=1033) was 2% compared to less than 1% in patients receiving placebo (n=609) (Prod Info EFFEXOR

3.3.13.A.2 Finding of frequency of urination

a) Incidence: 3% (Prod Info EFFEXOR(R) oral tablets, 2008)
b) During 4- to 8-week placebo-controlled trials of venlafaxine hydrochloride (dose ranging from 75 to 37 (n=1033) was 3% compared to 2% in patients receiving placebo (n=609) (Prod Info EFFEXOR(R) oral ta

3.3.14 Reproductive Effects

Venlafaxine

Venlafaxine Hydrochloride

3.3.14.A Venlafaxine

3.3.14.A.1 Sexual dysfunction

See Drug Consult reference: SELECTIVE SEROTONIN REUPTAKE INHIBITOR-INDUCED SEXUAL D

3.3.14.B Venlafaxine Hydrochloride

Abnormal ejaculation

Impotence

Orgasm disorder

Priapism

Reduced libido

3.3.14.B.1 Abnormal ejaculation

a) Incidence: 2.2% to 19% (Prod Info EFFEXOR(R) oral tablets, 2008; Prod Info EFFEXOR XR(R) exter
b) During 4- to 8-week placebo-controlled trials of venlafaxine hydrochloride (dose ranging from 75 to 3
receiving venlafaxine was 12% compared to less than 1% in patients receiving placebo (Prod Info EFFE
c) During a dose comparison trial involving 358 patients, the incidence of abnormal ejaculation/orgasm
venlafaxine 75, 225, and 375 milligrams/day, respectively (Prod Info EFFEXOR(R) oral tablets, 2008).
d) The table below provides the incidence rates of abnormal ejaculation in males on venlafaxine extend
oral capsules, 2008):

Studies	Percent of males with abnormal ejaculation	
	Venlafaxine ER	Placebo
Major depressive disorder *	16%	less than 1%
Generalized anxiety disorder (n=745) **	11%	less than 1%
Social anxiety disorder (n=811) **	19%	less than 1%
Panic disorder (n=573) ***	8%	less than 1%
Key: ER = extended-release; * = mostly delayed ejaculation; ** = includes delayed ejaculation and anorgasmia; *** = includes delayed or retarded ejaculation and anorgasmia		

3.3.14.B.2 Impotence

a) Incidence: 2.1% to 6% (Prod Info EFFEXOR(R) oral tablets, 2008; Prod Info EFFEXOR XR(R) exten
b) During 4- to 8-week placebo-controlled trials of venlafaxine hydrochloride (dose ranging from 75 to 3
6% compared to less than 1% in patients receiving placebo (Prod Info EFFEXOR(R) oral tablets, 2008).
c) During a dose comparison trial involving 219 male patients, the incidence of impotence was 0% for pl
375 milligrams/day, respectively (Prod Info EFFEXOR(R) oral tablets, 2008).
d) The table below provides the incidence rates of impotence in males on venlafaxine extended-release
capsules, 2008):

Studies	Percent of males with impotence	
	Venlafaxine ER	Placebo
Major depressive disorder	4%	less than 1%
Generalized anxiety disorder (n=745)	5%	less than 1%
Social anxiety disorder (n=811)	6%	less than 1%
Panic disorder (n=573)	4%	less than 1%
Key: ER = extended-release		

3.3.14.B.3 Orgasm disorder

a) Incidence: 2% to 5% (Prod Info EFFEXOR(R) oral tablets, 2008; Prod Info EFFEXOR XR(R) extende
b) During 4- to 8-week placebo-controlled trials of venlafaxine hydrochloride (dose ranging from 75 to 3
venlafaxine was 2% compared to less than 1% in patients receiving placebo (Prod Info EFFEXOR(R) ora

c) The table below provides the incidence rates of anorgasmia, delayed orgasm, or abnormal orgasm in EFFEXOR XR(R) extended-release oral capsules, 2008):

Studies	Percent of females with anorgasmia, delayed orgasm, or abnormal orgasm	
	Venlafaxine ER	Placebo
Major depressive disorder *	3%	less than 1%
Generalized anxiety disorder (n=1191) **	2%	0%
Social anxiety disorder (n=703) ***	5%	less than 1%
Panic disorder (n=1090) *	2%	less than 1%
Key: ER = extended-release; * = mostly delayed orgasm or anorgasmia; ** = includes delayed orgasm, abnormal orgasm and anorgasmia; *** = includes abnormal orgasm and anorgasmia		

3.3.14.B.4 Priapism

a) A 16-year-old boy developed priapism while being treated with venlafaxine (37.5 mg/day, titrated to 1 He had no problem with libido, erection, or ejaculation; however, after ejaculation, his erection persisted venlafaxine and experienced only one more episode of priapism, approximately three weeks after discor

3.3.14.B.5 Reduced libido

a) Incidence: 1.1% to 8% (Prod Info EFFEXOR(R) oral tablets, 2008; Prod Info EFFEXOR XR(R) extenc
b) During 4- to 8-week placebo-controlled trials of venlafaxine hydrochloride (dose ranging from 75 to 37 (n=1033) was 2% compared to less than 1% in patients receiving placebo (n=609) (Prod Info EFFEXOR
c) During a dose comparison trial involving 358 patients, the incidence of reduced libido was 1.1% for pl 375 milligrams/day, respectively (Prod Info EFFEXOR(R) oral tablets, 2008).
d) The table below provides the incidence rates of decreased libido during clinical trials of extended-rele

Studies	Incidence of Decreased Libido	
	Venlafaxine ER	Placebo
Major depressive disorder (n=642)	3%	less than 1%
Generalized anxiety disorder (n=1936)	4%	2%
Social anxiety disorder (n=1514)	8%	2%
Panic disorder (n=1663)	4%	2%
Key: ER = extended-release		

3.3.15 Respiratory Effects

3.3.15.A Venlafaxine Hydrochloride

Interstitial pneumonia

Simple pulmonary eosinophilia

Yawning

3.3.15.A.1 Interstitial pneumonia

a) Two cases of interstitial pneumonia with heart failure have been reported following the use of venlafa month) in combination with steroid treatment led to a complete recovery in a 21-year-old woman. Howev multiple-organ failure and died despite attempts at treatment (Drent et al, 2003). The possibility of interst progressive dyspnea, cough or chest discomfort. In these cases, prompt medical evaluation is necessary tablets, 2008; Prod Info EFFEXOR XR(R) extended-release oral capsules, 2008).

3.3.15.A.2 Simple pulmonary eosinophilia

a) Acute eosinophilic pneumonia developed in a man treated with venlafaxine for 17 days. On admissio crackles and rales; the oxygen saturation was 89.4%. The white blood cell count was elevated with 32.5 transbronchial biopsies showed accumulation of eosinophils and neutrophils within alveolar vessels. He methylprednisolone 1 gram daily for three days followed by tapering doses of prednisone for four weeks. within five days of beginning corticosteroids. All potential infectious causes were excluded with appropria pneumonia that resolved rapidly after starting corticosteroids (Fleisch et al, 2000). The possibility of eosi progressive dyspnea, cough or chest discomfort. In these cases, prompt medical evaluation is necessary tablets, 2008; Prod Info EFFEXOR XR(R) extended-release oral capsules, 2008).

3.3.15.A.3 Yawning

a) Incidence: 3% to 8% (Prod Info EFFEXOR(R) oral tablets, 2008; Prod Info EFFEXOR XR(R) extende

b) A dose increase of venlafaxine extended release (XR) led to excessive yawning in a patient who was or psychiatric disorders, suffered for 8 weeks from dysphoric mood, difficulty in concentration, loss of inte depressive disorder and prescribed venlafaxine XR 75 mg/day for 4 weeks. Due to an inadequate respo improved after 2 weeks of the dose increase. Excessive yawning not associated with drowsiness was nc occurrences of yawning per day, frequently in the morning, that interfered with his normal daily activities the patient's request, and the yawning completely disappeared 3 days after the dose decrease with no fu mechanism of excessive yawning was not clear, noradrenergic and dopaminergic mechanisms may play effect appeared to be dose-dependent (Chen & Lu, 2009).

c) During 4- to 8-week placebo-controlled trials of venlafaxine hydrochloride (dose ranging from 75 to 37 was 3% compared to less than 1% in patients receiving placebo (n=609) (Prod Info EFFEXOR(R) oral ta

d) During a dose comparison trial involving 358 patients, the incidence of yawning was 0% for placebo c milligrams/day, respectively (Prod Info EFFEXOR(R) oral tablets, 2008).

e) The table below provides the incidence rates of yawning during clinical trials of extended-release ven

Studies	Venlafaxine ER	Placebo
Major depressive disorder (n=642)	3%	0%
Generalized anxiety disorder (n=1936)	3%	less than 1%
Social anxiety disorder (n=1514)	5%	less than 1%
Key: ER = extended-release		

3.3.16 Other

Venlafaxine

Venlafaxine Hydrochloride

3.3.16.A Venlafaxine

3.3.16.A.1 Drug withdrawal

See Drug Consult reference: WITHDRAWAL SYNDROME OF SELECTIVE SEROTONIN REUPTAKE IN

3.3.16.B Venlafaxine Hydrochloride

Neuroleptic malignant syndrome

Serotonin syndrome

Withdrawal sign or symptom

3.3.16.B.1 Neuroleptic malignant syndrome

a) Neuroleptic malignant syndrome developed 12 hours after adding venlafaxine 75 mg daily to trifluope effects. The patient presented with profound anxiety, malaise, rigidity, tremor, and severe diaphoresis. O pulse was 163 beats per minute, temperature 38.3 degrees C, and respiratory rate 25 breaths/minute. Al concentration (11,320 international units/L)) and white blood cell count 23.5 x 10(9)/L. Treatment consist hours. Vital signs were normal 24 hours after admission, and trifluoperazine was restarted without proble

3.3.16.B.2 Serotonin syndrome

a) Serotonin syndrome, including life-threatening cases, or neuroleptic malignant syndrome (NMS)-like r serotonin syndrome include mental status changes (eg, agitation, hallucination, coma), autonomic instab hyperreflexia, incoordination) and/or gastrointestinal symptoms (eg, nausea, vomiting, diarrhea). Severe rigidity, autonomic instability with possible rapid fluctuation of vital signs, and mental status changes. Se including triptans, with drugs that impair metabolism of serotonin, including MAOIs, or with antipsychotics 2009; Prod Info Effexor(R) oral tablets, 2009).

b) Despite compliance with the recommended two week washout period, three patients were diagnosed after stopping treatment with phenelzine, a 25-year-old woman started venlafaxine 37.5 mg/day. Followi legs, shakiness, sweating, tachycardia, tachypnea, fever, and increased blood pressure. The woman wa hours later with no residual problems. A 49-year-old woman also started venlafaxine 14 days after disco The woman's symptoms subsided 3 hours later without treatment. Fourteen days after terminating phene tightness, anxiety, and emesis. Symptoms subsided without medical treatment. Finally, a 29-year-old fer

after ingestion of venlafaxine, the woman experienced shakiness, stomach pain, facial flushing, crying, d successfully treated with cyproheptadine and lorazepam and had no residual problems. A longer waiting (Diamond et al, 1998b).

c) A 44-year-old woman experienced serotonin syndrome after accidentally ingesting two 15 mg phenel anxious 30 minutes after ingesting the medications. Forty-five minutes later she experienced lower extre arrival had an elevated blood pressure, heart rate, respiratory rate, and temperature. The patient also ex was given 50 grams of charcoal with sorbitol, hydration therapy, benzodiazepines for muscle rigidity, anc woman showed improvements and an additional six days later was discharged from the hospital with no

d) A 60-year-old female presented to the emergency department obtunded, tachycardic, hyperthermic, h dose of venlafaxine while on maintenance tranylcypromine therapy. The patient recovered following supp

3.3.16.B.3 Withdrawal sign or symptom

a) Withdrawal symptoms such as agitation, anorexia, anxiety, confusion, impaired coordination and bala hypomania, insomnia, nausea, nervousness, nightmares, sensory disturbances (including shock-like ele with abrupt discontinuation or dose reduction of venlafaxine at various doses. The frequency of these eff EFFEXOR(R) oral tablets, 2008; Prod Info EFFEXOR XR(R) extended-release oral capsules, 2008).

b) A 45-year-old man and a 36-year-old woman reported electric shock-like sensations of the head shor experienced severe sensations of shock in his head and radiating to his back and arms on two occasions daily to 75 mg at bedtime and 150 mg at bedtime, respectively. The female patient was taking venlafaxin when trying to stop the medication on several occasions. Her dose was tapered to 37.5 mg three times a objects in her field of vision) when the medicine was withdrawn. For both patients, the sensations resolve

3.4 Teratogenicity/Effects in Pregnancy/Breastfeeding

A) Teratogenicity/Effects in Pregnancy

1) U.S. Food and Drug Administration's Pregnancy Category: Category C (Prod Info Effexor XR(R) extended-rele

a) Either studies in animals have revealed adverse effects on the fetus (teratogenic or embryocidal or other) available. Drugs should be given only if the potential benefit justifies the potential risk to the fetus.

2) Australian Drug Evaluation Committee's (ADEC) Category: B2(Australian Drug Evaluation Committee, 1999)

a) Drugs which have been taken by only a limited number of pregnant women and women of childbearing ag effects on the human fetus having been observed. Studies in animals are inadequate or may be lacking, but a

See Drug Consult reference: PREGNANCY RISK CATEGORIES

3) Crosses Placenta: Unknown

4) Clinical Management

a) Due to the lack of adequate, well-controlled studies in pregnant women, it is recommended that venlafaxir release oral capsules, 2009; Prod Info Effexor(R) oral tablets, 2009; Ferreira et al, 2007). Because adverse s the third trimester, the potential risks and benefits of venlafaxine therapy during this time should be taken into trimester (Prod Info Effexor XR(R) extended-release oral capsules, 2009; Prod Info Effexor(R) oral tablets, 20

5) Literature Reports

a) Neonates exposed to venlafaxine or other serotonin and norepinephrine reuptake inhibitors (SNRIs) or SS hospitalizations, respiratory support and tube feeding. These complications can occur immediately upon deliv difficulty, vomiting, hypoglycemia, hypotonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying or a drug discontinuation syndrome. In some cases, clinical findings have been consistent with serotonin syn (R) oral tablets, 2009).

b) A multicenter, prospective, controlled study comparing the results of pregnant women who called into the trimester and who were being treated with venlafaxine (n=150), an SSRI (n=150), or a nonteratogenic drug (r patients taking venlafaxine. Of the 150 patients in the venlafaxine group, all were treated with venlafaxine in t pregnancy. Of the patients treated with venlafaxine, 105 patients took 75 mg/day of the immediate-release fo (hypospadias and neural tube defect with club foot) reported in the venlafaxine group (1.6%), compared with not a significant difference in pregnancy outcomes among the three groups. An increase in spontaneous abo and the nonteratogenic drugs group (7.3%), but it did not reach statistical significance (Einarson et al, 2001).

c) Seventy-nine neonates of mothers treated with SSRIs or venlafaxine (n=76) during the third trimester exhi mothers (n=90). Treatment included paroxetine 5 to 40 mg (n=46), fluoxetine 10 to 40 mg (n=10), venlafaxine fluvoxamine 50 to 150 mg (n=2) with a mean duration of 32 months for SSRI use. In the treated group, 1 pati gestational age was reported in exposed infants (38.3 weeks) compared with 39.7 weeks; p less than 0.001). spasms, hypotonia, irritability, sleep disturbances, apnea/bradycardia and tachypnea. Respiratory effects, inc neonates. Exposed neonates also had a longer median length of hospitalization compared with unexposed in were hospitalized nearly 4 times longer than unexposed infants (14.5 days vs 3.7 days; p less than 0.001). Et potential risks and benefits in continuing SSRI or venlafaxine treatment during pregnancy on an individual ba

d) A study of prospectively collected data suggests antenatal use of SSRI antidepressants is associated with 2005, researchers compared 52 neonates exposed to SSRI antidepressants (paroxetine (n=25), citalopram (antenatal period to 52 matched neonates with no exposure. Prolonged QTc is defined as an interval of greate pediatric cardiology and neonatology). A pediatric cardiologist, blinded to drug exposure, interpreted all electr markedly prolonged mean QTc intervals in exposed neonates compared to unexposed neonates (mean; 409 longer among exposed neonates (mean; 280 +/- 31 msec vs 261 +/- 25 msec, p less than 0.001). Ten percer than 460 msec) compared to none of the unexposed neonates. The longest QTc interval observed was 543 r

e) Two cases of seizures were reported in neonates born to mothers using venlafaxine during pregnancy. Se found in either case. Both children had subsequently normal growth and development at one year follow-up (

f) A case report described development of necrotizing enterocolitis in dichorial, diamniotic, twin infants on the

throughout pregnancy until delivery. The mother, who experienced uneventful first and second trimesters, wa
was diagnosed for which she received azithromycin for 4 days. She received betamethasone 12 g twice in 24
section at 33+2 weeks. Twin A and B weighed 1700 g and 1980 g, respectively, with Apgar scores of 6, 7, an
intubated on day 1 of life. Twin A was successfully extubated on day 2. On day 6, signs of necrotizing enteroc
observed in the infants. Subsequently, oral feeding was withheld and IV amikacin and amoxicillin were given
continued to deteriorate and underwent surgery on day 10. Bowel necrosis was observed. Therefore, termina
was performed. He underwent a second surgery for stomal stenosis on day 22 of life. At 5 months of age, the
the remaining transverse colon and the proximal section of the descending colon for which an intestinal anas
2009).

B) Breastfeeding

1) Thomson Lactation Rating: Infant risk cannot be ruled out.

a) Available evidence and/or expert consensus is inconclusive or is inadequate for determining infant risk wh
potential risks before prescribing this drug during breastfeeding.

2) Clinical Management

a) Venlafaxine is excreted in human breast milk. Because of the potential for serious adverse effects in nursi
nursing, taking into consideration the importance of the drug to the mother (Prod Info Effexor XR(R) extended
administered to a nursing woman, the nursing infant should be monitored closely for adverse effects (Ilett et a

3) Literature Reports

a) A study of 78 breast-feeding mothers treated with antidepressants (3 took venlafaxine at a dose of 162.5 r
venlafaxine. The mean weights of all infants exposed to antidepressants in the study were 7.26 +/- 0.71 kg fo
normative growth data and remained similar in separate analyses of each antidepressant. However, infants o
months or more) despite antidepressant treatment weighed significantly less at 6 months (p=0.002) when cor
infants born to mothers who did not relapse to depression. The small venlafaxine sample size, maternal use
took psychotropics such as benzodiazepines or tricyclic antidepressants during the study), and absence of a

b) A study describing 3 lactating women treated with venlafaxine and their nursing infants found infant mean
concentrations for the sum of venlafaxine plus O-desmethylvenlafaxine (ODV). The maternal drug dose was
the mothers. The authors suggest that breast-feeding should generally not be discouraged in mothers treatec

c) Venlafaxine and its metabolite, O-desmethylvenlafaxine (ODV) were detected in six infant blood samples
venlafaxine dose of 255 mg/day in a study of 6 women taking venlafaxine and their 7 nursing infants (mean a
concentration of 5 mcg/L, while ODV was present in four infants in concentrations ranging from 3 to 38 mcg/r
2.74 (range 2.3 to 3.2), respectively. Although no adverse effects were noted in the infants, the authors recor
the potential risks and benefits of breast-feeding during venlafaxine therapy (Ilett et al, 2002).

d) Detectable levels of the metabolite O-desmethylvenlafaxine (ODV) were reported in three infants exposec
milk (milk-to-plasma concentration ratio of 4:1 and 3:1, respectively). Total infant exposure was 7.6% of the w
(Ilett et al, 1998).

4) Drug Levels in Breastmilk

a) Venlafaxine Hydrochloride

1) Parent Drug

a) Percent Adult Dose in Breastmilk

1) 7.6% (Ilett et al, 1998)

2) Active Metabolites

a) O-desmethylvenlafaxine (Prod Info EFFEXOR(R) oral tablets, 2008; Prod Info EFFEXOR XR(R)

1) Milk to Maternal Plasma Ratio

a) 3.06 +/- 0.08 (Ilett et al, 1998)

3.5 Drug Interactions

Drug-Drug Combinations

Drug-Food Combinations

3.5.1 Drug-Drug Combinations

Aceclofenac

Acemetacin

Acenocoumarol

Alclofenac

Almotriptan

Amitriptyline

Amoxapine

Amoxicillin

Anagrelide

Ancrod

Anisindione

Antithrombin III Human

Aspirin

Atazanavir

Benoxaprofen

Bivalirudin

Bromfenac

Bufexamac

Cannabis

Carprofen

Celecoxib

Cilostazol

Cimetidine

Clarithromycin

Clomipramine

Clonixin

Clopidogrel

Clozapine

Danaparoid

Defibrotide

Dermatan Sulfate

Desipramine

Desirudin

Desvenlafaxine

Dexfenfluramine

Dexketoprofen

Dextroamphetamine

Dibenzepin

Diclofenac

Dicumarol

Diflunisal

Dipyridamole

Dipyrone

Dothiepin

Doxepin

Droxicam

Duloxetine

Entacapone

Epoprostenol

Eptifibatide

Etodolac

Etofenamate

Etoricoxib

Felbinac

Fenbufen

Fenfluramine

Fenoprofen

Fentiazac

Floctafenine

Flufenamic Acid

Fluoxetine

Flurbiprofen

Fondaparinux

Frovatriptan

Furazolidone

Ginkgo

Haloperidol

Heparin

Ibuprofen

Iloprost

Imipramine

Indinavir

Indomethacin

Indoprofen

Iproniazid

Isocarboxazid

Isoxicam

Itraconazole

Jujube

Ketoconazole

Ketoprofen

Ketorolac

Lamifiban

Lexipafant

Linezolid

Lornoxicam

Meclofenamate

Mefenamic Acid

Meloxicam

Metoclopramide

Metoprolol

Mirtazapine

Moclobemide

Morniflumate

Nabumetone

Naproxen

Naratriptan

Nefazodone

Nelfinavir

Nialamide

Niflumic Acid

Nimesulide

Nortriptyline

Oxaprozin

Parecoxib

Pargyline

Pentosan Polysulfate Sodium

Phenelzine

Phenindione

Phenprocoumon

Phenylbutazone

Pirazolac

Piroxicam

Pirprofen

Procarbazine

Propyphenazone

Proquazone

Protriptyline

Rasagiline

Ritonavir

Rizatriptan

Rofecoxib

Saquinavir

Selegiline

Sibrafiban

Sibutramine

St John's Wort

Sulfinpyrazone

Sulindac

Sulodexide

Sumatriptan

Suprofen

Tapentadol

Telithromycin

Tenidap

Tenoxicam

Tiaprofenic Acid

Ticlopidine

Tirofiban

Tolmetin

Toloxatone

Tramadol

Tranylcypromine

Trazodone

Trifluoperazine

Trimipramine

Valdecoxib

Vasopressin

Warfarin

Xemilofiban

Zolmitriptan

Zolpidem

Zomepirac

3.5.1.A Aceclofenac

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control anc
NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ec
(R) oral tablets, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When venlafaxine and a nonsteroidal antiinflammatory agent are given concurrentl
2008).
7) Probable Mechanism: unknown

3.5.1.B Acemetacin

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control anc
NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ec
(R) oral tablets, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When venlafaxine and a nonsteroidal antiinflammatory agent are given concurrentl
2008).
7) Probable Mechanism: unknown

3.5.1.C Acenocoumarol

1) Interaction Effect: an increased risk of bleeding
2) Summary: Case reports and epidemiological studies have shown that use of selective serotonin reuptake
venlafaxine, is associated with gastrointestinal bleeding. Bleeding events with SSRIs and SNRIs included cas
have also occurred. Coadministration with warfarin or other anticoagulants may potentiate the risk of bleedin
phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased ris
Increases in prothrombin time, partial thromboplastin time, or INR have been reported when venlafaxine was
with warfarin or other drugs affecting coagulation should be undertaken with caution. Whenever venlafaxine i
coagulation parameters is recommended (Prod Info EFFEXOR XR(R) extended-release oral capsules, 2008a
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Use caution when venlafaxine is used concomitantly with warfarin or other drugs af
or discontinued in patients receiving anticoagulants, such as warfarin (Prod Info EFFEXOR XR(R) extended-
7) Probable Mechanism: additive adverse events
8) Literature Reports
a) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoum
increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospit
abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duratio
showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95
(adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).

3.5.1.D Alclofenac

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control anc
NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ec
(R) oral tablets, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When venlafaxine and a nonsteroidal antiinflammatory agent are given concurrentl
2008).
7) Probable Mechanism: unknown

3.5.1.E Almotriptan

1) Interaction Effect: an increased risk of serotonin syndrome
2) Summary: Concomitant use of almotriptan and selective serotonin reuptake inhibitors (SSRI's) has been r
Concurrent use of a triptan and an SSRI may result in serotonin syndrome which may be life-threatening. Sy
coordination, fast heart beat, rapid changes in blood pressure, increased body temperature, overreactive refl
commonly used intermittently and that either the triptan or the SSRI may be prescribed by a different physicia
combination and monitor them closely for symptoms of serotonin syndrome (US Food and Drug Administratic
3) Severity: major
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Coadministration of a triptan, such as almotriptan, and an SSRI may result in a life-
used intermittently and that either the triptan or the SSRI may be prescribed by a different physician. If these
monitor closely for symptoms of serotonin syndrome (restlessness, hyperthermia, hyperreflexia, incoordinatic
7) Probable Mechanism: additive pharmacologic effects resulting in excessive serotonergic stimulation
8) Literature Reports
a) Concomitant administration of fluoxetine and almotriptan is well tolerated and fluoxetine has only a m
pharmacokinetics are not significantly affected. A randomized, open-label, two-way crossover study invo
treatments with a minimum 3-week washout between periods: (1) three 20 mg fluoxetine capsules on da
on day 8 with no treatment on days 1 through 7. Peak almotriptan concentrations were 18% higher follov
This difference was statistically significant (p equal 0.023). Mean almotriptan area under the concentratic
treatment groups. Mean half-life was not statistically different between the treatment groups. During fluo
almotriptan may have been increased by fluoxetine. The author concludes that based on the results of th
and fluoxetine can be safely used concomitantly in migraine management (Fleishaker et al, 2001).

3.5.1.F Amitriptyline

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest
2) Summary: Tricyclic antidepressants (TCAs) and venlafaxine have been shown to prolong the QTc interval
1982). Even though no formal drug interaction studies have been done, the coadministration of tricyclic antid
recommended (Prod Info Elavil(R), 1999). In addition, venlafaxine and tricyclic antidepressants (TCAs) may c
(Perry, 2000; Prod Info Effexor(R) XR, 2003; Ellingrod & Perry, 1994a). Venlafaxine increased the AUC, Cma
increased by 2.5 and 4.5 fold when administered with venlafaxine 37.5 mg and 75 mg every 12 hours, respec
affected (Prod Info venlafaxine extended release oral tablets, 2008).
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Due to the potential for additive effects on the QT interval, the concurrent administra
7) Probable Mechanism: decreased TCA and venlafaxine metabolism; additive effects on QT prolongation
8) Literature Reports
a) When administered with imipramine, the pharmacokinetics of imipramine and the 2-hydroxy metaboli
(AUC), maximum concentration (Cmax), and minimum concentration (Cmin) of desipramine by approxim
12 hours) and by 4.5-fold (venlafaxine 75 mg every 12 hours). The clinical significance of this finding is u

3.5.1.G Amoxapine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest
2) Summary: Tricyclic antidepressants (TCAs) and venlafaxine have been shown to prolong the QTc interval
1982). Even though no formal drug interaction studies have been done, the coadministration of tricyclic antid
recommended (Prod Info Elavil(R), 1999). In addition, venlafaxine and tricyclic antidepressants (TCAs) may c
(Perry, 2000; Prod Info Effexor(R) XR, 2003; Ellingrod & Perry, 1994a). Venlafaxine increased the AUC, Cma
increased by 2.5 and 4.5 fold when administered with venlafaxine 37.5 mg and 75 mg every 12 hours, respec
affected (Prod Info venlafaxine extended release oral tablets, 2008).
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Due to the potential for additive effects on the QT interval, the concurrent administra
7) Probable Mechanism: decreased TCA and venlafaxine metabolism; additive effects on QT prolongation
8) Literature Reports
a) When administered with imipramine, the pharmacokinetics of imipramine and the 2-hydroxy metaboli

(AUC), maximum concentration (Cmax), and minimum concentration (Cmin) of desipramine by approxim
12 hours) and by 4.5-fold (venlafaxine 75 mg every 12 hours). The clinical significance of this finding is u

3.5.1.H Amoxicillin

1) Interaction Effect: an increased risk of serotonin syndrome

2) Summary: A 56-year-old male on venlafaxine experienced serotonin syndrome within 3 hours of taking an amoxicillin/clavulanate and venlafaxine are used concomitantly, monitor closely for symptoms of serotonin sy supportive care and other therapy as necessary (Boyer & Shannon, 2005).

3) Severity: major

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: A case of serotonin syndrome was reported with coadministration of amoxicillin/clav amoxicillin/clavulanate and venlafaxine are used concomitantly, monitor closely for symptoms of serotonin sy rigidity, clonus, peripheral hypertonicity, and shivering), autonomic hyperactivity (including tachycardia, mydri changes (including agitation and delirium). Serotonin syndrome can be life-threatening. If serotonin syndrome therapy as necessary (Boyer & Shannon, 2005).

7) Probable Mechanism: unknown

8) Literature Reports

a) A 56-year-old male on venlafaxine experienced serotonin syndrome within 3 hours of taking amoxicill mg twice daily for 10 months for depression. He experienced tingling in the tip of his tongue, intense para uncontrollable shivering and tremor, agitation, and he was frightened but not confused 2 hours after takir symptoms resolved after 6 hours and then he slept a further 8 hours. No further amoxicillin/clavulanate d same symptoms after the first dose. The patient continued on venlafaxine without further episodes. His r without any events (Connor, 2003).

3.5.1.I Anagrelide

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case reports and (SSRIs) and serotonin-norephinephrine reuptake inhibitors (SNRIs), including venlafaxine, is associated with ecchymoses, hematomas, epistaxis, and petechiae; life-threatening hemorrhages have also occurred. Coadr the risk of bleeding (Prod Info EFFEXOR XR(R) extended-release oral capsules, 2008a).

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: Use caution when venlafaxine is used concomitantly with antiplatelet agents. Close patients receiving antiplatelet agents concomitantly (Prod Info EFFEXOR XR(R) extended-release oral capsu

7) Probable Mechanism: unknown

3.5.1.J Ancrod

1) Interaction Effect: an increased risk of bleeding

2) Summary: Case reports and epidemiological studies have shown that use of selective serotonin reuptake venlafaxine, is associated with gastrointestinal bleeding. Bleeding events with SSRIs and SNRIs included cas have also occurred. Coadministration with warfarin or other anticoagulants may potentiate the risk of bleeding phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased ris Increases in prothrombin time, partial thromboplastin time, or INR have been reported when venlafaxine was with warfarin or other drugs affecting coagulation should be undertaken with caution. Whenever venlafaxine i coagulation parameters is recommended (Prod Info EFFEXOR XR(R) extended-release oral capsules, 2008a

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: Use caution when venlafaxine is used concomitantly with warfarin or other drugs af or discontinued in patients receiving anticoagulants, such as warfarin (Prod Info EFFEXOR XR(R) extended-

7) Probable Mechanism: additive adverse events

8) Literature Reports

a) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoum increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospit abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duratic showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95 (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).

3.5.1.K Anisindione

1) Interaction Effect: an increased risk of bleeding

2) Summary: Case reports and epidemiological studies have shown that use of selective serotonin reuptake venlafaxine, is associated with gastrointestinal bleeding. Bleeding events with SSRIs and SNRIs included cas have also occurred. Coadministration with warfarin or other anticoagulants may potentiate the risk of bleeding phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased ris Increases in prothrombin time, partial thromboplastin time, or INR have been reported when venlafaxine was with warfarin or other drugs affecting coagulation should be undertaken with caution. Whenever venlafaxine i

coagulation parameters is recommended (Prod Info EFFEXOR XR(R) extended-release oral capsules, 2008a
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Use caution when venlafaxine is used concomitantly with warfarin or other drugs af
or discontinued in patients receiving anticoagulants, such as warfarin (Prod Info EFFEXOR XR(R) extended-
7) Probable Mechanism: additive adverse events
8) Literature Reports
a) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoum
increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospit
abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duratic
showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95
(adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).

3.5.1.L Antithrombin III Human
1) Interaction Effect: an increased risk of bleeding
2) Summary: Case reports and epidemiological studies have shown that use of selective serotonin reuptake
venlafaxine, is associated with gastrointestinal bleeding. Bleeding events with SSRIs and SNRIs included cas
have also occurred. Coadministration with warfarin or other anticoagulants may potentiate the risk of bleeding
phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased ris
Increases in prothrombin time, partial thromboplastin time, or INR have been reported when venlafaxine was
with warfarin or other drugs affecting coagulation should be undertaken with caution. Whenever venlafaxine i
coagulation parameters is recommended (Prod Info EFFEXOR XR(R) extended-release oral capsules, 2008a
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Use caution when venlafaxine is used concomitantly with warfarin or other drugs af
or discontinued in patients receiving anticoagulants, such as warfarin (Prod Info EFFEXOR XR(R) extended-
7) Probable Mechanism: additive adverse events
8) Literature Reports
a) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoum
increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospit
abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duratic
showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95
(adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).

3.5.1.M Aspirin
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case reports and
(SSRIs) and serotonin-norephinephrine reuptake inhibitors (SNRIs), including venlafaxine, is associated with
ecchymoses, hematomas, epistaxis, and petechiae; life-threatening hemorrhages have also occurred. Coadr
the risk of bleeding (Prod Info EFFEXOR XR(R) extended-release oral capsules, 2008a).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Use caution when venlafaxine is used concomitantly with antiplatelet agents. Close
patients receiving antiplatelet agents concomitantly (Prod Info EFFEXOR XR(R) extended-release oral capsu
7) Probable Mechanism: unknown

3.5.1.N Atazanavir
1) Interaction Effect: increased plasma concentrations of venlafaxine
2) Summary: Caution is advised if a CYP3A4 inhibitor is administered with venlafaxine due to the possible in
(Prod Info venlafaxine extended release oral tablets, 2008). Patients should be monitored for venlafaxine toxi
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Patients should be monitored for signs of venlafaxine toxicity such as nausea, drow
7) Probable Mechanism: decreased venlafaxine clearance
8) Literature Reports
a) Caution is warranted with the concurrent use of CYP3A4 inhibitors, such as atazanavir, and venlafaxi
desvenlafaxine (ODV) (Prod Info venlafaxine extended release oral tablets, 2008).

3.5.1.O Benoxaprofen
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and
NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ec
(R) oral tablets, 2008).
3) Severity: moderate

4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When venlafaxine and a nonsteroidal antiinflammatory agent are given concurrentl
2008).
7) Probable Mechanism: unknown

3.5.1.P Bivalirudin
1) Interaction Effect: an increased risk of bleeding
2) Summary: Case reports and epidemiological studies have shown that use of selective serotonin reuptake
venlafaxine, is associated with gastrointestinal bleeding. Bleeding events with SSRIs and SNRIs included cas
have also occurred. Coadministration with warfarin or other anticoagulants may potentiate the risk of bleedin
phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased ris
Increases in prothrombin time, partial thromboplastin time, or INR have been reported when venlafaxine was
with warfarin or other drugs affecting coagulation should be undertaken with caution. Whenever venlafaxine i
coagulation parameters is recommended (Prod Info EFFEXOR XR(R) extended-release oral capsules, 2008a
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Use caution when venlafaxine is used concomitantly with warfarin or other drugs af
or discontinued in patients receiving anticoagulants, such as warfarin (Prod Info EFFEXOR XR(R) extended-
7) Probable Mechanism: additive adverse events
8) Literature Reports
a) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoum
increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospit
abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duratio
showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95
(adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).

3.5.1.Q Bromfenac
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control anc
NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ec
(R) oral tablets, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When venlafaxine and a nonsteroidal antiinflammatory agent are given concurrentl
2008).
7) Probable Mechanism: unknown

3.5.1.R Bufexamac
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control anc
NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ec
(R) oral tablets, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When venlafaxine and a nonsteroidal antiinflammatory agent are given concurrentl
2008).
7) Probable Mechanism: unknown

3.5.1.S Cannabis
1) Interaction Effect: manic symptoms
2) Summary: One case of mania following use of marijuana with fluoxetine therapy has been reported (Stoll
symptoms could have resulted from the fluoxetine or marijuana alone. Caution is advised for patients using m
3) Severity: moderate
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Caution patients taking selective serotonin reuptake inhibitors to avoid concomitant
7) Probable Mechanism: additive serotonergic stimulation
8) Literature Reports
a) A 21-year-old female presented with mania, agitation, and grandiose delusions following use of mariju
reported smoking 2 "joints" during a 36-hour period. Over the next 24 hours, she developed increased en
perphenazine were given for agitation and excitement which gradually resolved over 4 days. She remain
prior to discharge. One week after discharge, she discontinued fluoxetine due to insomnia and feeling "h
rapid switch to mania after smoking marijuana with fluoxetine, the manic symptoms were associated with
from either fluoxetine or marijuana alone (Stoll et al, 1991).

3.5.1.T Carprofen

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control anc NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ec (R) oral tablets, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When venlafaxine and a nonsteroidal antiinflammatory agent are given concurrentl 2008).
7) Probable Mechanism: unknown

3.5.1.U Celecoxib

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control anc NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ec (R) oral tablets, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When venlafaxine and a nonsteroidal antiinflammatory agent are given concurrentl 2008).
7) Probable Mechanism: unknown

3.5.1.V Cilostazol

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case reports anc (SSRIs) and serotonin-norephinephrine reuptake inhibitors (SNRIs), including venlafaxine, is associated with ecchymoses, hematomas, epistaxis, and petechiae; life-threatening hemorrhages have also occurred. Coadr the risk of bleeding (Prod Info EFFEXOR XR(R) extended-release oral capsules, 2008a).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Use caution when venlafaxine is used concomitantly with antiplatelet agents. Close patients receiving antiplatelet agents concomitantly (Prod Info EFFEXOR XR(R) extended-release oral capsu
7) Probable Mechanism: unknown

3.5.1.W Cimetidine

1) Interaction Effect: an increased risk of venlafaxine toxicity (nausea, drowsiness, dizziness, ejaculatory dis
2) Summary: Concurrent administration of cimetidine and venlafaxine (both at steady state) resulted in a 43 concentration of venlafaxine (Prod Info venlafaxine extended release oral tablets, 2008). The major metabolit amounts in the circulation than the parent drug. Because of this, it is unlikely that a clinically significant intera in patients with preexisting hepatic or renal dysfunction (Troy et al, 1998a). Therefore, caution is advised whe hepatic or renal function (Prod Info venlafaxine extended release oral tablets, 2008).
3) Severity: minor
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Concomitant use of cimetidine and venlafaxine may result in decreased venlafaxine as nausea, drowsiness, and dizziness; a decrease in dosage may be required with concomitant therapy. An a such as ranitidine or famotidine, may be an alternative.
7) Probable Mechanism: decreased venlafaxine clearance
8) Literature Reports
a) Eighteen healthy volunteers received venlafaxine 50 mg three times daily for five days alone and in c pharmacokinetics of venlafaxine. Venlafaxine has pharmacologic activity, and the metabolite O-desmeth cimetidine was coadministered, the average steady-state concentration of venlafaxine increased from a desmethylvenlafaxine did not change in the presence of cimetidine (388 ng/mL vs. 387 ng/mL). Therefor increased by an average of 13%. This increase is not expected to produce clinically significant alteration (Troy et al, 1998).

3.5.1.X Clarithromycin

1) Interaction Effect: increased plasma concentrations of venlafaxine
2) Summary: Caution is advised if a CYP3A4 inhibitor is administered with venlafaxine, due to the possible i (Prod Info venlafaxine extended release oral tablets, 2008). Patients should be monitored for venlafaxine toxi
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Patients should be monitored for signs of venlafaxine toxicity such as nausea, drow

7) Probable Mechanism: decreased venlafaxine clearance
8) Literature Reports
a) Caution is warranted with the concurrent use of CYP3A4 inhibitors, such as clarithromycin, and venla desvenlafaxine (ODV) (Prod Info venlafaxine extended release oral tablets, 2008).

3.5.1.Y Clomipramine
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Tricyclic antidepressants (TCAs) and venlafaxine have been shown to prolong the QTc interval 1982). Even though no formal drug interaction studies have been done, the coadministration of tricyclic antide recommended (Prod Info Elavil(R), 1999). In addition, venlafaxine and tricyclic antidepressants (TCAs) may c (Perry, 2000; Prod Info Effexor(R) XR, 2003; Ellingrod & Perry, 1994a). Venlafaxine increased the AUC, Cma increased by 2.5 and 4.5 fold when administered with venlafaxine 37.5 mg and 75 mg every 12 hours, respec affected (Prod Info venlafaxine extended release oral tablets, 2008).
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Due to the potential for additive effects on the QT interval, the concurrent administra
7) Probable Mechanism: decreased TCA and venlafaxine metabolism; additive effects on QT prolongation
8) Literature Reports
a) When administered with imipramine, the pharmacokinetics of imipramine and the 2-hydroxy metaboli (AUC), maximum concentration (Cmax), and minimum concentration (Cmin) of desipramine by approxim 12 hours) and by 4.5-fold (venlafaxine 75 mg every 12 hours). The clinical significance of this finding is u

3.5.1.Z Clonixin
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ec (R) oral tablets, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When venlafaxine and a nonsteroidal antiinflammatory agent are given concurrently 2008).
7) Probable Mechanism: unknown

3.5.1.AA Clopidogrel
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case reports and (SSRIs) and serotonin-norephinephrine reuptake inhibitors (SNRIs), including venlafaxine, is associated with ecchymoses, hematomas, epistaxis, and petechiae; life-threatening hemorrhages have also occurred. Coadr the risk of bleeding (Prod Info EFFEXOR XR(R) extended-release oral capsules, 2008a).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Use caution when venlafaxine is used concomitantly with antiplatelet agents. Close patients receiving antiplatelet agents concomitantly (Prod Info EFFEXOR XR(R) extended-release oral capsu
7) Probable Mechanism: unknown

3.5.1.AB Clozapine
1) Interaction Effect: increased serum concentrations of clozapine and venlafaxine
2) Summary: Coadministration of clozapine with other drugs that are metabolized by cytochrome P450 2D6, The hepatic P450IID6 isoenzyme is apparently involved with clozapine metabolism. Venlafaxine is a weak inl (Prod Info Effexor(R) XR, 1999c; Ellingrod & Perry, 1994b). With clozapine-venlafaxine coadministration, botl concentrations of both. Controlled studies are needed to validate these expectations and to document the cli
3) Severity: moderate
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Monitor patients receiving concurrent clozapine and venlafaxine for signs of clozapi venlafaxine toxicity (somnolence). Doses of either or both medications may need to be reduced.
7) Probable Mechanism: decreased clozapine and venlafaxine metabolism

3.5.1.AC Danaparoid
1) Interaction Effect: an increased risk of bleeding
2) Summary: Case reports and epidemiological studies have shown that use of selective serotonin reuptake venlafaxine, is associated with gastrointestinal bleeding. Bleeding events with SSRIs and SNRIs included cas have also occurred. Coadministration with warfarin or other anticoagulants may potentiate the risk of bleeding phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased ris Increases in prothrombin time, partial thromboplastin time, or INR have been reported when venlafaxine was

with warfarin or other drugs affecting coagulation should be undertaken with caution. Whenever venlafaxine i
coagulation parameters is recommended (Prod Info EFFEXOR XR(R) extended-release oral capsules, 2008a
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Use caution when venlafaxine is used concomitantly with warfarin or other drugs af
or discontinued in patients receiving anticoagulants, such as warfarin (Prod Info EFFEXOR XR(R) extended-
7) Probable Mechanism: additive adverse events
8) Literature Reports
a) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoum
increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospit
abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duratic
showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95
(adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).

3.5.1.AD Defibrotide

1) Interaction Effect: an increased risk of bleeding
2) Summary: Case reports and epidemiological studies have shown that use of selective serotonin reuptake
venlafaxine, is associated with gastrointestinal bleeding. Bleeding events with SSRIs and SNRIs included cas
have also occurred. Coadministration with warfarin or other anticoagulants may potentiate the risk of bleedin
phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased ris
Increases in prothrombin time, partial thromboplastin time, or INR have been reported when venlafaxine was
with warfarin or other drugs affecting coagulation should be undertaken with caution. Whenever venlafaxine i
coagulation parameters is recommended (Prod Info EFFEXOR XR(R) extended-release oral capsules, 2008a
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Use caution when venlafaxine is used concomitantly with warfarin or other drugs af
or discontinued in patients receiving anticoagulants, such as warfarin (Prod Info EFFEXOR XR(R) extended-
7) Probable Mechanism: additive adverse events
8) Literature Reports
a) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoum
increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospit
abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duratic
showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95
(adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).

3.5.1.AE Dermatan Sulfate

1) Interaction Effect: an increased risk of bleeding
2) Summary: Case reports and epidemiological studies have shown that use of selective serotonin reuptake
venlafaxine, is associated with gastrointestinal bleeding. Bleeding events with SSRIs and SNRIs included cas
have also occurred. Coadministration with warfarin or other anticoagulants may potentiate the risk of bleedin
phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased ris
Increases in prothrombin time, partial thromboplastin time, or INR have been reported when venlafaxine was
with warfarin or other drugs affecting coagulation should be undertaken with caution. Whenever venlafaxine i
coagulation parameters is recommended (Prod Info EFFEXOR XR(R) extended-release oral capsules, 2008a
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Use caution when venlafaxine is used concomitantly with warfarin or other drugs af
or discontinued in patients receiving anticoagulants, such as warfarin (Prod Info EFFEXOR XR(R) extended-
7) Probable Mechanism: additive adverse events
8) Literature Reports
a) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoum
increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospit
abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duratic
showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95
(adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).

3.5.1.AF Desipramine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest
2) Summary: Tricyclic antidepressants (TCAs) and venlafaxine have been shown to prolong the QTc interval
1982). Even though no formal drug interaction studies have been done, the coadministration of tricyclic antide
recommended (Prod Info Elavil(R), 1999). In addition, venlafaxine and tricyclic antidepressants (TCAs) may c
(Perry, 2000; Prod Info Effexor(R) XR, 2003; Ellingrod & Perry, 1994a). Venlafaxine increased the AUC, Cma
increased by 2.5 and 4.5 fold when administered with venlafaxine 37.5 mg and 75 mg every 12 hours, respec
affected (Prod Info venlafaxine extended release oral tablets, 2008).
3) Severity: major

4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Due to the potential for additive effects on the QT interval, the concurrent administr
7) Probable Mechanism: decreased TCA and venlafaxine metabolism; additive effects on QT prolongation
8) Literature Reports
a) When administered with imipramine, the pharmacokinetics of imipramine and the 2-hydroxy metaboli
(AUC), maximum concentration (Cmax), and minimum concentration (Cmin) of desipramine by approxim
12 hours) and by 4.5-fold (venlafaxine 75 mg every 12 hours). The clinical significance of this finding is u

3.5.1.AG Desirudin
1) Interaction Effect: an increased risk of bleeding
2) Summary: Case reports and epidemiological studies have shown that use of selective serotonin reuptake
venlafaxine, is associated with gastrointestinal bleeding. Bleeding events with SSRIs and SNRIs included cas
have also occurred. Coadministration with warfarin or other anticoagulants may potentiate the risk of bleedin
phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased ris
Increases in prothrombin time, partial thromboplastin time, or INR have been reported when venlafaxine was
with warfarin or other drugs affecting coagulation should be undertaken with caution. Whenever venlafaxine i
coagulation parameters is recommended (Prod Info EFFEXOR XR(R) extended-release oral capsules, 2008a
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Use caution when venlafaxine is used concomitantly with warfarin or other drugs af
or discontinued in patients receiving anticoagulants, such as warfarin (Prod Info EFFEXOR XR(R) extended-
7) Probable Mechanism: additive adverse events
8) Literature Reports
a) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoum
increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospit
abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duratic
showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95
(adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).

3.5.1.AH Desvenlafaxine
1) Interaction Effect: increased risk of serotonin syndrome (hypertension, hyperthermia, myoclonus, mental s
2) Summary: Desvenlafaxine is the major active metabolite of venlafaxine, and these agents should not be u
norepinephrine reuptake inhibitors, and their concomitant use may result in serotonin syndrome, which may b
hallucinations, loss of coordination, fast heart beat, rapid changes in blood pressure, increased body tempera
extended-release tablets, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of of desvenlafaxine and venlafaxine should be avoided, as desve
and norepinephrine reuptake inhibitors, and concomitant use increases the risk of serotonin syndrome (Prod
7) Probable Mechanism: additive serotonergic effect

3.5.1.AI Dexfenfluramine
1) Interaction Effect: serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)
2) Summary: Dexfenfluramine is a nonspecific serotonin agonist that both enhances the release of serotonin
selective serotonin reuptake inhibitor, such as venlafaxine, has the potential to cause serotonin syndrome (S
characterized by symptoms such as restlessness, myoclonus, changes in mental status, hyperreflexia, diaph
(Sternbach, 1991k). Dexfenfluramine should not be used in combination with venlafaxine (Prod Info Redux(R
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Concurrent use of dexfenfluramine and venlafaxine may result in an additive increa
syndrome (hypertension, hyperthermia, myoclonus, mental status changes). Dexfenfluramine should not be u
7) Probable Mechanism: additive serotonergic effects

3.5.1.AJ Dexketoprofen
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control anc
NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ec
(R) oral tablets, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When venlafaxine and a nonsteroidal antiinflammatory agent are given concurrentl
2008).
7) Probable Mechanism: unknown

3.5.1.AK Dextroamphetamine

1) Interaction Effect: an increased risk of serotonin syndrome

2) Summary: Two weeks of concurrent use of dextroamphetamine and venlafaxine resulted in symptoms of s venlafaxine are used concomitantly, monitor closely for symptoms of serotonin syndrome. Serotonin syndrom agents and provide supportive care and other therapy as necessary (Boyer & Shannon, 2005).

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: A case of serotonin syndrome was reported with coadministration of dextroamphetа concomitantly, monitor closely for symptoms of serotonin syndrome such as neuromuscular abnormalities (in shivering), autonomic hyperactivity (including tachycardia, mydriasis, diaphoresis, the presence of bowel sou Serotonin syndrome can be life-threatening. If serotonin syndrome develops, discontinue the offending agent

7) Probable Mechanism: additive pharmacologic effects

8) Literature Reports

a) A 32-year-old male on dextroamphetamine experienced serotonin syndrome approximately 2 weeks attention deficit hyperactivity disorder. He started 75 mg a day of venlafaxine for 1 week then the dose w experienced marked agitation, anxiety, shivering, and tremor. On admission he was alert and oriented. H per minute, blood pressure was 142/93 mmHg, and temperature was 37.3 degrees Celsius. No nystagm generalized hypertonia, hyperreflexia, inducible ankle clonus, frequent myoclonic jerking, and unilateral-t sinus tachycardia with a baseline tremor. Dextroamphetamine and venlafaxine were discontinued and cy and he was discharged the following morning. Dextroamphetamine was restarted 3 days later. Four days symptoms as he did with dextroamphetamine and venlafaxine. Agitation, nausea, diarrhea, and teeth cle cyproheptadine were given and within 2 days he was asymptomatic (Prior et al, 2002).

3.5.1.AL Dibenzepin

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest

2) Summary: Tricyclic antidepressants (TCAs) and venlafaxine have been shown to prolong the QTc interval 1982). Even though no formal drug interaction studies have been done, the coadministration of tricyclic antid recommended (Prod Info Elavil(R), 1999). In addition, venlafaxine and tricyclic antidepressants (TCAs) may c (Perry, 2000; Prod Info Effexor(R) XR, 2003; Ellingrod & Perry, 1994a). Venlafaxine increased the AUC, Cma increased by 2.5 and 4.5 fold when administered with venlafaxine 37.5 mg and 75 mg every 12 hours, respec affected (Prod Info venlafaxine extended release oral tablets, 2008).

3) Severity: major

4) Onset: rapid

5) Substantiation: theoretical

6) Clinical Management: Due to the potential for additive effects on the QT interval, the concurrent administra

7) Probable Mechanism: decreased TCA and venlafaxine metabolism; additive effects on QT prolongation

8) Literature Reports

a) When administered with imipramine, the pharmacokinetics of imipramine and the 2-hydroxy metaboli (AUC), maximum concentration (Cmax), and minimum concentration (Cmin) of desipramine by approxim 12 hours) and by 4.5-fold (venlafaxine 75 mg every 12 hours). The clinical significance of this finding is u

3.5.1.AM Diclofenac

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ec (R) oral tablets, 2008).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When venlafaxine and a nonsteroidal antiinflammatory agent are given concurrentl 2008).

7) Probable Mechanism: unknown

3.5.1.AN Dicumarol

1) Interaction Effect: an increased risk of bleeding

2) Summary: Case reports and epidemiological studies have shown that use of selective serotonin reuptake venlafaxine, is associated with gastrointestinal bleeding. Bleeding events with SSRIs and SNRIs included cas have also occurred. Coadministration with warfarin or other anticoagulants may potentiate the risk of bleeding phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased ris Increases in prothrombin time, partial thromboplastin time, or INR have been reported when venlafaxine was with warfarin or other drugs affecting coagulation should be undertaken with caution. Whenever venlafaxine i coagulation parameters is recommended (Prod Info EFFEXOR XR(R) extended-release oral capsules, 2008a

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: Use caution when venlafaxine is used concomitantly with warfarin or other drugs af

or discontinued in patients receiving anticoagulants, such as warfarin (Prod Info EFFEXOR XR(R) extended-
7) Probable Mechanism: additive adverse events
8) Literature Reports
a) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoum increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospit abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duratic showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95 (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).

3.5.1.AO Diflunisal
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control anc NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ec (R) oral tablets, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When venlafaxine and a nonsteroidal antiinflammatory agent are given concurrentl 2008).
7) Probable Mechanism: unknown

3.5.1.AP Dipyridamole
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case reports anc (SSRIs) and serotonin-norephinephrine reuptake inhibitors (SNRIs), including venlafaxine, is associated with ecchymoses, hematomas, epistaxis, and petechiae; life-threatening hemorrhages have also occurred. Coadr the risk of bleeding (Prod Info EFFEXOR XR(R) extended-release oral capsules, 2008a).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Use caution when venlafaxine is used concomitantly with antiplatelet agents. Close patients receiving antiplatelet agents concomitantly (Prod Info EFFEXOR XR(R) extended-release oral capsu
7) Probable Mechanism: unknown

3.5.1.AQ Dipyrone
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control anc NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ec (R) oral tablets, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When venlafaxine and a nonsteroidal antiinflammatory agent are given concurrentl 2008).
7) Probable Mechanism: unknown

3.5.1.AR Dothiepin
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest
2) Summary: Tricyclic antidepressants (TCAs) and venlafaxine have been shown to prolong the QTc interval 1982). Even though no formal drug interaction studies have been done, the coadministration of tricyclic antid recommended (Prod Info Elavil(R), 1999). In addition, venlafaxine and tricyclic antidepressants (TCAs) may c (Perry, 2000; Prod Info Effexor(R) XR, 2003; Ellingrod & Perry, 1994a). Venlafaxine increased the AUC, Cma increased by 2.5 and 4.5 fold when administered with venlafaxine 37.5 mg and 75 mg every 12 hours, respec affected (Prod Info venlafaxine extended release oral tablets, 2008).
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Due to the potential for additive effects on the QT interval, the concurrent administr
7) Probable Mechanism: decreased TCA and venlafaxine metabolism; additive effects on QT prolongation
8) Literature Reports
a) When administered with imipramine, the pharmacokinetics of imipramine and the 2-hydroxy metaboli (AUC), maximum concentration (Cmax), and minimum concentration (Cmin) of desipramine by approxim 12 hours) and by 4.5-fold (venlafaxine 75 mg every 12 hours). The clinical significance of this finding is u

3.5.1.AS Doxepin
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest
2) Summary: Tricyclic antidepressants (TCAs) and venlafaxine have been shown to prolong the QTc interval 1982). Even though no formal drug interaction studies have been done, the coadministration of tricyclic antid

recommended (Prod Info Elavil(R), 1999). In addition, venlafaxine and tricyclic antidepressants (TCAs) may c
(Perry, 2000; Prod Info Effexor(R) XR, 2003; Ellingrod & Perry, 1994a). Venlafaxine increased the AUC, Cma
increased by 2.5 and 4.5 fold when administered with venlafaxine 37.5 mg and 75 mg every 12 hours, respec
affected (Prod Info venlafaxine extended release oral tablets, 2008).
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Due to the potential for additive effects on the QT interval, the concurrent administra
7) Probable Mechanism: decreased TCA and venlafaxine metabolism; additive effects on QT prolongation
8) Literature Reports
a) When administered with imipramine, the pharmacokinetics of imipramine and the 2-hydroxy metaboli
(AUC), maximum concentration (Cmax), and minimum concentration (Cmin) of desipramine by approxim
12 hours) and by 4.5-fold (venlafaxine 75 mg every 12 hours). The clinical significance of this finding is u

3.5.1.AT Droxicam
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control anc
NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ec
(R) oral tablets, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When venlafaxine and a nonsteroidal antiinflammatory agent are given concurrently
2008).
7) Probable Mechanism: unknown

3.5.1.AU Duloxetine
1) Interaction Effect: an increased risk of serotonin syndrome
2) Summary: Duloxetine is a selective serotonin and norepinephrine reuptake inhibitor. The concomitant use
inhibitor, is not recommended due to the potential for serotonin syndrome (Prod Info CYMBALTA(R) delayed-
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concomitant use of duloxetine and venlafaxine is not recommended due to the
release oral capsules, 2008).
7) Probable Mechanism: additive serotonergic effects

3.5.1.AV Entacapone
1) Interaction Effect: an increased risk of tachycardia, hypertension, and arrhythmias
2) Summary: Entacapone is an inhibitor of catechol-o-methyltransferase (COMT), and inhibits the metabolisr
inhibitor; the concurrent administration of entacapone and venlafaxine may theoretically provoke a suprathera
cardiovascular adverse events (Prod Info Comtan(R), 2000; Prod Info Comtan(R), 2004).
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Coadministration of entacapone with venlafaxine is not recommended. Caution sho
be monitored for excessively increased heart rate, increased blood pressure, and cardiac arrhythmias.
7) Probable Mechanism: augmented inhibition of norepinephrine metabolism and clearance

3.5.1.AW Epoprostenol
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case reports anc
(SSRIs) and serotonin-norephinephrine reuptake inhibitors (SNRIs), including venlafaxine, is associated with
ecchymoses, hematomas, epistaxis, and petechiae; life-threatening hemorrhages have also occurred. Coadr
the risk of bleeding (Prod Info EFFEXOR XR(R) extended-release oral capsules, 2008a).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Use caution when venlafaxine is used concomitantly with antiplatelet agents. Close
patients receiving antiplatelet agents concomitantly (Prod Info EFFEXOR XR(R) extended-release oral capsu
7) Probable Mechanism: unknown

3.5.1.AX Eptifibatide
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case reports anc
(SSRIs) and serotonin-norephinephrine reuptake inhibitors (SNRIs), including venlafaxine, is associated with
ecchymoses, hematomas, epistaxis, and petechiae; life-threatening hemorrhages have also occurred. Coadr
the risk of bleeding (Prod Info EFFEXOR XR(R) extended-release oral capsules, 2008a).

3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Use caution when venlafaxine is used concomitantly with antiplatelet agents. Close patients receiving antiplatelet agents concomitantly (Prod Info EFFEXOR XR(R) extended-release oral capsu
7) Probable Mechanism: unknown

3.5.1.AY Etodolac
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control anc NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ec (R) oral tablets, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When venlafaxine and a nonsteroidal antiinflammatory agent are given concurrentl 2008).
7) Probable Mechanism: unknown

3.5.1.AZ Etofenamate
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control anc NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ec (R) oral tablets, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When venlafaxine and a nonsteroidal antiinflammatory agent are given concurrentl 2008).
7) Probable Mechanism: unknown

3.5.1.BA Etoricoxib
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control anc NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ec (R) oral tablets, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When venlafaxine and a nonsteroidal antiinflammatory agent are given concurrentl 2008).
7) Probable Mechanism: unknown

3.5.1.BB Felbinac
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control anc NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ec (R) oral tablets, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When venlafaxine and a nonsteroidal antiinflammatory agent are given concurrentl 2008).
7) Probable Mechanism: unknown

3.5.1.BC Fenbufen
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control anc NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ec (R) oral tablets, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When venlafaxine and a nonsteroidal antiinflammatory agent are given concurrentl 2008).
7) Probable Mechanism: unknown

3.5.1.BD Fenfluramine

1) Interaction Effect: serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)
2) Summary: Fenfluramine is a nonspecific serotonin agonist that both enhances the release of serotonin an serotonin reuptake inhibitor, such as venlafaxine, has the potential to cause serotonin syndrome (Schenck & symptoms such as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, more data are available, fenfluramine should not be used in combination with venlafaxine.
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Concurrent use of fenfluramine and venlafaxine may result in an additive increase i (hypertension, hyperthermia, myoclonus, mental status changes). Fenfluramine should not be used in combi
7) Probable Mechanism: additive serotonergic effects

3.5.1.BE Fenoprofen
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control anc NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ec (R) oral tablets, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When venlafaxine and a nonsteroidal antiinflammatory agent are given concurrentl 2008).
7) Probable Mechanism: unknown

3.5.1.BF Fentiazac
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control anc NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ec (R) oral tablets, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When venlafaxine and a nonsteroidal antiinflammatory agent are given concurrentl 2008).
7) Probable Mechanism: unknown

3.5.1.BG Floctafenine
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control anc NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ec (R) oral tablets, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When venlafaxine and a nonsteroidal antiinflammatory agent are given concurrentl 2008).
7) Probable Mechanism: unknown

3.5.1.BH Flufenamic Acid
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control anc NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ec (R) oral tablets, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When venlafaxine and a nonsteroidal antiinflammatory agent are given concurrentl 2008).
7) Probable Mechanism: unknown

3.5.1.BI Fluoxetine
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest mental status changes)
2) Summary: Venlafaxine and fluoxetine have been shown to prolong the QTc interval at the recommended though no formal drug interaction studies have been done, the coadministration of drugs known to prolong th fluoxetine may result in serotonin syndrome (Chan et al, 1998a).
3) Severity: major
4) Onset: rapid

5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of venlafaxine and fluoxetine is not recommended.
7) Probable Mechanism: additive effects on QT prolongation; additive serotonergic effect

3.5.1.BJ Flurbiprofen
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control anc NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ec (R) oral tablets, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When venlafaxine and a nonsteroidal antiinflammatory agent are given concurrentl 2008).
7) Probable Mechanism: unknown

3.5.1.BK Fondaparinux
1) Interaction Effect: an increased risk of bleeding
2) Summary: Case reports and epidemiological studies have shown that use of selective serotonin reuptake venlafaxine, is associated with gastrointestinal bleeding. Bleeding events with SSRIs and SNRIs included cas have also occurred. Coadministration with warfarin or other anticoagulants may potentiate the risk of bleedin phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased ris Increases in prothrombin time, partial thromboplastin time, or INR have been reported when venlafaxine was with warfarin or other drugs affecting coagulation should be undertaken with caution. Whenever venlafaxine i coagulation parameters is recommended (Prod Info EFFEXOR XR(R) extended-release oral capsules, 2008a
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Use caution when venlafaxine is used concomitantly with warfarin or other drugs af or discontinued in patients receiving anticoagulants, such as warfarin (Prod Info EFFEXOR XR(R) extended-
7) Probable Mechanism: additive adverse events
8) Literature Reports
a) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoum increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospit abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duratic showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95 (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).

3.5.1.BL Frovatriptan
1) Interaction Effect: increased risk of serotonin syndrome
2) Summary: A life-threatening condition known as serotonin syndrome may occur when triptans, such as fro (SNRI), such as venlafaxine. Symptoms of serotonin syndrome may include restlessness, hallucinations, loss temperature, overreactive reflexes, nausea, vomiting, and diarrhea. Clinicians should be aware that triptans r prescribed by a different physician. Discuss the risks of serotonin syndrome with patients who are prescribed and Drug Administration, 2006).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of a triptan, such as frovatriptan, and an SNRI, such as venlafaxir triptans may be commonly used intermittently and that either the triptan or the SNRI may be prescribed by a syndrome with the patient and monitor closely for symptoms of serotonin syndrome (restlessness, hypertherr
7) Probable Mechanism: additive pharmacologic effects resulting in excessive serotonergic stimulation

3.5.1.BM Furazolidone
1) Interaction Effect: weakness, hyperreflexia, and incoordination
2) Summary: Although not its primary mechanism of action, furazolidone has monoamine oxidase inhibitor a receiving selective serotonin reuptake inhibitors (SSRI) in combination with monoamine oxidase inhibitors (M fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium a SSRI, or within a minimum of 14 days of discontinuing therapy with a MAOI (Prod Info Furoxone(R), 1999).
3) Severity: contraindicated
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: If concurrent therapy with furazolidone and a selective serotonin reuptake inhibitor excess (mental status changes, diaphoresis, fever, weakness, hyperreflexia, incoordination).
7) Probable Mechanism: additive pharmacologic effects resulting in excessive serotonergic stimulation

3.5.1.BN Ginkgo
1) Interaction Effect: increased risk of serotonin syndrome (hypertension, hyperthermia, myoclonus, mental s

2) Summary: The addition of Ginkgo biloba and/or St. John's Wort to therapy with buspirone and fluoxetine r
is unclear if Ginkgo or St. John's Wort, the combination of both, or other patient factors, contributed to the eff
selective serotonin reuptake inhibitors (SSRIs). Caution is advised, especially when ginkgo is taken to counte
(Sloley et al, 2000; White et al, 1996), and has demonstrated serotonergic activity in animals (Ramassamy et
with SSRIs. The potential MAO inhibitory activity of ginkgo is questionable. A human study did not show MAC
extract inhibited MAO-A/MAO-B in the rat brain in vitro (Sloley et al, 2000; White et al, 1996) and MAO-B in h
following oral consumption (Porsolt et al, 2000).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor patients closely for symptoms of serotonin syndrome if ginkgo is combined
7) Probable Mechanism: additive pharmacologic effects resulting in excessive serotonergic stimulation
8) Literature Reports
a) A 42-year-old female experienced symptoms consistent with a mixed hypomanic episode following cc
symptoms resolved following discontinuation of Ginkgo and St. John's Wort. The patient was being treat
twice daily and buspirone 15 mg twice daily. Several weeks prior to presentation, buspirone was increas
melatonin, and St. John's Wort in unspecified doses. Melatonin was considered unlikely to have contribu
since they may potentiate antidepressants, and considering the temporal relationship between the use o
symptoms. However, the brain injury was considered a possible contributor (Spinella & Eaton, 2002).

3.5.1.BO Haloperidol
1) Interaction Effect: increased haloperidol serum concentrations and an increased risk of cardiotoxicity (QT
2) Summary: Venlafaxine may inhibit haloperidol metabolism (Prod Info Effexor(R) XR, 2003c). Haloperidol i
Prod Info Haldol(R), 2001). Venlafaxine has been shown to prolong the QTc interval at the recommended the
3) Severity: major
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: The concurrent administration of haloperidol and venlafaxine is not recommended.
7) Probable Mechanism: decreased haloperidol metabolism; theoretical additive effect on QT prolongation
8) Literature Reports
a) Under steady-state conditions, venlafaxine 150 mg daily decreased the total oral clearance of a singl
in the haloperidol area under the concentration-time curve (AUC). The haloperidol maximum concentrati
elimination half-life of haloperidol was not affected. The mechanism behind this interaction is not known
b) Numerous case reports have described significant QTc prolongation and torsades de pointes (TdP) a
ventricular fibrillation, asystole, and death have been reported. The risk of TdP appears to be greater wit
increases with doses greater than 35 milligrams (mg) over 24 hours, although TdP has been associated
haloperidol-induced TdP, screen patients for a history of dilated cardiomyopathy or alcohol abuse, testin
throughout therapy, and monitoring potassium, magnesium, and calcium. In patients with a baseline QTc
alternative agent should be used. Discontinue haloperidol if the QTc increases more than 25% from base
2003).

3.5.1.BP Heparin
1) Interaction Effect: an increased risk of bleeding
2) Summary: Case reports and epidemiological studies have shown that use of selective serotonin reuptake
venlafaxine, is associated with gastrointestinal bleeding. Bleeding events with SSRIs and SNRIs included cas
have also occurred. Coadministration with warfarin or other anticoagulants may potentiate the risk of bleedin
phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased ris
Increases in prothrombin time, partial thromboplastin time, or INR have been reported when venlafaxine was
with warfarin or other drugs affecting coagulation should be undertaken with caution. Whenever venlafaxine i
coagulation parameters is recommended (Prod Info EFFEXOR XR(R) extended-release oral capsules, 2008a
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Use caution when venlafaxine is used concomitantly with warfarin or other drugs af
or discontinued in patients receiving anticoagulants, such as warfarin (Prod Info EFFEXOR XR(R) extended-
7) Probable Mechanism: additive adverse events
8) Literature Reports
a) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoum
increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospit
abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duratic
showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95
(adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).

3.5.1.BQ Ibuprofen
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control anc
NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ec
(R) oral tablets, 2008).

3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When venlafaxine and a nonsteroidal antiinflammatory agent are given concurrentl
2008).
7) Probable Mechanism: unknown

3.5.1.BR Iloprost
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case reports anc
(SSRIs) and serotonin-norephinephrine reuptake inhibitors (SNRIs), including venlafaxine, is associated with
ecchymoses, hematomas, epistaxis, and petechiae; life-threatening hemorrhages have also occurred. Coadr
the risk of bleeding (Prod Info EFFEXOR XR(R) extended-release oral capsules, 2008a).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Use caution when venlafaxine is used concomitantly with antiplatelet agents. Close
patients receiving antiplatelet agents concomitantly (Prod Info EFFEXOR XR(R) extended-release oral capsu
7) Probable Mechanism: unknown

3.5.1.BS Imipramine
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest
2) Summary: Tricyclic antidepressants (TCAs) and venlafaxine have been shown to prolong the QTc interval
1982). Even though no formal drug interaction studies have been done, the coadministration of tricyclic antid
recommended (Prod Info Elavil(R), 1999). In addition, venlafaxine and tricyclic antidepressants (TCAs) may c
(Perry, 2000; Prod Info Effexor(R) XR, 2003; Ellingrod & Perry, 1994a). Venlafaxine increased the AUC, Cma
increased by 2.5 and 4.5 fold when administered with venlafaxine 37.5 mg and 75 mg every 12 hours, respec
affected (Prod Info venlafaxine extended release oral tablets, 2008).
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Due to the potential for additive effects on the QT interval, the concurrent administr
7) Probable Mechanism: decreased TCA and venlafaxine metabolism; additive effects on QT prolongation
8) Literature Reports
a) When administered with imipramine, the pharmacokinetics of imipramine and the 2-hydroxy metaboli
(AUC), maximum concentration (Cmax), and minimum concentration (Cmin) of desipramine by approxim
12 hours) and by 4.5-fold (venlafaxine 75 mg every 12 hours). The clinical significance of this finding is u

3.5.1.BT Indinavir
1) Interaction Effect: decreased indinavir serum concentrations
2) Summary: Venlafaxine 150 mg per day was administered under steady-state conditions to nine healthy vo
28% for a single 800 mg oral dose of indinavir, while the Cmax decreased by 36%. The pharmacokinetics of
administration of indinavir. The clinical significance of this has not been determined (Prod Info venlafaxine ex
3) Severity: minor
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Although the clinical significance of this interaction is unknown, monitor patient for a
7) Probable Mechanism: increased indinavir metabolism

3.5.1.BU Indomethacin
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control anc
NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ec
(R) oral tablets, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When venlafaxine and a nonsteroidal antiinflammatory agent are given concurrentl
2008).
7) Probable Mechanism: unknown

3.5.1.BV Indoprofen
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control anc
NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ec
(R) oral tablets, 2008).
3) Severity: moderate
4) Onset: unspecified

5) Substantiation: probable
6) Clinical Management: When venlafaxine and a nonsteroidal antiinflammatory agent are given concurrentl
2008).
7) Probable Mechanism: unknown

3.5.1.BW Iproniazid

1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental sta
2) Summary: Concurrent administration or overlapping therapy with venlafaxine and a monoamine oxidase (
state characterized by symptoms such as restlessness, myoclonus, changes in mental status, hyperreflexia,
concomitant use of serotonin specific reuptake inhibitors and MAO inhibitors (Prod Info Effexor(R) XR, 1999a
60-year old woman developed a serious case of serotonin syndrome after the inadvertent ingestion of a singl
Concomitant use is contraindicated.
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Concurrent use of venlafaxine and a MAO inhibitor is contraindicated. Wait at least
at least seven days after discontinuing venlafaxine before initiating therapy with a MAO inhibitor.
7) Probable Mechanism: inhibition of serotonin metabolism by monoamine oxidase
8) Literature Reports
a) Concomitant use of selective serotonin reuptake inhibitors and monoamine oxidase inhibitors can pro
syndrome is a condition of serotonergic hyperstimulation and manifests as restlessness, myoclonus, cha
not recognized and correctly treated, death can result.
b) A 26-year old woman who had been taking isocarboxazid for eight weeks stopped taking the drug for
the patient became restless and developed leg twitches. The patients was later admitted to the emergen
disturbances. After treatment with diazepam and propranolol the patient did not improve. The patient wa
symptoms after the second dose (Lappin & Auchincloss, 1994b).
c) A drug interaction was reported in a 61-year old woman in which sertraline 100 mg twice daily was ac
taking the first sertraline dose, the patient was found in a semicomatose state, with elevated body tempe
Hg. After transportation to the hospital, the patient was misdiagnosed as having neuroleptic malignant sy
sertraline and phenelzine. The authors suggest that monoamine oxidase inhibitor (MAOI) therapy should
serotonin reuptake inhibitor (SSRI) and that before starting a MAOI, SSRI therapy should be discontinue
1994b).
d) Two cases reports suggested a possible interaction between fluoxetine and selegiline (Suchowersky
approximately one month after adding selegiline to fluoxetine therapy. The patient improved two months
case involved diaphoresis, vasoconstriction, and cyanosis of the hands which occurred in close tempora
relatively quick resolution of symptoms. Rechallenge with fluoxetine alone occurred without incident.
e) A case of a 60-year old female who developed serotonin syndrome after the inadvertent ingestion of
Approximately four hours after taking the venlafaxine, the patient became weak, confused, and collapsed
hyperreflexia, and diaphoresis. After treatment with diazepam, dantrolene, and other supportive therapy,

3.5.1.BX Isocarboxazid

1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental sta
2) Summary: Concurrent administration or overlapping therapy with venlafaxine and a monoamine oxidase (
state characterized by symptoms such as restlessness, myoclonus, changes in mental status, hyperreflexia,
concomitant use of serotonin specific reuptake inhibitors and MAO inhibitors (Prod Info Effexor(R) XR, 2000;
Concomitant use is contraindicated (Prod Info Marplan(R), 1998).
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Concurrent use of venlafaxine and a MAO inhibitor is contraindicated. Wait at least
at least seven days after discontinuing venlafaxine before initiating therapy with a MAO inhibitor.
7) Probable Mechanism: inhibition of serotonin metabolism by monoamine oxidase
8) Literature Reports
a) Concomitant use of serotonin specific reuptake inhibitors and monoamine oxidase inhibitors can prod
syndrome is a condition of serotonergic hyperstimulation and manifests as restlessness, myoclonus, cha
not recognized and correctly treated, death can result.
b) A 26-year old woman who had been taking isocarboxazid for eight weeks stopped taking the drug for
the patient became restless and developed leg twitches. The patients was later admitted to the emergen
disturbances. After treatment with diazepam and propranolol the patient did not improve. The patient wa
symptoms after the second dose (Lappin & Auchincloss, 1994d).
c) A 43-year old man began taking venlafaxine 75 mg after showing only a partial response to isocarbox
agitation, hypomania, diaphoresis, shivering, and dilated pupils. The symptoms resolved after discontinu
venlafaxine and isocarboxazid. After approximately six weeks of treatment, the patient was admitted to t
The following day the patient continued to present with symptoms of serotonin syndrome, such as increa
was given every six hours and symptoms slowly resolved over the next six days (Klysner et al, 1995).
d) A drug interaction was reported in a 61-year old woman in which sertraline 100 mg twice daily was ac
taking the first sertraline dose, the patient was found in a semicomatose state, with elevated body tempe

Hg. After transportation to the hospital, the patient was misdiagnosed as having neuroleptic malignant sy sertraline and phenelzine. The authors suggest that monoamine oxidase inhibitor (MAOI) therapy should serotonin reuptake inhibitor (SSRI) and that before starting a MAOI, SSRI therapy should be discontinue 1994d).

e) Two cases reports suggested a possible interaction between fluoxetine and selegiline (Suchowersky approximately 1 month after adding selegiline to fluoxetine therapy. The patient improved 2 months after involved diaphoresis, vasoconstriction, and cyanosis of the hands which occurred in close temporal relat quick resolution of symptoms. Rechallenge with fluoxetine alone occurred without incident.

3.5.1.BY Isoxicam

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control anc NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ec (R) oral tablets, 2008).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When venlafaxine and a nonsteroidal antiinflammatory agent are given concurrentl 2008).

7) Probable Mechanism: unknown

3.5.1.BZ Itraconazole

1) Interaction Effect: increased plasma concentrations of venlafaxine

2) Summary: Caution is advised if a CYP3A4 inhibitor, such as itraconazole, is administered with venlafaxine desvenlafaxine (ODV) (Prod Info venlafaxine extended release oral tablets, 2008). Patients should be monito

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Patients should be monitored for signs of venlafaxine toxicity such as nausea, drow

7) Probable Mechanism: decreased venlafaxine clearance

8) Literature Reports

a) Caution is warranted with the concurrent use of CYP3A4 inhibitors, such as itraconazole, and venlafa desvenlafaxine (ODV) (Prod Info venlafaxine extended release oral tablets, 2008).

3.5.1.CA Jujube

1) Interaction Effect: an increased risk of serotonin syndrome

2) Summary: Serotonin syndrome developed within one hour in a 40-year-old female, when venlafaxine was nut) (Stewart, 2004). If Ziziphus jujube and venlafaxine are used concomitantly, monitor closely for symptoms syndrome develops, discontinue the offending agents and provide supportive care and other therapy as nece

3) Severity: major

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: A case of serotonin syndrome was reported with coadministration of Ziziphus jujube therefore, concomitant use is discouraged (Stewart, 2004). If Ziziphus jujube and venlafaxine are used concc abnormalities (including hyper-reflexia, tremor, muscle rigidity, clonus, peripheral hypertonicity, and shivering bowel sounds, and diarrhea), and mental status changes (including agitation and delirium). Serotonin syndro agents and provide supportive care and other therapy as necessary (Boyer & Shannon, 2005).

7) Probable Mechanism: additive pharmacologic effects

8) Literature Reports

a) Serotonin syndrome developed in a 40-year-old female, when venlafaxine was added to Ziziphus juju jujube 500 mg/day for insomnia, fatigue, nervousness, and poor appetite. After several weeks of treatme venlafaxine she experienced restlessness, nausea, dizziness, and ataxia. She then collapsed. She was and shivering. Peripheral pulses were absent but she had a carotid pulse of 50 bpm. Vital signs were 60/ signs were 180/100 mmHg, 80 beats/minute, and 14 breaths/minute. Vital signs and mental status norm venlafaxine at 150 mg/day, but did not restart jujube, and 1 month later remained stable (Stewart, 2004).

3.5.1.CB Ketoconazole

1) Interaction Effect: an increased risk of venlafaxine toxicity (nausea, drowsiness, dizziness, ejaculatory dis

2) Summary: Caution is advised if ketoconazole, a CYP3A4 inhibitor, is administered with venlafaxine. A pha the O-desvenlafaxine active metabolite with concomitant use (Prod Info EFFEXOR(R) oral tablets, 2008; Pro

3) Severity: minor

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: Patients should be monitored for signs of venlafaxine toxicity such as nausea, drow

7) Probable Mechanism: decreased venlafaxine clearance

8) Literature Reports

a) Higher plasma concentrations of both venlafaxine and the active metabolite O-desvenlafaxine (ODV) dose of venlafaxine (50 mg to 14 extensive metabolizers (EM) and 25 mg to 6 poor metabolizers (PM)).

metabolizers. Cmax of ODV increased by 29% in PM and 14% in EM subjects. Venlafaxine AUC increas
increased by 141% and 23% in PM and EM subjects, respectively, and the combined AUCs of venlafaxi
oral tablets, 2008; Prod Info EFFEXOR XR(R) extended-release oral capsules, 2008).

3.5.1.CC Ketoprofen

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control anc
NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ec
(R) oral tablets, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When venlafaxine and a nonsteroidal antiinflammatory agent are given concurrentl
2008).
7) Probable Mechanism: unknown

3.5.1.CD Ketorolac

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control anc
NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ec
(R) oral tablets, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When venlafaxine and a nonsteroidal antiinflammatory agent are given concurrentl
2008).
7) Probable Mechanism: unknown

3.5.1.CE Lamifiban

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case reports anc
(SSRIs) and serotonin-norephinephrine reuptake inhibitors (SNRIs), including venlafaxine, is associated with
ecchymoses, hematomas, epistaxis, and petechiae; life-threatening hemorrhages have also occurred. Coadr
the risk of bleeding (Prod Info EFFEXOR XR(R) extended-release oral capsules, 2008a).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Use caution when venlafaxine is used concomitantly with antiplatelet agents. Close
patients receiving antiplatelet agents concomitantly (Prod Info EFFEXOR XR(R) extended-release oral capsu
7) Probable Mechanism: unknown

3.5.1.CF Lexipafant

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case reports anc
(SSRIs) and serotonin-norephinephrine reuptake inhibitors (SNRIs), including venlafaxine, is associated with
ecchymoses, hematomas, epistaxis, and petechiae; life-threatening hemorrhages have also occurred. Coadr
the risk of bleeding (Prod Info EFFEXOR XR(R) extended-release oral capsules, 2008a).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Use caution when venlafaxine is used concomitantly with antiplatelet agents. Close
patients receiving antiplatelet agents concomitantly (Prod Info EFFEXOR XR(R) extended-release oral capsu
7) Probable Mechanism: unknown

3.5.1.CG Linezolid

1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental sta
2) Summary: Linezolid is a reversible, nonselective inhibitor of monoamine oxidase (MAO). Concurrent admi
toxicity or serotonin syndrome, a hyperserotonergic state characterized by symptoms such as restlessness, r
Serious, even fatal, reactions have been reported(Prod Info ZYVOX(R) IV injection, oral tablets, oral suspens
syndrome has been reported in 6 cases including 5 women (30, 36, 38, 58, and 81 years of age) and 1 man (
case, symptoms of serotonin syndrome abated when linezolid, venlafaxine, or both were discontinued (Maso
Berman, 2007; Jones et al, 2004). When concomitant use is warranted, monitoring the patient for serotonin s
both of the drugs should be considered (Prod Info ZYVOX(R) IV injection, oral tablets, oral suspension, 2008
waiting period of 14 days between administration of these drugs may be considered (Packer & Berman, 2007
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Concurrent use of linezolid and venlafaxine may result in serotonin syndrome. Mon

blushing, diaphoresis, and hyperpyrexia (Prod Info ZYVOX(R) IV injection, oral tablets, oral suspension, 2008
consider a waiting period of 14 days between administration of these drugs (Packer & Berman, 2007). If the u
symptoms of serotonin syndrome such as neuromuscular abnormalities (including hyper-reflexia, tremor, mus
(including tachycardia, mydriasis, diaphoresis, and diarrhea), and mental status changes (including agitation
develops, discontinue the offending agents and provide supportive care and other therapy as necessary (Boy
7) Probable Mechanism: inhibition of monamine oxidase-mediated serotonin metabolism
8) Literature Reports
a) A case report described serotonin toxicity in a 58-year-old woman following concomitant use of linezo
resection for transitional cell carcinoma 18 years earlier and had undergone a bilateral total hip arthropla
episodes of self-harm. She presented with symptoms of systemic infection. Increased activity at the site
Subsequently, the patient was initiated on vancomycin and rifampicin intravenously. A 2-stage revision T
antibiotic administration, her regimen was changed to oral linezolid and oral rifampicin 2 weeks postoper
examination and CT scan of the head did not reveal any abnormal findings or autonomic dysfunction. Ov
venlafaxine were stopped due to possible serotonin toxicity. The patient's condition normalized 48 hours
b) A case report described serotonin syndrome in a 36-year-old woman following the concomitant use o
regimen included lithium, venlafaxine, and imipramine for bipolar disorder, depression, and headaches, r
presenting to the ER, the patient received vancomycin for treatment of methicillin-resistant Staphylococc
before her ER visit. At presentation, she had a blood pressure (BP) of 234/196 mmHg, a heart rate of 16
with slow reaction to light and she was unresponsive to verbal instructions. The patient was intubated an
BP to 150/85 mmHg. Her serum lithium level was 1.2 mEq/L and there were no electrolyte abnormalities
patient was extubated. While both imipramine and venlafaxine were withheld, lithium was continued and
alert and oriented over the following days and had reduced anxiety. Three weeks following discharge, th
was postulated that her 3 chronic serotonergic medications led to a baseline hyperserotonergic state, wh
c) In one case report, a 30-year-old woman experienced symptoms of serotonin syndrome after concom
age of 15 years for depression, social anxiety, bulimia, and alcohol/benzodiazepine abuse, she had becc
After two weeks of treatment with linezolid, the patient complained of dizziness, syncope, and ataxia. At
discontinued and intensive therapy was instituted. Although her neurological symptoms dissipated, she c
quetiapine 25 mg 3 times daily was prescribed. Two weeks later, venlafaxine was gradually reinitiated (F
d) A retrospective chart review identified one highly probable case of serotonin syndrome in a patient wh
Charts of 72 inpatients who received linezolid and an SSRI or venlafaxine within 14 days of each other w
Hunter Serotonin Toxicity criteria. Of these patients, 52 (72%) were treated concomitantly with linezolid a
probability of SS. Of these, one case involved an 81-year-old woman who was diagnosed with a high pro
citalopram. Linezolid was given for a vancomycin-resistant Enterococcus urinary tract infection. When th
shouting. Although she appeared to have met 6 of the Sternbach criteria and 4 of the Hunter criteria for S
Hg with a heart rate of 120 beats/min, and a respiratory rate of 50 breaths/min. The following day, she ba
twitching and jerking, eyes rolled back in her head, and labored breathing. Linezolid was discontinued, a
after linezolid was stopped, she was extubated and had returned to baseline mental status with the abilit
e) A case report described serotonin toxicity in a 38-year-old woman following the concomitant administ
recent rib fracture was admitted after 3 weeks of coughing, progressive dyspnea, and green-colored spu
gabapentin 100 mg 3 times daily for one year, and hydromorphone 1 mg every 4 hours as needed for the
linezolid 600 mg IV every 12 hours for confirmed methicillin-resistant Staphylococcus aureus infection. F
hot flashes, dyspnea, and tiredness. Eight days following linezolid initiation, the venlafaxine dose was re
reported nervousness, muscle rigidity of the mouth, fine tremors (fingers), and involuntary arm, trunk, an
her BP normalized to 142/84 mmHg; other symptoms dissipated the next day. Upon discharge on day 10
150 mg once daily. In the subsequent 2-year period, the patient received two 10-day courses of linezolid
serotonin toxicity (Bergeron et al, 2005).
f) Serotonin syndrome was reported in the case of an 85-year-old man who was receiving venlafaxine 1
rifampicin for a closed wound due to the removal of a chronically infected hip prothesis. His medical histo
permanent pacemaker. After 20 days of receiving oral antibiotic therapy, the patient was reportedly confu
scan and serum chemistries were all normal with no evidence of sepsis; vital signs were also within norm
hospital due to drowsiness. He had a fever of 37.6 degrees Celsius and a decreased level of consciousn
venlafaxine were discontinued due to a suspected drug interaction. Within 2 days, the patient's mental st

3.5.1.CH Lornoxicam
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control anc
NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ec
(R) oral tablets, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When venlafaxine and a nonsteroidal antiinflammatory agent are given concurrentl
2008).
7) Probable Mechanism: unknown

3.5.1.CI Meclofenamate
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control anc

NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ec
(R) oral tablets, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When venlafaxine and a nonsteroidal antiinflammatory agent are given concurrentl
2008).
7) Probable Mechanism: unknown

3.5.1.CJ Mefenamic Acid
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control anc
NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ec
(R) oral tablets, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When venlafaxine and a nonsteroidal antiinflammatory agent are given concurrentl
2008).
7) Probable Mechanism: unknown

3.5.1.CK Meloxicam
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control anc
NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ec
(R) oral tablets, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When venlafaxine and a nonsteroidal antiinflammatory agent are given concurrentl
2008).
7) Probable Mechanism: unknown

3.5.1.CL Metoclopramide
1) Interaction Effect: an increased risk of developing extrapyramidal symptoms
2) Summary: A risk of serotonin syndrome with serious extrapyramidal reactions may occur with concomitan
developed extrapyramidal symptoms after metoclopramide was added to a regimen of venlafaxine (Fisher &
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Clinicians should be alerted to the possibility that patients may have an increased ri
metoclopramide. Close patient monitoring is warranted.
7) Probable Mechanism: synergistic dopaminergic inhibition
8) Literature Reports
a) Metoclopramide interacts with venlafaxine resulting in serotonin syndrome with serious dystonic-dysk
hospital after falling. She had been treated with venlafaxine 150 mg am and 75 mg pm for 3 years. The p
and clenching of the teeth after receiving metoclopramide intravenously. She was unresponsive for less
later, the patient developed mycolonic jerks and muscle rigidity and she became diaphoretic, confused a
and dilated pupils. Her temperature rose to 37.9 degrees Celsius, heart rate was 115 beats/min, respirat
values were normal. There was improvement in symptoms after intravenous diazepam was administered
increased muscle rigidity with intermittent forceful extensions of her legs and jerking of her arms. Two or
resolution of symptoms occurred on hospital day 3. Venlafaxine was reinstated without problems. Accord
was considered a probable cause of serotonin syndrome (Fisher & David, 2002).

3.5.1.CM Metoprolol
1) Interaction Effect: increased metoprolol plasma concentrations, but decreased metoprolol efficacy in lowe
2) Summary: Concomitant use of metoprolol and venlafaxine extended-release tablets may reduce the effica
administration. Some patients treated with venlafaxine have experienced dose-related increases in blood pre
extended-release tablets concomitantly (Prod Info Effexor XR(R) extended-release oral capsules, 2009).
3) Severity: major
4) Onset: unspecified
5) Substantiation: established
6) Clinical Management: Concurrent administration of metoprolol and venlafaxine extended-release tablets c
should be controlled before treatment with venlafaxine. Regularly monitor blood pressure in patients receiving
capsules, 2009).
7) Probable Mechanism: unknown
8) Literature Reports
a) In an interaction study of 18 healthy males, concomitant administration of metoprolol (100 mg every 2

increase in metoprolol plasma concentrations by approximately 30 to 40% without altering the plasma cc pharmacokinetic profile of venlafaxine or its O-desmethylvenlafaxine metabolite. It appeared that venlafa finding for hypertensive patients is unknown (Prod Info Effexor XR(R) extended-release oral capsules, 2(

3.5.1.CN Mirtazapine

1) Interaction Effect: an increased risk of serotonin syndrome

2) Summary: Concurrent use of mirtazapine and venlafaxine resulted in symptoms of serotonin syndrome in limbs, diaphoresis, hyperreflexia, tachycardia (greater than 100 beats per minute), and increased blood press symptoms of serotonin syndrome. Serotonin syndrome can be life-threatening. If serotonin syndrome develop necessary (Boyer & Shannon, 2005).

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: A case of serotonin syndrome was reported with concomitant use of mirtazapine ar mirtazapine and venlafaxine are used together, monitor closely for symptoms of serotonin syndrome such as peripheral hypertonicity, and shivering), autonomic hyperactivity (including tachycardia, mydriasis, diaphoresi agitation and delirium). Serotonin syndrome can be life-threatening. If serotonin syndrome develops, disconti (Boyer & Shannon, 2005).

7) Probable Mechanism: additive serotonergic pharmacologic effects

8) Literature Reports

a) A 31-year-old female on mirtazapine experienced serotonin syndrome after venlafaxine was added. S decided to slowly discontinue mirtazapine, with 30 mg/day, and start venlafaxine extended-release 75 m gross tremor of the upper limbs, diaphoresis, hyperreflexia, tachycardia (greater than 100 beats per minu tomography. Mirtazapine and venlafaxine were discontinued and she was administered oral lorazepam a resolved 24 hours later (Dimellis, 2002).

3.5.1.CO Moclobemide

1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental sta

2) Summary: Concurrent administration or overlapping therapy with venlafaxine and a monoamine oxidase (state characterized by symptoms such as restlessness, myoclonus, changes in mental status, hyperreflexia, concomitant use of serotonin specific reuptake inhibitors and MAO inhibitors (Prod Info Effexor(R) XR, 2000b & de Vries, 1990i). Concomitant use is contraindicated.

3) Severity: contraindicated

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: Concurrent use of venlafaxine and a MAO inhibitor is contraindicated. Wait at least at least seven days after discontinuing venlafaxine before initiating therapy with a MAO inhibitor.

7) Probable Mechanism: inhibition of serotonin metabolism by monoamine oxidase

8) Literature Reports

a) Concomitant use of selective serotonin reuptake inhibitors and monoamine oxidase inhibitors can pro syndrome is a condition of serotonergic hyperstimulation and manifests as restlessness, myoclonus, cha not recognized and correctly treated, death can result.

b) Two cases suggestive of an interaction between fluoxetine and selegiline, a selective monoamine oxi involved a first episode of mania being observed approximately one month after adding selegiline to fluo no further details were provided. The second case involved diaphoresis, vasoconstriction, and cyanosis selegiline. Both drugs were discontinued, with relatively quick resolution of symptoms. Rechallenge with

c) Five fatal overdose cases due to serotonin syndrome have been reported (Neuvonen et al, 1993). In moclobemide, a selective monoamine oxidase inhibitor, and citalopram. Of the three patients, blood con therapeutic level, and citalopram concentrations ranged from normal therapeutic levels to five times the t

d) A 34-year-old man experienced serotonin syndrome after ingesting venlafaxine 2.625 g and moclobe beats/min), tachypnea (26 breaths/min), altered mental status, hypertonia, and had a creatine phosphoki may act like an irreversible MAOI with large doses, increasing the level of serotonin in the synaptic cleft

e) A 32-year-old man taking moclobemide 20 mg twice daily and diazepam 15 mg daily was given venla vomiting, diaphoresis, hallucination and agitation. He also demonstrated muscle rigidity and ocular oscill mg and chlorpromazine 12.5 mg and his condition improved significantly (Chan et al, 1998).

3.5.1.CP Morniflumate

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control anc NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ec (R) oral tablets, 2008).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When venlafaxine and a nonsteroidal antiinflammatory agent are given concurrentl 2008).

7) Probable Mechanism: unknown

3.5.1.CQ Nabumetone

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control anc NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ec (R) oral tablets, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When venlafaxine and a nonsteroidal antiinflammatory agent are given concurrentl 2008).
7) Probable Mechanism: unknown

3.5.1.CR Naproxen

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control anc NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ec (R) oral tablets, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When venlafaxine and a nonsteroidal antiinflammatory agent are given concurrentl 2008).
7) Probable Mechanism: unknown

3.5.1.CS Naratriptan

1) Interaction Effect: an increased risk of serotonin syndrome
2) Summary: Rare incidences of weakness, hyperreflexia, and incoordination have been reported with the co 1 (5HT-1) agonist (Prod Info Amerge(TM), 2002). Concurrent use of a triptan and an SSRI may result in sero include restlessness, hallucinations, loss of coordination, fast heart beat, rapid changes in blood pressure, inc Clinicians should be aware that triptans may be commonly used intermittently and that either the triptan or the syndrome with patients who are prescribed this combination and monitor them closely for symptoms of seroto
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Coadministration of a triptan, such as naratriptan, and an SSRI may result in a life-t used intermittently and that either the triptan or the SSRI may be prescribed by a different physician. If these monitor closely for symptoms of serotonin syndrome (restlessness, hyperthermia, hyperreflexia, incoordinatic
7) Probable Mechanism: additive pharmacologic effects resulting in excessive serotonergic stimulation

3.5.1.CT Nefazodone

1) Interaction Effect: increased plasma concentrations of venlafaxine
2) Summary: Caution is advised if a CYP3A4 inhibitor, such as nefazodone, is administered with venlafaxine desvenlafaxine (ODV) (Prod Info venlafaxine extended release oral tablets, 2008). Patients should be monito
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Patients should be monitored for signs of venlafaxine toxicity such as nausea, drow
7) Probable Mechanism: decreased venlafaxine clearance
8) Literature Reports
  a) Caution is warranted with the concurrent use of CYP3A4 inhibitors, such as nefazodone, and venlafa desvenlafaxine (ODV) (Prod Info venlafaxine extended release oral tablets, 2008).

3.5.1.CU Nelfinavir

1) Interaction Effect: increased plasma concentrations of venlafaxine
2) Summary: Caution is advised if a CYP3A4 inhibitor, such as nelfinavir, is administered with venlafaxine, d desvenlafaxine (ODV) (Prod Info venlafaxine extended release oral tablets, 2008). Patients should be monito
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Patients should be monitored for signs of venlafaxine toxicity such as nausea, drow
7) Probable Mechanism: decreased venlafaxine clearance
8) Literature Reports
  a) Caution is warranted with the concurrent use of CYP3A4 inhibitors, such as nelfinavir, and venlafaxin desvenlafaxine (ODV) (Prod Info venlafaxine extended release oral tablets, 2008).

3.5.1.CV Nialamide

1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental st
2) Summary: Concurrent administration or overlapping therapy with venlafaxine and a monoamine oxidase (

state characterized by symptoms such as restlessness, myoclonus, changes in mental status, hyperreflexia, concomitant use of serotonin specific reuptake inhibitors and MAO inhibitors (Prod Info Effexor(R) XR, 1999b year old woman developed a serious case of serotonin syndrome after the inadvertent ingestion of a single d Concomitant use is contraindicated.

3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Concurrent use of venlafaxine and a MAO inhibitor is contraindicated. Wait at least at least seven days after discontinuing venlafaxine before initiating therapy with a MAO inhibitor.
7) Probable Mechanism: inhibition of serotonin metabolism by monoamine oxidase
8) Literature Reports

a) Concomitant use of selective serotonin reuptake inhibitors and monoamine oxidase inhibitors can pro syndrome is a condition of serotonergic hyperstimulation and manifests as restlessness, myoclonus, cha not recognized and correctly treated, death can result.

b) A 26-year old woman who had been taking isocarboxazid for eight weeks stopped taking the drug for the patient became restless and developed leg twitches. The patients was later admitted to the emergen disturbances. After treatment with diazepam and propranolol the patient did not improve. The patient wa symptoms after the second dose (Lappin & Auchincloss, 1994h).

c) A drug interaction was reported in a 61-year old woman in which sertraline 100 mg twice daily was ac taking the first sertraline dose, the patient was found in a semicomatose state, with elevated body tempe Hg. After transportation to the hospital, the patient was misdiagnosed as having neuroleptic malignant sy sertraline and phenelzine. The authors suggest that monoamine oxidase inhibitor (MAOI) therapy should serotonin reuptake inhibitor (SSRI) and that before starting a MAOI, SSRI therapy should be discontinue 1994i).

d) Two cases reports suggested a possible interaction between fluoxetine and selegiline (Suchowersky approximately one month after adding selegiline to fluoxetine therapy. The patient improved two months case involved diaphoresis, vasoconstriction, and cyanosis of the hands which occurred in close tempora relatively quick resolution of symptoms. Rechallenge with fluoxetine alone occurred without incident.

e) A case of a 60-year old female who developed serotonin syndrome after the inadvertent ingestion of Approximately four hours after taking the venlafaxine, the patient became weak, confused, and collapse hyperreflexia, and diaphoresis. After treatment with diazepam, dantrolene, and other supportive therapy,

3.5.1.CW Niflumic Acid

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control anc NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ec (R) oral tablets, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When venlafaxine and a nonsteroidal antiinflammatory agent are given concurrentl 2008).
7) Probable Mechanism: unknown

3.5.1.CX Nimesulide

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control anc NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ec (R) oral tablets, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When venlafaxine and a nonsteroidal antiinflammatory agent are given concurrentl 2008).
7) Probable Mechanism: unknown

3.5.1.CY Nortriptyline

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest
2) Summary: Tricyclic antidepressants (TCAs) and venlafaxine have been shown to prolong the QTc interval 1982). Even though no formal drug interaction studies have been done, the coadministration of tricyclic antid recommended (Prod Info Elavil(R), 1999). In addition, venlafaxine and tricyclic antidepressants (TCAs) may c (Perry, 2000; Prod Info Effexor(R) XR, 2003; Ellingrod & Perry, 1994a). Venlafaxine increased the AUC, Cma increased by 2.5 and 4.5 fold when administered with venlafaxine 37.5 mg and 75 mg every 12 hours, respec affected (Prod Info venlafaxine extended release oral tablets, 2008).
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Due to the potential for additive effects on the QT interval, the concurrent administr

7) Probable Mechanism: decreased TCA and venlafaxine metabolism; additive effects on QT prolongation
8) Literature Reports
a) When administered with imipramine, the pharmacokinetics of imipramine and the 2-hydroxy metaboli (AUC), maximum concentration (Cmax), and minimum concentration (Cmin) of desipramine by approxim 12 hours) and by 4.5-fold (venlafaxine 75 mg every 12 hours). The clinical significance of this finding is u

3.5.1.CZ Oxaprozin
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control anc NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ec (R) oral tablets, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When venlafaxine and a nonsteroidal antiinflammatory agent are given concurrentl 2008).
7) Probable Mechanism: unknown

3.5.1.DA Parecoxib
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control anc NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ec (R) oral tablets, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When venlafaxine and a nonsteroidal antiinflammatory agent are given concurrentl 2008).
7) Probable Mechanism: unknown

3.5.1.DB Pargyline
1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental st
2) Summary: Concurrent administration or overlapping therapy with venlafaxine and a monoamine oxidase (state characterized by symptoms such as restlessness, myoclonus, changes in mental status, hyperreflexia, concomitant use of serotonin specific reuptake inhibitors and MAO inhibitors (Prod Info Effexor(R) XR, 1999; 60-year old woman developed a serious case of serotonin syndrome after the inadvertent ingestion of a singl Concomitant use is contraindicated.
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Concurrent use of venlafaxine and a MAO inhibitor is contraindicated. Wait at least at least seven days after discontinuing venlafaxine before initiating therapy with a MAO inhibitor.
7) Probable Mechanism: inhibition of serotonin metabolism by monoamine oxidase
8) Literature Reports
a) Concomitant use of selective serotonin reuptake inhibitors and monoamine oxidase inhibitors can pro syndrome is a condition of serotonergic hyperstimulation and manifests as restlessness, myoclonus, cha not recognized and correctly treated, death can result.
b) A 26-year old woman who had been taking isocarboxazid for eight weeks stopped taking the drug for the patient became restless and developed leg twitches. The patients was later admitted to the emergen disturbances. After treatment with diazepam and propranolol the patient did not improve. The patient wa symptoms after the second dose (Lappin & Auchincloss, 1994).
c) A drug interaction was reported in a 61-year old woman in which sertraline 100 mg twice daily was ac taking the first sertraline dose, the patient was found in a semicomatose state, with elevated body tempe Hg. After transportation to the hospital, the patient was misdiagnosed as having neuroleptic malignant sy sertraline and phenelzine. The authors suggest that monoamine oxidase inhibitor (MAOI) therapy should serotonin reuptake inhibitor (SSRI) and that before starting a MAOI, SSRI therapy should be discontinue 1994).
d) Two cases reports suggested a possible interaction between fluoxetine and selegiline (Suchowersky approximately one month after adding selegiline to fluoxetine therapy. The patient improved two months case involved diaphoresis, vasoconstriction, and cyanosis of the hands which occurred in close tempora relatively quick resolution of symptoms. Rechallenge with fluoxetine alone occurred without incident.
e) A case of a 60-year old female who developed serotonin syndrome after the inadvertent ingestion of Approximately four hours after taking the venlafaxine, the patient became weak, confused, and collapse hyperreflexia, and diaphoresis. After treatment with diazepam, dantrolene, and other supportive therapy,

3.5.1.DC Pentosan Polysulfate Sodium
1) Interaction Effect: an increased risk of bleeding
2) Summary: Case reports and epidemiological studies have shown that use of selective serotonin reuptake

venlafaxine, is associated with gastrointestinal bleeding. Bleeding events with SSRIs and SNRIs included cas have also occurred. Coadministration with warfarin or other anticoagulants may potentiate the risk of bleeding phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased ris Increases in prothrombin time, partial thromboplastin time, or INR have been reported when venlafaxine was with warfarin or other drugs affecting coagulation should be undertaken with caution. Whenever venlafaxine i coagulation parameters is recommended (Prod Info EFFEXOR XR(R) extended-release oral capsules, 2008a

3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Use caution when venlafaxine is used concomitantly with warfarin or other drugs af or discontinued in patients receiving anticoagulants, such as warfarin (Prod Info EFFEXOR XR(R) extended-
7) Probable Mechanism: additive adverse events
8) Literature Reports

a) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoum increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospit abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duratic showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95 (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).

3.5.1.DD Phenelzine

1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental st
2) Summary: Serious, sometimes fatal, reactions have been seen with the combination of venlafaxine and m Effexor(R) XR, 2000c). Reports of adverse effects have included hyperthermia, rigidity, myoclonus, instability MAOIs and venlafaxine has also been reported to result in a condition termed serotonin syndrome (Klysner e potentially fatal condition of serotonergic hyperstimulation characterized by changes in mental status, restless one case serotonin syndrome occurred with initiation of venlafaxine therapy 16 days after discontinuation of another report, two additional patients were started on venlafaxine at least 14 days after discontinuation of ph 1998a).
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Concurrent use of venlafaxine and a MAO inhibitor is contraindicated. Wait at least at least seven days after discontinuing venlafaxine before initiating therapy with a MAO inhibitor. Even if initia for development of serotonin syndrome.
7) Probable Mechanism: inhibition of serotonin metabolism by monoamine oxidase
8) Literature Reports

a) Concomitant use of serotonin specific reuptake inhibitors and monoamine oxidase inhibitors can prod syndrome is a condition of serotonergic hyperstimulation and manifests as restlessness, myoclonus, cha not recognized and correctly treated, death can result.

b) A 46-year old man with depression was taking a regimen of phenelzine 30 mg three times daily and c initiating therapy with venlafaxine. The exact tapering regimen was not available. One day after the patie 60 minutes, the patient was confused, twitching, and had a full body tremor. The patient was also having propranolol, diphenhydramine, and lorazepam in the emergency room, with subsequent improvement in the intensive care unit with resolution of symptoms over the next day without further complications (Heisl

c) A 39-year old woman developed symptoms similar to serotonin syndrome due to an interaction betwe phenelzine 45 mg daily seven days earlier, took a single 37.5 mg dose of venlafaxine. The patient then e creatinine kinase level. After treatment with lorazepam and other supportive therapy, the patient's sympt dose (Phillips & Ringo, 1995).

d) A case of serotonin syndrome was reported in a 34-year old man due to an interaction between venla discontinued 16 days before the initiation of therapy with venlafaxine. Shortly after the first venlafaxine d tachycardia, and muscular rigidity. The patient had a temperature of 98.1 degrees F, a pulse of 115, and rigidity, and myoclonus in both feet, the patient was diagnosed with serotonin syndrome. The patient's sy three times daily for two days upon discharge. This case may be of major importance since phenelzine h venlafaxine. A longer washout period may be necessary (Kolecki, 1997).

e) A 44-year-old female was stabilized on phenelzine 30 mg twice daily and alprazolam 0.5 mg three tim phenelzine and alprazolam. Within 45 minutes she began to experience extremity shaking and rapid resp increased muscle tone, and diminished verbal responsiveness. Vital signs included blood pressure of 13 degrees Celsius. The diagnosis of serotonin syndrome was made. Following intubation and seven days (Weiner et al, 1998).

f) In a case report on four patients, symptoms of serotonin syndrome were noted, even in two cases wh patients ranged in age from 25 to 49 years, and all had been on phenelzine for co-existing migraine and of the four patients had been advised to wait 14 days after stopping phenelzine to start taking venlafaxin experienced symptoms including agitation, shaking, diaphoresis, hyperthermia, slight hypertension, dizzi one hour of administration of venlafaxine, and all the patients were returned to baseline within 24 hours

3.5.1.DE Phenindione

1) Interaction Effect: an increased risk of bleeding
2) Summary: Case reports and epidemiological studies have shown that use of selective serotonin reuptake

venlafaxine, is associated with gastrointestinal bleeding. Bleeding events with SSRIs and SNRIs included cas
have also occurred. Coadministration with warfarin or other anticoagulants may potentiate the risk of bleedinç
phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased ris
Increases in prothrombin time, partial thromboplastin time, or INR have been reported when venlafaxine was
with warfarin or other drugs affecting coagulation should be undertaken with caution. Whenever venlafaxine i
coagulation parameters is recommended (Prod Info EFFEXOR XR(R) extended-release oral capsules, 2008a
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Use caution when venlafaxine is used concomitantly with warfarin or other drugs af
or discontinued in patients receiving anticoagulants, such as warfarin (Prod Info EFFEXOR XR(R) extended-
7) Probable Mechanism: additive adverse events
8) Literature Reports
a) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoum
increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospit
abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duratic
showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95
(adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).

3.5.1.DF Phenprocoumon

1) Interaction Effect: an increased risk of bleeding
2) Summary: Case reports and epidemiological studies have shown that use of selective serotonin reuptake
venlafaxine, is associated with gastrointestinal bleeding. Bleeding events with SSRIs and SNRIs included cas
have also occurred. Coadministration with warfarin or other anticoagulants may potentiate the risk of bleedinç
phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased ris
Increases in prothrombin time, partial thromboplastin time, or INR have been reported when venlafaxine was
with warfarin or other drugs affecting coagulation should be undertaken with caution. Whenever venlafaxine i
coagulation parameters is recommended (Prod Info EFFEXOR XR(R) extended-release oral capsules, 2008a
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Use caution when venlafaxine is used concomitantly with warfarin or other drugs af
or discontinued in patients receiving anticoagulants, such as warfarin (Prod Info EFFEXOR XR(R) extended-
7) Probable Mechanism: additive adverse events
8) Literature Reports
a) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoum
increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospit
abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duratic
showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95
(adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).

3.5.1.DG Phenylbutazone

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control anc
NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ec
(R) oral tablets, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When venlafaxine and a nonsteroidal antiinflammatory agent are given concurrentl
2008).
7) Probable Mechanism: unknown

3.5.1.DH Pirazolac

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control anc
NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ec
(R) oral tablets, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When venlafaxine and a nonsteroidal antiinflammatory agent are given concurrentl
2008).
7) Probable Mechanism: unknown

3.5.1.DI Piroxicam

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control anc

NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ec
(R) oral tablets, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When venlafaxine and a nonsteroidal antiinflammatory agent are given concurrentl
2008).
7) Probable Mechanism: unknown

3.5.1.DJ Pirprofen
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control anc
NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ec
(R) oral tablets, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When venlafaxine and a nonsteroidal antiinflammatory agent are given concurrentl
2008).
7) Probable Mechanism: unknown

3.5.1.DK Procarbazine
1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental st
2) Summary: Concurrent administration or overlapping therapy with venlafaxine and a monoamine oxidase (
state characterized by symptoms such as restlessness, myoclonus, changes in mental status, hyperreflexia,
concomitant use of serotonin specific reuptake inhibitors and MAO inhibitors (Prod Info Effexor(R) XR, 1999d
60-year old woman developed a serious case of serotonin syndrome after the inadvertent ingestion of a singl
Concomitant use is contraindicated.
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Concurrent use of venlafaxine and a MAO inhibitor is contraindicated. Wait at least
at least seven days after discontinuing venlafaxine before initiating therapy with a MAO inhibitor.
7) Probable Mechanism: inhibition of serotonin metabolism by monoamine oxidase
8) Literature Reports
a) Concomitant use of selective serotonin reuptake inhibitors and monoamine oxidase inhibitors can pro
syndrome is a condition of serotonergic hyperstimulation and manifests as restlessness, myoclonus, cha
not recognized and correctly treated, death can result.
b) A 26-year old woman who had been taking isocarboxazid for eight weeks stopped taking the drug for
the patient became restless and developed leg twitches. The patients was later admitted to the emergen
disturbances. After treatment with diazepam and propranolol the patient did not improve. The patient wa
symptoms after the second dose (Lappin & Auchincloss, 1994j).
c) A drug interaction was reported in a 61-year old woman in which sertraline 100 mg twice daily was ac
taking the first sertraline dose, the patient was found in a semicomatose state, with elevated body tempe
Hg. After transportation to the hospital, the patient was misdiagnosed as having neuroleptic malignant sy
sertraline and phenelzine. The authors suggest that monoamine oxidase inhibitor (MAOI) therapy should
serotonin reuptake inhibitor (SSRI) and that before starting a MAOI, SSRI therapy should be discontinue
1994k).
d) Two cases reports suggested a possible interaction between fluoxetine and selegiline (Suchowersky
approximately one month after adding selegiline to fluoxetine therapy. The patient improved two months
case involved diaphoresis, vasoconstriction, and cyanosis of the hands which occurred in close tempora
relatively quick resolution of symptoms. Rechallenge with fluoxetine alone occurred without incident.
e) A case of a 60-year old female who developed serotonin syndrome after the inadvertent ingestion of
Approximately four hours after taking the venlafaxine, the patient became weak, confused, and collapsed
hyperreflexia, and diaphoresis. After treatment with diazepam, dantrolene, and other supportive therapy,

3.5.1.DL Propyphenazone
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control anc
NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ec
(R) oral tablets, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When venlafaxine and a nonsteroidal antiinflammatory agent are given concurrentl
2008).
7) Probable Mechanism: unknown

3.5.1.DM Proquazone

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control anc NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ec (R) oral tablets, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When venlafaxine and a nonsteroidal antiinflammatory agent are given concurrentl 2008).
7) Probable Mechanism: unknown

3.5.1.DN Protriptyline

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest
2) Summary: Tricyclic antidepressants (TCAs) and venlafaxine have been shown to prolong the QTc interval 1982). Even though no formal drug interaction studies have been done, the coadministration of tricyclic antid recommended (Prod Info Elavil(R), 1999). In addition, venlafaxine and tricyclic antidepressants (TCAs) may c (Perry, 2000; Prod Info Effexor(R) XR, 2003; Ellingrod & Perry, 1994a). Venlafaxine increased the AUC, Cma increased by 2.5 and 4.5 fold when administered with venlafaxine 37.5 mg and 75 mg every 12 hours, respec affected (Prod Info venlafaxine extended release oral tablets, 2008).
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Due to the potential for additive effects on the QT interval, the concurrent administr
7) Probable Mechanism: decreased TCA and venlafaxine metabolism; additive effects on QT prolongation
8) Literature Reports
a) When administered with imipramine, the pharmacokinetics of imipramine and the 2-hydroxy metaboli (AUC), maximum concentration (Cmax), and minimum concentration (Cmin) of desipramine by approxim 12 hours) and by 4.5-fold (venlafaxine 75 mg every 12 hours). The clinical significance of this finding is u

3.5.1.DO Rasagiline

1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental st
2) Summary: Concomitant use of rasagiline and venlafaxine, a serotonin-norepinephrine reuptake inhibitor (SSRIs and non-selective MAOIs has been reported to cause serious, sometimes fatal reactions. Signs and s sign fluctuations, and mental status changes progressing to extreme agitation, delirium, and coma. Similar re elapse after discontinuing rasagiline before initiating venlafaxine therapy (Prod Info AZILECT(R) oral tablets, therapy with rasagiline (Prod Info EFFEXOR(R) oral tablets, 2007).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concurrent use of rasagiline and venlafaxine is not recommended. Wait at least 14 least 7 days after discontinuing venlafaxine before initiating therapy with rasagiline (Prod Info AZILECT(R) or
7) Probable Mechanism: inhibition of serotonin metabolism by monoamine oxidase

3.5.1.DP Ritonavir

1) Interaction Effect: increased plasma concentrations of venlafaxine
2) Summary: Caution is advised if a CYP3A4 inhibitor, such as ritonavir, is administered with venlafaxine, du desvenlafaxine (ODV) (Prod Info venlafaxine extended release oral tablets, 2008). Patients should be monito
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Patients should be monitored for signs of venlafaxine toxicity such as nausea, drow
7) Probable Mechanism: decreased venlafaxine clearance
8) Literature Reports
a) Caution is warranted with the concurrent use of CYP3A4 inhibitors, such as ritonavir, and venlafaxine desvenlafaxine (ODV) (Prod Info venlafaxine extended release oral tablets, 2008).

3.5.1.DQ Rizatriptan

1) Interaction Effect: an increased risk of serotonin syndrome
2) Summary: There have been case reports of weakness, hyperreflexia, and incoordination following concon specific reuptake inhibitor (SSRI) (Prod Info Imitrex(R), 1998). Because rizatriptan is a 5HT 1B/1D receptor a 1998a). Concurrent use of a triptan and an SSRI may result in serotonin syndrome which may be life-threate coordination, fast heart beat, rapid changes in blood pressure, increased body temperature, overreactive refl commonly used intermittently and that either the triptan or the SSRI may be prescribed by a different physicia combination and monitor them closely for symptoms of serotonin syndrome (US Food and Drug Administratic
3) Severity: major
4) Onset: delayed

5) Substantiation: probable
6) Clinical Management: Coadministration of a triptan, such as rizatriptan, and an SSRI may result in a life-th used intermittently and that either the triptan or the SSRI may be prescribed by a different physician. If these monitor closely for symptoms of serotonin syndrome (restlessness, hyperthermia, hyperreflexia, incoordinatic
7) Probable Mechanism: additive pharmacologic effects resulting in excessive serotonergic stimulation
8) Literature Reports
a) Twelve healthy volunteers received paroxetine 20 mg daily for two weeks and a single dose of rizatrip paroxetine (Prod Info Maxalt(R), 1998).

3.5.1.DR Rofecoxib
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control anc NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ec (R) oral tablets, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When venlafaxine and a nonsteroidal antiinflammatory agent are given concurrentl 2008).
7) Probable Mechanism: unknown

3.5.1.DS Saquinavir
1) Interaction Effect: increased plasma concentrations of venlafaxine
2) Summary: Caution is advised if a CYP3A4 inhibitor, such as saquinavir, is administered with venlafaxine. desvenlafaxine (ODV) (Prod Info venlafaxine extended release oral tablets, 2008). Patients should be monito
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Patients should be monitored for signs of venlafaxine toxicity such as nausea, drow
7) Probable Mechanism: decreased venlafaxine clearance
8) Literature Reports
a) Caution is warranted with the concurrent use of CYP3A4 inhibitors, such as saquinavir, and venlafaxi desvenlafaxine (ODV) (Prod Info venlafaxine extended release oral tablets, 2008).

3.5.1.DT Selegiline
1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental sta
2) Summary: Concurrent administration or overlapping therapy with venlafaxine and a monoamine oxidase (state characterized by symptoms such as restlessness, myoclonus, changes in mental status, hyperreflexia, concomitant use of serotonin specific reuptake inhibitors and MAO inhibitors (Prod Info Effexor(R) XR, 2000f Concomitant administration of venlafaxine and selegiline is contraindicated, and a minimum of 14 days shoul minimum of 7 days should elapse after discontinuing venlafaxine before initiating therapy with selegiline (Pro reported 15 days after discontinuation of selegiline therapy and initiation of venlafaxine therapy, indicating tha
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Concurrent use of venlafaxine and selegiline is contraindicated. Wait at least 14 da seven days after discontinuing venlafaxine before initiating therapy with selegiline.
7) Probable Mechanism: inhibition of serotonin metabolism by monoamine oxidase
8) Literature Reports
a) Concomitant use of serotonin specific reuptake inhibitors and monoamine oxidase inhibitors can prod syndrome is a condition of serotonergic hyperstimulation and manifests as restlessness, myoclonus, cha not recognized and correctly treated, death can result.
b) A 26-year old woman who had been taking isocarboxazid for eight weeks stopped taking the drug for the patient became restless and developed leg twitches. The patient was later admitted to the emergenc disturbances. After treatment with diazepam and propranolol the patient did not improve. The patient wa symptoms after the second dose (Lappin & Auchincloss, 1994n).
c) A drug interaction was reported in a 61-year old woman in which sertraline 100 mg twice daily was ac taking the first sertraline dose, the patient was found in a semicomatose state, with elevated body tempe Hg. After transportation to the hospital, the patient was misdiagnosed as having neuroleptic malignant sy sertraline and phenelzine. The authors suggest that monoamine oxidase inhibitor (MAOI) therapy should serotonin reuptake inhibitor (SSRI) and that before starting a MAOI, SSRI therapy should be discontinue 1994o).
d) Two cases reports suggested a possible interaction between fluoxetine and selegiline (Suchowersky approximately one month after adding selegiline to fluoxetine therapy. The patient improved two months case involved diaphoresis, vasoconstriction, and cyanosis of the hands which occurred in close tempora relatively quick resolution of symptoms. Rechallenge with fluoxetine alone occurred without incident.
e) Although it has been suggested that MAOIs be discontinued for at least 14 days before the initiation c venlafaxine 15 days after cessation of selegiline. The patient had been treated previously with multiple a

50 mg. All medications were discontinued due to poor response and venlafaxine 37.5 mg was started 15 including profound anxiety, diarrhea, myoclonic jerks, shivering, tremor, and diaphoresis. These symptor further complications. The authors suggested that some patients may need a longer washout period betv

3.5.1.DU Sibrafiban

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case reports anc (SSRIs) and serotonin-norephinephrine reuptake inhibitors (SNRIs), including venlafaxine, is associated with ecchymoses, hematomas, epistaxis, and petechiae; life-threatening hemorrhages have also occurred. Coadr the risk of bleeding (Prod Info EFFEXOR XR(R) extended-release oral capsules, 2008a).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Use caution when venlafaxine is used concomitantly with antiplatelet agents. Close patients receiving antiplatelet agents concomitantly (Prod Info EFFEXOR XR(R) extended-release oral capsu
7) Probable Mechanism: unknown

3.5.1.DV Sibutramine

1) Interaction Effect: an increased risk of serotonin syndrome (hypertension, hyperthermia, myoclonus, ment
2) Summary: Sibutramine inhibits the reuptake of norepinephrine, dopamine, and serotonin. In addition, the t neurotransmitters. A hyperserotonergic state, termed serotonin syndrome, may result if sibutramine is given c and selective serotonin reuptake inhibitors is not recommended (Prod Info Meridia(R), 1997).
3) Severity: major
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Sibutramine should not be administered with serotonergic agents, including selectiv
7) Probable Mechanism: additive pharmacologic effects resulting in excessive serotonergic stimulation
8) Literature Reports
a) Serotonin syndrome is a condition of serotonergic hyperstimulation and manifests as restlessness, m the syndrome is not recognized and correctly treated, death can result (Sternbach, 1991a).

3.5.1.DW St John's Wort

1) Interaction Effect: an increased risk of serotonin syndrome (hypertension, hyperthermia, myoclonus, ment
2) Summary: One case of serotonin syndrome likely resulting from concomitant use of St. John's Wort and v of serotonin syndrome-like symptoms following the addition of St. John's Wort to sertraline or nefazodone the have mild monoamine oxidase inhibitory activity (Singer et al, 1999; Thiede & Walper, 1994), which when adc syndrome is a condition of serotonergic hyperstimulation and manifests as restlessness, myoclonus, changes Wort was initially characterized as a monoamine oxidase inhibitor (MAOI), it is now believed that insufficient I (Muller et al, 1997). It remains possible that the mild MAOI property of St. John's Wort may contribute to an ir (Demisch et al, 1989). Concomitant administration of monoamine oxidase inhibitors (MAOIs) with SSRIs has manufacturers. This contraindication may be extended to venlafaxine which, though not an SSRI, inhibits ser discontinuing St. John's Wort before starting a SSRI (Gordon, 1998), and may be applied to venlafaxine as w
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Avoid concomitant use. Given the half-life of venlafaxine of up to 11 hours, St. Johr discontinuation. A two-week washout period is suggested after discontinuing St. John's Wort before starting a
7) Probable Mechanism: additive serotonergic effect
8) Literature Reports
a) A 32-year-old male experienced symptoms of serotonin syndrome (malaise, anxiety, diaphoresis, trer and St. John's Wort tincture 200 drops three times daily (usual dose stated as 160 drops daily). The patie St. John's Wort after hearing of its benefits. St. John's Wort was discontinued on day 4 while venlafaxine

3.5.1.DX Sulfinpyrazone

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case reports anc (SSRIs) and serotonin-norephinephrine reuptake inhibitors (SNRIs), including venlafaxine, is associated with ecchymoses, hematomas, epistaxis, and petechiae; life-threatening hemorrhages have also occurred. Coadr the risk of bleeding (Prod Info EFFEXOR XR(R) extended-release oral capsules, 2008a).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Use caution when venlafaxine is used concomitantly with antiplatelet agents. Close patients receiving antiplatelet agents concomitantly (Prod Info EFFEXOR XR(R) extended-release oral capsu
7) Probable Mechanism: unknown

3.5.1.DY Sulindac

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control anc
NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ec
(R) oral tablets, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When venlafaxine and a nonsteroidal antiinflammatory agent are given concurrentl
2008).
7) Probable Mechanism: unknown

3.5.1.DZ Sulodexide
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case reports anc
(SSRIs) and serotonin-norephinephrine reuptake inhibitors (SNRIs), including venlafaxine, is associated with
ecchymoses, hematomas, epistaxis, and petechiae; life-threatening hemorrhages have also occurred. Coadr
the risk of bleeding (Prod Info EFFEXOR XR(R) extended-release oral capsules, 2008a).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Use caution when venlafaxine is used concomitantly with antiplatelet agents. Close
patients receiving antiplatelet agents concomitantly (Prod Info EFFEXOR XR(R) extended-release oral capsu
7) Probable Mechanism: unknown

3.5.1.EA Sumatriptan
1) Interaction Effect: an increased risk of serotonin syndrome
2) Summary: Concurrent use of a serotonin norepinephrine reuptake inhibitor, such as venlafaxine, and sum
serotonin syndrome may include restlessness, hallucinations, loss of coordination, fast heart beat, rapid char
vomiting, and diarrhea. Clinicians should be aware that triptans may be commonly used intermittently and tha
risks of serotonin syndrome with patients who are prescribed this combination and monitor them closely for s
EFFEXOR XR(R) extended-release oral capsules, 2008; Prod Info EFFEXOR(R) oral tablets, 2008; Prod Info
3) Severity: major
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Coadministration of a triptan, such as sumatriptan, and a serotonergic agent, such
aware that triptans may be commonly used intermittently and that either the triptan or the SSRI may be presc
serotonin syndrome with the patient and monitor closely for symptoms of serotonin syndrome (restlessness, I
7) Probable Mechanism: additive pharmacologic effects resulting in excessive serotonergic stimulation

3.5.1.EB Suprofen
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control anc
NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ec
(R) oral tablets, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When venlafaxine and a nonsteroidal antiinflammatory agent are given concurrentl
2008).
7) Probable Mechanism: unknown

3.5.1.EC Tapentadol
1) Interaction Effect: increased risk of serotonin syndrome (hypertension, hyperthermia, myoclonus, mental s
2) Summary: Concurrent use of tapentadol and venlafaxine may result in serotonin syndrome, which may be
hallucinations, loss of coordination, fast heart beat, rapid changes in blood pressure, increased body tempera
immediate release oral tablets, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of tapentadol and venlafaxine may result in a life-threatening conc
closely for symptoms of serotonin syndrome (restlessness, hyperthermia, hyperreflexia, incoordination), espe
release oral tablets, 2008).
7) Probable Mechanism: additive serotonergic effect

3.5.1.ED Telithromycin
1) Interaction Effect: increased plasma concentrations of venlafaxine
2) Summary: Caution is advised if a CYP3A4 inhibitor, such as telithromycin, is administered with venlafaxin
desvenlafaxine (ODV) (Prod Info venlafaxine extended release oral tablets, 2008). Patients should be monito
3) Severity: major

4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Patients should be monitored for signs of venlafaxine toxicity such as nausea, drow
7) Probable Mechanism: decreased venlafaxine clearance
8) Literature Reports
a) Caution is warranted with the concurrent use of CYP3A4 inhibitors, such as telithromycin, and venlafa desvenlafaxine (ODV) (Prod Info venlafaxine extended release oral tablets, 2008).

3.5.1.EE Tenidap
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control anc NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ec (R) oral tablets, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When venlafaxine and a nonsteroidal antiinflammatory agent are given concurrentl 2008).
7) Probable Mechanism: unknown

3.5.1.EF Tenoxicam
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control anc NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ec (R) oral tablets, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When venlafaxine and a nonsteroidal antiinflammatory agent are given concurrentl 2008).
7) Probable Mechanism: unknown

3.5.1.EG Tiaprofenic Acid
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control anc NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ec (R) oral tablets, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When venlafaxine and a nonsteroidal antiinflammatory agent are given concurrentl 2008).
7) Probable Mechanism: unknown

3.5.1.EH Ticlopidine
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case reports anc (SSRIs) and serotonin-norephinephrine reuptake inhibitors (SNRIs), including venlafaxine, is associated with ecchymoses, hematomas, epistaxis, and petechiae; life-threatening hemorrhages have also occurred. Coadr the risk of bleeding (Prod Info EFFEXOR XR(R) extended-release oral capsules, 2008a).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Use caution when venlafaxine is used concomitantly with antiplatelet agents. Close patients receiving antiplatelet agents concomitantly (Prod Info EFFEXOR XR(R) extended-release oral capsu
7) Probable Mechanism: unknown

3.5.1.EI Tirofiban
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case reports anc (SSRIs) and serotonin-norephinephrine reuptake inhibitors (SNRIs), including venlafaxine, is associated with ecchymoses, hematomas, epistaxis, and petechiae; life-threatening hemorrhages have also occurred. Coadr the risk of bleeding (Prod Info EFFEXOR XR(R) extended-release oral capsules, 2008a).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Use caution when venlafaxine is used concomitantly with antiplatelet agents. Close patients receiving antiplatelet agents concomitantly (Prod Info EFFEXOR XR(R) extended-release oral capsu

7) Probable Mechanism: unknown

3.5.1.EJ Tolmetin

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control anc NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ec (R) oral tablets, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When venlafaxine and a nonsteroidal antiinflammatory agent are given concurrentl 2008).
7) Probable Mechanism: unknown

3.5.1.EK Toloxatone

1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental st
2) Summary: Concurrent administration or overlapping therapy with venlafaxine and a monoamine oxidase (state characterized by symptoms such as restlessness, myoclonus, changes in mental status, hyperreflexia, concomitant use of serotonin specific reuptake inhibitors and MAO inhibitors (Prod Info Effexor(R) XR, 1999e 60-year old woman developed a serious case of serotonin syndrome after the inadvertent ingestion of a singl As a reversible and selective monoamine oxidase inhibitor, toloxatone may not potentiate the effects of selec with other MAOIs. However, until further studies confirm the safety and efficacy of this combined therapy, cor
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Concurrent use of venlafaxine and a MAO inhibitor is contraindicated. Wait at least at least seven days after discontinuing venlafaxine before initiating therapy with a MAO inhibitor.
7) Probable Mechanism: inhibition of serotonin metabolism by monoamine oxidase
8) Literature Reports
a) Concomitant use of selective serotonin reuptake inhibitors and monoamine oxidase inhibitors can pro syndrome is a condition of serotonergic hyperstimulation and manifests as restlessness, myoclonus, cha not recognized and correctly treated, death can result.
b) A 26-year old woman who had been taking isocarboxazid for eight weeks stopped taking the drug for the patient became restless and developed leg twitches. The patients was later admitted to the emergen disturbances. After treatment with diazepam and propranolol the patient did not improve. The patient wa symptoms after the second dose (Lappin & Auchincloss, 1994l).
c) A drug interaction was reported in a 61-year old woman in which sertraline 100 mg twice daily was ac taking the first sertraline dose, the patient was found in a semicomatose state, with elevated body tempe Hg. After transportation to the hospital, the patient was misdiagnosed as having neuroleptic malignant sy sertraline and phenelzine. The authors suggest that monoamine oxidase inhibitor (MAOI) therapy should serotonin reuptake inhibitor (SSRI) and that before starting a MAOI, SSRI therapy should be discontinue 1994m).
d) Two cases reports suggested a possible interaction between fluoxetine and selegiline (Suchowersky approximately one month after adding selegiline to fluoxetine therapy. The patient improved two months case involved diaphoresis, vasoconstriction, and cyanosis of the hands which occurred in close tempora relatively quick resolution of symptoms. Rechallenge with fluoxetine alone occurred without incident.
e) A case of a 60-year old female who developed serotonin syndrome after the inadvertent ingestion of Approximately four hours after taking the venlafaxine, the patient became weak, confused, and collapse hyperreflexia, and diaphoresis. After treatment with diazepam, dantrolene, and other supportive therapy,

3.5.1.EL Tramadol

1) Interaction Effect: an increased risk of serotonin syndrome
2) Summary: The use of tramadol concurrently with other serotonergic drugs may result in serotonin syndror tramadol with mirtazapine and venlafaxine resulted in symptoms of serotonin syndrome in 47-year-old male. hyperreflexia, and mydriasis (Houlihan, 2004). If tramadol is used concomitantly with venlafaxine, monitor clo serotonin syndrome develops, discontinue the offending agents and provide supportive care and other therap
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: There is potential for serotonin syndrome with the concomitant use of tramadol and release tablets, 2008). A case of serotonin syndrome was reported with coadministration of tramadol with ver If the use of tramadol concomitantly with venlafaxine is clinically warranted, monitor closely for symptoms of s muscle rigidity, clonus, peripheral hypertonicity, and shivering), autonomic hyperactivity (including tachycardi changes (including agitation and delirium). Serotonin syndrome can be life-threatening. If serotonin syndrome therapy as necessary (Boyer & Shannon, 2005).
7) Probable Mechanism: additive serotonergic pharmacologic effects
8) Literature Reports
a) Serotonin syndrome developed in a 47-year-old male when tramadol was added to a regimen of venl

and mirtazapine 30 mg/day for 4 months. Tramadol was added and over 4 weeks the dose was titrated u
mg/day of tramadol, he experienced agitation, confusion, severe shivering, diaphoresis, myoclonus, hype
the next 4 hours, tachycardia and a fever (39.2 degrees Celsius) developed. Intravenous fluids were adn
were restarted with dose titrations to original doses over 1 week without any recurrence of serotonin syn

3.5.1.EM Tranylcypromine

1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental sta
2) Summary: Concurrent administration or overlapping therapy with venlafaxine and a monoamine oxidase (
state characterized by symptoms such as restlessness, myoclonus, changes in mental status, hyperreflexia,
concomitant use of serotonin specific reuptake inhibitors and MAO inhibitors (Prod Info Effexor(R) XR, 2000a
60-year old woman developed a serious case of serotonin syndrome after the inadvertent ingestion of a singl
Concomitant use is contraindicated.
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Concurrent use of venlafaxine and a MAO inhibitor is contraindicated. Wait at least
at least seven days after discontinuing venlafaxine before initiating therapy with a MAO inhibitor.
7) Probable Mechanism: inhibition of serotonin metabolism by monoamine oxidase
8) Literature Reports

a) Concomitant use of serotonin specific reuptake inhibitors and monoamine oxidase inhibitors can prod
syndrome is a condition of serotonergic hyperstimulation and manifests as restlessness, myoclonus, cha
not recognized and correctly treated, death can result.

b) A drug interaction was reported in a 61-year old woman in which sertraline 100 mg twice daily was ac
taking the first sertraline dose, the patient was found in a semicomatose state, with elevated body tempe
Hg. After transportation to the hospital, the patient was misdiagnosed as having neuroleptic malignant sy
sertraline and phenelzine. The authors suggest that monoamine oxidase inhibitor (MAOI) therapy should
serotonin reuptake inhibitor (SSRI) and that before starting a MAOI, SSRI therapy should be discontinue
1994f).

c) Two cases reports suggested a possible interaction between fluoxetine and selegiline (Suchowersky
approximately one month after adding selegiline to fluoxetine therapy. The patient improved two months
case involved diaphoresis, vasoconstriction, and cyanosis of the hands which occurred in close tempora
relatively quick resolution of symptoms. Rechallenge with fluoxetine alone occurred without incident.

d) A case of a 60-year old female who developed serotonin syndrome after the inadvertent ingestion of
Approximately four hours after taking the venlafaxine, the patient became weak, confused, and collapsed
hyperreflexia, and diaphoresis. After treatment with diazepam, dantrolene, and other supportive therapy,

3.5.1.EN Trazodone

1) Interaction Effect: an increased risk of serotonin syndrome
2) Summary: Concurrent use of trazodone and venlafaxine resulted in symptoms of serotonin syndrome in a
and venlafaxine are used concomitantly, monitor closely for symptoms of serotonin syn
agents and provide supportive care and other therapy as necessary (Boyer & Shannon, 2005).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: A case of serotonin syndrome was reported with coadministration of trazodone and
concomitantly, monitor closely for symptoms of serotonin syndrome such as neuromuscular abnormalities (in
shivering), autonomic hyperactivity (including tachycardia, mydriasis, diaphoresis, the presence of bowel sou
Serotonin syndrome can be life-threatening. If serotonin syndrome develops, discontinue the offending agent
7) Probable Mechanism: additive pharmacologic effects
8) Literature Reports

a) A 50-year-old male experienced serotonin syndrome 18 days after starting venlafaxine and trazodone
opioid dependence, and docusate were started after he was admitted to the hospital for depressed mood
increased over 7 days to 225 mg/day. Eighteen days after hospitalization, he became disoriented, restles
afebrile. His other vital signs were unremarkable. All his drugs were discontinued because his symptoms
within 24 hours. Methadone and docusate were restarted and mirtazapine was started. He experienced r
inhibitors (SSRIs) while on methadone, without any similar symptoms (McCue & Joseph, 2001).

3.5.1.EO Trifluoperazine

1) Interaction Effect: an increased risk of neuroleptic malignant syndrome and an increased risk of cardiotoxi
2) Summary: Q and T wave distortions have been observed in patients taking phenothiazines (Prod Info Stel
that concomitant use with other drugs which prolong the QT interval is contraindicated (Prod Info Mellaril(R),
interval at the recommended therapeutic dose (Prod Info Effexor(R) XR, 2003a). In addition, concomitant use
(Nimmagadda et al, 2000a).
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: The concurrent administration of venlafaxine and trifluoperazine is contraindicated.

7) Probable Mechanism: dopamine-inhibition effect of venlafaxine augments dopamine-receptor inhibition by
8) Literature Reports
a) A 44-year-old male who had been receiving trifluoperazine 1 mg three times daily for ten years as an following his first dose, he presented with profound sweating, anxiety, tremor, and rigidity. Vital signs rev beats per minute. Urine and blood panels were within normal limits, with the exception of an elevated cre Neuroleptic malignant syndrome was diagnosed, and the patient was treated with dantrolene and bromo reintroduced without complications. Neuroleptic malignant syndrome may have developed in this patient venlafaxine which augmented dopamine-receptor inhibition by trifluoperazine (Nimmagadda et al, 2000).

3.5.1.EP Trimipramine
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest
2) Summary: Tricyclic antidepressants (TCAs) and venlafaxine have been shown to prolong the QTc interval 1982). Even though no formal drug interaction studies have been done, the coadministration of tricyclic antide recommended (Prod Info Elavil(R), 1999). In addition, venlafaxine and tricyclic antidepressants (TCAs) may c (Perry, 2000; Prod Info Effexor(R) XR, 2003; Ellingrod & Perry, 1994a). Venlafaxine increased the AUC, Cma increased by 2.5 and 4.5 fold when administered with venlafaxine 37.5 mg and 75 mg every 12 hours, respec affected (Prod Info venlafaxine extended release oral tablets, 2008).
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Due to the potential for additive effects on the QT interval, the concurrent administra
7) Probable Mechanism: decreased TCA and venlafaxine metabolism; additive effects on QT prolongation
8) Literature Reports
a) When administered with imipramine, the pharmacokinetics of imipramine and the 2-hydroxy metaboli (AUC), maximum concentration (Cmax), and minimum concentration (Cmin) of desipramine by approxim 12 hours) and by 4.5-fold (venlafaxine 75 mg every 12 hours). The clinical significance of this finding is u

3.5.1.EQ Valdecoxib
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ec (R) oral tablets, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When venlafaxine and a nonsteroidal antiinflammatory agent are given concurrently 2008).
7) Probable Mechanism: unknown

3.5.1.ER Vasopressin
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest
2) Summary: Venlafaxine and vasopressin have been shown to prolong the QTc interval at the recommende though no formal drug interaction studies have been done, the coadministration of drugs known to prolong th
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of venlafaxine and vasopressin is not recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.ES Warfarin
1) Interaction Effect: an increased risk of bleeding
2) Summary: Case reports and epidemiological studies have shown that use of selective serotonin reuptake venlafaxine, is associated with gastrointestinal bleeding. Bleeding events with SSRIs and SNRIs included cas have also occurred. Coadministration with warfarin or other anticoagulants may potentiate the risk of bleeding phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased ris Increases in prothrombin time, partial thromboplastin time, or INR have been reported when venlafaxine was with warfarin or other drugs affecting coagulation should be undertaken with caution. Whenever venlafaxine i coagulation parameters is recommended (Prod Info EFFEXOR XR(R) extended-release oral capsules, 2008a
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Use caution when venlafaxine is used concomitantly with warfarin or other drugs af or discontinued in patients receiving anticoagulants, such as warfarin (Prod Info EFFEXOR XR(R) extended-
7) Probable Mechanism: additive adverse events
8) Literature Reports
a) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoum increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospit abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duratic

showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95
(adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).

3.5.1.ET Xemilofiban

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case reports anc
(SSRIs) and serotonin-norephinephrine reuptake inhibitors (SNRIs), including venlafaxine, is associated with
ecchymoses, hematomas, epistaxis, and petechiae; life-threatening hemorrhages have also occurred. Coadr
the risk of bleeding (Prod Info EFFEXOR XR(R) extended-release oral capsules, 2008a).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Use caution when venlafaxine is used concomitantly with antiplatelet agents. Close
patients receiving antiplatelet agents concomitantly (Prod Info EFFEXOR XR(R) extended-release oral capsu
7) Probable Mechanism: unknown

3.5.1.EU Zolmitriptan

1) Interaction Effect: an increased risk of serotonin syndrome
2) Summary: Concurrent use of a serotonin norepinephrine reuptake inhibitor, such as venlafaxine, and zoln
serotonin syndrome may include restlessness, hallucinations, loss of coordination, fast heart beat, rapid char
vomiting, and diarrhea. Clinicians should be aware that triptans may be commonly used intermittently and tha
risks of serotonin syndrome with patients who are prescribed this combination and monitor them closely for s
EFFEXOR XR(R) extended-release oral capsules, 2008; Prod Info EFFEXOR(R) oral tablets, 2008).
3) Severity: major
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Coadministration of a triptan, such as zolmitriptan, and a serotonergic agent, such a
aware that triptans may be commonly used intermittently and that either the triptan or the SSRI may be presc
serotonin syndrome with the patient and monitor closely for symptoms of serotonin syndrome (restlessness, l
7) Probable Mechanism: additive pharmacologic effects resulting in excessive serotonergic stimulation

3.5.1.EV Zolpidem

1) Interaction Effect: an increased risk of hallucinations
2) Summary: The publication of five case reports from the Washington Poison Center elucidates potential int
reported hallucinations after concurrent use of zolpidem and antidepressant medication. The hallucination ep
1998a).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Observe patients for hallucinatory activity. Alternative anti-insomnia medication may
7) Probable Mechanism: unknown
8) Literature Reports
a) The Washington Poison Center reports that they received five different calls from patients experienci
the five reports came from patients taking serotonin-reuptake inhibitors in addition to zolpidem. The antic
and bupropion. In each case, the hallucinatory activity lasted longer than one hour, but the patients' sym
which zolpidem might cause hallucinations has not been firmly established (Elko et al, 1998).

3.5.1.EW Zomepirac

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control anc
NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ec
(R) oral tablets, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When venlafaxine and a nonsteroidal antiinflammatory agent are given concurrently
2008).
7) Probable Mechanism: unknown

3.5.2 Drug-Food Combinations

3.5.2.A Ethanol

1) Interaction Effect: an increased risk of CNS effects
2) Summary: Concomitant use of venlafaxine and ethanol did not potentiate psychomotor or psychometric ef
However, the manufacturer of venlafaxine recommends that patients be advised to avoid alcohol while using
3) Severity: minor
4) Onset: rapid
5) Substantiation: theoretical

6) Clinical Management: Patients receiving venlafaxine should be advised to avoid the use of alcohol.
7) Probable Mechanism: unknown
8) Literature Reports
a) The pharmacokinetic and pharmacodynamic effect of venlafaxine was tested in 16 healthy volunteers every eight hours for seven days. Ethanol or placebo was given on day 5 or 7 of venlafaxine administrati pharmacokinetics of venlafaxine when given with ethanol or placebo. In addition, no significant difference ethanol or placebo. It is not known if repeated administration of ethanol would have had a significant effe

4.0 Clinical Applications

Monitoring Parameters

Patient Instructions

Place In Therapy

Mechanism of Action / Pharmacology

Therapeutic Uses

Comparative Efficacy / Evaluation With Other Therapies

4.1 Monitoring Parameters

A) Venlafaxine Hydrochloride
1) Therapeutic
a) Physical Findings
1) Measures such as the Hamilton Depression Rating Scale, Hamilton depressed mood item, MADRS t Improvement item may be used to assess efficacy in patients receiving venlafaxine for major depressive extended-release oral capsules, 2008).
2) The Hamilton Rating Scale for Anxiety (HAM-A) total score, the HAM-A anxiety and tension items, an of venlafaxine extended-release in generalized anxiety disorder (Prod Info EFFEXOR XR(R) extended-re
3) The Liebowitz Social Anxiety Scale (LSAS) may be used to assess therapeutic efficacy of venlafaxine release oral capsules, 2008).
4) The Panic and Anticipatory Anxiety Scale (PAAS), Panic Disorder Severity Scale (PDSS) total score, therapeutic efficacy of venlafaxine extended-release in panic disorder (Prod Info EFFEXOR XR(R) exten
2) Toxic
a) Laboratory Parameters
1) Measurement of serum cholesterol levels should be considered during long-term treatment as clinical venlafaxine for at least 3 months during placebo-controlled trials (Prod Info EFFEXOR(R) oral tablets, 20
2) Hyponatremia may occur as a result of treatment with SSRIs and serotonine-norepinephrine reuptake diuretics. Consider monitoring serum sodium levels in these patients (Prod Info EFFEXOR(R) oral tablet
3) Liver function should be monitored as dosage adjustments are necessary in cases of cirrhosis of the release oral capsules, 2008).
4) Patients receiving warfarin therapy should be carefully monitored when venlafaxine is initiated or disc reported when SSRIs and serotonine-norepinephrine reuptake inhibitors were co-administered with warf release oral capsules, 2008).
5) Renal function should be monitored, particularly in the elderly, as dosage adjustments are necessary oral tablets, 2008; Prod Info EFFEXOR XR(R) extended-release oral capsules, 2008).
b) Physical Findings
1) Cough, progressive dyspnea, or chest discomfort may be indicative of interstitial lung disease and eo symptoms are observed, prompt medical evaluation and possible discontinuation of venlafaxine therapy extended-release oral capsules, 2008).
2) Increases in blood pressure have been reported in patients receiving venlafaxine. Preexisting hyperte monitoring of blood pressure should occur in patients receiving venlafaxine. Dose-reduction or discontinu pressure (Prod Info EFFEXOR(R) oral tablets, 2008; Prod Info EFFEXOR XR(R) extended-release oral c
3) Observe patients for discontinuation symptoms such as dysphoric mood, irritability, agitation, dizzines insomnia, hypomania, tinnitus, and seizures. Avoid abrupt discontinuation or dose-reduction of venlafaxi release oral capsules, 2008).
4) Observe patients (particularly the elderly, volume-depleted, and those receiving diuretics) for signs ar impairment, confusion, weakness, and unsteadiness. More severe and/or acute cases may lead to hallu oral tablets, 2008; Prod Info EFFEXOR XR(R) extended-release oral capsules, 2008).
5) Observe patients for signs and symptoms of serotonin syndrome. Symptoms may include mental stat blood pressure, hyperthermia), neuromuscular aberrations (hyperreflexia, incoordination), and/or gastroi 2008; Prod Info EFFEXOR XR(R) extended-release oral capsules, 2008).

6) Patients with depressive symptoms should be screened prior to initiating treatment with an antidepres
detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression (Prod In
capsules, 2008).
7) Patients receiving antidepressants should be monitored for worsening of depression, suicidality, or ur
increases or decreases. Such monitoring should include at least weekly face-to-face contact with patient
every other week for the next 4 weeks, then at 12 weeks, and then as clinically indicated beyond 12 wee
observation) of patients and communication with the prescriber (Prod Info EFFEXOR(R) oral tablets, 200
2004).
8) Patients who experience symptoms of anxiety, agitation, panic attacks, insomnia, irritability, hostility,
for worsening depression or suicidality. If these symptoms are observed, therapy should be re-evaluated
in onset, or were not part of the patient's initial symptoms (Anon, 2004; Anon, 2004; Prod Info EFFEXOF
9) Patients with raised ocular pressure or at risk of acute narrow angle glaucoma should have ocular pre
Info EFFEXOR XR(R) extended-release oral capsules, 2008).

4.2 Patient Instructions

A) Venlafaxine (By mouth)

Venlafaxine

Treats depression. Effexor XR® also treats panic disorder, social anxiety disorder, and generalized anxiety disorc

When This Medicine Should Not Be Used:
You should not use this medicine if you have had an allergic reaction to venlafaxine, or if you have used an MAO
days.

How to Use This Medicine:
Long Acting Capsule, Long Acting Tablet, Tablet

Your doctor will tell you how much of this medicine to use and how often. Your dose may need to be changed
use it more often than your doctor tells you to.
It is best to take this medicine with food or milk.
Swallow the extended-release capsule whole. Do not crush, break, or chew it.
If you cannot swallow the extended-release capsule, you may open it and pour the medicine into a small amo
it without chewing.
It is best to take this medicine at the same time each day.
This medicine should come with a Medication Guide. Read and follow these instructions carefully. Ask your d
Guide if you do not have one. Your doctor might ask you to sign some forms to show that you understand this

If a Dose is Missed:

If you miss a dose or forget to use your medicine, use it as soon as you can. If it is almost time for your next d
medicine to make up for a missed dose.

How to Store and Dispose of This Medicine:

Store the medicine in a closed container at room temperature, away from heat, moisture, and direct light.
Ask your pharmacist, doctor, or health caregiver about the best way to dispose of any leftover medicine after
expiration date has passed.
Keep all medicine away from children and never share your medicine with anyone.

Drugs and Foods to Avoid:
Ask your doctor or pharmacist before using any other medicine, including over-the-counter medicines, vitamins, a

Make sure your doctor knows if you are using an MAO inhibitor (such as isocarboxazid, phenelzine, selegilin
inhibitor within the last 14 days. Using these medicines with venlafaxine could cause serious health problems
Tell your doctor if you are also using St. John's Wort, tryptophan supplements, cimetidine (Tagamet®), halop
(Lithane®, Lithobid®, Eskalith®), or tramadol (Ultram®). Make sure your doctor knows if you are also using n
depression (such as desipramine, fluoxetine, paroxetine, Celexa®, Lexapro™, Norpramin®, Paxil®, Zoloft®),
for pain or arthritis, also called "NSAIDs" (such as aspirin, celecoxib, ibuprofen, Advil®, Aleve®, Celebrex®, E
Tell your doctor if you are using any medicines that make you sleepy. These include sleeping pills, cold and a
Do not drink alcohol while you are using this medicine.

Warnings While Using This Medicine:

Make sure your doctor knows if you are pregnant, trying to become pregnant, or breastfeeding.
Make sure your doctor knows if you have liver disease, kidney disease, heart disease, had a recent heart atta
high cholesterol in the blood, or a mineral imbalance (such as low sodium in the blood). Tell your doctor if you
For some children, teenagers, and young adults, this medicine can increase thoughts of suicide. Tell your do
have thoughts about hurting yourselves. Report any unusual thoughts or behaviors that trouble you or your c
you or your child have trouble sleeping, get upset easily, have a big increase in energy, or start to act reckles
nervous, angry, restless, violent, or scared. Let the doctor know if you, your child, or anyone in your family ha
This medicine may make you dizzy or drowsy. Avoid driving, using machines, or doing anything else that cou
Your doctor will need to check your progress at regular visits while you are using this medicine. Be sure to ke
Do not stop using this medicine suddenly without asking your doctor. You may need to slowly decrease your

Possible Side Effects While Using This Medicine:
Call your doctor right away if you notice any of these side effects:
Allergic reaction: Itching or hives, swelling in your face or hands, swelling or tingling in your mouth or throat, c
Change in how much or how often you urinate.
Chest pain.
Fast or uneven heartbeat.
Feeling confused, nervous, restless, or clumsy.
Feeling more excited or energetic than usual.
Fever, chills, cough, sore throat, and body aches.
Lightheadedness, dizziness, or fainting.
Muscle spasms, twitching, or stiffness.
Seizures or tremors.
Severe nausea or diarrhea.
Unexplained fever, sweating, or shivering.
Unusual behavior or thoughts of hurting yourself or others.
Unusual bleeding or bruising.
Unusual tiredness or weakness.

If you notice these less serious side effects, talk with your doctor:
Anxiety, trouble sleeping, or unusual dreams.
Blurred vision.
Constipation or dry mouth.
Headache.
Mild nausea, vomiting, loss of appetite, or weight loss.
Problems with sex.
Sleepiness.
Warmth or redness in your face, neck, arms, or upper chest.

If you notice other side effects that you think are caused by this medicine, tell your doctor.

4.3 Place In Therapy

A) Venlafaxine Hydrochloride

1) Like the SSRIs, venlafaxine does not cause the anticholinergic, sedative, or cardiovascular adverse effects typ activating effect, at least with acute administration. Although its clinical significance is unclear, it inhibits synaptos patients with previous experience with tricyclic antidepressants indicate that venlafaxine has a different adverse e

2) Despite availability of newer antidepressants, 30% to 40% of patients with severe depression fail to achieve co limited clinical trials, venlafaxine was comparable to tricyclic antidepressants and superior to selective serotonin r response rates may result from the dual action of venlafaxine on the norepinephrine and serotonin system. Furthe Venlafaxine extended-release was superior to placebo in the prevention of recurrent episodes of depression in pa maintenance phase trials (Kocsis et al, 2007; Keller et al, 2007).

3) One potential advantage of venlafaxine is its apparent rapid onset of action; significant improvement of depres 2 weeks of therapy. However, it has not been established that venlafaxine clearly works faster than other antidepr trials, rather than a distinguishing characteristic of this drug. If additional research including comparative trials sup should be considered.

4) Preliminary data suggest that venlafaxine may be useful in the treatment of obsessive-compulsive disorder an these disorders.

4.4 Mechanism of Action / Pharmacology

A) Venlafaxine Hydrochloride

1) MECHANISM OF ACTION

a) Venlafaxine hydrochloride is an antidepressant agent that potentiates the neurotransmitter activity in the c norepinephrine and dopamine reuptake. Venlafaxine and its active metabolite, O-desmethylvenlafaxine (ODV slightly less potent inhibitors of neuronal norepinephrine reuptake, and weak inhibitors of neuronal dopamine serotonin reuptake inhibitors (Prod Info EFFEXOR(R) oral tablets, 2008; Prod Info EFFEXOR XR(R) extende Perry, 1994; Saletu et al, 1992; Muth et al, 1991; Fabre & Putmann, 1987).

b) Venlafaxine is a bicyclic antidepressant that has been referred to as an atypical or "second-generation" ar dopamine in order of decreasing potency. It does not inhibit monoamine oxidase, and does not show the deg antidepressants have been shown to exhibit. No affinity for central muscarinic-cholinergic, dopaminergic, hist demonstrated for venlafaxine or its major active metabolite, O-desmethylvenlafaxine. In animal studies, venla Other antidepressant properties include its ability to reverse reserpine hypothermia and to cause pineal beta- Saletu et al, 1992a; Yardley et al, 1990).

c) Venlafaxine is a racemic mixture; while the pharmacologic profile of the levo(-) isomer is similar to that of 1992).

2) ELECTROENCEPHALOGRAPHIC EFFECTS

a) Electroencephalographic (EEG) analysis in patients receiving venlafaxine has shown that it exerts signific compared with placebo, alpha power is decreased, relative delta/theta and beta powers are increased, and th antidepressants such as imipramine (Saletu et al, 1992a).

3) NEUROPSYCHIATRIC EFFECTS
- **a)** Administration of venlafaxine has been shown to cause significant improvement in attention, concentratio to placebo in healthy volunteers. This is thought to be due to activation of all 3 neurotransmitter systems (i.e., with higher doses, most likely due to the drug's serotonergic activity (Saletu et al, 1992a).

4) REVIEW ARTICLES
- **a)** Two reviews provide a discussion of the efficacy of selective serotonin reuptake inhibitors and other antid
- **b)** The efficacy of antidepressants in reducing panic attack frequency, symptoms of depression, social avoid
- **c)** A review article discussed the rational treatment of depression and included a discussion of each class of
- **d)** The pharmacology and therapeutic potential of venlafaxine has been reviewed (Holliday & Benfield, 1995
- **e)** Drug-interactions of antidepressants are reviewed in German language (Zapotoczky & Simhandl, 1995).

4.5 Therapeutic Uses

4.5.A Venlafaxine Hydrochloride

Antineoplastic adverse reaction - Neurotoxicity

Attention deficit hyperactivity disorder

Binging - Eating disorder

Bipolar disorder, depressed phase

Cancer pain

Cerebrovascular accident - Depression

Depression - Perimenopausal disorder

Diabetic neuropathy

Dysthymia

Generalized anxiety disorder

Hot sweats, Breast cancer-related

Major depressive disorder

Menopausal flushing

Obsessive-compulsive disorder

Panic disorder, With or without agoraphobia

Posttraumatic stress disorder

Premenstrual dysphoric disorder

Recurrent major depressive episodes; Prophylaxis

Severe major depression with psychotic features

Social phobia

Tension-type headache; Prophylaxis

4.5.A.1 Antineoplastic adverse reaction - Neurotoxicity

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Venlafaxine extended-release completely resolved paclitaxel-neurosensory toxicity in a 69-year-old

c) Adult:

1) In a single case report, venlafaxine hydrochloride extended-release (XR) completely resolved paclitax milligrams (mg)/m(2) and carboplatin for ovarian cancer. After failure of clonazepam 1.5 mg, venlafaxine resolved pin-pricks and parerethises in both her hands and wrists (Durand & Goldwasser, 2002).

4.5.A.2 Attention deficit hyperactivity disorder

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Pediatric, Evidence favors efficacy
Recommendation: Pediatric, Class IIb
Strength of Evidence: Pediatric, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Results of a prospective, 6-week, open-label trial (n=13) demonstrate that venlafaxine therapy impro Abali, 2004).

c) Pediatric:

1) Symptoms of attention deficit hyperactivity disorder (ADHD) improved following venlafaxine treatment 6 to 15 years of age (mean age, 9.9 years) with ADHD and without comorbid depression received venlaf dose, 40.38 mg/day) for 6 weeks. No other psychotropic medications were allowed during the study. Res Clinical Global Impression (CGI)-Improvement scale. The total mean score of the Connor Parent Index w including significant improvement in individual index items such as "short attention span", "easily distract CGI-Severity rating was also significantly improved from baseline to endpoint (p less than 0.05) and ther who did not respond to venlafaxine treatment had comorbid conditions, including tic disorder or oppositic complicated by venlafaxine therapy. Transient adverse effects included stomachache (n=2), somnolence (56.25 mg/day) and one patient, with a comorbid tic disorder, experienced behavioral activation and wors safety and efficacy of venlafaxine in the treatment of ADHD in pediatric patients (Mukaddes & Abali, 200

4.5.A.3 Binging - Eating disorder

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Results of a retrospective study (n=35) indicate venlafaxine may be an effective treatment for binge-

c) Adult:

1) The results of a small, retrospective study indicate that venlafaxine may be an effective treatment for eating disorder (n=35) received venlafaxine alone (n=29) or as an adjunctive therapy (n=6) at a mean do (range, 28 to 300 days). Some patients also received behavioral dietary counseling (91%), formal psych amitriptyline, bupropion, paroxetine, or sertraline. Patients on single or combination venlafaxine therapy frequency, Clinical Global Impressions-Severity of Illness (CGI-S) scale scores for binge eating and depr 0.0001). Fifteen (43%) patients lost at least 5% of their baseline weight and 7 (20%) patients lost at least sexual dysfunction (14%), insomnia (14%), nausea (11%), and blood pressure changes (46%). A small i

4.5.A.4 Bipolar disorder, depressed phase

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

No significant difference between adjunctive bupropion, sertraline or venlafaxine was revealed amor risk of switching into (hypo)mania was significantly higher with venlafaxine in a randomized, double- Venlafaxine monotherapy was more effective than lithium for the initial treatment of bipolar II major d randomized, open-label, clinical trial (n=83) (Amsterdam & Shults, 2008).

Venlafaxine and paroxetine were both significantly effective adjunctive treatments for breakthrough observed with venlafaxine in a single-blind, randomized, comparative trial (n=60) (Vieta et al, 2002).

c) Adult:

1) General Information

a) The incidence of bipolar disorder is reported to occur in 1% to 3% of the population. Most importa comparison to (hypo)manic episodes and have a 10% to 20% lifetime risk of death by suicide (Post for reduction of morbidity and mortality in patients with bipolar affective disorder. However, practice inadequate. The American Psychiatric Association recommends that initial treatment of bipolar II ma stabilizer and the lowest-effective dose, short-term antidepressant therapy (Amsterdam & Shults, 20 antidepressant monotherapy may be considered in bipolar II major depressive episode in patients w mood stabilizer monotherapy for mild to moderate bipolar II depression and combination mood stabi treatment completely (Amsterdam & Shults, 2008). Historical studies have provided evidence that a (eg, venlafaxine, tricyclic antidepressants) may increase the risk of switch into a hypomanic or mani no significant differences between adjunctive bupropion, sertraline, or venlafaxine among response mania switch was significantly higher with venlafaxine compared with bupropion and sertraline (Pos treatment with venlafaxine or paroxetine were both significantly effective for the treatment of breakth or manic switch was observed with venlafaxine (Vieta et al, 2002). In contrast, venlafaxine monothe major depressive episode with low occurrence of hypomanic switch in a prospective, randomized tri sizes, distinguishing between inclusions of bipolar I or bipolar II patients, a clear definition of switch, would be beneficial for consistent and effective control of major depressive episode and minimizatio Shults, 2008; Vieta et al, 2002).

2) Clinical Trials

a) No significant difference between adjunctive bupropion, sertraline or venlafaxine was revealed a the risk of switching into (hypo)mania was significantly higher with venlafaxine compared with bupro (n=174). All patients were currently treated with at least 1 mood stabilizer or antimanic agent. Subje (n=51), sertraline 50 to 200 mg/day (n=58), or venlafaxine 37.5 to 375 mg/day (n=65) for 10 weeks. the study. Symptoms were assessed using the Inventory of Depression Symptomatology (IDS), the Disorder (CGI-BP). The outcome measures included antidepressant response (defined as either a 5 depression score), antidepressant remission (defined as an IDS score less than 12 and/or a CGI-BP hypomania (defined as either an increase of 2 points on the CGI-BP manic severity score during an at any time point). At week 10, the response rates for bupropion, sertraline and venlafaxine were 49 differences were not statistically significant between groups and controlling for lithium use did not alt venlafaxine. Based on at least a 2-point increase on the CGI-BP score, (hypo)manic switching occu respectively. When these data were analyzed using survival analysis in order to control for the effec treatment groups was significant (p=0.002), and controlling for lithium demonstrated similar results (the significant difference in the risk of switching-time between venlafaxine and sertraline (p=0.01, ac lithium), while there was no significant difference between sertraline and bupropion (p=0.9). The risk score (greater than 13) was analyzed. By study endpoint, 4%, 7%, and 15% of patients switched in for lithium did not change the results. The difference between venlafaxine, bupropion and sertraline mania of at least 3 or YMRS greater than 13 criteria were used (p=0.03 without controlling for lithium cycling was lower with bupropion when compared with venlafaxine (p less than 0.01) but there was venlafaxine. The percentages of patients who discontinued the study prematurely for any reason we Withdrawal for adverse events did not vary between the 3 groups. Limitations of the study include n

b) Venlafaxine monotherapy was more effective than lithium for the initial treatment of bipolar II ma randomized, open-label, clinical trial (n=83). DSM-IV bipolar II adult patients with an ongoing acute included in the trial. All patients had a baseline, 17-item Hamilton Depression Rating Scale (HAM-D psychosis in the preceding 3 months or if they were nonresponsive to venlafaxine or lithium during t neuroleptics, tranquilizers or over-the-counter antidepressant agents were not allowed. Any previous Concomitant zolpidem, zaleplon or trazodone was allowed for severe insomnia. Eligible patients age (n=40) for 12 weeks. Venlafaxine was initiated at 37.5 milligrams (mg)/day, increased to 75 mg/day mg/day by week 4. The highest tolerated dose was maintained for an additional 8 weeks. Lithium wa required serum lithium level of 0.5 millimoles (mmol)/L during week 2. Lithium dose was optimized t maintained for an additional 8 weeks. At baseline, study subjects had a history of bipolar II for 18.5 - 18.7 +/- 8.7 years and first hypomanic episode at age 20.7 +/- 8.2. The mean baseline HAM-D 28 sc group. At the end of the study, 79.1% of patients in the venlafaxine group and 37.5% of patients in t was a greater reduction in HAM-D 28 (primary endpoint) with venlafaxine monotherapy compared w (95% CI, -11.97 to -1.18; p=0.017). Venlafaxine monotherapy yielded a greater number of responde 20%; p less than 0.0005). The proportion of remitters (final HAM-D 28 score of 8 or less) was also s 0.0005). There was no significant difference between treatment groups in the mean Young Mania R each, experienced subsyndromal hypomanic and hypomanic symptoms (2.4% vs 2.6%; p=0.99). Or patient in the lithium group discontinued due to increasing suicidal ideation. Other common adverse mouth (32.6% vs 10%), somnolence (30.2% vs 22.5%) and difficulty thinking (16.3% vs 32.5%) in th of a placebo/control group, short treatment duration and small sample population size (Amsterdam &

c) Venlafaxine and paroxetine were both significantly effective adjunctive treatments for breakthrou manic switch was observed with venlafaxine in a single(rater)-blind, randomized, comparative trial (episode indicated by a score of greater than 17 on the 17-item Hamilton Rating Scale for Depressio carbamazepine, other) for at least 6 months prior to the current depressive episode, and required to throughout the study period. Recent treatment with antidepressant or antipsychotics during the prev attempt, currently abusing alcohol or other psychotropics, using concomitant anxiolytics, had previou Scale (YMRS). Eligible patients were randomly assigned to either venlafaxine (n=30; age 45.5 years

6 weeks. Based on response and tolerability, the venlafaxine group received 37.5 milligrams (mg) tv trial was 179.2 +/- 91 mg/day. The paroxetine group received 20 mg/day titrated by 10-mg/day incre modified intent-to-treat population, defined as all patients who took at least 1 dose of study medicati significant improvement in HAM-D 28 scores from baseline to endpoint (primary endpoint). The char to 13.8 +/- 6.7 for paroxetine (both p less than 0.0001). Venlafaxine was numerically superior to parc defined as a reduction in HAM-D 28 score by 50% or more from baseline, was 48% in the venlafaxir HAM-D score of less than 10 and a Clinical Global Impressions (CGI) severity score of 1 was 33% ir occurred in 4 patients (13%) in the venlafaxine group: 2 switched to hypomania (YMRS score = 12 a (3%) in the paroxetine group who switched to hypomania (YMRS score = 17) (p not significant). The treatment and antidepressant discontinuation. One manic episode required hospitalization. Commor vs 7%), headache (3% vs 10%) and insomnia (10% vs 0%) in the venlafaxine and paroxetine groups study design, small sample population size and short follow-up period (Vieta et al, 2002).

4.5.A.5 Cancer pain

See Drug Consult reference: MANAGEMENT OF CANCER-RELATED PAIN IN ADULT PATIENTS

4.5.A.6 Cerebrovascular accident - Depression

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

During an open study, 12 post-stroke patients benefited from venlafaxine treatment administered wi

c) Adult:

1) Twelve patients who received venlafaxine within 2 weeks of a stroke showed a decrease in depressiv (mg) daily with an increase to 150 mg daily after 2 days. Response was evaluated with the Hamilton Dep (MADRS). After 5 weeks of treatment, the HAM-D score decreased from 24.3 to 7.25, and the MADRS d dose was decreased in 1 patient due to agitation; 3 patients had nausea during initiation of treatment. Ba with depression secondary to stroke (Dahmen et al, 1999).

4.5.A.7 Depression - Perimenopausal disorder

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

In a small, open-label trial, extended-release venlafaxine therapy reduced depressive symptoms and

c) Adult:

1) In a small, 8-week, open-label trial, treatment with extended-release venlafaxine reduced depressive perimenopausal if they reported one or more climacteric symptoms (hot flushes, sweating, vaginal dryne criteria comprised of presence of current depressive disorder confirmed by the DSM-IV Axis I disorders, non-hormonal method of contraception. The study was initiated on day 10, 11, or 12 of the menstrual cyc orally once daily during week 1 and 75 mg daily during week 2. Data collection instruments included the global impression severity (CGI-S), and a standard measure of 4 subscales: psychiatric, somatic, vasom When clinically necessary, dosage was increased in 75-mg increments after the week 2 and week 4 visit observed by week 2 and were sustained through week 8. Antidepressant response (greater than 50% Ha equal to 7) was achieved in 12 subjects (75%) after 8 weeks of venlafaxine therapy (75 to 225 mg/day). 71%, and anxiety subscores reduced by 63%. Vasomotor and sexual dysfunction subscores were not sig vasomotor subscores greater than 0, a 37.5% decline was observed at week 8 (p less than 0.05). Howev vasomotor symptoms observed in women who had baseline vasomotor symptoms and that further studie depression (Ladd et al, 2005).

4.5.A.8 Diabetic neuropathy

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Dose-related, clinically significant reductions in pain were demonstrated with venlafaxine extended-r (Rowbotham et al, 2004).
One case report demonstrated the effectiveness of venlafaxine depot combined with gabapentin for Venlafaxine relieved the unremitting pain of diabetic peripheral neuropathy in 8 patients who found r

In a series of 11 patients, venlafaxine relieved the pain associated with diabetic peripheral neuropat

c) Adult:

1) The efficacy of venlafaxine extended-release (XR) for the treatment of painful diabetic neuropathy wa outpatients with metabolically stable type 1 or 2 diabetes and bilateral distal peripheral neuropathy of at l XR at a dose of 75 milligrams (mg) or 150 to 225 mg daily or placebo orally for 6 weeks. Primary efficacy and Pain Relief (VAS-PR) scales. Of the 244 patients randomized, 242 made up the intent-to-treat (ITT) in the venlafaxine XR 75 mg group, 67.3 mm in the venlafaxine XR 150 to 225 mg group, and 68.8 in the reductions in mean adjusted pain intensity scores were 32%, 50%, and 27% for venlafaxine XR 75 mg, v significantly more effective than placebo (p less than 0.001) and venlafaxine XR 75 mg (p =0.006) at wee venlafaxine 150 to 225 mg was significantly more effective than placebo by week 6 (59.9 mm versus 43. placebo (51 mm versus 43.6 mm). The percentages of patients who were considered responders (at leas placebo groups at week 6 (LOCF) were 56% and 34%, respectively (p less than 0.01). The number neec was 4.5 at week 6. The most common treatment-emergent adverse events associated with both venlafax occurred in 6%, 5%, and 1% of the venlafaxine XR 75 mg, venlafaxine XR 150 to 225 mg, and placebo g changes during treatment. Adverse events leading to study withdrawal did not significantly differ betweer

2) The combination of venlafaxine depot (75 milligrams (mg) three times daily) and gabapentin relieved history of type 1 diabetes. The patient developed burning pain and tenderness of the arms and legs and pain was not relieved despite the following treatments: paracetamol and dextropropoxyphene for 7 mont buprenorphine for 3 months; then eight different analgesics. Placing her legs in buckets of cold water for developed orthostatism, preproliferative retinopathy and moderate signs of distal sensory, autonomic, an 75 mg three times daily), and after 7 months was greatly improved with controllable distal pains. Analges

3) Venlafaxine relieved the unremitting pain of diabetic peripheral neuropathy in 8 patients who found nc acetaminophen, carbamazepine, capsaicin, and amitriptyline were not successful, either due to lack of e patients responded to venlafaxine 37.5 milligrams twice daily with dramatic relief in symptoms associatec rapidly without interruption of treatment. No serious side effects were observed (Kiayias et al, 2000).

4) Eleven patients with type 2 diabetes mellitus and painful diabetic neuropathy had a 75% to 100% red patients had been treated unsuccessfully with other medications known to alleviate the pain associated v 75 milligrams/day, all patients noted a 75% to 100% reduction in pain. No adverse effects were reported pain 2 to 3 days later. When venlafaxine was restarted, the pain was relieved promptly. This series sugg

4.5.A.9 Dysthymia

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

During 9-week, open study, venlafaxine was effective for treating dysthymic disorder in 14 patients (

c) Adult:

1) In a 9-week, open study, 10 and 4 patients showed a complete and modest response, respectively, tc determination of baseline Hamilton Rating Scale for Depression (HAM-D-17) and Beck Depression Inver was titrated to a maximum dose of 225 mg daily. Seven patients improved with venlafaxine 75 mg daily; weeks, and met proposed criteria for remission of dysthymic disorder. This study suggests that venlafaxi are needed.

4.5.A.10 Generalized anxiety disorder

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes (extended-release capsule only); Pediatric, no
Efficacy: Adult, Effective; Pediatric, Evidence favors efficacy
Recommendation: Adult, Class IIa; Pediatric, Class IIb
Strength of Evidence: Adult, Category B; Pediatric, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Venlafaxine extended-release is approved for treating generalized anxiety disorder (GAD), as define 2008).

Extended-release venlafaxine was more effective than placebo for improving the symptoms of depre generalized anxiety disorder; however, time to response was greater in patients with comorbidity tha

Venlafaxine extended-release was safe and effective for long-term treatment (6 months) of generali (n=251) (Gelenberg et al, 2000).

Extended-release venlafaxine was superior to placebo for relieving generalized anxiety disorder in n blind trial (n=349) (Rickels et al, 2000).

In two randomized, placebo-controlled, 8-week studies enrolling children with generalized anxiety di one individual trial and the pooled analysis (Rynn et al, 2007).

c) Adult:

1) Extended release (XR) venlafaxine was more effective than placebo for improving the symptoms of d generalized anxiety disorder (GAD). However, time to response was greater in patients with comorbidity

meeting DSM-IV criteria for major depressive disorder in a double-blind, randomized trial (n=368), results and compared to results of the noncomorbid patients. Patients took once-daily doses of venlafaxine XR increased to a maximum of 225 mg. According to the criteria of more than 50% reduction (from baseline) improvement with venlafaxine was significantly greater (p less than 0.05) than with placebo by 12 weeks however, overall, there was no evident trend for a placebo-drug difference until after the eighth week of t evident as early as week 2. By week 12, response rate was 66% on HAM-D and 59% on HAM-A for thos 2001a).

2) Venlafaxine extended-release (XR) was safe and effective for the long-term treatment of generalized (n=251) who met DSM-IV criteria for GAD without a diagnosis of major depressive disorder were random age, 41 years) or placebo (n=127; mean age, 38 years) for 28 weeks. Primary outcome measures includ HAM-A psychic anxiety factor score, and the Clinical Global Impressions (CGI) scale Severity of Illness a evaluable for the efficacy analysis. The overall dropout rate was 59%, with 60 and 44 patients in the venl observation-carried-forward (LOCF) method, the adjusted mean changes from baseline to week 28 for H changes for HAM-A psychic anxiety score were -7.4 for venlafaxine XR and -4.2 for placebo (p less than 0.001). Significant (p less than 0.01) changes in the HAM-A scores were seen as early as week 1 with ve differences between venlafaxine XR and placebo were maintained throughout the final assessment at we where significant reductions were noted with venlafaxine XR compared with placebo at week 1 (p=0.02) Illness scores for venlafaxine XR compared to placebo became initially noted at week 2, but became mo superior to placebo on the CGI-Global Improvement item at all times assessed beyond week 1. Respons or a CGI-Global Improvement score of 1 or 2) during weeks 6 through 28 were at least 69% in the venlaf most common adverse events occurring with at least twice the frequency with venlafaxine XR were anor sweating. Over time (days 57 to 196), these events subsided with continued therapy (Gelenberg et al, 20

3) Extended-release (XR) venlafaxine was superior to placebo for relieving generalized anxiety disorder double- blind trial, patients were given placebo (n=96) or venlafaxine XR (n=253) at one of 3 dose levels for the first week; during the second week, those assigned to the 150 and 225 mg/day groups were raise the end of week 1 and throughout the 8 weeks of treatment, efficacy measures for all doses of venlafaxir were indistinguishable for the 2 highest doses of venlafaxine, although, according to the Anxiety Subscal mg/day. Most discontinuations (29% of patients) were caused by adverse reactions and occurred within nausea, insomnia, dry mouth, somnolence, dizziness, and asthenia (Rickels et al, 2000).

d) Pediatric:

1) Extended-release venlafaxine may improve generalized anxiety disorder in children as evaluated in tw identical in design and were analyzed separately and in a pooled analysis. Children with generalized anx once daily (n=157) or placebo (n=163) and were titrated up according to body weight for 8 weeks, follow dose was 225 mg/day for children weighing greater than or equal to 50 kilograms (kg). Patients were stra equal to 20 on the severity component of the generalized anxiety section of the Columbia Schedule for A Patients were excluded if they had major depressive disorder, acute suicidality, social anxiety, or other p in the composite score of nine delineated items from the Columbia K-SADS (primary endpoint) was grea 12.4; p less than or equal 0.001); however, there was not a significant difference between treatment grou patients responded (defined as at least a 50% decrease from baseline in the nine-item Columbia K-SAD group (38%) compared to the placebo group (17%; p-value not reported) in the first study, but not in the of nine delineated items from the Columbia K-SADS generalized anxiety disorder section was 17.4 point ($p < 0.001$). In both studies, patients treated with extended-release venlafaxine experienced greater impr most common adverse events in the extended-release venlafaxine group that were twice as frequent as

4.5.A.11 Hot sweats, Breast cancer-related

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

In two randomized, double-blind, crossover trials, treatment with oral extended-release venlafaxine reductions in hot flash frequency, severity, and bother compared to placebo in breast cancer survivo In a randomized, double-blind German study (n=80), treatment with oral venlafaxine was significantl women with primary breast cancer (Loibl et al, 2007).

c) Adult:

1) General Information

a) Practice guidelines and limited clinical trials support short-term efficacy of oral venlafaxine in bre 2007; Loibl et al, 2007; Hickey et al, 2008). In two, 14-week, randomized, double-blind, placebo-con venlafaxine, primarily in Caucasian breast cancer survivors, both doses administered demonstrated physiologically-assessed), severity, and bother compared to placebo (Carpenter et al, 2007). Furthe evident in this study. In another 4-week, randomized, double-blind, controlled study in adult women frequency to a greater extent compared to clonidine (Loibl et al, 2007). Treatment-emergent adverse (Carpenter et al, 2007; Loibl et al, 2007).

2) Clinical Trials

a) Treatment with oral extended-release (ER) venlafaxine 37.5 milligrams (mg; low-dose) or 75 mg flash frequency, severity, and bother compared to placebo in breast cancer survivors in two random

cancer (the use of tamoxifen and/or aromatase inhibitors were not allowed), experiencing 1 or more
two, 14-week crossover trials. In the low-dose trial (n=52; mean age, 50.5 years; 91% Caucasian), p
(n=26) once daily for 6 weeks; subsequently, without a washout period, patients from each arm were
trial (n=18; mean age, 53 years; 90% Caucasian) had a similar design except venlafaxine ER (n=9)
during weeks 2 to 5. Hot flash frequency was evaluated using both a weekly, 24-hour (hr), ambulato
electronic event markers and written diaries that were completed during one 24-hr period each week
using separate 10-point numeric scales; range; 0=not at all and 10=extremely severe or bothersome
Interference Scale). Data for the 2 crossover trials were analyzed separately using mixed linear mod
(n=45 and n=15, respectively) provided 86% and 43% power, respectively (using a two-sided paired
detect a large effect size (equal to 0.78 standard deviation) in the high-dose group. At baseline, mea
study patients (pooled data from both studies) was 7.46 and 6.02, respectively. After 6 weeks of the
(adjusted mean reduction, -1.7) in the low-dose venlafaxine group compared to no change in the pla
(CI), 0.09 to 0.23). In the high-dose trial, venlafaxine-treated patients experienced a 14% (adjusted r
hr compared to a 13% (adjusted mean increase, +0.98) increase in the placebo group (p=0.013) (eff
baseline by 42% and 18% (p less than 0.001) in the venlafaxine ER and placebo groups, respective
(p=0.001), respectively, in the high-dose trial (effect size, 0.24; 95% CI, 0.1 to 0.38). Additionally, bo
vs -5%; p less than 0.001 for both) and bother (low-dose, -4% vs 10%; high-dose, -19% vs +6%; p le
greater improvements from baseline in hot flash interference occurred only in the high-dose venlafax
significant differences between the venlafaxine and placebo groups for secondary outcomes, which
adverse events was similar among venlafaxine- and placebo-treated patients, severe constipation a
compared to placebo. This study was limited by the placebo effect that was evident for self-reported
three-quarters of study patients were able to correctly identify receipt of placebo by study end (Carp
b) Treatment with oral venlafaxine was significantly more effective than clonidine in decreasing the
double-blind German study (n=80). Enrollees, who were required to have bothersome hot flashes at
either venlafaxine 37.5 mg (n=40) or clonidine 0.075 mg (n=40) orally twice daily for 4 weeks. Concu
was allowed provided patients were on it for at least a month and it was continued throughout the st
measure was the patient-recorded hot flash frequency at end of therapy. The hot flash severity scor
endpoint. At baseline 61% of patients in each group were over 50 years of age, with 90% and 82% r
respectively. At baseline, the median daily hot flash frequency was 11 (range, 3 to 23) and 9.7 (rang
flash severity was 1.7 (range, 1 to 3) and 1.8 (range, 1 to 3.1), respectively, and the median daily ho
Among the evaluable population (n=63), the median hot flash frequency decreased from baseline by
clonidine group at week 4 (p=0.025). Additionally, more patients in the venlafaxine group had a 75%
hot flashes occurred only in the venlafaxine group (n=6). The median daily hot flash score decrease
clonidine groups, respectively (p=0.043). Ten patients discontinued treatment due to adverse events
mouth (35.5% vs 51.1%), tiredness (35.5% vs 42.4%), and restless sleep (35.5% vs 51.5%) were th
were not statistically significant (Loibl et al, 2007).

4.5.A.12 Major depressive disorder

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes; Pediatric, no
Efficacy: Adult, Effective; Pediatric, Evidence is inconclusive
Recommendation: Adult, Class IIa; Pediatric, Class IIb
Strength of Evidence: Adult, Category B; Pediatric, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

The immediate-release and extended-release formulations of venlafaxine are indicated for the treatr
EFFEXOR XR(R) extended-release oral capsules, 2008; Prod Info venlafaxine extended release ora
Efficacy of venlafaxine immediate- and extended-release tablets for the treatment of major depressi
(Simon et al, 2004; Silverstone & Salinas, 2001a; Rudolph et al, 1998; Amsterdam et al, 1998) and i
Several open-label studies and individual case reports support the usefulness of venlafaxine as a pc
De Montigny et al, 1999; Fatemi et al, 1999; Sharma, 1998; Bader et al, 1998).
Venlafaxine combined with electroconvulsive therapy was efficacious in patients with treatment-resis
patients (Gonzalez-Pinto et al, 2002).
Separate results of 2 similar placebo-controlled, double-blind, randomized trials did not demonstrate
patients with major depressive disorder; pooled results showed greater improvement in adolescents

c) Adult:

1) Clinical Trials

a) Continuation of venlafaxine extended-release (ER) therapy following response to treatment appe
(MDD). In a prospective, multicenter study, patients (n=318) who responded to 8 weeks of open- lab
192 mg/day) entered a 6-month randomized, double-blind, continuation phase in which they either r
191 mg/day). During the 6-month relapse-prevention phase, significantly fewer patients treated with
0.001) and at study endpoint, the cumulative probability of relapse was higher for patients in the pla
of venlafaxine ER as compared with placebo (p less than 0.001) were also observed for secondary
D depressed mood item, Montgomery-Asberg Depression Rating Scale total score, and Clinical Glo
significantly more often with venlafaxine than with placebo included hypertension and sweating (p=0
withdrawn from the study due to increases in blood pressure (Simon et al, 2004).

b) Extended release (XR) venlafaxine was more effective than placebo for improving the symptoms

generalized anxiety disorder (GAD). However, time to response was greater in patients with comorb
criteria for MDD in a double-blind, randomized trial (n=368), results from the subset of patients who
noncomorbid patients. Patients took once-daily doses of venlafaxine XR 75 milligrams (mg), fluoxeti
of 225 mg. According to the criteria of more than 50% reduction (from baseline) in the Hamilton-Dep
was significantly greater (p less than 0.05) than with placebo by 12 weeks of treatment. About one tl
no evident trend for a placebo-drug difference until after the eighth week of treatment. Among patier
By week 12, response rate was 66% on HAM-D and 59% on HAM-A for those taking venlafaxine an
c) Venlafaxine was superior to placebo for treating depression during a 6-week, double-blind trial. F
(mg) daily, 225 mg daily, or 375 mg daily; the dose was titrated over 7 days in the 2 higher dosage g
the Montgomery-Asberg Depression Rating Scale (MADRS) total score, and the Clinical Global Imp
the CGI scale was significantly greater in all venlafaxine groups than the placebo group. Venlafaxine
the MADRS (p=0.005), and the CGI (p=0.0031). Of the 323 patients who began treatment, 194 com
withdrawal in the venlafaxine groups; whereas, failure to return and an unsatisfactory response were
d) In an open, community-based study, venlafaxine effectively treated depression in 62% of patient
149 were family physicians, and 62 were psychiatrists; each physician could enter a maximum of 5 p
scale, patients began treatment with venlafaxine 37.5 milligrams (mg) twice daily for about 2 weeks
patients who withdrew from the study, 134 (15%) withdrew due to adverse effects; whereas, only 17
Clinical Global Impressions (CGI) assessment; 522 (62%) patients achieved this outcome based on
week of treatment but declined over the remainder of the study (Joffe et al, 1998).
e) Once versus twice daily administration of venlafaxine immediate-release resulted in comparable
double-blind, randomized study (n=48), patients received the same dose of venlafaxine once or twic
groups. This dose was continued for 1 week in the once daily group; whereas, patients in the twice d
maximum dose of 225 mg daily was reached. At 2 weeks, a nonsignificant trend for greater improve
Depression Rating scale (MADRS) were observed in the twice daily versus once daily group; howev
were similar between treatments. This study suggests that once daily versus twice daily administrati
inconvenience of more frequent administration (Amsterdam et al, 1998).

2) Treatment-Resistant Depression

a) Nine out of 11 patients experienced a sustained improvement in depression with combined venla
recurrent depression while 1 patient had a severe major depressive episode. Two patients also had
Nine patients had failed fluoxetine or paroxetine therapy, and 9 had failed augmentation with lithium
clomipramine 150 to 375 milligrams (mg)/day, and 3 patients received imipramine 200 to 250 mg/da
daily to 150 mg every 12 hours. Using the Hamilton Rating Scale for Depression (HAM-D), 9 patient
patients with panic- agoraphobic symptoms also showed improvement; however, there was no impr
venlafaxine that allowed for maximum improvement was 75 to 300 mg/day (Gomez & Perramon, 20
b) In an 8-week, open trial (n=159), 58% and 28% of patients achieved a good response and remis
respond to at least 1 other antidepressant; 45% of patients had used 3 or more medications for this
titration to 375 mg/day over 4 weeks, if needed; the mean daily dose was 260 mg/day at 8 weeks. T
Rating Scale, and the Clinical Global Impression Scale scores were significantly lower at 8 weeks (p
Compared to many antidepressant trials, the number of patients who stopped treatment due to adve
c) Combination therapy with venlafaxine and bupropion was effective in a patient with treatment-res
times daily increased to 150 milligrams 3 times daily. Since her depressive symptoms did not respor
symptoms abated. The Beck Depression Inventory score decreased from 28 to 11.6 while the Globa
effects were sweating and a mild increase in heart rate which was controlled with atenolol 25 milligra
23 months (Fatemi et al, 1999).
d) A case report documents intermittent followed by sustained improvement with venlafaxine in a w
Treatment with venlafaxine 262.5 milligrams (mg) daily, in conjunction with several other medication
however, experienced relapse 4 months later. Attempts were made to increase the dose of venlafax
and venlafaxine was restarted. The patient reacted as she had before, with a relapse after 4 months
mg. Her symptoms resolved, and she had been maintained on that dose for 9 months (Sharma, 199
e) A 79-year-old man with several depressive episodes and a poor response to many antidepressa
venlafaxine titrated to 75 milligrams (mg) 3 times daily which increased his appetite but did not chan
morning and 5 mg at noon. Within 5 days, he began attending to activities of daily living; he continue
pressure and heart rate, this man was monitored carefully but therapy had no adverse cardiovascula

1) With Electroconvulsive Therapy

a) Venlafaxine combined with electroconvulsive therapy (ECT) proved to be efficacious in
was asystole in 4 of 13 patients. Mean score on the Hamilton Rating Scale for Depression
treatment (p less than 0.004, posttreatment compared with baseline). Overall, 10 of 13 (76.
improved' on the Clinical Global Impression (CGI) subscale for improvement and a 50% re
doses of venlafaxine were 265.38 milligrams (mg) (range 150 to 375 mg) and were not cha
Related to safety, rapid reduction in heart rate followed by asystole occurred in 4 of 110 se
the 4 affected patients. None of the study subjects had a history of cardiovascular disease.
(mean 337.5 mg, range 300 to 375 mg) compared with subjects in whom asystole did not c
succinylcholine were given immediately before ECT. No complications, such as prolonged
to 225 mg/day) were as responsive to combination venlafaxine-ECT treatment as those wh

d) Pediatric:

1) Separate results from two similar double-blind, randomized controlled trials indicated there was no sig
treatment of major depressive disorder (MDD) in pediatric patients aged 7 to 17 years, while pooled resu
(aged 12 to 17 years) only. After a single-blind, placebo lead-in phase, study participants (mean age, ap

body weight (n=184) or placebo (n=183) for up to 8 weeks. The primary efficacy measure was the chang
weeks. Secondary efficacy measures included the 21-Item Hamilton Rating Scale for Depression (HAM-
Impression-Severity (CGI-S), and CGI-Improvement scales. Efficacy and safety data from both studies w
pooled data from both studies. The combined study discontinuation rates were 27% and 32% for patients
changes from baseline, no statistically significant differences were seen between venlafaxine ER and pla
significant differences in secondary outcome measures or response rates. In the post hoc subgroup anal
groups on any outcome measure. Adolescents aged 12 to 17 years who received venlafaxine XR experi
to 32.5 at week 8 compared to a decrease from 56.9 to 36.9 at week 8 for the placebo group (p=0.022);
Adjusted mean change scores at week 8 also demonstrated greater improvement with venlafaxine XR o
(p=0.022) but not HAM-D-21 total. Additionally, there was a difference in responder rates based on CDR
reported adverse events for venlafaxine XR and placebo were abdominal pain (21% and 10%, respectiv
reported in 7% and 2% of patients receiving venlafaxine XR and placebo, respectively. Of the SAEs, ven
reaction (n=2). There were no completed suicides (Emslie et al, 2007).

4.5.A.13 Menopausal flushing

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

In a randomized, double-blind study (n=80), treatment with oral, extended-release venlafaxine 75 mi
postmenopausal hot flashes as well as improved mental health and vitality outcomes compared to p
Extended-release venlafaxine was effective for treating hot flashes in women with a history of breas
BC during a 4-week, double-blind, randomized, placebo-controlled trial (n=229) (Loprinzi et al, 2000
2002).
During a 4-week, open, pilot study (n=21), venlafaxine was effective in decreasing the incidence of h
1999).
Low-dose venlafaxine was effective in reducing the incidence and severity of hot flashes in women v
therapy (n=5) (Loprinzi et al, 1998).

c) Adult:

1) Treatment with oral, extended-release (ER) venlafaxine 75 milligrams (mg) per day for 12 weeks sign
improved mental health and vitality outcomes compared to placebo in a randomized, double-blind study
than 14 hot flashes per week were included. Women concurrently on antidepressants or chemotherapy v
(n=40; mean age, 52.7 years) or placebo (n=40; mean age, 51.6 years) for 12 weeks, and followed at 4,
for 1 week and then increased to 75 mg/day for the remainder of the study. The patient-perceived hot fla
visits using a 5-point Likert scale. Additionally, patients completed a daily hot flash diary, noting the frequ
majority of patients (approximately 80%) were in natural menopause, the mean patient-perceived hot flas
more common in the venlafaxine group (67.6% vs 36.8%; p=0.008). At the 3-month follow-up, the averag
was 21 points (95% confidence interval (CI), 11 to 32; p less than 0.001). Although reductions in the sco
month 2 visit, with a mean score of 35.3 in the venlafaxine group at month 3 compared with a rebound in
follow-up visits (p=0.01), the estimated treatment effect of venlafaxine remained significant compared to
score compared to a 15% reduction in the placebo group. Based on diary data, hot flash severity and fre
differences. Venlafaxine was associated with a mean reduction of 2.6 points (95% CI, -2.3 to 7.5; p=0.25
Quality of life measures, assessed monthly using a modified Short Form-36 Health Survey mood scale, s
group difference, 8.7; 95% CI, 2.8 to 14.6) and vitality (between-group difference, 8.5; 95% CI, 2.8 to 14.
occurring commonly and more frequently than placebo included dry mouth (81% vs 44%), sleeplessness
from the study (venlafaxine, n=11; placebo, n=8), difficulty sleeping, decreased libido, nausea, and anxie
of the venlafaxine-treated study participants chose to continue venlafaxine treatment following study com
2) Extended-release venlafaxine was effective for the treatment of hot flashes in breast cancer (BC) sur
four-week, double-blind, randomized, placebo-controlled trial. Eligible patients (n=229) were required to h
least 1 month prior to study entry, and a performance status of 0 to 1 on the Eastern Cooperative Oncolo
weeks treatment with placebo (n=56), 2) 4 weeks treatment with 37.5 milligrams (mg) venlafaxine daily (
week of 37.5 mg daily, 1 week of 75 mg daily, and 2 weeks of 150 mg daily (n=54). Use of antiestrogens
initiated 4 weeks prior to study entry and continued during the entire study duration. The primary endpoir
combined score of frequency and severity (range, 1=mild to 4=very severe). At baseline, study patients h
the modified intent-to-treat analysis of 191 evaluable patients at the end of the study, patients receiving v
activity scores at week 4 from baseline (37%, 61%, and 61% reduction in the venlafaxine 37.5 mg, 75 mg
than 0.001 vs placebo). A reduction of more than 50% in hot flash activity occurred in 45%, 63%, and 55
20% in the placebo group. No difference in efficacy was noted between the 75 mg and the 150 mg group
adverse events included dry mouth, nausea, decreased appetite, and constipation, which occurred more
2000).

a) An 8-week, open-label, longitudinal extension of this trial demonstrated that efficacy of venlafaxi
randomized, placebo-controlled trial that entered the open-label continuation phase, 102 patients we
37.5 to 150 milligrams (mg)/day. At 8 weeks, the venlafaxine doses used were 37.5 mg (n=26), 75 m
from baseline (week 1 of placebo-controlled phase) in hot flash frequency was reported at study enc
experienced an additional mean 26% reduction in hot flash scores, the approximate 60% reduction i

phase was maintained during the open-label extension. Common adverse events in the continuatior (Barton et al, 2002).

3) Low-dose venlafaxine decreased hot flash activity by 81% in men receiving androgen deprivation the 12.5 milligrams twice daily for 4 weeks. Using a diary, patients recorded the number and severity of daily daily hot flashes decreased from 10 at baseline to 6 after 4 weeks of treatment. This was accompanied b weeks, 52% of patients wished to continue venlafaxine treatment. Nausea was the primary adverse effec

4) Low-dose venlafaxine was effective in reducing the incidence and severity of hot flashes in women w therapy (n=5). Patients received venlafaxine 25 milligrams (mg) daily for 5 weeks. The average number (54%) patients reported a 50% or greater decrease in the incidence of hot flashes (P less than 0.0002). study were consistent with previous studies (Loprinzi et al, 1998).

4.5.A.14 Obsessive-compulsive disorder

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIa
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Venlafaxine extended-release (XR) was as effective as paroxetine in the primary treatment of patier (Denys et al, 2003a).

During a double-blind study (n=150), venlafaxine was effective as a crossover therapy in patients wi al, 2004).

Venlafaxine was effective for the treatment of obsessive compulsive disorder in two separate case s Hollander, 1996; Zajecka et al, 1990).

c) Adult:

1) Primary Therapy

a) Venlafaxine extended-release (XR) was as effective as paroxetine in the treatment of patients wi study, patients (n=150) with OCD and a score of at least 18 (or at least 12, if only obsessions or onl received either venlafaxine XR (initial, 75 milligrams (mg)/day, titrated to 300 mg/day by week 7) or Both paroxetine and venlafaxine XR treatments were effective, producing mean reductions of 7.8 ar decrease in the total Y-BOCS score from baseline was seen at week 3 for venlafaxine XR-treated p no significant differences in responder rates between treatment groups. In the venlafaxine XR group Similarly, in the paroxetine group, 44% and 22% of patients were partial responders and full respon treatments with regard to reduction of anxious or depressive symptoms (as measured by the Hamilt treatments, most adverse effects were of mild or moderate severity and included somnolence, swea

2) Crossover Therapy

a) Patients with obsessive-compulsive disorder (OCD) refractory to initial treatment with a selective a double-blind switch study, patients (n=150) with primary OCD received venlafaxine (titrated to 300 responders (n=43) were switched to the opposite therapy (venlafaxine, n=16; paroxetine, n=27) for a was defined as a reduction in the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) below 25%. (week 16) to endpoint, however the score was significantly reduced in paroxetine-treated patients (p statistically superior as compared with venlafaxine (p=0.017). The response rate during phase II of t group and a 56% (15/27) response rate in the paroxetine group (p=0.01). At the end of both phases between treatment groups including somnolence, sweating, headache, constipation, insomnia, naus

b) Venlafaxine was effective in the treatment of obsessive-compulsive disorder in a 28-year-old ma resulted in sedation, nausea, and dry mouth. A 3-week course of paroxetine 20 mg/d was discontinu anxiety, and agitation. Venlafaxine 25 mg 3 times daily was initiated and titrated up to 75 mg 3 times 24 to 7. Ten months later the patient was still responding well.

c) Venlafaxine may be useful in the treatment of obsessive-compulsive disorder. In one case report compulsive disorder refractory to amitriptyline, fluoxetine, and clomipramine was treated with venlafa baseline NIMH Global Obsessive-Compulsive Scale score was 12. At 4 weeks, there was significan dose of venlafaxine was increased to 375 mg/day over the next week; continued improvement in ob weeks (NIMH score=4). At that time, the patient requested discontinuation of venlafaxine due to per NIMH score went back to 12 (Zajecka et al, 1990).

4.5.A.15 Panic disorder, With or without agoraphobia

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes (extended-release capsule only); Pediatric, no
Efficacy: Adult, Effective
Recommendation: Adult, Class IIa
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Venlafaxine hydrochloride extended-release capsules are indicated for the treatment of panic disord extended-release oral capsules, 2008).

Results of a double-blind, randomized, controlled trial (n=664) comparing venlafaxine extended-rele

demonstrated greater improvement with venlafaxine XR and paroxetine than with placebo (Pollack e

c) Adult:

1) Results of a double-blind, randomized, controlled trial which compared venlafaxine extended-release greater improvement with venlafaxine XR and paroxetine than with placebo. Although paroxetine was inc placebo only. Nondepressed outpatients with a diagnosis of panic disorder with or without agoraphobia v median full-symptom panic attacks, 6), venlafaxine XR 150 mg/day (n=168; baseline median full-sympto attacks, 6), or placebo (n=163; baseline median full-symptom panic attacks, 6.1) orally for 12 weeks. The attacks in the last observation carried forward (LOCF) end point analysis, which was assessed using the Panic Disorder Severity Scale, Clinical Global Impressions-Severity (CGI-S) and -Improvement (CGI-I) s (no full-symptom panic attacks on the PAAS and CGI-S scores of 1 (not at all ill) or 2 (borderline ill). Res that patients who received venlafaxine XR or paroxetine experienced significantly greater improvement c groups had a significantly higher percentage of patients (p less than 0.001 for each active treatment grou study endpoint compared with the placebo group (venlafaxine XR 75 mg, 54.4%; venlafaxine XR 150 mg full-symptom panic attacks was also significantly greater in the three active treatment groups compared t venlafaxine XR 150 mg, (-6.5) p less than or equal to 0.001, paroxetine, (-6) p less than or equal to 0.01) in Panic Disorder Severity Scale total score compared with placebo at week 12 (p less than 0.001 for ea patients who responded to active treatments were 76.6% (venlafaxine XR 75 mg), 79.2% (venlafaxine X less than 0.001 for all three active treatment groups relative to placebo). The percentage of patients who mg), 43.4%% (venlafaxine XR 150 mg), and 44.4% (paroxetine) compared with 23.7% of patients receiv Adverse events were mild or moderate and similar between treatment groups. The most common advers tremor (Pollack et al, 2007).

2) In 2 double-blind, multicenter, placebo-controlled studies, venlafaxine hydrochloride extended-release patients with panic disorder. The 12-week studies included adult outpatients who met DSM-IV criteria for venlafaxine (75 or 150 milligrams (mg)/day in one study and 75 or 225 mg/day in the other study) or plac free of full-symptom panic attacks on the Panic and Anticipatory Anxiety Scale (PAAS); the mean change the percentage of patients who were much or very much improved (rated as responders) on the Clinical venlafaxine than with placebo. A dose-response relationship was not established in these fixed-dose stu phase study with venlafaxine extended-release capsules (75 to 225 mg/day) were randomly assigned to defined as having 2 or more full-symptom panic attacks per week for 2 consecutive weeks or discontinua average for 34 days. Results from the randomized phase indicated that patients who continued to receiv extended-release oral capsules, 2008).

4.5.A.16 Posttraumatic stress disorder

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Venlafaxine extended-release was somewhat effective and well tolerated for the treatment of posttra controlled trial (n=538) (Davidson et al, 2006) and a 6-month, double-blind, randomized controlled tr

c) Adult:

The efficacy and safety of venlafaxine extended-release (XR) were demonstrated in a 6-month, double-b diagnosis of posttraumatic stress disorder (PTSD). Patients were included in the study if they had a scor symptoms of PTSD for at least the previous 6 months. Following a washout period of at least 1 week, pa (n=161; mean age, 42.2 years) or placebo (n=168; mean age, 40.5 years) for 24 weeks. The primary out Secondary measures included the frequency of remission (defined as 20 or less on the CAPS-SX-17), ti 224 (68%) completed the study. The mean maximum daily dose of venlafaxine XR was 221.5 mg/day. Ir 29.2 at week 24 in the venlafaxine-XR group compared with a decrease from 82.9 to 38.1 in the placebo week 24 in completers were -59.2 and -54, for venlafaxine XR and placebo, respectively, and were not s improvement from week 4 onward (last observation carried forward (LOCF). Mean LOCF change scores 0.001). Efficacy measures related to symptom cluster scores are outlined in the table:

Outcome Measure	Venlafaxine XR Baseline	Venlafaxine XR Week 24
CAPS-SX-17 cluster B (reexperiencing) score	24.6	8
CAPS-SX-17 cluster C (avoidance/numbing) score	31.8	11.5
CAPS-SX-17 cluster D (hyperarousal) score	24.6	9.8

LOCF remission rates for venlafaxine XR and placebo were 50.9% and 37.5% (p=0.01), respectively, at were 44.7% and 33.3%, respectively (p=0.04). The most commonly reported adverse effects associated weight change of at least 7% occurred more frequently in venlafaxine-treated patients (12%) than placeb

The efficacy and safety of venlafaxine extended-release (XR) were demonstrated in a 12-week, double-b diagnosis of posttraumatic stress disorder (PTSD). Patients were included in the study if they had a scor symptoms of PTSD for at least the previous 6 months. Following a washout period of at least 1 week, pa (n=179), flexible-dose sertraline (50 to 200 mg/day) (n=173), or placebo (n=179) for 12 weeks. The prim baseline in the CAPS-SX-17 score week 12. Secondary efficacy measures included changes in CAPS-S (defined as a CAPS-SX-17 score of 20 or less). Of the 538 patients randomized, 531 received treatment venlafaxine XR was 224.6 mg compared with 151.4 mg for sertraline. Change scores for the primary out (LOCF) for venlafaxine and placebo are summarized in the table below. The magnitude of the difference to both primary and secondary efficacy values was minimal and clinically insignificant.

	Mean Change From Baseline (95% Confidence Interval)	
CAPS-SX-17 Outcome Measure	Venlafaxine XR	Pla
Total Score	-41.51	-3
Reexperiencing Cluster Score	-12.54	-1
Avoidance Cluster Score	-16.99	-1
Hyperarousal Cluster Score	-11.57	-9

Remission rates at week 12 were 30.2% for venlafaxine XR and 19.6% for placebo (p less than 0.05). Ve adverse effects being headache (29%), nausea (24%), and dry mouth (18%) (Davidson et al, 2006).

4.5.A.17 Premenstrual dysphoric disorder

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Venlafaxine was superior to placebo for alleviation of premenstrual dysphoric disorder symptoms du

c) Adult:

1) Venlafaxine was superior to placebo for alleviation of symptoms associated with premenstrual dysph dysphoric disorder (renamed PMDD in DSM-IV) after 3 levels of screening were randomly assigned to re cycles. The initial dose of venlafaxine was 25 milligrams (mg) twice daily. In the absence of response, th 200 mg daily. Data from 143 women were used in the efficacy analysis. The mean doses of venlafaxine cycle, venlafaxine was associated with a 42% decrease in symptoms, as assessed by the Daily Symptor the second cycle and thereafter, decrease from baseline was 57% for venlafaxine and 31% for placebo. symptoms. There was no difference between venlafaxine and placebo in effect on appetite. The rate of r venlafaxine group and 35% in the placebo group (p=0.003). There were no serious adverse effects. The from 36% in the first cycle to 15% in the second cycle; insomnia; dizziness; and decreased libido (Freem

4.5.A.18 Recurrent major depressive episodes; Prophylaxis

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Results from the Prevention of Recurrent Episodes of Depression with Venlafaxine for Two Years (P (ER) was effective in preventing recurrence of depression in patients who had been successfully tre maintenance (1 or 2 years) therapy (Keller et al, 2007a; Kocsis et al, 2007; Keller et al, 2007).

c) Adult:

1) Results of the double-blind, randomized PREVENT (Prevention of Recurrent Episodes of Depression (ER) was effective for the prevention of recurrent depressive episodes when given as long-term mainten depressive symptoms for at least 1 month prior to the start of the study and a score of at least 18 on the randomized to venlafaxine ER 75 to 300 milligrams (mg) per day (n=821) or fluoxetine 20 to 60 mg per d 37.5 mg per day or fluoxetine 10 mg per day and titrated based on response and tolerability. Patients wh 50% or more) or remission (defined as HDRS score of 7 or less), remained on double-blind venlafaxine E responders after the continuation phase were then enrolled into 2 consecutive 12-month maintenance ph acute and continuation phases, while overall the study was powered for the primary endpoint of time to r reduction from acute phase baseline that was not more than 50% at 2 consecutive visits or at last valid v reduction in HDRS score from acute phase baseline) in the maintenance phase for venlafaxine ER comp fluoxetine-treated patients being more severely depressed in the acute phase than venlafaxine-treated p venlafaxine ER and fluoxetine was 79% while remission rates were 49% and 50%, respectively (p=0.719

differences between treatment groups at end point with regard to the proportion of patients who maintain response rates for venlafaxine ER and fluoxetine at the end of the continuation phase were 90% and 92% overall comparison). Venlafaxine ER responders after the 6-month continuation phase were then randon placebo, while fluoxetine responders continued taking fluoxetine during the first one-year maintenance p 129 patients receiving venlafaxine ER and 129 patients receiving placebo. At study endpoint, venlafaxine and secondary definitions of recurrence (p=0.005 and p less than 0.001, respectively). The probability of confidence interval (CI), 31.8 to 52.2%) and 23.1% for venlafaxine ER (95% CI, 15.3 to 30.9%) (p=0.005 enrolled in another 12-month maintenance phase, and venlafaxine responders were randomized to venla responders continued taking fluoxetine. Placebo responders continued to receive placebo in the second longer time to recurrence compared with placebo (p less than 0.001). The probability of recurrence at mo 0 to 16.8%) (p less than 0.001). The rate of response or remission at 12 months was also significantly hi respectively; p=0.002) (Keller et al, 2007a; Kocsis et al, 2007; Keller et al, 2007).

4.5.A.19 Severe major depression with psychotic features

See Drug Consult reference: PSYCHOTIC DEPRESSION - DRUG THERAPY

4.5.A.20 Social phobia

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes (extended-release capsule and tablet only); Pediatric, no
Efficacy: Adult, Effective; Pediatric, Evidence favors efficacy
Recommendation: Adult, Class IIa; Pediatric, Class IIb
Strength of Evidence: Adult, Category B; Pediatric, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Venlafaxine extended-release capsules and tablets are approved for treating adults with social anxie (R) extended-release oral capsules, 2008; Prod Info venlafaxine extended release oral tablets, 2008 Low-dose (75 milligram (mg)/day) and high-dose (150 to 225 mg/day) venlafaxine extended-release month, randomized, placebo-controlled trial (n=395) (Stein et al, 2005).
Results of a randomized, placebo-controlled trial (n=293) demonstrated the efficacy and safety of ve al, 2007).

c) Adult:

1) Venlafaxine extended-release (XR) was safe and effective for the treatment of generalized social anx outpatients (n=395; mean age, approximately 37 years) diagnosed with GSAD as defined by DSM-IV we flexible higher dose of venlafaxine XR 150 to 225 mg per day (n=129), or placebo (n=129) for 28 weeks. (LSAS). Some secondary efficacy measures included the proportion of responders (ie, Clinical Global Im (ie, LSAS score of 30 or less). The proportion of patients who withdrew from the study for any reason wa XR groups, respectively (p less than 0.05 for both). The final intent to treat population was 364, and the m 213.7 mg for the flexible-dose group. The adjusted mean change from baseline in the LSAS total score a 37.8 for the combined venlafaxine XR groups, and -23.5 for the placebo group (p less than 0.001 for all c placebo and venlafaxine XR-treated patients (combined and at low- and high-dose), respectively, were r venlafaxine XR-treated patients (combined and at low- and high-dose), respectively, were remitters (p le groups, the study did not find significant differences in response or remission rates between the low and associated with venlafaxine XR at a higher rate than placebo included abnormal ejaculation (12 to 18% v 12%), dry mouth (19 to 23% vs 6%), nausea (34 to 37% vs 10%), and somnolence (24 to 29% vs 14%). attempts committed suicide on day 86 of the study. There were 3 other reports of suicidal ideation or atte receiving placebo (Stein et al, 2005).

d) Pediatric:

1) Results of a randomized, placebo-controlled trial (n=293) demonstrated the efficacy and safety of ver children and adolescents. Pediatric outpatients (aged 8 to 17 years) diagnosed with SAD were randomiz milligrams (mg) orally daily and was titrated based on patient weight to a maximum dose of 225 mg daily Anxiety Scale (SAS-CA) and the Clinical Global Impression Improvement (CGI-I) score which identified r improved) or 2 (much improved) at week 16. Of the 293 patients randomized, 285 were included in the in receiving venlafaxine XR and in 27% of patients receiving placebo. The most common reason for discon mg/kilogram. The mean SAS-CA scores improved from a baseline of 64.8 +/- 10.1 to 40.6 +/- 1.25 at we group. The ITT random regression analyses indicated a statistically significant improvement associated v adjusted for baseline SAS-CA score were 56% (95% confidence interval (CI), 47% to 64%) for patients r The effect of baseline SAS-CA score was not significant (p=0.172), whereas effect of treatment was (p=0 g=0.46) and number needed to treat (n=5; 95% CI, 3 to 13) indicate a moderately clinically meaningful b were more common than with placebo included asthenia (20% vs 9%; p=0.012), anorexia (22% vs 3%; p mild to moderate and most often resolved with continued therapy. Discontinuation of treatment due to ad respectively. There were 3 cases of suicidal ideation in patients receiving venlafaxine (two during treatm no suicides or suicide attempts reported during the study period (March et al, 2007).

4.5.A.21 Tension-type headache; Prophylaxis

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy

Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:
Treatment with venlafaxine extended-release resulted in less days with tension-type headache whe
et al, 2007).

c) Adult:
1) Results of a prospective, double-blind, randomized controlled trial demonstrated the efficacy and safe
(TTH) in outpatients (n=60) without a current diagnosis of depression or anxiety disorders or a history of
orally daily for 12 weeks. The dose of venlafaxine XR was 75 milligrams (mg) daily for 1 week and then
variable was the number of days with headache as assessed using patients' diaries. Diary completion ra
57.7% (15/25) for the group receiving placebo. The difference between venlafaxine XR and placebo in te
during period two (days 29 to 56) of the study and remained significant to study endpoint. The median da
and 11, respectively. The median days with headache for patients receiving venlafaxine XR and placebo
(p=0.033) during period three (days 57 to 84). The differences between treatment groups with regard to
significant at during any period. The median percentage change from baseline in headache frequency w
number of responders (defined as a reduction of at least 50% in days with headache, total hours, or HII s
15% for venlafaxine XR and placebo, respectively; p less than 0.05) but not for hours with headache or
(14.7%), nausea (8.8%), stomach ache (8.8%) and dizziness (8.8%) (Zissis et al, 2007).

4.6 Comparative Efficacy / Evaluation With Other Therapies

Bupropion

Buspirone

Clomipramine

Duloxetine

Fluoxetine

Imipramine

Medroxyprogesterone Acetate

Mirtazapine

Paroxetine

Pregabalin

Sertraline

Trazodone

4.6.A Bupropion

4.6.A.1 Bipolar disorder, depressed phase

a) There were no significant differences between bupropion, sertraline, and venlafaxine with regard to respo
switching into hypomania or mania was significantly higher with venlafaxine compared with bupropion and se
outpatients diagnosed with bipolar depression. All patients were receiving at least one mood stabilizer with in
bupropion 75 to 450 milligrams (mg)/day (n=51), sertraline 50 to 200 mg/day (n=58), or venlafaxine 37.5 to 3
Depression Symptomatology (IDS), the Young Mania Rating Scale (YMRS), and the Clinical Global Impressi
antidepressant response (defined as either a 50% or greater improvement in IDS score or a decrease of at le
IDS score less than 12 and/or a CGI-BP depression score of 1 at study endpoint), and antidepressant-relatec
score during any point of the trial or a CGI-BP manic severity score of 3 or more or a YMRS score above 13
were 49%, 53%, and 51%, respectively, while remission rates were 41%, 36%, and 34%, respectively. Differe
reported. Controlling for lithium use did not alter the results. Based on CGI-BP score, switching to mania or h
and sertraline (9%; p less than 0.01 overall). During post hoc analysis, it was demonstrated that the switch ef
venlafaxine and sertraline (p=0.01, adjusted for lithium) and bupropion (p less than 0.01, adjusted for lithium)

Based on YMRS score, switching occurred in 4%, 7%, and 15% of patients receiving bupropion, sertraline, a (31%) and bupropion (14%) and sertraline (16%) treatment groups remained significant when the combinatio for lithium; p=0.02 when controlled for lithium). Post hoc analysis results again showed that the difference wa history of rapid cycling was also higher with venlafaxine (43%) compared to bupropion (14%) and sertraline (for any reason were 31%, 41%, and 45% in the bupropion, sertraline and venlafaxine groups, respectively (P

4.6.B Buspirone

4.6.B.1 Generalized anxiety disorder

a) One small study suggests that venlafaxine could be an alternative to buspirone in patients with generalize of GAD received venlafaxine XR 75 milligrams (mg)/day (n=4), venlafaxine XR 150 mg/day (n=4), buspirone than 50% decline on the Hamilton Anxiety Scale. Improvement was seen in 2 venlafaxine 75 mg patients, 2 v size, no specific conclusions could be made (Rolland et al, 2000).

b) Venlafaxine XR was useful for treating generalized anxiety disorder (GAD); for many efficacy measures, i diagnosed by DSM-IV criteria were randomly assigned to blinded treatment with placebo, buspirone 30 millig treatment was titrated over 1 week. At study conclusion, the Hamilton Rating Scale for Anxiety (HAM-A) scor the HAM-A psychic anxiety, HAM-A anxious mood, and HAM-A tension scores were significantly lower for ve placebo and buspirone for selected weeks on the Clinical Global Impressions-Severity of Illness scale (CGI-S 10%, 22%, 28%, and 15% of patients treated with placebo, venlafaxine XR 75 mg, venlafaxine XR 150 mg, a

4.6.C Clomipramine

4.6.C.1 Depression

a) Venlafaxine 105 milligrams/day (average dose) tended to be more effective than clomipramine 105 milligr patients; however, the difference was not statistically significant (Holliday & Benfield, 1995b). Patients were a Rating Scale, and the Clinical Global Impressions scale. Venlafaxine was associated with fewer anticholinerg

4.6.D Duloxetine

4.6.D.1 Major depressive disorder

a) A meta-analysis of published, peer-reviewed, randomized, placebo-controlled, double-blind trials found th to placebo in remission and response rates for major depressive disorder and although there was a trend in f compared to duloxetine. A systematic literature search of Cochrane, EMBASE, and MEDLINE (1996 to Janua evaluate efficacy (n=1754) and discontinuation/safety (n=1791). Patients had a one week placebo lead-in per to 225 mg per day for a minimum of 8 weeks. The primary outcomes were remission and response rates. Re (HAM-D) score to less than or equal to 7 or to a Montgomery-Asberg Depression Rating Scale (MADRS) sco baseline in either the HAM-D or MADRS scores. The secondary outcomes evaluated were dropout rates and venlafaxine XR and were statistically significant compared to placebo (both p less than 0.001). No significant XR were compared. Patients receiving placebo had a higher dropout rate due to lack of efficacy compared to patients in the active drug treatment groups dropped out due to adverse effects compared to placebo (duloxe XR were compared, no statistically significant differences were found for dropout rates due to lack of efficacy A sensitivity analysis was also performed and included 2 additional studies, one study for venlafaxine XR dea with comorbid pain. Adding the 2 studies demonstrated similar results with both drugs having a statistically si

Outcome	Active Drug	Active Drug vs Placebo		
		Difference(a)	95% CI	p Value(b)
Remission	duloxetine	0.142	0.089 to 0.195	<0.001
	venlafaxine XR	0.178	0.09 to 0.265	<0.001
Response	duloxetine	0.186	0.13 to 0.242	<0.001
	venlafaxine XR	0.244	0.15 to 0.337	<0.001
Dropout rate due to ADRs	duloxetine	0.057	0.015 to 0.1	0.008
	venlafaxine XR	0.061	0.025 to 0.097	<0.001
Dropout rate due to lack of efficacy	duloxetine	-0.111 (c)	-0.159 to -0.63	<0.001
	venlafaxine XR	-0.107	-0.151 to -0.064	<0.001
ADRs = adverse drug reactions; XR = extended release; CI = confidence interval				
(a) The rate when meta-analytic rate of placebo is subtracted from the active drug rate.				
(b) Corresponding p value of the difference rate calculated with a Z-test.				
(c) Negative difference rates indicate a larger effect for placebo.				

4.6.E Fluoxetine

Depression

Mixed anxiety and depressive disorder

4.6.E.1 Depression

a) Analysis of pooled data from 8 randomized, double-blind studies (n=2045) showed a remission rate of dep (SSRIs), and 25% with placebo. Remission was defined as a total score of 7 or less on the 17-item Hamilton effective than SSRIs from 2 weeks onward and from placebo from 3 weeks onward. The end-of-therapy remi ratio for remission was 1.5, in favor of venlafaxine over SSRIs (Thase et al, 2001).

b) Venlafaxine and fluoxetine had similar efficacy in the treatment of major depression in an 8 week, double- 37.5 milligrams (mg) twice daily, and 186 patients were randomized to receive fluoxetine 20 mg daily. If patie 75 mg twice daily and fluoxetine to 20 mg twice daily. Primary outcome measures were scores on the Hamilt Scale (MADRS), the Clinical Global Impressions Severity of Illness Score (CGI-S), and the Clinical Global Im scores improved significantly after 8 weeks of therapy. CGI-I scores were also improved, 80.6% of patients s fluoxetine. Remission rates were equivalent in both groups, 60.2%, as determined by scores of 8 or less on t number of patients that required a dosage increase, fluoxetine (n=54) and venlafaxine (n=43). After treatmen greater in the venlafaxine group than the fluoxetine group. The frequency of adverse events associated with and tolerability between venlafaxine and fluoxetine (Cost e Silva, 1998).

c) Venlafaxine was effective in the treatment of major depression in an 8-week, open-label, comparative trial milligrams (mg) twice daily; 55 received fluoxetine 20 mg daily. If after 15 days of treatment response was ina daily. Both medications were significantly effective in treating major depression, as determined by improveme Asberg Depression Rating Scale (MADRS), and the Clinical Global Impressions Scale (CGI). There were no existed in patients requiring higher doses of venlafaxine than fluoxetine. Patients treated with venlafaxine we (Diaz-Martinez et al, 1998).

d) Venlafaxine 200 mg/day for 4 weeks tended to be more effective than fluoxetine 40 mg/day in the treatme significant by the end of the 6-week study period (Holliday & Benfield, 1995c). Patients were assessed using and the Clinical Global Impressions scale. The incidence of adverse effects was similar for both groups.

4.6.E.2 Mixed anxiety and depressive disorder

a) Extended release (XR) venlafaxine was more effective than placebo for improving the symptoms of depre anxiety disorder (GAD). However, time to response was greater in patients with comorbidity than in patients v better than placebo in patients with comorbidity. From the data of all the patients meeting DSM-IV criteria for subset of patients who had comorbid GAD (n=92) were analyzed separately and compared to results of the r (mg), fluoxetine 20 mg, or placebo for 12 weeks. Doses could be increased to a maximum of 225 mg for venl (from baseline) in the Hamilton-Depression (HAM-D) and Hamilton- Anxiety (HAM-A) scores, improvement w of treatment. There was a similar trend with fluoxetine, but at no time was fluoxetine statistically superior to pl however, overall, there was no evident trend for a placebo- drug difference until after the eighth week of treat as early as week 2. By week 12, response rate was 66% on HAM-D and 59% on HAM-A for those taking ven placebo (Silverstone & Salinas, 2001).

4.6.E.3 Adverse Effects

a) During a randomized, double-blind trial of elderly patients with major depression, the rate of study disconti venlafaxine (27%) compared with patients receiving placebo (9%; p=0.0017) but there were no significant diff (p=0.0666) or when fluoxetine was compared to venlafaxine (p=0.1838). Elderly patients (mean age, 71 year fluoxetine (n=100), or placebo (n=96) for 8 weeks. The dose of venlafaxine was titrated from 37.5 to 225 milli 29-day period. The most frequently reported adverse events in the venlafaxine and fluoxetine groups were na adverse events most frequently reported in the placebo group were headache (22%) and dry mouth (15%) (S

4.6.F Imipramine

4.6.F.1 Depression

a) Venlafaxine and imipramine resulted in similar improvement in depression with melancholia in hospitalize on 1 test (Benkert et al, 1996). Over 5 days, the dose of venlafaxine was rapidly increased from 75 to 375 mi mg/day. The dose of imipramine was increased from 50 to 200 mg/day over 5 days and was continued at this Montgomery-Asberg Depression Rating Scale (MADRS), but for the 21-item Hamilton Rating Scale for Depre (p=0.036). Adverse effects were reported in 69% and 76% of patients treated with venlafaxine and imipramin for imipramine (p less than 0.05) and nausea for venlafaxine (p=0.011). While this study enrolled 167 patients Additional studies are needed to provide conclusive evidence for a more rapid onset of effect with venlafaxine

b) Venlafaxine was found to have antidepressant efficacy comparable to imipramine in outpatients with mod double-blind placebo controlled study in 224 outpatients with depression of moderate to marked severity. Bas Rating Scale for Depression (HAM-D), the Montgomery-Asberg Depression Rating Scale (MADRS), the Clini daily dose of venlafaxine was 182 mg +/- 48 milligrams and the mean maximal total daily dose of imipramine times a day schedule after meals. Venlafaxine showed a significant clinical advantage over imipramine at the to the higher attrition rate for imipramine as compared to venlafaxine. Attrition rates due to adverse effects we mouth, and dizziness were the most prominently reported adverse effects for venlafazine (Schweizer et al, 19

4.6.G Medroxyprogesterone Acetate

4.6.G.1 Hot sweats

a) Single dose medroxyprogesterone acetate (MPA) significantly reduces hot flashes compared to venlafaxi old versus those older than 50), current tamoxifen and raloxifene use, duration of hot flash symptoms (less th flashes per day (two to three versus four to nine or more). Patients were then randomized to receive either ve

MPA 400 mg intramuscularly (IM) for one dose or MPA 500 mg IM at 2 week intervals for three total doses. T
this arm due to unexpectedly slow accrual rate. The completed study analysis refers mainly to the two major
and severity at 1 week of baseline and throughout the 6 week treatment period. After 6 weeks, if patients wer
randomized to MPA). Nurses contacted patients monthly for the next 5 months and then every other month fo
about the average number of mild, moderate, or severe hot flashes they were experiencing per day. At the er
baseline with MPA compared with 53% (n=94) in the venlafaxine group (p<0.0001). No hot flashes were repo
treatment week (p=<0.0001). During the first treatment week, venlafaxine group had significantly more nause
dryness (p=.01) and sleepiness (p=.02) in comparison to the MPA group. As measured by patient diaries and
symptom differences between the two study groups include constipation, hot flash distress and abnormal swe

4.6.H Mirtazapine

4.6.H.1 Major depression, melancholic type

a) Mirtazapine and venlafaxine both were effective in alleviating symptoms of depression in hospitalized pati
be superior with respect to both efficacy and dropout rate due to adverse reactions. In a randomized, double-
(mg)/day and increasing rapidly to as high as 60 mg/day, or venlafaxine, starting at 75 mg/day and increasing
Depression Rating Scale (MADRS) and the Hamilton Rating Scale for Depression (HAM-D-17) improved for b
mirtazapine, although differences were not statistically significant. Sleep disturbances improved more with mi
treated patients (74.4%) than venlafaxine-treated patients (65.8%) reported at least one adverse reaction. Ho
because of adverse events (15.3% vs 5.1%, p=0.037). The most common adverse events in the mirtazapine
sleepiness (7.7%), and nausea (6.4%). In the venlafaxine group, most common were increased sweating (19
(6.3%), and decreased salivation (6.3%) (Guelfi et al, 2001).

4.6.I Paroxetine

Bipolar disorder, depressed phase

Obsessive-compulsive disorder

4.6.I.1 Bipolar disorder, depressed phase

a) Paroxetine and venlafaxine had similar efficacy in the treatment of depression in bipolar patients taking co
week study demonstrated that paroxetine and venlafaxine produced responses in 43% and 48% of the patien
improvement in the Hamilton Rating Scale for Depression (HAM-D) and the Clinical Global Impressions (CGI
and -9.0 for the venlafaxine group. These responses were significantly different compared to baseline, but no
the HAM-D, the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fourth
All patients were being treated with 1 or more mood stabilizers for at least 6 months prior to onset of the curre
medication for at least 3 months prior to the start of the study. During the study, doses were adjusted for effic
which could be increased in increments of 75 mg per day (mg/d) every week. The starting dose of paroxetine
doses of venlafaxine and paroxetine were 179 mg/d and 32 mg/d, respectively. There were no significant diff
common adverse events were nausea (20% of all patients), and dizziness (8.3% of all patients). One patient
(13%) in the venlafaxine group switched to either hypomania (2 patients) or full mania (2 patients). Limitations
placebo group, a single-blind study design, and a short follow up period (Vieta et al, 2002).

4.6.I.2 Obsessive-compulsive disorder

a) Venlafaxine extended-release (XR) was as effective as paroxetine in the treatment of patients with obsess
patients (n=150) with OCD and a score of at least 18 (or at least 12, if only obsessions or only compulsions w
venlafaxine XR (initial, 75 milligrams (mg)/day, titrated to 300 mg/day by week 7) or paroxetine (initial, 15 mill
venlafaxine XR treatments were effective, producing mean reductions of 7.8 and 7.2 points, respectively, in th
score from baseline was seen at week 3 for venlafaxine XR- treated patients (p=0.008) and at week 5 for pat
rates between treatment groups. In the venlafaxine XR group, 37% and 25% of patients were partial respond
patients were partial responders and full responders, respectively. Additionally, no significant differences wer
symptoms (as measured by the Hamilton Anxiety Scale and the Hamilton Rating Scale for Depression, respe
included somnolence, sweating, insomnia, and nausea (Denys et al, 2003).

4.6.J Pregabalin

4.6.J.1 Generalized anxiety disorder

a) In a multicenter, randomized, double-blind, placebo-controlled, parallel-group study (n=374), treatment wit
compared with placebo in patients with generalized anxiety disorder (GAD). Patients who were 18 to 65 years
A) score of 20 or greater (with a HAM-A psychic and somatic anxiety factors score of 10 or greater) were elig
randomized to receive 8 weeks of oral pregabalin (150 milligrams (mg) twice daily for the first week then titrat
mg/day for the first week than titrated to a dose range of 75 to 225 mg/day administered in the morning with n
pregabalin arm but not the venlafaxine-XR arm had a significant improvement in least squares (LS) mean cha
treatment with pregabalin significantly improved some secondary investigator-rated efficacy measures includi
scale, and the Hamilton Depression Rating Scale (HAM-D) compared to placebo while treatment with venlafa

significantly improved LS mean change HAM-A total scores compared with venlafaxine-XR (p=0.008) or plac
patients (9.1%) compared with venlafaxine-XR-treated patients (20%) (Kasper et al, 2009).

Table 1			
	Pregabalin (n=121)		Venlafaxine
	LS mean +/- SE	p-value	LS mean +/- SE
HAM-A total score (primary endpoint)			
Baseline	27.6 +/- 0.4	0.028	27.4 +/- 0.4
Endpoint change	-14.5 +/- 0.9		-12 +/- 0.9
HAM-A psychic anxiety factor score			
Baseline	14.4 +/- 0.3	0.017	14 +/- 0.3
Endpoint change	-7.3 +/- 05		-5.9 +/- 0.5
HAM-A somatic anxiety factor score			
Baseline	13.3 +/- 0.3	0.11	13.4 +/- 0.3
Endpoint change	-7.3 +/- 0.4		-6.1 +/- 0.5
CGI severity score			
Baseline	4.7 +/- 0.1	0.14	4.6 +/- 0.1
Endpoint change	-2 +/- 0.2		-1.7 +/- 0.2
CGI improvement score			
Endpoint change	2.3 +/- 0.1	0.05	2.5 +/- 0.1
HAM-D score			
Baseline	11.5 +/- 0.2	0.018	11.5 +/- 0.2
Endpoint change	-4.4 +/- 0.5		-3.6 +/- 0.5
LS mean, least squares mean change; SE, standard error; HAM-A, Hamilton Anxiety Rating Scale; CGI Hamilton Depression Rating Scale			

b) Treatment with oral pregabalin at daily doses of 400 or 600 milligrams (mg) per day was comparable to ve
anxiety symptoms in adults with moderate to severe generalized anxiety disorder (GAD) in a randomized, do
years) meeting the DSM-IV criteria for primary GAD and who had total scores of 20 or greater on the Hamilto
Anxiety Scale, and 7 or lower on the Raskin Depression Scale were included. Patients were randomized to re
75 mg/day (n=113), or placebo (n=101) orally (given in divided doses twice daily) for 6 weeks, followed by a
600 mg/day groups, respectively) and titrated up to target doses over 1 week. Based on the modified intentio
the change in mean HAM-A total scores at endpoint from baseline (primary endpoint) was -14.7 +/- 0.8, -14.1
(n=104), and venlafaxine (n=110) arms, respectively, compared with -11.6 +/- 0.8 in the placebo (n=100) arm
A total scores occurred in both pregabalin arms compared with placebo during week 1 of treatment but not in
patients in the pregabalin 400 mg/day (61%; p=0.02) and venlafaxine 75 mg/day (62%; p=0.01) arms respon
difference in response in the pregabalin 600 mg/day (58%; p=0.06) was not significant. Among other seconda
placebo in HAM-A subscale scores of anxiety, tension, and insomnia, except a statistical insignificance on th
much improved or very much improved on the Clinical Global Impression-Improvement (CGI-I) scale was hig
venlafaxine (60.9%) arms compared with placebo (42%; all p less than or equal to 0.04). Treatment was well
commonly reported adverse events in the pregabalin arms and nausea, dizziness, and asthenia being the mo
were lower in the pregabalin 400 mg/day group (6.2%) compared with venlafaxine (20.4%; p less than 0.01) a

4.6.K Sertraline

Bipolar disorder, depressed phase

Depression

Depression, Elderly

4.6.K.1 Bipolar disorder, depressed phase

a) There were no significant differences between bupropion, sertraline, and venlafaxine with regard to respo switching into hypomania or mania was significantly higher with venlafaxine compared with bupropion and se outpatients diagnosed with bipolar depression. All patients were receiving at least one mood stabilizer with in bupropion 75 to 450 milligrams (mg)/day (n=51), sertraline 50 to 200 mg/day (n=58), or venlafaxine 37.5 to 3 Depression Symptomatology (IDS), the Young Mania Rating Scale (YMRS), and the Clinical Global Impressi antidepressant response (defined as either a 50% or greater improvement in IDS score or a decrease of at le IDS score less than 12 and/or a CGI-BP depression score of 1 at study endpoint), and antidepressant-relatec score during any point of the trial or a CGI-BP manic severity score of 3 or more or a YMRS score above 13 were 49%, 53%, and 51%, respectively, while remission rates were 41%, 36%, and 34%, respectively. Differe reported. Controlling for lithium use did not alter the results. Based on CGI-BP score, switching to mania or h and sertraline (9%; p less than 0.01 overall). During post hoc analysis, it was demonstrated that the switch ef venlafaxine and sertraline (p=0.01, adjusted for lithium) and bupropion (p less than 0.01, adjusted for lithium) Based on YMRS score, switching occurred in 4%, 7%, and 15% of patients receiving bupropion, sertraline, a (31%) and bupropion (14%) and sertraline (16%) treatment groups remained significant when the combinatio for lithium; p=0.02 when controlled for lithium). Post hoc analysis results again showed that the difference wa history of rapid cycling was also higher with venlafaxine (43%) compared to bupropion (14%) and sertraline (for any reason were 31%, 41%, and 45% in the bupropion, sertraline and venlafaxine groups, respectively (P

4.6.K.2 Depression

a) An 8-week, randomized, double-blind, active-control study of outpatient adults with major depressive diso not significantly different than that of venlafaxine XR (n=76). Patients were randomized to receive capsules c to 3 capsules/day. Primary outcome measure was the change in Quality of Life Enjoyment and Satisfaction C endpoint (8-weeks). Secondary outcome measures were the changes from baseline to endpoint in the scores Impressions - Severity of Illness scale (CGI-S), the Clinical Global Impressions - Improvement scale (CGI-I), 1 (very much improved) or 2 (much improved) on the CGI-I scale, or a reduction of HAM-D-17 score by at lea less. There were no significant differences between study groups with any outcome measures, including rem most common reported adverse effects during active treatment (10% or greater occurrence) were diarrhea, h scores, response rates, and remission rates for the outcome measures (Shelton et al, 2006):

	Endpoint Scores, Response Rates and Remiss
Measure/Sample	Sertraline (n=82)
Q-LES-Q score, mean (SD)	0.69 (0.12)
HAM-D-17 score, mean (SD)	10.8 (6.4)
HAM-D-17 response rate, (N/N)	55%(45/82)
HAM-D-17 remission rate, (N/N)	38% (31/82)
CGI-S score, mean (SD)	2.6 (1.1)
CGI-I score, mean (SD)	2.3 (1.1)
HAM-A score, mean (SD)	9.1 (5.4)
CGI-I = Clinical Global Impressions-Improvement scale; CGI-S = Clinical Global Impressions-Severity of Rating Scale for Depression; Q-LES-Q = Quality of Life Enjoyment and Satisfaction Questionnaire; XR =	

b) In patients with major depressive disorder, almost twice as many experienced a remission with venlafaxin depressive disorder randomly received venlafaxine 37.5 mg twice daily (n=75) or sertraline 50 mg daily (n=72 or the sertraline increased to 50 mg twice daily on day 15. After 8 weeks, patients in both groups showed sig Montgomery- Asberg Depression Rating Scale (p less than 0.05). In the venlafaxine group 83% were respon the venlafaxine group and in 45% of the sertraline group (p=0.008). The most common adverse events were with sertraline (Mehtonen et al, 2000).

4.6.K.3 Depression, Elderly

a) Treatment with venlafaxine had a lower tolerability, but was equally effective to sertraline therapy in elderl study, fifty-two elderly patients (mean age, 82.5 years) with depression received either sertraline (initial, 25 m mg/day, titrated to 150 mg/day) for 10 weeks. No significant differences were found in Hamilton Rating Scale groups. However, early termination and withdrawal rates due to serious adverse events were higher in venlaf tract infection, cerebrovascular accident, hypertension, decreased renal function, rapid atrial fibrillation, anem were observed in both treatment groups. From baseline to endpoint, heart rate increased in the venlafaxine g bpm to 70.9 bpm, respectively). The authors suggest that the lowered tolerability of venlafaxine may be relate

4.6.L Trazodone

4.6.L.1 Depression

a) Venlafaxine produced antidepressant efficacy comparable to trazodone in a double-blind, placebo controll milligrams (mg) per day, trazodone (mean = 300 mg/day) or placebo. Response rates were 72%, 60% and 5 cognitive disturbance and retardation factor as evidenced on the Hamilton Rating Scale for Depression (HAM Nausea was more common in the venlafaxine group compared to dizziness and somnolence in the trazodone

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242. Product Information: Comtan(R), entacapone. Novartis Pharmaceuticals Australia Pty Limited, North Ryde, New So
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244. Product Information: EFFEXOR XR(R) extended-release oral capsules, venlafaxine hydrochloride extended-releas
245. Product Information: EFFEXOR XR(R) extended-release oral capsules, venlafaxine hydrochloride extended-releas
246. Product Information: EFFEXOR(R) XR oral extended-release capsule, venlafaxine hydrochloride oral extended-rele
247. Product Information: EFFEXOR(R) XR oral extended-release capsules, venlafaxine hcl oral extended-release caps
248. Product Information: EFFEXOR(R) XR oral extended-release capsules, venlafaxine hcl oral extended-release caps
249. Product Information: EFFEXOR(R) oral tablets, venlafaxine hcl oral tablets. Wyeth Pharmaceuticals Inc, Philadelph

250. Product Information: EFFEXOR(R) oral tablets, venlafaxine hcl oral tablets. Wyeth Pharmaceuticals,Inc, Philadelph
251. Product Information: EMSAM(R) transdermal patch, selegiline transdermal patch. Bristol-Myers Squibb Company, I
252. Product Information: Effexor XR(R) extended-release oral capsules, venlafaxine hydrochloride extended-release or
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267. Product Information: Effexor(R) XR, venlafaxine. Wyeth-Ayerst Laboratories, Philadelphia, PA, 2000b.
268. Product Information: Effexor(R) XR, venlafaxine. Wyeth-Ayerst Laboratories, Philadelphia, PA, 2000c.
269. Product Information: Effexor(R) XR, venlafaxine. Wyeth-Ayerst Laboratories, Philadelphia, PA, 2000d.
270. Product Information: Effexor(R) XR, venlafaxine. Wyeth-Ayerst Laboratories, Philadelphia, PA, 2000e.
271. Product Information: Effexor(R) XR, venlafaxine. Wyeth-Ayerst Laboratories, Philadelphia, PA, 2000f.
272. Product Information: Effexor(R) XR, venlafaxine. Wyeth-Ayerst Laboratories, Philadelphia, PA, 2000g.
273. Product Information: Effexor(R) oral tablets, venlafaxine hydrochloride oral tablets. Wyeth Pharmaceuticals Inc., Ph
274. Product Information: Effexor. Wyeth-Ayerst, Canada, 94.
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281. Product Information: IMITREX(R) oral tablets, sumatriptan succinate oral tablets. GlaxoSmithKline, Research Trian
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283. Product Information: Lexapro(R) oral tablets, solution, escitalopram oxalate oral tablets, solution. Forest Pharmace
284. Product Information: MERIDIA(R) oral capsules, sibutramine hcl monohydrate oral capsules. Abbott Laboratories, N
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289. Product Information: Meridia(R), sibutramine hydrochloride monohydrate. Knoll Pharmaceutical Company, Mount C
290. Product Information: PAXIL CR(R) controlled release oral tablets, paroxetine hcl controlled release oral tablets. Gla
291. Product Information: PAXIL(R) tablets and oral suspension, paroxetine hydrochloride tablets and oral suspension. G
292. Product Information: PRISTIQ(TM) oral extended-release tablets, desvenlafaxine oral extended-release tablets. Wy
293. Product Information: PROZAC(R) delayed-release capsules, oral capsules, solution, fluoxetine delayed-release cap
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295. Product Information: Prozac(R), fluoxetine. Eli Lilly and Company, Indianapolis, IN, 2001.
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299. Product Information: Serentil(R), mesoridazine. Novartis Pharmaceuticals Corporation, East Hanover, NJ, 2000.
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301. Product Information: ULTRAM(R) ER oral extended-release tablets, tramadol HCl oral extended-release tablets. Pr
302. Product Information: ZOLOFT(R) concentrate, oral tablets, sertraline hcl concentrate, oral tablets. Roerig, Division
303. Product Information: ZYVOX(R) IV injection, oral tablets, oral suspension, linezolid IV injection, oral tablets, oral su
304. Product Information: fluvoxamine maleate oral tablets, fluvoxamine maleate oral tablets. Jazz Pharmaceuticals Inc,
305. Product Information: tapentadol immediate release oral tablets, tapentadol immediate release oral tablets. Ortho-M
306. Product Information: venlafaxine extended release oral tablets, venlafaxine extended release oral tablets. Upstate I
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Last Modified: June 08, 2009

DRUGDEX® Evaluations

DEXMETHYLPHENIDATE

0.0 Overview

1) Class
- **a)** This drug is a member of the following class(es):
  - Amphetamine Related
  - CNS Stimulant

2) Dosing Information
- **a)** Dexmethylphenidate Hydrochloride
  - **1)** Adult
    - **a)** Attention deficit hyperactivity disorder
      - **1)** extended-release: methylphenidate-naive patients, initial 10 mg ORALLY daily in the morning; adjust dose weekly in 10 mg increments; MAX 20 mg/day
      - **2)** extended-release: patients currently using methylphenidate, one-half the total daily dose of racemic methylphenidate; patients currently using dexmethylphenidate immediate-release may be switched to the same daily dose of dexmethylphenidate extended-release; MAX 20 mg/day
  - **2)** Pediatric
    - **a)** safety and efficacy not established in patients under 6 years of age
      - **1)** Attention deficit hyperactivity disorder
        - **a)** immediate-release (ages 6 years and older): methylphenidate-naive patients, initial 2.5 mg ORALLY twice daily; adjust dose weekly in 2.5 to 5 mg increments; MAX 20 mg/day (10 mg twice a day)
        - **b)** immediate-release (ages 6 years and older): patients currently using methylphenidate, one-half the dose of racemic methylphenidate; MAX 20 mg/day (10 mg twice a day)
        - **c)** extended-release (ages 6 years and older): methylphenidate-naive patients, initial 5 mg ORALLY in the morning; adjust dose weekly in 5 mg increments; MAX 20 mg/day(Prod Info FOCALIN XR(R) extended-release oral capsules, 2008)
        - **d)** extended-release (ages 6 years and older): patients currently using methylphenidate, one-half the total daily dose of racemic methylphenidate; patients currently using immediate release dexmethylphenidate may be switched to the same daily dose of dexmethylphenidate extended release (Prod Info FOCALIN XR(R) extended-release oral capsules, 2008)

3) Contraindications
- **a)** Dexmethylphenidate Hydrochloride
  - **1)** agitation, severe; anxiety; or tension; may aggravate symptoms (Prod Info FOCALIN(TM) XR extended-release oral capsules, 2006)
  - **2)** glaucoma (Prod Info FOCALIN(TM) XR extended-release oral capsules, 2006)
  - **3)** hypersensitivity to methylphenidate or other components of the product (Prod Info FOCALIN(TM) XR extended-release oral capsules, 2006)
  - **4)** MAOI use within 14 days; hypertensive crisis may result (Prod Info FOCALIN(TM) XR extended-release oral capsules, 2006)
  - **5)** motor tics (Prod Info FOCALIN(TM) XR extended-release oral capsules, 2006)
  - **6)** Tourette's syndrome, family history or diagnosis of (Prod Info FOCALIN(TM) XR extended-release oral capsules, 2006)

4) Serious Adverse Effects
- **a)** Dexmethylphenidate Hydrochloride
  - **1)** Mania
  - **2)** Psychotic disorder
  - **3)** Seizure

5) Clinical Applications
- **a)** Dexmethylphenidate Hydrochloride
  - **1)** FDA Approved Indications
    - **a)** Attention deficit hyperactivity disorder

1.0 Dosing Information

Drug Properties

Storage and Stability

Adult Dosage

Pediatric Dosage

1.1 Drug Properties

A) Information on specific products and dosage forms can be obtained by referring to the Tradename List (Product Index)

B) Synonyms

Dexmethylphenidate
Dexmethylphenidate HCl
Dexmethylphenidate Hydrochloride

C) Physicochemical Properties

1) Molecular Weight

a) 269.77(Prod Info Focalin™, 2001a)

2) Solubility

a) Systemic: Freely soluble in water and in methanol; soluble in alcohol; slightly soluble in chloroform and in acetone (Prod Info Focalin™, 2001a)

1.2 Storage and Stability

A) Oral route

1) The US manufacturer recommends storage of dexmethylphenidate tablets and capsules at 25 degrees C (77 degrees F), with excursions permitted to 15 to 30 degrees C (59 to 86 degrees F). Tablets should be protected from moisture (Prod Info FOCALIN(TM) XR, 2005; Prod Info Focalin(TM), 2001d).

1.3 Adult Dosage

Normal Dosage

Dosage in Renal Failure

Dosage in Hepatic Insufficiency

1.3.1 Normal Dosage

1.3.1.A Dexmethylphenidate Hydrochloride

1.3.1.A.1 Oral route

1.3.1.A.1.a Attention deficit hyperactivity disorder

1) Extended-Release

a) The recommended starting dose for patients not currently taking dexmethylphenidate or racemic methylphenidate, or for patients who are on stimulants other than methylphenidate, is 10 milligrams (mg)/day in the morning. The dose may be adjusted weekly in 10 mg increments to a maximum of 20 mg/day for adult patients. The patient should be observed for a sufficient duration at a given dose to ensure that a maximal benefit has been achieved before a dose increase is considered (Prod Info FOCALIN(TM) XR, 2005).

b) For patients currently using methylphenidate, the recommended starting dose is half the total daily dose of racemic methylphenidate. Patients using immediate-release dexmethylphenidate may be switched to the same daily dose of extended-release dexmethylphenidate. Maximum recommended dose is 20 milligrams/day (Prod Info FOCALIN (TM) XR, 2005).

c) The treatment duration is unclear, however, it is generally agreed that pharmacological treatment of ADHD may be needed for extended periods. The patient should be periodically reevaluated with periods off medication to assess patient's functioning without pharmacotherapy (Prod Info FOCALIN(TM) XR, 2005).

d) If paradoxical aggravation of symptoms or other adverse events occur, the dosage should be reduced or, if necessary, the drug should be discontinued (Prod Info FOCALIN(TM) XR, 2005).

e) If improvement is not observed after appropriate dosage adjustment over a 1-month period, the drug should be discontinued (Prod Info FOCALIN(TM) XR, 2005).

1.3.2 Dosage in Renal Failure

A) Dexmethylphenidate Hydrochloride

1) Pharmacokinetic data for dexmethylphenidate in renal impairment are unavailable. However, data for racemic methylphenidate indicate that only small amounts are excreted unchanged in the urine (about 1%)

(USPDI, 2001; Prod Info Focalin(TM), 2001); thus, dose adjustments of dexmethylphenidate do not appear to be necessary in this population.

1.3.3 Dosage in Hepatic Insufficiency

A) Dexmethylphenidate Hydrochloride

1) Similar to methylphenidate, dexmethylphenidate undergoes hepatic metabolism (USPDI, 2001); (Prod Info Focalin(TM), 2001). Dose adjustment should be considered in patients with moderate or greater hepatic dysfunction. Specific guidelines for dexmethylphenidate or the racemic compound are unavailable.

1.4 Pediatric Dosage

Normal Dosage

Dosage in Renal Failure

Dosage in Hepatic Insufficiency

1.4.1 Normal Dosage

1.4.1.A Dexmethylphenidate Hydrochloride

1.4.1.A.1 Oral route

1.4.1.A.1.a Attention deficit hyperactivity disorder

1) Immediate-Release

a) The efficacy of dexmethylphenidate has been demonstrated only in patients 6 to 17 years of age. The drug should be given twice daily, at least 4 hours apart; it can be given with or without food (Prod Info Focalin(TM), 2001).

b) In patients not currently receiving racemic methylphenidate, or for those who are on stimulants other than methylphenidate, the manufacturer recommends an initial dose of 2.5 milligrams (mg) twice daily, with dose adjustments in 2.5- to 5-mg increments to a maximum of 10 mg twice daily; dose adjustments may be undertaken at approximately weekly intervals (Prod Info Focalin(TM), 2001). An extended-release methylphenidate formulation (duration, 8 hours) may be preferable, as administration of doses during school can be eliminated; generic formulations are available.

c) For patients who are currently receiving racemic methylphenidate, the initial dose recommended by manufacturer is half the dose of methylphenidate, with a maximum daily dose of 20 mg (10 mg twice daily) (Prod Info Focalin(TM), 2001). However, available data suggest no clinical advantage in switching to the d-enantiomer.

d) The longest duration of effective treatment in clinical studies with dexmethylphenidate has been 6 weeks (Prod Info Focalin(TM), 2001). However, prolonged use may be indicated. Racemic methylphenidate has maintained improvement for up to 2 years.

2) Extended-Release

a) The recommended starting dose for patients not currently taking dexmethylphenidate or racemic methylphenidate, or for patients who are on stimulants other than methylphenidate, is 5 milligrams (mg)/day in the morning. The dose may be adjusted weekly in 5 mg increments to a maximum of 20 mg/day for pediatric patients. The patient should be observed for a sufficient duration at a given dose to ensure that a maximal benefit has been achieved before a dose increase is considered (Prod Info FOCALIN XR(R) extended-release oral capsules, 2008).

b) For patients currently using methylphenidate, the recommended starting dose is half the total daily dose of racemic methylphenidate. Patients using immediate-release dexmethylphenidate may be switched to the same daily dose of extended-release dexmethylphenidate. Maximum recommended dose is 20 milligrams/day (Prod Info FOCALIN XR(R) extended-release oral capsules, 2008).

c) The treatment duration is unclear, however, it is generally agreed that pharmacological treatment of ADHD may be needed for extended periods. The patient should be periodically reevaluated with periods off medication to assess patient's functioning without pharmacotherapy (Prod Info FOCALIN XR(R) extended-release oral capsules, 2008).

d) If paradoxical aggravation of symptoms or other adverse events occur, the dosage should be reduced or, if necessary, the drug should be discontinued (Prod Info FOCALIN XR(R) extended-release oral capsules, 2008).

e) If improvement is not observed after appropriate dosage adjustment over a 1-month period, the drug should be discontinued (Prod Info FOCALIN XR(R) extended-release oral capsules, 2008).

1.4.2 Dosage in Renal Failure

A) Dexmethylphenidate Hydrochloride

1) Pharmacokinetic data for dexmethylphenidate in renal impairment are unavailable. However, data for racemic methylphenidate indicate that only small amounts are excreted unchanged in the urine (about 1%) (USPDI, 2001; Prod Info Focalin(TM), 2001). Thus, dose adjustments of dexmethylphenidate do not appear necessary in this population.

1.4.3 Dosage in Hepatic Insufficiency

A) Dexmethylphenidate Hydrochloride

1) Similar to methylphenidate, dexmethylphenidate undergoes hepatic metabolism (USPDI, 2001; Prod Info Focalin(TM), 2001). Dose adjustment should be considered in patients with moderate or greater hepatic dysfunction. Specific guidelines for dexmethylphenidate or the racemic compound are unavailable.

2.0 Pharmacokinetics

Onset and Duration

Drug Concentration Levels

ADME

2.1 Onset and Duration

A) Onset

1) Dexmethylphenidate Hydrochloride

a) Initial Response

1) Attention-deficit hyperactivity disorder, oral extended-release tablets: 1 hour (Prod Info FOCALIN (TM) XR, 2005)

a) Value represents time to a significant treatment effect in pediatric patients after a single dose of 20 milligrams (Prod Info FOCALIN(TM) XR, 2005).

2) Attention-deficit hyperactivity disorder, oral immediate-release tablets: within 4 weeks (sustained improvement) (Anon, 2001).

a) Value represents time to significant symptom improvement during continuous twice-daily administration.

B) Duration

1) Dexmethylphenidate Hydrochloride

a) Multiple Dose

1) Attention deficit hyperactivity disorder, ORAL: up to 6.5 hours (acute effects) (Anon, 1999).

2) Attention deficit hyperactivity disorder, Oral: 12 hours in pediatric patients 6 to12 years old (Prod Info FOCALIN(TM) XR, 2005)

a) Represents interpretation of data from one unpublished study, which suggested a longer duration of action of dexmethylphenidate than racemic methylphenidate in ADHD (Anon, 1999). In this study, control of symptoms with dexmethylphenidate was seen at all time points, but there was failure of methylphenidate to control symptoms at the last measurements (5.5 to 6.5 hours postdose). However, specific time points evaluated in the study, the duration of action of methylphenidate, and statistical comparisons at these time points are not available; thus, the difference in duration between these agents in this study is unknown. In other studies, racemic methylphenidate has shown a duration of 4 to 6 hours, and the difference in durations between these agents must be small, and may not be clinically relevant. Extended-release methylphenidate is often used in ADHD, which has a longer duration than that reported for dexmethylphenidate (8 hours).

2.2 Drug Concentration Levels

A) Dexmethylphenidate Hydrochloride

1) Therapeutic Drug Concentration

a) Not established; plasma-level monitoring is not used clinically.

2) Time to Peak Concentration

a) Oral, immediate-release tablet: 1 to 1.5 hours (Prod Info Focalin™, 2001a).

1) This value is similar to that reported for racemic methylphenidate (about 2 hours).

2) Following oral doses of 2.5, 5, and 10 mg in children (as a capsule formulation), peak plasma levels and AUCs of dexmethylphenidate were proportional to the dose; plasma levels were similar to those observed after oral racemic methylphenidate 5, 10, and 20 mg (Prod Info Focalin™, 2001a).

3) No significant accumulation of dexmethylphenidate has been observed with repeated twice-daily doses compared to single doses in ADHD patients (Prod Info Focalin™, 2001a).

b) Oral, extended-release tablet: 1.5 hours (first peak) and 6.5 hours (second peak) (Prod Info FOCALIN (TM) XR, 2005).

1) The mean time to the first peak (tmax1) (1.5 hours) is similar to the tmax for the immediate-release formulation. The time to the second peak (tmax2) (6.5 hours) is slightly longer for the extended-release formulation given once-daily compared to the immediate-release formulation given in 2 doses 4 hours apart (Prod Info FOCALIN(TM) XR, 2005).

3) Area Under the Curve

a) The AUC after administration of dexmethylphenidate hydrochloride extended-release tablets given once daily is equivalent to the same total dose of dexmethylphenidate hydrochloride immediate-release tablets given in 2 doses 4 hours apart; variability in AUC is similar between the extended- and immediate-release tablets with approximately a three-fold range in each (Prod Info FOCALIN(TM) XR, 2005).

2.3 ADME

Absorption

Distribution

Metabolism

Excretion

Elimination Half-life

2.3.1 Absorption

A) Dexmethylphenidate Hydrochloride

1) Bioavailability

a) Oral, various: mean absolute bioavailability 22 to 25% (Prod Info FOCALIN(TM) XR, 2005).

1) Dexmethylphenidate is well absorbed after oral administration with approximately 90% recovered in the urine. However, due to first-pass metabolism, the mean absolute bioavailability when administered in various formulations was 22 to 25% (Prod Info FOCALIN(TM) XR, 2005).

2) Effects of Food

a) immediate-release tablet, delayed absorption (Prod Info Focalin™, 2001a).

1) In an unpublished study, administration of dexmethylphenidate with food had no significant effect on extent of absorption compared to the fasting state (based on peak plasma levels and AUC values); however, time to peak plasma levels was prolonged when given with food (mean, 2.9 versus 1.5 hours) (Prod Info Focalin™, 2001a). Dexmethylphenidate can be given with or without food.

b) extended-release tablet, unknown (Prod Info FOCALIN(TM) XR, 2005)

1) No food effect study was performed with the extended-release formulation; administration times relative to meals and meal composition may need to be individually titrated (Prod Info FOCALIN (TM) XR, 2005).

2) Effect of food: oral, racemic methylphenidate extended release tablets, following high fat breakfast, delayed absorption and second peak concentration is approximately 25% lower. Can be administered with or without food (Prod Info FOCALIN(TM) XR, 2005).

2.3.2 Distribution

A) Distribution Sites

1) Dexmethylphenidate Hydrochloride

a) Protein Binding

1) A specific value for dexmethylphenidate is unavailable. However, protein binding of racemic methylphenidate is minimal (12 to 15%) .(Prod Info FOCALIN(TM) XR, 2005)

B) Distribution Kinetics

1) Dexmethylphenidate Hydrochloride

a) Volume of Distribution

1) 2.65 L/kg (+/- 1.1 L/kg) (Prod Info FOCALIN(TM) XR, 2005).

2.3.3 Metabolism

A) Metabolism Sites and Kinetics

1) Dexmethylphenidate Hydrochloride

a) LIVER, extensive (Prod Info Focalin™, 2001a).

1) The primary metabolic pathway is deesterification to the inactive metabolite d-ritalinic acid (d-alpha-phenyl piperidine acetic acid) (Prod Info Focalin™, 2001a).

2) Inhibition of cytochrome P450 isozymes was not observed with dexmethylphenidate in vitro (Prod Info Focalin™, 2001a).

3) Bioconversion to l-dexmethylphenidate is negligible (Prod Info Focalin™, 2001a) and of no

clinical consequence.

B) Metabolites

1) Dexmethylphenidate Hydrochloride

a) d-Ritalinic acid (inactive) (Prod Info Focalin™, 2001a).

2.3.4 Excretion

A) Kidney

1) Dexmethylphenidate Hydrochloride

a) Renal Clearance (rate)

1) Intravenous dexmethylphenidate was eliminated with a mean clearance of 0.56 +/- 0.18 liter/minute (Prod Info FOCALIN(TM) XR, 2005)

b) Renal Excretion (%)

1) minimal unchanged (Prod Info Focalin™, 2001a).

c) Specific renal excretion data for dexmethylphenidate are unavailable. However, approximately 90% of an oral dose of racemic methylphenidate appears in the urine, mainly as ritalinic acid (about 80%); 0.5% appears as unchanged methylphenidate following an intravenous dose (Prod Info FOCALIN(TM) XR, 2005; Prod Info Focalin™, 2001a).

2.3.5 Elimination Half-life

A) Parent Compound

1) Dexmethylphenidate Hydrochloride

a) ELIMINATION HALF-LIFE

1) approximately 3 hours (Prod Info FOCALIN(TM) XR, 2005; Prod Info Focalin™, 2001a).

a) The mean terminal elimination half-life of dexmethylphenidate was just over 3 hours in healthy adults and typically varied between 2 and 4.5 hours; children displayed shorter half-lives with means of 2 to 3 hours (Prod Info FOCALIN(TM) XR, 2005).

3.0 Cautions

Contraindications

Precautions

Adverse Reactions

Teratogenicity/Effects in Pregnancy/Breastfeeding

Drug Interactions

3.0.A Black Box WARNING

1) Dexmethylphenidate Hydrochloride

a) Oral (Capsule, Extended Release; Tablet)

1) Dexmethylphenidate hydrochloride should be given cautiously to patients with a history of drug dependence or alcoholism. Chronic, abusive use can lead to marked tolerance and psychological dependence with varying degrees of abnormal behavior. Frank psychotic episodes can occur, especially with parenteral abuse. Careful supervision is required during drug withdrawal from abusive use since severe depression may occur. Withdrawal following chronic therapeutic use may unmask symptoms of the underlying disorder that may require follow-up (Prod Info FOCALIN(TM) XR extended-release oral capsules, 2006).

3.1 Contraindications

A) Dexmethylphenidate Hydrochloride

1) agitation, severe; anxiety; or tension; may aggravate symptoms (Prod Info FOCALIN(TM) XR extended-release oral capsules, 2006)

2) glaucoma (Prod Info FOCALIN(TM) XR extended-release oral capsules, 2006)

3) hypersensitivity to methylphenidate or other components of the product (Prod Info FOCALIN(TM) XR extended-release oral capsules, 2006)

4) MAOI use within 14 days; hypertensive crisis may result (Prod Info FOCALIN(TM) XR extended-release oral capsules, 2006)

5) motor tics (Prod Info FOCALIN(TM) XR extended-release oral capsules, 2006)

6) Tourette's syndrome, family history or diagnosis of (Prod Info FOCALIN(TM) XR extended-release oral capsules, 2006)

3.2 Precautions

A) Dexmethylphenidate Hydrochloride

1) cardiac abnormalities, structural; sudden death has been reported in association with CNS stimulant use(Prod Info FOCALIN(TM) XR extended-release oral capsules, 2006)
2) conditions which may be compromised by increases in blood pressure or heart rate, such as pre-existing hypertension, heart failure, recent myocardial infarction, or hyperthyroidism (Prod Info FOCALIN(TM) XR extended-release oral capsules, 2006)
3) depression, severe; do not use to treat (Prod Info FOCALIN(TM) XR extended-release oral capsules, 2006)
4) drug dependence or alcoholism, history of; potential for abuse (Prod Info FOCALIN(TM) XR extended-release oral capsules, 2006)
5) EEG abnormalities, especially history of; may lower convulsive threshold (Prod Info FOCALIN(TM) XR extended-release oral capsules, 2006)
6) fatigue, normal; do not use to treat (Prod Info FOCALIN(TM) XR extended-release oral capsules, 2006)
7) psychosis; may exacerbate behavior disturbance and thought disorder (Prod Info FOCALIN(TM) XR extended-release oral capsules, 2006)
8) seizures, especially history of; may lower convulsive threshold (Prod Info FOCALIN(TM) XR extended-release oral capsules, 2006)

3.3 Adverse Reactions

Cardiovascular Effects

Endocrine/Metabolic Effects

Gastrointestinal Effects

Hematologic Effects

Neurologic Effects

Ophthalmic Effects

Psychiatric Effects

Other

3.3.1 Cardiovascular Effects

3.3.1.A Dexmethylphenidate Hydrochloride

3.3.1.A.1 Cardiovascular finding

a) Modest increases in heart rate (up to 5 beats per minute) and systolic/diastolic blood pressure (up to 3 mmHg) have been reported during dexmethylphenidate therapy in children/adolescents with ADHD (unpublished clinical studies) (Prod Info Focalin(TM), 2001). TACHYCARDIA has rarely necessitated withdrawal of treatment (Prod Info Focalin(TM), 2001).

3.3.3 Endocrine/Metabolic Effects

3.3.3.A Dexmethylphenidate Hydrochloride

3.3.3.A.1 Metabolic finding

a) Whether prolonged use of methylphenidate (or dexmethylphenidate) can significantly limit height and body weight remains controversial. Monitoring of weight and height is indicated in preadolescent children. Early adolescent growth does not appear to be affected by methylphenidate.

3.3.4 Gastrointestinal Effects

3.3.4.A Dexmethylphenidate Hydrochloride

Abdominal pain

Loss of appetite

Nausea

3.3.4.A.1 Abdominal pain

a) Incidence: 15% (Prod Info FOCALIN(R) oral tablets, 2007)

b) In unpublished clinical-trial data for dexmethylphenidate in children/adolescents with ADHD, abdominal pain was reported at least once during treatment in 15% of patients. Incidences of these effects were at least 50% lower in placebo recipients (Prod Info FOCALIN(R) oral tablets, 2007). There is no demonstrated evidence of a lower frequency of GI effects in patients treated with dexmethylphenidate compared to racemic methylphenidate.

3.3.4.A.2 Loss of appetite

a) Incidence: 6% (Prod Info FOCALIN(R) oral tablets, 2007)

b) In unpublished clinical-trial data for dexmethylphenidate in children/adolescents with ADHD, anorexia was reported at least once during treatment in 6% of patients. Incidences of these effects were at least 50% lower in placebo recipients (Prod Info FOCALIN(R) oral tablets, 2007). There is no demonstrated evidence of a lower frequency of GI effects in patients treated with dexmethylphenidate compared to racemic methylphenidate.

3.3.4.A.3 Nausea

a) Incidence: 9% (Prod Info FOCALIN(R) oral tablets, 2007)

b) In unpublished clinical-trial data for dexmethylphenidate in children/adolescents with ADHD, nausea was reported at least once during treatment in 9% of patients. Incidences of these effects were at least 50% lower in placebo recipients (Prod Info FOCALIN(R) oral tablets, 2007). There is no demonstrated evidence of a lower frequency of GI effects in patients treated with dexmethylphenidate compared to racemic methylphenidate.

3.3.5 Hematologic Effects

3.3.5.A Dexmethylphenidate Hydrochloride

3.3.5.A.1 Hematology finding

a) Thrombocytopenia and anemia have occurred infrequently during racemic methylphenidate therapy (USPDI, 2001); (Prod Info Focalin(TM), 2001). The manufacturer of dexmethylphenidate has not disclosed the frequency of these effects in clinical trials, although this data is available from extensive premarketing safety evaluations (Prod Info Focalin(TM), 2001).

3.3.9 Neurologic Effects

3.3.9.A Dexmethylphenidate Hydrochloride

Insomnia

Spasmodic movement, Vocal or motor tics

3.3.9.A.1 Insomnia

a) Nervousness and insomnia have occurred relatively frequently with use of racemic methylphenidate in children and adolescents, and may be more common in children (USPDI, 2001); (Prod Info Focalin (TM), 2001).

b) In clinical studies specifically with dexmethylphenidate in ADHD, the manufacturer indicates that motor or vocal tics and insomnia have rarely (1%) necessitated therapy discontinuation (Prod Info Focalin(TM), 2001). However, the manufacturer has chosen not to disclose the frequency of other CNS effects in clinical trials, although this data was available from extensive premarketing safety evaluations (Prod Info Focalin(TM), 2001).

c) Although dexmethylphenidate is claimed to potentially produced fewer adverse CNS effects (eg, insomnia) than racemic methylphenidate (Anon, 2001a), this has not been demonstrated.

3.3.9.A.2 Spasmodic movement, Vocal or motor tics

a) In clinical studies specifically with dexmethylphenidate in ADHD, the manufacturer indicates that motor or vocal tics and insomnia have rarely (1%) necessitated therapy discontinuation (Prod Info Focalin(TM), 2001). However, the manufacturer has chosen not to disclose the frequency of other CNS effects in clinical trials, although this data was available from extensive premarketing safety evaluations (Prod Info Focalin(TM), 2001).

3.3.10 Ophthalmic Effects

3.3.10.A Dexmethylphenidate Hydrochloride

3.3.10.A.1 Eye / vision finding

a) Similar to racemic methylphenidate, dexmethylphenidate is capable of infrequently causing blurring of vision and other visual disturbances (USPDI, 2001); (Prod Info Focalin(TM), 2001). However, specific incidence data for these effects were not disclosed by the manufacturer of dexmethylphenidate.

3.3.12 Psychiatric Effects

3.3.12.A Dexmethylphenidate Hydrochloride

Mania

Psychotic disorder

Seizure

3.3.12.A.1 Mania

a) In a review of 49 randomized, controlled pediatric ADHD clinical trials involving pscyhostimulant medications (atomoxetine hydrochloride, methylphenidate hydrochloride, modafinil and dextromethylphenidate hydrochloride), the rate of psychosis/mania events in pediatric subjects receiving active drug was 1.48 (95% CI, 0.74 to 2.65) per 100 person-years, with no comparable adverse events recorded in the placebo group. A request from the US Food and Drug Administration to manufacturers of marketed ADHD drugs for submission of postmarketing case reports of psychosis or mania events between 2000 and 2005, yielded a total of 865 reports (pediatrics and adults) in which signs and/or symptoms of psychoses or mania were reported. The majority of reports involved pediatric subjects, with almost half of the reports in children 10 years-old or younger, and approximately 90% of cases involving no prior history of similar psychiatric conditions. Visual and/or tactile sensations of insects, snakes, or worms were commonly reported. Positive rechallenge was reported for each of the psychostimulant medications (methylphenidate hydrochloride, atomoxetine hydrochloride, and mixed salts of a single entity amphetamine product) included in the analysis; and in many cases a strong temporal association was identified. The onset of psychiatric symptoms ranged from days to weeks, but in some cases it was months or years from the start of ADHD treatment and symptom onset (Mosholder et al, 2009).

3.3.12.A.2 Psychotic disorder

a) In a review of 49 randomized, controlled pediatric ADHD clinical trials involving pscyhostimulant medications (atomoxetine hydrochloride, methylphenidate hydrochloride, modafinil and dextromethylphenidate hydrochloride), the rate of psychosis/mania events in pediatric subjects receiving active drug was 1.48 (95% CI, 0.74 to 2.65) per 100 person-years, with no comparable adverse events recorded in the placebo group. A request from the US Food and Drug Administration to manufacturers of marketed ADHD drugs for submission of postmarketing case reports of psychosis or mania events between 2000 and 2005, yielded a total of 865 reports (pediatrics and adults) in which signs and/or symptoms of psychoses or mania were reported. The majority of reports involved pediatric subjects, with almost half of the reports in children 10 years-old or younger, and approximately 90% of cases involving no prior history of similar psychiatric conditions. Visual and/or tactile sensations of insects, snakes, or worms were commonly reported. Positive rechallenge was reported for each of the psychostimulant medications (methylphenidate hydrochloride, atomoxetine hydrochloride, and mixed salts of a single entity amphetamine product) included in the analysis; and in many cases a strong temporal association was identified. The onset of psychiatric symptoms ranged from days to weeks, but in some cases it was months or years from the start of ADHD treatment and symptom onset (Mosholder et al, 2009).

b) Seizures and psychosis have occurred rarely with racemic methylphenidate (USPDI, 2001)

3.3.12.A.3 Seizure

a) Seizures and psychosis have occurred rarely with racemic methylphenidate (USPDI, 2001)

3.3.16 Other

3.3.16.A Dexmethylphenidate Hydrochloride

Drug dependence

Fever

3.3.16.A.1 Drug dependence

a) Similar to methylphenidate, both psychological and physical dependence can occur during high-dose and/or prolonged use of dexmethylphenidate. The manufacturer (Prod Info Focalin(TM), 2001) suggests only the risk of psychological dependence.

b) Slow tapering of the dose is required following long-term therapy or use of high doses to minimize withdrawal symptoms, which can include unusual tiredness, severe depression, and unusual behavior (USPDI, 2001).

3.3.16.A.2 Fever

a) In unpublished clinical-trial data for dexmethylphenidate in children/adolescents with ADHD, fever was reported at least once during treatment in 5% of patients; fever occurred in 1% of placebo recipients (Prod Info Focalin(TM), 2001).

3.4 Teratogenicity/Effects in Pregnancy/Breastfeeding

A) Teratogenicity/Effects in Pregnancy

1) U.S. Food and Drug Administration's Pregnancy Category: Category C (Prod Info FOCALIN XR, 2008) (All Trimesters)

a) Either studies in animals have revealed adverse effects on the fetus (teratogenic or embryocidal or other) and there are no controlled studies in women or studies in women and animals are not available. Drugs should be given only if the potential benefit justifies the potential risk to the fetus.

See Drug Consult reference: PREGNANCY RISK CATEGORIES

2) Crosses Placenta: Unknown

3) Clinical Management

a) Although a causal relationship between dexmethylphenidate and teratogenic effects have not been found, the safe use of dexmethylphenidate during pregnancy has yet to be confirmed. Until additional data are available, dexmethylphenidate should be used in pregnant women only if the benefit to the pregnant woman outweighs the potential risk to the fetus (Prod Info FOCALIN XR, 2008).

4) Literature Reports

a) No human studies of pregnancy outcomes after exposure to dexmethylphenidate have been published, and there are no reports of outcomes after inadvertent exposure during pregnancy. Adequate studies to establish safe use of dexmethylphenidate during pregnancy have not been conducted (Prod Info FOCALIN XR, 2008). One source describes a series of women (n=11) who used racemic methylphenidate (dose unspecified) during the first 4 months of pregnancy; no birth defects or other abnormalities were reported in any of the infants and all 11 were considered normal (Heinonen et al, 1977). A later report discussed the outcomes of another 38 women who used racemic methylphenidate during pregnancy (DeBooy et al, 1993). Although infants in these reports were more likely to be premature, growth retarded, and to show signs of neonatal withdrawal, no increase in congenital abnormalities was identified; however, this number is so small that no pattern or estimate of risk can be determined at this time. No teratogenicity was observed in rats and rabbits treated with dexmethylphenidate in doses up to 20 and 100 milligrams/kilogram (mg/kg) daily, respectively, during the period of organogenesis; however, delayed fetal skeletal ossification was seen at the highest dose in rats. However, doses of 200 mg/kg/day of racemic methylphenidate have produced teratogenic effects in rabbits throughout organogenesis (Prod Info FOCALIN XR, 2008).

B) Breastfeeding

1) Thomson Lactation Rating: Infant risk cannot be ruled out.

a) Available evidence and/or expert consensus is inconclusive or is inadequate for determining infant risk when used during breastfeeding. Weigh the potential benefits of drug treatment against potential risks before prescribing this drug during breastfeeding.

2) Clinical Management

a) It is not known whether dexmethylphenidate is excreted into human breast milk and the potential for adverse effects in the nursing infant from exposure to the drug are unknown (Prod Info FOCALIN XR, 2008).

3) Literature Reports

a) Four published case reports indicate that maternal doses of racemic methylphenidate of 35 to 80 mg/day during breastfeeding resulted in milk concentrations that ranged from undetectable to 15.4 ng/mL (calculated infant daily dose approximately 0.4 to 2.9 ug/kg/day or approximately 0.2% to 0.7% of the adjusted maternal weight dose) for an exclusively breastfed infant (Prod Info FOCALIN XR, 2008).

3.5 Drug Interactions

3.5.1 Drug-Drug Combinations

Amitriptyline

Amoxapine

Brofaromine

Clomipramine

Clorgyline

Desipramine

Dicumarol

Dothiepin

Doxepin

Furazolidone

Imipramine

Iproniazid

Isocarboxazid

Lazabemide

Linezolid

Lofepramine

Moclobemide

Nialamide

Nortriptyline

Opipramol

Pargyline

Phenelzine

Phenobarbital

Phenytoin

Primidone

Procarbazine

Protriptyline

Rasagiline

Selegiline

Toloxatone

Tranylcypromine

Trimipramine

Warfarin

3.5.1.A Amitriptyline

1) Interaction Effect: hypertension, other cardiac effects, and CNS stimulation

2) Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been reported to result in enhanced amphetamine effects from the release of norepinephrine (Beaumont, 1973; Raisfeld, 1972). A similar reaction might also occur with all drugs that have amphetamine-like effects. Acute elevations in blood pressure have been noted (Flemenbaum, 1971a). Some amphetamine-like drugs may inhibit the metabolism of TCAs, although most combinations have not been studied. When amphetamine analogs are being used to treat obesity, it should be noted that TCAs frequently lead to moderate weight gain (Russ & Ackerman, 1988). False positive urine tests for amphetamines have been reported during therapy with some TCAs (Merigian & Browning, 1993). Caution is advised when concurrent administration of amphetamine-like agents and TCAs is warranted. The patient should be closely monitored for increased cardiovascular effects (hypertension and dysrhythmias).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other sympathomimetic agents could lead to hypertension, increased cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006; Flemenbaum, 1972). Use caution if such therapy is warranted. Monitor the patient closely for hypertension and dysrhythmias.

7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission

8) Literature Reports

a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agents. Additionally, coadministration of d-amphetamine with TCAs such as desipramine or protriptyline results in sustained increases in d-amphetamine concentration in the brain (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006).

b) Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism of some tricyclic antidepressants, such as imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transdermal system, 2006).

c) Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases in blood pressure such that the hypotensive effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of combined therapy. Discontinuation of the methylphenidate usually results in the blood pressure returning to normotensive levels; reinstitution of the methylphenidate resulted in further blood pressure elevation (Flemenbaum, 1971; Flemenbaum, 1972).

d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine given for at least four weeks, were given fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical improvement. However, fenfluramine more than doubled steady-state plasma levels of desipramine (Price et al, 1990).

e) There have been claims based on uncontrolled studies that a better antidepressant response may occur with combined therapy (Garrettson et al, 1969). However, a systemic review of stimulants in the treatment of depression concluded that although uncontrolled studies were generally positive, the ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated little advantage of drug over placebo and did not appear to be as effective as the conventional antidepressants in primary depression (Satel & Nelson, 1989).

3.5.1.B Amoxapine

1) Interaction Effect: hypertension, other cardiac effects, and CNS stimulation

2) Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been reported to result in enhanced amphetamine effects from the release of norepinephrine (Beaumont, 1973; Raisfeld, 1972). A similar reaction might also occur with all drugs that have amphetamine-like effects. Acute elevations in blood pressure have been noted (Flemenbaum, 1971a). Some amphetamine-like drugs may inhibit the metabolism of TCAs, although most combinations have not been studied. When amphetamine analogs are being used to treat obesity, it should be noted that TCAs frequently lead to moderate weight gain (Russ & Ackerman, 1988). False positive urine tests for amphetamines have been reported during therapy with some TCAs (Merigian & Browning, 1993). Caution is advised when concurrent administration of amphetamine-like agents and TCAs is warranted. The patient should be closely monitored for increased cardiovascular effects (hypertension and dysrhythmias).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other

sympathomimetic agents could lead to hypertension, increased cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006; Flemenbaum, 1972). Use caution if such therapy is warranted. Monitor the patient closely for hypertension and dysrhythmias.
7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission
8) Literature Reports
a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agents. Additionally, coadministration of d-amphetamine with TCAs such as desipramine or protriptyline results in sustained increases in d-amphetamine concentration in the brain (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006).
b) Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism of some tricyclic antidepressants, such as imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transdermal system, 2006).
c) Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases in blood pressure such that the hypotensive effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of combined therapy. Discontinuation of the methylphenidate usually results in the blood pressure returning to normotensive levels; reinstitution of the methylphenidate resulted in further blood pressure elevation (Flemenbaum, 1971; Flemenbaum, 1972).
d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine given for at least four weeks, were given fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical improvement. However, fenfluramine more than doubled steady-state plasma levels of desipramine (Price et al, 1990).
e) There have been claims based on uncontrolled studies that a better antidepressant response may occur with combined therapy (Garrettson et al, 1969). However, a systemic review of stimulants in the treatment of depression concluded that although uncontrolled studies were generally positive, the ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated little advantage of drug over placebo and did not appear to be as effective as the conventional antidepressants in primary depression (Satel & Nelson, 1989).

3.5.1.C Brofaromine

1) Interaction Effect: hypertensive crisis (headache, palpitation, and neck stiffness)
2) Summary: Monoamine oxidase inhibitors should not be administered with sympathomimetic drugs such as dexmethylphenidate. Coadministration may result in hypertensive crisis, which is characterized by symptoms such as headache, palpitation, neck stiffness, nausea, and vomiting. Hypertensive crisis associated with monoamine oxidase inhibitors has been fatal (Prod Info Focalin(TM), 2001b).
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent use of monoamine oxidase inhibitors and dexmethylphenidate is contraindicated. If dexmethylphenidate is to be initiated, the monoamine oxidase inhibitor must be discontinued for a minimum of 14 days.
7) Probable Mechanism: unknown

3.5.1.D Clomipramine

1) Interaction Effect: hypertension, other cardiac effects, and CNS stimulation
2) Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been reported to result in enhanced amphetamine effects from the release of norepinephrine (Beaumont, 1973; Raisfeld, 1972). A similar reaction might also occur with all drugs that have amphetamine-like effects. Acute elevations in blood pressure have been noted (Flemenbaum, 1971a). Some amphetamine-like drugs may inhibit the metabolism of TCAs, although most combinations have not been studied. When amphetamine analogs are being used to treat obesity, it should be noted that TCAs frequently lead to moderate weight gain (Russ & Ackerman, 1988). False positive urine tests for amphetamines have been reported during therapy with some TCAs (Merigian & Browning, 1993). Caution is advised when concurrent administration of amphetamine-like agents and TCAs is warranted. The patient should be closely monitored for increased cardiovascular effects (hypertension and dysrhythmias).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other sympathomimetic agents could lead to hypertension, increased cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006; Flemenbaum, 1972). Use caution if such therapy is warranted. Monitor the patient closely for hypertension and dysrhythmias.
7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission
8) Literature Reports
a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agents. Additionally, coadministration of d-amphetamine with TCAs such as desipramine or protriptyline

results in sustained increases in d-amphetamine concentration in the brain (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006).

b) Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism of some tricyclic antidepressants, such as imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transdermal system, 2006).

c) Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases in blood pressure such that the hypotensive effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of combined therapy. Discontinuation of the methylphenidate usually results in the blood pressure returning to normotensive levels; reinstitution of the methylphenidate resulted in further blood pressure elevation (Flemenbaum, 1971; Flemenbaum, 1972).

d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine given for at least four weeks, were given fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical improvement. However, fenfluramine more than doubled steady-state plasma levels of desipramine (Price et al, 1990).

e) There have been claims based on uncontrolled studies that a better antidepressant response may occur with combined therapy (Garrettson et al, 1969). However, a systemic review of stimulants in the treatment of depression concluded that although uncontrolled studies were generally positive, the ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated little advantage of drug over placebo and did not appear to be as effective as the conventional antidepressants in primary depression (Satel & Nelson, 1989).

3.5.1.E Clorgyline

1) Interaction Effect: hypertensive crisis (headache, palpitation, and neck stiffness)

2) Summary: Monoamine oxidase inhibitors should not be administered with sympathomimetic drugs such as dexmethylphenidate. Coadministration may result in hypertensive crisis, which is characterized by symptoms such as headache, palpitation, neck stiffness, nausea, and vomiting. Hypertensive crisis associated with monoamine oxidase inhibitors has been fatal (Prod Info Focalin(TM), 2001b).

3) Severity: contraindicated

4) Onset: rapid

5) Substantiation: theoretical

6) Clinical Management: The concurrent use of monoamine oxidase inhibitors and dexmethylphenidate is contraindicated. If dexmethylphenidate is to be initiated, the monoamine oxidase inhibitor must be discontinued for a minimum of 14 days.

7) Probable Mechanism: unknown

3.5.1.F Desipramine

1) Interaction Effect: hypertension, other cardiac effects, and CNS stimulation

2) Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been reported to result in enhanced amphetamine effects from the release of norepinephrine (Beaumont, 1973; Raisfeld, 1972). A similar reaction might also occur with all drugs that have amphetamine-like effects. Acute elevations in blood pressure have been noted (Flemenbaum, 1971a). Some amphetamine-like drugs may inhibit the metabolism of TCAs, although most combinations have not been studied. When amphetamine analogs are being used to treat obesity, it should be noted that TCAs frequently lead to moderate weight gain (Russ & Ackerman, 1988). False positive urine tests for amphetamines have been reported during therapy with some TCAs (Merigian & Browning, 1993). Caution is advised when concurrent administration of amphetamine-like agents and TCAs is warranted. The patient should be closely monitored for increased cardiovascular effects (hypertension and dysrhythmias).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other sympathomimetic agents could lead to hypertension, increased cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006; Flemenbaum, 1972). Use caution if such therapy is warranted. Monitor the patient closely for hypertension and dysrhythmias.

7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission

8) Literature Reports

a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agents. Additionally, coadministration of d-amphetamine with TCAs such as desipramine or protriptyline results in sustained increases in d-amphetamine concentration in the brain (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006).

b) Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism of some tricyclic antidepressants, such as imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transdermal system, 2006).

c) Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases in blood pressure such that the hypotensive effects induced by TCAs may lead to blood pressures as

high as 170/120 mmHg within one day of combined therapy. Discontinuation of the methylphenidate usually results in the blood pressure returning to normotensive levels; reinstitution of the methylphenidate resulted in further blood pressure elevation (Flemenbaum, 1971; Flemenbaum, 1972).
d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine given for at least four weeks, were given fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical improvement. However, fenfluramine more than doubled steady-state plasma levels of desipramine (Price et al, 1990).
e) There have been claims based on uncontrolled studies that a better antidepressant response may occur with combined therapy (Garrettson et al, 1969). However, a systemic review of stimulants in the treatment of depression concluded that although uncontrolled studies were generally positive, the ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated little advantage of drug over placebo and did not appear to be as effective as the conventional antidepressants in primary depression (Satel & Nelson, 1989).

3.5.1.G Dicumarol

1) Interaction Effect: an increased risk of bleeding
2) Summary: Dexmethylphenidate may inhibit the metabolism of coumarin anticoagulants, such as dicumarol, potentially resulting in an increased risk of bleeding. Dicumarol dosage may need to be reduced during concurrent dexmethylphenidate therapy. When initiating or discontinuing dexmethylphenidate therapy, it may be necessary to adjust the dicumarol dose and monitor coagulation times (Prod Info FOCALIN(R) XR extended-release oral capsules, 2007).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Consider reducing the dicumarol dose during concomitant dexmethylphenidate therapy due to an increased risk of bleeding. Adjust the dose as needed and monitor coagulation times when initiating or discontinuing dexmethylphenidate treatment (Prod Info FOCALIN(R) XR extended-release oral capsules, 2007).
7) Probable Mechanism: inhibition of dicumarol metabolism

3.5.1.H Dothiepin

1) Interaction Effect: hypertension, other cardiac effects, and CNS stimulation
2) Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been reported to result in enhanced amphetamine effects from the release of norepinephrine (Beaumont, 1973; Raisfeld, 1972). A similar reaction might also occur with all drugs that have amphetamine-like effects. Acute elevations in blood pressure have been noted (Flemenbaum, 1971a). Some amphetamine-like drugs may inhibit the metabolism of TCAs, although most combinations have not been studied. When amphetamine analogs are being used to treat obesity, it should be noted that TCAs frequently lead to moderate weight gain (Russ & Ackerman, 1988). False positive urine tests for amphetamines have been reported during therapy with some TCAs (Merigian & Browning, 1993). Caution is advised when concurrent administration of amphetamine-like agents and TCAs is warranted. The patient should be closely monitored for increased cardiovascular effects (hypertension and dysrhythmias).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other sympathomimetic agents could lead to hypertension, increased cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006; Flemenbaum, 1972). Use caution if such therapy is warranted. Monitor the patient closely for hypertension and dysrhythmias.
7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission
8) Literature Reports
a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agents. Additionally, coadministration of d-amphetamine with TCAs such as desipramine or protriptyline results in sustained increases in d-amphetamine concentration in the brain (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006).
b) Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism of some tricyclic antidepressants, such as imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transdermal system, 2006).
c) Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases in blood pressure such that the hypotensive effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of combined therapy. Discontinuation of the methylphenidate usually results in the blood pressure returning to normotensive levels; reinstitution of the methylphenidate resulted in further blood pressure elevation (Flemenbaum, 1971; Flemenbaum, 1972).
d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine given for at least four weeks, were given fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical improvement. However, fenfluramine more than doubled

steady-state plasma levels of desipramine (Price et al, 1990).
e) There have been claims based on uncontrolled studies that a better antidepressant response may occur with combined therapy (Garrettson et al, 1969). However, a systemic review of stimulants in the treatment of depression concluded that although uncontrolled studies were generally positive, the ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated little advantage of drug over placebo and did not appear to be as effective as the conventional antidepressants in primary depression (Satel & Nelson, 1989).

3.5.1.I Doxepin

1) Interaction Effect: hypertension, other cardiac effects, and CNS stimulation
2) Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been reported to result in enhanced amphetamine effects from the release of norepinephrine (Beaumont, 1973; Raisfeld, 1972). A similar reaction might also occur with all drugs that have amphetamine-like effects. Acute elevations in blood pressure have been noted (Flemenbaum, 1971a). Some amphetamine-like drugs may inhibit the metabolism of TCAs, although most combinations have not been studied. When amphetamine analogs are being used to treat obesity, it should be noted that TCAs frequently lead to moderate weight gain (Russ & Ackerman, 1988). False positive urine tests for amphetamines have been reported during therapy with some TCAs (Merigian & Browning, 1993). Caution is advised when concurrent administration of amphetamine-like agents and TCAs is warranted. The patient should be closely monitored for increased cardiovascular effects (hypertension and dysrhythmias).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other sympathomimetic agents could lead to hypertension, increased cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006; Flemenbaum, 1972). Use caution if such therapy is warranted. Monitor the patient closely for hypertension and dysrhythmias.
7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission
8) Literature Reports
a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agents. Additionally, coadministration of d-amphetamine with TCAs such as desipramine or protriptyline results in sustained increases in d-amphetamine concentration in the brain (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006).
b) Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism of some tricyclic antidepressants, such as imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transdermal system, 2006).
c) Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases in blood pressure such that the hypotensive effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of combined therapy. Discontinuation of the methylphenidate usually results in the blood pressure returning to normotensive levels; reinstitution of the methylphenidate resulted in further blood pressure elevation (Flemenbaum, 1971; Flemenbaum, 1972).
d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine given for at least four weeks, were given fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical improvement. However, fenfluramine more than doubled steady-state plasma levels of desipramine (Price et al, 1990).
e) There have been claims based on uncontrolled studies that a better antidepressant response may occur with combined therapy (Garrettson et al, 1969). However, a systemic review of stimulants in the treatment of depression concluded that although uncontrolled studies were generally positive, the ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated little advantage of drug over placebo and did not appear to be as effective as the conventional antidepressants in primary depression (Satel & Nelson, 1989).

3.5.1.J Furazolidone

1) Interaction Effect: hypertensive crisis (headache, palpitation, and neck stiffness)
2) Summary: Monoamine oxidase inhibitors should not be administered with sympathomimetic drugs such as dexmethylphenidate. Coadministration may result in hypertensive crisis, which is characterized by symptoms such as headache, palpitation, neck stiffness, nausea, and vomiting. Hypertensive crisis associated with monoamine oxidase inhibitors has been fatal (Prod Info Focalin(TM), 2001b).
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent use of monoamine oxidase inhibitors and dexmethylphenidate is contraindicated. If dexmethylphenidate is to be initiated, the monoamine oxidase inhibitor must be discontinued for a minimum of 14 days.
7) Probable Mechanism: unknown

3.5.1.K Imipramine

1) Interaction Effect: hypertension, other cardiac effects, and CNS stimulation

2) Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been reported to result in enhanced amphetamine effects from the release of norepinephrine (Beaumont, 1973; Raisfeld, 1972). A similar reaction might also occur with all drugs that have amphetamine-like effects. Acute elevations in blood pressure have been noted (Flemenbaum, 1971a). Some amphetamine-like drugs may inhibit the metabolism of TCAs, although most combinations have not been studied. When amphetamine analogs are being used to treat obesity, it should be noted that TCAs frequently lead to moderate weight gain (Russ & Ackerman, 1988). False positive urine tests for amphetamines have been reported during therapy with some TCAs (Merigian & Browning, 1993). Caution is advised when concurrent administration of amphetamine-like agents and TCAs is warranted. The patient should be closely monitored for increased cardiovascular effects (hypertension and dysrhythmias).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other sympathomimetic agents could lead to hypertension, increased cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006; Flemenbaum, 1972). Use caution if such therapy is warranted. Monitor the patient closely for hypertension and dysrhythmias.

7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission

8) Literature Reports

a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agents. Additionally, coadministration of d-amphetamine with TCAs such as desipramine or protriptyline results in sustained increases in d-amphetamine concentration in the brain (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006).

b) Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism of some tricyclic antidepressants, such as imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transdermal system, 2006).

c) Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases in blood pressure such that the hypotensive effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of combined therapy. Discontinuation of the methylphenidate usually results in the blood pressure returning to normotensive levels; reinstitution of the methylphenidate resulted in further blood pressure elevation (Flemenbaum, 1971; Flemenbaum, 1972).

d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine given for at least four weeks, were given fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical improvement. However, fenfluramine more than doubled steady-state plasma levels of desipramine (Price et al, 1990).

e) There have been claims based on uncontrolled studies that a better antidepressant response may occur with combined therapy (Garrettson et al, 1969). However, a systemic review of stimulants in the treatment of depression concluded that although uncontrolled studies were generally positive, the ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated little advantage of drug over placebo and did not appear to be as effective as the conventional antidepressants in primary depression (Satel & Nelson, 1989).

3.5.1.L Iproniazid

1) Interaction Effect: hypertensive crisis (headache, palpitation, and neck stiffness)

2) Summary: Monoamine oxidase inhibitors should not be administered with sympathomimetic drugs such as dexmethylphenidate. Coadministration may result in hypertensive crisis, which is characterized by symptoms such as headache, palpitation, neck stiffness, nausea, and vomiting. Hypertensive crisis associated with monoamine oxidase inhibitors has been fatal (Prod Info Focalin(TM), 2001b).

3) Severity: contraindicated

4) Onset: rapid

5) Substantiation: theoretical

6) Clinical Management: The concurrent use of monoamine oxidase inhibitors and dexmethylphenidate is contraindicated. If dexmethylphenidate is to be initiated, the monoamine oxidase inhibitor must be discontinued for a minimum of 14 days.

7) Probable Mechanism: unknown

3.5.1.M Isocarboxazid

1) Interaction Effect: hypertensive crisis (headache, palpitation, and neck stiffness)

2) Summary: Monoamine oxidase inhibitors should not be administered with sympathomimetic drugs such as dexmethylphenidate. Coadministration may result in hypertensive crisis, which is characterized by symptoms such as headache, palpitation, neck stiffness, nausea, and vomiting. Hypertensive crisis associated with monoamine oxidase inhibitors has been fatal (Prod Info Focalin(TM), 2001b).

3) Severity: contraindicated

4) Onset: rapid

5) Substantiation: theoretical
6) Clinical Management: The concurrent use of monoamine oxidase inhibitors and dexmethylphenidate is contraindicated. If dexmethylphenidate is to be initiated, the monoamine oxidase inhibitor must be discontinued for a minimum of 14 days.
7) Probable Mechanism: unknown

3.5.1.N Lazabemide

1) Interaction Effect: hypertensive crisis (headache, palpitation, and neck stiffness)
2) Summary: Monoamine oxidase inhibitors should not be administered with sympathomimetic drugs such as dexmethylphenidate. Coadministration may result in hypertensive crisis, which is characterized by symptoms such as headache, palpitation, neck stiffness, nausea, and vomiting. Hypertensive crisis associated with monoamine oxidase inhibitors has been fatal (Prod Info Focalin(TM), 2001b).
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent use of monoamine oxidase inhibitors and dexmethylphenidate is contraindicated. If dexmethylphenidate is to be initiated, the monoamine oxidase inhibitor must be discontinued for a minimum of 14 days.
7) Probable Mechanism: unknown

3.5.1.O Linezolid

1) Interaction Effect: hypertensive crisis (headache, palpitation, and neck stiffness)
2) Summary: Monoamine oxidase inhibitors should not be administered with sympathomimetic drugs such as dexmethylphenidate. Coadministration may result in hypertensive crisis, which is characterized by symptoms such as headache, palpitation, neck stiffness, nausea, and vomiting. Hypertensive crisis associated with monoamine oxidase inhibitors has been fatal (Prod Info Focalin(TM), 2001b).
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent use of monoamine oxidase inhibitors and dexmethylphenidate is contraindicated. If dexmethylphenidate is to be initiated, the monoamine oxidase inhibitor must be discontinued for a minimum of 14 days.
7) Probable Mechanism: unknown

3.5.1.P Lofepramine

1) Interaction Effect: hypertension, other cardiac effects, and CNS stimulation
2) Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been reported to result in enhanced amphetamine effects from the release of norepinephrine (Beaumont, 1973; Raisfeld, 1972). A similar reaction might also occur with all drugs that have amphetamine-like effects. Acute elevations in blood pressure have been noted (Flemenbaum, 1971a). Some amphetamine-like drugs may inhibit the metabolism of TCAs, although most combinations have not been studied. When amphetamine analogs are being used to treat obesity, it should be noted that TCAs frequently lead to moderate weight gain (Russ & Ackerman, 1988). False positive urine tests for amphetamines have been reported during therapy with some TCAs (Merigian & Browning, 1993). Caution is advised when concurrent administration of amphetamine-like agents and TCAs is warranted. The patient should be closely monitored for increased cardiovascular effects (hypertension and dysrhythmias).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other sympathomimetic agents could lead to hypertension, increased cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006; Flemenbaum, 1972). Use caution if such therapy is warranted. Monitor the patient closely for hypertension and dysrhythmias.
7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission
8) Literature Reports

a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agents. Additionally, coadministration of d-amphetamine with TCAs such as desipramine or protriptyline results in sustained increases in d-amphetamine concentration in the brain (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006).

b) Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism of some tricyclic antidepressants, such as imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transdermal system, 2006).

c) Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases in blood pressure such that the hypotensive effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of combined therapy. Discontinuation of the methylphenidate usually results in the blood pressure returning to normotensive levels; reinstitution of the

methylphenidate resulted in further blood pressure elevation (Flemenbaum, 1971; Flemenbaum, 1972).
d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine given for at least four weeks, were given fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical improvement. However, fenfluramine more than doubled steady-state plasma levels of desipramine (Price et al, 1990).
e) There have been claims based on uncontrolled studies that a better antidepressant response may occur with combined therapy (Garrettson et al, 1969). However, a systemic review of stimulants in the treatment of depression concluded that although uncontrolled studies were generally positive, the ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated little advantage of drug over placebo and did not appear to be as effective as the conventional antidepressants in primary depression (Satel & Nelson, 1989).

3.5.1.Q Moclobemide

1) Interaction Effect: hypertensive crisis (headache, palpitation, and neck stiffness)
2) Summary: Monoamine oxidase inhibitors should not be administered with sympathomimetic drugs such as dexmethylphenidate. Coadministration may result in hypertensive crisis, which is characterized by symptoms such as headache, palpitation, neck stiffness, nausea, and vomiting. Hypertensive crisis associated with monoamine oxidase inhibitors has been fatal (Prod Info Focalin(TM), 2001b).
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent use of monoamine oxidase inhibitors and dexmethylphenidate is contraindicated. If dexmethylphenidate is to be initiated, the monoamine oxidase inhibitor must be discontinued for a minimum of 14 days.
7) Probable Mechanism: unknown

3.5.1.R Nialamide

1) Interaction Effect: hypertensive crisis (headache, palpitation, and neck stiffness)
2) Summary: Monoamine oxidase inhibitors should not be administered with sympathomimetic drugs such as dexmethylphenidate. Coadministration may result in hypertensive crisis, which is characterized by symptoms such as headache, palpitation, neck stiffness, nausea, and vomiting. Hypertensive crisis associated with monoamine oxidase inhibitors has been fatal (Prod Info Focalin(TM), 2001b).
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent use of monoamine oxidase inhibitors and dexmethylphenidate is contraindicated. If dexmethylphenidate is to be initiated, the monoamine oxidase inhibitor must be discontinued for a minimum of 14 days.
7) Probable Mechanism: unknown

3.5.1.S Nortriptyline

1) Interaction Effect: hypertension, other cardiac effects, and CNS stimulation
2) Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been reported to result in enhanced amphetamine effects from the release of norepinephrine (Beaumont, 1973; Raisfeld, 1972). A similar reaction might also occur with all drugs that have amphetamine-like effects. Acute elevations in blood pressure have been noted (Flemenbaum, 1971a). Some amphetamine-like drugs may inhibit the metabolism of TCAs, although most combinations have not been studied. When amphetamine analogs are being used to treat obesity, it should be noted that TCAs frequently lead to moderate weight gain (Russ & Ackerman, 1988). False positive urine tests for amphetamines have been reported during therapy with some TCAs (Merigian & Browning, 1993). Caution is advised when concurrent administration of amphetamine-like agents and TCAs is warranted. The patient should be closely monitored for increased cardiovascular effects (hypertension and dysrhythmias).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other sympathomimetic agents could lead to hypertension, increased cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006; Flemenbaum, 1972). Use caution if such therapy is warranted. Monitor the patient closely for hypertension and dysrhythmias.
7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission
8) Literature Reports
a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agents. Additionally, coadministration of d-amphetamine with TCAs such as desipramine or protriptyline results in sustained increases in d-amphetamine concentration in the brain (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006).
b) Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism

of some tricyclic antidepressants, such as imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transdermal system, 2006).
c) Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases in blood pressure such that the hypotensive effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of combined therapy. Discontinuation of the methylphenidate usually results in the blood pressure returning to normotensive levels; reinstitution of the methylphenidate resulted in further blood pressure elevation (Flemenbaum, 1971; Flemenbaum, 1972).
d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine given for at least four weeks, were given fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical improvement. However, fenfluramine more than doubled steady-state plasma levels of desipramine (Price et al, 1990).
e) There have been claims based on uncontrolled studies that a better antidepressant response may occur with combined therapy (Garrettson et al, 1969). However, a systemic review of stimulants in the treatment of depression concluded that although uncontrolled studies were generally positive, the ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated little advantage of drug over placebo and did not appear to be as effective as the conventional antidepressants in primary depression (Satel & Nelson, 1989).

3.5.1.T Opipramol

1) Interaction Effect: hypertension, other cardiac effects, and CNS stimulation
2) Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been reported to result in enhanced amphetamine effects from the release of norepinephrine (Beaumont, 1973; Raisfeld, 1972). A similar reaction might also occur with all drugs that have amphetamine-like effects. Acute elevations in blood pressure have been noted (Flemenbaum, 1971a). Some amphetamine-like drugs may inhibit the metabolism of TCAs, although most combinations have not been studied. When amphetamine analogs are being used to treat obesity, it should be noted that TCAs frequently lead to moderate weight gain (Russ & Ackerman, 1988). False positive urine tests for amphetamines have been reported during therapy with some TCAs (Merigian & Browning, 1993). Caution is advised when concurrent administration of amphetamine-like agents and TCAs is warranted. The patient should be closely monitored for increased cardiovascular effects (hypertension and dysrhythmias).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other sympathomimetic agents could lead to hypertension, increased cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006; Flemenbaum, 1972). Use caution if such therapy is warranted. Monitor the patient closely for hypertension and dysrhythmias.
7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission
8) Literature Reports
a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agents. Additionally, coadministration of d-amphetamine with TCAs such as desipramine or protriptyline results in sustained increases in d-amphetamine concentration in the brain (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006).
b) Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism of some tricyclic antidepressants, such as imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transdermal system, 2006).
c) Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases in blood pressure such that the hypotensive effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of combined therapy. Discontinuation of the methylphenidate usually results in the blood pressure returning to normotensive levels; reinstitution of the methylphenidate resulted in further blood pressure elevation (Flemenbaum, 1971; Flemenbaum, 1972).
d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine given for at least four weeks, were given fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical improvement. However, fenfluramine more than doubled steady-state plasma levels of desipramine (Price et al, 1990).
e) There have been claims based on uncontrolled studies that a better antidepressant response may occur with combined therapy (Garrettson et al, 1969). However, a systemic review of stimulants in the treatment of depression concluded that although uncontrolled studies were generally positive, the ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated little advantage of drug over placebo and did not appear to be as effective as the conventional antidepressants in primary depression (Satel & Nelson, 1989).

3.5.1.U Pargyline

1) Interaction Effect: hypertensive crisis (headache, palpitation, and neck stiffness)
2) Summary: Monoamine oxidase inhibitors should not be administered with sympathomimetic drugs such as dexmethylphenidate. Coadministration may result in hypertensive crisis, which is characterized by

symptoms such as headache, palpitation, neck stiffness, nausea, and vomiting. Hypertensive crisis associated with monoamine oxidase inhibitors has been fatal (Prod Info Focalin(TM), 2001b).
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent use of monoamine oxidase inhibitors and dexmethylphenidate is contraindicated. If dexmethylphenidate is to be initiated, the monoamine oxidase inhibitor must be discontinued for a minimum of 14 days.
7) Probable Mechanism: unknown

3.5.1.V Phenelzine
1) Interaction Effect: hypertensive crisis (headache, palpitation, and neck stiffness)
2) Summary: Monoamine oxidase inhibitors should not be administered with sympathomimetic drugs such as dexmethylphenidate. Coadministration may result in hypertensive crisis, which is characterized by symptoms such as headache, palpitation, neck stiffness, nausea, and vomiting. Hypertensive crisis associated with monoamine oxidase inhibitors has been fatal (Prod Info Focalin(TM), 2001b).
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent use of monoamine oxidase inhibitors and dexmethylphenidate is contraindicated. If dexmethylphenidate is to be initiated, the monoamine oxidase inhibitor must be discontinued for a minimum of 14 days.
7) Probable Mechanism: unknown

3.5.1.W Phenobarbital
1) Interaction Effect: increase in phenobarbital plasma concentrations
2) Summary: Pharmacologic studies have demonstrated that dexmethylphenidate may inhibit the metabolism of anticonvulsants, such as phenobarbital. Dose adjustments of phenobarbital may be necessary (Prod Info Focalin(TM), 2001c).
3) Severity: moderate
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Downward dose adjustments of phenobarbital may be required when given concomitantly with dexmethylphenidate.
7) Probable Mechanism: inhibition of phenobarbital metabolism by dexmethylphenidate

3.5.1.X Phenytoin
1) Interaction Effect: increase in phenytoin plasma concentrations
2) Summary: Pharmacologic studies have demonstrated that dexmethylphenidate may inhibit the metabolism of anticonvulsants, such as phenytoin. Dose adjustments of phenytoin may be necessary (Prod Info Focalin(TM), 2001).
3) Severity: moderate
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Downward dose adjustments of phenytoin may be required when given concomitantly with dexmethylphenidate.
7) Probable Mechanism: inhibition of phenytoin metabolism by dexmethylphenidate

3.5.1.Y Primidone
1) Interaction Effect: increase in primidone plasma concentrations
2) Summary: Pharmacologic studies have demonstrated that dexmethylphenidate may inhibit the metabolism of anticonvulsants, such as primidone. Dose adjustments of primidone may be necessary (Prod Info Focalin(TM), 2001a).
3) Severity: moderate
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Downward dose adjustments of primidone may be required when given concomitantly with dexmethylphenidate.
7) Probable Mechanism: inhibition of primidone metabolism by dexmethylphenidate

3.5.1.Z Procarbazine
1) Interaction Effect: hypertensive crisis (headache, palpitation, and neck stiffness)
2) Summary: Monoamine oxidase inhibitors should not be administered with sympathomimetic drugs such as dexmethylphenidate. Coadministration may result in hypertensive crisis, which is characterized by symptoms such as headache, palpitation, neck stiffness, nausea, and vomiting. Hypertensive crisis associated with monoamine oxidase inhibitors has been fatal (Prod Info Focalin(TM), 2001b).
3) Severity: contraindicated
4) Onset: rapid

5) Substantiation: theoretical
6) Clinical Management: The concurrent use of monoamine oxidase inhibitors and dexmethylphenidate is contraindicated. If dexmethylphenidate is to be initiated, the monoamine oxidase inhibitor must be discontinued for a minimum of 14 days.
7) Probable Mechanism: unknown

3.5.1.AA Protriptyline

1) Interaction Effect: hypertension, other cardiac effects, and CNS stimulation
2) Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been reported to result in enhanced amphetamine effects from the release of norepinephrine (Beaumont, 1973; Raisfeld, 1972). A similar reaction might also occur with all drugs that have amphetamine-like effects. Acute elevations in blood pressure have been noted (Flemenbaum, 1971a). Some amphetamine-like drugs may inhibit the metabolism of TCAs, although most combinations have not been studied. When amphetamine analogs are being used to treat obesity, it should be noted that TCAs frequently lead to moderate weight gain (Russ & Ackerman, 1988). False positive urine tests for amphetamines have been reported during therapy with some TCAs (Merigian & Browning, 1993). Caution is advised when concurrent administration of amphetamine-like agents and TCAs is warranted. The patient should be closely monitored for increased cardiovascular effects (hypertension and dysrhythmias).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other sympathomimetic agents could lead to hypertension, increased cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006; Flemenbaum, 1972). Use caution if such therapy is warranted. Monitor the patient closely for hypertension and dysrhythmias.
7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission
8) Literature Reports

a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agents. Additionally, coadministration of d-amphetamine with TCAs such as desipramine or protriptyline results in sustained increases in d-amphetamine concentration in the brain (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006).

b) Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism of some tricyclic antidepressants, such as imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transdermal system, 2006).

c) Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases in blood pressure such that the hypotensive effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of combined therapy. Discontinuation of the methylphenidate usually results in the blood pressure returning to normotensive levels; reinstitution of the methylphenidate resulted in further blood pressure elevation (Flemenbaum, 1971; Flemenbaum, 1972).

d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine given for at least four weeks, were given fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical improvement. However, fenfluramine more than doubled steady-state plasma levels of desipramine (Price et al, 1990).

e) There have been claims based on uncontrolled studies that a better antidepressant response may occur with combined therapy (Garrettson et al, 1969). However, a systemic review of stimulants in the treatment of depression concluded that although uncontrolled studies were generally positive, the ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated little advantage of drug over placebo and did not appear to be as effective as the conventional antidepressants in primary depression (Satel & Nelson, 1989).

3.5.1.AB Rasagiline

1) Interaction Effect: hypertensive crisis (headache, palpitation, and neck stiffness)
2) Summary: Monoamine oxidase inhibitors should not be administered with sympathomimetic drugs such as dexmethylphenidate. Coadministration may result in hypertensive crisis, which is characterized by symptoms such as headache, palpitation, neck stiffness, nausea, and vomiting. Hypertensive crisis associated with monoamine oxidase inhibitors has been fatal (Prod Info Focalin(TM), 2001b).
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent use of monoamine oxidase inhibitors and dexmethylphenidate is contraindicated. If dexmethylphenidate is to be initiated, the monoamine oxidase inhibitor must be discontinued for a minimum of 14 days.
7) Probable Mechanism: unknown

3.5.1.AC Selegiline

1) Interaction Effect: hypertensive crisis (headache, palpitation, and neck stiffness)

2) Summary: Monoamine oxidase inhibitors should not be administered with sympathomimetic drugs such as dexmethylphenidate. Coadministration may result in hypertensive crisis, which is characterized by symptoms such as headache, palpitation, neck stiffness, nausea, and vomiting. Hypertensive crisis associated with monoamine oxidase inhibitors has been fatal (Prod Info Focalin(TM), 2001b).
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent use of monoamine oxidase inhibitors and dexmethylphenidate is contraindicated. If dexmethylphenidate is to be initiated, the monoamine oxidase inhibitor must be discontinued for a minimum of 14 days.
7) Probable Mechanism: unknown

3.5.1.AD Toloxatone
1) Interaction Effect: hypertensive crisis (headache, palpitation, and neck stiffness)
2) Summary: Monoamine oxidase inhibitors should not be administered with sympathomimetic drugs such as dexmethylphenidate. Coadministration may result in hypertensive crisis, which is characterized by symptoms such as headache, palpitation, neck stiffness, nausea, and vomiting. Hypertensive crisis associated with monoamine oxidase inhibitors has been fatal (Prod Info Focalin(TM), 2001b).
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent use of monoamine oxidase inhibitors and dexmethylphenidate is contraindicated. If dexmethylphenidate is to be initiated, the monoamine oxidase inhibitor must be discontinued for a minimum of 14 days.
7) Probable Mechanism: unknown

3.5.1.AE Tranylcypromine
1) Interaction Effect: hypertensive crisis (headache, palpitation, and neck stiffness)
2) Summary: Monoamine oxidase inhibitors should not be administered with sympathomimetic drugs such as dexmethylphenidate. Coadministration may result in hypertensive crisis, which is characterized by symptoms such as headache, palpitation, neck stiffness, nausea, and vomiting. Hypertensive crisis associated with monoamine oxidase inhibitors has been fatal (Prod Info Focalin(TM), 2001b).
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent use of monoamine oxidase inhibitors and dexmethylphenidate is contraindicated. If dexmethylphenidate is to be initiated, the monoamine oxidase inhibitor must be discontinued for a minimum of 14 days.
7) Probable Mechanism: unknown

3.5.1.AF Trimipramine
1) Interaction Effect: hypertension, other cardiac effects, and CNS stimulation
2) Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been reported to result in enhanced amphetamine effects from the release of norepinephrine (Beaumont, 1973; Raisfeld, 1972). A similar reaction might also occur with all drugs that have amphetamine-like effects. Acute elevations in blood pressure have been noted (Flemenbaum, 1971a). Some amphetamine-like drugs may inhibit the metabolism of TCAs, although most combinations have not been studied. When amphetamine analogs are being used to treat obesity, it should be noted that TCAs frequently lead to moderate weight gain (Russ & Ackerman, 1988). False positive urine tests for amphetamines have been reported during therapy with some TCAs (Merigian & Browning, 1993). Caution is advised when concurrent administration of amphetamine-like agents and TCAs is warranted. The patient should be closely monitored for increased cardiovascular effects (hypertension and dysrhythmias).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other sympathomimetic agents could lead to hypertension, increased cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006; Flemenbaum, 1972). Use caution if such therapy is warranted. Monitor the patient closely for hypertension and dysrhythmias.
7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission
8) Literature Reports
a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agents. Additionally, coadministration of d-amphetamine with TCAs such as desipramine or protriptyline results in sustained increases in d-amphetamine concentration in the brain (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006).
b) Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism

of some tricyclic antidepressants, such as imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transdermal system, 2006).
c) Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases in blood pressure such that the hypotensive effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of combined therapy. Discontinuation of the methylphenidate usually results in the blood pressure returning to normotensive levels; reinstitution of the methylphenidate resulted in further blood pressure elevation (Flemenbaum, 1971; Flemenbaum, 1972).
d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine given for at least four weeks, were given fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical improvement. However, fenfluramine more than doubled steady-state plasma levels of desipramine (Price et al, 1990).
e) There have been claims based on uncontrolled studies that a better antidepressant response may occur with combined therapy (Garrettson et al, 1969). However, a systemic review of stimulants in the treatment of depression concluded that although uncontrolled studies were generally positive, the ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated little advantage of drug over placebo and did not appear to be as effective as the conventional antidepressants in primary depression (Satel & Nelson, 1989).

3.5.1.AG Warfarin
1) Interaction Effect: an increased risk of bleeding
2) Summary: Dexmethylphenidate may inhibit the metabolism of coumarin anticoagulants, such as warfarin, potentially resulting in an increased risk of bleeding. Warfarin dosage may need to be reduced during concurrent dexmethylphenidate therapy. When initiating or discontinuing dexmethylphenidate therapy, it may be necessary to adjust the warfarin dose and monitor coagulation times (Prod Info FOCALIN(R) XR extended-release oral capsules, 2007).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Consider reducing the warfarin dose during concomitant dexmethylphenidate therapy due to an increased risk of bleeding. Adjust the dose as needed and monitor coagulation times when initiating or discontinuing dexmethylphenidate treatment (Prod Info FOCALIN(R) XR extended-release oral capsules, 2007).
7) Probable Mechanism: inhibition of warfarin metabolism

4.0 Clinical Applications

Monitoring Parameters

Patient Instructions

Place In Therapy

Mechanism of Action / Pharmacology

Therapeutic Uses

Comparative Efficacy / Evaluation With Other Therapies

4.1 Monitoring Parameters
A) Dexmethylphenidate Hydrochloride
1) Therapeutic
a) Physical Findings
1) Improvement in mental and behavioral symptoms of attention deficit hyperactivity disorder (ADHD), including inappropriate inattention, impulsivity, hyperactivity, and cognitive performance.
a) For the inattentive type of ADHD, these include lack of sustained attention, no attention to details, inability to follow through on tasks, poor listener, avoidance of tasks requiring sustained mental effort, and easily distracted.
b) For the hyperactive-impulsive type, these include fidgeting or squirming, excessive talking, leaving seat, inappropriate climbing or running, intrusiveness, and difficulty with quiet activities.
c) If symptoms do not improve within one month (including appropriate dose adjustments), the drug should be discontinued (Prod Info FOCALIN(R) oral tablets, 2007a).
2) Periodic reassessment of the need for continued dexmethylphenidate treatment (by temporarily withdrawing therapy and monitoring for recurrence of behavioral symptoms and their severity; slow dose-tapering may be indicated to prevent withdrawal symptoms) (Prod Info FOCALIN(R) oral tablets,

2007a).

2) Toxic

a) Laboratory Parameters

1) Monitor complete blood count with differential and platelets periodically during extended therapy (Prod Info FOCALIN(R) oral tablets, 2007a).

b) Physical Findings

1) The American Academy of Pediatrics (AAP) does not recommend the routine use of electrocardiograms (ECGS) or routine subspecialty cardiology evaluations (which were previously recommended by the American Heart Association (AHA) scientific statement to detect cardiac conditions that might place the child at risk for sudden cardiac death) before initiating stimulant therapy to treat attention-deficit/hyperactivity disorder ADHD in most children. The APA cited specific reasons for changing the recommendation including: lack of evidence establishing a relationship between stimulant drugs used to treat ADHD and sudden cardiac death (SCD), the frequency of sudden unexpected deaths among patients taking stimulant drugs is not higher than that in the general population of children, and lack of cost-effective analysis to support ECG screening or special evaluation by pediatric cardiologist (Perrin et al, 2008).

2) Based on the American Academy of Pediatrics (AAP) and the American Heart Association (AHA) consensus statements, the following cardiac monitoring recommendations have been established to assist clinicians in the evaluation of children treated with stimulant drugs, including dexmethylphenidate, for ADHD (Perrin et al, 2008; Vetter et al, 2008):

- Conduct a thorough examination prior to initiating dexmethylphenidate therapy for a diagnosis of ADHD. Special attention should be given to symptoms indicative of a cardiac condition, including palpitations, near syncope, or syncope.
- Obtain a complete family and patient history for conditions associated with SCD, and determine current use of any other prescription or over-the-counter medications.
- Conduct a complete physical evaluation of the patient for hypertension, cardiac murmurs, physical findings associated with Marfan syndrome, and signs of irregular cardiac rhythms.
- Perform further evaluation if family history, patient history or physical exam is suggestive of cardiac disease during initial visit or at follow up visits, and if indicated, consult pediatric cardiologist .
- Continue to assess the patient for cardiac symptoms and any changes in family history at follow up visits.
- Blood pressure and heart rate should be evaluated at baseline, during routine follow-up within 1 to 3 months, and at follow up visits every 6 to 12 months. Increases in blood pressure and heart rate have been reported with stimulant use.

3) Assess growth determinations (body weight and height) periodically (Prod Info FOCALIN(R) oral tablets, 2007a).

4) Determine the amount and frequency of medication during prolonged treatment (for detection of potential tolerance/dependence).

4.2 Patient Instructions

A) Dexmethylphenidate (By mouth)

Dexmethylphenidate

Treats attention deficit hyperactivity disorder (ADHD).

When This Medicine Should Not Be Used:
You should not use this medicine if you or your child have had an allergic reaction to dexmethylphenidate. You should not use this medicine if you have glaucoma, or if you are anxious, tense, or agitated most of the time. You should not use this medicine if you have muscle tics or Tourette's syndrome, a condition that causes you to have muscle twitches or to makes sounds you are not able to control. Do not use this medicine if you have taken an MAO inhibitor (Eldepryl®, Marplan®, Nardil®, Parnate®) within the past 14 days. This medicine should not be given to a child under 6 years of age unless your doctor tells you otherwise.

How to Use This Medicine:
Tablet, Long Acting Capsule

Your doctor will tell you how much of this medicine to use and how often. Do not use more medicine or use it more often than your doctor tells you to.
This medicine should come with a Medication Guide. Read and follow these instructions carefully. Ask your doctor or pharmacist if you have any questions. Ask your pharmacist for the Medication Guide if you do not have one. Your doctor might ask you to sign some forms to show that you understand this information.
You may take this medicine with or without food.
This medicine is usually given once daily. Because dexmethylphenidate can cause a loss of appetite, it is best to take the medicine after eating or just before your morning meal, unless your doctor tells you otherwise.
Swallow the extended-release capsule whole. Do not crush, break, or chew it.
If you cannot swallow the extended-release capsule, you may open it and pour the medicine into a small amount of soft food such as pudding, yogurt, or applesauce. Stir this mixture well and swallow it without

chewing.
Always take this medicine with a full glass of liquid (water, milk, or juice).

If a Dose is Missed:
If you miss a dose or forget to use your medicine, use it as soon as you can. If it is almost time for your next dose, wait until then to use the medicine and skip the missed dose. Do not use extra medicine to make up for a missed dose.

How to Store and Dispose of This Medicine:
Store the medicine in a closed container at room temperature, away from heat, moisture, and direct light.
Ask your pharmacist, doctor, or health caregiver about the best way to dispose of any leftover medicine after you have finished your treatment. You will also need to throw away old medicine after the expiration date has passed.
Keep all medicine away from children and never share your medicine with anyone.

Drugs and Foods to Avoid:
Ask your doctor or pharmacist before using any other medicine, including over-the-counter medicines, vitamins, and herbal products.
Make sure your doctor knows if you are also using blood pressure medicines, blood thinners (such as Coumadin®, warfarin), clonidine (Catapres®, Clorpres®, Combipres®), or medicines to treat seizures (such as Dilantin®, Luminal®, Mysoline®). Tell your doctor if you use medicines for depression (such as amitriptyline, imipramine, trazodone, Celexa®, Effexor®, Luvox®, Norpramin®, Paxil®, Prozac®, Serzone®, Vivactil®, or Zoloft®).
Tell your doctor if you use cold or allergy medicines, or antacids or stomach acid reducers (such as Axid®, Prilosec®, Tagamet®, or Zantac®).

Warnings While Using This Medicine:
Make sure your doctor knows if you are pregnant, planning to become pregnant, or breastfeeding, or if you or your child have kidney problems, liver problems, heart disease, heart rhythm problems, or high blood pressure. Your doctor should know if you or your child have epilepsy, a history of seizures, depression or mental illness, or drug or alcohol problems. Also tell your doctor if you or anyone in your family has tried to commit suicide.
This medicine may be habit-forming. If you feel that the medicine is not working as well, do not use more than your prescribed dose. Call your doctor for instructions.
This medicine may make you dizzy or drowsy. Avoid driving, using machines, or doing anything else that could be dangerous if you are not alert.
This medicine may cause slow growth. If your child is using this medicine, the doctor will need to keep track of your child's height and weight to make sure that your child is growing properly.
Your doctor will need to check your progress at regular visits while you are using this medicine. Be sure to keep all appointments.

Possible Side Effects While Using This Medicine:
Call your doctor right away if you notice any of these side effects:
Allergic reaction: Itching or hives, swelling in your face or hands, swelling or tingling in your mouth or throat, chest tightness, trouble breathing.
Blurred vision, trouble seeing.
Chest pain or shortness of breath.
Fast, pounding, or irregular heartbeat.
Lightheadedness, dizziness, or fainting.
Mood or mental changes, confusion, or unusual behavior.
Seizures.
Tremors or shaking.
Uncontrollable muscle movements or twitching.
Unusual bleeding, bruising, or weakness.
Vomiting, agitation, confusion, sweating, fever.

If you notice these less serious side effects, talk with your doctor:
Dry mouth or nose.
Feeling restless or nervous.
Headache.
Nausea, loss of appetite, or stomach pain.
Trouble sleeping.

If you notice other side effects that you think are caused by this medicine, tell your doctor.

4.3 Place In Therapy

A) SUMMARY

1) Clinical data for dexmethylphenidate at present do not support its use over methylphenidate in ADHD. It is not

recommended for the hospital formulary.

B) ATTENTION-DEFICIT HYPERACTIVITY DISORDER

1) Pharmacologic therapy is indicated as an adjunct to other measures (eg, counseling) in patients with attention-deficit hyperactivity disorder (ADHD). The mainstays of drug therapy are the stimulants methylphenidate, dextroamphetamine, and pemoline; these agents are similarly effective, although pemoline is used less frequently initially due to its slow onset. In patients not responding well to stimulants, bupropion, desipramine, clonidine, or MAO inhibitors may find usefulness, although adverse effects may prove problematic.

2) Dexmethylphenidate, the d-enantiomer of methylphenidate, is indicated for the treatment of ADHD in patients aged 6 years and older. Two placebo-controlled studies in patients meeting DSM-IV criteria for ADHD demonstrated dexmethylphenidate's effectiveness in the treatment of ADHD in patients 6 years of age and older.

3) A slightly longer duration of action has been reported for dexmethylphenidate compared to regular-release methylphenidate, although this appears to be small and is probably of no clinical relevance; both agents are recommended twice daily at similar intervals. Extended-release methylphenidate is used commonly in children to eliminate the need for methylphenidate dosing at school, and has a duration exceeding that of methylphenidate and dexmethylphenidate by at least two hours. Both regular-release and extended-release methylphenidate products are available generically at a lower cost than dexmethylphenidate.

4.4 Mechanism of Action / Pharmacology

A) Dexmethylphenidate Hydrochloride

1) MECHANISM OF ACTION

a) Dexmethylphenidate is the d-enantiomer (also known as d-threo-enantiomer) of methylphenidate (Ritalin (R)), the latter of which exists as the racemate (d,l-enantiomers in a 1:1 ratio) (Anon, 1999; Prod Info Focalin™, 2001a). Dexmethylphenidate accounts for most or all clinical effects of racemic methylphenidate (Anon, 2001; Prod Info Focalin™, 2001a).

b) Dexmethylphenidate is claimed to have efficacy similar to or greater than methylphenidate in attention-deficit hyperactivity disorder (ADHD), with a lower propensity for adverse effects; as it is one of the quantitatively equal enantiomers, it can be given in half the dose of the racemic compound, and this is also claimed to be an advantage (Anon, 2001a; Anon, 2001; Anon, 2000).

c) The mechanism of racemic methylphenidate in ADHD has not been fully elucidated. Both methylphenidate and dexmethylphenidate appear to inhibit reuptake of dopamine and norepinephrine into presynaptic neurons (Prod Info Focalin™, 2001a), increasing availability of these neurotransmitters in the extraneuronal space.

4.5 Therapeutic Uses

4.5.A Dexmethylphenidate Hydrochloride

4.5.A.1 Attention deficit hyperactivity disorder

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes (extended-release only); Pediatric, yes (age 6 yr and older)
Efficacy: Adult, Evidence favors efficacy; Pediatric, Effective
Recommendation: Adult, Class IIa; Pediatric, Class IIa
Strength of Evidence: Adult, Category B; Pediatric, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Extended-release dexmethylphenidate was superior to placebo for the treatment of attention deficit/hyperactivity disorder (ADHD) in children (Silva et al, 2008; Brams et al, 2008; Prod Info FOCALIN XR(R) extended-release oral capsules, 2008).

Fixed-dose dexmethylphenidate extended-release (ER) was superior to placebo for the treatment of attention-deficit/hyperactivity disorder (ADHD) in adults in a 5-week, randomized double-blind, placebo-controlled trial (n=218) (Spencer et al, 2007).

Dexmethylphenidate extended-release (ER) was superior to placebo for the treatment of pediatric ADHD in a 7-week , randomized, double-blind, placebo-controlled study (n=97) (Greenhill et al, 2006).

Results of two unpublished studies suggest the efficacy of oral immediate-release dexmethylphenidate in children and adolescents with ADHD (Prod Info Focalin(TM), 2001)

The efficacy of dexmethylphenidate is similar to that of racemic methylphenidate

c) Adult:

1) Evaluated Data

a) There are no studies evaluating the efficacy of immediate-release dexmethylphenidate in adults with attention-deficit hyperactivity disorder (ADHD).

2) Clinical Study Summaries

a) In an unpublished study, dexmethylphenidate extended-release was found to be more effective than placebo for the treatment of adults (ages 18 to 60) who met DSM-IV criteria for attention-deficit hyperactivity disorder (ADHD). In a randomized, double-blind, parallel-group study, patients (n=221) were randomized to either a fixed dose (20, 30, or 40 milligrams (mg)/day) of dexmethylphenidate extended-release or placebo once daily for 5 weeks. Treatment was initiated

at 10 mg/day and was titrated in increments of 10 mg weekly to the assigned fixed dose. Efficacy was measured by comparing the mean change in signs and symptoms of ADHD from baseline to endpoint using an intent-to-treat analysis of the investigator-administered DSM-IV ADHD Disorder Rating Scale. All 3 doses were found to be superior to placebo, with no apparent advantage with increasing dose (Prod Info FOCALIN(TM) XR, 2005).

3) Extended-Release

a) Fixed-dose dexmethylphenidate extended-release (ER) was superior to placebo for the treatment of attention-deficit/hyperactivity disorder (ADHD) in adults in a 5-week, multicenter, randomized double-blind, parallel-group, placebo-controlled trial (n=218). Adult patients aged 18 to 60 years (yr) (mean, 38.7 years) who met the following criteria were included: a DSM-IV diagnosis of ADHD of any subtype with childhood onset of symptoms, a total score of at least 24 at screening and at baseline on the DSM-IV ADHD rating scale (RS), and a Global Assessment of Functioning (GAF) score of 60 or less. All patients were required to discontinue all psychotropic medications within 1 to 4 weeks prior to the screening visit. Patients were equally randomized to dexmethylphenidate ER 20 milligrams (mg) (n=58), 30 mg (n=55) or 40 mg (n=55) daily or to placebo (n=53) for 5 weeks. The primary outcome was the change from baseline to final visit in the DSM-IV ADHD-RS total score. Analysis was performed on the modified intent-to-treat population, defined as all randomized patients who received at least 1 dose of study medication and had at least 1 pre- and post randomization assessment for change in DSM-IV ADHD-RS total score. The analysis revealed that all doses of dexmethylphenidate ER were superior to placebo for improvement of DSM-IV ADHD-RS total score. The mean change from baseline to final visit in DSM-IV ADHD-RS total score was 13.7 (from 36.8 to 23.1; p=0.006) for dexmethylphenidate ER 20 mg, 13.4 (from 36.9 to 23.5; p=0.012) for 30 mg, 16.9 (36.9 to 20; p=0.001) for 40 mg, and 7.9 (37.5 to 29.6) for placebo. The most common adverse effects were headache (31.5% vs 18.9%), decreased appetite (18.2% vs 11.3%), insomnia (16.4% vs 11.3%), dry mouth (15.8% vs 3.8%; p less than 0.05), and jitteriness (12.1% vs 1.9%; p less than 0.05) in the consolidated dexmethylphenidate ER groups compared with the placebo group. The authors note limitations of short study duration and insufficient power for direct comparison between doses (Spencer et al, 2007).

d) Pediatric:

1) Evaluated Data

a) No studies with dexmethylphenidate immediate-release have been published. In studies sponsored by the manufacturer, dexmethylphenidate 5 to 20 milligrams (mg) daily was reported statistically superior to placebo in children/adolescents (6 to 17 years) with attention-deficit hyperactivity disorder (ADHD), based on various behavior scales (Anon, 1999; Anon, 1999a; Anon, 2001; Prod Info Focalin(TM), 2001). One of these studies employed short-term (2-week) drug withdrawal following open-label treatment, where failure rates were lower in children continuing dexmethylphenidate (about 20%) compared to those given placebo (63%)(Prod Info Focalin(TM), 2001).

b) However, data released for these studies are incomplete, and the actual number of trials conducted is unclear. Pertinent clinical details not provided include demographic data (importantly, baseline severity of ADHD in each group), doses associated with response (or mean or maximum effective doses), specific statistical-analysis data (or tests used), and details of evaluation methods.

c) Dexmethylphenidate has been compared with methylphenidate in at least one of these studies, although comparative efficacy results were not reported. Press releases from the manufacturer regarding these comparisons are unclear and confusing (Anon, 1999; Anon, 2001; Anon, 1999b). Overall, the two drugs appear similarly effective, with a similar adverse-effect profile. Although dexmethylphenidate can be given in half the dose of methylphenidate, this is not a clinical advantage.

2) Immediate Release

a) One unpublished, placebo-controlled study from the package insert involving 132 patients with ADHD (6 to 17 years) reported significantly greater improvement of symptom scores from baseline on the Swanson, Noland, and Pelham (SNAP)-ADHD rating scale with dexmethylphenidate 5 to 20 mg daily (two divided doses, 3.5 to 5.5 hours apart) than with placebo (mean change, -0.7 versus -0.2). This study assessed improvements over 4 weeks. Patients included had all subtypes of ADHD (combined type, inattentive type, hyperactive-impulsive type) (Prod Info Focalin(TM), 2001). This trial directly compared dexmethylphenidate to racemic methylphenidate (10 to 40 mg daily), although no results for methylphenidate were provided.

3) Extended-Release

a) A randomized, double-blind, placebo-controlled, crossover study revealed extended-release dexmethylphenidate was superior to placebo for the treatment of attention deficit/hyperactivity disorder (ADHD) in children (n=68). Children aged 6 to 12 years (mean 9.5 years; 66.2% male) who met Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV) criteria for any type of ADHD, who were clinically and behaviorally stable and without medication changes for at least 2 weeks were randomized to receive dexmethylphenidate extended release (d-MPH-ER) 20 milligram (mg) capsules daily for 7 days or to placebo, with treatment crossover, beginning on day 8 for an additional 7 days. Efficacy was assessed as change in the Swanson, Kotkin, Agler, M-Flynn and Pelham rating scale (SKAMP)-combined score from predose to time points 0.5, 1, 3, 4,

5, 7, 9, 10, 11 and 12 hours (hr), and math test performance in a laboratory classroom setting, with the SKAMP scale defined as 13 items of measurement that provides individual and combined scores on the core ADHD symptoms of attention and deportment. The intent-to-treat analysis revealed that d-MPH-ER was significantly superior to placebo in improvement of the SKAMP-combined score from predose to 0.5 hr postdose (adjusted mean change of score, -2.242 versus 3.493; p=0.001) and at all other time points (p less than or equal to 0.001). D-MPH-ER was associated with 8.6% improvement in SKAMP-combined score compared to 66.7% worsening with placebo. Change from predose in individual SKAMP attention scores (p less than or equal to 0.001) and deportment scores (p=0.003 or less) were significantly improved at all time points. Math test performance scores were significantly improved at all postdose time points in attempted test questions (p less than 0.001) and correctly-answered test questions (p less than 0.001). The most common adverse effect was upper respiratory tract infection, not otherwise specified (d-MPH-ER, 4.4% vs placebo, 7.4%). One serious adverse effect of 3+ proteinuria was reported during the d-MPH-ER phase, which was not attributed to study medication and resolved without sequelae (Silva et al, 2008).

b) A randomized, double-blind, placebo-controlled, crossover study revealed that extended-release dexmethylphenidate was superior to placebo for the treatment of attention deficit/hyperactivity disorder (ADHD) in children (n=86); however, the study was underpowered. Children (mean age 9.5 years (yr), range 6 to 12 yr, 61.6% male) diagnosed with any type of ADHD using the DSM-IV criteria, who were clinically and behaviorally stable and without medication changes for at least 2 weeks were randomized to receive dexmethylphenidate extended release (d-MPH-ER) 20 milligram (mg) capsules daily for 7 days or to placebo, with treatment crossover, beginning on day 8 for an additional 7 days. The primary outcome was change in the Swanson, Kotkin, Agler, M-Flynn and Pelham rating scale (SKAMP)-combined score from predose to 0.5 hours (hr) postdose, during an 8-hr laboratory classroom setting, with the SKAMP scale defined as 13 items of measurement that provides individual and combined scores on the core ADHD symptoms of attention and deportment. The intent-to-treat analysis revealed d-MPH-ER was significantly superior to placebo in improvement of the SKAMP-combined score from predose to 0.5 hr postdose with an adjusted mean change score of -0.969 vs 3.336 (p less than 0.001), and at all other postdose time points (1, 2, 4, 6, 8 hr) (p less than 0.001). Change in individual SKAMP attention and deportment scores were significantly improved at all time points (p less than or equal to 0.001). In addition, change from baseline in the Conners' ADHD/DSM-IV scale for parents (CADS-P), which assesses the childs' behavior with and without treatment, was significantly improved with d-MPH-ER compared with placebo (adjusted least-square mean -16.38 vs -4.62; difference, -11.76; 95% confidence interval (CI), -15.36 to -8.16; p less than 0.001). Dexmethylphenidate was associated with higher incidence of headache (3.5% vs 2.3%) compared with placebo (Brams et al, 2008).

c) Dexmethylphenidate extended-release (ER) was superior to placebo for the treatment of pediatric ADHD in a 7-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group, two-phase study (n=97). Pediatric patients aged 6 to 17 years (yr) who met DSM-IV criteria for ADHD of any type were eligible. All patients must be functioning at an age-appropriate academic level and the use of psychotropic medications or initiation of psychotropic medications within the past 3 months was not allowed. Any current treatment for ADHD was discontinued at least 7 days before baseline during the pre-randomization phase (up to 2 weeks). At the end of the pre-randomization phase, patients were randomized to receive either dexmethylphenidate ER 5 mg (n=52) or placebo (n=45) daily. In the double-blind treatment-phase, patients proceeded with dose titration to 5 or 10 mg/day for week 2; 5, 10 or 15 mg/day for week 3; then 5, 10, 15 or 20 mg/day for week 4. For treatment weeks 5 to 7, doses were titrated and maintained at optimal doses of 5, 10, 15, 20 or 30 mg/day. The mean final dexmethylphenidate ER dose was 24 +/- 7.1 mg/day. The primary outcome was the change from baseline to final visit in the Conners ADHD/DSM-IV Scale-Teacher version (CADS-T) total subscale score. Analysis was performed on the modified intent-to-treat population, defined as patients who received at least 1 dose of study medication and had at least 1 postbaseline CADS-T measurement. The analysis revealed that dexmethylphenidate ER was significantly superior to placebo in improvement from baseline to final visit in the CADS-T total score. The adjusted mean change in CADS-T total score from baseline to final visit was 16.3 in the dexmethylphenidate ER group compared with 5.7 in the placebo group (p less than 0.001). Similarly, dexmethylphenidate ER was superior to placebo in secondary outcome measures of mean change from baseline in the CADS-T Inattentive subscale score (8.1 vs 3.3; p=0.001) and in the Hyperactive-Impulsive subscale score (8.2 vs 2.5; p less than or equal to 0.001), respectively. The most common adverse effects attributed to study medication were decreased appetite (28.3% vs 6.4%), headache (24.5% vs 10.63%), nausea (11.3 vs 6.4%) and insomnia (7.5% vs 6.4%) in the dexmethylphenidate ER and placebo groups, respectively. No serious adverse events were reported. The authors note study limitations of short study duration and small sample size (Greenhill et al, 2006).

4.6 Comparative Efficacy / Evaluation With Other Therapies

4.6.A Methylphenidate

4.6.A.1 Attention deficit hyperactivity disorder

a) No comparisons with methylphenidate have been published, and data released by the manufacturer have not emphasized comparative efficacy, although this data is available. In a completed 4- week, placebo-controlled study described in the package insert (Prod Info Focalin(TM), 2001d), dexmethylphenidate 5 to 20 milligrams (mg) daily was compared to methylphenidate 10 to 40 mg daily (each in two divided doses) in patients with ADHD (n=132, 6 to 17 years of age). Patients included had all subtypes of ADHD (combined type, inattentive type, hyperactive-impulsive type). Dexmethylphenidate was reported to provide significantly greater improvement of symptom scores from baseline on the Swanson, Noland, and Pelham (SNAP)-ADHD rating scale compared to placebo (mean change, -0.7 versus -0.2). Although methylphenidate was the comparator, no results for methylphenidate were provided.

b) In manufacturer releases, apparently referring to the same package insert trial described above, the efficacy and safety of dexmethylphenidate were reported similar to methylphenidate (Anon, 2001)(Anon, 2001a). Earlier releases also did not indicate a significant difference in efficacy between the two drugs (Anon, 1999; Anon, 1999a), although they were carefully prepared to avoid this conclusion.

c) One manufacturer release suggested a longer duration of action of dexmethylphenidate in ADHD; in this study, control of symptoms with dexmethylphenidate was reportedly seen at all time points, but there was failure of methylphenidate to control symptoms at the last measurements (5.5 to 6.5 hours postdose) (Anon, 1999). However, the duration of action of methylphenidate was not given, precluding assessment of the duration of methylphenidate relative to dexmethylphenidate. The duration of dexmethylphenidate in this trial was similar to that of methylphenidate in other studies (4 to 6 hours), suggesting this difference is small. No study has provided comparative improvements in symptom scores from baseline, or statistical comparisons at all time points.

d) Available studies have not indicated a more favorable adverse- effect profile for dexmethylphenidate compared to methylphenidate (Anon, 1999a); (Anon, 2001).

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Last Modified: May 21, 2009

DRUGDEX® Evaluations

ZIPRASIDONE

0.0 Overview

1) Class

a) This drug is a member of the following class(es):
Antipsychotic
Benzisothiazoyl

2) Dosing Information

a) Ziprasidone Hydrochloride

1) Adult

a) Bipolar I disorder, acute manic or mixed episodes

1) day 1, 40 mg twice daily with food; day 2, 60 or 80 mg twice daily; then adjust to 40 to 80 mg twice daily (Prod Info GEODON(R) oral capsules, IM injection, 2007)

b) Schizophrenia

1) initial, 20 mg ORALLY twice a day with food; may increase dosage every 2 days up to 80 mg twice a day (Prod Info GEODON(R) oral capsules, IM injection, 2007)

2) maintenance, 20 to 80 mg ORALLY twice a day (MAX recommended dose is 80 mg twice a day); to ensure use of the lowest effective dose, observe for improvement for several weeks before upward dosage adjustment (Prod Info GEODON(R) oral capsules, IM injection, 2007)

[redacted] capsules, IM injection, 2007)

b) Ziprasidone Mesylate

1) Adult

a) Agitation, acute - Schizophrenia

1) 10 mg IM every 2 hr (MAX dose 40 mg/day) OR 20 mg IM every 4 hr (MAX dose 40 mg/day); oral ziprasidone should replace IM administration as soon as possible; IM administration for more than 3 consecutive days has not been studied (Prod Info GEODON(R) oral capsules, IM injection, 2007)

2) Pediatric

a) safety and effectiveness in pediatric patients have not been established (Prod Info GEODON(R) oral capsules, IM injection, 2007)

3) Contraindications

a) Ziprasidone Hydrochloride

1) cardiac arrhythmias, history (Prod Info GEODON(R) oral capsules, IM injection, 2008)

2) concomitant administration with arsenic trioxide, chlorpromazine, dofetilide, dolasetron mesylate, droperidol, gatifloxacin, halofantrine, levomethadyl acetate, mefloquine, mesoridazine, moxifloxacin, pentamidine, pimozide, probucol, quinidine, sotalol, sparfloxacin, tacrolimus, thioridazine, class Ia and III antiarrhythmics, and other drugs that cause QT prolongation; possible additive QT prolongation effect (Prod Info GEODON(R) oral capsules, IM injection, 2008)

3) heart failure, uncompensated (Prod Info GEODON(R) oral capsules, IM injection, 2008)

4) hypersensitivity to ziprasidone (Prod Info GEODON(R) oral capsules, IM injection, 2008)

5) myocardial infarction, acute and recent (Prod Info GEODON(R) oral capsules, IM injection, 2008)

6) QT prolongation history including congenital long QT syndrome (Prod Info GEODON(R) oral capsules, IM injection, 2008)

b) Ziprasidone Mesylate

1) cardiac arrhythmias, history (Prod Info GEODON(R) oral capsules, IM injection, 2007)

2) concomitant use with arsenic trioxide, chlorpromazine, dofetilide, dolasetron mesylate, droperidol, gatifloxacin, halofantrine, levomethadyl acetate, mefloquine, mesoridazine, moxifloxacin, pentamidine, pimozide, probucol, quinidine, sotalol, sparfloxacin, tacrolimus, thioridazine, Class Ia and III antiarrhythmics, and other drugs that cause QT prolongation; possible additive QT prolongation effect (Prod Info GEODON(R) oral capsules, IM injection, 2008)

3) heart failure, uncompensated (Prod Info GEODON(R) oral capsules, IM injection, 2008)

4) hypersensitivity to ziprasidone (Prod Info GEODON(R) oral capsules, IM injection, 2008)

5) myocardial infarction, acute and recent (Prod Info GEODON(R) oral capsules, IM injection, 2008)

6) QT prolongation, history including congenital long QT syndrome (Prod Info GEODON(R) oral capsules, IM injection, 2008)

4) Serious Adverse Effects

a) Ziprasidone Hydrochloride

1) Death

2) Diabetes mellitus

3) Hyperglycemia

4) Neuroleptic malignant syndrome

5) Priapism

6) Prolonged QT interval
7) Seizure
8) Syncope
9) Tardive dyskinesia
10) Torsades de pointes

b) Ziprasidone Mesylate
1) Death
2) Diabetes mellitus
3) Hyperglycemia
4) Priapism
5) Prolonged QT interval
6) Seizure
7) Syncope
8) Tardive dyskinesia
9) Torsades de pointes

5) Clinical Applications
a) Ziprasidone Hydrochloride
1) FDA Approved Indications
a) Bipolar I disorder, acute manic or mixed episodes
b) Schizophrenia

b) Ziprasidone Mesylate
1) FDA Approved Indications
a) Agitation, acute - Schizophrenia

1.0 Dosing Information

Drug Properties

Storage and Stability

Adult Dosage

1.1 Drug Properties

A) Information on specific products and dosage forms can be obtained by referring to the Tradename List (Product Index)

B) Synonyms
Ziprasidone
Ziprasidone HCl
Ziprasidone Hydrochloride
Ziprasidone Mesylate

C) Physicochemical Properties
1) Molecular Weight
a) 467.42(Prod Info Geodon™, 2001)

1.2 Storage and Stability

A) Ziprasidone Hydrochloride
1) Preparation
a) Oral route
1) Oral ziprasidone hydrochloride capsules should be taken with food (Prod Info GEODON(R) oral capsules, IM injection, 2007).

B) Ziprasidone Mesylate
1) Preparation
a) Intramuscular route
1) Preparation
a) Reconstitute 20 milligram (mg) ziprasidone mesylate vials with 1.2 milliliters (mL) of sterile water for injection. Shake vigorously until all drug is dissolved. Reconstituted solution contains 20 mg/mL, and any unused portion should be discarded (Prod Info GEODON(R) oral capsules, IM injection, 2007).
2) Administration
a) Ziprasidone mesylate injection should only be administered by intramuscular injection (IM) (Prod Info GEODON(R) oral capsules, IM injection, 2007).

C) Ziprasidone Hydrochloride
1) Oral route
a) Capsule
1) Ziprasidone hydrochloride capsules should be stored at 25 degrees Celsius (77 degrees

Fahrenheit); excursions permitted between 15 and 30 degrees Celsius (59 to 86 degrees Fahrenheit) (Prod Info GEODON(R) oral capsules, IM injection, 2007).

D) Ziprasidone Mesylate

1) Intramuscular route

a) Powder for Solution

1) Ziprasidone mesylate for injection, in dry form, should be protected from light and stored at 25 degrees Celsius (77 degrees Fahrenheit); excursions permitted between 15 and 30 degrees Celsius (59 to 86 degrees Fahrenheit). The reconstituted solution is stable for up to 7 days if refrigerated (2 to 8 degrees Celsius (36 to 46 degrees Fahrenheit)) or for up to 24 hours between 15 and 30 degrees Celsius (59 to 86 degrees Fahrenheit) (Prod Info GEODON(R) oral capsules, IM injection, 2007).

1.3 Adult Dosage

Normal Dosage

Dosage in Renal Failure

Dosage in Hepatic Insufficiency

Dosage in Geriatric Patients

1.3.1 Normal Dosage

Ziprasidone Hydrochloride

Ziprasidone Mesylate

1.3.1.A Ziprasidone Hydrochloride

1.3.1.A.1 Oral route

Bipolar I disorder, acute manic or mixed episodes

Schizophrenia

1.3.1.A.1.a Bipolar I disorder, acute manic or mixed episodes

1) For bipolar mania, the recommended initial dose is 40 milligrams twice daily with food. On the second day of treatment, the dose should be increased to 60 or 80 milligrams twice daily and thereafter adjusted according to tolerance and efficacy within the range of 40 to 80 milligrams twice daily. There are no recommendations for maintenance treatment (Prod Info GEODON(R) oral capsules, IM injection, 2007).

1.3.1.A.1.b Schizophrenia

1) For schizophrenia the initial daily dose is 20 milligrams (mg) twice daily with food. In some patients daily dosage may be adjusted up to 80 mg twice daily. Adjustments, if indicated, should occur at intervals of not less than 2 days. Efficacy in short-term clinical trials occurred with dosages between 20 to 100 mg twice daily. Initial dosages above 80 mg twice daily are not recommended and the safety of dosages above 100 mg twice daily have not been evaluated. To ensure the lowest effective dose, patients should be observed for improvement for several weeks before upward dosage adjustment (Prod Info GEODON(R) oral capsules, IM injection, 2007).

1.3.1.B Ziprasidone Mesylate

1.3.1.B.1 Intramuscular route

1.3.1.B.1.a Agitation, acute - Schizophrenia

1) For acute agitation in schizophrenia the recommended intramuscular dose of ziprasidone mesylate is 10 to 20 milligrams (mg) as needed to a maximum daily dose of 40 mg. The 10 mg dose may be given every 2 hours and 20 mg dose may be given every 4 hours (maximum dose=40 mg/day). Intramuscular dosing of ziprasidone for more than 3 days has not been studied. If long-

term therapy is indicated, oral ziprasidone should replace intramuscular administration as soon as possible (Prod Info GEODON(R) oral capsules, IM injection, 2007).
2) Ziprasidone 10 milligrams (mg) intramuscularly (IM) produced a rapid reduction in symptoms of acute agitation and was significantly more effective (p less than 0.01) compared to a 2 mg IM dose up to 4 hours after the first injection (Lesem et al, 2001).

1.3.2 Dosage in Renal Failure
A) Ziprasidone Hydrochloride
1) No dosage adjustment should be necessary for mild-to-moderate renal impairment. No clinically significant effect on oral ziprasidone pharmacokinetics was found in these patients (Prod Info GEODON(R) oral capsules, IM injection, 2007; Aweeka et al, 2000).
B) Ziprasidone Mesylate
1) Ziprasidone mesylate for injection should be used with caution in patients with impaired renal function as the injection contains a cyclodextrin sodium excipient that is eliminated by renal filtration (Prod Info GEODON(R) oral capsules, IM injection, 2007).

1.3.3 Dosage in Hepatic Insufficiency
A) Ziprasidone Hydrochloride
1) No dosage adjustment is necessary for mild-to-moderate hepatic impairment (chronic and stable, Child-Pugh classification A or B); the pharmacokinetics of ziprasidone were not significantly different in subjects with mild-to-moderate liver disease (Prod Info GEODON(R) oral capsules, IM injection, 2007; Everson et al, 2000).

1.3.4 Dosage in Geriatric Patients
A) Ziprasidone Hydrochloride
1) No dosage adjustment is thought to be necessary for elderly patients; no clinically significant difference in ziprasidone pharmacokinetics was found between healthy young and elderly volunteers (Prod Info GEODON(R) oral capsules, IM injection, 2007; Wilner et al, 2000).
B) Ziprasidone Mesylate
1) Intramuscular ziprasidone mesylate has not been systematically evaluated in elderly patients. Dosage adjustment is not necessary in the elderly for oral ziprasidone hydrochloride; no clinically significant difference in pharmacokinetics was found between healthy young and elderly volunteers (Prod Info GEODON(R) oral capsules, IM injection, 2007).

2.0 Pharmacokinetics

Onset and Duration

Drug Concentration Levels

ADME

2.1 Onset and Duration
A) Onset
1) Peak Response
a) SCHIZOPHRENIA, ORAL: 4 weeks (Harrigan et al, 1996).

2.2 Drug Concentration Levels
A) Time to Peak Concentration
1) ORAL: 4 to 5 hours (Miceli et al, 2000a; Ereshefsky, 1996; Miceli et al, 1995).
a) Fed, 4.5 hours; fasted, 3.6 hours (Hamelin et al, 1998).
2) INTRAMUSCULAR: 60 minutes (Prod Info Geodon(R), 2002ae).
B) Area Under the Curve
1) 627.2 ng x hr/mL fed; 371.0 ng x hr/mL fasted (Hamelin et al, 1998).
a) Oral, fed, multiple-dose: 109.8 to 1027.9 ng x hr/mL (10 to 120 mg/day) (Miceli et al, 2000a).
b) Steady-state pharmacokinetics of ziprasidone did not differ between genders (Caccia, 2000).

2.3 ADME

Absorption

Distribution

Metabolism

Excretion

Elimination Half-life

Extracorporeal Elimination

2.3.1 Absorption

A) Bioavailability
- **1)** ORAL: 60% (Ereshefsky, 1996; Miceli et al, 1995).
- **2)** INTRAMUSCULAR: 100% (Prod Info Geodon(R), 2002ae).

B) Effects of Food
- **1)** increased bioavailability (Ereshefsky, 1996; Miceli et al, 1995).
  - **a)** Dosing concurrent with high-fat meals increases systemic exposure to the drug, including area under the time-concentration curve, maximum concentration, and time to maximum concentration, while decreasing half-life (Caccia, 2000; Hamelin et al, 1998).

2.3.2 Distribution

A) Distribution Sites
- **1)** Protein Binding
  - **a)** Greater than 99% (Prod Info Geodon(R), 2002ae; Aweeka et al, 2000a; Everson et al, 2000a; Ereshefsky, 1996).

B) Distribution Kinetics
- **1)** Volume of Distribution
  - **a)** 1.5 L/kg (Prod Info Geodon(R), 2002ae).

2.3.3 Metabolism

A) Metabolism Sites and Kinetics
- **1)** LIVER, (Prod Info Geodon(R), 2002ae; Ereshefsky, 1996).
  - **a)** CYP3A4 is the predominant isoenzyme involved in ZIPRASIDONE metabolism (Prakash et al, 2000; Caccia, 2000).
  - **b)** ZIPRASIDONE does not cause clinically significant inhibition of CYP2D6 (Wilner et al, 2000a; Prakash et al, 2000).

B) Metabolites
- **1)** Metabolites inactive at 5HT-2A/dopamine D2 receptors (Ereshefsky, 1996).
- **2)** Ziprasidone sulfoxide (major) (Prod Info Geodon(R), 2002ae; Prakash et al, 2000).
- **3)** Benzisothiazole sulphoxide (Prod Info Geodon(R), 2002ae).
- **4)** Benzisothiazole sulphone (Prod Info Geodon(R), 2002ae).
- **5)** S-methyldihydroziprasidone (Prod Info Geodon(R), 2002ae).
- **6)** Ziprasidone sulfone (Prakash et al, 2000).
- **7)** Oxindole acetic acid (Prakash et al, 2000).
- **8)** Benzisothiazole piperazine (Prakash et al, 2000).

2.3.4 Excretion

A) Kidney
- **1)** RENAL EXCRETION: less than 1% (Prod Info Geodon(R), 2002ae).
  - **a)** Less than 1% of an oral dose of ziprasidone is renally excreted as unchanged drug (Prod Info Geodon(R), 2002ae).

2.3.5 Elimination Half-life

A) Parent Compound
- **1)** ELIMINATION HALF-LIFE
  - **a)** 7 hours oral; 2 to 5 hours intramuscular (Prod Info Geodon(R), 2002ae).
    - **1)** Fed, 4.65 hours; fasted, 6.63 hours (Hamelin et al, 1998).
    - **2)** Half-life dose-dependent at steady-state (not observed with single doses). Single doses, 5 to 60 mg: 3 to 4 hours. Multiple dosing: 4 to 5 hours with 5 mg twice daily, 20 mg twice daily; 8.8 hours with 40 mg twice daily; 10 hours with 60 mg twice daily (Miceli et al, 2000a; Miceli et al, 1995; Ereshefsky, 1996). These changes have minimal clinical relevance.
    - **3)** The half-life increased from 4 to 5 hours (10 to 40 mg/day-dose) to 9 to 10 hours at 80 to 120 mg/day dosing due to an additional elimination phase that becomes apparent only after repeated administration. The extended elimination period was not due to a decrease in clearance with higher doses (Caccia, 2000).

2.3.6 Extracorporeal Elimination

A) Hemodialysis
- **1)** Dialyzable: No (Aweeka et al, 2000a).

3.0 Cautions

Contraindications

Precautions

Adverse Reactions

Teratogenicity/Effects in Pregnancy/Breastfeeding

Drug Interactions

3.0.A Black Box WARNING

1) Ziprasidone Hydrochloride

a) Oral (Capsule)

1) Increased Mortality in Elderly Patients with Dementia-Related Psychosis: Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of seventeen placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of between 1.6 times to 1.7 times the risk of death in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (eg, heart failure, sudden death) or infectious (eg, pneumonia) in nature. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear. Ziprasidone hydrochloride is not approved for the treatment of patients with dementia-related psychosis (Prod Info GEODON(R) oral capsules, IM injection, 2008).

2) Ziprasidone Mesylate

a) Intramuscular (Powder for Solution)

1) Increased Mortality in Elderly Patients with Dementia-Related Psychosis: Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of seventeen placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of between 1.6 times to 1.7 times the risk of death in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (eg, heart failure, sudden death) or infectious (eg, pneumonia) in nature. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear. Ziprasidone mesylate is not approved for the treatment of patients with dementia-related psychosis (Prod Info GEODON(R) oral capsules, IM injection, 2008).

3.1 Contraindications

A) Ziprasidone Hydrochloride

1) cardiac arrhythmias, history (Prod Info GEODON(R) oral capsules, IM injection, 2008)

2) concomitant administration with arsenic trioxide, chlorpromazine, dofetilide, dolasetron mesylate, droperidol, gatifloxacin, halofantrine, levomethadyl acetate, mefloquine, mesoridazine, moxifloxacin, pentamidine, pimozide, probucol, quinidine, sotalol, sparfloxacin, tacrolimus, thioridazine, class Ia and III antiarrhythmics, and other drugs that cause QT prolongation; possible additive QT prolongation effect (Prod Info GEODON(R) oral capsules, IM injection, 2008)

3) heart failure, uncompensated (Prod Info GEODON(R) oral capsules, IM injection, 2008)

4) hypersensitivity to ziprasidone (Prod Info GEODON(R) oral capsules, IM injection, 2008)

5) myocardial infarction, acute and recent (Prod Info GEODON(R) oral capsules, IM injection, 2008)

6) QT prolongation history including congenital long QT syndrome (Prod Info GEODON(R) oral capsules, IM injection, 2008)

B) Ziprasidone Mesylate

1) cardiac arrhythmias, history (Prod Info GEODON(R) oral capsules, IM injection, 2007)

2) concomitant use with arsenic trioxide, chlorpromazine, dofetilide, dolasetron mesylate, droperidol, gatifloxacin, halofantrine, levomethadyl acetate, mefloquine, mesoridazine, moxifloxacin, pentamidine, pimozide, probucol, quinidine, sotalol, sparfloxacin, tacrolimus, thioridazine, Class Ia and III antiarrhythmics, and other drugs that cause QT prolongation; possible additive QT prolongation effect (Prod Info GEODON(R) oral capsules, IM injection, 2008)

3) heart failure, uncompensated (Prod Info GEODON(R) oral capsules, IM injection, 2008)
4) hypersensitivity to ziprasidone (Prod Info GEODON(R) oral capsules, IM injection, 2008)
5) myocardial infarction, acute and recent (Prod Info GEODON(R) oral capsules, IM injection, 2008)
6) QT prolongation, history including congenital long QT syndrome (Prod Info GEODON(R) oral capsules, IM injection, 2008)

3.2 Precautions

A) Ziprasidone Hydrochloride

1) elderly patients with dementia-related psychosis (unapproved use); increased risk of death; most deaths were attributed to cardiovascular events (eg, heart failure or sudden death) or infections (eg, pneumonia) (Prod Info GEODON(R) oral capsules, IM injection, 2008)
2) bradycardia; increased risk of torsades de pointes and/or sudden death (Prod Info GEODON(R) oral capsules, IM injection, 2008)
3) cardiovascular or cerebrovascular disease or conditions that predispose patients to hypotension (eg, dehydration, hypovolemia, antihypertensive medications); increased risk of orthostatic hypotension and syncope (Prod Info GEODON(R) oral capsules, IM injection, 2008)
4) conditions that may contribute to elevated body temperature (eg, strenuous exercise, extreme heat exposure, dehydration, concomitant anticholinergic use); disruption of body temperature regulation has been reported with antipsychotic agents (Prod Info GEODON(R) oral capsules, IM injection, 2008)
5) diabetes mellitus or risk factors for diabetes mellitus; increased risk of severe hyperglycemia; monitor blood glucose (Prod Info GEODON(R) oral capsules, IM injection, 2008)
6) esophageal dysmotility and aspiration may occur, use cautiously in patients at risk for aspiration pneumonia (Prod Info GEODON(R) oral capsules, IM injection, 2008)
7) elderly patients, especially elderly women are at increased risk of tardive dyskinesia (Prod Info GEODON(R) oral capsules, IM injection, 2008)
8) hyperglycemia (some cases extreme and associated with ketoacidosis, hyperosmolar coma, or death) is a risk (Prod Info GEODON(R) oral capsules, IM injection, 2008)
9) hypokalemia or hypomagnesemia, preexisting; increased risk of torsades de pointes and/or sudden death (Prod Info GEODON(R) oral capsules, IM injection, 2008)
10) increased duration of therapy and/or higher cumulative doses; increased risk of tardive dyskinesia (Prod Info GEODON(R) oral capsules, IM injection, 2008)
11) neuroleptic malignant syndrome, potentially fatal, has been reported in association with antipsychotics drugs; immediately discontinue drug (Prod Info GEODON(R) oral capsules, IM injection, 2008)
12) priapism has been reported rarely (Prod Info GEODON(R) oral capsules, IM injection, 2008)
13) rash and/or urticaria have been reported, discontinue if associated with systemic illness (eg, elevated WBC counts) (Prod Info GEODON(R) oral capsules, IM injection, 2008)
14) seizure disorder, history, or conditions which lower the seizure threshold (Prod Info GEODON(R) oral capsules, IM injection, 2008)
15) tardive dyskinesia, potentially irreversible, may occur (Prod Info GEODON(R) oral capsules, IM injection, 2008)

B) Ziprasidone Mesylate

1) elderly patients with dementia-related psychosis (unapproved use); increased risk of death; most deaths were attributed to cardiovascular events (eg, heart failure or sudden death) or infections (eg, pneumonia) (Prod Info GEODON(R) oral capsules, IM injection, 2008)
2) bradycardia; increased risk of torsades de pointes and/or sudden death (Prod Info GEODON(R) oral capsules, IM injection, 2008)
3) cardiovascular or cerebrovascular disease or conditions that predispose patients to hypotension (eg, dehydration, hypovolemia, antihypertensive medications); increased risk of orthostatic hypotension and syncope (Prod Info GEODON(R) oral capsules, IM injection, 2008)
4) conditions that may contribute to elevated body temperature (eg, strenuous exercise, extreme heat exposure, dehydration, concomitant anticholinergic use); disruption of body temperature regulation has been reported with antipsychotic agents (Prod Info GEODON(R) oral capsules, IM injection, 2008)
5) diabetes mellitus or risk factors for diabetes mellitus; increased risk of severe hyperglycemia; monitor blood glucose (Prod Info GEODON(R) oral capsules, IM injection, 2008)
6) esophageal dysmotility and aspiration may occur, use cautiously in patients at risk for aspiration pneumonia (Prod Info GEODON(R) oral capsules, IM injection, 2008)
7) elderly patients, especially elderly women are at increased risk of tardive dyskinesia (Prod Info GEODON(R) oral capsules, IM injection, 2008)
8) hyperglycemia (some cases extreme and associated with ketoacidosis, hyperosmolar coma, or death) is a risk (Prod Info GEODON(R) oral capsules, IM injection, 2008)
9) hypokalemia or hypomagnesemia, preexisting; increased risk of torsades de pointes and/or sudden death (Prod Info GEODON(R) oral capsules, IM injection, 2008)
10) increased duration of therapy and/or higher cumulative doses; increased risk of tardive dyskinesia (Prod Info GEODON(R) oral capsules, IM injection, 2008)
11) neuroleptic malignant syndrome, potentially fatal, has been reported in association with antipsychotics drugs; immediately discontinue drug (Prod Info GEODON(R) oral capsules, IM injection, 2008)
12) priapism has been reported rarely (Prod Info GEODON(R) oral capsules, IM injection, 2008)
13) rash and/or urticaria have been reported, discontinue if associated with systemic illness (eg, elevated WBC

counts) (Prod Info GEODON(R) oral capsules, IM injection, 2008)
14) seizure disorder, history, or conditions which lower the seizure threshold; use caution (Prod Info GEODON (R) oral capsules, IM injection, 2008)
15) tardive dyskinesia, potentially irreversible, may occur (Prod Info GEODON(R) oral capsules, IM injection, 2008)

3.3 Adverse Reactions

Cardiovascular Effects

Dermatologic Effects

Endocrine/Metabolic Effects

Gastrointestinal Effects

Hepatic Effects

Musculoskeletal Effects

Neurologic Effects

Ophthalmic Effects

Psychiatric Effects

Reproductive Effects

Respiratory Effects

Other

3.3.1 Cardiovascular Effects

Ziprasidone Hydrochloride

Ziprasidone Mesylate

3.3.1.A Ziprasidone Hydrochloride

Hypertension

Orthostatic hypotension

Prolonged QT interval

Syncope

Tachycardia

Torsades de pointes

3.3.1.A.1 Hypertension
a) Incidence: bipolar mania, 3%; schizophrenia, not reported (Prod Info GEODON(R) oral capsules, IM injection, 2007)

b) The incidence of hypertension reported in short-term trials of patients with bipolar mania was 3% for ziprasidone hydrochloride-treated subjects (n=279) versus 2% for placebo-treated patients (n=136) (Prod Info GEODON(R) oral capsules, IM injection, 2007).

3.3.1.A.2 Orthostatic hypotension

a) Incidence: frequent (Prod Info GEODON(R) oral capsules, IM injection, 2007)

b) Postural hypotension has been reported in both premarketing and postmarketing oral ziprasidone hydrochloride use and may be dose-dependent (Prod Info GEODON(R) oral capsules, IM injection, 2007).

3.3.1.A.3 Prolonged QT interval

a) Incidence: 0.06%(Prod Info GEODON(R) oral capsules, IM injection, 2007)

b) QT prolongation is dose-related. It is not yet known whether ziprasidone hydrochloride will cause torsades de pointes or increase the rate of sudden death. In clinical trials, oral ziprasidone increased the QTc interval, compared to placebo, by approximately 10 milliseconds (msec) at the highest dose (160 milligrams). Baseline QTc interval increased 9 to 14 msec more with oral ziprasidone than with risperidone, olanzapine, quetiapine, and haloperidol, but QTc interval was 14 msec less than that observed with thioridazine. During clinical trials, clinically significant QTc interval increases (defined as greater than 500 msec) occurred in 0.06% (2 out of 2988) of patients on ziprasidone hydrochloride compared with 0.23% (1 out of 440) patients on placebo. Ziprasidone was not suspected to have caused the QTc prolongation (Prod Info GEODON(R) oral capsules, IM injection, 2007).

1) The risk of QT prolongation and arrhythmia are increased when potassium and magnesium levels are low. Other risk factors include bradycardia, concomitant use of other drugs that prolong QTc interval, and presence of congenital prolongation of the QT interval. Baseline serum potassium and magnesium measurements should be obtained in patients who are at risk for significant electrolyte disturbances before starting ziprasidone. Before starting treatment with ziprasidone, hypokalemia and hypomagnesemia should be corrected. Electrolytes should be periodically monitored during therapy. Avoid ziprasidone in patients with histories of significant cardiovascular illness (QT prolongation, recent acute myocardial infarction, uncompensated heart failure, or cardiac arrhythmia). Further evaluation, such as Holter monitor, maybe be necessary in patients who experience symptoms (dizziness, palpitations, or syncope) suggestive of torsade de pointes. If the QTc measurement consistently exceeds 500 milliseconds, then ziprasidone should be discontinued (Prod Info GEODON(R) oral capsules, IM injection, 2007).

c) It has been shown that ziprasidone prolongs the QTc and that this represents a risk of potentially fatal ventricular dysrhythmias (Anon, 2000).

3.3.1.A.4 Syncope

a) Incidence: 0.6%(Prod Info GEODON(R) oral capsules, IM injection, 2007)

b) Syncope, which may be more prevalent during initial dose-titrations, was reported by 0.6% of patients taking ziprasidone. Patients experiencing syncope may need further evaluation, such as Holter monitoring, to rule out torsade de pointes (Prod Info GEODON(R) oral capsules, IM injection, 2007).

c) The rare occurrence of syncope has been reported during postmarketing use of ziprasidone (Prod Info GEODON(R) oral capsules, IM injection, 2007).

3.3.1.A.5 Tachycardia

a) Incidence: bipolar mania, not reported; schizophrenia, 2%(Prod Info GEODON(R) oral capsules, IM injection, 2007)

b) In short-term trials, the incidence of tachycardia was 2% among ziprasidone hydrochloride-treated schizophrenia subjects (n=702) versus 1% for placebo-treated subjects (n=273) (Prod Info GEODON(R) oral capsules, IM injection, 2007).

c) During schizophrenia trials, a mean increase in heart rate of 1.4 beats per minute in the ziprasidone group compared with 0.2 beats per minute in the placebo group. The occurrence of tachycardia has been reported during postmarketing use of ziprasidone (Prod Info GEODON(R) oral capsules, IM injection, 2007).

3.3.1.A.6 Torsades de pointes

a) Incidence: rare(Prod Info GEODON(R) oral capsules, IM injection, 2007)

b) Although the development of torsades de pointes, in the presence of other multiple confounding factors, has been observed during postmarketing use of ziprasidone, a causal relationship has not been confirmed. In premarketing studies, the development of torsades de pointes was not observed. Ziprasidone does have the capacity to prolong the QT/QTc interval and prolongation of the QTc interval has been associated with the development of torsade de pointes-type arrhythmias. However, the association between ziprasidone use and the possible development of torsades de pointes has yet to be determined (Prod Info GEODON(R) oral capsules, IM injection, 2007).

c) In a case report of a 28 year-old female, Q-T prolongation occurred separately during two hospital admissions, and asymptomatic non-sustained polymorphic ventricular tachycardia occurred during the second admission while using ziprasidone concurrently with other potentially arrhythmogenic medications (lithium, ciprofloxacin, fluconazole, fluoxetine, and trazodone). Upon discontinuation of

ziprasidone and the other medications, the patient's Q-T interval shortened. The patient had a medical history of systemic lupus erythematosus, hypothyroidism, and a complicated history of mood disorders with psychotic features, post traumatic stress disorder, and borderline personality disorder. During the first incidence of Q-T prolongation (600 milliseconds (msec) at 68 bpm) associated with ziprasidone, the patient was lithium toxic and hypokalemic; either of which have been associated with Q-T interval abnormalities and arrhythmias. Discontinuation of ziprasidone and lithium, coupled with emergency dialysis for lithium toxicity, resulted in a decrease in Q-T interval (440 msec at 77 bpm). Two weeks later, the patient was readmitted with complaints of chest pain and an electrocardiogram revealed prolonged Q-T interval (540 msec at 58 bpm). The patient experienced a gradual lowering of potassium levels and further prolongation of Q-T interval after the interchange of ziprasidone for olanzapine coupled with the concurrent initiation of fluconazole, ciprofloxacin, trazodone, and levetiracetam. On the third day, telemetry revealed an asymptomatic non-sustained polymorphic ventricular tachycardia. She was treated by discontinuing ziprasidone, trazodone, and fluconazole, and starting metoprolol. The QT interval remained prolonged at 455 to 480 msec for the remainder of her hospitalization with no subsequent arrhythmias (Heinrich et al, 2006).

3.3.1.B Ziprasidone Mesylate

Hypertension

Orthostatic hypotension

Prolonged QT interval

Syncope

Tachycardia

Torsades de pointes

3.3.1.B.1 Hypertension

a) Incidence: up to 2%(Prod Info GEODON(R) oral capsules, IM injection, 2007)

b) Hypertension was reported in up to 2% of patients during short-term fixed-dose intramuscular trials of ziprasidone mesylate (Prod Info GEODON(R) oral capsules, IM injection, 2007).

3.3.1.B.2 Orthostatic hypotension

a) Incidence: up to 5%(Prod Info GEODON(R) oral capsules, IM injection, 2007)

b) Postural hypotension, reported in up to 5% of patients during short-term fixed-dose intramuscular trials of ziprasidone mesylate, has also been observed during postmarketing use (Prod Info GEODON (R) oral capsules, IM injection, 2007).

3.3.1.B.3 Prolonged QT interval

a) In a study of the QT/QTc prolongation effects of intramuscular ziprasidone mesylate, the mean increase in QTc from baseline to time of maximum plasma concentration following two injections of intramuscular ziprasidone mesylate (20 mg then 30 mg, given four hours apart) was 4.6 msec and 12.8 msec following the first and second injections, respectively, compared to 6 msec and 14.7 msec for the first and second injections, respectively, of haloperidol (7.5 mg then 10 mg, given four hours apart). No patients experienced a QTc interval exceeding 500 msec in this study (Prod Info GEODON(R) oral capsules, IM injection, 2007).

b) QT prolongation is dose-related. It is not yet known whether ziprasidone mesylate will cause torsades de pointes or increase the rate of sudden death. In clinical trials, oral ziprasidone hydrochloride increased the QTc interval, compared to placebo, by approximately 10 milliseconds (msec) at the highest dose (160 milligrams). Baseline QTc interval increased 9 to 14 msec more with oral ziprasidone hydrochloride than with risperidone, olanzapine, quetiapine, and haloperidol, but QTc interval was 14 msec less than that observed with thioridazine. During clinical trials, clinically significant QTc interval increases (defined as greater than 500 msec) occurred in 0.06% (2 out of 2988) of patients on ziprasidone hydrochloride compared with 0.23% (1 out of 440) patients on placebo. Ziprasidone was not suspected to have caused the QTc prolongation (Prod Info GEODON(R) oral capsules, IM injection, 2007).

1) The risk of QT prolongation and arrhythmia are increased when potassium and magnesium levels are low. Other risk factors include bradycardia, concomitant use of other drugs that prolong QTc interval, and presence of congenital prolongation of the QT interval. Baseline serum potassium and magnesium measurements should be obtained in patients who are at risk for significant electrolyte disturbances before starting ziprasidone. Before starting treatment with ziprasidone,

hypokalemia and hypomagnesemia should be corrected. Electrolytes should be periodically monitored during therapy. Avoid ziprasidone in patients with histories of significant cardiovascular illness (QT prolongation, recent acute myocardial infarction, uncompensated heart failure, or cardiac arrhythmia). Further evaluation, such as Holter monitor, maybe be necessary in patients who experience symptoms (dizziness, palpitations, or syncope) suggestive of torsade de pointes. If the QTc measurement consistently exceeds 500 milliseconds, then ziprasidone should be discontinued (Prod Info GEODON(R) oral capsules, IM injection, 2007).

c) It has been shown that ziprasidone prolongs the QTc and that this represents a risk of potentially fatal ventricular dysrhythmias (Anon, 2000).

3.3.1.B.4 Syncope

a) Incidence: 0.6%(Prod Info GEODON(R) oral capsules, IM injection, 2007)

b) Syncope, which may be more prevalent during initial dose-titrations, was reported by 0.6% of patients taking ziprasidone. Patients experiencing syncope may need further evaluation, such as Holter monitoring, to rule out torsade de pointes (Prod Info GEODON(R) oral capsules, IM injection, 2007).

c) The rare occurrence of syncope has been reported during postmarketing use of ziprasidone (Prod Info GEODON(R) oral capsules, IM injection, 2007).

3.3.1.B.5 Tachycardia

a) Tachycardia, reported in 2% of patients with schizophrenia during short-term oral placebo-controlled trials, has been reported in postmarketing ziprasidone use (Prod Info GEODON(R) oral capsules, IM injection, 2007).

3.3.1.B.6 Torsades de pointes

a) Incidence: rare(Prod Info GEODON(R) oral capsules, IM injection, 2007)

b) Although the development of torsades de pointes, in the presence of other multiple confounding factors, has been observed during postmarketing use of ziprasidone, a causal relationship has not been confirmed. In premarketing studies, the development of torsades de pointes was not observed. Ziprasidone does have the capacity to prolong the QT/QTc interval and prolongation of the QTc interval has been associated with the development of torsade de pointes-type arrhythmias. However, the association between ziprasidone use and the possible development of torsades de pointes has yet to be determined (Prod Info GEODON(R) oral capsules, IM injection, 2007).

3.3.2 Dermatologic Effects

Ziprasidone Hydrochloride

Ziprasidone Mesylate

3.3.2.A Ziprasidone Hydrochloride

3.3.2.A.1 Rash

a) Incidence: 5%(Prod Info GEODON(R) oral capsules, IM injection, 2007)

b) Development of a dose-dependent rash and/or urticaria was reported in about 5% of patients during premarketing trials with ziprasidone hydrochloride and was one of the more common reasons given for study dropouts (Prod Info GEODON(R) oral capsules, IM injection, 2007).

3.3.2.B Ziprasidone Mesylate

Furunculosis

Injection site pain

Sweating symptom

3.3.2.B.1 Furunculosis

a) Incidence: up to 2%(Prod Info GEODON(R) oral capsules, IM injection, 2007)

b) Furunculosis was reported in up to 2% of patients during short-term fixed-dose intramuscular trials of ziprasidone mesylate (Prod Info GEODON(R) oral capsules, IM injection, 2007).

3.3.2.B.2 Injection site pain

a) Incidence: 7% to9%(Prod Info GEODON(R) oral capsules, IM injection, 2007)

b) Pain at the site of injection was reported in 7% to 9% of patients during short-term fixed-dose

intramuscular trials of ziprasidone mesylate (Prod Info GEODON(R) oral capsules, IM injection, 2007).

3.3.2.B.3 Sweating symptom

a) Incidence: up to 2%(Prod Info GEODON(R) oral capsules, IM injection, 2007)

b) Sweating was reported in up to 2% of patients during short-term fixed-dose intramuscular trials of ziprasidone mesylate (Prod Info GEODON(R) oral capsules, IM injection, 2007).

3.3.3 Endocrine/Metabolic Effects

Ziprasidone

Ziprasidone Hydrochloride

Ziprasidone Mesylate

3.3.3.A Ziprasidone

3.3.3.A.1 Diabetes mellitus

See Drug Consult reference: ATYPICAL ANTIPSYCHOTIC AGENTS - EFFECT ON GLUCOSE AND RISK OF DIABETES

3.3.3.B Ziprasidone Hydrochloride

Diabetes mellitus

Hyperglycemia

Increased prolactin level

Metabolic syndrome

Weight gain

3.3.3.B.1 Diabetes mellitus

a) Although there have been few reports of hyperglycemia or diabetes in patients treated with ziprasidone hydrochloride, increased risk has been clearly associated with other drugs of this class (atypical antipsychotics). Data are presently insufficient to exclude the possibility of increased risk of diabetes due to ziprasidone treatment. Before starting an atypical antipsychotic, patients with risk factors for diabetes should undergo fasting blood glucose testing, with periodic re-testing. All patients receiving an atypical antipsychotic should be monitored for symptoms of hyperglycemia (polydipsia, polyuria, polyphagia, weakness), and should be given blood glucose tests if such symptoms are seen. In some patients, resolution of hyperglycemia has occurred with discontinuation of the atypical antipsychotic; in other cases, it has not (Prod Info GEODON(R) oral capsules, IM injection, 2007).

3.3.3.B.2 Hyperglycemia

a) Although there have been few reports of hyperglycemia or diabetes in patients treated with ziprasidone hydrochloride, increased risk has been clearly associated with other drugs of this class (atypical antipsychotics). In the patients treated with atypical antipsychotics, ketoacidosis, hyperosmolar coma or death occurred. Data are presently insufficient to exclude the possibility of increased risk of diabetes due to ziprasidone treatment. Before starting an atypical antipsychotic, patients with risk factors for diabetes should undergo fasting blood glucose testing, with periodic re-testing. All patients receiving an atypical antipsychotic should be monitored for symptoms of hyperglycemia (polydipsia, polyuria, polyphagia, weakness), and should be given blood glucose tests if such symptoms are seen. In some patients, resolution of hyperglycemia has occurred with discontinuation of the atypical antipsychotic; in other cases, it has not (Prod Info GEODON(R) oral capsules, IM injection, 2007).

3.3.3.B.3 Increased prolactin level

a) Ziprasidone, like other drugs that antagonize dopamine D2 receptors, have the potential ot increase prolactin levels; however, the clinical significance is unknown (Prod Info GEODON(R) oral capsules, IM injection, 2007). Prolactin level increases are usually small and seen mainly with higher doses of ziprasidone (Anon, 1996a; Kerwin & Taylor, 1996a). The changes are transient and return to baseline

within 12 hours of ziprasidone administration (Miceli et al, 2000; Goff et al, 1998a).

3.3.3.B.4 Metabolic syndrome

See Drug Consult reference: ANTIPSYCHOTIC AGENTS - METABOLIC SYNDROME

3.3.3.B.5 Weight gain

a) Incidence: 0.4%(Prod Info GEODON(R) oral capsules, IM injection, 2007)

b) Weight gain was reported in 0.4% and 0.4% of patients on ziprasidone-treated and placebo-treated patients, respectively (Prod Info GEODON(R) oral capsules, IM injection, 2007).

c) Based on 4 short-term clinical trials (4 to 6 week duration) related to schizophrenia, incidence of weight gain amounting to 7% or more of baseline body weight was 10% for subjects receiving oral ziprasidone hydrochloride compared with 4% for those receiving placebo. Median weight gain of 0.5 kg and 0 kg occurred in the ziprasidone and placebo groups, respectively. Data collected during long-term therapy showed mean weight gain from baseline to be 1.4 kg for patients with initial low BMI (less than 23), no mean weight change for those with normal BMI (23 to 27), and 1.3 kg weight loss for patients with initially high BMI (greater than 27) (Prod Info GEODON(R) oral capsules, IM injection, 2007).

d) Compared to other atypical antipsychotics in a systemic review, ziprasidone is associated with a low risk of weight gain (Kingsbury et al, 2001; Taylor & McAskill, 2000).

3.3.3.C Ziprasidone Mesylate

Diabetes mellitus

Hyperglycemia

Increased prolactin level

Metabolic syndrome

3.3.3.C.1 Diabetes mellitus

a) Although there have been few reports of hyperglycemia or diabetes in patients treated with ziprasidone mesylate, increased risk has been clearly associated with other drugs of this class (atypical antipsychotics). Data are presently insufficient to exclude the possibility of increased risk of diabetes due to ziprasidone treatment. Before starting an atypical antipsychotic, patients with risk factors for diabetes should undergo fasting blood glucose testing, with periodic re-testing. All patients receiving an atypical antipsychotic should be monitored for symptoms of hyperglycemia (polydipsia, polyuria, polyphagia, weakness), and should be given blood glucose tests if such symptoms are seen. In some patients, resolution of hyperglycemia has occurred with discontinuation of the atypical antipsychotic; in other cases, it has not (Prod Info GEODON(R) oral capsules, IM injection, 2007).

3.3.3.C.2 Hyperglycemia

a) Although there have been few reports of hyperglycemia or diabetes in patients treated with ziprasidone mesylate, increased risk has been clearly associated with other drugs of this class (atypical antipsychotics). In the patients treated with atypical antipsychotics, ketoacidosis, hyperosmolar coma or death occurred. Data are presently insufficient to exclude the possibility of increased risk of diabetes due to ziprasidone treatment. Before starting an atypical antipsychotic, patients with risk factors for diabetes should undergo fasting blood glucose testing, with periodic re-testing. All patients receiving an atypical antipsychotic should be monitored for symptoms of hyperglycemia (polydipsia, polyuria, polyphagia, weakness), and should be given blood glucose tests if such symptoms are seen. In some patients, resolution of hyperglycemia has occurred with discontinuation of the atypical antipsychotic; in other cases, it has not (Prod Info GEODON(R) oral capsules, IM injection, 2007).

3.3.3.C.3 Increased prolactin level

a) Ziprasidone, like other drugs that antagonize dopamine D2 receptors, have the potential ot increase prolactin levels; however, the clinical significance is unknown (Prod Info GEODON(R) oral capsules, IM injection, 2007). Prolactin level increases are usually small and seen mainly with higher doses of ziprasidone (Anon, 1996a; Kerwin & Taylor, 1996a). The changes are transient and return to baseline within 12 hours of ziprasidone administration (Miceli et al, 2000; Goff et al, 1998a).

3.3.3.C.4 Metabolic syndrome

See Drug Consult reference: ANTIPSYCHOTIC AGENTS - METABOLIC SYNDROME

3.3.4 Gastrointestinal Effects

Ziprasidone Hydrochloride

Ziprasidone Mesylate

3.3.4.A Ziprasidone Hydrochloride

Abdominal pain

Constipation

Diarrhea

Indigestion

Loss of appetite

Nausea

Vomiting

Xerostomia

3.3.4.A.1 Abdominal pain

a) Incidence: bipolar mania, not reported; schizophrenia, frequent(Prod Info GEODON(R) oral capsules, IM injection, 2007)
b) Abdominal pain was frequently observed during premarketing schizophrenia clinical trials at multiple doses greater than 4 milligrams/day (Prod Info GEODON(R) oral capsules, IM injection, 2007).

3.3.4.A.2 Constipation

a) Incidence: bipolar mania, not reported; schizophrenia, 9%(Prod Info GEODON(R) oral capsules, IM injection, 2007)
b) In short-term trials, the incidence of constipation was 9% among ziprasidone hydrochloride-treated schizophrenia subjects (n=702) versus 8% for placebo-treated subjects (n=273) (Prod Info GEODON(R) oral capsules, IM injection, 2007).

3.3.4.A.3 Diarrhea

a) Incidence: bipolar mania and schizophrenia, 5%(Prod Info GEODON(R) oral capsules, IM injection, 2007)
b) The incidence of diarrhea reported in short-term trials of patients with bipolar mania was 5% for ziprasidone hydrochloride-treated subjects (n=279) versus 4% for placebo-treated patients (n=136) (Prod Info GEODON(R) oral capsules, IM injection, 2007).
c) In short-term trials, the incidence of diarrhea was 5% among ziprasidone hydrochloride-treated schizophrenia subjects (n=702) versus 4% for placebo-treated subjects (n=273) (Prod Info GEODON(R) oral capsules, IM injection, 2007).

3.3.4.A.4 Indigestion

a) Incidence: bipolar mania, not reported; schizophrenia, 8%(Prod Info GEODON(R) oral capsules, IM injection, 2007)
b) In short-term trials, the incidence of dyspepsia was 8% among ziprasidone hydrochloride-treated schizophrenia subjects (n=702) versus 7% for placebo-treated subjects (n=273) (Prod Info GEODON(R) oral capsules, IM injection, 2007).

3.3.4.A.5 Loss of appetite

a) Incidence: bipolar mania, not reported; schizophrenia, 2%(Prod Info GEODON(R) oral capsules, IM injection, 2007)
b) In short-term trials, the incidence of anorexia was 2% among ziprasidone hydrochloride-treated schizophrenia subjects (n=702) versus 1% for placebo-treated subjects (n=273). (Prod Info GEODON (R) oral capsules, IM injection, 2007).
c) Anorexia was frequently observed during premarketing schizophrenia clinical trials at multiple doses greater than 4 milligrams/day (Prod Info GEODON(R) oral capsules, IM injection, 2007).
d) An analysis of four short-term, fixed-dose, placebo-controlled studies of patients with schizophrenia

revealed a dependent relationship between the development of anorexia and the dose of ziprasidone hydrochloride (Prod Info GEODON(R) oral capsules, IM injection, 2007).

3.3.4.A.6 Nausea

a) Incidence: bipolar mania and schizophrenia, 10%(Prod Info GEODON(R) oral capsules, IM injection, 2007)

b) The incidence of nausea reported in short-term trials of patients with bipolar mania was 10% for ziprasidone hydrochloride-treated subjects (n=279) versus 7% for placebo-treated patients (n=136) (Prod Info GEODON(R) oral capsules, IM injection, 2007).

c) In short-term trials, the incidence of nausea was 10% among ziprasidone hydrochloride-treated schizophrenia subjects (n=702) versus 7% for placebo-treated subjects (n=273) (Prod Info GEODON(R) oral capsules, IM injection, 2007).

3.3.4.A.7 Vomiting

a) Incidence: bipolar mania, 5%; schizophrenia, frequent(Prod Info GEODON(R) oral capsules, IM injection, 2007)

b) The incidence of vomiting reported in short-term trials of patients with bipolar mania was 5% for ziprasidone hydrochloride-treated subjects (n=279) versus 2% for placebo-treated patients (n=136) (Prod Info GEODON(R) oral capsules, IM injection, 2007).

c) Vomiting was frequently observed during premarketing schizophrenia clinical trials at multiple doses greater than 4 milligrams/day and was one of the more common reasons given for study dropouts during the bipolar mania trials(Prod Info GEODON(R) oral capsules, IM injection, 2007).

3.3.4.A.8 Xerostomia

a) Incidence: bipolar mania, 5%; schizophrenia, 4%(Prod Info GEODON(R) oral capsules, IM injection, 2007)

b) The incidence of dry mouth reported in short-term trials of patients with bipolar mania was 5% for ziprasidone hydrochloride-treated subjects (n=279) versus 4% for placebo-treated patients (n=136) (Prod Info GEODON(R) oral capsules, IM injection, 2007).

c) In short-term trials, the incidence of dry mouth was 4% among ziprasidone hydrochloride-treated schizophrenia subjects (n=702) versus 2% for placebo-treated subjects (n=273) (Prod Info GEODON(R) oral capsules, IM injection, 2007).

d) An analysis of four short-term, fixed-dose, placebo-controlled studies of patients with schizophrenia revealed a dependent relationship between the development of dry mouth and the dose of ziprasidone hydrochloride (Prod Info GEODON(R) oral capsules, IM injection, 2007).

3.3.4.B Ziprasidone Mesylate

Abdominal pain

Constipation

Diarrhea

Indigestion

Loss of appetite

Nausea

Vomiting

3.3.4.B.1 Abdominal pain

a) Incidence: up to 2%(Prod Info GEODON(R) oral capsules, IM injection, 2007)

b) Abdominal pain was reported in up to 2% of patients during short-term fixed-dose intramuscular trials of ziprasidone mesylate (Prod Info GEODON(R) oral capsules, IM injection, 2007).

3.3.4.B.2 Constipation

a) Incidence: up to 2%(Prod Info GEODON(R) oral capsules, IM injection, 2007)

b) Constipation was reported in up to 2% of patients during short-term fixed-dose intramuscular trials of ziprasidone mesylate (Prod Info GEODON(R) oral capsules, IM injection, 2007).

3.3.4.B.3 Diarrhea

a) Incidence: up to 3%(Prod Info GEODON(R) oral capsules, IM injection, 2007)
b) Diarrhea was reported in up to 3% of patients during short-term fixed-dose intramuscular trials of ziprasidone mesylate (Prod Info GEODON(R) oral capsules, IM injection, 2007).

3.3.4.B.4 Indigestion
a) Incidence: 1% to 3%(Prod Info GEODON(R) oral capsules, IM injection, 2007)
b) Dyspepsia was reported in 1% to 3% of patients during short-term fixed-dose intramuscular trials of ziprasidone mesylate (Prod Info GEODON(R) oral capsules, IM injection, 2007).

3.3.4.B.5 Loss of appetite
a) Incidence: up to 2%(Prod Info GEODON(R) oral capsules, IM injection, 2007)
b) Anorexia was reported in up to 2% of patients during short-term fixed-dose intramuscular trials of ziprasidone mesylate (Prod Info GEODON(R) oral capsules, IM injection, 2007).

3.3.4.B.6 Nausea
a) Incidence: 4% to 12%(Prod Info GEODON(R) oral capsules, IM injection, 2007)
b) Nausea was reported in 4% to 12% of patients during short-term fixed-dose intramuscular trials of ziprasidone mesylate (Prod Info GEODON(R) oral capsules, IM injection, 2007).

3.3.4.B.7 Vomiting
a) Incidence: up to 3%(Prod Info GEODON(R) oral capsules, IM injection, 2007)
b) Vomiting was reported in up to 3% of patients during short-term fixed-dose intramuscular trials of ziprasidone mesylate (Prod Info GEODON(R) oral capsules, IM injection, 2007).

3.3.6 Hepatic Effects

Ziprasidone Hydrochloride

Ziprasidone Mesylate

3.3.6.A Ziprasidone Hydrochloride

3.3.6.A.1 Increased liver enzymes
a) No overt cases of hepatotoxicity have been reported. Occasional rises in liver enzymes have been reported with ziprasidone use but have not been clinically significant (Brown et al, 1999; Citrome, 1997; Kerwin & Taylor, 1996a).
b) Two patients in a clinical trial of ziprasidone were discontinued because of abnormal laboratory results. One patient had elevated gamma-glutamyl transpeptidase (GGT) and serum glutamic-pyruvic transaminase (SGPT/ALT) after 7 days of treatment with ziprasidone 10 milligrams/day, and one patient showed elevations of both serum glutamic-oxaloacetic transaminase (SGOT/AST) and SGPT/ALT after 8 days of treatment with ziprasidone 40 milligrams/day. Both patients had elevated GGT values at baseline. At follow-up, all values had returned or were returning to normal (Goff et al, 1998a).

3.3.6.B Ziprasidone Mesylate

3.3.6.B.1 Increased liver enzymes
a) No overt cases of hepatotoxicity have been reported. Occasional rises in liver enzymes have been reported with ziprasidone use but have not been clinically significant (Brown et al, 1999; Citrome, 1997; Kerwin & Taylor, 1996a).

3.3.8 Musculoskeletal Effects

3.3.8.A Ziprasidone Hydrochloride

Myalgia

Rhabdomyolysis, following correction of hyponatremia secondary to psychogenic polydipsia

3.3.8.A.1 Myalgia
a) Incidence: bipolar mania, 2%; schizophrenia, frequent(Prod Info GEODON(R) oral capsules, IM injection, 2007)
b) The incidence of myalgia reported in short-term trials of patients with bipolar mania was 2% for ziprasidone hydrochloride-treated subjects (n=279) versus 0% for placebo-treated patients (n=136)

(Prod Info GEODON(R) oral capsules, IM injection, 2007).
c) Myalgia was frequently observed during premarketing schizophrenia clinical trials at multiple doses greater than 4 milligrams/day (Prod Info GEODON(R) oral capsules, IM injection, 2007).

3.3.8.A.2 Rhabdomyolysis, following correction of hyponatremia secondary to psychogenic polydipsia

a) Rhabdomyolysis, possibly complicated by ziprasidone therapy, was observed in one patient following the correction of hyponatremia secondary to psychogenic polydipsia. The 50-year-old Caucasian male had begun ziprasidone therapy (40 mg twice daily) for the treatment of chronic paranoid schizophrenia three weeks before presenting with hyponatremia secondary to psychogenic polydipsia. Following the discontinuation of ziprasidone and the correction of hyponatremia via sodium chloride 0.9% administration and oral water restriction, the man developed rhabdomyolysis secondary to hyponatremia correction which manifested as an unexplained increase in serum alanine and aspartate aminotransferase levels and total serum creatine kinase elevated to 67,259 International Units/L. Following resolution of rhabdomyolysis, ziprasidone therapy was reinitiated at a dose of 80 mg twice daily with no recurrence of increased serum creatine kinase levels. While the author notes that hyponatremia secondary to psychogenic polydipsia or its correction was most likely the primary cause of rhabdomyolysis in this patient, he also asserts that a review of the literature allows supposition that the development of rhabdomyolysis may have been complicated by the prior use of ziprasidone. The use of the Naranjo probability scale indicated a possible relationship between the use of ziprasidone and the subsequent development of rhabdomyolysis (Zaidi, 2005).

3.3.9 Neurologic Effects

Ziprasidone Hydrochloride

Ziprasidone Mesylate

3.3.9.A Ziprasidone Hydrochloride

Akathisia

Asthenia

Disturbance in speech

Dizziness

Dystonia

Extrapyramidal disease

Headache

Insomnia

Neuroleptic malignant syndrome

Paresthesia

Seizure

Somnolence

Tardive dyskinesia

3.3.9.A.1 Akathisia

a) Incidence: bipolar mania, 10%; schizophrenia, 8%(Prod Info GEODON(R) oral capsules, IM

injection, 2008a)
b) The incidence of akathisia reported in short-term trials of patients with bipolar mania was 10% for ziprasidone hydrochloride-treated subjects (n=279) versus 5% for placebo-treated patients (n=136) (Prod Info GEODON(R) oral capsules, IM injection, 2008a).
c) In short-term trials, the incidence of akathisia was 8% among ziprasidone hydrochloride-treated schizophrenia subjects (n=702) versus 7% for placebo-treated subjects (n=273) (Prod Info GEODON(R) oral capsules, IM injection, 2008a).
d) Akathisia was one of the more common reasons given for study dropouts during the bipolar mania trials (Prod Info GEODON(R) oral capsules, IM injection, 2008a).

3.3.9.A.2 Asthenia
a) Incidence: bipolar mania, 6%; schizophrenia, 5%(Prod Info GEODON(R) oral capsules, IM injection, 2008a)
b) The incidence of asthenia reported in short-term trials of patients with bipolar mania was 6% for ziprasidone hydrochloride-treated subjects (n=279) versus 2% for placebo-treated patients (n=136) (Prod Info GEODON(R) oral capsules, IM injection, 2008a).
c) In short-term trials, the incidence of asthenia was 5% among ziprasidone hydrochloride-treated schizophrenia subjects (n=702) versus 3% for placebo-treated subjects (n=273) (Prod Info GEODON(R) oral capsules, IM injection, 2008a).

3.3.9.A.3 Disturbance in speech
a) Incidence: bipolar mania, 2%; schizophrenia, not reported(Prod Info GEODON(R) oral capsules, IM injection, 2008a)
b) The incidence of speech disorder reported in short-term trials of patients with bipolar mania was 2% for ziprasidone hydrochloride-treated subjects (n=279) versus 0% for placebo-treated patients (n=136) (Prod Info GEODON(R) oral capsules, IM injection, 2008a).

3.3.9.A.4 Dizziness
a) Incidence: bipolar mania, 16%; schizophrenia, 8%(Prod Info GEODON(R) oral capsules, IM injection, 2008a)
b) The incidence of dizziness and lightheadedness reported in short-term trials of patients with bipolar mania was 16% for ziprasidone hydrochloride-treated subjects (n=279) versus 7% for placebo-treated patients (n=136) (Prod Info GEODON(R) oral capsules, IM injection, 2008a).
c) In short-term trials, the incidence of dizziness and lightheadedness was 8% among ziprasidone hydrochloride-treated schizophrenia subjects (n=702) versus 6% for placebo-treated subjects (n=273) (Prod Info GEODON(R) oral capsules, IM injection, 2008a).
d) Dizziness may be more prevalent during initial ziprasidone hydrochloride dose-titrations and is dose-dependent. Patients experiencing continued dizziness may need further evaluation, such as Holter monitoring, to rule out torsade de pointes (Prod Info GEODON(R) oral capsules, IM injection, 2008a).

3.3.9.A.5 Dystonia
a) During the first few days after initiating treatment with an antipsychotic medication, symptoms of dystonia may occur in susceptible individuals. Symptoms may include spasm of neck muscles, which may progress to tightening of the throat, swallowing difficulty, breathing difficulty, and/or protrusion of the tongue. These symptoms can occur at low doses but most often occur (and occur with greater severity) with high potency and at higher doses of first generation antipsychotic medications. Males and younger age groups appear to be at greater risk for developing acute dystonia (Prod Info GEODON(R) oral capsules, IM injection, 2008a).

3.3.9.A.6 Extrapyramidal disease
a) Incidence: bipolar mania, 31%; schizophrenia, 14%(Prod Info GEODON(R) oral capsules, IM injection, 2008a)
b) General
1) In clinical trial adverse effect reports for ziprasidone hydrochloride, the manufacturer defines extrapyramidal symptoms to collectively include the following: Extrapyramidal syndrome, hypertonia, dystonia, dyskinesia, hypokinesia, tremor, paralysis, and twitching (Prod Info GEODON (R) oral capsules, IM injection, 2008a).
2) The incidence of extrapyramidal symptoms (EPS) reported in short-term trials of patients with bipolar mania was 31% for ziprasidone hydrochloride-treated subjects (n=279) versus 12% for placebo-treated patients (n=136) (Prod Info GEODON(R) oral capsules, IM injection, 2008a).
3) In short-term trials, the incidence of extrapyramidal symptoms (EPS) was 14% among ziprasidone hydrochloride -treated schizophrenia subjects (n=702) versus 8% for placebo-treated subjects (n=273). However, objectively collected data on the Simpson-Angus Rating Scale for EPS and the Barnes Akathisia Scale did not generally indicate a difference between the ziprasidone hydrochloride and placebo groups in these trials (Prod Info GEODON(R) oral capsules, IM injection, 2008a).
c) Hypertonia
1) Hypertonia occurred at a frequency of less than 10% in bipolar mania trials and less than 5% in

schizophrenia trials. Hypertonia was frequently (occurred in at least 1 of 100 people) observed during premarketing schizophrenia clinical trials at multiple doses greater than 4 milligrams/day (Prod Info GEODON(R) oral capsules, IM injection, 2008a).

2) An analysis of four short-term, fixed-dose, placebo-controlled studies of patients with schizophrenia revealed a dependent relationship between the development of hypertonia and the dose of ziprasidone hydrochloride (Prod Info GEODON(R) oral capsules, IM injection, 2008a).

d) Hypokinesia

1) Hypokinesia occurred at a frequency of less than 10% in bipolar mania trials and less than 5% in schizophrenia trials. Hypokinesia was frequently (occurred in at least 1 of 100 people) observed during premarketing schizophrenia clinical trials at multiple doses greater than 4 milligrams/day (Prod Info GEODON(R) oral capsules, IM injection, 2007).

e) Tremor

1) Tremor occurred at a frequency of less than 10% in bipolar mania trials and less than 5% in schizophrenia trials. Tremor was frequently (occurred in at least 1 of 100 people) observed during premarketing schizophrenia clinical trials at multiple doses greater than 4 milligrams/day (Prod Info GEODON(R) oral capsules, IM injection, 2008a).

2) An analysis of four short-term, fixed-dose, placebo-controlled studies of patients with schizophrenia revealed a dependent relationship between the development of tremor and the dose of ziprasidone hydrochloride (Prod Info GEODON(R) oral capsules, IM injection, 2008a).

f) Twitching

1) Twitching occurred at a frequency of less than 10% in bipolar mania trials and less than 5% in schizophrenia trials. Twitching was frequently (occurred in at least 1 of 100 people) observed during premarketing schizophrenia clinical trial at multiple doses greater than 4 milligrams/day (Prod Info GEODON(R) oral capsules, IM injection, 2008a).

See Drug Consult reference: NEUROLEPTIC-INDUCED EXTRAPYRAMIDAL REACTIONS

3.3.9.A.7 Headache

a) Incidence: bipolar mania, 18%; schizophrenia, not reported(Prod Info GEODON(R) oral capsules, IM injection, 2008a)

b) The incidence of headache reported in short-term trials of patients with bipolar mania was 18% for ziprasidone hydrochloride-treated subjects (n=279) versus 17% for placebo-treated patients (n=136) (Prod Info GEODON(R) oral capsules, IM injection, 2008a).

3.3.9.A.8 Insomnia

a) Incidence: rare(Prod Info GEODON(R) oral capsules, IM injection, 2008a)

b) Although no causal relationship has been established, rare postmarketing reports of insomnia with ziprasidone use have been observed (Prod Info GEODON(R) oral capsules, IM injection, 2008a).

3.3.9.A.9 Neuroleptic malignant syndrome

a) Incidence: rare(Murty et al, 2002)

b) Neuroleptic malignant syndrome (NMS) developed in a 49-year-old female patient after receiving ziprasidone (20 to 60 mg twice daily) for the treatment of recurrent psychotic depression. Symptoms included agitation, disorganized thoughts, sweating, tachycardia, hypertension, elevated liver enzymes, and hyponatremia. Although there was no evidence of fever or muscle rigidity, a diagnosis of rhabdomyolysis secondary to NMS was made. All medications were stopped and the symptoms resolved over the next 6 days following aggressive treatment including intravenous hydration and electrolyte replacement (Murty et al, 2002).

3.3.9.A.10 Paresthesia

a) Incidence: frequent(Prod Info GEODON(R) oral capsules, IM injection, 2008a)

b) Paresthesia was frequently (occurred in at least 1 of 100 people) reported in oral ziprasidone hydrochloride-treated patients during premarketing schizophrenia clinical trials at multiple doses greater than 4 milligrams/day, although causality was not determined (Prod Info GEODON(R) oral capsules, IM injection, 2008a).

3.3.9.A.11 Seizure

a) Incidence: 0.4%(Prod Info GEODON(R) oral capsules, IM injection, 2008a)

b) Seizures were reported in 0.4% of ziprasidone hydrochloride-treated patients during clinical trials, although confounding factors may have contributed to the occurrence in many of these cases (Prod Info GEODON(R) oral capsules, IM injection, 2008a).

3.3.9.A.12 Somnolence

a) Incidence: bipolar mania, 31%; schizophrenia, 14%(Prod Info GEODON(R) oral capsules, IM injection, 2008a)

b) The incidence of somnolence reported in short-term trials of patients with bipolar mania was 31% for ziprasidone hydrochloride-treated subjects (n=279) versus 12% for placebo-treated patients (n=136) (Prod Info GEODON(R) oral capsules, IM injection, 2008a).

c) In short-term trials, the incidence of somnolence was 14% among ziprasidone hydrochloride-treated

schizophrenia subjects (n=702) versus 7% for placebo-treated subjects (n=273). The frequency of somnolence appears to be dose-dependent (Prod Info GEODON(R) oral capsules, IM injection, 2008a).
d) Somnolence may be more prevalent during initial ziprasidone hydrochloride dose-titrations and is dose-dependent. During short-term clinical trials, 0.3% discontinued therapy due to somnolence (Prod Info GEODON(R) oral capsules, IM injection, 2008a).

3.3.9.A.13 Tardive dyskinesia

a) The use of antipsychotic drugs, such as ziprasidone hydrochloride, is a risk factor for the development of tardive dyskinesia. The risk of developing the syndrome increases with duration of treatment and total cumulative dose. The incidence of the syndrome appears to be highest among the elderly, particularly women. However, any patient may be at risk to develop the syndrome, even after a comparatively brief treatment period at a low dose (Prod Info GEODON(R) oral capsules, IM injection, 2008a).
b) Tardive dyskinesia developed in a 70-year-old woman nine weeks following the initiation of ziprasidone therapy (100 milligrams/day) for the treatment of major depression with mood-congruent psychotic features. Symptoms included repetitive, involuntary jaw and toe movements (Keck et al, 2004).

3.3.9.B Ziprasidone Mesylate

Akathisia

Asthenia

Disturbance in speech

Dizziness

Dystonia

Extrapyramidal disease

Headache

Insomnia

Paresthesia

Seizure

Somnolence

Tardive dyskinesia

3.3.9.B.1 Akathisia

a) Incidence: up to 2%(Prod Info GEODON(R) oral capsules, IM injection, 2008a)
b) Akathisia was reported in up to 2% of patients during short-term fixed-dose intramuscular trials of ziprasidone mesylate (Prod Info GEODON(R) oral capsules, IM injection, 2008a).

3.3.9.B.2 Asthenia

a) Incidence: up to 2%(Prod Info GEODON(R) oral capsules, IM injection, 2008a)
b) Asthenia was reported in up to 2% of patients during short-term fixed-dose intramuscular trials of ziprasidone mesylate (Prod Info GEODON(R) oral capsules, IM injection, 2008a).

3.3.9.B.3 Disturbance in speech

a) Incidence: up to 2%(Prod Info GEODON(R) oral capsules, IM injection, 2008a)
b) Speech disorder was reported in up to 2% of patients during short-term fixed-dose intramuscular trials of ziprasidone mesylate (Prod Info GEODON(R) oral capsules, IM injection, 2008a).

3.3.9.B.4 Dizziness

a) Incidence: 3% to 10%(Prod Info GEODON(R) oral capsules, IM injection, 2008a)

b) Dizziness was reported in 3% to 10% of patients during short-term fixed-dose intramuscular trials of ziprasidone mesylate (Prod Info GEODON(R) oral capsules, IM injection, 2008a).

3.3.9.B.5 Dystonia

a) During the first few days of treatment with an antipsychotic medication, symptoms of dystonia may occur in susceptible individuals. Symptoms may include spasm of neck muscles, which may progress to tightening of the throat, swallowing difficulty, breathing difficulty, and/or protrusion of the tongue. These symptoms can occur at low doses but most often occur (and occur with greater severity) with high potency and at higher doses of first generation antipsychotic medications. Males and younger age groups appear to be at greater risk for developing acute dystonia (Prod Info GEODON(R) oral capsules, IM injection, 2008a).

3.3.9.B.6 Extrapyramidal disease

a) Incidence: up to 2%(Prod Info GEODON(R) oral capsules, IM injection, 2008a)

b) Extrapyramidal syndrome was reported in up to 2% of patients during short-term fixed-dose intramuscular trials of ziprasidone mesylate (Prod Info GEODON(R) oral capsules, IM injection, 2008a). See Drug Consult reference: NEUROLEPTIC-INDUCED EXTRAPYRAMIDAL REACTIONS

3.3.9.B.7 Headache

a) Incidence: 3% to 13%(Prod Info GEODON(R) oral capsules, IM injection, 2008a)

b) Headache was reported in 3% to 13% of patients during short-term fixed-dose intramuscular trials of ziprasidone mesylate (Prod Info GEODON(R) oral capsules, IM injection, 2008a).

3.3.9.B.8 Insomnia

a) Incidence: up to 3%(Prod Info GEODON(R) oral capsules, IM injection, 2008a)

b) Insomnia was reported in up to 3% of patients during short-term fixed-dose intramuscular trials of ziprasidone mesylate (Prod Info GEODON(R) oral capsules, IM injection, 2008a).

c) Although no causal relationship has been established, postmarketing reports of insomnia with ziprasidone use have been observed (Prod Info GEODON(R) oral capsules, IM injection, 2008a).

3.3.9.B.9 Paresthesia

a) Incidence: up to 2%(Prod Info GEODON(R) oral capsules, IM injection, 2008a)

b) Paresthesia was reported in up to 2% of patients during short-term fixed-dose intramuscular trials of ziprasidone mesylate (Prod Info GEODON(R) oral capsules, IM injection, 2008a).

3.3.9.B.10 Seizure

a) Incidence: 0.4%(Prod Info GEODON(R) oral capsules, IM injection, 2008a)

b) Seizures were reported in 0.4% of ziprasidone mesylate-treated patients during clinical trials, although confounding factors may have contributed to the occurrence in many of these cases (Prod Info GEODON(R) oral capsules, IM injection, 2008a).

3.3.9.B.11 Somnolence

a) Incidence: 8% to 20%(Prod Info GEODON(R) oral capsules, IM injection, 2008a)

b) Somnolence was reported in 8% to 20% of patients during short-term fixed-dose intramuscular trials of ziprasidone mesylate (Prod Info GEODON(R) oral capsules, IM injection, 2008a).

3.3.9.B.12 Tardive dyskinesia

a) The use of antipsychotic drugs, such as ziprasidone mesylate, is a risk factor for the development of tardive dyskinesia. The risk of developing the syndrome increases with duration of treatment and total cumulative dose. The incidence of the syndrome appears to be highest among the elderly, particularly women. However, any patient may be at risk to develop the syndrome, even after a comparatively brief treatment period at a low dose (Prod Info GEODON(R) oral capsules, IM injection, 2008a).

3.3.10 Ophthalmic Effects

3.3.10.A Ziprasidone Hydrochloride

Abnormal vision

Oculogyric crisis

3.3.10.A.1 Abnormal vision

a) Incidence: bipolar mania, 6%; schizophrenia, 3%(Prod Info GEODON(R) oral capsules, IM injection, 2007)

b) The incidence of abnormal vision reported in short-term trials of patients with bipolar mania was 6%

for ziprasidone hydrochloride-treated subjects (n=279) versus 3% for placebo-treated patients (n=136) (Prod Info GEODON(R) oral capsules, IM injection, 2007).
c) In short-term trials, the incidence of abnormal vision was 3% among ziprasidone hydrochloride-treated schizophrenia subjects (n=702) versus 2% for placebo-treated subjects (n=273) (Prod Info GEODON(R) oral capsules, IM injection, 2007).
d) An analysis of four short-term, fixed-dose, placebo-controlled studies of patients with schizophrenia revealed a dependent relationship between the development of abnormal vision and the dose of ziprasidone hydrochloride (Prod Info GEODON(R) oral capsules, IM injection, 2007).

3.3.10.A.2 Oculogyric crisis

a) Oculogyric crisis developed in an 11-year-old boy after receiving ziprasidone 20 milligrams (mg) twice daily for the treatment of pervasive developmental disorder and psychotic symptoms. Six weeks following initiation of ziprasidone therapy, the child had a sudden onset of dystonic upward deviation of the eyes. Ziprasidone was discontinued and the patient was treated with oral diphenhydramine 50 mg every 4 hours. Symptoms subsided within 30 minutes of the first dose and completely resolved within 24 hours (Ramos et al, 2003).

3.3.12 Psychiatric Effects

Ziprasidone Hydrochloride

Ziprasidone Mesylate

3.3.12.A Ziprasidone Hydrochloride

At risk for suicide

Mania

3.3.12.A.1 At risk for suicide

a) Because an attempt at suicide is inherently possible in patients with a psychotic illness or bipolar disorder, high-risk patients on drug therapy should receive close supervision. Also, in order to reduce the risk of overdose, ziprasidone prescriptions should be written for the smallest quantity of capsules consistent with good patient management (Prod Info GEODON(R) oral capsules, IM injection, 2007).

3.3.12.A.2 Mania

a) Summary
1) There have been several case reports of mania/hypomania associated ziprasidone use, including reports during postmarketing use (Prod Info GEODON(R) oral capsules, IM injection, 2007; Brieger, 2004; Baldassano et al, 2003).
b) Hypomania developed in a 40-year-old man on two occasions following the initiation and reinitiation of ziprasidone therapy for the treatment bipolar schizoaffective disorder. Hypomania developed eight days after ziprasidone (100 milligrams (mg)/day) was initiated with ongoing venlafaxine (150 mg/day) and valproate (1200 mg/day) therapy. Symptoms included decreased need for sleep, recklessness, talkativeness, high self-esteem and racing thoughts. Ziprasidone was stopped on day 10 after a worsening of symptoms. However, 6 weeks later, the patient was restarted on ziprasidone treatment (120 mg/day) and again developed a hypomanic episode after eight days of treatment. A dysphoric mood rather than euphoric mood marked this episode and ziprasidone was again discontinued. Symptoms of hypomania resolved within 24 hours on both occasions (Brieger, 2004).
c) Four cases of mania related to the initiation of ziprasidone administration have been reported in bipolar patients. Three of the cases occurred in males 25, 26 and 45 years of age and the other case occurred in a 29-year-old female. In each case the patients were receiving multiple psychotropic medications prior to ziprasidone administration. Each patient received an initial ziprasidone dose of 20 milligrams (mg) twice a day. Manic symptoms occurred within 3 to 7 days in each of the male patients at this dosage. With the woman patient, ziprasidone dosage was increased to 100 mg/day over a period of 5 days and on the fifth day of treatment she developed manic symptoms. Within 3 to 7 days of dosage reduction or discontinuation of ziprasidone, all of the patient's manic symptoms improved. The authors speculated that ziprasidone's potent inhibition of noradrenergic and serotonergic reuptake sites may play a role in the observed switch from bipolar depression to mania (Baldassano et al, 2003).

3.3.12.B Ziprasidone Mesylate

Agitation

At risk for suicide

Personality disorder

3.3.12.B.1 Agitation

a) Incidence: up to 2%(Prod Info GEODON(R) oral capsules, IM injection, 2007)

b) Agitation was reported in up to 2% of patients during short-term fixed-dose intramuscular trials of ziprasidone mesylate (Prod Info GEODON(R) oral capsules, IM injection, 2007).

3.3.12.B.2 At risk for suicide

a) Because an attempt at suicide is inherently possible in patients with a psychotic illness or bipolar disorder, high-risk patients on drug therapy should receive close supervision (Prod Info GEODON(R) oral capsules, IM injection, 2007).

3.3.12.B.3 Personality disorder

a) Incidence: up to 2%(Prod Info GEODON(R) oral capsules, IM injection, 2007)

b) Personality disorder was reported in up to 2% of patients during short-term fixed-dose intramuscular trials of ziprasidone mesylate (Prod Info GEODON(R) oral capsules, IM injection, 2007).

3.3.14 Reproductive Effects

Ziprasidone Hydrochloride

Ziprasidone Mesylate

3.3.14.A Ziprasidone Hydrochloride

3.3.14.A.1 Priapism

a) Incidence: rare(Prod Info GEODON(R) oral capsules, IM injection, 2007)

b) Although no causal relationship has been established, rare postmarketing reports of priapism with ziprasidone use have been observed and one case was reported during premarketing trials. Surgical intervention may be required in severe cases (Prod Info GEODON(R) oral capsules, IM injection, 2007).

c) An African American male developed priapism on two occasions after receiving risperidone and again after receiving ziprasidone for the treatment of schizophrenia. Following risperidone treatment (4 milligrams (mg) twice daily) the man developed an erection lasting 13 hours, which resolved upon irrigation of the corpora with phenylephrine 200 micrograms. Following discontinuation of risperidone, the patient developed another unwanted erection after an increase in his ziprasidone dose from 20 mg twice daily to 40 mg twice daily. This erection lasted 2 hours and resolved upon urination. He experienced several more unwanted erections until the ziprasidone was discontinued and the priapism quickly resolved (Reeves et al, 2002).

3.3.14.B Ziprasidone Mesylate

Dysmenorrhea

Priapism

3.3.14.B.1 Dysmenorrhea

a) Incidence: up to 2%(Prod Info GEODON(R) oral capsules, IM injection, 2007)

b) Dysmenorrhea was reported in up to 2% of patients during short-term fixed-dose intramuscular trials of ziprasidone mesylate (Prod Info GEODON(R) oral capsules, IM injection, 2007).

3.3.14.B.2 Priapism

a) Incidence: up to 1%(Prod Info GEODON(R) oral capsules, IM injection, 2007)

b) Priapism, reported in up to 1% of patients during short-term fixed-dose intramuscular trials of ziprasidone mesylate, has also been observed during postmarketing use. Surgical intervention may be required in severe cases (Prod Info GEODON(R) oral capsules, IM injection, 2007).

3.3.15 Respiratory Effects

3.3.15.A Ziprasidone Hydrochloride

Cough

Dyspnea

Respiratory tract infection

Rhinitis

3.3.15.A.1 Cough

a) Incidence: bipolar mania, not reported; schizophrenia, 3%(Prod Info GEODON(R) oral capsules, IM injection, 2007)

b) In short-term trials, the incidence of cough was 3% among ziprasidone hydrochloride-treated schizophrenia subjects (n=702) versus 1% for placebo-treated subjects (n=273) (Prod Info GEODON(R) oral capsules, IM injection, 2007).

3.3.15.A.2 Dyspnea

a) Incidence: bipolar mania, 2%; schizophrenia, frequent(Prod Info GEODON(R) oral capsules, IM injection, 2007)

b) The incidence of dyspnea reported in short-term trials of patients with bipolar mania was 2% for ziprasidone hydrochloride-treated subjects (n=279) versus 1% for placebo-treated patients (n=136) (Prod Info GEODON(R) oral capsules, IM injection, 2007).

c) Dyspnea was frequently observed during premarketing schizophrenia clinical trials at multiple doses greater than 4 milligrams/day (Prod Info GEODON(R) oral capsules, IM injection, 2007).

3.3.15.A.3 Respiratory tract infection

a) Incidence: bipolar mania, not reported; schizophrenia, 8%(Prod Info GEODON(R) oral capsules, IM injection, 2007)

b) In short-term trials, the incidence of respiratory tract infection was 8% among ziprasidone hydrochloride-treated schizophrenia subjects (n=702) versus 3% for placebo-treated subjects (n=273) (Prod Info GEODON(R) oral capsules, IM injection, 2007).

3.3.15.A.4 Rhinitis

a) Incidence: bipolar mania, not reported; schizophrenia, 4%(Prod Info GEODON(R) oral capsules, IM injection, 2007)

b) In short-term trials, the incidence of rhinitis was 4% among ziprasidone hydrochloride-treated schizophrenia subjects (n=702) versus 2% for placebo-treated subjects (n=273) (Prod Info GEODON(R) oral capsules, IM injection, 2007).

c) An analysis of four short-term, fixed-dose, placebo-controlled studies of patients with schizophrenia revealed a dependent relationship between the development of rhinitis and the dose of ziprasidone hydrochloride (Prod Info GEODON(R) oral capsules, IM injection, 2007).

3.3.16 Other

Ziprasidone Hydrochloride

Ziprasidone Mesylate

3.3.16.A Ziprasidone Hydrochloride

Accidental injury

Death

3.3.16.A.1 Accidental injury

a) Incidence: bipolar mania and schizophrenia, 4%(Prod Info GEODON(R) oral capsules, IM injection, 2007)

b) The incidence of accidental injuries reported in short-term trials of patients with bipolar mania was 4% for ziprasidone hydrochloride-treated subjects (n=279) versus 1% for placebo-treated patients (n=136) (Prod Info GEODON(R) oral capsules, IM injection, 2007).

c) In short-term trials, the incidence of accidental injuries was 4% among ziprasidone hydrochloride-

treated schizophrenia subjects (n=702) versus 2% for placebo-treated subjects (n=273) (Prod Info GEODON(R) oral capsules, IM injection, 2007).

3.3.16.A.2 Death

a) Results of a population-based, retrospective cohort study demonstrated that the use of conventional antipsychotics was associated with an even greater risk for death than atypical antipsychotics when administered to elderly patients (aged 66 years and older) with dementia. Atypical versus no antipsychotic use and conventional versus atypical antipsychotic use pair-wise comparisons were made. A total of 27,259 matched pairs were identified and the dementia cohort was stratified based on place of residence (community versus long-term care facilities). In order to adjust for difference in baseline health status, propensity score matching was used. The primary outcome of the study was all-cause mortality. The risk for death was evaluated at 30, 60, 120, and 180 days after the antipsychotic medications were initially dispensed. There was a statistically significant increase in the risk for death at 30 days associated with new use of atypical antipsychotic medications compared with nonuse in both the community-dwelling cohort (adjusted hazard ratio (HR), 1.31 (95% confidence interval (CI), 1.02 to 1.70); absolute risk difference, 0.2 percentage point) and long-term care cohort (adjusted HR, 1.55 (95% CI, 1.15 to 2.07); absolute risk difference, 1.2 percentage points). For both cohorts, the risk associated with atypical antipsychotics appeared to persist to 180 days. The risk for death associated with conventional antipsychotics was even greater than the risk identified with atypical antipsychotics. At 30 days, the adjusted HR for the community-dwelling cohort was 1.55 (95% CI, 1.19 to 2.02) and 1.26 (95% CI, 1.04 to 1.53) for the long-term care cohort (adjusted risk difference for both was 1.1 percentage points). The risk appeared to persist to 180 days for both groups. Some important limitations to the study include unknown or unmeasured confounders may influence the results and cause of death could not be examined (Gill et al, 2007).

b) Results of a population-based, retrospective cohort study demonstrated comparable to possibly greater risk of death associated with the use of conventional antipsychotic medications in the elderly (aged 65 years and older) compared with atypical antipsychotic medications. The analysis excluded patients with cancer and included only new users of antipsychotic medications. The primary study outcome was 180-day all-cause mortality. A set of potential confounders was measured based on healthcare utilization data within 6 months before the initiation of antipsychotic medications. Of the 37,241 elderly patients identified, 12,882 and 24,359 received conventional and atypical antipsychotic medications, respectively. The risk of death in the conventional drug group within the first 180 days was 14.1% compared with 9.6% in the atypical drug group (unadjusted mortality ratio, 1.47; 95% confidence interval (CI), 1.39 to 1.56). In the multi-variable analysis which controlled for potential confounders, the adjusted mortality ratio for the risk of death within 180 days for conventional versus atypical drug therapy was 1.32 (95% CI, 1.23 to 1.42). When the most frequently prescribed conventional antipsychotic drugs were compared with risperidone, the mortality ratio associated with haloperidol was 2.14 (95% CI, 1.86 to 2.45) and loxapine was 1.29 (95% CI, 1.19 to 1.40), while there was no difference associated with olanzapine. The increased mortality risk for conventional versus atypical drug therapy was greatest when doses higher (above median) doses were used (mortality ratio 1.67; 95% CI, 1.5 to 1.86) and also during the first 40 days of therapy (mortality ratio 1.6; 95% CI, 1.42 to 1.8). Confirmatory analyses consisting of multi-variable Cox regression, propensity score, and instrumental variable estimation confirmed the results of the study (Schneeweiss et al, 2007).

c) The results of a retrospective cohort study indicate that conventional antipsychotic agents are at least as likely as atypical antipsychotic agents to increase the risk of death among elderly patients 65 years of age or older. The study included 9,142 new users of conventional agents (mean age, 83.2 years) and 13,748 new users of atypical agents (mean age, 83.5 years). A higher adjusted relative risk of death was associated with the use of conventional antipsychotics as compared with atypical antipsychotics at all time points studied after beginning therapy (within 180 days: RR, 1.37; 95% CI=1.27 to 1.49; less than 40 days: RR, 1.56; 95% CI=1.37 to 1.78; 40 to 79 days: RR, 1.37; 95% CI=1.19 to 1.59; 80 to 180 days: RR, 1.27; 95% CI=1.14 to 1.41). In addition, the adjusted risks of death observed in patients with dementia (RR, 1.29; 95% CI=1.15 to 1.45), without dementia (RR, 1.45; 95% CI=1.30 to 1.63), in a nursing home (RR, 1.26; 95% CI=1.08 to 1.47), or not in a nursing home (RR, 1.42; 95% CI=1.29 to 1.56) were also higher with the use of conventional antipsychotic therapy as compared with atypical antipsychotic use. This risk appeared to be dose-related and was greater with the use of higher dose (ie, greater than the median) conventional antipsychotics (RR, 1.73; 95% CI=1.57 to 1.90). Additional studies which specifically investigate the optimum care of elderly patients requiring antipsychotic therapy are needed so that appropriate guidance regarding therapeutic intervention can be provided (Wang et al, 2005).

3.3.16.B Ziprasidone Mesylate

3.3.16.B.1 Death

a) Results of a population-based, retrospective cohort study demonstrated that the use of conventional antipsychotics was associated with an even greater risk for death than atypical antipsychotics when administered to elderly patients (aged 66 years and older) with dementia. Atypical versus no antipsychotic use and conventional versus atypical antipsychotic use pair-wise comparisons were made. A total of 27,259 matched pairs were identified and the dementia cohort was stratified based on

place of residence (community versus long-term care facilities). In order to adjust for difference in baseline health status, propensity score matching was used. The primary outcome of the study was all-cause mortality. The risk for death was evaluated at 30, 60, 120, and 180 days after the antipsychotic medications were initially dispensed. There was a statistically significant increase in the risk for death at 30 days associated with new use of atypical antipsychotic medications compared with nonuse in both the community-dwelling cohort (adjusted hazard ratio (HR), 1.31 (95% confidence interval (CI), 1.02 to 1.70); absolute risk difference, 0.2 percentage point) and long-term care cohort (adjusted HR, 1.55 (95% CI, 1.15 to 2.07); absolute risk difference, 1.2 percentage points). For both cohorts, the risk associated with atypical antipsychotics appeared to persist to 180 days. The risk for death associated with conventional antipsychotics was even greater than the risk identified with atypical antipsychotics. At 30 days, the adjusted HR for the community-dwelling cohort was 1.55 (95% CI, 1.19 to 2.02) and 1.26 (95% CI, 1.04 to 1.53) for the long-term care cohort (adjusted risk difference for both was 1.1 percentage points). The risk appeared to persist to 180 days for both groups. Some important limitations to the study include unknown or unmeasured confounders may influence the results and cause of death could not be examined (Gill et al, 2007).

b) Results of a population-based, retrospective cohort study demonstrated comparable to possibly greater risk of death associated with the use of conventional antipsychotic medications in the elderly (aged 65 years and older) compared with atypical antipsychotic medications. The analysis excluded patients with cancer and included only new users of antipsychotic medications. The primary study outcome was 180-day all-cause mortality. A set of potential confounders was measured based on healthcare utilization data within 6 months before the initiation of antipsychotic medications. Of the 37,241 elderly patients identified, 12,882 and 24,359 received conventional and atypical antipsychotic medications, respectively. The risk of death in the conventional drug group within the first 180 days was 14.1% compared with 9.6% in the atypical drug group (unadjusted mortality ratio, 1.47; 95% confidence interval (CI), 1.39 to 1.56). In the multi-variable analysis which controlled for potential confounders, the adjusted mortality ratio for the risk of death within 180 days for conventional versus atypical drug therapy was 1.32 (95% CI, 1.23 to 1.42). When the most frequently prescribed conventional antipsychotic drugs were compared with risperidone, the mortality ratio associated with haloperidol was 2.14 (95% CI, 1.86 to 2.45) and loxapine was 1.29 (95% CI, 1.19 to 1.40), while there was no difference associated with olanzapine. The increased mortality risk for conventional versus atypical drug therapy was greatest when doses higher (above median) doses were used (mortality ratio 1.67; 95% CI, 1.5 to 1.86) and also during the first 40 days of therapy (mortality ratio 1.6; 95% CI, 1.42 to 1.8). Confirmatory analyses consisting of multi-variable Cox regression, propensity score, and instrumental variable estimation confirmed the results of the study (Schneeweiss et al, 2007).

3.4 Teratogenicity/Effects in Pregnancy/Breastfeeding

A) Teratogenicity/Effects in Pregnancy

1) U.S. Food and Drug Administration's Pregnancy Category: Category C (Prod Info Geodon(R), 2002ad) (All Trimesters)

a) Either studies in animals have revealed adverse effects on the fetus (teratogenic or embryocidal or other) and there are no controlled studies in women or studies in women and animals are not available. Drugs should be given only if the potential benefit justifies the potential risk to the fetus.

See Drug Consult reference: PREGNANCY RISK CATEGORIES

2) Crosses Placenta: Unknown

3) Clinical Management

a) There is insufficient clinical experience with the use of ziprasidone in pregnant patients to confirm its safety in that patient population. Until additional data are available, caution should be exercised with the use of ziprasidone in pregnancy. Detailed fetal ultrasonography is recommended for monitoring fetal outcome following inadvertent exposure (Schaefer, 2001).

4) Literature Reports

a) No human studies of pregnancy outcomes after exposure to ziprasidone have been published, and there are no reports of outcomes after inadvertent exposure during pregnancy.

B) Breastfeeding

1) Thomson Lactation Rating: Infant risk cannot be ruled out.

a) Available evidence and/or expert consensus is inconclusive or is inadequate for determining infant risk when used during breastfeeding. Weigh the potential benefits of drug treatment against potential risks before prescribing this drug during breastfeeding.

2) Clinical Management

a) It is not known whether ziprasidone or its metabolites are excreted into human breast milk, and the potential for adverse effects in the nursing infant from exposure to the drug are unknown. The manufacturer recommends that women receiving ziprasidone not breast feed their infants (Prod Info Ziprasidone(R), 2002).

3) Literature Reports

a) No reports describing the use of ziprasidone during human lactation or measuring the amount, if any, of the drug excreted into milk have been located.

3.5 Drug Interactions

3.5.1 Drug-Drug Combinations

Acecainide

Ajmaline

Ajmaline

Amiodarone

Amisulpride

Amitriptyline

Amoxapine

Aprindine

Arsenic Trioxide

Arsenic Trioxide

Astemizole

Azimilide

Bepridil

Bretylium

Carbamazepine

Chloral Hydrate

Chloroquine

Chlorpromazine

Chlorpromazine

Cisapride

Clarithromycin

Desipramine

Disopyramide

Disopyramide

Dofetilide

Dolasetron

Doxepin

Droperidol

Enflurane

Erythromycin

Flecainide

Fluconazole

Fluoxetine

Foscarnet

Gatifloxacin

Gemifloxacin

Halofantrine

Haloperidol

Halothane

Hydroquinidine

Hydroquinidine

Ibutilide

Iloperidone

Imipramine

Isoflurane

Isradipine

Lapatinib

Levofloxacin

Levomethadyl

Lidoflazine

Lorcainide

Lumefantrine

Mefloquine

Mesoridazine

Mesoridazine

Methadone

Moxifloxacin

Nilotinib

Nortriptyline

Octreotide

Pentamidine

Pimozide

Pirmenol

Pirmenol

Prajmaline

Prajmaline

Probucol

Procainamide

Procainamide

Prochlorperazine

Prochlorperazine

Propafenone

Protriptyline

Quinidine

Ranolazine

Sematilide

Sertindole

Sotalol

Sparfloxacin

Spiramycin

Sultopride

Sunitinib

Tacrolimus

Tedisamil

Telithromycin

Terfenadine

Tetrabenazine

Tetrabenazine

Thioridazine

Trifluoperazine

Trifluoperazine

Trimipramine

Vasopressin

Zolmitriptan

Zotepine

3.5.1.A Acecainide

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: The manufacturer of ziprasidone states that concomitant use of ziprasidone and Class III antiarrhythmic agents is contraindicated (Prod Info Geodon(TM), 2002m). Bretylium should not be used with other drugs known to prolong the QTc interval , including ziprasidone (Yamreudeewong et al, 2003a).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of ziprasidone and Class III antiarrhythmic agents is contraindicated.
7) Probable Mechanism: additive QT prolongation
8) Literature Reports
a) Concurrent use of class III antiarrhythmic agents, and other drugs that can prolong the QT interval, such as ziprasidone, is not recommended. Dofetilide should be stopped for at least 2 days before any interacting drug is initiated (Yamreudeewong et al, 2003).

3.5.1.B Ajmaline

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, the manufacturer of ziprasidone warns against its administration with other drugs which are also known to prolong the QTc interval, including Class IA antiarrhythmic agents (Prod Info Geodon(R), 2002j).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of a Class IA antiarrhythmic and ziprasidone is contraindicated.
7) Probable Mechanism: additive cardiac effects

3.5.1.C Ajmaline

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Several antipsychotic agents have demonstrated QT prolongation including amisulpride, haloperidol, iloperidone, paliperidone, quetiapine, risperidone, sertindole, sultopride, ziprasidone, and zotepine (Prod Info FANAPT(TM) oral tablets, 2009; Prod Info Solian(R), 1999e; O'Brien et al, 1999d; Prod Info INVEGA(TM) extended-release oral tablets, 2006; Owens, 2001i; Duenas-Laita et al, 1999f; Agelink et al, 2001d; Lande et al, 1992f; Prod Info GEODON(R) intramuscular injection, oral capsule, 2005; Sweetman,

2003). Because Class IA antiarrhythmic agents may also prolong the QT interval and increase the risk of arrhythmias, the concurrent administration of antipsychotics with a drug from this class is not recommended (Prod Info FANAPT(TM) oral tablets, 2009; Prod Info Quinaglute(R), 1999).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: The concurrent administration of a Class IA antiarrhythmic and an antipsychotic is not recommended.
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) In an open-label QTc study of patients with schizophrenia or schizoaffective disorder (n=160), iloperidone 12 mg twice a day was associated with QTc prolongation of 9 msec (Prod Info FANAPT(TM) oral tablets, 2009).
b) QRS widening, QTc interval prolongation, and torsades de pointes may occur with disopyramide therapy (Prod Info Norpace(R), 1997).
c) The effects of combined therapy with quinidine (Class IA antiarrhythmic agent) and haloperidol (antipsychotic agent) were studied by giving 12 healthy volunteers haloperidol 5 mg alone and with 250 mg of quinidine bisulfate. The study demonstrated significant increases in the plasma concentrations of haloperidol when given concurrently with quinidine versus haloperidol treatment alone. The mean area under the concentration curve (AUC) was increased from 54.3 ng/h/mL on haloperidol alone to 103.2 ng/h/mL on combined therapy. The peak concentration (Cmax) also showed an increase from 1.9 ng/mL on haloperidol to 3.8 ng/mL on combined therapy. Half-life (T1/2) and time to peak concentration (Tmax) were not significantly changed, thereby suggesting to the authors that a tissue binding mechanism is more likely responsible for the plasma level changes than an elimination alteration (Young et al, 1993).

3.5.1.D Amiodarone
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: The manufacturer of ziprasidone states that concomitant use of ziprasidone and Class III antiarrhythmic agents is contraindicated (Prod Info Geodon(TM), 2002m). Bretylium should not be used with other drugs known to prolong the QTc interval , including ziprasidone (Yamreudeewong et al, 2003a).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of ziprasidone and Class III antiarrhythmic agents is contraindicated.
7) Probable Mechanism: additive QT prolongation
8) Literature Reports
a) Concurrent use of class III antiarrhythmic agents, and other drugs that can prolong the QT interval, such as ziprasidone, is not recommended. Dofetilide should be stopped for at least 2 days before any interacting drug is initiated (Yamreudeewong et al, 2003).

3.5.1.E Amisulpride
1) Interaction Effect: cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Coadministration of ziprasidone with other drugs that potentially prolong the QTc interval, such as amisulpride, is contraindicated (Prod Info Solian(R), 1999d; Prod Info Geodon(R), 2002t).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of ziprasidone with agents that prolong the QT interval, such as amisulpride, is contraindicated.
7) Probable Mechanism: additive effects on QT prolongation
8) Literature Reports
a) Ziprasidone prolongs the QTc in some patients in a dose-related manner. It is not yet known whether ziprasidone will cause torsades de pointes or increase the rate of sudden death. In clinical trials ziprasidone increased the QTc interval, compared to placebo, by approximately 10 milliseconds (msec) at the highest dose (160 milligrams) (Prod Info Geodon(R), 2002s).

3.5.1.F Amitriptyline
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Ziprasidone use is associated with dose-related prolongation of the QTc interval. Even though no formal drug interaction studies have been done, it is recommended that concurrent use with other agents that may prolong QTc interval be avoided (Prod Info GEODON(R) oral capsules, IM injection, 2007; Marshall & Forker, 1982).
3) Severity: major
4) Onset: unspecified

5) Substantiation: theoretical
6) Clinical Management: Due to the potential for additive QTc interval prolongation, avoid the concurrent administration of ziprasidone and agents that can prolong the QTc interval (Prod Info GEODON(R) oral capsules, IM injection, 2007).
7) Probable Mechanism: additive cardiac effects

3.5.1.G Amoxapine
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Ziprasidone use is associated with dose-related prolongation of the QTc interval. Even though no formal drug interaction studies have been done, it is recommended that concurrent use with other agents that may prolong QTc interval be avoided (Prod Info GEODON(R) oral capsules, IM injection, 2007; Marshall & Forker, 1982).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Due to the potential for additive QTc interval prolongation, avoid the concurrent administration of ziprasidone and agents that can prolong the QTc interval (Prod Info GEODON(R) oral capsules, IM injection, 2007).
7) Probable Mechanism: additive cardiac effects

3.5.1.H Aprindine
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, the coadministration of Class I antiarrhythmics and other drugs known to prolong the QTc interval, such as ziprasidone is contraindicated (Prod Info Geodon(TM), 2002j; Prod Info Tambocor(R) flecainide acetate, 1998).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of ziprasidone and Class I antiarrhythmic agents is contraindicated.
7) Probable Mechanism: additive cardiac effects

3.5.1.I Arsenic Trioxide
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, ziprasidone should not be coadministered with other drugs, such as arsenic trioxide, which are also known to prolong the QTc interval (Prod Info Geodon(R), 2002i; Prod Info Trisenox(R), 2000).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of ziprasidone with other agents that can prolong the QT interval, such as arsenic trioxide, is contraindicated.
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) It has been shown that ziprasidone prolongs the QTc and that this represents a risk of potentially fatal ventricular dysrhythmias (Anon, 2000). QT prolongation is dose-related. It is not yet known whether ziprasidone will cause torsades de pointes or increase the rate of sudden death. In clinical trials ziprasidone increased the QTc interval, compared to placebo, by approximately 10 milliseconds (msec) at the highest dose (160 milligrams). Baseline QTc interval increased 9 to 14 msec more with ziprasidone than with risperidone, olanzapine, quetiapine, and haloperidol, but QTc interval was 14 msec less than that observed with thioridazine (Prod Info Geodon(R), 2002h).
b) QT/QTc prolongation should be expected during treatment with arsenic trioxide and torsade de pointes as well as complete heart block has been reported. Over 460 ECG tracings from 40 patients with refractory or relapsed APL treated with arsenic trioxide were evaluated for QTc prolongation. Sixteen of 40 patients (40%) had at least one ECG tracing with a QTc interval greater than 500 msec. Prolongation of the QTc was observed between 1 and 5 weeks after arsenic trioxide infusion, and then returned towards baseline by the end of 8 weeks after arsenic trioxide infusion. In these ECG evaluations, women did not experience more pronounced QT prolongation than men, and there was no correlation with age (Prod Info Trisenox(R), 2001).

3.5.1.J Arsenic Trioxide
1) Interaction Effect: prolongation of the QTc interval and/or torsades de pointes
2) Summary: Arsenic trioxide can prolong the QT interval in some patients, which may result in ventricular tachycardia, ventricular fibrillation, and torsades de pointes and should not be administered with other drugs that may prolong the QT interval (Prod Info Trisenox(R), 2001b). Several antipsychotic agents have

demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999a), haloperidol (O'Brien et al, 1999a), paliperidone (Prod Info INVEGA(TM) extended-release oral tablets, 2006), risperidone (Duenas-Laita et al, 1999c), sertindole (Agelink et al, 2001b), quetiapine (Owens, 2001d), sultopride (Lande et al, 1992c), ziprasidone (Prod Info GEODON(R) intramuscular injection, oral capsule, 2005), and zotepine (Sweetman, 2003).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of arsenic trioxide and antipsychotics is not recommended.
7) Probable Mechanism: additive effects on QTc prolongation
8) Literature Reports
a) QT/QTc prolongation should be expected during treatment with arsenic trioxide and torsade de pointes as well as complete heart block has been reported. Over 460 ECG tracings from 40 patients with refractory or relapsed APL treated with arsenic trioxide were evaluated for QTc prolongation. Sixteen of 40 patients (40%) had at least one ECG tracing with a QTc interval greater than 500 msec. Prolongation of the QTc was observed between 1 and 5 weeks after arsenic trioxide infusion, and then returned towards baseline by the end of 8 weeks after arsenic trioxide infusion. In these ECG evaluations, women did not experience more pronounced QT prolongation than men, and there was no correlation with age (Prod Info Trisenox(R), 2001a).

3.5.1.K Astemizole
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, the manufacturer of ziprasidone warns against its administration with other drugs which are also known to prolong the QTc interval, including astemizole (Prod Info Geodon(TM), 2002z).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of ziprasidone and astemizole is contraindicated.
7) Probable Mechanism: additive cardiac effects

3.5.1.L Azimilide
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: The manufacturer of ziprasidone states that concomitant use of ziprasidone and Class III antiarrhythmic agents is contraindicated (Prod Info Geodon(TM), 2002m). Bretylium should not be used with other drugs known to prolong the QTc interval , including ziprasidone (Yamreudeewong et al, 2003a).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of ziprasidone and Class III antiarrhythmic agents is contraindicated.
7) Probable Mechanism: additive QT prolongation
8) Literature Reports
a) Concurrent use of class III antiarrhythmic agents, and other drugs that can prolong the QT interval, such as ziprasidone, is not recommended. Dofetilide should be stopped for at least 2 days before any interacting drug is initiated (Yamreudeewong et al, 2003).

3.5.1.M Bepridil
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Some antipsychotic agents prolong the QT interval and an additive effect would be anticipated if administered with other agents which lengthen the QT interval (Prod Info Geodon(TM), 2002d; Agelink et al, 2001; Owens, 2001a; Prod Info Orap(R), 1999c; Prod Info Haldol(R), 1998). In U.S. clinical trials, bepridil increased QT and QTc intervals which was associated with torsades de pointes in approximately 1% of patients. Other drugs that increase the QT interval may exaggerate the prolongation of the QT interval observed with bepridil (Prod Info Vascor(R), 1997). Pimozide is contraindicated in patients taking other drugs which may prolong the QT interval (Prod Info Orap(R), 1999c).
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of antipsychotics and agents that prolong the QT interval, such as bepridil, is contraindicated. In particular, pimozide is contraindicated in individuals with congenital QT syndrome, patients with a history of cardiac arrhythmias, or patients taking other drugs which may prolong the QT interval.
7) Probable Mechanism: additive effects on QT prolongation

8) Literature Reports

a) Electrocardiographic changes that have occurred during clinical trials with pimozide have included prolongation of the corrected QT interval, flattening, notching, and inversion of the T wave and the appearance of U waves. In experimental studies, sudden, unexpected deaths have occurred while patients were receiving pimozide doses of 1 mg/kg. The proposed mechanism for these deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmias (Prod Info Orap(R), 1999b).

b) Sometimes fatal QRS prolongation and QTc prolongation have been reported in patients taking risperidone therapeutically (Duenas-Laita et al, 1999a; Ravin & Levenson, 1997a).

3.5.1.N Bretylium

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: The manufacturer of ziprasidone states that concomitant use of ziprasidone and Class III antiarrhythmic agents is contraindicated (Prod Info Geodon(TM), 2002m). Bretylium should not be used with other drugs known to prolong the QTc interval , including ziprasidone (Yamreudeewong et al, 2003a).

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of ziprasidone and Class III antiarrhythmic agents is contraindicated.

7) Probable Mechanism: additive QT prolongation

8) Literature Reports

a) Concurrent use of class III antiarrhythmic agents, and other drugs that can prolong the QT interval, such as ziprasidone, is not recommended. Dofetilide should be stopped for at least 2 days before any interacting drug is initiated (Yamreudeewong et al, 2003).

3.5.1.O Carbamazepine

1) Interaction Effect: decreased ziprasidone plasma concentrations

2) Summary: Ziprasidone is metabolized primarily by CYP3A4. The concomitant use of carbamazepine (a CYP3A4 inducer) 200 mg twice daily for 21 days decreased the ziprasidone AUC by approximately 35%. Therefore, caution should be used when carbamazepine and ziprasidone are coadministered due to the potential for reduced ziprasidone plasma concentrations (Prod Info GEODON(R) oral capsules, IM injection, 2008).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Use caution when prescribing carbamazepine to a patient who takes ziprasidone. Concomitant use of carbamazepine and ziprasidone has resulted in decreased ziprasidone plasma concentrations (Prod Info GEODON(R) oral capsules, IM injection, 2008).

7) Probable Mechanism: induction of CYP3A4-mediated ziprasidone metabolism by carbamazepine

3.5.1.P Chloral Hydrate

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Even though no formal drug interaction studies have been done, the manufacturer of ziprasidone warns against its administration with other drugs which are also known to prolong the QTc interval, including chloral hydrate (Prod Info Geodon(TM), 2002k; Young et al, 1986).

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of ziprasidone and chloral hydrate is contraindicated.

7) Probable Mechanism: additive cardiac effects

3.5.1.Q Chloroquine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Even though no formal drug interaction studies have been done, the manufacturer of ziprasidone warns against its administration with other drugs which are also known to prolong the QTc interval, including chloroquine (Prod Info Geodon(TM), 2002l). Chloroquine has been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Aralen(R), 1999).

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of ziprasidone and chloroquine is contraindicated.

7) Probable Mechanism: additive cardiac effects

3.5.1.R Chlorpromazine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Concomitant use of phenothiazines and antipsychotic agents may cause additive effects on the QT interval and is not recommended. Q and T wave distortions have been observed in patients taking phenothiazines (Prod Info Compazine(R), 2002; Prod Info Stelazine(R), 2002; Prod Info Thorazine(R), 2002). Other phenothiazines may have similar effects, though no reports are available. Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999), haloperidol (O'Brien et al, 1999), paliperidone (Prod Info INVEGA(TM) extended-release oral tablets, 2006), quetiapine (Owens, 2001c), risperidone (Duenas-Laita et al, 1999b), sertindole (Agelink et al, 2001a), sultopride (Lande et al, 1992), ziprasidone (Prod Info GEODON(R) intramuscular injection, oral capsule, 2005), and zotepine (Sweetman, 2003).

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of agents that prolong the QT interval, such as phenothiazines and antipsychotics, is not recommended.

7) Probable Mechanism: additive QT prolongation

3.5.1.S Chlorpromazine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: The manufacturer of ziprasidone states that concomitant use of ziprasidone and phenothiazines is contraindicated (Prod Info Compazine(R), 2002a; Prod Info Geodon(R), 2002w).

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of ziprasidone and other drugs that may prolong the QT interval, such as phenothiazines, is contraindicated.

7) Probable Mechanism: additive QT prolongation

3.5.1.T Cisapride

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Some antipsychotic agents prolong the QT interval and an additive effect would be anticipated if administered with other agents which lengthen the QT interval (Prod Info Geodon(TM), 2002c; Owens, 2001; Prod Info Orap(R), 1999a). Torsades de pointes and QT prolongation have been reported with cisapride (Prod Info Propulsid(R), 2000).

3) Severity: contraindicated

4) Onset: rapid

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of antipsychotics and agents that prolong the QT interval, such as cisapride, is contraindicated. In particular, pimozide is contraindicated in individuals with congenital QT syndrome, patients with a history of cardiac arrhythmias, or patients taking other drugs which may prolong the QT interval.

7) Probable Mechanism: additive effects on QT prolongation

8) Literature Reports

a) Electrocardiographic changes that have occurred during clinical trials with pimozide have included prolongation of the corrected QT interval, flattening, notching, and inversion of the T wave and the appearance of U waves. In experimental studies, sudden, unexpected deaths have occurred while patients were receiving pimozide doses of 1 mg/kg. The proposed mechanism for these deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmias (Prod Info Orap(R), 1999).

b) Fatal QRS prolongation and QTc prolongation have been reported in patients taking risperidone (Duenas-Laita et al, 1999; Ravin & Levenson, 1997).

3.5.1.U Clarithromycin

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Even though no formal drug interaction studies have been done, the manufacturer of ziprasidone warns against its administration with other drugs which are also known to prolong the QTc interval, including clarithromycin (Prod Info Geodon(TM), 2002s; Prod Info Biaxin(R), 2002).

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of ziprasidone and clarithromycin is contraindicated.

7) Probable Mechanism: additive cardiac effects

3.5.1.V Desipramine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Ziprasidone use is associated with dose-related prolongation of the QTc interval. Even though no formal drug interaction studies have been done, it is recommended that concurrent use with other agents that may prolong QTc interval be avoided (Prod Info GEODON(R) oral capsules, IM injection, 2007; Marshall & Forker, 1982).

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Due to the potential for additive QTc interval prolongation, avoid the concurrent administration of ziprasidone and agents that can prolong the QTc interval (Prod Info GEODON(R) oral capsules, IM injection, 2007).

7) Probable Mechanism: additive cardiac effects

3.5.1.W Disopyramide

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Even though no formal drug interaction studies have been done, the manufacturer of ziprasidone warns against its administration with other drugs which are also known to prolong the QTc interval, including Class IA antiarrhythmic agents (Prod Info Geodon(R), 2002j).

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of a Class IA antiarrhythmic and ziprasidone is contraindicated.

7) Probable Mechanism: additive cardiac effects

3.5.1.X Disopyramide

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Several antipsychotic agents have demonstrated QT prolongation including amisulpride, haloperidol, iloperidone, paliperidone, quetiapine, risperidone, sertindole, sultopride, ziprasidone, and zotepine (Prod Info FANAPT(TM) oral tablets, 2009; Prod Info Solian(R), 1999e; O'Brien et al, 1999d; Prod Info INVEGA(TM) extended-release oral tablets, 2006; Owens, 2001i; Duenas-Laita et al, 1999f; Agelink et al, 2001d; Lande et al, 1992f; Prod Info GEODON(R) intramuscular injection, oral capsule, 2005; Sweetman, 2003). Because Class IA antiarrhythmic agents may also prolong the QT interval and increase the risk of arrhythmias, the concurrent administration of antipsychotics with a drug from this class is not recommended (Prod Info FANAPT(TM) oral tablets, 2009; Prod Info Quinaglute(R), 1999).

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: The concurrent administration of a Class IA antiarrhythmic and an antipsychotic is not recommended.

7) Probable Mechanism: additive cardiac effects

8) Literature Reports

a) In an open-label QTc study of patients with schizophrenia or schizoaffective disorder (n=160), iloperidone 12 mg twice a day was associated with QTc prolongation of 9 msec (Prod Info FANAPT(TM) oral tablets, 2009).

b) QRS widening, QTc interval prolongation, and torsades de pointes may occur with disopyramide therapy (Prod Info Norpace(R), 1997).

c) The effects of combined therapy with quinidine (Class IA antiarrhythmic agent) and haloperidol (antipsychotic agent) were studied by giving 12 healthy volunteers haloperidol 5 mg alone and with 250 mg of quinidine bisulfate. The study demonstrated significant increases in the plasma concentrations of haloperidol when given concurrently with quinidine versus haloperidol treatment alone. The mean area under the concentration curve (AUC) was increased from 54.3 ng/h/mL on haloperidol alone to 103.2 ng/h/mL on combined therapy. The peak concentration (Cmax) also showed an increase from 1.9 ng/mL on haloperidol to 3.8 ng/mL on combined therapy. Half-life (T1/2) and time to peak concentration (Tmax) were not significantly changed, thereby suggesting to the authors that a tissue binding mechanism is more likely responsible for the plasma level changes than an elimination alteration (Young et al, 1993).

3.5.1.Y Dofetilide

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: The manufacturer of ziprasidone states that concomitant use of ziprasidone and Class III antiarrhythmic agents is contraindicated (Prod Info Geodon(TM), 2002m). Bretylium should not be used with other drugs known to prolong the QTc interval , including ziprasidone (Yamreudeewong et al, 2003a).

3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of ziprasidone and Class III antiarrhythmic agents is contraindicated.
7) Probable Mechanism: additive QT prolongation
8) Literature Reports
a) Concurrent use of class III antiarrhythmic agents, and other drugs that can prolong the QT interval, such as ziprasidone, is not recommended. Dofetilide should be stopped for at least 2 days before any interacting drug is initiated (Yamreudeewong et al, 2003).

3.5.1.Z Dolasetron
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, ziprasidone should not be coadministered with other drugs which are also known to prolong the QTc interval (Prod Info Geodon(R), 2002f).
3) Severity: contraindicated
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of ziprasidone with other agents that can prolong the QT interval, such as dolasetron, is contraindicated.
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) It has been shown that ziprasidone prolongs the QTc and that this represents a risk of potentially fatal ventricular dysrhythmias (Anon, 2000). QT prolongation is dose-related. It is not yet known whether ziprasidone will cause torsades de pointes or increase the rate of sudden death. In clinical trials ziprasidone increased the QTc interval, compared to placebo, by approximately 10 milliseconds (msec) at the highest dose (160 milligrams). Baseline QTc interval increased 9 to 14 msec more with ziprasidone than with risperidone, olanzapine, quetiapine, and haloperidol, but QTc interval was 14 msec less than that observed with thioridazine (Prod Info Geodon(R), 2002e).

3.5.1.AA Doxepin
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Ziprasidone use is associated with dose-related prolongation of the QTc interval. Even though no formal drug interaction studies have been done, it is recommended that concurrent use with other agents that may prolong QTc interval be avoided (Prod Info GEODON(R) oral capsules, IM injection, 2007; Marshall & Forker, 1982).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Due to the potential for additive QTc interval prolongation, avoid the concurrent administration of ziprasidone and agents that can prolong the QTc interval (Prod Info GEODON(R) oral capsules, IM injection, 2007).
7) Probable Mechanism: additive cardiac effects

3.5.1.AB Droperidol
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Droperidol has been shown to prolong the QTc interval at the recommended therapeutic dose. Even though no formal drug interaction studies have been done, the coadministration of droperidol and other drugs known to prolong the QTc interval, including ziprasidone, is contraindicated (Prod Info Inapsine(R), 2001; Prod Info Geodon(TM), 2002b).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of agents that prolong the QT interval, such as droperidol and ziprasidone, is contraindicated.
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) It has been shown that ziprasidone prolongs the QTc and that this represents a risk of potentially fatal ventricular dysrhythmias (Anon, 2000). QT prolongation is dose-related. It is not yet known whether ziprasidone will cause torsades de pointes or increase the rate of sudden death. In clinical trials ziprasidone increased the QTc interval, compared to placebo, by approximately 10 milliseconds (msec) at the highest dose (160 milligrams). Baseline QTc interval increased 9 to 14 msec more with ziprasidone than with risperidone, olanzapine, quetiapine, and haloperidol, but QTc interval was 14 msec less than that observed with thioridazine (Prod Info Geodon(TM), 2002a).

3.5.1.AC Enflurane

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Even though no formal drug interaction studies have been done, ziprasidone should not be coadministered with other drugs which may also prolong the QTc interval, including enflurane (Prod Info Geodon(R), 2002o; Owens, 2001f).

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of ziprasidone with other agents that can prolong the QT interval, such as enflurane, is contraindicated.

7) Probable Mechanism: additive effects on QT prolongation

8) Literature Reports

a) It has been shown that ziprasidone prolongs the QTc and that this represents a risk of potentially fatal ventricular dysrhythmias ((Anon, 2000)). QT prolongation is dose-related. It is not yet known whether ziprasidone will cause torsades de pointes or increase the rate of sudden death. In clinical trials ziprasidone increased the QTc interval, compared to placebo, by approximately 10 milliseconds (msec) at the highest dose (160 milligrams). Baseline QTc interval increased 9 to 14 msec more with ziprasidone than with risperidone, olanzapine, quetiapine, and haloperidol, but QTc interval was 14 msec less than that observed with thioridazine (Prod Info Geodon(R), 2002n).

3.5.1.AD Erythromycin

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Though no formal drug interaction studies have been done, ziprasidone should not be coadministered with other drugs which are also known to prolong the QTc interval (Prod Info Geodon(TM), 2002t). Erythromycin significantly increased the mean QTc interval versus baseline in a retrospective study of 49 patients (Oberg & Bauman, 1995a). Erythromycin has demonstrated QTc prolongation in combination with other drugs that prolong the QT interval (Prod Info PCE(R), 1997).

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of ziprasidone with other agents that can prolong the QT interval, such as erythromycin, is contraindicated.

7) Probable Mechanism: additive effects on QT prolongation

8) Literature Reports

a) Erythromycin significantly increased the QTc interval compared with baseline in a retrospective study of 49 patients. The erythromycin dose was 500 milligrams or 1 gram four times daily, with a mean of 15 doses received. Patients (n equal to 9) who received 60 mg/kg/day or more all developed increases in QT interval of 15% or greater. For all patients, the mean QTc interval increased from 432 milliseconds (msec) at baseline to 483 msec (p less than 0.01). In patients with delayed repolarization at baseline (n equal to 9), the QTc interval increased from 473 msec to 525 msec (p less than 0.01). In patients with heart disease (n equal to 30), all experienced an increase in QTc interval (mean of 15%), compared with an increase of 8% in patients without heart disease (p less than 0.05). In 5 patients (10%), the QTc interval was severely prolonged. One patient developed torsades de pointes attributed to erythromycin. Of 16 patients receiving cotrimoxazole concomitantly, 8 developed QT prolongation of 15% or greater (Oberg & Bauman, 1995).

3.5.1.AE Flecainide

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Even though no formal drug interaction studies have been done, the coadministration of Class I antiarrhythmics and other drugs known to prolong the QTc interval, such as ziprasidone is contraindicated (Prod Info Geodon(TM), 2002j; Prod Info Tambocor(R) flecainide acetate, 1998).

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of ziprasidone and Class I antiarrhythmic agents is contraindicated.

7) Probable Mechanism: additive cardiac effects

3.5.1.AF Fluconazole

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Even though no formal drug interaction studies have been done, ziprasidone should not be coadministered with other drugs which are also known to prolong the QTc interval (Prod Info Geodon(TM), 2002). Case reports have described QT prolongation and torsades de pointes associated with fluconazole

(Khazan & Mathis, 2002; Wassmann et al, 1999).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of ziprasidone with other agents that can prolong the QT interval, such as fluconazole, is contraindicated.
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) It has been shown that ziprasidone prolongs the QTc and that this represents a risk of potentially fatal ventricular dysrhythmias (Anon, 2000). QT prolongation is dose-related. It is not yet known whether ziprasidone will cause torsades de pointes or increase the rate of sudden death. In clinical trials ziprasidone increased the QTc interval, compared to placebo, by approximately 10 milliseconds (msec) at the highest dose (160 milligrams). Baseline QTc interval increased 9 to 14 msec more with ziprasidone than with risperidone, olanzapine, quetiapine, and haloperidol, but QTc interval was 14 msec less than that observed with thioridazine (Prod Info Geodon(R), 2002).

3.5.1.AG Fluoxetine
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, ziprasidone should not be coadministered with other drugs which are also known to prolong the QTc interval, including fluoxetine (Prod Info Geodon(TM), 2002v; Prod Info Prozac(R), 2001).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of ziprasidone with other agents that can prolong the QT interval, such as fluoxetine, is not recommended.
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) It has been shown that ziprasidone prolongs the QTc and that this represents a risk of potentially fatal ventricular dysrhythmias (Anon, 2000). QT prolongation is dose-related. It is not yet known whether ziprasidone will cause torsades de pointes or increase the rate of sudden death. In clinical trials ziprasidone increased the QTc interval, compared to placebo, by approximately 10 milliseconds (msec) at the highest dose (160 milligrams). Baseline QTc interval increased 9 to 14 msec more with ziprasidone than with risperidone, olanzapine, quetiapine, and haloperidol, but QTc interval was 14 msec less than that observed with thioridazine (Prod Info Geodon(R), 2002p).

3.5.1.AH Foscarnet
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, ziprasidone should not be coadministered with other drugs which are also known to prolong the QTc interval (Prod Info Geodon(TM), 2002u; Prod Info Foscavir(R), 2000).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of ziprasidone with other agents that can prolong the QT interval, such as foscarnet, is contraindicated.
7) Probable Mechanism: additive cardiac effects

3.5.1.AI Gatifloxacin
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, ziprasidone should not be coadministered with other drugs which are also known to prolong the QTc interval, including gatifloxacin (Prod Info Geodon(TM), 2002i).
3) Severity: contraindicated
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of ziprasidone and gatifloxacin is contraindicated.
7) Probable Mechanism: additive cardiac effects

3.5.1.AJ Gemifloxacin
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Although pharmacokinetic studies between ziprasidone and gemifloxacin, which may prolong the QT interval, have not been performed, gemifloxacin should not be used in patients receiving ziprasidone (Prod Info Factive(R), 2003; Prod Info Geodon(R), 2002a).

3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: The concurrent administration of ziprasidone with a drug that may prolong the QT interval, such as gemifloxacin, is contraindicated.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.AK Halofantrine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Halofantrine can prolong the QT interval in some patients, which may result in ventricular tachycardia, ventricular fibrillation, and torsades de pointes. Because ziprasidone may also prolong the QT interval and increase the risk of arrhythmias, the concurrent administration of halofantrine with ziprasidone is contraindicated (Prod Info Halfan(R), 1998; Prod Info Geodon(TM), 2002n).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of ziprasidone with other agents that can prolong the QT interval, such as halofantrine, is contraindicated.
7) Probable Mechanism: additive cardiac effects

3.5.1.AL Haloperidol

1) Interaction Effect: cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Haloperidol is associated with QTc prolongation and torsade de pointes (Hassaballa & Balk, 2003a; Prod Info Haldol(R), 2001). Coadministration of ziprasidone with drugs that potentially prolong the QTc interval, such as haloperidol, is contraindicated (Prod Info Geodon(R), 2002d).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of ziprasidone with agents that prolong the QT interval, such as haloperidol, is contraindicated.
7) Probable Mechanism: additive effects on QT prolongation
8) Literature Reports

a) Seven patients developed torsade de pointes after therapeutic use of haloperidol in high doses. Three patients developed the dysrhythmia after administration of 211 milligrams (mg) to 825 mg haloperidol over 1 to 2 days for agitated delirium. These 3 patients recovered from the initial episodes, but 1 patient subsequently died of cardiac arrest upon readministration of haloperidol (Metzger & Friedman, 1993; Wilt et al, 1993). Torsades de pointes developed in 8 of 223 critically ill patients in intensive care units. Patients who received intravenous haloperidol greater than 35 mg/day or had a QTc interval prolongation of greater than 500 milliseconds were at greatest risk (Sharma et al, 1998).

b) Numerous case reports have described significant QTc prolongation and torsades de pointes (TdP) associated with haloperidol. Hemodynamically significant ventricular tachyarrhythmias, ventricular fibrillation, asystole, and death have been reported. The risk of TdP appears to be greater with intravenous haloperidol, but has occurred with oral and intramuscular use. The risk increases with doses greater than 35 milligrams (mg) over 24 hours, although TdP has been associated with a dose as low as 10 mg administered intravenously over 4 hours. To prevent haloperidol-induced TdP, screen patients for a history of dilated cardiomyopathy or alcohol abuse, testing for hypothyroidism before therapy, obtaining an electrocardiogram at baseline and throughout therapy, and monitoring potassium, magnesium, and calcium. In patients with a baseline QTc greater than 450 milliseconds (msec), haloperidol should be used cautiously or an alternative agent should be used. Discontinue haloperidol if the QTc increases more than 25% from baseline or if flattening of T-waves or development of U-waves occurs (Hassaballa & Balk, 2003).

c) It has been shown that ziprasidone prolongs the QTc and that this represents a risk of potentially fatal ventricular dysrhythmias ((Anon, 2000)). QT prolongation is dose-related. It is not yet known whether ziprasidone will cause torsades de pointes or increase the rate of sudden death. In clinical trials ziprasidone increased the QTc interval, compared to placebo, by approximately 10 milliseconds (msec) at the highest dose (160 milligrams). Baseline QTc interval increased 9 to 14 msec more with ziprasidone than with risperidone, olanzapine, quetiapine, and haloperidol, but QTc interval was 14 msec less than that observed with thioridazine (Prod Info Geodon(R), 2002c).

3.5.1.AM Halothane

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, ziprasidone should not be coadministered with other drugs which may also prolong the QTc interval, including halothane (Prod Info Geodon(R), 2002ac; Owens, 2001j).
3) Severity: contraindicated
4) Onset: unspecified

5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of ziprasidone with other agents that can prolong the QT interval, such as halothane, is contraindicated.
7) Probable Mechanism: additive effect on QT interval
8) Literature Reports
a) It has been shown that ziprasidone prolongs the QTc and that this represents a risk of potentially fatal ventricular dysrhythmias ((Anon, 2000)). QT prolongation is dose-related. It is not yet known whether ziprasidone will cause torsades de pointes or increase the rate of sudden death. In clinical trials ziprasidone increased the QTc interval, compared to placebo, by approximately 10 milliseconds (msec) at the highest dose (160 milligrams). Baseline QTc interval increased 9 to 14 msec more with ziprasidone than with risperidone, olanzapine, quetiapine, and haloperidol, but QTc interval was 14 msec less than that observed with thioridazine (Prod Info Geodon(R), 2002ab).

3.5.1.AN Hydroquinidine
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, the manufacturer of ziprasidone warns against its administration with other drugs which are also known to prolong the QTc interval, including Class IA antiarrhythmic agents (Prod Info Geodon(R), 2002j).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of a Class IA antiarrhythmic and ziprasidone is contraindicated.
7) Probable Mechanism: additive cardiac effects

3.5.1.AO Hydroquinidine
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Several antipsychotic agents have demonstrated QT prolongation including amisulpride, haloperidol, iloperidone, paliperidone, quetiapine, risperidone, sertindole, sultopride, ziprasidone, and zotepine (Prod Info FANAPT(TM) oral tablets, 2009; Prod Info Solian(R), 1999e; O'Brien et al, 1999d; Prod Info INVEGA(TM) extended-release oral tablets, 2006; Owens, 2001i; Duenas-Laita et al, 1999f; Agelink et al, 2001d; Lande et al, 1992f; Prod Info GEODON(R) intramuscular injection, oral capsule, 2005; Sweetman, 2003). Because Class IA antiarrhythmic agents may also prolong the QT interval and increase the risk of arrhythmias, the concurrent administration of antipsychotics with a drug from this class is not recommended (Prod Info FANAPT(TM) oral tablets, 2009; Prod Info Quinaglute(R), 1999).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: The concurrent administration of a Class IA antiarrhythmic and an antipsychotic is not recommended.
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) In an open-label QTc study of patients with schizophrenia or schizoaffective disorder (n=160), iloperidone 12 mg twice a day was associated with QTc prolongation of 9 msec (Prod Info FANAPT(TM) oral tablets, 2009).
b) QRS widening, QTc interval prolongation, and torsades de pointes may occur with disopyramide therapy (Prod Info Norpace(R), 1997).
c) The effects of combined therapy with quinidine (Class IA antiarrhythmic agent) and haloperidol (antipsychotic agent) were studied by giving 12 healthy volunteers haloperidol 5 mg alone and with 250 mg of quinidine bisulfate. The study demonstrated significant increases in the plasma concentrations of haloperidol when given concurrently with quinidine versus haloperidol treatment alone. The mean area under the concentration curve (AUC) was increased from 54.3 ng/h/mL on haloperidol alone to 103.2 ng/h/mL on combined therapy. The peak concentration (Cmax) also showed an increase from 1.9 ng/mL on haloperidol to 3.8 ng/mL on combined therapy. Half-life (T1/2) and time to peak concentration (Tmax) were not significantly changed, thereby suggesting to the authors that a tissue binding mechanism is more likely responsible for the plasma level changes than an elimination alteration (Young et al, 1993).

3.5.1.AP Ibutilide
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: The manufacturer of ziprasidone states that concomitant use of ziprasidone and Class III antiarrhythmic agents is contraindicated (Prod Info Geodon(TM), 2002m). Bretylium should not be used with other drugs known to prolong the QTc interval , including ziprasidone (Yamreudeewong et al, 2003a).
3) Severity: contraindicated
4) Onset: unspecified

5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of ziprasidone and Class III antiarrhythmic agents is contraindicated.
7) Probable Mechanism: additive QT prolongation
8) Literature Reports
a) Concurrent use of class III antiarrhythmic agents, and other drugs that can prolong the QT interval, such as ziprasidone, is not recommended. Dofetilide should be stopped for at least 2 days before any interacting drug is initiated (Yamreudeewong et al, 2003).

3.5.1.AQ Iloperidone
1) Interaction Effect: an increased risk of QT interval prolongation
2) Summary: Due to the potential for additive effects on the QT interval and increased risk of torsade de pointes, caution should be used when iloperidone and drugs that prolong the QT interval are given concomitantly. Consideration should be given to monitoring cardiac function periodically with on-treatment ECGs and evaluating electrolyte (ie, magnesium, potassium) levels. Discontinue iloperidone in patients with persistent QTc measurements greater than 500 msec (Prod Info FANAPT(TM) oral tablets, 2009).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of iloperidone and drugs that prolong the QT interval may result in additive effects on the QT interval and an increased risk of torsade de pointes. Iloperidone should be avoided in patients with significant cardiovascular illness, eg, cardiac arrhythmia, QT prolongation, recent acute myocardial infarction, and uncompensated heart failure. If concomitant use is necessary, consider monitoring cardiac function periodically with on-treatment ECGs and evaluating electrolyte (ie, magnesium, potassium) levels. Discontinue iloperidone in patients with persistent QTc measurements greater than 500 msec(Prod Info FANAPT(TM) oral tablets, 2009).
7) Probable Mechanism: additive effects on the QT interval
8) Literature Reports
a) In an open-label QTc study of patients with schizophrenia or schizoaffective disorder (n=160), iloperidone 12 mg twice a day was associated with QTc prolongation of 9 msec (Prod Info FANAPT(TM) oral tablets, 2009).

3.5.1.AR Imipramine
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Ziprasidone use is associated with dose-related prolongation of the QTc interval. Even though no formal drug interaction studies have been done, it is recommended that concurrent use with other agents that may prolong QTc interval be avoided (Prod Info GEODON(R) oral capsules, IM injection, 2007; Marshall & Forker, 1982).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Due to the potential for additive QTc interval prolongation, avoid the concurrent administration of ziprasidone and agents that can prolong the QTc interval (Prod Info GEODON(R) oral capsules, IM injection, 2007).
7) Probable Mechanism: additive cardiac effects

3.5.1.AS Isoflurane
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, ziprasidone should not be coadministered with other drugs which may also prolong the QTc interval, including isoflurane (Prod Info Geodon(R), 2002v; Owens, 2001h).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of ziprasidone with other agents that can prolong the QT interval, such as isoflurane, is contraindicated.
7) Probable Mechanism: additive effect on QT interval
8) Literature Reports
a) It has been shown that ziprasidone prolongs the QTc and that this represents a risk of potentially fatal ventricular dysrhythmias (Anon, 2000). QT prolongation is dose-related. It is not yet known whether ziprasidone will cause torsades de pointes or increase the rate of sudden death. In clinical trials ziprasidone increased the QTc interval, compared to placebo, by approximately 10 milliseconds (msec) at the highest dose (160 milligrams). Baseline QTc interval increased 9 to 14 msec more with ziprasidone than with risperidone, olanzapine, quetiapine, and haloperidol, but QTc interval was 14 msec less than that observed with thioridazine (Prod Info Geodon(R), 2002u).

3.5.1.AT Isradipine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Even though no formal drug interaction studies have been done, ziprasidone should not be coadministered with other drugs which are also known to prolong the QTc interval, including isradipine (Prod Info Geodon(TM), 2002q; Prod Info DynaCirc(R), 2000).

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of ziprasidone with other agents that can prolong the QT interval, such as isradipine, is contraindicated.

7) Probable Mechanism: additive cardiac effects

8) Literature Reports

a) It has been shown that ziprasidone prolongs the QTc and that this represents a risk of potentially fatal ventricular dysrhythmias (Anon, 2000). QT prolongation is dose-related. It is not yet known whether ziprasidone will cause torsades de pointes or increase the rate of sudden death. In clinical trials ziprasidone increased the QTc interval, compared to placebo, by approximately 10 milliseconds (msec) at the highest dose (160 milligrams). Baseline QTc interval increased 9 to 14 msec more with ziprasidone than with risperidone, olanzapine, quetiapine, and haloperidol, but QTc interval was 14 msec less than that observed with thioridazine (Prod Info Geodon(TM), 2002p).

3.5.1.AU Lapatinib

1) Interaction Effect: an increased risk of QT interval prolongation

2) Summary: Due to the potential for additive effects on the QT interval and increased risk of torsade de pointes, caution should be used when lapatinib and drugs that prolong the QT interval are given concomitantly. Consideration should be given to monitoring cardiac function periodically with on-treatment ECGs and evaluating electrolyte (ie, magnesium, potassium) levels (Prod Info TYKERB oral tablets, 2008). Thirteen patients had either QTcF (corrected QT by the Friedericia method) greater than 480 msec or an increase in QTcF of greater than 60 msec in an uncontrolled, open-label, dose escalation study in advanced cancer patients (n=81) who received lapatinib doses ranging from 175 mg/day to 1800 mg/day, with serial ECGs collected on days 1 and 14 (Prod Info TYKERB oral tablets, 2008).

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concomitant use of lapatinib and drugs that prolong the QT interval may result in additive effects on the QT interval and an increased risk of torsade de pointes. Therefore, caution should be used when these agents are given concomitantly. Consider monitoring cardiac function periodically with on-treatment ECGs and evaluating electrolyte (ie, magnesium, potassium) levels (Prod Info TYKERB oral tablets, 2008).

7) Probable Mechanism: additive effects on the QT interval

3.5.1.AV Levofloxacin

1) Interaction Effect: increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Although no formal drug interaction studies have been done, ziprasidone should not be coadministered with other drugs which are also known to prolong the QTc interval, including levofloxacin (Prod Info Geodon(R) Capsules & Geodon(R) for Injection, 2004; Prod Info Levaquin, 2004).

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of ziprasidone and levofloxacin is not recommended.

7) Probable Mechanism: additive QT prolongation effects

3.5.1.AW Levomethadyl

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Any drug known to have the potential to prolong the QT interval should not be used with levomethadyl. Possible pharmacodynamic interactions can occur between levomethadyl and potentially arrhythmogenic agents such as ziprasidone that prolong the QT interval (Prod Info Orlaam(R), 2001).

3) Severity: contraindicated

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: Levomethadyl is contraindicated in patients being treated with ziprasidone as it may precipitate QT prolongation and interact with levomethadyl.

7) Probable Mechanism: additive cardiac effects

8) Literature Reports

a) It has been shown that ziprasidone prolongs the QTc and that this represents a risk of potentially fatal ventricular dysrhythmias (Anon, 2000). QT prolongation is dose-related. It is not yet known whether

ziprasidone will cause torsades de pointes or increase the rate of sudden death. In clinical trials ziprasidone increased the QTc interval, compared to placebo, by approximately 10 milliseconds (msec) at the highest dose (160 milligrams). Baseline QTc interval increased 9 to 14 msec more with ziprasidone than with risperidone, olanzapine, quetiapine, and haloperidol, but QTc interval was 14 msec less than that observed with thioridazine (Prod Info Geodon(R), 2002m).

3.5.1.AX Lidoflazine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Lidoflazine has been shown to prolong the QTc interval at the recommended therapeutic dose (Hanley & Hampton, 1983). Even though no formal drug interaction studies have been done, the coadministration of ziprasidone and other drugs known to prolong the QTc interval, including lidoflazine, is contraindicated (Prod Info Geodon(TM), 2002f).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of ziprasidone with other agents that can prolong the QT interval, such as lidoflazine, is contraindicated.
7) Probable Mechanism: additive cardiac effects

3.5.1.AY Lorcainide

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, the coadministration of Class I antiarrhythmics and other drugs known to prolong the QTc interval, such as ziprasidone is contraindicated (Prod Info Geodon(TM), 2002j; Prod Info Tambocor(R) flecainide acetate, 1998).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of ziprasidone and Class I antiarrhythmic agents is contraindicated.
7) Probable Mechanism: additive cardiac effects

3.5.1.AZ Lumefantrine

1) Interaction Effect: an increased risk of QT interval prolongation
2) Summary: Due to the potential for additive effects on QT interval prolongation, concomitant use of artemether/lumefantrine with drugs that prolong the QT interval should be avoided (Prod Info COARTEM(R) oral tablets, 2009).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of artemether/lumefantrine with drugs that prolong the QT interval should be avoided due to the potential for additive effects on QT interval prolongation (Prod Info COARTEM(R) oral tablets, 2009).
7) Probable Mechanism: additive effects on QT interval prolongation
8) Literature Reports
a) Concurrent administration of a single dose of IV quinine 10 mg/kg with the final dose of a 6-dose regimen of artemether/lumfantrine did not alter the systemic exposure to quinine, lumefantrine, or dihydroartemisinin (active metabolite of artemether). Although artemether exposure was decreased, it was not believed to be clinically significant. The effects on QT prolongation were not reported in this study (Prod Info COARTEM(R) oral tablets, 2009).

3.5.1.BA Mefloquine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, ziprasidone should not be coadministered with other drugs which are also known to prolong the QTc interval, including mefloquine (Prod Info Geodon(TM), 2002o; Davis et al, 1996).
3) Severity: contraindicated
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of ziprasidone and mefloquine is contraindicated.
7) Probable Mechanism: additive cardiac effects

3.5.1.BB Mesoridazine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Although citing no data, the manufacturer of mesoridazine states that concomitant use with

other drugs which prolong the QT interval is contraindicated (Prod Info Serentil(R), 2001). Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999c), haloperidol (O'Brien et al, 1999c), paliperidone (Prod Info INVEGA(TM) extended-release oral tablets, 2006), quetiapine (Owens, 2001g), risperidone (Duenas-Laita et al, 1999e), sertindole (Agelink et al, 2001c), sultopride (Lande et al, 1992e), ziprasidone (Prod Info GEODON(R) intramuscular injection, oral capsule, 2005), and zotepine (Sweetman, 2004).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of agents that prolong the QT interval, such as antipsychotics and mesoridazine, is contraindicated.
7) Probable Mechanism: additive QT prolongation

3.5.1.BC Mesoridazine
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: The manufacturer of ziprasidone states that concomitant use of ziprasidone and phenothiazines is contraindicated (Prod Info Compazine(R), 2002a; Prod Info Geodon(R), 2002w).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of ziprasidone and other drugs that may prolong the QT interval, such as phenothiazines, is contraindicated.
7) Probable Mechanism: additive QT prolongation

3.5.1.BD Methadone
1) Interaction Effect: an increased risk of QT interval prolongation
2) Summary: Cases of QT interval prolongation and serious arrhythmias, including torsade de pointes, have been reported with methadone use (Prod Info DOLOPHINE(R) HYDROCHLORIDE oral tablets, 2006). Ziprasidone use is associated with dose-related QT interval prolongation. Due to the potential for additive effects on QT interval prolongation, concurrent use of methadone and ziprasidone is contraindicated (Prod Info GEODON(R) oral capsule, GEODON(R) intramuscular powder for solution, 2005).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concurrent use of methadone and ziprasidone is contraindicated due to the potential for additive effects on QT interval prolongation (Prod Info GEODON(R) oral capsule, GEODON(R) intramuscular powder for solution, 2005).
7) Probable Mechanism: additive effects on QT interval prolongation

3.5.1.BE Moxifloxacin
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, ziprasidone should not be coadministered with other drugs which are also known to prolong the QTc interval, including moxifloxacin (Prod Info Geodon(TM), 2002g).
3) Severity: contraindicated
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of ziprasidone and moxifloxacin is contraindicated.
7) Probable Mechanism: additive cardiac effects

3.5.1.BF Nilotinib
1) Interaction Effect: an increased risk of QT interval prolongation
2) Summary: Due to the potential for additive effects on the QT interval and increased risk of torsade de pointes, concomitant use of nilotinib with drugs that prolong the QT interval should be avoided. However, if concomitant use is required, the patient should be closely monitored for prolongation of the QT interval (Prod Info TASIGNA(R) oral capsules, 2007).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of nilotinib with drugs that prolong the QT interval should be avoided due to the potential for additive effects on the QT interval and increased risk of torsade de pointes. However, if concurrent therapy is required, monitor patient closely for prolongation of the QT interval (Prod Info TASIGNA(R) oral capsules, 2007).
7) Probable Mechanism: additive effects on QT interval prolongation

3.5.1.BG Nortriptyline

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Ziprasidone use is associated with dose-related prolongation of the QTc interval. Even though no formal drug interaction studies have been done, it is recommended that concurrent use with other agents that may prolong QTc interval be avoided (Prod Info GEODON(R) oral capsules, IM injection, 2007; Marshall & Forker, 1982).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Due to the potential for additive QTc interval prolongation, avoid the concurrent administration of ziprasidone and agents that can prolong the QTc interval (Prod Info GEODON(R) oral capsules, IM injection, 2007).
7) Probable Mechanism: additive cardiac effects

3.5.1.BH Octreotide
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Octreotide has been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Sandostatin(R), 1999). Even though no formal drug interaction studies have been done, the coadministration of ziprasidone and other drugs known to prolong the QTc interval, including octreotide, is contraindicated (Prod Info Geodon(TM) ziprasidone, 2002b).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of ziprasidone with other agents that can prolong the QT interval, such as octreotide, is contraindicated.
7) Probable Mechanism: additive cardiac effects

3.5.1.BI Pentamidine
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: The manufacturer of ziprasidone states that concomitant use of ziprasidone and pentamidine is contraindicated (Prod Info Geodon(TM) ziprasidone, 2002). Pentamidine has been shown to prolong the QTc interval at the recommended therapeutic dose (Lindsay et al, 1990).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of ziprasidone with other agents that can prolong the QT interval, such as pentamidine, is contraindicated.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.BJ Pimozide
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, ziprasidone should not be coadministered with other drugs which are also known to prolong the QTc interval, including pimozide (Prod Info Geodon(TM), 2002w).
3) Severity: contraindicated
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of ziprasidone and pimozide is contraindicated.
7) Probable Mechanism: additive cardiac effects

3.5.1.BK Pirmenol
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, the manufacturer of ziprasidone warns against its administration with other drugs which are also known to prolong the QTc interval, including Class IA antiarrhythmic agents (Prod Info Geodon(R), 2002j).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of a Class IA antiarrhythmic and ziprasidone is contraindicated.
7) Probable Mechanism: additive cardiac effects

3.5.1.BL Pirmenol
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac

arrest)
2) Summary: Several antipsychotic agents have demonstrated QT prolongation including amisulpride, haloperidol, iloperidone, paliperidone, quetiapine, risperidone, sertindole, sultopride, ziprasidone, and zotepine (Prod Info FANAPT(TM) oral tablets, 2009; Prod Info Solian(R), 1999e; O'Brien et al, 1999d; Prod Info INVEGA(TM) extended-release oral tablets, 2006; Owens, 2001i; Duenas-Laita et al, 1999f; Agelink et al, 2001d; Lande et al, 1992f; Prod Info GEODON(R) intramuscular injection, oral capsule, 2005; Sweetman, 2003). Because Class IA antiarrhythmic agents may also prolong the QT interval and increase the risk of arrhythmias, the concurrent administration of antipsychotics with a drug from this class is not recommended (Prod Info FANAPT(TM) oral tablets, 2009; Prod Info Quinaglute(R), 1999).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: The concurrent administration of a Class IA antiarrhythmic and an antipsychotic is not recommended.
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) In an open-label QTc study of patients with schizophrenia or schizoaffective disorder (n=160), iloperidone 12 mg twice a day was associated with QTc prolongation of 9 msec (Prod Info FANAPT(TM) oral tablets, 2009).
b) QRS widening, QTc interval prolongation, and torsades de pointes may occur with disopyramide therapy (Prod Info Norpace(R), 1997).
c) The effects of combined therapy with quinidine (Class IA antiarrhythmic agent) and haloperidol (antipsychotic agent) were studied by giving 12 healthy volunteers haloperidol 5 mg alone and with 250 mg of quinidine bisulfate. The study demonstrated significant increases in the plasma concentrations of haloperidol when given concurrently with quinidine versus haloperidol treatment alone. The mean area under the concentration curve (AUC) was increased from 54.3 ng/h/mL on haloperidol alone to 103.2 ng/h/mL on combined therapy. The peak concentration (Cmax) also showed an increase from 1.9 ng/mL on haloperidol to 3.8 ng/mL on combined therapy. Half-life (T1/2) and time to peak concentration (Tmax) were not significantly changed, thereby suggesting to the authors that a tissue binding mechanism is more likely responsible for the plasma level changes than an elimination alteration (Young et al, 1993).

3.5.1.BM Prajmaline
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, the manufacturer of ziprasidone warns against its administration with other drugs which are also known to prolong the QTc interval, including Class IA antiarrhythmic agents (Prod Info Geodon(R), 2002j).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of a Class IA antiarrhythmic and ziprasidone is contraindicated.
7) Probable Mechanism: additive cardiac effects

3.5.1.BN Prajmaline
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Several antipsychotic agents have demonstrated QT prolongation including amisulpride, haloperidol, iloperidone, paliperidone, quetiapine, risperidone, sertindole, sultopride, ziprasidone, and zotepine (Prod Info FANAPT(TM) oral tablets, 2009; Prod Info Solian(R), 1999e; O'Brien et al, 1999d; Prod Info INVEGA(TM) extended-release oral tablets, 2006; Owens, 2001i; Duenas-Laita et al, 1999f; Agelink et al, 2001d; Lande et al, 1992f; Prod Info GEODON(R) intramuscular injection, oral capsule, 2005; Sweetman, 2003). Because Class IA antiarrhythmic agents may also prolong the QT interval and increase the risk of arrhythmias, the concurrent administration of antipsychotics with a drug from this class is not recommended (Prod Info FANAPT(TM) oral tablets, 2009; Prod Info Quinaglute(R), 1999).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: The concurrent administration of a Class IA antiarrhythmic and an antipsychotic is not recommended.
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) In an open-label QTc study of patients with schizophrenia or schizoaffective disorder (n=160), iloperidone 12 mg twice a day was associated with QTc prolongation of 9 msec (Prod Info FANAPT(TM) oral tablets, 2009).
b) QRS widening, QTc interval prolongation, and torsades de pointes may occur with disopyramide therapy (Prod Info Norpace(R), 1997).

c) The effects of combined therapy with quinidine (Class IA antiarrhythmic agent) and haloperidol (antipsychotic agent) were studied by giving 12 healthy volunteers haloperidol 5 mg alone and with 250 mg of quinidine bisulfate. The study demonstrated significant increases in the plasma concentrations of haloperidol when given concurrently with quinidine versus haloperidol treatment alone. The mean area under the concentration curve (AUC) was increased from 54.3 ng/h/mL on haloperidol alone to 103.2 ng/h/mL on combined therapy. The peak concentration (Cmax) also showed an increase from 1.9 ng/mL on haloperidol to 3.8 ng/mL on combined therapy. Half-life (T1/2) and time to peak concentration (Tmax) were not significantly changed, thereby suggesting to the authors that a tissue binding mechanism is more likely responsible for the plasma level changes than an elimination alteration (Young et al, 1993).

3.5.1.BO Probucol

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, ziprasidone should not be coadministered with other drugs which are also known to prolong the QTc interval, including probucol (Prod Info Geodon(TM), 2002y). Probucol has been shown to prolong the QTc interval (Gohn & Simmons, 1992; Prod Info Lorelco(R), 1991).
3) Severity: contraindicated
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of ziprasidone with other agents that can prolong the QT interval, such as probucol, is contraindicated.
7) Probable Mechanism: additive cardiac effects

3.5.1.BP Procainamide

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, the manufacturer of ziprasidone warns against its administration with other drugs which are also known to prolong the QTc interval, including Class IA antiarrhythmic agents (Prod Info Geodon(R), 2002j).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of a Class IA antiarrhythmic and ziprasidone is contraindicated.
7) Probable Mechanism: additive cardiac effects

3.5.1.BQ Procainamide

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Several antipsychotic agents have demonstrated QT prolongation including amisulpride, haloperidol, iloperidone, paliperidone, quetiapine, risperidone, sertindole, sultopride, ziprasidone, and zotepine (Prod Info FANAPT(TM) oral tablets, 2009; Prod Info Solian(R), 1999e; O'Brien et al, 1999d; Prod Info INVEGA(TM) extended-release oral tablets, 2006; Owens, 2001i; Duenas-Laita et al, 1999f; Agelink et al, 2001d; Lande et al, 1992f; Prod Info GEODON(R) intramuscular injection, oral capsule, 2005; Sweetman, 2003). Because Class IA antiarrhythmic agents may also prolong the QT interval and increase the risk of arrhythmias, the concurrent administration of antipsychotics with a drug from this class is not recommended (Prod Info FANAPT(TM) oral tablets, 2009; Prod Info Quinaglute(R), 1999).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: The concurrent administration of a Class IA antiarrhythmic and an antipsychotic is not recommended.
7) Probable Mechanism: additive cardiac effects
8) Literature Reports

a) In an open-label QTc study of patients with schizophrenia or schizoaffective disorder (n=160), iloperidone 12 mg twice a day was associated with QTc prolongation of 9 msec (Prod Info FANAPT(TM) oral tablets, 2009).

b) QRS widening, QTc interval prolongation, and torsades de pointes may occur with disopyramide therapy (Prod Info Norpace(R), 1997).

c) The effects of combined therapy with quinidine (Class IA antiarrhythmic agent) and haloperidol (antipsychotic agent) were studied by giving 12 healthy volunteers haloperidol 5 mg alone and with 250 mg of quinidine bisulfate. The study demonstrated significant increases in the plasma concentrations of haloperidol when given concurrently with quinidine versus haloperidol treatment alone. The mean area under the concentration curve (AUC) was increased from 54.3 ng/h/mL on haloperidol alone to 103.2 ng/h/mL on combined therapy. The peak concentration (Cmax) also showed an increase from 1.9 ng/mL on haloperidol to 3.8 ng/mL on combined therapy. Half-life (T1/2) and time to peak concentration

(Tmax) were not significantly changed, thereby suggesting to the authors that a tissue binding mechanism is more likely responsible for the plasma level changes than an elimination alteration (Young et al, 1993).

3.5.1.BR Prochlorperazine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Concomitant use of phenothiazines and antipsychotic agents may cause additive effects on the QT interval and is not recommended. Q and T wave distortions have been observed in patients taking phenothiazines (Prod Info Compazine(R), 2002; Prod Info Stelazine(R), 2002; Prod Info Thorazine(R), 2002). Other phenothiazines may have similar effects, though no reports are available. Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999), haloperidol (O'Brien et al, 1999), paliperidone (Prod Info INVEGA(TM) extended-release oral tablets, 2006), quetiapine (Owens, 2001c), risperidone (Duenas-Laita et al, 1999b), sertindole (Agelink et al, 2001a), sultopride (Lande et al, 1992), ziprasidone (Prod Info GEODON(R) intramuscular injection, oral capsule, 2005), and zotepine (Sweetman, 2003).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of agents that prolong the QT interval, such as phenothiazines and antipsychotics, is not recommended.
7) Probable Mechanism: additive QT prolongation

3.5.1.BS Prochlorperazine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: The manufacturer of ziprasidone states that concomitant use of ziprasidone and phenothiazines is contraindicated (Prod Info Compazine(R), 2002a; Prod Info Geodon(R), 2002w).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of ziprasidone and other drugs that may prolong the QT interval, such as phenothiazines, is contraindicated.
7) Probable Mechanism: additive QT prolongation

3.5.1.BT Propafenone

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, the coadministration of Class I antiarrhythmics and other drugs known to prolong the QTc interval, such as ziprasidone is contraindicated (Prod Info Geodon(TM), 2002j; Prod Info Tambocor(R) flecainide acetate, 1998).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of ziprasidone and Class I antiarrhythmic agents is contraindicated.
7) Probable Mechanism: additive cardiac effects

3.5.1.BU Protriptyline

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Ziprasidone use is associated with dose-related prolongation of the QTc interval. Even though no formal drug interaction studies have been done, it is recommended that concurrent use with other agents that may prolong QTc interval be avoided (Prod Info GEODON(R) oral capsules, IM injection, 2007; Marshall & Forker, 1982).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Due to the potential for additive QTc interval prolongation, avoid the concurrent administration of ziprasidone and agents that can prolong the QTc interval (Prod Info GEODON(R) oral capsules, IM injection, 2007).
7) Probable Mechanism: additive cardiac effects

3.5.1.BV Quinidine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, the manufacturer of ziprasidone warns against its administration with other drugs which are also known to prolong the QTc

interval, including Class IA antiarrhythmic agents (Prod Info Geodon(R), 2002j).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of a Class IA antiarrhythmic and ziprasidone is contraindicated.
7) Probable Mechanism: additive cardiac effects

3.5.1.BW Ranolazine
1) Interaction Effect: an increased risk of QT interval prolongation
2) Summary: Treatment with ranolazine has been associated with QTc prolongation (Prod Info RANEXA(R) extended-release oral tablets, 2008). Ziprasidone use is associated with dose-related QT interval prolongation (Prod Info GEODON(R) oral capsules, IM injection, 2008). Concurrent use of ranolazine and ziprasidone is contraindicated due to the potential for additive effects on QT interval prolongation (Prod Info GEODON(R) oral capsules, IM injection, 2008).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concurrent use of ranolazine and ziprasidone is contraindicated due to the potential for additive effects on QT interval prolongation (Prod Info GEODON(R) oral capsules, IM injection, 2008).
7) Probable Mechanism: additive effects on QT interval prolongation

3.5.1.BX Sematilide
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: The manufacturer of ziprasidone states that concomitant use of ziprasidone and Class III antiarrhythmic agents is contraindicated (Prod Info Geodon(TM), 2002m). Bretylium should not be used with other drugs known to prolong the QTc interval , including ziprasidone (Yamreudeewong et al, 2003a).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of ziprasidone and Class III antiarrhythmic agents is contraindicated.
7) Probable Mechanism: additive QT prolongation
8) Literature Reports
a) Concurrent use of class III antiarrhythmic agents, and other drugs that can prolong the QT interval, such as ziprasidone, is not recommended. Dofetilide should be stopped for at least 2 days before any interacting drug is initiated (Yamreudeewong et al, 2003).

3.5.1.BY Sertindole
1) Interaction Effect: cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, ziprasidone should not be coadministered with other drugs which are also known to prolong the QTc interval (Brown & Levin, 1998a; Prod Info Geodon(R), 2002aa).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of ziprasidone with agents that prolong the QT interval, such as sertindole is contraindicated.
7) Probable Mechanism: additive effects on QT prolongation
8) Literature Reports
a) The overall incidence of QT interval prolongation with sertindole is estimated at 1.9% to 4%, and the potential risk of developing torsades de pointes has been estimated at 0.13% to 0.21% (Brown & Levin, 1998). Periodic electrocardiographic monitoring is required in the United Kingdom per sertindole's official labeling (Cardoni & Myer, 1997).
b) Thirty, otherwise healthy, schizophrenic patients participated in an open, dose titration (4 to 16 mg/day) study to determine the cardiovascular effects of sertindole. At the end of the 3-week study it was concluded that resting heart rate and frequency corrected QT times increased in a dose-related manner, while there was no change in PQ-conduction times, autonomic parasympathetic tone, or blood pressure. Conduction times increased an average 3.5% to 6.5% over the dosing range (Agelink et al, 2001e).
c) Ziprasidone prolongs the QTc in some patients in a dose-related manner. It is not yet known whether ziprasidone will cause torsades de pointes or increase the rate of sudden death. In clinical trials ziprasidone increased the QTc interval, compared to placebo, by approximately 10 milliseconds (msec) at the highest dose (160 milligrams) (Prod Info Geodon(R), 2002z).

3.5.1.BZ Sotalol

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: The manufacturer of ziprasidone states that concomitant use of ziprasidone and Class III antiarrhythmic agents is contraindicated (Prod Info Geodon(TM), 2002m). Bretylium should not be used with other drugs known to prolong the QTc interval , including ziprasidone (Yamreudeewong et al, 2003a).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of ziprasidone and Class III antiarrhythmic agents is contraindicated.
7) Probable Mechanism: additive QT prolongation
8) Literature Reports
a) Concurrent use of class III antiarrhythmic agents, and other drugs that can prolong the QT interval, such as ziprasidone, is not recommended. Dofetilide should be stopped for at least 2 days before any interacting drug is initiated (Yamreudeewong et al, 2003).

3.5.1.CA Sparfloxacin
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, ziprasidone should not be coadministered with other drugs which are also known to prolong the QTc interval, including sparfloxacin (Prod Info Geodon(TM), 2002x).
3) Severity: contraindicated
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of ziprasidone and sparfloxacin is contraindicated.
7) Probable Mechanism: additive cardiac effects

3.5.1.CB Spiramycin
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Spiramycin has been shown to prolong the QTc interval at the recommended therapeutic dose (Stramba-Badiale et al, 1997). Even though no formal drug interaction studies have been done, the coadministration of ziprasidone and other drugs known to prolong the QTc interval, including spiramycin, is not recommended (Prod Info Geodon(TM) ziprasidone, 2002a).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of ziprasidone with other agents that can prolong the QT interval, such as spiramycin, is contraindicated.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.CC Sultopride
1) Interaction Effect: cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, ziprasidone should not be coadministered with other drugs which are also known to prolong the QTc interval (Lande et al, 1992b; Montaz et al, 1992a; Harry, 1997a; Prod Info Geodon(R), 2002l).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of ziprasidone with other agents that prolong the QT interval, such as sultopride, is contraindicated.
7) Probable Mechanism: additive effects on QT prolongation
8) Literature Reports
a) Sultopride may induce prolongation of the QT interval and ventricular arrhythmias including torsades de pointes following therapeutic or toxic doses (Lande et al, 1992a; Montaz et al, 1992; Harry, 1997).
b) Ziprasidone prolongs the QTc in some patients in a dose-related manner. It is not yet known whether ziprasidone will cause torsades de pointes or increase the rate of sudden death. In clinical trials ziprasidone increased the QTc interval, compared to placebo, by approximately 10 milliseconds (msec) at the highest dose (160 milligrams) (Prod Info Geodon(R), 2002k).

3.5.1.CD Sunitinib
1) Interaction Effect: an increased risk of QT interval prolongation
2) Summary: Sunitinib has been associated with prolongation of the QT interval in a dose dependent manner, with torsade de pointes occurring in less than 0.1% patients exposed to sunitinib. Due to the potential for additive effects on the QT interval and increased risk for torsade de pointes, caution should be used when sunitinib and ziprasidone are given concomitantly. Consideration should be given to monitoring cardiac function periodically with on-treatment ECGs and evaluating electrolyte (ie, magnesium, potassium)

levels (Prod Info SUTENT(R) oral capsules, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of sunitinib and ziprasidone may result in additive effects on the QT interval and an increased risk of torsade de pointes. Therefore, caution should be used when these agents are given concomitantly. Consider monitoring cardiac function periodically with on-treatment ECGs and evaluating electrolyte (ie, magnesium, potassium) levels (Prod Info SUTENT(R) oral capsules, 2008).
7) Probable Mechanism: additive effects on the QT interval

3.5.1.CE Tacrolimus
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, ziprasidone should not be coadministered with other drugs which are also known to prolong the QTc interval, including tacrolimus (Prod Info Geodon(TM), 2002r).
3) Severity: contraindicated
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of ziprasidone and tacrolimus is contraindicated.
7) Probable Mechanism: additive cardiac effects

3.5.1.CF Tedisamil
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: The manufacturer of ziprasidone states that concomitant use of ziprasidone and Class III antiarrhythmic agents is contraindicated (Prod Info Geodon(TM), 2002m). Bretylium should not be used with other drugs known to prolong the QTc interval , including ziprasidone (Yamreudeewong et al, 2003a).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of ziprasidone and Class III antiarrhythmic agents is contraindicated.
7) Probable Mechanism: additive QT prolongation
8) Literature Reports
a) Concurrent use of class III antiarrhythmic agents, and other drugs that can prolong the QT interval, such as ziprasidone, is not recommended. Dofetilide should be stopped for at least 2 days before any interacting drug is initiated (Yamreudeewong et al, 2003).

3.5.1.CG Telithromycin
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, ziprasidone should not be coadministered with other drugs which are also known to prolong the QTc interval, including telithromycin (Prod Info Geodon(TM), 2002h; Owens, 2001b).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of ziprasidone with other agents that can prolong the QT interval, such as telithromycin, is contraindicated.
7) Probable Mechanism: additive effect on QT interval
8) Literature Reports
a) It has been shown that ziprasidone prolongs the QTc and that this represents a risk of potentially fatal ventricular dysrhythmias (Anon, 2000). QT prolongation is dose-related. It is not yet known whether ziprasidone will cause torsades de pointes or increase the rate of sudden death. In clinical trials ziprasidone increased the QTc interval, compared to placebo, by approximately 10 milliseconds (msec) at the highest dose (160 milligrams). Baseline QTc interval increased 9 to 14 msec more with ziprasidone than with risperidone, olanzapine, quetiapine, and haloperidol, but QTc interval was 14 msec less than that observed with thioridazine (Prod Info Geodon(R), 2002g).

3.5.1.CH Terfenadine
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Some antipsychotics have been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Geodon(TM), 2002aa; Owens, 2001k; Prod Info Orap(R), 1999e). Even though no formal drug interaction studies have been done, the coadministration of terfenadine and other drugs known to prolong the QTc interval, including antipsychotics, is contraindicated (Anon, 1997).
3) Severity: contraindicated

4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of terfenadine with any drug that prolongs the QT interval, such as antipsychotic agents, is contraindicated.
7) Probable Mechanism: additive effect on QT interval
8) Literature Reports
a) Electrocardiographic changes that have occurred during clinical trials with pimozide have included prolongation of the corrected QT interval, flattening, notching, and inversion of the T wave and the appearance of U waves. In experimental studies, sudden, unexpected deaths have occurred while patients were receiving pimozide doses of 1 mg/kg. The proposed mechanism for these deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmias (Prod Info Orap(R), 1999d).

3.5.1.CI Tetrabenazine
1) Interaction Effect: an increased risk of QT interval prolongation
2) Summary: Due to the potential for additive effects on the QT interval and increased risk of torsade de pointes, concomitant use of tetrabenazine with drugs that prolong the QT interval should be avoided. However, if concomitant use is required, the patient should be closely monitored for prolongation of the QT interval (Prod Info XENAZINE(R) oral tablets, 2008). In a randomized, double-blind, placebo controlled crossover study of healthy subjects, the effect of a single 25 mg or 50 mg dose of tetrabenazine on the QT interval was studied with moxifloxacin as a positive control. The 50 mg dose of tetrabenazine caused an approximate 8 millisecond mean increase in QT (Prod Info XENAZINE(R) oral tablets, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of tetrabenazine with drugs that prolong the QT interval should be avoided due to the potential for additive effects on the QT interval and increased risk of torsade de pointes. However, if concurrent therapy is required, monitor patient closely for prolongation of the QT interval (Prod Info XENAZINE(R) oral tablets, 2008).
7) Probable Mechanism: additive effects on QT interval prolongation

3.5.1.CJ Tetrabenazine
1) Interaction Effect: increased risk of QT interval prolongation
2) Summary: Tetrabenazine causes a small increase in the corrected QT interval. As the degree of prolongation increases, QT prolongation can develop into torsade de pointes-type VT. The concomitant use of tetrabenazine with other drugs known for QT prolongation (eg, ziprasidone) should be avoided (Prod Info XENAZINE(R) oral tablets, 2008). In a randomized, double-blind, placebo controlled crossover study of healthy subjects, the effect of a single 25 mg or 50 mg dose of tetrabenazine on the QT interval was studied with moxifloxacin as a positive control. The 50 mg dose of tetrabenazine caused an approximate 8 millisecond mean increase in QT (Prod Info XENAZINE(R) oral tablets, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of tetrabenazine with ziprasidone or other drugs that prolong the QT interval should be avoided due to the potential for additive effects on the QT interval and increased risk of torsade de pointes (Prod Info XENAZINE(R) oral tablets, 2008). However, if concurrent therapy is required, monitor patient closely for prolongation of the QT interval.
7) Probable Mechanism: additive effects on QT interval prolongation

3.5.1.CK Thioridazine
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Although citing no data, the manufacturer of thioridazine states that concomitant use with other drugs which prolong the QT interval is contraindicated (Prod Info Mellaril(R), 2001). Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999b), haloperidol (O'Brien et al, 1999b), pimozide (Prod Info Orap(R), 2000), quetiapine (Owens, 2001e), paliperidone (Prod Info INVEGA(TM) extended-release oral tablets, 2006), risperidone (Duenas-Laita et al, 1999d), sertindole (Agelink et al, 2001c), sultopride (Lande et al, 1992d), ziprasidone (Prod Info GEODON (R) intramuscular injection, oral capsule, 2005), and zotepine (Sweetman, 2004).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of agents that prolong the QT interval, such as antipsychotics, and thioridazine, is contraindicated.
7) Probable Mechanism: additive QT prolongation

3.5.1.CL Trifluoperazine
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac

arrest)
2) Summary: Concomitant use of phenothiazines and antipsychotic agents may cause additive effects on the QT interval and is not recommended. Q and T wave distortions have been observed in patients taking phenothiazines (Prod Info Compazine(R), 2002; Prod Info Stelazine(R), 2002; Prod Info Thorazine(R), 2002). Other phenothiazines may have similar effects, though no reports are available. Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999), haloperidol (O'Brien et al, 1999), paliperidone (Prod Info INVEGA(TM) extended-release oral tablets, 2006), quetiapine (Owens, 2001c), risperidone (Duenas-Laita et al, 1999b), sertindole (Agelink et al, 2001a), sultopride (Lande et al, 1992), ziprasidone (Prod Info GEODON(R) intramuscular injection, oral capsule, 2005), and zotepine (Sweetman, 2003).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of agents that prolong the QT interval, such as phenothiazines and antipsychotics, is not recommended.
7) Probable Mechanism: additive QT prolongation

3.5.1.CM Trifluoperazine
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: The manufacturer of ziprasidone states that concomitant use of ziprasidone and phenothiazines is contraindicated (Prod Info Compazine(R), 2002a; Prod Info Geodon(R), 2002w).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of ziprasidone and other drugs that may prolong the QT interval, such as phenothiazines, is contraindicated.
7) Probable Mechanism: additive QT prolongation

3.5.1.CN Trimipramine
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Ziprasidone use is associated with dose-related prolongation of the QTc interval. Even though no formal drug interaction studies have been done, it is recommended that concurrent use with other agents that may prolong QTc interval be avoided (Prod Info GEODON(R) oral capsules, IM injection, 2007; Marshall & Forker, 1982).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Due to the potential for additive QTc interval prolongation, avoid the concurrent administration of ziprasidone and agents that can prolong the QTc interval (Prod Info GEODON(R) oral capsules, IM injection, 2007).
7) Probable Mechanism: additive cardiac effects

3.5.1.CO Vasopressin
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, ziprasidone should not be coadministered with other drugs which are also known to prolong the QTc interval, including vasopressin (Prod Info Geodon(TM), 2002e; Jacoby & Wiegman, 1990).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of ziprasidone with other agents that can prolong the QT interval, such as vasopressin, is contraindicated.
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) Ziprasidone prolongs the QTc and an increased risk of potentially fatal ventricular dysrhythmias (Anon, 2000). QT prolongation is dose-related. It is not yet known whether ziprasidone will cause torsades de pointes or increase the rate of sudden death. In clinical trials ziprasidone increased the QTc interval, compared to placebo, by approximately 10 milliseconds (msec) at the highest dose (160 milligrams). Baseline QTc interval increased 9 to 14 msec more with ziprasidone than with risperidone, olanzapine, quetiapine, and haloperidol, but QTc interval was 14 msec less than that observed with thioridazine (Prod Info Geodon(R), 2002b).

3.5.1.CP Zolmitriptan
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Even though no formal drug interaction studies have been done, ziprasidone should not be coadministered with other drugs which are also known to prolong the QTc interval, including zolmitriptan (Prod Info Geodon(R), 2002y; Prod Info Zomig(R), 2001).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of ziprasidone with other agents that can prolong the QT interval, such as zolmitriptan, is contraindicated.
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) It has been shown that ziprasidone prolongs the QTc and that this represents a risk of potentially fatal ventricular dysrhythmias ((Anon, 2000)). QT prolongation is dose-related. It is not yet known whether ziprasidone will cause torsades de pointes or increase the rate of sudden death. In clinical trials ziprasidone increased the QTc interval, compared to placebo, by approximately 10 milliseconds (msec) at the highest dose (160 milligrams). Baseline QTc interval increased 9 to 14 msec more with ziprasidone than with risperidone, olanzapine, quetiapine, and haloperidol, but QTc interval was 14 msec less than that observed with thioridazine (Prod Info Geodon(R), 2002x).

3.5.1.CQ Zotepine
1) Interaction Effect: cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Coadministration of ziprasidone with other drugs that potentially prolong the QTc interval, such as zotepine, is contraindicated (Prod Info Geodon(R), 2002r; Sweetman, 2003).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of ziprasidone with other agents that prolong the QT interval, such as zotepine, is contraindicated.
7) Probable Mechanism: additive effects on QT prolongation
8) Literature Reports
a) Ziprasidone prolongs the QTc in some patients in a dose-related manner. It is not yet known whether ziprasidone will cause torsades de pointes or increase the rate of sudden death. In clinical trials ziprasidone increased the QTc interval, compared to placebo, by approximately 10 milliseconds (msec) at the highest dose (160 milligrams) (Prod Info Geodon(R), 2002q).
b) Since zotepine can prolong the QT interval it is recommended that an ECG is performed before starting treatment. Patients with pre-existing prolongation of the QT interval should not be given zotepine (Sweetman, 2003).

4.0 Clinical Applications

Monitoring Parameters

Patient Instructions

Place In Therapy

Mechanism of Action / Pharmacology

Therapeutic Uses

Comparative Efficacy / Evaluation With Other Therapies

4.1 Monitoring Parameters
A) Ziprasidone Hydrochloride
1) Therapeutic
a) Physical Findings
1) Improvement of psychotic symptomatology (positive, negative symptoms) (Prod Info GEODON(R) oral capsules, IM injection, 2007).
2) Toxic
a) Laboratory Parameters
1) Torsade de Pointes
a) Ziprasidone may prolong the QT interval in some patients; ECG changes, blood pressure and heart rate monitoring may be warranted (Prod Info GEODON(R) oral capsules, IM injection, 2007).
b) Patients with hypokalemia or hypomagnesemia have an increased risk of the occurrence of torsade de pointes. Serum potassium and magnesium levels, at baseline and during ziprasidone

therapy, should be monitored for patients on concomitant diuretics or at risk for electrolyte disturbances (Prod Info GEODON(R) oral capsules, IM injection, 2007).

c) Further evaluation, such as Holter monitoring, should be initiated for any patient who experiences symptoms during ziprasidone therapy that may indicate the development of torsade de pointes (eg dizziness, palpitations, syncope) (Prod Info GEODON(R) oral capsules, IM injection, 2007).

2) Diabetes Mellitus

a) Atypical antipsychotics, such as ziprasidone, have been linked with the development of hyperglycemia, some cases extreme and associated with ketoacidosis or hyperosmolar coma or death. Patients diagnosed with or at risk of diabetes mellitus should be monitored regularly for worsening of glucose control (eg fasting blood glucose, polydipsia, polyuria, polyphagia, weakness) (Prod Info GEODON(R) oral capsules, IM injection, 2007).

b) Physical Findings

1) Tardive Dyskinesia

a) Patients being treated with antipsychotics, such as ziprasidone, may develop tardive dyskinesia. Severity and reversibility appear to be related to the duration of treatment and total cumulative dose administered, but may occur after brief treatment periods at low doses. The development of signs and symptoms of tardive dyskinesia should be monitored (Prod Info GEODON(R) oral capsules, IM injection, 2007).

2) Neuroleptic Malignant Syndrome

a) The development of Neuroleptic Malignant Syndrome (NMS) has been associated with antipsychotic therapy. Patients taking ziprasidone should be monitored for signs and symptoms of NMS (Prod Info GEODON(R) oral capsules, IM injection, 2007).

3) Body Temperature Dysregulation

a) Antipsychotics have been associated with disrupting the body's ability to regulate core body temperature. Patients taking ziprasidone should be monitored for changes in body temperature and dehydration (Prod Info GEODON(R) oral capsules, IM injection, 2007).

B) Ziprasidone Mesylate

1) Therapeutic

a) Physical Findings

1) Improvement of psychotic symptomatology (positive, negative symptoms) (Prod Info GEODON(R) oral capsules, IM injection, 2007).

2) Toxic

a) Laboratory Parameters

1) Torsade de Pointes

a) Ziprasidone may prolong the QT interval in some patients; ECG changes, blood pressure and heart rate monitoring may be warranted (Prod Info GEODON(R) oral capsules, IM injection, 2007).

b) Patients with hypokalemia or hypomagnesemia have an increased risk of the occurrence of torsade de pointes. Serum potassium and magnesium levels, at baseline and during ziprasidone therapy, should be monitored for patients on concomitant diuretics or at risk for electrolyte disturbances (Prod Info GEODON(R) oral capsules, IM injection, 2007).

c) Further evaluation, such as Holter monitoring, should be initiated for any patient who experiences symptoms during ziprasidone therapy that may indicate the development of torsade de pointes (eg dizziness, palpitations, syncope) (Prod Info GEODON(R) oral capsules, IM injection, 2007).

2) Diabetes Mellitus

a) Atypical antipsychotics, such as ziprasidone, have been linked with the development of hyperglycemia, some cases extreme and associated with ketoacidosis or hyperosmolar coma or death. Patients diagnosed with or at risk of diabetes mellitus should be monitored regularly for worsening of glucose control (eg fasting blood glucose, polydipsia, polyuria, polyphagia, weakness) (Prod Info GEODON(R) oral capsules, IM injection, 2007).

b) Physical Findings

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a) Patients being treated with antipsychotics, such as ziprasidone, may develop tardive dyskinesia. Severity and reversibility appear to be related to the duration of treatment and total cumulative dose administered, but may occur after brief treatment periods at low doses. The development of signs and symptoms of tardive dyskinesia should be monitored (Prod Info GEODON(R) oral capsules, IM injection, 2007).

2) Neuroleptic Malignant Syndrome

a) The development of Neuroleptic Malignant Syndrome (NMS) has been associated with antipsychotic therapy. Patients taking ziprasidone should be monitored for signs and symptoms of NMS (Prod Info GEODON(R) oral capsules, IM injection, 2007).

3) Body Temperature Dysregulation

a) Antipsychotics have been associated with disrupting the body's ability to regulate core body temperature. Patients taking ziprasidone should be monitored for changes in body temperature and dehydration (Prod Info GEODON(R) oral capsules, IM injection, 2007).

4.2 Patient Instructions

A) Ziprasidone (By mouth)
Ziprasidone

Treats schizophrenia and certain problems caused by bipolar disorder.

When This Medicine Should Not Be Used:
You should not use this medicine if you have had an allergic reaction to ziprasidone, or if you have severe heart failure or have recently had a heart attack. You should not use this medicine if you have a history of heart rhythm problems such as QT prolongation (including congenital long QT syndrome) or if you are using certain medicines that prolong the QT interval in the heart (such as dofetilide, sotalol, quinidine, disopyramide, procainamide, amiodarone, mesoridazine, thioridazine, chlorpromazine, droperidol, pimozide, sparfloxacin, gatifloxacin, moxifloxacin, halofantrine, mefloquine, pentamidine, arsenic trioxide, levomethadyl acetate, dolasetron mesylate, probucol, or tacrolimus). This medicine should not be used in elderly patients who have a mental illness called dementia-related psychosis.

How to Use This Medicine:
Capsule
Your doctor will tell you how much of this medicine to use and how often. Your dose may need to be changed several times in order to find out what works best for you. Do not use more medicine or use it more often than your doctor tells you to.
It is best to take this medicine with food or milk at the same time every day. Swallow the capsule whole. Do not break, crush, or chew it.
Keep using this medicine for the full treatment time, even if you feel better after the first few doses.

If a Dose is Missed:
If you miss a dose or forget to use your medicine, use it as soon as you can. If it is almost time for your next dose, wait until then to use the medicine and skip the missed dose. Do not use extra medicine to make up for a missed dose.

How to Store and Dispose of This Medicine:
Store the medicine in a closed container at room temperature, away from heat, moisture, and direct light.
Ask your pharmacist, doctor, or health caregiver about the best way to dispose of any leftover medicine after you have finished your treatment. You will also need to throw away old medicine after the expiration date has passed.
Keep all medicine away from children and never share your medicine with anyone.

Drugs and Foods to Avoid:
Ask your doctor or pharmacist before using any other medicine, including over-the-counter medicines, vitamins, and herbal products.
Make sure your doctor knows if you are using medicines to lower blood pressure, such as atenolol, lisinopril, metoprolol, quinapril, Accupril®, Cozaar®, Diovan®, Lotrel®, Norvasc®, Toprol®, or Zestril®. Tell your doctor if you are using diuretics or water pills (such as furosemide, Aldactazide®, Aldactone®, Dyazide®, Lasix®, Moduretic®, or Maxzide®), levodopa, carbamazepine (Carbatrol®, Tegretol®), or ketoconazole (Nizoral®).
Tell your doctor if you are also using levodopa (such as Dopart® or Larodopa®) or medicines such as bromocriptine (Parlodel®), Pramipexole (Mirapex®), ropinirole (Requip®), cabergoline (Dostinex®), or apomorphine (Apokyn®).
Tell your doctor if you are using any medicines that make you sleepy. These include sleeping pills, cold and allergy medicine, narcotic pain relievers, and sedatives.
Do not drink alcohol while you are using this medicine.

Warnings While Using This Medicine:
Make sure your doctor knows if you are pregnant or breastfeeding, or if you have heart problems, liver disease, Alzheimer's disease, trouble with swallowing, or dizziness or fainting problems. Tell your doctor if you have a history of stroke, seizures, breast cancer, or low potassium or magnesium levels in your blood.
Make sure your doctor knows if you have thoughts of hurting yourself. Tell your doctor if you or anyone in your family has a history of diabetes.
Make sure your doctor knows if you have a family history of a heart condition called congenital long QT syndrome. Tell your doctor if you have ever had Neuroleptic Malignant Syndrome (NMS) caused by other antipsychotic medicines.
Tardive dyskinesia (a movement disorder) may occur and may not go away after you stop using the medicine. Call your doctor if you are having signs of tardive dyskinesia such as rapid, worm-like movements of the tongue, or other uncontrolled movements of the mouth, tongue, cheeks, jaw, or arms and legs.
This medicine may cause an increase in your blood sugar. If you have diabetes, you may need to check your blood sugar more often. If you are using medicine for diabetes, your doctor may need to change your dose.
This medicine is not approved to treat behavior disorders in older people who have dementia. Using this medicine to treat this problem could increase the risk of death. This risk has not been shown for the

approved uses of this medicine.
This medicine may make you dizzy or drowsy. Avoid driving, using machines, or doing anything else that could be dangerous if you are not alert. This medicine may also make you feel lightheaded when you get up suddenly from a lying or sitting position, so get up slowly.
This medicine might reduce how much you sweat. Your body could get too hot if you do not sweat enough. If your body gets too hot, you might feel dizzy, weak, tired, or confused. You might vomit or have an upset stomach. Do not get too hot while you are exercising. Avoid places that are very hot. Call your doctor if you are too hot and cannot cool down.
Your doctor will need to check your progress at regular visits while you are using this medicine. Be sure to keep all appointments.
Some side effects are more likely to happen in elderly people who have memory problems or other reduced mental skills. Make sure the doctor knows if the person who will be using this medicine has Alzheimer's disease or similar problems (often called "dementia").

Possible Side Effects While Using This Medicine:
Call your doctor right away if you notice any of these side effects:
Allergic reaction: Itching or hives, swelling in your face or hands, swelling or tingling in your mouth or throat, chest tightness, trouble breathing.
Chest pain.
Fast, slow, irregular (uneven), or pounding heartbeat.
Fever, sweating, confusion, muscle stiffness.
In males: Painful, prolonged erection of your penis.
Increase in thirst, hunger, or urination.
Lightheadedness, dizziness, or fainting.
Problems with balance or walking.
Seizures.
Severe diarrhea, nausea, vomiting, or stomach pain.
Skin rash.
Trouble swallowing or talking, sticking out of the tongue, or spasm of neck muscles.
Twitching or muscle movements you cannot control (often in your face, tongue, or jaw).

If you notice these less serious side effects, talk with your doctor:
Anxiety or restlessness.
Changes in vision.
Constipation or upset stomach.
Dry mouth.
Headache.
Sleepiness or unusual drowsiness.
Sneezing, cough, or runny or stuffy nose.
Tiredness.
Weight gain.

If you notice other side effects that you think are caused by this medicine, tell your doctor.

B) Ziprasidone (Injection)
Ziprasidone

Treats agitation (excessive movement, tension, or anxiety) in a person who has schizophrenia.

When This Medicine Should Not Be Used:
You should not use this medicine if you have had an allergic reaction to ziprasidone, or if you have severe heart failure or have recently had a heart attack. You should not use this medicine if you have a history of heart rhythm problems such as QT prolongation (including congenital long QT syndrome) or if you are using certain medicines that prolong the QT interval in the heart (such as dofetilide, sotalol, quinidine, disopyramide, procainamide, amiodarone, mesoridazine, thioridazine, chlorpromazine, droperidol, pimozide, sparfloxacin, gatifloxacin, moxifloxacin, halofantrine, mefloquine, pentamidine, arsenic trioxide, levomethadyl acetate, dolasetron mesylate, probucol, or tacrolimus). This medicine should not be used in elderly patients who have a mental illness called dementia-related psychosis.

How to Use This Medicine:
Injectable
Your doctor will prescribe your exact dose and tell you how often it should be given. This medicine is given as a shot into one of your muscles.
A nurse or other trained health professional will give you this medicine.

Drugs and Foods to Avoid:
Ask your doctor or pharmacist before using any other medicine, including over-the-counter medicines, vitamins, and herbal products.
Make sure your doctor knows if you are using medicines to lower blood pressure, such as atenolol, lisinopril,

metoprolol, quinapril, Accupril®, Cozaar®, Diovan®, Lotrel®, Norvasc®, Toprol®, or Zestril®. Tell your doctor if you are using diuretics or water pills (such as furosemide, Aldactazide®, Aldactone®, Dyazide®, Lasix®, Moduretic®, or Maxzide®), levodopa, carbamazepine (Carbatrol®, Tegretol®), or ketoconazole (Nizoral®).
Tell your doctor if you are using levodopa (such as Dopart® or Larodopa®) or medicines such as bromocriptine (Parlodel®), Pramipexole (Mirapex®), ropinirole (Requip®), cabergoline (Dostinex®), or apomorphine (Apokyn®).
Tell your doctor if you are using any medicines that make you sleepy. These include sleeping pills, cold and allergy medicine, narcotic pain relievers, and sedatives.
Do not drink alcohol while you are using this medicine.

Warnings While Using This Medicine:
Make sure your doctor knows if you are pregnant or breastfeeding, or if you have heart problems, liver disease, Alzheimer's disease, trouble with swallowing, or dizziness or fainting problems. Tell your doctor if you have a history of stroke, seizures, breast cancer, or low potassium or magnesium levels in your blood.
Tell your doctor if you or anyone in your family has a history of diabetes.
Make sure your doctor knows if you have a family history of a heart condition called congenital long QT syndrome. Tell your doctor if you have ever had Neuroleptic Malignant Syndrome (NMS) caused by other antipsychotic medicines.
Tardive dyskinesia (a movement disorder) may occur and may not go away after you stop using the medicine. Call your doctor if you are having signs of tardive dyskinesia such as rapid, worm-like movements of the tongue, or other uncontrolled movements of the mouth, tongue, cheeks, jaw, or arms and legs.
This medicine is not approved to treat behavior disorders in older people who have dementia. Using this medicine to treat this problem could increase the risk of death. This risk has not been shown for the approved uses of this medicine.
This medicine may make you dizzy or drowsy. Avoid driving, using machines, or doing anything else that could be dangerous if you are not alert. This medicine may also make you feel lightheaded when you get up suddenly from a lying or sitting position, so get up slowly.
This medicine may cause an increase in your blood sugar. If you have diabetes, you may need to check your blood sugar more often. If you are taking medicine for diabetes, your doctor may need to change your dose.
This medicine may cause you to become overheated more easily than usual. Be careful when exercising, or when you are outdoors in hot or humid weather.
Your doctor will need to check your blood at regular visits while you are using this medicine. Be sure to keep all appointments.

Possible Side Effects While Using This Medicine:
Call your doctor right away if you notice any of these side effects:
Allergic reaction: Itching or hives, swelling in your face or hands, swelling or tingling in your mouth or throat, chest tightness, trouble breathing.
Anxiety, agitation, trouble sleeping, or changes in mood or behavior.
Fast, slow, uneven, or pounding heartbeat.
Fever, sweating, confusion, muscle stiffness.
In males: painful, prolonged erection of your penis.
Increase in thirst, hunger, or urination.
Lightheadedness, dizziness, or fainting.
Numbness, tingling, or burning pain in your hands, arms, legs, or feet.
Problems with balance or walking.
Red or black stools.
Seizures.
Severe diarrhea, nausea, vomiting, or stomach pain.
Skin rash.
Trouble swallowing or talking, sticking out of the tongue, or spasm of neck muscles.
Twitching or muscle movements you cannot control (often in your face, tongue, or jaw).

If you notice these less serious side effects, talk with your doctor:
Headache.
Pain where the shot was given.
Sleepiness or unusual drowsiness.
Sneezing, cough, or stuffy nose.
Tiredness.

If you notice other side effects that you think are caused by this medicine, tell your doctor.

4.3 Place In Therapy

A) Ziprasidone

1) Current users of atypical antipsychotic drugs (including ziprasidone) and typical antipsychotic drugs had a similar dose-dependent risk of sudden cardiac death, according to a retrospective cohort of 93,300 adult users of

antipsychotic drugs and 186,600 matched controls. The study included patients age 30 to 74 years (mean 45.7 +/- 11.8 years) with similar cardiovascular risk at baseline who had at least one filled prescription and had 1 outpatient visit in each of the 2 preceding years. Sudden cardiac death was defined as occurring in the community and excluded deaths of patients admitted to the hospital, non-sudden deaths, deaths due to extrinsic causes, or causes not related to ventricular tachyarrhythmia. Current use was defined as the interval between the time the prescription was filled and the end of the day's supply. Low and high doses was defined as comparable to less than 100 milligrams (mg) of chlorpromazine, and doses comparable to chlorpromazine 300 mg or greater, respectively. The adjusted rate of sudden cardiac death (incidence-rate ratio) in current users of atypical antipsychotic drugs in 79,589 person-years was 2.26 (95% CI, 1.88 to 2.72, p less than 0.001) which was similar to the risk in current users of typical antipsychotic drugs in 86,735 person-years which was 1.99 (95% CI, 1.68 to 2.34, p less than 0.001). The risk of sudden cardiac death significantly increased with increasing dose in both the typical and atypical antipsychotic drug groups. In atypical antipsychotic use, the incidence rate ratio increased from 1.59 (95% CI, 1.03 to 2.46) in low-dose use to 2.86 (95% CI, 2.25 to 3.65) in high-dose use. To limit the effects of confounding of the study results, there was a secondary analysis performed in a cohort of patients matched by propensity score, which resulted in a similar risk of sudden death as the primary cohort analysis (Ray et al, 2009). In an editorial in The New England Journal of Medicine, it has been suggested that antipsychotic drugs continue to be used in patients with clear evidence of benefit, but in vulnerable populations with cardiac risk profiles (eg, elderly patients), there should be an age-dependent justification required prior to administration. It has also been suggested (although not formally tested) that ECGs be performed before and shortly after initiation of antipsychotic therapy to screen for existing or emergent QT interval prolongation (Schneeweiss & Avorn, 2009).

2) General (atypical agents): patients resistant to standard antipsychotic agents; patients with therapy-limiting extrapyramidal symptoms, other adverse effects.

3) Specific: comparisons of ziprasidone with clozapine, risperidone, olanzapine, and sertindole in refractory patients are needed to determine potential advantages. Disadvantages of ziprasidone: prolongation of QT/QTc interval, shorter half-life, twice-daily dosing usually required (olanzapine, sertindole may be given once daily).

B) Ziprasidone Hydrochloride

See Drug Consult reference: FIRST- VS SECOND-GENERATION ANTIPSYCHOTIC AGENTS FOR SCHIZOPHRENIA

C) Ziprasidone Mesylate

See Drug Consult reference: FIRST- VS SECOND-GENERATION ANTIPSYCHOTIC AGENTS FOR SCHIZOPHRENIA

4.4 Mechanism of Action / Pharmacology

A) MECHANISM OF ACTION

1) Atypical antipsychotic (benzisothiazoyl piperazine derivative); serotonin (5HT)-2A/dopamine D2 antagonist. Also a 5HT-1A agonist (property may confer greater protection against adverse extrapyramidal effects) (Kerwin & Taylor, 1996; Bench et al, 1993; Fischman et al, 1996; Owens, 1996; Lieberman, 1993; Pickar, 1995; Anon, 1996a; Schotte et al, 1996).

2) Modest-to-low affinity for alpha-1, H1 receptors (Kerwin & Taylor, 1996). Inhibits norepinephrine reuptake (Pickar, 1995; Seeger et al, 1995).

3) In vitro: ratio of 5HT-2A/dopamine D2 receptor affinity greater than clozapine (2-fold), haloperidol (680-fold) (Seeger et al, 1995).

B) REVIEW ARTICLES

1) Focus on Ziprasidone (Green B, 2001).

2) Treatment of schizophrenia (includes use of atypical agents) (Marder, 1996; Fleischhacker, 1995; Meltzer et al, 1994; Lieberman, 1996; Weiden et al, 1996; Jeste et al, 1996).

3) Psychosis in mania (use of atypical agents) (McElroy et al, 1996).

4) Mechanism of action with respect to neurotransmitter pathways in the brain utilized by atypical antipsychotics, including ZIPRASIDONE (Kendrick, 1999).

5) A brief introductory review of ziprasidone is available (Tandon, 2000).

4.5 Therapeutic Uses

Ziprasidone

Ziprasidone Hydrochloride

Ziprasidone Mesylate

4.5.A Ziprasidone

4.5.A.1 Dementia

See Drug Consult reference: BEHAVIORAL AND PSYCHOLOGICAL SYMPTOMS OF DEMENTIA

4.5.B Ziprasidone Hydrochloride

Bipolar I disorder, acute manic or mixed episodes

Major depressive disorder, Treatment-resistant; Adjunct

Schizoaffective disorder

Schizophrenia

4.5.B.1 Bipolar I disorder, acute manic or mixed episodes

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIa
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Indicated for the treatment of acute manic or mixed episodes in patients with bipolar disorder, with or without psychotic features (Prod Info GEODON(R) oral capsules, IM injection, 2007)

c) Adult:

1) Ziprasidone was more effective than placebo for treating acute bipolar mania. In a randomized, double-blind, multicenter, placebo-controlled trial, 210 bipolar inpatients, currently in a manic or mixed episode, underwent single-blind placebo treatment for a one-week washout and were then randomized 2:1 to receive ziprasidone (n=140) or placebo (n=70) for 3 weeks. Ziprasidone, given with meals, was started at 40 milligrams (mg) twice daily on day 1, raised to 80 mg twice daily on day 2, and then adjusted if necessary during the trial to a final range of 80 to 160 mg/day. Data from 131 ziprasidone-treated patients and 66 placebo-treated patients were used for determining efficacy. On the 11-item Mania Rating Scale, a significantly greater improvement with ziprasidone compared to placebo was evident by day 2 (p less than 0.003) and remained apparent throughout the study (p less than 0.001 at the end of weeks 1, 2, and 3). By the end of the study, significant differences between the groups, favoring ziprasidone over placebo, were evident on the Clinical Global Impressions (CGI) severity scale, the CGI improvement scale, the Positive and Negative Syndrome Scale, and the Global Assessment of Functioning Scale. Fifty percent of patients receiving ziprasidone and 35% receiving placebo were classified as responders (p less than 0.05). In the ziprasidone group, 6.4% of patients (9 of 140) withdrew because of adverse events, compared to 4.3% (3 of 70) of the placebo group. None of the treatment-related adverse events in either group was serious. The most commonly occurring adverse events were somnolence (ziprasidone vs placebo: 37% vs 13%), headache (21% vs 19%), dizziness (22% vs 10%), and akathisia (11% vs 6%). Movement disorders were uncommon. No change in weight was associated with ziprasidone treatment. Ziprasidone treatment showed a mean prolongation in QT (c) interval of 11 milliseconds (msec). No patient had a QT(c) interval of 500 msec or higher (Keck et al, 2003).

4.5.B.2 Major depressive disorder, Treatment-resistant; Adjunct

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Ziprasidone augmentation may be effective in the treatment of major depression resistant to SSRI therapy

c) Adult:

1) Ziprasidone augmentation of selective serotonin reuptake inhibitor (SSRI) therapy may be an effective option for patients with treatment- resistant major depression. In a prospective, open-label trial (n=20), patients with major depressive disorder resistant to SSRI therapy and a Hamilton Rating Scale for Depression (HAM-D) score of at least 14 received ziprasidone (initial, 20 milligrams (mg) twice daily, titrated in 20 mg/week increments to a maximum of 80 mg twice daily; mean dose, 82.1 mg/day) in addition to continued SSRI therapy with citalopram, fluoxetine, paroxetine, or sertraline for 6 weeks. At endpoint, 10 (50%) patients achieved response (defined as at least a 50% reduction in the HAM-D score from baseline to endpoint) and 5 (25%) patients achieved remission (defined as a HAM-D score of 7 or less at endpoint). Overall, the mean HAM-D score was reduced from 21.8 to approximately 12

from baseline to week 6, respectively. The most common adverse events included fatigue (50%), sleep disturbance (30%), restlessness (15%), tremor (15%), bruxism (15%), headache (10%), dry mouth (20%), gastrointestinal distress (20%), and urinary frequency (10%). No patient had a QTc interval greater than 500 milliseconds; however, a QTc interval increase of 30 milliseconds was observed in two patients. Placebo-controlled trials are needed to clarify the efficacy of ziprasidone augmentation therapy in SSRI-resistant depression (Papakostas et al, 2004).

4.5.B.3 Schizoaffective disorder

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIa
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Oral ziprasidone has been shown to be effective in the short term treatment of patients with an acute episode of schizoaffective disorder.

c) Adult:

1) Significant dose-related improvements on all primary efficacy variables (BPRS total, BPRS Core, CGI-S and BPRS Manic scores) were observed in patients receiving ziprasidone compared to placebo in 2 multicenter double-blind placebo-controlled clinical trials (n=115). Inclusion criteria consisted of hospitalized patients with an acute exacerbation of schizoaffective disorder, bipolar or depressive subtype. Patients were required to have a minimum duration of illness of at least 6 months or 1 year. In one study patients were randomized to receive ziprasidone 20 milligrams (mg) twice daily or placebo for 4 weeks. In the second study, patients were randomized to receive ziprasidone 40 mg twice daily, 80 mg twice daily or placebo for 6 weeks. The incidence of individual adverse events was generally low in all treatment groups (Keck et al, 2001).

4.5.B.4 Schizophrenia

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes; Pediatric, no
Efficacy: Adult, Effective
Recommendation: Adult, Class I
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Positive/negative symptom improvement (Reeves & Harrigan, 1996; Harrigan et al, 1996a; Citrome, 1997a; Kerwin & Taylor, 1996b; Anon, 1996b)
Relatively low incidence of extrapyramidal symptoms (Reeves & Harrigan, 1996; Harrigan et al, 1996a; Citrome, 1997a; Kerwin & Taylor, 1996b; Anon, 1996b)
Causes more QT/QTc prolongation than risperidone, olanzapine, quetiapine, and haloperidol (Prod Info GEODON(R) oral capsules, IM injection, 2007)
Decreased the rate of relapse in patients with chronic, stable schizophrenia (Arato et al, 2002; Prod Info GEODON(R) oral capsules, IM injection, 2007)

c) Adult:

1) Results of the Ziprasidone Extended Use in Schizophrenia (ZEUS) study indicate that ziprasidone treatment decreased the rate of relapse in patients with chronic, stable schizophrenia. In this randomized, double-blind, placebo-controlled study, markedly ill (score of 5 or lower on the Clinical Global Impression Severity scale) patients with chronic, stable schizophrenia in extended-stay, inpatient settings received twice daily doses of ziprasidone 40 milligrams (mg)/day (n=72), ziprasidone 80 mg/day (n=68), ziprasidone 160 mg/day (n=67) or placebo (n=71) for up to 1 year. Patients were allowed to receive anticholinergics, lorazepam, and temazepam, but no other psychotropic medications were permitted during the study. The likelihood of relapse at 1 year was significantly lower in patients treated with ziprasidone 40 mg/day (43%), 80 mg/day (35%) or 160 mg/day (36%) as compared with placebo (77%) (p=0.002, p less than 0.001, p less than 0.001, respectively). Of the ziprasidone-treated patients who relapsed during the study, most (61/71) did so in the first 6 months. However, of patients who stayed in the study for at least 6 months only 9% (10/110) of patients in the ziprasidone groups eventually relapsed, as compared with 42% (8/19) of placebo-treated patients (p=0.001). Patients in all three ziprasidone treatment groups showed significantly better improvements in negative symptoms as compared with placebo beginning at week 16 and continuing until the end of the study. Ziprasidone was generally well tolerated, however, one patient had a grand mal seizure and another experienced extrapyramidal symptoms during treatment (Arato et al, 2002).

2) Placebo-controlled, double-blind studies of patients with acute exacerbation of schizophrenia or schizophreniform disorder found 80 to 160 milligrams (mg) daily to be effective in significantly improving positive and negative symptoms with a relatively low incidence of extrapyramidal symptoms (Reeves & Harrigan, 1996; Harrigan et al, 1996a; Citrome, 1997a; Kerwin & Taylor, 1996b; Anon, 1996b).

3) With 80/160 milligrams (mg) daily (6 weeks): reduction in Positive and Negative Syndrome Scale

(PANSS) total scores by 12.4/17.1 (-5.4 with placebo), negative subscale scores by 3.2/3.9 (-0.9 with placebo); significant improvement in BPRSd total score (18-item Brief Psychiatric Rating Scale derived from PANSS) (Reeves & Harrigan, 1996).
4) Ziprasidone was significantly superior to placebo in both time to relapse and rate of relapse, with no significant difference between the 2 dose groups in a 52-week, placebo-controlled trial (n = 294). Inpatients were randomized to receive ziprasidone 20 milligrams (mg) twice daily, 40 mg twice daily, 80 mg twice daily or placebo (Prod Info GEODON(R) oral capsules, IM injection, 2007).

4.5.C Ziprasidone Mesylate

4.5.C.1 Agitation, acute - Schizophrenia

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes; Pediatric, no
Efficacy: Adult, Effective
Recommendation: Adult, Class I
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Intramuscular ziprasidone mesylate is effective for the treatment of acute agitation in schizophrenic patients (Prod Info GEODON(R) oral capsules, IM injection, 2007)

c) Adult:

1) The efficacy of intramuscular ziprasidone mesylate for the treatment of acute agitation in schizophrenia was established in two double-blind, randomized, single-day trials. Acutely agitated schizophrenic patients with a score of 3 or higher on at least three Positive and Negative Syndrome Scale (PANSS) items (anxiety, tension, hostility, and excitement) received either a control dose (2 milligrams) or a higher dose of ziprasidone. In the first study, patients (n=79) received 20 mg or 2 mg of intramuscular ziprasidone up to four times in 24 hours at intervals of at least 4 hours. The higher dose of ziprasidone was statistically superior to the control dose as assessed by the area under the curve (AUC) of the Behavioral Activity Rating Scale (BARS) at 0 to 4 hours and by the Clinical Global Impression (CGI) severity rating at 4 hours and at endpoint. In the second study, patients (n=117) received 10 mg or 2 mg of intramuscular ziprasidone up to four times in 24 hours at intervals of at least 2 hours. The 10 mg dose of ziprasidone was statistically superior to the 2 mg dose as assessed by the AUC of the BARS at 0 to 2 hours , but not by the CGI severity rating (Prod Info GEODON(R) oral capsules, IM injection, 2007).

4.6 Comparative Efficacy / Evaluation With Other Therapies

Chlorpromazine

Haloperidol

Olanzapine

Perphenazine

Quetiapine

Risperidone

4.6.A Chlorpromazine

4.6.A.1 Schizophrenia

a) Based upon comparisons of minimum effective dosages identified in placebo- controlled, fixed-dose and fixed-dose-ranging drug development trials, the minimum effective dose of ziprasidone was 120 milligrams/day (equivalent to chlorpromazine 200 milligrams/day) (Woods SW, 2003).

4.6.B Haloperidol

Chronic schizophrenia

Schizophrenic episode, acute

4.6.B.1 Chronic schizophrenia

a) Ziprasidone was as effective as haloperidol in treating overall symptomatology, was more effective in the treatment of negative symptoms, and was better tolerated, in the long-term treatment of outpatients with stable schizophrenia. In a 28-week, double-blind, flexible-dose, parallel-group clinical trial, ziprasidone and haloperidol both improved overall symptomatology in 227 patients with chronic or subchronic schizophrenia. Patients who received ziprasidone had a significantly higher rate of improvement in the treatment of negative symptoms (48% of patients showed improvement) compared to patients who received haloperidol (33% of patients showed improvement). For patient assessment, the Positive and Negative Syndrome Scale (PANSS), the Clinical Global Impressions-Severity of Illness scale (CGI-S), and the Montgomery-Asberg Depression Rating Scale (MADRS) were used at baseline and weeks 3, 6, 16, and 28. In the ziprasidone group, patients received a starting dose of 40 milligrams per day (mg/d) on the first 2 days and 80 mg/d on day 3. The ziprasidone dose could be increased to a maximum of 120 mg/d in the second week and up to 160 mg/d in the third week. For the haloperidol group, patients received a starting dose of 5 mg/d, which could be increased to a maximum of 10 mg/d during the second week and 15 mg/d during the third week of treatment. At week 28, the mean doses of ziprasidone and haloperidol were 116.5 mg/d and 8.6 mg/d, respectively. Adverse events were evaluated using the Simpson-Angus scale, the Barnes Akathisia scale, and the Abnormal Involuntary Movement Scale (AIMS). Adverse events were reported in 85% of patients in the haloperidol group and 77% in the ziprasidone group; twice as many patients receiving haloperidol (16%) compared to ziprasidone (8%) discontinued the study due to treatment-related adverse events. There was also a distinct difference in the percentage of patients who developed movement disorders; 41% in the haloperidol group compared to 15% in the ziprasidone group, although this difference was not statistically significant (Hirsch et al, 2002).

4.6.B.2 Schizophrenic episode, acute

a) Acute exacerbations: ziprasidone 160 mg daily, haloperidol 15 mg daily comparable in efficacy (reduction of BPRS scores). Ziprasidone 4 to 40 mg/day less effective (Anon, 1996).

b) Ziprasidone 160 milligrams (mg) and haloperidol 15 mg were both effective in improving overall psychopathology in patients with an acute exacerbation of schizophrenia or schizoaffective disorder (Goff et al, 1998). In a double-blind, dose-ranging study, patients received either haloperidol 15 mg/day (n=17), or ziprasidone 4 mg (n=19), ziprasidone 10 mg (n=17), ziprasidone 40 mg (n=17), or ziprasidone 160 mg (n=20). Despite 46 patients failing to complete the study, intention-to-treat analysis showed a trend toward significance for the ziprasidone dose response on the Brief Psychiatric Rating scale (p=0.08) and a statistically significant dose response for the Clinical Global Impression (CGI) scale (p less than 0.001). Changes in the CGI severity score were significantly changed from baseline as compared to the ziprasidone 4 mg group for both the haloperidol group (p less than 0.01) and the ziprasidone 160 mg group (p=0.001). Study termination was due to 18 patients having a lack of efficacy (4 in the haloperidol group), 7 due to liver transaminase elevations in ziprasidone groups, and 23 for unrelated reasons.

c) In hospitalized patients, the mean reductions in BPRS total, BPRS agitation items, and CGI were statistically greater after INTRAMUSCULAR (IM) ziprasidone than IM haloperidol, and this continued following conversion to oral treatment. The study was a multicenter, 7-day, randomized, open-label, parallel-group study in 7 countries (n=132). Patients received either an initial dose of ziprasidone 10 milligrams (mg) IM, followed by up to 3 days of flexible-dose IM ziprasidone (5 mg to 20 mg every 4 to 6 hours prn) and continued with oral treatment (80 mg to 200 mg/day) to day 7 (n = 90), or haloperidol IM (2.5 mg to 10 mg) on entry, followed by 2.5 mg to 10 mg IM every 4 to 6 hours prn up to 3 days followed by oral haloperidol 10 mg/day to 80 mg/day to day 7 (n = 32). Ziprasidone was associated iwth a lower incidence of movement disorders compared to haloperidol (Brook et al, 2000).

4.6.C Olanzapine

Chronic schizophrenia

Schizophrenia

4.6.C.1 Chronic schizophrenia

a) When newer antipsychotic medications (olanzapine, quetiapine, risperidone, and ziprasidone) were compared with the first-generation antipsychotic, perphenazine, the majority of patients in each group discontinued their antipsychotic study medication before 18 months. Patients (n=1493) with chronic schizophrenia were randomized to receive olanzapine 7.5 to 30 milligrams/day (mg/day), perphenazine 8 to 32 mg/day, quetiapine 200 to 800 mg/day, risperidone 1.5 to 6.0 mg/day, or ziprasidone 40 to 160 mg/day for up to 19 months. Overall, 74% of patients discontinued treatment for any cause before 18 months; discontinuation rates ranged from 64 to 82%. Time to discontinuation ranged from 3.5 months for ziprasidone to 9.2 months with olanzapine. The time to discontinuation was significantly longer in the olanzapine group as compared with the quetiapine (hazard ratio (HR), 0.63; 95% confidence interval (CI), 0.52 to 0.76; p less than 0.001) or risperidone groups (HR, 0.75; 95% CI, 0.62 to 0.90; p=0.002). Time to

discontinuation due to adverse events were similar between all groups, but the rates ranged from 10% for risperidone to 19% for olanzapine (p=0.04). More patients discontinued olanzapine due to greater weight gain (average of 0.9 kilograms/month) and greater increases in glycosylated hemoglobin, total cholesterol, and triglycerides (Lieberman et al, 2005).

4.6.C.2 Schizophrenia

a) In a randomized, double-blind trial (n=269), six-week courses of OLANZAPINE and ZIPRASIDONE had comparable efficacy for treatment of schizophrenia or schizoaffective disorder (DSM-IV), while the side effects profile of ziprasidone appeared to be more favorable with respect to metabolic indicators but less favorable related to QT interval prolongation. Enrollees were acutely ill, recently admitted inpatients. During the first week, subjects received fixed doses of study drugs: olanzapine 5 milligrams (mg) on days 1 and 2 and 10 mg/day on days 3 to 7 (n=133); ziprasidone 40 mg twice daily on days 1 and 2 and 80 mg twice daily on days 3 to 7 (n=136). Dosing was flexible over weeks 2-6 (olanzapine 5 to 15 mg/day; ziprasidone 40 to 80 mg twice daily); overall median daily doses were 12.4 mg for olanzapine and 138.6 mg for ziprasidone (the latter in 2 divided doses daily). Efficacy measures included the Brief Psychiatric Rating Scale (BPRS), Clinical Global Impression (CGI) severity and improvement scales, Positive and Negative Syndrome Scale, and the Calgary Depression Scale for Schizophrenia. At study end, there were no significant differences on any rating scale between improvements in the olanzapine group and those in the ziprasidone group. At endpoint, 36.8% of the olanzapine group and 48.5% of the ziprasidone group had discontinued. Overall, 39.8% and 46.3% of the olanzapine and ziprasidone groups, respectively, had experienced adverse events that were considered treatment related. No between-group differences were seen related to dyskinesia, dystonia, or extrapyramidal symptoms. Weight gain amounted to approximately 3.5 kilograms (kg) and 1 kg for olanzapine- and ziprasidone-treated patients, respectively (p less than 0.0001). Total cholesterol, low-density lipoprotein cholesterol, and triglycerides increased by approximately 10%, 13%, and 25%, respectively, in the group receiving olanzapine; all the same measures decreased slightly in the ziprasidone group (p less than 0.0001; p=0.0004; p less than 0.003, respectively). Fasting serum insulin increased by median 3.3 and 0.25 micro- units/milliliter in the olanzapine and ziprasidone groups, respectively (p=0.051). Prolongation of the QTc interval amounted to 0.52 and 6.08 milliseconds for the same 2 groups, respectively (p less than 0.05) (Simpson et al, 2004).

b) A multicenter, randomized, double-blind, parallel-group, 28 week study (n=548) found that olanzapine therapy resulted in significantly greater psychopathology improvement and higher response and completion rates compared to ziprasidone, while ziprasidone therapy was superior for weight change and lipid profile. Patients with schizophrenia were randomized to receive olanzapine (n=277) 10 to 20 mg/day or ziprasidone (n=271) 80 to 160 mg/day. The primary efficacy measure, the Positive and Negative Syndrome Scale total score, showed that the olanzapine group had significantly greater improvement than the ziprasidone group (p less than 0.001). The olanzapine group also showed significant improvement from baseline to endpoint compared to ziprasidone in the Positive and Negative Syndrome subscales: positive symptoms, negative symptoms, general psychopathology, cognition, and excitability (all p less than 0.0001 except for negative symptoms p=0.003). Patients were allowed to take benzodiazepines or hypnotic monotherapy during the study, but were removed from the study if they required more than two concurrent benzodiazepine hypnotic medications. Significantly more patients in the ziprasidone group required at least one dose of a benzodiazepine compared to the olanzapine group (53.5% versus 40.4%; p=0.003). Response was defined as a 30% improvement in the Positive and Negative Syndrome Scale total score at endpoint, and the rate was significantly higher for the olanzapine group compared to the ziprasidone group (58.6% versus 42.5%) (p less than 0.001). There was no significant difference in exacerbation of symptoms between the two groups, which was defined as a decrease in the Positive and Negative Syndrome Scale total score by 20% or more and a decrease in the Clinical Global Impression severity of illness score of 1 point or more after week 8 (14.6% olanzapine and 25.3% ziprasidone; p=0.06). Significantly more patients in the olanzapine group (59.6%) than in the ziprasidone group (42.4%) completed the study (p less than 0.001). Reasons for discontinuation were only significant for lack of efficacy (olanzapine 7.2% versus ziprasidone 13.7%; p=0.02) and aggravation of psychosis (olanzapine 1.4% versus ziprasidone 4.4%; p=0.05). There were significantly greater increases in body weight and levels of total cholesterol, low-density lipoprotein cholesterol, and triglycerides (all p less than 0.001) and a significantly greater decrease in high-density lipoprotein cholesterol (p=0.001) in the olanzapine group than in the ziprasidone group (Breier et al, 2005).

4.6.D Perphenazine

4.6.D.1 Chronic schizophrenia

a) When newer antipsychotic medications (olanzapine, quetiapine, risperidone, and ziprasidone) were compared with the first-generation antipsychotic, perphenazine, the majority of patients in each group discontinued their antipsychotic study medication before 18 months. Patients (n=1493) with chronic schizophrenia were randomized to receive olanzapine 7.5 to 30 milligrams/day (mg/day), perphenazine 8 to 32 mg/day, quetiapine 200 to 800 mg/day, risperidone 1.5 to 6.0 mg/day, or ziprasidone 40 to 160 mg/day for up to 19 months. Overall, 74% of patients discontinued treatment for any cause before 18 months; discontinuation rates ranged from 64 to 82%. Time to discontinuation ranged from 3.5 months for ziprasidone to 9.2 months with olanzapine. The time to discontinuation was significantly longer in the olanzapine group as compared with the quetiapine (hazard ratio (HR), 0.63; 95% confidence interval (CI), 0.52 to 0.76; p less than 0.001) or risperidone groups (HR, 0.75; 95% CI, 0.62 to 0.90; p=0.002). Time to

discontinuation due to adverse events were similar between all groups, but the rates ranged from 10% for risperidone to 19% for olanzapine (p=0.04). More patients discontinued olanzapine due to greater weight gain (average of 0.9 kilograms/month) and greater increases in glycosylated hemoglobin, total cholesterol, and triglycerides (Lieberman et al, 2005).

4.6.E Quetiapine

4.6.E.1 Chronic schizophrenia

a) When newer antipsychotic medications (olanzapine, quetiapine, risperidone, and ziprasidone) were compared with the first-generation antipsychotic, perphenazine, the majority of patients in each group discontinued their antipsychotic study medication before 18 months. Patients (n=1493) with chronic schizophrenia were randomized to receive olanzapine 7.5 to 30 milligrams/day (mg/day), perphenazine 8 to 32 mg/day, quetiapine 200 to 800 mg/day, risperidone 1.5 to 6.0 mg/day, or ziprasidone 40 to 160 mg/day for up to 19 months. Overall, 74% of patients discontinued treatment for any cause before 18 months; discontinuation rates ranged from 64 to 82%. Time to discontinuation ranged from 3.5 months for ziprasidone to 9.2 months with olanzapine. The time to discontinuation was significantly longer in the olanzapine group as compared with the quetiapine (hazard ratio (HR), 0.63; 95% confidence interval (CI), 0.52 to 0.76; p less than 0.001) or risperidone groups (HR, 0.75; 95% CI, 0.62 to 0.90; p=0.002). Time to discontinuation due to adverse events were similar between all groups, but the rates ranged from 10% for risperidone to 19% for olanzapine (p=0.04). More patients discontinued olanzapine due to greater weight gain (average of 0.9 kilograms/month) and greater increases in glycosylated hemoglobin, total cholesterol, and triglycerides (Lieberman et al, 2005).

4.6.F Risperidone

4.6.F.1 Chronic schizophrenia

a) When newer antipsychotic medications (olanzapine, quetiapine, risperidone, and ziprasidone) were compared with the first-generation antipsychotic, perphenazine, the majority of patients in each group discontinued their antipsychotic study medication before 18 months. Patients (n=1493) with chronic schizophrenia were randomized to receive olanzapine 7.5 to 30 milligrams/day (mg/day), perphenazine 8 to 32 mg/day, quetiapine 200 to 800 mg/day, risperidone 1.5 to 6.0 mg/day, or ziprasidone 40 to 160 mg/day for up to 19 months. Overall, 74% of patients discontinued treatment for any cause before 18 months; discontinuation rates ranged from 64 to 82%. Time to discontinuation ranged from 3.5 months for ziprasidone to 9.2 months with olanzapine. The time to discontinuation was significantly longer in the olanzapine group as compared with the quetiapine (hazard ratio (HR), 0.63; 95% confidence interval (CI), 0.52 to 0.76; p less than 0.001) or risperidone groups (HR, 0.75; 95% CI, 0.62 to 0.90; p=0.002). Time to discontinuation due to adverse events were similar between all groups, but the rates ranged from 10% for risperidone to 19% for olanzapine (p=0.04). More patients discontinued olanzapine due to greater weight gain (average of 0.9 kilograms/month) and greater increases in glycosylated hemoglobin, total cholesterol, and triglycerides (Lieberman et al, 2005).

6.0 References

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167. Product Information: Geodon(R), ziprasidone capsules. Pfizer, Inc., New York, NY, 2002v.
168. Product Information: Geodon(R), ziprasidone capsules. Pfizer, Inc., New York, NY, 2002w.
169. Product Information: Geodon(R), ziprasidone for injection. Pfizer Inc., New York, NY, 2002.
170. Product Information: Geodon(R), ziprasidone for injection. Pfizer Inc., New York, NY, 2002b.
171. Product Information: Geodon(R), ziprasidone for injection. Pfizer Inc., New York, NY, 2002g.
172. Product Information: Geodon(R), ziprasidone for injection. Pfizer Inc., New York, NY, 2002h.
173. Product Information: Geodon(R), ziprasidone for injection. Pfizer Inc., New York, NY, 2002m.
174. Product Information: Geodon(R), ziprasidone for injection. Pfizer Inc., New York, NY, 2002n.
175. Product Information: Geodon(R), ziprasidone for injection. Pfizer Inc., New York, NY, 2002p.
176. Product Information: Geodon(R), ziprasidone for injection. Pfizer Inc., New York, NY, 2002u.
177. Product Information: Geodon(R), ziprasidone for injection. Pfizer Inc., New York, NY, 2002x.
178. Product Information: Geodon(R), ziprasidone for injection. Pfizer Inc., New York, NY, 2002y.
179. Product Information: Geodon(R), ziprasidone. Pfizer Inc, . New York, NY, 2002ad.
180. Product Information: Geodon(R), ziprasidone. Pfizer Inc, NY, NY, 2002aa.
181. Product Information: Geodon(R), ziprasidone. Pfizer Inc, NY, NY, 2002c.
182. Product Information: Geodon(R), ziprasidone. Pfizer Inc, NY, NY, 2002d.
183. Product Information: Geodon(R), ziprasidone. Pfizer Inc, NY, NY, 2002e.
184. Product Information: Geodon(R), ziprasidone. Pfizer Inc, NY, NY, 2002f.
185. Product Information: Geodon(R), ziprasidone. Pfizer Inc, NY, NY, 2002k.
186. Product Information: Geodon(R), ziprasidone. Pfizer Inc, NY, NY, 2002l.
187. Product Information: Geodon(R), ziprasidone. Pfizer Inc, NY, NY, 2002q.
188. Product Information: Geodon(R), ziprasidone. Pfizer Inc, NY, NY, 2002r.
189. Product Information: Geodon(R), ziprasidone. Pfizer Inc, NY, NY, 2002s.
190. Product Information: Geodon(R), ziprasidone. Pfizer Inc, NY, NY, 2002t.
191. Product Information: Geodon(R), ziprasidone. Pfizer Inc, NY, NY, 2002z.
192. Product Information: Geodon(R), ziprasidone. Pfizer Inc., NY, NY, 2002a.
193. Product Information: Geodon(R), ziprasidone. Pfizer Inc., NY, NY, 2002ac.
194. Product Information: Geodon(R), ziprasidone. Pfizer Inc., NY, NY, 2002j.
195. Product Information: Geodon(R), ziprasidone. Pfizer Inc., New York, NY, 2002ab.
196. Product Information: Geodon(R), ziprasidone. Pfizer, New York, NY, 2002ae.
197. Product Information: Geodon(TM) ziprasidone. Pfizer Inc., NY, NY, 2002.
198. Product Information: Geodon(TM) ziprasidone. Pfizer Inc., NY, NY, 2002a.
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201. Product Information: Geodon(TM), ziprasidone. Pfizer Inc., NY, NY, 2002.
202. Product Information: Geodon(TM), ziprasidone. Pfizer Inc., NY, NY, 2002aa.
203. Product Information: Geodon(TM), ziprasidone. Pfizer Inc., NY, NY, 2002b.
204. Product Information: Geodon(TM), ziprasidone. Pfizer Inc., NY, NY, 2002c.

205. Product Information: Geodon(TM), ziprasidone. Pfizer Inc., NY, NY, 2002d.
206. Product Information: Geodon(TM), ziprasidone. Pfizer Inc., NY, NY, 2002e.
207. Product Information: Geodon(TM), ziprasidone. Pfizer Inc., NY, NY, 2002f.
208. Product Information: Geodon(TM), ziprasidone. Pfizer Inc., NY, NY, 2002g.
209. Product Information: Geodon(TM), ziprasidone. Pfizer Inc., NY, NY, 2002h.
210. Product Information: Geodon(TM), ziprasidone. Pfizer Inc., NY, NY, 2002i.
211. Product Information: Geodon(TM), ziprasidone. Pfizer Inc., NY, NY, 2002j.
212. Product Information: Geodon(TM), ziprasidone. Pfizer Inc., NY, NY, 2002k.
213. Product Information: Geodon(TM), ziprasidone. Pfizer Inc., NY, NY, 2002l.
214. Product Information: Geodon(TM), ziprasidone. Pfizer Inc., NY, NY, 2002m.
215. Product Information: Geodon(TM), ziprasidone. Pfizer Inc., NY, NY, 2002n.
216. Product Information: Geodon(TM), ziprasidone. Pfizer Inc., NY, NY, 2002o.
217. Product Information: Geodon(TM), ziprasidone. Pfizer Inc., NY, NY, 2002p.
218. Product Information: Geodon(TM), ziprasidone. Pfizer Inc., NY, NY, 2002q.
219. Product Information: Geodon(TM), ziprasidone. Pfizer Inc., NY, NY, 2002r.
220. Product Information: Geodon(TM), ziprasidone. Pfizer Inc., NY, NY, 2002s.
221. Product Information: Geodon(TM), ziprasidone. Pfizer Inc., NY, NY, 2002t.
222. Product Information: Geodon(TM), ziprasidone. Pfizer Inc., NY, NY, 2002u.
223. Product Information: Geodon(TM), ziprasidone. Pfizer Inc., NY, NY, 2002v.
224. Product Information: Geodon(TM), ziprasidone. Pfizer Inc., NY, NY, 2002w.
225. Product Information: Geodon(TM), ziprasidone. Pfizer Inc., NY, NY, 2002x.
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240. Product Information: Orap(R), pimozide. Gate Pharmaceuticals, Sellersville, PA, 1999b.
241. Product Information: Orap(R), pimozide. Gate Pharmaceuticals, Sellersville, PA, 1999c.
242. Product Information: Orap(R), pimozide. Gate Pharmaceuticals, Sellersville, PA, 1999d.
243. Product Information: Orap(R), pimozide. Gate Pharmaceuticals, Sellersville, PA, 1999e.
244. Product Information: Orap(R), pimozide. Gate Pharmaceuticals, Sellersville, PA, 2000.
245. Product Information: Orlaam(R), levomethadyl. Roxane Laboratories, Inc., 2001.
246. Product Information: PCE(R), erythromycin particles in tablets. Abbott Laboratories, North Chicago, IL, 1997.
247. Product Information: Propulsid(R), cisapride. Janssen Pharmaceutica, Titusville, NJ, 2000.
248. Product Information: Prozac(R), fluoxetine. Eli Lilly and Company, Indianapolis, IN, 2001.
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250. Product Information: RANEXA(R) extended-release oral tablets, ranolazine extended-release oral tablets. CV Therapeutics Inc, Palo Alto, CA, 2008.
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252. Product Information: Sandostatin(R), octreotide. Novartis Pharmaceuticals, East Hanover, NJ, 1999.
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Last Modified: June 23, 2009

DRUGDEX® Evaluations

HALOPERIDOL

0.0 Overview

1) Class

a) This drug is a member of the following class(es):

Antipsychotic
Butyrophenone
Dopamine Antagonist

2) Dosing Information

a) Haloperidol

1) Adult

a) Gilles de la Tourette's syndrome

1) 0.5 to 2 mg (moderate symptoms) OR 3 to 5 mg (severe symptoms) ORALLY 2 to 3 times daily (Proc Info haloperidol oral tablets, 2008; Prod Info haloperidol oral solution, 2008)

b) Psychotic disorder

1) 0.5 to 2 mg (moderate symptoms) OR 3 to 5 mg (severe symptoms) ORALLY 2 to 3 times daily (Proc Info haloperidol oral tablets, 2006; Prod Info haloperidol oral solution, 2001)

c) Schizophrenia

1) 0.5 to 2 mg (moderate symptoms) OR 3 to 5 mg (severe symptoms) ORALLY 2 to 3 times daily (Proc Info haloperidol oral tablets, 2006; Prod Info haloperidol oral solution, 2001)

2) Pediatric

a) Not FDA approved in children less than 3 years of age (Prod Info haloperidol oral tablets, 2008; Prod Info haloperidol oral solution, 2008)

1) Gilles de la Tourette's syndrome

a) age 3 to 12 yr (weight range 15 to 40 kg), begin with the lowest possible dose (0.5 mg per day) c weight-based dose (0.05 to 0.075 mg/kg/day) ORALLY in 2 to 3 divided doses, whichever is less; increase by 0.5 mg at 5 to 7 day intervals to therapeutic effect (Prod Info haloperidol oral tablets, 20 Prod Info haloperidol oral solution, 2008)

b) over age 12 years, 0.5 to 2 mg (moderate symptoms) or 3 to 5 mg (severe symptoms) orally 2 to times daily (Prod Info haloperidol oral tablets, 2008; Prod Info haloperidol oral solution, 2008)

2) Hyperactive behavior, (Short-term treatment) after failure to respond to non-antipsychotic medication and psychotherapy

a) 3 to 12 yr (weight range 15 to 40 kg), 0.05 to 0.075 mg/kg/day ORALLY in 2 to 3 divided doses, increase by 0.5 mg at 5 to 7 day intervals to therapeutic effect; MAX daily dose 0.075 mg/kg/day (Pr Info haloperidol oral tablets, 2006; Prod Info haloperidol oral solution, 2001)

3) Psychotic disorder

a) 3 to 12 yr (weight range 15 to 40 kg), 0.05 mg/kg/day ORALLY in 2 to 3 divided doses, may increase by 0.5 mg/day at 5 to 7 day intervals to therapeutic effect; MAX daily dose 0.15 mg/kg/day (Prod Info haloperidol oral tablets, 2006; Prod Info haloperidol oral solution, 2001)

b) 12 yr and older, 0.5 to 2 mg (moderate symptoms) OR 3 to 5 mg (severe symptoms) ORALLY 2 3 times daily (Prod Info haloperidol oral tablets, 2006; Prod Info haloperidol oral solution, 2001)

4) Schizophrenia

a) 3 to 12 yr (weight range 15 to 40 kg), 0.05 mg/kg/day ORALLY in 2 to 3 divided doses, may increase by 0.5 mg/day at 5 to 7 day intervals to therapeutic effect; MAX daily dose 0.15 mg/kg/day (Prod Info haloperidol oral tablets, 2006; Prod Info haloperidol oral solution, 2001)

b) 12 yr and older, 0.5 to 2 mg (moderate symptoms) OR 3 to 5 mg (severe symptoms) ORALLY 2 3 times daily (Prod Info haloperidol oral tablets, 2006; Prod Info haloperidol oral solution, 2001)

b) Haloperidol Decanoate

1) Adult

a) Chronic schizophrenia

1) stabilized on low daily oral doses (up to 10 mg/day), 10 to 15 times previous daily oral dose IM month or every 4 wks; MAX initial dose 100 mg (Prod Info haloperidol decanoate injection, 2005)

2) stabilized on high daily oral doses, 20 times previous daily oral dose IM for the first month, then 10 to times previous daily oral dose IM monthly or every 4 wks; MAX initial dose 100 mg (Prod Info haloperido decanoate injection, 2005)

2) Pediatric

a) Safety and effectiveness have not been established in children

c) Haloperidol Lactate

1) Adult

a) Gilles de la Tourette's syndrome

1) 2 to 5 mg IM, may repeat every 4 to 8 hr depending on patient response; increase to every 1 hr if needed (Prod Info haloperidol lactate IM injection, 2005)

b) Schizophrenia

1) 2 to 5 mg IM, may repeat every 4 to 8 hr depending on patient response; increase to every 1 hr if needed (Prod Info HALDOL(R) immediate release IM injection, 2008)

2) Pediatric

a) safety and effectiveness have not been established in pediatric patients (Prod Info HALDOL(R) immediate release IM injection, 2008)

3) Contraindications

a) Haloperidol

1) comatose state from any cause (Prod Info haloperidol oral tablets, 2008)
2) hypersensitivity to haloperidol (Prod Info haloperidol oral tablets, 2008)
3) Parkinson's disease (Prod Info haloperidol oral tablets, 2008)
4) toxic central nervous system depression, severe (Prod Info haloperidol oral tablets, 2008)

b) Haloperidol Decanoate

1) comatose state from any cause (Prod Info HALDOL(R) Decanoate IM injection, 2008)
2) hypersensitivity to haloperidol (Prod Info HALDOL(R) Decanoate IM injection, 2008)
3) Parkinson's disease (Prod Info HALDOL(R) Decanoate IM injection, 2008)
4) toxic CNS depression, severe (Prod Info HALDOL(R) Decanoate IM injection, 2008)

c) Haloperidol Lactate

1) comatose state from any cause (Prod Info HALDOL(R) immediate release IM injection, 2008)
2) hypersensitivity to haloperidol lactate (Prod Info HALDOL(R) immediate release IM injection, 2008)
3) Parkinson's disease (Prod Info HALDOL(R) immediate release IM injection, 2008)
4) toxic CNS depression, severe (Prod Info HALDOL(R) immediate release IM injection, 2008)

4) Serious Adverse Effects

a) Haloperidol

1) Agranulocytosis
2) Dead - sudden death
3) Death
4) Neuroleptic malignant syndrome
5) Paralytic ileus
6) Priapism
7) Prolonged QT interval
8) Seizure
9) Sudden cardiac death
10) Tardive dyskinesia
11) Torsades de pointes

b) Haloperidol Decanoate

1) Agranulocytosis
2) Neuroleptic malignant syndrome
3) Paralytic ileus
4) Priapism
5) Prolonged QT interval
6) Seizure
7) Tardive dyskinesia
8) Torsades de pointes

5) Clinical Applications

a) Haloperidol

1) FDA Approved Indications

a) Gilles de la Tourette's syndrome
b) Hyperactive behavior, (Short-term treatment) after failure to respond to non-antipsychotic medication and psychotherapy
c) Psychotic disorder
d) Schizophrenia

b) Haloperidol Decanoate

1) FDA Approved Indications

a) Chronic schizophrenia

c) Haloperidol Lactate

1) FDA Approved Indications

a) Gilles de la Tourette's syndrome
b) Schizophrenia

1.0 Dosing Information

Drug Properties

Storage and Stability

Adult Dosage

Pediatric Dosage

1.1 Drug Properties

A) Information on specific products and dosage forms can be obtained by referring to the Tradename List (Product Index)

B) Synonyms
Haloperidol
Haloperidol Decanoate
Haloperidol Lactate

C) Physicochemical Properties

1) Molecular Weight

a) Haloperidol: 375.87 (Prod Info haloperidol oral tablets, 2008); haloperidol decanoate: 530.13 (Prod Info haloperidol decanoate injection, 2005)

2) pH

a) Haloperidol lactate: 3 to 3.6 (Prod Info HALDOL(R) immediate release IM injection, 2008)

3) Solubility

a) Haloperidol decanoate is soluble in most organic solvents and almost insoluble in water (0.01 mg/mL) (Pr Info haloperidol decanoate injection, 2005).

1.2 Storage and Stability

A) Haloperidol Decanoate

1) Preparation

a) Intramuscular route

1) Do not administer haloperidol decanoate intravenously (Prod Info haloperidol decanoate injection, 2005).

2) Haloperidol decanoate should be administered by deep intramuscular injection (21G needle) into the gluteal region. The maximum recommended volume is 3 milliliters per injection site (Prod Info haloperido decanoate injection, 2005).

B) Haloperidol Lactate

1) Preparation

a) General Information

1) Do NOT administer haloperidol lactate intravenously (Prod Info HALDOL(R) immediate release IM injection, 2008).

C) Haloperidol

1) Oral route

a) Tablet

1) Store at controlled room temperature, between 20 and 25 degrees C (68 and 77 degrees F), in a tigh light-resistant container (Prod Info haloperidol oral tablets, 2008).

D) Haloperidol Decanoate

1) Intramuscular route

a) Solution

1) Store at controlled room temperature, between 15 and 30 degrees C (59 and 86 degrees F). Protect from light. Do not refrigerate or freeze (Prod Info HALDOL(R) Decanoate IM injection, 2008).

2) Investigations of the stability of haloperidol decanoate when drawn into plastic syringes have not bee conducted. Preparation of individual doses of medication in disposable plastic syringes may be carried o a few hours prior to administration, provided these are protected from light. Because of unknown stability and because of concern for dosage sterility, such storage for longer periods is not recommended. Stabili in other types of syringes is also unknown (Pers Comm, 1987).

E) Haloperidol Lactate

1) Intramuscular route

a) Solution

1) Store at controlled room temperature, between 15 and 30 degrees C (59 and 86 degrees F). Protect from light. Do not freeze (Prod Info HALDOL(R) immediate release IM injection, 2008).

1.3 Adult Dosage

Normal Dosage

Dosage in Renal Failure

Dosage in Geriatric Patients

Dosage Adjustment During Dialysis

Dosage in Other Disease States

1.3.1 Normal Dosage

Important Note

Important Note

Important Note

Haloperidol

Haloperidol Decanoate

Haloperidol Lactate

1.3.1.A Important Note

The US Food and Drug Administration (FDA) issued an alert concerning reports of Torsades de Pointes and prolongation, some with fatal outcomes associated with the use of haloperidol, haloperidol decanoate, and haloperidol lactate, especially when administered intravenously (not an approved route of administration) or i higher doses than recommended. At least 28 published case reports exist, and case-control studies have demonstrated a dose-response relationship between intravenous haloperidol and the development of Torsad de Pointes (US Food and Drug Administration, 2007).

1.3.1.B Important Note

Haloperidol decanoate is in a sesame seed oil base and should not be given intravenously (Prod Info haloperidol decanoate injection, 2005).

The US Food and Drug Administration (FDA) issued an alert concerning reports of Torsades de Pointes and prolongation, some with fatal outcomes associated with the use of haloperidol, haloperidol decanoate, and haloperidol lactate, especially when administered intravenously (not an approved route of administration) or i higher doses than recommended. At least 28 published case reports exist, and case-control studies have demonstrated a dose-response relationship between intravenous haloperidol and the development of Torsad de Pointes (US Food and Drug Administration, 2007).

1.3.1.C Important Note

Haloperidol lactate should NOT be given intravenously (Prod Info HALDOL(R) immediate release IM injectior 2008).

The US Food and Drug Administration (FDA) issued an alert concerning reports of Torsades de Pointes and prolongation, some with fatal outcomes associated with the use of haloperidol, haloperidol decanoate, and haloperidol lactate, especially when administered intravenously (not an approved route of administration) or i higher doses than recommended. At least 28 published case reports exist, and case-control studies have demonstrated a dose-response relationship between intravenous haloperidol and the development of Torsad de Pointes (US Food and Drug Administration, 2007).

1.3.1.D Haloperidol

Intravenous route

Oral route

Chemotherapy-induced nausea and vomiting; Treatment and Prophylaxis

Hiccoughs

Ocular hypertension

Opioid withdrawal

1.3.1.D.1 Intravenous route

a) CONTINUOUS INTRAVENOUS DOSING

1) An initial bolus dose of 10 milligrams followed by continuous infusion beginning as 10 milligrams per hour is recommended. If control is not achieved, the bolus is repeated every 30 minutes, as well increasing the infusion rate by 5 milligrams per hour. Adjunctive sedative (benzodiazepines) doses should be adjusted as needed or discontinued if possible. After achieving control, infusion rates sho be titrated downward by 50% at each interval, seeking eventual return to bolus dosing. Continuous infusion haloperidol should be considered for patients receiving 80 mg of haloperidol daily (given in or more bolus doses) or who receive more than 10 mg/hour over 5 or more consecutive hours. Continuous dosing is also warranted in patients not effectively managed on other sedatives and in those in whom attempted reversal of the cause of agitation has been unsuccessful (Riker et al, 199

2) Initial infusion doses of 2 to 25 milligrams per hour haloperidol by continuous infusion have been cited in individual cases (Seneff & Mathews, 1995); (Dixon & Craven, 1993)(Fernandez et al, 1988).

3) Maximum infusion rate cited is 40 milligrams per hour (Riker et al, 1994a).

b) INTERMITTENT INTRAVENOUS DOSING

1) Total daily intermittent intravenous haloperidol doses of 80, 285, 130, 460, and 530 milligrams w generally well tolerated (Tesar et al, 1985).

c) SWITCHING FROM INJECTABLE TO ORAL HALOPERIDOL

1) For an initial approximation of the total daily dose required, the parenteral dose administered in t preceding 24 hours may be used; the first oral dose should be given within 12 to 24 hours following last parenteral dose (Prod Info HALDOL(R) injection, 2007).

1.3.1.D.2 Oral route

Behavioral syndrome - Dementia

Gilles de la Tourette's syndrome

Schizophrenia

1.3.1.D.2.a Behavioral syndrome - Dementia

1) A randomized, double-blind, placebo controlled crossover study demonstrated that standard-dos (2 to 3 milligrams (mg) daily) haloperidol was effective and superior to low-dose (0.05 to 0.75 mg da for treating psychosis and disruptive behaviors in patients with Alzheimer's disease. Seventy-one patients were treated with either standard-dose or low-dose haloperidol or placebo for 6 weeks. The patients taking placebo then crossed over to either standard or low- dose haloperidol while the haloperidol patients crossed over to placebo for another 6 weeks. Standard-dose haloperidol was efficacious and superior to low- dose haloperidol and placebo for the 60 patients who completed the first phase of the study. The same results were demonstrated in the second phase. Extrapyramidal side effects were greater with the standard dose however, low- dose haloperidol did not differ from placebo with regard to efficacy (Devanand et al, 1998).

1.3.1.D.2.b Gilles de la Tourette's syndrome

1) Manufacturer dose

a) The recommended dose in adults with moderate symptoms is haloperidol 0.5 to 2 milligrams (mg) orally 2 to 3 times daily, or with severe symptoms 3 to 5 mg orally 2 to 3 times daily (Prod Info haloperidol oral tablets, 2008; Prod Info haloperidol oral solution, 2008).

2) Tourette's syndrome is initially treated with haloperidol 6 to 15 mg/day orally in divided doses. Dosage is gradually increased in 2 mg increments until adverse effects are disabling. When sympto are controlled the dose is tapered to approximately 9 mg/day for maintenance (AMA Department of Drugs, 1980).

1.3.1.D.2.c Schizophrenia

1) SUMMARY

a) The usual daily oral dose range is from 1 to 15 milligrams; doses exceeding 100 milligrams have been used in severely resistant patients. Moderate doses of neuroleptic drugs, defined as between 165 and 375 milligram equivalent of chlorpromazine, were preferred in the maintenanc therapy of chronic psychosis in a meta-analysis of 22 randomized control trials (Bollini et al, 19 The association between dose and clinical effectiveness and side effects was assessed. At dos greater than 375 milligram equivalent of chlorpromazine, there was no incremental clinical improvement seen, and adverse reactions occurred at a significantly higher rate.

2) There is significant variation between patients in the amount of medication required; dosage mus be individualized. The normal dosage range for initiation of therapy for psychiatric indications is 1 to milligrams/day for moderate symptomatology and 6 to 15 milligrams/day for severe symptomatology divided into 2 to 3 doses. Adjustment of the dose up to 100 milligrams/day may be necessary for

severely resistant patients. When switching from parenteral to oral therapy, the first oral dose shoulc be given within 12 to 24 hours. The same oral as parenteral dose may be used with dosage adjustments made based on patient's response (Prod Info Haldol(R), 97a).

3) A 4-week prospective trial demonstrated that patients experiencing first-episode psychosis responded to haloperidol doses that were well below doses commonly prescribed. Patients (n=36) diagnosed with nonaffective psychosis began haloperidol treatment with 2 milligrams (mg) daily. The dose was increased weekly until either significant improvement or the onset of extrapyramidal symptoms occurred. The optimal dose for 42 percent of the patients was 2 mg daily and on average these patients exhibited the greatest improvement (Zhang- Wong et al, 1999).

4) Low dosage (16 milligrams/day) was compared with high dosage (80 milligrams/day) of haloperic in 40 newly admitted schizophrenia patients for 21 days. Upon evaluation on five occasions, the low dosage group showed significantly greater improvement (Winter et al, 1984). Similar results were found in another study (Rifkin et al, 1991).

5) A double-blind study was conducted in 42 patients treated with 10 milligrams, 30 milligrams, and milligrams per day of haloperidol. The researchers found no relationship between neuroleptic dose a outcome of mania, and no differences in side effects. These results suggest that there is no advanta to using more than 10 milligrams per day of haloperidol (Rifkin et al, 1990).

6) Haloperidol doses of 5, 10, and 20 milligrams per day were compared for 4 weeks in 80 newly admitted schizophrenic patients. The results after two weeks showed the 20 milligrams dose to be more effective than the 5 milligrams dose and the same as the 10 milligrams dose. Over the last two week period, the 20 milligrams dose per day did not control the patients. The researchers referred to this as "psychotoxic" side-effects. The researchers recommended 20 milligrams per day for short-ter therapy of psychotic disorders (Van Putten et al, 1990).

1.3.1.D.2.d Mania

1) In a double-blind, randomized study lasting six weeks, three dosage levels of haloperidol (10, 30 80 mg/day) were compared in 47 newly-diagnosed manic inpatients. All patients also received benztropine (2 mg three times per day). There were no significant differences in treatment outcomes side effects among patients at the three dosage levels. The authors concluded that haloperidol dose in excess of 10 mg/day offered no advantage in controlling symptoms of mania (Rifkin et al, 1994).

1.3.1.D.2.e SWITCHING FROM INJECTABLE TO ORAL HALOPERIDOL

1) For an initial approximation of the total daily dose required, the parenteral dose administered in t preceding 24 hours may be used; the first oral dose should be given within 12 to 24 hours following last parenteral dose (Prod Info HALDOL(R) injection, 2007).

1.3.1.D.3 Chemotherapy-induced nausea and vomiting; Treatment and Prophylaxis

See Drug Consult reference: CHEMOTHERAPY AND RADIOTHERAPY TREATMENT GUIDELINES FO NAUSEA AND VOMITING

1.3.1.D.4 Hiccoughs

See Drug Consult reference: HICCUPS - ETIOLOGY AND TREATMENT

1.3.1.D.5 Ocular hypertension

a) Topical administration of the haloperidol ophthalmic solution (0.125% and 1%) produced modest reductions in intraocular pressure in healthy volunteers, however, reductions were not considered statistically significant (Lavin & Andrews, 1986). These data do not suggest the role for topical haloperido in the treatment of glaucoma.

1.3.1.D.6 Opioid withdrawal

See Drug Consult reference: DRUG THERAPY OF OPIOID WITHDRAWAL

1.3.1.D.7 HIGH DOSE THERAPY

a) A randomized, double-blind study demonstrated that high-dose, long-term treatment with haloperidol may not be justified regardless if supported by clinical judgment (Volavka et al, 2000). Hospitalized patie (n=23) with the diagnosis of schizophrenia or schizoaffective disorder and with haloperidol plasma levels at least 15 nanograms per milliliter (ng/mL) were assigned to an experimental group (n=11) or a control group (n=12). The plasma level for the experimental group was reduced to 10 ng/mL via a gradual dose reduction while the control group was maintained at the original level. Over a period of 16 weeks, both groups demonstrated a slight reduction in symptoms and there were no significant differences in sympto severity. Additionally, the reduction in dose did not result in any apparent side effects. The authors conclude that high-dose therapy may be cautiously questioned since this study was small and biased.

b) Two studies failed to establish that a dosage of 100 milligrams/day was more effective than a dosage 10 milligrams/day in 63 acutely schizophrenic patients (Donlon et al, 1980; Ericksen et al, 1978). Howeve another study concluded that previously nonresponsive chronic schizophrenics may benefit from adequa high doses (median 100 milligrams/day) of haloperidol (Psaras et al, 1980).

c) Intravenous haloperidol ranging from 100 to 480 milligrams over 24 hours plus 36 to 480 milligrams o lorazepam has been shown to be effective in treatment of delirium in the critically ill cancer patient; the combination of haloperidol and lorazepam intravenously in a wide range of doses appears to be safe and effective (Adams et al, 1986).

d) The need for high-dose therapy was demonstrated in some chronic patients. By evaluating 100 patie

it was found that eight patients required more than 15 milligrams per day of haloperidol. When the streng was reduced, the eight patients lapsed back into their original psychiatric state. These authors conclude that dose-responsive patients should be examined on an individual basis (Brotman & McCormick, 1990).
e) High-dose therapy was used in a patient receiving treatment via an intra-aortic balloon pump. The patient was given a 50 milligrams bolus dose of haloperidol and 50 milligrams intravenously every hour thereafter. The patient received a total of 1200 milligrams of haloperidol in the first 24 hour period, and 1100 milligrams during the next 24 hour period. The doses were then decreased daily until day ten, when the pump was removed. No signs of extrapyramidal symptoms were exhibited (Sanders et al, 1991).

1.3.1.E Haloperidol Decanoate

1) ORAL TO DEPOT CONVERSION

a) The recommended initial dose of Haldol(R) decanoate is 10 to 20 times the previous daily dose in oral haloperidol equivalents but no more than a maximum initial dose of 100 milligrams given at monthly intervals. However, if initial conversion doses are more than 100 milligrams, the dose should be administered in 2 injections (ie, a maximum of 100 mg followed by the remaining balance in 3 to 7 days) (Prod Info haloperidol decanoate injection, 2005).
b) Clinical experience with depot injections greater than 450 milligrams/month is limited (Prod Info haloperidol decanoate injection, 2005).
c) The pharmacokinetic properties and therapeutic efficacy of haloperidol decanoate were studied in 21 chronic psychotic inpatients stabilized on oral haloperidol. The intramuscular dose was calculated from the oral dose, using standard equivalencies for those neuroleptics other than haloperidol. The depot form was administered for 4 months, the last 3 months given at one-half the original calculated loading dose. The depot form resulted in less fluctuation in blood levels, with levels approximating those on oral therapy. One third of the patients deteriorated, and there was no significant change in the incidence or severity of side effects. The authors concluded that there was no clinical advantage to the use of haloperidol decanoate over oral forms of therapy (de Cuyper et al, 1986).
d) Intramuscular haloperidol decanoate was compared with oral haloperidol in 30 chronic schizophrenic patients (Nair et al, 1986). Patients were stabilized for 2 weeks on an oral dose, which was then maintained for 2 weeks. Patients were then transferred to an intramuscular dose, stabilized, then continued on the dose for 5 months. Side effects were comparable and minimal. Therapeutic responses were also comparable. The monthly dose of haloperidol decanoate needed to achieve an equivalent therapeutic response was 15 times the daily dose of haloperidol in 17 patients, 10 times the daily oral dose of haloperidol in 7 patients, and ranged from 9.4 to 15 times the daily oral haloperidol dose in all patients. The authors concluded that intramuscular haloperidol decanoate is comparable to oral haloperidol in safety and efficacy and produces lower blood levels with less fluctuation.
e) Oral haloperidol given daily was compared with intramuscular haloperidol decanoate given every 28 days to establish pharmacokinetically and therapeutically equivalent dosages (Nayak et al, 1987). The study involved 20 patients and was of an open design. Results showed that haloperidol decanoate every 28 days required dosages 21.4 times higher than haloperidol given daily to achieve similar blood concentrations, but required dosages only 14.1 times higher to achieve similar clinical results. The authors recommended that dosages of haloperidol decanoate should be lower than what is calculated to achieve therapeutic blood levels. The dose is subsequently titrated upwards to achieve the desired therapeutic response.
f) Eighteen patients who were taking oral haloperidol and then switched to depot haloperidol were studied. The first month's mean haloperidol decanoate dose was 23.1 times the oral haloperidol dose, with a mean plasma concentration level of 3 +/- 1.9 mg/mL. The second month's dosing level regimen was decreased by 27.6 percent, giving a mean plasma concentration of 6.5 +/- 2.6 mg/mL. The patients improved during the conversion. The researchers concluded that haloperidol decanoate has less fluctuation than oral haloperidol because of constant absorption (Ereshefsky et al, 1990).
g) A method was described to convert from oral to depot intramuscular forms of haloperidol using a loading dose strategy (Ereshefsky et al, 1993). The method consisted of using a total dose of 20 times the oral dose, administered in consecutive divided doses of 100 to 200 milligrams every three to seven days. Oral haloperidol was discontinued prior to the first injection, except in cases where the daily haloperidol dose was 40 milligrams or greater where the dose was gradually reduced over two months. The depot dose was reduced, typically by 25% in both the second and third months to avoid excessive accumulation. The long-term maintenance dose was adjusted based on clinical response.

1.3.1.F Haloperidol Lactate

1.3.1.F.1 Intramuscular route

Gilles de la Tourette's syndrome

Schizophrenia

1.3.1.F.1.a Gilles de la Tourette's syndrome

1) The recommended dose for the control of tics and vocal utterances of Tourette's disorder is haloperidol lactate 2 to 5 milligrams intramuscularly. Depending on the clinical effect, the dose may repeated every 1 hour, although a 4- to 8-hour interval may be sufficient (Prod Info haloperidol lacta IM injection, 2005).

1.3.1.F.1.b Schizophrenia

1) In schizophrenic adults who are acutely agitated with moderately severe to very severe symptom the recommended dose is haloperidol lactate 2 to 5 milligrams intramuscularly. Depending on the clinical effect, the dose may be repeated every 1 hour, although a 4- to 8-hour interval may be sufficient (Prod Info HALDOL(R) immediate release IM injection, 2008).

1.3.2 Dosage in Renal Failure

A) Haloperidol

1) No specific dosage adjustment is necessary in patients with renal impairment (Bennett et al, 1994).

B) Haloperidol Decanoate

1) No specific dosage adjustment is necessary in patients with renal impairment (Bennett et al, 1994).

C) Haloperidol Lactate

1) No specific dosage adjustment is necessary in patients with renal impairment (Bennett et al, 1994).

1.3.4 Dosage in Geriatric Patients

A) Haloperidol

1) ORAL

a) Geriatric or debilitated patients may require a higher doses (0.5 to 2 milligrams 2 to 3 times daily) to achieve prompt response in some cases (Prod Info haloperidol oral tablets, 2006; Prod Info haloperidol c solution, 2001).

b) Elderly patients with chronic refractory schizophrenia should be initially treated with 0.5 to 1.5 milligram/day orally. Dosage may be gradually increased to a usual maintenance dose of 2 to 8 milligrams/day (AMA Department of Drugs, 1980).

c) Results of a double-blind, crossover study in 58 nursing-home residents suggest that the efficacy of long-term haloperidol, thioridazine, and lorazepam should be closely monitored and routine attempts at drug withdrawal should be considered (Cohen-Mansfield et al, 1999). The residents participating in the study were older than 70 years and had received haloperidol, thioridazine, or lorazepam for agitation for least 4 weeks. Half of the residents had their medication dose tapered over 3 weeks and then received placebo while the other half continued their usual medication dosage. After 7 weeks, the residents cross over and either titrated back on their medication or titrated off and began placebo for another 7 weeks. Analyses exhibited no effect of drug therapy discontinuation on behavior and withdrawal of medication h no impact on psychiatric symptom scores or agitation levels. More research is warranted to identify effective treatment for agitation and the appropriate duration of effectiveness.

d) Mentally retarded elderly patients with hyperkinesia are initially treated with 1.5 to 6 milligrams/day orally in divided doses. Doses may be gradually increased to a maximum of 15 milligrams/day to achieve control. Doses are then tapered to a minimally effective maintenance dose (AMA Department of Drugs, 1980).

B) Haloperidol Decanoate

1) INTRAMUSCULAR - DEPOT

a) Initial conversion from oral therapy for elderly patients, debilitated patients, or those on stable low dos of oral haloperidol, consists of a dose 10 to 15 times the previous oral daily dose. The dose is given at monthly intervals (Prod Info haloperidol decanoate injection, 2005).

C) Haloperidol Lactate

1) A lower dose may be required in the elderly, and titrated to clinical effect. In elderly women there has bee prevalence of tardive dyskinesia (Prod Info HALDOL(R) immediate release IM injection, 2008).

1.3.5 Dosage Adjustment During Dialysis

A) Haloperidol

1) It is unlikely that dosage adjustment is required during dialysis. Its large volume of distribution and low plasma levels suggest that little drug would be removed by dialysis (Anderson et al, 1976; Bennett et al, 1994

B) Haloperidol Decanoate

1) It is unlikely that dosage adjustment is required during dialysis. Its large volume of distribution and low plasma levels suggest that little drug would be removed by dialysis (Anderson et al, 1976; Bennett et al, 1994

C) Haloperidol Lactate

1) It is unlikely that dosage adjustment is required during dialysis. Its large volume of distribution and low plasma levels suggest that little drug would be removed by dialysis (Anderson et al, 1976; Bennett et al, 1994

1.3.6 Dosage in Other Disease States

A) Haloperidol Decanoate

1) DEBILITATED PATIENTS

a) Initial conversion from oral to depot injection in debilitated patients consists of a dose 10 to 15 times t previous oral daily dose. The dose is given at monthly intervals (Prod Info haloperidol decanoate injectio

2005).

B) Haloperidol Lactate

1) A lower dose may be required in debilitated patients or those with a history of adverse reactions to antipsychotic drugs, and titrated to clinical effect (Prod Info HALDOL(R) immediate release IM injection, 2008

1.4 Pediatric Dosage

Normal Dosage

Dosage in Renal Failure

Dosage Adjustment During Dialysis

1.4.1 Normal Dosage

Important Note

Important Note

Important Note

Haloperidol

Haloperidol Decanoate

Haloperidol Lactate

1.4.1.A Important Note

The US Food and Drug Administration (FDA) issued an alert concerning reports of Torsades de Pointes and prolongation, some with fatal outcomes associated with the use of haloperidol, haloperidol decanoate, and haloperidol lactate, especially when administered intravenously (not an approved route of administration) or i higher doses than recommended. At least 28 published case reports exist, and case-control studies have demonstrated a dose-response relationship between intravenous haloperidol and the development of Torsad de Pointes (US Food and Drug Administration, 2007).

1.4.1.B Important Note

Haloperidol decanoate is in a sesame seed oil base and should not be given intravenously (Prod Info haloperidol decanoate injection, 2005).

The US Food and Drug Administration (FDA) issued an alert concerning reports of Torsades de Pointes and prolongation, some with fatal outcomes associated with the use of haloperidol, haloperidol decanoate, and haloperidol lactate, especially when administered intravenously (not an approved route of administration) or i higher doses than recommended. At least 28 published case reports exist, and case-control studies have demonstrated a dose-response relationship between intravenous haloperidol and the development of Torsad de Pointes (US Food and Drug Administration, 2007).

1.4.1.C Important Note

Haloperidol lactate should NOT be given intravenously (Prod Info HALDOL(R) immediate release IM injectior 2008).

The US Food and Drug Administration (FDA) issued an alert concerning reports of Torsades de Pointes and prolongation, some with fatal outcomes associated with the use of haloperidol, haloperidol decanoate, and haloperidol lactate, especially when administered intravenously (not an approved route of administration) or i higher doses than recommended. At least 28 published case reports exist, and case-control studies have demonstrated a dose-response relationship between intravenous haloperidol and the development of Torsad de Pointes (US Food and Drug Administration, 2007).

1.4.1.D Haloperidol

Oral route

Anorexia nervosa

1.4.1.D.1 Oral route

1.4.1.D.1.a Gilles de la Tourette's syndrome

1) The recommended dose in pediatric patients age 3 to 12 years (weight range 15 to 40 kilograms for the treatment of Tourette's disorder is haloperidol 0.05 to 0.075 milligrams/kilogram/day (mg/kg/day) orally in 2 to 3 divided doses. Begin with the lowest possible dose (0.5 mg per day) or weight-based dose (0.05 to 0.075 mg/kg/day) ORALLY in 2 to 3 divided dose, whichever is less. Increases in dose are recommended at 0.5 mg increments at 5 to 7 day intervals to therapeutic effe to a maximum daily dose of 0.075 mg/kg/day (Prod Info haloperidol oral tablets, 2008; Prod Info haloperidol oral solution, 2008).

2) In children over age 12 years the recommended dose is haloperidol 0.5 to 2 mg (moderate symptoms) or 3 to 5 mg (severe symptoms) orally 2 to 3 times daily (Prod Info haloperidol oral table 2008; Prod Info haloperidol oral solution, 2008).

b) Haloperidol is not recommended for use in children under 3 years old (Prod Info haloperidol oral table 2008; Prod Info haloperidol oral solution, 2008).

1.4.1.D.2 Anorexia nervosa

See Drug Consult reference: ANOREXIA NERVOSA - DRUG THERAPY

1.4.1.E Haloperidol Decanoate

1.4.1.F Haloperidol Lactate

1) Safety and effectiveness have not been established in pediatric patients (Prod Info HALDOL(R) immediate release IM injection, 2008).

1.4.2 Dosage in Renal Failure

A) Haloperidol

1) No specific dosage adjustment is necessary in patients with renal impairment (Bennett et al, 1994).

B) Haloperidol Decanoate

1) No specific dosage adjustment is necessary in patients with renal impairment (Bennett et al, 1994).

1.4.4 Dosage Adjustment During Dialysis

A) Haloperidol

1) It is unlikely that dosage adjustment is required during dialysis. Its large volume of distribution and lov plasma levels suggest that little drug would be removed by dialysis (Anderson et al, 1976; Bennett et al, 1994).

B) Haloperidol Decanoate

1) It is unlikely that dosage adjustment is required during dialysis. Its large volume of distribution and lov plasma levels suggest that little drug would be removed by dialysis (Anderson et al, 1976; Bennett et al, 1994).

2.0 Pharmacokinetics

Onset and Duration

Drug Concentration Levels

ADME

2.1 Onset and Duration

A) Onset

1) Initial Response

a) Sedation, oral: greater than 1 hour (Forsman & Ohman, 1976).

b) Sedation, intravenous: 1 hour (Forsman & Ohman, 1976).

2.2 Drug Concentration Levels

A) Therapeutic Drug Concentration

1) Schizophrenic, schizoaffective and schizophreniform disorders, 5 to 15 ng/mL (Ulrich et al, 1998); (Van Patten et al, 1992)(Extein et al, 1983; Mavroidis et al, 1983; Morselli et al, 1982; Magliozzi et al, 1981).

a) In a 35-study meta-analysis and review, a lower threshold concentration for therapeutic effect was reported of 5.6 mcg/L (range: 3.1 to 8 mcg/L) and an upper threshold concentration of 16.9 mcg/L (range 11 to 26 mcg/L). A target concentration of 10 mcg/L was recommended (Ulrich et al, 1998).

b) A meta-analysis of 18 studies concluded that there was support for the existence of a therapeutic window between 4 and 26 nanograms/milliliter (de Oliveira et al, 1996a).

c) Increasing the haloperidol dose to achieve plasma levels above 18 ng/mL was not associated with improved response in a study of 66 adult inpatients with schizophrenia (Coryell et al, 1998). These result were supported by a study of 95 adults with acute psychosis (schizophrenia and schizoaffective disorder The probability of improvement among initial non-responders was significantly increased among patients titrated to plasma levels of 5 to 18 ng/mL, as opposed to those at lower or higher haloperidol levels (Janicak et al, 1997).

B) Time to Peak Concentration

1) Oral: 2 to 6 hours (Prod Info Haldol(R), 97).

a) The steady-state pharmacokinetics of oral haloperidol varies widely among different patients (Kudo & Ishizaki, 1999).

b) The steady state plasma concentrations of haloperidol and reduced haloperidol were not significantly different among 4 patient subgroups (n= 101) in a study designed to measure the effect of genetic polymorphism of CYP1A2 inducibility on the steady state plasma concentrations of oral haloperidol. Ther were no significant differences between the 4 subgroups, including age and weight, and smoking status not affect the steady state concentrations in the study. This suggests that CYP1A2 activity does not play key role in the steady state pharmacokinetics of haloperidol or reduced haloperidol (Mihara et al, 2000).

2) Intramuscular, haloperidol: 20 minutes (Prod Info Haldol(R), 97).

3) Intramuscular, haloperidol decanoate: 6 days (Prod Info Haldol(R) Decanoate, 2000).

2.3 ADME

Absorption

Distribution

Metabolism

Excretion

Elimination Half-life

2.3.1 Absorption

A) Bioavailability

1) Oral: 60 to 70% (Prod Info Haldol(R), 97; Cheng et al, 1987; Holley et al, 1983a).

2.3.2 Distribution

A) Distribution Sites

1) Protein Binding

a) greater than 90% (Tedeschi, 1981; Forsman & Ohman, 1977).

2) OTHER DISTRIBUTION SITES

a) Hair, less than 0.1% (Matsuno et al, 1990; Sato et al, 1989; Uematsu et al, 1989).

b) Saliva, levels are higher than serum levels and there is a significant correlation (Yamazumi & Muira, 1981).

B) Distribution Kinetics

1) Volume of Distribution

a) 9.5 to 21.7 liters/kilogram (Kudo & Ishizaki, 1999) or 1300 liters (Forsman & Ohman, 1976).

2.3.3 Metabolism

A) Metabolism Sites and Kinetics

1) Liver (Forsman et al, 1977; Forsman & Ohman, 1976).

a) Some evidence indicates extrahepatic metabolism (Forsman & Ohman, 1976; Forsman et al, 1977).

B) Metabolites

1) Hydroxy metabolite of HALOPERIDOL, active (Shostak et al, 1987) (Midha et al, 1989).

a) A significant correlation exists between the percent improvement and the plasma levels of the hydroxymetabolite reduced HALOPERIDOL (Shostak et al, 1987).

2) 4-fluorobenzol-propionic acid (Forsman et al, 1977).

3) 4-fluoro-phenylaceturic acid (Forsman et al, 1977).

4) Reduced haloperidol (Kudo & Ishizaki, 1999).

5) Pyridinium metabolites (Kudo & Ishizaki, 1999).

6) Haloperidol glucuronide (Kudo & Ishizaki, 1999).

2.3.4 Excretion

A) Kidney

1) Renal Excretion (%)
a) 33 to 40% (Prod Info Haldol(R), 97; Anderson et al, 1976a).
B) Other
1) Feces, 15% (Johnson et al, 1967).

2.3.5 Elimination Half-life
A) Parent Compound
1) ELIMINATION HALF-LIFE
a) 21 hours (range: 10 to 38 hours) (Forsman & Ohman, 1976; Cressman et al, 1974a).
1) HALOPERIDOL DECANOATE administered intramuscularly has a half-life of approximately weeks (Reyntjens et al, 1982).

3.0 Cautions

Contraindications

Precautions

Adverse Reactions

Teratogenicity/Effects in Pregnancy/Breastfeeding

Drug Interactions

3.0.A Black Box WARNING
1) Haloperidol
a) Oral (Tablet)
1) Increased Mortality in Elderly Patients with Dementia-Related Psychosis: Elderly patients with demen related psychosis treated with atypical antipsychotic drugs are at an increased risk of death. Analyses of seventeen placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of between 1.6 to 1.7 times the risk death in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (eg, heart failu sudden death) or infectious (eg, pneumonia) in nature. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear. Haloperidol is not approved for the treatment of patients with dementia-related psychosis (Prod Info haloperidol oral tablets 2008).
2) Haloperidol Decanoate
a) Intramuscular (Injectable)
1) Increased Mortality in Elderly Patients with Dementia-Related Psychosis: Elderly patients with demen related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of sevente placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of between 1.6 to 1.7 times the risk of death in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (eg, heart failure, sudden death) or infectious (eg, pneumonia) in nature. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear. Haloperidol decanoa is not approved for the treatment of patients with dementia-related psychosis (Prod Info HALDOL(R) Decanoate IM injection, 2008).
3) Haloperidol Lactate
a) Intramuscular (Solution)
Increased Mortality in Elderly Patients with Dementia-Related Psychosis:
Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increase risk of death. Analyses of seventeen placebo-controlled trials (modal duration of 10 weeks), largely i patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of between 1.6 to 1.7 times the risk of death in placebo-treated patients. Over the course of a typical 1 week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (eg, heart failure, sudden death) or infectious (eg, pneumonia)

nature. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increas mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear. Haloperidol injection is not approved for the treatment of patients with dementia-related psychosis (Prod Info HALDOL(R) immediate release IM injection, 20(

3.1 Contraindications

A) Haloperidol

1) comatose state from any cause (Prod Info haloperidol oral tablets, 2008)
2) hypersensitivity to haloperidol (Prod Info haloperidol oral tablets, 2008)
3) Parkinson's disease (Prod Info haloperidol oral tablets, 2008)
4) toxic central nervous system depression, severe (Prod Info haloperidol oral tablets, 2008)

B) Haloperidol Decanoate

1) comatose state from any cause (Prod Info HALDOL(R) Decanoate IM injection, 2008)
2) hypersensitivity to haloperidol (Prod Info HALDOL(R) Decanoate IM injection, 2008)
3) Parkinson's disease (Prod Info HALDOL(R) Decanoate IM injection, 2008)
4) toxic CNS depression, severe (Prod Info HALDOL(R) Decanoate IM injection, 2008)

C) Haloperidol Lactate

1) comatose state from any cause (Prod Info HALDOL(R) immediate release IM injection, 2008)
2) hypersensitivity to haloperidol lactate (Prod Info HALDOL(R) immediate release IM injection, 2008)
3) Parkinson's disease (Prod Info HALDOL(R) immediate release IM injection, 2008)
4) toxic CNS depression, severe (Prod Info HALDOL(R) immediate release IM injection, 2008)

3.2 Precautions

A) Haloperidol

1) elderly patients with dementia-related psychosis (unapproved use); increased risk of death; most deaths were attributed to cardiovascular events (eg, heart failure or sudden death) or infections (eg, pneumonia) (Pr Info haloperidol oral tablets, 2008)
2) allergies or allergic reactions to drugs, known (Prod Info haloperidol oral tablets, 2008)
3) bronchopneumonia, some fatal, have been reported (Prod Info haloperidol oral tablets, 2008)
4) cardiac abnormalities, underlying; increased risk of QT prolongation and torsades de pointes (Prod Info haloperidol oral tablets, 2008)
5) cardiovascular disorders, severe, preexisting; potential for transient hypotension and/or onset of anginal p (Prod Info haloperidol oral tablets, 2008)
6) concomitant lithium use; a few patients have experienced encephalopathic syndrome followed by irreversi brain damage; causality not established (Prod Info haloperidol oral tablets, 2008)
7) concomitant use with anticoagulants, anticholinergics (including antiparkinson drugs), anticonvulsants, an drugs known to prolong the QT interval (Prod Info haloperidol oral tablets, 2008)
8) EEG abnormalities; may increase risk of seizures due to possible lowered convulsive threshold (Prod Info haloperidol oral tablets, 2008)
9) elderly patients, especially elderly women are at increased risk of tardive dyskinesia (Prod Info haloperido oral tablets, 2008)
10) electrolyte imbalance, especially hypokalemia and hypomagnesemia; increased risk of QT prolongation and torsades de pointes (Prod Info haloperidol oral tablets, 2008)
11) hypothyroidism; increased risk of QT prolongation and torsades de pointes (Prod Info haloperidol oral tablets, 2008)
12) increased duration of therapy and/or higher cumulative doses; increased risk of tardive dyskinesia (Prod Info haloperidol oral tablets, 2008)
13) long QT syndrome, family history; increased risk of QT prolongation and torsades de pointes (Prod Info haloperidol oral tablets, 2008)
14) neuroleptic malignant syndrome, potentially fatal, has been reported; immediately discontinue (Prod Info haloperidol oral tablets, 2008)
15) QT prolongation, history; increased risk of QT prolongation and torsades de pointes (Prod Info haloperid oral tablets, 2008)
16) QT prolongation and torsades de pointes have been reported (Prod Info haloperidol oral tablets, 2008)
17) rapid mood fluctuation toward depression may occur when haloperidol is used for mania in bipolar disorders (Prod Info haloperidol oral tablets, 2008)
18) seizure disorder, history; may increase risk of seizures due to possible lowered convulsive threshold (Pr Info haloperidol oral tablets, 2008)
19) tardive dyskinesia, potentially irreversible, may occur (Prod Info haloperidol oral tablets, 2008)
20) thyrotoxicosis; severe neurotoxicity may occur (Prod Info haloperidol oral tablets, 2008)

B) Haloperidol Decanoate

1) elderly patients with dementia-related psychosis (unapproved use); increased risk of death; most deaths were attributed to cardiovascular events (eg, heart failure or sudden death) or infections (eg, pneumonia) (Pr Info HALDOL(R) Decanoate IM injection, 2008)
2) allergies or allergic reactions to drugs, known (Prod Info HALDOL(R) Decanoate IM injection, 2008)
3) bronchopneumonia, some fatal, have been reported (Prod Info HALDOL(R) Decanoate IM injection, 2008
4) cardiac abnormalities, underlying; increased risk of QT prolongation and torsades de pointes(Prod Info

HALDOL(R) Decanoate IM injection, 2008)
5) cardiovascular disorders, severe; potential for transient hypotension and/or onset of anginal pain(Prod Inf
HALDOL(R) Decanoate IM injection, 2008)
6) concomitant use with anticoagulants, anticholinergics (including antiparkinson drugs), anticonvulsants, an
drugs known to prolong the QT interval (Prod Info HALDOL(R) Decanoate IM injection, 2008)
7) EEG abnormalities; may increase risk of seizures due to possible lowered convulsive threshold(Prod Info
HALDOL(R) Decanoate IM injection, 2008)
8) elderly patients, especially elderly women are at increased risk of tardive dyskinesia (Prod Info HALDOL(
Decanoate IM injection, 2008)
9) electrolyte imbalance, especially hypokalemia and hypomagnesemia; increased risk of QT prolongation a
torsades de pointes(Prod Info HALDOL(R) Decanoate IM injection, 2008)
10) hypothyroidism; increased risk of QT prolongation and torsades de pointes(Prod Info HALDOL(R)
Decanoate IM injection, 2008)
11) increased duration of therapy and/or higher cumulative doses; increased risk of tardive dyskinesia (Prod
Info HALDOL(R) Decanoate IM injection, 2008)
12) long QT syndrome, family history; increased risk of QT prolongation and torsades de pointes (Prod Info
HALDOL(R) Decanoate IM injection, 2008)
13) neuroleptic malignant syndrome, potentially fatal, has been reported in association with antipsychotic
drugs; immediately discontinue drug (Prod Info HALDOL(R) Decanoate IM injection, 2008)
14) QT prolongation, history; increased risk of QT prolongation and torsades de pointes(Prod Info HALDOL(
Decanoate IM injection, 2008)
15) QT prolongation and torsades de pointes have been reported, especially when administered intravenous
or at doses higher than recommended (Prod Info HALDOL(R) Decanoate IM injection, 2008)
16) rapid mood fluctuation toward depression may occur when risperidone is used for mania in bipolar
disorders (Prod Info HALDOL(R) Decanoate IM injection, 2008)
17) seizure disorder, history; may increase risk of seizures due to possible lowered convulsive threshold(Pro
Info HALDOL(R) Decanoate IM injection, 2008)
18) tardive dyskinesia, potentially irreversible, may occur (Prod Info HALDOL(R) Decanoate IM injection, 20
19) thyrotoxicosis; severe neurotoxicity may occur (Prod Info HALDOL(R) Decanoate IM injection, 2008)

C) Haloperidol Lactate
1) elderly patients with dementia-related psychosis (unapproved use); increased risk of death; most deaths
were attributed to cardiovascular events (eg, heart failure or sudden death) or infections (eg, pneumonia) (Pr
Info HALDOL(R) immediate release IM injection, 2008)
2) allergies, known, or with a history of allergic reactions to drugs (Prod Info HALDOL(R) immediate release
injection, 2008)
3) bronchopneumonia, some cases fatal, has been reported (Prod Info HALDOL(R) immediate release IM
injection, 2008)
4) cardiovascular disorders, severe; potential for transient hypotension and/or onset of anginal pain (Prod In
HALDOL(R) immediate release IM injection, 2008)
5) concomitant use with anticoagulants, anticholinergics (including antiparkinson drugs), anticonvulsants, or
lithium (Prod Info HALDOL(R) immediate release IM injection, 2008)
6) EEG abnormalities; may increase risk of seizures due to lowered convulsive threshold (Prod Info HALDO
(R) immediate release IM injection, 2008)
7) elderly patients, especially elderly women, are at increased risk of tardive dyskinesia (Prod Info HALDOL(
immediate release IM injection, 2008)
8) increased duration of therapy and/or higher cumulative doses; increased risk of tardive dyskinesia (Prod I
HALDOL(R) immediate release IM injection, 2008)
9) neuroleptic malignant syndrome, potentially fatal, has been reported; immediately discontinue if
signs/symptoms develop (Prod Info HALDOL(R) immediate release IM injection, 2008)
10) QT prolongation and torsades de pointes have been reported; increased risk in patients with underlying
cardiac abnormalities, familial long QT syndrome, hypothyroidism, electrolyte imbalance (especially
hypokalemia and hypomagnesemia), and with other drugs that prolong the QT interval (Prod Info HALDOL(R
immediate release IM injection, 2008)
11) rapid mood swing toward depression may occur when haloperidol is used for mania in cyclic disorders
(Prod Info HALDOL(R) immediate release IM injection, 2008)
12) seizure, history of; may increase risk of seizures due to lowered convulsive threshold (Prod Info HALDO
(R) immediate release IM injection, 2008)
13) tardive dyskinesia, potentially irreversible, may occur (Prod Info HALDOL(R) immediate release IM
injection, 2008)
14) thyrotoxicosis; severe neurotoxicity may occur (Prod Info HALDOL(R) immediate release IM injection,
2008)

3.3 Adverse Reactions

Cardiovascular Effects

Dermatologic Effects

Endocrine/Metabolic Effects

Gastrointestinal Effects

Hematologic Effects

Hepatic Effects

Musculoskeletal Effects

Neurologic Effects

Ophthalmic Effects

Psychiatric Effects

Reproductive Effects

Respiratory Effects

Other

3.3.1 Cardiovascular Effects

Cardiac arrest

Heart block, third degree

Hypertension

Hypotension

Prolonged QT interval

Sudden cardiac death

Tachycardia

Torsades de pointes

Ventricular premature beats

3.3.1.A Cardiac arrest

1) Cases of cardiac arrest secondary to haloperidol administration have been reported. A 49-year-old female with normal vital signs was brought to the emergency department in an acute confusional state a was given 5 milligrams (mg) haloperidol intramuscularly upon admission. She was given 10 mg haloperic intramuscularly 5 hours later due to complaints of feeling sick and anxious. The patient remained disoriented and confused and received another dose of haloperidol 10 mg the next morning. Forty-five minutes later, the patient was found unresponsive, cyanotic, and in asystolic arrest. Electrocardiogram a resuscitation showed no evidence of ischemia or prolongation of corrected QT interval. The patient remained comatose and died one month after being transferred to a long-term care facility. Information l received from her treating psychiatrist revealed the patient had previous admissions for similar incidents confusion and had experienced severe reactions to neuroleptic agents. The authors suggest such patien are candidates for medical alert bracelets (Westlake & Rastegar, 1973). In addition, a 65-year-old male patient twice suffered asystolic cardiac arrest after separate intravenous injections of haloperidol 7.5 mg confusion. The authors suggest that extreme (greater than 50 mg) or intermittent intravenous doses nee to be restricted to those patients in intensive care units with cardiac monitoring facilities (Huyse & Van

Schijndel, 1988).

3.3.1.B Heart block, third degree

1) Intermittent third degree heart block occurred during the highest rate of infusion (40 mg/hour) (Riker e al, 1994).

2) Two patients experienced adverse reactions attributed to continuous infusion haloperidol. Intermittent third-degree heart block and prolonged qt interval with torsade de pointes occurred during the highest ra of infusion (40 mg/hour). Hemodynamically compromising tachycardia requiring cardioversion and lidoca occurred during infusion of 10 mg/hour over 5 days. Finally, extrapyramidal side effects appeared after abrupt discontinuation of benzodiazepine treatment, requiring its reinstatement for resolution (Riker et al 1994).

3.3.1.C Hypertension

1) Hypertension has been reported with haloperidol use, especially if excessive doses are ingested. Haloperidol in therapeutic doses rarely has an effect on blood pressure. Many neuroleptics cause hypotension. In overdosage, patients normally remain normotensive. However, a 22-month-old girl accidentally ingesting 15 to 20 mg haloperidol developed significant hypertension of 146/100 at 8 hours and 164/134 at 10 hours after a baseline level of 136/66 taken on admission. IV hydralazine was require to reduce pressures reaching as high as 180 systolic over the subsequent 5 days. This report substantia 2 other reports of hypertension recently received by the manufacturer (Cummingham & Challapalli, 1979

3.3.1.D Hypotension

1) Transient hypotension may occur. A vasopressor may be necessary to treat the hypotension. Epinephrine should not be the vasopressor selected because haloperidol blocks the vasopressor effects and paradoxical lowering of the blood pressure may occur (Prod Info HALDOL(R) injection, 2007).

3.3.1.E Prolonged QT interval

1) Summary

a) Torsades de Pointes and QT prolongation, including sudden death, have been reported especial when haloperidol is administered intravenously or at doses higher than recommended. Risk factors Torsades de Pointes or QT prolongation include QT-prolonging conditions such as electrolyte imbalance (especially, hypokalemia and hypomagnesemia); underlying cardiac abnormalities; hypothyroidism; familial long QT syndrome; and concomitant drugs that prolong the QT interval. Electrocardiogram monitoring is recommended in patients on intravenous haloperidol (US Food and Drug Administration, 2007).

b) The incidence of long QTc interval syndrome or torsade de pointes with haloperidol is small (Lawrence & Nasraway, 1997). The majority of cases occurred in critically ill patients with a history c cardiovascular disease prescribed more than 50 mg/day. It is recommended that before initiating therapy with haloperidol in critically ill patients that a baseline QTc interval and serum magnesium a potassium concentrations be measured. In cases where the baseline QTc interval is 440 millisecond or longer and they are receiving other drugs that may prolong the QTc interval, or they have an electrolyte disturbance, haloperidol or similar drugs should be used with caution. Electrocardiogram monitoring should be done in critically ill patients once haloperidol is initiated. If the QTc interval lengthens by 25% or more, the haloperidol should be discontinued or the dosage should be reduced

2) The medical literature includes 28 case reports of QT prolongation and Torsades de Pointes, includin cases of death when haloperidol was administered intravenously. Furthermore, a dose-response relationship between intravenous doses and subsequent Torsades de Pointes was demonstrated in case control studies (US Food and Drug Administration, 2007).

3) There were 229 cases of QT prolongation in patients administered injectable or oral haloperidol, including 73 cases of Torsades de Pointes of which 11 were fatal, reported in the manufacturer's worldw safety database received through June 30, 2005. Various doses of intravenous haloperidol were used in of the 11 fatal cases. QT-prolonging or medical conditions may have contributed to the events. A second postmarketing investigation, submitted to the Food and Drug Administration in March 2007, reported 13 Torsades de Points, QT prolongation, ventricular arrhythmias and/or sudden death (US Food and Drug Administration, 2007).

4) QT prolongation has been reported in clinical trials. Predisposed patients (long QT-syndrome, hypokalemia, electrolyte imbalance, drugs known to prolong QT, cardiovascular disease, family history c QT prolongation) or those being treated with high doses may have an increased risk of QT prolongation (Prod Info HALDOL(R) injection, 2007).

5) Two patients experienced adverse reactions attributed to continuous infusion haloperidol. Intermittent third-degree heart block and prolonged qt interval with Torsade de Pointes occurred during the highest ra of infusion (40 mg/hour). Hemodynamically compromising tachycardia requiring cardioversion and lidoca occurred during infusion of 10 mg/hour over 5 days (Riker et al, 1994).

6) Intermittent prolonged QT interval with torsades de pointes occurred during the highest rate of infusio (40 mg/hour) (Riker et al, 1994).

3.3.1.F Sudden cardiac death

1) In a large, retrospective, cohort study that included a primary cohort of 93,300 users of antipsychotic

drugs and 186,600 non-users of antipsychotic drugs, there was an increased risk of sudden cardiac deat in adult participants 30 to 74 years of age (mean age of 45.7 years) who were using haloperidol compare to those who were not using antipsychotic drugs (incidence-rate ratio, 1.61; 95% confidence interval (CI) 1.16 to 2.24; p=0.005). In participants being treated with typical antidepressants (haloperidol, thioridazine the incidence-rate ratio for sudden cardiac death increased from 1.31 (95% CI, 0.91 to 1.39) for those us low doses to 2.42 (95% CI, 1.91 to 3.06) for those using high doses (p less than 0.001) (Ray et al, 2009)

3.3.1.G Tachycardia

1) Hemodynamically compromising tachycardia requiring cardioversion and lidocaine occurred during infusion of 10 mg/hour over 5 days (Riker et al, 1994).

3.3.1.H Torsades de pointes

1) Summary

a) Torsades de Pointes and QT prolongation, including sudden death, have been reported especial when haloperidol is administered intravenously or at doses higher than recommended. Risk factors Torsades de Pointes or QT prolongation include QT-prolonging conditions such as electrolyte imbalance (especially, hypokalemia and hypomagnesemia); underlying cardiac abnormalities; hypothyroidism; familial long QT syndrome; and concomitant drugs that prolong the QT interval. Electrocardiogram monitoring is recommended in patients on intravenous haloperidol (US Food and Drug Administration, 2007).

b) The incidence of long QTc interval syndrome or torsade de pointes with haloperidol is small (Lawrence & Nasraway, 1997). The majority of cases occurred in critically ill patients with a history c cardiovascular disease prescribed more than 50 mg/day. It is recommended that before initiating therapy with haloperidol in critically ill patients that a baseline QTc interval and serum magnesium a potassium concentrations be measured. In cases where the baseline QTc interval is 440 millisecond or longer and they are receiving other drugs that may prolong the QTc interval, or they have an electrolyte disturbance, haloperidol or similar drugs should be used with caution. Electrocardiogram monitoring should be done in critically ill patients once haloperidol is initiated. If the QTc interval lengthens by 25% or more, the haloperidol should be discontinued or the dosage should be reduced

2) The medical literature includes 28 case reports of QT prolongation and Torsades de Pointes, includin cases of death when haloperidol was administered intravenously. Furthermore, a dose-response relationship between intravenous doses and subsequent Torsades de Pointes was demonstrated in case control studies (US Food and Drug Administration, 2007).

3) There were 229 cases of QT prolongation in patients administered injectable or oral haloperidol, including 73 cases of Torsades de Pointes of which 11 were fatal, reported in the manufacturer's worldw safety database received through June 30, 2005. Various doses of intravenous haloperidol were used in of the 11 fatal cases. QT-prolonging or medical conditions may have contributed to the events. A second postmarketing investigation, submitted to the Food and Drug Administration in March 2007, reported 13 Torsades de Points, QT prolongation, ventricular arrhythmias and/or sudden death (US Food and Drug Administration, 2007).

4) A case of haloperidol-induced torsade de pointes was reported in a 41-year-old woman with no predisposing factors. The patient developed torsade de pointes 55 minutes after receiving 80 milligrams (mg) of intravenous haloperidol. The patient was treated and the arrhythmia was controlled. She receive one more 80-mg dose of haloperidol without incident and then it was discontinued. The patient experienc no further arrhythmias (O'Brien et al, 1999t).

5) A total of 7 patients developed torsade de pointes after therapeutic use of haloperidol in high doses (Metzger & Friedman, 1993l; Wilt et al, 1993j). Three patients developed the dysrhythmia after administration of 211 to 825 mg haloperidol over 1 to 2 days for agitated delirium. These 3 patients recovered from the initial episodes, but 1 patient subsequently died of cardiac arrest upon readministrati of haloperidol. Four patients developed the dysrhythmia after administration of 170 to 580 mg over 1 to 4 days for delirium associated with bacterial meningitis (1), status asthmaticus (2) or respiratory insufficien (1). All 4 patients recovered with no adverse sequelae.

6) A case of torsade de pointes was reported in a 48-year-old woman who ingested 210 mg of haloperic and 1400 mg of orphenadrine. It was concluded that the haloperidol caused this reaction. The patient wa given gastric lavage, 50 grams of activated charcoal and a constant infusion of lidocaine administered at rate of 4 mg per minute. Later, the lidocaine was stopped and replaced by a pacing electrode. The patie was released eight days later in normal condition (Henderson et al, 1991).

7) A case of torsade de pointes caused by haloperidol was reported in a 36-year-old male chronic schizophrenic patient. The patient had been treated with oral haloperidol 20 mg/day for five days, and th 50 mg/day for two more days during hospitalization in a closed psychiatric department. The torsade de pointes was treated with an isoproterenol infusion 2 to 3 mg/minute until the electrocardiogram returned normal (Kriwisky et al, 1990).

8) In another report, the incidence of torsade de pointes was substantial, developing in 8 of 223 critically patients in intensive care units (Sharma et al, 1998f). Patients who received intravenous haloperidol grea than 35 mg/day or had a QTc interval prolongation of greater than 500 ms were at greatest risk.

3.3.1.I Ventricular premature beats

1) A patient who received 90 mg the first day and 60 mg the second day of this procedure developed

multifocal, premature ventricular beats after a 10 mg dose on the third day. The frequency of these beats decreased from one half to one tenth over a 3 day drug-free period. When the patient then received thiothixene over a 4 day course, the ECG was normal (Mehta et al, 1979).
2) Rapid neuroleptization with high dose haloperidol has been associated with few serious cardiovascul side effects. A patient who received 90 mg the first day and 60 mg the second day of this procedure developed multifocal, premature ventricular beats after a 10 mg dose on the third day. The frequency of these beats decreased from one half to one tenth over a 3 day drug-free period. When the patient then received thiothixene over a 4 day course, the ECG was normal (Mehta et al, 1979).

3.3.2 Dermatologic Effects

Dermatological finding

Hair finding

Photosensitivity

3.3.2.A Dermatological finding

1) The relationship between haloperidol-induced parkinsonism and development of SEBORRHEIC DERMATITIS was studied. In 42 patients with haloperidol-induced parkinsonism, 59.5% developed seborrheic dermatitis, while in 47 patients without the extrapyramidal reaction, only 15% had seborrheic dermatitis (Binder & Jonelis, 1983).
2) Haloperidol has also been reported to cause maculopapular and acneiform SKIN ERUPTIONS (Prod Info Haldol(R), 97a).
3) Four cases of injection site reactions after using haloperidol decanoate 100 mg/mL were reported. Ea of the four patients had been given 50 mg/mL strength and had no reaction. The researchers first though that the vehicle used in the 100 mg/mL strength was the problem, but the same vehicle is used in the 50 mg/mL injection. The conclusion was the concentration of 100 mg/mL created much local intolerance (Hamann et al, 1990).
4) Eight of 9 patients injected with haloperidol decanoate 100 mg/mL developed raised, firm, warm, erythematous nodules of 3.5 cm. Symptoms dissipated over three weeks, but nodules persisted for two months. The authors noted no similar reactions in patients receiving the 50 mg/mL strength (Reinke & Wiesert, 1992).

3.3.2.B Hair finding

1) A case of ALOPECIA areata was reported, possibly secondary to haloperidol therapy. The patient wa 56-year-old man who had taken haloperidol for one month (5 mg twice daily for one week, then 3 mg dai and began to experience hair loss on the back of his head. Haloperidol was discontinued and the patient switched to perphenazine. After one week, hair loss stopped and after one month hair growth was norma The patient was also receiving amoxapine and biperiden which may have contributed to the alopecia (Kubota et al, 1994).

3.3.2.C Photosensitivity

1) Isolated cases of photosensitivity has been reported (Prod Info HALDOL(R) injection, 2007).

3.3.3 Endocrine/Metabolic Effects

Gynecomastia

Hyperprolactinemia

Hypoglycemia

Metabolic syndrome

Syndrome of inappropriate antidiuretic hormone secretion

3.3.3.A Gynecomastia

1) Gynecomastia has been reported with haloperidol treatment (Prod Info HALDOL(R) Decanoate IM injection, 2008; Prod Info HALDOL(R) immediate release IM injection, 2008).

3.3.3.B Hyperprolactinemia

1) Overview

a) Antipsychotic-induced hyperprolactinemia was reported in 65.6%, 45.1%, and 42.4% of women c childbearing potential, postmenopausal women, and men, respectively, in an open-label, clinical tria patients treated with first-generation antipsychotics or risperidone at average doses of 4.2 to 5.2 mg/day. Compared to baseline, prolactin levels were significantly elevated (p less than 0.05) followir use of first-generation antipsychotics (ie, chlorpromazine, droperidol, flupenthixol, fluphenazine, haloperidol, paliperidone, perazine, perphenazine, pimozide, trifluoperazine, and zuclopenthixol) or risperidone in several clinical trials of patients with schizophrenia. Younger patients and women of childbearing potential have a greater risk for hyperprolactinemia following treatment with higher dos of these antipsychotics. Hyperprolactinemia may potentially result in menstrual disturbances, sexual dysfunction, bone mineral density (ie, osteopenia and osteoporosis), and breast and pituitary tumors (Bostwick et al, 2009).

2) Hyperprolactinemia has been reported with antipsychotic drugs; the elevation in prolactin persists dur chronic administration (Prod Info HALDOL(R) Decanoate IM injection, 2008; Prod Info HALDOL(R) immediate release IM injection, 2008).

3) Haloperidol use has been associated with an increased prolactin secretion. It appears that a correlati exists between haloperidol-induced prolactin secretion and antipsychotic effect, blood levels, and extrapyramidal side effects of haloperidol (Rao et al, 1980). However, there is a large intersubject variab in the timing and amount of prolactin secreted with a specific dose (Rubin & Forster, 1980). Furthermore other factors may influence prolactin secretion, the effect is blunted in cases of idiopathic hyperprolactinemia (Falaschi et al, 1980), and the effect may be diminished with high doses of haloperid (Bjorndal et al, 1980). Length of therapy apparently does not diminish the effect (Ohman, 1980).

4) In 15 subjects, with normal prolactin levels and beginning haloperidol therapy 1 to 10 mg twice daily, prolactin levels rapidly increased during the first 6 to 9 days. Thereafter, the level plateaued and in most subjects remained between 30 and 50 ng/mL for the 18 days that prolactin was measured. The level did not exceed 77 ng/mL (Spitzer et al, 1998).

5) Prolactin blood levels resulting from varying doses of haloperidol were studied. In their study, involvin 37 patients who received haloperidol 0.2 to 20 mg/day, the following findings were made; doses less tha mg did not produce elevation, doses of 5 to 20 mg produced increasing elevations of prolactin, and lithiu did not enhance the prolactin response (Mielke & Gallant, 1982).

6) The prolactin response to intramuscular haloperidol (0.5 mg, 1 mg, and 1.5 mg) was studied in 6 norr premenopausal women during the follicular and luteal phases of their menstrual cycles. These were compared to the prolactin response in normal young men at the same doses of haloperidol. The women had significantly greater prolactin responses to haloperidol 1 mg and 1.5 mg doses than the men. This w most likely due to a potentiating effect of estrogen. However, the prolactin response to haloperidol at the lower dose of 0.5 mg was significantly smaller in women than men. The women did not differ in their prolactin response to haloperidol during the early and late phase of their menstrual cycle, showing that a increase in endogenous estrogen did not augment the prolactin response to haloperidol (Asnis et al, 198

a) Management

1) Appropriate drug selection, monitoring and management are all important when prescribing antipsychotics that have the potential for inducing hyperprolactinemia. Prior to treatment with ar antipsychotic, question patients regarding changes in libido or galactorrhea. Female patients should be assessed for menstrual abnormalities and male patients, for erectile or ejaculatory dysfunction. In the event that any of these symptoms are present, consider obtaining baseline prolactin levels. Patients should be informed of the potential for sexual dysfunction with antipsychotic use. Several weeks after an antipsychotic is initiated, obtain a prolactin level measurement. In cases where the patient experiences troublesome adverse effects related to elevated prolactin levels and discontinuing the antipsychotic is not an option, treatment with a dopamine agonist (eg, bromocriptine or cabergoline) should be considered (Bostwick et al, 200

3.3.3.C Hypoglycemia

1) Hypoglycemia has been reported with haloperidol treatment (Prod Info HALDOL(R) Decanoate IM injection, 2008; Prod Info HALDOL(R) immediate release IM injection, 2008).

3.3.3.D Metabolic syndrome

See Drug Consult reference: ANTIPSYCHOTIC AGENTS - METABOLIC SYNDROME

3.3.3.E Syndrome of inappropriate antidiuretic hormone secretion

1) Syndrome of inappropriate antidiuretic hormone secretion (SIADH) developed in a lethargic 54-year-c patient following the administration of haloperidol 10 mg/day orally for 1 month. Serum sodium was 111 mEq/L and plasma and urine osmolalities were 225 and 325 mOsm/L, respectively. Renal, liver, and thyr function tests were normal. The response from an adrenocorticotropic hormone stimulation test was alsc normal. Discontinuation of haloperidol and water restriction resolved symptoms and improved serum sodium concentration. After several weeks had lapsed, haloperidol was reinitiated and after 5 days of therapy, the patient became lethargic and serum sodium was 115 mEq/L. The SIADH resolved following water restriction and discontinuation of haloperidol. The authors postulated two possible mechanisms for SIADH induced by haloperidol. Haloperidol may alter the central osmotic threshold for ADH (antidiuretic

hormone) levels, or haloperidol may act on the kidneys directly to increase their sensitivity to ADH (Peck Shenkman, 1979).
2) A 77-year-old female, receiving haloperidol 6 mg daily for 5 days, then 10 mg per day, developed SIADH on the eighth day. While she was taking digoxin and hydrochlorothiazide/triamterene, the tempor relationship to haloperidol suggested it as the cause (Husband et al, 1981).
3) A 25-year-old patient with a history of schizophrenia and mental retardation developed syndrome of inappropriate antidiuretic hormone secretion (SIADH). Prior to admission, the patient received haloperidc 30 mg/day for 4 months. Upon admission, serum sodium was 118 mEq/L, serum and urine osmolality we 254 and 299 mOsm/kg, respectively, and urine sodium was 23 mEq/L. To rule out other causes of SIADI serum calcium, magnesium, and phosphorus levels were determined, a hemogram, and renal, liver, adrenal, and thyroid function tests were performed, and all were normal. Roentgenograms of the chest a skull, an EEG, and CT and brain scan were also normal. The patient was treated with fluid restriction anc discharged 12 days following admission. The authors failed to state if haloperidol was discontinued or if t dose reduced, nor was a rechallenge with haloperidol performed, so the possibility of psychogenic water intake does exist for the etiology of SIADH in this case (Matuk & Kalyanaraman, 1977).

3.3.4 Gastrointestinal Effects

Constipation

Dysphagia

Gastrointestinal tract finding

Paralytic ileus

Xerostomia

3.3.4.A Constipation
1) Haloperidol has been reported to cause constipation (Prod Info Haldol(R), 97a).

3.3.4.B Dysphagia
See Drug Consult reference: ANTIPSYCHOTIC-INDUCED DYSPHAGIA

3.3.4.C Gastrointestinal tract finding
1) Haloperidol has been reported to cause ANOREXIA, DYSPEPSIA, NAUSEA and VOMITING, CONSTIPATION, DIARRHEA, and hypersalivation (Prod Info Haldol(R), 97a).
2) In one study of reported cases (n=192) of antipsychotic-induced PANCREATITIS, 12% of the cases were associated with the use of haloperidol at a mean daily dose of 8.2 milligrams. In most patients, time onset of pancreatitis was within 6 months after initiation of treatment (Koller et al, 2003c).

3.3.4.D Paralytic ileus
1) Incidence: rare
2) A case of ileus was reported in a 52-year-old female who received a mean dose of 41.4 mg haloperidol/day, raised to a mean dose of 53 mg/day the 5 days prior to onset. The resulting fecal impaction resolved over 6 days with discontinuation of haloperidol, IV fluids, and continuous nasogastric suction (Maltbie et al, 1981).

3.3.4.E Xerostomia
1) Dry mouth has been reported (Prod Info HALDOL(R) injection, 2007).

3.3.5 Hematologic Effects

Agranulocytosis

Leukopenia

3.3.5.A Agranulocytosis
1) Incidence: rare (Prod Info HALDOL(R) injection, 2007)
2) Agranulocytosis has occurred, rarely, in association with haloperidol and other medications (Prod Info HALDOL(R) injection, 2007).

3.3.5.B Leukopenia

1) Moderate doses of haloperidol have been associated with the development of mild and usually transi leukopenia (Prod Info Haldol(R), 97a).

2) A case of leukopenia (from 13,000 cu/mm to 3,200 cu/mm) 15 days after starting haloperidol 10 mg/d was reported. This followed a similar occurrence with thiothixene. The mechanism for this rare adverse effect could not be established, but the white count returned to normal within a few days after discontinuation of the drug, and subsequent treatment with fluphenazine has not caused a recurrence (Cutler & Heiser, 1979).

3.3.6 Hepatic Effects

3.3.6.A Hepatotoxicity

1) Chronic cholestatic LIVER DISEASE occurred in a 15-year-old black male following treatment with haloperidol (6 mg daily) and benztropine (8 mg daily) for 4 weeks. The patient was treated for an acute psychotic episode. At this time, the patient presented with jaundice to his psychiatrist and was admitted t the hospital approximately 2 months later. JAUNDICE and pruritus continued for over 7 months. Twenty- eight months after the occurrence of jaundice, the patient is asymptomatic but had mildly elevated alkalir phosphatase and transaminase levels (Dincsoy & Saelinger, 1982).

3.3.8 Musculoskeletal Effects

Musculoskeletal finding

Myasthenia gravis

Rhabdomyolysis

3.3.8.A Musculoskeletal finding

1) An increased incidence of hip fracture was reported in elderly patients receiving psychotropic agents (Ray et al, 1987). This study was a case-control evaluation of 1021 patients with hip fractures and 5606 controls, and indicated that an increased risk of hip fracture was observed with the use of hypnotic/anxiolytic agents with a long elimination half-life (greater than 24 hours), tricyclic antidepressant and antipsychotic agents. Current users were defined as subjects who had received a prescription in the day period prior to the admission date for index hospitalization. The long half-life hypnotic/anxiolytic ager studied were lorazepam, diazepam, chlordiazepoxide and barbiturates, excluding phenobarbital. The tricyclic antidepressants included amitriptyline, doxepin and imipramine; antipsychotic agents evaluated were thioridazine, haloperidol, chlorpromazine and perphenazine/amitriptyline. In contrast, shorter-acting hypnotic-anxiolytic agents (half-life of 24 hours or less) were not associated with an increased risk of hip fracture in these patients. The most frequently used agents in this category were diphenhydramine, hydroxyzine and chloral hydrate. The increased risk of hip fracture observed in this study was directly related to the doses of the drugs. Analysis for confounding by dementia did not alter the results. Addition studies are needed to confirm these results in this and other populations and to evaluate the effects of other psychotropic drugs that have less sedative effects.

3.3.8.B Myasthenia gravis

See Drug Consult reference: DRUG-INDUCED MYASTHENIA GRAVIS

3.3.8.C Rhabdomyolysis

1) A case of haloperidol-induced rhabdomyolysis in the absence of neuroleptic malignant syndrome was reported in a 6-year-old handicapped boy. Oral haloperidol (0.3 milligrams daily) was initiated to treat involuntary movements. The haloperidol was effective and the dose was increased to 0.8 milligrams twic daily. After haloperidol was begun, the patient's urine became dark brown on occasion and the myoglobi level in his urine increased. Mild rhabdomyolysis was suspected and haloperidol was discontinued. Subsequently, the myoglobin in the urine decreased, creatinine kinase decreased to normal, and the urir no longer become dark brown (Yoshikawa et al, 2000).

2) In a 23-year-old male a dystonic reaction occurred complicated by the occurrence of rhabdomyolysis. Ten hours following administration of haloperidol 5 mg PO TID, the patient experienced a dystonic reacti which was mistaken for psychotic behavior. Tonic activity continued into the second day and Benadryl 5(mg IV had minimal effect; the reaction was finally controlled with benztropine IV. On the third day, rhabdomyolysis was observed, and urinary myoglobin on minimal effect; the reaction was finally controlle with benztropine IV. On the third day, rhabdomyolysis was observed, and urinary myoglobin on day 4 wa 67 mcg/mL. Patient recovered following urinary alkalinization and IV fluid therapy (Cavanaugh & Finlays(1984).

3.3.9 Neurologic Effects

Akathisia

Dementia

Dysphoric mood

Dystonia

Encephalopathy

Extrapyramidal disease

Neuroleptic malignant syndrome

Parkinsonism

Phobia

Seizure

Tardive dyskinesia

Tic

3.3.9.A Akathisia

1) A study compared akathisia induced by haloperidol or thiothixene. The haloperidol group (5 mg as tes dose followed by 10 mg/day) experienced akathisia in 75% of cases. The thiothixene group (0.22 mg/kg test dose followed by 0.44 mg/kg/day) experienced akathisia in 46% of cases (Van Putten et al, 1984a; V Putten et al, 1984b).

3.3.9.B Dementia

1) Dementia, characterized by symptoms of confusion, memory impairment, disorientation, and slowing motor performance, has been reported (Thornton, 1976b; Cohen & Cohen, 1974a).

3.3.9.C Dysphoric mood

1) Dysphoria has been reported in patients treated with haloperidol for Gilles de la Tourette syndrome. C 72 patients being treated for Gilles de la Tourette syndrome, 3 patients developed pronounced and 3 patients developed mild dysphoria. The change in mood was not related to akinesia or other extrapyrami side effects, drowsiness, or cognitive impairment. Improvement was seen when dosage was reduced. Th report confirms 2 other case studies of similar nature (Caine & Polinsky, 1979).

2) Twenty-six cases of dysphoria, 13 of which were severe, were reported in patients being treated with haloperidol for Tourette syndrome. All appeared to have a threshold dose, above which dysphoria occur and below which symptoms subsided. The threshold dose was individualized and ranged from 1 to 30 mg/day (Bruun, 1982).

3.3.9.D Dystonia

1) During the first few days after initiating treatment with an antipsychotic medication, symptoms of dystonia may occur in susceptible individuals. Symptoms may include spasm of neck muscles, which ma progress to tightening of the throat, swallowing difficulty, breathing difficulty, and/or protrusion of the tongue. These symptoms can occur at low doses but most often occur (and occur with a greater severity with high potency and at higher doses of first generation antipsychotic medications. Males and younger a groups appear to be at greater risk for developing acute dystonia (Prod Info HALDOL(R) IM injection, 2008).

2) Extrapyramidal and dystonic reactions have occurred following usual therapeutic doses of haloperido The incidence of dystonias following haloperidol is reported to be as high as 16% (Swett, 1975) and for extrapyramidal symptoms as high as 25% (Anon, 1973a).

3) Laryngeal-pharyngeal dystonia was reported in a patient 16 hours after being treated with a single do of haloperidol 5 mg IM. The reaction was treated with benztropine 2 mg IV, repeated after 2 minutes, whereupon recovery without sequelae occurred in 5 minutes (Menuck, 1981).

4) Sudden death was reported in a woman receiving haloperidol 230 mg over less than 48 hours. The proposed mechanism was laryngeal-pharyngeal dystonia, followed by laryngospasm and cardiac arrest (Modestin et al, 1981). A similar case was reported after a patient received 340 mg over less than 96 hou

(Ketai et al, 1979).
5) Dystonic reactions were reported to persist for several weeks after a single dose of haloperidol in two patients (Anderson et al, 1981).
6) A high incidence of dystonic reactions was reported in cocaine abusers. Of 7 chronic heavy cocaine users, administration of intramuscular haloperidol (8 mg on 2 consecutive days) resulted in the occurrenc of acute dystonic reactions in 6; the onset of dystonia was approximately 22 hours following the first dos 4 patients and 3 hours following the second dose in 2 others. Diphenhydramine or benztropine was effective in alleviating dystonia in all patients. These data suggest a higher incidence of dystonic reactior in cocaine abusers treated with neuroleptic agents. However, controlled studies are required to confirm these findings, using a cocaine naive control group (Kumor et al, 1986).

3.3.9.E Encephalopathy
1) A case of post-surgical toxic encephalopathy has been attributed to high-dose haloperidol in a 54-yea old African-American male. The patient had a history of bipolar disorder, hypertension and a cerebrovascular accident. Despite increasing doses of haloperidol (up to 270 milligrams intravenously ov 24 hours) to treat agitation, mental status continued to worsen to the point of obtundation, with toxic encephalopathy diagnosed on day 14 after surgery. After haloperidol discontinuation, encephalopathy completely resolved within 8 days (Maxa et al, 1997).
2) An encephalopathic syndrome with irreversible brain syndrome has been reported (Thornton, 1976b; Cohen & Cohen, 1974a).

3.3.9.F Extrapyramidal disease
1) Incidence: frequent (Prod Info HALDOL(R) injection, 2007)
2) Extrapyramidal symptoms occur frequently. Parkinson-like symptoms, akathisia or dystonia may occu typically within the first few days of starting haloperidol. There is a greater association with higher doses. Dose reductions may alleviate symptoms. Antiparkinson drugs (such as benztropine mesylate or trihexyphenidyl hydrochloride) may be useful. Discontinuation of haloperidol may be necessary in patient with persistent extrapyramidal symptoms (Prod Info HALDOL(R) injection, 2007).
3) Extrapyramidal and dystonic reactions have occurred following usual therapeutic doses of haloperido The incidence of dystonias following haloperidol is reported to be as high as 16% (Swett, 1975) and for extrapyramidal symptoms as high as 25% (Anon, 1973a).
4) Extrapyramidal disturbances can present as mild to severe dyskinetic and dystonic reactions includin oculogyric crises, forced opening of the mouth, protrusion of tongue, spasm of facial muscles, opisthotor and scoliotic positioning, general muscle rigidity, cogwheel phenomenon, coarse tremors, oral dyskinesia restlessness, dystonic spasms and posturings of the neck, trunk, and limbs, aphonia and dysphagia (Ge et al, 1972; Walinder & Carlsson, 1973; Simpson, 1973; Lake & Fann, 1973; Yosselson & Kaplan, 1975; Shields & Bray, 1976; Loudon & Waring, 1976; Rice, 1977). Although a number of agents have been reported to be effective in treating these extrapyramidal disturbances including apomorphine, biperiden, procyclidine, and propranolol, conventional agents such as diphenhydramine, trihexyphenidyl, or benztropine may not always result in improvement of the dystonic reactions (Shields & Bray, 1976). Thes neurotoxic reactions have been reported in patients with thyrotoxicosis (Lake & Fann, 1973; Yosselson & Kaplan, 1975) as well as pediatric patients (Shields & Bray, 1976). Some reports indicate that concomita drug therapy such as with lithium may aggravate extrapyramidal reactions (Loudon & Waring, 1976). Son data suggests that, particularly in elderly patients, parkinsonism reactions induced by haloperidol may persist for up to 2 weeks (Rice, 1977). Parkinsonism-like symptoms (sialorrhea, dystonia, torticollis, and trismus) have occurred following discontinuation of haloperidol therapy (De Maio, 1973). Rigidity occurre in association with dyspnea, cyanosis, and dehydration in a thyrotoxic, 74-year-old female (Hamadah & Teggin, 1974).
5) The extrapyramidal side effects of haloperidol were shown to be lessened by joint administration of imipramine-like drugs (Butterworth, 1972).
6) The incidence of extrapyramidal reactions was lower in patients receiving intravenous as opposed to oral haloperidol (Menza et al, 1987). More studies are required to fully evaluate the potential mechanism for a lower incidence of EPS with the intravenous route. In addition, this study only involved 10 patients (received intravenous haloperidol, 6 received oral haloperidol) and more studies involving larger patient populations are necessary to confirm significant differences.
7) Four cases of severe muscle rigidity were reported in burn patients receiving haloperidol for the neuropsychiatric complications of thermal injury. The authors postulated that the seemingly high incidenc (greater than 30%) of this reaction could have resulted from an increased sensitivity of the neuromuscula receptors to acetylcholine, which is present in greater concentrations after haloperidol treatment (Huang al, 1987).
8) A 5-year-old female with Sydenham's chorea treated with doses of 0.5 to 0.7 mg orally 4 times daily c haloperidol developed side effects of dysphagia, aphonia, and dystonic posturing(Shields & Bray, 1976). Seven weeks later the patient was hospitalized and was noted to have abnormal head posture, left arm extension with fist clinched, inability to walk without falling frequently, and placement of her right thumb in the roof of her mouth causing pressure against the gingiva resulting in the exposure of 2 teeth's roots. Th haloperidol was discontinued and various drugs including diphenhydramine, benztropine, and levodopa were given without effect. The patient's condition deteriorated requiring frequent tube feeding with the patient being unable to walk and often assuming a fixed extensor posture. Due to circumstantial evidenc

the choreiform movements and dystonias were believed to be resulted to the haloperidol ingestion.
9) A 23-year-old woman receiving Lugol's solution, propylthiouracil (PTU), trihexyphenidyl, and haloperi developed facial rigidity, a fixed grin, aphasia, an inability to walk, severe weakness, diarrhea, and dryne of the lips and tongue. Four days prior to hospital admission when diarrhea developed, all drugs were discontinued except haloperidol. After 4 days, some improvement in her symptoms were noted. The authors suggested that this type of reaction is not necessarily idiosyncratic but expected in thyrotoxic patients (Yosselson & Kaplan, 1975).
10) A 32-year-old woman developed haloperidol toxicity because of manganese toxicity. The Parkinsonism-like neurotoxicity may be due to the free-radical formation in the presence of ionic manganese in the neuromelanin-containing regions of the brain (Mehta & Reilly, 1990).
11) The incidence and severity of tardive dyskinesia and extrapyramidal side effects was evaluated in 5 outpatients receiving either fluphenazine decanoate or haloperidol decanoate. Twenty-one patients had probable movement disorders based on the Involuntary Movement Scale and the Simpson-Angus Extrapyramidal symptoms (EPS) Rating Scale. Of these, only six had been previously identified by standard observational means. Frequency was higher with haloperidol decanoate, but these patients we also receiving higher doses (Bransgrove & Kelly, 1994).

See Drug Consult reference: NEUROLEPTIC-INDUCED EXTRAPYRAMIDAL REACTIONS

3.3.9.G Neuroleptic malignant syndrome

1) Incidence: rare
2) Neuroleptic malignant syndrome occurred in a 26-year-old male receiving 20 mg haloperidol TID for hypomania (Town, 1982). This patient developed profound rigidity and dystonia, tachycardia, hypertensi sweating, fever, confusion, depressed level of consciousness, incontinence, elevated CPK and leucocytosis. Withdrawal of the drug and treatment with anti-Parkinsonism drugs resulted in improvemer
3) Neuroleptic malignant syndrome was reported in 3 adults during haloperidol therapy of psychotic stat Discontinuation of haloperidol and institution of antiparkinson medications reversed the adverse effect (Cruz et al, 1983; Dosani, 1983; Henderson & Wooten, 1981). One proposed mechanism attributed dopamine receptor blockade in the striatum increasing thermogenesis and in the hypothalamus impairin heat dissipation (Henderson & Wooten, 1981).
4) Two cases of adverse reactions resembling neuroleptic malignant syndrome were reported in childre treated with haloperidol for psychiatric disorders. Therapy consisted of discontinuing haloperidol and administering fluids and antiparkinson medication (Geller & Greydanus, 1979).
5) Amantadine was used successfully to treat a case of neuroleptic malignant syndrome in a 19-year-ol female patient treated with haloperidol. The proposed mechanism for amantadine was dopaminergic agonist activity (Amdurski et al, 1983).
6) Neuroleptic malignant syndrome (NMS) was reported in a head injury patient treated with haloperidol control agitation. NMS began to develop by the third day and haloperidol was discontinued on the elever day. Improvement began to occur by the fourth day after discontinuation of haloperidol (Vincent et al, 1986).
7) Neuroleptic malignant syndrome (NMS) occurred in a chronic schizophrenic treated with haloperidol. The patient, having been treated with haloperidol for 10 years, was given 2 intramuscular doses to contr an abrupt increase in agitation accompanied by other mental changes. Characteristic signs and sympton of NMS occurred. These improved by the fourth day after haloperidol was discontinued, but recurred wh haloperidol was reinstituted on the twelfth day (Matthews & Cersosimo, 1986).
8) A fatal case of neuroleptic malignant syndrome was reported in an 84-year-old male being treated wi haloperidol for agitation associated with dementia. The patient had been taking haloperidol 6 mg/day, bu the dosage was rapidly increased by the family of the patient without informing the physician. Within 8 da the patient developed neuroleptic malignant syndrome. The authors postulated that the rapid increase in haloperidol dosage may have contributed to the severity of the case (Osser & Stewart, 1988).
9) Neuroleptic malignant syndrome (NMS) was reported in a 67-year-old female with parkinsonism bein treated with haloperidol for agitation. The patient having been treated with haloperidol 1 mg at bedtime fo five months was given a total of 12 mg haloperidol intramuscularly, with an additional 13 mg over the ensuing 48 hours. Within 2 days characteristic signs and symptoms of NMS occurred. Withdrawal of haloperidol and treatment with anti-Parkinsonism drugs resulted in improvement (Ryken & Merrell, 1989)
10) Neuroleptic malignant syndrome was reported in a 25-year-old male head injury patient being treate with haloperidol for agitation. Withdrawal of the haloperidol and treatment with dantrolene and bromocriptine resulted in improvement (Heird et al, 1989).
11) Neuroleptic malignant syndrome (NMS) secondary to haloperidol and subsequent to amantadine withdrawal occurred in a 75-year-old male with "senile" dementia and Parkinsonian symptoms (Hermesh al, 1984). The patient developed NMS approximately 2 days after initiation of therapy with haloperidol 0.5 mg orally 3 times daily to control delusions and aggressive behavior. Haloperidol was discontinued and therapy with amantadine 200 mg twice daily was initiated due to suspected NMS, resulting in subsidence NMS symptoms. Amantadine was withdrawn after approximately 1 month of treatment due to exacerbati of delusions, and NMS symptoms recurred approximately 2 days later. Amantadine and levodopa were given, resulting in abatement of NMS symptoms within several days. It is suggested that NMS occurred i this patient secondary to amantadine withdrawal as a result of decreased central dopamine activity, the same mechanism was implicated in the haloperidol induced NMS. It is speculated that Parkinson's disea may have increased this patient's vulnerability to further diminution of dopamine activity.

3.3.9.H Parkinsonism

1) Summary

a) Contrary to common belief, the results of a retrospective cohort study suggest that atypical antipsychotics may not be safer than typical antipsychotics when dose and potency are considered (Rochon et al, 2005).

2) The results of a cohort study indicate that high-dose atypical antipsychotic therapy carries a similar ris for the development of parkinsonism as does typical antipsychotic therapy. In a population-based, retrospective cohort study, adults (aged 66 years and older) with evidence of dementia were followed for to 1 year for the development of parkinsonism symptoms associated with typical or atypical antipsychotic use. As compared with older adults receiving atypical antipsychotic therapy (ie, olanzapine, risperidone, quetiapine), incident parkinsonism was 30% more likely to occur in those taking typical antipsychotics (ie chlorpromazine, haloperidol, perphenazine) (adjusted HR, 1.3; 95% (CI), 1.04 to 1.58), and 60% less like to occur in patient who did not receive either therapy (HR), 0.4; 95% CI, 0.29 to 0.43). Older adults using higher potency typical antipsychotics had almost a 50% greater risk of experiencing parkinsonism as compared with patients prescribed atypical antipsychotics (all were considered lower potency) (HR, 1.44 95% CI, 1.13 to 1.84); however, in patients receiving lower potency typical antipsychotics, the risk of developing parkinsonism was no different from that in adults taking atypical antipsychotics (HR, 0.75; 95 CI. 0.48 to 1.15). In addition, a positive dose-related relationship was observed between the occurrence incident parkinsonism and the use of atypical antipsychotics. The risk for developing parkinsonism was more than twice as great in patients using a high-dose atypical antipsychotic agent as compared with thc prescribed a low-dose atypical antipsychotic agent (HR, 2.07; 95% CI, 1.42 to 3.02). Furthermore, patier taking a typical antipsychotic were found to have a similar risk for the development of parkinsonism as patients receiving high-dose atypical antipsychotic therapy (p=ns). The authors conclude that atypical antipsychotics may not be safer than typical antipsychotics when dose and potency are considered (Rochon et al, 2005).

3.3.9.I Phobia

1) Phobia was triggered by use of haloperidol. After a psychotic depressive episode successfully treatec with haloperidol, the patient experienced severe anxiety when placed in stressful driving circumstances. Her symptoms resulted in her taking unusual precautions to avoid these situations. After five years of thi phobic situation, the symptoms gradually disappeared after haloperidol was discontinued (Bristol, 1982). Other similar cases have been reported (Mikkelson et al, 1981).

3.3.9.J Seizure

1) Incidence: rare

2) Convulsions, in association with parkinsonism symptoms, have occurred in pediatric patients treated with 1.5 to 2.5 mg of haloperidol or following a 6 mg overdose. Treatment with or without antiparkinsonis drugs was reported to result in complete recovery within a few days in all patients (Debray & Galland, 1970).

See Drug Consult reference: ANTIPSYCHOTICS - EFFECT ON SEIZURE THRESHOLD

3.3.9.K Tardive dyskinesia

1) Several cases of tardive dyskinesia or worsening of tardive dyskinesia have been reported, at doses ranging from 3 to 18 mg/day. Although features of the dyskinesias were different in each case, including onset, manifestations, concurrent therapy, and duration, all authors described a causal relationship with haloperidol (Kiloh et al, 1973; Moline, 1975); (Petty, 1980)(Faheem et al, 1982; Peabody et al, 1987).

2) The incidence of dyskinesias induced by neuroleptic agents was studied in 58 autistic children. Daily doses of haloperidol ranged from 0.02 to 0.22 mg/kg. Thirteen (22%) developed dyskinesias. There appeared to be no relationship between onset of symptoms and dose or administration schedule (Perry al, 1985).

3) Molindone was compared with haloperidol with regard to their ability to mask neuroleptic withdrawal-exacerbated tardive dyskinesia, using the theoretical proposition that agents less able to mask are less dyskinetogenic. In a parallel, double-blind study, 11 patients were given either molindone or haloperidol following discontinuation of previous neuroleptic therapy and at a point where involuntary movements showed a significant increase. Doses were based on standard relative potency assignments calculated from previous neuroleptic medications and ranged from 50% to 200% dose equivalency as compared to previous neuroleptics. Molindone was shown to be less effective than haloperidol in masking tardive dyskinesia, thereby suggesting lower dyskinetogenic potential (Glazer et al, 1985a).

3.3.9.L Tic

1) Nondystonic, nonakathisic TICs were reported in a hyperactive child. The reaction was similar to that seen when the boy was treated with amphetamine on one occasion and carbamazepine on another (Gualtieri & Patterson, 1986).

3.3.10 Ophthalmic Effects

Blurred vision

Eye / vision finding

3.3.10.A Blurred vision

1) Blurred vision has been reported (Prod Info HALDOL(R) injection, 2007).

3.3.10.B Eye / vision finding

1) A study was conducted in cooperation with Group Health Cooperative of Puget Sound using men and women born before 1931 to evaluate the risk of cataracts from exposure to phenothiazine drugs. A total 45,301 individuals were identified as potential patients in an effort to study a large population. A list of criteria was used to evaluate these patients, and the group was then whittled to 4,674 individuals. The results of the study showed there is no significant increase in risk of cataract extraction in patients who used haloperidol in either short or long-term cases (Isaac et al, 1991).

2) OCULOGYRIC CRISIS has been reported following the use of haloperidol (Dukes, 1975).

3.3.12 Psychiatric Effects

3.3.12.A Psychotic disorder

1) Psychotic exacerbation has been reported. Deterioration was correlated with dosage increase. An acutely psychotic patient, treated with haloperidol 30 mg/day for 10 days with no improvement, deteriora further over a 3 day period when the dose of haloperidol was increased to 60 mg/day. Upon reduction of the haloperidol dose, the patient gradually improved. When fluphenazine replaced haloperidol, the patier showed a gradual but dramatic recovery (Tornatore et al, 1981).

3.3.14 Reproductive Effects

3.3.14.A Priapism

1) Incidence: rare

2) PRIAPISM has been reported (Greenberg & Lee, 1987; Gomez, 1985).

3.3.15 Respiratory Effects

Pulmonary embolism

Respiratory finding

3.3.15.A Pulmonary embolism

1) The use of psychotropic medications has been linked to an increased risk of fatal pulmonary embolis In a case-control study including 62 cases of fatal pulmonary embolism and 243 matched controls, researchers found that compared to non-use, the current use of conventional antipsychotic medications (thioridazine and haloperidol) was associated with an increased risk of fatal pulmonary embolism (adjuste odds ratio, 13.3; 95% CI, 2.3 to 76.3). In addition, low potency antipsychotics, such as thioridazine, were associated with the highest risk, with an odds ratio of 20.8 (95% CI, 1.7 to 259). The current use of antidepressants was also associated with an increased risk of fatal pulmonary embolism (adjusted odds ratio, 4.9; 95% CI, 1.1 to 22.5); however, current or past use of other psychotropic drugs was not associated with an increased risk (adjusted odds ratio, 1.4; 95% CI, 0.3 to 5.8). (Parkin et al, 2003).

3.3.15.B Respiratory finding

1) A case of acute laryngeal dystonia was reported in a 26-year-old woman receiving haloperidol (no do reported) for management of schizophrenia. The patient received both diphenhydramine and lorazepam intravenously with subsequent resolution of symptoms. Haloperidol was discontinued and the patient wa discharged on oral diphenhydramine 24 hours later (Fines et al, 1999).

2) A 53-year-old female with a 25 year history of psychiatric illness was admitted to the ER after having discontinued all of her medications three weeks earlier. She had been taking trifluoperazine 5 mg daily, benztropine 2 mg daily and lithium in alternating daily doses of 600 and 900 mg. She had no known allergies. She was subsequently admitted to the psychiatric crisis unit where she was put on haloperidol mg every 8 hours. Two hours after the second dose, she experienced shortness of breath with audible wheezing. Physical examination findings included sinus tachycardia and auscultation of the chest reveal poor air entry with diffuse high pitched wheezing. There were no other adverse effects detected and she remained afebrile. The bronchospasm was treated and her breathing returned to normal within 30 minute Two hours later, she developed laryngeal stridor for which she was treated with benztropine. The haloperidol was discontinued and the patient was restarted on trifluoperazine. Allergy tests were done, b

skin testing revealed no significant wheal and flare responses. A tartrazine test was also done, but the results were negative. The cause and mechanism of the haloperidol induced bronchospasm remained unclear (Sethna et al, 1991).

3.3.16 Other

Dead - sudden death

Death

Drug dependence

Extrapyramidal disease

Hyperpyrexia

Withdrawal sign or symptom

3.3.16.A Dead - sudden death

1) Cases of sudden death have been reported in association with haloperidol treatment. Causality has n been determined; however, haloperidol cannot be ruled out. Sudden and unexpected death can occur in psychotic patients who may or may not be receiving treatment with other antipsychotic drugs (Prod Info HALDOL(R) injection, 2007).

2) A 59-year-old man admitted for an acute recurrence of a paranoid disorder died after admission (Turbott, 1984). Prior to admission, the patient had not received any neuroleptic medication. The patient was taking pindolol, hydrochlorothiazide, and amiloride for hypertension. The patient was also taking chlordiazepoxide and allopurinol. Physical examination was normal on admission. The patient received t 10-milligram doses of haloperidol orally three hours apart. Following the second dose, an ECG revealed normal sinus rhythm with a rate of 100 beats/minute, a QT interval of 0.42 seconds, and slight T-wave flattening. Shortly after the ECG, the patient was found cyanotic on the floor. A repeat ECG showed asystole, resuscitation efforts were unsuccessful. Autopsy revealed moderate left ventricular hypertrophy and 80% blockage of the right coronary artery and 70% blockage of the anterior descending left coronary artery. No other abnormalities were noted.

3) A 30-year-old male with a long history of multiple drug abuse died after receiving haloperidol (Mahutte 1982). Upon hospital admission, physical examination, routine laboratories and ECG were normal. Multip drug screens were negative. The patient's course over the next three weeks was varied. The patient was taking desipramine 100 milligrams (mg) each day and haloperidol 10 mg orally as needed for agitation. C the three days prior to his death, the patient received haloperidol 50 mg/day, 50 mg/day and 40 mg/day, respectively. After the last haloperidol dose, he was noted to be in respiratory distress, and bloody sputu was suctioned from the patient. The blood pressure at this time was 56/24 mmHg. Cardiac arrest followe and the patient expired. Autopsy revealed grossly congested lungs with diffuse alveolar hemorrhages. There was no evidence of pulmonary emboli, aspiration, or pneumonia. There was no evidence of significant cardiac disease or injury. The cause of death was thought to be transient pulmonary hypertension.

4) A 44-year-old woman with chronic paranoid schizophrenia, myopia, and obesity died 2 hours after a haloperidol dose (Modestin et al, 1981). All previous laboratories and ECGs were normal. The patient ha taken no medications for 6 weeks prior to admission. During the next two days the patient received 60 milligrams (mg) haloperidol intramuscularly and 160 mg orally. The patient experienced two dyskinetic episodes which were successfully treated by biperiden 2 mg. The patient's last dose of biperiden was tak the morning of the second day. Two hours after the patient's last dose of haloperidol (90 mg), vital signs were pulse regular at 84 beats/minute, blood pressure 120/80 mmHg, and respirations normal. Shortly thereafter, the patient cried out and was found unresponsive. The patient's pulse was not palpable and h breathing was labored, but she was not cyanotic. Her mouth was distorted and she bit her lower lip. Cardiopulmonary resuscitation was unsuccessful. Significant findings at autopsy were mild congestion of pulmonary and systemic circulation and large amounts of viscous mucus just above and below the epiglottis. The proposed mechanism was laryngeal-pharyngeal dystonia, followed by laryngospasm and cardiac arrest.

5) A 35-year-old woman with no prior psychiatric problems or significant medical history died in her slee hours after a total oral dose of haloperidol 80 milligrams (mg) (Ketai et al, 1979). In the previous 65 hours she had received haloperidol 260 mg orally. In response to a dystonic reaction 8 hours prior to her death the patient was given 2 mg of benztropine and started on 1 mg twice daily. The only significant finding or autopsy was mild, nonspecific edema of the lungs, brain and liver. This was thought due to attempts at cardiopulmonary resuscitation.

3.3.16.B Death

1) Results of a population-based, retrospective cohort study demonstrated that the use of conventional antipsychotics was associated with an even greater risk for death than atypical antipsychotics when administered to elderly patients (aged 66 years and older) with dementia. Atypical versus no antipsychot use and conventional versus atypical antipsychotic use pair-wise comparisons were made. A total of 27,259 matched pairs were identified and the dementia cohort was stratified based on place of residence (community versus long-term care facilities). In order to adjust for difference in baseline health status, propensity score matching was used. The primary outcome of the study was all-cause mortality. The risk for death was evaluated at 30, 60, 120, and 180 days after the antipsychotic medications were initially dispensed. There was a statistically significant increase in the risk for death at 30 days associated with n use of atypical antipsychotic medications compared with nonuse in both the community-dwelling cohort (adjusted hazard ratio (HR), 1.31 (95% confidence interval (CI), 1.02 to 1.70); absolute risk difference, 0. percentage point) and long-term care cohort (adjusted HR, 1.55 (95% CI, 1.15 to 2.07); absolute risk difference, 1.2 percentage points). For both cohorts, the risk associated with atypical antipsychotics appeared to persist to 180 days. The risk for death associated with conventional antipsychotics was ever greater than the risk identified with atypical antipsychotics. At 30 days, the adjusted HR for the communit dwelling cohort was 1.55 (95% CI, 1.19 to 2.02) and 1.26 (95% CI, 1.04 to 1.53) for the long-term care cohort (adjusted risk difference for both was 1.1 percentage points). The risk appeared to persist to 180 days for both groups. Some important limitations to the study include unknown or unmeasured confound may influence the results and cause of death could not be examined (Gill et al, 2007).

2) Results of a population-based, retrospective cohort study demonstrated comparable to possibly great risk of death associated with the use of conventional antipsychotic medications in the elderly (aged 65 years and older) compared with atypical antipsychotic medications. The analysis excluded patients with cancer and included only new users of antipsychotic medications. The primary study outcome was 180-c all-cause mortality. A set of potential confounders was measured based on healthcare utilization data wit 6 months before the initiation of antipsychotic medications. Of the 37,241 elderly patients identified, 12,8 and 24,359 received conventional and atypical antipsychotic medications, respectively. The risk of death the conventional drug group within the first 180 days was 14.1% compared with 9.6% in the atypical drug group (unadjusted mortality ratio, 1.47; 95% confidence interval (CI), 1.39 to 1.56). In the multi-variable analysis which controlled for potential confounders, the adjusted mortality ratio for the risk of death within 180 days for conventional versus atypical drug therapy was 1.32 (95% CI, 1.23 to 1.42). When the most frequently prescribed conventional antipsychotic drugs were compared with risperidone, the mortality rat associated with haloperidol was 2.14 (95% CI, 1.86 to 2.45) and loxapine was 1.29 (95% CI, 1.19 to 1.40 while there was no difference associated with olanzapine. The increased mortality risk for conventional versus atypical drug therapy was greatest when doses higher (above median) doses were used (mortalit ratio 1.67; 95% CI, 1.5 to 1.86) and also during the first 40 days of therapy (mortality ratio 1.6; 95% CI, 1 to 1.8). Confirmatory analyses consisting of multi-variable Cox regression, propensity score, and instrumental variable estimation confirmed the results of the study (Schneeweiss et al, 2007).

3) The results of a retrospective cohort study indicate that conventional antipsychotic agents are at leas likely as atypical antipsychotic agents to increase the risk of death among elderly patients 65 years of ag or older. The study included 9,142 new users of conventional agents (mean age, 83.2 years) and 13,748 new users of atypical agents (mean age, 83.5 years). A higher adjusted relative risk of death was associated with the use of conventional antipsychotics as compared with atypical antipsychotics at all tim points studied after beginning therapy (within 180 days: RR, 1.37; 95% CI, 1.27 to 1.49; less than 40 day RR, 1.56; 95% CI, 1.37 to 1.78; 40 to 79 days: RR, 1.37; 95% CI, 1.19 to 1.59; 80 to 180 days: RR, 1.27 95% CI, 1.14 to 1.41). In addition, the adjusted risks of death observed in patients with dementia (RR, 1. 95% CI, 1.15 to 1.45), without dementia (RR, 1.45; 95% CI, 1.3 to 1.63), in a nursing home (RR, 1.26; 95 CI, 1.08 to 1.47), or not in a nursing home (RR, 1.42; 95% CI, 1.29 to 1.56) were also higher with the use conventional antipsychotic therapy as compared with atypical antipsychotic use. This risk appeared to be dose-related and was greater with the use of higher dose (ie, greater than the median) conventional antipsychotics (RR, 1.73; 95% CI, 1.57 to 1.90). Additional studies which specifically investigate the optimum care of elderly patients requiring antipsychotic therapy are needed so that appropriate guidance regarding therapeutic intervention can be provided (Wang et al, 2005).

3.3.16.C Drug dependence

1) Several cases of intentional haloperidol ABUSE have been reported. Five patients treated for haloperidol toxicity had taken the drug for recreational purposes. All experienced severe extrapyramidal side effects. No reason was given for the choice of this agent for recreational use (Doenecke & Heuermann, 1980).

3.3.16.D Extrapyramidal disease

See Drug Consult reference: NEUROLEPTIC-INDUCED EXTRAPYRAMIDAL REACTIONS

3.3.16.E Hyperpyrexia

1) Hyperpyrexia has been reported with haloperidol treatment (Prod Info HALDOL(R) Decanoate IM injection, 2008; Prod Info HALDOL(R) immediate release IM injection, 2008). A case report described hyperpyrexia in a patient treated with haloperidol 2 mg four times daily. The patient was also receiving benztropine concomitantly (Westlake & Rastegar, 1973). The incidence of hyperthermia (37 to 37.9 C)

ranged from 3 to 13% following haloperidol doses of 10 to 15 mg/day (Harder et al, 1971).

3.3.16.F Withdrawal sign or symptom

1) Sudden discontinuation of haloperidol has been associated with a withdrawal syndrome. Tachycardia hypertension, restlessness, and abdominal distress occurred in a patient upon sudden discontinuation of haloperidol 40 mg/day and doxepin 150 mg/day (Pary et al, 1980). This was postulated to be due either cholinergic rebound or a hyperdopaminergic state (Gardos, 1980).

2) Physical agitation, epigastric distress with vomiting, pallor, diaphoresis, and other symptoms occurred days after discontinuation of haloperidol and benztropine. These symptoms persisted until the fifth day, when benztropine alleviated them (Lieberman, 1981).

3.4 Teratogenicity/Effects in Pregnancy/Breastfeeding

A) Teratogenicity/Effects in Pregnancy

1) U.S. Food and Drug Administration's Pregnancy Category: Category C (Prod Info HALDOL(R) injection, 2007) (All Trimesters)

a) Either studies in animals have revealed adverse effects on the fetus (teratogenic or embryocidal or other) and there are no controlled studies in women or studies in women and animals are not available. Drugs should be given only if the potential benefit justifies the potential risk to the fetus.

2) Australian Drug Evaluation Committee's (ADEC) Category: C(Australian Drug Evaluation Committee, 199

a) Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible. Accompanying texts should be consulted for further details.

See Drug Consult reference: PREGNANCY RISK CATEGORIES

3) Crosses Placenta: Unknown

4) Clinical Management

a) Although the teratogenicity of haloperidol has not been proven, its use during pregnancy is discourag It is suggested that haloperidol use during pregnancy be limited to psychotic patients requiring long-term therapy (Berkowitz et al, 1981). If use during pregnancy cannot be avoided, ultrasound with particular attention to limb formation should be considered in first trimester exposures (Diav-Citrin et al, 2005).

5) Literature Reports

a) A prospective, observational study of 54 women (mean age, 30.7 years), recruited from the Emory Women's Mental Health program exposed to antipsychotic medication during pregnancy, showed permeability of the placental barrier. Outcomes were determined by maternal and umbilical cord blood samples taken at delivery and through data collected from maternal reports and medical records. Placen passage ratios (defined as the ratio of umbilical cord to maternal plasma concentrations) showed a significant difference between antipsychotic medications, with olanzapine 72.1% (95% CI, 46.8%-97.5%) being the highest, followed by haloperidol 65.5% (95% CI, 40.3%-90.7%), risperidone 49.2% (95% CI, 13.6%-84.8%), and quetiapine 24.1% (95% CI, 18.7%-29.5%), showing the lowest placental passage rat There was a greater frequency of pre-term deliveries (21.4%, p=less than 0.23), low birth weights (30.8% p=less than 0.07), and neonatal intensive care admission (30.8%, p=less than 0.09) in infants exposed t olanzapine (Newport et al, 2007).

b) A multicenter, prospective, controlled study found no difference in the rate of congenital abnormalities the drug-exposed group and the control group. Haloperidol exposure occurred in 188 pregnancies and penfluridol in 27, with 161 of these known to be in the first trimester. The control group consisted of 631 pregnancies exposed to nonteratogens from 4 participating ENTIS (European Network of Teratology Information Services) centers. Other results include a higher rate of elective pregnancy terminations, hig rate of preterm birth, lower median birth rate and lower median birth weight of full-term infants in the drug exposed group. There were no significant differences in the rate of miscarriages, ectopic pregnancies or stillbirths between the control and haloperidol- or penfluridol-exposed groups(Diav-Citrin et al, 2005).

c) One case report describes a full-term, 3880 gram infant exposed to haloperidol in utero, who experienced "jitteriness" at birth. The mother, a 35-year-old woman with schizoaffective disorder, was maintained on haloperidol decanoate 200 mg every two weeks throughout pregnancy. The last dose was administered 3 weeks prior to delivery. By day 8 of life, the infant became increasingly irritable and experienced an episode of tonic-clonic movements in all extremities with tongue thrusting and torticollis. These episodes continued, but with treatment of clonazepam 0.02mg/kg/day, the tonic-clonic movement began to resolve by day 12. The infant was discharged following resolution of movement disorders and weaning of the clonazepam (Collins & Comer, 2003).

d) A 34-year-old pregnant woman ingested 300 mg haloperidol at 34 weeks gestation and presented CN depression, hypotonia, and involuntary spasms of the extremities. A biophysical profile of the fetus on admission was 2 of 10 (two points for amniotic fluid, no evidence of fetal movement, flexion-extension or fetal breathing, fetal heart rate 150 beats/minute, nonreactive with minimal long-term and short-term variability). The mother appeared fully recovered by 48 hours after admission, but a biophysical profile of was not achieved for the fetus until 5 days after admission. A healthy girl was delivered at 39 weeks gestation and she had normal developmental milestones and growth at 18 months of age (Hansen et al, 1997).

e) Although there are isolated cases of teratogenicity associated with haloperidol (McCullar & Heggenes 1975), no cause-effect relationship has been established. Haloperidol is transferred to the fetus via the placenta (Uematsu et al, 1991). Two cases of limb malformations have occurred in infants born to wome

given haloperidol with other potentially teratogenic drugs during the first trimester of pregnancy (Kopelma et al, 1975). Haloperidol has been used in the second and third trimesters, and during labor, without causing neonatal depression or other effects on the newborn (Ayd, 1976).

B) Breastfeeding

1) American Academy of Pediatrics Rating: Drugs for which the effect on nursing infants is unknown but may be of concern. (Anon, 2001)

2) World Health Organization Rating: Avoid breastfeeding if possible. Monitor infant for side effects. (Anon, 2002)

3) Thomson Lactation Rating: Infant risk cannot be ruled out.

a) Available evidence and/or expert consensus is inconclusive or is inadequate for determining infant ris when used during breastfeeding. Weigh the potential benefits of drug treatment against potential risks before prescribing this drug during breastfeeding.

4) Clinical Management

a) Haloperidol is excreted into human breastmilk, with a milk to plasma ratio estimated at 0.6 to 0.7 (Whalley et al, 1981). One group reported that the nursing infant receives a dose approximately equivale to 3% of the maternal dose (Yoshida et al, 1998). It is suggested that when the maternal dose is high, th infant's exposure to the drug may be minimized by limiting the number of feeds per day. There has been clear association between the small quantities of haloperidol in breastmilk and adverse effects in the exposed newborns (Whalley et al, 1981; Stewart et al, 1980), although a decline in developmental score has been reported (Anon, 2001).

5) Literature Reports

a) Animal studies have demonstrated that offspring exposed to haloperidol through breast milk experien drowsiness and impairment of motor activity (Iqbal et al, 2001).

b) A wide variation of haloperidol excretion into breast milk has been reported. This is most likely due to the different maternal doses and inter-individual variation in drug metabolism (Chisholm & Kuller, 1997). One study reported a breast milk concentration of 23.5 ng/mL following the administration of haloperidol milligrams twice daily (Whalley et al, 1981). The antipsychotic dose of haloperidol in children ranges from 0.02 to 0.07 milligrams/kilogram/day (Serrano, 1981). Assuming a newborn infant (3 kg) ingests 150 mL/kg/day of breast milk, the maximum dose received would be 0.01 milligram or one-sixth the therapeu dose. Another author reported a breast milk concentration of only 2 to 5 ng/mL following a maternal haloperidol dose of 12 to 30 mg/day (Stewart et al, 1980).

3.5 Drug Interactions

Drug-Drug Combinations

Intravenous Admixtures

3.5.1 Drug-Drug Combinations

Acecainide

Ajmaline

Amiodarone

Amisulpride

Amitriptyline

Amoxapine

Aprindine

Arsenic Trioxide

Astemizole

Azimilide

Belladonna

Belladonna Alkaloids

Benztropine

Bepridil

Betel Nut

Bretylium

Bupropion

Cabergoline

Carbamazepine

Chloral Hydrate

Chloroquine

Chlorpromazine

Cisapride

Clarithromycin

Dalfopristin

Dehydroepiandrosterone

Desipramine

Dextromethorphan

Dibenzepin

Dicumarol

Disopyramide

Dofetilide

Dolasetron

Doxepin

Droperidol

Encainide

Enflurane

Erythromycin

Flecainide

Fluconazole

Fluoxetine

Fluvoxamine

Foscarnet

Gemifloxacin

Halofantrine

Halothane

Hydroquinidine

Ibutilide

Imipramine

Isoflurane

Isradipine

Kava

Levodopa

Levomethadyl

Lidoflazine

Lithium

Lithospermum

Lorcainide

Mefloquine

Mesoridazine

Methyldopa

Nefazodone

Nortriptyline

Octreotide

Olanzapine

Pentamidine

Phenylalanine

Pimozide

Pirmenol

Prajmaline

Probucol

Procainamide

Prochlorperazine

Procyclidine

Propafenone

Propranolol

Protriptyline

Quetiapine

Quinupristin

Rifampin

Rifapentine

Risperidone

Sematilide

Sertindole

Sotalol

Sparfloxacin

Spiramycin

Sulfamethoxazole

Sultopride

Tacrine

Tedisamil

Telithromycin

Terfenadine

Tetrabenazine

Thioridazine

Tramadol

Trifluoperazine

Trihexyphenidyl

Trimethoprim

Trimipramine

Vasopressin

Venlafaxine

Vitex

Ziprasidone

Zolmitriptan

Zotepine

3.5.1.A Acecainide

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Concurrent use of acecainide and haloperidol is not recommended due to the risk of additi effects on the QT interval. If concurrent use cannot be avoided, cautious dosing and telemetric monitorin is advised (Yamreudeewong et al, 2003a).

3) Severity: major

4) Onset: rapid

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of acecainide and haloperidol is not recommend due to the potential for inducing life-threatening arrhythmias. If concurrent use cannot be avoided, cautio dosing and telemetric monitoring is advised.

7) Probable Mechanism: additive QT prolongation

8) Literature Reports

a) Class III antiarrhythmics have been shown to prolong the QT interval, which may result in ventricular tachycardia, ventricular fibrillation, and torsades de pointes. Several antipsychotic agents have demonstrated QT prolongation including haloperidol (O'Brien et al, 1999a). Concomitant use o Class III antiarrhythmic agents such as acecainide and haloperidol may have additive effects on the QT interval and is not recommended (Yamreudeewong et al, 2003).

3.5.1.B Ajmaline

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Several antipsychotic agents have demonstrated QT prolongation including amisulpride, haloperidol, iloperidone, paliperidone, quetiapine, risperidone, sertindole, sultopride, ziprasidone, and zotepine (Prod Info FANAPT(TM) oral tablets, 2009; Prod Info Solian(R), 1999z; O'Brien et al, 1999r; Pro Info INVEGA(TM) extended-release oral tablets, 2006; Owens, 2001z; Duenas-Laita et al, 1999y; Agelin et al, 2001x; Lande et al, 1992z; Prod Info GEODON(R) intramuscular injection, oral capsule, 2005; Sweetman, 2003). Because Class IA antiarrhythmic agents may also prolong the QT interval and increas the risk of arrhythmias, the concurrent administration of antipsychotics with a drug from this class is not recommended (Prod Info FANAPT(TM) oral tablets, 2009; Prod Info Quinaglute(R), 1999).

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: The concurrent administration of a Class IA antiarrhythmic and an antipsychoti not recommended.

7) Probable Mechanism: additive cardiac effects

8) Literature Reports

a) In an open-label QTc study of patients with schizophrenia or schizoaffective disorder (n=160), iloperidone 12 mg twice a day was associated with QTc prolongation of 9 msec (Prod Info FANAPT

(TM) oral tablets, 2009).
b) QRS widening, QTc interval prolongation, and torsades de pointes may occur with disopyramide therapy (Prod Info Norpace(R), 1997).
c) The effects of combined therapy with quinidine (Class IA antiarrhythmic agent) and haloperidol (antipsychotic agent) were studied by giving 12 healthy volunteers haloperidol 5 mg alone and with 250 mg of quinidine bisulfate. The study demonstrated significant increases in the plasma concentrations of haloperidol when given concurrently with quinidine versus haloperidol treatment alone. The mean area under the concentration curve (AUC) was increased from 54.3 ng/h/mL on haloperidol alone to 103.2 ng/h/mL on combined therapy. The peak concentration (Cmax) also show an increase from 1.9 ng/mL on haloperidol to 3.8 ng/mL on combined therapy. Half-life (T1/2) and tir to peak concentration (Tmax) were not significantly changed, thereby suggesting to the authors that tissue binding mechanism is more likely responsible for the plasma level changes than an eliminatio alteration (Young et al, 1993).

3.5.1.C Amiodarone
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Concurrent use of amiodarone and haloperidol is not recommended due to the risk of additive effects on the QT interval. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised (Yamreudeewong et al, 2003a).
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of amiodarone and haloperidol is not recommended due to the potential for inducing life-threatening arrhythmias. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised.
7) Probable Mechanism: additive QT prolongation
8) Literature Reports
a) Patients who received concurrent administration of amiodarone and haloperidol experienced a potentially significant QTc interval prolongation. All adult patients admitted to a tertiary teaching hospital between January 2005 and December 2006 who received both amiodarone and haloperido were included in a retrospective analysis of data collected to assess patients' risk, cardiac effects, a baseline statistics to determine change in QT interval. Of the 49 patients (age, 68 +/- 10 years) who met inclusion criteria, there were 381 amiodarone and haloperidol distinct exposures, of which 36.2 (138 of 381) exposures included at least one additional QT-interval prolonging drug. Duration of concomitant amiodarone-haloperidol exposure per patient averaged 3 days (range, 1 to 17 days), a the daily dose of haloperidol was 11 +/- 12 mg (range, 1 to 65 mg). There was no apparent affiliatior between longer QTc intervals and the increased number of concomitant QT-interval prolonging drug but QTc intervals were longer with higher daily doses on average. Nearly 55% of patients receiving amiodarone alone had a QTc interval greater than 450 msec and 38% patients had a QTc interval greater than 500 msec. The mean increase in QTc interval following exposure to haloperidol was 9.8 msec (95% CI, 0.6 to 19 msec). Notably, no ventricular arrhythmia was observed (Bush et al, 2008).
b) Class III antiarrhythmics have been shown to prolong the QT interval, which may result in ventricular tachycardia, ventricular fibrillation, and torsades de pointes. Several antipsychotic agents have demonstrated QT prolongation including haloperidol (O'Brien et al, 1999a). Concomitant use o Class III antiarrhythmic agents such as amiodarone and haloperidol may have additive effects on th QT interval and is not recommended (Yamreudeewong et al, 2003).

3.5.1.D Amisulpride
1) Interaction Effect: cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Haloperidol is associated with QTc prolongation and torsade de pointes (Hassaballa & Bal 2003c; Prod Info Haldol(R), 2001a). Amisulpride has rarely caused QT prolongation (Prod Info Solian(R) 1999e). Caution is advised with coadministration of drugs that potentially prolong the QTc interval.
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Caution is advised if haloperidol and amisulpride are used concomitantly. Scre patients for conditions that may predispose to QT prolongation and torsade de pointes (i.e. cardiomyopathy, alcohol abuse, hypothyroidism). Monitor the ECG and electrolytes at baseline and throughout therapy.
7) Probable Mechanism: additive effects on QT prolongation
8) Literature Reports
a) Numerous case reports have described significant QTc prolongation and torsades de pointes (Tc associated with haloperidol. Hemodynamically significant ventricular tachyarrhythmias, ventricular fibrillation, asystole, and death have been reported. The risk of TdP appears to be greater with intravenous haloperidol, but has occurred with oral and intramuscular use. The risk increases with doses greater than 35 milligrams (mg) over 24 hours, although TdP has been associated with a dos as low as 10 mg administered intravenously over 4 hours. To prevent haloperidol-induced TdP, scre

patients for a history of dilated cardiomyopathy or alcohol abuse, testing for hypothyroidism before therapy, obtaining an electrocardiogram at baseline and throughout therapy, and monitoring potassium, magnesium, and calcium. In patients with a baseline QTc greater than 450 milliseconds (msec), haloperidol should be used cautiously or an alternative agent should be used. Discontinue haloperidol if the QTc increases more than 25% from baseline or if flattening of T-waves or development of U-waves occurs (Hassaballa & Balk, 2003b).

b) Seven patients developed torsade de pointes after therapeutic use of haloperidol in high doses. Three patients developed the dysrhythmia after administration of 211 milligrams (mg) to 825 mg haloperidol over 1 to 2 days for agitated delirium. These 3 patients recovered from the initial episode but 1 patient subsequently died of cardiac arrest upon readministration of haloperidol (Metzger & Friedman, 1993b; Wilt et al, 1993a). Torsades de pointes developed in 8 of 223 critically ill patients i intensive care units. Patients who received intravenous haloperidol greater than 35 mg/day or had a QTc interval prolongation of greater than 500 milliseconds were at greatest risk (Sharma et al, 1998

3.5.1.E Amitriptyline

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999b), haloperidol (O'Brien et al, 1999b), risperidone (Duenas-Laita et al, 1999b), sertindole (Agelink et al, 2001a), quetiapine (Owens, 2001b), sultopride (Lande et al, 1992a), and zotepi (Sweetman, 2003). Even though no formal drug interaction studies have been done, the coadministratio a tricyclic antidepressant and an antipsychotic is not recommended (Prod Info Pamelor(R), 2001; Marsh & Forker, 1982).

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of a tricyclic antidepressant and an antipsychoti not recommended.

7) Probable Mechanism: additive cardiac effects

8) Literature Reports

a) Electrocardiographic changes that have occurred during clinical trials with pimozide have include prolongation of the corrected QT interval, flattening, notching, and inversion of the T wave and the appearance of U waves. In experimental studies, sudden, unexpected deaths have occurred while patients were receiving pimozide doses of 1 mg/kg. The proposed mechanism for these deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmias (Prod Info Orap(R), 1999).

3.5.1.F Amoxapine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999b), haloperidol (O'Brien et al, 1999b), risperidone (Duenas-Laita et al, 1999b), sertindole (Agelink et al, 2001a), quetiapine (Owens, 2001b), sultopride (Lande et al, 1992a), and zotepi (Sweetman, 2003). Even though no formal drug interaction studies have been done, the coadministratio a tricyclic antidepressant and an antipsychotic is not recommended (Prod Info Pamelor(R), 2001; Marsh & Forker, 1982).

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of a tricyclic antidepressant and an antipsychoti not recommended.

7) Probable Mechanism: additive cardiac effects

8) Literature Reports

a) Electrocardiographic changes that have occurred during clinical trials with pimozide have include prolongation of the corrected QT interval, flattening, notching, and inversion of the T wave and the appearance of U waves. In experimental studies, sudden, unexpected deaths have occurred while patients were receiving pimozide doses of 1 mg/kg. The proposed mechanism for these deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmias (Prod Info Orap(R), 1999).

3.5.1.G Aprindine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Coadministration of haloperidol with other drugs that potentially prolong the QTc interval, such as aprindine, should be approached with caution. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised (Owens, 2001f; Prod Info Haldol(R), 1998b; Larochelle et al, 1984).

3) Severity: major

4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of aprindine and haloperidol is not recommende due to the potential for inducing life-threatening arrhythmias. If concurrent use cannot be avoided, cautio dosing and telemetric monitoring is advised.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.H Arsenic Trioxide

1) Interaction Effect: prolongation of the QTc interval and/or torsades de pointes
2) Summary: Arsenic trioxide can prolong the QT interval in some patients, which may result in ventricul tachycardia, ventricular fibrillation, and torsades de pointes and should not be administered with other drugs that may prolong the QT interval (Prod Info Trisenox(R), 2001a). Several antipsychotic agents hav demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999o), haloperidol (O'Brien e al, 1999j), paliperidone (Prod Info INVEGA(TM) extended-release oral tablets, 2006), risperidone (Duena Laita et al, 1999p), sertindole (Agelink et al, 2001m), quetiapine (Owens, 2001p), sultopride (Lande et al 1992o), ziprasidone (Prod Info GEODON(R) intramuscular injection, oral capsule, 2005), and zotepine (Sweetman, 2003).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of arsenic trioxide and antipsychotics is not recommended.
7) Probable Mechanism: additive effects on QTc prolongation
8) Literature Reports
a) QT/QTc prolongation should be expected during treatment with arsenic trioxide and torsade de pointes as well as complete heart block has been reported. Over 460 ECG tracings from 40 patients with refractory or relapsed APL treated with arsenic trioxide were evaluated for QTc prolongation. Sixteen of 40 patients (40%) had at least one ECG tracing with a QTc interval greater than 500 mse Prolongation of the QTc was observed between 1 and 5 weeks after arsenic trioxide infusion, and th returned towards baseline by the end of 8 weeks after arsenic trioxide infusion. In these ECG evaluations, women did not experience more pronounced QT prolongation than men, and there was no correlation with age (Prod Info Trisenox(R), 2001).

3.5.1.I Astemizole

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999n), haloperidol (O'Brien et al, 1999i), quetiapine (Owens, 2001o), risperidone (Duenas-Laita et al, 1999m; Prod Info Risperdal(R) risperidone, 2002a), sertindole (Agelink et al, 2001l), sultopride (Lande et al, 1992l), and zotepine (Sweetman, 2003). Even though no formal drug interaction studies have been done, the coadministration of astemizole and other drugs known to prolong the QTc interval, including antipsychotics, is not recommended (Prod Info Hismanal(R), 1996).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of astemizole and agents that prolong the QT interval, such as antipsychotics, is not recommended.
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) A total of 7 patients developed torsade de pointes after therapeutic use of haloperidol in high dos (Metzger & Friedman, 1993g; Wilt et al, 1993e). Three patients developed the dysrhythmia after administration of 211 to 825 mg haloperidol over 1 to 2 days for agitated delirium. These 3 patients recovered from the initial episodes, but 1 patient subsequently died of cardiac arrest upon readministration of haloperidol. Four patients developed the dysrhythmia after administration of 170 580 mg over 1 to 4 days for delirium associated with bacterial meningitis (1), status asthmaticus (2) respiratory insufficiency (1). All 4 patients recovered with no adverse sequelae.

3.5.1.J Azimilide

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Concurrent use of azimilide and haloperidol is not recommended due to the risk of additive effects on the QT interval. If concurrent use cannot be avoided, cautious dosing and telemetric monitorin is advised (Yamreudeewong et al, 2003a).
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of azimilide and haloperidol is not recommende due to the potential for inducing life-threatening arrhythmias. If concurrent use cannot be avoided, cautio

dosing and telemetric monitoring is advised.
7) Probable Mechanism: additive QT prolongation
8) Literature Reports
a) Class III antiarrhythmics have been shown to prolong the QT interval, which may result in ventricular tachycardia, ventricular fibrillation, and torsades de pointes. Several antipsychotic agents have demonstrated QT prolongation including haloperidol (O'Brien et al, 1999a). Concomitant use o Class III antiarrhythmic agents such as azimilide and haloperidol may have additive effects on the Q interval and is not recommended (Yamreudeewong et al, 2003).

3.5.1.K Belladonna
1) Interaction Effect: excessive anticholinergic activity (severe dry mouth, constipation, decreased urination, excessive sedation, blurred vision)
2) Summary: The anticholinergic activity of the active alkaloids present in belladonna may predispose th patient to excessive anticholinergic activity if taken with haloperidol. Belladonna contains L-hyoscyamine atropine, and scopolamine with a total alkaloid content of at least 0.3% in the leaves and 0.5% in the roo (Blumenthal et al, 1998). Because belladonna is typically available as a homeopathic preparation, the clinical severity of the interaction with haloperidol is unknown. Caution is advised.
3) Severity: minor
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Excessive anticholinergic activity may be manifested by dry mouth, constipatio urinary retention, tachycardia, decreased sweating, mydriasis, blurred vision, elevated temperature, muscular weakness, and sedation. If such effects are noted, belladonna should be discontinued immediately. In severe cases, paralytic ileus, confusion, psychoses, agitation, delusions, delirium, and paranoia may be encountered as well as tachycardia, dysrhythmia, and hypertension. In severe cases, immediate medical attention should be obtained.
7) Probable Mechanism: additive anticholinergic effect

3.5.1.L Belladonna Alkaloids
1) Interaction Effect: excessive anticholinergic activity (severe dry mouth, constipation, decreased urination, excessive sedation, blurred vision)
2) Summary: The anticholinergic activity of the active alkaloids present in belladonna may predispose th patient to excessive anticholinergic activity if taken with haloperidol. Belladonna contains L-hyoscyamine atropine, and scopolamine with a total alkaloid content of at least 0.3% in the leaves and 0.5% in the roo (Blumenthal et al, 1998). Because belladonna is typically available as a homeopathic preparation, the clinical severity of the interaction with haloperidol is unknown. Caution is advised.
3) Severity: minor
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Excessive anticholinergic activity may be manifested by dry mouth, constipatio urinary retention, tachycardia, decreased sweating, mydriasis, blurred vision, elevated temperature, muscular weakness, and sedation. If such effects are noted, belladonna should be discontinued immediately. In severe cases, paralytic ileus, confusion, psychoses, agitation, delusions, delirium, and paranoia may be encountered as well as tachycardia, dysrhythmia, and hypertension. In severe cases, immediate medical attention should be obtained.
7) Probable Mechanism: additive anticholinergic effect

3.5.1.M Benztropine
1) Interaction Effect: excessive anticholinergic effects (sedation, constipation, dry mouth)
2) Summary: Combined use of haloperidol and anticholinergics may result in excessive anticholinergic effects (Prod Info Haldol(R), 2000a). In a number of case reports, the use of haloperidol with benztropine trihexyphenidyl, or procyclidine, has resulted in a worsening of schizophrenic symptoms. In addition, whe anticholinergics are used with phenothiazines or haloperidol, there may be an increased incidence of tardive dyskinesia (Linnoila et al, 1980a; Singh & Kay, 1979a).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor signs of excessive anticholinergic effects. Adjust the doses or discontir the medications as needed.
7) Probable Mechanism: additive anticholinergic effects
8) Literature Reports
a) Concomitant haloperidol and benztropine therapy has been reported to result in inhibition of antipsychotic effects of haloperidol and increased "social avoidance" behavior in several schizophre patients (Singh & Smith, 1973; Prod Info Cogentin(R), 1994).
b) Routine use of antiparkinson medication with neuroleptic agents is controversial and there is evidence that these agents should only be administered at the occurrence of extrapyramidal symptoms, and then only for a short period of time thereafter. This interaction, although not well-documented, supports recommendations by many investigators that routine use of anticholinergic

medications with phenothiazines and haloperidol is not warranted and may be deleterious (Perry et 1991).

c) In a study to evaluate the prophylactic use of benztropine in haloperidol-induced dystonic reactio 29 psychotic patients were treated with haloperidol and either benztropine or a placebo. The results showed no significant difference in side-effects between benztropine or the placebo, except increas dry mouth with benztropine. The occurrence of dystonic reactions with the use of benztropine dropp from 33% to 14%. The researchers conclude that the increased side-effects of benztropine are of litt consequence when compared to the positive effects of the drug (Goff et al, 1991b).

d) Acute intestinal pseudo-obstruction may occur in patients receiving benztropine and haloperidol concomitantly. A 68-year-old female with mild multi-infarct dementia developed acute intestinal pseudo-obstruction after receiving 2 doses of benztropine to treat extrapyramidal symptoms associated with haloperidol therapy. Treatment with haloperidol 0.5 mg 3 times daily was initiated af the patient developed psychotic behavior and agitation. She was hospitalized three days later with extrapyramidal symptoms and was treated with intravenous benztropine. Her abdomen became significantly distended within 3-4 hours. Upon examination, she was dehydrated and had reduced bowel sounds. Dilation of her large bowel and some distention of her small bowel loops were appare on x-ray. Haloperidol and benztropine were discontinued and supportive therapy was initiated. Her abdominal distention had resolved within 24 hours. Benztropine may acutely potentiate the effect of haloperidol, causing acute pseudo-obstruction (Sheikh, 2001).

3.5.1.N Bepridil

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Some antipsychotic agents prolong the QT interval and an additive effect would be anticipated if administered with other agents which lengthen the QT interval (Prod Info Geodon(TM), 200 Agelink et al, 2001c; Owens, 2001d; Prod Info Orap(R), 1999b; Prod Info Haldol(R), 1998a). In U.S. clini trials, bepridil increased QT and QTc intervals which was associated with torsades de pointes in approximately 1% of patients. Other drugs that increase the QT interval may exaggerate the prolongatio the QT interval observed with bepridil (Prod Info Vascor(R), 1997). Pimozide is contraindicated in patient taking other drugs which may prolong the QT interval (Prod Info Orap(R), 1999b).

3) Severity: contraindicated

4) Onset: rapid

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of antipsychotics and agents that prolong the QT interval, such as bepridil, is contraindicated. In particular, pimozide is contraindicated in individuals with congenital QT syndrome, patients with a history of cardiac arrhythmias, or patients taking other drugs wh may prolong the QT interval.

7) Probable Mechanism: additive effects on QT prolongation

8) Literature Reports

a) Electrocardiographic changes that have occurred during clinical trials with pimozide have include prolongation of the corrected QT interval, flattening, notching, and inversion of the T wave and the appearance of U waves. In experimental studies, sudden, unexpected deaths have occurred while patients were receiving pimozide doses of 1 mg/kg. The proposed mechanism for these deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmias (Prod Info Orap(R), 1999a).

b) Sometimes fatal QRS prolongation and QTc prolongation have been reported in patients taking risperidone therapeutically (Duenas-Laita et al, 1999c; Ravin & Levenson, 1997).

3.5.1.O Betel Nut

1) Interaction Effect: increased extrapyramidal side effects of haloperidol (difficulty with movement or abnormal movement of muscles)

2) Summary: Case reports have described increased extrapyramidal side effects when betel nut was chewed by patients taking fluphenazine and fluphenthixol for schizophrenia (Deahl, 1989a). The extrapyramidal effects were not improved with anticholinergic therapy with procyclidine, and resolved wit betel nut discontinuation (Deahl, 1989a). A similar effect may occur if betel nut is chewed with concomita haloperidol therapy. The cholinergic activity of betel nut has been attributed to the arecoline content. Wh given with peripheral anticholinergics, arecoline increased the heart rate due to central muscarinic agoni activity (Nutt et al, 1978a). Case reports suggest the onset of betel nut activity to be within 3 weeks with resolution within 4 to 7 days after discontinuation (Deahl, 1989a).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: It is unclear to what extent the cholinergic effect of betel nut may increase the incidence of extrapyramidal side effects of haloperidol, especially if patients are treated with anticholiner agents to control these side effects. Deterioration in symptoms of patients with Parkinson's disease or ot extrapyramidal movement disorders may be expected. Persons who have been chewing betel nut have characteristic red stain on the teeth which may help the clinician discover betel nut use.

7) Probable Mechanism: cholinergic effect of betel nut

8) Literature Reports

a) Within 3 weeks of initiating betel nut chewing, a 51-year-old Indian man experienced marked rigidity, bradykinesia, and jaw tremor. This patient had been stabilized for the previous 2 years on fluphenazine decanoate depot 50 milligrams (mg) every 3 weeks for schizophrenia and procyclidine mg twice daily for a mild Parkinsonian tremor. Within one week of discontinuation of betel nut chewi the patient's condition returned to baseline. This report appears to demonstrate decreased anticholinergic effects of procyclidine when coadministered with betel nut (Deahl, 1989).

b) Following betel nut ingestion, a 45-year-old Indian man developed akathisia, tremor and stiffness which was not affected by dosage escalations of up to 20 mg daily of procyclidine. This patient had been previously stabilized on fluphenthixol 60 mg depot every two weeks for the previous year for schizoaffective disorder without extrapyramidal side effects. His symptoms resolved over 4 days afte discontinuing betel nut. It appears that the anticholinergic effects of procyclidine were diminished wh betel nut was chewed concomitantly (Deahl, 1989).

c) High doses (5 mg, 10 mg, and 20 mg) of subcutaneous (SC) arecoline given one hour after SC administration of 0.5 mg of the peripheral anticholinergic agent methscopolamine increased the hea rate and blood pressure of six patients with Huntington's disease. Significant increases in blood pressure occurred at doses of 5 mg, 10 mg (p less than 0.01) and 20 mg (p less than 0.05). Heart ra increased at doses of 5 mg and 20 mg (p less than 0.01), and 10 mg (p less than 0.05). Subjective effects in some patients included tremor, flushing or pallor at the time of peak drug effect and nause weakness, and mental changes at the higher doses. No peripheral cholinergic effects were noted. T results indicated a central muscarinic effect for arecoline (Nutt et al, 1978).

d) A low dose (0.5 mg) of arecoline given intravenously 3 minutes after the peripheral anticholinergi agent glycopyrrolate 0.15 mg to 8 patients with major depressive disorder increased their heart rates The peak heart rate increase in a non-REM portion of the sleep cycle during the 10 minute post-infusion period was 6.75 +/- 12.9 beats per minute for placebo and 25 +/- 10.3 beats per minute for arecoline. The peak heart rates all began 1 to 8 minutes after the arecoline infusion, and the mean heart rate was significantly elevated over placebo from 2 to 10 minutes after arecoline infusion (p les than 0.05) (Abramson et al, 1985).

e) Though chewing betel nut alone does not significantly increase catecholamine levels, a popular betel nut preparation does. Six to eight minutes after chewing betel nut, 4 subjects had only a moderate increase in plasma noradrenaline from 266.2 +/- 105.7 picograms/milliliter (pg/mL) to 313. +/- 92.9 pg/mL (p equal to 0.0607). Combining betel nut with lime, catechu and Piper betel flower as commonly done caused significant elevation of norepinephrine in nine subjects from 292.2 +/- 59.5 pg/mL to 375.1 +/- 130.0 pg/mL (p equal to 0.0244) and epinephrine from 62.5 +/- 23.9 pg/mL to 10 +/- 45.0 pg/mL (p equal to 0.0226). In this group dopamine was also elevated in 8 of 9 subjects, but mean was not significant (Chu, 1995).

3.5.1.P Bretylium

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Concurrent use of bretylium and haloperidol is not recommended due to the risk of additive effects on the QT interval. If concurrent use cannot be avoided, cautious dosing and telemetric monitorin is advised (Yamreudeewong et al, 2003a).

3) Severity: major

4) Onset: rapid

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of bretylium and haloperidol is not recommende due to the potential for inducing life-threatening arrhythmias. If concurrent use cannot be avoided, cautio dosing and telemetric monitoring is advised.

7) Probable Mechanism: additive QT prolongation

8) Literature Reports

a) Class III antiarrhythmics have been shown to prolong the QT interval, which may result in ventricular tachycardia, ventricular fibrillation, and torsades de pointes. Several antipsychotic agents have demonstrated QT prolongation including haloperidol (O'Brien et al, 1999a). Concomitant use o Class III antiarrhythmic agents such as bretylium and haloperidol may have additive effects on the C interval and is not recommended (Yamreudeewong et al, 2003).

3.5.1.Q Bupropion

1) Interaction Effect: increased plasma levels of haloperidol

2) Summary: It is recommended that haloperidol, an antipsychotic metabolized by the cytochrome P450 2D6 isoenzyme, be initiated at the lower end of the dose range when administered concomitantly with bupropion (Prod Info Wellbutrin XL(TM), 2003; Prod Info Zyban(R), 2000).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Coadministration of bupropion and haloperidol should be approached with caution and should be initiated at the lower end of the dose range of haloperidol. If bupropion is added tc the treatment regimen of a patient already receiving haloperidol, consider decreasing the dose of

haloperidol.
7) Probable Mechanism: inhibition of cytochrome P450 2D6-mediated haloperidol metabolism

3.5.1.R Cabergoline
1) Interaction Effect: the decreased therapeutic effect of both drugs
2) Summary: Cabergoline is a long-acting dopamine receptor agonist with a high affinity for dopamine-2 receptors. It should not be administered concomitantly with dopamine-2 antagonists, such as phenothiazines, butyrophenones, thioxanthines, and metoclopramide (Prod Info Dostinex(R), 1996).
3) Severity: moderate
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Cabergoline, a dopamine-2 receptor agonist, should not be used concurrently with a dopamine-2 antagonist, such as haloperidol.
7) Probable Mechanism: antagonistic pharmacologic effects

3.5.1.S Carbamazepine
1) Interaction Effect: decreased haloperidol effectiveness
2) Summary: In a case report, the addition of carbamazepine to patients stabilized with haloperidol resulted in mean reductions of haloperidol levels by 60%. Two other case reports and a clinical study supported this finding, while a third case report did not (Kahn et al, 1990a; Arana et al, 1986a; Fast et al, 1986; Klein et al, 1984; Hesslinger et al, 1999a).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor for the therapeutic efficacy of haloperidol following the addition of carbamazepine; higher haloperidol dosage may be required in some clinical situations.
7) Probable Mechanism: increased cytochrome P450 2D6 and 3A4-mediated haloperidol metabolism
8) Literature Reports
a) Serum haloperidol levels of 14 schizophrenic patients dropped an average of 50% when carbamazepine was added to their therapy. Haloperidol doses ranged from 2 mg to 20 mg daily and the carbamazepine dose was adjusted to yield levels of 8 to 12 mcg/mL. The drop in haloperidol lev resulted in the worsening of one patient's condition. Two patients had significant symptom reduction while on carbamazepine, despite the decrease in the haloperidol levels. Their improvement may hav been due to direct effects of the carbamazepine, or as a secondary effect due to the lowering of the haloperidol levels. The authors recommend monitoring serum medication levels when administering haloperidol in combination with carbamazepine (Kahn et al, 1990).
b) Serum haloperidol levels of seven patients treated for psychosis fell when carbamazepine was added to their therapy. Haloperidol doses ranged from 10 mg to 40 mg daily and carbamazepine do ranged from 400 mg to 1000 mg daily. After carbamazepine was added, haloperidol levels decrease by 19% to 100%. The two patients whose blood levels fell to undetectable levels had a marked worsening of symptoms. Careful monitoring should take place if carbamazepine is added to haloper therapy (Arana et al, 1986).
c) Concomitant administration of haloperidol and carbamazepine as reported to result in neurotoxic (drowsiness, slurred speech, concentration difficulties) in a 37-year-old woman with cerebral palsy a dipolar disorder (Brayley & Yellowlees, 1987). Withdrawal of carbamazepine resulted in subsidence symptoms on this second occasion. It is speculated that the interaction occurred at the level of the CNS, as opposed to toxic effects of either drug alone, as carbamazepine serum levels were subtherapeutic during the toxic episodes and due to the fact that carbamazepine is reported to enhance haloperidol metabolism. In addition, the patient received higher doses of carbamazepine following withdrawal of haloperidol without the occurrence of toxic effects. Cerebral palsy may have been a predisposing factor to the interaction.
d) Twenty-seven schizophrenic patients enrolled in a study to determine the effects of carbamazepi and valproic acid on the plasma levels of haloperidol and the psychopathologic outcome. Following four-day washout period, patients were assigned to receive treatment for four weeks with haloperidc monotherapy, haloperidol with carbamazepine, or haloperidol with valproic acid. Doses of haloperidc remained stable throughout the study, and the doses of carbamazepine and valproic acid were titrat to a plasma level of 6 to 12 mg/L and 50 to 100 mg/L, respectively. When administered with carbamazepine, haloperidol plasma levels decreased by 45% (from 7.6 ng/mL to 4.6 ng/mL) over th 28-day period. Decreases in the rating scores on the Positive subscale of the Positive and Negative Syndrome Scale (pPANSS) were significant during the carbamazepine phase of the study, indicatin that the coadministration of carbamazepine and haloperidol may worsen the clinical outcome compared to haloperidol monotherapy (Hesslinger et al, 1999).

3.5.1.T Chloral Hydrate
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Chloral hydrate has been shown to prolong the QTc interval at the recommended therapeu dose (Young et al, 1986). Even though no formal drug interaction studies have been done, the

administration of drugs known to prolong the QTc interval, such as antipsychotics and chloral hydrate is recommended. Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999m), haloperidol (O'Brien et al, 1999h), quetiapine (Owens, 2001n), risperidone (Duenas-Laita et al, 1999l), sertindole (Agelink et al, 2001k), sultopride (Lande et al, 1992k), and zotepin (Sweetman, 2003).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of chloral hydrate and antipsychotics is not recommended.
7) Probable Mechanism: additive effects on QT prolongation
8) Literature Reports
a) The overall incidence of QT interval prolongation with sertindole is estimated at 1.9% to 4%, and the potential risk of developing torsades de pointes has been estimated at 0.13% to 0.21% (Brown & Levin, 1998b). Periodic electrocardiographic monitoring is required in the United Kingdom per sertindole's official labeling (Cardoni & Myer, 1997).
b) A total of 7 patients developed torsade de pointes after therapeutic use of haloperidol in high dos (Metzger & Friedman, 1993f; Wilt et al, 1993d). Three patients developed the dysrhythmia after administration of 211 to 825 mg haloperidol over 1 to 2 days for agitated delirium. These 3 patients recovered from the initial episodes, but 1 patient subsequently died of cardiac arrest upon readministration of haloperidol.

3.5.1.U Chloroquine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Chloroquine has been shown to prolong the QTc interval at the recommended therapeutic dose and an additive effect would be anticipated if administered with other agents which lengthen the QT interval (Prod Info Aralen(R), 2001). Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999w), haloperidol (O'Brien et al, 1999p), quetiapine (Owens 2001x), risperidone (Duenas-Laita et al, 1999w), sertindole (Agelink et al, 2001u), sultopride (Lande et a 1992w), and zotepine (Sweetman, 2004).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of antipsychotics and agents that prolong the QT interval, such as chloroquine is not recommended.
7) Probable Mechanism: additive effect on QT prolongation
8) Literature Reports
a) Sometimes fatal QRS prolongation and QTc prolongation have been reported in patients taking risperidone therapeutically (Duenas-Laita et al, 1999v; Ravin & Levenson, 1997e).

3.5.1.V Chlorpromazine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Concomitant use of phenothiazines and antipsychotic agents may cause additive effects o the QT interval and is not recommended. Q and T wave distortions have been observed in patients takin phenothiazines (Prod Info Compazine(R), 2002; Prod Info Stelazine(R), 2002; Prod Info Thorazine(R), 2002). Other phenothiazines may have similar effects, though no reports are available. Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999k), haloperidol (O'Brien et al, 1999g), paliperidone (Prod Info INVEGA(TM) extended-release oral tablets, 2006), quetiapine (Owens, 2001m), risperidone (Duenas-Laita et al, 1999k), sertindole (Agelink e al, 2001j), sultopride (Lande et al, 1992i), ziprasidone (Prod Info GEODON(R) intramuscular injection, or capsule, 2005), and zotepine (Sweetman, 2003).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of agents that prolong the QT interval, such as phenothiazines and antipsychotics, is not recommended.
7) Probable Mechanism: additive QT prolongation

3.5.1.W Cisapride

1) Interaction Effect: worsening of psychotic symptoms and/or an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Concomitant therapy of cisapride with any drug that prolongs the QT interval, such as haloperidol, is contraindicated (Prod Info Propulsid(R), 2000a). Haloperidol is associated with QTc prolongation and torsade de pointes (Hassaballa & Balk, 2003n; Prod Info Haldol(R), 2001h). No pharmacokinetic interaction was observed in a study of 15 schizophrenic patients taking cisapride with haloperidol, though psychiatric symptoms worsened (Mihara et al, 1999a).

3) Severity: contraindicated
4) Onset: delayed
5) Substantiation: established
6) Clinical Management: The concurrent administration of cisapride and agents that prolong the QT interval, such as haloperidol, is contraindicated.
7) Probable Mechanism: inhibition of haloperidol metabolism by cisapride; accelerated haloperidol absorption; additive effect on QT interval
8) Literature Reports
a) Psychiatric symptoms significantly increased with concomitant cisapride therapy in 15 schizophrenic patients receiving haloperidol, although no pharmacokinetic interaction was observed Patients received cisapride 5 milligrams (mg) twice daily along with haloperidol 12 mg to 36 mg daily for one week. No significant changes in the mean plasma concentrations of haloperidol or reduced haloperidol were observed during cisapride coadministration. Side effects, measured by the UKU rating scale, were not significantly affected. The authors noted that higher doses of cisapride may affect haloperidol concentrations (Mihara et al, 1999).
b) Prolonged QT interval, ventricular arrhythmias, and torsades de pointes have been reported in 2 cases from July 1993 through May 1999. Of these cases, 70 have resulted in death. A majority (85% of patients experiencing cardiotoxicity had risk factors that predisposed them to arrhythmias (Prod Ir Propulsid(R), 2000).
c) Numerous case reports have described significant QTc prolongation and torsades de pointes (Tc associated with haloperidol. Hemodynamically significant ventricular tachyarrhythmias, ventricular fibrillation, asystole, and death have been reported. The risk of TdP appears to be greater with intravenous haloperidol, but has occurred with oral and intramuscular use. The risk increases with doses greater than 35 milligrams (mg) over 24 hours, although TdP has been associated with a dos as low as 10 mg administered intravenously over 4 hours. To prevent haloperidol-induced TdP, scre patients for a history of dilated cardiomyopathy or alcohol abuse, testing for hypothyroidism before therapy, obtaining an electrocardiogram at baseline and throughout therapy, and monitoring potassium, magnesium, and calcium. In patients with a baseline QTc greater than 450 milliseconds (msec), haloperidol should be used cautiously or an alternative agent should be used. Discontinue haloperidol if the QTc increases more than 25% from baseline or if flattening of T-waves or development of U-waves occurs (Hassaballa & Balk, 2003m).

3.5.1.X Clarithromycin
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999d), haloperidol (O'Brien et al, 1999c), quetiapine (Owens, 2001e), risperidone (Duenas-Laita et al, 1999d), sertindole (Agelink et al, 2001d), sultopride (Lande et al, 1992c), and zotepi (Sweetman, 2004). Even though no formal drug interaction studies have been done, concomitant use of clarithromycin and antipsychotic agents may cause additive effects on the QT interval and is not recommended (Prod Info Biaxin(R), 2002).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of clarithromycin and agents that prolong the QT interval, such as antipsychotics, is not recommended.
7) Probable Mechanism: additive effects on QT prolongation
8) Literature Reports
a) A 32-year-old male with schizoaffective disorder and metabolic syndrome experienced a significa increase in plasma concentration following administration of quetiapine. The patient, hospitalized for acute psychotic symptoms was treated with 50 mg quetiapine daily, with a gradual increase in dosag to 700 mg over 10 days. Psychotic symptoms dissipated within 3 weeks. On day 28, the patient developed a lower airway infection, and was orally treated with 750 mg sultamicillin, 500 mg clarithromycin along with his evening dose of quetiapine 400 mg. The following morning, 750 mg sultamicillin, 500 mg clarithromycin, and the morning 300-mg quetiapine dose were given. Within ho the patient became somnolent, and plasma sample testing resulted in 826.8 microgram/L (normal range, 70 to 170 microgram/L). The patient developed severe impaired consciousness and respirato depression. Quetiapine overdose was suspected and treatment was discontinued. Plasma levels we continually measured over the course of a week until complete recovery was achieved (Schulz-Du E et al, 2008).
b) A total of 7 patients developed torsade de pointes after therapeutic use of haloperidol in high dos (Metzger & Friedman, 1993a; Wilt et al, 1993). Three patients developed the dysrhythmia after administration of 211 to 825 mg haloperidol over 1 to 2 days for agitated delirium. These 3 patients recovered from the initial episodes, but 1 patient subsequently died of cardiac arrest upon readministration of haloperidol. Four patients developed the dysrhythmia after administration of 170 580 mg over 1 to 4 days for delirium associated with bacterial meningitis (1), status asthmaticus (2) respiratory insufficiency (1). All 4 patients recovered with no adverse sequelae.
c) Prolongation of the QTc interval was reported in 8 patients receiving risperidone (Prod Info

Risperdal(R) risperidone, 2002).

3.5.1.Y Dalfopristin

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Quinupristin/dalfopristin is a major inhibitor of cytochrome P450 3A4 (CYP3A4) isoenzyme and haloperidol is a CYP3A4 substrate. Coadministration of these two agents may likely result in increas plasma concentrations of haloperidol, which may lead to QTc interval prolongation and risk of torsades d pointes (Prod Info SYNERCID(R) intravenous injection, 2003; Prod Info Haldol(R) Injection, 2001).

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: The concurrent administration of quinupristin/dalfopristin and haloperidol shoul be avoided. Monitor ECG if used concomitantly.

7) Probable Mechanism: inhibition of cytochrome P450 3A4-mediated haloperidol metabolism

3.5.1.Z Dehydroepiandrosterone

1) Interaction Effect: reduced effectiveness of haloperidol

2) Summary: Dehydroepiandrosterone (DHEA) levels within the normal range of 100 to 400 microgram/deciliter (mcg/dL) are conducive to optimal treatment of patients with psychosis (Howard, 1992a). In case reports, patients have been resistant to antipsychotics when DHEA levels were elevated (Howard, 1992a). Patient being treated with haloperidol should avoid DHEA supplementation.

3) Severity: moderate

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: Avoid concomitant use of dehydroepiandrosterone (DHEA) and haloperidol. If DHEA is elevated, treatment with dexamethasone 1 mg orally per day may be used to normalize DHEA levels.

7) Probable Mechanism: elevated dehydroepiandrosterone (DHEA) blood levels may reduce responsiveness to haloperidol

8) Literature Reports

a) A 24-year-old female diagnosed with schizophrenia was resistant to daily doses of haloperidol 20 milligrams (mg), fluphenazine 40 mg, lithium carbonate 1200 mg, and lithium carbonate 900 mg plus thioridazine 300 mg. The patient appeared Cushinoid with moon face, acne, facial hair, abdominal h and a 40 pound weight gain in the previous 8 months. Dehydroepiandrosterone (DHEA) measured a part of an endocrine panel was 725 micrograms/deciliter (mcg/dL) (normal: 100 to 400 mcg/dL). Dexamethasone 1 mg orally at bedtime resulted in substantial improvement within one week. The patient appeared calmer, more alert with improved psychotic symptoms and ability to concentrate. A two weeks, a repeated DHEA level was within normal range (328 mcg/dL). The author concluded th elevated DHEA levels were associated with severe psychosis resistant to conventional antipsychotic therapy (Howard, 1992).

b) A 13-year-old male decompensated with a subsequent two-year period of emotional problems accompanied by heavy use of LSD, hashish, barbiturates, and alcohol. His mental status included bizarre, disorganized, delusional thinking, auditory and visual hallucinations, paranoia, lack of attent to personal hygiene, agitation, and combativeness. He was diagnosed with chronic paranoid schizophrenia; schizophrenia, chronic undifferentiated type, and schizoaffective disorder, excited typ He was resistant to daily doses of trifluoperazine 40 mg, chlorpromazine 400 mg, and imipramine 10 mg. He was also resistant to combination therapy with chlorpromazine 400 mg with thiothixene 80 m thioridazine 1000 mg, perphenazine 48 mg with lithium carbonate 1200 mg, clonazepam 4 mg, and carbamazepine 1200 mg daily. Baseline DHEA level exceeded 900 mcg/dL. A seven-day suppressi test with dexamethasone 1 mg orally at bedtime resulted in a normal DHEA level of 200 mcg/dL. By day 5, psychosis improved and the patient was well-oriented, conversational, and was making good eye contact. Once dexamethasone was discontinued, rapid decompensation and florid psychosis ensued despite "substantial amounts of psychotropic medications." DHEA increased to 536 mcg/dL. The author concluded that elevated DHEA levels were associated with florid psychosis resistant to conventional antipsychotic therapy (Howard, 1992).

3.5.1.AA Desipramine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999b), haloperidol (O'Brien et al, 1999b), risperidone (Duenas-Laita et al, 1999b), sertindole (Agelink et al, 2001a), quetiapine (Owens, 2001b), sultopride (Lande et al, 1992a), and zotepi (Sweetman, 2003). Even though no formal drug interaction studies have been done, the coadministration a tricyclic antidepressant and an antipsychotic is not recommended (Prod Info Pamelor(R), 2001; Marsha & Forker, 1982).

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of a tricyclic antidepressant and an antipsychotic not recommended.
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) Electrocardiographic changes that have occurred during clinical trials with pimozide have include prolongation of the corrected QT interval, flattening, notching, and inversion of the T wave and the appearance of U waves. In experimental studies, sudden, unexpected deaths have occurred while patients were receiving pimozide doses of 1 mg/kg. The proposed mechanism for these deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmias (Prod Info Orap(R), 1999).

3.5.1.AB Dextromethorphan
1) Interaction Effect: exacerbation of dextromethorphan adverse effects (CNS excitement, mental confusion, respiratory depression, nervousness, tremors, insomnia, diarrhea)
2) Summary: Dextromethorphan is metabolized by the cytochrome P450IID6 isoenzyme in humans. Haloperidol is an inhibitor of CYP2D6 (Shen, 1995; Slaughter & Edwards, 1995). Coadministration of dextromethorphan and haloperidol may result in elevated concentrations of dextromethorphan and increased adverse effects.
3) Severity: moderate
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Monitor patient for signs and symptoms of dextromethorphan toxicity (CNS excitement, mental confusion, respiratory depression, nervousness, tremors, insomnia, diarrhea). A reduction of dextromethorphan doses may reduce or resolve adverse effects.
7) Probable Mechanism: inhibition of dextromethorphan metabolism

3.5.1.AC Dibenzepin
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999b), haloperidol (O'Brien et al, 1999b), risperidone (Duenas-Laita et al, 1999b), sertindole (Agelink et al, 2001a), quetiapine (Owens, 2001b), sultopride (Lande et al, 1992a), and zotepi (Sweetman, 2003). Even though no formal drug interaction studies have been done, the coadministratio a tricyclic antidepressant and an antipsychotic is not recommended (Prod Info Pamelor(R), 2001; Marsh & Forker, 1982).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of a tricyclic antidepressant and an antipsychotic not recommended.
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) Electrocardiographic changes that have occurred during clinical trials with pimozide have include prolongation of the corrected QT interval, flattening, notching, and inversion of the T wave and the appearance of U waves. In experimental studies, sudden, unexpected deaths have occurred while patients were receiving pimozide doses of 1 mg/kg. The proposed mechanism for these deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmias (Prod Info Orap(R), 1999).

3.5.1.AD Dicumarol
1) Interaction Effect: decreased anticoagulant effectiveness
2) Summary: Haloperidol may increase the metabolism of dicumarol and reduce the hypoprothrombine effect of oral anticoagulants (Prod Info Dicumarol, 1995).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: In patients receiving oral anticoagulant therapy, the prothrombin time ratio or I (international normalized ratio) should be closely monitored with the addition and withdrawal of treatmen with haloperidol, and should be reassessed periodically during concurrent therapy. Adjustments of the dicumarol dose may be necessary in order to maintain the desired level of anticoagulation.
7) Probable Mechanism: increased dicumarol metabolism

3.5.1.AE Disopyramide
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Several antipsychotic agents have demonstrated QT prolongation including amisulpride, haloperidol, iloperidone, paliperidone, quetiapine, risperidone, sertindole, sultopride, ziprasidone, and

zotepine (Prod Info FANAPT(TM) oral tablets, 2009; Prod Info Solian(R), 1999z; O'Brien et al, 1999r; Pro Info INVEGA(TM) extended-release oral tablets, 2006; Owens, 2001z; Duenas-Laita et al, 1999y; Agelin et al, 2001x; Lande et al, 1992z; Prod Info GEODON(R) intramuscular injection, oral capsule, 2005; Sweetman, 2003). Because Class IA antiarrhythmic agents may also prolong the QT interval and increas the risk of arrhythmias, the concurrent administration of antipsychotics with a drug from this class is not recommended (Prod Info FANAPT(TM) oral tablets, 2009; Prod Info Quinaglute(R), 1999).

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: The concurrent administration of a Class IA antiarrhythmic and an antipsychoti not recommended.

7) Probable Mechanism: additive cardiac effects

8) Literature Reports

a) In an open-label QTc study of patients with schizophrenia or schizoaffective disorder (n=160), iloperidone 12 mg twice a day was associated with QTc prolongation of 9 msec (Prod Info FANAPT (TM) oral tablets, 2009).

b) QRS widening, QTc interval prolongation, and torsades de pointes may occur with disopyramide therapy (Prod Info Norpace(R), 1997).

c) The effects of combined therapy with quinidine (Class IA antiarrhythmic agent) and haloperidol (antipsychotic agent) were studied by giving 12 healthy volunteers haloperidol 5 mg alone and with 250 mg of quinidine bisulfate. The study demonstrated significant increases in the plasma concentrations of haloperidol when given concurrently with quinidine versus haloperidol treatment alone. The mean area under the concentration curve (AUC) was increased from 54.3 ng/h/mL on haloperidol alone to 103.2 ng/h/mL on combined therapy. The peak concentration (Cmax) also show an increase from 1.9 ng/mL on haloperidol to 3.8 ng/mL on combined therapy. Half-life (T1/2) and tir to peak concentration (Tmax) were not significantly changed, thereby suggesting to the authors that tissue binding mechanism is more likely responsible for the plasma level changes than an eliminatio alteration (Young et al, 1993).

3.5.1.AF Dofetilide

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Concurrent use of dofetilide and haloperidol is not recommended due to the risk of additive effects on the QT interval. If concurrent use cannot be avoided, cautious dosing and telemetric monitorin is advised. Dofetilide should be stopped for at least 2 days before any interacting drug is initiated (Yamreudeewong et al, 2003a).

3) Severity: major

4) Onset: rapid

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of dofetilide and haloperidol is not recommende due to the potential for inducing life-threatening arrhythmias. Dofetilide should be stopped for at least 2 days before any interacting drug is initiated. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised.

7) Probable Mechanism: additive QT prolongation

8) Literature Reports

a) Class III antiarrhythmics have been shown to prolong the QT interval, which may result in ventricular tachycardia, ventricular fibrillation, and torsades de pointes. Several antipsychotic agents have also demonstrated QT prolongation including haloperidol (O'Brien et al, 1999a). Concomitant u of Class III antiarrhythmic agents such as dofetilide and haloperidol may have additive effects on the QT interval and is not recommended (Yamreudeewong et al, 2003).

3.5.1.AG Dolasetron

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999i), haloperidol (O'Brien et al, 1999f), quetiapine (Owens, 2001k), risperidone (Duenas-Laita et al, 1999i), sertindole (Agelink et al, 2001h), sultopride (Lande et al, 1992g), and zotepir (Sweetman, 2003). Even though no formal drug interaction studies have been done, the coadministration dolasetron and other drugs known to prolong the QTc interval, including antipsychotics, is not recommended (Prod Info Anzemet(R), 1997a).

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of dolasetron and agents that prolong the QT interval, such as antipsychotics, is not recommended.

7) Probable Mechanism: additive effects on QT prolongation

8) Literature Reports

a) In several studies, dolasetron resulted in significant, dose-related increases in mean PR, QRS, a

QTc intervals compared to baseline values. Measured changes in ECG parameters were transient, reversible, and asymptomatic. Increases in PR and QRS intervals may be due to prolongation of maximum upstroke velocity (Vmax) due to binding of dolasetron to fast sodium channels. The cause QTc interval prolongation appears to be due to prolongation of the QRS interval, increases in heart rate, or both (Prod Info Anzemet(R), 1997; Hunt et al, 1995; Kris et al, 1994).
b) A total of 7 patients developed torsade de pointes after therapeutic use of haloperidol in high dos (Metzger & Friedman, 1993e; Wilt et al, 1993c). Three patients developed the dysrhythmia after administration of 211 to 825 mg haloperidol over 1 to 2 days for agitated delirium. These 3 patients recovered from the initial episodes, but 1 patient subsequently died of cardiac arrest upon readministration of haloperidol. Four patients developed the dysrhythmia after administration of 170 580 mg over 1 to 4 days for delirium associated with bacterial meningitis (1), status asthmaticus (2) respiratory insufficiency (1). All 4 patients recovered with no adverse sequelae.
c) Prolongation of the QTc interval was reported in 8 patients receiving risperidone (Prod Info Risperdal(R) risperidone, 1999).

3.5.1.AH Doxepin

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999b), haloperidol (O'Brien et al, 1999b), risperidone (Duenas-Laita et al, 1999b), sertindole (Agelink et al, 2001a), quetiapine (Owens, 2001b), sultopride (Lande et al, 1992a), and zotepi (Sweetman, 2003). Even though no formal drug interaction studies have been done, the coadministratio a tricyclic antidepressant and an antipsychotic is not recommended (Prod Info Pamelor(R), 2001; Marsh & Forker, 1982).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of a tricyclic antidepressant and an antipsychoti not recommended.
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) Electrocardiographic changes that have occurred during clinical trials with pimozide have include prolongation of the corrected QT interval, flattening, notching, and inversion of the T wave and the appearance of U waves. In experimental studies, sudden, unexpected deaths have occurred while patients were receiving pimozide doses of 1 mg/kg. The proposed mechanism for these deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmias (Prod Info Orap(R), 1999).

3.5.1.AI Droperidol

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999t), haloperidol (O'Brien et al, 1999m), quetiapine (Owens, 2001u), risperidone (Duenas-Laita et al, 1999s), sertindole (Agelink et al, 2001p), sultopride (Lande et al, 1992t), and zotepir (Sweetman, 2003). Droperidol has been shown to prolong the QTc interval at the recommended therapeutic dose. Even though no formal drug interaction studies have been done, the coadministration droperidol and other drugs known to prolong the QTc interval, including antipsychotics is not recommend (Prod Info Inapsine(R), 2002).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of droperidol and antipsychotics is not recommended.
7) Probable Mechanism: additive cardiac effects

3.5.1.AJ Encainide

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Coadministration of haloperidol with other drugs that potentially prolong the QTc interval, such as encainide, should be approached with caution. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised (Owens, 2001f; Prod Info Haldol(R), 1998b; Larochelle et al, 1984).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of encainide and haloperidol is not recommende due to the potential for inducing life-threatening arrhythmias. If concurrent use cannot be avoided, cautio dosing and telemetric monitoring is advised.

7) Probable Mechanism: additive effects on QT prolongation

3.5.1.AK Enflurane

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Some antipsychotic agents prolong the QT interval and an additive effect would be anticipated if administered with other agents which lengthen the QT interval (Agelink et al, 2001aa; Owe 2001ad; Prod Info Haldol(R), 1998j; Lande et al, 1992ac). Even though no formal drug interaction studie have been done, antipsychotic agents should not be coadministered with other drugs which are also kno to prolong the QTc interval, including enflurane (Owens, 2001ad).

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of enflurane and agents that prolong the QT interval, such as antispychotics, is not recommended.

7) Probable Mechanism: additive effects on QT prolongation

8) Literature Reports

a) Sometimes fatal QRS prolongation and QTc prolongation have been reported in patients taking risperidone therapeutically (Duenas-Laita et al, 1999ab; Ravin & Levenson, 1997h).

3.5.1.AL Erythromycin

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Erythromycin significantly increased the mean QTc interval versus baseline in a retrospect study of 49 patients (Oberg & Bauman, 1995a). Erythromycin has demonstrated QTc prolongation in combination with other drugs that prolong the QT interval (Prod Info PCE(R), 1997). Several antipsychot agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999x), haloperic (O'Brien et al, 1999q), risperidone (Duenas-Laita et al, 1999x), sertindole (Agelink et al, 2001v), sultopric (Lande et al, 1992x), and zotepine (Sweetman, 2003). Caution is advised with coadministration of drugs that potentially prolong the QTc interval.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Caution is advised if erythromycin and antipsychotics are used concomitantly. Monitor QT interval at baseline and periodically during treatment.

7) Probable Mechanism: additive effects on QT prolongation

8) Literature Reports

a) Erythromycin significantly increased the QTc interval compared with baseline in a retrospective study of 49 patients. The erythromycin dose was 500 milligrams or 1 gram four times daily, with a mean of 15 doses received. Patients (n equal to 9) who received 60 mg/kg/day or more all develope increases in QT interval of 15% or greater. For all patients, the mean QTc interval increased from 4 milliseconds (msec) at baseline to 483 msec (p less than 0.01). In patients with delayed repolarizatic at baseline (n equal to 9), the QTc interval increased from 473 msec to 525 msec (p less than 0.01). patients with heart disease (n equal to 30), all experienced an increase in QTc interval (mean of 15% compared with an increase of 8% in patients without heart disease (p less than 0.05). In 5 patients (10%), the QTc interval was severely prolonged. One patient developed torsades de pointes attribut to erythromycin. Of 16 patients receiving cotrimoxazole concomitantly, 8 developed QT prolongatior 15% or greater (Oberg & Bauman, 1995).

3.5.1.AM Flecainide

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Coadministration of haloperidol with other drugs that potentially prolong the QTc interval, such as flecainide, should be approached with caution. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised (Owens, 2001f; Prod Info Haldol(R), 1998b; Prod Info Tambocor(R), 1998; Larochelle et al, 1984).

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of flecainide and haloperidol is not recommende due to the potential for inducing life-threatening arrhythmias. If concurrent use cannot be avoided, cautio dosing and telemetric monitoring is advised.

7) Probable Mechanism: additive effects on QT prolongation

3.5.1.AN Fluconazole

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Case reports have described QT prolongation and torsades de points associated with

fluconazole (Khazan & Mathis, 2002; Wassmann et al, 1999). Haloperidol (Prod Info Haldol(R), 1998e), risperidone (Prod Info Risperdal(R) risperidone, 2000), amisulpride (Prod Info Solian(R), 1999l), sertindo (Brown & Levin, 1998a); sultopride (Lande et al, 1992j), and zotepine (Sweetman, 2004) have been shov to prolong the QT interval at therapeutic doses. Even though no formal drug interaction studies have bee done, caution is advised if drugs known to prolong the QT interval are used concomitantly.
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Caution is advised if fluconazole and antipsychotics are used concomitantly.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.AO Fluoxetine
1) Interaction Effect: haloperidol toxicity (pseudoparkinsonism, akathisia, tongue stiffness) and an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Haloperidol is associated with QTc prolongation and torsade de pointes (Hassaballa & Bal 2003f; Prod Info Haldol(R), 2001d). Fluoxetine has been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Prozac(R), 2001). Caution is advised with coadministration of drugs that potentially prolong the QTc interval. In addition, several case reports describe development of extrapyramidal symptoms when fluoxetine and haloperidol were taken together, possibly due to inhibitior haloperidol metabolism (Benazzi, 1996a; Goff et al, 1991a; Stein, 1991a; Tate, 1989a).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: The concurrent administration of fluoxetine and haloperidol is not recommende
7) Probable Mechanism: inhibition of haloperidol metabolism by fluoxetine; theoretical additive effects or QT prolongation
8) Literature Reports
a) Fluoxetine increased plasma concentrations of haloperidol in 8 outpatients. Patients received fluoxetine 20 mg daily for 10 days with maintenance doses of haloperidol (average dose, 14 mg per day). After ten days, mean plasma concentrations of haloperidol had increased by 20%. Extrapyramidal symptom scores did not change appreciably after the addition of fluoxetine although one patient developed mild akathisia and another developed tremors. Extrapyramidal symptoms we expected to increase because of indirect inhibition of dopamine synthesis by fluoxetine (Goff et al, 1991).
b) A 39-year-old male experienced tardive dyskinesia with concomitant fluoxetine and haloperidol therapy. He was taking fluoxetine 20 mg daily for 2 months, then haloperidol 2 mg twice daily was started and later lowered to 1 mg per day. Five months later during a routine examination, tardive dyskinesia was diagnosed. The suggested mechanism was the down-regulation of dopamine activit (Stein, 1991).
c) A 39-year-old female developed tardive dyskinesia associated with concomitant fluoxetine and haloperidol therapy. She had been taking haloperidol 2 to 5 mg a day for two years (both with and without benztropine) with occasional mild, reversible extrapyramidal symptoms. Five days before stopping haloperidol, she started taking fluoxetine, which was increased over several days to 40 mg twice a day. After two weeks of fluoxetine she took haloperidol 5 mg each on two consecutive days (along with continuation of fluoxetine). She then experienced severe tongue stiffness, parkinsonism, and akathisia. Both fluoxetine and haloperidol were withdrawn. During the next seven days her extrapyramidal symptoms gradually disappeared (Tate, 1989).
d) A 40-year-old male developed urinary retention while taking fluoxetine and haloperidol. During a recurrence of depression, the patient was treated with fluoxetine 20 mg per day, alprazolam 1.5 mg day, and haloperidol 1 mg per day. The patient had previously taken fluoxetine and alprazolam with incident. Approximately one week after beginning therapy, the patient developed difficulty in voiding urine, dilated pupils, dry mouth, palpitations, restlessness, hand tremors, and insomnia. After discontinuation of haloperidol and alprazolam, side effects ceased within one week. The authors postulated that the interaction was due to fluoxetine inhibition of cytochrome CYP2D6, which metabolizes haloperidol (Benazzi, 1996).

3.5.1.AP Fluvoxamine
1) Interaction Effect: an increased risk of haloperidol toxicity
2) Summary: Haloperidol serum concentrations were increased by the coadministration of fluvoxamine i small double blind, randomized, placebo controlled, crossover study (Daniel et al, 1994a).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Caution should be used when fluvoxamine is administered with haloperidol. Monitor serum concentrations of haloperidol and adjust the dose accordingly. Also monitor the patient fo signs and symptoms of worsening clinical and cognitive assessments.
7) Probable Mechanism: inhibition of cytochrome P450-mediated metabolism of haloperidol
8) Literature Reports

a) Four inpatient males with chronic schizophrenia were stabilized on haloperidol and benztropine orally. In randomized order, the patients were then placed on fluvoxamine for six weeks or identicall appearing placebo. Results showed that the addition of fluvoxamine to haloperidol therapy significar elevated serum concentrations of haloperidol. In addition, haloperidol concentrations did not plateau during the six-week period of fluvoxamine treatment, indicating that the haloperidol concentrations n have continued to increase at a constant dose of fluvoxamine. The coadministration of haloperidol a fluvoxamine also worsened all measures of clinical and cognitive function assessments, including delayed recall memory and attentional function. It is possible that haloperidol may require the cytochrome P450 1A2 system for metabolism, and fluvoxamine is known to be a potent inhibitor of t enzyme pathway (Daniel et al, 1994).

3.5.1.AQ Foscarnet

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Foscarnet can prolong the QT interval in some patients, which may result in ventricular tachycardia, ventricular fibrillation, and torsades de pointes. Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999ab), haloperidol (O'Brien al, 1999s), quetiapine (Owens, 2001ac), risperidone (Duenas-Laita et al, 1999aa), sertindole (Agelink et 2001z), sultopride (Lande et al, 1992ab), and zotepine (Sweetman, 2003). Because antipsychotics may also prolong the QT interval and increase the risk of arrhythmias, the concurrent administration of foscar and antipsychotics is not recommended (Prod Info Foscavir(R), 1998; Ravin & Levenson, 1997g).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of foscarnet and antipsychotics is not recommended.
7) Probable Mechanism: additive cardiac effects

3.5.1.AR Gemifloxacin

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Although pharmacokinetic studies between gemifloxacin and drugs that prolong the QT interval, such as antipsychotics, have not been performed, gemifloxacin should be used cautiously in patients receiving antipsychotic medications (Prod Info Factive(R), 2003).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of two drugs that prolong the QT interval, such a gemifloxacin and antipsychotics, is not recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.AS Halofantrine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Halofantrine can prolong the QT interval in some patients, which may result in ventricular tachycardia, ventricular fibrillation, and torsades de pointes. Some antipsychotic agents prolong the QT interval and an additive effect would be anticipated if administered with other agents which lengthen the interval (Agelink et al, 2001b; Owens, 2001c; Prod Info Solian(R), 1999c; Prod Info Haldol(R), 1998; Lan et al, 1992b). The concurrent administration of halofantrine with antipsychotics is not recommended (Pro Info Halfan(R), 1998).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of halofantrine and an antipsychotic is not recommended.
7) Probable Mechanism: additive cardiac effects

3.5.1.AT Halothane

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Some antipsychotic agents prolong the QT interval and an additive effect would be anticipated if administered with other agents which lengthen the QT interval (Agelink et al, 2001i; Owens 2001l; Prod Info Solian(R), 1999j; Prod Info Haldol(R), 1998d; Lande et al, 1992h). Even though no form drug interaction studies have been done, antipsychotic agents should not be coadministered with other drugs which may also prolong the QTc interval, including halothane (Owens, 2001l).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of halothane and agents that prolong the QT interval, such as antispychotics, is not recommended.
7) Probable Mechanism: additive effect on QT interval
8) Literature Reports
a) Sometimes fatal QRS prolongation and QTc prolongation have been reported in patients taking risperidone therapeutically (Duenas-Laita et al, 1999j; Ravin & Levenson, 1997b).

3.5.1.AU Hydroquinidine
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Several antipsychotic agents have demonstrated QT prolongation including amisulpride, haloperidol, iloperidone, paliperidone, quetiapine, risperidone, sertindole, sultopride, ziprasidone, and zotepine (Prod Info FANAPT(TM) oral tablets, 2009; Prod Info Solian(R), 1999z; O'Brien et al, 1999r; Prc Info INVEGA(TM) extended-release oral tablets, 2006; Owens, 2001z; Duenas-Laita et al, 1999y; Agelin et al, 2001x; Lande et al, 1992z; Prod Info GEODON(R) intramuscular injection, oral capsule, 2005; Sweetman, 2003). Because Class IA antiarrhythmic agents may also prolong the QT interval and increas the risk of arrhythmias, the concurrent administration of antipsychotics with a drug from this class is not recommended (Prod Info FANAPT(TM) oral tablets, 2009; Prod Info Quinaglute(R), 1999).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: The concurrent administration of a Class IA antiarrhythmic and an antipsychoti not recommended.
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) In an open-label QTc study of patients with schizophrenia or schizoaffective disorder (n=160), iloperidone 12 mg twice a day was associated with QTc prolongation of 9 msec (Prod Info FANAPT (TM) oral tablets, 2009).
b) QRS widening, QTc interval prolongation, and torsades de pointes may occur with disopyramide therapy (Prod Info Norpace(R), 1997).
c) The effects of combined therapy with quinidine (Class IA antiarrhythmic agent) and haloperidol (antipsychotic agent) were studied by giving 12 healthy volunteers haloperidol 5 mg alone and with 250 mg of quinidine bisulfate. The study demonstrated significant increases in the plasma concentrations of haloperidol when given concurrently with quinidine versus haloperidol treatment alone. The mean area under the concentration curve (AUC) was increased from 54.3 ng/h/mL on haloperidol alone to 103.2 ng/h/mL on combined therapy. The peak concentration (Cmax) also show an increase from 1.9 ng/mL on haloperidol to 3.8 ng/mL on combined therapy. Half-life (T1/2) and tir to peak concentration (Tmax) were not significantly changed, thereby suggesting to the authors that tissue binding mechanism is more likely responsible for the plasma level changes than an eliminatio alteration (Young et al, 1993).

3.5.1.AV Ibutilide
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Concurrent use of ibutilide and haloperidol is not recommended due to the risk of additive effects on the QT interval. If concurrent use cannot be avoided, cautious dosing and telemetric monitorin is advised (Yamreudeewong et al, 2003a).
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of ibutilide and haloperidol is not recommended due to the potential for inducing life-threatening arrhythmias. If concurrent use cannot be avoided, cautio dosing and telemetric monitoring is advised.
7) Probable Mechanism: additive QT prolongation
8) Literature Reports
a) Class III antiarrhythmics have been shown to prolong the QT interval, which may result in ventricular tachycardia, ventricular fibrillation, and torsades de pointes. Several antipsychotic agents have demonstrated QT prolongation including haloperidol (O'Brien et al, 1999a). Concomitant use o Class III antiarrhythmic agents such as ibutilide and haloperidol may have additive effects on the QT interval and is not recommended (Yamreudeewong et al, 2003).

3.5.1.AW Imipramine
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999b), haloperidol (O'Brien et al, 1999b), risperidone (Duenas-Laita et al, 1999b), sertindole (Agelink et al, 2001a), quetiapine (Owens, 2001b), sultopride (Lande et al, 1992a), and zotepi (Sweetman, 2003). Even though no formal drug interaction studies have been done, the coadministratior

a tricyclic antidepressant and an antipsychotic is not recommended (Prod Info Pamelor(R), 2001; Marsha & Forker, 1982).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of a tricyclic antidepressant and an antipsychotic not recommended.
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) Electrocardiographic changes that have occurred during clinical trials with pimozide have include prolongation of the corrected QT interval, flattening, notching, and inversion of the T wave and the appearance of U waves. In experimental studies, sudden, unexpected deaths have occurred while patients were receiving pimozide doses of 1 mg/kg. The proposed mechanism for these deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmias (Prod Info Orap(R), 1999).

3.5.1.AX Isoflurane
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Some antipsychotic agents prolong the QT interval and an additive effect would be anticipated if administered with other agents which lengthen the QT interval (Agelink et al, 2001y; Owens 2001aa; Prod Info Solian(R), 1999aa; Prod Info Haldol(R), 1998i; Lande et al, 1992aa). Even though no formal drug interaction studies have been done, antipsychotic agents should not be coadministered with other drugs which are also known to prolong the QTc interval, including isoflurane (Owens, 2001aa).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of isoflurane and agents that prolong the QT interval, such as antipsychotics, is not recommended.
7) Probable Mechanism: additive effect on QT interval
8) Literature Reports
a) Sometimes fatal QRS prolongation and QTc prolongation have been reported in patients taking risperidone therapeutically (Duenas-Laita et al, 1999z; Ravin & Levenson, 1997f).

3.5.1.AY Isradipine
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Isradipine can prolong the QT interval in some patients, which may result in ventricular tachycardia, ventricular fibrillation, and torsades de pointes, and its use with other drugs known to cause QT prolongation is not recommended (Prod Info DynaCirc(R), 2000). Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999g), haloperidol (O'Brien et al, 1999d), quetiapine (Owens, 2001h), risperidone (Duenas-Laita et al, 1999f), sertindole (Agelink et al, 2001b), and zotepine (Sweetman, 2004).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of isradipine and an antipsychotic is not recommended.
7) Probable Mechanism: additive cardiac effects

3.5.1.AZ Kava
1) Interaction Effect: additive dopamine antagonist effects
2) Summary: Theoretically, kava may add to the effect of dopamine antagonists, increasing the risk for adverse effects. Case reports describe what appears to be dopamine-blocking activity of kava manifested in patients as dystonia, dyskinesias, and Parkinsonism (Spillane et al, 1997a; Schelosky et al, 1995a). Kava extracts antagonized apomorphine-induced hyperreactivity to external stimuli in mice, suggesting dopamine blockade activity (Jamieson et al, 1989).
3) Severity: moderate
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Avoid concomitant use of kava with dopamine antagonists. The desired effect and/or adverse effects of the dopamine antagonist may be increased or may be variable depending on the time of administration of kava and the quality of the kava product (i.e., whether it contains a standardized amount of kava).
7) Probable Mechanism: dopamine antagonist effect of kava
8) Literature Reports
a) A 27-year-old Aboriginal Australian male presented three times following heavy kava use with symptoms of severe choreoathetosis of the limbs, trunk, neck, and facial musculature, and athetosis

the tongue. Level of consciousness was not impaired. Symptoms resolved within 12 hours of intravenous diazepam on each occasion. Acute rheumatic fever was excluded, cerebrospinal fluid a computed tomography of the brain was normal, and urinary drug screen was negative. The only abnormalities found in hematological and biochemical tests were a serum alkaline phosphatase of 1 international units/liter (IU/L) (normal: 35-135 IU/L) and serum gamma-glutamyltransferase of 426 IU (normal less than 60 IU/L). These were attributed to kava use. The patient did not drink alcohol (Spillane et al, 1997).

b) A 76-year-old female with idiopathic Parkinson's disease of 17 years' duration treated for 8 years with levodopa 500 milligrams (mg) and benserazide 125 mg was prescribed kava extract (Kavaspor Forte(R)) 150 mg twice daily for complaints of inner tension. Within 10 days, she noted a pronounce increase in her daily "off" periods both in terms of duration and number. Within 2 days of discontinui the kava product, symptoms had returned to her normal baseline (Schelosky et al, 1995).

c) A 63-year-old female experienced sudden and acute forceful involuntary oral and lingual dyskinesias on the fourth day of self-initiated therapy with kava extract (Kavasporal Forte(R)) 150 m three times daily. She was treated successfully in the emergency room with biperiden 5 mg intravenously. She denied taking any other medications in the months preceding this event (Schelos et al, 1995).

d) A 22-year-old female took kava extract (Laitan(R)) 100 mg once for anxiety and nervousness. Within four hours she experienced oral and lingual dyskinesias, tonic rotation of the head, and painf twisting trunk movements. She was treated successfully with biperiden 2.5 mg intravenously. She denied taking any other medications in the months preceding this event (Schelosky et al, 1995).

e) A 28-year-old male experienced acute involuntary neck extension with forceful upward deviation the eyes within 90 minutes of taking kava extract (Laitan(R)) 100 mg. Symptoms resolved spontaneously within 40 minutes. This man had a history of acute dystonic reactions following exposure to promethacin (50 mg) and fluspirilene (1.5 mg), which had responded biperiden 5 mg intravenously 9 and 12 years previously (Schelosky et al, 1995).

3.5.1.BA Levodopa

1) Interaction Effect: decreased levodopa effectiveness

2) Summary: The therapeutic effects of levodopa may be reduced when coadministered with haloperido (Prod Info Stalevo(TM), 2003).

3) Severity: moderate

4) Onset: rapid

5) Substantiation: theoretical

6) Clinical Management: Monitor for clinical response to levodopa. The therapeutic effects of levodopa may be reduced with concomitant administration of haloperidol.

7) Probable Mechanism: antagonistic pharmacologic effect

3.5.1.BB Levomethadyl

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Haloperidol is associated with QTc prolongation and torsade de pointes (Hassaballa & Bal 2003a; Prod Info Haldol(R), 2001). Coadministration of levomethadyl with drugs that potentially prolong t QTc interval, such as haloperidol, is contraindicated (Prod Info Orlaam(R), 2001).

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of levomethadyl with agents that prolong the QT interval, such as haloperidol, is contraindicated.

7) Probable Mechanism: additive effects on QT prolongation

8) Literature Reports

a) Numerous case reports have described significant QTc prolongation and torsades de pointes (Tc associated with haloperidol. Hemodynamically significant ventricular tachyarrhythmias, ventricular fibrillation, asystole, and death have been reported. The risk of TdP appears to be greater with intravenous haloperidol, but has occurred with oral and intramuscular use. The risk increases with doses greater than 35 milligrams (mg) over 24 hours, although TdP has been associated with a dos as low as 10 mg administered intravenously over 4 hours. To prevent haloperidol-induced TdP, scre patients for a history of dilated cardiomyopathy or alcohol abuse, testing for hypothyroidism before therapy, obtaining an electrocardiogram at baseline and throughout therapy, and monitoring potassium, magnesium, and calcium. In patients with a baseline QTc greater than 450 milliseconds (msec), haloperidol should be used cautiously or an alternative agent should be used. Discontinue haloperidol if the QTc increases more than 25% from baseline or if flattening of T-waves or development of U-waves occurs (Hassaballa & Balk, 2003).

3.5.1.BC Lidoflazine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Lidoflazine has been shown to prolong the QTc interval at the recommended therapeutic

dose (Hanley & Hampton, 1983). Even though no formal drug interaction studies have been done, the coadministration of antipsychotics and other drugs known to prolong the QTc interval is not recommende Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Soliar (R), 1999), haloperidol (O'Brien et al, 1999), quetiapine (Owens, 2001), risperidone (Duenas-Laita et al, 1999), sertindole (Agelink et al, 2001), sultopride (Lande et al, 1992), and zotepine (Sweetman, 2003).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of lidoflazine and antipsychotics is not recommended.
7) Probable Mechanism: additive cardiac effects

3.5.1.BD Lithium
1) Interaction Effect: weakness, dyskinesias, increased extrapyramidal symptoms, encephalopathy, and brain damage
2) Summary: An encephalopathic syndrome followed by irreversible brain damage has occurred in a fev patients treated with lithium plus a dopamine-2 antagonist, particularly haloperidol. A causal relationship between these events and the concomitant administration of a dopamine-2 antagonist and lithium has nc been established (Prod Info LITHOBID(R) slow-release oral tablets, 2005). Coadministration of lithium ar a number of antipsychotic drugs has caused a wide variety of encephalopathic symptoms, brain damage extrapyramidal symptoms, and dyskinesias in isolated case reports. In most cases, these effects have occurred with therapeutic lithium levels (Amdisen, 1982; Prakash, 1982; Addonizio et al, 1988a). Howeve many series and trials have reported using such combinations with no severe adverse consequences (Goldney & Spence, 1986). The mechanism is not fully understood, but chronic lithium treatment decreas neostriatal dopaminergic activity, probably through a direct action on the G protein and the capacity of th G proteins, once activated, to stimulate adenyl cyclase (Carli et al, 1994). Hyperglycemic reactions have also occurred during combined phenothiazine and lithium use (Zall et al, 1968).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor patients closely for any signs of toxicity or extrapyramidal symptoms, especially if high doses of dopamine-2 antagonists, particularly haloperidol, and lithium are used. Serum lithium levels should be monitored periodically. Some clinicians advocate maintaining levels in the low therapeutic range.
7) Probable Mechanism: unknown
8) Literature Reports
a) Concomitant haloperidol and lithium therapy has resulted in symptoms of encephalopathy, confusion, extrapyramidal symptoms, and fever in several patients with mania (Cohen & Cohen, 197 Loudon & Waring, 1976; Thomas, 1979). Irreversible neurological injuries have been reported (Sanc & Hurwitz, 1983; Keitner & Rahman, 1984).
b) Seizures, encephalopathy, delirium, and abnormal EEG occurred in four patients during combine lithium and thioridazine therapy (Spring, 1979). Serum lithium levels were below 1 mEq/L at the time the toxic reaction in all cases. All patients had previously tolerated lithium in combination with anothe phenothiazine. Three of these patients developed symptoms within eight days of initiating combinati therapy.
c) The addition of lithium to neuroleptic therapy exacerbated extrapyramidal symptoms (EPS) in a small study (Addonizio et al, 1988). The patients had received at least five days of treatment with eit oral thiothixene, haloperidol, or fluphenazine in mean doses of 607.5 chlorpromazine equivalents pri to initiation of the lithium and were experiencing drug-induced extrapyramidal symptoms. Oral lithiun was added when clinically indicated in sufficient doses to achieve a therapeutic serum concentration The maximum levels attained were 0.65 to 1.27 mEq/L. The EPS ratings increased in all ten patients following the addition of lithium. However, only three patients developed marked symptoms and no patient developed lithium toxicity. Significantly increased symptoms included gait, shoulder shaking, elbow rigidity, and tremor.
d) Ten patients treated with clozapine and lithium were studied (Blake et al, 1992). Of the ten patier four experienced significant neurologic effects, including jerking of limbs, facial spasms and tics, trer of hands and arms, tongue twitching, and stumbling gait. One of these also experienced delirium. These effects reversed when lithium was discontinued or given at a lower dose. On rechallenge, one two patients suffered recurrence of symptoms. By keeping serum lithium no greater than 0.5 mEq/L, clozapine could be safely coadministered.
e) Chlorpromazine serum levels can be significantly reduced in the presence of lithium treatment. If used concurrently, abrupt cessation of lithium may result in rebound elevation of chlorpromazine levels, resulting in chlorpromazine toxicity. In patients on a lithium-chlorpromazine combination, abru withdrawal of the lithium may precipitate chlorpromazine cardiotoxicity. In this report, such toxicity w manifested as sudden ventricular fibrillation associated with prolongation of the QTc interval. Hypotension and EPS are also possible in this situation (Stevenson et al, 1989).
f) However, other data do not support that such adverse events are frequent or indeed causally related to combination therapy. Combination of dopamine antagonist antipsychotic drugs and lithium

have been used successfully in many patients with manic-depressive illness. It has been proposed t the interaction may only become significant with very high doses of one or both drugs or with failure discontinue dosing in the presence of toxic symptoms (Miller & Menninger, 1987).

g) A 69-year-old patient with oxygen-dependent chronic obstructive pulmonary disorder and a 25-y history of bipolar disorder was started on risperidone 3 mg for the treatment of new-onset auditory a visual hallucinations. She had also been maintained on a regimen of lithium (450 mg daily) for more than 10 years. In addition, she was given amantadine (100 mg twice daily) for tremor. Three weeks after the start of risperidone, the patient experienced a decline in mental status in addition to dizzine worsening tremors, nausea and vomiting, polyuria, depression, and visual and auditory hallucinatior She was then admitted to the hospital for delirium. Her lithium serum level was 1.36 mEq/L at the tir of the admission. All medications were discontinued. Although her lithium level decreased to 0.41 mEq/L, she continued to experience profound delirium, tremors, lethargy, and hallucinations for alm one week. After she started to respond to commands, she was restarted on lithium (300 mg at bedtime) because of the onset of mild hypomania. Five days later, she was discharged with a regim of lithium and low-dose lorazepam for treatment of insomnia. It is suggested that delirium could have been caused by the concurrent use of lithium and risperidone. Other factors could also have caused delirium, such as the patient's serum lithium level and the underlying pulmonary pathology. In additi amantadine, which facilitates the release of presynaptic dopamine and has a mild anticholinergic effect, may have contributed (Chen & Cardasis, 1996).

3.5.1.BE Lithospermum

1) Interaction Effect: decreased effectiveness of dopamine antagonists

2) Summary: Theoretically, the dopamine agonist activity of lithospermum may oppose that of dopamine antagonists, decreasing their effectiveness. Lithospermum likely decreases prolactin secretion via dopamine stimulation (Sourgens et al, 1982a). Animal data suggest that the effect occurs rapidly within 3 hours after injection, subsiding within 6 to 9 hours (Sourgens et al, 1980a). The magnitude and clinical significance of this phenomenon has yet to be determined in humans. Furthermore, it is not known if the ability to stimulate dopamine receptors is limited to the hypothalamic region or if such an effect will be nc elsewhere (i.e., if patients with psychosis will experience worsening of their condition due to dopamine stimulation secondary to lithospermum). Caution is recommended until the effects on humans and possil implications of a drug-herb interaction with dopamine antagonists can be fully determined.

3) Severity: minor

4) Onset: rapid

5) Substantiation: theoretical

6) Clinical Management: If therapy is initiated with lithospermum and a dopamine antagonist, monitor closely for return of symptoms previously controlled by the dopamine antagonist.

7) Probable Mechanism: dopamine agonism of lithospermum may counteract dopamine antagonists

8) Literature Reports

a) Administration of freeze dried extracts (FDE) of Lithospermum officinale (Boraginaceae) by intravenous injection to rats resulted in reduced prolactin serum levels and hypophyseal stores. Whe administered diluent, prolactin levels decreased from 36 +/- 8 nanograms/milliliter (ng/mL) serum to +/- 4 ng/mL serum (p less than 0.005) when administered Lithospermum officinale FDE (40 milligrar (mg)/100 grams body weight) within 3 hours post intravenous administration. The authors concluded that Lithospermum officinale possibly impacted prolactin secretion at the hypothalamic site via dopamine stimulation (Sourgens et al, 1982).

b) Prolactin levels decreased rapidly below basal values in rats within the first 3 hours following a single intravenous injection of Lithospermum officinale. Prolactin levels returned to control levels wit 6 to 9 hours after the injection (Sourgens et al, 1980).

3.5.1.BF Lorcainide

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Coadministration of haloperidol with other drugs that potentially prolong the QTc interval, such as lorcainide, should be approached with caution. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised (Owens, 2001f; Prod Info Haldol(R), 1998b; Larochelle et al, 1984).

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of lorcainide and haloperidol is not recommende due to the potential for inducing life-threatening arrhythmias. If concurrent use cannot be avoided, cautio dosing and telemetric monitoring is advised.

7) Probable Mechanism: additive effects on QT prolongation

3.5.1.BG Mefloquine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Even though no formal drug interaction studies have been done, caution is advised if

mefloquine is used with other drugs which can prolong the QTc interval (Prod Info Lariam(R), 1999). Mefloquine was associated with significant QT prolongation in a study of 46 healthy subjects (Davis et al 1996). Antipsychotics including haloperidol (Prod Info Haldol(R), 1998g), quetiapine (Owens, 2001s), risperidone (Prod Info Risperdal(R) risperidone, 2000b), amisulpride (Prod Info Solian(R), 1999r), sertinc (Agelink et al, 2001o); sultopride (Lande et al, 1992r), and zotepine (Sweetman, 2004) have been showr prolong the QT interval at therapeutic doses.
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Caution is advised if mefloquine and antipsychotics are used concomitantly.
7) Probable Mechanism: additive effect on QT interval

3.5.1.BH Mesoridazine
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Although citing no data, the manufacturer of mesoridazine states that concomitant use witl other drugs which prolong the QT interval is contraindicated (Prod Info Serentil(R), 2001). Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999s), haloperidol (O'Brien et al, 1999l), paliperidone (Prod Info INVEGA(TM) extended-release oral tablets, 2006), quetiapine (Owens, 2001t), risperidone (Duenas-Laita et al, 1999r), sertindole (Agelink et 2001n), sultopride (Lande et al, 1992s), ziprasidone (Prod Info GEODON(R) intramuscular injection, oral capsule, 2005), and zotepine (Sweetman, 2004).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of agents that prolong the QT interval, such as antipsychotics and mesoridazine, is contraindicated.
7) Probable Mechanism: additive QT prolongation

3.5.1.BI Methyldopa
1) Interaction Effect: CNS toxicity (dementia) or reversible parkinsonism
2) Summary: Cases of marked increases of psychotic behavior or newly developed bizarre behavior hav developed within one week after the addition of haloperidol to an established methyldopa regimen. The abnormal behavior dramatically improved within days upon discontinuation of either agent. The few case reported do not establish a cause-effect relationship, but the combination should be used with caution ar the patient observed closely for several days (Thornton, 1976a; Nadel & Wallach, 1979a).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: established
6) Clinical Management: Monitor psychiatric symptoms. Discontinue haloperidol if necessary.
7) Probable Mechanism: increased dopamine inhibition
8) Literature Reports
a) Two male patients experienced adverse mental effects resulting from combined methyldopa and haloperidol therapy (Thornton, 1976). The first case was a 48-year-old male with hypertension treate with 1 gram per day of methyldopa for three years. Following initiation of 8 milligrams per day of haloperidol for anxiety, the patient developed symptoms of psychomotor retardation, memory impairment, ideas of reference with accompanying inappropriate suspiciousness, and inability to do mathematical calculations. Discontinuing the haloperidol resulted in resolution of these symptoms within 48 hours. The second case was a 43-year-old male with hypertension treated with 1.5 grams day of methyldopa for 18 months who developed symptoms of disorientation, inability to recognize c handwriting, inability to concentrate and marked slowing of both motor and muscle performance with three days after starting 6 milligrams per day of haloperidol for anxiety. Following discontinuation of haloperidol, the symptoms disappeared completely within 72 hours.
b) A patient became irritable, aggressive, assaultive and unmanageable several days after receivin combination therapy with haloperidol and methyldopa (Nadel & Wallach, 1979). Improvement in symptoms occurred as soon as methyldopa was discontinued.
c) The potentiation of haloperidol by methyldopa was studied in schizophrenic patients (Chouinard al, 1973). Ten patients were maintained on haloperidol 10 milligrams and methyldopa 500 milligram daily from day 2 until the end of the 4-week trial. Among the ten patients, 20 incidences of extrapyramidal side effects were reported, which exceeds the expected incidence of extrapyramidal side effects of 25% following therapeutic doses of haloperidol (Anon, 1973). Antiparkinsonian medication was needed in eight out of 10 patients to control these drug-induced extrapyramidal effe Somnolence was noted in eight patients and considered severe in two.

3.5.1.BJ Nefazodone
1) Interaction Effect: an increased risk of extrapyramidal effects, hypotension, and sedation
2) Summary: A single dose of haloperidol administered with steady-state nefazodone decreased haloperidol clearance. Pharmacodynamic effects of haloperidol were not significantly altered (Prod Info

Serzone(R), 1998; DeVane, 1995).
3) Severity: moderate
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Patients receiving combined haloperidol with nefazodone should be monitored closely for signs of excessive haloperidol side effects. Reductions in haloperidol dosage may be necessa
7) Probable Mechanism: decreased haloperidol metabolism and clearance
8) Literature Reports
a) The effect of nefazodone on the pharmacokinetics and pharmacodynamics of haloperidol was studied in 12 healthy males. Nefazodone 200 mg every 12 hours had a slight effect on the pharmacokinetics of a single dose of haloperidol 5 mg. The average area under the plasma concentration curve (AUC), highest concentration, and 12-hour concentration of haloperidol were increased 36%, 13%, and 37%, respectively. Only the effect on the AUC reached statistical significance. The pharmacodynamics of haloperidol were not effected by nefazodone consistently (Barbhaiya et al, 1996).

3.5.1.BK Nortriptyline
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999b), haloperidol (O'Brien et al, 1999b), risperidone (Duenas-Laita et al, 1999b), sertindole (Agelink et al, 2001a), quetiapine (Owens, 2001b), sultopride (Lande et al, 1992a), and zotepi (Sweetman, 2003). Even though no formal drug interaction studies have been done, the coadministratio a tricyclic antidepressant and an antipsychotic is not recommended (Prod Info Pamelor(R), 2001; Marsh & Forker, 1982).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of a tricyclic antidepressant and an antipsychoti not recommended.
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) Electrocardiographic changes that have occurred during clinical trials with pimozide have include prolongation of the corrected QT interval, flattening, notching, and inversion of the T wave and the appearance of U waves. In experimental studies, sudden, unexpected deaths have occurred while patients were receiving pimozide doses of 1 mg/kg. The proposed mechanism for these deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmias (Prod Info Orap(R), 1999).

3.5.1.BL Octreotide
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Octreotide has been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Sandostatin(R), 1999). Even though no formal drug interaction studies have been done, the coadministration of antipsychotics and other drugs known to prolong the QTc interval, including octreotide, is not recommended. Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999u), haloperidol (O'Brien et al, 1999n), risperidone (Duen Laita et al, 1999t), sertindole (Agelink et al, 2001q), quetiapine (Owens, 2001v), sultopride (Lande et al, 1992u), and zotepine (Sweetman, 2003).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of octreotide and antipsychotics is not recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.BM Olanzapine
1) Interaction Effect: an increased risk of parkinsonism (cogwheeling rigidity, unstable gait)
2) Summary: A patient receiving haloperidol experienced extreme parkinsonism following the addition o olanzapine therapy. Possible explanations include a pharmacokinetic interaction between olanzapine, a weak cytochrome P450 2D6 (CYP2D6) inhibitor, and haloperidol, a CYP2D6 substrate. Pharmacodynamically, the small amount of dopamine (D2) blockade from olanzapine may have been enough to increase the patient's parkinsonism (Gomberg, 1999a).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Patients should be closely monitored for signs and symptoms of increased parkinsonian adverse effects when olanzapine is added to haloperidol therapy. Doses of haloperidol ma

need to be decreased.
7) Probable Mechanism: competitive inhibition of cytochrome P450 2D6-mediated haloperidol metabolis increased dopamine D2 blockade
8) Literature Reports
a) A 67-year-old hospitalized male with bipolar disorder who had stopped taking his medications wa restarted on haloperidol 10 mg nightly, benztropine 1 mg nightly, and valproate 750 mg twice daily. H had been experiencing some mild parkinsonian symptoms at baseline, but these symptoms did not worsen when haloperidol was reinstituted. Following stabilization on this regimen, it was decided to change his antipsychotic medication to olanzapine to minimize any parkinsonism that was a result o his medications. While tapering the haloperidol and initiating olanzapine, the patient experienced extreme parkinsonism that resulted in an inability to walk. His mental status remained unchanged. Haloperidol was discontinued on day 7 of combination therapy, and two days later the patient's parkinsonism side effects had resolved back to baseline. Benztropine was then discontinued, and th parkinsonian symptoms did not reoccur while on olanzapine (Gomberg, 1999).

3.5.1.BN Pentamidine
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Pentamidine has been shown to prolong the QTc interval at the recommended therapeutic dose (Lindsay et al, 1990). Even though no formal drug interaction studies have been done, the coadministration of antipsychotics and other drugs known to prolong the QTc interval, including pentamidine, is not recommended (Agelink et al, 2001e; Owens, 2001g; Prod Info Haldol(R), 2001b; Pro Info Solian(R), 1999f; Duenas-Laita et al, 1999e; Duenas-Laita et al, 1999e; Prod Info Nipolept(R), 1996 Metzger & Friedman, 1993c; Lande et al, 1992d).
3) Severity: major
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of pentamidine and antipsychotics is not recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.BO Phenylalanine
1) Interaction Effect: increased incidence of tardive dyskinesia
2) Summary: Taking phenylalanine concomitantly with certain neuroleptic drugs may exacerbate tardive dyskinesia (Gardos et al, 1992a). Abnormal phenylalanine metabolism in certain patients may lead to phenylalanine accumulation in the brain and in turn, reduced brain availability of other large neutral amin acids. This may interfere with the synthesis of catecholamines (Gardos et al, 1992a).
3) Severity: moderate
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Caution is advised if phenylalanine is administered with a neuroleptic agent. Monitor the patient closely for signs of tardive dyskinesia.
7) Probable Mechanism: reduced brain availability of other large neutral amino acids and interference w catecholamine synthesis
8) Literature Reports
a) Phenylalanine tended to increase the incidence of tardive dyskinesia in patients taking neurolept in an open study. Three groups of patients were studied: (1) patients with unipolar depression with tardive dyskinesia (n=11), (2) patients with no tardive dyskinesia with current or past exposure to greater than or equal to 100 milligrams (mg) of a chlorpromazine equivalent for at least 3 months (n=10), and (3) patients with no tardive dyskinesia not previously exposed to a neuroleptic drug (n=1 Neuroleptic agents were taken during the study by 6 patients in group 1, and 5 patients in group 2. Patients received powdered phenylalanine 100 mg/kilogram dissolved in orange juice after an overnight fast. Blood samples were obtained just prior to phenylalanine administration and 2 hours after administration. Three patients in group 1 (with tardive dyskinesia) had the highest postloading phenylalanine plasma levels, this group as a whole had higher (though nonsignificant) mean phenylalanine levels than the other groups. Tardive dyskinesia score (measured using the Abnorma Involuntary Movements Scale (AIMS)) nonsignificantly increased in group 1. Postloading phenylalar level and postloading AIMS scores were significantly positively correlated in group 1 (rs=0.347, p les than 0.05; Spearman correlation coefficient 0.543, p less than 0.05). Postloading phenylalanine leve and baseline AIMS scores demonstrated a trend toward correlation (rs=0.246, p=0.092; Spearman correlation coefficient 0.679, p less than 0.05). In all patients, phenylalanine loading increased plasn phenylalanine levels approximately eight-fold, and plasma tyrosine increased 2.5 times as a result o conversion of phenylalanine to tyrosine. Plasma levels of competing large neutral amino acids such tryptophan decreased slightly (Gardos et al, 1992).

3.5.1.BP Pimozide
1) Interaction Effect: cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Haloperidol is associated with QTc prolongation and torsade de pointes (Hassaballa & Bal

2003x; Prod Info Haldol(R), 2001m). According to the manufacturer, coadministration of pimozide with drugs that potentially prolong the QTc interval, such as haloperidol, is contraindicated (Prod Info Orap(R) 1999e).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of agents that prolong the QT interval, such as haloperidol and pimozide, is contraindicated.
7) Probable Mechanism: additive effects on QT prolongation
8) Literature Reports
a) Numerous case reports have described significant QTc prolongation and torsades de pointes (Tc associated with haloperidol. Hemodynamically significant ventricular tachyarrhythmias, ventricular fibrillation, asystole, and death have been reported. The risk of TdP appears to be greater with intravenous haloperidol, but has occurred with oral and intramuscular use. The risk increases with doses greater than 35 milligrams (mg) over 24 hours, although TdP has been associated with a dos as low as 10 mg administered intravenously over 4 hours. To prevent haloperidol-induced TdP, scre patients for a history of dilated cardiomyopathy or alcohol abuse, testing for hypothyroidism before therapy, obtaining an electrocardiogram at baseline and throughout therapy, and monitoring potassium, magnesium, and calcium. In patients with a baseline QTc greater than 450 milliseconds (msec), haloperidol should be used cautiously or an alternative agent should be used. Discontinue haloperidol if the QTc increases more than 25% from baseline or if flattening of T-waves or development of U-waves occurs (Hassaballa & Balk, 2003w).
b) Seven patients developed torsade de pointes after therapeutic use of haloperidol in high doses. Three patients developed the dysrhythmia after administration of 211 milligrams (mg) to 825 mg haloperidol over 1 to 2 days for agitated delirium. These 3 patients recovered from the initial episode but 1 patient subsequently died of cardiac arrest upon readministration of haloperidol (Metzger & Friedman, 1993k; Wilt et al, 1993i). Torsades de pointes developed in 8 of 223 critically ill patients ir intensive care units. Patients who received intravenous haloperidol greater than 35 mg/day or had a QTc interval prolongation of greater than 500 milliseconds were at greatest risk (Sharma et al, 1998
c) In experimental studies of conditions other than Tourette's Disorder, sudden, unexpected deaths have occurred. The patients were receiving pimozide dosages of approximately 1 mg/kg. One possi mechanism for such deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmia. The manufacturer recommends that an electrocardiogram be performed before pimozid treatment is initiated and periodically thereafter, especially during the period of dose adjustment (Pro Info Orap(R) pimozide, 1999).

3.5.1.BQ Pirmenol
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Several antipsychotic agents have demonstrated QT prolongation including amisulpride, haloperidol, iloperidone, paliperidone, quetiapine, risperidone, sertindole, sultopride, ziprasidone, and zotepine (Prod Info FANAPT(TM) oral tablets, 2009; Prod Info Solian(R), 1999z; O'Brien et al, 1999r; Pro Info INVEGA(TM) extended-release oral tablets, 2006; Owens, 2001z; Duenas-Laita et al, 1999y; Agelin et al, 2001x; Lande et al, 1992z; Prod Info GEODON(R) intramuscular injection, oral capsule, 2005; Sweetman, 2003). Because Class IA antiarrhythmic agents may also prolong the QT interval and increas the risk of arrhythmias, the concurrent administration of antipsychotics with a drug from this class is not recommended (Prod Info FANAPT(TM) oral tablets, 2009; Prod Info Quinaglute(R), 1999).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: The concurrent administration of a Class IA antiarrhythmic and an antipsychoti not recommended.
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) In an open-label QTc study of patients with schizophrenia or schizoaffective disorder (n=160), iloperidone 12 mg twice a day was associated with QTc prolongation of 9 msec (Prod Info FANAPT (TM) oral tablets, 2009).
b) QRS widening, QTc interval prolongation, and torsades de pointes may occur with disopyramide therapy (Prod Info Norpace(R), 1997).
c) The effects of combined therapy with quinidine (Class IA antiarrhythmic agent) and haloperidol (antipsychotic agent) were studied by giving 12 healthy volunteers haloperidol 5 mg alone and with 250 mg of quinidine bisulfate. The study demonstrated significant increases in the plasma concentrations of haloperidol when given concurrently with quinidine versus haloperidol treatment alone. The mean area under the concentration curve (AUC) was increased from 54.3 ng/h/mL on haloperidol alone to 103.2 ng/h/mL on combined therapy. The peak concentration (Cmax) also show an increase from 1.9 ng/mL on haloperidol to 3.8 ng/mL on combined therapy. Half-life (T1/2) and ti to peak concentration (Tmax) were not significantly changed, thereby suggesting to the authors that tissue binding mechanism is more likely responsible for the plasma level changes than an eliminatio

alteration (Young et al, 1993).

3.5.1.BR Prajmaline

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Several antipsychotic agents have demonstrated QT prolongation including amisulpride, haloperidol, iloperidone, paliperidone, quetiapine, risperidone, sertindole, sultopride, ziprasidone, and zotepine (Prod Info FANAPT(TM) oral tablets, 2009; Prod Info Solian(R), 1999z; O'Brien et al, 1999r; Prc Info INVEGA(TM) extended-release oral tablets, 2006; Owens, 2001z; Duenas-Laita et al, 1999y; Agelin et al, 2001x; Lande et al, 1992z; Prod Info GEODON(R) intramuscular injection, oral capsule, 2005; Sweetman, 2003). Because Class IA antiarrhythmic agents may also prolong the QT interval and increas the risk of arrhythmias, the concurrent administration of antipsychotics with a drug from this class is not recommended (Prod Info FANAPT(TM) oral tablets, 2009; Prod Info Quinaglute(R), 1999).

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: The concurrent administration of a Class IA antiarrhythmic and an antipsychoti not recommended.

7) Probable Mechanism: additive cardiac effects

8) Literature Reports

a) In an open-label QTc study of patients with schizophrenia or schizoaffective disorder (n=160), iloperidone 12 mg twice a day was associated with QTc prolongation of 9 msec (Prod Info FANAPT (TM) oral tablets, 2009).

b) QRS widening, QTc interval prolongation, and torsades de pointes may occur with disopyramide therapy (Prod Info Norpace(R), 1997).

c) The effects of combined therapy with quinidine (Class IA antiarrhythmic agent) and haloperidol (antipsychotic agent) were studied by giving 12 healthy volunteers haloperidol 5 mg alone and with 250 mg of quinidine bisulfate. The study demonstrated significant increases in the plasma concentrations of haloperidol when given concurrently with quinidine versus haloperidol treatment alone. The mean area under the concentration curve (AUC) was increased from 54.3 ng/h/mL on haloperidol alone to 103.2 ng/h/mL on combined therapy. The peak concentration (Cmax) also show an increase from 1.9 ng/mL on haloperidol to 3.8 ng/mL on combined therapy. Half-life (T1/2) and tir to peak concentration (Tmax) were not significantly changed, thereby suggesting to the authors that tissue binding mechanism is more likely responsible for the plasma level changes than an eliminatio alteration (Young et al, 1993).

3.5.1.BS Probucol

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Even though no formal drug interaction studies have been done, the coadministration of drugs known to prolong the QTc interval is not recommended. Probucol has been shown to prolong the QTc interval (Gohn & Simmons, 1992; Prod Info Lorelco(R), 1991). Antipsychotics including haloperidol (Prod Info Haldol(R), 1998f), quetiapine (Owens, 2001q), risperidone (Prod Info Risperdal(R) risperidone 2000a), amisulpride (Prod Info Solian(R), 1999p), sertindole (Brown & Levin, 1998c); sultopride (Lande e al, 1992p), and zotepine (Sweetman, 2004) have been shown to prolong the QT interval at therapeutic doses.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Caution is advised if probucol and antipsychotics are used concomitantly.

7) Probable Mechanism: additive effect on QT interval

3.5.1.BT Procainamide

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Several antipsychotic agents have demonstrated QT prolongation including amisulpride, haloperidol, iloperidone, paliperidone, quetiapine, risperidone, sertindole, sultopride, ziprasidone, and zotepine (Prod Info FANAPT(TM) oral tablets, 2009; Prod Info Solian(R), 1999z; O'Brien et al, 1999r; Prc Info INVEGA(TM) extended-release oral tablets, 2006; Owens, 2001z; Duenas-Laita et al, 1999y; Agelin et al, 2001x; Lande et al, 1992z; Prod Info GEODON(R) intramuscular injection, oral capsule, 2005; Sweetman, 2003). Because Class IA antiarrhythmic agents may also prolong the QT interval and increas the risk of arrhythmias, the concurrent administration of antipsychotics with a drug from this class is not recommended (Prod Info FANAPT(TM) oral tablets, 2009; Prod Info Quinaglute(R), 1999).

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: The concurrent administration of a Class IA antiarrhythmic and an antipsychoti not recommended.

7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) In an open-label QTc study of patients with schizophrenia or schizoaffective disorder (n=160), iloperidone 12 mg twice a day was associated with QTc prolongation of 9 msec (Prod Info FANAPT (TM) oral tablets, 2009).
b) QRS widening, QTc interval prolongation, and torsades de pointes may occur with disopyramide therapy (Prod Info Norpace(R), 1997).
c) The effects of combined therapy with quinidine (Class IA antiarrhythmic agent) and haloperidol (antipsychotic agent) were studied by giving 12 healthy volunteers haloperidol 5 mg alone and with 250 mg of quinidine bisulfate. The study demonstrated significant increases in the plasma concentrations of haloperidol when given concurrently with quinidine versus haloperidol treatment alone. The mean area under the concentration curve (AUC) was increased from 54.3 ng/h/mL on haloperidol alone to 103.2 ng/h/mL on combined therapy. The peak concentration (Cmax) also show an increase from 1.9 ng/mL on haloperidol to 3.8 ng/mL on combined therapy. Half-life (T1/2) and tir to peak concentration (Tmax) were not significantly changed, thereby suggesting to the authors that tissue binding mechanism is more likely responsible for the plasma level changes than an eliminatio alteration (Young et al, 1993).

3.5.1.BU Prochlorperazine
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Concomitant use of phenothiazines and antipsychotic agents may cause additive effects o the QT interval and is not recommended. Q and T wave distortions have been observed in patients takin phenothiazines (Prod Info Compazine(R), 2002; Prod Info Stelazine(R), 2002; Prod Info Thorazine(R), 2002). Other phenothiazines may have similar effects, though no reports are available. Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999k), haloperidol (O'Brien et al, 1999g), paliperidone (Prod Info INVEGA(TM) extended-release oral tablets, 2006), quetiapine (Owens, 2001m), risperidone (Duenas-Laita et al, 1999k), sertindole (Agelink e al, 2001j), sultopride (Lande et al, 1992i), ziprasidone (Prod Info GEODON(R) intramuscular injection, or capsule, 2005), and zotepine (Sweetman, 2003).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of agents that prolong the QT interval, such as phenothiazines and antipsychotics, is not recommended.
7) Probable Mechanism: additive QT prolongation

3.5.1.BV Procyclidine
1) Interaction Effect: excessive anticholinergic effects (sedation, constipation, dry mouth)
2) Summary: Use of haloperidol in combination with anticholinergics may result in excessive anticholinergic effects (Prod Info Haldol(R), 2000). A significant reduction in haloperidol serum levels occurred following the addition of procyclidine in patients who were previously well stabilized. Following discontinuation of procyclidine haloperidol serum levels returned to baseline (Bamrah et al, 1986). In a number of case reports, the use of haloperidol with benztropine, trihexyphenidyl, or procyclidine has resulted in a worsening of schizophrenic symptoms. In addition, when anticholinergics are used with phenothiazines or haloperidol, there may be an increased incidence of tardive dyskinesia (Singh & Kay, 1979; Linnoila et al, 1980).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Use this combination only when clearly indicated. Monitor for excessive anticholinergic effects. A dosage adjustment for haloperidol may be required in order to maintain or achie a therapeutic effect.
7) Probable Mechanism: additive anticholinergic effects

3.5.1.BW Propafenone
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Coadministration of haloperidol with other drugs that potentially prolong the QTc interval, such as propafenone, should be approached with caution. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised (Owens, 2001f; Prod Info Haldol(R), 1998b; Larochelle et al, 1984).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of haloperidol and propafenone is not recommended due to the potential for inducing life-threatening arrhythmias. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised.

7) Probable Mechanism: additive effects on QT prolongation

3.5.1.BX Propranolol

1) Interaction Effect: an increased risk of hypotension and cardiac arrest

2) Summary: A case report described 3 hypotensive episodes and 2 cardiopulmonary arrests in a patier who received haloperidol and propranolol concomitantly on 3 separate occasions. Alpha-receptor bindin by haloperidol and an additive relaxant effect on peripheral blood vessels by haloperidol and propranolol possibly blunting sympathetic heart stimulation is a postulated mechanism for this interaction. The autho advise caution in coadministering haloperidol and propranolol or other beta blockers (Alexander et al, 1984). Monitoring the patient for signs of hypotension is warranted.

3) Severity: major

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: Concomitant use of haloperidol and propranolol may increase the risk of hypotension and cardiac arrest. Caution is advised when coadministering haloperidol and propranolol or other beta blockers (Prod Info INDERAL(R) LA oral capsules, 2007; Alexander et al, 1984). Monitor the patient for signs of hypotension.

7) Probable Mechanism: unknown

8) Literature Reports

a) A case report described 3 hypotensive episodes and 2 cardiopulmonary arrests with concomitan haloperidol and propranolol use in a 48-year-old woman with schizophrenia and hypertension. Two years after starting haloperidol 20 mg/day and trichlormethiazide 4 mg/day, the patient was admitte with psychosis due to discontinuing haloperidol. Her blood pressure (BP) was 205/100 mmHg. Propranolol 80 mg was initiated followed by haloperidol 10 mg nine hours later. Ninety minutes later she was unresponsive with shallow breathing and a BP of 80/0 mmHg. The patient recovered and w discharged with haloperidol 30 mg/day and trichlormethiazide 4 mg/day. Ten months later, the patie was admitted with agitation after stopping her medicine. Haloperidol 10 mg was administered. Ten hours later, she was given haloperidol 10 mg and propranolol 40 mg. Hypotension and cardiopulmonary arrest occurred 2.5 hours later. She was discharged the next day with loxapine 25 mg/day, trichlormethiazide 4 mg/day, and propranolol 80 mg twice per day. Five months later, the patient presented with acute psychosis and a BP of 210/110 mmHg. Because her chart could not be located to assess prior treatment, she was given propranolol 80 mg and 15 minutes later, haloperido 10 mg. Hypotension and cardiac arrest occurred 30 minutes later. After discharge, she continued to successfully maintained on trichlormethiazide 4 mg/day, propranolol 80 mg twice daily, and loxapine 30 mg/day. A postulated mechanism is alpha-receptor binding by haloperidol and an additive relaxa effect on peripheral blood vessels by haloperidol and propranolol that may blunt sympathetic heart stimulation (Alexander et al, 1984).

3.5.1.BY Protriptyline

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999b), haloperidol (O'Brien et al, 1999b), risperidone (Duenas-Laita et al, 1999b), sertindole (Agelink et al, 2001a), quetiapine (Owens, 2001b), sultopride (Lande et al, 1992a), and zotepi (Sweetman, 2003). Even though no formal drug interaction studies have been done, the coadministratio a tricyclic antidepressant and an antipsychotic is not recommended (Prod Info Pamelor(R), 2001; Marsh & Forker, 1982).

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of a tricyclic antidepressant and an antipsychoti not recommended.

7) Probable Mechanism: additive cardiac effects

8) Literature Reports

a) Electrocardiographic changes that have occurred during clinical trials with pimozide have include prolongation of the corrected QT interval, flattening, notching, and inversion of the T wave and the appearance of U waves. In experimental studies, sudden, unexpected deaths have occurred while patients were receiving pimozide doses of 1 mg/kg. The proposed mechanism for these deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmias (Prod Info Orap(R), 1999).

3.5.1.BZ Quetiapine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Haloperidol is associated with QTc prolongation and torsade de pointes (Hassaballa & Bal 2003h; Prod Info Haldol(R), 2001e). Quetiapine may prolong the QT interval at therapeutic and toxic dos Coadministration of haloperidol 7.5 mg twice daily with quetiapine 300 mg twice daily did not alter the steady-state pharmacokinetics of quetiapine (Prod Info Seroquel(R), 2003). Caution is advised with

coadministration of drugs that potentially prolong the QTc interval.
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Caution is advised if haloperidol and quetiapine are used concomitantly. Scree patients for conditions that may predispose to QT prolongation and torsade de pointes (i.e. cardiomyopathy, alcohol abuse, hypothyroidism). Monitor the ECG and electrolytes at baseline and throughout therapy.
7) Probable Mechanism: additive effects on QT prolongation
8) Literature Reports
a) Numerous case reports have described significant QTc prolongation and torsades de pointes (Tc associated with haloperidol. Hemodynamically significant ventricular tachyarrhythmias, ventricular fibrillation, asystole, and death have been reported. The risk of TdP appears to be greater with intravenous haloperidol, but has occurred with oral and intramuscular use. The risk increases with doses greater than 35 milligrams (mg) over 24 hours, though TdP has been associated with a dose low as 10 mg administered intravenously over 4 hours. To prevent haloperidol-induced TdP, screen patients for a history of dilated cardiomyopathy or alcohol abuse, testing for hypothyroidism before therapy, obtaining an electrocardiogram at baseline and throughout therapy, and monitoring potassium, magnesium, and calcium. In patients with a baseline QTc greater than 450 milliseconds (msec), haloperidol should be used cautiously or an alternative agent should be used. Discontinue haloperidol if the QTc increases more than 25% from baseline or if flattening of T-waves or development of U-waves occurs (Hassaballa & Balk, 2003g).

3.5.1.CA Quinupristin
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Quinupristin/dalfopristin is a major inhibitor of cytochrome P450 3A4 (CYP3A4) isoenzyme and haloperidol is a CYP3A4 substrate. Coadministration of these two agents may likely result in increas plasma concentrations of haloperidol, which may lead to QTc interval prolongation and risk of torsades d pointes (Prod Info SYNERCID(R) intravenous injection, 2003; Prod Info Haldol(R) Injection, 2001).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: The concurrent administration of quinupristin/dalfopristin and haloperidol shoul be avoided. Monitor ECG if used concomitantly.
7) Probable Mechanism: inhibition of cytochrome P450 3A4-mediated haloperidol metabolism

3.5.1.CB Rifampin
1) Interaction Effect: decreased haloperidol effectiveness
2) Summary: Haloperidol blood levels and half-life were examined in 7 patients treated concurrently with haloperidol and rifampin(Takeda et al, 1986). Blood levels and half-lives of haloperidol were significantly decreased compared to controls.
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor the patient for a decreased clinical response to haloperidol when rifam is added to the drug therapy. The haloperidol dose may need to be increased while receiving rifampin ar decreased when rifampin is discontinued.
7) Probable Mechanism: increased hepatic metabolism

3.5.1.CC Rifapentine
1) Interaction Effect: decreased haloperidol effectiveness
2) Summary: Rifapentine is known to induce hepatic enzymes involved in the metabolism of haloperidol When haloperidol and rifapentine are administered together, it may be necessary to increase the dose o haloperidol used (Prod Info Priftin(R), 2000).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor the patient for a decreased clinical response to haloperidol when rifapentine is added to the drug therapy. The haloperidol dose may need to be increased while receiving rifapentine and decreased when rifapentine is discontinued.
7) Probable Mechanism: increased hepatic metabolism

3.5.1.CD Risperidone
1) Interaction Effect: cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Haloperidol is associated with QTc prolongation and torsade de pointes (Hassaballa & Bal 2003j; Prod Info Haldol(R), 2001f). Sometimes fatal QRS prolongation and QTc prolongation have been reported in patients taking risperidone therapeutically (Duenas-Laita et al, 1999o; Ravin & Levenson,

1997d; Gesell & Stephen, 1997a) and in overdose situations (Lo Vecchio et al, 1996a; Brown et al, 1993
Caution is advised with coadministration of drugs that potentially prolong the QTc interval.
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Caution is advised if haloperidol and risperidone are used concomitantly. Scree
patients for conditions that may predispose to QT prolongation and torsade de pointes (i.e.
cardiomyopathy, alcohol abuse, hypothyroidism). Monitor the ECG and electrolytes at baseline and
throughout therapy.
7) Probable Mechanism: additive effects on QT prolongation
8) Literature Reports
a) Sometimes fatal QRS prolongation and QTc prolongation have been reported in patients taking
risperidone therapeutically (Duenas-Laita et al, 1999n; Ravin & Levenson, 1997c; Gesell & Stephen
1997) and in overdose situations (Lo Vecchio et al, 1996; Brown et al, 1993).
b) Numerous case reports have described significant QTc prolongation and torsades de pointes (Tc
associated with haloperidol. Hemodynamically significant ventricular tachyarrhythmias, ventricular
fibrillation, asystole, and death have been reported. The risk of TdP appears to be greater with
intravenous haloperidol, but has occurred with oral and intramuscular use. The risk increases with
doses greater than 35 milligrams (mg) over 24 hours, although TdP has been associated with a dos
as low as 10 mg administered intravenously over 4 hours. To prevent haloperidol-induced TdP, scre
patients for a history of dilated cardiomyopathy or alcohol abuse, testing for hypothyroidism before
therapy, obtaining an electrocardiogram at baseline and throughout therapy, and monitoring
potassium, magnesium, and calcium. In patients with a baseline QTc greater than 450 milliseconds
(msec), haloperidol should be used cautiously or an alternative agent should be used. Discontinue
haloperidol if the QTc increases more than 25% from baseline or if flattening of T-waves or
development of U-waves occurs (Hassaballa & Balk, 2003i).

3.5.1.CE Sematilide
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac
arrest)
2) Summary: Concurrent use of sematilide and haloperidol is not recommended due to the risk of additiv
effects on the QT interval. If concurrent use cannot be avoided, cautious dosing and telemetric monitorin
is advised (Yamreudeewong et al, 2003a).
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of sematilide and haloperidol is not recommende
due to the potential for inducing life-threatening arrhythmias. If concurrent use cannot be avoided, cautio
dosing and telemetric monitoring is advised.
7) Probable Mechanism: additive QT prolongation
8) Literature Reports
a) Class III antiarrhythmics have been shown to prolong the QT interval, which may result in
ventricular tachycardia, ventricular fibrillation, and torsades de pointes. Several antipsychotic agents
have demonstrated QT prolongation including haloperidol (O'Brien et al, 1999a). Concomitant use o
Class III antiarrhythmic agents such as sematilide and haloperidol may have additive effects on the
interval and is not recommended (Yamreudeewong et al, 2003).

3.5.1.CF Sertindole
1) Interaction Effect: cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Haloperidol is associated with QTc prolongation and torsade de pointes (Hassaballa & Bal
2003r; Prod Info Haldol(R), 2001j). Sertindole has demonstrated QTc prolongation (Agelink et al, 2001t;
Brown & Levin, 1998e; Cardoni & Myer, 1997b). Caution is advised with coadministration of drugs that
potentially prolong the QTc interval.
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Caution is advised if haloperidol and sertindole are used concomitantly. Screer
patients for conditions that may predispose to QT prolongation and torsade de pointes (i.e.
cardiomyopathy, alcohol abuse, hypothyroidism). Monitor the ECG and electrolytes at baseline and
throughout therapy.
7) Probable Mechanism: additive effects on QT prolongation
8) Literature Reports
a) Seven patients developed torsade de pointes after therapeutic use of haloperidol in high doses.
Three patients developed the dysrhythmia after administration of 211 milligrams (mg) to 825 mg
haloperidol over 1 to 2 days for agitated delirium. These 3 patients recovered from the initial episode
but 1 patient subsequently died of cardiac arrest upon readministration of haloperidol (Metzger &
Friedman, 1993i; Wilt et al, 1993g). Torsades de pointes developed in 8 of 223 critically ill patients ir
intensive care units. Patients who received intravenous haloperidol greater than 35 mg/day or had a

QTc interval prolongation of greater than 500 milliseconds were at greatest risk (Sharma et al, 1998

b) Numerous case reports have described significant QTc prolongation and torsades de pointes (Tc associated with haloperidol. Hemodynamically significant ventricular tachyarrhythmias, ventricular fibrillation, asystole, and death have been reported. The risk of TdP appears to be greater with intravenous haloperidol, but has occurred with oral and intramuscular use. The risk increases with doses greater than 35 milligrams (mg) over 24 hours, although TdP has been associated with a dos as low as 10 mg administered intravenously over 4 hours. To prevent haloperidol-induced TdP, scre patients for a history of dilated cardiomyopathy or alcohol abuse, testing for hypothyroidism before therapy, obtaining an electrocardiogram at baseline and throughout therapy, and monitoring potassium, magnesium, and calcium. In patients with a baseline QTc greater than 450 milliseconds (msec), haloperidol should be used cautiously or an alternative agent should be used. Discontinue haloperidol if the QTc increases more than 25% from baseline or if flattening of T-waves or development of U-waves occurs (Hassaballa & Balk, 2003q).

c) The overall incidence of QT interval prolongation with sertindole is estimated at 1.9% to 4%, and the potential risk of developing torsade de pointes has been estimated at 0.13% to 0.21% (Brown & Levin, 1998d). Periodic electrocardiographic monitoring is required in the United Kingdom per sertindole's official labeling (Cardoni & Myer, 1997a).

d) Thirty, otherwise healthy, schizophrenic patients participated in an open, dose titration (4 to 16 mg/day) study to determine the cardiovascular effects of sertindole. At the end of the 3-week study i was concluded that resting heart rate and frequency corrected QT intervals increased in a dose-rela manner, while there was no change in PQ-conduction times, autonomic parasympathetic tone, or blood pressure. Conduction times increased an average 3.5% to 6.5% over the dosing range (Agelir et al, 2001s).

3.5.1.CG Sotalol

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Concurrent use of sotalol and haloperidol is not recommended due to the risk of additive effects on the QT interval. If concurrent use cannot be avoided, cautious dosing and telemetric monitorin is advised (Yamreudeewong et al, 2003a).

3) Severity: major

4) Onset: rapid

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of sotalol and haloperidol is not recommended d to the potential for inducing life-threatening arrhythmias. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised.

7) Probable Mechanism: additive QT prolongation

8) Literature Reports

a) Class III antiarrhythmics have been shown to prolong the QT interval, which may result in ventricular tachycardia, ventricular fibrillation, and torsades de pointes. Several antipsychotic agents have demonstrated QT prolongation including haloperidol (O'Brien et al, 1999a). Concomitant use o Class III antiarrhythmic agents such as sotalol and haloperidol may have additive effects on the QT interval and is not recommended (Yamreudeewong et al, 2003).

3.5.1.CH Sparfloxacin

1) Interaction Effect: prolongation of the QTc interval and/or torsades de pointes

2) Summary: Haloperidol is associated with QTc prolongation and torsade de pointes (Hassaballa & Bal 2003v; Prod Info Haldol(R), 2001l). Coadministration of sparfloxacin with drugs that potentially prolong th QTc interval, such as haloperidol, is contraindicated (Prod Info Zagam(R), 1998a).

3) Severity: contraindicated

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of sparfloxacin with agents that prolong the QT interval, such as haloperidol, is contraindicated.

7) Probable Mechanism: additive effects on QTc prolongation

8) Literature Reports

a) In clinical trials involving 1489 patients with a baseline QTc measurement, the mean prolongation the QTc interval at sparfloxacin steady-state was 10 msec (2.5%). Of these subjects, 0.7% had a QT interval greater than 500 msec at steady-state. However, no arrhythmic effects were seen in any of t patients. The magnitude of the QTc effect does not increase with repeated administration of sparfloxacin, and the QTc interval returns to baseline within 48 hours after discontinuation of sparfloxacin (Prod Info Zagam(R), 1998).

b) A 47-year-old woman treated with sparfloxacin went into cardiac arrest as a result of torsade de pointes and required cardiopulmonary resuscitation. dizziness and lost consciousness. Her pre-treatment electrocardiogram showed QT and QTc intervals of 0.34 and 0.46 seconds, respectively. A electrocardiogram post-arrest revealed QT and QTc intervals of 0.35 and 0.60 seconds, respectively Continuous electrocardiography confirmed numerous episodes of torsade de pointes. Sparfloxacin w discontinued and the QTc returned to baseline within a week. Upon further testing, it was determine

that the patient suffered from a mild idiopathic long QT syndrome. Due to the onset of symptoms wit administration of sparfloxacin and the relief of symptoms following discontinuation of the drug, it is highly probable that sparfloxacin contributed to the torsades de pointes (Dupont et al, 1996).
c) Numerous case reports have described significant QTc prolongation and torsades de pointes (Tc associated with haloperidol. Hemodynamically significant ventricular tachyarrhythmias, ventricular fibrillation, asystole, and death have been reported. The risk of TdP appears to be greater with intravenous haloperidol, but has occurred with oral and intramuscular use. The risk increases with doses greater than 35 milligrams (mg) over 24 hours, although TdP has been associated with a dos as low as 10 mg administered intravenously over 4 hours. To prevent haloperidol-induced TdP, scre patients for a history of dilated cardiomyopathy or alcohol abuse, testing for hypothyroidism before therapy, obtaining an electrocardiogram at baseline and throughout therapy, and monitoring potassium, magnesium, and calcium. In patients with a baseline QTc greater than 450 milliseconds (msec), haloperidol should be used cautiously or an alternative agent should be used. Discontinue haloperidol if the QTc increases more than 25% from baseline or if flattening of T-waves or development of U-waves occurs (Hassaballa & Balk, 2003u).

3.5.1.CI Spiramycin

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Spiramycin has been shown to prolong the QTc interval at the recommended therapeutic dose (Stramba-Badiale et al, 1997). Even though no formal drug interaction studies have been done, the coadministration of antipsychotics and other drugs known to prolong the QTc interval, including spiramyc is not recommended. Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999v), haloperidol (O'Brien et al, 1999o), quetiapine (Owens, 2001w), risperidone (Duenas-Laita et al, 1999u), sertindole (Agelink et al, 2001r), sultopride (Lande et al, 1992v), and zotepine (Sweetman, 2003).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of spiramycin and antipsychotics is not recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.CJ Sulfamethoxazole

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Cotrimoxazole has been shown to prolong the QTc interval at the recommended therapeu dose (Lopez et al, 1987). Even though no formal drug interaction studies have been done, the coadministration of antipsychotics and other drugs known to prolong the QTc interval, including cotrimoxazole, is not recommended. Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999h), haloperidol (O'Brien et al, 1999e), quetiapine (Owens 2001i), risperidone (Duenas-Laita et al, 1999g), sertindole (Agelink et al, 2001f), sultopride (Lande et al, 1992e), and zotepine (Sweetman, 2003).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of cotrimoxazole and antipsychotics is not recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.CK Sultopride

1) Interaction Effect: cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Haloperidol is associated with QTc prolongation and torsade de pointes (Hassaballa & Bal 2003l; Prod Info Haldol(R), 2001g). Sultopride may induce prolongation of the QT interval and ventricula arrhythmias including torsades de pointes following therapeutic or toxic doses (Harry, 1997b; Lande et a 1992n; Montaz et al, 1992a). Caution is advised with coadministration of drugs that potentially prolong th QTc interval.
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Caution is advised if haloperidol and sultopride are used concomitantly. Screer patients for conditions that may predispose to QT prolongation and torsade de pointes (i.e. cardiomyopathy, alcohol abuse, hypothyroidism). Monitor the ECG and electrolytes at baseline and throughout therapy.
7) Probable Mechanism: additive effects on QT prolongation
8) Literature Reports
a) Seven patients developed torsade de pointes after therapeutic use of haloperidol in high doses. Three patients developed the dysrhythmia after administration of 211 milligrams (mg) to 825 mg

haloperidol over 1 to 2 days for agitated delirium. These 3 patients recovered from the initial episode but 1 patient subsequently died of cardiac arrest upon readministration of haloperidol (Metzger & Friedman, 1993h; Wilt et al, 1993f). Torsades de pointes developed in 8 of 223 critically ill patients i intensive care units. Patients who received intravenous haloperidol greater than 35 mg/day or had a QTc interval prolongation of greater than 500 milliseconds were at greatest risk (Sharma et al, 1998

b) Numerous case reports have described significant QTc prolongation and torsades de pointes (T associated with haloperidol. Hemodynamically significant ventricular tachyarrhythmias, ventricular fibrillation, asystole, and death have been reported. The risk of TdP appears to be greater with intravenous haloperidol, but has occurred with oral and intramuscular use. The risk increases with doses greater than 35 milligrams (mg) over 24 hours, although TdP has been associated with a dos as low as 10 mg administered intravenously over 4 hours. To prevent haloperidol-induced TdP, scre patients for a history of dilated cardiomyopathy or alcohol abuse, testing for hypothyroidism before therapy, obtaining an electrocardiogram at baseline and throughout therapy, and monitoring potassium, magnesium, and calcium. In patients with a baseline QTc greater than 450 milliseconds (msec), haloperidol should be used cautiously or an alternative agent should be used. Discontinue haloperidol if the QTc increases more than 25% from baseline or if flattening of T-waves or development of U-waves occurs (Hassaballa & Balk, 2003k).

c) Sultopride may induce prolongation of the QT interval and ventricular arrhythmias including torsades de pointes following therapeutic or toxic doses (Harry, 1997a; Lande et al, 1992m; Montaz al, 1992).

3.5.1.CL Tacrine

1) Interaction Effect: Parkinsonian syndrome (akinesia, shuffling gait, masked facies, slurred speech, lea pipe rigidity, cogwheel signs)

2) Summary: Parkinsonian syndrome with concomitant use of tacrine and haloperidol has been reportec two separate case reports. Both patients were able to tolerate one of the drugs when the other was discontinued. Both of these drugs increase acetylcholine activity in the striatal region of the brain, which may have caused the effects observed (McSwain & Forman, 1995a; Maany, 1996a).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Patients should be closely monitored for signs of a Parkinsonian syndrome wh being treated with haloperidol and tacrine. Discontinuation of one agent may be required.

7) Probable Mechanism: increased striatal acetylcholine activity

8) Literature Reports

a) The first case report of tacrine and haloperidol resulting in a parkinsonian syndrome was in an 87 year old male (McSwain & Forman, 1995). Haloperidol doses of 5 mg daily were being administered for agitation and paranoia. When tacrine 10 mg four times daily was added to his regimen, he developed severe parkinsonian symptoms within 72 hours, including akinesia, masked facies, shuffl gait, and lead-pipe rigidity. When both tacrine and haloperidol were discontinued, the symptoms resolved within approximately eight hours. Haloperidol was successfully reinitiated at a dose of 4 mg daily without recurrence of the parkinsonian syndrome.

b) A 72-year old female with agitated paranoid psychosis became controlled on haloperidol 10 mg daily without undue side effects, including extrapyramidal syndrome. When tacrine 10 mg four times daily was added to her regimen for dementia, she developed a disabling parkinsonian syndrome wit a week. Symptoms included severe akinesia, shuffling gait, masked facies, slurred speech, and pronounced rigidity and cogwheel signs. The haloperidol regimen was tapered off and replaced with risperidone 1 mg twice daily, with resolution of the parkinsonian syndrome within a few days. She di not experience further extrapyramidal signs, even after the tacrine dose was increased to 20 mg fou times daily (Maany, 1996).

3.5.1.CM Tedisamil

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Concurrent use of tedisamil and haloperidol is not recommended due to the risk of additive effects on the QT interval. If concurrent use cannot be avoided, cautious dosing and telemetric monitorin is advised (Yamreudeewong et al, 2003a).

3) Severity: major

4) Onset: rapid

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of haloperidol and tedisamil is not recommende due to the potential for inducing life-threatening arrhythmias. If concurrent use cannot be avoided, cautio dosing and telemetric monitoring is advised.

7) Probable Mechanism: additive QT prolongation

8) Literature Reports

a) Class III antiarrhythmics have been shown to prolong the QT interval, which may result in ventricular tachycardia, ventricular fibrillation, and torsades de pointes. Several antipsychotic agents have demonstrated QT prolongation including haloperidol (O'Brien et al, 1999a). Concomitant use o

Class III antiarrhythmic agents such as tedisamil and haloperidol may have additive effects on the C interval and is not recommended (Yamreudeewong et al, 2003).

3.5.1.CN Telithromycin

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Some antipsychotic agents prolong the QT interval and an additive effect would be anticipated if administered with other agents which lengthen the QT interval (Agelink et al, 2001g; Owens 2001j; Prod Info Haldol(R), 1998c; Lande et al, 1992f). Even though no formal drug interaction studies ha been done, antipsychotic agents should not be coadministered with other drugs which are also known to prolong the QTc interval, including telithromycin (Owens, 2001j).

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Due to the potential for additive effects on the QT interval, the concurrent administration of telithromycin and an antipsychotic is not recommended.

7) Probable Mechanism: additive effect on QT interval

8) Literature Reports

a) Fatal QRS prolongation and QTc prolongation have been reported in patients taking risperidone therapeutically (Duenas-Laita et al, 1999h; Ravin & Levenson, 1997a).

3.5.1.CO Terfenadine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Some antipsychotics have been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Geodon(TM), 2002a; Owens, 2001ab; Prod Info Orap(R), 1999d). Even thou no formal drug interaction studies have been done, the coadministration of terfenadine and other drugs known to prolong the QTc interval, including antipsychotics, is contraindicated (Anon, 1997).

3) Severity: contraindicated

4) Onset: rapid

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of terfenadine with any drug that prolongs the Q interval, such as antipsychotic agents, is contraindicated.

7) Probable Mechanism: additive effect on QT interval

8) Literature Reports

a) Electrocardiographic changes that have occurred during clinical trials with pimozide have include prolongation of the corrected QT interval, flattening, notching, and inversion of the T wave and the appearance of U waves. In experimental studies, sudden, unexpected deaths have occurred while patients were receiving pimozide doses of 1 mg/kg. The proposed mechanism for these deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmias (Prod Info Orap(R), 1999c).

3.5.1.CP Tetrabenazine

1) Interaction Effect: increased risk of QT interval prolongation, neuroleptic malignant syndrome, extrapyramidal disorders

2) Summary: Tetrabenazine causes a small increase in the correct QT interval. As the degree of prolongation increases, QT prolongation can develop into torsade de pointes-type VT. The concomitant u of tetrabenazine with other drugs known for QT prolongation (eg, haloperidol) should be avoided. In a randomized, double-blind, placebo controlled crossover study of healthy subjects, the effect of a single 2 mg or 50 mg dose of tetrabenazine on the QT interval was studied with moxifloxacin as a positive contro The 50 mg dose of tetrabenazine caused an approximate 8 millisecond mean increase in QT (Prod Info XENAZINE(R) oral tablets, 2008). In addition to QT prolongation, tetrabenazine may also cause adverse reactions such as neuroleptic malignant syndrome and extrapyramidal disorders, which may be exaggerated when coadministered with neuroleptic drugs (eg, haloperidol) (Prod Info XENAZINE(R) oral tablets, 2008)

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Coadministration of tetrabenazine with haloperidol or other neuroleptic drugs m increase tetrabenazine adverse reactions, such as QT interval prolongation and increased risk of torsade de pointes. Other adverse reactions, such as neuroleptic malignant syndrome and extrapyramidal disord may be enhanced when given with a dopamine agonist such as haloperidol (Prod Info XENAZINE(R) ora tablets, 2008).

7) Probable Mechanism: increased dopamine levels; additive effects on QT interval prolongation

3.5.1.CQ Thioridazine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Although citing no data, the manufacturer of thioridazine states that concomitant use with other drugs which prolong the QT interval is contraindicated (Prod Info Mellaril(R), 2001). Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999q), haloperidol (O'Brien et al, 1999k), pimozide (Prod Info Orap(R), 2000), quetiapine (Owens, 2001 paliperidone (Prod Info INVEGA(TM) extended-release oral tablets, 2006), risperidone (Duenas-Laita et 1999q), sertindole (Agelink et al, 2001n), sultopride (Lande et al, 1992q), ziprasidone (Prod Info GEODC (R) intramuscular injection, oral capsule, 2005), and zotepine (Sweetman, 2004).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of agents that prolong the QT interval, such as antipsychotics, and thioridazine, is contraindicated.
7) Probable Mechanism: additive QT prolongation

3.5.1.CR Tramadol
1) Interaction Effect: an increased risk of seizures
2) Summary: Seizures have been reported in patients using tramadol. The manufacturer of tramadol sta that combining neuroleptic medications with tramadol may enhance the risk of seizures (Prod Info Ultran (R), 1998).
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Caution should be used if tramadol is to be administered to patients receiving neuroleptic therapy. If possible, avoid this combination, especially in patients with underlying conditions t might predispose to seizures.
7) Probable Mechanism: unknown

3.5.1.CS Trifluoperazine
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Concomitant use of phenothiazines and antipsychotic agents may cause additive effects o the QT interval and is not recommended. Q and T wave distortions have been observed in patients takin phenothiazines (Prod Info Compazine(R), 2002; Prod Info Stelazine(R), 2002; Prod Info Thorazine(R), 2002). Other phenothiazines may have similar effects, though no reports are available. Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999k), haloperidol (O'Brien et al, 1999g), paliperidone (Prod Info INVEGA(TM) extended-release oral tablets, 2006), quetiapine (Owens, 2001m), risperidone (Duenas-Laita et al, 1999k), sertindole (Agelink e al, 2001j), sultopride (Lande et al, 1992i), ziprasidone (Prod Info GEODON(R) intramuscular injection, or capsule, 2005), and zotepine (Sweetman, 2003).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of agents that prolong the QT interval, such as phenothiazines and antipsychotics, is not recommended.
7) Probable Mechanism: additive QT prolongation

3.5.1.CT Trihexyphenidyl
1) Interaction Effect: excessive anticholinergic effects (sedation, constipation, dry mouth)
2) Summary: Use of haloperidol in combination with anticholinergics may result in additive anticholinergi effects (Prod Info Haldol(R), 2000b). In a number of case reports, the use of haloperidol with benztropine trihexyphenidyl, or procyclidine has resulted in a worsening of schizophrenic symptoms. In addition, whe anticholinergics are used with phenothiazines or haloperidol, there may be increased incidence of tardive dyskinesia (Singh & Kay, 1979b; Linnoila et al, 1980b).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Use this combination only when clearly indicated. Monitor for excessive anticholinergic effects. Dosage adjustments may be required.
7) Probable Mechanism: additive anticholinergic effects

3.5.1.CU Trimethoprim
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Cotrimoxazole has been shown to prolong the QTc interval at the recommended therapeu dose (Lopez et al, 1987). Even though no formal drug interaction studies have been done, the coadministration of antipsychotics and other drugs known to prolong the QTc interval, including cotrimoxazole, is not recommended. Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999h), haloperidol (O'Brien et al, 1999e), quetiapine (Owens

2001i), risperidone (Duenas-Laita et al, 1999g), sertindole (Agelink et al, 2001f), sultopride (Lande et al, 1992e), and zotepine (Sweetman, 2003).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of cotrimoxazole and antipsychotics is not recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.CV Trimipramine
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999b), haloperidol (O'Brien et al, 1999b), risperidone (Duenas-Laita et al, 1999b), sertindole (Agelink et al, 2001a), quetiapine (Owens, 2001b), sultopride (Lande et al, 1992a), and zotepi (Sweetman, 2003). Even though no formal drug interaction studies have been done, the coadministratio a tricyclic antidepressant and an antipsychotic is not recommended (Prod Info Pamelor(R), 2001; Marsh & Forker, 1982).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of a tricyclic antidepressant and an antipsychoti not recommended.
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) Electrocardiographic changes that have occurred during clinical trials with pimozide have include prolongation of the corrected QT interval, flattening, notching, and inversion of the T wave and the appearance of U waves. In experimental studies, sudden, unexpected deaths have occurred while patients were receiving pimozide doses of 1 mg/kg. The proposed mechanism for these deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmias (Prod Info Orap(R), 1999).

3.5.1.CW Vasopressin
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Antipsychotics and vasopressin have been shown to prolong the QTc interval at the recommended therapeutic dose (Owens, 2001a; Prod Info Solian(R), 1999a; Duenas-Laita et al, 1999a; Brown & Levin, 1998; Harry, 1997; Prod Info Nipolept(R), 1996; Metzger & Friedman, 1993; Mauro et al, 1988). Even though no formal drug interaction studies have been done, the coadministration of drugs known to prolong the QTc interval is not recommended.
3) Severity: major
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of drugs that prolong the QT interval, such as antipsychotics and vasopressin, is not recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.CX Venlafaxine
1) Interaction Effect: increased haloperidol serum concentrations and an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Venlafaxine may inhibit haloperidol metabolism (Prod Info Effexor(R) XR, 2003a). Haloperidol is associated with QTc prolongation and torsade de pointes (Hassaballa & Balk, 2003p; Proc Info Haldol(R), 2001i). Venlafaxine has been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Effexor(R) XR, 2003a). Concomitant use is not recommended.
3) Severity: major
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: The concurrent administration of haloperidol and venlafaxine is not recommended.
7) Probable Mechanism: decreased haloperidol metabolism; theoretical additive effect on QT prolongati
8) Literature Reports
a) Under steady-state conditions, venlafaxine 150 mg daily decreased the total oral clearance of a single 2 mg dose of haloperidol by 42% in 24 healthy subjects. This resulted in a 70% increase in th haloperidol area under the concentration-time curve (AUC). The haloperidol maximum concentratio (Cmax) was increased by 88% when venlafaxine was coadministered, but the elimination half-life of haloperidol was not affected. The mechanism behind this interaction is not known (Prod Info Effexor XR, 2003).
b) Numerous case reports have described significant QTc prolongation and torsades de pointes (Tc

associated with haloperidol. Hemodynamically significant ventricular tachyarrhythmias, ventricular fibrillation, asystole, and death have been reported. The risk of TdP appears to be greater with intravenous haloperidol, but has occurred with oral and intramuscular use. The risk increases with doses greater than 35 milligrams (mg) over 24 hours, although TdP has been associated with a dos as low as 10 mg administered intravenously over 4 hours. To prevent haloperidol-induced TdP, scre patients for a history of dilated cardiomyopathy or alcohol abuse, testing for hypothyroidism before therapy, obtaining an electrocardiogram at baseline and throughout therapy, and monitoring potassium, magnesium, and calcium. In patients with a baseline QTc greater than 450 milliseconds (msec), haloperidol should be used cautiously or an alternative agent should be used. Discontinue haloperidol if the QTc increases more than 25% from baseline or if flattening of T-waves or development of U-waves occurs (Hassaballa & Balk, 2003o).

3.5.1.CY Vitex

1) Interaction Effect: decreased effectiveness of dopamine antagonists

2) Summary: Theoretically, the dopamine agonist activity of Vitex may oppose that of dopamine antagonists, decreasing their effectiveness. Vitex has been effective in alleviating luteal phase defects du to hyperprolactinemia and in relieving symptoms related to premenstrual tension syndrome (Milewicz et a 1993a; Lauritzen et al, 1997a). Vitex reduced prolactin secretion in humans (Milewicz et al, 1993a). In vit Vitex inhibited prolactin release by binding to the D2 receptor (Jarry et al, 1994a).

3) Severity: minor

4) Onset: delayed

5) Substantiation: established

6) Clinical Management: If therapy is initiated with Vitex and a dopamine antagonist, monitor closely for return of symptoms previously controlled by the dopamine antagonist.

7) Probable Mechanism: dopamine agonism of Vitex may counteract dopamine antagonists

8) Literature Reports

a) Vitex agnus castus (Vitex) effectively normalized prolactin release in a randomized double-blind, placebo-controlled trial of 52 women with luteal phase defects due to latent hyperprolactinemia. Administration of Vitex agnus castus 20 mg daily for three months reduced prolactin release (from 2 to 22.5 nanogram (ng)/mL; p equal to 0.23), normalized shortened luteal phases (from 5.5 days to 1 days; p less than 0.005), and eliminated deficits in luteal progesterone synthesis (from 2.46 ng/mL t 9.69 ng/mL; p less than 0.001). No side effects were noted (Milewicz et al, 1993).

b) Vitex agnus castus and pyridoxine caused a similar reduction on the premenstrual tension scale (PMTS) in a randomized, controlled trial of 127 women with PMTS. Patients taking Vitex agnus cast (Agnolyt(R)) experienced more relief from breast tenderness, inner tension, headache, edema, constipation, and depression than those taking pyridoxine. Patients in the Vitex agnus castus group receive one capsule of Agnolyt(R) and one placebo capsule daily for 3 menstrual cycles. Patients in the pyridoxine group received one placebo capsule twice daily on days 1-15 of the menstrual cycle a pyridoxine 100 mg twice daily on days 16 to 35 of the menstrual cycle for 3 menstrual cycles. Unspecified gastrointestinal disturbances occurred in the treatment group along with two cases of sk reaction and one transient headache (Lauritzen et al, 1997).

c) In vitro, Vitex (Agnus castus) was found to bind to the D2 receptor in rat pituitary cell cultures. Ba prolactin release was significantly inhibited by 0.5 milligram (mg) and 1 mg of vitex extract/mL cultur medium (p less than 0.05). Agnus castus extract doses from 0.125 mg/mL to 1 mg/mL significantly suppressed prolactin release in cells stimulated by thyrothropin releasing hormone (TRH) (p less tha 0.05). Dopaminergic action was demonstrated in the rat corpus striatum membrane dopamine recep assay. Agnus castus extract did not affect basal luteinizing hormone (LH) or follicle-stimulating hormone (FSH), indicating selectivity for prolactin secretion, and not generalized inhibition of pituitar hormone secretion. The effect was not due to a cytotoxic effect as demonstrated by the lack of effec on the MTT-conversion test. The authors concluded that Agnus castus exerted its prolactin inhibiting effect via stimulation of D2 receptors in the pituitary (Jarry et al, 1994).

3.5.1.CZ Ziprasidone

1) Interaction Effect: cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Haloperidol is associated with QTc prolongation and torsade de pointes (Hassaballa & Bal 2003e; Prod Info Haldol(R), 2001c). Coadministration of ziprasidone with drugs that potentially prolong th QTc interval, such as haloperidol, is contraindicated (Prod Info Geodon(R), 2002a).

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of ziprasidone with agents that prolong the QT interval, such as haloperidol, is contraindicated.

7) Probable Mechanism: additive effects on QT prolongation

8) Literature Reports

a) Seven patients developed torsade de pointes after therapeutic use of haloperidol in high doses. Three patients developed the dysrhythmia after administration of 211 milligrams (mg) to 825 mg haloperidol over 1 to 2 days for agitated delirium. These 3 patients recovered from the initial episode but 1 patient subsequently died of cardiac arrest upon readministration of haloperidol (Metzger &

Friedman, 1993d; Wilt et al, 1993b). Torsades de pointes developed in 8 of 223 critically ill patients i intensive care units. Patients who received intravenous haloperidol greater than 35 mg/day or had a QTc interval prolongation of greater than 500 milliseconds were at greatest risk (Sharma et al, 1998

b) Numerous case reports have described significant QTc prolongation and torsades de pointes (Tc associated with haloperidol. Hemodynamically significant ventricular tachyarrhythmias, ventricular fibrillation, asystole, and death have been reported. The risk of TdP appears to be greater with intravenous haloperidol, but has occurred with oral and intramuscular use. The risk increases with doses greater than 35 milligrams (mg) over 24 hours, although TdP has been associated with a dos as low as 10 mg administered intravenously over 4 hours. To prevent haloperidol-induced TdP, scre patients for a history of dilated cardiomyopathy or alcohol abuse, testing for hypothyroidism before therapy, obtaining an electrocardiogram at baseline and throughout therapy, and monitoring potassium, magnesium, and calcium. In patients with a baseline QTc greater than 450 milliseconds (msec), haloperidol should be used cautiously or an alternative agent should be used. Discontinue haloperidol if the QTc increases more than 25% from baseline or if flattening of T-waves or development of U-waves occurs (Hassaballa & Balk, 2003d).

c) It has been shown that ziprasidone prolongs the QTc and that this represents a risk of potentially fatal ventricular dysrhythmias ((Anon, 2000)). QT prolongation is dose-related. It is not yet known whether ziprasidone will cause torsades de pointes or increase the rate of sudden death. In clinical trials ziprasidone increased the QTc interval, compared to placebo, by approximately 10 millisecond (msec) at the highest dose (160 milligrams). Baseline QTc interval increased 9 to 14 msec more wit ziprasidone than with risperidone, olanzapine, quetiapine, and haloperidol, but QTc interval was 14 msec less than that observed with thioridazine (Prod Info Geodon(R), 2002).

3.5.1.DA Zolmitriptan

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Zolmitriptan has been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Zomig(R), 2001). Antipsychotics including haloperidol (Prod Info Haldol(R), 1998h), quetiapine (Owens, 2001y), risperidone (Prod Info Risperdal(R) risperidone, 2000c), amisulpride (Prod In Solian(R), 1999y), sertindole (Agelink et al, 2001w); sultopride (Lande et al, 1992y), and zotepine (Sweetman, 2004) have been shown to prolong the QT interval at therapeutic doses. Even though no formal drug interaction studies have been done, the coadministration of drugs known to prolong the QT interval is not recommended.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of zolmitriptan and antipsychotics is not recommended.

7) Probable Mechanism: additive effect on QT interval

3.5.1.DB Zotepine

1) Interaction Effect: increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arres

2) Summary: Haloperidol is associated with QTc prolongation and torsade de pointes (Hassaballa & Bal 2003t; Prod Info Haldol(R), 2001k). Zotepine may cause QT prolongation (Sweetman, 2003). Caution is advised with coadministration of drugs that potentially prolong the QTc interval.

3) Severity: major

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: Caution is advised if haloperidol and zotepine are used concomitantly. Screen patients for conditions that may predispose to QT prolongation and torsade de pointes (i.e. cardiomyopathy, alcohol abuse, hypothyroidism). Monitor the ECG and electrolytes at baseline and throughout therapy.

7) Probable Mechanism: additive effects on QT prolongation

8) Literature Reports

a) Numerous case reports have described significant QTc prolongation and torsades de pointes (Tc associated with haloperidol. Hemodynamically significant ventricular tachyarrhythmias, ventricular fibrillation, asystole, and death have been reported. The risk of TdP appears to be greater with intravenous haloperidol, but has occurred with oral and intramuscular use. The risk increases with doses greater than 35 milligrams (mg) over 24 hours, although TdP has been associated with a dos as low as 10 mg administered intravenously over 4 hours. To prevent haloperidol-induced TdP, scre patients for a history of dilated cardiomyopathy or alcohol abuse, testing for hypothyroidism before therapy, obtaining an electrocardiogram at baseline and throughout therapy, and monitoring potassium, magnesium, and calcium. In patients with a baseline QTc greater than 450 milliseconds (msec), haloperidol should be used cautiously or an alternative agent should be used. Discontinue haloperidol if the QTc increases more than 25% from baseline or if flattening of T-waves or development of U-waves occurs (Hassaballa & Balk, 2003s).

b) Seven patients developed torsade de pointes after therapeutic use of haloperidol in high doses. Three patients developed the dysrhythmia after administration of 211 milligrams (mg) to 825 mg

haloperidol over 1 to 2 days for agitated delirium. These 3 patients recovered from the initial episode but 1 patient subsequently died of cardiac arrest upon readministration of haloperidol (Metzger & Friedman, 1993j; Wilt et al, 1993h). Torsades de pointes developed in 8 of 223 critically ill patients in intensive care units. Patients who received intravenous haloperidol greater than 35 mg/day or had a QTc interval prolongation of greater than 500 milliseconds were at greatest risk (Sharma et al, 1998
c) Since zotepine can prolong the QT interval it is recommended that an ECG is performed before starting treatment. Patients with pre-existing prolongation of the QT interval should not be given zotepine (Sweetman, 2003).

3.5.5 Intravenous Admixtures

Drugs

Solutions

3.5.5.1 Drugs

Haloperidol

Haloperidol Lactate

3.5.5.1.A Haloperidol

Amitriptyline

Amsacrine

Benztropine

Biperiden

Buprenorphine

Chlorpromazine

Cimetidine

Diacetylmorphine

Diazepam

Dobutamine

Dopamine

Famotidine

Filgrastim

Fluconazole

Fludarabine

Fluphenazine

Foscarnet

Heparin Sodium

Imipramine

Lidocaine

Lorazepam

Mesoridazine

Nitroglycerin

Nitroprusside

Norepinephrine

Ondansetron

Paclitaxel

Phenylephrine

Prochlorperazine

Sargramostim

Tacrolimus

Theophylline

Trifluoperazine

3.5.5.1.A.1 Amitriptyline

a) Compatible

1) Amitriptyline in a 1:1 or 3:1 mixture with haloperidol, visually compatible with no decreas in haloperidol concentration in 4 hours at room temperature; drug concentrations not specif (Pers Comm, 1990)

3.5.5.1.A.2 Amsacrine

a) Compatible

1) Amsacrine 1 mg/mL with haloperidol 0.2 mg/mL visually compatible in Dextrose 5% in water for a 4-hour study period at room temperature under fluorescent lighting (Trissel et al 1990)

3.5.5.1.A.3 Benztropine

a) Incompatible

1) Benztropine in a 1:1 or 2:1 mixture with haloperidol, precipitate formation reported in 1 hour at room temperature and 53% haloperidol decomposition reported in 4 hours; drug concentrations not specified (Pers Comm, 1990)

3.5.5.1.A.4 Biperiden

a) Compatible

1) Biperiden in a 1:1 mixture with haloperidol, visually compatible with no decrease in haloperidol concentration in 4 hours at room temperature; drug concentrations not specifie (Pers Comm, 1990)

3.5.5.1.A.5 Buprenorphine

a) Compatible

1) Buprenorphine in a 1:1 volume ratio with haloperidol, physically and chemically compati for up to 7 hours at room temperature (Pers Comm, 1990)

3.5.5.1.A.6 Chlorpromazine

a) Conflicting Data

1) Incompatible

a) Chlorpromazine in a 2:1 mixture with haloperidol, visually compatible for 4 hours at room temperature, but 44% decrease in haloperidol concentration reported (Pers Com 1990); however, chlorpromazine in a 1:1 mixture with haloperidol, visually compatible with no decrease in haloperidol concentration in 4 hours at room temperature; drug concentrations not specified (Pers Comm, 1990)

2) Compatible

a) Chlorpromazine in a 1:1 mixture with haloperidol, visually compatible with no decrease in haloperidol concentration in 4 hours at room temperature; drug concentrations not specified (Pers Comm, 1990)

b) Chlorpromazine in a 2:1 mixture with haloperidol, visually compatible for 4 hours at room temperature, but 44% decrease in haloperidol concentration reported (Pers Com 1990)

3.5.5.1.A.7 Cimetidine

a) Compatible

1) Cimetidine 6 mg/mL with haloperidol 5 or 0.5 mg/mL visually compatible in Dextrose 5% water for 24 hours at 21 degrees C under fluorescent light (Outman & Monolakis, 1991b)

3.5.5.1.A.8 Diacetylmorphine

a) Conflicting Data

1) Incompatible

a) Diacetylmorphine in high concentration incompatible with haloperidol; drug concentrations and conditions not specified (Allwood, 1991)

2) Compatible

a) Diacetylmorphine (up to 1 g with haloperidol 7.5 mg compatible in a 10-mL syringe; conditions not specified) (Allwood, 1991a)

3.5.5.1.A.9 Diazepam

a) Incompatible

1) Diazepam in a 1:1 or 2:1 mixture with haloperidol, precipitate formation reported within 2 hours at room temperature; drug concentrations not specified (Pers Comm, 1990)

3.5.5.1.A.10 Dobutamine

a) Compatible

1) Dobutamine 4 mg/mL with haloperidol 5 or 0.5 mg/mL visually compatible in Dextrose 5 in water for 24 hours at 21 degrees C under fluorescent light (Outman & Monolakis, 1991e)

3.5.5.1.A.11 Dopamine

a) Compatible

1) Dopamine 1.6 mg/mL with haloperidol 5 or 0.5 mg/mL visually compatible in Dextrose 5 in water for 24 hours at 21 degrees C under fluorescent light (Outman & Monolakis, 1991a)

3.5.5.1.A.12 Famotidine

a) Compatible

1) Famotidine 0.267 mg/mL with haloperidol 5 or 0.5 mg/mL visually compatible in Dextros 5% in water for 24 hours at 21 degrees C under fluorescent light (Outman & Monolakis, 1991g)

3.5.5.1.A.13 Filgrastim

a) Compatible

1) Filgrastim 30 mcg/mL in Dextrose 5% in water with haloperidol 0.2 mg/mL in Dextrose 5 in water, compatible for up to 4 hours at 22 degrees C (Trissel & Martinez, 1994)

3.5.5.1.A.14 Fluconazole

a) Incompatible

1) Fluconazole 2 milligrams/milliliter (mg/mL) with haloperidol 5 mg/mL, visually incompatil delayed precipitation reported (Lor et al, 1991)

3.5.5.1.A.15 Fludarabine

a) Compatible

1) Fludarabine 1 mg/mL with haloperidol 0.2 mg/mL, both in Dextrose 5% in water, visually compatible for a 4-hour study period at room temperature under fluorescent light (Trissel et 1991a)

3.5.5.1.A.16 Fluphenazine

a) Incompatible

1) Fluphenazine in a 1:1 mixture with haloperidol, immediate precipitate formation reported with 65% haloperidol decomposition in 4 hours at room temperature; drug concentrations n specified (Pers Comm, 1990)

3.5.5.1.A.17 Foscarnet

a) Incompatible

1) Foscarnet 24 mg/mL with haloperidol 5 mg/mL, delayed formation of a fine white precipitated reported (Lor & Takagi, 1990)

3.5.5.1.A.18 Heparin Sodium

a) Incompatible

1) Heparin sodium 100 or 200 U/mL in a Dextrose 5% in water or Sodium chloride 0.9% infusion running at 1000 U/hr, with haloperidol 5 mg/1 mL injected over 1 minute, formation a white precipitate reported immediately; the authors recommend that heparin infusions be stopped and the line flushed with Dextrose 5% in water or Sodium chloride 0.9% before an after the injection of haloperidol and that a similar flushing procedure be followed for administration of haloperidol through a heparin lock (Solomon & Nasinnyk, 1982)

2) Heparin sodium 50 U/mL in a Sodium chloride 0.9% infusion running at 1 mL/min with haloperidol 5 mg/1 mL given over 3 minutes, formation of white turbidity reported (Trissel, 1990)

3) Heparin sodium 2500 U/1 mL with haloperidol 5 mg/1 mL, turbidity or precipitate formati reported within 5 minutes in syringe (Trissel, 1990)

3.5.5.1.A.19 Imipramine

a) Conflicting Data

1) Incompatible

a) Haloperidol in a 1:1 or 1:2 mixture with imipramine, compatibility is questionable because the mixture exhibited no visual changes in 1 hour, was slightly cloudy and viscous in 2 hours, was clear and very viscous in 4 hours at room temperature, but no haloperidol decomposition was observed in a 4 hour study period; drug concentrations not specified (Pers Comm, 1990)

2) Compatible

a) Haloperidol in a 1:1 or 1:2 mixture with imipramine, compatibility is questionable because the mixture exhibited no visual changes in 1 hour, was slightly cloudy and viscous in 2 hours, was clear and very viscous in 4 hours at room temperature, but no haloperidol decomposition was observed in a 4 hour study period; drug concentrations not specified (Pers Comm, 1990)

3.5.5.1.A.20 Lidocaine

a) Compatible

1) Haloperidol 5 or 0.5 mg/mL with lidocaine 4 mg/mL visually compatible in Dextrose 5% water for 24 hours at 21 degrees C under fluorescent light (Outman & Monolakis, 1991f)

3.5.5.1.A.21 Lorazepam

a) Compatible

1) Haloperidol 5 mg/1 mL with lorazepam 2 or 4 mg/1 mL, physically compatible for 4 hour in syringe; temperature not specified (Prod Info Ativan(R) Injection compatibility charts, 198

2) Haloperidol in a 1:1 mixture with lorazepam, physically compatible for 16 hours at room temperature; drug concentrations not specified (Pers Comm, 1990)

3.5.5.1.A.22 Mesoridazine

a) Incompatible

1) Haloperidol in a 1:1 mixture with mesoridazine, immediate precipitate formation reported drug concentrations not specified (Pers Comm, 1990)

3.5.5.1.A.23 Nitroglycerin

a) Compatible

1) Haloperidol 5 or 0.5 mg/mL with nitroglycerin 0.4 mg/mL visually compatible in Dextrose 5% in water for 24 hours at 21 degrees C under fluorescent light (Outman & Monolakis, 1991h)

3.5.5.1.A.24 Nitroprusside

a) Conflicting Data

1) Incompatible

a) Haloperidol 5 mg/mL with nitroprusside 0.2 mg/mL, immediate formation of cloudy solution reported in Dextrose 5% in water; however, nitroprusside 0.2 mg/mL has beer

reported to be compatible with haloperidol 0.5 mg/mL in Dextrose 5% (Outman & Monolakis, 1991i)

2) Compatible

a) Haloperidol 0.5 mg/mL with nitroprusside 0.2 mg/mL visually compatible in Dextros 5% in water for 24 hours at 21 degrees C under fluorescent light; however, nitroprussi 0.2 mg/mL has been reported to be incompatible with haloperidol 5 mg/mL in Dextrose 5% (Outman & Monolakis, 1991)

3.5.5.1.A.25 Norepinephrine

a) Compatible

1) Haloperidol 5 or 0.5 mg/mL with norepinephrine 0.032 mg/mL visually compatible in Dextrose 5% in water for 24 hours at 21 degrees C under fluorescent light (Outman & Monolakis, 1991j)

3.5.5.1.A.26 Ondansetron

a) Compatible

1) Haloperidol 0.2 mg/mL in Dextrose 5% in water with ondansetron 1 mg/mL in Sodium chloride 0.9% was physically compatible for 4 hours at 22 degrees C under ambient lightin (Trissel et al, 1991b; Prod Info Zofran(R), 1999)

3.5.5.1.A.27 Paclitaxel

a) Compatible

1) Haloperidol 0.2 mg/mL in Dextrose 5% injection with paclitaxel 1.2 mg/mL in Dextrose 5 injection in glass container, no visual or turbidimetric evidence of incompatibility in simulate Y-site injection for a 4-hour study period, admixture stored at room temperature under fluorescent light (Trissel & Bready, 1992). However, this admixture was not tested for chemical stability.

3.5.5.1.A.28 Phenylephrine

a) Compatible

1) Haloperidol 5 or 0.5 mg/mL with phenylephrine 0.02 mg/mL visually compatible in Dextrose 5% in water for 24 hours at 21 degrees C under fluorescent light (Outman & Monolakis, 1991d)

3.5.5.1.A.29 Prochlorperazine

a) Incompatible

1) Haloperidol in a 1:1 or 1:2 mixture with prochlorperazine, immediate formation of cloudy solution reported with precipitate formation reported in 1 to 2 hours at room temperature; d concentrations not specified (Pers Comm, 1990)

3.5.5.1.A.30 Sargramostim

a) Incompatible

1) Haloperidol lactate 0.2 mg/mL with sargramostim 10 mcg/mL, both in sodium chloride 0.9%, formation of small particles reported in 1 of 2 samples within 4 hours at 22 degrees C under fluorescent light (Trissel et al, 1992)

3.5.5.1.A.31 Tacrolimus

a) Compatible

1) Haloperidol 2.5 mg/mL in 5% Dextrose injection with tacrolimus 1 mg/mL in 0.9% Sodiu chloride injection, visually compatible for 24 hours at room temperature under fluorescent li (Min et al, 1992)

3.5.5.1.A.32 Theophylline

a) Compatible

1) Haloperidol 5 or 0.5 mg/mL with theophylline, premixed 1.6 mg/mL visually compatible i Dextrose 5% in water for 24 hours at 21 degrees C under fluorescent light (Outman & Monolakis, 1991c)

3.5.5.1.A.33 Trifluoperazine

a) Incompatible

1) Haloperidol in a 1:1 mixture with trifluoperazine, immediate formation of a cloudy solutio reported; drug concentrations not specified (Pers Comm, 1990)

3.5.5.1.B Haloperidol Lactate

Allopurinol Sodium

Amifostine

Aztreonam

Cyclizine Lactate

Fenoldopam Mesylate

Gallium Nitrate

Granisetron Hydrochloride

Piperacillin Sodium/Tazobactam

Propofol

Vinorelbine

3.5.5.1.B.1 Allopurinol Sodium

a) Incompatible

1) Haloperidol lactate is physically incompatible in solution with allopurinol sodium for injection; conditions not specified; do not mix with or administer through the same intravenc port (Prod Info Aloprim(TM), 1999).

2) Allopurinol sodium 3 mg/mL in Sodium chloride 0.9% injection with haloperidol lactate 0 mg/mL in Sodium chloride 0.9% injection, heavy turbidity formed immediately and develope into crystalline particles within 1 hour (Trissel & Martinez, 1994a)

3.5.5.1.B.2 Amifostine

a) Compatible

1) Amifostine 10 mg/mL in Dextrose 5% in water with haloperidol lactate 0.2 mg/mL in 5% Dextrose injection, compatible during simulated Y-site administration (Trissel & Martinez, 1995a)

3.5.5.1.B.3 Aztreonam

a) Compatible

1) Aztreonam 40 mg/mL in 5% Dextrose in water with haloperidol lactate 0.2 mg/mL in Dextrose 5% in water, compatible for up to 4 hours at 23 degrees C (Trissel & Martinez, 1995)

3.5.5.1.B.4 Cyclizine Lactate

a) Incompatible

1) Cyclizine lactate 50 mg/mL (3 mL) with haloperidol lactate 5 mg/mL (0.3 mL) in 0.9% Sodium chloride injection (17 mL), crystals were seen within 24 hours when mixed in syring driver; however, no crystals were noted when water for injection or Dextrose 5% injection were used and stored at 25 degrees C for 24 hours (Fawcett et al, 1994).

3.5.5.1.B.5 Fenoldopam Mesylate

a) Compatible

1) Fenoldopam mesylate 80 mcg/mL in Sodium chloride 0.9% injection with haloperidol lactate 0.2 mg/mL in Sodium chloride 0.9% injection, visually and physically compatible for to 4 hours at 23 degrees C in a clear glass tube under constant fluorescent light during simulated Y- site administration (Trissel et al, 2003).

3.5.5.1.B.6 Gallium Nitrate

a) Incompatible

1) Gallium nitrate (Ganite(R)) 1 mg/mL in Sodium chloride 0.9% admixed from a plastic syringe in a 1:1 ratio simulating Y-site administration with haloperidol lactate (undiluted) 5 mg/mL, immediate white haze that adhered to test tube after centrifugation, leaving a clear liquid at 15 minutes which remained clear for 24-hour study period, stored at room temperature under fluorescent light in a glass container; chemical stability not tested (Lobe Dollard, 1993)

3.5.5.1.B.7 Granisetron Hydrochloride

a) Compatible

1) Granisetron hydrochloride diluted with 5% dextrose injection to a concentration of 50 mcg/mL is compatible with haloperidol lactate at a concentration of 0.2 mg/mL (D5W) durin simulated Y-site injection. Compatibility was measured using visual examinations in fluorescent light and in high-intensity monodirectional light. Turbidity, particle size and parti counts were completed for certain solutions. The mixtures were assessed at 1 and 4 hours (Trissel, 1997).

3.5.5.1.B.8 Piperacillin Sodium/Tazobactam

a) Incompatible

1) Piperacillin sodium 40 mg/mL plus tazobactam 5 mg/mL in Dextrose 5% in water with haloperidol lactate 0.2 mg/mL in Dextrose 5% in water, white turbidity and numerous white particles formed immediately (Trissel & Martinez, 1994b)

3.5.5.1.B.9 Propofol

a) Compatible

1) Propofol 1% injectable emulsion and haloperidol lactate 0.2 milligrams/milliliter in a 1:1 volume mixture (simulated Y-site administration) are visually compatible in polycarbonate t tubes at 15 minutes and 1 hour at approximately 23 degrees Celsius as determined by visualization with fluorescent light and a high-intensity, mono-directional light source (Tynd beam) (Trissel et al, 1997).

3.5.5.1.B.10 Vinorelbine

a) Compatible

1) Haloperidol lactate 0.2 mg/mL in Sodium chloride 0.9% with vinorelbine 1 mg/mL in Sodium chloride 0.9%, compatible for up to 4 hours at 22 degrees C (Trissel & Martinez, 1994c)

3.5.5.2 Solutions

Haloperidol

Haloperidol Lactate

3.5.5.2.A Haloperidol

Dextrose 5% in water

Total Parenteral Nutrition

3.5.5.2.A.1 Dextrose 5% in water

a) Compatible

1) Dextrose 5% in water with haloperidol 100 mg/L stable for 38 days at 24 degrees C in a amber glass bottle or a plastic container (Das Gupta & Stewart, 1982)

3.5.5.2.A.2 Total Parenteral Nutrition

a) Compatible

1) Haloperidol 0.2 mg/mL in Dextrose 5% in water added to total parenteral nutrition soluti compatible in simulated Y-site administration for 4 hours at 23 degrees C; specific composition of total parenteral nutrition solution listed below (Trissel et al, 1997a):

Amino acids 10% (Aminosyn(R) II)	3.5%
Dextrose	5%
Sterile water for injection	516.8 mL
Potassium phosphates	3.5 mM
Sodium chloride	25 mEq
Potassium chloride	35 mEq
Magnesium sulfate	8 mEq
Multivitamins	10 mL
Trace elements	1 mL
Calcium gluconate	9.3 mEq

2) Haloperidol 0.2 mg/mL in Dextrose 5% in water added to total parenteral nutrition soluti compatible in simulated Y-site administration for 4 hours at 23 degrees C; specific composition of total parenteral nutrition solution listed below (Trissel et al, 1997a):

Amino acids 10% (FreAmine(R) III)	3.5%
Dextrose	5%
Sterile water for injection	516.75 mL
Sodium chloride	37.5 mEq
Potassium chloride	40 mEq
Magnesium sulfate	8 mEq
Multivitamins	10 mL
Trace elements	1 mL
Calcium gluconate	5 mEq

3) Haloperidol 0.2 mg/mL in Dextrose 5% in water added to total parenteral nutrition soluti compatible in simulated Y-site administration for 4 hours at 23 degrees C; specific composition of total parenteral nutrition solution listed below (Trissel et al, 1997a):

Amino acids 10% (Aminosyn(R) II)	4.25%
Dextrose	25%
Sterile water for injection	161 mL
Potassium phosphates	15 mM
Sodium chloride	25 mEq
Potassium chloride	18 mEq
Magnesium sulfate	8 mEq
Multivitamins	10 mL
Trace elements	1 mL
Calcium gluconate	9.15 mEq

4) Haloperidol 0.2 mg/mL in Dextrose 5% in water added to total parenteral nutrition soluti compatible in simulated Y-site administration for 4 hours at 23 degrees C; specific composition of total parenteral nutrition solution listed below (Trissel et al, 1997a):

Amino acids 10% (FreAmine(R) III)	4.25%
Dextrose	25%
Sterile water for injection	158.6 mL
Potassium phosphates	5.75 mM
Sodium chloride	40 mEq
Potassium chloride	25 mEq
Magnesium sulfate	8 mEq
Multivitamins	10 mL
Trace elements	1 mL
Calcium gluconate	7.5 mEq

3.5.5.2.B Haloperidol Lactate

Dextrose 5% and Sodium chloride 0.225%

Dextrose 5% in water

lactated Ringer's injection

Lactated Ringer's injection

Sodium chloride 0.45%

Sodium chloride 0.9%

3.5.5.2.B.1 Dextrose 5% and Sodium chloride 0.225%

a) Conflicting Data

1) Incompatible

a) Haloperidol 3 mg/mL (as the lactate salt) in 10 mL of Dextrose 5% and Sodium chloride 0.225%, precipitated by 0.5 hour (Fraser & Riker, 1994a)
b) Haloperidol 2 mg/mL (as the lactate salt) in 10 mL of Dextrose 5% and Sodium chloride 0.225%, precipitated by 1 hour (Fraser & Riker, 1994a)

2) Compatible
a) Haloperidol 0.1, 0.5, 0.75, 1 mg/mL (as the lactate salt) in 10 mL of Dextrose 5% a Sodium chloride 0.225%, visually compatible for up to 7 days at 21 degrees C (Fraser Riker, 1994)

3.5.5.2.B.2 Dextrose 5% in water

a) Compatible
1) Haloperidol 0.1, 0.5, 0.75, 1, 2, 3 mg/mL (as the lactate salt) in 10 mL of Dextrose 5% i water, visually compatible for up to 7 days at 21 degrees C (Fraser & Riker, 1994)

3.5.5.2.B.3 lactated Ringer's injection

a) Incompatible
1) Haloperidol 3 mg/mL (as the lactate salt) in 10 mL of lactated Ringer's injection, precipitated immediately (Fraser & Riker, 1994c)
2) Haloperidol 2 mg/mL (as the lactate salt) in 10 mL of lactated Ringer's injection, precipitated by 0.25 hour (Fraser & Riker, 1994c)

3.5.5.2.B.4 Lactated Ringer's injection

a) Compatible
1) Haloperidol 0.1, 0.5, 0.75, 1 mg/mL (as the lactate salt) of 10 mL of lactated Ringer's injection, visually compatible for up to 7 days at 21 degrees C (Fraser & Riker, 1994b).

3.5.5.2.B.5 Sodium chloride 0.45%

a) Conflicting Data
1) Incompatible
a) Haloperidol 3 mg/mL (as the lactate salt) in 10 mL Sodium chloride 0.45%, precipitated immediately, and haloperidol 2 mg/mL, precipitated by 0.25 hour (Fraser & Riker, 1994e)

2) Compatible
a) Haloperidol 0.1, 0.5, 0.75, 1 mg/mL (as the lactate salt) in 10 mL of Sodium chlorid 0.45%, visually compatible for up to 7 days at 21 degrees C (Fraser & Riker, 1994d)

3.5.5.2.B.6 Sodium chloride 0.9%

a) Conflicting Data
1) Incompatible
a) Haloperidol 1,2,3 mg/mL (as the lactate salt) in 10mL of Sodium chloride 0.9% precipitated immediately, and the precipitate became more dense over time (Fraser & Riker, 1994e)
b) Haloperidol 10,20, or 30 mg/mL with sodium chloride 0.9%, slight precipitate formation reported with the precipitate increasing with time in the larger concentrations however, sodium chloride 0.9% has been reported to be compatible with haloperidol 1 5 mg/mL (Outman & Monolakis, 1991l).

2) Compatible
a) Haloperidol 0.1, 0.5, 0.75 mg/mL (as the lactate salt) in 10 mL of Sodium chloride 0.9%, visually compatible for up to 7 days at 21 degrees C (Fraser & Riker, 1994d)
b) Haloperidol 1 or 5 mg/10mL with sodium chloride 0.9%, visually compatible for an hour study period at 21 degrees C under fluorescent light; however, sodium chloride 0.9% has been reported to be incompatible with haloperidol 10, 20 or 30 mg/10 mL (Outman & Monolakis, 1991k)

4.0 Clinical Applications

Monitoring Parameters

Patient Instructions

Place In Therapy

Mechanism of Action / Pharmacology

Therapeutic Uses

Comparative Efficacy / Evaluation With Other Therapies

4.1 Monitoring Parameters

A) Haloperidol

1) Therapeutic

a) Physical Findings

1) Decrease in severity or elimination of target psychotic symptoms:

a) Positive psychotic symptoms (delusions, auditory hallucinations, racing thoughts)

b) Negative psychotic symptoms (anhedonia, apathy, amotivation, ambivalence).

2) Improvement in socialization, grooming, and attention to activities of daily living.

2) Toxic

a) Laboratory Parameters

1) Complete blood counts (every 6 months)

2) Electrocardiogram at baseline and periodically while on therapy, especially if administered intravenously (US Food and Drug Administration, 2007; Pacher & Kecskemeti, 2004).

a) Torsades de Pointes and QT prolongation, including sudden death, have been reported especially when haloperidol is administered intravenously or at doses higher than recommende (US Food and Drug Administration, 2007; Pacher & Kecskemeti, 2004)

3) Hepatic function tests (every 6 months)

b) Physical Findings

1) Abnormal involuntary movement scale (AIMS) examination or similar test for tardive dyskinesia every 6 months.

2) Assessment for extrapyramidal symptoms (EPS) during dose adjustment and every 3 months.

B) Haloperidol Lactate

1) Therapeutic

a) Physical Findings

1) Control of agitation is indicative of clinical response.

2) Toxic

a) Physical Findings

1) Allergic reactions should be monitored, especially in patients with known allergies, or a history of drug-induced allergic reactions.

2) Bronchopneumonia with symptoms including lethargy, decreased thirst, and reduced pulmonary ventilation should be monitored, especially in the elderly.

3) Electrocardiogram at baseline and periodically while on therapy to monitor for arrhythmias (including Torsades de Pointes) and QT prolongation, especially when haloperidol is administered intravenously (route not approved) or at doses higher than recommended (Prod Info HALDOL(R) immediate release IM injection, 2008; US Food and Drug Administration, 2007; Pacher & Kecskeme 2004).

4) Hypotension and/or anginal pain should be monitored in patients with comorbid cardiovascular disorders.

5) Involuntary dyskinetic movements (including tardive dyskinesia), which are potentially irreversible should be monitored, especially in elderly women or patients receiving longer durations of treatment

6) Neuroleptic malignant syndrome (NMS) should be monitored and includes symptoms of hyperpyrexia, muscle rigidity, altered mental status, irregular pulse or blood pressure, tachycardia, diaphoresis and cardiac dysrhythmias. If confirmed, haloperidol therapy may need to be discontinue and medical management instituted. Following recovery from NMS, if therapy is to be reinstituted, careful monitoring is recommended to prevent recurrences (Prod Info HALDOL(R) immediate releas IM injection, 2008).

7) Seizure monitoring is recommended especially in patients with a history of seizures or EEG abnormalities.

4.2 Patient Instructions

A) Haloperidol (By mouth)

Haloperidol

Treats symptoms of mental and emotional disorders. Helps patients with Tourette's syndrome and children w severe behavior problems, including hyperactivity.

When This Medicine Should Not Be Used:
You should not use this medicine if you have had an allergic reaction to haloperidol, or if you have Parkinson disease. This medicine should not be given to patients with severe brain disease.

How to Use This Medicine:
Tablet

Your doctor will tell you how much of this medicine to use and how often. Your dose may need to be changed several times in order to find out what works best for you. Do not use more medicine or use it

more often than your doctor tells you to.

If a Dose is Missed:
If you miss a dose or forget to use your medicine, use it as soon as you can. If it is almost time for your r dose, wait until then to use the medicine and skip the missed dose. Do not use extra medicine to make u for a missed dose.

How to Store and Dispose of This Medicine:
Store the medicine in a closed container at room temperature, away from heat, moisture, and direct light
Ask your pharmacist, doctor, or health caregiver about the best way to dispose of any leftover medicine after you have finished your treatment. You will also need to throw away old medicine after the expiratior date has passed.
Keep all medicine away from children and never share your medicine with anyone.

Drugs and Foods to Avoid:
Ask your doctor or pharmacist before using any other medicine, including over-the-counter medicines, vitamii and herbal products.
You must be careful if you are also using other medicine that might cause similar side effects as haloperidol. This includes medicine that might cause low blood pressure, overheating, or liver problems.
Make sure your doctor knows about all other medicines you are using.
Tell you doctor if you are also using lithium, phenindione, medicine for seizures, or medicine to treat Parkinson's disease.
Tell your doctor if you are using any medicines that make you sleepy. These include sleeping pills, cold a allergy medicine, narcotic pain relievers, and sedatives.
Do not drink alcohol while you are using this medicine.

Warnings While Using This Medicine:
Make sure your doctor knows if you are pregnant or breastfeeding, or if you have liver disease, kidney disease, heart or blood vessel disease, blood pressure problems, overactive thyroid, or history of seizure or breast cancer.
Tell your doctor about any other medicine you have used to treat a mental disorder, especially if the medicine caused problems.
This medicine may make you dizzy or drowsy. Avoid driving, using machines, or doing anything else that could be dangerous if you are not alert.
You might get overheated more easily while using this medicine. Be aware of this if you are exercising o the weather is hot. Drinking water might help. If you get too hot and feel dizzy, weak, tired, confused, or sick to your stomach, you need to cool down.
Do not stop using this medicine suddenly without asking your doctor. You may need to slowly decrease your dose before stopping it completely.
Your doctor will need to check your progress at regular visits while you are using this medicine. Be sure keep all appointments.

Possible Side Effects While Using This Medicine:
Call your doctor right away if you notice any of these side effects:
Allergic reaction: Itching or hives, swelling in your face or hands, swelling or tingling in your mouth or thro chest tightness, trouble breathing.
Change in how much or how often you urinate.
Changes in vision.
Fast or pounding heartbeat.
Fever or chills.
Jerky muscle movement you cannot control (often in your face, tongue, or jaw).
Headache, confusion, lightheadedness, or fainting.
Painful, prolonged erection of your penis.
Problems with balance or walking.
Seeing or hearing things which are not there.
Seizures or tremors.
Severe muscle stiffness.
Troubled breathing.
Unusual bleeding, bruising, or weakness.
Yellowing of skin and eyes.

If you notice these less serious side effects, talk with your doctor:
Breast pain or swelling.
Change in menstrual periods.
Decreased thirst or dry mouth.
Loss of appetite.
Nausea, vomiting, diarrhea, or constipation.
Skin rash.

Trouble sleeping, restlessness.

If you notice other side effects that you think are caused by this medicine, tell your doctor.

B) Haloperidol (Injection)

Haloperidol

Treats mental illness (such as schizophrenia), behavior problems, agitation, and symptoms of Tourette's syndrome.

When This Medicine Should Not Be Used:
You should not use this medicine if you have had an allergic reaction to haloperidol, or if you have Parkinson disease. This medicine should not be given to patients with severe brain disease.

How to Use This Medicine:
Injectable

Your doctor will prescribe your exact dose and tell you how often it should be given. This medicine is giv as a shot into one of your muscles.
A nurse or other trained health professional will give you this medicine.

Drugs and Foods to Avoid:
Ask your doctor or pharmacist before using any other medicine, including over-the-counter medicines, vitami and herbal products.

Make sure your doctor knows if you are also using lithium (Eskalith®, Lithane®, Lithobid®), rifampin (Rimactane®, Rifadin®), a blood thinner (such as phenindione), or medicine for Parkinson's disease (su as carbidopa, levodopa, Sinemet®).
Tell your doctor if you are using any medicines that make you sleepy. These include sleeping pills, cold a allergy medicine, narcotic pain relievers, and sedatives.
Do not drink alcohol while you are using this medicine.

Warnings While Using This Medicine:

Make sure your doctor knows if you are pregnant or breastfeeding, or if you have liver disease, kidney disease, lung disease, glaucoma, an overactive thyroid, or a history of seizures or neuroleptic malignant syndrome (NMS). Your doctor needs to know if you have any kind of heart or blood vessel problems, including blood pressure problems, heart rhythm problems, or mineral imbalance.
Older adults may be more sensitive to the side effects of this medicine, including heart failure or pneumonia. This medicine is not used to treat behavioral problems in older adults with dementia.
Tardive dyskinesia (a movement disorder) may occur and may not go away after you stop using the medicine. Check with your doctor right away if you or your child have any of the following symptoms whil taking this medicine: lip smacking or puckering, puffing of the cheeks, rapid or worm-like movements of t tongue, uncontrolled chewing movements, or uncontrolled movements of the arms and legs.
This medicine may make you more sensitive to sunlight and heat. Avoid sunlamps, hot tubs, tanning bec and saunas. Take care not to get overheated during exercise or outdoor activity. Use a sunscreen when outdoors.
This medicine may make you dizzy or drowsy. Avoid driving, using machines, or doing anything else tha could be dangerous if you are not alert. You may also feel lightheaded when getting up suddenly from a lying or sitting position, so stand up slowly.
Do not stop using this medicine suddenly without asking your doctor. You may need to slowly decrease your dose before stopping it completely.
Your doctor will need to check your progress at regular visits while you are using this medicine. Be sure keep all appointments.

Possible Side Effects While Using This Medicine:
Call your doctor right away if you notice any of these side effects:

Allergic reaction: Itching or hives, swelling in your face or hands, swelling or tingling in your mouth or thro chest tightness, trouble breathing.
Change in how much or how often you urinate.
Chills, cough, sore throat, and body aches.
Fast, slow, or irregular heartbeat.
Feeling very thirsty or hungry.
Fever, sweating, confusion, uneven heartbeat, or muscle stiffness.
Jerky muscle movement you cannot control (often in your face, tongue, or jaw).
Lightheadedness or fainting.
Painful, prolonged erection of your penis.
Problems with vision, speech, or walking.
Seeing or hearing things which are not there.
Seizures or tremors.
Trouble breathing or swallowing.
Twitching or muscle movements you cannot control.

Unexplained fever or muscle stiffness.
Unusual facial expressions.
Unusual bleeding, bruising, or weakness.
Yellowing of your skin or the whites of your eyes.

If you notice these less serious side effects, talk with your doctor:
Breast pain or swelling.
Drowsiness, depression, or headache.
Dry mouth.
Hair loss.
Irregular menstrual periods.
Loss of appetite.
Nausea, vomiting, constipation, or stomach upset.
Skin rash.
Trouble having sex.
Trouble sleeping, restlessness.

If you notice other side effects that you think are caused by this medicine, tell your doctor.

C) Haloperidol Decanoate (Injection)

Haloperidol Decanoate

Treats mental disorders such as schizophrenia.

When This Medicine Should Not Be Used:
You should not use this medicine if you have had an allergic reaction to haloperidol decanoate, or if you have Parkinson's disease. This medicine should not be given to patients with severe brain disease.

How to Use This Medicine:
Injectable
Your doctor will prescribe your exact dose and tell you how often it should be given. This medicine is giv as a shot into one of your muscles.
A nurse or other trained health professional will give you this medicine.

Drugs and Foods to Avoid:
Ask your doctor or pharmacist before using any other medicine, including over-the-counter medicines, vitamir and herbal products.
Make sure your doctor knows if you are also using lithium (Eskalith®, Lithane®, Lithobid®), rifampin (Rimactane®, Rifadin®), a blood thinner (such as phenindione), or medicine for Parkinson's disease (suc as carbidopa, levodopa, Sinemet®).
Do not drink alcohol while you are using this medicine.
Tell your doctor if you are using any medicines that make you sleepy. These include sleeping pills, cold a allergy medicine, narcotic pain relievers, and sedatives.

Warnings While Using This Medicine:
Make sure your doctor knows if you are pregnant or breastfeeding, or if you have liver disease, kidney disease, lung disease, glaucoma, an overactive thyroid, or a history of seizures or neuroleptic malignant syndrome (NMS). Your doctor needs to know if you have any kind of heart or blood vessel problems, including blood pressure problems, heart rhythm problems, or mineral imbalance.
Older adults may be more sensitive to the side effects of this medicine, including heart failure or pneumonia. This medicine is not used to treat behavioral problems in older adults with dementia.
Tardive dyskinesia (a movement disorder) may occur and may not go away after you stop using the medicine. Check with your doctor right away if you or your child have any of the following symptoms whil taking this medicine: lip smacking or puckering, puffing of the cheeks, rapid or worm-like movements of t tongue, uncontrolled chewing movements, or uncontrolled movements of the arms and legs.
This medicine may make you more sensitive to sunlight and heat. Avoid sunlamps, hot tubs, tanning bec and saunas. Take care not to get overheated during exercise or outdoor activity. Use a sunscreen when outdoors.
This medicine may make you drowsy or dizzy. Avoid driving, using machines, or doing anything else that could be dangerous if you are not alert. You may also feel lightheaded when getting up suddenly from a lying or sitting position, so stand up slowly.
Do not stop using this medicine suddenly without asking your doctor. You may need to slowly decrease your dose before stopping it completely.
Your doctor will need to check your progress at regular visits while you are using this medicine. Be sure keep all appointments.

Possible Side Effects While Using This Medicine:
Call your doctor right away if you notice any of these side effects:
Allergic reaction: Itching or hives, swelling in your face or hands, swelling or tingling in your mouth or thro

chest tightness, trouble breathing.
Blood in your urine.
Chills, sore throat, and body aches.
Decreased thirst.
Fast or uneven heartbeat.
Feeling very thirsty or hungry.
Fever, sweating, confusion, or muscle stiffness.
Lightheadedness or fainting.
Problems with vision, speech, balance, or walking.
Seeing or hearing things which are not there.
Seizures (convulsions).
Tremors or movements that you cannot control in the tongue, face, neck, jaw, or eyes
Trouble breathing or swallowing.
Unusual bleeding, bruising, or weakness.
Unusual facial expressions.
Yellowing of your skin or the whites of your eyes.

If you notice these less serious side effects, talk with your doctor:
Anxiety, drowsiness, or depression.
Decrease in how much or how often you urinate.
Dry mouth, cough, or headache.
Hair loss.
Loss of appetite.
Nausea, vomiting, diarrhea, or stomach upset.
Pain in the breast, irregular menstrual periods.
Skin rash, sunburn, or pain at the injection site.
Trouble having sex, or increased development of breasts (in men).
Trouble sleeping, restlessness.

If you notice other side effects that you think are caused by this medicine, tell your doctor.

4.3 Place In Therapy

A) Current users of atypical antipsychotic drugs and typical antipsychotic drugs (including haloperidol) had a simi dose-dependent risk of sudden cardiac death, according to a retrospective cohort of 93,300 adult users of antipsychotic drugs and 186,600 matched controls. The study included patients age 30 to 74 years (mean 45.7 +/ 11.8 years) with similar cardiovascular risk at baseline who had at least one filled prescription and had 1 outpatier visit in each of the 2 preceding years. Sudden cardiac death was defined as occurring in the community and excluded deaths of patients admitted to the hospital, non-sudden deaths, deaths due to extrinsic causes, or cause not related to ventricular tachyarrhythmia. Current use was defined as the interval between the time the prescripti was filled and the end of the day's supply. Low and high doses was defined as comparable to less than 100 milligrams (mg) of chlorpromazine, and doses comparable to chlorpromazine 300 mg or greater, respectively. The adjusted rate of sudden cardiac death (incidence-rate ratio) in current users of atypical antipsychotic drugs in 79,5 person-years was 2.26 (95% CI, 1.88 to 2.72, p less than 0.001) which was similar to the risk in current users of typical antipsychotic drugs in 86,735 person-years which was 1.99 (95% CI, 1.68 to 2.34, p less than 0.001). The risk of sudden cardiac death in current haloperidol users in 21,728 person-years was 1.61 (95% CI, 1.16 to 2.24, p=0.005). The risk of sudden cardiac death significantly increased with increasing dose in both the typical and atypical antipsychotic drug groups. In typical antipsychotic use, the incidence rate ratio increased from 1.31 (95% 0.97 to 1.77) in low-dose use to 2.42 (95% CI, 1.91 to 3.06) in high-dose use. To limit the effects of confounding c the study results, there was a secondary analysis performed in a cohort of patients matched by propensity score, which resulted in a similar risk of sudden death as the primary cohort analysis (Ray et al, 2009). In an editorial in The New England Journal of Medicine, it has been suggested that antipsychotic drugs continue to be used in patients with clear evidence of benefit, but in vulnerable populations with cardiac risk profiles (eg, elderly patients) there should be an age-dependent justification required prior to administration. It has also been suggested (althou not formally tested) that ECGs be performed before and shortly after initiation of antipsychotic therapy to screen fo existing or emergent QT interval prolongation (Schneeweiss & Avorn, 2009).

B) Haloperidol is a butyrophenone-derivative antipsychotic agent with a very low incidence of sedative, anticholinergic, and cardiovascular adverse effects; however, it may produce a very high incidence of extrapyrami symptoms. The drug is useful in treating a variety of psychiatric disorders including schizophrenia and Tourette's syndrome. Haloperidol decanoate is a long-acting depot dosage form, which may be administered in up to 4-week intervals, which is a potential advantage in noncompliant patients.

C) Clinical evidence demonstrates that all the commonly marketed neuroleptic agents have therapeutic equivaler when adequate doses are utilized (Appleton et al, 1980). When a flexible dosage regimen is used to titrate the chosen agent to maximum effect, all neuroleptics will demonstrate statistical equivalence in a study population. However, one agent may be effective while another will not in any given individual patient. Pharmacokinetic and pharmacodynamic differences as well as possible multiple etiologies of the patient's schizophrenia may be reasor for the individual inequivalence (Young & Koda-Kimble, 1988). The patient's past medication history of neuroleptic agents should play an important role in drug selection. The patient's subjective response to neuroleptics should al be used in deciding on a specific agent. A reduction in symptoms or a pleasurable response following the first

neuroleptic dose will improve patient compliance better than if the patient has a bad experience after the first dose (May, 1978). The last factor in deciding which neuroleptic agent to use is its adverse effect profile. Almost all neuroleptic agents possess similar adverse effects; however, the overall incidence of a particular category of adverse effects varies between the agents.

D) The US Food and Drug Administration (FDA) issued an alert concerning reports of Torsades de Pointes and C prolongation, some with fatal outcomes associated with the use of haloperidol, haloperidol decanoate, and haloperidol lactate, especially when administered intravenously (not an approved route of administration) or in higher doses than recommended. At least 28 published case reports exist, and case-control studies have demonstrated a dose-response relationship between intravenous haloperidol use and the development of Torsad de Pointes. Two post-marketing analyses of the association of QT prolongation or Torsades de Pointes with oral c injectable haloperidol revealed 242 cases, with at least 8 fatalities involving intravenous administration. Risk facto for the development of QT prolongation or Torsades de Pointes include concomitant QT-prolonging conditions, su as electrolyte imbalance; underlying cardiac abnormalities; hypothyroidism; familial long QT syndromes; or concomitant use of drugs known to prolong the QT interval. However, some cases have occurred in patients with predisposing factors. The true incidence of QT prolongation or Torsades de Pointes cannot be determined at this time (US Food and Drug Administration, 2007).

E) Based upon a critical review of the literature, it is suggested that haloperidol decanoate provides no advantage and safety and is more expensive (Hemstrom et al, 1988). It is recommended that haloperidol decanoate be reserved for schizophrenic patients who have responded to oral haloperidol and who may significantly benefit fror long-acting preparation. Haloperidol and haloperidol decanoate are effective agents in the treatment of certain psychiatric disorders and should be included on hospital formularies where these types of patients are routinely treated.

See Drug Consult reference: CHEMOTHERAPY AND RADIOTHERAPY TREATMENT GUIDELINES FOR NAUS AND VOMITING

See Drug Consult reference: FIRST- VS SECOND-GENERATION ANTIPSYCHOTIC AGENTS FOR SCHIZOPHRENIA

4.4 Mechanism of Action / Pharmacology

A) MECHANISM OF ACTION

1) Haloperidol is pharmacologically related to the piperazine phenothiazines (Ayd, 1978). Similar to other neuroleptics, haloperidol centrally blocks the action of dopamine by binding previously to DA-2 receptors, anc a lesser extent, DA-1 receptors. The potency of all antipsychotic drugs correlates well with their affinity for DA receptors (AMA Department of Drugs, 1983; Snyder, 1981).

2) Haloperidol is relatively non-sedating but is more likely to produce extrapyramidal symptoms as compared other antipsychotic agents; autonomic side effects are less than with other agents (AMA Department of Drugs 1983).

3) Haloperidol 2 mg is approximately equivalent to 100 mg chlorpromazine, 2 mg fluphenazine, 10 mg loxapi and 4 mg thiothixine in antipsychotic potency (AMA Department of Drugs, 1983). The drug is used primarily i schizophrenia and acute psychosis. Other indications are schizoaffective disorders, paranoid syndrome, and Tourette's syndrome (AMA Department of Drugs, 1983).

B) REVIEW ARTICLES

1) A pharmacokinetics update of haloperidol has been reviewed (Kudo & Ishizaki, 1999).

2) The pharmacokinetics and therapeutic use of IM haloperidol decanoate in the treatment of psychosis have been reviewed (Beresford & Ward, 1987a).

3) A comprehensive review of haloperidol pharmacokinetics has been published and included all factors whi have the potential of influencing the serum levels of haloperidol (Froemming et al, 1989a).

4) The use of haloperidol in the treatment of psychotic symptoms in the elderly has been reviewed, including pharmacokinetics, indications and principles for use, side effects, and advantages of haloperidol (Steinhart, 1983).

5) Practice guidelines for the treatment of schizophrenia have been developed by the American Psychiatric Association (Anon, 1997).

4.5 Therapeutic Uses

Haloperidol

Haloperidol Decanoate

Haloperidol Lactate

4.5.A Haloperidol

Agitation

Alcohol withdrawal syndrome

Anorexia nervosa

Behavioral syndrome - Dementia

Chemotherapy-induced nausea and vomiting; Treatment and Prophylaxis

Delirium

Dementia

Flashbacks, LSD

Gilles de la Tourette's syndrome

Hiccoughs

Hiccoughs, Intractable

Hyperactive behavior, (Short-term treatment) after failure to respond to non-antipsychotic medication and psychotherapy

Migraine

Nausea and vomiting; Treatment and Prophylaxis

Obsessive-compulsive disorder; Adjunct

Ocular hypertension

Opioid withdrawal

Pain

Postoperative nausea and vomiting; Prophylaxis

Problematic behavior in children (Severe), With failure to respond non-antipsychotic medication or psychotherapy

Psychotic disorder

Rheumatoid arthritis

Schizophrenia

Severe major depression with psychotic features

Sneezing

4.5.A.1 Agitation

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive; Pediatric, Evidence is inconclusive
Recommendation: Adult, Class IIb; Pediatric, Class IIb
Strength of Evidence: Adult, Category B; Pediatric, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:
Effective treatment for agitated, critical care patients (Ziehm, 1991)
Controlled studies are needed to identify the most effective and safe method of haloperidol administration

c) Adult:

1) HALOPERIDOL given intramuscularly (IM), intravenously (IV), or orally has been reported effecti in the management of disruptive patients in the emergency room setting (Clinton et al, 1987). The average total doses of HALOPERIDOL administered were 8 mg, 6 mg, and 9 mg for the IM, IV, and oral routes, respectively.

d) Pediatric:

1) Haloperidol provided effective sedation for a 9-month-old girl during mechanical ventilation after bone marrow transplant. Sedation with fentanyl 18 micrograms/kilogram (mcg/kg) per hour and midazolam 1 milligram (mg) per hour was not adequate. By day 33 of mechanical ventilation, she wa receiving fentanyl 30 mcg/kg/hour, methadone 1.4 mg/kg intravenously (IV) every 6 hours, and lorazepam 1.1 mg/kg IV every 4 hours. Eleven doses of pancuronium over 24 hours were needed to minimize movement. Intravenous haloperidol 0.06 mg/kg was administered, followed 6 hours later b maintenance regimen of 0.015 mg/kg IV every 6 hours. Twelve hours after the loading dose, the patient was reported to be calm, with no thrashing. She required 2 additional doses of haloperidol during the next 8 hours in response to intermittent agitation, and, during the 24 hours after the loadi dose, a dose of pancuronium and 2 extra doses of fentanyl were administered. Two days after initiat of haloperidol, she needed no extra doses of fentanyl, lorazepam, or pancuronium. She was successfully extubated 3 days after starting haloperidol, after which haloperidol was discontinued ar the other sedatives tapered. Similar, successful treatments with haloperidol were reported for 4 othe pediatric cases (ages 11 months, 12 years, 14 years, and 16 years) (Harrison et al, 2002).

4.5.A.2 Alcohol withdrawal syndrome

a) Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:
bolus doses of haloperidol and clonidine provided better patient outcome than continuous infusion doses

c) Adult:

1) Severity and duration of alcohol withdrawal syndrome (AWS) was significantly lower in patients receiving bolus rather than infusions of haloperidol and clonidine. In a prospective, randomized, stuc adult patients with AWS who had trauma or gastrointestinal surgery, a history of alcohol abuse (grea than 60 grams per day), and a clinical withdrawal assessment for alcohol score (CIWA-Ar) greater th 20 were randomized to the infusion-titrated group (ITG) or the bolus-titrated group (BTG). All patient received bolus doses of flunitrazepam (for agitation), haloperidol (for hallucinations), and clonidine (autonomic signs) to achieve a CIMA- Ar score less than 20. An infusion of flunitrazepam infusion (25 100 micrograms/kilogram/hour (mg/kg/hr)) was started to prevent convulsions. Patients were then randomized to the ITG (n=21) or the BTG (n=23), in which, haloperidol plus clonidine was administe as infusion or bolus doses to achieve a CIWA-Ar score of less than 10 and Ramsey Sedation Score (RSS) of 2 to 4. Doses were dependent on the initial need for the drug and ranged from 50 to 200 mcg/kg/hr or bolus doses less than 20 milligrams (mg), 20 to 40 mg, or greater than 40 mg for haloperidol and 150 to 300 mcg/kg/hr or bolus doses less than 150 mcg, 150 to 300 mcg, or greater than 300 mcg for clonidine. Propofol 50 to 400 mg was given as a rescue medication. The primary outcome, severity and duration of AWS, favored the BTG. CIWA-Ar scores increased following ITG from approximately 21 to 29, p less than or equal to 0.01, but not in the BTG where scores remained approximately 23 (p less than or equal to 0.01 compared to ITG). The duration of AWS was significantly longer for patients in the ITG (median interquartile range: 4 to 10 days) than patients in BTG (median interquartile range: 2 to 4 days), p less than or equal to 0.01. In addition, the days spe in the intensive care unit (ICU) were significantly longer for ITG patients (median interquartile range: to 25 days) than BTG patients (median interquartile range: 5 to 10 days), p less than or equal to 0.0 Pneumonia developed in 9 of 23 (39%) of BTG patients and 15 of 21 (71%) of ITG patients, p less th or equal to 0.01 (Spies et al, 2003).

4.5.A.3 Anorexia nervosa

See Drug Consult reference: ANOREXIA NERVOSA - DRUG THERAPY

4.5.A.4 Behavioral syndrome - Dementia

a) Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:
May be efficacious for treating behavioral problems associated with Alzheimer's disease
Use may expose the patient to unnecessary adverse reactions

c) Adult:
1) HALOPERIDOL 1 to 5 milligrams orally each day was effective in improving psychotic and behavioral symptoms in patients with probable ALZHEIMER'S DISEASE during a single-blind pilot study (Devanand et al, 1989). However, severe adverse effects were observed during therapy, primarily extrapyramidal symptoms, and no patient could be maintained on the maximum dose of 5 milligrams daily. The average daily dose at the end of the 8-week haloperidol phase (preceded and followed by 4-week placebo phases) was 2.44 milligrams daily. Cognitive function deteriorated durin HALOPERIDOL therapy, with only partial recovery by the end of the subsequent 4-week placebo phase. This small study suggests that HALOPERIDOL is effective in treating psychosis and other behavioral disturbances in Alzheimer's patients, but that severe extrapyramidal adverse effects and adverse effects on cognitive function can compromise efficacy. However, in most cases, benefits of therapy appear to outweigh adverse effects (based upon opinions of physician and family members) Larger controlled studies are required to further evaluate neuroleptic therapy in Alzheimer's disease

4.5.A.5 Chemotherapy-induced nausea and vomiting; Treatment and Prophylaxis
See Drug Consult reference: CHEMOTHERAPY AND RADIOTHERAPY TREATMENT GUIDELINES FC NAUSEA AND VOMITING

4.5.A.6 Delirium

a) Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:
Effective in controlling patients with delirium and agitation

c) Adult:
1) Haloperidol, administered via continuous infusion, was effective in controlling delirium and agitati in a series of three critically ill intensive care unit patients. In all of the three patients, symptoms wer previously not adequately controlled with high doses of benzodiazepines and narcotics and bolus injections of intravenous haloperidol. Control of delirium was rapidly attained following initiation of continuous intravenous haloperidol (4 to 24 mg/hour) which allowed other sedatives to be discontinu and facilitated weaning from the ventilator. Two of the patients had underlying psychiatric illness (Seneff & Mathews, 1995).
2) Eight critically ill, mechanically ventilated patients with severe agitation unresponsive to benzodiazepines, narcotics, and intermittent bolus haloperidol were eventually controlled with haloperidol by continuous intravenous infusion. Initial infusion rates ranged from 3 to 25 milligrams (mg)/hour (mean 9 mg/hour), with titration as high as 40 mg/hour for control (mean maintenance infusion 18 mg/hour). Control of agitation was demonstrated by a decline in the number of daily supplemental sedative doses (from 23 to 7) and by declines in the Sedation-Agitation Scale. Nursing time per patient decreased from 320 to 96 minutes, although one patient still required 2 nurses and adjunctive sedative doses daily (Riker et al, 1994a).
3) AIDS patients with organic mental disorders were treated for their delirium with high-dose intravenous haloperidol in combination with lorazepam (Fernandez et al, 1989). Although effective ir treating symptoms of delirium, half of the 38 patients treated developed extrapyramidal symptoms. A subsequent study randomized hospitalized AIDS patients with delirium to either haloperidol, chlorpromazine, or lorazepam (Breitbart et al, 1996b). Both neuroleptic agents significantly improvec symptoms of delirium with a low incidence of side effects. Lorazepam, however, was not effective, a the majority of patients treated with this agent developed treatment-limiting adverse effects. The me dose of haloperidol used was 2.8 mg during the first 24 hours of treatment and 1.4 mg for the remainder of the protocol.
4) In a prospective study of 14 delirious, medically ill patients with severe agitation, it was shown th those patients receiving intravenous (IV) HALOPERIDOL 4 milligrams/day plus at least 1 mg of benzodiazepine had fewer extrapyramidal symptoms than those patients receiving intravenous HALOPERIDOL 4 mg/day alone (Menza et al, 1988). DIAZEPAM, LORAZEPAM, OXAZEPAM, and ALPRAZOLAM were used with the dosage reported in milligram equivalents of DIAZEPAM. Doses were oral except four cases of IV LORAZEPAM. The approximate ratio of milligram of HALOPERIDC to milligram equivalents of DIAZEPAM was 4:1. In the HALOPERIDOL plus benzodiazepine treated patients, only one patient suffered very mild parkinsonian-like extrapyramidal symptoms, and there were no cases of akathisia or dystonia. The authors concluded that IV HALOPERIDOL combined wi benzodiazepines may be safely and effectively used to control severe agitation in delirious, medicall patients in critical care areas.

5) Intravenous HALOPERIDOL (100 to 480 milligrams/day) with LORAZEPAM (36 to 480 mg/day) successfully treated delirium in critically ill cancer patients. Mild to moderate levels of sedation were achieved in 24 of 25 patients within 90 minutes; most within 20 minutes. Seven patients died from underlying disease within 1 month of institution of therapy, and 18 patients recovered after correctio of the underlying problem. The longest duration of therapy was 3 months. Only 1 of the 25 patients experienced side effects (a dystonic reaction) serious enough to discontinue therapy (Adams et al, 1986).

4.5.A.7 Dementia

See Drug Consult reference: BEHAVIORAL AND PSYCHOLOGICAL SYMPTOMS OF DEMENTIA

4.5.A.8 Flashbacks, LSD

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Useful in decreasing flashbacks associated with LSD

c) Adult:

1) Oral doses of 1 to 2 milligrams 3 times daily were effective in decreasing the frequency, intensity and duration of flashbacks associated with LSD ingestion. In a series of 8 patients, 3 patients were noted to have an increase in the number of flashbacks when HALOPERIDOL was discontinued (Moskowitz, 1971).

4.5.A.9 Gilles de la Tourette's syndrome

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes; Pediatric, yes (3 yr and older)
Efficacy: Adult, Evidence favors efficacy; Pediatric, Evidence favors efficacy
Recommendation: Adult, Class IIb; Pediatric, Class IIb
Strength of Evidence: Adult, Category B; Pediatric, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Indicated for the control of tics and vocal utterances of Tourette's disorder in adults and childrer age 3 years and older (Prod Info haloperidol oral tablets, 2008; Prod Info haloperidol oral soluti 2008).

In pediatric patients (n=22) haloperidol was not significantly more effective on the Tourette Syndrome Global Scale compared with placebo, and was associated with a significantly greate incidence of extrapyramidal symptoms, while pimozide demonstrated effectiveness over placeb according to a 24-week, randomized, crossover study (Sallee et al, 1997a).

More effective than pimozide on the Gilles de la Tourette's syndrome severity scale and more effective than placebo on 4 of 6 measurement scales, according to a randomized, placebo-controlled, double-blind parallel and crossover study (n=57) in adults and children (Shapiro et a 1989a).

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c) Adult:

1) Haloperidol was more effective than pimozide on the Gilles de la Tourette's syndrome (TS) seve scale and was more effective than placebo on 4 of 6 measurement scales according to a randomize placebo-controlled, double-blind, parallel-group and crossover study (n=57). Patients with DSM-III criteria for TS, aged 8 to 46 years (mean 21.1 +/- 11 years) were randomized to receive haloperidol (n=20), pimozide (n=18), or placebo (n=19) during the 6-week, parallel-phase study (period 1), followed by a 3-week single-blind placebo or drug-free period. The study included previously untreat patients, and patients with inadequate prior response or history of adverse effects from haloperidol, clonidine, or other drugs. In the crossover phase (period 2), patients who received 6 weeks of active treatment (haloperidol or pimozide) were crossed over to the alternate study drug while patients initi assigned to placebo during the parallel phase were randomized to either haloperidol or pimozide an then crossed-over to the alternate drug for an additional 6 weeks. Patients received once daily dosir titrated to clinical effect up to a maximum dose of pimozide 0.3 milligram/kilogram (mg/kg) or 20 mg, whichever was smaller, or haloperidol 10 mg. Haloperidol was more effective than pimozide on the physician-rated TS severity scale (p=0.011). Haloperidol was also more effective than placebo on 1) the physician-rated TS severity scale (p=0.01), 2) total vocal tics (p=0.019), 3) Clinical Global Impression Scale (CGI scale) of therapeutic effects (rated by physician p=0.009, rated by patient p=0.01), and 4) the CGI scale of adverse effects (rated by physician p=0.01, rated by patient p=0.01 There was not a significant difference in the incidence of QTc interval greater than 0.44 sec (pimozi n=9 vs haloperidol n=1). The results of the study may have been limited by the short duration of treatment (Shapiro et al, 1989a).

2) Although haloperidol is the drug of choice in the treatment of Tourette's syndrome, more than on drug has been effective (Shapiro & Shapiro, 1981a). In some cases, combination therapy with haloperidol and nicotine or nifedipine has been effective (McConville et al, 1991); (Sandberg et al, 1989)(Alessi et al, 1989). The goal of treatment is to determine the lowest dosage that results in 70% improvement and the fewest side effects (Erenberg, 1992).

3) Nine out of 10 patients with Tourette's syndrome, not adequately controlled with haloperidol, wer successfully treated with adjunct nicotine gum (McConville et al, 1991). The patients began a therap of a 2 mg nicotine gum in conjunction with a mean dose of 2.8 mg per day of haloperidol. The numb of vocal and motor tics were recorded after chewing the gum 30 and 60 minutes. Nine out of the ten patients experienced reduced tic frequency. The mechanism of action is still under investigation.

d) Pediatric:

1) Haloperidol was not significantly more effective on the Tourette Syndrome (TS) Global Scale compared with placebo, and was associated with a significantly greater incidence of extrapyramidal symptoms, while pimozide demonstrated effectiveness over placebo, according to a 24-week, randomized, crossover study in pediatric patients (n=22). Patients with DSM-III-R criteria for TS, age 7 to 16 years (mean 10.2 +/- 2.5 years) were included in the study. Following an initial 2-week place baseline period, patients were randomized to receive 6 weeks of treatment with either haloperidol 1 milligram (mg), pimozide 1 mg, or placebo with dose titration of 2 mg/week to produce a 70% reduct in tic symptoms. Each 6-week treatment period was followed by a 2-week placebo washout period prior to crossing over to alternate therapy. A 70% tic reduction on the total TS global scale was achieved in 64% (14/22) with equivalent mean effective doses of pimozide 3.4 +/- 1.6 mg or haloperidol 3.5 +/- 2.2 mg/day compared with 23% (5/22) who received placebo (p=0.02 for treatme group effect). In a post hoc analysis, pimozide was significantly more effective than placebo on the total TS global scale , TS global tic subscale, the TS symptom list tic subscale score, Clinical Global Impression (CGI) tic severity scale, and on the clinician-rated Children's Global Assessment Scale (less than 0.05 on all scores). Haloperidol was significantly more effective than placebo on the CGI ti severity scale and on the clinician-rated Children's Global Assessment Scale (p less than 0.05 for bo scores). The number of extrapyramidal symptoms was higher during the haloperidol-treatment perio (mean 4.1 +/- 6.9) compared with the pimozide-treatment period (mean 2 +/- 3) (p less than 0.05), o placebo (mean 1.4 +/- 3) (p less than 0.01). Moderate to severe adverse events including depressio anxiety, or severe dyskinesias occurred in 9 of 22 patients during the haloperidol-treatment phase compared with 3 of 22 patients during the pimozide-treatment phase. There were no significant electrocardiovascular effects on heart rate, rhythm, or waveform in either the pimozide or haloperidc treatment phases compared with placebo (Sallee et al, 1997a).

2) Nicotine potentiated the effects of haloperidol in the treatment of Tourette's syndrome (Sandberg al, 1989). Ten children between the ages of 7 and 17 years (mean 12 years) who were taking haloperidol in doses ranging from 1 to 3 mg/day (mean 1 mg/day) were given nicotine gum 2 mg thr times daily. Eighty percent of the children showed both decreases of tics and improvement of concentration and attention span. This positive effect lasted from 45 to 60 minutes. However, 70% o the children discontinued the gum due to side effects. The side effects included stomach pain, naus decreased appetite, complaints of bitter taste and burning sensation in the mouth, and weight loss. T mechanism of action by which nicotine potentiates haloperidol is not known and more studies are needed. Two cases were reported of children in which NICOTINE gum 2 mg helped control Tourette syndrome that could not be adequately controlled with haloperidol alone (Sandberg et al, 1988).

3) The combination of haloperidol (1 milligram orally twice daily) plus nifedipine (10 milligrams orally times daily) was effective in the treatment of Gilles de la Tourette's syndrome in a 9-year-old boy wh was refractory to both nifedipine and haloperidol when administered as single agent therapy (Alessi al, 1989). The mechanism of apparent synergism in this patient is unclear, however, the authors postulate that the combination results in a relative reduction in D2 receptor-binding sites, causing a relative increase in the site specific potency of haloperidol. More studies are required to investigate t combination in Tourette's patients.

4.5.A.10 Hiccoughs

See Drug Consult reference: HICCUPS - ETIOLOGY AND TREATMENT

4.5.A.11 Hiccoughs, Intractable

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class III
Strength of Evidence: Adult, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Intramuscular HALOPERIDOL 2 mg successfully treated intractable hiccups in 2 patients (Ives et al, 1985)

4.5.A.12 Hyperactive behavior, (Short-term treatment) after failure to respond to non-antipsychotic medication and psychotherapy

FDA Labeled Indication

a) Overview

FDA Approval: Adult, no; Pediatric, yes (3 yr and older)
Efficacy: Pediatric, Evidence favors efficacy
Recommendation: Pediatric, Class IIb
Strength of Evidence: Pediatric, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Indicated for short-term treatment of hyperactive children with excessive motor activity and concomitant conduct disorders such as impulsivity, difficulty sustaining attention, aggressivity, mood lability and poor frustration tolerance (Prod Info haloperidol oral tablets, 2006; Prod Info haloperidol oral solution, 2001)

4.5.A.13 Migraine

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive; Pediatric, Evidence is inconclusive
Recommendation: Adult, Class III; Pediatric, Class III
Strength of Evidence: Adult, Category C; Pediatric, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

In case reports, intravenous haloperidol has been effective in relieving symptoms of migraine headache

c) Adult:

1) Intravenous haloperidol was effective in relieving symptoms of migraine headache in a series of s cases. Haloperidol was primarily administered for the relief of nausea and vomiting, but was also fou to alleviate headache pain. Following an intravenous bolus of 500 to 1000 milliliters of normal saline haloperidol was given as a dose of 5 mg over 2 to 3 minutes. Headache pain was better after 25 to (minutes, and none of the six patients returned for additional treatment within the next two days (Fish 1995). Randomized prospective trials are needed to validate these findings.

d) Pediatric:

1) HALOPERIDOL 0.05 to 0.1 milligrams/kilogram/day orally has been effective in relieving hemiple episodes of MIGRAINE HEADACHE in children (Salmon & Wilson, 1984).

4.5.A.14 Nausea and vomiting; Treatment and Prophylaxis

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Prevents nausea and vomiting due to numerous causes

c) Adult:

1) Numerous studies have indicated that HALOPERIDOL in 1 to 4 milligram doses, intramuscular o oral, is an effective ANTIEMETIC in the prevention or treatment of nausea and vomiting due to varic causes including POSTOPERATIVE NAUSEA and vomiting, CANCER CHEMOTHERAPY, IRRADIATION, and GASTROINTESTINAL DISORDERS (Barton et al, 1975; Robbins & Nagel, 197 Cole & Duffy, 1974; Christman et al, 1974; Plotkin et al, 1973; Tornetta, 1972); (Shields et al, 1971). postoperative nausea, HALOPERIDOL by the intravenous route was more rapid in onset than either DROPERIDOL or PROCHLORPERAZINE (Loeser et al, 1979).

2) Two cases were reported of HALOPERIDOL combined with LORAZEPAM to successfully treat nausea and vomiting associated with the intravenous use of DIHYDROERGOTAMINE for treatment intractable migraine headaches (Backonja et al, 1989). The authors found that the intravenous administration of 0.5 to 1 mg each of HALOPERIDOL and LORAZEPAM 15 minutes prior to the intravenous administration of DIHYDROERGOTAMINE prevents nausea and vomiting. HALOPERIDOL and LORAZEPAM cause marked sedation and the authors therefore recommend th 0.25 mg of each drug be given initially and an additional 0.25 to 0.5 mg be added as needed.

3) HALOPERIDOL gave better results in emesis induced by platinol and NITROGEN MUSTARD; BENZQUINAMIDE gave better results with DOXORUBICIN. This was in a study where BENZQUINAMIDE was compared with HALOPERIDOL for relief of emesis due to specific antineoplastic agents in 64 patients. In patients not being relieved by the first agent, crossover usua resulted in some relief. More PROCHLORPERAZINE resistant patients obtained relief with HALOPERIDOL than with BENZQUINAMIDE (Neidhart et al, 1981b).

4.5.A.15 Obsessive-compulsive disorder; Adjunct

a) Overview

FDA Approval: Adult, no; Pediatric, no

Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class III
Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:
Useful as adjunct therapy in treating refractory obsessive compulsive disorder

c) Adult:
1) The addition of haloperidol was useful in treating refractory obsessive compulsive disorder. In a double-blind, randomized, placebo-controlled trial lasting four weeks, 34 patients receiving, but refractory to, fluvoxamine (maximum 300 mg/day) for obsessive compulsive disorder had either haloperidol (maximum 10 mg/day) or placebo added to their regimen (McDougle et al, 1994). Severa scales used to assess obsessive compulsive symptoms, tics, depression, and related symptoms showed that the addition of haloperidol was significantly better than the addition of placebo in reduci the severity of obsessive compulsive symptoms with chronic tic disorders. The only significant adver effect occurring with haloperidol was akathisia in 9 of 31 patients. Haloperidol addition was of limitec benefit in treating obsessive compulsive disorder patients without tics.

4.5.A.16 Ocular hypertension

a) Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class III
Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:
Not effective

c) Adult:
1) Topical administration of the HALOPERIDOL ophthalmic solution (0.125% and 1%) produced modest reductions in intraocular pressure in healthy volunteers; however, reductions were not considered statistically significant (Lavin & Andrews, 1986).
2) HALOPERIDOL 3 milligrams orally was reported to produce significant decreases in intraocular pressure in non-glaucomatous volunteers at 3 to 4 hours post-administration (Sheppard & Schaid, 1986). However, significant reductions in intraocular pressure were not observed in glaucomatous patients receiving topical antiglaucoma medications, and more studies are required to determine benefits in glaucomatous patients; the authors suggest that lack of response in this group was relate to use of the concurrent topical medications.

4.5.A.17 Opioid withdrawal

See Drug Consult reference: DRUG THERAPY OF OPIOID WITHDRAWAL

4.5.A.18 Pain

a) Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class III
Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:
Questionable effects on pain control

c) Adult:
1) No shift to the left in dosage histograms was found in 424 cancer patients treated with MORPHIN vs MORPHINE plus HALOPERIDOL. The authors concluded that HALOPERIDOL did not potentiate MORPHINE analgesia (Hanks et al, 1983).
2) In a single case report (Daw & Cohen-Cale, 1981), HALOPERIDOL was shown to have an independent analgesic effect as well as a narcotic-potentiating effect in the treatment of severe pelv pain.
3) In intractable pain, HALOPERIDOL has successfully been used as an analgesic. A review of the cases reveals that it has been used for terminal cancer pain, intractable arthritic pain, and severe denervation dysesthesia. Some of these patients have been able to greatly decrease their consumption of narcotics; others have managed on HALOPERIDOL alone. The rationale for use of HALOPERIDOL for this purpose rests with its structural similarity to MEPERIDINE, its effectiveness preventing withdrawal symptoms upon removal of narcotics in addicts, a recognition of an analgesic dose-response seen at doses which, until recently, were rarely used (ie, 20 to 40 mg/day), and the demonstration that HALOPERIDOL binds to the opiate receptor. Further study of the analgesic effec of HALOPERIDOL is warranted (Maltbie et al, 1979a).
4) In chronic facial pain, nonmigranous and nonneuralgiform in nature, HALOPERIDOL along with relaxation therapy was successful in relieving pain in 12 of 12 patients. Although this type of pain ha very high psychogenic component and improvement in the psychiatric well-being of the patient coul

be the rationale of successful therapy, HALOPERIDOL has also been shown to have analgesic properties. The author suggests that further study might elucidate more clearly the use of HALOPERIDOL in these patients (Raft et al, 1979).

4.5.A.19 Postoperative nausea and vomiting; Prophylaxis

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

The administration of haloperidol after spinal anesthesia reduced the incidence of postoperative nausea and vomiting

c) Adult:

1) Prophylactic administration of haloperidol after spinal anesthesia reduced the incidence of postoperative nausea and vomiting during the first 24 hours after surgery. In a randomized, double-blind, placebo- controlled study (n=108), patients undergoing lower limb orthopedic or endoscopic urologic surgery under spinal anesthesia received a single intramuscular dose of haloperidol 1 milligram (mg), haloperidol 2 mg, or placebo after spinal anesthesia with local anesthetic and morph 0.3 mg for the prophylaxis of postoperative nausea and vomiting. Treatment failure was defined as a nausea score of 1 (mild) or higher, any episode of vomiting, or a request for rescue antiemetic. Over 60% of patients met criteria for treatment failure within the first 12 hours following surgery, with both haloperidol doses demonstrating a significant dose-related reduction in incidence of postoperative nausea, vomiting, or antiemetic use (treatment failure, placebo 76%, haloperidol 1 mg 56%, haloperidol 2 mg 50%; p=0.012). The total treatment failure rate at 24 hours was 65% (placebo 76% haloperidol 1 mg 64%, haloperidol 2 mg 55%; p=0.03). No difference was found between the two haloperidol doses. No extrapyramidal effects were observed with the use of haloperidol during the study (Parlow et al, 2004).

4.5.A.20 Problematic behavior in children (Severe), With failure to respond non-antipsychotic medication or psychotherapy

FDA Labeled Indication

a) Overview

FDA Approval: Adult, no; Pediatric, yes (3 yr and older)
Efficacy: Pediatric, Effective
Recommendation: Pediatric, Class IIb
Strength of Evidence: Pediatric, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Indicated in the treatment of severe behavior problems in children with combative, explosive hyperexcitability which is not accounted for by immediate provocation
Also effective in the short-term treatment of hyperactive children who show excessive motor activity with accompanying conduct disorders (i.e. impulsivity, difficulty sustaining attention, aggressivity, mood lability and poor frustration tolerance)
Recommended for children unresponsive to psychotherapy or medications other than antipsychotics

c) Pediatric:

1) Symptomatic improvement was seen with HALOPERIDOL in 12 hospitalized patients 7 to 11 yea old who suffered from childhood-onset PERVASIVE DEVELOPMENTAL DISORDER. The average dose of HALOPERIDOL was 0.04 milligrams/kilogram per day. There was remarkable improvement peer interaction, reduction in autistic-like behavior, improved reality testing, and decreased impulsivi and hyperactivity. This low-dose treatment with HALOPERIDOL produced minimal side effects. Thre children exhibited transient drowsiness in the initial phase of treatment, but this decreased over time and did not interfere with their cognitive performance. Two children suffered mild extrapyramidal symptoms with rigidity and cogwheeling. These symptoms were treated with oral DIPHENHYDRAMINE and did not recur when the drug was withdrawn (Joshi et al, 1988).

2) HALOPERIDOL (0.5 to 4 milligrams/kilogram) was more effective than placebo in a double-blind crossover study of 41 patients aged 2.3 to 6.9 years with INFANTILE AUTISM. HALOPERIDOL resulted in a significant decrease in behavioral symptoms and significant increases in facilitation and retention of discrimination (Anderson et al, 1984).

3) HALOPERIDOL 0.5 to 4 milligrams was compared with placebo in a double-blind, crossover stud in nine autistic children, ages 2 to 7 years, confirming the efficacy of HALOPERIDOL in autism (Coh et al, 1980). It was found effective in reducing rates of stereotypy and facilitating low rates of orientir to the rater, while not affecting other behaviors, including motor activity, speech, affect, or irritability. The results of this ongoing study, involving 33 patients, have been updated (Campbell et al, 1982a).

4.5.A.21 Psychotic disorder

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes; Pediatric, yes (3 yr and older (oral formulations only))
Efficacy: Adult, Evidence favors efficacy; Pediatric, Evidence favors efficacy
Recommendation: Adult, Class IIb; Pediatric, Class IIb
Strength of Evidence: Adult, Category B; Pediatric, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Indicated for management of manifestations of psychotic disorders (Prod Info haloperidol oral tablets, 2006; Prod Info haloperidol oral solution, 2001)

4.5.A.22 Rheumatoid arthritis

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class III
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Improves clinical features and laboratory parameters of RHEUMATOID ARTHRITIS

c) Adult:

1) Patients with rheumatoid arthritis previously treated only with nonsteroidal antiinflammatory drugs were found to have no significant difference in responses to either 150 milligrams (mg)/day indomethacin or 1.5 mg/day HALOPERIDOL. A proposed mechanism for this effect of HALOPERID is membrane-stabilization on platelets (Grimaldi & Bergonzi, 1980). A follow-up study (Grimaldi, 198 suggested a specific antirheumatic activity of HALOPERIDOL, based on increased serum sulfphydry levels and decreased PIP joints technetium index, ESR, and joint count.

4.5.A.23 Schizophrenia

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes; Pediatric, yes (3 yr and older (oral formulations only))
Efficacy: Adult, Evidence favors efficacy; Pediatric, Evidence favors efficacy
Recommendation: Adult, Class IIa; Pediatric, Class IIa
Strength of Evidence: Adult, Category B; Pediatric, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Indicated in the management of schizophrenia

c) Adult:

1) Haloperidol is effective in the treatment of SCHIZOPHRENIA and ACUTE PSYCHOSIS, as well schizoaffective disorders and paranoid syndrome. Usual oral haloperidol doses range from 5 to 20 milligrams/day, but doses of 100 mg/day or more may be indicated (Carter, 1986).

2) Intravenous HALOPERIDOL was used successfully in five severely regressed, nonviolent, psychiatric inpatients with psychotic disorders (Plotnick & Brown, 1991). Five psychiatric patients unable to thrive without intravenous fluids and nutrition and incapable of ingesting oral medications were given intravenous HALOPERIDOL in therapeutic doses to alleviate psychotic symptoms and were studied in retrospect. All five cases showed significant improvement in symptoms shortly following use of intravenous HALOPERIDOL. Four of the five patients were discharged in complete remission of symptoms after brief hospital stays. The authors suggested that HALOPERIDOL given a slow intravenous push was a safe and rapidly effective treatment for severely regressed, nonviole psychotic inpatients.

3) A double-blind study with 20 patients suffering manic or schizomanic psychoses determined that CARBAMAZEPINE and HALOPERIDOL in combination were as effective as HALOPERIDOL alone. The doses were haloperidol 24 mg/day and CARBAMAZEPINE 600 mg/day. No evidence was foun to show that the combination was more effective than HALOPERIDOL alone (Moller et al, 1989). Similarly, the combination of CARBAMAZEPINE plus HALOPERIDOL was compared with HALOPERIDOL plus placebo in a controlled study involving 43 patients with excited psychoses. Combination therapy was reported superior to HALOPERIDOL alone with clinical benefits being as apparent in excited schizophrenia as in mania (Klein et al, 1984a).

4) The positive correlation between early response and clinical outcome in schizophrenic patients treated with HALOPERIDOL was reported. Doses were not reported, but averaged 26 and 32 mg at hours in dysphoric and nondysphoric patients, respectively. Eighty-two percent of patients classified nondysphoric after 24 hours had good clinical results after 3 weeks, while 23% of dysphoric patients after 24 hours had poor clinical results after 3 weeks. The authors concluded that early subjective ar symptom improvement is an indicator of therapeutic outcome (Awad & Hogan, 1985).

5) Amphetamine was beneficial when added to chronic haloperidol therapy in 21 patients with undifferentiated or paranoid schizophrenia (Goldberg et al, 1991). Thirty-two percent reflected negat symptoms, 46% displayed positive symptoms, and 11% had paranoid symptoms. The study assess

changes in neuropsychological function such as positive effects on affect and cognition. A single dos of 0.25 milligrams/kilogram of dextroamphetamine was administered and the patients were evaluate for cognitive function, performance and comprehension. Six patients showed improvement after administration of the amphetamine. Increases in spontaneous eye-blink rate and enlarged cerebral ventricles were associated with improvement. The authors concluded that amphetamine paired with haloperidol had a positive effect on symptoms of schizophrenia; however, no definite conclusions co be drawn because no long term study was done.

4.5.A.24 Severe major depression with psychotic features

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Successfully used in combination with tricyclic antidepressants to treat psychotic depression

c) Adult:

1) Two cases were reported of patients suffering from PSYCHOTIC DEPRESSION successfully be treated with a combination of low dose HALOPERIDOL (1 to 3 mg/day) and DESIPRAMINE (100 mg/day). The HALOPERIDOL serum levels of the patients were 1.5 to 2.4 ng/mL. The authors concluded that the higher doses of neuroleptics commonly used to treat this condition may not be necessary (Lin et al, 1989).

4.5.A.25 Sneezing

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class III
Strength of Evidence: Adult, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Effective in 1 case report

c) Adult:

1) A single case of intractable sneezing of 139 days (every 4 to 5 seconds except when sleeping or talking) was slowed to every 30 seconds with a dose of haloperidol 1.5 milligrams (mg) twice daily. T rate continued to slow as the dose was increased and stopped altogether at a dose of 5 mg 3 times daily. The dose was then gradually reduced over 6 months without recurrence (Davison, 1982).

4.5.B Haloperidol Decanoate

Chronic schizophrenia

Gilles de la Tourette's syndrome

4.5.B.1 Chronic schizophrenia

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Indicated for the treatment of schizophrenic patients who require prolonged parenteral antipsychotic therapy (Prod Info haloperidol decanoate injection, 2005)

c) Adult:

1) Monthly intramuscular injections of HALOPERIDOL DECANOATE 50 milligrams for 5 months wa reported effective in the treatment of chronic schizophrenic patients, many of whom showed poor compliance to oral medication (Bucci & Marini, 1985).

4.5.B.2 Gilles de la Tourette's syndrome

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy

Recommendation: Adult, Class IIa
Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:
Effective in treatment of severe, intractable Tourette's syndrome unresponsive to oral haloperid in 1 case report (Clarke & Ford, 1988)

c) Adult:
1) HALOPERIDOL DECANOATE intramuscularly was reported effective in the treatment of severe, intractable Tourette's syndrome unresponsive to oral HALOPERIDOL in a 23-year-old male (Clarke Ford, 1988). The patient had been unresponsive to oral HALOPERIDOL (doses of up to 10 milligran orally four times daily) for several years. Oral HALOPERIDOL was discontinued and a test dose of HALOPERIDOL DECANOATE 100 milligrams intramuscularly was administered, resulting in a reduction in tics, coprolalia, and copropraxic gestures over the ensuing two weeks. HALOPERIDOL DECANOATE was continued in doses of up to 400 milligrams intramuscularly monthly, then was subsequently reduced to 200 milligram maintenance doses. Tourette's symptoms disappeared completely after 4 months of treatment.

4.5.C Haloperidol Lactate

Gilles de la Tourette's syndrome

Schizophrenia

4.5.C.1 Gilles de la Tourette's syndrome

FDA Labeled Indication

a) Overview
FDA Approval: Adult, yes; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:
Indicated for the control of tics and vocal utterances of Tourette's disorder (Prod Info HALDOL(I immediate release IM injection, 2008)

c) Adult:
1) Indicated for the control of tics and vocal utterances of Tourette's disorder (Prod Info HALDOL(R immediate release IM injection, 2008).
2) In some cases, combination therapy with haloperidol and nicotine or nifedipine has been effectiv the treatment of Tourette's syndrome (McConville et al, 1991); (Sandberg et al, 1989)(Alessi et al, 1989). The goal of treatment is to determine the lowest dosage that results in 70% improvement and the fewest side effects (Erenberg, 1992).
3) Nine out of 10 patients with Tourette's syndrome, not adequately controlled with haloperidol, wer successfully treated with adjunct nicotine gum (McConville et al, 1991). The patients began a therap of a 2 mg nicotine gum in conjunction with a mean dose of 2.8 mg per day of haloperidol. The numb of vocal and motor tics were recorded after chewing the gum 30 and 60 minutes. Nine out of the ten patients experienced reduced tic frequency. The mechanism of action is still under investigation.

4.5.C.2 Schizophrenia

FDA Labeled Indication

a) Overview
FDA Approval: Adult, yes; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:
Indicated for the treatment of schizophrenia in adult patients (Prod Info HALDOL(R) immediate release IM injection, 2008).

c) Adult:
1) Haloperidol is effective in the treatment of schizophrenia and acute psychosis, as well as schizoaffective disorders and paranoid syndrome (Carter, 1986).
2) A double-blind study with 20 patients suffering manic or schizomanic psychoses determined that carbamazepine and haloperidol in combination were as effective as haloperidol alone. The doses w haloperidol 24 mg/day and carbamazepine 600 mg/day. No evidence was found to show that the combination was more effective than haloperidol alone (Moller et al, 1989). Similarly, the combinatio

of carbamazepine plus haloperidol was compared with haloperidol plus placebo in a controlled study involving 43 patients with excited psychoses. Combination therapy was reported superior to haloperidol alone with clinical benefits being as apparent in excited schizophrenia as in mania (Kleir al, 1984a).
3) The positive correlation between early response and clinical outcome in schizophrenic patients treated with haloperidol was reported. Doses were not reported, but averaged 26 and 32 mg at 24 hours in dysphoric and nondysphoric patients, respectively. Eighty-two percent of patients classified nondysphoric after 24 hours had good clinical results after 3 weeks, while 23% of dysphoric patients after 24 hours had poor clinical results after 3 weeks. The authors concluded that early subjective ar symptom improvement is an indicator of therapeutic outcome (Awad & Hogan, 1985).
4) Amphetamine was beneficial when added to chronic haloperidol therapy in 21 patients with undifferentiated or paranoid schizophrenia (Goldberg et al, 1991). Thirty-two percent reflected negat symptoms, 46% displayed positive symptoms, and 11% had paranoid symptoms. The study assesse changes in neuropsychological function such as positive effects on affect and cognition. A single dos of 0.25 milligrams/kilogram of dextroamphetamine was administered and the patients were evaluate for cognitive function, performance and comprehension. Six patients showed improvement after administration of the amphetamine. Increases in spontaneous eye-blink rate and enlarged cerebral ventricles were associated with improvement. The authors concluded that amphetamine paired with haloperidol had a positive effect on symptoms of schizophrenia; however, no definite conclusions co be drawn because no long term study was done.

4.6 Comparative Efficacy / Evaluation With Other Therapies

Alizapride

Alprazolam

Amisulpride

Amitriptyline

Amobarbital

Aripiprazole

Ascorbic Acid

Benzquinamide

Bromperidol

Carbamazepine

Chlorpromazine

Chlorprothixene

Clocapramine

Clomipramine

Clonazepam

Clonidine

Clozapine

Diazepam

Diphenhydramine

Droperidol

Flunitrazepam

Flupenthixol

Fluphenazine

Imipramine

Lithium

Lorazepam

Loxapine

Melperone

Mesoridazine

Metoclopramide

Midazolam

Molindone

Olanzapine

Oxazepam

Oxcarbazepine

Penfluridol

Perazine

Periciazine

Perphenazine

Phenelzine

Physostigmine

Pimozide

Pramipexole

Prochlorperazine

Quetiapine

Remoxipride

Risperidone

Sertindole

Sulpiride

Sultopride

Tetrabenazine

Tetrahydrocannabinol

Thioridazine

Thiothixene

Timiperone

Trifluoperazine

Trimethobenzamide

Valproic Acid

Ziprasidone

Zotepine

Zuclopenthixol

4.6.A Alizapride

4.6.A.1 Nausea

a) The combination of tropisetron and haloperidol was compared with alizapride to treat nausea and vomiting in high-dose alkylating agent cancer chemotherapy. Twenty-six patients received only alizapride therapy. In the initial 24-hour period, six patients on tropisetron and haloperidol experienced no nausea o vomiting, opposed to one patient taking alizapride. At the end of the study period (72 hours), six patients taking tropisetron plus haloperidol showed no signs of nausea and vomiting compared with zero patients receiving alizapride (Bregni et al, 1991).

4.6.B Alprazolam

4.6.B.1 Dementia - Problem behavior

a) Alprazolam was as effective as low-dose haloperidol in a double-blind, cross-over trial in elderly, nurs home patients with disruptive behaviors associated with delirium, dementia, amnestic disorders, and oth cognitive disorders (Christensen & Benfield, 1998). Patients (n=48) currently receiving haloperidol 1 milligram (mg) or less on a scheduled basis had behavioral episodes measured at baseline. Thereafter patients either continued haloperidol for 6 weeks or entered a 2-week washout period followed by alprazolam 0.5 mg daily for 4 weeks. Both groups were reassessed and then crossed-over into the other group. There was no significant difference in the number of behavioral episodes for patients taking alprazolam compared to patients receiving haloperidol. There was also no difference in either group as compared to baseline. Since no placebo was used in this study, it is difficult to determine whether the patients actually benefited from either therapy.

4.6.C Amisulpride

4.6.C.1 Schizophrenia

a) Amisulpride was superior to haloperidol for the treatment of acute exacerbations of schizophrenia, in regard to both efficacy and safety. In a randomized, double-blind study, patients aged 18 to 45 years witl paranoid schizophrenia or schizophreniform disorder (by DSM-IV criteria) were treated for 4 months with oral haloperidol 10 to 30 milligrams (mg) per day (n=105) or amisulpride 400 to 1200 mg/day (n=94). Starting doses were 20 mg/day for haloperidol and 800 mg/day for amisulpride. Doses were then adjuste according to the patient's condition. Significantly more patients in the haloperidol group than in the

amisulpride group withdrew from the study, due mainly to adverse effects (21% vs 4%) and lack of effica (9% vs 6%). At the end of the study, scores on the Positive and Negative Syndrome Scale (PANSS) had improved more in the amisulpride group than in the haloperidol group, with the difference reaching significance on the negative PANSS score (p=0.01). The percentage of responders ("much" or "very muc improved on the Clinical Global Impressions (CGI) global improvement scale) was 71% in the amisulprid group and 47% in the haloperidol group (p=0.0006). Five percent of the patients in the amisulpride group were considered "worse" after treatment, compared to 15% of those in the haloperidol group. At the end the study, 40% of the amisulpride group were considered "normal," "borderline," or "mildly ill," vs 25% of the haloperidol group. Half of the patients who received haloperidol reported at least one extrapyramidal adverse event, compared to 33% of those who received amisulpride. At least one serious adverse event (mainly psychotic disorders and extrapyramidal effects) occurred in 16% of patients receiving haloperido and 4% of those receiving amisulpride. Weight gain (increase of 5% or more from baseline) was more frequent in the amisulpride group (33% vs 17%, p=0.051) (Carriere et al, 2000).

b) SUMMARY: AMISULPRIDE has been shown to be as effective as HALOPERIDOL in short-term and long-term treatment of schizophrenia. In some studies, AMISULPRIDE demonstrated greater efficacy related to negative symptomatology and improved tolerability (eg, fewer extrapyramidal effects).

c) In an open-label, randomized, multi-center trial (n=488), a 12-month course of AMISULPRIDE produc a similar incidence of drug-related adverse effects (69%) compared to HALOPERIDOL (70%), with amisulpride inducing lower rates of extrapyramidal side effects than haloperidol (13% vs 28%), in patient with subchronic or chronic schizophrenia with acute exacerbation (DSM-III-R). Amisulpride showed simil efficacy to haloperidol on positive symptoms of schizophrenia and significantly greater effectiveness thar haloperidol on negative symptoms (p=0.0001). Enrollees included patients with at least moderate scores 2 or more of the 4 positive items of the Brief Psychiatric Rating Scale (BPRS). Randomization was in a 3 1 ratio, amisulpride (n=370) to haloperidol (n=118). Scores on the Simpson-Angus extrapyramidal scale, Barnes Akathisia Scale, and the Abnormal Involuntary Movement Scale (AIMS) favored amisulpride ove haloperidol (p=0.0001; p less than 0.0001; and p=0.014, respectively). Serious adverse events (primarily psychiatric, including psychosis, agitation, aggression, and suicide attempts) occurred in 10% and 7%, respectively, of amisulpride- and haloperidol-treated patients. Rates of weight gain and amenorrhea were 11% and 6% for amisulpride compared with 3% and 0, respectively, for haloperidol. Discontinuations due adverse effects were 8% and 10%, respectively (amisulpride vs haloperidol). Withdrawals due to lack of efficacy were significantly less in the amisulpride group (12% vs 22%; p=0.009). At the end of 12 months the rate of change in BPRS scores was 44.8% and 33.7% from baseline in the amisulpride and haloperic groups, respectively. Mean decreases in the Positive and Negative Syndrome Scale (PANSS) positive scores were similar across groups (amisulpride, 48.4%; haloperidol 44.2%), whereas changes in PANSS negative scores were significantly greater for amisulpride (35.1% decrease vs 12% decrease; p=0.0001) Dosing was flexible, based on efficacy and tolerability. Maximum doses permitted during acute episodes were 1200 milligrams/day (mg/d) for amisulpride and 30 mg/d for haloperidol; during stable periods, dose were to fall between 200 and 800 mg for amisulpride and between 5 and 20 mg for haloperidol (mean da doses by study end were amisulpride 605 mg and haloperidol 14.6 mg) (Colonna et al, 2000).

d) In a double-blind, randomized study, AMISULPRIDE 800 milligrams (mg)/day over 6 weeks was shov to be as effective as HALOPERIDOL 20 mg/day for the treatment of subchronic schizophrenia or chronic schizophrenia with an acute exacerbation (DSM-III-R criteria), with AMISULPRIDE showing possibly greater efficacy in improving negative symptoms, as well as greater tolerability (n=191). On the Positive and Negative Symptom Scales (PANSS), negative symptoms were significantly improved in amisulpride-treated patients compared with the haloperidol group (mean change, 7.5 vs 5.1; p=0.038). Results on so parts of the Clinical Global Impression (CGI) rating also favored amisulpride (p=0.01 and p less than 0.0 respectively). Overall, 54 of 95 patients (56.8%) in the amisulpride group had at least one adverse event (mostly extrapyramidal symptoms) compared with 72 of 96 patients (75%) in the haloperidol group; 25 a 39 patients, respectively, dropped out of the study (p=0.04) (Moller et al, 1997).

e) Amisulpride was as effective for relapse prevention as haloperidol over a 1-year period in long-term i patients with predominantly negative symptoms of schizophrenia (Speller et al, 1997). Patients were randomly allocated to receive either amisulpride (n=29) or haloperidol (n=31) at a dose calculated to be equivalent to their previous antipsychotic medication. Amisulpride doses were 800 milligrams (mg), 600 450 mg, 300 mg, 150 mg, and 100 mg daily. For haloperidol doses were 20 mg, 16 mg, 11.5 mg, 8 mg, 4 mg, and 3 mg daily. Dose reductions were undertaken every 3 months with the trial medication reduced the next lowest level, unless the lowest dose had been achieved or there was evidence of psychotic exacerbation. During the year, 18% of the amisulpride group and 35% of the haloperidol group experienc psychotic exacerbations (not statistically significant). At the end of the year, 76% of the amisulpride grou had achieved the lowest dose while 58% of the haloperidol group were on the lowest dose (either 3 mg c 4.5 mg). Amisulpride patients did show a greater reduction of the affective flattening and the avolition-apathy global items on the Scale for the Assessment of Negative Symptoms but it was again not significa

f) In a double-blind study, 41 schizophrenic patients were treated, with flexible doses, of haloperidol (n= and amisulpride (n=21) over a period of 42 days (Delcker et al, 1990). On the basis of the Brief Psychiat Rating Scale subscore for anxiety-depression syndrome, and the Arbeitsgemeinschaft fuer Methodik unc Dokumentation in der Psychiatrie (AMDP) system subscore for the somatic depressive syndrome and th hypochondriac syndrome, the amisulpride group showed better results than the haloperidol group. No difference between the two drugs was found in improvement of psychotic symptoms. Amisulpride showe tendency to cause fewer extrapyramidal adverse effects.

g) In a double-blind study, amisulpride (10 milligrams/kilogram (mg/kg) daily) was compared to haloperic (0.5 mg/kg daily) in treatment over one month of patients with acute schizophrenia. The 9 patients in the amisulpride group completed the study, whereas 5 of 10 patients of haloperidol group dropped out of the trial, 3 because of adverse effects. Both drugs significantly improved the acute psychotic symptomatolog and were tolerated in a comparable manner. Extrapyramidal effects were much more pronounced in the haloperidol group (Ruther et al, 1989).

h) In a comparative, double-blind study, 40 patients hospitalized for acute psychosis were treated with amisulpride (800 to 1200 milligrams (mg)/day, 20 patients) or haloperidol (20 to 30 mg/day, 20 patients) 21 days (Costa & Silva, 1989). No significant difference in efficacy was reported between the two drugs according to the Brief Psychiatric Rating Scale. Amisulpride showed less frequent and less intense extrapyramidal adverse effects. Larger, long-term comparative studies are needed to more clearly asses the efficacy, safety and therapeutic role of amisulpride in schizophrenia.

i) A double-blind trial evaluated the therapeutic effects and tolerance of high doses of amisulpride (800 t 1200 milligrams (mg) daily) (20 patients) versus haloperidol (20 to 30 mg daily) (19 patients) in acute psychotic disorders (acute delusional attacks and positive symptoms of schizophrenia). Both drugs exhibited good antipsychotic activity, but amisulpride had a prompt effect, provided more improvement o symptoms (particularly on the anergy, thought disorder, and activation items of the Brief Psychiatric Rati Scale), and exhibited a better tolerance (Pichot & Boyer, 1988).

4.6.C.2 Adverse Effects

a) AMISULPRIDE appears to have better tolerability compared with HALOPERIDOL in both short-term a long-term regimens.

b) In an open-label, randomized, multi-center trial (n=488), a 12-month course of AMISULPRIDE produc a similar incidence of drug-related adverse effects (69%) compared to HALOPERIDOL (70%), with amisulpride inducing lower rates of extrapyramidal side effects than haloperidol (13% vs 28%), in patient with subchronic or chronic schizophrenia with acute exacerbation (DSM-III-R). Amisulpride showed simil efficacy to haloperidol on positive symptoms of schizophrenia and significantly greater effectiveness thar haloperidol on negative symptoms (p=0.0001). Enrollees included patients with at least moderate scores 2 or more of the 4 positive items of the Brief Psychiatric Rating Scale (BPRS). Randomization was in a 3 1 ratio, amisulpride (n=370) to haloperidol (n=118). Scores on the Simpson-Angus extrapyramidal scale, Barnes Akathisia Scale, and the Abnormal Involuntary Movement Scale (AIMS) favored amisulpride ove haloperidol (p=0.0001; p less than 0.0001; and p=0.014, respectively). Serious adverse events (primarily psychiatric, including psychosis, agitation, aggression, and suicide attempts) occurred in 10% and 7%, respectively, of amisulpride- and haloperidol-treated patients. Rates of weight gain and amenorrhea were 11% and 6% for amisulpride compared with 3% and 0, respectively, for haloperidol. Discontinuations due adverse effects were 8% and 10%, respectively (amisulpride vs haloperidol). Withdrawals due to lack of efficacy were significantly less in the amisulpride group (12% vs 22%; p=0.009). At the end of 12 months the rate of change in BPRS scores was 44.8% and 33.7% from baseline in the amisulpride and haloperic groups, respectively. Mean decreases in the Positive and Negative Syndrome Scale (PANSS) positive scores were similar across groups (amisulpride, 48.4%; haloperidol 44.2%), whereas changes in PANSS negative scores were significantly greater for amisulpride (35.1% decrease vs 12% decrease; p=0.0001) Dosing was flexible, based on efficacy and tolerability. Maximum doses permitted during acute episodes were 1200 milligrams/day (mg/d) for amisulpride and 30 mg/d for haloperidol; during stable periods, dose were to fall between 200 and 800 mg for amisulpride and between 5 and 20 mg for haloperidol (mean da doses by study end were amisulpride 605 mg and haloperidol 14.6 mg) (Colonna et al, 2000).

c) AMISULPRIDE produces fewer disturbances of psychomotor, cognitive, extrapyramidal, and affective functions compared with HALOPERIDOL, according to a double-blind, randomized, cross-over study in healthy volunteers (n=21). Enrollees received 4 different 5-day regimens, with at least 10 days of washo between treatments. On days 1 and 5, subjects ingested 2 capsules in the morning: (1)placebo plus placebo; (2)amisulpride 50 milligrams (mg) plus placebo; (3)amisulpride 200 mg plus amisulpride 200 mg (400 mg/day); or (4)haloperidol 2 mg plus haloperidol 2 mg (4 mg/day). On days 2, 3, and 4, the same dosages were given but divided between morning and evening. Amisulpride 50 mg/day had no effect comparing baseline with post-treatment measurements. Amisulpride 400 mg was associated with a few adverse effects on psychomotor and cognitive performance (on day 5 only). Haloperidol was problematic from day 1; it induced several affective disturbances, including higher ratings for depression on the Hamilton Scale, lower feelings of well-being on the Subjective Well-Being under Neuroleptics Scale, and more negative symptoms on the Positive and Negative Symptoms Scale. With respect to affective measures, only drowsiness was significantly greater after amisulpride 400 mg than after placebo (p=0.01 Mean ratings of extrapyramidal symptoms and akathisia were always significantly higher after haloperidc than amisulpride 400 mg (Simpson-Angus Extrapyramidal Side Effect Scale, p equal or less than 0.01; Barnes Akathisia Scale, p equal or less than 0.02). Five times more patients requested anti-cholinergic agents while receiving haloperidol than during amisulpride 400-mg treatment. Two patients dropped out due to side effects of haloperidol vs no drop-outs for amisulpride (Ramaekers et al, 1999).

4.6.D Amitriptyline

4.6.D.1 Schizoaffective disorder

a) Amitriptyline (mean 148 mg/day, maximum 150 mg/day), haloperidol (mean 7.2 mg/day, maximum 12 mg/day), and placebo were compared in 64 patients with unstable and schizotypal borderline disorders.

a wide variety of psychological tests, haloperidol was shown to be significantly more effective than amitriptyline in these disorders, including disorders with a depressive component (Soloff et al, 1986).

4.6.E Amobarbital

4.6.E.1 Psychotic disorder

a) A single-blind study of 15 healthy male schizophrenic patients showed that intramuscular administrati of sodium amytal 250 mg or midazolam 5 milligrams was significantly more effective than haloperidol 10 mg in controlling motor agitation. They were also more effective than haloperidol in controlling hostility, though this did not reach statistic significance (Wyant et al, 1990).

4.6.F Aripiprazole

4.6.F.1 Schizophrenia

a) SUMMARY: Aripiprazole (up to 30 mg daily) and haloperidol (up to 20 mg daily) appear similarly effective in patients with acutely relapsed schizophrenia or schizoaffective disorder; adverse effects may less with aripiprazole.

b) Haloperidol 5 to 20 mg daily, but not aripiprazole (5 to 30 mg daily), was superior to placebo with respect to improvement in BPRS scores in a 4-week study involving acutely relapsed inpatients with DSI III/IV schizophrenia (n=103). Both haloperidol and aripiprazole were more effective than placebo in responder analysis based on CGI-severity scores (Prod Info Abilify(TM), 2002).

c) In a placebo-controlled, phase III study involving relapsed schizophrenic or schizoaffective patients (n=414), aripiprazole 15 or 30 mg daily and haloperidol 10 mg daily (fixed doses) were each statistically superior to placebo with regard to changes in PANSS-total and BPRS-total scores; based on responder analysis (a 30% reduction in PANSS-total scores from baseline at last visit), each dose of aripiprazole w significantly more effective than placebo, whereas haloperidol was not. There was evidence of better tolerability with aripiprazole compared to haloperidol (eg, benztropine requirements for extrapyramidal effects, prolactin increases, weight increase). Extrapyramidal symptoms were reportedly similar with aripiprazole and placebo, and fewer patients receiving aripiprazole discontinued treatment due to advers events compared to haloperidol and placebo (Kane et al, 2000). However, this study did not report statistical comparisons of aripiprazole and haloperidol for any parameter (efficacy versus baseline or adverse effects); responder-analysis data revealed only a small difference between the two drugs. Overa this study does not provide evidence that aripiprazole is significantly more efficacious than haloperidol.

d) Results of phase II studies also suggested fewer adverse effects with aripiprazole compared to haloperidol (Saha et al, 1999; Anon, 2000). In these studies, lower changes from baseline in Simpson-Angus Scale scores (parkinsonian symptoms) and less requirement for benztropine were observed with doses of aripiprazole (2, 10, or 30 mg daily) than with haloperidol 10 mg daily; prolactin levels were not increased by aripiprazole, compared to significant increases with haloperidol, and significantly less weigl gain was evident in the aripiprazole groups (all doses). Comparative efficacy data were not presented.

4.6.G Ascorbic Acid

4.6.G.1 PCP intoxication

a) Four treatment regimens for phencyclidine intoxication were compared: 10 patients received placebo 10 received 1 gram intramuscular ascorbic acid, 10 received 5 mg intramuscular haloperidol, and 10 received both the haloperidol and ascorbic acid. Treatments were administered at 0 and 30 minutes and assessments were made at 0, 30, and 60 minutes by blinded evaluators. The order of responses, each being significantly better than the previous by statistical analysis, was ascorbic acid, placebo, haloperido and the combination therapy. The authors concluded that ascorbic acid potentiated the action of haloperidol, either by inhibiting the binding of phencyclidine to the dopamine receptor or by interfering wi the metabolism of haloperidol (Giannini et al, 1987).

4.6.H Benzquinamide

4.6.H.1 Vomiting

a) Although benzquinamide may be a useful antiemetic for some conditions, haloperidol appears to be superior. Effectiveness of antiemetic agents may vary in the treatment of nausea and vomiting due to different chemotherapeutic agents. The efficacy of haloperidol was compared with that of benzquinamide 64 patients receiving cancer chemotherapy. In a randomized, cross-over, double-blind study, 36 patients received haloperidol 2 milligrams (mg) or benzquinamide 50 mg intramuscularly, 10 minutes before chemotherapy administration. Patients preferred haloperidol over benzquinamide for control of emesis induced by cisplatin (78% versus 22%) or nitrogen mustard (67% versus 16%). However, patients receiv doxorubicin preferred benzquinamide (46% versus 38%). In patients previously unrelieved by prochlorperazine, haloperidol was more effective than benzquinamide (54% versus 29%). Complete relie of vomiting was achieved in 14 of 45 and 5 of 41 patients receiving haloperidol and benzquinamide, respectively (Neidhart et al, 1981a).

4.6.I Bromperidol

4.6.I.1 Psychotic disorder

a) In a double-blind 4-week study, bromperidol was compared with haloperidol in the initial treatment of psychotic patients (Denijs, 1980). The median daily oral dose was 9 to 12 mg for bromperidol and 12 mg haloperidol. Brief Psychiatric Rating Scale scores showed marked intragroup improvements for both bromperidol and haloperidol. Differences between the drugs were slight at all times. Nurses' Observatior Scale for Inpatient Evaluation-30 scores also showed intragroup improvement without significant intergrc differences. Bromperidol had more of an activating effect, while haloperidol was more antimanic. Most frequent side effects were tremor, parkinsonism, akathisia and increased salivation. For the bromperidol group, paroxysmal dyskinesia, sedation and orthostatic hypotension were also noted. Overall results showed that all bromperidol patients were either improved or unchanged (similar for haloperidol) and 19 20 patients tolerated bromperidol well. Bromperidol is equally effective as haloperidol in treating psychos

b) Bromperidol was compared with haloperidol in a double-blind study with 40 psychotic (mostly schizophrenic) patients (Poeldinger et al, 1977). Initial doses were 5 mg/day orally of either bromperidol haloperidol, with subsequent dosage adjustments At study end, the mean daily dose of each drug was 6 mg/day, with a range of 5 to 12 mg/day for bromperidol and 5 to 9 mg/day for haloperidol. Sixty-five perc of patients showed improvement with bromperidol and 50% with haloperidol, with negligible differences between the two drugs when directly compared. Global evaluation revealed that a majority of patients (1 out of 20 for each drug) had either very good, good, or moderate improvement, with only one bromperidc patient showing no improvement and one haloperidol patient having deteriorated. Parkinsonian side effe were observed in four bromperidol and three haloperidol patients. There were no autonomic or psychic s effects. Bromperidol is at least as effective a treatment for psychic disorders as haloperidol, on the basis its quicker onset of action.

c) The efficacy of bromperidol was compared with that of haloperidol in a 12-week double-blind controlle study involving 164 schizophrenic patients. Dosages were started at 3 to 6 mg daily and individually adjusted for best therapeutic response. Fifty-five percent of the bromperidol patients showed improveme compared to 38% for haloperidol. Bromperidol was judged to be a better form of treatment than the previous neuroleptic in 42.9% of the cases versus 23.8% for haloperidol. General improvement scores showed that bromperidol was more effective and had a quicker onset of action. Specific symptoms on th Brief Psychiatric Rating Scale were improved significantly more with bromperidol. Side effects reported (dystonia, akathisia, parkinsonism) were either less with bromperidol, or equal to haloperidol (Itoh, 1985)

4.6.J Carbamazepine

4.6.J.1 Drug-induced psychosis, Inhalant

a) Carbamazepine demonstrated comparable efficacy to haloperidol in the treatment of inhalant-induced psychotic disorder (Hernandez- Avila et al, 1998). Patients received either 1 capsule of carbamazepine 2 milligrams (mg) 3 times daily (n=20) or 1 capsule of haloperidol 5 mg 3 times daily (n=20) for 5 weeks. Doses were increased at weekly intervals by 1 capsule if the patient failed to show a 25% decrease in th Brief Psychiatric Rating Scale (BPRS). At the end of the study, mean daily doses were carbamazepine 9 mg (serum level of 10.8 micrograms/liter) and haloperidol 21.7 mg. Similar improvements were found in both groups with 48.3% improvement in the carbamazepine group and 52.7% improvement in the haloperidol group.

4.6.K Chlorpromazine

Delirium

Drug-induced psychosis - Phencyclidine-related disorder

Schizophrenia

4.6.K.1 Delirium

a) Chlorpromazine (n=13) and haloperidol (n=11) were effective and had few side effects in the treatmer of delirium in AIDS patients in a double-blind study; lorazepam (n=6) was not effective and was associat with adverse effects (Breitbart et al, 1996a). Average doses for the first 24 hours of treatment were lorazepam 3 mg, chlorpromazine 50 milligrams, and haloperidol 1.4 milligram. There was significant improvement in the 2 neuroleptic-treated groups in the first 24 hours as measured by the Delirium Ratinç Scale scores (p less than 0.001 for both groups). Very little further improvement was seen after day 2. Delirium symptoms did not improve in the lorazepam-treated group. Cognitive status as measured by the Mini-Mental State scale improved in the chlorpromazine group (p less than 0.001) and haloperidol group (NS), but did not improve in the lorazepam group. Few extrapyramidal side effects were associated with either neuroleptic drug, but all lorazepam-treated patients developed adverse effects that led to the remc of this drug from the protocol. The authors recommend further study to confirm their finding that early intervention with low-dose neuroleptics is effective in managing delirium in AIDS patients (Breitbart et al,

1996a).

4.6.K.2 Drug-induced psychosis - Phencyclidine-related disorder

a) Haloperidol was reported more effective than chlorpromazine in treating signs of psychosis secondary phencyclidine in one uncontrolled report (Giannini & Eighan, 1984). Haloperidol 5 milligrams intramuscularly (IM) was given in 2 separate doses 20 minutes apart or chlorpromazine 50 milligrams IM was administered in 2 separate doses according to the same schedule. The authors suspect that the greater benefits of haloperidol were attributable to specificity for DA-2 presynaptic sites.

4.6.K.3 Schizophrenia

a) Based upon comparisons of minimum effective dosages identified in placebo- controlled , fixed-dose and fixed-dose-ranging drug development trials, the minimum effective dose of haloperidol was 4 milligrams/day (equivalent to chlorpromazine 200 milligrams/day) (Woods SW, 2003).

b) Haloperidol was compared with placebo, chlorpromazine, diazepam, and imipramine as prophylactic agents to prevent relapse of schizophrenic patients. At the end of the three year trial, haloperidol and chlorpromazine significantly prolonged remission as compared to the other three treatments. Daily doses haloperidol were 3 milligrams; chlorpromazine doses were 75 milligrams (Nishikawa et al, 1982b).

4.6.K.4 Adverse Effects

a) Haloperidol, chlorpromazine, and sulpiride were compared in normal volunteers to test mood state (McClelland et al, 1990a). The twelve volunteers were assessed using sixteen visual analogue scales su as elapsed time estimation, tapping rate, body sway and tremor. The volunteers were divided into four groups: haloperidol (3 milligrams per day), chlorpromazine (50 milligrams per day), sulpiride (400 milligrams per day) and a placebo group. The results showed chlorpromazine and haloperidol users experienced reduced alertness and contentedness. Haloperidol reduced feelings of "calmness" in the volunteers. Sulpiride did not significantly alter vision in the volunteers. Haloperidol affected the informatic processing function, but did not affect motor ability and speed in the group taking this drug.

4.6.L Chlorprothixene

Schizophrenia

Tardive dyskinesia

4.6.L.1 Schizophrenia

a) Chlorprothixene was compared with (mean dose 251 milligrams/day; dose range 100 to 400 mg/day) haloperidol (mean dose 9 milligrams/day; dose range 5 to 16 mg/day) and placebo in a 3-week randomized, double-blind, crossover study of 34 patients with acute schizophrenia. There were no statistically significant differences in relation to efficacy (Marjerrison et al, 1971).

4.6.L.2 Tardive dyskinesia

a) The Nordic Dyskinesia Study Group (Anon, 1986) compared the effects of several neuroleptic drugs c tardive dyskinesia and parkinsonian symptoms in 33 chronic psychiatric patients in a crossover, randomized, open study. Treatment consisted of 6 months of therapy in each of 4 groups, preceded by a week, placebo-washout period. Treatment groups were chlorprothixene 132 to 142 milligrams/day, haloperidol 5.5 to 5.6 milligrams/day, perphenazine 16.8 to 24.2 mg/day, and haloperidol 11 milligrams/d in combination with biperiden 7 mg/day. Doses were chosen to be relatively equipotent according to established tables. Perphenazine, haloperidol, and haloperidol/biperiden all caused a reduction in tardive dyskinesia and an increase in parkinsonian symptoms. Chlorprothixene reduced tardive dyskinesia sligh and had no effect on parkinsonian symptoms. All drugs were equally effective at controlling psychotic symptoms. The authors concluded that long-term therapy with low-potency drugs presented a minimal ris of potentially irreversible tardive dyskinesia and a lower likelihood of inducing acute parkinsonian symptoms.

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4.6.M Clocapramine

4.6.M.1 Schizophrenia

a) In 26 chronic schizophrenia patients, clocapramine (75 mg/day initially, to a maximum of 700 mg/day) was compared with haloperidol (3 mg/day, to a maximum of 30 mg/day) in a double-blind, crossover stud lasting 28 weeks. There was no significant difference between the 2 drugs. Although no side effects were significant enough to terminate therapy, clocapramine produced fewer and milder side effects. The author concluded that clocapramine was equivalent to haloperidol in antipsychotic efficacy but superior in terms safety (Yamagami, 1985).

4.6.N Clomipramine

4.6.N.1 Autistic disorder

a) Among subjects who completed full therapeutic trials of haloperidol and clomipramine for treatment of autistic disorder, the two drugs were comparable; however, haloperidol was superior to clomipramine on intent-to-treat basis, because of the large proportion of patients who were unable to complete clomipram treatment due to side effects and behavior problems. In a double- blind, placebo-controlled crossover study, 36 subjects with a DSM- IV diagnosis of autism were given placebo, haloperidol, and clomipramin for periods of 7 weeks each. Clomipramine was begun at 25 milligrams (mg) at bedtime for 2 days and increased to 25 mg twice a day for 2 days, 25 mg 3 times a day for 2 days, and finally 50 mg twice a day Haloperidol was begun at 0.25 mg at bedtime for 2 days and increased to 0.25 mg twice a day for 2 days 0.25 mg 3 times a day for 2 days, and finally 0.5 mg twice a day. For both drugs, adjustments of the final dose could be made as clinically indicated. During week 7 of each period, drug dosages were tapered in preparation for the next treatment. Percentages of subjects completing each trial were 70% for haloperid 38% for clomipramine, and 66% for placebo. In the haloperidol trials, 7 of 10 discontinuations were for si effects (fatigue or lethargy, dystonia, depression) and the remainder for behavior problems. With clomipramine, 12 of 20 discontinuations were for side effects (fatigue or lethargy, tremors, tachycardia, insomnia, diaphoresis, nausea or vomiting, and decreased appetite) and the remainder for behavior problems. In the placebo trials, 10 of 11 discontinuations were for behavior problems. On an intent-to-tre basis, significant improvement in irritability (p less than 0.05) and hyperactivity (p less than 0.05) was see with haloperidol only (versus baseline). No differences among treatments were observed for stereotypic behavior, lethargy, or inappropriate speech. When data only from patients completing full therapeutic tria were assessed, both haloperidol and clomipramine were superior to baseline with regard to irritability and stereotypy (Remington et al, 2001).

4.6.O Clonazepam

Gilles de la Tourette's syndrome

Psychotic disorder

4.6.O.1 Gilles de la Tourette's syndrome

a) In a retrospective study, haloperidol, clonazepam, and clonidine were compared in the treatment of 8 patients suffering multifocal tic disorders, either Tourette's syndrome or chronic motor tics. The most effective drug for treating Tourette's syndrome was haloperidol, mean dose of 5.8 milligrams/day. The m effective drug for treating chronic motor tics was clonazepam, mean dose of 4.8 milligrams/day. Clonidin was effective in six patients, but only in combination with either haloperidol or clonazepam. The authors recommend treatment with clonazepam first, due to the risk of tardive dyskinesia associated with haloperidol. Then clonazepam in combination with clonidine, if clonazepam alone is not effective. Then in nonresponsive patients haloperidol should be used (Troung et al, 1988a).

4.6.O.2 Psychotic disorder

a) Clonazepam and haloperidol (both given by the intramuscular route) were compared for tranquilizatio of agitated psychotic patients with manic symptoms. Fifteen patients received three doses of either clonazepam 1 to 2 milligrams or haloperidol 5 to 10 milligrams at 30 minute intervals. Both drugs successfully controlled the agitation, but haloperidol gave a more rapid response (Chouinard et al, 1993a Better results may have been obtained by administering single higher doses of intramuscular (IM) clonazepam: 4 to 5 milligrams of IM clonazepam every 30 to 60 minutes seems to be effective, safe and rapid for the control of acute psychotic agitation and onset of action may be similar to IM haloperidol (Benazzi & Mazzoli, 1994).

4.6.P Clonidine

4.6.P.1 Gilles de la Tourette's syndrome

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4.6.Q Clozapine

Hostile behavior

Schizophrenia, Refractory

4.6.Q.1 Hostile behavior

a) Clozapine reduced hostility in patients with schizophrenia and was superior to haloperidol and risperidone in that regard. One hundred fifty seven patients with a diagnosis of schizophrenia or schizoaffective disorder and a history of poor response to drug treatment were randomly assigned to receive clozapine, olanzapine, risperidone, or haloperidol in cross-titration with the antipsychotic drug us prior to the start of the study. Concomitant mood stabilizers and antidepressants had been phased out earlier. Daily doses of olanzapine, risperidone, and haloperidol were escalated within the first week to th target doses of 20, 8, and 20 milligrams (mg), respectively. Patients receiving clozapine were scheduled achieve the target daily dose of 500 mg on day 24. Doses remained fixed for the remainder of the initial 8 week period. In a second (6-week) period, doses were allowed to vary: 200 to 800 mg for clozapine, 10 t 40 mg for olanzapine, 4 to 16 mg for risperidone, and 10 to 30 mg for haloperidol. Hostility, measured by the hostility item of the Positive and Negative Syndrome Scale (PANSS), improved significantly (in comparison to baseline) in the clozapine group only (p=0.019). This effect was independent of effects on psychotic symptoms (delusional thinking, hallucinations) or on sedation. The effect of clozapine on hostil was superior to that of haloperidol (p=0.021) or risperidone (p=0.012) but not to that of olanzapine (Citro et al, 2001).

4.6.Q.2 Schizophrenia, Refractory

a) Olanzapine and risperidone improved neurocognitive deficits more than did haloperidol or clozapine i patients with schizophrenia or schizoaffective disorder that was refractory to treatment with typical antipsychotics. In a randomized, double-blind study, inpatients were given clozapine (n=24) 200 to 800 milligrams (mg) per day, olanzapine (n=26) 10 to 40 mg/day, risperidone (n=26) 4 to 16 mg day, or haloperidol (n=25) 10 to 30 mg/day. Dose escalation and fixed-dose treatment (target doses: olanzapine mg/day, risperidone 8 mg/day, haloperidol 20 mg/day, clozapine 500 mg/day) occurred during the first 8 weeks of the 14-week study; during the last 6 weeks, dosages were adjusted individually (generally increased if response was insufficient, but sometimes reduced because of adverse effects). Improvemer over time in global neurocognitive score was seen for olanzapine and risperidone. In general executive a perceptual organization and in processing speed and attention, improvement was seen with olanzapine. simple motor function, there was improvement with clozapine. Changes in global neurocognitive performance with olanzapine and risperidone were of medium magnitude (approximately 8 to 9 "IQ equivalents") but large enough to be clinically significant. Beneficial changes with clozapine were modes Despite cognitive gains, patients still had significant impairments of cognitive ability and social/vocationa functioning. Improvements in neurocognitive deficits were associated with improvements in negative symptoms (Bilder et al, 2002b).

b) Schizophrenic patients treated with clozapine were more likely to be rated as improved and less likel discontinue treatment due to lack of efficacy than a matched group treated with haloperidol. Seventy-one patients between the ages of 20 to 55 years with a diagnosis of schizophrenic or schizoaffective disorde were enrolled in this 6-month, double-blind, prospective, randomized trial. These outpatients, were documented as poor or partial responders to antipsychotic therapy and had a rating of at least moderate 1 of 4 Brief Psychiatric Rating Scale (BSRS) items (conceptual disorganization, suspiciousness, hallucinatory behavior, or unusual thought content). The two major outcome measures for this study wer time to discontinuation of study medication due to lack of clinical response and 20% improvement in the item BPRS cluster during two consecutive rating periods. The haloperidol group (n=34) was targeted to receive 10 milligrams (mg)/day, along with 2 mg/day of benztropine, while the clozapine group was to receive 500 mg/day (n=37). Doses could be adjusted in either group to a range of 4 to 16 mg/day for the haloperidol group and 200 to 800 mg/day for the clozapine group depending upon the patient's clinical course. At the end of 29 weeks, 50.5% of the haloperidol-treated group (mean dose 18.9 mg/day) and 11.6% of the clozapine group (mean dose 523 mg/day) had discontinued treatment due to lack of efficac (p=0.02). The mean BPRS ratings at the end of the study were 3.2 and 4.2 for the clozapine and haloperidol groups respectively (p less than 0.001). There was no difference found between the groups a

measured by the Schedule for Assessment of Negative Symptoms (SANS) score using the sum of the 4 global ratings. Haloperidol-treated patients experienced more dry mouth and decreased appetite, while t clozapine-treated group reported more salivation, sweating, and dizziness. Three haloperidol and 2 clozapine-treated patients dropped-out of the study due to adverse drug effects (Kane et al, 2001).

c) Clozapine exhibited improved efficacy with fewer adverse effects as compared to haloperidol in a randomized, double-blind, 12-month study conducted at Veterans Affairs medical centers (n=423 with refractory schizophrenia). Using intention-to-treat analysis, schizophrenia symptom scores were significantly improved with clozapine over haloperidol at 6 weeks (p equals 0.008) and 6 months (p equa 0.001), with no statistical difference in quality of life measures. When crossover cases were excluded, quality of life measures were significantly better in the clozapine group at 3 months and 1 year (p equals 0.02). Clozapine also reduced scores for tardive dyskinesia, akathisia and extrapyramidal syndrome. Clozapine's higher costs for drug acquisition and laboratory monitoring were offset by decreased inpatie hospital stays (Rosenheck et al, 1997).

d) These investigators later evaluated compliance with clozapine versus haloperidol. The results confirm that clozapine established better medication continuation and regimen compliance. Patients taking clozapine continued taking the study drug for a mean of 35.5 weeks as compared with on 27.2 weeks among haloperidol patients (p=0.0001). No differences were found between the groups in the proportion prescribed pills that were returned at any time point. Continuation with medication is greater with clozapi than haloperidol and is partly explained by greater symptom improvement and reduced side effects. No differences were discovered in regimen compliance (Rosenheck et al, 2000).

4.6.Q.3 Adverse Effects

a) The results of one study suggest that patients receiving atypical antipsychotics have a higher inciden of PANCREATITIS than patients receiving a conventional antipsychotic medication. In a retrospective, pharmacovigilance study, 192 cases of pancreatitis were identified in patients taking clozapine (mean do 306.7 milligrams (mg)/day), olanzapine (mean dose, 15 mg/day), risperidone, (mean dose, 4 mg/day) or haloperidol (mean dose, 8.2 mg/day). Of the identified cases, 40%, 33%, and 16% were related to treatment with the atypical antipsychotic medications clozapine, olanzapine, or risperidone, respectively, compared with 12% of the cases which were related to the conventional neuroleptic, haloperidol. In most patients, time to onset of pancreatitis was within 6 months after initiation of treatment (Koller et al, 2003b

b) No significant difference was found in sexual disturbances occurring in clozapine-treated versus haloperidol-treated patients (Hummer et al, 1999). Inpatients receiving either clozapine (n=100) or haloperidol (n=53) were screened. The most common adverse event in both groups was diminished sexu desire occurring in 4 (33.3%) of the haloperidol-treated women, 26 (63.4%) of the haloperidol-treated me 7 (28%) of the clozapine-treated women, and 43 (57.3%) of the clozapine-treated men. Among women treated, amenorrhea occurred in 4 (33.3%) of the haloperidol patients and in 3 (12%) of the clozapine patients. Larger studies may be needed to show differences.

c) In a prospective study, the incidence of alanine aminotransferase (ALT) elevation to more than twice upper normal limit was statistically greater with clozapine (37%, n=167) than with haloperidol (17%, n=71 Among those receiving clozapine, the rates of elevations in aspartate aminotransferase (AST) and gamm glutamyl transpeptidase (GGT) to more than twice the upper normal limit were 12% and 15%, respective No such increases in bilirubin or alkaline phosphatase occurred in clozapine-treated patients. These effe were transient in the majority of patients (disappearing by week 13) with no clinical manifestations report (Hummer et al, 1997).

4.6.R Diazepam

4.6.R.1 Schizophrenia

a) Haloperidol was compared with placebo, chlorpromazine, diazepam, and imipramine as prophylactic agents to prevent relapse of schizophrenic patients. At the end of the three year trial, haloperidol and chlorpromazine significantly prolonged remission as compared to the other three treatments. Daily doses haloperidol were 3 mg; chlorpromazine doses were 75 mg (Nishikawa et al, 1982a).

4.6.S Diphenhydramine

4.6.S.1 Dementia - Restlessness and agitation

a) Oxazepam, haloperidol, and diphenhydramine were equally efficacious in the treatment of agitated behavior in 59 elderly demented inpatients in an 8-week, double-blind study (Coccaro et al, 1990a). The mean daily doses were oxazepam 30 +/- 19.4 mg, haloperidol 1.5 +/- 0.9 mg, and diphenhydramine 81.3 +/- 48.5 mg. Chloral hydrate was given if the study medication did not adequately control agitation. Ratin scale scores indicated that diphenhydramine and haloperidol were more effective than oxazepam, but no of the differences in scores among the groups was significant. Only modest improvement was seen in terms of agitated behavior and activities of daily living. There was only a slight decrease in the use of chloral hydrate in all 3 groups during the study and no difference among the groups.

4.6.T Droperidol

Agitation

Postoperative nausea and vomiting

4.6.T.1 Agitation

a) In equal doses, intramuscular (IM) droperidol controlled agitation more rapidly than haloperidol withou difference in side effect occurrence. A randomized, double-blind, prospective study (Thomas et al, 1992) compared haloperidol versus droperidol for chemical restraint in agitated or violent patients. Sixty-eight patients randomly received 5 mg of haloperidol or droperidol by the intravenous (IV) or IM routes and we monitored for behavior control on a combativeness scale ranging 1 to 5. Patients were also monitored fo side effects and vital sign changes. Patients were compared at 5, 10, 15, 30 and 60 minutes after injectic of drug. Intramuscular droperidol controlled combativeness significantly more than IM haloperidol at ten, and 30 minutes while no significant difference was noted at 60 minutes in equal doses. No significant difference in behavior control was seen when the drugs were given IV.

b) In a double-blind study (Resnick & Burton, 1984), intramuscular droperidol and haloperidol were compared in the treatment of 27 acutely agitated patients. Patients received either droperidol 5 milligram or haloperidol 5 milligrams intramuscularly, and were psychologically evaluated at 15 minutes following initial injection and at 30-minute intervals for 3 hours thereafter. At 30 minutes following the initial treatme 36% of the droperidol-treated and 81% of the haloperidol-treated patients required a second injection. Bo agents were well tolerated. The investigators recognize the greater sedative effect associated with droperidol, and admit that this property may explain the more rapid control of patients in the droperidol-treated group.

4.6.T.2 Postoperative nausea and vomiting

a) Intramuscular (IM) droperidol 5 mg was compared with a single IM dose of haloperidol 2 mg and prochlorperazine 10 mg as a premedicant in a group of 65 patients. The incidence of vomiting with droperidol at 0.5 to 1 hour postoperatively was 50% compared to 7% with haloperidol. However, droperic exerted its antiemetic effect up to 24 hours as compared with haloperidol and prochlorperazine, which ha a duration of only 4 hours. Ideally a combination of droperidol and haloperidol should be used to provide rapid onset with a long duration of effect (Loeser et al, 1979).

4.6.U Flunitrazepam

4.6.U.1 Aggressive behavior - Psychotic disorder

a) Intramuscularly administered flunitrazepam and haloperidol were similarly effective in controlling agitated or aggressive behavior in emergency psychiatric situations (Dorevitch et al, 1999). In the study group of 28 patients, 19 with schizophrenia, 7 with schizoaffective disorder, and 2 with bipolar disorder), intramuscular injection of either flunitrazepam 1 milligram (mg) or haloperidol 5 mg during an acute aggressive outburst significantly reduced Overt Aggression Scale scores (p less than 0.001, time effect). 90 minutes post-administration, the rate of response reduction in total Overt Aggression Scale score was 80% (12/15) in the flunitrazepam group and 92% (12/13) in the haloperidol group (p=0.34). Flunitrazepar reached its maximal antiaggressive effect 30 minutes after administration, while haloperidol increased its activity more gradually, and the difference in antiaggressive effect over time was significant (p less than 0.01, time-by-group interaction). In both groups, the reduction in aggression level lasted for at least 120 minutes after drug administration. Each drug induced marked sedation in 3 patients.

4.6.V Flupenthixol

Psychotic disorder

Schizophrenia

4.6.V.1 Psychotic disorder

a) An open trial of flupenthixol versus haloperidol was conducted in 40 acutely psychotic patients in an open, 28-day controlled study. Patients received oral flupenthixol 32 to 192 milligrams/day (mean dose 1 mg/day) or oral haloperidol 2 to 50 milligrams/day (mean dose 18 mg/day) as required for control of psychotic symptoms. While global assessment revealed a significant reduction in severity of symptoms i both groups, 5 patients receiving flupenthixol had complete or almost complete remission of symptoms a the 28-day assessment, whereas none of those taking haloperidol had achieved this degree of remissior In addition, anxiety/depression scores improved considerably with flupenthixol, whereas haloperidol had little effect. Flupenthixol also had an activating effect, but haloperidol did not. The authors felt that while both drug were effective, flupenthixol had a faster onset of symptom control than haloperidol. However, a these doses it caused more extrapyramidal symptoms than haloperidol (Parent & Toussaint, 1983).

4.6.V.2 Schizophrenia

a) Haloperidol decanoate (mean dose 131 to 151 milligrams/4 weeks) was compared with flupenthixol

decanoate (mean dose 56 to 66 milligrams/4 weeks) in 32 schizophrenic patients in a 48 week, double-blind, crossover study. Side effects of the two drugs were comparable, but therapeutic efficacy near the e of each dosing period was significantly better for haloperidol than flupenthixol. The investigators recommended a shorter dosing interval for flupenthixol (Eberhard & Hellbom, 1986).
b) Haloperidol was reported superior to flupenthixol in producing lower levels of psychopathology in chronic schizophrenic inpatients in a double-blind, crossover study (Ehmann et al, 1987). Average doses haloperidol and flupenthixol at the time of final assessments were 33 milligrams daily (range, 10 to 84 milligrams) and 27 mg daily (range, 8 to 84 mg daily), respectively. Significantly less psychiatric disturba was observed during haloperidol therapy as determined by the Rating Scale of the Mental State (RSMS) and the BPRS Agitation-Excitement Scale: Less psychopathology was also observed with haloperidol or total scores for BPRS but this was not significant. Side effects were similar with both agents, primarily extrapyramidal symptoms. In addition, no evidence was observed to suggest that flupenthixol is useful in "activating" chronic schizophrenic patients, or in alleviating affective symptoms.

4.6.W Fluphenazine

Gilles de la Tourette's syndrome

Schizophrenia

4.6.W.1 Gilles de la Tourette's syndrome

a) In 23 patients with Tourette's syndrome who had previously been treated with haloperidol, fluphenazi treatment was equally efficacious but fluphenazine produced fewer side effects. The previous treatment consisted of haloperidol 1.5 to 9 milligrams/day for 2 months to 9 years and was replaced with fluphenzir 1 to 16 milligrams/day for 1 month to 2.75 years (Singer et al, 1986).

4.6.W.2 Schizophrenia

a) Haloperidol decanoate and fluphenazine decanoate were equally efficacious in an 8-month study in schizophrenic patients (Chouinard et al, 1984). Haloperidol decanoate was given in doses of 15 to 900 milligrams (median, 225 mg) every 2 to 4 weeks with fluphenazine decanoate administered in doses of 2 to 300 milligrams per injection (median, 75 mg) every 2 to 4 weeks. No significant differences between th 2 drugs were observed with regard to therapeutic efficacy; however, tardive dyskinetic movements of the tongue and jaw were more severe in haloperidol-treated patients.
b) Haloperidol decanoate was compared with fluphenazine decanoate in 38 schizophrenic inpatients in parallel, single-blind study which lasted for 60 weeks. Doses were based on standard relative potency assignments calculated from previous neuroleptic medication, and haloperidol and fluphenazine were considered equipotent. The haloperidol patients had better mental states but poorer ward behavior and lower parkinsonism scores compared with the fluphenazine group (McKane et al, 1987).

4.6.X Imipramine

4.6.X.1 Schizophrenia

a) Haloperidol was compared with placebo, chlorpromazine, diazepam, and imipramine as prophylactic agents to prevent relapse of schizophrenic patients. At the end of the three-year trial, haloperidol and chlorpromazine significantly prolonged remission as compared to the other three treatments. Daily doses haloperidol were 3 milligrams; chlorpromazine doses were 75 mg (Nishikawa et al, 1982).

4.6.Y Lithium

4.6.Y.1 Aggressive behavior

a) The same results of the same study were published in two different journals (Platt et al, 1984, 1984a) (Campbell et al, 1984). They compared the effects of lithium (mean dose 1,166 mg/day) to haloperidol (mean dose 2.95 mg/day) on cognition in hospitalized school-age children with conduct disorder. After a two week placebo period to eliminate placebo responders, 61 children were divided into haloperidol, lithium, or placebo groups. Both drugs gave better responses by a variety of tests and were equally effective. Haloperidol produced significantly more side effects.

4.6.Z Lorazepam

Agitation - Psychotic disorder

Delirium

4.6.Z.1 Agitation - Psychotic disorder

a) The combination of haloperidol and lorazepam was suggested to be more effective than lorazepam alone in agitated patients presenting to the psychiatric emergency service (Bieniek et al, 1998). Patients who met clinical criteria for the use of chemical restraints and had a minimum score of 4 on the Overt Aggression Scale received either lorazepam 2 milligrams (mg) (n=11) or haloperidol 5 mg and lorazepan mg (n=9). Combination therapy was significantly better than lorazepam alone after 1 hour according to th Overt Aggression Scale and the visual analog scale (p less than 0.05). However, on the Clinical Global Impressions severity scale, the comparison was not significant. With repeated measures of analyses of variance, both groups improved over time.

b) Repeated doses of either lorazepam 2 milligrams or haloperidol 5 milligrams were equally effective fo the early treatment of acute agitation in psychotic patients (Battaglia et al, 1997). In a double-blind, randomized study, 98 patients received either intramuscular lorazepam, haloperidol, or both. Patients received 1 to 6 injections in a 12-hour period depending upon clinical need. Effective symptom reduction was achieved in each treatment group with significant decreases from baseline at every hourly evaluatio (p less than 0.01). Mean differences on the Agitated Behavior Scale and modified Brief Psychiatric Ratin Scale suggested that tranquilization was most rapid in patients receiving the combination therapy (p less than 0.05).

4.6.Z.2 Delirium

a) Chlorpromazine (n=13) and haloperidol (n=11) were effective and had few side effects in the treatmer of delirium in AIDS patients in a double-blind study; lorazepam (n=6) was not effective and was associat with adverse effects (Breitbart et al, 1996). Average doses for the first 24 hours of treatment were lorazepam 3 mg, chlorpromazine 50 mg, and haloperidol 1.4 mg. There was significant improvement in t 2 neuroleptic-treated groups in the first 24 hours as measured by the Delirium Rating Scale scores (p les than 0.001 for both groups). Very little further improvement was seen after day 2. Delirium symptoms did not improve in the lorazepam-treated group. Cognitive status as measured by the Mini-Mental State scal improved in the chlorpromazine group (p less than 0.001) and haloperidol group (NS), but did not improv in the lorazepam group. Few extrapyramidal side effects were associated with either neuroleptic drug, bu all lorazepam-treated patients developed adverse effects that led to the removal of this drug from the protocol. Breitbart et al recommend further study to confirm their finding that early intervention with low-dose neuroleptics is effective in managing delirium in AIDS patients.

4.6.AA Loxapine

4.6.AA.1 Schizophrenia

a) Intramuscular loxapine and intramuscular haloperidol at the usual therapeutic doses were shown to b comparable in the initial management of hostile and aggressive schizophrenic patients. Both drugs resul in rapid improvement in symptoms of hostility and uncooperativeness, and produced desirable sedation. The maintenance of therapeutic response after conversion to oral medication was also comparable between the 2 drugs (Tuason, 1986).

4.6.AB Melperone

4.6.AB.1 Anxiety

a) The effects of melperone, chlorpromazine, haloperidol, and diazepam on artificially-induced anxiety were compared in normal subjects. Autonomic (skin conductance) response evoked during aversive classical conditioning was measured in eleven healthy subjects. Single oral doses of placebo, melperone 10 mg, melperone 50 mg, chlorpromazine 50 mg, diazepam 10 mg, and haloperidol were administered randomly to each member of the study group. There was a minimum of 10 days between tests. Judging from the data which indicates a subject's anxiety level in this experimental setting, ie, skin conductance level during habituation and reinforcement, its pattern of changes and fluctuations, etc, it may be conclud that diazepam, the higher (50 mg) dose of melperone and chlorpromazine are effective anxiolytics. Whereas melperone 50 mg reduced skin conductance level, and eliminated anticipatory responses, melperone 10 mg (as well as haloperidol) had no effect upon conditioned and unconditioned responses (Molander, 1982).

4.6.AC Mesoridazine

4.6.AC.1 Schizophrenia

a) Mesoridazine was compared with haloperidol in a group of 39 schizophrenic patients in an attempt to correlate the response seen in the first 48 hours, as measured by the Dysphoric Response Index (DRI) v ultimate outcome of therapy (White et al, 1981). The daily dosage of haloperidol was 2 to 100 milligrams (mean 28 mg) and of mesoridazine was 100 to 800 milligrams (mean 421 mg). The outcome as measure by BPRS (Brief Psychiatric Rating Scale and CGI (Clinical Global Impressions Scale), was equivalent fo the two regimens. Side effects for the two regimens were significantly different. Correlation of the DRI to ultimate outcome was poor.

4.6.AD Metoclopramide

4.6.AD.1 Chemotherapy-induced nausea and vomiting

a) Metoclopramide (2 mg/kg) was compared with haloperidol (3 mg total dose) for the control of cisplatir induced emesis (Grunberg et al, 1984). Both drugs were administered intravenously two hours for five doses beginning one-half hour before cisplatin therapy. Twenty-eight patients completed the cross-over study. Metoclopramide resulted in 1.92 vomiting episodes (range 0-5) with 36% exhibiting no vomiting. Haloperidol resulted in 3.04 vomiting episodes (range 0-8) with 20% having no vomiting. Metoclopramide showed a minor but not significant advantage.

4.6.AE Midazolam

4.6.AE.1 Psychotic disorder

a) A single-blind study of fifteen healthy male schizophrenic patients found intramuscular administration 250 milligrams (mg) of sodium amytal or 5 mg of midazolam significantly more effective than 10 mg of haloperidol in controlling motor agitation. Midazolam and sodium amytal were also more effective than haloperidol in controlling hostility, though this did not reach statistical significance. No significant differen in controlling auditory hallucinations or flight of ideas was noted (Wyant et al, 1990a).

4.6.AF Molindone

Psychotic disorder

Tardive dyskinesia

4.6.AF.1 Psychotic disorder

a) Molindone and haloperidol were comparable in a study of 24 acutely psychotic patients (Binder et al, 1981). The dose of molindone was 25 milligrams 2 to 4 times/day (+ as needed) the dose of haloperidol was 5 milligrams 2 to 4 times/day (+ as needed). Both drugs were given intramuscularly. Evaluation of results was based on Brief Psychiatric Rating Scale, Target Symptom Rating Scale, and Clinical Global Impression.

b) Molindone (up to 225 milligrams/day by injection followed by up to 500 mg/day orally) was compared with haloperidol (up to 45 milligrams/day by injection followed by 100 mg/day orally) in 35 acutely schizophrenic patients in a double-blind study. There were no significant differences in efficacy or safety over the 4 weeks of the study (Escobar et al, 1985).

4.6.AF.2 Tardive dyskinesia

a) Haloperidol was more effective than molindone at masking tardive dyskinesia which was exacerbatec by withdrawal of neuroleptic medication. Molindone was compared with haloperidol with regard to their ability to mask neuroleptic withdrawal-exacerbated tardive dyskinesia, using the theoretical proposition th agents less able to mask are less dyskinetogenic (Glazer et al, 1985). In a parallel, double-blind study, 1 patients were given either molindone or haloperidol in doses ranging from 50% to 200% dose equivalenc to the neuroleptics from which they had been removed, at a point after discontinuation where involuntary movements showed a significant increase. At doses that were equivalent to 200% of the prestudy neuroleptic dose, molindone was shown to be less able to mask neuroleptic withdrawal-exacerbated tarc dyskinesia than was haloperidol, thereby suggesting lower dyskinetogenic potential.

4.6.AG Olanzapine

Adverse reaction to cannabis - Drug-induced psychosis

Mania

Schizophrenia

Tardive dyskinesia

4.6.AG.1 Adverse reaction to cannabis - Drug-induced psychosis

a) Olanzapine was as effective as haloperidol in the treatment of cannabis-induced psychotic disorder (Berk et al, 1999). In a double- blind study, patients with a psychotic episode associated with cannabis u were randomized to receive either olanzapine 10 milligrams (n=15) or haloperidol 10 mg (n=15). After 4 weeks there was a significant improvement in both groups as compared to baseline measured on the Bri Psychiatric Rating Scale (p=0.0002 for olanzapine, p=0.0001 for haloperidol). There was no significant

difference between the 2 groups. Olanzapine was associated with fewer extrapyramidal side effects.

4.6.AG.2 Mania

a) Olanzapine and haloperidol therapies were similarly effective in the treatment of acute mania in patie with bipolar disorder. In a randomized, double-blind study, patients with bipolar I disorder, mixed or mani episode and a Young-Mania Rating Scale (Y-MRS) score of at least 20 received either olanzapine (5 to 2 milligram (mg)/day) or haloperidol (3 to 15 mg/day) at flexible doses for 6 weeks. Patients showing symptom improvement entered a 6-week continuation phase in which they received ongoing treatment. Symptomatic remission was defined as a Y-MRS score of 12 or less and a Hamilton Rating Scale for Depression score (HAM-D) of 8 or less at week 6. Symptomatic remission rates for patients in the olanzapine group were similar to those of patients in the haloperidol group at week 6 (52.1% vs 46.1%, respectively; p=NS) and week 12 (51.7% vs 43.8%, respectively; p=NS). However, olanzapine treatment produced greater improvements in health- related quality of life factors as compared with haloperidol treatment (Shi et al, 2002).

4.6.AG.3 Schizophrenia

a) SUMMARY: Olanzapine is more effective than haloperidol for the treatment of negative symptoms of schizophrenia; both agents are similarly effective in managing positive symptoms. Olanzapine is less like to induce extrapyramidal reactions or elevation of serum prolactin levels.

b) Olanzapine and risperidone improved neurocognitive deficits more than did haloperidol or clozapine i patients with schizophrenia or schizoaffective disorder that was refractory to treatment with typical antipsychotics. In a randomized, double-blind study, inpatients were given clozapine (n=24) 200 to 800 milligrams (mg) per day, olanzapine (n=26) 10 to 40 mg/day, risperidone (n=26) 4 to 16 mg day, or haloperidol (n=25) 10 to 30 mg/day. Dose escalation and fixed-dose treatment (target doses: olanzapine mg/day, risperidone 8 mg/day, haloperidol 20 mg/day, clozapine 500 mg/day) occurred during the first 8 weeks of the 14-week study; during the last 6 weeks, dosages were adjusted individually (generally increased if response was insufficient, but sometimes reduced because of adverse effects). Improvemer over time in global neurocognitive score was seen for olanzapine and risperidone. In general executive a perceptual organization and in processing speed and attention, improvement was seen with olanzapine. simple motor function, there was improvement with clozapine. Changes in global neurocognitive performance with olanzapine and risperidone were of medium magnitude (approximately 8 to 9 "IQ equivalents") but large enough to be clinically significant. Beneficial changes with clozapine were modes Despite cognitive gains, patients still had significant impairments of cognitive ability and social/vocationa functioning. Improvements in neurocognitive deficits were associated with improvements in negative symptoms (Bilder et al, 2002).

c) Olanzapine was at least as effective as and safer than haloperidol for the treatment of schizophrenia a large population of Japanese patients with positive and negative symptoms resistant to treatment with typical antipsychotics. In a randomized, double-blind trial, 182 patients were given olanzapine, starting at milligrams (mg) per day and increased to a maximum of 15 mg/day, or haloperidol, starting at 4 mg/day a increasing to 12 mg/day, for 8 weeks. Mean modal daily doses were 10.5 mg for olanzapine and 8 mg fo haloperidol. The proportion of olanzapine-treated patients who showed moderate to remarkable improvement was 44.5%, compared to 40.5% of haloperidol-treated patients. The 95% confidence interv was -8% to 16% favoring olanzapine. Thus, olanzapine was not inferior to haloperidol in efficacy. Total a subscale scores on the Positive and Negative Symptom Scale (PANSS) were numerically better in the olanzapine group than in the haloperidol group, but only on the negative symptoms subscale did the difference reach statistical significance (p=0.024). Eighty-one percent of olanzapine-treated patients and 66% of haloperidol-treated patients finished the study, with fewer dropping out of the olanzapine group because of adverse events or abnormal laboratory values (8 vs 22). Olanzapine-treated patients showe an improvement in extrapyramidal symptoms, whereas haloperidol-treated patients showed a worsening less than 0.001). Treatment-emergent parkinsonism occurred in 3.2% of the olanzapine group and 18.8% of the haloperidol group. By the end of treatment, parkinsonism had resolved in all patients in the olanzapine group but was sustained in 7.8% of the haloperidol group. There was a significantly greater incidence of insomnia, akathisia, tremor, anorexia, increased salivation, bradykinesia, abnormal gait, nausea, and weight decrease in haloperidol-treated patients than in olanzapine-treated patients. Only weight gain was significantly greater with olanzapine (0.96 kilogram vs -0.71 kilogram, p less than 0.001) Thirty-two percent of olanzapine-treated patients showed no adverse drug reaction and no laboratory abnormality, compared to 15.5% of haloperidol-treated patients (p=0.008) (Ishigooka et al, 2001).

d) Olanzapine has been at least as effective as haloperidol, each given for six weeks, in the treatment o schizophrenia (Tollefson et al, 1997); (Beasley et al, 1996)(Anon, 1996; Anon, 1995). Overall improveme based on Brief Psychiatric Rating Scale (BPRS) total scores, has been greater with olanzapine; this reached significance in the largest trial (Anon, 1996). Both agents have produced similar decreases in positive symptoms, and the superior overall improvement with olanzapine is attributed to a greater reduction in negative symptoms in these patients, particularly in higher dosages (12.5 to 17.5 mg daily); decreases in negative symptoms have been significantly greater with olanzapine on the Scale for the Assessment of Negative Symptoms (SANS) and Positive and Negative Syndrome Scale (PANSS), although significance was not achieved on the BPRS-negative scale in one study (Beasley et al, 1996). Significantly more patients have demonstrated greater than 80% improvement in BPRS-total scores with olanzapine, whereas the percentage with lower levels of improvement has not always differed significant

between drugs.
e) Intramuscular (IM) olanzapine successfully treated acutely agitated patients with schizophrenia in 3 clinical trials. Two open-label, single-blind trials evaluated 108 patients receiving fixed or variable doses 2.5, 5.0, 7.5, or 10.0 milligram (mg) given as 1 to 4 injections daily (QD) for 3 days, followed by 10 to 20 orally (PO) QD for 2 days. Response was assessed using the Brief Psychiatric Rating Scale (BPRS); the positive subscale improved during both IM and PO Administration (no statistical analysis was performed) The third study was a multicenter, double-blind, placebo-controlled trial that compared IM olanzapine wit IM haloperidol in the treatment of acute agitation. Patients (n=311) received up to 3 doses of olanzapine (10 mg), haloperidol (7.5 mg) or placebo in 24 hours. Thereafter, patients were treated with oral olanzapi (5 to 20 mg QD) or oral haloperidol (5 to 20 mg QD) for 4 days. Patients treated with IM olanzapine or haloperidol showed significantly greater improvement over placebo at 2 and 24 hours as measured by th BPRS positive subscale, but no differences were observed between olanzapine- and haloperidol-treated patients. Patients treated with intramuscular olanzapine continued to improve to day 5; but, there was nc significant difference between patients treated with IM drug between baseline and day 5 (Jones et al, 20
f) In a study of 300 patients with schizoaffective disorder, olanzapine treated patients showed significant greater improvement than haloperidol treated patients on the Brief Psychiatric Rating Scale (BPRS) total (p=0.002), Positive and Negative Syndrome Scale (PANSS) total (p=0.003), PANSS negative (p=0.006), and Montgomery-Asberg Depression Rating Scale (MADRS) total (p less than 0.001). Patients were take from a larger prospective, double blind study. Patients were assessed weekly for a six week acute phase with responders followed for up to 1-year. Among acute phase patients with bipolar subtype, olanzapine to 20 milligrams) was superior to haloperidol (5 to 20 milligrams) in the BPRS (p=0.012), PANSS negativ (p=0.031) and total (p=0.028), and MADRS (p less than 0.001); however, in depressed subtype patients, no significant differences were seen when compared to haloperidol treated patients. During the double-blind extension phase, the only significant difference between treatment groups was in the MADRS total score in favor of olanzapine (p=0.045). Extrapyramidal symptoms were less severe among olanzapine treated patients (p=0.016), but weight gain was more problematic (p=0.032) (Tran et al, 1997).
g) In a 6-week randomized study of 83 patients with first-episode psychosis (schizophrenia, schizophreniform disorder, or schizoaffective disorder), patients receiving olanzapine showed significantl greater improvement on the Brief Psychiatric Rating Scale (BPRS) and the Positive and Negative Symptoms Scale (PANSS) as compared to patients receiving haloperidol. Patients greater than 45 years age at onset of symptoms with a disease duration of greater than 5 years received olanzapine or haloperidol 5 milligrams (mg) per day and adjusted every 7 days within the range of 5 to 20 mg per day. the BPRS, 67.2% of olanzapine treated patients experienced a 40% or greater improvement from baseli compared to 29.2% of haloperidol treated patients (p=0.003). Olanzapine treated patients also improved more on the PANSS total score (p=0.02) and positive symptom score (p=0.03) compared to haloperidol treated patients. Using the Simpson-Angus scale, olanzapine patients showed improvement in extrapyramidal symptoms, whereas haloperidol treated patients worsened (p less than 0.001). Somnoler was more common in olanzapine treated patients, whereas akathisia and hypertonia were more commor with haloperidol (Sanger et al, 1999).
h) Olanzapine showed a superior and broader spectrum of efficacy over haloperidol in the treatment of schizophrenia and also had a more favorable safety profile (Tollefson et al, 1997). In a large internationa multicenter double-blind trial, olanzapine (N=1336) was compared to haloperidol (N=660) over 6 weeks. Starting doses were 5 milligrams (mg) for both drugs which could be increased by 5 mg increments at th investigator's discretion to a maximum of 20 mg/day. Olanzapine was significantly superior to haloperido on the Brief Psychiatric Rating Scale (p less than 0.02), the Positive and Negative Syndrome Scale (p=0.05), the clinical Global Impression severity score (p less than 0.03), and the Montgomery-Asberg Depression Rating Scale total score (p=0.001). Significant advantages were also seen in the extrapyramidal profiles and effects on prolactin levels. Further analyses revealed that depressive signs a symptoms were also better controlled with olanzapine therapy (Tollefson et al, 1998). On the Montgomer Asberg Depression Rating Scale, olanzapine was significantly more effective than haloperidol (p = 0.001
i) In multiple clinical trials of olanzapine, the incidence of self-directed aggression among patients receiv olanzapine, haloperidol, or placebo, was not significantly different (Keck et al, 2000). These trials indicate a significantly greater improvement in suicidal thoughts in olanzapine-treated patients compared with haloperidol-treated patients. Another analysis demonstrated a 2.3-fold reduction in the annual suicide attempt rate among chronic psychotic patients receiving olanzapine versus haloperidol.

4.6.AG.4 Tardive dyskinesia
a) Olanzapine was associated with a lower incidence of tardive dyskinesia when compared to haloperid (Tollefson, 1997a). Data combined from 3 controlled and blinded studies evaluating patients with schizophrenia, schizophreniform disorder, or schizoaffective disorder treated with olanzapine (n=707) or haloperidol (n=197) were compared. Patients had no evidence of tardive dyskinesia at baseline. At any v after baseline 7.1% of patients in the olanzapine group and 16.2% of patients in the haloperidol group manifested treatment-emergent tardive dyskinesia (p less than 0.001). At the last study visit, 2.3% of olanzapine patients and 7.6% of haloperidol patients manifested tardive dyskinesia (p equal to 0.001). Similar results have been reported (Beasley et al, 1999).
4.6.AG.5 Efficacy
a) Results of a retrospective analysis showed that olanzapine treatment was associated with a lower rat of extrapyramidal symptoms (EPS) than haloperidol, but was similar to rates occurring with risperidone a

clozapine therapy. In a pooled analysis of 23 randomized, controlled clinical trials in 4611 patients with schizophrenia, frequency and severity of EPS associated with olanzapine therapy (2.5 to 20 milligrams (mg)/day) was compared with that of haloperidol (1 to 20 mg/day), risperidone (4 to 12 mg/day), clozapir (25 to 625 mg/day), and placebo. Dystonic events (ie, dystonia, oculogyric crisis, opisthotonos, torticollis occurred in significantly fewer patients during olanzapine treatment as compared with haloperidol (0.5% 5.6%, respectively; p less than 0.001) or risperidone (1% vs 3.2%, respectively; p=0.047) treatment, whil no significant difference was found between olanzapine- and clozapine-treated patients. As compared w olanzapine-treated patients, a significantly higher percentage of haloperidol-treated patients experiencec parkinsonian events (ie, akinesia, cogwheel rigidity, extrapyramidal syndrome, hypertonia, hypokinesia, masked facies, and tremor) (9.3% vs 28.3%, respectively; p less than 0.001) or akathisia events (ie, akathisia, hyperkinesia) (6.7% vs 20.4%, respectively; p less than 0.001) during therapy. However, no significant difference was observed between the olanzapine group as compared with the placebo, risperidone, or clozapine groups in regard to the occurrence of parkinsonian or akathisia events. Overall, EPS occurred in significantly more patients treated with haloperidol as compared with olanzapine (44.4% vs 16.2%, respectively; p less than 0.001) and in fewer patients treated with clozapine as compared with olanzapine (2.6% vs 6.8%, respectively; p=0.047). The overall rate of EPS was similar between the placebo and risperidone groups as compared with olanzapine. Significantly fewer patients received anticholinergic medications in the olanzapine group as compared with the haloperidol (p less than 0.001) risperidone (p=0.018) groups. No difference was found between olanzapine-treated patients as compare with placebo or clozapine in regard to percentage of patients given anticholinergic drugs during therapy (Carlson et al, 2003).

b) Pooled safety results from 3 large double-blind, controlled trials in 2606 patients demonstrated that olanzapine had a significantly lower rate of any extrapyramidal symptoms (EPS) occurring versus haloperidol (p less than 0.001) (Tran et al, 1997). Also statistically fewer patients treated with olanzapine discontinued the study because of EPS (p less than 0.001). This suggests that the use of olanzapine ma be associated with better long-term compliance due to fewer adverse effects.

c) The risk of extrapyramidal adverse effects is lower with olanzapine compared to haloperidol, especial dystonic reactions. Increases in serum prolactin have been significantly less with olanzapine (Tollefson e al, 1997); (Beasley et al, 1996)(Anon, 1996; Anon, 1995).

4.6.AG.6 Adverse Effects

a) The results of one study suggest that patients receiving atypical antipsychotics have a higher incidenc of PANCREATITIS than patients receiving a conventional antipsychotic medication. In a retrospective, pharmacovigilance study, 192 cases of pancreatitis were identified in patients taking clozapine (mean do 306.7 milligrams (mg)/day), olanzapine (mean dose, 15 mg/day), risperidone, (mean dose, 4 mg/day) or haloperidol (mean dose, 8.2 mg/day). Of the identified cases, 40%, 33%, and 16% were related to treatment with the atypical antipsychotic medications clozapine, olanzapine, or risperidone, respectively, compared with 12% of the cases which were related to the conventional neuroleptic, haloperidol. In most patients, time to onset of pancreatitis was within 6 months after initiation of treatment (Koller et al, 2003).

4.6.AH Oxazepam

4.6.AH.1 Dementia - Restlessness and agitation

a) Oxazepam, haloperidol, and diphenhydramine were equally efficacious in the treatment of agitated behavior in 59 elderly demented inpatients in an 8-week, double-blind study (Coccaro et al, 1990). The mean daily doses were oxazepam 30 +/- 19.4 milligrams, haloperidol 1.5 +/- 0.9 milligrams, and diphenhydramine 81.3 +/- 48.5 mg. Chloral hydrate was given if the study medication did not adequately control agitation. Ratings scale scores indicated that diphenhydramine and haloperidol were more effecti than oxazepam, but none of the differences in scores among the groups was significant. Only modest improvement was seen in terms of agitated behavior and activities of daily living. There was only a slight decrease in the use of chloral hydrate in all 3 groups during the study and no difference among the grou

4.6.AI Oxcarbazepine

4.6.AI.1 Bipolar disorder

a) Oxcarbazepine has been compared with with haloperidol in 42 patients with acute mania; mean dose used were 2400 mg/day and 42 mg/day respectively. Although the response to oxcarbazepine was slow by the end of the second week of treatment, results were similar in both treatment groups. Haloperidol-treated patients had a significantly higher incidence of adverse effects (Emrich, 1990).

4.6.AJ Penfluridol

Gilles de la Tourette's syndrome

Schizophrenia

4.6.AJ.1 Gilles de la Tourette's syndrome

a) Haloperidol has been the drug of choice for Tourette's syndrome for many years, producing beneficia effects in up to 90% of patients treated (Shapiro & Shapiro, 1981; Shapiro et al, 1983). However, advers effects with haloperidol, mainly extrapyramidal symptoms, have limited its use in many patients. Penfluri and pimozide have both been evaluated in the treatment of Tourette's syndrome, based upon animal studies suggesting that each drug has catecholamine blocking effects that differ from haloperidol (Nose Takemoto, 1975). Penfluridol is presumed to be a more specific blocker of dopamine than haloperidol. In addition, it is postulated that penfluridol produces less frequent and less severe extrapyramidal toxicity th haloperidol (Ayd, 1972). However, the differences in extrapyramidal symptoms between the 2 agents remain unclear.

b) Penfluridol was evaluated in the treatment of Tourette's syndrome (Shapiro et al, 1983). The study involved 8 patients with Tourette's syndrome and the results with penfluridol were compared to previous therapy with haloperidol or pimozide (6 of 8 patients). There were 7 males and 1 female aged 10 to 33 years. Penfluridol was given initially in oral doses of 10 mg weekly, increasing by 10 mg weekly for 3 to 1 months (mean, 10 months). Dosage during treatment ranged from 20 to 160 mg weekly, with penfluridol being taken every 3 to 7 days. The percent decrease in tic symptoms was significantly higher for penfluri (mean, 74.4%) than previous haloperidol treatment (mean, 61%). Penfluridol was considered to be slight superior to previous pimozide treatment, however, these differences were not considered significant. Sid effects, including extrapyramidal symptoms, were less in penfluridol patients as compared to previous pimozide or haloperidol therapy. The number of patients using antiparkinson drugs was less with penfluridol.

4.6.AJ.2 Schizophrenia

a) Penfluridol administered once weekly is probably as effective as haloperidol administered daily in the treatment of chronic schizophrenia as well as Tourette's syndrome. An investigational preparation of haloperidol decanoate (McNeil Laboratories) can be given IM and has a duration of action of 4 weeks. B haloperidol decanoate and oral penfluridol will have advantages over oral haloperidol for the manageme of chronic schizophrenia, each improving compliance significantly. Other controlled studies have also reported the equivalent efficacy of daily chlorpromazine as compared to weekly penfluridol (Chouinard e 1977; Chouinard & Annable, 1976; Claghorn et al, 1979). Thus, penfluridol appears to be as effective as chlorpromazine with the advantage of once weekly administration. The incidence of extrapyramidal reactions is greater with penfluridol. Penfluridol will be useful in the patients who are non-compliant on chlorpromazine given daily and in some patients who are not responding optimally to chlorpromazine alo

4.6.AJ.3 Efficacy

a) Although penfluridol is considered a diphenylbutylpiperidine derivative, it does have structural similarities to haloperidol, and both drugs have essentially indistinguishable pharmacologic effects (AMA Department of Drugs, 1986). However, the one-week duration of action of penfluridol is significantly long than haloperidol. Although there is some evidence that penfluridol produces a lower incidence of extrapyramidal side effects than haloperidol (Ayd, 1972; Shapiro et al, 1983), there are no direct comparative studies to support these claims.

4.6.AK Perazine

4.6.AK.1 Schizophrenia

a) High-dose haloperidol was not found to be more effective than standard-dose perazine in treating acutely psychotic schizophrenic patients in a double-blind randomized clinical trial of 32 male patients. Patients received between 15 to 45 milligrams (mg) daily of haloperidol or 300 to 900 mg/day of perazine According to the Clinical Global Impression scale 60% of all examined patients achieved satisfactory improvement after 4 weeks of therapy with an average 65% reduction in their symptoms. The number of responders in the haloperidol group (9 of 15) was not statistically different from the responders in the perazine group (9 of 17). Symptoms were measured according to the AMP scale. As expected, the high-dose haloperidol group reported a significantly higher frequency of extrapyramidal symptoms, rigor, and acute dyskinesia; the perazine group had a higher incidence of dry mouth. Overall 4 patients discontinue the study: 2 in the haloperidol group due to extrapyramidal symptoms and 2 in the perazine group who h to be switched to high-dose haloperidol therapy because of uncontrolled symptoms (Schmidt et al, 1982)

4.6.AL Periciazine

4.6.AL.1 Schizophrenia

a) Maintenance therapy with oral periciazine in doses of 10 to 60 milligrams daily has been less effectiv than haloperidol 1 to 6 mg daily in symptom-free schizophrenic patients. This was attributed in part to lac of dose-dependent decreases in relapse rates with periciazine; although the drug increased symptom-fre days over doses of 10 to 30 mg daily, a significant decrease in this parameter (placebo levels) was seen with 60 mg daily, in association with a high incidence of adverse effects (eg, dysarthria, malaise, hypersomnia). These combined results are suggestive of an inverted U-shaped dose-response curve for periciazine. In contrast, haloperidol significantly and dose-dependently increased symptom-free days ov the range of 1 to 6 mg daily, without an increase in adverse effects (Nishikawa et al, 1984).

4.6.AM Perphenazine

Psychotic disorder

Schizophrenia

4.6.AM.1 Psychotic disorder

a) One double-blind study reported the similar efficacy of intramuscular haloperidol 5 milligrams every 8 hours and intramuscular perphenazine 5 milligrams every 8 hours in the treatment of acute psychiatric episodes (Fitzgerald, 1969). Total doses (mean) of haloperidol and perphenazine were 26 mg and 27 mg respectively, over a period of 48 hours.

4.6.AM.2 Schizophrenia

a) Haloperidol decanoate (100 milligrams/4 weeks) was compared with perphenazine enanthate (100 milligrams/2 weeks) in 20 schizophrenic patients in a 48-week, double-blind crossover study. There were no significant differences in either safety or efficacy (Rapp et al, 1986).

b) Perphenazine decanoate and haloperidol decanoate were compared in a 51-week, randomized, double blind, cross-over, multicenter study. There were no significant differences between the two drugs in antipsychotic efficacy or side effects (Dencker et al, 1994).

4.6.AN Phenelzine

4.6.AN.1 Personality disorder

a) Haloperidol was compared to phenelzine in a placebo-controlled, randomized, double-blind study of 1 patients with borderline personality disorder over a 5 week period (Soloff et al, 1993). Thirty-six patients received 4 mg haloperidol, 38 received 60 mg phenelzine and 34 received look-alike placebo tablets. Several measures of effectiveness were evaluated. Haloperidol was found to be ineffective and phenelzi was effective in comparison to both placebo and haloperidol. This study was not able to establish a dissection of borderline personality disorders into affective and schizotypal subtypes.

4.6.AO Physostigmine

4.6.AO.1 Alzheimer's disease

a) Physostigmine was compared with haloperidol in the treatment of behavioral disturbances in 15 patie diagnosed with Alzheimer's disease (Gorman et al, 1993). Physostigmine 15 milligrams/day in two-hourly divided doses was compared to haloperidol to 3 milligrams/day. Both drugs were effective in controlling t behavioral disturbances. Haloperidol produced a high incidence of adverse effects.

b) Physostigmine 6 mg/day was compared with haloperidol 3 mg/day in a double-blind study of two patients with Alzheimer's Disease and prominent delusions. Both patients responded to each treatment with a decrease in delusions and associated hallucinations and agitated behavior. Physostigmine was w tolerated in both patients (Cummings et al, 1993).

4.6.AP Pimozide

Gilles de la Tourette's syndrome

Schizophrenia

4.6.AP.1 Gilles de la Tourette's syndrome

a) The efficacy of pimozide in Tourette's syndrome was evaluated (Colvin & Tankanow, 1985). Although effective, superiority of the drug over haloperidol has not been adequately demonstrated. The drug is indicated as reserve therapy for Tourette's syndrome in patients who have not responded to haloperidol who cannot tolerate toxicity of haloperidol.

b) In a 6-month, controlled crossover trial of children and adolescents (n=22) with Tourette's syndrome, only pimozide demonstrated statistical improvement over placebo on the global rating scale (p less than 0.05). However, pimozide and haloperidol did not differ statistically in efficacy from each other. Overall, 64% of subjects attained the goal of 70% tic reduction with active therapy as compared to only 23% with placebo. The mean effective doses of pimozide and haloperidol were equivalent (3.4 and 3.5 milligrams daily, respectively). Haloperidol was associated with a greater incidence of extrapyramidal symptoms (Sallee et al, 1997).

c) Haloperidol was compared with pimozide in 9 patients with Gilles de la Tourette syndrome (Ross & Moldofsky, 1978). In this double-blind study, patients were assigned to pimozide or haloperidol, each in doses of 2 milligrams (mg) initially every morning, increasing by 2 mg every second day until symptoms

disappeared or until side effects were observed or until maximum doses of 12 mg daily were obtained. A follow-up period of 420 months was undertaken. Both pimozide and haloperidol significantly reduced me 5-minute tic counts, with no significant difference between the 2 drugs. Both haloperidol and pimozide w more effective than placebo. Follow-up at 4 to 20 months indicated that 6 of 7 patients continuing on pimozide and one of 2 patients continuing on haloperidol had a greater than 75% improvement in symptoms. Significantly fewer days of lethargy or tiredness was associated with pimozide than haloperid Anticholinergic and extrapyramidal effects were similar with both agents. Pimozide may be an effective alternative to haloperidol in Gilles de la Tourette syndrome, particularly in haloperidol non-responders or patients receiving haloperidol but developing incapacitating side effects.

d) Haloperidol was compared with pimozide in a double-blind, parallel, crossover study lasting 6 weeks 57 patients with Tourette's syndrome. The maximum dose of haloperidol was 10 milligrams (mg)/day, an for pimozide it was 20 mg/day. Haloperidol was slightly more effective than pimozide in the treatment of Tourette's syndrome. Adverse effects of haloperidol were not significantly different than those of pimozid Clinically significant cardiac effects did not occur. However, due to the potential of pimozide prolonging QTC intervals, haloperidol is the drug of choice for initial treatment of Tourette's syndrome (Shapiro et al 1989).

4.6.AP.2 Schizophrenia

a) SUMMARY: Pimozide is at least as effective as haloperidol in the treatment of chronic schizophrenia.

b) Pimozide was compared with haloperidol (5 to 50 milligrams/day (mg/day) of either) in relation to dopaminergic blockade and clinical response in 22 patients with schizophrenia. The drugs were equally effective. There was no correlation between either dopaminergic blockade or blood level and therapeutic response (Silverstone et al, 1984).

c) Pimozide 306 mg daily was superior to haloperidol 7 to 14 mg daily in chronic schizophrenia in a sma double-blind study. A subsequent report has indicated the equivalent efficacy of pimozide 10 to 60 mg da and haloperidol 10 to 60 mg daily in acute schizophrenia (Haas & Beckmann, 1982). In this study, howev extrapyramidal effects were more pronounced in patients using pimozide (Gowardman et al, 1973).

4.6.AQ Pramipexole

4.6.AQ.1 Schizophrenia

a) Haloperidol 15 mg daily has been superior to pramipexole (0.3, 0.75, or 3 mg daily) in the treatment o schizophrenia (Lecrubier, 1994).

4.6.AR Prochlorperazine

4.6.AR.1 Chemotherapy-induced nausea and vomiting

a) Butyrophenones such as haloperidol and droperidol are more effective than phenothiazines such as prochlorperazine in moderate to highly emetogenic chemotherapy, particularly when used in combinatior with steroids and antihistamines (Wood, 1993; Sridhar & Donnelly, 1988; Kelley et al, 1986); (Mason, 1982).

b) Haloperidol combined with dexamethasone was compared to prochlorperazine combined with dexamethasone in controlling nausea and vomiting in breast cancer patients (Silvey et al, 1988). The prospective study was nonblinded and randomized. The patients received either intravenous cyclophosphamide, doxorubicin, and fluorouracil (a chemotherapy regimen known as CAF) or cyclophosphamide, methotrexate, and fluorouracil) (a chemotherapy regimen known as CMF). Patients received either prochlorperazine 6 mg/m(2) plus dexamethasone 5 mg/m(2) or haloperidol 2 mg/m(2) plu dexamethasone 5 mg/m(2). The patients received the first dose intravenously 30 minutes before the administration of cytotoxic drug, the same dose orally 3.5 hours after therapy and then every 4 hours for hours. Neither the prochlorperazine plus dexamethasone or haloperidol plus dexamethasone was highly effective in preventing nausea and vomiting in the doses and schedules used, although the haloperidol a dexamethasone regimen did reduce the severity of vomiting and nausea to some extent. Based upon thi information, neither regimen can be recommended as standard antiemetic therapy for this patient population.

4.6.AS Quetiapine

4.6.AS.1 Schizophrenia

a) In a study involving 361 patients, quetiapine (across 5 fixed doses) was found to be superior to placel in improving depressive symptoms in schizophrenic patients, while haloperidol (12 milligrams/day) was r Additionally, depressive symptoms were improved in a greater proportion of patients treated with quetiap versus haloperidol or placebo. None of the quetiapine patients withdrew from the study due to extrapyramidal symptoms, while 4 haloperidol and 1 placebo patient withdrew (Keck et al, 2000a; Glazer 2000).

b) A 6-week, multicenter, double-blind trial comparing quetiapine and haloperidol (mean total daily dose of 455 milligrams and 8 milligrams, respectively) in the treatment of acute exacerbation of schizophrenia concluded that quetiapine in as effective and better tolerated than haloperidol. Both agents produced cle reductions in the Positive and Negative Syndrome Scale scores and Clinical Global Impression Severity

Illness and Global Improvement scores. Quetiapine was better tolerated in terms of extrapyramidal symptoms. In addition, mean serum prolactin concentration decreased in quetiapine patients and increas in haloperidol patients (Copolov et al, 2000).

4.6.AT Remoxipride

4.6.AT.1 Schizophrenia

a) SUMMARY: REMOXIPRIDE and HALOPERIDOL have been shown to achieve equal efficacy for the treatment of schizophrenia. In some studies, REMOXIPRIDE produced a lower frequency of extrapyrami or other adverse symptoms.

b) Controlled-release (CR) REMOXIPRIDE and HALOPERIDOL were shown to produce comparable efficacy in the treatment of chronic schizophrenia patients with a preponderance of negative symptoms (ratings based on the Positive and Negative Symptoms Scale (PANSS)) in a multi-center, double-blind tr Following a run-in period, patients were randomized to a 24-week course of remoxipride CR 150 to 600 milligrams (mg)/day (n=97) or haloperidol 5 to 20 mg/day (n=108), given in 2 divided doses. Mean daily doses were 334.1 mg for remoxipride and 10.44 mg for haloperidol during the last study-week. A reducti of 20% in the PANSS negative symptoms scores occurred in 49.4% and 47.6%, respectively, of remoxipride- and haloperidol-treated patients. Clinical Global Impression evaluations rated 33.7% of remoxipride and 30.8% of haloperidol patients much or very much improved. Tolerability was similar for both medications with the overall adverse effects profile of remoxipride not statistically different from haloperidol. The authors noted that the generally low-dosages of haloperidol used in this study may have enhanced its tolerability (Lapierre et al, 1999).

c) Remoxipride showed equal efficacy to haloperidol in a double-blind study using 80 patients with schizophrenia (Ahlfors et al, 1990). Remoxipride is a dopamine D2 receptor blocking agent that shows n effect on serotonin, noradrenaline, histamine, acetylcholine, or GABA receptors. Because remoxipride ha receptor specificity, it suggests low extrapyramidal side-effects. A total of 50 patients were used in the study and were then evaluated at the end of the treatment. The mean daily dose of remoxipride was 316 milligrams as opposed to 8.7 milligrams of haloperidol. The results showed comparable effectiveness in treating schizophrenia. Only 14 patients exhibited extrapyramidal effects, and of these, only three were remoxipride patients. The researchers conclude that remoxipride is a comparable antipsychotic to haloperidol. Similar results have been reported (Andersen et al, 1990; Deo et al, 1990; den Boer et al, 1990; den Boer & Westenberg, 1990); (Lindrom et al, 1990)(Mendlewicz et al, 1990).

d) Haloperidol and remoxipride were equally efficacious in one study (Laux et al, 1990). The study grou was divided into three groups: remoxipride (53 patients) twice daily, remoxipride (52 patients) three times daily, and haloperidol (52 patients) three times daily. The results showed no significant differences in effectiveness. No extrapyramidal effects were noticed in remoxipride patients opposed to 4% affected patients using haloperidol. The researchers' conclusion is that remoxipride is as effective as haloperidol i acute schizophrenia with fewer side-effects. Similar results have been reported by others (Lapierre et al, 1990; Patris et al, 1990).

e) A double-blind multicenter study of 150 schizophrenic or schizophreniform patients compared the efficacy and safety of oral forms of remoxipride immediate-release (IR), remoxipride controlled-release (CR), and haloperidol. Patients randomly received one of the three drugs in mean daily doses of 332 milligrams and 12.5 milligrams, respectively, and were evaluated for a four-week period using two standa neuroleptic efficacy scales as well as the Simpson & Angus scale for extrapyramidal symptoms. There were no statistically significant differences among the treatment groups. The authors concluded that the three drugs were equal in antipsychotic efficacy in treating schizophrenia or schizophreniform behavior while remoxipride, IR and CR had less frequent side effects than haloperidol in therapeutic doses (Hebenstreit et al, 1991).

f) In a four-week study involving 51 previously untreated patients with schizophrenia, remoxipride (mean dose 375 milligrams/day), haloperidol (mean dose 16 milligrams/day), and clozapine (mean dose 350 milligrams/day) were compared (Klieser et al, 1994). There was no significant difference in efficacy amor the three drugs. The incidence of extrapyramidal side effects (EPS) was most frequent with haloperidol a least frequent with clozapine, with remoxipride causing EPS with intermediate frequency.

4.6.AU Risperidone

Cognitive function finding

Dementia

Extrapyramidal disease

Mania

Schizophrenia

4.6.AU.1 Cognitive function finding

a) Results of a multicenter, randomized, double blind trial assessing cognitive function in patients experiencing their first schizophrenic episode or a related psychosis demonstrated that overall improvement in cognitive functioning was superior with risperidone than with haloperidol. Patients (n=53 were randomized to receive either risperidone or haloperidol on a one-to-one randomization basis for a period of 2 years or more. There were no significant differences in sex, race or ethnicity, age, diagnosis, previous neuroleptic treatment in either group. Dosing strategies were equivalent in both groups where patients were started on 1 milligram per day (mg/day) of the study drug and titrated up to 4 mg/day, or in some cases, to a maximum of 8 mg/day. Patients in the risperidone group received the trial medication (mean modal total dose 3.3 mg/day) for an average of 192 days while patients in the haloperidol group received treatment (mean modal total dose 2.9 mg/day) for an average of 218 days. Cognitive assessments, performed at several different follow-up intervals, included examinations of verbal and visuospatial episodic memory, vigilance, executive functioning, processing speed, and verbal fluency. Ar intention-to-treat analysis conducted with a focus on the 3-month assessment revealed that there was significant improvement from baseline in the risperidone group (n=169) for all measures except category verbal fluency and letter verbal fluency (p less than 0.05). In the haloperidol group (n=169), statistically significant improvements from baseline were noted in episodic memory, vigilance, and visuomotor speec but not in executive functioning and verbal fluency. Comparison between the two groups showed that, af 3 months of treatment, the risperidone group was significantly more beneficial than the haloperidol group on the composite measure of cognitive functioning. In addition, cognitive improvement as a result of treatment with risperidone was not affected by changes in symptoms. Risperidone therapy also proved t be superior than haloperidol in relapse prevention and extrapyramidal side effects (Harvey et al, 2005).

b) Risperidone therapy appeared to exert a more favorable effect on verbal working memory in treatmer resistant schizophrenic patients than did haloperidol therapy (Green et al, 1997). In a randomized, doubl blind comparison of treatment with risperidone (n = 30) and haloperidol (n = 29), verbal working memory was measured at baseline and after 4 weeks of both a fixed dose and flexible dose regimen. Risperidone patients showed a significant improvement in memory using a Digit Span Distractibility Test from baselin performance at both the fixed-dose (p less than 0.0001) and the flexible dose (p less than 0.0003) phase The haloperidol-treated patients did not change significantly. Results suggest that treatment of schizophrenia could be broadened to include the impact on neurocognitive abilities.

4.6.AU.2 Dementia

a) Some Chinese patients with dementia, who were non-responders to haloperidol, responded to risperidone with decreased behavioral disturbances and improved mood. Thirty-five Chinese patients wh had shown insufficient response to an 8- week trial with haloperidol (i.e., having a total score of more tha 10 on the Brief Psychiatric Rating Scale (BPRS) at the end of 8 weeks) (typical dose 1 gram/day) were switched abruptly from haloperidol to risperidone 0.5 milligrams (mg) at bedtime for weeks 1 to 4 and the (if tolerated) to 1 mg at bedtime for weeks 5 to 12. At week 13, the regimen was shifted again to haloperi at the dose used in the earlier trial. Twenty-nine patients completed the trial. Sixteen patients responded the end of the risperidone trial (response = a decrease of 25% in the BPRS score). After haloperidol resumption, the mean BPRS score stayed the same, but the number of responders decreased to 15. Patients with vascular dementia were almost 6 times more likely to respond to risperidone than patients with Alzheimer's disease. Mean scores on the Behavioral Pathology in Alzheimer's Disease Rating Scale decreased (6.1 at baseline to 1.9 at 12 weeks of risperidone treatment) and increased after switching ba to haloperidol (to 2.4 after 4 weeks of haloperidol). Thirty- four of the 35 patients tolerated both doses of risperidone and haloperidol 1 mg/day. One patient experienced moderate rigidity with risperidone 1 mg/c which was relieved by reduction of the dose to 0.5 mg/day. Patients experienced fewer extrapyramidal symptoms with risperidone than with haloperidol (Lane et al, 2002).

b) Both risperidone and haloperidol in low doses reduced the severity and frequency of behavioral and psychological symptoms of elderly Chinese patients with dementia. Risperidone was associated with les severe exacerbation of extrapyramidal symptoms (EPS). In a randomized, double-blind trial, 55 elderly Chinese patients (mean age 80 years) with Alzheimer's dementia or vascular dementia and with behavic disturbance, were given either risperidone or haloperidol for 12 weeks after a 2-week washout period for elimination of psychotropic and antiparkinsonian drugs. The starting dose for both treatment drugs was 0 milligrams (mg) at night; doses were adjusted individually in increments of 0.5 mg no faster than every other day, to a maximum of 2 mg/day. At 12 weeks, the mean daily dose of haloperidol was 0.9 mg, and that of risperidone, 0.85 mg. Significant improvements on the Cohen- Mansfield Agitation Inventory (CMA were evident in both groups (haloperidol, p less than 0.001; risperidone, p=0.002). Significant reduction was seen at 2 weeks in the risperidone group and at 4 weeks in the haloperidol group. With risperidone, there were significant improvements in scores for psychosis, activity disturbances, aggressiveness and diurnal rhythm disturbances, whereas with haloperidol, improvement in only the aggressiveness score reached statistical significance. However, none of the measures showed a significant difference betweer the treatment groups. With haloperidol, there was a significant worsening of EPS (p less than 0.001), whereas, with risperidone, EPS scores were only modestly worsened. Final EPS scores were significant higher for haloperidol (p=0.001) (Chan et al, 2001).

4.6.AU.3 Extrapyramidal disease

a) Data from a multicenter comparative study of risperidone, placebo, and haloperidol revealed that risperidone caused few or no extrapyramidal symptoms (Simpson & Lindenmayer, 1997). Mean changes Extrapyramidal Symptom Rating Scale (ESRS) scores from baseline to worst score were significantly lov in each risperidone group than the haloperidol group (P less than 0.001).

4.6.AU.4 Mania

a) A small, controlled study, compared the efficacy and safety of risperidone versus lithium and haloperi in mania and found comparable results with risperidone. Patients (n=45) were assigned to take risperido (as monotherapy), dosed at 6 mg per day, haloperidol at 10mg per day, or 800 to 1000 mg daily of lithiur All 3 groups showed a similar improvement on Brief Psychiatric Rating Scale and Young Mania Rating Scale scores. The EPS of risperidone and haloperidol were not significantly different and mania did not worsen in any of the risperidone treated patients (Segal et al, 1998).

4.6.AU.5 Schizophrenia

a) Olanzapine and risperidone improved neurocognitive deficits more than did haloperidol or clozapine i patients with schizophrenia or schizoaffective disorder that was refractory to treatment with typical antipsychotics. In a randomized, double-blind study, inpatients were given clozapine (n=24) 200 to 800 milligrams (mg) per day, olanzapine (n=26) 10 to 40 mg/day, risperidone (n=26) 4 to 16 mg day, or haloperidol (n=25) 10 to 30 mg/day. Dose escalation and fixed-dose treatment (target doses: olanzapine mg/day, risperidone 8 mg/day, haloperidol 20 mg/day, clozapine 500 mg/day) occurred during the first 8 weeks of the 14-week study; during the last 6 weeks, dosages were adjusted individually (generally increased if response was insufficient, but sometimes reduced because of adverse effects). Improvemer over time in global neurocognitive score was seen for olanzapine and risperidone. In general executive a perceptual organization and in processing speed and attention, improvement was seen with olanzapine. simple motor function, there was improvement with clozapine. Changes in global neurocognitive performance with olanzapine and risperidone were of medium magnitude (approximately 8 to 9 "IQ equivalents") but large enough to be clinically significant. Beneficial changes with clozapine were modes Despite cognitive gains, patients still had significant impairments of cognitive ability and social/vocationa functioning. Improvements in neurocognitive deficits were associated with improvements in negative symptoms (Bilder et al, 2002a).

b) The risk of relapse of schizophrenia was significantly less with long-term treatment with risperidone th with haloperidol. In a randomized, double-blind study, 365 patients meeting DSM-IV criteria for schizophrenia or schizoaffective disorder and in a stable condition were given flexible doses of either risperidone or haloperidol. The trial was continued until the last enrolled patient had completed one year treatment. Means of modal daily doses were 4.9 milligrams (mg) for risperidone and 11.7 mg for haloperidol. At the end of the study, 25% of the risperidone group and 40% of the haloperidol group had relapsed. The risk of relapse was significantly higher among patients assigned to haloperidol (risk ratio 1.93, p less than 0.001). The risk of premature discontinuation was greater for the haloperidol group thar for the risperidone group (risk ratio 1.52), mainly because of relapse. Median duration of treatment for th risperidone group was 364 days and for the haloperidol group, 238 days (p=0.02). The subtypes of relap (psychiatric hospitalization, clinical deterioration, increase in level of care, suicidal or homicidal ideation) were similar in the 2 groups. In the risperidone group, there were improvements from baseline in positive and negative symptoms, disorganized thoughts, and anxiety- depression, whereas symptoms were not improved with haloperidol. The severity of extrapyramidal symptoms was reduced from baseline in the risperidone group and increased in the haloperidol group. Differences between the groups were significa (p less than 0.02 for total score on the Extrapyramidal Symptom Rating Scale). The most frequent adver events were somnolence (14% with risperidone and 25% with haloperidol), agitation (10% and 18% respectively), and hyperkinesia (5% and 20%, respectively). Those taking risperidone had a mean increa in body weight of 2.3 kilograms (kg) and those taking haloperidol had a mean decrease of 0.73 kg (p less than 0.001) (Csernansky et al, 2002).

c) Risperidone was more efficacious and had fewer adverse effects than haloperidol when used to treat refractory schizophrenia in Chinese patients. Chinese patients, meeting DSM-III-R criteria for schizophre and having a history of treatment failure with 3 conventional neuroleptics given at least 3 months at full dose, were randomly assigned to receive risperidone (n=41) or haloperidol (n=37) for a 12-week, double blind trial. The dose of risperidone was increased during the first week to 6 milligrams (mg) per day, and dose of haloperidol to 20 mg/day. By the end of the study, the average score on the Positive and Negativ Syndrome Scale (PANSS) had decreased by 39.8% for the risperidone group and by 28.3% for the haloperidol group (p=0.03). The general psychopathology and negative subscores of the PANSS showe greater improvement with risperidone, but there was no difference between treatments in the positive subscore. The proportion of patients rated as responders was higher in the risperidone group (31 of 41 v 20 of 37, p=0.046). Total scores on the Treatment Emergent Symptoms Scale (TESS) were significantly lower with risperidone than with haloperidol (2.9 vs 6.9, p=0.01). Particular subscores significantly favori risperidone were those showing symptoms of the nervous system (rigidity, tremor, dystonia, and akathisi and of the cardiovascular system (hypotension, dizziness, tachycardia, hypertension and electrocardiogr abnormalities) (p=0.02 and p=0.04, respectively). Patients in the risperidone group required less medicat for extrapyramidal symptoms during the study than did patients in the haloperidol group. The authors mentioned that the dose of haloperidol was higher than the dose recommended in the United States and Europe and may have accounted for some of the difference between treatments in efficacy and adverse

effects (Zhang et al, 2001).
d) Results of a subanalysis of data from the multinational risperidone trial (double-blind, randomized, parallel-group) reported that the reduction in negative symptoms was significantly better in patients receiving risperidone 16 mg/day than haloperidol 10 mg/day (p less than 0.05) (Moller et al, 1997a). Patients with chronic schizophrenia (n=169) were treated with risperidone 1 mg, 4 mg, 8 mg, 12 mg, or 1 mg, or haloperidol 10 mg/day for 8 weeks. Improvement was noted in each group. Risperidone onset wa faster than haloperidol. An analysis of the Positive and Negative Syndrome Scale cluster scores revealed significantly greater improvement in the risperidone-treated patients than in the haloperidol group on 2 clusters: activity and anxiety/depression (p less than 0.05).
e) Risperidone was significantly better than haloperidol in the treatment of chronic schizophrenia using combined data from 2 studies (Chouinard et al, 1993; Marder & Meibach, 1994) to evaluate five factors o the Positive and Negative Syndrome Scale (Marder et al, 1997). Data from 513 patients showed that afte to 8 weeks of therapy, patients receiving risperidone 6 to 16 milligrams had significantly higher adjusted mean changes in total Positive and Negative Syndrome Scale than patients treated with haloperidol (p le than 0.01). The 5 specific symptom areas that risperidone was significantly superior to haloperidol includ negative symptoms (p less than 0.01), positive symptoms (p less than 0.05), disorganized thought (p les than 0.05), uncontrolled hostility/excitement (p less than 0.01), and anxiety/depression (p less than 0.01) One author, however, noted some positive symptoms that reemerged after an initial response to risperidone (Cung & Stimmel, 1997).
f) In a meta-analysis, risperidone (4 to 8 milligrams(mg)/day) was found to be more effective and produc fewer extrapyramidal effects than haloperidol (4 to 20 mg/day). Seven studies done in a double-blind, randomized fashion were included. The primary outcome measure was clinical improvement defined as a 20% reduction in the total scores on the Brief Psychiatric Rating Scale or the Positive and Negative Syndrome Scale. Results showed that patients identified as treatment failures were 50% of those taking risperidone, 66% on haloperidol, and 83% on placebo. There was a highly significant need for anticholinergic medication in the haloperidol-treated patients as compared to risperidone (P less than 0.00001) (de Oliveira et al, 1996).
g) Risperidone was more effective than haloperidol in a double-blind, placebo-controlled, multicenter stu (Marder & Meibach, 1994). 388 schizophrenic patients were randomly assigned to receive 4 fixed doses risperidone (2, 6, 10, and 16 milligrams/day, on a BID schedule), haloperidol 20 milligrams daily or place for 8-weeks (Marder and Meibach, 1994). Patients receiving risperidone 6 to 16 milligrams showed statistically greater improvement than placebo or haloperidol in Clinical Global Impression (CGI) and tota Positive and Negative Syndrome Scale (PANSS) scores. Of the four doses studied, the 6, 10, and 16 milligram doses were all effective with the 6 milligram dose being the most effective. Similar results have been reported (Chouinard et al, 1993; Marder, 1992).
h) In an 8-week, double-blind study, 1362 schizophrenic patients were randomly assigned to receive eit risperidone 1, 4, 8, 12, 16 milligrams/day, on a BID schedule, or haloperidol 10 milligrams daily (Muller-Spahn, 1992). Significantly greater improvement in Positive and Negative Syndrome Scale (PANSS) and Brief Psychiatric Rating Scale (BPRS) total score, the PANSS General Psychopathology subscale, the BPRS Activity and Anxiety/Depression cluster, was observed in the risperidone 4 milligram and 8 milligra groups versus the haloperidol-treated patients. In addition, a greater percentage of patients treated with risperidone 4 and 8 milligrams achieved clinical improvement on the PANSS and BPRS as compared wi the haloperidol group.
i) Risperidone was faster acting, more effective, and had fewer side effects than haloperidol in a study t determine efficacy in treating negative symptoms of schizophrenia (Claus et al, 1992). The multicenter double-blind study that took place over a period of 15 weeks included a two-week run-in period and a on week washout period. The patients (n=42) took one to 5 mg bid of either drug for a period of 12 weeks. T Positive and Negative Syndrome Scale for Schizophrenia was the key efficacy parameter. The Schedule for Affective Disorders and Schizophrenia Change Conversion was used as a diagnostic aid and sympto severity measure. The Clinical Global Impression Scale was complete as a global rating. In addition, the occurrence of extrapyramidal side effects was also monitored. The improvement in PANSS was approximately three times greater in the risperidone group, both at week six and at endpoint. In addition, the onset of therapeutic effects was quicker in the risperidone group. Finally, the risperidone group need 10 times less anticholinergic medication to control the extrapyramidal side effects than did the haloperido group. According to this study, risperidone showed a greater improvement in schizophrenic symptoms th haloperidol.
j) Risperidone was less effective as monotherapy when compared to combination therapy of haloperidol and amitriptyline in patients with coexisting psychotic and depressive disorders. In this double-blind multicenter study, 123 patients were randomized to receive either risperidone (dose titrated to 8 milligram (mg) by the end of week 1) or the combination of haloperidol and amitriptyline (doses titrated to 10 mg a 200 mg by the end of week 1). For all patients, doses were then adjusted under double blind conditions over the next 5 weeks based on response. At endpoint, the mean effective daily dose was 6.9 mg risperidone, and 9 mg haloperidol in combination with 180 mg amitriptyline. In the 98 patients who completed at least 3 weeks of treatment, Brief Psychiatric Rating Scale (BPRS) scores decreased in both treatment groups, but the reduction in the combination treatment group was significantly greater than the risperidone treated group (p=0.004). The proportion of patients achieving at least 50% improvement in BPRS scores was also significantly higher with combination therapy (p = 0.002). Greater benefit by combination therapy was still observed in an intent-to-treat analyses of the 123 patients. Use of

anticholinergic medication for extrapyramidal symptoms was higher in the risperidone group (Muller-Siecheneder et al, 1998)

4.6.AU.6 Adverse Effects

a) The results of one study suggest that patients receiving atypical antipsychotics have a higher incidenc of PANCREATITIS than patients receiving a conventional antipsychotic medication. In a retrospective, pharmacovigilance study, 192 cases of pancreatitis were identified in patients taking clozapine (mean do 306.7 milligrams (mg)/day), olanzapine (mean dose, 15 mg/day), risperidone, (mean dose, 4 mg/day) or haloperidol (mean dose, 8.2 mg/day). Of the identified cases, 40%, 33%, and 16% were related to treatment with the atypical antipsychotic medications clozapine, olanzapine, or risperidone, respectively, compared with 12% of the cases which were related to the conventional neuroleptic, haloperidol. In most patients, time to onset of pancreatitis was within 6 months after initiation of treatment (Koller et al, 2003a

4.6.AV Sertindole

4.6.AV.1 Schizophrenia

a) Sertindole appears to be as effective as haloperidol in the treatment of schizophrenia. In a placebo-controlled, double-blind, multicenter trial involving 497 hospitalized patients, sertindole 12 milligrams (n=76), 20 mg (n=68), or 24 mg (n=72) was compared with haloperidol 4 mg (n=71), 8 mg (n=67), or 16 (n=70) and placebo (n=73). All doses of both sertindole and haloperidol were significantly more effective than placebo in treating the positive symptoms of schizophrenia (hallucinations, delusions and disorganiz thinking) as measured by Positive and Negative Symptom Scale (PANSS) scores. With negative sympto (emotional withdrawal and paucity of thoughts), only sertindole 20 mg was significantly more effective tha placebo in reducing PANSS negative scale scores. Extrapyramidal symptoms (EPS) were not observed with sertindole; in contrast, patients receiving any dose of haloperidol experienced significantly more EPS than patients receiving placebo or any dose of sertindole. The most common adverse effects associated with sertindole included nasal congestion and decreased ejaculatory volume, thought to be related to its alpha-1 activity; other adverse effects were mild prolongation and mild weight gain (Anon, 1996a; Anon, 1996b).

4.6.AW Sulpiride

4.6.AW.1 Schizophrenia

a) Sulpiride in doses of 300 to 1200 milligrams daily has been comparable in efficacy to chlorpromazine 150 to 675 mg daily (Peselow & Stanley, 1982; Bratfos & Haug, 1979), trifluoperazine 15 to 45 mg daily (Edwards et al, 1980), haloperidol 0.5 to 10.5 milligrams daily (Cassano et al, 1975), and perphenazine 4 80 mg daily) (Peselow & Stanley, 1982) in patients with acute or chronic schizophrenia. One study (Taverna et al, 1972) reported the superiority of sulpiride 200 to 800 mg/day over haloperidol 1 to 4 mg/d with regard to overall global improvement, as well as improvement of thought content and mood state; however, the doses of haloperidol in this study may have been too low to enable a fair comparison.

b) In patients with severe chronic schizophrenia, higher doses of sulpiride (800 to 3200 milligrams daily) were as effective as haloperidol 6 to 24 milligrams daily in controlling symptoms (Gerlach et al, 1985; Munk-Andersen et al, 1984). Median doses in these studies were 1600 to 2000 mg sulpiride and 12 mg haloperidol daily.

c) In some studies, greater benefits of sulpiride have been observed on certain target symptoms, includi more improvement in thought content and mood state as compared with haloperidol (Taverna et al, 1972 and greater reductions in aggressiveness and hyperactivity as compared with chlorpromazine (Peselow Stanley, 1982). However, haloperidol tended to be more effective than sulpiride in a subgroup of chronic disturbed patients who had received long-term neuroleptic therapy in one study (Munk-Andersen et al, 1984), and perphenazine had a greater effect on hallucinations in another (Peselow & Stanley, 1982).

4.6.AW.2 Adverse Effects

a) Haloperidol, chlorpromazine, and sulpiride were compared in normal volunteers to test mood state (McClelland et al, 1990). The twelve volunteers were assessed using sixteen visual analog scales such a elapsed time estimation, tapping rate, body sway and tremor, etc. The volunteers were divided into four groups: haloperidol (3 milligrams per day), chlorpromazine (50 mg per day), sulpiride (400 milligrams per day), and a placebo group. The results showed chlorpromazine and haloperidol users experienced reduc alertness and well-being. Haloperidol reduced feelings of "calmness" in the volunteers. Sulpiride did not significantly alter vision in the volunteers. Haloperidol affected the information processing function, but di not affect motor ability and speed in the group taking this drug.

4.6.AX Sultopride

4.6.AX.1 Psychotic disorder, acute

a) A double-blind, randomized, multicenter study was carried out in a total of 64 acutely psychotic inpatients (32 on sultopride 800 milligrams (mg), and 32 on haloperidol 20 mg daily) over a 15-day perio Efficacy of treatment was assessed using Diagnostic Statistical Manual (DSM) III criteria, a visual analog scale evaluating overall symptom severity, a positive symptom scale, the Arbeitsgemeinschaft fuer Methodik und Dokumentation in der Psychatrie (AMDP)-4 and -5 scales, and an alertness scale. At study end, both groups had improved significantly and comparably. Sultopride was more effective than

haloperidol after 3 days of treatment on several AMDP items, such as mental dissociation, anxiety, cognitive disturbances, depression and apathy. According to the CHESS list of somatic symptoms, haloperidol induced more extrapyramidal symptoms than sultopride (Ropert et al, 1989).

4.6.AY Tetrabenazine

4.6.AY.1 Tardive dyskinesia

a) Tetrabenazine and haloperidol were similarly effective in an 18-week randomized study (n=13); haloperidol tended to be more effective during the first two weeks of therapy (Kazamatsuri et al, 1973). T small patient population in this study limits adequate comparison.

4.6.AZ Tetrahydrocannabinol

4.6.AZ.1 Chemotherapy-induced nausea and vomiting

a) Tetrahydrocannabinol was compared with haloperidol in 52 patients experiencing nausea and vomitir resulting from cancer chemotherapy. Subjective evaluation was made by the patient with regard to numb of vomiting episodes, preference, "efficacy", and adverse reactions. Doses were 10 mg tetrahydrocannabinol and 2 mg haloperidol, given 2 hours prior and 30 minutes prior to cancer chemotherapy then at 1 hour and then 3 to 4 hour intervals times 8 doses after cancer chemotherapy. Efficacy was judged equal for the two regimens, and about one-half had relief with the crossover regime when the first regimen failed. Adverse effects were more frequent and more severe in the tetrahydrocannabinol group (Neidhart et al, 1981).

4.6.BA Thioridazine

4.6.BA.1 Psychotic disorder

a) In a single-blind, randomized parallel study lasting six weeks, haloperidol (mean dose of 2.9 milligrams/day) was compared with thioridazine (mean dose of 145 milligrams/day) in 13 patients with psychosis associated with HIV infection. Based on several scales for assessing psychoses, the two drug produced modest improvement, but were not statistically different in the outcomes produced. All haloperidol-treated patients developed extrapyramidal side effects, while 60% of those taking thioridazin developed them (Sewell et al, 1994).

4.6.BB Thiothixene

4.6.BB.1 Psychotic disorder

a) Thiothixene is not as useful as haloperidol in the treatment of psychotic symptomatology including schizophrenia, manic-depression, psychotic reactions secondary to trauma, and psychosis with mental deficiencies (Howard, 1974).

b) A single-blind study compared the efficacy of haloperidol and thiothixene in the treatment of acute organic mental syndromes in 14 patients in a general hospital setting (Peterson & Bongar, 1989). The do of haloperidol was 4.8 to 15 milligrams and for thiothixene, 2 to 7 milligrams. Evaluations were performed using the Brief Psychiatric Rating Scale (BPRS). There was a trend toward greater reductions in magnitu of BPRS scores in patients treated with thiothixene. Symptoms most affected by treatment included: anergia, thought disturbance, level of activity, hostility, and suspicion. The small sample size was a limitation of this study and larger studies are needed to adequately compare the 2 agents.

c) In a double-blind study of borderline and schizotypal patients treated with thiothixene or haloperidol, 84% of patients improved markedly or moderately by 3 months (Serban & Siegel, 1984). A better respon was seen in those patients receiving thiothixene as compared with haloperidol. Mean dosages were 9.4 7.6 milligrams/day for thiothixene and 3 +/- 0.8 milligrams/day for haloperidol.

d) A 24-week, double-blind study compared the safety and efficacy of haloperidol and thiothixene in 46 schizophrenic outpatients (Abuzzahab & Zimmerman, 1982). Mean dosages used were 17.5 milligrams/ for haloperidol and 31.8 milligrams/day for thiothixene. Haloperidol was equal to, and in some parameter superior to, thiothixene in these patients. Haloperidol also appeared to produce fewer central nervous system adverse effects.

4.6.BC Timiperone

4.6.BC.1 Schizophrenia

a) Haloperidol (maximum dose 18 mg/day) was compared with timiperone (maximum dose 12 mg/day) i 206 patients treated for schizophrenia for up to 12 weeks. The authors concluded that timiperone was superior to haloperidol in efficacy and that the drugs were comparable in safety (Kariya et al, 1983).

4.6.BD Trifluoperazine

4.6.BD.1 Psychotic disorder

a) Trifluoperazine 1 mg milligram orally twice a day was reported similarly effective as haloperidol 0.5 milligram orally twice a day in the treatment of behavioral symptoms associated with chronic brain

syndrome and senile psychosis in a controlled study involving 54 elderly patients (Lovett et al, 1987). Based upon CGI scores, improvement was observed in 86% and 90% of patients receiving trifluoperazin and haloperidol, respectively. Several other rating scales demonstrated significant advantages of trifluoperazine. Due to the small number of patients in this trial, it is unclear if these findings are significa and more studies are required in larger patient populations.

4.6.BE Trimethobenzamide

4.6.BE.1 Vomiting

a) SUMMARY: Trimethobenzamide does not appear to be as effective as the phenothiazines for reducti of nausea and vomiting (Purkis, 1965; Bardfeld, 1966; Shields et al, 1971).

b) Trimethobenzamide was compared with haloperidol and prochlorperazine for emesis. In this study of males, aged 17 to 49 years, 6 patients received trimethobenzamide in a dose of 2.5 mg/kg IM as a single dose. Emesis was induced with a threshold emetic dose of apomorphine. Trimethobenzamide was found be effective in only 50% of the cases at the recommended dose. All patients responded to prochlorperaz 0.1 mg/kg and haloperidol 0.007 mg/kg (Shields et al, 1971).

4.6.BF Valproic Acid

4.6.BF.1 Mania

a) Divalproex and haloperidol were found to be equally efficacious in the management of acute psychoti mania in patients with bipolar disorder. In this study, patients (n=36) were randomized to therapy with divalproex (20 mg/kg/day) or haloperidol (0.2 mg/kg/day) for a period of six days. Divalproex was given a dosage considered to be a loading dose to produce valproate concentrations of approximately 80 mg/L after one day of treatment. Improvement was greatest during the first three days of treatment; extrapyramidal side effects were observed much more often in patients treated with haloperidol (McElroy al, 1996).

4.6.BG Ziprasidone

Chronic schizophrenia

Schizophrenic episode, acute

4.6.BG.1 Chronic schizophrenia

a) Ziprasidone was as effective as haloperidol in treating overall symptomatology, was more effective in the treatment of negative symptoms, and was better tolerated, in the long-term treatment of outpatients v stable schizophrenia. In a 28-week, double-blind, flexible-dose, parallel-group clinical trial, ziprasidone a haloperidol both improved overall symptomatology in 227 patients with chronic or subchronic schizophrenia. Patients who received ziprasidone had a significantly higher rate of improvement in the treatment of negative symptoms (48% of patients showed improvement) compared to patients who received haloperidol (33% of patients showed improvement). For patient assessment, the Positive and Negative Syndrome Scale (PANSS), the Clinical Global Impressions-Severity of Illness scale (CGI-S), a the Montgomery-Asberg Depression Rating Scale (MADRS) were used at baseline and weeks 3, 6, 16, a 28. In the ziprasidone group, patients received a starting dose of 40 milligrams per day (mg/d) on the firs days and 80 mg/d on day 3. The ziprasidone dose could be increased to a maximum of 120 mg/d in the second week and up to 160 mg/d in the third week. For the haloperidol group, patients received a startin dose of 5 mg/d, which could be increased to a maximum of 10 mg/d during the second week and 15 mg/ during the third week of treatment. At week 28, the mean doses of ziprasidone and haloperidol were 116 mg/d and 8.6 mg/d, respectively. Adverse events were evaluated using the Simpson-Angus scale, the Barnes Akathisia scale, and the Abnormal Involuntary Movement Scale (AIMS). Adverse events were reported in 85% of patients in the haloperidol group and 77% in the ziprasidone group; twice as many patients receiving haloperidol (16%) compared to ziprasidone (8%) discontinued the study due to treatment-related adverse events. There was also a distinct difference in the percentage of patients who developed movement disorders; 41% in the haloperidol group compared to 15% in the ziprasidone group although this difference was not statistically significant (Hirsch et al, 2002).

4.6.BG.2 Schizophrenic episode, acute

a) Acute exacerbations: ziprasidone 160 mg daily, haloperidol 15 mg daily comparable in efficacy (reduction of BPRS scores). Ziprasidone 4 to 40 mg/day less effective (Anon, 1996a).

b) Ziprasidone 160 milligrams (mg) and haloperidol 15 mg were both effective in improving overall psychopathology in patients with an acute exacerbation of schizophrenia or schizoaffective disorder (Go et al, 1998). In a double-blind, dose-ranging study, patients received either haloperidol 15 mg/day (n=17) or ziprasidone 4 mg (n=19), ziprasidone 10 mg (n=17), ziprasidone 40 mg (n=17), or ziprasidone 160 mg (n=20). Despite 46 patients failing to complete the study, intention-to-treat analysis showed a trend towa

significance for the ziprasidone dose response on the Brief Psychiatric Rating scale (p=0.08) and a statistically significant dose response for the Clinical Global Impression (CGI) scale (p less than 0.001). Changes in the CGI severity score were significantly changed from baseline as compared to the ziprasidone 4 mg group for both the haloperidol group (p less than 0.01) and the ziprasidone 160 mg gro (p=0.001). Study termination was due to 18 patients having a lack of efficacy (4 in the haloperidol group) due to liver transaminase elevations in ziprasidone groups, and 23 for unrelated reasons.
c) In hospitalized patients, the mean reductions in BPRS total, BPRS agitation items, and CGI were statistically greater after INTRAMUSCULAR (IM) ziprasidone than IM haloperidol, and this continued following conversion to oral treatment. The study was a multicenter, 7-day, randomized, open-label, parallel-group study in 7 countries (n=132). Patients received either an initial dose of ziprasidone 10 milligrams (mg) IM, followed by up to 3 days of flexible-dose IM ziprasidone (5 mg to 20 mg every 4 to 6 hours prn) and continued with oral treatment (80 mg to 200 mg/day) to day 7 (n = 90), or haloperidol IM (2.5 mg to 10 mg) on entry, followed by 2.5 mg to 10 mg IM every 4 to 6 hours prn up to 3 days followed oral haloperidol 10 mg/day to 80 mg/day to day 7 (n = 32). Ziprasidone was associated iwth a lower incidence of movement disorders compared to haloperidol (Brook et al, 2000).

4.6.BH Zotepine

Delusional disorder - Depression

Schizophrenia

4.6.BH.1 Delusional disorder - Depression

a) Zotepine 150 to 200 mg/day was as effective as a butyrophenone (haloperidol or bromperidol) approximately 10 mg/day, and had a better adverse effect profile than the butyrophenones, in two open, four-week studies of 31 patients with delusional depression (Wolfersdorf et al, 1994). All patients receive an antidepressant (maprotiline or amitriptyline, 150 mg/day) in addition to zotepine or the butyrophenone According to a 24-item version of the Hamilton depression scale, significant overall improvement was obtained with both zotepine and haloperidol or bromperidol. After one and two weeks of treatment, the improvement was significantly greater with zotepine. For a six-item list of delusional symptoms alone, bo groups improved significantly, and for the remaining non-delusional symptoms, the improvement was significant for both groups again (with significantly greater improvement with zotepine in the first two weeks). Zotepine, with its greater tolerability, is thus in many instances a viable alternative to highly pote butyrophenones in the treatment of delusional depression.

4.6.BH.2 Schizophrenia

a) There was no difference in efficacy between zotepine 50 milligrams (mg) 3 times daily and haloperido mg 3 times daily in the treatment of positive symptoms of schizophrenia in Chinese patients. After a washout period, patients (n=70) were randomly assigned to double-blind treatment with fixed doses of zotepine or haloperidol for 6 weeks. Although all of the efficacy measures tended to have greater score changes for haloperidol than for zotepine, there were no statistically significant differences between grou The greater score changes with haloperidol may have represented a lack of equivalency of doses. Dizziness, weight gain, and pulse rate were significantly higher with zotepine than with haloperidol, while the haloperidol group reported significantly more akathisia (Hwang et al, 2001).
b) Zotepine (mean dosage 309 mg/day) was as effective as haloperidol (mean dosage 14.5 mg/day) ora for six weeks in a randomized, double-blind study of 40 schizophrenics, and had a better side effect profi than haloperidol. Improvement measured according to the Brief Psychiatric Rating Scale (BPRS) total score reached statistical significance for both drugs on day 3, and at no point was there a significant difference between the two groups. For the individual BPRS factors, anxiety/depression was significantly improved in the zotepine group on day 14, as compared to haloperidol. Clinical Global Impression scores decreased similarly for both groups. Anticholinergic and extrapyramidal side effects were more common the haloperidol group. Liver function abnormalities were recorded in 12 and 6 patients from the zotepine and haloperidol groups, respectively, with one zotepine patient withdrawing from the study due to elevate liver enzymes (Fleischhacker et al, 1989).
c) Zotepine was more effective than haloperidol in controlling the negative effects of schizophrenia, and demonstrated better tolerability than haloperidol in a randomized, double-blind study of thirty schizophrer patients with similar characteristics (Barnas et al, 1992). The patients randomly received either zotepine to 150 mg/day (mean 94.4 mg/day) or haloperidol 2 to 6 mg/day (mean 4.2 mg/day) in oral capsule form the study period of seven weeks. Only zotepine significantly decreased schizophrenic behavior scores in the rating scales. Eight haloperidol patients did not complete the course due to side effects, while none o the zotepine patients experienced significant adverse effects. The authors noted that as most improved symptomatology was seen in the zotepine group after many haloperidol patients had already dropped ou of the study, longer therapy with haloperidol may have been more effective. However, zotepine was mor useful as it was better tolerated, and this must be recognized as a benefit of zotepine over haloperidol.
d) Similar advantages for zotepine (150 to 300 mg/day) versus haloperidol (10 to 20 mg/day) were

obtained in an 8-week, randomized, double-blind study of 126 schizophrenic patients. The mean reductic in Brief Psychiatric Rating Scale score was greater for zotepine compared to haloperidol (17.03 vs 13.45 not statistically significant). According to the Scale for Assessment of Negative Symptoms, zotepine was significantly more effective (p less than 0.05), and the adverse effect profile favored zotepine, particularly with respect to extrapyramidal symptoms. There were no occurrences of akathisia in patients treated wit zotepine compared with seven for haloperidol (Petit et al, 1996). Fixed doses of zotepine (225 mg/day) a haloperidol (12 mg/day) for four weeks in 26 schizophrenic patients resulted in comparable therapeutic efficacy with a clear advantage for zotepine with respect to global tolerability and extrapyramidal adverse effects (Klieser et al, 1991).

4.6.BI Zuclopenthixol

Dementia

Psychotic disorder

Tardive dyskinesia

4.6.BI.1 Dementia

a) Zuclopenthixol 4 to 5 milligrams orally daily was at least as effective as the combination of haloperido to 1.5 milligrams daily plus levomepromazine 6 to 8 milligrams daily in the treatment of elderly demented patients (over 80 years of age) with primary symptoms of agitation and aggressiveness in a 4-week, double-blind study (Fuglum et al, 1989). Zuclopenthixol was significantly superior to the combination at 2 weeks of treatment, but not at 4 weeks.

b) In an earlier double-blind study, oral zuclopenthixol 5 milligrams daily and oral haloperidol 0.5 milligra daily were associated with similar but minimal improvement in several rating scales (Clinical Global Impressions, Gottfries-Cronholm geriatric rating scale, Crichton geriatric rating scale) in elderly patients with dementia (Gotestam et al, 1981). Trends toward the superiority of zuclopenthixol were reported in some areas but these differences are of doubtful clinical significance.

4.6.BI.2 Psychotic disorder

a) Oral zuclopenthixol was similarly as effective as oral haloperidol in the treatment of chronic schizophrenia in a double-blind study involving 63 inpatients (Heikkila et al, 1981a). Mean daily doses of zuclopenthixol at week 1 and week 12 of therapy were 36 mg and 40 mg, respectively; corresponding doses of haloperidol were 7 mg and 10 mg, respectively. Adverse effects occurred with similar frequency although there was a trend toward a lower incidence of extrapyramidal effects in zuclopenthixol-treated patients. Similar findings were reported in another controlled study comparing oral haloperidol and zuclopenthixol in acute psychosis (Wistedt et al, 1991).

b) In 1 randomized study, intramuscular zuclopenthixol acetate was reported comparable in efficacy to parenteral haloperidol in treating patients with acute psychosis or an exacerbation of chronic psychosis; extrapyramidal symptoms were more frequent in haloperidol-treated patients (Bobon & De Bleeker, 1989

c) Intramuscular zuclopenthixol decanoate and haloperidol decanoate were similarly effective in the maintenance treatment of chronic schizophrenia in a 9-month double-blind study involving 64 patients (Wistedt et al, 1991). The average doses of zuclopenthixol decanoate and haloperidol decanoate at wee 36 of treatment were 284 milligrams and 92 milligrams, respectively; most patients received injections every 4 weeks. The incidence of extrapyramidal reactions was similar with both agents in this study, whic is in contrast to studies comparing shorter-acting formulations of haloperidol and zuclopenthixol. Other adverse effects also occurred with similar frequency; however, autonomic symptoms (eg, orthostatic dizziness, palpitations) tended to decrease with zuclopenthixol decanoate over the 9 months of treatmen whereas they increased with haloperidol decanoate during this period.

d) A double-blind, randomized study in 49 hospitalized patients with acute psychosis or exacerbation of chronic psychosis compared the clinical profile and frequency and severity of unwanted effects of oral zuclopenthixol and haloperidol (Heikkila et al, 1992). Patients initially received one of the two drugs with average daily dose of 33.5 milligrams or 7.6 milligrams, respectively, with doses titrated depending on patient response. Clinical efficacy scales and a side effect monitor were employed to evaluate efficacy a safety at baseline, one, two, four, six, and eight weeks with four weeks being the minimum study period analyzed. Both drugs were found to be effective in controlling psychotic episodes with no significant difference, and no difference in the incidence of side effects was seen. Zuclopenthixol had a slightly mor rapid onset of action as well as an earlier onset and elimination of extrapyramidal symptoms. Zuclopenthixol also appeared to have a stronger anxiolytic-antidepressant effect than haloperidol. The authors suggested that this study confirmed previous studies that both zuclopenthixol and haloperidol ar very efficacious and equally safe in treating acute psychoses.

e) Haloperidol (53 to 120 milligrams intramuscularly or orally over 6 days), zuclopenthixol (64 to 259 milligrams intramuscularly and orally over 6 days) and zuclopenthixol acetate (162 to 220 milligrams intramuscularly over 6 days) were compared in the treatment of acute psychoses (48 patients), mania (2

patients) and exacerbation of chronic psychoses (73 patients). Several measures of effectiveness, differi according to the initial diagnosis, were evaluated. The number of doses administered was significantly different in the zuclopenthixol acetate group (1 to 4) versus the haloperidol group (1 to 26) and the zuclopenthixol group (1 to 22). There was no significant difference in efficacy among any treatment regimens or initial diagnoses. Haloperidol caused significantly more hypokinesia during the first 24 hours but after that period there were no significant differences in any adverse effects. Based on the decreased number of doses administered, the authors concluded that zuclopenthixol acetate would be a useful addition to the therapeutic armamentarium (Baastrup et al, 1993).

4.6.BI.3 Tardive dyskinesia

a) It has been hypothesized that neuroleptics with both D1 and D2 antagonist activity are better drugs fo suppressing tardive dyskinesia than pure D2 antagonists. A study compared the effects of the mixed D1/ antagonist zuclopenthixol to that of the pure D2 antagonist haloperidol (Lublin et al, 1991). The double-blind crossover study consisted of 15 patients, who took each drug for three weeks. There was a six wee washout period. The subjects took either oral haloperidol 0.5 milligram twice a day, or oral zuclopenthixo milligrams twice a day. During treatment, benzodiazepines were prescribed on a prn basis for anxiety. Tardive dyskinesia and Parkinson-like symptoms were recorded on video tape and were scored by two raters. The changes and differences in the two groups regarding aggravation and suppression of tardive dyskinesia and Parkinson-like symptoms were compared using a paired t-test. There was no significant difference in the induction of tardive dyskinesia suppression and tardive dyskinesia withdrawal. Both drug induced or aggravated Parkinson-like symptoms. There were no differences between the groups. This study did not support the animal findings that a D1 component in a neuroleptic drug would lead to a stronger tardive dyskinesia suppression and to less withdrawal tardive dyskinesia.

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Last Modified: June 23, 2009

DRUGDEX® Evaluations

PALIPERIDONE

0.0 Overview

1) Class
- **a)** This drug is a member of the following class(es):
  Antipsychotic
  Benzisoxazole

2) Dosing Information
- **a)** Adult
  - **1)** Schizophrenia
    - **a)** extended-release tablets, initial 6 mg/day ORALLY; may increase by 3 mg/day increments at intervals of r maximum of 12 mg/day (Prod Info INVEGA(TM) extended-release oral tablets, 2006)

3) Contraindications
- **a)** hypersensitivity to paliperidone, risperidone, or to any product component (Prod Info INVEGA(R) extended-release

4) Serious Adverse Effects
- **a)** Death
- **b)** Ischemia
- **c)** Tachyarrhythmia

5) Clinical Applications
- **a)** FDA Approved Indications
  - **1)** Schizophrenia

1.0 Dosing Information

Drug Properties

Storage and Stability

Adult Dosage

1.1 Drug Properties

A) Information on specific products and dosage forms can be obtained by referring to the Tradename List (Product In

B) Synonyms
Paliperidone

C) Physicochemical Properties
- **1)** Molecular Weight
  - **a)** 426.49 (Prod Info INVEGA(TM) extended-release oral tablets, 2006)
- **2)** Solubility
  - **a)** Paliperidone is practically insoluble in water, 0.1N sodium hydroxide solution, and hexane; slightly soluble dimethylformamide; and sparingly soluble in 0.1N hydrochloric acid and methylene chloride (Prod Info INVEG release oral tablets, 2006).

1.2 Storage and Stability

A) Preparation
- **1)** Oral route
  - **a)** ADMINISTRATION
    - **1)** Paliperidone may be taken without regard to meals (Prod Info INVEGA(TM) extended-release oral tal
    - **2)** Extended-release tablets must be swallowed whole with liquid, do not chew, divide, or crush (Prod In extended-release oral tablets, 2006)

B) Oral route
- **1)** Tablet, Extended Release
  - **a)** Store paliperidone extended-release tablets at 25 degrees Celsius (77 degrees Fahrenheit), with excursio 30 degrees Celsius (59 to 86 degrees Fahrenheit). Protect from moisture (Prod Info INVEGA(TM) extended-r 2006).

1.3 Adult Dosage

Normal Dosage

Dosage in Renal Failure

1.3.1 Normal Dosage

1.3.1.A Oral route

1.3.1.A.1 Schizophrenia

a) The recommended dose of extended-release oral tablets is 6 milligrams/day (mg/day) with increases intervals of at least 5 days, to a maximum of 12 mg/day. In some patients, a lower starting dose of 3 mg/ Dose increases above 6 mg/day should only be made after clinical reassessment (Prod Info INVEGA(TM oral tablets, 2006).

1.3.2 Dosage in Renal Failure

A) In mild renal impairment (creatinine clearance 50 to less than 80 milliliters/minute (mL/minute)), the maximum 6 mg once daily. In moderate to severe renal impairment (creatinine clearance 10 to less than 50 mL/minute), the recommended dose is 3 mg once daily (Prod Info INVEGA(TM) extended-release oral tablets, 2006).

2.0 Pharmacokinetics

Drug Concentration Levels

ADME

2.2 Drug Concentration Levels

A) Peak Concentration

1) 8.85 ng/mL (single-dose, oral solution) (Vermeir et al, 2008)

a) The mean Cmax (standard deviation) was 8.85 ng/mL (+/- 1.31 ng/mL) after a single, 1-mg dose of palipe administered to healthy, caucasian, male volunteers in the fasted state, in an open-label pharmacokinetic stu were 40 to 63 years of age (mean, 51.2 years) and weighed 68.7 kg to 78.6 kg (mean, 73.38 kg) with a mean 25.5 kg/m(2) (range, 24 to 28 kg/m(2)). There was no difference in the Cmax between the 2 poor and 3 exten metabolizers. Nor was there a difference in Cmax and the genotypic expression of UGT1A1 and UGT1A6 me (Vermeir et al, 2008).

B) Time to Peak Concentration

1) 24 hours (extended-release tablets) (Prod Info INVEGA(TM) extended-release oral tablets, 2006)

a) After a single dose of paliperidone, plasma concentration reaches its peak in approximately 24 hours (Pro extended-release oral tablets, 2006).

b) The median Tmax was 1.5 hr (range, 1 to 1.5 hr) after a single, 1-mg dose of paliperidone solution admini caucasian, male volunteers in the fasted state, in an open-label pharmacokinetic study (n=5). The males wer age (mean, 51.2 years) and weighed 68.7 kg to 78.6 kg (mean, 73.38 kg) with a mean body mass index of 25 to 28 kg/m(2) (Vermeir et al, 2008).

C) Steady State

1) 4 to 5 days (Prod Info INVEGA(TM) extended-release oral tablets, 2006)

a) Paliperidone reaches steady-state concentration within 4 to 5 days after initiation of therapy. The steady-s ratio for a 9-mg dose was 1.7 (range, 1.2 to 3.1) (Prod Info INVEGA(TM) extended-release oral tablets, 2006

D) Area Under the Curve

1) 187 ng x hr/mL (Vermeir et al, 2008)

a) The mean AUC (0 to infinity) was 187 ng x hr/mL (standard deviation of +/- 29.3 ng x hr/mL) after a single paliperidone solution administered to healthy, caucasian, male volunteers in the fasted state, in an open-labe study (n=5). The males were 40 to 63 years of age (mean, 51.2 years) and weighed 68.7 kg to 78.6 kg (mean mean body mass index of 25.5 kg/m(2) (range, 24 to 28 kg/m(2)). There was no difference in the AUC (0 to in 24 hr) between the 2 poor and 3 extensive CYP2D6 metabolizers. Nor was there a difference in AUC and the of UGT1A1 and UGT1A6 metabolizing enzymes (Vermeir et al, 2008).

b) The area under the curve concentration (AUC) of paliperidone was not reported in patients with normal re the average AUC was increased among patients with renal impairment due to reduced clearance. Following a milligram dose of paliperidone extended-release, there was a 1.5-fold increase in drug exposure among patie impairment (creatinine clearance (CrCl) 50 to less than 80 milliliters/minute (mL/min)); a 2.6-fold increase am moderate renal impairment (CrCl 30 to less than 50 mL/min); and a 4.8-fold increase among those with severe (CrCl 10 to less than 30 mL./min) (Prod Info INVEGA(TM) extended-release oral tablets, 2006).

2.3 ADME

Absorption

Distribution

Metabolism

Excretion

Elimination Half-life

2.3.1 Absorption

A) Bioavailability

1) 28% (extended-release tablet) (Prod Info INVEGA(TM) extended-release oral tablets, 2006)

a) The absolute oral bioavailability of paliperidone extended-release tablet is 28% (Prod Info INVEGA(TM oral tablets, 2006).

B) Effects of Food

1) Increase peak concentration (Cmax) by 60% and mean area under the curve (AUC) by 54% (Prod Info IN release oral tablets, 2006)

a) After administration of paliperidone extended-release 12 milligrams to healthy ambulatory individuals, calorie meal increased mean peak concentration (Cmax) and mean area under the curve concentration (by 60% and 54%, respectively, compared with administration under fasting states (Prod Info INVEGA(TM oral tablets, 2006).

2.3.2 Distribution

A) Distribution Sites

1) Protein Binding

a) 74% (Prod Info INVEGA(TM) extended-release oral tablets, 2006)

1) The plasma protein binding of paliperidone is 74% (Prod Info INVEGA(TM) extended-release ora

B) Distribution Kinetics

1) Volume of Distribution

a) 487 L (Prod Info INVEGA(TM) extended-release oral tablets, 2006)

1) Paliperidone has a volume of distribution (Vd) of 487 liters (L) (Prod Info INVEGA(TM) extended- 2006).

2.3.3 Metabolism

A) Metabolism Sites and Kinetics

1) Liver: limited (Vermeir et al, 2008; Prod Info INVEGA(TM) extended-release oral tablets, 2006)

a) While in vitro data indicated that paliperidone was metabolized by cytochrome P450 2D6 (CYP2D6) a isozymes, these isozymes played a limited role in the overall elimination of paliperidone based on in vivo was found between extensive and poor metabolizers of CYP2D6 substrates in the clearance or exposure Info INVEGA(TM) extended-release oral tablets, 2006).

b) There were 4 primary metabolic pathways identified in vivo, each accounting for no more than 10% o dealkylation, hydroxylation, dehydrogenation, and benzisoxazole scission (Vermeir et al, 2008).

c) Metabolism was limited after a single, 1-mg dose of paliperidone solution administered to healthy, cau volunteers in the fasted state, in an open-label pharmacokinetic study (n=5). On average the 4 identified accounted for approximately 3% to 5% of the dose. The males were 40 to 63 years of age (mean, 51.2 y 68.7 kg to 78.6 kg (mean, 73.38 kg) with a mean body mass index of 25.5 kg/m(2) (range, 24 to 28 kg/m 2008).

B) Metabolites

1) M1 (Vermeir et al, 2008)

a) The pathway for paliperidone to M1 formation was oxidative N-dealkylation, after a single, 1-mg dose solution administered to healthy, caucasian, male volunteers in the fasted state, in an open-label pharma The males were 40 to 63 years of age (mean, 51.2 years) and weighed 68.7 kg to 78.6 kg (mean, 73.38 mass index of 25.5 kg/m(2) (range, 24 to 28 kg/m(2)). A mean of 4.55% (standard deviation, +/-1.42%) o excreted in the urine as M1 metabolite (Vermeir et al, 2008).

2) M9 (Vermeir et al, 2008)

a) The pathway for paliperidone to M9 formation was monohydroxylation, after a single, 1-mg dose of pa administered to healthy, caucasian, male volunteers in the fasted state, in an open-label pharmacokineti males were 40 to 63 years of age (mean, 51.2 years) and weighed 68.7 kg to 78.6 kg (mean, 73.38 kg) w mass index of 25.5 kg/m(2) (range, 24 to 28 kg/m(2)). A mean of 3.75% (standard deviation, +/-1.42%) o excreted in the urine as M1 metabolite. The detection of M9 was in the urine of extensive metabolizers b metabolizers (Vermeir et al, 2008).

3) M10 (Vermeir et al, 2008)

a) The pathway for paliperidone to M10 formation was benzisoxazole scission and hydroxylation, after a paliperidone solution administered to healthy, caucasian, male volunteers in the fasted state, in an open- study (n=5). The males were 40 to 63 years of age (mean, 51.2 years) and weighed 68.7 kg to 78.6 kg (m mean body mass index of 25.5 kg/m(2) (range, 24 to 28 kg/m(2)). M10 was excreted in the feces (Verme

4) M11 (Vermeir et al, 2008)

a) The pathway for paliperidone to M11 formation was benzisoxazole scission, after a single, 1-mg dose

solution administered to healthy, caucasian, male volunteers in the fasted state, in an open-label pharma
The males were 40 to 63 years of age (mean, 51.2 years) and weighed 68.7 kg to 78.6 kg (mean, 73.38
mass index of 25.5 kg/m(2) (range, 24 to 28 kg/m(2)). M11 was excreted in the feces (Vermeir et al, 200

5) M12 (Vermeir et al, 2008)

a) The pathways for paliperidone to M12 formation was alcohol dehydrogenation and also nonenzymati
mg dose of paliperidone solution administered to healthy, caucasian, male volunteers in the fasted state,
pharmacokinetic study (n=5). The males were 40 to 63 years of age (mean, 51.2 years) and weighed 68
(mean, 73.38 kg) with a mean body mass index of 25.5 kg/m(2) (range, 24 to 28 kg/m(2)). A mean of 2.7
deviation, +/-1.66%) of the dose was excreted in the urine as M12 metabolite (Vermeir et al, 2008).

6) M16 (Vermeir et al, 2008)

a) The pathway for paliperidone to M16 formation was glucuronidation, after a single, 1-mg dose of palip
administered to healthy, caucasian, male volunteers in the fasted state, in an open-label pharmacokineti
males were 40 to 63 years of age (mean, 51.2 years) and weighed 68.7 kg to 78.6 kg (mean, 73.38 kg) v
mass index of 25.5 kg/m(2) (range, 24 to 28 kg/m(2)). A mean of 4.06% (standard deviation, +/-1.03%) c
excreted in the urine as M16 metabolite (Vermeir et al, 2008).

2.3.4 Excretion

A) Kidney

1) Renal Clearance (rate)

a) 53.1 +/- 9.47 mL/min (Vermeir et al, 2008)

1) The mean renal clearance was 53.1 +/- 9.47 mL/min after a single, 1-mg dose of paliperidone so
healthy, caucasian, male volunteers in the fasted state, in an open-label pharmacokinetic study (n=5
to 63 years of age (mean, 51.2 years) and weighed 68.7 kg to 78.6 kg (mean, 73.38 kg) with a mean
25.5 kg/m(2) (range, 24 to 28 kg/m(2)). The mean clearances (standard deviation) were as follow: cr
113 +/- 10.3 mL/min, glomerular filtration rate, 25.9 +/- 2.36 mL/min; and active renal clearance, 27.
(Vermeir et al, 2008).

2) Renal Excretion (%)

a) 59% (range, 51% to 67%) unchanged (Vermeir et al, 2008; Prod Info INVEGA(TM) extended-release

1) One week following administration of a single oral dose of immediate-release radioactive-paliperi
in 5 healthy volunteers, 59% (range, 51% to 67%) of the dose was excreted into the urine unchange
26% to 41%) was recovered as metabolites, 6% to 12% of the dose was not recovered (Prod Info IN
release oral tablets, 2006).

2) The mean total dose excreted in the urine was 59.4% (standard deviation +/- 7.12%) after a sing
paliperidone solution administered to healthy, caucasian, male volunteers in the fasted state, in an o
pharmacokinetic study (n=5). About half of the renal excretion occurred by active secretion. The M1
metabolites were detected in the urine. The males were 40 to 63 years of age (mean, 51.2 years) ar
78.6 kg (mean, 73.38 kg) with a mean body mass index of 25.5 kg/m(2) (range, 24 to 28 kg/m(2)) (V

B) Feces

1) Not detected (Vermeir et al, 2008)

a) No unchanged drug was recovered in the feces. Fecal excretion did not differ between poor and exte
metabolizers. The M10 and M11 metabolites were detected in the feces (Vermeir et al, 2008).

C) Total Body Clearance

1) Not reported (Prod Info INVEGA(TM) extended-release oral tablets, 2006)

a) Clearance of paliperidone was not reported in patients with normal renal function. However, total clea
was reduced with decreasing estimated creatinine clearance (CrCl). Following administration of a 3-milli
paliperidone extended release, there was a 32% reduction in patients with mild renal impairment (CrCl 5
milliliters/minute (mL/min)); a 64% reduction in patients with moderate renal impairment (CrCl 30 to less
a 71% reduction in patients with severe renal impairment (CrCl 10 to less than 30 mL./min) (Prod Info IN
release oral tablets, 2006).

b) The mean total plasma clearance was 91 +/- 15 mL/min after a single, 1-mg dose of paliperidone solu
healthy, caucasian, male volunteers in the fasted state, in an open-label pharmacokinetic study (n=5). Th
63 years of age (mean, 51.2 years) and weighed 68.7 kg to 78.6 kg (mean, 73.38 kg) with a mean body
kg/m(2) (range, 24 to 28 kg/m(2)) (Vermeir et al, 2008).

2.3.5 Elimination Half-life

A) Parent Compound

1) approximately 23 hours (Prod Info INVEGA(TM) extended-release oral tablets, 2006)

a) The terminal elimination half-life of paliperidone is approximately 23 hours (Prod Info INVEGA(TM) ex
tablets, 2006).

2) renal impairment, 24 hours to 51 hours

a) The mean terminal elimination half-lives of paliperidone following administration of a 3-milligram dose
extended-release were increased to 24 hours, 40 hours, and 51 hours among individuals with mild (creat
50 to less than 80 milliliters/minute (mL/min)), moderate renal impairment (CrCl 30 to less than 50 mL/mi
10 to less than 30 mL./min) renal impairment, respectively. The elimination half-life was 23 hours among
renal function (CrCl at or above 80 mL/min) (Prod Info INVEGA(TM) extended-release oral tablets, 2006

3.0 Cautions

Contraindications

Precautions

Adverse Reactions

Teratogenicity/Effects in Pregnancy/Breastfeeding

Drug Interactions

3.0.A Black Box WARNING

1) Oral (Tablet, Extended Release)

a) Increased Mortality in Elderly Patients with Dementia-Related Psychosis: Elderly patients with dementia-relate with antipsychotic drugs are at an increased risk of death. Analyses of 17 placebo-controlled trials (modal duratio in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of between 1.6 to 1 death in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-tr about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, m appeared to be either cardiovascular (eg, heart failure, sudden death) or infectious (eg, pneumonia) in nature. Ob suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as characteristic(s) of the patients is not clear. Paliperidone is not approved for the treatment of patients with dement (Prod Info INVEGA(R) extended-release oral tablets, 2008).

3.1 Contraindications

A) hypersensitivity to paliperidone, risperidone, or to any product component (Prod Info INVEGA(R) extended-release

3.2 Precautions

A) elderly patients with dementia-related psychosis (unapproved use); increased risk of death; most deaths were attri cardiovascular events (eg, heart failure or sudden death) or infections (eg, pneumonia) (Prod Info INVEGA(R) extende 2008)

B) bradycardia; increased risk of torsade de pointes and/or sudden death (Prod Info INVEGA(R) extended-release or

C) cardiac arrhythmias; use should be avoided due to risk of prolonged QT interval (Prod Info INVEGA(R) extended-r 2008)

D) cardiovascular or cerebrovascular disease or conditions that predispose patients to hypotension (eg, dehydration, antihypertensive medications); increased risk of orthostatic hypotension and syncope (Prod Info INVEGA(R) extended 2008)

E) concomitant use of other drugs known to prolong the QTc interval, such as Class IA (eg, quinidine, procainamide) amiodarone, sotalol) antiarrhythmics, antibiotics (eg, gatifloxacin, moxifloxacin), and antipsychotics (eg, chlorpromazin should be avoided (Prod Info INVEGA(R) extended-release oral tablets, 2008)

F) conditions that may contribute to elevated body temperature (eg, strenuous exercise, extreme heat exposure, dehy anticholinergic use); may disrupt body temperature regulation (Prod Info INVEGA(R) extended-release oral tablets, 20

G) congenital long QT syndrome; increased risk of torsade de pointes and/or sudden death (Prod Info INVEGA(R) ex tablets, 2008)

H) diabetes mellitus or risk factors for diabetes mellitus; increased risk of severe hyperglycemia; monitor blood glucos (R) extended-release oral tablets, 2008)

I) elderly patients, especially elderly women are at increased risk of tardive dyskinesia (Prod Info INVEGA(R) extende 2008)

J) esophageal dysmotility and aspiration may occur; use cautiously in patients at risk for aspiration pneumonia (Prod extended-release oral tablets, 2008)

K) gastrointestinal narrowing, severe (eg, esophageal motility disorders, small bowel inflammatory disease, short gut adhesions or decreased transit time, peritonitis, cystic fibrosis, chronic intestinal pseudoobstruction, or Meckel's diverti swallow a tablet whole; ingestion of drugs in nondeformable controlled-release formulations may cause obstructive sy INVEGA(R) extended-release oral tablets, 2008)

L) hyperglycemia (some cases extreme and associated with ketoacidosis, hyperosmolar coma, or death) is a risk (Pr extended-release oral tablets, 2008)

M) hypokalemia or hypomagnesemia; increased risk of torsade de pointes and/or sudden death (Prod Info INVEGA(R oral tablets, 2008)

N) increased duration of therapy and/or higher cumulative doses; increased risk of tardive dyskinesia (Prod Info INVE release oral tablets, 2008)

O) neuroleptic malignant syndrome, potentially fatal, has been reported in association with antipsychotic drugs; imme drug (Prod Info INVEGA(R) extended-release oral tablets, 2008)

P) Parkinson's disease or dementia with Lewy bodies; increased sensitivity to antipsychotic medications (Prod Info IN release oral tablets, 2008)

Q) seizure disorder, history, or conditions that lower the seizure threshold (Prod Info INVEGA(R) extended-release or

R) suicide risk (Prod Info INVEGA(R) extended-release oral tablets, 2008)

S) tardive dyskinesia, potentially irreversible, may occur (Prod Info INVEGA(R) extended-release oral tablets, 2008)

3.3 Adverse Reactions

Cardiovascular Effects

Endocrine/Metabolic Effects

Gastrointestinal Effects

Hematologic Effects

Immunologic Effects

Neurologic Effects

Other

3.3.1 Cardiovascular Effects

Bradyarrhythmia

Hypotension

Ischemia

Orthostatic hypotension

Prolonged QT interval

Tachyarrhythmia

Tachycardia

3.3.1.A Bradyarrhythmia

1) During the pre-marketing phase, bradycardia was reported infrequently (1 in 100 to 1 in 1000) in patients t paliperidone doses ranging from 3 mg to 12 mg orally once daily (n=2,720); however, causal relationship to p been determined (Prod Info INVEGA(TM) extended-release oral tablets, 2006).

3.3.1.B Hypotension

1) Incidence: 5% geriatric (Tzimos et al, 2008)

2) Geriatric

a) During the double-blind phase of a safety trial in 114 geriatric patients, the incidence of hypotension v patients receiving paliperidone extended-release (ER), compared with 0% (0/38) in patients receiving pla prospective, 6-week, double-blind, randomized, placebo-controlled, optional 24-week open-label extensi the open-label phase, the incidence of hypotension was 0% (0/30) of patients switched to paliperidone E was 2% (1/58) in patients continuing with paliperidone ER treatment from the double-blind phase. In gen was well tolerated in the geriatric population compared with placebo. The study included 114 patients (m with 99% having moderate to severe schizophrenia, receiving either placebo or median mean dose of pa milligrams/day (mg/day) during the double-blind phase and median mean doses of 7.4 mg and 8.5 mg in placebo/paliperidone ER and paliperidone ER/paliperidone ER groups, respectively, during the open-lab 2008).

3.3.1.C Ischemia

1) Incidence: rare (Prod Info INVEGA(TM) extended-release oral tablets, 2006)

2) During the pre-marketing phase, ischemia was reported rarely (less than 1 in 1000) in patients treated wit ranging from 3 mg to 12 mg orally once daily (n=2,720); however, causal relationship to paliperidone has not (Prod Info INVEGA(TM) extended-release oral tablets, 2006).

3.3.1.D Orthostatic hypotension

1) Incidence: 1% to 4% (Prod Info INVEGA(TM) extended-release oral tablets, 2006)

2) In 3 short-term (6-week), fixed-dose, placebo-controlled trials, orthostatic hypotension occurred in 1% to 4 with paliperidone doses ranging from 3 mg to 12 mg orally once daily (n=850) compared to 1% in placebo-tre The incidence of orthostatic hypotension increased with the dose, occurring particularly at the 9-mg and 12-m INVEGA(TM) extended-release oral tablets, 2006).

3) Geriatric

a) During the double-blind phase of a safety trial in 114 geriatric patients, the incidence of orthostatic hy (3/76) in patients receiving paliperidone extended-release (ER), compared with 0% (0/38) in patients rec according to a prospective, 6-week, double-blind, randomized, placebo-controlled, optional 24-week ope safety trial. In general, paliperidone ER was well tolerated in the geriatric population compared with place included 114 patients (mean age of 70 years), with 99% having moderate to severe schizophrenia, recei median mean dose of paliperidone ER 8.4 milligrams/day (mg/day) during the double-blind phase and m 7.4 mg and 8.5 mg in the placebo/paliperidone ER and paliperidone ER/paliperidone ER groups, respect label phase (Tzimos et al, 2008).

3.3.1.E Prolonged QT interval

1) Incidence: 3% to 7% (Tzimos et al, 2008; Prod Info INVEGA(TM) extended-release oral tablets, 2006)

2) In 3 short-term (6-week), fixed-dose, placebo-controlled trials, prolongation of QTc interval occurred in 3% treated with paliperidone doses ranging from 3 mg to 12 mg orally once daily (n=850) compared to 3% in plac (n=355). Among ECG measurements taken during these trials, a change in QTc interval exceeding 60 millise occurred only in 1 subject in the 12-mg group. Overall, none of the subjects had a QTc interval exceeding 50 time point (Prod Info INVEGA(TM) extended-release oral tablets, 2006).

3) Geriatric

a) During the double-blind phase of a safety trial in 114 geriatric patients, the incidence of electrocardiog prolongation was 7% (5/76) in patients receiving paliperidone extended-release (ER), compared with 3% receiving placebo according to a prospective, 6-week, double-blind, randomized, placebo-controlled, opt label extension safety trial. During the open-label phase, the incidence of QTc interval prolongation was switched to paliperidone ER from placebo, and 3% (2/58) in patients continuing with paliperidone ER trea double-blind phase. Prolonged QTcB prolongation of 500 milliseconds or greater led to discontinuation o patients assigned to paliperidone ER. In general, paliperidone ER was well tolerated in the geriatric popu placebo. The study included 114 patients (mean age of 70 years), with 99% having moderate to severe s receiving either placebo or median mean dose of paliperidone ER 8.4 milligrams/day (mg/day) during the and median mean doses of 7.4 mg and 8.5 mg in the placebo/paliperidone ER and paliperidone ER/palip respectively, during the open-label phase (Tzimos et al, 2008).

3.3.1.F Tachyarrhythmia

1) Incidence: 12% to 14% (Prod Info INVEGA(TM) extended-release oral tablets, 2006)

2) In 3 short-term (6-week), fixed-dose, placebo-controlled trials, tachyarrhythmia occurred in 12% to 14% of paliperidone doses ranging from 3 mg to 12 mg orally once daily (n=850) compared to 7% in placebo-treated Additional cardiac disorders occurring at a higher incidence than placebo included first-degree atrioventricula block, and sinus arrhythmia (Prod Info INVEGA(TM) extended-release oral tablets, 2006).

3.3.1.G Tachycardia

1) Incidence: 16% geriatric (Tzimos et al, 2008)

2) Geriatric

a) During the double-blind phase of a safety trial in 114 geriatric patients, the incidence of tachycardia w patients receiving paliperidone extended-release (ER), compared with 0% (0/38) in patients receiving pla prospective, 6-week, double-blind, randomized, placebo-controlled, optional 24-week open-label extensi the open-label phase, the incidence of tachycardia was 13% (4/30) of patients switched to paliperidone E was 10% (6/58) in patients continuing with paliperidone ER treatment from the double-blind phase. Hear beats/minute or greater occurred in 25% in the paliperidone ER group compared with 5% in placebo duri phase. During the open-label phase, the incidence of heart rates of 100 beats/minute or greater was 20% to paliperidone ER from placebo, and was 16% in patients continuing with paliperidone ER treatment fro phase. Pulse rate increases were more prominent in patients aged 70 to 75 years compared with age 64 general, paliperidone ER was well tolerated in the geriatric population compared with placebo. The study (mean age of 70 years), with 99% having moderate to severe schizophrenia, receiving either placebo or paliperidone ER 8.4 milligrams/day (mg/day) during the double-blind phase and median mean doses of 7 the placebo/paliperidone ER and paliperidone ER/paliperidone ER groups, respectively, during the open et al, 2008).

3.3.3 Endocrine/Metabolic Effects

Hyperprolactinemia

Metabolic syndrome

Weight gain

3.3.3.A Hyperprolactinemia

1) Incidence: geriatric, 45% to 49% (Tzimos et al, 2008)

2) Antipsychotic-induced hyperprolactinemia was reported in 65.6%, 45.1%, and 42.4% of women of childbe postmenopausal women, and men, respectively, in an open-label, clinical trial of patients treated with first-ge or risperidone at average doses of 4.2 to 5.2 mg/day. Compared to baseline, prolactin levels were significantl 0.05) following use of first-generation antipsychotics (ie, chlorpromazine, droperidol, flupenthixol, fluphenazin paliperidone, perazine, perphenazine, pimozide, trifluoperazine, and zuclopenthixol) or risperidone in several patients with schizophrenia. Younger patients and women of childbearing potential have a greater risk for hyp following treatment with higher doses of these antipsychotics. Hyperprolactinemia may potentially result in m sexual dysfunction, bone mineral density (ie, osteopenia and osteoporosis), and breast and pituitary tumors (

3) Geriatric

a) During the double-blind phase of a safety trial in 114 geriatric patients, the incidence of increased pro male patients and 49% in female patients receiving paliperidone extended-release (ER), according to a p double-blind, randomized, placebo-controlled, optional 24-week open-label extension safety trial. The ma was 75.3 +/- 10.8 nanograms/mL in females and 27.2 +/- 8.7 nanograms/mL in males. During the open-l levels increased in patients switched to paliperidone ER from placebo, and was stable for patients contin ER treatment from the double-blind phase. In general, paliperidone ER was well tolerated in the geriatric with placebo. The study included 114 patients (mean age of 70 years), with 99% having moderate to sev receiving either placebo or median mean dose of paliperidone ER 8.4 mg/day during the double-blind ph doses of 7.4 mg and 8.5 mg in the placebo/paliperidone ER and paliperidone ER/paliperidone ER group the open-label phase (Tzimos et al, 2008).

4) Management

a) Appropriate drug selection, monitoring and management are all important when prescribing antipsych potential for inducing hyperprolactinemia. Prior to treatment with an antipsychotic, question patients rega or galactorrhea. Female patients should be assessed for menstrual abnormalities and male patients, for dysfunction. In the event that any of these symptoms are present, consider obtaining baseline prolactin l be informed of the potential for sexual dysfunction with antipsychotic use. Several weeks after an antipsy obtain a prolactin level measurement. In cases where the patient experiences troublesome adverse effe prolactin levels and discontinuing the antipsychotic is not an option, treatment with a dopamine agonist (cabergoline) should be considered (Bostwick et al, 2009).

3.3.3.B Metabolic syndrome

See Drug Consult reference: ANTIPSYCHOTIC AGENTS - METABOLIC SYNDROME

3.3.3.C Weight gain

1) Incidence: 6% to 9% (Prod Info INVEGA(R) extended-release oral tablets, 2008a)

2) In 3 short-term (6-week), fixed-dose, placebo-controlled trials, weight gain of at least 7% of body weight w 9% of patients treated with paliperidone doses ranging from 3 mg to 12 mg orally once daily (n=850) compare treated patients (n=355). The incidence of weight gain increased with the dose, particularly at the 9-mg and 1 INVEGA(R) extended-release oral tablets, 2008a).

3.3.4 Gastrointestinal Effects

Abdominal pain

Xerostomia

3.3.4.A Abdominal pain

1) Incidence: 1% to 3% (Prod Info INVEGA(TM) extended-release oral tablets, 2006)

2) In 3 short-term (6-week), fixed-dose, placebo-controlled trials, upper abdominal pain occurred in 1% to 3% with paliperidone doses ranging from 3 mg to 12 mg orally once daily (n=850) compared to 1% in placebo-tre (Prod Info INVEGA(TM) extended-release oral tablets, 2006).

3.3.4.B Xerostomia

1) Incidence: 1% to 3% (Prod Info INVEGA(TM) extended-release oral tablets, 2006)

2) In 3 short-term (6-week), fixed-dose, placebo-controlled trials, dry mouth occurred in 1% to 3% of patients paliperidone doses ranging from 3 mg to 12 mg orally once daily (n=850) compared to 1% in placebo-treated (Prod Info INVEGA(TM) extended-release oral tablets, 2006).

3.3.5 Hematologic Effects

3.3.5.A Thrombocytopenia

1) Incidence: rare (Prod Info INVEGA(TM) extended-release oral tablets, 2006)
2) During the pre-marketing phase, thrombocytopenia was reported rarely (less than 1 in 1000) in patients tr paliperidone doses ranging from 3 mg to 12 mg orally once daily (n=2,720); however, causal relationship to p been determined (Prod Info INVEGA(TM) extended-release oral tablets, 2006).

3.3.7 Immunologic Effects

3.3.7.A Anaphylaxis

1) Incidence: rare (Prod Info INVEGA(TM) extended-release oral tablets, 2006)
2) During the pre-marketing phase, anaphylactic shock occurred rarely (less than 1 in 1000) in patients treat doses ranging from 3 mg to 12 mg orally once daily (n=2,720); however, causal relationship to paliperidone h determined (Prod Info INVEGA(TM) extended-release oral tablets, 2006).

3.3.9 Neurologic Effects

Akathisia

Dizziness

Dystonia

Extrapyramidal disease

Headache

Somnolence

Tremor

3.3.9.A Akathisia

1) Incidence: 3% to 10% (Prod Info INVEGA(TM) extended-release oral tablets, 2006)
2) In 3 short-term (6-week), fixed-dose, placebo-controlled trials, akathisia occurred in 3% to 10% of patients paliperidone doses ranging from 3 mg to 12 mg orally once daily (n=850) compared to 4% in placebo-treated incidence of akathisia increased with the dose, occurring particularly at the 9-mg and 12-mg doses (Prod Info extended-release oral tablets, 2006).

3.3.9.B Dizziness

1) Incidence: 7% geriatric (Tzimos et al, 2008)
2) Geriatric
a) During the double-blind phase of a safety trial in 114 geriatric patients, the incidence of dizziness was receiving paliperidone extended-release (ER), compared with 0% (0/38) in patients receiving placebo ac prospective, 6-week, double-blind, randomized, placebo-controlled, optional 24-week open-label extensi the open-label phase, the incidence of dizziness was 3% (1/30) of patients switched to paliperidone ER f 10% (6/58) in patients continuing with paliperidone ER treatment from the double-blind phase. In genera well tolerated in the geriatric population compared with placebo. The study included 114 patients (mean 99% having moderate to severe schizophrenia, receiving either placebo or median mean dose of paliper milligrams/day (mg/day) during the double-blind phase and median mean doses of 7.4 mg and 8.5 mg in placebo/paliperidone ER and paliperidone ER/paliperidone ER groups, respectively, during the open-lab 2008).

3.3.9.C Dystonia

1) Incidence: 1% to 5% (Prod Info INVEGA(R) extended-release oral tablets, 2008b)
2) In 3 short-term (6-week), fixed-dose, placebo-controlled trials, dystonia occurred in 1% to 5% of patients t paliperidone doses ranging from 3 mg to 12 mg orally once daily (n=850) compared with 1% in placebo-treate Dystonic reactions included muscle spasms, oculogyration, and trismus. The incidence of dystonia increased occurring particularly at the 9-mg and 12-mg doses (Prod Info INVEGA(R) extended-release oral tablets, 200
3) During the first few days after initiating treatment with an antipsychotic medication, symptoms of dystonia susceptible individuals. Symptoms may include spasm of neck muscles, which may progress to tightening of difficulty, breathing difficulty, and/or protrusion of the tongue. These symptoms can occur at low doses but m occur with a greater severity) with high potency and at higher doses of first generation antipsychotic medicati younger age groups appear to be at greater risk for developing acute dystonia (Prod Info INVEGA(R) extend 2008b).

3.3.9.D Extrapyramidal disease

1) Incidence: 2% to 7% (Prod Info INVEGA(TM) extended-release oral tablets, 2006)

2) In 3 short-term (6-week), fixed-dose, placebo-controlled trials, extrapyramidal disorders occurred in 2% to with paliperidone doses ranging from 3 mg to 12 mg orally once daily (n=850) compared to 2% in placebo-tre Extrapyramidal symptoms (EPS) included akathisia, dyskinesia, dystonia, hyperkinesia, and tremor, and Parl involved bradykinesia, cogwheel rigidity, drooling, hypertonia, hypokinesia, muscle rigidity, and musculoskele incidence of EPS increased with the dose, occurring particularly at the 9-mg and 12-mg doses (Prod Info INV release oral tablets, 2006).

See Drug Consult reference: NEUROLEPTIC-INDUCED EXTRAPYRAMIDAL REACTIONS

3.3.9.E Headache

1) Incidence: 11% to 14% (Prod Info INVEGA(TM) extended-release oral tablets, 2006)

2) In 3 short-term (6-week), fixed-dose, placebo-controlled trials, headache occurred in 11% to 14% of patier paliperidone doses ranging from 3 mg to 12 mg orally once daily (n=850) compared to 12% in placebo-treate (Prod Info INVEGA(TM) extended-release oral tablets, 2006).

3.3.9.F Somnolence

1) Incidence: 6% to 11% (Prod Info INVEGA(TM) extended-release oral tablets, 2006)

2) In 3 short-term (6-week), fixed-dose, placebo-controlled trials, somnolence occurred in 6% to 11% of patie paliperidone doses ranging from 3 mg to 12 mg orally once daily (n=850) compared to 7% in placebo-treated incidence of somnolence increased with the dose, particularly at the 9-mg and 12-mg doses (Prod Info INVE release oral tablets, 2006).

3) Geriatric

a) During the double-blind phase of a safety trial in 114 geriatric patients, the incidence of somnolence v patients receiving paliperidone extended-release (ER), compared with 5% (2/38) in patients receiving pla prospective, 6-week, double-blind, randomized, placebo-controlled, optional 24-week open-label extensi the open-label phase, the incidence of somnolence was 7% (2/30) of patients switched to paliperidone E was 0% (0/58) in patients continuing with paliperidone ER treatment from the double-blind phase. During phase, an age-related increase in the incidence of somnolence was seen in patients receiving paliperido to 69 years, 11% in age 70 to 75 years, and 14% in age greater than 75 years. In general, paliperidone E in the geriatric population compared with placebo. The study included 114 patients (mean age of 70 yea moderate to severe schizophrenia, receiving either placebo or median mean dose of paliperidone ER 8.4 (mg/day) during the double-blind phase and median mean doses of 7.4 mg and 8.5 mg in the placebo/pa paliperidone ER/paliperidone ER groups, respectively, during the open-label phase (Tzimos et al, 2008).

3.3.9.G Tremor

1) Incidence: 3% to 4% (Prod Info INVEGA(TM) extended-release oral tablets, 2006)

2) In 3 short-term (6-week), fixed-dose, placebo-controlled trials, tremor occurred in 3% to 4% of patients tre doses ranging from 3 mg to 12 mg orally once daily (n=850) compared to 3% in placebo-treated patients (n=3 INVEGA(TM) extended-release oral tablets, 2006).

3.3.16 Other

Death

Extrapyramidal disease

3.3.16.A Death

1) Results of a population-based, retrospective cohort study demonstrated that the use of conventional antip associated with an even greater risk for death than atypical antipsychotics when administered to elderly patie and older) with dementia. Atypical versus no antipsychotic use and conventional versus atypical antipsychoti comparisons were made. A total of 27,259 matched pairs were identified and the dementia cohort was stratifi residence (community versus long-term care facilities). In order to adjust for difference in baseline health stat matching was used. The primary outcome of the study was all-cause mortality. The risk for death was evalua 180 days after the antipsychotic medications were initially dispensed. There was a statistically significant incr death at 30 days associated with new use of atypical antipsychotic medications compared with nonuse in bot dwelling cohort (adjusted hazard ratio (HR), 1.31 (95% confidence interval (CI), 1.02 to 1.70); absolute risk di percentage point) and long-term care cohort (adjusted HR, 1.55 (95% CI, 1.15 to 2.07); absolute risk differen points). For both cohorts, the risk associated with atypical antipsychotics appeared to persist to 180 days. Th associated with conventional antipsychotics was even greater than the risk identified with atypical antipsycho adjusted HR for the community-dwelling cohort was 1.55 (95% CI, 1.19 to 2.02) and 1.26 (95% CI, 1.04 to 1.5 care cohort (adjusted risk difference for both was 1.1 percentage points). The risk appeared to persist to 180 Some important limitations to the study include unknown or unmeasured confounders may influence the resu could not be examined (Gill et al, 2007).

2) Results of a population-based, retrospective cohort study demonstrated comparable to possibly greater ris

with the use of conventional antipsychotic medications in the elderly (aged 65 years and older) compared wit
antipsychotic medications. The analysis excluded patients with cancer and included only new users of antips
The primary study outcome was 180-day all-cause mortality. A set of potential confounders was measured ba
utilization data within 6 months before the initiation of antipsychotic medications. Of the 37,241 elderly patien
and 24,359 received conventional and atypical antipsychotic medications, respectively. The risk of death in th
group within the first 180 days was 14.1% compared with 9.6% in the atypical drug group (unadjusted mortali
confidence interval (CI), 1.39 to 1.56). In the multi-variable analysis which controlled for potential confounders
mortality ratio for the risk of death within 180 days for conventional versus atypical drug therapy was 1.32 (95
When the most frequently prescribed conventional antipsychotic drugs were compared with risperidone, the r
associated with haloperidol was 2.14 (95% CI, 1.86 to 2.45) and loxapine was 1.29 (95% CI, 1.19 to 1.40), wh
difference associated with olanzapine. The increased mortality risk for conventional versus atypical drug thera
when doses higher (above median) doses were used (mortality ratio 1.67; 95% CI, 1.5 to 1.86) and also durin
therapy (mortality ratio 1.6; 95% CI, 1.42 to 1.8). Confirmatory analyses consisting of multi-variable Cox regre
score, and instrumental variable estimation confirmed the results of the study (Schneeweiss et al, 2007).

3.3.16.B Extrapyramidal disease

See Drug Consult reference: NEUROLEPTIC-INDUCED EXTRAPYRAMIDAL REACTIONS

3.4 Teratogenicity/Effects in Pregnancy/Breastfeeding

A) Teratogenicity/Effects in Pregnancy

1) U.S. Food and Drug Administration's Pregnancy Category: Category C (Prod Info INVEGA(TM) extended-relea
(All Trimesters)

a) Either studies in animals have revealed adverse effects on the fetus (teratogenic or embryocidal or other)
controlled studies in women or studies in women and animals are not available. Drugs should be given only if
justifies the potential risk to the fetus.

See Drug Consult reference: PREGNANCY RISK CATEGORIES

2) Crosses Placenta: Unknown

3) Clinical Management

a) Adequate and well controlled studies with paliperidone have not been conducted in pregnant women. Whi
generation antipsychotic drugs during the last trimester of pregnancy has been linked to extrapyramidal symp
unknown whether paliperidone could lead to similar neonatal effects. Until further data are available, it is recc
paliperidone be used during pregnancy only if the potential benefit to the mother justifies the potential risk to
INVEGA(TM) extended-release oral tablets, 2006).

4) Literature Reports

a) No human studies of pregnancy outcomes after exposure to paliperidone have been published, and there
of outcomes after inadvertent exposure during pregnancy. In studies in rats and rabbits, no increases in fetal
noted at the highest oral paliperidone dose, which was approximately 8 times the maximum recommended hu
Paliperidone is the major active metabolite of risperidone. In rat reproduction studies with risperidone, increas
noted at oral doses that were less than the MRHD of risperidone. Use of first-generation antipsychotic drugs
trimester of pregnancy has been linked to extrapyramidal symptoms in neonates. However, it is unknown whe
could lead to similar neonatal effects (Prod Info INVEGA(TM) extended-release oral tablets, 2006).

B) Breastfeeding

1) Thomson Lactation Rating: Infant risk cannot be ruled out.

a) Available evidence and/or expert consensus is inconclusive or is inadequate for determining infant risk wh
breastfeeding. Weigh the potential benefits of drug treatment against potential risks before prescribing this dr
breastfeeding.

2) Literature Reports

a) Lactation studies with paliperidone have not been conducted in humans. In animal studies, paliperidone w
milk. Paliperidone is the major active metabolite of risperidone, which is excreted into human milk. Therefore,
paliperidone recommended that women receiving paliperidone should not breast-feed infants (Prod Info INVE
release oral tablets, 2006).

3.5 Drug Interactions

3.5.1 Drug-Drug Combinations

Acecainide

Ajmaline

Amiodarone

Arsenic Trioxide

Azimilide

Bretylium

Carbamazepine

Chlorpromazine

Disopyramide

Dofetilide

Gatifloxacin

Hydroquinidine

Ibutilide

Iloperidone

Lapatinib

Levodopa

Mesoridazine

Methadone

Moxifloxacin

Nilotinib

Paroxetine

Pirmenol

Prajmaline

Procainamide

Prochlorperazine

Ranolazine

Sematilide

Sotalol

Tedisamil

Tetrabenazine

Thioridazine

Trifluoperazine

3.5.1.A Acecainide

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Class III antiarrhythmics have been shown to prolong the QT interval, which may result in ventr ventricular fibrillation, and torsades de pointes (Prod Info CORDARONE(R) oral tablets, 2006; Prod Info sotal 2005). Modest increases in the QTc interval have been noted with paliperidone use (Prod Info INVEGA(TM) e tablets, 2006). Due to the risk of additive QTc prolongation, the concurrent administration of paliperidone and antiarrhythmic agents should be avoided (Prod Info INVEGA(TM) extended-release oral tablets, 2006).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of paliperidone and class III antiarrhythmic agents sh this may result in additive QTc interval prolongation (Prod Info INVEGA(TM) extended-release oral tablets, 2(
7) Probable Mechanism: additive QT prolongation

3.5.1.B Ajmaline

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Several antipsychotic agents have demonstrated QT prolongation including amisulpride, halop paliperidone, quetiapine, risperidone, sertindole, sultopride, ziprasidone, and zotepine (Prod Info FANAPT(TM Prod Info Solian(R), 1999b; O'Brien et al, 1999b; Prod Info INVEGA(TM) extended-release oral tablets, 2006 Duenas-Laita et al, 1999b; Agelink et al, 2001b; Lande et al, 1992b; Prod Info GEODON(R) intramuscular inj 2005; Sweetman, 2003). Because Class IA antiarrhythmic agents may also prolong the QT interval and incre arrhythmias, the concurrent administration of antipsychotics with a drug from this class is not recommended ((TM) oral tablets, 2009; Prod Info Quinaglute(R), 1999).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: The concurrent administration of a Class IA antiarrhythmic and an antipsychotic is r
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) In an open-label QTc study of patients with schizophrenia or schizoaffective disorder (n=160), iloperic day was associated with QTc prolongation of 9 msec (Prod Info FANAPT(TM) oral tablets, 2009).
b) QRS widening, QTc interval prolongation, and torsades de pointes may occur with disopyramide ther Norpace(R), 1997).
c) The effects of combined therapy with quinidine (Class IA antiarrhythmic agent) and haloperidol (antip studied by giving 12 healthy volunteers haloperidol 5 mg alone and with 250 mg of quinidine bisulfate. Th significant increases in the plasma concentrations of haloperidol when given concurrently with quinidine treatment alone. The mean area under the concentration curve (AUC) was increased from 54.3 ng/h/mL to 103.2 ng/h/mL on combined therapy. The peak concentration (Cmax) also showed an increase from 1 haloperidol to 3.8 ng/mL on combined therapy. Half-life (T1/2) and time to peak concentration (Tmax) we changed, thereby suggesting to the authors that a tissue binding mechanism is more likely responsible fo changes than an elimination alteration (Young et al, 1993).

3.5.1.C Amiodarone

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Class III antiarrhythmics have been shown to prolong the QT interval, which may result in ventr ventricular fibrillation, and torsades de pointes (Prod Info CORDARONE(R) oral tablets, 2006; Prod Info sotal 2005). Modest increases in the QTc interval have been noted with paliperidone use (Prod Info INVEGA(TM) e tablets, 2006). Due to the risk of additive QTc prolongation, the concurrent administration of paliperidone and antiarrhythmic agents should be avoided (Prod Info INVEGA(TM) extended-release oral tablets, 2006).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of paliperidone and class III antiarrhythmic agents sh this may result in additive QTc interval prolongation (Prod Info INVEGA(TM) extended-release oral tablets, 2(
7) Probable Mechanism: additive QT prolongation

3.5.1.D Arsenic Trioxide

1) Interaction Effect: prolongation of the QTc interval and/or torsades de pointes
2) Summary: Arsenic trioxide can prolong the QT interval in some patients, which may result in ventricular ta fibrillation, and torsades de pointes and should not be administered with other drugs that may prolong the QT Trisenox(R), 2001a). Several antipsychotic agents have demonstrated QT prolongation including amisulpride 1999), haloperidol (O'Brien et al, 1999), paliperidone (Prod Info INVEGA(TM) extended-release oral tablets, 2 (Duenas-Laita et al, 1999), sertindole (Agelink et al, 2001), quetiapine (Owens, 2001), sultopride (Lande et al (Prod Info GEODON(R) intramuscular injection, oral capsule, 2005), and zotepine (Sweetman, 2003).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of arsenic trioxide and antipsychotics is not recomme
7) Probable Mechanism: additive effects on QTc prolongation

8) Literature Reports

a) QT/QTc prolongation should be expected during treatment with arsenic trioxide and torsade de pointe heart block has been reported. Over 460 ECG tracings from 40 patients with refractory or relapsed APL t trioxide were evaluated for QTc prolongation. Sixteen of 40 patients (40%) had at least one ECG tracing greater than 500 msec. Prolongation of the QTc was observed between 1 and 5 weeks after arsenic triox returned towards baseline by the end of 8 weeks after arsenic trioxide infusion. In these ECG evaluations experience more pronounced QT prolongation than men, and there was no correlation with age (Prod Inf

3.5.1.E Azimilide

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Class III antiarrhythmics have been shown to prolong the QT interval, which may result in ventri ventricular fibrillation, and torsades de pointes (Prod Info CORDARONE(R) oral tablets, 2006; Prod Info sotal 2005). Modest increases in the QTc interval have been noted with paliperidone use (Prod Info INVEGA(TM) e tablets, 2006). Due to the risk of additive QTc prolongation, the concurrent administration of paliperidone and antiarrhythmic agents should be avoided (Prod Info INVEGA(TM) extended-release oral tablets, 2006).

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of paliperidone and class III antiarrhythmic agents sh this may result in additive QTc interval prolongation (Prod Info INVEGA(TM) extended-release oral tablets, 20

7) Probable Mechanism: additive QT prolongation

3.5.1.F Bretylium

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Class III antiarrhythmics have been shown to prolong the QT interval, which may result in ventri ventricular fibrillation, and torsades de pointes (Prod Info CORDARONE(R) oral tablets, 2006; Prod Info sotal 2005). Modest increases in the QTc interval have been noted with paliperidone use (Prod Info INVEGA(TM) e tablets, 2006). Due to the risk of additive QTc prolongation, the concurrent administration of paliperidone and antiarrhythmic agents should be avoided (Prod Info INVEGA(TM) extended-release oral tablets, 2006).

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of paliperidone and class III antiarrhythmic agents sh this may result in additive QTc interval prolongation (Prod Info INVEGA(TM) extended-release oral tablets, 20

7) Probable Mechanism: additive QT prolongation

3.5.1.G Carbamazepine

1) Interaction Effect: decreased paliperidone concentration

2) Summary: Concomitant use of paliperidone and carbamazepine decreased the maximum concentration (C under the concentration-time curve (AUC) values of paliperidone by 37%. Coadministration with carbamazep inducer, could increase paliperidone renal clearance by 35%. The dose of paliperidone should be evaluated v concurrently with carbamazepine. If therapy with carbamazepine is discontinued, the dose of paliperidone sh necessary (Prod Info INVEGA(TM) extended-release oral tablets, 2007).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Coadministration of paliperidone and carbamazepine resulted in decreased paliperi Dosing of paliperidone should be evaluated when it is administered concurrently with carbamazepine. If thera carbamazepine is discontinued, the dose of paliperidone should be decreased if necessary(Prod Info INVEGA release oral tablets, 2007).

7) Probable Mechanism: induction of paliperidone metabolism

8) Literature Reports

a) Coadministration of paliperidone 6 mg daily and carbamazepine 200 mg twice daily decreased the pa steady-state maximum concentration (Cmax) and area under the concentration-time curve (AUC) by app decrease is caused by a 35% increase in renal clearance of paliperidone. There is little effect on the met bioavailability of paliperidone when coadministered with carbamazepine. Carefully evaluate paliperidone discontinuation of carbamazepine (Prod Info INVEGA(TM) extended-release oral tablets, 2007).

3.5.1.H Chlorpromazine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Concomitant use of phenothiazines and antipsychotic agents may cause additive effects on the recommended. Q and T wave distortions have been observed in patients taking phenothiazines (Prod Info Co Prod Info Stelazine(R), 2002; Prod Info Thorazine(R), 2002). Other phenothiazines may have similar effects, available. Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info haloperidol (O'Brien et al, 1999a), paliperidone (Prod Info INVEGA(TM) extended-release oral tablets, 2006), 2001a), risperidone (Duenas-Laita et al, 1999a), sertindole (Agelink et al, 2001a), sultopride (Lande et al, 199 (Prod Info GEODON(R) intramuscular injection, oral capsule, 2005), and zotepine (Sweetman, 2003).

3) Severity: major

4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of agents that prolong the QT interval, such as phen antipsychotics, is not recommended.
7) Probable Mechanism: additive QT prolongation

3.5.1.I Disopyramide
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest
2) Summary: Several antipsychotic agents have demonstrated QT prolongation including amisulpride, halop paliperidone, quetiapine, risperidone, sertindole, sultopride, ziprasidone, and zotepine (Prod Info FANAPT(TM Prod Info Solian(R), 1999b; O'Brien et al, 1999b; Prod Info INVEGA(TM) extended-release oral tablets, 2006 Duenas-Laita et al, 1999b; Agelink et al, 2001b; Lande et al, 1992b; Prod Info GEODON(R) intramuscular inj 2005; Sweetman, 2003). Because Class IA antiarrhythmic agents may also prolong the QT interval and incre arrhythmias, the concurrent administration of antipsychotics with a drug from this class is not recommended ((TM) oral tablets, 2009; Prod Info Quinaglute(R), 1999).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: The concurrent administration of a Class IA antiarrhythmic and an antipsychotic is r
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) In an open-label QTc study of patients with schizophrenia or schizoaffective disorder (n=160), iloperi day was associated with QTc prolongation of 9 msec (Prod Info FANAPT(TM) oral tablets, 2009).
b) QRS widening, QTc interval prolongation, and torsades de pointes may occur with disopyramide ther Norpace(R), 1997).
c) The effects of combined therapy with quinidine (Class IA antiarrhythmic agent) and haloperidol (antip studied by giving 12 healthy volunteers haloperidol 5 mg alone and with 250 mg of quinidine bisulfate. Th significant increases in the plasma concentrations of haloperidol when given concurrently with quinidine treatment alone. The mean area under the concentration curve (AUC) was increased from 54.3 ng/h/mL to 103.2 ng/h/mL on combined therapy. The peak concentration (Cmax) also showed an increase from 1 haloperidol to 3.8 ng/mL on combined therapy. Half-life (T1/2) and time to peak concentration (Tmax) we changed, thereby suggesting to the authors that a tissue binding mechanism is more likely responsible fo changes than an elimination alteration (Young et al, 1993).

3.5.1.J Dofetilide
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest
2) Summary: Class III antiarrhythmics have been shown to prolong the QT interval, which may result in ventr ventricular fibrillation, and torsades de pointes (Prod Info CORDARONE(R) oral tablets, 2006; Prod Info sotal 2005). Modest increases in the QTc interval have been noted with paliperidone use (Prod Info INVEGA(TM) e tablets, 2006). Due to the risk of additive QTc prolongation, the concurrent administration of paliperidone and antiarrhythmic agents should be avoided (Prod Info INVEGA(TM) extended-release oral tablets, 2006).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of paliperidone and class III antiarrhythmic agents sh this may result in additive QTc interval prolongation (Prod Info INVEGA(TM) extended-release oral tablets, 2
7) Probable Mechanism: additive QT prolongation

3.5.1.K Gatifloxacin
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest
2) Summary: Gatifloxacin may prolong the QTc interval in some patients, which may result in ventricular tach ventricular fibrillation. Additionally, rare cases of torsades de pointes have been reported with quinolones, inc post-marketing surveillance (Prod Info TEQUIN(R) tablets, injection, 2006). Modest increases in the QTc inte with paliperidone use (Prod Info INVEGA(TM) extended-release oral tablets, 2006). Although pharmacokineti gatifloxacin and other drugs which prolong the QT interval have not been performed, an additive effect canno Therefore, the concurrent administration of gatifloxacin and paliperidone should be avoided (Prod Info INVEG release oral tablets, 2006).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of gatifloxacin and paliperidone should be avoided as additive QTc interval prolongation (Prod Info INVEGA(TM) extended-release oral tablets, 2006).
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.L Hydroquinidine
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest
2) Summary: Several antipsychotic agents have demonstrated QT prolongation including amisulpride, halop paliperidone, quetiapine, risperidone, sertindole, sultopride, ziprasidone, and zotepine (Prod Info FANAPT(TM

Prod Info Solian(R), 1999b; O'Brien et al, 1999b; Prod Info INVEGA(TM) extended-release oral tablets, 2006 Duenas-Laita et al, 1999b; Agelink et al, 2001b; Lande et al, 1992b; Prod Info GEODON(R) intramuscular inj 2005; Sweetman, 2003). Because Class IA antiarrhythmic agents may also prolong the QT interval and incre arrhythmias, the concurrent administration of antipsychotics with a drug from this class is not recommended ((TM) oral tablets, 2009; Prod Info Quinaglute(R), 1999).

3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: The concurrent administration of a Class IA antiarrhythmic and an antipsychotic is r
7) Probable Mechanism: additive cardiac effects
8) Literature Reports

a) In an open-label QTc study of patients with schizophrenia or schizoaffective disorder (n=160), iloperic day was associated with QTc prolongation of 9 msec (Prod Info FANAPT(TM) oral tablets, 2009).

b) QRS widening, QTc interval prolongation, and torsades de pointes may occur with disopyramide ther Norpace(R), 1997).

c) The effects of combined therapy with quinidine (Class IA antiarrhythmic agent) and haloperidol (antip studied by giving 12 healthy volunteers haloperidol 5 mg alone and with 250 mg of quinidine bisulfate. Th significant increases in the plasma concentrations of haloperidol when given concurrently with quinidine treatment alone. The mean area under the concentration curve (AUC) was increased from 54.3 ng/h/mL to 103.2 ng/h/mL on combined therapy. The peak concentration (Cmax) also showed an increase from 1 haloperidol to 3.8 ng/mL on combined therapy. Half-life (T1/2) and time to peak concentration (Tmax) we changed, thereby suggesting to the authors that a tissue binding mechanism is more likely responsible fo changes than an elimination alteration (Young et al, 1993).

3.5.1.M Ibutilide

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Class III antiarrhythmics have been shown to prolong the QT interval, which may result in ventr ventricular fibrillation, and torsades de pointes (Prod Info CORDARONE(R) oral tablets, 2006; Prod Info sotal 2005). Modest increases in the QTc interval have been noted with paliperidone use (Prod Info INVEGA(TM) e tablets, 2006). Due to the risk of additive QTc prolongation, the concurrent administration of paliperidone and antiarrhythmic agents should be avoided (Prod Info INVEGA(TM) extended-release oral tablets, 2006).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of paliperidone and class III antiarrhythmic agents sh this may result in additive QTc interval prolongation (Prod Info INVEGA(TM) extended-release oral tablets, 20
7) Probable Mechanism: additive QT prolongation

3.5.1.N Iloperidone

1) Interaction Effect: an increased risk of QT interval prolongation
2) Summary: Due to the potential for additive effects on the QT interval and increased risk of torsade de poin used when iloperidone and drugs that prolong the QT interval are given concomitantly. Consideration should cardiac function periodically with on-treatment ECGs and evaluating electrolyte (ie, magnesium, potassium) le iloperidone in patients with persistent QTc measurements greater than 500 msec (Prod Info FANAPT(TM) ora
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of iloperidone and drugs that prolong the QT interval may result in the QT interval and an increased risk of torsade de pointes. Iloperidone should be avoided in patients with sig cardiovascular illness, eg, cardiac arrhythmia, QT prolongation, recent acute myocardial infarction, and uncon failure. If concomitant use is necessary, consider monitoring cardiac function periodically with on-treatment E electrolyte (ie, magnesium, potassium) levels. Discontinue iloperidone in patients with persistent QTc measur 500 msec(Prod Info FANAPT(TM) oral tablets, 2009).
7) Probable Mechanism: additive effects on the QT interval
8) Literature Reports

a) In an open-label QTc study of patients with schizophrenia or schizoaffective disorder (n=160), iloperic day was associated with QTc prolongation of 9 msec (Prod Info FANAPT(TM) oral tablets, 2009).

3.5.1.O Lapatinib

1) Interaction Effect: an increased risk of QT interval prolongation
2) Summary: Due to the potential for additive effects on the QT interval and increased risk of torsade de poin used when lapatinib and drugs that prolong the QT interval are given concomitantly. Consideration should be cardiac function periodically with on-treatment ECGs and evaluating electrolyte (ie, magnesium, potassium) le TYKERB oral tablets, 2008). Thirteen patients had either QTcF (corrected QT by the Friedericia method) grea an increase in QTcF of greater than 60 msec in an uncontrolled, open-label, dose escalation study in advanc (n=81) who received lapatinib doses ranging from 175 mg/day to 1800 mg/day, with serial ECGs collected on Info TYKERB oral tablets, 2008).
3) Severity: major

4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of lapatinib and drugs that prolong the QT interval may result in ac QT interval and an increased risk of torsade de pointes. Therefore, caution should be used when these agent concomitantly. Consider monitoring cardiac function periodically with on-treatment ECGs and evaluating elec magnesium, potassium) levels (Prod Info TYKERB oral tablets, 2008).
7) Probable Mechanism: additive effects on the QT interval

3.5.1.P Levodopa
1) Interaction Effect: loss of levodopa efficacy
2) Summary: Because paliperidone is an antagonist with a high affinity for dopamine type 2 receptors, it is ex the effects of levodopa and other dopamine agonists (Prod Info INVEGA(TM) extended-release oral tablets, 2 paliperidone is used concurrently in patients receiving levodopa. Monitor patients for loss of levodopa efficacy
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concurrent use with paliperidone is expected to antagonize the effects of levodopa agonists due to pharmacologic antagonism (Prod Info INVEGA(TM) extended-release oral tablets, 2006). Us paliperidone is used concurrently in patients receiving levodopa. Monitor patients for loss of levodopa efficacy
7) Probable Mechanism: pharmacologic antagonism

3.5.1.Q Mesoridazine
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Although citing no data, the manufacturer of mesoridazine states that concomitant use with oth prolong the QT interval is contraindicated (Prod Info Serentil(R), 2001). Several antipsychotic agents have de prolongation including amisulpride (Prod Info Solian(R), 1999d), haloperidol (O'Brien et al, 1999d), paliperido (TM) extended-release oral tablets, 2006), quetiapine (Owens, 2001d), risperidone (Duenas-Laita et al, 1999 et al, 2001c), sultopride (Lande et al, 1992d), ziprasidone (Prod Info GEODON(R) intramuscular injection, ora zotepine (Sweetman, 2004).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of agents that prolong the QT interval, such as antips mesoridazine, is contraindicated.
7) Probable Mechanism: additive QT prolongation

3.5.1.R Methadone
1) Interaction Effect: an increased risk of QT interval prolongation
2) Summary: Cases of QT interval prolongation and serious arrhythmias, including torsade de pointes, have methadone use (Prod Info DOLOPHINE(R) HYDROCHLORIDE oral tablets, 2006). Treatment with paliperido associated with QTc prolongation (Prod Info INVEGA(TM) extended-release oral tablets, 2006a). The coadm paliperidone and other drugs known to prolong the QTc interval, including methadone, should be avoided due additive QT interval prolongation (Prod Info INVEGA(TM) extended-release oral tablets, 2006a).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Due to the potential for additive effects on the QT interval, avoid concomitant use of methadone (Prod Info INVEGA(TM) extended-release oral tablets, 2006a).
7) Probable Mechanism: additive effects on QT interval prolongation

3.5.1.S Moxifloxacin
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Moxifloxacin has been shown to prolong the QTc interval in some patients (Prod Info AVELOX injection, 2005). Modest increases in the QTc interval have been noted with paliperidone use (Prod Info INVE release oral tablets, 2006). Although pharmacokinetic studies between moxifloxacin and paliperidone have no additive effect cannot be excluded. Therefore, the concurrent administration of moxifloxacin and paliperidone (Prod Info INVEGA(TM) extended-release oral tablets, 2006).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of moxifloxacin and paliperidone should be avoided a additive QTc interval prolongation (Prod Info INVEGA(TM) extended-release oral tablets, 2006).
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.T Nilotinib
1) Interaction Effect: an increased risk of QT interval prolongation
2) Summary: Due to the potential for additive effects on the QT interval and increased risk of torsade de poin of nilotinib with drugs that prolong the QT interval should be avoided. However, if concomitant use is required

closely monitored for prolongation of the QT interval (Prod Info TASIGNA(R) oral capsules, 2007).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of nilotinib with drugs that prolong the QT interval should be avoid for additive effects on the QT interval and increased risk of torsade de pointes. However, if concurrent therap patient closely for prolongation of the QT interval (Prod Info TASIGNA(R) oral capsules, 2007).
7) Probable Mechanism: additive effects on QT interval prolongation

3.5.1.U Paroxetine
1) Interaction Effect: increased plasma concentrations of paliperidone
2) Summary: Concurrent use of paliperidone and paroxetine may result in increased paliperidone plasma co Paliperidone (9-hydroxyrisperidone) is the major active metabolite of risperidone (Prod Info INVEGA(TM) exte tablets, 2007). Concomitant use of paroxetine and risperidone has resulted in increased plasma concentratio and 9-hydroxyrisperidone, particularly at higher (40 mg) paroxetine doses (Saito et al, 2005; Spina et al, 200 paliperidone and paroxetine are used concomitantly. Consider monitoring for increased paliperidone side effe neuroleptic malignant syndrome, QTc prolongation, or tardive dyskinesia.
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Use caution when paliperidone and paroxetine are used concomitantly as this may paliperidone plasma concentrations (Prod Info INVEGA(TM) extended-release oral tablets, 2007). Consider r increased paliperidone side effects, including neuroleptic malignant syndrome, QTc prolongation, or tardive d
7) Probable Mechanism: inhibition of the CYP2D6-mediated metabolism of paliperidone
8) Literature Reports
a) In a drug interaction study, paliperidone exposures were a significant 16% (90% confidence interval, average in CYP2D6 extensive metabolizers who were treated concomitantly with a single dose of palipe paroxetine 20 mg/day. Studies with higher paroxetine doses have not been conducted. The clinical relev (Prod Info INVEGA(TM) extended-release oral tablets, 2007).
b) Paroxetine, a potent inhibitor of cytochrome CYP2D6, may impair the elimination of risperidone, prim CYP2D6-mediated alpha-hydroxylation and, to a lesser extent, by simultaneously affecting the further m hydroxyrisperidone (9-OH-risperidone) or other pathways of risperidone biotransformation. In a study inc diagnosed with schizophrenia (n=7) or schizoaffective disorder depressive type (n=3), risperidone plasm increased when paroxetine was coadministered with risperidone. Patients were stabilized on risperidone and received adjunctive paroxetine 20 mg/day to treat negative symptoms, concomitant depression, or b dosage remained constant throughout the duration of the study. A significant elevation in risperidone pla less than 0.01) and a slight, nonsignificant decrease in 9-OH-risperidone occurred. After 4 weeks of parc total concentration of risperidone and 9-OH-risperidone was increased by 45% (p less than 0.05). The m risperidone to 9-OH-risperidone ratio also changed significantly (p less than 0.001) with concomitant par Extrapyramidal side effects occurred in one patient during the second week of paroxetine coadministratio of risperidone in this patient increased 62% over baseline values during paroxetine coadministration. The extrapyramidal symptoms in patients after addition of SSRIs to antipsychotics might also be caused by a pharmacodynamic effect of paroxetine (Spina et al, 2001).
c) Risperidone plasma concentrations increased when risperidone-treated inpatients (n=12) with schizo symptoms were coadministered incremental doses of paroxetine. Prior to initiating paroxetine, patients w risperidone 2 mg twice daily for at least 6 weeks and steady-state plasma concentrations of risperidone a hydroxyrisperidone (9-OH-risperidone) had been achieved. Paroxetine doses were administered in 3 cor increments of 10 mg/day, 20 mg/day, and 40 mg/day. Mean risperidone plasma concentrations during 1(paroxetine treatment were 3.8- (95% confidence interval (CI), 3.2 to 5.8; p less than 0.01) , 7.1- (95% CI than 0.01), and 9.7-fold (95% CI, 7.8 to 22.5; p less than 0.01) higher compared with baseline. Increases concentrations were not significant with paroxetine use. Mean active moiety (risperidone plus 9-OH-rispe concentrations increased by 1.8-fold (95% CI, 1.4 to 2.7; p less than 0.05) during the 40-mg paroxetine c not significant with 10- or 20-mg doses. Metabolic ratio was significantly increased (p less than 0.01) by to 6.2) with 10 mg of paroxetine, by 8.2-fold (95% CI, 6 to 16) with 20 mg, and by 12.6-fold (95% CI, 9.6 Negative symptom scores were significantly improved during all paroxetine doses; however, extrapyrami were significantly higher during 20- and 40-mg doses. The authors suggest that low-dose coadministratio risperidone may be safe and effective for treating schizophrenia with negative symptoms (Saito et al, 20(

3.5.1.V Pirmenol
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Several antipsychotic agents have demonstrated QT prolongation including amisulpride, halop paliperidone, quetiapine, risperidone, sertindole, sultopride, ziprasidone, and zotepine (Prod Info FANAPT(TM Prod Info Solian(R), 1999b; O'Brien et al, 1999b; Prod Info INVEGA(TM) extended-release oral tablets, 2006 Duenas-Laita et al, 1999b; Agelink et al, 2001b; Lande et al, 1992b; Prod Info GEODON(R) intramuscular inj 2005; Sweetman, 2003). Because Class IA antiarrhythmic agents may also prolong the QT interval and incre arrhythmias, the concurrent administration of antipsychotics with a drug from this class is not recommended ((TM) oral tablets, 2009; Prod Info Quinaglute(R), 1999).
3) Severity: major

4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: The concurrent administration of a Class IA antiarrhythmic and an antipsychotic is r
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) In an open-label QTc study of patients with schizophrenia or schizoaffective disorder (n=160), iloperic day was associated with QTc prolongation of 9 msec (Prod Info FANAPT(TM) oral tablets, 2009).
b) QRS widening, QTc interval prolongation, and torsades de pointes may occur with disopyramide ther Norpace(R), 1997).
c) The effects of combined therapy with quinidine (Class IA antiarrhythmic agent) and haloperidol (antip studied by giving 12 healthy volunteers haloperidol 5 mg alone and with 250 mg of quinidine bisulfate. Th significant increases in the plasma concentrations of haloperidol when given concurrently with quinidine treatment alone. The mean area under the concentration curve (AUC) was increased from 54.3 ng/h/mL to 103.2 ng/h/mL on combined therapy. The peak concentration (Cmax) also showed an increase from 1 haloperidol to 3.8 ng/mL on combined therapy. Half-life (T1/2) and time to peak concentration (Tmax) we changed, thereby suggesting to the authors that a tissue binding mechanism is more likely responsible fo changes than an elimination alteration (Young et al, 1993).

3.5.1.W Prajmaline

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Several antipsychotic agents have demonstrated QT prolongation including amisulpride, halop paliperidone, quetiapine, risperidone, sertindole, sultopride, ziprasidone, and zotepine (Prod Info FANAPT(TM Prod Info Solian(R), 1999b; O'Brien et al, 1999b; Prod Info INVEGA(TM) extended-release oral tablets, 2006 Duenas-Laita et al, 1999b; Agelink et al, 2001b; Lande et al, 1992b; Prod Info GEODON(R) intramuscular inj 2005; Sweetman, 2003). Because Class IA antiarrhythmic agents may also prolong the QT interval and incre arrhythmias, the concurrent administration of antipsychotics with a drug from this class is not recommended ((TM) oral tablets, 2009; Prod Info Quinaglute(R), 1999).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: The concurrent administration of a Class IA antiarrhythmic and an antipsychotic is r
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) In an open-label QTc study of patients with schizophrenia or schizoaffective disorder (n=160), iloperic day was associated with QTc prolongation of 9 msec (Prod Info FANAPT(TM) oral tablets, 2009).
b) QRS widening, QTc interval prolongation, and torsades de pointes may occur with disopyramide ther Norpace(R), 1997).
c) The effects of combined therapy with quinidine (Class IA antiarrhythmic agent) and haloperidol (antip studied by giving 12 healthy volunteers haloperidol 5 mg alone and with 250 mg of quinidine bisulfate. Th significant increases in the plasma concentrations of haloperidol when given concurrently with quinidine treatment alone. The mean area under the concentration curve (AUC) was increased from 54.3 ng/h/mL to 103.2 ng/h/mL on combined therapy. The peak concentration (Cmax) also showed an increase from 1 haloperidol to 3.8 ng/mL on combined therapy. Half-life (T1/2) and time to peak concentration (Tmax) we changed, thereby suggesting to the authors that a tissue binding mechanism is more likely responsible fo changes than an elimination alteration (Young et al, 1993).

3.5.1.X Procainamide

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Several antipsychotic agents have demonstrated QT prolongation including amisulpride, halop paliperidone, quetiapine, risperidone, sertindole, sultopride, ziprasidone, and zotepine (Prod Info FANAPT(TM Prod Info Solian(R), 1999b; O'Brien et al, 1999b; Prod Info INVEGA(TM) extended-release oral tablets, 2006 Duenas-Laita et al, 1999b; Agelink et al, 2001b; Lande et al, 1992b; Prod Info GEODON(R) intramuscular inj 2005; Sweetman, 2003). Because Class IA antiarrhythmic agents may also prolong the QT interval and incre arrhythmias, the concurrent administration of antipsychotics with a drug from this class is not recommended ((TM) oral tablets, 2009; Prod Info Quinaglute(R), 1999).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: The concurrent administration of a Class IA antiarrhythmic and an antipsychotic is r
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) In an open-label QTc study of patients with schizophrenia or schizoaffective disorder (n=160), iloperic day was associated with QTc prolongation of 9 msec (Prod Info FANAPT(TM) oral tablets, 2009).
b) QRS widening, QTc interval prolongation, and torsades de pointes may occur with disopyramide ther Norpace(R), 1997).
c) The effects of combined therapy with quinidine (Class IA antiarrhythmic agent) and haloperidol (antip studied by giving 12 healthy volunteers haloperidol 5 mg alone and with 250 mg of quinidine bisulfate. Th significant increases in the plasma concentrations of haloperidol when given concurrently with quinidine

treatment alone. The mean area under the concentration curve (AUC) was increased from 54.3 ng/h/mL to 103.2 ng/h/mL on combined therapy. The peak concentration (Cmax) also showed an increase from 1 haloperidol to 3.8 ng/mL on combined therapy. Half-life (T1/2) and time to peak concentration (Tmax) we changed, thereby suggesting to the authors that a tissue binding mechanism is more likely responsible fo changes than an elimination alteration (Young et al, 1993).

3.5.1.Y Prochlorperazine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Concomitant use of phenothiazines and antipsychotic agents may cause additive effects on the recommended. Q and T wave distortions have been observed in patients taking phenothiazines (Prod Info Co Prod Info Stelazine(R), 2002; Prod Info Thorazine(R), 2002). Other phenothiazines may have similar effects, available. Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info haloperidol (O'Brien et al, 1999a), paliperidone (Prod Info INVEGA(TM) extended-release oral tablets, 2006), 2001a), risperidone (Duenas-Laita et al, 1999a), sertindole (Agelink et al, 2001a), sultopride (Lande et al, 199 (Prod Info GEODON(R) intramuscular injection, oral capsule, 2005), and zotepine (Sweetman, 2003).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of agents that prolong the QT interval, such as phen antipsychotics, is not recommended.
7) Probable Mechanism: additive QT prolongation

3.5.1.Z Ranolazine

1) Interaction Effect: an increased risk of QT interval prolongation
2) Summary: Paliperidone causes an increase of QTc interval and ranolazine prolongs the QTc interval in a If concomitant administration is unavoidable, use caution when paliperidone is coadministered with ranolazin for additive effects on QT interval prolongation (Prod Info INVEGA(R) extended-release oral tablets, 2008a).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Paliperidone causes an increase of QTc interval and ranolazine prolongs the QTc i related manner. If concomitant administration is unavoidable, use caution when paliperidone is coadministere to the potential for additive effects on QT interval prolongation (Prod Info INVEGA(R) extended-release oral t
7) Probable Mechanism: additive effects on QT interval prolongation

3.5.1.AA Sematilide

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Class III antiarrhythmics have been shown to prolong the QT interval, which may result in venti ventricular fibrillation, and torsades de pointes (Prod Info CORDARONE(R) oral tablets, 2006; Prod Info sotal 2005). Modest increases in the QTc interval have been noted with paliperidone use (Prod Info INVEGA(TM) tablets, 2006). Due to the risk of additive QTc prolongation, the concurrent administration of paliperidone and antiarrhythmic agents should be avoided (Prod Info INVEGA(TM) extended-release oral tablets, 2006).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of paliperidone and class III antiarrhythmic agents sh this may result in additive QTc interval prolongation (Prod Info INVEGA(TM) extended-release oral tablets, 2
7) Probable Mechanism: additive QT prolongation

3.5.1.AB Sotalol

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Class III antiarrhythmics have been shown to prolong the QT interval, which may result in venti ventricular fibrillation, and torsades de pointes (Prod Info CORDARONE(R) oral tablets, 2006; Prod Info sotal 2005). Modest increases in the QTc interval have been noted with paliperidone use (Prod Info INVEGA(TM) tablets, 2006). Due to the risk of additive QTc prolongation, the concurrent administration of paliperidone and antiarrhythmic agents should be avoided (Prod Info INVEGA(TM) extended-release oral tablets, 2006).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of paliperidone and class III antiarrhythmic agents sh this may result in additive QTc interval prolongation (Prod Info INVEGA(TM) extended-release oral tablets, 2
7) Probable Mechanism: additive QT prolongation

3.5.1.AC Tedisamil

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Class III antiarrhythmics have been shown to prolong the QT interval, which may result in venti ventricular fibrillation, and torsades de pointes (Prod Info CORDARONE(R) oral tablets, 2006; Prod Info sotal 2005). Modest increases in the QTc interval have been noted with paliperidone use (Prod Info INVEGA(TM)

tablets, 2006). Due to the risk of additive QTc prolongation, the concurrent administration of paliperidone and antiarrhythmic agents should be avoided (Prod Info INVEGA(TM) extended-release oral tablets, 2006).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of paliperidone and class III antiarrhythmic agents sh this may result in additive QTc interval prolongation (Prod Info INVEGA(TM) extended-release oral tablets, 2(
7) Probable Mechanism: additive QT prolongation

3.5.1.AD Tetrabenazine
1) Interaction Effect: an increased risk of QT interval prolongation
2) Summary: Due to the potential for additive effects on the QT interval and increased risk of torsade de poir of tetrabenazine with drugs that prolong the QT interval should be avoided. However, if concomitant use is re should be closely monitored for prolongation of the QT interval (Prod Info XENAZINE(R) oral tablets, 2008). I double-blind, placebo controlled crossover study of healthy subjects, the effect of a single 25 mg or 50 mg do the QT interval was studied with moxifloxacin as a positive control. The 50 mg dose of tetrabenazine caused millisecond mean increase in QT (Prod Info XENAZINE(R) oral tablets, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of tetrabenazine with drugs that prolong the QT interval should be potential for additive effects on the QT interval and increased risk of torsade de pointes. However, if concurre monitor patient closely for prolongation of the QT interval (Prod Info XENAZINE(R) oral tablets, 2008).
7) Probable Mechanism: additive effects on QT interval prolongation

3.5.1.AE Thioridazine
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Although citing no data, the manufacturer of thioridazine states that concomitant use with other the QT interval is contraindicated (Prod Info Mellaril(R), 2001). Several antipsychotic agents have demonstra including amisulpride (Prod Info Solian(R), 1999c), haloperidol (O'Brien et al, 1999c), pimozide (Prod Info Ora quetiapine (Owens, 2001c), paliperidone (Prod Info INVEGA(TM) extended-release oral tablets, 2006), risper et al, 1999c), sertindole (Agelink et al, 2001c), sultopride (Lande et al, 1992c), ziprasidone (Prod Info GEODO injection, oral capsule, 2005), and zotepine (Sweetman, 2004).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of agents that prolong the QT interval, such as antips thioridazine, is contraindicated.
7) Probable Mechanism: additive QT prolongation

3.5.1.AF Trifluoperazine
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Concomitant use of phenothiazines and antipsychotic agents may cause additive effects on the recommended. Q and T wave distortions have been observed in patients taking phenothiazines (Prod Info Co Prod Info Stelazine(R), 2002; Prod Info Thorazine(R), 2002). Other phenothiazines may have similar effects, available. Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info haloperidol (O'Brien et al, 1999a), paliperidone (Prod Info INVEGA(TM) extended-release oral tablets, 2006), 2001a), risperidone (Duenas-Laita et al, 1999a), sertindole (Agelink et al, 2001a), sultopride (Lande et al, 199 (Prod Info GEODON(R) intramuscular injection, oral capsule, 2005), and zotepine (Sweetman, 2003).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of agents that prolong the QT interval, such as phen antipsychotics, is not recommended.
7) Probable Mechanism: additive QT prolongation

4.0 Clinical Applications

Monitoring Parameters

Patient Instructions

Place In Therapy

Mechanism of Action / Pharmacology

Therapeutic Uses

Comparative Efficacy / Evaluation With Other Therapies

4.1 Monitoring Parameters

A) Therapeutic

1) Physical Findings

a) Schizophrenia

1) Patients should be monitored for signs of improvement in the target positive and negative symptoms as improved communication, decreased hallucinations and delusions, improved socialization, and decrea of improvement in socialization, grooming, and attention to activities of daily living should also be monito

B) Toxic

1) Laboratory Parameters

a) Fasting glucose test in patients with a diagnosis or with risk factors for diabetes mellitus at the initiation of periodically during treatment (Prod Info INVEGA(TM) extended-release oral tablets, 2006)

2) Physical Findings

a) Hyperglycemia symptom monitoring in all patients for polydipsia, polyuria, polyphagia, and weakness (Prc extended-release oral tablets, 2006)

b) Neuroleptic malignant syndrome has been reported and patients should be monitored for the signs and sy syndrome (hyperpyrexia, muscle rigidity, altered mental status, and autonomic instability) (Prod Info INVEGA release oral tablets, 2006).

c) Orthostatic vital sign monitoring in patients susceptible to hypotension (Prod Info INVEGA(TM) extended-r 2006)

d) QT prolongation has been reported with paliperidone, a baseline EKG may be considered (Prod Info INVE release oral tablets, 2006)

e) Suicide monitoring in high-risk patients (Prod Info INVEGA(TM) extended-release oral tablets, 2006)

4.2 Patient Instructions

A) Paliperidone (By mouth)

Paliperidone

Treats schizophrenia (a mental disorder).

When This Medicine Should Not Be Used:
You should not use this medicine if you have had an allergic reaction to paliperidone or risperidone.

How to Use This Medicine:
Long Acting Tablet

Your doctor will tell you how much of this medicine to use and how often. Your dose may need to be changed order to find out what works best for you. Do not use more medicine or use it more often than your doctor tell
You may take this medicine with or without food.
Swallow the extended-release tablet whole. Do not crush, break, or chew it. Swallow the tablet with a liquid, s
While taking the extended-release form of this medicine, part of the tablet may pass into your stools. This is r to worry about.

If a Dose is Missed:

If you miss a dose or forget to use your medicine, use it as soon as you can. If it is almost time for your next d use the medicine and skip the missed dose. Do not use extra medicine to make up for a missed dose.

How to Store and Dispose of This Medicine:

Store the medicine in a closed container at room temperature, away from heat, moisture, and direct light.
Ask your pharmacist, doctor, or health caregiver about the best way to dispose of any leftover medicine after your treatment. You will also need to throw away old medicine after the expiration date has passed.
Keep all medicine away from children and never share your medicine with anyone.

Drugs and Foods to Avoid:
Ask your doctor or pharmacist before using any other medicine, including over-the-counter medicines, vitamins, a

Make sure your doctor knows if you are using medicines for heart rhythm problems (such as amiodarone, qui sotalol, Betapace®, Cordarone®, Procanbid®) or a diuretic, also called a "water pill" (such as furosemide, hy Aldactazide®, Aldactone®, Lasix®, Maxzide®).
Tell your doctor if you are using levodopa (Dopar®, Larodopa®), any medicine for mental illness (such as chl thioridazine, Thorazine®, Mellaril®), or certain antibiotic medicines (such as gatifloxacin, moxifloxacin, Tequi
Tell your doctor if you are using any medicines that make you sleepy. These include sleeping pills, cold and a narcotic pain relievers, and sedatives.
Do not drink alcohol while you are using this medicine.

Warnings While Using This Medicine:

Make sure your doctor knows if you are pregnant, planning to become pregnant, or if you are breastfeeding. T
have a history of seizures, heart disease, kidney disease, stroke, or breast cancer. Make sure your doctor kn
Parkinson's disease, any trouble with swallowing, or a history of blocked bowels or stomach and intestine pro
doctor if you have ever had thoughts of hurting yourself.

Make sure your doctor knows if you or a family member has a heart condition called congenital long QT synd
if you have ever had a condition called neuroleptic malignant syndrome (NMS) that was caused by a medicin
disorders.

This medicine may cause an increase in your blood sugar. If you have diabetes, you may need to check your
often. If you are using medicine for diabetes, your doctor may need to change your dose.

This medicine is not approved to treat behavior disorders in older people who have dementia. Using this med
problem could increase the risk of death. This risk has not been shown for the approved uses of this medicin
Some side effects are more likely to happen in elderly people who have memory problems or other reduced r
sure the doctor knows if the person who will be using this medicine has Alzheimer's disease or similar proble
"dementia").

This medicine may cause tardive dyskinesia, which is a movement disorder. If you have muscle spasms, twit
body, or uncontrolled tongue or jaw movements, stop taking this medicine and call your doctor right away. Ta
the risk of this side effect.

This medicine may make you dizzy or drowsy. Avoid driving, using machines, or doing anything else that cou
are not alert. You may also feel lightheaded or dizzy when you get up quickly from a sitting or lying position. I
should get up slowly.

This medicine might reduce how much you sweat. Your body could get too hot if you do not sweat enough. If
hot, you might feel dizzy, weak, tired, or confused. You might vomit or have an upset stomach. Do not get too
exercising. Avoid places that are very hot. Call your doctor if you are too hot and cannot cool down.

Your doctor will need to check your progress at regular visits while you are using this medicine. Be sure to ke

If your symptoms do not improve or if they get worse, call your doctor.

Possible Side Effects While Using This Medicine:

Call your doctor right away if you notice any of these side effects:

Allergic reaction: Itching or hives, swelling in your face or hands, swelling or tingling in your mouth or throat, c
breathing.

Dry mouth, increased thirst, muscle cramps, nausea, or vomiting.

Fast, slow, pounding, or irregular heartbeat.

Fever, confusion, sweating, or muscle stiffness.

Lightheadedness, dizziness, or fainting.

Neck muscle spasm, throat tightness, difficulty swallowing or breathing, or sticking out of the tongue.

Painful or prolonged erection of the penis.

Pinpoint red spots on skin.

Problems with speech, balance, or walking.

Seizures or tremors.

Swelling of breasts or unusual milk production.

Twitching or muscle movements you cannot control (often in your face, tongue, or jaw).

If you notice these less serious side effects, talk with your doctor:

Anxiety or restlessness.

Drooling.

Headache.

Sleepiness or unusual drowsiness.

Stomach pain or upset stomach.

Unusual tiredness or weakness.

Weight gain.

If you notice other side effects that you think are caused by this medicine, tell your doctor.

4.3 Place In Therapy

A) Current users of atypical antipsychotic drugs (including paliperidone) and typical antipsychotic drugs had a similar
of sudden cardiac death, according to a retrospective cohort of 93,300 adult users of antipsychotic drugs and 186,600
The study included patients age 30 to 74 years (mean 45.7 +/- 11.8 years) with similar cardiovascular risk at baseline
filled prescription and had 1 outpatient visit in each of the 2 preceding years. Sudden cardiac death was defined as oc
community and excluded deaths of patients admitted to the hospital, non-sudden deaths, deaths due to extrinsic caus
related to ventricular tachyarrhythmia. Current use was defined as the interval between the time the prescription was f
the day's supply. Low and high doses was defined as comparable to less than 100 milligrams (mg) of chlorpromazine,
comparable to chlorpromazine 300 mg or greater, respectively. The adjusted rate of sudden cardiac death (incidence-
users of atypical antipsychotic drugs in 79,589 person-years was 2.26 (95% CI, 1.88 to 2.72, p less than 0.001) which
in current users of typical antipsychotic drugs in 86,735 person-years which was 1.99 (95% CI, 1.68 to 2.34, p less tha
sudden cardiac death significantly increased with increasing dose in both the typical and atypical antipsychotic drug gr
antipsychotic use, the incidence rate ratio increased from 1.59 (95% CI, 1.03 to 2.46) in low-dose use to 2.86 (95% CI
dose use. To limit the effects of confounding of the study results, there was a secondary analysis performed in a coho

by propensity score, which resulted in a similar risk of sudden death as the primary cohort analysis (Ray et al, 2009). I New England Journal of Medicine, it has been suggested that antipsychotic drugs continue to be used in patients with benefit, but in vulnerable populations with cardiac risk profiles (eg, elderly patients), there should be an age-dependen prior to administration. It has also been suggested (although not formally tested) that ECGs be performed before and s of antipsychotic therapy to screen for existing or emergent QT interval prolongation (Schneeweiss & Avorn, 2009).
B) Paliperidone is a benzisoxazole derivative, and an active metabolite of risperidone. It is indicated for the treatment efficacy in improving positive symptoms, negative symptoms, disorganized thoughts, uncontrolled hostility/excitement, anxiety/depression among patients with schizophrenia has been established in three 6-week, multinational, fixed-dose and active-controlled (olanzapine) trials. While the mechanism of action of paliperidone is unclear, it is thought to bloc dopamine Type 2 (D(2)) and serotonin Type 2 (5HT(2A)) receptors, and has antagonistic effects on the alpha-1 adren adrenergic, and H1 histaminergic receptors (Prod Info INVEGA(TM) extended-release oral tablets, 2006). Due to the l efficacy data with haloperidol, fluphenazine, risperidone, and other conventional neuroleptics, the role of paliperidone i schizophrenia is unclear. Concomitant use of paliperidone with risperidone has not been studied.
C) Paliperidone extended-release is also being investigated as a monotherapy and as an adjunctive therapy to lithium treatment of acute manic and mixed episodes associated with bipolar I disorder, as well as in schizoaffective disorder.
See Drug Consult reference: FIRST- VS SECOND-GENERATION ANTIPSYCHOTIC AGENTS FOR SCHIZOPHREN

4.4 Mechanism of Action / Pharmacology

A) Paliperidone is the major active metabolite of risperidone. While the mechanism of action is unknown, its proposed antagonism of both the central dopamine Type 2 (D(2)) and serotonin Type 2 (5HT(2A)) receptors. It also has antagon alpha-1 adrenergic, alpha-2 adrenergic, and H1 histaminergic receptors; however, the degree of affinity is unclear. Pal known affinity for cholinergic muscarinic or beta-1 and beta-2 adrenergic receptors (Prod Info INVEGA(TM) extended- 2006).

4.5 Therapeutic Uses

4.5.A Schizophrenia

FDA Labeled Indication

1) Overview

FDA Approval: Adult, yes; Pediatric, no
Efficacy: Adult, Effective
Recommendation: Adult, Class IIa
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Paliperidone is indicated for the treatment of schizophrenia (Prod Info INVEGA(TM) extended-release or
A 6-week, randomized, double-blind, placebo- and active-controlled, dose-response study (n=630) demo daily paliperidone (6 milligrams (mg), 9 mg, and 12 mg) extended-release (ER) was effective in significar schizophrenia symptoms, personal functioning, and social functioning (Kane et al, 2007).
In a randomized, double-blind, placebo-controlled study (n=113), paliperidone extended-release (ER) tab delayed time-to-recurrence of schizophrenia symptoms and maintained symptom stability relative to plac 2007).
Geriatric patients (n=114) were safely treated with paliperidone extended-release tablets and although n for efficacy or safety and tolerability, clinical improvements were seen, according to a prospective, 6-wee randomized, placebo-controlled, optional 24-week open-label extension safety trial (Tzimos et al, 2008).

3) Adult:

a) Acute Therapy

1) A 6-week, randomized, double-blind, placebo- and active-controlled, dose-response study demonstra paliperidone (6 milligrams (mg), 9 mg, and 12 mg) extended-release (ER) was effective in significantly in symptoms, personal functioning, and social functioning. The enrolled patients (n=630) were greater than of age (mean age, 37.1 years), experiencing an acute episode of schizophrenia (Positive and Negative S (PANSS) score between 70 and 120), and had a diagnosis of schizophrenia according to the Diagnostic of Mental Disorders Fourth Edition (DSM-IV) for at least 1 year. After discontinuation of previous medicat antiparkinsonian drugs, beta-blockers or other psychotropic agents) for three days prior to randomization group (n=628) received either paliperidone ER 6 mg (n=123), paliperidone ER 9 mg (n=122), paliperidon olanzapine 10 mg (n=128), or placebo (n=126) once daily for 6 weeks. The primary efficacy variable was PANSS score from baseline to 6 weeks for each dose of paliperidone ER compared to placebo. The mea deviation (SD)) decrease in PANSS score was 17.9 (+/-22.2), 17.2 (+/-20.2), 23.3 (+/-20.1) for the 6 mg, paliperidone ER groups (p less than 0.001 vs placebo), respectively, compared with 4.1 (+/-23.2), and 19 placebo and olanzapine groups, respectively. All doses of paliperidone ER resulted in statistically signific placebo (p less than 0.001) in all PANSS Marder factor scores. Clinical response (defined as a greater th decrease in PANSS total score) was achieved in 56%, 51%, 61%, and 30% for the paliperidone ER 6 mg placebo groups, respectively (p less than 0.001 for all groups vs placebo). Improvement in personal and (+/- SD) scores was 9.1 (+/-15.5), 8.1 (+/-14.5), 11.5 (+/-16), and 0.5 (+/-15.5) for the paliperidone 6 mg, placebo groups, respectively (p less than 0.001). At 6 weeks, fewer patients were classified as marked o the Clinical and Global Impressions-Severity scale scores (paliperidone ER 6 mg: 62.6% at baseline vs 2 paliperidone ER 9 mg: 57.3% at baseline vs 23% at 6 weeks, paliperidone ER 12 mg: 64.4% at baseline placebo: 59.5% at baseline vs 50.8% at 6 weeks, p less than 0.001 for all doses vs placebo). The numbe

adverse effects in the safety analysis group (n=629) was similar among all groups. The most common ac
to discontinuation of the study was tachycardia (2% for paliperidone ER 12 mg, 1% in all other groups). F
showed no observable dose-response relationship for the severity of adverse events. The most common
effect was psychosis which occurred in 2% of the paliperidone ER 12 mg group, 1% of the placebo, palip
olanzapine groups, and in 0% of the paliperidone ER 9 mg group. Most movement disorder-related adve
to moderate in severity; 3 patients discontinued the study because of movement disorder-related adverse
paliperidone ER 6 mg group, 2 in the 12 mg group) (Kane et al, 2007).

b) Maintenance Therapy

1) In a randomized, double-blind, placebo-controlled study, paliperidone extended-release (ER) tablets s
time-to-recurrence of schizophrenia symptoms and maintained symptom stability relative to placebo. The
65 years old and had a diagnosis of schizophrenia according to the Diagnostic and Statistical Manual of
Fourth Edition (DSM-IV) for at least 1 year. The patients were also experiencing an acute episode of sch
and Negative Syndrome Scale (PANSS) total score of 70-120). The study consisted of an 8-week run-in
patients received open-label paliperidone ER, starting at 9 milligrams (mg) once daily and adjusted until
for at least 2 weeks (dose range: 3 to 15 mg once daily). This was followed by a 6-week open-label stabi
they remained on their stabilized dose. Patients then entered a double-blinded treatment phase in which
randomized to receive paliperidone ER or placebo for maintenance therapy. The patients remained in th
until they experienced a recurrence event (defined as: psychiatric hospitalization, a pre-defined increase
Clinical and Global Impression-Severity (CGI-S) score, deliberate self-injury, aggressive behavior, suicid
homicidal ideation), until they withdrew from the study or until the end of the study. The time to first recur
double-blind phase was the primary efficacy variable. At the interim analysis (n=113), the study was term
significant efficacy was established; 14 patients (25%) in the paliperidone ER group experienced a recur
to 29 patients (53%) in the placebo group. In the final analysis (n=205), paliperidone ER significantly dela
recurrence (25% quantile of time-to-recurrence was 83 days for paliperidone ER vs 23 days for placebo,
open-label phases of the trial, 73% of patients reported treatment-related adverse events while 37% of p
treatment-related adverse events in the double-blind phase. A 2 fold increase in treatment-related advers
reported for the placebo group than for the paliperidone ER group; most related to the underlying psycho
psychosis and aggressive reaction occurred more frequently in the placebo group (n=102, 23% and 6%,
the paliperidone ER group (n=104, 7% and 1%, respectively) (Kramer et al, 2007).

c) Geriatric

1) According to a prospective, 6-week, double-blind, randomized, placebo-controlled, optional 24-week
safety trial, paliperidone treatment was well tolerated in the geriatric population compared with placebo.
adverse events in geriatric patients receiving paliperidone extended-release tablets in general were simil
increased age-related incidences of somnolence and elevated pulse rate. Although the study was not su
efficacy or safety and tolerability, clinical improvements were seen in the Positive and Negative Syndrom
paliperidone-treated (n=76) versus placebo-treated patients (n=38) during the 6-week double-blind perio
difference in the change from baseline of -14.6 vs -9.9, respectively yielding a difference between groups
confidence interval, -9.9 to -1.1, p=0.014). There were nonsignificant differences seen between treatmen
Clinical Global Impressions Severity (CGI-S) scale, Personal and Social Performance Scale, and the Scl
Life Scale. The study included 114 patients (mean age of 70 years) with 99% having moderate to severe
receiving either placebo or median mean dose of paliperidone ER 8.4 milligrams/day (mg/day) during the
and median mean doses of 7.4 mg and 8.5 mg in the placebo/paliperidone ER and paliperidone ER/palip
respectively during the open-label phase (Tzimos et al, 2008).

4.6 Comparative Efficacy / Evaluation With Other Therapies

4.6.A Quetiapine Fumarate

4.6.A.1 Schizophrenia, Recent exacerbation, in hospitalized patients

a) In a randomized, double-blind, placebo- and active-controlled clinical trial (n=394), treatment with paliperid
(ER) produced significantly improved Positive and Negative Syndrome Scale (PANSS) total scores compared
hospitalized patients with a recent exacerbation of schizophrenia. Hospitalized patients 18 to 65 years of age
(defined as lasting less than 4 weeks but more than 4 days) of schizophrenia (paranoid, disorganized, or und
diagnosed using Diagnostic and Statistical Manual of Mental Disorders Fourth edition (DSM-IV)), a Clinical G
Severity (CGI-S) scale score of 5 or greater, and symptom scores of 4 or greater on 2 or more of the following
hostility, excitement, tension, uncooperativeness, and poor impulse control (with a combined score of these it
were eligible for enrollment. Following the discontinuation of all psychotropic agents, patients were randomize
paliperidone ER (n=157; baseline mean PANSS total score, 102.8 +/- 13.1 points), quetiapine (n=157; baseli
score, 101.3 +/- 13.3 points), or placebo (n=80; baseline mean PANSS total score, 103.8 +/- 15.7 points). In a
phase, paliperidone ER was initiated at 6 milligrams (mg)/day on days 1 to 3 and then increased to 9 mg/day
an optional dose increase to 12 mg/day starting on day 8 if necessary (mean dose, 10.4 +/- 1.7 mg/day) and
at 50 mg/day on day 1, 100 mg/day on day 2, 200 mg/day on day 3, 400 mg/day on day 4, 600 mg/day on da
dose increase to 800 mg/day on day 8 (mean dose, 690.9 +/- 134.3 mg/day). Psychotropic medications (excl
additional paliperidone ER or quetiapine) could be added following the 14-day monotherapy phase (one or m
agents: paliperidone ER, 52.9%; quetiapine, 55.4%; placebo, 66.7%). The least-squares mean PANSS total s
baseline to day 14 was significantly decreased in the paliperidone ER arm (-23.4 +/- 1.8 (standard error (SE)
with the quetiapine arm (-17.1 +/- 1.8 (SE) points; p less than 0.001) (primary endpoint) and the placebo arm
between group analyses (using a least-squares mean differences in change scores with the last observation

patients in the paliperidone ER arm had significantly improved PANSS total score, PANSS scale negative sy
PANSS scale disorganized thoughts scores, PANSS scale uncontrolled hostility/excitement scores, and CGI-
with patients in the quetiapine and placebo arms at day 14 and at the end of 6 weeks of treatment (day 42) (T
the PANSS scale positive symptoms score (PANSS-P) and Clinical Global Impression of Change (CGI-C) sc
improved in the paliperidone ER arm compared with the quetiapine and placebo arms at day 14 and paliperic
improved PANSS-P and CGI-C compared with placebo at day 42 (Table 1). Serious adverse events were rep
and 2.5% of patients in the paliperidone ER, quetiapine, and placebo arms, respectively. Extrapyramidal sym
significantly (p less than 0.001) higher in the paliperidone ER arm following the 14-day monotherapy phase c
quetiapine using the Simpson-Angus Rating Scale (total score). The incidence of movement disorders at day
significantly different between the 3 arms using the Barnes Akathisia Rating Scale and the Abnormal Involunt
(Canuso et al, 2009).

Table 1: Between Group Analyses

Outcome measures	Day 14			Day 42	
PANSS score Mean (SE)	Paliperidone ER versus Quetiapine	Paliperidone ER versus Placebo	Quetiapine versus Placebo	Paliperidone ER versus Quetiapine	Paliperidc ER versus Placebc
Total	-6.3* (1.8)	-8.4* (2.2)	-2.1 (2.2)	-4.7* (2)	-7.8* (2.
Positive symptoms	-1.6* (0.6)	-2.1* (0.7)	-0.5 (0.7)	-1.1 (0.6)	-1.9* (0.
Negative symptoms	-1.3* (0.5)	-2.2* (0.6)	-0.9 (0.6)	-1.2* (0.5)	-2.1* (0.
Anxiety/depression	-0.5 (0.3)	-0.6 (0.4)	-0.1 (0.4)	-0.4 (0.3)	-0.5 (0.4
Disorganized thoughts	-1.3* (0.4)	-2.1* (0.5)	-0.8 (0.5)	-1* (0.5)	-2* (0.6
Uncontrolled hostility/excitement	-1.5* (0.4)	-1.6* (0.5)	-0.1 (0.5)	-1* (0.4)	-1.3* (0.
CGI-S (Mean SE)	-0.3* (0.1)	-0.4* (0.1)	-0.1 (0.1)	-0.3* (0.1)	-0.5* (0.
CGI-C (Mean SE)	-0.4* (0.1)	-0.5* (0.1)	-0.2 (0.1)	-0.1 (0.1)	-0.4* (0.

*p less than 0.05

PANSS, Positive and Negative Syndrome Scale; SE, standard error; CGI-S, Clinical Global Impression
Clinical Global Impression of Change

6.0 References

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Last Modified: June 25, 2009

DRUGDEX® Evaluations

LAMOTRIGINE

0.0 Overview

1) Class

a) This drug is a member of the following class(es):
Anticonvulsant
Phenyltriazine

2) Dosing Information

a) Adult

1) caution for potential for dispensing errors involving similarly named medications (Prod Info LAMICTAL chewab disintegrating tablets, 2009)

2) safety and efficacy as initial monotherapy, for conversion to monotherapy from a non-enzyme-inducing antiepi conversion to monotherapy from 2 or more concomitant antiepileptic drugs has not been established (Prod Info L orally disintegrating tablets, 2009)

a) Bipolar I disorder

1) (patients not taking enzyme-inducing drugs or valproic acid) 25 mg/day orally for 2 weeks, then 50 m 200 mg/day; usual maintenance dose of lamotrigine in patients not taking enzyme-inducing drugs or valp dispersible oral tablets, oral tablets, orally disintegrating tablets, 2009)

2) (added to valproic acid regimen) 25 mg/day orally every other day for 2 weeks, then 25 mg/day for 2 usual maintenance dose of lamotrigine in patients taking valproic acid is 100 mg/day (Prod Info LAMICT disintegrating tablets, 2009)

3) (added to enzyme-inducing antiepileptic drug regimen without valproic acid) 50 mg/day orally for 2 we then 200 mg/day for 1 week (in divided doses), then 300 mg/day for 1 week (in divided doses), then may mg/day (in divided doses) (Prod Info LAMICTAL chewable dispersible oral tablets, oral tablets, orally disi

b) Lennox-Gastaut syndrome; Adjunct

1) (added to antiepileptic drug regimen with valproic acid) 25 mg/day ORALLY every OTHER day for 2 dosage by 25 to 50 mg/day ORALLY every 1 to 2 weeks to the usual maintenance dose of 100 to 400 m of patients adding lamotrigine to valproic acid ALONE ranges from 100 to 200 mg/day (Prod Info LAMIC disintegrating tablets, 2009)

2) (added to antiepileptic drug regimen not containing enzyme-inducing antiepileptic drugs or valproic ac 2 weeks; may increase dosage by 50 mg/day every 1 to 2 weeks to the usual maintenance dose of 225 chewable dispersible oral tablets, oral tablets, orally disintegrating tablets, 2009)

3) (added to enzyme-inducing antiepileptic drug regimen without valproic acid) 50 mg/day ORALLY for 2 weeks; may increase dosage by 100 mg/day ORALLY every 1 to 2 weeks to the usual maintenance dos LAMICTAL chewable dispersible oral tablets, oral tablets, orally disintegrating tablets, 2009)

c) Partial seizure, Adjunct or monotherapy

1) (chewable dispersible or orally disintegrating tablets; added to antiepileptic drug regimen with valproic then 25 mg/day for 2 weeks; may increase dosage by 25 to 50 mg/day ORALLY every 1 to 2 weeks to th 2 divided doses; usual maintenance dose of patients adding lamotrigine to valproic acid ALONE ranges dispersible oral tablets, oral tablets, orally disintegrating tablets, 2009)

2) (chewable dispersible or orally disintegrating tablets; added to antiepileptic drug regimen not containi ORALLY for 2 weeks, then 50 mg/day for 2 weeks; may increase dosage by 50 mg/day every 1 to 2 wee in 2 divided doses (Prod Info LAMICTAL chewable dispersible oral tablets, oral tablets, orally disintegrati

3) (chewable dispersible or orally disintegrating tablets; added to antiepileptic drug regimen containing e mg/day orally for 2 weeks, then 100 mg/day (in 2 divided doses) for 2 weeks; may increase dosage by 1 maintenance dose of 300 to 500 mg/day (in 2 divided doses) (Prod Info LAMICTAL chewable dispersible 2009)

4) (chewable dispersible or orally disintegrating tablets; conversion to monotherapy in patients, 16 yr an inducing antiepileptic drug) 500 mg/day orally (in 2 divided doses); titrate lamotrigine to the targeted dos withdraw the other drug by 20% decrements each week over a 4-week period (Prod Info LAMICTAL che disintegrating tablets, 2009)

5) (chewable dispersible or orally disintegrating tablets; conversion to monotherapy in patients, 16 yr an lamotrigine to 200 mg/day while maintaining valproic acid dose, the maintain lamotrigine dose at 200 mg by decrements no greater than 500 mg/day per week and then maintain the dose at 500 mg/day for 1 we while simultaneously decreasing the valproic acid to 250 mg/day and maintain this for 1 week, finally dis 100 mg/day each week until the maintenance dose of 500 mg/day is reached(Prod Info LAMICTAL chew disintegrating tablets, 2009)

6) (extended-release tablets; added to antiepileptic drug regimen with valproic acid) weeks 1 and 2, 25 mg/day; week 5, 50 mg/day; week 6, 100 mg/day; week 7, 150 mg/day; weeks 8 onwards to maintenanc 200 to 250 mg/day (Prod Info LAMICTAL XR oral extended-release tablets, 2009)

7) (extended-release tablets; added to antiepileptic drug regimen not containing enzyme-inducing drugs weeks 3 and 4, 50 mg/day; week 5, 100 mg/day; week 6, 150 mg/day; week 7, 200 mg/day; weeks 8 on at weekly intervals), 300 to 400 mg/day (Prod Info LAMICTAL XR oral extended-release tablets, 2009)

8) (extended-release tablets; added to antiepileptic drug regimen containing enzyme-inducing drugs and ORALLY; weeks 3 and 4, 100 mg/day; week 5, 200 mg/day; week 6, 300 mg/day; week 7, 400 mg/day; v 100 mg/day at weekly intervals), 400 to 600 mg/day (Prod Info LAMICTAL XR oral extended-release tab
9) (extended-release tablets; conversion from immediate-release lamotrigine tablets) initial, should matc need adjustments depending on therapeutic response after conversion (Prod Info LAMICTAL XR oral ex

d) Tonic-clonic seizure, Primary generalized; Adjunct

1) (added to antiepileptic drug regimen with valproic acid) 25 mg/day orally every other day for 2 weeks, 25 to 50 mg/day orally every 1 to 2 weeks to the usual maintenance dose of 100 to 400 mg/day in 1 to 2 adding lamotrigine to valproic acid alone ranges from 100 to 200 mg/day (Prod Info LAMICTAL chewable disintegrating tablets, 2009)
2) (added to antiepileptic drug regimen not containing enzyme-inducing antiepileptic drugs or valproic ac weeks; may increase dosage by 50 mg/day every 1 to 2 weeks to the usual maintenance dose of 225 to chewable dispersible oral tablets, oral tablets, orally disintegrating tablets, 2009)
3) (added to enzyme-inducing antiepileptic drug regimen without valproic acid) 50 mg/day orally for 2 we may increase dosage by 100 mg/day orally every 1 to 2 weeks to the usual maintenance dose of 300 to chewable dispersible oral tablets, oral tablets, orally disintegrating tablets, 2009)

b) Pediatric

1) safety and efficacy of extended-release lamotrigine in patients below 13 years of age has not been established tablets, 2009)
2) safety and efficacy in pediatric patients with acute mood disorders has not been established (Prod Info LAMIC 2007)
3) efficacy in pediatric patients (age range, 1 to 24 months) for the treatment of partial seizures was not demonst tablets, oral tablets, orally disintegrating tablets, 2009)

a) Lennox-Gastaut syndrome; Adjunct

1) (2 to 12 yr; added to antiepileptic drug regimen with valproic acid) 0.15 mg/kg/day (rounded down to t doses for 2 weeks, then 0.3 mg/kg/day (rounded down to the nearest whole tablet) in 1 to 2 divided dose every 1 to 2 weeks (rounded down to the nearest whole tablet) to the usual maintenance dose of 1 to 5 r usual maintenance dose for children adding lamotrigine to valproic acid ALONE ranges from 1 to 3 mg/k tablets, oral tablets, orally disintegrating tablets, 2009)
2) (2 to 12 yr; added to antiepileptic drug regimen not containing enzyme-inducing antiepileptic drugs or nearest whole tablet) ORALLY in 1 to 2 divided doses for 2 weeks, then 0.6 mg/kg/day (rounded down to weeks; may increase dosage by 0.6 mg/kg/day every 1 to 2 weeks (rounded down to the nearest whole t mg/kg/day in 2 divided doses (max 300 mg/day) (Prod Info LAMICTAL chewable dispersible oral tablets,
3) (2 to 12 yr; added to enzyme-inducing antiepileptic drug regimen without valproic acid) 0.6 mg/kg/day 2 divided doses for 2 weeks, then 1.2 mg/kg/day (rounded down to the nearest whole tablet) in 2 divided mg/kg/day every 1 to 2 weeks (rounded down to the nearest whole tablet) to the usual maintenance dose mg/day) (Prod Info LAMICTAL chewable dispersible oral tablets, oral tablets, orally disintegrating tablets
4) (over age 12; added to antiepileptic drug regimen with valproic acid) 25 mg/day ORALLY every OTHE increase dosage by 25 to 50 mg/day ORALLY every 1 to 2 weeks to the usual maintenance dose of 100 maintenance dose of patients adding lamotrigine to valproic acid ALONE ranges from 100 to 200 mg/day tablets, oral tablets, orally disintegrating tablets, 2009)
5) (over age 12; added to antiepileptic drug regimen not containing enzyme-inducing antiepileptic drugs 50 mg/day for 2 weeks; may increase dosage by 50 mg/day every 1 to 2 weeks to the usual maintenanc Info LAMICTAL chewable dispersible oral tablets, oral tablets, orally disintegrating tablets, 2009)
6) (over age 12; added to enzyme-inducing antiepileptic drug regimen without valproic acid) 50 mg/day doses) for 2 weeks; may increase dosage by 100 mg/day ORALLY every 1 to 2 weeks to the usual main (Prod Info LAMICTAL chewable dispersible oral tablets, oral tablets, orally disintegrating tablets, 2009)

b) Partial seizure, Adjunct or monotherapy

1) (chewable dispersible or orally disintegrating tablets; 2 to 12 yr; added to antiepileptic drug regimen w nearest whole tablet) ORALLY in 1 to 2 divided doses for 2 weeks, then 0.3 mg/kg/day (rounded down to weeks; may increase dosage by 0.3 mg/kg/day every 1 to 2 weeks (rounded down to the nearest whole t mg/kg/day in 1 to 2 divided doses (max 200 mg/day); usual maintenance dose for children adding lamotr mg/kg/day (Prod Info LAMICTAL chewable dispersible oral tablets, oral tablets, orally disintegrating table
2) (chewable dispersible or orally disintegrating tablets; 2 to 12 yr; added to antiepileptic drug regimen n valproic acid) 0.3 mg/kg/day (rounded down to the nearest whole tablet) ORALLY in 1 to 2 divided doses nearest whole tablet) in 2 divided doses for 2 weeks; may increase dosage by 0.6 mg/kg/day every 1 to 2 the usual maintenance dose of 4.5 to 7.5 mg/kg/day in 2 divided doses (max 300 mg/day) (Prod Info LAM orally disintegrating tablets, 2009)
3) (chewable dispersible or orally disintegrating tablets; 2 to 12 yr; added to enzyme-inducing antiepilept (rounded down to the nearest whole tablet) ORALLY in 2 divided doses for 2 weeks, then 1.2 mg/kg/day doses for 2 weeks; may increase dosage by 1.2 mg/kg/day every 1 to 2 weeks (rounded down to the nea 15 mg/kg/day in 2 divided doses (max 400 mg/day) (Prod Info LAMICTAL chewable dispersible oral table
4) (chewable dispersible or orally disintegrating tablets, over age 12; added to antiepileptic drug regimen day for 2 weeks, then 25 mg/day for 2 weeks; may increase dosage by 25 to 50 mg/day ORALLY every 400 mg/day in 1 to 2 divided doses; usual maintenance dose of patients adding lamotrigine to valproic ac LAMICTAL chewable dispersible oral tablets, oral tablets, orally disintegrating tablets, 2009)
5) (chewable dispersible or orally disintegrating tablets; over age 12; added to antiepileptic drug regimen valproic acid) 25 mg/day ORALLY for 2 weeks, then 50 mg/day for 2 weeks; may increase dosage by 50

dose of 225 to 375 mg/day in 2 divided doses (Prod Info LAMICTAL chewable dispersible oral tablets, or
6) (chewable dispersible or orally disintegrating tablets; over age 12; added to enzyme-inducing antiepil
ORALLY for 2 weeks, then 100 mg/day (in 2 divided doses) for 2 weeks; may increase dosage by 100 m
maintenance dose of 300 to 500 mg/day (in 2 divided doses) (Prod Info LAMICTAL chewable dispersible
2009)
7) (extended-release tablets; age 13 and older; added to antiepileptic drug regimen with valproic acid) w
weeks 3 and 4, 25 mg/day; week 5, 50 mg/day; week 6, 100 mg/day; week 7, 150 mg/day; week 8 onwa
100 mg/day at weekly intervals), 200 to 250 mg/day (Prod Info LAMICTAL XR oral extended-release tab
8) (extended-release tablets; age 13 and older; added to antiepileptic drug regimen not containing enzy
mg/day ORALLY; weeks 3 and 4, 50 mg/day; week 5, 100 mg/day; week 6, 150 mg/day; week 7, 200 mg
should not exceed 100 mg/day at weekly intervals), 300 to 400 mg/day (Prod Info LAMICTAL XR oral ex
9) (extended-release tablets; age 13 and older; added to antiepileptic drug regimen containing enzyme-i
2, 50 mg/day ORALLY; weeks 3 and 4, 100 mg/day; week 5, 200 mg/day; week 6, 300 mg/day; week 7,
increase should not exceed 100 mg/day at weekly intervals), 400 to 600 mg/day (Prod Info LAMICTAL X
10) (extended-release tablets; age 13 and older; conversion from immediate-release lamotrigine tablets)
release lamotrigine; may need adjustments depending on therapeutic response after conversion (Prod In

c) Tonic-clonic seizure, Primary generalized; Adjunct
1) (2 to 12 yr; added to antiepileptic drug regimen with valproic acid) 0.15 mg/kg/day (rounded down to t
for 2 weeks, then 0.3 mg/kg/day (rounded down to the nearest whole tablet) in 1 to 2 divided doses for 2
to 2 weeks (rounded down to the nearest whole tablet) to the usual maintenance dose of 1 to 5 mg/kg/da
maintenance dose for children adding lamotrigine to valproic acid ALONE ranges from 1 to 3 mg/kg/day
oral tablets, orally disintegrating tablets, 2009)
2) (2 to 12 yr; added to antiepileptic drug regimen not containing enzyme-inducing antiepileptic drugs or
nearest whole tablet) ORALLY in 1 to 2 divided doses for 2 weeks, then 0.6 mg/kg/day (rounded down to
weeks; may increase dosage by 0.6 mg/kg/day every 1 to 2 weeks (rounded down to the nearest whole t
mg/kg/day in 2 divided doses (max 300 mg/day) (Prod Info LAMICTAL chewable dispersible oral tablets,
3) (2 to 12 yr; added to enzyme-inducing antiepileptic drug regimen without valproic acid) 0.6 mg/kg/day
divided doses for 2 weeks, then 1.2 mg/kg/day (rounded down to the nearest whole tablet) in 2 divided d
mg/kg/day every 1 to 2 weeks (rounded down to the nearest whole tablet) to the usual maintenance dose
mg/day) (Prod Info LAMICTAL chewable dispersible oral tablets, oral tablets, orally disintegrating tablets
4) (over age 12; added to antiepileptic drug regimen with valproic acid) 25 mg/day orally every other day
increase dosage by 25 to 50 mg/day ORALLY every 1 to 2 weeks to the usual maintenance dose of 100
maintenance dose of patients adding lamotrigine to valproic acid alone ranges from 100 to 200 mg/day (
oral tablets, orally disintegrating tablets, 2009)
5) (over age 12; added to antiepileptic drug regimen not containing enzyme-inducing antiepileptic drugs
mg/day for 2 weeks; may increase dosage by 50 mg/day every 1 to 2 weeks to the usual maintenance d
LAMICTAL chewable dispersible oral tablets, oral tablets, orally disintegrating tablets, 2009)
6) (over age 12; added to enzyme-inducing antiepileptic drug regimen without valproic acid) 50 mg/day
for 2 weeks; may increase dosage by 100 mg/day ORALLY every 1 to 2 weeks to the usual maintenance
Info LAMICTAL chewable dispersible oral tablets, oral tablets, orally disintegrating tablets, 2009)

3) Contraindications
a) hypersensitivity to lamotrigine or any component of the product (Prod Info LAMICTAL chewable dispersible oral tab
Prod Info LAMICTAL XR oral extended-release tablets, 2009)

4) Serious Adverse Effects
a) Anemia
b) Angioedema
c) Disseminated intravascular coagulation
d) Eosinophil count raised
e) Erythema multiforme
f) Leukopenia
g) Liver failure
h) Stevens-Johnson syndrome
i) Thrombocytopenia
j) Toxic epidermal necrolysis

5) Clinical Applications
a) FDA Approved Indications
1) Bipolar I disorder
2) Lennox-Gastaut syndrome; Adjunct
3) Partial seizure, Adjunct or monotherapy
4) Tonic-clonic seizure, Primary generalized; Adjunct

1.0 Dosing Information

Drug Properties

Storage and Stability

Adult Dosage

Pediatric Dosage

1.1 Drug Properties

A) Information on specific products and dosage forms can be obtained by referring to the Tradename List (Product In

B) Synonyms

Lamotrigine

C) Orphan Drug Status

1) Lamotrigine has been designated an orphan product for use in the treatment of Lennox-Gastaut syndrome.

D) Physicochemical Properties

1) Molecular Weight

a) 256.09 (Prod Info LAMICTAL XR oral extended-release tablets, 2009)

2) pKa

a) 5.7 (Prod Info LAMICTAL XR oral extended-release tablets, 2009)

3) Solubility

a) Lamotrigine is very slightly soluble in water (0.17 mg/mL at 25 degrees C) and slightly soluble in 0.1 mola LAMICTAL XR oral extended-release tablets, 2009).

1.2 Storage and Stability

A) Preparation

1) Oral route

a) Chewable Dispersible Tablets

1) Chewable dispersible tablets may be swallowed whole, chewed, or dispersed in water or diluted fruit nearest whole tablet. Disperse by adding tablets to a small amount of liquid (1 teaspoon, or enough to co dispersed (approximately 1 min), swirl solution and consume entire volume immediately (Prod Info LAMI orally disintegrating tablets, 2009).

b) Orally Disintegrating Tablets

1) Orally disintegrating tablets should be placed onto the tongue and moved around in the mouth. The ta without water and may be taken with or without food (Prod Info LAMICTAL chewable dispersible oral tab

c) Extended-Release Tablets

1) Extended-release tablets must be swallowed whole with or without food. The tablet must not be chew extended-release tablets, 2009).

B) Lamotrigine 25 milligrams (mg) tablets and lamotrigine chewable dispersible 2 mg, 5 mg and 25 mg tablets should Fahrenheit (F)) with excursions permitted between 15 and 30 degrees C (59 to 86 degrees F) in a dry place. Lamotrigi stored at 25 degrees C (77 degrees F) with excursions permitted between 15 to 30 degrees C (59 to 86 degrees F) in (R), 2003f).

1.3 Adult Dosage

Normal Dosage

Dosage in Renal Failure

Dosage in Hepatic Insufficiency

Dosage in Other Disease States

1.3.1 Normal Dosage

1.3.1.A Oral route

Bipolar I disorder

Lennox-Gastaut syndrome; Adjunct

Partial seizure, Adjunct or monotherapy

Tonic-clonic seizure, Primary generalized; Adjunct

1.3.1.A.1 Bipolar I disorder

a) Not Taking Enzyme-Inducing Antiepileptic Drugs or Valproic Acid

1) The target dose of lamotrigine is 200 milligrams (mg)/day. Doses up to 400 mg/day as monothera benefit was observed at 400 mg/day as compared to 200 mg/day (Prod Info LAMICTAL chewable di tablets, 2009)

2) For patients not taking carbamazepine (or other enzyme-inducing drugs) or valproic acid:

Weeks 1 and 2:	25 mg/day
Weeks 3 and 4:	50 mg/day
Week 5:	100 mg/day
Week 6:	200 mg/day
Week 7:	200 mg/day (target dose)

b) Added to Valproic Acid Regimen

1) The target dose of lamotrigine in combination with valproic acid is 100 mg/day (Prod Info LAMIC disintegrating tablets, 2009):

2) For patients taking valproic acid:

Weeks 1 and 2:	25 mg every other day
Weeks 3 and 4:	25 mg/day
Week 5:	50 mg/day
Week 6:	100 mg/day
Week 7:	100 mg/day (target dose)

c) Added to Enzyme-Inducing Antiepileptic Drug Regimen (Without Valproic Acid)

1) The target dose of lamotrigine in combination with carbamazepine or other enzyme-inducing dru dispersible oral tablets, oral tablets, orally disintegrating tablets, 2009).

2) For patients taking carbamazepine (or other enzyme-inducing drugs), but not taking valproic acid

Weeks 1 and 2:	50 mg/day
Weeks 3 and 4:	100 mg/day (divided doses)
Week 5:	200 mg/day (divided doses)
Week 6:	300 mg/day (divided doses)
Week 7:	400 mg/day (divided doses) (target dose)

d) Adjustment - Discontinuation of Psychotropics

1) For discontinuation of psychotropic drugs excluding valproic acid, carbamazepine, or other enzyr dose (Prod Info LAMICTAL chewable dispersible oral tablets, oral tablets, orally disintegrating tablet

e) Adjustment - Discontinuation of Valproic Acid

1) For patients discontinuing valproic acid, the dose of lamotrigine should be doubled over a 2-weel LAMICTAL chewable dispersible oral tablets, oral tablets, orally disintegrating tablets, 2009):

AFTER DISCONTINUATION OF VALPROIC ACID	
Current lamotrigine dose:	100 mg/day
Week 1:	150 mg/day
Week 2:	200 mg/day
Week 3 and onward:	200 mg/day

f) Adjustment - Discontinuation of Carbamazepine

1) For patients discontinuing carbamazepine or other enzyme-inducing agents, the dose of lamotrig should be decreased by half over a 2-week period in equal weekly decrements. The dose may then mg/day (Prod Info LAMICTAL chewable dispersible oral tablets, oral tablets, orally disintegrating tab

AFTER DISCONTINUATION OF CARBAMAZEPINE OR OTHER ENZYME-INDUCING DRUGS	
Current lamotrigine dose:	400 mg/day
Week 1:	400 mg/day
Week 2:	300 mg/day
Week 3 and onward:	200 mg/day

1.3.1.A.2 Lennox-Gastaut syndrome; Adjunct

a) With Valproic Acid

1) For adult patients adding lamotrigine to an antiepileptic drug (AED) regimen containing valproic a tablets, oral tablets, orally disintegrating tablets, 2009):

Lamotrigine added to antiepileptic drug (AED) regimen containing valproic acid:

Weeks 1 and 2: 25 milligrams (mg) every other day

Weeks 3 and 4: 25 mg every day

Week 5 and onward: Doses may be increased by 25 to 50 mg/day every 1 to 2 weeks to ac
Usual maintenance dose: 100 to 400 mg/day (1 or 2 divided doses)
The usual maintenance dose in patients adding lamotrigine to valproic acid alone rang

b) Without Valproic Acid

1) For adult patients receiving enzyme-inducing antiepileptic drugs (EIAED) (carbamazepine, phen
(Prod Info LAMICTAL chewable dispersible oral tablets, oral tablets, orally disintegrating tablets, 20(
Lamotrigine added to EIAED regimen without valproic acid:
Weeks 1 and 2: 50 mg/day
Weeks 3 and 4: 100 mg/day (in 2 divided doses)
Week 5 and onward: Doses may be increased by 100 mg/day every 1 to 2 weeks to achiev
Usual maintenance dose: 300 to 500 mg/day (in two divided doses)

c) With Antiepileptic Drugs Not Containing Enzyme-Inducing Properties or Valproic Acid

1) For adult patients adding lamotrigine to an antiepileptic drug (AED) regimen not containing enzyr
LAMICTAL chewable dispersible oral tablets, oral tablets, orally disintegrating tablets, 2009) :
Lamotrigine added to AED regimen not containing drug-inducing AED or valproic acid:
Weeks 1 and 2: 25 mg/day
Weeks 3 and 4: 50 mg/day
Wee 5 and onward: Doses may be increased by 50 mg/day every 1 to 2 weeks to achieve
Usual maintenance dose: 225 to 375 mg/day (in 2 divided doses)

1.3.1.A.3 Partial seizure, Adjunct or monotherapy

a) With Valproic Acid

1) For patients age 13 years or older adding extended-release lamotrigine to an antiepileptic drug (A
LAMICTAL XR oral extended-release tablets, 2009):
Extended-release lamotrigine added to AED regimen containing valproic acid:
Weeks 1 and 2: 25 milligrams (mg) once every other day
Weeks 3 and 4: 25 mg once daily
Week 5: 50 mg once daily
Week 6: 100 mg once daily
Week 7: 150 mg once daily
Week 8 onwards to maintenance: 200 to 250 mg once daily
Dose increase at week 8 or later should not exceed 100 mg daily at weekly intervals

2) For adult patients adding chewable dispersible or orally disintegrating lamotrigine to an antiepilep
Info LAMICTAL chewable dispersible oral tablets, oral tablets, orally disintegrating tablets, 2009):
Chewable dispersible or orally disintegrating lamotrigine added to AED regimen containing valp
Weeks 1 and 2: 25 milligrams (mg) every other day
Weeks 3 and 4: 25 mg every day
Week 5 and onward: Doses may be increased by 25 to 50 mg/day every 1 to 2 weeks to ac
Usual maintenance dose: 100 to 400 mg/day (1 or 2 divided doses)
The usual maintenance dose in patients adding lamotrigine to valproic acid alone rang

b) Without Valproic Acid

1) (extended-release tablets) For patients 13 years or older receiving enzyme-inducing antiepileptic
phenobarbital, or primidone) without valproic acid (Prod Info LAMICTAL XR oral extended-release ta
Extended-release lamotrigine added to EIAED regimen without valproic acid:
Weeks 1 and 2: 50 mg once daily
Weeks 3 and 4: 100 mg once daily
Week 5: 200 mg once daily
Week 6: 300 mg once daily
Week 7: 400 mg once daily
Week 8 onwards to maintenance: 400 to 600 mg once daily
Dose increase at week 8 or later should not exceed 100 mg daily at weekly intervals

2) (chewable dispersible or orally disintegrating tablets) For adult patients receiving enzyme-inducir
phenytoin, phenobarbital, or primidone) without valproic acid (Prod Info LAMICTAL chewable disper
tablets, 2009):
Chewable dispersible or orally disintegrating lamotrigine added to EIAED regimen without valpr
Weeks 1 and 2: 50 mg/day
Weeks 3 and 4: 100 mg/day (in 2 divided doses)
Week 5 and onward: Doses may be increased by 100 mg/day every 1 to 2 weeks to achiev
Usual maintenance dose: 300 to 500 mg/day (in two divided doses)

c) With Antiepileptic Drugs Not Containing Enzyme-Inducing Properties or Valproic Acid

1) For patients 13 years or older adding extended-release lamotrigine to an antiepileptic drug (AED)
valproic acid (Prod Info LAMICTAL XR oral extended-release tablets, 2009):
Extended-release lamotrigine added to EIAED regimen without valproic acid:
Weeks 1 and 2: 25 mg once daily
Weeks 3 and 4: 50 mg once daily
Week 5: 100 mg once daily
Week 6: 150 mg once daily
Week 7: 200 mg once daily

Week 8 onwards to maintenance: 300 to 400 mg once daily
Dose increase at week 8 or later should not exceed 100 mg daily at weekly intervals

2) For adult patients adding chewable dispersible or orally disintegrating lamotrigine to an antiepilep properties or valproic acid (Prod Info LAMICTAL chewable dispersible oral tablets, oral tablets, orall

Chewable dispersible or orally disintegrating lamotrigine added to AED regimen not containing

Weeks 1 and 2: 25 mg/day
Weeks 3 and 4: 50 mg/day
Week 5 and onward: Doses may be increased by 50 mg/day every 1 to 2 weeks to achieve
Usual maintenance dose: 225 to 375 mg/day (in 2 divided doses)

d) Conversion from Immediate-Release to Extended-Release Formulation

1) The initial dose of extended-release lamotrigine in patients age 13 years and older should match Depending on the therapeutic response after conversion, the total daily dose may need to be adjust Info LAMICTAL XR oral extended-release tablets, 2009).

e) Conversion to Monotherapy, With Enzyme-Inducing Antiepileptic Drug

1) The recommended dose for conversion from adjunctive therapy with a single-enzyme-inducing a patients 16 years-old and older, is 500 milligrams/day (mg/day) given in 2 divided doses. Lamotrigin maintaining the first drug at a fixed level. Lamotrigine should be titrated as follows (Prod Info LAMIC orally disintegrating tablets, 2009):

Weeks 1 and 2: 50 mg/day
Weeks 3 and 4: 100 mg/day (in two divided doses)
Doses may be increased by 100 mg/day every 1 to 2 weeks to achieve maintenance.
After achieving a dose of 500 mg/day of lamotrigine, withdrawal of the concomitant drug should each week.

f) Conversion to Monotherapy, With Valproic Acid

The recommended dose for conversion from adjunctive therapy with valproic acid to monotherapy w 500 milligrams/day (mg/day) given in 2 divided doses. The conversion regimen involves 4 steps. Firs dose while maintaining the valproic acid dose at a fixed level. Lamotrigine should be titrated as follo tablets, oral tablets, orally disintegrating tablets, 2009):

Weeks 1 and 2: 25 mg every other day
Weeks 3 and 4: 25 mg every day
Doses may be increased by 25 to 50 mg/day every 1 to 2 weeks to achieve the target dose.

Secondly, while maintaining the lamotrigine dose at 200 mg/day, valproic acid should be gradually d 500 mg/day per week. This regimen should be maintained for 1 week. Thirdly, the lamotrigine dose acid is simultaneously decreased to 250 mg/day. This regimen should also be maintained for 1 weel completely and lamotrigine should be increased by 100 mg/day every week until the recommended LAMICTAL chewable dispersible oral tablets, oral tablets, orally disintegrating tablets, 2009).

g) Conversion to Monotherapy, With Non-Enzyme-Inducing Antiepileptic Drug

1) The effects of non-enzyme-inducing antiepileptic drugs other than valproic acid on the metabolis no dosing guidelines can be provided for the safe and effective conversion to monotherapy with lam tablets, oral tablets, orally disintegrating tablets, 2009).

h) Partial Seizures - Refractory

1) In the treatment of simple and complex partial seizures refractory to multiple combinations of ant milligrams/day has been effective. Dose adjustments are made based on clinical response rather th had trough plasma levels in the range of 1 to 4 micrograms/milliliter (Graves & Leppik, 1991; Jawad

1.3.1.A.4 Tonic-clonic seizure, Primary generalized; Adjunct

a) With Valproic Acid

1) For adult patients adding lamotrigine to an antiepileptic drug (AED) regimen containing valproic a tablets, oral tablets, orally disintegrating tablets, 2009):

Lamotrigine added to antiepileptic drug (AED) regimen containing valproic acid:

Weeks 1 and 2: 25 milligrams (mg) every other day
Weeks 3 and 4: 25 mg every day
Week 5 and onward: Doses may be increased by 25 to 50 mg/day every 1 to 2 weeks to ac
Usual maintenance dose: 100 to 400 mg/day (1 or 2 divided doses)
The usual maintenance dose in patients adding lamotrigine to valproic acid alone rang

b) Without Valproic Acid

1) For adult patients receiving enzyme-inducing antiepileptic drugs (EIAED) (carbamazepine, pheny (Prod Info LAMICTAL chewable dispersible oral tablets, oral tablets, orally disintegrating tablets, 20

Lamotrigine added to EIAED regimen without valproic acid:

Weeks 1 and 2: 50 mg/day
Weeks 3 and 4: 100 mg/day (in 2 divided doses)
Week 5 and onward: Doses may be increased by 100 mg/day every 1 to 2 weeks to achiev
Usual maintenance dose: 300 to 500 mg/day (in two divided doses)

c) With Antiepileptic Drugs Not Containing Enzyme-Inducing Properties or Valproic Acid

1) For adult patients adding lamotrigine to an antiepileptic drug (AED) regimen not containing enzyr LAMICTAL chewable dispersible oral tablets, oral tablets, orally disintegrating tablets, 2009):

Lamotrigine added to AED regimen not containing drug-inducing AED or valproic acid:

Weeks 1 and 2: 25 mg/day

Weeks 3 and 4: 50 mg/day
Wee 5 and onward: Doses may be increased by 50 mg/day every 1 to 2 weeks to achieve
Usual maintenance dose: 225 to 375 mg/day (in 2 divided doses)

1.3.1.B Important Note

1) Use caution when dispensing lamotrigine (Lamictal(R), Lamisil(R), lamivudine, Ludiomil(R), labetalol, and errors involving these similarly named medications (Prod Info LAMICTAL chewable dispersible oral tablets, o

2) Safety and efficacy of lamotrigine has not been established (Prod Info LAMICTAL chewable dispersible or 2009):

- as initial monotherapy
- for conversion to monotherapy from a non-enzyme-inducing antiepileptic agent other than valproic acid
- for simultaneous conversion to monotherapy from 2 or more concomitant antiepileptic drugs

1.3.1.C Withdrawal

1) In patients requiring discontinuation of lamotrigine, the dosage should be decreased by about 50% per we patient's safety require a more rapid withdrawal. Discontinuing an enzyme-inducing antiepileptic agent should valproic acid should shorten the half-life of lamotrigine (Prod Info LAMICTAL(R) oral tablets, chewable disper extended-release tablets, 2009).

1.3.2 Dosage in Renal Failure

A) Use reduced maintenance doses in patients with significant renal impairment. Use with caution in patients with Prod Info LAMICTAL XR oral extended-release tablets, 2009).

B) Twenty volunteers with chronic renal failure (mean creatinine clearance 13 milliliters/minute) were given a sing prolonged compared to that observed in volunteers with normal renal function (50 hours vs 25 hours). Another 6 p milligram dose of lamotrigine. On average, approximately 17% (range 5.6% to 35.1%) of lamotrigine was removed life in these patients during hemodialysis was 12.2 hours, while that between sessions was 59.6 hours (Fillastre e

C) Dosage of lamotrigine need not be altered in the presence of impaired renal function since lamotrigine disposi the pharmacokinetics of lamotrigine in 10 subjects with renal failure (estimated creatinine clearance of 10.6 to 25. maximum concentration and area-under-the curve were similar since lamotrigine was largely cleared by metabolis to accumulate. Therefore, impaired renal function would have little effect on the plasma concentrations of lamotrig

1.3.3 Dosage in Hepatic Insufficiency

A) The manufacturer recommends that in patients with moderate and severe liver impairment without ascites, the reduced by approximately 25%. In patients with severe hepatic impairment with ascites, the initial, escalation, and approximately 50%. Clinical response should also be considered during escalation and maintenance dosing (Prod oral tablets, 2006) (Prod Info LAMICTAL XR oral extended-release tablets, 2009).

1.3.6 Dosage in Other Disease States

A) Hyperbilirubinemia

1) Elimination of lamotrigine is not significantly impaired in patients with Gilbert's syndrome (unconjugated hy

B) Pregnancy

1) Dose-normalized lamotrigine concentrations progressively decreased during pregnancy with a 40% and 6 women on lamotrigine monotherapy in 2 retrospective studies (n=12 and n=11. respectively). Lamotrigine cle trimester in a retrospective (n=12) and prospective (n=14) study, respectively. The clearance and concentrati delivery. Other evidence suggest that there was a less pronounced reduction in lamotrigine plasma concentra enzyme-inducing antiepileptic drugs or valproic acid (Tomson & Battino, 2007).

2) Lamotrigine clearance increased by more than 50% in some women at the onset of pregnancy with a drar reversed soon after delivery. Increased doses of lamotrigine may be required to maintain therapeutic levels d following pregnancy (Tran et al, 2002a).

1.4 Pediatric Dosage

Normal Dosage

Dosage in Renal Failure

Dosage in Hepatic Insufficiency

Dosage in Other Disease States

1.4.1 Normal Dosage

1.4.1.A Oral route

Convulsions in the newborn, Intractable

Epilepsy, Refractory

Lennox-Gastaut syndrome; Adjunct

Partial seizure, Adjunct or monotherapy

Status epilepticus

Tonic-clonic seizure, Primary generalized; Adjunct

1.4.1.A.1 Convulsions in the newborn, Intractable

a) Adjunctive lamotrigine was successful in reducing the number of seizures in patients with intractable | label study. In neonates who were taking enzyme-inducing agents, doses up to 10 milligrams per kilogra between 1 and 12 months of age, who were taking enzyme- inducing agents, final doses ranged betwee of age, taking valproate and enzyme inducers, were dosed between 5 to 10 mg/kg/day. In infants betwee mg/kg/day was the final dose (Mikati et al, 2002).

1.4.1.A.2 Epilepsy, Refractory

a) Lamotrigine is effective in intractable childhood epilepsy. Doses of lamotrigine 2 to 15 milligrams/kilog (maximum of 15 milligrams/kilogram/day used in patients on enzyme-inducing antiepileptic drugs (AEDs) valproate only) (Gibbs et al, 1992); (Yven et al, 1992)(Mims, 1992; Hosking, 1993; Pons, 1993).

1.4.1.A.3 Lennox-Gastaut syndrome; Adjunct

a) Age 2 to 12 Years

1) With Valproic Acid

a) For patients 2 to 12 years of age adding lamotrigine to an antiepileptic drug (AED) regimen dispersible oral tablets, oral tablets, orally disintegrating tablets, 2009):

Lamotrigine added to AED regimen containing valproic acid in patients 2 to 12 years of age

Weeks 1 and 2: 0.15 milligram/kilogram/day (mg/kg/day) in one or two divided doses, tablets should be used for dosing

Weeks 3 and 4: 0.3 mg/kg/day in one or two divided doses, rounded down to the neare

Week 5 and onward: Doses may be increased every 1 to 2 weeks by 0.3 mg/kg/day, r the previously administered daily dose to achieve maintenance.

Usual maintenance dose: 1 to 5 mg/kg/day (maximum 200 mg/day in 1 or 2 divided do

The usual maintenance dose in patients adding lamotrigine to valproic acid alone

Maintenance doses in patients weighing less than 30 kg may need to be increase

INITIAL WEIGHT BASED DOSING GUIDE:

Patient weight 6.7 to 14 kg, dose for weeks 1 and 2 is 2 mg every other day; dose

Patient weight 14.1 to 27 kg, dose for weeks 1 and 2 is 2 mg every day; dose for

Patient weight 27.1 to 34 kg, dose for weeks 1 and 2 is 4 mg every day; dose for

Patient weight 34.1 to 40 kg, dose for weeks 1 and 2 is 5 mg every day; dose for

2) Without Valproic Acid

a) For patients age 2 to 12 years old receiving enzyme-inducing antiepileptic drugs (EIAED) (c without valproic acid (Prod Info LAMICTAL chewable dispersible oral tablets, oral tablets, orally

Lamotrigine added to EIAED regimen without valproic acid in patients 2 to 12 years of age:

Weeks 1 and 2: 0.6 milligram/kilogram/day (mg/kg/day) in two divided doses, rounded

Weeks 3 and 4: 1.2 mg/kg/day in two divided doses, rounded down to the nearest whc

Week 5 and onward: Doses may be increased every 1 to 2 weeks by 1.2 mg/kg/day, r the previously administered daily dose to achieve maintenance.

Usual maintenance dose: 5 to 15 mg/kg/day (maximum 400 mg/day in 2 divided doses

Maintenance doses in patients weighing less than 30 kg may need to be increase

3) With Antiepileptic Drugs Not Containing Enzyme-Inducing Properties or Valproic Acid

a) For patients 2 to 12 years of age adding lamotrigine to an antiepileptic drug (AED) regimen acid (Prod Info LAMICTAL chewable dispersible oral tablets, oral tablets, orally disintegrating ta

Lamotrigine added to an antiepileptic drug (AED) regimen not containing drug-inducing AE

Weeks 1 and 2: 0.3 milligram/kilogram/day (mg/kg/day) in one or two divided doses, r tablets should be used for dosing.

Weeks 3 and 4: 0.6 mg/kg/day in two divided doses, rounded down to the nearest whc

Week 5 and onward: Doses may be increased every 1 to 2 weeks by 0.6 mg/kg/day, r the previously administered daily dose to achieve maintenance.

Usual maintenance dose: 4.5 to 7.5 mg/kg/day (maximum 300 mg/day in 2 divided dos

Maintenance doses in patients weighing less than 30 kg may need to be increase

b) Age 12 Years and Older

1) With Valproic Acid

a) For patients 12 years and older adding lamotrigine to an antiepileptic drug (AED) regimen cc
dispersible oral tablets, oral tablets, orally disintegrating tablets, 2009):
Lamotrigine added to antiepileptic drug (AED) regimen containing valproic acid:
Weeks 1 and 2: 25 milligrams (mg) every other day
Weeks 3 and 4: 25 mg every day
Week 5 and onward: Doses may be increased by 25 to 50 mg/day every 1 to 2 weeks
Usual maintenance dose: 100 to 400 mg/day (1 or 2 divided doses)
The usual maintenance dose in patients adding lamotrigine to valproic acid alone

2) Without Valproic Acid
a) For patients 12 years and older receiving enzyme-inducing antiepileptic drugs (EIAED) (carb
without valproic acid (Prod Info LAMICTAL chewable dispersible oral tablets, oral tablets, orally
Lamotrigine added to EIAED regimen without valproic acid:
Weeks 1 and 2: 50 mg/day
Weeks 3 and 4: 100 mg/day (in 2 divided doses)
Week 5 and onward: Doses may be increased by 100 mg/day every 1 to 2 weeks to ac
Usual maintenance dose: 300 to 500 mg/day (in two divided doses)

3) With Antiepileptic Drugs Not Containing Enzyme-Inducing Properties or Valproic Acid
a) For patients 12 years and older adding lamotrigine to an antiepileptic drug (AED) regimen nc
acid (Prod Info LAMICTAL chewable dispersible oral tablets, oral tablets, orally disintegrating ta
Lamotrigine added to AED regimen not containing drug-inducing AED or valproic acid:
Weeks 1 and 2: 25 mg/day
Weeks 3 and 4: 50 mg/day
Wee 5 and onward: Doses may be increased by 50 mg/day every 1 to 2 weeks to achi
Usual maintenance dose: 225 to 375 mg/day (in 2 divided doses)

1.4.1.A.4 Partial seizure, Adjunct or monotherapy

a) Extended-release Tablets, Age 13 Years and Older

1) With Valproic Acid
a) For patients 13 years of age and older adding extended-release lamotrigine to an antiepilept
Info LAMICTAL XR oral extended-release tablets, 2009):
Extended-release lamotrigine added to AED regimen containing valproic acid:
Weeks 1 and 2: 25 milligrams (mg) once every other day
Weeks 3 and 4: 25 mg once daily
Week 5: 50 mg once daily
Week 6: 100 mg once daily
Week 7: 150 mg once daily
Week 8 onwards to maintenance: 200 to 250 mg once daily
Dose increase at week 8 or later should not exceed 100 mg daily at weekly intervals

1) Without Valproic Acid
a) (extended-release tablets) For patients 13 years or older receiving enzyme-inducing ant
phenobarbital, or primidone) without valproic acid (Prod Info LAMICTAL XR oral extended-
Extended-release lamotrigine added to EIAED regimen without valproic acid:
Weeks 1 and 2: 50 mg once daily
Weeks 3 and 4: 100 mg once daily
Week 5: 200 mg once daily
Week 6: 300 mg once daily
Week 7: 400 mg once daily
Week 8 onwards to maintenance: 400 to 600 mg once daily
Dose increase at week 8 or later should not exceed 100 mg daily at weekly interva

2) With Antiepileptic Drugs Not Containing Enzyme-Inducing Properties or Valproic Acid
a) For patients 13 years or older adding extended-release lamotrigine to an antiepileptic dr
properties or valproic acid (Prod Info LAMICTAL XR oral extended-release tablets, 2009):
Extended-release lamotrigine added to EIAED regimen without valproic acid:
Weeks 1 and 2: 25 mg once daily
Weeks 3 and 4: 50 mg once daily
Week 5: 100 mg once daily
Week 6: 150 mg once daily
Week 7: 200 mg once daily
Week 8 onwards to maintenance: 300 to 400 mg once daily
Dose increase at week 8 or later should not exceed 100 mg daily at weekly interva

2) Conversion from Immediate-Release to Extended-Release Formulation
a) The initial dose of extended-release lamotrigine in patients age 13 years and older should m
lamotrigine. Depending on the therapeutic response after conversion, the total daily dose may r
instructions (Prod Info LAMICTAL XR oral extended-release tablets, 2009).

b) Chewable Dispersible or Orally Disintegrating Tablets, Age 2 to 12 Years

1) With Valproic Acid
a) For patients 2 to 12 years of age adding chewable dispersible or orally disintegrating lamotri
valproic acid (Prod Info LAMICTAL chewable dispersible oral tablets, oral tablets, orally disinteg

Chewable dispersible or orally disintegrating lamotrigine added to AED regimen containing
Weeks 1 and 2: 0.15 milligram/kilogram/day (mg/kg/day) in one or two divided doses,
tablets should be used for dosing
Weeks 3 and 4: 0.3 mg/kg/day in one or two divided doses, rounded down to the neare
Week 5 and onward: Doses may be increased every 1 to 2 weeks by 0.3 mg/kg/day, r
the previously administered daily dose to achieve maintenance.
Usual maintenance dose: 1 to 5 mg/kg/day (maximum 200 mg/day in 1 or 2 divided do
The usual maintenance dose in patients adding lamotrigine to valproic acid alone
Maintenance doses in patients weighing less than 30 kg may need to be increase
INITIAL WEIGHT BASED DOSING GUIDE:
Patient weight 6.7 to 14 kg, dose for weeks 1 and 2 is 2 mg every OTHER day; do
Patient weight 14.1 to 27 kg, dose for weeks 1 and 2 is 2 mg every day; dose for
Patient weight 27.1 to 34 kg, dose for weeks 1 and 2 is 4 mg every day; dose for
Patient weight 34.1 to 40 kg, dose for weeks 1 and 2 is 5 mg every day; dose for

2) Without Valproic Acid

a) For patients age 2 to 12 years old receiving enzyme-inducing antiepileptic drugs (EIAED) (ca
without valproic acid (Prod Info LAMICTAL chewable dispersible oral tablets, oral tablets, orally
Chewable dispersible or orally disintegrating lamotrigine added to EIAED regimen without
Weeks 1 and 2: 0.6 milligram/kilogram/day (mg/kg/day) in two divided doses, rounded
Weeks 3 and 4: 1.2 mg/kg/day in two divided doses, rounded down to the nearest whc
Week 5 and onward: Doses may be increased every 1 to 2 weeks by 1.2 mg/kg/day, r
the previously administered daily dose to achieve maintenance.
Usual maintenance dose: 5 to 15 mg/kg/day (maximum 400 mg/day in 2 divided doses
Maintenance doses in patients weighing less than 30 kg may need to be increase

3) With Antiepileptic Drugs Not Containing Enzyme-Inducing Properties or Valproic Acid

a) For patients 2 to 12 years of age adding chewable dispersible or orally disintegrating lamotri
containing enzyme-inducing properties or valproic acid (Prod Info LAMICTAL chewable dispers
2009):
Chewable dispersible or orally disintegrating lamotrigine added to an antiepileptic drug (AE
valproic acid in patients 2 to 12 years of age:
Weeks 1 and 2: 0.3 milligram/kilogram/day (mg/kg/day) in one or two divided doses, r
tablets should be used for dosing.
Weeks 3 and 4: 0.6 mg/kg/day in two divided doses, rounded down to the nearest whc
Week 5 and onward: Doses may be increased every 1 to 2 weeks by 0.6 mg/kg/day, r
the previously administered daily dose to achieve maintenance.
Usual maintenance dose: 4.5 to 7.5 mg/kg/day (maximum 300 mg/day in 2 divided dos
Maintenance doses in patients weighing less than 30 kg may need to be increase

c) Chewable Dispersible or Orally Disintegrating Tablets, Age 12 Years and Older

1) With Valproic Acid

a) For patients 12 years and older adding chewable dispersible or orally disintegrating lamotrig
valproic acid (Prod Info LAMICTAL chewable dispersible oral tablets, oral tablets, orally disinteg
Chewable dispersible or orally disintegrating lamotrigine added to antiepileptic drug (AED)
Weeks 1 and 2: 25 milligrams (mg) every other day
Weeks 3 and 4: 25 mg every day
Week 5 and onward: Doses may be increased by 25 to 50 mg/day every 1 to 2 weeks
Usual maintenance dose: 100 to 400 mg/day (1 or 2 divided doses)
The usual maintenance dose in patients adding lamotrigine to valproic acid alone

2) Without Valproic Acid

a) For patients 12 years and older receiving enzyme-inducing antiepileptic drugs (EIAED) (carb
without valproic acid (Prod Info LAMICTAL chewable dispersible oral tablets, oral tablets, orally
Chewable dispersible or orally disintegrating lamotrigine added to EIAED regimen without
Weeks 1 and 2: 50 mg/day
Weeks 3 and 4: 100 mg/day (in 2 divided doses)
Week 5 and onward: Doses may be increased by 100 mg/day every 1 to 2 weeks to a
Usual maintenance dose: 300 to 500 mg/day (in two divided doses)

3) With Antiepileptic Drugs Not Containing Enzyme-Inducing Properties or Valproic Acid

a) For patients 12 years and older adding chewable dispersible or orally disintegrating lamotrig
containing enzyme-inducing properties or valproic acid (Prod Info LAMICTAL chewable dispers
2009):
Chewable dispersible or orally disintegrating lamotrigine added to AED regimen not contair
Weeks 1 and 2: 25 mg/day
Weeks 3 and 4: 50 mg/day
Wee 5 and onward: Doses may be increased by 50 mg/day every 1 to 2 weeks to achi
Usual maintenance dose: 225 to 375 mg/day (in 2 divided doses)

1.4.1.A.5 Status epilepticus

a) Successful control of status epilepticus refractory to parenteral diazepam was achieved in one 17-yea
over 24 hours followed by 200 milligrams twice a day. Although this case report was encouraging, more

lamotrigine in status epilepticus (Pisani et al, 1991).

1.4.1.A.6 Tonic-clonic seizure, Primary generalized; Adjunct

a) Age 2 to 12 Years

1) With Valproic Acid

a) For patients 2 to 12 years of age adding lamotrigine to an antiepileptic drug (AED) regimen c
dispersible oral tablets, oral tablets, orally disintegrating tablets, 2009):

Lamotrigine added to AED regimen containing valproic acid in patients 2 to 12 years of age

Weeks 1 and 2: 0.15 milligram/kilogram/day (mg/kg/day) in one or two divided doses,
tablets should be used for dosing

Weeks 3 and 4: 0.3 mg/kg/day in one or two divided doses, rounded down to the neare

Week 5 and onward: Doses may be increased every 1 to 2 weeks by 0.3 mg/kg/day, r
the previously administered daily dose to achieve maintenance.

Usual maintenance dose: 1 to 5 mg/kg/day (maximum 200 mg/day in 1 or 2 divided do

The usual maintenance dose in patients adding lamotrigine to valproic acid alone

Maintenance doses in patients weighing less than 30 kg may need to be increase

INITIAL WEIGHT BASED DOSING GUIDE:

Patient weight 6.7 to 14 kg, dose for weeks 1 and 2 is 2 mg every other day; dose

Patient weight 14.1 to 27 kg, dose for weeks 1 and 2 is 2 mg every day; dose for

Patient weight 27.1 to 34 kg, dose for weeks 1 and 2 is 4 mg every day; dose for

Patient weight 34.1 to 40 kg, dose for weeks 1 and 2 is 5 mg every day; dose for

2) Without Valproic Acid

a) For patients age 2 to 12 years old receiving enzyme-inducing antiepileptic drugs (EIAED) (ca
without valproic acid (Prod Info LAMICTAL chewable dispersible oral tablets, oral tablets, orally

Lamotrigine added to EIAED regimen without valproic acid in patients 2 to 12 years of age:

Weeks 1 and 2: 0.6 milligram/kilogram/day (mg/kg/day) in two divided doses, rounded

Weeks 3 and 4: 1.2 mg/kg/day in two divided doses, rounded down to the nearest whc

Week 5 and onward: Doses may be increased every 1 to 2 weeks by 1.2 mg/kg/day, r
the previously administered daily dose to achieve maintenance.

Usual maintenance dose: 5 to 15 mg/kg/day (maximum 400 mg/day in 2 divided doses

Maintenance doses in patients weighing less than 30 kg may need to be increase

3) With Antiepileptic Drugs Not Containing Enzyme-Inducing Properties or Valproic Acid

a) For patients 2 to 12 years of age adding lamotrigine to an antiepileptic drug (AED) regimen
acid (valproic acid) (Prod Info LAMICTAL chewable dispersible oral tablets, oral tablets, orally d

Lamotrigine added to an antiepileptic drug (AED) regimen not containing drug-inducing AE

Weeks 1 and 2: 0.3 milligram/kilogram/day (mg/kg/day) in one or two divided doses, rc
tablets should be used for dosing.

Weeks 3 and 4: 0.6 mg/kg/day in two divided doses, rounded down to the nearest whc

Week 5 and onward: Doses may be increased every 1 to 2 weeks by 0.6 mg/kg/day, r
the previously administered daily dose to achieve maintenance.

Usual maintenance dose: 4.5 to 7.5 mg/kg/day (maximum 300 mg/day in 2 divided dos

Maintenance doses in patients weighing less than 30 kg may need to be increase

b) Age 12 Years and Older

1) With Valproic Acid

a) For patients 12 years and older adding lamotrigine to an antiepileptic drug (AED) regimen cc
tablets, chewable dispersible oral tablets, 2006):

Lamotrigine added to antiepileptic drug (AED) regimen containing valproic acid:

Weeks 1 and 2: 25 milligrams (mg) every other day

Weeks 3 and 4: 25 mg every day

Week 5 and onward: Doses may be increased by 25 to 50 mg/day every 1 to 2 weeks

Usual maintenance dose: 100 to 400 mg/day (1 or 2 divided doses)

The usual maintenance dose in patients adding lamotrigine to valproic acid alone

2) Without Valproic Acid

a) For patients 12 years and older receiving enzyme-inducing antiepileptic drugs (EIAED) (carb
without valproic acid (Prod Info LAMICTAL(R) oral tablets, chewable dispersible oral tablets, 20

Lamotrigine added to EIAED regimen without valproic acid:

Weeks 1 and 2: 50 mg/day

Weeks 3 and 4: 100 mg/day (in 2 divided doses)

Week 5 and onward: Doses may be increased by 100 mg/day every 1 to 2 weeks to ac

Usual maintenance dose: 300 to 500 mg/day (in two divided doses)

3) With Antiepileptic Drugs Not Containing Enzyme-Inducing Properties or Valproic Acid

a) For patients 12 years and older adding lamotrigine to an antiepileptic drug (AED) regimen nc
acid (Prod Info LAMICTAL chewable dispersible oral tablets, oral tablets, orally disintegrating ta

Lamotrigine added to AED regimen not containing drug-inducing AED or valproic acid:

Weeks 1 and 2: 25 mg/day

Weeks 3 and 4: 50 mg/day

Wee 5 and onward: Doses may be increased by 50 mg/day every 1 to 2 weeks to achi

Usual maintenance dose: 225 to 375 mg/day (in 2 divided doses)

1.4.1.B Important Note

1) Safety and efficacy of extended-release lamotrigine has not been established in patients below 13 years c tablets, 2009)

2) The risk of developing a potentially life-threatening rash is appreciably higher in children than in adults. Do escalation regimens (Prod Info LAMICTAL(R) oral tablets, chewable dispersible oral tablets, 2007) (Prod Info may also be higher with concomitant valproic acid and divalproex sodium use (Prod Info LAMICTAL(R) oral t Info LAMICTAL XR oral extended-release tablets, 2009).

3) Only whole tablets of the chewable dispersible tablets should be used. Doses should be rounded down to tablets, chewable dispersible oral tablets, 2007).

1.4.2 Dosage in Renal Failure

A) Use reduced maintenance doses in patients with significant renal impairment. Use with caution in patients with (Prod Info LAMICTAL XR oral extended-release tablets, 2009).

B) Dosage of lamotrigine need not be altered in the presence of impaired renal function since lamotrigine disposi the pharmacokinetics of lamotrigine in 10 subjects with renal failure (estimated creatinine clearance of 10.6 to 25. maximum concentration and area-under-the curve were similar since lamotrigine was largely cleared by metabolis to accumulate. Therefore, impaired renal function would have little effect on the plasma concentrations of lamotrig

C) Twenty volunteers with chronic renal failure (mean creatinine clearance 13 milliliters/min) were given a single prolonged compared to that observed in volunteers with normal renal function (50 hours vs 25 hours). Another 6 p milligrams dose of lamotrigine. On average, approximately 17% (range 5.6 to 35.1%) of lamotrigine was removed life in these patients during hemodialysis was 12.2 hours, while that between sessions was 59.6 hr (Fillastre et al,

1.4.3 Dosage in Hepatic Insufficiency

A) The manufacturer recommends that in patients with moderate and severe liver impairment without ascites, the reduced by approximately 25%. In patients with severe hepatic impairment with ascites, the initial, escalation, and approximately 50%. Clinical response should also be considered during escalation and maintenance dosing (Prod oral tablets, 2006; Prod Info LAMICTAL XR oral extended-release tablets, 2009).

1.4.5 Dosage in Other Disease States

A) Hyperbilirubinemia

1) Elimination of lamotrigine is not significantly impaired in patients with Gilbert's syndrome (unconjugated hy

2.0 Pharmacokinetics

Onset and Duration

Drug Concentration Levels

ADME

2.1 Onset and Duration

A) Onset

1) Initial Response

a) Seizure, oral: 3 months (Gibbs et al, 1992a; Jawad et al, 1989c).

B) Duration

1) Multiple Dose

a) Seizure, oral: at least 6 months (Gibbs et al, 1992a).

2.2 Drug Concentration Levels

A) Therapeutic Drug Concentration

1) Seizure, 1 to 4 mcg/mL (not well-established) (Garnett, 1997; Cohen et al, 1987a).

a) The therapeutic concentration range for lamotrigine has not been determined (Brodie, 1992) (Goa et al, 19 dosage titration should be based on clinical response rather than plasma concentrations (Goa et al, 1993b; M

b) Many patients have required higher levels (Garnett, 1997).

c) In children optimal levels have been between 0.5 to 5.4 mcg/ml (Battino et al, 1996)(Battino et al, 1995a).

d) Pharmacokinetics remained approximately linear within individuals (Battino et al, 1997; Bartoli et al, 1997;

e) Adults have a higher concentration to dose ratio than children (Battino et al, 1997; Bartoli et al, 1997).

f) Extended Release Tablets

1) In an open-label, crossover study of 44 epileptic patients on concomitant ant-epileptic drugs (AEDs) a extended-release lamotrigine once daily with immediate-release lamotrigine twice daily showed that stea lamotrigine were not significantly different from those of the immediate-release product. The degree of flu decreased by 17%, 34% and 37% for extended-release lamotrigine administered concomitantly with enz phenytoin, phenobarbital, and primidone), valproic acid, or all other AEDS, respectively, compared with t release lamotrigine was associated with lower peaks, longer time to peaks and lower peak-to-trough fluc lamotrigine (Prod Info LAMICTAL XR oral extended-release tablets, 2009).

B) Peak Concentration
1) Oral, single dose: 0.58 to 4.63 mg/L (50 to 400 mg)(Goa et al, 1993b; Prod Info Lamictal, 94; Prod Info Lamicta
a) Peak plasma concentrations increased linearly from 0.58 to 4.63 mg/L in healthy subjects administered si
mg(Goa et al, 1993b; Prod Info Lamictal, 94; Prod Info Lamictal, 97; Goa et al, 1993b).
b) In two small studies of patients with epilepsy, plasma concentrations increased linearly with doses of 50 to
11/22/95.).
c) Extended Release Tablet
1) In an open-label, crossover study of 44 epileptic patients on concomitant anti-epileptic drugs (AEDs) a
extended-release lamotrigine once daily with immediate-release lamotrigine twice daily showed a mean r
release lamotrigine. Analysis of the data based on concomitant AED use showed, the decrease in Cmax
inducing AEDs (ie, carbamazepine, phenytoin, phenobarbital, and primidone), 12% for patients receiving
receiving all other AEDs. Some of the patients receiving the extended-release lamotrigine with concomita
reduction in Cmax (Prod Info LAMICTAL XR oral extended-release tablets, 2009).
d) Rectal Administration
1) A peak concentration of 0.54 mcg/mL was achieved in 6.5 hours in 12 healthy adults after rectal adm
with a peak concentration of 1.43 mcg/mL in 0.79 hour after oral administration of lamotrigine 100 mg ch
2001).
C) Time to Peak Concentration
1) Oral: (adult) 1.4 hours to 4.8 hours (Prod Info LAMICTAL chewable dispersible oral tablets, oral tablets, orally
hours (extended-release) (Prod Info LAMICTAL XR oral extended-release tablets, 2009).
2) Oral: (pediatric) 1.6 hours to 5.2 hours (Prod Info LAMICTAL chewable dispersible oral tablets, oral tablets, ora
(Mikati et al, 2003)
a) Adults
1) Immediate-Release
a) In healthy volunteers and adult patients with epilepsy, peak plasma concentration was achieved
administration (Prod Info LAMICTAL chewable dispersible oral tablets, oral tablets, orally disintegrat
b) A second peak has been reported at 4 to 6 hours, possibly due to enterohepatic recycling (Garne
2) Extended Release Tablet
a) In an open-label, crossover study of 44 epileptic patients on concomitant anti-epileptic drugs (AE
comparison of extended-release lamotrigine once daily with immediate-release lamotrigine twice dai
(Tmax) following administration of extended-release lamotrigine was 4 to 11 hours compared with 1
Specifically, in patients receiving concomitant enzyme inducing AEDs (ie carbamazepine, phenytoin
approximately 4 to 6 hours; in patients receiving concomitant valproic acid, the Tmax was 9 to 11 ho
was 6 to 10 hours (Prod Info LAMICTAL XR oral extended-release tablets, 2009).
3) Rectal Administration
a) A peak concentration of 0.54 mcg/mL was achieved in 6.5 hours in 12 healthy adults after rectal
compared with a peak concentration of 1.43 mcg/mL in 0.79 hour after oral administration of lamotri
(Birnbaum et al, 2001).
b) Pediatrics
1) In pediatric patients with epilepsy, ages 10 months to 5.3 years old, the peak concentration was achie
concomitant carbamazepine, phenytoin, phenobarbital or valproate. The mean time to peak was 5.2 hou
drugs with no known effect on the apparent clearance of lamotrigine (Prod Info LAMICTAL chewable disp
tablets, 2009).
2) In pediatric patients with epilepsy, ages 5 to 11 years old, the mean peak concentration of lamotrigine
concomitant carbamazepine, phenytoin, phenobarbital, or primidone; to 4.5 hours among patients taking
dispersible oral tablets, oral tablets, orally disintegrating tablets, 2009).
3) Peak concentrations in 3 neonates between the ages of 3 and 4 weeks, were obtained at 4 hours, wit
lamotrigine (Mikati et al, 2003).
D) Area Under the Curve
1) Oral, (adult) 56.6 mg x hr/L (Garnett, 1997).
2) Oral (elderly) 91.8 mg x hr/L (Garnett, 1997)
3) Oral (pediatric) 61 mcg x hr/mL (Chen et al, 1999)
a) The AUC in adults was 56.6 mg x hr/L (Garnett, 1997)
b) Area under the curve was 55% higher in the elderly (91.8 mg x hr/L) (Garnett, 1997).
c) The AUC in children was 61 mcg x hr/mL (Chen et al, 1999).
d) Extended Release Tablet
1) In an open-label, crossover study of 44 epileptic patients on concomitant anti-epileptic drugs (AEDs) a
extended-release lamotrigine once daily with immediate-release lamotrigine twice daily, showed the mea
lamotrigine was approximately 21% lower than immediate-release lamotrigine in patients receiving conc
phenytoin, phenobarbital, and primidone), 6% lower in patients receiving concomitant valproic acid, and
patients in this study, experienced up to 70% decrease in AUC when switched to the extended-release la
release tablets, 2009).

2.3 ADME

Absorption

Distribution

Metabolism

Excretion

Elimination Half-life

Extracorporeal Elimination

2.3.1 Absorption

A) Bioavailability

1) Oral tablets: 98% (Prod Info LAMICTAL chewable dispersible oral tablets, oral tablets, orally disintegrating

a) Lamotrigine is rapidly and completely absorbed after oral administration with an absolute bioavailabili oral tablets, oral tablets, orally disintegrating tablets, 2009).

b) Lamotrigine chewable/dispersible tablets are equivalent to the compressed tablets in terms of rate an dispersed in water, chewed, swallowed as whole or disintegrated in the mouth (Prod Info LAMICTAL che disintegrating tablets, 2009).

c) The relative bioavailability was 0.52 when a lamotrigine 100-mg chewable dispersible tablet was adm orally and swallowed whole in 12 healthy adults (Birnbaum et al, 2001). The rectal suspension was prepa and placing it into 6 mL of tap water (room temperature), followed by two 2-mL syringe-tubing rinses, wit under the curve (AUC) for rectally administered lamotrigine was 29.68 mcg/mL x hr compared with 54.94 than 0.001).

B) Effects of Food

1) No effect on systemic availability (Prod Info LAMICTAL chewable dispersible oral tablets, oral tablets, oral

a) The bioavailability of lamotrigine is not affected by food (Prod Info LAMICTAL chewable dispersible o 2009; Prod Info LAMICTAL XR oral extended-release tablets, 2009).

2.3.2 Distribution

A) Distribution Sites

1) Protein Binding

a) Plasma protein: 55% (Prod Info LAMICTAL chewable dispersible oral tablets, oral tablets, orally disin

1) Lamotrigine is approximately 55% bound to human plasma proteins at concentration from 1 to 10 oral tablets, oral tablets, orally disintegrating tablets, 2009).

B) Distribution Kinetics

1) Volume of Distribution

a) adult, 0.9 to 1.3 L/kg(Prod Info LAMICTAL chewable dispersible oral tablets, oral tablets, orally disinte 1999)

1) The mean apparent volume of distribution of lamotrigine after oral administration ranges from 0.9 volunteers (Prod Info LAMICTAL chewable dispersible oral tablets, oral tablets, orally disintegrating

2) The volume of distribution in patients receiving concurrent antiepileptic therapy is 1.2 to 1.5 L/kg

3) The volume of distribution in children was 1.5 L/kg (Chen et al, 1999).

2.3.3 Metabolism

A) Metabolism Sites and Kinetics

1) Liver, extensive (Prod Info LAMICTAL chewable dispersible oral tablets, oral tablets, orally disintegrating t

2) Lamotrigine is metabolized primarily by glucuronic acid conjugation into inactive metabolites. When given metabolism; however, in patients receiving other anticonvulsants this may not occur (Prod Info LAMICTAL ch disintegrating tablets, 2009).

2.3.4 Excretion

A) Kidney

1) Renal Clearance (rate)

a) Adult, (healthy volunteers) 0.18 to 0.58 mL/min/kg; (epilepsy), 0.28 to 1.21 mL/min/kg(Prod Info LAMI orally disintegrating tablets, 2009)

1) The mean apparent plasma clearance of lamotrigine was between 0.44 and 0.58 mL/min/kg in he medications, between 0.18 and 0.3 mL/min/kg in patients taking concomitant valproic acid (n=24) (P oral tablets, orally disintegrating tablets, 2009).

2) The mean apparent plasma clearance of lamotrigine in adult patients with epilepsy taking concor When lamotrigine was taken concomitantly with valproic acid and an enzyme-inducing antiepileptic r 0.53 mL/min/kg (n=25). When taken concomitantly with an enzyme-inducing antiepileptic medicatior mL/min/kg (n=41) (Prod Info LAMICTAL chewable dispersible oral tablets, oral tablets, orally disinte

b) Elderly, 0.26 to 0.48 mL/min/kg (Prod Info LAMICTAL chewable dispersible oral tablets, oral tablets, o

1) In 12 elderly volunteers between the ages of 65 and 76 years (mean creatinine clearance, 61 mL

was 0.40 mL/min/kg (range, 0.26 to 0.48 mL/min/kg) following a single 150-mg dose of lamotrigine (oral tablets, orally disintegrating tablets, 2009).

c) Gender, no effect(Prod Info LAMICTAL chewable dispersible oral tablets, oral tablets, orally disintegra

1) In general, the clearance of lamotrigine is not affected by gender. However, during dose escalati dose of valproic acid (n=77), the mean trough lamotrigine concentrations, unadjusted for weight, we than in males (Prod Info LAMICTAL chewable dispersible oral tablets, oral tablets, orally disintegrati

d) Hepatic Impairment, 0.15 to 0.3 mL/min/kg (Prod Info LAMICTAL chewable dispersible oral tablets, o

1) Following a single 100-mg dose of lamotrigine the mean apparent clearances of lamotrigine in pa ascites (n=2), and severe with ascites (n=5) hepatic impairment were 0.30 +/- 0.09, 0.24 +/- 0.1, 0.2 compared with 0.37 +/- 0.1 mL/min/kg in the healthy control patients (Prod Info LAMICTAL chewable disintegrating tablets, 2009).

e) Pediatric, 0.24 to 3.62 mL/min/kg (Prod Info LAMICTAL chewable dispersible oral tablets, oral tablets

1) The mean apparent plasma clearance of lamotrigine in pediatric patients with epilepsy (age rang enzyme-inducing antiepileptic medication regimen was 3.62 mL/min/kg (n=10). When lamotrigine wa antiepileptic medication regimen, the mean plasma clearance was 1.2 mL/min/kg (n=7), and was 0.4 acid (n=8) (Prod Info LAMICTAL chewable dispersible oral tablets, oral tablets, orally disintegrating

2) The mean apparent plasma clearance of lamotrigine in pediatric patients with epilepsy (age rang inducing antiepileptic medication regimen was 2.54 mL/min/kg (n=7). When lamotrigine was taken c antiepileptic medication regime, the mean plasma clearance was 0.89 mL/min/kg (n=8), and was 0.2 acid (n=3) (Prod Info LAMICTAL chewable dispersible oral tablets, oral tablets, orally disintegrating

3) The mean apparent plasma clearance of lamotrigine in pediatric patients with epilepsy (age rang inducing antiepileptic medication regimen was 1.3 mL/min/kg (n=11). When lamotrigine was taken c antiepileptic medication regimen, the mean plasma clearance was 0.5 mL/min/kg (n=8), and was 0.3 (n=4) (Prod Info LAMICTAL chewable dispersible oral tablets, oral tablets, orally disintegrating table

4) The mean apparent clearance in infants less than 2 months old was 0.119 liter per hour per kilog 2 to 12 months old and who were administered oral lamotrigine (Mikati et al, 2003).

f) Race, 25% lower in non-Caucasians (Prod Info LAMICTAL chewable dispersible oral tablets, oral tabl

1) The apparent clearance of lamotrigine was 25% lower in non-Caucasians than in Caucasians (Pr oral tablets, orally disintegrating tablets, 2009).

g) Renal Impairment, 2 mL/min (Garnett, 1997)

1) The clearance was reduced to 2 mL/min in patients with renal failure (Garnett, 1997).

2) Renal Excretion (%)

a) 94% (Prod Info LAMICTAL chewable dispersible oral tablets, oral tablets, orally disintegrating tablets,

1) Following oral administration in healthy volunteers, 94% of the drug was recovered in the urine (P oral tablets, orally disintegrating tablets, 2009; Peck, 1991e).

B) Feces

1) Feces, 2% (Prod Info LAMICTAL chewable dispersible oral tablets, oral tablets, orally disintegrating tablet

a) After oral administration of lamotrigine, 2% was recovered in the feces (Prod Info LAMICTAL chewab disintegrating tablets, 2009).

2.3.5 Elimination Half-life

A) Parent Compound

1) ELIMINATION HALF-LIFE

a) Adult, (healthy volunteers) 25.4 to 70.3 hours; (epilepsy), 12.6 to 58.8 hours (Prod Info LAMICTAL ch disintegrating tablets, 2009)

1) The elimination half-life of lamotrigine in healthy adult volunteers (n=215) taking no other medica between 48.3 and 70.3 hours taken concomitantly with valproic acid (n=24) (Prod Info LAMICTAL ch disintegrating tablets, 2009).

2) The elimination half-life of lamotrigine in adult patients with epilepsy taking lamotrigine concomita when taken concomitantly with valproic acid and an enzyme-inducing antiepileptic medication regim concomitantly with an enzyme-inducing antiepileptic medication regimen (n=41) (Prod Info LAMICTA disintegrating tablets, 2009).

b) Elderly, 31.2 hours(Prod Info LAMICTAL chewable dispersible oral tablets, oral tablets, orally disinteg

1) In 12 elderly volunteers between the ages of 65 and 76 years (mean creatinine clearance, 61 mL half-life was 31.2 hours (range, 24.5 to 43.4 hours) following a single 150-mg dose of lamotrigine (P oral tablets, orally disintegrating tablets, 2009).

c) Hepatic Impairment, 46 +/- 20 hours to 100 +/- 48 hours(Prod Info LAMICTAL chewable dispersible o 2009)

1) Following a single 100-mg dose of lamotrigine the mean half-life elimination of lamotrigine in pati ascites (n=2), and severe with ascites (n=5) hepatic impairment were 46 +/- 20 hours, 72 +/- 44 hou as compared with 33 +/- 7 hours in healthy control patients (Prod Info LAMICTAL chewable dispersi 2009).

d) Pediatric, 7 hours to 65.8 hours (Prod Info LAMICTAL chewable dispersible oral tablets, oral tablets,

1) The elimination half-life of lamotrigine in pediatric patients with epilepsy (age range, 10 months t concomitantly with an enzyme-inducing antiepileptic medication regimen (n=10). When taken conco medication regimen, the half-life was 19 hours (n=7). When taken concomitantly with valproic acid (dispersible oral tablets, oral tablets, orally disintegrating tablets, 2009).

2) The mean elimination half-life of lamotrigine in pediatric patients with epilepsy (age range, 5 to 1

antiepileptic medication regimen was 7 hours (n=7). When lamotrigine was taken concomitantly with
medication regimen, the elimination half-life was 19.1 hours (n=8). When taken concomitantly with v
LAMICTAL chewable dispersible oral tablets, oral tablets, orally disintegrating tablets, 2009).
3) The estimated half-life of lamotrigine in neonates taking enzyme-inducing agents was 23.4 hours
e) Renal Impairment, 13 hours to 57.4 hours (Prod Info LAMICTAL chewable dispersible oral tablets, or
1) Following a single 100-mg dose of lamotrigine, volunteers with chronic renal failure (n=12; mean
patients undergoing hemodialysis (n=6) the mean plasma half-lives were 42.9 hours (chronic renal f
(between hemodialysis) compared with 26.2 hours in healthy volunteers (Prod Info LAMICTAL chew
disintegrating tablets, 2009).

2.3.6 Extracorporeal Elimination

A) Hemodialysis

1) Dialyzable: Yes (Prod Info Lamictal(R), 2003g; Garnett, 1997).

a) Approximately 20% (range, 5.6% to 35.1%) of the amount of lamotrigine present in the body was elim
Info LAMICTAL chewable dispersible oral tablets, oral tablets, orally disintegrating tablets, 2009).

3.0 Cautions

Contraindications

Precautions

Adverse Reactions

Teratogenicity/Effects in Pregnancy/Breastfeeding

Drug Interactions

3.0.A Black Box WARNING

1) Oral (Tablet; Tablet, Chewable; Tablet, Disintegrating; Tablet, Extended Release)

a) Serious Skin Rashes: Lamotrigine can cause serious rashes requiring hospitalization and discontinuation of tre
included Stevens-Johnson syndrome, is approximately 0.8% (8 per 1,000) in pediatric patients (2 to 16 years of a
lamotrigine as adjunctive therapy for epilepsy and 0.3% (3 per 1,000) in adults on adjunctive therapy for epilepsy.
patients (2 to 16 years of age) with epilepsy taking adjunctive immediate-release formulation of lamotrigine, there
experience, rare cases of toxic epidermal necrolysis and/or rash-related death have been reported in adult and pe
a precise estimate of the rate.

b) The risk of serious rash caused by treatment with lamotrigine is not expected to differ from that with the immed
relatively limited treatment experience with lamotrigine makes it difficult to characterize the frequency and risk of s

c) Other than age, there are as yet no factors identified that are known to predict the risk of occurrence or the sev
suggestions, yet to be proven, that the risk of rash may also be increased by (1) coadministration of lamotrigine w
sodium), (2) exceeding the recommended initial dose of lamotrigine, or (3) exceeding the recommended dose esc
in the absence of these factors.

d) Nearly all cases of life-threatening rashes caused by the immediate-release formulation of lamotrigine have oc
However, isolated cases have occurred after prolonged treatment (eg, 6 months). Accordingly, duration of therapy
potential risk heralded by the first appearance of a rash.

e) Although benign rashes are also caused by lamotrigine, it is not possible to predict reliably which rashes will p
lamotrigine should ordinarily be discontinued at the first sign of rash, unless the rash is clearly not drug-related. D
becoming life-threatening or permanently disabling or disfiguring (Prod Info LAMICTAL chewable dispersible oral
Prod Info LAMICTAL XR oral extended-release tablets, 2009).

3.1 Contraindications

A) hypersensitivity to lamotrigine or any component of the product (Prod Info LAMICTAL chewable dispersible oral tal
Prod Info LAMICTAL XR oral extended-release tablets, 2009)

3.2 Precautions

A) skin rash, serious and potentially life-threatening, has been reported; discontinue drug if alternate etiology for react
dispersible oral tablets, oral tablets, orally disintegrating tablets, 2009; Prod Info LAMICTAL XR oral extended-release
B) concomitant use with valproic acid; dose adjustment may be required (Prod Info LAMICTAL chewable dispersible
2009; Prod Info LAMICTAL XR oral extended-release tablets, 2009)
C) pediatric patients (2 to 16 years of age); higher rate of serious rash (Prod Info LAMICTAL chewable dispersible ora
Prod Info LAMICTAL XR oral extended-release tablets, 2009)
D) abrupt drug discontinuation should be avoided due to the potential for increased seizure frequency (Prod Info LAM
orally disintegrating tablets, 2009; Prod Info LAMICTAL XR oral extended-release tablets, 2009)
E) allergy to other antiepileptic drugs, preexisting; lamotrigine may increase risk of nonserious rash (Prod Info LAMIC
disintegrating tablets, 2009; Prod Info LAMICTAL XR oral extended-release tablets, 2009)

F) bipolar disorder, treatment of; possible increased risk for worsening depression or suicidality (Prod Info LAMICTAL disintegrating tablets, 2009; Prod Info LAMICTAL XR oral extended-release tablets, 2009)
G) blood dyscrasias (ie, neutropenia, anemia, leukopenia, pancytopenia, thrombocytopenia, aplastic anemia, pure red LAMICTAL chewable dispersible oral tablets, oral tablets, orally disintegrating tablets, 2009; Prod Info LAMICTAL XR
H) hypersensitivity reactions, including life-threatening or fatal reactions, have occurred; discontinuation of therapy ma dispersible oral tablets, oral tablets, orally disintegrating tablets, 2009; Prod Info LAMICTAL XR oral extended-release
I) multiorgan failure, acute, including fatal and irreversible cases, has occurred (Prod Info LAMICTAL chewable dispe tablets, 2009; Prod Info LAMICTAL XR oral extended-release tablets, 2009)
J) status epilepticus, sudden and unexplained deaths, may occur (Prod Info LAMICTAL chewable dispersible oral tab Info LAMICTAL XR oral extended-release tablets, 2009)
K) suicidality, increased risk of; monitoring recommended (Prod Info LAMICTAL XR oral extended-release tablets, 20 tablets, 2009; US Food and Drug Administration, 2008)

3.3 Adverse Reactions

Cardiovascular Effects

Dermatologic Effects

Endocrine/Metabolic Effects

Gastrointestinal Effects

Hematologic Effects

Hepatic Effects

Immunologic Effects

Musculoskeletal Effects

Neurologic Effects

Ophthalmic Effects

Psychiatric Effects

Renal Effects

Reproductive Effects

Respiratory Effects

Other

3.3.1 Cardiovascular Effects

Chest pain

EKG finding

Hypotension

3.3.1.A Chest pain

1) Incidence: 3% (extended-release) (Prod Info LAMICTAL XR oral extended-release tablets, 2009)
2) In a 19-week, double-blind, placebo-controlled study of patients with partial onset seizure, chest pain was treatment with lamotrigine extended-release (n=118) compared with 1% who received placebo (n=121) (Prod

2009).

3.3.1.B EKG finding

1) Premarketing studies have shown a minor incidence of increased PR interval, which were not clinically sig (Matsuo et al, 1993a). One case of a patient who had first-degree heart block was also reported (Betts et al,

2) Literature Reports

a) First-degree heart block was reported in one patient receiving lamotrigine therapy; however, this was an athlete, continued to run marathons while continuing lamotrigine treatment. Another patient had invert electrocardiogram (EKG) performed 2 weeks after discontinuing lamotrigine was still abnormal, so this e 1991).

3.3.1.C Hypotension

1) Two children had hypotensive episodes, with blood pressure 77/45 millimeters of mercury in one child, aft Both children subsequently suffered multiorgan dysfunction, which reversed several days following discontinu represents lamotrigine-associated anticonvulsant hypersensitivity syndrome (Chattergoon et al, 1997b).

3.3.2 Dermatologic Effects

Alopecia

Erythema multiforme

Fixed drug eruption

Flushing

Rash

Stevens-Johnson syndrome

Summary

Toxic epidermal necrolysis

3.3.2.A Alopecia

1) Incidence: 2% (extended-release) (Prod Info LAMICTAL XR oral extended-release tablets, 2009)

2) In a 19-week, double-blind, placebo-controlled study of patients with partial onset seizure, alopecia was e treatment with lamotrigine extended-release (n=118) compared with 1% who received placebo (n=121) (Prod 2009).

3.3.2.B Erythema multiforme

1) Summary

a) Multiforme erythema has been rarely reported during clinical trials of pediatric and adult patients rece tablets, chewable dispersible oral tablets, 2006).

2) Incidence: rare (Prod Info LAMICTAL(R) oral tablets, chewable dispersible oral tablets, 2006)

3.3.2.C Fixed drug eruption

1) Case Report

a) Lamotrigine was associated with an extensive fixed drug eruption developed in a 54-year-old man. La Rapid improvement occurred (Hsiao et al, 2001).

2) Literature Reports

a) A 54-year-old man developed an extensive fixed drug eruption caused by lamotrigine. His medical his spinocerebellar degeneration; his medications were haloperidol 1 to 5 milligrams (mg) as required, baclo daily, and bisacodyl 10 mg at bedtime. For the previous month and one-half, the patient had been taking seizures. Due to poor control of his seizures, lamotrigine 50 mg twice daily was added to the valproate. T developed a rash, described as red to violaceous, round patches and plaques with central erosions or ve periorbital area and subsequently spread to the trunk and extremities. Skin biopsy revealed extensive va infiltration of lymphocytes, histiocytes, eosinophils, and melanophages. Fixed drug eruption due to lamot withdrawn, and Solu-Medrol 40 mg/day initiated. Rapid improvement occurred. Nine weeks later, patch t lamotrigine was the causal agent. When patch-test lamotrigine was applied to previously uninvolved area appeared only on the previously involved areas (Hsiao et al, 2001).

3.3.2.D Flushing

1) Incidence: 3% (extended-release) (Prod Info LAMICTAL XR oral extended-release tablets, 2009)
2) In a 19-week, double-blind, placebo-controlled study of patients with partial onset seizure, hot flush was e
treatment with lamotrigine extended-release (n=118) compared with 0% who received placebo (n=121) (Prod
2009).

3.3.2.E Rash

1) Incidence: 10% adult; 14% pediatric (immediate-release) (Prod Info LAMICTAL(R) oral tablets, chewable
(Prod Info LAMICTAL XR oral extended-release tablets, 2009)
2) Immediate Release
a) Maculopapular and erythematous rashes have been reported with therapeutic doses of lamotrigine (F
dispersible oral tablets, 2006; Messenheimer et al, 1998; Matsuo et al, 1993a). Retrospective evaluation
United Kingdom epilepsy clinics identified 12 cases of serious skin rash (1.1%). Nonserious rashes occu
determined the following significant (p less than 0.05) risk factors: higher starting dose, concomitant sodi
Reports from clinical use have suggested (although not proven) that, besides age below 16 years, the fo
developing a severe potentially life-threatening rash (Prod Info LAMICTAL(R) oral tablets, chewable disp
Concomitant use of valproic acid or antibiotics known to cause skin rashes; 2) Administration of lamotrigi
manufacturer; 3) Escalating the lamotrigine dose at a faster rate than recommended by the manufacture
3) Literature Reports
a) Retrospective evaluation of 1050 records of lamotrigine recipients from five United Kingdom epilepsy
The relative risk of lamotrigine- related rash in females compared to males was 1.83 (95% confidence int
serious rash included concomitant sodium valproate (n=12), female gender (n=10), and starting daily dos
serious rash decreased following the manufacturer- recommended initial dose reduction in 1994, the ove
after this time point (Wong et al, 1999).
b) PEDIATRIC REVIEW - A comprehensive review of manufacturer data encompassing 13 clinical trials
profile in the pediatric population. As add-on therapy, the mean lamotrigine dose and duration were 5.5 r
respectively. As monotherapy, the mean dose and duration were 2.9 mg/kg/day and 22 weeks, respectiv
effect was rash. (Messenheimer et al, 2000). One such add-on study, involving 1983 pediatric patients, r
oral tablets, chewable dispersible oral tablets, 2006). In all monotherapy trials, the corresponding event v
rash was 12.6%, leading to discontinuation in 4.7% of children (Messenheimer et al, 2000).
c) In a series of 68 consecutive children treated with lamotrigine at a pediatric medical center, five (7%)
hospitalization, one with Stevens-Johnson syndrome. The authors conclude that lamotrigine should be d
within two to eight weeks of initiation of therapy; if rechallenge is considered, it should be done with a ver
In a study of 14 children, lamotrigine was withdrawn due to rash (two cases) and hirsutism (one case) (B
d) A 25-year-old man who had developed rash with lamotrigine was rechallenged and developed the ras
previously started on lamotrigine 25 milligrams/day titrated by 25 mg every 3 days for 2 weeks, and then
to a daily dose of 300 mg/day. A slower titration was attempted and again after reaching 300 mg (after 7
made to decrease the dose to 150 mg and begin prednisone 20 mg, however, the rash persisted and lan
4) Management
a) Among 44 patients rechallenged with lamotrigine following lamotrigine-induced rash, 39 were succes
systematic review including 2 case series, 2 case reports, and 1 retrospective record review of adults wit
2 case reports of adults with bipolar disorder. The authors concluded that very slow titration is essential i
The following table outlines the number of successful lamotrigine rash rechallenges and the titration sche

Patients/study design	Total patients rechallenged or continued	Successful rechallenge/ continuation	
Children epilepsy case series (age 5 to 19 years)	7	7	Re-initiated after a m mg/day; week 2: 0.1 and 5: 1 mg/day; wee 10: 6.25 mg/day; wee doubled in increment dose of 50 mg/day. T mg/day.
Adult epilepsy case series	6	6	Rechallenged with 12 specified
Adult epilepsy case series	8	7	Titration doses varied varying from 24 days
Adult epilepsy case reports	2	2	Re-initiated at a dose dose of 50 mg/day
Adult epilepsy retrospective review	19	16	5 mg/day or every se weeks to 25 mg/day.
Adult bipolar disorder case report	1	0	Rechallenged with 5 dose of 300 mg/day
Adult bipolar disorder case	1	1	Restarted at 12.5 mg

report			wks, 50 mg/day for 2
Total	44	39	

(Lorberg et al, 2009)

5) Extended Release

a) In a 19-week, double-blind, placebo-controlled study of patients with partial onset seizure, rash was e treatment with lamotrigine extended-release (n=118) compared with 1% who received placebo (n=121). extended-release is not expected to be different from the immediate-release formulation (Prod Info LAMI

3.3.2.F Stevens-Johnson syndrome

1) Incidence: 0.08% to 0.8% (Prod Info LAMICTAL(R) oral tablets, chewable dispersible oral tablets, 2006)

2) Severe and potentially life-threatening rashes, including Stevens-Johnson syndrome, have been reported and 0.8% of pediatric epilepsy patients. Serious rashes were also reported in clinical trials of adult patients w lamotrigine as initial monotherapy and 0.13% for adjunctive therapy. Most cases have presented within 2 to 8 occurred after long-term treatment (Prod Info LAMICTAL(R) oral tablets, chewable dispersible oral tablets, 20

3) A Stevens-Johnson-like syndrome appeared in one of 16 patients during the first year of lamotrigine treatr discontinuation (Cocito et al, 1994).

4) Literature Reports

a) A case of Stevens-Johnson-Syndrome associated with lamotrigine therapy in a 30-year-old male was initiation of lamotrigine, which was added to valproic acid therapy (2500 milligrams/day) and was diagnos to the drug. The patient developed a skin eruption and had complaints of influenza-like symptoms (Sachs

3.3.2.G Summary

1) Lamotrigine should be discontinued at the first sign of a rash, unless the rash is clearly not drug related. P also been noted. The risk of severe rash may be increased by the coadministration of lamotrigine with valproi lamotrigine or by exceeding the recommended dose escalation recommendations. However, cases have bee manufacturer recommends that lamotrigine not be restarted in patients who have previously discontinued lam drug clearly outweigh the risks. If a patient has discontinued lamotrigine for greater than 5 half-lives, the initia LAMICTAL(R) oral tablets, chewable dispersible oral tablets, 2006).

3.3.2.H Toxic epidermal necrolysis

1) Incidence: 0.08% to 0.8% (Prod Info LAMICTAL(R) oral tablets, chewable dispersible oral tablets, 2006)

2) Severe and potentially life-threatening rashes, including toxic epidermal necrolysis (TEN), have been repo adult and 0.8% of pediatric epilepsy patients. Serious rashes were also reported in clinical trials of adult patie receiving lamotrigine as initial monotherapy and 0.13% for adjunctive therapy. Most cases have presented wi but some occurred after long-term treatment (Prod Info LAMICTAL(R) oral tablets, chewable dispersible oral

3) Literature Reports

a) A 54-year-old man developed fatal toxic epidermal necrolysis (TEN) 4 weeks after beginning lamotrig glioblastoma multiforme brain tumor. The patient was also receiving allopurinol, captopril, and valproic a started and was then increased to 50 mg twice daily within 1 week. He died 17 days after the onset of TE

b) A 74-year-old man developed toxic epidermal necrolysis (TEN) 14 days after beginning lamotrigine th rash, which progressed in 4 days to TEN. After 5 days the lamotrigine was discontinued and the patient & Davis, 1997).

c) A 22-month-old child developed toxic epidermal necrolysis 14 days after the addition of lamotrigine to maculopapular rash developed and worsened involving the conjunctivae, oral cavity and trachea. Lamot weeks (Vukelic et al, 1997).

d) Three cases of toxic epidermal necrolysis (TEN), verified by skin biopsies, were reported, which deve were treated in burn units of hospitals. The authors speculated immune sensitization occurred; however, incidence of rash with lamotrigine is especially high when combined with valproic acid, but it is unknown 1996).

3.3.3 Endocrine/Metabolic Effects

Hyponatremia

Weight gain

3.3.3.A Hyponatremia

1) Hyponatremia occurred in 2 young girls (12 and 15 years of age) with cranial diabetes insipidus who were had primary panhypopituitarism, and the second patient developed panhypopituitarism secondary to removal desmopressin therapy at the time lamotrigine was introduced. The first patient was given lamotrigine 50 millig had lamotrigine dose increases of 7 milligrams/kilogram (mg/kg) (initial dose not specified). In both cases, the requirements as lamotrigine doses increased. The authors suggested that the effect of lamotrigine on fluid ba 2000).

3.3.3.B Weight gain

1) Incidence: 2% (extended-release) (Prod Info LAMICTAL XR oral extended-release tablets, 2009)

2) In a 19-week, double-blind, placebo-controlled study of patients with partial onset seizure, weight gain was treatment with lamotrigine extended-release (n=118) compared with 1% who received placebo (n=121) (Prod 2009).

3) Lamotrigine is not associated with clinically significant weight gain. Based on a retrospective review of ma the average weight change was only 0.5 kilogram at a mean lamotrigine daily dose and duration of 259 millig age- or gender-related differences in body weight changes (Devinsky et al, 2000).

3.3.4 Gastrointestinal Effects

Abdominal pain

Constipation

Diarrhea

Indigestion

Loss of appetite

Nausea

Vomiting

Xerostomia

3.3.4.A Abdominal pain

1) Incidence: 10% (Prod Info LAMICTAL(R) oral tablets, chewable dispersible oral tablets, 2006)

2) Abdominal pain has been reported in 10% of pediatric epilepsy patients receiving lamotrigine compared w tablets, chewable dispersible oral tablets, 2006).

3) Incidence: 6% (extended-release) (Prod Info LAMICTAL XR oral extended-release tablets, 2009)

4) In a 19-week, double-blind, placebo-controlled study of patients with partial onset seizure, abdominal pain treatment with lamotrigine extended-release (n=118) compared with 4% who received placebo (n=121) (Prod 2009).

3.3.4.B Constipation

1) Incidence: 3% (extended-release) (Prod Info LAMICTAL XR oral extended-release tablets, 2009)

2) In a 19-week, double-blind, placebo-controlled study of patients with partial onset seizure, constipation wa treatment with lamotrigine extended-release (n=118) compared with 1% who received placebo (n=121) (Prod 2009).

3.3.4.C Diarrhea

1) Incidence: 8% (extended-release) (Prod Info LAMICTAL XR oral extended-release tablets, 2009)

2) In a 19-week, double-blind, placebo-controlled study of patients with partial onset seizure, diarrhea was ev treatment with lamotrigine extended-release (n=118) compared with 5% who received placebo (n=121) (Prod 2009).

3.3.4.D Indigestion

1) Incidence: 7% (Prod Info LAMICTAL(R) oral tablets, chewable dispersible oral tablets, 2006)

2) In a monotherapy trial for adults with partial seizures, 7% of patients receiving lamotrigine reported dyspep valproate (Prod Info LAMICTAL(R) oral tablets, chewable dispersible oral tablets, 2006).

3.3.4.E Loss of appetite

1) Incidence: 3% (extended-release) (Prod Info LAMICTAL XR oral extended-release tablets, 2009)

2) In a 19-week, double-blind, placebo-controlled study of patients with partial onset seizure, decreased appe adjunctive treatment with lamotrigine extended-release (n=118) compared with 2% who received placebo (n= tablets, 2009).

3.3.4.F Nausea

1) Incidence: 7% to 25%(immediate-release) (Prod Info LAMICTAL(R) oral tablets, chewable dispersible ora LAMICTAL XR oral extended-release tablets, 2009)

2) Immediate Release

a) Nausea has been reported in 7% of adult partial seizure patients treated with lamotrigine compared w
epilepsy patients receiving lamotrigine compared with 10% of placebo patients, and in 10% of pediatric e
2% of placebo patients. A randomized trial of adult epilepsy patients found that incidence of nausea was
with 500 mg, compared with 11% with placebo (Prod Info LAMICTAL(R) oral tablets, chewable dispersib

3) Extended Release

a) In a 19-week, double-blind, placebo-controlled study of patients with partial onset seizure, nausea wa
treatment with lamotrigine extended-release (n=118) compared with 2% who received placebo (n=121) (
2009)

3.3.4.G Vomiting

1) Incidence: 9%(immediate-release) (Prod Info LAMICTAL(R) oral tablets, chewable dispersible oral tablets

2) Immediate Release

a) Vomiting has been reported in 9% of adult epilepsy patients receiving lamotrigine compared with 4%
seizure patients treated with lamotrigine compared with none of the patients treated with low-dose valproc
that incidence of vomiting was dose-related, increasing from 11% with 300 mg to 18% with 500 mg, com
oral tablets, chewable dispersible oral tablets, 2006).

3) Extended Release

a) In a 19-week, double-blind, placebo-controlled study of patients with partial onset seizure, vomiting w
treatment with lamotrigine extended-release (n=118) compared with 2% who received placebo (n=121) (
2009).

3.3.4.H Xerostomia

1) Incidence: 3% (extended-release) (Prod Info LAMICTAL XR oral extended-release tablets, 2009)

2) In a 19-week, double-blind, placebo-controlled study of patients with partial onset seizure, dry mouth was
treatment with lamotrigine extended-release (n=118) compared with 2% who received placebo (n=121) (Prod
2009).

3.3.5 Hematologic Effects

Anemia

Disseminated intravascular coagulation

Eosinophil count raised

Leukopenia

Neutropenia

Pure red cell aplasia

Thrombocytopenia

Thrombocytosis

3.3.5.A Anemia

1) Anemia has been reported as an uncommon adverse effect of lamotrigine. Anemias (aplastic anemia, her
reversible after discontinuation of lamotrigine. Patients with anemias were also taking other anticonvulsants,
LAMICTAL(R) oral tablets, chewable dispersible oral tablets, 2006; Pulik et al, 2000; Esfahani & Dasheiff, 19

2) Literature Reports

a) Complete erythroblastopenia occurred several weeks after initiation of lamotrigine (50 milligrams (mg
for uncontrolled epilepsia in a 29- year-old woman who had been diagnosed at age 4 months with Diamo
aplasia). Treatment with folinic acid 25 mg/day returned hemoglobin levels to normal within 2 months, ar
et al, 2000).

b) In one patient, lamotrigine treatment was stopped after 23 months due to macrocytic anemia (Cocito

3.3.5.B Disseminated intravascular coagulation

1) Two children (3.5- and 11-years-old) suffered multiorgan dysfunction and disseminated intravascular coag
current valproic acid therapy. Symptoms began 9 days after starting lamotrigine therapy and included a syndr
urticarial/maculopapular rash, hepatic, and renal dysfunction, hypoalbuminemia, and changes in alertness. D
were also reported, along with evidence of rhabdomyolysis in one patient. No seizures were noted during this
lamotrigine. This probably represents lamotrigine- associated anticonvulsant hypersensitivity syndrome (Chat

2) Disseminated intravascular coagulation has been reported in a 45-year-old female after 2 weeks of upwar

previously been maintained on carbamazepine and clonazepam for seizures with poor control prior to lamotri
partial thromboplastin times were significantly prolonged, fibrinogen was decreased, and fibrin degradation pr

3.3.5.C Eosinophil count raised

1) Eosinophilia has been infrequently reported with lamotrigine use (Prod Info LAMICTAL(R) oral tablets, che

3.3.5.D Leukopenia

1) Although uncommon, leukopenia has resulted from therapeutic dosages of lamotrigine. Neutropenia, panc
in postmarketing experiences, causality has not been established (Prod Info LAMICTAL(R) oral tablets, chew
2) Leukopenia progressing to agranulocytosis occurred within days of discontinuing lamotrigine due to rash i
lamotrigine 50 milligrams/day two weeks prior to this event. No concomitant medications were taken. The agr
count of 3.1 x 10(9)/liter (92% lymphocytes and 8% monocytes) and accompanied by slight transaminase ele
improved to 6.5 x 10(9)/liter with 50% neutrophils (Kraus de Camargo & Bode, 1999).
3) A 35-year-old woman presented with leukopenia, which progressed to sepsis following 10 days of therapy
valproate sodium and propranolol. On admission to the hospital she was hypoxic, hypotensive and feverish, v
therapy, her condition stabilized and she fully recovered (Nicholson et al, 1995).

3.3.5.E Neutropenia

1) Neutropenia induced by lamotrigine was experienced by a 50-year-old woman with schizoaffective disorde
the patient presented with mood swings, alopecia, and weight gain. Lamotrigine was administered at 12.5 mg
and then by 50 mg/day every 2 weeks until a total of 150 mg twice daily was reached. Sodium valproate was
in mood symptoms. Her WBC count and absolute neutrophil count was 4.9 x 10(9) and 2.8 x 10(9)/L, respect
months later, her WBC count was 3.8 x 10(9)/L and absolute neutrophil count was 2.2 x 10(9)/L. Due to decli
decreased by 50 mg/day. Briefly her counts returned to baseline only to continue downward. Consequently, l
on therapy for approximately 10 months. Her WBC count and neutrophil count at discontinuation was 2.8 x 10
returned to baseline without any recurrence of neutropenia. A year and a half later, the patient was rechallen
decreased once again after 2 months of lamotrigine therapy. Following discontinuation, her counts returned t
al, 2007).

3.3.5.F Pure red cell aplasia

1) Incidence: rare (Prod Info LAMICTAL(R) oral tablets, chewable dispersible oral tablets, 2006)
2) Pure red cell aplasia, possibly related to hypersensitivity syndrome, has been noted as an adverse reactio
experiences (Prod Info LAMICTAL(R) oral tablets, chewable dispersible oral tablets, 2006).

3.3.5.G Thrombocytopenia

1) A 15-year-old female with therapy-resistant Lennox-Gastaut syndrome experienced severe thrombocytop
mucosal edema two weeks after initiation of add-on lamotrigine therapy (25 milligrams every other day). The
valproate sodium 2400 milligrams/day. After discontinuation of lamotrigine and introduction of prednisone 10
edema cleared and the thrombocyte level returned to the normal range. The authors assume that the thromb
close time relationship involved, although other possible causes (hypersensitivity reaction, bone marrow aller
(Laengler & Meusers, 1995).

3.3.5.H Thrombocytosis

1) Two cases of decreased hematocrit with thrombocytosis were reported approximately 2 months after begi
reversed after discontinuation of lamotrigine.

3.3.6 Hepatic Effects

Hepatitis

Hyperbilirubinemia

Increased liver enzymes

Liver failure

3.3.6.A Hepatitis

1) Acute hepatitis occurred in a 28-year-old woman after lamotrigine (25 milligrams every other day) was adc
had used for 12 years to treat a generalized seizure disorder (Sauve et al, 2000).
2) Twelve days after initiation of lamotrigine, a 28-year-old patient developed headache, fever, and diplopia a
day. The lamotrigine had been added to her current dose of valproate 14 milligrams/kilogram/day. Clinical sy
amoxicillin therapy, and the patient was admitted. An atypical headache, hyperthermia, drowsiness, and majc
results showed a 10-fold increase in aspartate aminotransferase and alanine aminotransferase, plus a low pr
indicating coagulopathy). All medications were immediately withdrawn. To prevent seizures, gabapentin (400

by clonazepam (1 milligram/day continuous intravenous infusion). Two days after admission, the patient bega peaked on day 3, then declined and became normal within 2 weeks, when she was discharged. A liver biopsy lymphocytes and eosinophils; focal acidophil hepatocellular necrosis was also noted (Sauve et al, 2000).

3.3.6.B Hyperbilirubinemia

1) Slight elevations in plasma bilirubin have been reported with lamotrigine (Cohen et al, 1987b); however, th

3.3.6.C Increased liver enzymes

1) A case report described acute liver failure with significant elevations in liver enzymes in a 21-year-old mal time of admission to the inpatient psychiatry unit for paranoid delusions, home medications included aripiprazo nonadherence to aripiprazole was reported by the patient's family. Although the overall duration and titration 200 mg/day for 2 months prior to admission. While acute findings were not present on physical examination, based on aspartate aminotransferase (AST) and alanine aminotransferase (ALT) serum levels of 960 units/L were normal, and the patient was afebrile with no signs of infection. Liver function tests 2 months prior to adm serology and autoimmune tests ruled out other etiologies of hepatic failure, lamotrigine was determined to be Instead, the patient was restarted on aripiprazole, titrating up to 25 mg/day. Five days after stopping lamotrigi (102 units/L). The Naranjo Probability Scale indicated a probable causative relationship of lamotrigine and ac

2) Elevated aspartate transaminase (AST) (1,066 units/liter (L)), alanine aminotransferase (ALT) (279 units/L units/L), and alkaline phosphatase (ALP) (145 units/L) serum levels were reported in an 11-year-old female a therapy. Multiorgan dysfunction developed, with rhabdomyolysis and no seizures. After discontinuation of her returned to normal over 10 days (Chattergoon et al, 1997b). This probably represents lamotrigine-associated

3.3.6.D Liver failure

1) A case report described acute liver failure with significant elevations in liver enzymes in a 21-year-old mal time of admission to the inpatient psychiatry unit for paranoid delusions, home medications included aripiprazo nonadherence to aripiprazole was reported by the patient's family. Although the overall duration and titration 200 mg/day for 2 months prior to admission. While acute findings were not present on physical examination, based on aspartate aminotransferase (AST) and alanine aminotransferase (ALT) serum levels of 960 units/L were normal, and the patient was afebrile with no signs of infection. Liver function tests 2 months prior to adm serology and autoimmune tests ruled out other etiologies of hepatic failure, lamotrigine was determined to be Instead, the patient was restarted on aripiprazole, titrating up to 25 mg/day. Five days after stopping lamotrigi (102 units/L). The Naranjo Probability Scale indicated a probable causative relationship of lamotrigine and ac

2) A 35-year-old woman, with a history of bipolar disorder and poly substance abuse, developed a fatal prog treatment. Thirty-nine days after starting lamotrigine 400 milligrams/day, she had a four-day history of fevers, addition to lamotrigine she was also receiving Tylenol 3, chloral hydrate, olanzapine, topiramate, and trazodo papular rash, fever (104 degrees Farenheit) and elevated liver function tests were noted. On day 48 lamotrigi chloral hydrate, olanzapine, and trazodone were discontinued. On day 55, a liver biopsy showed centrilobular hepatocytes. Despite treatment, the liver necrosis progressed over the next 3 weeks and the patient died. An extensive, well developed, bile duct proliferation which was suggestive of a protracted and subacute course. damage, the authors suspected that lamotrigine was the cause of the hepatic necrosis due to the rash preced 2002).

3) An 8-year-old boy developed acute hepatic failure 2 weeks after beginning lamotrigine therapy. The patien 50 milligrams, 3 times daily (6 milligrams/kilogram/day) with 3 days of overlapping drugs. Two weeks later, he coagulopathy. His lamotrigine level was 30.2 micrograms/milliliter (mcg/mL) (normal 1 to 3 mcg/mL). He reco and supportive care (Arnon, 1998).

3.3.7 Immunologic Effects

3.3.7.A Immune hypersensitivity reaction

1) Some fatal or life-threatening hypersensitivity reactions have occurred which included clinical features of r vasculitis, lupus-like syndrome, flu-like symptoms and/or disseminated intravascular coagulation. Even thoug hypersensitivity are present, such as fever, or lymphadenopathy, the patient should be evaluated immediately dispersible oral tablets, 2006; Schlienger et al, 1998).

2) Literature Reports

a) Anticonvulsant hypersensitivity syndrome (AHS) - consisting of fever, skin eruption or lymphadenopat associated with lamotrigine therapy in 26 reported cases. Effects appear similar to AHS induced by other have fever (100%), exanthematous rashes (77%), eosinophilia (19%) and lymphadenopathy (12%). Four intravascular coagulopathy. The most commonly reported internal organ toxicities were hematologic and followed by renal (23%) and musculoskeletal (8%). Concomitant anticonvulsant drugs were used in all 26

b) Acute granulomatous interstitial nephritis, along with colitis and ileitis, occurred in a 17-year-old woma weeks after the start of lamotrigine, she developed an pruritic rash; lamotrigine was withdrawn. A week la she developed a fever and progressing flu-like symptoms (sore throat, nausea/vomiting, diarrhea, and ur Lymphadenopathy was found to be present, and liver enzymes were abnormal. Occult blood was found i necrotizing epithelioid granuloma. Renal function deteriorated, with development of oliguria requiring her steroid treatment. The authors concluded that this was a case of anticonvulsant hypersensitivity syndrom

c) A 6-year-old boy being treated with lamotrigine and valproic acid for generalized tonic-clonic seizures lamotrigine, he developed a pruritic eruption (predominantly trunk and extremities), facial swelling, nause white blood cell count had increased to 9500 cells/cubic millimeter, liver enzymes were elevated, and che

Lamotrigine was discontinued but the symptoms persisted until valproic acid was discontinued 2 days lat
laboratory abnormalities (Brown et al, 1999).
d) A 27-year-old female developed multisystem hypersensitivity reaction, with disseminated intravascula
dysfunction, 11 days after starting lamotrigine therapy. Adjunctive therapy included phenobarbital. After s
spontaneously with no interventions other than steroid therapy (Sarris & Wong, 1999).
e) A 47-year-old man developed a hypersensitivity syndrome to lamotrigine that included neuralgic amy
valproate and had lamotrigine titrated to 50 milligrams/day over 1 month. He developed a rash, fever, an
was discontinued but 3 days later he developed left shoulder pain and numbness. Neuralgic amyotrophy
followed by focal neurologic symptoms restricted to that limb. It resolved over 8 months (Hennessy et al,
f) A 35-year-old man developed pseudolymphoma (which may develop as a hypersensitivity reaction to
patient was receiving lamotrigine 225 milligrams along with valproic acid, carbamazepine, and clobazam
The frozen section diagnosis was consistent with lymphoma. With further testing a pathologic diagnosis
of lymphoid hyperplasia was established. Lymphadenopathy resolved 1 month after lamotrigine was disc

3.3.8 Musculoskeletal Effects

Asthenia

Myalgia

Rhabdomyolysis

3.3.8.A Asthenia

1) Summary

a) In premarketing clinical trials of monotherapy for epilepsy, asthenia has been reported in at least 5%
(Prod Info LAMICTAL(R) oral tablets, chewable dispersible oral tablets, 2006).

b) Asthenia led to discontinuation of therapy in 2.4% of adult patients (n=420)(Prod Info LAMICTAL(R) o

2) Incidence: 5% or greater (Prod Info LAMICTAL(R) oral tablets, chewable dispersible oral tablets, 2006)

3.3.8.B Myalgia

1) Incidence: 3% (extended-release) (Prod Info LAMICTAL XR oral extended-release tablets, 2009)

2) In a 19-week, double-blind, placebo-controlled study of patients with partial onset seizure, muscle pain wa
treatment with lamotrigine extended-release (n=118) compared with 0% who received placebo (n=121) (Prod
2009).

3.3.8.C Rhabdomyolysis

1) Rhabdomyolysis has been reported in hypersensitive patients during postmarketing surveillance (Prod Inf
tablets, 2006).

2) Rhabdomyolysis in the absence of seizures is reported in an 11-year-old female 9 days after the addition
dose was halved). Serum creatine kinase level was reported to be 40,952 units/liter (normal less than 255 un
creatine kinase levels returned to normal. This probably represents lamotrigine-associated anticonvulsant hy

3) A case of myopathy with elevated creatine kinase levels (7770 International Units/liter) and myoglobin lev
absence of generalized seizures following a 2 week period of lamotrigine initialization and increasing therape

3.3.9 Neurologic Effects

Amnesia

Aphasia

Aseptic meningitis

Ataxia

Aura, Loss

Blepharospasm

Coordination problem

Dizziness

Drug withdrawal seizure

Encephalopathy

Gilles de la Tourette's syndrome

Headache

Insomnia

Myoclonus

Nystagmus

Somnolence

Status epilepticus

Tremor

Unsteady gait

Vertigo

3.3.9.A Amnesia

1) Incidence: greater than 1% to less than 5% (Prod Info LAMICTAL(R) chewable dispersible oral tablets, or

2) Amnesia has been reported in greater than 2% and less than 5% of adult patients with epilepsy who recei received placebo (Prod Info LAMICTAL(R) chewable dispersible oral tablets, oral tablets, 2009).

3) Amnesia has also been reported in greater than 1% and less than 5% of adult patients with bipolar disord more frequently than in those who received placebo (Prod Info LAMICTAL(R) oral tablets, chewable dispersib

3.3.9.B Aphasia

1) An 11-year-old girl with atypical, benign partial epilepsy showed a loss of previously acquired communicat milligrams/kilogram/day for a recurrence of absence seizures. An increase in the dose of lamotrigine to 2.5 m age 5, she had been treated successfully for absence seizures with valproate and phenobarbital. At the onse the normal range. The girl at age 6 had shown mild learning difficulties, and tests showed low normal intellige was accompanied by marked electroencephalographic (EEG) activation, especially during sleep, when a patt weaning from lamotrigine, EEG patterns and language function returned to pre-lamotrigine levels (Battaglia e

3.3.9.C Aseptic meningitis

1) A 25-year-old woman developed aseptic meningitis 8 days after starting lamotrigine 25 mg/day for epileps resolved; however the symptoms returned upon rechallenge with lamotrigine. The patient presented with mer glutamyl transpeptidase (GGT), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) and cerebros erythrocytes, and leukocytes were elevated; however, CSF cultures for bacteria, fungi, and viruses were nega empiric ceftriaxone 2 g twice daily was initiated The patient had mild leukopenia and thrombocytopenia were viral meningitis. One hour after lamotrigine was re-initiated on day 19, the patient experienced a severe head dysesthesia, tachycardia, and a fever of 39.9 degrees C. Lab findings showed leukopenia, an elevated GGT Again, the CSF cultures for bacteria, fungi, and viruses were negative. Subsequently, lamotrigine was discon initiated until CSF results were negative. Symptoms improved; however, a mild right abducens nerve palsy w good recovery with the exception of incomplete resolution of the abducens palsy. Upon questioning, the patie eyes and mouth, was diagnosed with Sjogren's syndrome that was confirmed by a positive antinuclear antibo with a stabilized erythrocyte sedimentation rate. (Boot, 2009).

2) Lamotrigine-induced aseptic meningitis was reported in a 50-year-old female after the first dose of lamotri mixed episode of bipolar disorder with suicidal thoughts. Within a few hours of the first dose of lamotrigine 25 40.1 degrees C, difficult breathing, tachycardia, headache, photophobia, neck stiffness and increasing myalg inflammation; however, cerebrospinal fluid (CSF) Gram-stains and bacterial cultures found no evidence of an subsequently discontinued and the symptoms improved over the next few days. It was then discovered that t was started on lamotrigine 25 mg daily 7 months prior to the current incident. Lamotrigine was also discontinu subsequently discharged with a presumptive diagnosis of aseptic meningitis. The time between the administr of meningitis, which completely resolved upon discontinuation, as well as recurrence of symptoms upon rech aseptic meningitis in this patient. Aseptic meningitis is a rare side effect of lamotrigine with only 4 cases previ

3.3.9.D Ataxia

1) Incidence: adults, greater than 2% to 28%; children, 11% (Prod Info LAMICTAL(R) chewable dispersible o

2) In premarketing clinical trials of adjunctive epilepsy therapy, ataxia was reported in 22% of adult patients r those receiving placebo (n=419) (Prod Info LAMICTAL(R) chewable dispersible oral tablets, oral tablets, 200

3) In a randomized, placebo-controlled, parallel study, ataxia was one of the more common dose-related adv adult patients with epilepsy treated with lamotrigine 300 mg/day (n=71), lamotrigine 500 mg/day (n=72), and chewable dispersible oral tablets, oral tablets, 2009).

4) In a controlled, monotherapy trial, ataxia was reported in greater than 2% and less than 5% of adult patier (n=43) following discontinuation of carbamazepine or phenytoin and was reported at a greater frequency thar (Prod Info LAMICTAL(R) chewable dispersible oral tablets, oral tablets, 2009).

5) In placebo-controlled, adjunctive trials, ataxia was reported in 11% of pediatric patients with epilepsy rece 750 mg/day (n=168) compared to 3% of patients receiving placebo (n=171) (Prod Info LAMICTAL(R) chewab

3.3.9.E Aura, Loss

1) Three patients experienced loss of aura after switching from conventional antiepileptic therapy to lamotrig had been refractory to conventional therapy. Two of the patients sustained injuries due to loss of aura (Deleu

3.3.9.F Blepharospasm

1) Blepharospasm was attributed to lamotrigine monotherapy in a 51-year-old male with secondarily general blepharospasm appeared 4 months after lamotrigine initiation, his current dose and serum level were 500 mg remitted after a 4-week gradual taper and withdrawal of lamotrigine. The authors discuss possible mechanisn inhibitory effect on glutamate release, which may indirectly affect basal ganglia function (Verma et al, 1999).

3.3.9.G Coordination problem

1) Incidence: 5% (extended-release) (Prod Info LAMICTAL XR oral extended-release tablets, 2009)

2) In a 19-week, double-blind, placebo-controlled study of patients with partial onset seizure, cerebellar coor who received adjunctive treatment with lamotrigine extended-release (n=118) compared with 0% who receive extended-release tablets, 2009).

3.3.9.H Dizziness

1) Incidence: adults, 7% to 54%; children, 14% (immediate-release) (Prod Info LAMICTAL(R) chewable disp release)

2) Immediate Release

a) In premarketing clinical trials of adjunctive epilepsy therapy, dizziness was reported in 38% of adult p 13% of those receiving placebo (n=419) (Prod Info LAMICTAL(R) chewable dispersible oral tablets, oral

b) In a randomized, placebo-controlled, parallel study, dizziness was one of the more common dose-rel and 27% of adult patients with epilepsy treated with lamotrigine 300 mg/day (n=71), lamotrigine 500 mg/ LAMICTAL(R) chewable dispersible oral tablets, oral tablets, 2009).

c) In a controlled, monotherapy trial, dizziness was reported in 7% of adult patients with epilepsy who re discontinuation of carbamazepine or phenytoin compared to 0% of those who received valproate monoth dispersible oral tablets, oral tablets, 2009).

d) In placebo-controlled, adjunctive trials, dizziness was reported in 14% of pediatric patients with epilep maximum of 750 mg/day (n=168) compared to 4% of patients receiving placebo (n=171) (Prod Info LAM 2009).

3) Extended Release

a) In a 19-week, double-blind, placebo-controlled study of patients with partial onset seizure, dizziness v treatment with lamotrigine extended-release (n=118) compared with 5% who received placebo (n=121) (2009).

3.3.9.I Drug withdrawal seizure

1) Drug withdrawal seizure has been reported in patients with bipolar disorder in clinical trials (Prod Info LAM tablets, 2009; Guerrini et al, 1999).

3.3.9.J Encephalopathy

1) Reversible encephalopathy associated with high lamotrigine blood levels (19 mg/L), with a concurrent urir Concomitant medication included valproic acid, which remained at therapeutic blood levels. Symptoms includ incontinence and primitive reflexes. Symptoms improved concurrent with a fall in lamotrigine levels after her l mg/day (Hennessy & Wiles, 1996).

3.3.9.K Gilles de la Tourette's syndrome

1) Lamotrigine caused dose-related symptoms of Tourette syndrome in 3 children (Lombroso, 1999).

2) A 7-year-old girl with partial motor seizures with secondary generalization was treated with valproic acid a developed tic-like movements and vocalizations. Lamotrigine was discontinued and all symptoms abated. Se up to 250 mg daily. Vocalizations were worse but abated after lamotrigine was reduced to 175 mg daily. A 12 lamotrigine 450 mg added to carbamazepine. He began tic-like movements, vocalizations, and rituals consist Lamotrigine was discontinued and the ticks resolved within 2 weeks and the OCD symptoms resolved over s and the symptoms have not returned. An 8-year-old boy with complex partial seizures received lamotrigine 2 repetitive head shaking, hand rubbing, throat clearing, and facial grimaces. His tics abated within a few days

remained under control with lamotrigine 200 mg daily (Lombroso, 1999).

3.3.9.L Headache

1) Incidence: 29% (Prod Info LAMICTAL(R) chewable dispersible oral tablets, oral tablets, 2009)

2) In a premarketing clinical trial, headache was reported in 29% of adult epilepsy patients receiving lamotrig patients, and resulted in drug discontinuation in 3.1% of lamotrigine patients (Prod Info LAMICTAL(R) chewal

3.3.9.M Insomnia

1) Incidence: 5% to 10% (Prod Info LAMICTAL(R) chewable dispersible oral tablets, oral tablets, 2009)

2) In premarketing clinical trials of adjunctive epilepsy therapy, insomnia was reported in 6% of adult patients those receiving placebo (n=419) (Prod Info LAMICTAL(R) chewable dispersible oral tablets, oral tablets, 200

3) In a controlled, monotherapy trial, insomnia was reported in 5% of adult patients with epilepsy who receive discontinuation of carbamazepine or phenytoin compared to 2% of those who received valproate monotherap oral tablets, oral tablets, 2009).

4) In two placebo-controlled trials, insomnia was reported in 10% of adults with bipolar I disorder receiving la after being converted from add-on therapy with other psychotropic medications compared to 6% of those rec chewable dispersible oral tablets, oral tablets, 2009).

3.3.9.N Myoclonus

1) Three case reports describe lamotrigine-associated myoclonus. Two cases involved young adult males (a epilepsies since early childhood. After 2 to 3 years of lamotrigine-valproic acid therapy resulting in a seizure-f myoclonic jerking. In both cases, the lamotrigine serum level was higher than usual (16.5 and 17.7 mg/L). My yet greatly diminished after lamotrigine was stopped or its dose reduced (Janszky et al, 2000).

3.3.9.O Nystagmus

1) Incidence: 3% (extended-release) (Prod Info LAMICTAL XR oral extended-release tablets, 2009)

2) In a 19-week, double-blind, placebo-controlled study of patients with partial onset seizure nystagmus was lamotrigine extended-release (n=118) compared with 1% who received placebo (n=121) (Prod Info LAMICTA

3.3.9.P Somnolence

1) Incidence: adults, 9% to 14%; children, 17% (immediate-release) (Prod Info LAMICTAL(R) chewable disp release) (Prod Info LAMICTAL XR oral extended-release tablets, 2009)

2) Immediate Release

a) In premarketing clinical trials of adjunctive epilepsy therapy, somnolence was reported in 14% of adul patients receiving placebo (n=419) (Prod Info LAMICTAL(R) chewable dispersible oral tablets, oral table

b) In placebo-controlled, adjunctive trials, somnolence was reported in 17% of pediatric patients with ep maximum of 750 mg/day (n=168) compared to 15% of patients receiving placebo (n=171) (Prod Info LA tablets, 2009)

c) In two placebo-controlled trials, somnolence was reported in 9% of adults with bipolar I disorder recei monotherapy after being converted from add-on therapy with other psychotropic medications compared LAMICTAL(R) chewable dispersible oral tablets, oral tablets, 2009).

d) Somnolence and ataxia were also reported in a 45-year-old female following a 2-week upward titratio signs were present. Her neurological status improved over the next 2 weeks following discontinuation of

3) Extended Release

a) In a 19-week, double-blind, placebo-controlled study of patients with partial onset seizure, somnolenc treatment with lamotrigine extended-release (n=118) compared with 5% who received placebo (n=121) (2009)

3.3.9.Q Status epilepticus

1) Status epilepticus has been reported in a minimum of 7 of 2,343 adult patients receiving lamotrigine (Prod oral tablets, 2009; Guerrini et al, 1999).

2) An 8-year-old female diagnosed 4 years previously with Lennox-Gastaut syndrome developed myoclonic clobazam/vigabatrin regimen. Lamotrigine had been initiated at 2 mg/kg, then gradually increased to 20 mg/k the parents reported increasingly frequent episodes of irregular multifocal jerks. Long-term electroencephalo myoclonus, which resolved shortly upon lamotrigine discontinuation (Guerrini et al, 1999).

3.3.9.R Tremor

1) Incidence: adults, 4%; children, 10% (immediate-release) (Prod Info LAMICTAL(R) chewable dispersible (Prod Info LAMICTAL XR oral extended-release tablets, 2009)

2) Immediate Release

a) In premarketing clinical trials of adjunctive epilepsy therapy, tremor was reported in 4% of adult patie those receiving placebo (n=419) (Prod Info LAMICTAL(R) chewable dispersible oral tablets, oral tablets,

b) In placebo-controlled, adjunctive trials, tremor was reported in 10% of pediatric patients with epilepsy of 750 mg/day (n=168) compared to 1% of patients receiving placebo (n=171) (Prod Info LAMICTAL(R)

c) Disabling tremors with dysarthria and mild truncal ataxia have also been reported in 3 patients followi valproate sodium. Tremor resolved with reduction in dose of lamotrigine or valproate sodium (Reutens e

3) Extended Release

a) In a 19-week, double-blind, placebo-controlled study of patients with partial onset seizure, tremor was

treatment with lamotrigine extended-release (n=118) compared with 2% who received placebo (n=121) (2009).

3.3.9.S Unsteady gait

1) Incidence: 2% (extended-release) (Prod Info LAMICTAL XR oral extended-release tablets, 2009)

2) In a 19-week, double-blind, placebo-controlled study of patients with partial onset seizure, gait disturbance treatment with lamotrigine extended-release (n=118) compared with 0% who received placebo (n=121) (Prod 2009).

3.3.9.T Vertigo

1) Incidence: 4% (extended-release) (Prod Info LAMICTAL XR oral extended-release tablets, 2009)

2) In a 19-week, double-blind, placebo-controlled study of patients with partial onset seizure, vertigo was evi treatment with lamotrigine extended-release (n=118) compared with 0% who received placebo (n=121) (Prod 2009).

3.3.10 Ophthalmic Effects

Blurred vision

Diplopia

3.3.10.A Blurred vision

1) Incidence: 11% to 25% (immediate-release) (Prod Info LAMICTAL(R) oral tablets, chewable dispersible o LAMICTAL XR oral extended-release tablets, 2009)

2) Immediate Release

a) In an adjunctive trial, blurred vision was reported in 16% of adult epilepsy patients receiving lamotrigi trial of adult epilepsy patients found that incidence of blurred vision was dose-related, increasing from 11 10% with placebo (Prod Info LAMICTAL(R) oral tablets, chewable dispersible oral tablets, 2006).

3) Extended Release

a) In a 19-week, double-blind, placebo-controlled study of patients with partial onset seizure, blurred visi adjunctive treatment with lamotrigine extended-release (n=118) compared with 2% who received placeb release tablets, 2009).

3.3.10.B Diplopia

1) Incidence: 24% to 49% (immediate-release) (Prod Info LAMICTAL(R) oral tablets, chewable dispersible o LAMICTAL XR oral extended-release tablets, 2009)

2) Immediate Release

a) In an adjunctive trial, diplopia was reported in 28% of adult epilepsy patients receiving lamotrigine co of adult epilepsy patients found that incidence of diplopia was dose-related, increasing from 24% with 30 placebo (Prod Info LAMICTAL(R) oral tablets, chewable dispersible oral tablets, 2006).

3) A comprehensive review of manufacturer data encompassing 13 clinical trials (n=1096) characterize lamo population. As add-on therapy, the mean lamotrigine dose and duration were 5.5 milligrams/kilogram/day (m the mean dose and duration were 2.9 mg/kg/day and 22 weeks, respectively. In placebo-controlled studies, a frequency among lamotrigine recipients included diplopia at 5.4% (Messenheimer et al, 2000).

a) Extended Release

1) In a 19-week, double-blind, placebo-controlled study of patients with partial onset seizure, diplop adjunctive treatment with lamotrigine extended-release (n=118) compared with 0% who received pla release tablets, 2009).

3.3.12 Psychiatric Effects

Anxiety

Depression

Dyssomnia

Suicidal thoughts

Visual hallucinations

3.3.12.A Anxiety

1) Incidence: 5% (immediate release)(Prod Info LAMICTAL(R) oral tablets, chewable dispersible oral tablets XR oral extended-release tablets, 2009)
2) Immediate Release
a) In a monotherapy trial of adult partial seizure patients, anxiety was reported in 5% of patients treated treated with low-dose valproate (Prod Info LAMICTAL(R) oral tablets, chewable dispersible oral tablets, 2
3) Extended Release
a) In a 19-week, double-blind, placebo-controlled study of patients with partial onset seizure, anxiety wa treatment with lamotrigine extended-release (n=118) compared with 0% who received placebo (n=121) (2009).

3.3.12.B Depression
1) Incidence: 4% (extended-release) (Prod Info LAMICTAL XR oral extended-release tablets, 2009)
2) In a 19-week, double-blind, placebo-controlled study of patients with partial onset seizure, depression was treatment with lamotrigine extended-release (n=118) compared with 1% who received placebo (n=121) (Prod 2009).

3.3.12.C Dyssomnia
1) A 42-year-old healthy woman experienced dose-related visual hallucinations as well as sleep disturbance citalopram 40 mg/day for 6 months for depression. She was then diagnosed with bipolar affective disorder typ subsequent dose increase to 50 mg/day, then 100 mg/day in 2 week intervals. Initial symptoms after dose inc wakening and vivid dream-like experiences without being completely asleep. Five days later she experienced headaches and hypersensitivity to noise. The hallucinations resolved over 2 to 3 days after reducing the lamo disturbances and nightmares returned within 1 week of a dose increase to 75 mg/day. Three months later, th disturbed sleep and nightmares. She continued on 100 mg/day, which resulted in visual hallucinations descri that she perceived as real. The events occurred at times of clear consciousness during both daytime and nigl in hallucinations resolving over 3 days. Hallucinations and nightmares have not recurred despite continued tr mg/day. She had no past history of hallucinations (Uher & Jones, 2006).

3.3.12.D Suicidal thoughts
1) Data reviewed by the US Food and Drug Administration suggest an increased risk of suicidal behavior or antiepileptic drugs (AEDs). The analysis included 199 placebo-controlled clinical studies covering 11 different epilepsy, selected psychiatric illnesses, and other conditions, including migraine and neuropathic pain syndro AEDs and 16,029 patients who received placebo, and patients were aged 5 years and older. There were 4 co groups versus (vs) none in the placebo groups. Suicidal behavior or ideation occurred in 0.43% of patients in patients in the placebo groups. This corresponded to an estimated 2.1 per 1000 (95% confidence interval, 0.7 having suicidal behavior or ideation than the placebo groups. The increased risk of suicidality was noted at 1 weeks. When compared to placebo, results were generally consistent among the drugs and were seen in all psychiatric disorders, or other conditions were all at an increased risk for suicidality compared to placebo. Clo or worsening of depression, suicidality and other unusual changes in behavior, which may include symptoms hypomania (US Food and Drug Administration, 2008).

3.3.12.E Visual hallucinations
1) A 42-year-old healthy woman experienced dose-related visual hallucinations as well as sleep disturbance citalopram 40 mg/day for 6 months for depression. She was then diagnosed with bipolar affective disorder typ subsequent dose increase to 50 mg/day, then 100 mg/day in 2 week intervals. Initial symptoms after dose inc wakening and vivid dream-like experiences without being completely asleep. Five days later she experienced headaches and hypersensitivity to noise. The hallucinations resolved over 2 to 3 days after reducing the lamo disturbances and nightmares returned within 1 week of a dose increase to 75 mg/day. Three months later, th disturbed sleep and nightmares. She continued on 100 mg/day, which resulted in visual hallucinations descri that she perceived as real. The events occurred at times of clear consciousness during both daytime and nigl in hallucinations resolving over 3 days. Hallucinations and nightmares have not recurred despite continued tr mg/day. She had no past history of hallucinations (Uher & Jones, 2006).

3.3.13 Renal Effects

Hematuria

Renal failure

3.3.13.A Hematuria
1) Hematuria was reported in 5% of patients receiving lamotrigine in one clinical trial (Jawad et al, 1989d); h In overall clinical experience with the drug, hematuria infrequently occurred (1% or less) (Prod Info LAMICTA 2006).

3.3.13.B Renal failure

1) Acute renal failure, in the absence of predisposing factors, occurred in a 45-year-old female after 14 days for complex partial seizures. Carbamazepine and clonazepam had been used previously by this patient. Seru Rhabdomyolysis developed and may have contributed to the renal failure. Generalized seizures were not rep

3.3.14 Reproductive Effects

3.3.14.A Dysmenorrhea

1) Incidence: 5% (Prod Info LAMICTAL(R) oral tablets, chewable dispersible oral tablets, 2006)

2) In a monotherapy trial for adults with partial seizures, 5% of female patients receiving lamotrigine reportec low-dose valproate (Prod Info LAMICTAL(R) oral tablets, chewable dispersible oral tablets, 2006).

3.3.15 Respiratory Effects

Apnea

Congestion of nasal sinus

Epistaxis

Influenza

Pain in throat

Rhinitis

Sinusitis

3.3.15.A Apnea

1) Summary

a) Apnea has been reported in postmarketing surveys, but causality has not been established (Prod Infc tablets, 2006).

3.3.15.B Congestion of nasal sinus

1) Incidence: 3% (extended-release) (Prod Info LAMICTAL XR oral extended-release tablets, 2009)

2) In a 19-week, double-blind, placebo-controlled study of patients with partial onset seizure, sinus congestic adjunctive treatment with lamotrigine extended-release (n=118) compared with 0% respectively who receivec extended-release tablets, 2009).

3.3.15.C Epistaxis

1) Incidence: 2% (extended-release) (Prod Info LAMICTAL XR oral extended-release tablets, 2009)

2) In a 19-week, double-blind, placebo-controlled study of patients with partial onset seizure, epistaxis was e treatment with lamotrigine extended-release (n=118) compared with 1% who received placebo (n=121) (Prod 2009).

3.3.15.D Influenza

1) Incidence: 3% (extended-release) (Prod Info LAMICTAL XR oral extended-release tablets, 2009)

2) In a 19-week, double-blind, placebo-controlled study of patients with partial onset seizure, influenza or infl received adjunctive lamotrigine extended-release (n=118) compared with 2% who received placebo (n=121) 2009).

3.3.15.E Pain in throat

1) Incidence: 3% (extended-release) (Prod Info LAMICTAL XR oral extended-release tablets, 2009)

2) In a 19-week, double-blind, placebo-controlled study of patients with partial onset seizure, pharyngolaryng adjunctive treatment with lamotrigine extended-release (n=118) compared with 2% who received placebo (n= tablets, 2009).

3.3.15.F Rhinitis

1) Incidence: 7% (Prod Info LAMICTAL(R) oral tablets, chewable dispersible oral tablets, 2006)

2) In a monotherapy trial of adult partial seizure patients, rhinitis was reported in 7% of patients treated with l low-dose valproate (Prod Info LAMICTAL(R) oral tablets, chewable dispersible oral tablets, 2006).

3.3.15.G Sinusitis

1) Incidence: 3% (extended-release) (Prod Info LAMICTAL XR oral extended-release tablets, 2009)

2) In a 19-week, double-blind, placebo-controlled study of patients with partial onset seizure, sinusitis was ev
treatment with lamotrigine extended-release (n=118) compared with 1% who received placebo (n=121) (Prod
2009).

3.3.16 Other

Angioedema

Asthenia

Drug withdrawal

Fever

Multiorgan failure, acute

Pain

3.3.16.A Angioedema

1) Incidence: rare (Prod Info LAMICTAL(R) oral tablets, chewable dispersible oral tablets, 2006)
2) Angioedema has been rarely reported with lamotrigine therapy (Prod Info LAMICTAL(R) oral tablets, chev

3.3.16.B Asthenia

1) Incidence: 9% (extended-release) (Prod Info LAMICTAL XR oral extended-release tablets, 2009)
2) In a 19-week, double-blind, placebo-controlled study of patients with partial onset seizure, asthenia condit
adjunctive treatment with lamotrigine extended-release (n=118) compared with 5% who received placebo (n=
tablets, 2009).

3.3.16.C Drug withdrawal

1) A 26-year-old man developed anhedonia, visual hallucinations, tremor, slight tachycardia, and hyperhidros
discontinuation of his antiepileptic medications (valproic acid 1220 milligrams (mg) per day, lamotrigine 200 n
mg/day for the first 7 days and 2000 mg/day thereafter) in combination with valproic acid was prescribed to re
psychomotor symptoms had begun before he took the first dose of levetiracetam. Therefore, the authors attri
symptoms resolved within a few days (Gelisse et al, 2002).

3.3.16.D Fever

1) Increased temperature related to leukopenia and sepsis has been reported in a patient following 10 days
included valproate sodium and propranolol (Nicholson et al, 1995). Another case was reported of a 45-year-o
disseminated intravascular coagulation, and acute renal failure 14 days after beginning lamotrigine therapy. C
carbamazepine (Schaub et al, 1994).

3.3.16.E Multiorgan failure, acute

1) Acute multiorgan failure, which has sometimes been fatal or irreversible, has been reported in patients tak
associated with multiorgan failure and hepatic failure in 2 of 3,796 adult patients and 4 of 2,435 pediatric pati
other serious medical complications (Prod Info LAMICTAL(R) oral tablets, chewable dispersible oral tablets, 2
2) Two children (3.5- and 11-years-old) suffered multiorgan dysfunction and disseminated intravascular coag
current valproic acid therapy. Symptoms began 9 days after starting lamotrigine therapy and included a syndi
urticarial/maculopapular rash, hepatic, and renal dysfunction, hypoalbuminemia, and changes in alertness. D
were also reported, along with evidence of rhabdomyolysis in one patient. No seizures were noted during this
lamotrigine. This probably represents lamotrigine- associated anticonvulsant hypersensitivity syndrome (Chat

3.3.16.F Pain

1) Incidence: 5% (immediate-release)(Prod Info LAMICTAL(R) oral tablets, chewable dispersible oral tablets
XR oral extended-release tablets, 2009)
2) Immediate Release
a) In a monotherapy trial of adult partial seizure patients, nonspecific body pain was reported in 5% of pa
the patients treated with low-dose valproate (Prod Info LAMICTAL(R) oral tablets, chewable dispersible c
3) Extended Release
a) In a 19-week, double-blind, placebo-controlled study of patients with partial onset seizure, pain was e
treatment with lamotrigine extended-release (n=118) compared with 1% who received placebo (n=121) (
2009).

3.4 Teratogenicity/Effects in Pregnancy/Breastfeeding

A) Teratogenicity/Effects in Pregnancy

1) U.S. Food and Drug Administration's Pregnancy Category: Category C (Prod Info LAMICTAL(R) oral tablets, c
a) Either studies in animals have revealed adverse effects on the fetus (teratogenic or embryocidal or other) in women and animals are not available. Drugs should be given only if the potential benefit justifies the poten
2) Australian Drug Evaluation Committee's (ADEC) Category: B3(Australian Drug Evaluation Committee, 1999)
a) Drugs which have been taken by only a limited number of pregnant women and women of childbearing ag or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have damage, the significance of which is considered uncertain in humans.
See Drug Consult reference: PREGNANCY RISK CATEGORIES
3) Crosses Placenta: Yes
4) Clinical Management
a) A major risk for congenital malformations or fetal loss after first trimester exposure to lamotrigine is not ev Inherently epileptic women have a greater risk of delivering a malformed infant than those without epilepsy, b with maternal seizures or with the treatment drug (Hvas et al, 2000; Morrell, 1996). Based on preliminary data Pregnancy, a possible link may exist between exposure to lamotrigine monotherapy during the first trimester and Drug Administration, 2006). A, large, case-controlled study showed a nonsignificant difference in risk of c compared with non-exposed infants(Dolk et al, 2008). In animal studies, lamotrigine decreases folate concen further data are available, lamotrigine should be used during pregnancy only if the potential benefit to the mot manufacturer maintains a Lamotrigine Pregnancy Registry to monitor outcomes of exposure to lamotrigine du encouraged to report such prenatal exposure, before fetal outcome (eg, ultrasound, amniocentesis results, bi 1-800-336-2176. Patients or prescribers may also enroll in the NAAED by calling (888) 233-2334 (Prod Info L tablets, 2007).
5) Literature Reports
a) There was not an increased risk of isolated orofacial cleft (OC) relative to other malformations in neonates with those who were not exposed to any antiepileptic drugs in a population-based, case-control study (n=85,5 5511 orofacial cleft (OC) cases and 80,052 non-OC controls. For isolated OC in lamotrigine-exposed neonate malformations (odds ratio adjusted for maternal age (adjOR) equal to 0.8, 95% confidence interval (CI), 0.11 other malformations for any of the other 3 OC categories: isolated and multiply malformed OC (adjOR equal t (adjOR equal to 1.01, 95% CI, 0.03 to 5.57), and isolated and multiply malformed CP (adjOR equal to 0.79, 9 exposure. There were 72 lamotrigine mono- or polytherapy-exposed registrations, 40 of which were lamotrigi total cases corresponded to a prevalence of 0.47 cases of OC per 1000 registrations (Dolk et al, 2008).
b) As of September 2006, preliminary data collected by the North American Antiepileptic Drug (NAAED) preg prevalence of isolated, non-syndromic, cleft palate and/or cleft lip in infants of women exposed to lamotrigine Five cases of oral cleft (2 isolated cleft lip, 3 isolated cleft palate) occurred among 564 women who received l resulting in a total prevalence of 8.9 per 1000. However, other pregnancy registries have not reported a simila until further data are available (US Food and Drug Administration, 2006).
c) A July 2005 report from the Lamotrigine Pregnancy Registry, established by the manufacturer to collect da 648 instances of mothers treated with lamotrigine monotherapy during the first trimester of pregnancy. Sixtee abnormalities were noted in this group. In mothers treated with lamotrigine plus one or more other anticonvuls presented with anomalies. However, there was no consistent pattern of anomalies among the birth defects re
d) A series of observational cohort studies suggested that lamotrigine does not cause an increased rate of c 68 pregnant women who took the drug, three discontinued the drug before the last menstrual period; 59 were second or third trimester. Of the 59 exposed during the first trimester, there were 39 births (31 without congen abortion, and nine pregnancies intentionally terminated. Three infants were delivered full term with congenita (mother also exposed to phenytoin), palatal cleft, hypospadias, and undescended testes (mother also expose ventricular septal defect (mother also exposed to phenobarbitone and valproic acid). One infant was delivered abdominal intestinal obstruction. The mother had been exposed to labetalol and had experienced pre-eclamp
e) Lamotrigine clearance increased by more than 50% in some women at the onset of pregnancy with a sign reversed soon after delivery. Increased doses of lamotrigine may be required to maintain therapeutic levels d following pregnancy (Tran et al, 2002).

B) Breastfeeding
1) Thomson Lactation Rating: Infant risk cannot be ruled out.
a) Available evidence and/or expert consensus is inconclusive or is inadequate for determining infant risk wh benefits of drug treatment against potential risks before prescribing this drug during breastfeeding.
2) Clinical Management
a) Lamotrigine milk to plasma (M/P) ratio was 41.3% (range, 5.7% to 147.1%) and infant/maternal ratio of tot prospective, observational study of 30 nursing mothers treated with lamotrigine and their infants (Newport et exposed to lamotrigine from the mother's breast milk are not known, breast-feeding is not recommended in w oral tablets, chewable dispersible oral tablets, 2007).
3) Literature Reports
a) Lamotrigine milk to plasma (M/P) ratio was 41.3% (95% confidence interval (CI), 33% to 49.6%) and infan 18.3% (95% CI, 9.5% to 27%) in a prospective, observational study of 30 nursing mothers treated with lamotr M/P ratio, calculated using each participant's mean breast milk concentration, ranged from 5.7% to 147.1%. U concentrations for each participant, M/P ratios were 26.5% (95% CI, 20.2% to 32.9%) and 63.1% (95% CI, 47 free lamotrigine concentration was 30.9% (95% CI, 13.4% to 48.3%), 1.7 times higher than the total. Infants h lamotrigine compared with their mothers (53.5% vs 29.5%, paired t=2.91, p less than 0.02). Theoretical infant mg/kg/d (95% CI, 0.37 to 0.65 mg/kg/d) and 9.2% (95% CI, 7.4% to 10.9%), respectively. Univariate Pearson p values less than 0.0001) positive correlations of lamotrigine concentration in breast milk with maternal daily plasma (r=0.37), and free lamotrigine in maternal plasma (r=0.51). Maternal dose (F(1147)=25.62) and free la

=17.31) were significant predictors of lamotrigine breast milk concentration (p values less than 0.0001) in a m
predictors was also significant (F(1147)=6.44, p less than 0.02). The final regression model accounted for 45
concentrations (F(3147)=41.11; p less than 0.0001) (Newport et al, 2008).
b) Evaluation of six infants who were breast fed by mothers treated with lamotrigine (mean doses of 400 mg/
infant dose of lamotrigine received through breast milk was 0.45 mg/kg/day. The mean infant plasma concen
concentration was 18% (Page-Sharp et al, 2006).
c) Lamotrigine levels were measured on day 10 of life in 4 full-term nursing infants born to epileptic mothers
ranged from less than 1 to 2 mcg/mL, and were an average of 30% (range 20 to 43%) of maternal lamotrigine
with repeated levels at 2 months. Both infants were nursing with supplemental formula 2 to 3 times a day. Th
levels in the neonate were a result of immature enzyme systems in the infants, specifically hepatic glucuronic
the infants (Liporace et al, 2004).
d) Serum lamotrigine levels in three women and their nursed infants were measured and the infants' intake c
None of the infants experienced adverse effects (Ohman & Vitols, 2000).

4) Drug Levels in Breastmilk
- **a)** Parent Drug
  - **1)** Percent Adult Dose in Breastmilk
    - **a)** 9% (2-20%) (Ohman & Vitols, 2000)
  - **2)** Milk to Maternal Plasma Ratio
    - **a)** 0.61 (0.5-0.77) (Ohman & Vitols, 2000)

3.5 Drug Interactions

3.5.1 Drug-Drug Combinations

Acetaminophen

Carbamazepine

Desogestrel

Escitalopram

Estradiol Cypionate

Ethinyl Estradiol

Ethynodiol Diacetate

Etonogestrel

Evening Primrose

Fosphenytoin

Ginkgo

Levonorgestrel

Lopinavir

Mestranol

Methsuximide

Norethindrone

Norgestimate

Norgestrel

Oxcarbazepine

Phenobarbital

Phenytoin

Primidone

Rifampin

Risperidone

Ritonavir

Rufinamide

Sertraline

Valproic Acid

3.5.1.A Acetaminophen

1) Interaction Effect: decreased lamotrigine effectiveness

2) Summary: In a randomized study, the effect of acetaminophen on the pharmacokinetics of lamotrigine wa area under the plasma concentration-time curve of lamotrigine decreased by 15% and 20% respectively. Rer al, 1990a).

3) Severity: minor

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: Monitor the clinical effectiveness of lamotrigine therapy. Routine increases in lamot failure occurs. An occasional dose of acetaminophen is unlikely to significantly decrease lamotrigine concent

7) Probable Mechanism: increased renal clearance

8) Literature Reports

a) Acetaminophen enhances the urinary elimination of lamotrigine after single doses of the anticonvulsa mg dose of lamotrigine followed by acetaminophen 900 mg 3 times a day resulted in a decrease in AUC compared to administration of lamotrigine with placebo. No differences in peak plasma concentration or t lamotrigine recovered in the urine was also higher when administered with acetaminophen. It was sugge lamotrigine from the circulation (Depot et al, 1990).

3.5.1.B Carbamazepine

1) Interaction Effect: reduced lamotrigine efficacy, loss of seizure control, and a potential risk of neurotoxicity

2) Summary: The clearance of lamotrigine may double during concomitant therapy with carbamazepine (Goa 1991a; Mikati et al, 1989a; Jawad et al, 1987a). In addition, increased serum concentrations of carbamazepir carbamazepine) and neurotoxicity have been reported during concomitant administration of carbamazepine a investigators have found that lamotrigine had no effect on either carbamazepine or its metabolite (Schapel et While lamotrigine has no appreciable effect on the steady-state carbamazepine concentration, carbamazepin (Prod Info Lamictal(R), 2003e).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Monitor seizure control and follow patients for signs of neurotoxicity (nausea, vertig increase lamotrigine doses and/or reduce carbamazepine doses. It may be advantageous to monitor the seru metabolite, carbamazepine-10,11-epoxide. Increased side effects have been associated with carbamazepine When given in combination with an enzyme-inducing antiepileptic agent, the manufacturer recommends an ir two weeks for adult patients, followed by 50 mg twice daily for the third and fourth weeks, advancing by 100 r to 500 mg administered in two divided doses.

7) Probable Mechanism: hepatic induction by carbamazepine of lamotrigine metabolism; possible alteration

8) Literature Reports

a) While lamotrigine alone has a steady-state elimination half-life of between 25 to 37 hours, coadminist approximately 14 or 15 hours (Binnie et al, 1986c; Jawad et al, 1987; Peck, 1991d). Lamotrigine clearan mL/min/kg) in healthy volunteers given lamotrigine alone (Cohen et al, 1987; Posner et al, 1989; Posner therapy ranged from 0.044 to 0.084 L/h/kg (0.73 to 1.4 mL/min/kg) (Jawad et al, 1987; Mikati et al, 1989; decrease incrementally the half-life of lamotrigine by 1.7 hours for every 100 mg of carbamazepine withir

1987).

b) If phenytoin or carbamazepine (or any prodrugs) is used in pregnant women, there is a substantially i of other anticonvulsants. The teratogenicity of these drugs is largely or wholly related to the levels of the Dyke et al, 1991b; Finnell et al, 1992b). The epoxide/parent drug ratio is generally increased when phen any other drugs that induce cytochrome P450 enzymes (3A4, 2C9, 2C19), or drugs which inhibit epoxide lamotrigine (Bianchetti et al, 1987b; Ramsay et al, 1990b; Spina et al, 1996b). Such combinations increa monotherapy and about 10-fold over background rates.

c) No pharmacokinetic interaction between carbamazepine and lamotrigine was found in children. Three generalized epilepsy who had been treated with carbamazepine for longer than one year started lamotrig lamotrigine dose was increased by 1 mg/kg/day every other week until clinical response or side effects o change significantly from baseline when lamotrigine was coadministered (29.9 mmol/L vs. 28.8 mmol/L). metabolite of carbamazepine, carbamazepine-10,11-epoxide, significantly decreased from 6.4 mmol/L to Boreus, 1997).

d) Carbamazepine reduces the plasma levels of lamotrigine. A 65-year-old male suffering from complex carbamazepine (400 mg three times daily) and lamotrigine (200 mg three times daily). Seizures occurred and a beta-agonist were used for an obstructive lung disease. A current pneumonia was being treated w was 1.7 mcmol/mL and a trough carbamazepine was 11 mcmol/mL. The patient continued to suffer from levitiracetam (1500 mg twice daily) within 4 weeks. After 4 weeks of levitiracetam therapy the patient's ca lamotrigine plasma levels were 12.1 mcmol/mL. Lamotrigine levels increased rapidly after reductions in t combination was well tolerated and seizures stopped completely after 4 weeks. A drug interaction should result in ineffective antiepileptic therapy (Koch et al, 2003).

3.5.1.C Desogestrel

1) Interaction Effect: decreased plasma lamotrigine concentrations

2) Summary: The concomitant use of combined hormonal contraceptives and lamotrigine has resulted in sig Info ORTHO EVRA(R) transdermal system patch, 2008). A sudden change in a patient's clinical condition an the use or changes in the use of oral contraceptives (Christensen et al, 2007; Sabers et al, 2003; Sabers et a lamotrigine concentrations following introduction of oral contraceptives and reports of increased lamotrigine c contraceptives in women taking lamotrigine. Dosage adjustments may be necessary when starting or discont maintain clinical response (Prod Info LAMICTAL(R) oral tablets, chewable dispersible oral tablets, 2006).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: established

6) Clinical Management: Estrogen-containing oral contraceptives have been shown to significantly decrease use. Carefully monitor and adjust lamotrigine doses in women who choose estrogen-containing hormonal cor system patch, 2008; Prod Info LAMICTAL(R) oral tablets, chewable dispersible oral tablets, 2006).

7) Probable Mechanism: induction of lamotrigine glucuronidation by combination contraceptive

8) Literature Reports

a) Evidence from a double-blind, placebo-controlled trial involving 7 women with epilepsy suggests that lamotrigine. All patients were treated with lamotrigine monotherapy and taking combination oral contrace a crossover fashion to receive either placebo or contraceptive (35 mcg ethinyl estradiol/250 mcg norgest a 7-day pause). Steady-state blood samples were collected as trough levels (just prior to the next dose) and morning doses. Mean lamotrigine plasma concentrations increased by 84% (95% CI, 45% to 134%) contraceptive treatment for 21 days. Urine excretion of lamotrigine metabolites, measured as the N-2-glu (95% CI, -20% to 61%) when placebo was taken instead of oral contraceptive. Seizures occurred in 3 pa seizures occurred during placebo therapy. The mechanism of the interaction is likely the induction of gluc lamotrigine and ethinyl estradiol (Christensen et al, 2007).

b) Several cases in which oral contraceptives changed the plasma levels of lamotrigine as well as the pa patients who were seizure-free (one with epilepsy, two with complex partial seizures, and two with absen concentrations after oral contraceptives were initiated. Two other patients, one with simple partial seizure discontinued their oral contraceptives. Plasma levels of lamotrigine in these two patients had increased s plasma levels of lamotrigine 41% to 64% (mean 49%). As a result, seizure control deteriorated when ora when oral contraceptives were discontinued. These effects were independent of whether the oral contrac norethindrone. The author concludes that there is a need for careful monitoring and adjustment of the lar combination contraceptives (Sabers et al, 2001).

c) Lamotrigine plasma levels are reduced by greater than 50% during oral contraceptive co-medication. used oral contraceptives, and 30 who did not. The mean lamotrigine dose was 349 mg/day among wome those who did not. Mean plasma level of lamotrigine was 13 mcmol/L in patients on oral contraceptives a (p less than 0.0001). Oral contraceptives markedly decrease plasma concentrations of lamotrigine (Sabe

d) In a study of 16 female volunteers, estrogen-containing oral contraceptive (30 mcg ethinyl estradiol/1 clearance of 300 mg/day lamotrigine by approximately 2-fold with a mean decrease in AUC of 52% and i concentrations gradually increased and were approximately 2-fold higher at the end of the week of inacti serum lamotrigine concentrations at the end of the active hormone cycle. This increase occurred in wom lamotrigine (carbamazepine, phenytoin, phenobarbital, primidone, or rifampin). Dosage adjustment of lar containing oral contraceptives (Prod Info LAMICTAL(R) oral tablets, chewable dispersible oral tablets, 20

3.5.1.D Escitalopram

1) Interaction Effect: an increased risk of myoclonus

2) Summary: Myoclonus occurred in 2 patients receiving escitalopram and lamotrigine concomitantly, where escitalopram in 1 patient. There was no evidence of a metabolic enzyme interaction with lamotrigine, and the additive/synergistic effect of lamotrigine and escitalopram on the 5-HT1A receptors, or by an additive inhibitio (Rosenhagen et al, 2006). Exercise caution when using both drugs concurrently and monitor for signs and sy and jerking.
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Use caution if escitalopram and lamotrigine are used concurrently as this resulted i resolved after escitalopram was withdrawn (Rosenhagen et al, 2006). Monitor for signs and symptoms of myo
7) Probable Mechanism: additive inhibition of voltage-gated calcium channels; additive or synergistic effects
8) Literature Reports
a) Myoclonus occurred in 2 patients following concomitant treatment with escitalopram and lamotrigine. escitalopram 30 mg/day for depression, developed daytime and nighttime myoclonus after 8 weeks of re treatment of bipolar type II disorder. Serum levels of both drugs, measured after the onset of myoclonus, escitalopram levels remained stable compared to a baseline level drawn prior to starting lamotrigine ther continued to have myoclonus while on escitalopram and lamotrigine therapy. Further analysis revealed t CYP2C19, and CYP2D6 enzymes. The second patient, a 28-year-old woman taking lamotrigine 300 mg/ nighttime myoclonus after 2 weeks of receiving escitalopram (titrated to 20 mg/day) for generalized anxie same frequency of myoclonus while on both therapies; however, the myoclonus resolved 2 weeks after e measured at the onset and after the myoclonus resolved, did not change. Although escitalopram is meta CYP2D6, there was no evidence of a metabolic enzyme interaction with lamotrigine. It was postulated th or synergistic effect of lamotrigine and escitalopram on the 5-HT1A receptors, or by an additive inhibition (Rosenhagen et al, 2006).

3.5.1.E Estradiol Cypionate

1) Interaction Effect: decreased plasma lamotrigine concentrations
2) Summary: The concomitant use of combined hormonal contraceptives and lamotrigine has resulted in sig Info ORTHO EVRA(R) transdermal system patch, 2008). A sudden change in a patient's clinical condition an the use or changes in the use of oral contraceptives (Christensen et al, 2007; Sabers et al, 2003; Sabers et a lamotrigine concentrations following introduction of oral contraceptives and reports of increased lamotrigine c contraceptives in women taking lamotrigine. Dosage adjustments may be necessary when starting or discont maintain clinical response (Prod Info LAMICTAL(R) oral tablets, chewable dispersible oral tablets, 2006).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: established
6) Clinical Management: Estrogen-containing oral contraceptives have been shown to significantly decrease use. Carefully monitor and adjust lamotrigine doses in women who choose estrogen-containing hormonal cor system patch, 2008; Prod Info LAMICTAL(R) oral tablets, chewable dispersible oral tablets, 2006).
7) Probable Mechanism: induction of lamotrigine glucuronidation by combination contraceptive
8) Literature Reports
a) Evidence from a double-blind, placebo-controlled trial involving 7 women with epilepsy suggests that lamotrigine. All patients were treated with lamotrigine monotherapy and taking combination oral contrace a crossover fashion to receive either placebo or contraceptive (35 mcg ethinyl estradiol/250 mcg norgest a 7-day pause). Steady-state blood samples were collected as trough levels (just prior to the next dose) and morning doses. Mean lamotrigine plasma concentrations increased by 84% (95% CI, 45% to 134%) contraceptive treatment for 21 days. Urine excretion of lamotrigine metabolites, measured as the N-2-glu (95% CI, -20% to 61%) when placebo was taken instead of oral contraceptive. Seizures occurred in 3 pa seizures occurred during placebo therapy. The mechanism of the interaction is likely the induction of gluc lamotrigine and ethinyl estradiol (Christensen et al, 2007).
b) Several cases in which oral contraceptives changed the plasma levels of lamotrigine as well as the p patients who were seizure-free (one with epilepsy, two with complex partial seizures, and two with absen concentrations after oral contraceptives were initiated. Two other patients, one with simple partial seizure discontinued their oral contraceptives. Plasma levels of lamotrigine in these two patients had increased s plasma levels of lamotrigine 41% to 64% (mean 49%). As a result, seizure control deteriorated when ora when oral contraceptives were discontinued. These effects were independent of whether the oral contrac norethindrone. The author concludes that there is a need for careful monitoring and adjustment of the lar combination contraceptives (Sabers et al, 2001).
c) Lamotrigine plasma levels are reduced by greater than 50% during oral contraceptive co-medication. used oral contraceptives, and 30 who did not. The mean lamotrigine dose was 349 mg/day among wome those who did not. Mean plasma level of lamotrigine was 13 mcmol/L in patients on oral contraceptives a (p less than 0.0001). Oral contraceptives markedly decrease plasma concentrations of lamotrigine (Sabe
d) In a study of 16 female volunteers, estrogen-containing oral contraceptive (30 mcg ethinyl estradiol/1 clearance of 300 mg/day lamotrigine by approximately 2-fold with a mean decrease in AUC of 52% and i concentrations gradually increased and were approximately 2-fold higher at the end of the week of inacti serum lamotrigine concentrations at the end of the active hormone cycle. This increase occurred in wom lamotrigine (carbamazepine, phenytoin, phenobarbital, primidone, or rifampin). Dosage adjustment of lar containing oral contraceptives (Prod Info LAMICTAL(R) oral tablets, chewable dispersible oral tablets, 20

3.5.1.F Ethinyl Estradiol

1) Interaction Effect: decreased plasma lamotrigine concentrations

2) Summary: The concomitant use of combined hormonal contraceptives and lamotrigine has resulted in sig
Info ORTHO EVRA(R) transdermal system patch, 2008). A sudden change in a patient's clinical condition an
the use or changes in the use of oral contraceptives (Christensen et al, 2007; Sabers et al, 2003; Sabers et a
lamotrigine concentrations following introduction of oral contraceptives and reports of increased lamotrigine c
contraceptives in women taking lamotrigine. Dosage adjustments may be necessary when starting or discont
maintain clinical response (Prod Info LAMICTAL(R) oral tablets, chewable dispersible oral tablets, 2006).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: established

6) Clinical Management: Estrogen-containing oral contraceptives have been shown to significantly decrease
use. Carefully monitor and adjust lamotrigine doses in women who choose estrogen-containing hormonal cor
system patch, 2008; Prod Info LAMICTAL(R) oral tablets, chewable dispersible oral tablets, 2006).

7) Probable Mechanism: induction of lamotrigine glucuronidation by combination contraceptive

8) Literature Reports

a) Evidence from a double-blind, placebo-controlled trial involving 7 women with epilepsy suggests that
lamotrigine. All patients were treated with lamotrigine monotherapy and taking combination oral contrace
a crossover fashion to receive either placebo or contraceptive (35 mcg ethinyl estradiol/250 mcg norgest
a 7-day pause). Steady-state blood samples were collected as trough levels (just prior to the next dose)
and morning doses. Mean lamotrigine plasma concentrations increased by 84% (95% CI, 45% to 134%)
contraceptive treatment for 21 days. Urine excretion of lamotrigine metabolites, measured as the N-2-glu
(95% CI, -20% to 61%) when placebo was taken instead of oral contraceptive. Seizures occurred in 3 pa
seizures occurred during placebo therapy. The mechanism of the interaction is likely the induction of glu
lamotrigine and ethinyl estradiol (Christensen et al, 2007).

b) Several cases in which oral contraceptives changed the plasma levels of lamotrigine as well as the p
patients who were seizure-free (one with epilepsy, two with complex partial seizures, and two with absen
concentrations after oral contraceptives were initiated. Two other patients, one with simple partial seizure
discontinued their oral contraceptives. Plasma levels of lamotrigine in these two patients had increased s
plasma levels of lamotrigine 41% to 64% (mean 49%). As a result, seizure control deteriorated when ora
when oral contraceptives were discontinued. These effects were independent of whether the oral contrac
norethindrone. The author concludes that there is a need for careful monitoring and adjustment of the lar
combination contraceptives (Sabers et al, 2001).

c) Lamotrigine plasma levels are reduced by greater than 50% during oral contraceptive co-medication.
used oral contraceptives, and 30 who did not. The mean lamotrigine dose was 349 mg/day among wome
those who did not. Mean plasma level of lamotrigine was 13 mcmol/L in patients on oral contraceptives a
(p less than 0.0001). Oral contraceptives markedly decrease plasma concentrations of lamotrigine (Sabe

d) In a study of 16 female volunteers, estrogen-containing oral contraceptive (30 mcg ethinyl estradiol/1
clearance of 300 mg/day lamotrigine by approximately 2-fold with a mean decrease in AUC of 52% and i
concentrations gradually increased and were approximately 2-fold higher at the end of the week of inacti
serum lamotrigine concentrations at the end of the active hormone cycle. This increase occurred in wom
lamotrigine (carbamazepine, phenytoin, phenobarbital, primidone, or rifampin). Dosage adjustment of lar
containing oral contraceptives (Prod Info LAMICTAL(R) oral tablets, chewable dispersible oral tablets, 20

3.5.1.G Ethynodiol Diacetate

1) Interaction Effect: decreased plasma lamotrigine concentrations

2) Summary: The concomitant use of combined hormonal contraceptives and lamotrigine has resulted in sig
Info ORTHO EVRA(R) transdermal system patch, 2008). A sudden change in a patient's clinical condition an
the use or changes in the use of oral contraceptives (Christensen et al, 2007; Sabers et al, 2003; Sabers et a
lamotrigine concentrations following introduction of oral contraceptives and reports of increased lamotrigine c
contraceptives in women taking lamotrigine. Dosage adjustments may be necessary when starting or discont
maintain clinical response (Prod Info LAMICTAL(R) oral tablets, chewable dispersible oral tablets, 2006).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: established

6) Clinical Management: Estrogen-containing oral contraceptives have been shown to significantly decrease
use. Carefully monitor and adjust lamotrigine doses in women who choose estrogen-containing hormonal cor
system patch, 2008; Prod Info LAMICTAL(R) oral tablets, chewable dispersible oral tablets, 2006).

7) Probable Mechanism: induction of lamotrigine glucuronidation by combination contraceptive

8) Literature Reports

a) Evidence from a double-blind, placebo-controlled trial involving 7 women with epilepsy suggests that
lamotrigine. All patients were treated with lamotrigine monotherapy and taking combination oral contrace
a crossover fashion to receive either placebo or contraceptive (35 mcg ethinyl estradiol/250 mcg norgest
a 7-day pause). Steady-state blood samples were collected as trough levels (just prior to the next dose)
and morning doses. Mean lamotrigine plasma concentrations increased by 84% (95% CI, 45% to 134%)
contraceptive treatment for 21 days. Urine excretion of lamotrigine metabolites, measured as the N-2-glu
(95% CI, -20% to 61%) when placebo was taken instead of oral contraceptive. Seizures occurred in 3 pa

seizures occurred during placebo therapy. The mechanism of the interaction is likely the induction of glu
lamotrigine and ethinyl estradiol (Christensen et al, 2007).
b) Several cases in which oral contraceptives changed the plasma levels of lamotrigine as well as the p
patients who were seizure-free (one with epilepsy, two with complex partial seizures, and two with abser
concentrations after oral contraceptives were initiated. Two other patients, one with simple partial seizur
discontinued their oral contraceptives. Plasma levels of lamotrigine in these two patients had increased s
plasma levels of lamotrigine 41% to 64% (mean 49%). As a result, seizure control deteriorated when ora
when oral contraceptives were discontinued. These effects were independent of whether the oral contrac
norethindrone. The author concludes that there is a need for careful monitoring and adjustment of the la
combination contraceptives (Sabers et al, 2001).
c) Lamotrigine plasma levels are reduced by greater than 50% during oral contraceptive co-medication.
used oral contraceptives, and 30 who did not. The mean lamotrigine dose was 349 mg/day among wom
those who did not. Mean plasma level of lamotrigine was 13 mcmol/L in patients on oral contraceptives a
(p less than 0.0001). Oral contraceptives markedly decrease plasma concentrations of lamotrigine (Sabe
d) In a study of 16 female volunteers, estrogen-containing oral contraceptive (30 mcg ethinyl estradiol/1
clearance of 300 mg/day lamotrigine by approximately 2-fold with a mean decrease in AUC of 52% and i
concentrations gradually increased and were approximately 2-fold higher at the end of the week of inacti
serum lamotrigine concentrations at the end of the active hormone cycle. This increase occurred in wom
lamotrigine (carbamazepine, phenytoin, phenobarbital, primidone, or rifampin). Dosage adjustment of lar
containing oral contraceptives (Prod Info LAMICTAL(R) oral tablets, chewable dispersible oral tablets, 20

3.5.1.H Etonogestrel

1) Interaction Effect: decreased plasma lamotrigine concentrations
2) Summary: The concomitant use of combined hormonal contraceptives and lamotrigine has resulted in sig
Info ORTHO EVRA(R) transdermal system patch, 2008). A sudden change in a patient's clinical condition an
the use or changes in the use of oral contraceptives (Christensen et al, 2007; Sabers et al, 2003; Sabers et a
lamotrigine concentrations following introduction of oral contraceptives and reports of increased lamotrigine c
contraceptives in women taking lamotrigine. Dosage adjustments may be necessary when starting or discont
maintain clinical response (Prod Info LAMICTAL(R) oral tablets, chewable dispersible oral tablets, 2006).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: established
6) Clinical Management: Estrogen-containing oral contraceptives have been shown to significantly decrease
use. Carefully monitor and adjust lamotrigine doses in women who choose estrogen-containing hormonal cor
system patch, 2008; Prod Info LAMICTAL(R) oral tablets, chewable dispersible oral tablets, 2006).
7) Probable Mechanism: induction of lamotrigine glucuronidation by combination contraceptive
8) Literature Reports
a) Evidence from a double-blind, placebo-controlled trial involving 7 women with epilepsy suggests that
lamotrigine. All patients were treated with lamotrigine monotherapy and taking combination oral contrace
a crossover fashion to receive either placebo or contraceptive (35 mcg ethinyl estradiol/250 mcg norgest
a 7-day pause). Steady-state blood samples were collected as trough levels (just prior to the next dose)
and morning doses. Mean lamotrigine plasma concentrations increased by 84% (95% CI, 45% to 134%)
contraceptive treatment for 21 days. Urine excretion of lamotrigine metabolites, measured as the N-2-glu
(95% CI, -20% to 61%) when placebo was taken instead of oral contraceptive. Seizures occurred in 3 pa
seizures occurred during placebo therapy. The mechanism of the interaction is likely the induction of glu
lamotrigine and ethinyl estradiol (Christensen et al, 2007).
b) Several cases in which oral contraceptives changed the plasma levels of lamotrigine as well as the p
patients who were seizure-free (one with epilepsy, two with complex partial seizures, and two with abser
concentrations after oral contraceptives were initiated. Two other patients, one with simple partial seizur
discontinued their oral contraceptives. Plasma levels of lamotrigine in these two patients had increased s
plasma levels of lamotrigine 41% to 64% (mean 49%). As a result, seizure control deteriorated when ora
when oral contraceptives were discontinued. These effects were independent of whether the oral contrac
norethindrone. The author concludes that there is a need for careful monitoring and adjustment of the la
combination contraceptives (Sabers et al, 2001).
c) Lamotrigine plasma levels are reduced by greater than 50% during oral contraceptive co-medication.
used oral contraceptives, and 30 who did not. The mean lamotrigine dose was 349 mg/day among wom
those who did not. Mean plasma level of lamotrigine was 13 mcmol/L in patients on oral contraceptives a
(p less than 0.0001). Oral contraceptives markedly decrease plasma concentrations of lamotrigine (Sabe
d) In a study of 16 female volunteers, estrogen-containing oral contraceptive (30 mcg ethinyl estradiol/1
clearance of 300 mg/day lamotrigine by approximately 2-fold with a mean decrease in AUC of 52% and i
concentrations gradually increased and were approximately 2-fold higher at the end of the week of inacti
serum lamotrigine concentrations at the end of the active hormone cycle. This increase occurred in wom
lamotrigine (carbamazepine, phenytoin, phenobarbital, primidone, or rifampin). Dosage adjustment of lar
containing oral contraceptives (Prod Info LAMICTAL(R) oral tablets, chewable dispersible oral tablets, 20

3.5.1.I Evening Primrose

1) Interaction Effect: reduced anticonvulsant effectiveness
2) Summary: Theoretically, evening primrose oil may reduce the effectiveness of anticonvulsants by lowering

contraindicated in patients with epilepsy (Barber, 1998; Newall et al, 1996).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Avoid concomitant use of evening primrose oil with anticonvulsants.
7) Probable Mechanism: evening primrose oil may reduce the seizure threshold

3.5.1.J Fosphenytoin
1) Interaction Effect: reduced lamotrigine efficacy
2) Summary: Fosphenytoin is a prodrug of phenytoin and the same interactions that occur with phenytoin are Cerebyx(R), 1999). Potent hepatic enzyme-inducing drugs including phenytoin enhance the metabolic cleara steady-state elimination half-life of approximately 24 to 30 hours, coadministration of phenytoin reduces the h et al, 1986; Jawad et al, 1989; Peck, 1991).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Higher doses of lamotrigine are needed when given concurrently with enzyme-indu When given in combination with an enzyme-inducing antiepileptic agent, the manufacturer recommends an ir two weeks for adult patients, followed by 50 mg twice daily for the third and fourth weeks, advancing by 100 r to 500 mg administered in two divided doses.
7) Probable Mechanism: increased lamotrigine metabolism
8) Literature Reports
a) If phenytoin or carbamazepine (or any prodrugs) is used in pregnant women, there is a substantially i of other anticonvulsants. The teratogenicity of these drugs is largely or wholly related to the levels of the Dyke et al, 1991; Finnell et al, 1992). The epoxide/parent drug ratio is generally increased when phenyto other drugs that induce cytochrome P450 enzymes (3A4, 2C9, 2C19), or drugs which inhibit epoxide hyc lamotrigine (Bianchetti et al, 1987; Ramsay et al, 1990; Spina et al, 1996). Such combinations increase t monotherapy and about 10-fold over background rates.

3.5.1.K Ginkgo
1) Interaction Effect: decreased anticonvulsant effectiveness
2) Summary: In a case report, 2 patients with epilepsy previously well controlled by valproate sodium develo extract. Seizure control was regained after ginkgo was withdrawn (Granger, 2001a). An infant developed seiz from ingestion of ginkgo seeds (Yagi et al, 1993a). The compound 4'-O-methylpyridoxine, a neurotoxin, is fou in leaves, the ginkgo component from which commercially available extracts are derived (Arenz et al, 1996a). sufficient amounts of 4'-O-methylpyridoxine to cause seizures. However, ginkgo products are not commonly a contained in the commercial product. Of concern are those instances where, depending on the harvest seasc methylpyridoxine may be present in sufficient amounts to be problematic in vulnerable populations (eg, infant
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Avoid concomitant use of ginkgo and anticonvulsants in patients with epilepsy. If se previously controlled by anticonvulsant medication, inquire about the use of ginkgo seed or leaf extract. If pos product to ascertain if 4'-O-methylpyridoxine is present.
7) Probable Mechanism: neurotoxin 4'-O-methylpyridoxine (found in leaves and seeds of ginkgo biloba) may
8) Literature Reports
a) The serum of a 21-month-old patient with gin-nan food poisoning was assayed for 4'-O-methylpyridox micrograms/milliliter (mcg/mL) at 8.5 hours after ingesting ginkgo seeds, decreasing to 0.05 mcg/mL at 1 methylpyridoxine content was responsible for the tonic/clonic convulsions and loss of consciousness obs particularly vulnerable (Yagi et al, 1993).
b) Four to six milligrams of the neurotoxin 4'-O-methylpyridoxine have been isolated from 2 kilograms of commercially-available products. Highest amounts were found in seeds (85 micrograms (mcg)/seed) and July and beginning of August. The albumen of the seed can contain 105.15 mcg/gram dry weight, but thi boiled. The unprocessed seed coats contain from 5.44-7.15 mcg/gram dry weight. The neurotoxin in gink detectable in homeopathic preparations. Specifically, 8.13 mcg/mL of 4'-O-methylpyridoxine was found in mcg/mL in Kaveri Forte(R), and 7.18 mcg/mL in Gingium(R). Based on recommended daily intake, this tr methylpyridoxine of 48.78 mcg, 58.62 mcg, 11.40 mcg, and 43.08 mcg for Tebonin Forte(R), Rokan(R), the homeopathic products, Ginkgo biloba Urtinktur Hanosan(R) and Ginkgo biloba Urtinktur DHU(R) con methylpyridoxine, respectively. However, the authors note that the amount contained in medicinal extrac significance. Concern remains with the variance in 4'-O-methylpyridoxine content depending on the seas 1996).
c) Seizures recurred in 2 patients, both with epilepsy that was well controlled prior to ingesting ginkgo bi 78-year-old man) had been free of seizures for at least 18 months prior to beginning therapy with Gb 120 developed seizures within 2 weeks of beginning Gb therapy, and both remained seizure-free (without cha (Granger, 2001).

3.5.1.L Levonorgestrel
1) Interaction Effect: decreased plasma lamotrigine concentrations

2) Summary: The concomitant use of combined hormonal contraceptives and lamotrigine has resulted in sig
Info ORTHO EVRA(R) transdermal system patch, 2008). A sudden change in a patient's clinical condition an
the use or changes in the use of oral contraceptives (Christensen et al, 2007; Sabers et al, 2003; Sabers et a
lamotrigine concentrations following introduction of oral contraceptives and reports of increased lamotrigine c
contraceptives in women taking lamotrigine. Dosage adjustments may be necessary when starting or discont
maintain clinical response (Prod Info LAMICTAL(R) oral tablets, chewable dispersible oral tablets, 2006).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: established
6) Clinical Management: Estrogen-containing oral contraceptives have been shown to significantly decrease
use. Carefully monitor and adjust lamotrigine doses in women who choose estrogen-containing hormonal cor
system patch, 2008; Prod Info LAMICTAL(R) oral tablets, chewable dispersible oral tablets, 2006).
7) Probable Mechanism: induction of lamotrigine glucuronidation by combination contraceptive
8) Literature Reports

a) Evidence from a double-blind, placebo-controlled trial involving 7 women with epilepsy suggests that
lamotrigine. All patients were treated with lamotrigine monotherapy and taking combination oral contrace
a crossover fashion to receive either placebo or contraceptive (35 mcg ethinyl estradiol/250 mcg norgest
a 7-day pause). Steady-state blood samples were collected as trough levels (just prior to the next dose)
and morning doses. Mean lamotrigine plasma concentrations increased by 84% (95% CI, 45% to 134%)
contraceptive treatment for 21 days. Urine excretion of lamotrigine metabolites, measured as the N-2-glu
(95% CI, -20% to 61%) when placebo was taken instead of oral contraceptive. Seizures occurred in 3 pa
seizures occurred during placebo therapy. The mechanism of the interaction is likely the induction of gluc
lamotrigine and ethinyl estradiol (Christensen et al, 2007).

b) Several cases in which oral contraceptives changed the plasma levels of lamotrigine as well as the p
patients who were seizure-free (one with epilepsy, two with complex partial seizures, and two with absen
concentrations after oral contraceptives were initiated. Two other patients, one with simple partial seizure
discontinued their oral contraceptives. Plasma levels of lamotrigine in these two patients had increased s
plasma levels of lamotrigine 41% to 64% (mean 49%). As a result, seizure control deteriorated when ora
when oral contraceptives were discontinued. These effects were independent of whether the oral contrac
norethindrone. The author concludes that there is a need for careful monitoring and adjustment of the lar
combination contraceptives (Sabers et al, 2001).

c) Lamotrigine plasma levels are reduced by greater than 50% during oral contraceptive co-medication.
used oral contraceptives, and 30 who did not. The mean lamotrigine dose was 349 mg/day among wome
those who did not. Mean plasma level of lamotrigine was 13 mcmol/L in patients on oral contraceptives a
(p less than 0.0001). Oral contraceptives markedly decrease plasma concentrations of lamotrigine (Sabe

d) In a study of 16 female volunteers, estrogen-containing oral contraceptive (30 mcg ethinyl estradiol/1
clearance of 300 mg/day lamotrigine by approximately 2-fold with a mean decrease in AUC of 52% and i
concentrations gradually increased and were approximately 2-fold higher at the end of the week of inacti
serum lamotrigine concentrations at the end of the active hormone cycle. This increase occurred in wom
lamotrigine (carbamazepine, phenytoin, phenobarbital, primidone, or rifampin). Dosage adjustment of lar
containing oral contraceptives (Prod Info LAMICTAL(R) oral tablets, chewable dispersible oral tablets, 20

3.5.1.M Lopinavir

1) Interaction Effect: decreased lamotrigine serum concentrations
2) Summary: Coadministration of lamotrigine and lopinavir/ritonavir in healthy subjects significantly decrease
lamotrigine clearance in an open-label, sequential, 3-period trial. The postulated mechanism of action is enha
and/or lopinavir on lamotrigine, which is metabolized by direct glucuronidation. A doubling of the lamotrigine d
lopinavir/ritonavir in this study (vanderLee et al, 2006). Monitor patients for loss of lamotrigine efficacy and ac
3) Severity: moderate
4) Onset: delayed
5) Substantiation: established
6) Clinical Management: Coadministration of lamotrigine and lopinavir/ritonavir in healthy subjects significant
increased lamotrigine clearance. A doubling of the lamotrigine dose was required to overcome the interaction
al, 2006). If these agents are coadministered, monitor patients for loss of lamotrigine efficacy and adjust lamo
7) Probable Mechanism: increased lamotrigine metabolism
8) Literature Reports

a) In an open-label, sequential, 3-period trial, coadministration of lamotrigine and lopinavir/ritonavir in he
exposure and half-life, and increased lamotrigine clearance; a doubling of the lamotrigine dose is require
to 65 years (n=24) received oral lamotrigine 50 mg once daily for days 1 and 2, followed by 100 mg twice
100 mg twice daily was added on day 11. Lamotrigine trough levels (Cmin) were measured between day
300 mg twice daily depending on the percentage of decrease. Among 18 patients who completed the stu
day 20 (lamotrigine plus lopinavir/ritonavir) compared to day 10 (lamotrigine alone). The median AUC, C
were not bioequivalent to those on day 10, with a geometric mean ratio (GMR) for lamotrigine AUC (day
0.54). Consequently, the lamotrigine dose was increased to 200 mg twice daily from day 23 to day 31 in
bioequivalent to that on day 10, with a GMR (day 31/day 10) of 0.91 (90% CI, 0.82 to 1.02). The median
metabolite to lamotrigine on day 20 was almost double to that on day 10 (0.57 on day 10 versus 1.12 on
induction of glucuronidation of lamotrigine by ritonavir, and possibly also due to lopinavir. The pharmacol
altered (vanderLee et al, 2006).

3.5.1.N Mestranol

1) Interaction Effect: decreased plasma lamotrigine concentrations

2) Summary: The concomitant use of combined hormonal contraceptives and lamotrigine has resulted in sig
Info ORTHO EVRA(R) transdermal system patch, 2008). A sudden change in a patient's clinical condition an
the use or changes in the use of oral contraceptives (Christensen et al, 2007; Sabers et al, 2003; Sabers et a
lamotrigine concentrations following introduction of oral contraceptives and reports of increased lamotrigine c
contraceptives in women taking lamotrigine. Dosage adjustments may be necessary when starting or discont
maintain clinical response (Prod Info LAMICTAL(R) oral tablets, chewable dispersible oral tablets, 2006).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: established

6) Clinical Management: Estrogen-containing oral contraceptives have been shown to significantly decrease
use. Carefully monitor and adjust lamotrigine doses in women who choose estrogen-containing hormonal cor
system patch, 2008; Prod Info LAMICTAL(R) oral tablets, chewable dispersible oral tablets, 2006).

7) Probable Mechanism: induction of lamotrigine glucuronidation by combination contraceptive

8) Literature Reports

a) Evidence from a double-blind, placebo-controlled trial involving 7 women with epilepsy suggests that
lamotrigine. All patients were treated with lamotrigine monotherapy and taking combination oral contrace
a crossover fashion to receive either placebo or contraceptive (35 mcg ethinyl estradiol/250 mcg norgest
a 7-day pause). Steady-state blood samples were collected as trough levels (just prior to the next dose)
and morning doses. Mean lamotrigine plasma concentrations increased by 84% (95% CI, 45% to 134%)
contraceptive treatment for 21 days. Urine excretion of lamotrigine metabolites, measured as the N-2-glu
(95% CI, -20% to 61%) when placebo was taken instead of oral contraceptive. Seizures occurred in 3 pa
seizures occurred during placebo therapy. The mechanism of the interaction is likely the induction of gluc
lamotrigine and ethinyl estradiol (Christensen et al, 2007).

b) Several cases in which oral contraceptives changed the plasma levels of lamotrigine as well as the p
patients who were seizure-free (one with epilepsy, two with complex partial seizures, and two with absen
concentrations after oral contraceptives were initiated. Two other patients, one with simple partial seizure
discontinued their oral contraceptives. Plasma levels of lamotrigine in these two patients had increased s
plasma levels of lamotrigine 41% to 64% (mean 49%). As a result, seizure control deteriorated when ora
when oral contraceptives were discontinued. These effects were independent of whether the oral contrac
norethindrone. The author concludes that there is a need for careful monitoring and adjustment of the lar
combination contraceptives (Sabers et al, 2001).

c) Lamotrigine plasma levels are reduced by greater than 50% during oral contraceptive co-medication.
used oral contraceptives, and 30 who did not. The mean lamotrigine dose was 349 mg/day among wome
those who did not. Mean plasma level of lamotrigine was 13 mcmol/L in patients on oral contraceptives a
(p less than 0.0001). Oral contraceptives markedly decrease plasma concentrations of lamotrigine (Sabe

d) In a study of 16 female volunteers, estrogen-containing oral contraceptive (30 mcg ethinyl estradiol/1
clearance of 300 mg/day lamotrigine by approximately 2-fold with a mean decrease in AUC of 52% and i
concentrations gradually increased and were approximately 2-fold higher at the end of the week of inacti
serum lamotrigine concentrations at the end of the active hormone cycle. This increase occurred in wom
lamotrigine (carbamazepine, phenytoin, phenobarbital, primidone, or rifampin). Dosage adjustment of lar
containing oral contraceptives (Prod Info LAMICTAL(R) oral tablets, chewable dispersible oral tablets, 20

3.5.1.O Methsuximide

1) Interaction Effect: reduced lamotrigine concentrations and possible loss of seizure control

2) Summary: During a retrospective study, it was determined that methsuximide significantly decreases lamo
receiving combination therapy, lamotrigine concentrations were 69.7% lower than compared to lamotrigine m
induces lamotrigine metabolism (May et al, 1999a).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Monitor seizure control and anticipate a possible need to increase lamotrigine dose
methsuximide is withdrawn from therapy, doses of lamotrigine may need to be reduced.

7) Probable Mechanism: hepatic induction by methsuximide of lamotrigine metabolism

8) Literature Reports

a) Lamotrigine serum concentrations from 222 patients receiving lamotrigine monotherapy (n = 64) or co
evaluated. Thirteen patients were being treated with lamotrigine and methsuximide. In the lamotrigine mo
7.14 mcg/mL while the mean dose was 7.27 mg/dose/kg. The lamotrigine level-to-dose ratio (LDR) in thi
subjects receiving methsuximide in addition to lamotrigine, the plasma concentration was 3.06 mcg/mL v
lamotrigine LDR in this group was 0.31 mcg/mL/mg/kg, demonstrating the inducing properties of methsu

3.5.1.P Norethindrone

1) Interaction Effect: decreased plasma lamotrigine concentrations

2) Summary: The concomitant use of combined hormonal contraceptives and lamotrigine has resulted in sig
Info ORTHO EVRA(R) transdermal system patch, 2008). A sudden change in a patient's clinical condition an
the use or changes in the use of oral contraceptives (Christensen et al, 2007; Sabers et al, 2003; Sabers et a

lamotrigine concentrations following introduction of oral contraceptives and reports of increased lamotrigine c
contraceptives in women taking lamotrigine. Dosage adjustments may be necessary when starting or discont
maintain clinical response (Prod Info LAMICTAL(R) oral tablets, chewable dispersible oral tablets, 2006).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: established
6) Clinical Management: Estrogen-containing oral contraceptives have been shown to significantly decrease
use. Carefully monitor and adjust lamotrigine doses in women who choose estrogen-containing hormonal cor
system patch, 2008; Prod Info LAMICTAL(R) oral tablets, chewable dispersible oral tablets, 2006).
7) Probable Mechanism: induction of lamotrigine glucuronidation by combination contraceptive
8) Literature Reports
a) Evidence from a double-blind, placebo-controlled trial involving 7 women with epilepsy suggests that
lamotrigine. All patients were treated with lamotrigine monotherapy and taking combination oral contrace
a crossover fashion to receive either placebo or contraceptive (35 mcg ethinyl estradiol/250 mcg norgest
a 7-day pause). Steady-state blood samples were collected as trough levels (just prior to the next dose)
and morning doses. Mean lamotrigine plasma concentrations increased by 84% (95% CI, 45% to 134%)
contraceptive treatment for 21 days. Urine excretion of lamotrigine metabolites, measured as the N-2-glu
(95% CI, -20% to 61%) when placebo was taken instead of oral contraceptive. Seizures occurred in 3 pa
seizures occurred during placebo therapy. The mechanism of the interaction is likely the induction of gluc
lamotrigine and ethinyl estradiol (Christensen et al, 2007).
b) Several cases in which oral contraceptives changed the plasma levels of lamotrigine as well as the pa
patients who were seizure-free (one with epilepsy, two with complex partial seizures, and two with absen
concentrations after oral contraceptives were initiated. Two other patients, one with simple partial seizure
discontinued their oral contraceptives. Plasma levels of lamotrigine in these two patients had increased s
plasma levels of lamotrigine 41% to 64% (mean 49%). As a result, seizure control deteriorated when ora
when oral contraceptives were discontinued. These effects were independent of whether the oral contrac
norethindrone. The author concludes that there is a need for careful monitoring and adjustment of the lar
combination contraceptives (Sabers et al, 2001).
c) Lamotrigine plasma levels are reduced by greater than 50% during oral contraceptive co-medication.
used oral contraceptives, and 30 who did not. The mean lamotrigine dose was 349 mg/day among wome
those who did not. Mean plasma level of lamotrigine was 13 mcmol/L in patients on oral contraceptives a
(p less than 0.0001). Oral contraceptives markedly decrease plasma concentrations of lamotrigine (Sabe
d) In a study of 16 female volunteers, estrogen-containing oral contraceptive (30 mcg ethinyl estradiol/1
clearance of 300 mg/day lamotrigine by approximately 2-fold with a mean decrease in AUC of 52% and i
concentrations gradually increased and were approximately 2-fold higher at the end of the week of inacti
serum lamotrigine concentrations at the end of the active hormone cycle. This increase occurred in wom
lamotrigine (carbamazepine, phenytoin, phenobarbital, primidone, or rifampin). Dosage adjustment of lar
containing oral contraceptives (Prod Info LAMICTAL(R) oral tablets, chewable dispersible oral tablets, 20

3.5.1.Q Norgestimate

1) Interaction Effect: decreased plasma lamotrigine concentrations
2) Summary: The concomitant use of combined hormonal contraceptives and lamotrigine has resulted in sig
Info ORTHO EVRA(R) transdermal system patch, 2008). A sudden change in a patient's clinical condition an
the use or changes in the use of oral contraceptives (Christensen et al, 2007; Sabers et al, 2003; Sabers et a
lamotrigine concentrations following introduction of oral contraceptives and reports of increased lamotrigine c
contraceptives in women taking lamotrigine. Dosage adjustments may be necessary when starting or discont
maintain clinical response (Prod Info LAMICTAL(R) oral tablets, chewable dispersible oral tablets, 2006).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: established
6) Clinical Management: Estrogen-containing oral contraceptives have been shown to significantly decrease
use. Carefully monitor and adjust lamotrigine doses in women who choose estrogen-containing hormonal cor
system patch, 2008; Prod Info LAMICTAL(R) oral tablets, chewable dispersible oral tablets, 2006).
7) Probable Mechanism: induction of lamotrigine glucuronidation by combination contraceptive
8) Literature Reports
a) Evidence from a double-blind, placebo-controlled trial involving 7 women with epilepsy suggests that
lamotrigine. All patients were treated with lamotrigine monotherapy and taking combination oral contrace
a crossover fashion to receive either placebo or contraceptive (35 mcg ethinyl estradiol/250 mcg norgest
a 7-day pause). Steady-state blood samples were collected as trough levels (just prior to the next dose)
and morning doses. Mean lamotrigine plasma concentrations increased by 84% (95% CI, 45% to 134%)
contraceptive treatment for 21 days. Urine excretion of lamotrigine metabolites, measured as the N-2-glu
(95% CI, -20% to 61%) when placebo was taken instead of oral contraceptive. Seizures occurred in 3 pa
seizures occurred during placebo therapy. The mechanism of the interaction is likely the induction of gluc
lamotrigine and ethinyl estradiol (Christensen et al, 2007).
b) Several cases in which oral contraceptives changed the plasma levels of lamotrigine as well as the pa
patients who were seizure-free (one with epilepsy, two with complex partial seizures, and two with absen
concentrations after oral contraceptives were initiated. Two other patients, one with simple partial seizure
discontinued their oral contraceptives. Plasma levels of lamotrigine in these two patients had increased s

plasma levels of lamotrigine 41% to 64% (mean 49%). As a result, seizure control deteriorated when ora
when oral contraceptives were discontinued. These effects were independent of whether the oral contrac
norethindrone. The author concludes that there is a need for careful monitoring and adjustment of the lar
combination contraceptives (Sabers et al, 2001).

c) Lamotrigine plasma levels are reduced by greater than 50% during oral contraceptive co-medication.
used oral contraceptives, and 30 who did not. The mean lamotrigine dose was 349 mg/day among wome
those who did not. Mean plasma level of lamotrigine was 13 mcmol/L in patients on oral contraceptives a
(p less than 0.0001). Oral contraceptives markedly decrease plasma concentrations of lamotrigine (Sabe

d) In a study of 16 female volunteers, estrogen-containing oral contraceptive (30 mcg ethinyl estradiol/1
clearance of 300 mg/day lamotrigine by approximately 2-fold with a mean decrease in AUC of 52% and i
concentrations gradually increased and were approximately 2-fold higher at the end of the week of inacti
serum lamotrigine concentrations at the end of the active hormone cycle. This increase occurred in wom
lamotrigine (carbamazepine, phenytoin, phenobarbital, primidone, or rifampin). Dosage adjustment of lar
containing oral contraceptives (Prod Info LAMICTAL(R) oral tablets, chewable dispersible oral tablets, 20

3.5.1.R Norgestrel

1) Interaction Effect: decreased plasma lamotrigine concentrations

2) Summary: The concomitant use of combined hormonal contraceptives and lamotrigine has resulted in sig
Info ORTHO EVRA(R) transdermal system patch, 2008). A sudden change in a patient's clinical condition an
the use or changes in the use of oral contraceptives (Christensen et al, 2007; Sabers et al, 2003; Sabers et a
lamotrigine concentrations following introduction of oral contraceptives and reports of increased lamotrigine c
contraceptives in women taking lamotrigine. Dosage adjustments may be necessary when starting or discont
maintain clinical response (Prod Info LAMICTAL(R) oral tablets, chewable dispersible oral tablets, 2006).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: established

6) Clinical Management: Estrogen-containing oral contraceptives have been shown to significantly decrease
use. Carefully monitor and adjust lamotrigine doses in women who choose estrogen-containing hormonal cor
system patch, 2008; Prod Info LAMICTAL(R) oral tablets, chewable dispersible oral tablets, 2006).

7) Probable Mechanism: induction of lamotrigine glucuronidation by combination contraceptive

8) Literature Reports

a) Evidence from a double-blind, placebo-controlled trial involving 7 women with epilepsy suggests that
lamotrigine. All patients were treated with lamotrigine monotherapy and taking combination oral contrace
a crossover fashion to receive either placebo or contraceptive (35 mcg ethinyl estradiol/250 mcg norgest
a 7-day pause). Steady-state blood samples were collected as trough levels (just prior to the next dose)
and morning doses. Mean lamotrigine plasma concentrations increased by 84% (95% CI, 45% to 134%)
contraceptive treatment for 21 days. Urine excretion of lamotrigine metabolites, measured as the N-2-glu
(95% CI, -20% to 61%) when placebo was taken instead of oral contraceptive. Seizures occurred in 3 pa
seizures occurred during placebo therapy. The mechanism of the interaction is likely the induction of gluc
lamotrigine and ethinyl estradiol (Christensen et al, 2007).

b) Several cases in which oral contraceptives changed the plasma levels of lamotrigine as well as the pa
patients who were seizure-free (one with epilepsy, two with complex partial seizures, and two with absen
concentrations after oral contraceptives were initiated. Two other patients, one with simple partial seizure
discontinued their oral contraceptives. Plasma levels of lamotrigine in these two patients had increased s
plasma levels of lamotrigine 41% to 64% (mean 49%). As a result, seizure control deteriorated when ora
when oral contraceptives were discontinued. These effects were independent of whether the oral contrac
norethindrone. The author concludes that there is a need for careful monitoring and adjustment of the lar
combination contraceptives (Sabers et al, 2001).

c) Lamotrigine plasma levels are reduced by greater than 50% during oral contraceptive co-medication.
used oral contraceptives, and 30 who did not. The mean lamotrigine dose was 349 mg/day among wome
those who did not. Mean plasma level of lamotrigine was 13 mcmol/L in patients on oral contraceptives a
(p less than 0.0001). Oral contraceptives markedly decrease plasma concentrations of lamotrigine (Sabe

d) In a study of 16 female volunteers, estrogen-containing oral contraceptive (30 mcg ethinyl estradiol/1
clearance of 300 mg/day lamotrigine by approximately 2-fold with a mean decrease in AUC of 52% and i
concentrations gradually increased and were approximately 2-fold higher at the end of the week of inacti
serum lamotrigine concentrations at the end of the active hormone cycle. This increase occurred in wom
lamotrigine (carbamazepine, phenytoin, phenobarbital, primidone, or rifampin). Dosage adjustment of lar
containing oral contraceptives (Prod Info LAMICTAL(R) oral tablets, chewable dispersible oral tablets, 20

3.5.1.S Oxcarbazepine

1) Interaction Effect: reduced lamotrigine concentrations and possible loss of seizure control

2) Summary: Oxcarbazepine is structurally similar to carbamazepine but does not form an epoxide metabolit
effects of carbamazepine. When lamotrigine and oxcarbazepine were administered concurrently to 14 epilept
decreased 28.7% compared to lamotrigine monotherapy (May et al, 1999c). In two patients who had received
ulcers occurred several weeks after oxcarbazepine discontinuation or dose reduction. Induction of lamotrigine
the mechanism, such oxcarbazepine discontinuation or a dose reduction may have resulted in a slow increas
(O'Neill & deLeon, 2007). Concomitant use of lamotrigine and oxcarbazepine may require monitoring the pati
lamotrigine dose as necessary. Conversely, in patients receiving these agents concurrently, if oxcarbazepine

doses may need to be reduced. Additionally, the patient may need to be monitored over several weeks for sig
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor seizure control and anticipate a possible need to increase lamotrigine dose oxcarbazepine is withdrawn from therapy or if dosage is reduced, lamotrigine doses may need to be reduced weeks for symptoms of lamotrigine toxicity.
7) Probable Mechanism: hepatic induction by oxcarbazepine of lamotrigine metabolism
8) Literature Reports
a) Two patients, receiving lamotrigine and oxcarbazepine concurrently, experienced oral ulcers several reduction. In the first case, a 35-year-old woman being treated for bipolar II disorder (BD II), hypothyroidi experiencing one week of worsening depression and two days of suicidal thoughts and treated with oxca aripiprazole, quetiapine, lithium, naproxen, pantoprazole, amoxicillin, and levothyroxine. On day 2, lamot mg/day by day 6. Oxcarbazepine dose was decreased and stopped by day 5, and she was discharged o aripiprazole, escitalopram, naproxen, pantoprazole, levothyroxine, and hydroxyzine. On day 42 (41 days oxcarbazepine), she developed painful tongue ulcers. Subsequently, lamotrigine was stopped and the ul old man with BD II, hypertension, and GERD was admitted following a suicide attempt and prescribed ox venlafaxine, mirtazapine, metoprolol, and famotidine. Lamotrigine 50 mg/day was initiated on day 11 and discharged on day 14 with lamotrigine 100 mg and oxcarbazepine 1200 mg (along with other medication mg/day after discharge. On day 44 (22 days after oxcarbazepine dose decrease), he developed several lamotrigine and oxcarbazepine were discontinued and the ulcers resolved completely (O'Neill & deLeon,
b) Lamotrigine serum concentrations from 222 patients receiving lamotrigine monotherapy (n = 64) or co evaluated. Fourteen patients were being treated with lamotrigine and oxcarbazepine. In the lamotrigine r 7.14 mcg/mL while the mean dose was 7.27 mg/dose/kg. The lamotrigine level-to-dose ratio (LDR) in thi subjects receiving oxcarbazepine in addition to lamotrigine, the plasma concentration was 4.73 mcg/mL lamotrigine LDR in this group was 0.71 mcg/mL/mg/kg, demonstrating the inducing properties of oxcarba

3.5.1.T Phenobarbital
1) Interaction Effect: reduced lamotrigine efficacy, loss of seizure control
2) Summary: Potent hepatic enzyme-inducing drugs including phenobarbital enhance the metabolic clearanc state elimination half-life of approximately 24 to 30 hours, coadministration of phenobarbital reduces the half- al, 1989a; Peck, 1991a) and decreases the lamotrigine steady-state concentration by approximately 40% (Pr therapy with lamotrigine, valproic acid, and an enzyme inducer on lamotrigine metabolism does not appear to
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Higher doses of lamotrigine are needed when given concurrently with enzyme-indu given in combination with an enzyme-inducing antiepileptic agent, the manufacturer recommends an initial la weeks for adult patients, followed by 50 mg twice daily for the third and fourth weeks, advancing by 100 mg d 500 mg administered in two divided doses.
7) Probable Mechanism: hepatic induction by phenobarbital of lamotrigine metabolism
8) Literature Reports
a) In 13 patients treated with either carbamazepine or phenobarbital with lamotrigine, the half-life of lam children over the age of 2 years and young adults with epilepsy that was not controlled with a single age subjects taking lamotrigine alone has been 25.4 hours with repeated dosing (Prod Info Lamictal(R), 2003

3.5.1.U Phenytoin
1) Interaction Effect: reduced lamotrigine efficacy
2) Summary: Potent hepatic enzyme-inducing drugs including phenytoin enhance the metabolic clearance o elimination half-life of approximately 24 to 30 hours, coadministration of phenytoin reduces the half-life of lam Jawad et al, 1989b; Peck, 1991b). The addition of phenytoin decreases the lamotrigine steady-state concentr phenytoin. Lamotrigine has no significant effect on steady-state phenytoin concentrations (Prod Info Lamictal
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Higher doses of lamotrigine are needed when given concurrently with enzyme-indu When given in combination with an enzyme-inducing antiepileptic agent, the manufacturer recommends an ir two weeks for adult patients, followed by 50 mg twice daily for the third and fourth weeks, advancing by 100 r to 500 mg administered in two divided doses.
7) Probable Mechanism: increased lamotrigine metabolism
8) Literature Reports
a) If phenytoin or carbamazepine (or any prodrugs) is used in pregnant women, there is a substantially i of other anticonvulsants. The teratogenicity of these drugs is largely or wholly related to the levels of the Dyke et al, 1991a; Finnell et al, 1992a). The epoxide/parent drug ratio is generally increased when pheny any other drugs that induce cytochrome P450 enzymes (3A4, 2C9, 2C19), or drugs which inhibit epoxide lamotrigine (Bianchetti et al, 1987a; Ramsay et al, 1990a; Spina et al, 1996a). Such combinations increa monotherapy and about 10-fold over background rates.

3.5.1.V Primidone

1) Interaction Effect: decreased lamotrigine efficacy

2) Summary: When primidone is added to lamotrigine therapy, the steady-state lamotrigine concentration de 2003).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Higher doses of lamotrigine are needed when given concurrently with enzyme-indu given in combination with an enzyme-inducing antiepileptic agent, the manufacturer recommends an initial la weeks for adult patients, followed by 50 mg twice daily for the third and fourth weeks, advancing by 100 mg d 500 mg administered in two divided doses.

7) Probable Mechanism: hepatic enzyme induction

3.5.1.W Rifampin

1) Interaction Effect: decreased lamotrigine exposure

2) Summary: Coadministration of a single 25-mg dose of lamotrigine in healthy volunteers receiving rifampin increased apparent clearance of lamotrigine (approximately 2-fold). Lamotrigine's AUC decreased by approxi chewable dispersible oral tablets, 2006). Use caution if these agents are coadministered. Monitor patients for doses accordingly.

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: Coadministration of lamotrigine and rifampin has led to significantly increased lamo LAMICTAL(R) oral tablets, chewable dispersible oral tablets, 2006). Monitor patients for loss of lamotrigine ef

7) Probable Mechanism: increased lamotrigine clearance

3.5.1.X Risperidone

1) Interaction Effect: increased risperidone plasma concentrations and risk of adverse effects

2) Summary: Increased risperidone plasma concentrations, with signs of toxicity, developed in a patient adm regimen of risperidone and clozapine (Bienentreu & Kronmuller, 2005).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Clinicians should be aware of the increased risk of risperidone adverse effects in pa When concomitant lamotrigine is initiated, discontinued, or the dose of lamotrigine is changed, re-evaluate th

7) Probable Mechanism: unknown

8) Literature Reports

a) Increased risperidone plasma concentrations and subsequent toxicity were reported in a patient recei risperidone and clozapine. The patient, a 26-year-old woman diagnosed with schizophrenia, had sustain clozapine 550 milligrams (mg) daily and risperidone 8 mg daily. Baseline plasma concentrations of risper (ng/mL) and 800-1100 ng/mL, respectively. Lamotrigine was initiated, with the dose incrementally titrated concentrations increased to 1300 ng/mL and 263 ng/mL, respectively; no symptoms of intoxication were of 225 mg daily, after which risperidone plasma concentration increased to 412 ng/mL, accompanied by dose was reduced to 2 mg daily and completely withdrawn shortly thereafter (Bienentreu & Kronmuller, 2

3.5.1.Y Ritonavir

1) Interaction Effect: decreased lamotrigine serum concentrations

2) Summary: Coadministration of ritonavir and lamotrigine may result in decreased serum concentrations of solution, 2006). Coadministration of lamotrigine and lopinavir/ritonavir in healthy subjects significantly decrea lamotrigine clearance in an open-label, sequential, 3-period trial. The postulated mechanism of action is enha drugs that are metabolized by direct glucuronidation (vanderLee et al, 2006). If lamotrigine and ritonavir are a need to be increased (Prod Info NORVIR(R) oral capsules, solution, 2006). In one study, a doubling of the la effect (vanderLee et al, 2006). Monitor patients for loss of lamotrigine efficacy.

3) Severity: moderate

4) Onset: delayed

5) Substantiation: established

6) Clinical Management: Coadministration of lamotrigine and ritonavir may result in decreased lamotrigine se be increased (Prod Info NORVIR(R) oral capsules, solution, 2006). In one study, a doubling of the lamotrigine (vanderLee et al, 2006). Monitor patients for loss of lamotrigine efficacy.

7) Probable Mechanism: increased lamotrigine metabolism

8) Literature Reports

a) In an open-label, sequential, 3-period trial, coadministration of lamotrigine and lopinavir/ritonavir in he exposure and half-life, and increased lamotrigine clearance; a doubling of the lamotrigine dose is require to 65 years (n=24) received oral lamotrigine 50 mg once daily for days 1 and 2, followed by 100 mg twice 100 mg twice daily was added on day 11. Lamotrigine trough levels (Cmin) were measured between day 300 mg twice daily depending on the percentage of decrease. Among 18 patients who completed the stu day 20 (lamotrigine plus lopinavir/ritonavir) compared to day 10 (lamotrigine alone). The median AUC, C were not bioequivalent to those on day 10, with a geometric mean ratio (GMR) for lamotrigine AUC (day

0.54). Consequently, the lamotrigine dose was increased to 200 mg twice daily from day 23 to day 31 in bioequivalent to that on day 10, with a GMR (day 31/day 10) of 0.91 (90% CI, 0.82 to 1.02). The median metabolite to lamotrigine on day 20 was almost double to that on day 10 (0.57 on day 10 versus 1.12 on induction of glucuronidation of lamotrigine by ritonavir, and possibly also due to lopinavir. The pharmacol altered (vanderLee et al, 2006).

3.5.1.Z Rufinamide

1) Interaction Effect: decreased lamotrigine plasma concentrations

2) Summary: Concomitant administration of lamotrigine and rufinamide may result in lamotrigine concentrati dependent on the concentration of rufinamide, so maximum changes will most likely occur in children and oth rufinamide (Prod Info BANZEL(TM) oral tablets, 2008).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: Caution is advised if lamotrigine and rufinamide are coadministered as this may res Risk is increased in children and in other patients who achieve significantly higher levels of rufinamide (Prod

7) Probable Mechanism: unknown

3.5.1.AA Sertraline

1) Interaction Effect: an increased risk of lamotrigine toxicity (fatigue, sedation, confusion, decreased cogniti

2) Summary: Two case reports describe epileptic patients who experienced lamotrigine toxicity when sertrali primarily via glucuronidation, while sertraline relies on N-demethylation, hydroxylation, oxidative deamination decreases lamotrigine metabolism through competitive inhibition of glucuronidation (Kaufman & Gerner, 199

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Caution should be exercised when combining sertraline and lamotrigine therapy. La dosages adjusted accordingly.

7) Probable Mechanism: inhibition of lamotrigine glucuronidation

8) Literature Reports

a) A 39-year-old female with epilepsy was maintained on lamotrigine 200 mg daily with a baseline lamot intermittent explosive disorder, sertraline 25 mg daily was initiated. Six weeks later, the lamotrigine level confusion and cognitive impairment. Sertraline was increased to 50 mg daily while lamotrigine was decre eliminated the patient's confusion and impaired cognition, and the blood level of lamotrigine stabilized at

b) Lamotrigine 450 mg daily was not controlling seizures in a 17-year-old female with mixed epileptic dis and titrated to 75 mg daily without any side effects. Lamotrigine was also increased to 600 mg daily, and fatigue, and decreased cognition. The lamotrigine blood level was 19.3 mcg/mL at this time. The sertralir lamotrigine level was increased to 800 mg daily, resulting in a new steady-state lamotrigine level of 9.8 n decreased to approximately 50% with a 33% decrease in the sertraline daily dose, even though the lamo Gerner, 1998).

3.5.1.AB Valproic Acid

1) Interaction Effect: increased elimination half-life of lamotrigine leading to lamotrigine toxicity (fatigue, drow rashes

2) Summary: Valproic acid interferes with the metabolic clearance of lamotrigine. The normal elimination half receiving concomitant valproic acid therapy, the half-life increases to approximately 40 to 60 hours. The mecl the two drugs for hepatic metabolism (Binnie et al, 1986b; Peck, 1991c; Eriksson et al, 1996a; Sallustio & Mo disseminated intravascular coagulation, and fatal toxic necrolysis have been reported with this combination ir Page II et al, 1998a). Given the increased risk of rash in pediatric patients, careful monitoring of lamotrigine s younger than 16 years of age, for whom the indication for lamotrigine is restricted to those who have been dia syndrome. The dose of lamotrigine should be reduced when coadministered with valproate (Prod Info Depak 2006).

3) Severity: major

4) Onset: delayed

5) Substantiation: established

6) Clinical Management: Dosage reductions of lamotrigine are necessary with concurrent valproic acid thera inducing medications. The manufacturer recommends a lamotrigine dose of 25 mg every other day for the firs next two weeks, advancing to a maintenance dose of 100 mg to 400 mg daily in increments of 25 mg to 50 m only other antiepileptic medication, the usual maintenance dose of lamotrigine is 100 to 200 mg daily. Discon the rash is clearly not drug related (Prod Info lamotrigine oral tablets, 2006).

7) Probable Mechanism: decreased lamotrigine metabolism

8) Literature Reports

a) A 23-year-old woman presented to the emergency room with generalized rash, redness and swelling sore throat 3 weeks after lamotrigine was added to her anti-epilepsy regimen. Her initial regimen consist 500 mg twice daily was added 2 months and lamotrigine 50 mg twice daily was added 3 weeks prior to c erythrocyte sedimentation rate and C-reactive protein. However, serum carbamazepine and valproic acic lamotrigine concentrations were not measured. She was diagnosed with lamotrigine-induced Stevens-Jo Reactions Probability Scale score of 6 (probably drug induced). Lamotrigine was discontinued and treatn

day 18 on oral carbamazepine 400 mg twice daily and oral valproic acid 1500 mg/day. At the one month
oromucosal and skin lesions, with areas of hyperpigmentation. The patient's increased risk of developing
combination of lamotrigine and valproic acid leading to decreased metabolism of lamotrigine, or due to ir
manufacturer's recommended starting dose of 25 mg per day (Kocak et al, 2007).
b) Fever, rash, multiorgan dysfunction, and disseminated intravascular coagulation were reported in two
Both children were receiving valproic acid for treatment of seizures. Lamotrigine was added because of p
starting lamotrigine, but did not abate after lamotrigine was discontinued (Chattergoon et al, 1997).
c) A 54-year-old male presented to the hospital with a five-day history of facial swelling, intermittent feve
extremities, neck, and back. He had been taking allopurinol 100 mg daily and captopril 50 mg daily for fo
multiforme brain tumor, valproic acid and lamotrigine therapy was begun and the doses were titrated to v
50 mg twice daily approximately four weeks prior to his hospital admission. By hospital day 7, the patient
his back, face, and trunk, accounting for more than 60% of his total body surface area. He continued to d
hospital day 12. His death was attributed to toxic epidermal necrolysis probably due to lamotrigine therap
1998).
d) A study including 28 patients with intractable epilepsy was conducted to determine whether the dose
acid were inversely related to lamotrigine clearance. Valproic acid was initiated at 500 mg/day for 3 days
tolerance and response. The valproic acid dose was increased 125 to 250 mg every 3 weeks, until patien
Upon initiation of valproic acid, the dose of lamotrigine was decreased by 50%, so as to maintain lamotri
monotherapy. A 50% reduction in lamotrigine clearance was reported in these patients. The dose of lam
valproic acid therapy to maintain comparable lamotrigine Css. However, additional increases in valproic
lamotrigine to maintain stable lamotrigine Css. Seizure-free periods were significantly longer during treat
lamotrigine monotherapy, an indication that therapeutic synergism exists between lamotrigine and valpro
e) A study involving eight patients with epilepsy found a significant increase in lamotrigine area under th
with concomitant valproic acid administration. Dosages of valproic acid of up to 1,000 mg/day resulted in
fold. Even low doses of valproic acid (200 mg/day) resulted in significant increases in lamotrigine AUC (r
concentrations by inhibiting lamotrigine metabolism and increased half-life has been achieved with the us
al, 2000).
f) Lamotrigine decreased valproic acid steady-state concentrations by 25% in 18 healthy volunteers ove
lamotrigine to the existing therapy did not cause a change in plasma valproate concentrations in adult or
addition of valproate increased lamotrigine steady-state concentrations in normal volunteers by more tha
g) In a black box warning from the manufacturer, the incidence of severe rash may be higher in patients
Info Lamictal(R), 2003d).

4.0 Clinical Applications

Monitoring Parameters

Patient Instructions

Place In Therapy

Mechanism of Action / Pharmacology

Therapeutic Uses

Comparative Efficacy / Evaluation With Other Therapies

4.1 Monitoring Parameters

A) Therapeutic

1) Laboratory Parameters

a) A therapeutic plasma concentration range has not been established for lamotrigine. Dosing of lamotrigine
plasma concentration. Monitoring of plasma levels of lamotrigine and concomitant antiepileptic drugs may be
Info LAMICTAL chewable dispersible oral tablets, oral tablets, orally disintegrating tablets, 2009).
b) Due to the possibility of increased clearance during pregnancy lamotrigine serum levels should be monito
Battino, 2007; Tran et al, 2002a). Although, therapeutic concentrations have not been established, prepregna
provide a reference concentration for comparison to concentrations during pregnancy, when concentrations d
characteristics of lamotrigine (Tomson & Battino, 2007).

2) Physical Findings

a) Patients receiving lamotrigine for the treatment of epilepsy should be monitored for a therapeutic respons
of seizures(Prod Info LAMICTAL chewable dispersible oral tablets, oral tablets, orally disintegrating tablets, 2
b) Patients receiving lamotrigine for the treatment of bipolar 1 disorder should be assessed for a therapeutic
episodes (eg, depression, mania, hypomania, mixed episodes) (Prod Info LAMICTAL chewable dispersible o
2009).

B) Toxic

1) Laboratory Parameters
a) Although, lamotrigine has no significant effects on the plasma levels of other antiepileptic drugs, serum lev
especially during dosage adjustments (Prod Info LAMICTAL chewable dispersible oral tablets, oral tablets, or
2) Physical Findings
a) Observe patient for signs of rash or skin reaction (Prod Info LAMICTAL chewable dispersible oral tablets,
1) Discontinue lamotrigine therapy at the first sign of a rash. If the cause of rash has been clearly identif
to be discontinued (Prod Info LAMICTAL chewable dispersible oral tablets, oral tablets, orally disintegrat
b) Evaluate patient for signs of hypersensitivity reaction, such as fever and lymphadenopathy. Hypersensitiv
multiorgan failure/dysfunction. Lamotrigine should be discontinued if other causes of the symptoms are not id
tablets, oral tablets, orally disintegrating tablets, 2009).
c) Assess patient for worsening of depressive symptoms and/or development of suicidality at the initiation of
requiring the closest monitoring for suicide risk are those with a history or presence of suicidal behavior or th
chewable dispersible oral tablets, oral tablets, orally disintegrating tablets, 2009).
d) Data reviewed by the US Food and Drug Administration suggest an increased risk of suicidal behavior or
antiepileptic drugs (AEDs). The increased risk of suicidality was noted at 1 week after starting an AED and co
epilepsy, psychiatric disorders, or other conditions were all at an increased risk for suicidality compared to pla
emergence or worsening of depression, suicidality, and other unusual changes in behavior, which may includ
and hypomania (US Food and Drug Administration, 2008).

4.2 Patient Instructions

A) Lamotrigine (By mouth)
Lamotrigine

Treats certain types of seizures and mood disorders. Often used along with other medicines.

When This Medicine Should Not Be Used:
You should not use this medicine if you have had an allergic reaction to lamotrigine.

How to Use This Medicine:
Tablet, Chewable Tablet, Dissolving Tablet, Long Acting Tablet
Your doctor will tell you how much of this medicine to use and how often. Your dose may need to be changed
you. Do not use more medicine or use it more often than your doctor tells you to.
You may take this medicine with or without food.
It is best to swallow the regular tablet whole. You may break or crush the tablet if your doctor tells you to, but
The chewable tablet may be swallowed whole, or chewed and taken with a small amount of water or diluted f
a teaspoon of water or fruit juice and swallow the mixture after 1 minute.
If you are using the disintegrating tablet, make sure your hands are dry before you handle the tablet. Do not o
are ready to take it. Remove the tablet from the blister pack by peeling back the foil, then taking the tablet out
in your mouth. It should melt quickly. After the tablet has melted, swallow or take a drink of water.
Swallow the extended-release tablet whole. Do not crush, break, or chew it.
Use only the brand of this medicine that your doctor prescribed. Different brands may not work the same way
This medicine can be used with other seizure medicines. Keep using all of your seizure medicines unless you
This medicine should come with a Medication Guide. Read and follow these instructions carefully. Ask your d
pharmacist for the Medication Guide if you do not have one. Your doctor might ask you to sign some forms to
This medicine comes with patient instructions. Read and follow these instructions carefully. Ask your doctor o

If a Dose is Missed:
If you miss a dose or forget to use your medicine, use it as soon as you can. If it is almost time for your next o
missed dose. Do not use extra medicine to make up for a missed dose.

How to Store and Dispose of This Medicine:
Store the medicine in a closed container at room temperature, away from heat, moisture, and direct light.
Ask your pharmacist, doctor, or health caregiver about the best way to dispose of any leftover medicine after
throw away old medicine after the expiration date has passed.
Keep all medicine away from children and never share your medicine with anyone.

Drugs and Foods to Avoid:
Ask your doctor or pharmacist before using any other medicine, including over-the-counter medicines, vitamins, a
Make sure your doctor knows if you are using any other medicine to control seizures (such as carbamazepine
primidone, valproic acid, valproate, Depakene®, Depakote®, Dilantin®, Mysoline®, or Tegretol®). Make sure
(Rimactane®, Rifadin®). Tell your doctor if you are also using birth control pills, or if you are also using hormo
Ask your doctor before you start or stop using any medicines, including birth control pills and hormone replac
Make sure your doctor knows if you are receiving methotrexate (Rheumatrex®, Trexall®) or pemetrexed (Alim

Warnings While Using This Medicine:
Make sure your doctor knows if you are pregnant or breastfeeding, or if you have kidney problems, liver prob
problems, or depression.
It is important to tell your doctor if you become pregnant while using this medicine. Your doctor may want you

seizure medicine.
This medicine may make you dizzy or drowsy. Avoid driving, using machines, or doing anything else that cou
Do not stop using this medicine suddenly without asking your doctor. You may need to slowly decrease your
If you have a skin rash while using this medicine, call your doctor right away. Sometimes a rash is a sign of a
This medicine may cause serious allergic reactions affecting multiple body organs (e.g., liver or kidney). Che
symptoms: fever, dark urine, headache, hives, muscle pain or stiffness, stomach pain, unusual tiredness, or
For some children, teenagers, and young adults, this medicine can increase thoughts of suicide. Tell your do
start to feel more depressed and have thoughts about hurting yourselves. Report any unusual thoughts or be
are new or get worse quickly. Make sure the doctor knows if you or your child have trouble sleeping, get upse
reckless. Also tell the doctor if you or your child have sudden or strong feelings, such as feeling nervous, ang
you, your child, or anyone in your family has bipolar disorder (manic-depressive) or has tried to commit suicid
This medicine lowers the number of some types of blood cells in your body. Because of this, you may bleed
problems, avoid being near people who are sick or have infections. Wash your hands often. Stay away from
bruised, cut, or injured. Brush and floss your teeth gently. Be careful when using sharp objects, including raz
If your symptoms do not improve or if they get worse, call your doctor.
Your doctor will need to check your progress at regular visits while you are using this medicine. Be sure to ke

Possible Side Effects While Using This Medicine:
Call your doctor right away if you notice any of these side effects:
Allergic reaction: Itching or hives, swelling in your face or hands, swelling or tingling in your mouth or throat,
Blistering, peeling, or red skin rash.
Bloody stools.
Blurred or double vision.
Changes in your menstrual cycle (period).
Chest pain.
Extreme weakness, dizziness, or fainting.
Feeling unusually sleepy, sad, grouchy, moody, or nervous.
Fever, chills, cough, sore throat, and body aches.
Nosebleed.
Pain, soreness, or itching in your vagina.
Painful sores in your mouth or around your eyes.
Painful urination or a change in how much or how often you urinate.
Problems with balance or walking.
Swelling in your face, hands, ankles, or feet.
Swollen, painful, or tender lymph glands in your neck, armpit, or groin.
Thoughts of killing yourself.
Tremors.
Unusual bleeding, bruising, or weakness.
Wheezing or troubled breathing.
Yellowing of your skin or the whites of your eyes.

If you notice these less serious side effects, talk with your doctor:
Dry mouth.
Eye twitching or eye movements you cannot control.
Headache, neck pain, back pain, or joint pain.
Increased sexual desire.
Loss of appetite, or weight loss.
Mild rash.
Nausea, vomiting, diarrhea, stomach upset or pain, or passing gas.
Runny or stuffy nose, or nose irritation.
Unable to concentrate or remember things.
Unable to sleep, or sleeping too much.

If you notice other side effects that you think are caused by this medicine, tell your doctor.

4.3 Place In Therapy

A) Bipolar I Disorder

1) Lamotrigine is indicated as maintenance treatment of Bipolar I Disorder to delay the time to occurrence of moc
acute mood episodes (Prod Info LAMICTAL chewable dispersible oral tablets, oral tablets, orally disintegrating tab

B) Seizure

1) Extended-release lamotrigine is indicated as adjunctive therapy for partial onset seizures with or without secor
(Prod Info LAMICTAL XR oral extended-release tablets, 2009). Chewable dispersible or orally disintegrating lamo
seizures, the generalized seizures of Lennox-Gastaut syndrome, and primary tonic-clonic seizures in adults and
indicated as monotherapy in the treatment of epilepsy in patients 16 years or older who are being converted from
valproic acid as the single antiepileptic agent (Prod Info LAMICTAL chewable dispersible oral tablets, oral tablets,
efficacy in controlling partial and tonic-clonic seizures, primarily generalized seizures (absence and myoclonic), ju
syndrome (Trevathan et al, 2006)

2) Lamotrigine is an anticonvulsant with excellent potential in the management of various types of seizures. Its ar

carbamazepine; however, it is associated with less sedative effects and other neurotoxicity than many existing an
lamotrigine, including its rapid and complete oral absorption, long elimination half-life, relatively low protein bindin
lack of active or toxic metabolites, makes it desirable as an anticonvulsant.
3) The major drawback to the use of lamotrigine is that Stevens-Johnson syndrome occurs in approximately 1/10
4) Initiating lamotrigine at conservative doses and titrating lamotrigine slowly when added to concomitant valproic
(Prod Info LAMICTAL chewable dispersible oral tablets, oral tablets, orally disintegrating tablets, 2009).

4.4 Mechanism of Action / Pharmacology

A) MECHANISM OF ACTION

1) The exact mechanism of action of lamotrigine has not been fully elucidated. It is thought to act by inhibiting rel
inhibition of voltage-sensitive sodium channels (Prod Info LAMICTAL chewable dispersible oral tablets, oral tablet
1987a; Meldrum, 1991; O'Donohoe, 1991; Porter, 1989; Reynolds, 1993; Perucca, 1993). In animals, plasma con
(mcg/mL) are of similar protective efficacy as therapeutic concentrations of phenytoin and carbamazepine in the m
tests. It also reduces or abolishes the afterdischarge induced by focal stimulation of the cortex or hippocampus in
not block or reduce the rate of development of kindling, it does decrease the number of kindled responses and the
Lamotrigine is not effective in threshold tests (Jawad et al, 1989c; Leach et al, 1991; Peck, 1991e).
2) Further evidence that lamotrigine inhibits glutamate release is exhibited in the rat model, in which kainic acid n
inhibited, whereas quinolinic acid and ibotenic acid neurotoxicity, mediated by N-methyl-D-aspartate (NMDA) rece
3) The pharmacological profile of lamotrigine is similar to that of phenytoin. In vitro animal studies have shown it t
release in brain tissue, with no effect on potassium-induced amino acid release. This suggests that the drug acts a
neuronal membranes and inhibit neurotransmitter release, namely glutamate (Leach et al, 1986).
4) Single doses of lamotrigine cause an acute reduction in or abolition of photosensitivity in patients with epilepsy
hallmarks of epileptic activity (Binnie et al, 1986d; Jawad et al, 1986).

4.5 Therapeutic Uses

Absence seizure; Adjunct

Bipolar disorder, depressed phase

Bipolar I disorder

Brain injury

Cancer pain

Convulsions in the newborn, Intractable

Dementia of frontal lobe type

Depersonalization disorder

Depression, Treatment-resistant; Adjunct

Epilepsy, Refractory

Epileptic psychosis

Infantile neuronal ceroid lipofuscinosis

Juvenile myoclonic epilepsy

Lennox-Gastaut syndrome; Adjunct

Migraine

Mood swings

Neuropathic pain

Obesity

Pain

Palatal myoclonus

Parkinson's disease, Idiopathic

Paroxysmal choreoathetosis, Paroxysmal

Partial seizure, Adjunct or monotherapy

Reflex epilepsy

Rett's disorder

Schizophrenia, Refractory

Sexual dysfunction

Shortlasting, unilateral, neuralgiform pain with conjunctival injection and tearing syndrome

Status epilepticus

Tinnitus

Tonic-clonic seizure, Primary generalized; Adjunct

Trigeminal neuralgia

West syndrome

4.5.A Absence seizure; Adjunct

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Pediatric, Evidence favors efficacy
Recommendation: Pediatric, Class IIb
Strength of Evidence: Pediatric, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Preliminary results for add-on therapy in resistant cases and for initial monotherapy are encouraging (Bu

3) Pediatric:

a) In a pediatric case series, patients meeting strict diagnostic criteria for isolated typical absence epilepsy in age: 7 years) whose absence seizures were refractory to standard therapy received add-on lamotrigine and e dosage of 2.9 milligrams/kilogram/day (mg/kg/day) for a median follow-up of 3.1 years. Five of eight children months (median) and remain seizure-free on lamotrigine alone, with only one relapse necessitating resumptic treated with lamotrigine monotherapy after initial diagnosis also attained complete seizure control at a mediar years. One child had to discontinue lamotrigine due to rash. Electroencephalographic abnormalities resolved

4.5.B Bipolar disorder, depressed phase

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Pediatric, Evidence favors efficacy
Recommendation: Pediatric, Class IIb
Strength of Evidence: Pediatric, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

In an 8-week open-label study (n=20) of lamotrigine in adolescents ages 12 to 17 years (mean age 15.8; depressive episode, lamotrigine was effective, whether as adjunctive or monotherapy, in decreasing dep

3) Pediatric:

a) In an 8-week open-label study (n=20) of lamotrigine in adolescents ages 12 to 17 years (mean age 15.8; 7 depressive episode, lamotrigine was effective, whether as adjunctive or monotherapy, in decreasing depress lamotrigine with a mean final dose of 132 +/- 31 milligrams (mg)/day. Seven patients had the diagnosis of bip patients had bipolar disorder not otherwise specified. The primary measure for response was a "1" or "2" on t secondary measure for response was at least a 50% decrease in the Children's Depression Rating Scale-Re were 19 evaluable patients with 16 (84%) considered responders by primary criteria and 12 (63%) considered of 28 or less on the CDRS-R and a CGI Severity scale (CGI-S) score of 1 or 2) was attained by 11 of 19 (58% R scores from baseline to study end (mean change -30.1 +/- 11.9; p less than 0.001). Patients with a baseline than 20 were less likely to be responders by secondary criteria (p=0.04), but YMRS scores did decrease sign on adjunctive medication (n=7) showed no significant differences in CADRES scores compared with those or week 8 (p=0.35). Patients on adjunctive medication did not have a better response than those on monotherap Modified also improved from baseline to week 8 with decreases in total aggression (48.9 +/- 50.2 to 16.7 +/- 2 +/- 2.5; p less than 0.001), and suicide (1.56 +/- 2.1 to 0.26 +/- 0.65; p=0.02). There was no significant weight (kg); p=0.34). Adverse events reported were headache (84%), fatigue (58%), nausea (53%), sweating (47%) reported rash, but on further investigation, it was concluded that they experienced skin irritations, not true ras events, and no patients had any significant laboratory abnormalities during the study (Chang et al, 2006).

4.5.C Bipolar I disorder

FDA Labeled Indication

1) Overview

FDA Approval: Adult, yes; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIa
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Indicated for the maintenance therapy of bipolar 1 disorder to delay the time to occurrence of mood episo standard therapy (Prod Info LAMICTAL chewable dispersible oral tablets, oral tablets, orally disintegratin Effective in refractory bipolar disorder in case reports and open studies (Robillard & Conn, 2002; Calabre Some patients with rapid-cycling bipolar disorder succeeded on lamotrigine maintenance monotherapy (

3) Adult:

a) The results of a small, open label study indicate that adjunctive lamotrigine therapy may be effective in the this uncontrolled study, five hospitalized, geriatric patients (ages 65 to 85 years) with bipolar disorder in the d milligrams (mg) at bedtime, titrated weekly in 12.5 mg/day increments to a total dose of 75 or 100 mg) in addi receiving both lithium and valproate therapy for at least 4 months prior to beginning the study and were nonre selective serotonin reuptake inhibitor or a tricyclic antidepressant. Following six weeks of treatment, at least a Rating Scale scores of 3 patients. All three patients had rapid- cycling bipolar disorder. Nonresponsive patien bipolar disorder. Lamotrigine was well tolerated, however one patient developed coarse hand tremor that imp randomized studies are needed to confirm these findings (Robillard & Conn, 2002).

b) Oral lamotrigine as maintenance monotherapy was effective prophylactic treatment for some patients with placebo-controlled trial (n=180). Prior to the double-blind phase of the study, patients entered an open-label p 8 weeks to a target of 200 milligrams (mg)/day (weeks 1 and 2: 25 mg/day; weeks 3 and 4: 50 mg/day; week up to 300 mg/day); after 4 to 8 weeks of lamotrigine, all other psychotropic medications were tapered off. The to vary; after the preliminary phase, mean daily dose was 287.9 mg/day. Randomization placed patients on p proportion of patients who were able to maintain on placebo or lamotrigine without requiring added pharmacc the difference was not significant (p=0.177). Median survival time without added treatment was 18 weeks and patients, respectively. The percentage of patients able to complete 6 months of the randomized phase withou group (41% versus 26%, p=0.03), and especially among those with bipolar II subtype. Most adverse events w most common side effects (Calabrese et al, 2000).

c) Data from a 48-week open-label trial lend support to lamotrigine's effectiveness as add-on (n=60) or monc other therapies for bipolar I or II disorder. Of 40 evaluable subjects with depressive symptoms, 48% and 20% respectively, with a mean 42% decrease in Hamilton Depression Scale scores. Of 31 evaluable subjects with marked and moderate improvement, respectively, with a mean 74% decrease in Mania Rating Scale scores. Adverse effects included dizziness (29%), tremor (23%), somnolence (21%), headache (19%), nausea (15%) rate was 51%. Controlled trials are in progress (Calabrese et al, 1999).

d) Lamotrigine appeared to have some mood-stabilizing and antidepressant effects in 5 rapid-cycling bipolar lamotrigine at an average dose of 185 milligrams/day. Three scales were used to measure improvement with improvement after therapy as compared to before therapy (p less than 0.006). The other scales did not show less than 0.289) and Young Mania Rating Scale (p less than 0.552). Further randomized studies are needed

e) In an open trial of lamotrigine therapy in 7 patients with treatment-refractory mood disorder, mixed results used with 2 patients showing marked improvement, 2 had a moderate response, 2 had no response and 1 di Sternbach, 1997).

f) In a 41-year-old female with longstanding bipolar disorder, add-on lamotrigine effectively substituted for lit high-dose steroid therapy. Prednisone was necessary to treat lithium-induced interstitial nephritis. Lamotrigin increased to 200 mg every 12 hours within 9 days. Despite escalating prednisone doses to 120 mg/day, her r concurrent medications included perphenazine, temazepam, clonazepam, and nifedipine (Preda et al, 1999).

g) A 48-year-old man with treatment-refractory bipolar disorder had a good response to lamotrigine titrated t psychotic mania and depression and responded to a combination of lamotrigine, paroxetine and levothyroxin

4.5.D Brain injury

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Provided improvement in a series of patients with severe brain injury (Chatham Showalter & Kimmel, 20

3) Adult:

a) Lamotrigine therapy in a case series of 13 patients with severe brain injury brought better than expected s retrospective chart review . Use of lamotrigine was triggered by significant unexpected improvement in 1 case and an allergic reaction to phenytoin. The patient was on day 268 after a subarachnoid hemorrhage (SAH); s oriented and animated, his short-term memory improved, his conversation became coherent, and his ability t discharged to his home. On the Rancho Los Amigos Cognitive Scale, he improved from level III to level VIII. the cohort of 13 patients, all were severely impaired (due to SAH (5), motor vehicle accidents (4), falls from 1 resection (1)); the Rancho level was II to III for all; 3 had a Glasgow Coma Scale score of 3. Mean starting da been on an anticonvulsant prior to lamotrigine. Mean lamotrigine final daily dose was 250 milligrams (range 1 showed more cognitive improvement than expected; 4 improved at an expected modest rate. After mean 72 1 to a son's home, and 1 to a community residential program; after rehabilitation of mean 117 days, 3 were di Kimmel, 2000).

4.5.E Cancer pain

See Drug Consult reference: MANAGEMENT OF CANCER-RELATED PAIN IN ADULT PATIENTS

4.5.F Convulsions in the newborn, Intractable

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Pediatric, Evidence favors efficacy
Recommendation: Pediatric, Class IIa
Strength of Evidence: Pediatric, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

May be effective as adjunct therapy in decreasing the number of infantile spasms (Mikati et al, 2002)

3) Pediatric:

a) In part of an open-label, prospective study, adjunctive lamotrigine therapy decreased the daily number of seizures per day (p=0.028) in patients diagnosed with intractable seizures. Enrolled infants had to have been the 13 patients were diagnosed with infantile spasms, 1 was diagnosed with both infantile spasms and partial partial seizures. In this study, one infant had no response and no infants became seizure free. Doses were ba neonates who were taking enzyme-inducing agents, doses up to 10 milligrams per kilogram per day (mg/kg/d months of age, who were taking enzyme- inducing agents, final doses ranged between 10 to 20 mg/kg/day. I valproate and enzyme inducers, were dosed between 5 to 10 mg/kg/day. In infants between 1 and 12 months final dose. One case of skin rash, which subsided after a day, and one case of elevated liver enzymes, which reported. Eleven of the 13 infants had no observed adverse effects (Mikati et al, 2002).

4.5.G Dementia of frontal lobe type

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Lamotrigine successfully treated severely aggressive behavior resulting from frontal lobe dementia in a s

3) Adult:

a) A 65-year-old female psychiatric inpatient with frontal lobe dementia (presenile condition) and resultant ag psychotropic medications greatly benefited from add-on lamotrigine. With dosing of 12.5 milligrams/day (mg/d showed "dramatic" improvement in all symptoms, with no further aggressive episodes through 6 months of fo

4.5.H Depersonalization disorder

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Ineffective
Recommendation: Adult, Class III
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Lamotrigine did not show any benefit in the treatment of depersonalization disorder (Sierra et al, 2003)

3) Adult:

a) In a pilot, double-blinded, randomized, placebo- controlled, crossover study, lamotrigine did not show any
Fourteen men and women were randomized to one arm of lamotrigine then placebo or another arm of placeb
two-week wash out period before crossing over to the other arm. Lamotrigine was dose escalated over sever
Each month patients were assessed using the Present State Examination and the Cambridge Depersonaliza
study due to nonadherence to the study protocol. One other patient dropped out due to developing neutroper
These individuals were not included in the statistical analyses. Analysis of the administered scale scores reve
endpoint scores in both arms. Mild nausea, dizziness, and muscle aches were reported with lamotrigine use

4.5.I Depression, Treatment-resistant; Adjunct

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Treatment with add-on oral lamotrigine led to similar efficacy results as lithium augmentation in patients v
label, randomized, prospective study (n=34) (Schindler & Anghelescu, 2007)
Results of a retrospective chart review (n=37) showed that adjunctive lamotrigine was efficacious and we
refractory, unipolar depression in adults (Barbee & Jamhour, 2002)

3) Adult:

a) General Information

1) Treatment with oral lamotrigine used as an add-on to antidepressant therapy was safe and demonstra
treatment-refractory, unipolar depression (Schindler & Anghelescu, 2007; Barbee & Jamhour, 2002; Roc
prospective study (n=34), lamotrigine, initiated at 25 milligrams (mg) per day and titrated up to 250 mg/da
augmentation (Schindler & Anghelescu, 2007). Two other retrospective chart reviews found similar impro
mg/day (Barbee & Jamhour, 2002; Rocha & Hara, 2003). Notably, responses in both reviews were base
scores, which were culled retrospectively from chart notes. Patients included in the open-label study as v
anxiety comorbidity and had received a variety of prior antidepressant and/or combination augmentation
studies and there were no instances of skin rash or other dermatological toxicity.

b) Clinical Trials

1) In an open-label, randomized, prospective study (n=34), treatment with add-on oral lamotrigine was v
augmentation in patients with treatment-resistant, unipolar depression. Patients who had experienced a
according to the DSM-IV (Text Revised), with a minimum score of 17 points on the Hamilton Rating Scal
study purposes, treatment-resistant depression was defined as non-response (less than 50% reduction o
classes of antidepressants for at least 6 weeks. Patients were randomized to receive augmentation with
lithium (n=17; mean age, 50.3 years) orally for 8 weeks. Lamotrigine was initiated at 25 milligrams (mg) o
week 3) and 50 mg (at weeks 5 and 6) to a target daily dosage of 150 mg. In cases of non-response or p
Lithium was titrated over several days to a blood level of 0.6 to 0.8 millimoles/liter. Prior antidepressant th
augmentation strategies were discontinued. Based on clinical need, concomitant use of benzodiazepines
(n=27) were treated as inpatients during this study. Weekly assessments were conducted using the HRS
Prior to study initiation, most patients had received treatment with a variety of augmentation or combinati
therapy (n=20), atypical antipsychotics (n=27), and right unilateral electroconvulsive therapy (n=5), and 4
axis I or II disorder. At baseline, the mean duration of current depressive episode (lamotrigine, 6.9 month
prior episodes (lamotrigine, 2.94; lithium, 2.76; p=0.84) was similar between the groups. An intention-to-t
in HRSD scores in both groups. The mean +/- standard deviation (SD) HRSD score decreased from 22.7
group and from 21.5 +/- 3.8 at baseline to 13.3 +/- 5.7 in the lithium group (p=0.11 between groups at we
regards to the time point of onset of symptom resolution. The mean +/- SD CGI scores decreased from 6
(mildly ill) in the lamotrigine group and from 6.24 +/- 0.66 (severely ill) at baseline to 4.12 +/- 1.22 (moder
score of 7 points or less) occurred in 23% (n=4) and 18% (n=3) of lamotrigine- and lithium-treated patien
treated patients versus 41% (n=7) of lithium-treated patients responded (ie, 50% or greater reduction in i
(ie, 25%-49% reduction in HRSD score) occurred in 47% (n=8) and 35% (n=6) of lamotrigine- and lithium
side effects were dry mouth, blurred vision, headache, tremor, weight gain, vertigo, constipation, and dia
tremor (lamotrigine, n=2; lithium, n=5), frequencies for all effects were similar in both groups. Dermatolog
study (Schindler & Anghelescu, 2007).

2) A retrospective chart review (n=37) revealed that add-on treatment with lamotrigine was efficacious a
depression. Charts of patients (mean age 50.22 years; range, 18-75 years) with a diagnosis of major dep
who had received lamotrigine augmentation following failure of at least two adequate trials (minimum of
antidepressants were reviewed. Patients with current psychotic symptoms, or hypomania/mania were ex
at bedtime for 2 weeks and then increased to 50 mg/day for 2 weeks; further dosage increases were ma
improved or the patient was no longer able to tolerate further dosage increases. Patients included in the
continued on treatment with their primary antidepressant or concomitant augmentation medications with
those agents; one patient discontinued all antidepressant therapy prior to initiation of lamotrigine treatme
generalized anxiety disorder (n=16), panic disorder (n=5), social or specific phobia (n=5, n=2), posttraum
disorder (n=3), and anxiety not otherwise specified (n=1). With the exception of two patients, none of the
initiation of lamotrigine, study patients had received a mean of 13.27 (range, 2-29) antidepressant trials a

medications during lamotrigine therapy. The mean duration of lamotrigine treatment was 35.41 weeks (ra
Functioning (GAF) scores were recorded at the time of each visit. Prior to initiation of lamotrigine, the me
+/- 8.27. There was a statistically significant improvement in GAF scores following lamotrigine therapy (d
Rating Scale (CGI) scores were evaluated retrospectively based on extensive, detailed progress notes re
augmentation, intent-to-treat analysis found that 15 (40.5%) patients were rated as much or very much ir
as unchanged. The mean +/- SD lamotrigine dose among responders was 113.33 +/- 93.48 mg, which d
of current depressive episode, number of prior antidepressant trials, stage of treatment resistance, and C
CGI rating scores in the intent-to-treat analysis. The most commonly reported treatment-emergent side e
nausea (n=5), and tremor (n=4). There were no instances of skin rash during this study (Barbee & Jamh

4.5.J Epilepsy, Refractory

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy; Pediatric, Evidence favors efficacy
Recommendation: Adult, Class IIa; Pediatric, Class IIa
Strength of Evidence: Adult, Category B; Pediatric, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Effective as add-on therapy in treatment-resistant focal and generalized epilepsy (Huber et al, 1998)
May be useful in the treatment of intractable childhood epilepsy (Lerman-Sagie & Lerman, 1998)

3) Adult:

a) In an observational study, lamotrigine was useful as add-on therapy in a group of 125 multi-handicapped, epilepsy . Although most effects were only partial, 28.8% of patients had a reduction of 50% or more in seizu epilepsies, 26.7% with generalized epilepsies, and 22.4% with both. A mean lamotrigine dose of 391 milligra combination of valproic acid and lamotrigine was particularly effective(Huber et al, 1998).

b) Lamotrigine was reported to be useful in treating 10 adult patients (23 to 44 years old) with intractable abs started in childhood and persisted into adulthood . Lamotrigine was initially started at 0.2 milligrams/kilogram maximum of 5 mg/kg. All patients were receiving valproic acid. Except for valproic acid, all other antiepileptic optimal lamotrigine dose. Valproic acid doses ranged from 600 to 2000 mg/day and lamotrigine doses were 1 tonic-clonic seizures was achieved in all patients; 7 patients achieved cessation of absence seizures with 3 p Sagie & Lerman, 1998).

4) Pediatric:

a) In an open-label, long-term study (n=41), add-on lamotrigine therapy proved successful in 44% of study su years of age; mean 12 years) with refractory severe partial epilepsy (mean seizure frequency 3.6/day). All en major antiepileptic drugs. Eighteen patients (44%) remained on lamotrigine after 12 to 48 months of follow-up occurred in 15 patients (34%) (p less than 0.00006), with 6 of these subjects remaining seizure-free. Three of marked improvement in behavior, although seizure frequency was unchanged. Higher response rates were o symptomatic of cerebral malformation. Seizure worsening occurred in 9 patients; transient rash developed in starting daily dose was 0.2 to 2.5 milligrams/kilogram (mg/kg) titrated over 2 to 4 weeks to an initial maintena subsequently adjusted based on clinical response up to a maximum of 1.8 to 15 mg/kg/day; mean dose was valproate, median dose was 4.8 mg/kg/day; for those on enzyme-inducing drugs except valproate, median do

b) In an open trial, 16 out of 63 children had a complete response to lamotrigine add-on treatment for their re types with a mean of 1.72 seizure types per child. Seizure types included infantile spasms, simple partial seiz seizures, myoclonic seizures, typical absence seizures, and atypical absence seizures. A complete response achieved a 50% to 90% decrease in seizures (Buoni et al, 1998).

c) In an open, prospective trial, 30 of 56 children with generalized epilepsies were improved with lamotrigine than 18 years old and suffered from Lennox-Gastaut syndrome (15), childhood absence (4), severe myocloni symptomatic generalized (24) and other epilepsies (5). An improvement of greater than 50% was observed ir in 11 of 24 children with other symptomatic generalized epilepsy (p less than 0.09). Rash occurred in 4 patier was discontinued and lamotrigine was restarted without recurrence of rash (Farrell et al, 1997).

d) In an open trial, lamotrigine was useful as add-on therapy in about one-third of patients (2 to 22 years old) lamotrigine 5 to 15 milligrams/kilogram/day (lower doses for patients receiving concomitant valproic acid). Aft seizure frequency of more than 50% and 8 of these patients became seizure-free. Lamotrigine was most effe absences, and atonic seizures (Coppola & Pascotto, 1997).

e) Fourteen children suffering from refractory epilepsy received lamotrigine as add-on therapy. A decrease ir lamotrigine was observed in 6 of the 7 patients who completed the study. The median total seizure frequency study, seizure frequency had decreased by more than 50% in 2 patients, by more than 75% in 2 patients, and seizure frequency was unchanged (Battino et al, 1996)(Battino et al, 1995b).

f) In one series, 8 of 10 children with various seizure disorders had decreased total seizure count when lamo used in increasing doses up to 2 milligrams/kilogram/day (mg/kg/day) in patients taking valproic acid, and in c phenytoin, phenobarbital, or carbamazepine. After 3 months, the dose was increased by 50%. The median to 21 to 916) to 46/month (range 6 to 644) after 6 months. Patients with atypical absence and complex partial se patients, respectively, experiencing greater than 50% reduction in seizure frequency. Myoclonic seizures dec remission; however, 4 patients had an increased frequency of myoclonic seizures. Tonic-clonic seizures decr significant adverse effect noted was drowsiness in 3 patients; however, this did not require dosage reduction

g) In 161 patients remaining on lamotrigine during a 2-year follow-up, 21 of the first 55 patients evaluated ha free. Best response was in generalized epilepsy, particularly absence seizures. Rash was the most commonl valproate (Yuen, 1992).

h) Twelve children with severe or life-threatening epilepsy received lamotrigine (250 to 900 milligrams/day). S
for 12 to 61 months with 4 on monotherapy. No patient was hospitalized for status epilepticus. No adverse ef

4.5.K Epileptic psychosis

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Effective in 2 case reports (DeLeon & Furmaga, 1999)

3) Adult:

a) Two cases were presented describing patients with epilepsy-related psychosis that was resistant to antips
lamotrigine. The first was a 39-year-old woman with seizures and psychosis that included thought broadcasti
clonazepam, phenytoin and gabapentin without improvement in seizure control or decrease in psychotic sym
closed head injury, seizures, delusions of persecution, and aggressive behavior. His treatment consisted of c
improvement in seizure control and relief from psychotic symptoms occurred with the addition of lamotrigine t
twice daily and the man was titrated to 450 mg daily. Also in both cases risperidone was tapered and disconti
the need for antipsychotic therapy (DeLeon & Furmaga, 1999).

4.5.L Infantile neuronal ceroid lipofuscinosis

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Pediatric, Evidence favors efficacy
Recommendation: Pediatric, Class IIb
Strength of Evidence: Pediatric, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

In 1 study, lamotrigine was useful as adjunctive therapy for seizures associated with infantile neuronal ce

3) Pediatric:

a) Lamotrigine was useful in treating seizures associated with infantile neuronal ceroid lipofuscinosis . Lamot
16 children (2.5 to 12 years old) at a dose of 0.5 milligrams/kilogram and increased every 2 weeks as needed
10 patients seizure frequency decreased by more than 50%. In 4 children seizures decreased by 100%. Mon
successful (Aberg et al, 1997).

4.5.M Juvenile myoclonic epilepsy

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Ineffective; Pediatric, Ineffective
Recommendation: Adult, Class III; Pediatric, Class III
Strength of Evidence: Adult, Category C; Pediatric, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Exacerbation of myoclonus reported in juvenile myoclonic epileptic patients treated with lamotrigine (Bira

3) Adult:

a) A group of 7 patients 16 to 32 years of age with juvenile myoclonic epilepsy (JME) experienced immediate
of the cohort had previously used valproic acid. Three patients began lamotrigine as add-on therapy to valpro
therapy. In either instance, JME deteriorated, with worsening of myoclonus in all 7 patients and appearance o
the patients were switched back to valproic acid or to topiramate without further adverse sequelae. Dosing of
given as monotherapy and 150 to 200 mg/day when combined with valproate (Biraben et al, 2000).

4) Pediatric:

a) A group of 7 patients 16 to 32 years of age with juvenile myoclonic epilepsy (JME) experienced immediate
of the cohort had previously used valproic acid. Three patients began lamotrigine as add-on therapy to valpro
therapy. In either instance, JME deteriorated, with worsening of myoclonus in all 7 patients and appearance o
the patients were switched back to valproic acid or to topiramate without further adverse sequelae. Dosing of
given as monotherapy and 150 to 200 mg/day when combined with valproate (Biraben et al, 2000).

4.5.N Lennox-Gastaut syndrome; Adjunct

FDA Labeled Indication

1) Overview

FDA Approval: Adult, yes; Pediatric, yes (2 years and older)
Efficacy: Adult, Effective; Pediatric, Effective
Recommendation: Adult, Class IIa; Pediatric, Class IIa
Strength of Evidence: Adult, Category B; Pediatric, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Indicated as adjunctive therapy for the generalized seizures of Lennox-Gastaut syndrome (Prod Info LAM

orally disintegrating tablets, 2009)

3) Adult:

a) In a double-blind, placebo-controlled study, lamotrigine as add-on therapy was effective for seizures asso
years old) received placebo (n=90) or lamotrigine (n=79) with a maximum dose of 100 to 200 milligrams for p
milligrams for other patients. For all seizure types, the median frequency changed from 16.4 and 13.5 per we
to 9.9 and 14.2 per week after 16 weeks of treatment, respectively (p less than 0.002). Reduction of seizure f
lamotrigine group and in 16% of the placebo group (p less than 0.01). The results were similar for drop attack
absence seizures did not significantly change. Two patients on lamotrigine and valproic acid developed rash

b) Thirteen patients with Lennox-Gastaut syndrome (age 5.5 to 27 years) received lamotrigine 100 to 400 mi
seizure-free after 2 months to 2 years of treatment. Eight of 13 achieved control of at least 1 seizure type. Six
1991).

4) Pediatric:

a) In a double-blind, placebo-controlled study, lamotrigine as add-on therapy was effective for seizures asso
years old) received placebo (n=90) or lamotrigine (n=79) with a maximum dose of 100 to 200 milligrams for p
milligrams for other patients. For all seizure types, the median frequency changed from 16.4 and 13.5 per we
to 9.9 and 14.2 per week after 16 weeks of treatment, respectively (p less than 0.002). Reduction of seizure f
lamotrigine group and in 16% of the placebo group (p less than 0.01). The results were similar for drop attack
absence seizures did not significantly change. Two patients on lamotrigine and valproic acid developed rash

b) As part of a larger open, prospective trial, 11 of 15 children with Lennox-Gastaut syndrome were improved
milligrams/kilogram/day (Farrell et al, 1997).

c) Thirteen patients with Lennox-Gastaut syndrome (age 5.5 to 27 years) received lamotrigine 100 to 400 mi
seizure-free after 2 months to 2 years of treatment. Eight of 13 achieved control of at least 1 seizure type. Six
1991).

4.5.O Migraine

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Appears to be effective only in patients with an aura before their migraine (Lampl et al, 1999)

3) Adult:

a) Lamotrigine appears to act specifically on the aura mechanism in relieving migraine headaches and appe
headache (D'Andrea et al, 1999)(Lampl et al, 1999). In one study, 21 patients receiving lamotrigine 100 millig
their attacks from 6.1/month at baseline to 0.7/month after 3 months (p less than 0.0001). In 13 patients the a
reduced. In 5 patients with migraine without aura, there was no change (D'Andrea et al, 1999). Similarly, in 1
migraine, lamotrigine 25 to 100 mg daily produced a significant decrease in aura episodes after 4 months (p l
months from 23 minutes at baseline to 3 minutes (p less than 0.001) (Lampl et al, 1999). In the treatment of g
than placebo in 77 patients (Steiner et al, 1997).

4.5.P Mood swings

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Lamotrigine was beneficial in post-stroke pathological laughing and crying in 1 case study (Ramasubbu,

3) Adult:

a) In a single case report, lamotrigine improved symptoms of pathological laughing and crying in a 60-year-o
affecting the left frontal and temporal lobes. The patient had developed symptoms 3 to 4 weeks after the strok
and inappropriate to the stimuli or felt emotion. Twelve months after the onset of symptoms, lamotrigine was
increased to 75 mg during weeks 3 and 4, and to 100 mg during weeks 5 and 6. Laughing spells gradually de
no spells after week 4 of therapy. Crying spells gradually decreased from 7 to 8 spells per day, lasting for 3 to
therapy. After 8 weeks of follow-up, clinical improvements were still maintained. The patient did not report any
(Ramasubbu, 2003).

4.5.Q Neuropathic pain

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Ineffective for the treatment of chemotherapy-induced peripheral neuropathy in a randomized, placebo-c
Mixed results observed in neuropathic pain due to diabetes (Eisenberg et al, 2001) and HIV (Simpson et
controlled trials
No appreciable effect seen with lamotrigine for intractable neuropathic pain (McCleane, 1999) or neurop
2002) in randomized, double-blind, placebo-controlled trials, although lamotrigine was promising for a sm
(Finnerup et al, 2002)

3) Adult:

a) Lamotrigine was not effective for relieving neuropathic pain symptoms in 125 patients with chemotherapy-
phase 3 randomized, placebo-controlled study. Patients with symptomatic CIPN with pain scores of either gre
Group (ECOG) neuropathy scale (ENS), or greater than 3 on a 0 to 10 Numerical Rating Scale (NRS) were e
numbers correspond to greater severity of symptoms. Participants were randomized to treatment with lamotri
mg/day over 10 weeks; n=63) or placebo (n=62). The primary efficacy measure, patient-reported "average" d
ENS, was assessed weekly. Secondary efficacy measures, such as the World Health Organization (WHO) cl
decreased tendon reflexes, 2 = severe paresthesias and/or mild weakness, 3 = intolerable paresthesias and/
evaluate changes in CIPN symptoms related to, but distinct from, pain. At the time of enrollment, the proporti
chemotherapy was 38% and 45% (p=0.47) for the lamotrigine and placebo arms, respectively, with the remai
arm was similar with regard to demographic factors and chemotherapy drugs responsible for CIPN at baselin
and 3.6 (p=0.22), and symptoms using ENS were 2 and 1.9 (p=0.31) for lamotrigine and placebo, respectivel
severity decreased in both groups without significant differences between them. According to the NRS, the m
units (p=0.56) and symptom severity (by ENS) decreased by 0.4 and 0.3 units (p=0.36) in treatment and plac
least pain scores by NRS (-0.2 and 0.1), and by WHO pain scales (-0.2 and -0.1) were similar between treatm
differences were noted between the 2 groups with regard to some of the secondary endpoints, these were nc
according to those patients still receiving chemotherapy and those who had completed chemotherapy, neithe
compared with placebo. Adverse events were similar for both groups, although patients receiving lamotrigine
adverse events compared to placebo (33% vs 18% respectively, p=0.06). The most common toxicities (grade
placebo groups, respectively, included ataxia (24% vs 16%), rash (6% vs 5%), constipation (0% vs 2%), arthr
vomiting (0% vs 2%), pruritis (2% vs 0%), fatigue (2% each), and headache (0% vs 4%) (Rao et al, 2008).

b) Lamotrigine effectively improved numerical pain scores in patients with diabetic neuropathy but failed to p
indices in a randomized, double-blind, placebo-controlled clinical trial conducted in Israel. Patients (n=53) wit
neuropathy of at least 6 months duration, and pain scores of at least 4 on a scale of 0 (no pain) to 10 (worst i
analgesics for 3 days prior to starting a diary during the baseline period. Patients were randomized to an 8-w
daily for 2 weeks, then 50 mg daily for 2 weeks, and then 100 mg, 200 mg, 300 mg, and 400 mg daily for one
placebo (n=26; mean age, 57.8 +/- 1.7 years). Doses were administered as once daily for the first 2 weeks ar
primary endpoint was a patient-recorded pain intensity score, using the same 0 to 10 numerical pain scale ac
the morning and evening, and patients were instructed not to take any rescue medication for at least 2 hours
characteristics were similar between groups except patients in the lamotrigine group had a significantly longe
patients in the placebo group (9.6 +/- 1.1 years; p=0.04). Distal symmetric pain in the legs (stocking-like distri
abnormal neurologic examinations that indicated peripheral neuropathy. Patients in the lamotrigine group exp
6.4 +/- 0.1 to 4.2 +/- 0.1, while patients in the placebo group had an overall decline of 6.5 +/- 0.1 to 5.3 +/- 0.1
pain intensity scores were observed at lamotrigine doses of 200, 300, and 400 mg compared to placebo. Dur
pain was seen in 12 patients receiving lamotrigine and 5 patients receiving placebo (p=0.05), while the overa
arm compared to 20% in the placebo arm. Of 7 patients in the lamotrigine group who required rescue analge
their use during the last 4 weeks of treatment compared to no changes in analgesic requirements in the 3 pat
No significant differences were found between groups in the McGill Pain Questionnaire, the Beck Depression
assessment of efficacy and tolerability, which were completed at baseline and at week 8. Rash occurred in 2
7th weeks of treatment, although both cases resolved upon discontinuation of lamotrigine (Eisenberg et al, 20

c) Results from a randomized, double-blind, placebo-controlled study demonstrated lamotrigine was well-tole
in patients receiving neurotoxic antiretroviral therapy (ART). Two groups of patients were randomized to plac
those not receiving ART (n=135). The study included a 7-week dose escalation phase followed by a 4-week m
to induce the metabolism of lamotrigine started the dose escalation phase at 25 milligrams (mg) every other d
known to induce metabolism of lamotrigine started at a dose of 25 mg daily. During the 4-week maintenance
for patients not receiving enzyme-inducing drugs and 600 mg/day for patients receiving enzyme-inducing dru
Scale did not differ between lamotrigine and placebo for either group at the end of the maintenance phase. H
Scale reflected greater improvement with lamotrigine than with placebo in the group receiving ART (p=0.004)
also showed greater improvement on the Visual Analogue Scale for Pain Intensity and the McGill Pain Asses
of global impression of change in pain (p less than or equal to 0.02). The incidence of adverse events was sir
2003).

d) In a randomized, double-blind, placebo-controlled crossover trial, lamotrigine treatment had no effect on th
(n=22) of patients with spinal cord injury (SCI) but did reduce pain in a subset of the sample, which was chara
with or without motor function, preserved below the lesion level and including sacral segments S4-S5). Patien
were given lamotrigine, beginning with 25 milligrams (mg) and increasing to a target dose of 400 mg/day, or p
period, crossed over to the other treatment for 9 weeks. The dose of lamotrigine was limited by individual tole
dose of 300 mg/day, and 5 had a final dose of 200 mg/day. Among the 12 patients with incomplete SCI lesion
an 11-point pain scale) to lamotrigine. Three patients also responded to placebo. The median difference in pa
in the group with incomplete lesions. All patients who had evoked pain (brush allodynia or wind-up-like pain) v
evoked pain was a responder (p less than 0.001), suggesting that the presence of evoked pain may be a pre
et al, 2002).

e) In a randomized, placebo-controlled, double-blind trial of 100 adults with intractable neuropathic pain, lam

mg/day exhibited no appreciable analgesic efficacy. Subjects completed daily diaries with visual analog score into weekly scores. With mean scores from week 8 compared to week 1, there were no statistically significant analgesic consumption, overall pain, burning pain, numbness, "pins and needles," shooting pain, skin sensitivity points out that this study does not rule out lamotrigine's efficacy using a different dosing scheme or in other n

4.5.R Obesity

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

In a single center, double-blind, placebo-controlled, randomized study (n=40) of healthy adult volunteers greater or equal to 30 but less than 40), while there was no statistically significant mean change in body subjects who took placebo, lamotrigine showed a statistically significant difference in mean change in BM (Merideth, 2006).

3) Adult:

a) In a single center, double-blind, placebo-controlled, randomized study (n=40) of healthy adult volunteers v greater or equal to 30 but less than 40), while there was no statistically significant mean change in body weig subjects who took placebo, lamotrigine showed a statistically significant difference in mean change in BMI an were randomized to receive lamotrigine 200 milligrams (mg)/day (n=20) or placebo (n=20) for 26 weeks. Initia weeks until the maintenance dose of 150 to 200 mg/day was reached. All patients were titrated to lamotrigine mg/day and was discontinued early from the study. Of those subjects randomly assigned, 28 completed the 2 placebo). Subjects completed the Impact of Weight on Quality of Life (IWQOL) scale at baseline and endpoin difference in baseline body weight between the 2 groups (lamotrigine mean +/- standard deviation (SD) equa equal 225 +/- 32.7 lb; p=0.0588). The primary study outcome of change in body weight from baseline to endp lamotrigine and placebo, respectively (p=0.0623). There was a statistically significant difference in mean chan and -0.1 +/- 1.05 for lamotrigine and placebo, respectively (p=0.0421). A greater change in quality of life satis lamotrigine group (p=0.0065). Other secondary outcomes showed no significant differences. No serious adve in the placebo group discontinued treatment due to edema. No lamotrigine subjects discontinued treatment d the most frequently reported adverse event with a 15% incidence across the study group (Merideth, 2006).

4.5.S Pain

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Possibly effective for different pain syndromes (Eisenberg et al, 2003; Vestergaard et al, 2001; Cianchett
Lamotrigine provided moderate analgesia for central post-stroke pain (Vestergaard et al, 2001)
Open-label data suggest possible benefit in treating resistant paroxysmal limb pain and painful tonic spa 1999)
Possibly effective in treating sciatica (Eisenberg et al, 2003)

3) Adult:

a) Multiple Sclerosis-Related Pain

1) Open-label add-on lamotrigine 25 milligrams/day (mg/day) titrated slowly to a maximum dose of 400 Multiple sclerosis-related pain syndromes refractory to multiple other medications. Improvement in parox eight of 21 (38%) patients, with five of 21 (24%) experiencing improvement in painful tonic spasms. The year in some cases. These results require confirmation in a placebo-controlled trial (Cianchetti et al, 199

b) Postoperative Pain

1) Lamotrigine may be effective in reducing postoperative pain In a double-blind, placebo-controlled stu either lamotrigine 200 milligrams or placebo 1 hour before receiving spinal anesthesia for transurethral p were lower in the lamotrigine group than in the placebo group at 2 hours (p equal to 0.04), 4 hours (p les (Bonicalzi et al, 1997).

c) Post-stroke Pain

1) In a double-blind, randomized, crossover trial (n=30), patients with central post-stroke pain experienc milligrams/day. Subjects were randomized to 8-week courses of lamotrigine and placebo, separated by a lamotrigine was titrated at 2-week intervals from 25 milligrams (mg)/day to 50 mg/day, 100 mg/day, and pain score over the last week of treatment from 7 to 5 (p=0.01 compared with placebo). Twelve of 27 sub defined as a pain score 2 or more points lower than their score using placebo. No significant analgesia o secondary end points, including global physical pain score over last 4 weeks and pain stimulated by a co lamotrigine (p=0.02 and p=0.01, respectively); the trend favored lamotrigine on other secondary end poir events occurred at similar rates in the 2 periods. Mild rash was associated with lamotrigine use in 2 patie during the lamotrigine period due to mild rash, severe headache, and severe pain (Vestergaard et al, 20

d) Sciatica

1) An open-label, non-comparative study involving 14 patients suggests that lamotrigine may be effectiv radiculopathy for 12 to 36 months. They underwent a 1 week washout period from previous analgesics a was initiated at 25 milligrams (mg) once daily and was doubled weekly up to the maintenance dose of 40 dose for 4 weeks. Of the 14 patients, only 7 completed the full 11 weeks. Diarrhea, dizziness and person discontinuation. In patients who received at least 1 week of lamotrigine and in whom drug plasma concer numerical pain scale scores for spontaneous pain decreased from 7.6 to 4.5 at the end of 11 weeks (p le spontaneous pain also decreased from 7.9 to 4.1 (p less than 0.05). Scores from the Short Form of the M less than 0.05). A linear correlation was found between lamotrigine concentrations and the mean weekly analog measurements (both p=0.001). Due to high dropout rates and the open-label design of the study, (Eisenberg et al, 2003).

4.5.T Palatal myoclonus

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Eliminated ear clicks associated with palatal myoclonus in one case (Nasr & Brown, 2002)

3) Adult:

a) Ear-clicking associated with palatal myoclonus (PM) was stopped by lamotrigine treatment in a 37-year-ol admitted to psychiatric services because of an acute psychotic episode associated with excessive alcohol co After alcohol detoxification and antipsychotic treatment (thioridazine 100 milligrams (mg) 3 times daily), he wa patient reported gradual improvement, with disappearance of ear-clicking and slowing of the frequency of pal clinical examination. After discharge, the man began again to drink alcohol and stopped taking lamotrigine, re Brown, 2002).

4.5.U Parkinson's disease, Idiopathic

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Ineffective
Recommendation: Adult, Class III
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

No beneficial effect (Shinotoh et al, 1997)

3) Adult:

a) Lamotrigine had no beneficial effects on patients with Parkinson's disease treated either during a single d (n=12) (Shinotoh et al, 1997).

4.5.V Paroxysmal choreoathetosis, Paroxysmal

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Pediatric, Evidence favors efficacy
Recommendation: Pediatric, Class IIb
Strength of Evidence: Pediatric, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Effective in 3 children with paroxysmal kinesigenic choreoathetosis (Uberall & Wenzel, 2000)

3) Pediatric:

a) Low-dose lamotrigine was safe and effective in 3 children with idiopathic paroxysmal kinesigenic choreoat year-old girl, and a 10-year-old boy. The first boy was started on lamotrigine 5 milligrams (mg)/day, with titrati mg/kilogram (kg); titration from 5 to 10 to 25 to 50 mg). On that dosage, his attacks were significantly decreas was attack-free. The girl received increasing doses, starting from 5 mg/day ranging up to 100 mg/day (4.7 mg dose, she was attack-free also. The second boy began taking lamotrigine 10 mg/day, with titration biweekly t point his dystonic attacks ceased. In all cases, lamotrigine was well tolerated. Previous medications which ha carbamazepine, phenobarbital, and flunarizine. The patients had used lamotrigine for 16, 19, and 27 months,

4.5.W Partial seizure, Adjunct or monotherapy

FDA Labeled Indication

1) Overview

FDA Approval: Adult, yes; Pediatric, yes (13 years and older, extended-release only; 2 years and older, only)
Efficacy: Adult, Effective; Pediatric, Effective
Recommendation: Adult, Class IIa; Pediatric, Class IIa
Strength of Evidence: Adult, Category A; Pediatric, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Extended-release formulation is indicated as adjunctive therapy for partial onset seizures with or without older (Prod Info LAMICTAL XR oral extended-release tablets, 2009)

Indicated as adjunctive therapy in the treatment of partial seizures in adults and pediatric patients with ep tablets, oral tablets, orally disintegrating tablets, 2009)

Indicated for conversion to monotherapy in patients receiving treatment with a single enzyme-inducing a chewable dispersible oral tablets, oral tablets, orally disintegrating tablets, 2009)

Beneficial in patients with seizures resistant to various combinations of carbamazepine, phenobarbital, p

3) Adult:

a) Extended-release formulation is indicated as adjunctive therapy for partial onset seizures with or without s older (Prod Info LAMICTAL XR oral extended-release tablets, 2009).

b) Of the 527 patients enrolled in a 6-year, open-label, continuation study examining the use of lamotrigine n partial seizures, the clinical status of 58% of patients were judged to have improved from baseline and the lor incidence of adverse effects. Patients were recruited from 5 primary clinical studies of adjunctive lamotrigine. milligrams per day (range 100 to 730 mg per day). Forty-three percent (n=229) of patients completed the stuc 37% of patients, miscellaneous reasons (7%), adverse events (5%) and administrative reasons (5%; eg, prot Overall clinical status was judged on a 7 point scale by the investigators. Mild, moderate, and marked improv the time of discontinuation when compared to pre-lamotrigine clinical status. No change was seen in 30% of and marked deterioration) was seen in 12% of patients. Adverse events were noted in 98% of patients. The n diplopia, ataxia, headache, somnolence, nausea, amblyopia and accidental injury. Serious adverse events w a serious adverse event by 0.4% of patients. No patients developed Stevens-Johnson syndrome (Faught et a

c) As an add-on treatment, lamotrigine (LTG) was effective in the treatment of epileptic drop attacks (EDA) ir patients being treated with antiepileptic drugs but still experiencing at least one EDA per month and at least 4 were observed for 3 months (baseline), given LTG over a 4-month period during which the dose was increase months while taking the maintenance dose. Prior medications were continued throughout the study. In patien milligrams/day (mg/day), which was increased incrementally every 2 weeks to a final dose of 150 mg/day. In was 25 mg/day, which was increased to 300 mg/day. In the last month of the titration period, if necessary, do tolerated dose. Of the 12 patients who completed the study, all had more than a 50% reduction in their total s 75% decrease in seizure frequency. EDA disappeared in 6 patients, improved by 80% in 3 patients and by 50 improvement in EDA frequency. The average maximum LTG dosages were 200 mg/day with valproic acid an al, 2001).

d) Monotherapy with lamotrigine was successful in most patients with partial seizures converted from adjunc double-blind trial, 156 patients who had experienced at least 4 seizures during each of 2 consecutive 4-week monotherapy were randomized to receive adjunct therapy with either valproate 1000 milligrams (mg)/day or l week period with patients then converted to monotherapy with lamotrigine or valproate over the next 4 weeks had: doubling of average monthly seizure count, doubling of highest consecutive 2-day seizure frequency, en prolongation of generalized tonic-clonic seizures. Percentage of patients failing monotherapy in the lamotrigir was 69%. A low dose of valproate was used to demonstrate the efficacy of lamotrigine and provide some pro demonstrate lamotrigine superiority or equivalence.(Gilliam et al, 1998)

e) Double-blind, placebo-controlled add-on trials demonstrated that lamotrigine is efficacious in treating refra produced a 26% or greater reduction in seizure frequency in 48% of patients and 50% or greater reduction in (n=216), observed median reductions in seizures relative to baseline were 8%, 20%, and 36% in patients rec and lamotrigine 500 mg/d, respectively (Matsuo et al, 1993b). In addition, preliminary data indicate that lamot generalized seizures (Binnie et al, 1989); (Sander et al, 1990; Pers Comm, 1993). In one trial, 15 of 19 adult reduction in seizure frequency; some patients were able to withdraw one or more anticonvulsants while maint 1992).

f) In a long-term study, 38% of 16 adult patients with refractory epilepsy had a reduction of seizure frequency year. Further follow-up indicates some decline in efficacy, since the percentage of improved patients droppec al, 1994a).

g) Ten of the 27 patients with refractory complex partial, secondarily generalized tonic clonic, atypical absen 12 months due to lack of efficacy . Patients were studied over a 2-year period with 11 of the remaining patien frequency. Only 3 patients with atypical absence and atonic seizures showed a significant response.

h) In 104 patients remaining in an 11-month, open-label study evaluating add-on lamotrigine for severe refra reduction in seizure frequency (Sander et al, 1990). Nineteen patients withdrew from the study due to advers drowsiness, and rash or due to an increase in seizure frequency (Pisani et al, 1991).

i) In a double-blind, placebo-controlled trial of add-on lamotrigine therapy, 15 of 23 adult patients with refract experienced a 50% or greater reduction in seizure frequency. The blood levels of concomitantly administered adverse effects were noted (Loiseau et al, 1990).

j) Lamotrigine is useful in controlling simple and complex partial seizures and secondarily generalized tonic c crossover trial, 21 patients refractory to multiple anticonvulsants including phenobarbital, phenytoin, primidon 100 milligrams/day (dosage adjusted to produce trough plasma concentrations of 1.5 to 2 micrograms/millilite showed improvement with lamotrigine treatment; the mean reduction in seizure frequency was 59% (confider improvement in simple and complex partial seizures; 8 of 15 showed improvement in secondarily generalizec common adverse reactions included fatigue, diplopia, drowsiness, ataxia, and headache. These were not cor

4) Pediatric:

a) Extended-release formulation is indicated as adjunctive therapy for partial onset seizures with or without s older (Prod Info LAMICTAL XR oral extended-release tablets, 2009).

b) In part of an open-label, prospective study, adjunctive lamotrigine therapy decreased the daily number of

per day (p=0.027) in patients diagnosed with intractable seizures. Enrolled infants had to have been previous
patients were diagnosed with partial seizures, 1 was diagnosed with both infantile spasms and partial seizure
spasms. In this study, one infant had no response and no infants became seizure free. Doses were based up
neonates who were taking enzyme-inducing agents, doses up to 10 milligrams per kilogram per day (mg/kg/d
months of age, who were taking enzyme-inducing agents, final doses ranged between 10 to 20 mg/kg/day. In
and enzyme inducers, were dosed between 5 to 10 mg/kg/day. In infants between 1 and 12 months of age, ta
One case of skin rash, which subsided after a day, and one case of elevated liver enzymes, which subsided
Eleven of the 15 infants had no observed adverse effects (Mikati et al, 2003).

c) In an open-label, long-term study (n=41), add-on lamotrigine therapy proved successful in 44% of study s
years of age; mean 12 years) with refractory severe partial epilepsy (mean seizure frequency 3.6/day). All en
major antiepileptic drugs. Eighteen patients (44%) remained on lamotrigine after 12 to 48 months of follow-up
occurred in 15 patients (34%) (p less than 0.00006), with 6 of these subjects remaining seizure-free. Three of
marked improvement in behavior, although seizure frequency was unchanged. Higher response rates were o
symptomatic of cerebral malformation. Seizure worsening occurred in 9 patients; transient rash developed in
starting daily dose was 0.2 to 2.5 milligrams/kilogram (mg/kg) titrated over 2 to 4 weeks to an initial maintena
subsequently adjusted based on clinical response up to a maximum of 1.8 to 15 mg/kg/day; mean dose was
valproate, median dose was 4.8 mg/kg/day; for those on enzyme-inducing drugs except valproate, median do

d) The efficacy and safety of add-on lamotrigine for treatment of partial seizures in children were demonstrat
entered an 8-week baseline phase to confirm the presence of intractable seizures with their current antiepilep
dose escalation phase and a 12-week maintenance phase. The median reductions in seizure frequency durin
were 36% and 6.7% in lamotrigine and placebo recipients, respectively (p=0.008). Secondarily generalized s
respectively (p=0.003). A decline in seizure frequency of at least 50% occurred in 42% and 16% of the lamot
0.001). Dizziness, tremor, nausea and ataxia were significantly more common with lamotrigine than with plac

4.5.X Reflex epilepsy

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Pilot data from a small case series suggest possible efficacy in startle/noise-induced reflex epilepsy (Fau

3) Adult:

a) Four adults with debilitating, refractory startle-induced seizure disorders gained relief from add-on lamotrig
eliminated "drop attacks" brought on by sudden noise, yet one patient had to discontinue lamotrigine after 10
drop attacks resumed. The other patients maintained excellent seizure control with no adverse effects noted

4.5.Y Rett's disorder

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Pediatric, Evidence favors efficacy
Recommendation: Pediatric, Class IIb
Strength of Evidence: Pediatric, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Lamotrigine controlled seizures and modulated symptoms of Rett syndrome in 2 case reports (Kumanda

3) Pediatric:

a) Two young girls (4.5 and 2.5 years of age) diagnosed with Rett syndrome showed marked improvement o
therapy. In the 4.5-year-old girl, myoclonic seizures were present, along with microcephaly, mental retardatio
unsteadiness, hypertonia, hyperactive deep tendon reflexes, and stereotypical wringing hand movements. La
lamotrigine 3 milligrams/kilogram (mg/kg) daily. At 6 months, she was seizure-free. Hand movements and au
respiratory function was improved. The younger girl exhibited tonic-clonic seizures, hypotonia, hyperactive de
movements. Phenobarbital and valproic acid were given, but did not control the seizures. With lamotrigine 3 m
the girl became seizure-free. Her abnormal hand movements, though continuing, were appreciably decrease
pyruvate in cerebrospinal fluid (CSF) were all normal. The authors suggested that the remedial effects of lam
release (glutamate concentrations in CSF were reported to be elevated in Rett syndrome) (Kumandas et al, 2

4.5.Z Schizophrenia, Refractory

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Adjunctive lamotrigine improved positive symptoms scores but did not improve total symptom scores in a
schizophrenia (Tiihonen et al, 2003)

When added to clozapine treatment, improved psychiatric symptoms in 3 patients (Saba et al, 2002)

3) Adult:

a) In a randomized, double-blinded, placebo-controlled, crossover trial, adjunctive lamotrigine improved the p total symptom scores in patients resistant to clozapine therapy. Patients (n=34) were diagnosed with schizop with no epilepsy or current anticonvulsant or lithium therapy and who had an unsatisfactory response with clo period lasted 14 weeks and started with a 1-week placebo lead-in. Lamotrigine was initiated at 25 milligrams/ followed by 100 mg/d for 2 weeks, 150 mg/d for 2 weeks and then 200 mg/d for 4 weeks. Doses were then ta Negative Syndrome Scale (PANSS) scores changed from 68.55 to 64.31 in the lamotrigine arm and from 69. analysis). PANSS negative symptoms scores changed from 19.97 to 18.69 in the lamotrigine arm and 19.8 tc However, PANSS positive symptom scores improved from 17.24 to 16.24 the lamotrigine arm compared to a intent to treat) and general psychopathological symptoms scores changed from 31.34 to 29.38 in the lamotrig (p=0.03, intent to treat) (Tiihonen et al, 2003).

b) In 3 patients who had responded poorly to 6 months of treatment with clozapine, addition of lamotrigine fo and 28% decrease in BPRS (Brief Psychiatric Rating Scale) scores). Patient 1: clozapine dosage 700 mg/day 50 mg/day), 43 on day 56 (lamotrigine 100 mg/day), 30 on day 84 (lamotrigine 150 mg/day). His degree of im hospitalization. Steady-state concentrations of clozapine, norclozapine, and lamotrigine in plasma were 235 r micrograms/mL (mcg/mL), respectively, on day 83. Patient 2: clozapine 500 mg/day. BPRS score 66 on day (with lamotrigine dose increasing to 75 mg/day. Steady state plasma concentrations for clozapine, norclozapir 0.57 mcg/mL, respectively, at day 56. Patient 3: clozapine dosage 700 mg/day. BPRS score 43 on day 0, 35 (lamotrigine 75 mg/day), and 31 on day 84 (lamotrigine 200 mg/day). Steady-state concentrations of clozapin ng/mL, 420 ng/mL, and 1.28 mcg/mL, respectively, on day 85. No marked side effects, rash, or hematologica 2002).

4.5.AA Sexual dysfunction

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

In three case reports, substitution of lamotrigine for gabapentin resolved impotence in men with epilepsy

3) Adult:

a) Three men who developed impotence while being treated with multiple anticonvulsants for long-standing e on lamotrigine. In each case, lamotrigine was initiated and escalated while gabapentin was tapered and witho frequency in these individuals (Husain et al, 2000).

4.5.AB Shortlasting, unilateral, neuralgiform pain with conjunctival injection and tearing syndrome

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Lamotrigine appeared to be curative in case reports of SUNCT syndrome (short-lasting unilateral neuralg tearing syndrome) (Malik et al, 2002)

3) Adult:

a) Symptoms of SUNCT syndrome resolved following lamotrigine treatment in one female patient. An 80-yea pain with episodes occurring every 15 to 20 minutes failed to respond to treatment with carbamazepine, gaba hydrocodone/acetaminophen. Lamotrigine therapy was initiated at 25 milligrams (mg)/day for 1 week and titra The intensity of her attacks shrunk by half within 1 week of beginning lamotrigine. Her episodes were comple year of follow-up (Malik et al, 2002).

b) A 66-year-old female with SUNCT SYNDROME of 6 months duration with recent worsening (up to 15 atta therapy. SUNCT syndrome was resistant to aspirin and other nonsteroidal agents and carbamazepine. After sudden exacerbation of attacks occurred, which then abated completely following lamotrigine dose escalation 3-month course of therapy, with no further episodes through 15 months of follow-up (D'Andrea et al, 1999).

4.5.AC Status epilepticus

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Pediatric, Evidence favors efficacy
Recommendation: Pediatric, Class IIb
Strength of Evidence: Pediatric, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Successful control of status epilepticus has been reported in one case refractory to intravenous diazepar More data are needed to ascertain the role of lamotrigine in the therapy of status epilepticus (Pisani et al

3) Pediatric:

a) Lamotrigine may be an important adjunct to other drugs in the treatment of status epilepticus. In one case carbamazepine 1200 milligrams/day (mg) and phenobarbital 200 mg/day experienced an unexplained increas generalized convulsive status epilepticus refractory to multiple boluses and continuous infusion of diazepam. followed by 200 mg twice a day, with prompt resolution of status epilepticus and a resulting decrease in seizu discharged on lamotrigine, phenobarbital 100 mg twice a day, and carbamazepine 400 mg 3 times a day (Pis

4.5.AD Tinnitus

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Lamotrigine's effects on chronic tinnitus were equivocal in a placebo-controlled, crossover trial (Simpson

3) Adult:

a) Lamotrigine did not clearly demonstrate efficacy in ameliorating chronic tinnitus in a randomized, double-b patient received lamotrigine in an escalating regimen (25 to 100 milligrams/day) and placebo in two different Patients assessed the loudness, annoyance and awareness of tinnitus on visual analog scales (VAS) at base observed between lamotrigine and placebo in terms of VAS scores or audiometry. According to patient quest (35%) and 6 (19%) patients while on lamotrigine and placebo, respectively. The majority reported "no change correlate with response to lamotrigine (Simpson et al, 1999).

4.5.AE Tonic-clonic seizure, Primary generalized; Adjunct

FDA Labeled Indication

1) Overview

FDA Approval: Adult, yes; Pediatric, yes (2 years and older)
Efficacy: Adult, Effective; Pediatric, Effective
Recommendation: Adult, Class IIa; Pediatric, Class IIa
Strength of Evidence: Adult, Category B; Pediatric, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Indicated as adjunctive therapy for primary generalized tonic-clonic seizures in adults and pediatric patie chewable dispersible oral tablets, oral tablets, orally disintegrating tablets, 2009)

The efficacy of lamotrigine as adjunctive therapy for primary generalized tonic-clonic seizures was demo involving 117 adult and pediatric patients (Prod Info LAMICTAL chewable dispersible oral tablets, oral ta

3) Adult:

a) The efficacy of lamotrigine as adjunctive therapy for primary generalized tonic-clonic seizures was demon involving 117 adult and pediatric (at least 2 years of age) patients. The study included an 8-week baseline ph generalized tonic-clonic seizures during the baseline phase were randomized to oral lamotrigine therapy (n=5 their existing antiepileptic drug (AED) regimen of up to 2 drugs. The adult target dose of lamotrigine ranged fr concomitant antiepileptic therapy. Efficacy was based on the percent change from baseline in primary genera primary generalized tonic-clonic seizures in the intent-to-treat population, which included both adult and pedia lamotrigine and placebo, respectively (p=0.006) (Prod Info LAMICTAL chewable dispersible oral tablets, oral

4) Pediatric:

a) The efficacy of lamotrigine as adjunctive therapy for primary generalized tonic-clonic (PGTC) seizures was trial involving a total of 117 adult and pediatric (aged 2 to 19 years; mean age, 11 years) patients with PGTC drugs (AED). The study included an 8-week baseline phase after which patients who had at least 3 primary g phase were randomized. The pediatric subgroup was randomized to oral lamotrigine therapy (n=21) or placel study consisted of an escalation phase (12 weeks for patients 2 to 12 years and 7 weeks for patients greater with a pediatric target dose of lamotrigine ranging from 3 milligrams/kilogram/day (mg/kg/day) to 12 mg/kg/da The most common concomitant antiepileptic drug was valproate which was used in 67% of the lamotrigine gr reduction in PGTC seizures from baseline (primary efficacy measure) was 77% and 40% in patients receiving median percent decrease in PGTC seizures during the escalation phase was 72% and 30% in the lamotrigine decrease during the maintenance phase was 83% and 42%, respectively (p=0.058). The overall median PGT group and 2.5 in the placebo group (p=0.007) (Trevathan et al, 2006; Prod Info LAMICTAL chewable dispers 2009).

4.5.AF Trigeminal neuralgia

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Effective for essential and symptomatic trigeminal neuralgia (Zakrzewska et al, 1997; Lunardi et al, 1997

3) Adult:

a) Lamotrigine demonstrated antineuralgic properties in 13 patients with trigeminal neuralgia . In a double-bli compared to placebo in patients receiving steady doses of carbamazepine or phenytoin. Each drug was give therapies. Lamotrigine was superior to placebo (p less than 0.011) on a composite efficacy index score which scores, and global evaluations. Interestingly, during the second phase of the trial, those receiving placebo aft improvement observed during lamotrigine therapy. The authors speculated that lamotrigine may have produc drug, or this could have occurred randomly since there were relatively small patient numbers. More studies a (Zakrzewska et al, 1997).

b) In an open, prospective trial, lamotrigine showed impressive results in the treatment of 20 patients with tri to 75 years old) with an "essential" form of trigeminal neuralgia while the second group consisted of 5 patient associated with multiple sclerosis. In the first group, 11 patients had a complete remission with 1 patient attai with 150 to 250 mg/day and 2 patients requiring 400 mg/day. Four patients continued to have pain at the 400 group had full relief of pain with lamotrigine 150 to 200 mg/day. Patients with relief continued to be pain-free a

4.5.AG West syndrome

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Pediatric, Evidence favors efficacy
Recommendation: Pediatric, Class IIb
Strength of Evidence: Pediatric, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Spasms resolved in three infants following treatment with low-dose lamotrigine (Cianchetti et al, 2002).

3) Pediatric:

a) Symptoms of West syndrome in three infants resolved following treatment with low-dose lamotrigine. Spas following the initiation of lamotrigine therapy (1.25 milligrams (mg) one to three times daily) after unsuccessfu ACTH). The infants remained seizure-free at maintenance doses of lamotrigine 1.25 mg/day to 2.5 mg twice

4.6 Comparative Efficacy / Evaluation With Other Therapies

Carbamazepine

Gabapentin

Lithium

Topiramate

4.6.A Carbamazepine

4.6.A.1 Seizure

a) Carbamazepine and lamotrigine are equally effective as monotherapy in patients with newly diagnosed ep randomly assigned to a fixed dosage titration of either carbamazepine or lamotrigine. After four weeks, all pa lamotrigine or 600 mg/day of carbamazepine; for the next 24 weeks, doses were adjusted according to effica patients who were seizure-free for the last 6 months of the study were 39% and 38% for lamotrigine and carb was better tolerated, and more patients were able to complete the study period than patients treated with carb common with carbamazepine than lamotrigine (22% versus 12%, respectively) (Brodie et al, 1995).

b) As initial monotherapy in elderly patients newly diagnosed with epilepsy, lamotrigine demonstrated a supe carbamazepine. Subjects (n=150) were randomized in a double-blinded 2:1 ratio to lamotrigine 25 milligrams medications were titrated slowly upward over 6 weeks to 50 mg twice daily and 200 mg twice daily, respectiv duration. The median doses of lamotrigine and carbamazepine in study completers were 100 mg/day and 40 concentrations at week 24 were 2.3 mg/liter (L) and 6.9 mg/L, respectively. Somnolence (29% versus 12%) a often in the carbamazepine versus lamotrigine groups, respectively. The corresponding withdrawal rates wer 42% and 18% of discontinuations, respectively. The hazard ratio for withdrawal with carbamazepine compare to 4). Efficacy measures were considered secondary endpoints in this trial. While no between-group differenc significantly more lamotrigine recipients remained seizure-free over the last 16 weeks of the study (39% vers

4.6.B Gabapentin

4.6.B.1 Mood disorder

a) Preliminary results from a cross-over study (randomized, double- blinded) suggest that LAMOTRIGINE m the improvement of refractory mood disorders (n=31) (Frye et al, 2000). Study subjects included bipolar I (11 23 were rapid-cycling); all had tried other mood stabilizing agents previously. Percentages of those who had for gabapentin, and 23% for placebo based on the Clinical Global Impression (CGI) scale modified for bipolar

responders were defined as those who were much or very much improved on the CGI scale. Both agents we
developed a rash caused by lamotrigine; the rash progressed to toxic epidermal necrolysis, requiring treatme
trend showed that subjects tended to lose weight on lamotrigine relative to the weight gained on gabapentin.
(mg) daily in week 1, titrated to 50 mg/day in week 2, 50 to 100 mg/day in week 3, 150 to 300 mg for weeks 4
was given at an initial daily dose of 900 mg, titrated to 1500 mg by the end of week 1, 2700 mg by the end of
and 4800 mg by week 5 to 6. Mean daily doses as of week 6 were 274 mg for lamotrigine and 3987 mg for ga

4.6.B.2 Adverse Effects

a) In healthy volunteers, cognitive difficulties were associated with topiramate while gabapentin and lamotrig
Healthy young adults (n=17) were randomized to receive topiramate 5.7 milligrams/kilogram (mg/kg), lamotrig
titrated up over 4 weeks. Neurobehavioral performances were then compared at baseline, 2 weeks, and 4 we
group made significantly more errors during week 2 (p less than 0.02) and during week 4 (p less than 0.004)
symbol digits modalities test, the topiramate group performed poorer than the lamotrigine and gabapentin at
lamotrigine group at week 4 (p less than 0.04). On memory tests at week 2 the topiramate group was worse t
lamotrigine group was below that of the gabapentin group but above the topiramate group. At week 4 the gro
more symptoms of depressed mood at week 4 compared to the lamotrigine and gabapentin groups (p less th
the lamotrigine group at week 4 (p less than 0.02). Further long-term drug effects should be evaluated.

4.6.C Lithium

4.6.C.1 Bipolar disorder

a) In a double-blinded study (GW606), lamotrigine and lithium were both statistically superior to placebo in th
mood episode in recently (within 60 days) MANIC or HYPOMANIC patients with bipolar I disorder. During an
lamotrigine therapy while other psychotropic drugs were discontinued. Patients who tolerated the open-label
lithium (n=46) or placebo (n=70) as the sole agent for maintenance therapy for 18 months. Lamotrigine doses
was titrated to serum levels of 0.8 to 1.1 mEq/L. The median time to intervention due to a mood episode was
in the lithium arm (p=0.46) and 85 days in the placebo arm (p=0.02). The difference in the median time to inte
placebo as well as between lithium and placebo (p=0.003). Of the mood events, 20 lamotrigine patients, 8 lith
This difference was statistically significant between the lithium and placebo arms (p=0.006). Of the mood eve
placebo patients developed depression. This was statistically different between the lamotrigine and placebo a
of depression were not statistically different between lamotrigine and lithium (p=0.09 and 0.36, respectively).
discontinue therapy early due to adverse events compared to placebo and lamotrigine (p=0.01 and 0.003, res
the number of patients enrolled was lower than projected and patients randomized into each study arm had r
could bias results (Bowden et al, 2003).

b) In a double-blinded study (GW605), both lamotrigine and lithium were statistically superior to placebo in th
mood episode in recently (within 60 days) DEPRESSED PATIENTS with bipolar I disorder. During an 8- to 16
therapy while other psychotropic drugs were discontinued. Patients who tolerated lamotrigine were then rand
or placebo (n=121) as the sole agent for maintenance therapy for up to 18 months. Lamotrigine doses range
evaluations were performed in patients who received 200 to 400 mg daily (n=169). Lithium was titrated to ser
intervention due to a mood episode was 200 days in the lamotrigine arm compared to 170 days in the lithium
(p=0.029). The difference in the median time to intervention was significant between lamotrigine and placebo
Interventions for emerging depression occurred nearly 3 times more often than interventions for manic sympt
symptoms of mania after 1 year compared to 86% of lithium patients and 72% of placebo patients. This differ
and placebo arms (p=0.026). Of the lamotrigine patients, 57% did not develop symptoms of depression after
placebo patients. This was statistically different between the lamotrigine and placebo arms (p=0.047). Develo
not statistically different between lamotrigine and lithium (p=0.125 and 0.434, respectively). Results should be
each study arm had responded to lamotrigine in the open-label phase which could bias results (Calabrese et

4.6.D Topiramate

1) Adverse Effects

a) In healthy volunteers, cognitive difficulties were associated with topiramate while gabapentin and lamotrig
Healthy young adults (n=17) were randomized to receive topiramate 5.7 milligrams/kilogram (mg/kg), lamotrig
titrated up over 4 weeks. Neurobehavioral performances were then compared at baseline, 2 weeks, and 4 we
group made significantly more errors during week 2 (p less than 0.02) and during week 4 (p less than 0.004)
symbol digits modalities test, the topiramate group performed poorer than the lamotrigine and gabapentin at
lamotrigine group at week 4 (p less than 0.04). On memory tests at week 2 the topiramate group was worse t
lamotrigine group was below that of the gabapentin group but above the topiramate group. At week 4 the gro
more symptoms of depressed mood at week 4 compared to the lamotrigine and gabapentin groups (p less th
the lamotrigine group at week 4 (p less than 0.02). Further long-term drug effects should be evaluated.

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Last Modified: June 25, 2009

DRUGDEX® Evaluations

ESCITALOPRAM

0.0 Overview

1) Class
- **a)** This drug is a member of the following class(es):
  Antianxiety
  Antidepressant
  Serotonin Reuptake Inhibitor

2) Dosing Information
- **a)** Escitalopram Oxalate
  - **1)** Adult
    - **a)** Generalized anxiety disorder
      1) initial, 10 mg/day ORALLY as a single dose in the morning or ev
      Info LEXAPRO(R) Oral solution, Oral tablets, 2009)
      2) maintenance, 10 mg/day ORALLY, may increase to 20 mg/day (
      after a minimum of one week (Prod Info LEXAPRO(R) Oral solution
      2009)
    - **b)** Major depressive disorder
      1) initial, 10 mg/day ORALLY as a single dose in the morning or ev
      Info LEXAPRO(R) Oral solution, Oral tablets, 2009)
      2) maintenance, 10 mg/day ORALLY, may increase to 20 mg/day (
      after a minimum of one week (Prod Info LEXAPRO(R) Oral solution
      2009)
  - **2)** Pediatric
    a) safety and effectiveness in children for the acute treatment of genera
    disorder have not been established (Prod Info LEXAPRO(R) Oral solutic
    tablets, 2009)
    b) safety and effectiveness in children under the age of 12 years for the
    maintenance treatment of major depressive disorder have not been esta
    Info LEXAPRO(R) Oral solution, Oral tablets, 2009)
    - **1)** Major depressive disorder
      a) age 12 years and older: initial, 10 mg/day ORALLY as a sin
      morning or evening (Prod Info LEXAPRO(R) Oral solution, Oral
      2009)
      b) age 12 years and older: maintenance, 10 mg/day ORALLY,
      to 20 mg/day ORALLY only after a minimum of 3 weeks (Prod I
      LEXAPRO(R) Oral solution, Oral tablets, 2009)

3) Contraindications
- **a)** Escitalopram Oxalate
  1) concomitant use of pimozide or monoamine oxidase inhibitors (MAOIs) (F
  Lexapro(R) oral tablets, solution, 2009)
  2) hypersensitivity to citalopram, escitalopram, or any other component of th
  (Prod Info Lexapro(R) oral tablets, solution, 2009)

4) Serious Adverse Effects
- **a)** Escitalopram Oxalate
  1) Depression, worsening
  2) Diabetes mellitus
  3) Grand mal seizure
  4) Heart failure
  5) Myocardial infarction
  6) Neuroleptic malignant syndrome
  7) Pancreatitis

8) Prolonged QT interval
9) Rectal hemorrhage
10) Serotonin syndrome
11) Suicidal thoughts
12) Suicide
13) Syndrome of inappropriate antidiuretic hormone secretion
14) Torsades de pointes

5) Clinical Applications
a) Escitalopram Oxalate
1) FDA Approved Indications
a) Generalized anxiety disorder
b) Major depressive disorder

1.0 Dosing Information

Drug Properties

Storage and Stability

Adult Dosage

Pediatric Dosage

1.1 Drug Properties

A) Information on specific products and dosage forms can be obtained by referri
Tradename List (Product Index)
B) Synonyms
Escitalopram
Escitalopram Oxalate
C) Physicochemical Properties
1) Molecular Weight
a) 414.40 (Prod Info Lexapro™, 2002a)
2) Solubility
a) Systemic: Escitalopram is freely soluble in methanol and dimethylsulf
(DMSO), sparingly soluble in water and in ethanol, slightly soluble in eth
and insoluble in heptane.(Prod Info Lexapro™, 2002a)

1.2 Storage and Stability

A) Escitalopram Oxalate
1) Preparation
a) Oral route
1) Allow at least 14 days between the discontinuation of an MAOI a
escitalopram or the discontinuation of escitalopram and initiation of
MAO inhibitors (Prod Info LEXAPRO(R) Oral solution, Oral tablets,
2) Administer without regard to meals (Prod Info LEXAPRO(R) Ora
tablets, 2009).
B) Oral route
1) Tablets should be stored at 77 degrees Fahrenheit (25 degrees Celsius);
permitted to 59 to 86 degrees Fahrenheit (15 to 30 degrees Celsius)(Prod In
(TM), 2002g).

1.3 Adult Dosage

Normal Dosage

Dosage in Renal Failure

Dosage in Hepatic Insufficiency

Dosage in Geriatric Patients

Dosage in Other Disease States

1.3.1 Normal Dosage

1.3.1.A Escitalopram Oxalate

1.3.1.A.1 Oral route

Generalized anxiety disorder

Major depressive disorder

1.3.1.A.1.a Generalized anxiety disorder

1) The initial recommended dose in the acute treatment of gen
anxiety disorder in adults is escitalopram 10 milligrams (mg) or
(morning or evening). After one week, the dose may be increas
orally once daily. The efficacy of escitalopram in the treatment
anxiety disorder for longer than 8 weeks has not been establish
on long-term treatment should be reevaluated periodically to de
long term usefulness of escitalopram (Prod Info LEXAPRO(R)
Oral tablets, 2009).

1.3.1.A.1.b Major depressive disorder

1) The initial recommended dose in the acute and maintenanc
major depressive disorder in adults is escitalopram 10 milligram
once daily (morning or evening). After one week the dose may
to 20 mg once daily; however, there were no statistically signific
improvements in efficacy at the higher dose, and higher rates o
effects were reported (Prod Info LEXAPRO(R) Oral solution, O
2009; Wade et al, 2002; Gorman, 2001a).

1.3.1.A.2 Switching To Or From a Monoamine Oxidase Inhibitor

a) Because of a potential interaction, at least 14 days should elaps
discontinuation of a monoamine oxidase inhibitor (MAOI) and the in
escitalopram therapy or between the cessation of escitalopram and
of MAOI therapy (Prod Info LEXAPRO(R) Oral solution, Oral tablets

1.3.2 Dosage in Renal Failure

A) Escitalopram Oxalate

1) In patients with mild to moderate renal impairment, there is no dose a
recommended. Caution should be used in patients with severe renal imp
Info LEXAPRO(R) Oral solution, Oral tablets, 2009).

1.3.3 Dosage in Hepatic Insufficiency

A) Escitalopram Oxalate

1) Escitalopram is extensively metabolized in the liver. The recommend
patients with hepatic impairment is 10 milligrams (mg) orally once daily (
LEXAPRO(R) Oral solution, Oral tablets, 2009).

1.3.4 Dosage in Geriatric Patients

A) Escitalopram Oxalate

1) In pharmacokinetic studies, escitalopram half-life was increased by a
50% in elderly patients as compared with young patients. The recomme
elderly patients is 10 milligrams (mg) of escitalopram once daily (Prod In
(R) Oral solution, Oral tablets, 2009).

1.3.6 Dosage in Other Disease States

A) Escitalopram Oxalate

1) Discontinuation of Treatment

a) Patients should be monitored for withdrawal symptoms when dis
escitalopram treatment and a gradual tapering of the dose, rather th
discontinuation, is recommended whenever possible. If intolerable s
occur after a dose reduction or upon cessation of treatment, the pre
prescribed dose may be reinstated and then the dose may be reduc
gradual rate (Prod Info LEXAPRO(R) Oral solution, Oral tablets, 20

2) Pregnancy

a) Neonates exposed to escitalopram and other selective serotonin

inhibitors (SSRI) or selective noradrenaline reuptake inhibitors (SNR
third trimester have developed complications requiring prolonged ho
tube feeding, and respiratory support. The potential risks and benef
carefully considered when treating pregnant women with escitalopra
third trimester. Tapering escitalopram in the third trimester may be c
(Prod Info LEXAPRO(R) Oral solution, Oral tablets, 2009).

1.4 Pediatric Dosage

Normal Dosage

Dosage in Renal Failure

Dosage in Hepatic Insufficiency

Dosage in Other Disease States

1.4.1 Normal Dosage

1.4.1.A Escitalopram Oxalate

1.4.1.A.1 Oral route

1.4.1.A.1.a Major depressive disorder

1) The initial recommended dose in the acute and maintenanc
major depressive disorder in adolescents age 12 years and old
escitalopram 10 milligrams (mg) orally once daily (morning or e
3 weeks the dose may be increased to 20 mg once daily; howe
were no statistically significant improvements in efficacy at the
and higher rates of adverse effects were reported (Prod Info LE
Oral solution, Oral tablets, 2009).

2) The safety and effectiveness in children for the acute treatment of ge
anxiety disorder have not been established (Prod Info LEXAPRO(R) Ora
Oral tablets, 2009).

3) The safety and effectiveness in children under the age of 12 years fo
and maintenance treatment of major depressive disorder have not been
(Prod Info LEXAPRO(R) Oral solution, Oral tablets, 2009).

1.4.2 Dosage in Renal Failure

A) Escitalopram Oxalate

1) In patients with mild to moderate renal impairment, there is no dose a
recommended. Caution should be used in patients with severe renal imp
Info LEXAPRO(R) Oral solution, Oral tablets, 2009).

1.4.3 Dosage in Hepatic Insufficiency

A) Escitalopram Oxalate

1) Escitalopram is extensively metabolized in the liver. The recommend
patients with hepatic impairment is 10 milligrams (mg) orally once daily (
LEXAPRO(R) Oral solution, Oral tablets, 2009).

1.4.5 Dosage in Other Disease States

A) Escitalopram Oxalate

1) Discontinuation of Treatment

a) Patients should be monitored for withdrawal symptoms when dis
escitalopram treatment and a gradual tapering of the dose, rather th
discontinuation, is recommended whenever possible. If intolerable s
occur after a dose reduction or upon cessation of treatment, the pre
prescribed dose may be reinstated and then the dose may be reduc
gradual rate (Prod Info LEXAPRO(R) Oral solution, Oral tablets, 20

2.0 Pharmacokinetics

Onset and Duration

Drug Concentration Levels

ADME

2.1 Onset and Duration

A) Onset

1) Initial Response

a) DEPRESSION, ORAL: 1 to 2 weeks (Montgomery et al, 2001; Wade Burke, 2001a).

1) Indicates time to a significant antidepressant effect compared to doses of 10 or 20 mg daily.

b) ANXIETY IN DEPRESSION, ORAL: 1 week (Lydiard, 2001b).

2.2 Drug Concentration Levels

A) Therapeutic Drug Concentration

1) Not established.

B) Time to Peak Concentration

1) ORAL, TABLET: 3 to 6 hours (single 20-mg dose) (Prod Info Lexapro(TM Drewes et al, 2001; Gutierrez et al, 2001).

a) In healthy subjects, a mean peak plasma level of 18.8 ng/mL was ob hours after single oral doses of escitalopram 20 mg in healthy subjects. its major metabolite, S(+)-desmethylcitalopram, occurred in 14 hours (m ng/mL) (Drewes et al, 2001). After 40-mg oral doses of racemic citalopra study, nearly identical peak levels and times to peak levels of escitalopra in 3.2 hours) and S(+)-desmethylcitalopram (3.5 ng/mL in 14.2 hours) w other pharmacokinetic parameters were also very similar (eg, AUC, half- excretion). These data collectively suggest that 20 mg escitalopram is bi 40 mg citalopram with respect to escitalopram and S(+)-desmethylcitalo

b) Duration: Following single oral doses of escitalopram 20 mg, plasma fallen from a peak of about 19 ng/mL to approximately 1 ng/mL at 120 h et al, 2001).

C) Area Under the Curve

1) 600 to 635 hr x ng/mL (20-mg single dose) (Drewes et al, 2001); (Gutierre

a) AUC (infinity) values for both escitalopram and S(+)-desmethylcitalop similar after oral doses of escitalopram 20 mg and citalopram 40 mg in c S(+)-desmethylcitalopram specifically, the mean AUC was approximatel ng/mL after 20 mg escitalopram (Drewes et al, 2001).

2.3 ADME

Absorption

Distribution

Metabolism

Excretion

Elimination Half-life

2.3.1 Absorption

A) Bioavailability

1) ORAL, TABLET: 80% for citalopram; no data available for escitalopra Lexapro(TM), 2002h)

a) Escitalopram 20 mg and citalopram 40 mg appear bioequivalent escitalopram and S(+)-desmethylcitalopram (peak plasma levels ac to peak levels, other pharmacokinetic parameters) (Drewes et al, 20

B) Effects of Food

1) None (Prod Info Lexapro(TM), 2002h)

2.3.2 Distribution

A) Distribution Sites

1) Protein Binding
a) 56% (Prod Info Lexapro(TM), 2002h).
B) Distribution Kinetics
1) Volume of Distribution
a) approximately 1330 L (single 20-mg oral dose) (Drewes et al, 20
1) Similar to the value for escitalopram after 40 mg of oral cital (Drewes et al, 2001).

2.3.3 Metabolism

A) Metabolism Sites and Kinetics
1) LIVER, extensive (Prod Info Lexapro(TM), 2002h; Greenblatt et al, 2(Moltke et al, 2001; Greenblatt et al, 2000); (Gutierrez et al, 2001).
a) Escitalopram (S(+)-citalopram) is metabolized to S(+)-desmethyl which is mediated by cytochrome P450 isozymes 2D6, 2C19, and 3 metabolism of S(+)-desmethylcitalopram to S(+)-didesmethylcitalop via cytochrome P450-2D6 (von Moltke et al, 2001; Greenblatt et al, Greenblatt et al, 2000).
b) Studies with human liver microsomes (Greenblatt et al, 2001) ha that escitalopram and S(+)-desmethylcitalopram are only weak or n inhibitors of cytochrome P450 isozymes 1A2, 2C19, 2C9, 2D6, 2E1 (+)-Didesmethylcitalopram was also only a weak inhibitor of 1A2, 2D 3A, although moderate inhibition of the 2C9 and 2C19 isozymes wa with this metabolite; these latter effects do not appear clinically relev the low plasma levels of S(+)-didesmethylcitalopram observed after escitalopram.
c) There is no apparent in vivo interconversion from S-enantiomers enantiomers following oral doses of escitalopram (Drewes et al, 200
B) Metabolites
1) S(+)-Desmethylcitalopram (active in vitro) (von Moltke et al, 2001).
a) Major metabolite; 7 times less potent than escitalopram. Despite evidence of serotonin reuptake inhibition, the contribution of this me clinical activity of escitalopram is considered minimal (Prod Info Lex 2002h).
2) S(+)-Didesmethylcitalopram (active in vitro) (Greenblatt et al, 2001).
a) Twenty-seven times less potent than escitalopram. Despite evid serotonin reuptake inhibition, the contribution of this metabolite to th activity of escitalopram is doubtful as it is present in very low concer plasma (Prod Info Lexapro(TM), 2002h).

2.3.4 Excretion

A) Kidney
1) Renal Clearance (rate)
a) 2.7 L/hr (single 20-mg oral dose) (Drewes et al, 2001).
1) Similar to the value for escitalopram after oral citalopram 40
2) For S(+)-desmethylcitalopram, a value of 6.9 L/hr was repor mg oral escitalopram (Drewes et al, 2001); this was similar to th (+)-desmethylcitalopram after oral citalopram 40 mg.
2) Renal Excretion (%)
a) 8% unchanged (single 20-mg oral dose) (Drewes et al, 2001).
1) Identical to the escitalopram value observed after oral doses 40 mg.
2) Approximately 10% of an oral dose of escitalopram 20 mg is S(+)-desmethylcitalopram (Drewes et al, 2001). This is similar t S(+)-desmethylcitalopram excretion after oral citalopram 40 mg
B) Total Body Clearance
1) 600 mL/min (Prod Info Lexapro(TM), 2002h).
a) Similar to the value for escitalopram clearance after oral doses c 40 mg (Drewes et al, 2001).

2.3.5 Elimination Half-life

A) Parent Compound
1) ELIMINATION HALF-LIFE
a) 22 to 32 hours (single 20-mg oral dose) (Prod Info Lexapro(TM), (Gutierrez et al, 2001)(Drewes et al, 2001).
1) Escitalopram half-life is increased by approximately 50% in patients as compared with young patients. (Prod Info Lexapro(T
2) Similar to the value for escitalopram after oral citalopram 40

et al, 2001).

B) Metabolites

1) S(+)-Desmethylcitalopram, 59 hours (Drewes et al, 2001).

a) Represents value after 20 mg oral escitalopram.

b) This value is similar to that observed for the metabolite following citalopram 40 mg (Drewes et al, 2001).

3.0 Cautions

Contraindications

Precautions

Adverse Reactions

Teratogenicity/Effects in Pregnancy/Breastfeeding

Drug Interactions

3.0.A Black Box WARNING

1) Escitalopram Oxalate

a) Oral (Tablet; Solution)

Suicidality and Antidepressant Drugs

Antidepressants increased the risk compared to placebo of suicidal think behavior (suicidality) in children, adolescents, and young adults in short- of major depressive disorder (MDD) and other psychiatric disorders. Any considering the use of escitalopram oxalate or any other antidepressant adolescent, or young adult must balance this risk with the clinical need. studies did not show an increase in the risk of suicidality with antidepres compared to placebo in adults beyond age 24; there was a reduction in antidepressants compared to placebo in adults aged 65 and older. Depr certain other psychiatric disorders are themselves associated with increa of suicide. Patients of all ages who are started on antidepressant therap monitored appropriately and observed closely for clinical worsening, suic unusual changes in behavior. Families and caregivers should be advise for close observation and communication with the prescriber. Escitalopra not approved for use in pediatric patients (Prod Info Lexapro(R) oral tabl 2009).

3.1 Contraindications

A) Escitalopram Oxalate

1) concomitant use of pimozide or monoamine oxidase inhibitors (MAOIs) (P Lexapro(R) oral tablets, solution, 2009)

2) hypersensitivity to citalopram, escitalopram, or any other component of th (Prod Info Lexapro(R) oral tablets, solution, 2009)

3.2 Precautions

A) Escitalopram Oxalate

1) suicidal ideation and behavior or worsening depression; increased risk, pa children, adolescents, and young adults, during the first few months of therap changes in dosage (Prod Info Lexapro(R) oral tablets, solution, 2009)

2) abnormal bleeding has been reported, including life-threatening hemorrha Info Lexapro(R) oral tablets, solution, 2009)

3) abrupt withdrawal; serious discontinuation symptoms have been reported Lexapro(R) oral tablets, solution, 2009)

4) bipolar disorder; increased risk of precipitation of a mixed/manic episode Lexapro(R) oral tablets, solution, 2009)

5) concomitant use of NSAIDs, aspirin, or other drugs that affect coagulation bleeding, particularly the gastrointestinal tract, may occur (Prod Info Lexapro tablets, solution, 2009)

6) concomitant serotonergic drug use (serotonin precursors (tryptophan), SS serotonin-norepinephrine reuptake inhibitors); monitoring recommended duri escitalopram initiation and discontinuation (Prod Info Lexapro(R) oral tablets, 2009)

7) diseases or conditions that produce altered metabolism or hemodynamic

(Prod Info Lexapro(R) oral tablets, solution, 2009)
8) hepatic impairment; reduced drug clearance; lower or less frequent dose required (Prod Info Lexapro(R) oral tablets, solution, 2009)
9) mania history; risk of activation of mania/hypomania (Prod Info Lexapro(F solution, 2009)
10) seizure disorder, history (Prod Info Lexapro(R) oral tablets, solution, 200
11) serotonin syndrome has been reported, including cases that are life-thre that resemble neuroleptic malignant syndrome; monitoring recommended (Pr Lexapro(R) oral tablets, solution, 2009)
12) use of escitalopram within 14 days of MAOI discontinuation (Prod Info L tablets, solution, 2009)
13) use of MAOIs within 14 days after escitalopram discontinuation (Prod Int oral tablets, solution, 2009)
14) volume-depleted, elderly, or concurrent diuretic therapy; hyponatremia, s inappropriate antidiuretic hormone secretion (SIADH) has occurred; discontir symptoms develop (Prod Info Lexapro(R) oral tablets, solution, 2009)

3.3 Adverse Reactions

Cardiovascular Effects

Dermatologic Effects

Endocrine/Metabolic Effects

Gastrointestinal Effects

Hematologic Effects

Hepatic Effects

Immunologic Effects

Musculoskeletal Effects

Neurologic Effects

Ophthalmic Effects

Psychiatric Effects

Renal Effects

Respiratory Effects

Other

3.3.1 Cardiovascular Effects

3.3.1.A Escitalopram Oxalate

Bradyarrhythmia

Heart failure

Hypertension

INR raised

Myocardial infarction

Palpitations

Prolonged QT interval

Sudden cardiac death

Torsades de pointes

3.3.1.A.1 Bradyarrhythmia

a) Incidence: 1% or less (Prod Info LEXAPRO(R), 2008)

b) No significant effects on blood pressure, heart rate, or the ECG v observed with therapeutic doses in studies monitoring these parame Info LEXAPRO(R), 2008; Burke, 2001; Burke, 2000).

c) A 60-year-old post-stroke female experienced severe bradycardi consciousness and respiratory failure within 45 minutes of escitalop Upon admission to the stroke unit 3 days prior, neurological examin a left brachiofacial hemiparesis and ECG was normal. Acute ischem the right temporo-insular cortex was confirmed by MRI, while dopple ultrasonography and cerebral angiography revealed 90% stenosis o internal carotid artery and complete occlusion of the right internal ca Because she had a history of depression (untreated at the time) tha after her stroke, she was treated with escitalopram. The episode of (20-30 beats/min) was successfully treated and the patient survived retrospectively remembered experiencing dizziness and fainting foll of citalopram 20 mg several years prior. The exact cause of the life- bradycardia is unclear, but stroke involving the insular cortex has be to induce ECG abnormalities, increasing the risk for cardiac abnorm death (Beyenburg & Schonegger, 2007).

3.3.1.A.2 Heart failure

a) Cardiac failure has been reported in postmarketing spontaneous trials (Prod Info LEXAPRO(R), 2008).

3.3.1.A.3 Hypertension

a) Incidence: 1% (Prod Info LEXAPRO(R), 2008)

b) Hypertension has been reported in at least 1% of patients follow escitalopram treatment (Prod Info LEXAPRO(R), 2008).

c) No significant effects on blood pressure, heart rate, or the ECG v with therapeutic doses in studies monitoring these parameters (Proc LEXAPRO(R), 2008; Burke, 2001; Burke, 2000).

3.3.1.A.4 INR raised

a) Increased INR has been reported in postmarketing spontaneous trials (Prod Info LEXAPRO(R), 2008).

3.3.1.A.5 Myocardial infarction

a) Myocardial infarction has been reported in postmarketing sponta clinical trials (Prod Info LEXAPRO(R), 2008).

3.3.1.A.6 Palpitations

a) Incidence: 1% (Prod Info LEXAPRO(R), 2008)

b) Palpitations have been reported in at least 1% of patients followi escitalopram treatment (Prod Info LEXAPRO(R), 2008).

c) No significant effects on blood pressure, heart rate, or the ECG v with therapeutic doses in studies monitoring these parameters (Proc LEXAPRO(R), 2008; Burke, 2001; Burke, 2000).

3.3.1.A.7 Prolonged QT interval

a) Electrocardiogram QT prolongation has been reported in postma spontaneous and clinical trials (Prod Info LEXAPRO(R), 2008).

3.3.1.A.8 Sudden cardiac death

a) In a large cohort study including 481,744 persons and 1487 case cardiac death occurring in a community setting, the use of selective reuptake inhibitors was not associated with an increased risk of sud death (rate ratio, 0.95; 95% CI, 0.42 to 2.15). In contrast, users of tr antidepressants in doses of 100 mg or higher (amitriptyline or its eq a 41% increased rate of sudden cardiac death (rate ratio, 1.41; 95% 1.95) (Ray et al, 2004).

3.3.1.A.9 Torsades de pointes

a) Torsades de pointes has been reported in postmarketing sponta clinical trials (Prod Info LEXAPRO(R), 2008).

3.3.2 Dermatologic Effects

3.3.2.A Escitalopram Oxalate

Diaphoresis

Erythroderma

Rash

3.3.2.A.1 Diaphoresis

a) Incidence: 4% to 5% (Prod Info Lexapro(R) oral tablets, solution,
b) Increased sweating was observed in 4% to 5% of patients during treatment compared with 1% to 2% in matched placebo groups (Pro Lexapro(R) oral tablets, solution, 2009; Montgomery et al, 2001a).

3.3.2.A.2 Erythroderma

a) A 49-year-old female reported a case of photo-induced erythrode escitalopram therapy. The patient was initiated on escitalopram 10 r reactive depression. She was exposed to UV rays for 15 minutes in tanning bed about 4 hours following her first dose. Thirty-six hours l developed a skin rash which covered her face and body. Escitalopra discontinued 5 days later. Examination revealed diffuse erythema, c sparing only medallion, and string. Skin biopsy results revealed sing necrosis of keratinocytes with mild infiltrate of lymphocytes in the su dermis. Immunological evaluation was unremarkable. Photo-induce erythroderma was diagnosed and a regimen of betamethasone dipr 0.05% was initiated. The rash resolved within 3 weeks but with cont pigmentation (Ram-Wolf et al, 2008).

3.3.2.A.3 Rash

a) Incidence: at least 1% (Prod Info Lexapro(R) oral tablets, solutio
b) Rash has been reported in at least 1% of patients treated with es (Prod Info Lexapro(R) oral tablets, solution, 2009; Montgomery et al

3.3.3 Endocrine/Metabolic Effects

3.3.3.A Escitalopram Oxalate

Diabetes mellitus

Hyponatremia

Syndrome of inappropriate antidiuretic hormone secretion

Weight increased

3.3.3.A.1 Diabetes mellitus

a) Diabetes mellitus has been reported in postmarketing spontaneo

clinical trials (Prod Info LEXAPRO(R), 2008).

3.3.3.A.2 Hyponatremia

a) Individual case reports have described development of hyponatr initiation of escitalopram therapy (Grover et al, 2007; Nirmalani et al Nahshoni et al, 2004). The incidence of hyponatremia associated w SSRI therapy ranges between 0.5% to 25%. Risk factors for the dev hyponatremia include older age, female gender, low body weight, hi SSRI, and concomitant use of diuretics, antipsychotics, narcotics, a hypoglycemic agents. Routine monitoring of electrolyte levels espec elderly during the first 2 to 4 weeks of therapy may be warranted (G 2007).

b) A case report described development of hyponatremia following therapy in a 67-year-old female. The patient, who had a history of h diabetes mellitus, and late-onset bipolar affective disorder, had pres acute-onset, severe depression without psychotic symptoms of 4 m duration. Escitalopram was initiated at 10 mg/day and after 3 weeks escalated to 15 mg/day. The patient had normal electrolyte levels pr of escitalopram, and concomitant drug therapy included sodium valp hydrochlorothiazide, gliclazide, aspirin, losartan, and metoprolol. Wi of the escalated escitalopram dose, the patient became delirious, ar to have serum sodium levels of 127 mEq/L and increased urine sod concentration 160 mmol/L. Following discontinuation of escitaloprar thiazides, and provision of supportive therapy, the patient level and consciousness gradually improved (Grover et al, 2007).

c) Hyponatremia occurred in a 65-year-old male patient subsequer of escitalopram. The patient, who had a history of generalized anxie and hypertension was initiated on escitalopram 10 mg/day after he p anxiety symptoms. Concurrent medications included amlodipine and Within 10 days of initiating escitalopram, the patient experienced on generalized tonic-clonic seizures and was found to have a serum so 126 mEq/L. Following discontinuation of escitalopram and provision care, the patient gradually improved over the next 2 weeks (Grover

d) A 50-year-old black male experienced the syndrome of inapprop antidiuretic hormone (SIADH) within 4 weeks of initiating escitalopra depression. Upon admission to the hospital, he was on no other me physical exam was normal, and all diagnostic tests for acute illness Serum sodium was within the normal range at 138 mmol/L. Escitalo at bedtime and olanzapine 10 mg at bedtime were begun on hospita the doses increased over the next 3 weeks. The patient was taking escitalopram by day 13. Due to lack of efficacy, olanzapine was disc day 23, and risperidone 2 mg/day was initiated. Over the next week patient's depression improved, but by day 28, he complained of wea dizziness, and appeared diaphoretic. The results of a complete mec were unremarkable except for serum sodium of 121 mmol/L, serum mmol/L, and serum osmolality of 254 mOsm/kg (normal 275-300 m Urine osmolality was 617 mOsm/kg (normal 50-1,200 mOsm/kg) an sodium was 115 mmol/L. Following a diagnosis of SIADH, the patie on fluid restriction. Escitalopram 20 mg/day and risperidone 2 mg/da continued. By day 32 the patient's sodium rose to 130 mmol/L, but b had again decreased to 124 mmol/L. The escitalopram was then dis and the patient improved by day 39. Sodium returned to normal at 1 day 41. Depression was successfully treated with mirtazapine 30 m risperidone 2 mg/day and the patient was discharged on day 46 (Ni 2006).

e) The syndrome of inappropriate antidiuretic hormone (SIADH) an hyponatremia was reported in a 62-year-old female patient 3 weeks initiation of escitalopram 10 mg/day for depression. She was admitt hospital following a syncopal fall resulting in head trauma. Upon adr serum sodium level was 110 mmol/L, serum osmolality was 261 mn sodium was 53 mmol/L, and urine osmolality was 286 mmol/kg. The identified for possible causes of SIADH was the use of escitalopram was discontinued. The patient was treated with intravenous normal her sodium levels slowly normalized. At discharge her serum sodiur mmol/L; one week later it was stabilized at 135 mmol/L and serum a osmolality returned to normal levels. The patient's depression was s treated with mirtazapine 30 mg/day without recurrence of hyponatre

(Nahshoni et al, 2004).

3.3.3.A.3 Syndrome of inappropriate antidiuretic hormone secretic

a) A 50-year-old black male experienced the syndrome of inapprop antidiuretic hormone (SIADH) within 4 weeks of initiating escitalopra depression. Upon admission to the hospital, he was on no other me physical exam was normal, and all diagnostic tests for acute illness Serum sodium was within the normal range at 138 mmol/L. Escitalo at bedtime and olanzapine 10 mg at bedtime were begun on hospita the doses increased over the next 3 weeks. The patient was taking escitalopram by day 13. Due to lack of efficacy, olanzapine was disc day 23, and risperidone 2 mg/day was initiated. Over the next week patient's depression improved, but by day 28, he complained of wea dizziness, and appeared diaphoretic. The results of a complete mec were unremarkable except for serum sodium of 121 mmol/L, serum mmol/L, and serum osmolality of 254 mOsm/kg (normal 275-300 m Urine osmolality was 617 mOsm/kg (normal 50-1,200 mOsm/kg) an sodium was 115 mmol/L. Following a diagnosis of SIADH, the patie on fluid restriction. Escitalopram 20 mg/day and risperidone 2 mg/da continued. By day 32 the patient's sodium rose to 130 mmol/L, but b had again decreased to 124 mmol/L. The escitalopram was then dis and the patient improved by day 39. Sodium returned to normal at 1 day 41. Depression was successfully treated with mirtazapine 30 m risperidone 2 mg/day and the patient was discharged on day 46 (Ni 2006).

b) The syndrome of inappropriate antidiuretic hormone (SIADH) an hyponatremia was reported in a 62-year-old female patient 3 weeks initiation of escitalopram 10 mg/day for depression. She was admitt hospital following a syncopal fall resulting in head trauma. Upon adr serum sodium level was 110 mmol/L, serum osmolality was 261 mn sodium was 53 mmol/L, and urine osmolality was 286 mmol/kg. The identified for possible causes of SIADH was the use of escitalopram was discontinued. The patient was treated with intravenous normal her sodium levels slowly normalized. At discharge her serum sodiur mmol/L; one week later it was stabilized at 135 mmol/L and serum a osmolality returned to normal levels. The patient's depression was s treated with mirtazapine 30 mg/day without recurrence of hyponatre (Nahshoni et al, 2004).

3.3.3.A.4 Weight increased

a) Incidence: 1% (Prod Info LEXAPRO(R), 2008)

b) Increased weight has been reported in at least 1% of patients re escitalopram therapy (Prod Info LEXAPRO(R), 2008).

3.3.4 Gastrointestinal Effects

3.3.4.A Escitalopram Oxalate

Abdominal pain

Constipation

Diarrhea

Gastroenteritis

Gastrointestinal hemorrhage

Heartburn

Indigestion

Nausea

Pancreatitis

Rectal hemorrhage

Vomiting

Xerostomia

3.3.4.A.1 Abdominal pain

a) Incidence: 1% to 2% (Prod Info LEXAPRO(R), 2008)

b) Abdominal pain has been reported in 1% to 2% of patients recei escitalopram therapy (Prod Info LEXAPRO(R), 2008; Wade et al, 2(2000; Montgomery et al, 2001a; Gorman, 2001; Burke, 2001) (Lepo 2001).

3.3.4.A.2 Constipation

a) Incidence: 3% to 6% (Prod Info LEXAPRO(R), 2008)

b) Constipation has been reported in 3% to 6% of patients receivin (10 to 20 mg) therapy, at a greater incidence than placebo (Prod Inf (R), 2008; Wade et al, 2001; Burke, 2000; Montgomery et al, 2001a 2001; Burke, 2001) (Lepola et al, 2001).

3.3.4.A.3 Diarrhea

a) Incidence: 6% to 14% (Prod Info LEXAPRO(R), 2008)

b) Diarrhea has been reported in 6% to 14% of patients receiving e (10 to 20 mg) therapy, at a greater incidence than placebo (Prod Inf (R), 2008; Wade et al, 2001; Burke, 2000; Montgomery et al, 2001a 2001; Burke, 2001) (Lepola et al, 2001).

3.3.4.A.4 Gastroenteritis

a) Incidence: 1% (Prod Info LEXAPRO(R), 2008)

b) Gastroenteritis has been reported in at least 1% patients receivi escitalopram therapy (Prod Info LEXAPRO(R), 2008; Wade et al, 2(2000; Montgomery et al, 2001a; Gorman, 2001; Burke, 2001) (Lepo 2001).

3.3.4.A.5 Gastrointestinal hemorrhage

See Drug Consult reference: CONCOMITANT USE OF SSRIs AND INCREASED RISK OF GASTROINTESTINAL BLEEDING

3.3.4.A.6 Heartburn

a) Incidence: 1% (Prod Info LEXAPRO(R), 2008)

b) Heartburn has been reported in at least 1% patients receiving es therapy (Prod Info LEXAPRO(R), 2008; Wade et al, 2001; Burke, 2(Montgomery et al, 2001a; Gorman, 2001; Burke, 2001) (Lepola et a

3.3.4.A.7 Indigestion

a) Incidence: 2% to 6% (Prod Info LEXAPRO(R), 2008)

b) Indigestion has been reported in 2% to 6% of patients receiving (10 to 20 mg) therapy, at a greater incidence than placebo (Prod Inf (R), 2008; Wade et al, 2001; Burke, 2000; Montgomery et al, 2001a 2001; Burke, 2001) (Lepola et al, 2001).

3.3.4.A.8 Nausea

a) Incidence: 15% to 18% (Prod Info LEXAPRO(R), 2008)

b) Nausea has been reported in 15% to 18% of patients receiving e (10 to 20 mg) therapy, at a greater incidence than placebo (Prod Inf (R), 2008; Wade et al, 2001; Burke, 2000; Montgomery et al, 2001a 2001; Burke, 2001) (Lepola et al, 2001).

3.3.4.A.9 Pancreatitis

a) Pancreatitis has been reported in postmarketing spontaneous ar trials (Prod Info LEXAPRO(R), 2008).

3.3.4.A.10 Rectal hemorrhage

a) Rectal hemorrhage has been reported in postmarketing spontan clinical trials (Prod Info LEXAPRO(R), 2008).

3.3.4.A.11 Vomiting

a) Incidence: 3% (Prod Info LEXAPRO(R), 2008)

b) Vomiting has been reported in 3% of patients receiving escitalop mg) therapy, at a greater incidence than placebo (Prod Info LEXAP Wade et al, 2001; Burke, 2000; Montgomery et al, 2001a; Gorman, 2001) (Lepola et al, 2001).

3.3.4.A.12 Xerostomia

a) Incidence: 6% to 9% (Prod Info LEXAPRO(R), 2008)

b) Dry mouth has been reported in 6% to 9% of patients receiving e (10 to 20 mg) therapy, at a greater incidence than placebo (Prod Inf (R), 2008; Wade et al, 2001; Burke, 2000; Montgomery et al, 2001a 2001; Burke, 2001) (Lepola et al, 2001).

3.3.5 Hematologic Effects

3.3.5.A Escitalopram Oxalate

Anemia

Contusion

Epistaxis

Hematoma

3.3.5.A.1 Anemia

a) Incidence: 1% or less (Prod Info LEXAPRO(R), 2008)

b) Anemia has been reported in less than 1% of patients receiving therapy (Prod Info LEXAPRO(R), 2008).

3.3.5.A.2 Contusion

a) Incidence: 1% or less (Prod Info LEXAPRO(R), 2008)

b) Bruising has been reported in less than 1% of patients receiving therapy (Prod Info LEXAPRO(R), 2008).

3.3.5.A.3 Epistaxis

a) Incidence: 1% or less (Prod Info LEXAPRO(R), 2008)

b) Nosebleed has been reported in 1% or less of patients receiving therapy, and has been associated with SSRI and serotonin norepine reuptake inhibitor (SNRI) therapy in general (Prod Info LEXAPRO(F

3.3.5.A.4 Hematoma

a) Incidence: 1% or less(Prod Info LEXAPRO(R), 2008)

b) Hematoma has been reported in 1% or less of patients receiving therapy (Prod Info LEXAPRO(R), 2008).

3.3.6 Hepatic Effects

3.3.6.A Escitalopram Oxalate

Fulminant hepatitis

Hepatic necrosis

Liver failure

3.3.6.A.1 Fulminant hepatitis

a) Fulminant hepatitis has been reported in postmarketing spontan clinical trials (Prod Info LEXAPRO(R), 2008).

3.3.6.A.2 Hepatic necrosis

a) Hepatic necrosis has been reported in postmarketing spontaneo trials (Prod Info LEXAPRO(R), 2008).

3.3.6.A.3 Liver failure

a) Hepatic failure has been reported in postmarketing spontaneous trials (Prod Info LEXAPRO(R), 2008).

3.3.7 Immunologic Effects

3.3.7.A Escitalopram Oxalate

3.3.7.A.1 Anaphylaxis

a) Oculogyric crisis with mixed anaphylactic features developed in female after ingestion of 20 milligrams (mg) of escitalopram in addit mg daily dose. The patient experienced a dystonic upward deviatior eye along with diaphoresis, dyspnea, palpitations, and swelling of th tongue. She self-administered a 0.3-mg dose of intramuscular epine autoinjector and symptoms temporarily resolved, but recurred after Resolution of all symptoms was achieved with administration of lora hydroxyzine. The patient had previously reported an episode of ana being treated with sertraline 50 mg daily. It is unclear if the dystonic symptoms of anaphylaxis are related (Patel & Simon, 2006).

3.3.8 Musculoskeletal Effects

3.3.8.A Escitalopram Oxalate

Arthralgia

Fracture of bone

Fracture of bone, Nonvertebral

Myalgia

Rhabdomyolysis

3.3.8.A.1 Arthralgia

a) Incidence: 1% (Prod Info LEXAPRO(R), 2008)

b) Arthralgia has been reported in at least 1% of patients following treatment (Prod Info LEXAPRO(R), 2008).

3.3.8.A.2 Fracture of bone

a) In a population-based, randomly selected, prospective cohort stu for potential covariates, an increased risk of fragility fracture was re 5-year follow-up in patients 50 years of age and older who used dai (n=137; mean age of 65.1 years), including citalopram (escitalopran in this study), compared with those who did not use an SSRI (n=487 of 65.7 years). Daily SSRI use was associated with a significant 2.1 increased risk of fragility fracture (95% confidence interval (CI), 1.3 dose of SSRI use was associated with a 1.5-fold increased risk of fr (95% CI, 1.1 to 2.1). Daily SSRI users who were recurrent (ie, treate at baseline and at 5-year follow-up) had a significant 2.1-fold increa fragility fracture (95% CI, 1.1 to 4). Fractures were reported at the fo forearm (40%), ankle and foot (21%), hip (13%), rib (13%), femur (9 (4%). None were reported at the skull, toes, or fingers (Richards et increased risk of fragility fracture has been reported in a prospective of SSRIs, including citalopram (Richards et al, 2007). Escitalopram included in this study

3.3.8.A.3 Fracture of bone, Nonvertebral

a) In a prospective, population-based, cohort study (n=7983) with a up of 8.4 years, there was an increased risk of nonvertebral fracture participants older than 55 years of age (mean age of 77.5 years) wh currently using an SSRI (citalopram, escitalopram, fluoxetine, fluvox paroxetine, or sertraline) compared to those who were not exposed antidepressants. Current SSRI use was associated with an increase nonvertebral fracture (adjusted hazard ratio (HR), 2.35; 95% confide (CI), 1.32 to 4.18) compared with no antidepressant use. Current SS also associated with an increased risk of nonvertebral fracture (adju 2.07; 95% CI, 1.23 to 3.5) compared with past antidepressant use (addition, duration of SSRI use showed a 9% increase in fracture risk month on an SSRI (95% CI, 3% to 16%; p for trend=0.004). Fractur (most frequent), wrist, humerus, and pelvis were reported (Ziere et a

3.3.8.A.4 Myalgia

a) Incidence: 1% (Prod Info LEXAPRO(R), 2008)

b) Myalgia has been reported in at least 1% of patients following es treatment (Prod Info LEXAPRO(R), 2008).

3.3.8.A.5 Rhabdomyolysis

a) Rhabdomyolysis has been reported in postmarketing spontaneo trials (Prod Info LEXAPRO(R), 2008).

3.3.9 Neurologic Effects

3.3.9.A Escitalopram Oxalate

Agitation

Dizziness

Feeling nervous

Grand mal seizure

Headache

Insomnia

Lightheadedness

Neuroleptic malignant syndrome

Restless legs syndrome

Serotonin syndrome

Somnolence

Tremor

3.3.9.A.1 Agitation

a) Incidence: 1% or less (Lydiard, 2001a)

b) Agitation has occurred in less than 1% of patients treated with es placebo (Lydiard, 2001a).

3.3.9.A.2 Dizziness

a) Incidence: 4% to 7%(Prod Info LEXAPRO(R), 2008)

b) Dizziness has been reported in 4% to 7% of patients receiving e

(10 to 20 mg) therapy, at a greater incidence than placebo (Prod Inf (R), 2008; Wade et al, 2001; Montgomery et al, 2001b; Montgomery Burke, 2001; Gorman, 2001).

3.3.9.A.3 Feeling nervous

a) Incidence: 1% or less (Lydiard, 2001a)

b) Nervousness has occurred in less than 1% of patients treated w escitalopram or placebo (Lydiard, 2001a).

3.3.9.A.4 Grand mal seizure

a) Grand mal seizures have been reported in postmarketing sponta clinical trials (Prod Info LEXAPRO(R), 2008).

3.3.9.A.5 Headache

a) Incidence: 24% (Prod Info LEXAPRO(R), 2008)

b) Headache has been reported in 24% of patients receiving escita 20 mg) therapy, at a greater incidence than placebo (Prod Info LEX 2008; Wade et al, 2001; Montgomery et al, 2001b; Montgomery et a Burke, 2001; Gorman, 2001).

3.3.9.A.6 Insomnia

a) Incidence: 7% to 14% (Prod Info LEXAPRO(R), 2008)

b) Insomnia has been reported in 7% to 14% of patients receiving e (10 to 20 mg) therapy, at a greater incidence than placebo (Prod Inf (R), 2008; Wade et al, 2001; Montgomery et al, 2001b; Montgomery Burke, 2001; Gorman, 2001).

3.3.9.A.7 Lightheadedness

a) Incidence: 1% (Prod Info LEXAPRO(R), 2008)

b) Lightheadedness has been reported in at least 1% of patients re escitalopram therapy (Prod Info LEXAPRO(R), 2008).

3.3.9.A.8 Neuroleptic malignant syndrome

a) Neuroleptic malignant syndrome has been reported in postmarke spontaneous and clinical trials (Prod Info LEXAPRO(R), 2008).

3.3.9.A.9 Restless legs syndrome

a) In a prospective, naturalistic study of patients (median age, 46 y 18 to 87 years) treated with antidepressants, 24 of 271 (9%) subjec experienced new-onset restless leg syndrome (RLS) or worsening o RLS as a side effect related to treatment. Antidepressants included paroxetine, citalopram, sertraline, escitalopram, venlafaxine, duloxe reboxetine, and mirtazapine. Mirtazapine led to a marked decline of of subjects compared with reboxetine which had none. The other ar showed RLS symptoms (newly occurred or deteriorated) at the rate 10%. Subjects stated symptoms occurred early in treatment (media range 1 to 23 days) (Rottach et al, 2008).

3.3.9.A.10 Serotonin syndrome

a) Serotonin syndrome has been reported in postmarketing sponta clinical trials (Prod Info LEXAPRO(R), 2008).

3.3.9.A.11 Somnolence

a) Incidence: 4% to 13% (Prod Info LEXAPRO(R), 2008)

b) Somnolence has been reported in 4% to 13% of patients receivi escitalopram (10 to 20 mg) therapy, at a greater incidence than plac Info LEXAPRO(R), 2008; Wade et al, 2001; Montgomery et al, 2001 Montgomery et al, 2001a; Burke, 2001; Gorman, 2001).

3.3.9.A.12 Tremor

a) Incidence: 1% or less (Lydiard, 2001a)

b) Tremors have occurred in less than 1% of patients treated with e or placebo (Lydiard, 2001a).

3.3.10 Ophthalmic Effects

3.3.10.A Escitalopram Oxalate

Angle-closure glaucoma

Oculogyric crisis

3.3.10.A.1 Angle-closure glaucoma

a) A case of acute bilateral angle closure glaucoma with choroidal e occurred in a 41-year-old woman following escitalopram use. The w had a history of depression and seasonal allergies, was placed on e 20 mg/day. Four weeks later, she presented with blurry vision in bot had lasted several hours. Ophthalmic examinations revealed elevat pressures of 47 and 45 millimeters of mercury in both eyes and a be visual acuity of 20/40 in both eyes, with a myopic shift of approxima from her current spectacle prescription. In addition, bilaterally shallo chambers and closed angles for 360 degrees in both eyes were not treatments, which consisted of topical timolol, dorzolamide, brimonic acetazolamide, and glycerin, followed by a laser peripheral iridotom eye, were not successful. The patient's corneas became edematous acuity declining from 20/40 to 20/400 in both eyes, over the next 3 h Additional testing confirmed the presence of choroidal effusions with detachments and diffuse choroidal thickening in each eye. Subsequ treatment was initiated oral prednisone (1 mg/kg), topical prednisolc and cycloplegic drops, and escitalopram was discontinued. Over the the patient's clinical symptoms resolved as evidenced by 20/20 visic eyes, normal intraocular pressures, and deepening of anterior cham postulated that escitalopram induced bilateral uveal effusions which angle closure in the patient (Zelefsky et al, 2006).

3.3.10.A.2 Oculogyric crisis

a) Oculogyric crisis with mixed anaphylactic features developed in a female after ingestion of 20 milligrams (mg) of escitalopram in addit mg daily dose. The patient experienced a dystonic upward deviation eye along with diaphoresis, dyspnea, palpitations, and swelling of th tongue. She self-administered a 0.3-mg dose of intramuscular epine autoinjector and symptoms temporarily resolved, but recurred after Resolution of all symptoms was achieved with administration of lora hydroxyzine. The patient had previously reported an episode of ana being treated with sertraline 50 mg daily. It is unclear if the dystonic symptoms of anaphylaxis are related (Patel & Simon, 2006).

3.3.12 Psychiatric Effects

3.3.12.A Escitalopram Oxalate

Depression, exacerbation

Depression, worsening

Psychotic disorder, acute

Suicidal thoughts

Suicide

3.3.12.A.1 Depression, exacerbation

a) Adult and pediatric patients who experience symptoms of anxiety panic attacks, insomnia, irritability, hostility (aggressiveness), impuls akathisia (psychomotor restlessness), hypomania, or mania may be worsening of their depression. This same concern applies to treating other psychiatric and nonpsychiatric disorders. If these symptoms a therapy should be reevaluated and it may be necessary to discontin medications when symptoms are severe, sudden in onset, or were n patient's initial symptoms (Prod Info LEXAPRO(R) Oral solution, Or

2009; Anon, 2004; Prod Info LEXAPRO(R), 2008).

3.3.12.A.2 Depression, worsening

a) Incidence: rare

b) Clinical worsening of depression has been reported in patients r escitalopram therapy, particularly during the initial few months of tre during dose adjustments. It may persist until significant remission oc patients treated with antidepressants for any indication should be m signs of clinical worsening (Prod Info LEXAPRO(R) Oral solution, O 2009).

3.3.12.A.3 Psychotic disorder, acute

a) Acute psychosis has been reported during postmarketing use of (Prod Info LEXAPRO(R) Oral solution, Oral tablets, 2009).

3.3.12.A.4 Suicidal thoughts

a) Incidence: rare

b) Adult and pediatric patients being treated with antidepressants f depressive disorder who experience symptoms of anxiety, agitation attacks, insomnia, irritability, hostility (aggressiveness), impulsivity, (psychomotor restlessness), hypomania, or mania may be at risk of ideation and behavior (suicidality). This same concern applies to tre with other psychiatric and nonpsychiatric disorders. If these sympto observed, therapy should be reevaluated and it may be necessary t medications when symptoms are severe, sudden in onset, or were n patient's initial symptoms. Patients and their caregivers should be p the Medication Guide that is available for this drug. Closely monitor especially during the initial few months of therapy or at times of dos (Prod Info LEXAPRO(R) Oral solution, Oral tablets, 2009; Anon, 20 2004).

c) A causal role for antidepressants in inducing suicidality has beer in pediatric patients. Anyone considering the use of antidepressants adolescent must balance this risk with the clinical need. In pooled a short-term, placebo-controlled trials of nine antidepressants (citalop fluoxetine, fluvoxamine, paroxetine, sertraline, bupropion, mirtazapi nefazodone, and venlafaxine extended-release) including over 440 patients with major depressive disorder (MDD), obsessive compulsi (OCD), or other psychiatric disorders, a greater risk of suicidal beha ideation during the first few months of therapy was demonstrated in receiving antidepressants as compared with placebo (4% vs 2%). T suicidality was most consistently observed in the trials that included MDD, but there were signs of risk emerging from trials in other psyc indications, such as obsessive compulsive disorder and social anxie (Anon, 2004).

1) In a pooled analyses of placebo-controlled trials in adults wi other psychiatric disorders including 295 short-term trials (medi 2 months) of 11 antidepressant drugs in greater than 77,000 pa of suicidality varied among the drugs studied. However, for alm studied, there was a tendency toward increasing suicidality in y patients. The risk difference (drug versus placebo in the numbe suicidality per 1000 patients treated) was 14 additional cases ir than 18 years of age, 5 additional cases in patients 18 to 24 ye case in patients 25 to 64 years, and 6 fewer cases in patients 6 older. No suicides occurred in the pediatric trials. Suicides did o adult trials; however, the number of suicides was insufficient to causality. The risk of suicidality during longer-term use (ie, beyo months) in pediatric patients is not known. However, evidence placebo-controlled, maintenance trials in adults with depressior substantiate a delay in the recurrence of depression with antide (Prod Info LEXAPRO(R) Oral solution, Oral tablets, 2009; Anor

3.3.12.A.5 Suicide

a) Incidence: rare

b) Suicide has been reported in adult patients receiving escitalopra clinical trials; however, the number of suicides was insufficient to de causality (Prod Info LEXAPRO(R) Oral solution, Oral tablets, 2009).

3.3.13 Renal Effects

3.3.13.A Escitalopram Oxalate

3.3.13.A.1 Urogenital finding

a) EJACULATION DISTURBANCES (primary ejaculatory delay) ha
reported in 9% to 14% of patients during escitalopram treatment in
studies compared with 2% to less than 1% in matched placebo grou
DECREASED LIBIDO (7%) and ANORGASMIA (6%) have also bee
following treatment with escitalopram (Prod Info Lexapro(TM), 2004
Gorman, 2001; Wade et al, 2001; Montgomery et al, 2001a).

3.3.15 Respiratory Effects

3.3.15.A Escitalopram Oxalate

3.3.15.A.1 Respiratory finding

a) BRONCHITIS, SINUS CONGESTION, COUGH, NASAL CONGI
SINUS HEADACHE have occurred in at least 1% of patients treatec
escitalopram (Prod Info Lexapro(TM), 2004).

3.3.16 Other

3.3.16.A Escitalopram Oxalate

Drug withdrawal

Fatigue

Serotonin syndrome

3.3.16.A.1 Drug withdrawal

See Drug Consult reference: WITHDRAWAL SYNDROME OF SEL
SEROTONIN REUPTAKE INHIBITORS

3.3.16.A.2 Fatigue

a) Incidence: 2% to 8% (Prod Info LEXAPRO(R), 2008)

b) Fatigue has been reported in 2% to 8% of patients receiving esc
to 20 mg) therapy, at a greater incidence than placebo (Prod Info LE
2008; Wade et al, 2001; Montgomery et al, 2001b; Montgomery et a
Burke, 2001; Gorman, 2001).

3.3.16.A.3 Serotonin syndrome

a) Serotonin syndrome, including life-threatening cases, or neurole
syndrome (NMS)-like reactions have been reported with the use of
alone. Signs and symptoms of serotonin syndrome include mental s
(eg, agitation, hallucination, coma), autonomic instability (eg, tachyc
blood pressure, hyperthermia), neuromuscular aberrations (eg, hyp
incoordination) and/or gastrointestinal symptoms (eg, nausea, vomi
Severe serotonin syndrome can resemble NMS with symptoms incl
hyperthermia, muscle rigidity, autonomic instability with possible rap
of vital signs, and mental status changes. Serotonin syndrome occu
commonly with the concomitant use of serotonergic drugs, including
drugs that impair metabolism of serotonin, including MAOIs, or with
or other dopamine antagonists (Prod Info Lexapro(R) oral tablets, s

3.4 Teratogenicity/Effects in Pregnancy/Breastfeeding

A) Teratogenicity/Effects in Pregnancy

1) U.S. Food and Drug Administration's Pregnancy Category: Category C (P
LEXAPRO(R) oral tablets, solution, 2007) (All Trimesters)

a) Either studies in animals have revealed adverse effects on the fetus
embryocidal or other) and there are no controlled studies in women or st
women and animals are not available. Drugs should be given only if the
benefit justifies the potential risk to the fetus.

2) Australian Drug Evaluation Committee's (ADEC) Category: C (Australian Department of Health and Ageing Therapeutic Goods Administration, 2006)

a) Drugs which, owing to their pharmacological effects, have caused or suspected of causing harmful effects on the human fetus or neonate witl malformations. These effects may be reversible. Accompanying texts sh consulted for further details.

See Drug Consult reference: PREGNANCY RISK CATEGORIES

3) Crosses Placenta: Yes

4) Clinical Management

a) There are no data on the use of escitalopram, the S(+)-enantiomer o during human pregnancy at this time. However, complications have bee neonates exposed to other SSRIs or serotonin and norepinephrine reupt (SNRIs) in the third trimester. Nonteratogenic effects (pulmonary hyperte newborn (PPHN) and clinical findings consistent with serotonin syndrom increased special or intensive unit care of the infant were demonstrated maternal use of SSRIs during the third trimester of pregnancy (Chamber One study revealed that women who discontinued antidepressant medic pregnancy had a greater likelihood of relapse compared with those who antidepressant therapy throughout the pregnancy (Prod Info LEXAPRO(tablets, solution, 2007). Animal studies of escitalopram and citalopram u gestation have shown adverse effects only with doses much higher than to humans. When deciding whether to treat a pregnant woman with esci during the third trimester, evaluate the potential risk to the fetus and the benefit to the mother. Consider tapering the escitalopram dose during th trimester of pregnancy (Prod Info LEXAPRO(R) oral tablets, solution, 20

5) Literature Reports

a) Neonates exposed to escitalopram and other SSRIs or serotonin-nor reuptake inhibitors (SNRIs) late in the third trimester have developed co some arising immediately upon delivery, including respiratory distress, s vomiting, tremor, and irritability, that were consistent with either direct S selective SNRI toxicity or a possible drug discontinuation syndrome. In s clinical findings were consistent with serotonin syndrome (Prod Info LEX tablets, solution, 2007).

b) In a case control study of women who delivered infants with pulmona hypertension of the newborn (PPHN; n=377) and women who delivered infants (n=836), the risk for developing PPHN was approximately six-fol infants exposed to SSRIs after week 20 of gestation compared with infa exposed to SSRIs during gestation. This study demonstrates a potential of PPHN, associated with considerable neonatal morbidity and mortality exposed to SSRIs later in the pregnancy. Because this is the first study PPHN with SSRI use during pregnancy and there are not enough cases to individual SSRIs, it can not be determined if all SSRIs posed similar le risk. In the general population, PPHN occurs in 1 to 2 per 1000 live birth LEXAPRO(R) oral tablets, solution, 2007; Chambers et al, 2006).

c) In a prospective longitudinal study of 201 women with a history of ma depression and no signs of depression at the beginning of pregnancy, th greater likelihood of relapse of major depression in those who discontinu antidepressant drugs during pregnancy compared with those who contin antidepressant drugs throughout the pregnancy (Prod Info LEXAPRO(R solution, 2007).

d) Fetal structural abnormalities, reduced fetal body weight, growth reta death were reported in the offspring of rats and rabbits treated with eithe escitalopram or racemic citalopram during pregnancy at doses considera than the maximum recommended human dose. Mild maternal toxicity wa reported in rat studies of escitalopram use during pregnancy (Prod Info L oral tablets, solution, 2007).

B) Breastfeeding

1) Thomson Lactation Rating: Infant risk has been demonstrated.

a) Evidence and/or expert consensus has demonstrated harmful infant used during breastfeeding. An alternative to this drug should be prescrib should be advised to discontinue breastfeeding.

2) Clinical Management

a) Escitalopram is the S(+)-enantiomer of citalopram. Citalopram is sec human breast milk and has been associated with some adverse effects infants. Although there is no specific data on escitalopram, effects can b be similar to that seen with citalopram. Bottle feeding is suggested durin escitalopram therapy, and for at least 5 days after therapy discontinuatic

1998). The American Academy of Pediatrics considers antidepressants
that warrant concern in the nursing infant, particularly if used for long pe
2001). A decision should be made whether to discontinue nursing or dis
drug, taking into consideration the potential risks of citalopram exposure
and the benefits of treatment for the mother (Prod Info LEXAPRO(R) ora
solution, 2007). If the use of escitalopram in a nursing mother is necessa
monitoring the infant for unusual sleepiness, changes in appetite, and w
The long-term effects of exposure to SSRIs via breast milk on the cognit
development of the infant have not been determined.

3) Literature Reports

a) In a study describing 8 lactating women treated with an escitalopram
daily dose of 10 mg (range, 10 to 20 mg) that began 55 days before the
the infant plasma concentrations of escitalopram and its active metabolit
demethylescitalopram, were undetectable (n=4), low (n=1), or not measu
The total relative infant dose for escitalopram and its metabolite was a m
(95% confidence interval (CI), 4.2% to 6.2%) of the maternal weight-adju
and the absolute doses were 7.6 mcg/kg/day (95% CI, 5.2 to 10) and 3 m
(95% CI, 2.4 to 3.6) for escitalopram and demethylescitalopram, respect
mean milk/plasma ratio was 2.2 for both escitalopram (95% confidence i
to 2.4) and demethylescitalopram (95% CI, 1.9 to 2.5). The authors sugg
escitalopram is safe for use in nursing mothers; however, individual case
decided based on a risk/benefit analysis (Rampono et al, 2006).

b) Although specific data are not available for escitalopram, racemic cita
appears in breast milk. There have been two case reports of excessive s
weight loss, and decreased feeding in nursing infants whose mothers we
citalopram. One infant reportedly recovered completely upon maternal c
discontinuation; follow-up information was not available for the other infa
LEXAPRO(R) oral tablets, solution, 2007; Anon, 1998).

3.5 Drug Interactions

Drug-Drug Combinations

Drug-Food Combinations

3.5.1 Drug-Drug Combinations

Abciximab

Aceclofenac

Acemetacin

Acenocoumarol

Alclofenac

Almotriptan

Anagrelide

Ancrod

Anisindione

Antithrombin III Human

Ardeparin

Aspirin

Benoxaprofen

Bivalirudin

Bromfenac

Bufexamac

Cannabis

Carprofen

Celecoxib

Certoparin

Cilostazol

Cimetidine

Clonixin

Clopidogrel

Clorgyline

Cyclobenzaprine

Dalteparin

Danaparoid

Defibrotide

Dehydroepiandrosterone

Dermatan Sulfate

Desipramine

Desirudin

Desvenlafaxine

Dexketoprofen

Diclofenac

Dicumarol

Diflunisal

Dipyridamole

Dipyrone

Droxicam

Duloxetine

Eletriptan

Enoxaparin

Epoprostenol

Eptifibatide

Etodolac

Etofenamate

Etoricoxib

Felbinac

Fenbufen

Fenoprofen

Fentiazac

Floctafenine

Flufenamic Acid

Flurbiprofen

Fondaparinux

Frovatriptan

Furazolidone

Ginkgo

Heparin

Hydrocodone

Hydroxytryptophan

Ibuprofen

Iloprost

Indomethacin

Indoprofen

Isocarboxazid

Isoxicam

Ketoconazole

Ketoprofen

Ketorolac

Lamifiban

Lamotrigine

Lazabemide

Lexipafant

Linezolid

Lithium

Lornoxicam

Meclofenamate

Mefenamic Acid

Meloxicam

Methylphenidate

Metoprolol

Milnacipran

Moclobemide

Morniflumate

Nabumetone

Nadroparin

Naproxen

Naratriptan

Niflumic Acid

Nimesulide

Oxaprozin

Oxycodone

Parecoxib

Parnaparin

Pentosan Polysulfate Sodium

Phenelzine

Phenindione

Phenprocoumon

Phenylbutazone

Pirazolac

Piroxicam

Pirprofen

Propyphenazone

Proquazone

Rasagiline

Reviparin

Rizatriptan

Rofecoxib

Selegiline

Sibrafiban

Sibutramine

St John's Wort

Sulfinpyrazone

Sulindac

Sulodexide

Sumatriptan

Suprofen

Tapentadol

Tapentadol

Tenidap

Tenoxicam

Tiaprofenic Acid

Ticlopidine

Tinzaparin

Tirofiban

Tolmetin

Tramadol

Tranylcypromine

Valdecoxib

Warfarin

Xemilofiban

Zolmitriptan

Zomepirac

3.5.1.A Abciximab

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maint
hemostasis. Case-control and cohort studies have shown that the combi
SSRIs and antiplatelet agents has been associated with an increased ris
Bleeding events reported have included epistaxis, ecchymosis, hematon
and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, susp
Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an antiplatelet agent are g
concurrently, monitor patient for signs of increased bleeding (Prod Info P
tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed
capsules, solution, 2008)

7) Probable Mechanism: unknown

3.5.1.B Aceclofenac

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maint
hemostasis. Case-control and cohort studies have shown that the combi
SSRIs and NSAIDs has been associated with an increased risk of bleed
events have included epistaxis, ecchymosis, hematoma, petechiae, and
threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension,
Info Lexapro(TM), 2003a; Dalton et al, 2003a; Prod Info CELEXA (R) ora
solution, 2005).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an NSAID are given concu
monitor patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and th
potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospi
upper gastrointestinal bleeding were searched among 26,005 users
antidepressant medications and compared with the number of hosp

those patients who did not receive prescriptions for antidepressants
of upper GI bleeding episodes was 3.6 times more than expected (9
confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSA
dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1
5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of
demonstrate an increased risk of upper GI bleeding during the use
Combined use of SSRIs and NSAIDs or low-dose aspirin increased
further (Dalton et al, 2003).

b) Coadministration of ketorolac with psychoactive drugs (such as
been associated with hallucinations in some patients (Prod Info TOF
oral tablets, 2007).

3.5.1.C Acemetacin

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for main
hemostasis. Case-control and cohort studies have shown that the combi
SSRIs and NSAIDs has been associated with an increased risk of bleed
events have included epistaxis, ecchymosis, hematoma, petechiae, and
threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension,
Info Lexapro(TM), 2003a; Dalton et al, 2003a; Prod Info CELEXA (R) ora
solution, 2005).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an NSAID are given concu
monitor patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and th
potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospi
upper gastrointestinal bleeding were searched among 26,005 users
antidepressant medications and compared with the number of hosp
those patients who did not receive prescriptions for antidepressants
of upper GI bleeding episodes was 3.6 times more than expected (9
confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSA
dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1
5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of
demonstrate an increased risk of upper GI bleeding during the use
Combined use of SSRIs and NSAIDs or low-dose aspirin increased
further (Dalton et al, 2003).

b) Coadministration of ketorolac with psychoactive drugs (such as
been associated with hallucinations in some patients (Prod Info TOF
oral tablets, 2007).

3.5.1.D Acenocoumarol

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for main
hemostasis. Case-control and cohort studies have shown that the combi
SSRIs and anticoagulants has been associated with an increased risk of
(Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info LEXAPRO(R
solution, 2008). Bleeding events reported have included epistaxis, ecchy
hematoma, petechiae, and life-threatening hemorrhages. Altered anticoa
(including increased bleeding) have been reported with the coadministra
with warfarin (Schalekamp et al, 2008; Prod Info LEXAPRO(R) oral table
2008).

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When escitalopram and an anticoagulant are g
concurrently, monitor patients for signs of increased bleeding. Patients v
warfarin should be monitored closely for altered anticoagulant effects, in
increased bleeding, when escitalopram therapy is initiated or discontinue
LEXAPRO(R) oral tablets, solution, 2008).

7) Probable Mechanism: unknown

8) Literature Reports

a) According to a retrospective cohort study (n=234), there was an
of clinically relevant bleeding (hospital admission due to bleeding) ir

receiving warfarin for atrial fibrillation during concomitant SSRI thera
weeks following SSRI therapy termination. Patients with a mean ag
years receiving warfarin plus SSRI (n=117) were matched with ranc
patients who received warfarin only (n=117). SSRI included fluoxeti
citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nin
experienced 11 bleeding episodes during 213.9 treatment years in t
plus SSRI group, and 10 patients experienced 14 bleedings during
treatment years in the warfarin-only group. The corresponding total
bleedings were 51.4 and 23.9 per 1000 treatment years, respectivel
ratio for first bleedings during treatment with warfarin plus SSRI was
CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI ir
patients experiencing bleeding at the time of concomitant administra
sertraline or citalopram. The addition of an SSRI was not associatec
change in warfarin dose or INR (p=0.48 and p=0.31 respectively). T
the study may be limited by earlier bleeding events, unknown patier
and exclusion of clopidogrel, dipyridamol, corticosteroids and antico
other than warfarin in the model (Wallerstedt et al, 2009).

b) A population-based, case-controlled study of new coumarin user
(acenocoumarol and phenprocoumon) with concomitant selective se
reuptake inhibitors (SSRIs) resulted in an increased risk of hospitali
nongastrointestinal bleeding. Using national pharmacy and hospitali
records, Netherlands researchers identified 1848 cases that were a
abnormal bleeding and compared them with 5818 control subjects a
coumarins. Median duration of treatment in patients was 220 days (
4690 days). Patients on SSRIs showed greater risk for hospitalizatic
nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% cor
interval (CI), 1.1 to 2.5), however, the rate of gastrointestinal bleedir
OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schaleka
2008).

3.5.1.E Alclofenac

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for main
hemostasis. Case-control and cohort studies have shown that the combi
SSRIs and NSAIDs has been associated with an increased risk of bleed
events have included epistaxis, ecchymosis, hematoma, petechiae, and
threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension,
Info Lexapro(TM), 2003a; Dalton et al, 2003a; Prod Info CELEXA (R) ora
solution, 2005).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an NSAID are given concu
monitor patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and th
potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospi
upper gastrointestinal bleeding were searched among 26,005 users
antidepressant medications and compared with the number of hosp
those patients who did not receive prescriptions for antidepressants
of upper GI bleeding episodes was 3.6 times more than expected (9
confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSA
dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1
5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of
demonstrate an increased risk of upper GI bleeding during the use
Combined use of SSRIs and NSAIDs or low-dose aspirin increased
further (Dalton et al, 2003).

b) Coadministration of ketorolac with psychoactive drugs (such as
been associated with hallucinations in some patients (Prod Info TOF
oral tablets, 2007).

3.5.1.F Almotriptan

1) Interaction Effect: an increased risk of serotonin syndrome

2) Summary: Concomitant use of almotriptan and selective serotonin re
inhibitors (SSRI's) has been reported to cause weakness, hyperreflexia,
incoordination (Prod Info Axert(TM), 2001). Concurrent use of a triptan a

may result in serotonin syndrome which may be life-threatening. Sympto
serotonin syndrome may include restlessness, hallucinations, loss of co
heart beat, rapid changes in blood pressure, increased body temperatur
overreactive reflexes, nausea, vomiting, and diarrhea. Clinicians should
triptans may be commonly used intermittently and that either the triptan
may be prescribed by a different physician. Discuss the risks of serotoni
with patients who are prescribed this combination and monitor them clos
symptoms of serotonin syndrome (US Food and Drug Administration, 20
3) Severity: major
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Coadministration of a triptan, such as almotript
SSRI may result in a life-threatening condition called serotonin syndrom
that triptans may be commonly used intermittently and that either the trip
SSRI may be prescribed by a different physician. If these agents are use
discuss the risks of serotonin syndrome with the patient and monitor clos
symptoms of serotonin syndrome (restlessness, hyperthermia, hyperrefl
incoordination).
7) Probable Mechanism: additive pharmacologic effects resulting in exc
serotonergic stimulation
8) Literature Reports
a) Concomitant administration of fluoxetine and almotriptan is well
fluoxetine has only a modest effect on almotriptan maximum plasma
concentration (Cmax). Other almotriptan pharmacokinetics are not s
affected. A randomized, open-label, two-way crossover study involv
volunteers has been conducted. Subjects received each of the follo
treatments with a minimum 3-week washout between periods: (1) th
fluoxetine capsules on day 1 to 8 and one dose almotriptan 12.5 mg
one dose of almotriptan 12.5 mg on day 8 with no treatment on days
Peak almotriptan concentrations were 18% higher following concom
administration of fluoxetine than after almotriptan administration alo
difference was statistically significant (p equal 0.023). Mean almotrip
under the concentration-time curve (AUC) and oral clearance were
statistically different between treatment groups. Mean half-life was n
different between the treatment groups. During fluoxetine coadminis
was shorter, suggesting that the absorption rate of almotriptan may
increased by fluoxetine. The author concludes that based on the res
study and the lack of effect of fluoxetine on almotriptan pharmacoki
almotriptan and fluoxetine can be safely used concomitantly in migr
management (Fleishaker et al, 2001).

3.5.1.G Anagrelide

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for main
hemostasis. Case-control and cohort studies have shown that the combi
SSRIs and antiplatelet agents has been associated with an increased ris
Bleeding events reported have included epistaxis, ecchymosis, hematon
and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, susp
Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an antiplatelet agent are g
concurrently, monitor patient for signs of increased bleeding (Prod Info P
tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed
capsules, solution, 2008)
7) Probable Mechanism: unknown

3.5.1.H Ancrod

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for main
hemostasis. Case-control and cohort studies have shown that the combi
SSRIs and anticoagulants has been associated with an increased risk of
(Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info LEXAPRO(P
solution, 2008). Bleeding events reported have included epistaxis, ecchy
hematoma, petechiae, and life-threatening hemorrhages. Altered anticoa
(including increased bleeding) have been reported with the coadministra

with warfarin (Schalekamp et al, 2008; Prod Info LEXAPRO(R) oral table 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When escitalopram and an anticoagulant are g concurrently, monitor patients for signs of increased bleeding. Patients v warfarin should be monitored closely for altered anticoagulant effects, in increased bleeding, when escitalopram therapy is initiated or discontinue LEXAPRO(R) oral tablets, solution, 2008).
7) Probable Mechanism: unknown
8) Literature Reports
a) According to a retrospective cohort study (n=234), there was an of clinically relevant bleeding (hospital admission due to bleeding) ir receiving warfarin for atrial fibrillation during concomitant SSRI thera weeks following SSRI therapy termination. Patients with a mean ag years receiving warfarin plus SSRI (n=117) were matched with rand patients who received warfarin only (n=117). SSRI included fluoxeti citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nin experienced 11 bleeding episodes during 213.9 treatment years in t plus SSRI group, and 10 patients experienced 14 bleedings during treatment years in the warfarin-only group. The corresponding total bleedings were 51.4 and 23.9 per 1000 treatment years, respectivel ratio for first bleedings during treatment with warfarin plus SSRI was CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI ir patients experiencing bleeding at the time of concomitant administra sertraline or citalopram. The addition of an SSRI was not associated change in warfarin dose or INR (p=0.48 and p=0.31 respectively). T the study may be limited by earlier bleeding events, unknown patier and exclusion of clopidogrel, dipyridamol, corticosteroids and antico other than warfarin in the model (Wallerstedt et al, 2009).
b) A population-based, case-controlled study of new coumarin user (acenocoumarol and phenprocoumon) with concomitant selective se reuptake inhibitors (SSRIs) resulted in an increased risk of hospitali nongastrointestinal bleeding. Using national pharmacy and hospitali records, Netherlands researchers identified 1848 cases that were a abnormal bleeding and compared them with 5818 control subjects a coumarins. Median duration of treatment in patients was 220 days (4690 days). Patients on SSRIs showed greater risk for hospitalizatio nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% cor interval (CI), 1.1 to 2.5), however, the rate of gastrointestinal bleedir OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schaleka 2008).

3.5.1.l Anisindione

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maint hemostasis. Case-control and cohort studies have shown that the combi SSRIs and anticoagulants has been associated with an increased risk of (Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info LEXAPRO(R solution, 2008). Bleeding events reported have included epistaxis, ecchy hematoma, petechiae, and life-threatening hemorrhages. Altered anticoa (including increased bleeding) have been reported with the coadministra with warfarin (Schalekamp et al, 2008; Prod Info LEXAPRO(R) oral table 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When escitalopram and an anticoagulant are g concurrently, monitor patients for signs of increased bleeding. Patients v warfarin should be monitored closely for altered anticoagulant effects, in increased bleeding, when escitalopram therapy is initiated or discontinue LEXAPRO(R) oral tablets, solution, 2008).
7) Probable Mechanism: unknown
8) Literature Reports
a) According to a retrospective cohort study (n=234), there was an of clinically relevant bleeding (hospital admission due to bleeding) ir

receiving warfarin for atrial fibrillation during concomitant SSRI thera
weeks following SSRI therapy termination. Patients with a mean ag
years receiving warfarin plus SSRI (n=117) were matched with ranc
patients who received warfarin only (n=117). SSRI included fluoxeti
citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nin
experienced 11 bleeding episodes during 213.9 treatment years in t
plus SSRI group, and 10 patients experienced 14 bleedings during
treatment years in the warfarin-only group. The corresponding total
bleedings were 51.4 and 23.9 per 1000 treatment years, respectivel
ratio for first bleedings during treatment with warfarin plus SSRI was
CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI ir
patients experiencing bleeding at the time of concomitant administra
sertraline or citalopram. The addition of an SSRI was not associated
change in warfarin dose or INR (p=0.48 and p=0.31 respectively). T
the study may be limited by earlier bleeding events, unknown patier
and exclusion of clopidogrel, dipyridamol, corticosteroids and antico
other than warfarin in the model (Wallerstedt et al, 2009).

b) A population-based, case-controlled study of new coumarin user
(acenocoumarol and phenprocoumon) with concomitant selective se
reuptake inhibitors (SSRIs) resulted in an increased risk of hospitali
nongastrointestinal bleeding. Using national pharmacy and hospitali
records, Netherlands researchers identified 1848 cases that were a
abnormal bleeding and compared them with 5818 control subjects a
coumarins. Median duration of treatment in patients was 220 days (
4690 days). Patients on SSRIs showed greater risk for hospitalizatio
nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% cor
interval (CI), 1.1 to 2.5), however, the rate of gastrointestinal bleedir
OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schaleka
2008).

3.5.1.J Antithrombin III Human

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for main
hemostasis. Case-control and cohort studies have shown that the combi
SSRIs and anticoagulants has been associated with an increased risk o
(Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info LEXAPRO(R
solution, 2008). Bleeding events reported have included epistaxis, ecchy
hematoma, petechiae, and life-threatening hemorrhages. Altered anticoa
(including increased bleeding) have been reported with the coadministra
with warfarin (Schalekamp et al, 2008; Prod Info LEXAPRO(R) oral table
2008).

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When escitalopram and an anticoagulant are g
concurrently, monitor patients for signs of increased bleeding. Patients v
warfarin should be monitored closely for altered anticoagulant effects, in
increased bleeding, when escitalopram therapy is initiated or discontinue
LEXAPRO(R) oral tablets, solution, 2008).

7) Probable Mechanism: unknown

8) Literature Reports

a) According to a retrospective cohort study (n=234), there was an
of clinically relevant bleeding (hospital admission due to bleeding) ir
receiving warfarin for atrial fibrillation during concomitant SSRI thera
weeks following SSRI therapy termination. Patients with a mean ag
years receiving warfarin plus SSRI (n=117) were matched with ranc
patients who received warfarin only (n=117). SSRI included fluoxeti
citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nin
experienced 11 bleeding episodes during 213.9 treatment years in t
plus SSRI group, and 10 patients experienced 14 bleedings during
treatment years in the warfarin-only group. The corresponding total
bleedings were 51.4 and 23.9 per 1000 treatment years, respectivel
ratio for first bleedings during treatment with warfarin plus SSRI was
CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI ir
patients experiencing bleeding at the time of concomitant administra
sertraline or citalopram. The addition of an SSRI was not associated
change in warfarin dose or INR (p=0.48 and p=0.31 respectively). T

the study may be limited by earlier bleeding events, unknown patier
and exclusion of clopidogrel, dipyridamol, corticosteroids and antico
other than warfarin in the model (Wallerstedt et al, 2009).

b) A population-based, case-controlled study of new coumarin user
(acenocoumarol and phenprocoumon) with concomitant selective se
reuptake inhibitors (SSRIs) resulted in an increased risk of hospitali
nongastrointestinal bleeding. Using national pharmacy and hospitali
records, Netherlands researchers identified 1848 cases that were a
abnormal bleeding and compared them with 5818 control subjects a
coumarins. Median duration of treatment in patients was 220 days (
4690 days). Patients on SSRIs showed greater risk for hospitalizatio
nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% cor
interval (CI), 1.1 to 2.5), however, the rate of gastrointestinal bleedir
OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schaleka
2008).

3.5.1.K Ardeparin

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maint
hemostasis. Case-control and cohort studies have shown that the combi
SSRIs and anticoagulants has been associated with an increased risk of
(Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info LEXAPRO(R
solution, 2008). Bleeding events reported have included epistaxis, ecchy
hematoma, petechiae, and life-threatening hemorrhages. Altered anticoa
(including increased bleeding) have been reported with the coadministra
with warfarin (Schalekamp et al, 2008; Prod Info LEXAPRO(R) oral table
2008).

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When escitalopram and an anticoagulant are g
concurrently, monitor patients for signs of increased bleeding. Patients v
warfarin should be monitored closely for altered anticoagulant effects, in
increased bleeding, when escitalopram therapy is initiated or discontinue
LEXAPRO(R) oral tablets, solution, 2008).

7) Probable Mechanism: unknown

8) Literature Reports

a) According to a retrospective cohort study (n=234), there was an
of clinically relevant bleeding (hospital admission due to bleeding) ir
receiving warfarin for atrial fibrillation during concomitant SSRI thera
weeks following SSRI therapy termination. Patients with a mean age
years receiving warfarin plus SSRI (n=117) were matched with rand
patients who received warfarin only (n=117). SSRI included fluoxeti
citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nin
experienced 11 bleeding episodes during 213.9 treatment years in t
plus SSRI group, and 10 patients experienced 14 bleedings during 5
treatment years in the warfarin-only group. The corresponding total
bleedings were 51.4 and 23.9 per 1000 treatment years, respectivel
ratio for first bleedings during treatment with warfarin plus SSRI was
CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI ir
patients experiencing bleeding at the time of concomitant administra
sertraline or citalopram. The addition of an SSRI was not associated
change in warfarin dose or INR (p=0.48 and p=0.31 respectively). T
the study may be limited by earlier bleeding events, unknown patier
and exclusion of clopidogrel, dipyridamol, corticosteroids and antico
other than warfarin in the model (Wallerstedt et al, 2009).

b) A population-based, case-controlled study of new coumarin user
(acenocoumarol and phenprocoumon) with concomitant selective se
reuptake inhibitors (SSRIs) resulted in an increased risk of hospitali
nongastrointestinal bleeding. Using national pharmacy and hospitali
records, Netherlands researchers identified 1848 cases that were a
abnormal bleeding and compared them with 5818 control subjects a
coumarins. Median duration of treatment in patients was 220 days (
4690 days). Patients on SSRIs showed greater risk for hospitalizatio
nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% cor
interval (CI), 1.1 to 2.5), however, the rate of gastrointestinal bleedir
OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schaleka

2008).

3.5.1.L Aspirin

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maint hemostasis. Case-control and cohort studies have shown that the combi SSRIs and antiplatelet agents has been associated with an increased ris Bleeding events reported have included epistaxis, ecchymosis, hematon and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, susp Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an antiplatelet agent are g concurrently, monitor patient for signs of increased bleeding (Prod Info F tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed capsules, solution, 2008)

7) Probable Mechanism: unknown

3.5.1.M Benoxaprofen

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maint hemostasis. Case-control and cohort studies have shown that the combi SSRIs and NSAIDs has been associated with an increased risk of bleed events have included epistaxis, ecchymosis, hematoma, petechiae, and threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, Info Lexapro(TM), 2003a; Dalton et al, 2003a; Prod Info CELEXA (R) ora solution, 2005).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an NSAID are given concu monitor patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and th potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospi upper gastrointestinal bleeding were searched among 26,005 users antidepressant medications and compared with the number of hosp those patients who did not receive prescriptions for antidepressants of upper GI bleeding episodes was 3.6 times more than expected (9 confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSA dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of demonstrate an increased risk of upper GI bleeding during the use Combined use of SSRIs and NSAIDs or low-dose aspirin increased further (Dalton et al, 2003).

b) Coadministration of ketorolac with psychoactive drugs (such as been associated with hallucinations in some patients (Prod Info TOR oral tablets, 2007).

3.5.1.N Bivalirudin

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maint hemostasis. Case-control and cohort studies have shown that the combi SSRIs and anticoagulants has been associated with an increased risk of (Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info LEXAPRO(R solution, 2008). Bleeding events reported have included epistaxis, ecchy hematoma, petechiae, and life-threatening hemorrhages. Altered anticoa (including increased bleeding) have been reported with the coadministra with warfarin (Schalekamp et al, 2008; Prod Info LEXAPRO(R) oral table 2008).

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When escitalopram and an anticoagulant are g concurrently, monitor patients for signs of increased bleeding. Patients v

warfarin should be monitored closely for altered anticoagulant effects, in
increased bleeding, when escitalopram therapy is initiated or discontinue
LEXAPRO(R) oral tablets, solution, 2008).
7) Probable Mechanism: unknown
8) Literature Reports
a) According to a retrospective cohort study (n=234), there was an
of clinically relevant bleeding (hospital admission due to bleeding) ir
receiving warfarin for atrial fibrillation during concomitant SSRI thera
weeks following SSRI therapy termination. Patients with a mean ag
years receiving warfarin plus SSRI (n=117) were matched with ranc
patients who received warfarin only (n=117). SSRI included fluoxeti
citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nin
experienced 11 bleeding episodes during 213.9 treatment years in t
plus SSRI group, and 10 patients experienced 14 bleedings during
treatment years in the warfarin-only group. The corresponding total
bleedings were 51.4 and 23.9 per 1000 treatment years, respectivel
ratio for first bleedings during treatment with warfarin plus SSRI was
CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI ir
patients experiencing bleeding at the time of concomitant administra
sertraline or citalopram. The addition of an SSRI was not associated
change in warfarin dose or INR (p=0.48 and p=0.31 respectively). T
the study may be limited by earlier bleeding events, unknown patier
and exclusion of clopidogrel, dipyridamol, corticosteroids and antico
other than warfarin in the model (Wallerstedt et al, 2009).
b) A population-based, case-controlled study of new coumarin user
(acenocoumarol and phenprocoumon) with concomitant selective se
reuptake inhibitors (SSRIs) resulted in an increased risk of hospitali
nongastrointestinal bleeding. Using national pharmacy and hospitali
records, Netherlands researchers identified 1848 cases that were a
abnormal bleeding and compared them with 5818 control subjects a
coumarins. Median duration of treatment in patients was 220 days (
4690 days). Patients on SSRIs showed greater risk for hospitalizatio
nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% cor
interval (CI), 1.1 to 2.5), however, the rate of gastrointestinal bleedir
OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schaleka
2008).

3.5.1.O Bromfenac
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for main
hemostasis. Case-control and cohort studies have shown that the combi
SSRIs and NSAIDs has been associated with an increased risk of bleed
events have included epistaxis, ecchymosis, hematoma, petechiae, and
threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension,
Info Lexapro(TM), 2003a; Dalton et al, 2003a; Prod Info CELEXA (R) ora
solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concu
monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and th
potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospi
upper gastrointestinal bleeding were searched among 26,005 users
antidepressant medications and compared with the number of hosp
those patients who did not receive prescriptions for antidepressants
of upper GI bleeding episodes was 3.6 times more than expected (9
confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSA
dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1
5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of
demonstrate an increased risk of upper GI bleeding during the use
Combined use of SSRIs and NSAIDs or low-dose aspirin increased
further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as
been associated with hallucinations in some patients (Prod Info TOF

oral tablets, 2007).

3.5.1.P Bufexamac

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for main hemostasis. Case-control and cohort studies have shown that the combi SSRIs and NSAIDs has been associated with an increased risk of bleed events have included epistaxis, ecchymosis, hematoma, petechiae, and threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, Info Lexapro(TM), 2003a; Dalton et al, 2003a; Prod Info CELEXA (R) ora solution, 2005).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an NSAID are given concu monitor patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and th potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospi upper gastrointestinal bleeding were searched among 26,005 users antidepressant medications and compared with the number of hosp those patients who did not receive prescriptions for antidepressants of upper GI bleeding episodes was 3.6 times more than expected (9 confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSA dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of demonstrate an increased risk of upper GI bleeding during the use Combined use of SSRIs and NSAIDs or low-dose aspirin increased further (Dalton et al, 2003).

b) Coadministration of ketorolac with psychoactive drugs (such as been associated with hallucinations in some patients (Prod Info TOF oral tablets, 2007).

3.5.1.Q Cannabis

1) Interaction Effect: manic symptoms

2) Summary: One case of mania following use of marijuana with fluoxet has been reported (Stoll et al, 1991a). Although an interaction is propose authors also state the manic symptoms could have resulted from the fluo marijuana alone. Caution is advised for patients using marijuana and tak or other serotonin reuptake inhibitors.

3) Severity: moderate

4) Onset: rapid

5) Substantiation: theoretical

6) Clinical Management: Caution patients taking selective serotonin reu inhibitors to avoid concomitant use of marijuana.

7) Probable Mechanism: additive serotonergic stimulation

8) Literature Reports

a) A 21-year-old female presented with mania, agitation, and grand delusions following use of marijuana with fluoxetine therapy. She ha fluoxetine 20 mg daily for 4 weeks and reported smoking 2 "joints" o hour period. Over the next 24 hours, she developed increased ener hypersexuality, pressured speech, and grandiose delusions. Loraze perphenazine were given for agitation and excitement which gradua over 4 days. She remained hospitalized for 36 days. Fluoxetine 20 m other day was reintroduced one week prior to discharge. One week discharge, she discontinued fluoxetine due to insomnia and feeling These symptoms resolved rapidly upon discontinuation of fluoxetine rapid switch to mania after smoking marijuana with fluoxetine, the m symptoms were associated with the concomitant use of fluoxetine a though mania could have developed from either fluoxetine or mariju (Stoll et al, 1991).

3.5.1.R Carprofen

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for main hemostasis. Case-control and cohort studies have shown that the combi

SSRIs and NSAIDs has been associated with an increased risk of bleed
events have included epistaxis, ecchymosis, hematoma, petechiae, and
threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension,
Info Lexapro(TM), 2003a; Dalton et al, 2003a; Prod Info CELEXA (R) ora
solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concu
monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and th
potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospi
upper gastrointestinal bleeding were searched among 26,005 users
antidepressant medications and compared with the number of hosp
those patients who did not receive prescriptions for antidepressants
of upper GI bleeding episodes was 3.6 times more than expected (9
confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSA
dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1
5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of
demonstrate an increased risk of upper GI bleeding during the use
Combined use of SSRIs and NSAIDs or low-dose aspirin increased
further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as
been associated with hallucinations in some patients (Prod Info TOF
oral tablets, 2007).

3.5.1.S Celecoxib
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for main
hemostasis. Case-control and cohort studies have shown that the combi
SSRIs and NSAIDs has been associated with an increased risk of bleed
events have included epistaxis, ecchymosis, hematoma, petechiae, and
threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension,
Info Lexapro(TM), 2003a; Dalton et al, 2003a; Prod Info CELEXA (R) ora
solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concu
monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and th
potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospi
upper gastrointestinal bleeding were searched among 26,005 users
antidepressant medications and compared with the number of hosp
those patients who did not receive prescriptions for antidepressants
of upper GI bleeding episodes was 3.6 times more than expected (9
confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSA
dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1
5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of
demonstrate an increased risk of upper GI bleeding during the use
Combined use of SSRIs and NSAIDs or low-dose aspirin increased
further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as
been associated with hallucinations in some patients (Prod Info TOF
oral tablets, 2007).

3.5.1.T Certoparin
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for main
hemostasis. Case-control and cohort studies have shown that the combi
SSRIs and anticoagulants has been associated with an increased risk o
(Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info LEXAPRO(F
solution, 2008). Bleeding events reported have included epistaxis, ecchy

hematoma, petechiae, and life-threatening hemorrhages. Altered anticoa
(including increased bleeding) have been reported with the coadministra
with warfarin (Schalekamp et al, 2008; Prod Info LEXAPRO(R) oral table
2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When escitalopram and an anticoagulant are g
concurrently, monitor patients for signs of increased bleeding. Patients v
warfarin should be monitored closely for altered anticoagulant effects, in
increased bleeding, when escitalopram therapy is initiated or discontinue
LEXAPRO(R) oral tablets, solution, 2008).
7) Probable Mechanism: unknown
8) Literature Reports
a) According to a retrospective cohort study (n=234), there was an
of clinically relevant bleeding (hospital admission due to bleeding) ir
receiving warfarin for atrial fibrillation during concomitant SSRI thera
weeks following SSRI therapy termination. Patients with a mean ag
years receiving warfarin plus SSRI (n=117) were matched with rand
patients who received warfarin only (n=117). SSRI included fluoxeti
citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nin
experienced 11 bleeding episodes during 213.9 treatment years in t
plus SSRI group, and 10 patients experienced 14 bleedings during
treatment years in the warfarin-only group. The corresponding total
bleedings were 51.4 and 23.9 per 1000 treatment years, respectivel
ratio for first bleedings during treatment with warfarin plus SSRI was
CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI ir
patients experiencing bleeding at the time of concomitant administra
sertraline or citalopram. The addition of an SSRI was not associated
change in warfarin dose or INR (p=0.48 and p=0.31 respectively). T
the study may be limited by earlier bleeding events, unknown patier
and exclusion of clopidogrel, dipyridamol, corticosteroids and antico
other than warfarin in the model (Wallerstedt et al, 2009).
b) A population-based, case-controlled study of new coumarin user
(acenocoumarol and phenprocoumon) with concomitant selective se
reuptake inhibitors (SSRIs) resulted in an increased risk of hospitali
nongastrointestinal bleeding. Using national pharmacy and hospitali
records, Netherlands researchers identified 1848 cases that were a
abnormal bleeding and compared them with 5818 control subjects a
coumarins. Median duration of treatment in patients was 220 days (
4690 days). Patients on SSRIs showed greater risk for hospitalizatio
nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% cor
interval (CI), 1.1 to 2.5), however, the rate of gastrointestinal bleedir
OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schaleka
2008).

3.5.1.U Cilostazol
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for main
hemostasis. Case-control and cohort studies have shown that the combi
SSRIs and antiplatelet agents has been associated with an increased ris
Bleeding events reported have included epistaxis, ecchymosis, hematon
and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, susp
Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an antiplatelet agent are g
concurrently, monitor patient for signs of increased bleeding (Prod Info P
tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed
capsules, solution, 2008)
7) Probable Mechanism: unknown

3.5.1.V Cimetidine
1) Interaction Effect: increased bioavailability of escitalopram
2) Summary: In a clinical study, citalopram maximum plasma concentra
under the concentration-time curve increased by 39% and 43%, respect

subjects treated for 21 days with racemic citalopram 40 mg/day concurre
8-day regimen of cimetidine 400 mg/day (Prod Info LEXAPRO(R) Oral T
Solution, 2005).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor patients for signs of escitalopram toxic
serotonin syndrome. Doses of escitalopram may need to be reduced.
7) Probable Mechanism: unknown

3.5.1.W Clonixin

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for main
hemostasis. Case-control and cohort studies have shown that the combi
SSRIs and NSAIDs has been associated with an increased risk of bleed
events have included epistaxis, ecchymosis, hematoma, petechiae, and
threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension,
Info Lexapro(TM), 2003a; Dalton et al, 2003a; Prod Info CELEXA (R) ora
solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concu
monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and th
potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospi
upper gastrointestinal bleeding were searched among 26,005 users
antidepressant medications and compared with the number of hosp
those patients who did not receive prescriptions for antidepressants
of upper GI bleeding episodes was 3.6 times more than expected (9
confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSA
dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1
5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of
demonstrate an increased risk of upper GI bleeding during the use
Combined use of SSRIs and NSAIDs or low-dose aspirin increased
further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as
been associated with hallucinations in some patients (Prod Info TOR
oral tablets, 2007).

3.5.1.X Clopidogrel

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for main
hemostasis. Case-control and cohort studies have shown that the combi
SSRIs and antiplatelet agents has been associated with an increased ris
Bleeding events reported have included epistaxis, ecchymosis, hematon
and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, susp
Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an antiplatelet agent are g
concurrently, monitor patient for signs of increased bleeding (Prod Info P
tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed
capsules, solution, 2008)
7) Probable Mechanism: unknown

3.5.1.Y Clorgyline

1) Interaction Effect: CNS toxicity and/or serotonin syndrome (hypertens
hyperthermia, myoclonus, mental status changes)
2) Summary: Concurrent administration or overlapping therapy with esc
a monoamine oxidase (MAO) inhibitor may result in CNS toxicity or sero
syndrome, a hyperserotonergic state characterized by symptoms such a
restlessness, myoclonus, changes in mental status, hyperreflexia, diaph
shivering, and tremor. Serious, even fatal, reactions have been reported

Lexapro(TM), 2002b). Concomitant use is contraindicated.
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Concurrent use of escitalopram and clorgyline contraindicated. Wait at least two weeks after discontinuing a MAO inhib initiating escitalopram therapy. In addition, wait at least five weeks after escitalopram before initiating therapy with a MAO inhibitor.
7) Probable Mechanism: inhibition of serotonin metabolism by monoam

3.5.1.Z Cyclobenzaprine
1) Interaction Effect: an increased risk of serotonin syndrome
2) Summary: Clinical symptoms of serotonin syndrome have been repo concurrent use of cyclobenzaprine with escitalopram. (Day & Jeanmono Caution is advised if cyclobenzaprine and escitalopram are coadminister patients for signs and symptoms of serotonin syndrome.
3) Severity: moderate
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: A case of serotonin syndrome was reported wi concomitant use of cyclobenzaprine and escitalopram, and therefore, co is discouraged (Day & Jeanmonod, 2008).
7) Probable Mechanism: additive serotonergic effects
8) Literature Reports
a) A 27-year-old female admitted to the hospital for possible overdo experienced serotonin syndrome following coadministration of cyclo and escitalopram. The patient stated she had taken "5 or 6" 10 mg cyclobenzaprine tablets and 2 rum beverages the previous evening currently being treated with escitalopram 10 mg daily for mild depre Lortab(R) and cyclobenzaprine as needed for lower back pain. The initially responsive, but quickly became stuporous, marked by eye o pain, nonsensical speech, and localization to painful stimuli. Her ten 101.7, pulse of 140, blood pressure of 159/76, respirations of 24, ar oximetry of 94% on 6 L. Physical exam showed skin flushing, diaph tremors, rigidity in lower extremities, horizontal nystagmus and hype the patella. Laboratory results showed a respiratory acidosis (7.29/5 creatinine kinase fraction of 3862 units/L, serum ethanol of 44 mg/d positive tricyclic and opiate screens. An ECG showed tachycardia w morphology or interval changes. A diagnosis of serotonin syndrome and the patient was treated accordingly. Over the next 12 hours, the temperature, tachycardia, tremors, and creatinine kinase fraction de mental status improved and she was oriented. After a psychiatric ev was discharged with direction to discontinue cyclobenzaprine while escitalopram (Day & Jeanmonod, 2008).

3.5.1.AA Dalteparin
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for main hemostasis. Case-control and cohort studies have shown that the combi SSRIs and anticoagulants has been associated with an increased risk of (Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info LEXAPRO(R solution, 2008). Bleeding events reported have included epistaxis, ecchy hematoma, petechiae, and life-threatening hemorrhages. Altered anticoa (including increased bleeding) have been reported with the coadministra with warfarin (Schalekamp et al, 2008; Prod Info LEXAPRO(R) oral table 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When escitalopram and an anticoagulant are g concurrently, monitor patients for signs of increased bleeding. Patients v warfarin should be monitored closely for altered anticoagulant effects, in increased bleeding, when escitalopram therapy is initiated or discontinue LEXAPRO(R) oral tablets, solution, 2008).
7) Probable Mechanism: unknown
8) Literature Reports
a) According to a retrospective cohort study (n=234), there was an

of clinically relevant bleeding (hospital admission due to bleeding) ir
receiving warfarin for atrial fibrillation during concomitant SSRI thera
weeks following SSRI therapy termination. Patients with a mean ag
years receiving warfarin plus SSRI (n=117) were matched with ranc
patients who received warfarin only (n=117). SSRI included fluoxeti
citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nin
experienced 11 bleeding episodes during 213.9 treatment years in t
plus SSRI group, and 10 patients experienced 14 bleedings during
treatment years in the warfarin-only group. The corresponding total
bleedings were 51.4 and 23.9 per 1000 treatment years, respectivel
ratio for first bleedings during treatment with warfarin plus SSRI was
CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI ir
patients experiencing bleeding at the time of concomitant administra
sertraline or citalopram. The addition of an SSRI was not associatec
change in warfarin dose or INR (p=0.48 and p=0.31 respectively). T
the study may be limited by earlier bleeding events, unknown patier
and exclusion of clopidogrel, dipyridamol, corticosteroids and antico
other than warfarin in the model (Wallerstedt et al, 2009).

b) A population-based, case-controlled study of new coumarin user
(acenocoumarol and phenprocoumon) with concomitant selective se
reuptake inhibitors (SSRIs) resulted in an increased risk of hospitali
nongastrointestinal bleeding. Using national pharmacy and hospitali
records, Netherlands researchers identified 1848 cases that were a
abnormal bleeding and compared them with 5818 control subjects a
coumarins. Median duration of treatment in patients was 220 days (
4690 days). Patients on SSRIs showed greater risk for hospitalizatic
nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% cor
interval (CI), 1.1 to 2.5), however, the rate of gastrointestinal bleedir
OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schaleka
2008).

3.5.1.AB Danaparoid

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for main
hemostasis. Case-control and cohort studies have shown that the combi
SSRIs and anticoagulants has been associated with an increased risk o
(Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info LEXAPRO(R
solution, 2008). Bleeding events reported have included epistaxis, ecchy
hematoma, petechiae, and life-threatening hemorrhages. Altered anticoa
(including increased bleeding) have been reported with the coadministra
with warfarin (Schalekamp et al, 2008; Prod Info LEXAPRO(R) oral table
2008).

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When escitalopram and an anticoagulant are g
concurrently, monitor patients for signs of increased bleeding. Patients v
warfarin should be monitored closely for altered anticoagulant effects, in
increased bleeding, when escitalopram therapy is initiated or discontinue
LEXAPRO(R) oral tablets, solution, 2008).

7) Probable Mechanism: unknown

8) Literature Reports

a) According to a retrospective cohort study (n=234), there was an
of clinically relevant bleeding (hospital admission due to bleeding) ir
receiving warfarin for atrial fibrillation during concomitant SSRI thera
weeks following SSRI therapy termination. Patients with a mean ag
years receiving warfarin plus SSRI (n=117) were matched with ranc
patients who received warfarin only (n=117). SSRI included fluoxeti
citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nin
experienced 11 bleeding episodes during 213.9 treatment years in t
plus SSRI group, and 10 patients experienced 14 bleedings during
treatment years in the warfarin-only group. The corresponding total
bleedings were 51.4 and 23.9 per 1000 treatment years, respectivel
ratio for first bleedings during treatment with warfarin plus SSRI was
CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI ir
patients experiencing bleeding at the time of concomitant administra
sertraline or citalopram. The addition of an SSRI was not associatec

change in warfarin dose or INR (p=0.48 and p=0.31 respectively). T
the study may be limited by earlier bleeding events, unknown patier
and exclusion of clopidogrel, dipyridamol, corticosteroids and antico
other than warfarin in the model (Wallerstedt et al, 2009).

b) A population-based, case-controlled study of new coumarin user
(acenocoumarol and phenprocoumon) with concomitant selective se
reuptake inhibitors (SSRIs) resulted in an increased risk of hospitali
nongastrointestinal bleeding. Using national pharmacy and hospitali
records, Netherlands researchers identified 1848 cases that were a
abnormal bleeding and compared them with 5818 control subjects a
coumarins. Median duration of treatment in patients was 220 days (
4690 days). Patients on SSRIs showed greater risk for hospitalizatio
nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% cor
interval (CI), 1.1 to 2.5), however, the rate of gastrointestinal bleedir
OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schaleka
2008).

3.5.1.AC Defibrotide

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for main
hemostasis. Case-control and cohort studies have shown that the combi
SSRIs and anticoagulants has been associated with an increased risk of
(Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info LEXAPRO(R
solution, 2008). Bleeding events reported have included epistaxis, ecchy
hematoma, petechiae, and life-threatening hemorrhages. Altered anticoa
(including increased bleeding) have been reported with the coadministra
with warfarin (Schalekamp et al, 2008; Prod Info LEXAPRO(R) oral table
2008).

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When escitalopram and an anticoagulant are g
concurrently, monitor patients for signs of increased bleeding. Patients v
warfarin should be monitored closely for altered anticoagulant effects, in
increased bleeding, when escitalopram therapy is initiated or discontinue
LEXAPRO(R) oral tablets, solution, 2008).

7) Probable Mechanism: unknown

8) Literature Reports

a) According to a retrospective cohort study (n=234), there was an
of clinically relevant bleeding (hospital admission due to bleeding) ir
receiving warfarin for atrial fibrillation during concomitant SSRI thera
weeks following SSRI therapy termination. Patients with a mean age
years receiving warfarin plus SSRI (n=117) were matched with rand
patients who received warfarin only (n=117). SSRI included fluoxeti
citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nin
experienced 11 bleeding episodes during 213.9 treatment years in t
plus SSRI group, and 10 patients experienced 14 bleedings during 5
treatment years in the warfarin-only group. The corresponding total
bleedings were 51.4 and 23.9 per 1000 treatment years, respectivel
ratio for first bleedings during treatment with warfarin plus SSRI was
CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI ir
patients experiencing bleeding at the time of concomitant administra
sertraline or citalopram. The addition of an SSRI was not associated
change in warfarin dose or INR (p=0.48 and p=0.31 respectively). T
the study may be limited by earlier bleeding events, unknown patier
and exclusion of clopidogrel, dipyridamol, corticosteroids and antico
other than warfarin in the model (Wallerstedt et al, 2009).

b) A population-based, case-controlled study of new coumarin user
(acenocoumarol and phenprocoumon) with concomitant selective se
reuptake inhibitors (SSRIs) resulted in an increased risk of hospitali
nongastrointestinal bleeding. Using national pharmacy and hospitali
records, Netherlands researchers identified 1848 cases that were a
abnormal bleeding and compared them with 5818 control subjects a
coumarins. Median duration of treatment in patients was 220 days (
4690 days). Patients on SSRIs showed greater risk for hospitalizatio
nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% cor
interval (CI), 1.1 to 2.5), however, the rate of gastrointestinal bleedir

OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schaleka 2008).

3.5.1.AD Dehydroepiandrosterone

1) Interaction Effect: development of manic symptoms

2) Summary: A case has been reported in which concomitant dehydroepiandrosterone (DHEA) and sertraline use was suggested to p manic episode in a patient with a history of bipolar disorder (Dean, 2000 also noted to cause mania in a patient with no previous personal or fami bipolar disorder (Markowitz et al, 1999). Elevated DHEA levels have bee patients with mental disorders; DHEA suppression has lead to improvem psychotic symptoms (Howard, 1992). DHEA possesses proserotonergic may predispose patients to manic episodes (Majewska, 1995). DHEA is androgenic steroids, which in high doses may precipitate mania (Markov 1999). Patients taking medication for bipolar disorder or patients with a p and/or family history of bipolar disorder should not take DHEA until furth available to characterize this drug-herb interaction. Concomitant use of D selective serotonin reuptake inhibitors (SSRIs) should be avoided due to additive precipitation of mania.

3) Severity: moderate

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: Avoid concomitant use of dehydroepiandroster and selective serotonin reuptake inhibitors. If patients present with mani (i.e. agitation, anger, irritability, aggressive behavior), determine if the pa DHEA and discontinue DHEA.

7) Probable Mechanism: serotonergic activity of dehydroepiandrosteron increased androgen levels

8) Literature Reports

a) A 31-year-old male was admitted following threats to commit sui family members. He had self-initiated sertraline 100 milligrams (mg) previous 2 to 3 weeks for depression. Sertraline had been prescribe prior when he was diagnosed with bipolar disorder, which he discon weeks. He had also taken dehydroepiandrosterone (DHEA) 300 mg daily for the previous 2 months apparently for weight training. Follov DHEA for a short time, he became more irritable, was not sleeping v began threatening a female friend and family members. He also dra occasionally and reportedly had difficulty controlling his anger when Sertraline was stopped and the patient was treated with valproic aci dose titrated to 500 mg twice daily. The combination of DHEA, sertr alcohol was suggested responsible for the developing of the manic (Dean, 2000).

3.5.1.AE Dermatan Sulfate

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for main hemostasis. Case-control and cohort studies have shown that the combi SSRIs and anticoagulants has been associated with an increased risk of (Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info LEXAPRO(R solution, 2008). Bleeding events reported have included epistaxis, ecchy hematoma, petechiae, and life-threatening hemorrhages. Altered anticoa (including increased bleeding) have been reported with the coadministra with warfarin (Schalekamp et al, 2008; Prod Info LEXAPRO(R) oral table 2008).

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When escitalopram and an anticoagulant are g concurrently, monitor patients for signs of increased bleeding. Patients v warfarin should be monitored closely for altered anticoagulant effects, in increased bleeding, when escitalopram therapy is initiated or discontinue LEXAPRO(R) oral tablets, solution, 2008).

7) Probable Mechanism: unknown

8) Literature Reports

a) According to a retrospective cohort study (n=234), there was an of clinically relevant bleeding (hospital admission due to bleeding) ir receiving warfarin for atrial fibrillation during concomitant SSRI thera

weeks following SSRI therapy termination. Patients with a mean ag
years receiving warfarin plus SSRI (n=117) were matched with ranc
patients who received warfarin only (n=117). SSRI included fluoxeti
citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nin
experienced 11 bleeding episodes during 213.9 treatment years in t
plus SSRI group, and 10 patients experienced 14 bleedings during
treatment years in the warfarin-only group. The corresponding total
bleedings were 51.4 and 23.9 per 1000 treatment years, respectivel
ratio for first bleedings during treatment with warfarin plus SSRI was
CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI ir
patients experiencing bleeding at the time of concomitant administra
sertraline or citalopram. The addition of an SSRI was not associatec
change in warfarin dose or INR (p=0.48 and p=0.31 respectively). T
the study may be limited by earlier bleeding events, unknown patier
and exclusion of clopidogrel, dipyridamol, corticosteroids and antico
other than warfarin in the model (Wallerstedt et al, 2009).

b) A population-based, case-controlled study of new coumarin user
(acenocoumarol and phenprocoumon) with concomitant selective se
reuptake inhibitors (SSRIs) resulted in an increased risk of hospitali
nongastrointestinal bleeding. Using national pharmacy and hospitali
records, Netherlands researchers identified 1848 cases that were a
abnormal bleeding and compared them with 5818 control subjects a
coumarins. Median duration of treatment in patients was 220 days (
4690 days). Patients on SSRIs showed greater risk for hospitalizatic
nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% cor
interval (CI), 1.1 to 2.5), however, the rate of gastrointestinal bleedir
OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schaleka
2008).

3.5.1.AF Desipramine

1) Interaction Effect: increase in the bioavailability and plasma concentr
desipramine

2) Summary: Desipramine plasma concentration and area under the co
time curve increased by 40% and 100%, respectively, when a single dos
desipramine 50 milligrams (mg) was administered concurrently with a 21
of escitalopram 20 mg/day (Prod Info LEXAPRO(R) Oral Tablet, Oral Sc

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: Caution is indicated in the coadministration of
and escitalopram due to the risk for increased desipramine plasma conc

7) Probable Mechanism: escitalopram inhibition of cytochrome P450-2D
desipramine metabolism

3.5.1.AG Desirudin

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maint
hemostasis. Case-control and cohort studies have shown that the combi
SSRIs and anticoagulants has been associated with an increased risk of
(Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info LEXAPRO(R
solution, 2008). Bleeding events reported have included epistaxis, ecchy
hematoma, petechiae, and life-threatening hemorrhages. Altered anticoa
(including increased bleeding) have been reported with the coadministra
with warfarin (Schalekamp et al, 2008; Prod Info LEXAPRO(R) oral table
2008).

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When escitalopram and an anticoagulant are g
concurrently, monitor patients for signs of increased bleeding. Patients v
warfarin should be monitored closely for altered anticoagulant effects, in
increased bleeding, when escitalopram therapy is initiated or discontinue
LEXAPRO(R) oral tablets, solution, 2008).

7) Probable Mechanism: unknown

8) Literature Reports

a) According to a retrospective cohort study (n=234), there was an
of clinically relevant bleeding (hospital admission due to bleeding) ir

receiving warfarin for atrial fibrillation during concomitant SSRI thera
weeks following SSRI therapy termination. Patients with a mean ag
years receiving warfarin plus SSRI (n=117) were matched with ranc
patients who received warfarin only (n=117). SSRI included fluoxeti
citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nin
experienced 11 bleeding episodes during 213.9 treatment years in t
plus SSRI group, and 10 patients experienced 14 bleedings during
treatment years in the warfarin-only group. The corresponding total
bleedings were 51.4 and 23.9 per 1000 treatment years, respectivel
ratio for first bleedings during treatment with warfarin plus SSRI was
CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI ir
patients experiencing bleeding at the time of concomitant administra
sertraline or citalopram. The addition of an SSRI was not associatec
change in warfarin dose or INR (p=0.48 and p=0.31 respectively). T
the study may be limited by earlier bleeding events, unknown patier
and exclusion of clopidogrel, dipyridamol, corticosteroids and antico
other than warfarin in the model (Wallerstedt et al, 2009).

b) A population-based, case-controlled study of new coumarin user
(acenocoumarol and phenprocoumon) with concomitant selective se
reuptake inhibitors (SSRIs) resulted in an increased risk of hospitali
nongastrointestinal bleeding. Using national pharmacy and hospitali
records, Netherlands researchers identified 1848 cases that were a
abnormal bleeding and compared them with 5818 control subjects a
coumarins. Median duration of treatment in patients was 220 days (
4690 days). Patients on SSRIs showed greater risk for hospitalizatic
nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% cor
interval (CI), 1.1 to 2.5), however, the rate of gastrointestinal bleedir
OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schaleka
2008).

3.5.1.AH Desvenlafaxine

1) Interaction Effect: increased risk of serotonin syndrome (hypertensio
hyperthermia, myoclonus, mental status changes)

2) Summary: Concurrent use of desvenlafaxine and a selective seroton
inhibitor (SSRI) may result in serotonin syndrome, which may be life-thre
Symptoms of serotonin syndrome may include restlessness, hallucinatio
coordination, fast heart beat, rapid changes in blood pressure, increasec
temperature, overreactive reflexes, nausea, vomiting, and diarrhea (Proc
PRISTIQ(TM) oral extended-release tablets, 2008).

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Coadministration of desvenlafaxine and an SS
in a life-threatening condition called serotonin syndrome. If these agents
together, discuss the risks of serotonin syndrome with the patient and m
for symptoms of serotonin syndrome (restlessness, hyperthermia, hyper
incoordination), especially during treatment initiation and dose increases
PRISTIQ(TM) oral extended-release tablets, 2008).

7) Probable Mechanism: additive serotonergic effect

3.5.1.AI Dexketoprofen

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for main
hemostasis. Case-control and cohort studies have shown that the combi
SSRIs and NSAIDs has been associated with an increased risk of bleed
events have included epistaxis, ecchymosis, hematoma, petechiae, and
threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension,
Info Lexapro(TM), 2003a; Dalton et al, 2003a; Prod Info CELEXA (R) ora
solution, 2005).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an NSAID are given concu
monitor patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and th

potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospi
upper gastrointestinal bleeding were searched among 26,005 users
antidepressant medications and compared with the number of hosp
those patients who did not receive prescriptions for antidepressants
of upper GI bleeding episodes was 3.6 times more than expected (9
confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSA
dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1
5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of
demonstrate an increased risk of upper GI bleeding during the use
Combined use of SSRIs and NSAIDs or low-dose aspirin increased
further (Dalton et al, 2003).

b) Coadministration of ketorolac with psychoactive drugs (such as
been associated with hallucinations in some patients (Prod Info TOF
oral tablets, 2007).

3.5.1.AJ Diclofenac

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for main
hemostasis. Case-control and cohort studies have shown that the combi
SSRIs and NSAIDs has been associated with an increased risk of bleed
events have included epistaxis, ecchymosis, hematoma, petechiae, and
threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension,
Info Lexapro(TM), 2003a; Dalton et al, 2003a; Prod Info CELEXA (R) ora
solution, 2005).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an NSAID are given concu
monitor patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and th
potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospi
upper gastrointestinal bleeding were searched among 26,005 users
antidepressant medications and compared with the number of hosp
those patients who did not receive prescriptions for antidepressants
of upper GI bleeding episodes was 3.6 times more than expected (9
confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSA
dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1
5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of
demonstrate an increased risk of upper GI bleeding during the use
Combined use of SSRIs and NSAIDs or low-dose aspirin increased
further (Dalton et al, 2003).

b) Coadministration of ketorolac with psychoactive drugs (such as
been associated with hallucinations in some patients (Prod Info TOF
oral tablets, 2007).

3.5.1.AK Dicumarol

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for main
hemostasis. Case-control and cohort studies have shown that the combi
SSRIs and anticoagulants has been associated with an increased risk of
(Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info LEXAPRO(F
solution, 2008). Bleeding events reported have included epistaxis, ecchy
hematoma, petechiae, and life-threatening hemorrhages. Altered anticoa
(including increased bleeding) have been reported with the coadministra
with warfarin (Schalekamp et al, 2008; Prod Info LEXAPRO(R) oral table
2008).

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When escitalopram and an anticoagulant are g
concurrently, monitor patients for signs of increased bleeding. Patients v
warfarin should be monitored closely for altered anticoagulant effects, in
increased bleeding, when escitalopram therapy is initiated or discontinue
LEXAPRO(R) oral tablets, solution, 2008).

7) Probable Mechanism: unknown

8) Literature Reports

a) According to a retrospective cohort study (n=234), there was an of clinically relevant bleeding (hospital admission due to bleeding) ir receiving warfarin for atrial fibrillation during concomitant SSRI thera weeks following SSRI therapy termination. Patients with a mean ag years receiving warfarin plus SSRI (n=117) were matched with ranc patients who received warfarin only (n=117). SSRI included fluoxeti citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nin experienced 11 bleeding episodes during 213.9 treatment years in t plus SSRI group, and 10 patients experienced 14 bleedings during treatment years in the warfarin-only group. The corresponding total bleedings were 51.4 and 23.9 per 1000 treatment years, respectivel ratio for first bleedings during treatment with warfarin plus SSRI was CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI ir patients experiencing bleeding at the time of concomitant administra sertraline or citalopram. The addition of an SSRI was not associatec change in warfarin dose or INR (p=0.48 and p=0.31 respectively). T the study may be limited by earlier bleeding events, unknown patier and exclusion of clopidogrel, dipyridamol, corticosteroids and antico other than warfarin in the model (Wallerstedt et al, 2009).

b) A population-based, case-controlled study of new coumarin user (acenocoumarol and phenprocoumon) with concomitant selective se reuptake inhibitors (SSRIs) resulted in an increased risk of hospitali nongastrointestinal bleeding. Using national pharmacy and hospitali records, Netherlands researchers identified 1848 cases that were a abnormal bleeding and compared them with 5818 control subjects a coumarins. Median duration of treatment in patients was 220 days (4690 days). Patients on SSRIs showed greater risk for hospitalizatic nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% cor interval (CI), 1.1 to 2.5), however, the rate of gastrointestinal bleedir OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schaleka 2008).

3.5.1.AL Diflunisal

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for main hemostasis. Case-control and cohort studies have shown that the combi SSRIs and NSAIDs has been associated with an increased risk of bleed events have included epistaxis, ecchymosis, hematoma, petechiae, and threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, Info Lexapro(TM), 2003a; Dalton et al, 2003a; Prod Info CELEXA (R) ora solution, 2005).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an NSAID are given concu monitor patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and th potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospi upper gastrointestinal bleeding were searched among 26,005 users antidepressant medications and compared with the number of hosp those patients who did not receive prescriptions for antidepressants of upper GI bleeding episodes was 3.6 times more than expected (9 confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSA dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of demonstrate an increased risk of upper GI bleeding during the use Combined use of SSRIs and NSAIDs or low-dose aspirin increased further (Dalton et al, 2003).

b) Coadministration of ketorolac with psychoactive drugs (such as been associated with hallucinations in some patients (Prod Info TOF oral tablets, 2007).

3.5.1.AM Dipyridamole

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maint
hemostasis. Case-control and cohort studies have shown that the combi
SSRIs and antiplatelet agents has been associated with an increased ris
Bleeding events reported have included epistaxis, ecchymosis, hematon
and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, susp
Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an antiplatelet agent are g
concurrently, monitor patient for signs of increased bleeding (Prod Info P
tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed
capsules, solution, 2008)
7) Probable Mechanism: unknown

3.5.1.AN Dipyrone

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maint
hemostasis. Case-control and cohort studies have shown that the combi
SSRIs and NSAIDs has been associated with an increased risk of bleed
events have included epistaxis, ecchymosis, hematoma, petechiae, and
threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension,
Info Lexapro(TM), 2003a; Dalton et al, 2003a; Prod Info CELEXA (R) ora
solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concu
monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and th
potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospi
upper gastrointestinal bleeding were searched among 26,005 users
antidepressant medications and compared with the number of hosp
those patients who did not receive prescriptions for antidepressants
of upper GI bleeding episodes was 3.6 times more than expected (9
confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSA
dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1
5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of
demonstrate an increased risk of upper GI bleeding during the use
Combined use of SSRIs and NSAIDs or low-dose aspirin increased
further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as
been associated with hallucinations in some patients (Prod Info TOR
oral tablets, 2007).

3.5.1.AO Droxicam

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maint
hemostasis. Case-control and cohort studies have shown that the combi
SSRIs and NSAIDs has been associated with an increased risk of bleed
events have included epistaxis, ecchymosis, hematoma, petechiae, and
threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension,
Info Lexapro(TM), 2003a; Dalton et al, 2003a; Prod Info CELEXA (R) ora
solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concu
monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and th
potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospi
upper gastrointestinal bleeding were searched among 26,005 users
antidepressant medications and compared with the number of hosp

those patients who did not receive prescriptions for antidepressants of upper GI bleeding episodes was 3.6 times more than expected (9 confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSA dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of demonstrate an increased risk of upper GI bleeding during the use Combined use of SSRIs and NSAIDs or low-dose aspirin increased further (Dalton et al, 2003).

b) Coadministration of ketorolac with psychoactive drugs (such as been associated with hallucinations in some patients (Prod Info TOR oral tablets, 2007).

3.5.1.AP Duloxetine

1) Interaction Effect: an increased risk of serotonin syndrome

2) Summary: Duloxetine is a selective serotonin and norepinephrine reu inhibitor. The concomitant use of duloxetine with escitalopram, a selectiv reuptake inhibitor, is not recommended due to the potential for serotonin (Prod Info CYMBALTA(R) delayed-release oral capsules, 2008).

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concomitant use of duloxetine and escitalo recommended due to the potential for development of serotonin syndron CYMBALTA(R) delayed-release oral capsules, 2008).

7) Probable Mechanism: additive serotonergic effects

3.5.1.AQ Eletriptan

1) Interaction Effect: an increased risk of serotonin syndrome

2) Summary: There have been case reports of weakness, hyperreflexia incoordination following concomitant use of sumatriptan, a 5-hydroxytryp (5HT-1) agonist, and a serotonin specific reuptake inhibitor (SSRI) (Proc (R) Nasal Spray, 2003). Because eletriptan is a 5HT 1B/1D agonist, a si interaction between SSRIs and eletriptan may occur (Prod Info Relpax(R Concurrent use of a triptan and an SSRI may result in serotonin syndron be life-threatening. Symptoms of serotonin syndrome may include restle hallucinations, loss of coordination, fast heart beat, rapid changes in blo increased body temperature, overreactive reflexes, nausea, vomiting, ar Clinicians should be aware that triptans may be commonly used intermit either the triptan or the SSRI may be prescribed by a different physician risks of serotonin syndrome with patients who are prescribed this combi monitor them closely for symptoms of serotonin syndrome (US Food and Administration, 2006).

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Coadministration of a triptan, such as eletriptan SSRI may result in a life-threatening condition called serotonin syndrom that triptans may be commonly used intermittently and that either the trip SSRI may be prescribed by a different physician. If these agents are use discuss the risks of serotonin syndrome with the patient and monitor clos symptoms of serotonin syndrome (restlessness, hyperthermia, hyperrefl incoordination).

7) Probable Mechanism: additive pharmacologic effects resulting in exc serotonergic stimulation

3.5.1.AR Enoxaparin

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for main hemostasis. Case-control and cohort studies have shown that the combi SSRIs and anticoagulants has been associated with an increased risk of (Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info LEXAPRO(R solution, 2008). Bleeding events reported have included epistaxis, ecchy hematoma, petechiae, and life-threatening hemorrhages. Altered anticoa (including increased bleeding) have been reported with the coadministra with warfarin (Schalekamp et al, 2008; Prod Info LEXAPRO(R) oral table 2008).

3) Severity: major

4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When escitalopram and an anticoagulant are g concurrently, monitor patients for signs of increased bleeding. Patients v warfarin should be monitored closely for altered anticoagulant effects, in increased bleeding, when escitalopram therapy is initiated or discontinue LEXAPRO(R) oral tablets, solution, 2008).
7) Probable Mechanism: unknown
8) Literature Reports
a) According to a retrospective cohort study (n=234), there was an of clinically relevant bleeding (hospital admission due to bleeding) ir receiving warfarin for atrial fibrillation during concomitant SSRI thera weeks following SSRI therapy termination. Patients with a mean ag years receiving warfarin plus SSRI (n=117) were matched with ranc patients who received warfarin only (n=117). SSRI included fluoxeti citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nin experienced 11 bleeding episodes during 213.9 treatment years in t plus SSRI group, and 10 patients experienced 14 bleedings during treatment years in the warfarin-only group. The corresponding total bleedings were 51.4 and 23.9 per 1000 treatment years, respectivel ratio for first bleedings during treatment with warfarin plus SSRI was CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI ir patients experiencing bleeding at the time of concomitant administra sertraline or citalopram. The addition of an SSRI was not associated change in warfarin dose or INR (p=0.48 and p=0.31 respectively). T the study may be limited by earlier bleeding events, unknown patier and exclusion of clopidogrel, dipyridamol, corticosteroids and antico other than warfarin in the model (Wallerstedt et al, 2009).
b) A population-based, case-controlled study of new coumarin user (acenocoumarol and phenprocoumon) with concomitant selective se reuptake inhibitors (SSRIs) resulted in an increased risk of hospitali nongastrointestinal bleeding. Using national pharmacy and hospitali records, Netherlands researchers identified 1848 cases that were a abnormal bleeding and compared them with 5818 control subjects a coumarins. Median duration of treatment in patients was 220 days (4690 days). Patients on SSRIs showed greater risk for hospitalizatio nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% cor interval (CI), 1.1 to 2.5), however, the rate of gastrointestinal bleedir OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schaleka 2008).

3.5.1.AS Epoprostenol
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for main hemostasis. Case-control and cohort studies have shown that the combi SSRIs and antiplatelet agents has been associated with an increased ris Bleeding events reported have included epistaxis, ecchymosis, hematon and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, susp Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an antiplatelet agent are g concurrently, monitor patient for signs of increased bleeding (Prod Info P tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed capsules, solution, 2008)
7) Probable Mechanism: unknown

3.5.1.AT Eptifibatide
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for main hemostasis. Case-control and cohort studies have shown that the combi SSRIs and antiplatelet agents has been associated with an increased ris Bleeding events reported have included epistaxis, ecchymosis, hematon and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, susp Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution
3) Severity: major

4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an antiplatelet agent are g
concurrently, monitor patient for signs of increased bleeding (Prod Info F
tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayec
capsules, solution, 2008)
7) Probable Mechanism: unknown

3.5.1.AU Etodolac

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for main
hemostasis. Case-control and cohort studies have shown that the combi
SSRIs and NSAIDs has been associated with an increased risk of bleed
events have included epistaxis, ecchymosis, hematoma, petechiae, and
threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension,
Info Lexapro(TM), 2003a; Dalton et al, 2003a; Prod Info CELEXA (R) ora
solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concu
monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and th
potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospi
upper gastrointestinal bleeding were searched among 26,005 users
antidepressant medications and compared with the number of hosp
those patients who did not receive prescriptions for antidepressants
of upper GI bleeding episodes was 3.6 times more than expected (9
confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSA
dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1
5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of
demonstrate an increased risk of upper GI bleeding during the use
Combined use of SSRIs and NSAIDs or low-dose aspirin increased
further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as
been associated with hallucinations in some patients (Prod Info TOF
oral tablets, 2007).

3.5.1.AV Etofenamate

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for main
hemostasis. Case-control and cohort studies have shown that the combi
SSRIs and NSAIDs has been associated with an increased risk of bleed
events have included epistaxis, ecchymosis, hematoma, petechiae, and
threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension,
Info Lexapro(TM), 2003a; Dalton et al, 2003a; Prod Info CELEXA (R) ora
solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concu
monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and th
potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospi
upper gastrointestinal bleeding were searched among 26,005 users
antidepressant medications and compared with the number of hosp
those patients who did not receive prescriptions for antidepressants
of upper GI bleeding episodes was 3.6 times more than expected (9
confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSA
dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1
5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of
demonstrate an increased risk of upper GI bleeding during the use
Combined use of SSRIs and NSAIDs or low-dose aspirin increased

further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as t
been associated with hallucinations in some patients (Prod Info TOF
oral tablets, 2007).

3.5.1.AW Etoricoxib
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maint
hemostasis. Case-control and cohort studies have shown that the combi
SSRIs and NSAIDs has been associated with an increased risk of bleed
events have included epistaxis, ecchymosis, hematoma, petechiae, and
threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2
Info Lexapro(TM), 2003a; Dalton et al, 2003a; Prod Info CELEXA (R) ora
solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concu
monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and th
potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospi
upper gastrointestinal bleeding were searched among 26,005 users
antidepressant medications and compared with the number of hosp
those patients who did not receive prescriptions for antidepressants
of upper GI bleeding episodes was 3.6 times more than expected (9
confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSA
dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1
5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of
demonstrate an increased risk of upper GI bleeding during the use o
Combined use of SSRIs and NSAIDs or low-dose aspirin increased
further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as t
been associated with hallucinations in some patients (Prod Info TOF
oral tablets, 2007).

3.5.1.AX Felbinac
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maint
hemostasis. Case-control and cohort studies have shown that the combi
SSRIs and NSAIDs has been associated with an increased risk of bleed
events have included epistaxis, ecchymosis, hematoma, petechiae, and
threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2
Info Lexapro(TM), 2003a; Dalton et al, 2003a; Prod Info CELEXA (R) ora
solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concu
monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and th
potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospi
upper gastrointestinal bleeding were searched among 26,005 users
antidepressant medications and compared with the number of hosp
those patients who did not receive prescriptions for antidepressants
of upper GI bleeding episodes was 3.6 times more than expected (9
confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSA
dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1
5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of
demonstrate an increased risk of upper GI bleeding during the use o
Combined use of SSRIs and NSAIDs or low-dose aspirin increased
further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as t
been associated with hallucinations in some patients (Prod Info TOF

oral tablets, 2007).

3.5.1.AY Fenbufen

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maint hemostasis. Case-control and cohort studies have shown that the combi SSRIs and NSAIDs has been associated with an increased risk of bleed events have included epistaxis, ecchymosis, hematoma, petechiae, and threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, Info Lexapro(TM), 2003a; Dalton et al, 2003a; Prod Info CELEXA (R) ora solution, 2005).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an NSAID are given concu monitor patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and th potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospi upper gastrointestinal bleeding were searched among 26,005 users antidepressant medications and compared with the number of hosp those patients who did not receive prescriptions for antidepressants of upper GI bleeding episodes was 3.6 times more than expected (9 confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSA dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of demonstrate an increased risk of upper GI bleeding during the use Combined use of SSRIs and NSAIDs or low-dose aspirin increased further (Dalton et al, 2003).

b) Coadministration of ketorolac with psychoactive drugs (such as been associated with hallucinations in some patients (Prod Info TOF oral tablets, 2007).

3.5.1.AZ Fenoprofen

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maint hemostasis. Case-control and cohort studies have shown that the combi SSRIs and NSAIDs has been associated with an increased risk of bleed events have included epistaxis, ecchymosis, hematoma, petechiae, and threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, Info Lexapro(TM), 2003a; Dalton et al, 2003a; Prod Info CELEXA (R) ora solution, 2005).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an NSAID are given concu monitor patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and th potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospi upper gastrointestinal bleeding were searched among 26,005 users antidepressant medications and compared with the number of hosp those patients who did not receive prescriptions for antidepressants of upper GI bleeding episodes was 3.6 times more than expected (9 confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSA dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of demonstrate an increased risk of upper GI bleeding during the use Combined use of SSRIs and NSAIDs or low-dose aspirin increased further (Dalton et al, 2003).

b) Coadministration of ketorolac with psychoactive drugs (such as been associated with hallucinations in some patients (Prod Info TOF oral tablets, 2007).

3.5.1.BA Fentiazac

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for main
hemostasis. Case-control and cohort studies have shown that the combi
SSRIs and NSAIDs has been associated with an increased risk of bleed
events have included epistaxis, ecchymosis, hematoma, petechiae, and
threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension,
Info Lexapro(TM), 2003a; Dalton et al, 2003a; Prod Info CELEXA (R) ora
solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concu
monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and th
potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospi
upper gastrointestinal bleeding were searched among 26,005 users
antidepressant medications and compared with the number of hosp
those patients who did not receive prescriptions for antidepressants
of upper GI bleeding episodes was 3.6 times more than expected (9
confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSA
dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1
5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of
demonstrate an increased risk of upper GI bleeding during the use
Combined use of SSRIs and NSAIDs or low-dose aspirin increased
further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as
been associated with hallucinations in some patients (Prod Info TOR
oral tablets, 2007).

3.5.1.BB Floctafenine

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for main
hemostasis. Case-control and cohort studies have shown that the combi
SSRIs and NSAIDs has been associated with an increased risk of bleed
events have included epistaxis, ecchymosis, hematoma, petechiae, and
threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension,
Info Lexapro(TM), 2003a; Dalton et al, 2003a; Prod Info CELEXA (R) ora
solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concu
monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and th
potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospi
upper gastrointestinal bleeding were searched among 26,005 users
antidepressant medications and compared with the number of hosp
those patients who did not receive prescriptions for antidepressants
of upper GI bleeding episodes was 3.6 times more than expected (9
confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSA
dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1
5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of
demonstrate an increased risk of upper GI bleeding during the use
Combined use of SSRIs and NSAIDs or low-dose aspirin increased
further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as
been associated with hallucinations in some patients (Prod Info TOR
oral tablets, 2007).

3.5.1.BC Flufenamic Acid

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for main
hemostasis. Case-control and cohort studies have shown that the combi

SSRIs and NSAIDs has been associated with an increased risk of bleed
events have included epistaxis, ecchymosis, hematoma, petechiae, and
threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension,
Info Lexapro(TM), 2003a; Dalton et al, 2003a; Prod Info CELEXA (R) ora
solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concu
monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and th
potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospi
upper gastrointestinal bleeding were searched among 26,005 users
antidepressant medications and compared with the number of hosp
those patients who did not receive prescriptions for antidepressants
of upper GI bleeding episodes was 3.6 times more than expected (9
confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSA
dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1
5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of
demonstrate an increased risk of upper GI bleeding during the use
Combined use of SSRIs and NSAIDs or low-dose aspirin increased
further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as
been associated with hallucinations in some patients (Prod Info TOR
oral tablets, 2007).

3.5.1.BD Flurbiprofen

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for main
hemostasis. Case-control and cohort studies have shown that the combi
SSRIs and NSAIDs has been associated with an increased risk of bleed
events have included epistaxis, ecchymosis, hematoma, petechiae, and
threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension,
Info Lexapro(TM), 2003a; Dalton et al, 2003a; Prod Info CELEXA (R) ora
solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concu
monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and th
potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospi
upper gastrointestinal bleeding were searched among 26,005 users
antidepressant medications and compared with the number of hosp
those patients who did not receive prescriptions for antidepressants
of upper GI bleeding episodes was 3.6 times more than expected (9
confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSA
dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1
5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of
demonstrate an increased risk of upper GI bleeding during the use
Combined use of SSRIs and NSAIDs or low-dose aspirin increased
further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as
been associated with hallucinations in some patients (Prod Info TOR
oral tablets, 2007).

3.5.1.BE Fondaparinux

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for main
hemostasis. Case-control and cohort studies have shown that the combi
SSRIs and anticoagulants has been associated with an increased risk o
(Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info LEXAPRO(R
solution, 2008). Bleeding events reported have included epistaxis, ecchy

hematoma, petechiae, and life-threatening hemorrhages. Altered anticoa
(including increased bleeding) have been reported with the coadministra
with warfarin (Schalekamp et al, 2008; Prod Info LEXAPRO(R) oral table
2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When escitalopram and an anticoagulant are g
concurrently, monitor patients for signs of increased bleeding. Patients v
warfarin should be monitored closely for altered anticoagulant effects, in
increased bleeding, when escitalopram therapy is initiated or discontinue
LEXAPRO(R) oral tablets, solution, 2008).
7) Probable Mechanism: unknown
8) Literature Reports
a) According to a retrospective cohort study (n=234), there was an
of clinically relevant bleeding (hospital admission due to bleeding) ir
receiving warfarin for atrial fibrillation during concomitant SSRI thera
weeks following SSRI therapy termination. Patients with a mean ag
years receiving warfarin plus SSRI (n=117) were matched with rand
patients who received warfarin only (n=117). SSRI included fluoxeti
citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nin
experienced 11 bleeding episodes during 213.9 treatment years in t
plus SSRI group, and 10 patients experienced 14 bleedings during
treatment years in the warfarin-only group. The corresponding total
bleedings were 51.4 and 23.9 per 1000 treatment years, respectivel
ratio for first bleedings during treatment with warfarin plus SSRI was
CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI ir
patients experiencing bleeding at the time of concomitant administra
sertraline or citalopram. The addition of an SSRI was not associated
change in warfarin dose or INR (p=0.48 and p=0.31 respectively). T
the study may be limited by earlier bleeding events, unknown patier
and exclusion of clopidogrel, dipyridamol, corticosteroids and antico
other than warfarin in the model (Wallerstedt et al, 2009).
b) A population-based, case-controlled study of new coumarin user
(acenocoumarol and phenprocoumon) with concomitant selective se
reuptake inhibitors (SSRIs) resulted in an increased risk of hospitali
nongastrointestinal bleeding. Using national pharmacy and hospitali
records, Netherlands researchers identified 1848 cases that were a
abnormal bleeding and compared them with 5818 control subjects a
coumarins. Median duration of treatment in patients was 220 days (
4690 days). Patients on SSRIs showed greater risk for hospitalizatio
nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% cor
interval (CI), 1.1 to 2.5), however, the rate of gastrointestinal bleedir
OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schaleka
2008).

3.5.1.BF Frovatriptan
1) Interaction Effect: an increased risk of serotonin syndrome
2) Summary: There have been case reports of weakness, hyperreflexia
incoordination following concomitant use of sumatriptan, a 5-hydroxytryp
(5HT-1) agonist, and a serotonin specific reuptake inhibitor (SSRI) (Proc
(R) Nasal Spray, 2003). Because frovatriptan is a 5HT 1B/1D agonist, a
interaction between SSRIs and frovatriptan may occur (Prod Info Frova(
Concurrent use of frovatriptan and an SSRI may result in serotonin synd
may be life-threatening. Symptoms of serotonin syndrome may include r
hallucinations, loss of coordination, fast heart beat, rapid changes in blo
increased body temperature, overreactive reflexes, nausea, vomiting, ar
Clinicians should be aware that triptans may be commonly used intermit
either the triptan or the SSRI may be prescribed by a different physician.
risks of serotonin syndrome with patients who are prescribed this combi
monitor them closely for symptoms of serotonin syndrome (US Food and
Administration, 2006).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Coadministration of a triptan, such as frovatrip
SSRI may result in a life-threatening condition called serotonin syndrom

that triptans may be commonly used intermittently and that either the trip
SSRI may be prescribed by a different physician. If these agents are use
discuss the risks of serotonin syndrome with the patient and monitor clos
symptoms of serotonin syndrome (restlessness, hyperthermia, hyperrefl
incoordination).
7) Probable Mechanism: additive pharmacologic effects resulting in exc
serotonergic stimulation

3.5.1.BG Furazolidone

1) Interaction Effect: weakness, hyperreflexia, and incoordination
2) Summary: Although not its primary mechanism of action, furazolidon
monoamine oxidase inhibitor activity. Cases of serious sometimes fatal r
been reported in patients receiving selective serotonin reuptake inhibitor
combination with monoamine oxidase inhibitors (MAOIs). Hyperthermia,
myoclonus, autonomic instability with possible rapid fluctuations of vital s
mental status changes that include extreme agitation progressing to deli
coma have been reported. Furazolidone should not be used in combinat
SSRI, or within a minimum of 14 days of discontinuing therapy with a MA
Furoxone(R), 1999).
3) Severity: contraindicated
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: If concurrent therapy with furazolidone and a s
serotonin reuptake inhibitor (SSRI) is deemed to be necessary, closely r
patient for signs of serotonergic excess (mental status changes, diaphor
weakness, hyperreflexia, incoordination).
7) Probable Mechanism: additive pharmacologic effects resulting in exc
serotonergic stimulation

3.5.1.BH Ginkgo

1) Interaction Effect: increased risk of serotonin syndrome (hypertensio
hyperthermia, myoclonus, mental status changes)
2) Summary: The addition of Ginkgo biloba and/or St. John's Wort to th
buspirone and fluoxetine may have precipitated a hypomanic episode in
(Spinella & Eaton, 2002a). It is unclear if Ginkgo or St. John's Wort, the
both, or other patient factors, contributed to the effect. Theoretically, Gin
increase the risk of serotonin syndrome when taken with selective seroto
inhibitors (SSRIs). Caution is advised, especially when ginkgo is taken to
sexual dysfunction associated with SSRIs. Ginkgo may inhibit monoamin
(Sloley et al, 2000; White et al, 1996), and has demonstrated serotonerg
animals (Ramassamy et al, 1992) which might increase the risk of seroto
when ginkgo is combined with SSRIs. The potential MAO inhibitory activ
is questionable. A human study did not show MAO inhibition in the brain
consumption (Fowler et al, 2000). Ginkgo biloba extract inhibited MAO-A
the rat brain in vitro (Sloley et al, 2000; White et al, 1996) and MAO-B in
platelets in vitro (White et al, 1996). No significant MAO inhibition was fo
following oral consumption (Porsolt et al, 2000).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor patients closely for symptoms of seroto
if ginkgo is combined with selective serotonin reuptake inhibitors (SSRIs
7) Probable Mechanism: additive pharmacologic effects resulting in exc
serotonergic stimulation
8) Literature Reports
a) A 42-year-old female experienced symptoms consistent with a m
hypomanic episode following concomitant use of fluoxetine, buspiro
biloba, and St. John's Wort. The symptoms resolved following disco
Ginkgo and St. John's Wort. The patient was being treated for depre
following a mild traumatic brain injury with fluoxetine 20 milligrams (
daily and buspirone 15 mg twice daily. Several weeks prior to prese
buspirone was increased to 20 mg twice daily for persistent anxiety
patient began taking Ginkgo biloba, melatonin, and St. John's Wort
doses. Melatonin was considered unlikely to have contributed to her
Ginkgo and St. John's Wort were considered possible contributors s
potentiate antidepressants, and considering the temporal relationsh
the use of the herbs and onset of symptoms and discontinuation of

resolution of symptoms. However, the brain injury was considered a contributor (Spinella & Eaton, 2002).

3.5.1.BI Heparin

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maint hemostasis. Case-control and cohort studies have shown that the combi SSRIs and anticoagulants has been associated with an increased risk of (Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info LEXAPRO(R solution, 2008). Bleeding events reported have included epistaxis, ecchy hematoma, petechiae, and life-threatening hemorrhages. Altered anticoa (including increased bleeding) have been reported with the coadministra with warfarin (Schalekamp et al, 2008; Prod Info LEXAPRO(R) oral table 2008).

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When escitalopram and an anticoagulant are g concurrently, monitor patients for signs of increased bleeding. Patients v warfarin should be monitored closely for altered anticoagulant effects, in increased bleeding, when escitalopram therapy is initiated or discontinue LEXAPRO(R) oral tablets, solution, 2008).

7) Probable Mechanism: unknown

8) Literature Reports

a) According to a retrospective cohort study (n=234), there was an of clinically relevant bleeding (hospital admission due to bleeding) ir receiving warfarin for atrial fibrillation during concomitant SSRI thera weeks following SSRI therapy termination. Patients with a mean ag years receiving warfarin plus SSRI (n=117) were matched with ranc patients who received warfarin only (n=117). SSRI included fluoxeti citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nin experienced 11 bleeding episodes during 213.9 treatment years in t plus SSRI group, and 10 patients experienced 14 bleedings during 5 treatment years in the warfarin-only group. The corresponding total bleedings were 51.4 and 23.9 per 1000 treatment years, respectivel ratio for first bleedings during treatment with warfarin plus SSRI was CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI ir patients experiencing bleeding at the time of concomitant administra sertraline or citalopram. The addition of an SSRI was not associated change in warfarin dose or INR (p=0.48 and p=0.31 respectively). T the study may be limited by earlier bleeding events, unknown patier and exclusion of clopidogrel, dipyridamol, corticosteroids and antico other than warfarin in the model (Wallerstedt et al, 2009).

b) A population-based, case-controlled study of new coumarin user (acenocoumarol and phenprocoumon) with concomitant selective se reuptake inhibitors (SSRIs) resulted in an increased risk of hospitali nongastrointestinal bleeding. Using national pharmacy and hospitali records, Netherlands researchers identified 1848 cases that were a abnormal bleeding and compared them with 5818 control subjects a coumarins. Median duration of treatment in patients was 220 days (4690 days). Patients on SSRIs showed greater risk for hospitalizatio nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% cor interval (CI), 1.1 to 2.5), however, the rate of gastrointestinal bleedir OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schaleka 2008).

3.5.1.BJ Hydrocodone

1) Interaction Effect: an increased risk of serotonin syndrome (tachycard hyperthermia, myoclonus, mental status changes)

2) Summary: Coadministration of escitalopram and hydrocodone has re development of visual hallucinations in a 90-year-old woman. While no c symptoms suggestive of serotonin syndrome were reported for this patie symptoms such as visual hallucinations are usually reported less commo serotonin syndrome (approximately 10% of cases). Clinical symptoms of syndrome have been reported with concurrent use of escitalopram with c (Gnanadesigan et al, 2005). Caution is advised if escitalopram and hydr coadministered. Monitor patients for signs and symptoms of serotonin sy

(tachycardia, hyperthermia, myoclonus, mental status changes).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Concomitant administration of escitalopram an hydrocodone may increase the risk of developing serotonin syndrome. If are coadministered, monitor patients for symptoms of serotonin syndrom (tachycardia, hyperthermia, myoclonus, mental status changes).
7) Probable Mechanism: additive pharmacologic effects resulting in exc serotonergic stimulation
8) Literature Reports
a) Visual hallucinations developed in an 90-year-old woman followi administration of hydrocodone and escitalopram. The woman was b with hydrocodone and citalopram 10 mg/day. Citalopram was chang escitalopram 10 mg once daily and a few weeks later, the patient be experiencing visual hallucinations. Improvement in pain symptoms c hydrocodone to be subsequently discontinued. One month later, the hallucinations had resolved. Prior to escitalopram therapy, the patie treated with paroxetine and later, citalopram along with the same hy dose. However, this had not resulted in any hallucinations or any se syndrome-related symptoms (Gnanadesigan et al, 2005).

3.5.1.BK Hydroxytryptophan

1) Interaction Effect: an increased risk of serotonin syndrome (hyperten hyperthermia, myoclonus, mental status changes)
2) Summary: Hydroxytryptophan (5-HTP) may potentiate the serotonerg selective serotonin reuptake inhibitors (SSRIs) (Meltzer et al, 1997a). Si increases serotonin levels, when combined with an SSRI, the serotonin increased sufficiently to produce serotonin syndrome. Caution is advised concomitant use of 5-HTP and SSRIs.
3) Severity: moderate
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: No cases have been reported of serotonin syn resulting from this combination. Caution is advised if hydroxytryptophan selective serotonin reuptake inhibitor (SSRI) are used concomitantly. Mo patient for early signs of serotonin syndrome such as anxiety, confusion, disorientation.
7) Probable Mechanism: additive serotonergic effect
8) Literature Reports
a) Hydroxytryptophan (5-HTP) (200 milligrams (mg) orally) as a sin increased plasma cortisol and prolactin levels in both medicated and unmedicated patients with major depression or obsessive compulsiv (OCD). These responses were greater if the patient was also taking = 16) (p less than 0.0001). Mean fluoxetine dose for depressed pati mg/day,and for OCD patients it was 60 mg/day. Cortisol or prolactin in patients taking 5-HTP with tricyclic antidepressants (n = 14) or the no medication (n = 83) were not significantly different from each oth measurement of serotonergic effects of antidepressants can be eva measuring hypothalamic-pituitary-adrenal (HPA) axis or PRL respon clinical manifestations of serotonin syndrome were reported in patie HTP concomitantly with fluoxetine (Meltzer et al, 1997).

3.5.1.BL Ibuprofen

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for main hemostasis. Case-control and cohort studies have shown that the combi SSRIs and NSAIDs has been associated with an increased risk of bleed events have included epistaxis, ecchymosis, hematoma, petechiae, and threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, Info Lexapro(TM), 2003a; Dalton et al, 2003a; Prod Info CELEXA (R) ora solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concu monitor patient for signs of increased bleeding.

7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and th potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospi upper gastrointestinal bleeding were searched among 26,005 users antidepressant medications and compared with the number of hosp those patients who did not receive prescriptions for antidepressants of upper GI bleeding episodes was 3.6 times more than expected (9 confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSA dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of demonstrate an increased risk of upper GI bleeding during the use Combined use of SSRIs and NSAIDs or low-dose aspirin increased further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as been associated with hallucinations in some patients (Prod Info TOR oral tablets, 2007).

3.5.1.BM Iloprost
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for main hemostasis. Case-control and cohort studies have shown that the combi SSRIs and antiplatelet agents has been associated with an increased ris Bleeding events reported have included epistaxis, ecchymosis, hematon and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, susp Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an antiplatelet agent are g concurrently, monitor patient for signs of increased bleeding (Prod Info F tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed capsules, solution, 2008)
7) Probable Mechanism: unknown

3.5.1.BN Indomethacin
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for main hemostasis. Case-control and cohort studies have shown that the combi SSRIs and NSAIDs has been associated with an increased risk of bleed events have included epistaxis, ecchymosis, hematoma, petechiae, and threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, Info Lexapro(TM), 2003a; Dalton et al, 2003a; Prod Info CELEXA (R) ora solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concu monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and th potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospi upper gastrointestinal bleeding were searched among 26,005 users antidepressant medications and compared with the number of hosp those patients who did not receive prescriptions for antidepressants of upper GI bleeding episodes was 3.6 times more than expected (9 confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSA dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of demonstrate an increased risk of upper GI bleeding during the use Combined use of SSRIs and NSAIDs or low-dose aspirin increased further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as been associated with hallucinations in some patients (Prod Info TOR oral tablets, 2007).

3.5.1.BO Indoprofen

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for main hemostasis. Case-control and cohort studies have shown that the combi SSRIs and NSAIDs has been associated with an increased risk of bleed events have included epistaxis, ecchymosis, hematoma, petechiae, and threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, Info Lexapro(TM), 2003a; Dalton et al, 2003a; Prod Info CELEXA (R) ora solution, 2005).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an NSAID are given concu monitor patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and th potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospi upper gastrointestinal bleeding were searched among 26,005 users antidepressant medications and compared with the number of hosp those patients who did not receive prescriptions for antidepressants of upper GI bleeding episodes was 3.6 times more than expected (9 confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSA dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of demonstrate an increased risk of upper GI bleeding during the use Combined use of SSRIs and NSAIDs or low-dose aspirin increased further (Dalton et al, 2003).

b) Coadministration of ketorolac with psychoactive drugs (such as been associated with hallucinations in some patients (Prod Info TOR oral tablets, 2007).

3.5.1.BP Isocarboxazid

1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, myoclonus, mental status changes)

2) Summary: Concurrent administration or overlapping therapy with esc a monoamine oxidase (MAO) inhibitor may result in CNS toxicity or sero syndrome, a hyperserotonergic state characterized by symptoms such a restlessness, myoclonus, changes in mental status, hyperreflexia, diaph shivering, and tremor. Serious, even fatal, reactions have been reported Lexapro(TM), 2002a). Concomitant use is contraindicated.

3) Severity: contraindicated

4) Onset: rapid

5) Substantiation: theoretical

6) Clinical Management: Concurrent use of escitalopram and isocarbox contraindicated. Wait at least two weeks after discontinuing a MAO inhib initiating escitalopram therapy. In addition, wait at least five weeks after escitalopram before initiating therapy with a MAO inhibitor.

7) Probable Mechanism: inhibition of serotonin metabolism by monoam

3.5.1.BQ Isoxicam

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for main hemostasis. Case-control and cohort studies have shown that the combi SSRIs and NSAIDs has been associated with an increased risk of bleed events have included epistaxis, ecchymosis, hematoma, petechiae, and threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, Info Lexapro(TM), 2003a; Dalton et al, 2003a; Prod Info CELEXA (R) ora solution, 2005).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an NSAID are given concu monitor patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and th

potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospi
upper gastrointestinal bleeding were searched among 26,005 users
antidepressant medications and compared with the number of hosp
those patients who did not receive prescriptions for antidepressants
of upper GI bleeding episodes was 3.6 times more than expected (9
confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSA
dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1
5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of
demonstrate an increased risk of upper GI bleeding during the use
Combined use of SSRIs and NSAIDs or low-dose aspirin increased
further (Dalton et al, 2003).

b) Coadministration of ketorolac with psychoactive drugs (such as
been associated with hallucinations in some patients (Prod Info TOF
oral tablets, 2007).

3.5.1.BR Ketoconazole

1) Interaction Effect: decreased ketoconazole bioavailability

2) Summary: Concomitant administration of escitalopram 40 milligrams
ketoconazole 200 mg induced reductions in ketoconazole maximum plas
concentrations and area under the concentration-time curve by 21% and
respectively; escitalopram pharmacokinetics were unaffected by coadmi
(Prod Info LEXAPRO(R) Oral Tablet, Oral Solution, 2005).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: If concurrent therapy is required, a dosage adj
be required for ketoconazole in order to achieve and maintain a consiste
effect.

7) Probable Mechanism: unknown

3.5.1.BS Ketoprofen

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for main
hemostasis. Case-control and cohort studies have shown that the combi
SSRIs and NSAIDs has been associated with an increased risk of bleed
events have included epistaxis, ecchymosis, hematoma, petechiae, and
threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension,
Info Lexapro(TM), 2003a; Dalton et al, 2003a; Prod Info CELEXA (R) ora
solution, 2005).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an NSAID are given concu
monitor patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and th
potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospi
upper gastrointestinal bleeding were searched among 26,005 users
antidepressant medications and compared with the number of hosp
those patients who did not receive prescriptions for antidepressants
of upper GI bleeding episodes was 3.6 times more than expected (9
confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSA
dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1
5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of
demonstrate an increased risk of upper GI bleeding during the use
Combined use of SSRIs and NSAIDs or low-dose aspirin increased
further (Dalton et al, 2003).

b) Coadministration of ketorolac with psychoactive drugs (such as
been associated with hallucinations in some patients (Prod Info TOF
oral tablets, 2007).

3.5.1.BT Ketorolac

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for main
hemostasis. Case-control and cohort studies have shown that the combi
SSRIs and NSAIDs has been associated with an increased risk of bleed

events have included epistaxis, ecchymosis, hematoma, petechiae, and threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, Info Lexapro(TM), 2003a; Dalton et al, 2003a; Prod Info CELEXA (R) ora solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concu monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and th potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospi upper gastrointestinal bleeding were searched among 26,005 users antidepressant medications and compared with the number of hosp those patients who did not receive prescriptions for antidepressants of upper GI bleeding episodes was 3.6 times more than expected (9 confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSA dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of demonstrate an increased risk of upper GI bleeding during the use Combined use of SSRIs and NSAIDs or low-dose aspirin increased further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as been associated with hallucinations in some patients (Prod Info TOR oral tablets, 2007).

3.5.1.BU Lamifiban

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for main hemostasis. Case-control and cohort studies have shown that the combi SSRIs and antiplatelet agents has been associated with an increased ris Bleeding events reported have included epistaxis, ecchymosis, hematon and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, susp Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an antiplatelet agent are g concurrently, monitor patient for signs of increased bleeding (Prod Info P tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed capsules, solution, 2008)
7) Probable Mechanism: unknown

3.5.1.BV Lamotrigine

1) Interaction Effect: an increased risk of myoclonus
2) Summary: Myoclonus occurred in 2 patients receiving escitalopram a lamotrigine concomitantly, where symptoms resolved following withdraw escitalopram in 1 patient. There was no evidence of a metabolic enzyme with lamotrigine, and the interaction was believed to be due to an additiv effect of lamotrigine and escitalopram on the 5-HT1A receptors, or by ar inhibition of voltage-gated calcium channels by both agents (Rosenhage Exercise caution when using both drugs concurrently and monitor for sig symptoms of myoclonus including involuntary twitching and jerking.
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Use caution if escitalopram and lamotrigine are concurrently as this resulted in myoclonus in 2 patients. In one patient, n resolved after escitalopram was withdrawn (Rosenhagen et al, 2006). M signs and symptoms of myoclonus including involuntary twitching and je
7) Probable Mechanism: additive inhibition of voltage-gated calcium cha additive or synergistic effects on the 5-HT1A receptor
8) Literature Reports
a) Myoclonus occurred in 2 patients following concomitant treatmer escitalopram and lamotrigine. The first patient, a 22-year-old woma escitalopram 30 mg/day for depression, developed daytime and nig

myoclonus after 8 weeks of receiving lamotrigine (titrated to 100 mg treatment of bipolar type II disorder. Serum levels of both drugs, me the onset of myoclonus, were within the expected drug reference ra escitalopram levels remained stable compared to a baseline level d starting lamotrigine therapy. Neither drug was discontinued and the continued to have myoclonus while on escitalopram and lamotrigine Further analysis revealed that the patient was a normal metabolizer CYP2C19, and CYP2D6 enzymes. The second patient, a 28-year-o taking lamotrigine 300 mg/day for a seizure disorder, developed day nighttime myoclonus after 2 weeks of receiving escitalopram (titrate mg/day) for generalized anxiety disorder. For 6 months, the patient the same frequency of myoclonus while on both therapies; however myoclonus resolved 2 weeks after escitalopram was withdrawn. Lar serum levels, measured at the onset and after the myoclonus resolv change. Although escitalopram is metabolized by hepatic enzymes CYP2C19, and CYP2D6, there was no evidence of a metabolic enz interaction with lamotrigine. It was postulated that the myoclonus ma caused by an additive or synergistic effect of lamotrigine and escital 5-HT1A receptors, or by an additive inhibition of voltage-gated calci by both agents (Rosenhagen et al, 2006).

3.5.1.BW Lazabemide

1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, myoclonus, mental status changes)

2) Summary: Concurrent administration or overlapping therapy with esc a monoamine oxidase (MAO) inhibitor may result in CNS toxicity or sero syndrome, a hyperserotonergic state characterized by symptoms such a restlessness, myoclonus, changes in mental status, hyperreflexia, diaph shivering, and tremor. Serious, even fatal, reactions have been reported Lexapro(TM), 2002d). Concomitant use is contraindicated.

3) Severity: contraindicated

4) Onset: rapid

5) Substantiation: theoretical

6) Clinical Management: Concurrent use of escitalopram and lazabemic contraindicated. Wait at least two weeks after discontinuing a MAO inhib initiating escitalopram therapy. In addition, wait at least five weeks after escitalopram before initiating therapy with a MAO inhibitor.

7) Probable Mechanism: inhibition of serotonin metabolism by monoam

3.5.1.BX Lexipafant

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maint hemostasis. Case-control and cohort studies have shown that the combi SSRIs and antiplatelet agents has been associated with an increased ris Bleeding events reported have included epistaxis, ecchymosis, hematon and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, susp Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an antiplatelet agent are g concurrently, monitor patient for signs of increased bleeding (Prod Info P tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed capsules, solution, 2008)

7) Probable Mechanism: unknown

3.5.1.BY Linezolid

1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, myoclonus, mental status changes)

2) Summary: Linezolid is a reversible, nonselective inhibitor of monoam Concurrent administration or overlapping therapy with escitalopram and oxidase (MAO) inhibitor may result in CNS toxicity or serotonin syndrom hyperserotonergic state characterized by symptoms such as restlessnes changes in mental status, hyperreflexia, diaphoresis, shivering, and trem even fatal, reactions have been reported. There have been spontaneous serotonin syndrome associated with concomitant use of linezolid and se agents (Prod Info ZYVOX(R) IV injection, oral tablets, oral suspension, 2

Info Lexapro(R), 2002). If escitalopram and linezolid are used concomita
closely for symptoms of serotonin syndrome. Serotonin syndrome can b
threatening. If serotonin syndrome develops, discontinue the offending a
provide supportive care and other therapy as necessary (Boyer & Shanr
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Unless carefully monitored for serotonin syndr
should not be administered to patients taking escitalopram (Prod Info ZY
injection, oral tablets, oral suspension, 2008) If escitalopram and linezoli
concomitantly, monitor closely for symptoms of serotonin syndrome such
neuromuscular abnormalities (including hyper-reflexia, tremor, muscle ri
peripheral hypertonicity, and shivering), autonomic hyperactivity (includi
tachycardia, mydriasis, diaphoresis, and diarrhea), and mental status ch
(including agitation and delirium). Serotonin syndrome can be life-threate
serotonin syndrome develops, discontinue the offending agents and pro
supportive care and other therapy as necessary (Boyer & Shannon, 200
7) Probable Mechanism: inhibition of serotonin metabolism by monoam

3.5.1.BZ Lithium

1) Interaction Effect: possible increased lithium concentrations and/or a
risk of SSRI-related serotonin syndrome (hypertension, hyperthermia, m
mental status changes)
2) Summary: Concomitant use of lithium and various SSRIs has been a
enhanced side effects of either or both drugs, and with or without elevat
levels. The combination has resulted in neurotoxicity and increased lithi
one case report (Salama & Shafey, 1989a). Signs and symptoms of lithi
and serotonin syndrome have also been reported in patients who demor
therapeutic serum lithium levels while on concurrent fluoxetine and lithiu
1993a; Noveske et al, 1989a). Two studies have failed to identify a phar
interaction between lithium and citalopram (Gram et al, 1993a; Baumann
1996a). Combined administration of citalopram (40 mg daily for 10 days)
(30 mmol/day for 5 days) had no significant effect on the pharmacokinet
citalopram or lithium. However, plasma lithium levels should be monitore
appropriate adjustment to the lithium dose in accordance with standard c
practice. Lithium may enhance the serotonergic effects of citalopram, the
caution should be exercised when citalopram and lithium are coadminist
Info Celexa(R), 2004). Concurrent use of fluvoxamine and lithium has le
reports of increased lithium levels and neurotoxicity, serotonin syndrome
somnolence, and mania (Salama & Shafey, 1989a; Ohman & Spigset, 1
& Marwick, 1990; Burrai et al, 1991a). No pharmacokinetic interference
during a multiple-dose study of coadministered lithium and paroxetine (P
CR(TM), 2003). If these two agents are to be given concomitantly, the m
suggests that caution be used until more clinical experience is available.
interactions leading to lithium toxicity have been reported when lithium w
coadministered with fluoxetine and fluvoxamine (both in the same pharm
class as paroxetine, eg, selective serotonin reuptake inhibitors) (Ohman
1993a; Salama & Shafey, 1989a).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: established
6) Clinical Management: Monitor patients on concurrent lithium and sele
serotonin reuptake inhibitor therapy for increased plasma concentrations
addition, monitor patients for signs and symptoms associated with seroto
(hypertension, hyperthermia, myoclonus, mental status changes).
7) Probable Mechanism: unknown
8) Literature Reports
a) Concomitant administration of oral lithium carbonate and oral flu
resulted in increased lithium serum levels with lithium toxicity in a 4
woman with a bipolar affective disorder (Salama & Shafey, 1989). F
mg daily was added to a regimen of lithium 1200 mg daily following
complaints of weakness, tiredness, decreased concentration, and e
awakening. Lithium serum levels increased to 1.7 mEq/L from a ran
1.15 mEq/L prior to fluoxetine. Fluoxetine was discontinued and the
lithium decreased; this resulted in a decrease in the lithium serum le
hours to 1.2 mEq/L. The neurologic symptoms subsided within seve
lithium serum level decreased to 0.9 mEq/L. The contribution of fluo

lithium toxicity in this patient was obscured by the fact that the lithiu
reduced at the time of fluoxetine withdrawal.
b) A 53-year old woman who had been taking fluoxetine 20 mg dail
lorazepam 0.5 mg four times daily for a major depressive disorder h
mg per day added to her regimen in order to augment her response
Within 48 hours, the patient became confused, ataxic, and develope
tremor in her right arm. Vital signs showed a rectal temperature of 1
and laboratory values were normal except for an elevated leukocyte
slightly elevated bilirubin level. After discontinuation of lithium and fl
patient's symptoms resolved over the next four days. At no point dic
levels reach a toxic level, suggesting that the patient's symptoms w
toxic reaction between fluoxetine and lithium (Noveske et al, 1989).
c) Serotonin syndrome was precipitated when lithium 300 mg twice
added to a three-month regimen of fluoxetine 40 mg per day. Five d
patient's lithium level was measured at 0.65 mEq/L and the dose wa
to 300 mg three times daily. Two days after this dosage change, the
experienced akathisia, myoclonus, hyperreflexia, shivering, tremor,
incoordination. After discontinuation of lithium and initiation of cypro
therapy, the patient's symptoms began to improve. The patient was
on a regimen of fluoxetine 40 mg per day without further symptoms
syndrome (Muly et al, 1993).
d) Eight healthy male volunteers completed three phases of an inte
to determine the effects of coadministered lithium and citalopram. A
were extensive metabolizers of sparteine, indicating normal cytochr
2D6 enzyme activity. Although lithium is not influenced by drug oxid
citalopram metabolites are excreted by the kidney, as is lithium. Eac
received citalopram 40 mg alone as a single daily dose for 10 days,
mmol (1980 mg) alone daily for five days, and lithium coadministere
citalopram on days 3-7. At least two weeks separated each treatme
Results showed that the concurrent administration of citalopram and
not significantly alter the pharmacokinetics of lithium (Gram et al, 19
e) Twenty-four patients experiencing depression (DSM III criteria) v
randomized under double-blind conditions to receive citalopram (40
daily) and lithium carbonate (800 mg daily) or placebo. All of the sub
failed to respond to four weeks of citalopram monotherapy. Lithium
coadministered on days 29 to 42. No evidence of a pharmacokinetic
between lithium and citalopram was noted, and cotherapy was well
(Baumann et al, 1996).
f) Serotonin syndrome was described in a 53-year-old patient who
on lithium 1400 mg daily (serum level 0.71 mmol/L) and was given f
50 mg daily. Over a 10-day period the fluvoxamine dose was increa
daily; tremor and difficulty with fine hand movements developed. Aft
tremor, impaired motor function coordination, marked bilateral hype
biceps and knee jerks, and clonus in both ankles were seen. After 1
continued therapy, during which time no further deterioration occurr
nortriptyline 100 mg daily replaced fluvoxamine, and the neuromusc
symptoms abated over a 2-week period. After four weeks the patier
neurological exam was normal (Ohman & Spigset, 1993).
g) Three cases of mania were reported in patients who were treate
and fluvoxamine. The mania appeared 10 days, four weeks, and fiv
respectively, after cotherapy was begun. Fluvoxamine was discontir
two of the three patients, the mania resolved, and successful treatm
depression occurred with lithium alone. The third patient improved,
depression reappeared within a month of fluvoxamine discontinuatic
al, 1991).
h) In an open-labeled, placebo-controlled study, lithium 600 mg wa
administered to 16 subjects orally twice daily on days one through e
in the morning on day nine. In addition, oral sertraline 100 mg or pla
given twice, ten hours and two hours prior to lithium dosing on day r
steady-state lithium level was only decreased by 1.4% (0.01 mEq/L)
lithium renal clearance increased by 6.9% (0.11 L/hour) when sertra
coadministered. Seven subjects experienced side effects, mainly tre
receiving lithium and sertraline, whereas no subjects who ingested p
lithium experienced side effects (Wilner et al, 1991).

3.5.1.CA Lornoxicam

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maint
hemostasis. Case-control and cohort studies have shown that the combi
SSRIs and NSAIDs has been associated with an increased risk of bleed
events have included epistaxis, ecchymosis, hematoma, petechiae, and
threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension,
Info Lexapro(TM), 2003a; Dalton et al, 2003a; Prod Info CELEXA (R) ora
solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concu
monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and th
potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospi
upper gastrointestinal bleeding were searched among 26,005 users
antidepressant medications and compared with the number of hosp
those patients who did not receive prescriptions for antidepressants
of upper GI bleeding episodes was 3.6 times more than expected (9
confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSA
dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1
5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of
demonstrate an increased risk of upper GI bleeding during the use
Combined use of SSRIs and NSAIDs or low-dose aspirin increased
further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as
been associated with hallucinations in some patients (Prod Info TOF
oral tablets, 2007).

3.5.1.CB Meclofenamate

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maint
hemostasis. Case-control and cohort studies have shown that the combi
SSRIs and NSAIDs has been associated with an increased risk of bleed
events have included epistaxis, ecchymosis, hematoma, petechiae, and
threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension,
Info Lexapro(TM), 2003a; Dalton et al, 2003a; Prod Info CELEXA (R) ora
solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concu
monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and th
potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospi
upper gastrointestinal bleeding were searched among 26,005 users
antidepressant medications and compared with the number of hosp
those patients who did not receive prescriptions for antidepressants
of upper GI bleeding episodes was 3.6 times more than expected (9
confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSA
dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1
5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of
demonstrate an increased risk of upper GI bleeding during the use
Combined use of SSRIs and NSAIDs or low-dose aspirin increased
further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as
been associated with hallucinations in some patients (Prod Info TOF
oral tablets, 2007).

3.5.1.CC Mefenamic Acid

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maint
hemostasis. Case-control and cohort studies have shown that the combi
SSRIs and NSAIDs has been associated with an increased risk of bleed

events have included epistaxis, ecchymosis, hematoma, petechiae, and threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, Info Lexapro(TM), 2003a; Dalton et al, 2003a; Prod Info CELEXA (R) ora solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concu monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and th potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospi upper gastrointestinal bleeding were searched among 26,005 users antidepressant medications and compared with the number of hosp those patients who did not receive prescriptions for antidepressants of upper GI bleeding episodes was 3.6 times more than expected (9 confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSA dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of demonstrate an increased risk of upper GI bleeding during the use Combined use of SSRIs and NSAIDs or low-dose aspirin increased further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as been associated with hallucinations in some patients (Prod Info TOF oral tablets, 2007).

3.5.1.CD Meloxicam

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for main hemostasis. Case-control and cohort studies have shown that the combi SSRIs and NSAIDs has been associated with an increased risk of bleed events have included epistaxis, ecchymosis, hematoma, petechiae, and threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, Info Lexapro(TM), 2003a; Dalton et al, 2003a; Prod Info CELEXA (R) ora solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concu monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and th potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospi upper gastrointestinal bleeding were searched among 26,005 users antidepressant medications and compared with the number of hosp those patients who did not receive prescriptions for antidepressants of upper GI bleeding episodes was 3.6 times more than expected (9 confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSA dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of demonstrate an increased risk of upper GI bleeding during the use Combined use of SSRIs and NSAIDs or low-dose aspirin increased further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as been associated with hallucinations in some patients (Prod Info TOF oral tablets, 2007).

3.5.1.CE Methylphenidate

1) Interaction Effect: increased selective serotonin reuptake inhibitor pla concentrations
2) Summary: Human pharmacologic studies have demonstrated that me may inhibit the metabolism of selective serotonin reuptake inhibitors (SS Downward dose adjustments of the SSRI may be necessary when it is u concurrently with methylphenidate. Additionally, when initiating or discor methylphenidate, the SSRI dose may need to be adjusted as needed (P

METADATE CD(R) extended-release oral capsules, 2007).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Use caution when prescribing methylphenidate who take an selective serotonin reuptake inhibitor (SSRI). Concomitant u methylphenidate and an SSRI may cause elevated SSRI plasma concer Consider a decrease in the dose of SSRI when these agents are coadm Additionally, consider adjusting the SSRI dose if necessary when initiatir discontinuing methylphenidate therapy (Prod Info METADATE CD(R) ex release oral capsules, 2007).
7) Probable Mechanism: inhibition of selective serotonin reuptake inhibi metabolism by methylphenidate

3.5.1.CF Metoprolol
1) Interaction Effect: increased metoprolol plasma concentrations and p metoprolol cardioselectivity
2) Summary: Administration of a single dose of metoprolol 100 milligran following administration of escitalopram 20 mg daily for 21 days produce 50% and 82% in metoprolol maximum plasma concentrations and area u concentration-time curve, respectively. No clinically significant changes i pressure or heart rate were observed; however, increased metoprolol pl have been associated with decreased cardioselectivity (Prod Info LEXAI Tablet, Oral Solution, 2005).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Patients stabilized on metoprolol who are adm escitalopram should be observed for signs of increased beta blockade s bradycardia, hypotension or heart failure. At higher metoprolol concentra cardioselectivity may be diminished; monitor appropriate measures of di when escitalopram and metoprolol are used concomitantly.
7) Probable Mechanism: unknown

3.5.1.CG Milnacipran
1) Interaction Effect: increased risk of serotonin syndrome (hypertensio hyperthermia, myoclonus, mental status changes)
2) Summary: Concurrent use of milnacipran and an SSRI or a serotonir norepinephrine reuptake inhibitor (SNRI) may result in hypertension, cor vasoconstriction or serotonin syndrome, which may be life-threatening. S serotonin syndrome may include restlessness, hallucinations, loss of coo heart beat, rapid changes in blood pressure, increased body temperatur overreactive reflexes, nausea, vomiting, and diarrhea (Prod Info SAVEL tablets, 2009).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of milnacipran and an SSRI o norepinephrine reuptake inhibitor (SNRI) may result in hypertension and artery vasoconstriction through the additive serotonergic effects. If these used together, discuss the risks of serotonin syndrome with the patient a closely for symptoms of serotonin syndrome (restlessness, hyperthermia hyperreflexia, incoordination), especially during treatment initiation and o increases (Prod Info SAVELLA(R) oral tablets, 2009).
7) Probable Mechanism: additive serotonergic effect

3.5.1.CH Moclobemide
1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, myoclonus, mental status changes)
2) Summary: Concurrent administration or overlapping therapy with esc a monoamine oxidase (MAO) inhibitor may result in CNS toxicity or sero syndrome, a hyperserotonergic state characterized by symptoms such a restlessness, myoclonus, changes in mental status, hyperreflexia, diaph shivering, and tremor. Serious, even fatal, reactions have been reported Lexapro(TM), 2002e). Concomitant use is contraindicated.
3) Severity: contraindicated
4) Onset: rapid

5) Substantiation: theoretical
6) Clinical Management: Concurrent use of escitalopram and moclobem contraindicated. Wait at least two weeks after discontinuing a MAO inhib initiating escitalopram therapy. In addition, wait at least five weeks after escitalopram before initiating therapy with a MAO inhibitor.
7) Probable Mechanism: inhibition of serotonin metabolism by monoam

3.5.1.CI Morniflumate

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for main hemostasis. Case-control and cohort studies have shown that the combi SSRIs and NSAIDs has been associated with an increased risk of bleed events have included epistaxis, ecchymosis, hematoma, petechiae, and threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, Info Lexapro(TM), 2003a; Dalton et al, 2003a; Prod Info CELEXA (R) ora solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concu monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and th potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospi upper gastrointestinal bleeding were searched among 26,005 users antidepressant medications and compared with the number of hosp those patients who did not receive prescriptions for antidepressants of upper GI bleeding episodes was 3.6 times more than expected (9 confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSA dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of demonstrate an increased risk of upper GI bleeding during the use Combined use of SSRIs and NSAIDs or low-dose aspirin increased further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as been associated with hallucinations in some patients (Prod Info TOF oral tablets, 2007).

3.5.1.CJ Nabumetone

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for main hemostasis. Case-control and cohort studies have shown that the combi SSRIs and NSAIDs has been associated with an increased risk of bleed events have included epistaxis, ecchymosis, hematoma, petechiae, and threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, Info Lexapro(TM), 2003a; Dalton et al, 2003a; Prod Info CELEXA (R) ora solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concu monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and th potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospi upper gastrointestinal bleeding were searched among 26,005 users antidepressant medications and compared with the number of hosp those patients who did not receive prescriptions for antidepressants of upper GI bleeding episodes was 3.6 times more than expected (9 confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSA dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of demonstrate an increased risk of upper GI bleeding during the use Combined use of SSRIs and NSAIDs or low-dose aspirin increased further (Dalton et al, 2003).

b) Coadministration of ketorolac with psychoactive drugs (such as t
been associated with hallucinations in some patients (Prod Info TOF
oral tablets, 2007).

3.5.1.CK Nadroparin

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maint
hemostasis. Case-control and cohort studies have shown that the combi
SSRIs and anticoagulants has been associated with an increased risk of
(Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info LEXAPRO(R
solution, 2008). Bleeding events reported have included epistaxis, ecchy
hematoma, petechiae, and life-threatening hemorrhages. Altered anticoa
(including increased bleeding) have been reported with the coadministra
with warfarin (Schalekamp et al, 2008; Prod Info LEXAPRO(R) oral table
2008).

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When escitalopram and an anticoagulant are g
concurrently, monitor patients for signs of increased bleeding. Patients v
warfarin should be monitored closely for altered anticoagulant effects, in
increased bleeding, when escitalopram therapy is initiated or discontinue
LEXAPRO(R) oral tablets, solution, 2008).

7) Probable Mechanism: unknown

8) Literature Reports

a) According to a retrospective cohort study (n=234), there was an
of clinically relevant bleeding (hospital admission due to bleeding) in
receiving warfarin for atrial fibrillation during concomitant SSRI thera
weeks following SSRI therapy termination. Patients with a mean age
years receiving warfarin plus SSRI (n=117) were matched with rand
patients who received warfarin only (n=117). SSRI included fluoxeti
citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nin
experienced 11 bleeding episodes during 213.9 treatment years in t
plus SSRI group, and 10 patients experienced 14 bleedings during 5
treatment years in the warfarin-only group. The corresponding total
bleedings were 51.4 and 23.9 per 1000 treatment years, respectivel
ratio for first bleedings during treatment with warfarin plus SSRI was
CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI in
patients experiencing bleeding at the time of concomitant administra
sertraline or citalopram. The addition of an SSRI was not associated
change in warfarin dose or INR (p=0.48 and p=0.31 respectively). T
the study may be limited by earlier bleeding events, unknown patien
and exclusion of clopidogrel, dipyridamol, corticosteroids and antico
other than warfarin in the model (Wallerstedt et al, 2009).

b) A population-based, case-controlled study of new coumarin user
(acenocoumarol and phenprocoumon) with concomitant selective se
reuptake inhibitors (SSRIs) resulted in an increased risk of hospitali
nongastrointestinal bleeding. Using national pharmacy and hospitali
records, Netherlands researchers identified 1848 cases that were a
abnormal bleeding and compared them with 5818 control subjects a
coumarins. Median duration of treatment in patients was 220 days (
4690 days). Patients on SSRIs showed greater risk for hospitalizatio
nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% cor
interval (CI), 1.1 to 2.5), however, the rate of gastrointestinal bleedi
OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schaleka
2008).

3.5.1.CL Naproxen

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maint
hemostasis. Case-control and cohort studies have shown that the combi
SSRIs and NSAIDs has been associated with an increased risk of bleed
events have included epistaxis, ecchymosis, hematoma, petechiae, and
threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension,
Info Lexapro(TM), 2003a; Dalton et al, 2003a; Prod Info CELEXA (R) ora
solution, 2005).

3) Severity: moderate

4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concu
monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and th
potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospi
upper gastrointestinal bleeding were searched among 26,005 users
antidepressant medications and compared with the number of hosp
those patients who did not receive prescriptions for antidepressants
of upper GI bleeding episodes was 3.6 times more than expected (9
confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSA
dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1
5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of
demonstrate an increased risk of upper GI bleeding during the use
Combined use of SSRIs and NSAIDs or low-dose aspirin increased
further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as
been associated with hallucinations in some patients (Prod Info TOF
oral tablets, 2007).

3.5.1.CM Naratriptan
1) Interaction Effect: an increased risk of serotonin syndrome
2) Summary: Rare incidences of weakness, hyperreflexia, and incoordi
been reported with the concurrent use of a selective serotonin reuptake
(SSRI) and a 5-hydroxytryptamine-1 (5HT-1) agonist (Prod Info Amerge
Concurrent use of a triptan and an SSRI may result in serotonin syndron
be life-threatening. Symptoms of serotonin syndrome may include restle
hallucinations, loss of coordination, fast heart beat, rapid changes in blo
increased body temperature, overreactive reflexes, nausea, vomiting, ar
Clinicians should be aware that triptans may be commonly used intermit
either the triptan or the SSRI may be prescribed by a different physician.
risks of serotonin syndrome with patients who are prescribed this combi
monitor them closely for symptoms of serotonin syndrome (US Food and
Administration, 2006).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Coadministration of a triptan, such as naratript
SSRI may result in a life-threatening condition called serotonin syndrom
that triptans may be commonly used intermittently and that either the trip
SSRI may be prescribed by a different physician. If these agents are use
discuss the risks of serotonin syndrome with the patient and monitor clos
symptoms of serotonin syndrome (restlessness, hyperthermia, hyperrefl
incoordination).
7) Probable Mechanism: additive pharmacologic effects resulting in exc
serotonergic stimulation

3.5.1.CN Niflumic Acid
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for main
hemostasis. Case-control and cohort studies have shown that the combi
SSRIs and NSAIDs has been associated with an increased risk of bleed
events have included epistaxis, ecchymosis, hematoma, petechiae, and
threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension,
Info Lexapro(TM), 2003a; Dalton et al, 2003a; Prod Info CELEXA (R) ora
solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concu
monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and th
potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospi

upper gastrointestinal bleeding were searched among 26,005 users antidepressant medications and compared with the number of hosp those patients who did not receive prescriptions for antidepressants of upper GI bleeding episodes was 3.6 times more than expected (9 confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSA dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of demonstrate an increased risk of upper GI bleeding during the use Combined use of SSRIs and NSAIDs or low-dose aspirin increased further (Dalton et al, 2003).

b) Coadministration of ketorolac with psychoactive drugs (such as been associated with hallucinations in some patients (Prod Info TOF oral tablets, 2007).

3.5.1.CO Nimesulide

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for main hemostasis. Case-control and cohort studies have shown that the combi SSRIs and NSAIDs has been associated with an increased risk of bleed events have included epistaxis, ecchymosis, hematoma, petechiae, and threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, Info Lexapro(TM), 2003a; Dalton et al, 2003a; Prod Info CELEXA (R) ora solution, 2005).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an NSAID are given concu monitor patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and th potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospi upper gastrointestinal bleeding were searched among 26,005 users antidepressant medications and compared with the number of hosp those patients who did not receive prescriptions for antidepressants of upper GI bleeding episodes was 3.6 times more than expected (9 confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSA dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of demonstrate an increased risk of upper GI bleeding during the use Combined use of SSRIs and NSAIDs or low-dose aspirin increased further (Dalton et al, 2003).

b) Coadministration of ketorolac with psychoactive drugs (such as been associated with hallucinations in some patients (Prod Info TOF oral tablets, 2007).

3.5.1.CP Oxaprozin

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for main hemostasis. Case-control and cohort studies have shown that the combi SSRIs and NSAIDs has been associated with an increased risk of bleed events have included epistaxis, ecchymosis, hematoma, petechiae, and threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, Info Lexapro(TM), 2003a; Dalton et al, 2003a; Prod Info CELEXA (R) ora solution, 2005).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an NSAID are given concu monitor patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and th potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospi upper gastrointestinal bleeding were searched among 26,005 users antidepressant medications and compared with the number of hosp those patients who did not receive prescriptions for antidepressants

of upper GI bleeding episodes was 3.6 times more than expected (9
confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSA
dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1
5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of
demonstrate an increased risk of upper GI bleeding during the use
Combined use of SSRIs and NSAIDs or low-dose aspirin increased
further (Dalton et al, 2003).

b) Coadministration of ketorolac with psychoactive drugs (such as
been associated with hallucinations in some patients (Prod Info TOI
oral tablets, 2007).

3.5.1.CQ Oxycodone

1) Interaction Effect: an increased risk of serotonin syndrome (tachycar
hyperthermia, myoclonus, mental status changes)

2) Summary: Coadministration of oxycodone and escitalopram resulted
development of serotonin syndrome in an 88-year-old woman (Gnanade
2005). Caution is advised if escitalopram and oxycodone are coadminist
patients for signs and symptoms of serotonin syndrome (tachycardia, hy
myoclonus, mental status changes).

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Concomitant administration of escitalopram an
may increase the risk of developing serotonin syndrome. If these agents
coadministered, monitor patients for symptoms of serotonin syndrome (t
hyperthermia, myoclonus, mental status changes).

7) Probable Mechanism: additive pharmacologic effects resulting in exc
serotonergic stimulation

8) Literature Reports

a) Symptoms of serotonin syndrome developed in an 88-year-old w
following concurrent administration of oxycodone and escitalopram.
was taking escitalopram 10 mg/day and extended-release oxycodor
twice daily. Approximately 5 weeks prior to the current presentation,
extended-release oxycodone had been doubled. She presented to t
room with acutely elevated blood pressure (200/90 millimeters of m
frequent myoclonic jerks in the lower extremities. Both escitalopram
oxycodone were stopped and the patient was treated with intraveno
which led to resolution of the myoclonic jerks and a return to baselir
pressure in less than a day. Subsequent re-initiation of extended-re
oxycodone (20 mg twice daily), but not escitalopram, did not result i
or blood pressure elevation (Gnanadesigan et al, 2005).

3.5.1.CR Parecoxib

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for main
hemostasis. Case-control and cohort studies have shown that the combi
SSRIs and NSAIDs has been associated with an increased risk of bleed
events have included epistaxis, ecchymosis, hematoma, petechiae, and
threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension,
Info Lexapro(TM), 2003a; Dalton et al, 2003a; Prod Info CELEXA (R) ora
solution, 2005).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an NSAID are given concu
monitor patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and th
potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospi
upper gastrointestinal bleeding were searched among 26,005 users
antidepressant medications and compared with the number of hosp
those patients who did not receive prescriptions for antidepressants
of upper GI bleeding episodes was 3.6 times more than expected (9
confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSA
dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1
5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of

demonstrate an increased risk of upper GI bleeding during the use c
Combined use of SSRIs and NSAIDs or low-dose aspirin increased
further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as f
been associated with hallucinations in some patients (Prod Info TOF
oral tablets, 2007).

3.5.1.CS Parnaparin

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maint
hemostasis. Case-control and cohort studies have shown that the combi
SSRIs and anticoagulants has been associated with an increased risk of
(Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info LEXAPRO(R
solution, 2008). Bleeding events reported have included epistaxis, ecchy
hematoma, petechiae, and life-threatening hemorrhages. Altered anticoa
(including increased bleeding) have been reported with the coadministra
with warfarin (Schalekamp et al, 2008; Prod Info LEXAPRO(R) oral table
2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When escitalopram and an anticoagulant are g
concurrently, monitor patients for signs of increased bleeding. Patients v
warfarin should be monitored closely for altered anticoagulant effects, in
increased bleeding, when escitalopram therapy is initiated or discontinue
LEXAPRO(R) oral tablets, solution, 2008).
7) Probable Mechanism: unknown
8) Literature Reports
a) According to a retrospective cohort study (n=234), there was an
of clinically relevant bleeding (hospital admission due to bleeding) ir
receiving warfarin for atrial fibrillation during concomitant SSRI thera
weeks following SSRI therapy termination. Patients with a mean age
years receiving warfarin plus SSRI (n=117) were matched with rand
patients who received warfarin only (n=117). SSRI included fluoxeti
citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nin
experienced 11 bleeding episodes during 213.9 treatment years in t
plus SSRI group, and 10 patients experienced 14 bleedings during 5
treatment years in the warfarin-only group. The corresponding total
bleedings were 51.4 and 23.9 per 1000 treatment years, respectivel
ratio for first bleedings during treatment with warfarin plus SSRI was
CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI ir
patients experiencing bleeding at the time of concomitant administra
sertraline or citalopram. The addition of an SSRI was not associated
change in warfarin dose or INR (p=0.48 and p=0.31 respectively). T
the study may be limited by earlier bleeding events, unknown patier
and exclusion of clopidogrel, dipyridamol, corticosteroids and antico
other than warfarin in the model (Wallerstedt et al, 2009).
b) A population-based, case-controlled study of new coumarin user
(acenocoumarol and phenprocoumon) with concomitant selective se
reuptake inhibitors (SSRIs) resulted in an increased risk of hospitali
nongastrointestinal bleeding. Using national pharmacy and hospitali
records, Netherlands researchers identified 1848 cases that were a
abnormal bleeding and compared them with 5818 control subjects a
coumarins. Median duration of treatment in patients was 220 days (
4690 days). Patients on SSRIs showed greater risk for hospitalizatio
nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% cor
interval (CI), 1.1 to 2.5), however, the rate of gastrointestinal bleedir
OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schaleka
2008).

3.5.1.CT Pentosan Polysulfate Sodium

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maint
hemostasis. Case-control and cohort studies have shown that the combi
SSRIs and anticoagulants has been associated with an increased risk of
(Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info LEXAPRO(R
solution, 2008). Bleeding events reported have included epistaxis, ecchy

hematoma, petechiae, and life-threatening hemorrhages. Altered anticoa
(including increased bleeding) have been reported with the coadministra
with warfarin (Schalekamp et al, 2008; Prod Info LEXAPRO(R) oral table
2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When escitalopram and an anticoagulant are g
concurrently, monitor patients for signs of increased bleeding. Patients v
warfarin should be monitored closely for altered anticoagulant effects, in
increased bleeding, when escitalopram therapy is initiated or discontinue
LEXAPRO(R) oral tablets, solution, 2008).
7) Probable Mechanism: unknown
8) Literature Reports
a) According to a retrospective cohort study (n=234), there was an
of clinically relevant bleeding (hospital admission due to bleeding) ir
receiving warfarin for atrial fibrillation during concomitant SSRI thera
weeks following SSRI therapy termination. Patients with a mean ag
years receiving warfarin plus SSRI (n=117) were matched with rand
patients who received warfarin only (n=117). SSRI included fluoxeti
citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nin
experienced 11 bleeding episodes during 213.9 treatment years in t
plus SSRI group, and 10 patients experienced 14 bleedings during
treatment years in the warfarin-only group. The corresponding total
bleedings were 51.4 and 23.9 per 1000 treatment years, respectivel
ratio for first bleedings during treatment with warfarin plus SSRI was
CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI ir
patients experiencing bleeding at the time of concomitant administra
sertraline or citalopram. The addition of an SSRI was not associated
change in warfarin dose or INR (p=0.48 and p=0.31 respectively). T
the study may be limited by earlier bleeding events, unknown patier
and exclusion of clopidogrel, dipyridamol, corticosteroids and antico
other than warfarin in the model (Wallerstedt et al, 2009).
b) A population-based, case-controlled study of new coumarin user
(acenocoumarol and phenprocoumon) with concomitant selective se
reuptake inhibitors (SSRIs) resulted in an increased risk of hospitali
nongastrointestinal bleeding. Using national pharmacy and hospitali
records, Netherlands researchers identified 1848 cases that were a
abnormal bleeding and compared them with 5818 control subjects a
coumarins. Median duration of treatment in patients was 220 days (
4690 days). Patients on SSRIs showed greater risk for hospitalizatio
nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% cor
interval (CI), 1.1 to 2.5), however, the rate of gastrointestinal bleedir
OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schaleka
2008).

3.5.1.CU Phenelzine
1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension,
myoclonus, mental status changes)
2) Summary: Concurrent administration or overlapping therapy with esc
a monoamine oxidase (MAO) inhibitor may result in CNS toxicity or sero
syndrome, a hyperserotonergic state characterized by symptoms such a
restlessness, myoclonus, changes in mental status, hyperreflexia, diaph
shivering, and tremor. Serious, even fatal, reactions have been reported
Lexapro(TM), 2002f). Concomitant use is contraindicated.
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Concurrent use of escitalopram and phenelzin
contraindicated. Wait at least two weeks after discontinuing a MAO inhib
initiating escitalopram therapy. In addition, wait at least five weeks after
escitalopram before initiating therapy with a MAO inhibitor.
7) Probable Mechanism: inhibition of serotonin metabolism by monoam

3.5.1.CV Phenindione
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for main

hemostasis. Case-control and cohort studies have shown that the combi
SSRIs and anticoagulants has been associated with an increased risk o
(Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info LEXAPRO(R
solution, 2008). Bleeding events reported have included epistaxis, ecchy
hematoma, petechiae, and life-threatening hemorrhages. Altered anticoa
(including increased bleeding) have been reported with the coadministra
with warfarin (Schalekamp et al, 2008; Prod Info LEXAPRO(R) oral table
2008).

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When escitalopram and an anticoagulant are g
concurrently, monitor patients for signs of increased bleeding. Patients v
warfarin should be monitored closely for altered anticoagulant effects, in
increased bleeding, when escitalopram therapy is initiated or discontinue
LEXAPRO(R) oral tablets, solution, 2008).

7) Probable Mechanism: unknown

8) Literature Reports

a) According to a retrospective cohort study (n=234), there was an
of clinically relevant bleeding (hospital admission due to bleeding) ir
receiving warfarin for atrial fibrillation during concomitant SSRI thera
weeks following SSRI therapy termination. Patients with a mean ag
years receiving warfarin plus SSRI (n=117) were matched with ranc
patients who received warfarin only (n=117). SSRI included fluoxeti
citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nin
experienced 11 bleeding episodes during 213.9 treatment years in t
plus SSRI group, and 10 patients experienced 14 bleedings during
treatment years in the warfarin-only group. The corresponding total
bleedings were 51.4 and 23.9 per 1000 treatment years, respectivel
ratio for first bleedings during treatment with warfarin plus SSRI was
CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI ir
patients experiencing bleeding at the time of concomitant administra
sertraline or citalopram. The addition of an SSRI was not associated
change in warfarin dose or INR (p=0.48 and p=0.31 respectively). T
the study may be limited by earlier bleeding events, unknown patier
and exclusion of clopidogrel, dipyridamol, corticosteroids and antico
other than warfarin in the model (Wallerstedt et al, 2009).

b) A population-based, case-controlled study of new coumarin user
(acenocoumarol and phenprocoumon) with concomitant selective se
reuptake inhibitors (SSRIs) resulted in an increased risk of hospitali
nongastrointestinal bleeding. Using national pharmacy and hospitali
records, Netherlands researchers identified 1848 cases that were a
abnormal bleeding and compared them with 5818 control subjects a
coumarins. Median duration of treatment in patients was 220 days (
4690 days). Patients on SSRIs showed greater risk for hospitalizatio
nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% cor
interval (CI), 1.1 to 2.5), however, the rate of gastrointestinal bleedir
OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schaleka
2008).

3.5.1.CW Phenprocoumon

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for main
hemostasis. Case-control and cohort studies have shown that the combi
SSRIs and anticoagulants has been associated with an increased risk o
(Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info LEXAPRO(R
solution, 2008). Bleeding events reported have included epistaxis, ecchy
hematoma, petechiae, and life-threatening hemorrhages. Altered anticoa
(including increased bleeding) have been reported with the coadministra
with warfarin (Schalekamp et al, 2008; Prod Info LEXAPRO(R) oral table
2008).

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When escitalopram and an anticoagulant are g
concurrently, monitor patients for signs of increased bleeding. Patients v
warfarin should be monitored closely for altered anticoagulant effects, in

increased bleeding, when escitalopram therapy is initiated or discontinue
LEXAPRO(R) oral tablets, solution, 2008).
7) Probable Mechanism: unknown
8) Literature Reports
a) According to a retrospective cohort study (n=234), there was an
of clinically relevant bleeding (hospital admission due to bleeding) ir
receiving warfarin for atrial fibrillation during concomitant SSRI thera
weeks following SSRI therapy termination. Patients with a mean ag
years receiving warfarin plus SSRI (n=117) were matched with ranc
patients who received warfarin only (n=117). SSRI included fluoxeti
citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nin
experienced 11 bleeding episodes during 213.9 treatment years in t
plus SSRI group, and 10 patients experienced 14 bleedings during
treatment years in the warfarin-only group. The corresponding total
bleedings were 51.4 and 23.9 per 1000 treatment years, respectivel
ratio for first bleedings during treatment with warfarin plus SSRI was
CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI ir
patients experiencing bleeding at the time of concomitant administra
sertraline or citalopram. The addition of an SSRI was not associated
change in warfarin dose or INR (p=0.48 and p=0.31 respectively). T
the study may be limited by earlier bleeding events, unknown patier
and exclusion of clopidogrel, dipyridamol, corticosteroids and antico
other than warfarin in the model (Wallerstedt et al, 2009).
b) A population-based, case-controlled study of new coumarin user
(acenocoumarol and phenprocoumon) with concomitant selective se
reuptake inhibitors (SSRIs) resulted in an increased risk of hospitali
nongastrointestinal bleeding. Using national pharmacy and hospitali
records, Netherlands researchers identified 1848 cases that were a
abnormal bleeding and compared them with 5818 control subjects a
coumarins. Median duration of treatment in patients was 220 days (
4690 days). Patients on SSRIs showed greater risk for hospitalizatio
nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% cor
interval (CI), 1.1 to 2.5), however, the rate of gastrointestinal bleedir
OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schaleka
2008).

3.5.1.CX Phenylbutazone
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for main
hemostasis. Case-control and cohort studies have shown that the combi
SSRIs and NSAIDs has been associated with an increased risk of bleed
events have included epistaxis, ecchymosis, hematoma, petechiae, and
threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension,
Info Lexapro(TM), 2003a; Dalton et al, 2003a; Prod Info CELEXA (R) ora
solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concu
monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and th
potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospi
upper gastrointestinal bleeding were searched among 26,005 users
antidepressant medications and compared with the number of hosp
those patients who did not receive prescriptions for antidepressants
of upper GI bleeding episodes was 3.6 times more than expected (9
confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSA
dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1
5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of
demonstrate an increased risk of upper GI bleeding during the use
Combined use of SSRIs and NSAIDs or low-dose aspirin increased
further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as
been associated with hallucinations in some patients (Prod Info TOF
oral tablets, 2007).

3.5.1.CY Pirazolac

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maint hemostasis. Case-control and cohort studies have shown that the combi SSRIs and NSAIDs has been associated with an increased risk of bleed events have included epistaxis, ecchymosis, hematoma, petechiae, and threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, Info Lexapro(TM), 2003a; Dalton et al, 2003a; Prod Info CELEXA (R) ora solution, 2005).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an NSAID are given concu monitor patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and th potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospi upper gastrointestinal bleeding were searched among 26,005 users antidepressant medications and compared with the number of hosp those patients who did not receive prescriptions for antidepressants of upper GI bleeding episodes was 3.6 times more than expected (9 confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSA dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of demonstrate an increased risk of upper GI bleeding during the use Combined use of SSRIs and NSAIDs or low-dose aspirin increased further (Dalton et al, 2003).

b) Coadministration of ketorolac with psychoactive drugs (such as been associated with hallucinations in some patients (Prod Info TOR oral tablets, 2007).

3.5.1.CZ Piroxicam

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maint hemostasis. Case-control and cohort studies have shown that the combi SSRIs and NSAIDs has been associated with an increased risk of bleed events have included epistaxis, ecchymosis, hematoma, petechiae, and threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, Info Lexapro(TM), 2003a; Dalton et al, 2003a; Prod Info CELEXA (R) ora solution, 2005).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an NSAID are given concu monitor patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and th potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospi upper gastrointestinal bleeding were searched among 26,005 users antidepressant medications and compared with the number of hosp those patients who did not receive prescriptions for antidepressants of upper GI bleeding episodes was 3.6 times more than expected (9 confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSA dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of demonstrate an increased risk of upper GI bleeding during the use Combined use of SSRIs and NSAIDs or low-dose aspirin increased further (Dalton et al, 2003).

b) Coadministration of ketorolac with psychoactive drugs (such as been associated with hallucinations in some patients (Prod Info TOR oral tablets, 2007).

3.5.1.DA Pirprofen

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maint
hemostasis. Case-control and cohort studies have shown that the combi
SSRIs and NSAIDs has been associated with an increased risk of bleed
events have included epistaxis, ecchymosis, hematoma, petechiae, and
threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension,
Info Lexapro(TM), 2003a; Dalton et al, 2003a; Prod Info CELEXA (R) ora
solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concu
monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and th
potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospi
upper gastrointestinal bleeding were searched among 26,005 users
antidepressant medications and compared with the number of hosp
those patients who did not receive prescriptions for antidepressants
of upper GI bleeding episodes was 3.6 times more than expected (9
confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSA
dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1
5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of
demonstrate an increased risk of upper GI bleeding during the use
Combined use of SSRIs and NSAIDs or low-dose aspirin increased
further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as
been associated with hallucinations in some patients (Prod Info TOF
oral tablets, 2007).

3.5.1.DB Propyphenazone

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maint
hemostasis. Case-control and cohort studies have shown that the combi
SSRIs and NSAIDs has been associated with an increased risk of bleed
events have included epistaxis, ecchymosis, hematoma, petechiae, and
threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension,
Info Lexapro(TM), 2003a; Dalton et al, 2003a; Prod Info CELEXA (R) ora
solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concu
monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and th
potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospi
upper gastrointestinal bleeding were searched among 26,005 users
antidepressant medications and compared with the number of hosp
those patients who did not receive prescriptions for antidepressants
of upper GI bleeding episodes was 3.6 times more than expected (9
confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSA
dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1
5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of
demonstrate an increased risk of upper GI bleeding during the use
Combined use of SSRIs and NSAIDs or low-dose aspirin increased
further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as
been associated with hallucinations in some patients (Prod Info TOF
oral tablets, 2007).

3.5.1.DC Proquazone

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maint
hemostasis. Case-control and cohort studies have shown that the combi
SSRIs and NSAIDs has been associated with an increased risk of bleed

events have included epistaxis, ecchymosis, hematoma, petechiae, and threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, Info Lexapro(TM), 2003a; Dalton et al, 2003a; Prod Info CELEXA (R) ora solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concu monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and th potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospi upper gastrointestinal bleeding were searched among 26,005 users antidepressant medications and compared with the number of hosp those patients who did not receive prescriptions for antidepressants of upper GI bleeding episodes was 3.6 times more than expected (9 confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSA dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of demonstrate an increased risk of upper GI bleeding during the use Combined use of SSRIs and NSAIDs or low-dose aspirin increased further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as been associated with hallucinations in some patients (Prod Info TOR oral tablets, 2007).

3.5.1.DD Rasagiline

1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, myoclonus, mental status changes)
2) Summary: Concomitant use of rasagiline and escitalopram should be Concurrent administration or overlapping therapy with SSRIs and non-se MAOIs has been reported to cause serious, sometimes fatal reactions. S symptoms included hyperthermia, rigidity, myoclonus, autonomic instabi vital sign fluctuations, and mental status changes progressing to extrem delirium, and coma. Data from clinical studies, where rasagiline-treated (n=141) were concomitantly exposed to SSRIs, are insufficient to rule ou interaction. At least 14 days should elapse after discontinuing rasagiline initiating escitalopram therapy (Prod Info AZILECT(R) oral tablets, 2006) least 14 days should also elapse after discontinuing escitalopram before therapy with rasagiline (Prod Info CELEXA(R) oral tablets, solution, 200
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concurrent use of escitalopram and rasagiline recommended. Wait at least 14 days after discontinuing rasagiline befor therapy with escitalopram (Prod Info AZILECT(R) oral tablets, 2006). Sin least 14 days after discontinuing escitalopram before initiating therapy w (Prod Info CELEXA(R) oral tablets, solution, 2007).
7) Probable Mechanism: inhibition of serotonin metabolism by monoam

3.5.1.DE Reviparin

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for main hemostasis. Case-control and cohort studies have shown that the combi SSRIs and anticoagulants has been associated with an increased risk of (Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info LEXAPRO(R solution, 2008). Bleeding events reported have included epistaxis, ecchy hematoma, petechiae, and life-threatening hemorrhages. Altered anticoa (including increased bleeding) have been reported with the coadministra with warfarin (Schalekamp et al, 2008; Prod Info LEXAPRO(R) oral table 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When escitalopram and an anticoagulant are g concurrently, monitor patients for signs of increased bleeding. Patients v

warfarin should be monitored closely for altered anticoagulant effects, in increased bleeding, when escitalopram therapy is initiated or discontinue LEXAPRO(R) oral tablets, solution, 2008).

7) Probable Mechanism: unknown

8) Literature Reports

a) According to a retrospective cohort study (n=234), there was an of clinically relevant bleeding (hospital admission due to bleeding) ir receiving warfarin for atrial fibrillation during concomitant SSRI thera weeks following SSRI therapy termination. Patients with a mean ag years receiving warfarin plus SSRI (n=117) were matched with ranc patients who received warfarin only (n=117). SSRI included fluoxeti citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nin experienced 11 bleeding episodes during 213.9 treatment years in t plus SSRI group, and 10 patients experienced 14 bleedings during 5 treatment years in the warfarin-only group. The corresponding total bleedings were 51.4 and 23.9 per 1000 treatment years, respectivel ratio for first bleedings during treatment with warfarin plus SSRI was CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI ir patients experiencing bleeding at the time of concomitant administra sertraline or citalopram. The addition of an SSRI was not associated change in warfarin dose or INR (p=0.48 and p=0.31 respectively). T the study may be limited by earlier bleeding events, unknown patier and exclusion of clopidogrel, dipyridamol, corticosteroids and antico other than warfarin in the model (Wallerstedt et al, 2009).

b) A population-based, case-controlled study of new coumarin user (acenocoumarol and phenprocoumon) with concomitant selective se reuptake inhibitors (SSRIs) resulted in an increased risk of hospitali nongastrointestinal bleeding. Using national pharmacy and hospitali records, Netherlands researchers identified 1848 cases that were a abnormal bleeding and compared them with 5818 control subjects a coumarins. Median duration of treatment in patients was 220 days (4690 days). Patients on SSRIs showed greater risk for hospitalizatio nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% cor interval (CI), 1.1 to 2.5), however, the rate of gastrointestinal bleedir OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schaleka 2008).

3.5.1.DF Rizatriptan

1) Interaction Effect: an increased risk of serotonin syndrome

2) Summary: There have been case reports of weakness, hyperreflexia incoordination following concomitant use of sumatriptan, a 5-hydroxytryp (5HT-1) agonist, and a serotonin specific reuptake inhibitor (SSRI) (Proc (R), 1998). Because rizatriptan is a 5HT 1B/1D receptor agonist, a simila between SSRIs and rizatriptan may occur (Prod Info Maxalt(R), 1998a). use of a triptan and an SSRI may result in serotonin syndrome which ma threatening. Symptoms of serotonin syndrome may include restlessness hallucinations, loss of coordination, fast heart beat, rapid changes in blo increased body temperature, overreactive reflexes, nausea, vomiting, ar Clinicians should be aware that triptans may be commonly used intermit either the triptan or the SSRI may be prescribed by a different physician. risks of serotonin syndrome with patients who are prescribed this combi monitor them closely for symptoms of serotonin syndrome (US Food and Administration, 2006).

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Coadministration of a triptan, such as rizatripta SSRI may result in a life-threatening condition called serotonin syndrom that triptans may be commonly used intermittently and that either the trip SSRI may be prescribed by a different physician. If these agents are use discuss the risks of serotonin syndrome with the patient and monitor clos symptoms of serotonin syndrome (restlessness, hyperthermia, hyperrefl incoordination).

7) Probable Mechanism: additive pharmacologic effects resulting in exc serotonergic stimulation

8) Literature Reports

a) Twelve healthy volunteers received paroxetine 20 mg daily for tw

a single dose of rizatriptan 10 mg. Plasma concentrations of rizatrip
altered by the administration of paroxetine (Prod Info Maxalt(R), 19

3.5.1.DG Rofecoxib

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for main
hemostasis. Case-control and cohort studies have shown that the combi
SSRIs and NSAIDs has been associated with an increased risk of bleed
events have included epistaxis, ecchymosis, hematoma, petechiae, and
threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension,
Info Lexapro(TM), 2003a; Dalton et al, 2003a; Prod Info CELEXA (R) ora
solution, 2005).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an NSAID are given concu
monitor patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and th
potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospi
upper gastrointestinal bleeding were searched among 26,005 users
antidepressant medications and compared with the number of hosp
those patients who did not receive prescriptions for antidepressants
of upper GI bleeding episodes was 3.6 times more than expected (9
confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSA
dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1
5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of
demonstrate an increased risk of upper GI bleeding during the use
Combined use of SSRIs and NSAIDs or low-dose aspirin increased
further (Dalton et al, 2003).

b) Coadministration of ketorolac with psychoactive drugs (such as
been associated with hallucinations in some patients (Prod Info TOF
oral tablets, 2007).

3.5.1.DH Selegiline

1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension,
myoclonus, mental status changes)

2) Summary: Concurrent administration or overlapping therapy with esc
a monoamine oxidase (MAO) inhibitor may result in CNS toxicity or sero
syndrome, a hyperserotonergic state characterized by symptoms such a
restlessness, myoclonus, changes in mental status, hyperreflexia, diaph
shivering, and tremor. Serious, even fatal, reactions have been reported
Lexapro(TM), 2002c). Concomitant use is contraindicated.

3) Severity: contraindicated

4) Onset: rapid

5) Substantiation: theoretical

6) Clinical Management: Concurrent use of escitalopram and selegiline
contraindicated. Wait at least two weeks after discontinuing a MAO inhib
initiating escitalopram therapy. In addition, wait at least five weeks after
escitalopram before initiating therapy with a MAO inhibitor.

7) Probable Mechanism: inhibition of serotonin metabolism by monoam

3.5.1.DI Sibrafiban

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for main
hemostasis. Case-control and cohort studies have shown that the combi
SSRIs and antiplatelet agents has been associated with an increased ris
Bleeding events reported have included epistaxis, ecchymosis, hematon
and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, susp
Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an antiplatelet agent are g
concurrently, monitor patient for signs of increased bleeding (Prod Info F
tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed

capsules, solution, 2008)
7) Probable Mechanism: unknown

3.5.1.DJ Sibutramine
1) Interaction Effect: an increased risk of serotonin syndrome (hyperten
hyperthermia, myoclonus, mental status changes)
2) Summary: Sibutramine inhibits the reuptake of norepinephrine, dopa
serotonin. In addition, the two major metabolites of sibutramine, M1 and
inhibit the reuptake of these neurotransmitters. A hyperserotonergic stat
serotonin syndrome, may result if sibutramine is given concurrently with
serotonin reuptake inhibitor. Coadministration of sibutramine and selecti
reuptake inhibitors is not recommended (Prod Info Meridia(R), 1997).
3) Severity: major
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Sibutramine should not be administered with s
agents, including selective serotonin reuptake inhibitors, because of the
of serotonin syndrome.
7) Probable Mechanism: additive pharmacologic effects resulting in exc
serotonergic stimulation
8) Literature Reports
a) Serotonin syndrome is a condition of serotonergic hyperstimulati
manifests as restlessness, myoclonus, changes in mental status, hy
diaphoresis, shivering, and tremor. If the syndrome is not recognize
correctly treated, death can result (Sternbach, 1991).

3.5.1.DK St John's Wort
1) Interaction Effect: an increased risk of serotonin syndrome (hyperten
hyperthermia, myoclonus, mental status changes)
2) Summary: Case reports describe the onset of serotonin syndrome-lik
mania, and hypomania following the addition of St. John's Wort to sertra
fluoxetine, and paroxetine therapy (Spinella & Eaton, 2002c; Barbanel e
Waksman et al, 2000a; Lantz et al, 1999a). A patient exhibited a syndro
resembling sedative/hypnotic intoxication after adding St. John's Wort to
therapy (Gordon, 1998a). St. John's Wort is thought to inhibit serotonin r
may have mild monoamine oxidase inhibitory activity (Singer et al, 1999
Walper, 1994), which when added to selective serotonin reuptake inhibit
in serotonin syndrome.
3) Severity: major
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Patients should be advised to wait two weeks
St. John's Wort before restarting selective serotonin reuptake inhibitor th
patient plans to replace selective serotonin reuptake inhibitor (SSRI) the
John's Wort, the half-life of the specific SSRI should be taken into consid
waiting at least 5 half-lives for the SSRI to be metabolized out of the boc
7) Probable Mechanism: additive serotonergic effect
8) Literature Reports
a) Five cases have been reported of serotonin syndrome in the eld
combining prescription antidepressants and St. John's Wort. Case 1
dizziness, nausea, vomiting and a headache 4 days after starting St
300 milligrams (mg) three times daily combined with sertraline 50 m
symptoms resolved 2 to 3 days after stopping all medications. Case
nausea, epigastric pain and anxiety 3 days after starting St. John's
twice daily combined with sertraline 75 mg daily. His symptoms reso
week after discontinuing both medications, and he resumed sertralin
complications. The third case developed nausea, vomiting, anxiety,
2 days after starting St. John's Wort 300 mg twice daily combined w
50 mg daily. His symptoms improved in 4 to 5 days after stopping b
medications and taking cyproheptadine 4 mg three times daily. Cas
nausea, anxiety, restless, and irritability 2 days after starting St. Joh
mg three times daily combined with sertraline 50 mg daily. Cyprohe
twice daily was administered for seven days, and his symptoms imp
week after stopping the medication. Cases 1 through 4 resumed the
sertraline after symptoms subsided and had no further problems. Ca
developed nausea, vomiting and restlessness 3 days after starting S
Wort 300 mg three times daily combined with nefazodone 100 mg tw

She continued to take St. John's Wort but discontinued the nefazod
1 week her symptoms Improved. She refused to resume therapy wi
nefazodone, but continued therapy with St. John's Wort and mild to
symptoms of depression and anxiety returned (Lantz et al, 1999).
b) A 50-year-old female taking St. John's Wort 600 mg daily experi
symptoms of sedative intoxication when she ingested a single dose
20 mg. She was incoherent, groggy, slow-moving, and complained
weakness. Prior to starting St. John's Wort, she had been receiving
mg daily for eight months without adverse effects. After a night of sl
returned to her baseline mental status (Gordon, 1998).
c) A 61-year-old female experienced restlessness and involuntary
her extremities after beginning paroxetine 20 milligrams (mg) two da
discontinuing St. John's Wort 600 mg daily. The patient reported ag
akathisia 8 hours after taking the first dose of paroxetine. She prese
diaphoresis and involuntary movement of all extremities with hyperr
rigidity. Blood pressure, heart rate, and temperature were normal. A
admission, blood pressure increased to 200/116 mmHg and heart ra
to 145 beats per minute. Creatine kinase increased from 212 units/l
initially to 1024 U/L. The patient was managed with supportive care
lorazepam and discharged after two days (Waksman et al, 2000).
d) A 28-year-old male developed a manic syndrome following com
St. John's Wort and sertraline. The patient was also on testosterone
therapy following bilateral orchidectomy 2 years earlier, but testoste
were subtherapeutic. The patient was prescribed sertraline 50 millig
depression following a 2 week trial of St. John's Wort per patient pre
not specified). Before sertraline was started, the patient was instruc
discontinue St. John'sWort, but continued it despite this advice. The
experienced improved mood so did not see his physician, believing
not need further treatment. Over 2 months, the patient had elated m
irritable, and overspent, buying a car he could not afford, and was u
arrested for stealing fuel for the car. On arrest, he was referred to ps
services due to irritability and disinhibition. He was observed to be d
distractible, have flight of ideas, and grandiose delusions, leading to
of a manic episode. The authors state the possibility of the manic st
from sertraline therapy alone, and that St. John's Wort may have inc
risk as a result of monoamine oxidase inhibition. Since the patient's
level was subnormal, the possibility of its contribution to the manic s
considered low. However, the patient had elevated gonadotropin lev
(luteinizing hormone and follicle-stimulating hormone) which may ha
predisposed the patient to mania (Barbanel et al, 2000).
e) A 42-year-old female experienced symptoms consistent with a m
hypomanic episode following concomitant use of fluoxetine, buspiro
biloba, and St. John's Wort. The symptoms resolved following disco
Ginkgo and St. John's Wort. The patient was being treated for depre
following a mild traumatic brain injury with fluoxetine 20 milligrams (
daily and buspirone 15 mg twice daily. Several weeks prior to prese
buspirone was increased to 20 mg twice daily for persistent anxiety
patient began taking Ginkgo biloba, melatonin, and St. John's Wort
doses. Melatonin was considered unlikely to have contributed to her
Ginkgo and St. John's Wort were considered possible contributors s
potentiate antidepressants, and considering the temporal relationsh
the use of the herbs and onset of symptoms and discontinuation of
resolution of symptoms. However, the brain injury was considered a
contributor (Spinella & Eaton, 2002b).

3.5.1.DL Sulfinpyrazone

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for main
hemostasis. Case-control and cohort studies have shown that the combi
SSRIs and antiplatelet agents has been associated with an increased ris
Bleeding events reported have included epistaxis, ecchymosis, hematon
and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, susp
Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an antiplatelet agent are g

concurrently, monitor patient for signs of increased bleeding (Prod Info F tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayec capsules, solution, 2008)
7) Probable Mechanism: unknown

3.5.1.DM Sulindac
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for main hemostasis. Case-control and cohort studies have shown that the combi SSRIs and NSAIDs has been associated with an increased risk of bleed events have included epistaxis, ecchymosis, hematoma, petechiae, and threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, Info Lexapro(TM), 2003a; Dalton et al, 2003a; Prod Info CELEXA (R) ora solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concu monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and th potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospi upper gastrointestinal bleeding were searched among 26,005 users antidepressant medications and compared with the number of hosp those patients who did not receive prescriptions for antidepressants of upper GI bleeding episodes was 3.6 times more than expected (9 confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSA dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of demonstrate an increased risk of upper GI bleeding during the use Combined use of SSRIs and NSAIDs or low-dose aspirin increased further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as been associated with hallucinations in some patients (Prod Info TOF oral tablets, 2007).

3.5.1.DN Sulodexide
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for main hemostasis. Case-control and cohort studies have shown that the combi SSRIs and antiplatelet agents has been associated with an increased ris Bleeding events reported have included epistaxis, ecchymosis, hematon and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, susp Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an antiplatelet agent are g concurrently, monitor patient for signs of increased bleeding (Prod Info F tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayec capsules, solution, 2008)
7) Probable Mechanism: unknown

3.5.1.DO Sumatriptan
1) Interaction Effect: an increased risk of serotonin syndrome
2) Summary: There have been rare postmarketing reports describing pa weakness, hyperreflexia, and incoordination following the use of a selec reuptake inhibitor and sumatriptan (Prod Info Lexapro(TM), 2003). Conc a triptan and an SSRI may result in serotonin syndrome which may be lif Symptoms of serotonin syndrome may include restlessness, hallucinatio coordination, fast heart beat, rapid changes in blood pressure, increasec temperature, overreactive reflexes, nausea, vomiting, and diarrhea. Clin be aware that triptans may be commonly used intermittently and that eitl or the SSRI may be prescribed by a different physician. Discuss the risk syndrome with patients who are prescribed this combination and monito for symptoms of serotonin syndrome (US Food and Drug Administration

3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Coadministration of a triptan, such as sumatrip SSRI, such as escitalopram, may result in a life-threatening condition ca syndrome. Be aware that triptans may be commonly used intermittently the triptan or the SSRI may be prescribed by a different physician. If thes used together, discuss the risks of serotonin syndrome with the patient a closely for symptoms of serotonin syndrome (restlessness, hyperthermia hyperreflexia, incoordination).
7) Probable Mechanism: additive pharmacologic effects resulting in exc serotonergic stimulation

3.5.1.DP Suprofen
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for main hemostasis. Case-control and cohort studies have shown that the combi SSRIs and NSAIDs has been associated with an increased risk of bleed events have included epistaxis, ecchymosis, hematoma, petechiae, and threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, Info Lexapro(TM), 2003a; Dalton et al, 2003a; Prod Info CELEXA (R) ora solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concu monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and th potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospi upper gastrointestinal bleeding were searched among 26,005 users antidepressant medications and compared with the number of hosp those patients who did not receive prescriptions for antidepressants of upper GI bleeding episodes was 3.6 times more than expected (9 confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSA dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of demonstrate an increased risk of upper GI bleeding during the use Combined use of SSRIs and NSAIDs or low-dose aspirin increased further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as been associated with hallucinations in some patients (Prod Info TOR oral tablets, 2007).

3.5.1.DQ Tapentadol
1) Interaction Effect: increased risk of serotonin syndrome (hypertensio hyperthermia, myoclonus, mental status changes)
2) Summary: Concurrent use of tapentadol and a selective serotonin re inhibitor (SSRI) may result in serotonin syndrome, which may be life-thre Symptoms of serotonin syndrome may include restlessness, hallucinatio coordination, fast heart beat, rapid changes in blood pressure, increased temperature, overreactive reflexes, nausea, vomiting, and diarrhea (Proc tapentadol immediate release oral tablets, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of tapentadol and an SSRI m life-threatening condition called serotonin syndrome. If these agents are together, monitor the patient closely for symptoms of serotonin syndrom (restlessness, hyperthermia, hyperreflexia, incoordination), especially du initiation and dose increases (Prod Info tapentadol immediate release or 2008).
7) Probable Mechanism: additive serotonergic effect

3.5.1.DR Tapentadol
1) Interaction Effect: an increase in central nervous system and respirat

depression
2) Summary: The concomitant use of tapentadol with central nervous sy
depressants including sedatives (eg, alprazolam, midazolam, or zolpider
in additive CNS and respiratory depressant effects, including hypotensio
sedation and/or coma. When administering tapentadol and a sedative to
dosage of one or both agents may be reduced (Prod Info NUCYNTA(TM
release oral tablets, 2009).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Consider monitoring the patient for cardiorespi
depression when tapentadol and sedatives are used in combination. A r
dose of one or both drugs may be necessary (Prod Info NUCYNTA(TM)
release oral tablets, 2009).
7) Probable Mechanism: additive effects

3.5.1.DS Tenidap
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for main
hemostasis. Case-control and cohort studies have shown that the combi
SSRIs and NSAIDs has been associated with an increased risk of bleed
events have included epistaxis, ecchymosis, hematoma, petechiae, and
threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension,
Info Lexapro(TM), 2003a; Dalton et al, 2003a; Prod Info CELEXA (R) ora
solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concu
monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and th
potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospi
upper gastrointestinal bleeding were searched among 26,005 users
antidepressant medications and compared with the number of hosp
those patients who did not receive prescriptions for antidepressants
of upper GI bleeding episodes was 3.6 times more than expected (9
confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSA
dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1
5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of
demonstrate an increased risk of upper GI bleeding during the use
Combined use of SSRIs and NSAIDs or low-dose aspirin increased
further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as
been associated with hallucinations in some patients (Prod Info TOR
oral tablets, 2007).

3.5.1.DT Tenoxicam
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for main
hemostasis. Case-control and cohort studies have shown that the combi
SSRIs and NSAIDs has been associated with an increased risk of bleed
events have included epistaxis, ecchymosis, hematoma, petechiae, and
threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension,
Info Lexapro(TM), 2003a; Dalton et al, 2003a; Prod Info CELEXA (R) ora
solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concu
monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and th
potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospi
upper gastrointestinal bleeding were searched among 26,005 users

antidepressant medications and compared with the number of hosp
those patients who did not receive prescriptions for antidepressants
of upper GI bleeding episodes was 3.6 times more than expected (9
confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSA
dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1
5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of
demonstrate an increased risk of upper GI bleeding during the use
Combined use of SSRIs and NSAIDs or low-dose aspirin increased
further (Dalton et al, 2003).

b) Coadministration of ketorolac with psychoactive drugs (such as
been associated with hallucinations in some patients (Prod Info TOF
oral tablets, 2007).

3.5.1.DU Tiaprofenic Acid

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for main
hemostasis. Case-control and cohort studies have shown that the combi
SSRIs and NSAIDs has been associated with an increased risk of bleed
events have included epistaxis, ecchymosis, hematoma, petechiae, and
threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension,
Info Lexapro(TM), 2003a; Dalton et al, 2003a; Prod Info CELEXA (R) ora
solution, 2005).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an NSAID are given concu
monitor patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and th
potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospi
upper gastrointestinal bleeding were searched among 26,005 users
antidepressant medications and compared with the number of hosp
those patients who did not receive prescriptions for antidepressants
of upper GI bleeding episodes was 3.6 times more than expected (9
confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSA
dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1
5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of
demonstrate an increased risk of upper GI bleeding during the use
Combined use of SSRIs and NSAIDs or low-dose aspirin increased
further (Dalton et al, 2003).

b) Coadministration of ketorolac with psychoactive drugs (such as
been associated with hallucinations in some patients (Prod Info TOF
oral tablets, 2007).

3.5.1.DV Ticlopidine

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for main
hemostasis. Case-control and cohort studies have shown that the combi
SSRIs and antiplatelet agents has been associated with an increased ris
Bleeding events reported have included epistaxis, ecchymosis, hematon
and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, susp
Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an antiplatelet agent are g
concurrently, monitor patient for signs of increased bleeding (Prod Info P
tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed
capsules, solution, 2008)

7) Probable Mechanism: unknown

3.5.1.DW Tinzaparin

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for main
hemostasis. Case-control and cohort studies have shown that the combi
SSRIs and anticoagulants has been associated with an increased risk of

(Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info LEXAPRO(R
solution, 2008). Bleeding events reported have included epistaxis, ecchy
hematoma, petechiae, and life-threatening hemorrhages. Altered anticoa
(including increased bleeding) have been reported with the coadministra
with warfarin (Schalekamp et al, 2008; Prod Info LEXAPRO(R) oral table
2008).

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When escitalopram and an anticoagulant are g
concurrently, monitor patients for signs of increased bleeding. Patients v
warfarin should be monitored closely for altered anticoagulant effects, in
increased bleeding, when escitalopram therapy is initiated or discontinue
LEXAPRO(R) oral tablets, solution, 2008).

7) Probable Mechanism: unknown

8) Literature Reports

a) According to a retrospective cohort study (n=234), there was an
of clinically relevant bleeding (hospital admission due to bleeding) ir
receiving warfarin for atrial fibrillation during concomitant SSRI thera
weeks following SSRI therapy termination. Patients with a mean ag
years receiving warfarin plus SSRI (n=117) were matched with ranc
patients who received warfarin only (n=117). SSRI included fluoxeti
citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nin
experienced 11 bleeding episodes during 213.9 treatment years in t
plus SSRI group, and 10 patients experienced 14 bleedings during
treatment years in the warfarin-only group. The corresponding total
bleedings were 51.4 and 23.9 per 1000 treatment years, respectivel
ratio for first bleedings during treatment with warfarin plus SSRI was
CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI ir
patients experiencing bleeding at the time of concomitant administra
sertraline or citalopram. The addition of an SSRI was not associated
change in warfarin dose or INR (p=0.48 and p=0.31 respectively). T
the study may be limited by earlier bleeding events, unknown patier
and exclusion of clopidogrel, dipyridamol, corticosteroids and antico
other than warfarin in the model (Wallerstedt et al, 2009).

b) A population-based, case-controlled study of new coumarin user
(acenocoumarol and phenprocoumon) with concomitant selective se
reuptake inhibitors (SSRIs) resulted in an increased risk of hospitali
nongastrointestinal bleeding. Using national pharmacy and hospitali
records, Netherlands researchers identified 1848 cases that were a
abnormal bleeding and compared them with 5818 control subjects a
coumarins. Median duration of treatment in patients was 220 days (
4690 days). Patients on SSRIs showed greater risk for hospitalizatio
nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% cor
interval (CI), 1.1 to 2.5), however, the rate of gastrointestinal bleedir
OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schaleka
2008).

3.5.1.DX Tirofiban

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for main
hemostasis. Case-control and cohort studies have shown that the combi
SSRIs and antiplatelet agents has been associated with an increased ris
Bleeding events reported have included epistaxis, ecchymosis, hematon
and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, susp
Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an antiplatelet agent are g
concurrently, monitor patient for signs of increased bleeding (Prod Info F
tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed
capsules, solution, 2008)

7) Probable Mechanism: unknown

3.5.1.DY Tolmetin

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maint
hemostasis. Case-control and cohort studies have shown that the combi
SSRIs and NSAIDs has been associated with an increased risk of bleed
events have included epistaxis, ecchymosis, hematoma, petechiae, and
threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension,
Info Lexapro(TM), 2003a; Dalton et al, 2003a; Prod Info CELEXA (R) ora
solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concu
monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and th
potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospi
upper gastrointestinal bleeding were searched among 26,005 users
antidepressant medications and compared with the number of hosp
those patients who did not receive prescriptions for antidepressants
of upper GI bleeding episodes was 3.6 times more than expected (9
confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSA
dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1
5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of
demonstrate an increased risk of upper GI bleeding during the use
Combined use of SSRIs and NSAIDs or low-dose aspirin increased
further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as
been associated with hallucinations in some patients (Prod Info TOR
oral tablets, 2007).

3.5.1.DZ Tramadol
1) Interaction Effect: an increased risk of seizures and serotonin syndro
(hypertension, hyperthermia, myoclonus, mental status changes)
2) Summary: Seizures and serotonin syndrome have been reported in p
tramadol. The risk of seizures and serotonin syndrome may be enhance
escitalopram and tramadol therapy are combined (Prod Info Ultram(R),
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Caution should be used if tramadol is to be adı
patients receiving concomitant escitalopram therapy. If possible, avoid th
combination, especially in patients with underlying conditions that might
them to seizures . Observe the patient closely for signs and symptoms o
syndrome.
7) Probable Mechanism: increased concentration of serotonin in the ner
and periphery

3.5.1.EA Tranylcypromine
1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension,
myoclonus, mental status changes)
2) Summary: Concurrent administration or overlapping therapy with esc
a monoamine oxidase (MAO) inhibitor may result in CNS toxicity or sero
syndrome, a hyperserotonergic state characterized by symptoms such a
restlessness, myoclonus, changes in mental status, hyperreflexia, diaph
shivering, and tremor. Serious, even fatal, reactions have been reported
Lexapro(TM), 2002). Concomitant use is contraindicated.
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Concurrent use of escitalopram and tranylcypr
contraindicated. Wait at least two weeks after discontinuing a MAO inhib
initiating escitalopram therapy. In addition, wait at least five weeks after
escitalopram before initiating therapy with a MAO inhibitor.
7) Probable Mechanism: inhibition of serotonin metabolism by monoam

3.5.1.EB Valdecoxib
1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maint
hemostasis. Case-control and cohort studies have shown that the combi
SSRIs and NSAIDs has been associated with an increased risk of bleed
events have included epistaxis, ecchymosis, hematoma, petechiae, and
threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension,
Info Lexapro(TM), 2003a; Dalton et al, 2003a; Prod Info CELEXA (R) ora
solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concu
monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and th
potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospi
upper gastrointestinal bleeding were searched among 26,005 users
antidepressant medications and compared with the number of hosp
those patients who did not receive prescriptions for antidepressants
of upper GI bleeding episodes was 3.6 times more than expected (9
confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSA
dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1
5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of
demonstrate an increased risk of upper GI bleeding during the use
Combined use of SSRIs and NSAIDs or low-dose aspirin increased
further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as
been associated with hallucinations in some patients (Prod Info TOR
oral tablets, 2007).

3.5.1.EC Warfarin
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maint
hemostasis. Case-control and cohort studies have shown that the combi
SSRIs and anticoagulants has been associated with an increased risk of
(Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info LEXAPRO(R
solution, 2008). Bleeding events reported have included epistaxis, ecchy
hematoma, petechiae, and life-threatening hemorrhages. Altered anticoa
(including increased bleeding) have been reported with the coadministra
with warfarin (Schalekamp et al, 2008; Prod Info LEXAPRO(R) oral table
2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When escitalopram and an anticoagulant are g
concurrently, monitor patients for signs of increased bleeding. Patients v
warfarin should be monitored closely for altered anticoagulant effects, in
increased bleeding, when escitalopram therapy is initiated or discontinue
LEXAPRO(R) oral tablets, solution, 2008).
7) Probable Mechanism: unknown
8) Literature Reports
a) According to a retrospective cohort study (n=234), there was an
of clinically relevant bleeding (hospital admission due to bleeding) ir
receiving warfarin for atrial fibrillation during concomitant SSRI thera
weeks following SSRI therapy termination. Patients with a mean ag
years receiving warfarin plus SSRI (n=117) were matched with ranc
patients who received warfarin only (n=117). SSRI included fluoxeti
citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nin
experienced 11 bleeding episodes during 213.9 treatment years in t
plus SSRI group, and 10 patients experienced 14 bleedings during
treatment years in the warfarin-only group. The corresponding total
bleedings were 51.4 and 23.9 per 1000 treatment years, respectivel
ratio for first bleedings during treatment with warfarin plus SSRI was
CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI ir
patients experiencing bleeding at the time of concomitant administra
sertraline or citalopram. The addition of an SSRI was not associated
change in warfarin dose or INR (p=0.48 and p=0.31 respectively). T

the study may be limited by earlier bleeding events, unknown patier and exclusion of clopidogrel, dipyridamol, corticosteroids and antico other than warfarin in the model (Wallerstedt et al, 2009).

b) A population-based, case-controlled study of new coumarin user (acenocoumarol and phenprocoumon) with concomitant selective se reuptake inhibitors (SSRIs) resulted in an increased risk of hospitali nongastrointestinal bleeding. Using national pharmacy and hospitali records, Netherlands researchers identified 1848 cases that were a abnormal bleeding and compared them with 5818 control subjects a coumarins. Median duration of treatment in patients was 220 days (4690 days). Patients on SSRIs showed greater risk for hospitalizatic nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% cor interval (CI), 1.1 to 2.5), however, the rate of gastrointestinal bleedir OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schaleka 2008).

3.5.1.ED Xemilofiban

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for main hemostasis. Case-control and cohort studies have shown that the combi SSRIs and antiplatelet agents has been associated with an increased ris Bleeding events reported have included epistaxis, ecchymosis, hematon and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, susp Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an antiplatelet agent are g concurrently, monitor patient for signs of increased bleeding (Prod Info P tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed capsules, solution, 2008)

7) Probable Mechanism: unknown

3.5.1.EE Zolmitriptan

1) Interaction Effect: an increased risk of serotonin syndrome

2) Summary: There have been case reports of weakness, hyperreflexia incoordination following concomitant use of sumatriptan, a 5-hydroxytryp (5HT-1) agonist, and a serotonin specific reuptake inhibitor (SSRI) (Proc (R), 1998a; Prod Info Zomig(TM), 1997). Because zolmitriptan is a 5HT agonist, a similar interaction between SSRIs and zolmitriptan may occur Zomig(TM), 1997). Concurrent use of zolmitriptan and an SSRI may resu syndrome which may be life-threatening. Symptoms of serotonin syndro include restlessness, hallucinations, loss of coordination, fast heart beat changes in blood pressure, increased body temperature, overreactive re nausea, vomiting, and diarrhea. Clinicians should be aware that triptans commonly used intermittently and that either the triptan or the SSRI may prescribed by a different physician. Discuss the risks of serotonin syndrc patients who are prescribed this combination and monitor them closely f of serotonin syndrome (US Food and Drug Administration, 2006).

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Coadministration of a triptan, such as zolmitrip SSRI may result in a life-threatening condition called serotonin syndrom that triptans may be commonly used intermittently and that either the trip SSRI may be prescribed by a different physician. If these agents are use discuss the risks of serotonin syndrome with the patient and monitor clos symptoms of serotonin syndrome (restlessness, hyperthermia, hyperrefl incoordination).

7) Probable Mechanism: additive pharmacologic effects resulting in exc serotonergic stimulation

8) Literature Reports

a) The pharmacokinetics of a single 10 mg dose of zolmitriptan wer by four weeks of fluoxetine 20 mg daily pretreatment in healthy volu effects of zolmitriptan on blood pressure were also not changed by t therapy (Prod Info Zomig(R), 2002).

3.5.1.EF Zomepirac

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maint hemostasis. Case-control and cohort studies have shown that the combi SSRIs and NSAIDs has been associated with an increased risk of bleed events have included epistaxis, ecchymosis, hematoma, petechiae, and threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, Info Lexapro(TM), 2003a; Dalton et al, 2003a; Prod Info CELEXA (R) ora solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concu monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and th potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospi upper gastrointestinal bleeding were searched among 26,005 users antidepressant medications and compared with the number of hosp those patients who did not receive prescriptions for antidepressants of upper GI bleeding episodes was 3.6 times more than expected (9 confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSA dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of demonstrate an increased risk of upper GI bleeding during the use Combined use of SSRIs and NSAIDs or low-dose aspirin increased further (Dalton et al, 2003).

b) Coadministration of ketorolac with psychoactive drugs (such as been associated with hallucinations in some patients (Prod Info TOR oral tablets, 2007).

3.5.2 Drug-Food Combinations

3.5.2.A Ethanol

1) Interaction Effect: potentiation of the cognitive and motor effects of al
2) Summary: According to the manufacturer, escitalopram did not poter cognitive and motor effects of alcohol. The concomitant use, however, is recommended (Prod Info Lexapro(TM), 2003b).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The use of alchohol by patients taking escitalo recommended.
7) Probable Mechanism: unknown

4.0 Clinical Applications

4.1 Monitoring Parameters

A) Escitalopram Oxalate
1) Therapeutic

a) Physical Findings
1) Symptoms of depression or anxiety/depression (improvement)
2) Maintenance therapy should be periodically reevaluated during l to determine the clinical need (Prod Info LEXAPRO(R) Oral solutior 2009).

2) Toxic
a) Laboratory Parameters
1) Serum sodium levels should be monitored (levels lower than 11(been reported) as medically warranted. There is an increased risk o hyponatremia (as a result of the syndrome of inappropriate antidiure secretion) in patients receiving concomitant diuretics, patients who a depleted, and the elderly. If hyponatremia is confirmed, escitaloprar discontinued and medical management may be necessary.

b) Physical Findings
1) Abnormal bleeding should be monitored for ecchymoses, hemat epistaxis and petechiae especially in patients receiving concomitant NSAIDs, warfarin or other anticoagulants.
2) Hyponatremia (as a result of SIADH) should be monitored includ of headache, difficulty concentrating, memory impairment, confusion and unsteadiness. More severe symptoms include hallucination, syı seizure, coma, and respiratory arrest including fatalities. There is ar risk of hyponatremia in patients receiving concomitant diuretics, pat volume depleted, and the elderly. If hyponatremia is confirmed, esci should be discontinued and medical management may be necessar
3) If intolerable withdrawal symptoms occur following a decrease in therapy is being discontinued, it may be necessary to resume the pı prescribed dose and taper the dose at a more gradual rate (Prod Int (R) Oral solution, Oral tablets, 2009).
4) Mania/hypomania may be activated in patients with undiagnosec disorder. Monitoring is recommended especially in patients with a h mania. Escitalopram is not indicated for use in bipolar disorder.
5) Monitor patients receiving antidepressants for worsening of depr suicidality, or unusual changes in behavior, especially at the initiatio or when the dose increases or decreases (Prod Info LEXAPRO(R) (Oral tablets, 2009). Such monitoring should include at least weekly contact with patients or their family members or caregivers during th weeks of treatment, then visits every other week for the next 4 weel weeks, and then as clinically indicated beyond 12 weeks. Families a should be advised of the need for close observation (i.e., daily obse patients and communication with the prescriber (Anon, 2004)
6) Patients who experience symptoms of anxiety, agitation, panic a insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia, or mania may be at an increased risk for worsening depression or s these symptoms are observed, therapy should be reevaluated and i necessary to discontinue medications when symptoms are severe, s onset, or were not part of the patient's initial symptoms (Prod Info LI Oral solution, Oral tablets, 2009; Anon, 2004)
7) Seizures should be monitored, especially in patients with a histo disorder.
8) Serotonin syndrome or neuroleptic malignant syndrome-like reac be monitored including mental status changes, autonomic instability labile blood pressure, hyperthermia), neuromuscular aberrations (m hyperreflexia, incoordination) and/or gastrointestinal symptoms. The increased risk of this reaction with concomitant use of serotonergic ((including triptans), drugs which impair metabolism of serotonin, or a or dopamine antagonists, all of which are not recommended during therapy. Treatment should be discontinued if serotonin syndrome or malignant syndrome-like reactions occur (Prod Info LEXAPRO(R) C Oral tablets, 2009).

4.2 Patient Instructions

A) Escitalopram (By mouth)
Escitalopram

Treats severe depression and generalized anxiety disorder (GAD). This med selective serotonin reuptake inhibitor (SSRI).

When This Medicine Should Not Be Used:
You should not use this medicine if you have had an allergic reaction to escit
citalopram (Celexa®), or if you are using pimozide (Orap®). You should not u
medicine if you have used an MAO inhibitor (such as Eldepryl®, Marplan®, M
Parnate®) within the past 14 days. Do not use an MAO inhibitor for at least 1
you stop using escitalopram.

How to Use This Medicine:
Liquid, Tablet
Your doctor will tell you how much of this medicine to use and how often
more medicine or use it more often than your doctor tells you to.
You may take this medicine with or without food.
Measure the oral liquid medicine with a marked measuring spoon, oral s
medicine cup.
This medicine should come with a Medication Guide. Read and follow th
instructions carefully. Ask your doctor or pharmacist if you have any que
your pharmacist for the Medication Guide if you do not have one. Your d
ask you to sign some forms to show that you understand this information

If a Dose is Missed:
If you miss a dose or forget to use your medicine, use it as soon as you
almost time for your next dose, wait until then to use the medicine and s
dose. Do not use extra medicine to make up for a missed dose.

How to Store and Dispose of This Medicine:
Store the medicine in a closed container at room temperature, away fror
moisture, and direct light.
Ask your pharmacist, doctor, or health caregiver about the best way to d
leftover medicine after you have finished your treatment. You will also ne
away old medicine after the expiration date has passed.
Keep all medicine away from children and never share your medicine wi

Drugs and Foods to Avoid:
Ask your doctor or pharmacist before using any other medicine, including ove
medicines, vitamins, and herbal products.
Do not use citalopram (Celexa®) while you are using escitalopram. Thes
medicines are closely related and using both could be dangerous.
Make sure your doctor knows if you are using linezolid (Zyvox®), lithium
St. John's Wort, pain or migraine medicines (such as aspirin, tramadol, s
zolmitriptan, rizatriptan, Ultram®, Imitrex®, Zomig®, or Maxalt®), pain or
medicines called NSAIDs (such as diclofenac, ibuprofen, naproxen, Adv
Feldene®, Daypro®, Motrin®, Orudis®, Relafen®, or Voltaren®), or a bl
such as warfarin (Coumadin®). Tell your doctor if you are also using cim
(Tagamet®), carbamazepine (Tegretol®), ketoconazole (Nizoral®), meto
(Lopressor®), or other medicines for depression (such as amitriptyline, i
Norpramin®, or Tofranil®).
Tell your doctor if you are using any medicines that make you sleepy. Th
sleeping pills, cold and allergy medicine, narcotic pain relievers, and sed
Do not drink alcohol while you are using this medicine.

Warnings While Using This Medicine:
Make sure your doctor knows if you are pregnant or breastfeeding, or if y
bleeding problems, kidney disease, liver disease, heart disease, hypona
sodium in the blood), or a history of seizure disorder (such as epilepsy) o
your doctor if you have a history of neuroleptic malignant syndrome (NM
serotonin syndrome.
For some children, teenagers, and young adults, this medicine can incre
of suicide. Tell your doctor or your child's doctor right away if you or you
feel more depressed and have thoughts about hurting yourselves. Repo
thoughts or behaviors that trouble you or your child, especially if they are
getting worse quickly. Make sure the doctor knows if you or your child ha
sleeping, get upset easily, have a big increase in energy, or start to act r
tell the doctor if you or your child have sudden or strong feelings, such a
nervous, angry, restless, violent, or scared. Let the doctor know if you, y
anyone in your family has bipolar disorder (manic-depressive) or has trie
suicide.
You may need to take this medicine for up to 4 weeks before you feel be

using this medicine for the full treatment time. If you feel that the medicir
working well, do not take more than your prescribed dose. Call your doc
instructions.
This medicine may make you dizzy or drowsy. Avoid driving, using mach
anything else that could be dangerous if you are not alert.
Do not stop using this medicine suddenly without asking your doctor. Yo
slowly decrease your dose before stopping it completely.
Your doctor will need to check your progress at regular visits while you a
medicine. Be sure to keep all appointments.

Possible Side Effects While Using This Medicine:
Call your doctor right away if you notice any of these side effects:
Allergic reaction: Itching or hives, swelling in your face or hands, swellin
your mouth or throat, chest tightness, trouble breathing.
Blistering, peeling, or red skin rash.
Change in how much or how often you urinate, or painful urination.
Chest pain or shortness of breath.
Confusion, weakness, or muscle twitching.
Fast, pounding, or uneven heartbeat.
Fever, chills, cough, sore throat, and body aches.
Painful, prolonged erection of the penis.
Swelling in your hands, ankles, or feet.
Unusual behavior or thoughts of hurting yourself or others.
Unusual bleeding or bruising.

If you notice these less serious side effects, talk with your doctor:
Dry mouth.
Headache, dizziness, or drowsiness.
Nausea, diarrhea, constipation, or upset stomach.
Problems with sex.
Runny or stuffy nose.
Sweating.
Tiredness.
Trouble with sleeping.

If you notice other side effects that you think are caused by this medicine, tel

4.3 Place In Therapy

A) Depression

1) Escitalopram is indicated for the acute and maintenance treatment of maj
disorder in adults and adolescents age 12 years and older (Prod Info LEXAP
solution, Oral tablets, 2009).

2) The selective serotonin (5-HT) reuptake inhibitors (SSRIs) are considered
choice for mild or moderate depression by many specialists. More severe de
depression unresponsive to the SSRIs, is usually treated by tricyclic antidepr
inhibitors, or bupropion or venlafaxine. There is no consistent evidence that c
superior to another.

3) In several studies, escitalopram has been reported effective in major depr
pooled analysis of placebo-controlled trials escitalopram demonstrated a stat
significant improvement in depressive symptoms compared to placebo at one
compared to 4 weeks for citalopram. The actual improvement in depressive s
escitalopram compared to placebo at weeks one and 2 was an approximately
decrease (out of a possible 60) as measured on the Montgomery Asberg De
Rating Scale (Gorman et al, 2002). The clinical significance of this change is
There was no statistically significant difference between escitalopram 10 mg
placebo in regards to discontinuation rates due to adverse effects or in the ra
treatment-emergent adverse events. Both escitalopram 20 mg per day and c
mg per day did show statistically significant higher rates for discontinuation d
effects and in treatment-emergent adverse events (Burke et al, 2002). A com
equivalent doses of escitalopram 10 mg per day and citalopram 20 mg per da
to determine if escitalopram offers clinical advantages over citalopram in the
adverse drug effects.

B) Generalized Anxiety Disorder

1) Escitalopram is indicated in the acute treatment of generalized anxiety dis
adults (Prod Info LEXAPRO(R) Oral solution, Oral tablets, 2009).

2) For the acute treatment of generalized anxiety disorder (GAD), SSRIs suc
paroxetine, sertraline, and escitalopram, as well as venlafaxine, benzodiazep

alprazolam and diazepam, and the tricyclic antidepressant (TCA) imipramine
The SSRIs and venlafaxine are preferred to benzodiazepines and TCAs due
tolerability. Studies have shown that long-term treatment with SSRIs or venla
increases response rates and prevents relapse (Baldwin & Nair, 2005).
3) Escitalopram has been shown to be effective for the acute and chronic tre
GAD, as well as in the prevention of relapse (Goodman et al, 2005; Davidsor
Allgulander et al, 2006). In three 8-week randomized controlled trials, patient
escitalopram 10 milligrams (mg) daily showed statistically significant improve
placebo as early as 1 week, as measured by change from baseline Hamilton
for Anxiety (HAMA) scores (Goodman et al, 2005). Patients completing the 8
were invited to participate in a 24-week, open-label extension in which all pat
escitalopram. Initially, patients who received escitalopram in the lead-in trials
improvements than patients who received placebo, but by week 4 of the exte
patients were at the same level of improvement regardless of previous treatn
76% of patients were considered responders and 49% achieved remission (D
2005). In a relapse prevention study lasting 24 to 76 weeks, patients on place
times more likely to relapse than patients who were treated with escitalopram
(Allgulander et al, 2006). A comparison study found escitalopram to be as eff
paroxetine in the treatment of GAD; however, escitalopram was better tolerat
al, 2005).

4.4 Mechanism of Action / Pharmacology

A) MECHANISM OF ACTION

1) Antidepressant effects are secondary to inhibition of reuptake of serotonir
serotonergic neurons via binding to the serotonin transporter, resulting in incr
synaptic availability of 5-HT (Owens et al, 2001; Owens & Knight, 2000).

B) PHARMACOLOGY

1) The antidepressant citalopram is a selective serotonin (5-HT) reuptake inl
it is available for clinical use as a racemic mixture (S(+)-citalopram and R(-)-c
1:1 ratio) (Montgomery et al, 2001; Sanchez & Hogg, 2000). Escitalopram is
enantiomer of citalopram, and appears responsible for most or all antidepres
the racemic compound (Sanchez & Hogg, 2000; Sanchez & Brennum, 2000;
al, 2001; Mitchell & Hogg, 2001). In vitro, escitalopram was about twice as po
racemic citalopram and 130 times as potent as R(-)-citalopram as an inhibito
reuptake (Sanchez & Brennum, 2000; Sanchez & Hogg, 2000; Owens et al,
Bergqvist et al, 2001) and exhibited minimal-to-no effect on norepinephrine c
reuptake (Sanchez & Brennum, 2000).
2) Subcutaneous escitalopram was reported effective in an animal model pr
antidepressant activity, and at least twice as potent as subcutaneous citalopr
& Hogg, 2001). The onset of antidepressant activity with escitalopram was fa
of racemic citalopram (Montgomery et al, 2001) or tricyclic antidepressants (I
Sanchez, 2001) in rat models of depression.
3) Escitalopram has demonstrated anxiolytic activity in animal models of ger
panic anxiety, whereas the R(-)-enantiomer was essentially inactive (Sanche
These data suggest that the clinical anxiolytic actions observed with racemic
are due to escitalopram.

4.5 Therapeutic Uses

4.5.A Escitalopram Oxalate

Cerebrovascular accident - Depression; Prophylaxis

Generalized anxiety disorder

Major depressive disorder

Mixed anxiety and depressive disorder

Obsessive-compulsive disorder

Panic disorder

Trichotillomania

4.5.A.1 Cerebrovascular accident - Depression; Prophylaxis

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENC

b) Summary:

In a 12-month, multicenter, randomized, double-blind study (n= prophylaxis with oral escitalopram 5 or 10 milligrams/day was n than placebo or problem-solving therapy in reducing the freque onset depression in adults with recent ischemic or hemorrhagic (Robinson et al, 2008)

c) Adult:

1) Prophylaxis with oral escitalopram was more effective than place lowering incidence of depression in nondepressed patients with rec 12-month, multicenter, randomized, double-blind study (n=176); hov benefit seen in patients exposed to nonblinded problem-solving ther not statistically significant compared to placebo. Patients older than less than 90 years of age (mean age, 62 years) who had experience ischemic or hemorrhagic stroke within 3 months were included, prov not meet the DSM-IV diagnostic criteria for major or minor depressiv had a Hamilton-17 Depression Rating Scale (HDRS) score of greate (mean score range at baseline, 7 to 7.22). Patients were randomize double-blinded therapy with either escitalopram 5 milligrams (mg)/d patients older than 65 years) or 10 mg/day (for patients 65 years or or placebo (n=58), or nonblinded problem-solving therapy (n=59) fo In the problem-solving therapy arm, patients selected a problem and through 7 steps to form a course of action; therapy involved 6 treatm over the first 12 weeks and 6 reinforcement sessions over the rema months. Assessments were conducted at 3 month intervals using th Clinical Interview for DSM-IV, and patients meeting major or minor d diagnostic criteria and with a HDRS score of greater than 12 were d depression (primary outcome measure). At 12 months, there are 11 minor cases of depression (total, 22.4%) in the placebo arm compar and 2 minor cases (total, 8.5%) in the escitalopram arm. Excluding ((13.5%) of the study patients who dropped out for various reasons p receiving treatment and after adjusting for prior history of mood disc each arm), patients in the placebo group were significantly more like depression compared to patients in the escitalopram group (adjuste (HR), 4.5; 95% confidence interval (CI), 2.4 to 8.2; p less than 0.001 number needed to treat (NNT) of 7.2 acute stroke patients. In the pr therapy group, there were 5 major and 2 minor cases of depression adjusted HR (vs placebo), 2.2; 95% CI, 1.4 to 3.5; p less than 0.001 NNT of 9.1 acute stroke patients. Notably, an intention-to-treat analy included post-randomization dropouts (n=27), with the assumption t developed depression, revealed statistical significance compared to the escitalopram group (34.5% vs 23.1%, respectively; adjusted HR 1.2 to 3.9; p=0.007) but not for the problem-solving therapy group (3 30.5%, respectively; adjusted HR, 1.1; 95% CI, 0.8 to 1.5; p=0.51). secondary efficacy variables, activities of daily living (measured usir Functional Independence Measure) as well as social functioning (m the Social Functioning Exam scores) improved across all 3 groups, significant time to treatment interaction. Additionally, there were no differences in frequency of adverse events, including all-cause hosp and gastrointestinal effects, between the groups (Robinson et al, 20

4.5.A.2 Generalized anxiety disorder

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes; Pediatric, no
Efficacy: Adult, Effective
Recommendation: Adult, Class IIa
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENC

b) Summary:

Indicated in the acute treatment of generalized anxiety disorder (Prod Info LEXAPRO(R) Oral solution, Oral tablets, 2009).
Treatment with escitalopram in older adults (60 years or older) generalized anxiety disorder (GAD) was associated with improv clinical response rates in anxiety symptoms and self-reported r compared to placebo, in a 12 week, randomized, double-blind, controlled, phase 2 study (n=179); however, statistical significa observed only in the modified intent-to-treat analysis (Lenze et

c) Adult:

1) A pooled analysis of three short-term double-blind, placebo-cont flexible-dose studies showed that escitalopram is more effective tha treating generalized anxiety disorder (GAD). Patients (mean age, a 39 years) with a diagnosis of GAD and a Hamilton Rating Scale for (HAMA) total score of at least 18 and at least a score of 2 on the te anxiety items were included. Those with diagnoses of major depres schizophrenia, psychosis, bipolar disorder, developmental or cognit and substance abuse within the past 6 months were excluded. Follo week placebo lead-in period, patients were randomized to receive e escitalopram 10 milligrams (mg) daily (n=429) or placebo (n=427). T escitalopram dose could be increased to 20 mg daily after 4 weeks was judged to be insufficient by the investigator. The primary endpo change in HAMA total score from baseline to week 8. The mean cha baseline for HAMA total score was a 10.1-point decrease (+/-0.3) fo and a 7.6-point decrease (+/-0.3) for placebo (p less than 0.001). At response, defined as a decrease of at least 50% in mean HAMA sc in 47.5% of escitalopram-treated patients and 28.6% of placebo-trea (p less than 0.001). Remission, defined as a HAMA score of 7 or les 26.4% of escitalopram-treated patients and 14.1% of placebo-treate less than 0.001). Clinical Global Impressions of Improvement (CGI- defined as a CGI-I score of 1 or 2, occurred in 52% of escitalopram- patients and 37% of placebo-treated patients (p less than 0.001). In trials, the most commonly reported adverse effects were nausea (es 18.2%; placebo, 7.5%), ejaculation disorder (escitalopram, 14.3%; p 1.5%), insomnia (escitalopram, 11.9%; placebo, 5.6%), fatigue (esc 7.7%; placebo, 2.1%), decreased libido (escitalopram, 6.8%; placeb anorgasmia (escitalopram, 5.7%; placebo, 0.4%) (Goodman et al, 2
Patients who completed 8-week trials comparing escitalopram were invited to participate in a 24-week, open-label, flexible-dos study (n=526) of escitalopram. Inclusion and exclusion criteria as for the previous trials, with the added requirement that the p participated in and completed one of the three 8-week trials wit 72 hours. All patients, regardless of treatment received in the s trials, were given escitalopram 10 milligrams (mg) daily for 4 we weeks of treatment, the dose could be increased to 20 mg daily patient's response was unsatisfactory. The primary endpoint of study was improvement in Hamilton Rating Scale for Anxiety (H Baseline HAMA scores in the placebo-treated group from the le were higher than in those patients who had been treated with e the lead-in trials. However, within 4 weeks of open-label escital treatment, the improvement had equalized between the two gro remained similar throughout the rest of the study. Of the patien 56.8% completed the extension study. For the intent-to-treat (IT (n=521), the mean change in HAMA score at 24 weeks was -3. and 76% of patients were considered responders and 49% rem (Davidson et al, 2005).

2) Escitalopram was effective in the prevention of relapse of genera disorder (GAD) in a clinical trial that began with a 12-week, open-lab (n=491) followed by a double-blind, randomized treatment period (n between 24 and 76 weeks. Patients included were those between th and 65 with a primary diagnosis of GAD and a Hamilton Rating Sca (HAMA) score of 20 or greater. Those with a diagnosis of major dep disorder, panic disorder, social anxiety disorder, bipolar disorder, ea disorders, suicidal ideations, psychoses, and substance abuse diso excluded. Patients were given escitalopram 10 milligrams (mg) daily week of the open-label period, then doses were increased to 20 mg remainder of the 12-week period. At 12 weeks, responders were ra continue escitalopram 20 mg daily or placebo for the maintenance p

double-blind period ended on the same date for all patients (24 to 7
treatment), then was followed by a 2-week taper. The primary endp
to relapse during the double-blind period, as defined by an increase
total score of 15 or greater or investigator-determined lack of efficac
HAMA total score at the beginning of the open-label period was 27.
standard deviation (SD). At the start of the double-blind period, the
total score for the placebo group was 5 +/-3.1, and the mean HAMA
for the escitalopram group was 5.7 +/-2.9. Escitalopram was benefic
to placebo with regard to time to relapse (p less than 0.001; log-ranl
Escitalopram was associated with decreased relapse compared to p
versus 56%, respectively; p less than 0.001). The hazard ratio for re
4.04 (95% confidence interval (CI), 2.75 to 5.94). The change in tota
score from the beginning of the double-blind period to the end of 24
decrease of 0.83 in the escitalopram group and an increase of 0.39
group (treatment difference, -1.22; 95% CI, -2.28 to -0.17). The mos
side effects reported during the open-label period of treatment with
include nausea (24.2%), headache (16.7%), ejaculation dysfunction
dizziness (11.6%), fatigue (11.2%), insomnia (11%), and dry mouth
most common side effects reported during the double-blind portion
were headache (escitalopram, 11.2%; placebo, 3.7%), rhinitis (escit
13.9%; placebo, 5.9%), and upper respiratory tract infections (escita
placebo, 2.7%), and the withdrawal rate for adverse effects was sim
the two groups (escitalopram, 7%; placebo, 8.5%) (Allgulander et al

a) Geriatric Populations

1) Treatment with escitalopram in older adults (60 years o
generalized anxiety disorder (GAD) was associated with im
cumulative clinical response rates in anxiety symptoms an
role functioning compared to placebo, in a 12-week, rando
double-blind, placebo-controlled, phase 2 study (n=179); h
statistical significance was observed only in the modified ir
analysis. Patients with a principal diagnosis of GAD accorc
Diagnostic and Statistical Manual of Mental Disorders, Fou
(DSM-IV) criteria, and clinically significant anxiety sympton
a score of 17 or greater in the Hamilton Anxiety Rating Sca
total anxiety score range from 0 to 56) were enrolled. Patie
excluded from the study if they had a history of lifetime psy
bipolar disorder, dementia, increased suicide risk, medical
ongoing psychotherapy, and current antidepressant or anx
(with the exception of benzodiazepine use equivalent to lo
milligrams/day (mg/day)). Eligible patients were randomize
fashion to receive escitalopram 10 mg orally daily (mean a
7.4 years (yr); n=85) or matching placebo (mean age, 72.2
n=92) for 12 weeks. Patients who did not achieve a clinical
after 4 weeks of escitalopram 10 mg orally daily were give
escitalopram dose of 20 mg orally daily, as tolerated. Outc
defined as changes in symptoms of anxiety on the Clinical
Impressions Improvement Scale (CGI-I), HARS, Penn Stat
Questionnaire (PSWQ), and role functioning. The primary
a response defined as CGI-I of 1 (very much improved) or
improved). In the modified intent-to-treat (ITT) analysis am
participants who provided at least 1 follow-up data point (n
response was higher in the escitalopram arm (60%; 95% C
71%) compared with the placebo arm (45%; 95% CI, 36%
p=0.048). However, in the ITT analysis (n=179), the respor
statistically different between the escitalopram and placebo
arms (57%; 95% CI, 46% to 67% vs 45%; 95% CI, 35% to
Overall, cumulative incidence of response was higher in th
escitalopram arm versus placebo arm (mean response rate
CI, 58% to 80% vs 51%; 95% CI, 40% to 62%, respectively
Treatment with escitalopram also significantly improved the
activity limitations subscale scores compared to placebo. F
somnolence (41.1%) were the most common adverse effec
with escitalopram and appeared to be dose-related (Lenze

4.5.A.3 Major depressive disorder

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes; Pediatric, yes (age 12 years and old
Efficacy: Adult, Evidence favors efficacy; Pediatric, Evidence fa
Recommendation: Adult, Class IIa; Pediatric, Class IIb
Strength of Evidence: Adult, Category B; Pediatric, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENC

b) Summary:

Indicated for the acute and maintenance treatment of major de disorder in adults and adolescents age 12 years and older (Pro LEXAPRO(R) Oral solution, Oral tablets, 2009).

Escitalopram has been more effective than placebo in alleviatir of major depression in adults (Burke et al, 2002b; Gorman et al Wade et al, 2002; Montgomery et al, 2001a; Anon, 2000; Wade Burke, 2000a; Gorman, 2001a).

Escitalopram was not statistically better than placebo in the trea major depressive disorder (MDD) among pediatric patients age years (n=261) (Wagner et al, 2006); however, in a multicenter, randomized, placebo-controlled study (n=316), escitalopram wa more effective than placebo among adolescent patients with M al, 2009).

The efficacy of escitalopram for maintenance treatment of majc disorder in adolescents age 12 to 17 years was extrapolated fr (Prod Info LEXAPRO(R) Oral solution, Oral tablets, 2009).

c) Adult:

1) Randomized studies (published and unpublished) have reported greater efficacy of escitalopram 10 or 20 milligrams (mg) daily comp placebo in the treatment of major depressive disorder, based on imp the Montgomery Asberg Depression Rating Scale (MADRS), the Cli Impressions (CGI) scale, and the Hamilton Depression Rating Scale (Burke et al, 2002b; Gorman et al, 2002b; Wade et al, 2002; Montg 2001a; Anon, 2000; Wade et al, 2001b; Burke, 2000a; Gorman, 200 these studies appeared to involve the same patient populations, wit reinterpretation of data; others were the same population with varie treatment. The three published studies were all of short duration (8 et al, 2002b; Gorman et al, 2002b; Wade et al, 2002). Differences ir of escitalopram (10 and 20 mg) relative to placebo at endpoint in the depression were statistically significant and amounted to decreases points on the MADRS (Burke et al, 2002b; Wade et al, 2002).

2) In studies providing response rates (50% reduction in MADRS s compared to baseline) (Burke et al, 2002b; Gorman et al, 2002b; W 2002; Wade et al, 2001b; Gorman, 2001a), 42% to 44% of patients placebo with 56% to 61% responding to escitalopram 10 or 20 millig this difference reached statistical significance in favor of escitalopra

3) In direct comparisons (unpublished studies), escitalopram 10 or has not been statistically superior to citalopram 20 or 40 mg daily (G 2001a; Burke, 2001b; Montgomery et al, 2001c). However, in an an pooled data from placebo-controlled trials, escitalopram 10 or 20 mg statistically significant (p less than 0.05) decrease in Montgomery A Depression Rating Scale scores compared to citalopram 40 mg dail weeks, but not at weeks 2, 4, or 8 (Gorman et al, 2002b).

4) In a randomized, double-blind study involving patients with majo disorder of at least one month in duration (n=366), Montgomery Asb Depression Rating scale (MADRS), Clinical Global Impression (CGI Hamilton Rating Scale for Depression (HAMD) scores were improve significantly greater extent with escitalopram 10 or 20 milligrams (m placebo. This difference was first noted at one week on the mood ite HAMD scale and on the CGI scale. At week 2 there was also a stati significant difference noted on the MADRS and HAMD scales; impr remained statistically significant in favor of escitalopram throughout of therapy. Discontinuation of treatment due to adverse events was frequent in the 20-mg group compared to 10 mg daily or placebo gr al, 2002b).

d) Pediatric:

1) In a multicenter, double-blind, randomized, placebo-controlled st escitalopram was significantly more effective than placebo in the tre adolescent patients with major depressive disorder (MDD). Adolesc diagnosed with MDD as defined by the Diagnostic and Statistical M Mental Disorders (DSM-IV) criteria and Kiddie Schedule for Affectiv

and Schizophrenia for School-Age Children - Present and Lifetime v
current MDD episode of at least 12 weeks duration, a score of at lea
Children's Depression Rating Scale-Revised (CDRS-R) at both scre
baseline visits, a Clinical Global Impressions-Severity (CGI-S) Scale
least 4 at baseline, a Kaufman Brief Intelligence Test score of 80 or
eligible for the study. There was a 2-week screening period and all p
received single-blind placebo during the second week. Following the
period, eligible patients were randomized to receive escitalopram 10
milligrams/day (mg/day) for the first 3 weeks (n=158; mean age, 14.
years (yr)) or placebo (n=158; mean age, 14.5 +/- 1.5 yr). After 3 or
escitalopram dose could be adjusted to 20 mg/day or remain at 10 m
patients developed intolerance at higher doses. Baseline characteri
similar between the escitalopram arm (mean duration of depressive
+/- 17.4 months; antidepressant naive, 81.3%) and the placebo arm
duration of depressive episode, 16.5 +/- 15.4 months; antidepressa
85.4%). The mean baseline CDRS-R scores (57.6 vs 56; p=0.034) a
scores (4.6 vs 4.4; p=0.007) indicated greater severity of depressio
escitalopram arm compared with the placebo arm, but the difference
clinically significant. A total of 81.3% (126 of 154) of patients in the e
group completed the 8 weeks of treatment compared to 84.7% (133
patients who received placebo. The mean dose of escitalopram was
mg/day and 68.4% patients who received escitalopram had a dose
compared to 76.4% of patients in the placebo arm. Based on the int
analysis, patients who received escitalopram experienced a greater
in the CDRS-R scores at week 8 (primary endpoint) compared with
received placebo (mean +/- standard error of mean, -22.1 +/- 1.22 v
1.27; difference, -3.356; 95% CI, -6.226 to -0.486; p=0.22). Addition
change from baseline to week 8 for the CGI-S scores (secondary en
greater for the patients who received escitalopram compared with p
+/- 0.11 vs 1.4 +/- 0.12; difference, -0.37; 95% CI, -0.64 to -0.1; p=0
Escitalopram was associated with a higher incidence of insomnia (1
6.4%), nausea (10.3% vs 8.3%) and influenza-like symptoms (7.1%
Relative to escitalopram, placebo was associated with a higher incid
menstrual cramps (15.2% vs 10.9%) and inflicted injury (13.4% vs 9
al, 2009).

2) In an 8-week, multicenter, double-blind, randomized, placebo-co
among children and adolescents aged 6 to 17 years with major dep
disorder (n=261; 6 to 11 years, n=104; 12 to 17 years, n=157), escit
not statistically better than placebo in outcome measures. All patien
12.3 +/- 3 years) were free of other psychiatric disorders, of whom 5
female. Patients were randomly assigned to either escitalopram 10
(mg) once daily for the first 4 weeks, followed flexible dosing of 10 t
(n=129) or matching placebo (n=132). The median dose of escitalop
+/- 2.3 mg per day. Baseline Children's Depression Rating Scale-Re
R) scores were 54.5 for escitalopram-treatment patients and 56.6 fo
treated patients, with higher scores indicating worsening of depress
the intent-to-treat analysis using the last observation-carried-forwar
approach, the improvement from baseline at week 8 in the CDRS-R
(primary outcome) was similar between the escitalopram and the pl
(mean change, -21.9 vs -20.2; p=0.31). Escitalopram was not statis
than placebo in Clinical Global Impressions-Improvement (CGI-I) (p
Clinical Global Impressions-Severity (CGI-S) (p=0.057), and Childre
Assessment Scale (CGAS) Compliance (p=0.065) scores. In the su
analysis among adolescents aged 12 to 17 years (n=157) using the
approach, escitalopram demonstrated significant improvements fro
compared with placebo in CGI-I (2.4 vs 2.8; p=0.038), CGI-S (-1.5 v
and CGAS scores (15.7 vs 10; p=0.005). Compliance rates were no
different, at 77.9% and 86.5% for the escitalopram and the placebo
respectively. Headache (22.9% vs 21.8%), abdominal pain (10.7% v
nausea (7.6% vs 4.5%) were more frequently associated with escita
placebo. Suicidal ideation and intent were reported in one escitalop
patients and 2 placebo-treated patients, none of which was success
et al, 2006).

4.5.A.4 Mixed anxiety and depressive disorder

a) Overview

FDA Approval: Adult, no; Pediatric, no

Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENC

b) Summary:
Effective in treating anxiety in patients with major depression in studies (Burke et al, 2002b; Lydiard, 2001c)

c) Adult:
1) Escitalopram 10 or 20 milligrams (mg) daily was reported to be s placebo in treating both anxiety and depression in outpatients with r depression in an 8-week, placebo-controlled, double-blind study. Th statistically significant decreases in anxiety scores relative to placeb treatment groups; 1.1 points (p=0.04) for the 10 mg escitalopram gr points (p less than 0.01) for the 20 mg escitalopram group. These d represented the change from baseline to endpoint (week 8) as mea Hamilton Rating Scale for Anxiety (Burke et al, 2002b).
2) In an unpublished, 8-week, placebo-controlled studies, escitalop milligrams (mg) daily was reported to be superior to placebo in treat anxiety and depression in outpatients with major depression. Antian were demonstrated by improvements in the anxiety subscale of the Depression Rating Scale (HAMD), the inner tension component of t Montgomery-Asberg Depression Rating Scale (MADRS), and the H Anxiety Scale (HAMA). Doses of 20 mg tended to be more effective Combined data for both doses indicated antianxiety and antidepres comparable to citalopram 20 or 40 mg daily; slightly faster improver symptoms was seen with escitalopram versus citalopram, although statistically significant (Lydiard, 2001c).

4.5.A.5 Obsessive-compulsive disorder

a) Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENC

b) Summary:
In patients with obsessive-compulsive disorder, continued treat escitalopram during a 24-week, randomized, double-blind, plac phase maintained clinical response observed after 16 weeks of treatment, and yielded higher relapse prevention than placebo al, 2007).
In a 24-week, randomized, double-blind study (n=466), treatme escitalopram 20 milligrams (mg) per day was more effective tha and achieved comparable efficacy to paroxetine in treating adu to-severe obsessive-compulsive disorder (Stein et al, 2007).

c) Adult:
1) General Information
a) Treatment with oral escitalopram was more effective than pl treating adult moderate-to-severe obsessive-compulsive disord 24-week, randomized, double-blind study (n=466) (Stein et al, 2 study also employed paroxetine as an active-comparator and e efficacy was comparable to that observed with paroxetine. Com effects included nausea, headache, and fatigue among the acti arms. In another study in adults with moderate-to-severe OCD, weeks of open-label treatment with escitalopram 10 or 20 mg/d responders randomized to 24 weeks of continued treatment wit escitalopram at the same doses during the subsequent double- maintained clinical response and had lower relapse rates (52% compared to placebo (Fineberg et al, 2007). Notably, exclusion with other primary or axis I psychiatric disorders and/or significa comorbidity in both studies may limit the generalizability of thes

2) Clinical Trials
a) Twenty-four weeks of continued treatment with escitalopram randomized, double-blind, placebo-controlled phase maintained response observed after 16 weeks of open-label treatment and higher relapse prevention in patients with obsessive compulsive (OCD). Patients with moderate-to-severe OCD diagnosed acco

DSM-IV (Third Revision) criteria (aged 18 to 65 years; mean, 3
were required to have a Yale-Brown Obsessive Compulsive Sc
total score of 20 or higher, with an OCD duration of at least 1 y
symptoms for at least 6 months, and no other primary psychiat
significant somatic comorbidity. Patients (n=468; mean +/- stan
(SD) Y-BOCS total score, 26.4 +/- 3.7) were first enrolled in a 1
open-label phase, receiving oral escitalopram 10 mg/day for th
and then titrated up to 20 mg/day based on tolerability and effic
was fixed from weeks 12 to 16. Of the 374 patients completing
phase, 320 who responded to treatment (ie, had a 25% or grea
from baseline Y-BOCS total score; mean +/- SD Y-BOCS total
weeks, 15 +/- 8.5) were entered into the double-blind phase an
to receive either escitalopram 10 or 20 mg/day (n=163) or place
for 24 weeks. Escitalopram was tapered off in patients assigne
as well as in the escitalopram group at the end of the study (we
of patients in the escitalopram group received the 20 mg/day d
the double-blind phase, trained raters assessed patients using
National Institute of Mental Health-Obsessive Compulsive Scal
OCS), and Clinical Global Impressions-Severity of Illness (CGI-
Improvement of Illness (CGI-I) every 2 weeks until week 8 and
weeks. Relapse was defined as an increase in the Y-BOCS tot
or greater, or lack of efficacy based on the investigator's judgm
Meier survival analysis revealed that the primary efficacy meas
relapse of OCD from the start of the double-blind phase (baseli
significantly in favor of escitalopram compared to placebo (p les
log-rank test). The relapse rate was significantly higher in the p
compared to the escitalopram group (52% vs 23%; p less than
yielding an estimated hazard ratio of 2.74 (p less than 0.001). A
significant between-group difference in Y-BOCS total score was
week 4 of the double-blind phase, which was maintained throug
While the mean +/- SD Y-BOCS total scores in the placebo gro
from 11.2 +/- 5.3 at baseline to 14.8 +/- 7.5, Y-BOCS total scor
escitalopram group were essentially unchanged (10.8 +/- 5.4 at
10.7 +/- 7.3 at 24 weeks), yielding an adjusted mean change (p
escitalopram) of -3.67 (95% confidence interval, -4.91 to 2.42).
secondary efficacy measures, the mean NIMH-OCS, CGI-S, ar
scores in the escitalopram group, all of which had reduced sign
baseline during the open-label phase, remained either unchang
decreased compared to values at randomization. In the placebo
measures were increased at week 24 compared to randomizati
adjusted mean change from randomization was statistically sig
favor of escitalopram for all measures. Of the 20% (n=94/468)
who withdrew from the study during the open-label phase, 28 p
withdrew due to adverse events. During the double-blind phase
rates were comparable between the groups (escitalopram, 7.9%
8.9%). Adverse events occurred in 39% of escitalopram-treated
compared to 31.6% of placebo-treated patients, with the majori
being mild to moderate. Despite the taper, discontinuation effec
(5.7% vs 0.6%; p less than 0.001) and dizziness (15.9% vs 0.6%
frequently reported in the placebo group during the first 2 week
double-blind phase (p less than 0.001 for both) (Fineberg et al,

b) Treatment with oral escitalopram 20 milligrams (mg) per day
effective than placebo and achieved comparable efficacy to pa
treating adult moderate to severe obsessive-compulsive disord
24-week, randomized, double-blind study (n=466). Outpatients
years (mean, 38 years) with a primary diagnosis of OCD accor
DSM-IV (Third Revision) criteria, with a Yale-Brown Obsessive
Scale (Y-BOCS) total score of 20 or higher, an OCD duration o
year and stable symptoms for at least 6 months, and no other c
psychiatric disorders were included. Patients were randomized
either escitalopram 10 mg/day (n=116) or 20 mg/day (n=116), p
mg/day (n=119), or placebo (n=115) for 24 weeks, followed by
taper period. Trained raters assessed efficacy primarily using th
total score every 2 weeks until week 12 and every 4 weeks sub
Secondary efficacy measures included the National Institute of
Health-Obsessive Compulsive Scale (NIMH-OCS), and Clinical
Impressions-Severity of Illness (CGI-S) and Improvement of Illn

Response was defined as a score of 2 or less on the CGI-I, and reduction in the Y-BOCS total score at week 12 and 24; remiss score of 1 or 2 on the CGI-S, and a Y-BOCS total score of 10 o weeks 12 and 24. At baseline, the mean +/- standard deviation total scores were 27.7 +/- 4.2, 26.6 +/- 3.7, 26.6 +/- 3.9, and 27 placebo, escitalopram 10 mg/day, escitalopram 20 mg/day, and 40 mg/day groups, respectively. Compared to placebo, the mea Y-BOCS total score from baseline to week 12 (primary efficacy statistically significant for the escitalopram 20 mg/day group (m difference, -3.21; 95% confidence interval (CI), -5.19 to -1.23; p 0.01) and the paroxetine group (mean difference, -2.47; 95% C 0.51; p less than 0.05). For the escitalopram 20 mg/day group, treatment difference from placebo in Y-BOCS total scores eme 6 (p less than 0.05) and continued through week 24 (p less tha Analysis of the per-protocol population revealed statistically sig +/- SD changes from baseline to week 12 in Y-BOCS total scor to placebo (-8.46 +/- 0.76; n=97) for the escitalopram 10 mg/da 0.78; p less than 0.01; n=92), escitalopram 20 mg/day (-12.14 - than 0.001; n=95), and the paroxetine 40 mg/day groups (-11.6 less than 0.01; n=90). For the escitalopram 20 mg/day group, a responder status and remitter status from placebo emerged at week 12, respectively, based on the Y-BOCS total score criteria other secondary endpoints, all active treatment groups showed significant improvement versus placebo in NIMH-OCS, CGI-S, scores at both weeks 12 and 24. Of 131 study withdrawals, a s higher proportion of patients withdrew from the placebo group (lack of efficacy compared to the escitalopram 20 mg/day (6.1% paroxetine 40 mg/day (7.7%) groups (p less than 0.05 for both) (19% to 27%), headache (17% to 22%), and fatigue (12% to 19 most commonly reported adverse events in the active treatmen (Stein et al, 2007).

4.5.A.6 Panic disorder

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIa
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENC

b) Summary:

Reduced panic attack frequency in patients with panic disorder 2003)

c) Adult:

1) Escitalopram treatment reduced panic attack frequency in patien disorder. In a randomized, double-blind, placebo-controlled, flexible multicenter study, patients with panic disorder with or without agora received escitalopram (n=128; mean dose, 10.8 milligrams (mg)/day (n=119; mean dose, 21.3 mg/day), or placebo for 10 weeks. Panic a frequency in escitalopram-treated patients was significantly reduced baseline to endpoint as compared with patients who received placel 0.32, respectively; p=0.04). Additionally, the percentage of patients escitalopram group with zero panic attacks at endpoint as compared approached statistical significance (50% vs 38%, respectively; p=0.(citalopram group was not statistically different from placebo on eithe measures. However, patients in both the escitalopram and citalopra show significant improvements in numerous other efficacy measure placebo including, Panic and Agoraphobia Scale total score, Clinica Impression- Improvement (CGI-I) and -Severity of Illness (CGI-S) sc Phobic avoidance score, Patient Global Evaluation score, and Qual Enjoyment and Satisfaction Questionnaire score (p less than or equ values). The most commonly reported adverse events included hea mouth, nausea, insomnia, fatigue, dizziness, and somnolence (Stah

4.5.A.7 Trichotillomania

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy

Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENC

b) Summary:

Treatment with escitalopram led to significant improvement in s trichotillomania in adult women (mean age, 32.5 years) in a sm open-label, prospective trial (n=20) (Gadde et al, 2007)

c) Adult:

1) In a small, 12-week, open-label, prospective trial (n=20), treatme escitalopram led to significant improvement in symptoms of trichotill adult women. Enrollees (mean age, 32.5 years; 17 Caucasian) had DSM-IV-TR diagnosis of trichotillomania and were required to have or higher on the National Institute of Mental Health (NIMH) trichotillo severity scale (TSS) and 4 or higher on the NIMH trichotillomania in scale (TIS). Patients with a history of mania, hypomania, schizophre psychotic disorders, with a primary diagnosis of obsessive-compuls or those with recent (4 weeks prior) use of antidepressants or other medications were excluded. Study patients received escitalopram 1 (mg) orally once daily in the evening. Based on clinical response an the dose was increased in 10-mg increments at 4-week intervals up maximum dose of 30 mg/day by week 8. Patients kept diaries detail pulling behavior prior to study initiation and maintained them during study duration. Assessments were conducted every 2 weeks using Massachusetts General Hospital (MGH) Hair Pulling scale, clinician rated Clinical Global Impression improvement scale (CGI-I). The TS (range, 0 to 25), assessing the frequency of hair pulling, resistance, urge, distress, and interference, was the primary efficacy measure. a clinician-rated CGI-I score of 1 (very much improved) or 2 (much i at least 50% reduction in TSS total score were classified as respond baseline, most study patients displayed hair pulling from more than the scalp being the most common site (n=16). The mean +/- standa duration of trichotillomania was 15.3 +/- 2.1 years, and an equal nur patients displayed relaxation- and stress-associated trichotillomania The mean +/- SE escitalopram dose was 21.9 +/- 2.1 mg/day. Base intention-to-treat (ITT) analysis (including all patients with at least 1 assessment), 50% (8/16) of patients were responders. Of the 8 resp were rated as very much improved and 5 were rated as much impro the clinician- and patient-rated CGI-I. In the ITT population, the mea total score decreased over time from 15.4 +/- 0.9 at baseline to 9.4 week 12 (p less than 0.0001); scores were similar among study com (n=12; 15.8 +/- 1 at baseline to 7.5 +/- 1.2 at week 12; p less than 0 Among secondary outcomes, significant improvements occurred in +/- 0.3 to 3.3 +/- 0.4; p less than 0.0001) and MGH hair pulling scale to 10.6 +/- 1.2; p less than 0.0015) scores for the ITT set. Results w among study completers. Specific predictors of response were not e this small study set. Treatment-emergent adverse events were mos included nausea (n=6), insomnia (n=4), fatigue (n=2), decreased lib orgasmic dysfunction (n=2). Bruising, which resolved after discontin was reported in 1 patient (Gadde et al, 2007).

4.6 Comparative Efficacy / Evaluation With Other Therapies

Citalopram

Duloxetine

Paroxetine

4.6.A Citalopram

Depression

Mixed anxiety and depressive disorder

4.6.A.1 Depression

a) Direct placebo-controlled comparisons of escitalopram 10 or 20 millig daily and citalopram 20 or 40 mg daily in patients with major depression revealed a trend toward the superiority of escitalopram in improving sym although this did not reach statistical significance (Gorman et al, 2002a; et al, 2001a; Burke et al, 2002a). In all studies, improvements from base escitalopram versus placebo tended to be greater than citalopram versu leading the investigators to indicate greater efficacy of escitalopram; hov statistical superiority of escitalopram versus citalopram for baseline impr not demonstrated. Using placebo-effect versus baseline comparisons, th action of escitalopram was judged faster than that of citalopram; statistic between escitalopram and citalopram were not applied.

b) In pooled data from three 8-week, placebo-controlled studies compar 20 to 40 mg daily and escitalopram 10 to 20 mg daily in patients with ma disorder, improvement of Montgomery Asberg Depression Rating Scale scores was significantly greater with escitalopram versus placebo after c whereas borderline significance (p=0.068) versus placebo was seen for week 4. Similar trends were reported for Clinical Global Impressions (CG scores. In patients completing 8 weeks of treatment, MADRS scores had at least 50% in 59%, 53%, and 41% of patients receiving escitalopram, c and placebo, respectively; MADRS response rates for both escitalopram citalopram were significantly greater compared to placebo, although ther significant difference between active drug groups (Gorman et al, 2002a)

4.6.A.2 Mixed anxiety and depressive disorder

a) In unpublished, 8-week placebo-controlled studies, escitalopram 10 c milligrams (mg) daily was comparable in efficacy to citalopram 20 or 40 r treating both anxiety and depression in outpatients with major depressio 2001). A trend toward faster improvement of anxiety symptoms was see escitalopram, although this was not statistically significant. Adverse-effe provided only for escitalopram.

4.6.A.3 Adverse Effects

a) In one large study (N=491) adverse effects occurred in 71%, 79%, 86 of patients treated with placebo, escitalopram 10 mg daily, escitalopram and citalopram 40 mg daily, respectively; corresponding incidences of th discontinuation due to adverse effects were 2.5%, 4.2%, 10.4%, and 8.8 no significant statistical difference in the number of adverse effects betw and escitalopram 10 mg daily. There was also no significant statistical di the number of adverse effects reported for escitalopram 20 mg daily and 40 mg daily, but both groups had statistically (p less than 0.01) higher ra treatment-emergent adverse effects than placebo or escitalopram 10 mg et al, 2002a).

4.6.B Duloxetine

4.6.B.1 Major depressive disorder

a) In an 8-week randomized, double-blind, placebo- and active-compara multicenter, noninferiority trial in adult patients (n=684) with major depre (MDD), onset of efficacy for duloxetine 60 milligrams (mg) daily was at le onset for escitalopram 10 mg daily, and patients in both active treatment more likely to meet onset criteria than placebo patients. Patients aged 1 older (range, 18 to 79 years), meeting the DSM-IV criteria for MDD and Montgomery-Asberg Depression Rating Scale (MADRS) total score of 2 and a Clinical Global Impression Scale-Severity (CGI-S) score of 4 or gr included. Patients were randomized to receive either duloxetine 60 mg c mean age, 41.1 years; mean baseline Hamilton Rating Scale for Depres Maier subscale score, 17.6), escitalopram 10 mg daily (n=274; mean ag mean baseline HAMD score, 17.8), or placebo (n=137; mean age, 42.5 baseline HAMD score, 17.7) during an 8-week, acute treatment period. efficacy (primary endpoint) was defined as achieving a 20% or greater d HAMD score by week 2 that was sustained for the remainder of the acut period. In the intent-to-treat analysis, the probability of meeting efficacy was similar in the duloxetine and escitalopram groups (42.6% vs 35.2%, difference, 7.4%; 95% confidence interval (CI), -1.3% to 16.2%; p=0.097 patients in both groups were more likely to achieve efficacy onset compa placebo patients (21.5%; duloxetine vs placebo, p less than 0.001; escit

placebo, p=0.008). The noninferiority of duloxetine to escitalopram was
following a per-protocol analysis. In an analysis for the main treatment e
data from all visits were pooled, a significantly greater proportion of dulo
patients achieved efficacy onset vs escitalopram patients (p=0.026), and
proportion of patients in both active treatment groups achieved efficacy
placebo patients (p less than or equal to 0.018 for both). The median tim
was significantly shorter among duloxetine-treated patients than both es
and placebo-treated patients (23 days vs 41 days vs 55 days, respective
vs escitalopram, p=0.032; duloxetine vs placebo, p less than 0.001), and
to onset did not differ between escitalopram and placebo patients (p=0.0
probability of achieving a treatment response (secondary endpoint) by w
as a 50% or greater improvement in HAMD total score, was similar amo
duloxetine (48.7%), escitalopram (45.3%), and placebo (36.9%) groups,
probability of remission (HAMD total score of 7 or less) also did not diffe
groups (40.1% vs 33% vs 27.7%, respectively). The 191 subjects who fa
complete the study were evenly distributed among the groups, and a sim
percentage in each group discontinued due to adverse effects. Nausea
commonly caused discontinuation among duloxetine patients compared
escitalopram patients (2.9% vs 0.4%, respectively; p=0.02). Both nausea
mouth occurred more often in duloxetine patients compared to escitalop
placebo patients and at a rate greater than 10% (nausea, 23.8% vs 12%
mouth, 21.6% vs 10.9% vs 10.9%; p less than 0.05 for all). Although this
focused on the acute 8-week treatment period, subjects completing this
continued with blinded treatment for an additional 6 months (Nierenberg
During the 6-month extension phase, the duloxetine dose ranged from 6
mg/day and the escitalopram dose ranged from 10 to 20 mg/day; placeb
responders from the acute treatment phase were assigned in a double-b
active treatment. Among the 431 patients (63%) continuing on in the ext
there were no significant differences in antidepressant efficacy between
and escitalopram groups based on HAMD total scores. The probability o
was 70% and 75% among the duloxetine and escitalopram groups, resp
(p=0.44). The only statistically significant difference between the groups
HAMD sleep subscale, where escitalopram-treated patients had greater
in insomnia than duloxetine-treated patients (mean change from baselin
1.55; p less than 0.05). Although discontinuation rates over the 8-month
higher in the duloxetine group vs escitalopram (62% vs 55%; p=0.02), ra
discontinuation due to adverse events were similar (12.8% vs 12%, resp
(Pigott et al, 2007).

b) In a randomized, double-blind, fixed-dose, noninferiority trial (n=294)
duloxetine was at least as effective as escitalopram for the long term tre
major depressive disorder (MDD), escitalopram was superior in acute tre
study included outpatients aged 18 to 73 years old with MDD according
(Third Revision) criteria, with a Montgomery-Asberg Depression Rating S
(MADRS) total score of 26 or greater, and with a Clinical Global Impress
Severity (CGI-S) score of 4 or greater were included. With the exception
compulsive disorder, posttraumatic stress disorder, or panic disorder, pa
secondary, current, comorbid anxiety disorder were included. Study pati
randomized to receive either duloxetine 60 milligrams (n=151) or escitalo
(initial dose, 10 mg/day; increased after 2 weeks; n=143) orally once dai
weeks. At baseline, the MADRS scores were 32.1 +/- 4.4 and 32.5 +/- 4.
duloxetine and escitalopram groups, respectively. At the end of the 24 w
mean change from baseline in MADRS score in the intent-to-treat popul
endpoint) for escitalopram and duloxetine were -23.4 and -21.7, respecti
(p=0.055). Based on a per-protocol analysis (n=287), the between-group
(escitalopram minus duloxetine) in MADRS scores at 24 weeks was 0.67
confidence interval (CI), -1.06 to 2.41; p not significant), which met the p
noninferiority criteria (ie, upper limit of the one-sided CI did not include 2
Furthermore, superiority of escitalopram was evident (ie, upper limit of th
CI did not include zero) at week 8 and week 24 based on a between-gro
differences of 2.54 (95% CI, p=0.011) and 2.21 (p=0.027), respectively,
per-protocol population. At 24 weeks, 81.6% (n=115) of escitalopram-tre
were considered to be responders (ie, 50% or greater decrease from ba
MADRS total score) compared with 73% (n=112) of duloxetine-treated p
Among secondary endpoints, escitalopram was significantly more effecti
duloxetine in CGI-I (p=0.039) score reduction from baseline to week 8. E
also was significantly better than duloxetine in the Sheehan Disability Sc
work score reduction at week 24, and SDS total score reduction at week

less than 0.05 for all). Significantly more patients on duloxetine reported
(12.6% vs 4.9%) and constipation (8.6% vs 2.8%) compared to escitalop
almost twice the withdrawal rate due to adverse events in the duloxetine
vs 9%; p less than 0.05) (Wade et al, 2007).

4.6.C Paroxetine

4.6.C.1 Generalized anxiety disorder

a) In a randomized, double-blind, multi-center trial involving patients (m
approximately 37 years) with moderate to severe generalized anxiety dis
treatment with either escitalopram (10 to 20 milligrams (mg) per day), or
(20 to 50 mg per day) lead to improvements over time in all efficacy mea
however, escitalopram was better tolerated. The primary efficacy endpoi
change in Hamilton Anxiety Scale (HAMA) total score from baseline to w
intent -to-treat (ITT) population. Mean baseline HAMA scores were 23.7
standard error of the mean (SEM) for the escitalopram-treated patients (
23.4 +/- 0.4 SEM for the paroxetine-treated patients (n=61). Upon analys
data, there were no statistically significant differences between treatmen
week 8 or week 24. At week 24, mean changes in HAMA scores were -1
SEM and -13.3 +/- 1 SEM for the escitalopram and paroxetine groups, re
The proportions of patients who met the response criterion (Clinical Glob
Impressions of Improvement (CGI-I) of 1 or 2) at week 8 were 65% for e
and 55.7% for paroxetine and at week 24 were 78.3% and 62.3%, respe
differences were not statistically significant. A greater proportion of patie
with paroxetine withdrew from the study due to adverse events compare
receiving escitalopram (22.6% vs. 6.6%, respectively; p=0.02). While no
adverse event was reported as the reason for discontinuation of escitalo
by more than one patient, headache, insomnia, and nausea each lead to
discontinuation of paroxetine in 2 or more patients. Upper respiratory tra
and diarrhea were reported more frequently with escitalopram than with
(14.8% vs. 4.8% and 21.3% vs. 8.1%, respectively). Insomnia (25.8% vs
constipation (14.5% vs. 1.6%), ejaculation disorder (30% vs. 14.8%), an
(26.2% vs. 5.9%) and decreased libido (22.6% vs. 4.9%) occurred more
the paroxetine group compared to the escitalopram group, respectively.
incidence of treatment emergent adverse events was 88.7% for paroxeti
for escitalopram (Bielski et al, 2005).

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Last Modified: July 24, 2009

DRUGDEX® Evaluations

FLUVOXAMINE

0.0 Overview

1) Class

a) This drug is a member of the following class(es):
Antidepressant
Central Nervous System Agent
Serotonin Reuptake Inhibitor

2) Dosing Information

a) Fluvoxamine Maleate

1) Adult

a) Depression

1) 50 to 300 mg/day ORALLY

b) Obsessive-compulsive disorder

1) immediate-release, 50 mg/day ORALLY at bedtime; may increase by 50 mg increments every 4-7 days to a MAX dosage of 300 mg/day (usual effective range 100 to 300 mg/day) (Prod Info LUVOX(R) oral tablets, 2007)

2) extended-release, 100 mg/day ORALLY at bedtime; may increase by 50 mg increments every week to a MAX dosage of 300 mg/day (usual effective range 100 to 300 mg/day) (Prod Info LUVOX(R) CR extended-release oral capsules, 2008)

c) Panic disorder

1) 50-300 mg/day ORALLY (mean effective dose is 225 mg/day)

d) Social phobia

1) extended-release, 100 mg/day ORALLY at bedtime; may increase by 50 mg increments every week to a MAX dosage of 300 mg/day (usual effective range 100 to 300 mg/day) (Prod Info LUVOX(R) CR extended-release oral capsules, 2008)

2) Pediatric

a) extended-release fluvoxamine maleate has not been evaluated for use in pediatric patients (Prod Info LUVOX(R) CR extended-release oral capsules, 2008)

b) safety and efficacy of immediate release fluvoxamine maleate has not been studied in patients with obsessive compulsive disorder (OCD) less than 8 years of age (Prod Info LUVOX(R) oral tablets, 2007)

1) Obsessive-compulsive disorder

a) immediate-release (ages 8-11 yr), 25 mg/day ORALLY at bedtime; may increase by 25 mg increments every 4-7 days to a MAX dosage of 200 mg/day (usual effective range 50 to 200 mg/day) (Prod Info LUVOX(R) oral tablets, 2007)

b) immediate-release (ages 12-17 yr), 25 mg/day ORALLY at bedtime; may increase by 25 mg increments every 4-7 days to a MAX dosage of 300 mg/day (usual effective range 50 to 200 mg/day) (Prod Info LUVOX(R) oral tablets, 2007)

3) Contraindications

a) Fluvoxamine Maleate

1) concomitant use with alosetron, pimozide, thioridazine, or tizanidine (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007)

2) concomitant use with a monoamine oxidase inhibitor (MAOI) or within 14 days following treatment with a MAOI (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007)

3) hypersensitivity to fluvoxamine maleate or any other component of the product (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007)

4) Serious Adverse Effects

a) Fluvoxamine Maleate

1) Bleeding, Abnormal
2) Depression, worsening
3) Extrapyramidal disease
4) Hyponatremia
5) Neuroleptic malignant syndrome
6) Psychotic disorder
7) Seizure
8) Serotonin syndrome
9) Stevens-Johnson syndrome
10) Stevens-Johnson syndrome
11) Suicidal thoughts
12) Syndrome of inappropriate antidiuretic hormone secretion
13) Toxic epidermal necrolysis
14) Withdrawal sign or symptom

5) Clinical Applications

a) Fluvoxamine Maleate
1) FDA Approved Indications
a) Obsessive-compulsive disorder
b) Social phobia
2) Non-FDA Approved Indications
a) Depression
b) Panic disorder

1.0 Dosing Information

Drug Properties

Adult Dosage

Pediatric Dosage

1.1 Drug Properties

A) Information on specific products and dosage forms can be obtained by referring to the Tradename List (Product Index)
B) Synonyms
Fluvoxamine
Fluvoxamine Maleate
C) Physicochemical Properties
1) Molecular Weight
a) Fluvoxamine base: 318.3 (Fleeger, 1994); Fluvoxamine maleate: 434.41 (Canada, 1997)
2) Solubility
a) Systemic: Fluvoxamine maleate is sparingly soluble in water (Prod Info Luvox, 97) and freely soluble in ethanol (Prod Info Luvox, 97).

1.3 Adult Dosage

Normal Dosage

Dosage in Renal Failure

Dosage in Hepatic Insufficiency

Dosage in Geriatric Patients

1.3.1 Normal Dosage

1.3.1.A Fluvoxamine Maleate

1.3.1.A.1 Oral route

Depression

Obsessive-compulsive disorder

Social phobia

1.3.1.A.1.a Depression
1) Doses of 50 to 300 milligrams/day administered orally have been found effective in clinical trials (Ottevanger, 1994; Martin et al, 1987a) (Porro et al, 1988). A single night time dose of fluvoxamine appears to be best tolerated (Siddigui et al, 1985).

1.3.1.A.1.b Obsessive-compulsive disorder
1) Immediate-release Formulation
a) The recommended dose of fluvoxamine maleate for the treatment of obsessions and

compulsions in adult patients with obsessive compulsive disorder (OCD) is 50 milligrams (mg) orally once daily at bedtime initially, titrated by 50 mg increments every 4 to 7 days, as tolerated, to the target dose range of 100 to 300 mg/day. The maximum dose should not exceed 300 mg/day. Treatment with fluvoxamine maleate beyond 10 weeks for OCD has not been studied in controlled trials; therefore, if treatment is necessary beyond 10 weeks, maintain the patient on the lowest effective dose and periodically reassess the need for treatment (Prod Info LUVOX(R) oral tablets, 2007).

2) Extended-release Formulation

a) The recommended dose of extended-release fluvoxamine maleate for the treatment of obsessions and compulsions in adult patients with obsessive compulsive disorder (OCD) is 100 milligrams (mg) orally once daily at bedtime initially, titrated by 50 mg increments every week, as tolerated, to the target dose range of 100 to 300 mg/day. The maximum dose should not exceed 300 mg/day. Treatment with extended-release fluvoxamine maleate beyond 12 weeks for OCD has not been studied in controlled trials; therefore, if treatment is necessary beyond 12 weeks, maintain the patient on the lowest effective dose and periodically reassess the need for treatment (Prod Info LUVOX(R) CR extended-release oral capsules, 2008).

3) Therapy Withdrawal

a) When discontinuing therapy, a gradual reduction in dose is preferred over abrupt cessation of therapy due to risk of withdrawal symptoms. Monitor for withdrawal symptoms when stopping fluvoxamine maleate therapy (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007).

1.3.1.A.1.c Social phobia

1) The recommended dose of extended-release fluvoxamine maleate for the treatment of social anxiety disorder (social phobia) in adult patients is 100 milligrams (mg) orally once daily at bedtime initially, titrated by 50 mg increments every week, as tolerated, to the target dose range of 100 to 300 mg/day. The maximum dose should not exceed 300 mg/day. Treatment with extended-release fluvoxamine maleate beyond 12 weeks for social anxiety disorder has not been studied in controlled trials; therefore, if treatment is necessary beyond 12 weeks, maintain the patient on the lowest effective dose and periodically reassess the need for treatment. When discontinuing therapy, a gradual withdrawal is preferred to an abrupt cessation of therapy due to risk of withdrawal symptoms. Monitor for withdrawal symptoms when stopping fluvoxamine maleate therapy (Prod Info LUVOX(R) CR extended-release oral capsules, 2008).

1.3.2 Dosage in Renal Failure

A) Fluvoxamine Maleate

1) Renal impairment does not appear to affect the pharmacokinetics of fluvoxamine (Raghoebar & Roseboom, 1988). However, a low starting dosage along with careful monitoring is recommended, especially during the first month of treatment.

1.3.3 Dosage in Hepatic Insufficiency

A) Fluvoxamine Maleate

1) Because fluvoxamine undergoes extensive hepatic metabolism, a reduction in the initial dose and slower dose titration may be required in patients with hepatic insufficiency (Prod Info Luvox(R), 1998); (Harten et al, 1993)(DeBree et al, 1983; Doogan, 1980). A 30% decrease in fluvoxamine clearance was noted in patients with hepatic insufficiency (Prod Info Luvox(R), 1998).

2) The pharmacokinetics of fluvoxamine were studied in 13 patients with biopsy-proven liver cirrhosis (van Harten et al, 1993a). They received a single oral 100 mg dose as an enteric-coated tablet and plasma samples were collected up to one week after administration. The mean elimination half-life was 25 hours and it increased with higher plasma bilirubin levels although no relationship between bilirubin and AUC was observed. The AUC was about 50% higher in patients than in healthy volunteers. The authors recommended that in patients with signs of active liver disease, it is wise to initiate fluvoxamine treatment at a lower daily dose and to carefully monitor the patient during subsequent dose increases.

1.3.4 Dosage in Geriatric Patients

A) Fluvoxamine Maleate

1) Mean fluvoxamine plasma concentrations are reported to be 40% higher in elderly versus young subjects following doses of 50 or 100 mg. Fluvoxamine clearance is also reduced by 50% in the elderly. Fluvoxamine dosage should be slowly titrated in elderly patients (Prod Info Luvox(R), 1998).

1.4 Pediatric Dosage

1.4.1 Normal Dosage

1.4.1.A Fluvoxamine Maleate

1.4.1.A.1 Oral route

1.4.1.A.1.a Obsessive-compulsive disorder

1) The recommended dose of fluvoxamine maleate (immediate-release) for the treatment of obsessions and compulsions in patients aged 8 to 11 years with obsessive compulsive disorder (OCD) is 25 milligrams (mg) orally once daily at bedtime initially, titrated by 25 mg increments every 4 to 7 days, as tolerated, to the target dose range of 50 to 200 mg/day (maximum dose not to exceed 200 mg/day). The recommended dose of fluvoxamine maleate (immediate-release) for the treatment of obsessions and compulsions in patients aged 12 to 17 years with OCD is 25 mg orally once daily at bedtime initially, titrated by 25 mg increments every 4 to 7 days, as tolerated, to the target dose range of 50 to 200 mg/day (maximum dose not to exceed 300 mg/day). Treatment with fluvoxamine maleate beyond 10 weeks for OCD has not been studied in controlled trials; therefore, if treatment is necessary beyond 10 weeks, maintain the patient on the lowest effective dose and periodically reassess the need for treatment. When discontinuing therapy, a gradual withdrawal is preferred to an abrupt cessation of therapy due to risk of withdrawal symptoms. Monitor for withdrawal symptoms when stopping fluvoxamine maleate therapy (Prod Info LUVOX(R) oral tablets, 2007).

2) Extended-release fluvoxamine maleate has not been evaluated for use in pediatric patients and is not indicated for use in this population (Prod Info LUVOX(R) CR extended-release oral capsules, 2008).

3) The safety and efficacy of immediate-release fluvoxamine maleate has not been evaluated in patients with obsessive compulsive disorder (OCD) less than 8 years of age (Prod Info LUVOX(R) oral tablets, 2007).

2.0 Pharmacokinetics

Onset and Duration

Drug Concentration Levels

ADME

2.1 Onset and Duration

A) Onset

1) Fluvoxamine Maleate

a) Initial Response

1) Obsessions: 3 to 10 weeks (Jenike et al, 1990; Goodman et al, 1990).

2) Depression: 2 to 3 weeks (Wilde et al, 1993a).

2.2 Drug Concentration Levels

A) Fluvoxamine Maleate

1) Peak Concentration

a) Immediate-release, Age Differences

1) Adults, 5.7 nanogram/mL; children (6 to 11 years), 14.8 nanogram/mL; adolescents (12 to 17 years), 4.2 to 6.7 nanogram/mL (Prod Info LUVOX(R) oral tablets, 2007).

a) In a multiple-dose study of immediate-release fluvoxamine maleate tablets in children age 6 to 11 years, adolescents age 12 to 17 years, and adults, peak concentrations were widely variable. Following oral administration of 100 mg twice daily, children exhibited a mean Cmax of 14.8 nanogram/milliliter (ng/mL) compared to 4.2 ng/mL in adolescents. Following oral administration of 150 mg twice daily, adolescents exhibited a mean Cmax of 6.7 ng/mL compared to 5.7 ng/mL in adults (Prod Info LUVOX(R) oral tablets, 2007).

b) In a dose proportionality study, following administration of fluvoxamine maleate 100, 200, and 300 mg/day for 10 days in 30 healthy volunteers, the mean maximum plasma concentrations at steady state were 88, 283, and 546 nanograms/mL, respectively (Prod Info LUVOX(R) oral tablets, 2007).

c) In a pharmacokinetics study, mean maximum plasma concentrations were 40% higher in elderly patients (66 to 73 years of age) than in younger subjects (19 to 35 years of age) following administration of immediate-release fluvoxamine 50 mg and 100 mg tablets (Prod Info LUVOX(R) oral tablets, 2007).

d) Immediate-release, Gender Differences

1) Children (6 to 11 years), females, 28.1 nanogram/milliliter; males, 9.1 nanogram/milliliter (Prod Info LUVOX(R) oral tablets, 2007).

a) In a multiple-dose study of 100 mg immediate-release fluvoxamine maleate tablets administered orally twice daily in children age 6 to 11 years and adolescents age 12 to 17 years, female children exhibited a higher mean Cmax compared to male children (28.1 ng/mL versus 9.1 ng/mL, respectively). Gender differences were not noted in adolescents (Prod Info LUVOX(R) oral tablets, 2007).

b) Extended-release

1) In a single-dose crossover study in 28 healthy volunteers, the mean Cmax was 38% lower following administration of extended-release capsules compared with immediate-release tablets. In a dose proportionality study, following administration of fluvoxamine maleate extended-release capsules 100, 200, and 300 mg/day in 20 healthy volunteers, the mean maximum plasma concentrations were 47, 161, and 319 nanograms/mL, respectively. The Cmax increased 5.7-fold following the 3-fold increase in dose from 100 to 300 mg (Prod Info LUVOX(R) CR extended-release oral capsules, 2008).

2) In a study of 28 healthy volunteers receiving extended-release fluvoxamine 100 mg, the Cmax was increased by approximately 60% in females compared with males (Prod Info LUVOX(R) CR extended-release oral capsules, 2008).

2) Time to Peak Concentration

a) Immediate-release

1) 3 to 8 hours (Prod Info LUVOX(R) oral tablets, 2007)

a) In a dose proportionality study, following administration of 100, 200, and 300 milligrams/day for 10 days in 30 healthy volunteers, the maximum plasma concentrations at steady state were reached within 3 to 8 hours (Prod Info LUVOX(R) oral tablets, 2007).

3) Steady State

a) 7 to 10 days (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007)

1) Steady-state plasma concentrations were reached following 1 week of dosing with either immediate-release or extended release fluvoxamine maleate according to dose proportionality studies of 100 to 300 mg/day of either extended-release capsules (n=20), or immediate-release tablets (n=30) (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007).

2) In additional studies, steady-state plasma concentrations of fluvoxamine were attained in about 10 days of multiple dosing (Harten, 1995; Wilde et al, 1993a; Vries et al, 1992; Wright et al, 1991).

4) Area Under the Curve

a) Immediate-release, Age Differences

1) Adults, 59.4 nanogram x hour/milliliter; children (6 to 11 years), 155.1 nanogram x hour/milliliter; adolescents (12 to 17 years), 43.9 to 69.6 nanogram x hour/milliliter (Prod Info LUVOX(R) oral tablets, 2007).

a) In a multiple-dose study of immediate-release fluvoxamine maleate tablets in children age 6 to 11 years, adolescents age 12 to 17 years, and adults, AUCs were widely variable. Following oral administration of 100 mg twice daily, children exhibited a mean AUC of 155.1 nanogram x hour/milliliter (ng x hr/mL) compared to 43.9 ng x hr/mL in adolescents. Following oral administration of 150 mg twice daily, adolescents exhibited a mean AUC of 69.6 ng x hr/mL compared to 59.4 ng x hr/mL in adults (Prod Info LUVOX(R) oral tablets, 2007).

b) Immediate-release, Gender Differences

1) Children (6 to 11 years), females, 293.5 nanogram x hour/milliliter; males, 95.8 nanogram x hour/milliliter (Prod Info LUVOX(R) oral tablets, 2007).

a) In a multiple-dose study of 100 mg immediate-release fluvoxamine maleate tablets administered orally twice daily in children age 6 to 11 years and adolescents age 12 to 17 years, female children exhibited a higher AUC compared to male children (293.5 ng x hr/mL versus 95.8 ng x hr/mL, respectively). Gender differences were not noted in adolescents (Prod Info LUVOX(R) oral tablets, 2007).

c) Extended-release

1) In a multiple-dose proportionality study, following administration of fluvoxamine maleate extended-release capsules 100, 200, and 300 mg/day in 20 healthy volunteers, the AUC increased 5.7-fold following the 3-fold increase in dose from 100 to 300 mg (Prod Info LUVOX(R) CR extended-release oral capsules, 2008).

2) In a study of healthy volunteers receiving extended-release fluvoxamine 100 mg, the AUC was increased by approximately 60% in females (n=13) compared with males (n=15) (Prod Info LUVOX(R) CR extended-release oral capsules, 2008).

2.3 ADME

Absorption

Distribution

Metabolism

Excretion

Elimination Half-life

2.3.1 Absorption

A) Fluvoxamine Maleate

1) Bioavailability

a) Oral, immediate-release: 53% (Prod Info LUVOX(R) oral tablets, 2007); extended-release: 84% relative to immediate-release (Prod Info LUVOX(R) CR extended-release oral capsules, 2008).

1) The absolute bioavailability of fluvoxamine maleate immediate-release tablets is 53% (Prod Info LUVOX(R) oral tablets, 2007). The bioavailability of fluvoxamine maleate extended-release capsules is 84% relative to immediate-release tablets (Prod Info LUVOX(R) CR extended-release oral capsules, 2008).

2) Effects of Food

a) No significant effect (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007).

1) Food causes the mean AUC and Cmax of fluvoxamine to increase only slightly and does not significantly affect the absorption of fluvoxamine maleate (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007).

2.3.2 Distribution

A) Distribution Sites

1) Fluvoxamine Maleate

a) Protein Binding

1) 80% (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007).

a) Fluvoxamine maleate is 80% bound to plasma protein, primarily albumin, over a concentration range of 20 to 2000 nanograms/mL (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007).

B) Distribution Kinetics

1) Fluvoxamine Maleate

a) Volume of Distribution

1) 25 L/kg (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007).

a) Fluvoxamine maleate exhibits extensive tissue distribution, with a mean apparent Vd of approximately 25 L/kg (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007).

2.3.3 Metabolism

A) Metabolism Sites and Kinetics

1) Fluvoxamine Maleate

a) Liver, extensive (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX (R) oral tablets, 2007).

1) Fluvoxamine is extensively metabolized in the liver (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007) (DeBree et al, 1983a; Doogan, 1980a) via oxidative demethylation and deamination (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007).

B) Metabolites

1) Fluvoxamine Maleate

a) Fluvoxamine acid (active) (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007).

1) Nine mostly inactive metabolites of fluvoxamine maleate have been identified. One metabolite, fluvoxamine acid, has a weak effect (1-2 orders of magnitude less potent than the parent compound) on the inhibition of serotonin uptake (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007).

2.3.4 Excretion

A) Kidney

1) Fluvoxamine Maleate

a) Renal Excretion (%)

1) 94% (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007; DeBree et al, 1983a; Doogan, 1980a).

a) Following a dose of fluvoxamine maleate 5 mg orally, an average of 94% of drug-related products was recovered in the urine within 71 hours. Two percent is excreted unchanged in the urine (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007).

b) The mean minimum concentrations were similar after 4 and 6 weeks of treatment with fluvoxamine maleate 50 mg twice day day (n=13) in renally impaired patients with creatinine clearance of 5 to 45 mL/minute, suggesting no accumulation of fluvoxamine in this group (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007).

B) Total Body Clearance

1) Fluvoxamine Maleate

a) Hepatic Impairment
1) There was a 30% decrease in fluvoxamine clearance in patients with hepatic dysfunction compared with healthy subjects in a cross study (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007).
b) Elderly
1) In elderly patients the clearance of fluvoxamine was reduced by 50% so initiation of therapy should be titrated slowly (Prod Info LUVOX(R) oral tablets, 2007)

2.3.5 Elimination Half-life
A) Parent Compound
1) Fluvoxamine Maleate
a) Immediate-release, 15.6 hours (Prod Info LUVOX(R) oral tablets, 2007); extended-release, 16.3 hours (Prod Info LUVOX(R) CR extended-release oral capsules, 2008).
1) Immediate-release
a) The mean plasma half-life of fluvoxamine at steady state following multiple dose oral administration of immediate-release tablets 100 mg/day in young, healthy volunteers was 15.6 hours (Prod Info LUVOX(R) oral tablets, 2007).
b) In a study comparing administration of immediate-release fluvoxamine 50 mg and 100 mg to elderly patients (66 to 73 years of age) and younger subjects (19 to 35 years of age), the elimination half-life following multiple doses was 17.4 and 25.9 hours in elderly patients compared with 13.6 and 15.6 hours in younger subjects, respectively (Prod Info LUVOX(R) oral tablets, 2007).
2) Extended-release
a) The mean plasma half-life of fluvoxamine following a single oral dose of a 100-mg extended release capsule in healthy volunteers was 16.3 hours (Prod Info LUVOX(R) CR extended-release oral capsules, 2008).

3.0 Cautions

Contraindications

Precautions

Adverse Reactions

Teratogenicity/Effects in Pregnancy/Breastfeeding

Drug Interactions

3.0.A Black Box WARNING
1) Fluvoxamine Maleate
a) Oral (Capsule, Extended Release; Tablet)
Suicidality and Antidepressant Drugs
Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of fluvoxamine maleate extended-release capsules or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007). Fluvoxamine maleate extended-release capsules are not approved for use in pediatric patients (Prod Info LUVOX(R) CR extended-release oral capsules, 2008). Fluvoxamine maleate tablets are not approved for use in pediatric patients except for patients with obsessive compulsive disorder (OCD) (Prod Info LUVOX(R) oral tablets, 2007).

3.1 Contraindications
A) Fluvoxamine Maleate
1) concomitant use with alosetron, pimozide, thioridazine, or tizanidine (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007)
2) concomitant use with a monoamine oxidase inhibitor (MAOI) or within 14 days following treatment with a

MAOI (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007)
3) hypersensitivity to fluvoxamine maleate or any other component of the product (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007)

3.2 Precautions

A) Fluvoxamine Maleate

1) suicidal ideation and behavior or worsening depression has been reported, particularly in children, adolescents, and young adults during the first few months of therapy or following changes in dosage; monitoring recommended (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007)
2) abnormal bleeding, sometimes fatal, has occurred; risk may be increased with concomitant use of drugs that affect coagulation (eg, NSAIDs, aspirin, warfarin) (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007)
3) abrupt discontinuation; serious discontinuation symptoms have been reported with abrupt fluvoxamine maleate withdrawal; monitoring recommended; reduce dose gradually if possible (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007)
4) bipolar disorder, in patients at risk (eg, major depressive disorder (MDD) may be the initial presentation of bipolar disorder); may cause a mixed/manic episode (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007)
5) concomitant use with antipsychotic agents; may increase the risk of neuroleptic malignant syndrome (NMS) or NMS-like events (eg, hyperthermia, muscle rigidity, autonomic instability, mental status changes); use with caution (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007)
6) concomitant use with serotonergic drugs (eg, SSRIs, serotonin-norepinephrine reuptake inhibitors), diazepam, ramelteon, or serotonin precursors (eg, tryptophan) is not recommended (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007)
7) concomitant use with 5-hydroxytryptamine receptor agonists (triptans); risk of serotonin syndrome; monitoring recommended if concurrent use is clinically warranted (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007)
8) hyponatremia and/or syndrome of inappropriate antidiuretic hormone secretion (SIADH) has occurred, greater risk in patients who are volume-depleted, elderly, or receiving concurrent diuretic therapy; discontinue if symptomatic hyponatremia occurs (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007)
9) liver dysfunction; lower doses may be necessary (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007)
10) mania, history of; may cause an activation of mania or hypomania (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007)
11) seizure disorder, history of (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007)

3.3 Adverse Reactions

Cardiovascular Effects

Dermatologic Effects

Endocrine/Metabolic Effects

Gastrointestinal Effects

Hematologic Effects

Hepatic Effects

Immunologic Effects

Musculoskeletal Effects

Neurologic Effects

Ophthalmic Effects

Psychiatric Effects

Renal Effects

Reproductive Effects

Respiratory Effects

Other

3.3.1 Cardiovascular Effects

3.3.1.A Fluvoxamine Maleate

Abnormal ECG

Hypotension

Pulse irregular

Sudden cardiac death

3.3.1.A.1 Abnormal ECG

a) Fluvoxamine maleate use was not associated with important changes in ECG variables during short-term, placebo-controlled trials involving patients with obsessive-compulsive disorder or depression (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007).

b) Premature ventricular contractions (PVCs) not requiring therapy have been occasionally reported (Garnier et al, 1993).

c) In a pooled analysis of ECG data from several studies, fluvoxamine caused slight increases in the R-R, QT, and QTc intervals (Guelfi et al, 1983a; DeWilde & Doogan, 1982; De Wilde et al, 1983a; Benfield & Ward, 1986b). Fluvoxamine did not change T wave configurations as seen after tricyclic antidepressant administration (Roos, 1983a).

d) In 25 healthy males, fluvoxamine 50 to 100 mg three times daily for 9 days produced a mean decrease in heart rate of 5 beats/minute compared with placebo (Robinson & Doogan, 1982).

3.3.1.A.2 Hypotension

a) Incidence: 1% (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007)

b) Hypotension was reported in at least 1% of patients with major depressive disorder or obsessive-compulsive disorder who took immediate-release fluvoxamine maleate during premarketing clinical trials (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007).

c) Orthostatic hypotension, which improved upon dose reduction, was reported with fluvoxamine therapy in patients with obsessive-compulsive disorder (Price et al, 1987).

d) Fluvoxamine did not produce any significant changes in systolic and diastolic blood pressure or mean arterial pressure in a study using single doses of 50, 75, and 100 mg administered to 17 healthy volunteers (Wilson et al, 1983).

3.3.1.A.3 Pulse irregular

a) Incidence: 0.1% to 1% (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007)

b) Irregular pulse was reported in 0.1% to 1% of patients with major depressive disorder or obsessive-compulsive disorder who took immediate-release fluvoxamine maleate during premarketing clinical trials (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007).

c) fluvoxamine maleate did not produce any significant changes in pulse rate in a study using single doses of 50, 75, and 100 mg administered to 17 healthy volunteers (Wilson et al, 1983).

3.3.1.A.4 Sudden cardiac death

a) In a large cohort study including 481,744 persons and 1487 cases of sudden cardiac death occurring in a community setting, the use of SSRIs was not associated with an increased risk of sudden cardiac death (rate ratio, 0.95; 95% CI, 0.42 to 2.15). In contrast, users of tricyclic antidepressants in doses of 100 mg or higher (amitriptyline or its equivalent) had a 41% increased rate of sudden cardiac death

(rate ratio, 1.41; 95% CI, 1.02 to 1.95) (Ray et al, 2004).

3.3.2 Dermatologic Effects

3.3.2.A Fluvoxamine Maleate

Alopecia

Rash

Stevens-Johnson syndrome

Sweating

Toxic epidermal necrolysis

3.3.2.A.1 Alopecia

a) Incidence: 0.1% to 1% (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007)

b) Alopecia was reported in between 0.1% and 1% of patients with major depressive disorder or obsessive-compulsive disorder who took immediate-release fluvoxamine maleate during premarketing clinical trials (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007).

c) A case of patchy baldness was observed following 6 months of therapy with fluvoxamine. A 41-year-old male had taken the medication in varying dosages from 50 to 250 mg/day for treatment of obsessive-compulsive disorder. Three months following discontinuation of fluvoxamine, regrowth of fine white hair was noted over the alopecic patches (Parameshwar, 1996).

3.3.2.A.2 Rash

a) In a placebo-controlled study involving pediatric patients with obsessive-compulsive disorder, rash was reported in 5% or more of patients treated with immediate-release fluvoxamine maleate. This was at least twice the rate found in placebo-treated patients (Prod Info LUVOX(R) oral tablets, 2007).

3.3.2.A.3 Stevens-Johnson syndrome

a) Stevens-Johnson syndrome has been reported during postmarketing use of immediate-release fluvoxamine maleate, although a causal relationship has not been established (Prod Info LUVOX(R) oral tablets, 2007; Prod Info LUVOX(R) CR extended-release oral capsules, 2008).

3.3.2.A.4 Sweating

a) Incidence: immediate-release, 7%; extended-release (social anxiety disorder), 6%; extended-release (obsessive-compulsive disorder), 7% (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007)

b) In short-term, placebo-controlled clinical trials evaluating immediate-release fluvoxamine maleate (100 mg/day to 300 mg/day) for the treatment of obsessive-compulsive disorder (OCD) or depression, sweating was reported in 7% of fluvoxamine maleate patients (n=892) compared with 3% of placebo patients (n=778) (Prod Info LUVOX(R) oral tablets, 2007). The use of 100 mg/day to 300 mg/day extended-release fluvoxamine maleate has been evaluated in short-term, placebo-controlled trials of social anxiety disorder (SAD) and OCD. For use in SAD treatment, 6% of fluvoxamine maleate patients (n=279) reported sweating compared with 2% of placebo patients (n=276). For use in OCD treatment, 7% of fluvoxamine maleate patients (n=124) reported sweating compared with less than 1% of placebo patients (n=124) (Prod Info LUVOX(R) CR extended-release oral capsules, 2008).

3.3.2.A.5 Toxic epidermal necrolysis

a) Toxic epidermal necrolysis has been reported during postmarketing use of immediate-release fluvoxamine maleate, although a causal relationship has not been established (Prod Info LUVOX(R) oral tablets, 2007; Prod Info LUVOX(R) CR extended-release oral capsules, 2008).

b) A case of severe toxic epidermal necrolysis (TEN) was reported in a 16-year-old girl following treatment with fluvoxamine. The patient had been treated with clomipramine 100 mg/day and clorazepate 50 mg/day, and metoclopramide had been given once. After one week of clomipramine, it was withdrawn and replaced by fluvoxamine 100 mg/day. Within 8 days of fluvoxamine, the patient developed a widespread bullous eruption with mucous membrane involvement. Two days later, she showed epidermal detachment of the trunk, face, and proximal limbs involving 30% of the body surface area. This rapidly progressed to include 60% of body surface area. Histological examination of the skin showed total necrosis of the epidermis typical of TEN. Extensive epidemiologic data ruled out other

drugs as causative agents. Fluvoxamine has been previously associated with a case of Stevens-Johnson syndrome (Wolkenstein et al, 1993).

3.3.3 Endocrine/Metabolic Effects

3.3.3.A Fluvoxamine Maleate

Excessive thirst

Galactorrhea

Hyperglycemia

Hyponatremia

Ineffective thermoregulation

Syndrome of inappropriate antidiuretic hormone secretion

Weight loss

3.3.3.A.1 Excessive thirst

a) There was a two-fold increase in the rate of thirst during studies of obsessive-compulsive disorder (OCD) treatment compared with studies of OCD and depression (Prod Info LUVOX(R) oral tablets, 2007).

b) Polydipsia occurred in 3 women after taking fluvoxamine 100 mg/day. One patient developed polydipsia on the second day of treatment. She was also taking levosulpiride and alprazolam. The symptoms disappeared on withdrawal of fluvoxamine but recurred when the drug was restarted 2 weeks later. The adverse effect disappeared when the drug was stopped 1 week later. Water ingestion also increased markedly in a 30-year-old woman with dysthymia and a 40-year-old woman with panic disorder and agoraphobia shortly after they started fluvoxamine treatment. Symptoms rapidly disappeared in these 2 women after the drug was discontinued (Benazzi & Mazzoli, 1993).

3.3.3.A.2 Galactorrhea

a) Galactorrhea and amenorrhea associated with fluvoxamine were reported in a 38-year-old woman with refractory bipolar affective disorder; this patient had been treated for over a decade with several psychotropic agents. The patient had been maintained for an undetermined length of time on loxapine 150 mg daily, oxazepam 30 mg three times daily, and zopiclone 7.5 mg at bedtime. Fluvoxamine was prescribed for depression, and the dose was titrated to 150 mg daily while the loxapine dosage was decreased to 75 mg daily. Six weeks after starting fluvoxamine, she complained of amenorrhea followed soon by galactorrhea. Thorough evaluation ruled out an underlying organic etiology; however, the serum prolactin level was 80 mcg/L (normal, 4 to 30 mcg/L). Galactorrhea resolved 3 weeks after stopping fluvoxamine, and menstruation resumed a week later. The temporal relationship between fluvoxamine and the onset of galactorrhea and amenorrhea suggests a possible etiologic role for fluvoxamine (Jeffries et al, 1992). The probable mechanism for SSRI-induced galactorrhea is an increase in serum prolactin. This may result from direct stimulation of postsynaptic serotonin receptors in the hypothalamus or presynaptic serotonin receptor mediated inhibition of dopamine release (Bronzo & Stahl, 1993).

3.3.3.A.3 Hyperglycemia

a) Incidence: less than 0.01% (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007)

b) Hyperglycemia was reported in less than 0.1% of patients with major depressive disorder or obsessive-compulsive disorder who took immediate-release fluvoxamine maleate during premarketing clinical trials (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007).

c) A 60-year-old woman with well-controlled insulin-dependent diabetes developed hyperglycemia following fluvoxamine administration for the treatment of major depression. Five days following initiation of fluvoxamine (100 mg/day) therapy, the woman's blood glycemia began to increase significantly without change in diet or compliance. Glycemia increased from 120 mg/dL at baseline to 210 mg/dL at days 19 and 21. Hyperglycemia persisted for 9 days before the patient discontinued fluvoxamine and the blood glycemia returned to baseline level. Twenty-two days later, fluvoxamine therapy was reinitiated and glycemia increased to the same range as the initial episode. Fluvoxamine was again

stopped and glycemia returned to normal within 2 days (Oswald et al, 2003).

3.3.3.A.4 Hyponatremia

a) Hyponatremia (serum sodium less than 110 mmol/L) has occurred in patients receiving fluvoxamine maleate, possibly as a result of SIADH. Symptoms included headache, difficulty concentrating, memory impairment, confusion, weakness, and unsteadiness. Severe hyponatremia signs/symptoms have included hallucination, syncope, seizure, coma, respiratory arrest, and death. Patients at highest risk include the elderly, volume-depleted, or those taking diuretics. Consider drug discontinuation with symptomatic hyponatremia (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007).

b) Of the 63 case reports of fluoxetine-induced SIADH reported to the US Food and Drug Administration, the majority occurred in patients over 70 years of age. Based on published reports, the onset of the SIADH was between 3 days and 4 months after starting therapy. Symptoms included confusion, lethargy, dizziness, fatigue, anorexia, delirium, and abdominal pain. Abnormal laboratory findings consisted of a decreased serum osmolality (median 251 milliosmoles/liter (mOsm/L); range 214 to 272 mOsm/L), decreased serum sodium concentration (median 118 mEq/L; range 98 to 130 milliequivalents/liter (mEq/L)), and urine osmolality (median 392.5 mOsm/L; 229 to 613 mOsm/L). In all but 1 case report, the SSRI was stopped, and fluid restriction was required before hyponatremia resolved; 1 patient was also treated with sodium chloride 3%. Patients in their fifties generally recovered in 2 to 4 days versus patients in their eighties who required up to 14 days for complete recovery. Of the 6 patients rechallenged with an SSRI, 3 developed a decrease in serum sodium consistent with SIADH, and 3 tolerated rechallenge without adverse events. In many case reports, inadequate reporting of symptoms, laboratory results, and exclusion of other causes were NOT included making it difficult to attribute SIADH to the SSRI (Woo & Smythe, 1997).

3.3.3.A.5 Ineffective thermoregulation

a) Three women developed diaphoresis, shivering, restlessness, anxiety, and subnormal body temperature, followed by low-grade fever, within 30 minutes of taking a first dose of fluvoxamine 25 mg in combination with a benzodiazepine (medazepam or ethyl loflazepate) in the evening. The women were being treated for either panic disorder or anxiety disorder, with associated depressive symptoms. Symptoms abated and disappeared by the next morning. One woman took a second dose and had the same experience. In all cases, symptoms did not reappear after discontinuation of fluvoxamine (Okada & Okajima, 2001).

3.3.3.A.6 Syndrome of inappropriate antidiuretic hormone secretion

a) SIADH with hyponatremia (serum sodium less than 110 mmol/L) has occurred in patients receiving fluvoxamine maleate. Symptoms included headache, difficulty concentrating, memory impairment, confusion, weakness, and unsteadiness. Severe hyponatremia signs/symptoms have included hallucination, syncope, seizure, coma, respiratory arrest, and death. Patients at highest risk include the elderly, volume-depleted, or those taking diuretics. Consider drug discontinuation with symptomatic hyponatremia (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007).

b) Of the 63 case reports of fluoxetine-induced SIADH reported to the US Food and Drug Administration, the majority occurred in patients over 70 years of age. Based on published reports, the onset of the SIADH was between 3 days and 4 months after starting therapy. Symptoms included confusion, lethargy, dizziness, fatigue, anorexia, delirium, and abdominal pain. Abnormal laboratory findings consisted of a decreased serum osmolality (median 251 milliosmoles/liter (mOsm/L); range 214 to 272 mOsm/L), decreased serum sodium concentration (median 118 mEq/L; range 98 to 130 milliequivalents/liter (mEq/L)), and urine osmolality (median 392.5 mOsm/L; 229 to 613 mOsm/L). In all but 1 case report, the SSRI was stopped, and fluid restriction was required before hyponatremia resolved; 1 patient was also treated with sodium chloride 3%. Patients in their fifties generally recovered in 2 to 4 days versus patients in their eighties who required up to 14 days for complete recovery. Of the 6 patients rechallenged with an SSRI, 3 developed a decrease in serum sodium consistent with SIADH, and 3 tolerated rechallenge without adverse events. In many case reports, inadequate reporting of symptoms, laboratory results, and exclusion of other causes were NOT included making it difficult to attribute SIADH to the SSRI (Woo & Smythe, 1997).

c) A patient treated with fluvoxamine developed SIADH, which presented as profound confusion. Drug withdrawal resulted in rapid resolution of the CNS and biochemical abnormalities (McHardy, 1993).

3.3.3.A.7 Weight loss

a) Incidence: immediate-release, at least 1%; extended-release (obsessive-compulsive disorder), 2% (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007)

b) Weight loss was reported in at least 1% of patients with major depressive disorder or obsessive-compulsive disorder (OCD) who took immediate-release fluvoxamine maleate during premarketing clinical trials. There was a two-fold increase in the rate of weight loss in studies of OCD treatment compared with studies of OCD and depression (Prod Info LUVOX(R) oral tablets, 2007). The use of 100 mg/day to 300 mg/day extended-release fluvoxamine maleate has been evaluated in short-term,

placebo-controlled trials of social anxiety disorder (SAD) and OCD. Weight loss was not reported during SAD treatment. For use in OCD treatment, 2% of fluvoxamine maleate patients (n=124) reported weight loss compared with less than 1% of placebo patients (n=124) (Prod Info LUVOX(R) CR extended-release oral capsules, 2008).
c) Decreased appetite and weight loss have occurred in children taking SSRIs, including fluvoxamine maleate. Regular monitoring of growth is recommended. Weight loss was more frequent in pediatric OCD patients (n=57) taking immediate-release fluvoxamine maleate than in patients taking placebo (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007).

3.3.4 Gastrointestinal Effects

3.3.4.A Fluvoxamine Maleate

Constipation

Diarrhea

Dysphagia

Flatulence

Gastrointestinal hemorrhage

Indigestion

Loss of appetite

Nausea

Taste sense altered

Vomiting

Xerostomia

3.3.4.A.1 Constipation
a) Incidence: immediate-release, 10%; extended-release (social anxiety disorder), 6%; extended-release (obsessive-compulsive disorder), 4% (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007)
b) In short-term, placebo-controlled clinical trials evaluating immediate-release fluvoxamine maleate (100 mg/day to 300 mg/day) for the treatment of obsessive-compulsive disorder (OCD) or depression, constipation was reported in 10% of fluvoxamine maleate patients (n=892) compared with 8% of placebo patients (n=778) (Prod Info LUVOX(R) oral tablets, 2007). The use of 100 mg/day to 300 mg/day extended-release fluvoxamine maleate has been evaluated in short-term, placebo-controlled trials of social anxiety disorder (SAD) and OCD. For use in SAD treatment, 6% of fluvoxamine maleate patients (n=279) reported constipation compared with 5% of placebo patients (n=276). For use in OCD treatment, 4% of fluvoxamine maleate patients (n=124) reported constipation compared with less than 1% of placebo patients (n=124) (Prod Info LUVOX(R) CR extended-release oral capsules, 2008).
c) Constipation was reported by 18% of fluvoxamine-treated patients (n=222) from pooled data of 10 double-blind, placebo-controlled studies comparing fluvoxamine and imipramine. Constipation was reported by 20% and 7% of patients treated with imipramine and placebo, respectively (Benfield & Ward, 1986b).

3.3.4.A.2 Diarrhea
a) Incidence: immediate-release, 11%; extended-release (social anxiety disorder), 14%; extended-release (obsessive-compulsive disorder), 18% (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007)
b) In short-term, placebo-controlled clinical trials evaluating immediate-release fluvoxamine maleate (100 mg/day to 300 mg/day) for the treatment of obsessive-compulsive disorder (OCD) or depression, diarrhea was reported in 11% of fluvoxamine maleate patients (n=892) compared with 7% of placebo patients (n=778) (Prod Info LUVOX(R) oral tablets, 2007). The use of 100 mg/day to 300 mg/day

extended-release fluvoxamine maleate has been evaluated in short-term, placebo-controlled trials of social anxiety disorder (SAD) and OCD. For use in SAD treatment, 14% of fluvoxamine maleate patients (n=279) reported diarrhea compared with 5% of placebo patients (n=276). For use in OCD treatment, 18% of fluvoxamine maleate patients (n=124) reported diarrhea compared with 8% of placebo patients (n=124) (Prod Info LUVOX(R) CR extended-release oral capsules, 2008).

3.3.4.A.3 Dysphagia

a) Incidence: immediate-release, 2% (Prod Info LUVOX(R) oral tablets, 2007)

b) In short-term, placebo-controlled clinical trials evaluating immediate-release fluvoxamine maleate (100 mg/day to 300 mg/day) for the treatment of obsessive-compulsive disorder (OCD) or depression, dysphagia was reported in 2% of fluvoxamine maleate patients (n=892) compared with 1% of placebo patients (n=778). There was a two-fold decrease in the rate of dysphagia in studies of OCD treatment compared with studies of OCD and depression (Prod Info LUVOX(R) oral tablets, 2007).

3.3.4.A.4 Flatulence

a) Incidence: immediate-release, at least 4% (Prod Info LUVOX(R) oral tablets, 2007)

b) In short-term, placebo-controlled clinical trials evaluating immediate-release fluvoxamine maleate (100 mg/day to 300 mg/day) for the treatment of obsessive-compulsive disorder (OCD) or depression, flatulence was reported in 4% of fluvoxamine maleate patients (n=892) compared with 3% of placebo patients (n=778) (Prod Info LUVOX(R) oral tablets, 2007).

c) In a placebo-controlled study involving pediatric patients with obsessive-compulsive disorder, flatulence was reported in 5% or more of patients treated with immediate-release fluvoxamine maleate. This was at least twice the rate found in placebo-treated patients (Prod Info LUVOX(R) oral tablets, 2007).

3.3.4.A.5 Gastrointestinal hemorrhage

See Drug Consult reference: CONCOMITANT USE OF SSRIs AND NSAIDs - INCREASED RISK OF GASTROINTESTINAL BLEEDING

3.3.4.A.6 Indigestion

a) Incidence: immediate-release, 10%; extended-release (social anxiety disorder), 10%; extended-release (obsessive-compulsive disorder), 8% (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007)

b) In short-term, placebo-controlled clinical trials evaluating immediate-release fluvoxamine maleate (100 mg/day to 300 mg/day) for the treatment of obsessive-compulsive disorder (OCD) or depression, dyspepsia was reported in 10% of fluvoxamine maleate patients (n=892) compared with 5% of placebo patients (n=778) (Prod Info LUVOX(R) oral tablets, 2007). The use of 100 mg/day to 300 mg/day extended-release fluvoxamine maleate has been evaluated in short-term, placebo-controlled trials of social anxiety disorder (SAD) and OCD. For use in SAD treatment, 10% of fluvoxamine maleate patients (n=279) reported dyspepsia compared with 4% of placebo patients (n=276). For use in OCD treatment, 8% of fluvoxamine maleate patients (n=124) reported dyspepsia compared with 5% of placebo patients (n=124) (Prod Info LUVOX(R) CR extended-release oral capsules, 2008).

3.3.4.A.7 Loss of appetite

a) Incidence: immediate-release, 6%; extended-release (social anxiety disorder), 14%; extended-release (obsessive-compulsive disorder), 13% (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007)

b) In short-term, placebo-controlled clinical trials evaluating immediate-release fluvoxamine maleate (100 mg/day to 300 mg/day) for the treatment of obsessive-compulsive disorder (OCD) or depression, anorexia was reported in 6% of fluvoxamine maleate patients (n=892) compared with 2% of placebo patients (n=778) (Prod Info LUVOX(R) oral tablets, 2007). The use of 100 mg/day to 300 mg/day extended-release fluvoxamine maleate has been evaluated in short-term, placebo-controlled trials of social anxiety disorder (SAD) and OCD. For use in SAD treatment, 14% of fluvoxamine maleate patients (n=279) reported anorexia compared with 1% of placebo patients (n=276). For use in OCD treatment, 13% of fluvoxamine maleate patients (n=124) reported anorexia compared with 5% of placebo patients (n=124) (Prod Info LUVOX(R) CR extended-release oral capsules, 2008).

c) Anorexia was reported by 15% of patients receiving fluvoxamine, according to the pooled results of 10 placebo-controlled, double-blind studies comparing fluvoxamine and imipramine (Benfield & Ward, 1986b).

3.3.4.A.8 Nausea

a) Incidence: immediate-release, 40%; extended-release (social anxiety disorder), 39%; extended-release (obsessive-compulsive disorder), 34% (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007)

b) In short-term, placebo-controlled clinical trials evaluating immediate-release fluvoxamine maleate (100 mg/day to 300 mg/day) for the treatment of obsessive-compulsive disorder (OCD) or depression, nausea was reported in 40% of fluvoxamine maleate patients (n=892) compared with 14% of placebo patients (n=778). There was an approximate 25% decrease in the rate of nausea in studies of OCD

treatment compared with studies of OCD and depression (Prod Info LUVOX(R) oral tablets, 2007). The use of 100 mg/day to 300 mg/day extended-release fluvoxamine maleate has been evaluated in short-term, placebo-controlled trials of social anxiety disorder (SAD) and OCD. For use in SAD treatment, 39% of fluvoxamine maleate patients (n=279) reported nausea compared with 11% of placebo patients (n=276). For use in OCD treatment, 34% of fluvoxamine maleate patients (n=124) reported nausea compared with 13% of placebo patients (n=124) (Prod Info LUVOX(R) CR extended-release oral capsules, 2008).

c) SSRIs produce nausea and vomiting in 20% to 25% and 2% to 3% of patients, respectively. In the majority of patients, nausea gradually decreases or resolves over approximately 3 weeks. However, in others, reduction of the dose or discontinuation of the drug is required. For this group, ondansetron or cisapride administered for a few weeks may facilitate continued treatment with the SSRI. Limited data suggest that ondansetron is more effective; however, it is also more expensive. Use of cisapride with careful monitoring for arrhythmias may be more cost effective and open therapy to a broader group of patients. The proposed mechanism for SSRI-induced nausea and vomiting is increased serotonin levels within the chemoreceptor trigger zone and area postrema in the brainstem, the primary areas within the brain associated with nausea and vomiting (McManis & Talley, 1997).

d) Approximately 12.7% of patients with depression receiving fluvoxamine reported nausea as an adverse effect during an open, large-scale study of over 5000 patients. Nausea was the stated reason for withdrawing from this study in 5.6% of all patients (Martin et al, 1987).

e) Event monitoring in Great Britain of fluvoxamine use in 10,401 patients revealed the most commonly reported individual event to be nausea and vomiting (13%) (Edwards et al, 1994).

3.3.4.A.9 Taste sense altered

a) Incidence: immediate-release, 3%; extended-release, 2% (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007)

b) In short-term, placebo-controlled clinical trials evaluating immediate-release fluvoxamine maleate (100 mg/day to 300 mg/day) for the treatment of obsessive-compulsive disorder (OCD) or depression, taste perversion was reported in 3% of fluvoxamine maleate patients (n=892) compared with 1% of placebo patients (n=778) (Prod Info LUVOX(R) oral tablets, 2007). The use of 100 mg/day to 300 mg/day extended-release fluvoxamine maleate has been evaluated in short-term, placebo-controlled trials of social anxiety disorder (SAD) and OCD. For use in SAD treatment, 2% of fluvoxamine maleate patients (n=279) reported taste perversion compared with less than 1% of placebo patients (n=276). For use in OCD treatment, 2% of fluvoxamine maleate patients (n=124) reported taste perversion compared with less than 1% of placebo patients (n=124) (Prod Info LUVOX(R) CR extended-release oral capsules, 2008).

3.3.4.A.10 Vomiting

a) Incidence: immediate-release, 5%; extended-release (social anxiety disorder), 0%; extended-release (obsessive-compulsive disorder), 6% (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007)

b) In short-term, placebo-controlled clinical trials evaluating immediate-release fluvoxamine maleate (100 mg/day to 300 mg/day) for the treatment of obsessive-compulsive disorder (OCD) or depression, vomiting was reported in 5% of fluvoxamine maleate patients (n=892) compared with 2% of placebo patients (n=778) (Prod Info LUVOX(R) oral tablets, 2007). The use of 100 mg/day to 300 mg/day extended-release fluvoxamine maleate has been evaluated in short-term, placebo-controlled trials of social anxiety disorder (SAD) and OCD. Vomiting did not occur during SAD treatment. For use in OCD treatment, 6% of fluvoxamine maleate patients (n=124) reported vomiting compared with 2% of placebo patients (n=124) (Prod Info LUVOX(R) CR extended-release oral capsules, 2008).

c) SSRIs produce nausea and vomiting in 20% to 25% and 2% to 3% of patients, respectively. In the majority of patients, nausea gradually decreases or resolves over approximately 3 weeks. However, in others, reduction of the dose or discontinuation of the drug is required. For this group, ondansetron or cisapride administered for a few weeks may facilitate continued treatment with the SSRI. Limited data suggest that ondansetron is more effective; however, it is also more expensive. Use of cisapride with careful monitoring for arrhythmias may be more cost effective and open therapy to a broader group of patients. The proposed mechanism for SSRI-induced nausea and vomiting is increased serotonin levels within the chemoreceptor trigger zone and area postrema in the brainstem, the primary areas within the brain associated with nausea and vomiting (McManis & Talley, 1997).

d) Vomiting was reported by 3.6% of patients and led to the discontinuation of therapy in 2.8% of all patients in a open, large-scale study of over 5000 patients with depression (Martin et al, 1987).

e) Event monitoring in Great Britain of fluvoxamine use in 10,401 patients revealed the most commonly reported individual event to be nausea and vomiting (13%) (Edwards et al, 1994).

3.3.4.A.11 Xerostomia

a) Incidence: immediate-release, 14%; extended-release (social anxiety disorder), 11%; extended-release (obsessive-compulsive disorder), 10% (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007)

b) In short-term, placebo-controlled clinical trials evaluating immediate-release fluvoxamine maleate (100 mg/day to 300 mg/day) for the treatment of obsessive-compulsive disorder (OCD) or depression,

dry mouth was reported in 14% of fluvoxamine maleate patients (n=892) compared with 10% of placebo patients (n=778) (Prod Info LUVOX(R) oral tablets, 2007). The use of 100 mg/day to 300 mg/day extended-release fluvoxamine maleate has been evaluated in short-term, placebo-controlled trials of social anxiety disorder (SAD) and OCD. For use in SAD treatment, 11% of fluvoxamine maleate patients (n=279) reported dry mouth compared with 8% of placebo patients (n=276). For use in OCD treatment, 10% of fluvoxamine maleate patients (n=124) reported dry mouth compared with 9% of placebo patients (n=124) (Prod Info LUVOX(R) CR extended-release oral capsules, 2008).
c) From pooled data of 10 double-blind, placebo-controlled studies comparing fluvoxamine and imipramine, dry mouth was experienced by 26% of the patients treated with fluvoxamine (n=222), which was significantly less than the incidence of 51% in patients who were receiving imipramine (n=221). Twenty-six percent of patients receiving placebo also complained of dry mouth (Benfield & Ward, 1986b).
d) During an open, large-scale study of over 5000 patients with depression, dry mouth was reported by 3.7% of patients but led to the discontinuation of therapy in only 0.8% of all patients (Martin et al, 1987).
e) Fluvoxamine failed to demonstrate any significant differences in salivary flow when compared to placebo. The study administered single doses of fluvoxamine 50, 75, and 100 mg to 17 healthy volunteers (Wilson et al, 1983).

3.3.5 Hematologic Effects

3.3.5.A Fluvoxamine Maleate

3.3.5.A.1 Bleeding, Abnormal

a) In case reports and epidemiological studies, drugs which interfere with serotonin reuptake (eg, SSRIs and serotonin-norepinephrine-reuptake inhibitors (SNRIs)) have been associated with an increased incidence of gastrointestinal bleeding. Bleeding events, including ecchymoses, hematomas, epistaxis, petechiae, gastrointestinal bleeding, and life-threatening hemorrhages have been reported with SSRI and SNRI use. Because the risk of bleeding may be increased by the concomitant use of drugs that affect coagulation (eg, NSAIDs, aspirin, warfarin), use caution when these agents are co-administered with fluvoxamine maleate. Additionally, patients receiving concurrent warfarin therapy should be monitored when fluvoxamine maleate is started or discontinued (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007).
b) Epistaxis was more frequent in pediatric obsessive-compulsive disorder patients (n=57) taking immediate-release fluvoxamine maleate than in patients taking placebo (Prod Info LUVOX(R) oral tablets, 2007).
c) SSRIs reduce uptake of serotonin by platelets; therefore, reduction in granular storage of serotonin is observed. Serotonin-mediated platelet aggregation may be decreased. For minor bleeding diatheses (ie, bruising), treatment is usually unnecessary because it usually resolves with continued treatment. However, if bleeding is clinically significant, occurs with other underlying medical illnesses, or fails to improve with time, the drug should be discontinued. Many cases of bleeding have occurred in patients taking doses at the higher end of the dose range. Bleeding is more common in patients with underlying diseases; 1 case occurred in a patient with HIV (Berk & Jacobson, 1998).
d) A 33-year-old woman began taking paroxetine 40 mg daily for panic attacks and noted spontaneous bruising on her arms and legs and excessive menstrual bleeding within 2 weeks. No gynecologic or hematologic abnormalities were identified. Vitamin C added to paroxetine stopped bleeding in 3 weeks; discontinuation of vitamin C resulted in recurrent bleeding. Her medication was switched to fluvoxamine which also caused bleeding that resolved with vitamin C (Tielens, 1997).

3.3.6 Hepatic Effects

3.3.6.A Fluvoxamine Maleate

3.3.6.A.1 Liver function tests abnormal

a) Incidence: extended-release, 2% (Prod Info LUVOX(R) CR extended-release oral capsules, 2008)
b) In 2 short-term, placebo-controlled clinical trials evaluating extended-release fluvoxamine maleate (100 mg/day to 300 mg/day) for the treatment of social anxiety disorder, abnormal results of liver function tests were reported in 2% of fluvoxamine maleate patients (n=279) compared with less than 1% of placebo patients (n=276) (Prod Info LUVOX(R) CR extended-release oral capsules, 2008).
c) A 57-year-old man experienced a 3-fold increase in gamma glutamyl transferase (GGT) of 176 international units/L over baseline (50 international units/L) after 3 weeks of fluvoxamine maleate 100 mg twice daily. An enlarged liver with evidence of fatty changes was observed on abdominal ultrasound and examination. GGT levels returned to near baseline levels 5 weeks after discontinuing therapy (Green, 1988).

3.3.7 Immunologic Effects

3.3.7.A Fluvoxamine Maleate

3.3.7.A.1 Stevens-Johnson syndrome

a) Stevens-Johnson syndrome has been reported during postmarketing use of immediate-release fluvoxamine maleate, although a causal relationship has not been established (Prod Info LUVOX(R) oral tablets, 2007; Prod Info LUVOX(R) CR extended-release oral capsules, 2008).

3.3.8 Musculoskeletal Effects

3.3.8.A Fluvoxamine Maleate

Fracture of bone

Fracture of bone, Nonvertebral

Leg cramp

Myalgia

3.3.8.A.1 Fracture of bone

a) Incidence: less than 0.1% (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007)

b) Pathological fracture was reported in less than 0.1% of patients with major depressive disorder or obsessive-compulsive disorder who took immediate-release fluvoxamine maleate during premarketing clinical trials (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007).

c) In a population-based, randomized, prospective cohort study adjusted for potential covariates, an increased risk of fragility fracture was reported at the 5-year follow-up in patients 50 years of age and older who used daily SSRIs (n=137; mean age of 65.1 years), including fluvoxamine, compared with those who did not use an SSRI (n=4871; mean age of 65.7 years). Daily SSRI use was associated with a significant 2.1-fold increased risk of fragility fracture (95% confidence interval (CI), 1.3 to 3.4). Daily SSRI users who were recurrent (ie, treated with SSRIs at baseline and at 5-year follow-up) had a significant 2.1-fold increased risk of fragility fracture (95% CI, 1.1 to 4.0). Fractures were reported at the following sites: forearm (40%), ankle and foot (21%), hip (13%), rib (13%), femur (9%), and back (4%). None were reported at the skull, toes, or fingers (Richards et al, 2007).

3.3.8.A.2 Fracture of bone, Nonvertebral

a) In a prospective, population-based, cohort study (n=7983) with a mean follow-up of 8.4 years, there was an increased risk of nonvertebral fracture in adult participants older than 55 years of age (mean age of 77.5 years) who were currently using an SSRI (citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, or sertraline) compared to those who were not exposed to antidepressants. Current SSRI use was associated with an increased risk of nonvertebral fracture (adjusted hazard ratio (HR), 2.35; 95% confidence interval (CI), 1.32 to 4.18) compared with no antidepressant use. Current SSRI use was also associated with an increased risk of nonvertebral fracture (adjusted HR, 2.07; 95% CI, 1.23 to 3.5) compared with past antidepressant use (n=1217). In addition, duration of SSRI use showed a 9% increase in fracture risk per extra month on an SSRI (95% CI, 3% to 16%; p for trend=0.004). Fractures of the hip (most frequent), wrist, humerus, and pelvis were reported (Ziere et al, 2008).

3.3.8.A.3 Leg cramp

a) There was a two-fold increase in the rate of leg cramps in studies of obsessive-compulsive disorder (OCD) treatment compared with studies of OCD and depression (Prod Info LUVOX(R) oral tablets, 2007).

3.3.8.A.4 Myalgia

a) Incidence: extended-release (obsessive-compulsive disorder), 5% (Prod Info LUVOX(R) CR extended-release oral capsules, 2008)

b) The use of 100 mg/day to 300 mg/day extended-release fluvoxamine maleate has been evaluated in short-term, placebo-controlled trials of social anxiety disorder (SAD) and obsessive-compulsive disorder (OCD). For use in OCD treatment, 5% of fluvoxamine maleate patients (n=124) reported myalgia compared with 2% of placebo patients (n=124). Myalgia was not reported during SAD treatment (Prod Info LUVOX(R) CR extended-release oral capsules, 2008). In short-term, placebo-controlled clinical trials evaluating immediate-release fluvoxamine maleate (100 mg/day to 300 mg/day) for the treatment of OCD, myalgia was reported at a rate that was two-fold higher than the rate reported in OCD and depression trials (Prod Info LUVOX(R) oral tablets, 2007).

3.3.9 Neurologic Effects

Fluvoxamine

Fluvoxamine Maleate

3.3.9.A Fluvoxamine

3.3.9.A.1 Seizure

See Drug Consult reference: COMPARATIVE INCIDENCE OF SEIZURES FROM ANTIDEPRESSANTS

3.3.9.B Fluvoxamine Maleate

Asthenia

Dizziness

EEG abnormality

Extrapyramidal disease

Headache

Hyperactive behavior

Insomnia

Myoclonus

Seizure

Serotonin syndrome

Sleep disorder

Somnolence

Tremor

3.3.9.B.1 Asthenia

a) Incidence: immediate-release, 14%; extended-release (social anxiety disorder), 24%; extended-release (obsessive-compulsive disorder), 26% (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007)

b) In short-term, placebo-controlled clinical trials evaluating immediate-release fluvoxamine maleate (100 mg/day to 300 mg/day) for the treatment of obsessive-compulsive disorder (OCD) or depression, asthenia was reported in 14% of fluvoxamine maleate patients (n=892) compared with 6% of placebo patients (n=778). There was a two-fold increase in the rate of asthenia in studies of OCD treatment compared with studies of OCD and depression (Prod Info LUVOX(R) oral tablets, 2007). The use of 100 mg/day to 300 mg/day extended-release fluvoxamine maleate has been evaluated in short-term, placebo-controlled trials of social anxiety disorder (SAD) and OCD. For use in SAD treatment, 24% of fluvoxamine maleate patients (n=279) reported asthenia compared with 10% of placebo patients (n=276). For use in OCD treatment, 26% of fluvoxamine maleate patients (n=124) reported asthenia compared with 8% of placebo patients (n=124) (Prod Info LUVOX(R) CR extended-release oral capsules, 2008).

3.3.9.B.2 Dizziness

a) Incidence: immediate-release, 11%; extended-release (social anxiety disorder), 15%; extended-release (obsessive-compulsive disorder), 12% (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007)

b) In short-term, placebo-controlled clinical trials evaluating immediate-release fluvoxamine maleate

(100 mg/day to 300 mg/day) for the treatment of obsessive-compulsive disorder (OCD) or depression, dizziness was reported in 11% of fluvoxamine maleate patients (n=892) compared with 6% of placebo patients (n=778) (Prod Info LUVOX(R) oral tablets, 2007). The use of 100 mg/day to 300 mg/day extended-release fluvoxamine maleate has been evaluated in short-term, placebo-controlled trials of social anxiety disorder (SAD) and OCD. For use in SAD treatment, 15% of fluvoxamine maleate patients (n=279) reported dizziness compared with 7% of placebo patients (n=276). For use in OCD treatment, 12% of fluvoxamine maleate patients (n=124) reported dizziness compared with 10% of placebo patients (n=124) (Prod Info LUVOX(R) CR extended-release oral capsules, 2008).

c) Event monitoring in Great Britain of fluvoxamine use in 10,401 patients revealed the most common category of adverse events to be neuropsychiatric. Dizziness was reported in 3.3% of patients (Edwards et al, 1994).

d) In an open study of more than 5000 patients with depression, dizziness was reported by 4.5% of patients (Martin et al, 1987).

e) Dizziness was reported in 14% of patients who received fluvoxamine (n=222) during 10 double-blind, placebo-controlled studies comparing fluvoxamine and imipramine in patients with depression (Benfield & Ward, 1986b).

3.3.9.B.3 EEG abnormality

a) EEG profiles of patients being treated with fluvoxamine showed concomitant increases of slow and fast activities and a decrease in alpha activity indicating sedative qualities. Single doses of fluvoxamine 75 mg were administered to 10 healthy volunteers. The EEG studies showed that fluvoxamine induced less augmentation of slow activity than imipramine, indicating fewer sedative properties with fluvoxamine (Saletu et al, 1983).

3.3.9.B.4 Extrapyramidal disease

a) Incidence: 0.1% to 1% (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007)

b) Extrapyramidal syndrome was reported in 0.1% to 1% of patients with major depressive disorder or obsessive-compulsive disorder who took immediate-release fluvoxamine maleate during premarketing clinical trials (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007).

c) Dystonic reactions, parkinsonism, akathisia, and dyskinesias have been described, with the earliest onset noted at 5 days (Bronner & Vanneste, 1998) and latest onset at 4 months (Chong, 1995).

d) Extrapyramidal reactions (EPR) have been reported with 1 or more SSRIs. The majority of case reports involved fluoxetine; however, all of the SSRIs were implicated in at least 1 EPR. Duration of symptoms with treatment was usually a few days. Symptoms occurred weekly for the first 4 weeks of treatment and periodically thereafter. For most cases, treatment was limited to reducing the dose or stopping the SSRI (Caley, 1997; Gill et al, 1997).

e) In a limited number of case reports, propranolol and/or benzodiazepines were used to treat SSRI-induced akathisia; the dose of propranolol ranged from 40 to 90 mg daily (Gill et al, 1997).

f) In case reports, dystonic reactions responded to an unspecified dose of intramuscular trihexyphenidyl or diphenhydramine 50 mg (Gill et al, 1997; George & Trimble, 1993).

g) Possible mechanisms by which SSRIs cause extrapyramidal reactions (EPR) include: (1) central serotonergic activity which inhibits dopaminergic activity; and (2) concurrent use of an SSRI and antipsychotic may cause EPRs by a pharmacokinetic interaction, a pharmacodynamic interaction, or a combination of the two (Caley, 1997).

h) Three days after starting concomitant fluvoxamine and metoclopramide, a 14-year-old boy developed acute dystonia of the extensor muscles of the neck, back, and upper extremities; jaw rigidity; horizontal nystagmus; dysarthria; and uncontrolled movement of the tongue. He was treated with fluvoxamine 50 mg/day and metoclopramide 10 mg 3 times daily. Treatment with intramuscular biperiden 5 mg completely relieved symptoms within 30 minutes. Previous treatment with metoclopramide did NOT produce dystonia (Palop et al, 1999).

i) A 71-year-old woman developed involuntary movements of the head, neck, and extremities, especially the arms, 5 days after she began taking fluvoxamine 50 mg daily for depression. Upon examination in the emergency department, the movements occurred at rest and were NOT suppressible; they were described as dystonic contractures and myoclonic jerks. Treatment consisted of IV clonazepam 1 mg which resulted in improvement within 10 minutes; 2 hours later, myoclonus recurred and responded to oral clonazepam 2 mg. Fluvoxamine was stopped and myoclonus resolved. One week later, this woman was rechallenged with fluvoxamine 50 mg daily which resulted in a similar reaction 11 days later. The abnormal movements resolved after administering oral clonazepam 2 mg. After stopping fluvoxamine, the movements disappeared and did NOT recur during 6 months of follow-up. Of note, this woman was also taking diltiazem, which inhibits the cytochrome P450 enzyme 1A2 (the enzyme responsible for metabolizing fluvoxamine). This may have resulted in increased fluvoxamine bioavailability (Bronner & Vanneste, 1998).

j) About 4 months after starting fluvoxamine 100 mg daily, a 38-year-old woman complained of periauricular pain and headache which progressed to tightening of jaw muscles and teeth clenching over the next month. She also had difficulty chewing solid foods. Upon reduction of the fluvoxamine dose to 50 mg, her complaints lessened but did NOT completely resolve until she stopped fluvoxamine.

This patient did NOT have a history of previous psychiatric illnesses or dystonias (Chong, 1995).

3.3.9.B.5 Headache

a) Incidence: immediate-release, 22%; extended-release (social anxiety disorder), 35%; extended-release (obsessive-compulsive disorder), 32% (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007)

b) In short-term, placebo-controlled clinical trials evaluating immediate-release fluvoxamine maleate (100 mg/day to 300 mg/day) for the treatment of obsessive-compulsive disorder (OCD) or depression, headache was reported in 22% of fluvoxamine maleate patients (n=892) compared with 20% of placebo patients (n=778) (Prod Info LUVOX(R) oral tablets, 2007). The use of 100 mg/day to 300 mg/day extended-release fluvoxamine maleate has been evaluated in short-term, placebo-controlled trials of social anxiety disorder (SAD) and OCD. For use in SAD treatment, 35% of fluvoxamine maleate patients (n=279) reported headache compared with 30% of placebo patients (n=276). For use in OCD treatment, 32% of fluvoxamine maleate patients (n=124) reported headache compared with 31% of placebo patients (n=124) (Prod Info LUVOX(R) CR extended-release oral capsules, 2008).

c) Event monitoring in Great Britain of fluvoxamine use in 10,401 patients revealed the most common category of adverse events to be neuropsychiatric. Headache was reported in 3.9% of patients (Edwards et al, 1994).

d) In an open study of more than 5000 patients with depression, headache was reported by 5% of patients, causing withdrawal from the study in 2.7% (Martin et al, 1987).

e) Headache was reported in 22% of patients who received fluvoxamine (n=222) during 10 double-blind, placebo-controlled studies comparing fluvoxamine and imipramine in patients with depression (Benfield & Ward, 1986b).

3.3.9.B.6 Hyperactive behavior

a) In a placebo-controlled study involving pediatric patients with obsessive-compulsive disorder, hyperkinesia was reported in 5% or more of patients treated with immediate-release fluvoxamine maleate. This was at least twice the rate found in placebo-treated patients (Prod Info LUVOX(R) oral tablets, 2007).

3.3.9.B.7 Insomnia

a) Incidence: immediate-release, 21%; extended-release (social anxiety disorder), 32%; extended-release (obsessive-compulsive disorder), 35% (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007)

b) In short-term, placebo-controlled clinical trials evaluating immediate-release fluvoxamine maleate (100 mg/day to 300 mg/day) for the treatment of obsessive-compulsive disorder (OCD) or depression, insomnia was reported in 21% of fluvoxamine maleate patients (n=892) compared with 10% of placebo patients (n=778) (Prod Info LUVOX(R) oral tablets, 2007). The use of 100 mg/day to 300 mg/day extended-release fluvoxamine maleate has been evaluated in short-term, placebo-controlled trials of social anxiety disorder (SAD) and OCD. For use in SAD treatment, 32% of fluvoxamine maleate patients (n=279) reported insomnia compared with 13% of placebo patients (n=276). For use in OCD treatment, 35% of fluvoxamine maleate patients (n=124) reported insomnia compared with 20% of placebo patients (n=124) (Prod Info LUVOX(R) CR extended-release oral capsules, 2008).

c) Event monitoring in Great Britain of fluvoxamine use in 10,401 patients revealed the most common category of adverse events to be neuropsychiatric. Insomnia was reported in 2.4% of patients (Edwards et al, 1994).

d) Insomnia was reported in 15% of patients who received fluvoxamine (n=222) during 10 double-blind, placebo-controlled studies comparing fluvoxamine and imipramine in patients with depression (Benfield & Ward, 1986b).

3.3.9.B.8 Myoclonus

a) There was a two-fold increase in the rate of myoclonus/twitch in studies of obsessive-compulsive disorder (OCD) treatment compared with studies of OCD and depression. Myoclonus was reported in at least 1% and twitching was reported in 0.1% to 1% of patients with major depressive disorder or OCD who took immediate-release fluvoxamine maleate during premarketing clinical trials (Prod Info LUVOX (R) oral tablets, 2007). Twitching was reported in 2% of patients with OCD who were treated with fluvoxamine maleate extended-release 100 mg/day to 300 mg/day (n=124) compared with 0% of placebo-treated patients (n=124) during short-term, placebo-controlled trials of social anxiety disorder (SAD) and OCD. Twitching was not reported in patients with SAD (Prod Info LUVOX(R) CR extended-release oral capsules, 2008).

b) A 71-year-old woman developed involuntary movements of the head, neck, and extremities, especially the arms, 5 days after she began taking fluvoxamine 50 mg daily for depression. Upon examination in the emergency department, the movements occurred at rest and were NOT suppressible; they were described as dystonic contractures and myoclonic jerks. Treatment consisted of IV clonazepam 1 mg which resulted in improvement within 10 minutes; 2 hours later, myoclonus recurred and responded to oral clonazepam 2 mg. Fluvoxamine was stopped and myoclonus resolved. One week later, this woman was rechallenged with fluvoxamine 50 mg daily which resulted in a similar reaction 11 days later. The abnormal movements resolved after administering oral clonazepam 2 mg.

After stopping fluvoxamine, the movements disappeared and did NOT recur during 6 months of follow-up. Of note, this woman was also taking diltiazem, which inhibits the cytochrome P450 enzyme 1A2 (the enzyme responsible for metabolizing fluvoxamine). This may have resulted in increased fluvoxamine bioavailability (Bronner & Vanneste, 1998).

3.3.9.B.9 Seizure

a) Incidence: 0.2% (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX (R) oral tablets, 2007)

b) Seizures occurred in 0.2% of patients treated with immediate-release fluvoxamine maleate during premarketing trials. Cautious administration is recommended in patients with controlled epilepsy or a history of convulsions. Avoid treatment in unstable epilepsy. Discontinue fluvoxamine maleate if seizures occur or increase in frequency (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007).

c) A 49-year-old male who had been seizure-free for 10 years with anticonvulsant therapy experienced a generalized seizure 3 days after beginning fluvoxamine therapy, 150 mg at bedtime. Following an increase in dose of the anticonvulsant therapy, the patient did not experience any more seizures (Kim et al, 2000).

3.3.9.B.10 Serotonin syndrome

a) Serotonin syndrome, which may include mental status changes (eg, agitation, hallucination, and coma), autonomic instability (eg, tachycardia, hyperthermia, and labile blood pressure), neuromuscular aberrations, and gastrointestinal symptoms (eg, nausea, vomiting, and diarrhea), may occur with fluvoxamine maleate. This syndrome could be life-threatening. Risk is increased with concomitant use of SSRIs, serotonin norepinephrine reuptake inhibitors (SNRI), triptans, and MAOIs (contraindicated). If concomitant use with SSRIs, SNRIs, or a triptan is warranted, increased monitoring is advised (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007).

b) A serotonin syndrome has been described with administration of fluvoxamine. Symptoms include anxiety, coma, confusion, diaphoresis, disorientation, hyperreflexia, hypertension, hyperthermia, myoclonus, rigidity, seizures, and tremor. Incidence is rare (less than 0.1%). In severe cases, hospitalization has been required for treatment (Gill et al, 1999).

c) An 11-year-old boy developed serotonin syndrome (SS) 1 hour after receiving fluvoxamine 50 mg for attention deficit disorder. He was also receiving perphenazine and benztropine, which had been used for 2 years. Symptoms of SS included agitation, unresponsiveness to verbal or painful stimuli, fluctuating blood pressure and heart rate, jaw myoclonus, shivering, fever to 103.5 degrees Fahrenheit, and hyperreflexia with rigidity of the lower extremities. Initial treatment consisted of diazepam 10 mg and lorazepam 21 mg in incremental intravenous doses. Due to a rise in temperature, he was paralyzed with rocuronium 50 mg and intubated; sedation and pharmacologic paralysis were continued for 24 hours. Full recovery occurred 48 hours after hospitalization (Gill et al, 1999).

3.3.9.B.11 Sleep disorder

a) Incidence: 0.1% to 1% (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007)

b) Sleep disorder was reported in 0.1% to 1% of patients with major depressive disorder or obsessive-compulsive disorder who took immediate-release fluvoxamine maleate during premarketing clinical trials (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007).

c) Fluvoxamine 100 to 150 mg tended to increase rapid eye movement (REM) sleep latency, increase stage 3 sleep, and shorten REM time in a placebo-controlled trial of healthy volunteers. The overall quality of sleep deteriorated, and subjects complained of feeling worse in the mornings (Benfield & Ward, 1986b).

3.3.9.B.12 Somnolence

a) Incidence: immediate-release, 22%; extended-release (social anxiety disorder), 26%; extended-release (obsessive-compulsive disorder), 27% (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007)

b) In short-term, placebo-controlled clinical trials evaluating immediate-release fluvoxamine maleate (100 mg/day to 300 mg/day) for the treatment of obsessive-compulsive disorder (OCD) or depression, somnolence was reported in 22% of fluvoxamine maleate patients (n=892) compared with 8% of placebo patients (n=778) (Prod Info LUVOX(R) oral tablets, 2007). The use of 100 mg/day to 300 mg/day extended-release fluvoxamine maleate has been evaluated in short-term, placebo-controlled trials of social anxiety disorder (SAD) and OCD. For use in SAD treatment, 26% of fluvoxamine maleate patients (n=279) reported somnolence compared with 9% of placebo patients (n=276). For use in OCD treatment, 27% of fluvoxamine maleate patients (n=124) reported somnolence compared with 11% of placebo patients (n=124) (Prod Info LUVOX(R) CR extended-release oral capsules, 2008).

c) In an open study of more than 5000 patients with depression, somnolence was reported by 3.8% of patients (Martin et al, 1987).

d) Somnolence was reported in 26% of patients who received fluvoxamine (n=222) during 10 double-blind, placebo-controlled studies comparing fluvoxamine and imipramine in patients with depression

(Benfield & Ward, 1986b).

3.3.9.B.13 Tremor

a) Incidence: immediate-release, 5%; extended-release (social anxiety disorder), 8%; extended-release (obsessive-compulsive disorder), 6% (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007)

b) In short-term, placebo-controlled clinical trials evaluating immediate-release fluvoxamine maleate (100 mg/day to 300 mg/day) for the treatment of obsessive-compulsive disorder (OCD) or depression, tremor was reported in 5% of fluvoxamine maleate patients (n=892) compared with 1% of placebo patients (n=778) (Prod Info LUVOX(R) oral tablets, 2007). The use of 100 mg/day to 300 mg/day extended-release fluvoxamine maleate has been evaluated in short-term, placebo-controlled trials of social anxiety disorder (SAD) and OCD. For use in SAD treatment, 8% of fluvoxamine maleate patients (n=279) reported tremor compared with less than 1% of placebo patients (n=276). For use in OCD treatment, 6% of fluvoxamine maleate patients (n=124) reported tremor compared with 0% of placebo patients (n=124) (Prod Info LUVOX(R) CR extended-release oral capsules, 2008).

3.3.10 Ophthalmic Effects

3.3.10.A Fluvoxamine Maleate

Blurred vision

Raised intraocular pressure

3.3.10.A.1 Blurred vision

a) Incidence: immediate-release, 3%; extended-release (obsessive-compulsive disorder), 2%(Prod Info LUVOX(R) oral tablets, 2007; Prod Info LUVOX(R) CR extended-release oral capsules, 2008)

b) In short-term, placebo-controlled clinical trials evaluating immediate-release fluvoxamine maleate (100 mg/day to 300 mg/day) for the treatment of obsessive-compulsive disorder (OCD) or depression, amblyopia (mostly "blurred vision") was reported in 3% of fluvoxamine maleate patients (n=892) compared with 2% of placebo patients (n=778). There was a two-fold decrease in the rate of amblyopia (mostly "blurred vision") in studies of OCD treatment compared with studies of OCD and depression (Prod Info LUVOX(R) oral tablets, 2007). Amblyopia was reported in 2% of patients with OCD who were treated with fluvoxamine maleate (n=124) compared with less than 1% of placebo-treated patients (n=124) during short-term, placebo-controlled trials of social anxiety disorder (SAD) and OCD. Amblyopia was not reported in patients with SAD (Prod Info LUVOX(R) oral tablets, 2007).

3.3.10.A.2 Raised intraocular pressure

a) Aggravation of glaucoma and mydriasis in one patient was attributed to fluvoxamine given to treat tension headache. A 66-year-old woman who was being treated with timolol 0.25% twice per day for narrow-angle glaucoma developed severe orbital pain and blurred vision 2 months after initiation of treatment with fluvoxamine 50 mg/day for tension headache and depression. The headache and mood disorder improved with fluvoxamine. However, she was found to have increased ocular pressure, mydriasis, and a closed angle. The eye problems were treated with intravenous glycerol 50%, acetazolamide 1.5 mg/kg, and pilocarpine 2% 4 applications/day for 1 day. The usual dose of timolol was continued. Intraocular pressure was reduced by the treatment but rose again after 3 days. Discontinuation of fluvoxamine resulted in normalization of intraocular pressure and resolution of orbital pain and blurred vision within 2 days (Jimenez-Jimenez et al, 2001).

3.3.12 Psychiatric Effects

3.3.12.A Fluvoxamine Maleate

Agitation

Anxiety

Depression, worsening

Feeling nervous

Frontal lobe syndrome

Hypomania

Mania

Psychiatric sign or symptom

Psychotic disorder

Suicidal thoughts

3.3.12.A.1 Agitation

a) Incidence: immediate-release, 2%; extended-release (social anxiety disorder), 3%; extended-release (obsessive-compulsive disorder), 2% (Prod Info LUVOX(R) oral tablets, 2007; Prod Info LUVOX(R) CR extended-release oral capsules, 2008)

b) In short-term, placebo-controlled clinical trials evaluating immediate-release fluvoxamine maleate (100 mg/day to 300 mg/day) for the treatment of obsessive-compulsive disorder (OCD) or depression, agitation was reported in 2% of fluvoxamine maleate patients (n=892) compared with 1% of placebo patients (n=778). There was a two-fold increase in the rate of agitation in studies of OCD treatment compared with studies of OCD and depression(Prod Info LUVOX(R) oral tablets, 2007). The use of 100 mg/day to 300 mg/day extended-release fluvoxamine maleate has been evaluated in short-term, placebo-controlled trials of social anxiety disorder (SAD) and OCD. For use in SAD treatment, 3% of fluvoxamine maleate patients (n=279) reported agitation compared with less than 1% of placebo patients (n=276). For use in OCD treatment, 2% of fluvoxamine maleate patients (n=124) reported agitation compared with less than 1% of placebo patients (n=124) (Prod Info LUVOX(R) CR extended-release oral capsules, 2008).

c) Severe agitation was reported in an 11-year-old boy following the ingestion of one therapeutic (50 mg) fluvoxamine tablet (Gill et al, 1999).

d) A 68-year-old male experienced severe agitation and restlessness within one week of beginning fluvoxamine therapy, 50 mg daily. The akathisia began to subside gradually following discontinuation of the fluvoxamine and administration of diazepam (Chong & Cheong, 1999).

e) Agitation was noted in 16% of patients taking fluvoxamine therapeutically (Benfield & Ward, 1986b).

3.3.12.A.2 Anxiety

a) Incidence: immediate-release, 5%; extended-release (social anxiety disorder), 8%; extended-release (obsessive-compulsive disorder), 6% (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007)

b) In short-term, placebo-controlled clinical trials evaluating immediate-release fluvoxamine maleate (100 mg/day to 300 mg/day) for the treatment of obsessive-compulsive disorder (OCD) or depression, anxiety was reported in 5% of fluvoxamine maleate patients (n=892) compared with 3% of placebo patients (n=778). There was a two-fold increase in the rate of anxiety in studies of OCD treatment compared with studies of OCD and depression(Prod Info LUVOX(R) oral tablets, 2007). The use of 100 mg/day to 300 mg/day extended-release fluvoxamine maleate has been evaluated in short-term, placebo-controlled trials of social anxiety disorder (SAD) and OCD. For use in SAD treatment, 8% of fluvoxamine maleate patients (n=279) reported anxiety compared with 5% of placebo patients (n=276). For use in OCD treatment, 6% of fluvoxamine maleate patients (n=124) reported anxiety compared with 2% of placebo patients (n=124) (Prod Info LUVOX(R) CR extended-release oral capsules, 2008).

c) Event monitoring in Great Britain of fluvoxamine use in 10,401 patients revealed the most common category of adverse events to be neuropsychiatric. Anxiety was reported in 2.6% of patients (Edwards et al, 1994).

3.3.12.A.3 Depression, worsening

a) Adult and pediatric patients being treated with antidepressants for major depressive disorder who experience symptoms of anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, or mania may be at risk of suicidal ideation and behavior (suicidality). This same concern applies to patients being treated for other psychiatric and nonpsychiatric disorders. If these symptoms are observed, therapy should be re-evaluated, and it may be necessary to discontinue medications when symptoms are severe, sudden in onset, or were not part of the patient's initial symptoms. The dose should be tapered off, avoiding abrupt discontinuation whenever possible. Patients and their caregivers should be provided with the Medication Guide that is available for this drug (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007; Anon, 2004).

3.3.12.A.4 Feeling nervous

a) Incidence: immediate-release, 12%; extended-release (social anxiety disorder), 10% (Prod Info

LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007)
b) In short-term, placebo-controlled clinical trials evaluating immediate-release fluvoxamine maleate (100 mg/day to 300 mg/day) for the treatment of obsessive-compulsive disorder (OCD) or depression, nervousness was reported in 12% of fluvoxamine maleate patients (n=892) compared with 5% of placebo patients (n=778) (Prod Info LUVOX(R) oral tablets, 2007). The use of 100 mg/day to 300 mg/day extended-release fluvoxamine maleate has been evaluated in short-term, placebo-controlled trials of social anxiety disorder (SAD) and OCD. For use in SAD treatment, 10% of fluvoxamine maleate patients (n=279) reported nervousness compared with 9% of placebo patients (n=276). Nervousness was not reported as an adverse effect in OCD treatment (Prod Info LUVOX(R) CR extended-release oral capsules, 2008).

3.3.12.A.5 Frontal lobe syndrome
a) A patient developed a frontal lobe syndrome (apathy, indifference) while taking moderate doses of fluvoxamine 150 mg/day and sulpiride, a dopamine (D-2) antagonist, at 400 mg/day. It was theorized that serotonergic agents may cause this syndrome via reduction of frontal blood flow and that dopamine-blocking agents may modulate this effect (George & Trimble, 1992).
b) Apathy, indifference, loss of initiative, and disinhibition were reported in association with fluvoxamine treatment of 2 patients with panic disorder. The effects appeared to be dose-related and disappeared rapidly when the dose of fluvoxamine, which has a short elimination half-life, was reduced. Patients' behavior seemed to resemble that of people with frontal lobe dysfunction (Hoehn-Saric et al, 1990).

3.3.12.A.6 Hypomania
a) Incidence: 1% (Prod Info LUVOX(R) oral tablets, 2007; Prod Info LUVOX(R) CR extended-release oral capsules, 2008)
b) Mania or hypomania was reported in 1% of patients with primarily depression who took fluvoxamine maleate during premarketing clinical trials (Prod Info LUVOX(R) oral tablets, 2007; Prod Info LUVOX(R) CR extended-release oral capsules, 2008).
c) During an 8-week, placebo-controlled study of fluvoxamine for obsessive-compulsive disorder (OCD), 5 of 20 patients became manic (2) or hypomanic (3). This is inconsistent with prior experience with other serotonin re-uptake inhibitors. The rate of hypomania associated with fluvoxamine when treating major depression is 0.4%, that for clomipramine when treating OCD is 0.4%, and that for fluoxetine in the treatment of depression is 0.98%. The high percentage (25%) in this study may reflect the presence of bipolar type II patients in the sample as these patients show a greater frequency of cycling (Jefferson et al, 1991).

3.3.12.A.7 Mania
a) Incidence: 1% to 4% (Prod Info LUVOX(R) oral tablets, 2007; Prod Info LUVOX(R) CR extended-release oral capsules, 2008)
b) Mania or hypomania was reported in 1% of patients with primarily depression who took fluvoxamine maleate during premarketing clinical trials. Manic reactions were reported in 4% of pediatric patients with obsessive-compulsive disorder who were given fluvoxamine maleate (n=57) during a ten-week study, compared with no manic reactions in patients who received placebo (n=63). Caution is advised when fluvoxamine maleate is used in patients with a history of mania (Prod Info LUVOX(R) oral tablets, 2007; Prod Info LUVOX(R) CR extended-release oral capsules, 2008).
c) Mania occurred in 3 patients who were treated with a combination of fluvoxamine and lithium. Dosage of fluvoxamine was 100 to 200 mg/day and lithium levels were low, ie, 0.5, 0.55, 0.6 mmol/L. This may represent a "switch" from depression into mania induced by fluvoxamine (Burrai et al, 1991c).
d) During an 8-week, placebo-controlled study of fluvoxamine for obsessive-compulsive disorder (OCD), 5 of 20 patients became manic (2) or hypomanic (3). This is inconsistent with prior experience with other serotonin re-uptake inhibitors. The rate of hypomania associated with fluvoxamine when treating major depression is 0.4%, that for clomipramine when treating OCD is 0.4%, and that for fluoxetine in the treatment of depression is 0.98%. The high percentage (25%) in this study may reflect the presence of bipolar type II patients in the sample as these patients show a greater frequency of cycling (Jefferson et al, 1991).

3.3.12.A.8 Psychiatric sign or symptom
a) Behavioral and mood changes (such as motor activation, impulsivity, aggression, and dysphoria) were observed in 5 patients treated with fluvoxamine (200 to 300 mg/day) for obsessive-compulsive disorders. The authors recommended reduction, but not discontinuation, of fluvoxamine, with addition of carbamazepine (Diaferia et al, 1994).

3.3.12.A.9 Psychotic disorder
a) Incidence: at least 1% (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007)
b) Psychotic reaction was reported in at least 1% of patients with major depressive disorder or obsessive-compulsive disorder who took immediate-release fluvoxamine maleate during premarketing clinical trials (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007).

c) Acute exacerbation of schizophrenic symptoms (hallucinations, attacks of anger) occurred in a 53-year-old woman with chronic schizophrenia since age 30 when fluvoxamine 150 mg/day was added to her treatment program for depression. After discontinuation of fluvoxamine and increase of perphenazine (from 16 to 32 mg/day), the patient was free of psychotic symptoms (Rocco & De Leo, 1992).
d) A 17-year-old male with mild mental retardation experienced an acute psychotic reaction resulting in hospitalization for 6 days following a single dose of fluvoxamine 50 mg for depression and anxiety symptoms. The subject experienced agitation, insomnia, auditory and visual hallucinations, fearful mood, paranoid delusions, and episodes of catatonia within 24 hours of taking fluvoxamine. Forty-eight hours after the fluvoxamine dose the subject was hospitalized with an unremarkable physical examination, negative drug screen, and normal laboratories. He was treated with haloperidol 2 mg, lorazepam 1 mg, and chlorpromazine 50 mg. Psychotic symptoms improved within 72 hours of admission and after an additional 72 hours of observation, the subject was discharged on no medication. Medical history was negative for past psychotic presentations and substance abuse history (Sim & Massabki, 2000).

3.3.12.A.10 Suicidal thoughts

a) Adult and pediatric patients being treated with antidepressants for major depressive disorder who experience symptoms of anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, or mania may be at risk of suicidal ideation and behavior (suicidality). This same concern applies to patients being treated for other psychiatric and nonpsychiatric disorders. If these symptoms are observed, therapy should be re-evaluated, and it may be necessary to discontinue medications when symptoms are severe, sudden in onset, or were not part of the patient's initial symptoms. The dose should be tapered off, avoiding abrupt discontinuation whenever possible. Patients and their caregivers should be provided with the Medication Guide that is available for this drug (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007; Anon, 2004; Anon, 2004).
b) A causal role for antidepressants in inducing suicidality has been established in children, adolescents, and young adults (up to 24 years old). Anyone considering the use of antidepressants in a child, adolescent, or young adult must balance this risk with the clinical need. Families and caregivers should be encouraged to observe the patient carefully for emerging symptoms and unexpected behavior. This causal role in children and adolescents was determined from pooled analyses of 24 short-term, placebo-controlled trials of 9 antidepressants (SSRIs and others) which included over 4400 patients with major depressive disorder, obsessive-compulsive disorder (OCD), or other psychiatric disorders. The causal role in adults was determined from pooled analyses of 295 short-term, placebo-controlled trials of 11 antidepressants which included over 77,000 patients with major depressive disorder or other psychiatric disorders. The risk of suicidal thinking and behavior was increased in children, adolescents, and young adults up to 24 years old. This increased risk did not exist in adults over 24 years old, and the risk was lower in adults over 65 years old. The risk was highest in patients with major depressive disorder, but there were signs of risk emerging from trials in other psychiatric indications, such as OCD and social anxiety disorder. No suicides occurred in the pediatric trials. The risk of suicidality during longer-term use (ie, beyond several months) is not known (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007; Anon, 2004).

3.3.13 Renal Effects

3.3.13.A Fluvoxamine Maleate

3.3.13.A.1 Urinary retention

a) Incidence: immediate-release, 1% (Prod Info LUVOX(R) oral tablets, 2007)
b) In short-term, placebo-controlled clinical trials evaluating immediate-release fluvoxamine maleate (100 mg/day to 300 mg/day) for the treatment of obsessive-compulsive disorder (OCD) or depression, urinary retention was reported in 1% of fluvoxamine maleate patients (n=892) compared with 0% of placebo patients (n=778). There was a two-fold increase in the rate of urinary retention in studies of OCD treatment compared with studies of OCD and depression (Prod Info LUVOX(R) oral tablets, 2007).

3.3.14 Reproductive Effects

Fluvoxamine

Fluvoxamine Maleate

3.3.14.A Fluvoxamine

3.3.14.A.1 Sexual dysfunction

See Drug Consult reference: DRUG-INDUCED SEXUAL DYSFUNCTION
See Drug Consult reference: SELECTIVE SEROTONIN REUPTAKE INHIBITOR-INDUCED SEXUAL DYSFUNCTION

3.3.14.B Fluvoxamine Maleate

Abnormal ejaculation

Amenorrhea

Dysmenorrhea

Impotence

Increased libido

Orgasm incapacity

Priapism

Reduced libido

Sexual dysfunction

3.3.14.B.1 Abnormal ejaculation

a) Incidence: immediate-release, 8%; extended-release (social anxiety disorder), 11%; extended-release (obsessive-compulsive disorder), 10% (Prod Info LUVOX(R) oral tablets, 2007; Prod Info LUVOX(R) CR extended-release oral capsules, 2008)

b) In short-term, placebo-controlled clinical trials evaluating immediate-release fluvoxamine maleate (100 mg/day to 300 mg/day) for the treatment of obsessive-compulsive disorder (OCD) or depression, abnormal ejaculation (mostly delayed ejaculation) was reported in 8% of male fluvoxamine maleate patients compared with 1% of placebo patients. There was a two-fold increase in the rate of abnormal ejaculation (mostly delayed ejaculation) in studies of OCD treatment compared with studies of OCD and depression(Prod Info LUVOX(R) oral tablets, 2007). The use of 100 mg/day to 300 mg/day extended-release fluvoxamine maleate has been evaluated in short-term, placebo-controlled trials of social anxiety disorder (SAD) and OCD. For use in SAD treatment, 11% of male fluvoxamine maleate patients reported abnormal ejaculation compared with 2% of placebo patients (n=276). For use in OCD treatment, 10% of male fluvoxamine maleate patients reported abnormal ejaculation compared with 0% of placebo patients (n=124) (Prod Info LUVOX(R) CR extended-release oral capsules, 2008).

c) Cyproheptadine, 1 mg per 25 mg of fluvoxamine taken 2 hours prior to intercourse was effective in reversing ejaculatory failure secondary to fluvoxamine in a 63-year-old man with recurrent unipolar depression. Eventually, 150 mg fluvoxamine per day was effective in controlling the patient's affective symptoms and 6 mg of cyproheptadine was effective in preventing ejaculatory failure (Arnatt & Nutt, 1994).

3.3.14.B.2 Amenorrhea

a) Amenorrhea has been listed in postmarketing reports of immediate-release fluvoxamine maleate use, although a causal relationship has not been established (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007).

b) Galactorrhea and amenorrhea associated with fluvoxamine were reported in a 38-year-old woman with refractory bipolar affective disorder; this patient had been treated for over a decade with several psychotropic agents. The patient had been maintained for an undetermined length of time on loxapine 150 mg daily, oxazepam 30 mg three times daily, and zopiclone 7.5 mg at bedtime. Fluvoxamine was prescribed for depression, and the dose was titrated to 150 mg daily while the loxapine dosage was decreased to 75 mg daily. Six weeks after starting fluvoxamine, she complained of amenorrhea followed soon by galactorrhea. Thorough evaluation ruled out an underlying organic etiology; however, the serum prolactin level was 80 mcg/L (normal, 4 to 30 mcg/L). Galactorrhea resolved 3 weeks after stopping fluvoxamine, and menstruation resumed a week later. The temporal relationship between fluvoxamine and the onset of galactorrhea and amenorrhea suggests a possible etiologic role for fluvoxamine (Jeffries et al, 1992).

3.3.14.B.3 Dysmenorrhea

a) In a placebo-controlled study involving pediatric patients with obsessive-compulsive disorder, dysmenorrhea was reported in 5% or more of patients treated with immediate-release fluvoxamine maleate. This was at least twice the rate found in placebo-treated patients (Prod Info LUVOX(R) oral tablets, 2007).

3.3.14.B.4 Impotence

a) Incidence: immediate-release, 2% (Prod Info LUVOX(R) oral tablets, 2007)

b) In short-term, placebo-controlled clinical trials evaluating immediate-release fluvoxamine maleate (100 mg/day to 300 mg/day) for the treatment of obsessive-compulsive disorder (OCD) or depression, impotence was reported in 2% of male fluvoxamine maleate patients compared with 1% of male placebo patients. There was a two-fold increase in the rate of impotence in studies of OCD treatment compared with studies of OCD and depression (Prod Info LUVOX(R) oral tablets, 2007). Impotence was reported in 2% of males treated with extended-release fluvoxamine maleate (n=403) compared with 3% of males treated with placebo (n=400) in trials of social anxiety disorder and OCD treatment (Prod Info LUVOX(R) CR extended-release oral capsules, 2008).

3.3.14.B.5 Increased libido

a) A 65-year-old female experienced increased sexual desire after 1 week of treatment with fluvoxamine 25 mg twice daily, medazepam 5 mg twice daily, and flunitrazepam 2 mg once daily for the treatment of depression and insomnia. Her depressive symptoms dramatically improved; however, sexual desire increased daily over the second week of therapy. Fluvoxamine was discontinued and treatment with sulpiride 100 mg twice daily, amoxapine 10 mg twice daily, medazepam 5 mg twice daily, and flunitrazepam 2 mg once daily were initiated. Symptoms of increased sexual desire disappeared and did not recur. The subject's past sexual history included cessation of her sexual relationship with her husband for 10 years prior to this event (Okada & Ikajima, 2000).

3.3.14.B.6 Orgasm incapacity

a) Incidence: immediate-release, 2%; extended-release, 5% (Prod Info LUVOX(R) oral tablets, 2007; Prod Info LUVOX(R) CR extended-release oral capsules, 2008)

b) In short-term, placebo-controlled clinical trials evaluating immediate-release fluvoxamine maleate (100 mg/day to 300 mg/day) for the treatment of obsessive-compulsive disorder (OCD) or depression, anorgasmia was reported in 2% of fluvoxamine maleate patients (n=892) compared with 0% of placebo patients (n=778). There was a two-fold increase in the rate of anorgasmia (in males) in studies of OCD treatment compared with studies of OCD and depression(Prod Info LUVOX(R) oral tablets, 2007). The use of 100 mg/day to 300 mg/day extended-release fluvoxamine maleate has been evaluated in short-term, placebo-controlled trials of social anxiety disorder (SAD) and OCD. For use in SAD treatment, 5% of fluvoxamine maleate patients (n=279) reported anorgasmia compared with 1% of placebo patients (n=276). For use in OCD treatment, 5% of fluvoxamine maleate patients (n=124) reported anorgasmia compared with 0% of placebo patients (n=124) (Prod Info LUVOX(R) CR extended-release oral capsules, 2008).

c) A 22-year-old woman who had been taking fluvoxamine for 2 months experienced anorgasmia which was unresponsive to treatment with cyproheptadine 8 and 12 mg; therefore, a reduction in fluvoxamine dosage was tried. Decreasing the weekend dose to 150 or 200 mg did NOT result in normal sexual function; a reduction in dose to fluvoxamine 200 mg daily resulted in a return of obsessive symptoms. In this patient, a partial drug holiday resulted in normal sexual function (Nemeth et al, 1996).

3.3.14.B.7 Priapism

a) Incidence: immediate release, 2% (Prod Info LUVOX(R) oral tablets, 2007)

b) In short-term, placebo-controlled clinical trials evaluating immediate-release fluvoxamine maleate (100 mg/day to 300 mg/day) for the treatment of obsessive-compulsive disorder (OCD) or depression, priapism was reported in 2% of fluvoxamine maleate patients (n=892) compared with 1% of placebo patients (n=778) (Prod Info LUVOX(R) oral tablets, 2007).

3.3.14.B.8 Reduced libido

a) Incidence: immediate-release, 2%; extended-release (social anxiety disorder), 6%; extended-release (obsessive-compulsive disorder), 6% (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007)

b) In short-term, placebo-controlled clinical trials evaluating immediate-release fluvoxamine maleate (100 mg/day to 300 mg/day) for the treatment of obsessive-compulsive disorder (OCD) or depression, decreased libido was reported in 2% of fluvoxamine maleate patients (n=892) compared with 1% of placebo patients (n=778). There was a two-fold increase in the rate of decreased libido in studies of OCD treatment compared with studies of OCD and depression(Prod Info LUVOX(R) oral tablets, 2007). The use of 100 mg/day to 300 mg/day extended-release fluvoxamine maleate has been evaluated in short-term, placebo-controlled trials of social anxiety disorder (SAD) and OCD. For use in SAD treatment, 6% of fluvoxamine maleate patients (n=279) reported decreased libido (8% in males and 4% in females) compared with 4% of placebo patients (n=276) (6% in males and 3% in females). For use in OCD treatment, 6% of fluvoxamine maleate patients (n=124) reported decreased libido (10% in males

and 4% in females) compared with 2% of placebo patients (n=124) (5% in males and 1% in females) (Prod Info LUVOX(R) CR extended-release oral capsules, 2008).

3.3.14.B.9 Sexual dysfunction

a) Incidence: extended-release (social anxiety disorder), 2% (males), 3% (females); extended-release (obsessive-compulsive disorder), 4% (males)(Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007)

b) The use of 100 mg/day to 300 mg/day extended-release fluvoxamine maleate has been evaluated in short-term, placebo-controlled trials of social anxiety disorder (SAD) and OCD. For use in SAD treatment, 3% of fluvoxamine maleate patients (n=279) reported abnormal sexual function (2% in males and 3% in females) compared with less than 1% of placebo patients (n=276) (1% in males). For use in OCD treatment, 4% of male fluvoxamine maleate patients reported abnormal sexual function compared with 3% of male placebo patients. The incidence was 0% in females (Prod Info LUVOX(R) CR extended-release oral capsules, 2008).

c) Of 20 healthy volunteers enrolled in a phenotyping study using fluvoxamine, 7 (35%) reported sexual dysfunction after 4 weeks of fluvoxamine treatment. Fluvoxamine 100 mg daily on Friday and Saturday followed by 300 mg daily Sunday through Thursday resulted in normal sexual function with adequate control of depression and obsessive-compulsive symptoms. In humans, it is postulated that serotonin has an inhibitory effect on sexual function by direct effects on the central, spinal, or peripheral receptors (Nafziger et al, 1999).

3.3.15 Respiratory Effects

3.3.15.A Fluvoxamine Maleate

Pharyngitis

Rhinitis

Upper respiratory infection

Yawning

3.3.15.A.1 Pharyngitis

a) Incidence: extended-release (obsessive-compulsive disorder), 6% (Prod Info LUVOX(R) CR extended-release oral capsules, 2008)

b) The use of 100 mg/day to 300 mg/day extended-release fluvoxamine maleate has been evaluated in short-term, placebo-controlled trials of social anxiety disorder (SAD) and obsessive-compulsive disorder (OCD). For use in OCD treatment, 6% of fluvoxamine maleate patients (n=124) reported pharyngitis compared with less than 1% of placebo patients (n=124). For use in SAD treatment, the incidence was less than or equal to placebo (Prod Info LUVOX(R) CR extended-release oral capsules, 2008). In short-term, placebo-controlled clinical trials evaluating immediate-release fluvoxamine maleate (100 mg/day to 300 mg/day) for the treatment of OCD, pharyngitis was reported at a rate that was two-fold higher than the rate reported in OCD and depression trials (Prod Info LUVOX(R) oral tablets, 2007).

3.3.15.A.2 Rhinitis

a) Incidence: immediate-release (obsessive-compulsive disorder), at least 5% (Prod Info LUVOX(R) oral tablets, 2007)

b) In 2 short-term, placebo-controlled studies involving patients with obsessive-compulsive disorder, rhinitis was reported in 5% or more of patients treated with immediate-release fluvoxamine maleate. This was at least twice the rate found in placebo-treated patients, and there was a two-fold increase in the rate of rhinitis in studies of OCD treatment compared with studies of OCD and depression(Prod Info LUVOX(R) oral tablets, 2007).

3.3.15.A.3 Upper respiratory infection

a) Incidence: immediate-release, 9% (Prod Info LUVOX(R) oral tablets, 2007)

b) In short-term, placebo-controlled clinical trials evaluating immediate-release fluvoxamine maleate (100 mg/day to 300 mg/day) for the treatment of obsessive-compulsive disorder (OCD) or depression, upper respiratory infection was reported in 9% of fluvoxamine maleate patients (n=892) compared with 5% of placebo patients (n=778) (Prod Info LUVOX(R) oral tablets, 2007).

3.3.15.A.4 Yawning

a) Incidence: immediate-release, 2%; extended-release (social anxiety disorder), 5%; extended-release (obsessive-compulsive disorder), 2% (Prod Info LUVOX(R) oral tablets, 2007; Prod Info LUVOX(R) CR

extended-release oral capsules, 2008)
b) In short-term, placebo-controlled clinical trials evaluating immediate-release fluvoxamine maleate (100 mg/day to 300 mg/day) for the treatment of obsessive-compulsive disorder (OCD) or depression, yawning was reported in 2% of fluvoxamine maleate patients (n=892) compared with 0% of placebo patients (n=778) (Prod Info LUVOX(R) oral tablets, 2007). The use of 100 mg/day to 300 mg/day extended-release fluvoxamine maleate has been evaluated in short-term, placebo-controlled trials of social anxiety disorder (SAD) and OCD. For use in SAD treatment, 5% of fluvoxamine maleate patients (n=279) reported yawning compared with less than 1% of placebo patients (n=276). For use in OCD treatment, 2% of fluvoxamine maleate patients (n=124) reported yawning compared with 0% of placebo patients (n=124) (Prod Info LUVOX(R) CR extended-release oral capsules, 2008).

3.3.16 Other

Fluvoxamine

Fluvoxamine Maleate

3.3.16.A Fluvoxamine

3.3.16.A.1 Drug withdrawal
See Drug Consult reference: WITHDRAWAL SYNDROME OF SELECTIVE SEROTONIN REUPTAKE INHIBITORS

3.3.16.B Fluvoxamine Maleate

Accidental injury

Neuroleptic malignant syndrome

Withdrawal sign or symptom

3.3.16.B.1 Accidental injury
a) Incidence: immediate-release, at least 1%; extended-release (obsessive-compulsive disorder), 5% (Prod Info LUVOX(R) oral tablets, 2007; Prod Info LUVOX(R) CR extended-release oral capsules, 2008)
b) Accidental injury was reported in at least 1% of patients with major depressive disorder or obsessive-compulsive disorder (OCD) who took immediate-release fluvoxamine maleate during premarketing clinical trials (Prod Info LUVOX(R) oral tablets, 2007). The use of 100 mg/day to 300 mg/day extended-release fluvoxamine maleate has been evaluated in short-term, placebo-controlled trials of social anxiety disorder (SAD) and OCD. For use in OCD treatment, 5% of fluvoxamine maleate patients (n=124) reported accidental injury compared with 3% of placebo patients (n=124). For use in SAD treatment, the incidence was less than or equal to placebo (Prod Info LUVOX(R) CR extended-release oral capsules, 2008).

3.3.16.B.2 Neuroleptic malignant syndrome
a) Incidence: rare (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX (R) oral tablets, 2007)
b) While most reports of neuroleptic malignant syndrome (NMS) involved concomitant administration of fluvoxamine maleate and an antipsychotic drug, a small number of NMS cases have been associated with the administration of fluvoxamine maleate alone. Symptoms included hyperthermia, muscle rigidity, autonomic instability, changes in vital signs, and mental status changes (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007).
c) Neuroleptic malignant syndrome has been described, with the earliest onset noted at 5 days (Bronner & Vanneste, 1998), and latest onset at 4 months (Chong, 1995). Duration of symptoms with treatment is usually a few days (Caley, 1997; Gill et al, 1997).

3.3.16.B.3 Withdrawal sign or symptom
a) Withdrawal symptoms including dysphoric mood, irritability, agitation, dizziness, sensory disturbances (eg, paresthesias, including electric shock sensations), anxiety, confusion, headache, lethargy, emotional lability, insomnia, and hypomania have occurred when immediate-release fluvoxamine maleate was discontinued, primarily if discontinuation is abrupt. These events may be serious, although they are usually self-limiting. A gradual reduction in dose is recommended and, if intolerable symptoms develop, a temporary resumption of therapy with the prescribed dose may be

warranted, followed by a more gradual reduction (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007).

b) On the fourth day following the abrupt discontinuation of fluvoxamine (200 mg/day), a 12-year-old boy experienced nausea, poor concentration, lightheadedness, fatigue, headache, gait instability, and insomnia. Fluvoxamine was restarted at the same dose and the patient's discontinuation symptoms resolved within 2 days. A second 12-year-old boy developed discontinuation symptoms of headache, poor concentration, irritability, dizziness, fatigue, and shock-like sensation in the brain 5 days after stopping fluvoxamine 200 mg/day. Reinstitution of fluvoxamine at the former dose resulted in resolution of withdrawal symptoms in 3 days (Diler & Avci, 2002).

3.4 Teratogenicity/Effects in Pregnancy/Breastfeeding

A) Teratogenicity/Effects in Pregnancy

1) U.S. Food and Drug Administration's Pregnancy Category: Category C (Prod Info LUVOX(R) oral tablets, 2008) (All Trimesters)

a) Either studies in animals have revealed adverse effects on the fetus (teratogenic or embryocidal or other) and there are no controlled studies in women or studies in women and animals are not available. Drugs should be given only if the potential benefit justifies the potential risk to the fetus.

2) Australian Drug Evaluation Committee's (ADEC) Category: C(Australian Drug Evaluation Committee, 1999)

a) Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible. Accompanying texts should be consulted for further details.

See Drug Consult reference: PREGNANCY RISK CATEGORIES

3) Crosses Placenta: Unknown

4) Clinical Management

a) Although human and animal studies of fluvoxamine use during pregnancy did not reveal substantial teratogenicity (Kulin et al, 1998), nonteratogenic effects (pulmonary hypertension of the newborn (PPHN) and clinical findings consistent with serotonin syndrome) and increased special or intensive unit care of the infant were demonstrated following maternal use of fluvoxamine during the third trimester of pregnancy (Prod Info LUVOX(R) oral tablets, 2008; Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Malm et al, 2005). A study of prospectively collected data suggests antenatal use of selective serotonin-reuptake inhibitor (SSRI) antidepressants is associated with QTc interval prolongation in exposed neonates (Dubnov-Raz et al, 2008). One study revealed that women who discontinued antidepressant medication during pregnancy had a greater likelihood of relapse compared with those who continued antidepressant therapy throughout the pregnancy (Prod Info LUVOX(R) oral tablets, 2008; Prod Info LUVOX(R) CR extended-release oral capsules, 2008). Therefore, when deciding whether to treat a pregnant woman with fluvoxamine during the third trimester, evaluate the potential risk to the fetus and the potential benefit to the mother. Consider tapering the fluvoxamine dose during the third trimester of pregnancy (Prod Info LUVOX (R) oral tablets, 2008; Prod Info LUVOX(R) CR extended-release oral capsules, 2008).

5) Literature Reports

a) A study of prospectively collected data suggests antenatal use of selective serotonin-reuptake inhibitor (SSRI) antidepressants is associated with QTc interval prolongation in exposed neonates. Between January 2000 and December 2005, researchers compared 52 neonates exposed to SSRI antidepressants (paroxetine (n=25), citalopram (n=13), fluoxetine (n=12), fluvoxamine (n=1), and venlafaxine (n=1)) in the immediate antenatal period to 52 matched neonates with no exposure. Prolonged QTc is defined as an interval of greater than 460 milliseconds (msec) (the widely used upper limit cited by authorities in both pediatric cardiology and neonatology). A pediatric cardiologist blinded to drug exposure, interpreted all electrocardiograms (ECGs) using standard statistical analyses. ECG recordings revealed markedly prolonged mean QTc intervals in exposed neonates compared to unexposed neonates (mean; 409 +/- 42 msec versus 392 +/- 29 msec, p=0.02). The mean uncorrected QT interval was 7.5% longer among exposed neonates (mean; 280 +/- 31 msec versus 261 +/- 25 msec, p less than 0.001). Ten percent (n=5) of exposed neonates had a notable increase in QTc interval prolongation (greater than 460 msec) compared to none of the unexposed neonates. The longest QTc interval observed was 543 msec (Dubnov-Raz et al, 2008).

b) Neonates exposed to fluvoxamine and other SSRIs late in the third trimester have developed complications, including respiratory distress, seizures, vomiting, tremor, and irritability that were consistent with either SSRI toxicity or a possible drug discontinuation syndrome. In some cases, clinical findings were consistent with serotonin syndrome (Prod Info LUVOX(R) oral tablets, 2008; Prod Info LUVOX(R) CR extended-release oral capsules, 2008).

c) In a case control study of women who delivered infants with pulmonary hypertension of the newborn (PPHN; n=377) and women who delivered healthy infants (n=836), the risk for developing PPHN was approximately six-fold higher in infants exposed to SSRIs after week 20 of gestation compared with infants not exposed to SSRIs during gestation. This study demonstrates a potential increased risk of PPHN, associated with considerable neonatal morbidity and mortality, in infants exposed to SSRIs later in the pregnancy. In the general population, PPHN occurs in 1 to 2 per 1000 live births (Prod Info LUVOX(R) oral tablets, 2008; Prod Info LUVOX(R) CR extended-release oral capsules, 2008).

d) In a prospective longitudinal study of 201 women with a history of major depression and no signs of depression at the beginning of pregnancy, there was a greater likelihood of relapse of major depression in those who discontinued antidepressant drugs during pregnancy compared with those who continued antidepressant drugs throughout the pregnancy (Prod Info LUVOX(R) oral tablets, 2008; Prod Info LUVOX

(R) CR extended-release oral capsules, 2008).

e) A population-based study of 1782 pregnant women exposed to SSRIs found no increased risk of adverse perinatal outcome except for treatment in the neonatal intensive or special care unit, particularly with third trimester exposure. Using 1996-2001 data derived from a government project involving 4 birth or medication registries in Finland, women who had at least one purchase (a 3-month supply) of an SSRI during the period of one month before pregnancy and the day pregnancy ended were compared with 1782 controls with no reimbursed drug purchases during the same peripartum period. The mean age of both cohorts was 30 years (+/- 7). There were more than twice as many smokers and six times as many pregnancies induced by artificial reproductive techniques in the SSRI group compared to controls (p less than 0.001), and mean length of gestation and birth weight were lower (p less than 0.001) in the SSRI group. Malformations, however, were not more common in the SSRI group (p = 0.4). Purchases of SSRIs (citalopram, fluoxetine, paroxetine, sertraline and fluvoxamine) were more common in the first trimester than later in pregnancy, with 65 women purchasing fluvoxamine during the first trimester, 23 during the second trimester, 27 during the third, and 10 throughout pregnancy. When compared with first trimester exposure, treatment in a special or intensive care unit was more common for the infants exposed during the third trimester (11.2% and 15.7%, respectively; p = 0.009). Even after adjusting for confounding variables, this difference remained statistically significant (OR 1.6; 95% CI 1.1-2.2) (Malm et al, 2005).

f) In a cohort study (n=267), the pregnancy outcome did not differ between women treated with sertraline (n=147), paroxetine (n=97), or fluvoxamine (n=26) versus controls. Rates of major malformations, stillbirth, and spontaneous and elective abortions were similar between the 2 groups as were the mean birth rate and gestational age. Nine major malformations were detected in infants exposed to a selective serotonin reuptake inhibitor (SSRI) and in control infants. Of the 49 women who were treated throughout pregnancy with an SSRI, there were also no differences in outcome compared to women treated only during the first trimester. The majority of women took sertraline 50 mg/day, paroxetine 30 mg/day, and fluvoxamine 50 mg/day (Kulin et al, 1998).

g) Treatment with fluvoxamine 200 mg/day and quetiapine 400 mg/day in a 33-year-old woman during her second pregnancy resulted in an uneventful pregnancy and the birth of a healthy female infant. The patient was being treated with fluvoxamine and quetiapine when she was diagnosed with a severe postpartum psychotic depression after the birth of her first child; multiple attempts at reducing her medication led to relapse. After being informed of the risks-benefits of fluvoxamine/quetiapine exposure during pregnancy, the patient decided to go forward with a second pregnancy while maintaining her drug regimen of fluvoxamine and quetiapine with the addition of folate 5 mg/day throughout the pregnancy. The patient gained 9 kg with no symptoms of psychiatric instability. Routine biochemical tests were within the normal range and 5 echographic reports found no fetal abnormalities. The presence of an intrauterine myoma led to an elective caesarean-section. A healthy female infant weighing 2600 g and measuring 49 cm in length was delivered, with Apgar scores of 9 and 10 at 1 minute and 5 minutes, respectively (Gentile, 2006).

B) Breastfeeding

1) American Academy of Pediatrics Rating: Drugs for which the effect on nursing infants is unknown but may be of concern. (Anon, 2001)

2) Thomson Lactation Rating: Infant risk cannot be ruled out.

a) Available evidence and/or expert consensus is inconclusive or is inadequate for determining infant risk when used during breastfeeding. Weigh the potential benefits of drug treatment against potential risks before prescribing this drug during breastfeeding.

3) Clinical Management

a) The American Academy of Pediatrics considers antidepressants to be drugs worthy of concern in the nursing infant, particularly during long-term use (Anon, 2001). The long-term effects of exposure to SSRIs via breast milk on the cognitive development of the infant have not been determined. Although fluvoxamine appeared in the breast milk of two nursing mothers, the drug was not observed in the plasma of either infant and both developed normally with no adverse effects (Kristensen et al, 2002). Similarly, in a case report of a nursing woman being treated with fluvoxamine/quetiapine, the nursing infant received breast milk supplemented with formula for 3 months and showed no developmental abnormalities (Gentile, 2006). Because fluvoxamine is secreted in human breast milk and there is potential for serious adverse effects in the nursing infant, a decision should be made whether to discontinue the drug or discontinue nursing, taking into consideration the potential risk to the fetus as well as the potential benefit to the mother (Prod Info LUVOX(R) oral tablets, 2008; Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Kristensen et al, 2002).

4) Literature Reports

a) Treatment with fluvoxamine 200 mg/day and quetiapine 400 mg/day in a 33-year-old woman during her second pregnancy resulted in an uneventful pregnancy and the birth of a healthy female infant weighing 2600 g and measuring 49 cm in length with Apgar scores of 9 and 10 at 1 minute and 5 minutes, respectively. The patient chose to breast-feed; however, formula was required to supplement her breast milk due to insufficient milk production. In the 3 months that the infant received breast milk supplemented with formula, no adverse effects were detected and the infant continues to develop normally (Gentile, 2006).

b) In a study of 2 mother-infant pairs, there were no adverse effects from fluvoxamine found in either nursing infant. The infants were 26 months and 0.75 months of age at the time of the study, which involved collecting venous blood samples and breast milk over a 24 hour dosing interval. Assuming a milk intake for both infants of 0.15 L/kg/day, the infant dose calculated as a percentage of the weight-adjusted maternal dose were 1.38% (26 month old infant) and 0.8% (0.75 month old infant). The milk to plasma ratios were

1.34 and 1.21, respectively. Fluvoxamine was not detected in the plasma of either infant. The 26-month-old infant had a Denver developmental assessment with a quotient of 115, indicating that the infant achieved the anticipated milestones. The 0.75-month-old infant was too young to have a meaningful Denver assessment, so a detailed pediatric examination was performed and found no abnormalities. Both mothers reported that the health and progress of their infants was satisfactory (Kristensen et al, 2002).

5) Drug Levels in Breastmilk

a) Fluvoxamine Maleate

1) Parent Drug

a) Percent Adult Dose in Breastmilk

1) In a study of 2 mother-infant pairs, the infant dose calculated as a percentage of the weight adjusted maternal dose were 0.8% (0.75 month old infant) and 1.38% (26 month old infant). These values assume an average milk intake of 0.15 liters/kilogram (L/kg) per day (Kristensen et al, 2002).

b) Milk to Maternal Plasma Ratio

1) In a study of 2 mother-infant pairs, the milk to maternal plasma ratio were 1.21 (0.75 month old infant) and 1.34 (26 month old infant) (Kristensen et al, 2002).

c) Time to Peak Concentration in Milk

1) In a study of 2 mother-infant pairs, the time after dose at which maximum fluvoxamine concentrations were achieved in breast milk were 2.1 hours (0.75 month old infant) and 4.2 hours (26 month old infant) (Kristensen et al, 2002).

3.5 Drug Interactions

Drug-Drug Combinations

Drug-Food Combinations

Drug-Tobacco Combinations

3.5.1 Drug-Drug Combinations

Abciximab

Aceclofenac

Acemetacin

Acenocoumarol

Alclofenac

Almotriptan

Alosetron

Alprazolam

Amitriptyline

Anagrelide

Ancrod

Anisindione

Antithrombin III Human

Ardeparin

Aspirin

Astemizole

Bendamustine

Benoxaprofen

Bivalirudin

Bromfenac

Bufexamac

Bupropion

Cannabis

Carbamazepine

Carprofen

Celecoxib

Certoparin

Cilostazol

Cisapride

Clomipramine

Clonixin

Clopidogrel

Clopidogrel

Clorgyline

Clozapine

Cyclosporine

Dalteparin

Danaparoid

Defibrotide

Dehydroepiandrosterone

Dermatan Sulfate

Desipramine

Desirudin

Desvenlafaxine

Dexfenfluramine

Dexketoprofen

Diazepam

Diclofenac

Dicumarol

Diflunisal

Dihydroergotamine

Diltiazem

Dipyridamole

Dipyrone

Droperidol

Droxicam

Duloxetine

Eletriptan

Eltrombopag

Enoxaparin

Epoprostenol

Eptifibatide

Ergoloid Mesylates

Ergonovine

Ergotamine

Estazolam

Etodolac

Etofenamate

Etoricoxib

Felbinac

Fenbufen

Fenfluramine

Fenoprofen

Fentiazac

Floctafenine

Flufenamic Acid

Flurbiprofen

Fondaparinux

Fosphenytoin

Frovatriptan

Furazolidone

Galantamine

Ginkgo

Glimepiride

Guarana

Haloperidol

Heparin

Hydroxytryptophan

Ibuprofen

Iloprost

Imipramine

Indomethacin

Indoprofen

Iproniazid

Isocarboxazid

Isoxicam

Ketoprofen

Ketorolac

Lamifiban

Levomethadyl

Lexipafant

Linezolid

Lithium

Lornoxicam

Maprotiline

Mate

Meclofenamate

Mefenamic Acid

Melatonin

Meloxicam

Methadone

Methylergonovine

Methylphenidate

Metoprolol

Mexiletine

Midazolam

Milnacipran

Mirtazapine

Moclobemide

Morniflumate

Nabumetone

Nadroparin

Naproxen

Naratriptan

Nialamide

Niflumic Acid

Nimesulide

Olanzapine

Oxaprozin

Oxycodone

Parecoxib

Pargyline

Parnaparin

Pentosan Polysulfate Sodium

Phenelzine

Phenindione

Phenprocoumon

Phenylbutazone

Phenytoin

Pirazolac

Piroxicam

Pirprofen

Procarbazine

Propranolol

Propyphenazone

Proquazone

Ramelteon

Rasagiline

Reviparin

Rizatriptan

Rofecoxib

Ropivacaine

Selegiline

Sibrafiban

Sibutramine

St John's Wort

Sulfinpyrazone

Sulindac

Sulodexide

Sumatriptan

Suprofen

Tacrine

Tapentadol

Tenidap

Tenoxicam

Terfenadine

Theophylline

Thioridazine

Tiaprofenic Acid

Ticlopidine

Tinzaparin

Tirofiban

Tizanidine

Tolmetin

Toloxatone

Tramadol

Tranylcypromine

Triazolam

Tryptophan

Valdecoxib

Warfarin

Xemilofiban

Zolmitriptan

Zomepirac

3.5.1.A Abciximab

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and antiplatelet agents has been associated with an increased risk of bleeding. Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an antiplatelet agent are given concurrently, monitor patient for signs of increased bleeding (Prod Info PAXIL(R) oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008)

7) Probable Mechanism: unknown

3.5.1.B Aceclofenac

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).

b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.C Acemetacin

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate

an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).

b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.D Acenocoumarol

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info LUVOX(R) CR extended-release oral capsules, 2008). Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with warfarin. In patients receiving warfarin and fluvoxamine concomitantly for 2 weeks, warfarin plasma concentrations increased by 98% and prothrombin times were prolonged. Fluvoxamine appears to inhibit several cytochrome P450 isoenzymes which may include 1A2 and 2C9 isozymes, which are responsible for warfarin metabolism (Schalekamp et al, 2008; Prod Info LUVOX(R) CR extended-release oral capsules, 2008).

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: When fluvoxamine and an anticoagulant are given concurrently, monitor patient for signs of increased bleeding. Patients who are taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, when fluvoxamine therapy is initiated or discontinued. Periodically reassess the prothrombin time ratio and INR in patients receiving fluvoxamine and anticoagulant therapy (Prod Info LUVOX(R) CR extended-release oral capsules, 2008).

7) Probable Mechanism: unknown

8) Literature Reports

a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bleeding (hospital admission due to bleeding) in patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patients with a mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients experienced 11 bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experiencing bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model (Wallerstedt et al, 2009).

b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5), however, the rate of gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).

c) A hospitalized 80-year-old female was started on intravenous heparin and oral warfarin therapy due to an embolic stroke secondary to atrial fibrillation and mitral stenosis. Her warfarin dose was maintained at 1 mg daily, with her INR between 2.5 and 3. Fluvoxamine 25 mg daily was started for depression, and her warfarin dose was increased to 1.5 mg daily 3 days later due to worsening of the left hemiparesis. Three days later, her INR was 9.96, and a repeat INR to rule out laboratory error was 11.3. Warfarin was discontinued, fresh frozen plasma was given, and fluvoxamine was discontinued. Six days later, warfarin was again started at 1 mg daily, and the INR increased over 4 days to 11.8. The elevated INR was attributed to the persisting effect of fluvoxamine. She was eventually stabilized on warfarin 1 mg daily with INR values between 2 and 2.5 (Yap & Low, 1999).

3.5.1.E Alclofenac

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).

3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.F Almotriptan

1) Interaction Effect: an increased risk of serotonin syndrome
2) Summary: Concomitant use of almotriptan and selective serotonin reuptake inhibitors (SSRI's) has been reported to cause weakness, hyperreflexia, and incoordination (Prod Info Axert(TM), 2001). Concurrent use of a triptan and an SSRI may result in serotonin syndrome which may be life-threatening. Symptoms of serotonin syndrome may include restlessness, hallucinations, loss of coordination, fast heart beat, rapid changes in blood pressure, increased body temperature, overreactive reflexes, nausea, vomiting, and diarrhea. Clinicians should be aware that triptans may be commonly used intermittently and that either the triptan or the SSRI may be prescribed by a different physician. Discuss the risks of serotonin syndrome with patients who are prescribed this combination and monitor them closely for symptoms of serotonin syndrome (US Food and Drug Administration, 2006).
3) Severity: major
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Coadministration of a triptan, such as almotriptan, and an SSRI may result in a life-threatening condition called serotonin syndrome. Be aware that triptans may be commonly used intermittently and that either the triptan or the SSRI may be prescribed by a different physician. If these agents are used together, discuss the risks of serotonin syndrome with the patient and monitor closely for symptoms of serotonin syndrome (restlessness, hyperthermia, hyperreflexia, incoordination).
7) Probable Mechanism: additive pharmacologic effects resulting in excessive serotonergic stimulation
8) Literature Reports
a) Concomitant administration of fluoxetine and almotriptan is well tolerated and fluoxetine has only a modest effect on almotriptan maximum plasma concentration (Cmax). Other almotriptan pharmacokinetics are not significantly affected. A randomized, open-label, two-way crossover study involving 14 healthy volunteers has been conducted. Subjects received each of the following treatments with a minimum 3-week washout between periods: (1) three 20 mg fluoxetine capsules on day 1 to 8 and one dose almotriptan 12.5 mg on day 8, (2) one dose of almotriptan 12.5 mg on day 8 with no treatment on days 1 through 7. Peak almotriptan concentrations were 18% higher following concomitant administration of fluoxetine than after almotriptan administration alone. This difference was statistically significant (p equal 0.023). Mean almotriptan area under the concentration-time curve (AUC) and oral clearance were borderline statistically different between treatment groups. Mean half-life was not statistically different between the treatment groups. During fluoxetine coadministration, Tmax was shorter, suggesting that the absorption rate of almotriptan may have been increased by fluoxetine. The author concludes that based on the results of this study and the lack of effect of fluoxetine on almotriptan pharmacokinetics, almotriptan and fluoxetine can be safely used concomitantly in migraine management (Fleishaker et al, 2001).

3.5.1.G Alosetron

1) Interaction Effect: increased alosetron exposure and increased side effects
2) Summary: Fluvoxamine is a potent inhibitor of the CYP1A2-mediated metabolism of alosetron. In a pharmacokinetic study of 40 healthy female subjects, fluvoxamine increased mean alosetron AUC by 6-fold and prolonged alosetron half-life by 3-fold. Concomitant use of fluvoxamine and alosetron is contraindicated due to the increased risk of serious bowel side effects, including ischemic colitis (Prod Info LOTRONEX(R), 2005).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: established
6) Clinical Management: Concomitant use of alosetron and fluvoxamine is contraindicated. Monitor patient for bowel side effects including constipation, abdominal or gastrointestinal pain or discomfort, nausea,

abdominal distention, reflux and hemorrhoids. Watch for signs and symptoms of ischemic colitis including rectal bleeding, bloody diarrhea or new or worsening abdominal pain.
7) Probable Mechanism: inhibition by fluvoxamine of CYP1A2-mediated alosetron metabolism
8) Literature Reports
a) Fluvoxamine inhibits the CYP1A2-mediated metabolism of alosetron. In a pharmacokinetic study involving 40 healthy female subjects, participants received an escalating dose of fluvoxamine 50 to 200 mg daily for 16 days. On the final day, participants also received a single 1 mg dose of alosetron. The area under the concentration-time curve (AUC) and half-life of alosetron increased 6-fold and 3-fold, respectively (Prod Info LOTRONEX(R), 2005).

3.5.1.H Alprazolam
1) Interaction Effect: elevated plasma alprazolam levels and an increased risk of side effects (CNS depression)
2) Summary: Fluvoxamine coadministration (100 mg daily) with alprazolam 1 mg four times daily resulted in a 2-fold increase in alprazolam steady-state plasma concentrations, area under the concentration-time curve (AUC), maximum concentration (Cmax), and half-life. Elevated plasma levels of alprazolam were associated with impaired psychomotor performance and memory. This effect may be even more pronounced with higher fluvoxamine doses (300 mg daily) (Prod Info Luvox(R), 1997x).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: If alprazolam is given to a patient already on fluvoxamine, the initial alprazolam dose should be reduced by 50% due to the possibility of significant alprazolam accumulation. Monitor for signs of alprazolam intoxication (eg, sedation, dizziness, ataxia, weakness, decreased cognition or motor performance) or consider switching to a benzodiazepine eliminated by glucuronidation (eg, lorazepam, oxazepam, temazepam).
7) Probable Mechanism: inhibition by fluvoxamine of cytochrome P4503A4-mediated alprazolam metabolism

3.5.1.I Amitriptyline
1) Interaction Effect: amitriptyline toxicity (dry mouth, urinary retention, sedation)
2) Summary: Coadministration of fluvoxamine and amitriptyline was found to significantly increase plasma levels of amitriptyline (Bertschy et al, 1991a). A bidirectional effect was suggested in which fluvoxamine increased amitriptyline concentrations (by interfering with N-demethylation) and amitriptyline increased fluvoxamine levels (Hartter et al, 1993a).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor patients for signs of amitriptyline and fluvoxamine toxicity; lower doses of one or both agents may be required with concomitant therapy.
7) Probable Mechanism: decreased amitriptyline metabolism
8) Literature Reports
a) Fluvoxamine has been shown to significantly increase plasma levels of amitriptyline and clomipramine and to mildly increase levels of their metabolites nortriptyline and desmethylclomipramine, respectively. This may be due to competitive inhibition of oxidative metabolism in the liver (Bertschy et al, 1991).
b) Metabolism of tricyclic antidepressants coadministered with fluvoxamine was studied in eight depressed patients (one patient received amitriptyline) (Hartter et al, 1993). Fluvoxamine was found to interfere with N-demethylation of amitriptyline. The combination of fluvoxamine and amitriptyline led to increased plasma levels of amitriptyline and decreased concentrations of amitriptyline's N-demethylated metabolite, nortriptyline. In addition, plasma levels of fluvoxamine were increased.

3.5.1.J Anagrelide
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and antiplatelet agents has been associated with an increased risk of bleeding. Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an antiplatelet agent are given concurrently, monitor patient for signs of increased bleeding (Prod Info PAXIL(R) oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008)
7) Probable Mechanism: unknown

3.5.1.K Ancrod

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info LUVOX(R) CR extended-release oral capsules, 2008). Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with warfarin. In patients receiving warfarin and fluvoxamine concomitantly for 2 weeks, warfarin plasma concentrations increased by 98% and prothrombin times were prolonged. Fluvoxamine appears to inhibit several cytochrome P450 isoenzymes which may include 1A2 and 2C9 isozymes, which are responsible for warfarin metabolism (Schalekamp et al, 2008; Prod Info LUVOX(R) CR extended-release oral capsules, 2008).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When fluvoxamine and an anticoagulant are given concurrently, monitor patient for signs of increased bleeding. Patients who are taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, when fluvoxamine therapy is initiated or discontinued. Periodically reassess the prothrombin time ratio and INR in patients receiving fluvoxamine and anticoagulant therapy (Prod Info LUVOX(R) CR extended-release oral capsules, 2008).
7) Probable Mechanism: unknown
8) Literature Reports

a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bleeding (hospital admission due to bleeding) in patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patients with a mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients experienced 11 bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experiencing bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model (Wallerstedt et al, 2009).

b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5), however, the rate of gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).

c) A hospitalized 80-year-old female was started on intravenous heparin and oral warfarin therapy due to an embolic stroke secondary to atrial fibrillation and mitral stenosis. Her warfarin dose was maintained at 1 mg daily, with her INR between 2.5 and 3. Fluvoxamine 25 mg daily was started for depression, and her warfarin dose was increased to 1.5 mg daily 3 days later due to worsening of the left hemiparesis. Three days later, her INR was 9.96, and a repeat INR to rule out laboratory error was 11.3. Warfarin was discontinued, fresh frozen plasma was given, and fluvoxamine was discontinued. Six days later, warfarin was again started at 1 mg daily, and the INR increased over 4 days to 11.8. The elevated INR was attributed to the persisting effect of fluvoxamine. She was eventually stabilized on warfarin 1 mg daily with INR values between 2 and 2.5 (Yap & Low, 1999).

3.5.1.L Anisindione

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info LUVOX(R) CR extended-release oral capsules, 2008). Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with warfarin. In patients receiving warfarin and fluvoxamine concomitantly for 2 weeks, warfarin plasma concentrations increased by 98% and prothrombin times were prolonged. Fluvoxamine appears to inhibit several cytochrome P450 isoenzymes which may include 1A2 and 2C9 isozymes, which are responsible for warfarin metabolism (Schalekamp et al, 2008; Prod Info LUVOX(R) CR extended-release oral capsules, 2008).
3) Severity: major

4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When fluvoxamine and an anticoagulant are given concurrently, monitor patient for signs of increased bleeding. Patients who are taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, when fluvoxamine therapy is initiated or discontinued. Periodically reassess the prothrombin time ratio and INR in patients receiving fluvoxamine and anticoagulant therapy (Prod Info LUVOX(R) CR extended-release oral capsules, 2008).
7) Probable Mechanism: unknown
8) Literature Reports
a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bleeding (hospital admission due to bleeding) in patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patients with a mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients experienced 11 bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experiencing bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model (Wallerstedt et al, 2009).
b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5), however, the rate of gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).
c) A hospitalized 80-year-old female was started on intravenous heparin and oral warfarin therapy due to an embolic stroke secondary to atrial fibrillation and mitral stenosis. Her warfarin dose was maintained at 1 mg daily, with her INR between 2.5 and 3. Fluvoxamine 25 mg daily was started for depression, and her warfarin dose was increased to 1.5 mg daily 3 days later due to worsening of the left hemiparesis. Three days later, her INR was 9.96, and a repeat INR to rule out laboratory error was 11.3. Warfarin was discontinued, fresh frozen plasma was given, and fluvoxamine was discontinued. Six days later, warfarin was again started at 1 mg daily, and the INR increased over 4 days to 11.8. The elevated INR was attributed to the persisting effect of fluvoxamine. She was eventually stabilized on warfarin 1 mg daily with INR values between 2 and 2.5 (Yap & Low, 1999).

3.5.1.M Antithrombin III Human

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info LUVOX(R) CR extended-release oral capsules, 2008). Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with warfarin. In patients receiving warfarin and fluvoxamine concomitantly for 2 weeks, warfarin plasma concentrations increased by 98% and prothrombin times were prolonged. Fluvoxamine appears to inhibit several cytochrome P450 isoenzymes which may include 1A2 and 2C9 isozymes, which are responsible for warfarin metabolism (Schalekamp et al, 2008; Prod Info LUVOX(R) CR extended-release oral capsules, 2008).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When fluvoxamine and an anticoagulant are given concurrently, monitor patient for signs of increased bleeding. Patients who are taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, when fluvoxamine therapy is initiated or discontinued. Periodically reassess the prothrombin time ratio and INR in patients receiving fluvoxamine and anticoagulant therapy (Prod Info LUVOX(R) CR extended-release oral capsules, 2008).
7) Probable Mechanism: unknown
8) Literature Reports
a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bleeding (hospital admission due to bleeding) in patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patients with a mean

age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients experienced 11 bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experiencing bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model (Wallerstedt et al, 2009).

b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5), however, the rate of gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).

c) A hospitalized 80-year-old female was started on intravenous heparin and oral warfarin therapy due to an embolic stroke secondary to atrial fibrillation and mitral stenosis. Her warfarin dose was maintained at 1 mg daily, with her INR between 2.5 and 3. Fluvoxamine 25 mg daily was started for depression, and her warfarin dose was increased to 1.5 mg daily 3 days later due to worsening of the left hemiparesis. Three days later, her INR was 9.96, and a repeat INR to rule out laboratory error was 11.3. Warfarin was discontinued, fresh frozen plasma was given, and fluvoxamine was discontinued. Six days later, warfarin was again started at 1 mg daily, and the INR increased over 4 days to 11.8. The elevated INR was attributed to the persisting effect of fluvoxamine. She was eventually stabilized on warfarin 1 mg daily with INR values between 2 and 2.5 (Yap & Low, 1999).

3.5.1.N Ardeparin

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info LUVOX(R) CR extended-release oral capsules, 2008). Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with warfarin. In patients receiving warfarin and fluvoxamine concomitantly for 2 weeks, warfarin plasma concentrations increased by 98% and prothrombin times were prolonged. Fluvoxamine appears to inhibit several cytochrome P450 isoenzymes which may include 1A2 and 2C9 isozymes, which are responsible for warfarin metabolism (Schalekamp et al, 2008; Prod Info LUVOX(R) CR extended-release oral capsules, 2008).

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: When fluvoxamine and an anticoagulant are given concurrently, monitor patient for signs of increased bleeding. Patients who are taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, when fluvoxamine therapy is initiated or discontinued. Periodically reassess the prothrombin time ratio and INR in patients receiving fluvoxamine and anticoagulant therapy (Prod Info LUVOX(R) CR extended-release oral capsules, 2008).

7) Probable Mechanism: unknown

8) Literature Reports

a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bleeding (hospital admission due to bleeding) in patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patients with a mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients experienced 11 bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experiencing bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model (Wallerstedt et al, 2009).

b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5), however, the rate of gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).
c) A hospitalized 80-year-old female was started on intravenous heparin and oral warfarin therapy due to an embolic stroke secondary to atrial fibrillation and mitral stenosis. Her warfarin dose was maintained at 1 mg daily, with her INR between 2.5 and 3. Fluvoxamine 25 mg daily was started for depression, and her warfarin dose was increased to 1.5 mg daily 3 days later due to worsening of the left hemiparesis. Three days later, her INR was 9.96, and a repeat INR to rule out laboratory error was 11.3. Warfarin was discontinued, fresh frozen plasma was given, and fluvoxamine was discontinued. Six days later, warfarin was again started at 1 mg daily, and the INR increased over 4 days to 11.8. The elevated INR was attributed to the persisting effect of fluvoxamine. She was eventually stabilized on warfarin 1 mg daily with INR values between 2 and 2.5 (Yap & Low, 1999).

3.5.1.O Aspirin

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and antiplatelet agents has been associated with an increased risk of bleeding. Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an antiplatelet agent are given concurrently, monitor patient for signs of increased bleeding (Prod Info PAXIL(R) oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008)
7) Probable Mechanism: unknown

3.5.1.P Astemizole

1) Interaction Effect: cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Fluvoxamine should not be used in combination with astemizole. Fluvoxamine appears to be a potent inhibitor of the cytochrome P450IIIA4 isozyme, the enzyme primarily responsible for metabolizing astemizole. Inhibition of this enzyme may result in elevated astemizole concentrations; increased plasma concentrations of astemizole are associated with QT prolongation and torsades de pointes, which can be fatal (Prod Info Luvox(R), 1997j; Prod Info Hismanal(R), 1998).
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Concurrent use of astemizole and fluvoxamine is contraindicated.
7) Probable Mechanism: inhibition by fluvoxamine of astemizole metabolism

3.5.1.Q Bendamustine

1) Interaction Effect: increased bendamustine levels and decreased levels of active minor metabolites of bendamustine
2) Summary: Alternative treatments should be considered when concomitant use of bendamustine with a CYP1A2 inhibitor is necessary. Based on in vitro data, bendamustine is primarily metabolized via CYP1A2 into 2 active minor metabolites (M3 and M4). However, the cytotoxic efficacy is primarily due to the parent compound as the active metabolites have very low plasma concentrations. Concomitant administration of a strong CYP1A2 inhibitor, such as fluvoxamine, may result in increased bendamustine concentrations and decreased concentrations of the metabolites (Prod Info TREANDA(R) IV injection, 2008). If used concomitantly, patients should be closely monitored for increased incidence of bendamustine adverse events (myelosuppression, infection, skin reactions) and doses should be adjusted appropriately.
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Consider alternative treatment when concomitant use of bendamustine with a strong CYP1A2 inhibitor, such as fluvoxamine, is required. However, use caution if bendamustine and fluvoxamine are coadministered (Prod Info TREANDA(R) IV injection, 2008). Monitor the patient for increased bendamustine adverse events (myelosuppression, infection, skin reactions) and adjust doses as necessary.
7) Probable Mechanism: inhibition of the CYP1A2-mediated bendamustine metabolism

3.5.1.R Benoxaprofen

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).

b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.S Bivalirudin

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info LUVOX(R) CR extended-release oral capsules, 2008). Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with warfarin. In patients receiving warfarin and fluvoxamine concomitantly for 2 weeks, warfarin plasma concentrations increased by 98% and prothrombin times were prolonged. Fluvoxamine appears to inhibit several cytochrome P450 isoenzymes which may include 1A2 and 2C9 isozymes, which are responsible for warfarin metabolism (Schalekamp et al, 2008; Prod Info LUVOX(R) CR extended-release oral capsules, 2008).

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: When fluvoxamine and an anticoagulant are given concurrently, monitor patient for signs of increased bleeding. Patients who are taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, when fluvoxamine therapy is initiated or discontinued. Periodically reassess the prothrombin time ratio and INR in patients receiving fluvoxamine and anticoagulant therapy (Prod Info LUVOX(R) CR extended-release oral capsules, 2008).

7) Probable Mechanism: unknown

8) Literature Reports

a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bleeding (hospital admission due to bleeding) in patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patients with a mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients experienced 11 bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experiencing bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model (Wallerstedt et al, 2009).

b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of

treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5), however, the rate of gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).

c) A hospitalized 80-year-old female was started on intravenous heparin and oral warfarin therapy due to an embolic stroke secondary to atrial fibrillation and mitral stenosis. Her warfarin dose was maintained at 1 mg daily, with her INR between 2.5 and 3. Fluvoxamine 25 mg daily was started for depression, and her warfarin dose was increased to 1.5 mg daily 3 days later due to worsening of the left hemiparesis. Three days later, her INR was 9.96, and a repeat INR to rule out laboratory error was 11.3. Warfarin was discontinued, fresh frozen plasma was given, and fluvoxamine was discontinued. Six days later, warfarin was again started at 1 mg daily, and the INR increased over 4 days to 11.8. The elevated INR was attributed to the persisting effect of fluvoxamine. She was eventually stabilized on warfarin 1 mg daily with INR values between 2 and 2.5 (Yap & Low, 1999).

3.5.1.T Bromfenac

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).

b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.U Bufexamac

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).

b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.V Bupropion

1) Interaction Effect: increased plasma levels of bupropion

2) Summary: In vitro studies suggest that fluvoxamine inhibits the hydroxylation of bupropion which may result in increased bupropion concentrations when the two agents are used concurrently. Use caution when bupropion and fluvoxamine are coadministered and monitor patients for excessive bupropion adverse effects (agitation, anxiety, insomnia, hallucinations) (Prod Info WELLBUTRIN(R) oral tablets, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of bupropion and fluvoxamine may cause elevated bupropion concentrations. Monitor patients for excessive bupropion adverse effects (agitation, anxiety, insomnia, hallucinations) when fluvoxamine is being administered concurrently (Prod Info WELLBUTRIN(R) oral tablets, 2008).
7) Probable Mechanism: inhibition of the hydroxylation of bupropion by fluvoxamine
8) Literature Reports
a) In vitro studies suggest that fluvoxamine inhibits the hydroxylation of bupropion. No clinical studies have been conducted to verify this finding (Prod Info WELLBUTRIN(R) oral tablets, 2008).

3.5.1.W Cannabis

1) Interaction Effect: manic symptoms
2) Summary: One case of mania following use of marijuana with fluoxetine therapy has been reported (Stoll et al, 1991a). Although an interaction is proposed, the authors also state the manic symptoms could have resulted from the fluoxetine or marijuana alone. Caution is advised for patients using marijuana and taking fluoxetine or other serotonin reuptake inhibitors.
3) Severity: moderate
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Caution patients taking selective serotonin reuptake inhibitors to avoid concomitant use of marijuana.
7) Probable Mechanism: additive serotonergic stimulation
8) Literature Reports
a) A 21-year-old female presented with mania, agitation, and grandiose delusions following use of marijuana with fluoxetine therapy. She had been taking fluoxetine 20 mg daily for 4 weeks and reported smoking 2 "joints" during a 36-hour period. Over the next 24 hours, she developed increased energy, hypersexuality, pressured speech, and grandiose delusions. Lorazepam and perphenazine were given for agitation and excitement which gradually resolved over 4 days. She remained hospitalized for 36 days. Fluoxetine 20 mg every other day was reintroduced one week prior to discharge. One week after discharge, she discontinued fluoxetine due to insomnia and feeling "hyper". These symptoms resolved rapidly upon discontinuation of fluoxetine. Due to the rapid switch to mania after smoking marijuana with fluoxetine, the manic symptoms were associated with the concomitant use of fluoxetine and marijuana, though mania could have developed from either fluoxetine or marijuana alone (Stoll et al, 1991).

3.5.1.X Carbamazepine

1) Interaction Effect: carbamazepine toxicity (ataxia, nystagmus, diplopia, headache, vomiting, apnea, seizures, coma)
2) Summary: Several cases have been reported in which fluvoxamine appeared to cause increased carbamazepine levels and symptoms of carbamazepine toxicity (Martinelli et al, 1993; Fritze et al, 1991a). However, one study of eight epileptic patients found no such increase in carbamazepine levels with three weeks of concurrent use (Spina et al, 1993e).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Due to the potential to increase carbamazepine levels, patients should be monitored for evidence of carbamazepine toxicity when fluvoxamine is added to therapy. Carbamazepine levels should be considered when adding or discontinuing fluvoxamine, with dosage adjustments made as indicated.
7) Probable Mechanism: decreased carbamazepine metabolism
8) Literature Reports
a) The addition of fluvoxamine to a constant dosage of carbamazepine in three patients caused an increase in carbamazepine levels resulting in symptoms of toxicity (Fritze et al, 1991). The authors concluded that this resulted from inhibition of carbamazepine metabolism. However, (Spina et al, 1993d) found no increase in carbamazepine levels in eight epileptic patients who were given fluvoxamine 100 mg daily or fluoxetine 20 mg daily with carbamazepine for three weeks.

3.5.1.Y Carprofen

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM),

2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.Z Celecoxib
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.AA Certoparin
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info LUVOX(R) CR extended-release oral capsules, 2008). Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with warfarin. In patients receiving warfarin and fluvoxamine concomitantly for 2 weeks, warfarin plasma concentrations increased by 98% and prothrombin times were prolonged. Fluvoxamine appears to inhibit several cytochrome P450 isoenzymes which may include 1A2 and 2C9 isozymes, which are responsible for warfarin metabolism (Schalekamp et al, 2008; Prod Info LUVOX(R) CR extended-release oral capsules, 2008).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When fluvoxamine and an anticoagulant are given concurrently, monitor patient for signs of increased bleeding. Patients who are taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, when fluvoxamine therapy is initiated or discontinued. Periodically reassess the prothrombin time ratio and INR in patients receiving fluvoxamine and anticoagulant therapy (Prod Info LUVOX(R) CR extended-release oral capsules, 2008).
7) Probable Mechanism: unknown
8) Literature Reports

a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bleeding (hospital admission due to bleeding) in patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patients with a mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients experienced 11 bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experiencing bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model (Wallerstedt et al, 2009).

b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5), however, the rate of gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).

c) A hospitalized 80-year-old female was started on intravenous heparin and oral warfarin therapy due to an embolic stroke secondary to atrial fibrillation and mitral stenosis. Her warfarin dose was maintained at 1 mg daily, with her INR between 2.5 and 3. Fluvoxamine 25 mg daily was started for depression, and her warfarin dose was increased to 1.5 mg daily 3 days later due to worsening of the left hemiparesis. Three days later, her INR was 9.96, and a repeat INR to rule out laboratory error was 11.3. Warfarin was discontinued, fresh frozen plasma was given, and fluvoxamine was discontinued. Six days later, warfarin was again started at 1 mg daily, and the INR increased over 4 days to 11.8. The elevated INR was attributed to the persisting effect of fluvoxamine. She was eventually stabilized on warfarin 1 mg daily with INR values between 2 and 2.5 (Yap & Low, 1999).

3.5.1.AB Cilostazol

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and antiplatelet agents has been associated with an increased risk of bleeding. Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an antiplatelet agent are given concurrently, monitor patient for signs of increased bleeding (Prod Info PAXIL(R) oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008)

7) Probable Mechanism: unknown

3.5.1.AC Cisapride

1) Interaction Effect: cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Fluvoxamine should not be used in combination with cisapride. Although there is no direct experience with this combination, fluvoxamine appears to be a potent inhibitor of the cytochrome P450 3A4 isozyme, the enzyme primarily responsible for the metabolism of cisapride. Inhibition of this enzyme may result in elevated cisapride concentrations; increased plasma concentrations of cisapride are associated with QT prolongation and torsades de pointes, which can be fatal (Prod Info Luvox(R), 1997u).

3) Severity: contraindicated

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: Concurrent use of fluvoxamine and cisapride is contraindicated.

7) Probable Mechanism: inhibition of cytochrome P450 3A4-mediated cisapride metabolism

3.5.1.AD Clomipramine

1) Interaction Effect: clomipramine toxicity (dry mouth, urinary retention, sedation)

2) Summary: Coadministration of fluvoxamine and clomipramine was found to significantly increase plasma levels of clomipramine (Bertschy et al, 1991c). A bidirectional effect was suggested in which fluvoxamine increased clomipramine concentrations (by interfering with N-demethylation) and clomipramine increased fluvoxamine levels (Hartter et al, 1993c).

3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor patients for signs of clomipramine and fluvoxamine toxicity; lower doses of one or both agents may be required with concomitant therapy.
7) Probable Mechanism: decreased clomipramine metabolism
8) Literature Reports
a) Fluvoxamine has been shown to significantly increase plasma levels of amitriptyline and clomipramine and to mildly increase levels of their metabolites nortriptyline and desmethylclomipramine, respectively. This may be due to competitive inhibition of oxidative metabolism in the liver (Bertschy et al, 1991b).
b) Metabolism of tricyclic antidepressants coadministered with fluvoxamine was studied in eight depressed patients (four patients received clomipramine). Fluvoxamine was found to interfere with N-demethylation and 8-hydroxylation of clomipramine. The combination of fluvoxamine and clomipramine led to increased plasma levels of clomipramine and decreased concentrations of clomipramine's N-demethylated metabolite, desmethylclomipramine. In addition, plasma levels of fluvoxamine were increased (Hartter et al, 1993b).

3.5.1.AE Clonixin
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.AF Clopidogrel
1) Interaction Effect: reduction in clinical efficacy of clopidogrel
2) Summary: Clopidogrel is metabolized to its active metabolite by CYP2C19. Concomitant use of CYP2C19 inhibitors, such as fluvoxamine, would be expected to result in reduced levels of the active metabolite, and therefore a reduction the clinical efficacy of clopidogrel. Concomitant use of CYP2C19 inhibitors with clopidogrel is discouraged (Prod Info PLAVIX(R) oral tablet, 2009).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of clopidogrel and fluvoxamine is discouraged (Prod Info PLAVIX (R) oral tablet, 2009).
7) Probable Mechanism: inhibition of CYP2C19- mediated clopidogrel metabolism by fluvoxamine

3.5.1.AG Clopidogrel
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and antiplatelet agents has been associated with an increased risk of bleeding. Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an antiplatelet agent are given concurrently, monitor patient for

signs of increased bleeding (Prod Info PAXIL(R) oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008)
7) Probable Mechanism: unknown

3.5.1.AH Clorgyline
1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)
2) Summary: Concurrent administration or overlapping therapy with fluvoxamine and a monoamine oxidase (MAO) inhibitor may result in CNS toxicity or serotonin syndrome, a hyperserotonergic state characterized by symptoms such as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. Serious, even fatal, reactions have been reported with concomitant use of serotonin specific reuptake inhibitors and MAO inhibitors (Prod Info Luvox(R), 1997k; Lappin & Auchincloss, 1994e; Graber et al, 1994e; Suchowersky & de Vries, 1990e). Concomitant use is not recommended.
3) Severity: major
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Concurrent use of fluvoxamine and a MAO inhibitor should be avoided. Wait at least two weeks after discontinuing an MAO inhibitor before initiating therapy with fluvoxamine. Wait at least two weeks after discontinuing fluvoxamine before initiating therapy with a MAO inhibitor.
7) Probable Mechanism: serotonin reuptake inhibition
8) Literature Reports
a) Concomitant use of serotonin specific reuptake inhibitors and monoamine oxidase inhibitors can produce a toxic reaction known as serotonin syndrome (Sternbach, 1991d). Serotonin syndrome is a condition of serotonergic hyperstimulation and manifests as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. If the syndrome is not recognized and correctly treated, death can result.
b) A 26-year old woman who had been taking isocarboxazid for eight weeks stopped taking the drug for 11 days before beginning therapy with sertraline. After a single 100 mg sertraline dose, the patient became restless and developed leg twitches. The patients was later admitted to the emergency room with diaphoresis, tachycardia, hyperreflexia, and various neuromuscular disturbances. After treatment with diazepam and propranolol the patient did not improve. The patient was then given two 4 mg doses of cyproheptadine an hour apart, with notable improvement in symptoms after the second dose (Lappin & Auchincloss, 1994d).
c) A drug interaction occurred in a 61-year old woman whose regimen of sertraline 100 mg twice daily was added to a regimen of lithium, phenelzine, thioridazine, and doxepin. Three hours after taking the first sertraline dose, the patient was found in a semicomatose state, with elevated body temperature, increased pulse, increased respiration rate, and a blood pressure of 140/110 mm Hg. After transportation to the hospital, the patient was misdiagnosed as having neuroleptic malignant syndrome (NMS) which was later changed to serotonin syndrome due to a reaction between sertraline and phenelzine. The authors suggest that monoamine oxidase inhibitor (MAOI) therapy should be discontinued for at least two weeks before initiation of therapy with a selective serotonin reuptake inhibitor (SSRI) and that before starting a MAOI, SSRI therapy should be discontinued for at least 5 half-lives of the parent drug and any active metabolites (Graber et al, 1994d).
d) Two cases reports suggested a possible interaction between fluoxetine and selegiline (Suchowersky & de Vries, 1990d). One case involved a first episode of mania being observed approximately one month after adding selegiline to fluoxetine therapy. The patient improved two months after both drugs were discontinued, and no further details were provided. The second case involved diaphoresis, vasoconstriction, and cyanosis of the hands which occurred in close temporal relationship to adding fluoxetine and selegiline. Both drugs were discontinued, with relatively quick resolution of symptoms. Rechallenge with fluoxetine alone occurred without incident.

3.5.1.AI Clozapine
1) Interaction Effect: increased serum clozapine concentrations
2) Summary: Coadministration of clozapine with fluvoxamine has been reported to result in increased clozapine levels and worsening of psychotic symptoms (Prod Info Clozaril(R), 2002; Chong et al, 1997a; Jerling et al, 1994a). Extrapyramidal symptoms have also been reported with this drug combination (Kuo et al, 1998a). Fluvoxamine, a potent inhibitor of CYP1A2, may decrease metabolism of clozapine, resulting in increased serum concentrations (Chong et al, 1997a; Wetzel et al, 1998a).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Clinicians should be aware of a potential interaction between clozapine and fluvoxamine. If these drugs are given concurrently, monitor patients for increased serum clozapine concentrations, worsening of psychosis, and the development of extrapyramidal symptoms. Downward dosage adjustments of clozapine may be necessary.
7) Probable Mechanism: inhibition of cytochrome P450 1A2-mediated clozapine metabolism
8) Literature Reports
a) Therapeutic drug monitoring data showed higher clozapine concentration/dose ratios in three of four

patients when concurrent fluvoxamine was used compared with clozapine alone. In two of these patients, clozapine concentrations were 5 to 10 times higher when fluvoxamine was coadministered. One patient experienced adverse effects, including sedation and urinary incontinence. Inhibition of the CYP1A2 enzyme by fluvoxamine was thought to be the mechanism in this drug interaction (Jerling et al, 1994).

b) One study presented two case reports in which addition of a selective serotonin reuptake inhibitor (SSRI) to clozapine therapy resulted in exacerbation of psychotic symptoms. The first patient, a 26-year old woman with schizophrenia, had been taking clozapine 175 mg per day. Other medications included propranolol for tachycardia and trihexyphenidyl for hypersalivation. After marked improvement in psychotic symptoms but continued compulsive behavior, sertraline 50 mg per day was added. Within four weeks, the patient's obsessive-compulsive symptoms and psychotic symptoms worsened. Plasma clozapine concentrations increased from 325 ng/mL before sertraline therapy to 695 ng/mL after sertraline therapy. Patient 2, a 24-year old woman with schizophrenia, was placed on a regimen of clozapine 500 mg per day which was later increased to 600 mg per day. After fluvoxamine 50 mg per day was started as adjunctive treatment, the patient's clozapine level rose from 1146 ng/mL before fluvoxamine treatment to 2750 ng/mL after 28 days of fluvoxamine treatment. During this time the patient's compulsive symptoms remained unchanged, but psychotic symptoms worsened. The authors postulated that the worsening of psychotic symptoms could be due to SSRI inhibition of clozapine metabolism by cytochrome P450 isozymes, or an imbalance of the serotonergic and dopaminergic blockade caused by coadministration the two drugs (Chong et al, 1997).

c) Fluvoxamine significantly increased serum levels of clozapine in 16 patients with schizophrenia. Clozapine 2.5 to 3 mg/kg/day was given for 14 days, then fluvoxamine 50 mg daily was added for 14 days. Serum concentrations of clozapine and two metabolites were measured on days 1, 7, and 14. The increase in clozapine serum concentration was approximately 3-fold when given with fluvoxamine compared to clozapine alone (Wetzel et al, 1998).

d) Two patients experienced the onset of extrapyramidal symptoms (EPS) when fluvoxamine was added to an existing regimen that included clozapine. The first patient, a 46-year-old male, was stabilized on clozapine 400 mg daily for more than a year when fluvoxamine 25 mg daily was started. No signs of EPS were present before fluvoxamine therapy, and the clozapine plasma level was 686.2 ng/mL. Four days after fluvoxamine was initiated, the patient experienced rigidity and an Extrapyramidal Symptom Rating Scale (ESRS) score of 6. Three weeks later, the ESRS had increased to 8 and the clozapine level was 817.9 ng/mL. Fluvoxamine was discontinued, and the ESRS score and clozapine level decreased to 1 and 686.8 ng/mL, respectively, three weeks later. The second patient, a 46-year-old female, was maintained on clozapine 600 mg daily for more than two years with a plasma level of 1292.5 ng/mL and no signs of EPS. Fluvoxamine was started at 25 mg daily and six days later she developed moderate akathisia and tremors (ESRS of 7). Three weeks and six weeks into combination therapy, her clozapine plasma levels were 1438.2 ng/mL and 1548.9 ng/mL, respectively. The ESRS increased to 9, but the patient preferred the combination therapy due to the efficacy in alleviating psychotic symptoms (Kuo et al, 1998).

3.5.1.AJ Cyclosporine

1) Interaction Effect: an increased risk of cyclosporine toxicity (renal dysfunction, cholestasis, paresthesias)

2) Summary: Fluvoxamine was reported to increase cyclosporine trough serum levels in a 62-year-old female. Fluvoxamine is an inhibitor of cytochrome P450 3A4 enzymes, which are required for cyclosporine metabolism (Vella & Sayegh, 1998a).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Closely monitor cyclosporine serum concentrations when fluvoxamine therapy is initiated, altered, or discontinued.

7) Probable Mechanism: inhibition of cytochrome P450 3A4 enzymes by fluvoxamine decreases cyclosporine metabolism

8) Literature Reports

a) A 62-year-old female received a cadaveric renal allograft nine years prior to initiating fluvoxamine therapy for depression. Her baseline cyclosporine trough level ranged from 200 ng/mL to 250 ng/mL, and serum creatinine was 1.5 mg/dL. Medications included cyclosporine 300 mg daily, prednisone, atenolol, levothyroxine, bumetanide, rocaltrol, and omeprazole. Fluvoxamine 100 mg daily was started for symptoms of depression, and two weeks later the patient complained of shivering and exhibited a fine tremor. Cyclosporine trough level was 380 ng/mL and serum creatinine had increased to 1.9 mg/dL. Cyclosporine dosage was decreased to 200 mg daily, and both the cyclosporine trough level and serum creatinine returned to their baseline values (Vella & Sayegh, 1998).

3.5.1.AK Dalteparin

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info LUVOX(R) CR extended-release oral capsules, 2008). Bleeding events reported have included epistaxis, ecchymosis,

hematoma, petechiae, and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with warfarin. In patients receiving warfarin and fluvoxamine concomitantly for 2 weeks, warfarin plasma concentrations increased by 98% and prothrombin times were prolonged. Fluvoxamine appears to inhibit several cytochrome P450 isoenzymes which may include 1A2 and 2C9 isozymes, which are responsible for warfarin metabolism (Schalekamp et al, 2008; Prod Info LUVOX(R) CR extended-release oral capsules, 2008).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When fluvoxamine and an anticoagulant are given concurrently, monitor patient for signs of increased bleeding. Patients who are taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, when fluvoxamine therapy is initiated or discontinued. Periodically reassess the prothrombin time ratio and INR in patients receiving fluvoxamine and anticoagulant therapy (Prod Info LUVOX(R) CR extended-release oral capsules, 2008).
7) Probable Mechanism: unknown
8) Literature Reports
a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bleeding (hospital admission due to bleeding) in patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patients with a mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients experienced 11 bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experiencing bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model (Wallerstedt et al, 2009).
b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5), however, the rate of gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).
c) A hospitalized 80-year-old female was started on intravenous heparin and oral warfarin therapy due to an embolic stroke secondary to atrial fibrillation and mitral stenosis. Her warfarin dose was maintained at 1 mg daily, with her INR between 2.5 and 3. Fluvoxamine 25 mg daily was started for depression, and her warfarin dose was increased to 1.5 mg daily 3 days later due to worsening of the left hemiparesis. Three days later, her INR was 9.96, and a repeat INR to rule out laboratory error was 11.3. Warfarin was discontinued, fresh frozen plasma was given, and fluvoxamine was discontinued. Six days later, warfarin was again started at 1 mg daily, and the INR increased over 4 days to 11.8. The elevated INR was attributed to the persisting effect of fluvoxamine. She was eventually stabilized on warfarin 1 mg daily with INR values between 2 and 2.5 (Yap & Low, 1999).

3.5.1.AL Danaparoid
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info LUVOX(R) CR extended-release oral capsules, 2008). Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with warfarin. In patients receiving warfarin and fluvoxamine concomitantly for 2 weeks, warfarin plasma concentrations increased by 98% and prothrombin times were prolonged. Fluvoxamine appears to inhibit several cytochrome P450 isoenzymes which may include 1A2 and 2C9 isozymes, which are responsible for warfarin metabolism (Schalekamp et al, 2008; Prod Info LUVOX(R) CR extended-release oral capsules, 2008).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When fluvoxamine and an anticoagulant are given concurrently, monitor patient for signs of increased bleeding. Patients who are taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, when fluvoxamine therapy is initiated or discontinued.

Periodically reassess the prothrombin time ratio and INR in patients receiving fluvoxamine and anticoagulant therapy (Prod Info LUVOX(R) CR extended-release oral capsules, 2008).

7) Probable Mechanism: unknown

8) Literature Reports

a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bleeding (hospital admission due to bleeding) in patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patients with a mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients experienced 11 bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experiencing bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model (Wallerstedt et al, 2009).

b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5), however, the rate of gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).

c) A hospitalized 80-year-old female was started on intravenous heparin and oral warfarin therapy due to an embolic stroke secondary to atrial fibrillation and mitral stenosis. Her warfarin dose was maintained at 1 mg daily, with her INR between 2.5 and 3. Fluvoxamine 25 mg daily was started for depression, and her warfarin dose was increased to 1.5 mg daily 3 days later due to worsening of the left hemiparesis. Three days later, her INR was 9.96, and a repeat INR to rule out laboratory error was 11.3. Warfarin was discontinued, fresh frozen plasma was given, and fluvoxamine was discontinued. Six days later, warfarin was again started at 1 mg daily, and the INR increased over 4 days to 11.8. The elevated INR was attributed to the persisting effect of fluvoxamine. She was eventually stabilized on warfarin 1 mg daily with INR values between 2 and 2.5 (Yap & Low, 1999).

3.5.1.AM Defibrotide

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info LUVOX(R) CR extended-release oral capsules, 2008). Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with warfarin. In patients receiving warfarin and fluvoxamine concomitantly for 2 weeks, warfarin plasma concentrations increased by 98% and prothrombin times were prolonged. Fluvoxamine appears to inhibit several cytochrome P450 isoenzymes which may include 1A2 and 2C9 isozymes, which are responsible for warfarin metabolism (Schalekamp et al, 2008; Prod Info LUVOX(R) CR extended-release oral capsules, 2008).

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: When fluvoxamine and an anticoagulant are given concurrently, monitor patient for signs of increased bleeding. Patients who are taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, when fluvoxamine therapy is initiated or discontinued. Periodically reassess the prothrombin time ratio and INR in patients receiving fluvoxamine and anticoagulant therapy (Prod Info LUVOX(R) CR extended-release oral capsules, 2008).

7) Probable Mechanism: unknown

8) Literature Reports

a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bleeding (hospital admission due to bleeding) in patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patients with a mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients experienced 11 bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4

and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experiencing bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model (Wallerstedt et al, 2009).

b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5), however, the rate of gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).

c) A hospitalized 80-year-old female was started on intravenous heparin and oral warfarin therapy due to an embolic stroke secondary to atrial fibrillation and mitral stenosis. Her warfarin dose was maintained at 1 mg daily, with her INR between 2.5 and 3. Fluvoxamine 25 mg daily was started for depression, and her warfarin dose was increased to 1.5 mg daily 3 days later due to worsening of the left hemiparesis. Three days later, her INR was 9.96, and a repeat INR to rule out laboratory error was 11.3. Warfarin was discontinued, fresh frozen plasma was given, and fluvoxamine was discontinued. Six days later, warfarin was again started at 1 mg daily, and the INR increased over 4 days to 11.8. The elevated INR was attributed to the persisting effect of fluvoxamine. She was eventually stabilized on warfarin 1 mg daily with INR values between 2 and 2.5 (Yap & Low, 1999).

3.5.1.AN Dehydroepiandrosterone

1) Interaction Effect: development of manic symptoms

2) Summary: A case has been reported in which concomitant dehydroepiandrosterone (DHEA) and sertraline use was suggested to precipitate a manic episode in a patient with a history of bipolar disorder (Dean, 2000a). DHEA was also noted to cause mania in a patient with no previous personal or family history of bipolar disorder (Markowitz et al, 1999). Elevated DHEA levels have been found in patients with mental disorders; DHEA suppression has lead to improvement in psychotic symptoms (Howard, 1992). DHEA possesses proserotonergic activity which may predispose patients to manic episodes (Majewska, 1995). DHEA is a precursor to androgenic steroids, which in high doses may precipitate mania (Markowitz et al, 1999). Patients taking medication for bipolar disorder or patients with a personal and/or family history of bipolar disorder should not take DHEA until further data is available to characterize this drug-herb interaction. Concomitant use of DHEA with selective serotonin reuptake inhibitors (SSRIs) should be avoided due to the potential additive precipitation of mania.

3) Severity: moderate

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: Avoid concomitant use of dehydroepiandrosterone (DHEA) and selective serotonin reuptake inhibitors. If patients present with manic symptoms (i.e. agitation, anger, irritability, aggressive behavior), determine if the patient is using DHEA and discontinue DHEA.

7) Probable Mechanism: serotonergic activity of dehydroepiandrosterone, possibly increased androgen levels

8) Literature Reports

a) A 31-year-old male was admitted following threats to commit suicide and injure family members. He had self-initiated sertraline 100 milligrams (mg) daily for the previous 2 to 3 weeks for depression. Sertraline had been prescribed 3 years prior when he was diagnosed with bipolar disorder, which he discontinued after 2 weeks. He had also taken dehydroepiandrosterone (DHEA) 300 mg to 500 mg daily for the previous 2 months apparently for weight training. Following use of DHEA for a short time, he became more irritable, was not sleeping well, and began threatening a female friend and family members. He also drank alcohol occasionally and reportedly had difficulty controlling his anger when intoxicated. Sertraline was stopped and the patient was treated with valproic acid with the dose titrated to 500 mg twice daily. The combination of DHEA, sertraline, and alcohol was suggested responsible for the developing of the manic episode (Dean, 2000).

3.5.1.AO Dermatan Sulfate

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info LUVOX(R) CR extended-release oral capsules, 2008). Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with warfarin. In patients receiving warfarin and fluvoxamine concomitantly for 2 weeks, warfarin plasma concentrations increased by 98% and

prothrombin times were prolonged. Fluvoxamine appears to inhibit several cytochrome P450 isoenzymes which may include 1A2 and 2C9 isozymes, which are responsible for warfarin metabolism (Schalekamp et al, 2008; Prod Info LUVOX(R) CR extended-release oral capsules, 2008).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When fluvoxamine and an anticoagulant are given concurrently, monitor patient for signs of increased bleeding. Patients who are taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, when fluvoxamine therapy is initiated or discontinued. Periodically reassess the prothrombin time ratio and INR in patients receiving fluvoxamine and anticoagulant therapy (Prod Info LUVOX(R) CR extended-release oral capsules, 2008).
7) Probable Mechanism: unknown
8) Literature Reports
a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bleeding (hospital admission due to bleeding) in patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patients with a mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients experienced 11 bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experiencing bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model (Wallerstedt et al, 2009).
b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5), however, the rate of gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).
c) A hospitalized 80-year-old female was started on intravenous heparin and oral warfarin therapy due to an embolic stroke secondary to atrial fibrillation and mitral stenosis. Her warfarin dose was maintained at 1 mg daily, with her INR between 2.5 and 3. Fluvoxamine 25 mg daily was started for depression, and her warfarin dose was increased to 1.5 mg daily 3 days later due to worsening of the left hemiparesis. Three days later, her INR was 9.96, and a repeat INR to rule out laboratory error was 11.3. Warfarin was discontinued, fresh frozen plasma was given, and fluvoxamine was discontinued. Six days later, warfarin was again started at 1 mg daily, and the INR increased over 4 days to 11.8. The elevated INR was attributed to the persisting effect of fluvoxamine. She was eventually stabilized on warfarin 1 mg daily with INR values between 2 and 2.5 (Yap & Low, 1999).

3.5.1.AP Desipramine
1) Interaction Effect: desipramine toxicity (dry mouth, urinary retention, sedation)
2) Summary: While an early report on fluvoxamine combined with desipramine or imipramine found increased TCA concentrations (Spina et al, 1992a), later studies by the same investigators reported that fluvoxamine caused no significant alterations in desipramine pharmacokinetics (Spina et al, 1993a; Spina et al, 1993aa).
3) Severity: minor
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Monitor patients for signs of desipramine and fluvoxamine toxicity; lower doses of one or both agents may be required with concomitant therapy.
7) Probable Mechanism: decreased desipramine metabolism
8) Literature Reports
a) The addition of fluvoxamine to imipramine or desipramine in four patients was reported to result in greatly increased tricyclic antidepressant plasma levels (Spina et al, 1992). Three of the four patients showed signs of tricyclic toxicity.
b) A controlled study in eight depressed patients found a slight, but insignificant, increase in desipramine concentrations, after 10 days, when fluvoxamine was added to desipramine therapy (Spina et al, 1993a).
c) A pharmacokinetic study in 12 healthy volunteers reviewed concurrent use of desipramine and fluvoxamine (Spina et al, 1993). No significant alterations in the pharmacokinetics of either drug were

found.

3.5.1.AQ Desirudin

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info LUVOX(R) CR extended-release oral capsules, 2008). Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with warfarin. In patients receiving warfarin and fluvoxamine concomitantly for 2 weeks, warfarin plasma concentrations increased by 98% and prothrombin times were prolonged. Fluvoxamine appears to inhibit several cytochrome P450 isoenzymes which may include 1A2 and 2C9 isozymes, which are responsible for warfarin metabolism (Schalekamp et al, 2008; Prod Info LUVOX(R) CR extended-release oral capsules, 2008).

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: When fluvoxamine and an anticoagulant are given concurrently, monitor patient for signs of increased bleeding. Patients who are taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, when fluvoxamine therapy is initiated or discontinued. Periodically reassess the prothrombin time ratio and INR in patients receiving fluvoxamine and anticoagulant therapy (Prod Info LUVOX(R) CR extended-release oral capsules, 2008).

7) Probable Mechanism: unknown

8) Literature Reports

a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bleeding (hospital admission due to bleeding) in patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patients with a mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients experienced 11 bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experiencing bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model (Wallerstedt et al, 2009).

b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5), however, the rate of gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).

c) A hospitalized 80-year-old female was started on intravenous heparin and oral warfarin therapy due to an embolic stroke secondary to atrial fibrillation and mitral stenosis. Her warfarin dose was maintained at 1 mg daily, with her INR between 2.5 and 3. Fluvoxamine 25 mg daily was started for depression, and her warfarin dose was increased to 1.5 mg daily 3 days later due to worsening of the left hemiparesis. Three days later, her INR was 9.96, and a repeat INR to rule out laboratory error was 11.3. Warfarin was discontinued, fresh frozen plasma was given, and fluvoxamine was discontinued. Six days later, warfarin was again started at 1 mg daily, and the INR increased over 4 days to 11.8. The elevated INR was attributed to the persisting effect of fluvoxamine. She was eventually stabilized on warfarin 1 mg daily with INR values between 2 and 2.5 (Yap & Low, 1999).

3.5.1.AR Desvenlafaxine

1) Interaction Effect: increased risk of serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)

2) Summary: Concurrent use of desvenlafaxine and a selective serotonin reuptake inhibitor (SSRI) may result in serotonin syndrome, which may be life-threatening. Symptoms of serotonin syndrome may include restlessness, hallucinations, loss of coordination, fast heart beat, rapid changes in blood pressure, increased body temperature, overreactive reflexes, nausea, vomiting, and diarrhea (Prod Info PRISTIQ(TM) oral extended-release tablets, 2008).

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical
6) Clinical Management: Coadministration of desvenlafaxine and an SSRI may result in a life-threatening condition called serotonin syndrome. If these agents are used together, discuss the risks of serotonin syndrome with the patient and monitor closely for symptoms of serotonin syndrome (restlessness, hyperthermia, hyperreflexia, incoordination), especially during treatment initiation and dose increases (Prod Info PRISTIQ(TM) oral extended-release tablets, 2008).
7) Probable Mechanism: additive serotonergic effect

3.5.1.AS Dexfenfluramine

1) Interaction Effect: serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)
2) Summary: Dexfenfluramine is a nonspecific serotonin agonist that both enhances the release of serotonin and inhibits serotonin reuptake. Combination therapy with dexfenfluramine and another selective serotonin reuptake inhibitor, such as fluvoxamine, has the potential to cause serotonin syndrome (Schenck & Mahowald, 1996a). Serotonin syndrome is a hyperserotonergic state characterized by symptoms such as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. Serious, even fatal, reactions have been reported (Sternbach, 1991k). Dexfenfluramine should not be used in combination with fluvoxamine (Prod Info Redux(R), 1997).
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Concurrent use of dexfenfluramine and fluvoxamine may result in an additive increase in serotonin levels in the central nervous system, and could result in serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes). Dexfenfluramine should not be used in combination with fluvoxamine or other serotonin specific reuptake inhibitors.
7) Probable Mechanism: additive serotonergic effects

3.5.1.AT Dexketoprofen

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.AU Diazepam

1) Interaction Effect: diazepam and N-desmethyldiazepam accumulation
2) Summary: Coadministration of fluvoxamine 150 mg daily with a single oral dose of diazepam 10 mg resulted in a 65% decrease in clearance of diazepam. The clearance of diazepam's primary active metabolite, N-desmethyldiazepam, is reduced to immeasurable levels. This effect may be more pronounced with increasing doses of fluvoxamine (Prod Info Luvox(R), 1997g).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Diazepam and fluvoxamine should not be taken concurrently due to the possibility of significant diazepam accumulation. Consider switching to a benzodiazepine eliminated by glucuronidation (eg, lorazepam, oxazepam, temazepam) and monitor for signs of benzodiazepine intoxication (eg, sedation, dizziness, ataxia, weakness, decreased cognition or motor performance).
7) Probable Mechanism: reduced diazepam clearance

3.5.1.AV Diclofenac

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.AW Dicumarol

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info LUVOX(R) CR extended-release oral capsules, 2008). Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with warfarin. In patients receiving warfarin and fluvoxamine concomitantly for 2 weeks, warfarin plasma concentrations increased by 98% and prothrombin times were prolonged. Fluvoxamine appears to inhibit several cytochrome P450 isoenzymes which may include 1A2 and 2C9 isozymes, which are responsible for warfarin metabolism (Schalekamp et al, 2008; Prod Info LUVOX(R) CR extended-release oral capsules, 2008).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When fluvoxamine and an anticoagulant are given concurrently, monitor patient for signs of increased bleeding. Patients who are taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, when fluvoxamine therapy is initiated or discontinued. Periodically reassess the prothrombin time ratio and INR in patients receiving fluvoxamine and anticoagulant therapy (Prod Info LUVOX(R) CR extended-release oral capsules, 2008).
7) Probable Mechanism: unknown
8) Literature Reports
a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bleeding (hospital admission due to bleeding) in patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patients with a mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients experienced 11 bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experiencing bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model (Wallerstedt et al, 2009).
b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for

hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5), however, the rate of gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).

c) A hospitalized 80-year-old female was started on intravenous heparin and oral warfarin therapy due to an embolic stroke secondary to atrial fibrillation and mitral stenosis. Her warfarin dose was maintained at 1 mg daily, with her INR between 2.5 and 3. Fluvoxamine 25 mg daily was started for depression, and her warfarin dose was increased to 1.5 mg daily 3 days later due to worsening of the left hemiparesis. Three days later, her INR was 9.96, and a repeat INR to rule out laboratory error was 11.3. Warfarin was discontinued, fresh frozen plasma was given, and fluvoxamine was discontinued. Six days later, warfarin was again started at 1 mg daily, and the INR increased over 4 days to 11.8. The elevated INR was attributed to the persisting effect of fluvoxamine. She was eventually stabilized on warfarin 1 mg daily with INR values between 2 and 2.5 (Yap & Low, 1999).

3.5.1.AX Diflunisal

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).

b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.AY Dihydroergotamine

1) Interaction Effect: an increased risk of ergotism (nausea, vomiting, vasospastic ischemia)

2) Summary: Because of the potential for serious toxicity including vasospasm that can occur with increased plasma concentrations of ergot derivatives, the concurrent use of fluvoxamine and ergot derivatives is contraindicated. Fluvoxamine and ergot derivatives are both metabolized by cytochrome P450 3A4 enzymes, and the competition for metabolism could result in an increased plasma concentration of the ergot derivative (Prod Info Cafergot(R), 2002).

3) Severity: contraindicated

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: The concurrent use of fluvoxamine and ergot derivatives is contraindicated.

7) Probable Mechanism: inhibition of cytochrome P450 3A4- mediated ergot metabolism by fluvoxamine

3.5.1.AZ Diltiazem

1) Interaction Effect: bradycardia

2) Summary: Fluvoxamine may inhibit the metabolism of diltiazem, causing elevated diltiazem levels and bradycardia (Prod Info Luvox(R), 1997s).

3) Severity: minor

4) Onset: rapid

5) Substantiation: theoretical

6) Clinical Management: Monitor patients for appropriate cardiovascular response to calcium channel blockade, with dose titration as required to achieve desired effect.

7) Probable Mechanism: decreased diltiazem metabolism

3.5.1.BA Dipyridamole

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and antiplatelet agents has been associated with an increased risk of bleeding. Bleeding events reported have included epistaxis, ecchymosis,

hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an antiplatelet agent are given concurrently, monitor patient for signs of increased bleeding (Prod Info PAXIL(R) oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008)
7) Probable Mechanism: unknown

3.5.1.BB Dipyrone
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.BC Droperidol
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Any drug known to have the potential to prolong the QT interval should not be used together with droperidol. Possible pharmacodynamic interactions can occur between droperidol and potentially arrhythmogenic agents such as antidepressants that prolong the QT interval (Prod Info Inapsine(R), 2002).
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Droperidol should be administered with extreme caution in the presence of risk factors for development of prolonged QT syndrome, such as treatment with antidepressants.
7) Probable Mechanism: additive cardiac effects

3.5.1.BD Droxicam
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined

use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.BE Duloxetine
1) Interaction Effect: increased duloxetine bioavailability and an increased risk of serotonin syndrome
2) Summary: Duloxetine is a selective serotonin and norepinephrine reuptake inhibitor (SSNRI) that is primarily metabolized by the CYP1A2 and CYP2D6 isozymes. The concomitant use of duloxetine with fluvoxamine, a SSRI, is not recommended due to the potential for serotonin syndrome. In addition, coadministration of fluvoxamine 100 mg (a CYP1A2 inhibitor) with duloxetine 40 mg twice a day in 14 CYP2D6 poor metabolizer subjects resulted in a 6-fold increase in duloxetine AUC and Cmax. Also, when 14 male patients were given duloxetine 60 mg together with fluvoxamine 100 mg, duloxetine AUC, Cmax, and half-life increased by 6-fold, about 2.5-fold, and 3-fold, respectively (Prod Info CYMBALTA(R) delayed-release oral capsules, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: established
6) Clinical Management: The concomitant use of duloxetine and fluvoxamine is not recommended due to the potential for development of serotonin syndrome. Additionally, concomitant use has resulted in significantly increased duloxetine exposure and serum levels (Prod Info CYMBALTA(R) delayed-release oral capsules, 2008).
7) Probable Mechanism: inhibition of CYP1A2-mediated duloxetine metabolism; additive serotonergic effects

3.5.1.BF Eletriptan
1) Interaction Effect: an increased risk of serotonin syndrome
2) Summary: There have been case reports of weakness, hyperreflexia, and incoordination following concomitant use of sumatriptan, a 5-hydroxytryptamine-1 (5HT-1) agonist, and a serotonin specific reuptake inhibitor (SSRI) (Prod Info Imitrex(R) Nasal Spray, 2003). Because eletriptan is a 5HT 1B/1D agonist, a similar interaction between SSRIs and eletriptan may occur (Prod Info Relpax(R), 2003). Concurrent use of a triptan and an SSRI may result in serotonin syndrome which may be life-threatening. Symptoms of serotonin syndrome may include restlessness, hallucinations, loss of coordination, fast heart beat, rapid changes in blood pressure, increased body temperature, overreactive reflexes, nausea, vomiting, and diarrhea. Clinicians should be aware that triptans may be commonly used intermittently and that either the triptan or the SSRI may be prescribed by a different physician. Discuss the risks of serotonin syndrome with patients who are prescribed this combination and monitor them closely for symptoms of serotonin syndrome (US Food and Drug Administration, 2006).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Coadministration of a triptan, such as eletriptan, and an SSRI may result in a life-threatening condition called serotonin syndrome. Be aware that triptans may be commonly used intermittently and that either the triptan or the SSRI may be prescribed by a different physician. If these agents are used together, discuss the risks of serotonin syndrome with the patient and monitor closely for symptoms of serotonin syndrome (restlessness, hyperthermia, hyperreflexia, incoordination).
7) Probable Mechanism: additive pharmacologic effects resulting in excessive serotonergic stimulation

3.5.1.BG Eltrombopag
1) Interaction Effect: increased eltrombopag plasma concentrations
2) Summary: Concomitant use of eltrombopag and fluvoxamine, a strong CYP1A2 inhibitor, may result in elevated eltrombopag plasma concentrations due to inhibition of CYP1A2-mediated eltrombopag metabolism. The patient should be monitored for excessive eltrombopag exposure when eltrombopag and fluvoxamine are coadministered (Prod Info PROMACTA(R) oral tablets, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of eltrombopag and fluvoxamine, a strong CYP1A2 inhibitor, may result in elevated eltrombopag plasma concentrations. Monitor the patient for excessive eltrombopag exposure when eltrombopag and fluvoxamine are coadministered (Prod Info PROMACTA(R) oral tablets, 2008).
7) Probable Mechanism: inhibition of CYP1A2-mediated eltrombopag metabolism by fluvoxamine

3.5.1.BH Enoxaparin
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control

and cohort studies have shown that the combined use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info LUVOX(R) CR extended-release oral capsules, 2008). Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with warfarin. In patients receiving warfarin and fluvoxamine concomitantly for 2 weeks, warfarin plasma concentrations increased by 98% and prothrombin times were prolonged. Fluvoxamine appears to inhibit several cytochrome P450 isoenzymes which may include 1A2 and 2C9 isozymes, which are responsible for warfarin metabolism (Schalekamp et al, 2008; Prod Info LUVOX(R) CR extended-release oral capsules, 2008).

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: When fluvoxamine and an anticoagulant are given concurrently, monitor patient for signs of increased bleeding. Patients who are taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, when fluvoxamine therapy is initiated or discontinued. Periodically reassess the prothrombin time ratio and INR in patients receiving fluvoxamine and anticoagulant therapy (Prod Info LUVOX(R) CR extended-release oral capsules, 2008).

7) Probable Mechanism: unknown

8) Literature Reports

a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bleeding (hospital admission due to bleeding) in patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patients with a mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients experienced 11 bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experiencing bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model (Wallerstedt et al, 2009).

b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5), however, the rate of gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).

c) A hospitalized 80-year-old female was started on intravenous heparin and oral warfarin therapy due to an embolic stroke secondary to atrial fibrillation and mitral stenosis. Her warfarin dose was maintained at 1 mg daily, with her INR between 2.5 and 3. Fluvoxamine 25 mg daily was started for depression, and her warfarin dose was increased to 1.5 mg daily 3 days later due to worsening of the left hemiparesis. Three days later, her INR was 9.96, and a repeat INR to rule out laboratory error was 11.3. Warfarin was discontinued, fresh frozen plasma was given, and fluvoxamine was discontinued. Six days later, warfarin was again started at 1 mg daily, and the INR increased over 4 days to 11.8. The elevated INR was attributed to the persisting effect of fluvoxamine. She was eventually stabilized on warfarin 1 mg daily with INR values between 2 and 2.5 (Yap & Low, 1999).

3.5.1.BI Epoprostenol

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and antiplatelet agents has been associated with an increased risk of bleeding. Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an antiplatelet agent are given concurrently, monitor patient for signs of increased bleeding (Prod Info PAXIL(R) oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008)

7) Probable Mechanism: unknown

3.5.1.BJ Eptifibatide

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and antiplatelet agents has been associated with an increased risk of bleeding. Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an antiplatelet agent are given concurrently, monitor patient for signs of increased bleeding (Prod Info PAXIL(R) oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008)
7) Probable Mechanism: unknown

3.5.1.BK Ergoloid Mesylates

1) Interaction Effect: an increased risk of ergotism (nausea, vomiting, vasospastic ischemia)
2) Summary: Because of the potential for serious toxicity including vasospasm that can occur with increased plasma concentrations of ergot derivatives, the concurrent use of fluvoxamine and ergot derivatives is contraindicated. Fluvoxamine and ergot derivatives are both metabolized by cytochrome P450 3A4 enzymes, and the competition for metabolism could result in an increased plasma concentration of the ergot derivative (Prod Info Cafergot(R), 2002).
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: The concurrent use of fluvoxamine and ergot derivatives is contraindicated.
7) Probable Mechanism: inhibition of cytochrome P450 3A4- mediated ergot metabolism by fluvoxamine

3.5.1.BL Ergonovine

1) Interaction Effect: an increased risk of ergotism (nausea, vomiting, vasospastic ischemia)
2) Summary: Because of the potential for serious toxicity including vasospasm that can occur with increased plasma concentrations of ergot derivatives, the concurrent use of fluvoxamine and ergot derivatives is contraindicated. Fluvoxamine and ergot derivatives are both metabolized by cytochrome P450 3A4 enzymes, and the competition for metabolism could result in an increased plasma concentration of the ergot derivative (Prod Info Cafergot(R), 2002).
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: The concurrent use of fluvoxamine and ergot derivatives is contraindicated.
7) Probable Mechanism: inhibition of cytochrome P450 3A4- mediated ergot metabolism by fluvoxamine

3.5.1.BM Ergotamine

1) Interaction Effect: an increased risk of ergotism (nausea, vomiting, vasospastic ischemia)
2) Summary: Because of the potential for serious toxicity including vasospasm that can occur with increased plasma concentrations of ergot derivatives, the concurrent use of fluvoxamine and ergot derivatives is contraindicated. Fluvoxamine and ergot derivatives are both metabolized by cytochrome P450 3A4 enzymes, and the competition for metabolism could result in an increased plasma concentration of the ergot derivative (Prod Info Cafergot(R), 2002).
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: The concurrent use of fluvoxamine and ergot derivatives is contraindicated.
7) Probable Mechanism: inhibition of cytochrome P450 3A4- mediated ergot metabolism by fluvoxamine

3.5.1.BN Estazolam

1) Interaction Effect: increased estazolam plasma concentrations and risk of estazolam toxicity
2) Summary: Fluvoxamine is a inhibitor of CYP3A and estazolam metabolism is catalyzed by CYP3A, therefore fluvoxamine is expected to increase plasma estazolam concentration resulting in an increased risk of estazolam toxicity and associated adverse effects (Prod Info ProSom(TM), 2004).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Monitor for signs of benzodiazepine intoxication (eg, sedation, dizziness, ataxia, weakness, decreased cognition or motor performance). If symptoms are present, reduce estazolam dose or consider switching to a benzodiazepine eliminated by glucuronidation (eg, lorazepam, oxazepam, temazepam).
7) Probable Mechanism: fluvoxamine inhibition of P450-3A isoform-mediated estazolam metabolism

3.5.1.BO Etodolac

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).

b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.BP Etofenamate

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).

b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.BQ Etoricoxib

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched

among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).

b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.BR Felbinac

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).

b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.BS Fenbufen

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).

b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.BT Fenfluramine

1) Interaction Effect: serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)

2) Summary: Fenfluramine is a nonspecific serotonin agonist that both enhances the release of serotonin and inhibits serotonin reuptake. Combination therapy with fenfluramine and another selective serotonin reuptake inhibitor, such as fluvoxamine, has the potential to cause serotonin syndrome (Schenck & Mahowald, 1996). Serotonin syndrome is a hyperserotonergic state characterized by symptoms such as

restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. Serious, even fatal, reactions have been reported (Sternbach, 1991j). Until more data are available, fenfluramine should not be used in combination with fluvoxamine.
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Concurrent use of fenfluramine and fluvoxamine may result in an additive increase in serotonin levels in the central nervous system, and could result in serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes). Fenfluramine should not be used in combination with fluvoxamine or other serotonin specific reuptake inhibitors.
7) Probable Mechanism: additive serotonergic effects

3.5.1.BU Fenoprofen
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.BV Fentiazac
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.BW Floctafenine
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an

increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.BX Flufenamic Acid
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.BY Flurbiprofen
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1

to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).

b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.BZ Fondaparinux

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info LUVOX(R) CR extended-release oral capsules, 2008). Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with warfarin. In patients receiving warfarin and fluvoxamine concomitantly for 2 weeks, warfarin plasma concentrations increased by 98% and prothrombin times were prolonged. Fluvoxamine appears to inhibit several cytochrome P450 isoenzymes which may include 1A2 and 2C9 isozymes, which are responsible for warfarin metabolism (Schalekamp et al, 2008; Prod Info LUVOX(R) CR extended-release oral capsules, 2008).

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: When fluvoxamine and an anticoagulant are given concurrently, monitor patient for signs of increased bleeding. Patients who are taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, when fluvoxamine therapy is initiated or discontinued. Periodically reassess the prothrombin time ratio and INR in patients receiving fluvoxamine and anticoagulant therapy (Prod Info LUVOX(R) CR extended-release oral capsules, 2008).

7) Probable Mechanism: unknown

8) Literature Reports

a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bleeding (hospital admission due to bleeding) in patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patients with a mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients experienced 11 bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experiencing bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model (Wallerstedt et al, 2009).

b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5), however, the rate of gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).

c) A hospitalized 80-year-old female was started on intravenous heparin and oral warfarin therapy due to an embolic stroke secondary to atrial fibrillation and mitral stenosis. Her warfarin dose was maintained at 1 mg daily, with her INR between 2.5 and 3. Fluvoxamine 25 mg daily was started for depression, and her warfarin dose was increased to 1.5 mg daily 3 days later due to worsening of the left hemiparesis. Three days later, her INR was 9.96, and a repeat INR to rule out laboratory error was 11.3. Warfarin was discontinued, fresh frozen plasma was given, and fluvoxamine was discontinued. Six days later, warfarin was again started at 1 mg daily, and the INR increased over 4 days to 11.8. The elevated INR was attributed to the persisting effect of fluvoxamine. She was eventually stabilized on warfarin 1 mg daily with INR values between 2 and 2.5 (Yap & Low, 1999).

3.5.1.CA Fosphenytoin

1) Interaction Effect: an increased risk of phenytoin toxicity (ataxia, hyperreflexia, nystagmus, tremors)

2) Summary: Fosphenytoin is a prodrug of phenytoin and the same interactions that occur with phenytoin are expected to occur with fosphenytoin (Prod Info Cerebyx(R), 1999). Fluvoxamine inhibits several of the isoenzymes of the cytochrome P450 enzyme system (oxidative metabolism); IA2, IIC9, and IIIA4. Since phenytoin is eliminated at least partially via the CYP450 IIC9 pathway, it is possible that coadministration

with fluvoxamine may cause elevations in phenytoin plasma levels (Prod Info Luvox(R), 1997t). During an in vitro study, the inhibitory effects of fluvoxamine on cytochrome P450 2C9 were evaluated using p-hydroxylation of phenytoin as an established index reaction reflecting CYP2C9 activity. In vivo, p-hydroxylation of phenytoin depends on the formation of 5-(p-hydroxy-phenyl)-5-phenylhydantoin (HPPH). Fluvoxamine, a strong inhibitor of HPPH, impaired the formation of HPPH, which can lead to an increase in steady-state phenytoin levels (Schmider et al, 1997a).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Consideration should be given to monitoring of phenytoin serum levels when fluvoxamine is added or withdrawn from therapy and dosage adjustments made accordingly. Patients should be counseled to be aware of the potential side effects of phenytoin toxicity such as drowsiness, ataxia, and nystagmus, and to notify their physician if such side effects occur.
7) Probable Mechanism: decreased oxidative metabolism

3.5.1.CB Frovatriptan
1) Interaction Effect: an increased risk of serotonin syndrome
2) Summary: There have been case reports of weakness, hyperreflexia, and incoordination following concomitant use of sumatriptan, a 5-hydroxytryptamine-1 (5HT-1) agonist, and a serotonin specific reuptake inhibitor (SSRI) (Prod Info Imitrex(R) Nasal Spray, 2003). Because frovatriptan is a 5HT 1B/1D agonist, a similar interaction between SSRIs and frovatriptan may occur (Prod Info Frova(R), 2004). Concurrent use of frovatriptan and an SSRI may result in serotonin syndrome which may be life-threatening. Symptoms of serotonin syndrome may include restlessness, hallucinations, loss of coordination, fast heart beat, rapid changes in blood pressure, increased body temperature, overreactive reflexes, nausea, vomiting, and diarrhea. Clinicians should be aware that triptans may be commonly used intermittently and that either the triptan or the SSRI may be prescribed by a different physician. Discuss the risks of serotonin syndrome with patients who are prescribed this combination and monitor them closely for symptoms of serotonin syndrome (US Food and Drug Administration, 2006).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Coadministration of a triptan, such as frovatriptan, and an SSRI may result in a life-threatening condition called serotonin syndrome. Be aware that triptans may be commonly used intermittently and that either the triptan or the SSRI may be prescribed by a different physician. If these agents are used together, discuss the risks of serotonin syndrome with the patient and monitor closely for symptoms of serotonin syndrome (restlessness, hyperthermia, hyperreflexia, incoordination).
7) Probable Mechanism: additive pharmacologic effects resulting in excessive serotonergic stimulation

3.5.1.CC Furazolidone
1) Interaction Effect: weakness, hyperreflexia, and incoordination
2) Summary: Although not its primary mechanism of action, furazolidone has monoamine oxidase inhibitor activity. Cases of serious sometimes fatal reactions have been reported in patients receiving selective serotonin reuptake inhibitors (SSRI) in combination with monoamine oxidase inhibitors (MAOIs). Hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma have been reported. Furazolidone should not be used in combination with an SSRI, or within a minimum of 14 days of discontinuing therapy with a MAOI (Prod Info Furoxone(R), 1999).
3) Severity: contraindicated
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: If concurrent therapy with furazolidone and a selective serotonin reuptake inhibitor (SSRI) is deemed to be necessary, closely monitor the patient for signs of serotonergic excess (mental status changes, diaphoresis, fever, weakness, hyperreflexia, incoordination).
7) Probable Mechanism: additive pharmacologic effects resulting in excessive serotonergic stimulation

3.5.1.CD Galantamine
1) Interaction Effect: increased galantamine plasma concentrations
2) Summary: Based upon in vitro studies, the major enzymes involved in galantamine metabolism are CYP3A4 and CYP2D6. Fluvoxamine is a known inhibitor of CYP2D6. In a population pharmacokinetic analysis using a database of 852 Alzheimer's disease patients, several drugs which inhibit CYP2D6, including fluvoxamine (N=14), demonstrated a 25-33% decrease in galantamine clearance. The resulting plasma concentration increase of galantamine may warrant caution when it is coadministered with fluvoxamine. Monitor for galantamine toxicity including anorexia, nausea, vomiting, dizziness, arrhythmias or gastrointestinal bleeding (Prod Info RAZADYNE(R) ER extended release oral capsules, oral tablets, oral solution, 2007).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable

6) Clinical Management: Increased galantamine plasma concentrations may result from fluvoxamine inhibition of galantamine CYP2D6-mediated metabolism. Monitor for galantamine toxicity including anorexia, nausea, vomiting, dizziness, arrhythmias, or gastrointestinal bleeding (Prod Info RAZADYNE(R) ER extended release oral capsules, oral tablets, oral solution, 2007).
7) Probable Mechanism: inhibition of cytochrome CYP2D6-mediated galantamine metabolism

3.5.1.CE Ginkgo

1) Interaction Effect: increased risk of serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)
2) Summary: The addition of Ginkgo biloba and/or St. John's Wort to therapy with buspirone and fluoxetine may have precipitated a hypomanic episode in a case report (Spinella & Eaton, 2002a). It is unclear if Ginkgo or St. John's Wort, the combination of both, or other patient factors, contributed to the effect. Theoretically, Ginkgo may increase the risk of serotonin syndrome when taken with selective serotonin reuptake inhibitors (SSRIs). Caution is advised, especially when ginkgo is taken to counteract sexual dysfunction associated with SSRIs. Ginkgo may inhibit monoamine oxidase (Sloley et al, 2000; White et al, 1996), and has demonstrated serotonergic activity in animals (Ramassamy et al, 1992) which might increase the risk of serotonin syndrome when ginkgo is combined with SSRIs. The potential MAO inhibitory activity of ginkgo is questionable. A human study did not show MAO inhibition in the brain following oral consumption (Fowler et al, 2000). Ginkgo biloba extract inhibited MAO-A/MAO-B in the rat brain in vitro (Sloley et al, 2000; White et al, 1996) and MAO-B in human platelets in vitro (White et al, 1996). No significant MAO inhibition was found in mice following oral consumption (Porsolt et al, 2000).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor patients closely for symptoms of serotonin syndrome if ginkgo is combined with selective serotonin reuptake inhibitors (SSRIs).
7) Probable Mechanism: additive pharmacologic effects resulting in excessive serotonergic stimulation
8) Literature Reports
a) A 42-year-old female experienced symptoms consistent with a mixed hypomanic episode following concomitant use of fluoxetine, buspirone, Ginkgo biloba, and St. John's Wort. The symptoms resolved following discontinuation of Ginkgo and St. John's Wort. The patient was being treated for depression following a mild traumatic brain injury with fluoxetine 20 milligrams (mg) twice daily and buspirone 15 mg twice daily. Several weeks prior to presentation, buspirone was increased to 20 mg twice daily for persistent anxiety and the patient began taking Ginkgo biloba, melatonin, and St. John's Wort in unspecified doses. Melatonin was considered unlikely to have contributed to her symptoms. Ginkgo and St. John's Wort were considered possible contributors since they may potentiate antidepressants, and considering the temporal relationship between the use of the herbs and onset of symptoms and discontinuation of the herbs and resolution of symptoms. However, the brain injury was considered a possible contributor (Spinella & Eaton, 2002).

3.5.1.CF Glimepiride

1) Interaction Effect: an increase in plasma concentrations of glimepiride
2) Summary: Caution is advised when fluvoxamine is coadministered with glimepiride. An increase in plasma concentrations of glimepiride has been documented in healthy patients when used concomitantly with fluvoxamine without a significant effect on blood glucose concentrations (Niemi et al, 2001).
3) Severity: minor
4) Onset: rapid
5) Substantiation: established
6) Clinical Management: Use glimepiride and fluvoxamine concomitantly with caution or use therapeutic alternative. Monitor the patient for hypoglycemia if used concurrently.
7) Probable Mechanism: inhibition of the metabolism of glimepiride through the cytochrome P450 2C9 enzyme
8) Literature Reports
a) Plasma concentrations of glimepiride were moderately increased when used concomitantly with fluvoxamine. A double-blind, randomized, crossover study with three phases including a 4-week washout period between the phases was conducted in twelve healthy volunteers. The aim of the study is to investigate the effects of fluvoxamine on the pharmacokinetics and pharmacodynamics of glimepiride. Subjects received fluvoxamine 100 mg or placebo orally once daily for 4 days. On day 4, a single oral dose of 0.5 mg of glimepiride was administered after the patients fasted overnight. Meals were served 15 minutes after, 3 hours after, and 7 hours after glimepiride administration. For the fluvoxamine phase, the peak concentration (Cmax) was 143% (p less than 0.05) of the respective placebo value, and the half-life was increased from 2 to 2.3 hours (p less than 0.01). The increase in the area under the concentration-time curve (AUC) was not significant, and differences in blood glucose levels were not statistically significant (Niemi et al, 2001).

3.5.1.CG Guarana

1) Interaction Effect: symptoms of excessive caffeine (insomnia, headache, restlessness, nervousness, palpitations, and arrhythmias)

2) Summary: The primary pharmacologically-active ingredient of guarana is caffeine. Fluvoxamine inhibits CYP1A2 and CYP2D6 which are responsible for caffeine metabolism. Decreased caffeine clearance and increased half-life have been demonstrated in humans. Signs and symptoms of caffeine excess may result if the compounds are taken together. Patients should avoid guarana use during therapy with fluvoxamine in order to avoid complications (Jeppesen et al, 1996c).
3) Severity: moderate
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Patients should be advised of the caffeine content of guarana, and of symptoms of excess if taken with fluvoxamine (insomnia, headache, restlessness, nervousness, palpitations, and arrhythmias) as well as symptoms of caffeine withdrawal which may accompany abrupt discontinuation of guarana (headache, fatigue, depression, anxiety, and insomnia). Patients should avoid guarana use during therapy with fluvoxamine in order to avoid complications.
7) Probable Mechanism: fluvoxamine may inhibit the metabolism of the caffeine content of guarana
8) Literature Reports
a) In an open, randomized, cross-over study of 8 volunteers, fluvoxamine significantly decreased caffeine total clearance and increased caffeine half-life. Fluvoxamine was administered as 50 milligrams (mg) for 4 days, then 100 mg for 8 days while subjects abstained from all caffeine intake. Caffeine 200 mg was then administered orally. Total clearance of caffeine decreased from 107 milliliters/minute (ml/min) to 21 ml/min, and half-life increased from 5 hours to 31 hours. Patients taking fluvoxamine should restrict caffeine intake (Jeppesen et al, 1996b).
b) In vitro, fluvoxamine was found to be a very potent inhibitor of the formation of N-demethylated caffeine metabolites with K1 values of 0.08 micromoles (mcmol) to 0.28 mcmol. The formation of 1,7-dimethylxanthine was abolished by 10 mcmol of fluvoxamine, implying the N3-demethylation of caffeine is almost entirely catalyzed by CYP1A2 (Rasmussen et al, 1998a).
c) At least 14 metabolites are formed from caffeine whose main route of elimination is N3-demethylation to paraxanthine (1,7-methylxanthine) which accounts for greater than 80% of caffeine elimination (Lelo et al, 1986a).
d) CYP1A2 is the major enzyme metabolizing caffeine to 1,7-dimethylxanthine (Berthou et al, 1991a; Sesardic et al, 1990a; Butler et al, 1989a). CYP1A2 is also a major enzyme in the formation of 3,7-dimethylxanthine and 1,3-dimethylxantihine from caffeine (Gu et al, 1992a; Berthou et al, 1991a; Grant et al, 1987a).

3.5.1.CH Haloperidol
1) Interaction Effect: an increased risk of haloperidol toxicity
2) Summary: Haloperidol serum concentrations were increased by the coadministration of fluvoxamine in a small double blind, randomized, placebo controlled, crossover study (Daniel et al, 1994a).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Caution should be used when fluvoxamine is administered with haloperidol. Monitor serum concentrations of haloperidol and adjust the dose accordingly. Also monitor the patient for signs and symptoms of worsening clinical and cognitive assessments.
7) Probable Mechanism: inhibition of cytochrome P450-mediated metabolism of haloperidol
8) Literature Reports
a) Four inpatient males with chronic schizophrenia were stabilized on haloperidol and benztropine orally. In randomized order, the patients were then placed on fluvoxamine for six weeks or identically appearing placebo. Results showed that the addition of fluvoxamine to haloperidol therapy significantly elevated serum concentrations of haloperidol. In addition, haloperidol concentrations did not plateau during the six-week period of fluvoxamine treatment, indicating that the haloperidol concentrations may have continued to increase at a constant dose of fluvoxamine. The coadministration of haloperidol and fluvoxamine also worsened all measures of clinical and cognitive function assessments, including delayed recall memory and attentional function. It is possible that haloperidol may require the cytochrome P450 1A2 system for metabolism, and fluvoxamine is known to be a potent inhibitor of this enzyme pathway (Daniel et al, 1994).

3.5.1.CI Heparin
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info LUVOX(R) CR extended-release oral capsules, 2008). Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with warfarin. In patients receiving warfarin and fluvoxamine concomitantly for 2 weeks, warfarin plasma concentrations increased by 98% and prothrombin times were prolonged. Fluvoxamine appears to inhibit several cytochrome P450 isoenzymes which may include 1A2 and 2C9 isozymes, which are responsible for warfarin metabolism (Schalekamp et al, 2008; Prod Info LUVOX(R) CR extended-release oral capsules, 2008).

3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When fluvoxamine and an anticoagulant are given concurrently, monitor patient for signs of increased bleeding. Patients who are taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, when fluvoxamine therapy is initiated or discontinued. Periodically reassess the prothrombin time ratio and INR in patients receiving fluvoxamine and anticoagulant therapy (Prod Info LUVOX(R) CR extended-release oral capsules, 2008).
7) Probable Mechanism: unknown
8) Literature Reports

a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bleeding (hospital admission due to bleeding) in patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patients with a mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients experienced 11 bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experiencing bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model (Wallerstedt et al, 2009).

b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5), however, the rate of gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).

c) A hospitalized 80-year-old female was started on intravenous heparin and oral warfarin therapy due to an embolic stroke secondary to atrial fibrillation and mitral stenosis. Her warfarin dose was maintained at 1 mg daily, with her INR between 2.5 and 3. Fluvoxamine 25 mg daily was started for depression, and her warfarin dose was increased to 1.5 mg daily 3 days later due to worsening of the left hemiparesis. Three days later, her INR was 9.96, and a repeat INR to rule out laboratory error was 11.3. Warfarin was discontinued, fresh frozen plasma was given, and fluvoxamine was discontinued. Six days later, warfarin was again started at 1 mg daily, and the INR increased over 4 days to 11.8. The elevated INR was attributed to the persisting effect of fluvoxamine. She was eventually stabilized on warfarin 1 mg daily with INR values between 2 and 2.5 (Yap & Low, 1999).

3.5.1.CJ Hydroxytryptophan

1) Interaction Effect: an increased risk of serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)
2) Summary: Hydroxytryptophan (5-HTP) may potentiate the serotonergic effect of selective serotonin reuptake inhibitors (SSRIs) (Meltzer et al, 1997a). Since 5-HTP increases serotonin levels, when combined with an SSRI, the serotonin level may be increased sufficiently to produce serotonin syndrome. Caution is advised with concomitant use of 5-HTP and SSRIs.
3) Severity: moderate
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: No cases have been reported of serotonin syndrome resulting from this combination. Caution is advised if hydroxytryptophan (5-HTP) and a selective serotonin reuptake inhibitor (SSRI) are used concomitantly. Monitor the patient for early signs of serotonin syndrome such as anxiety, confusion, and disorientation.
7) Probable Mechanism: additive serotonergic effect
8) Literature Reports

a) Hydroxytryptophan (5-HTP) (200 milligrams (mg) orally) as a single dose increased plasma cortisol and prolactin levels in both medicated and unmedicated patients with major depression or obsessive compulsive disorder (OCD). These responses were greater if the patient was also taking fluoxetine (n = 16) (p less than 0.0001). Mean fluoxetine dose for depressed patients was 44 mg/day,and for OCD patients it was 60 mg/day. Cortisol or prolactin (PRL) levels in patients taking 5-HTP with tricyclic antidepressants (n = 14) or those receiving no medication (n = 83) were not significantly different from each other. A measurement of serotonergic effects of antidepressants can be evaluated by measuring hypothalamic-pituitary-adrenal (HPA) axis or PRL response. No clinical manifestations of serotonin

syndrome were reported in patients taking 5-HTP concomitantly with fluoxetine (Meltzer et al, 1997).

3.5.1.CK Ibuprofen

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).

b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.CL Iloprost

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and antiplatelet agents has been associated with an increased risk of bleeding. Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an antiplatelet agent are given concurrently, monitor patient for signs of increased bleeding (Prod Info PAXIL(R) oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008)

7) Probable Mechanism: unknown

3.5.1.CM Imipramine

1) Interaction Effect: imipramine toxicity (dry mouth, urinary retention, sedation)

2) Summary: Addition of fluvoxamine to imipramine or desipramine therapy can result in significantly increased tricyclic antidepressant plasma levels and signs of tricyclic toxicity (Spina et al, 1992c; Spina et al, 1993ac; Spina et al, 1993c). Fluvoxamine significantly increases imipramine half-life and reduces clearance (Spina et al, 1993c). The addition of fluvoxamine to imipramine or desipramine therapy may result in greatly increased tricyclic antidepressant plasma levels and tricyclic toxicity (Spina et al, 1992c; Spina et al, 1993ac). A bidirectional effect is suggested, in which fluvoxamine increases imipramine concentrations (by interfering with N-demethylation), and imipramine increases fluvoxamine levels (Hartter et al, 1993e).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Monitor patients for signs of imipramine and fluvoxamine toxicity; lower doses of one or both agents may be required with concomitant therapy.

7) Probable Mechanism: decreased imipramine metabolism

8) Literature Reports

a) The pharmacokinetics of combined imipramine and fluvoxamine were studied in healthy volunteers (Spina et al, 1993b). After a 7-day course of fluvoxamine, imipramine half-life was significantly increased (from 23 to 41 hours) and clearance decreased (from 1.02 to 0.28 L/h/kg).

b) The addition of fluvoxamine to imipramine or desipramine in four patients was reported to result in greatly increased tricyclic antidepressant plasma levels (Spina et al, 1992b). Three of four patients showed signs of tricyclic toxicity. The effect of fluvoxamine 100 mg daily for 10 days on plasma concentrations of imipramine was studied in seven depressed patients on maintenance therapy (Spina et al, 1993ab). Imipramine plasma levels were three to four times higher during fluvoxamine coadministration. One patient complained of anticholinergic effects, along with tremor and confusion.

The mechanism of this drug interaction was inhibition of demethylation of imipramine. A pharmacokinetic study in healthy volunteers demonstrated a significantly increased imipramine half-life and reduced clearance (Spina et al, 1993b).

c) Metabolism of tricyclic antidepressants coadministered with fluvoxamine was studied in eight depressed patients (two patients received imipramine) (Hartter et al, 1993d). Fluvoxamine was found to interfere with N-demethylation of imipramine. The combination of fluvoxamine and imipramine led to increased plasma levels of imipramine and decreased concentrations of the N-demethylated imipramine metabolite desimipramine. In addition, TCA-fluvoxamine coadministration apparently raised plasma levels of fluvoxamine.

3.5.1.CN Indomethacin

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).

b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.CO Indoprofen

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).

b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.CP Iproniazid

1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)

2) Summary: Concurrent administration or overlapping therapy with fluvoxamine and a monoamine oxidase (MAO) inhibitor may result in CNS toxicity or serotonin syndrome, a hyperserotonergic state characterized by symptoms such as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis,

shivering, and tremor. Serious, even fatal, reactions have been reported with concomitant use of selective serotonin reuptake inhibitors and MAO inhibitors (Prod Info Luvox(R), 1997f; Lappin & Auchincloss, 1994c; Graber et al, 1994c; Suchowersky & de Vries, 1990c). Concomitant use is not recommended.
3) Severity: major
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Concurrent use of fluvoxamine and a MAO inhibitor should be avoided. Wait at least two weeks after discontinuing an MAO inhibitor before initiating therapy with fluvoxamine. Wait at least two weeks after discontinuing fluvoxamine before initiating therapy with a MAO inhibitor.
7) Probable Mechanism: serotonin reuptake inhibition
8) Literature Reports
a) Concomitant use of serotonin specific reuptake inhibitors and monoamine oxidase inhibitors can produce a toxic reaction known as serotonin syndrome (Sternbach, 1991c). Serotonin syndrome is a condition of serotonergic hyperstimulation and manifests as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. If the syndrome is not recognized and correctly treated, death can result.
b) A 26-year old woman who had been taking isocarboxazid for eight weeks stopped taking the drug for 11 days before beginning therapy with sertraline. After a single 100 mg sertraline dose, the patient became restless and developed leg twitches. The patients was later admitted to the emergency room with diaphoresis, tachycardia, hyperreflexia, and various neuromuscular disturbances. After treatment with diazepam and propranolol the patient did not improve. The patient was then given two 4 mg doses of cyproheptadine an hour apart, with notable improvement in symptoms after the second dose (Lappin & Auchincloss, 1994b).
c) A drug interaction occurred in a 61-year old woman whose regimen of sertraline 100 mg twice daily was added to a regimen of lithium, phenelzine, thioridazine, and doxepin. Three hours after taking the first sertraline dose, the patient was found in a semicomatose state, with elevated body temperature, increased pulse, increased respiration rate, and a blood pressure of 140/110 mm Hg. After transportation to the hospital, the patient was misdiagnosed as having neuroleptic malignant syndrome (NMS) which was later changed to serotonin syndrome due to a reaction between sertraline and phenelzine. The authors suggest that monoamine oxidase inhibitor (MAOI) therapy should be discontinued for at least two weeks before initiation of therapy with a selective serotonin reuptake inhibitor (SSRI) and that before starting a MAOI, SSRI therapy should be discontinued for at least five half-lives of the parent drug and any active metabolites (Graber et al, 1994b).
d) Two cases reports suggested a possible interaction between fluoxetine and selegiline (Suchowersky & de Vries, 1990b). One case involved a first episode of mania being observed approximately one month after adding selegiline to fluoxetine therapy. The patient improved two months after both drugs were discontinued, and no further details were provided. The second case involved diaphoresis, vasoconstriction, and cyanosis of the hands which occurred in close temporal relationship to adding fluoxetine and selegiline. Both drugs were discontinued, with relatively quick resolution of symptoms. Rechallenge with fluoxetine alone occurred without incident.

3.5.1.CQ Isocarboxazid
1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)
2) Summary: Concurrent administration or overlapping therapy with fluvoxamine and a monoamine oxidase (MAO) inhibitor may result in CNS toxicity or serotonin syndrome, a hyperserotonergic state characterized by symptoms such as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. Serious, even fatal, reactions have been reported with concomitant use of serotonin specific reuptake inhibitors and MAO inhibitors (Prod Info Luvox(R), 1997z; Lappin & Auchincloss, 1994s; Graber et al, 1994s; Suchowersky & de Vries, 1990s). Concomitant use is contraindicated (Prod Info Marplan(R), 1998).
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Concurrent use of fluvoxamine and isocarboxazid is contraindicated. Wait at least two weeks after discontinuing isocarboxazid before initiating therapy with fluvoxamine. Wait at least two weeks after discontinuing fluvoxamine before initiating therapy with isocarboxazid.
7) Probable Mechanism: serotonin reuptake inhibition
8) Literature Reports
a) Concomitant use of serotonin specific reuptake inhibitors and monoamine oxidase inhibitors can produce a toxic reaction known as serotonin syndrome (Sternbach, 1991m). Serotonin syndrome is a condition of serotonergic hyperstimulation and manifests as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. If the syndrome is not recognized and correctly treated, death can result.
b) A 26-year old woman who had been taking isocarboxazid for eight weeks stopped taking the drug for 11 days before beginning therapy with sertraline. After a single 100 mg sertraline dose, the patient became restless and developed leg twitches. The patients was later admitted to the emergency room with diaphoresis, tachycardia, hyperreflexia, and various neuromuscular disturbances. After treatment

with diazepam and propranolol the patient did not improve. The patient was then given two 4 mg doses of cyproheptadine an hour apart, with notable improvement in symptoms after the second dose (Lappin & Auchincloss, 1994r).

c) A drug interaction was reported in a 61-year old woman in which sertraline 100 mg twice daily was added to a regimen of lithium, phenelzine, thioridazine, and doxepin. Three hours after taking the first sertraline dose, the patient was found in a semicomatose state, with elevated body temperature, increased pulse, increased respiration rate, and a blood pressure of 140/110 mm Hg. After transportation to the hospital, the patient was misdiagnosed as having neuroleptic malignant syndrome (NMS) which was later changed to serotonin syndrome due to a reaction between sertraline and phenelzine. The authors suggest that monoamine oxidase inhibitor (MAOI) therapy should be discontinued for at least two weeks before initiation of therapy with a selective serotonin reuptake inhibitor (SSRI) and that before starting a MAOI, SSRI therapy should be discontinued for at least 5 half-lives of the parent drug and any active metabolites (Graber et al, 1994r).

d) Two cases reports suggested a possible interaction between fluoxetine and selegiline (Suchowersky & de Vries, 1990r). One case involved a first episode of mania being observed approximately one month after adding selegiline to fluoxetine therapy. The patient improved two months after both drugs were discontinued, and no further details were provided. The second case involved diaphoresis, vasoconstriction, and cyanosis of the hands which occurred in close temporal relationship to adding fluoxetine and selegiline. Both drugs were discontinued, with relatively quick resolution of symptoms. Rechallenge with fluoxetine alone occurred without incident.

3.5.1.CR Isoxicam

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).

b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.CS Ketoprofen

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate

an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.CT Ketorolac
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.CU Lamifiban
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and antiplatelet agents has been associated with an increased risk of bleeding. Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an antiplatelet agent are given concurrently, monitor patient for signs of increased bleeding (Prod Info PAXIL(R) oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008)
7) Probable Mechanism: unknown

3.5.1.CV Levomethadyl
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Any drug known to have the potential to prolong the QT interval should not be used with levomethadyl. Possible pharmacodynamic interactions can occur between levomethadyl and potentially arrhythmogenic agents such as fluvoxamine that prolong the QT interval (Prod Info Orlaam(R), 2001).
3) Severity: contraindicated
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Levomethadyl is contraindicated in patients being treated with fluvoxamine as it may precipitate QT prolongation and interact with levomethadyl.
7) Probable Mechanism: unknown

3.5.1.CW Lexipafant
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and antiplatelet agents has been associated with an increased risk of bleeding. Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
3) Severity: major
4) Onset: unspecified

5) Substantiation: probable
6) Clinical Management: When an SSRI and an antiplatelet agent are given concurrently, monitor patient for signs of increased bleeding (Prod Info PAXIL(R) oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008)
7) Probable Mechanism: unknown

3.5.1.CX Linezolid

1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)
2) Summary: Linezolid is a reversible, nonselective inhibitor of monoamine oxidase. Concurrent administration or overlapping therapy with fluvoxamine and a monoamine oxidase (MAO) inhibitor may result in CNS toxicity or serotonin syndrome, a hyperserotonergic state characterized by symptoms such as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. There have been spontaneous reports of serotonin syndrome associated with concomitant use of linezolid and serotonergic agents (Prod Info ZYVOX(R) IV injection, oral tablets, oral suspension, 2008; Prod Info Luvox (R), 2000). If fluvoxamine and linezolid are used concomitantly, monitor closely for symptoms of serotonin syndrome. Serotonin syndrome can be life-threatening. If serotonin syndrome develops, discontinue the offending agents and provide supportive care and other therapy as necessary (Boyer & Shannon, 2005).
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: If fluoxamine and linezolid are used concomitantly, monitor closely for symptoms of serotonin syndrome such as neuromuscular abnormalities (including hyper-reflexia, tremor, muscle rigidity, clonus, peripheral hypertonicity, and shivering), autonomic hyperactivity (including tachycardia, mydriasis, diaphoresis, the presence of bowel sounds, and diarrhea), and mental status changes (including agitation and delirium). Serotonin syndrome can be life-threatening. If serotonin syndrome develops, discontinue the offending agents and provide supportive care and other therapy as necessary (Boyer & Shannon, 2005)
7) Probable Mechanism: inhibition of serotonin metabolism by monoamine oxidase

3.5.1.CY Lithium

1) Interaction Effect: possible increased lithium concentrations and/or an increased risk of SSRI-related serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)
2) Summary: Concomitant use of lithium and various SSRIs has been associated with enhanced side effects of either or both drugs, and with or without elevated lithium levels. The combination has resulted in neurotoxicity and increased lithium levels in one case report (Salama & Shafey, 1989a). Signs and symptoms of lithium toxicity and serotonin syndrome have also been reported in patients who demonstrated therapeutic serum lithium levels while on concurrent fluoxetine and lithium (Muly et al, 1993a; Noveske et al, 1989a). Two studies have failed to identify a pharmacokinetic interaction between lithium and citalopram (Gram et al, 1993a; Baumann et al, 1996a). Combined administration of citalopram (40 mg daily for 10 days) and lithium (30 mmol/day for 5 days) had no significant effect on the pharmacokinetics of citalopram or lithium. However, plasma lithium levels should be monitored with appropriate adjustment to the lithium dose in accordance with standard clinical practice. Lithium may enhance the serotonergic effects of citalopram, therefore caution should be exercised when citalopram and lithium are coadministered (Prod Info Celexa(R), 2004). Concurrent use of fluvoxamine and lithium has led to case reports of increased lithium levels and neurotoxicity, serotonin syndrome, somnolence, and mania (Salama & Shafey, 1989a; Ohman & Spigset, 1993a; Evans & Marwick, 1990; Burrai et al, 1991a). No pharmacokinetic interference was apparent during a multiple-dose study of coadministered lithium and paroxetine (Prod Info Paxil CR(TM), 2003). If these two agents are to be given concomitantly, the manufacturer suggests that caution be used until more clinical experience is available. Drug interactions leading to lithium toxicity have been reported when lithium was coadministered with fluoxetine and fluvoxamine (both in the same pharmacological class as paroxetine, eg, selective serotonin reuptake inhibitors) (Ohman & Spigset, 1993a; Salama & Shafey, 1989a).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: established
6) Clinical Management: Monitor patients on concurrent lithium and selective serotonin reuptake inhibitor therapy for increased plasma concentrations of lithium. In addition, monitor patients for signs and symptoms associated with serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes).
7) Probable Mechanism: unknown
8) Literature Reports
a) Concomitant administration of oral lithium carbonate and oral fluoxetine resulted in increased lithium serum levels with lithium toxicity in a 44-year-old woman with a bipolar affective disorder (Salama & Shafey, 1989). Fluoxetine 20 mg daily was added to a regimen of lithium 1200 mg daily following patient complaints of weakness, tiredness, decreased concentration, and early morning awakening. Lithium serum levels increased to 1.7 mEq/L from a range of 0.75 to 1.15 mEq/L prior to fluoxetine. Fluoxetine was discontinued and the dose of lithium decreased; this resulted in a decrease in the lithium serum level within 48 hours to 1.2 mEq/L. The neurologic symptoms subsided within seven days as the lithium serum level decreased to 0.9 mEq/L. The contribution of fluoxetine to lithium toxicity in this patient was

obscured by the fact that the lithium was reduced at the time of fluoxetine withdrawal.
b) A 53-year old woman who had been taking fluoxetine 20 mg daily and lorazepam 0.5 mg four times daily for a major depressive disorder had lithium 900 mg per day added to her regimen in order to augment her response to fluoxetine. Within 48 hours, the patient became confused, ataxic, and developed a coarse tremor in her right arm. Vital signs showed a rectal temperature of 101 degrees F, and laboratory values were normal except for an elevated leukocyte count and slightly elevated bilirubin level. After discontinuation of lithium and fluoxetine, the patient's symptoms resolved over the next four days. At no point did the lithium levels reach a toxic level, suggesting that the patient's symptoms were due to a toxic reaction between fluoxetine and lithium (Noveske et al, 1989).
c) Serotonin syndrome was precipitated when lithium 300 mg twice daily was added to a three-month regimen of fluoxetine 40 mg per day. Five days later, the patient's lithium level was measured at 0.65 mEq/L and the dose was increased to 300 mg three times daily. Two days after this dosage change, the patient experienced akathisia, myoclonus, hyperreflexia, shivering, tremor, diarrhea, and incoordination. After discontinuation of lithium and initiation of cyproheptadine therapy, the patient's symptoms began to improve. The patient was discharged on a regimen of fluoxetine 40 mg per day without further symptoms of serotonin syndrome (Muly et al, 1993).
d) Eight healthy male volunteers completed three phases of an interaction study to determine the effects of coadministered lithium and citalopram. All subjects were extensive metabolizers of sparteine, indicating normal cytochrome P450 2D6 enzyme activity. Although lithium is not influenced by drug oxidation, citalopram metabolites are excreted by the kidney, as is lithium. Each subject received citalopram 40 mg alone as a single daily dose for 10 days, lithium 30 mmol (1980 mg) alone daily for five days, and lithium coadministered with citalopram on days 3-7. At least two weeks separated each treatment phase. Results showed that the concurrent administration of citalopram and lithium did not significantly alter the pharmacokinetics of lithium (Gram et al, 1993).
e) Twenty-four patients experiencing depression (DSM III criteria) were randomized under double-blind conditions to receive citalopram (40 mg to 60 mg daily) and lithium carbonate (800 mg daily) or placebo. All of the subjects had failed to respond to four weeks of citalopram monotherapy. Lithium was coadministered on days 29 to 42. No evidence of a pharmacokinetic interaction between lithium and citalopram was noted, and cotherapy was well tolerated (Baumann et al, 1996).
f) Serotonin syndrome was described in a 53-year-old patient who was stabilized on lithium 1400 mg daily (serum level 0.71 mmol/L) and was given fluvoxamine 50 mg daily. Over a 10-day period the fluvoxamine dose was increased to 200 mg daily; tremor and difficulty with fine hand movements developed. After two weeks, tremor, impaired motor function coordination, marked bilateral hyperreflexia of biceps and knee jerks, and clonus in both ankles were seen. After 12 weeks of continued therapy, during which time no further deterioration occurred, nortriptyline 100 mg daily replaced fluvoxamine, and the neuromuscular symptoms abated over a 2-week period. After four weeks the patient's neurological exam was normal (Ohman & Spigset, 1993).
g) Three cases of mania were reported in patients who were treated with lithium and fluvoxamine. The mania appeared 10 days, four weeks, and five weeks, respectively, after cotherapy was begun. Fluvoxamine was discontinued and, in two of the three patients, the mania resolved, and successful treatment of depression occurred with lithium alone. The third patient improved, but depression reappeared within a month of fluvoxamine discontinuation (Burrai et al, 1991).
h) In an open-labeled, placebo-controlled study, lithium 600 mg was administered to 16 subjects orally twice daily on days one through eight and once in the morning on day nine. In addition, oral sertraline 100 mg or placebo was given twice, ten hours and two hours prior to lithium dosing on day nine. The steady-state lithium level was only decreased by 1.4% (0.01 mEq/L) and the lithium renal clearance increased by 6.9% (0.11 L/hour) when sertraline was coadministered. Seven subjects experienced side effects, mainly tremors, after receiving lithium and sertraline, whereas no subjects who ingested placebo and lithium experienced side effects (Wilner et al, 1991).

3.5.1.CZ Lornoxicam

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI

bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).

b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.DA Maprotiline

1) Interaction Effect: maprotiline toxicity (dry mouth, urinary retention, sedation)

2) Summary: An interaction of fluvoxamine with tricyclic antidepressants (TCAs) was reported (Hartter et al, 1993g). Plasma concentrations of TCAs were increased when combined with fluvoxamine. This effect was less prominent with maprotiline compared with imipramine, clomipramine, or amitriptyline. In addition, TCAs appeared to increase fluvoxamine levels.

3) Severity: minor

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Monitor patients for excess tricyclic antidepressant side effects such as dry mouth and lethargy. Maprotiline doses may need to be reduced in some clinical situations.

7) Probable Mechanism: decreased maprotiline metabolism

8) Literature Reports

a) Metabolism of tricyclic antidepressants coadministered with fluvoxamine was studied in eight depressed patients (one patient received maprotiline) (Hartter et al, 1993f). Fluvoxamine was found to interfere with N-demethylation of maprotiline. The combination of fluvoxamine and maprotiline led to increased plasma levels of maprotiline and decreased concentrations of maprotiline's N-demethylated metabolite, desmethylmaprotiline. Also, plasma levels of fluvoxamine were increased.

3.5.1.DB Mate

1) Interaction Effect: increased caffeine levels (insomnia, headache, restlessness, nervousness, palpitations, and arrhythmias)

2) Summary: The primary pharmacologically-active ingredient of mate is caffeine. Fluvoxamine inhibits CYP1A2 and CYP2D6 which are responsible for caffeine metabolism. Decreased caffeine clearance and increased half-life have been demonstrated in humans (Jeppesen et al, 1996a). Signs and symptoms of caffeine excess may result if the compounds are taken together. Patients should avoid mate use during therapy with fluvoxamine in order to avoid possible complications.

3) Severity: moderate

4) Onset: rapid

5) Substantiation: theoretical

6) Clinical Management: Patients should be advised of the caffeine content of mate, and of symptoms of excess if taken with fluvoxamine (insomnia, headache, restlessness, nervousness, palpitations, and arrhythmias), as well as symptoms of caffeine withdrawal which may accompany abrupt discontinuation of mate (e.g., headache, fatigue, depression, anxiety, and insomnia). Patients should avoid mate use during therapy with fluvoxamine in order to avoid possible complications.

7) Probable Mechanism: inhibition of caffeine metabolism

8) Literature Reports

a) In an open, randomized, cross-over study of 8 volunteers, fluvoxamine significantly decreased caffeine total clearance and increased caffeine half-life. Fluvoxamine was administered as 50 milligrams (mg) for 4 days, then 100 mg for 8 days while subjects abstained from all caffeine intake. Caffeine 200 mg was then administered orally. Total clearance of caffeine decreased from 107 milliliters/minute (mL/min) to 21 mL/min, and half-life increased from 5 hours to 31 hours. Patients taking fluvoxamine should restrict caffeine intake (Jeppesen et al, 1996).

b) In vitro, fluvoxamine was found to be a very potent inhibitor of the formation of N-demethylated caffeine metabolites with K1 values of 0.08 micromoles (mcmol) to 0.28 mcmol. The formation of 1,7-dimethylxanthine was abolished by 10 mcmol of fluvoxamine, implying the N3-demethylation of caffeine is almost entirely catalyzed by CYP1A2 (Rasmussen et al, 1998).

c) At least 14 metabolites are formed from caffeine whose main route of elimination is N3-demethylation to paraxanthine (1,7-methylxanthine) which accounts for greater than 80% of caffeine elimination (Lelo et al, 1986). CYP1A2 is the major enzyme metabolizing caffeine to 1,7-dimethylxanthine (Berthou et al, 1991; Sesardic et al, 1990; Butler et al, 1989). CYP1A2 is also a major enzyme in the formation of 3,7-dimethylxanthine and 1,3-dimethylxantihine from caffeine (Gu et al, 1992; Berthou et al, 1991; Grant et al, 1987).

3.5.1.DC Meclofenamate

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM),

2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.DD Mefenamic Acid
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.DE Melatonin
1) Interaction Effect: increased central nervous system depression
2) Summary: Fluvoxamine significantly increased melatonin levels and increased drowsiness when given with melatonin in a study of 5 healthy volunteers (Hartter et al, 2000a). Endogenous melatonin levels increased following fluvoxamine administration in 7 healthy subjects (Von Bahr et al, 2000). Fluvoxamine may inhibit melatonin elimination (Hartter et al, 2000a), or metabolism via cytochrome P450 1A2 or 2C19 (Von Bahr et al, 2000). Patients taking fluvoxamine with or without melatonin supplementation should be monitored for changes in sleep and central nervous system depression.
3) Severity: minor
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Monitor patients taking fluvoxamine with melatonin supplementation for changes in sleep patterns and signs of excessive central nervous system depression. Downward titration of melatonin dosages may be required during concomitant administration with fluvoxamine.
7) Probable Mechanism: inhibition of cytochrome P450 enzymes, possibly CYP1A2 and CYP2C19, responsible for melatonin metabolism
8) Literature Reports
a) The bioavailability of oral melatonin was significantly increased after coadministration of fluvoxamine. Five volunteers (one CYP2D6 poor metabolizer) were included in a study that was designed to evaluate the effects of fluvoxamine on the pharmacokinetics of melatonin. A single dose of melatonin 5 mg was administered to all subjects. One week later a single oral dose of fluvoxamine 50 mg was administered to all subjects. Blood samples were evaluated at certain time points after

administration of each agent. An increase in melatonin serum concentrations occurred in all subjects with a 23-fold increase in area under the concentration-time curve (AUC) (6.2 to 141.3 mcg h/L) and a twelve-fold increase in maximum serum concentration (Cmax) (2.18 to 25.1 ng/ml) of melatonin. The effects of fluvoxamine on melatonin pharmacokinetics were effectively greater in the poor CYP2D6 metabolizer. The author suggests that this is most likely due to inhibition of the elimination of melatonin rather than an increased production of melatonin (Hartter et al, 2000).

3.5.1.DF Meloxicam

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).

b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.DG Methadone

1) Interaction Effect: increased plasma methadone levels

2) Summary: When fluvoxamine is added to patients receiving maintenance methadone therapy, significantly increased methadone plasma level:dose ratios are seen. Symptoms of opioid toxicity were observed in one patient. In another patient, opioid withdrawal symptoms were observed following discontinuation of fluvoxamine (Prod Info Luvox(R), 1997w).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Monitor closely if adding or withdrawing fluvoxamine in patients on chronic methadone.

7) Probable Mechanism: inhibition by fluvoxamine of cytochrome P450 3A4-mediated methadone metabolism

8) Literature Reports

a) A 28-year-old female who was admitted to a hospital for the management of an acute exacerbation of asthma had a stabilized medication regimen which included methadone 70 mg daily, diazepam 2 mg twice daily, albuterol, ipratropium, ranitidine, and spironolactone. Three weeks before admission, she had started fluvoxamine 100 mg daily. The patient's asthma was not considered to be in a significant exacerbation upon further testing, although hypoxemia and hypercapnia indicating hypoventilation was present. Methadone was decreased to 50 mg daily and diazepam was discontinued. Analysis of a blood sample taken at admission showed that the serum methadone concentration was 262 ng/mL. Twelve days later, oxygenation had improved and the methadone concentration was measured at 202 ng/mL. The reduction in serum methadone concentration and clinical improvement observed after methadone was decreased suggest that fluvoxamine may have inhibited the cytochrome P450 3A4-mediated metabolism of methadone, although diazepam may have compounded this interaction (Alderman & Frith, 1999).

3.5.1.DH Methylergonovine

1) Interaction Effect: an increased risk of ergotism (nausea, vomiting, vasospastic ischemia)

2) Summary: Because of the potential for serious toxicity including vasospasm that can occur with increased plasma concentrations of ergot derivatives, the concurrent use of fluvoxamine and ergot derivatives is contraindicated. Fluvoxamine and ergot derivatives are both metabolized by cytochrome P450 3A4 enzymes, and the competition for metabolism could result in an increased plasma concentration of the ergot derivative (Prod Info Cafergot(R), 2002).

3) Severity: contraindicated

4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: The concurrent use of fluvoxamine and ergot derivatives is contraindicated.
7) Probable Mechanism: inhibition of cytochrome P450 3A4- mediated ergot metabolism by fluvoxamine

3.5.1.DI Methylphenidate

1) Interaction Effect: increased selective serotonin reuptake inhibitor plasma concentrations
2) Summary: Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism of selective serotonin reuptake inhibitors (SSRIs). Downward dose adjustments of the SSRI may be necessary when it is used concurrently with methylphenidate. Additionally, when initiating or discontinuing methylphenidate, the SSRI dose may need to be adjusted as needed (Prod Info METADATE CD(R) extended-release oral capsules, 2007).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Use caution when prescribing methylphenidate to patients who take an selective serotonin reuptake inhibitor (SSRI). Concomitant use of methylphenidate and an SSRI may cause elevated SSRI plasma concentrations. Consider a decrease in the dose of SSRI when these agents are coadministered. Additionally, consider adjusting the SSRI dose if necessary when initiating or discontinuing methylphenidate therapy (Prod Info METADATE CD(R) extended-release oral capsules, 2007).
7) Probable Mechanism: inhibition of selective serotonin reuptake inhibitor metabolism by methylphenidate

3.5.1.DJ Metoprolol

1) Interaction Effect: bradycardia and hypotension
2) Summary: Fluvoxamine may inhibit the metabolism of metoprolol, which resulted in bradycardia and/or hypotension in one case (Prod Info Luvox(R), 1997o).
3) Severity: moderate
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: If metoprolol is coadministered with fluvoxamine, it is recommended that the initial dose be reduced and that dose titration proceed more cautiously than usual. No dose change is required for fluvoxamine. Monitor heart rate and blood pressure carefully.
7) Probable Mechanism: decreased metoprolol metabolism

3.5.1.DK Mexiletine

1) Interaction Effect: decreased mexiletine metabolism
2) Summary: In a single-dose study, concurrent administration of fluvoxamine and mexiletine reduced the clearance of mexiletine by 37%, significantly increasing the mean serum peak concentration and area under the concentration-time curve (Kusumoto et al, 2001a; Prod Info Mexitil(R), 2003).
3) Severity: moderate
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Monitor patients for signs and symptoms of mexiletine toxicity (nausea, dizziness, cardiac arrhythmias). Monitor liver function, complete blood count, and electrocardiogram if mexiletine toxicity is suspected, and reduce mexiletine dose as required.
7) Probable Mechanism: fluvoxamine-induced inhibition of CYP1A2-mediated mexiletine metabolism
8) Literature Reports
a) Co-administration of fluvoxamine with mexiletine significantly reduced the metabolism and clearance of mexiletine. In a randomized, cross-over study, healthy Japanese men (n=6) received either a single oral dose of mexiletine 200 milligrams (mg) or a 7-day regimen of oral fluvoxamine 50 mg twice daily followed by fluvoxamine plus a single dose of mexiletine 200 mg on day 8. Serial blood samples were measured over the 24 hours following each mexiletine dose. Thereafter, each subject crossed over to the opposing study arm following a 7-day wash-out period. Compared with control values, concurrent administration of fluvoxamine with mexiletine provoked a significant increase in the mean maximum serum concentration (0.536 versus 0.623 micrograms/milliliter (mcg/mL), p=0.0074) and area under the concentration-time curve (5.71 versus 7.46 mcg x hour/mL, p=0.0028). Co-administration significantly decreased mean oral clearance by 37% (0.551 versus 0.341 L/hour/kilogram, p=0.015). The study authors proposed fluvoxamine-induced inhibition of CYP1A2 metabolism as the mechanism of action (Kusumoto et al, 2001).

3.5.1.DL Midazolam

1) Interaction Effect: elevated serum midazolam concentrations
2) Summary: Fluvoxamine coadministration (100 mg daily) with alprazolam 1 mg four times daily resulted in a 2-fold increase in alprazolam steady-state plasma concentrations, AUC, Cmax, and half-life. Elevated plasma levels of alprazolam were associated with impaired psychomotor performance and memory. This suggests that fluvoxamine is a potent inhibitor of cytochrome P450 3A4 enzymes, which are responsible for alprazolam metabolism. Because midazolam also relies on CYP3A4 for metabolism, a similar interaction with fluvoxamine seems likely (Prod Info Luvox(R), 1997aa).

3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When midazolam and fluvoxamine are coadministered, monitor patients for benzodiazepine toxicity (sedation, lethargy, slurred speech). Midazolam doses may need to be reduced, or consider switching to a benzodiazepine eliminated by glucuronidation (eg, lorazepam, oxazepam, temazepam).
7) Probable Mechanism: inhibition of midazolam metabolism due to cytochrome P450 3A4 enzyme inhibition

3.5.1.DM Milnacipran

1) Interaction Effect: increased risk of serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)
2) Summary: Concurrent use of milnacipran and an SSRI may result in hypertension, coronary artery vasoconstriction or serotonin syndrome, which may be life-threatening. Symptoms of serotonin syndrome may include restlessness, hallucinations, loss of coordination, fast heart beat, rapid changes in blood pressure, increased body temperature, overreactive reflexes, nausea, vomiting, and diarrhea (Prod Info SAVELLA(R) oral tablets, 2009).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of milnacipran and an SSRI may result in hypertension and coronary artery vasoconstriction, through the additive serotonergic effects. If these agents are used together, discuss the risks of serotonin syndrome with the patient and monitor closely for symptoms of serotonin syndrome (restlessness, hyperthermia, hyperreflexia, incoordination), especially during treatment initiation and dose increases (Prod Info SAVELLA(R) oral tablets, 2009).
7) Probable Mechanism: additive serotonergic effect

3.5.1.DN Mirtazapine

1) Interaction Effect: an increased risk of serotonin syndrome
2) Summary: Mirtazapine increases serotonin release and fluvoxamine inhibits the CYP450 1A2, 2C9, 2D6, and 3A3/4-mediated mirtazapine metabolism. Concurrent use of fluvoxamine and mirtazapine resulted in symptoms of serotonin syndrome in a 26-year-old female (Demers & Malone, 2001). If fluvoxamine and mirtazapine are used together, monitor closely for symptoms of serotonin syndrome. Serotonin syndrome can be life-threatening. If serotonin syndrome develops, discontinue the offending agents and provide supportive care and other therapy as necessary (Boyer & Shannon, 2005).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: A case of serotonin syndrome was reported with concomitant use of fluvoxamine and mirtazapine and therefore, concomitant use is discouraged(Demers & Malone, 2001). If fluvoxamine and mirtazapine are used together, monitor closely for symptoms of serotonin syndrome such as neuromuscular abnormalities (including hyper-reflexia, tremor, muscle rigidity, clonus, peripheral hypertonicity, and shivering), autonomic hyperactivity (including tachycardia, mydriasis, diaphoresis, the presence of bowel sounds, and diarrhea), and mental status changes (including agitation and delirium). Serotonin syndrome can be life-threatening. If serotonin syndrome develops, discontinue the offending agents and provide supportive care and other therapy as necessary (Boyer & Shannon, 2005).
7) Probable Mechanism: additive pharmacologic effects and inhibition of CYP1A2, 2C9, 2D6, and 3A3/4-mediated metabolism of mirtazapine by fluvoxamine
8) Literature Reports
a) A 26-year-old woman with anorexia nervosa on fluvoxamine for a total of 4 months developed symptoms of serotonin syndrome after mirtazapine was added. She was on fluvoxamine 150 mg/day for 2 months with a subsequent increase to 200 mg/day for 2 months before starting mirtazapine. The symptoms of twitching, tremors, agitation, restlessness, and "feeling like she could crawl out of her skin" developed over a period of 4 days after starting mirtazapine 30 mg/day. Symptoms rapidly progressed to twitching, tremors, and restlessness. She was hospitalized with further symptoms of diaphoresis, flushing, fasciculations, and nausea and treated with cyproheptadine 4 mg every 6 hours, acetaminophen, and intravenous fluids. She remained afebrile throughout the event. Symptoms completely resolved within 24 hours. She was discharged on 50 mg/day of fluvoxamine and no recurrence the following day. The interaction was attributed to multiple mechanisms. Mirtazapine increases the release of serotonin via the 5-hydroxytryptamine (serotonin) (5-HT) 1 receptors but it is also a 5-HT2 and 5-HT3 receptors blocker. Fluvoxamine decreases mirtazapine metabolism by inhibiting cytochrome P-450 1A2, 2C9, 2D6, and 3A3/4 enzymes, and may have increased the mirtazapine serum levels resulting in increased mirtazapine adverse effects (Demers & Malone, 2001).
b) A letter to the editor (Isbister et al, 2001) disagreed with the case report that fluvoxamine and mirtazapine resulted in serotonin syndrome (Demers & Malone, 2001). Their argument is that the diagnostic criteria used was unreliable; mirtazapine, a 5-hydroxytryptamine 2A receptor blocker, is unlikely to cause serotonin syndrome and may actually offer benefit in treating it; and the symptoms

were adverse effects related to increased concentrations of mirtazapine from inhibition of metabolism by fluvoxamine (Isbister et al, 2001).

3.5.1.DO Moclobemide

1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)

2) Summary: Concurrent administration or overlapping therapy with fluvoxamine and a monoamine oxidase (MAO) inhibitor may result in CNS toxicity or serotonin syndrome, a hyperserotonergic state characterized by symptoms such as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. Serious, even fatal, reactions have been reported with concomitant use of serotonin specific reuptake inhibitors and MAO inhibitors (Prod Info Luvox(R), 1997e; Neuvonen et al, 1993a). Although not reported specifically with moclobemide in therapeutic doses, a similar reaction may occur. Concomitant use is not recommended.

3) Severity: major

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: In general, concurrent use of a serotonin specific reuptake inhibitor and a MAO inhibitor should be avoided. Wait at least 14 days after discontinuing a MAO inhibitor before initiating therapy with fluvoxamine. Wait at least 14 days after discontinuing fluvoxamine before initiating therapy with a MAO inhibitor.

7) Probable Mechanism: inhibition of serotonin metabolism by monoamine oxidase

8) Literature Reports

a) Concomitant use of selective serotonin reuptake inhibitors and monoamine oxidase inhibitors can produce a toxic reaction known as serotonin syndrome (Sternbach, 1991a). Serotonin syndrome is a condition of serotonergic hyperstimulation and manifests as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. If the syndrome is not recognized and correctly treated, death can result.

b) A study reported five fatal overdose cases due to serotonin syndrome. In three of the five cases, the drug combination that induced the fatal syndrome was moclobemide, a selective monoamine oxidase inhibitor, and citalopram. Of the three patients, blood concentrations of moclobemide ranged from five times the therapeutic level to 50 times the therapeutic level, and citalopram concentrations ranged from normal therapeutic levels to five times the therapeutic level (Neuvonen et al, 1993).

3.5.1.DP Morniflumate

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).

b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.DQ Nabumetone

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.DR Nadroparin
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info LUVOX(R) CR extended-release oral capsules, 2008). Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with warfarin. In patients receiving warfarin and fluvoxamine concomitantly for 2 weeks, warfarin plasma concentrations increased by 98% and prothrombin times were prolonged. Fluvoxamine appears to inhibit several cytochrome P450 isoenzymes which may include 1A2 and 2C9 isozymes, which are responsible for warfarin metabolism (Schalekamp et al, 2008; Prod Info LUVOX(R) CR extended-release oral capsules, 2008).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When fluvoxamine and an anticoagulant are given concurrently, monitor patient for signs of increased bleeding. Patients who are taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, when fluvoxamine therapy is initiated or discontinued. Periodically reassess the prothrombin time ratio and INR in patients receiving fluvoxamine and anticoagulant therapy (Prod Info LUVOX(R) CR extended-release oral capsules, 2008).
7) Probable Mechanism: unknown
8) Literature Reports
a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bleeding (hospital admission due to bleeding) in patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patients with a mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients experienced 11 bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experiencing bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model (Wallerstedt et al, 2009).
b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5), however, the rate of gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).
c) A hospitalized 80-year-old female was started on intravenous heparin and oral warfarin therapy due to an embolic stroke secondary to atrial fibrillation and mitral stenosis. Her warfarin dose was maintained at 1 mg daily, with her INR between 2.5 and 3. Fluvoxamine 25 mg daily was started for depression, and her warfarin dose was increased to 1.5 mg daily 3 days later due to worsening of the left hemiparesis. Three days later, her INR was 9.96, and a repeat INR to rule out laboratory error was

11.3. Warfarin was discontinued, fresh frozen plasma was given, and fluvoxamine was discontinued. Six days later, warfarin was again started at 1 mg daily, and the INR increased over 4 days to 11.8. The elevated INR was attributed to the persisting effect of fluvoxamine. She was eventually stabilized on warfarin 1 mg daily with INR values between 2 and 2.5 (Yap & Low, 1999).

3.5.1.DS Naproxen

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).

b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.DT Naratriptan

1) Interaction Effect: an increased risk of serotonin syndrome

2) Summary: Rare incidences of weakness, hyperreflexia, and incoordination have been reported with the concurrent use of a selective serotonin reuptake inhibitor (SSRI) and a 5-hydroxytryptamine-1 (5HT-1) agonist (Prod Info Amerge(TM), 2002). Concurrent use of a triptan and an SSRI may result in serotonin syndrome which may be life-threatening. Symptoms of serotonin syndrome may include restlessness, hallucinations, loss of coordination, fast heart beat, rapid changes in blood pressure, increased body temperature, overreactive reflexes, nausea, vomiting, and diarrhea. Clinicians should be aware that triptans may be commonly used intermittently and that either the triptan or the SSRI may be prescribed by a different physician. Discuss the risks of serotonin syndrome with patients who are prescribed this combination and monitor them closely for symptoms of serotonin syndrome (US Food and Drug Administration, 2006).

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Coadministration of a triptan, such as naratriptan, and an SSRI may result in a life-threatening condition called serotonin syndrome. Be aware that triptans may be commonly used intermittently and that either the triptan or the SSRI may be prescribed by a different physician. If these agents are used together, discuss the risks of serotonin syndrome with the patient and monitor closely for symptoms of serotonin syndrome (restlessness, hyperthermia, hyperreflexia, incoordination).

7) Probable Mechanism: additive pharmacologic effects resulting in excessive serotonergic stimulation

3.5.1.DU Nialamide

1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)

2) Summary: Concurrent administration or overlapping therapy with fluvoxamine and a monoamine oxidase (MAO) inhibitor may result in CNS toxicity or serotonin syndrome, a hyperserotonergic state characterized by symptoms such as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. Serious, even fatal, reactions have been reported with concomitant use of selective serotonin reuptake inhibitors and MAO inhibitors (Prod Info Luvox(R), 1997y; Lappin & Auchincloss, 1994q; Graber et al, 1994q; Suchowersky & de Vries, 1990q). Concomitant use is not recommended.

3) Severity: major

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: Concurrent use of fluvoxamine and a MAO inhibitor should be avoided. Wait at least two weeks after discontinuing an MAO inhibitor before initiating therapy with fluvoxamine. Wait at least two weeks after discontinuing fluvoxamine before initiating therapy with a MAO inhibitor.

7) Probable Mechanism: serotonin reuptake inhibition

8) Literature Reports

a) Concomitant use of serotonin specific reuptake inhibitors and monoamine oxidase inhibitors can produce a toxic reaction known as serotonin syndrome (Sternbach, 1991l). Serotonin syndrome is a condition of serotonergic hyperstimulation and manifests as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. If the syndrome is not recognized and correctly treated, death can result.

b) A 26-year old woman who had been taking isocarboxazid for eight weeks stopped taking the drug for 11 days before beginning therapy with sertraline. After a single 100 mg sertraline dose, the patient became restless and developed leg twitches. The patients was later admitted to the emergency room with diaphoresis, tachycardia, hyperreflexia, and various neuromuscular disturbances. After treatment with diazepam and propranolol the patient did not improve. The patient was then given two 4 mg doses of cyproheptadine an hour apart, with notable improvement in symptoms after the second dose (Lappin & Auchincloss, 1994p).

c) A drug interaction occurred in a 61-year old woman whose regimen of sertraline 100 mg twice daily was added to a regimen of lithium, phenelzine, thioridazine, and doxepin. Three hours after taking the first sertraline dose, the patient was found in a semicomatose state, with elevated body temperature, increased pulse, increased respiration rate, and a blood pressure of 140/110 mm Hg. After transportation to the hospital, the patient was misdiagnosed as having neuroleptic malignant syndrome (NMS) which was later changed to serotonin syndrome due to a reaction between sertraline and phenelzine. The authors suggest that monoamine oxidase inhibitor (MAOI) therapy should be discontinued for at least two weeks before initiation of therapy with a selective serotonin reuptake inhibitor (SSRI) and that before starting a MAOI, SSRI therapy should be discontinued for at least five half-lives of the parent drug and any active metabolites (Graber et al, 1994p).

d) Two cases reports suggested a possible interaction between fluoxetine and selegiline (Suchowersky & de Vries, 1990p). One case involved a first episode of mania being observed approximately one month after adding selegiline to fluoxetine therapy. The patient improved two months after both drugs were discontinued, and no further details were provided. The second case involved diaphoresis, vasoconstriction, and cyanosis of the hands which occurred in close temporal relationship to adding fluoxetine and selegiline. Both drugs were discontinued, with relatively quick resolution of symptoms. Rechallenge with fluoxetine alone occurred without incident.

3.5.1.DV Niflumic Acid

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).

b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.DW Nimesulide

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of

increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.DX Olanzapine
1) Interaction Effect: an increased risk of olanzapine adverse effects
2) Summary: Fluvoxamine inhibits cytochrome P450 1A2 enzymes and may inhibit olanzapine elimination (Prod Info Zyprexa(R), 1999). The clinical significance of this interaction is unknown since olanzapine is metabolized by multiple enzyme systems.
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor patients for excessive olanzapine adverse effects (orthostatic hypotension, tachycardia, transaminase elevations, seizures).
7) Probable Mechanism: inhibition of olanzapine elimination
8) Literature Reports
a) A patient experienced elevated olanzapine plasma levels during coadministration of fluvoxamine. The patient was taking fluvoxamine and olanzapine for several months for schizophrenia and secondary depression. She appeared to move rigidly, had a slight tremor of both hands and mydriasis. Olanzapine concentration was 120 mcg/L and fluvoxamine concentration was 70 mcg/L. Olanzapine was decreased in increments from 15 mg/day to 5 mg/day. Fourteen days after the last decrease in dose, olanzapine plasma levels were 38 mcg/L. Tremor and rigidity disappeared, however, mydriasis persisted. Fluvoxamine was replaced by paroxetine which resulted in paroxetine concentration of 0.027 mg/L and olanzapine concentration of 22 mcg/L (de Jong et al, 2001).
b) Addition of fluvoxamine to olanzapine therapy may result in olanzapine-induced side effects or intoxication. Eight chronic schizophrenic patients were being treated for not less than 3 months with 10-20 mg/day of olanzapine. The dose of olanzapine was unchanged for not less than 8 weeks prior to the study and remained stable throughout the study period. Fluvoxamine 100 mg/day was added to olanzapine treatment at the start of the study (week 0) and continued for 8 weeks. Olanzapine concentrations increased during fluvoxamine treatment 1.58-fold from week 0 to week 1, 1.42-fold from week 0 to week 4, and 1.81-fold from week 0 to week 8. Percentage change from week 0 to week 8 ranged from 12% to 112%. Mean concentrations of the N-demethylated metabolite were not significantly changed. Even though all eight patients had higher olanzapine blood serum concentrations on week 8 than on week 1, the ratio of increase of olanzapine blood serum concentrations from week 0 to week 8 did not correlate significantly with fluvoxamine serum levels (p greater than 0.05). This study confirmed that the addition of fluvoxamine to a stable dose of olanzapine increased olanzapine concentrations in the blood serum. Combined olanzapine and fluvoxamine should be used cautiously and controlled clinically and by therapeutic drug monitoring to avoid olanzapine-induced side effects or intoxication (Hiemke et al, 2002).

3.5.1.DY Oxaprozin
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations

in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).

b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.DZ Oxycodone

1) Interaction Effect: an increased risk of serotonin syndrome (tachycardia, hyperthermia, myoclonus, mental status changes)

2) Summary: Coadministration of oxycodone and fluvoxamine has resulted in the development of serotonin syndrome in a 70-year-old woman. Presenting symptoms included confusion, nausea, fever, clonus, hyperreflexia, and tachycardia. Caution is advised if fluvoxamine and oxycodone are coadministered. Monitor patients for signs and symptoms of serotonin syndrome (tachycardia, hyperthermia, myoclonus, mental status changes) (Karunatilake & Buckley, 2006).

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Concomitant administration of fluvoxamine and oxycodone may increase the risk of developing serotonin syndrome. If these agents are coadministered, monitor patients for symptoms of serotonin syndrome (tachycardia, hyperthermia, myoclonus, mental status changes).

7) Probable Mechanism: additive pharmacologic effects resulting in excessive serotonergic stimulation

8) Literature Reports

a) Concurrent administration of oxycodone and fluvoxamine resulted in a serotonin syndrome in a 70-year-old woman. The patient was receiving fluvoxamine 200 mg and doxepin 50 mg for several months for treatment of depression. Subsequent to a fall, the patients was started on slow-release oral oxycodone 40 mg twice daily, and 2 days later, short-acting oral oxycodone 10 mg, to be used on an "as needed" basis, was added to her regimen. After a dose of about 60 mg oxycodone taken over 24 hours, the patient presented to the emergency department in a state of confusion, with symptoms including nausea, fever, clonus, hyperreflexia, and shivering. The patient also had mydriasis, transient atrial fibrillation, tachycardia, and an elevated creatinine kinase level. Fluvoxamine, doxepin, and oxycodone were discontinued and the patient was treated with 5 doses of oral acetaminophen 1,000 mg over the next 2 days. The patient's neurologic and cardiovascular symptoms improved steadily over the next 48 hours. Prior to discharge, doxepin therapy was re-initiated with no apparent adverse effects. However, patient was not rechallenged with either fluvoxamine or oxycodone while she was in the hospital. According to the Naranjo probability scale, the interaction falls into the probable category (Karunatilake & Buckley, 2006).

3.5.1.EA Parecoxib

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).

b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.EB Pargyline

1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental

status changes)
2) Summary: Concurrent administration or overlapping therapy with fluvoxamine and a monoamine oxidase (MAO) inhibitor may result in CNS toxicity or serotonin syndrome, a hyperserotonergic state characterized by symptoms such as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. Serious, even fatal, reactions have been reported with concomitant use of selective serotonin reuptake inhibitors and MAO inhibitors (Prod Info Luvox(R), 1997l; Lappin & Auchincloss, 1994g; Graber et al, 1994g; Suchowersky & de Vries, 1990g). Concomitant use is not recommended.
3) Severity: major
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Concurrent use of fluvoxamine and a MAO inhibitor should be avoided. Wait at least two weeks after discontinuing an MAO inhibitor before initiating therapy with fluvoxamine. Wait at least two weeks after discontinuing fluvoxamine before initiating therapy with a MAO inhibitor.
7) Probable Mechanism: serotonin reuptake inhibition
8) Literature Reports
a) Concomitant use of serotonin specific reuptake inhibitors and monoamine oxidase inhibitors can produce a toxic reaction known as serotonin syndrome (Sternbach, 1991e). Serotonin syndrome is a condition of serotonergic hyperstimulation and manifests as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. If the syndrome is not recognized and correctly treated, death can result.
b) A 26-year old woman who had been taking isocarboxazid for eight weeks stopped taking the drug for 11 days before beginning therapy with sertraline. After a single 100 mg sertraline dose, the patient became restless and developed leg twitches. The patients was later admitted to the emergency room with diaphoresis, tachycardia, hyperreflexia, and various neuromuscular disturbances. After treatment with diazepam and propranolol the patient did not improve. The patient was then given two 4 mg doses of cyproheptadine an hour apart, with notable improvement in symptoms after the second dose (Lappin & Auchincloss, 1994f).
c) A drug interaction occurred in a 61-year old woman whose regimen of sertraline 100 mg twice daily was added to a regimen of lithium, phenelzine, thioridazine, and doxepin. Three hours after taking the first sertraline dose, the patient was found in a semicomatose state, with elevated body temperature, increased pulse, increased respiration rate, and a blood pressure of 140/110 mm Hg. After transportation to the hospital, the patient was misdiagnosed as having neuroleptic malignant syndrome (NMS) which was later changed to serotonin syndrome due to a reaction between sertraline and phenelzine. The authors suggest that monoamine oxidase inhibitor (MAOI) therapy should be discontinued for at least two weeks before initiation of therapy with a selective serotonin reuptake inhibitor (SSRI) and that before starting a MAOI, SSRI therapy should be discontinued for at least five half-lives of the parent drug and any active metabolites (Graber et al, 1994f).
d) Two cases reports suggested a possible interaction between fluoxetine and selegiline (Suchowersky & de Vries, 1990f). One case involved a first episode of mania being observed approximately one month after adding selegiline to fluoxetine therapy. The patient improved two months after both drugs were discontinued, and no further details were provided. The second case involved diaphoresis, vasoconstriction, and cyanosis of the hands which occurred in close temporal relationship to adding fluoxetine and selegiline. Both drugs were discontinued, with relatively quick resolution of symptoms. Rechallenge with fluoxetine alone occurred without incident.

3.5.1.EC Parnaparin
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info LUVOX(R) CR extended-release oral capsules, 2008). Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with warfarin. In patients receiving warfarin and fluvoxamine concomitantly for 2 weeks, warfarin plasma concentrations increased by 98% and prothrombin times were prolonged. Fluvoxamine appears to inhibit several cytochrome P450 isoenzymes which may include 1A2 and 2C9 isozymes, which are responsible for warfarin metabolism (Schalekamp et al, 2008; Prod Info LUVOX(R) CR extended-release oral capsules, 2008).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When fluvoxamine and an anticoagulant are given concurrently, monitor patient for signs of increased bleeding. Patients who are taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, when fluvoxamine therapy is initiated or discontinued. Periodically reassess the prothrombin time ratio and INR in patients receiving fluvoxamine and anticoagulant therapy (Prod Info LUVOX(R) CR extended-release oral capsules, 2008).
7) Probable Mechanism: unknown
8) Literature Reports
a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant

bleeding (hospital admission due to bleeding) in patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patients with a mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients experienced 11 bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experiencing bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model (Wallerstedt et al, 2009).

b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5), however, the rate of gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).

c) A hospitalized 80-year-old female was started on intravenous heparin and oral warfarin therapy due to an embolic stroke secondary to atrial fibrillation and mitral stenosis. Her warfarin dose was maintained at 1 mg daily, with her INR between 2.5 and 3. Fluvoxamine 25 mg daily was started for depression, and her warfarin dose was increased to 1.5 mg daily 3 days later due to worsening of the left hemiparesis. Three days later, her INR was 9.96, and a repeat INR to rule out laboratory error was 11.3. Warfarin was discontinued, fresh frozen plasma was given, and fluvoxamine was discontinued. Six days later, warfarin was again started at 1 mg daily, and the INR increased over 4 days to 11.8. The elevated INR was attributed to the persisting effect of fluvoxamine. She was eventually stabilized on warfarin 1 mg daily with INR values between 2 and 2.5 (Yap & Low, 1999).

3.5.1.ED Pentosan Polysulfate Sodium

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info LUVOX(R) CR extended-release oral capsules, 2008). Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with warfarin. In patients receiving warfarin and fluvoxamine concomitantly for 2 weeks, warfarin plasma concentrations increased by 98% and prothrombin times were prolonged. Fluvoxamine appears to inhibit several cytochrome P450 isoenzymes which may include 1A2 and 2C9 isozymes, which are responsible for warfarin metabolism (Schalekamp et al, 2008; Prod Info LUVOX(R) CR extended-release oral capsules, 2008).

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: When fluvoxamine and an anticoagulant are given concurrently, monitor patient for signs of increased bleeding. Patients who are taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, when fluvoxamine therapy is initiated or discontinued. Periodically reassess the prothrombin time ratio and INR in patients receiving fluvoxamine and anticoagulant therapy (Prod Info LUVOX(R) CR extended-release oral capsules, 2008).

7) Probable Mechanism: unknown

8) Literature Reports

a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bleeding (hospital admission due to bleeding) in patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patients with a mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients experienced 11 bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experiencing bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding

events, unknown patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model (Wallerstedt et al, 2009).

b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5), however, the rate of gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).

c) A hospitalized 80-year-old female was started on intravenous heparin and oral warfarin therapy due to an embolic stroke secondary to atrial fibrillation and mitral stenosis. Her warfarin dose was maintained at 1 mg daily, with her INR between 2.5 and 3. Fluvoxamine 25 mg daily was started for depression, and her warfarin dose was increased to 1.5 mg daily 3 days later due to worsening of the left hemiparesis. Three days later, her INR was 9.96, and a repeat INR to rule out laboratory error was 11.3. Warfarin was discontinued, fresh frozen plasma was given, and fluvoxamine was discontinued. Six days later, warfarin was again started at 1 mg daily, and the INR increased over 4 days to 11.8. The elevated INR was attributed to the persisting effect of fluvoxamine. She was eventually stabilized on warfarin 1 mg daily with INR values between 2 and 2.5 (Yap & Low, 1999).

3.5.1.EE Phenelzine

1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)

2) Summary: Concurrent administration or overlapping therapy with fluvoxamine and a monoamine oxidase (MAO) inhibitor may result in CNS toxicity or serotonin syndrome, a hyperserotonergic state characterized by symptoms such as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. Serious, even fatal, reactions have been reported with concomitant use of serotonin specific reuptake inhibitors and MAO inhibitors (Prod Info Luvox(R), 1997m; Lappin & Auchincloss, 1994i; Graber et al, 1994i; Suchowersky & de Vries, 1990i). Concomitant use of phenelzine and fluvoxamine is contraindicated (Prod Info Nardil(R), 1997).

3) Severity: contraindicated

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: Concurrent use of fluvoxamine and phenelzine is contraindicated . Wait at least two weeks after discontinuing an MAO inhibitor before initiating therapy with fluvoxamine. Wait at least two weeks after discontinuing fluvoxamine before initiating therapy with a MAO inhibitor.

7) Probable Mechanism: serotonin reuptake inhibition

8) Literature Reports

a) Concomitant use of serotonin specific reuptake inhibitors and monoamine oxidase inhibitors can produce a toxic reaction known as serotonin syndrome (Sternbach, 1991f). Serotonin syndrome is a condition of serotonergic hyperstimulation and manifests as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. If the syndrome is not recognized and correctly treated, death can result.

b) A 26-year old woman who had been taking isocarboxazid for eight weeks stopped taking the drug for 11 days before beginning therapy with sertraline. After a single 100 mg sertraline dose, the patient became restless and developed leg twitches. The patients was later admitted to the emergency room with diaphoresis, tachycardia, hyperreflexia, and various neuromuscular disturbances. After treatment with diazepam and propranolol the patient did not improve. The patient was then given two 4 mg doses of cyproheptadine an hour apart, with notable improvement in symptoms after the second dose (Lappin & Auchincloss, 1994h).

c) A drug interaction was reported in a 61-year old woman in which sertraline 100 mg twice daily was added to a regimen of lithium, phenelzine, thioridazine, and doxepin. Three hours after taking the first sertraline dose, the patient was found in a semicomatose state, with elevated body temperature, increased pulse, increased respiration rate, and a blood pressure of 140/110 mm Hg. After transportation to the hospital, the patient was misdiagnosed as having neuroleptic malignant syndrome (NMS) which was later changed to serotonin syndrome due to a reaction between sertraline and phenelzine. The authors suggest that monoamine oxidase inhibitor (MAOI) therapy should be discontinued for at least two weeks before initiation of therapy with a selective serotonin reuptake inhibitor (SSRI) and that before starting a MAOI, SSRI therapy should be discontinued for at least 5 half-lives of the parent drug and any active metabolites (Graber et al, 1994h).

d) Two cases reports suggested a possible interaction between fluoxetine and selegiline (Suchowersky & de Vries, 1990h). One case involved a first episode of mania being observed approximately one month after adding selegiline to fluoxetine therapy. The patient improved two months after both drugs were discontinued, and no further details were provided. The second case involved diaphoresis, vasoconstriction, and cyanosis of the hands which occurred in close temporal relationship to adding fluoxetine and selegiline. Both drugs were discontinued, with relatively quick resolution of symptoms. Rechallenge with fluoxetine alone occurred without incident.

3.5.1.EF Phenindione

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info LUVOX(R) CR extended-release oral capsules, 2008). Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with warfarin. In patients receiving warfarin and fluvoxamine concomitantly for 2 weeks, warfarin plasma concentrations increased by 98% and prothrombin times were prolonged. Fluvoxamine appears to inhibit several cytochrome P450 isoenzymes which may include 1A2 and 2C9 isozymes, which are responsible for warfarin metabolism (Schalekamp et al, 2008; Prod Info LUVOX(R) CR extended-release oral capsules, 2008).

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: When fluvoxamine and an anticoagulant are given concurrently, monitor patient for signs of increased bleeding. Patients who are taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, when fluvoxamine therapy is initiated or discontinued. Periodically reassess the prothrombin time ratio and INR in patients receiving fluvoxamine and anticoagulant therapy (Prod Info LUVOX(R) CR extended-release oral capsules, 2008).

7) Probable Mechanism: unknown

8) Literature Reports

a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bleeding (hospital admission due to bleeding) in patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patients with a mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients experienced 11 bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experiencing bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model (Wallerstedt et al, 2009).

b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5), however, the rate of gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).

c) A hospitalized 80-year-old female was started on intravenous heparin and oral warfarin therapy due to an embolic stroke secondary to atrial fibrillation and mitral stenosis. Her warfarin dose was maintained at 1 mg daily, with her INR between 2.5 and 3. Fluvoxamine 25 mg daily was started for depression, and her warfarin dose was increased to 1.5 mg daily 3 days later due to worsening of the left hemiparesis. Three days later, her INR was 9.96, and a repeat INR to rule out laboratory error was 11.3. Warfarin was discontinued, fresh frozen plasma was given, and fluvoxamine was discontinued. Six days later, warfarin was again started at 1 mg daily, and the INR increased over 4 days to 11.8. The elevated INR was attributed to the persisting effect of fluvoxamine. She was eventually stabilized on warfarin 1 mg daily with INR values between 2 and 2.5 (Yap & Low, 1999).

3.5.1.EG Phenprocoumon

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info LUVOX(R) CR extended-release oral capsules, 2008). Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with warfarin. In patients receiving warfarin and fluvoxamine concomitantly for 2 weeks, warfarin plasma concentrations increased by 98% and prothrombin times were prolonged. Fluvoxamine appears to inhibit several cytochrome P450 isoenzymes which may include 1A2 and 2C9 isozymes, which are responsible for warfarin metabolism (Schalekamp et

al, 2008; Prod Info LUVOX(R) CR extended-release oral capsules, 2008).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When fluvoxamine and an anticoagulant are given concurrently, monitor patient for signs of increased bleeding. Patients who are taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, when fluvoxamine therapy is initiated or discontinued. Periodically reassess the prothrombin time ratio and INR in patients receiving fluvoxamine and anticoagulant therapy (Prod Info LUVOX(R) CR extended-release oral capsules, 2008).
7) Probable Mechanism: unknown
8) Literature Reports
a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bleeding (hospital admission due to bleeding) in patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patients with a mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients experienced 11 bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experiencing bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model (Wallerstedt et al, 2009).
b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5), however, the rate of gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).
c) A hospitalized 80-year-old female was started on intravenous heparin and oral warfarin therapy due to an embolic stroke secondary to atrial fibrillation and mitral stenosis. Her warfarin dose was maintained at 1 mg daily, with her INR between 2.5 and 3. Fluvoxamine 25 mg daily was started for depression, and her warfarin dose was increased to 1.5 mg daily 3 days later due to worsening of the left hemiparesis. Three days later, her INR was 9.96, and a repeat INR to rule out laboratory error was 11.3. Warfarin was discontinued, fresh frozen plasma was given, and fluvoxamine was discontinued. Six days later, warfarin was again started at 1 mg daily, and the INR increased over 4 days to 11.8. The elevated INR was attributed to the persisting effect of fluvoxamine. She was eventually stabilized on warfarin 1 mg daily with INR values between 2 and 2.5 (Yap & Low, 1999).

3.5.1.EH Phenylbutazone
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).

b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.EI Phenytoin

1) Interaction Effect: an increased risk of phenytoin toxicity (ataxia, hyperreflexia, nystagmus, tremors)
2) Summary: Fluvoxamine inhibits several of the isoenzymes of the cytochrome P450 enzyme system (oxidative metabolism); IA2, IIC9, and IIIA4. Since phenytoin is eliminated at least partially via the CYP450 IIC9 pathway, it is possible that coadministration with fluvoxamine may cause elevations in phenytoin plasma levels (Prod Info Luvox(R), 1997).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Consideration should be given to monitoring of phenytoin serum levels when fluvoxamine is added or withdrawn from therapy and dosage adjustments made accordingly. Patients should be counseled to be aware of the potential side effects of phenytoin toxicity such as drowsiness, ataxia, and nystagmus, and to notify their physician if such side effects occur.
7) Probable Mechanism: decreased oxidative metabolism
8) Literature Reports

a) During an in vitro study, the inhibitory effects of fluvoxamine on cytochrome P450 2C9 were evaluated using p-hydroxylation of phenytoin as an established index reaction reflecting CYP2C9 activity. In vivo, p-hydroxylation of phenytoin depends on the formation of 5-(p-hydroxy-phenyl)-5-phenylhydantoin (HPPH). Fluvoxamine, a strong inhibitor of HPPH, impaired the formation of HPPH, which can lead to an increase in steady-state phenytoin levels (Schmider et al, 1997).

b) Phenytoin intoxication occurred in a patient after administration of fluvoxamine. Serum phenytoin concentration dramatically increased from 16.6 to 49.1 mcg/mL during treatment with fluvoxamine. Fluvoxamine may inhibit the metabolism of PHT, mediated by cytochrome P450 2C9 (CYP2C9) and CYP 2C19 enzymes (Mamiya et al, 2000).

3.5.1.EJ Pirazolac

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).

b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.EK Piroxicam

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.EL Pirprofen

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.EM Procarbazine

1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)
2) Summary: Concurrent administration or overlapping therapy with fluvoxamine and a monoamine oxidase (MAO) inhibitor may result in CNS toxicity or serotonin syndrome, a hyperserotonergic state characterized by symptoms such as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. Serious, even fatal, reactions have been reported with concomitant use of selective serotonin reuptake inhibitors and MAO inhibitors (Prod Info Luvox(R), 1997p; Lappin & Auchincloss, 1994m; Graber et al, 1994m; Suchowersky & de Vries, 1990m). Concomitant use is not recommended.
3) Severity: major
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Concurrent use of fluvoxamine and a MAO inhibitor should be avoided. Wait at least two weeks after discontinuing an MAO inhibitor before initiating therapy with fluvoxamine. Wait at least two weeks after discontinuing fluvoxamine before initiating therapy with a MAO inhibitor.
7) Probable Mechanism: serotonin reuptake inhibition
8) Literature Reports

a) Concomitant use of serotonin specific reuptake inhibitors and monoamine oxidase inhibitors can produce a toxic reaction known as serotonin syndrome (Sternbach, 1991i). Serotonin syndrome is a condition of serotonergic hyperstimulation and manifests as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. If the syndrome is not recognized and correctly treated, death can result.
b) A 26-year old woman who had been taking isocarboxazid for eight weeks stopped taking the drug for 11 days before beginning therapy with sertraline. After a single 100 mg sertraline dose, the patient became restless and developed leg twitches. The patients was later admitted to the emergency room with diaphoresis, tachycardia, hyperreflexia, and various neuromuscular disturbances. After treatment with diazepam and propranolol the patient did not improve. The patient was then given two 4 mg doses of cyproheptadine an hour apart, with notable improvement in symptoms after the second dose (Lappin & Auchincloss, 1994l).
c) A drug interaction was reported in a 61-year old woman in which sertraline 100 mg twice daily was

added to a regimen of lithium, phenelzine, thioridazine, and doxepin. Three hours after taking the first sertraline dose, the patient was found in a semicomatose state, with elevated body temperature, increased pulse, increased respiration rate, and a blood pressure of 140/110 mm Hg. After transportation to the hospital, the patient was misdiagnosed as having neuroleptic malignant syndrome (NMS) which was later changed to serotonin syndrome due to a reaction between sertraline and phenelzine. The authors suggest that monoamine oxidase inhibitor (MAOI) therapy should be discontinued for at least two weeks before initiation of therapy with a selective serotonin reuptake inhibitor (SSRI) and that before starting a MAOI, SSRI therapy should be discontinued for at least five half-lives of the parent drug and any active metabolites (Graber et al, 1994l).

d) Two cases reports suggested a possible interaction between fluoxetine and selegiline (Suchowersky & de Vries, 1990l). One case involved a first episode of mania being observed approximately one month after adding selegiline to fluoxetine therapy. The patient improved two months after both drugs were discontinued, and no further details were provided. The second case involved diaphoresis, vasoconstriction, and cyanosis of the hands which occurred in close temporal relationship to adding fluoxetine and selegiline. Both drugs were discontinued, with relatively quick resolution of symptoms. Rechallenge with fluoxetine alone occurred without incident.

3.5.1.EN Propranolol

1) Interaction Effect: bradycardia and hypotension

2) Summary: Propranolol serum concentrations may increase significantly during concomitant therapy with fluvoxamine. Elevated propranolol serum concentrations may be associated with an increased risk of bradycardia and hypotension (Prod Info Luvox(R), 1997c).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Carefully monitor heart rate and blood pressure. The propranolol does may need to be reduced if bradycardia or hypotension develop. Alternatively, use of atenolol, a beta-blocker which does not undergo hepatic metabolism and is not affected by fluvoxamine, may be considered.

7) Probable Mechanism: reduced beta blocker metabolism

8) Literature Reports

a) Coadministration of propranolol (160 mg per day) and fluvoxamine (100 mg per day) in healthy volunteers resulted in a mean 5-fold increase in minimum propranolol serum concentrations. This was associated with a slight reduction in heart rate and blood pressure (Prod Info Luvox(R), 1997b; van Harten, 1993).

3.5.1.EO Propyphenazone

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).

b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.EP Proquazone

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).

3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.EQ Ramelteon
1) Interaction Effect: increased ramelteon plasma concentrations with increased risk of side effects
2) Summary: Concurrent administration of fluvoxamine and ramelteon is contraindicated due to significantly increased ramelteon plasma concentrations with concurrent fluvoxamine use (Prod Info ROZEREM(R) oral tablets, 2008).
3) Severity: contraindicated
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Concurrent administration of fluvoxamine and ramelteon is contraindicated (Prod Info ROZEREM(R) oral tablets, 2008).
7) Probable Mechanism: inhibition of CYP1A2-mediated ramelteon metabolism by fluvoxamine
8) Literature Reports
a) Fluvoxamine, a strong CYP1A2 inhibitor, significantly increases ramelteon plasma concentrations when used concurrently. When a single dose of ramelteon 16 mg was coadministered to subjects who received fluvoxamine 100 mg twice daily for 3 days prior, the ramelteon AUC and Cmax increased approximately 190-fold and 70-fold, respectively (Prod Info ROZEREM(R) oral tablets, 2008).

3.5.1.ER Rasagiline
1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)
2) Summary: Concurrent administration or overlapping therapy with selective serotonin reuptake inhibitors, including fluvoxamine, and non-selective MAOIs or the selective MAO-B inhibitor selegiline, has been reported to cause serious, sometimes fatal reactions. Signs and symptoms included hyperthermia, rigidity, myoclonus, autonomic instability with rapid vital sign fluctuations, and mental status changes progressing to extreme agitation, delirium, and coma. Similar reactions have been reported with serotonin-norepinephrine reuptake inhibitors (SNRIs) and non-selective MAOIs or selegiline. Rasagiline clinical trials did not allow concomitant use of fluvoxamine; the combination of rasagiline and fluvoxamine should be avoided. Wait at least two weeks after discontinuing rasagiline before initiating therapy with fluvoxamine (Prod Info AZILECT (R) oral tablets, 2006).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Concurrent use of fluvoxamine and rasagiline should be avoided. Wait at least two weeks after discontinuing rasagiline before initiating therapy with fluvoxamine.
7) Probable Mechanism: inhibition of serotonin metabolism by monoamine oxidase
8) Literature Reports
a) Concomitant use of serotonin specific reuptake inhibitors and monoamine oxidase inhibitors can produce a toxic reaction known as serotonin syndrome (Sternbach, 1991g). Serotonin syndrome is a condition of serotonergic hyperstimulation and manifests as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. If the syndrome is not recognized and correctly treated, death can result.

3.5.1.ES Reviparin
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info LUVOX(R) CR extended-release oral capsules, 2008). Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Altered anticoagulant effects (including increased

bleeding) have been reported with the coadministration of SSRIs with warfarin. In patients receiving warfarin and fluvoxamine concomitantly for 2 weeks, warfarin plasma concentrations increased by 98% and prothrombin times were prolonged. Fluvoxamine appears to inhibit several cytochrome P450 isoenzymes which may include 1A2 and 2C9 isozymes, which are responsible for warfarin metabolism (Schalekamp et al, 2008; Prod Info LUVOX(R) CR extended-release oral capsules, 2008).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When fluvoxamine and an anticoagulant are given concurrently, monitor patient for signs of increased bleeding. Patients who are taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, when fluvoxamine therapy is initiated or discontinued. Periodically reassess the prothrombin time ratio and INR in patients receiving fluvoxamine and anticoagulant therapy (Prod Info LUVOX(R) CR extended-release oral capsules, 2008).
7) Probable Mechanism: unknown
8) Literature Reports
a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bleeding (hospital admission due to bleeding) in patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patients with a mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients experienced 11 bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experiencing bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model (Wallerstedt et al, 2009).
b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5), however, the rate of gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).
c) A hospitalized 80-year-old female was started on intravenous heparin and oral warfarin therapy due to an embolic stroke secondary to atrial fibrillation and mitral stenosis. Her warfarin dose was maintained at 1 mg daily, with her INR between 2.5 and 3. Fluvoxamine 25 mg daily was started for depression, and her warfarin dose was increased to 1.5 mg daily 3 days later due to worsening of the left hemiparesis. Three days later, her INR was 9.96, and a repeat INR to rule out laboratory error was 11.3. Warfarin was discontinued, fresh frozen plasma was given, and fluvoxamine was discontinued. Six days later, warfarin was again started at 1 mg daily, and the INR increased over 4 days to 11.8. The elevated INR was attributed to the persisting effect of fluvoxamine. She was eventually stabilized on warfarin 1 mg daily with INR values between 2 and 2.5 (Yap & Low, 1999).

3.5.1.ET Rizatriptan
1) Interaction Effect: an increased risk of serotonin syndrome
2) Summary: There have been case reports of weakness, hyperreflexia, and incoordination following concomitant use of sumatriptan, a 5-hydroxytryptamine-1 (5HT-1) agonist, and a serotonin specific reuptake inhibitor (SSRI) (Prod Info Imitrex(R), 1998). Because rizatriptan is a 5HT 1B/1D receptor agonist, a similar interaction between SSRIs and rizatriptan may occur (Prod Info Maxalt(R), 1998a). Concurrent use of a triptan and an SSRI may result in serotonin syndrome which may be life-threatening. Symptoms of serotonin syndrome may include restlessness, hallucinations, loss of coordination, fast heart beat, rapid changes in blood pressure, increased body temperature, overreactive reflexes, nausea, vomiting, and diarrhea. Clinicians should be aware that triptans may be commonly used intermittently and that either the triptan or the SSRI may be prescribed by a different physician. Discuss the risks of serotonin syndrome with patients who are prescribed this combination and monitor them closely for symptoms of serotonin syndrome (US Food and Drug Administration, 2006).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Coadministration of a triptan, such as rizatriptan, and an SSRI may result in a life-threatening condition called serotonin syndrome. Be aware that triptans may be commonly used intermittently and that either the triptan or the SSRI may be prescribed by a different physician. If these

agents are used together, discuss the risks of serotonin syndrome with the patient and monitor closely for symptoms of serotonin syndrome (restlessness, hyperthermia, hyperreflexia, incoordination).
7) Probable Mechanism: additive pharmacologic effects resulting in excessive serotonergic stimulation
8) Literature Reports
a) Twelve healthy volunteers received paroxetine 20 mg daily for two weeks and a single dose of rizatriptan 10 mg. Plasma concentrations of rizatriptan were not altered by the administration of paroxetine (Prod Info Maxalt(R), 1998).

3.5.1.EU Rofecoxib
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.EV Ropivacaine
1) Interaction Effect: increased plasma levels of ropivacaine
2) Summary: Ropivacaine is metabolized in the liver by the cytochrome P450 1A2 (CYP1A2) enzyme system to 3-hydroxyropivacaine, the major metabolite. Drugs which inhibit CYP1A2, such as fluvoxamine, can potentially interact with the metabolism of ropivacaine. This would result in decreased renal clearance and increased plasma concentrations of ropivacaine (Jokinen et al, 2000a; Prod Info Naropin(TM), 1996).
3) Severity: moderate
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Care must be taken to monitor the patient for signs of local anesthetic toxicity with the coadministration of ropivacaine and fluvoxamine.
7) Probable Mechanism: inhibition by fluvoxamine of cytochrome P450 1A2-mediated ropivacaine metabolism
8) Literature Reports
a) In a randomized, three-way crossover study, 12 healthy volunteers received a single dose of ropivacaine 40 mg as an intravenous infusion alone or combined with either oral fluvoxamine 25 mg or ketoconazole 100 mg twice daily for two days. The combined therapy with ropivacaine and ketoconazole demonstrated no clinically significant differences in the pharmacokinetic measurements obtained. The authors theorized that cytochrome P450 3A4 (CYP3A4) inhibition, as measured by ketoconazole, has little effect on the pharmacokinetics of ropivacaine. However, CYP1A2 inhibition, as measured by fluvoxamine, may result in a clinically relevant drug interaction with repeated administration. In the presence of fluvoxamine, ropivacaine total plasma clearance decreased by 68% (from 354 mL/min to 112 mL/min). The observed reduction in the total plasma clearance after fluvoxamine arises from a decrease in 3-hydroxyropivacaine formation, which is likely mediated by CYP1A2. Additionally, the half-life of ropivacaine increased from 1.9 hours to 3.6 hours when given with fluvoxamine. The reduction in ropivacaine clearance during fluvoxamine administration is likely to be of minor relevance when ropivacaine is given as a single dose. However, repeated administration of ropivacaine in a patient also receiving fluvoxamine may result in toxic ropivacaine plasma concentrations (Arlander et al, 1998).
b) Inhibition of cytochrome P450 1A2 (CYP1A2) by fluvoxamine considerably reduced elimination of ropivacaine. The eight patients in this randomized, double-blind, cross-over, four phase study ingested erythromycin 1500 mg daily for 6 days, fluvoxamine 100 mg for 5 days, both erythromycin and fluvoxamine, or placebo. Each subject received ropivacaine 0.6 mg/kg IV over 30 minutes as a single dose. Fluvoxamine increased both the AUC (p less than 0.001) of ropivacaine 3.7-fold, prolonged the

half-life from 2.3 to 7.4 h (p less than 0.01), and decreased clearance 77% (p less than 0.001) when compared with placebo. Fluvoxamine increased the AUC of 2,6-pipecoloxylidide (PPX), a ropivacaine metabolite, 2.5-fold (p less than 0.001) and the Cmax of PPX 2.8-fold (p less than 0.001) and decreased the plasma levels of 3-OH-ropivacaine to below the limit of quantitation. Erythromycin had minor effects on the pharmacokinetics of ropivacaine. The combination of fluvoxamine and erythromycin, however, when compared with fluvoxamine alone, further increased the AUC of ropivacaine by 50% (p less than 0.01), and prolonged the half-life from 7.4 to 11.9 h (p less than 0.01). The author concludes that fluvoxamine-induced cytochrome P450 1A2 inhibition considerably reduces elimination of ropivacaine. Coadministration of fluvoxamine and erythromycin increases plasma ropivacaine levels further by decreasing its clearance (Jokinen et al, 2000).

3.5.1.EW Selegiline

1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)

2) Summary: Concurrent administration or overlapping therapy with fluvoxamine and a monoamine oxidase (MAO) inhibitor may result in CNS toxicity or serotonin syndrome, a hyperserotonergic state characterized by symptoms such as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. Serious, even fatal, reactions have been reported with concomitant use of serotonin specific reuptake inhibitors and MAO inhibitors (Prod Info Luvox(R), 1997v; Lappin & Auchincloss, 1994o; Graber et al, 1994o; Suchowersky & de Vries, 1990o). Concomitant use is not recommended.

3) Severity: major

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: Concurrent use of fluvoxamine and a MAO inhibitor should be avoided. Wait at least two weeks after discontinuing an MAO inhibitor before initiating therapy with fluvoxamine. Wait at least two weeks after discontinuing fluvoxamine before initiating therapy with a MAO inhibitor.

7) Probable Mechanism: serotonin reuptake inhibition

8) Literature Reports

a) Concomitant use of serotonin specific reuptake inhibitors and monoamine oxidase inhibitors can produce a toxic reaction known as serotonin syndrome (Sternbach, 1991g). Serotonin syndrome is a condition of serotonergic hyperstimulation and manifests as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. If the syndrome is not recognized and correctly treated, death can result.

b) A 26-year old woman who had been taking isocarboxazid for eight weeks stopped taking the drug for 11 days before beginning therapy with sertraline. After a single 100 mg sertraline dose, the patient became restless and developed leg twitches. The patients was later admitted to the emergency room with diaphoresis, tachycardia, hyperreflexia, and various neuromuscular disturbances. After treatment with diazepam and propranolol the patient did not improve. The patient was then given two 4 mg doses of cyproheptadine an hour apart, with notable improvement in symptoms after the second dose (Lappin & Auchincloss, 1994n).

c) A drug interaction occurred in a 61-year old woman whose regimen of sertraline 100 mg twice daily was added to a regimen of lithium, phenelzine, thioridazine, and doxepin. Three hours after taking the first sertraline dose, the patient was found in a semicomatose state, with elevated body temperature, increased pulse, increased respiration rate, and a blood pressure of 140/110 mm Hg. After transportation to the hospital, the patient was misdiagnosed as having neuroleptic malignant syndrome (NMS) which was later changed to serotonin syndrome due to a reaction between sertraline and phenelzine. The authors suggest that monoamine oxidase inhibitor (MAOI) therapy should be discontinued for at least two weeks before initiation of therapy with a selective serotonin reuptake inhibitor (SSRI) and that before starting a MAOI, SSRI therapy should be discontinued for at least 5 half-lives of the parent drug and any active metabolites (Graber et al, 1994n).

d) Two cases reports suggested a possible interaction between fluoxetine and selegiline (Suchowersky & de Vries, 1990n). One case involved a first episode of mania being observed approximately one month after adding selegiline to fluoxetine therapy. The patient improved two months after both drugs were discontinued, and no further details were provided. The second case involved diaphoresis, vasoconstriction, and cyanosis of the hands which occurred in close temporal relationship to adding fluoxetine and selegiline. Both drugs were discontinued, with relatively quick resolution of symptoms. Rechallenge with fluoxetine alone occurred without incident.

3.5.1.EX Sibrafiban

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and antiplatelet agents has been associated with an increased risk of bleeding. Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an antiplatelet agent are given concurrently, monitor patient for signs of increased bleeding (Prod Info PAXIL(R) oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008)
7) Probable Mechanism: unknown

3.5.1.EY Sibutramine

1) Interaction Effect: an increased risk of serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)
2) Summary: Sibutramine inhibits the reuptake of norepinephrine, dopamine, and serotonin. In addition, the two major metabolites of sibutramine, M1 and M2, also inhibit the reuptake of these neurotransmitters. A hyperserotonergic state, termed serotonin syndrome, may result if sibutramine is given concurrently with a selective serotonin reuptake inhibitor. Coadministration of sibutramine and selective serotonin reuptake inhibitors is not recommended (Prod Info Meridia(R), 1997).
3) Severity: major
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Sibutramine should not be administered with serotonergic agents, including selective serotonin reuptake inhibitors, because of the increased risk of serotonin syndrome.
7) Probable Mechanism: additive pharmacologic effects resulting in excessive serotonergic stimulation
8) Literature Reports
a) Serotonin syndrome is a condition of serotonergic hyperstimulation and manifests as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. If the syndrome is not recognized and correctly treated, death can result (Sternbach, 1991b).

3.5.1.EZ St John's Wort

1) Interaction Effect: an increased risk of serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)
2) Summary: Case reports describe the onset of serotonin syndrome-like symptoms, mania, and hypomania following the addition of St. John's Wort to sertraline, fluoxetine, and paroxetine therapy (Spinella & Eaton, 2002c; Barbanel et al, 2000a; Waksman et al, 2000a; Lantz et al, 1999a). A patient exhibited a syndrome resembling sedative/hypnotic intoxication after adding St. John's Wort to paroxetine therapy (Gordon, 1998a). St. John's Wort is thought to inhibit serotonin reuptake and may have mild monoamine oxidase inhibitory activity (Singer et al, 1999; Thiede & Walper, 1994), which when added to selective serotonin reuptake inhibitors may result in serotonin syndrome.
3) Severity: major
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Patients should be advised to wait two weeks after stopping St. John's Wort before restarting selective serotonin reuptake inhibitor therapy. If a patient plans to replace selective serotonin reuptake inhibitor (SSRI) therapy with St. John's Wort, the half-life of the specific SSRI should be taken into consideration, waiting at least 5 half-lives for the SSRI to be metabolized out of the body.
7) Probable Mechanism: additive serotonergic effect
8) Literature Reports
a) Five cases have been reported of serotonin syndrome in the elderly after combining prescription antidepressants and St. John's Wort. Case 1 developed dizziness, nausea, vomiting and a headache 4 days after starting St. John's Wort 300 milligrams (mg) three times daily combined with sertraline 50 mg daily. Her symptoms resolved 2 to 3 days after stopping all medications. Case 2 developed nausea, epigastric pain and anxiety 3 days after starting St. John's Wort 300 mg twice daily combined with sertraline 75 mg daily. His symptoms resolved in one week after discontinuing both medications, and he resumed sertraline use without complications. The third case developed nausea, vomiting, anxiety, and confusion 2 days after starting St. John's Wort 300 mg twice daily combined with sertraline 50 mg daily. His symptoms improved in 4 to 5 days after stopping both medications and taking cyproheptadine 4 mg three times daily. Case 4 developed nausea, anxiety, restless, and irritability 2 days after starting St. John's Wort 300 mg three times daily combined with sertraline 50 mg daily. Cyproheptadine 4 mg twice daily was administered for seven days, and his symptoms improved in 1 week after stopping the medication. Cases 1 through 4 resumed their prescriptive sertraline after symptoms subsided and had no further problems. Case 5 developed nausea, vomiting and restlessness 3 days after starting St. John's Wort 300 mg three times daily combined with nefazodone 100 mg twice daily. She continued to take St. John's Wort but discontinued the nefazodone and over 1 week her symptoms Improved. She refused to resume therapy with nefazodone, but continued therapy with St. John's Wort and mild to moderate symptoms of depression and anxiety returned (Lantz et al, 1999).
b) A 50-year-old female taking St. John's Wort 600 mg daily experienced symptoms of sedative intoxication when she ingested a single dose of paroxetine 20 mg. She was incoherent, groggy, slow-moving, and complained of nausea and weakness. Prior to starting St. John's Wort, she had been receiving paroxetine 40 mg daily for eight months without adverse effects. After a night of sleep, she returned to her baseline mental status (Gordon, 1998).
c) A 61-year-old female experienced restlessness and involuntary movements of her extremities after beginning paroxetine 20 milligrams (mg) two days after discontinuing St. John's Wort 600 mg daily. The

patient reported agitation and akathisia 8 hours after taking the first dose of paroxetine. She presented with diaphoresis and involuntary movement of all extremities with hyperreflexia and rigidity. Blood pressure, heart rate, and temperature were normal. After admission, blood pressure increased to 200/116 mmHg and heart rate increased to 145 beats per minute. Creatine kinase increased from 212 units/liter (U/L) initially to 1024 U/L. The patient was managed with supportive care and lorazepam and discharged after two days (Waksman et al, 2000).

d) A 28-year-old male developed a manic syndrome following comedication with St. John's Wort and sertraline. The patient was also on testosterone replacement therapy following bilateral orchidectomy 2 years earlier, but testosterone levels were subtherapeutic. The patient was prescribed sertraline 50 milligrams daily for depression following a 2 week trial of St. John's Wort per patient preference (dose not specified). Before sertraline was started, the patient was instructed to discontinue St. John'sWort, but continued it despite this advice. The patient experienced improved mood so did not see his physician, believing that he did not need further treatment. Over 2 months, the patient had elated mood, was irritable, and overspent, buying a car he could not afford, and was ultimately arrested for stealing fuel for the car. On arrest, he was referred to psychiatric services due to irritability and disinhibition. He was observed to be over-aroused, distractible, have flight of ideas, and grandiose delusions, leading to a diagnosis of a manic episode. The authors state the possibility of the manic state resulting from sertraline therapy alone, and that St. John's Wort may have increased the risk as a result of monoamine oxidase inhibition. Since the patient's testosterone level was subnormal, the possibility of its contribution to the manic state was considered low. However, the patient had elevated gonadotropin levels (luteinizing hormone and follicle-stimulating hormone) which may have predisposed the patient to mania (Barbanel et al, 2000).

e) A 42-year-old female experienced symptoms consistent with a mixed hypomanic episode following concomitant use of fluoxetine, buspirone, Ginkgo biloba, and St. John's Wort. The symptoms resolved following discontinuation of Ginkgo and St. John's Wort. The patient was being treated for depression following a mild traumatic brain injury with fluoxetine 20 milligrams (mg) twice daily and buspirone 15 mg twice daily. Several weeks prior to presentation, buspirone was increased to 20 mg twice daily for persistent anxiety and the patient began taking Ginkgo biloba, melatonin, and St. John's Wort in unspecified doses. Melatonin was considered unlikely to have contributed to her symptoms. Ginkgo and St. John's Wort were considered possible contributors since they may potentiate antidepressants, and considering the temporal relationship between the use of the herbs and onset of symptoms and discontinuation of the herbs and resolution of symptoms. However, the brain injury was considered a possible contributor (Spinella & Eaton, 2002b).

3.5.1.FA Sulfinpyrazone

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and antiplatelet agents has been associated with an increased risk of bleeding. Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an antiplatelet agent are given concurrently, monitor patient for signs of increased bleeding (Prod Info PAXIL(R) oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008)

7) Probable Mechanism: unknown

3.5.1.FB Sulindac

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined

use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).

b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.FC Sulodexide

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and antiplatelet agents has been associated with an increased risk of bleeding. Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an antiplatelet agent are given concurrently, monitor patient for signs of increased bleeding (Prod Info PAXIL(R) oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008)

7) Probable Mechanism: unknown

3.5.1.FD Sumatriptan

1) Interaction Effect: an increased risk of serotonin syndrome

2) Summary: There have been case reports of weakness, hyperreflexia, and incoordination following concomitant use of a triptan, such as sumatriptan, and a serotonin specific reuptake inhibitor (SSRI), such as fluvoxamine (Prod Info Imitrex(R), 2002). Concurrent use of a triptan and an SSRI may result in serotonin syndrome which may be life-threatening. Symptoms of serotonin syndrome may include restlessness, hallucinations, loss of coordination, fast heart beat, rapid changes in blood pressure, increased body temperature, overreactive reflexes, nausea, vomiting, and diarrhea. Clinicians should be aware that triptans may be commonly used intermittently and that either the triptan or the SSRI may be prescribed by a different physician. Discuss the risks of serotonin syndrome with patients who are prescribed this combination and monitor them closely for symptoms of serotonin syndrome (US Food and Drug Administration, 2006).

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Coadministration of a triptan, such as sumatriptan, and an SSRI, such as fluvoxamine, may result in a life-threatening condition called serotonin syndrome. Be aware that triptans may be commonly used intermittently and that either the triptan or the SSRI may be prescribed by a different physician. If these agents are used together, discuss the risks of serotonin syndrome with the patient and monitor closely for symptoms of serotonin syndrome (restlessness, hyperthermia, hyperreflexia, incoordination).

7) Probable Mechanism: additive pharmacologic effects resulting in excessive serotonergic stimulation

3.5.1.FE Suprofen

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).

b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with

hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.FF Tacrine

1) Interaction Effect: an increase in the plasma concentration of tacrine

2) Summary: Two studies involving healthy volunteers and single doses of tacrine found that fluvoxamine inhibited the metabolism of tacrine, causing an increase in the area under the concentration-time curve (AUC) of tacrine and three of its metabolites. Fluvoxamine inhibits cytochrome P450 1A2 enzymes, and these same enzymes are responsible for tacrine metabolism. Whether this interaction would be present in Alzheimer's patients receiving multiple tacrine doses is not known (Becquemont et al, 1997a; Teilmann Larsen et al, 1999a).

3) Severity: moderate

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: While the exact clinical implication of this drug interaction is uncertain, monitor patients receiving tacrine and fluvoxamine concurrently for excessive tacrine adverse effects, including cholinergic effects. Also monitor liver function for increased hepatotoxicity.

7) Probable Mechanism: inhibition of cytochrome P450 1A2 enzymes by fluvoxamine

8) Literature Reports

a) A randomized, double-blind, two-period cross-over study involving 14 healthy male volunteers investigated the influence of fluvoxamine on the pharmacokinetics of a single-dose of tacrine. Study subjects received either fluvoxamine 100 mg or placebo once daily for six days, and a single dose of tacrine 40 mg was coadministered on day 6. The tacrine area under the concentration-time curve (AUC) increased from 27 ng/hr/mL to 224 ng/hr/mL in the presence of fluvoxamine. Maximum concentration (Cmax) of tacrine also increased from 7 ng/mL to 39 ng/mL during the fluvoxamine period. No significant changes in the time to reach Cmax (tmax) and the half-life of tacrine were observed. The AUC values of three tacrine metabolites were also significantly increased, but to a lesser extent than the AUC of tacrine. Whether these same results are seen in Alzheimer's patients receiving multiple doses of tacrine is not known (Becquemont et al, 1997).

b) Eighteen healthy male volunteers participated in an open, randomized crossover study to establish whether fluvoxamine in clinically relevant doses was able to inhibit the formation of tacrine metabolites. Volunteers received tacrine 40 mg as a single dose and fluvoxamine 50 mg or 100 mg once daily for five days, followed by a dose of tacrine 20 mg. Fluvoxamine reduced the apparent oral clearance of tacrine by 85%. Specifically, fluvoxamine reduced the formation of 1- and 2-hydroxytacrine, but the formation of 4-hydroxytacrine was not affected. Whether the inhibition of these metabolites reduced tacrine-induced hepatotoxicity requires further investigation (Teilmann Larsen et al, 1999).

3.5.1.FG Tapentadol

1) Interaction Effect: increased risk of serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)

2) Summary: Concurrent use of tapentadol and a selective serotonin reuptake inhibitor (SSRI) may result in serotonin syndrome, which may be life-threatening. Symptoms of serotonin syndrome may include restlessness, hallucinations, loss of coordination, fast heart beat, rapid changes in blood pressure, increased body temperature, overreactive reflexes, nausea, vomiting, and diarrhea (Prod Info tapentadol immediate release oral tablets, 2008).

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Coadministration of tapentadol and an SSRI may result in a life-threatening condition called serotonin syndrome. If these agents are used together, monitor the patient closely for symptoms of serotonin syndrome (restlessness, hyperthermia, hyperreflexia, incoordination), especially during treatment initiation and dose increases (Prod Info tapentadol immediate release oral tablets, 2008).

7) Probable Mechanism: additive serotonergic effect

3.5.1.FH Tenidap

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent

use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).

b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.FI Tenoxicam

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).

b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.FJ Terfenadine

1) Interaction Effect: cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Fluvoxamine should not be used in combination with terfenadine. Although there is no direct experience with this combination, fluvoxamine appears to be a potent inhibitor of the cytochrome P450IIIA4 isozyme, the enzyme primarily responsible for the metabolism of terfenadine. Inhibition of this enzyme may result in elevated terfenadine concentrations; increased plasma concentrations of terfenadine are associated with QT prolongation and torsades de pointes, which can be fatal (Prod Info Luvox(R), 1997h).

3) Severity: contraindicated

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: Concurrent use of fluvoxamine and terfenadine is contraindicated.

7) Probable Mechanism: inhibition by fluvoxamine of terfenadine metabolism

3.5.1.FK Theophylline

1) Interaction Effect: theophylline toxicity (nausea, vomiting, palpitations, seizures)

2) Summary: Fluvoxamine-theophylline combination therapy has produced toxic serum concentrations of theophylline (Sperber, 1991a; van den Brekel & Harrington, 1994; Perucca et al, 1994; Lorenz et al, 1996a). The reported mechanism of action is fluvoxamine's inhibitory effect on the hepatic cytochrome P4501A2 (CYP1A2), the microsome responsible for catalyzing theophylline metabolism (Prod Info Luvox(R), 1997r).

3) Severity: major

4) Onset: delayed

5) Substantiation: established

6) Clinical Management: Careful monitoring of theophylline serum concentration is required. Theophylline doses should be reduced to one-third of the usual daily maintenance dose if fluvoxamine is coadministered. No dose adjustment is necessary for fluvoxamine.

7) Probable Mechanism: decreased theophylline metabolism

8) Literature Reports

a) Fluvoxamine appeared to be responsible for substantially increased serum theophylline levels and symptoms of theophylline toxicity in an 11-year-old boy taking sustained-release theophylline 300 mg twice daily (Sperber, 1991). Both drugs were discontinued, and theophylline was later reinstated (dose not specified) with no further evidence of toxicity.

b) An increase in theophylline plasma concentrations from 13 mg/L to 40 mg/L was found after fluvoxamine was added to therapy. The patient was an 83-year-old man who was receiving sustained release theophylline 600 mg per day (Diot et al, 1991).
c) Fluvoxamine 50 mg twice a day given concurrently with theophylline 1000 mg daily resulted in a theophylline plasma concentration of 32 mcg/mL and nausea and tachycardia in a 75-year-old male with normal liver function (Lorenz et al, 1996). Theophylline clearance was calculated to be 43 mL/h before the addition of fluvoxamine and 22 mL/h after four doses.
d) In 12 healthy nonsmoking volunteers with steady-state fluvoxamine levels, the pharmacokinetics of a single dose of theophylline 375 mg were evaluated. Theophylline clearance decreased three-fold. Therefore, it is recommended that the daily maintenance dose of theophylline be reduced by two-thirds in a patient also receiving fluvoxamine (Prod Info Luvox(R), 1997q).

3.5.1.FL Thioridazine

1) Interaction Effect: an increased risk of thioridazine toxicity, cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Fluvoxamine inhibits the metabolism of thioridazine, possibly through the inhibition of cytochrome P450 2D6 (CYP2D6) resulting in toxicity. The resulting elevated levels of thioridazine would be expected to enhance the prolongation of the QT interval associated with thioridazine and may increase the risk of serious, potentially fatal, cardiac arrhythmias, such as torsade de pointes-type arrhythmias (Prod Info Mellaril(R), 2000a).
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Due to the potential for significant, possibly life-threatening, proarrhythmic effects, concurrent administration of thioridazine and fluvoxamine is contraindicated.
7) Probable Mechanism: inhibition of cytochrome P450 2D6-mediated thioridazine metabolism
8) Literature Reports
a) The serum concentrations of thioridazine and its two metabolites, mesoridazine and sulforidazine, were evaluated in ten male schizophrenic patients aged 36 to 78 years at three separate time points. All patients were receiving thioridazine monotherapy for the management of schizophrenia at a mean dose of 88 mg daily. Fluvoxamine 50 mg daily was coadministered for one week. Plasma levels of thioridazine and its metabolites were measured during monotherapy with thioridazine, after one week of concurrent therapy with thioridazine and fluvoxamine, and two weeks after fluvoxamine was discontinued. Following one week of combination therapy with fluvoxamine and thioridazine, thioridazine levels increased 225%, mesoridazine levels increased 219%, and sulforidazine concentrations rose 258%. Even two weeks after the discontinuation of fluvoxamine, three patients continued to show elevated thioridazine and metabolite levels. No clinical symptoms were attributed to the interaction between these two agents (Carrillo et al, 1999).
b) The metabolism of thioridazine is inhibited by drugs such as fluvoxamine due to reduced cytochrome P450 2D6 and 1A2 isozyme activity. The elevated levels of thioridazine would be expected to enhance the prolongation of the QT interval associated with thioridazine. This, in turn, may increase the risk of serious, potentially fatal, cardiac arrhythmias, such as torsade de pointes-type arrhythmias (Prod Info Mellaril(R), 2000).

3.5.1.FM Tiaprofenic Acid

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with

hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.FN Ticlopidine

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and antiplatelet agents has been associated with an increased risk of bleeding. Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an antiplatelet agent are given concurrently, monitor patient for signs of increased bleeding (Prod Info PAXIL(R) oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008)
7) Probable Mechanism: unknown

3.5.1.FO Tinzaparin

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info LUVOX(R) CR extended-release oral capsules, 2008). Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with warfarin. In patients receiving warfarin and fluvoxamine concomitantly for 2 weeks, warfarin plasma concentrations increased by 98% and prothrombin times were prolonged. Fluvoxamine appears to inhibit several cytochrome P450 isoenzymes which may include 1A2 and 2C9 isozymes, which are responsible for warfarin metabolism (Schalekamp et al, 2008; Prod Info LUVOX(R) CR extended-release oral capsules, 2008).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When fluvoxamine and an anticoagulant are given concurrently, monitor patient for signs of increased bleeding. Patients who are taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, when fluvoxamine therapy is initiated or discontinued. Periodically reassess the prothrombin time ratio and INR in patients receiving fluvoxamine and anticoagulant therapy (Prod Info LUVOX(R) CR extended-release oral capsules, 2008).
7) Probable Mechanism: unknown
8) Literature Reports

a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bleeding (hospital admission due to bleeding) in patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patients with a mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients experienced 11 bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experiencing bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model (Wallerstedt et al, 2009).

b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5), however, the rate of gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).

c) A hospitalized 80-year-old female was started on intravenous heparin and oral warfarin therapy due to an embolic stroke secondary to atrial fibrillation and mitral stenosis. Her warfarin dose was maintained at 1 mg daily, with her INR between 2.5 and 3. Fluvoxamine 25 mg daily was started for depression, and her warfarin dose was increased to 1.5 mg daily 3 days later due to worsening of the left hemiparesis. Three days later, her INR was 9.96, and a repeat INR to rule out laboratory error was

11.3. Warfarin was discontinued, fresh frozen plasma was given, and fluvoxamine was discontinued. Six days later, warfarin was again started at 1 mg daily, and the INR increased over 4 days to 11.8. The elevated INR was attributed to the persisting effect of fluvoxamine. She was eventually stabilized on warfarin 1 mg daily with INR values between 2 and 2.5 (Yap & Low, 1999).

3.5.1.FP Tirofiban

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and antiplatelet agents has been associated with an increased risk of bleeding. Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an antiplatelet agent are given concurrently, monitor patient for signs of increased bleeding (Prod Info PAXIL(R) oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008)
7) Probable Mechanism: unknown

3.5.1.FQ Tizanidine

1) Interaction Effect: increased tizanidine plasma concentrations
2) Summary: Concomitant use of fluvoxamine and tizanidine is contraindicated. Use of these drugs together has resulted in increased plasma concentrations and half-life of tizanidine (Prod Info tizanidine hcl tablets, 2006).(Prod Info Zanaflex (R) Tablets, 2004). Concurrent administration of fluvoxamine, a potent CYP1A2 inhibitor, and tizanidine induced a profound increase in tizanidine bioavailability. The inhibition of CYP1A2-mediated tizanidine metabolism provokes clinically significant hypotension and alteration of consciousness (Granfors et al, 2004). In a retrospective case series, tizanidine-associated adverse events occurred significantly more often in patients treated concomitantly with fluvoxamine and tizanidine compared with tizanidine monotherapy (Momo et al, 2004).
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: established
6) Clinical Management: The concomitant use of fluvoxamine and tizanidine is contraindicated. Use of tizanidine with fluvoxamine can increase the plasma concentrations of tizanidine (Prod Info tizanidine hcl tablets, 2006) which may lead to decreased blood pressure, psychomotor impairment, and excessive drowsiness (Granfors et al, 2004).
7) Probable Mechanism: inhibition of CYP1A2-mediated tizanidine metabolism by fluvoxamine
8) Literature Reports

a) In a study of 10 healthy volunteers treated with fluvoxamine and tizanidine, the half-life, Cmax, and AUC of tizanidine increased by 12-fold, 33-fold, and 3-fold, respectively (Prod Info tizanidine hcl tablets, 2006).

b) Coadministration of fluvoxamine with tizanidine resulted in profound increases in tizanidine bioavailability due to P450 CYP1A2-mediated inhibition of tizanidine metabolism and was associated with multiple adverse clinical effects. In a randomized, double-blind, crossover study (4-week wash out period), healthy subjects (n=10) received a 4-day regimen of fluvoxamine 100 milligrams (mg) or placebo once daily. On day 4, each subject received a single oral dose of tizanidine 4 mg. Serial blood pharmacokinetic analysis was performed over the next 24 hours, in conjunction with measurement of pharmacodynamic response. When compared with placebo, the presence of fluvoxamine dramatically increased tizanidine mean maximum serum concentration (by 1210% (from 2.2 to 26.6 nanograms/milliliter), p=0.000001), mean area under the concentration-time curve (AUC 0-infinity; by 3260%, p=0.000002), and mean elimination half-life from 1.5 hours to 4.3 hours (by 290%, p=0.00004). Pharmacodynamic responses to fluvoxamine-enhanced tizanidine exposure were also dramatic: mean systolic blood pressure declined by 35 millimeters mercury (mmHg; from 115 to 79 mmHg), mean diastolic blood pressure decreased by 20 mmHg (from 66 to 46 mmHg), heart rate decreased by 4 beats per minute, and subjectively perceived drowsiness (0-100 visual analogue scale) increased by a mean of 42 points compared with the placebo-tizanidine phase (p=0.000009, p=0.00002, p=0.007, and p=0.0002, respectively). During the fluvoxamine-tizanidine phase, all subjects experienced somnolence and dizziness for between 3 and 6 hours after the dose of tizanidine. There was no compensatory tachycardic response to the treatment-associated hypotension (Granfors et al, 2004).

c) In a retrospective case series review of patients treated with tizanidine (n=913), tizanidine-related adverse events occurred with significantly greater frequency in patients treated concurrently with fluvoxamine and tizanidine (n=23) when compared with tizanidine monotherapy (26.1% (6/23) versus 5.3%, respectively; p less than 0.0001). Bradycardia occurred in the 6 affected patients, with dizziness, hypothermia, drowsiness, hypotension, and impaired speech occurring in order of descending frequency (Momo et al, 2004).

3.5.1.FR Tolmetin

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.FS Toloxatone

1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)
2) Summary: Concurrent administration or overlapping therapy with fluvoxamine and a monoamine oxidase (MAO) inhibitor may result in CNS toxicity or serotonin syndrome, a hyperserotonergic state characterized by symptoms such as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. Serious, even fatal, reactions have been reported with concomitant use of selective serotonin reuptake inhibitors and MAO inhibitors (Prod Info Luvox(R), 1997n; Lappin & Auchincloss, 1994k; Graber et al, 1994k; Suchowersky & de Vries, 1990k). As a reversible and selective monoamine oxidase inhibitor, toloxatone may not potentiate the effects of selective serotonin reuptake inhibitors to the same frequency, extent, and duration observed with other MAOIs. However, until further studies confirm the safety and efficacy of this combined therapy, caution should be used.
3) Severity: major
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Concurrent use of fluvoxamine and a MAO inhibitor should be avoided. Wait at least two weeks after discontinuing an MAO inhibitor before initiating therapy with fluvoxamine. Wait at least two weeks after discontinuing fluvoxamine before initiating therapy with a MAO inhibitor.
7) Probable Mechanism: serotonin reuptake inhibition
8) Literature Reports
a) Concomitant use of serotonin specific reuptake inhibitors and monoamine oxidase inhibitors can produce a toxic reaction known as serotonin syndrome (Sternbach, 1991h). Serotonin syndrome is a condition of serotonergic hyperstimulation and manifests as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. If the syndrome is not recognized and correctly treated, death can result.
b) A 26-year old woman who had been taking isocarboxazid for eight weeks stopped taking the drug for 11 days before beginning therapy with sertraline. After a single 100 mg sertraline dose, the patient became restless and developed leg twitches. The patients was later admitted to the emergency room with diaphoresis, tachycardia, hyperreflexia, and various neuromuscular disturbances. After treatment with diazepam and propranolol the patient did not improve. The patient was then given two 4 mg doses of cyproheptadine an hour apart, with notable improvement in symptoms after the second dose (Lappin & Auchincloss, 1994j).
c) A drug interaction occurred in a 61-year old woman whose regimen of sertraline 100 mg twice daily was added to a regimen of lithium, phenelzine, thioridazine, and doxepin. Three hours after taking the first sertraline dose, the patient was found in a semicomatose state, with elevated body temperature, increased pulse, increased respiration rate, and a blood pressure of 140/110 mm Hg. After transportation to the hospital, the patient was misdiagnosed as having neuroleptic malignant syndrome (NMS) which was later changed to serotonin syndrome due to a reaction between sertraline and phenelzine. The authors suggest that monoamine oxidase inhibitor (MAOI) therapy should be discontinued for at least two weeks before initiation of therapy with a selective serotonin reuptake inhibitor (SSRI) and that before starting a MAOI, SSRI therapy should be discontinued for at least five half-lives of the parent drug and any active metabolites (Graber et al, 1994j).
d) Two cases reports suggested a possible interaction between fluoxetine and selegiline (Suchowersky

& de Vries, 1990j). One case involved a first episode of mania being observed approximately one month after adding selegiline to fluoxetine therapy. The patient improved two months after both drugs were discontinued, and no further details were provided. The second case involved diaphoresis, vasoconstriction, and cyanosis of the hands which occurred in close temporal relationship to adding fluoxetine and selegiline. Both drugs were discontinued, with relatively quick resolution of symptoms. Rechallenge with fluoxetine alone occurred without incident.

3.5.1.FT Tramadol

1) Interaction Effect: an increased risk of seizures and serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)
2) Summary: Seizures and serotonin syndrome have been reported in patients using tramadol. The risk of seizures and serotonin syndrome may be enhanced when fluvoxamine and tramadol therapy are combined (Prod Info Ultram(R), 2001).
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Caution should be used if tramadol is to be administered to patients receiving concomitant fluvoxamine therapy. If possible, avoid this combination, especially in patients with underlying conditions that might predispose to seizures. Observe the patient closely for signs and symptoms of serotonin syndrome.
7) Probable Mechanism: increased concentration of serotonin in the nervous system and periphery

3.5.1.FU Tranylcypromine

1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)
2) Summary: Concurrent administration or overlapping therapy with fluvoxamine and a monoamine oxidase (MAO) inhibitor may result in CNS toxicity or serotonin syndrome, a hyperserotonergic state characterized by symptoms such as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. Serious, even fatal, reactions have been reported with concomitant use of serotonin specific reuptake inhibitors and MAO inhibitors (Prod Info Luvox(R), 1997a; Lappin & Auchincloss, 1994a; Graber et al, 1994a; Suchowersky & de Vries, 1990a). Concomitant use is not recommended.
3) Severity: major
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Concurrent use of a selective serotonin reuptake inhibitors, such as fluvoxamine, and tranylcypromine is contraindicated. Wait at least two weeks after discontinuing an MAO inhibitor before initiating therapy with fluvoxamine. Wait at least two weeks after discontinuing fluvoxamine before initiating therapy with a MAO inhibitor.
7) Probable Mechanism: serotonin reuptake inhibition
8) Literature Reports

a) Concomitant use of serotonin specific reuptake inhibitors and monoamine oxidase inhibitors can produce a toxic reaction known as serotonin syndrome (Sternbach, 1991). Serotonin syndrome is a condition of serotonergic hyperstimulation and manifests as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. If the syndrome is not recognized and correctly treated, death can result.

b) A 26-year old woman who had been taking isocarboxazid for eight weeks stopped taking the drug for 11 days before beginning therapy with sertraline. After a single 100 mg sertraline dose, the patient became restless and developed leg twitches. The patients was later admitted to the emergency room with diaphoresis, tachycardia, hyperreflexia, and various neuromuscular disturbances. After treatment with diazepam and propranolol the patient did not improve. The patient was then given two 4 mg doses of cyproheptadine an hour apart, with notable improvement in symptoms after the second dose (Lappin & Auchincloss, 1994).

c) A drug interaction occurred in a 61-year old woman whose regimen of sertraline 100 mg twice daily was added to a regimen of lithium, phenelzine, thioridazine, and doxepin. Three hours after taking the first sertraline dose, the patient was found in a semicomatose state, with elevated body temperature, increased pulse, increased respiration rate, and a blood pressure of 140/110 mm Hg. After transportation to the hospital, the patient was misdiagnosed as having neuroleptic malignant syndrome (NMS) which was later changed to serotonin syndrome due to a reaction between sertraline and phenelzine. The authors suggest that monoamine oxidase inhibitor (MAOI) therapy should be discontinued for at least two weeks before initiation of therapy with a selective serotonin reuptake inhibitor (SSRI) and that before starting a MAOI, SSRI therapy should be discontinued for at least 5 half-lives of the parent drug and any active metabolites (Graber et al, 1994).

d) Two cases reports suggested a possible interaction between fluoxetine and selegiline (Suchowersky & de Vries, 1990). One case involved a first episode of mania being observed approximately one month after adding selegiline to fluoxetine therapy. The patient improved two months after both drugs were discontinued, and no further details were provided. The second case involved diaphoresis, vasoconstriction, and cyanosis of the hands which occurred in close temporal relationship to adding fluoxetine and selegiline. Both drugs were discontinued, with relatively quick resolution of symptoms.

Rechallenge with fluoxetine alone occurred without incident.

3.5.1.FV Triazolam

1) Interaction Effect: elevated serum triazolam concentrations
2) Summary: Fluvoxamine coadministration (100 mg daily) with alprazolam 1 mg four times daily resulted in a 2-fold increase in alprazolam steady-state plasma concentrations, AUC, Cmax, and half-life. Elevated plasma levels of alprazolam were associated with impaired psychomotor performance and memory. This suggests that fluvoxamine is a potent inhibitor of cytochrome P450 3A4 enzymes, which are responsible for alprazolam metabolism. Because triazolam also relies on CYP3A4 for metabolism, a similar interaction with fluvoxamine seems likely (Prod Info Luvox(R), 1997d).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When triazolam and fluvoxamine are coadministered, monitor patients for benzodiazepine toxicity (sedation, lethargy, slurred speech). Triazolam doses may need to be reduced, or consider switching to a benzodiazepine eliminated by glucuronidation (eg, lorazepam, oxazepam, temazepam).
7) Probable Mechanism: inhibition of triazolam metabolism and clearance due to cytochrome P450 3A4 enzyme inhibition

3.5.1.FW Tryptophan

1) Interaction Effect: severe vomiting
2) Summary: Tryptophan enhances the serotonergic effect of fluvoxamine and has been reported to cause severe vomiting. Use the combination cautiously (Prod Info Luvox(R), 1997i).
3) Severity: moderate
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Concurrent use of fluvoxamine and tryptophan should be avoided.
7) Probable Mechanism: enhanced serotonergic effects

3.5.1.FX Valdecoxib

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.FY Warfarin

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info LUVOX(R) CR extended-release oral capsules, 2008). Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with warfarin. In patients receiving warfarin and fluvoxamine concomitantly for 2 weeks, warfarin plasma concentrations increased by 98% and prothrombin times were prolonged. Fluvoxamine appears to inhibit several cytochrome P450 isoenzymes which may include 1A2 and 2C9 isozymes, which are responsible for warfarin metabolism (Schalekamp et al, 2008; Prod Info LUVOX(R) CR extended-release oral capsules, 2008).

3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When fluvoxamine and an anticoagulant are given concurrently, monitor patient for signs of increased bleeding. Patients who are taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, when fluvoxamine therapy is initiated or discontinued. Periodically reassess the prothrombin time ratio and INR in patients receiving fluvoxamine and anticoagulant therapy (Prod Info LUVOX(R) CR extended-release oral capsules, 2008).
7) Probable Mechanism: unknown
8) Literature Reports

a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bleeding (hospital admission due to bleeding) in patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patients with a mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients experienced 11 bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experiencing bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model (Wallerstedt et al, 2009).

b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5), however, the rate of gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).

c) A hospitalized 80-year-old female was started on intravenous heparin and oral warfarin therapy due to an embolic stroke secondary to atrial fibrillation and mitral stenosis. Her warfarin dose was maintained at 1 mg daily, with her INR between 2.5 and 3. Fluvoxamine 25 mg daily was started for depression, and her warfarin dose was increased to 1.5 mg daily 3 days later due to worsening of the left hemiparesis. Three days later, her INR was 9.96, and a repeat INR to rule out laboratory error was 11.3. Warfarin was discontinued, fresh frozen plasma was given, and fluvoxamine was discontinued. Six days later, warfarin was again started at 1 mg daily, and the INR increased over 4 days to 11.8. The elevated INR was attributed to the persisting effect of fluvoxamine. She was eventually stabilized on warfarin 1 mg daily with INR values between 2 and 2.5 (Yap & Low, 1999).

3.5.1.FZ Xemilofiban

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and antiplatelet agents has been associated with an increased risk of bleeding. Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an antiplatelet agent are given concurrently, monitor patient for signs of increased bleeding (Prod Info PAXIL(R) oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008)
7) Probable Mechanism: unknown

3.5.1.GA Zolmitriptan

1) Interaction Effect: an increased risk of serotonin syndrome
2) Summary: There have been case reports of weakness, hyperreflexia, and incoordination following concomitant use of sumatriptan, a 5-hydroxytryptamine-1 (5HT-1) agonist, and a serotonin specific reuptake inhibitor (SSRI) (Prod Info Imitrex(R), 1998a; Prod Info Zomig(TM), 1997). Because zolmitriptan is a 5HT 1B/1D agonist, a similar interaction between SSRIs and zolmitriptan may occur (Prod Info Zomig(TM), 1997). Concurrent use of zolmitriptan and an SSRI may result in serotonin syndrome which may be life-threatening. Symptoms of serotonin syndrome may include restlessness, hallucinations, loss of coordination, fast heart beat, rapid changes in blood pressure, increased body temperature, overreactive reflexes,

nausea, vomiting, and diarrhea. Clinicians should be aware that triptans may be commonly used intermittently and that either the triptan or the SSRI may be prescribed by a different physician. Discuss the risks of serotonin syndrome with patients who are prescribed this combination and monitor them closely for symptoms of serotonin syndrome (US Food and Drug Administration, 2006).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Coadministration of a triptan, such as zolmitriptan, and an SSRI may result in a life-threatening condition called serotonin syndrome. Be aware that triptans may be commonly used intermittently and that either the triptan or the SSRI may be prescribed by a different physician. If these agents are used together, discuss the risks of serotonin syndrome with the patient and monitor closely for symptoms of serotonin syndrome (restlessness, hyperthermia, hyperreflexia, incoordination).
7) Probable Mechanism: additive pharmacologic effects resulting in excessive serotonergic stimulation
8) Literature Reports
a) The pharmacokinetics of a single 10 mg dose of zolmitriptan were not altered by four weeks of fluoxetine 20 mg daily pretreatment in healthy volunteers. The effects of zolmitriptan on blood pressure were also not changed by fluoxetine therapy (Prod Info Zomig(R), 2002).

3.5.1.GB Zomepirac
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.2 Drug-Food Combinations

3.5.2.A Grapefruit Juice
1) Interaction Effect: increased fluvoxamine exposure
2) Summary: Grapefruit juice significantly increased fluvoxamine exposure when co-administered to healthy volunteers (n=10), in a randomized, placebo-controlled crossover study. Compared with baseline, grapefruit juice produced a 1.3-fold increase in the serum mean concentration of fluvoxamine, by 33 nanograms/milliliter (ng/mL; plus/minus 10 to 44 ng/mL) (p=0.049) and increased the fluvoxamine mean area under the concentration-time curve from 550 ng hours/mL to 881 ng hours/mL (p=0.014) (Hori et al, 2003a).
3) Severity: minor
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Counsel patients to avoid grapefruit juice while taking fluvoxamine. Orange juice may be substituted as it provides the same basic nutrients but is not known to inhibit drug metabolism.
7) Probable Mechanism: inhibition of intestinal CYP3A4 and P-glycoprotein-mediated fluvoxamine metabolism
8) Literature Reports
a) Grapefruit juice significantly increased exposure to fluvoxamine, when co-administered to healthy volunteers. In a randomized, crossover study, healthy men (n=10) received 250 milliliters of either regular-strength grapefruit juice or water 3 times daily for 5 days. On day 6, oral fluvoxamine 75 milligrams was given to each subject along with the grapefruit juice or water regimen. Serial blood sampling then occurred over the next 24 hours. After 2 weeks, subjects crossed over to the opposing study arm. Compared with baseline, grapefruit juice produced a 1.3-fold increase in the mean serum

concentration of fluvoxamine, by 33 nanograms/milliliter (ng/mL; plus/minus 10 to 44 ng/mL) (p=0.049). In 8 subjects, the fluvoxamine mean area under the concentration-time curve increased from 550 ng hours/mL to 881 ng hours/mL (p=0.014); additionally, 2 subjects showed a rebound increase in fluvoxamine plasma concentration at 24 hours after fluvoxamine administration (Hori et al, 2003).

3.5.4 Drug-Tobacco Combinations

3.5.4.A Tobacco

1) Interaction Effect: increased fluvoxamine metabolism
2) Summary: In comparison to nonsmokers, fluvoxamine metabolism is increased by 25% in smokers (Prod Info Luvox(R), 1997ab).
3) Severity: minor
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor fluvoxamine efficacy in patients who smoke. Larger doses of fluvoxamine may be required.
7) Probable Mechanism: hepatic enzyme induction

4.0 Clinical Applications

Monitoring Parameters

Patient Instructions

Place In Therapy

Mechanism of Action / Pharmacology

Therapeutic Uses

Comparative Efficacy / Evaluation With Other Therapies

4.1 Monitoring Parameters

A) Fluvoxamine Maleate

1) Therapeutic

a) Decreases in depressive or obsessive-compulsive behavior by both subjective and objective assessments.

2) Toxic

a) Laboratory Parameters

1) Regularly monitor serum electrolytes, especially sodium, blood urea nitrogen, and serum creatinine in the following patients or disease states (Prod Info fluvoxamine maleate oral tablets, 2005):

elderly
concomitant diuretics
syndrome of inappropriate secretion of antidiuretic hormone
displacement syndromes
edematous states
adrenal disease
fluid depleted patients

b) Physical Findings

1) Monitor patients receiving antidepressants for worsening of depression, suicidality, or unusual changes in behavior, especially at the initiation of therapy or when the dose increases or decreases. Such monitoring should include at least weekly face-to-face contact with patients or their family members or caregivers during the initial 4 weeks of treatment, then visits every other week for the next 4 weeks, then at 12 weeks, and then as clinically indicated beyond 12 weeks. Families and caregivers should be advised of the need for close observation (i.e., daily observation) of patients and communication with the prescriber (Prod Info fluvoxamine maleate oral tablets, 2005).

2) Patients who experience symptoms of anxiety, agitation, panic attacks, insomnia, irritability, hostility, impulsivity, akathisia, hypomania, or mania may be at an increased risk for worsening depression or suicidality. If these symptoms are observed, therapy should be re-evaluated and it may be necessary to discontinue medications when symptoms are severe, sudden in onset, or were not part of the patient's initial symptoms (Prod Info fluvoxamine maleate oral tablets, 2005).

3) Nausea and/or vomiting seen early during fluvoxamine therapy may be alleviated by reducing the dose and then gradually increasing the dose to therapeutic effect.

4.2 Patient Instructions

A) Fluvoxamine (By mouth)

Fluvoxamine

Treats symptoms of obsessive compulsive disorder (OCD) and social anxiety disorder (social phobia).

When This Medicine Should Not Be Used:
You should not use this medicine if you have had an allergic reaction to fluvoxamine. You should not use fluvoxamine if you are also using alosetron (Lotronex®), thioridazine (Mellaril®), terfenadine (Seldane®), astemizole (Hismanal®), cisapride (Propulsid®), pimozide (Orap®), or tizanidine (Zanaflex®). Make sure your doctor knows if you have taken an MAO inhibitor (such as isocarboxazid, phenelzine, selegiline, tranylcypromine, Eldepryl®, Nardil®, Marplan®, or Parnate®) within the past 2 weeks.

How to Use This Medicine:
Long Acting Capsule, Tablet

Your doctor will tell you how much of this medicine to use and how often. Your dose may need to be changed several times in order to find out what works best for you. Do not use more medicine or use it more often than your doctor tells you to.
You may take this medicine with or without food.
Take this medicine at bedtime, unless your doctor tells you otherwise.
Do not use this medicine for longer than 10 weeks unless your doctor tells you otherwise.
Swallow the extended-release capsule whole. Do not crush, break, or chew it.
This medicine should come with a Medication Guide. Read and follow these instructions carefully. Ask your doctor or pharmacist if you have any questions. Ask your pharmacist for the Medication Guide if you do not have one. Your doctor might ask you to sign some forms to show that you understand this information.

If a Dose is Missed:

If you miss a dose or forget to use your medicine, use it as soon as you can. If it is almost time for your next dose, wait until then to use the medicine and skip the missed dose. Do not use extra medicine to make up for a missed dose.

How to Store and Dispose of This Medicine:

Store the medicine in a closed container at room temperature, away from heat, moisture, and direct light.
Ask your pharmacist, doctor, or health caregiver about the best way to dispose of any outdated medicine or medicine no longer needed.
Keep all medicine away from children and never share your medicine with anyone.

Drugs and Foods to Avoid:
Ask your doctor or pharmacist before using any other medicine, including over-the-counter medicines, vitamins, and herbal products.

There are many other drugs that can interact with fluvoxamine. Make sure your doctor knows about ALL other medicines you are using, especially medicines to treat depression or mental illness.
Tell your your doctor if you are using blood thinners (warfarin or Coumadin®), diuretics (water pills), or pain or arthritis medicine (sometimes called “NSAIDs”) such as aspirin, ibuprofen, Aleve®, or Motrin®. Tell your doctor if you use a tranquilizer or sedative such as alprazolam (Xanax®), diazepam (Valium®), midazolam (Versed®), ramelteon (Rozerem®), or triazolam (Halcion®).
Your doctor should know if you use blood pressure medicine (such as atenolol, metoprolol, propranolol, Corgard®, Inderal®, Lopressor®, Toprol®, or Tenormin®) or medicine to treat headaches (such as eletriptan, sumatriptan, Imitrex®, or Relpax®).
Tell your doctor if you also use carbamazepine (Tegretol®), clozapine (Clozaril®), diltiazem (Cardizem®), linezolid (Zyvox®), lithium (Eskalith®), methadone (Dolophine®), mexiletine (Mexitil®), quinidine, omeprazole (Prilosec®), phenytoin (Dilantin®), St. John's wort, Tacrine (Cognex®), theophylline (Theo-Dur®), tramadol (Ultram®), or tryptophan supplements.
Do not drink alcohol while you are using this medicine.

Warnings While Using This Medicine:

Make sure your doctor knows if you are pregnant or breastfeeding, or if you have diabetes, liver disease, heart disease or a recent heart attack, epilepsy or seizures, bleeding problems, or a history of mania. Tell your doctor if you smoke.
For some children, teenagers, and young adults, this medicine can increase thoughts of suicide. Tell your doctor or your child's doctor right away if you or your child start to feel more depressed and have thoughts about hurting yourselves. Report any unusual thoughts or behaviors that trouble you or your child, especially if they are new or are getting worse quickly. Make sure the doctor knows if you or your child have trouble sleeping, get upset easily, have a big increase in energy, or start to act reckless. Also tell the doctor if you or your child have sudden or strong feelings, such as feeling nervous, angry, restless, violent, or scared. Let the doctor know if you, your child, or anyone in your family has bipolar disorder (manic-depressive) or has tried to commit suicide.
While you are using this medicine, be sure to keep all appointments with your caregiver or mental health

counselor. It is very important that your caregivers observe you for changes in your mental status or behavior.
Fluvoxamine should not be used to treat depression. It should not be given to a child unless that child has been diagnosed with OCD.
This medicine may make you dizzy or drowsy. Avoid driving, using machines, or doing anything else that could be dangerous if you are not alert.
Do not stop using this medicine suddenly without asking your doctor. You may need to slowly decrease your dose before stopping it completely.

Possible Side Effects While Using This Medicine:
Call your doctor right away if you notice any of these side effects:
Allergic reaction: Itching or hives, swelling in your face or hands, swelling or tingling in your mouth or throat, chest tightness, trouble breathing.
Anxiety, agitation, aggression, trouble sleeping, or panic attack.
Blurred vision, shallow breathing, trouble standing or walking.
Change in how much or how often you urinate.
Chest pain.
Confusion, extreme weakness, muscle twitching.
Fast, slow, or uneven heartbeat.
Feeling irritable, nervous, or shaky.
Fever, chills, cough, sore throat, and body aches.
Lightheadedness or fainting.
Numbness, tingling, or burning pain in your hands, arms, legs, or feet.
Seizures or tremors.
Sudden and severe stomach pain, nausea, or vomiting.
Swelling in your hands, feet, or ankles.
Unusual behavior, thoughts of hurting yourself or others.
Unusual bleeding or bruising.
Yellowing of your skin or the whites of your eyes.

If you notice these less serious side effects, talk with your doctor:
Diarrhea, constipation, stomach upset, or loss of appetite.
Dry mouth.
Headache or dizziness.
Mood or behavior changes after you stop using the medicine.
Muscle pain.
Pain during monthly periods.
Problems having sex.
Prolonged erection of the penis.
Skin rash.
Sleepiness.
Sweating more than usual.
Weakness.

If you notice other side effects that you think are caused by this medicine, tell your doctor.

4.3 Place In Therapy

A) Fluvoxamine Maleate

1) Obsessive-compulsive Disorder

a) The extended-release formulation of fluvoxamine maleate is indicated for the treatment of obsessions and compulsions in adult patients with obsessive compulsive disorder (OCD) (Prod Info LUVOX(R) CR extended-release oral capsules, 2008), and the immediate-release formulation of fluvoxamine maleate is indicated for the treatment of obsessions and compulsions in patients with OCD aged 8 years and older (Prod Info LUVOX(R) oral tablets, 2007).

b) Treatment with extended-release fluvoxamine maleate at once-daily doses of 100 to 300 milligrams was safe and led to clinical improvement in adult patients with obsessive-compulsive disorder compared to placebo in a 12-week, multicenter, randomized, double-blind study (n=253) (Hollander et al, 2003).

c) A 10-week study demonstrated that immediate-release fluvoxamine and behavior therapy were more efficacious for treating obsessive compulsive disorder (OCD) compared to placebo and behavior therapy (Hohagen et al, 1998).

d) Immediate-release fluvoxamine was significantly more effective than placebo in children (8 years or older) and adolescents with obsessive compulsive disorder (OCD) in a 10-week, double-blind study in 120 children with at least a 6-month history of OCD (Riddle, 1996).

2) Social Anxiety Disorder

a) Extended-release fluvoxamine maleate is indicated for social anxiety disorder, also known as social phobia (Prod Info LUVOX(R) CR extended-release oral capsules, 2008).

b) In a randomized, double-blind, multicenter, placebo-controlled study (n=300), patients with generalized social anxiety disorder (GSAD) who received fluvoxamine extended-release (ER) demonstrated a

significantly greater reduction in the mean Liebowitz Social Anxiety Scale (LSAS) total score from baseline compared with patients who received placebo (Westenberg et al, 2004), with a trend towards continued clinical benefit with fluvoxamine ER compared to placebo in a 12-week double-blind extension phase of this study (Stein et al, 2003).

3) Depression

a) All of the selective serotonin reuptake inhibitors (SSRIs) are effective for treating depression, although selected characteristics of each agent may offer greater benefit in some patients. Fluvoxamine does not have any major therapeutic benefits over other SSRIs; however, discontinuation of therapy among patients treated with fluvoxamine appeared higher than for other SSRIs during clinical trials. Gastrointestinal symptoms and drowsiness/sedation were more common especially early in therapy than with other SSRIs. Ultimately, the selection of an SSRI is dependent on clinical judgement and response of patients to previous therapy (Edwards & Anderson, 1999).

b) Data suggest that a trial of a second serotonin reuptake inhibitor (SSRI) is a viable clinical alternative in depressed patients who have failed to respond to an adequate trial of the first SSRI used. In a retrospective review of 55 patients who had failed to respond to at least five weeks of therapy with either fluoxetine, sertraline, fluvoxamine, or paroxetine (all at therapeutic dosages), 51% responded to a trial of an alternative agent. The choice of the second agent was based on clinician preference; no difference between response rates of the different drugs was noted (Joffe et al, 1996).

4.4 Mechanism of Action / Pharmacology

A) Fluvoxamine Maleate

1) Mechanism of Action

a) Fluvoxamine maleate is a potent selective serotonin (5-HT) reuptake inhibitor (SSRI) belonging to the 2-aminoethyl oxime ethers of aralkylketones series and is unrelated to other SSRIs and clomipramine. In obsessive compulsive disorder the clinical effect is presumed to be from its specific inhibition of serotonin reuptake in brain neurons. In-vitro studies have shown that fluvoxamine maleate has no significant affinity for histaminergic, alpha or beta adrenergic, muscarinic, or dopaminergic receptors (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007).

2) Review Articles

a) Fluvoxamine is a compound in the series of 2-aminoethyloxime ethers of aralkylketones. The drug acts as an antidepressant and has no structural similarities to tricyclic antidepressants. Fluvoxamine is a potent selective inhibitor of presynaptic serotonin (5-hydroxytryptamine or 5-HT) reuptake (Claassen et al, 1977). Following a single dose of fluvoxamine, the serotonin turnover in the rat forebrain was reduced (Claassen et al, 1977). Also, in the raphe nuclei the intraneuronal and extraneuronal concentrations of serotonin decreased and increased, respectively (Constantinidis et al, 1981). In vitro and in vivo experiments demonstrated that fluvoxamine fails to facilitate noradrenergic neurotransmission, similar to other specific inhibitors of serotonin uptake (Bradford, 1983; Claassen, 1983). Unlike the tricyclic antidepressants, fluvoxamine demonstrates a very low in vitro affinity for alpha-1, alpha-2, beta-1, dopamine-2, histamine-1, serotonin-1, serotonin-2 or muscarinic receptors (Richelson & Nelson, 1984; Benfield & Ward, 1986). In vitro and in vivo studies have not demonstrated any monoamine oxidase inhibitor activity (Lapierre et al, 1983; Benfield & Ward, 1986).

b) The exact relationship of serotonin uptake inhibition and its effects on depression are not known. It is proposed that fluvoxamine's antidepressant activity is initiated by enhanced serotoninergic input to other neuronal systems in the brain. This may lead to primary and secondary changes in receptors and rates of firing and rates of release of neurotransmitters which may result in remission of depressive symptoms (Fuller & Wong, 1987).

c) The effects of treatment with fluvoxamine on platelet and plasma serotonin were studied in 11 drug-free patients with major depression (Celeda et al, 1992). Single-dose fluvoxamine (50 mg) was without effect on serotonin, whereas treatment with 100 to 150 mg/day for 12 weeks reduced both platelet (-89%) and plasma (-60%) serotonin. Patients who responded to the treatment at 6 weeks had significantly lower pretreatment values of platelet serotonin than the rest. This suggests that "low serotonin" patients may respond more rapidly to fluvoxamine. Platelet serotonin and Hamilton Depression Scale scores correlated significantly during treatment. These data demonstrate a marked action of fluvoxamine as a serotonin reuptake inhibitor at therapeutic doses and confirm that this mechanism is relevant for its efficacy as an antidepressant.

d) Fluvoxamine does not have significant effects on central norepinephrine function in human depressed patients, as determined by measurement of MHPG, VMA, NMN, and HVA in urine and NE in plasma (Johnson et al, 1993).

e) The possible relationship between plasma tryptophan (Trp) to large neutral amino acid (LNAA) ratio, thought to reflect brain serotonin (5-HT) formation, was estimated in 47 patients with major depression (unipolar and bipolar) before and after 6 weeks of fluvoxamine. The authors found a significant difference between responders (n=39) and nonresponders (n=8) for Trp/LNAA ratio, whereas no difference emerged between the two groups for the mean plasma steady-state fluvoxamine levels. These data suggest that a specific plasma amino acid profile may be a useful indicator of good clinical response to fluvoxamine (Lucca et al, 1994).

4.5 Therapeutic Uses

4.5.A Fluvoxamine Maleate

Alcoholism

Asperger's disorder

Autistic disorder

Body dysmorphic disorder

Compulsive buying

Compulsive exhibitionism

Compulsive gambling

Depression

Eating disorder

Fibromyalgia

Hypochondriasis

Mixed anxiety and depressive disorder

Myocardial infarction; Prophylaxis

Obsessive-compulsive disorder

Panic disorder

Posttraumatic stress disorder

Premenstrual dysphoric disorder

Prostatic pain

Repetitive self-excoriation

Severe major depression with psychotic features

Social phobia

Stereotypy habit disorder

Trichotillomania

Wernicke-Korsakoff syndrome

4.5.A.1 Alcoholism

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Adverse effects limit the usefulness of fluvoxamine for treating alcoholism (Kranzler et al, 1993).

c) Adult:

1) Adverse effects limit the usefulness of fluvoxamine for treating alcoholism. Results of open-label and placebo-controlled trials of fluvoxamine as an adjunct to relapse prevention psychotherapy in alcoholics were reported (Kranzler et al, 1993). In the open trial, 16 inpatient alcoholics began a 12-week treatment program, with 10 patients dropping out during the first 4 weeks of treatment. In the controlled trial, 8 of 10 patients on fluvoxamine dropped out during the first 4 weeks of treatment, compared with only 1 of 9 patients on placebo. Baseline patient characteristics did not explain the baseline differential attrition in the controlled trial, although the placebo-treated patients are more alcohol-dependent. In both trials, patients taking fluvoxamine complained of a variety of adverse effects, which they identified as the basis for early termination of treatment. The most commonly reported adverse effects were nausea, headache, and sedation. More severe effects included hepatitis (1), depigmenting dermatitis (1), and focal seizures (1).

4.5.A.2 Asperger's disorder

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Pediatric, Evidence is inconclusive
Recommendation: Pediatric, Class IIb
Strength of Evidence: Pediatric, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Fluvoxamine treatment improved sleep and reduced excessive fears and interests in a case report of a boy with Asperger's syndrome (Furusho et al, 2001).

c) Pediatric:

1) Fluvoxamine treatment improved sleep and reduced excessive fears and interests of an 8-year-old boy with Asperger's syndrome, a pervasive developmental disorder with similarities to autism. In addition to poor sleep, the boy showed an inability to communicate with school classmates and teachers and displayed anxiety about remembered unpleasant occurrences. Although language development was normal, he sometimes spoke in a peculiar voice. He was given fluvoxamine 25 milligrams twice daily (after breakfast and supper). Within 4 weeks, his excessive fears and interests were reduced, his sleep improved, hyperactivity declined, and he gained control over unusual behaviors, such as using the peculiar voice. After 7 months of treatment, he continued to have some difficulty communicating with others. No adverse effects were observed (Furusho et al, 2001).

4.5.A.3 Autistic disorder

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

In adults, fluvoxamine was more effective than placebo for improving symptoms of autism (McDougle et al, 1996).

c) Adult:

1) In a 12-week, placebo-controlled trial (n=30), fluvoxamine was more effective than placebo for reducing repetitive thoughts/behavior and aggression and for improving some aspects of social interaction and language usage. Patients assigned to fluvoxamine were initially treated with 50 milligrams (mg) per day which was adjusted to a maximum of 300 mg daily over 3 weeks; the dosage was 276 mg versus 283 mg in patients treated with fluvoxamine versus placebo, respectively, at the conclusion of the study. Using the Clinical Global Impression Scale, fluvoxamine was statistically superior to placebo (p less than 0.001); statistically significant differences were also noted for other assessment scales. In addition, 4 of 15 patients treated with fluvoxamine showed clinically significant improvements in social functioning, including full-time employment (n=1), participation in a wedding (n=1), and a move from a group home to a supervised apartment (n=2). Adverse effects were mild and did NOT require treatment discontinuation. Based on the positive results obtained in these adult patients with autism, further study is required in children and adolescents with autism (McDougle et al, 1996).

4.5.A.4 Body dysmorphic disorder

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Fluvoxamine produced a significant response in patients with body dysmorphic disorder in an open-

label study (n=30) (Phillips et al, 2001).

c) Adult:

1) In a 16-week, open-label study, fluvoxamine appeared effective in the treatment of body dysmorphic disorder (BDD). After establishing the diagnosis of BDD, patients (n=30, 21 females) were treated with fluvoxamine 50 milligrams (mg) daily with increases to 150 mg twice daily by day 9, if tolerated. Using an intent-to-treat analysis, it was found that there were statistically significant (p less than 0.001) decreases in the Brown Assessment of Beliefs Scale (BABS), 66%; the Yale-Brown Obsessive Compulsive Scale modified for BDD (BDD-YBOCS), 46.6%; the Hamilton Rating Scale for Depression (HAM-D), 38%; and the Montgomery-Asberg Depression Rating Scale (MADRS), 38%; at study end-point. Additionally, the Clinical Global Impressions Scale (CGI) rated 63% of patients as responders. Five of 7 delusional patients were responders; and response was not related to initial severity of illness. The mean dose of fluvoxamine was 238.3 mg/day (range 50-300 mg/day) and the mean response time was 6.1 weeks (range, 1 to 16 weeks). Only 60% of the patients completed the study (reasons for drop-outs not stated). This preliminary study suggests that fluvoxamine is effective for BDD, but blinded, placebo-controlled studies are needed to determine efficacy (Phillips et al, 2001).

4.5.A.5 Compulsive buying

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Ineffective
Recommendation: Adult, Class III
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Treatment with fluvoxamine did not alter the buying behavior of subjects prone to compulsive buying in a randomized, placebo-controlled trial (n=37) (Ninan et al, 2000).

c) Adult:

1) Results of a prospective, randomized, double-blind, placebo- controlled study demonstrated no benefit with fluvoxamine therapy in the number of shopping episodes, amount of time spent shopping, amount of money spent, or number of items purchased in 37 subjects with compulsive buying disorder. Forty-two subjects entered the study beginning with a 1-week single-blind placebo lead-in. Five subjects who experienced more than a 50% improvement in the Yale-Brown Obsessive Compulsive Scale modified for compulsive buying (YBOCS-CB) scores after this first week were excluded. Seventy-four percent of the 42 enrolled patients were diagnosed with comorbid psychiatric disorders. Subjects were randomized to placebo or daily fluvoxamine 50 milligrams (mg) increased weekly up to 300 mg according to subject response and tolerance. The average dose of fluvoxamine was 215 mg. The most commonly reported adverse events with fluvoxamine therapy were gastrointestinal distress (25%) and insomnia (20%), compared with headache (29%) and sedation (18%) with placebo. Each of the efficacy variables, YBOCS-CB, Global Assessment of Functioning (GAF), and Hamilton Rating Scale for Depression (HAM-D) improved with time for both treatment groups, yet no difference between treatment groups was observed (Ninan et al, 2000).

4.5.A.6 Compulsive exhibitionism

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Fluvoxamine was effective in one case of compulsive exhibitionist behavior (Zohar et al, 1994).

c) Adult:

1) Fluvoxamine was effective in extinguishing inappropriate compulsive exhibitionist behavior in a 36-year-old patient who was persistently masturbating in front of women in public. After 2 weeks of fluvoxamine at a dose of 300 milligrams daily, the behavior and impulses had disappeared completely (Zohar et al, 1994).

4.5.A.7 Compulsive gambling

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

In a small, open study, fluvoxamine reduced pathological gambling (Hollander et al, 1998).

c) Adult:

1) Of 10 patients who completed 8 weeks of fluvoxamine therapy, total abstinence of gambling was

achieved in 7. Sixteen patients began treatment with placebo for 8 weeks but 4 and 2 were terminated due to noncompliance and lack of efficacy, respectively. The remaining patients received fluvoxamine; the mean fluvoxamine dose was 220 milligrams/day at study endpoint. The Yale-Brown scale gambling behavior scores were reduced by 25%, and 7 of 10 patients were considered treatment responders by the clinician-rated Clinical Global Impression scores. While fluvoxamine appeared effective, this study was small, non-blinded, and of short duration; therefore, a randomized, controlled trial is needed to verify the results (Hollander et al, 1998).

4.5.A.8 Depression

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIa
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Fluvoxamine was more effective than placebo during double-blind trials for the treatment of depression (Ottevanger, 1994; Martin et al, 1987a) (Porro et al, 1988).

A single night time dose of fluvoxamine appears to be best tolerated (Siddigui et al, 1985).

c) Adult:

1) Fluvoxamine is effective in the treatment of DELUSIONAL DEPRESSION (Gatti et al, 1996). In a group of 59 patients, 84.2% responded favorably within the six-week study period. The dose of fluvoxamine used was 100 mg daily days 1 through 3; 200 mg daily days 4 through 7; and 300 mg daily from day 8. No other psychotropic drugs were used, except for eight patients who continued to receive maintenance therapy with lithium.

2) Fluvoxamine was effective in the treatment of severely depressed patients in a re-evaluation of a double-blind study of fluvoxamine, imipramine, and placebo in 308 patients (Ottevanger, 1994). Improvement was superior in severely depressed patients to that of moderately depressed patients, which in turn was superior to mildly depressed patients. Anticholinergic side effects were more common for imipramine, while gastrointestinal effects were more frequent with fluvoxamine.

3) Fluvoxamine was safe and effective for treating depression during a 6-week, large-scale, open trial of 5625 depressed patients (Martin et al, 1987a). All patients were started on fluvoxamine 50 to 100 milligrams at night, increasing after the first week, if necessary, to a maximum of 300 milligrams per day. Of the original 5625 patients admitted, 73% completed the study. In 6.4% (358 patients), withdrawal was not considered to be drug related. Other reasons for withdrawal included adverse effects in 16.2% (912 patients) and lack of efficacy in 2.1% (117 patients). The most commonly reported adverse effect was nausea (12.7%), followed by headache (5%), dizziness (4.5%), and somnolence (3.8%).

4) Fluvoxamine produced a more significant reduction in the global score of the Hamilton Rating Scale of Depression than placebo during a 4-week, double-blind study of 41 patients with depression (Porro et al, 1988). Patients randomized to receive fluvoxamine started at doses of 100 milligrams/day and were increased to 150 milligrams/day after 3 days. A significant reduction in the partial scores connected with anxiety and depression was observed in the fluvoxamine-treated patients after 7 days of therapy when compared with baseline scores. This trend became greater during the course of the treatment. Placebo-treated patients demonstrated a reduction in anxiety-related scores during the first 7 days; however, this disappeared over the course of treatment. The most commonly reported adverse effects associated with fluvoxamine therapy were nausea, vomiting, tremor, dry mouth, and increased salivation; however, they were only slightly-to-moderately severe and usually resolved by the end of the study.

5) An uncontrolled, non-randomized study of fluvoxamine 100 milligrams/day in 16 depressed HIV-1-infected patients revealed that fluvoxamine should not be used as first line treatment in this clinical setting. Good efficacy was reported in 6 patients, whereas the other 10 discontinued the drug due to severe adverse effects (acute total insomnia, gastrointestinal disturbance, aggressive and impulsive behavior, and excessive sedation) (Grassi et al, 1995).

4.5.A.9 Eating disorder

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIa
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

In small open-label and larger double-blind, placebo-controlled trials, fluvoxamine has been effective for reducing the number of binge-eating episodes and for bulimia nervosa (Aynso-Gutierrez et al, 1994), (Brambilla et al, 1995a; Hudson et al, 1998).

c) Adult:

1) In a 9-week study, fluvoxamine effectively reduced the frequency of binges in patients with binge-eating disorder. In this double-blind, flexible-dose study (n=85), patients were randomly assigned to

placebo or fluvoxamine 50 milligrams (mg) daily titrated to a maximum dose of 300 mg daily. Fluvoxamine compared to placebo resulted in a significant reduction in frequency of binges (p=0.006), Clinical Global Impression severity scale score (p=0.002), and body mass index (p=0.04). Of the 67 patients who completed 9 weeks of treatment, 15 and 12 were in remission (no binges) or markedly improved (75% or greater improvement) in the fluvoxamine and placebo groups, respectively (p=0.04). Significantly more patients treated with fluvoxamine than placebo discontinued treatment due to adverse effects (p=0.03); however, none of the adverse effects were serious. Of interest, the placebo response was between 42% and 44% which suggests that a conservative approach should be used in offering drug therapy for this disorder (Hudson et al, 1998).

2) A review article discussing BINGE EATING DISORDER found that fluvoxamine was effective in isolated cases and a few small trials (Hudson et al, 1996). A significant reduction in the frequency of binge eating was noted by one investigator in 10 patients who did not self-induce vomiting. This was conducted over an 8 week course. Another investigator found similar reductions in the frequency of binge eating episodes, in addition to a significant overall improvement compared to placebo over a 9-week course. In a case report, fluvoxamine was effective for binge-eating disorder. A 58-year-old female sought treatment for binge-eating 4 episodes per week. She suffered from chronic binges for 18 years. Previous unsuccessful therapy included psychotherapy, and over-the-counter appetite suppressants. Randomized to fluvoxamine 100 milligrams daily, she reported no binge eating episodes by the second week of therapy. She reported only 1 binge episode during the following seven weeks of treatment. Her binge eating relapsed after 2 weeks without fluvoxamine. She was unable to restart fluvoxamine however, as it was not commercially available at the time.

3) Fluvoxamine was effective in the treatment of 20 patients with bulimia nervosa when used in doses of 50 to 150 mg per day for eight weeks (Aynso-Gutierrez et al, 1994). Four patients showed drowsiness and 3 insomnia.

4) In an uncontrolled, non-randomized study, 15 women with bulimia nervosa were administered 4 months of combined cognitive-behavioral and nutritional therapy along with either fluvoxamine 300 milligrams (mg) per day or amineptine 300 mg/day. Bulimic Investigation Test symptoms and gravity improved significantly and equally in both groups, whereas Eating Disorders Inventory scores and depression and anxiety according to the Hamilton Rating Scale for Depression and Anxiety decreased, but not significantly. Body mass index was normal before therapy and did not change during treatment. These preliminary results need to be validated in larger and better designed studies (Brambilla et al, 1995a).

4.5.A.10 Fibromyalgia

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Fluvoxamine may be helpful for patients with fibromyalgia (Nishikai & Akiya, 2003).

c) Adult:

1) Fluvoxamine was equally effective to amitriptyline in reducing pain associated with fibromyalgia. In an open-label, uncontrolled study, 68 Japanese patients with fibromyalgia received either amitriptyline at a mean dose of 20 milligrams (mg)/day or fluvoxamine at a mean dose of 25 mg/day for 4 weeks. Patients evaluated pain relief by means of a visual analog scale and efficacy was defined as a decrease in pain by at least 50%. At 4 weeks, 50% of patients in the amitriptyline group and 41% of patients in the fluvoxamine group reported effective relief of pain (p=NS). Drowsiness was the most commonly reported adverse event with amitriptyline treatment and nausea was most frequently reported with fluvoxamine. The authors hypothesize that because the efficacy of amitriptyline for the treatment of fibromyalgia-related pain has been established in previous, controlled trials and because fluvoxamine showed similar efficacy to amitriptyline in this open-label study; fluvoxamine may be helpful for patients with fibromyalgia (Nishikai & Akiya, 2003).

4.5.A.11 Hypochondriasis

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Fluvoxamine may be beneficial in the treatment of hypochondriasis (Fallon et al, 2003).

c) Adult:

1) The results of one study suggest that fluvoxamine may be a beneficial treatment in reducing symptoms of patients with hypochondriasis. In a small, 12-week, open-label study, patients with at least a moderate hypochondriasis rating on the Heightened Illness Concern Severity Scale (HICSS) received

daily divided doses of fluvoxamine (50 milligrams (mg) initially, increased every 7 days to a maximum dose of 300 mg by the sixth week) for 10 weeks following a 2-week placebo run-in phase. Response was defined as a clinician-rated change in score of "much improved" or "very much improved" on the Clinical Global Impressions (CGI) scale. In the intent-to-treat analysis, 57.1% of patients responded to fluvoxamine treatment. In patients who completed 6 or more weeks of treatment, 72.7% were responders and mean scores on the HICSS were significantly reduced from baseline to endpoint (5 vs 3.64, p=0.001). Fluvoxamine was generally well tolerated. Further, well- controlled studies are needed to substantiate these findings (Fallon et al, 2003).

4.5.A.12 Mixed anxiety and depressive disorder

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Fluvoxamine was effective for treating depression accompanied by an anxiety disorder in a small, open-label study (n=30) (Sonawalla et al, 1999).

c) Adult:

1) Eighteen (60%) of 30 patients achieved a score of 2 or less on the Clinical Global Impressions-Improvement (CGI-I) scale for both anxiety and depression. All patients had major depression with at least 1 co-morbid anxiety disorder. Fluvoxamine was initiated at 50 milligrams (mg)/day and was titrated to 200 mg/day as needed and tolerated; the mean dose was 143 mg/day at 12 weeks (study endpoint). Twenty (67%) and 23 (77%) patients showed a response on the CGI-I depression and CGI-I anxiety scales at endpoint, respectively. Twelve patients withdrew from the study before 12 weeks. This small open study suggests that fluvoxamine is effective for treating depression accompanied by an anxiety disorder, but these results must be confirmed in a controlled clinical trial (Sonawalla et al, 1999).

4.5.A.13 Myocardial infarction; Prophylaxis

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class III
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

SSRIs, including fluvoxamine, may confer a protective effect against first MI (Sauer et al, 2001).

c) Adult:

1) In a case-control study comprised of 653 cases of first myocardial infarction (MI) and 2990 control subjects, results indicated that selective serotonin reuptake inhibitors (SSRIs) may confer a protective effect against first MI. The subjects in this study were smokers, between the ages of 30 to 65 years, with a first MI hospitalized between September 1995 and December 1997. The four SSRIs investigated in this study were fluoxetine, fluvoxamine, paroxetine, and sertraline; doses taken by participants were not stated. The odds ratio of patients who were taking SSRIs having a first MI compared to controls (after adjustment for potential confounders) was 0.35 (95% CI 0.18, 0.68; p less than 0.01). The authors suggested that this effect was possibly attributable to an inhibitory effect on serotonin-medicated platelet activation or amelioration of other factors associated with increased risk for MI in depression (Sauer et al, 2001).

4.5.A.14 Obsessive-compulsive disorder

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes; Pediatric, yes (8 years and older (immediate-release formulation only))
Efficacy: Adult, Effective; Pediatric, Effective
Recommendation: Adult, Class IIa; Pediatric, Class IIa
Strength of Evidence: Adult, Category B; Pediatric, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

The extended-release formulation of fluvoxamine maleate is indicated for the treatment of obsessions and compulsions in adult patients with obsessive compulsive disorder (OCD) (Prod Info LUVOX(R) CR extended-release oral capsules, 2008), and the immediate-release formulation of fluvoxamine maleate is indicated for the treatment of obsessions and compulsions in patients with OCD aged 8 years and older (Prod Info LUVOX(R) oral tablets, 2007).

A 10-week study demonstrated that immediate-release fluvoxamine and behavior therapy were more efficacious for treating obsessive compulsive disorder compared to placebo and behavior therapy (Hohagen et al, 1998).

Immediate-release fluvoxamine was significantly more effective than placebo in children (8 years or

older) and adolescents with obsessive compulsive disorder (OCD) in a 10-week, double-blind study in 120 children with at least a 6-month history of OCD (Riddle, 1996).
Treatment with extended-release fluvoxamine maleate at once-daily doses of 100 to 300 milligrams was safe and led to clinical improvement in adult patients with obsessive-compulsive disorder compared to placebo in a 12-week, multicenter, randomized, double-blind study (n=253) (Hollander et al, 2003).

c) Adult:

1) General Information

a) Of the selective serotonin reuptake inhibitors (SSRIs) (ie, fluoxetine, sertraline, paroxetine, fluvoxamine) with U.S. Food and Drug Administration approval for treating OCD, all are effective. Limited clinical studies also suggest that the SSRIs are comparable to clomipramine; however, results of a meta-analysis found that clomipramine may be more effective than the SSRIs (Flament & Bisserbe, 1997; Leonard, 1997). Selection of initial treatment is often based on the side effect profile of the individual drug; in general, the SSRIs are tolerated better than clomipramine (Leonard, 1997). Early studies used near maximal doses of an SSRI which resulted in a high incidence of adverse effects; however, initial low doses with gradual dose adjustment result in a good response in some patients and better tolerance in most (Leonard, 1997). While the optimal duration of treatment has NOT been defined, most patients require long-term treatment. A few small studies have shown relapse rates between 65% and 90% when pharmacologic treatment was stopped (Rasmussen & Eisen, 1997). Patients who do NOT respond to 10 to 12 weeks of maximum doses of an SSRI and/or behavioral therapy are considered refractory to treatment. In about 20% of this group, a trial of a second SSRI will be effective. In the remaining patients, augmentation therapy with haloperidol or clonazepam may be beneficial (Rasmussen & Eisen, 1997).

2) Clinical Trials

a) Immediate-release Formulation

1) Fluvoxamine and behavior therapy are efficacious for treating obsessive compulsive disorder (OCD). Patients were randomized to receive fluvoxamine 300 milligrams (mg) daily, initiated at doses of 50 mg daily and titrated as tolerated in 50 mg increments weekly, and behavior therapy (n=24) or placebo and behavior therapy (n=25). After 10 weeks of treatment, both groups showed significant improvements in scores on the Structured Clinical Interview (SCID), Yale-Brown Obsessive-Compulsive Scale (Y-BOCS), Hamilton Depression Scale (HAM-D), Clinical Anxiety Scale (CAS), Global Assessment Scale (GAS), and the Clinical Global Improvement Scale (CGIS). Fluvoxamine and behavioral therapy were significantly more effective in treating obsessions than placebo and behavior therapy, as defined by improvements in total Y-BOCS scores and Y-BOCS obsession scores. Treatment with fluvoxamine and behavior therapy also showed a significantly greater improvement than placebo and behavior therapy in patients with secondary depression. Treatment with fluvoxamine and behavior therapy may be advantageous in patients whose obsessions, not compulsions, dictate their clinical profile and for patients that have depression secondary to OCD (Hohagen et al, 1998).

2) Data from small, short-term or non-blinded studies indicate that patients with obsessive-compulsive disorder (OCD) may tolerate substantial reductions in fluvoxamine dosage without a relapse (Mundo et al, 1997; Ravizza et al, 1996). In a double-blind study, patients with stable OCD tolerated reductions in the dosage of fluvoxamine or clomipramine of 33% to 67% without relapses for up to 102 days. Thirty patients were randomly assigned to group I (same dosage), group II (33% to 40% reduction in dosage), or group III (60% to 67% reduction in dosage). Five patients relapsed during the study; 3 were in the control group, and 1 each was in groups II and III. No statistical difference was identified between treatment groups for the cumulative number of patients who completed the study without a relapse. Larger studies are needed to confirm these results (Mundo et al, 1997).

3) Long-term outcome at 18 months posttreatment favored exposure therapy with or without fluvoxamine for treating OCD. Drug effects did not last while exposure therapy did. At 18 months, a smaller number of exposure therapy patients were receiving antidepressant treatment, but all three groups showed comparable improvement. Sixty outpatients with OCD treated for six months with either 1) fluvoxamine and antiexposure therapy (F), 2) fluvoxamine and exposure therapy (FE), or 3) placebo and exposure therapy (PE) (20 patients per group) were followed up one year after these treatments were stopped to determine their clinical status. Fluvoxamine dosage ranged up to 300 mg per day, and the drug was taken for 24 weeks. It was gradually tapered from week 24 to 28. Antiexposure therapy was a mild form of behavior therapy using relaxation instead of confrontation with feared situations. Thirty-three of 60 patients were rated at 18 months. FE and F produced a greater reduction in rituals at 8 weeks and in depression at 24 weeks than did PE, but this difference disappeared at 12 months (Cottraux et al, 1993).

4) OCD patients with co-morbid chronic tic disorder may require addition of a neuroleptic to fluvoxamine for effective symptom reduction (McDougle et al, 1994). A 25-year-old male patient with a history of Tourette's syndrome was treated with fluvoxamine for OCD symptoms. Fluvoxamine worsened tics, led to coprolalia (use of feces-related foul language) and did not help the OCD. The addition of pimozide dramatically reduced both the OCD and Tourette's

symptoms. Double-blind sequential discontinuation of fluvoxamine and pimozide confirmed that pimozide alone reduced only tics and the combination of fluvoxamine and pimozide was required for improvement in OCD. Tics may reflect a subtype of OCD and OCD patients unresponsive to a serotonin-reuptake inhibitor alone may benefit from the addition of a dopamine antagonist (Delgado et al, 1990).

b) Extended-release Formulation

1) In a 12-week, multicenter, randomized, double-blind, placebo-controlled study (n=253), treatment with extended-release (ER) fluvoxamine maleate was safe and led to a statistically significant and clinical relevant decrease in obsessive-compulsive disorder (OCD) severity in adult patients. Patients meeting the DSM-IV criteria for OCD (mean duration, approximately 16 years), and with scores of 21 or higher on the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) and 16 or lower on the 17-item Hamilton Rating Scale for Depression randomly received either fluvoxamine ER (n=127; mean age, 38.1 years) or placebo (n=126; mean age, 36.7 years) orally once daily for 12 weeks. Fluvoxamine ER was initiated at a nightly dose of 100 milligrams (mg) and titrated in weekly 50-mg increments over 6 weeks to a target dose of 100 to 300 mg/day. The dose remained constant during the remaining 6 weeks of the study (mean daily dose at endpoint, 271 mg). Patients were assessed every 2 weeks using the Y-BOCS (primary efficacy measure) and the Clinical Global Impressions-Severity of Illness (CGI-S) and -Improvement (CGI-I) scales. At baseline, the Y-BOCS scores were 26.6 and 26.3 in the fluvoxamine ER and placebo groups, respectively. A modified intent-to-treat (including patients with at least 1 postbaseline efficacy measurement) analysis of Y-BOCS total score revealed a mean +/- standard error (SE) decrease from baseline to week 12 of 8.5 +/- 0.7 (31.7% change) in the fluvoxamine ER group compared to 5.6 +/- 0.7 (21.2% change) in the placebo group (F=10.48; df=1218; p=0.001). There were significant treatment differences in favor of fluvoxamine ER group for both the obsession (39.6% change vs 24.4% change; p less than 0.001) and compulsion (34.3% vs 24.8%; p=0.048) subtotals of the Y-BOCS. Notably, treatment differences were evident at week 2 and were sustained throughout the 12-week study. Among secondary efficacy measures, compared to placebo, significant improvements occurred in fluvoxamine ER-treated patients for both the CGI-S (-1 +/- 0.1 vs -0.6 +/- 0.1; p=0.002) and the CGI-I (endpoint, 2.7 +/- 0.1 (range, 1 to 5) vs 3.2 +/- 0.1 (range, 1-6); p less than 0.001) scores. More patients discontinued treatment due to adverse events in the fluvoxamine ER versus placebo group (19% vs 6%). The most common adverse events occurring with fluvoxamine ER at a higher frequency than placebo included nausea (34% vs 13%), insomnia (35% vs 20%), somnolence (27% vs 11), asthenia (25% vs 8%), diarrhea (18% vs 8%), and anorexia (13% vs 5%). Abnormal ejaculation and anorgasmia (8% and 5%, respectively) only occurred in the fluvoxamine ER group, and decreased libido was also reported more frequently in the fluvoxamine ER group (7% vs 3%) (Hollander et al, 2003).

d) Pediatric:

1) Fluvoxamine maleate was significantly more effective than placebo in children (8 years or older) and adolescents with obsessive compulsive disorder (OCD). In this 10-week, double-blind study, 120 children with at least a 6-month history of OCD were randomized to receive fluvoxamine or placebo. During the first 4 weeks, the dose was titrated to patient response; the dose at 4 weeks was continued for the last 6 weeks of the study. Efficacy was assessed via the Children's Yale-Brown Obsessive Compulsive Scale which showed significant improvement at weeks 1 to 4, 6, and 10. No serious adverse effects were reported. Fluvoxamine was safe and effective in children with OCD (Riddle, 1996).

2) Fluvoxamine maleate was effective in decreasing depression and bulimic symptoms, but its impact on impulsive, suicidal, and anorectic symptoms was less clear. The safety and efficacy of fluvoxamine were evaluated in the treatment of adolescent patients with obsessive compulsive disorder (n=14) and major depression (n=6). Patients were age 13 to 18 and were treated for 8 weeks in an open-label trial. They were rated at 2-week intervals using Y-BOCS (Yale-Brown Obsessive Compulsive Scale) and other rating scales. Fluvoxamine maleate was more effective in OCD patients than in depressed patients, as evidenced by significant decreases in Y-BOCS scores. The most common side effects were dermatitis, insomnia, hyperactivity, excitement, anxiety, tremor and nausea. The drug was discontinued in 4 patients because of more severe side effects (delirium, hallucinations) (Apter et al, 1994).

4.5.A.15 Panic disorder

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

In uncontrolled or placebo-controlled studies, fluvoxamine was effective for treating panic disorder in patients with and without depression (Spiegel et al, 1996; Black et al, 1993a).

c) Adult:

1) Fluvoxamine was effective for treating panic disorder complicated by depression. In an 8-week, open-label, flexible-dose trial, fluvoxamine was administered to 17 patients. Thirteen patients had panic

disorder with agoraphobia; 14 patients had an additional anxiety disorder; 15 patients had a major depressive disorder; and 5 patients also had obsessive-compulsive disorder. Fluvoxamine was initiated at 40 milligrams per day, increased to 100 milligrams on day 5 and to 150 milligrams on day 9. The dose was increased at 50 milligram intervals each week until side effects occurred; the maximum dose of 300 milligrams was reached; or panic attack and depression resolved. Fifteen patients completed the study. One patient dropped out due to side effects and one for unknown reasons. The most common adverse events were nausea, insomnia, anxiety/restlessness, headache, drowsiness and dry mouth. At the study's end (at a mean fluvoxamine dose of 213 milligrams), there was a statistically significant difference from baseline in the number of panic attacks, anticipatory anxiety, general anxiety, depression and a self-rating of disability; however, fluvoxamine did NOT affect agoraphobia avoidance (Spiegel et al, 1996).

2) Fluvoxamine was superior to cognitive therapy (CT) and placebo (PL) in the treatment of seventy-five outpatients with moderate-to-severe panic disorder. CT subjects also showed improvement but the degree of improvement was not different from that of PL patients. Fluvoxamine also produced improvement earlier than CT; at week 4, 57% of fluvoxamine patients were rated moderately improved or better compared to 40% for the CT group and 22% for the PL group. At the same time point, 43% of fluvoxamine patients were free of panic attacks compared with 25% of CT and 4% of PL patients (Black et al, 1993a).

3) In a case report, fluvoxamine 150 milligrams/day for 6 weeks prevented panic attacks and decreased obsessive-compulsive symptoms in a 36-year-old woman (Servant et al, 1988). The patient had a 12-year history of recurrent panic attacks. The patient had most recently been treated with imipramine 150 mg/day and lorazepam 2.5 mg/day without improvement.

4) In a placebo-controlled, double-blind study, fluvoxamine significantly reduced the number of panic attacks compared to placebo. The severity of attacks was not affected by fluvoxamine. There was no difference between drug and placebo until 6 weeks of treatment when placebo lost its effect on anxiety, depressive mood, and disability (Hoehn-Saric, 1993).

4.5.A.16 Posttraumatic stress disorder

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Open trials suggest that fluvoxamine may be useful for treating post-traumatic stress disorder (Escalona et al, 2002; Davidson et al, 1998; Marmar et al, 1996).

c) Adult:

1) Some symptoms of combat-related post-traumatic stress disorder (PTSD) improved during treatment with fluovoxamine; however, there was a high drop-out rate from the study due to side effects and lack of perceived therapeutic benefit. Fifteen Vietnam combat veterans with no other psychiatric diagnosis than PTSD and depression were treated with fluvoxamine, starting at a dose of 50 milligrams (mg) twice daily and increasing to a maximum of 300 mg/day, in an open-label, 14- week study. The study was preceded by a 30-day washout period. The mean daily dose of fluvoxamine at week 14 was 150 mg. Only 8 patients completed 8 weeks of the study and 5 completed the entire study. In intent-to-treat analysis, scores on intrusion and avoidance scales of the Clinician PTSD Scale (CAPS) showed significant improvement (p less than 0.001), as did scores on the Hamilton Anxiety Scale (p less than 0.001). However, measures of depression showed no significant changes. Hyperarousal scores also were unchanged. Gastrointestinal side effects and dizziness were the most common adverse effects reported (Escalona et al, 2002).

2) In an open, 8-week trial, fluvoxamine resulted in symptom improvement in 64.2% of civilian patients with post-traumatic stress disorder (PTSD). Fifteen patients with confirmed PTSD were treated with fluvoxamine 50 milligrams (mg) daily with adjustment of dose to a maximum of 200 mg daily depending on symptom improvement and side effects. Using assessment scales including the Structured Interview for PTSD, Treatment-Outcome PTSD Scale, and the Duke Global Rating Scale for PTSD, the symptom score improved by 40% to 50%; this difference was clinically and statistically significant. Five patients left the trial early due to adverse effects (n=2) and administrative reasons (n=3); however, 14 of 15 patients were included in the efficacy analysis. Positive results of this and an earlier trial indicate that a double-blind, placebo-controlled trial should be performed with fluvoxamine for PTSD (Davidson et al, 1998).

3) In an open-label trial, fluvoxamine improved stress-related symptoms in 10 Vietnam combat veterans with post-traumatic stress disorder. The 12-week study consisted of a drug wash out and DSM-IIIR diagnoses screening during weeks 0 to 2, followed by fluvoxamine 50 milligrams (mg) daily starting at week 2. Fluvoxamine was increased weekly by 50 mg to a therapeutic dose; the (modal) daily dose was 150 mg, (range 100 to 250 mg daily). Self-report and clinician ratings of stress-specific and general psychiatric symptomatology improved significantly over the first 6 weeks and continued at this level for the duration of the study. These included the intrusion, avoidance and hyperarousal symptoms of PTSD. The comorbid features of depression and anxiety were also significantly affected;

however, hostility was unaffected. The most commonly reported side effects were sedation, headache, nausea, and insomnia (Marmar et al, 1996).

4.5.A.17 Premenstrual dysphoric disorder

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

With the exception of food cravings, symptoms associated with premenstrual syndrome were significantly improved by the use of fluvoxamine in an open-label study (Freeman et al, 1996).

c) Adult:

1) With the exception of food cravings, symptoms associated with premenstrual syndrome were significantly improved by the use of fluvoxamine (Freeman et al, 1996). In an open-label, pilot study, fluvoxamine was examined for the treatment of premenstrual dysphoric disorder (PDD), commonly referred to as PREMENSTRUAL SYNDROME. Twelve women who met the DSM-IV criteria for PDD were treated with fluvoxamine for 2 menstrual cycles. Fluvoxamine was started at 50 milligrams per day on day 1 of the menstrual cycle. At 4 weeks, the mean daily dose was 85 milligrams and at 8 weeks, all women took 100 milligrams daily. Eight of the 10 women completing the study reported side effects. Commonly reported side effects included insomnia, fatigue, dry mouth, nausea and loss of libido. Most effects were transient and were only experienced early in the treatment. Improvement in the daily symptom reports (DSR) was significant at both 4 and 8 weeks. Four factors, mood, function, pain and physical changes made up the DSR. Seventeen individual items were contained within these 4 factors. Further controlled studies are needed to substantiate these findings. It would also be helpful to determine if fluvoxamine is needed on a daily basis throughout the menstrual cycle.

4.5.A.18 Prostatic pain

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Fluvoxamine reduced pain and normalized urinary flow rates in patients with prostatodynia in a randomized, double-blind, placebo-controlled study (n=42) (Turkington et al, 2002).

c) Adult:

1) Fluvoxamine treatment was more likely than placebo to reduce pain and normalize urinary flow rates in patients with prostatodynia. In this randomized, double-blind, placebo-controlled study (n=42), patients with at least a one-year history of perigenital pain without local or systemic infection and without local inflammation were assigned to receive placebo or fluvoxamine for 8 weeks. Treatment medication was initiated at 50 milligrams (mg) daily, then increased by 50 mg every 2 weeks, as needed (median dose, 150 mg; range, 50-300 mg). Patients treated with fluvoxamine reported significant improvements in pain as compared with placebo-treated patients (p=0.01). Significantly more patients in the fluvoxamine group showed improvement in urinary flow rate as compared with the placebo group (7 of 8 vs 1 of 6, respectively; p=0.03). Larger studies are needed to address the efficacy of fluvoxamine for all symptoms of prostatodynia and to identify the optimal dose (Turkington et al, 2002).

4.5.A.19 Repetitive self-excoriation

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class III
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

A response rate of 50% was seen in patients treated with fluvoxamine in an open-label study (Arnold et al, 1999).

c) Adult:

1) In an open, 12-week study, patients with psychogenic excoriation improved during treatment with fluvoxamine; however, 7 patients withdrew early due to adverse effects (n=4) or unrelated reasons. Response defined as a 30% or greater decrease in the total score on the modified Yale-Brown Obsessive Compulsive Scale (Y-BOCS) was achieved in 50% of enrolled patients. The modified Y-BOCS score was reduced from 17.9 at baseline to 10.9 at termination. Adverse effects were common and included those normally expected with fluvoxamine. This study suggests that fluvoxamine may be useful for psychogenic excoriation; however, controlled clinical trials are needed to confirm this (Arnold

et al, 1999).

4.5.A.20 Severe major depression with psychotic features

See Drug Consult reference: PSYCHOTIC DEPRESSION - DRUG THERAPY

4.5.A.21 Social phobia

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes (extended-release formulation only); Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIa
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Extended-release fluvoxamine maleate is indicated for social anxiety disorder, also known as social phobia (Prod Info LUVOX(R) CR extended-release oral capsules, 2008).
In a randomized, double-blind, multicenter, placebo-controlled study (n=300), patients with generalized social anxiety disorder (GSAD) who received fluvoxamine controlled-release (CR) demonstrated a significantly greater reduction in the mean Liebowitz Social Anxiety Scale (LSAS) total score from baseline compared with patients who received placebo (Westenberg et al, 2004); there was a trend towards continued clinical benefit with fluvoxamine ER compared to placebo in a 12-week double-blind extension phase of this study (Stein et al, 2003).

c) Adult:

1) Fluvoxamine extended-release (ER) was an effective therapy in the treatment of patients with generalized social anxiety disorder (GSAD). In a randomized, double-blind, placebo-controlled, multicenter study, patients (n=300) with GSAD and a score of at least 60 on the Liebowitz Social Anxiety Scale (LSAS) received fluvoxamine ER (initial, 100 milligrams (mg)/day, titrated weekly in 50 mg increments, as needed, to maximum of 300 mg/day; mean dose, 209 mg/day) for 12 weeks. A significantly greater reduction in the mean LSAS total score was observed from baseline to endpoint in the fluvoxamine ER group as compared with the placebo group (37% vs 28%, respectively; p=0.02). The mean LSAS total score for patients in the fluvoxamine ER group was significantly more improved as compared with placebo at weeks 4, 8, 10, and 12 (p less than 0.05, all values), but not at week 6 (p=0.066). Reductions on the fear and avoidance subscales of the LSAS were also significantly greater for fluvoxamine ER-treated patients as compared with placebo-treated patients (p=0.015 and p=0.04, respectively). Additionally, fluvoxamine ER was superior to placebo in three of four secondary measures including the Clinical Global Impression Improvement (CGI-I) Scale, CGI-Severity (CGI-S) of Illness Scale, and the Sheehan Disability Scale (SDS) (p=0.026, p=0.022, and p=0.036, respectively). Nausea (47%), headache (35%), insomnia (32%), asthenia (28%), and somnolence (22%) were the most commonly reported adverse events. Adverse effects related to sexual dysfunction were not significantly different between treatment groups, however these effects included abnormal ejaculation, anorgasmia, impotence, and decreased libido (Westenberg et al, 2004).

a) In a 12-week double-blind extension of the aforementioned study, there was a trend towards continued clinical benefit with fluvoxamine ER (n=56) compared to placebo (n=53) among patients with generalized social anxiety disorder. Patients completing the 12-week acute phase study and achieving at least minimal improvement (ie, a CGI-I score of 3 or less) continued to receive study medications as assigned in the acute phase; the mean fluvoxamine ER dose in the extension phase was 181 milligrams/day. Notably, the extension phase was not powered to detect statistical significance due to the small number of patients expected to continue into the extension study. At the end of 24 weeks of treatment, the mean +/- standard error (SE) LSAS total scores continued to decline in the fluvoxamine ER group compared to placebo (difference from week 12, -6.3 +/- 1.6 for fluvoxamine ER versus (vs) -1.6 +/- 1.6 for placebo; p=0.109). Although not statistically significant, greater improvements were seen in the fluvoxamine ER group compared to placebo for the secondary measures of CGI-S and SDS scores during the 12-week extension. The percentage of responders (ie, score of 1 or 2 on the CGI-I; 80% vs 74%; p=0.322) and remitters (ie, score of 1 on the CGI-I; 38% vs 28%; p=0.318) was numerically higher in the fluvoxamine ER group than the placebo group. During the extension phase, 9% (5/56) and 4% (2/53) of fluvoxamine ER- and placebo-treated patients, respectively, discontinued treatment due to adverse events. Common adverse events occurring more frequently than placebo included sweating (9% vs 4%), nausea (7% vs 2%), and sexual dysfunction (16% vs 5%), with 7% of fluvoxamine ER-treated patients reporting abnormal ejaculation (0% in the placebo group) (Stein et al, 2003).

2) Fluvoxamine was superior to placebo for treating social phobia. Patients diagnosed with DSM-IV social anxiety disorder were randomly assigned to 12 weeks of double-blind treatment with placebo (n=44) or fluvoxamine 50 milligrams daily (n=42) with titration at weekly intervals to a maximum dose of 300 milligrams daily. Response was defined by a score of 1 (very much improved) or 2 (much improved) on the Clinical Global Impression scale (CGI). Of the patients (n=64) who completed the full 12 weeks of the study, 53.3% and 23.5% treated with fluvoxamine and placebo, respectively, were considered responders on the CGI scale (p=0.01). In addition, evaluation using specialized social phobia scales demonstrated significant improvement in the fluvoxamine versus placebo group (ie, Brief

Social Phobia Scale, p less than 0.01; Social Phobia Inventory, p=0.02; Liebowitz Social Anxiety Scale subscales for work and family life, p=0.006 and p=0.02). The mean fluvoxamine dose was 202 milligrams/day at study end. Treatment was withdrawn due to adverse effects in 25% and 9.1% of patients treated with fluvoxamine and placebo, respectively; nausea and insomnia were the primary adverse effects that led to treatment discontinuation. Treatment benefit was first observed at 6 weeks and continued through week 12 of the study. Comparison of fluvoxamine with other accepted treatments is needed (Stein et al, 1999).

3) Fluvoxamine was effective in a small group of patients who met DSM-III-R criteria for social phobia. Fifteen patients were treated with fluvoxamine 50 milligrams (mg)/day with titration to 150 mg/day as needed; treatment was continued for 6 weeks. Five patients discontinued treatment due to adverse effects or difficulty traveling for appointments. Assessment scales including the Hamilton Rating for Anxiety, Brief Social Phobia Scale, Marks-Sheehan Phobia Scale, Fear Questionnaire, and Sheehan Patient Rated Anxiety Scale showed a significant reduction from baseline to week 7. Patients also reported a reduction in anxiety associated with giving a speech at baseline and conclusion of the study. This small, open study suggests that fluvoxamine is effective for social anxiety disorder (DeVane et al, 1999).

4.5.A.22 Stereotypy habit disorder

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Three patients responded to fluvoxamine with complete cessation of stereotypic behavior in 1 patient

c) Adult:

1) Of 3 elderly women with stereotypic behavior, 2 almost completely stopped the behavior, and 1 had a partial response to fluvoxamine (Trappler & Vinuela, 1997). Pretreatment assessment with the Abnormal Involuntary Movement Scales (AIMS) yielded a score of 13 to 16. The first patient gnawed on her fingers, clothing, and towels but stopped this behavior after receiving fluvoxamine 50 milligrams (mg) daily for 4 weeks; the AIMS decreased to 1. Treatment was continued for 10 weeks; this patient remained symptom-free 6 months after stopping fluvoxamine. The second patient had almost complete resolution of chewing on her sweater and finger sucking 3 weeks after increasing fluvoxamine to 100 mg daily; her AIMS also decreased to 1. The third patient caused constant irritation and infection to her left eyelid due to constantly wiping it with her sleeve. This behavior partially abated after treatment with fluvoxamine 150 mg daily; the AIMS went from 16 to 7. Therapy was tolerated well by all patients who ranged in age from 81 to 88 years. Since 2 patients maintained a response after treatment withdrawal, this behavior was considered responsive to fluvoxamine and is likely related to a serotonergic mechanism.

4.5.A.23 Trichotillomania

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Fluvoxamine may have beneficial effects in patients with trichotillomania (Stanley et al, 1997).

c) Adult:

1) In a 12-week, open trial, fluvoxamine treatment resulted in some improvement in trichotillomania. Twenty-one patients were treated with fluvoxamine 50 milligrams (mg) daily with dosage adjustment to a maximum of 300 mg daily. Of the 21 patients treated, only 13 completed the entire 12 weeks of treatment. When the data were analyzed including patients completing the study, few statistically significant differences were found in symptoms on the assessment scales; however, when all patients were included, significant differences were found in several symptoms on the assessment scales. One possible explanation for this difference includes early treatment withdrawal in patients with a good response; another possible reason is the assessment scales were NOT well validated for trichotillomania. Since some symptomatic improvement occurred in both groups (completers and non-completers), controlled clinical trials are needed to assess fluvoxamine treatment for trichotillomania (Stanley et al, 1997).

4.5.A.24 Wernicke-Korsakoff syndrome

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class III

Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Results of studies have been mixed when fluvoxamine was used for treating alcoholic Korsakoff syndrome. Available studies have included only a few patients; therefore, larger, well-controlled studies may resolve the controversy (O'Carroll et al, 1994; Stapleton et al, 1988).

c) Adult:

1) Fluvoxamine 200 milligrams/day was ineffective in the treatment of alcoholic Korsakoff syndrome in 8 patients who were treated for 4 weeks in a double-blind, placebo-controlled, crossover trial. Fluvoxamine had no cognitive-enhancing effect as measured by a detailed neuropsychological battery on a weekly basis. There was significant impairment in verbal fluency. Two patients developed a major depressive episode in the fluvoxamine group; within 3 days of fluvoxamine discontinuation, their mood returned to normal (O'Carroll et al, 1994).

2) Fluvoxamine 100 to 200 milligrams/day improved episodic memory in 7 patients with alcohol amnestic disorder (Korsakoff's psychosis) in a 4-week, double-blind, crossover design study. These improvements were significantly correlated with reductions in cerebrospinal fluid 5-HIAA levels, suggesting that facilitation of serotonergic neurotransmission may ameliorate the episodic memory failure in patients with alcohol amnestic disorder (Martin, 1989).

3) Fluvoxamine produced a small but significant improvement in memory performance in 5 alcoholic ORGANIC BRAIN SYNDROME patients during a double-blind, crossover study. Fluvoxamine 200 milligrams/day for 4 weeks was administered to all patients. Overall improvement in performance was associated with higher levels of fluvoxamine and lower levels of 5-hydroxy-indole-acetic acid (5HIAA), a metabolite of serotonin, in the cerebrospinal fluid (Stapleton et al, 1988).

4.6 Comparative Efficacy / Evaluation With Other Therapies

Amineptine

Amitriptyline

Clomipramine

Clovoxamine

Desipramine

Dothiepin

Fluoxetine

Flupenthixol

Imipramine

Lithium

Lorazepam

Maprotiline

Mianserin

Milnacipran

Oxaprotiline

Paroxetine

Sertraline

4.6.A Amineptine

4.6.A.1 Bulimia nervosa

a) Fifteen women with bulimia nervosa were treated with a combined cognitive-behavioral, nutritional and antidepressant therapy (either amineptine 300 milligrams (mg) per day or fluvoxamine 300 mg/day) for 4 months. The combination of psychotherapeutic and pharmacologic therapy showed rapid, good effects and improvement was stable in most of the patients until the end of the observations. Prior to therapy, the patients had high global Eating Disorders Inventory (EDI) scores; these did not change during fluvoxamine therapy and decreased during amineptine administration in some patients (not statistically significant). No statistically significant improvement (p=0.4) was found in depression or anxiety in the two groups. The Bulimic Investigation Test Edinburgh (BITE) symptoms and gravity scores improved significantly (p=0.001) in both groups and gravity was more significantly (p=0.05) improved with amineptine than fluvoxamine. Optimum dosage and duration of treatment for this condition have not been determined. The data of this study are preliminary and the results need to be validated in a larger population over a longer observation period (Brambilla et al, 1995).

4.6.B Amitriptyline

Depression

Fibromyalgia

4.6.B.1 Depression

a) SUMMARY: In two clinical studies, amitriptyline and fluvoxamine were equally effective in treating patients with depression (Gasperini et al, 1992; Remick et al, 1994). A greater percentage of the amitriptyline group discontinued therapy due to side effects (Remick et al, 1994).

b) In a double-blind, randomized parallel study lasting seven weeks, fluvoxamine (mean dose 175 mg/day) was compared to amitriptyline (mean dose 135 mg/day) in 33 outpatients with moderate degrees of depression. There was no statistically significant difference between the two drugs as judged using the Hamilton Rating Scale for Depression and the Clinical Global Impression Scale. The two drugs had a comparable safety profile, although a greater percentage of the amitriptyline group discontinued therapy due to side effects (Remick et al, 1994).

c) In another study, amitriptyline was compared to fluvoxamine in a double-blind trial of 56 patients with major depressive disorders. The study lasted 6 weeks and doses of amitriptyline and fluvoxamine escalated from 50 to 300 mg and 100 to 300 mg, respectively. Patients were divided into responders and non-responders based on the Hamilton rating scale for depression and the Montgomery-Asberg depression rating scale. Overall, the drugs were found equally effective, but there was some symptom specificity which might guide the selection of one or the other drug in the clinical setting (Gasperini et al, 1992).

4.6.B.2 Fibromyalgia

a) Fluvoxamine was equally effective to amitriptyline in reducing pain associated with fibromyalgia. In an open-label, uncontrolled study, 68 Japanese patients with fibromyalgia received either amitriptyline at a mean dose of 20 milligrams (mg)/day or fluvoxamine at a mean dose of 25 mg/day for 4 weeks. Patients evaluated pain relief by means of a visual analog scale and efficacy was defined as a decrease in pain by at least 50%. At 4 weeks, 50% of patients in the amitriptyline group and 41% of patients in the fluvoxamine group reported effective relief of pain (p=NS). Drowsiness was the most commonly reported adverse event with amitriptyline treatment and nausea was most frequently reported with fluvoxamine. The authors hypothesize that because the efficacy of amitriptyline for the treatment of fibromyalgia-related pain has been established in previous, controlled trials and because fluvoxamine showed similar efficacy to amitriptyline in this open-label study; fluvoxamine may be helpful for patients with fibromyalgia (Nishikai & Akiya).

4.6.C Clomipramine

Anxiety

Cataplexy

Depression

Obsessive-compulsive disorder

Panic disorder

4.6.C.1 Anxiety

a) Fluvoxamine and clomipramine were comparable in reducing anxiety symptoms in patients with agoraphobia with panic attacks (APA), generalized anxiety disorders (GAD), and obsessive-compulsive disorders (OCD) as classified by DSM-III during a randomized, double-blind study (Westenberg et al, 1987). Of the 50 patients in this study, 39 diagnosed with APA, 5 with GAD, and 6 with OCD. Patients were randomly assigned to receive either clomipramine, up to 150 milligrams/day, or fluvoxamine, up to 100 milligrams/day, for the 6-week study. Both drugs demonstrated significant improvement in anxiety symptoms after drug therapy when compared to pretreatment.

4.6.C.2 Cataplexy

a) Both fluvoxamine and clomipramine improved cataplexy, but not narcolepsy, in 18 patients with these diseases during a cross-over study (Schachter & Parkes, 1980). It was not revealed if either the patients or researchers were blinded to drug therapy. It should be noted that 15 of the 18 patients were receiving clomipramine 25 to 100 milligrams/daily at the start of the trial, and may have been accustomed to the adverse effects of clomipramine. Also, if the patients were not blinded to drug therapy, some patients may have associated more adverse effects with a new drug, fluvoxamine. Patients were randomly allocated to receive fluvoxamine or clomipramine for a 3-week interval. After a 1-week drug-free period, the patients crossed over to the other drug. The daily dosing range for both drugs ranged from 25 to 200 milligrams/day. All patients were clinically assessed by observers on 5 occasions. The observers' impression was that fluvoxamine caused a moderate reduction in the frequency of attacks of cataplexy and sleep paralysis in most subjects. Fluvoxamine abolished cataplexy in 4 patients and sleep paralysis in 2 patients; only 12 of the 18 patients completed the fluvoxamine-treatment period. The observers felt that clomipramine was more effective than fluvoxamine in preventing both cataplexy and sleep paralysis. Clomipramine abolished cataplexy in 4 patients and sleep paralysis in 5 patients.

4.6.C.3 Depression

a) SUMMARY: Several double-blind, short-term studies have demonstrated fluvoxamine to be as effective as clomipramine in the treatment of depression (De Wilde et al, 1983; Klok et al, 1981). Anticholinergic adverse effects appear to be less common with fluvoxamine therapy.

b) Fluvoxamine and clomipramine were compared for antidepressant activity in a 6-week, randomized, double-blind study of 43 outpatients with major depression (De Wilde et al, 1983). Oral fluvoxamine 100 to 300 milligrams or oral clomipramine 50 to 150 milligrams was administered once daily in the evening. Assessments of the HAM-D (Hamilton Rating Scale for Depression) during the study and at the end failed to demonstrate any significant differences in antidepressant activity between the 2 drugs. The incidence of anticholinergic adverse effects were slightly more significant in the clomipramine-treated group.

c) Clomipramine and fluvoxamine appeared to be equally effective in the treatment of depression for 36 female inpatients during a 4-week, randomized, double-blind study (Klok et al, 1981). Patients were randomized to receive either oral clomipramine or oral fluvoxamine 50 milligrams 3 times daily. Diazepam 10 to 30 mg/day for severe agitation and/or anxiety was the only other psychotropic agent administered. Significant improvements in the Hamilton Rating Scale for Depression, the Clinical Global Impression, and the Zung Self-Rating Depression scale were seen in both treatment groups. Anticholinergic adverse effects appeared more frequently in the clomipramine-treated patients, while gastrointestinal effects were more prevalent in the fluvoxamine group.

d) Fluvoxamine and clomipramine appeared to have similar clinical efficacy in the treatment of endogenous depression for 30 unipolar and bipolar inpatients during a 4-week, randomized, double-blind study (De Wilde et al, 1983). Both drugs were administered orally in doses of 150 to 300 milligrams/day in 3 divided doses. At the end of the study, the fluvoxamine-treated patients demonstrated a 73% improvement on the Hamilton Rating Scale for Depression, while the clomipramine-treated patients had a 62% improvement. In the bipolar patients, 3 of 4 on fluvoxamine responded, while only 1 of 5 on clomipramine demonstrated a good response on the CGI Global Change Scale. Overall, the differences in efficacy between the 2 drugs were not statistically significant. Adverse anticholinergic effects were significantly more prevalent in the clomipramine-treated group.

e) Both clomipramine and fluvoxamine produced significant improvements on the Hamilton Rating Scale for Depression (HAM-D) in 32 patients with mixed depression during a 4-week, randomized, double-blind study (Dick & Ferrero, 1983). The average daily dosage was 130 milligrams and 132.8 milligrams for fluvoxamine and clomipramine, respectively. The mean percentage improvement on the HAM-D for the fluvoxamine-treated patients was 63.8%, and for the clomipramine-treated patients it was 66.3%.

4.6.C.4 Obsessive-compulsive disorder

a) Fluvoxamine (150 to 125 milligrams/day) and clomipramine (100 to 250 milligrams/day were equally effective in the treatment (10 weeks) of 66 outpatients with obsessive compulsive disorder. Both treatments were well-tolerated. Fluvoxamine produced fewer anticholinergic adverse effects and caused less sexual dysfunction than clomipramine, but caused more headache and insomnia (Freeman et al, 1994). under OBSESSIVE COMPULSIVE DISORDER add:

b) In a randomized, double-blind study of 26 patients with obsessive compulsive disorder without comorbid diseases, fluvoxamine and clomipramine, each titrated from an initial dose of 50 milligrams (mg) in the evening up to a maximum of 300 mg daily within two weeks, were equally effective (38% improvement over

baseline with fluvoxamine versus 40% for clomipramine). Efficacy was assessed according to the Yale-Brown Obsessive Compulsive Scale and Clinical Global Impression Scale. Fluvoxamine was better tolerated, with less anticholinergic adverse effects while clomipramine had a quicker onset of action. Further studies are needed to demonstrate a time-related effect that might differentiate these drugs (Milanfranchi et al, 1997).

4.6.C.5 Panic disorder

a) Clomipramine (10 milligrams (mg) for three days and 20 mg for four days) and fluvoxamine (50 mg/day for seven days) were both effective in decreasing the hypersensitivity to 35% carbon dioxide, supporting the serotonergic effect of these drugs to decrease panic attacks through modification of carbon dioxide sensitivity. Thirty-nine panic disorder patients were enrolled in a double-blind, randomized, placebo-controlled study, where each patient was given the 35% carbon dioxide challenge on days 0, 3, and 7. Patients on clomipramine and fluvoxamine showed significant reduction in sensitivity over placebo after seven days as seen by the percent change on a visual analogue for anxiety scale (p=0.027) (Perna et al, 1997).

4.6.D Clovoxamine

1) Efficacy

a) SUMMARY: Clovoxamine induces only minor electroencephalographic changes in healthy subjects; whereas, changes produced by fluvoxamine more closely resemble those of imipramine, including an increase of slow activity. Clovoxamine appears less sedating than fluvoxamine, and may possess mild alerting effects.

b) In computerized electroencephalographic studies involving healthy subjects (Saletu et al, 1980), oral clovoxamine 50 to 125 mg was primarily associated with an increase in very fast beta-activity (predominant 6 hours postdose), suggesting an activating effect of the drug. Although an increase in fast beta-activity was also observed with fluvoxamine 75 mg, this agent also produced a concomitant increase of slow activity and a decrease of alpha-activity. Imipramine 75 mg produced the most marked electroencephalographic changes, characterized by a concomitant increase of slow and fast activities and a decrease of alpha-activity. Augmentation of slow activity was, however, less with fluvoxamine than imipramine, suggesting less sedative properties of the former. Overall, pharmacodynamic data based on both electroencephalographic and psychometric parameters indicated that imipramine 75 mg produced the most central nervous system changes, followed by fluvoxamine 75 mg, clovoxamine 125 mg, clovoxamine 75 mg, and clovoxamine 50 mg. Peak effects occurred 4 to 6 hours after clovoxamine and fluvoxamine, compared to 2 to 4 hours following imipramine. Adverse effects were minimal with clovoxamine, with euphoria occurring in a few subjects; in contrast, tiredness was common after fluvoxamine (50% of subjects) and imipramine (80%).

c) The results of a further placebo-controlled study in healthy volunteers also suggested a lower propensity of clovoxamine to induce sedation in comparison with fluvoxamine. In doses of 50 mg twice daily (8 am and 6 pm), fluvoxamine was associated with changes suggestive of enhanced nighttime sedation; fluvoxamine-treated were significantly less refreshed upon awakening and had greater difficulty in achieving morning alertness compared to placebo, and there were trends toward fewer nocturnal awakenings and shorter sleep latency in the fluvoxamine group. In contrast, these effects were not observed clovoxamine 150 mg daily (100 mg at 8 am and 50 mg at 6 pm); depth of sleep was reduced significantly with clovoxamine compared to placebo (Ochs et al, 1989).

4.6.E Desipramine

4.6.E.1 Depression

a) The efficacy of fluvoxamine was compared to that of desipramine in a multicenter, double-blind, placebo-controlled six-week flexible dose trial of 90 outpatients with major depressive disorder. Dosage range for each active medication was 100 to 300 milligrams/d. The Montgomery-Asberg Depression Rating Scale, the Hamilton Rating Scale for Depression, and the Clinical Global Impression Scale were used to assess response. There was no significant difference in efficacy among the three treatments until week six, when both active drug groups continued to improve while the placebo group remained at the same level of depression. The authors concluded that 6 weeks was too short a time to identify the differences between active drug and placebo in the patient population (Roth et al, 1990).

b) An immediate increase in pain threshold (polysynaptic R-III reflex and subjective pain rating to electric shock) was seen in a single-dose, placebo-controlled study comparing desipramine, fluvoxamine, and moclobemide in healthy volunteers (n=10) (Coquoz et al, 1993).

4.6.F Dothiepin

4.6.F.1 Depression

a) Fluvoxamine and dothiepin were comparable in reducing symptoms of depression in 73 patients during a 6-week, double-blind study (Mullin et al, 1988). The patients were randomized to receive initial starting doses of either fluvoxamine 100 milligrams or dothiepin 75 milligrams daily. The doses were increased gradually, as tolerated, to a maximum of fluvoxamine 300 milligrams or dothiepin 225 milligrams/day. At the conclusion of the study, both drugs demonstrated efficacy in treating depression as measured by the Hamilton Depression Rating Scale (HAMD), Clinical Global Impression, and Clinical Global Improvement

scales. There were no significant differences in efficacy between the 2 drugs. Dothiepin was associated with more anticholinergic adverse effects, while fluvoxamine was associated with more nausea and vomiting.
b) Fluvoxamine (25 to 200 mg/d) was equivalent to dothiepin (25 to 200 mg/d) in efficacy in 52 elderly inpatients with major depressive disorder. Patients were treated for 6 weeks with weekly assessments for therapeutic response and presence of adverse effects. The mean dosage during the last 2 weeks of the study was 157 mg/d for fluvoxamine and 159 mg/d for dothiepin. Sixty-three percent of fluvoxamine patients and 60% of dothiepin patients showed marked improvement at six weeks (Rahman et al, 1991).

4.6.G Fluoxetine

4.6.G.1 Depression
a) In a randomized, double-blind study (n=100), fluvoxamine and fluoxetine demonstrated comparable efficacy and side effects in out-patients with major depression. After randomization, patients were treated initially with fluvoxamine 50 milligrams (mg) daily adjusted to a maximum of 150 mg daily or fluoxetine 20 mg daily adjusted to a maximum of 80 mg daily. Throughout the study, significant differences in efficacy were NOT detected on several depression scales including the Hamilton depression scale and clinical global impressions scale. Adverse effects were common with both drugs but the severity was mild in the majority of patients. Even though this study included 100 patients, it may NOT have detected subtle differences between the 2 treatments (Rapaport et al, 1996).

4.6.H Flupenthixol

4.6.H.1 Depression
a) Flupenthixol was as effective as fluvoxamine in the treatment of depression, and had a more favorable adverse effect profile (Hamilton et al, 1989). In a multicenter trial, 72 patients with depression were randomized to receive either flupenthixol 1 milligram/day (n=36) or fluvoxamine 100 milligram/day (n=36) for 4 weeks. Patients were evaluated objectively on days 1, 8, 15, and 29 using the Hamilton Depression Rating Scale, the Clinical Global Impressions Scale, and a self-assessment analog scale. At the end of the first week, the dose was doubled if response was judged to be insufficient. While both drugs were shown to be effective, mean improvement scores were higher at all evaluation times as measured by any of the 3 parameters in the group receiving flupenthixol. At the end of the first week, 89% of the flupenthixol group showed at least minimal improvement, compared with 75% of the fluvoxamine group. At the end of the study, all patients receiving flupenthixol had responded to treatment, compared with 83% of the fluvoxamine group. Four patients taking fluvoxamine were withdrawn due to adverse effects, but no patients receiving flupenthixol were withdrawn.

4.6.I Imipramine

4.6.I.1 Depression
a) SUMMARY: Fluvoxamine and imipramine appear to be equally efficacious in the treatment of depression (Lapierre et al, 1987; Guelfi et al, 1983; Guy et al, 1984; Itil et al, 1983); (March, 1990)(Lydiard et al, 1989).
b) Fluvoxamine demonstrated a trend toward superiority over imipramine in treating 63 patients with major depression during a 4- to 6-week, randomized, placebo-controlled, double-blind study (Lapierre et al, 1987). All drugs were started at 50 milligrams/day, and were gradually increased to a maximum of 300 mg/day. The mean daily dose of fluvoxamine at the the end of the study was 207 mg, and 192 mg for imipramine. At the end of the study, the total Hamilton Rating Scale for Depression (HAM-D) score had decreased by 75%, 55%, and 6% in the fluvoxamine-, imipramine-, and placebo-treated groups, respectively. At the end of the study there were 8, 3, and 1 responders from the fluvoxamine, imipramine, and placebo groups, respectively. Only 1 patient in each active treatment group withdrew from the study because of adverse effects.
c) Fluvoxamine was comparable to imipramine in antidepressant activity during a 4-week, double-blind, multicenter study of 151 patients (Guelfi et al, 1983). Drug therapy was administered in twice daily dosing in the range of 100 to 300 milligrams daily for fluvoxamine and 50 to 200 milligrams daily for imipramine. At the end of the study there was a mean improvement in the Hamilton Rating Scale for Depression (HAM-D) of 67.2% in the fluvoxamine-treated group and a 62.1% improvement in the imipramine-treated group. A similar improvement was detected with both drugs on the Clinical Global Impression Scale. At the end of the study, the mean daily dose of fluvoxamine was 221 mg and 112 mg for imipramine. A total of 37 patients withdrew from the study prematurely; 19 on fluvoxamine and 18 on imipramine. The reasons for early withdrawal appeared to be similar between both drugs.
d) Fluvoxamine and imipramine were comparable in efficacy for the treatment of depression in 36 patients diagnosed with unipolar or bipolar depression during a 4- to 6-week, randomized, double-blind study (Guy et al, 1984). Both medications were administered at bedtime with a maximal dosage range between 150 to 225 milligrams/day. In the unipolar depressed fluvoxamine-treated patients, 92% were judged "improved" at the end of the study compared to 81% of the imipramine group. However, the imipramine-treated group appeared to have a higher percent of patients rated as "much" or "very much" improved, 75% compared to 54% of the fluvoxamine group.
e) A double-blind comparative study of fluvoxamine and imipramine was carried out in 20 outpatients with depressive disorder. Patients received randomly-assigned medication over a 4-week period in a dosage

range of 50 of 300 mg given in 2 divided doses. There was a significant symptom severity reduction in both groups at the end of 4 weeks, and fluvoxamine was more effective than imipramine in reducing suicidal ideas and anxiety/somatic symptoms. Anticholinergic-type adverse reactions predominated for imipramine and gastrointestinal effects for fluvoxamine (Gonella et al, 1990).

f) In a 6-week, double-blind, placebo-controlled, variable-dose study assessing the comparative antidepressant efficacy of fluvoxamine (FLU), imipramine (IMI), and placebo (PBO), 45 patients with major depressive disorder were evaluated for response and side effects. Dosage ranged between 100 to 300 milligrams/day for active medications. No statistically significant differences between either the FLU (N=17) and PBO or the FLU and IMI groups were found. Side effects were present in all three groups: IMI(N=18): constipation (83%), dry mouth (55%), and sweating, dizziness, and nausea, all 39%. FLU(N=18): diarrhea, headache, dry mouth, all 41%, nausea (35%), and flatus (29%). PBO(N=18): pruritus (29%, nausea (23%), headache (18%), asthenia and somnolence, both 12%. This study revealed a high placebo response, with a 50% improvement at week 6. Thus, it is difficult to show differences from active medication unless the study is carried out for a longer time. In addition, the numbers of patients are too small to detect a true difference. Second, patients seemed to either respond or not respond to FLU, while the response to IMI appeared to be more graded. This may reflect a subgroup of depressed patients that have a serotonin-deficient type of depression (Lydiard et al, 1989).

g) Other double-blind, placebo-controlled studies comparing imipramine and fluvoxamine have only demonstrated slightly more improvement in depression with either drug when compared with placebo (Dominguez et al, 1985; Norton et al, 1984).

4.6.I.2 Adverse Effects

a) SUMMARY: Fluvoxamine produces less cardiovascular and anticholinergic adverse effects than imipramine; however, nausea and vomiting are more common with fluvoxamine therapy (Benfield & Ward, 1986a; Roos, 1983; Saletu et al, 1980a; Laird et al, 1993).

b) Adverse effects data was pooled from the results of 10 double-blind, placebo-controlled trials comparing fluvoxamine (n=222) with imipramine (n=221) (Benfield & Ward, 1986a). Anticholinergic effects such as dry mouth, dizziness/syncope, sweating, and abnormal accommodation were much more prevalent in patients receiving imipramine. Nausea/vomiting was the only adverse effect to be much more prevalent in the fluvoxamine-treated patients.

c) The cardiac effects of tricyclic antidepressants were compared with fluvoxamine. The major cardiac adverse effects observed with tricyclic antidepressants include postural hypotension, heart rate increase, and slight prolongation of the intraventricular conduction time and QT interval. The only cardiac effect observed with fluvoxamine was a statistically, but not clinically, significant slowing of heart rate (Roos, 1983).

d) Fluvoxamine produced less psychomotor impairment than imipramine. Fluvoxamine was superior to imipramine 75 milligrams in regards to concentration, reaction time, mood, psychomotor activity, and affectivity. Following the administration of fluvoxamine 75 milligrams to 10 healthy volunteers, psychometric tests demonstrated a tendency towards an improvement in psychomotor activity, concentration, attention, after-effect, and mood and a significant increase in critical flicker fusion frequency when compared to placebo (Saletu et al, 1980a).

4.6.J Lithium

4.6.J.1 Depression

a) The rate of recurrence of unipolar depressive episodes was lower for fluvoxamine 200 milligrams (mg) per day than lithium salts 600 to 900 mg/day in a randomized study of 64 unipolar patients. Follow-up continued for 24 months (Franchini et al, 1994). Further follow-up at 36 months showed no additional recurrences of depression in either the fluvoxamine or the lithium group (Franchini et al, 1996). Due to methodological limitations, further studies are needed.

4.6.K Lorazepam

4.6.K.1 Depression

a) Fluvoxamine (50 to 300 mg/d) was compared with lorazepam (1 to 6 mg/d) in a multi-center, double-blind, parallel group study in 112 general practice patients with mixed anxiety and depression. Response was assessed over a 6-week period using the Montgomery-Asberg Depression Rating Scale (MADRS) and the Clinical Anxiety Scale (CAS). There were no significant differences between treatments at any point except in an elderly subgroup where anxiety improved more rapidly with lorazepam. There were significant improvements in MADRS and CAS, and global ratings compared with baseline at all subsequent assessments. Lorazepam produced more sedation while fluvoxamine produced more nausea and vomiting (Laws et al, 1990).

4.6.L Maprotiline

4.6.L.1 Schizophrenia

a) Fluvoxamine was more effective than maprotiline for improving negative symptoms associated with schizophrenia. Patients entered in this study had schizophrenia of at least 2 years duration and received more than 1 antipsychotic with anticholinergics (stable dose maintained during study). Patients (n=38) were

randomly assigned to fluvoxamine or maprotiline 50 milligrams (mg) daily which was increased to 100 mg during the remaining 5 weeks of the study. Thirteen patients left the study within 2 weeks due to personal reasons, side effects, or worsening symptoms; these patients were NOT included in the efficacy analysis. The total score for the Scale for the Assessment of Negative Symptoms was significantly (p=0.045) lower in the fluvoxamine (65.6 to 57.1) versus maprotiline (80.3 to 78) group; similar results were obtained for the Brief Psychiatric Rating Scale for negative factors. Five (38.5%) patients in the fluvoxamine group were responders (defined by 20% improvement in total SANS score) versus none in the maprotiline group. The authors suggest that the serotonergic versus the antidepressant effect of fluvoxamine are responsible for the change in negative symptoms. Further study is needed since the sample size was small, and many patients left the study (Silver & Shmugliakov, 1998).

4.6.M Mianserin

4.6.M.1 Depression

a) Both fluvoxamine and mianserin are effective for the treatment of depressive illness (Perez & Ashford, 1990). Efficacy and CNS effects of fluvoxamine were compared with those of mianserin in depressed outpatients in a 6-week double-blind trial. The study included active treatment with 100 to 300 milligrams/d of fluvoxamine or 60 to 180 milligrams/d of mianserin. Data from 63 patients (30 fluvoxamine) showed comparable efficacy at the end of 6 weeks. MADRS scores (Montgomery-Asburg Depression Rating Scale) improved 65.6% with fluvoxamine and 60.8% with mianserin with no significant differences between treatments at any assessment. Mianserin produced more sedation during the first week of treatment but this difference resolved for the remainder of the study.

b) Fluvoxamine 50 to 200 milligrams and mianserin 20 to 80 milligrams/d were equivalent in efficacy and tolerability in a study of 57 elderly patients with major depressive episode. Seven of 25 fluvoxamine patients and 4 of 25 mianserin patients had to leave the study because of intolerable side effects (Phanjoo et al, 1991).

4.6.N Milnacipran

4.6.N.1 Depression

a) Although there was no significant difference in efficacy between groups of patients treated with fluvoxamine or milnacipran when viewed overall, among the subset of severely depressed patients, significantly more who were treated with milnacipran responded to treatment (50% or greater improvement in Hamilton Depression Rating Scale (HDRS) score) than who were treated with fluvoxamine. The groups comprised patients who had been treated with milnacipran (maximum dose 15 milligrams (mg) per day) for at least 22 months (n=102) or with fluvoxamine (maximum dose 250 mg/day) for the same period (n=90). Overall, 53% of milnacipran-treated patients and 47% of fluvoxamine-treated patients responded to treatment. Among patients with an initial HDRS score of 19 or greater, 69% of those treated with milnacipran and 46% of those treated with fluvoxamine responded (p=0.046). Scores showing improvement in insomnia and agitation significantly favored milnacipran. There were no significant differences between groups for individual or total adverse events. However, urological adverse events occurred more frequently in the milnacipran group and gastrointestinal symptoms in the fluvoxamine group. Palpitations occurred only in the milnacipran group (3%) (Fukuchi & Kanemoto, 2002).

b) Several comparative trials (mainly unpublished) have indicated no significant difference in efficacy between milnacipran 50 to 150 mg twice daily and fluvoxamine 100 mg twice daily or fluoxetine 20 mg once daily in major depression (Guelfi et al, 1998; Anon, 1997). One study reported the superiority of fluoxetine 20 mg once daily (statistically significant for most parameters) over milnacipran 100 mg once daily in major depressive outpatients (Ansseau et al, 1994); however, this study suffered from methodological problems, the most significant being once-daily dosing of milnacipran, which may not achieve therapeutic levels.

c) Meta-analyses of studies comparing milnacipran and fluoxetine/fluvoxamine have been performed by the manufacturer; greater improvements (eg, Hamilton, Montgomery-Asberg) were described for milnacipran, which were usually statistically significant (Lopez-Ibor et al, 1996; Anon, 1997; Elwood, 1997). However, only a few trials were selected for analysis, and not all patients in these trials were evaluated; the superiority of milnacipran was demonstrated only after results were subjected to multiple reanalysis (Anon, 1997).

d) Comparisons with other similar agents (eg, sertraline) are lacking.

4.6.O Oxaprotiline

4.6.O.1 Depression

a) Oxaprotiline appeared to be more efficacious than fluvoxamine in 71 depressed patients resistant to prior tricyclic antidepressants during a randomized, double-blind, partial crossover study (Nolen et al, 1988). Patients were randomized to receive either fluvoxamine or oxaprotiline at a starting dose of 50 mg BID, which was gradually increased to a maximum of 150 mg BID as tolerated. The mean daily doses of oxaprotiline and fluvoxamine at the end of 4 weeks were 260 mg and 288 mg, respectively. Only 9 of 33 (27%) patients receiving oxaprotiline demonstrated a response, while none of the fluvoxamine-treated patients responded. During the second treatment phase, 55 patients were crossed over to the other drug. The mean daily doses of oxaprotiline and fluvoxamine at the end of the second phase were 267 mg and 286 mg, respectively. Of the 31 patients completing at least 2 weeks of oxaprotiline therapy, 12 (38%)

responded; however, 6 (19%) relapsed within 6 months for a long-term response rate of only 19%. Of the 21 patients completing at least 2 weeks of fluvoxamine therapy, 2 patients (9%) responded with lasting effects.

4.6.P Paroxetine

4.6.P.1 Depression

a) Fluvoxamine and paroxetine produced similar improvements in depressive symptoms in patients with an initial or recurrent episode of major depression. Adverse effects occurred in 100% and 97% of patients treated with paroxetine and fluvoxamine, respectively. Fluvoxamine was associated with a higher incidence of asthenia, dry mouth, somnolence, and insomnia; whereas, paroxetine caused a higher incidence of headache, nausea, diarrhea, sweating, abnormal dreams, and sexual dysfunction. In this 7-week, randomized, double-blind study, 58 patients were assigned to receive fluvoxamine 50 milligrams(mg)/day or paroxetine 20 mg/day initially; the protocol allowed for dosage titration to fluvoxamine 150 mg/day or paroxetine 50 mg/day. An additional 10 fluvoxamine- and 8 paroxetine-treated patients dropped out of the study for various reasons, but all of the patients were included in the intent-to-treat efficacy analysis. Due to the small sample size of this study, only large differences between treatments would be detectable; therefore, larger studies are needed to detect differences in treatment effects between these drugs (Kiev & Feiger, 1997).

b) The pharmacology, pharmacokinetics, adverse effects, drug interactions, efficacy, and dosage and administration of fluvoxamine (FVX), sertraline (SRT) and paroxetine (PRX) were compared in a comprehensive review (Grimsley & Jann, 1992). All three agents have large volumes of distribution and are highly protein-bound. In contrast to fluoxetine, FVX, SRT, and PRX all have shorter elimination half-lives (approximately 24 hours) and are metabolized to clinically-inactive compounds. Nausea was the most commonly reported adverse effect for all three agents. Other reported adverse effects include sedation, headache, dry mouth, insomnia, sexual dysfucntion, and constipation. FVX has been found to be superior to placebo and equivalent to imipramine, clomipramine, desipramine, mianserin, and maprotiline in the treatment of depression and both FVX and SRT have been shown to be superior to placebo in the treatment of obsessive-compulsive disorder (OCD). PRX has been found to be superior to placebo and equivalent to amitriptyline, imipramine, clomipramine, and doxepin in the treatment of depression while SRT has been found to be superior to placebo and equivalent to amitriptyline. Clinical experience has demonstrated all three drugs to be effective in the treatment of depression. They may be especially useful in elderly patients, in those who cannot tolerate alternate treatments, and in those who do not respond to adequate trials of other antidepressant therapies.

4.6.Q Sertraline

4.6.Q.1 Depression

a) In a small study (n=64), the incidence of recurrent depression was similar between patients treated prophylactically with sertraline and fluvoxamine. Sixty-four patients entered the study and received either sertraline 100 milligrams(mg)/day or fluvoxamine 200 mg/day for 2 years; increases in dose were allowed if depression recurred. During the study period, 7 sertraline-treated and 6 fluvoxamine-treated patients had a new episode of depression (p=0.88). Adverse effects were minor and transient for both treatments. Results of this study suggest that sertraline and fluvoxamine were effective for preventing recurrent depression episodes, but are limited by the absence of a placebo control group(Franchini et al, 1997).

b) The pharmacology, pharmacokinetics, adverse effects, drug interactions, efficacy, and dosage of fluvoxamine (FVX), sertraline (SRT) and paroxetine (PRX) were compared in a comprehensive review (Grimsley & Jann, 1992a). All three agents have large volumes of distribution and are highly protein-bound. In comparison to fluoxetine, FVX, SRT, and PRX all have shorter elimination half-lives (approximately 24 hours) and are metabolized to clinically-inactive compounds. These agents, therefore, are less likely than fluoxetine to interact with other drugs. Nausea was the most commonly reported adverse effect for all three agents. Other reported adverse effects include sedation, headache, dry mouth, insomnia, sexual dysfunction, and constipation. FVX has been found to be superior to placebo and equivalent to imipramine, clomipramine, desipramine, mianserin, and maprotiline in the treatment of depression and both FVX and SRT have been shown to be superior to placebo in the treatment of obsessive-compulsive disorder (OCD). PRX has been found to be superior to placebo and equivalent to amitriptyline, imipramine, clomipramine, and doxepin in the treatment of depression while SRT has been found to be superior to placebo and equivalent to amitriptyline. Clinical experience has demonstrated all three drugs to be effective in the treatment of depression. They may be especially useful in elderly patients, in those who cannot tolerate alternate treatments, and in those who do not respond to adequate trials of other antidepressant therapies.

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Last Modified: June 23, 2009

DRUGDEX® Evaluations

THIORIDAZINE

0.0 Overview

1) Class
- **a)** This drug is a member of the following class(es):
  - Antipsychotic
  - Phenothiazine
  - Piperidine

2) Dosing Information
- **a)** Thioridazine Hydrochloride
  - **1)** Adult
    - **a)** Schizophrenia, Refractory
      - **1)** initial, 50 to 100 mg ORALLY 3 times a day; may increase gradually to a MAX of 800 mg/day in 2 to 4 divided doses (Prod Info Mellaril(R), 2000)
      - **2)** maintenance, once effective control of symptoms achieved, may gradually reduce dose to determine the minimum maintenance dose (range from 200 to 800 mg/day in 2 to 4 divided doses) (Prod Info Mellaril(R), 2000)
  - **2)** Pediatric
    - **a)** Safety and effectiveness not established in children under 2 years of age
      - **1)** Schizophrenia, Refractory
        - **a)** initial, 0.5 mg/kg/day in divided doses; may increase gradually to a MAX of 3 mg/kg/day (Prod Info Mellaril(R), 2000)

3) Contraindications
- **a)** Thioridazine Hydrochloride
  - **1)** abnormal serum potassium concentration
  - **2)** central nervous system (CNS) depression, coma, or drug-induced CNS depression
  - **3)** co-administration with other drugs that cause QTc-interval prolongation or drugs that inhibit thioridazine metabolism or clearance
  - **4)** history of cardiac arrhythmias or QTc-interval prolongation
  - **5)** hypersensitivity to thioridazine
  - **6)** patients with a QTc-interval greater than 450 milliseconds
  - **7)** patients with reduced hepatic cytochrome P450 2D6 enzyme activity
  - **8)** patients with severe hypertensive or hypotensive heart disease

4) Serious Adverse Effects
- **a)** Thioridazine Hydrochloride
  - **1)** Agranulocytosis
  - **2)** Cholestatic jaundice syndrome
  - **3)** Death
  - **4)** Disorder of hematopoietic structure
  - **5)** Drug-induced lupus erythematosus, Systemic
  - **6)** Ineffective thermoregulation, Heatstroke or hypothermia
  - **7)** Leukopenia
  - **8)** Neuroleptic malignant syndrome
  - **9)** Obstipation
  - **10)** Paralytic ileus
  - **11)** Priapism
  - **12)** Prolonged QT interval
  - **13)** Seizure
  - **14)** Sudden cardiac death
  - **15)** Thrombocytopenia
  - **16)** Torsades de pointes

5) Clinical Applications
- **a)** Thioridazine Hydrochloride
  - **1)** FDA Approved Indications
    - **a)** Schizophrenia, Refractory

1.0 Dosing Information

Drug Properties

Storage and Stability

Adult Dosage

Pediatric Dosage

1.1 Drug Properties

A) Information on specific products and dosage forms can be obtained by referring to the Tradename List (Product Index)

B) Synonyms

Thioridazine
Thioridazine HCl
Thioridazine Hydrochloride

1.2 Storage and Stability

A) Thioridazine Hydrochloride

1) Oral route

a) Thioridazine tablets should be stored at 25 degrees Celsius (77 degrees Fahrenheit); excursions permitted to 15 to 30 degrees Celsius (59 to 86 degrees Fahrenheit) (Prod Info Mellaril(R), 2000ae).

b) Thioridazine oral solution should be stored below 30 degrees Celsius (86 degrees Fahrenheit) in a tightly sealed, amber bottle. The solution can be diluted in distilled water, tap water, or juices; storage of bulk dilutions is not recommended (Prod Info Mellaril(R), 2000ae).

c) Thioridazine when mixed with lithium citrate syrup (5 and 10 mL) is visually incompatible. Centrifugation of this mixture yielded two liquid phases, a clear supernatant and a viscous hydrophobic sediment. This mixture should be avoided due to the possibility that underdosing could occur (Theesen et al, 1981).

1.3 Adult Dosage

Normal Dosage

Dosage in Geriatric Patients

1.3.1 Normal Dosage

1.3.1.A Thioridazine Hydrochloride

1.3.1.A.1 Oral route

1.3.1.A.1.a Schizophrenia, Refractory

1) The usual oral starting dose of thioridazine for schizophrenia unresponsive to other agents is 50 to 100 milligrams three times daily with gradual incremental increases to a maximum of 800 milligrams/day if necessary. The dose should be reduced gradually to determine the minimum maintenance dose once effective control of symptoms has been achieved (Prod Info Mellaril(R), 2000ae).

1.3.1.A.2 IMPORTANT NOTE

a) Patients being considered for thioridazine therapy should have baseline electrocardiograms and measurement of serum potassium concentrations. Thioridazine is contraindicated in patients with a QTc-interval greater than 450 milliseconds and in patients with a history of cardiac arrhythmias. The drug should not be given until serum potassium levels are within the normal range (Prod Info Mellaril(R), 2000ae).

1.3.1.A.3 MAXIMUM DOSE

a) Thioridazine doses should not exceed 800 milligrams/day as higher doses have been associated with pigmentation retinopathy and irreversible blindness (Prod Info Mellaril(R), 2000ae).

1.3.1.A.4 ORAL SOLUTION PREPARATION

a) The oral concentrate of thioridazine may be diluted with distilled water, acidified tap water, or suitable juices. Each dose should be diluted just prior to administration. The preparation and storage of bulk dilutions is not recommended (Prod Info Mellaril(R), 2000ae).

1.3.4 Dosage in Geriatric Patients

A) Thioridazine Hydrochloride

1) Elderly patients should be treated with reduced doses of phenothiazine drugs and monitored closely for excessive parkinsonism side effects. This patient population has a higher incidence of these side effects which may be irreversible and unresponsive to conventional anti-parkinsonian drugs (Ayd, 1961; Paulson, 1968). Unless there are compelling reasons to the contrary, thioridazine use in the elderly should be avoided because of side effect-related complications.

2) Significantly higher plasma concentrations of thioridazine (1.5- to 2-fold higher) were reported in elderly patients (mean age, 76 years) as compared with young adults (mean age, 28 years). Adverse effects (postural hypotension, dry mouth) were more frequent and severe in the elderly subjects. These data suggest that dosing reductions are indicated in elderly patients receiving thioridazine (Cohen & Sommer, 1988).

1.4 Pediatric Dosage

1.4.1 Normal Dosage

1.4.1.A Thioridazine Hydrochloride

1.4.1.A.1 Oral route

1.4.1.A.1.a Schizophrenia, Refractory

1) For children who suffer from schizophrenia unresponsive to other agents, the recommended dose of oral thioridazine is 0.5 milligram/kilogram/day in divided doses. Dosage may be titrated gradually to optimum clinical response or to the maximum dose of 3 milligrams/kilogram/day (Prod Info Mellaril(R), 2000ae).

1.4.1.A.2 IMPORTANT NOTE

a) Patients being considered for thioridazine therapy should have baseline electrocardiograms and measurement of serum potassium concentrations. Thioridazine is contraindicated in patients with a QTc-interval greater than 450 milliseconds and in patients with a history of cardiac arrhythmias. The drug should not be given until serum potassium levels are within the normal range (Prod Info Mellaril(R), 2000ae).

1.4.1.A.3 MAXIMUM DOSE

a) Thioridazine doses should not exceed 3 milligrams/kilogram/day as higher doses have been associated with pigmentation retinopathy and irreversible blindness (Prod Info Mellaril(R), 2000ae).

1.4.1.A.4 ORAL SOLUTION PREPARATION

a) The oral concentrate of thioridazine may be diluted with distilled water, acidified tap water, or suitable juices. Each dose should be diluted just prior to administration. The preparation and storage of bulk dilutions is not recommended (Prod Info Mellaril(R), 2000ae).

2.0 Pharmacokinetics

Drug Concentration Levels

ADME

2.2 Drug Concentration Levels

A) Thioridazine Hydrochloride

1) Therapeutic Drug Concentration

a) Schizophrenia, not established (Smith et al, 1985; Sajadi et al, 1984; Shvartsburd et al, 1984a).

2.3 ADME

Distribution

Metabolism

Excretion

Elimination Half-life

2.3.2 Distribution

A) Distribution Sites

1) Thioridazine Hydrochloride

a) OTHER DISTRIBUTION SITES

1) CEREBROSPINAL FLUID (Nyberg et al, 1981).

B) Distribution Kinetics

1) Thioridazine Hydrochloride

a) Volume of Distribution

1) 17.8 L/kg (Axelsson, 1977).

2.3.3 Metabolism

A) Metabolism Sites and Kinetics
1) Thioridazine Hydrochloride
a) LIVER, extensive (Sakalis, 1977; Axelsson & Martensson, 1977).
1) Thioridazine disposition was found to be influenced by debrisoquin hydroxylation phenotype (von Bahr et al, 1991).

B) Metabolites
1) Thioridazine Hydrochloride
a) MESORIDAZINE, active (Cohen et al, 1979; Aguilar, 1975).
1) MESORIDAZINE is twice as potent as THIORIDAZINE and is commercially available as Serentil (R) (Cohen et al, 1979; Aguilar, 1975).
b) Sulforidazine, (active) (Chakraborty et al, 1989).
c) 5-sulfoxide (ring), inactive (Sakalis, 1977; Axelsson & Martensson, 1977).

2.3.4 Excretion

A) Kidney
1) Thioridazine Hydrochloride
a) Renal Excretion (%)
1) small amounts (Sakalis, 1977; Axelsson & Martensson, 1977).

2.3.5 Elimination Half-life

A) Parent Compound
1) Thioridazine Hydrochloride
a) ELIMINATION HALF-LIFE
1) 21 to 24 hours (Shvartsburd et al, 1984a; Axelsson, 1977).

3.0 Cautions

Contraindications

Precautions

Adverse Reactions

Teratogenicity/Effects in Pregnancy/Breastfeeding

Drug Interactions

3.0.A Black Box WARNING
1) Thioridazine Hydrochloride
a) Oral (Tablet; Solution)
1) Thioridazine hydrochloride has been shown to prolong the QTc interval in a dose related manner, and drugs with this potential, including thioridazine hydrochloride, have been associated with torsades de pointes-type arrhythmias and sudden death. Due to its potential for significant, possibly life-threatening, proarrhythmic effects, thioridazine hydrochloride should be reserved for use in the treatment of schizophrenic patients who fail to show an acceptable response to adequate courses of treatment with other antipsychotic drugs, either because of insufficient effectiveness or the inability to achieve an effective dose due to intolerable adverse effects from those drugs (Prod Info MELLARIL(R) oral tablet, solution, USP, MELLARIL-S(R) oral suspension, USP, 2000).

3.1 Contraindications

A) Thioridazine Hydrochloride
1) abnormal serum potassium concentration
2) central nervous system (CNS) depression, coma, or drug-induced CNS depression
3) co-administration with other drugs that cause QTc-interval prolongation or drugs that inhibit thioridazine metabolism or clearance
4) history of cardiac arrhythmias or QTc-interval prolongation
5) hypersensitivity to thioridazine
6) patients with a QTc-interval greater than 450 milliseconds
7) patients with reduced hepatic cytochrome P450 2D6 enzyme activity
8) patients with severe hypertensive or hypotensive heart disease

3.2 Precautions

A) Thioridazine Hydrochloride
1) elderly patients with dementia-related psychosis (unapproved use); increased risk of death reported with both conventional and atypical antipsychotics when used to treat behavorial and psychological symptoms associated with dementia (US Food and Drug Administration, 2008)
2) history of breast cancer (can elevate prolactin levels)
3) history of myasthenia gravis
4) history of neuroleptic malignant syndrome or tardive dyskinesia
5) leukopenia or agranulocytosis
6) patients participating in activities requiring complete mental alertness
7) seizure disorders

3.3 Adverse Reactions

Cardiovascular Effects

Dermatologic Effects

Endocrine/Metabolic Effects

Gastrointestinal Effects

Hematologic Effects

Hepatic Effects

Neurologic Effects

Ophthalmic Effects

Reproductive Effects

Respiratory Effects

Other

3.3.1 Cardiovascular Effects

3.3.1.A Thioridazine Hydrochloride

Cardiac dysrhythmia

EKG finding

Hypotension

Prolonged QT interval

Sudden cardiac death

Torsades de pointes

3.3.1.A.1 Cardiac dysrhythmia

a) Ventricular and supraventricular arrhythmias have been reported following therapeutic use of thioridazine and acute overdose. Arrhythmias have often been associated with conduction defects manifested by prolonged QRS interval and slight prolongation of the QT interval in association with either sinus bradycardia or tachycardia (Fletcher et al, 1969). Although in some cases discontinuation of the drug results in resolution of the cardiac arrhythmias and the return of a normal EKG within 2 weeks to 4 months (Fletcher et al, 1969), on occasion ventricular tachycardia may be refractory to conventional

modes of therapy including cardioversion, procainamide, and lidocaine. Electrical pacing with a transvenous electrical pacemaker has been reported to stabilize refractory arrhythmias (Annane et al, 1996) The increased cardiotoxicity of thioridazine over other neuroleptics was confirmed in a prospective study of neuroleptic overdosage (poisoning) in adult patients presenting to Newcastle (Australia) Hospitals between 1987-1993 (Buckley et al, 1996).
b) In a retrospective analysis of 141 adult thioridazine mono-intoxications, sinus tachycardia was a symptom of toxicity in 21% of the cases. The arrhythmia occurred after ingestion of 1125 mg (median; range 250 to 8000 mg) (Schuerch et al, 1996).
c) A 68-year-old male suffered central nervous, cardiovascular, and gastrointestinal adverse effects over 9 days after a severe thioridazine intoxication. During high toxic thioridazine plasma concentrations (6061 to 6480 nanograms/mL), the patient developed life-threatening ventricular arrhythmias followed by bradycardia. The electrocardiogram showed delays in all parts of the conduction system. A transitory atrial pacemaker was inserted to maintain a hemodynamically favorable rhythm (Schmidt & Lang, 1997).

3.3.1.A.2 EKG finding
a) Use of thioridazine was found to carry a significant risk for QT interval prolongation in patients on psychotropic medications, with an odds ratio of 5.4 linking thioridazine therapy with QT interval abnormalities (p less than 0.001). This conclusion was based on a study using logistic regression and backwards stepwise regression to determine risk factors for QT interval lengthening in patients enrolled in psychiatric treatment programs (n=495). Overall, 64 of 495 patients were taking thioridazine. Of the 64 thioridazine-users, 15 (almost 25%) were found to have abnormally lengthened QT intervals. QT intervals of 456 msec or greater were defined as abnormal, based on a review of electrocardiograms for 101 healthy volunteers. When dose-levels were looked at, only 4 thioridazine-treated patients were considered to be in the high-dose range (eg, 600 mg/day or greater); however, two of these 4 patients had abnormally prolonged QT intervals. It was suggested that thioridazine causes this effect by blocking the delayed rectifier potassium channel in the myocardium, resulting in abnormal repolarization. The authors concluded that thioridazine confers an increased risk of drug-induced arrhythmias (Reilly et al, 2000).
b) Some data indicate that ECG changes induced by thioridazine, particularly those involving T-waves, become more severe with increasing age. Although these changes are in most cases asymptomatic, elderly patients and particularly those with cardiac disease should be monitored (Thornton & Wendkos, 1971).
c) T-wave changes have been reported to represent a reversible benign repolarization disturbance rather than any indication of cardiotoxic effects. Administration of isosorbide dinitrate, ergotamine, potassium salts or isoproterenol have been reported to resolve T-wave abnormalities (Pietro, 1981).
d) EKG and serum thioridazine concentrations were studied in 43 patients with paranoid psychosis. Significant positive correlations were found between serum drug concentrations and type I changes (rounded, leveled, or notched T-waves) while Type II changes (diphasic waves) showed no concentration dependence (Axelsson & Asperstrom, 1982).

3.3.1.A.3 Hypotension
a) Labile hypertension occurred in a 62-year-old patient who was treated with thioridazine 200 mg per day. Within 3 weeks after stopping the thioridazine, episodes of hypertension (systolic 150 to 180, diastolic 100 to 120) lasting 4 to 8 hours were noted. After reinstituting thioridazine dosage at 300 mg per day, blood pressure was lowered to normal with no further hypertensive episodes (Thaker et al, 1985).

3.3.1.A.4 Prolonged QT interval
a) Summary
1) Prolongation of the QT interval, along with ventricular and supraventricular arrhythmias, have been reported following therapeutic use of thioridazine and acute overdose (Reilly et al, 2000; Prod Info Mellaril(R), 2000ae; Buckley et al, 1996). Due to the association between thioridazine therapy and QT interval prolongation, the US Food and Drug Administration requested a labeling change as of July 2000, such that use of thioridazine should be reserved for schizophrenic patients who have failed to respond to other antipsychotic agents (Anon, 2000). Occasionally, prolongation of the QT interval has led to the development of torsade de pointes (Kiriike et al, 1987). Rare cases of hypotension have also occurred (Prod Info Mellaril(R), 2000ae).
b) Incidence: rare
c) Thioridazine lengthens the QTc-interval in a dose-related manner, and drugs with this potential, including thioridazine, have been associated with arrhythmias of the torsade de pointes-type and sudden death. In 9 healthy males, QTc-interval increased by 23 milliseconds following a 50-mg dose of thioridazine (Prod Info Mellaril(R), 2000ae).

3.3.1.A.5 Sudden cardiac death
a) In a large, retrospective, cohort study that included a primary cohort of 93,300 users of antipsychotic drugs and 186,600 non-users of antipsychotic drugs, there was an increased risk of sudden cardiac death in adult participants 30 to 74 years of age (mean age of 45.7 years) who were using thioridazine

compared to those who were not using antipsychotic drugs (incidence-rate ratio, 3.19; 95% confidence interval (CI), 2.41 to 4.21; p less than 0.001). In participants being treated with typical antidepressants (haloperidol, thioridazine), the incidence-rate ratio for sudden cardiac death increased from 1.31 (95% CI, 0.97 to 1.77) for those using low doses to 2.42 (95% CI, 1.91 to 3.06) for those using high doses (p less than 0.001) (Ray et al, 2009).

3.3.1.A.6 Torsades de pointes

a) Incidence: rare

b) Atypical ventricular tachycardia (torsade de pointes) presumably secondary to thioridazine was reported in a 53-year-old male and was successfully treated with isoproterenol infusion after unsuccessful use of other agents (Kemper et al, 1983).

c) A 56-year-old schizophrenic patient receiving thioridazine, trifluoperazine, and benztropine experienced syncope (Raehl et al, 1985). The patient experienced episodes of ventricular tachycardia with multifocal PVCs and torsade de pointes.

d) A patient had a preexisting prolonged QT interval that led to the development of potentially fatal ventricular arrhythmia (torsade de pointes) during low-dose, short-term therapy with thioridazine. The recurrent ventricular tachyarrhythmia was exacerbated by lidocaine and procainamide therapy but was effectively controlled by cardiac pacing (Kiriike et al, 1987).

e) Complete heart block and torsade de pointes was associated with thioridazine poisoning (3 grams). A 72-year-old female was semi comatose and had persistent third degree atrioventricular block, progressive hypotension and torsade de pointes. These symptoms resolved within 48 hours and no adverse sequelae persisted (Hulisz et al, 1994).

3.3.2 Dermatologic Effects

3.3.2.A Thioridazine Hydrochloride

Erythema multiforme

Pseudolymphoma

3.3.2.A.1 Erythema multiforme

a) Thioridazine 400 and 800 mg orally daily for 17 days was associated with the occurrence of erythema multiforme of the oral cavity in a 22-year-old patient with psychosis (Rees, 1985). Improvement of lesions was observed within 48 hours after the discontinuation of thioridazine and symptomatic treatment.

3.3.2.A.2 Pseudolymphoma

a) A case of pseudolymphoma, manifested by itchy, slightly infiltrated erythemato-popular lesions in the face exacerbating after sun exposure, was reported in a patient taking thioridazine for 5 1/2 years (Kardaun et al, 1988). All lesions disappeared four weeks after the drug was discontinued.

3.3.3 Endocrine/Metabolic Effects

3.3.3.A Thioridazine Hydrochloride

Body temperature above normal

Hirsutism

Hyperprolactinemia

Syndrome of inappropriate antidiuretic hormone secretion

Weight gain

3.3.3.A.1 Body temperature above normal

a) Apparent hyperpyrexia was induced by thioridazine in 43-year-old schizophrenic. The patient was taking 100 mg three times/day and was exposed to a non-air-conditioned environment during prolonged hot, humid weather (Jacknowitz, 1979).

b) Treatment with thioridazine resulted in hyperpyrexia and ventricular tachycardia in a young woman who was later shown to have thyrotoxicosis. Authors concluded that hyperthyroidism may enhance

thioridazine toxicity (Murphy & Fitzgerald, 1984).
c) In a study of hypothermia in the elderly, the effects of chlormethiazole, thioridazine, and lormetazepam were compared. Three out of 14 patients experienced postural hypotension (chlormethiazole group) while 11 of 14 developed the same reaction following thioridazine. Chlormethiazole was equal to placebo in hypothermia, while thioridazine and lormetazepam caused a fall in temperature. For behavior control in the elderly, and for use as a hypnotic, chlormethiazole seems to be safer than thioridazine or lormetazepam (McCarthy et al, 1986).

3.3.3.A.2 Hirsutism
a) A case of hirsutism associated with long-term thioridazine use (100 mg three times/day for 10 years) was reported (Phillips et al, 1979).

3.3.3.A.3 Hyperprolactinemia
a) Increased tumor size of a prolactin-secreting pituitary chromophobe adenoma occurred in a 42-year-old schizophrenic male who was receiving thioridazine. Thioridazine was discontinued and the patient started on bromocriptine 7.5 mg/day to decrease tumor size and diazepam to control anxiety. Peripheral vision improved and prolactin levels decreased over the next 6 months (Weingarten & Thompson, 1985).

3.3.3.A.4 Syndrome of inappropriate antidiuretic hormone secretion
a) Summary
1) The syndrome of inappropriate antidiuretic hormone secretion (SIADH) has been infrequently reported with phenothiazines.
b) SIADH was reported in a 42-year-old male receiving thioridazine 400 milligrams daily. The patient presented with symptoms of hyponatremia (serum sodium of 113 mEq/L), metabolic alkalosis, and coma. The sodium level returned to normal following discontinuation of thioridazine and supportive therapy, which included a normal saline infusion. The patient had similar hyponatremic episodes with other phenothiazine derivatives (Ananth & Lin, 1987).
c) A 58-year-old woman with chronic depression became acutely agitated and received 500 milligrams of thioridazine within an hour. It was noted that her water consumption increased during a 9-hour period. The patient was found unresponsive with intermittent seizure activity. Serum sodium was 114 mEq/L, while plasma and urine osmolality were 235 and 512 mOsm/kg, respectively. Fluid restriction improved the signs and symptoms of SIADH (Vincent & Emery, 1978).
d) One case of syndrome of inappropriate antidiuretic hormone secretion (SIADH) was reported in a 60-year-old schizophrenic patient who received thioridazine 150 milligrams/day for several months. The patient was comatose, possessed a serum sodium of 112 mEq/L, urine sodium of 17 mEq/L, and serum and urine osmolality of 239 and 257 mOsm/kg, respectively. A hemogram, ECG, brain scan, and roentgenograms of the skull, chest, and spine were normal. Thyroid, adrenal, liver, and kidney function tests were also within normal limits. An EEG revealed a diffuse slow-wave abnormality. The patient was treated with fluid restriction, regained consciousness, and was subsequently discharged (Matuk & Kalyanaraman, 1977).

3.3.3.A.5 Weight gain
a) Thioridazine administration was associated with weight gain in acute paranoid psychotic patients. Participants were divided into 3 subgroups: male patients (25 to 68 years old); female patients younger than 50 years old; and female patients older than 50 years old. Doses ranged from 80 to 1000 milligrams/day. Out of 8 male patients, 5 experienced a 1% to 10% increase in weight, while 3 demonstrated a 1 to 5% reduction in weight. All 9 female patients, younger than 50 years old, displayed a 1% to 20% increase in body weight. Eight of 16 female patients older than 50 years old experienced a 1% to 15% increase in weight, 4 individuals maintained their weight, and 3 subjects demonstrated a 1% to 5% reduction in weight. No specific doses were mentioned to determine if a dose response relationship existed (Ohman & Axelsson, 1980).

3.3.4 Gastrointestinal Effects

3.3.4.A Thioridazine Hydrochloride

Constipation

Dysphagia

Parotitis

Vomiting

Xerostomia

3.3.4.A.1 Constipation

a) Constipation and DIARRHEA have been reported with thioridazine therapy (Prod Info Mellaril(R), 2000ae).

3.3.4.A.2 Dysphagia

See Drug Consult reference: ANTIPSYCHOTIC-INDUCED DYSPHAGIA

3.3.4.A.3 Parotitis

a) A 21-year-old female treated with doses of up to 2 g/day of thioridazine with trifluoperazine developed an enlargement of the parotid glands. Discontinuation of thioridazine resulted in the glands returning to normal despite continued trifluoperazine administration. Readministration of thioridazine resulted in gland enlargement. The author postulated that passive congestion as a result of the atropine-like effects of the phenothiazine caused SALIVARY GLAND ENLARGEMENT (Worthington, 1965).

3.3.4.A.4 Vomiting

a) Vomiting and symptoms of irritability have been associated with abrupt withdrawal of thioridazine therapy. A 9-year-old male with minimal brain dysfunction treated with 125 mg/day of thioridazine for 18 months developed symptoms of IRRITABILITY, STOMACH PAINS, NAUSEA and vomiting 1 to 3 weeks following abrupt withdrawal of the drug. In addition, dyskinetic movements including choreoathetotic movements of the hands and fingers associated with facial grimacing also developed on the fourteenth day post-withdrawal but decreased in frequency lasting up to 90 days (Yepes & Winsburg, 1977).

3.3.4.A.5 Xerostomia

a) Dryness of the mouth has been reported with thioridazine therapy (Prod Info Mellaril(R), 2000ae).

3.3.5 Hematologic Effects

3.3.5.A Thioridazine Hydrochloride

3.3.5.A.1 Agranulocytosis

a) Summary

1) Leukopenia and agranulocytosis are the most common hematopoietic adverse drug reactions reported with thioridazine, and the phenothiazine derivatives are frequently implicated in this reaction. Estimates of the incidence of phenothiazine-induced agranulocytosis vary from 1 to 300 per 100,000 patients.

b) Incidence: rare

c) A female was treated with thioridazine and developed agranulocytosis and THROMBOCYTOPENIA and subsequently died due to cerebral hemorrhage (Ekblom & Walinder, 1965).

3.3.6 Hepatic Effects

3.3.6.A Thioridazine Hydrochloride

3.3.6.A.1 Hepatotoxicity

a) Summary

1) Nearly all the phenothiazines have been associated with the picture of cholestatic jaundice or mixed cholestatic-hepatocellular jaundice. Onset of clinical jaundice usually occurs during the second to fourth week of therapy, but the reaction is not necessarily related to either dose or duration of therapy.

b) Possible thioridazine-induced hepatic dysfunction was reported in a 38-year-old female who received thioridazine 300 milligrams/day. Six days following the initiation of thioridazine the patient became delusional, edematous, and serum AST (aspartate aminotransferase) was 104 units/L (normal 0 to 41 units/L), while ALT (alanine aminotransferase) was 48 units/L (normal 0 to 45 units/L), and LDH (lactate dehydrogenase) was 376 units/L (normal 100 to 225 units/L). Thioridazine was discontinued and the serum levels of AST and ALT normalized within 7 days, however the LDH remained elevated (305 units/L). It is difficult to assess the relationship of thioridazine to the development of transient hepatic dysfunction, as amitriptyline was administered concurrently (Pies, 1982).

c) Hepatic dysfunction associated with thioridazine which presented with normal bilirubin and normal liver enzyme levels was reported in a 34-year-old male schizophrenic (Urberg, 1990).

3.3.9 Neurologic Effects

3.3.9.A Thioridazine Hydrochloride

Central nervous system finding

Confusion

Extrapyramidal sign

Neuroleptic malignant syndrome

Parkinsonism

Seizure

Tardive dyskinesia

3.3.9.A.1 Central nervous system finding

a) Summary

1) Drowsiness is common, especially with large doses, but tends to diminish with continued therapy (Prod Info Mellaril(R), 2000ae). Extrapyramidal symptoms, tardive dyskinesia, and confusion occur less frequently; however, these side effects are more serious and may require a reduction in dosage (Theofilopolous et al, 1984; Jeste et al, 1982; Meyer et al, 1983).

b) In a retrospective analysis of 141 adult thioridazine mono-intoxications, the most frequent symptoms of toxicity, were DROWSINESS and sinus tachycardia (Schuerch et al, 1996). Drowsiness occurred after ingestion of 1225 mg (median; range 100 to 5000 mg) and sinus tachycardia occurred after ingestion of 1125 mg (median; range 250 to 8000 mg). The most frequent symptom of intoxication in 61 pediatric cases was drowsiness, which occurred after a median thioridazine ingestion of 4 mg/kg (range 2.2 to 27 mg/kg).

c) A 10-year-old boy treated concurrently with thioridazine and methylphenidate developed persistent TICS of the head and shoulders. Clonidine did not reduce the tics, suggesting the site of dysfunction is not within the noradrenergic system (Casat & Wilson, 1986).

d) Two hyperactive boys, who had developed motor and phonic tics during stimulant treatment, reacted similarly to low doses of haloperidol and thioridazine. Neuroleptic-induced tics may be a consequence of presynaptic dopamine blockade (Gualtieri & Patterson, 1986).

3.3.9.A.2 Confusion

a) A case of a 35-year-old female treated with thioridazine 25 mg orally 3 times/day developed a toxic confusion state. Discontinuation of thioridazine and institution of chlordiazepoxide resulted in clearing of the symptoms (De Hart, 1969).

b) A 67-year-old male treated with thioridazine for chronic brain syndrome developed, at higher dosages (25 to 50 mg twice a day), a toxic confusional state characterized as hyperactivity, startle reaction, coma, and Cheyne-Stokes respiration. Lowering of the dosage of the drug to 25 mg/day resulted in the patient becoming less comatose and less stuporous (Hader & Schulman, 1965).

c) The influence of thioridazine (1 and 1.5 mg/kg) on human cognitive, psychomotor, and reaction performance as well as subjective feelings was studied. Equivalent doses ranged from 65 to 80 mg and 97 to 120 mg. Performance was reduced in all areas and the most pronounced effects occurred in the subjective state of well-being. Reaction performance was impaired only at the higher dose. Effects on cognitive performance varied and showed least correlation with dose (Meyer et al, 1983).

d) Confusion, memory impairment, and cognitive deficits were reported in a 17-year-old female schizophrenic patient who was treated with thioridazine 200 mg per day and lithium carbonate 1200 mg/day. Lithium levels were nontoxic (0.8 to 0.9 mEq/L) (Bailine & Doft, 1986).

3.3.9.A.3 Extrapyramidal sign

a) Thioridazine has been shown to cause significant impairment of psychomotor performance as measured by pencil-and-paper tests, critical flicker fusion frequency, wire-maze tracing and tapping. Doses of 50 mg were evaluated in healthy volunteers (Theofilopolous et al, 1984).

3.3.9.A.4 Neuroleptic malignant syndrome

a) Incidence: rare

b) A case of neuroleptic malignant syndrome (NMS) was reported in a 70-year-old psychiatric patient who had taken 100 to 300 mg of thioridazine per day for 18 months (Twemlow & Bair, 1983).

c) A neuroleptic malignant syndrome was described in a 22-year-old woman with psychosis following an increase of her dose of thioridazine to 75 mg daily (Zammit & Sullivan, 1987). The patient responded

initially to withdrawal of thioridazine, however haloperidol administration for 1 day was followed by return of symptoms. Withdrawal of haloperidol resulted in stabilization; however, the patient remained psychotic and was eventually treated successfully with chlorpromazine without adverse sequelae. These data suggest that thioridazine may also cause the neuroleptic malignant syndrome.

3.3.9.A.5 Parkinsonism

a) Summary

1) Contrary to common belief, the results of a retrospective cohort study suggest that atypical antipsychotics may not be safer than typical antipsychotics when dose and potency are considered (Rochon et al, 2005).

b) LITERATURE REPORTS

1) The results of a cohort study indicate that high-dose atypical antipsychotic therapy carries a similar risk for the development of parkinsonism as does typical antipsychotic therapy. In a population-based, retrospective cohort study, adults (aged 66 years and older) with evidence of dementia were followed for up to 1 year for the development of parkinsonism symptoms associated with typical or atypical antipsychotic use. As compared with older adults receiving atypical antipsychotic therapy (ie, olanzapine, risperidone, quetiapine), incident parkinsonism was 30% more likely to occur in those taking typical antipsychotics (ie, chlorpromazine, haloperidol, perphenazine) (adjusted HR, 1.3; 95% CI, 1.04 to 1.58), and 60% less likely to occur in patient who did not receive either therapy (HR, 0.4; 95% CI, 0.29 to 0.43). Older adults using higher potency typical antipsychotics had almost a 50% greater risk of experiencing parkinsonism as compared with patients prescribed atypical antipsychotics (all were considered lower potency) (HR, 1.44; 95% CI, 1.13 to 1.84); however, in patients receiving lower potency typical antipsychotics, the risk of developing parkinsonism was no different from that in adults taking atypical antipsychotics (HR, 0.75; 95% CI. 0.48 to 1.15). In addition, a positive dose-related relationship was observed between the occurrence of incident parkinsonism and the use of atypical antipsychotics. The risk for developing parkinsonism was more than twice as great in patients using a high-dose atypical antipsychotic agent as compared with those prescribed a low-dose atypical antipsychotic agent (HR, 2.07; 95% CI, 1.42 to 3.02). Furthermore, patients taking a typical antipsychotic were found to have a similar risk for the development of parkinsonism as patients receiving high-dose atypical antipsychotic therapy (p=ns). The authors conclude that atypical antipsychotics may not be safer than typical antipsychotics when dose and potency are considered (Rochon et al, 2005).

3.3.9.A.6 Seizure

See Drug Consult reference: ANTIPSYCHOTICS - EFFECT ON SEIZURE THRESHOLD

3.3.9.A.7 Tardive dyskinesia

a) The risk of developing tardive dyskinesia and the likelihood it will become irreversible are thought to be associated with the duration of therapy and the cumulative dose; the elderly, especially elderly women, appear to be more prone to this syndrome (Prod Info Mellaril(R), 2000ae).

b) A 17-year-old female treated with 100 to 800 mg/day of thioridazine over a 2-year period developed tardive dyskinesia. Discontinuation of thioridazine and initiation of Deanol(R) therapy in doses of up to 1200 mg/day resulted in gradual improvement of the condition. After 3 months of deanol therapy the drug was discontinued, and the symptoms did not return (Kumar, 1976).

c) There was no correlation between serum concentrations of thioridazine and its major metabolites, THD-2-sulfoxide, THD-2-sulfone, and THD-5-oxide and presence of symptoms of tardive dyskinesia (TD) in elderly chronic schizophrenic patients (Widerlov et al, 1982). However, another study reported higher serum concentration-to-dose ratios in 16 middle aged or elderly female patients. Sulforidazine was significantly elevated in serum of TD patients compared to control (Jeste et al, 1982).

3.3.10 Ophthalmic Effects

3.3.10.A Thioridazine Hydrochloride

Oculogyric crisis

Retinopathy

3.3.10.A.1 Oculogyric crisis

a) Oculogyric crisis has been reported following the use of thioridazine 10 milligrams (Fitzgerald & Jankovic, 1989).

3.3.10.A.2 Retinopathy

a) Thioridazine has produced pigmentary retinopathy with visual impairment. This effect appears to be dose related. Patients develop pigmentary changes within 2 to 8 weeks after initiation of therapy with

acute symptoms including blurred vision, night blindness, and partial color blindness. After thioridazine is discontinued, pigmentary changes may still progress, however, visual function usually improves. Thioridazine appears to bind to the melanin granules in the retinal pigment epithelium which alters retinal enzyme kinetics (Shah et al, 1998). The manufacturer cautions not to exceed a maximum daily dose of 800 mg/day to avoid this adverse effect (Prod Info Mellaril(R), 2000ae).
b) A 28-year-old woman experienced decreased vision in both eyes for 2 weeks after receiving thioridazine 800 milligrams 4 times daily for 8 weeks. Her dilated fundus revealed a diffuse pigmentary retinopathy of the entire post-equatorial fundus. With fluorescein angiography, confluent areas of punctate hyperfluorescence consistent with diffuse retinal pigment epithelial alterations were seen (Shah et al, 1998).
c) Yellow vision occurred in a patient after receiving thioridazine 25 mg three times/day for 4 days (Giannini & Mahar, 1980, 1981).
d) Measurement of the oscillatory potentials of the electroretinogram (ERG) and the O2 wavelet may be necessary to detect early changes of the retina caused by thioridazine therapy. The investigators feel a daily dosage of 160 mg over the long term or 400 mg for shorter periods are critical levels of drug administration (Miyata et al, 1980).
e) Two of 18 mentally retarded institutionalized subjects who had received long-term, high dose treatment with thioridazine or chlorpromazine developed corneal and ventricular opacities (Gualtieri et al, 1982).
f) PIGMENTARY RETINOPATHY was reported in a 57-year-old woman receiving low doses of thioridazine (400 mg daily for approximately 15 years) (Lam & Remick, 1985).
g) Three cases of NUMMULAR RETINOPATHY caused by thioridazine were reported. This retinopathy is a clinical subset of classic thioridazine pigmentation retinopathy. Nummular areas of retinal pigment epithelial atrophy separated by relatively intact pigment epithelium are found in the midretinal periphery with sparing of central vision. This can occur with doses of thioridazine previously considered safe (Kozy et al, 1984). Severe nummular retinopathy and visual dysfunction were reported in a 52-year-old male with paranoid schizophrenia taking thioridazine 200 milligrams or less, over the past 13 years (Tekell et al, 1996).
h) A 51-year-old female patient developed pigmentation retinopathy after taking 400 to 800 mg thioridazine for 2 months. This is below the 800 mg ceiling dose recommended by the manufacturer and suggests that clinicians should carefully investigate visual complaints of patients taking thioridazine in the upper end of the approved dosage range (Hamilton, 1985).
i) Thioridazine toxicity to the eye has been described as "progressive chorioretinopathy", but this designation can be misleading. During the first year after TDZ exposure, retinal pigmentation evolves from a granular to a patchy or nummular appearance. However, visual function and the electroretinogram typically improve during this period. Some cases may show chorioretinal atrophy and functional loss many years later, but there is little evidence for drug-related progression. Late atrophy may represent degeneration of cells that were injured subclinically during the time of initial drug exposure. Although TDZ toxicity produces an evolving pigmentary disturbance, functional changes must be monitored independently of fundus appearance (Marmor, 1990).

3.3.14 Reproductive Effects

3.3.14.A Thioridazine Hydrochloride

Breast cancer

Sexual dysfunction

3.3.14.A.1 Breast cancer

a) Benign INTRADUCTAL PAPILLOMA occurred in a 71-year-old male following approximately 10 years of treatment of thioridazine for a chronic psychiatric disorder (Sara & Gottfried, 1987). Examination revealed a subareolar mass distending the left nipple with no discharge; the right breast was unaffected. Six months later, recurrence of a mass in the same breast was observed without pain or discharge, presumably during continued thioridazine therapy. No data were presented regarding effects of withdrawal of Mellaril(R) or substitution therapy with other non-phenothiazine psychotropic agents, and it is impossible to definitely attribute the papilloma to phenothiazine therapy.

3.3.14.A.2 Sexual dysfunction

a) INHIBITION OF EJACULATION related to thioridazine occurred in a 32-year-old patient 1 week after starting the drug at a dose of 200 mg/day (Yassa, 1983).
b) Four cases of male patients, age range 20 to 40 years, treated with oral thioridazine 100 mg four times/day developed histories of prolonged PAINFUL ERECTIONS (PRIAPISM) which persisted for 1 to 2 days. All patients were treated with corporeal aspiration and corpus cavernosum-corpus spongiosum shunts with good results. The authors postulated the mechanism to be due to peripheral adrenergic

blockade (Dorman & Schmidt, 1976).
c) An 11-year-old boy receiving thioridazine for attention deficit disorder presented to the emergency room with PRIAPISM 30 hours in duration. A penile block with 1% lidocaine was performed. Using a 27 gauge needle inserted into 1 corporeal body, 0.2 to 0.4 milliliters of phenylephrine 1 milligram/milliliter was instilled every 15 minutes until detumescence occurred. No adverse effects were observed (Siegel & Reda, 1997).
See Drug Consult reference: DRUG-INDUCED SEXUAL DYSFUNCTION

3.3.15 Respiratory Effects

3.3.15.A Thioridazine Hydrochloride

3.3.15.A.1 Pulmonary embolism
a) The use of psychotropic medications has been linked to an increased risk of fatal pulmonary embolism. In a case-control study including 62 cases of fatal pulmonary embolism and 243 matched controls, researchers found that compared to non-use, the current use of conventional antipsychotic medications (ie, thioridazine and haloperidol) was associated with an increased risk of fatal pulmonary embolism (adjusted odds ratio, 13.3; 95% confidence interval (CI), 2.3 to 76.3). In addition, low potency antipsychotics, such as thioridazine, were associated with the highest risk, with an odds ratio of 20.8 (95% CI, 1.7 to 259). The current use of antidepressants was also associated with an increased risk of fatal pulmonary embolism (adjusted odds ratio, 4.9; 95% CI, 1.1 to 22.5); however, current or past use of other psychotropic drugs was not associated with an increased risk (adjusted odds ratio, 1.4; 95% CI, 0.3 to 5.8). (Parkin et al, 2003).

3.3.16 Other

3.3.16.A Thioridazine Hydrochloride

Dead - sudden death

Death

Extrapyramidal disease

Withdrawal sign or symptom

3.3.16.A.1 Dead - sudden death
a) Sudden death has been associated with phenothiazines such as thioridazine (Shader & Greenblatt, 1998). Deaths are most likely of cardiac origin and may be attributable to phenothiazine-induced ventricular tachyarrhythmias.
b) A 68-year-old man being treated with thioridazine 25 milligrams 3 times daily for behavioral problems was found dead on the fifth day of treatment (Thomas & Cooper, 1998). His post-mortem examination revealed no coronary thrombosis, myocardial infarction, or other significant pathology except for ischemic heart disease. The certificate of death noted the cause of death as cardiac arrhythmia due to ischemic heart disease.
c) Thioridazine was associated with sudden death syndrome in a 20-year-old female hospitalized for bizarre behavior of 1 week duration and treated initially with chlorpromazine but with subsequent development of a skin rash (Goodson & Litkenhous, 1976). Therapy was changed to thioridazine 500 mg/day, and the patient remained hospitalized for 1 month, then was discharged. Approximately 7 months later, the patient was again admitted for bizarre behavior and received four 100-mg doses of chlorpromazine within 2 days before it was discovered that the patient was allergic to the drug. Treatment was immediately changed to thioridazine in a dose of 200 mg 4 times a day and following 4 days of treatment with thioridazine, the patient was found dead in bed. Autopsy revealed no cause of death.

3.3.16.A.2 Death
a) Results of a population-based, retrospective cohort study demonstrated that the use of conventional antipsychotics was associated with an even greater risk for death than atypical antipsychotics when administered to elderly patients (aged 66 years and older) with dementia. Atypical versus no antipsychotic use and conventional versus atypical antipsychotic use pair-wise comparisons were made. A total of 27,259 matched pairs were identified and the dementia cohort was stratified based on place of residence (community versus long-term care facilities). In order to adjust for difference in baseline health status, propensity score matching was used. The primary outcome of the study was all-cause mortality. The risk for death was evaluated at 30, 60, 120, and 180 days after the antipsychotic

medications were initially dispensed. There was a statistically significant increase in the risk for death at 30 days associated with new use of atypical antipsychotic medications compared with nonuse in both the community-dwelling cohort (adjusted hazard ratio (HR), 1.31 (95% confidence interval (CI), 1.02 to 1.70); absolute risk difference, 0.2 percentage point) and long-term care cohort (adjusted HR, 1.55 (95% CI, 1.15 to 2.07); absolute risk difference, 1.2 percentage points). For both cohorts, the risk associated with atypical antipsychotics appeared to persist to 180 days. The risk for death associated with conventional antipsychotics was even greater than the risk identified with atypical antipsychotics. At 30 days, the adjusted HR for the community-dwelling cohort was 1.55 (95% CI, 1.19 to 2.02) and 1.26 (95% CI, 1.04 to 1.53) for the long-term care cohort (adjusted risk difference for both was 1.1 percentage points). The risk appeared to persist to 180 days for both groups. Some important limitations to the study include unknown or unmeasured confounders may influence the results and cause of death could not be examined (Gill et al, 2007).

b) Results of a population-based, retrospective cohort study demonstrated comparable to possibly greater risk of death associated with the use of conventional antipsychotic medications in the elderly (aged 65 years and older) compared with atypical antipsychotic medications. The analysis excluded patients with cancer and included only new users of antipsychotic medications. The primary study outcome was 180-day all-cause mortality. A set of potential confounders was measured based on healthcare utilization data within 6 months before the initiation of antipsychotic medications. Of the 37,241 elderly patients identified, 12,882 and 24,359 received conventional and atypical antipsychotic medications, respectively. The risk of death in the conventional drug group within the first 180 days was 14.1% compared with 9.6% in the atypical drug group (unadjusted mortality ratio, 1.47; 95% confidence interval (CI), 1.39 to 1.56). In the multi-variable analysis which controlled for potential confounders, the adjusted mortality ratio for the risk of death within 180 days for conventional versus atypical drug therapy was 1.32 (95% CI, 1.23 to 1.42). When the most frequently prescribed conventional antipsychotic drugs were compared with risperidone, the mortality ratio associated with haloperidol was 2.14 (95% CI, 1.86 to 2.45) and loxapine was 1.29 (95% CI, 1.19 to 1.40), while there was no difference associated with olanzapine. The increased mortality risk for conventional versus atypical drug therapy was greatest when doses higher (above median) doses were used (mortality ratio 1.67; 95% CI, 1.5 to 1.86) and also during the first 40 days of therapy (mortality ratio 1.6; 95% CI, 1.42 to 1.8). Confirmatory analyses consisting of multi-variable Cox regression, propensity score, and instrumental variable estimation confirmed the results of the study (Schneeweiss et al, 2007).

c) The results of a retrospective cohort study indicate that conventional antipsychotic agents are at least as likely as atypical antipsychotic agents to increase the risk of death among elderly patients 65 years of age or older. The study included 9142 new users of conventional agents (mean age, 83.2 years) and 13,748 new users of atypical agents (mean age, 83.5 years). A higher adjusted relative risk of death was associated with the use of conventional antipsychotics as compared with atypical antipsychotics at all timepoints studied after beginning therapy (within 180 days: relative risk (RR), 1.37; 95% confidence interval (CI), 1.27 to 1.49; less than 40 days: RR, 1.56; 95% CI, 1.37 to 1.78; 40 to 79 days: RR, 1.37; 95% CI, 1.19 to 1.59; 80 to 180 days: RR, 1.27; 95% CI, 1.14 to 1.41). In addition, the adjusted risks of death observed in patients with dementia (RR, 1.29; 95% CI, 1.15 to 1.45), without dementia (RR, 1.45; 95% CI, 1.30 to 1.63), in a nursing home (RR, 1.26; 95% CI, 1.08 to 1.47), or not in a nursing home (RR, 1.42; 95% CI, 1.29 to 1.56) were also higher with the use of conventional antipsychotic therapy as compared with atypical antipsychotic use. This risk appeared to be dose-related and was greater with the use of higher dose (ie, greater than the median) conventional antipsychotics (RR, 1.73; 95% CI, 1.57 to 1.9). Additional studies which specifically investigate the optimum care of elderly patients requiring antipsychotic therapy are needed so that appropriate guidance regarding therapeutic intervention can be provided (Wang et al, 2005).

3.3.16.A.3 Extrapyramidal disease

See Drug Consult reference: NEUROLEPTIC-INDUCED EXTRAPYRAMIDAL REACTIONS

3.3.16.A.4 Withdrawal sign or symptom

a) Labile hypertension occurred in a 62-year-old patient who was treated with thioridazine 200 mg per day (Thaker et al, 1985). Within 3 weeks after stopping the thioridazine episodes of hypertension (systolic pressure 150 to 180 mmHg, diastolic pressure 100 to 120 mmHg) lasting 4 to 8 hours were noted. After reinstituting thioridazine dosage at 300 mg per day, blood pressure was lowered to normal with no further hypertensive episodes.

3.4 Teratogenicity/Effects in Pregnancy/Breastfeeding

A) Teratogenicity/Effects in Pregnancy

1) Australian Drug Evaluation Committee's (ADEC) Category: C (Batagol, 1996)

a) Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible. Accompanying texts should be consulted for further details.

See Drug Consult reference: PREGNANCY RISK CATEGORIES

2) Crosses Placenta: Yes

3) Clinical Management

a) In general, schizophrenia in pregnant patients represents a difficult clinical problem, for which few optimal

treatment options are available. If the benefits of treatment outweigh possible teratogenic risks (ie, if reality testing demonstrates a risk to life and limb, if the mother demonstrates gross inability to care for herself, and/or if supportive intervention including hospitalization is inadequate), antipsychotics should be used at the lowest effective dose to achieve adequate improvement in symptoms (Cohen et al, 1989; Spielvogel & Wile, 1986). Cautious use of high potency antipsychotics may yield the best therapeutic benefit with the least anticholinergic and sedative effects, however, clinical evaluations of comparative efficacy and safety are unavailable in this setting.

4) Literature Reports

a) In pooled data of 2,948 women exposed to phenothiazines during pregnancy, no increased risk for fetal malformations was demonstrated (relative risk: 1.03; 95% confidence interval: 0.88-1.22). One study did show a relationship between phenothiazine use and teratogenicity, but the study had many confounders (Magee et al, 2002).

b) Although phenothiazines have been implicated in several cases of congenital malformations (Freeman, 1972; Rafla, 1987), establishing a definite cause-effect relationship is extremely difficult; the incidence of malformations does not appear to be greater than that seen in the general population. Most studies have found phenothiazines to be safe for both mother and fetus if used in low doses during pregnancy (Ayd, 1976; Kris, 1965; Miklovich & van den Berg, 1976).

c) Extrapyramidal symptoms, including hypertonia, tremor, and abnormal hand posturing, which resolved between 10 and 22 months of age, were reported in an infant maternally exposed to thioridazine, trifluoperazine, and chlorpromazine (Hill et al, 1966).

B) Breastfeeding

1) Thomson Lactation Rating: Infant risk cannot be ruled out.

a) Available evidence and/or expert consensus is inconclusive or is inadequate for determining infant risk when used during breastfeeding. Weigh the potential benefits of drug treatment against potential risks before prescribing this drug during breastfeeding.

2) Clinical Management

a) No reports describing the use of thioridazine during human lactation are available and the effects on the nursing infant from exposure to the drug in milk are unknown. It is not known if thioridazine affects the quantity and composition of breastmilk. Until more data is available, use caution when considering the use of thioridazine in lactating women.

3) Literature Reports

a) No reports describing the use of thioridazine during human lactation or measuring the amount, if any, of the drug excreted into milk have been located.

4) Drug Levels in Breastmilk

a) Thioridazine Hydrochloride

1) Active Metabolites

a) mesoridazine (Cohen et al, 1979a)

3.5 Drug Interactions

Drug-Drug Combinations

Drug-Food Combinations

Drug-Lab Modifications

3.5.1 Drug-Drug Combinations

Acecainide

Acetylcholine

Ajmaline

Amantadine

Amiodarone

Amisulpride

Amitriptyline

Amoxapine

Aprindine

Arsenic Trioxide

Astemizole

Azimilide

Belladonna

Belladonna Alkaloids

Benztropine

Bepridil

Betel Nut

Bretylium

Bromocriptine

Bupropion

Cabergoline

Chloral Hydrate

Chloroquine

Chlorpromazine

Cinacalcet

Cisapride

Clarithromycin

Clozapine

Darifenacin

Darunavir

Dehydroepiandrosterone

Desipramine

Dibenzepin

Diethylpropion

Disopyramide

Dofetilide

Dolasetron

Doxepin

Droperidol

Duloxetine

Encainide

Enflurane

Erythromycin

Evening Primrose

Fentanyl

Flecainide

Fluconazole

Fluoxetine

Fluvoxamine

Foscarnet

Fosphenytoin

Gatifloxacin

Gemifloxacin

Grepafloxacin

Halofantrine

Haloperidol

Halothane

Hydroquinidine

Ibutilide

Iloperidone

Imipramine

Iopamidol

Isoflurane

Isradipine

Kava

Ketanserin

Lapatinib

Levodopa

Levofloxacin

Levomethadyl

Levorphanol

Lidoflazine

Lithium

Lithospermum

Lorcainide

Lubeluzole

Lumefantrine

Mefloquine

Meperidine

Methadone

Methadone

Metoprolol

Metrizamide

Morphine

Morphine Sulfate Liposome

Moxifloxacin

Nortriptyline

Octreotide

Ondansetron

Orphenadrine

Oxycodone

Paliperidone

Paroxetine

Pentamidine

Phenobarbital

Phenylalanine

Phenytoin

Pimozide

Pindolol

Pirmenol

Porfimer

Prajmaline

Probucol

Procainamide

Procarbazine

Procaterol

Prochlorperazine

Procyclidine

Propafenone

Propranolol

Protirelin

Protriptyline

Quetiapine

Quinidine

Ranolazine

Rilonacept

Risperidone

Ritonavir

Roxithromycin

Sematilide

Sertindole

Sotalol

Sparfloxacin

Spiramycin

Sulfamethoxazole

Sultopride

Sunitinib

Tapentadol

Tedisamil

Telithromycin

Terfenadine

Tetrabenazine

Tramadol

Trazodone

Trifluoperazine

Trihexyphenidyl

Trimethoprim

Trimipramine

Vasopressin

Vitex

Ziprasidone

Zolmitriptan

Zotepine

Zotepine

3.5.1.A Acecainide

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Although no drug interaction studies have been performed, the manufacturer of thioridazine states that the concurrent use of thioridazine with other drugs known to prolong the QTc interval is contraindicated (Prod Info Thioridazine tablets, 2002). Class III antiarrhythmic agents may prolong the QT

interval in some patients, which may result in ventricular tachycardia, ventricular fibrillation, and torsades de pointes (Yamreudeewong et al, 2003; Prod Info Betapace(R), 2001; Prod Info Corvert(R), 2000; Corey et al, 1999; Karam et al, 1998).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of thioridazine and agents that prolong the QT interval such as Class III antiarrhythmic agents is contraindicated.
7) Probable Mechanism: additive effect on QT interval

3.5.1.B Acetylcholine
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, thioridazine should not be coadministered with other drugs which are also known to prolong the QTc interval, including acetylcholine (Prod Info Mellaril(R), 2000f).
3) Severity: contraindicated
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of thioridazine and agents that prolong the QT interval is contraindicated.
7) Probable Mechanism: additive cardiac effects

3.5.1.C Ajmaline
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Class Ia antiarrhythmics have been shown to prolong the QTc interval at the recommended therapeutic dose. Even though no formal drug interaction studies have been done, the coadministration of thioridazine with other drugs known to prolong the QTc interval, including Class Ia antiarrhythmic agents, is not recommended (Prod Info Mellaril(R), 2002a; Prod Info Procanbid(R), 2000; Prod Info Quinaglute(R), 1999; Desai et al, 1981).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of a Class IA antiarrhythmic and thioridazine is contraindicated.
7) Probable Mechanism: additive cardiac effects

3.5.1.D Amantadine
1) Interaction Effect: worsening tremor
2) Summary: Worsening of tremor has occurred in elderly patients with Parkinson's disease when amantadine was co-administered with thioridazine (Prod Info Symmetrel(R), 2002).
3) Severity: minor
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: If amantadine and thioridazine are co-administered, monitor the patient for signs of tremor emergence or recurrence.
7) Probable Mechanism: unknown

3.5.1.E Amiodarone
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Although no drug interaction studies have been performed, the manufacturer of thioridazine states that the concurrent use of thioridazine with other drugs known to prolong the QTc interval is contraindicated (Prod Info Thioridazine tablets, 2002). Class III antiarrhythmic agents may prolong the QT interval in some patients, which may result in ventricular tachycardia, ventricular fibrillation, and torsades de pointes (Yamreudeewong et al, 2003; Prod Info Betapace(R), 2001; Prod Info Corvert(R), 2000; Corey et al, 1999; Karam et al, 1998).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of thioridazine and agents that prolong the QT interval such as Class III antiarrhythmic agents is contraindicated.
7) Probable Mechanism: additive effect on QT interval

3.5.1.F Amisulpride
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Although citing no data, the manufacturer of thioridazine states that concomitant use with other drugs which prolong the QT interval is contraindicated (Prod Info Mellaril(R), 2001b). Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999), haloperidol (O'Brien et al, 1999), pimozide (Prod Info Orap(R), 2000), quetiapine (Owens, 2001c), paliperidone (Prod Info INVEGA(TM) extended-release oral tablets, 2006), risperidone (Duenas-Laita et al, 1999), sertindole (Agelink et al, 2001), sultopride (Lande et al, 1992), ziprasidone (Prod Info GEODON(R) intramuscular injection, oral capsule, 2005), and zotepine (Sweetman, 2004).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of agents that prolong the QT interval, such as antipsychotics, and thioridazine, is contraindicated.
7) Probable Mechanism: additive QT prolongation

3.5.1.G Amitriptyline
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Although citing no data, the manufacturer of thioridazine states that concomitant use with other drugs which prolong the QT interval is contraindicated (Prod Info Mellaril(R), 2001). Tricyclic antidepressants (TCAs) at therapeutic doses can cause QT prolongation (Marshall & Forker, 1982).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concurrent administration of a tricyclic antidepressant and thioridazine is contraindicated.
7) Probable Mechanism: additive effect on QT interval

3.5.1.H Amoxapine
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Although citing no data, the manufacturer of thioridazine states that concomitant use with other drugs which prolong the QT interval is contraindicated (Prod Info Mellaril(R), 2001). Tricyclic antidepressants (TCAs) at therapeutic doses can cause QT prolongation (Marshall & Forker, 1982).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concurrent administration of a tricyclic antidepressant and thioridazine is contraindicated.
7) Probable Mechanism: additive effect on QT interval

3.5.1.I Aprindine
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Class I antiarrhythmic agents may prolong the QT interval in some patients, which may result in ventricular tachycardia, ventricular fibrillation, and torsades de pointes. Although pharmacokinetic studies between thioridazine and other drugs which prolong the QT interval have not been performed, an additive effect cannot be excluded. Therefore, the concurrent administration of thioridazine with a Class I antiarrhythmic agent is contraindicated (Prod Info Rythmol(R), 2002; Prod Info Mellaril(R), 2002; Prod Info Tambocor(R), 1998).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of thioridazine and agents that prolong the QT interval, such as Class I antiarrhythmic agents, is contraindicated.
7) Probable Mechanism: additive cardiac effects

3.5.1.J Arsenic Trioxide
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, neither thioridazine nor arsenic trioxide should be coadministered with other drugs which are also known to prolong the QTc interval (Prod Info Mellaril(R), 2000l; Prod Info Trisenox(R), 2001a).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of thioridazine and agents that prolong the QT interval, such as arsenic trioxide, is contraindicated.
7) Probable Mechanism: additive effects on QT prolongation

8) Literature Reports

a) QT/QTc prolongation should be expected during treatment with arsenic trioxide and torsade de pointes as well as complete heart block has been reported. Over 460 ECG tracings from 40 patients with refractory or relapsed APL treated with arsenic trioxide were evaluated for QTc prolongation. Sixteen of 40 patients (40%) had at least one ECG tracing with a QTc interval greater than 500 msec. Prolongation of the QTc was observed between 1 and 5 weeks after arsenic trioxide infusion, and then returned towards baseline by the end of 8 weeks after arsenic trioxide infusion. In these ECG evaluations, women did not experience more pronounced QT prolongation than men, and there was no correlation with age (Prod Info Trisenox(R), 2001).

3.5.1.K Astemizole

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Even though no formal drug interaction studies have been done, thioridazine should not be coadministered with other drugs which are also known to prolong the QTc interval, including astemizole (Prod Info Mellaril(R), 2002; Prod Info Hismanal(R), 1998).

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of thioridazine and agents that prolong the QT interval, such as astemizole, is contraindicated.

7) Probable Mechanism: additive cardiac effects

3.5.1.L Azimilide

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Although no drug interaction studies have been performed, the manufacturer of thioridazine states that the concurrent use of thioridazine with other drugs known to prolong the QTc interval is contraindicated (Prod Info Thioridazine tablets, 2002). Class III antiarrhythmic agents may prolong the QT interval in some patients, which may result in ventricular tachycardia, ventricular fibrillation, and torsades de pointes (Yamreudeewong et al, 2003; Prod Info Betapace(R), 2001; Prod Info Corvert(R), 2000; Corey et al, 1999; Karam et al, 1998).

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of thioridazine and agents that prolong the QT interval such as Class III antiarrhythmic agents is contraindicated.

7) Probable Mechanism: additive effect on QT interval

3.5.1.M Belladonna

1) Interaction Effect: increased manic, agitated reactions, or enhanced anticholinergic effects resulting in cardiorespiratory failure, especially in cases of belladonna overdose

2) Summary: Belladonna contains L-hyoscyamine, atropine, and scopolamine with a total alkaloid content of at least 0.3% in the leaves and 0.5% in the roots (Blumenthal et al, 1998). The anticholinergic activity of the active alkaloids present in belladonna may predispose the patient to excessive anticholinergic activity if taken with a phenothiazine (Shader & Greenblatt, 1971; Taylor et al, 1970a; Louria, 1969a). Because belladonna is typically available as a homeopathic preparation, the clinical severity of the interaction with phenothiazines is unknown. Belladonna alkaloids have been used as "spiking" agents in illicit drugs. In the amount of belladonna used for this purpose, the interaction is well known and severe (Taylor et al, 1970a). Phenothiazines should not be used to sedate patients with belladonna toxicity; alternatives include short-acting barbiturates, benzodiazepines, or chloral hydrate (Shader & Greenblatt, 1971; Louria, 1969a).

3) Severity: moderate

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: Excessive anticholinergic activity may be manifested by dry mouth, constipation, urinary retention, tachycardia, decreased sweating, mydriasis, blurred vision, elevated temperature, muscular weakness, and sedation. If such effects are noted, belladonna should be discontinued immediately. In severe cases, paralytic ileus, confusion, psychoses, agitation, delusions, delirium, and paranoia may be encountered as well as tachycardia, dysrhythmia, and hypertension. In severe cases, immediate medical attention should be obtained. Benzodiazepines, short-acting barbiturates, or chloral hydrate may be used to sedate patients with anticholinergic toxicity (Shader & Greenblatt, 1971).

7) Probable Mechanism: additive anticholinergic effect

8) Literature Reports

a) Central nervous system depression occurred in patients taking an anticholinergic agent with a phenothiazine. Belladonna alkaloids have been used for "spiking" of illicit drugs. Treatment of toxicity from such use with a phenothiazine enhances the anticholinergic effects and may lead to coma and cardiorespiratory failure (Taylor et al, 1970).

b) Use of chlorpromazine to treat drug overdose with the illicit anticholinergic drug 2,5-dimethoxy-4-

methyl amphetamine (STP) enhances mania and agitation, and may result in respiratory failure of cardiovascular collapse. Diazepam, chlordiazepoxide, or short-acting barbiturates may be treatment of choice for anticholinergic toxicity (Louria, 1969).

3.5.1.N Belladonna Alkaloids

1) Interaction Effect: increased manic, agitated reactions, or enhanced anticholinergic effects resulting in cardiorespiratory failure, especially in cases of belladonna overdose

2) Summary: Belladonna contains L-hyoscyamine, atropine, and scopolamine with a total alkaloid content of at least 0.3% in the leaves and 0.5% in the roots (Blumenthal et al, 1998). The anticholinergic activity of the active alkaloids present in belladonna may predispose the patient to excessive anticholinergic activity if taken with a phenothiazine (Shader & Greenblatt, 1971; Taylor et al, 1970a; Louria, 1969a). Because belladonna is typically available as a homeopathic preparation, the clinical severity of the interaction with phenothiazines is unknown. Belladonna alkaloids have been used as "spiking" agents in illicit drugs. In the amount of belladonna used for this purpose, the interaction is well known and severe (Taylor et al, 1970a). Phenothiazines should not be used to sedate patients with belladonna toxicity; alternatives include short-acting barbiturates, benzodiazepines, or chloral hydrate (Shader & Greenblatt, 1971; Louria, 1969a).

3) Severity: moderate

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: Excessive anticholinergic activity may be manifested by dry mouth, constipation, urinary retention, tachycardia, decreased sweating, mydriasis, blurred vision, elevated temperature, muscular weakness, and sedation. If such effects are noted, belladonna should be discontinued immediately. In severe cases, paralytic ileus, confusion, psychoses, agitation, delusions, delirium, and paranoia may be encountered as well as tachycardia, dysrhythmia, and hypertension. In severe cases, immediate medical attention should be obtained. Benzodiazepines, short-acting barbiturates, or chloral hydrate may be used to sedate patients with anticholinergic toxicity (Shader & Greenblatt, 1971).

7) Probable Mechanism: additive anticholinergic effect

8) Literature Reports

a) Central nervous system depression occurred in patients taking an anticholinergic agent with a phenothiazine. Belladonna alkaloids have been used for "spiking" of illicit drugs. Treatment of toxicity from such use with a phenothiazine enhances the anticholinergic effects and may lead to coma and cardiorespiratory failure (Taylor et al, 1970).

b) Use of chlorpromazine to treat drug overdose with the illicit anticholinergic drug 2,5-dimethoxy-4-methyl amphetamine (STP) enhances mania and agitation, and may result in respiratory failure of cardiovascular collapse. Diazepam, chlordiazepoxide, or short-acting barbiturates may be treatment of choice for anticholinergic toxicity (Louria, 1969).

3.5.1.O Benztropine

1) Interaction Effect: decreased phenothiazine serum concentrations, decreased phenothiazine effectiveness, enhanced anticholinergic effects (ileus, hyperpyrexia, sedation, dry mouth)

2) Summary: The concurrent use of anticholinergic agents (benztropine, orphenadrine, procyclidine, trihexyphenidyl) to control extrapyramidal side effects may reduce oral absorption of phenothiazines, antagonize the behavioral and antipsychotic effects of the phenothiazine, and enhance anticholinergic side effects (Rivera-Calimlim et al, 1976e; Mann & Boger, 1978g; Singh & Kay, 1979c; Gershon et al, 1965g; Buckle & Guillebaud, 1967c).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: Anticholinergics (benztropine, orphenadrine, procyclidine, trihexyphenidyl) should not be used routinely with phenothiazine derivatives as prophylaxis against possible extrapyramidal symptoms; use should be reserved for situations where EPS occur and lowering of the antipsychotic dosage is not possible. Anticholinergic use should be reevaluated at least every three months.

7) Probable Mechanism: delayed gastric emptying, increased gut wall metabolism of phenothiazine, decreased absorption

8) Literature Reports

a) The concomitant administration of trihexyphenidyl and chlorpromazine has been shown to result in a decrease in chlorpromazine plasma levels (Rivera-Calimlim et al, 1973c; Gershon et al, 1965f). A crossover controlled study of the chlorpromazine-trihexyphenidyl interaction in psychiatric patients showed conclusively that trihexyphenidyl lowers plasma levels of chlorpromazine from 13% to 100% (Rivera-Calimlim et al, 1973c). The mechanism by which trihexyphenidyl lowers plasma levels of chlorpromazine was shown in rats to be an inhibition of gastric emptying by trihexyphenidyl, probably as a result of its anticholinergic activity (Rivera-Calimlim, 1976c). Slow gastric emptying will delay the transport of chlorpromazine to intestinal absorption sites and favor enhanced gastrointestinal metabolism.

b) Trihexyphenidyl may also directly reverse some of the therapeutic effects of chlorpromazine. A toxic psychosis has been commonly reported following usual therapeutic doses of anticholinergic drugs, particularly when these agents are used in conjunction with other drugs with anticholinergic properties. Symptoms may include visual hallucinations, confusion, disorientation, speech difficulty, emotional

lability and psychotic thinking (Perry et al, 1985c).
c) The chlorpromazine-trihexyphenidyl interaction may also include additive anticholinergic effects including constipation or paralytic ileus, dry mouth, blurred vision, increased intraocular pressure and urinary retention (Perry et al, 1985c). Hyperpyrexia has been reported, presumably due to blocking of exocrine sweat glands in combination with the hypothalamic dysregulation produced by antipsychotics (Mann & Boger, 1978f).
d) A significant reduction in fluphenazine serum levels occurred following addition of procyclidine in patients who were previously well stabilized. Following discontinuation of procyclidine, fluphenazine serum levels returned to baseline (Bamrah et al, 1986c). However, the addition of orphenadrine to perphenazine therapy resulted in no clinically relevant pharmacokinetic changes in the absorption, distribution, or elimination of perphenazine (Bolvig Hansen et al, 1979c).

3.5.1.P Bepridil
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, bepridil should not be coadministered with other drugs which are also known to prolong the QTc interval, including phenothiazines (Prod Info Compazine(R), 2002; Prod Info Mellaril(R), 2002d; Prod Info Stelazine(R), 2002; Prod Info Thorazine(R), 2002; Prod Info Serentil(R), 2001; Prod Info Vascor(R), 2000).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of bepridil and agents that prolong the QT interval, such as phenothiazines, is contraindicated.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.Q Betel Nut
1) Interaction Effect: increased extrapyramidal side effects of phenothiazines
2) Summary: Case reports have described increased extrapyramidal side effects when betel nut was chewed by patients taking fluphenazine and fluphenthixol for schizophrenia (Deahl, 1989a). The extrapyramidal effects were not improved with anticholinergic therapy with procyclidine, and resolved with betel nut discontinuation (Deahl, 1989a). A similar effect may occur if betel nut is chewed with other phenothiazine therapy. The cholinergic activity of betel nut has been attributed to the arecoline content. When given with peripheral anticholinergics, arecoline increased the heart rate due to central muscarinic agonist activity (Nutt et al, 1978a). Case reports suggest the onset of betel nut activity to be within 3 weeks with resolution within 4 to 7 days after discontinuation (Deahl, 1989a).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: It is unclear to what extent the cholinergic effect of betel nut may increase the incidence of extrapyramidal side effects of phenothiazines, especially if patients are treated with anticholinergic agents to control these side effects. Deterioration in symptoms of patients with Parkinson's disease or other extrapyramidal movement disorders may be expected. Persons who have been chewing betel nut have a characteristic red stain on the teeth which may help the clinician discover betel nut use.
7) Probable Mechanism: cholinergic effect of betel nut
8) Literature Reports
a) Within 3 weeks of initiating betel nut chewing, a 51-year-old Indian man experienced marked rigidity, bradykinesia, and jaw tremor. This patient had been stabilized on fluphenazine decanoate depot 50 milligrams (mg) every 3 weeks for schizophrenia and procyclidine 5 mg twice daily for a mild Parkinsonian tremor for the previous 2 years. Within one week of discontinuation of betel nut chewing, the patient's condition returned to baseline. This report appears to demonstrate decreased anticholinergic effects of procyclidine when coadministered with betel nut (Deahl, 1989).
b) A 45-year-old Indian man developed akathisia, tremor and stiffness following betel nut ingestion which was not affected by dosage escalations of up to 20 mg daily of procyclidine. This patient had been previously stabilized on fluphenthixol 60 mg depot every two weeks for the previous year for schizoaffective disorder without extrapyramidal side effects. His symptoms resolved over 4 days after discontinuing betel nut. It appears that the anticholinergic effects of procyclidine were diminished when betel nut was chewed concomitantly (Deahl, 1989).
c) High doses (5 mg, 10 mg, and 20 mg) of subcutaneous (SC) arecoline given one hour after SC administration of 0.5 mg of the peripheral anticholinergic agent methscopolamine increased the heart rate and blood pressure of six Huntington disease patients. Significant increases in blood pressure occurred at doses of 5 mg, 10 mg (p less than 0.01) and 20 mg (p less than 0.05). Heart rate increased at doses of 5 mg and 20 mg (p less than 0.01), and 10 mg (p less than 0.05). Subjective effects in some patients included tremor, flushing or pallor at the time of peak drug effect and nausea, weakness, and mental changes at the higher doses. No peripheral cholinergic effects were noted. The results indicated a central muscarinic effect for arecoline (Nutt et al, 1978).
d) A low dose (0.5 mg) of arecoline given intravenously 3 minutes after the peripheral anticholinergic agent glycopyrrolate 0.15 mg to 8 patients with major depressive disorder increased their heart rates.

The peak heart rate increase in a non-REM portion of the sleep cycle during the 10 minute post-infusion period was 6.75 +/- 12.9 beats per minute for placebo and 25 +/- 10.3 beats per minute for arecoline. The peak heart rates all began 1 to 8 minutes after the arecoline infusion, and the mean heart rate was significantly elevated over placebo from 2 to 10 minutes after arecoline infusion (p less than 0.05) (Abramson et al, 1985).
e) Though chewing betel nut alone does not significantly increase catecholamine levels, a popular betel nut preparation does. Six to eight minutes after chewing betel nut, 4 subjects had only a moderate increase in plasma noradrenaline from 266.2 +/- 105.7 picograms/milliliter (pg/mL) to 313.7 +/- 92.9 pg/mL (p equal to 0.0607). Combining betel nut with lime, catechu and Piper betel flower as is commonly done caused significant elevation of norepinephrine in nine subjects from 292.2 +/- 59.5 pg/mL to 375.1 +/- 130.0 pg/mL (p equal to 0.0244) and epinephrine from 62.5 +/- 23.9 pg/mL to 102.2 +/- 45.0 pg/mL (p equal to 0.0226). In this group dopamine was also elevated in 8 of 9 subjects, but the mean was not significant (Chu, 1995).

3.5.1.R Bretylium

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Although no drug interaction studies have been performed, the manufacturer of thioridazine states that the concurrent use of thioridazine with other drugs known to prolong the QTc interval is contraindicated (Prod Info Thioridazine tablets, 2002). Class III antiarrhythmic agents may prolong the QT interval in some patients, which may result in ventricular tachycardia, ventricular fibrillation, and torsades de pointes (Yamreudeewong et al, 2003; Prod Info Betapace(R), 2001; Prod Info Corvert(R), 2000; Corey et al, 1999; Karam et al, 1998).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of thioridazine and agents that prolong the QT interval such as Class III antiarrhythmic agents is contraindicated.
7) Probable Mechanism: additive effect on QT interval

3.5.1.S Bromocriptine

1) Interaction Effect: decreased bromocriptine effectiveness
2) Summary: Concomitant therapy with thioridazine and bromocriptine was reported to result in interference of the prolactin lowering effects of bromocriptine. In addition, a deterioration in visual fields was observed after 3 months of concurrent use, which resolved within 5 days of discontinuing thioridazine (Robbins et al, 1984).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Because bromocriptine and thioridazine have opposite effects on dopamine receptors, the concurrent use of these two drugs is illogical. Alternative therapy to either drug should be considered.
7) Probable Mechanism: antagonism at dopamine receptors

3.5.1.T Bupropion

1) Interaction Effect: increased plasma levels of thioridazine
2) Summary: It is recommended that thioridazine, an antipsychotic metabolized by the cytochrome P450 2D6 isoenzyme, be initiated at the lower end of the dose range when administered concomitantly with bupropion (Prod Info Wellbutrin XL(TM), 2003; Prod Info Zyban(R), 2000).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Coadministration of bupropion and thioridazine should be approached with caution and should be initiated at the lower end of the dose range of thioridazine. If bupropion is added to the treatment regimen of a patient already receiving thioridazine, consider decreasing the dose of thioridazine.
7) Probable Mechanism: inhibition of cytochrome P450 2D6-mediated thioridazine metabolism

3.5.1.U Cabergoline

1) Interaction Effect: the decreased therapeutic effect of both drugs
2) Summary: Cabergoline is a long-acting dopamine receptor agonist with a high affinity for dopamine-2 receptors. It should not be administered concomitantly with dopamine-2 antagonists, such as phenothiazines, butyrophenones, thioxanthines, and metoclopramide (Prod Info Dostinex(R), 1996).
3) Severity: moderate
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Cabergoline, a dopamine-2 receptor agonist, should not be used concurrently with a dopamine-2 antagonist, such as thioridazine.
7) Probable Mechanism: antagonistic pharmacologic effects

3.5.1.V Chloral Hydrate

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, thioridazine should not be coadministered with other drugs which are also known to prolong the QTc interval, including chloral hydrate (Prod Info Mellaril(R), 2000s; Young et al, 1986).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of chloral hydrate and thioridazine is contraindicated.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.W Chloroquine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, thioridazine should not be coadministered with other drugs which are also known to prolong the QTc interval, including chloroquine (Prod Info Mellaril(R), 2000ad; Prod Info Aralen(R), 1999).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of chloroquine and agents that prolong the QT interval, such as thioridazine, is contraindicated.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.X Chlorpromazine

1) Interaction Effect: an increased risk of cardiotoxicity (QT interval prolongation, torsades de pointes, cardiac arrest)
2) Summary: Because thioridazine may prolong the QT interval and increase the risk of arrhythmias, the concurrent administration of thioridazine and other phenothiazines is contraindicated (Prod Info Mellaril(R), 2000l). Q and T wave distortions have been observed in patients taking phenothiazines (Prod Info Compazine(R), 2002a; Prod Info Stelazine(R), 2002a; Prod Info Thorazine(R), 2002a). Other phenothiazines may have similar effects, though no reports are available.
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of agents that prolong the QT interval, such as thioridazine and other phenothiazines, is contraindicated.
7) Probable Mechanism: additive effect on QT interval

3.5.1.Y Cinacalcet

1) Interaction Effect: increased thioridazine plasma concentrations
2) Summary: Cinacalcet is partially metabolized by and is a strong inhibitor of the CYP2D6 isozyme. Cinacalcet may increase blood concentrations of drugs that are predominantly metabolized by CYP2D6 and have a narrow therapeutic index, such as thioridazine. Therefore, if cinacalcet and thioridazine are coadministered, dose adjustments of thioridazine may be required (Prod Info SENSIPAR(TM) oral tablets, 2007).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: If cinacalcet, a strong CYP2D6 inhibitor, is coadministered with a drug that is primarily metabolized by CYP2D6 and has a narrow therapeutic index, such as thioridazine, dose adjustments of the CYP2D6-metabolized drug may be necessary (Prod Info SENSIPAR(TM) oral tablets, 2007).
7) Probable Mechanism: inhibition of CYP2D6-mediated thioridazine metabolism

3.5.1.Z Cisapride

1) Interaction Effect: cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Cisapride therapy has resulted in serious cardiac arrhythmias, including ventricular tachycardia, ventricular fibrillation, torsades de pointes, and QT prolongation. Because phenothiazines also may prolong the QT interval and increase the risk of arrhythmias, the concurrent administration of cisapride with a drug from this class is contraindicated (Prod Info Propulsid(R), 2000).
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: The concurrent use of cisapride and phenothiazines is contraindicated.

7) Probable Mechanism: additive effects on QT prolongation

3.5.1.AA Clarithromycin

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Clarithromycin can prolong the QT interval in some patients, which may result in ventricular tachycardia, ventricular fibrillation, and torsades de pointes (Prod Info Biaxin(R), 2000). Because thioridazine may also prolong the QT interval and increase the risk of arrhythmias, the concurrent administration of clarithromycin and thioridazine is contraindicated (Prod Info Mellaril(R), 2000ac).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of agents that prolong the QT interval, such as clarithromycin and thioridazine, is contraindicated.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.AB Clozapine

1) Interaction Effect: increased plasma concentrations of clozapine and or the phenothiazine
2) Summary: Coadministration of clozapine with other drugs that are metabolized by cytochrome P450 2D6, such as phenothiazines, should be approached with caution (Prod Info Clozaril(R), 2002).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Concomitant use of clozapine with other drugs metabolized by cytochrome P450 2D6, such as phenothiazines, may require lower doses than usually prescribed for either clozapine or the phenothiazine.
7) Probable Mechanism: competitive substrate inhibition

3.5.1.AC Darifenacin

1) Interaction Effect: increased thioridazine exposure with an increased risk of QT prolongation and other side effects
2) Summary: Coadministered darifenacin may increase thioridazine exposure, causing a potential risk of QT prolongation or other serious adverse effects. Thioridazine, like imipramine, is metabolized primarily by the CYP2D6 isoenzyme and it has a narrow therapeutic window. The mean maximum concentration (Cmax) and area under the concentration-time curve (AUC) of imipramine increased 57% and 70%, respectively, when used together with darifenacin 30 mg once daily at steady-state. Note: The recommended dose of darifenacin is 7.5 or 15 mg once daily. The AUC of desipramine, the active metabolite of imipramine, increased 3.6-fold. Caution should be used with the coadministration of darifenacin and CYP2D6 substrates with a narrow therapeutic window, such as thioridazine (Prod Info Enablex, 2004).
3) Severity: major
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Use caution with the coadministration of darifenacin and other CYP2D6 substrates with a narrow therapeutic window, such as thioridazine. Monitor for thioridazine toxicity including QT prolongation.
7) Probable Mechanism: competitive inhibition of CYP2D6-mediated thioridazine metabolism

3.5.1.AD Darunavir

1) Interaction Effect: increased thioridazine plasma concentrations
2) Summary: Coadministration of ritonavir-boosted darunavir, a CYP2D6 inhibitor, and thioridazine, a CYP2D6 substrate, may result in increased plasma concentrations of thioridazine, possibly due to inhibition of CYP2D6-mediated thioridazine metabolism by darunavir/ritonavir. As this may result in thioridazine adverse effects, a lower dose of thioridazine should be considered with concomitant use is necessary (Prod Info PREZISTA(R) film coated oral tablets, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concurrent administration of ritonavir-boosted darunavir and thioridazine may increase thioridazine plasma concentrations. Consider using a lower thioridazine dose when these agents are coadministered (Prod Info PREZISTA(R) film coated oral tablets, 2008).
7) Probable Mechanism: inhibition of CYP2D6-mediated thioridazine metabolism by darunavir/ritonavir

3.5.1.AE Dehydroepiandrosterone

1) Interaction Effect: reduced effectiveness of phenothiazines
2) Summary: Dehydroepiandrosterone (DHEA) levels within the normal range of 100 to 400 microgram/deciliter (mcg/dL) are conducive to optimal treatment of patients with psychosis (Howard, 1992a). In case reports, patients have been resistant to antipsychotics when DHEA levels were elevated (Howard, 1992a). Patients being treated with phenothiazines for psychosis should avoid DHEA supplementation.

3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Avoid concomitant use of dehydroepiandrosterone (DHEA) and phenothiazines. If DHEA is elevated, treatment with dexamethasone 1 mg orally per day may be used to normalize DHEA levels.
7) Probable Mechanism: elevated dehydroepiandrosterone (DHEA) blood levels may reduce responsiveness to phenothiazines
8) Literature Reports
a) A 24-year-old female diagnosed with schizophrenia was resistant to daily doses of haloperidol 20 milligrams (mg), fluphenazine 40 mg, lithium carbonate 1200 mg, and lithium carbonate 900 mg plus thioridazine 300 mg. The patient appeared Cushinoid with moon face, acne, facial hair, abdominal hair, and a 40 pound weight gain in the previous 8 months. Dehydroepiandrosterone (DHEA) measured as part of an endocrine panel was 725 micrograms/deciliter (mcg/dL) (normal: 100 to 400 mcg/dL). Dexamethasone 1 mg orally at bedtime resulted in substantial improvement within one week. The patient appeared calmer, more alert with improved psychotic symptoms and ability to concentrate. At two weeks, a repeated DHEA level was within normal range (328 mcg/dL). The author concluded that elevated DHEA levels were associated with severe psychosis resistant to conventional antipsychotic therapy (Howard, 1992).
b) A 13-year-old male decompensated with a subsequent two-year period of emotional problems accompanied by heavy use of LSD, hashish, barbiturates, and alcohol. His mental status included bizarre, disorganized, delusional thinking, auditory and visual hallucinations, paranoia, lack of attention to personal hygiene, agitation, and combativeness. He was diagnosed with chronic paranoid schizophrenia; schizophrenia, chronic undifferentiated type, and schizoaffective disorder, excited type. He was resistant to daily doses of trifluoperazine 40 mg, chlorpromazine 400 mg, and imipramine 100 mg. He was also resistant to combination therapy with chlorpromazine 400 mg with thiothixene 80 mg, thioridazine 1000 mg, perphenazine 48 mg with lithium carbonate 1200 mg, clonazepam 4 mg, and carbamazepine 1200 mg daily. Baseline DHEA level exceeded 900 mcg/dL. A seven-day suppression test with dexamethasone 1 mg orally at bedtime resulted in a normal DHEA level of 200 mcg/dL. By day 5, psychosis improved and the patient was well-oriented, conversational, and was making good eye contact. Once dexamethasone was discontinued, rapid decompensation and florid psychosis ensued despite "substantial amounts of psychotropic medications." DHEA increased to 536 mcg/dL. The author concluded that elevated DHEA levels were associated with florid psychosis resistant to conventional antipsychotic therapy (Howard, 1992).

3.5.1.AF Desipramine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Although citing no data, the manufacturer of thioridazine states that concomitant use with other drugs which prolong the QT interval is contraindicated (Prod Info Mellaril(R), 2001). Tricyclic antidepressants (TCAs) at therapeutic doses can cause QT prolongation (Marshall & Forker, 1982).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concurrent administration of a tricyclic antidepressant and thioridazine is contraindicated.
7) Probable Mechanism: additive effect on QT interval

3.5.1.AG Dibenzepin

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Although citing no data, the manufacturer of thioridazine states that concomitant use with other drugs which prolong the QT interval is contraindicated (Prod Info Mellaril(R), 2001). Tricyclic antidepressants (TCAs) at therapeutic doses can cause QT prolongation (Marshall & Forker, 1982).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concurrent administration of a tricyclic antidepressant and thioridazine is contraindicated.
7) Probable Mechanism: additive effect on QT interval

3.5.1.AH Diethylpropion

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, thioridazine should not be coadministered with other drugs which are also known to prolong the QTc interval, including diethylpropion (Prod Info Mellaril(R), 2000z).
3) Severity: contraindicated

4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of thioridazine and agents that prolong the QT interval is contraindicated.
7) Probable Mechanism: additive cardiac effects

3.5.1.AI Disopyramide
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Class Ia antiarrhythmics have been shown to prolong the QTc interval at the recommended therapeutic dose. Even though no formal drug interaction studies have been done, the coadministration of thioridazine with other drugs known to prolong the QTc interval, including Class Ia antiarrhythmic agents, is not recommended (Prod Info Mellaril(R), 2002a; Prod Info Procanbid(R), 2000; Prod Info Quinaglute(R), 1999; Desai et al, 1981).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of a Class IA antiarrhythmic and thioridazine is contraindicated.
7) Probable Mechanism: additive cardiac effects

3.5.1.AJ Dofetilide
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Although no drug interaction studies have been performed, the manufacturer of thioridazine states that the concurrent use of thioridazine with other drugs known to prolong the QTc interval is contraindicated (Prod Info Thioridazine tablets, 2002). Class III antiarrhythmic agents may prolong the QT interval in some patients, which may result in ventricular tachycardia, ventricular fibrillation, and torsades de pointes (Yamreudeewong et al, 2003; Prod Info Betapace(R), 2001; Prod Info Corvert(R), 2000; Corey et al, 1999; Karam et al, 1998).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of thioridazine and agents that prolong the QT interval such as Class III antiarrhythmic agents is contraindicated.
7) Probable Mechanism: additive effect on QT interval

3.5.1.AK Dolasetron
1) Interaction Effect: cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Dolasetron can cause QTc interval prolongation. These changes are related in magnitude and frequency to the blood levels of the active metabolite, hydrodolasetron. Although the changes in QTc interval are self-limiting with declining blood levels of hydrodolasetron, some patients may experience prolonged QTc intervals for 24 hours or longer. Because of dolasetron's ability to cause QTc prolongation, its use with thioridazine is contraindicated (Prod Info Anzemet(R), 1997; Prod Info Mellaril(R), 2002g).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of dolasetron and thioridazine is contraindicated, since each of these agents can cause prolongation of the QTc interval.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.AL Doxepin
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Although citing no data, the manufacturer of thioridazine states that concomitant use with other drugs which prolong the QT interval is contraindicated (Prod Info Mellaril(R), 2001). Tricyclic antidepressants (TCAs) at therapeutic doses can cause QT prolongation (Marshall & Forker, 1982).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concurrent administration of a tricyclic antidepressant and thioridazine is contraindicated.
7) Probable Mechanism: additive effect on QT interval

3.5.1.AM Droperidol
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Although citing no data, the manufacturers of some phenothiazines state that concomitant use

with other drugs which prolong the QT interval is contraindicated (Prod Info Thioridazine tablets, 2002). QT prolongation has been observed in patients treated with droperidol (Prod Info Inapsine(R), 2001). Other phenothiazines may have similar effects, though no reports are available.
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of droperidol and thioridazine is contraindicated as it may precipitate QT prolongation.
7) Probable Mechanism: additive cardiac effects

3.5.1.AN Duloxetine
1) Interaction Effect: increased thioridazine serum concentrations and risk of cardiac arrhythmia
2) Summary: Given thioridazine's tendency to prolong the QTc-interval in a dose-dependent manner, the attendant risk for developing serious or fatal ventricular arrhythmias precludes the safe concomitant use of duloxetine and thioridazine. Duloxetine is a moderately potent inhibitor of CYP2D6 (for which thioridazine is a substrate) and therefore, the coadministration of duloxetine with thioridazine is likely to produce elevated thioridazine plasma concentrations with attendant cardiotoxicity (Prod Info Mellaril(R), 2000c; Prod Info CYMBALTA(R) delayed-release oral capsules, 2008).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of duloxetine and thioridazine is contraindicated (Prod Info Mellaril(R), 2000c).
7) Probable Mechanism: duloxetine inhibition of CYP2D6-mediated thioridazine metabolism

3.5.1.AO Encainide
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Class I antiarrhythmic agents may prolong the QT interval in some patients, which may result in ventricular tachycardia, ventricular fibrillation, and torsades de pointes. Although pharmacokinetic studies between thioridazine and other drugs which prolong the QT interval have not been performed, an additive effect cannot be excluded. Therefore, the concurrent administration of thioridazine with a Class I antiarrhythmic agent is contraindicated (Prod Info Rythmol(R), 2002; Prod Info Mellaril(R), 2002; Prod Info Tambocor(R), 1998).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of thioridazine and agents that prolong the QT interval, such as Class I antiarrhythmic agents, is contraindicated.
7) Probable Mechanism: additive cardiac effects

3.5.1.AP Enflurane
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, thioridazine should not be coadministered with other drugs which may also prolong the QTc interval, including enflurane (Owens, 2001; Prod Info Mellaril(R), 2002b).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of thioridazine and agents that may prolong the QT interval, such as enflurane, is contraindicated.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.AQ Erythromycin
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Erythromycin significantly increased the mean QTc interval versus baseline in a retrospective study of 49 patients (Oberg & Bauman, 1995). Erythromycin has demonstrated QTc prolongation in combination with other drugs that prolong the QT interval (Prod Info PCE(R), 1997). Thioridazine has been shown to prolong the QT interval; the manufacturer states that the concurrent administration of thioridazine with other drugs known to prolong the QTc interval is contraindicated (Prod Info Mellaril(R), 2002e).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of thioridazine with other agents that can prolong the QT interval, such as erythromycin, is contraindicated.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.AR Evening Primrose

1) Interaction Effect: increased risk of seizures
2) Summary: Evening primrose oil may reduce the seizure threshold when taken with phenothiazines. Seizures have been reported when evening primrose oil was added to phenothiazine therapy in schizophrenic patients (Holman & Bell, 1983a; Vaddadi, 1981a). Avoid concomitant use of evening primrose oil with anticonvulsants.
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Avoid concomitant use of evening primrose oil with phenothiazines.
7) Probable Mechanism: evening primrose oil may reduce the seizure threshold
8) Literature Reports
a) A 43-year-old male on fluphenazine decanoate 50 mg every two weeks experienced a grand mal seizure after 12 weeks of using EPO 4 grams daily. After withdrawing EPO, no further seizure episodes occurred in the next 7 months (Holman & Bell, 1983).
b) Three schizophrenic patients unresponsive to phenothiazines were given evening primrose oil (EPO), which exacerbated symptoms and led to seizures. EPO was discontinued and carbamazepine initiated when electroencephalogram (EEG) showed temporal lobe epileptic disorders. Phenothiazine therapy was discontinued or reduced in all patients (Vaddadi, 1981).

3.5.1.AS Fentanyl

1) Interaction Effect: an increase in central nervous system and respiratory depression
2) Summary: The concomitant use of fentanyl and other central nervous system depressants including phenothiazines (e.g. chlorpromazine, promethazine, thioridazine) may result in additive CNS and respiratory depressant effects, including hypotension, profound sedation and/or coma . When administering fentanyl and a phenothiazine together, one or both agents dosage should be significantly reduced (Prod Info Duragesic(R), 2005). Monitor patient carefully for signs of respiratory depression, CNS depression, and hypotension.
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Monitor patients for signs of respiratory depression, CNS depression, and hypotension. A dosage reduction of one or both drugs should be made.
7) Probable Mechanism: additive effects

3.5.1.AT Flecainide

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Class I antiarrhythmic agents may prolong the QT interval in some patients, which may result in ventricular tachycardia, ventricular fibrillation, and torsades de pointes. Although pharmacokinetic studies between thioridazine and other drugs which prolong the QT interval have not been performed, an additive effect cannot be excluded. Therefore, the concurrent administration of thioridazine with a Class I antiarrhythmic agent is contraindicated (Prod Info Rythmol(R), 2002; Prod Info Mellaril(R), 2002; Prod Info Tambocor(R), 1998).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of thioridazine and agents that prolong the QT interval, such as Class I antiarrhythmic agents, is contraindicated.
7) Probable Mechanism: additive cardiac effects

3.5.1.AU Fluconazole

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Although citing no data, the manufacturer of thioridazine states that concomitant use with other drugs which prolong the QT interval is contraindicated (Prod Info Mellaril(R), 2000i). Other phenothiazines may have similar effects, though no reports are available. Case reports have described QT prolongation and torsades de pointes associated with fluconazole (Khazan & Mathis, 2002; Wassmann et al, 1999).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Due to the possibility of additive effects on the QT interval, the concomitant administration of fluconazole and thioridazine is contraindicated.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.AV Fluoxetine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Fluoxetine inhibits the metabolism of thioridazine through inhibition of CYP2D6. The resulting elevated levels of thioridazine may enhance QT prolongation (Prod Info Mellaril(R), 2000w). Fluoxetine has been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Prozac(R), 2001). Although citing no data, the manufacturer of thioridazine states that concomitant use with other drugs which prolong the QT interval is contraindicated (Prod Info Mellaril(R), 2000w).
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: The concurrent administration of fluoxetine and thioridazine is contraindicated.
7) Probable Mechanism: inhibition of cytochrome P450 2D6-mediated thioridazine metabolism; additive effects on QT prolongation

3.5.1.AW Fluvoxamine
1) Interaction Effect: an increased risk of thioridazine toxicity, cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Fluvoxamine inhibits the metabolism of thioridazine, possibly through the inhibition of cytochrome P450 2D6 (CYP2D6) resulting in toxicity. The resulting elevated levels of thioridazine would be expected to enhance the prolongation of the QT interval associated with thioridazine and may increase the risk of serious, potentially fatal, cardiac arrhythmias, such as torsade de pointes-type arrhythmias (Prod Info Mellaril(R), 2000r).
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Due to the potential for significant, possibly life-threatening, proarrhythmic effects, concurrent administration of thioridazine and fluvoxamine is contraindicated.
7) Probable Mechanism: inhibition of cytochrome P450 2D6-mediated thioridazine metabolism
8) Literature Reports
a) The serum concentrations of thioridazine and its two metabolites, mesoridazine and sulforidazine, were evaluated in ten male schizophrenic patients aged 36 to 78 years at three separate time points. All patients were receiving thioridazine monotherapy for the management of schizophrenia at a mean dose of 88 mg daily. Fluvoxamine 50 mg daily was coadministered for one week. Plasma levels of thioridazine and its metabolites were measured during monotherapy with thioridazine, after one week of concurrent therapy with thioridazine and fluvoxamine, and two weeks after fluvoxamine was discontinued. Following one week of combination therapy with fluvoxamine and thioridazine, thioridazine levels increased 225%, mesoridazine levels increased 219%, and sulforidazine concentrations rose 258%. Even two weeks after the discontinuation of fluvoxamine, three patients continued to show elevated thioridazine and metabolite levels. No clinical symptoms were attributed to the interaction between these two agents (Carrillo et al, 1999).
b) The metabolism of thioridazine is inhibited by drugs such as fluvoxamine due to reduced cytochrome P450 2D6 and 1A2 isozyme activity. The elevated levels of thioridazine would be expected to enhance the prolongation of the QT interval associated with thioridazine. This, in turn, may increase the risk of serious, potentially fatal, cardiac arrhythmias, such as torsade de pointes-type arrhythmias (Prod Info Mellaril(R), 2000q).

3.5.1.AX Foscarnet
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Foscarnet can prolong the QT interval in some patients, which may result in ventricular tachycardia, ventricular fibrillation, and torsades de pointes (Prod Info Foscavir(R), 1998). Because thioridazine may also prolong the QT interval and increase the risk of arrhythmias, the concurrent administration of foscarnet and thioridazine is contraindicated (Prod Info Mellaril(R), 2000g).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of foscarnet and thioridazine is contraindicated.
7) Probable Mechanism: additive cardiac effects

3.5.1.AY Fosphenytoin
1) Interaction Effect: increased or decreased phenytoin levels and possibly reduced phenothiazine levels
2) Summary: Fosphenytoin is a prodrug of phenytoin and the same interactions that occur with phenytoin are expected to occur with fosphenytoin (Prod Info Cerebyx(R), 1999). Concurrent phenothiazine and phenytoin therapy has been reported to increase, decrease, or cause no change in the serum levels of phenytoin (Sands et al, 1987; Vincent, 1980; Siris et al, 1974; Houghton & Richens, 1975). In one study, concomitant phenytoin reduced the serum levels of mesoridazine, but not thioridazine (Linnoila et al, 1980a).
3) Severity: minor
4) Onset: delayed

5) Substantiation: probable
6) Clinical Management: Consider monitoring phenytoin levels when a phenothiazine is added or discontinued from therapy; dosage adjustments may be needed in some cases. The patient should also be observed for any signs of phenytoin toxicity (ataxia, nystagmus, tremor, hyperreflexia), particularly in the case of adjustments to the phenothiazine dosage. Observe patients for phenothiazine efficacy.
7) Probable Mechanism: induction or inhibition of phenytoin metabolism; induction of phenothiazine metabolism
8) Literature Reports
a) Compelling data were reported suggesting that phenothiazines as a group decrease serum phenytoin concentrations, but the effect of individual phenothiazines was not evaluated. A total of 92 cases (institutionalized patients) who were receiving constant phenytoin doses and who were either initiating, discontinuing, increasing, or decreasing a phenothiazine were retrospectively reviewed. Approximately half of the patients received thioridazine, while the other half received either chlorpromazine or mesoridazine. Phenytoin concentrations decreased by 44% (p=0.001) when a phenothiazine was added; similarly, increases in phenothiazine dose caused a 33% decrease in phenytoin concentrations (p=0.001). In patients who discontinued a phenothiazine, phenytoin concentrations increased by 71% (p=0.001); similarly, decreases in phenothiazine dose caused a 55% increase in phenytoin concentrations (p=0.001). Although the combined results cannot be applied clinically to a particular phenothiazine, this study does suggest a remarkably strong trend among phenothiazines which is contrary to some individual case reports. Further study is needed (Haidukewych & Rodin, 1985).
b) The effects of concomitant treatment with phenytoin and/or phenobarbital on the steady-state serum concentrations of haloperidol, thioridazine, and mesoridazine were investigated in 2 groups of patients. The investigators found that concomitant anticonvulsant medication significantly reduced the plasma level of haloperidol and mesoridazine, but not thioridazine (Linnoila et al, 1980).

3.5.1.AZ Gatifloxacin
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Gatifloxacin may prolong the QT interval in some patients, which may result in ventricular tachycardia, ventricular fibrillation, and torsades de pointes (Prod Info Tequin(TM), 1999). Although pharmacokinetic studies between gatifloxacin and other drugs which prolong the QT interval have not been performed, an additive effect cannot be excluded. According to the manufacturer, thioridazine should not be administered with other drugs which are also known to prolong the QTc interval (Prod Info Mellaril(R), 2000h).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of gatifloxacin and thioridazine is contraindicated.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.BA Gemifloxacin
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Although pharmacokinetic studies between thioridazine and gemifloxacin, which may prolong the QT interval, have not been performed, gemifloxacin should not be used in patients receiving thioridazine (Prod Info Factive(R), 2003).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: The concurrent administration of thioridazine with other drugs that prolong the QT interval, such as gemifloxacin, is contraindicated.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.BB Grepafloxacin
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Healthy volunteers who received grepafloxacin during a Phase I study experienced prolongation of the QTc interval. On an outpatient basis, grepafloxacin is contraindicated with other drugs that are known to also prolong the QTc interval or cause torsades de pointes, including phenothiazines. When appropriate cardiac monitoring can be assured, such as in the hospitalized patient, these two agents should be coadministered with caution (Prod Info Raxar(R), 1999).
3) Severity: contraindicated
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: The concurrent use of grepafloxacin and phenothiazines is contraindicated unless appropriate cardiac monitoring can be assured, such as in the hospitalized patient.
7) Probable Mechanism: additive cardiac effects

3.5.1.BC Halofantrine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Halofantrine can prolong the QT interval in some patients, which may result in ventricular tachycardia, ventricular fibrillation, and torsades de pointes (Prod Info Halfan(R), 1998). Because thioridazine may also prolong the QT interval and increase the risk of arrhythmias, the concurrent administration of halofantrine with thioridazine is contraindicated (Prod Info Thioridazine tablets, 2002).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Due to the potential for additive effects on the QT interval, the concurrent administration of halofantrine and thioridazine is contraindicated.
7) Probable Mechanism: additive cardiac effects

3.5.1.BD Haloperidol

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Although citing no data, the manufacturer of thioridazine states that concomitant use with other drugs which prolong the QT interval is contraindicated (Prod Info Mellaril(R), 2001b). Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999), haloperidol (O'Brien et al, 1999), pimozide (Prod Info Orap(R), 2000), quetiapine (Owens, 2001c), paliperidone (Prod Info INVEGA(TM) extended-release oral tablets, 2006), risperidone (Duenas-Laita et al, 1999), sertindole (Agelink et al, 2001), sultopride (Lande et al, 1992), ziprasidone (Prod Info GEODON(R) intramuscular injection, oral capsule, 2005), and zotepine (Sweetman, 2004).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of agents that prolong the QT interval, such as antipsychotics, and thioridazine, is contraindicated.
7) Probable Mechanism: additive QT prolongation

3.5.1.BE Halothane

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, thioridazine should not be coadministered with other drugs which may also prolong the QTc interval, including halothane (Owens, 2001b; Prod Info Mellaril(R), 2002).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of thioridazine and agents that may prolong the QT interval, such as halothane, is contraindicated.
7) Probable Mechanism: additive effects on the QT interval

3.5.1.BF Hydroquinidine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Class Ia antiarrhythmics have been shown to prolong the QTc interval at the recommended therapeutic dose. Even though no formal drug interaction studies have been done, the coadministration of thioridazine with other drugs known to prolong the QTc interval, including Class Ia antiarrhythmic agents, is not recommended (Prod Info Mellaril(R), 2002a; Prod Info Procanbid(R), 2000; Prod Info Quinaglute(R), 1999; Desai et al, 1981).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of a Class IA antiarrhythmic and thioridazine is contraindicated.
7) Probable Mechanism: additive cardiac effects

3.5.1.BG Ibutilide

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Although no drug interaction studies have been performed, the manufacturer of thioridazine states that the concurrent use of thioridazine with other drugs known to prolong the QTc interval is contraindicated (Prod Info Thioridazine tablets, 2002). Class III antiarrhythmic agents may prolong the QT interval in some patients, which may result in ventricular tachycardia, ventricular fibrillation, and torsades de pointes (Yamreudeewong et al, 2003; Prod Info Betapace(R), 2001; Prod Info Corvert(R), 2000; Corey et al,

1999; Karam et al, 1998).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of thioridazine and agents that prolong the QT interval such as Class III antiarrhythmic agents is contraindicated.
7) Probable Mechanism: additive effect on QT interval

3.5.1.BH Iloperidone
1) Interaction Effect: an increased risk of QT interval prolongation
2) Summary: Due to the potential for additive effects on the QT interval and increased risk of torsade de pointes, caution should be used when iloperidone and drugs that prolong the QT interval are given concomitantly. Consideration should be given to monitoring cardiac function periodically with on-treatment ECGs and evaluating electrolyte (ie, magnesium, potassium) levels. Discontinue iloperidone in patients with persistent QTc measurements greater than 500 msec (Prod Info FANAPT(TM) oral tablets, 2009).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of iloperidone and drugs that prolong the QT interval may result in additive effects on the QT interval and an increased risk of torsade de pointes. Iloperidone should be avoided in patients with significant cardiovascular illness, eg, cardiac arrhythmia, QT prolongation, recent acute myocardial infarction, and uncompensated heart failure. If concomitant use is necessary, consider monitoring cardiac function periodically with on-treatment ECGs and evaluating electrolyte (ie, magnesium, potassium) levels. Discontinue iloperidone in patients with persistent QTc measurements greater than 500 msec(Prod Info FANAPT(TM) oral tablets, 2009).
7) Probable Mechanism: additive effects on the QT interval
8) Literature Reports
a) In an open-label QTc study of patients with schizophrenia or schizoaffective disorder (n=160), iloperidone 12 mg twice a day was associated with QTc prolongation of 9 msec (Prod Info FANAPT(TM) oral tablets, 2009).

3.5.1.BI Imipramine
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Although citing no data, the manufacturer of thioridazine states that concomitant use with other drugs which prolong the QT interval is contraindicated (Prod Info Mellaril(R), 2001). Tricyclic antidepressants (TCAs) at therapeutic doses can cause QT prolongation (Marshall & Forker, 1982).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concurrent administration of a tricyclic antidepressant and thioridazine is contraindicated.
7) Probable Mechanism: additive effect on QT interval

3.5.1.BJ Iopamidol
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, thioridazine should not be coadministered with other drugs which are also known to prolong the QTc interval, including iopamidol (Prod Info Mellaril(R), 2000d).
3) Severity: contraindicated
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of thioridazine and agents that prolong the QT interval is contraindicated.
7) Probable Mechanism: additive cardiac effects

3.5.1.BK Isoflurane
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, thioridazine should not be coadministered with other drugs which may also prolong the QTc interval, including isoflurane (Owens, 2001a; Prod Info Mellaril(R), 2002c).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of thioridazine and agents that may prolong the QT interval, such as isoflurane, is contraindicated.

7) Probable Mechanism: additive effects on the QT interval

3.5.1.BL Isradipine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Isradipine can prolong the QT interval in some patients, which may result in ventricular tachycardia, ventricular fibrillation, and torsades de pointes (Prod Info DynaCirc(R), 2000). Because thioridazine may also prolong the QT interval and increase the risk of arrhythmias, the concurrent administration of isradipine with thioridazine is contraindicated (Prod Info Mellaril(R), 2000v).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of isradipine and thioridazine is contraindicated.
7) Probable Mechanism: additive cardiac effects

3.5.1.BM Kava

1) Interaction Effect: additive dopamine antagonist side effects
2) Summary: Theoretically, kava may add to the dopamine antagonism of phenothiazines, increasing the risk for adverse effects. Case reports describe what appears to be dopamine-blocking activity of kava manifested in patients as dystonia, dyskinesias, and Parkinsonism (Spillane et al, 1997a; Schelosky et al, 1995a). Kava extracts antagonized apomorphine-induced hyperreactivity to external stimuli in mice, suggesting dopamine blockade activity (Jamieson et al, 1989a).
3) Severity: moderate
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Avoid concomitant use of kava with phenothiazines. The desired effect and/or adverse effects of phenothiazines may be increased or may be variable depending on the time of administration of kava and the quality of the kava product (i.e., whether it consistently contains a standardized amount of kava).
7) Probable Mechanism: additive dopamine antagonism
8) Literature Reports
a) A 27-year-old Aboriginal Australian male presented three times following heavy kava use with symptoms of severe choreoathetosis of the limbs, trunk, neck, and facial musculature, and athetosis of the tongue. Level of consciousness was not impaired. Symptoms resolved within 12 hours of intravenous diazepam on each occasion. Acute rheumatic fever was excluded, cerebrospinal fluid and computed tomography of the brain was normal, and urinary drug screen was negative. The only abnormalities found in hematological and biochemical tests were a serum alkaline phosphatase of 162 international units/liter (IU/L) (normal: 35-135 IU/L) and serum gamma-glutamyltransferase of 426 IU/L (normal less than 60 IU/L). These were attributed to kava use. The patient did not drink alcohol (Spillane et al, 1997).
b) A 76-year-old female with idiopathic Parkinson's disease of 17 years' duration treated for 8 years with levodopa 500 milligrams (mg) and benserazide 125 mg was prescribed kava extract (Kavasporal Forte(R)) 150 mg twice daily for complaints of inner tension. Within 10 days, she noted a pronounced increase in her daily "off" periods both in terms of duration and number. Within 2 days of discontinuing the kava product, symptoms had returned to her normal baseline (Schelosky et al, 1995).
c) A 63-year-old female experienced sudden and acute forceful involuntary oral and lingual dyskinesias on the fourth day of self-initiated therapy with kava extract (Kavasporal Forte(R)) 150 mg three times daily. She was treated successfully in the emergency room with biperiden 5 mg intravenously. She denied taking any other medications in the months preceding this event (Schelosky et al, 1995).
d) A 22-year-old female took kava extract (Laitan(R)) 100 mg once for anxiety and nervousness. Within four hours she experienced oral and lingual dyskinesias, tonic rotation of the head, and painful twisting trunk movements. She was treated successfully with biperiden 2.5 mg intravenously. She denied taking any other medications in the months preceding this event (Schelosky et al, 1995).
e) A 28-year-old male experienced acute involuntary neck extension with forceful upward deviation of the eyes within 90 minutes of taking kava extract (Laitan(R)) 100 mg. Symptoms resolved spontaneously within 40 minutes. This man had a history of acute dystonic reactions following exposure to promethacin (50 mg) and fluspirilene (1.5 mg), which had responded biperiden 5 mg intravenously 9 and 12 years previously (Schelosky et al, 1995).
f) In mice, kava extracts antagonized apomorphine-induced hyperreactivity to external stimuli. The number of hyperreactive mice after apomorphine 20 milligrams/kilogram (mg/kg) intraperitoneal administration was 6/6 in the saline treated group versus 0/6 in the group treated with kava resin (120 mg/kg) (p less than 0.005) or aqueous kava extract (p less than 0.001) (Jamieson et al, 1989).

3.5.1.BN Ketanserin

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, thioridazine should not be coadministered with other drugs which are also known to prolong the QTc interval, including ketanserin

(Prod Info Mellaril(R), 2000a).
3) Severity: contraindicated
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of thioridazine and agents that prolong the QT interval is contraindicated.
7) Probable Mechanism: additive cardiac effects

3.5.1.BO Lapatinib
1) Interaction Effect: an increased risk of QT interval prolongation
2) Summary: Due to the potential for additive effects on the QT interval and increased risk of torsade de pointes, caution should be used when lapatinib and drugs that prolong the QT interval are given concomitantly. Consideration should be given to monitoring cardiac function periodically with on-treatment ECGs and evaluating electrolyte (ie, magnesium, potassium) levels (Prod Info TYKERB oral tablets, 2008). Thirteen patients had either QTcF (corrected QT by the Friedericia method) greater than 480 msec or an increase in QTcF of greater than 60 msec in an uncontrolled, open-label, dose escalation study in advanced cancer patients (n=81) who received lapatinib doses ranging from 175 mg/day to 1800 mg/day, with serial ECGs collected on days 1 and 14 (Prod Info TYKERB oral tablets, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of lapatinib and drugs that prolong the QT interval may result in additive effects on the QT interval and an increased risk of torsade de pointes. Therefore, caution should be used when these agents are given concomitantly. Consider monitoring cardiac function periodically with on-treatment ECGs and evaluating electrolyte (ie, magnesium, potassium) levels (Prod Info TYKERB oral tablets, 2008).
7) Probable Mechanism: additive effects on the QT interval

3.5.1.BP Levodopa
1) Interaction Effect: loss of levodopa efficacy
2) Summary: Because thioridazine is a dopamine antagonist, it is expected to antagonize the pharmacologic effects of levodopa (Prod Info Stalevo(TM), 2003; Prod Info Sinemet(R), 1998). In general, concomitant use should be avoided (Yahr & Duvoisin, 1972).
3) Severity: moderate
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Concurrent use of thioridazine and levodopa should be avoided. If concomitant use is necessary, monitor the patient for loss of levodopa therapeutic efficacy.
7) Probable Mechanism: pharmacologic antagonism

3.5.1.BQ Levofloxacin
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Coadministration of levofloxacin and thioridazine may produce additive prolongation of the QTc interval and, thus, such use is contraindicated (Prod Info Mellaril(R), 2002; Prod Info Levaquin(R), 2000).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of thioridazine and agents that prolong the QT interval, such as levofloxacin, is contraindicated.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.BR Levomethadyl
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, thioridazine should not be coadministered with other drugs which are also known to prolong the QTc interval, including levomethadyl (Prod Info Mellaril(R), 2002; Prod Info Orlaam(R), 2001).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Levomethadyl is contraindicated in patients being treated with thioridazine as it may precipitate QT prolongation.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.BS Levorphanol
1) Interaction Effect: an increase in central nervous system and respiratory depression

2) Summary: The concomitant use of levorphanol and other central nervous system depressants including phenothiazines (e.g. chlorpromazine, promethazine, thioridazine) may result in additive CNS and respiratory depressant effects, including hypotension, profound sedation and/or coma . When administering levorphanol and a phenothiazine together, one or both agents dosage should be significantly reduced (Prod Info LEVO-DROMORAN(TM) injection, oral tablets, 2004). Monitor patient carefully for signs of respiratory depression, CNS depression, and hypotension.
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Monitor patients for signs of respiratory depression, CNS depression, and hypotension. A dosage reduction of one or both drugs should be made.
7) Probable Mechanism: additive effects

3.5.1.BT Lidoflazine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, thioridazine should not be coadministered with other drugs which are also known to prolong the QTc interval, including lidoflazine (Prod Info Mellaril(R), 2000b; Hanley & Hampton, 1983).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of lidoflazine and thioridazine is contraindicated.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.BU Lithium

1) Interaction Effect: weakness, dyskinesias, increased extrapyramidal symptoms, encephalopathy, and brain damage
2) Summary: An encephalopathic syndrome followed by irreversible brain damage has occurred in a few patients treated with lithium plus a dopamine-2 antagonist, particularly haloperidol. A causal relationship between these events and the concomitant administration of a dopamine-2 antagonist and lithium has not been established (Prod Info LITHOBID(R) slow-release oral tablets, 2005). Coadministration of lithium and a number of antipsychotic drugs has caused a wide variety of encephalopathic symptoms, brain damage, extrapyramidal symptoms, and dyskinesias in isolated case reports. In most cases, these effects have occurred with therapeutic lithium levels (Amdisen, 1982; Prakash, 1982; Addonizio et al, 1988a). However, many series and trials have reported using such combinations with no severe adverse consequences (Goldney & Spence, 1986). The mechanism is not fully understood, but chronic lithium treatment decreases neostriatal dopaminergic activity, probably through a direct action on the G protein and the capacity of the G proteins, once activated, to stimulate adenyl cyclase (Carli et al, 1994). Hyperglycemic reactions have also occurred during combined phenothiazine and lithium use (Zall et al, 1968).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor patients closely for any signs of toxicity or extrapyramidal symptoms, especially if high doses of dopamine-2 antagonists, particularly haloperidol, and lithium are used. Serum lithium levels should be monitored periodically. Some clinicians advocate maintaining levels in the low therapeutic range.
7) Probable Mechanism: unknown
8) Literature Reports

a) Concomitant haloperidol and lithium therapy has resulted in symptoms of encephalopathy, confusion, extrapyramidal symptoms, and fever in several patients with mania (Cohen & Cohen, 1974; Loudon & Waring, 1976; Thomas, 1979). Irreversible neurological injuries have been reported (Sandyk & Hurwitz, 1983; Keitner & Rahman, 1984).

b) Seizures, encephalopathy, delirium, and abnormal EEG occurred in four patients during combined lithium and thioridazine therapy (Spring, 1979). Serum lithium levels were below 1 mEq/L at the time of the toxic reaction in all cases. All patients had previously tolerated lithium in combination with another phenothiazine. Three of these patients developed symptoms within eight days of initiating combination therapy.

c) The addition of lithium to neuroleptic therapy exacerbated extrapyramidal symptoms (EPS) in a small study (Addonizio et al, 1988). The patients had received at least five days of treatment with either oral thiothixene, haloperidol, or fluphenazine in mean doses of 607.5 chlorpromazine equivalents prior to initiation of the lithium and were experiencing drug-induced extrapyramidal symptoms. Oral lithium was added when clinically indicated in sufficient doses to achieve a therapeutic serum concentration. The maximum levels attained were 0.65 to 1.27 mEq/L. The EPS ratings increased in all ten patients following the addition of lithium. However, only three patients developed marked symptoms and no patient developed lithium toxicity. Significantly increased symptoms included gait, shoulder shaking, elbow rigidity, and tremor.

d) Ten patients treated with clozapine and lithium were studied (Blake et al, 1992). Of the ten patients,

four experienced significant neurologic effects, including jerking of limbs, facial spasms and tics, tremor of hands and arms, tongue twitching, and stumbling gait. One of these also experienced delirium. These effects reversed when lithium was discontinued or given at a lower dose. On rechallenge, one of two patients suffered recurrence of symptoms. By keeping serum lithium no greater than 0.5 mEq/L, clozapine could be safely coadministered.

e) Chlorpromazine serum levels can be significantly reduced in the presence of lithium treatment. If used concurrently, abrupt cessation of lithium may result in rebound elevation of chlorpromazine levels, resulting in chlorpromazine toxicity. In patients on a lithium-chlorpromazine combination, abrupt withdrawal of the lithium may precipitate chlorpromazine cardiotoxicity. In this report, such toxicity was manifested as sudden ventricular fibrillation associated with prolongation of the QTc interval. Hypotension and EPS are also possible in this situation (Stevenson et al, 1989).

f) However, other data do not support that such adverse events are frequent or indeed causally related to combination therapy. Combination of dopamine antagonist antipsychotic drugs and lithium have been used successfully in many patients with manic-depressive illness. It has been proposed that the interaction may only become significant with very high doses of one or both drugs or with failure to discontinue dosing in the presence of toxic symptoms (Miller & Menninger, 1987).

g) A 69-year-old patient with oxygen-dependent chronic obstructive pulmonary disorder and a 25-year history of bipolar disorder was started on risperidone 3 mg for the treatment of new-onset auditory and visual hallucinations. She had also been maintained on a regimen of lithium (450 mg daily) for more than 10 years. In addition, she was given amantadine (100 mg twice daily) for tremor. Three weeks after the start of risperidone, the patient experienced a decline in mental status in addition to dizziness, worsening tremors, nausea and vomiting, polyuria, depression, and visual and auditory hallucinations. She was then admitted to the hospital for delirium. Her lithium serum level was 1.36 mEq/L at the time of the admission. All medications were discontinued. Although her lithium level decreased to 0.41 mEq/L, she continued to experience profound delirium, tremors, lethargy, and hallucinations for almost one week. After she started to respond to commands, she was restarted on lithium (300 mg at bedtime) because of the onset of mild hypomania. Five days later, she was discharged with a regimen of lithium and low-dose lorazepam for treatment of insomnia. It is suggested that delirium could have been caused by the concurrent use of lithium and risperidone. Other factors could also have caused delirium, such as the patient's serum lithium level and the underlying pulmonary pathology. In addition, amantadine, which facilitates the release of presynaptic dopamine and has a mild anticholinergic effect, may have contributed (Chen & Cardasis, 1996).

3.5.1.BV Lithospermum

1) Interaction Effect: increased dopaminergic side effects

2) Summary: Theoretically, the dopamine agonist activity of lithospermum may add to that of other dopamine agonists, increasing the risk of dopaminergic adverse effects. Lithospermum likely decreases prolactin secretion via dopamine stimulation (Sourgens et al, 1982a). Animal data suggest that the effect occurs rapidly within 3 hours after injection, subsiding within 6 to 9 hours (Sourgens et al, 1980a). The magnitude and clinical significance of this phenomenon has yet to be determined in humans. Furthermore, it is not known if the ability to stimulate dopamine receptors is limited to the hypothalamic region or if such an effect will be noted elsewhere (i.e., if patients with psychosis will experience worsening of their condition due to dopamine stimulation secondary to lithospermum). Caution is recommended until the effects on humans and possible implications of a drug-herb interaction with dopamine agonists can be fully determined.

3) Severity: minor

4) Onset: rapid

5) Substantiation: theoretical

6) Clinical Management: Avoid concomitant use of lithospermum with phenothiazines. If the patient chooses to take lithospermum, monitor closely for symptoms of additive dopamine agonism such as nausea, headache, dizziness, fatigue, vomiting, and postural hypotension.

7) Probable Mechanism: additive dopaminergic effect

8) Literature Reports

a) Administration of freeze dried extracts (FDE) of Lithospermum officinale (Boraginaceae) by intravenous injection to rats resulted in reduced prolactin serum levels and hypophyseal stores. When administered diluent, prolactin levels decreased from 36 +/- 8 nanograms/milliliter (ng/mL) serum to 10 +/- 4 ng/mL serum (p less than 0.005) when administered Lithospermum officinale FDE (40 milligrams (mg)/100 grams body weight) within 3 hours post intravenous administration. The authors concluded that Lithospermum officinale possibly impacted prolactin secretion at the hypothalamic site via dopamine stimulation (Sourgens et al, 1982).

b) Prolactin levels decreased rapidly below basal values in rats within the first 3 hours following a single intravenous injection of Lithospermum officinale. Prolactin levels returned to control levels within 6 to 9 hours after the injection (Sourgens et al, 1980).

3.5.1.BW Lorcainide

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Class I antiarrhythmic agents may prolong the QT interval in some patients, which may result in ventricular tachycardia, ventricular fibrillation, and torsades de pointes. Although pharmacokinetic studies

between thioridazine and other drugs which prolong the QT interval have not been performed, an additive effect cannot be excluded. Therefore, the concurrent administration of thioridazine with a Class I antiarrhythmic agent is contraindicated (Prod Info Rythmol(R), 2002; Prod Info Mellaril(R), 2002; Prod Info Tambocor(R), 1998).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of thioridazine and agents that prolong the QT interval, such as Class I antiarrhythmic agents, is contraindicated.
7) Probable Mechanism: additive cardiac effects

3.5.1.BX Lubeluzole
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, thioridazine should not be coadministered with other drugs which are also known to prolong the QTc interval, including lubeluzole (Prod Info Mellaril(R), 2000t).
3) Severity: contraindicated
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of thioridazine and agents that prolong the QT interval is contraindicated.
7) Probable Mechanism: additive cardiac effects

3.5.1.BY Lumefantrine
1) Interaction Effect: an increased risk of QT interval prolongation
2) Summary: Due to the potential for additive effects on QT interval prolongation, concomitant use of artemether/lumefantrine with drugs that prolong the QT interval should be avoided (Prod Info COARTEM(R) oral tablets, 2009).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of artemether/lumefantrine with drugs that prolong the QT interval should be avoided due to the potential for additive effects on QT interval prolongation (Prod Info COARTEM(R) oral tablets, 2009).
7) Probable Mechanism: additive effects on QT interval prolongation
8) Literature Reports
a) Concurrent administration of a single dose of IV quinine 10 mg/kg with the final dose of a 6-dose regimen of artemether/lumfantrine did not alter the systemic exposure to quinine, lumefantrine, or dihydroartemisinin (active metabolite of artemether). Although artemether exposure was decreased, it was not believed to be clinically significant. The effects on QT prolongation were not reported in this study (Prod Info COARTEM(R) oral tablets, 2009).

3.5.1.BZ Mefloquine
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, the manufacturer of thioridazine states that concomitant use with other drugs which prolong the QT interval is contraindicated (Prod Info Mellaril(R), 2000u). Mefloquine was associated with significant QT prolongation in a study of 46 healthy subjects (Davis et al, 1996).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of thioridazine and any other drug which prolongs the QT interval, such as mefloquine, is contraindicated.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.CA Meperidine
1) Interaction Effect: an increase in central nervous system and respiratory depression
2) Summary: Phenothiazines may potentiate the analgesic effects of meperidine, resulting in CNS depression, hypotension, and respiratory depression. Several studies report the potentiation of analgesia by the addition of promethazine, chlorpromazine, and propiomazine to narcotic analgesics (Fromhagen & Carswell, 1961a; Winne, 1961a; Glessner & Allis, 1964a; Jackson & Smith, 1956; Eisenstein, 1964). Other studies and reviews however, do not confirm these findings (Dundee, 1963a; Siker et al, 1966; Keats, 1961; McGee & Alexander, 1979). When administered concomitantly with phenothiazines, the dose of meperidine may need to be reduced by 25% to 50% (Prod Info Demerol(R), 1997).
3) Severity: moderate
4) Onset: rapid

5) Substantiation: probable
6) Clinical Management: Monitor patients for signs of respiratory depression, CNS depression, and hypotension. A dosage reduction or discontinuation of one or both drugs may be necessary.
7) Probable Mechanism: additive effects
8) Literature Reports
a) Promethazine and meperidine combinations have been the most widely studied. It has been concluded from a controlled study in 296 patients during labor that meperidine 50 mg and promethazine 25 mg produced significantly greater analgesia than 50 mg of meperidine alone (Fromhagen & Carswell, 1961).
b) No difference in analgesic efficacy was found when promethazine 25 mg and meperidine 50 mg was alternated with meperidine 100 mg in 26 post-surgical patients (Glessner & Allis, 1964).
c) A controlled study in 51 post-operative hemorrhoidectomy patients concluded that injections of 50 mg of meperidine combined with 50 mg of promethazine gave the same amount of pain relief as a 100 mg injection of meperidine (Winne, 1961). Even though these studies were controlled, response to pain was still subjective in nature and only post-operative pain was being measured. Pain of this type varies considerably from patient to patient and no definite conclusions can be drawn from these studies.
d) In opposition to these studies is the detailed investigation by other researchers (Dundee, 1963). By applying various amounts of pressure to the anterior surface of the tibia, they measured the analgesic effects of 13 phenothiazines given by deep intramuscular injection. Using this technique, promethazine alone was shown to have an antianalgesic effect (increased the patients' sensitivity to somatic pain). It was shown that injections of meperidine 100 mg combined with promethazine 50 mg has less analgesic effect than 100 mg of meperidine alone. Promazine was the only phenothiazine that showed an additive analgesic effect with meperidine.
e) Arterial blood gases were measured to determine the effect of methotrimeprazine in 31 healthy volunteers (Zsigmond & Flynn, 1988). Methotrimeprazine, administered alone, caused no significant respiratory depression but was found to potentiate the respiratory depression caused by meperidine. When methotrimeprazine (0.15 mg per kg intravenously) was given alone, PaO2, PaCO2, pH, and base excess remained unchanged. When methotrimeprazine and meperidine were combined, significant increases in PaCO2 and pH reductions were observed, which confirms the potentiation of meperidine-induced respiratory depression by methotrimeprazine.
f) The pharmacokinetics of meperidine were not significantly altered when chlorpromazine was administered concomitantly in a two-way crossover study of 10 healthy patients. Subjects were given meperidine (26 mg per meter squared) with either chlorpromazine (30 mg per meter squared) or placebo. The effect of chlorpromazine on the serum concentration-time curve and metabolism of meperidine was investigated in order to determine if concomitant administration of a phenothiazine and meperidine alters the metabolism of meperidine, resulting in additive CNS and respiratory depression. When the two drugs were combined, N-demethylation activity was increased as evidenced by elevated urinary excretion of normeperidine (a toxic metabolite) and normeperidinic acid. Excretion of normeperidine is slower than that of meperidine, thus repeated dosing of the combination (chlorpromazine and meperidine) could lead to increased cardiac and central nervous system toxicity (Stambaugh & Wainer, 1981).

3.5.1.CB Methadone
1) Interaction Effect: an increase in central nervous system and respiratory depression
2) Summary: The concomitant use of methadone and other central nervous system depressants including phenothiazines (e.g. chlorpromazine, promethazine, thioridazine) may result in additive CNS and respiratory depressant effects, including hypotension, profound sedation and/or coma (Prod Info METHADOSE(R) oral concentrate, sugar-free oral concentrate, 2005). Monitor patient carefully for signs of respiratory depression, CNS depression, and hypotension.
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Monitor patients for signs of respiratory depression, CNS depression, and hypotension.
7) Probable Mechanism: additive effects

3.5.1.CC Methadone
1) Interaction Effect: an increased risk of QTc interval prolongation
2) Summary: Cases of QT interval prolongation and serious arrhythmias, including torsade de pointes, have been reported with methadone use (Prod Info DOLOPHINE(R) HYDROCHLORIDE oral tablets, 2006). Treatment with thioridazine has also been associated with QTc prolongation and sudden death due to torsade de pointes-type arrhythmias. Concurrent administration of methadone and thioridazine is contraindicated due to the potential for additive effects on QTc interval prolongation (Prod Info Mellaril(R), 2000n).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concurrent use of methadone and thioridazine is contraindicated due to the

potential for additive effects on QT interval prolongation (Prod Info Mellaril(R), 2000n).
7) Probable Mechanism: additive effects on QTc interval prolongation

3.5.1.CD Metoprolol
1) Interaction Effect: increased plasma levels of metoprolol
2) Summary: Concurrent use of metoprolol, a CYP2D6 enzyme substrate, and thioridazine, a potent CYP2D6 enzyme inhibitor, may increase metoprolol exposure. Use caution when metoprolol is administered concomitantly with thioridazine, and monitor closely for metoprolol adverse effects (such as bradycardia) (Prod Info LOPRESSOR(R) oral tablets, IV injection, 2006).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Coadministration of metoprolol with thioridazine, a potent CYP2D6-inhibitor, should be approached with caution. Monitor adverse reactions related to metoprolol toxicity, such as bradycardia (Prod Info LOPRESSOR(R) oral tablets, IV injection, 2006).
7) Probable Mechanism: inhibition of CYP2D6-mediated metoprolol metabolism

3.5.1.CE Metrizamide
1) Interaction Effect: an increased seizure risk
2) Summary: Concomitant administration of metrizamide and phenothiazines has predisposed patients to metrizamide-induced seizure activity (Hindmarsh & Brucher, 1975a). However, most available data supporting this interaction is anecdotal in nature, and specific documentation of the interaction is lacking. Animal studies demonstrate that concurrent administration of phenothiazines and metrizamide results in a significantly higher frequency of seizures compared to when these drugs are administered alone (Gonsette & Brucher, 1977a).
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Chlorpromazine (and possibly other phenothiazines) should be discontinued at least five days prior to using metrizamide. Halothane, isoflurane, or narcotic/relaxant techniques are appropriate if general anesthesia is necessary in patients receiving metrizamide.
7) Probable Mechanism: decreased seizure threshold
8) Literature Reports
a) A patient who had a seizure after being injected with metrizamide was the only patient in well over 1,000 patients in this series having major complications (Hindmarsh & Brucher, 1975). The patient had been on chlorpromazine for 4 months due to a psychiatric disorder. Medication was reduced to 50 mg from his normal 75 mg the day before the metrizamide injection and reduced again to 25 mg the day of the procedure. This patient had no prior history of epileptic seizures. Three and a half hours after the administration of metrizamide the patient sustained a grand mal seizure that lasted 1 minute and stopped without treatment. Five hours after the first attack the patient exhibited a second attack which was brought under control by 10 mg of diazepam. This was a single case that suggested the possibility of a correlation between subarachnoid use of metrizamide and phenothiazines.
b) Over 500,000 applications of metrizamide were reviewed (Ahlgren, 1980). There were 42 reported convulsions after treatment. A causal relationship between phenothiazine pretreatment and development of seizures could not be established. The author further stated that the addition of levomepromazine 40 mg may actually decrease the number of side effects such as headaches and nausea. One study examined 77 patients, 26 receiving pretreatment with levomepromazine and 51 without the medication (Standness, 1982). EEGs were taken before, during and after treatment. There were no differences between the groups.
c) In a study of rabbits, pericerebral injection of metrizamide and intravenous injection of chlorpromazine administered separately produced no clinical seizure activity, but the combination produced clinical seizures in 66% of the animals (Gonsette & Brucher, 1977). Upon histologic examination, inflammatory reactions were found in 66% of the animals receiving the combination, compared to 5% seen with chlorpromazine alone and 0% seen with metrizamide alone. Animals pretreated with phenobarbital were protected from the enhanced seizure activity of the combination while animals pretreated with diazepam were not.

3.5.1.CF Morphine
1) Interaction Effect: an increase in central nervous system and respiratory depression
2) Summary: The concomitant use of morphine and other central nervous system depressants including phenothiazines (e.g. chlorpromazine, promethazine, thioridazine) may result in additive CNS and respiratory depressant effects, including hypotension, profound sedation and/or coma . When administering morphine and a phenothiazine together, one or both agents dosage should be significantly reduced (Prod Info MS CONTIN(R) controlled-release oral tablets, 2005). Monitor patient carefully for signs of respiratory depression, CNS depression, and hypotension.
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical

6) Clinical Management: Monitor patients for signs of respiratory depression, CNS depression, and hypotension. A dosage reduction of one or both drugs should be made.
7) Probable Mechanism: additive effects

3.5.1.CG Morphine Sulfate Liposome
1) Interaction Effect: an increase in central nervous system and respiratory depression
2) Summary: The concomitant use of morphine sulfate liposome and other central nervous system depressants including phenothiazines (e.g. chlorpromazine, promethazine, thioridazine) may result in additive CNS and respiratory depressant effects, including hypotension, profound sedation and/or coma (Prod Info DEPODUR(TM) extended release liposome injection, 2005). Monitor patient carefully for signs of respiratory depression, CNS depression, and hypotension.
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Monitor patients for signs of respiratory depression, CNS depression, and hypotension.
7) Probable Mechanism: additive effects

3.5.1.CH Moxifloxacin
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, thioridazine should not be coadministered with other drugs which are also known to prolong the QTc interval, including moxifloxacin (Prod Info Mellaril(R), 2002; Prod Info Avelox(TM), 2000).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of thioridazine and agents that prolong the QT interval, such as moxifloxacin, is contraindicated.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.CI Nortriptyline
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Although citing no data, the manufacturer of thioridazine states that concomitant use with other drugs which prolong the QT interval is contraindicated (Prod Info Mellaril(R), 2001). Tricyclic antidepressants (TCAs) at therapeutic doses can cause QT prolongation (Marshall & Forker, 1982).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concurrent administration of a tricyclic antidepressant and thioridazine is contraindicated.
7) Probable Mechanism: additive effect on QT interval

3.5.1.CJ Octreotide
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Although citing no data, the manufacturers of some phenothiazines state that concomitant use with other drugs which prolong the QT interval is contraindicated (Prod Info Thioridazine tablets, 2002). QT prolongation has been observed in patients treated with octreotide (Prod Info Sandostatin(R), 1999). Other phenothiazines may have similar effects, though no reports are available.
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of octreotide and thioridazine is contraindicated as it may precipitate QT prolongation.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.CK Ondansetron
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Rarely, and predominantly with the intravenous formulation, transient ECG changes including QT interval prolongation have occurred with ondansetron (Prod Info ZOFRAN(R) oral tablets, oral solution, ZOFRAN ODT(R) orally disintegrating tablets, 2006). Thioridazine has been shown to prolong the QTc interval in a dose related manner, and should be avoided in combination with other drugs that are known to prolong the QTc interval, including ondansetron (Prod Info Mellaril(R), 2000k).
3) Severity: contraindicated
4) Onset: unspecified

5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of ondansetron and agents that may prolong the QT interval, such as thioridazine, is contraindicated.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.CL Orphenadrine
1) Interaction Effect: decreased phenothiazine serum concentrations, decreased phenothiazine effectiveness, enhanced anticholinergic effects (ileus, hyperpyrexia, sedation, dry mouth)
2) Summary: The concurrent use of anticholinergic agents (benztropine, orphenadrine, procyclidine, trihexyphenidyl) to control extrapyramidal side effects may reduce oral absorption of phenothiazines, antagonize the behavioral and antipsychotic effects of the phenothiazine, and enhance anticholinergic side effects (Rivera-Calimlim et al, 1976a; Mann & Boger, 1978a; Singh & Kay, 1979; Gershon et al, 1965a; Buckle & Guillebaud, 1967).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Anticholinergics (benztropine, orphenadrine, procyclidine, trihexyphenidyl) should not be used routinely with phenothiazine derivatives as prophylaxis against possible extrapyramidal symptoms; use should be reserved for situations where EPS occur and lowering of the antipsychotic dosage is not possible. Anticholinergic use should be reevaluated at least every three months.
7) Probable Mechanism: delayed gastric emptying, increased gut wall metabolism of phenothiazine, decreased absorption
8) Literature Reports
a) The concomitant administration of trihexyphenidyl and chlorpromazine has been shown to result in a decrease in chlorpromazine plasma levels (Rivera-Calimlim et al, 1973; Gershon et al, 1965). A crossover controlled study of the chlorpromazine-trihexyphenidyl interaction in psychiatric patients showed conclusively that trihexyphenidyl lowers plasma levels of chlorpromazine from 13% to 100% (Rivera-Calimlim et al, 1976). The mechanism by which trihexyphenidyl lowers plasma levels of chlorpromazine was shown in rats to be an inhibition of gastric emptying by trihexyphenidyl, probably as a result of its anticholinergic activity (Rivera-Calimlim, 1976). Slow gastric emptying will delay the transport of chlorpromazine to intestinal absorption sites and favor enhanced gastrointestinal metabolism.
b) Trihexyphenidyl may also directly reverse some of the therapeutic effects of chlorpromazine. A toxic psychosis has been commonly reported following usual therapeutic doses of anticholinergic drugs, particularly when these agents are used in conjunction with other drugs with anticholinergic properties. Symptoms may include visual hallucinations, confusion, disorientation, speech difficulty, emotional lability and psychotic thinking (Perry et al, 1985).
c) The chlorpromazine-trihexyphenidyl interaction may also include additive anticholinergic effects including constipation or paralytic ileus, dry mouth, blurred vision, increased intraocular pressure and urinary retention (Perry et al, 1985). Hyperpyrexia has been reported, presumably due to blocking of exocrine sweat glands in combination with the hypothalamic dysregulation produced by antipsychotics (Mann & Boger, 1978).
d) A significant reduction in fluphenazine serum levels occurred following addition of procyclidine in patients who were previously well stabilized. Following discontinuation of procyclidine, fluphenazine serum levels returned to baseline (Bamrah et al, 1986). However, the addition of orphenadrine to perphenazine therapy resulted in no clinically relevant pharmacokinetic changes in the absorption, distribution, or elimination of perphenazine (Bolvig Hansen et al, 1979).

3.5.1.CM Oxycodone
1) Interaction Effect: an increase in central nervous system and respiratory depression
2) Summary: The concomitant use of oxycodone and other central nervous system depressants including phenothiazines (e.g. chlorpromazine, promethazine, thioridazine) may result in additive CNS and respiratory depressant effects, including hypotension, profound sedation and/or coma . When administering oxycodone and a phenothiazine together, the oxycodone dose should be reduced by 1/3 to 1/2 (Prod Info OXYCONTIN (R) controlled release tablets, 2005). Monitor patient carefully for signs of respiratory depression, CNS depression, and hypotension.
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Monitor patients for signs of respiratory depression, CNS depression, and hypotension. A dosage reduction of 1/3 to 1/2 of oxycodone should be made.
7) Probable Mechanism: additive effects

3.5.1.CN Paliperidone
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Although citing no data, the manufacturer of thioridazine states that concomitant use with other drugs which prolong the QT interval is contraindicated (Prod Info Mellaril(R), 2001b). Several

antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999), haloperidol (O'Brien et al, 1999), pimozide (Prod Info Orap(R), 2000), quetiapine (Owens, 2001c), paliperidone (Prod Info INVEGA(TM) extended-release oral tablets, 2006), risperidone (Duenas-Laita et al, 1999), sertindole (Agelink et al, 2001), sultopride (Lande et al, 1992), ziprasidone (Prod Info GEODON(R) intramuscular injection, oral capsule, 2005), and zotepine (Sweetman, 2004).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of agents that prolong the QT interval, such as antipsychotics, and thioridazine, is contraindicated.
7) Probable Mechanism: additive QT prolongation

3.5.1.CO Paroxetine
1) Interaction Effect: an increased risk of thioridazine toxicity, cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Paroxetine inhibits the metabolism of thioridazine, possibly through the inhibition of cytochrome P450 2D6 (CYP2D6) resulting in toxicity. The resulting elevated levels of thioridazine would be expected to enhance the prolongation of the QT interval and may increase the risk of serious, potentially fatal, cardiac arrhythmias, such as torsade de pointes-type arrhythmias (Prod Info Paxil(R), 2003; Prod Info Mellaril(R), 2000p).
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Due to the potential for significant, possibly life-threatening, proarrhythmic effects, concurrent administration of thioridazine and paroxetine is contraindicated.
7) Probable Mechanism: inhibition of cytochrome P450 2D6-mediated thioridazine metabolism
8) Literature Reports
a) The metabolism of thioridazine is inhibited by drugs such as paroxetine due to reduced cytochrome P450 2D6 isozyme activity. The elevated levels of thioridazine would be expected to enhance the prolongation of the QTc interval associated with thioridazine. This, in turn, may increase the risk of serious, potentially fatal, cardiac arrhythmias, such as torsade de pointes-type arrhythmias (Prod Info Mellaril(R), 2000o).

3.5.1.CP Pentamidine
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Although citing no data, the manufacturers of some phenothiazines state that concomitant use with other drugs which prolong the QT interval is contraindicated (Prod Info Thioridazine tablets, 2002). Torsades de pointes has been associated with pentamidine (Lindsay et al, 1990).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Pentamidine is contraindicated in patients being treated with thioridazine as it may precipitate QT prolongation.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.CQ Phenobarbital
1) Interaction Effect: decreased phenobarbital or thioridazine effectiveness
2) Summary: Phenobarbital may decrease thioridazine concentrations due to its ability to induce hepatic microsomal enzymes (Ellenor et al, 1978a). Phenobarbital and thioridazine have also been reported to produce lower serum levels of both drugs when given concomitantly (Gay & Madsen, 1983a).
3) Severity: moderate
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: If concurrent therapy is required, a dosage adjustment for thioridazine or phenobarbital may be required in order to maintain or achieve a therapeutic effect.
7) Probable Mechanism: induction of hepatic microsomal enzymes
8) Literature Reports
a) Seven retarded patients on concurrent phenobarbital and thioridazine therapy experienced an increase in their thioridazine and metabolite levels when phenobarbital was withdrawn. The most likely explanation is that withdrawal of phenobarbital resulted in a reversal of the phenobarbital-induced increase in hepatic drug metabolizing enzyme activity (Ellenor et al, 1978).
b) Retarded adults on phenobarbital and thioridazine 100 mg to 200 mg per day were matched to retarded adults on antiepileptic therapy alone. When given concomitantly, phenobarbital and thioridazine produced lower serum levels of both drugs than when either drug was given alone. The presumed mechanism was induction of microsomal enzymes (Gay & Madsen, 1983).

3.5.1.CR Phenylalanine

1) Interaction Effect: increased incidence of tardive dyskinesia
2) Summary: Taking phenylalanine concomitantly with certain neuroleptic drugs may exacerbate tardive dyskinesia (Gardos et al, 1992a). Abnormal phenylalanine metabolism in certain patients may lead to phenylalanine accumulation in the brain and in turn, reduced brain availability of other large neutral amino acids. This may interfere with the synthesis of catecholamines. It was hypothesized that some patients with depression may have deficient phenylalanine hydroxylase (as in phenylketonuria (PKU)), or deficient dihydropteridine reductase (as in atypical PKU) (Gardos et al, 1992a).
3) Severity: moderate
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Caution is advised if phenylalanine is administered with a neuroleptic agent. Monitor the patient closely for signs of tardive dyskinesia.
7) Probable Mechanism: reduced brain availability of other large neutral amino acids and interference with catecholamine synthesis
8) Literature Reports
a) Phenylalanine tended to increase the incidence of tardive dyskinesia in patients taking neuroleptics in an open study. Three groups of patients were studied: (1) patients with unipolar depression with tardive dyskinesia (n=11), (2) patients with no tardive dyskinesia with current or past exposure to greater than or equal to 100 milligrams (mg) of a chlorpromazine equivalent for at least 3 months (n=10), and (3) patients with no tardive dyskinesia not previously exposed to a neuroleptic drug (n=10). Neuroleptic agents were taken during the study by 6 patients in group 1, and 5 patients in group 2. Patients received powdered phenylalanine 100 mg/kilogram dissolved in orange juice after an overnight fast. Blood samples were obtained just prior to phenylalanine administration and 2 hours after administration. Three patients in group 1 (with tardive dyskinesia) had the highest postloading phenylalanine plasma levels; this group as a whole had higher (though nonsignificant) mean phenylalanine levels than the other groups. Tardive dyskinesia score (measured using the Abnormal Involuntary Movements Scale (AIMS)) nonsignificantly increased in group 1. Postloading phenylalanine level and postloading AIMS scores were significantly positively correlated in group 1 (rs=0.347, p less than 0.05; Spearman correlation coefficient 0.543, p less than 0.05). Postloading phenylalanine level and baseline AIMS scores demonstrated a trend toward correlation (rs=0.246, p=0.092; Spearman correlation coefficient 0.679, p less than 0.05). In all patients, phenylalanine loading increased plasma phenylalanine levels approximately eight-fold, and plasma tyrosine increased 2.5 times as a result of conversion of phenylalanine to tyrosine. Plasma levels of competing large neutral amino acids such as tryptophan decreased slightly (Gardos et al, 1992).

3.5.1.CS Phenytoin

1) Interaction Effect: increased or decreased phenytoin levels and possibly reduced phenothiazine levels
2) Summary: Concurrent phenothiazine and phenytoin therapy has been reported to increase, decrease, or cause no change in the serum levels of phenytoin (Sands et al, 1987a; Vincent, 1980a; Siris et al, 1974a; Houghton & Richens, 1975a). In one study, concomitant phenytoin reduced the serum levels of mesoridazine, but not thioridazine (Linnoila et al, 1980c).
3) Severity: minor
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Consider monitoring phenytoin levels when a phenothiazine is added or discontinued from therapy; dosage adjustments may be needed in some cases. The patient should also be observed for any signs of phenytoin toxicity (ataxia, nystagmus, tremor, hyperreflexia), particularly in the case of adjustments to the phenothiazine dosage. Observe patients for phenothiazine efficacy.
7) Probable Mechanism: induction or inhibition of phenytoin metabolism; induction of phenothiazine metabolism
8) Literature Reports
a) Compelling data was reported suggesting that phenothiazines as a group decrease serum phenytoin concentrations, but the effect of individual phenothiazines was not evaluated. A total of 92 cases (institutionalized patients) who were receiving constant phenytoin doses and who were either initiating, discontinuing, increasing, or decreasing a phenothiazine were retrospectively reviewed. Approximately half of the patients received thioridazine, while the other half were about evenly split between chlorpromazine and mesoridazine. Phenytoin concentrations decreased by 44% (p=0.001) when a phenothiazine was added; similarly, increases in phenothiazine dose caused a 33% decrease in phenytoin concentrations (p=0.001). In patients who discontinued a phenothiazine, phenytoin concentrations increased by 71% (p=0.001); similarly, decreases in phenothiazine dose caused a 55% increase in phenytoin concentrations (p=0.001). Although the combined results cannot be applied clinically to a particular phenothiazine, this study does suggest a remarkably strong trend among phenothiazines which is contrary to some individual case reports. Further study is needed (Haidukewych & Rodin, 1985a).
b) The effects of concomitant treatment with phenytoin and/or phenobarbital on the steady-state serum concentrations of haloperidol, thioridazine, and mesoridazine were investigated in two groups of patients. The investigators found that concomitant anticonvulsant medication significantly reduced the plasma level of haloperidol and mesoridazine, but not thioridazine (Linnoila et al, 1980b).

3.5.1.CT Pimozide

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Although citing no data, the manufacturer of thioridazine states that concomitant use with other drugs which prolong the QT interval is contraindicated (Prod Info Mellaril(R), 2001b). Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999), haloperidol (O'Brien et al, 1999), pimozide (Prod Info Orap(R), 2000), quetiapine (Owens, 2001c), paliperidone (Prod Info INVEGA(TM) extended-release oral tablets, 2006), risperidone (Duenas-Laita et al, 1999), sertindole (Agelink et al, 2001), sultopride (Lande et al, 1992), ziprasidone (Prod Info GEODON(R) intramuscular injection, oral capsule, 2005), and zotepine (Sweetman, 2004).

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of agents that prolong the QT interval, such as antipsychotics, and thioridazine, is contraindicated.

7) Probable Mechanism: additive QT prolongation

3.5.1.CU Pindolol

1) Interaction Effect: an increased risk of thioridazine toxicity, cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Pindolol has been beneficial in the treatment of patients with behavior and management problems secondary to organic brain disease (Greendyke & Gulya, 1988a). Fluoxetine inhibits the metabolism of thioridazine, possibly through the inhibition of cytochrome P450 2D6 (CYP2D6) resulting in toxicity. The resulting elevated levels of thioridazine would be expected to enhance the prolongation of the QT interval and may increase the risk of serious, potentially fatal, cardiac arrhythmias, such as torsade de pointes-type arrhythmias (Prod Info Mellaril(R), 2000ab).

3) Severity: contraindicated

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Due to the potential for significant, possibly life-threatening, proarrhythmic effects, concurrent administration of thioridazine and pindolol is contraindicated.

7) Probable Mechanism: inhibition of cytochrome P450 2D6-mediated thioridazine metabolism

8) Literature Reports

a) Twenty-six male patients with intermittent explosive disorder secondary to organic brain disease were studied to determine the effect of pindolol and thioridazine coadministration. All patients were already receiving treatment with thioridazine, haloperidol, phenytoin, or phenobarbital. Pindolol therapy was started at 5 mg twice daily with total daily increments of 10 mg every three days for a total dose of 40 mg. It was then reduced by 10 mg increments to zero with a reversal of the schedule. Results showed moderate, dose-related increases in serum levels of thioridazine and two of its metabolites when coadministered with pindolol. Serum pindolol levels were also higher than expected in patients receiving thioridazine. No serum level increases were found for phenytoin, phenobarbital, or haloperidol. This fact led the authors to believe that the elevation in thioridazine and pindolol levels was due to mutually competitive interference with their hepatic metabolism (Greendyke & Gulya, 1988).

b) The metabolism of thioridazine is inhibited by drugs such as pindolol due to reduced cytochrome P450 2D6 isozyme activity. The elevated levels of thioridazine would be expected to enhance the prolongation of the QTc interval associated with thioridazine. This, in turn, may increase the risk of serious, potentially fatal, cardiac arrhythmias, such as torsade de pointes-type arrhythmias (Prod Info Mellaril(R), 2000h).

3.5.1.CV Pirmenol

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Class Ia antiarrhythmics have been shown to prolong the QTc interval at the recommended therapeutic dose. Even though no formal drug interaction studies have been done, the coadministration of thioridazine with other drugs known to prolong the QTc interval, including Class Ia antiarrhythmic agents, is not recommended (Prod Info Mellaril(R), 2002a; Prod Info Procanbid(R), 2000; Prod Info Quinaglute(R), 1999; Desai et al, 1981).

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of a Class IA antiarrhythmic and thioridazine is contraindicated.

7) Probable Mechanism: additive cardiac effects

3.5.1.CW Porfimer

1) Interaction Effect: excessive intracellular damage in photosensitized tissues

2) Summary: Coadministration of porfimer with other photosensitizing agents, including phenothiazines,

may increase the severity of photosensitivity reactions and lead to excessive tissue damage (Prod Info Photofrin(R), 1995). Caution should be used if thioridazine is to be given to patients receiving porfimer for photodynamic therapy.
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Patients who are receiving phenothiazine therapy along with photodynamic therapy should be counseled to avoid exposure of skin and eyes to direct sunlight or bright indoor light for 30 days after administration of porfimer. Application of sunscreens does not protect against photosensitivity reactions.
7) Probable Mechanism: additive photosensitizing effects

3.5.1.CX Prajmaline
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Class Ia antiarrhythmics have been shown to prolong the QTc interval at the recommended therapeutic dose. Even though no formal drug interaction studies have been done, the coadministration of thioridazine with other drugs known to prolong the QTc interval, including Class Ia antiarrhythmic agents, is not recommended (Prod Info Mellaril(R), 2002a; Prod Info Procanbid(R), 2000; Prod Info Quinaglute(R), 1999; Desai et al, 1981).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of a Class IA antiarrhythmic and thioridazine is contraindicated.
7) Probable Mechanism: additive cardiac effects

3.5.1.CY Probucol
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, thioridazine should not be coadministered with other drugs which are also known to prolong the QTc interval (Prod Info Mellaril(R), 2000j). Probucol has been shown to prolong the QTc interval (Gohn & Simmons, 1992; Prod Info Lorelco(R), 1991).
3) Severity: contraindicated
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of thioridazine and agents that prolong the QT interval, such as probucol, is contraindicated.
7) Probable Mechanism: additive cardiac effects

3.5.1.CZ Procainamide
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Class Ia antiarrhythmics have been shown to prolong the QTc interval at the recommended therapeutic dose. Even though no formal drug interaction studies have been done, the coadministration of thioridazine with other drugs known to prolong the QTc interval, including Class Ia antiarrhythmic agents, is not recommended (Prod Info Mellaril(R), 2002a; Prod Info Procanbid(R), 2000; Prod Info Quinaglute(R), 1999; Desai et al, 1981).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of a Class IA antiarrhythmic and thioridazine is contraindicated.
7) Probable Mechanism: additive cardiac effects

3.5.1.DA Procarbazine
1) Interaction Effect: CNS depression
2) Summary: The combined use of phenothiazines and monoamine oxidase inhibitors (MAOI) has resulted in prolonged phenothiazine effects (Sjoqvist, 1965). To minimize CNS depression and possible potentiation, coadministration of procarbazine and phenothiazines should be approached with caution (Prod Info Matulane(R), 2002).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: The coadministration of procarbazine and phenothiazines should be approached with caution.
7) Probable Mechanism: unknown

3.5.1.DB Procaterol

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, thioridazine should not be coadministered with other drugs which are also known to prolong the QTc interval, including procaterol (Prod Info Mellaril(R), 2000x).
3) Severity: contraindicated
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of thioridazine and agents that prolong the QT interval is contraindicated.
7) Probable Mechanism: additive cardiac effects

3.5.1.DC Prochlorperazine

1) Interaction Effect: an increased risk of cardiotoxicity (QT interval prolongation, torsades de pointes, cardiac arrest)
2) Summary: Because thioridazine may prolong the QT interval and increase the risk of arrhythmias, the concurrent administration of thioridazine and other phenothiazines is contraindicated (Prod Info Mellaril(R), 2000l). Q and T wave distortions have been observed in patients taking phenothiazines (Prod Info Compazine(R), 2002a; Prod Info Stelazine(R), 2002a; Prod Info Thorazine(R), 2002a). Other phenothiazines may have similar effects, though no reports are available.
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of agents that prolong the QT interval, such as thioridazine and other phenothiazines, is contraindicated.
7) Probable Mechanism: additive effect on QT interval

3.5.1.DD Procyclidine

1) Interaction Effect: decreased phenothiazine serum concentrations, decreased phenothiazine effectiveness, enhanced anticholinergic effects (ileus, hyperpyrexia, sedation, dry mouth)
2) Summary: The concurrent use of anticholinergic agents (benztropine, orphenadrine, procyclidine, trihexyphenidyl) to control extrapyramidal side effects may reduce oral absorption of phenothiazines, antagonize the behavioral and antipsychotic effects of the phenothiazine, and enhance anticholinergic side effects (Rivera-Calimlim et al, 1976d; Mann & Boger, 1978e; Singh & Kay, 1979b; Gershon et al, 1965e; Buckle & Guillebaud, 1967b).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Anticholinergics (benztropine, orphenadrine, procyclidine, trihexyphenidyl) should not be used routinely with phenothiazine derivatives as prophylaxis against possible extrapyramidal symptoms; use should be reserved for situations where EPS occur and lowering of the antipsychotic dosage is not possible. Anticholinergic use should be reevaluated at least every three months.
7) Probable Mechanism: delayed gastric emptying, increased gut wall metabolism of phenothiazine, decreased absorption
8) Literature Reports

a) The concomitant administration of trihexyphenidyl and chlorpromazine has been shown to result in a decrease in chlorpromazine plasma levels (Rivera-Calimlim et al, 1973b; Gershon et al, 1965d). A crossover controlled study of the chlorpromazine-trihexyphenidyl interaction in psychiatric patients showed conclusively that trihexyphenidyl lowers plasma levels of chlorpromazine from 13% to 100% (Rivera-Calimlim et al, 1973b). The mechanism by which trihexyphenidyl lowers plasma levels of chlorpromazine was shown in rats to be an inhibition of gastric emptying by trihexyphenidyl, probably as a result of its anticholinergic activity (Rivera-Calimlim, 1976b). Slow gastric emptying will delay the transport of chlorpromazine to intestinal absorption sites and favor enhanced gastrointestinal metabolism.

b) Trihexyphenidyl may also directly reverse some of the therapeutic effects of chlorpromazine. A toxic psychosis has been commonly reported following usual therapeutic doses of anticholinergic drugs, particularly when these agents are used in conjunction with other drugs with anticholinergic properties. Symptoms may include visual hallucinations, confusion, disorientation, speech difficulty, emotional lability and psychotic thinking (Perry et al, 1985b).

c) The chlorpromazine-trihexyphenidyl interaction may also include additive anticholinergic effects including constipation or paralytic ileus, dry mouth, blurred vision, increased intraocular pressure and urinary retention (Perry et al, 1985b). Hyperpyrexia has been reported, presumably due to blocking of exocrine sweat glands in combination with the hypothalamic dysregulation produced by antipsychotics (Mann & Boger, 1978d).

d) A significant reduction in fluphenazine serum levels occurred following addition of procyclidine in patients who were previously well stabilized. Following discontinuation of procyclidine, fluphenazine

serum levels returned to baseline (Bamrah et al, 1986b). However, the addition of orphenadrine to perphenazine therapy resulted in no clinically relevant pharmacokinetic changes in the absorption, distribution, or elimination of perphenazine (Bolvig Hansen et al, 1979b).

3.5.1.DE Propafenone

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Class I antiarrhythmic agents may prolong the QT interval in some patients, which may result in ventricular tachycardia, ventricular fibrillation, and torsades de pointes. Although pharmacokinetic studies between thioridazine and other drugs which prolong the QT interval have not been performed, an additive effect cannot be excluded. Therefore, the concurrent administration of thioridazine with a Class I antiarrhythmic agent is contraindicated (Prod Info Rythmol(R), 2002; Prod Info Mellaril(R), 2002; Prod Info Tambocor(R), 1998).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of thioridazine and agents that prolong the QT interval, such as Class I antiarrhythmic agents, is contraindicated.
7) Probable Mechanism: additive cardiac effects

3.5.1.DF Propranolol

1) Interaction Effect: an increased risk of thioridazine toxicity, cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: In two case reports, large doses of propranolol (more than 400 mg daily) resulted in a 3-fold to 5-fold increase of thioridazine concentration in patients on large doses of thioridazine (more than 500 mg daily) (Silver et al, 1986). Long-acting propranolol resulted in significant dose-related increases in thioridazine plasma levels in five patients (Greendyke & Kanter, 1987). Fluoxetine inhibits the metabolism of thioridazine, possibly through the inhibition of cytochrome P450 2D6 (CYP2D6) resulting in toxicity. The resulting elevated levels of thioridazine would be expected to enhance the prolongation of the QT interval and may increase the risk of serious, potentially fatal, cardiac arrhythmias, such as torsade de pointes-type arrhythmias (Prod Info Mellaril(R), 2000y).
3) Severity: contraindicated
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Due to the potential for significant, possibly life-threatening, proarrhythmic effects, concurrent administration of thioridazine and propranolol is contraindicated.
7) Probable Mechanism: inhibition of cytochrome P450 2D6-mediated thioridazine metabolism
8) Literature Reports
a) The metabolism of thioridazine is inhibited by drugs such as propranolol due to reduced cytochrome P450 2D6 isozyme activity. The elevated levels of thioridazine would be expected to enhance the prolongation of the QT interval associated with thioridazine. This, in turn, may increase the risk of serious, potentially fatal, cardiac arrhythmias, such as torsade de pointes-type arrhythmias (Prod Info Mellaril(R), 2000c).

3.5.1.DG Protirelin

1) Interaction Effect: decreased TSH response
2) Summary: Chronic thioridazine therapy in psychiatric patients may significantly decrease the thyroid-stimulating hormone (TSH) response to protirelin (Lamberg et al, 1977). Protirelin 200 mcg was administered intravenously to 10 patients receiving thioridazine 100 mg to 700 mg daily for over one year. The mean change in serum TSH levels from baseline was 5.8 microunits/mL in patients on thioridazine, which was significantly less than those seen in healthy controls (12.5 micrograms/mL).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor patients for a decreased response to thyroid-stimulating hormone (TSH).
7) Probable Mechanism: unknown

3.5.1.DH Protriptyline

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Although citing no data, the manufacturer of thioridazine states that concomitant use with other drugs which prolong the QT interval is contraindicated (Prod Info Mellaril(R), 2001). Tricyclic antidepressants (TCAs) at therapeutic doses can cause QT prolongation (Marshall & Forker, 1982).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concurrent administration of a tricyclic antidepressant and thioridazine is contraindicated.

7) Probable Mechanism: additive effect on QT interval

3.5.1.DI Quetiapine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Although citing no data, the manufacturer of thioridazine states that concomitant use with other drugs which prolong the QT interval is contraindicated (Prod Info Mellaril(R), 2001b). Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999), haloperidol (O'Brien et al, 1999), pimozide (Prod Info Orap(R), 2000), quetiapine (Owens, 2001c), paliperidone (Prod Info INVEGA(TM) extended-release oral tablets, 2006), risperidone (Duenas-Laita et al, 1999), sertindole (Agelink et al, 2001), sultopride (Lande et al, 1992), ziprasidone (Prod Info GEODON(R) intramuscular injection, oral capsule, 2005), and zotepine (Sweetman, 2004).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of agents that prolong the QT interval, such as antipsychotics, and thioridazine, is contraindicated.
7) Probable Mechanism: additive QT prolongation

3.5.1.DJ Quinidine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Class Ia antiarrhythmics have been shown to prolong the QTc interval at the recommended therapeutic dose. Even though no formal drug interaction studies have been done, the coadministration of thioridazine with other drugs known to prolong the QTc interval, including Class Ia antiarrhythmic agents, is not recommended (Prod Info Mellaril(R), 2002a; Prod Info Procanbid(R), 2000; Prod Info Quinaglute(R), 1999; Desai et al, 1981).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of a Class IA antiarrhythmic and thioridazine is contraindicated.
7) Probable Mechanism: additive cardiac effects

3.5.1.DK Ranolazine

1) Interaction Effect: an increase in thioridazine serum concentration and an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Ranolazine, and/or its metabolites, partially inhibit cytochrome P450-2D6-mediated thioridazine metabolism resulting in increased thioridazine exposure. Ranolazine and thioridazine have been shown to increase QTc interval in a dose-dependent manner. Concurrent administration of ranolazine and thioridazine is contraindicated (Prod Info thioridazine hcl oral tablets, 2003).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Using ranolazine and thioridazine together is contraindicated due to the additive effects on QTc prolongation.(Prod Info thioridazine hcl oral tablets, 2003).
7) Probable Mechanism: ranolazine inhibition of cytochrome P450-2D6-mediated metabolism of thioridazine and additive effects on QTc prolongation

3.5.1.DL Rilonacept

1) Interaction Effect: altered thioridazine plasma concentrations
2) Summary: In states of chronic inflammation, the formation of CYP450 enzymes is suppressed by increased levels of cytokines such as interleukin-1 (IL-1). Upon administration of an IL-1 blocker, such as rilonacept, the formation of CYP450 enzymes could be normalized. In patients receiving CYP450 substrates with a narrow therapeutic index concomitantly, such normalization may have a clinically relevant effect on the CYP450 substrate levels. If rilonacept therapy is initiated in a patient being treated with a CYP450 substrate that has a narrow therapeutic index, such as thioridazine, the therapeutic effect of thioridazine should be monitored and thioridazine dose should be adjusted if necessary (Prod Info ARCALYST(TM) subcutaneous injection, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: If rilonacept therapy is initiated in a patient being treated with a CYP450 substrate with a narrow therapeutic index, such as thioridazine, monitor for therapeutic effect of thioridazine and adjust thioridazine dose as needed (Prod Info ARCALYST(TM) subcutaneous injection, 2008).
7) Probable Mechanism: interference with CYP450-mediated thioridazine metabolism

3.5.1.DM Risperidone

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Although citing no data, the manufacturer of thioridazine states that concomitant use with other drugs which prolong the QT interval is contraindicated (Prod Info Mellaril(R), 2001b). Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999), haloperidol (O'Brien et al, 1999), pimozide (Prod Info Orap(R), 2000), quetiapine (Owens, 2001c), paliperidone (Prod Info INVEGA(TM) extended-release oral tablets, 2006), risperidone (Duenas-Laita et al, 1999), sertindole (Agelink et al, 2001), sultopride (Lande et al, 1992), ziprasidone (Prod Info GEODON(R) intramuscular injection, oral capsule, 2005), and zotepine (Sweetman, 2004).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of agents that prolong the QT interval, such as antipsychotics, and thioridazine, is contraindicated.
7) Probable Mechanism: additive QT prolongation

3.5.1.DN Ritonavir
1) Interaction Effect: increased thioridazine serum concentrations and potential toxicity (hypotension, sedation, extrapyramidal effects, arrhythmias)
2) Summary: Coadministered ritonavir may increase serum concentrations of thioridazine, resulting in thioridazine toxicity (Prod Info NORVIR(R), 2005).
3) Severity: moderate
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Use caution and monitor patients for signs and symptoms of neuroleptic toxicity (hypotension, sedation, extrapyramidal effects, arrhythmias). Reduce doses of thioridazine as required.
7) Probable Mechanism: decreased thioridazine metabolism

3.5.1.DO Roxithromycin
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, thioridazine should not be coadministered with other drugs which are also known to prolong the QTc interval, including roxithromycin (Prod Info Mellaril(R), 2000e).
3) Severity: contraindicated
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of thioridazine and agents that prolong the QT interval is contraindicated.
7) Probable Mechanism: additive cardiac effects

3.5.1.DP Sematilide
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Although no drug interaction studies have been performed, the manufacturer of thioridazine states that the concurrent use of thioridazine with other drugs known to prolong the QTc interval is contraindicated (Prod Info Thioridazine tablets, 2002). Class III antiarrhythmic agents may prolong the QT interval in some patients, which may result in ventricular tachycardia, ventricular fibrillation, and torsades de pointes (Yamreudeewong et al, 2003; Prod Info Betapace(R), 2001; Prod Info Corvert(R), 2000; Corey et al, 1999; Karam et al, 1998).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of thioridazine and agents that prolong the QT interval such as Class III antiarrhythmic agents is contraindicated.
7) Probable Mechanism: additive effect on QT interval

3.5.1.DQ Sertindole
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Although citing no data, the manufacturer of thioridazine states that concomitant use with other drugs which prolong the QT interval is contraindicated (Prod Info Mellaril(R), 2001b). Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999), haloperidol (O'Brien et al, 1999), pimozide (Prod Info Orap(R), 2000), quetiapine (Owens, 2001c), paliperidone (Prod Info INVEGA(TM) extended-release oral tablets, 2006), risperidone (Duenas-Laita et al, 1999), sertindole (Agelink et al, 2001), sultopride (Lande et al, 1992), ziprasidone (Prod Info GEODON(R) intramuscular injection, oral capsule, 2005), and zotepine (Sweetman, 2004).
3) Severity: contraindicated

4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of agents that prolong the QT interval, such as antipsychotics, and thioridazine, is contraindicated.
7) Probable Mechanism: additive QT prolongation

3.5.1.DR Sotalol

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Although no drug interaction studies have been performed, the manufacturer of thioridazine states that the concurrent use of thioridazine with other drugs known to prolong the QTc interval is contraindicated (Prod Info Thioridazine tablets, 2002). Class III antiarrhythmic agents may prolong the QT interval in some patients, which may result in ventricular tachycardia, ventricular fibrillation, and torsades de pointes (Yamreudeewong et al, 2003; Prod Info Betapace(R), 2001; Prod Info Corvert(R), 2000; Corey et al, 1999; Karam et al, 1998).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of thioridazine and agents that prolong the QT interval such as Class III antiarrhythmic agents is contraindicated.
7) Probable Mechanism: additive effect on QT interval

3.5.1.DS Sparfloxacin

1) Interaction Effect: prolongation of the QTc interval and/or torsades de pointes
2) Summary: Torsades de pointes has been reported in patients receiving sparfloxacin concomitantly with disopyramide and amiodarone. The use of sparfloxacin is contraindicated with drugs which produce an increase in the QTc interval and/or torsades de pointes, including phenothiazines. Sparfloxacin is also contraindicated in persons with known QTc prolongation (Prod Info Zagam(R), 1998).
3) Severity: contraindicated
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Sparfloxacin is contraindicated in individuals with known QTc prolongation or in patients being treated concurrently with drugs that are known to increase the QTc interval and/or cause torsades de pointes.
7) Probable Mechanism: additive effects on QTc prolongation
8) Literature Reports
a) In clinical trials involving 1489 patients with a baseline QTc measurement, the mean prolongation of the QTc interval at sparfloxacin steady-state was 10 msec (2.5%). Of these subjects, 0.7% had a QTc interval greater than 500 msec at steady-state. However, no arrhythmic effects were seen in any of the patients. The magnitude of the QTc effect does not increase with repeated administration of sparfloxacin, and the QTc interval returns to baseline within 48 hours after discontinuation of sparfloxacin (Prod Info Zagam(R), 1996).
b) A case of sparfloxacin-induced torsades de pointes is described (Dupont et al, 1996). A 47-year old woman hospitalized for suppurative otitis media and mastoiditis was treated with sparfloxacin due to an allergy to betalactam antibiotics. On day six of treatment she felt dizzy and lost consciousness. This was attributed to torsades de pointes on the cardioscope and was followed by cardiac arrest which required cardiopulmonary resuscitation. Her pre-treatment electrocardiogram showed QT and QTc intervals of 0.34 and 0.46 seconds, respectively. An electrocardiogram post-arrest revealed QT and QTc intervals of 0.35 and 0.60 seconds, respectively. A 24-hour continuous electrocardiography confirmed numerous episodes of torsades de pointes occurring after episodes of sino-auricular block. Sparfloxacin was discontinued and the QTc returned to baseline within a week. Upon further testing, it was determined that the patient suffered from a mild idiopathic long QT syndrome. Due to the onset of symptoms with administration of sparfloxacin and the relief of symptoms following discontinuation of the drug, it is highly probable that sparfloxacin contributed to the torsades de pointes.

3.5.1.DT Spiramycin

1) Interaction Effect: cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Although citing no data, the manufacturer of thioridazine states that concomitant use with other drugs which prolong the QT interval is contraindicated (Prod Info Mellaril(R), 2000aa). QT prolongation has been reported with spiramycin (Stramba-Badiale et al, 1997).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of spiramycin and thioridazine is contraindicated.
7) Probable Mechanism: additive cardiac effects

3.5.1.DU Sulfamethoxazole

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac

arrest)
2) Summary: Although citing no data, the manufacturer of thioridazine states that concomitant use with other drugs which prolong the QT interval is contraindicated (Prod Info Mellaril(R), 2000m). Q and T wave distortions have been observed in patients taking cotrimoxazole (Lopez et al, 1987). Other phenothiazines may have similar effects, though no reports are available.
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Due to the potential for additive effects on the QT interval, the concurrent administration of cotrimoxazole and thioridazine is contraindicated.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.DV Sultopride
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Although citing no data, the manufacturer of thioridazine states that concomitant use with other drugs which prolong the QT interval is contraindicated (Prod Info Mellaril(R), 2001b). Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999), haloperidol (O'Brien et al, 1999), pimozide (Prod Info Orap(R), 2000), quetiapine (Owens, 2001c), paliperidone (Prod Info INVEGA(TM) extended-release oral tablets, 2006), risperidone (Duenas-Laita et al, 1999), sertindole (Agelink et al, 2001), sultopride (Lande et al, 1992), ziprasidone (Prod Info GEODON(R) intramuscular injection, oral capsule, 2005), and zotepine (Sweetman, 2004).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of agents that prolong the QT interval, such as antipsychotics, and thioridazine, is contraindicated.
7) Probable Mechanism: additive QT prolongation

3.5.1.DW Sunitinib
1) Interaction Effect: an increased risk of QT interval prolongation
2) Summary: Sunitinib has been associated with prolongation of the QT interval in a dose dependent manner, with torsade de pointes occurring in less than 0.1% patients exposed to sunitinib (Prod Info SUTENT(R) oral capsules, 2008). Thioridazine has also been shown to prolong the QT interval in a dose dependent manner. Due to the potential for additive effects on the QT interval and increased risk for torsade de pointes, the concomitant use of thioridazine and other drugs that prolong the QT interval is contraindicated (Prod Info MELLARIL(R) oral tablet, solution, USP, MELLARIL-S(R) oral suspension, USP, 2000).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of thioridazine and drugs that prolong the QT interval, such as sunitinib, is contraindicated due to the potential for additive effects on the QT interval and an increased risk of torsade de pointes (Prod Info MELLARIL(R) oral tablet, solution, USP, MELLARIL-S(R) oral suspension, USP, 2000).
7) Probable Mechanism: additive effects on the QT interval

3.5.1.DX Tapentadol
1) Interaction Effect: an increase in central nervous system and respiratory depression
2) Summary: The concomitant use of tapentadol with central nervous system depressants including phenothiazines (e.g. chlorpromazine, promethazine, thioridazine) may result in additive CNS and respiratory depressant effects, including hypotension, profound sedation and/or coma. When administering tapentadol and a phenothiazine together, dosage of one or both agents may be reduced (Prod Info tapentadol immediate release oral tablets, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Consider monitoring the patient for cardiorespiratory depression when tapentadol and phenothiazines are used in combination. A reduction in dose of one or both drugs may be necessary (Prod Info tapentadol immediate release oral tablets, 2008).
7) Probable Mechanism: additive effects

3.5.1.DY Tedisamil
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Although no drug interaction studies have been performed, the manufacturer of thioridazine states that the concurrent use of thioridazine with other drugs known to prolong the QTc interval is contraindicated (Prod Info Thioridazine tablets, 2002). Class III antiarrhythmic agents may prolong the QT

interval in some patients, which may result in ventricular tachycardia, ventricular fibrillation, and torsades de pointes (Yamreudeewong et al, 2003; Prod Info Betapace(R), 2001; Prod Info Corvert(R), 2000; Corey et al, 1999; Karam et al, 1998).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of thioridazine and agents that prolong the QT interval such as Class III antiarrhythmic agents is contraindicated.
7) Probable Mechanism: additive effect on QT interval

3.5.1.DZ Telithromycin
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, thioridazine should not be coadministered with other drugs which are also known to prolong the QTc interval, including telithromycin (Owens, 2001d; Prod Info Mellaril(R), 2002h).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of thioridazine and agents that may prolong the QT interval, such as telithromycin, is contraindicated.
7) Probable Mechanism: additive effects on the QT interval

3.5.1.EA Terfenadine
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Although citing no data, the manufacturers of some phenothiazines state that concomitant use with other drugs which prolong the QT interval is contraindicated (Prod Info Mellaril(R), 2002f; Prod Info Serentil(R), 2000). Q and T wave distortions have been observed in patients taking phenothiazines (Prod Info Compazine(R), 2002b; Prod Info Stelazine(R), 2002b; Prod Info Thorazine(R), 2002b). Other phenothiazines may have similar effects, though no reports are available. Even though no formal drug interaction studies have been done, the coadministration of terfenadine and other drugs known to prolong the QTc interval, including phenothiazines, is contraindicated (Anon, 1997).
3) Severity: contraindicated
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of terfenadine and a phenothiazine is contraindicated.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.EB Tetrabenazine
1) Interaction Effect: increased risk of QT interval prolongation
2) Summary: Tetrabenazine causes a small increase in the corrected QT interval. As the degree of prolongation increases, QT prolongation can develop into torsade de pointes-type VT. The concomitant use of tetrabenazine with other drugs known for QT prolongation (eg, thioridazine) should be avoided (Prod Info XENAZINE(R) oral tablets, 2008). In a randomized, double-blind, placebo controlled crossover study of healthy subjects, the effect of a single 25 mg or 50 mg dose of tetrabenazine on the QT interval was studied with moxifloxacin as a positive control. The 50 mg dose of tetrabenazine caused an approximate 8 millisecond mean increase in QT (Prod Info XENAZINE(R) oral tablets, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of tetrabenazine with thioridazine or other drugs that prolong the QT interval should be avoided due to the potential for additive effects on the QT interval and increased risk of torsade de pointes (Prod Info XENAZINE(R) oral tablets, 2008). However, if concurrent therapy is required, monitor patient closely for prolongation of the QT interval.
7) Probable Mechanism: additive effects on QT interval prolongation

3.5.1.EC Tramadol
1) Interaction Effect: an increased risk of seizures
2) Summary: Seizures have been reported in patients using tramadol. The manufacturer of tramadol states that combining phenothiazine medications with tramadol may enhance the risk of seizures and CNS and respiratory depression (Prod Info Ultram(R), 1998).
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Caution should be used if tramadol is to be administered to patients receiving phenothiazine therapy. If possible, avoid this combination, especially in patients with underlying conditions

that might predispose to seizures.
7) Probable Mechanism: unknown

3.5.1.ED Trazodone
1) Interaction Effect: hypotension
2) Summary: Concomitant administration of trazodone with chlorpromazine or trifluoperazine resulted in additive hypotensive effects in two case reports. Withdrawal of trazodone resulted in resolution of the hypotension (Asayesh, 1986).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor blood pressure, particularly in patients who might be sensitive to this effect. Advise patient to rise slowly from laying or sitting position.
7) Probable Mechanism: additive hypotensive effects
8) Literature Reports
a) In one study, 11 depressed patients received trazodone 150 mg or 300 mg at bedtime for one to 18 weeks. In addition, thioridazine 40 mg daily was given for one week, and blood samplings were obtained prior to and after the coadministration. Thioridazine significantly increased plasma concentrations of both trazodone and m-chlorophenylpiperazine, the active metabolite of trazodone. These results suggest the involvement of cytochrome P4502D6 (CYP2D6) in the metabolism of trazodone, since thioridazine is a known inhibitor of this isozyme (Yasui et al, 1995).

3.5.1.EE Trifluoperazine
1) Interaction Effect: an increased risk of cardiotoxicity (QT interval prolongation, torsades de pointes, cardiac arrest)
2) Summary: Because thioridazine may prolong the QT interval and increase the risk of arrhythmias, the concurrent administration of thioridazine and other phenothiazines is contraindicated (Prod Info Mellaril(R), 2000l). Q and T wave distortions have been observed in patients taking phenothiazines (Prod Info Compazine(R), 2002a; Prod Info Stelazine(R), 2002a; Prod Info Thorazine(R), 2002a). Other phenothiazines may have similar effects, though no reports are available.
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of agents that prolong the QT interval, such as thioridazine and other phenothiazines, is contraindicated.
7) Probable Mechanism: additive effect on QT interval

3.5.1.EF Trihexyphenidyl
1) Interaction Effect: decreased phenothiazine serum concentrations, decreased phenothiazine effectiveness, enhanced anticholinergic effects (ileus, hyperpyrexia, sedation, dry mouth)
2) Summary: The concurrent use of anticholinergic agents (benztropine, orphenadrine, procyclidine, trihexyphenidyl) to control extrapyramidal side effects may reduce oral absorption of phenothiazines, antagonize the behavioral and antipsychotic effects of the phenothiazine, and enhance anticholinergic side effects (Rivera-Calimlim et al, 1976c; Mann & Boger, 1978c; Singh & Kay, 1979a; Gershon et al, 1965c; Buckle & Guillebaud, 1967a).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Anticholinergics (benztropine, orphenadrine, procyclidine, trihexyphenidyl) should not be used routinely with phenothiazine derivatives as prophylaxis against possible extrapyramidal symptoms; use should be reserved for situations where EPS occur and lowering of the antipsychotic dosage is not possible. Anticholinergic use should be reevaluated at least every three months.
7) Probable Mechanism: delayed gastric emptying, increased gut wall metabolism of phenothiazine, decreased absorption
8) Literature Reports
a) The concomitant administration of trihexyphenidyl and chlorpromazine has been shown to result in a decrease in chlorpromazine plasma levels (Rivera-Calimlim et al, 1973a; Gershon et al, 1965b). A crossover controlled study of the chlorpromazine-trihexyphenidyl interaction in psychiatric patients showed conclusively that trihexyphenidyl lowers plasma levels of chlorpromazine from 13% to 100% (Rivera-Calimlim et al, 1976b). The mechanism by which trihexyphenidyl lowers plasma levels of chlorpromazine was shown in rats to be an inhibition of gastric emptying by trihexyphenidyl, probably as a result of its anticholinergic activity (Rivera-Calimlim, 1976a). Slow gastric emptying will delay the transport of chlorpromazine to intestinal absorption sites and favor enhanced gastrointestinal metabolism.
b) Trihexyphenidyl may also directly reverse some of the therapeutic effects of chlorpromazine. A toxic psychosis has been commonly reported following usual therapeutic doses of anticholinergic drugs, particularly when these agents are used in conjunction with other drugs with anticholinergic properties. Symptoms may include visual hallucinations, confusion, disorientation, speech difficulty, emotional

lability and psychotic thinking (Perry et al, 1985a).
c) The chlorpromazine-trihexyphenidyl interaction may also include additive anticholinergic effects including constipation or paralytic ileus, dry mouth, blurred vision, increased intraocular pressure and urinary retention (Perry et al, 1985a). Hyperpyrexia has been reported, presumably due to blocking of exocrine sweat glands in combination with the hypothalamic dysregulation produced by antipsychotics (Mann & Boger, 1978b).
d) A significant reduction in fluphenazine serum levels occurred following addition of procyclidine in patients who were previously well stabilized. Following discontinuation of procyclidine, fluphenazine serum levels returned to baseline (Bamrah et al, 1986a). However, the addition of orphenadrine to perphenazine therapy resulted in no clinically relevant pharmacokinetic changes in the absorption, distribution, or elimination of perphenazine (Bolvig Hansen et al, 1979a).

3.5.1.EG Trimethoprim
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Although citing no data, the manufacturer of thioridazine states that concomitant use with other drugs which prolong the QT interval is contraindicated (Prod Info Mellaril(R), 2000m). Q and T wave distortions have been observed in patients taking cotrimoxazole (Lopez et al, 1987). Other phenothiazines may have similar effects, though no reports are available.
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Due to the potential for additive effects on the QT interval, the concurrent administration of cotrimoxazole and thioridazine is contraindicated.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.EH Trimipramine
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Although citing no data, the manufacturer of thioridazine states that concomitant use with other drugs which prolong the QT interval is contraindicated (Prod Info Mellaril(R), 2001). Tricyclic antidepressants (TCAs) at therapeutic doses can cause QT prolongation (Marshall & Forker, 1982).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concurrent administration of a tricyclic antidepressant and thioridazine is contraindicated.
7) Probable Mechanism: additive effect on QT interval

3.5.1.EI Vasopressin
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Thioridazine and vasopressin have been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Mellaril(R), 2000n; Mauro et al, 1988). Even though no formal drug interaction studies have been done, the coadministration of drugs known to prolong the QTc interval is not recommended.
3) Severity: contraindicated
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of drugs that prolong the QT interval, such as thioridazine and vasopressin, is contraindicated.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.EJ Vitex
1) Interaction Effect: increased dopaminergic side effects
2) Summary: Theoretically, the dopamine agonist activity of Vitex may add to that of other dopamine agonists, increasing the risk of dopaminergic adverse effects. Vitex has been effective in alleviating luteal phase defects due to hyperprolactinemia and in relieving symptoms related to premenstrual tension syndrome (Milewicz et al, 1993a; Lauritzen et al, 1997a). Vitex reduced prolactin secretion in humans (Milewicz et al, 1993a). In vitro, Vitex inhibited prolactin release by binding to the D2 receptor (Jarry et al, 1994a).
3) Severity: minor
4) Onset: delayed
5) Substantiation: established
6) Clinical Management: Avoid concomitant use of Vitex with phenothiazines. If the patient chooses to take Vitex, monitor closely for symptoms of additive dopamine agonism such as nausea, headache, dizziness, fatigue, vomiting, and postural hypotension.
7) Probable Mechanism: additive dopaminergic effect

8) Literature Reports

a) Vitex agnus castus effectively normalized prolactin release in a randomized double-blind, placebo-controlled trial of 52 women with luteal phase defects due to latent hyperprolactinemia. Administration of Vitex agnus castus 20 mg daily for three months reduced prolactin release (from 23.7 to 22.5 nanogram (ng)/mL; p equal to 0.23), normalized shortened luteal phases (from 5.5 days to 10.5 days; p less than 0.005), and eliminated deficits in luteal progesterone synthesis (from 2.46 ng/mL to 9.69 ng/mL; p less than 0.001). No side effects were noted (Milewicz et al, 1993).

b) Vitex agnus castus and pyridoxine caused a similar reduction on the premenstrual tension scale (PMTS) in a randomized, controlled trial of 127 women with PMTS. Patients taking Vitex agnus castus (Agnolyt(R)) experienced more relief from breast tenderness, inner tension, headache, edema, constipation, and depression than those taking pyridoxine. Patients in the Vitex agnus castus group receive one capsule of Agnolyt(R) and one placebo capsule daily for 3 menstrual cycles. Patients in the pyridoxine group received one placebo capsule twice daily on days 1-15 of the menstrual cycle and pyridoxine 100 mg twice daily on days 16 to 35 of the menstrual cycle for 3 menstrual cycles. Unspecified gastrointestinal disturbances occurred in the treatment group along with two cases of skin reaction and one transient headache (Lauritzen et al, 1997).

c) In vitro, Vitex (Agnus castus) was found to bind to the D2 receptor in rat pituitary cell cultures. Basal prolactin release was significantly inhibited by 0.5 milligram (mg) and 1 mg of Vitex extract/mL culture medium (p less than 0.05). Agnus castus extract doses from 0.125 mg/mL to 1 mg/mL significantly suppressed prolactin release in cells stimulated by thyrothropin releasing hormone (TRH) (p less than 0.05). Dopaminergic action was demonstrated in the rat corpus striatum membrane dopamine receptor assay. Agnus castus extract did not affect basal luteinizing hormone (LH) or follicle-stimulating hormone (FSH), indicating selectivity for prolactin secretion, and not generalized inhibition of pituitary hormone secretion. The effect was not due to a cytotoxic effect as demonstrated by the lack of effect on the MTT-conversion test. The authors concluded that Agnus castus exerted its prolactin inhibiting effect via stimulation of D2 receptors in the pituitary (Jarry et al, 1994).

3.5.1.EK Ziprasidone

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Although citing no data, the manufacturer of thioridazine states that concomitant use with other drugs which prolong the QT interval is contraindicated (Prod Info Mellaril(R), 2001b). Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999), haloperidol (O'Brien et al, 1999), pimozide (Prod Info Orap(R), 2000), quetiapine (Owens, 2001c), paliperidone (Prod Info INVEGA(TM) extended-release oral tablets, 2006), risperidone (Duenas-Laita et al, 1999), sertindole (Agelink et al, 2001), sultopride (Lande et al, 1992), ziprasidone (Prod Info GEODON(R) intramuscular injection, oral capsule, 2005), and zotepine (Sweetman, 2004).

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of agents that prolong the QT interval, such as antipsychotics, and thioridazine, is contraindicated.

7) Probable Mechanism: additive QT prolongation

3.5.1.EL Zolmitriptan

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Even though no formal drug interaction studies have been done, the manufacturer of thioridazine states that thioridazine should not be coadministered with other drugs which are also known to prolong the QTc interval (Prod Info Thioridazine tablets, 2002). Zolmitriptan has been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Zomig(R), 2001).

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of thioridazine and agents that prolong the QT interval, such as zolmitriptan, is contraindicated.

7) Probable Mechanism: additive effects on QT prolongation

3.5.1.EM Zotepine

1) Interaction Effect: increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Although no drug interaction studies have been performed, the manufacturer of thioridazine states that coadministration of thioridazine with drugs known to prolong the QTc interval is contraindicated (Prod Info Mellaril(R), 2001a). Zotepine can prolong the QTc interval (Sweetman, 2004).

3) Severity: contraindicated

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: Concurrent administration of agents that prolong the QT interval, such as zotepine and thioridazine, is contraindicated.

7) Probable Mechanism: additive effects on QT prolongation
8) Literature Reports
a) Since zotepine can prolong the QT interval it is recommended that an ECG is performed before starting treatment. Patients with pre-existing prolongation of the QT interval should not be given zotepine (Sweetman, 2004).

3.5.1.EN Zotepine
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Although citing no data, the manufacturer of thioridazine states that concomitant use with other drugs which prolong the QT interval is contraindicated (Prod Info Mellaril(R), 2001b). Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999), haloperidol (O'Brien et al, 1999), pimozide (Prod Info Orap(R), 2000), quetiapine (Owens, 2001c), paliperidone (Prod Info INVEGA(TM) extended-release oral tablets, 2006), risperidone (Duenas-Laita et al, 1999), sertindole (Agelink et al, 2001), sultopride (Lande et al, 1992), ziprasidone (Prod Info GEODON(R) intramuscular injection, oral capsule, 2005), and zotepine (Sweetman, 2004).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of agents that prolong the QT interval, such as antipsychotics, and thioridazine, is contraindicated.
7) Probable Mechanism: additive QT prolongation

3.5.2 Drug-Food Combinations

3.5.2.A Ethanol
1) Interaction Effect: increased central nervous system depression and an increased risk of extrapyramidal reactions
2) Summary: Concomitant administration of ethanol and phenothiazines has been reported to result in additive central nervous system depression (Zirkle et al, 1959; Milner & Landauer, 1971; Fazekas et al, 1955; Sutherland et al, 1960). Neuroleptic-induced extrapyramidal side effects triggered by alcohol have also been reported (Lutz, 1976; Freed, 1981).
3) Severity: moderate
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Counsel patients on potential for increased risk of central nervous system depression and extrapyramidal side effects, including akathisia and dystonia, when alcohol is ingested with phenothiazines. Patients should be instructed to avoid alcohol consumption while taking phenothiazines.
7) Probable Mechanism: unknown; probable additive CNS depression

3.5.3 Drug-Lab Modifications

Salicylate measurement

Urine chorionic gonadotrophin measurement

3.5.3.A Salicylate measurement
1) Interaction Effect: false positives on salicylate assay in urine
2) Summary: Thioridazine at a concentration of greater than or equal to 2 mg/dl in urine has been demonstrated to result in interference with spectrophotometric screening tests based upon the method of Trinder (Frings, 1973). Thioridazine causes a green color change under these conditions, whereas the screening test is based upon a purple color change caused by salicylates.
3) Severity: minor
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Salicylate spectrophotometric screening tests based upon the method of Trinder should be avoided in patients receiving thioridazine.
7) Probable Mechanism: salicylate assay interference

3.5.3.B Urine chorionic gonadotrophin measurement
1) Interaction Effect: falsely positive or negative pregnancy test results
2) Summary: Interpret pregnancy test results with caution in patients receiving phenothiazines due to the possibility of false-negative or false-positive results for tests based on immunological reactions between human chorionic gonadotropin (HCG) and anti-HCG (Prod Info promethazine hcl oral tablets, 2005). Promethazine administration produced false-positive pregnancy results with the Gravindex(R) method and

false-negative results with the Prepuerin(R) and DAP-test(R) methods when administered to patients or added to urine specimens or serum in vitro (Tait, 1971). In one study, where 3 major phenothiazine groups (dimethylamines (chlorpromazine), piperazines (perphenazine, carphenazine, trifluoperazine, fluphenazine), and piperidines (thioridazine)), were given to both male and female subjects as monotherapy for at least one week, HCG(R) tests consistently gave false positive results for all 3 categories of phenothiazines in both males and females (Ravel et al, 1969).

3) Severity: moderate

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: Phenothiazines may cause false-negative or false-positive results for pregnancy tests based on immunological reactions between human chorionic gonadotropin (HCG) and anti-HCG (Prod Info promethazine hcl oral tablets, 2005; Tait, 1971). Drug therapy should be evaluated when interpreting pregnancy test results.

7) Probable Mechanism: interference based on immunological reactions between human chorionic gonadotropin (HCG) and anti-HCG

8) Literature Reports

a) Promethazine administration produced false-positive results with the Gravindex(R) method and false-negative results with the Prepuerin(R) and DAP-test(R) methods when administered to patients or added to urine specimens or serum in vitro (Tait, 1971). Results indicate promethazine may interfere with latex agglutination with the Gravindex(R) and DAP-tests(R), leading to false-positive and false-negative results, respectively. With the Prepuerin(R) method, promethazine inhibited disagglutination of red cells, causing false-negative results. Of the three tests, the DAP-test(R) was most affected by promethazine, giving false results 50% of the time. In the DAP-test(R), agglutination is reduced by promethazine as it reacts with HCG, thereby not permitting it to bind the anti-HCG on the latex particles, leading to false-negative results.

b) Urine pregnancy tests were evaluated on both men and nonpregnant women who were receiving a phenothiazine as monotherapy for at least one week. All three major phenothiazine groups were represented in this study: dimethylamines (chlorpromazine), piperazines (perphenazine, carphenazine, trifluoperazine, fluphenazine), and piperidines (thioridazine). Commercially available urine pregnancy tests which were used included Gravindex(R), HCG(R) test, Natatel(R), UCG(R), Pregslide(R), and DAP(R). Results showed that the HCG(R) test consistently gave false positive results in all three categories of phenothiazines, both in male and female subjects. In some of the false-positive HCG(R) cases, retesting the same urine specimen produced negative findings, while others confirmed the initial false-positive result. The authors concluded that drug effects should be thoroughly evaluated on any pregnancy test (Ravel et al, 1969).

4.0 Clinical Applications

Monitoring Parameters

Patient Instructions

Place In Therapy

Mechanism of Action / Pharmacology

Therapeutic Uses

Comparative Efficacy / Evaluation With Other Therapies

4.1 Monitoring Parameters

A) Thioridazine Hydrochloride

1) Therapeutic

a) Physical Findings

1) Decrease in severity or elimination of target psychotic symptoms:

a) Positive psychotic symptoms (delusions, auditory hallucinations, racing thoughts)

b) Negative psychotic symptoms (anhedonia, apathy, lack of motivation, ambivalence).

2) Improvement in socialization, grooming, and attention to activities of daily living.

2) Toxic

a) Laboratory Parameters

1) Complete blood counts (every 6 months)

2) Hepatic function tests (every 6 months)

3) Baseline serum potassium levels with periodic evaluations during therapy, especially when making dose adjustments

b) Physical Findings
1) Abnormal involuntary movement scale (AIMS) examination or similar test for tardive dyskinesia every 6 months.
2) Assessment for extrapyramidal symptoms (EPS) during dose adjustment and every 3 months.
3) Periodic eye examination for ocular changes (retinopathy)
4) Baseline EKG evaluation for QTc-interval prolongation with periodic evaluations during therapy, especially when making dose adjustments

4.2 Patient Instructions

A) Thioridazine (By mouth)

Thioridazine

Treats the symptoms of schizophrenia.

When This Medicine Should Not Be Used:
You should not use this medicine if you have had an allergic reaction to thioridazine, if you have a history of heart rhythm problems or extreme high or low blood pressure, or if you have a genetic defect involving an enzyme called cytochrome P450. You should not take thioridazine if you are also taking medicines for depression (such as amitriptyline, Paxil®, Prozac®, Zoloft®), blood pressure medicine (such as atenolol, metoprolol, propranolol), medicines for heart rhythm problems, or other antipsychotic medicines (Haldol®, Risperdal®). There are many other medicines, including over-the-counter medicines, that you should not use while you are taking thioridazine. Make sure your doctor knows about all other medicines you are using.

How to Use This Medicine:
Tablet, Liquid
Your doctor will tell you how much of this medicine to take and how often. Your dose may need to be changed several times in order to find out the what works best for you. Do not take more medicine or take it more often than your doctor tells you to.
Measure the oral liquid medicine with a marked measuring spoon or medicine cup, or use the dropper that came with the medicine.
You may mix the oral liquid concentrate with a half glass of distilled water or orange juice. Mix only enough medicine for one dose and drink all the liquid right away.

If a Dose is Missed:
If you miss a dose or forget to take your medicine, take it as soon as you can. If it is almost time for your next dose, wait until then to take the medicine and skip the missed dose.
Do not use extra medicine to make up for a missed dose.

How to Store and Dispose of This Medicine:
Store the medicine at room temperature in a closed container, away from heat, moisture, and direct light. Do not freeze.
Keep all medicine out of the reach of children and never share your medicine with anyone.

Drugs and Foods to Avoid:
Ask your doctor or pharmacist before using any other medicine, including over-the-counter medicines, vitamins, and herbal products.
Certain drugs should not be used while using thioridazine. Using these drugs can cause very serious medical problems, heart problems, or even death.
Avoid drinking alcohol.
Make sure your doctor knows if you are using any medicines that make you sleepy (such as sleeping pills, cold and allergy medicine, narcotic pain killers, or sedatives).

Warnings While Using This Medicine:
If you are pregnant or breast feeding, talk to your doctor before taking this medicine. False positive (incorrect) pregnancy tests have been reported in patients taking this medicine.
Check with your doctor before taking thioridazine if you have an unusually slow heartbeat, low levels of potassium in your blood, seizures, or heart disease, or if you have ever had breast cancer. Also, tell your doctor if you have ever had a reaction to similar medicines, such as Thorazine® or Trilafon®.
Thioridazine can make some people feel dizzy or drowsy. Be careful if driving a car or operating machinery.

Possible Side Effects While Using This Medicine:
Call your doctor right away if you notice any of these side effects:
Dizziness, fainting
Fever, severe muscle stiffness, excessive sweating
Irregular or fast heartbeat
Muscle spasms of the neck, face, or tongue, or other body movements you cannot control
Severe chest pain
Trouble breathing

Unusual bleeding or bruising, seizures (convulsions)

If you notice these less serious side effects, talk with your doctor:
Changes in menstrual cycle
Changes in vision, such as trouble focusing, changes in how you see colors, or trouble seeing at night
Dry mouth
Lightheadedness, especially when standing up
Nausea, vomiting, diarrhea, or constipation
Sleepiness
Tremors or shaking

If you notice other side effects that you think are caused by this medicine, tell your doctor.

4.3 Place In Therapy

A) Thioridazine

See Drug Consult reference: FIRST- VS SECOND-GENERATION ANTIPSYCHOTIC AGENTS FOR SCHIZOPHRENIA

B) Thioridazine Hydrochloride

1) Current users of atypical antipsychotic drugs and typical antipsychotic drugs (including thioridazine) had a similar dose-dependent risk of sudden cardiac death, according to a retrospective cohort of 93,300 adult users of antipsychotic drugs and 186,600 matched controls. The study included patients age 30 to 74 years (mean 45.7 +/- 11.8 years) with similar cardiovascular risk at baseline who had at least one filled prescription and had 1 outpatient visit in each of the 2 preceding years. Sudden cardiac death was defined as occurring in the community and excluded deaths of patients admitted to the hospital, non-sudden deaths, deaths due to extrinsic causes, or causes not related to ventricular tachyarrhythmia. Current use was defined as the interval between the time the prescription was filled and the end of the day's supply. Low and high doses was defined as comparable to less than 100 milligrams (mg) of chlorpromazine, and doses comparable to chlorpromazine 300 mg or greater, respectively. The adjusted rate of sudden cardiac death (incidence-rate ratio) in current users of atypical antipsychotic drugs in 79,589 person-years was 2.26 (95% CI, 1.88 to 2.72, p less than 0.001) which was similar to the risk in current users of typical antipsychotic drugs in 86,735 person-years which was 1.99 (95% CI, 1.68 to 2.34, p less than 0.001). The risk of sudden cardiac death in current thioridazine users in 15,715 person-years was 3.19 (95% CI, 2.41 to 4.21, p less than 0.001). The risk of sudden cardiac death significantly increased with increasing dose in both the typical and atypical antipsychotic drug groups. In typical antipsychotic use, the incidence rate ratio increased from 1.31 (95% CI, 0.97 to 1.77) in low-dose use to 2.42 (95% CI, 1.91 to 3.06) in high-dose use. To limit the effects of confounding of the study results, there was a secondary analysis performed in a cohort of patients matched by propensity score, which resulted in a similar risk of sudden death as the primary cohort analysis (Ray et al, 2009). In an editorial in The New England Journal of Medicine, it has been suggested that antipsychotic drugs continue to be used in patients with clear evidence of benefit, but in vulnerable populations with cardiac risk profiles (eg, elderly patients), there should be an age-dependent justification required prior to administration. It has also been suggested (although not formally tested) that ECGs be performed before and shortly after initiation of antipsychotic therapy to screen for existing or emergent QT interval prolongation (Schneeweiss & Avorn, 2009).

2) Thioridazine (Mellaril(R)) is FDA labeled for use ONLY in schizophrenic patients who fail to respond adequately to treatment with other antipsychotic drugs. These restrictions are due to the increased risk of significant, potentially life-threatening, proarrhythmic effects associated with thioridazine therapy. The manufacturer recommends at least 2 drug trials, each with a different antipsychotic, be conducted prior to the initiation of treatment with thioridazine (Prod Info Mellaril(R), 2000).

3) Thioridazine is a phenothiazine with weak potency as an antipsychotic agent. It also has a low incidence of extrapyramidal symptoms, but has a high incidence of sedation, anticholinergic effects, and cardiovascular effects.

4) Clinical evidence demonstrates that all of the commonly marketed neuroleptic agents have therapeutic equivalence when adequate doses are utilized (Baldessarini, 1985). When a flexible dosage regimen is used to titrate the chosen agent to maximum effect, all neuroleptics will demonstrate statistical equivalence in a study population. However, one agent may be effective while another will not. Pharmacokinetic and pharmacodynamic differences as well as possible multiple etiologies of the patient's schizophrenia may be reasons for the individual variance (Young & Koda-Kimble, 1988). The patient's past medication history of neuroleptic agents should play an important role in drug selection. The patient's subjective response to neuroleptics should also be used in deciding on a specific agent. Lastly, adverse effects may determine drug selection. Side effects vary in incidence and severity among antipsychotic agents and avoidance of specific effects may determine drug selection.

4.4 Mechanism of Action / Pharmacology

A) Thioridazine Hydrochloride

1) MECHANISM OF ACTION

a) Thioridazine is a piperidine phenothiazine, which is effective in controlling psychotic symptoms of schizophrenia. It is believed to work by blocking post synaptic dopamine (D2) receptors in the brain, especially in the mesolimbic and mesocortical tracts. Thioridazine possesses calcium antagonist activity which may relate to its cardiac and sexual side effects (Gould et al, 1984).

4.5 Therapeutic Uses

4.5.A Thioridazine Hydrochloride

Behavioral syndrome

Borderline personality disorder

Dementia

Depression

Female infertility

Schizophrenia, Refractory

4.5.A.1 Behavioral syndrome

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive; Pediatric, Evidence is inconclusive
Recommendation: Adult, Class III; Pediatric, Class III
Strength of Evidence: Adult, Category A; Pediatric, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Thioridazine (Mellaril(R)) is no longer approved by the FDA for the treatment of behavioral problems due to its potential for significant proarrhythmic effects
Has been used for the treatment of multiple symptoms such as agitation, anxiety, depressed mood, tension, sleep disturbances, and fears in geriatric patients
Use with caution in the treatment of agitation or behavior problems in cognitively impaired patients
Overall efficacy has been modest and use exposes patients to major risks (Eimer, 1992)

c) Adult:

1) A meta-analysis of 7 double-blind studies showed that thioridazine is not more effective than placebo or other neuroleptic drugs for improving behavioral-, global clinical-, or cognitive-states of elderly patients with dementia (Kirchner et al, 1999). Anxiety scores were improved in more patients receiving thioridazine than placebo (p less than 0.0001) or diazepam (p=0.03). However, no comparisons were reported regarding adverse effects of thioridazine versus diazepam.

2) Two agitated patients with ALZHEIMER'S DISEASE failed to respond or worsened with conventional, low-dose neuroleptic treatment (thioridazine 25 milligrams as needed). Both patients showed sustained improvement with very low-dose neuroleptics (haloperidol 0.125 milligram, thioridazine 5 milligrams). Clinical, pharmacokinetic and pharmacodynamic factors may have been responsible for this positive response (Risse et al, 1987).

3) Chlormethiazole and thioridazine were found to be equally effective in the management of the agitation component of agitated confusional states in the elderly. Confusion and nocturnal awakening were controlled more effectively with chlormethiazole than with thioridazine. Chlormethiazole also caused less physical disability than thioridazine (Ather et al, 1986a).

4) Thioridazine and loxapine were only modestly effective in controlling anxiety, excitement, emotional lability, and uncooperativeness in nursing home patients with dementia. Patients with the most severe symptoms responded the best. Sedation, EPS, and hypotension were commonly occurring side effects (Barnes et al, 1982).

d) Pediatric:

1) Thioridazine has been used to control SELF-ABUSIVE BEHAVIOR in mentally retarded patients in daily doses up to 400 milligrams (Heistad et al, 1982). Thioridazine tablets were shown to be equally effective to thioridazine suspension in the treatment of emotionally-disturbed/retarded children (Jakab, 1984).

2) In a double-blind study of 30 children with subaverage IQs and psychiatric diagnoses of attention deficit disorder (ADD) and/or conduct disorder (CD), clinical response to METHYLPHENIDATE (MP) was greater than the response to THIORIDAZINE (TDZ). Each treatment was given for 3 weeks. The dosage of MP was 0.4 mg/kg/day and that for TDZ was 1.75 milligrams/kilogram/day. Significant improvements were confined to conduct and hyperactivity problems according to teacher ratings (Aman et al, 1991).

4.5.A.2 Borderline personality disorder

a) Overview

FDA Approval: Adult, no; Pediatric, no

Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class III
Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:
Patients with borderline personality disorder were less symptomatic while on thioridazine

c) Adult:
1) Thioridazine (TDZ) exerted prominent effects on 11 outpatients (8 female, 3 male) with Borderline Personality Disorder (BPD) in a 12-week open study. Mean TDZ dose was 92 milligrams/day for the duration of the study. At endpoint, there was a significant reduction in BPRS scores and patients appeared to be less symptomatic on the impulse action patterns, affects, and psychosis subscales of the Diagnostic Interview for Borderline Patients (DIB). Subjects completing the entire study (N=6) also showed improvement in interpersonal relations. Weight gain was not a significant problem, but sedation and erectile dysfunction were problematic (Teicher et al, 1989).

4.5.A.3 Dementia
See Drug Consult reference: BEHAVIORAL AND PSYCHOLOGICAL SYMPTOMS OF DEMENTIA

4.5.A.4 Depression

a) Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class III
Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:
Thioridazine (Mellaril(R)) is no longer approved by the FDA for the treatment of depression due to its potential for significant proarrhythmic effects
Has been used for the short-term treatment of moderate to marked depression with variable degrees of anxiety
First and second generation antidepressants are preferred

c) Adult:
1) Combination therapy with thioridazine and desipramine was reported to produce greater improvement in depressive symptoms than desipramine alone (Bennett et al, 1984a). Fourteen patients received a constant dose of DESIPRAMINE (200 milligrams daily) for 21 days, while 7 patients received additional thioridazine (100 milligrams daily) for the first 7 days of treatment. Greater improvement over baseline on the Hamilton Depression Scale was observed during the first 7 days with concomitant therapy.

4.5.A.5 Female infertility

a) Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class III
Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:
Improve infertility in one study
Effect may be explained by anxiolytic properties at low dosage

c) Adult:
1) Thioridazine was used to treat unexplained infertility (Sharma & Sharma, 1992). From a total of 452 women with unexplained infertility, 310 were given one 5-milligram thioridazine tablet one hour after dinner from the eighth to the 18th day of the menstrual cycle. Coitus was advised 1 to 2 hours after ingestion of the tablet. One hundred forty-two patients were given placebo along with the same instructions. At one-year follow-up, 30% of the study group conceived compared with 15% of the control group. Incidence of abortions, congenital malformations, and mode of delivery were not significantly different in the two groups.

4.5.A.6 Schizophrenia, Refractory
FDA Labeled Indication

a) Overview
FDA Approval: Adult, yes; Pediatric, yes
Efficacy: Adult, Evidence favors efficacy; Pediatric, Evidence favors efficacy
Recommendation: Adult, Class IIb; Pediatric, Class IIb
Strength of Evidence: Adult, Category B; Pediatric, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:
Indicated for the management of schizophrenia in patients who have failed to respond to other

antipsychotic agents
The association between thioridazine and QT interval prolongation resulted in the designation of the drug for use following failure of treatment with other antipsychotic agents
The efficacy of thioridazine in refractory schizophrenia is not known

c) Adult:

1) Thioridazine therapy for new-onset psychosis in five HIV-positive men produced modest, but significant reduction in overall level of psychosis and in positive symptoms, but not in negative symptoms (Sewell et al, 1994a). The mean daily dose of thioridazine was 145 milligrams. Three of the five patients developed noticeable side effects.

2) Seven patients with refractory schizophrenia who failed to respond to chlorpromazine 1800 milligrams/day responded to mesoridazine 400 milligrams/day (3 patients) and thioridazine 800 milligrams/day (4 patients) as assessed by the Brief Psychiatric Rating Scale. A higher neuroleptic blood level was achieved with mesoridazine or thioridazine at less than half the reference chlorpromazine dosage. Correlations between neuroleptic blood level and clinical response were positive for mesoridazine, negative for chlorpromazine, and non-significant for thioridazine. Drug-resistant schizophrenic patients seem to improve with mesoridazine or thioridazine. This difference may be a function of the selective dopamine receptor blockade by mesoridazine (Vital-Herne et al, 1986).

d) Pediatric:

1) Of 21 schizophrenic adolescents given thiothixene or thioridazine, many responded poorly or experienced sedation. Because sedation necessitates dose reductions which limit therapeutic response, high potency neuroleptics may be preferable to the more sedating, low potency drugs for schizophrenic adolescents (Realmuto et al, 1984a).

4.6 Comparative Efficacy / Evaluation With Other Therapies

Bromazepam

Chlormethiazole

Chlorprothixene

Desipramine

Diazepam

Haloperidol

Mesoridazine

Methylphenidate

Molindone

Periciazine

Remoxipride

Thiothixene

4.6.A Bromazepam

4.6.A.1 Anxiety

a) Thioridazine was inferior to bromazepam in a study of 80 outpatients with various anxiety, phobic, and obsessive-compulsive disorders. Bromazepam was more effective in controlling anxiety symptoms and was more "activating" than thioridazine. Symptoms of hostility responded better to thioridazine (Dencker & Fasth, 1986).

4.6.B Chlormethiazole

4.6.B.1 Delirium

a) Chlormethiazole and thioridazine were found to be equally effective in the management of the agitational

component of agitated confusional states in the elderly. Confusion and nocturnal awakening were controlled more effectively with chlormethiazole than with thioridazine. Chlormethiazole also caused less physical disability than thioridazine (Ather et al, 1986).

4.6.C Chlorprothixene

4.6.C.1 Behavioral syndrome

a) Chlorprothixene was more effective than thioridazine in controlling behavioral symptoms such as aggressiveness, hostility, and hyperactivity. Chlorprothixene (up to 375 milligrams/day) was compared with thioridazine (up to 375 milligrams/day) in a 12-week, double-blind, crossover study involving 59 patients with mental retardation (LeVann, 1970).

4.6.D Desipramine

4.6.D.1 Depression

a) Combination therapy with thioridazine and desipramine was reported to produce greater improvement in depressive symptoms than desipramine alone (Bennett et al, 1984). Fourteen patients received a constant dose of desipramine (200 milligrams daily) for 21 days, while 7 patients received additional thioridazine (100 milligrams daily) for the first 7 days of treatment. Greater improvement over baseline on the Hamilton Depression Scale was observed during the first 7 days with concomitant therapy.

4.6.E Diazepam

Anxiety

Behavioral syndrome

4.6.E.1 Anxiety

a) Diazepam was more effective for anxiety symptoms in 47 patients who were treated with diazepam 4 to 40 milligrams every day and thioridazine 20 to 200 milligrams every day to relieve mixed anxiety depressive symptoms (Rosenthal & Bowden, 1973).

b) In 36 patients with anxiety or depression, no difference was found between diazepam 5 to 10 milligrams 3 to 4 times daily and thioridazine 25 to 50 milligrams 3 to 4 times daily in the relief of symptoms (Schuster et al, 1972).

4.6.E.2 Behavioral syndrome

a) One study reported the superiority of oral thioridazine (10 to 200 milligrams daily) over oral diazepam (2 to 40 milligrams daily), and placebo, in the treatment of emotional and behavioral disorders in elderly, non-psychotic patients in geriatric wards, state hospitals, or nursing homes (Stotsky, 1984). Greater improvement in the majority of symptoms assessed by the Hamilton Anxiety Scale and NOSIE were observed in patients receiving thioridazine.

4.6.F Haloperidol

4.6.F.1 Psychotic disorder

a) In a single-blind, randomized parallel study lasting six weeks, haloperidol (mean dose of 2.9 milligrams/day) was compared with thioridazine (mean dose of 145 milligrams/day) in 13 patients with psychosis associated with HIV infection. Based on several scales for assessing psychoses, the two drugs produced modest improvement, but were not statistically different in the outcomes produced. All haloperidol-treated patients developed extrapyramidal side effects, while 60% of those taking thioridazine developed them (Sewell et al, 1994).

4.6.G Mesoridazine

4.6.G.1 Schizophrenia

a) Mesoridazine has been compared with its parent compound, thioridazine, and has been found to be similar in therapeutic effect and toxicity in the treatment of chronic schizophrenia. Available data indicate that, although the drug appears to be 2 to 3 times more potent on a milligram basis, there appears to be no significant or marked clinical differences or advantages with either of the 2 drugs (Prusmack, 1966; Mena et al, 1966).

b) Mesoridazine 50 to 400 milligrams daily provided a significantly greater improvement in somatic concern, hostility, suspiciousness, and retardation factor in chronic schizophrenic patients compared with thioridazine 100 to 800 milligrams daily (Gardos et al, 1978).

c) Mesoridazine may be effective in schizophrenic patients refractory to treatment with thioridazine. This may be related to its slow rate of inactivation and to the relatively large proportion of free mesoridazine that

is available for penetration to the target sites in the brain (Gershon, 1981).

4.6.H Methylphenidate

1) Adverse Effects

a) One group of investigators reported a controlled study of methylphenidate and thioridazine in improving cognitive and motor performance in intellectually subaverage children. Twenty-seven children with subaverage IQs participated in a double-blind, placebo-controlled, cross-over study comparing methylphenidate (0.4 milligrams/kilogram/day and thioridazine (1.75 milligrams/kilogram/day. The children were tested for IQ performance, breadth of attention, and performance on a series of electronically-controlled cognitive-motor tests. Methylphenidate improved accuracy on a memory task, reduced omission errors on an attentional task, and reduced seat movements on two tasks. Thioridazine had no significant effects in improving cognitive-motor performance. It did not produce deleterious effects on IQ performance when subjects received reinforcers for correct answers. Thioridazine at the given dose did not adversely effect performance on any of the cognitive-motor performance tests (Aman et al, 1991).

4.6.I Molindone

4.6.I.1 Disruptive behavior disorder

a) Molindone and thioridazine were equally efficacious in an 8-week, double-blind, placebo-controlled, parallel design study that compared molindone (n=15) with thioridazine (n=16) in 31 aggressive male children with conduct disorder (Greenhill et al, 1985). Both drugs resulted in significant improvement in Aggression Scale score and CPRS evaluation of hostility and antisocial and violent behavior when compared to the placebo periods before and after the 4-week treatment cycle. The overall mean molindone dose was 1.3 milligrams/kilogram/day and the thioridazine mean dose was 4.64 milligrams/kilogram/day.

4.6.J Periciazine

Psychotic disorder, chronic

Schizophrenia

4.6.J.1 Psychotic disorder, chronic

a) Neither periciazine (40 to 60 mg daily) nor thioridazine (200 to 300 mg daily) produced significant improvement (BPRS scales) in the symptomatology of chronic psychosis patients in one study (Deutsch et al, 1971). Failure was ascribed to subtherapeutic doses of each agent.

4.6.J.2 Schizophrenia

a) Available comparisons do not suggest any advantage of oral periciazine daily over oral thioridazine in the management of chronic schizophrenic patients (Anon, 1967; Barker & Miller, 1969; Deutsch et al, 1971). Periciazine has tended to be superior for paranoid delusions, although the significance of this is doubtful.

4.6.K Remoxipride

4.6.K.1 Schizophrenia

a) SUMMARY: One controlled study has reported the overall similar efficacy of remoxipride and thioridazine in schizophrenia; however, definite trends toward the superiority of thioridazine were observed.

b) The efficacy of remoxipride and thioridazine were compared in the treatment of acute schizophrenia in a double-blind study involving 61 patients (McCreadil et al, 1988). Following discontinuance of previous medication and a 7-day placebo period, patients were randomized to receive either remoxipride 25 to 125 mg three times daily or thioridazine 50 to 250 mg three times daily for a 6-week period. All patients were inpatients for the first 4 weeks of therapy. No statistically significant difference was seen between the 2 agents on the Brief Psychiatric Rating Scale (BPRS), although there was a definite trend in favor of thioridazine over remoxipride. Both drugs produced similar reductions in positive symptoms, including hallucinations and unusual thought content. Mean maintenance doses during the study were 238 mg daily for remoxipride and 440 mg daily for thioridazine. General adverse effects were observed more frequently in thioridazine patients, including sedation, anticholinergic effects, autonomic dysfunction, and weight gain. Akathisia appeared more severe in remoxipride treated patients. Sleep disorder was more frequent in the remoxipride group, and breast swelling and galactorrhea were observed with remoxipride but not with thioridazine. Orthostatic hypotension (n=1) and ECG changes (n=2) were reported in remoxipride-treated patients. ECG abnormalities were seen in 2 thioridazine-treated patients. This study suggests that in the doses employed remoxipride is, at best, as effective as thioridazine. Definite trends toward the superiority of thioridazine were observed. Adverse effects in general were less with remoxipride; extrapyramidal effects appeared similar with each drug.

c) The efficacy and safety of remoxipride (RMX) were compared with that of thioridazine (TDZ) in 18 hospitalized elderly psychotic patients. Patients ranged in age from 66 to 90 years (median=78). Over the 6-

week study period, 9 patients each received either RMX or TDZ in a dosage range of 50 to 200 milligrams/day. Responses using the BPRS and CGI indicated that both treatments were effective in reducing psychotic symptoms over the 6-week study. Adverse effects were "low" in both groups with the exception of severe drowsiness in 3 TDZ patients. It was concluded that remoxipride was well-tolerated in the elderly and its efficacy in the dosage used was promising (Phanjoo & Link, 1990).

4.6.L Thiothixene

4.6.L.1 Schizophrenia

a) Thiothixene and thioridazine had comparable efficacy in a double-blind study in 21 adolescent schizophrenic patients. Many in both groups responded poorly. The patients in the thioridazine group experienced much more sedation which necessitated dosage reductions which could potentially limit therapeutic response. The results suggest that the two drugs were equally effective, but that high potency neuroleptics (such as thiothixene) may be preferred in adolescents because of less dose-limiting sedation as opposed to low potency drugs (such as thioridazine) (Realmuto et al, 1984).

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Last Modified: June 23, 2009

DRUGDEX® Evaluations

GABAPENTIN

0.0 Overview

1) Class
- **a)** This drug is a member of the following class(es):
  Anticonvulsant
  Gamma Aminobutyric Acid (class)
  Neuropathic Pain Agent

2) Dosing Information
- **a)** Adult
  - **1)** Diabetic peripheral neuropathy
    - **a)** 900 to 3600 mg/day ORALLY in 3 divided doses (Backonja et al, 1998
  - **2)** Partial seizure; Adjunct
    - **a)** 12 yr and older, 300 mg ORALLY 3 times a day; may increase up to 1
      doses). Dosages up to 2400 mg/day have been well tolerated and doses
      administered to a small number of patients for a relatively short duration
  - **3)** Postherpetic neuralgia
    - **a)** 300 mg ORALLY on Day 1, 300 mg twice a day on Day 2, and 300 mg
      increase dosage up to 1800 mg/day (divided into 3 doses) (Prod Info NEU
      capsules, oral solution, 2007)
- **b)** Pediatric
  - **1)** Partial seizure; Adjunct
    - **a)** age 3 to 12 yr, initial, 10 to 15 mg/kg/day ORALLY in 3 divided doses
    - **b)** age 3 to 4 yr, maintenance, titrate upwards over 3 days to 40 mg/kg/da
    - **c)** age 5 to 12 yr, maintenance, titrate upwards over 3 days to 25 to 35 m

3) Contraindications
- **a)** hypersensitivity to gabapentin

4) Serious Adverse Effects
- **a)** Drug-induced coma
- **b)** Seizure
- **c)** Stevens-Johnson syndrome

5) Clinical Applications
- **a)** FDA Approved Indications
  - **1)** Partial seizure; Adjunct
  - **2)** Postherpetic neuralgia
- **b)** Non-FDA Approved Indications
  - **1)** Diabetic peripheral neuropathy

1.0 Dosing Information

1.1 Drug Properties

A) Information on specific products and dosage forms can be obtained by referring Index)
B) Synonyms
Gabapentin
C) Orphan Drug Status
1) Gabapentin has been designated an orphan product for use in the treatmer
D) Physicochemical Properties
1) Molecular Weight
a) 171.24 (Prod Info Neurontin, 94) (Levy, 1989) (Prod Info Neurontin, 94
2) Partition Coefficient
a) The log of the partition coefficient (n-octanol/0.05M phosphate buffer) Neurontin®, 2003)
3) pKa
a) 3.68 and 10.7 (Levy, 1989) (Prod Info Neurontin, 94a)
4) Solubility
a) Systemic: Freely soluble in water and both basic and acidic aqueous s 2003)

1.2 Storage and Stability

A) Tablets and capsules should be stored at a controlled room temperature of 25 Fahrenheit). Excursions to 15 to 30 degrees Celsius (59 to 86 degrees Fahrenheit) Neurontin(R), 2003a).
B) The oral solution should be kept refrigerated; 2 to 8 degrees Celsius (36 to 46 Neurontin(R), 2003a).
1) Extemporaneous Formulation - Oral route
a) Oral suspensions of gabapentin have been developed (Nahata, 1999). powder the contents of 67 capsules of gabapentin 300 milligrams (mg) us mixed in a 1:1 ratio of simple syrup NF with 1% methylcellulose. Similarly, gabapentin 300 mg may be mixed with 1:1 Ora Sweet: Ora Plus. Both pro gabapentin of 100 mg/milliliter in suspension. Both suspensions retained for 91 days at 4 degrees Celsius and for 56 days at 25 degrees Celsius. T drug was stable for 8 weeks at 25 degrees Celsius, this not recommende growth. Microbiological studies were not performed.

1.3 Adult Dosage

Normal Dosage

Dosage in Renal Failure

Dosage Adjustment During Dialysis

Dosage in Other Disease States

1.3.1 Normal Dosage

Oral route

Tinnitus

1.3.1.A Oral route

Diabetic peripheral neuropathy

Partial seizure; Adjunct

Postherpetic neuralgia

Social phobia

1.3.1.A.1 Diabetic peripheral neuropathy

a) Doses of 900 to 3600 milligrams/day administered orally in 3 divid treatment of pain and sleep difficulties associated with diabetic periph 1998).

1.3.1.A.2 Partial seizure; Adjunct

a) INITIAL THERAPY

1) 300 milligrams (mg) 3 times daily (Prod Info Neurontin(R), 20

a) gabapentin has been given in lower doses during initiatic milligrams 3 times daily was administered initially for 2 week times daily for the ensuing 3 months (Anon, 1990c). Others times a day on the first day of treatment; the dose was incre day on the second day (Sivenius et al, 1991b).

b) In a brief tolerability study, initiation of gabapentin at 900 associated with more dizziness on day 1 and throughout the was initiation at 300 milligrams per day, with titration to 900 However, incidences of the other common adverse events (were not different for the 2 initiation protocols (Fisher et al, 2

b) TITRATION

1) The dose may be increased using 300- or 400-mg capsules c Info Neurontin(R), 2003a).

c) MAINTENANCE THERAPY

1) 900 to 1800 milligrams given in 3 divided doses. In long-term mg have been well tolerated. The maximum time between doses (Prod Info Neurontin(R), 2003a).

d) As add-on therapy in patients with drug-refractory partial seizures reported with gabapentin 1200 milligrams daily in 3 divided doses (Ar 1991b). gabapentin 900 milligrams daily has not been consistently ef milligrams/day are usually ineffective (Crawford et al, 1987b; Sivenius

1) MAXIMUM DOSE

a) 2400 to 3600 milligrams/day has been administered (Pro

2) WITHDRAWAL

a) Discontinuation of gabapentin therapy should be done sl prevent rebound phenomena. Abrupt discontinuation may pr Info Neurontin(R), 2003a).

1.3.1.A.3 Postherpetic neuralgia

a) In adults with postherpetic neuralgia, the recommended initial dos milligram (mg) dose on Day 1, 600 mg/day on Day 2 (divided twice da (divided three times daily). The dose can then be titrated up as neede 1800 mg (divided three times daily). In clinical studies, efficacy was d doses from 1800 mg/day to 3600 mg/day, however no additional ben doses above 1800 mg/day (Prod Info NEURONTIN(R) oral tablets, or

1.3.1.A.4 Social phobia

a) Doses of 900 to 3600 milligrams/day divided in 3 doses have beer al, 1999).

1.3.1.B Tinnitus

See Drug Consult reference: DRUG THERAPY OF TINNITUS

C) Dose reductions, gabapentin discontinuation or substitutions with alternativ performed gradually over a minimum of 1 week (Prod Info Neurontin(R), 2003a

1.3.2 Dosage in Renal Failure

Dosage Based Upon Renal Function:

Creatinine Clearance (mL/min)	Total Daily Dose Range (mg/day)	Dose Frequency
60 or greater	900 - 3600	Equally divided (doses/day)
30 to 59	400 - 1400	Equally divided (doses/day)
15 to 29	200 - 700	Single dose
15 or less*	100 - 300	Single dose

* For patients with creatinine clearances (CrCl) of 15 mL/min or less, the dosag proportionally (patients with a CrCl of 7.5 mL/min should receive one-half the c

mL/min) (Prod Info Neurontin(R), 2003a).

1.3.5 Dosage Adjustment During Dialysis

A) Patients receiving hemodialysis should receive maintenance gabapentin d creatinine clearance (see dosage in renal failure) and a supplemental post-he after each 4 hours of hemodialysis (Prod Info Neurontin(R), 2003a).

Post-Hemodialysis Supplemental Dose	
Maintenance Dose Range (mg/day)	Supplemental Dose (mg)
100 - 900	125
125 - 1200	150
150 - 1800	200
200 - 2400	250
300 - 3600	350

1.3.6 Dosage in Other Disease States

A) In high-risk patients (eg, poor general status, low body weight, post- transp should take place in no more than 100-milligram increments (Fachinfo Neuron

1.4 Pediatric Dosage

Normal Dosage

Dosage in Renal Failure

Dosage Adjustment During Dialysis

1.4.1 Normal Dosage

Oral route

Rectal route

1.4.1.A Oral route

1.4.1.A.1 Partial seizure; Adjunct

a) INITIAL THERAPY

1) The starting dose for patients between 3 and 12 years of age milligrams/kilogram/day in 3 divided doses (Prod Info Neurotin(R

2) Initial doses should be 40 milligrams/kilogram/day in 3 divide up to under 5 years, based on a pharmacokinetic study in 48 chi (evenly distributed over the age range). For children 5 to 12 year be 30 milligrams/kilogram/day (Haig et al, 2001).

3) In a brief tolerability study, initiation of gabapentin at 900 milli with more dizziness on day 1 and throughout the 5 days of active 300 milligrams per day, with titration to 900 milligrams/day over 3 the other common adverse events (fatigue, ataxia, and somnole initiation protocols (Fisher et al, 2001).

b) TITRATION

1) The dose may be increased using 300- or 400-mg capsules, solution (Prod Info Neurontin(R), 2002.

c) MAINTENANCE THERAPY

For patients between 3 and 4 years of age:

40 milligrams/kilogram/day in 3 divided doses (Prod Info Ne

For patients 5 years of age and older:

25 to 35 milligrams/kilogram/day in 3 divided doses (Prod In

For patients over 12 years of age:

900 to 1800 milligrams given in 3 divided doses Prod Info N

2) Dosage interval between doses should not exceed 12 hours (Prod Info

1.4.1.B Rectal route

1) A study on two children found that gabapentin plasma concentrations a of gabapentin solution (capsule contents mixed with 5 milliliters mL of wat oral administration. Relative bioavailability was 0.29 and 0.17. The author administration of gabapentin is not satisfactory when oral dosing is interru

1.4.2 Dosage in Renal Failure

Dosage Based Upon Renal Function for patients 12 years old and older:

Creatinine Clearance(mL/min)	Total Daily Dose Range (mg/day)	Dose Frequenc
60 or greater	900 - 3600	Equally divided doses/day)
30 to 59	400 - 1400	Equally divided doses/day)
15 to 29	200 - 700	Single dose
15 or less	100 - 300*	Single dose

* For patients with creatinine clearances (CrCl) of 15 mL/min or less, the dosa proportionally (patients with a CrCl of 7.5 mL/min should receive one-half the d mL/min) (Prod Info Neurontin(R), 2003a). Gabapentin use in patients less thar compromised renal function has not been studied.

1.4.4 Dosage Adjustment During Dialysis

A) Patients 12 years or older receiving hemodialysis should receive maintena estimates of creatinine clearance (see dosage in renal failure) and a supplem administered after each 4 hours of hemodialysis. Gabapentin use in patients le compromised renal function has not been studied (Prod Info Neurontin(R), 200

Post-Hemodialysis Supplemental Dose	
Maintenance Dose Range (mg/day)	Supplemental Dose (mg)
100 - 900	125
125 - 1200	150
150 - 1800	200
200 - 2400	250
300 - 3600	350
(Prod Info Neurontin(R), 2002).	

2.0 Pharmacokinetics

Drug Concentration Levels

ADME

2.2 Drug Concentration Levels

A) Therapeutic Drug Concentration

1) Partial Seizures, greater than 2 mcg/mL (Sivenius et al, 1991).

a) Optimal plasma concentrations have not been established (Prod Info N Woster, 1995).

B) Time to Peak Concentration

1) Oral: 1.5 to 4 hours (Gidal et al, 1998; Andrews & Fischer, 1994; Hooper et

a) Time to peak concentration (t-max) was 2.31 hours after a single oral d month to 12 years (evenly distributed over the age range). Maximum conc 4.52 mcg/mL for those 1 to 59 months old (n=27) and 60 to 155 months (r those 2 years or younger was gabapentin syrup 10 mg/kg; subjects over 2 based on weight: 200 mg for 16 to 25 kg; 300 mg for 26 to 36 kg; 400 mg 2001a).

C) Area Under the Curve

1) 35 to 47 mcg/mL x hr (Gidal et al, 1998).

a) Determined with a single 600-mg dose (Gidal et al, 1998).

b) AUC values were 25.6 and 36.0 mcg x h/mL after a single oral dose in under 5 years (n=27) and 5 to 12 years (n=21), respectively. Dosing for th gabapentin syrup 10 mg/kg; subjects over 2 years received oral capsules to 25 kg; 300 mg for 26 to 36 kg; 400 mg for 37 to 50 kg (Haig et al, 2001a

2.3 ADME

Absorption

Distribution

Metabolism

Excretion

Elimination Half-life

Extracorporeal Elimination

2.3.1 Absorption

A) Bioavailability

1) Tablets/capsules (900 mg dose): 60% (Prod Info Neurontin(R), 2003)

a) Bioavailability decreases with increasing doses:

DOSAGE (3 divided doses)	ORAL BIOAVAILABILITY
900 milligrams	60%
1200 milligrams	47%
2400 milligrams	34%
3600 milligrams	33%
4800 milligrams	27%
(Prod Info Neurontin(R), 2002)	

b) Approximately 50% to 60% is absorbed from the gastrointestinal t

c) Gabapentin plasma concentrations attained after rectal administra (capsule contents mixed with 5 milliliters mL of water) were much low administration. Relative bioavailability was 0.29 and 0.17 (Kriel et al,

B) Effects of Food

1) Slight (Prod Info Neurontin(R), 2003).

a) A 14% increase in area under the curve (AUC) and Cmax has bee taken with food (Prod Info Neurontin(R), 2003).

b) Gabapentin capsules that were opened and mixed with food did n (Gidal et al, 1998). Protein may actually favorably influence gabapent

2.3.2 Distribution

A) Distribution Sites

1) Protein Binding

a) less than 3% (Vollmer et al, 1986; Prod Info Neurontin(R), 2003).

2) OTHER DISTRIBUTION SITES

a) BRAIN, a lobectomy revealed GABAPENTIN concentrations in ep mcg/g and 6.75 mcg/mL, respectively (cortex/serum ratio of 0.8) (Oje

b) CEREBROSPINAL FLUID, steady-state cerebrospinal fluid levels approximately 20% of plasma concentrations (Prod Info Neurontin(R)

c) TISSUES, animal studies revealed highest concentrations in the p adipose tissue (Vollmer et al, 1986).

B) Distribution Kinetics

1) Distribution Half-Life

a) 0.1 hr (Graves & Leppik, 1991).

2) Volume of Distribution

a) 58 to 61 liters (Prod Info Neurontin(R), 2003; Vollmer et al, 1986).

1) Vd values were 2.76 L/kg and 1.80 L/kg after a single oral do under 5 years (n=27) and 5 to 12 years (n=21), respectively. Dos was gabapentin syrup 10 mg/kg; subjects over 2 years received 200 mg for 16 to 25 kg; 300 mg for 26 to 36 kg; 400 mg for 37 to

2.3.3 Metabolism

A) Metabolism Sites and Kinetics

1) Not metabolized (Prod Info Neurontin(R), 2003; Vollmer et al, 1986).
a) Excreted unchanged in the urine (Haig et al, 2001a).

2.3.4 Excretion
A) Kidney
1) Renal Clearance (rate)
a) 150 mL/minute (Vollmer et al, 1986).
1) In a study examining gabapentin pharmacokinetics in patients were administered a single 400 milligram dose of gabapentin. In clearance greater than 60 milliliter/minute (mL/min) had a gabap mL/min. Patients with a creatinine clearance less than 30 mL/mi clearance of 10 mL/min (Prod Info Neurontin(R), 2003).
2) Renal clearance rates were 7.40 mL/min/kg and 4.41 mL/min CHILDREN ages 1 month to under 5 years (n=27) and 5 to 12 ye for those 2 years or younger was gabapentin syrup 10 mg/kg; su capsules based on weight: 200 mg for 16 to 25 kg; 300 mg for 2((Haig et al, 2001a).
2) Renal Excretion (%)
a) 76% to 81% (Vollmer et al, 1986).
1) Percentage of dose excreted unchanged in the urine was 41. CHILDREN ages 5 to 12 years (n=21). Dosing of oral capsules v 16 to 25 kg; 300 mg for 26 to 36 kg; 400 mg for 37 to 50 kg (Haig
B) Other
1) OTHER EXCRETION
a) Feces, 10% to 23% (Vollmer et al, 1986).

2.3.5 Elimination Half-life
A) Parent Compound
1) ELIMINATION HALF-LIFE
a) 5 to 7 hours (Prod Info Neurontin(R), 2003; Hooper et al, 1991a; A 1986).
1) The elimination rate constant, plasma clearance, and renal cl proportional to creatine clearance (Prod Info Neurontin(R), 2003)
2) In patients with decreased renal function the elimination half l 400 mg oral dose, the mean gabapentin half life was 6.5 hours ir clearance greater than 60 milliliters/minute (mL/min) and was 52 clearance less than 30 mL/min (Prod Info Neurontin(R), 2003).
3) Elimination half-life was 4.44 hours after a single oral dose in 12 years (evenly distributed over the age range). Dosing for thos gabapentin syrup 10 mg/kg; subjects over 2 years received oral mg for 16 to 25 kg; 300 mg for 26 to 36 kg; 400 mg for 37 to 50 k

2.3.6 Extracorporeal Elimination
A) Hemodialysis
1) Dialyzable: Yes (Prod Info Neurontin(R), 2003; Prod Info Neurontin(R)
a) In anuric patients the apparent elimination half-life of gababentin v days and was reduced to 3.8 hours during dialysis (Prod Info Neuron

3.0 Cautions

3.1 Contraindications
A) hypersensitivity to gabapentin

3.2 Precautions

A) abrupt discontinuation may precipitate status epilepticus
B) renal insufficiency
C) suicidality, increased risk of; based on data analysis of 199 placebo-controlled s
small elevated risk occurred as early as 1 week after starting therapy and continue
and Drug Administration, 2008)

3.3 Adverse Reactions

Cardiovascular Effects

Dermatologic Effects

Endocrine/Metabolic Effects

Gastrointestinal Effects

Hematologic Effects

Hepatic Effects

Musculoskeletal Effects

Neurologic Effects

Ophthalmic Effects

Psychiatric Effects

Renal Effects

Reproductive Effects

Respiratory Effects

Other

3.3.1 Cardiovascular Effects

Cardiovascular finding

Edema

Hypertension

Vasodilatation

3.3.1.A Cardiovascular finding
1) Hypertension, vasodilation and edema may develop with gabapentin tl

3.3.1.B Edema
1) Summary
a) Peripheral edema and facial edema were reported in gabapentin-t
Neurontin(R), 2003a).

3.3.1.C Hypertension
1) Summary
a) It may be advisable to monitor blood pressure in overdoses, as hy

a frequent adverse event following therapeutic doses of gabapentin (

3.3.1.D Vasodilatation

1) Summary

a) Vasodilation (1.1%) was reported in gabapentin-treated patients (

3.3.2 Dermatologic Effects

Alopecia

Dermatological finding

Drug-induced rash

Rash

Stevens-Johnson syndrome

3.3.2.A Alopecia

1) Summary

a) Acute alopecia has been described as an adverse event following 1997).

3.3.2.B Dermatological finding

1) Acne, alopecia, eczema, pruritus, skin rashes and Stevens- Johnson s

3.3.2.C Drug-induced rash

1) Summary

a) Acne, eczema and pruritus have occasionally occurred with gabap Neurontin(R), 2003a; Sivenius et al, 1991a; Anon, 1990b; Crawford e

3.3.2.D Rash

1) Summary

a) Skin rashes have been occasionally associated with gabapentin th due to a maculopapular skin rash has also occurred (Prod Info Neurc 1991a; Anon, 1990b; Crawford et al, 1987a).

2) LITERATURE REPORTS

a) 58-year-old man, after beginning therapy with gabapentin 300 mill developed a mild pruritic, erythematous, macular rash. Therapy conti excellent pain control with increased gabapentin (2400 mg/daily). At 5 the rash spread to thighs and forearms. Gabapentin was reduced to Gabapentin was discontinued but restarted after the neuropathic pair other drugs. A similar rash reoccurred despite a slower titration. Topi pruritus and intensity of the rash (Gould, 1998).

3.3.2.E Stevens-Johnson syndrome

1) Summary

a) Several cases of Stevens-Johnson syndrome have been reported et al, 1999; Gonzalez-Sicilia et al, 1998)

2) Incidence: rare

3) LITERATURE REPORTS

a) A 26-year-old woman with a history of Stevens-Johnson Syndrom carbamazepine therapy developed a skin eruption with gabapentin th Gabapentin had been titrated up in 300-mg increments. On the eighth developed a pruriginous, erythematous eruption on the proximal thigh distal lower extremities. There was no systemic involvement. The ras discontinued.

b) A 32-year-old, HIV-positive woman developed Stevens-Johnson s gabapentin therapy. It spread to her face and upper trunk with a skin necrolysis with slight perivascular infiltrates of lymphocytes in the der gabapentin was discontinued (Gonzalez-Sicilia et al, 1998).

3.3.3 Endocrine/Metabolic Effects

Blood glucose abnormal

Endocrine finding

Gynecomastia

Thyroiditis

Weight change finding

3.3.3.A Blood glucose abnormal

1) Summary

a) Fluctuations in blood sugar levels below 3.3 millimole/Liter and ab
to 5.5) have been reported in clinical studies. Caution should be exer
Info Neurontin(R), 1998).

3.3.3.B Endocrine finding

1) The most commonly reported adverse effects are glucose level chang
weight fluctuations.

3.3.3.C Gynecomastia

1) Summary

a) CASE REPORT - Gynecomastia, along with weight gain, occurrec
GABAPENTIN for thoracic pain. The patient had undergone thoracot
metastasized, poorly differentiated cancerous tumor was found in his
Afterwards he experienced severe post-thoracotomy pain. He was ur
morphine, fentanyl, diclofenac, amitriptyline, venlafaxine, bupivacaine
10%. A year or more later, gabapentin 2100 mg/day was introduced i
patient reported a significant decrease in pain (from 8 to 3 on a 10-pc
several weeks, the patient complained of painful gynecomastia. He w
testosterone, FSH, and LH levels, though he had a normal response
that gabapentin may have produced selective hypothalamic insufficie
hormone axis in this terminal cancer patient and that effect may have
et al, 2000).

3.3.3.D Thyroiditis

1) Summary

a) A 28-year-old woman being treated for bipolar II disorder develop
gabapentin 4800 milligrams daily (Frye et al, 1999). Physical sympto
nonsustained sinus tachycardia, mild hand tremor, and heat intoleran
microunits/milliliter. An I-123 uptake scan revealed a normal-sized ho
uptake of 1% at 24 hours. Gabapentin was discontinued and her sym
function tests returned to baseline.

3.3.3.E Weight change finding

1) Summary

a) Weigh loss associated with anorexia and weight gain related to in
reported in up to 5% of gabapentin- treated patients (Prod Info Neuro

2) LITERATURE REPORTS

a) Twenty-eight of 44 patients treated for seizure disorder with gabap
(Toledo et al, 1997). Ten patients gained more than 10% of their bas
5% to 10%, 16 patients had no change, and 3 patients lost 5% to 10%
increase started between the second and third months of therapy and

3.3.4 Gastrointestinal Effects

Abdominal discomfort

Gastrointestinal tract finding

Pancreatitis

3.3.4.A Abdominal discomfort

1) Summary

a) Abdominal pain and flatulence have been reported (Prod Info Neu has been noted infrequently during gabapentin therapy (Sivenius et a et al, 1987a).

3.3.4.B Gastrointestinal tract finding

1) Summary

a) Nausea and vomiting have been reported infrequently during gaba 1991a; Anon, 1990b; Crawford et al, 1987a). Constipation, diarrhea, and gingivitis have been reported with gabapentin therapy (Prod Info

2) Abdominal pain, constipation, diarrhea, dental abnormalities, dry mout been reported with gabapentin therapy. Gastric upset, nausea and vomiti case of pancreatitis was also noted.

3.3.4.C Pancreatitis

1) Summary

a) A case of pancreatitis has occurred with gabapentin treatment (Pr

3.3.5 Hematologic Effects

Hematology finding

Leukopenia

Purpuric disorder

3.3.5.A Hematology finding

1) Leukopenia and purpura have been reported with therapeutic doses of

3.3.5.B Leukopenia

1) Summary

a) Leukopenia has been reported in approximately 1.1% of gabapen with 0.3% of a placebo-controlled group (Prod Info Neurontin(R), 200

3.3.5.C Purpuric disorder

1) Summary

a) The manufacturer reports that purpura has frequently occurred wi most often described as bruises resulting from physical trauma (Prod

3.3.6 Hepatic Effects

3.3.6.A Hepatotoxicity

1) Summary

a) A 60-year-old man taking many concomitant medications develop attributed to gabapentin treatment (for pain). An earlier skin eruption, toxicoderma, cleared with 5 days of steroid treatment after discontinu metamizole. Jaundice and palpable hepatomegaly developed severa metamizole had been discontinued. Gabapentin (oral), which had bee 1800 milligrams per day, was then progressively reduced. Improveme leukocyte and eosinophil counts followed. None of the other concomi before improvement was evident (Lasso-de-la-Vega et al, 2001).

3.3.8 Musculoskeletal Effects

Backache

Fracture of bone

Myalgia

Myasthenia gravis

Rhabdomyolysis

3.3.8.A Backache

1) Incidence: 1.8% (Prod Info NEURONTIN(R) oral tablets, oral capsules
2) Backpain has been reported in 1.8% of the patients receiving gabaper ongoing antiepileptic treatment compared with 0.5% with placebo add-on NEURONTIN(R) oral tablets, oral capsules, oral solution, 2007).

3.3.8.B Fracture of bone

1) Incidence: 1.1% (Prod Info NEURONTIN(R) oral tablets, oral capsules
2) Fracture has been reported in 1.1% of the patients receiving gabapent ongoing antiepileptic treatment compared with 0.8% with placebo add-on NEURONTIN(R) oral tablets, oral capsules, oral solution, 2007).

3.3.8.C Myalgia

1) Incidence: 2% (Prod Info NEURONTIN(R) oral tablets, oral capsules, c
2) Myalgia has been reported in 2% of the patients receiving gabapentin ongoing antiepileptic treatment compared with 1.9% with placebo add-on NEURONTIN(R) oral tablets, oral capsules, oral solution, 2007).

3.3.8.D Myasthenia gravis

See Drug Consult reference: DRUG-INDUCED MYASTHENIA GRAVIS

3.3.8.E Rhabdomyolysis

1) In a single case report, the administration of gabapentin appeared to ir year-old diabetic female. The patient had a history of type 2 diabetes mell dyslipidemia. She was taking multiple insulin injections daily, irbesartan 15 mg thrice daily, of which gabapentin was prescribed three weeks earlier fo initiation of gabapentin, her creatinine was 1.2 mg/dL, CPK was 142 units 21 units/L, and microalbuminuria was 170 mg/24 hours. On admission, th weakness of her lower extremities, muscle pain, fatigue along with decrea urine. Physical examination revealed proximal muscle tenderness and we reflexes, and decreased vibration sensation. Laboratory testing revealed e mg/dL, CPK of 75,680 units/L, AST of 1451 units/L, ALT of 453 units/L, LD level of 6.3 mmol/L, and positive for myoglobin in urine; indicative of acute thyroid hormones and troponin-I were in normal ranges. Muscle biopsy co rhabdomyolysis. Hemodialysis was initiated to remedy hyperkalemia and discontinued and parenteral fluids along with furosemide were initiated to showing gradual renal improvement. Six months following hospital discha asymptomatic, and her renal function and muscle enzymes were normaliz

3.3.9 Neurologic Effects

Abnormal reflex

Amnesia

Asthenia

Ataxia

Choreoathetosis

Dizziness

Drug-induced coma

Dysarthria

Dyskinesia

Headache

Hyperactive behavior

Insomnia

Nystagmus

Polyneuropathy

Seizure

Somnolence

Stuttering

Tremor

Vertigo

3.3.9.A Abnormal reflex

1) Incidence: 0.1% or greater (Prod Info NEURONTIN(R) oral tablets, ora

2) Abnormal reflex (increased, decreased, or absent reflex) was reported epilepsy patients greater than 12 years of age who received gabapentin (antiepileptic drug therapy in all adjunctive therapy clinical trials (except ne Info NEURONTIN(R) oral tablets, oral capsules, oral solution, 2007).

3) In double-blind and open-label clinical trials, decreased reflex was rep patients who received gabapentin (n=1173) for treatment of neuropathic p was not established (Prod Info NEURONTIN(R) oral tablets, oral capsules

3.3.9.B Amnesia

1) Incidence: postherpetic neuralgia, 1.2%; epilepsy, 2.2% (Prod Info NE capsules, oral solution, 2007)

2) Amnesia has been reported in 1.2% of patients treated with gabapenti those treated with placebo (n=227) in controlled trials of patients with pos NEURONTIN(R) oral tablets, oral capsules, oral solution, 2007).

3) Amnesia has been reported in 2.2% of patients treated with gabapenti treated with placebo (n=378) in controlled add-on trials of patients greater epilepsy (Prod Info NEURONTIN(R) oral tablets, oral capsules, oral soluti

3.3.9.C Asthenia

1) Incidence: 1% to 5.7% (Prod Info NEURONTIN(R) oral tablets, oral ca

2) Asthenia was reported in 5.7% of patients treated with gabapentin (n= with placebo (n=227) in controlled trials of patients with postherpetic neur oral tablets, oral capsules, oral solution, 2007).

3) Asthenia was reported in at least 1% (1 of 100) of epilepsy patients gr received gabapentin (n=4717) in addition to current antiepileptic drug ther clinical trials (except neuropathic pain trials) (Prod Info NEURONTIN(R) o solution, 2007).

3.3.9.D Ataxia

1) Incidence: postherpetic neuralgia, 3.3%; epilepsy, 12.5% (Prod Info NI capsules, oral solution, 2007)

2) Ataxia has been reported in 3.3% of patients treated with gabapentin (those treated with placebo (n=227) in controlled trials of patients with pos NEURONTIN(R) oral tablets, oral capsules, oral solution, 2007).

3) Ataxia has been reported in 12.5% of patients treated with gabapentin treated with placebo (n=378) in controlled add-on trials of patients greater epilepsy. Ataxia was one of the adverse effects most frequently associate (0.8%) (Prod Info NEURONTIN(R) oral tablets, oral capsules, oral solutio

4) Truncal ataxia was reported in 48 children treated with gabapentin syr younger) or oral capsules in 200-mg doses for those 16 to 25 kg, 300-mg

400-mg doses for those 37 to 50 kg (over 2 years of age) in a single-dose
pediatric patients age 1 month to 12 years (evenly distributed over the ag

3.3.9.E Choreoathetosis

1) Incidence: less than 0.1% (Prod Info NEURONTIN(R) oral tablets, oral
2) Choreoathetosis was reported in less than 0.1% (1 of 1000) of epileps
age who received gabapentin (n=4717) in addition to current antiepileptic
therapy clinical trials (except neuropathic pain trials) (Prod Info NEURON
oral solution, 2007).
3) Two case reports described choreoathetosis related to adjunctive gab
mg/day in 2 institutionalized, mentally retarded patients. In one case, the
the severity of choreoathetoid movements lessening with decreasing dos
movements occurred intermittently for 10 weeks after discontinuation. In t
was attempted after discontinuation. Upon rechallenge, the patient develo
reaching a gabapentin dose of 1800 mg/day. The movements occurred 1
persisted for 1 to 2 hours. Increasing the dose to 3600 mg/day had no eff
the movements. Because the movements were not disabling and seizure
a decision was made to continue gabapentin therapy (Chudnow et al, 199

3.3.9.F Dizziness

1) Incidence: pediatrics, 2.5%; adults, 17.1% to 28% (Prod Info NEURON
capsules, oral solution, 2007)
2) Dizziness has been reported in 28% of patients treated with gabapenti
those treated with placebo (n=227) in controlled trials of patients with pos
NEURONTIN(R) oral tablets, oral capsules, oral solution, 2007).
3) In controlled add-on trials of epilepsy patients greater than 12 years of
17.1% of patients who received gabapentin (n=543) compared with 6.9%
(n=378) in addition to current antiepileptic drug therapy. Dizziness was on
frequently associated with gabapentin discontinuation (0.6%) (Prod Info N
capsules, oral solution, 2007).
4) Dizziness was reported in 2.5% of pediatric patients who received gab
1.6% of patients who received placebo (n=128) in addition to current antie
trials of patients 3 to 12 years of age with epilepsy (Prod Info NEURONTI
oral solution, 2007).

3.3.9.G Drug-induced coma

1) A case report described a drug-induced coma in a 65-year-old woman
patient, who had a history of untreated hypertension, was admitted to the
aneurysmal subarachnoid hemorrhage. The Glasgow coma scale was 15
initial generalized tonic clonic seizure. Subsequently, gabapentin 600 mg
initiated along with IV nimodipine, paracetamol, and oral omeprazole. A C
subarachnoid hemorrhage without clot. Six hours after ICU admission, an
communicating artery was treated by coil. Dilation of the ventricles was re
leading to the insertion of an external ventricular drainage which was linke
intracranial pressure. Because the patient was conscious with no motor sl
performed on day 1. Several hours later, the patient gradually progressed
Intracranial pressure, transcranial Doppler and PaCO(2) were all normal.
ventilatory assistance was provided, and a continuous infusion of sufenta
sedate her. Rebleeding or ischemic complication were ruled out by CT sc
4), sedation was maintained; sedatives were stopped temporarily each da
There was no improvement in consciousness. At day 8, vasospasm was
performed without sedation, revealed evidence of a reactive alternating c
down with less reactivity and rare spike foci on the anterior region indicati
of seizure resulted in a gabapentin dose increase to 900 mg 3 times daily
triphasic slow waves in addition to the previously described spike foci. He
and she became deeply comatose. Due to the consistent presence of slo
a diagnosis of metabolic encephalopathy was made. Gabapentin, omepra
paracetamol were discontinued on day 15. Oxcarbazepine was initiated ir
300 mg twice daily. Her neurological status improved and she gained con
21 and 28, controlled EEGs no longer showed the slow triphasic waves. M
after gabapentin discontinuation), 34, and 58 showed a progression towa
2007).

3.3.9.H Dysarthria

1) Incidence: 2.4% (Prod Info NEURONTIN(R) oral tablets, oral capsules
2) In controlled add-on trials of patients greater than 12 years of age with
in 2.4% of patients who received gabapentin (n=543) compared with 0.5%

placebo (n=378) in addition to current antiepileptic drug therapy (Prod Info oral capsules, oral solution, 2007).

3.3.9.I Dyskinesia

1) Two men developed generalized dyskinetic movements of the face an gabapentin 900 or 1200 mg/day. The men were being treated for anxiety. in resolution of abnormal movements within 1.5 to 3 days (Norton & Quarl

3.3.9.J Headache

1) Incidence: 3.3% (Prod Info NEURONTIN(R) oral tablets, oral capsules
2) Headache has been reported in 3.3% of patients treated with gabapen treated with placebo (n=227) in controlled trials of patients with postherpe NEURONTIN(R) oral tablets, oral capsules, oral solution, 2007).

3.3.9.K Hyperactive behavior

1) Incidence: 1% to 4.7% (Prod Info NEURONTIN(R) oral tablets, oral ca
2) Hyperkinesia was reported in 2.5% of pediatric patients who received with 0.8% of patients who received placebo (n=128) in addition to current controlled trials of patients 3 to 12 years of age with epilepsy (Prod Info N capsules, oral solution, 2007).
3) In controlled trials of pediatric patients 3 to 12 years of age with epilep restlessness and hyperactivity) was reported in 4.7% of patients who rece compared with 2.9% of patients who received placebo (n=128) in addition therapy (Prod Info NEURONTIN(R) oral tablets, oral capsules, oral solutic
4) Hyperkinesia was reported in at least 1% (1 of 100) of epilepsy patient who received gabapentin (n=4717) in addition to current antiepileptic drug clinical trials (except neuropathic pain trials) (Prod Info NEURONTIN(R) o solution, 2007).

3.3.9.L Insomnia

1) Incidence: 0.1% or greater (Prod Info NEURONTIN(R) oral tablets, ora
2) Insomnia has been reported in more than 1% of patients treated with more frequent in those treated with placebo (n=378) in controlled add-on years of age with epilepsy (Prod Info NEURONTIN(R) oral tablets, oral ca
3) In double-blind and open-label clinical trials, insomnia was reported in received gabapentin (n=1173) for treatment of neuropathic pain condition established (Prod Info NEURONTIN(R) oral tablets, oral capsules, oral so
4) Insomnia is one of the most frequently reported adverse events followi gabapentin (Prod Info NEURONTIN(R) oral tablets, oral capsules, oral so

3.3.9.M Nystagmus

1) Incidence: 0.1% to 8.3% (Prod Info NEURONTIN(R) oral tablets, oral
2) In controlled add-on trials of epilepsy patients greater than 12 years of 8.3% of patients who received gabapentin (n=543) compared with 4% of t (n=378) in addition to current antiepileptic drug therapy (Prod Info NEURO capsules, oral solution, 2007).
3) In double-blind and open-label clinical trials, nystagmus was reported who received gabapentin (n=1173) for treatment of neuropathic pain conc established (Prod Info NEURONTIN(R) oral tablets, oral capsules, oral so

3.3.9.N Polyneuropathy

1) A case report described polyneuropathy in a 58-year-old man being tre neuropathic pain in his head, neck, and back. After beginning therapy with he developed a mild pruritic, erythematous, macular rash. Therapy contin control with increased gabapentin (2400 mg/daily). At 5 months, pruritus i thighs and forearms. Gabapentin was reduced to 1200 mg daily with no c discontinued but restarted after the neuropathic pain returned without resp rash reoccurred despite a slower titration. Topical triamcinolone relieved t rash; however, the patient was left with a constant burning sensation in hi Sedimentation rate was elevated at 35. Toxic polyneuropathy was suspec discontinued. After 1 month, the burning dysesthesia had decreased but p and light-touch below the mid-calf was decreased. Seven months later, th improved and were present only in the soles of his feet (Gould, 1998).

3.3.9.O Seizure

1) A case report described an exacerbation of seizures in a child with Ler adjunctive use of gabapentin. Both absence and myoclonic seizures recu

increase in dosage. After discontinuation of gabapentin, and addition of pl
myoclonic seizures occurred (Vossler, 1996).
2) Absence status was described in one patient during initiation of gabap
discontinued in this patient (Crawford et al, 1987a).

3.3.9.P Somnolence

1) Incidence: 8.4% to 21.4% (Prod Info NEURONTIN(R) oral tablets, oral
2) Somnolence was reported in 21.4% of patients treated with gabapentir
those treated with placebo (n=227) in controlled trials of patients with post
NEURONTIN(R) oral tablets, oral capsules, oral solution, 2007).
3) In controlled add-on trials of epilepsy patients greater than 12 years of
19.3% of patients who received gabapentin (n=543) compared with 8.7%
(n=378) in addition to current antiepileptic drug therapy. Somnolence was
frequently associated with gabapentin discontinuation (1.2%) (Prod Info N
capsules, oral solution, 2007).
4) Somnolence was reported in 8.4% of pediatric patients who received g
with 4.7% of patients who received placebo (n=128) in addition to current
controlled trials of epilepsy patients 3 to 12 years of age (Prod Info NEUR
capsules, oral solution, 2007).

3.3.9.Q Stuttering

1) A case report described stuttering in a 58-year-old woman after being
intractable seizures. Gabapentin therapy was discontinued and within 4 d
(Nissani & Sanchez, 1997).

3.3.9.R Tremor

1) Incidence: postherpetic neuralgia, more than 1%; epilepsy, 6.8% (Proc
tablets, oral capsules, oral solution, 2007)
2) Tremor was reported in more than 1% of patients treated with gabaper
frequent in those treated with placebo (n=227) in controlled trials of patier
(Prod Info NEURONTIN(R) oral tablets, oral capsules, oral solution, 2007
3) In controlled add-on trials of epilepsy patients greater than 12 years of
of patients who received gabapentin (n=543) compared with 3.2% of thos
in addition to current antiepileptic drug therapy (Prod Info NEURONTIN(R
solution, 2007).

3.3.9.S Vertigo

1) Incidence: 0.1% or greater (Prod Info NEURONTIN(R) oral tablets, ora
2) Vertigo was reported in at least 1% (1 of 100) of epilepsy patients grea
received gabapentin (n=4717) in addition to current antiepileptic drug ther
clinical trials (except neuropathic pain trials) (Prod Info NEURONTIN(R) o
solution, 2007).
3) In double-blind and open-label clinical trials, vertigo was reported in 0.
received gabapentin (n=1173) for treatment of neuropathic pain condition
established (Prod Info NEURONTIN(R) oral tablets, oral capsules, oral so

3.3.10 Ophthalmic Effects

Blurred vision

Diplopia

Visual field constriction

3.3.10.A Blurred vision

1) Blurred vision, amblyopia, and abnormal vision have been reported oc
therapy (Sivenius et al, 1991a; Prod Info Neurontin(R), 2003a).

3.3.10.B Diplopia

1) Diplopia has been reported following therapeutic doses of gabapentin
Neurontin(R), 2003a).

3.3.10.C Visual field constriction

1) A case of reversible concentric visual field constriction occurred in a 5

use. The woman had been diagnosed with polyneuropathy, which was ini
However, persistent dizziness with carbamazepine led to its discontinuati
gabapentin, which was initiated at 400 mg twice daily and titrated to 800 r
months of gabapentin therapy, the patient experienced episodes of disturl
and dizziness. Ophthalmological examination revealed concentric visual f
reduction of gabapentin dosage to 400 mg three times daily. Four months
worsened despite the reduced dosing and gabapentin was subsequently
visual evoked responses, and a brain MRI were normal, excluding conditi
in the hypophysial area. Improvements occurred over the following 9 mon
examinations. A follow-up examination 2 years after symptom-onset revea
complete resolution of the visual defects were noted at the 5 year follow-u
2006).

3.3.12 Psychiatric Effects

Disturbance in mood

Suicidal thoughts

Unable to concentrate

3.3.12.A Disturbance in mood

1) Summary

a) Gabapentin was associated with the occurrence of neuropsychiatr
involving pediatric epilepsy patients between 3 to 12 years of age. Th
the following categories: emotional lability (primarily behavioral proble
aggressive behaviors), thought disorder (including concentration prob
performance), and hyperkinesia (primarily restlessness and hyperacti
2003a).

b) There are reports of symptoms including anxiety, depression, emo
nervousness with gabapentin therapy. A case of mania has also beer
(R), 2003a; Leweke et al, 1999).

2) LITERATURE REPORTS

a) A 35-year-old woman receiving gabapentin 3200 mg/day monothe
(Leweke et al, 1999). Psychiatric symptoms disappeared within 5 day
discontinuation.

3.3.12.B Suicidal thoughts

1) Data reviewed by the US Food and Drug Administration suggest an in
or ideation may exist in patients receiving therapy with antiepileptic drugs
199 placebo-controlled clinical studies covering 11 different AEDs used fo
such as epilepsy, selected psychiatric illnesses, and other conditions, incl
pain syndromes. The analysis included 27,863 patients treated with AEDs
received placebo, and patients were aged 5 years and older. There were
patients in the AED treatment groups versus (vs) none in the placebo grou
occurred in 0.43% of patients in the AED treatment groups compared to 0
groups. This corresponded to an estimated 2.1 per 1000 (95% confidence
in the AED treatment groups having suicidal behavior or ideation than the
risk of suicidality was noted at 1 week after starting an AED and continued
compared to placebo, results were generally consistent among the drugs
subgroups. Patients treated for epilepsy, psychiatric disorders, or other co
risk for suicidality compared to placebo. Closely monitor patients treated w
worsening of depression, suicidality and other unusual changes in behavi
such as anxiety, agitation, hostility, mania, and hypomania (US Food and

3.3.12.C Unable to concentrate

1) Summary

a) Impaired concentration or memory has been reported within three
therapy (Prod Info Neurontin(R), 2003a; Ramsay, 1994a).

3.3.13 Renal Effects

Incontinence

Serum creatinine raised

3.3.13.A Incontinence

1) Summary

a) Three cases of bladder and rectal incontinence were reported whi
(Gil-Nagel et al, 1997). All occurred within 1 to 4 weeks of starting ga
upon discontinuation.

3.3.13.B Serum creatinine raised

1) A 59-year-old woman and a 49-year-old male with a history of renal ins
experienced a 47.8% and 30% increase in serum creatinine, respectively
discontinuation of lithium (Silvia & Spitznas, 2007).

a) Significant past medical history for the 59-year-old woman include
(dose range of 450 mg/day to 2100 mg/day) and an episode of lithiun
nephrogenic diabetes insipidus requiring hospitalization. Serum urea
continued to rise and therefore, lithium was discontinued 6 years afte
months prior to lithium discontinuation, the serum creatinine was 2.3
was started 1 week prior to discontinuation of lithium. The dose was t
months later. Her serum creatinine continued to rise and reached a p
5.5 months after gabapentin initiation (a 47.8% increase). Clinical ber
gabapentin was continued. The dose was reduced but the creatinine
least 3 months (Silvia & Spitznas, 2007).

b) Significant past medical history for the 49-year-old male includes
3 years. At some point in time, amiloride was added, presumably for
discontinued due to worsening renal function (serum creatinine of 4 n
interstitial fibrosis/nephritis secondary to lithium and possibly amilorid
divalproex sodium was started but subsequently discontinued 6 mont
patient refusal. Carbamazepine was started but gradually discontinue
patient refusal. Gabapentin 100 mg/day was started 1 month prior to
Gabapentin was titrated up to 300 mg/day within 1 month. His serum
and plateaued at a peak of 5.2 mg/dL, after approximately 10 months
increase). Clinical benefit was achieved; therefore, gabapentin was c
2007).

3.3.14 Reproductive Effects

Amenorrhea

Sexual dysfunction

3.3.14.A Amenorrhea

1) LITERATURE REPORT

a) Amenorrhea occurred in a 35-year-old women treated with gabap
syndrome type 2. Gabapentin had been initiated at a dose of 300 mg
gabapentin dose was increased to a total dose of 1800 mg/day. Thre
reported complete cessation of menses with no other changes in sex
cycles were normal and the patient had not experienced any prior ep
measured follicle stimulating hormone level at the time was 4.8 Interr
estradiol level was 55 IU/mL, both at the lower end of normal. At this
down by 300 mg/day over 6 days. Two weeks later, the patient's mer
2004).

3.3.14.B Sexual dysfunction

1) Summary

a) Impotence has been reported in 1.5% of patients treated with ther
(Prod Info Neurontin(R), 2003a). Anorgasmia has been reported in 2
2002; Montes & Ferrando, 2001; Labbate & Rubey, 1999).

2) LITERATURE REPORTS

a) Anorgasmia and decreased libido was reported in 2 women who r
day (Grant & Oh, 2002).

b) A 41-year-old man being treated with gabapentin for hypomania f
attain (Labbate & Rubey, 1999). He initially noted the problem with a
the dose was increased to 600 mg 3 times daily, he found ejaculation

to achieve. One week after gabapentin discontinuation, he reported r
c) Anorgasmia occurred in a 36-year-old man after a short course of
bipolar I disorder. Due to this adverse drug-induced side effect, the p
Initially the patient was on lithium therapy (1200 mg/day). However, h
therapy after experiencing a first-degree atrioventricular block. He sta
with titration of 400 mg every 2 days to 400 mg 3 times a day. This th
episode which occurred after withdrawal of lithium. Two weeks later,
because it caused him difficulty in attaining orgasm. His sex drive and
discontinuation of gabapentin, he returned to normal orgasmic functio
the gabapentin dosing regimen, he relapsed into a new episode of hy
Ferrando, 2001).

3.3.15 Respiratory Effects

Disorder of upper respiratory system

Respiratory failure

Respiratory finding

3.3.15.A Disorder of upper respiratory system

1) Summary

a) Rhinitis and pharyngitis have occurred with gabapentin use (Prod

3.3.15.B Respiratory failure

1) Summary

a) Gabapentin therapy was associated with hypoventilation, hyperca
69-year-old man under treatment for chronic obstructive pulmonary d
anxiety disorder (Batoon et al, 2001) and hypoventilation requiring int
woman with end-stage renal disease on long-term hemodialysis (Jon

2) LITERATURE REPORTS

a) After taking multiple doses of gabapentin over two days, without ir
year-old woman with end-stage renal disease became hypoxic and s
was 80% on room air and she was subsequently intubated. She had
and a gabapentin level of 22.6 micrograms per milliliter. Following he
rapidly improved and she was extubated. This gabapentin level is les
of toxicity and suggests that gabapentin toxicity should be considered
gabapentin with end-stage renal disease show signs of impaired mer
2002).

b) Gabapentin therapy was associated with hypoventilation, hyperca
69-year-old man under treatment for chronic obstructive pulmonary d
anxiety disorder. The patient was admitted with shortness of breath a
he had started gabapentin 300 mg 3 times a day for painful peripher
initiation of gabapentin, he was hospitalized for severe hypercapnia, r
(MV). His other medications were albuterol, ipratropium, clonazepam
hospitalization, he was again put on MV due to lethargy, respiratory d
attempts at extubation failed. On day 10, gabapentin was withdrawn
steroid, levofloxacin, clonazepam, and zolpidem were continued). Tw
and his carbon dioxide levels normalized. He continued to improve, a
remained stable. The authors suggest that caution be exercised if ga
COPD patients (Batoon et al, 2001).

3.3.15.C Respiratory finding

1) Summary

a) Viral infection, fever, coughing and pneumonia have been associa
(Prod Info Neurontin(R), 2003a).

2) Coughing, pharyngitis, respiratory failure, pneumonia, rhinitis and viral
gabapentin therapy.

3.3.16 Other

Summary

Drug withdrawal

Fatigue

3.3.16.A Summary

1) OTHER EFFECTS

a) Rebound and withdrawal symptoms may occur upon discontinuati

3.3.16.B Drug withdrawal

1) Five patients being treated with gabapentin augmentation for obsessiv experienced a rebound of symptoms after abruptly discontinuing gabapen Patients complained of markedly more pronounced and intense problems obsessional thinking, depression, and decreased sleep over their baseline

2) A 48-year-old woman with bipolar affective disorder developed catator discontinued (Rosebush et al, 1999). She had begun gabapentin during h hypomania. She has a history of intolerance to lithium, carbamazepine, va Gabapentin was slowly increased to 500 mg/day, but after 3 weeks, she b was tapered off over several days. Within 48 hours, she became immobile drink, rigidity, and absence of spontaneous movement. She remained cat with lorazepam eventually reversed the catatonia.

3.3.16.C Fatigue

1) Summary

a) In available studies, the most common adverse effects of gabaper tiredness/fatigue usually within three days of initiating therapy (Crawf Hooper et al, 1991b; Sivenius et al, 1991a; Prod Info Neurontin(R), 2 Drowsiness has been reported in patients ranging from 15% to 45%. in 13% of patients in one large study (Sivenius et al, 1991a; Anon, 19

2) LITERATURE REPORTS

a) CHILDREN - Drowsiness was a side effects of oral gabapentin ex month to 12 years (evenly distributed over the age range) involved in study. Dosing for children 2 years or younger was gabapentin syrup children over 2 years old received oral capsules based on weight: 20 26 to 36 kg; 400 mg for 37 to 50 kg (Haig et al, 2001).

b) Increased tiredness was seen with gabapentin 2400 milligrams/da (p=0.03). Cognition, dysphoria, temper, fatigue, and worry were not s gabapentin therapy even at the highest dose (Leach, 1997).

c) In a small study drowsiness has been observed in up to 45% of pa 1991a). Tiredness and drowsiness have occasionally required withdr tiredness/fatigue were reported in 15% and 13% of patients, respecti (Anon, 1990b)

3.4 Teratogenicity/Effects in Pregnancy/Breastfeeding

A) Teratogenicity/Effects in Pregnancy

1) U.S. Food and Drug Administration's Pregnancy Category: Category C (Pr capsules, oral tablets, oral solution, 2005) (All Trimesters)

a) Either studies in animals have revealed adverse effects on the fetus (t other) and there are no controlled studies in women or studies in women Drugs should be given only if the potential benefit justifies the potential ris

2) Australian Drug Evaluation Committee's (ADEC) Category: B1 (Batagol, 19

a) Drugs which have been taken by only a limited number of pregnant wo age, without an increase in the frequency of malformation or other direct human fetus having been observed. Studies in animals have not shown e occurrence of fetal damage.

See Drug Consult reference: PREGNANCY RISK CATEGORIES

3) Crosses Placenta: Yes

4) Clinical Management

a) There is insufficient clinical experience with gabapentin in pregnancy t population. Since gabapentin is frequently prescribed with other anticonvu between maternal gabapentin use and fetal adverse effects can not be de adequate, well-controlled studies, the manufacturer recommends that gab pregnancy only if the the potential benefit outweighs the potential risk to t (R) oral capsules, oral tablets, oral solution, 2005).

5) Literature Reports

a) There are no well-designed studies in pregnant women that have eval the growing fetus. However, the Gabapentin Pregnancy Registry has colle fetuses exposed to the drug. In the women, one case of hypertension, on one case of eclampsia were reported during the pregnancies. There were

miscarriages and one elective abortion. Full term babies accounted for 77
deliveries occurred between weeks 32 to 36. Median birth weight (n of 29
(oz) (range 3 lb 7 oz to 9 lb 8 oz). The time and length of gabapentin expo
fully described. The following malformations were reported: hypospadia in
and valproate, congenital solitary kidney in a baby exposed to gabapentin
thereafter phenobarbital, and minor malformation of the left external ear c
gabapentin and lamotrigine throughout gestation. The above birth statistic
women with epilepsy and in the general population. The effects of gabape
elucidated from these results and caution should still used when consideri
individuals (Montouris, 2003).

b) Data from a limited study of 6 women who were administered gabaper
lactation demonstrated fetal accumulation of gabapentin. The women wer
from 900 to 3,200 milligrams (mg)/day. While 1 woman had a premature d
deliveries were uneventful and resulted in healthy children. At the time of
maternal gabapentin plasma concentration ratio was 1.74. The study inve
indicative of an active transplacental transport of gabapentin (Ohman et a

c) In rodent studies, gabapentin, dosed at 1 to 4 times the maximum dos
a mg per square meter (mg/mg(2)) to pregnant females has been shown t
ossification of several bones in the skull, vertebrae, forelimbs, and hindlim
approximately one-half the human dose of gabapentin (Prod Info NEURO
tablets, oral solution, 2005).

d) In reproductive studies, rats dosed prior to and during mating, and thro
approximately 1 to 5 times the maximum human dose of 3,600 milligrams
increased incidence of hydroureter and/or hydronephrosis and the offsprir
affected. In a teratology study, an increased incidence of postimplantation
pregnant rabbits exposed to 60, 300, and 1,500 milligrams/kilogram/day (
than 0.25 to 8 times the maximum human dose) (Prod Info NEURONTIN(
solution, 2005).

B) Breastfeeding

1) Thomson Lactation Rating: Infant risk cannot be ruled out.

a) Available evidence and/or expert consensus is inconclusive or is inade
when used during breastfeeding. Weigh the potential benefits of drug trea
before prescribing this drug during breastfeeding.

2) Clinical Management

a) Gabapentin is secreted into human milk after oral administration. Limit
infants exposed to gabapentin through breast milk had minimal serum cor
effects. However, extensive studies are warranted and it is advisable that
through breast milk should be closely monitored to potential adverse effec
et al, 2006). Although a nursed infant may be exposed to a maximum dos
milligram/kilogram/day of gabapentin, until further data are available, the r
gabapentin should be used in nursing women only if the potential benefit t
to the infant (Prod Info NEURONTIN(R) oral capsules, oral tablets, oral so

3) Literature Reports

a) Data from a limited study of 6 women who were administered gabaper
lactation demonstrated extensive transfer of gabapentin to breast milk but
nursed infant. The women were given gabapentin doses ranging from 900
the time of delivery, the mean umbilical-to-maternal gabapentin plasma co
hours postpartum, the mean gabapentin plasma concentrations in the infa
levels (range 12 to 36%) with an estimated elimination half-life in the neor
Sampling of the breast milk was conducted before maternal intake of the r
approximately 10 to 15 hours following the last gabapentin dose. Based o
pairs, mean milk/maternal plasma gabapentin ratio was 1.0 (range 0.7 to
from delivery and the relative infant gabapentin dose was approximated to
(kg)/day, which was equivalent to 1.3 to 3.8% of the weight normalized do
No adverse effects were observed in the infants (Ohman et al, 2005).

b) A case report described gabapentin transfer into the breast milk of a la
administered gabapentin for chronic back pain. The 34-year-old woman h
milligrams (mg) three times daily (36.7 milligrams/kilogram/day (mg/kg/da
her 1.6-month-old male infant, weighing 3.1 kg, were studied over a 24-ho
determine the milk-plasma ratio and relative infant dose of gabapentin. Th
the relative infant dose was 2.34% of the weight-adjusted maternal dose.
0.86 mg/kg/day, which is approximately 3% of the children's dose of 25 to
plasma concentration in the infant was 0.4 milligrams/liter (mg/L), which w
mother's average drug plasma concentration of 6.7 mg/L. No adverse effe
(Kristensen et al, 2006).

4) Drug Levels in Breastmilk

a) Parent Drug

1) Peak Concentration in Infant
a) Following oral administration, gabapentin is secreted into hun
exposed to a maximum gabapentin dose of 1 milligram per kilogı
exposure on the nursing infant is unknown (Prod Info Neurontin(

3.5 Drug Interactions

Drug-Drug Combinations

Drug-Lab Modifications

3.5.1 Drug-Drug Combinations

Aluminum Carbonate, Basic

Aluminum Hydroxide

Aluminum Phosphate

Dihydroxyaluminum Aminoacetate

Dihydroxyaluminum Sodium Carbonate

Evening Primrose

Ginkgo

Hydrocodone

Magaldrate

Magnesium Carbonate

Magnesium Hydroxide

Magnesium Oxide

Magnesium Trisilicate

Morphine

Morphine Sulfate Liposome

3.5.1.A Aluminum Carbonate, Basic

1) Interaction Effect: decreased gabapentin effectiveness
2) Summary: The manufacturer reports that an antacid (Maalox(R)) giver
reduced gabapentin bioavailability by 20%. Bioavailability was reduced by
given two hours after the antacid. Therefore, gabapentin should be admin
antacid (Prod Info Neurontin(R), 2002).
3) Severity: moderate
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Patients receiving gabapentin should be instruct
hours of taking gabapentin due to the potential to decrease the effectiven
7) Probable Mechanism: decreased gabapentin bioavailability

3.5.1.B Aluminum Hydroxide

1) Interaction Effect: decreased gabapentin effectiveness
2) Summary: The manufacturer reports that an antacid (Maalox(R)) giver reduced gabapentin bioavailability by 20%. Bioavailability was reduced by given two hours after the antacid. Therefore, gabapentin should be admin antacid (Prod Info Neurontin(R), 2002).
3) Severity: moderate
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Patients receiving gabapentin should be instruct hours of taking gabapentin due to the potential to decrease the effectiven
7) Probable Mechanism: decreased gabapentin bioavailability

3.5.1.C Aluminum Phosphate
1) Interaction Effect: decreased gabapentin effectiveness
2) Summary: The manufacturer reports that an antacid (Maalox(R)) giver reduced gabapentin bioavailability by 20%. Bioavailability was reduced by given two hours after the antacid. Therefore, gabapentin should be admin antacid (Prod Info Neurontin(R), 2002).
3) Severity: moderate
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Patients receiving gabapentin should be instruct hours of taking gabapentin due to the potential to decrease the effectiven
7) Probable Mechanism: decreased gabapentin bioavailability

3.5.1.D Dihydroxyaluminum Aminoacetate
1) Interaction Effect: decreased gabapentin effectiveness
2) Summary: The manufacturer reports that an antacid (Maalox(R)) giver reduced gabapentin bioavailability by 20%. Bioavailability was reduced by given two hours after the antacid. Therefore, gabapentin should be admin antacid (Prod Info Neurontin(R), 2002).
3) Severity: moderate
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Patients receiving gabapentin should be instruct hours of taking gabapentin due to the potential to decrease the effectiven
7) Probable Mechanism: decreased gabapentin bioavailability

3.5.1.E Dihydroxyaluminum Sodium Carbonate
1) Interaction Effect: decreased gabapentin effectiveness
2) Summary: The manufacturer reports that an antacid (Maalox(R)) giver reduced gabapentin bioavailability by 20%. Bioavailability was reduced by given two hours after the antacid. Therefore, gabapentin should be admin antacid (Prod Info Neurontin(R), 2002).
3) Severity: moderate
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Patients receiving gabapentin should be instruct hours of taking gabapentin due to the potential to decrease the effectiven
7) Probable Mechanism: decreased gabapentin bioavailability

3.5.1.F Evening Primrose
1) Interaction Effect: reduced anticonvulsant effectiveness
2) Summary: Theoretically, evening primrose oil may reduce the effective lowering the seizure threshold. Evening primrose oil is contraindicated in 1998; Newall et al, 1996).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Avoid concomitant use of evening primrose oil w
7) Probable Mechanism: evening primrose oil may reduce the seizure thr

3.5.1.G Ginkgo
1) Interaction Effect: decreased anticonvulsant effectiveness
2) Summary: In a case report, 2 patients with epilepsy previously well co developed a recurrence of seizures after ingesting ginkgo extract. Seizure ginkgo was withdrawn (Granger, 2001a). An infant developed seizures aft

methylpyridoxine arising from ingestion of ginkgo seeds (Yagi et al, 1993a
methylpyridoxine, a neurotoxin, is found in ginkgo seeds (used as food in
ginkgo component from which commercially available extracts are derivec
majority of ginkgo leaf products should not contain sufficient amounts of 4
seizures. However, ginkgo products are not commonly assayed to assure
contained in the commercial product. Of concern are those instances whe
season and the potential introduction of contamination, 4'-O-methylpyrido
amounts to be problematic in vulnerable populations (eg, infants or those
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Avoid concomitant use of ginkgo and anticonvul
seizures occur for the first time or recur in patients previously controlled b
inquire about the use of ginkgo seed or leaf extract. If possible, an assay
specific product to ascertain if 4'-O-methylpyridoxine is present.
7) Probable Mechanism: neurotoxin 4'-O-methylpyridoxine (found in leav
may cause seizures
8) Literature Reports
a) The serum of a 21-month-old patient with gin-nan food poisoning
methylpyridoxine levels. The serum concentration was 0.9 microgram
after ingesting ginkgo seeds, decreasing to 0.05 mcg/mL at 15.5 hou
the 4'-O-methylpyridoxine content was responsible for the tonic/clonic
consciousness observed. They further observed that infants are parti
1993).
b) Four to six milligrams of the neurotoxin 4'-O-methylpyridoxine hav
of Ginkgo biloba leaves which is the source of commercially-available
found in seeds (85 micrograms (mcg)/seed) and leaves (5 mcg/leaf)
July and beginning of August. The albumen of the seed can contain 1
this is reduced to 0.75-1.32 mcg/gram dry weight when boiled. The u
from 5.44-7.15 mcg/gram dry weight. The neurotoxin in ginkgo leaf w
was even detectable in homeopathic preparations. Specifically, 8.13
was found in Tebonin Forte(R), 9.77 mcg/mL in Rokan(R), 3.80 mcg/
mcg/mL in Gingium(R). Based on recommended daily intake, this tra
intake of 4'-O-methylpyridoxine of 48.78 mcg, 58.62 mcg, 11.40 mcg,
(R), Rokan(R), Kaveri Forte(R), and Gingium(R), respectively. Among
Ginkgo biloba Urtinktur Hanosan(R) and Ginkgo biloba Urtinktur DHU
0.589 mcg/mL of 4'-O-methylpyridoxine, respectively. However, the a
contained in medicinal extracts of ginkgo leaves may be too low to be
remains with the variance in 4'-O-methylpyridoxine content dependin
ginkgo was harvested (Arenz et al, 1996).
c) Seizures recurred in 2 patients, both with epilepsy that was well c
biloba (Gb). The patients (an 84-year-old woman and a 78-year-old n
at least 18 months prior to beginning therapy with Gb 120 milligrams
Both patients developed seizures within 2 weeks of beginning Gb the
free (without changing anticonvulsant therapy) after discontinuing Gb

3.5.1.H Hydrocodone

1) Interaction Effect: decreased bioavailability of hydrocodone
2) Summary: Coadministration of gabapentin and hydrocodone has been
concentration and area under the curve (AUC) values of hydrocodone in a
minimally increase gabapentin AUC (Prod Info NEURONTIN(R) oral table
2007). Therefore, caution is advised if these agents are coadministered a
monitored for lack of hydrocodone efficacy.
3) Severity: minor
4) Onset: unspecified
5) Substantiation: established
6) Clinical Management: Concomitant use of gabapentin and hydrocodor
peak concentration of hydrocodone in a dose-dependent manner; gabape
(Prod Info NEURONTIN(R) oral tablets, oral capsules, oral solution, 2007
coadministered and consider monitoring patients for lack of hydrocodone
7) Probable Mechanism: unknown
8) Literature Reports
a) Coadministration of gabapentin 125 to 500 mg (n=48) and hydroc
the Cmax and AUC values of hydrocodone in a dose-dependent fash
of hydrocodone alone. Following administration of gabapentin 125 m
hydrocodone decreased by 3% and 4%, respectively. After a gabape
hydrocodone Cmax and AUC were 21% and 22% lower, respectively

increased by 14% with concomitant use of hydrocodone and gabapen
interaction is not known (Prod Info NEURONTIN(R) oral tablets, oral

3.5.1.I Magaldrate

1) Interaction Effect: decreased gabapentin effectiveness
2) Summary: The manufacturer reports that an antacid (Maalox(R)) given reduced gabapentin bioavailability by 20%. Bioavailability was reduced by given two hours after the antacid. Therefore, gabapentin should be admin antacid (Prod Info Neurontin(R), 2002).
3) Severity: moderate
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Patients receiving gabapentin should be instruct hours of taking gabapentin due to the potential to decrease the effectiven
7) Probable Mechanism: decreased gabapentin bioavailability

3.5.1.J Magnesium Carbonate

1) Interaction Effect: decreased gabapentin effectiveness
2) Summary: The manufacturer reports that an antacid (Maalox(R)) given reduced gabapentin bioavailability by 20%. Bioavailability was reduced by given two hours after the antacid. Therefore, gabapentin should be admin antacid (Prod Info Neurontin(R), 2002).
3) Severity: moderate
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Patients receiving gabapentin should be instruct hours of taking gabapentin due to the potential to decrease the effectiven
7) Probable Mechanism: decreased gabapentin bioavailability

3.5.1.K Magnesium Hydroxide

1) Interaction Effect: decreased gabapentin effectiveness
2) Summary: The manufacturer reports that an antacid (Maalox(R)) given reduced gabapentin bioavailability by 20%. Bioavailability was reduced by given two hours after the antacid. Therefore, gabapentin should be admin antacid (Prod Info Neurontin(R), 2002).
3) Severity: moderate
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Patients receiving gabapentin should be instruct hours of taking gabapentin due to the potential to decrease the effectiven
7) Probable Mechanism: decreased gabapentin bioavailability

3.5.1.L Magnesium Oxide

1) Interaction Effect: decreased gabapentin effectiveness
2) Summary: The manufacturer reports that an antacid (Maalox(R)) given reduced gabapentin bioavailability by 20%. Bioavailability was reduced by given two hours after the antacid. Therefore, gabapentin should be admin antacid (Prod Info Neurontin(R), 2002).
3) Severity: moderate
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Patients receiving gabapentin should be instruct hours of taking gabapentin due to the potential to decrease the effectiven
7) Probable Mechanism: decreased gabapentin bioavailability

3.5.1.M Magnesium Trisilicate

1) Interaction Effect: decreased gabapentin effectiveness
2) Summary: The manufacturer reports that an antacid (Maalox(R)) given reduced gabapentin bioavailability by 20%. Bioavailability was reduced by given two hours after the antacid. Therefore, gabapentin should be admin antacid (Prod Info Neurontin(R), 2002).
3) Severity: moderate
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Patients receiving gabapentin should be instruct hours of taking gabapentin due to the potential to decrease the effectiven
7) Probable Mechanism: decreased gabapentin bioavailability

3.5.1.N Morphine

1) Interaction Effect: an increase in gabapentin plasma concentrations
2) Summary: Patients who require concomitant treatment with morphine gabapentin concentrations (Prod Info Neurontin(R), 2002a).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Patients should be carefully observed for signs somnolence or dizziness. The dose of gabapentin or morphine should be
7) Probable Mechanism: additive CNS depression

3.5.1.O Morphine Sulfate Liposome

1) Interaction Effect: an increase in gabapentin plasma concentrations
2) Summary: Patients who require concomitant treatment with morphine gabapentin concentrations (Prod Info Neurontin(R), 2002a).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Patients should be carefully observed for signs somnolence or dizziness. The dose of gabapentin or morphine should be
7) Probable Mechanism: additive CNS depression

3.5.3 Drug-Lab Modifications

3.5.3.A Urine total protein measurement

1) Interaction Effect: false-positive urine protein measurement using Ame
2) Summary: In patients receiving gabapentin with other antiepileptic dru measurements with the Ames N-Multistix SG(R) dipstick test have been n of urine protein in patients on gabapentin therapy, the more specific sulfos procedure is recommended (Prod Info NEURONTIN(R) oral capsules, sol
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: False-positive readings for urinary protein have Multistix SG(R) dipstick test when gabapentin was used in conjunction wit the more specific sulfosalicylic acid precipitation procedure is recommend patients receiving gabapentin (Prod Info NEURONTIN(R) oral capsules, s
7) Probable Mechanism: mechanism unknown

4.0 Clinical Applications

4.1 Monitoring Parameters

A) Therapeutic

1) Laboratory Parameters

a) There is no well-defined therapeutic range for GABAPENTIN and optir not been established.

b) In women who plan on becoming pregnant, obtaining concentrations c pregnant and during the pregnancy may be beneficial. Although, therapeu established, prepregnancy concentrations in an optimally-treated woman for comparison to concentrations during pregnancy, when concentrations

2007).
2) Physical Findings
a) Reduction in seizure frequency
B) Toxic
1) Laboratory Parameters
a) Routine monitoring of clinical laboratory parameters is not recommend
2) Physical Findings
a) Data reviewed by the US Food and Drug Administration suggest an in
or ideation may exist in patients receiving therapy with antiepileptic drugs
suicidality was noted at 1 week after starting an AED and continued to at
for epilepsy, psychiatric disorders, or other conditions were all at an increa
to placebo. Closely monitor patients treated with AEDs for emergence or
suicidality, and other unusual changes in behavior, which may include syr
hostility, mania, and hypomania (US Food and Drug Administration, 2008

4.2 Patient Instructions

A) Gabapentin (By mouth)

Gabapentin

Controls certain types of seizures in people who have epilepsy. Also treats pai
shingles (postherpetic neuralgia).

When This Medicine Should Not Be Used:
You should not use this medicine if you have ever had an allergic reaction to g

How to Use This Medicine:
Capsule, Tablet, Liquid
Your doctor will tell you how much of this medicine to take and how often.
take it more often than your doctor tells you to.
You may take this medicine with or without food.
Do not allow more than 12 hours between doses.
Measure the oral liquid medicine with a marked measuring spoon or medi
When used to treat seizures, gabapentin is usually taken with other anticc
other medicines your doctor has prescribed as part of your combination tr

If a Dose is Missed:
If you miss a dose or forget to take your medicine, take it as soon as you
next dose, wait until then to take the medicine and skip the missed dose.
Do not use extra medicine to make up for a missed dose.

How to Store and Dispose of This Medicine:
Store the medicine at room temperature, away from heat, moisture, and d
the refrigerator. Do not freeze.
Keep all medicine out of the reach of children and never share your medic

Drugs and Foods to Avoid:
Ask your doctor or pharmacist before using any other medicine, including over
and herbal products.
Make sure your doctor knows if you are also using morphine or hydrocodc
If you take an antacid (such as Maalox®), wait at least 2 hours before taki

Warnings While Using This Medicine:
Make sure your doctor knows if you are pregnant or breastfeeding, or if yc
Do not stop using this medicine suddenly without asking your doctor. You
your dose before stopping it completely.
This medicine may make you dizzy or drowsy. Avoid driving, using machi
could be dangerous if you are not alert.
If you have a test done for protein in your urine, tell the healthcare provide

Possible Side Effects While Using This Medicine:
Call your doctor right away if you notice any of these side effects:
Allergic reaction: Itching or hives, swelling in face or hands, swelling or tin
tightness in chest, trouble breathing
Clumsiness, problems with coordination
Extreme tiredness, slurred speech
Uncontrolled eye movement

If you notice these less serious side effects, talk with your doctor:
Behavior problems, hostility, restlessness, trouble concentrating, moodine
Blurred or double vision
Fever, cough, sneezing, sore throat, stuffy nose (especially in children)
Nausea, vomiting (especially in children)
Rapid weight gain
Shakiness
Swelling in your hands, ankles, or feet

If you notice other side effects that you think are caused by this medicine, tell

4.3 Place In Therapy

A) Gabapentin has been demonstrated effective as an add-on anticonvulsant age partial seizures. The drug also appears effective in generalized seizures. Adverse gabapentin have been minimal. The ultimate place in therapy of gabapentin will de controlled add-on studies comparing the efficacy and safety of the drug with other

B) One potential advantage of gabapentin over other antiepileptic agents is its app most common adverse effects of the drug have been drowsiness, fatigue, and dizz hematologic, hepatic, or renal function tests have been observed, and the drug doe significantly with concomitant antiepileptic regimens. In 1 small study, gabapentin u no adverse effects on cognition (Mortimore et al, 1998).

4.4 Mechanism of Action / Pharmacology

A) MECHANISM OF ACTION

1) Gabapentin is an amino acid structurally-related to the inhibitory neurotrans (GABA); however, its antiepileptic activity appears unrelated to any direct effec (Andrews & Fischer, 1994).

2) Animal studies have demonstrated the anticonvulsant activity of gabapentii by interference with GABAergic transmission or provoked by excitatory amino al, 1987). Although gabapentin appears to possess GABA-mimetic properties mechanism of action remains unclear. The drug has no significant effect on G not bind to GABA or benzodiazepine receptors or influence the neural uptake pharmacologically active doses (Crawford et al, 1987; Sivenius et al, 1991). In 1996) in which in vivo measurements of GABA in human brain were made usi spectroscopy, occipital lobe concentrations were higher in patients taking gab that gabapentin increases GABA synthesis. An effect of gabapentin on central been postulated by some investigators (Rao et al, 1988).

3) GABA is the major inhibitory neurotransmitter in the central nervous systen transmission is involved in the pathogenesis of epilepsy (AMA Department of addition to valproic acid, several other agents have been developed in an effo inhibition, including progabide (GABA prodrug and GABA agonist) (Crawford & (GABA transaminase inhibitor) (Rimmer & Richens, 1984; Gram, 1988). The r of epilepsy will ultimately depend upon how well it compares with all of these a

4) The analgesic action of gabapentin has been demonstrated in animal mode prevented allodynia and hyperaglesia. Pain related responses in neuropathic p inflammation models were prevented or decreased by gabapentin. Immediate altered. The mechanism by which gabapentin exerts its analgesic effects is un 2003).

B) REVIEW ARTICLES

1) Dosages and formulations of antiepileptic drugs used to treat pediatric epil (Bourgeois, 2002).

2) Basic reviews of the treatment of seizures have been written; these include status epilepticus (Willmore, 1998), treatment of the elderly (Rowan, 1998), an adults (Feely, 1999; Mattson, 1998). Pediatric seizure management has also b Pellock, 1998).

3) With the addition of the newer antiepileptic drugs, polypharmacy in epilepsy (Schneiderman, 1998; Guberman, 1998).

4) Reviews on the use of gabapentin for bipolar disorder have been published Botts & Raskind, 1999).

5) The role of gabapentin for pain management has been discussed (Wetzel &

6) Reviews of the pharmacology and clinical use and safety of gabapentin are Ramsay, 1994).

7) Reviews of newer antiepileptic medications, including a summary of clinica recommendations for use, are available (Bauer, 1997 (German)). (Dichter & B

4.5 Therapeutic Uses

Acute intermittent porphyria - Seizure

Alcohol withdrawal syndrome

Amyotrophic lateral sclerosis

Antineoplastic adverse reaction, Taxane - Myalgia

Bipolar disorder

Cancer pain - Neuropathic pain

Charles Bonnet syndrome

Ciguatoxin causing toxic effect

Clozapine adverse reaction - Drug-induced epilepsy

Cluster headache

Cocaine dependence

Complex regional pain syndrome, type I - Pain

Dementia

Dementia - Problem behavior

Diabetic peripheral neuropathy

Essential tremor

Fibromyalgia

Generalized seizure

Hemifacial spasm

Hiccoughs, Intractable

Hot sweats

Intracranial tumor - Seizure

Mania

Migraine; Prophylaxis

Multiple sclerosis, Complications

Neuropathic pain

Neuropathy due to human immunodeficiency virus

Nystagmus

Orthostatic tremor

Panic disorder

Partial seizure

Partial seizure, Refractory

Partial seizure; Adjunct

Phantom limb syndrome

Postherpetic neuralgia

Postoperative pain

Priapism

Pruritus

Restless legs syndrome

Sensory disorder

Shortlasting, unilateral, neuralgiform pain with conjunctival injection and tearing sy

Social phobia

Spasticity

Spinal muscular atrophy

Tardive dyskinesia

Tinnitus

4.5.A Acute intermittent porphyria - Seizure

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RA

2) Summary:

Appears to be safe when used in patients with porphyria (Zadra et al, 199

3) Adult:

a) A 23-year-old woman was safely treated with gabapentin 1200 milligra associated with acute intermittent porphyria (Zadra et al, 1998). She beca abdominal pains. She had previously experienced attacks while on pheny valproate.

4.5.B Alcohol withdrawal syndrome

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RA

2) Summary:

In a randomized, double-blind trial (n=100), high-dose gabapentin led Institute Withdrawal Assessment for Alcohol-revised (CIWA-Ar) score outpatients with alcohol withdrawal (Myrick et al, 2009).
In a randomized, double-blinded, placebo-controlled trial, gabapentin reducing the amount of rescue medications received in the first 24 ho Mainz Alcohol Withdrawal Scores (MAWS), or in reducing the numbe discontinuations within the first 48 hours of therapy in patients with al to severe alcohol withdrawal syndrome (Bonnet et al, 2003).

3) Adult:

a) In a randomized, double-blind trial (n=100), high-dose gabapentin led Institute Withdrawal Assessment for Alcohol-revised (CIWA-Ar) scores co outpatients with alcohol withdrawal. Patients with alcohol dependence and and Statistical Manual of Mental Disorders Fourth Edition (DSM-IV) criteri score of 26 or higher, and a CIWA-Ar score of 10 or greater who voluntee withdrawal received 4 days of gabapentin or lorazepam. One of the follow gabapentin were administered: 1) 200 milligrams (mg) 3 times daily for 3 day 4 (600 mg arm; n=16); 2) 300 mg 3 times daily for 3 days, then 300 m arm; n=28; mean age, 38.4 +/- 1.82 years (yr); mean drinks/day in previou or 3) 400 mg 3 times daily for 3 days, then 400 mg twice daily on day 4 (h 40.5 +/- 2.25 yr; mean drinks/day in previously 14 days, 16.8 +/- 2.18 drin was discontinued after one near syncopal event and 2 patient-reported se patients in this arm were not included in the final analysis. The lorazepam administered as 2 mg 3 times daily for 3 days, then 2 mg twice daily on da 1.83 yr; mean drinks/day in previously 14 days, 11.4 +/- 1.11 drinks). CIW daily during the medication phase and on 1, 2, and 7 days posttreatment received oral thiamine 100 mg daily for 12 days. Patients could take blind gabapentin or lorazepam as needed on days 1 to 4 to treat subjective syn there were no significant differences (p=0.75) in supplemental medication lorazepam-treated patients. The mean CIWA-Ar score was significantly lo arm but not the low-dose gabapentin arm compared with the lorazepam a (gabapentin: low-dose, 4.52 +/- 39 (standard error (SE)); high-dose, 3.14 0.38 (SE); high-dose gabapentin versus (vs) lorazepam p less than 0.05) (gabapentin: low-dose, 1.79 +/- 0.32 (SE); high-dose, 1.03 +/- 0.31 (SE); high-dose gabapentin vs lorazepam p less than 0.01). Mean alcohol cravi analog scale of zero millimeters (mm) (no discomfort) to 100 mm (greates less than 0.05) lower in patients who received gabapentin (gabapentin: lo dose, 28.73 +/- 4.6 (SE)) compared with lorazepam (42.7 +/- 4.7 (SE)) du however, alcohol craving scores were not significantly different between th phase (gabapentin: low-dose, 13.9 +/- 5.3 (SE); high-dose, 20.4 +/- 4.8 (S Mean anxiety scores (evaluated using the Zung Anxiety Scale) were signi patients who received gabapentin (gabapentin: low-dose, 32.11 +/- 1.74 ((SE)) compared with lorazepam (36.98 +/- 1.5 (SE)) during the medicatior score was significantly (p less than 0.01) improved in the high-dose gabap gabapentin arm compared with lorazepam arm during the follow-up phase 1.3 (SE); high-dose, 28.8 +/- 1.2 (SE); lorazepam: 33.9 +/- 1.1 (SE)). Duri in the low-dose gabapentin arm had significantly (p less than 0.01) improv (BDI) scores and patients in the high-dose gabapentin arm had significant sleep scores evaluated using the Epworth Sleepiness Scale compared wi The incidence of patient-reported adverse effects did not differ between th arms (p=0.74) (Myrick et al, 2009).

b) Gabapentin was not better than placebo in reducing the amount of res first 24 hours of treatment, in decreasing patient's Mainz Alcohol Withdrav reducing the number of premature trial discontinuation within the first 48 h treat alcohol withdrawal. A double-blinded, randomized, placebo-controlle milligrams 4 times daily (n=32) with placebo (n=29) in patients with alcoho severe alcohol withdrawal syndrome (as defined by a MAWS greater than administered full doses for 3 days and then treatments were tapered dow of rescue medication (clomethiazole) doses required in the first 24 hours gabapentin and placebo arms, respectively (p=0.96). The differences betv not statistically different in the first 48 hours of the study (p=0.4). Frequen statistically different between treatment arms (p=0.74). However, nausea frequently with the use of gabapentin. Mean gabapentin levels were 4.63, micrograms/milliliter at day 1, 2, and day 5, respectively (Bonnet et al, 20(

c) Six patients were successfully treated with gabapentin for alcohol with patients had an average score of 17 on the Clinical Institute Withdrawal fo R, 10 or higher indicates moderate withdrawal). Gabapentin 400 milligram the first 3 days, followed by 400 mg twice daily for 1 day, and 400 mg dail

decreased on the CIWA-R to 11 on day 1, 2 on day 2, and 0 on day 3.
d) A 38-year-old man with obsessive-compulsive disorder (OCD) and alc
craving after being treated with gabapentin (Chatterjee & Ringold, 1999).
his paroxetine to augment his OCD therapy. Gabapentin was started at 3(
increased to 1200 mg 3 times daily over 2 months. He stopped drinking w
approximately 3 weeks after beginning gabapentin. His avoidant OCD bel

4.5.C Amyotrophic lateral sclerosis

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RAT

2) Summary:

Possible efficacy was found in a phase II study (Miller et al, 1996); howev
gabapentin therapy in a follow-up phase III study (Miller et al, 2001)

3) Adult:

a) A 9-month course of oral gabapentin failed to provide beneficial effects
lateral sclerosis (ALS), according to a controlled, multicenter phase III tria
Enrollees were randomized to placebo (n=96) or gabapentin 1200 milligra
months (gabapentin titrated over 4 to 6 weeks to total 3600 mg/day). The
decline was not significantly different between groups (maximum voluntar
arm muscles measured bilaterally for shoulder and elbow flexion and exte
0.021 units/week; gabapentin group minus 0.020 units/week. There were
differences on the ALS Functional Rating Scale (p=0.2), rapid foot tap exe
protocol (p=0.17). ALS symptoms (such as cramps, fasciculations, stiffnes
gabapentin, nor was the mortality rate (deaths: 7 placebo, 6 gabapentin).
more frequently in the gabapentin group were lightheadedness, drowsines
difference in dropout rates occurred across the 2 groups. The results of th
phase II trial in which gabapentin 2400 mg/day appeared to slow the rate
et al, 1996).
b) In a randomized, double-blinded study of 117 patients, gabapentin wa
of arm strength (as measured by mean arm score) in patients with amyotr
compared to placebo, although the difference was not statistically significa
gabapentin was 800 milligrams 3 times daily over the course of 6 months
well tolerated. Gabapentin was not found to have any effect on forced vita

4.5.D Antineoplastic adverse reaction, Taxane - Myalgia

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RAT

2) Summary:

Effective in 2 case reports (van Deventer & Bernard, 1999)

3) Adult:

a) Gabapentin successfully allowed the continuation of 2 taxane-based c
been limited by the development of severe myalgias (van Deventer & Ber
48-year-old woman with breast cancer with pulmonary nodules developec
arms, back and neck after 2 cycles of paclitaxel. She had no improvemen
acetaminophen. Gabapentin 400 milligrams (mg) 3 times daily on the day
then for 4 to 5 days afterward significantly improved her symptoms. The s
woman with uterine leiomyosarcoma who developed pulmonary and hepa
with docetaxel but by the fourth cycle she developed grade III myalgias. T
acetaminophen and dexamethasone. Gabapentin 300 mg twice daily beg
and continuing to the eighth day dramatically improved her symptoms.

4.5.E Bipolar disorder

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RAT

2) Summary:

Demonstrates efficacy in bipolar disorder in case reports, retrospectiv
(Cabras et al, 1999; Ghaemi et al, 1998; Sheldon et al, 1998; Schaffe
Further case-controlled studies are warranted

3) Adult:

a) In this open-label, safety and varying dosage study, gabapentin was fc
mania and hypomania in patients with bipolar and schizoaffective disorde
(n=22) were initially started on gabapentin 300 milligrams/day (mg/day). D
every 4 days as tolerated to a maximum daily dose of 2400 mg/day. The r
mg/day. Any benzodiazepines and neuroleptics were continued at a cons
Mood stabilizers such as lithium, carbamazepine, and valproate were tape
compared to baseline, significant reductions were seen in Clinical Global
versus 2.1; p less than 0.0001) and Brief Psychiatric Rating Scale (BPRS
than 0.0001) after 16 weeks of treatment. Sedation was the most commor
improved with continued treatment.

b) In a naturalistic and retrospective study, gabapentin add-on therapy w
of patients with mood disorders (Ghaemi et al, 1998). Patients suffered fr
disorder (n=10), bipolar disorder type I (n=13), bipolar disorder type II (n=
otherwise specified (NOS) (n=8). Moderate or marked response on the Cl
Improvement scale was seen in 30% of patients. Patients with bipolar disc
response with 11 out of 27 patients (41%) improving. Response rates for
out of 13 (15%) and for unipolar major depressive disorder were only 2 ou
responses between the groups were not clinically significant.

c) A 73-year-old woman with severe bipolar disorder benefited from gaba
1998). She had been unable to tolerate lithium and valproate. Gabapentin
twice daily. She did well on a combination of gabapentin, venlafaxine, anc

d) In an open study, a positive response to gabapentin therapy was dem
patients. All patients had been refractory to standard mood stabilizing dru
combination with other medicines including antianxiety agents, antidepres
anticonvulsants. The response was judged by both the treating psychiatris
Schaffer, 1997).

4.5.F Cancer pain - Neuropathic pain

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RAT

2) Summary:

Effective in case reports (Caraceni et al, 1999)

3) Adult:

a) Gabapentin provided pain relief in most patients with neuropathic canc
analgesics (Caraceni et al, 1999). Consecutive cancer patients with neuro
treated with gabapentin doses of 600 to 1200 milligrams added to their op
scales for the assessment, global pain scores, burning pain intensity, and
decreased. In 9 patients with allodynia, 7 patients reported disappearance
Twenty out of 22 patients judged gabapentin as efficacious in reducing the

4.5.G Charles Bonnet syndrome

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RAT

2) Summary:

A case of Charles Bonnet syndrome resolved with low-dose gabapentin th

3) Adult:

a) Complex visual hallucinations completely remitted after use of gabape
a diagnosis of Charles Bonnet's syndrome. The patient had a 10-year hist
degeneration, and for 2 years, she had experienced persistent and daily v
hallucinations included visions of medieval women, knights in bright colors
or torsos; they occurred most frequently in the morning and evening, only
moved when her eyes moved. The patient had no psychiatric history and
her visions. Her medications included an angiotensin II antagonist and diu
hypertension, and pain killers (tilidine) for polyarthrosis. She had tried per
treat her hallucinations, but without effect. Electroencephalography and cr

abnormalities. Gabapentin 300 milligrams/day was initiated. The patient e
episode on each of the next 2 days. After that, the hallucinations stopped.
further episodes of hallucinations were reported, no visual deterioration ha
caused no side effects (Paulig & Mentrup, 2001).

4.5.H Ciguatoxin causing toxic effect

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RAT

2) Summary:

Symptomatic improvement in 2 cases (Perez et al, 2001)

3) Adult:

a) Two patients, stricken with ciguatera poisoning, had significant improv
with GABAPENTIN. The patients were a 30 year-old woman and a 37-yea
dusky grouper in the Dominican Republic and both were disabled for wee
neurotoxin. The first patient had an episode of diarrhea, followed in severa
intense pruritus of the hands, legs, and breasts, especially with exposure
generalized pruritus and sharp, shooting pains in her legs. Gabapentin 40
was begun a month after the onset of symptoms. Improvement was rapid.
stopped. Within a few hours, both women had a return of symptoms; on re
relief occurred. Gabapentin was given for an additional 21 days. After the
the first patient had only minor dysesthesia and the second patient had sc
continue the medication (Perez et al, 2001).

4.5.I Clozapine adverse reaction - Drug-induced epilepsy

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RAT

2) Summary:

Gabapentin prevented clozapine-induced seizures in a 65-year-old, chron
2001)

3) Adult:

a) Gabapentin was effective as a prophylactic agent in the prevention of
year-old chronic schizophrenic women, with no prior history of seizures, h
medication regimen of haloperidol 10 milligrams (mg) per day and procycl
four week period clozapine was gradually increased to 37.5 mg daily. The
clonic seizure 2 days after the last increase in dose and the clozapine was
mg/day, was added prophylactically to prevent seizures and the clozapine
mg per day. Due to a lack of therapeutic response the clozapine was to be
clozapine taper, gabapentin was also decreased to 600 mg/day due to co
day the patient had a second tonic-clonic seizure and the clozapine was w

4.5.J Cluster headache

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RAT

2) Summary:

Mitigated cluster headache in one case refractory to other agents (Ta
Further study is needed

3) Adult:

a) Oral gabapentin provided complete relief of cluster headache in a 38-y
had been only slightly diminished with other therapeutic agents; gabapent
for prophylaxis of his headaches. The patient had a 24-year history of hea
by neurologists who diagnosed cluster headache, according to criteria of t
Society. His right-sided headaches occurred in a temporal pattern, only in
warm to cold weather. The 2-hour headache episodes typically appeared
going to bed, and continued for a period of 14 to 21 days. Amitriptyline, m
blockers, phenytoin, and indomethacin brought some partial relief (on a sc

from 100 to between 70 and 85). Gabapentin 300 milligrams twice daily w
after the time his headaches had begun. After 2 doses, his pain had decre
possible 100), and after 3 doses, he experienced complete resolution of p
gabapentin successfully aborted his headaches. The fourth year, the patie
gabapentin (300 mg twice daily) before November, and had no headache
headache period. The only side effect was transient drowsiness. The auth
in additional patients before gabapentin can be recommended for cluster

4.5.K Cocaine dependence

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RAT

2) Summary:

Possibly reduces cocaine craving and use in cocaine-dependent patients
2001) (Raby, 2000)

3) Adult:

a) Investigators from a 24-week, open-label trial reported that the averag
urine screens decreased in patients with cocaine dependence treated with
initiated as 200 milligrams (mg) twice daily for 2 days, then increased to 4
600 mg twice daily for 2 days, and then increased to 1200 mg twice daily.
800 to 2400 mg/day. Of the original 11 patients, 2 dropped out after week
Seven of the 9 remaining patients also participated in a structured substa
were obtained up to 3 times a week as part of the substance use program
considered to be cocaine positive and the average proportion of missed s
and 21% during treatment (p greater than 0.5). Baseline urine screens we
to starting gabapentin and were cocaine positive an average of 53.11 time
were collected in the 24 weeks after gabapentin initiation and were cocair
less than 0.01 when compared to baseline). Sedation was reported in 2 p

b) Oral GABAPENTIN therapy was apparently well-tolerated and may re
cocaine use in some cocaine- dependent subjects (DSM-IV), based on a
al, 2001). Gabapentin was initiated as 300 milligrams (mg) twice daily for
twice daily, for a course of therapy expected to last for 8 weeks. Of 30 sub
return after week 1; of 18 remaining, 14 completed week 4, and 6 comple
completed week 4 were included in the intent-to- treat analysis. Eighty-six
14) were positive for cocaine at baseline compared to 29% (4 of 14) at we
frequency of cocaine craving decreased from baseline to week 8 (78% to
frequency; p=0.004). Mean number of days till relapse was 21 days. The
were transient nausea and sedation, which occurred in 1 subject each. Th
subject-retention rate.

c) Two cocaine users experienced markedly reduced cravings for cocain
gabapentin therapy (Raby, 2000). A 42-year-old man had been addicted t
to heroin since the age of 28. His treatment for drug withdrawal had includ
imipramine for depression (75 to 300 milligrams (mg)/day). He continued
especially in times of difficulties. While continuing imipramine (200 mg/da
titration over a week to 400 mg twice daily (serum concentration 12.4 mg/
cocaine had disappeared. A 31- year-old woman was diagnosed with schi
abuse. Bimonthly injections of fluphenazine 50 mg controlled her psychoti
(up to 20 mg/day) was also given as supplementation to control auditory h
use of crack cocaine. She began gabapentin and reached a dose of 1200
mg/L). Over a 9-month course of gabapentin, her only relapse was a one-
cigarettes. Neither patient reported significant side effects, such as ataxia
postulated to restore the GABA- mediated inhibitory feedback action of nu
ascending mesolimbic dopaminergic neurons, resulting in decreased activ
projecting to the nucleus accumbens (a site identified with addictive beha

4.5.L Complex regional pain syndrome, type I - Pain

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy; Pediatric, Evidence favors e
Recommendation: Adult, Class IIb; Pediatric, Class IIb
Strength of Evidence: Adult, Category C; Pediatric, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RAT

2) Summary:

Patients experience dramatic results in pain associated with reflex sy

Mellick, 1997; McGraw & Kosek, 1997)
Controlled studies are needed to define the role for REFLEX SYMPA

3) Adult:

a) In a case series, 6 patients who had experienced years of severe, intra multiple treatments including nerve blocks and drug therapy for their reflex experienced dramatic results with gabapentin therapy (Mellick & Mellick, 1 900 milligrams (mg) per day, however, some patients required higher dos Specific improvements were reduced hyperpathia, allodynia, hyperalgesia soft tissue manifestations.

4) Pediatric:

a) Two cases of improved pain relief in patients with REFLEX SYMPATH described including one of a 9-year-old girl (McGraw & Kosek, 1997). She her feet which was initially treated with gabapentin 100 mg three times pe mg three times daily for 4 months. At that time the medication was tapere for 6 months.

4.5.M Dementia

See Drug Consult reference: BEHAVIORAL AND PSYCHOLOGICAL SYMPT

4.5.N Dementia - Problem behavior

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RAT

2) Summary:

Gabapentin use improved behavioral symptom scores in 20 patients dementia
Effective in case reports of disruptive behavior and agitation

3) Adult:

a) Gabapentin use in 20 patients with probable Alzheimer's and dementia as measured with the Neuro-Psychiatric Inventory and the Cohen-Mansfie 15 months of therapy. Patients were between 68 and 76 years old (mean with dementia (DSM IV) and probable Alzheimer's. Patients had been trea therapy (donepezil or rivastigmine) for a mean duration of 8.8 months. Ag with delusions had become evident an average of 6 months after the initia therapy. Gabapentin was initiated at 100 milligrams (mg) twice daily. After was titrated to 300 mg twice daily and then after 2 weeks, 300 mg three ti gabapentin was 980 mg daily. The NeuroPsychiatric Inventory (NPI) and Inventory (CMAI) were used to assess behavioral symptoms. At 7 months scores had improved significantly (p less than 0.001 for both measures). S demonstrated significant improvements in agitation, anxiety, apathy, aggr disturbance scores (p less than 0.05). However, hallucination, depression eating disturbances scores were not significantly changed. Sedation and adverse events reported (Moretti et al, 2003)(Pers Comm, 2004).

b) In a case series, gabapentin was associated with at least minimal impr for the treatment of behavioral disorders in dementia (Herrmann et al, 200 years, with behavioral problems and Alzheimer's disease (n=7), vascular dementia (n=1), or alcoholic dementia (n=1) received gabapentin at an ini twice daily. Over 8 weeks, gabapentin was given in doses ranging from 2 (average dose was 900 mg/day). Two patients completed only 2 weeks of emergent adverse events. Utilizing the Neuropsychiatric Inventory and the Inventory, 2 patients were rated as much improved, 3 as minimally improv minimally worse after 8 weeks. Adverse events included gait instability, se sweating. The authors concluded that there may be a subgroup of patient that might respond to gabapentin.

c) Improvement with gabapentin therapy was reported in 4 patients with (Roane et al, 2000). Three of the patients had Alzheimer's disease and 1 was used in doses of 300 to 2400 milligrams daily. Clinical improvement cursing, threatening, moaning, crying, task perseverating, and hitting. One due to sedation and disorientation. Other adverse effects included headac ambulation.

d) A 62-year-old man with dementia, not otherwise specified, became les gabapentin (Low & Brandes, 1999). He also had a history of cerebrovascu a possible head injury. His other psychiatric medications included haloper trial of paroxetine. He continued to be agitated until gabapentin was starte

(mg) daily and increased to 300 mg 3 times daily. Within 10 days, he beca
e) A 92-year-old woman with disruptive behavior secondary to Alzheimer
gabapentin 200 milligrams every 8 hours (Goldenberg et al, 1998). Her di
as ceaseless vocalization and insomnia with restlessness. Trazodone hac
haloperidol caused increased confusion. During a 2-month follow-up her b
with no adverse effects.
f) Two cases of gabapentin being useful for behavior problems have bee
An 87-year-old male with Alzheimer's disease had his agitation and assau
weeks of receiving gabapentin titrated to 100 milligrams (mg) 3 times daily
Alzheimer's disease exhibited improved functioning with gabapentin titrate
a progressive agitation and displayed behaviors such as striking out.

4.5.O Diabetic peripheral neuropathy

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RAT

2) Summary:

As effective as amitriptyline for the treatment of pain associated with
1 study (Morello et al, 1999a)
Low doses of 900 milligrams/day are only minimally effective (Gorsor

3) Adult:

a) Gabapentin was effective for the treatment of pain and sleep difficulties
peripheral neuropathy (DPN) (Backonja et al, 1998). In a double-blind, 8-v
(mean age 53 years) with painful DPN for 1 to 5 years were randomized t
(n=82) or placebo (n=80). During the first 4 weeks, gabapentin was increa
milligrams (mg) to 3600 mg. Doses were only decreased if intolerable adv
3600 mg/day dose was achieved by 67% of the gabapentin-treated patier
was a daily pain score measured on an 11-point Likert scale. There was a
the gabapentin scores and placebo from week 2 through week 8 (p less th
significant differences seen in mean sleep interference scores at week 1 t
Also using the short-form McGill Pain Questionnaire, gabapentin patients
pain scores (p less than 0.01). The gabapentin group did experience more
dizziness, somnolence, and confusion. This study shows that gabapentin
those patients able to tolerate it.
b) There was no difference as measured by pain scales and global pain s
gabapentin in the treatment of diabetics with peripheral neuropathy pain (
patients with stable glycemic control (n=21) received either gabapentin or
were then crossed-over to the other arm of therapy for 6 weeks with a 1-w
Dosage was adjusted based on the patient's response with gabapentin do
milligrams (mean dose 1565 mg) and amitriptyline doses ranging from 25
Both drugs significantly decreased pain scores from baseline (both p less
provided moderate or greater pain relief in 67% of patients while gabapen
patients (p=0.26). There was no statistically significant difference in occur
the drugs except for increased weight gain with amitriptyline.
c) Gabapentin was only minimally effective for the treatment of painful dia
900 milligrams/day . In a double-blind, crossover trial, patients received ei
and then were crossed-over to the other therapy with a 3-week washout p
by 300 mg every 3 days to a stable dosage of 900 mg daily. Patients were
questionnaire, global assessment of pain relief, a visual analogue scale, a
A significant difference in pain relief with gabapentin over placebo was se
questionnaire (p=0.03). Moderate or excellent pain relief was reported by
6 in placebo only, and 3 with both agents (p=0.11). The authors suggest t
are needed (Gorson et al, 1999).

4.5.P Essential tremor

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RAT

2) Summary:

Mixed results have occurred (Gironell et al, 1999a; Pahwa et al, 1998)

3) Adult:

a) In a comparative, double-blind, crossover, placebo-controlled study, ga three times daily was as effective as propranolol 40 mg three times daily v treatment of patients with essential tremor (Gironell et al, 1999a). Patients initially receive either gabapentin, propranolol, or placebo for a two-week crossed-over to the other 2 arms with a 1-week washout period between t with gabapentin and propranolol treatment were seen in the Tremor Clinic clinical examination and motor task performance as compared to placebo respectively). No differences in self-reported subjective disability scale or from accelerometry were noted between the 3 groups.
b) In a double-blind, placebo-controlled crossover study of 20 patients wi 1800 milligrams (mg) per day was no different than placebo at improving t assessed at baseline and after 2 weeks of therapy using the Fahn-Tolosa Patients were crossed over to the opposite treatment after at least a five d differences in tremor symptoms, patient-rated global disability or global im treatment when compared to baseline. Two patients withdrew from the stu therapy with gabapentin (Pahwa et al, 1998).

4.5.Q Fibromyalgia

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RAT

2) Summary:

In a 12-week, randomized, double-blind, placebo-controlled, multicen 1200 to 2400 milligrams/day was safe and efficacious in the treatmer associated with fibromyalgia in adults (Arnold et al, 2007)

3) Adult:

a) Gabapentin was safe and efficacious in the treatment of pain and othe fibromyalgia in adults in a randomized, double-blind, placebo-controlled, r 90% women; 97% Caucasian) meeting the American College of Rheumat who had a score of 4 or greater on the average pain severity item of the B included. Patients with pain from structural or regional rheumatic disease, arthritis, or autoimmune disease were among those excluded. Patients we oral gabapentin (n=75) or placebo (n=75) for 12 weeks. Gabapentin was i bedtime and titrated weekly for 6 weeks up to a maximum dose of 2400 m 1200 mg at bedtime). Dosage reductions to a minimum 1200 mg/day dos not tolerate 2400 mg/day; however, the study dose was stable for at least Following the 12-week study period, gabapentin was decreased by 300 m median gabapentin dose was 1800 mg/day (interquartile range, 1200 to 2 of acetaminophen or over-the-counter NSAIDs, and occasional use of sed concomitant medications or herbal agents with CNS effects and other ana the study. The primary efficacy outcome measure was pain severity meas (short form) average pain severity score (0-10 scale; 0=no pain, 10=pain response to treatment was defined as a 30% or greater reduction in the B Based on longitudinal analysis, the mean +/- SD BPI average pain severit decreased from 5.7 +/- 1.4 at baseline to 3.2 +/- 2 at 12 weeks in the gaba a decrease from 6 +/- 1.5 at baseline to 4.6 +/- 2.6 at 12 weeks in the plac mean difference between groups for the primary endpoint was -0.86 (95% -0.04; p=0.039). In the intent-to-treat population, the estimated mean diffe primary endpoint was -0.92 (95% CI, -1.75 to -0.71; p=0.015). Intent-to-tre (38/75) of gabapentin-treated patients responded compared to 31% (23/7 (p=0.014). Among secondary endpoints, patients in the gabapentin group reductions compared to placebo in Fibromyalgia Impact Questionnaire tot groups, -8.4; 95% CI, -13 to -3.3; p=0.001), Clinical Global Impression of between groups, -0.66; 95% CI, -1.08 to -0.24; p=0.002), and Medical Ou Index score (difference between groups, -11.5; 95% CI, -18.6 to -4.4; p=0 treatment differences observed in the gabapentin group for depressive sy pressure pain thresholds were not statistically significant compared to pla with gabapentin were mostly mild to moderate and included dizziness (25 lightheadedness (14.7%), which occurred more frequently than with place

4.5.R Generalized seizure

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy

Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RAT

2) Summary:
Demonstrates efficacy as add-on therapy in patients with generalized seiz
et al, 1991b; Crawford et al, 1987b; Crawford et al, 1987b)

3) Adult:
a) GABAPENTIN has shown efficacy in the treatment of secondarily gene
1991b; Crawford et al, 1987b). A reduction in tonic-clonic seizures by 50%
patients in 1 small study (n=11) employing a lower dose of GABAPENTIN
et al, 1987b). A median reduction in tonic-clonic seizures of 36% with GAI
1800 milligrams is reported. A significant reduction in absence seizures w
investigators. Additional placebo-controlled and comparative studies are r
the drug in primary generalized seizures (Bauer, 1987).

4.5.S Hemifacial spasm

1) Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category C
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RAT

2) Summary:
Effective in case reports of hemifacial spasm (Bandini & Mazzella, 1999)

3) Adult:
a) In a series of case reports, gabapentin was effective in 5 patients (34 t
spasm (Bandini & Mazzella, 1999). Patients received gabapentin 900 to 1
improvement of spasms. One patient complained of mild somnolence and
giddiness. Neither discontinued medication due to these effects.

4.5.T Hiccoughs, Intractable

1) Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category C
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RAT

2) Summary:
May be effective as add-on or sole treatment for intractable hiccups (Porz
2000)

3) Adult:
a) Gabapentin partially improved symptoms in 3 cases involving hiccup ir
Two of the 3 patients had previously tried combinations of metoclopramid
chlorpromazine, or haloperidol with mixed success. Gabapentin 300 millig
starting dose in all cases. In 1 case, it was added to metoclopramide and
cases it was started as the sole agent. In all cases, the response was pro
occurred in 2 patients and in 1 patient the hiccup returned 10 days later w
efficacy was not assessed as patients could only be followed between 6 t
b) Clinicians reported 4 cases of IDIOPATHIC CHRONIC HICCUPS in w
occurred after the addition of GABAPENTIN to cisapride and omeprazole
baclofen (Petroianu et al, 2000). The recommended protocol includes initi
milligrams (mg) 3 times daily and omeprazole 20 mg once daily. If this du
times daily would be added, and if the triple therapy fails, gabapentin 400
The therapy, if successful, would be continued for 6 months, then gradual
the 4 reported cases (males; 55, 58, 74, and 75 years of age), medication
unsuccessfully included carbamazepine, promethazine, levomepromazine
meperidine, tiapride, flunitrazepam, nordazepam, clorazepate, amitriptylin
pantoprazole, as well as mistletoe extract, other herbal remedies, and acu

4.5.U Hot sweats

1) Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RAT

2) Summary:

Reduced the frequency and severity of hot flashes in postmenopausa
May be effective in treating tamoxifen-induced hot flashes (Pandya e

3) Adult:

a) Low-dose gabapentin effectively controlled hot flashes in postmenopa double-blind, placebo- controlled trial, women (n=59) experiencing an ave day accompanied by sweating received gabapentin 300 milligrams (mg) t weeks. Following 12 weeks of treatment, gabapentin-treated patients had mean hot flash frequency and a 54% decrease in the mean hot flash com frequency and severity) from baseline as compared with 29% and 31% re (p=0.02 and p=0.01, respectively). After the blinded trial, patients were gi 5-week open-label treatment period in which the gabapentin dose could b Similar results were found in the open- label study. The most common ad somnolence (20%), dizziness (13%), and rash with or without peripheral e 2003).

b) In a randomized, double-blind, placebo controlled trial (n=420), gabap hot flashes in women with breast cancer at a dose of 300 mg three times assigned placebo (n=137), gabapentin 100 milligrams (mg) (n=139), or ga to be taken three times a day for 8 weeks. The mean age of the patients v an average of two or more hot flashes per day and most of them were tak patients kept a journal and reported symptoms severity and duration of th the study and during weeks 4 and 8 of treatment. Evaluable data was ava (119 placebo, 123 gabapentin 300 mg, and 129 gabapentin 900 mg) and placebo, 114 gabapentin 300 mg, and 120 gabapentin 900 mg). A higher from the gabapentin 900 mg group due to side-effects, but only a very sm ineffective treatment. The opposite was found in the placebo group with m treatment not being helpful. It was found that gabapentin 300 mg per day any comparison. There was no significant difference among all the groups episodes. The differences in severity and frequency of hot-flash episodes 900 mg per day group compared to either of the other study groups . The flash severity score from baseline in the placebo, gabapentin 300 mg and -21% (-5.45), -33% (-7.50), and -49% (-9.97), respectively, at week 4 (p=0 7.75) and -46% (-9.94), respectively, at week 8 (p=0.007). The percentag frequency from baseline in the same 3 groups were -18% (1.98), -28% (-2 respectively, at week 4 (p=0.0002), and -15% (-2.25), -30% (-2.86), and - 8 (p=0006). Somnolence or fatigue was the main reason for patients to wi gabapentin 900 mg group (Pandya et al, 2005).

c) In a pilot, non-comparative study, gabapentin decreased the severity, TAMOXIFEN-INDUCED HOT FLASHES. Patients (n=22) were postmeno tamoxifen for breast cancer for at least 1 month who experienced more th Following a 1-week baseline period, gabapentin was administered as 300 1 month. Daily diaries were used to evaluate the hot flashes. Four patient nausea, rash and excessive sleepiness and 2 patients were not evaluable remaining patients, the mean frequency and duration of hot flashes decre 0.001 for both measures). Daily severity scores based upon the number a experienced in a day also decreased 52.6% (p less than 0.001). Of the 16 study, 50% had a complete elimination of hot flashes (Pandya et al, 2004)

4.5.V Intracranial tumor - Seizure

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RAT

2) Summary:

Effective as adjunct therapy in an open trial of patients with refractory intracranial tumors (Perry & Sawka, 1996)
Controlled studies are needed to validate these results

3) Adult:

a) Add-on therapy with GABAPENTIN was effective in an open-label trial refractory seizures associated with intracranial tumors. The majority of pa (glioblastomas, metastases, and malignant astrocytoma). Gabapentin wa 2400 milligrams per day; all of the patients responded with at least a 50% and half of the patients became seizure-free. Most of the patients were al cranial irradiation which may have contributed to improvement in their clin 1996).

4.5.W Mania

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive; Pediatric, Evidence is incon
Recommendation: Adult, Class IIb; Pediatric, Class IIb
Strength of Evidence: Adult, Category C; Pediatric, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RAT

2) Summary:

Possibly effective in moderate cases (Erfurth et al, 1998)

3) Adult:

a) In a case series report, gabapentin therapy was useful in 3 out of 6 pa add-on therapy and in 4 out of 8 patients as monotherapy (Erfurth et al, 1 4800 milligrams daily. In the add-on group scores on the Bech-Rafaelsen declined from 37.7 to 7.8; additional valproic acid was used in 3 out of 6 p scores declined from 27.8 to 9 in 4 out of 8 patients completing the study.

4) Pediatric:

a) A 13-year-old boy with manic episode, bipolar I disorder, and attention the addition of gabapentin 1500 milligrams to his carbamazepine therapy previously failed divalproex and could not tolerate lithium. His initial Young 27 and decreased to 6 after 7 months of gabapentin.

4.5.X Migraine; Prophylaxis

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RAT

2) Summary:

Efficacy and safety demonstrated in a controlled trial (Mathew et al, 2001)

3) Adult:

a) Oral GABAPENTIN 2400 milligrams (mg)/day taken in 3 divided doses frequency of migraine headaches and was generally well tolerated, basec trial (n=87). Enrollees had 3 to 8 migraine headache episodes per month months (with or without aura); subjects were randomized to gabapentin or dosing occurred during a 4-week baseline period. The first 4 weeks of the considered the titration phase. Gabapentin dosing on day 1 was 300 mg; 7, 1500 mg on day 14, 2100 mg on day 21, and 2400 mg on day 28 (all di gabapentin-treated patients stabilized on 2400 mg/day. During the last 4 v period, the median rate of migraine was 2.7 for the gabapentin 2400-mg/c group (p=0.006). A 50% reduction rate for migraines in the last 4 weeks c was achieved by 46.4% and 16.1% of the gabapentin 2400- mg/day and c (p=0.008). Average number of days with migraine during the last 4 weeks groups, respectively (p=0.006). Drug-related adverse events (somnolence commonly) occurred in 67.3% of the treatment group and 48.9% of the co adverse events amounted to 13.3% and 6.7% of the gabapentin and plac authors believe that gabapentin therapy represents an advance in the pro (Mathew et al, 2001).

4.5.Y Multiple sclerosis, Complications

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RAT

2) Summary:

Effective for multiple sclerosis complications including trigeminal neuralgia dysesthetic or paresthetic symptoms, and spasticity (Khan, 1998; Solaro e Dunevsky & Perel, 1998)

3) Adult:

a) Refractory trigeminal neuralgia completely resolved in 6 out of 7 multip gabapentin (Khan, 1998). Patients were started on gabapentin 300 milligr until effective. Effective doses ranged from 900 to 2400 mg/day. In 6 patie resolved while 1 patient had a marked improvement.

b) Gabapentin was useful for paroxysmal symptoms in multiple sclerosis 1998). In an open study, MS patients with trigeminal neuralgia, painful ton

paresthetic symptoms refractory to other treatments received gabapentin
patients dropped out due to nausea or poor compliance. In the trigeminal
patients experienced complete resolution of symptoms. Improvement beg
Painful tonic spasm was relieved in 9 out of 11 patients completing the stu
being seen within 3 days. Only partial improvement was seen in the 2 pati
disturbances completing the study.

c) Gabapentin 900 to 2700 milligrams (mg) daily in 3 divided doses was s
on subjective and objective spasticity measures in 22 multiple sclerosis (M
randomized, placebo-controlled, double-masked, crossover trial. All subje
form of MS and were divided into two groups which received either gabap
fashion. Gabapentin was dosed initially at 300 mg three times daily and in
to a maximum dose of 900 mg three times a day. Interference with functio
(p=0.003), Modified Ashworth (p=0.04), painful spasm (p=0.03), plantar st
spasm severity (p=0.01) scores were significantly improved when patients
compared to when they were assigned placebo. Significant improvements
scales, including fatigue impact (p=0.006), global assessment (p=0.0001)
(p=0.002), painful spasm (p=0.002), spasm frequency (p=0.0001), and sp
compared to baseline. Gabapentin treatment also yielded improved score
physician-administered scales including clonus score (p=0.002), deep ten
Ashworth Scale (p=0.0005), and plantar stimulation scale (p=0.008). Plac
gabapentin in measures of fatigue reduction (p=0.03) and decreases in de
Subjects reported improvements in activities of daily living and in appetite
adverse events were reported (Cutter et al, 2000).

d) Two patients with multiple sclerosis obtained marked improvement in s
spasm with gabapentin therapy (Dunevsky & Perel, 1998). A 41-year-old
(modified Ashworth Scale) in the left lower limb and grade 2 for the right lo
take a few steps with a walker. After 3 months of gabapentin 400 milligrar
+1 for the left and 1 for the right limb. She could walk 75 to 100 meters wi
a 52-year-old male, had grade 2 spasticity for both lower limbs and upper
meters with a cane. After 3 months of gabapentin 300 mg 3 times daily, sp
lower limbs and normal in the left upper limb. The patient could ambulate

e) A 36-year-old woman with multiple sclerosis had her continuous "tight"
gabapentin (Samkoff et al, 1997). The pain had been refractory to amitript
carbamazepine. Gabapentin 300 milligrams/day (mg/day) was titrated to 3
improvement in pain.

4.5.Z Neuropathic pain

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy; Pediatric, Evidence favors e
Recommendation: Adult, Class IIb; Pediatric, Class IIb
Strength of Evidence: Adult, Category B; Pediatric, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RAT

2) Summary:

Pain associated with multiple neuropathic syndromes including: DYSESTH
NEURALGIA, and direct nerve injury has been relieved (Serpell, 2002) (T
(Otley, 1999)

3) Adult:

a) Mean weekly pain diary scores were reduced in patients given gabape
neuropathic pain. In a randomized, double-blinded, placebo-controlled stu
receive gabapentin (n=153), at an initial dose of 900 milligrams/day (mg/d
placebo (n=152). Gabapentin was increased to 1800 mg/day and then 24
in patients who did not show at least a 50% reduction in overall pain. Pati
By the end of the titration period, 101 patients were taking 2400 mg/day o
1800 mg/day and 27 were taking 900 mg/day. Certain concomitant medic
patients were reported as taking prohibited medications during the study.
stable doses, which may have affected efficacy estimates. Investigators d
patients belonged. Efficacy was assessed using mean weekly pain dairy s
from daily patient assessments of pain on an 11-point Likert scale. In the
diary score decreased from 7.1 at baseline to 5.6 at week 8 (21% decreas
7.3 to 6.3 (14%) in the placebo arm (p=0.048). At weeks 1, 3, 4, 5, and 6,
diary scores between the arms were significantly different (p less than 0.0
there was no longer a statistical difference between the 2 arms. By week
pain symptoms were not different between the two arms (p greater than 0
were associated with the use of gabapentin (Serpell, 2002).

b) A retrospective analysis of 2 years of patient data (n=38) in one practi
some relief to 76% of patients with neuropathic pain that resulted from spi

of gabapentin was 900 milligrams (mg) per day and the median maintena
(range 900 mg to 4800 mg). Nine of 38 patients discontinued treatment w
adverse effects and 5 for lack of efficacy. Among those patients for whom
months of therapy (n=11), mean pain scores on a zero-to-10-point scale c
5.23 at 1 month, 4.59 at 3 months, and 4.13 at 6 months (p less than 0.00
c) A 19-year-old woman was successfully treated for chronic neuropathic
woman had a history of chronic right eye pain, which was refractory to tria
nonsteroidal antiinflammatory drugs, opioids, multiple corrective surgeries
block with local anesthetic. Post-enucleation of the eye, the women report
character of the pain. Gabapentin was initiated at 300 milligrams (mg) dai
300 mg three times a day. By 2 weeks, the patient reported complete pair
the 3 months of follow-up (Sloan et al, 2003).
d) Gabapentin relieved the pain caused by PILOLEIOMYOMAS in 54- ye
undergone a hysterectomy at age 41 for dysfunctional uterine bleeding as
leiomyomatosis, which had first been noticed when she was pregnant at a
numerous painful, red-brown, oval nodules on her right side, including her
woman rated her pain 8 on a scale of 1 to 10 (10 being the most severe).
gabapentin 300 milligrams daily for 3 days, twice daily for 3 days, and the
end of 2 weeks, there was nearly complete resolution of leiomyoma-relate
where the pain was remarkably reduced (pain rating, 3 on a scale of 10).
were mild dizziness and fatigue. The woman continued the same dose as
2002).
e) A 69-year-old woman had her dysesthetic pain after reconstructive sur
(Otley, 1999). The woman had a basal cell carcinoma of the right upper lip
cheek transposition flap. She developed disturbing dysesthetic pain 2 mo
antidepressant therapy and acetaminophen had no effect. She was starte
daily and titrated up to 300 mg 3 times daily. Within 2 weeks the pain had
taper off the gabapentin without reoccurrence of the pain. After 10 weeks
of the gabapentin with only minimal pain reoccurring.
f) A 60-year-old woman suffered exquisite facial pain secondary to being
which was relieved by gabapentin (Lucier & Franm, 1997). Gabapentin 15
increased to 300 mg provided relief after 2 days. The dose was eventually
discontinued after 5 months without recurrence.
g) Two cases of trigeminal neuralgia responsive to gabapentin have beer
one case, the patient reported gabapentin 300 milligrams (mg) 3 times da
baclofen without the dizziness she had experienced. In another case, the
gabapentin 2400 mg/day. She had been refractory to carbamazepine and
and baclofen.

4) Pediatric:

a) Neuropathic pain secondary to pacemaker revision surgery in a 12-yea
block responded to gabapentin therapy (McGraw & Stacey, 1998). Two m
suffered from constant knifelike pain. The pain worsened despite diazepa
antiinflammatory agents. It was somewhat alleviated by amitriptyline and
milligrams infused intravenously over 20 minutes relieved the pain for 6 h
gabapentin increased over 3 weeks to 300 milligrams 3 times daily with a
months the gabapentin was weaned without recurrence of pain.

4.5.AA Neuropathy due to human immunodeficiency virus

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RAT

2) Summary:

Gabapentin was superior to placebo for the treatment of HIV-associa
multicenter, prospective, randomized, double-blind, placebo-controlle
(n=26) (Hahn et al, 2004).
Efficacy documented by case series (La Spina et al, 2001)

3) Adult:

a) Gabapentin was superior to placebo for the treatment of HIV-associate
multicenter, prospective, randomized, double-blind, placebo-controlled tria
(n=26). Adult patients must be diagnosed with symptomatic HIV-associate
by a neurologist and had completed a baseline pain diary over 1 week pri
definition for HIV-SN diagnosis included distal sensory symptoms (paresth
abnormal sensory signs (elevated vibratory threshold or pin hyperalgesia)
reflexes. Prestudy and during-study use of central analgesics was not per

analgesics (paracetamol, diclofenac) must be decreased to a minimum or
randomized to receive gabapentin (GBP) 400 milligrams (mg) daily titrate
1200 or 2400 mg/day in 3 divided doses (n=15; median age 46 years (yr);
4-week, double-blind treatment phase or to placebo (n=11; median age 4
After the double-blind treatment phase, the study was unblinded and the
increase GBP up to 3600 mg/day and the placebo group could initiate GB
primary outcome was improvement in pain, measured by the difference in
to week 4 based on the Visual Analogue Scale of the Short-Form McGill P
patients had a significant change in median pain score from baseline to w
to 2.85 (p less than 0.05) vs 4.7 to 3.3 (p=0.646), respectively. The chang
baseline to week 4 correlated with a 44.1% improvement vs a 29.8% impr
compared with placebo arm, respectively. Further, GBP was associated w
interference score at week 4 from baseline (-48.9% vs -11.6%) relative to
with common adverse events of somnolence (80% vs 18.2%) dizziness (6
vs 27.3%), nausea (33.3% vs 18.2%) and headache (6.7% vs 9.1%) in the
respectively (Hahn et al, 2004).
b) GABAPENTIN as sole analgesic was effective in ameliorating neuropa
Pain symptomology was due to the disease itself (n=6), neurotoxic drugs
(n=4). Gabapentin was started at 300 milligrams (mg)/day and titrated by
3600 mg/day or highest tolerated dose. Mean dose during the study was
reporting analgesia at 300 mg/day. Pain was improved within mean 6 day
Mean pain score as assessed by a visual analog scale (VAS) decreased f
(p=0.0001). Pain which interfered with sleep decreased from baseline 60.
was at least 4 months in the majority of patients. Overall 1 of 19 patients e
gabapentin. The drug was well tolerated, and the only adverse event was
After the study ended, 15 patients were still on gabapentin; 4 patients stop
months due to complete or nearly complete pain relief. Another advantage
low potential for drug interactions with gabapentin as the drug is not meta
eliminated by renal secretion as unchanged drug (La Spina et al, 2001).
c) Oral GABAPENTIN 300 milligrams (mg) three times a day proved to b
POLYNEUROPATHY in a 41-year-old man positive for HIV infection but n
treatment. The patient was diagnosed with Mycobacterium tuberculosis, a
month history of paresthesias in his legs. His tuberculosis was successful
neurologic deficits in his lower extremities progressively worsened. He de
his legs, hard leg pain, and proprioceptor alterations. An electromyogram
symmetric sensorimotor polyneuropathy. Carbamazepine 400 mg 3 times
Low-dose gabapentin was introduced and gradually increased while carba
deficits slowly improved and in 1 month, the patient was able to walk with

4.5.AB Nystagmus

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RAT

2) Summary:

Improves nystagmus (Averbuch-Heller et al, 1997) (Stahl et al, 1996)

3) Adult:

a) In a double-blind, crossover trial, gabapentin (up to 900 milligrams/day
baclofen (up to 30 milligrams/day) for acquired pendular nystagmus, howe
effective for downbeat nystagmus (Averbuch-Heller et al, 1997). In 15 pat
nystagmus, gabapentin significantly improved visual acuity and median ey
produced no significant change in visual acuity and only affected eye spe
patients with downbeat or torsional downbeat nystagmus, changes in me
less consistent with both drugs. In all 21 patients, gabapentin produced a
near visual acuity (p less than 0.05) and decrease in median eye speed (p
significant effect on visual acuity but did reduce median, vertical eye spee
b) In a pilot study, three patients with acquired forms of nystagmus exper
and improvement in vision with GABAPENTIN. In two of the patients, nyst
multiple sclerosis; the third patient experienced nystagmus following a bra
administered as a single 600-milligram dose which resulted in improveme
two of the patients who continued to take the drug, at doses of 900 to 150
improvement in vision was sustained after 5 weeks of treatment (Stahl et

4.5.AC Orthostatic tremor

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RAT

2) Summary:
Improves orthostatic tremor symptoms in doses of 300 to 2400 milligrams Onofrj et al, 1998)

3) Adult:
a) In an open-label study of seven consecutive patients presenting with o doses of 300 to 1800 milligrams (mg) per day subjectively improved symp Patients were similarly diagnosed using strict clinical criteria and five patie with clonazepam, four without improvement. Subjectively, patients reporte to 80% (mean 73%). In one patient, gabapentin was added to clonazepan was 11 months and no patients had to discontinue therapy due to side eff included sedation, nausea, diplopia, unsteadiness, and constipation (Evid
b) Orthostatic tremor almost disappeared with gabapentin treatment in 3 1998). Patients were started on gabapentin 300 milligrams and increased increased to 2400 mg. Utilizing self-monitoring scales, tremor rating scale gabapentin was shown to improve tremor during the 1800 to 2400 mg trea (p less than 0.01).

4.5.AD Panic disorder

1) Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RAT

2) Summary:
GABAPENTIN was more effective in patients with greater illness severity, more efficacious than placebo (Pande et al, 2000)

3) Adult:
a) According to an 8-week, randomized, double-blind trial (n=103), impro disorder (DSM-IV) was not significantly greater comparing GABAPENTIN however, when study subjects were stratified for illness severity, the more receiving gabapentin showed significantly more improvement than those g Stratification divided patients according to scores on the Panic and Agora or more (n=53) versus scores of less than 20 (n=41). Of those with scores PAS-score reduction in gabapentin-treated subjects and a 4.88-point redu patients (p=0.04, least-squares mean change in scores). Women with scc likely to respond than men, regardless of treatment. Doses of gabapentin ranged from 600 to 3600 milligrams/day, and were increased as long as tl no limiting adverse effects were present. Side effects of gabapentin were dizziness; approximately 12% of gabapentin- and 4% of placebo-treated p adverse event. One serious event (an automobile accident) in a gabapent the investigator as unlikely to be medication-related (Pande et al, 2000).

4.5.AE Partial seizure

1) Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Effective; Pediatric, Evidence favors efficacy
Recommendation: Adult, Class IIb; Pediatric, Class IIb
Strength of Evidence: Adult, Category B; Pediatric, Category C
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RAT

2) Summary:
Effective as monotherapy for partial seizures (Chadwick et al, 1998; Heilb 1997)

3) Adult:
a) In a randomized, double-blind clinical trial of 292 patients (12 years an partial seizures, gabapentin monotherapy at doses of 900 milligrams (mg) superior to gabapentin 300 mg per day and comparable in efficacy to ope per day. Patients were randomized to one of the three gabapentin regime for 24 weeks. The primary outcome of the study was the time to an exit ev tonic-clonic seizure, 3 simple or complex partial seizures, or status epilept significantly longer for patients receiving 900 mg or 1800 mg per day of ga mg per day gabapentin regimen (p=0.018; p=0.04, respectively). For the c

or withdrawal due to side effects, gabapentin 900 mg per day had the high
the 24 week evaluation. Dizziness, headache, and fatigue were the most
(Chadwick et al, 1998).
b) Gabapentin was effective as monotherapy for partial seizures in 23 of
a retrospective review (Heilbroner & Devinsky, 1997). Median duration of
months with a median dose of 1200 milligrams. During gabapentin therap
than 90% seizure reduction, 6 patients had a 50% to 89% reduction, 2 pa
reduction, 12 had no change and 1 had a 25% increase in seizures. Six o
in seizure frequency, had already experienced good seizure control and t
Specific seizure type did not predict response. Four patients discontinued
effects.

4) Pediatric:

a) In a case report concerning a 15-year-old female with focal epilepsy, g
three times daily was as effective and better tolerated than previous carba
caused allergic dermatologic reactions after successful treatment initially.
reduced from 600 mg/day to 200 mg/day for six months, at which point it
monotherapy was then continued, and the patient was seizure-free withou
months (Kindler, 1997).

4.5.AF Partial seizure, Refractory

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Pediatric, Evidence is inconclusive
Recommendation: Pediatric, Class III
Strength of Evidence: Pediatric, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RAT

2) Summary:

Ineffective as adjunctive therapy for refractory partial seizures (Korn-Merk

3) Pediatric:

a) Gabapentin showed little to no benefit in an open label trial in 52 childr
treated concomitantly with gabapentin 26 to 78 milligrams/kilogram (mg/k
other antiepileptic agent. Thirty four patients discontinued due to inadequa
increased seizure frequency while being treated with gabapentin, and 12
beginning of the trial but subsequently became tolerant to gabapentin anc
seizure control. Only 3 children continued to benefit from gabapentin thera
throughout the trial. Adverse events were minimal and most commonly inc
hyperactivity (Korn-Merker et al, 2000).

4.5.AG Partial seizure; Adjunct

FDA Labeled Indication

1) Overview

FDA Approval: Adult, yes; Pediatric, yes (3 to 12 years)
Efficacy: Adult, Effective; Pediatric, Evidence favors efficacy
Recommendation: Adult, Class IIb; Pediatric, Class IIb
Strength of Evidence: Adult, Category B; Pediatric, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RAT

2) Summary:

Indicated as adjunctive therapy in the treatment of partial seizures wi
generalization in adults with epilepsy
Indicated for adjunctive therapy in the treatment of partial seizures wi
generalization for children over 12 years old and for adjunctive therap
seizures in children between 3 and 12 years old

3) Adult:

a) GENERAL INFORMATION: In open and controlled clinical studies, ad
oral doses of 900 to greater than 1600 milligrams daily has been effective
resistant partial epilepsy (simple partial seizures, complex partial seizures
seizures) (Baulac et al, 1998; Anon, 1998); (Hardin et al, 1998)(Sivenius e
Handforth et al, 1989; Bauer, 1987; Crawford et al, 1987b). With gabapen
reduction in the frequency of partial seizures by at least 50% has been re
(Sivenius et al, 1991b; Anon, 1990c). In studies investigating gabapentin
frequency has been halved in only 12% to 20% (Sivenius et al, 1991b; Cr
1200 to 2400 milligrams in patients with partial seizures refractory to othe
43% of patients reducing their seizure frequency by at least 50% (Leach,
studies are lacking, indirect analysis suggests that the efficacy of gabape
of valproic acid or vigabatrin as add-on therapy (Mumford, 1988; Gram, 1
al, 1987b).

b) Gabapentin was shown to be effective as add-on therapy in patients w

(Mayer et al, 1999). In this 26-week, open-label multicenter study, patients
partial seizures with or without secondary generalization (n=110) after pric
therapy were initiated on gabapentin, in addition to their existing AED regi
1200 milligrams/day (mg/day) within the first 5 days and was further titrate
2400 mg/day in increments of 400 mg after every second seizure for the f
frequency during the last 8 weeks of treatment was compared to that duri
59.7% of patients demonstrated a reduction in seizure frequency of 50% c
specific seizure types, simple partial seizures, complex partial seizures, a
clonic seizures, occurred in 63.3%, 60%, and 76.8% of patients, respectiv
reported in quality of life, and no correlation was found between trough pla
reduction in seizure frequency.

c) Gabapentin was shown to be effective as add-on therapy in patients w
(Mayer et al, 1999). In this 26-week, open-label multicenter study, patients
partial seizures with or without secondary generalization (n=110) after pric
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59.7% of patients demonstrated a reduction in seizure frequency of 50% c
specific seizure types, simple partial seizures, complex partial seizures, a
clonic seizures, occurred in 63.3%, 60%, and 76.8% of patients, respectiv
reported in quality of life, and no correlation was found between trough pla
reduction in seizure frequency.

d) In an open-label six-month observational study of 610 patients (mean
epilepsy, gabapentin add-on therapy (mean dose 1739 milligrams per day
50% or more in 34% of patients, with a median reduction of seizure freque
baseline seizure frequency of 7.2 per month and were taking 2.3 concomi
During the last 4- week evaluation period, 79 patients remained seizure fr
seizure-free patients at baseline. At six months, 57 patients (9.7%) had di
effects and 368 patients (62%) continued on gabapentin therapy. The mo
were somnolence, asthenia, and weight gain (Baulac et al, 1998).

e) A 20-week, open-label study of gabapentin add-on therapy (mean 160
patients with partial epilepsy reduced the combined frequency of complex
generalized seizures by half or more in 71% of patients (p=0.0001). Patie
eight or more complex partial seizures with or without secondarily general
months and taking stable doses of either carbamazepine, phenytoin, or b
improvements were also observed in the Quality of Life in Epilepsy (QOLI
Analysis by the type of seizure showed significant reductions only for com
Somnolence and dizziness were the most frequently reported side effects
discontinued therapy due to side effects prior to the end of the 20-week st

f) In a retrospective evaluation of 90 patients (7 months to 78 years) with
disorders, the addition of gabapentin therapy reduced seizure frequency i
gabapentin dose was found to be 1700 milligrams (mg) per day and 95%
drugs. The duration of treatment ranged from one to 14 months and gaba
patients due to side effects or lack of efficacy. The most frequently reporte
dizziness, headache, and weight gain (Hardin et al, 1998).

g) In one 14-week study, maximal reductions in partial seizure frequency
after 3 to 6 weeks of gabapentin therapy (600 to 1200 milligrams daily); af
in seizure frequency tended to be less (approximately 27%) (Anon, 1990c
tolerance development.

4) Pediatric:

a) The safety and efficacy of adjunctive gabapentin demonstrated in a 3-
controlled trial was sustained in an added 6-month open-label extension c
children 3 to 12 years of age with refractory partial seizures (n=237). Stud
as 24 to 70 milligrams/kilogram/day (initial dosing was 24 to 35 mg/kg/day
subjects were receiving sodium valproate or carbamazepine; other medic
lamotrigine, clobazam, phenytoin, or (rarely) phenobarbitone. Mean durat
154 days. For all partial seizures, 80 of 237 patients (34%) showed a posi
reduction in baseline partial seizure frequency (baseline as the period bef
177 patients with complex partial seizures, 103 (58%) were positive respo
generalized tonic-clonic seizures responded positively. Four patients were
label phase, while 42 patients had a 75% or greater reduction in seizure fr
phase, 12 patients (5%) experienced at least 1 episode of status epileptic
episodes (more than 4). Somnolence was the most commonly associated
Thirteen patients withdrew due to adverse effects; these effects included
lability, fatigue, ataxia, hyperkinesia, urinary incontinence, or confusion (A

4.5.AH Phantom limb syndrome

1) Overview

FDA Approval: Adult, no; Pediatric, no

Efficacy: Adult, Evidence is inconclusive; Pediatric, Evidence favors e

Recommendation: Adult, Class IIb; Pediatric, Class IIb

Strength of Evidence: Adult, Category B; Pediatric, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RAT

2) Summary:

In a randomized, double-blind, placebo-controlled, crossover clinical s gabapentin was more effective than placebo in alleviating postamputa weeks of therapy (Bone et al, 2002).

In a randomized, double-blind, placebo-controlled, crossover clinical s in patients with phantom limb pain and/or residual limb pain, gabaper measures of pain intensity compared to placebo (Smith et al, 2005).

There was no significant difference between gabapentin and placebo stump and phantom pain in a prospective, randomized, placebo-cont al, 2006).

Gabapentin reduced phantom limb pain in a case series of seven chil al, 2001).

3) Adult:

a) In a randomized, double-blind, placebo-controlled, crossover clinical st gabapentin was more effective than placebo in alleviating postamputation of therapy. Patients with established phantom limb pain for a minimum of amputation and a pain score of at least 40 millimeters (mm) on a 100-mm eligible for inclusion, and received 6 weeks of gabapentin therapy and 6 w 1-week washout interval followed the first period. Gabapentin was initiated with titration up to a maximum of 2400 mg daily in 3 divided doses. The pr pain intensity difference (PID) at the end of each treatment compared to b completed both arms of the study; analyses were performed using the inte least 1 dose of study drug). A large placebo effect was observed as there pain in weeks 2, 4, and 5 in the placebo group and in weeks 2, 3, and 5 in with baseline pain scores. Up to week 5 of the study, there was no signific scores between placebo and gabapentin. However, at week 6, there was receiving gabapentin at the end of the study period relative to placebo (VA p=0.025). There were no significant differences in the secondary outcome needed, sleep interference, HAD depression scale scores, and activities o (Bone et al, 2002).

b) In a randomized, double-blind, placebo-controlled, crossover clinical st in patients with phantom limb pain (PLP) and/or residual limb pain (RLP), affect measures of pain intensity compared to placebo. Patients with lowe months prior and an average pain score of at least 3 on a 0 to 10 numeric eligible for inclusion, and received 6 weeks of gabapentin therapy and 6 w random order; with a 5-week washout interval followed the first period. Ga milligrams (mg) on day 1 with titration up to a maximum of 3600 mg daily dose of 3600 mg was attained by 82% of patients during the first phase an second phase. The primary efficacy outcome was PLP (painful sensations amputated) and RLP (pain in the residual limb) measured using the NRS. differences observed in pre- to posttreatment pain intensity change scores versus placebo for any of the four types of pain intensity (average and wo RLP). There were also no significant differences noted for change scores depressive symptoms (CES-D), or pain interference (BPI) between the ga (Smith et al, 2005).

c) There was no significant difference between gabapentin and placebo i stump and phantom pain in a prospective, randomized, placebo-controlled required lower limb amputation due to peripheral vascular disease were e amputation of the foot or toes only were excluded. Eligible patients were r (n=21; age 70.8 +/- 11.9 years (yr); 52% male) or placebo (n=20; age 69.8 gabapentin arm received 300 milligrams (mg) orally on postoperative day mg on days 2 to 4, then by 300-mg increments every 2 days to a goal dos 13 to 30. Patients with a creatinine clearance (CrCl) between 30 and 60 m a maximum gabapentin dose of 1200 mg. Lower doses of gabapentin wer not tolerated; however, patients who received doses lower than 900 mg fo from the analysis. The study medication was provided in 3 divided doses days. The primary outcome was the incidence of phantom pain and the in pain on day 30. Intensity of pain was measured by a numeric scale of 0 to Questionnaire. The data analysis revealed no significant difference betwe incidence of phantom pain or in the intensity of stump and phantom pain.

phantom pain was 55% and 52.6% (risk difference, 2.4%; 95% CI, -28.9%
gabapentin compared with placebo group, respectively. At day 30, the me
was 1.5 (range, 0 to 9) and 1.2 (range, 0 to 6.6) in the gabapentin and pla
(p=0.6). The corresponding median intensity of stump pain was 0.85 (rang
5.4), respectively (p=0.68). Common adverse effects, which were transier
study medication were nausea, stomach ache, fatigue, confusion, nightma
gabapentin (n=9) and placebo (n=8) groups. The author's note a study lim
size (Nikolajsen et al, 2006).

4) Pediatric:

a) Gabapentin therapy provided successful control of phantom limb pain
from 4 to 28 years of age. Within 2 months of beginning gabapentin, pain
in 6 of 7 patients; in the seventh patient, pain was reduced to a tolerable l
ranged from 14 to 40 milligrams/kilogram; commonly when the right dose
occurred suddenly. Mean follow-up time with the cohort was 1.74 years. F
taper the gabapentin, and had no recurrence of pain when the drug was t
used gabapentin on an occasional basis when the phantom sensations w
had reached almost complete resolution of phantom pain when his cance
shortly thereafter. One patient who did not have resolution of pain reques
Tapering was begun; when the dose had dropped from 800 to 600 mg thr
a dramatic increase in phantom pain, and the dose was returned to 800 m
receive maintenance doses of gabapentin, varying the dose between 800
There were minimal side effects with gabapentin therapy; 4 patients had r
after several doses (Rusy et al, 2001).

4.5.AI Postherpetic neuralgia

FDA Labeled Indication

1) Overview

FDA Approval: Adult, yes; Pediatric, no
Efficacy: Adult, Effective
Recommendation: Adult, Class IIa
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RAT

2) Summary:

Gabapentin is indicated for the management of postherpetic neuralgi
NEURONTIN(R) oral tablets, oral capsules, oral solution, 2007).
In a randomized, double-blind, parallel-group, 9-week study (n=76) in
neuralgia (PMH), gabapentin was as effective, but was tolerated bett
compared to nortriptyline (Chandra et al, 2006).
Gabapentin treatment reduced the pain of postherpetic neuralgia, imp
improved patients' quality of life in a randomized, double-blind, multic
et al, 2001).
Two cases of acute herpetic neuralgia pain and 3 cases of postherpe
responded to gabapentin therapy have been reported (Filadora et al,
Gabapentin was useful for postherpetic neuralgia and direct peripher
chart review of pain patients receiving gabapentin for at least 30 days

3) Adult:

a) In a randomized, double-blind, parallel-group, 9-week study (n=76) in p
neuralgia (PMH), gabapentin was as effective, but was tolerated better wi
nortriptyline. Adult PMH patients with a history of greater than 8 weeks of
pain intensity of at least 40 millimeters (mm) on a 100 mm visual analog s
randomization, and average pain score of at least 4 on the Likert scale du
randomized after a 1-week run-in period to receive nortriptyline 25 milligra
age 52.5 years; n=38) or gabapentin 300 mg orally three times daily (mea
weeks. Doses were escalated based on tolerability and pain relief every 2
nortriptyline 50 mg three times daily and gabapentin 900 mg three times d
pain score on the Likert scale was 5.8 +/- 1.4 and 5.6 +/- 1.1 in the nortrip
respectively. VAS pain score was also comparable between treatment arr
5.3 +/- 1.3 and 4.8 +/- 1.2, respectively. Results of the study were based o
population (n=70). For the primary efficacy outcome of change in pain sco
baseline to study end, there was a 47.6% and 42.8% reduction in average
and gabapentin groups, respectively, with 38.8% (n=14) and 38.2% (n=13
and gabapentin groups, respectively, showing improvement in their baseli
than 50% improvement in baseline pain scores on the Likert scale was re
patients, respectively, in the nortriptyline and gabapentin groups. For seco
significant improvement in sleep scores (46% vs 52%, for nortriptyline and
and Short Form McGill Pain Questionnaire (SF-MPQ) scores for pain were
groups. Clinical effectiveness was improved (27.8% vs 23.8%, for nortript

respectively). Approximately two-thirds of patients in both groups moved t
in the categorical scale, and disability rating improved (41.5% vs 39.6%, f
respectively). The results of the primary and secondary outcomes, howev
significant differences between the 2 groups. In the nortriptyline group, 58
adverse events, with dry mouth (50%), constipation (22.2%), postural hyp
(16.7%) being the most common. Gabapentin was well tolerated with slee
(11.8%) adverse event reported (Chandra et al, 2006).

b) Gabapentin treatment reduced the pain of postherpetic neuralgia, impr
improved patients' quality of life. In a randomized, double-blind, multicente
underwent a week-long run-in period before beginning treatment with gab
(mg) per day or placebo. Gabapentin doses were started at 300 mg/day a
days. Dosing was stable at 1200 mg/day for days 4 to 7 and then titrated
doses were further titrated for patients randomized to 2400 mg/day. All dc
continued for a total of 7 weeks of treatment. Pain relievers other than ace
acetaminophen/codeine were disallowed. Changes in pain scores from ba
significantly greater in the gabapentin groups (p less than 0.01). Reductio
the placebo group, 34.5% for gabapentin 1800 mg and 34.5% for gabape
scores were evident as early as one week after the start of treatment (whe
The proportion of patients experiencing more than a 50% reduction in pai
gabapentin 1800 mg and 2400 mg, respectively, and 14% with placebo. S
pattern similar to that of pain. Quality of life measures showed greater imp
with placebo. Gabapentin-treated patients experienced more adverse effe
The most common adverse events with gabapentin were dizziness and dr

c) Gabapentin reduced pain in patients with postherpetic neuralgia prese
healing of the rash. In a multicenter, double-blind study, patients received
over 4 weeks to the maximum tolerable dose (maximum dose 3600 milligr
After 8 weeks, the average pain score (11-point Likert scale) was significa
group (33.3%) versus placebo (7.7%; p less than 0.001). Mean scores for
Questionnaire also markedly improved for total pain (p less 0.001) and sp
sensory pain and affective pain (p less than 0.001). At the end of the stud
gabapentin categorized their pain as much or moderately improved versus
(Rowbotham et al, 1998).

d) Two cases of acute herpetic neuralgia pain and 3 cases of postherpeti
to gabapentin therapy were described. All occurred in the head and neck
unresponsive to narcotics, amitriptyline, acetaminophen, and ibuprofen. D
600 to 1800 milligrams (Filadora et al, 1999).

e) Gabapentin was useful for postherpetic neuralgia and direct peripheral
chart review of pain patients receiving gabapentin for at least 30 days. Th
was to rapidly increase gabapentin to 1600 milligrams/day and further incr
benefits were evident. Self-reported visual analog scales were reviewed.
score was observed in patients with neuropathic pain (p less than 0.0001)
0.04). No difference was seen for back pain. Further subgroup analysis sh
postherpetic neuralgia pain scores (53%, p less than 0.004) and diabetic
0.03). Patients with a greater than 75% decrease in pain score included 9
with postherpetic neuralgia (Rosenberg et al, 1997).

f) Gabapentin may be of benefit in the treatment of postherpetic neuralgia
woman whose pain was refractory to capsaicin, desipramine, and both pa
administered narcotic analgesics, therapy with gabapentin 300 milligrams
marked relief of symptoms (Segal & Rordorf, 1996).

4.5.AJ Postoperative pain

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class III
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RAT

2) Summary:

Gabapentin reduced morphine consumption during the first 24 hours
however, it did not effect patient rated pain scores (Dierking et al, 200
Pre-incision or post-incision administration of gabapentin for open do
and rescue analgesic requirements (Pandey et al, 2005)

3) Adult:

a) Although pain scores did not differ, morphine consumption was reduce
abdominal hysterectomy in patients administered gabapentin. In a double
randomized to receive gabapentin or placebo. The study recruited 80 wor
subtotal abdominal hysterectomy with or without salpingo-oophorectomy.

patients were received 1200 milligrams (mg) of oral gabapentin or placeb
or placebo 8, 16, and 24 hours after the initial dose. Morphine (0.15 mg/ki
intravenously at wound closure. Postoperative pain was controlled using p
morphine with a bolus dose of 2.5 mg and a 10 minute lock out period. If r
administered additional morphine (2.5 mg) in the first postoperative hour.
time 0 to 24 hours was a median 63 mg (interquartile range 53 to 88 mg) i
43 mg (interquartile range 28 to 60 mg) in the gabapentin arm (p less thar
significant differences in reported adverse effects between the 2 arms (p g
scores taken at time 2, 4, 22 and 24 hours were not significantly different
inverse association between plasma levels of gabapentin at 2 hours and r
was also reported (R(2)=0.24, p=0.008) (Dierking et al, 2004).
b) A double-blind, prospective, randomized, placebo-controlled study fou
pre-incision or post-incision for open donor nephrectomy was superior to p
using the visual analog scale (VAS) and rescue analgesic requirements. A
open donor nephrectomy, were randomized into three groups: the pre-inc
gabapentin 600 milligrams (mg) two hours before surgery and two placeb
tube after surgical incision; the post-incision group (n=20) received two pl
and gabapentin 600 mg through a nasogastric tube after surgical incision;
received two placebo capsules before surgery and two placebo capsules
surgical incision. Pain scores were recorded at rest using the VAS after ar
care unit and at six hour intervals until 24 hours post-surgery. All patients
controlled analgesia (PCA) pump (fentanyl 1 microgram/kilogram (mcg/kg
interval of 5 minutes). The pre-incision and post-incision groups had signi
time points compared to the placebo group (p less than 0.05). In addition,
groups also used less fentanyl compared to the placebo group (563.3 +/-
924.7 +/- 417.5 mcg, respectively) (p less than 0.05). There were no differ
group and the post-incision group in total fentanyl use and pain scores at
0.05 at all time points). Side effects were comparable in all study groups,
the most commonly reported (Pandey et al, 2005).

4.5.AK Priapism

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RAT

2) Summary:

Gabapentin was useful in the treatment of priapism in 3 cases (Perimenis

3) Adult:

a) Gabapentin was useful in the treatment of recurrent, refractory, idiopat
patients. A case series reported the use of gabapentin in patients who ha
episodes of priapism that was refractory to several oral treatments or alph
etilephrine intracavernosal injections. Gabapentin was initiated at 400 mill
Maintenance doses ranged from 900 to 2400 mg per day. Detumescence
and 2 patients have not had a repeat episode for 16 to 24 months. The thi
gabapentin after 6 months and had another priapism episode. He again re
gabapentin and is currently maintained at 900 mg/day. He has not had an
et al, 2004).

4.5.AL Pruritus

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RAT

2) Summary:

Effective in case report of refractory brachioradial itching (Bueller et al, 19

3) Adult:

a) Gabapentin 300 milligrams (mg) six times daily was effective in elimina
year-old woman with severe, refractory pruritus of the left forearm. Acupu
antihistamines, and dietary modifications were all ineffective. Intramuscula
for a short time, as were ice packs. An escalating gabapentin dose, startir
increasing to 300 mg six times daily, eliminated the symptoms (Bueller et

4.5.AM Restless legs syndrome

1) Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RAT

2) Summary:
Results of a small study showed improvement of restless legs syndrome v hemodialysis patients (Thorp et al, 2001)

3) Adult:
a) Oral GABAPENTIN therapy may improve symptoms of restless legs sy based on a small double-blind, cross- over trial (n=16). Subjects were ran gabapentin (300 milligrams administered 3 times weekly at the end of her Following a 1-week washout period, subjects crossed over to the other th criteria developed by the International Restless Legs Syndrome Study Gr and after each treatment period. Mean baseline score on the questionnair were 5.8 after placebo therapy compared with 3.0 after gabapentin therap response to treatment as a score less than 6, there were 11 patients who to placebo (p less than 0.01), 1 who responded to placebo and not to gab both. Three subjects failed to complete the study; in 2 cases, somnolence was the cause; a third participant died of myocardial infarction on placebo 2001).

4.5.AN Sensory disorder

1) Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category C
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RAT

2) Summary:
Sensory deficits were ameliorated in 3 of 5 patients being treated with gab (Chong et al, 2002)

3) Adult:
a) Of 5 patients with sensory deficits in addition to neuropathic pain, 3 ex sensation while their neuropathies were being treated with gabapentin. Tv diabetic neuropathy and one had neuropathic pain secondary to trigemina gabapentin 400 to 600 milligrams 3 times per day, all 3 patients experienc and/or area of neuropathic pain. In addition, sensation returned to areas p unresponsive to temperature or touch (Chong et al, 2002).

4.5.AO Shortlasting, unilateral, neuralgiform pain with conjunctival injection

1) Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category C
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RAT

2) Summary:
Improvement of symptoms in 1 case report (Graff-Radford, 2000)

3) Adult:
a) A 48-year-old man suffering from SUNCT SYNDROME (severe unilate conjunctival injection and tearing, rhinorrhea, and subclinical sweating) fo free when treated with oral GABAPENTIN. Symptoms included ocular, fac left side; attacks consisted of burning, sharp, shooting pain with tearing ar for 2 to 3 minutes and occurring up to 25 times a day. Under the direction tried prednisone 60 milligrams (mg)/day for 4 weeks; the steroid relieved l prednisone, his pain returned. He had also tried carbamazepine, verapam dihydroergotamine, and indomethacin without benefit. Gabapentin was st The patient experienced dramatic relief. Doses were increased to 600 mg nearly complete pain relief. The patient had then moved to another area, syndrome when his gabapentin prescription ran out. On returning to the a became pain-free at doses of 900 mg three times daily, and, with these m be pain-free at 1 year. When he attempted to stop the gabapentin, his pai 2000).

4.5.AP Social phobia

1) Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RAT
2) Summary:
Appears beneficial in the treatment of social phobia (Pande et al, 199
3) Adult:
a) Patients with social phobia appeared to benefit from gabapentin therap double-blind, 14-week study, patients randomly received either gabapenti (mg) twice daily (n=34) or placebo (n=35). During the first week the dose mg 3 times daily; thereafter, the dose could be increased in increments of maximum of 3600 mg/day. The gabapentin group improved significantly b the Liebowitz Social Anxiety Scale (LSAS) (p=0.008). Approximately 77% received doses of greater than 2100 mg/day. Also, patients over 35 years treatment effect than younger patients (p less than 0.05). LSAS scores pla 14. Dry mouth and dizziness were significantly more common in the gaba group (p=0.05).

4.5.AQ Spasticity
1) Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class III
Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RAT
2) Summary:
Reduced spasticity in five patients with spinal cord injury (Priebe et al, 199
3) Adult:
a) Gabapentin 1200 milligrams three times daily clinically reduced spastic injury (Priebe et al, 1997). This result occurred during the open-label stud double-blind study of gabapentin 400 mg three times daily versus placebo not significantly improve spasticity. However, when patients were allowed higher dose, the patients reported improvement. A further control trial is w

4.5.AR Spinal muscular atrophy
1) Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RAT
2) Summary:
An open-label study suggests possible benefit in patients with type II or ty ATROPHY (Merlini et al, 2003)
3) Adult:
a) After 12 months of gabapentin therapy, there were modest improveme three-point pinch scores (calculated as an arm mega-score) and statistica knee flexion, knee extension and foot flexion (calculated as a leg mega-sc type III spinal muscular atrophy. In an open-label, non- placebo-controllec to receive either gabapentin (n=61) or no treatment (n=59) for 12 months. was 1590 milligrams divided twice daily. Arm mega-scores at 6 months w between the gabapentin and the non-treatment arms (5.77% versus 0% n baseline, p greater than 0.05). By 12 months, the median percent change baseline were 7.27% in the gabapentin group and 0% in the non-treatmer percent changes in leg mega-scores were 11.11% at 6 months and 12% a arm and 0% at 6 and 12 months for the non- treatment arm (p=0.02 and 0 use did not have any effect on forced vital capacity or most timed function

4.5.AS Tardive dyskinesia
1) Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RAT

2) Summary:
May have a role in the treatment of antipsychotic- induced tardive dyskine
3) Adult:
a) In an open-label, non-comparative study, gabapentin improved Abnorr (AIMS) scores in patients with antipsychotic-induced tardive dyskinesia. T at least 1 year (mean 5.2 years) and concomitant drug therapy was stable Gabapentin was initiated at 300 milligrams/day (mg/day), increased to 60(increased to 900 to 1200 mg/day by day 7. Patients were followed for 1 ye complete the study due to poor adherence (n=1), poor efficacy (n=1), and weight gain, dizziness, confusion, irritability and dysphoria were reported gabapentin. Mean AIMS scores showed statistically significant, time-relate decreased from 24.3 at baseline to 13.0 at 1 year (p less than 0.000). The improvement was 47.5% (range 14.3 to 72.4%). Larger clinical studies are effectiveness of gabapentin in this patient population (Hardoy et al, 2003)

4.5.AT Tinnitus
1) Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Ineffective
Recommendation: Adult, Class III
Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RAT
2) Summary:
In an 8-week, double-blind, randomized, placebo-controlled trial (n=1 between gabapentin and placebo in the relief of idiopathic tinnitus (Pi In a single-center, double-blind, randomized, placebo-controlled trial difference between gabapentin and placebo in the relief of moderate
See Drug Consult reference: DRUG THERAPY OF TINNITUS
3) Adult:
a) General Information
1) Gabapentin was ineffective in treating tinnitus based on reviewed al, 2007; Witsell et al, 2007; Bauer & Brozoski, 2006). According to 2 placebo-controlled trials involving nearly 200 patients with idiopathic there was no statistically significant difference in the primary outcome Inventory score improvement between gabapentin therapy (at doses placebo. Furthermore, no difference in subjective perceived improver between treatment arms (Piccirillo et al, 2007; Witsell et al, 2007). Th symptomatic relief of tinnitus is questionable.
b) Clinical Trials
1) In an 8-week, double-blind, randomized, placebo-controlled trial (r between gabapentin and placebo in the relief of idiopathic tinnitus. Pa years (mean, 57 +/- 8.2 years), with a history of tinnitus for at least 6 Additionally, enrolled patients were required to have a Tinnitus Handi 0 to 100; higher score indicative of a more severe condition) of 38 or randomized to receive gabapentin at a maintenance dose of 900 to 3 or matching placebo (n=56) for 8 weeks. Gabapentin was initiated at doses daily for 1 week, followed by gradual dose titration in 900-mg v weeks until reaching a maximum daily dose of 3600 mg that was mai While 86% of the patients in the active treatment arm reached a dosa of the patients achieved a maintenance dosage of 2700 mg/day and Approximately 65% of the patients had history of tinnitus for 6 years experienced bilateral tinnitus. The vast majority of the subjects also r disturbances. At baseline, approximately 50% of patients had THI sc scores were 49.53 +/- 17.85 and 51.77 +/- 18.03 in the gabapentin ar Based on the modified intent-to-treat analysis of 115 patients who ha study medication during the maintenance-dose period and provided a assessment, there was no statistical difference in the primary outcom improvement from baseline to study end point at week 8 between the (difference from baseline, 11.3 vs 11; between-group difference, 0.3; Furthermore, the between-group difference in the number of patients meaningful change in THI score (difference of 20 or greater from bas significant (gabapentin, 37% vs placebo, 32%; p=0.56). Statistically n gabapentin and placebo were not affected by age, sex, race, or histo efficacy outcomes, there were no significant between-group differenc bother and global improvement (Piccirillo et al, 2007).
2) In a single-center, double-blind, randomized, placebo-controlled tr significant difference between gabapentin and placebo in the relief of

range, 29 to 84 years; mean, 55 +/- 11 years), with a history of nonpu
tinnitus for at least 3 months of duration were randomized to receive
matching placebo (n=24) for 6 weeks. Gabapentin was initiated at 30
then 900 mg/day given in 3 divided doses daily for 1 week, followed b
mg/day that was maintained for an additional 2 weeks. During week 5
tapered to 900 mg and 300 mg per day, respectively. Efficacy was ev
month after the end of the study medication taper. The vast majority
of tinnitus for 6 months or longer, with 59% experiencing bilateral tinn
tinnitus symptoms of moderate or worse bother. The mean baseline
score (primary outcome measure) was 37.8 +/- 23 in the gabapentin
placebo arm (p not significant). While both groups reported a significa
end of week 4, there was no statistically significant difference in the c
gabapentin and placebo arm at corresponding intervals (p above 0.9
Total Mood Score change was noted between treatment arms (p abo
absence of hearing loss did not affect efficacy outcomes (Witsell et a

4.6 Comparative Efficacy / Evaluation With Other Therapies

Amitriptyline

Baclofen

Lamotrigine

Lorazepam

Nortriptyline Hydrochloride

Propranolol

Ropinirole

Topiramate

4.6.A Amitriptyline

4.6.A.1 Diabetic peripheral neuropathy

a) There was no difference as measured by pain scales and global pain s
gabapentin in the treatment of diabetics with peripheral neuropathy pain (
patients with stable glycemic control (n=21) received either gabapentin or
were then crossed-over to the other arm of therapy for 6 weeks with a 1-w
Dosage was adjusted based on the patient's response with gabapentin do
milligrams (mean dose 1565 mg) and amitriptyline doses ranging from 25
Both drugs significantly decreased pain scores from baseline (both p less
provided moderate or greater pain relief in 67% of patients while gabapen
patients (p=0.26). There was no statistically significant difference in occur
the drugs except for increased weight gain with amitriptyline.

4.6.B Baclofen

4.6.B.1 Nystagmus

a) In a double-blind, cross-over trial, gabapentin (up to 900 milligrams/da
baclofen (up to 30 milligrams/day) for acquired pendular nystagmus, howe
effective for downbeat nystagmus (Averbuch-Heller et al, 1997). In 15 pat
nystagmus, gabapentin significantly improved visual acuity and median ey
produced no significant change in visual acuity and only affected eye spe
patients with downbeat or torsional downbeat nystagmus, changes in mec
less consistent with both drugs. In all 21 patients, gabapentin produced a
near visual acuity (p less than 0.05) and decrease in median eye speed (p
no significant effect on visual acuity but did reduce median, vertical eye sp

4.6.C Lamotrigine

4.6.C.1 Mood disorder

a) Preliminary results from a cross-over study (randomized, double- blind may be superior to GABAPENTIN, as well as placebo, for the improveme (n=31) (Frye et al, 2000). Study subjects included bipolar I (11), bipolar II the bipolar, 23 were rapid-cycling); all had tried other mood stabilizing age those who had responded by 6 weeks were 52% for lamotrigine, 26% for based on the Clinical Global Impression (CGI) scale modified for bipolar il gabapentin); responders were defined as those who were much or very m Both agents were well-tolerated. The one exception was a patient who de lamotrigine; the rash progressed to toxic epidermal necrolysis, requiring tr made a full recovery. A trend showed that subjects tended to lose weight weight gained on gabapentin. Lamotrigine was initiated at a dose of 25 mi titrated to 50 mg/day in week 2, 50 to 100 mg/day in week 3, 150 to 300 n 500 mg for weeks 5 to 6. Gabapentin was given at an initial daily dose of the end of week 1, 2700 mg by the end of the second week, 3600 mg by v 4800 mg by week 5 to 6. Mean daily doses as of week 6 were 274 mg for gabapentin.

4.6.C.2 Adverse Effects

a) In healthy volunteers, cognitive difficulties were associated with topirar lamotrigine had only minimal effects (Martin et al, 1999a). Healthy young receive topiramate 5.7 milligrams/kilogram (mg/kg), lamotrigine 7.1 mg/kg were titrated up over 4 weeks. Neurobehavioral performances were then and 4 weeks. For the visual serial addition test, the topiramate group mad week 2 (p less than 0.02) and during week 4 (p less than 0.004) than the On the symbol digits modalities test, the topiramate group performed poor gabapentin at week 2 (p less than 0.005) and worse than the lamotrigine 0.04). On memory tests at week 2 the topiramate group was worse than th 0.05). The lamotrigine group was below that of the gabapentin group but a week 4 the groups were similar. The topiramate group also reported more week 4 compared to the lamotrigine and gabapentin groups (p less than 0 hostility symptoms than the lamotrigine group at week 4 (p less than 0.02) should be evaluated.

4.6.D Lorazepam

4.6.D.1 Alcohol withdrawal syndrome

a) In a randomized, double-blind trial (n=100), high-dose gabapentin led Institute Withdrawal Assessment for Alcohol-revised (CIWA-Ar) scores co outpatients with alcohol withdrawal. Patients with alcohol dependence and and Statistical Manual of Mental Disorders Fourth Edition (DSM-IV) criteri score of 26 or higher, and a CIWA-Ar score of 10 or greater who voluntee withdrawal received 4 days of gabapentin or lorazepam. One of the follow gabapentin were administered: 1) 200 milligrams (mg) 3 times daily for 3 day 4 (600 mg arm; n=16); 2) 300 mg 3 times daily for 3 days, then 300 m arm; n=28; mean age, 38.4 +/- 1.82 years (yr); mean drinks/day in previou or 3) 400 mg 3 times daily for 3 days, then 400 mg twice daily on day 4 (h 40.5 +/- 2.25 yr; mean drinks/day in previously 14 days, 16.8 +/- 2.18 drin was discontinued after one near syncopal event and 2 patient-reported se patients in this arm were not included in the final analysis. The lorazepam administered as 2 mg 3 times daily for 3 days, then 2 mg twice daily on da 1.83 yr; mean drinks/day in previously 14 days, 11.4 +/- 1.11 drinks). CIW daily during the medication phase and on 1, 2, and 7 days posttreatment received oral thiamine 100 mg daily for 12 days. Patients could take blind gabapentin or lorazepam as needed on days 1 to 4 to treat subjective syn there were no significant differences (p=0.75) in supplemental medication lorazepam-treated patients. The mean CIWA-Ar score was significantly lo arm but not the low-dose gabapentin arm compared with the lorazepam a (gabapentin: low-dose, 4.52 +/- 39 (standard error (SE)); high-dose, 3.14 0.38 (SE); high-dose gabapentin versus (vs) lorazepam p less than 0.05) (gabapentin: low-dose, 1.79 +/- 0.32 (SE); high-dose, 1.03 +/- 0.31 (SE); high-dose gabapentin vs lorazepam p less than 0.01). Mean alcohol cravi analog scale of zero millimeters (mm) (no discomfort) to 100 mm (greates less than 0.05) lower in patients who received gabapentin (gabapentin: lo dose, 28.73 +/- 4.6 (SE)) compared with lorazepam (42.7 +/- 4.7 (SE)) du however, alcohol craving scores were not significantly different between th phase (gabapentin: low-dose, 13.9 +/- 5.3 (SE); high-dose, 20.4 +/- 4.8 (S

Mean anxiety scores (evaluated using the Zung Anxiety Scale) were signi
patients who received gabapentin (gabapentin: low-dose, 32.11 +/- 1.74 (
(SE)) compared with lorazepam (36.98 +/- 1.5 (SE)) during the medicatio
score was significantly (p less than 0.01) improved in the high-dose gaba
gabapentin arm compared with lorazepam arm during the follow-up phase
1.3 (SE); high-dose, 28.8 +/- 1.2 (SE); lorazepam: 33.9 +/- 1.1 (SE)). Duri
in the low-dose gabapentin arm had significantly (p less than 0.01) improv
(BDI) scores and patients in the high-dose gabapentin arm had significant
sleep scores evaluated using the Epworth Sleepiness Scale compared wi
The incidence of patient-reported adverse effects did not differ between th
arms (p=0.74) (Myrick et al, 2009).

4.6.E Nortriptyline Hydrochloride

4.6.E.1 Postherpetic neuralgia

a) In a randomized, double-blind, parallel-group, 9-week study (n=76) in p
neuralgia (PMH), gabapentin was as effective, but was tolerated better wi
nortriptyline. Adult PMH patients with a history of greater than 8 weeks of
pain intensity of at least 40 millimeters (mm) on a 100 mm visual analog s
randomization, and average pain score of at least 4 on the Likert scale du
randomized after a 1-week run-in period to receive nortriptyline 25 milligra
age 52.5 years; n=38) or gabapentin 300 mg orally three times daily (mea
weeks. Doses were escalated based on tolerability and pain relief every 2
nortriptyline 50 mg three times daily and gabapentin 900 mg three times d
pain score on the Likert scale was 5.8 +/- 1.4 and 5.6 +/- 1.1 in the nortrip
respectively. VAS pain score was also comparable between treatment arr
5.3 +/- 1.3 and 4.8 +/- 1.2, respectively. Results of the study were based o
population (n=70). For the primary efficacy outcome of change in pain sco
baseline to study end, there was a 47.6% and 42.8% reduction in average
and gabapentin groups, respectively, with 38.8% (n=14) and 38.2% (n=13
and gabapentin groups, respectively, showing improvement in their baseli
than 50% improvement in baseline pain scores on the Likert scale was re
patients, respectively, in the nortriptyline and gabapentin groups. For seco
significant improvement in sleep scores (46% vs 52%, for nortriptyline and
and Short Form McGill Pain Questionnaire (SF-MPQ) scores for pain were
groups. Clinical effectiveness was improved (27.8% vs 23.8%, for nortripty
respectively). Approximately two-thirds of patients in both groups moved t
in the categorical scale, and disability rating improved (41.5% vs 39.6%, f
respectively). The results of the primary and secondary outcomes, howev
significant differences between the 2 groups. In the nortriptyline group, 58
adverse events, with dry mouth (50%), constipation (22.2%), postural hyp
(16.7%) being the most common. Gabapentin was well tolerated with slee
(11.8%) adverse event reported (Chandra et al, 2006).

4.6.F Propranolol

4.6.F.1 Essential tremor

a) In a comparative, double-blind, crossover, placebo-controlled study, ga
three times daily was as effective as propranolol 40 mg three times daily v
treatment of patients with essential tremor (Gironell et al, 1999). Patients
initially receive either gabapentin, propranolol, or placebo for a two-week
crossed-over to the other 2 arms with a 1-week washout period between t
with gabapentin and propranolol treatment were seen in the Tremor Clinic
clinical examination and motor task performance as compared to placebo
respectively). No differences in self-reported subjective disability scale or
from accelerometry were noted between the 3 groups.

4.6.G Ropinirole

4.6.G.1 Restless legs syndrome

a) Investigators of an open-label, pilot study did not find significant differe
efficacy of ropinirole and gabapentin for treatment of idiopathic restless le
randomized to receive either gabapentin 300 milligrams (mg) 2 hours befo
0.25 mg in the late afternoon and 2 hours before bedtime (n=8). Doses we
gabapentin and 0.25 mg for ropinirole until symptoms of restless leg synd
disappeared. After 4 weeks of therapy, mean gabapentin doses were 750
and mean ropinirole doses were 0.78 mg (range 0.25 to 1.5 mg). Polysom

number of periodic leg movements per hour of sleep time (PLMS index) h
arm from 39.2 times to 22.6 (p=0.012) and the number of arousals, due to
sleep, per hour of sleep time (PLMS arousal index) decreased from 6.7 to
efficiency, total sleep time, sleep latency and duration of slow wave sleep
the ropinirole arm, the PLMS index decreased from 48.4 to 13.2 times (p=
arousal index did not significantly change (8.6 versus 9.3, p=0.123). Unlik
the ropinirole arm had significant changes in their sleep architecture comp
sleep (p=0.007), less deep (p=0.001) and REM sleep (p=0.003), less tota
efficiency (p=0.01). Six to 10 months later, gabapentin patients were still
900 mg per day). Of the 8 patients on ropinirole, only 3 were still on thera
experience sufficient relief and was switched to gabapentin and the other
take any medications. Mild and transient numbness, dizziness, sleepiness
with gabapentin use. Ropinirole was associated with nausea and sleepine
transient (Happe et al, 2003).

4.6.H Topiramate

1) Adverse Effects

a) In healthy volunteers, cognitive difficulties were associated with topirar
lamotrigine had only minimal effects (Martin et al, 1999). Healthy young a
receive topiramate 5.7 milligrams/kilogram (mg/kg), lamotrigine 7.1 mg/kg
were titrated up over 4 weeks. Neurobehavioral performances were then
and 4 weeks. For the visual serial addition test, the topiramate group mad
week 2 (p less than 0.02) and during week 4 (p less than 0.004) than the
On the symbol digits modalities test, the topiramate group performed poo
gabapentin at week 2 (p less than 0.005) and worse than the lamotrigine
0.04). On memory tests at week 2 the topiramate group was worse than t
0.05). The lamotrigine group was below that of the gabapentin group but
week 4 the groups were similar. The topiramate group also reported more
week 4 compared to the lamotrigine and gabapentin groups (p less than
hostility symptoms than the lamotrigine group at week 4 (p less than 0.02
should be evaluated.

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Last Modified: August 11, 2009

DRUGDEX® Evaluations

PIMOZIDE

0.0 Overview

1) Class
- **a)** This drug is a member of the following class(es):
  Antipsychotic
  Diphenylbutylpiperidine
  Dopamine Antagonist

2) Dosing Information
- **a)** Adult
  - **1)** Gilles de la Tourette's syndrome
    - **a)** initial, 1-2 mg a day ORALLY in divided doses; may increase dosage gradually every other day to a MAX dose of 10 mg/day or 0.2 mg/kg/day whichever is smaller
- **b)** Pediatric
  - **1)** Safety and effectiveness not established in children under age 12
    - **a)** Gilles de la Tourette's syndrome
      - **1)** initial, 0.05 mg/kg/day ORALLY preferably taken once at bedtime; the dosage may be increased every third day to a maximum of 0.2 mg/kg/day not to exceed 10 mg/day

3) Contraindications
- **a)** aggressive schizophrenics when sedation is required
- **b)** concurrent administration of pemoline, methylphenidate or amphetamines that may cause motor and phonic tics
- **c)** concurrent administration with dofetilide, sotalol, quinidine, other Class Ia and III anti-arrhythmics, mesoridazine, thioridazine, chlorpromazine, and droperidol
- **d)** concurrent administration with sparfloxacin, gatifloxacin, moxifloxacin, halofantrine, mefloquine, pentamidine, arsenic trioxide, levomethadyl acetate, dolasetron mesylate, probucol, tacrolimus, ziprasidone, sertraline, and macrolide antibiotics
- **e)** concurrent administration with drugs that have demonstrated QT prolongation as one of their pharmacodynamic effects, and less potent inhibitors of CYP3A4 (zileuton, fluvoxamine)
- **f)** congenital or drug-induced long QT syndrome
- **g)** high doses (greater than 10 mg/day)
- **h)** history of cardiac arrhythmias
- **i)** hypersensitivity to pimozide
- **j)** Parkinson's disease
- **k)** patients with known hypokalemia or hypomagnesemia
- **l)** severe central nervous system depression
- **m)** simple tics or tics not associated with Tourette's syndrome

4) Serious Adverse Effects
- **a)** Agranulocytosis
- **b)** Cholestatic jaundice syndrome
- **c)** Death
- **d)** Disorder of hematopoietic structure
- **e)** Drug-induced lupus erythematosus, Systemic
- **f)** Ineffective thermoregulation, Heatstroke or hypothermia
- **g)** Leukopenia
- **h)** Neuroleptic malignant syndrome
- **i)** Obstipation
- **j)** Paralytic ileus
- **k)** Priapism
- **l)** Prolonged QT interval
- **m)** Seizure
- **n)** Thrombocytopenia
- **o)** Torsades de pointes

5) Clinical Applications
- **a)** FDA Approved Indications
  - **1)** Gilles de la Tourette's syndrome

1.0 Dosing Information

Drug Properties

Storage and Stability

Adult Dosage

Pediatric Dosage

1.1 Drug Properties

A) Information on specific products and dosage forms can be obtained by referring to the Tradename List (Product Index)

B) Synonyms
Pimozide

C) Physicochemical Properties

1) Molecular Weight

a) 461.56 (Canada, 1997)

2) Solubility

a) Systemic: Less than 0.01 mg per mL in water (Prod Info Orap, 96).

1.2 Storage and Stability

A) Oral route

1) Store Orap(R) tablets at controlled room temperature, 15 to 30 degrees Celsius (59 to 86 degrees Fahrenheit) (Prod Info Orap(R), 2003). Dispense in a light resistant container.

1.3 Adult Dosage

Normal Dosage

Dosage in Renal Failure

Dosage in Hepatic Insufficiency

Dosage in Geriatric Patients

1.3.1 Normal Dosage

Chronic schizophrenia

Gilles de la Tourette's syndrome

1.3.1.A Chronic schizophrenia

1) SUMMARY

a) Usual daily oral doses range from 2 to 12 milligrams and doses up to 20 mg have been used. Moderate doses of neuroleptic drugs, defined as between 165 and 375 milligram equivalent of chlorpromazine, were preferred in the maintenance therapy of chronic psychosis in a meta-analysis of 22 randomized control trials (Bollini et al, 1994). The association between dose and clinical effectiveness and side effects was assessed. At doses greater than 375 milligram equivalent of chlorpromazine, there was no incremental clinical improvement seen, and adverse reactions occurred at a significantly higher rate.

2) Effective doses in chronic schizophrenia have been 2 to 12 milligrams daily (Kolivakis et al, 1974b; Cesarec et al, 1974); (Lapierre & Lavallee, 1975; Simms & Burnside, 1975)(Claghorn, 1974a; Gross, 1974b; DeSilva & Masheter, 1971; Janssen et al, 1972a). The optimal maintenance dose for patients previously maintained on other psychotic agents appears to be 6 mg daily (Pinder et al, 1976b). In all studies, lower doses are initiated (2 mg daily) and increased based upon clinical response.

3) Evidence from clinical studies suggest that pimozide may be more effective in the treatment of autistic patients with chronic schizophrenia and associated emotional withdrawal, delusions and hallucinations, as opposed to the agitated and aggressive patients (Janssen et al, 1972a; Pinder et al, 1976b).

4) There is no relationship between types of previous antipsychotic medications and response to pimozide (Pinder et al, 1976b).

5) Pimozide was equally effective in doses of 3 or 8 milligrams daily in the treatment of schizophrenia; however, extrapyramidal symptoms were significantly higher in patients taking 8 milligram doses. The author recommends initial doses of 3 milligrams daily (Fleischhauer, 1978).

1.3.1.B Gilles de la Tourette's syndrome

1) A slow and gradual introduction of pimozide is required to suppress tics; the dose should be carefully titrated to balance tic suppression with the untoward side effects of the drug. The manufacturer recommends initial doses of 1 to 2 milligrams/day in divided doses, increasing thereafter every other day; most patients are maintained effectively on doses of less than 0.2 milligram/kilogram/day, or 10 milligram/day, whichever is less. Doses of 0.2 milligram/kilogram/day or 10 milligrams/day should not be exceeded (Prod Info Orap (R), 2003).
2) Doses of 2 to 12 milligrams daily have been effective in GILLES DE LA TOURETTE SYNDROME (Ross & Moldofsky, 1978b).

1.3.1.C IMPORTANT NOTE
1) Sudden, unexpected deaths have occurred in patients receiving HIGH DOSES of Orap(R), ie, doses greater than 10 milligrams (Mulcahy, 1999).

1.3.1.D SINGLE DAILY DOSE
1) Due to the long half-life of pimozide, the drug may be administered once daily (Pinder et al, 1976b). Other reports have indicated that 4 times the initial single daily dose was effective when administered weekly in chronic schizophrenia (once weekly to a maximum of 60 milligrams). In one study, the average dose of pimozide weekly was 40 milligrams (range, 10 to 60 milligrams) (McCreadie et al, 1982b).

1.3.2 Dosage in Renal Failure
A) Reductions in dose do not appear necessary in renal failure due to the small amount of pimozide excreted unchanged in the urine (less than 1% unchanged drug) (Baro et al, 1972a).

1.3.3 Dosage in Hepatic Insufficiency
A) Reductions in dose should be considered in severe hepatic insufficiency since a large portion of the drug is metabolized in the liver (Baro et al, 1972a).

1.3.4 Dosage in Geriatric Patients
A) An initial dosage of 1 milligram/day is recommended in geriatric patients (Semla et al, 1997).

1.4 Pediatric Dosage

Normal Dosage

Dosage in Renal Failure

Dosage in Hepatic Insufficiency

1.4.1 Normal Dosage

Oral route

Gilles de la Tourette's syndrome

1.4.1.A Oral route
1) Doses of 1 to 2 milligrams daily have been effective in the treatment of schizophrenic and behavioral symptoms in children age 9 to 14 years (Pangalila-Ratulangi, 1973). Other data indicate the efficacy of 1 to 3 milligrams pimozide daily in adolescents 13 to 20 years of age with childhood or juvenile schizophrenia (LeVann, 1971).

1.4.1.B Gilles de la Tourette's syndrome
1) The manufacturer recommends an initial dose of 0.05 milligram/kilogram taken at bedtime. Every third day the dose may be increased to a maximum of 0.2 mg/kg but should not exceed 10 mg/day. Dose-response data concerning the effects of pimozide on tic manifestations in children younger than 12 years are unavailable (Prod Info Orap(R), 2003).
2) PIMOZIDE had a similar safety profile in 36 children ages 2 to 12 years as it did in older patients, according to a 24-week open label study. Thus, there are no safety findings that would preclude its use in pediatric patients 2 to 12 years of age. However, the manufacturer does not recommend its use in pediatric patients for any condition other than Tourette's syndrome as the drug has not been evaluated in other childhood disorders (Prod Info Orap(R), 2003).
3) Others recommend starting doses in both adults and children of 1 milligram pimozide at bedtime, with dose increases of 1 milligram every 5 to 7 days until symptoms are observed to decrease by at least 70%, or adverse effects occur without symptomatic benefit (or if symptoms decrease and adverse effects occur at the same time). If toxicity interferes slightly with functioning, dose reductions of 1 milligram weekly are suggested. If toxicity is severe, the dose should be reduced by one half immediately; titration should be

reinstituted at intervals ranging from 7 to 30 days after disappearance of severe adverse effects (Shapiro et al, 1987).

1.4.1.C IMPORTANT NOTE

1) Sudden, unexpected deaths have occurred in patients receiving HIGH DOSES of Orap(R), ie, doses greater than 10 milligrams (Mulcahy, 1999).

1.4.2 Dosage in Renal Failure

A) Reductions in dose do not appear necessary in renal failure due to the small amount of pimozide excreted unchanged in the urine (less than 1% unchanged drug) (Baro et al, 1972a).

1.4.3 Dosage in Hepatic Insufficiency

A) Reductions in dose should be considered in severe hepatic insufficiency since a large portion of the drug is metabolized in the liver (Baro et al, 1972a).

2.0 Pharmacokinetics

Onset and Duration

Drug Concentration Levels

ADME

2.1 Onset and Duration

A) Onset

1) Peak Response

a) Schizophrenia: 1 to 3 weeks (Fleischhauer, 1978a); (Chouinard, 1970).

B) Duration

1) Single Dose

a) Schizophrenia, oral: 24 to 48 hours (Pinder et al, 1976a).

2.2 Drug Concentration Levels

A) Time to Peak Concentration

1) Oral: 6 to 8 hours (Prod Info Orap(R), 2003a; McCreadie et al, 1979; Baro et al, 1972).

a) Peak plasma levels following single 6 mg and 24 mg doses were 4 ng/mL and 16 ng/mL at 6 hours, respectively (McCreadie et al, 1979).

b) Following multiple doses of 6 mg once daily for 4 days, peak plasma concentrations were 4, 5, 8, and 10 ng/mL on each successive day (McCreadie et al, 1979).

c) Following a single 2 mg oral dose of pimozide in children with Tourette's syndrome, peak plasma concentrations of 7.2 ng/mL were achieved in approximately 7 hours (Sallee et al, 1987).

2.3 ADME

Absorption

Metabolism

Excretion

Elimination Half-life

2.3.1 Absorption

A) Bioavailability

1) More than 50% (Prod Info Orap(R), 2003a).

a) More than 50% of an oral dose of pimozide is absorbed and the drug undergoes significant hepatic first- pass metabolism (Prod Info Orap(R), 2003a).

2.3.3 Metabolism

A) Metabolism Sites and Kinetics

1) Liver: Eextensive (Prod Info Orap(R), 2003a; Pinder et al, 1976a; Baro et al, 1972).

a) Metabolized via N-dealkylation (Prod Info Orap(R), 2003a; Pinder et al, 1976a; Baro et al, 1972).

b) PIMOZIDE is metabolized at least in part by cytochrome P450 IIIA (CYP3A) isoenzymes. Significant drug interactions may occur if pimozide is co-administered with drugs that inhibit CYP3A enzymes, ie,

macrolides (clarithromycin, erythromycin, dirithromycin, troleandomycin), azole antifungals (ketoconazole, itraconazole), protease inhibitors (ritonavir, saquinavir, indinavir, nelfinavir), nefazodone, and zileuton. Pimozide may also be metabolized by CYP1A2 isoenzymes and a theoretical potential exists for drug interactions between pimozide and drugs which inhibit CYP1A2 (Prod Info Orap(R), 2003a; Mulcahy, 1999).

B) Metabolites
1) 4, 4-bis-(4-fluorophenyl) butyric acid, (Prod Info Orap(R), 2003a; Baro et al, 1972).
2) 1-(4-piperidyl)-2-benzimidazolinone, (Prod Info Orap(R), 2003a; Baro et al, 1972).

2.3.4 Excretion
A) Kidney
1) Renal Excretion (%)
a) 38% to 45% (Pinder et al, 1976a; Baro et al, 1972).
2) Excreted drug is 1% unchanged drug and two-thirds the 4-bis-(4-fluorophenyl) butyric acid metabolite (Baro et al, 1972).
3) Renal excretion is the major route of elimination of pimozide and its metabolites (Prod Info Orap(R), 2003a).

2.3.5 Elimination Half-life
A) Parent Compound
1) ELIMINATION HALF-LIFE
a) 53 to 55 hours (Prod Info Orap(R), 2003a; McCreadie et al, 1979).
1) An elimination half-life of 66 hours was reported in children with Tourette's syndrome following a single 2 mg oral dose (Sallee et al, 1987).

3.0 Cautions

Contraindications

Precautions

Adverse Reactions

Teratogenicity/Effects in Pregnancy/Breastfeeding

Drug Interactions

3.1 Contraindications
A) aggressive schizophrenics when sedation is required
B) concurrent administration of pemoline, methylphenidate or amphetamines that may cause motor and phonic tics
C) concurrent administration with dofetilide, sotalol, quinidine, other Class Ia and III anti-arrhythmics, mesoridazine, thioridazine, chlorpromazine, and droperidol
D) concurrent administration with sparfloxacin, gatifloxacin, moxifloxacin, halofantrine, mefloquine, pentamidine, arsenic trioxide, levomethadyl acetate, dolasetron mesylate, probucol, tacrolimus, ziprasidone, sertraline, and macrolide antibiotics
E) concurrent administration with drugs that have demonstrated QT prolongation as one of their pharmacodynamic effects, and less potent inhibitors of CYP3A4 (zileuton, fluvoxamine)
F) congenital or drug-induced long QT syndrome
G) high doses (greater than 10 mg/day)
H) history of cardiac arrhythmias
I) hypersensitivity to pimozide
J) Parkinson's disease
K) patients with known hypokalemia or hypomagnesemia
L) severe central nervous system depression
M) simple tics or tics not associated with Tourette's syndrome

3.2 Precautions
A) elderly patients with dementia-related psychosis (unapproved use); increased risk of death reported with both conventional and atypical antipsychotics when used to treat behavorial and psychological symptoms associated with dementia (US Food and Drug Administration, 2008)
B) concomitant administration with inhibitors of cytochrome P450 IA2 (CYP1A2) and CYP 3A4 enzymes
C) concomitant use of CNS depressants (exaggerated depression)
D) concomitant use of fluoxetine and pimozide may cause bradycardia
E) elderly patients (increased sensitivity)

F) epileptic patients (may exacerbate seizures)
G) grapefruit juice consumption
H) history of neuroleptic malignant syndrome, tardive dyskinesia
I) impaired liver or kidney function

3.3 Adverse Reactions

Cardiovascular Effects

Dermatologic Effects

Endocrine/Metabolic Effects

Gastrointestinal Effects

Hepatic Effects

Neurologic Effects

Ophthalmic Effects

Psychiatric Effects

Renal Effects

Reproductive Effects

Other

3.3.1 Cardiovascular Effects

Cardiovascular finding

Dead - sudden death

Hypotension

3.3.1.A Cardiovascular finding

1) Sudden cardiac death, prolongation of the QT interval with possible ventricular arrhythmias, and hypotension are described with the administration of pimozide.

3.3.1.B Dead - sudden death

1) Summary

a) Sudden death is described with administration of pimozide. The mechanism may be due to PROLONGED QT INTERVAL and the development of VENTRICULAR ARRHYTHMIAS (Prod Info Orap(R), 2003; Fulop et al, 1987; Anon, 1985; Pinder et al, 1976; Huber et al, 1971).

2) LITERATURE REPORTS

a) During experimental studies of pimozide for conditions other than Tourette's syndrome, sudden, unexpected deaths occurred. Pimozide dosages were approximately 1 milligram/kilogram (mg/kg). It is speculated that prolongation of the QT interval predisposed patients to ventricular arrhythmia. The manufacturer recommends performing an electrocardiogram (ECG) before initiation of pimozide therapy and periodically thereafter, especially during periods of dose adjustment (Prod Info Orap(R), 2003).

b) Electrocardiogram (ECG) changes seen during clinical trials in Tourette's syndrome and schizophrenia patients include prolongation of the QT interval, flattening, notching, and inversion of the T wave, and the appearance of U waves. Sudden, unexpected deaths have occurred at doses greater than 20 milligrams/day (Prod Info Orap(R), 2003).

c) The manufacturer of pimozide has reported sudden, unexpected deaths in some patients taking doses greater than 10 milligrams (mg). Deaths are due to ventricular dysrhythmia probably as a result of prolongation of the QT interval. Drug interactions with drugs inhibiting metabolism of pimozide and

resulting in increased plasma concentrations could result in QT prolongation (Anon, 1999).
d) An association with sudden death in schizophrenic patients has been postulated from doses in the 1 milligram/kilogram (mg/kg) range. The mechanism may be from prolongation of the QT interval (Anon, 1985; Fulop et al, 1987).
e) About 25% of patients taking therapeutic dosages of pimozide have prolonged QT intervals similar to those caused by the phenothiazines (Anon, 1985).
f) Most studies have reported no significant effect of pimozide therapy, in high or low doses, on the electrocardiogram (Pinder et al, 1976).
g) One report of T WAVE CHANGES on electrocardiogram has been reported with pimozide therapy; however, a definite cause/effect relationship was not established (Huber et al, 1971).

3.3.1.C Hypotension
1) Summary
a) Isolated reports of hypotension have been reported during treatment with pimozide (Pinder et al, 1976; Arfwidsson et al, 1971; Chouinard et al, 1970a).

3.3.2 Dermatologic Effects

Acne

Dermatological finding

Facial edema

Rash

3.3.2.A Acne
1) Summary
a) CASE REPORT - One case of ACNE VULGARIS has been reported possibly in association with pimozide administration (Chouinard et al, 1970a).

3.3.2.B Dermatological finding
1) Skin rashes, acne, and facial edema are described with the administration of pimozide.

3.3.2.C Facial edema
1) Summary
a) Facial edema has been reported with administration of pimozide (Morris et al, 1970a).

3.3.2.D Rash
1) Summary
a) ERYTHEMATOUS SKIN RASHES occurred infrequently during pimozide administration (Pinder et al, 1976).

3.3.3 Endocrine/Metabolic Effects

Hyperprolactinemia

Hyponatremia

Weight gain

Weight loss

3.3.3.A Hyperprolactinemia
1) Overview
a) Antipsychotic-induced hyperprolactinemia was reported in 65.6%, 45.1%, and 42.4% of women of childbearing potential, postmenopausal women, and men, respectively, in an open-label, clinical trial of patients treated with first-generation antipsychotics or risperidone at average doses of 4.2 to 5.2 mg/day. Compared to baseline, prolactin levels were significantly elevated (p less than 0.05) following use of first-generation antipsychotics (ie, chlorpromazine, droperidol, flupenthixol, fluphenazine, haloperidol, paliperidone, perazine, perphenazine, pimozide, trifluoperazine, and zuclopenthixol) or

risperidone in several clinical trials of patients with schizophrenia. Younger patients and women of childbearing potential have a greater risk for hyperprolactinemia following treatment with higher doses of these antipsychotics. Hyperprolactinemia may potentially result in menstrual disturbances, sexual dysfunction, bone mineral density (ie, osteopenia and osteoporosis), and breast and pituitary tumors (Bostwick et al, 2009).

2) Hyperprolactinemia has been reported with antipsychotic drugs; the elevation in prolactin persists during chronic administration (Prod Info Orapred(R), 2004). Pimozide is associated with increased serum prolactin (Delitala, 1977).

3) The effect of pimozide on hypothalamo-pituitary functions was studied in 13 children with behavior disorders. Pimozide was associated with an increase in serum prolactin levels. No significant influence on growth hormone or cortisol secretion was induced by hypoglycemia. Serum thyroxine and triiodothyronine were not influenced by pimozide (Suwa et al, 1984).

a) Management

1) Appropriate drug selection, monitoring and management are all important when prescribing antipsychotics that have the potential for inducing hyperprolactinemia. Prior to treatment with an antipsychotic, question patients regarding changes in libido or galactorrhea. Female patients should be assessed for menstrual abnormalities and male patients, for erectile or ejaculatory dysfunction. In the event that any of these symptoms are present, consider obtaining baseline prolactin levels. Patients should be informed of the potential for sexual dysfunction with antipsychotic use. Several weeks after an antipsychotic is initiated, obtain a prolactin level measurement. In cases where the patient experiences troublesome adverse effects related to elevated prolactin levels and discontinuing the antipsychotic is not an option, treatment with a dopamine agonist (eg, bromocriptine or cabergoline) should be considered (Bostwick et al, 2009).

3.3.3.B Hyponatremia

1) Hyponatremia has been reported during post-marketing use of pimozide; causality cannot be established (Prod Info Orapred(R), 2004).

3.3.3.C Weight gain

1) Weight gain has been reported in patients treated with pimozide for conditions other than Tourette's disorder (Prod Info Orapred(R), 2004).

3.3.3.D Weight loss

1) Weight loss has been reported in patients treated with pimozide for conditions other than Tourette's disorder (Prod Info Orapred(R), 2004).

3.3.4 Gastrointestinal Effects

Gastrointestinal tract finding

Loss of appetite

3.3.4.A Gastrointestinal tract finding

1) Summary

a) Pimozide has infrequently been associated with gastrointestinal side effects including anorexia, NAUSEA, ABDOMINAL PAIN, DIARRHEA, and CONSTIPATION (Kline et al, 1977a; Pinder et al, 1976; Singh, 1971).

2) Nausea, abdominal pain, diarrhea, constipation, and anorexia are associated with the administration of pimozide.

3.3.4.B Loss of appetite

1) Summary

a) Significant weight loss (average 5.4 kilograms) was reported in all patients receiving pimozide for maintenance treatment of chronic schizophrenia (McCreadie et al, 1982a).

3.3.6 Hepatic Effects

3.3.6.A Hepatotoxicity

1) Transient increases in alkaline phosphatase have occurred during pimozide treatment; however, a cause/effect relationship has not been established. No cases of hepatic damage have been reported (Huber et al, 1971).

3.3.9 Neurologic Effects

Extrapyramidal disease

Neuroleptic malignant syndrome

Neurological finding

Parkinsonism

Seizure

3.3.9.A Extrapyramidal disease

1) Summary

a) Extrapyramidal reactions to pimozide are the most frequent side effects of the drug, primarily TARDIVE DYSKINESIA, AKATHISIA, DYSTONIC REACTIONS, TREMORS and PARKINSONIAN SYMPTOMS, occurring in up to 15% of patients treated. Extrapyramidal reactions are generally dose-related in most patients and have been reversed by dose reduction in the majority (Prod Info Orap(R), 2003; Pinder et al, 1976).

2) LITERATURE REPORTS

a) Tardive dyskinesia (TD) due to pimozide seems to be rare, occurring in some patients on long-term therapy or after drug therapy has been discontinued. The risk may be greater for elderly patients on high-dose therapy (Prod Info Orap(R), 2003).

b) A 6-year-old autistic boy developed repeated episodes of ACUTE DYSTONIC REACTION while receiving pimozide and subsequently thioridazine. Acute dystonic reactions occur within the first few days of neuroleptic administration and they are well controlled with diphenhydramine in children (Ernst et al, 1993).

c) Tardive dyskinesia appeared in a 17-year-old boy following withdrawal from a combination of pimozide and thioridazine. The CHOREODYSKINETIC MOVEMENT of the limbs and the trunk cleared with anticholinergic drugs but were dramatically worsened by dopaminergic receptor blockers (Monteiro, 1985).

d) A case is reported of a 16-year-old female treated with pimozide 4 milligrams/day (mg/day) for 1 day, the dose increased to 6 mg/day for 1 day. She developed neck stiffness and OCULOGYRIC CRISIS, which resolved with benztropine 2 milligrams intramuscularly. The dose was reduced to 4 milligrams/day (mg/day) on day 3 but later in the day she suffered a tonic-clonic seizure. Pimozide was discontinued and no further seizures occurred (Larkin, 1983).

e) Some evidence indicates that pimozide exerts more prolific extrapyramidal effects than haloperidol (Haas & Beckmann, 1982a).

f) Extrapyramidal reactions respond readily to anticholinergic agents. Tardive dyskinesia was reported in 35% of patients receiving pimozide in one study (McCreadie et al, 1982a).

g) Pimozide has been mentioned as the causal agent in tardive dyskinesia (TD) in one review (Burke et al, 1982).

h) A single case of a 50-year-old alcoholic with late onset extrapyramidal side effects thought related to pimozide and alcohol withdrawal or alcohol intake was reported (Freed, 1982).

i) A severe dystonic reaction requiring discontinuance of pimozide and treatment with benztropine and diazepam was reported in a patient taking 4 milligrams/day for approximately 6 weeks (Logan et al, 1982).

j) Sixteen patients were given pimozide doses up to 60 milligrams/day for 28 days with few side effects. Most notable were mild extrapyramidal effects (tremors and PERIORAL DYSKINESIAS) which responded to antiparkinsonian medication. Side effects were never prominent enough to require discontinuance of therapy (Shopin & Selzer, 1977).

k) Extrapyramidal effects may occur with therapeutic use. Extrapyramidal effects appeared only in the pimozide group in a placebo-controlled trial (Huber et al, 1971).

3.3.9.B Neuroleptic malignant syndrome

1) Summary

a) Neuroleptic malignant syndrome has been reported after pimozide administration (Prod Info Orap (R), 2003).

2) Incidence: rare

3.3.9.C Neurological finding

1) Summary

a) AKATHISIA, SEDATION, and DROWSINESS, are described with the administration of pimozide (Prod Info Orap(R), 2003; Bloch et al, 1997; Kenway, 1973; Pinder et al, 1976; Singh, 1971; Kenway, 1973; Chouinard et al, 1970a).

2) Excitement, insomnia, sedation, tinnitus, headache, extrapyramidal effects, dystonic reactions and seizures are described with the administration of pimozide.

3) LITERATURE REPORTS

a) Drowsiness was reported in one 35-year-old patient receiving pimozide (Kenway, 1973).

b) Infrequently, pimozide has been associated with excitement, insomnia, anxiety, agitation, tinnitus, and headache (Pinder et al, 1976; Singh, 1971; Kenway, 1973; Chouinard et al, 1970a).

3.3.9.D Parkinsonism

1) Summary

a) Contrary to common belief, the results of a retrospective cohort study suggest that atypical antipsychotics may not be safer than typical antipsychotics when dose and potency are considered (Rochon et al, 2005).

2) LITERATURE REPORTS

a) The results of a cohort study indicate that high-dose atypical antipsychotic therapy carries a similar risk for the development of parkinsonism as does typical antipsychotic therapy. In a population-based, retrospective cohort study, adults (aged 66 years and older) with evidence of dementia were followed for up to 1 year for the development of parkinsonism symptoms associated with typical or atypical antipsychotic use. As compared with older adults receiving atypical antipsychotic therapy (ie, olanzapine, risperidone, quetiapine), incident parkinsonism was 30% more likely to occur in those taking typical antipsychotics (ie, chlorpromazine, haloperidol, perphenazine) (adjusted HR, 1.3; 95% CI, 1.04 to 1.58), and 60% less likely to occur in patient who did not receive either therapy (HR, 0.4; 95% CI, 0.29 to 0.43). Older adults using higher potency typical antipsychotics had almost a 50% greater risk of experiencing parkinsonism as compared with patients prescribed atypical antipsychotics (all were considered lower potency) (HR, 1.44; 95% CI, 1.13 to 1.84); however, in patients receiving lower potency typical antipsychotics, the risk of developing parkinsonism was no different from that in adults taking atypical antipsychotics (HR, 0.75; 95% CI. 0.48 to 1.15). In addition, a positive dose-related relationship was observed between the occurrence of incident parkinsonism and the use of atypical antipsychotics. The risk for developing parkinsonism was more than twice as great in patients using a high-dose atypical antipsychotic agent as compared with those prescribed a low-dose atypical antipsychotic agent (HR, 2.07; 95% CI, 1.42 to 3.02). Furthermore, patients taking a typical antipsychotic were found to have a similar risk for the development of parkinsonism as patients receiving high-dose atypical antipsychotic therapy (p=ns). The authors conclude that atypical antipsychotics may not be safer than typical antipsychotics when dose and potency are considered (Rochon et al, 2005).

3.3.9.E Seizure

1) Summary

a) Seizures are described with the administration of pimozide (Larkin, 1983; Burkitt & Faulkner, 1972; Pinder et al, 1976; Morris et al, 1970a).

2) Incidence: rare

3) LITERATURE REPORTS

a) A case report described a GRAND MAL SEIZURE in a 16-year-old girl during treatment of anorexia nervosa with pimozide. The seizure occurred after receiving 4 to 6 milligrams/day for 3 days. On the second day of treatment, the patient developed an oculogyric crisis which responded to benztropine (Larkin, 1983).

b) Pimozide may lower the seizure threshold in both epileptic and non-epileptic patients (Pinder et al, 1976).

c) Seizure activity has been reported during pimozide therapy. It is unclear if pimozide possesses epileptogenic potential, but the drug should be used cautiously in epileptic patients (Burkitt & Faulkner, 1972).

d) Seizures are described in three patients with no prior history of seizures and no exposure to epileptogenic drugs. All had been given pimozide and all had the dosage reduced or stopped prior to the seizures. The interval between the dosage change and the onset of seizures was 13 to 31 days. The dose given was not stated (Burkitt & Faulkner, 1972).

e) 13.3% (n=30) of patients given pimozide developed slight tremor and two of these had slight rigidity on doses increasing to 9 milligrams per day (Morris et al, 1970a).

3.3.10 Ophthalmic Effects

Blurred vision

Edema of eyelid

Eye / vision finding

Pupillary paralysis

Retinal pigment deposits

3.3.10.A Blurred vision

1) Summary

a) Blurred vision has occurred infrequently with pimozide therapy (Piyakulmala et al, 1977; Kline et al, 1977a).

3.3.10.B Edema of eyelid

1) Summary

a) Blurred vision has occurred infrequently with pimozide therapy (Piyakulmala et al, 1977; Kline et al, 1977a).

3.3.10.C Eye / vision finding

1) Blurred vision, edema of the eyelids (blepharedema), pupillary paralysis, OCULOGYRIC CRISIS, and retinal pigmentation are described with the administration of pimozide (Sharma et al, 1974).

3.3.10.D Pupillary paralysis

1) Summary

a) Pupillary paralysis was reported in a 24-year-old female following several weeks of therapy with pimozide 6 to 8 milligrams daily for schizophrenia (Crawford, 1971).

2) LITERATURE REPORTS

a) A patient developed parkinsonian tremor of the hands and legs and poor visual acuity followed by paralysis of the ciliary muscle of the eyes with fixed dilated pupils and paralysis of accommodation after pimozide administration. Benztropine 2 milligrams three times a day was administered resulting in alleviation of parkinsonian symptoms. The dose of pimozide was reduced to 2 milligrams daily and orphenadrine 50 milligrams (mg) three times a day was substituted for benztropine. Pupillary response gradually returned to normal over a period of 2 weeks (Crawford, 1971).

3.3.10.E Retinal pigment deposits

1) Summary

a) CASE REPORT - A single case of retinal pigmentation was reported in a patient on long-term fluphenazine who also received pimozide and haloperidol (McQueen, 1983). Other authors indicated no changes in ocular pigmentation with pimozide use as noted by slit-lamp examination (Pinder et al, 1976).

3.3.12 Psychiatric Effects

3.3.12.A Psychiatric sign or symptom

1) Summary

a) DEPRESSION, PHOBIAS and ANXIETY are described with the administration of pimozide (Prod Info Orap(R), 2003; Bloch et al, 1997; Kenway, 1973; Pinder et al, 1976; Singh, 1971; Kenway, 1973; Chouinard et al, 1970a).

2) Depression, anxiety, agitation and phobias are described with the administration of pimozide.

3) LITERATURE REPORTS

a) Four of 7 men being treated for stuttering with pimozide developed depression as measured on the Beck Depression Inventory (Bloch et al, 1997). Pimozide was started at 2 milligrams (mg)/day and increased, as tolerated, to 10 milligrams (mg). Three subjects became euthymic at 7 to 15 days after discontinuation. One subject was successfully treated with an antidepressant. Also, of these 4 subjects, 1 developed akathisia and 3 developed mild parkinsonian symptoms.

b) One of the main advantages of pimozide over other neuroleptics is its low propensity to produce sedation and drowsiness. Very few clinical studies have reported sedation as a significant side effect. Infrequently, pimozide has been associated with excitement, insomnia, anxiety, agitation, tinnitus, and headache (Pinder et al, 1976; Singh, 1971; Kenway, 1973; Chouinard et al, 1970a).

c) SCHOOL PHOBIA induced by pimozide was reported in an 11- year-old boy being treated for Tourette syndrome. This type of pimozide-induced SEPARATION ANXIETY may be unique to patients with Tourette syndrome (Linet, 1985).

d) Several patients developed dose-related dysphoria or depression with administration of pimozide (Bruun, 1988). In every case a "threshold dose" could be identified above which the patient complained of dysphoria.

e) Depression, and dysphoria are described as frequent adverse effects of pimozide (Shapiro et al, 1983).

3.3.13 Renal Effects

Nocturnal enuresis

Urinary incontinence

Urogenital finding

3.3.13.A Nocturnal enuresis

1) Summary

a) CASE REPORT - Nocturnal enuresis has been reported in one patient (9-year-old male) with Gilles de la Tourette syndrome during the 18 months of treatment with pimozide 1 to 4 milligrams at bedtime (specific onset not described). Enuresis was controlled by administering pimozide as a single dose in the morning instead of the evening (Shapiro, 1981).

3.3.13.B Urinary incontinence

1) Summary

a) CASE REPORT ? Shapiro reported on a 9 year old with Tourette's syndrome treated with pimozide (3 milligrams at night) and methylphenidate (5 milligrams twice daily) for 1 1/2 years. Although the child had a history of night time enuresis prior to using the drug, when given the drug at bedtime control was lost. Methylphenidate was discontinued without effect on enuresis. When pimozide was stopped or when given in the morning, night time enuresis did not occur (Shapiro, 1981).

3.3.13.C Urogenital finding

1) Nocturnal enuresis, urinary incontinence, and sexual dysfunction are described with the administration of pimozide.

3.3.14 Reproductive Effects

3.3.14.A Sexual dysfunction

1) Summary

a) IMPOTENCE was reported in a 37-year-old male following 2 months of treatment with pimozide 60 milligrams daily for psychosis. The patient could not maintain an erection and this persisted for one month. Pimozide was discontinued and erection was possible 2 weeks later. However, psychosis recurred resulting in readministration of pimozide. The patient exhibited EJACULATION DISTURBANCES when the dose was increased gradually from 4 to 12 milligrams daily. With doses of 16 milligrams daily the patient again became impotent (Ananth, 1982).

3.3.16 Other

Death

Fever

3.3.16.A Death

1) Results of a population-based, retrospective cohort study demonstrated that the use of conventional antipsychotics was associated with an even greater risk for death than atypical antipsychotics when administered to elderly patients (aged 66 years and older) with dementia. Atypical versus no antipsychotic use and conventional versus atypical antipsychotic use pair-wise comparisons were made. A total of 27,259 matched pairs were identified and the dementia cohort was stratified based on place of residence (community versus long-term care facilities). In order to adjust for difference in baseline health status, propensity score matching was used. The primary outcome of the study was all-cause mortality. The risk for death was evaluated at 30, 60, 120, and 180 days after the antipsychotic medications were initially dispensed. There was a statistically significant increase in the risk for death at 30 days associated with new use of atypical antipsychotic medications compared with nonuse in both the community-dwelling cohort (adjusted hazard ratio (HR), 1.31 (95% confidence interval (CI), 1.02 to 1.70); absolute risk difference, 0.2 percentage point) and long-term care cohort (adjusted HR, 1.55 (95% CI, 1.15 to 2.07); absolute risk difference, 1.2 percentage points). For both cohorts, the risk associated with atypical antipsychotics appeared to persist to 180 days. The risk for death associated with conventional antipsychotics was even greater than the risk identified with atypical antipsychotics. At 30 days, the adjusted HR for the community-dwelling cohort was 1.55 (95% CI, 1.19 to 2.02) and 1.26 (95% CI, 1.04 to 1.53) for the long-term care cohort (adjusted risk difference for both was 1.1 percentage points). The risk appeared to persist to 180 days for both groups. Some important limitations to the study include unknown or unmeasured confounders may influence the results and cause of death could not be examined (Gill et al, 2007).

2) Results of a population-based, retrospective cohort study demonstrated comparable to possibly greater risk of death associated with the use of conventional antipsychotic medications in the elderly (aged 65 years and older) compared with atypical antipsychotic medications. The analysis excluded patients with cancer and included only new users of antipsychotic medications. The primary study outcome was 180-day all-cause mortality. A set of potential confounders was measured based on healthcare utilization data within 6 months before the initiation of antipsychotic medications. Of the 37,241 elderly patients identified, 12,882

and 24,359 received conventional and atypical antipsychotic medications, respectively. The risk of death in the conventional drug group within the first 180 days was 14.1% compared with 9.6% in the atypical drug group (unadjusted mortality ratio, 1.47; 95% confidence interval (CI), 1.39 to 1.56). In the multi-variable analysis which controlled for potential confounders, the adjusted mortality ratio for the risk of death within 180 days for conventional versus atypical drug therapy was 1.32 (95% CI, 1.23 to 1.42). When the most frequently prescribed conventional antipsychotic drugs were compared with risperidone, the mortality ratio associated with haloperidol was 2.14 (95% CI, 1.86 to 2.45) and loxapine was 1.29 (95% CI, 1.19 to 1.40), while there was no difference associated with olanzapine. The increased mortality risk for conventional versus atypical drug therapy was greatest when doses higher (above median) doses were used (mortality ratio 1.67; 95% CI, 1.5 to 1.86) and also during the first 40 days of therapy (mortality ratio 1.6; 95% CI, 1.42 to 1.8). Confirmatory analyses consisting of multi-variable Cox regression, propensity score, and instrumental variable estimation confirmed the results of the study (Schneeweiss et al, 2007).

3) The results of a retrospective cohort study indicate that conventional antipsychotic agents are at least as likely as atypical antipsychotic agents to increase the risk of death among elderly patients 65 years of age or older. The study included 9,142 new users of conventional agents (mean age, 83.2 years) and 13,748 new users of atypical agents (mean age, 83.5 years). A higher adjusted relative risk of death was associated with the use of conventional antipsychotics as compared with atypical antipsychotics at all timepoints studied after beginning therapy (within 180 days: RR, 1.37; 95% CI, 1.27 to 1.49; less than 40 days: RR, 1.56; 95% CI, 1.37 to 1.78; 40 to 79 days: RR, 1.37; 95% CI, 1.19 to 1.59; 80 to 180 days: RR, 1.27; 95% CI, 1.14 to 1.41). In addition, the adjusted risks of death observed in patients with dementia (RR, 1.29; 95% CI, 1.15 to 1.45), without dementia (RR, 1.45; 95% CI, 1.30 to 1.63), in a nursing home (RR, 1.26; 95% CI, 1.08 to 1.47), or not in a nursing home (RR, 1.42; 95% CI, 1.29 to 1.56) were also higher with the use of conventional antipsychotic therapy as compared with atypical antipsychotic use. This risk appeared to be dose-related and was greater with the use of higher dose (ie, greater than the median) conventional antipsychotics (RR, 1.73; 95% CI, 1.57 to 1.90). Additional studies which specifically investigate the optimum care of elderly patients requiring antipsychotic therapy are needed so that appropriate guidance regarding therapeutic intervention can be provided (Wang et al, 2005).

3.3.16.B Fever

1) Summary

a) Severe HYPERPYREXIA requiring discontinuance of therapy was reported in one of twenty patients receiving pimozide (Huber et al, 1971).

3.4 Teratogenicity/Effects in Pregnancy/Breastfeeding

A) Teratogenicity/Effects in Pregnancy

1) U.S. Food and Drug Administration's Pregnancy Category: Category C (Prod Info Orap(R), 1999bl) (All Trimesters)

a) Either studies in animals have revealed adverse effects on the fetus (teratogenic or embryocidal or other) and there are no controlled studies in women or studies in women and animals are not available. Drugs should be given only if the potential benefit justifies the potential risk to the fetus.

2) Australian Drug Evaluation Committee's (ADEC) Category: B1(Batagol, 1996)

a) Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have not shown evidence of an increased occurrence of fetal damage.

See Drug Consult reference: PREGNANCY RISK CATEGORIES

3) Crosses Placenta: Unknown

4) Clinical Management

a) There has not been sufficient clinical experience to establish the safety of pimozide in general during pregnancy. If possible, use of pimozide during pregnancy should be avoided.

5) Literature Reports

a) There are no studies or published case reports on the use of pimozide in pregnant women. Although studies conducted in rats and rabbits have shown that pimozide is not teratogenic, oral doses up to 8 times the maximum human dose resulted in decreased pregnancies and in the retarded development of fetuses. These effects are thought to be due to an inhibition or delay in implantation and is similarly observed in rodents administered other antipsychotic drugs (Prod Info Orap(R), 1999bl).

B) Breastfeeding

1) Thomson Lactation Rating: Infant risk cannot be ruled out.

a) Available evidence and/or expert consensus is inconclusive or is inadequate for determining infant risk when used during breastfeeding. Weigh the potential benefits of drug treatment against potential risks before prescribing this drug during breastfeeding.

2) Clinical Management

a) No reports describing the use of pimozide during human lactation are available and the effects on the nursing infant from exposure to the drug in milk are unknown. It is not known if pimozide affects the quantity and composition of breastmilk. Until more data is available, use caution when considering the use of pimozide in lactating women.

3) Literature Reports

a) No reports describing the use of pimozide during human lactation or measuring the amount, if any, of the

drug excreted into milk have been located.

3.5 Drug Interactions

Drug-Drug Combinations

Drug-Food Combinations

3.5.1 Drug-Drug Combinations

Acecainide

Ajmaline

Ajmaline

Amiodarone

Amisulpride

Amitriptyline

Amoxapine

Amprenavir

Aprepitant

Aprindine

Arsenic Trioxide

Arsenic Trioxide

Astemizole

Atazanavir

Azimilide

Azithromycin

Belladonna

Belladonna Alkaloids

Bepridil

Betel Nut

Bretylium

Chloral Hydrate

Chloroquine

Chlorpromazine

Chlorpromazine

Cisapride

Clarithromycin

Dalfopristin

Darunavir

Dasatinib

Delavirdine

Desipramine

Dibenzepin

Dirithromycin

Disopyramide

Disopyramide

Dofetilide

Dolasetron

Doxepin

Droperidol

Efavirenz

Encainide

Enflurane

Erythromycin

Flecainide

Fluconazole

Fluoxetine

Fosamprenavir

Fosaprepitant

Foscarnet

Gemifloxacin

Halofantrine

Haloperidol

Halothane

Hydroquinidine

Hydroquinidine

Ibutilide

Imatinib

Imipramine

Indinavir

Isoflurane

Isradipine

Itraconazole

Kava

Ketoconazole

Lapatinib

Levomethadyl

Lidoflazine

Lithium

Lithospermum

Lorcainide

Lumefantrine

Mefloquine

Mesoridazine

Mesoridazine

Methadone

Miconazole

Moxifloxacin

Nefazodone

Nelfinavir

Nilotinib

Nortriptyline

Octreotide

Ondansetron

Paroxetine

Pentamidine

Phenylalanine

Pirmenol

Pirmenol

Posaconazole

Prajmaline

Prajmaline

Probucol

Procainamide

Procainamide

Prochlorperazine

Prochlorperazine

Propafenone

Protriptyline

Quinidine

Quinupristin

Ranolazine

Rilonacept

Risperidone

Ritonavir

Roxithromycin

Saquinavir

Sematilide

Sertindole

Sertraline

Sotalol

Spiramycin

Sulfamethoxazole

Sultopride

Sunitinib

Tedisamil

Telithromycin

Terfenadine

Tetrabenazine

Thioridazine

Tipranavir

Tramadol

Trifluoperazine

Trifluoperazine

Trimethoprim

Trimipramine

Troleandomycin

Vasopressin

Vitex

Voriconazole

Zileuton

Ziprasidone

Zolmitriptan

Zotepine

3.5.1.A Acecainide

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Class III antiarrhythmics have been shown to prolong the QT interval, which may result in ventricular tachycardia, ventricular fibrillation, and torsades de pointes. Even though no formal drug interaction studies have been done, the coadministration of pimozide and other drugs known to prolong the QTc interval, including class III antiarrhythmics is contraindicated (Yamreudeewong et al, 2003a; Prod Info Orap(R), 1999k).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of pimozide with other agents that can prolong the QT interval, such as Class III antiarrhythmic agents, is contraindicated.
7) Probable Mechanism: additive effects on QT prolongation
8) Literature Reports
a) In experimental studies of conditions other than Tourette's Disorder, sudden, unexpected deaths have occurred. The patients were receiving pimozide dosages of approximately 1 mg per kg. One possible mechanism for such deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmia. The manufacturer recommends that an electrocardiogram be performed before pimozide treatment is initiated and periodically thereafter, especially during the period of dose adjustment (Prod Info Orap(R), 1999j).
b) Concurrent use of class III antiarrhythmic agents, and other drugs that can prolong the QT interval, such as pimozide, is not recommended. Dofetilide should be stopped for at least 2 days before any interacting drug is initiated. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised (Yamreudeewong et al, 2003).

3.5.1.B Ajmaline
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Because Class Ia antiarrhythmic agents may also prolong the QT interval and increase the risk of arrhythmias, the concurrent administration of pimozide with a drug from this class is contraindicated (Prod Info Orap(R), 1999q; Prod Info Quinaglute Dura-tabs(R), 1999; Stratmann et al, 1985; Chow et al, 1984).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of pimozide with other agents that can prolong the QT interval, such as Class Ia antiarrhythmic agents, is contraindicated.
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) In experimental studies of conditions other than Tourette's Disorder, sudden, unexpected deaths have occurred. The patients were receiving pimozide dosages of approximately 1 mg per kg. One possible mechanism for such deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmia. The manufacturer recommends that an electrocardiogram be performed before pimozide treatment is initiated and periodically thereafter, especially during the period of dose adjustment (Prod Info Orap(R), 1999p).
b) QRS widening, QTc interval prolongation, and torsades de pointes may occur with disopyramide therapy (Prod Info Norpace(R), 1997).
c) Several cases of recurrent irregular ventricular tachycardia also known as torsade de pointes have been reported with conventional doses of disopyramide. This condition is more likely to occur with severe repolarization delay and sinus bradycardia or atrioventricular block, especially when disopyramide therapy is combined with other QT interval prolonging agents (Tzivoni et al, 1981; Commerford & Beck, 1980; Croft & Kennelly, 1981). Others have retrospectively determined that women, irrespective of the presence or absence of other underlying heart conditions, are more at risk than men of developing torsades de pointes, in the setting of prolonged QT interval, following disopyramide therapy (Makkar et al, 1993).

3.5.1.C Ajmaline
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Several antipsychotic agents have demonstrated QT prolongation including amisulpride, haloperidol, iloperidone, paliperidone, quetiapine, risperidone, sertindole, sultopride, ziprasidone, and zotepine (Prod Info FANAPT(TM) oral tablets, 2009; Prod Info Solian(R), 1999e; O'Brien et al, 1999d; Prod Info INVEGA(TM) extended-release oral tablets, 2006; Owens, 2001i; Duenas-Laita et al, 1999g; Agelink et al, 2001d; Lande et al, 1992f; Prod Info GEODON(R) intramuscular injection, oral capsule, 2005; Sweetman, 2003). Because Class IA antiarrhythmic agents may also prolong the QT interval and increase the risk of arrhythmias, the concurrent administration of antipsychotics with a drug from this class is not recommended (Prod Info FANAPT(TM) oral tablets, 2009; Prod Info Quinaglute(R), 1999).
3) Severity: major

4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: The concurrent administration of a Class IA antiarrhythmic and an antipsychotic is not recommended.
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) In an open-label QTc study of patients with schizophrenia or schizoaffective disorder (n=160), iloperidone 12 mg twice a day was associated with QTc prolongation of 9 msec (Prod Info FANAPT(TM) oral tablets, 2009).
b) QRS widening, QTc interval prolongation, and torsades de pointes may occur with disopyramide therapy (Prod Info Norpace(R), 1997a).
c) The effects of combined therapy with quinidine (Class IA antiarrhythmic agent) and haloperidol (antipsychotic agent) were studied by giving 12 healthy volunteers haloperidol 5 mg alone and with 250 mg of quinidine bisulfate. The study demonstrated significant increases in the plasma concentrations of haloperidol when given concurrently with quinidine versus haloperidol treatment alone. The mean area under the concentration curve (AUC) was increased from 54.3 ng/h/mL on haloperidol alone to 103.2 ng/h/mL on combined therapy. The peak concentration (Cmax) also showed an increase from 1.9 ng/mL on haloperidol to 3.8 ng/mL on combined therapy. Half-life (T1/2) and time to peak concentration (Tmax) were not significantly changed, thereby suggesting to the authors that a tissue binding mechanism is more likely responsible for the plasma level changes than an elimination alteration (Young et al, 1993).

3.5.1.D Amiodarone
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Class III antiarrhythmics have been shown to prolong the QT interval, which may result in ventricular tachycardia, ventricular fibrillation, and torsades de pointes. Even though no formal drug interaction studies have been done, the coadministration of pimozide and other drugs known to prolong the QTc interval, including class III antiarrhythmics is contraindicated (Yamreudeewong et al, 2003a; Prod Info Orap(R), 1999k).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of pimozide with other agents that can prolong the QT interval, such as Class III antiarrhythmic agents, is contraindicated.
7) Probable Mechanism: additive effects on QT prolongation
8) Literature Reports
a) In experimental studies of conditions other than Tourette's Disorder, sudden, unexpected deaths have occurred. The patients were receiving pimozide dosages of approximately 1 mg per kg. One possible mechanism for such deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmia. The manufacturer recommends that an electrocardiogram be performed before pimozide treatment is initiated and periodically thereafter, especially during the period of dose adjustment (Prod Info Orap(R), 1999j).
b) Concurrent use of class III antiarrhythmic agents, and other drugs that can prolong the QT interval, such as pimozide, is not recommended. Dofetilide should be stopped for at least 2 days before any interacting drug is initiated. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised (Yamreudeewong et al, 2003).

3.5.1.E Amisulpride
1) Interaction Effect: cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Coadministration of drugs that potentially prolong the QTc interval, such as amisulpride and pimozide, is contraindicated (Prod Info Solian(R), 1999b; Prod Info Orap(R), 1999ar).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of agents that prolong the QT interval, such as amisulpride and pimozide, is contraindicated.
7) Probable Mechanism: additive effects on QT prolongation
8) Literature Reports
a) In experimental studies of conditions other than Tourette's Disorder, sudden, unexpected deaths have occurred. The patients were receiving pimozide dosages of approximately 1 mg per kg. One possible mechanism for such deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmia. The manufacturer recommends that an electrocardiogram be performed before pimozide treatment is initiated and periodically thereafter, especially during the period of dose adjustment (Prod Info Orap(R) pimozide, 1999l).

3.5.1.F Amitriptyline
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac

arrest)
2) Summary: Although citing no data, the manufacturer of pimozide states that concomitant use with other drugs which prolong the QT interval is contraindicated (Prod Info Orap(R), 1999ap). Tricyclic antidepressants (TCAs) at therapeutic doses can cause QT prolongation (Prod Info Norpramin(R), 2000; Marshall & Forker, 1982).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Because of the potential to prolong the QT interval, concurrent administration of a tricyclic antidepressant and pimozide is contraindicated.
7) Probable Mechanism: additive effects on QT interval
8) Literature Reports
a) Electrocardiogram (ECG) changes seen during clinical trials of pimozide in Tourette's syndrome and schizophrenia patients include prolongation of the QT interval, flattening, notching, and inversion of the T wave, and the appearance of U waves. Sudden, unexpected deaths have occurred at doses greater than 20 milligrams/day (Prod Info Orap(R) pimozide, 1999k).

3.5.1.G Amoxapine
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Although citing no data, the manufacturer of pimozide states that concomitant use with other drugs which prolong the QT interval is contraindicated (Prod Info Orap(R), 1999ap). Tricyclic antidepressants (TCAs) at therapeutic doses can cause QT prolongation (Prod Info Norpramin(R), 2000; Marshall & Forker, 1982).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Because of the potential to prolong the QT interval, concurrent administration of a tricyclic antidepressant and pimozide is contraindicated.
7) Probable Mechanism: additive effects on QT interval
8) Literature Reports
a) Electrocardiogram (ECG) changes seen during clinical trials of pimozide in Tourette's syndrome and schizophrenia patients include prolongation of the QT interval, flattening, notching, and inversion of the T wave, and the appearance of U waves. Sudden, unexpected deaths have occurred at doses greater than 20 milligrams/day (Prod Info Orap(R) pimozide, 1999k).

3.5.1.H Amprenavir
1) Interaction Effect: an increased risk of cardiotoxicity (QT interval prolongation, torsades de pointes, cardiac arrest)
2) Summary: Amprenavir is an inhibitor of the isoenzyme cytochrome P450 3A; concomitant use with pimozide may result in inhibition of pimozide metabolism. Elevated pimozide serum concentrations have been associated with an increased risk of cardiotoxicity. The concurrent administration of amprenavir and pimozide is contraindicated (Prod Info AGENERASE(R) Capsules, 2004).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Concomitant use of amprenavir and pimozide is contraindicated.
7) Probable Mechanism: increased pimozide serum concentrations due to inhibition of cytochrome P450 3A-mediated pimozide metabolism

3.5.1.I Aprepitant
1) Interaction Effect: an increase in pimozide plasma concentrations
2) Summary: Inhibition of cytochrome P450 isoenzyme 3A4 (CYP3A4) by aprepitant could result in elevated pimozide plasma concentrations. The concomitant use of pimozide and aprepitant is contraindicated (Prod Info EMEND(R) oral capsules, 2008).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Concurrent use of aprepitant and pimozide is contraindicated (Prod Info EMEND (R) oral capsules, 2008).
7) Probable Mechanism: inhibition of cytochrome P450 3A4-mediated metabolism of pimozide by aprepitant

3.5.1.J Aprindine
1) Interaction Effect: cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, the coadministration of pimozide and other drugs known to prolong the QTc interval, including Class I antiarrhythmic agents, is contraindicated (Prod Info Orap(R) pimozide, 1999a; Prod Info Tambocor(TM), 1998; Prod Info Enkaid(R), 1988; Larochelle et al, 1984).

3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of pimozide with other agents that can prolong the QT interval, such as Class I antiarrhythmic agents, is contraindicated.
7) Probable Mechanism: additive effects on QT prolongation
8) Literature Reports
a) In experimental studies of conditions other than Tourette's Disorder, sudden, unexpected deaths have occurred. The patients were receiving pimozide dosages of approximately 1 mg per kg. One possible mechanism for such deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmia. The manufacturer recommends that an electrocardiogram be performed before pimozide treatment is initiated and periodically thereafter, especially during the period of dose adjustment (Prod Info Orap(R) pimozide, 1999).

3.5.1.K Arsenic Trioxide
1) Interaction Effect: prolongation of the QTc interval and/or torsades de pointes
2) Summary: Arsenic trioxide can prolong the QT interval in some patients, which may result in ventricular tachycardia, ventricular fibrillation, and torsades de pointes. The concurrent administration of pimozide and other agents that can prolong the QT interval, such as arsenic trioxide is contraindicated (Prod Info Trisenox (R), 2001a; Prod Info Orap(R), 1999ak).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of arsenic trioxide and pimozide is contraindicated.
7) Probable Mechanism: additive effects on QTc prolongation
8) Literature Reports
a) QT/QTc prolongation should be expected during treatment with arsenic trioxide and torsade de pointes as well as complete heart block has been reported. Over 460 ECG tracings from 40 patients with refractory or relapsed APL treated with arsenic trioxide were evaluated for QTc prolongation. Sixteen of 40 patients (40%) had at least one ECG tracing with a QTc interval greater than 500 msec. Prolongation of the QTc was observed between 1 and 5 weeks after arsenic trioxide infusion, and then returned towards baseline by the end of 8 weeks after arsenic trioxide infusion. In these ECG evaluations, women did not experience more pronounced QT prolongation than men, and there was no correlation with age (Prod Info Trisenox(R), 2001).

3.5.1.L Arsenic Trioxide
1) Interaction Effect: prolongation of the QTc interval and/or torsades de pointes
2) Summary: Arsenic trioxide can prolong the QT interval in some patients, which may result in ventricular tachycardia, ventricular fibrillation, and torsades de pointes and should not be administered with other drugs that may prolong the QT interval (Prod Info Trisenox(R), 2001c). Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999a), haloperidol (O'Brien et al, 1999a), paliperidone (Prod Info INVEGA(TM) extended-release oral tablets, 2006), risperidone (Duenas-Laita et al, 1999d), sertindole (Agelink et al, 2001b), quetiapine (Owens, 2001f), sultopride (Lande et al, 1992a), ziprasidone (Prod Info GEODON(R) intramuscular injection, oral capsule, 2005), and zotepine (Sweetman, 2003).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of arsenic trioxide and antipsychotics is not recommended.
7) Probable Mechanism: additive effects on QTc prolongation
8) Literature Reports
a) QT/QTc prolongation should be expected during treatment with arsenic trioxide and torsade de pointes as well as complete heart block has been reported. Over 460 ECG tracings from 40 patients with refractory or relapsed APL treated with arsenic trioxide were evaluated for QTc prolongation. Sixteen of 40 patients (40%) had at least one ECG tracing with a QTc interval greater than 500 msec. Prolongation of the QTc was observed between 1 and 5 weeks after arsenic trioxide infusion, and then returned towards baseline by the end of 8 weeks after arsenic trioxide infusion. In these ECG evaluations, women did not experience more pronounced QT prolongation than men, and there was no correlation with age (Prod Info Trisenox(R), 2001b).

3.5.1.M Astemizole
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Pimozide prolongs the QT interval and an additive effect would be anticipated if administered with other agents which lengthen the QT interval (Prod Info Orap(R), 1999f). Astemizole alone has caused QT prolongation and torsades de pointes in patients receiving greater than the recommended dose (Prod Info Hismanal(R), 1997). Pimozide is contraindicated in patients taking other drugs which may prolong the

QT interval (Prod Info Orap(R), 1999f).
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Pimozide is contraindicated in individuals with congenital QT syndrome, patients with a history of cardiac arrhythmias, or patients taking other drugs which may prolong the QT interval.
7) Probable Mechanism: additive effects on QT prolongation
8) Literature Reports
a) Electrocardiographic changes that have occurred during clinical trials with pimozide have included prolongation of the corrected QT interval, flattening, notching, and inversion of the T wave and the appearance of U waves. In experimental studies, sudden, unexpected deaths have occurred while patients were receiving pimozide doses of 1 mg/kg. The proposed mechanism for these deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmias (Prod Info Orap(R), 1999e).

3.5.1.N Atazanavir
1) Interaction Effect: an increased risk of cardiac arrhythmias
2) Summary: Coadministration of atazanavir is contraindicated with drugs that are metabolized by cytochrome P450 3A and for which elevated plasma concentrations are associated with serious and/or life threatening events. Side effects may include cardiac arrhythmias (Prod Info Reyataz(TM), 2003).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Coadministration of atazanavir and pimozide is contraindicated.
7) Probable Mechanism: inhibition of cytochrome P450 3A-mediated pimozide metabolism by atazanavir

3.5.1.O Azimilide
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Class III antiarrhythmics have been shown to prolong the QT interval, which may result in ventricular tachycardia, ventricular fibrillation, and torsades de pointes. Even though no formal drug interaction studies have been done, the coadministration of pimozide and other drugs known to prolong the QTc interval, including class III antiarrhythmics is contraindicated (Yamreudeewong et al, 2003a; Prod Info Orap(R), 1999k).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of pimozide with other agents that can prolong the QT interval, such as Class III antiarrhythmic agents, is contraindicated.
7) Probable Mechanism: additive effects on QT prolongation
8) Literature Reports
a) In experimental studies of conditions other than Tourette's Disorder, sudden, unexpected deaths have occurred. The patients were receiving pimozide dosages of approximately 1 mg per kg. One possible mechanism for such deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmia. The manufacturer recommends that an electrocardiogram be performed before pimozide treatment is initiated and periodically thereafter, especially during the period of dose adjustment (Prod Info Orap(R), 1999j).
b) Concurrent use of class III antiarrhythmic agents, and other drugs that can prolong the QT interval, such as pimozide, is not recommended. Dofetilide should be stopped for at least 2 days before any interacting drug is initiated. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised (Yamreudeewong et al, 2003).

3.5.1.P Azithromycin
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Azithromycin may inhibit the metabolism of pimozide, resulting in increased serum concentrations of this agent. Elevated serum levels of pimozide have been associated with adverse cardiovascular effects including QT interval prolongation, cardiac arrhythmia, and sudden death (Flockhart et al, 1996d). The concurrent administration of azithromycin and pimozide is contraindicated (Prod Info Orap (R), 1999bj).
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Concurrent use of pimozide and azithromycin is contraindicated.
7) Probable Mechanism: inhibition of cytochrome P450 3A-mediated pimozide metabolism

3.5.1.Q Belladonna
1) Interaction Effect: excessive anticholinergic activity (severe dry mouth, constipation, decreased urination,

excessive sedation, blurred vision)
2) Summary: The anticholinergic activity of the active alkaloids present in belladonna may predispose the patient to excessive anticholinergic activity if taken with pimozide. Belladonna contains L-hyoscyamine, atropine, and scopolamine with a total alkaloid content of at least 0.3% in the leaves and 0.5% in the roots (Blumenthal et al, 1998). Because belladonna is typically available as a homeopathic preparation, the clinical severity of the interaction with pimozide is unknown. Caution is advised.
3) Severity: minor
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Excessive anticholinergic activity may be manifested by dry mouth, constipation, urinary retention, tachycardia, decreased sweating, mydriasis, blurred vision, elevated temperature, muscular weakness, and sedation. If such effects are noted, belladonna should be discontinued immediately. In severe cases, paralytic ileus, confusion, psychoses, agitation, delusions, delirium, and paranoia may be encountered as well as tachycardia, dysrhythmia, and hypertension. In severe cases, immediate medical attention should be obtained.
7) Probable Mechanism: additive anticholinergic effect

3.5.1.R Belladonna Alkaloids
1) Interaction Effect: excessive anticholinergic activity (severe dry mouth, constipation, decreased urination, excessive sedation, blurred vision)
2) Summary: The anticholinergic activity of the active alkaloids present in belladonna may predispose the patient to excessive anticholinergic activity if taken with pimozide. Belladonna contains L-hyoscyamine, atropine, and scopolamine with a total alkaloid content of at least 0.3% in the leaves and 0.5% in the roots (Blumenthal et al, 1998). Because belladonna is typically available as a homeopathic preparation, the clinical severity of the interaction with pimozide is unknown. Caution is advised.
3) Severity: minor
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Excessive anticholinergic activity may be manifested by dry mouth, constipation, urinary retention, tachycardia, decreased sweating, mydriasis, blurred vision, elevated temperature, muscular weakness, and sedation. If such effects are noted, belladonna should be discontinued immediately. In severe cases, paralytic ileus, confusion, psychoses, agitation, delusions, delirium, and paranoia may be encountered as well as tachycardia, dysrhythmia, and hypertension. In severe cases, immediate medical attention should be obtained.
7) Probable Mechanism: additive anticholinergic effect

3.5.1.S Bepridil
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Some antipsychotic agents prolong the QT interval and an additive effect would be anticipated if administered with other agents which lengthen the QT interval (Prod Info Geodon(TM), 2002a; Agelink et al, 2001; Owens, 2001c; Prod Info Orap(R), 1999o; Prod Info Haldol(R), 1998). In U.S. clinical trials, bepridil increased QT and QTc intervals which was associated with torsades de pointes in approximately 1% of patients. Other drugs that increase the QT interval may exaggerate the prolongation of the QT interval observed with bepridil (Prod Info Vascor(R), 1997). Pimozide is contraindicated in patients taking other drugs which may prolong the QT interval (Prod Info Orap(R), 1999o).
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of antipsychotics and agents that prolong the QT interval, such as bepridil, is contraindicated. In particular, pimozide is contraindicated in individuals with congenital QT syndrome, patients with a history of cardiac arrhythmias, or patients taking other drugs which may prolong the QT interval.
7) Probable Mechanism: additive effects on QT prolongation
8) Literature Reports
a) Electrocardiographic changes that have occurred during clinical trials with pimozide have included prolongation of the corrected QT interval, flattening, notching, and inversion of the T wave and the appearance of U waves. In experimental studies, sudden, unexpected deaths have occurred while patients were receiving pimozide doses of 1 mg/kg. The proposed mechanism for these deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmias (Prod Info Orap(R), 1999n).
b) Sometimes fatal QRS prolongation and QTc prolongation have been reported in patients taking risperidone therapeutically (Duenas-Laita et al, 1999a; Ravin & Levenson, 1997a).

3.5.1.T Betel Nut
1) Interaction Effect: increased extrapyramidal side effects of pimozide
2) Summary: Case reports have described increased extrapyramidal side effects when betel nut was chewed by patients taking fluphenazine and fluphenthixol for schizophrenia (Deahl, 1989a). The

extrapyramidal effects were not improved with anticholinergic therapy with procyclidine, and resolved with betel nut discontinuation (Deahl, 1989a). A similar effect may occur if betel nut is chewed with concomitant pimozide therapy. The cholinergic activity of betel nut has been attributed to the arecoline content. When given with peripheral anticholinergics, arecoline increased the heart rate due to central muscarinic agonist activity (Nutt et al, 1978a). Case reports suggest the onset of betel nut activity to be within 3 weeks with resolution within 4 to 7 days after discontinuation (Deahl, 1989a).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: It is unclear to what extent the cholinergic effect of betel nut may increase the incidence of extrapyramidal side effects of pimozide, especially if patients are treated with anticholinergic agents to control these side effects. Deterioration in symptoms of patients with Parkinson's disease or other extrapyramidal movement disorders may be expected. Persons who have been chewing betel nut have a characteristic red stain on the teeth which may help the clinician discover betel nut use.

7) Probable Mechanism: cholinergic effect of betel nut

8) Literature Reports

a) Within 3 weeks of initiating betel nut chewing, a 51-year-old Indian man experienced marked rigidity, bradykinesia, and jaw tremor. This patient had been stabilized on fluphenazine decanoate depot 50 milligrams (mg) every 3 weeks for schizophrenia and procyclidine 5 mg twice daily for a mild Parkinsonian tremor for the previous 2 years. Within one week of discontinuation of betel nut chewing, the patient's condition returned to baseline. This report appears to demonstrate decreased anticholinergic effects of procyclidine when coadministered with betel nut (Deahl, 1989).

b) A 45-year-old Indian man developed akathisia, tremor and stiffness following betel nut ingestion which was not affected by dosage escalations of up to 20 mg daily of procyclidine. This patient had been previously stabilized on fluphenthixol 60 mg depot every two weeks for the previous year for schizoaffective disorder without extrapyramidal side effects. His symptoms resolved over 4 days after discontinuing betel nut. It appears that the anticholinergic effects of procyclidine were diminished when betel nut was chewed concomitantly (Deahl, 1989).

c) High doses (5 mg, 10 mg, and 20 mg) of subcutaneous (SC) arecoline given one hour after SC administration of 0.5 mg of the peripheral anticholinergic agent methscopolamine increased the heart rate and blood pressure of six Huntington disease patients. Significant increases in blood pressure occurred at doses of 5 mg, 10 mg (p less than 0.01) and 20 mg (p less than 0.05). Heart rate increased at doses of 5 mg and 20 mg (p less than 0.01), and 10 mg (p less than 0.05). Subjective effects in some patients included tremor, flushing or pallor at the time of peak drug effect and nausea, weakness, and mental changes at the higher doses. No peripheral cholinergic effects were noted. The results indicated a central muscarinic effect for arecoline (Nutt et al, 1978).

d) A low dose (0.5 mg) of arecoline given intravenously 3 minutes after the peripheral anticholinergic agent glycopyrrolate 0.15 mg to 8 patients with major depressive disorder increased their heart rates. The peak heart rate increase in a non-REM portion of the sleep cycle during the 10 minute post-infusion period was 6.75 +/- 12.9 beats per minute for placebo and 25 +/- 10.3 beats per minute for arecoline. The peak heart rates all began 1 to 8 minutes after the arecoline infusion, and the mean heart rate was significantly elevated over placebo from 2 to 10 minutes after arecoline infusion (p less than 0.05) (Abramson et al, 1985).

e) Though chewing betel nut alone does not significantly increase catecholamine levels, a popular betel nut preparation does. Six to eight minutes after chewing betel nut, 4 subjects had only a moderate increase in plasma noradrenaline from 266.2 +/- 105.7 picograms/milliliter (pg/mL) to 313.7 +/- 92.9 pg/mL (p equal to 0.0607). Combining betel nut with lime, catechu and Piper betel flower as is commonly done caused significant elevation of norepinephrine in nine subjects from 292.2 +/- 59.5 pg/mL to 375.1 +/- 130.0 pg/mL (p equal to 0.0244) and epinephrine from 62.5 +/- 23.9 pg/mL to 102.2 +/- 45.0 pg/mL (p equal to 0.0226). In this group dopamine was also elevated in 8 of 9 subjects, but the mean was not significant (Chu, 1995).

3.5.1.U Bretylium

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Class III antiarrhythmics have been shown to prolong the QT interval, which may result in ventricular tachycardia, ventricular fibrillation, and torsades de pointes. Even though no formal drug interaction studies have been done, the coadministration of pimozide and other drugs known to prolong the QTc interval, including class III antiarrhythmics is contraindicated (Yamreudeewong et al, 2003a; Prod Info Orap(R), 1999k).

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of pimozide with other agents that can prolong the QT interval, such as Class III antiarrhythmic agents, is contraindicated.

7) Probable Mechanism: additive effects on QT prolongation

8) Literature Reports

a) In experimental studies of conditions other than Tourette's Disorder, sudden, unexpected deaths

have occurred. The patients were receiving pimozide dosages of approximately 1 mg per kg. One possible mechanism for such deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmia. The manufacturer recommends that an electrocardiogram be performed before pimozide treatment is initiated and periodically thereafter, especially during the period of dose adjustment (Prod Info Orap(R), 1999j).

b) Concurrent use of class III antiarrhythmic agents, and other drugs that can prolong the QT interval, such as pimozide, is not recommended. Dofetilide should be stopped for at least 2 days before any interacting drug is initiated. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised (Yamreudeewong et al, 2003).

3.5.1.V Chloral Hydrate

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Chloral hydrate has been shown to prolong the QTc interval at the recommended therapeutic dose (Young et al, 1986). Even though no formal drug interaction studies have been done, the administration of drugs known to prolong the QTc interval, such as pimozide and chloral hydrate is contraindicated (Prod Info Orap(R), 1999d).

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Due to the potential for additive effects on the QT interval, the concurrent administration of chloral hydrate and pimozide is contraindicated.

7) Probable Mechanism: additive effects on QT prolongation

8) Literature Reports

a) In experimental studies of conditions other than Tourette's Disorder, sudden, unexpected deaths have occurred. The patients were receiving pimozide dosages of approximately 1 mg per kg. One possible mechanism for such deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmia. The manufacturer recommends that an electrocardiogram be performed before pimozide treatment is initiated and periodically thereafter, especially during the period of dose adjustment (Prod Info Orap(R) pimozide, 1999b).

3.5.1.W Chloroquine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Chloroquine has been shown to prolong the QTc interval at the recommended therapeutic dose and an additive effect would be anticipated if administered with other agents which lengthen the QT interval (Prod Info Aralen(R), 1999). Several antipsychotic agents have demonstrated QT prolongation including pimozide (Prod Info Orap(R), 1999x).

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of pimozide and agents that prolong the QT interval, such as chloroquine is contraindicated.

7) Probable Mechanism: additive effects on QT prolongation

8) Literature Reports

a) In experimental studies of conditions other than Tourette's Disorder, sudden, unexpected deaths have occurred. The patients were receiving pimozide dosages of approximately 1 mg per kg. One possible mechanism for such deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmia. The manufacturer recommends that an electrocardiogram be performed before pimozide treatment is initiated and periodically thereafter, especially during the period of dose adjustment (Prod Info Orap(R) pimozide, 1999d).

3.5.1.X Chlorpromazine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Even though no formal drug interaction studies have been done, the manufacturer of pimozide warns against its administration with other drugs which are also known to prolong the QTc interval, including phenothiazines (Prod Info Thorazine(R), 2002; Prod Info Compazine(R), 2002; Prod Info Stelazine(R), 2002; Prod Info Orap(R), 1999t). The manufacturers of mesoridazine and thioridazine state that concomitant use is contraindicated with other agents known to prolong the QT interval (Prod Info Mellaril(R), 2002; Prod Info Serentil(R), 2001).

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of pimozide and other drugs that may prolong the QT interval, such as phenothiazines is contraindicated.

7) Probable Mechanism: additive effects on QT prolongation

8) Literature Reports

a) Electrocardiogram (ECG) changes seen during clinical trials of pimozide in Tourette's syndrome and schizophrenia patients include prolongation of the QT interval, flattening, notching, and inversion of the T wave, and the appearance of U waves. Sudden, unexpected deaths have occurred at doses greater than 20 milligrams/day (Prod Info Orap(R), 1999s).

3.5.1.Y Chlorpromazine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Concomitant use of phenothiazines and antipsychotic agents may cause additive effects on the QT interval and is not recommended. Q and T wave distortions have been observed in patients taking phenothiazines (Prod Info Compazine(R), 2002a; Prod Info Stelazine(R), 2002a; Prod Info Thorazine(R), 2002a). Other phenothiazines may have similar effects, though no reports are available. Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999), haloperidol (O'Brien et al, 1999), paliperidone (Prod Info INVEGA(TM) extended-release oral tablets, 2006), quetiapine (Owens, 2001e), risperidone (Duenas-Laita et al, 1999c), sertindole (Agelink et al, 2001a), sultopride (Lande et al, 1992), ziprasidone (Prod Info GEODON(R) intramuscular injection, oral capsule, 2005), and zotepine (Sweetman, 2003).

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of agents that prolong the QT interval, such as phenothiazines and antipsychotics, is not recommended.

7) Probable Mechanism: additive QT prolongation

3.5.1.Z Cisapride

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Some antipsychotic agents prolong the QT interval and an additive effect would be anticipated if administered with other agents which lengthen the QT interval (Prod Info Geodon(TM), 2002; Owens, 2001; Prod Info Orap(R), 1999a). Torsades de pointes and QT prolongation have been reported with cisapride (Prod Info Propulsid(R), 2000).

3) Severity: contraindicated

4) Onset: rapid

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of antipsychotics and agents that prolong the QT interval, such as cisapride, is contraindicated. In particular, pimozide is contraindicated in individuals with congenital QT syndrome, patients with a history of cardiac arrhythmias, or patients taking other drugs which may prolong the QT interval.

7) Probable Mechanism: additive effects on QT prolongation

8) Literature Reports

a) Electrocardiographic changes that have occurred during clinical trials with pimozide have included prolongation of the corrected QT interval, flattening, notching, and inversion of the T wave and the appearance of U waves. In experimental studies, sudden, unexpected deaths have occurred while patients were receiving pimozide doses of 1 mg/kg. The proposed mechanism for these deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmias (Prod Info Orap(R), 1999).

b) Fatal QRS prolongation and QTc prolongation have been reported in patients taking risperidone (Duenas-Laita et al, 1999; Ravin & Levenson, 1997).

3.5.1.AA Clarithromycin

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Clarithromycin may inhibit the metabolism of pimozide, resulting in increased serum concentrations of this agent (Prod Info Biaxin(R), 2001). Elevated serum levels of pimozide have been associated with adverse cardiovascular effects including QT interval prolongation, cardiac arrhythmia, and sudden death (Flockhart et al, 1996b). One patient being treated with therapeutic doses of pimozide for Tourette's syndrome died five days after clarithromycin was prescribed for bronchitis. The patient had toxic plasma levels of pimozide (greater than 50 ng/mL) and a prolonged QTc interval (Flockhart et al, 2000a). A 27-year-old patient being treated with pimozide for Tourette's syndrome was prescribed clarithromycin for bronchopneumonia. The patient died five days later from a cardiac arrhythmia. Blood pimozide concentrations were 50 ng/ml (4-20 ng/ml). The concurrent use of clarithromycin and pimozide is contraindicated (Prod Info Orap(R), 1999ah).

3) Severity: contraindicated

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: Concurrent use of pimozide and clarithromycin is contraindicated.

7) Probable Mechanism: inhibition by clarithromycin of cytochrome P450 3A-mediated pimozide metabolism

8) Literature Reports

a) In a randomized, double-blind, placebo-controlled crossover design study, twelve healthy volunteers were given a single oral dose of pimozide 6 mg after five days of pretreatment with placebo or clarithromycin 500 mg twice daily. With respect to cytochrome P450 2D6 (CYP2D6) phenotyping, five study subjects were poor metabolizers and seven were extensive metabolizers. All participants had a corrected QTc shorter than 470 ms prior to inclusion in the study. Clarithromycin pretreatment increased the pimozide maximum concentration (Cmax) from 4.4 ng/mL to 6.1 ng/mL and increased the area under the concentration-time curve (AUC) by 113% (146 ng/mL/h vs. 310 ng/mL/h). Pimozide half-life, clearance, and apparent volume of distribution were also significantly increased by clarithromycin. Pimozide prolonged the QT interval in all study subjects, and these increases coincided with plasma concentrations. In the first 20 hours after administration, the clarithromycin group had a more prolonged QTc interval (increased by 15.7 ms) than the placebo group (increased by 13.3 ms). There was no significant effect of CYP2D6 phenotyping or gender on the pharmacodynamics or pharmacokinetics of pimozide. Clarithromycin inhibits cytochrome P450 3A (CYP3A) enzymes, which are responsible for pimozide metabolism. Inhibition of pimozide metabolism leads to cardiotoxicity, which is an effect of the parent drug (Desta et al, 1999).
b) A case report describes a 27-year-old male with a history of Tourette syndrome who experienced sudden cardiac death after being coprescribed pimozide and clarithromycin. The patient was currently taking pimozide 14 mg/day, but due to an increase in the number of tics he was experiencing, it was decided that his dose of pimozide be slowly increased by one 2 mg tablet per day. Two days after the increase in dose, he was diagnosed with bronchopneumonia. Clarithromycin 500 mg per day was prescribed. Four days after he presented to the emergency department he complained of a racing heart and felt a "head rush". He was observed without incident. An ECG showed a corrected QT interval of 0.506 seconds. He was discharged with instructions to follow-up with his neurologist. The following day he was found unconscious, apneic, and unresponsive without the ability to be resuscitated. Blood pimozide concentrations were 50 ng/ml (4-20 ng/ml). Cardiac arrhythmia resulting from an excessive concentration of pimozide was the most likely cause of death (Flockhart et al, 2000).
c) Electrocardiogram (ECG) changes seen during clinical trials of pimozide in Tourette's syndrome and schizophrenia patients include prolongation of the QT interval, flattening, notching, and inversion of the T wave, and the appearance of U waves. Sudden, unexpected deaths have occurred at doses greater than 20 milligrams/day (Prod Info Orap(R), 1999ag).

3.5.1.AB Dalfopristin

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Quinupristin/dalfopristin is a major inhibitor of cytochrome P450 3A4 (CYP3A4) isoenzymes, and pimozide is a CYP3A4 substrate. Coadministration of these two agents may likely result in increased plasma concentrations of pimozide, which may lead to QTc interval prolongation and risk of torsades de pointes (Prod Info SYNERCID(R) intravenous injection, 2003; Prod Info ORAP(R) Tablets, 2004).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: The concurrent administration of pimozide and quinupristin/dalfopristin is contraindicated.
7) Probable Mechanism: inhibition of cytochrome P450 3A4-mediated pimozide metabolism

3.5.1.AC Darunavir

1) Interaction Effect: an increased risk of serious and/or life-threatening reactions such as cardiac arrhythmias
2) Summary: The coadministration of darunavir/ritonavir and pimozide is contraindicated as this may result in inhibition of the CYP3A-mediated pimozide metabolism, leading to increased pimozide plasma concentrations and creating the potential for serious and/or life-threatening reactions such as cardiac arrhythmias (Prod Info PREZISTA(TM) oral tablets, 2006).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of darunavir/ritonavir and pimozide is contraindicated.
7) Probable Mechanism: inhibition of CYP3A-mediated pimozide metabolism

3.5.1.AD Dasatinib

1) Interaction Effect: altered pimozide plasma concentrations
2) Summary: Use caution when coadministering dasatinib (a CYP3A4 inhibitor) and pimozide (a CYP3A4 substrate with a narrow therapeutic index), as this may result in altered plasma concentrations of pimozide (Prod Info SPRYCEL(R) oral tablets, 2008). Monitoring patients for pimozide-related adverse effects (cardiotoxicity including QT interval prolongation, torsades de pointes, and cardiac arrest) may be warranted when these drugs are used concomitantly.
3) Severity: moderate
4) Onset: unspecified

5) Substantiation: theoretical
6) Clinical Management: Use caution if dasatinib and pimozide are coadministered (Prod Info SPRYCEL(R) oral tablets, 2008). Consider monitoring the patient for pimozide-related adverse effects (cardiotoxicity including QT interval prolongation, torsades de pointes, and cardiac arrest) when these drugs are used concomitantly.
7) Probable Mechanism: altered CYP3A4-mediated metabolism of pimozide

3.5.1.AE Delavirdine
1) Interaction Effect: an increased risk of cardiotoxicity
2) Summary: Delavirdine and pimozide are both metabolized by the CYP3A4 enzyme system. Competition for this pathway could result in inhibition of pimozide metabolism, creating the potential for pimozide toxicity and cardiac arrhythmias. Concurrent administration of delavirdine and pimozide is contraindicated (Prod Info RESCRIPTOR(R) oral tablets, 2006).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of delavirdine and pimozide is contraindicated due to the potential for serious or life-threatening cardiac arrhythmias.
7) Probable Mechanism: inhibition of cytochrome P450 3A-mediated pimozide metabolism

3.5.1.AF Desipramine
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Although citing no data, the manufacturer of pimozide states that concomitant use with other drugs which prolong the QT interval is contraindicated (Prod Info Orap(R), 1999ap). Tricyclic antidepressants (TCAs) at therapeutic doses can cause QT prolongation (Prod Info Norpramin(R), 2000; Marshall & Forker, 1982).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Because of the potential to prolong the QT interval, concurrent administration of a tricyclic antidepressant and pimozide is contraindicated.
7) Probable Mechanism: additive effects on QT interval
8) Literature Reports
a) Electrocardiogram (ECG) changes seen during clinical trials of pimozide in Tourette's syndrome and schizophrenia patients include prolongation of the QT interval, flattening, notching, and inversion of the T wave, and the appearance of U waves. Sudden, unexpected deaths have occurred at doses greater than 20 milligrams/day (Prod Info Orap(R) pimozide, 1999k).

3.5.1.AG Dibenzepin
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Although citing no data, the manufacturer of pimozide states that concomitant use with other drugs which prolong the QT interval is contraindicated (Prod Info Orap(R), 1999ap). Tricyclic antidepressants (TCAs) at therapeutic doses can cause QT prolongation (Prod Info Norpramin(R), 2000; Marshall & Forker, 1982).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Because of the potential to prolong the QT interval, concurrent administration of a tricyclic antidepressant and pimozide is contraindicated.
7) Probable Mechanism: additive effects on QT interval
8) Literature Reports
a) Electrocardiogram (ECG) changes seen during clinical trials of pimozide in Tourette's syndrome and schizophrenia patients include prolongation of the QT interval, flattening, notching, and inversion of the T wave, and the appearance of U waves. Sudden, unexpected deaths have occurred at doses greater than 20 milligrams/day (Prod Info Orap(R) pimozide, 1999k).

3.5.1.AH Dirithromycin
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Dirithromycin may inhibit the metabolism of pimozide, resulting in increased serum concentrations of this agent. Elevated serum levels of pimozide have been associated with adverse cardiovascular effects including QT interval prolongation, cardiac arrhythmia, and sudden death. The concomitant administration of pimozide and dirithromycin is contraindicated (Flockhart et al, 1996; Prod Info Orap(R), 1999l).
3) Severity: contraindicated
4) Onset: rapid

5) Substantiation: theoretical
6) Clinical Management: Concurrent use of pimozide and dirithromycin is contraindicated.
7) Probable Mechanism: inhibition of cytochrome P450 3A-mediated pimozide metabolism

3.5.1.AI Disopyramide

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Because Class Ia antiarrhythmic agents may also prolong the QT interval and increase the risk of arrhythmias, the concurrent administration of pimozide with a drug from this class is contraindicated (Prod Info Orap(R), 1999q; Prod Info Quinaglute Dura-tabs(R), 1999; Stratmann et al, 1985; Chow et al, 1984).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of pimozide with other agents that can prolong the QT interval, such as Class Ia antiarrhythmic agents, is contraindicated.
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) In experimental studies of conditions other than Tourette's Disorder, sudden, unexpected deaths have occurred. The patients were receiving pimozide dosages of approximately 1 mg per kg. One possible mechanism for such deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmia. The manufacturer recommends that an electrocardiogram be performed before pimozide treatment is initiated and periodically thereafter, especially during the period of dose adjustment (Prod Info Orap(R), 1999p).
b) QRS widening, QTc interval prolongation, and torsades de pointes may occur with disopyramide therapy (Prod Info Norpace(R), 1997).
c) Several cases of recurrent irregular ventricular tachycardia also known as torsade de pointes have been reported with conventional doses of disopyramide. This condition is more likely to occur with severe repolarization delay and sinus bradycardia or atrioventricular block, especially when disopyramide therapy is combined with other QT interval prolonging agents (Tzivoni et al, 1981; Commerford & Beck, 1980; Croft & Kennelly, 1981). Others have retrospectively determined that women, irrespective of the presence or absence of other underlying heart conditions, are more at risk than men of developing torsades de pointes, in the setting of prolonged QT interval, following disopyramide therapy (Makkar et al, 1993).

3.5.1.AJ Disopyramide

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Several antipsychotic agents have demonstrated QT prolongation including amisulpride, haloperidol, iloperidone, paliperidone, quetiapine, risperidone, sertindole, sultopride, ziprasidone, and zotepine (Prod Info FANAPT(TM) oral tablets, 2009; Prod Info Solian(R), 1999e; O'Brien et al, 1999d; Prod Info INVEGA(TM) extended-release oral tablets, 2006; Owens, 2001i; Duenas-Laita et al, 1999g; Agelink et al, 2001d; Lande et al, 1992f; Prod Info GEODON(R) intramuscular injection, oral capsule, 2005; Sweetman, 2003). Because Class IA antiarrhythmic agents may also prolong the QT interval and increase the risk of arrhythmias, the concurrent administration of antipsychotics with a drug from this class is not recommended (Prod Info FANAPT(TM) oral tablets, 2009; Prod Info Quinaglute(R), 1999).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: The concurrent administration of a Class IA antiarrhythmic and an antipsychotic is not recommended.
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) In an open-label QTc study of patients with schizophrenia or schizoaffective disorder (n=160), iloperidone 12 mg twice a day was associated with QTc prolongation of 9 msec (Prod Info FANAPT(TM) oral tablets, 2009).
b) QRS widening, QTc interval prolongation, and torsades de pointes may occur with disopyramide therapy (Prod Info Norpace(R), 1997a).
c) The effects of combined therapy with quinidine (Class IA antiarrhythmic agent) and haloperidol (antipsychotic agent) were studied by giving 12 healthy volunteers haloperidol 5 mg alone and with 250 mg of quinidine bisulfate. The study demonstrated significant increases in the plasma concentrations of haloperidol when given concurrently with quinidine versus haloperidol treatment alone. The mean area under the concentration curve (AUC) was increased from 54.3 ng/h/mL on haloperidol alone to 103.2 ng/h/mL on combined therapy. The peak concentration (Cmax) also showed an increase from 1.9 ng/mL on haloperidol to 3.8 ng/mL on combined therapy. Half-life (T1/2) and time to peak concentration (Tmax) were not significantly changed, thereby suggesting to the authors that a tissue binding mechanism is more likely responsible for the plasma level changes than an elimination alteration (Young et al, 1993).

3.5.1.AK Dofetilide

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Class III antiarrhythmics have been shown to prolong the QT interval, which may result in ventricular tachycardia, ventricular fibrillation, and torsades de pointes. Even though no formal drug interaction studies have been done, the coadministration of pimozide and other drugs known to prolong the QTc interval, including class III antiarrhythmics is contraindicated (Yamreudeewong et al, 2003a; Prod Info Orap(R), 1999k).

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of pimozide with other agents that can prolong the QT interval, such as Class III antiarrhythmic agents, is contraindicated.

7) Probable Mechanism: additive effects on QT prolongation

8) Literature Reports

a) In experimental studies of conditions other than Tourette's Disorder, sudden, unexpected deaths have occurred. The patients were receiving pimozide dosages of approximately 1 mg per kg. One possible mechanism for such deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmia. The manufacturer recommends that an electrocardiogram be performed before pimozide treatment is initiated and periodically thereafter, especially during the period of dose adjustment (Prod Info Orap(R), 1999j).

b) Concurrent use of class III antiarrhythmic agents, and other drugs that can prolong the QT interval, such as pimozide, is not recommended. Dofetilide should be stopped for at least 2 days before any interacting drug is initiated. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised (Yamreudeewong et al, 2003).

3.5.1.AL Dolasetron

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Although no formal interaction studies have been conducted, the manufacturer of pimozide considers its coadministration with other drugs when may prolong the QT interval to be contraindicated (Prod Info Orap(R), 1999ax; Prod Info Anzemet(R), 1997a).

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of agents that prolong the QT interval, such as dolasetron and pimozide, is contraindicated.

7) Probable Mechanism: additive effects on QT prolongation

8) Literature Reports

a) In experimental studies of conditions other than Tourette's Disorder, sudden, unexpected deaths have occurred. The patients were receiving pimozide dosages of approximately 1 mg per kg. One possible mechanism for such deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmia. The manufacturer recommends that an electrocardiogram be performed before pimozide treatment is initiated and periodically thereafter, especially during the period of dose adjustment (Prod Info Orap(R) pimozide, 1999o).

b) In several studies, dolasetron resulted in significant, dose-related increases in mean PR, QRS, and QTc intervals compared to baseline values. Measured changes in ECG parameters were transient, reversible, and asymptomatic. Increases in PR and QRS intervals may be due to prolongation of maximum upstroke velocity (Vmax) due to binding of dolasetron to fast sodium channels. The cause of QTc interval prolongation appears to be due to prolongation of the QRS interval, increases in heart rate, or both (Prod Info Anzemet(R), 1997; Hunt et al, 1995; Kris et al, 1994).

3.5.1.AM Doxepin

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Although citing no data, the manufacturer of pimozide states that concomitant use with other drugs which prolong the QT interval is contraindicated (Prod Info Orap(R), 1999ap). Tricyclic antidepressants (TCAs) at therapeutic doses can cause QT prolongation (Prod Info Norpramin(R), 2000; Marshall & Forker, 1982).

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Because of the potential to prolong the QT interval, concurrent administration of a tricyclic antidepressant and pimozide is contraindicated.

7) Probable Mechanism: additive effects on QT interval

8) Literature Reports

a) Electrocardiogram (ECG) changes seen during clinical trials of pimozide in Tourette's syndrome and

schizophrenia patients include prolongation of the QT interval, flattening, notching, and inversion of the T wave, and the appearance of U waves. Sudden, unexpected deaths have occurred at doses greater than 20 milligrams/day (Prod Info Orap(R) pimozide, 1999k).

3.5.1.AN Droperidol

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Droperidol has been shown to prolong the QTc interval at the recommended therapeutic dose. Even though no formal drug interaction studies have been done, the coadministration of droperidol and other drugs known to prolong the QTc interval, including pimozide, is contraindicated (Prod Info Inapsine(R), 2001; Prod Info Orap(R), 1999w).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of agents that prolong the QT interval, such as droperidol and pimozide, is contraindicated.
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) In experimental studies of conditions other than Tourette's Disorder, sudden, unexpected deaths have occurred. The patients were receiving pimozide dosages of approximately 1 mg per kg. One possible mechanism for such deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmia. The manufacturer recommends that an electrocardiogram be performed before pimozide treatment is initiated and periodically thereafter, especially during the period of dose adjustment (Prod Info Orap(R), 1999v).

3.5.1.AO Efavirenz

1) Interaction Effect: an increased risk of cardiac arrhythmias
2) Summary: Efavirenz and pimozide are both metabolized by the CYP3A4 enzyme system. Competition for this pathway could result in inhibition of pimozide metabolism, creating the potential for serious and/or life-threatening reactions such as cardiac arrhythmias. Concurrent administration of efavirenz and pimozide is contraindicated (Prod Info SUSTIVA(R) oral capsules, tablets, 2008).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The coadministration of efavirenz and pimozide is contraindicated as this may result in competitive inhibition of pimozide metabolism, thereby increasing the risk for serious and/or potentially life-threatening adverse events such as cardiac arrhythmias (Prod Info SUSTIVA(R) oral capsules, tablets, 2008).
7) Probable Mechanism: competition for CYP3A4-mediated pimozide metabolism by efavirenz

3.5.1.AP Encainide

1) Interaction Effect: cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, the coadministration of pimozide and other drugs known to prolong the QTc interval, including Class I antiarrhythmic agents, is contraindicated (Prod Info Orap(R) pimozide, 1999a; Prod Info Tambocor(TM), 1998; Prod Info Enkaid(R), 1988; Larochelle et al, 1984).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of pimozide with other agents that can prolong the QT interval, such as Class I antiarrhythmic agents, is contraindicated.
7) Probable Mechanism: additive effects on QT prolongation
8) Literature Reports
a) In experimental studies of conditions other than Tourette's Disorder, sudden, unexpected deaths have occurred. The patients were receiving pimozide dosages of approximately 1 mg per kg. One possible mechanism for such deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmia. The manufacturer recommends that an electrocardiogram be performed before pimozide treatment is initiated and periodically thereafter, especially during the period of dose adjustment (Prod Info Orap(R) pimozide, 1999).

3.5.1.AQ Enflurane

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Pimozide prolongs the QT interval and an additive effect would be anticipated if administered with other agents which lengthen the QT interval (Prod Info Orap(R) pimozide, 1999c). Even though no formal drug interaction studies have been done, pimozide should not be coadministered with other drugs which are also known to prolong the QTc interval, including enflurane (Owens, 2001b).
3) Severity: contraindicated

4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Pimozide is contraindicated in individuals with congenital QT syndrome, patients with a history of cardiac arrhythmias, or patients taking other drugs which may prolong the QT interval.
7) Probable Mechanism: additive effects on QT prolongation
8) Literature Reports
a) Electrocardiographic changes that have occurred during clinical trials with pimozide have included prolongation of the corrected QT interval, flattening, notching, and inversion of the T wave and the appearance of U waves. In experimental studies, sudden, unexpected deaths have occurred while patients were receiving pimozide doses of 1 mg/kg. The proposed mechanism for these deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmias (Prod Info Orap(R), 1999m).

3.5.1.AR Erythromycin
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Erythromycin significantly increased the mean QTc interval versus baseline in a retrospective study of 49 patients (Oberg & Bauman, 1995a). Erythromycin has demonstrated QTc prolongation in combination with other drugs that prolong the QT interval (Prod Info PCE(R), 1997). Even though no formal drug interaction studies have been done, pimozide should not be coadministered with other drugs which are also known to prolong the QTc interval, including erythromycin (Prod Info Orap(R) pimozide, 1999q).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of pimozide with other agents that can prolong the QT interval, such as erythromycin, is contraindicated.
7) Probable Mechanism: additive effects on QT prolongation
8) Literature Reports
a) In experimental studies of conditions other than Tourette's Disorder, sudden, unexpected deaths have occurred. The patients were receiving pimozide dosages of approximately 1 mg per kg. One possible mechanism for such deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmia. The manufacturer recommends that an electrocardiogram be performed before pimozide treatment is initiated and periodically thereafter, especially during the period of dose adjustment (Prod Info Orap(R) pimozide, 1999p).
b) Erythromycin significantly increased the QTc interval compared with baseline in a retrospective study of 49 patients. The erythromycin dose was 500 milligrams or 1 gram four times daily, with a mean of 15 doses received. Patients (n equal to 9) who received 60 mg/kg/day or more all developed increases in QT interval of 15% or greater. For all patients, the mean QTc interval increased from 432 milliseconds (msec) at baseline to 483 msec (p less than 0.01). In patients with delayed repolarization at baseline (n equal to 9), the QTc interval increased from 473 msec to 525 msec (p less than 0.01). In patients with heart disease (n equal to 30), all experienced an increase in QTc interval (mean of 15%), compared with an increase of 8% in patients without heart disease (p less than 0.05). In 5 patients (10%), the QTc interval was severely prolonged. One patient developed torsades de pointes attributed to erythromycin. Of 16 patients receiving cotrimoxazole concomitantly, 8 developed QT prolongation of 15% or greater (Oberg & Bauman, 1995).

3.5.1.AS Flecainide
1) Interaction Effect: cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, the coadministration of pimozide and other drugs known to prolong the QTc interval, including Class I antiarrhythmic agents, is contraindicated (Prod Info Orap(R) pimozide, 1999a; Prod Info Tambocor(TM), 1998; Prod Info Enkaid(R), 1988; Larochelle et al, 1984).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of pimozide with other agents that can prolong the QT interval, such as Class I antiarrhythmic agents, is contraindicated.
7) Probable Mechanism: additive effects on QT prolongation
8) Literature Reports
a) In experimental studies of conditions other than Tourette's Disorder, sudden, unexpected deaths have occurred. The patients were receiving pimozide dosages of approximately 1 mg per kg. One possible mechanism for such deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmia. The manufacturer recommends that an electrocardiogram be performed before pimozide treatment is initiated and periodically thereafter, especially during the period of dose adjustment (Prod Info Orap(R) pimozide, 1999).

3.5.1.AT Fluconazole
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac

arrest)
2) Summary: Even though no formal drug interaction studies have been done, pimozide should not be coadministered with other drugs which are also known to prolong the QTc interval (Prod Info Orap(R) pimozide, 1999u). Case reports have described QT prolongation and torsades de pointes associated with fluconazole (Khazan & Mathis, 2002; Wassmann et al, 1999).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of pimozide with other agents that can prolong the QT interval, such as fluconazole, is contraindicated.
7) Probable Mechanism: additive cardiac effects

3.5.1.AU Fluoxetine
1) Interaction Effect: bradycardia, somnolence, and potentially increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: One case of bradycardia and somnolence resulting from concomitant fluoxetine and pimozide therapy has been reported (Ahmed et al, 1993). Although a specific interaction study has not been conducted with these agents, due to the potential for additive QT prolongation effects, the concomitant use of fluoxetine and pimozide is contraindicated (Prod Info PROZAC(R) oral capsule, oral pulvule, oral solution, oral tablet, 2005).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Due to the possibility of additive effects on the QT interval, the concurrent administration of fluoxetine and pimozide is contraindicated.
7) Probable Mechanism: additive effects on QT prolongation
8) Literature Reports
a) One case has been reported in which concurrent use of pimozide 5 mg daily and fluoxetine 20 mg daily in an elderly patient resulted in severe bradycardia and somnolence. The pulse rate gradually returned to normal after discontinuation of pimozide; rechallenge with a lower pimozide dose and a higher fluoxetine dose also resulted in bradycardia (Ahmed et al, 1993).

3.5.1.AV Fosamprenavir
1) Interaction Effect: an increased risk of cardiotoxicity (QT interval prolongation, torsades de pointes, cardiac arrest)
2) Summary: Fosamprenavir is an inhibitor of the isoenzyme cytochrome P450 3A; concomitant use with pimozide may result in inhibition of pimozide metabolism. Elevated pimozide serum concentrations have been associated with an increased risk of cardiotoxicity. The concurrent administration of fosamprenavir and pimozide is contraindicated (Prod Info Lexiva(R), 2004).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Concomitant use of fosamprenavir and pimozide is contraindicated.
7) Probable Mechanism: inhibition of cytochrome P450 3A-mediated pimozide metabolism

3.5.1.AW Fosaprepitant
1) Interaction Effect: increased plasma concentrations of pimozide
2) Summary: Fosaprepitant is a prodrug of aprepitant, which is a moderate CYP3A4 inhibitor. Coadministration with pimozide, a CYP3A4 substrate, could result in elevated plasma pimozide levels and potentially cause serious or life-threatening reactions. The concomitant use of pimozide and fosaprepitant is contraindicated (Prod Info EMEND(R) IV injection, 2008).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of fosaprepitant and pimozide is contraindicated (Prod Info EMEND(R) IV injection, 2008).
7) Probable Mechanism: inhibition of CYP3A4-mediated metabolism of pimozide by aprepitant

3.5.1.AX Foscarnet
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Coadministration of drugs that potentially prolong the QTc interval, such as foscarnet and pimozide, is contraindicated (Prod Info Orap(R), 1999az; Prod Info Foscavir(R), 1998).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of agents that prolong the QT interval, such as foscarnet and pimozide, is contraindicated.

7) Probable Mechanism: additive effects on QT prolongation
8) Literature Reports
a) In experimental studies of conditions other than Tourette's Disorder, sudden, unexpected deaths have occurred. The patients were receiving pimozide dosages of approximately 1 mg per kg. One possible mechanism for such deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmia. The manufacturer recommends that an electrocardiogram be performed before pimozide treatment is initiated and periodically thereafter, especially during the period of dose adjustment (Prod Info Orap(R), 1999ay).

3.5.1.AY Gemifloxacin
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Although pharmacokinetic studies between gemifloxacin and pimozide, which has the potential to prolong the QT interval, have not been performed, gemifloxacin should not be used in patients receiving pimozide (Prod Info Factive(R), 2003; Prod Info Orap(R), 1999i).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: The concurrent administration of pimozide with other drugs that prolong the QT interval, such as gemifloxacin, is contraindicated.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.AZ Halofantrine
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Halofantrine can prolong the QT interval in some patients, which may result in ventricular tachycardia, ventricular fibrillation, and torsades de pointes. Because pimozide may also prolong the QT interval and increase the risk of arrhythmias, the concurrent administration of halofantrine with pimozide is contraindicated (Prod Info Orap(R) pimozide, 1999n; Prod Info Halfan(R), 1998).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Due to the potential additive effects on the QT interval, the concurrent administration of halofantrine and pimozide is contraindicated.
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) In experimental studies of conditions other than Tourette's Disorder, sudden, unexpected deaths have occurred. The patients were receiving pimozide dosages of approximately 1 mg per kg. One possible mechanism for such deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmia. The manufacturer recommends that an electrocardiogram be performed before pimozide treatment is initiated and periodically thereafter, especially during the period of dose adjustment (Prod Info Orap(R) pimozide, 1999m).

3.5.1.BA Haloperidol
1) Interaction Effect: cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Haloperidol is associated with QTc prolongation and torsade de pointes (Hassaballa & Balk, 2003a; Prod Info Haldol(R), 2001). According to the manufacturer, coadministration of pimozide with drugs that potentially prolong the QTc interval, such as haloperidol, is contraindicated (Prod Info Orap(R), 1999bi).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of agents that prolong the QT interval, such as haloperidol and pimozide, is contraindicated.
7) Probable Mechanism: additive effects on QT prolongation
8) Literature Reports
a) Numerous case reports have described significant QTc prolongation and torsades de pointes (TdP) associated with haloperidol. Hemodynamically significant ventricular tachyarrhythmias, ventricular fibrillation, asystole, and death have been reported. The risk of TdP appears to be greater with intravenous haloperidol, but has occurred with oral and intramuscular use. The risk increases with doses greater than 35 milligrams (mg) over 24 hours, although TdP has been associated with a dose as low as 10 mg administered intravenously over 4 hours. To prevent haloperidol-induced TdP, screen patients for a history of dilated cardiomyopathy or alcohol abuse, testing for hypothyroidism before therapy, obtaining an electrocardiogram at baseline and throughout therapy, and monitoring potassium, magnesium, and calcium. In patients with a baseline QTc greater than 450 milliseconds (msec), haloperidol should be used cautiously or an alternative agent should be used. Discontinue haloperidol if the QTc increases more than 25% from baseline or if flattening of T-waves or development of U-waves occurs (Hassaballa & Balk, 2003).
b) Seven patients developed torsade de pointes after therapeutic use of haloperidol in high doses.

Three patients developed the dysrhythmia after administration of 211 milligrams (mg) to 825 mg haloperidol over 1 to 2 days for agitated delirium. These 3 patients recovered from the initial episodes, but 1 patient subsequently died of cardiac arrest upon readministration of haloperidol (Metzger & Friedman, 1993; Wilt et al, 1993). Torsades de pointes developed in 8 of 223 critically ill patients in intensive care units. Patients who received intravenous haloperidol greater than 35 mg/day or had a QTc interval prolongation of greater than 500 milliseconds were at greatest risk (Sharma et al, 1998).
c) In experimental studies of conditions other than Tourette's Disorder, sudden, unexpected deaths have occurred. The patients were receiving pimozide dosages of approximately 1 mg/kg. One possible mechanism for such deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmia. The manufacturer recommends that an electrocardiogram be performed before pimozide treatment is initiated and periodically thereafter, especially during the period of dose adjustment (Prod Info Orap(R) pimozide, 1999v).

3.5.1.BB Halothane

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Pimozide prolongs the QT interval and an additive effect would be anticipated if administered with other agents which lengthen the QT interval (Prod Info Orap(R), 1999h). Even though no formal drug interaction studies have been done, pimozide should not be coadministered with other drugs which are also known to prolong the QTc interval, including halothane (Owens, 2001a).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Pimozide is contraindicated in individuals with congenital QT syndrome, patients with a history of cardiac arrhythmias, or patients taking other drugs which may prolong the QT interval.
7) Probable Mechanism: additive effect on QT interval
8) Literature Reports
a) Electrocardiographic changes that have occurred during clinical trials with pimozide have included prolongation of the corrected QT interval, flattening, notching, and inversion of the T wave and the appearance of U waves. In experimental studies, sudden, unexpected deaths have occurred while patients were receiving pimozide doses of 1 mg/kg. The proposed mechanism for these deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmias (Prod Info Orap(R), 1999g).

3.5.1.BC Hydroquinidine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Because Class Ia antiarrhythmic agents may also prolong the QT interval and increase the risk of arrhythmias, the concurrent administration of pimozide with a drug from this class is contraindicated (Prod Info Orap(R), 1999q; Prod Info Quinaglute Dura-tabs(R), 1999; Stratmann et al, 1985; Chow et al, 1984).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of pimozide with other agents that can prolong the QT interval, such as Class Ia antiarrhythmic agents, is contraindicated.
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) In experimental studies of conditions other than Tourette's Disorder, sudden, unexpected deaths have occurred. The patients were receiving pimozide dosages of approximately 1 mg per kg. One possible mechanism for such deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmia. The manufacturer recommends that an electrocardiogram be performed before pimozide treatment is initiated and periodically thereafter, especially during the period of dose adjustment (Prod Info Orap(R), 1999p).
b) QRS widening, QTc interval prolongation, and torsades de pointes may occur with disopyramide therapy (Prod Info Norpace(R), 1997).
c) Several cases of recurrent irregular ventricular tachycardia also known as torsade de pointes have been reported with conventional doses of disopyramide. This condition is more likely to occur with severe repolarization delay and sinus bradycardia or atrioventricular block, especially when disopyramide therapy is combined with other QT interval prolonging agents (Tzivoni et al, 1981; Commerford & Beck, 1980; Croft & Kennelly, 1981). Others have retrospectively determined that women, irrespective of the presence or absence of other underlying heart conditions, are more at risk than men of developing torsades de pointes, in the setting of prolonged QT interval, following disopyramide therapy (Makkar et al, 1993).

3.5.1.BD Hydroquinidine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Several antipsychotic agents have demonstrated QT prolongation including amisulpride, haloperidol, iloperidone, paliperidone, quetiapine, risperidone, sertindole, sultopride, ziprasidone, and zotepine (Prod Info FANAPT(TM) oral tablets, 2009; Prod Info Solian(R), 1999e; O'Brien et al, 1999d; Prod Info INVEGA(TM) extended-release oral tablets, 2006; Owens, 2001i; Duenas-Laita et al, 1999g; Agelink et al, 2001d; Lande et al, 1992f; Prod Info GEODON(R) intramuscular injection, oral capsule, 2005; Sweetman, 2003). Because Class IA antiarrhythmic agents may also prolong the QT interval and increase the risk of arrhythmias, the concurrent administration of antipsychotics with a drug from this class is not recommended (Prod Info FANAPT(TM) oral tablets, 2009; Prod Info Quinaglute(R), 1999).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: The concurrent administration of a Class IA antiarrhythmic and an antipsychotic is not recommended.
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) In an open-label QTc study of patients with schizophrenia or schizoaffective disorder (n=160), iloperidone 12 mg twice a day was associated with QTc prolongation of 9 msec (Prod Info FANAPT(TM) oral tablets, 2009).
b) QRS widening, QTc interval prolongation, and torsades de pointes may occur with disopyramide therapy (Prod Info Norpace(R), 1997a).
c) The effects of combined therapy with quinidine (Class IA antiarrhythmic agent) and haloperidol (antipsychotic agent) were studied by giving 12 healthy volunteers haloperidol 5 mg alone and with 250 mg of quinidine bisulfate. The study demonstrated significant increases in the plasma concentrations of haloperidol when given concurrently with quinidine versus haloperidol treatment alone. The mean area under the concentration curve (AUC) was increased from 54.3 ng/h/mL on haloperidol alone to 103.2 ng/h/mL on combined therapy. The peak concentration (Cmax) also showed an increase from 1.9 ng/mL on haloperidol to 3.8 ng/mL on combined therapy. Half-life (T1/2) and time to peak concentration (Tmax) were not significantly changed, thereby suggesting to the authors that a tissue binding mechanism is more likely responsible for the plasma level changes than an elimination alteration (Young et al, 1993).

3.5.1.BE Ibutilide

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Class III antiarrhythmics have been shown to prolong the QT interval, which may result in ventricular tachycardia, ventricular fibrillation, and torsades de pointes. Even though no formal drug interaction studies have been done, the coadministration of pimozide and other drugs known to prolong the QTc interval, including class III antiarrhythmics is contraindicated (Yamreudeewong et al, 2003a; Prod Info Orap(R), 1999k).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of pimozide with other agents that can prolong the QT interval, such as Class III antiarrhythmic agents, is contraindicated.
7) Probable Mechanism: additive effects on QT prolongation
8) Literature Reports
a) In experimental studies of conditions other than Tourette's Disorder, sudden, unexpected deaths have occurred. The patients were receiving pimozide dosages of approximately 1 mg per kg. One possible mechanism for such deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmia. The manufacturer recommends that an electrocardiogram be performed before pimozide treatment is initiated and periodically thereafter, especially during the period of dose adjustment (Prod Info Orap(R), 1999j).
b) Concurrent use of class III antiarrhythmic agents, and other drugs that can prolong the QT interval, such as pimozide, is not recommended. Dofetilide should be stopped for at least 2 days before any interacting drug is initiated. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised (Yamreudeewong et al, 2003).

3.5.1.BF Imatinib

1) Interaction Effect: increased plasma levels of pimozide
2) Summary: Plasma concentrations of pimozide may be altered when coadministration with imatinib. Caution should be utilized when administering imatinib with cytochrome P450 3A4 substrates, such as pimozide, that have narrow therapeutic windows (Prod Info Gleevec(TM), 2002).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Caution is recommended when administering imatinib with pimozide, a cytochrome P450 3A4 substrate with a narrow therapeutic window.
7) Probable Mechanism: inhibition of cytochrome P450 3A4 metabolism of pimozide by imatinib

3.5.1.BG Imipramine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Although citing no data, the manufacturer of pimozide states that concomitant use with other drugs which prolong the QT interval is contraindicated (Prod Info Orap(R), 1999ap). Tricyclic antidepressants (TCAs) at therapeutic doses can cause QT prolongation (Prod Info Norpramin(R), 2000; Marshall & Forker, 1982).

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Because of the potential to prolong the QT interval, concurrent administration of a tricyclic antidepressant and pimozide is contraindicated.

7) Probable Mechanism: additive effects on QT interval

8) Literature Reports

a) Electrocardiogram (ECG) changes seen during clinical trials of pimozide in Tourette's syndrome and schizophrenia patients include prolongation of the QT interval, flattening, notching, and inversion of the T wave, and the appearance of U waves. Sudden, unexpected deaths have occurred at doses greater than 20 milligrams/day (Prod Info Orap(R) pimozide, 1999k).

3.5.1.BH Indinavir

1) Interaction Effect: an increased risk of cardiotoxicity (QT interval prolongation, torsades de pointes, cardiac arrest)

2) Summary: Indinavir is an inhibitor of cytochrome P450 3A may result in inhibition of pimozide metabolism. Elevated pimozide serum concentrations have been associated with an increased risk of cardiotoxicity. The concurrent administration of indinavir and pimozide is contraindicated (Prod Info Orap(R), 1999u).

3) Severity: contraindicated

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: Concomitant use of pimozide and indinavir is contraindicated.

7) Probable Mechanism: inhibition of cytochrome P450 3A-mediated pimozide metabolism

3.5.1.BI Isoflurane

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Pimozide prolongs the QT interval and an additive effect would be anticipated if administered with other agents which lengthen the QT interval (Prod Info Orap(R), 1999bf). Even though no formal drug interaction studies have been done, pimozide should not be coadministered with other drugs which are also known to prolong the QTc interval, including isoflurane (Owens, 2001j).

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Pimozide is contraindicated in individuals with congenital QT syndrome, patients with a history of cardiac arrhythmias, or patients taking other drugs which may prolong the QT interval.

7) Probable Mechanism: additive effect on QT interval

8) Literature Reports

a) Electrocardiographic changes that have occurred during clinical trials with pimozide have included prolongation of the corrected QT interval, flattening, notching, and inversion of the T wave and the appearance of U waves. In experimental studies, sudden, unexpected deaths have occurred while patients were receiving pimozide doses of 1 mg/kg. The proposed mechanism for these deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmias (Prod Info Orap(R), 1999be).

3.5.1.BJ Isradipine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Coadministration of drugs that potentially prolong the QTc interval, such as isradipine and pimozide, is contraindicated (Prod Info DynaCirc(R), 2000; Prod Info Orap(R), 1999ai).

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of agents that prolong the QT interval, such as isradipine and pimozide, is contraindicated.

7) Probable Mechanism: additive cardiac effects

8) Literature Reports

a) In experimental studies of conditions other than Tourette's Disorder, sudden, unexpected deaths have occurred. The patients were receiving pimozide dosages of approximately 1 mg per kg. One

possible mechanism for such deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmia. The manufacturer recommends that an electrocardiogram be performed before pimozide treatment is initiated and periodically thereafter, especially during the period of dose adjustment (Prod Info Orap(R) pimozide, 1999h).

3.5.1.BK Itraconazole

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Itraconazole may inhibit the metabolism of pimozide, resulting in increased serum concentrations of this agent. Elevated serum levels of pimozide have been associated with adverse cardiovascular effects including QT interval prolongation, cardiac arrhythmia, and sudden death. The concurrent use of itraconazole and pimozide is contraindicated (Prod Info Orap(R), 1999af; Prod Info Sporanox(R), 2002).
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: The concurrent administration of itraconazole and pimozide is contraindicated.
7) Probable Mechanism: inhibition by itraconazole of cytochrome P450 3A4-mediated pimozide metabolism

3.5.1.BL Kava

1) Interaction Effect: additive dopamine antagonist effects
2) Summary: Theoretically, kava may add to the effect of dopamine antagonists, increasing the risk for adverse effects. Case reports describe what appears to be dopamine-blocking activity of kava manifested in patients as dystonia, dyskinesias, and Parkinsonism (Spillane et al, 1997a; Schelosky et al, 1995a). Kava extracts antagonized apomorphine-induced hyperreactivity to external stimuli in mice, suggesting dopamine blockade activity (Jamieson et al, 1989).
3) Severity: moderate
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Avoid concomitant use of kava with dopamine antagonists. The desired effect and/or adverse effects of the dopamine antagonist may be increased or may be variable depending on the time of administration of kava and the quality of the kava product (i.e., whether it contains a standardized amount of kava).
7) Probable Mechanism: dopamine antagonist effect of kava
8) Literature Reports

a) A 27-year-old Aboriginal Australian male presented three times following heavy kava use with symptoms of severe choreoathetosis of the limbs, trunk, neck, and facial musculature, and athetosis of the tongue. Level of consciousness was not impaired. Symptoms resolved within 12 hours of intravenous diazepam on each occasion. Acute rheumatic fever was excluded, cerebrospinal fluid and computed tomography of the brain was normal, and urinary drug screen was negative. The only abnormalities found in hematological and biochemical tests were a serum alkaline phosphatase of 162 international units/liter (IU/L) (normal: 35-135 IU/L) and serum gamma-glutamyltransferase of 426 IU/L (normal less than 60 IU/L). These were attributed to kava use. The patient did not drink alcohol (Spillane et al, 1997).
b) A 76-year-old female with idiopathic Parkinson's disease of 17 years' duration treated for 8 years with levodopa 500 milligrams (mg) and benserazide 125 mg was prescribed kava extract (Kavasporal Forte(R)) 150 mg twice daily for complaints of inner tension. Within 10 days, she noted a pronounced increase in her daily "off" periods both in terms of duration and number. Within 2 days of discontinuing the kava product, symptoms had returned to her normal baseline (Schelosky et al, 1995).
c) A 63-year-old female experienced sudden and acute forceful involuntary oral and lingual dyskinesias on the fourth day of self-initiated therapy with kava extract (Kavasporal Forte(R)) 150 mg three times daily. She was treated successfully in the emergency room with biperiden 5 mg intravenously. She denied taking any other medications in the months preceding this event (Schelosky et al, 1995).
d) A 22-year-old female took kava extract (Laitan(R)) 100 mg once for anxiety and nervousness. Within four hours she experienced oral and lingual dyskinesias, tonic rotation of the head, and painful twisting trunk movements. She was treated successfully with biperiden 2.5 mg intravenously. She denied taking any other medications in the months preceding this event (Schelosky et al, 1995).
e) A 28-year-old male experienced acute involuntary neck extension with forceful upward deviation of the eyes within 90 minutes of taking kava extract (Laitan(R)) 100 mg. Symptoms resolved spontaneously within 40 minutes. This man had a history of acute dystonic reactions following exposure to promethacin (50 mg) and fluspirilene (1.5 mg), which had responded biperiden 5 mg intravenously 9 and 12 years previously (Schelosky et al, 1995).

3.5.1.BM Ketoconazole

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Ketoconazole may inhibit the metabolism of pimozide, resulting in increased serum concentrations of this agent. Elevated serum levels of pimozide have been associated with adverse

cardiovascular effects including QT interval prolongation, cardiac arrhythmia, and sudden death. The concurrent use of ketoconazole and pimozide is contraindicated (Prod Info Orap(R), 1999ao).
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: The concurrent administration of ketoconazole and pimozide is contraindicated.
7) Probable Mechanism: inhibition by ketoconazole of cytochrome P450 3A-mediated pimozide metabolism

3.5.1.BN Lapatinib
1) Interaction Effect: an increased risk of QT interval prolongation
2) Summary: Due to the potential for additive effects on the QT interval and increased risk of torsade de pointes, caution should be used when lapatinib and drugs that prolong the QT interval are given concomitantly. Consideration should be given to monitoring cardiac function periodically with on-treatment ECGs and evaluating electrolyte (ie, magnesium, potassium) levels (Prod Info TYKERB oral tablets, 2008). Thirteen patients had either QTcF (corrected QT by the Friedericia method) greater than 480 msec or an increase in QTcF of greater than 60 msec in an uncontrolled, open-label, dose escalation study in advanced cancer patients (n=81) who received lapatinib doses ranging from 175 mg/day to 1800 mg/day, with serial ECGs collected on days 1 and 14 (Prod Info TYKERB oral tablets, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of lapatinib and drugs that prolong the QT interval may result in additive effects on the QT interval and an increased risk of torsade de pointes. Therefore, caution should be used when these agents are given concomitantly. Consider monitoring cardiac function periodically with on-treatment ECGs and evaluating electrolyte (ie, magnesium, potassium) levels (Prod Info TYKERB oral tablets, 2008).
7) Probable Mechanism: additive effects on the QT interval

3.5.1.BO Levomethadyl
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Any drug known to have the potential to prolong the QT interval should not be used with levomethadyl. Possible pharmacodynamic interactions can occur between levomethadyl and potentially arrhythmogenic agents such as pimozide that prolong the QT interval (Prod Info Orlaam(R), 2001).
3) Severity: contraindicated
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Levomethadyl is contraindicated in patients being treated with pimozide as it may precipitate QT prolongation and interact with levomethadyl.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.BP Lidoflazine
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Lidoflazine has been shown to prolong the QTc interval at the recommended therapeutic dose (Hanley & Hampton, 1983). Even though no formal drug interaction studies have been done, the coadministration of lidoflazine with other drugs known to prolong the QTc interval, including pimozide, is contraindicated (Prod Info Orap(R), 1999bc).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of agents that prolong the QT interval, such as lidoflazine and pimozide, is contraindicated.
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) In experimental studies of conditions other than Tourette's Disorder, sudden, unexpected deaths have occurred. The patients were receiving pimozide dosages of approximately 1 mg per kg. One possible mechanism for such deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmia. The manufacturer recommends that an electrocardiogram be performed before pimozide treatment is initiated and periodically thereafter, especially during the period of dose adjustment (Prod Info Orap(R) pimozide, 1999t).

3.5.1.BQ Lithium
1) Interaction Effect: weakness, dyskinesias, increased extrapyramidal symptoms, encephalopathy, and brain damage
2) Summary: An encephalopathic syndrome followed by irreversible brain damage has occurred in a few patients treated with lithium plus a dopamine-2 antagonist, particularly haloperidol. A causal relationship between these events and the concomitant administration of a dopamine-2 antagonist and lithium has not

been established (Prod Info LITHOBID(R) slow-release oral tablets, 2005). Coadministration of lithium and a number of antipsychotic drugs has caused a wide variety of encephalopathic symptoms, brain damage, extrapyramidal symptoms, and dyskinesias in isolated case reports. In most cases, these effects have occurred with therapeutic lithium levels (Amdisen, 1982; Prakash, 1982; Addonizio et al, 1988a). However, many series and trials have reported using such combinations with no severe adverse consequences (Goldney & Spence, 1986). The mechanism is not fully understood, but chronic lithium treatment decreases neostriatal dopaminergic activity, probably through a direct action on the G protein and the capacity of the G proteins, once activated, to stimulate adenyl cyclase (Carli et al, 1994). Hyperglycemic reactions have also occurred during combined phenothiazine and lithium use (Zall et al, 1968).

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Monitor patients closely for any signs of toxicity or extrapyramidal symptoms, especially if high doses of dopamine-2 antagonists, particularly haloperidol, and lithium are used. Serum lithium levels should be monitored periodically. Some clinicians advocate maintaining levels in the low therapeutic range.

7) Probable Mechanism: unknown

8) Literature Reports

a) Concomitant haloperidol and lithium therapy has resulted in symptoms of encephalopathy, confusion, extrapyramidal symptoms, and fever in several patients with mania (Cohen & Cohen, 1974; Loudon & Waring, 1976; Thomas, 1979). Irreversible neurological injuries have been reported (Sandyk & Hurwitz, 1983; Keitner & Rahman, 1984).

b) Seizures, encephalopathy, delirium, and abnormal EEG occurred in four patients during combined lithium and thioridazine therapy (Spring, 1979). Serum lithium levels were below 1 mEq/L at the time of the toxic reaction in all cases. All patients had previously tolerated lithium in combination with another phenothiazine. Three of these patients developed symptoms within eight days of initiating combination therapy.

c) The addition of lithium to neuroleptic therapy exacerbated extrapyramidal symptoms (EPS) in a small study (Addonizio et al, 1988). The patients had received at least five days of treatment with either oral thiothixene, haloperidol, or fluphenazine in mean doses of 607.5 chlorpromazine equivalents prior to initiation of the lithium and were experiencing drug-induced extrapyramidal symptoms. Oral lithium was added when clinically indicated in sufficient doses to achieve a therapeutic serum concentration. The maximum levels attained were 0.65 to 1.27 mEq/L. The EPS ratings increased in all ten patients following the addition of lithium. However, only three patients developed marked symptoms and no patient developed lithium toxicity. Significantly increased symptoms included gait, shoulder shaking, elbow rigidity, and tremor.

d) Ten patients treated with clozapine and lithium were studied (Blake et al, 1992). Of the ten patients, four experienced significant neurologic effects, including jerking of limbs, facial spasms and tics, tremor of hands and arms, tongue twitching, and stumbling gait. One of these also experienced delirium. These effects reversed when lithium was discontinued or given at a lower dose. On rechallenge, one of two patients suffered recurrence of symptoms. By keeping serum lithium no greater than 0.5 mEq/L, clozapine could be safely coadministered.

e) Chlorpromazine serum levels can be significantly reduced in the presence of lithium treatment. If used concurrently, abrupt cessation of lithium may result in rebound elevation of chlorpromazine levels, resulting in chlorpromazine toxicity. In patients on a lithium-chlorpromazine combination, abrupt withdrawal of the lithium may precipitate chlorpromazine cardiotoxicity. In this report, such toxicity was manifested as sudden ventricular fibrillation associated with prolongation of the QTc interval. Hypotension and EPS are also possible in this situation (Stevenson et al, 1989).

f) However, other data do not support that such adverse events are frequent or indeed causally related to combination therapy. Combination of dopamine antagonist antipsychotic drugs and lithium have been used successfully in many patients with manic-depressive illness. It has been proposed that the interaction may only become significant with very high doses of one or both drugs or with failure to discontinue dosing in the presence of toxic symptoms (Miller & Menninger, 1987).

g) A 69-year-old patient with oxygen-dependent chronic obstructive pulmonary disorder and a 25-year history of bipolar disorder was started on risperidone 3 mg for the treatment of new-onset auditory and visual hallucinations. She had also been maintained on a regimen of lithium (450 mg daily) for more than 10 years. In addition, she was given amantadine (100 mg twice daily) for tremor. Three weeks after the start of risperidone, the patient experienced a decline in mental status in addition to dizziness, worsening tremors, nausea and vomiting, polyuria, depression, and visual and auditory hallucinations. She was then admitted to the hospital for delirium. Her lithium serum level was 1.36 mEq/L at the time of the admission. All medications were discontinued. Although her lithium level decreased to 0.41 mEq/L, she continued to experience profound delirium, tremors, lethargy, and hallucinations for almost one week. After she started to respond to commands, she was restarted on lithium (300 mg at bedtime) because of the onset of mild hypomania. Five days later, she was discharged with a regimen of lithium and low-dose lorazepam for treatment of insomnia. It is suggested that delirium could have been caused by the concurrent use of lithium and risperidone. Other factors could also have caused delirium, such as the patient's serum lithium level and the underlying pulmonary pathology. In addition, amantadine, which facilitates the release of presynaptic dopamine and has a mild anticholinergic effect,

may have contributed (Chen & Cardasis, 1996).

3.5.1.BR Lithospermum

1) Interaction Effect: decreased effectiveness of dopamine antagonists
2) Summary: Theoretically, the dopamine agonist activity of lithospermum may oppose that of dopamine antagonists, decreasing their effectiveness. Lithospermum likely decreases prolactin secretion via dopamine stimulation (Sourgens et al, 1982a). Animal data suggest that the effect occurs rapidly within 3 hours after injection, subsiding within 6 to 9 hours (Sourgens et al, 1980a). The magnitude and clinical significance of this phenomenon has yet to be determined in humans. Furthermore, it is not known if the ability to stimulate dopamine receptors is limited to the hypothalamic region or if such an effect will be noted elsewhere (i.e., if patients with psychosis will experience worsening of their condition due to dopamine stimulation secondary to lithospermum). Caution is recommended until the effects on humans and possible implications of a drug-herb interaction with dopamine antagonists can be fully determined.
3) Severity: minor
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: If therapy is initiated with lithospermum and a dopamine antagonist, monitor closely for return of symptoms previously controlled by the dopamine antagonist.
7) Probable Mechanism: dopamine agonism of lithospermum may counteract dopamine antagonists
8) Literature Reports
a) Administration of freeze dried extracts (FDE) of Lithospermum officinale (Boraginaceae) by intravenous injection to rats resulted in reduced prolactin serum levels and hypophyseal stores. When administered diluent, prolactin levels decreased from 36 +/- 8 nanograms/milliliter (ng/mL) serum to 10 +/- 4 ng/mL serum (p less than 0.005) when administered Lithospermum officinale FDE (40 milligrams (mg)/100 grams body weight) within 3 hours post intravenous administration. The authors concluded that Lithospermum officinale possibly impacted prolactin secretion at the hypothalamic site via dopamine stimulation (Sourgens et al, 1982).
b) Prolactin levels decreased rapidly below basal values in rats within the first 3 hours following a single intravenous injection of Lithospermum officinale. Prolactin levels returned to control levels within 6 to 9 hours after the injection (Sourgens et al, 1980).

3.5.1.BS Lorcainide

1) Interaction Effect: cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, the coadministration of pimozide and other drugs known to prolong the QTc interval, including Class I antiarrhythmic agents, is contraindicated (Prod Info Orap(R) pimozide, 1999a; Prod Info Tambocor(TM), 1998; Prod Info Enkaid(R), 1988; Larochelle et al, 1984).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of pimozide with other agents that can prolong the QT interval, such as Class I antiarrhythmic agents, is contraindicated.
7) Probable Mechanism: additive effects on QT prolongation
8) Literature Reports
a) In experimental studies of conditions other than Tourette's Disorder, sudden, unexpected deaths have occurred. The patients were receiving pimozide dosages of approximately 1 mg per kg. One possible mechanism for such deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmia. The manufacturer recommends that an electrocardiogram be performed before pimozide treatment is initiated and periodically thereafter, especially during the period of dose adjustment (Prod Info Orap(R) pimozide, 1999).

3.5.1.BT Lumefantrine

1) Interaction Effect: an increased risk of QT interval prolongation
2) Summary: Due to the potential for additive effects on QT interval prolongation, concomitant use of artemether/lumefantrine with drugs that prolong the QT interval should be avoided (Prod Info COARTEM(R) oral tablets, 2009).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of artemether/lumefantrine with drugs that prolong the QT interval should be avoided due to the potential for additive effects on QT interval prolongation (Prod Info COARTEM(R) oral tablets, 2009).
7) Probable Mechanism: additive effects on QT interval prolongation
8) Literature Reports
a) Concurrent administration of a single dose of IV quinine 10 mg/kg with the final dose of a 6-dose regimen of artemether/lumfantrine did not alter the systemic exposure to quinine, lumefantrine, or dihydroartemisinin (active metabolite of artemether). Although artemether exposure was decreased, it was not believed to be clinically significant. The effects on QT prolongation were not reported in this

study (Prod Info COARTEM(R) oral tablets, 2009).

3.5.1.BU Mefloquine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, pimozide should not be coadministered with other drugs which are also known to prolong the QTc interval (Prod Info Orap(R), 1999ae). Mefloquine was associated with significant QT prolongation in a study of 46 healthy subjects (Davis et al, 1996).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of pimozide with other agents that can prolong the QT interval, such as mefloquine, is contraindicated.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.BV Mesoridazine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, the manufacturer of pimozide warns against its administration with other drugs which are also known to prolong the QTc interval, including phenothiazines (Prod Info Thorazine(R), 2002; Prod Info Compazine(R), 2002; Prod Info Stelazine(R), 2002; Prod Info Orap(R), 1999t). The manufacturers of mesoridazine and thioridazine state that concomitant use is contraindicated with other agents known to prolong the QT interval (Prod Info Mellaril(R), 2002; Prod Info Serentil(R), 2001).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of pimozide and other drugs that may prolong the QT interval, such as phenothiazines is contraindicated.
7) Probable Mechanism: additive effects on QT prolongation
8) Literature Reports
a) Electrocardiogram (ECG) changes seen during clinical trials of pimozide in Tourette's syndrome and schizophrenia patients include prolongation of the QT interval, flattening, notching, and inversion of the T wave, and the appearance of U waves. Sudden, unexpected deaths have occurred at doses greater than 20 milligrams/day (Prod Info Orap(R), 1999s).

3.5.1.BW Mesoridazine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Although citing no data, the manufacturer of mesoridazine states that concomitant use with other drugs which prolong the QT interval is contraindicated (Prod Info Serentil(R), 2001a). Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999d), haloperidol (O'Brien et al, 1999c), paliperidone (Prod Info INVEGA(TM) extended-release oral tablets, 2006), quetiapine (Owens, 2001h), risperidone (Duenas-Laita et al, 1999f), sertindole (Agelink et al, 2001c), sultopride (Lande et al, 1992c), ziprasidone (Prod Info GEODON(R) intramuscular injection, oral capsule, 2005), and zotepine (Sweetman, 2004).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of agents that prolong the QT interval, such as antipsychotics and mesoridazine, is contraindicated.
7) Probable Mechanism: additive QT prolongation

3.5.1.BX Methadone

1) Interaction Effect: an increased risk of QT interval prolongation
2) Summary: Cases of QT interval prolongation and serious arrhythmias, including torsade de pointes, have been reported with methadone use (Prod Info DOLOPHINE(R) HYDROCHLORIDE oral tablets, 2006). Treatment with pimozide has also been associated with QTc prolongation (Prod Info ORAP(R) oral tablets, 2005). Concurrent administration of methadone and pimozide is contraindicated due to the potential for additive effects on QTc prolongation (Prod Info ORAP(R) oral tablets, 2005).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concurrent use of methadone and pimozide is contraindicated due to the potential for additive effects on QT interval prolongation (Prod Info ORAP(R) oral tablets, 2005).
7) Probable Mechanism: additive effects on QT interval prolongation

3.5.1.BY Miconazole

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Miconazole may inhibit the metabolism of pimozide, resulting in increased serum concentrations of this agent. Elevated serum levels of pimozide have been associated with adverse cardiovascular effects including QT interval prolongation, cardiac arrhythmia, and sudden death. The concurrent use of miconazole and pimozide is contraindicated (Prod Info Orap(R), 1999al).
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of miconazole and pimozide is contraindicated.
7) Probable Mechanism: inhibition by miconazole of cytochrome P450 3A4-mediated pimozide metabolism

3.5.1.BZ Moxifloxacin

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Prolongation of the QTc interval has occurred with oral and intravenous moxifloxacin (Prod Info AVELOX(R) oral tablets, IV injection, 2005). Treatment with pimozide has also been associated with QTc prolongation. Concurrent administration of moxifloxacin and pimozide is contraindicated due to the potential for additive effects on QTc prolongation (Prod Info ORAP(R) oral tablets, 2005).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concurrent use of moxifloxacin and pimozide is contraindicated due to the potential for additive effects on QT interval prolongation (Prod Info ORAP(R) oral tablets, 2005).
7) Probable Mechanism: additive cardiac effects

3.5.1.CA Nefazodone

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Nefazodone may inhibit the metabolism of pimozide, resulting in increased serum concentrations of this agent. Elevated serum levels of pimozide have been associated with adverse cardiovascular effects including QT interval prolongation, cardiac arrhythmia, and sudden death. The concurrent use of nefazodone and pimozide is contraindicated (Prod Info Orap(R), 1999an).
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: The concurrent administration of nefazodone and pimozide is contraindicated.
7) Probable Mechanism: inhibition by nefazodone of cytochrome P450 3A-mediated pimozide metabolism

3.5.1.CB Nelfinavir

1) Interaction Effect: an increased risk of cardiotoxicity (QT interval prolongation, torsades de pointes, cardiac arrest)
2) Summary: Nelfinavir is an inhibitor of cytochrome P450 3A may result in inhibition of pimozide metabolism. Elevated pimozide serum concentrations have been associated with an increased risk of cardiotoxicity. The concurrent administration of nelfinavir and pimozide is contraindicated (Prod Info Orap (R), 1999aq).
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Concomitant use of pimozide and nelfinavir is contraindicated.
7) Probable Mechanism: inhibition of cytochrome P450 3A-mediated pimozide metabolism

3.5.1.CC Nilotinib

1) Interaction Effect: an increased risk of QT interval prolongation
2) Summary: Due to the potential for additive effects on the QT interval and increased risk of torsade de pointes, concomitant use of nilotinib with drugs that prolong the QT interval should be avoided. However, if concomitant use is required, the patient should be closely monitored for prolongation of the QT interval (Prod Info TASIGNA(R) oral capsules, 2007).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of nilotinib with drugs that prolong the QT interval should be avoided due to the potential for additive effects on the QT interval and increased risk of torsade de pointes. However, if concurrent therapy is required, monitor patient closely for prolongation of the QT interval (Prod Info TASIGNA(R) oral capsules, 2007).
7) Probable Mechanism: additive effects on QT interval prolongation

3.5.1.CD Nortriptyline

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Although citing no data, the manufacturer of pimozide states that concomitant use with other drugs which prolong the QT interval is contraindicated (Prod Info Orap(R), 1999ap). Tricyclic antidepressants (TCAs) at therapeutic doses can cause QT prolongation (Prod Info Norpramin(R), 2000; Marshall & Forker, 1982).

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Because of the potential to prolong the QT interval, concurrent administration of a tricyclic antidepressant and pimozide is contraindicated.

7) Probable Mechanism: additive effects on QT interval

8) Literature Reports

a) Electrocardiogram (ECG) changes seen during clinical trials of pimozide in Tourette's syndrome and schizophrenia patients include prolongation of the QT interval, flattening, notching, and inversion of the T wave, and the appearance of U waves. Sudden, unexpected deaths have occurred at doses greater than 20 milligrams/day (Prod Info Orap(R) pimozide, 1999k).

3.5.1.CE Octreotide

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Octreotide has been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Sandostatin(R), 1999). Even though no formal drug interaction studies have been done, the coadministration of pimozide and other drugs known to prolong the QTc interval, including octreotide, is contraindicated (Prod Info Orap(R) pimozide, 1999s).

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of pimozide with other agents that can prolong the QT interval, such as octreotide, is contraindicated.

7) Probable Mechanism: additive effects on QT prolongation

8) Literature Reports

a) In experimental studies of conditions other than Tourette's Disorder, sudden, unexpected deaths have occurred. The patients were receiving pimozide dosages of approximately 1 mg per kg. One possible mechanism for such deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmia. The manufacturer recommends that an electrocardiogram be performed before pimozide treatment is initiated and periodically thereafter, especially during the period of dose adjustment (Prod Info Orap(R) pimozide, 1999r).

3.5.1.CF Ondansetron

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Rarely, and predominantly with the intravenous formulation, transient ECG changes including QT interval prolongation have occurred with ondansetron (Prod Info ZOFRAN(R) oral tablets, oral solution, ZOFRAN ODT(R) orally disintegrating tablets, 2006). Pimozide has been shown to prolong the QTc interval and coadministration with other drugs which prolong the QT interval is contraindicated (Prod Info ORAP(R) oral tablets, 2004).

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of pimozide and agents that may prolong the QT interval, such as ondansetron, is contraindicated.

7) Probable Mechanism: additive effects on QT prolongation

3.5.1.CG Paroxetine

1) Interaction Effect: an increased risk of pimozide toxicity including cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Coadministration of paroxetine and pimozide is contraindicated. A controlled study involving concurrent administration of pimozide and paroxetine to healthy volunteers resulted in a mean increase in AUC and Cmax of 151% and 62%, respectively. The consequence of such an extreme increase of pimozide plasma concentrations may be pimozide toxicity, including risk of QT prolongation leading to torsades de pointes (Prod Info PAXIL CR(R) CONTROLLED-RELEASE TABLETS, 2005).

3) Severity: contraindicated

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: The concurrent administration of paroxetine and pimozide is contraindicated due to the possibility of significantly increased pimozide plasma concentrations resulting in a dangerous risk of

pimozide toxicity.
7) Probable Mechanism: unknown
8) Literature Reports
a) A group of healthy volunteers in a controlled study received a single dose of 2 mg pimozide after being titrated up to a daily dose of 60 mg of immediate-release paroxetine hydrochloride. The study resulted in a mean increase of pimozide area under the concentration time-curve (AUC) and maximum concentration (Cmax) of 151% and 62%, respectively (Prod Info PAXIL CR(R) CONTROLLED-RELEASE TABLETS, 2005).

3.5.1.CH Pentamidine
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Pentamidine has been shown to prolong the QTc interval at the recommended therapeutic dose (Lindsay et al, 1990). Even though no formal drug interaction studies have been done, the coadministration of pimozide and other drugs known to prolong the QTc interval, including pentamidine, is contraindicated (Prod Info Orap(R), 1999at).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of pimozide with other agents that can prolong the QT interval, such as pentamidine, is contraindicated.
7) Probable Mechanism: additive effects on QT prolongation
8) Literature Reports
a) In experimental studies of conditions other than Tourette's Disorder, sudden, unexpected deaths have occurred. The patients were receiving pimozide dosages of approximately 1 mg per kg. One possible mechanism for such deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmia. The manufacturer recommends that an electrocardiogram be performed before pimozide treatment is initiated and periodically thereafter, especially during the period of dose adjustment (Prod Info Orap(R), 1999as).

3.5.1.CI Phenylalanine
1) Interaction Effect: increased incidence of tardive dyskinesia
2) Summary: Taking phenylalanine concomitantly with certain neuroleptic drugs may exacerbate tardive dyskinesia (Gardos et al, 1992a). Abnormal phenylalanine metabolism in certain patients may lead to phenylalanine accumulation in the brain and in turn, reduced brain availability of other large neutral amino acids. This may interfere with the synthesis of catecholamines (Gardos et al, 1992a).
3) Severity: moderate
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Caution is advised if phenylalanine is administered with a neuroleptic agent. Monitor the patient closely for signs of tardive dyskinesia.
7) Probable Mechanism: reduced brain availability of other large neutral amino acids and interference with catecholamine synthesis
8) Literature Reports
a) Phenylalanine tended to increase the incidence of tardive dyskinesia in patients taking neuroleptics in an open study. Three groups of patients were studied: (1) patients with unipolar depression with tardive dyskinesia (n=11), (2) patients with no tardive dyskinesia with current or past exposure to greater than or equal to 100 milligrams (mg) of a chlorpromazine equivalent for at least 3 months (n=10), and (3) patients with no tardive dyskinesia not previously exposed to a neuroleptic drug (n=10). Neuroleptic agents were taken during the study by 6 patients in group 1, and 5 patients in group 2. Patients received powdered phenylalanine 100 mg/kilogram dissolved in orange juice after an overnight fast. Blood samples were obtained just prior to phenylalanine administration and 2 hours after administration. Three patients in group 1 (with tardive dyskinesia) had the highest postloading phenylalanine plasma levels, this group as a whole had higher (though nonsignificant) mean phenylalanine levels than the other groups. Tardive dyskinesia score (measured using the Abnormal Involuntary Movements Scale (AIMS)) nonsignificantly increased in group 1. Postloading phenylalanine level and postloading AIMS scores were significantly positively correlated in group 1 (rs=0.347, p less than 0.05; Spearman correlation coefficient 0.543, p less than 0.05). Postloading phenylalanine level and baseline AIMS scores demonstrated a trend toward correlation (rs=0.246, p=0.092; Spearman correlation coefficient 0.679, p less than 0.05). In all patients, phenylalanine loading increased plasma phenylalanine levels approximately eight-fold, and plasma tyrosine increased 2.5 times as a result of conversion of phenylalanine to tyrosine. Plasma levels of competing large neutral amino acids such as tryptophan decreased slightly (Gardos et al, 1992).

3.5.1.CJ Pirmenol
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Because Class Ia antiarrhythmic agents may also prolong the QT interval and increase the

risk of arrhythmias, the concurrent administration of pimozide with a drug from this class is contraindicated (Prod Info Orap(R), 1999q; Prod Info Quinaglute Dura-tabs(R), 1999; Stratmann et al, 1985; Chow et al, 1984).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of pimozide with other agents that can prolong the QT interval, such as Class Ia antiarrhythmic agents, is contraindicated.
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) In experimental studies of conditions other than Tourette's Disorder, sudden, unexpected deaths have occurred. The patients were receiving pimozide dosages of approximately 1 mg per kg. One possible mechanism for such deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmia. The manufacturer recommends that an electrocardiogram be performed before pimozide treatment is initiated and periodically thereafter, especially during the period of dose adjustment (Prod Info Orap(R), 1999p).
b) QRS widening, QTc interval prolongation, and torsades de pointes may occur with disopyramide therapy (Prod Info Norpace(R), 1997).
c) Several cases of recurrent irregular ventricular tachycardia also known as torsade de pointes have been reported with conventional doses of disopyramide. This condition is more likely to occur with severe repolarization delay and sinus bradycardia or atrioventricular block, especially when disopyramide therapy is combined with other QT interval prolonging agents (Tzivoni et al, 1981; Commerford & Beck, 1980; Croft & Kennelly, 1981). Others have retrospectively determined that women, irrespective of the presence or absence of other underlying heart conditions, are more at risk than men of developing torsades de pointes, in the setting of prolonged QT interval, following disopyramide therapy (Makkar et al, 1993).

3.5.1.CK Pirmenol
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Several antipsychotic agents have demonstrated QT prolongation including amisulpride, haloperidol, iloperidone, paliperidone, quetiapine, risperidone, sertindole, sultopride, ziprasidone, and zotepine (Prod Info FANAPT(TM) oral tablets, 2009; Prod Info Solian(R), 1999e; O'Brien et al, 1999d; Prod Info INVEGA(TM) extended-release oral tablets, 2006; Owens, 2001i; Duenas-Laita et al, 1999g; Agelink et al, 2001d; Lande et al, 1992f; Prod Info GEODON(R) intramuscular injection, oral capsule, 2005; Sweetman, 2003). Because Class IA antiarrhythmic agents may also prolong the QT interval and increase the risk of arrhythmias, the concurrent administration of antipsychotics with a drug from this class is not recommended (Prod Info FANAPT(TM) oral tablets, 2009; Prod Info Quinaglute(R), 1999).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: The concurrent administration of a Class IA antiarrhythmic and an antipsychotic is not recommended.
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) In an open-label QTc study of patients with schizophrenia or schizoaffective disorder (n=160), iloperidone 12 mg twice a day was associated with QTc prolongation of 9 msec (Prod Info FANAPT(TM) oral tablets, 2009).
b) QRS widening, QTc interval prolongation, and torsades de pointes may occur with disopyramide therapy (Prod Info Norpace(R), 1997a).
c) The effects of combined therapy with quinidine (Class IA antiarrhythmic agent) and haloperidol (antipsychotic agent) were studied by giving 12 healthy volunteers haloperidol 5 mg alone and with 250 mg of quinidine bisulfate. The study demonstrated significant increases in the plasma concentrations of haloperidol when given concurrently with quinidine versus haloperidol treatment alone. The mean area under the concentration curve (AUC) was increased from 54.3 ng/h/mL on haloperidol alone to 103.2 ng/h/mL on combined therapy. The peak concentration (Cmax) also showed an increase from 1.9 ng/mL on haloperidol to 3.8 ng/mL on combined therapy. Half-life (T1/2) and time to peak concentration (Tmax) were not significantly changed, thereby suggesting to the authors that a tissue binding mechanism is more likely responsible for the plasma level changes than an elimination alteration (Young et al, 1993).

3.5.1.CL Posaconazole
1) Interaction Effect: increased risk of QT prolongation and torsade de pointes
2) Summary: Concurrent use of pimozide and posaconazole is contraindicated. Posaconazole is an inhibitor of CYP3A4 enzymes. Coadministration of posaconazole and pimozide, a CYP3A4 substrate, may result in increased pimozide plasma concentrations, thereby leading to QT prolongation and rarely, torsade de pointes (Prod Info NOXAFIL(R) oral suspension, 2006).
3) Severity: contraindicated

4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of pimozide and posaconazole may result in increased pimozide plasma concentration and can lead to QT prolongation and rarely, torsade de pointes. Therefore, concurrent use of pimozide and posaconazole is contraindicated (Prod Info NOXAFIL(R) oral suspension, 2006).
7) Probable Mechanism: increased plasma pimozide levels due to inhibition of CYP3A4-mediated pimozide metabolism

3.5.1.CM Prajmaline

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Because Class Ia antiarrhythmic agents may also prolong the QT interval and increase the risk of arrhythmias, the concurrent administration of pimozide with a drug from this class is contraindicated (Prod Info Orap(R), 1999q; Prod Info Quinaglute Dura-tabs(R), 1999; Stratmann et al, 1985; Chow et al, 1984).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of pimozide with other agents that can prolong the QT interval, such as Class Ia antiarrhythmic agents, is contraindicated.
7) Probable Mechanism: additive cardiac effects
8) Literature Reports

a) In experimental studies of conditions other than Tourette's Disorder, sudden, unexpected deaths have occurred. The patients were receiving pimozide dosages of approximately 1 mg per kg. One possible mechanism for such deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmia. The manufacturer recommends that an electrocardiogram be performed before pimozide treatment is initiated and periodically thereafter, especially during the period of dose adjustment (Prod Info Orap(R), 1999p).
b) QRS widening, QTc interval prolongation, and torsades de pointes may occur with disopyramide therapy (Prod Info Norpace(R), 1997).
c) Several cases of recurrent irregular ventricular tachycardia also known as torsade de pointes have been reported with conventional doses of disopyramide. This condition is more likely to occur with severe repolarization delay and sinus bradycardia or atrioventricular block, especially when disopyramide therapy is combined with other QT interval prolonging agents (Tzivoni et al, 1981; Commerford & Beck, 1980; Croft & Kennelly, 1981). Others have retrospectively determined that women, irrespective of the presence or absence of other underlying heart conditions, are more at risk than men of developing torsades de pointes, in the setting of prolonged QT interval, following disopyramide therapy (Makkar et al, 1993).

3.5.1.CN Prajmaline

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Several antipsychotic agents have demonstrated QT prolongation including amisulpride, haloperidol, iloperidone, paliperidone, quetiapine, risperidone, sertindole, sultopride, ziprasidone, and zotepine (Prod Info FANAPT(TM) oral tablets, 2009; Prod Info Solian(R), 1999e; O'Brien et al, 1999d; Prod Info INVEGA(TM) extended-release oral tablets, 2006; Owens, 2001i; Duenas-Laita et al, 1999g; Agelink et al, 2001d; Lande et al, 1992f; Prod Info GEODON(R) intramuscular injection, oral capsule, 2005; Sweetman, 2003). Because Class IA antiarrhythmic agents may also prolong the QT interval and increase the risk of arrhythmias, the concurrent administration of antipsychotics with a drug from this class is not recommended (Prod Info FANAPT(TM) oral tablets, 2009; Prod Info Quinaglute(R), 1999).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: The concurrent administration of a Class IA antiarrhythmic and an antipsychotic is not recommended.
7) Probable Mechanism: additive cardiac effects
8) Literature Reports

a) In an open-label QTc study of patients with schizophrenia or schizoaffective disorder (n=160), iloperidone 12 mg twice a day was associated with QTc prolongation of 9 msec (Prod Info FANAPT(TM) oral tablets, 2009).
b) QRS widening, QTc interval prolongation, and torsades de pointes may occur with disopyramide therapy (Prod Info Norpace(R), 1997a).
c) The effects of combined therapy with quinidine (Class IA antiarrhythmic agent) and haloperidol (antipsychotic agent) were studied by giving 12 healthy volunteers haloperidol 5 mg alone and with 250 mg of quinidine bisulfate. The study demonstrated significant increases in the plasma concentrations of haloperidol when given concurrently with quinidine versus haloperidol treatment alone. The mean area under the concentration curve (AUC) was increased from 54.3 ng/h/mL on haloperidol alone to 103.2 ng/h/mL on combined therapy. The peak concentration (Cmax) also showed an increase from 1.9

ng/mL on haloperidol to 3.8 ng/mL on combined therapy. Half-life (T1/2) and time to peak concentration (Tmax) were not significantly changed, thereby suggesting to the authors that a tissue binding mechanism is more likely responsible for the plasma level changes than an elimination alteration (Young et al, 1993).

3.5.1.CO Probucol

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, pimozide should not be coadministered with other drugs which are also known to prolong the QTc interval (Prod Info Orap(R), 1999r). Probucol has been shown to prolong the QTc interval (Gohn & Simmons, 1992; Prod Info Lorelco (R), 1991).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of pimozide with other agents that can prolong the QT interval, such as probucol, is contraindicated.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.CP Procainamide

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Because Class Ia antiarrhythmic agents may also prolong the QT interval and increase the risk of arrhythmias, the concurrent administration of pimozide with a drug from this class is contraindicated (Prod Info Orap(R), 1999q; Prod Info Quinaglute Dura-tabs(R), 1999; Stratmann et al, 1985; Chow et al, 1984).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of pimozide with other agents that can prolong the QT interval, such as Class Ia antiarrhythmic agents, is contraindicated.
7) Probable Mechanism: additive cardiac effects
8) Literature Reports

a) In experimental studies of conditions other than Tourette's Disorder, sudden, unexpected deaths have occurred. The patients were receiving pimozide dosages of approximately 1 mg per kg. One possible mechanism for such deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmia. The manufacturer recommends that an electrocardiogram be performed before pimozide treatment is initiated and periodically thereafter, especially during the period of dose adjustment (Prod Info Orap(R), 1999p).
b) QRS widening, QTc interval prolongation, and torsades de pointes may occur with disopyramide therapy (Prod Info Norpace(R), 1997).
c) Several cases of recurrent irregular ventricular tachycardia also known as torsade de pointes have been reported with conventional doses of disopyramide. This condition is more likely to occur with severe repolarization delay and sinus bradycardia or atrioventricular block, especially when disopyramide therapy is combined with other QT interval prolonging agents (Tzivoni et al, 1981; Commerford & Beck, 1980; Croft & Kennelly, 1981). Others have retrospectively determined that women, irrespective of the presence or absence of other underlying heart conditions, are more at risk than men of developing torsades de pointes, in the setting of prolonged QT interval, following disopyramide therapy (Makkar et al, 1993).

3.5.1.CQ Procainamide

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Several antipsychotic agents have demonstrated QT prolongation including amisulpride, haloperidol, iloperidone, paliperidone, quetiapine, risperidone, sertindole, sultopride, ziprasidone, and zotepine (Prod Info FANAPT(TM) oral tablets, 2009; Prod Info Solian(R), 1999e; O'Brien et al, 1999d; Prod Info INVEGA(TM) extended-release oral tablets, 2006; Owens, 2001i; Duenas-Laita et al, 1999g; Agelink et al, 2001d; Lande et al, 1992f; Prod Info GEODON(R) intramuscular injection, oral capsule, 2005; Sweetman, 2003). Because Class IA antiarrhythmic agents may also prolong the QT interval and increase the risk of arrhythmias, the concurrent administration of antipsychotics with a drug from this class is not recommended (Prod Info FANAPT(TM) oral tablets, 2009; Prod Info Quinaglute(R), 1999).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: The concurrent administration of a Class IA antiarrhythmic and an antipsychotic is not recommended.
7) Probable Mechanism: additive cardiac effects
8) Literature Reports

a) In an open-label QTc study of patients with schizophrenia or schizoaffective disorder (n=160), iloperidone 12 mg twice a day was associated with QTc prolongation of 9 msec (Prod Info FANAPT(TM) oral tablets, 2009).
b) QRS widening, QTc interval prolongation, and torsades de pointes may occur with disopyramide therapy (Prod Info Norpace(R), 1997a).
c) The effects of combined therapy with quinidine (Class IA antiarrhythmic agent) and haloperidol (antipsychotic agent) were studied by giving 12 healthy volunteers haloperidol 5 mg alone and with 250 mg of quinidine bisulfate. The study demonstrated significant increases in the plasma concentrations of haloperidol when given concurrently with quinidine versus haloperidol treatment alone. The mean area under the concentration curve (AUC) was increased from 54.3 ng/h/mL on haloperidol alone to 103.2 ng/h/mL on combined therapy. The peak concentration (Cmax) also showed an increase from 1.9 ng/mL on haloperidol to 3.8 ng/mL on combined therapy. Half-life (T1/2) and time to peak concentration (Tmax) were not significantly changed, thereby suggesting to the authors that a tissue binding mechanism is more likely responsible for the plasma level changes than an elimination alteration (Young et al, 1993).

3.5.1.CR Prochlorperazine
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, the manufacturer of pimozide warns against its administration with other drugs which are also known to prolong the QTc interval, including phenothiazines (Prod Info Thorazine(R), 2002; Prod Info Compazine(R), 2002; Prod Info Stelazine(R), 2002; Prod Info Orap(R), 1999t). The manufacturers of mesoridazine and thioridazine state that concomitant use is contraindicated with other agents known to prolong the QT interval (Prod Info Mellaril(R), 2002; Prod Info Serentil(R), 2001).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of pimozide and other drugs that may prolong the QT interval, such as phenothiazines is contraindicated.
7) Probable Mechanism: additive effects on QT prolongation
8) Literature Reports
a) Electrocardiogram (ECG) changes seen during clinical trials of pimozide in Tourette's syndrome and schizophrenia patients include prolongation of the QT interval, flattening, notching, and inversion of the T wave, and the appearance of U waves. Sudden, unexpected deaths have occurred at doses greater than 20 milligrams/day (Prod Info Orap(R), 1999s).

3.5.1.CS Prochlorperazine
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Concomitant use of phenothiazines and antipsychotic agents may cause additive effects on the QT interval and is not recommended. Q and T wave distortions have been observed in patients taking phenothiazines (Prod Info Compazine(R), 2002a; Prod Info Stelazine(R), 2002a; Prod Info Thorazine(R), 2002a). Other phenothiazines may have similar effects, though no reports are available. Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999), haloperidol (O'Brien et al, 1999), paliperidone (Prod Info INVEGA(TM) extended-release oral tablets, 2006), quetiapine (Owens, 2001e), risperidone (Duenas-Laita et al, 1999c), sertindole (Agelink et al, 2001a), sultopride (Lande et al, 1992), ziprasidone (Prod Info GEODON(R) intramuscular injection, oral capsule, 2005), and zotepine (Sweetman, 2003).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of agents that prolong the QT interval, such as phenothiazines and antipsychotics, is not recommended.
7) Probable Mechanism: additive QT prolongation

3.5.1.CT Propafenone
1) Interaction Effect: cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, the coadministration of pimozide and other drugs known to prolong the QTc interval, including Class I antiarrhythmic agents, is contraindicated (Prod Info Orap(R) pimozide, 1999a; Prod Info Tambocor(TM), 1998; Prod Info Enkaid(R), 1988; Larochelle et al, 1984).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of pimozide with other agents that can prolong the QT interval, such as Class I antiarrhythmic agents, is contraindicated.
7) Probable Mechanism: additive effects on QT prolongation

8) Literature Reports

a) In experimental studies of conditions other than Tourette's Disorder, sudden, unexpected deaths have occurred. The patients were receiving pimozide dosages of approximately 1 mg per kg. One possible mechanism for such deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmia. The manufacturer recommends that an electrocardiogram be performed before pimozide treatment is initiated and periodically thereafter, especially during the period of dose adjustment (Prod Info Orap(R) pimozide, 1999).

3.5.1.CU Protriptyline

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Although citing no data, the manufacturer of pimozide states that concomitant use with other drugs which prolong the QT interval is contraindicated (Prod Info Orap(R), 1999ap). Tricyclic antidepressants (TCAs) at therapeutic doses can cause QT prolongation (Prod Info Norpramin(R), 2000; Marshall & Forker, 1982).

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Because of the potential to prolong the QT interval, concurrent administration of a tricyclic antidepressant and pimozide is contraindicated.

7) Probable Mechanism: additive effects on QT interval

8) Literature Reports

a) Electrocardiogram (ECG) changes seen during clinical trials of pimozide in Tourette's syndrome and schizophrenia patients include prolongation of the QT interval, flattening, notching, and inversion of the T wave, and the appearance of U waves. Sudden, unexpected deaths have occurred at doses greater than 20 milligrams/day (Prod Info Orap(R) pimozide, 1999k).

3.5.1.CV Quinidine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Because Class Ia antiarrhythmic agents may also prolong the QT interval and increase the risk of arrhythmias, the concurrent administration of pimozide with a drug from this class is contraindicated (Prod Info Orap(R), 1999q; Prod Info Quinaglute Dura-tabs(R), 1999; Stratmann et al, 1985; Chow et al, 1984).

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of pimozide with other agents that can prolong the QT interval, such as Class Ia antiarrhythmic agents, is contraindicated.

7) Probable Mechanism: additive cardiac effects

8) Literature Reports

a) In experimental studies of conditions other than Tourette's Disorder, sudden, unexpected deaths have occurred. The patients were receiving pimozide dosages of approximately 1 mg per kg. One possible mechanism for such deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmia. The manufacturer recommends that an electrocardiogram be performed before pimozide treatment is initiated and periodically thereafter, especially during the period of dose adjustment (Prod Info Orap(R), 1999p).

b) QRS widening, QTc interval prolongation, and torsades de pointes may occur with disopyramide therapy (Prod Info Norpace(R), 1997).

c) Several cases of recurrent irregular ventricular tachycardia also known as torsade de pointes have been reported with conventional doses of disopyramide. This condition is more likely to occur with severe repolarization delay and sinus bradycardia or atrioventricular block, especially when disopyramide therapy is combined with other QT interval prolonging agents (Tzivoni et al, 1981; Commerford & Beck, 1980; Croft & Kennelly, 1981). Others have retrospectively determined that women, irrespective of the presence or absence of other underlying heart conditions, are more at risk than men of developing torsades de pointes, in the setting of prolonged QT interval, following disopyramide therapy (Makkar et al, 1993).

3.5.1.CW Quinupristin

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Quinupristin/dalfopristin is a major inhibitor of cytochrome P450 3A4 (CYP3A4) isoenzymes, and pimozide is a CYP3A4 substrate. Coadministration of these two agents may likely result in increased plasma concentrations of pimozide, which may lead to QTc interval prolongation and risk of torsades de pointes (Prod Info SYNERCID(R) intravenous injection, 2003; Prod Info ORAP(R) Tablets, 2004).

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: The concurrent administration of pimozide and quinupristin/dalfopristin is contraindicated.
7) Probable Mechanism: inhibition of cytochrome P450 3A4-mediated pimozide metabolism

3.5.1.CX Ranolazine
1) Interaction Effect: an increased risk of QT interval prolongation
2) Summary: Pimozide and ranolazine have both been shown to prolong the QT interval. Concurrent administration of pimozide and ranolazine is contraindicated due to the potential for additive effects on QTc prolongation (Prod Info ORAP(R) oral tablets, 2005).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concurrent use of pimozide and ranolazine is contraindicated due to the potential for additive effects on QT interval prolongation (Prod Info ORAP(R) oral tablets, 2005).
7) Probable Mechanism: additive effects on QT interval prolongation

3.5.1.CY Rilonacept
1) Interaction Effect: altered pimozide plasma concentrations
2) Summary: In states of chronic inflammation, the formation of CYP450 enzymes is suppressed by increased levels of cytokines such as interleukin-1 (IL-1). Upon administration of an IL-1 blocker, such as rilonacept, the formation of CYP450 enzymes could be normalized. In patients receiving CYP450 substrates with a narrow therapeutic index concomitantly, such normalization may have a clinically relevant effect on the CYP450 substrate levels. If rilonacept therapy is initiated in a patient being treated with a CYP450 substrate that has a narrow therapeutic index, such as pimozide, the therapeutic effect of pimozide should be monitored and pimozide dose should be adjusted if necessary (Prod Info ARCALYST(TM) subcutaneous injection, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: If rilonacept therapy is initiated in a patient being treated with a CYP450 substrate with a narrow therapeutic index, such as pimozide, monitor for therapeutic effect of pimozide and adjust pimozide dose as needed (Prod Info ARCALYST(TM) subcutaneous injection, 2008).
7) Probable Mechanism: interference with CYP450-mediated pimozide metabolism

3.5.1.CZ Risperidone
1) Interaction Effect: cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Although no drug interaction studies have been performed, the manufacturer of pimozide states that coadministration of pimozide with drugs known to prolong the QTc interval should be approached with caution (Prod Info Orap(R) pimozide, 1999f). Risperidone has been reported to prolong the QTc interval (Prod Info Risperdal(R), 2002).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of agents that prolong the QT interval, such as pimozide and risperidone, is contraindicated.
7) Probable Mechanism: additive effects on QT prolongation
8) Literature Reports
a) In experimental studies of conditions other than Tourette's Disorder, sudden, unexpected deaths have occurred. The patients were receiving pimozide dosages of approximately 1 mg per kg. One possible mechanism for such deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmia. The manufacturer recommends that an electrocardiogram be performed before pimozide treatment is initiated and periodically thereafter, especially during the period of dose adjustment (Prod Info Orap(R), 1999z).
b) Sometimes fatal QRS prolongation and QTc prolongation have been reported in patients taking risperidone therapeutically (Duenas-Laita et al, 1999b; Ravin & Levenson, 1997b; Gesell & Stephen, 1997; Lo Vecchio et al, 1996; Brown et al, 1993).

3.5.1.DA Ritonavir
1) Interaction Effect: an increased risk of cardiotoxicity (QT interval prolongation, torsades de pointes, cardiac arrest)
2) Summary: Ritonavir is an inhibitor of cytochrome P450 3A may result in inhibition of pimozide metabolism. Elevated pimozide serum concentrations have been associated with an increased risk of cardiotoxicity. The concurrent administration of ritonavir and pimozide is contraindicated (Prod Info Norvir (R), 2000; Prod Info Orap(R), 1999aj).
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Concomitant use of pimozide and ritonavir is contraindicated.

7) Probable Mechanism: inhibition of cytochrome P450 3A-mediated pimozide metabolism

3.5.1.DB Roxithromycin

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Roxithromycin may inhibit the metabolism of pimozide, resulting in increased serum concentrations of this agent. Elevated serum levels of pimozide have been associated with adverse cardiovascular effects including QT interval prolongation, cardiac arrhythmia, and sudden death. The concomitant administration of roxithromycin and pimozide is contraindicated (Flockhart et al, 1996a; Prod Info Orap(R), 1999aa).
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Concurrent use of pimozide and roxithromycin is contraindicated.
7) Probable Mechanism: inhibition of cytochrome P450 3A-mediated pimozide metabolism

3.5.1.DC Saquinavir

1) Interaction Effect: an increased risk of cardiotoxicity (QT interval prolongation, torsades de pointes, cardiac arrest)
2) Summary: Saquinavir is an inhibitor of cytochrome P450 3A may result in inhibition of pimozide metabolism. Elevated pimozide serum concentrations have been associated with an increased risk of cardiotoxicity. The concurrent administration of saquinavir and pimozide is contraindicated (Prod Info Orap (R), 1999au).
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Concomitant use of pimozide and saquinavir is contraindicated.
7) Probable Mechanism: inhibition of cytochrome P450 3A-mediated pimozide metabolism

3.5.1.DD Sematilide

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Class III antiarrhythmics have been shown to prolong the QT interval, which may result in ventricular tachycardia, ventricular fibrillation, and torsades de pointes. Even though no formal drug interaction studies have been done, the coadministration of pimozide and other drugs known to prolong the QTc interval, including class III antiarrhythmics is contraindicated (Yamreudeewong et al, 2003a; Prod Info Orap(R), 1999k).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of pimozide with other agents that can prolong the QT interval, such as Class III antiarrhythmic agents, is contraindicated.
7) Probable Mechanism: additive effects on QT prolongation
8) Literature Reports

a) In experimental studies of conditions other than Tourette's Disorder, sudden, unexpected deaths have occurred. The patients were receiving pimozide dosages of approximately 1 mg per kg. One possible mechanism for such deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmia. The manufacturer recommends that an electrocardiogram be performed before pimozide treatment is initiated and periodically thereafter, especially during the period of dose adjustment (Prod Info Orap(R), 1999j).

b) Concurrent use of class III antiarrhythmic agents, and other drugs that can prolong the QT interval, such as pimozide, is not recommended. Dofetilide should be stopped for at least 2 days before any interacting drug is initiated. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised (Yamreudeewong et al, 2003).

3.5.1.DE Sertindole

1) Interaction Effect: cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Although no drug interaction studies have been performed, the manufacturer of pimozide states that coadministration of pimozide with drugs known to prolong the QTc interval should be approached with caution (Prod Info Orap(R), 1999bd). Sertindole has been reported to prolong the QTc interval (Brown & Levin, 1998a).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of pimozide with agents that prolong the QT interval, such as sertindole, is contraindicated.
7) Probable Mechanism: additive effects on QT prolongation
8) Literature Reports

a) In experimental studies of conditions other than Tourette's Disorder, sudden, unexpected deaths have occurred. The patients were receiving pimozide dosages of approximately 1 mg per kg. One possible mechanism for such deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmia. The manufacturer recommends that an electrocardiogram be performed before pimozide treatment is initiated and periodically thereafter, especially during the period of dose adjustment (Prod Info Orap(R) pimozide tablets, 1999).
b) Thirty, otherwise healthy, schizophrenic patients participated in an open, dose titration (4 to 16 milligrams per day (mg/day)) study to determine the cardiovascular effects of sertindole. At the end of the 3-week study it was concluded that resting heart rate and frequency corrected QT times increased in a dose-related manner, while there was no change in PQ-conduction times, autonomic parasympathetic tone, or blood pressure. Conduction times increased an average 3.5% to 6.5% over the dosing range (Agelink et al, 2001e).
c) The overall incidence of QT interval prolongation with sertindole is estimated at 1.9% to 4% (Brown & Levin, 1998). The potential risk of developing torsades de pointes has been estimated at 0.13% to 0.21% (Brown & Levin, 1998). Periodic electrocardiographic monitoring is required in the United Kingdom per sertindole's official labeling (Cardoni & Myer, 1997).

3.5.1.DF Sertraline

1) Interaction Effect: an increase in plasma pimozide levels
2) Summary: Due to the narrow therapeutic index of pimozide and due to the interaction noted at low dose of pimozide, concomitant administration of sertraline and pimozide is contraindicated (Prod Info Zoloft(R), 2002a).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Concomitant use of sertraline in patients taking pimozide is contraindicated.
7) Probable Mechanism: unknown
8) Literature Reports
a) In a controlled trial of a single 2 mg dose of pimozide, sertraline 200 mg daily coadministration to steady state was associated with a mean increase in pimozide area under the concentration-time curve (AUC) and maximum plasma concentrations (Cmax) of about 40%, but was not associated with any changes in EKG. Since the highest recommended pimozide dose (10 mg) has not been evaluated in combination with sertraline, the effect on QT interval and pharmacokinetic parameters at higher than 2 mg are not known. Considering the narrow therapeutic index of pimozide and observed interaction data with low doses, the combination should be avoided (Prod Info Zoloft(R), 2002).

3.5.1.DG Sotalol

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Class III antiarrhythmics have been shown to prolong the QT interval, which may result in ventricular tachycardia, ventricular fibrillation, and torsades de pointes. Even though no formal drug interaction studies have been done, the coadministration of pimozide and other drugs known to prolong the QTc interval, including class III antiarrhythmics is contraindicated (Yamreudeewong et al, 2003a; Prod Info Orap(R), 1999k).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of pimozide with other agents that can prolong the QT interval, such as Class III antiarrhythmic agents, is contraindicated.
7) Probable Mechanism: additive effects on QT prolongation
8) Literature Reports
a) In experimental studies of conditions other than Tourette's Disorder, sudden, unexpected deaths have occurred. The patients were receiving pimozide dosages of approximately 1 mg per kg. One possible mechanism for such deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmia. The manufacturer recommends that an electrocardiogram be performed before pimozide treatment is initiated and periodically thereafter, especially during the period of dose adjustment (Prod Info Orap(R), 1999j).
b) Concurrent use of class III antiarrhythmic agents, and other drugs that can prolong the QT interval, such as pimozide, is not recommended. Dofetilide should be stopped for at least 2 days before any interacting drug is initiated. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised (Yamreudeewong et al, 2003).

3.5.1.DH Spiramycin

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Spiramycin has been shown to prolong the QTc interval at the recommended therapeutic dose (Stramba-Badiale et al, 1997). Even though no formal drug interaction studies have been done, the coadministration of pimozide and other drugs known to prolong the QTc interval, including spiramycin, is

contraindicated (Prod Info Orap(R) pimozide, 1999j).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Due to the potential additive effects on the QT interval, the concurrent administration of spiramycin and pimozide is contraindicated.
7) Probable Mechanism: additive effects on QT prolongation
8) Literature Reports
a) In experimental studies of conditions other than Tourette's Disorder, sudden, unexpected deaths have occurred. The patients were receiving pimozide dosages of approximately 1 mg per kg. One possible mechanism for such deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmia. The manufacturer recommends that an electrocardiogram be performed before pimozide treatment is initiated and periodically thereafter, especially during the period of dose adjustment (Prod Info Orap(R) pimozide, 1999i).

3.5.1.DI Sulfamethoxazole
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Cotrimoxazole has been shown to prolong the QTc interval at the recommended therapeutic dose (Lopez et al, 1987). Even though no formal drug interaction studies have been done, the manufacturer of pimozide warns against its administration with other drugs which are also known to prolong the QTc interval, including cotrimoxazole (Prod Info Orap(R), 1999ad).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of agents that prolong the QT interval, such as cotrimoxazole and pimozide, is contraindicated.
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) In experimental studies of conditions other than Tourette's Disorder, sudden, unexpected deaths have occurred. The patients were receiving pimozide dosages of approximately 1 mg per kg. One possible mechanism for such deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmia. The manufacturer recommends that an electrocardiogram be performed before pimozide treatment is initiated and periodically thereafter, especially during the period of dose adjustment (Prod Info Orap(R) pimozide, 1999g).

3.5.1.DJ Sultopride
1) Interaction Effect: cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Coadministration of drugs that potentially prolong the QTc interval, such as pimozide and sultopride, should be approached with caution (Lande et al, 1992e; Montaz et al, 1992a; Harry, 1997a; Prod Info Orap(R), 1999bb).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of pimozide and other agents that prolong the QT interval, such as sultopride, is contraindicated.
7) Probable Mechanism: additive effects on QT prolongation
8) Literature Reports
a) In experimental studies of conditions other than Tourette's Disorder, sudden, unexpected deaths have occurred. The patients were receiving pimozide dosages of approximately 1 mg per kg. One possible mechanism for such deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmia. The manufacturer recommends that an electrocardiogram be performed before pimozide treatment is initiated and periodically thereafter, especially during the period of dose adjustment (Prod Info Orap(R), 1999ba).
b) Sultopride may induce prolongation of the QT interval and ventricular arrhythmias including torsades de pointes following therapeutic or toxic doses (Lande et al, 1992d; Montaz et al, 1992; Harry, 1997).

3.5.1.DK Sunitinib
1) Interaction Effect: an increased risk of QT interval prolongation
2) Summary: Sunitinib has been associated with prolongation of the QT interval in a dose dependent manner, with torsade de pointes occurring in less than 0.1% patients exposed to sunitinib (Prod Info SUTENT(R) oral capsules, 2008). Pimozide is also known to prolong the QT interval. Due to the potential for additive effects on the QT interval and increased risk for torsade de pointes, the concomitant use of pimozide and other drugs that prolong the QT interval is contraindicated (Prod Info ORAP(R) oral tablets, 2005a).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical

6) Clinical Management: Concomitant use of pimozide and drugs that prolong the QT interval, such as sunitinib, is contraindicated due to the potential for additive effects on the QT interval and an increased risk of torsade de pointes (Prod Info ORAP(R) oral tablets, 2005a).
7) Probable Mechanism: additive effects on the QT interval

3.5.1.DL Tedisamil

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Class III antiarrhythmics have been shown to prolong the QT interval, which may result in ventricular tachycardia, ventricular fibrillation, and torsades de pointes. Even though no formal drug interaction studies have been done, the coadministration of pimozide and other drugs known to prolong the QTc interval, including class III antiarrhythmics is contraindicated (Yamreudeewong et al, 2003a; Prod Info Orap(R), 1999k).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of pimozide with other agents that can prolong the QT interval, such as Class III antiarrhythmic agents, is contraindicated.
7) Probable Mechanism: additive effects on QT prolongation
8) Literature Reports
a) In experimental studies of conditions other than Tourette's Disorder, sudden, unexpected deaths have occurred. The patients were receiving pimozide dosages of approximately 1 mg per kg. One possible mechanism for such deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmia. The manufacturer recommends that an electrocardiogram be performed before pimozide treatment is initiated and periodically thereafter, especially during the period of dose adjustment (Prod Info Orap(R), 1999j).
b) Concurrent use of class III antiarrhythmic agents, and other drugs that can prolong the QT interval, such as pimozide, is not recommended. Dofetilide should be stopped for at least 2 days before any interacting drug is initiated. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised (Yamreudeewong et al, 2003).

3.5.1.DM Telithromycin

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Pimozide prolongs the QT interval and an additive effect would be anticipated if administered with other agents which lengthen the QT interval (Prod Info Orap(R), 1999ac). Even though no formal drug interaction studies have been done, pimozide should not be coadministered with other drugs which are also known to prolong the QTc interval, including telithromycin (Prod Info Ketek(TM), 2004; Owens, 2001d).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Pimozide is contraindicated in individuals with congenital QT syndrome, patients with a history of cardiac arrhythmias, or patients taking other drugs which may prolong the QT interval, including telithromycin.
7) Probable Mechanism: additive effect on QT interval
8) Literature Reports
a) Electrocardiographic changes that have occurred during clinical trials with pimozide have included prolongation of the corrected QT interval, flattening, notching, and inversion of the T wave and the appearance of U waves. In experimental studies, sudden, unexpected deaths have occurred while patients were receiving pimozide doses of 1 mg/kg. The proposed mechanism for these deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmias (Prod Info Orap(R), 1999ab).

3.5.1.DN Terfenadine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Some antipsychotics have been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Geodon(TM), 2002c; Owens, 2001k; Prod Info Orap(R), 1999bh). Even though no formal drug interaction studies have been done, the coadministration of terfenadine and other drugs known to prolong the QTc interval, including antipsychotics, is contraindicated (Anon, 1997).
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of terfenadine with any drug that prolongs the QT interval, such as antipsychotic agents, is contraindicated.
7) Probable Mechanism: additive effect on QT interval
8) Literature Reports
a) Electrocardiographic changes that have occurred during clinical trials with pimozide have included

prolongation of the corrected QT interval, flattening, notching, and inversion of the T wave and the appearance of U waves. In experimental studies, sudden, unexpected deaths have occurred while patients were receiving pimozide doses of 1 mg/kg. The proposed mechanism for these deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmias (Prod Info Orap(R), 1999bg).

3.5.1.DO Tetrabenazine

1) Interaction Effect: an increased risk of QT interval prolongation
2) Summary: Due to the potential for additive effects on the QT interval and increased risk of torsade de pointes, concomitant use of tetrabenazine with drugs that prolong the QT interval should be avoided. However, if concomitant use is required, the patient should be closely monitored for prolongation of the QT interval (Prod Info XENAZINE(R) oral tablets, 2008). In a randomized, double-blind, placebo controlled crossover study of healthy subjects, the effect of a single 25 mg or 50 mg dose of tetrabenazine on the QT interval was studied with moxifloxacin as a positive control. The 50 mg dose of tetrabenazine caused an approximate 8 millisecond mean increase in QT (Prod Info XENAZINE(R) oral tablets, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of tetrabenazine with drugs that prolong the QT interval should be avoided due to the potential for additive effects on the QT interval and increased risk of torsade de pointes. However, if concurrent therapy is required, monitor patient closely for prolongation of the QT interval (Prod Info XENAZINE(R) oral tablets, 2008).
7) Probable Mechanism: additive effects on QT interval prolongation

3.5.1.DP Thioridazine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Although citing no data, the manufacturer of thioridazine states that concomitant use with other drugs which prolong the QT interval is contraindicated (Prod Info Mellaril(R), 2001). Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999c), haloperidol (O'Brien et al, 1999b), pimozide (Prod Info Orap(R), 2000), quetiapine (Owens, 2001g), paliperidone (Prod Info INVEGA(TM) extended-release oral tablets, 2006), risperidone (Duenas-Laita et al, 1999e), sertindole (Agelink et al, 2001c), sultopride (Lande et al, 1992b), ziprasidone (Prod Info GEODON (R) intramuscular injection, oral capsule, 2005), and zotepine (Sweetman, 2004).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of agents that prolong the QT interval, such as antipsychotics, and thioridazine, is contraindicated.
7) Probable Mechanism: additive QT prolongation

3.5.1.DQ Tipranavir

1) Interaction Effect: serious and/or life-threatening reactions such as cardiac arrhythmias
2) Summary: Because of the potential for serious and/or life-threatening cardiac arrhythmias that can occur with increased plasma concentrations of pimozide, the concurrent use of tipranavir and ritonavir with pimozide is contraindicated. Tipranavir, coadministered with 200 milligrams of ritonavir, is a net inhibitor of cytochrome P450 3A. Concomitant administration of tipranavir and ritonavir with pimozide, which is metabolized by cytochrome P450 3A4 enzymes, could result in an increased plasma concentration of pimozide and is contraindicated (Prod Info Aptivus (R) capsules, 2005).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of tipranavir and ritonavir, when coadministered with pimozide is contraindicated.
7) Probable Mechanism: inhibition of cytochrome P450 3A-mediated pimozide metabolism

3.5.1.DR Tramadol

1) Interaction Effect: an increased risk of seizures
2) Summary: Seizures have been reported in patients using tramadol. The manufacturer of tramadol states that combining neuroleptic medications with tramadol may enhance the risk of seizures (Prod Info Ultram(R), 1998).
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Caution should be used if tramadol is to be administered to patients receiving neuroleptic therapy. If possible, avoid this combination, especially in patients with underlying conditions that might predispose to seizures.
7) Probable Mechanism: unknown

3.5.1.DS Trifluoperazine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Even though no formal drug interaction studies have been done, the manufacturer of pimozide warns against its administration with other drugs which are also known to prolong the QTc interval, including phenothiazines (Prod Info Thorazine(R), 2002; Prod Info Compazine(R), 2002; Prod Info Stelazine(R), 2002; Prod Info Orap(R), 1999t). The manufacturers of mesoridazine and thioridazine state that concomitant use is contraindicated with other agents known to prolong the QT interval (Prod Info Mellaril(R), 2002; Prod Info Serentil(R), 2001).

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of pimozide and other drugs that may prolong the QT interval, such as phenothiazines is contraindicated.

7) Probable Mechanism: additive effects on QT prolongation

8) Literature Reports

a) Electrocardiogram (ECG) changes seen during clinical trials of pimozide in Tourette's syndrome and schizophrenia patients include prolongation of the QT interval, flattening, notching, and inversion of the T wave, and the appearance of U waves. Sudden, unexpected deaths have occurred at doses greater than 20 milligrams/day (Prod Info Orap(R), 1999s).

3.5.1.DT Trifluoperazine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Concomitant use of phenothiazines and antipsychotic agents may cause additive effects on the QT interval and is not recommended. Q and T wave distortions have been observed in patients taking phenothiazines (Prod Info Compazine(R), 2002a; Prod Info Stelazine(R), 2002a; Prod Info Thorazine(R), 2002a). Other phenothiazines may have similar effects, though no reports are available. Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999), haloperidol (O'Brien et al, 1999), paliperidone (Prod Info INVEGA(TM) extended-release oral tablets, 2006), quetiapine (Owens, 2001e), risperidone (Duenas-Laita et al, 1999c), sertindole (Agelink et al, 2001a), sultopride (Lande et al, 1992), ziprasidone (Prod Info GEODON(R) intramuscular injection, oral capsule, 2005), and zotepine (Sweetman, 2003).

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of agents that prolong the QT interval, such as phenothiazines and antipsychotics, is not recommended.

7) Probable Mechanism: additive QT prolongation

3.5.1.DU Trimethoprim

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Cotrimoxazole has been shown to prolong the QTc interval at the recommended therapeutic dose (Lopez et al, 1987). Even though no formal drug interaction studies have been done, the manufacturer of pimozide warns against its administration with other drugs which are also known to prolong the QTc interval, including cotrimoxazole (Prod Info Orap(R), 1999ad).

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of agents that prolong the QT interval, such as cotrimoxazole and pimozide, is contraindicated.

7) Probable Mechanism: additive cardiac effects

8) Literature Reports

a) In experimental studies of conditions other than Tourette's Disorder, sudden, unexpected deaths have occurred. The patients were receiving pimozide dosages of approximately 1 mg per kg. One possible mechanism for such deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmia. The manufacturer recommends that an electrocardiogram be performed before pimozide treatment is initiated and periodically thereafter, especially during the period of dose adjustment (Prod Info Orap(R) pimozide, 1999g).

3.5.1.DV Trimipramine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Although citing no data, the manufacturer of pimozide states that concomitant use with other drugs which prolong the QT interval is contraindicated (Prod Info Orap(R), 1999ap). Tricyclic antidepressants (TCAs) at therapeutic doses can cause QT prolongation (Prod Info Norpramin(R), 2000;

Marshall & Forker, 1982).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Because of the potential to prolong the QT interval, concurrent administration of a tricyclic antidepressant and pimozide is contraindicated.
7) Probable Mechanism: additive effects on QT interval
8) Literature Reports
a) Electrocardiogram (ECG) changes seen during clinical trials of pimozide in Tourette's syndrome and schizophrenia patients include prolongation of the QT interval, flattening, notching, and inversion of the T wave, and the appearance of U waves. Sudden, unexpected deaths have occurred at doses greater than 20 milligrams/day (Prod Info Orap(R) pimozide, 1999k).

3.5.1.DW Troleandomycin
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Troleandomycin may inhibit the metabolism of pimozide, resulting in increased serum concentrations of this agent. Elevated serum concentrations of pimozide have been associated with adverse cardiovascular effects, including QT interval prolongation, cardiac arrhythmias, and sudden death. The concomitant administration of pimozide and troleandomycin is contraindicated (Flockhart et al, 1996c; Prod Info Orap(R), 1999am).
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Concurrent use of pimozide and troleandomycin is contraindicated.
7) Probable Mechanism: inhibition of cytochrome P450 3A-mediated pimozide metabolism

3.5.1.DX Vasopressin
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Pimozide and vasopressin have been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Orap(R), 1999c; Mauro et al, 1988). Even though no formal drug interaction studies have been done, the coadministration of these two drugs, known to prolong the QTc interval, is contraindicated.
3) Severity: contraindicated
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of drugs that prolong the QT interval, such as pimozide and vasopressin, is contraindicated.
7) Probable Mechanism: additive effects on QT prolongation
8) Literature Reports
a) In experimental studies of conditions other than Tourette's Disorder, sudden, unexpected deaths have occurred. The patients were receiving pimozide dosages of approximately 1 mg per kg. One possible mechanism for such deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmia.The manufactuer recommends that an electrocardiogram be performed before pimozide treatment is initiated and periodically thereafter, especially during the period of dose adjustment (Prod Info Orap(R), 1999b).

3.5.1.DY Vitex
1) Interaction Effect: decreased effectiveness of dopamine antagonists
2) Summary: Theoretically, the dopamine agonist activity of Vitex may oppose that of dopamine antagonists, decreasing their effectiveness. Vitex has been effective in alleviating luteal phase defects due to hyperprolactinemia and in relieving symptoms related to premenstrual tension syndrome (Milewicz et al, 1993a; Lauritzen et al, 1997a). Vitex reduced prolactin secretion in humans (Milewicz et al, 1993a). In vitro, Vitex inhibited prolactin release by binding to the D2 receptor (Jarry et al, 1994a).
3) Severity: minor
4) Onset: delayed
5) Substantiation: established
6) Clinical Management: If therapy is initiated with Vitex and a dopamine antagonist, monitor closely for return of symptoms previously controlled by the dopamine antagonist.
7) Probable Mechanism: dopamine agonism of Vitex may counteract dopamine antagonists
8) Literature Reports
a) Vitex agnus castus (Vitex) effectively normalized prolactin release in a randomized double-blind, placebo-controlled trial of 52 women with luteal phase defects due to latent hyperprolactinemia. Administration of Vitex agnus castus 20 mg daily for three months reduced prolactin release (from 23.7 to 22.5 nanogram (ng)/mL; p equal to 0.23), normalized shortened luteal phases (from 5.5 days to 10.5 days; p less than 0.005), and eliminated deficits in luteal progesterone synthesis (from 2.46 ng/mL to 9.69 ng/mL; p less than 0.001). No side effects were noted (Milewicz et al, 1993).

b) Vitex agnus castus and pyridoxine caused a similar reduction on the premenstrual tension scale (PMTS) in a randomized, controlled trial of 127 women with PMTS. Patients taking Vitex agnus castus (Agnolyt(R)) experienced more relief from breast tenderness, inner tension, headache, edema, constipation, and depression than those taking pyridoxine. Patients in the Vitex agnus castus group receive one capsule of Agnolyt(R) and one placebo capsule daily for 3 menstrual cycles. Patients in the pyridoxine group received one placebo capsule twice daily on days 1-15 of the menstrual cycle and pyridoxine 100 mg twice daily on days 16 to 35 of the menstrual cycle for 3 menstrual cycles. Unspecified gastrointestinal disturbances occurred in the treatment group along with two cases of skin reaction and one transient headache (Lauritzen et al, 1997).
c) In vitro, Vitex (Agnus castus) was found to bind to the D2 receptor in rat pituitary cell cultures. Basal prolactin release was significantly inhibited by 0.5 milligram (mg) and 1 mg of vitex extract/mL culture medium (p less than 0.05). Agnus castus extract doses from 0.125 mg/mL to 1 mg/mL significantly suppressed prolactin release in cells stimulated by thyrothropin releasing hormone (TRH) (p less than 0.05). Dopaminergic action was demonstrated in the rat corpus striatum membrane dopamine receptor assay. Agnus castus extract did not affect basal luteinizing hormone (LH) or follicle-stimulating hormone (FSH), indicating selectivity for prolactin secretion, and not generalized inhibition of pituitary hormone secretion. The effect was not due to a cytotoxic effect as demonstrated by the lack of effect on the MTT-conversion test. The authors concluded that Agnus castus exerted its prolactin inhibiting effect via stimulation of D2 receptors in the pituitary (Jarry et al, 1994).

3.5.1.DZ Voriconazole
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsade de pointes, cardiac arrest)
2) Summary: The systemic exposure to pimozide may be significantly increased by concomitant administration of voriconazole. The metabolism of pimozide may be inhibited by concomitant administration of voriconazole. Increased plasma concentrations of pimozide can lead to QT prolongation and rare occurrence of torsade de pointes (Prod Info VFEND(R) IV injection, oral tablets, suspension, 2008).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of voriconazole and pimozide is contraindicated (Prod Info VFEND(R) IV injection, oral tablets, suspension, 2008).
7) Probable Mechanism: inhibition by voriconazole of cytochrome P450 3A4-mediated pimozide metabolism

3.5.1.EA Zileuton
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Zileuton may inhibit the metabolism of pimozide, resulting in increased serum concentrations of this agent. Elevated serum levels of pimozide have been associated with adverse cardiovascular effects including QT interval prolongation, cardiac arrhythmia, and sudden death. The concurrent use of zileuton or any inhibitor of cytochrome P450 3A enzymes and pimozide is not recommended (Prod Info Orap(R), 1999av).
3) Severity: major
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: The concurrent administration of pimozide with an inhibitor of cytochrome P450 3A enzymes, such as zileuton, should be avoided.
7) Probable Mechanism: inhibition by zileuton of cytochrome P450 3A-mediated pimozide metabolism

3.5.1.EB Ziprasidone
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, ziprasidone should not be coadministered with other drugs which are also known to prolong the QTc interval, including pimozide (Prod Info Geodon(TM), 2002b).
3) Severity: contraindicated
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of ziprasidone and pimozide is contraindicated.
7) Probable Mechanism: additive cardiac effects

3.5.1.EC Zolmitriptan
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Pimozide and zolmitriptan have been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Zomig(R), 2002; Prod Info Orap(R), 1999y). Even though no formal drug interaction studies have been done, the coadministration of these two drugs, known to prolong the QTc interval, is contraindicated.
3) Severity: contraindicated

4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of drugs that prolong the QT interval, such as pimozide and zolmitriptan, is contraindicated.
7) Probable Mechanism: additive effects on QT prolongation
8) Literature Reports
a) In experimental studies of conditions other than Tourette's Disorder, sudden, unexpected deaths have occurred. The patients were receiving pimozide dosages of approximately 1 mg per kg. One possible mechanism for such deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmia. The manufacturer recommends that an electrocardiogram be performed before pimozide treatment is initiated and periodically thereafter, especially during the period of dose adjustment (Prod Info Orap(R) pimozide, 1999e).

3.5.1.ED Zotepine
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Though no drug interaction studies have been performed, the manufacturer of pimozide states that coadministration pimozide with other drugs that potentially prolong the QTc interval is contraindicated (Prod Info Orap(R), 1999aw). Zotepine can prolong the QTc interval (Sweetman, 2004).
3) Severity: contraindicated
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Concurrent administration of agents that prolong the QT interval, such as zotepine and pimozide, is contraindicated.
7) Probable Mechanism: additive effects on QT prolongation

3.5.2 Drug-Food Combinations

3.5.2.A Grapefruit Juice
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Grapefruit juice may inhibit the metabolism of pimozide, resulting in increased serum concentrations of this agent. Elevated serum levels of pimozide have been associated with adverse cardiovascular effects including QT interval prolongation, cardiac arrhythmia, and sudden death. The concurrent use of pimozide and grapefruit juice should be avoided (Prod Info Orap(R), 1999bk).
3) Severity: major
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Counsel patients to avoid grapefruit juice during pimozide therapy. Orange juice may be substituted as it provides the same basic nutrients but is not known to inhibit drug metabolism.
7) Probable Mechanism: inhibition by grapefruit juice of cytochrome P450 3A-mediated pimozide metabolism

4.0 Clinical Applications

Monitoring Parameters

Patient Instructions

Place In Therapy

Mechanism of Action / Pharmacology

Therapeutic Uses

Comparative Efficacy / Evaluation With Other Therapies

4.1 Monitoring Parameters
A) Therapeutic
1) Physical Findings
a) Decrease in severity or elimination of target psychotic symptoms:
1) Positive psychotic symptoms (delusions, auditory hallucinations, racing thoughts)
2) Negative psychotic symptoms (anhedonia, apathy, amotivation, ambivalence).
b) Improvement in socialization, grooming, and attention to activities of daily living.

B) Toxic
1) Physical Findings
a) An ECG should be performed before initiation of pimozide therapy and periodically thereafter, especially during periods of dose adjustment. The QTc interval should not exceed 0.47 seconds in children or 0.52 seconds in adults, or more than 25% above the patient's original baseline (Prod Info Orap(R), 2003).
b) Abnormal involuntary movement scale (AIMS) examination or similar test for tardive dyskinesia every 6 months.
c) Assessment for extrapyramidal symptoms (EPS) during dose adjustment and every 3 months.

4.2 Patient Instructions

A) Pimozide (By mouth)

Pimozide

Treats symptoms of Tourette's syndrome such as uncontrolled body movements or vocal sounds. It is used when these symptoms are severe.

When This Medicine Should Not Be Used:
You should not use this medicine if you have had an allergic reaction to pimozide or medicines to treat mental problems such as haloperidol, molindone, loxapine, thiothixene, perphenazine, thioridazine, and others. You should not use this medicine if you are using itraconazole, ketoconazole, ritonavir, saquinavir, indinavir, nelfinavir, nefazodone, or zileuton. You should not use this medicine if you have an irregular heartbeat or if you are using any of these antibiotic medicines: clarithromycin, erythromycin, azithromycin, dirithromycin, or troleandomycin. Pimozide used with certain antibiotics can cause severe heart problems.

How to Use This Medicine:
Tablet
Your doctor will tell you how much medicine to use and how often. You should not use more of the medicine than your doctor ordered.

If a Dose is Missed:
Use the missed dose as soon as possible, unless it is almost time for your next dose.
Skip the missed dose if it is almost time for your next regular dose.
You should not use two doses at the same time.

How to Store and Dispose of This Medicine:
Store the tablets at room temperature, away from heat, moisture, and direct light.
Keep all medicine out of the reach of children.

Drugs and Foods to Avoid:
Ask your doctor or pharmacist before using any other medicine, including over-the-counter medicines, vitamins, and herbal products.
Tell your doctor if you are also using pemoline (Cylert®), methylphenidate (Ritalin®), or amphetamines (Dexedrine®).
Make sure your doctor knows if you are using other drugs that could make you sleepy, such as sleeping pills, tranquilizers, antidepressants, strong pain killers, or cold or allergy medicine. Avoid drinking alcohol while using this medicine. You may get too drowsy or sedated if you drink alcohol or use medicines that cause drowsiness with pimozide.
Some antidepressants, tranquilizers, and medicines to treat mental problems, emotional problems, or an irregular heartbeat can cause or worsen heart problems if used with pimozide. Talk with your doctor about this.
Do not drink grapefruit juice while using this medicine.

Warnings While Using This Medicine:
Check with your doctor before using pimozide if you have seizures, an enlarged prostate, trouble urinating, glaucoma, or heart, liver, or kidney disease.
If you are pregnant or breastfeeding, talk to your doctor before using this medicine.
This medicine may make you drowsy or dizzy. Be careful if driving or using machinery.
Do not suddenly stop using pimozide without checking with your doctor. You may need to use smaller and smaller doses before completely stopping the medicine.
This medicine may cause side effects that include muscle spasms, twitching in the face and body, and uncontrolled tongue or jaw movement. Talk to your doctor about this.
Your doctor may want to check your heart rhythm while you are using this medicine. Make sure to keep all appointments.

Possible Side Effects While Using This Medicine:
Call your doctor right away if you notice any of these side effects:
Fast or irregular heartbeat, fast breathing
Fever, severe muscle stiffness

Muscle spasms, twitching, uncontrolled tongue or jaw movement
Restlessness or feeling as if you need to be moving constantly
Spasms or cramps in the neck, face, or back

If you notice these less serious side effects, talk with your doctor:
Constipation
Drowsiness, dizziness, headache
Dry mouth
Vision changes, such as trouble focusing

If you notice other side effects that you think are caused by this medicine, tell your doctor.

4.3 Place In Therapy

A) Pimozide's primary place in therapy is in the treatment of Tourette's syndrome in patients who are refractory to haloperidol or who develop incapacitating side effects during haloperidol therapy (Shapiro & Shapiro, 1984).
B) Clinical studies have demonstrated no significant advantage of pimozide over other antipsychotic agents in the treatment of chronic schizophrenic patients (Clark et al, 1975). The drug may find usefulness due to its long half-life, when given orally once weekly in chronic schizophrenia as an alternative to intramuscular fluphenazine decanoate given every 2 weeks. The drug should also be considered in patients where sedation is a problem with other antipsychotic agents. Pimozide may prove useful as an adjuvant to maintenance therapy with other antipsychotic agents in chronic schizophrenia. Also, pimozide may be effective in schizophrenic patients unresponsive to other antipsychotic medications.
C) Most controlled studies have indicated that pimozide is equally effective as other antipsychotic agents in the treatment of chronic schizophrenia (Kolivakis et al, 1974; Cesarec et al, 1974; Kenway & Masheter, 1971; Hellon, 1971; Kline et al, 1975; Clark et al, 1975). However, there appears to be an advantage of pimozide over other agents in the treatment of patients with poor social adjustment with symptoms of emotional withdrawal, disturbed thought content, hallucinations and blunted affect (Pinder et al, 1976). Pimozide is less effective than the other antipsychotic agents, in general, for the excited, agitated chronic schizophrenic patient.
D) Pimozide is a useful addition to the formulary of institutions which handle Tourette's syndrome and other difficult-to-treat psychiatric patients.

4.4 Mechanism of Action / Pharmacology

A) MECHANISM OF ACTION

1) Pimozide is a potent neuroleptic agent, a diphenylbutylpiperidine derivative, structurally dissimilar from phenothiazines, butyrophenones, and thioxanthenes that elicits antipsychotic effects via central antidopaminergic activity. The drug is effective orally and has a long serum half-life (greater than 50 hours). It has been primarily evaluated in the maintenance treatment of chronic schizophrenia (Andersen et al, 1974; Gross, 1974; Janssen et al, 1972).
2) Pimozide, similar to other neuropsychotic agents, is a central antidopaminergic agent which increases dopamine turnover in the brain, but may be more potent than other agents. The drug concentrates in areas rich in dopaminergic neurons (Janssen et al, 1968; Anden et al, 1970). There is evidence that pimozide exhibits more specific antipsychotic effects than other antipsychotic agents with respect to delusions, autism, emotional withdrawal and apathy in chronic schizophrenia (Janssen et al, 1968; Smythies & Beaton, 1974; Stier et al, 1978).
3) Pimozide has also been effective in the treatment of Gilles de la Tourette syndrome, with benefits being similar to those of haloperidol but producing less sedation (Ross & Moldofsky, 1978). The drug's mechanism of action in Tourette's syndrome is related to its dopaminergic blocking activity. The drug may also produce secondary alterations in central dopamine metabolism and function, accompanying receptor blockade, which may contribute to its therapeutic effects (Prod Info Haldol(R), 1984).

4.5 Therapeutic Uses

Anorexia nervosa

Anxiety

Chronic schizophrenia

Gilles de la Tourette's syndrome

Huntington's disease

Obsessive-compulsive disorder

Trigeminal trophic syndrome

4.5.A Anorexia nervosa

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Pediatric, Evidence is inconclusive
Recommendation: Pediatric, Class III
Strength of Evidence: Pediatric, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Unclear efficacy
See Drug Consult reference: ANOREXIA NERVOSA - DRUG THERAPY

3) Pediatric:

a) All 10 adolescent anorectic females studied for a period of 20 weeks succeeded in gaining body weight with or without pimozide (Weizman et al, 1985; Plantey, 1977). Five patients were treated by behavior therapy programs and the other 5 were treated with pimozide. Serum prolactin levels were increased in the 5 patients receiving pimozide, while no elevation was observed in patients undergoing behavior therapy.

b) One report has described the successful use of pimozide 4 milligrams orally 3 times daily for one month in anorexia nervosa in a 17-year-old male. Dramatic improvement was observed in 3 weeks with the patient gaining 9 kg. Obsession with weight disappeared at this time as well as bradycardia and overactivity (Plantey, 1977).

4.5.B Anxiety

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class III
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

As effective as chlordiazepoxide and diazepam in the treatment of non-psychotic patients with anxiety
However, offers no advantage over benzodiazepines

3) Adult:

a) Pimozide has been shown to be more effective than placebo in anxiety (Van Mierlo, 1972), and as effective as haloperidol (Kenway, 1973a). Pimozide 2 milligrams daily has produced similar effects to diazepam 10 milligrams daily or chlordiazepoxide 40 milligrams daily (Anon, 1972; Reyntjens & Van Mierlo, 1972).

b) The addition of pimozide 2 milligrams daily to chlordiazepoxide 30 to 60 milligrams daily did not result in a more rapid antianxiety effect, enhanced antianxiety effect or reduction of chlordiazepoxide dose, or a decrease in the incidence of side effects (Anon, 1975).

4.5.C Chronic schizophrenia

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Efficacious in chronic SCHIZOPHRENIA (Kline et al, 1977; Donlon et al, 1977; Singh, 1971; Sugarman, 1971; Masheter, 1971; Arfwidsson et al, 1971)
Doses range from 2 to 40 milligrams (mean: 6 milligrams daily)

3) Adult:

a) Pimozide has been reported to be more specific than other antipsychotic agents for autistic patients with emotional withdrawal, delusions, and hallucinations as opposed to agitated or aggressive type patients with chronic schizophrenia (Pinder et al, 1976b; Janssen et al, 1972a). Pimozide may have special usefulness, as opposed to other agents, in improving emotional withdrawal and assisting in resocialization of chronic schizophrenic patients (Gross, 1974b; Kolivakis et al, 1974b; Janssen et al, 1972a; Huber et al, 1971a; Kenway & Masheter, 1971b). However, at least one report has indicated that pimozide was no more effective than chlorpromazine in improving emotional withdrawal and social competence in chronic schizophrenia (Wilson et al, 1982).

b) A significant improvement in negative symptoms, but not positive symptoms was observed with pimozide in schizophrenic patients (Feinberg et al, 1988). The dose of pimozide was started at 4 milligrams/day and increased over 4 weeks to an average dose of 12.6 milligrams/day.

c) Pimozide given intermittently has proven effective in the management of schizophrenia, due to its long half-life (McCreadie et al, 1982b; McCreadie et al, 1980a). The drug has been administered orally once weekly, producing equivalent clinical effects as that of fluphenazine decanoate administered once every 2 weeks (McCreadie et al, 1982b).

d) Pimozide has been successful when used concurrently with maintenance antipsychotic medications on

improving work behavior, work habits, and mental status in chronic schizophrenics following its addition to maintenance therapy (8 milligrams daily) (Nakra & Wickramasinghe, 1980). The drug has been used successfully as replacement therapy in patients unresponsive to other neuroleptic agents, resulting in improvement in apathy and withdrawal in many patients who were unresponsive to other agents prior to pimozide therapy (Stirling, 1979).

e) Pimozide in combination with other antipsychotic medications improved social behavior in chronic schizophrenia (Nakra et al, 1980). Pimozide was administered in oral doses of 8 milligrams daily for 12 weeks to 20 patients receiving other medications (haloperidol, flupenthixol, trifluoperazines, thiothixine, fluphenazine, promazine, or chlorpromazine). Pimozide significantly improved social behavior in terms of work behavior, work habits, and mental status after 8 weeks of treatment.

f) Pimozide was effective as single agent therapy for chronic schizophrenia in patients who were primarily withdrawn. Patients were administered pimozide 8 to 20 milligrams daily after withdrawal of all other medications for a period of one month. General improvement was observed after assessment at 4 and 6 months (Cheadle & Freedman, 1979). Marked improvement was reported in 6 of 12 patients with chronic schizophrenia undergoing acute exacerbations with pimozide in doses up to 16 milligrams daily over a period of 10 weeks. Patients demonstrated improvement with thought disorders, apathy, emotional withdrawal, motor retardation and depression. This study supports the antiautistic and antidelusional effects of pimozide (Stier et al, 1978a).

4.5.D Gilles de la Tourette's syndrome

FDA Labeled Indication

1) Overview

FDA Approval: Adult, yes; Pediatric, yes (12 years and older)
Efficacy: Adult, Evidence favors efficacy; Pediatric, Evidence favors efficacy
Recommendation: Adult, Class IIa; Pediatric, Class IIa
Strength of Evidence: Adult, Category B; Pediatric, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Effective Gilles de la Tourette syndrome
Effective in patients who were unable to tolerate or were unresponsive to haloperidol (Shapiro & Shapiro, 1984; Shapiro et al, 1983)

3) Adult:

a) Haloperidol has been the drug of choice in Gilles de la Tourette syndrome, its efficacy being related to dopamine receptor blocking activity in the CNS. Pimozide is a more specific antidopaminergic agent. Although effective, superiority of pimozide over haloperidol has not been adequately demonstrated (Colvin & Tankanow, 1985a). The drug is indicated as reserve therapy for Tourette's syndrome in patients who have not responded to haloperidol or who cannot tolerate toxicity of haloperidol. A review of the efficacy and toxicity of pimozide in the treatment of tic and Tourette disorders is available (Shapiro et al, 1987).

b) In 9 patients with Gilles de la Tourette syndrome both haloperidol and pimozide were effective (Ross & Moldofsky, 1978b). In this double-blind study, patients were assigned to pimozide or haloperidol, each in doses of 2 milligrams initially every morning, increasing by 2 milligrams every second day until symptoms disappeared or until side effects were observed or until maximum doses of 12 milligrams daily were obtained. A follow-up period of 420 months was undertaken. Both pimozide and haloperidol significantly reduced mean 5-minute tic counts, with no significant difference between the 2 drugs. Both haloperidol and pimozide were more effective than placebo. Follow-up at 4 to 20 months indicated that 6 of 7 patients continuing on pimozide and one of 2 patients continuing on haloperidol had a greater than 75% improvement in symptoms. Significantly fewer days of lethargy or tiredness was associated with pimozide than haloperidol. Anticholinergic and extrapyramidal effects were similar with both agents. Pimozide is an effective alternative to haloperidol in Gilles de la Tourette syndrome, particularly in haloperidol nonresponders or patients receiving haloperidol but developing incapacitating side effects.

4.5.E Huntington's disease

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Effective in the treatment of Huntington's chorea (Siegmund et al, 1982; Fog & Pakkenberg, 1970)

3) Adult:

a) Oral pimozide 16 milligrams daily (in 3 to 4 divided doses; maximum 40 milligrams daily) produced good long-term results in 9 of 11 patients with Huntington's chorea, with significant improvement in hyperkinesia. These patients were discharged from the hospital indicating therapy may permit social reintegration and improved quality of life for Huntington's patients. However, both haloperidol and chlorpromazine have been utilized with some degree of success in Huntington's chorea (Pinder et al, 1976b) and controlled studies are required to determine any benefits of pimozide.

4.5.F Obsessive-compulsive disorder

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Useful in treating some subtypes of obsessive compulsive disorder

3) Adult:

a) The addition of pimozide was useful in treating a possible subtype of obsessive compulsive disorder (OCD) in a patient with a dual diagnosis of OCD and chronic multiple tics or Tourette's Syndrome. A 25-year-old man with a history of Tourette's Syndrome presented for treatment of OCD symptoms (Delgado et al, 1990). Fluvoxamine alone appeared to exacerbate tics leading to the onset of coprolalia, without improving OCD symptoms. Pimozide alone reduced tics very slightly. In this patient, the combination of fluvoxamine (150 to 250 milligram/day) and pimozide (1 milligram/day) appeared to be necessary for clinical improvement of OCD symptoms, suggesting that both the dopamine and serotonin systems were involved in the near remission of OCD symptoms and the reduction of tics.

b) Pimozide was used successfully for 7 months in ONYCHOTILLOMANIA. The condition was reported to be a manifestation of obsessive compulsive disorder (Hamann, 1982).

4.5.G Trigeminal trophic syndrome

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

In one case, successfully treated severe trigeminal neurotrophic ulceration

3) Adult:

a) A rare case was described of an 82-year-old woman with severe trigeminal neurotrophic ulceration which improved substantially with pimozide, given for treatment of unrelated paranoid symptoms. The established use of pimozide in delusional parasitosis in relationship to this case was discussed (Mayer & Smith, 1993).

4.6 Comparative Efficacy / Evaluation With Other Therapies

Chlorpromazine

Fluphenazine

Haloperidol

Levosulpiride

Trifluoperazine

4.6.A Chlorpromazine

Mania

Schizophrenia

4.6.A.1 Mania

a) SUMMARY: Pimozide is at least as effective as chlorpromazine in the treatment of mania (Cookson et al, 1979; Cookson et al, 1981; Cookson et al, 1980a). In a double-blind, randomized fashion, 23 mania patients received either pimozide 2 milligrams (mg) or chlorpromazine 100 milligrams (mg), with adjustments to a maximum of 32 mg/day and 1600 mg/day, respectively. The patients were evaluated for 14 days using two scales, the Mania Rating Scale (MRS) and the Petterson Rating Scale (PRS). MRS evaluation demonstrated chlorpromazine to be more effective than pimozide, probable due to greater sedative effects (Cookson et al, 1981).

4.6.A.2 Schizophrenia

a) Similar clinical effects were reported with pimozide (mean dose, 7 milligrams (mg) daily) and chlorpromazine sustained-release (mean dose, 216 mg daily) in the treatment of chronic schizophrenia (Kolivakis et al, 1974a). Similar results were observed in chronic schizophrenic patients in a double-blind study over 52 weeks (Wilson et al, 1982a). Average daily doses of pimozide 7.3 mg were as effective as chlorpromazine 381 mg. There was no significant difference in improvement or side effects between the two drug treatment groups except for a higher incidence of skin reactions with chlorpromazine. However, the authors were unable to replicate previous data indicating the special utility of pimozide for improvement of emotional withdrawal and social competence in schizophrenia in this long-term study. All patients in this study were stable, compliant patients which may not be the optimal group for the evaluation of these effects.

4.6.B Fluphenazine

4.6.B.1 Schizophrenia

a) SUMMARY: Clinical studies have reported the equivalent effects of fluphenazine and pimozide in chronic schizophrenia (Cesarec et al, 1974a; Chouinard et al, 1970; Kenway & Masheter, 1971a; Lapierre & Lavellee, 1975; Donlon et al, 1977; Morris et al, 1970; Shepherd, 1979).
b) The comparative efficacy of fluphenazine HCl (12.5 milligrams daily, average) and pimozide (9.6 milligrams daily, average) were reported in the treatment of chronic schizophrenia in a 12-month study. Both drugs were equally effective in maintaining control of symptomatology at a better level than previous medication (Donlon et al, 1977).
c) Other reports have reported the comparability of long-acting fluphenazine and pimozide. There was equivalent efficacy with fluphenazine decanoate given biweekly and pimozide 4 days each week (McCreadie et al, 1980). In a subsequent report, pimozide once weekly (in doses up to 60 milligrams) and fluphenazine decanoate (up to 50 milligrams every 2 weeks) were equally effective in the management of chronic schizophrenia (McCreadie et al, 1982). Tardive dyskinesia was more frequent in pimozide patients. Pimozide may be considered an alternative to intramuscular fluphenazine for chronic schizophrenia.
d) Depot fluphenazine decanoate and oral pimozide were compared in 36 schizophrenic outpatients over 1 year in a double-blind, placebo-controlled trial. Analyses of Social Behavior Assessment Schedule (SBAS) data from pre-trial and end of study assessments revealed no significant advantage for either of the treatments (Barnes et al, 1983).

4.6.C Haloperidol

Gilles de la Tourette's syndrome

Schizophrenia

4.6.C.1 Gilles de la Tourette's syndrome

a) The efficacy of pimozide in Tourette's syndrome was evaluated (Colvin & Tankanow, 1985). Although effective, superiority of the drug over haloperidol has not been adequately demonstrated. The drug is indicated as reserve therapy for Tourette's syndrome in patients who have not responded to haloperidol or who cannot tolerate toxicity of haloperidol.
b) In a 6-month, controlled crossover trial of children and adolescents (n=22) with Tourette's syndrome, only pimozide demonstrated statistical improvement over placebo on the global rating scale (p less than 0.05). However, pimozide and haloperidol did not differ statistically in efficacy from each other. Overall, 64% of subjects attained the goal of 70% tic reduction with active therapy as compared to only 23% with placebo. The mean effective doses of pimozide and haloperidol were equivalent (3.4 and 3.5 milligrams daily, respectively). Haloperidol was associated with a greater incidence of extrapyramidal symptoms (Sallee et al, 1997).
c) Haloperidol was compared with pimozide in 9 patients with Gilles de la Tourette syndrome (Ross & Moldofsky, 1978a). In this double-blind study, patients were assigned to pimozide or haloperidol, each in doses of 2 milligrams (mg) initially every morning, increasing by 2 mg every second day until symptoms disappeared or until side effects were observed or until maximum doses of 12 mg daily were obtained. A follow-up period of 420 months was undertaken. Both pimozide and haloperidol significantly reduced mean 5-minute tic counts, with no significant difference between the 2 drugs. Both haloperidol and pimozide were more effective than placebo. Follow-up at 4 to 20 months indicated that 6 of 7 patients continuing on pimozide and one of 2 patients continuing on haloperidol had a greater than 75% improvement in symptoms. Significantly fewer days of lethargy or tiredness was associated with pimozide than haloperidol. Anticholinergic and extrapyramidal effects were similar with both agents. Pimozide may be an effective alternative to haloperidol in Gilles de la Tourette syndrome, particularly in haloperidol non-responders or patients receiving haloperidol but developing incapacitating side effects.
d) Haloperidol was compared with pimozide in a double-blind, parallel, crossover study lasting 6 weeks in 57 patients with Tourette's syndrome. The maximum dose of haloperidol was 10 milligrams (mg)/day, and for pimozide it was 20 mg/day. Haloperidol was slightly more effective than pimozide in the treatment of

Tourette's syndrome. Adverse effects of haloperidol were not significantly different than those of pimozide. Clinically significant cardiac effects did not occur. However, due to the potential of pimozide prolonging QTC intervals, haloperidol is the drug of choice for initial treatment of Tourette's syndrome (Shapiro et al, 1989).

4.6.C.2 Schizophrenia

a) SUMMARY: Pimozide is at least as effective as haloperidol in the treatment of chronic schizophrenia.
b) Pimozide was compared with haloperidol (5 to 50 milligrams/day (mg/day) of either) in relation to dopaminergic blockade and clinical response in 22 patients with schizophrenia. The drugs were equally effective. There was no correlation between either dopaminergic blockade or blood level and therapeutic response (Silverstone et al, 1984).
c) Pimozide 306 mg daily was superior to haloperidol 7 to 14 mg daily in chronic schizophrenia in a small double-blind study. A subsequent report has indicated the equivalent efficacy of pimozide 10 to 60 mg daily and haloperidol 10 to 60 mg daily in acute schizophrenia (Haas & Beckmann, 1982). In this study, however, extrapyramidal effects were more pronounced in patients using pimozide (Gowardman et al, 1973).

4.6.D Levosulpiride

4.6.D.1 Schizophrenia

a) A single-blind, randomized clinical study compared the therapeutic efficacy of levosulpiride and pimozide in the treatment of schizophrenic patients with negative symptoms not relieved by haloperidol. Following Andreasen's diagnostic criteria based on the Scale of Assessment of Positive Symptoms and the Scale of Assessment of Negative Symptoms, the study showed that the therapeutic activity of low doses of levosulpiride (200 milligrams/day (mg/day) orally) was higher than pimozide 4 mg/day orally (De Ronchi et al, 1996).

4.6.E Trifluoperazine

4.6.E.1 Schizophrenia

a) Comparative studies have reported the similarity of trifluoperazine (5 to 30 milligrams daily) and pimozide (2 to 80 milligrams daily) in the management of chronic schizophrenia (Claghorn, 1974; Kline et al, 1975a). Other reports have indicated the superiority of pimozide over trifluoperazine for retardation, emotional withdrawal and unusual thought content in chronic schizophrenia (Andersen et al, 1971; Andersen et al, 1974a; Gross, 1974a). A more recent report has confirmed these observations (Kline et al, 1977), with pimozide being reported superior to trifluoperazine in improving anxiety, motor retardation, suspiciousness and emotional adjustment, indicating its preferability in certain apathic schizophrenic patients.

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335. Product Information: Orap(R), pimozide. Gate Pharmaceuticals, Sellersville, PA, 1999r.
336. Product Information: Orap(R), pimozide. Gate Pharmaceuticals, Sellersville, PA, 1999s.
337. Product Information: Orap(R), pimozide. Gate Pharmaceuticals, Sellersville, PA, 1999u.
338. Product Information: Orap(R), pimozide. Gate Pharmaceuticals, Sellersville, PA, 1999v.
339. Product Information: Orap(R), pimozide. Gate Pharmaceuticals, Sellersville, PA, 1999w.
340. Product Information: Orap(R), pimozide. Gate Pharmaceuticals, Sellersville, PA, 1999x.
341. Product Information: Orap(R), pimozide. Gate Pharmaceuticals, Sellersville, PA, 2000.
342. Product Information: Orap(R), pimozide. Gate Pharmaceuticals, Sellersville, PA, 2003.
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345. Product Information: Orap(R), pimozide. TEVA Pharmaceuticals, Sellersville, PA, 1999ai.
346. Product Information: Orap(R), pimozide. TEVA Pharmaceuticals, Sellersville, PA, 1999ak.
347. Product Information: Orap(R), pimozide. TEVA Pharmaceuticals, Sellersville, PA, 1999aq.
348. Product Information: Orap(R), pimozide. TEVA Pharmaceuticals, Sellersville, PA, 1999ar.
349. Product Information: Orap(R), pimozide. TEVA Pharmaceuticals, Sellersville, PA, 1999as.
350. Product Information: Orap(R), pimozide. TEVA Pharmaceuticals, Sellersville, PA, 1999aw.
351. Product Information: Orap(R), pimozide. TEVA Pharmaceuticals, Sellersville, PA, 1999az.
352. Product Information: Orap(R), pimozide. TEVA Pharmaceuticals, Sellersville, PA, 1999b.
353. Product Information: Orap(R), pimozide. TEVA Pharmaceuticals, Sellersville, PA, 1999ba.
354. Product Information: Orap(R), pimozide. TEVA Pharmaceuticals, Sellersville, PA, 1999bb.
355. Product Information: Orap(R), pimozide. TEVA Pharmaceuticals, Sellersville, PA, 1999bc.

356. Product Information: Orap(R), pimozide. TEVA Pharmaceuticals, Sellersville, PA, 1999bd.
357. Product Information: Orap(R), pimozide. TEVA Pharmaceuticals, Sellersville, PA, 1999bi.
358. Product Information: Orap(R), pimozide. TEVA Pharmaceuticals, Sellersville, PA, 1999j.
359. Product Information: Orap(R), pimozide. TEVA Pharmaceuticals, Sellersville, PA, 1999k.
360. Product Information: Orap(R), pimozide. TEVA Pharmaceuticals, Sellersville, PA, 1999p.
361. Product Information: Orap(R), pimozide. TEVA Pharmaceuticals, Sellersville, PA, 1999q.
362. Product Information: Orap(R), pimozide. TEVA Pharmaceuticals, Sellersville, PA, 1999y.
363. Product Information: Orap(R), pimozide. TEVA Pharmaceuticals, Sellersville, PA, 1999z.
364. Product Information: Orap(R), pimozide. Teva Pharmaceuticals USA, Sellersville, PA, 1999t.
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367. Product Information: Orapred(R), prednisolone sodium phosphate. Ascent Pediatrics, Brockton, MA, 2004.
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369. Product Information: PAXIL CR(R) CONTROLLED-RELEASE TABLETS, paroxetine hydrochloride controlled-release tablets. GlaxoSmithKline, Research Triangle Park, NC, 2005.
370. Product Information: PCE(R), erythromycin particles in tablets. Abbott Laboratories, North Chicago, IL, 1997.
371. Product Information: PREZISTA(TM) oral tablets, darunavir oral tablets. Tibotec Therapeutics,Inc, Raritan, NJ, 2006.
372. Product Information: PROZAC(R) oral capsule, oral pulvule, oral solution, oral tablet, fluoxetine hcl oral capsule, oral pulvule, oral solution, oral tablet. Eli Lilly and Company, Indianapolis, IN, 2005.
373. Product Information: Propulsid(R), cisapride. Janssen Pharmaceutica, Titusville, NJ, 2000.
374. Product Information: Quinaglute Dura-tabs(R), quinidine gluconate. Berlex Laboratories, Wayne, NJ, 1999.
375. Product Information: Quinaglute(R), quinidine gluconate. Berlex Laboratories, Wayne, NJ, 1999.
376. Product Information: RESCRIPTOR(R) oral tablets, delavirdine mesylate oral tablets. Pfizer,Inc, New York, NY, 2006.
377. Product Information: Reyataz(TM), atazanavir. Bristol-Myers Squibb Company, Princeton, NJ, 2003.
378. Product Information: Risperdal(R), risperidone. Janssen Pharmaceutica Products, L.P., Titusville, NJ, 2002.
379. Product Information: SPRYCEL(R) oral tablets, dasatinib oral tablets. Bristol-Myers Squibb, Princeton, NJ, 2008.
380. Product Information: SUSTIVA(R) oral capsules, tablets, efavirenz oral capsules, tablets. Bristol-Myers Squibb Company, Princeton, NJ, 2008.
381. Product Information: SUTENT(R) oral capsules, sunitinib malate oral capsules. Pfizer Labs, New York, NY, 2008.
382. Product Information: SYNERCID(R) intravenous injection, dalfopristin/quinupristin intravenous injection. Monarch Pharmaceuticals, Inc, Bristol, TN, 2003.
383. Product Information: Sandostatin(R), octreotide acetate injection. Novartis Pharmaceuticals Corporation, East Hanover, NJ, 1999.
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389. Product Information: Solian(R), amisulpride tablets. Lorex Synthelabo, Maidenhead, Berkshire, UK, 1999c.
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Last Modified: May 19, 2009

DRUGDEX® Evaluations

PAROXETINE

0.0 Overview

1) Class

a) This drug is a member of the following class(es):

Antidepressant
Central Nervous System Agent
Serotonin Reuptake Inhibitor

2) Dosing Information

a) Paroxetine Hydrochloride

1) Adult

a) Generalized anxiety disorder

1) 20 mg/day ORALLY in the morning

b) Major depressive disorder

1) 20 mg/day ORALLY in the morning; may increase dosage by 10 mg/day increments each week to a max dose of 50 mg/day

2) controlled release, 25 mg/day ORALLY in the morning; may increase dosage by 12.5 mg/day increments each week to a max dose of 62.5 mg/day

c) Obsessive-compulsive disorder

1) 20 mg/day ORALLY in the morning; may increase dosage by 10 mg/day increments each week to a max dose of 60 mg/day; usual effective dose is 40 mg/day

d) Panic disorder

1) 10 mg/day ORALLY in the morning; may increase dosage by 10 mg/day increments each week to a max dose of 60 mg/day; usual effective dose is 40 mg/day

2) controlled release, 12.5 mg/day ORALLY in the morning; may increase dosage by 12.5 mg/day increments each week to a max dose of 75 mg/day

e) Posttraumatic stress disorder

1) 20 mg/day ORALLY in the morning

f) Premenstrual dysphoric disorder

1) controlled release, 12.5 mg/day ORALLY in the morning; may increase to 25 mg/day at interval of at least one week; may be administered daily throughout the menstrual cycle or limited to daily administration during the luteal phase of the menstrual cycle

g) Social phobia

1) 20 mg/day ORALLY in the morning

2) Pediatric

a) Safety and effectiveness in pediatric patients have not been established

3) Contraindications

a) Paroxetine Hydrochloride

1) concomitant use of linezolid (Prod Info PAXIL CR(R) controlled-release oral tablets, 2009; Prod Info PAXIL(R) oral tablets, suspension, 2009)

2) concomitant use of monoamine oxidase inhibitors (MAOIs) (Prod Info PAXIL CR(R) controlled-release oral tablets, 2009; Prod Info PAXIL(R) oral tablets, suspension, 2009)

3) concomitant use of pimozide (Prod Info PAXIL CR(R) controlled-release oral tablets, 2009; Prod Info PAXIL (R) oral tablets, suspension, 2009)

4) concomitant use of thioridazine (Prod Info PAXIL CR(R) controlled-release oral tablets, 2009; Prod Info PAXIL(R) oral tablets, suspension, 2009)

5) hypersensitivity to paroxetine or any component of the product (Prod Info PAXIL CR(R) controlled-release oral tablets, 2009; Prod Info PAXIL(R) oral tablets, suspension, 2009)

4) Serious Adverse Effects

a) Paroxetine Hydrochloride

1) Acute hepatitis
2) Bleeding, Abnormal
3) Depression, exacerbation
4) Hypomania
5) Hyponatremia
6) Mania
7) Seizure
8) Serotonin syndrome
9) Suicidal thoughts
10) Suicide
11) Toxic epidermal necrolysis

5) Clinical Applications

a) Paroxetine Hydrochloride

1) FDA Approved Indications
- **a)** Generalized anxiety disorder
- **b)** Major depressive disorder
- **c)** Obsessive-compulsive disorder
- **d)** Panic disorder
- **e)** Posttraumatic stress disorder
- **f)** Premenstrual dysphoric disorder
- **g)** Social phobia

1.0 Dosing Information

Drug Properties

Adult Dosage

1.1 Drug Properties

A) Information on specific products and dosage forms can be obtained by referring to the Tradename List (Product Index)

B) Synonyms

Paroxetine
Paroxetine HCl
Paroxetine Hydrochloride
Paroxetine Mesylate

C) Physicochemical Properties

1) Molecular Weight

a) Paroxetine base: 329.37 (Fleeger, 1996); Paroxetine hydrochloride: 374.8 (Prod Info Paroxetine, 97) (Prod Info Paroxetine, 95)

2) Solubility

a) Systemic: 5.4 mg of paroxetine hydrochloride per mL water (Prod Info Paroxetine, 97).

1.3 Adult Dosage

Normal Dosage

Dosage in Renal Failure

Dosage in Hepatic Insufficiency

Dosage in Geriatric Patients

1.3.1 Normal Dosage

1.3.1.A Paroxetine Hydrochloride

1.3.1.A.1 Oral route

Generalized anxiety disorder

Major depressive disorder

Obsessive-compulsive disorder

Panic disorder

Posttraumatic stress disorder

Premenstrual dysphoric disorder

Social phobia

1.3.1.A.1.a Generalized anxiety disorder

1) The usual initial dosage is 20 milligrams (mg) daily. For generalized anxiety disorder, additional benefit has NOT been shown for doses above 20 mg daily; therefore, the recommended dosage is 20 mg daily. Paroxetine is usually taken in the morning and may be taken with or without food (Prod Info Paxil(R), 2002e).

1.3.1.A.1.b Major depressive disorder

1) The usual initial dosage is 20 milligrams (mg) daily. For patients who have an inadequate response, the dose may be increased in increments of 10 mg daily at intervals of 1 week or more. The maximum recommended dose is 50 mg daily. Paroxetine is usually taken in the morning and may be taken with or without food (Prod Info Paxil(R), 2002e; Gagiano et al, 1989a; Rickels et al, 1989a; Feighner & Boyer, 1989a; Byrne, 1989a; Oswald & Adam, 1986; Battegay et al, 1985b).
2) For the controlled-release tablet, the usual initial dosage is 25 milligrams (mg) daily. For patients who have an inadequate response, the dose may be increased in increments of 12.5 mg daily at intervals of 1 week or more. The maximum recommended dose is 62.5 mg daily. Paroxetine is usually taken in the morning and may be taken with or without food (Prod Info Paxil(R) CR(TM), 2002).
3) Allow a 14-day washout period when switching a patient from a monoamine oxidase inhibitor (MAOI) to paroxetine, or from paroxetine to a MAOI (Prod Info Paxil(R), 2002e); (Prod Info Paxil CR(TM),2002).

1.3.1.A.1.c Obsessive-compulsive disorder

1) The usual initial dosage is 20 milligrams (mg) daily; however, for this indication, the recommended dosage is 40 mg daily. The dose should be increased in increments of 10 mg daily at intervals of 1 week. The maximum recommended dose is 60 mg daily. Paroxetine is usually taken in the morning and may be taken with or without food (Prod Info Paxil(R), 2002e).
2) For maintenance therapy, the dose should be adjusted to the lowest effective dosage. Long-term treatment is usually necessary because OCD is a chronic condition (Prod Info Paxil(R), 2002e).

1.3.1.A.1.d Panic disorder

1) The usual initial dosage is 10 milligrams (mg) daily; however, for this indication, the recommended dosage is 40 mg daily. The dose should be increased in increments of 10 mg daily at intervals of 1 week. The maximum recommended dose is 60 mg daily. Paroxetine is usually taken in the morning and may be taken with or without food (Prod Info Paxil(R), 2002e).
2) For the controlled-release tablet, the usual initial dosage is 12.5 milligrams (mg) daily. For patients who have an inadequate response, the dose may be increased in increments of 12.5 mg daily at intervals of 1 week or more. The maximum recommended dose is 75 mg daily. Paroxetine is usually taken in the morning and may be taken with or without food (Prod Info Paxil CR(TM), 2002).
3) For maintenance therapy, the dose should be adjusted to the lowest effective dose. Long-term treatment is usually necessary because panic disorder is a chronic condition (Prod Info Paxil(R), 2002e); (Prod Info Paxil CR(TM), 2002).

1.3.1.A.1.e Posttraumatic stress disorder

1) The recommended dose is 20 milligrams per day (mg/day), in the morning, with or without food. There is insufficient evidence to suggest that a higher dose would provide increased benefit. Dosing adjustments, if desired, should be made in 10 mg increments (Prod Info Paxil(R), 2002e). Paroxetine in doses of 20 or 40 mg/day effectively treated all three components of posttraumatic stress disorder (reexperiencing, avoidance/numbing and hyperarousal) when compared to a matched placebo group (Marshall et, al, 2001).

1.3.1.A.1.f Premenstrual dysphoric disorder

1) Paroxetine controlled-release may be administered daily throughout the menstrual cycle or limited to daily administration during the luteal phase of the menstrual cycle. The usual initial dosage is 12.5 milligrams (mg) controlled- release as a single daily dose; the dose may be increased to 25 mg/day at intervals of at least 1 week. Doses of 12.5 mg/day and 25 mg/day have both been shown to be effective. Paroxetine controlled-release is usually taken in the morning and may be taken with or without food (Prod Info Paxil CR(TM), 2004b).
2) The effectiveness of paroxetine controlled-release for maintenance therapy beyond 3 menstrual cycles has not been evaluated; however, the continuation of treatment in a responding patient is reasonable due to the usual persistence of symptoms until menopause. Patients should be reassessed occasionally to determine the need for ongoing treatment (Prod Info Paxil CR (TM), 2003).

1.3.1.A.1.g Social phobia

1) The usual initial dosage is 20 milligrams (mg) daily. For social anxiety disorder, additional

benefit has NOT been shown for doses above 20 mg daily; therefore, the recommended dosage is 20 mg daily. Paroxetine is usually taken in the morning and may be taken with or without food (Prod Info Paxil(R), 2002e).

2) For the controlled-release tablet, the usual initial dosage is 12.5 milligrams (mg) daily; the dose may be increased in increments of 12.5 mg/day at intervals of 1 week or more. Doses of 12.5 mg/day to 37.5 mg/day have been shown to be effective. The maximum recommended dose is 37.5 mg daily. Paroxetine is usually taken in the morning and may be taken with or without food (Prod Info Paxil(R) CR(TM), 2002).

3) For maintenance therapy, the dose should be adjusted to the lowest effective dose and patients should be reassessed occasionally to determine the need for ongoing treatment. Long-term treatment is usually necessary because social anxiety disorder is a chronic condition (Prod Info Paxil CR (TM), 2003).

1.3.1.A.2 DRUG DISCONTINUATION

a) It is recommended that paroxetine dosage be reduced gradually when treatment is going to be discontinued. In some clinical trials paroxetine was decreased by 10 milligrams (mg) per day at weekly intervals. When a daily dose of 20 mg/day was reached, patients were continued on this dose for 1 week before treatment was stopped. If intolerable symptoms occur following a reduction in dose or upon discontinuation of treatment, then resuming the previously prescribed dose maybe be considered. Decreasing the dose at a more gradual rate is then recommended (Prod Info Paxil(R), 2002e); (Prod Info Paxil CR(TM), 2002).

1.3.1.A.3 MAXIMUM RECOMMENDED DOSAGE

a) The maximum recommended dosage is 60 milligrams daily (Prod Info Paxil(R), 2002e). For the controlled-release tablet, the maximum recommended dosage is 75 milligrams daily (Prod Info Paxil(R), 2002e); (Prod Info Paxil CR(TM), 2002).

1.3.2 Dosage in Renal Failure

A) Paroxetine Hydrochloride

1) The initial recommended dosage is 10 milligrams (mg) daily, and the maximum recommended dosage is 40 mg daily (Prod Info Paxil(R), 2002e). For paroxetine controlled release, the initial recommended dose is 12.5 mg daily with a maximum recommended dose of 50 mg daily; these dosing guidelines also apply to debilitated patients (Prod Info Paxil(R) CR(TM), 2002).

2) In a single-dose study involving subjects with varying degrees of renal impairment, maximum serum levels and area under the concentration-time curve (AUC) values of paroxetine tended to increase as renal function declined. The elimination half-life was prolonged significantly only in severe renal impairment (creatinine clearance less than 30 milliliters/minute) (Doyle et al, 1989a).

1.3.3 Dosage in Hepatic Insufficiency

A) Paroxetine Hydrochloride

1) The initial recommended dosage is 10 milligrams (mg) daily, and the maximum recommended dosage is 40 mg daily (Prod Info Paxil(R), 2002e). For paroxetine controlled release, the initial recommended dose is 12.5 mg daily with a maximum recommended dose of 50 mg daily; these dosing guidelines also apply to debilitated patients (Prod Info Paxil CR (TM), 2002).

2) Higher plasma levels and slower elimination of paroxetine were observed in patients with cirrhosis (Dalhoff et al, 1991a). This was observed in a 14-day multiple-dose study in 12 patients with alcoholic cirrhosis and 6 patients with no liver disease. The trough paroxetine concentration at steady state and AUC were significantly higher in patients with liver disease.

1.3.4 Dosage in Geriatric Patients

A) Paroxetine Hydrochloride

1) The initial recommended dosage is 10 milligrams (mg) daily, and the maximum recommended dosage is 40 mg daily for elderly or debilitated patients (Prod Info Paxil(R), 2002e). For paroxetine controlled release, the initial recommended dose is 12.5 mg daily with a maximum recommended dose of 50 mg daily; these dosing guidelines also apply to debilitated patients (Prod Info Paxil CR(TM), 2002).

2) Although considerable interindividual variation in paroxetine pharmacokinetics has been observed, higher plasma levels of paroxetine have been observed, as well as slowed elimination in the elderly, compared with younger subjects (Kaye et al, 1989d; Ghose, 1989a; Bayer et al, 1989a; Lundmark et al, 1989a). In 1 study of elderly depressed patients receiving paroxetine 20 milligrams daily, pharmacokinetic parameters observed were similar to those in younger subjects receiving 30 milligrams daily (Lundmark et al, 1989a).

3) It is recommended that paroxetine dosage be reduced gradually when treatment is going to be discontinued. In some clinical trials paroxetine was decreased by 10 milligrams (mg) per day at weekly intervals. When a daily dose of 20 mg/day was reached, patients were continued on this dose for 1 week before treatment was stopped. If intolerable symptoms occur following a reduction in dose or upon discontinuation of treatment, then resuming the previously prescribed dose maybe be considered. Decreasing the dose at a more gradual rate is then recommended (Prod Info Paxil(R), 2002e); (Prod Info Paxil CR(TM), 2002).

2.0 Pharmacokinetics

Onset and Duration

Drug Concentration Levels

ADME

2.1 Onset and Duration

A) Onset

1) Initial Response

a) Depression, regular release: 2 weeks (Feighner & Boyer, 1989c; Rickels et al, 1989b).

b) Depression, controlled release and regular release: 1 to 4 weeks (Prod Info Paxil(R), 2002d); (Prod Info Paxil CR(TM), 2002).

2.2 Drug Concentration Levels

A) Time to Peak Concentration

1) Oral, regular release: 3 to 8 hours (Kaye et al, 1989c).

a) After oral administration of paroxetine 20 milligrams (mg), mean peak serum concentrations were 10.7 nanograms/milliliter (ng/mL) (range, 0.8 to 32.5 ng/mL). With oral doses of 30 mg and 40 mg, mean peak concentrations were 17.6 ng/mL and 26.6 ng/mL, respectively, each occurring in approximately 6 hours (Kaye et al, 1989c). After oral administration of 30 mg paroxetine tablets daily for 30 days, the mean peak steady state concentration was 61.7 ng/mL (Prod Info Paxil(R), 2002d).

b) Steady-state plasma concentrations have not correlated with clinical improvement in depressed patients (Tasker et al, 1989a).

2) Oral, controlled release: 6 to 10 hours (Prod Info Paxil CR(TM), 2002).

a) After oral administration of paroxetine CR 12.5 mg, 25 mg, 37.5 mg, and 50 mg, the Cmax was 2, 5.5, 9, and 12.5 ng/mL, respectively (Prod Info Paxil CR(TM), 2002).

B) Area Under the Curve

1) 121 TO 540 ng x hr/mL (controlled release) (Prod Info Paxil CR(TM), 2002).

2.3 ADME

Absorption

Distribution

Metabolism

Excretion

Elimination Half-life

2.3.1 Absorption

A) Bioavailability

1) Oral, regular release: well-absorbed (Kaye et al, 1989c).

B) Effects of Food

1) Minimal (Prod Info Paxil(R), 2002d); (Prod Info Paxil CR(TM), 2002).

a) When administered with food, the Cmax and AUC increased by 6% and 29%, respectively (Prod Info Paxil(R), 2002d).

2.3.2 Distribution

A) Distribution Sites

1) Protein Binding

a) 95% (Kaye et al, 1989c).

B) Distribution Kinetics

1) Volume of Distribution

a) 8.7 L/kg (Kaye et al, 1989c).

1) The Vd, 17.2 L/kg (range, 8 to 28 L/kg), was greater following an intravenous infusion of paroxetine 23 to 28 mg over 24 to 30 minutes versus a bolus dose (Kaye et al, 1989c).

2.3.3 Metabolism

A) Metabolism Sites and Kinetics

1) Liver, extensive (Kaye et al, 1989c).

a) The cytochrome P4502D6 enzymes responsible in part for metabolizing paroxetine are saturable, resulting in non-linear kinetics at increased doses (Prod Info Paxil(R), 2002d).

B) Metabolites

1) Conjugates of paroxetine, inactive (Prod Info Paxil(R), 2002d; Kaye et al, 1989c).

2.3.4 Excretion

A) Kidney

1) Renal Excretion (%)

a) 65% to 67% (Kaye et al, 1989c).

2) Less than 2% of an oral dose of paroxetine is excreted unchanged in urine. Approximately 65% of a dose appears in the urine as metabolites (conjugates and other unknown polar metabolites) (Kaye et al, 1989c).

B) Total Body Clearance

1) 0.5 to 1 L/kg (Kaye et al, 1989c).

C) Other

1) Feces 36% to 37% (Prod Info Paxil(R), 2002d; Kaye et al, 1989c).

a) Excreted as metabolites (36%) and as parent drug (less than 1%) (Prod Info Paxil(R), 2002d; Kaye et al, 1989c).

2.3.5 Elimination Half-life

A) Parent Compound

1) ELIMINATION HALF-LIFE

a) 15 to 22 hours (Prod Info Paxil(R), 2002d); (Prod Info Paxil CR(TM), 2002)(Kaye et al, 1989c).

1) Considerable intersubject variation is observed as demonstrated by the range of half-lives between 3.8 to 65 hours (Kaye et al, 1989c).

3.0 Cautions

Contraindications

Precautions

Adverse Reactions

Teratogenicity/Effects in Pregnancy/Breastfeeding

Drug Interactions

3.0.A Black Box WARNING

1) Paroxetine Hydrochloride

a) Oral (Tablet; Tablet, Extended Release; Suspension)

Suicidality and Antidepressant Drugs

Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of paroxetine hydrochloride or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Paroxetine hydrochloride is not approved for use in pediatric patients (Prod Info PAXIL(R) oral tablets, suspension, 2009; Prod Info PAXIL CR(R) controlled-release oral tablets, 2009).

3.1 Contraindications

A) Paroxetine Hydrochloride

1) concomitant use of linezolid (Prod Info PAXIL CR(R) controlled-release oral tablets, 2009; Prod Info PAXIL(R) oral tablets, suspension, 2009)

2) concomitant use of monoamine oxidase inhibitors (MAOIs) (Prod Info PAXIL CR(R) controlled-release oral tablets, 2009; Prod Info PAXIL(R) oral tablets, suspension, 2009)

3) concomitant use of pimozide (Prod Info PAXIL CR(R) controlled-release oral tablets, 2009; Prod Info PAXIL (R) oral tablets, suspension, 2009)

4) concomitant use of thioridazine (Prod Info PAXIL CR(R) controlled-release oral tablets, 2009; Prod Info PAXIL(R) oral tablets, suspension, 2009)

5) hypersensitivity to paroxetine or any component of the product (Prod Info PAXIL CR(R) controlled-release oral tablets, 2009; Prod Info PAXIL(R) oral tablets, suspension, 2009)

3.2 Precautions

A) Paroxetine Hydrochloride

1) suicidal ideation and behavior or worsening depression; increased risk, particularly in children, adolescents, and young adults with major depressive disorder during the first few months of therapy or following changes in dosage (Prod Info PAXIL CR(R) controlled-release oral tablets, 2009; Prod Info PAXIL(R) oral tablets, suspension, 2009)

2) abnormal bleeding has been reported, including life-threatening hemorrhages (Prod Info PAXIL CR(R) controlled-release oral tablets, 2009; Prod Info PAXIL(R) oral tablets, suspension, 2009)

3) abrupt withdrawal; serious discontinuation symptoms have been reported (Prod Info PAXIL CR(R) controlled-release oral tablets, 2009; Prod Info PAXIL(R) oral tablets, suspension, 2009)

4) bipolar disorder; increased risk of precipitation of a mixed/manic episode (Prod Info PAXIL CR(R) controlled-release oral tablets, 2009; Prod Info PAXIL(R) oral tablets, suspension, 2009)

5) concomitant alcohol use; should be avoided (Prod Info PAXIL CR(R) controlled-release oral tablets, 2009; Prod Info PAXIL(R) oral tablets, suspension, 2009)

6) concomitant use of NSAIDs, aspirin, warfarin, or other drugs that affect coagulation; monitoring recommended during paroxetine initiation and discontinuation (Prod Info PAXIL CR(R) controlled-release oral tablets, 2009; Prod Info PAXIL(R) oral tablets, suspension, 2009)

7) concomitant serotonergic drug use (serotonin precursors (tryptophan), SSRIs, serotonin-norepinephrine reuptake inhibitors); use is not recommended (Prod Info PAXIL CR(R) controlled-release oral tablets, 2009; Prod Info PAXIL(R) oral tablets, suspension, 2009)

8) glaucoma, narrow-angle; increased risk of mydriasis (Prod Info PAXIL CR(R) controlled-release oral tablets, 2009; Prod Info PAXIL(R) oral tablets, suspension, 2009)

9) hepatic impairment, severe; lower or less frequent dose may be required (Prod Info PAXIL CR(R) controlled-release oral tablets, 2009; Prod Info PAXIL(R) oral tablets, suspension, 2009)

10) mania, history; risk of activation of mania/hypomania (Prod Info PAXIL CR(R) controlled-release oral tablets, 2009; Prod Info PAXIL(R) oral tablets, suspension, 2009)

11) medical diseases or conditions that could affect metabolism or hemodynamic responses (Prod Info PAXIL CR(R) controlled-release oral tablets, 2009; Prod Info PAXIL(R) oral tablets, suspension, 2009)

12) renal impairment, severe; lower or less frequent dose may be required (Prod Info PAXIL CR(R) controlled-release oral tablets, 2009; Prod Info PAXIL(R) oral tablets, suspension, 2009)

13) seizures, history (Prod Info PAXIL(R) oral tablets, suspension, 2007; Prod Info PAXIL CR(R) controlled-release oral tablets, 2007)

14) serotonin syndrome has been reported, including cases that are life-threatening or that resemble neuroleptic malignant syndrome; monitoring recommended (Prod Info PAXIL CR(R) controlled-release oral tablets, 2009; Prod Info PAXIL(R) oral tablets, suspension, 2009)

15) use of MAOI (including linezolid) within 14 days of paroxetine discontinuation (Prod Info PAXIL CR(R) controlled-release oral tablets, 2009; Prod Info PAXIL(R) oral tablets, suspension, 2009)

16) use of paroxetine within 14 days of MAOI (including linezolid) discontinuation (Prod Info PAXIL CR(R) controlled-release oral tablets, 2009; Prod Info PAXIL(R) oral tablets, suspension, 2009)

17) volume-depleted, elderly, or concurrent diuretic therapy; hyponatremia, syndrome of inappropriate antidiuretic hormone secretion (SIADH) has occurred with paroxetine hydrochloride (Prod Info PAXIL CR(R) controlled-release oral tablets, 2009; Prod Info PAXIL(R) oral tablets, suspension, 2009)

3.3 Adverse Reactions

Cardiovascular Effects

Dermatologic Effects

Endocrine/Metabolic Effects

Gastrointestinal Effects

Hematologic Effects

Hepatic Effects

Immunologic Effects

Musculoskeletal Effects

Neurologic Effects

Ophthalmic Effects

Psychiatric Effects

Renal Effects

Reproductive Effects

Respiratory Effects

Other

3.3.1 Cardiovascular Effects

3.3.1.A Paroxetine Hydrochloride

Cardiac dysrhythmia

Cardiovascular finding

ECG: extrasystole

EKG finding

Hypotension

Transient ischemic attack

3.3.1.A.1 Cardiac dysrhythmia

a) Summary

1) The occurrence of VENTRICULAR FIBRILLATION, VENTRICULAR TACHYCARDIA, and TORSADE DE POINTES have been documented in paroxetine postmarketing reports (Prod Info Paxil(R), 2002e); (Prod Info Paxil CR(TM), 2002).

3.3.1.A.2 Cardiovascular finding

a) Summary

1) During clinical trials of paroxetine regular-release, PALPITATION (2% to 3%) and VASODILATION (3% to 4%) were the primary cardiovascular adverse effects (Prod Info Paxil(R), 2002e; Edwards et al, 1989b; Feighner & Boyer, 1989b; Rickels et al, 1989; Warrington et al, 1989b). In some studies, cardiovascular effects (increase in heart rate, decrease in left ventricular ejection time index) have been less with paroxetine compared to amitriptyline (Kuhs & Rudolf, 1989a; Warrington et al, 1989b). In other studies, the incidence of cardiovascular adverse effects was similar for both agents (Byrne, 1989b). TACHYCARDIA (1%) and vasodilation (2%; FLUSHING) were also observed in clinical trials of paroxetine controlled-release (Prod Info Paxil CR(TM), 2002).

2) In a large cohort study including 481,744 persons and 1487 cases of SUDDEN CARDIAC DEATH occurring in a community setting, the use of selective serotonin reuptake inhibitors was not associated with an increased risk of sudden cardiac death (rate ratio, 0.95; 95% CI, 0.42 to 2.15). In contrast, users of tricyclic antidepressants in doses of 100 mg or higher (amitriptyline or its equivalent) had a 41% increased rate of sudden cardiac death (rate ratio, 1.41; 95% CI, 1.02 to 1.95) (Ray et al, 2004).

b) Palpitation, vasodilation, hypotension, tachycardia, arrhythmias, transient ischemic attack, premature ventricular contractions (PVC's), and minor electrocardiogram changes have been reported with paroxetine therapy.

3.3.1.A.3 ECG: extrasystole

a) Summary

1) Multiple preventricular contractions (PVCs) without associated symptoms developed in one

patient taking therapeutic doses of paroxetine (Battegay et al, 1985a).

3.3.1.A.4 EKG finding

a) Summary

1) Paroxetine 30 milligrams daily produced no significant effect on the electrocardiogram (EKG) in a 4-week, placebo-controlled study involving 20 depressed patients. Paroxetine therapy produced no significant effect on heart rate, PR or QT(c) intervals, or T-wave height. A small increase in QRS width was observed at week 4 of therapy, although this was of no clinical relevance. Blood pressure was unchanged during the study. These data suggest the lack of significant cardiac effects induced by paroxetine (Edwards et al, 1989b).

b) LITERATURE REPORTS

1) In 1 study comparing the electrocardiogram (EKG) effects of amitriptyline and paroxetine, amitriptyline was associated with increases in heart rate, prolongation of the PR interval, and a reduction in T-wave amplitude, whereas paroxetine produced no significant EKG abnormalities (Warrington et al, 1989b).

3.3.1.A.5 Hypotension

a) Summary

1) An asymptomatic decrease in systolic blood pressure was noted in patients taking therapeutic doses of paroxetine after 4 weeks on therapy (Battegay et al, 1985a). Orthostatic dizziness was reported in 6 of 19 patients taking therapeutic doses (Laurson et al, 1985).

b) LITERATURE REPORTS

1) SYNCOPE associated with a sudden fall in blood pressure and pulse developed in a 71 year-old-woman taking therapeutic doses (Lundmark et al, 1989a).

3.3.1.A.6 Transient ischemic attack

a) Transient ischemic attack occurred in a 57-year-old male patient with a history of high cholesterol and intermittent atrial fibrillation following the initiation of paroxetine therapy for the treatment of chronic hip pain. The man presented with right side facial droop and slurred speech after taking four doses of 20-milligram paroxetine at a twice-daily dosing regimen. On the day of presentation and subsequent admission to the hospital, the patient described residual bilateral paresthesia and "burning" pain that spread from the top of his head downward to his groin. He had experienced "burning" chest pain, sweating, and lightheadedness two days prior to admission. Paroxetine was stopped upon admission; anticoagulation therapy (ie, heparin and oral warfarin) was initiated and the patient's symptoms resolved. Two days later paroxetine was restarted at a dose of 10 mg twice daily. After two doses of medication, the patient experienced two more episodes similar to the initial one. Paroxetine was again discontinued and symptoms resolved with no recurrence of episodes over a 4-month follow-up period (Manos & Wechsler, 2004).

3.3.2 Dermatologic Effects

3.3.2.A Paroxetine Hydrochloride

Diaphoresis

Eczema

Photosensitivity

Rash

Toxic epidermal necrolysis

Vasculitis of the skin

3.3.2.A.1 Diaphoresis

a) Summary

1) Sweating has been reported with paroxetine regular- and controlled-release use in clinical trials including patients treated for the following disorders: major depressive, obsessive-compulsive, panic, social anxiety, generalized anxiety, posttraumatic stress, and premenstrual dysphoric (Prod Info PAXIL(R) oral tablets, suspension, 2009; Prod Info PAXIL CR(R) controlled-release oral tablets, 2009). In some reports, diaphoresis has occurred less frequently with paroxetine than with amitriptyline (Battegay et al, 1985a; Bascara, 1989a).

b) Incidence: 5% to 14% (Prod Info PAXIL(R) oral tablets, suspension, 2009; Prod Info PAXIL CR(R)

controlled-release oral tablets, 2009; Claghorn et al, 1992a; Dunbar, 1989; Rickels et al, 1989; Miller et al, 1989)
c) In 6-week, placebo-controlled, clinical trials for major depressive disorder, sweating was reported in 11% of patients treated with regular-release paroxetine 20 to 50 mg/day (n=421) and 2% of patients treated with placebo (n=421) (Prod Info PAXIL(R) oral tablets, suspension, 2009).
d) In placebo-controlled, clinical trials, sweating was reported in a greater percentage of patients treated with regular-release paroxetine 10 to 60 mg/day compared with patients treated with placebo for panic disorder (14% vs 6%), for social anxiety disorder (9% vs 2%), for generalized anxiety disorder (6% vs 2%), and for posttraumatic stress disorder (5% vs 1%) (Prod Info PAXIL(R) oral tablets, suspension, 2009).
e) In phase 3 double-blind, controlled, outpatient studies, sweating was reported in a greater percentage of patients treated with controlled-release paroxetine compared with patients treated with placebo for major depressive disorder (MDD; 6% vs 2%), MDD in the elderly (10% vs less than 1%), panic disorder (7% vs 2%), social anxiety disorder (14% vs 3%), premenstrual dysphoric disorder (PMDD) with continuous dosing (7% vs 1%), and PMDD with fixed dosing (8.9% vs 0.9%) (Prod Info PAXIL CR(R) controlled-release oral tablets, 2009).
f) Diaphoresis has been a fairly common adverse effect during paroxetine therapy, occurring in up to 12% of patients treated (Claghorn et al, 1992a; Dunbar, 1989; Rickels et al, 1989; Miller et al, 1989). The incidence of diaphoresis has been less than that observed with amitriptyline in some reports (Battegay et al, 1985a; Bascara, 1989a).

3.3.2.A.2 Eczema
a) Incidence: 1% (Prod Info PAXIL CR(R) controlled-release oral tablets, 2009)
b) In a clinical trial of patients with social anxiety disorder, eczema was reported in 1% of patients treated with paclitaxel controlled-release (n=186) and 0% of patients treated with placebo (n=184) (Prod Info PAXIL CR(R) controlled-release oral tablets, 2009).

3.3.2.A.3 Photosensitivity
a) Incidence: 2% (Prod Info PAXIL CR(R) controlled-release oral tablets, 2009)
b) In a pool of 2 studies including patients with major depressive disorder, photosensitivity was reported in 2% of patients treated with paclitaxel controlled-release (n=212) and 0% of patients treated with placebo (n=211) (Prod Info PAXIL CR(R) controlled-release oral tablets, 2009).

3.3.2.A.4 Rash
a) Summary
1) Rash has been reported in clinical, placebo-controlled trials with regular- and controlled-release paroxetine (Prod Info PAXIL(R) oral tablets, suspension, 2009; Prod Info PAXIL(R) oral tablets, suspension, 2009). A case report also described rash and pruritus in a 47-year-old woman treated with paroxetine (Sannicandro et al, 2002).
b) Incidence: up to 3% (Prod Info PAXIL(R) oral tablets, suspension, 2009; Prod Info PAXIL CR(R) controlled-release oral tablets, 2009)
c) In 6-week, placebo-controlled, clinical trials for major depressive disorder, rash was reported in 2% of patients treated with regular-release paroxetine 20 to 50 mg/day (n=421) and 1% of patients treated with placebo (n=421) (Prod Info PAXIL(R) oral tablets, suspension, 2009).
d) In 12-week, placebo-controlled, clinical trials for obsessive compulsive disorder, rash was reported in 3% of patients treated with regular-release paroxetine 20 to 60 mg/day (n=542) and 2% of patients treated with placebo (n=265) (Prod Info PAXIL(R) oral tablets, suspension, 2009).
e) In phase 3 double-blind, controlled, outpatient studies for major depressive disorder, panic disorder, social anxiety disorder, and premenstrual dysphoric disorder (n=1627), rash was reported in greater than 1% of patients treated with multiple doses of controlled-release paroxetine (Prod Info PAXIL CR(R) controlled-release oral tablets, 2009).
f) Skin rashes and pruritus have each been reported in 2% of patients treated with paroxetine (Claghorn et al, 1992a; Dunbar, 1989).
g) A 47-year-old African American woman developed a morbilliform-type rash and pruritus 3 days after beginning treatment with paroxetine for depression. At admission to hospital, she was started on paroxetine 20 mg at bedtime for major depression and lorazepam for potential alcohol withdrawal symptoms and for anxiety. The rash that developed on day 3 was generalized to her trunk, extremities, and neck, with some facial involvement but no palm or sole involvement. Paroxetine was discontinued and she was given diphenhydramine 25 mg every 6 hours as needed plus topical hydrocortisone 1% for treatment of pruritus. Venlafaxine extended-release was administered for treatment of depression. The rash resolved 3 to 4 days after discontinuation of paroxetine. Hydrocortisone was discontinued on day 10 and she was discharged on day 15. The woman had previously experienced a similar rash when treated with fluoxetine (Sannicandro et al, 2002).

3.3.2.A.5 Toxic epidermal necrolysis
a) Toxic epidermal necrolysis has been reported during postmarketing use of paroxetine; causality and frequency cannot be established (Prod Info PAXIL CR(R) controlled-release oral tablets, 2009)
b) A case report described toxic epidermal necrolysis in a 71-year-old woman following treatment with

paroxetine. The patient, who had been treated for 3 years with diltiazem, trimetazidine, lysine acetylsalicylate, rosuvastatin, and topical latanoprost, was initiated on alprazolam and tianeptine due to a recent depressive disorder. Because the tianeptine was not adequately controlling her depression, the drug was switched to paroxetine 60 mg/day. Fourteen days after paroxetine was initiated, she presented with malaise and pruritic cutaneous rash on her arms. Topical corticosteroids, antiseptic chlorhexidine, oral fusidic acid and betamethasone plus dexchlorpheniramine were prescribed. Over the following days, she presented to the emergency room with lesions on her thighs, lower back, abdomen, and axillae which her doctor thought to be TEN. Bacteriological samples showed Klebsiella pneumoniae and Morganella morganii on in the axillae and skin biopsy was indicative of TEN. Subsequently, all medications were discontinued and the patient was prescribed paracetamol and nalbuphine for pain for 2 days. The following day, all medications were reinitiated with the exception of paroxetine. On day 11, the patient was discharged after a complete recovery with the exception of hyperpigmentation and no further lesions were reported (Tudela et al, 2009).

3.3.2.A.6 Vasculitis of the skin

a) A case report described multiple painful purple lesions of the extremities of fingers on both hands in a 20-year-old woman with obsessive-compulsive disorder and a history of migraines 15 weeks after beginning treatment with paroxetine. After 6 weeks of treatment and while on a stable dose of 20 mg/day, she developed insomnia, a worsening of migraine headaches, and a "shaking feeling all over." Her dose was reduced to 10 mg/day at 10 weeks. Paroxetine was discontinued when cutaneous vasculitis developed, and the lesions vanished within a week. Reintroduction of paroxetine resulted in reappearance of cutaneous vasculitis lesions within 2 days. Paroxetine was again discontinued, and lesions again disappeared within a week (Margolese et al, 2001).

3.3.3 Endocrine/Metabolic Effects

3.3.3.A Paroxetine Hydrochloride

Disorder of fluid AND/OR electrolyte

Endocrine finding

Galactorrhea

Hyponatremia

Metabolic finding

Pheochromocytoma

Porphyria

Syndrome of inappropriate antidiuretic hormone secretion

3.3.3.A.1 Disorder of fluid AND/OR electrolyte

a) Hyponatremia (occasionally severe) has occurred with paroxetine therapy.

3.3.3.A.2 Endocrine finding

a) Drug induced syndrome of inappropriate antidiuretic hormone, galactorrhea, syndrome of inappropriate secretion of antidiuretic hormone (SIADH) and pheochromocytoma have been reported with therapeutic paroxetine use.

3.3.3.A.3 Galactorrhea

a) Summary

1) From the manufacturer's premarketing database, 3 cases of galactorrhea were reported in 4126 paroxetine-treated patients over 4 years. After paroxetine was marketed in the United States (2/93), the manufacturer received 9 reports of galactorrhea or nonpuerperal lactation. Eleven additional cases have been reported to the manufacturer since paroxetine was introduced in Europe (Pers Comm, 1994).

b) LITERATURE REPORTS

1) Over a 10-year period, the Netherlands Pharmacovigilance Foundation received 38 reports of NON-PUERPERAL LACTATION related to medications of which 15 cases were attributed to antidepressants primarily the selective serotonin reuptake inhibitors (SSRIs). The odds ratio for the

risk of galactorrhea due to all antidepressants versus other medications was 8.3 (95% confidence interval (CI), 4.3 to 16.1). The odds ratio for SSRIs was 12.7 (95% CI, 6.4 to 25.4) versus 1.6 (95% CI, 0.2 to 11.6) for other antidepressants. Of the 15 reports, 5, 4, and 4 were related to fluvoxamine, fluoxetine, and paroxetine, respectively. Women developing galactorrhea were significantly younger (mean age, 33 years) than women without galactorrhea (mean age, 51 years). Galactorrhea developed from 2 weeks to 2 years after starting the SSRI. In all cases, galactorrhea resolved with continuation of the SSRI, a reduction in the dose, or discontinuation of the SSRI. Several patients were taking other medications, which have caused galactorrhea, concurrently with the SSRI but galactorrhea only developed after adding the SSRI. While this is not a serious adverse reaction, increased awareness may prevent unnecessary diagnostic procedures (Pers Comm, 1994).

2) The probable mechanism for selective serotonin reuptake inhibitor-induced galactorrhea is an increase in serum prolactin. This may result from direct stimulation of postsynaptic serotonin receptors in the hypothalamus or presynaptic serotonin receptor mediated inhibition of dopamine release (Bronzo & Stahl, 1993).

3.3.3.A.4 Hyponatremia

a) Summary

1) Hyponatremia has been reported in several patients taking therapeutic doses and has been severe in some cases (Odeh et al, 1999); (Goddard & Patton, 1992)(Chua & Vong, 1994; Chua & Vong, 1993). An unusually rapid onset of hyponatremia, following only 3 doses, was reported in an 82-year-old female (Paul & Sankaran, 1998).

2) Hyponatremia developed in 12% of elderly, depressed patients taking paroxetine for the treatment of a major depressive episode. In this 12-week, prospective study, 9 of 75 patients ages 63 to 90 years (mean age, 75.3 years) developed hyponatremia (sodium level less than 135 milliequivalents/liter (mEq/L)) within 1 to 14 days (mean, 9.3 days; median 9 days) of beginning paroxetine therapy at a mean dose of 12.5 milligrams. The authors identified lower body mass index and lower baseline plasma sodium level (138 mEq/L or less) as significant risk factors in the development of hyponatremia in elderly patients treated with paroxetine (Fabian et al, 2004).

b) Incidence: rare

3.3.3.A.5 Metabolic finding

a) Porphyria has occurred with paroxetine therapy.

3.3.3.A.6 Pheochromocytoma

a) Summary

1) After increasing paroxetine to 40 milligrams daily, a 55-year-old man had variable blood pressure readings between 240/130 millimeters of mercury (mmHg) and 80/40 mmHg; after performing appropriate tests, a pheochromocytoma was diagnosed. Pathologic examination after a left-sided adrenalectomy was also compatible with a pheochromocytoma. The only other medications taken by this man were atenolol and a benzodiazepine. Possible explanations for the rapid change in blood pressure include increased inhibition of noradrenalin reuptake after increasing the dose or slow metabolism by cytochrome P450 which resulted in increased noradrenalin levels. These factors combined with increased catecholamines from the pheochromocytoma may have produced the hemodynamic changes in this patient (Seelen et al, 1997).

3.3.3.A.7 Porphyria

a) Summary

1) The occurrence of porphyria has been documented in post marketing paroxetine reports (Prod Info Paxil(R), 2002e); (Prod Info Paxil CR(TM), 2002).

3.3.3.A.8 Syndrome of inappropriate antidiuretic hormone secretion

a) Summary

1) Paroxetine may occasionally induce a SYNDROME OF INAPPROPRIATE SECRETION OF ANTIDIURETIC HORMONE (SIADH) with resultant hyponatremia. Elderly patients may be more susceptible to SIADH. Cases following therapeutic paroxetine use have been reported (Monmany et al, 1999; Odeh et al, 1999; Paul & Sankaran, 1998; Van Campen & Voets, 1996). Of the 63 case reports of selective serotonin reuptake inhibitor (SSRI)-induced SIADH reported to the Food and Drug Administration, the majority occurred in patients over 70 years of age, patients taking diuretics, or patients who were dehydrated (Chua & Vong, 1993; Goddard & Paton, 1992). Based on published reports, the onset of the SIADH was between 3 days and 4 months after starting therapy. Symptoms included confusion, lethargy, dizziness, fatigue, anorexia, delirium, and abdominal pain.

b) LITERATURE REPORTS

1) Abnormal laboratory findings in case report review consisted of a decreased serum osmolality (median 251 milliosmole/liter (mOsm/L); range 214 to 272 mOsm/L), decreased serum sodium concentration (median 118 milliequivalents/liter (mEq/L); range 98 to 130 mEq/L), and urine

osmolality (median 392.5 mOsm/L; 229 to 613 mOsm/L). In all but 1 case report, the selective serotonin reuptake inhibitor (SSRI) was stopped, and fluid restriction was required before hyponatremia resolved; 1 patient was also treated with sodium chloride 3%. Patients in their fifties generally recovered in 2 to 4 days versus patients in their eighties who required up to 14 days for complete recovery. Of the 6 patients rechallenged with an SSRI, 3 developed a decrease in serum sodium consistent with SIADH, and 3 tolerated rechallenge without adverse events. In many case reports, inadequate reporting of symptoms, laboratory results, and exclusion of other causes were NOT included, making it difficult to attribute SIADH to the SSRI (Woo & Smythe, 1997).
2) Nine days after starting paroxetine 20 milligrams daily, a 72-year-old man was diagnosed with paroxetine-induced syndrome of inappropriate secretion of antidiuretic hormone (SIADH). He presented to the emergency department with disorientation, confusion, verbal incoherence, and a depressed level of consciousness. Laboratory studies revealed a plasma sodium concentration of 118 millimoles/liter (mmol/L), plasma osmolality of 262 millimoles/kilogram (mmol/kg) water, urinary sodium concentration of 53 mmol/L, and urine osmolality of 940 mmol/kg water. Other drugs and medical causes of SIADH were excluded. Paroxetine was stopped, and his level of consciousness and plasma sodium returned to normal (Monmany et al, 1999).
3) An 89-year-old woman developed the syndrome of inappropriate antidiuretic hormone (SIADH) possibly due to paroxetine 10 milligrams daily added the previous week. At hospital admission, she had abdominal distention and lethargy; abnormal laboratory values included a serum sodium of 116 millimoles/liter (mmol/L), serum osmolality 250 milliosmole/liter (mOsm/L), urinary sodium excretion 97 mmol/24 hours, and urine osmolality of 410 mOsm/L. Paroxetine was stopped, and the patient was treated with an intravenous saline infusion. Medical causes for SIADH were ruled out; thus, the authors attributed the SIADH to paroxetine. It is recommended that patients treated with a selective serotonin reuptake inhibitor who develop symptoms of weakness, lethargy, headache, anorexia, weight gain, confusion, or constipation have a serum sodium measured (Meynaar et al, 1997).

3.3.4 Gastrointestinal Effects

3.3.4.A Paroxetine Hydrochloride

Constipation

Diarrhea

Gastric hemorrhage

Gastrointestinal hemorrhage

Gastrointestinal tract finding

Grinding teeth

Loss of appetite

Nausea and vomiting

Xerostomia

3.3.4.A.1 Constipation

a) Summary

1) Constipation is a commonly reported side effect of paroxetine therapy (Dunbar et al, 1993a; Claghorn et al, 1992a; Rickels et al, 1989). Constipation (5% TO 16%) occurred with paroxetine at a higher incidence than placebo (Prod Info Paxil(R), 2002e). The incidence of constipation was less with paroxetine than amitriptyline in some studies (Kuhs & Rudolf, 1989a; Hassan et al, 1985b; Laursen et al, 1985b); however, other studies did NOT show a significant difference between the 2 drugs (Bascara, 1989a; Battegay et al, 1985a). Constipation (10%) also occurred at a higher incidence than placebo in clinical trials of Paxil CR(TM) (Prod Info Paxil CR(TM), 2002).

3.3.4.A.2 Diarrhea

a) Summary

1) Diarrhea is reported at therapeutic paroxetine doses (Claghorn et al, 1992a). Diarrhea (9% TO 12%) occurred at a higher incidence than placebo (Prod Info Paxil(R), 2002e). Diarrhea (18%) also

occurred at a higher incidence than placebo in clinical trials of Paxil CR(TM) (Prod Info Paxil CR (TM), 2002). Paroxetine increases GI motility and reduces orocecal transit time at therapeutic doses (Gorard et al, 1994).

3.3.4.A.3 Gastric hemorrhage

a) Summary

1) In a retrospective cohort study of 317,824 elderly patients, it was reported that high inhibition of serotonin reuptake increased the risk of upper GI bleeding. An overall risk of 7.3 per 1000 person years was reported. Elderly patients and those with previous GI bleeding were at increased risk (van Walraven et al, 2001).

3.3.4.A.4 Gastrointestinal hemorrhage

See Drug Consult reference: CONCOMITANT USE OF SSRIs AND NSAIDs - INCREASED RISK OF GASTROINTESTINAL BLEEDING

3.3.4.A.5 Gastrointestinal tract finding

a) Summary

1) Gastrointestinal adverse effects that occurred at a higher incidence than placebo included FLATULENCE (4%) and DYSPEPSIA (2% to 4%), (Prod Info Paxil(R), 2002e). Flatulence (6%) also occurred at a higher incidence than placebo in clinical trials of Paxil CR(TM) (Prod Info Paxil CR(TM), 2002).

b) Anorexia, constipation, dry mouth, diarrhea, flatulence, dyspepsia, gastric bleeding, nausea and vomiting have been reported with paroxetine therapy.

3.3.4.A.6 Grinding teeth

a) Possible paroxetine-induced bruxism (ie, grinding and clenching of the teeth, usually during sleep) followed treatment with paroxetine 10 milligrams (mg) daily in the morning for 5 days, increasing to 20 mg daily. Four months later, routine dental cleaning revealed damaged teeth consistent with bruxism. Tooth damage or temporomandibular joint dysfunction were not observed at previous dental visits. The 20-year-old woman's only other medication was tetracycline 250 mg twice daily for acne. On the fourth day after addition of oral buspirone 5 mg at bedtime the patient reported a significant reduction of gritting, tooth pain, and jaw tenderness (Romanelli et al, 1996). A 67-year-old woman was given oral paroxetine 20 mg each morning. Eleven months later she reported diurnal bruxism and jaw clenching and her jaws and gums ached. Oral buspirone (dosage not noted) did not have any beneficial effects (Fitzgerald & Healy, 1995).

3.3.4.A.7 Loss of appetite

a) Summary

1) Anorexia and WEIGHT LOSS have been reported with therapeutic paroxetine doses (Feighner et al, 1993; Ohrberg et al, 1992) DECREASED APPETITE (4% TO 6%) occurred with paroxetine at a higher incidence than placebo (Prod Info Paxil(R), 2002e); (Prod Info Paxil CR(TM), 2002).

3.3.4.A.8 Nausea and vomiting

a) Summary

1) Gastrointestinal adverse effects that occurred at a higher incidence than placebo included nausea (23% to 26%) and vomiting (2%) (Prod Info Paxil(R), 2002e); (Prod Info Paxil CR(TM), 2002). In the majority of patients, nausea gradually decreases or resolves over approximately 3 weeks. However, in others, reduction of the dose or discontinuation of the drug is required. The proposed mechanism for SSRI- induced nausea and vomiting is increased serotonin levels within the chemoreceptor trigger zone and area postrema in the brainstem, the primary areas within the brain associated with nausea and vomiting (McManis & Talley, 1997).

b) LITERATURE REPORTS

1) The selective serotonin reuptake inhibitors (SSRIs) produce nausea and vomiting in 20% to 25% and 2% to 3% of patients, respectively. In the majority of patients, nausea gradually decreases or resolves over approximately 3 weeks. However, in others, reduction of the dose or discontinuation of the drug is required. For this group, ondansetron or cisapride administered for a few weeks may facilitate continued treatment with the SSRI. Limited data suggest that ondansetron is more effective than cisapride; however, it is also more expensive. Use of cisapride with careful monitoring for arrhythmias may be more cost effective, and open therapy to a broader group of patients (McManis & Talley, 1997).

3.3.4.A.9 Xerostomia

a) Summary

1) Dry mouth occurs with therapeutic paroxetine doses (Miller et al, 1989; Battegay et al, 1985a). Dry mouth (9% TO 18%) occurred with paroxetine at a higher incidence than placebo (Prod Info Paxil(R), 2002e); (Prod Info Paxil CR(TM), 2002). The incidence of dry mouth was less with paroxetine than amitriptyline in some studies (Kuhs & Rudolf, 1989a; Hassan et al, 1985b; Laursen et al, 1985b); however, other studies did NOT show a significant difference between the 2 drugs

(Bascara, 1989a; Battegay et al, 1985a).

3.3.5 Hematologic Effects

3.3.5.A Paroxetine Hydrochloride

Ecchymosis

Hematology finding

3.3.5.A.1 Ecchymosis

a) Summary

1) Spontaneous ecchymosis has been reported in two patients taking therapeutic paroxetine doses (Ottervanger et al, 1994). Routine coagulation studies were normal in these patients, but in one patient there was no spontaneous platelet aggregation. Spontaneous ecchymoses due to therapeutic paroxetine doses occurred in a 47-year-old patient. Discontinuation of paroxetine resulted in resolution of ecchymoses (Cooper et al, 1998).

3.3.5.A.2 Hematology finding

a) Summary

1) The incidence of hemostatic disturbances is rare (0.1%) with paroxetine therapy. Common adverse effects include; APLASTIC ANEMIA, AGRANULOCYTOSIS, bone marrow aplasia, BRUISING, EOSINOPHILIA, EPISTAXIS, HEMOLYTIC ANEMIA, LEUKOCYTOSIS, LEUKOPENIA, PANCYTOPENIA, PROLONGED BLEEDING TIME, and RECTAL BLEEDING. Many cases have occurred in patients taking doses at the higher end of the dose range and are mild (Berk & Jacobson, 1998). Vitamin C 500 milligrams (mg) daily stopped bleeding and bruising associated with paroxetine and fluvoxamine therapy (Teilens, 1997).

b) Aplastic anemia, agranulocytosis, bone marrow aplasia, eosinophilia, epistaxis, hemolytic anemia, leukocytosis, leukopenia, pancytopenia, prolonged bleeding time, ecchymoses and rectal bleeding have occurred with paroxetine therapy.

c) LITERATURE REPORTS

1) INCIDENCE - Rare (incidence less than 0.1%).

a) The majority cases have been reported in patients taking fluoxetine but case reports are also available for paroxetine, sertraline, and fluvoxamine (Berk & Jacobson, 1998).

2) OUTCOME - Mild (treatment continued with/without other management) (Berk & Jacobson, 1998).

3) ASSOCIATED SYMPTOMS - Symptoms include: aplastic anemia, agranulocytosis, bone marrow aplasia, bruising, ecchymoses, eosinophilia, epistaxis, hemolytic anemia, leukocytosis, leukopenia, pancytopenia, prolonged bleeding time, rectal bleeding.

a) ONSET/DURATION

1) EARLIEST ONSET - 2 weeks (Tielens, 1997).

b) CLINICAL MANAGEMENT

1) PHARMACOLOGIC: For minor bleeding diatheses (ie, bruising), treatment is usually unnecessary because it usually resolves with continued treatment. However, if bleeding is clinically significant, occurs with other underlying medical illnesses, or fails to improve with time, the drug should be discontinued (Berk & Jacobson, 1998). Vitamin C 500 milligrams/day effectively reduced bleeding and bruising in 1 woman (Tielens, 1997).

c) PREDISPOSING RISK FACTORS

1) DOSE-RELATED ? YES. Many cases have occurred in patients taking doses at the higher end of the dose range (Berk & Jacobson, 1998).

2) DISEASE STATES: More common in patients with underlying diseases; 1 case occurred in a patient with HIV (Berk & Jacobson, 1998).

d) PROBABLE MECHANISM

1) Pharmacologic (extension of the expected effects of the drug). Selective serotonin reuptake inhibitors reduce uptake of serotonin by platelets; therefore, reduction in granular storage of serotonin is observed. Serotonin-mediated platelet aggregation may be decreased (Berk & Jacobson, 1998).

e) DOCUMENTATION QUALITY

1) Fair

f) CASE REPORTS

1) Vitamin C 500 milligrams (mg) daily stopped bleeding and bruising associated with paroxetine and fluvoxamine therapy (Teilens, 1997). A 33-year-old woman began taking paroxetine 40 mg daily for panic attacks and noted spontaneous bruising on her arms and legs and excessive menstrual BLEEDING within 2 weeks. No gynecologic or hematologic abnormalities were identified. Vitamin C added to paroxetine therapy stopped bleeding in

3 weeks; discontinuation of vitamin C resulted in recurrent bleeding. Her medication was switched to fluvoxamine which also caused bleeding that resolved with vitamin C (Tielens, 1997).

3.3.6 Hepatic Effects

3.3.6.A Paroxetine Hydrochloride

Acute hepatitis

Hepatitis

Hepatotoxicity

Liver finding

3.3.6.A.1 Acute hepatitis

a) Incidence: rare

b) An 84-year-old woman developed clinical symptoms of acute hepatitis after the first dose of paroxetine 10 mg/day prescribed for chronic mild depression. Symptoms of mental confusion, hyporexia, nausea and vomiting began after the first dose of paroxetine which was 3 days prior to hospitalization. The patient's medical history included chronic mild depression, chronic atrial fibrillation, arterial hypertension, brain atherosclerosis (two previous episodes of transitory ischemic attacks), and medications included verapamil 80 mg/day, tilopidine 500 mg/day, spironolactone 25 mg/day, and nimodipine 60 mg/day. Results from a clinical evaluation from 1 week prior to hospitalization, reported normal physical examination and normal serum levels of common biochemical markers, and serum transaminase levels (eg, AST (13 international units/L), ALT (17 international units/L), alkaline phosphatase (180 international units/L) and total bilirubin (1.03 mg/dL)). Upon hospitalization, the laboratory analysis revealed abnormal serum transaminase levels, including AST (186 international units/L), ALT (245 international units/L), mild hyperbilirubinemia (1.5 mg/dL), mild renal failure, and increased WBC levels without eosinophilia. The paroxetine was discontinued immediately. The next day, the laboratory analysis revealed a marked increase in serum transaminase levels (eg, AST (2208 international units/L), ALT (2110 international units/L)), normal alkaline phosphatase (277 international units/L), hyperbilirubinemia (2.5 mg/dL), hematochemical signs of liver failure and the patient developed clinical signs of hepatic encephalopathy stage I (bilateral asterixis, confusion and lethargy). An ultrasound study showed normal finding of the liver, spleen, pancrease and kidneys. The serum markers of viral, autoimmune and metabolic liver disease were negative. The patient was treated with parenteral administration of branched chain amino acids and lactulose given by retention enema. Within three days after hospitalization, the patient's clinical condition and mental status improved, and serum transaminase and ammonia levels were decreased. After 15 days, all liver-related laboratory values normalized and the patient was discharged in good clinical condition. The Naranjo probability scale suggests that paroxetine was the probable cause of the acute hepatitis (total score of 7) (Pompili et al, 2008).

3.3.6.A.2 Hepatitis

a) Summary

1) CASE REPORT - Chronic active hepatitis attributed to paroxetine was reported in a 54-year-old woman with depression. About 10 months after starting paroxetine 20 milligrams daily, the aspartate transaminase was elevated at 256 international units/liter (IU/L); 6 months later, it was 299 IU/L with an elevated alkaline phosphatase. Liver ultrasonography and serological tests for hepatitis were normal; however, a liver biopsy showed chronic active hepatitis with eosinophilic infiltration suggesting a drug reaction. Paroxetine was stopped, and laboratory tests returned to normal within 13 weeks (Benbow & Gill, 1997).

3.3.6.A.3 Hepatotoxicity

a) Summary

1) Rare cases of severe hepatotoxicity with jaundice associated with paroxetine therapy have been reported. Hepatotoxicity has been of the hepatocellular type or hepatocellular and cholestatic mixed type. Liver damage is generally reversible on discontinuation of the drug. Liver damage is most likely idiosyncratic (Odeh et al, 2001).

2) Although no causal relationship to paroxetine was established, deaths with liver necrosis and cases of severe hepatic dysfunction with gross elevations of transaminase levels were reported in non-US postmarketing reports (Prod Info Paxil(R), 2001). Isolated reports of elevations in liver enzymes (transaminases) have been observed during paroxetine therapy of depression (Dunbar,

1989); (Kuhs & Rudoff, 1989)(Rickels et al, 1989). Transaminases normalized after withdrawal of the drug in 1 patient (Kuhs & Rudoff, 1989).

3.3.6.A.4 Liver finding

a) Hepatitis and elevations of liver enzymes have been noted with paroxetine therapy. Deaths due to liver necrosis and severe hepatic dysfunction have been reported but without an established causal relationship to paroxetine therapy.

3.3.7 Immunologic Effects

3.3.7.A Paroxetine Hydrochloride

Anaphylaxis

Immune hypersensitivity reaction, Delayed

Immunology finding

3.3.7.A.1 Anaphylaxis

a) Summary

1) The occurrence of anaphylaxis has been documented in postmarketing paroxetine reports (Prod Info Paxil(R), 2002e); (Prod Info Paxil CR(TM), 2002).

3.3.7.A.2 Immune hypersensitivity reaction, Delayed

a) Summary

1) CASE REPORT - A 63-year-old woman, with a history of arterial hypertension and major depression, who was treated with atenolol and hydrochlorothiazide (for 3 years) and paroxetine (for 18 months), developed abdominal pain associated with intermittent fever, vomiting, and constipation. Laboratory tests showed leucocytosis, eosinophilia, monocytosis, lymphopenia, normocytic anemia, and hypoalbuminemia. Exploratory laparotomy revealed a gelatin-like abdominal fluid and a fibrotic omentum, which, on biopsy, showed massive infiltrates of eosinophils and mononuclear cells. During treatment with hydrocortisone 750 milligrams for 2 days, the fever, eosinophilia, and pain disappeared , only to recur. Atenolol and paroxetine were discontinued. Symptoms resolved with a 6-week course of oral prednisone. Three months later, drug hypersensitivity testing showed a positive reaction to paroxetine in the interferon-gamma release test in vitro and to atenolol in a histamine release test. At one year, there had been no relapse. The authors concluded that the delayed-type hypersensitivity was probably cause by paroxetine (Rozin et al, 2000).

3.3.7.A.3 Immunology finding

a) Anaphylaxis and delayed hypersensitivity have been reported with paroxetine therapy.

3.3.8 Musculoskeletal Effects

3.3.8.A Paroxetine Hydrochloride

Arthralgia

Arthritis

Arthropathy

Bursitis

Fracture of bone

Fracture of bone, Nonvertebral

Myositis

Osteoporosis

Spasm

Summary

Tenosynovitis

3.3.8.A.1 Arthralgia

a) Incidence: 1% or greater (Prod Info PAXIL(R) oral tablets, suspension, 2009)

b) Arthralgia was reported in at least 1% of patients exposed to multiple doses of paroxetine (n=9089) in clinical trials; a causal relationship cannot be determined (Prod Info PAXIL(R) oral tablets, suspension, 2009).

3.3.8.A.2 Arthritis

a) Incidence: 0.1% to 1% (Prod Info PAXIL(R) oral tablets, suspension, 2009)

b) Arthritis was reported in 0.1 to 1% of patients exposed to multiple doses of paroxetine (n=9089) in clinical trials; a causal relationship cannot be determined (Prod Info PAXIL(R) oral tablets, suspension, 2009).

3.3.8.A.3 Arthropathy

a) Incidence: 0.1% to 1% (Prod Info PAXIL(R) oral tablets, suspension, 2009)

b) Arthrosis was reported in 0.1 to 1% of patients exposed to multiple doses of paroxetine (n=9089) in clinical trials; a causal relationship cannot be determined (Prod Info PAXIL(R) oral tablets, suspension, 2009).

3.3.8.A.4 Bursitis

a) Incidence: less than 0.1% (Prod Info PAXIL(R) oral tablets, suspension, 2009)

b) Bursitis was reported in fewer than 0.1% of patients exposed to multiple doses of paroxetine (n=9089) in clinical trials; a causal relationship cannot be determined (Prod Info PAXIL(R) oral tablets, suspension, 2009).

3.3.8.A.5 Fracture of bone

a) In a case-control study including fracture cases (n=124,655) during the year 2000 and age- and gender-matched controls (n=373,962), there was an increased risk of any fracture in participants who were using an average standard daily dose of paroxetine (adjusted odds ratio (OR), 1.21; 95% CI, 1.1 to 1.33) compared to those who were not exposed to paroxetine. Paroxetine use was associated with an increased risk of hip fracture (adjusted OR, 1.39; 95% CI, 1.04 to 1.84) and forearm fracture (adjusted OR, 1.64; 95% CI, 1.28 to 2.11), but not spine fracture (adjusted OR, 1.38; CI, 0.8 to 2.4) (Vestergaard et al, 2008).

b) In a population-based, randomly selected, prospective cohort study adjusted for potential covariates, an increased risk of fragility fracture was reported at the 5-year follow-up in patients 50 years of age and older who used daily SSRIs (n=137; mean age of 65.1 years), including paroxetine, compared with those who did not use an SSRI (n=4871; mean age of 65.7 years). Daily SSRI use was associated with a significant 2.1-fold increased risk of fragility fracture (95% confidence interval (CI), 1.3 to 3.4). Daily dose of SSRI use was associated with a 1.5-fold increased risk of fragility fracture (95% CI, 1.1 to 2.1). Daily SSRI users who were recurrent (ie, treated with SSRIs at baseline and at 5-year follow-up) had a significant 2.1-fold increased risk of fragility fracture (95% CI, 1.1 to 4.0). Fractures were reported at the following sites: forearm (40%), ankle and foot (21%), hip (13%), rib (13%), femur (9%), and back (4%). None were reported at the skull, toes, or fingers (Richards et al, 2007).

3.3.8.A.6 Fracture of bone, Nonvertebral

a) In a prospective, population-based, cohort study (n=7983) with a mean follow-up of 8.4 years, there was an increased risk of nonvertebral fracture in adult participants older than 55 years of age (mean age of 77.5 years) who were currently using an SSRI (citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, or sertraline) compared to those who were not exposed to antidepressants. Current SSRI use was associated with an increased risk of nonvertebral fracture (adjusted hazard ratio (HR), 2.35; 95% confidence interval (CI), 1.32 to 4.18) compared with no antidepressant use. Current SSRI use was also associated with an increased risk of nonvertebral fracture (adjusted HR, 2.07; 95% CI, 1.23 to 3.5) compared with past antidepressant use (n=1217). In addition, duration of SSRI use showed a 9% increase in fracture risk per extra month on an SSRI (95% CI, 3% to 16%; p for trend=0.004). Fractures of the hip (most frequent), wrist, humerus, and pelvis were reported (Ziere et al, 2008).

3.3.8.A.7 Myositis

a) Incidence: less than 0.1% (Prod Info PAXIL(R) oral tablets, suspension, 2009)

b) Myositis was reported in fewer than 0.1% of patients exposed to multiple doses of paroxetine (n=9089) in clinical trials; a causal relationship cannot be determined (Prod Info PAXIL(R) oral tablets,

suspension, 2009).

3.3.8.A.8 Osteoporosis

a) Incidence: less than 0.1% (Prod Info PAXIL(R) oral tablets, suspension, 2009)

b) Osteoporosis was reported in fewer than 0.1% of patients exposed to multiple doses of paroxetine (n=9089) in clinical trials; a causal relationship cannot be determined (Prod Info PAXIL(R) oral tablets, suspension, 2009).

3.3.8.A.9 Spasm

a) Incidence: less than 0.1% (Prod Info PAXIL(R) oral tablets, suspension, 2009)

b) Generalized spasm was reported in fewer than 0.1% of patients exposed to multiple doses of paroxetine (n=9089) in clinical trials; a causal relationship cannot be determined (Prod Info PAXIL(R) oral tablets, suspension, 2009).

3.3.8.A.10 Summary

a) Arthralgia, arthritis, arthrosis, bursitis, generalized spasm, myositis, osteoporosis, and tenosynovitis have been reported following paroxetine treatment (Prod Info PAXIL(R) oral tablets, suspension, 2009). Paroxetine use was associated with an increased risk of hip and forearm fracture, but not spine fracture in a case-control study (Vestergaard et al, 2008). An increased risk of fragility fracture has been reported in a prospective cohort study of SSRIs, including paroxetine (Richards et al, 2007). An increased risk of nonvertebral fracture has been reported in a prospective cohort study of SSRI use, including paroxetine, in adult participants older than 55 years of age (Ziere et al, 2008).

3.3.8.A.11 Tenosynovitis

a) Incidence: 0.1% to 1% (Prod Info PAXIL(R) oral tablets, suspension, 2009)

b) Tenosynovitis was reported in 0.1 to 1% of patients exposed to multiple doses of paroxetine (n=9089) in clinical trials; a causal relationship cannot be determined (Prod Info PAXIL(R) oral tablets, suspension, 2009).

3.3.9 Neurologic Effects

Paroxetine

Paroxetine Hydrochloride

3.3.9.A Paroxetine

3.3.9.A.1 Seizure

See Drug Consult reference: COMPARATIVE INCIDENCE OF SEIZURES FROM ANTIDEPRESSANTS

3.3.9.B Paroxetine Hydrochloride

Akathisia

Central nervous system depression

Chorea

Cognitive function finding

Confusion

Decreased serotonin level

Dizziness

EEG finding

Extrapyramidal sign

Headache

Impaired psychomotor performance

Paresthesia

Parkinson's disease

Restless legs syndrome

Seizure

Sleep walking disorder

Somnolence

Summary

Tetany

Tremor

3.3.9.B.1 Akathisia

a) Summary

1) In a retrospective review of a series of patients treated with paroxetine, akathisia was reported to occur at an incidence of 4% (Baldassano et al, 1996). In two of the reported cases, akathisia occurred within a week of initiation of paroxetine therapy (20 milligrams/day) in which the patients described feelings of inner restlessness, insomnia, and the inability to stay still. Akathisia resolved in both cases following the addition of propranolol (40 to 80 milligrams/day) (Baldassano et al, 1996; Adler & Angrist, 1995).

b) LITERATURE REPORTS

1) A 38-year-old man who had been treated with paroxetine 70 milligrams (mg) once daily for 2 years for obsessive-compulsive disorder developed a subjective inner restlessness. Three years earlier, he had a similar reaction shortly after starting pimozide treatment; pimozide was discontinued. Because of that previous experience, the current episode was diagnosed as TARDIVE AKATHISIA and attributed to paroxetine. Treatment with lorazepam 1 mg 3 times daily eliminated, within 4 days, the restlessness without further changes in medication (Boffa & Lofchy, 2000).

2) A 33-year-old man treated for depression with paroxetine 20 milligrams (mg) daily developed an intense restlessness in both legs which began as he was falling asleep. Restlessness of the arms and hands also appeared. Only physical exercise helped in relieving the symptoms. Due to the restless leg syndrome, he stopped treatment, and symptoms disappeared within days. Two months later, he presented with a recurrence of depression. Paroxetine 20 mg was restarted and resulted in improvement in depression; however, the nocturnal leg restlessness occurred with greater intensity. Treatment with paroxetine was continued for 3 months and then stopped. Restlessness of the legs disappeared after stopping paroxetine. This patient reported worsening when alcohol was consumed and also reported that his mother had experienced similar symptoms (Sanz-Fuentenebro et al, 1996).

3) Akathisia developed in a 63-year-old man treated with paroxetine 20 milligrams/day (Adler & Angrist, 1995). The Adverse Drug Reactions Advisory Committee has received several reports of akathisia (restlessness, constant need to pace), including one case which began 5 months after starting paroxetine and resolved on discontinuation of the drug (Anon, 1996).

3.3.9.B.2 Central nervous system depression

a) Summary

1) TIREDNESS, LETHARGY, and difficulty concentrating are commonly reported adverse effects of paroxetine therapy (Feighner et al, 1993)(Dunbar et al, 1993a); (Calghorn et al, 1992)(Rickels et al, 1989); (Laurson et al, 1985).

b) LITERATURE REPORTS

1) Profound psychomotor retardation developed in a mentally retarded 67-year-old woman taking paroxetine 20 milligrams/day (Lewis et al, 1993).

3.3.9.B.3 Chorea

a) Summary

1) Of 246 suspected cases of extrapyramidal reactions submitted to the Committee on Safety of Medicines in the United Kingdom, only 3 described chorea associated with paroxetine. The manufacturer has received only 12 reports of chorea from all countries where paroxetine is available. None of the previously reported cases occurred after the first dose (Fox et al, 1997).

b) LITERATURE REPORTS

1) A 42-year-old woman presented with choreiform movements of all 4 limbs and an inability to communicate after taking 1 dose of paroxetine 20 milligrams for depression. On examination, she also had oculogyric crisis, hypertension (220/120 mmHg), and tachycardia. Three doses of procyclidine 5 milligrams relieved symptoms after 30 minutes (Fox et al, 1997).

3.3.9.B.4 Cognitive function finding

a) Summary

1) Use of FLUOXETINE or PAROXETINE was not associated with degradation of cognitive function in depressed non-demented elderly patients (Cassano et al, 2002).

b) LITERATURE REPORTS

1) A 1-year course of FLUOXETINE or PAROXETINE did NOT have detrimental effects on cognitive function in depressed non-demented elderly patients; in fact, tests of cognition showed improved results after 1 year of treatment compared with baseline, according to a randomized, double-blind trial (n=242; mean age 75.4 years). Both active treatments were well tolerated, and both significantly reduced symptoms of depression. Memory, learning, and attention improved over the year of therapy, and improved scores were seen on the Mini-Mental State Exam (MMSE), the Blessed Information and Memory Test (BIMT), the Cancellation Task Test (CTT), the Clifton Assessment Schedule (CLAS), and the Wechsler Paired Word Test (WPW). Some parameters on the Buschke Selective Reminding Test (BSRT) were better treatment. Daily doses of fluoxetine were in the range of 20 to 60 mg, and paroxetine dosages ranged from 20 to 40 mg/day (Cassano et al, 2002).

3.3.9.B.5 Confusion

a) Summary

1) CONFUSION (1%) was reported during clinical trials with paroxetine (Prod Info Paxil(R), 2002e); (Prod Info Paxil CR(TM), 2002)(Dunbar, 1989; Rickels et al, 1989).

3.3.9.B.6 Decreased serotonin level

a) Summary

1) Serum serotonin concentrations decreased in 3 healthy volunteers following 1 to 2 weeks of paroxetine 10 to 25 milligrams/day. Pretreatment levels were 0.3 micrograms/milliliter (mcg/mL) in one subject and 0.1 mcg/mL in the other two. Serotonin levels decreased to 0.02 to 0.04 mcg/mL following treatment with paroxetine. A drug-free period of 3 to 4 weeks was necessary to return to pretreatment serum serotonin concentrations (Lund et al, 1979).

3.3.9.B.7 Dizziness

a) Summary

1) Dizziness (11% to 14%) was reported during clinical trials with paroxetine (Prod Info Paxil(R), 2002e); (Prod Info Paxil CR(TM), 2002)(Dunbar, 1989; Rickels et al, 1989). The incidence of dizziness is lower after treatment with paroxetine than amitriptyline (Kuhs & Rudolf, 1989a); (Lund et al, 1985).

3.3.9.B.8 EEG finding

a) Summary

1) At therapeutic doses paroxetine induces a decrease in delta and theta activity, and in increase in beta activity (McClelland & Raptopoulos, 1984).

3.3.9.B.9 Extrapyramidal sign

a) Summary

1) Extrapyramidal reactions, particularly dystonic reactions involving the face or mouth, appear to occur more frequently with paroxetine than with other serotonin reuptake inhibitors (Gerber & Lynd, 1998; Romanelli et al, 1996); (Anon, 1996). The majority of extrapyramidal reactions (EPRs) occur within the first few days to month of treatment. Therefore, careful monitoring for EPRs is recommended weekly during the first 4 weeks of treatment with selective serotonin reuptake inhibitors (SSRIs) and periodically thereafter. EPRs generally resolve within a few days after reducing the dose or stopping the SSRI (Caley, 1997; Gill et al, 1997).

b) LITERATURE REPORTS

1) Orolingual movements (intermittent facial movements, initially involving the tongue and lips) have been described as an adverse effect of selective serotonin reuptake inhibitors (SSRIs), including paroxetine (Gerber & Lynd, 1998); (Anon, 1996). BRUXISM has also been described as an adverse effect of paroxetine (Gerber & Lynd, 1998; Romanelli et al, 1996).

2) Extrapyramidal reactions (EPRs) including acute DYSTONIC REACTIONS, PARKINSONISM, NEUROLEPTIC MALIGNANT SYNDROME, and DYSKINESIAS were reported with 1 or more selective serotonin reuptake inhibitors (SSRI). The majority of case reports involve fluoxetine; however, all of the SSRIs were implicated in at least 1 EPR (Caley, 1997; Gill et al, 1997). Reactions occurred primarily in women (about 75%) possibly due to use of SSRIs for treating mental disorders common to women (ie, depression). In many, but not all, case reports, the dose of the SSRI was increased to the maximum recommended dose within 7 days or near maximum doses were used. The majority of reactions occurred within the first week or during the second to fourth week of treatment. Possible mechanisms by which SSRIs cause EPRs include: (1) Central serotonergic activity which inhibits dopaminergic activity resulting in clinically significant effects; and (2) Concurrent use of an SSRI and antipsychotic may cause EPRs by a pharmacokinetic interaction, a pharmacodynamic interaction, or a combination of the two (Caley, 1997).
3) TREATMENT - In a limited number of case reports, propranolol and/or benzodiazepines were used to treat akathisia; the dose of propranolol ranged from 40 to 90 milligrams (mg) daily, and the dose of clonazepam was 1.5 mg daily (Gill et al, 1997). In single case reports, dystonic reactions responded to an unspecified dose of intramuscular trihexyphenidyl or diphenhydramine 50 mg. Parkinsonism characterized by increasing rigidity and tremor frequently occurred with high doses of the SSRI or during concomitant treatment with a neuroleptic agent. In all cases, symptoms disappeared after reducing the dose or stopping the SSRI. In contrast to neuroleptic-induced dyskinesias including tardive dyskinesia, SSRI-induced dyskinesias resolve spontaneously over days to weeks after the SSRI is stopped (Gill et al, 1997).
4) A 35-year-old woman with early-onset parkinsonism developed worsening symptoms (tremor, rigidity, postural instability) after taking paroxetine 20 milligrams/day. Symptoms returned to baseline after discontinuing paroxetine (Jimenez-Jimenez et al, 1994).

3.3.9.B.10 Headache

a) Summary

1) Headache is reported in (18%) of patients with therapeutic paroxetine doses (Prod Info Paxil(R), 2002e); (Ohrberg et al, 1992)(Dunbar, 1989; Mertens & Pintens, 1988b; Laursen et al, 1985b). In clinical trials with Paxil CR(TM), headache (27%) was reported at an incidence higher than placebo (Prod Info Paxil CR(TM), 2002).

3.3.9.B.11 Impaired psychomotor performance

a) Summary

1) No significant effects on psychomotor performance have been observed in single- or multiple-dose studies with paroxetine in healthy subjects (Warrington et al, 1989b; McClelland & Raptopoulos, 1985). In 1 study, a significant increase in cerebrospinal fluid (CSF) threshold was observed with paroxetine, suggesting an alerting effect of the drug. In this study, amitriptyline reduced the CSF threshold, indicative of sedation (Warrington et al, 1989b). Recently, in a large retrospective review, it was found that nursing home patients treated with fluoxetine and other selective serotonin-reuptake inhibitors (SSRIs) including paroxetine and sertraline have an increased risk of falls compared to patients who are not on antidepressants (Thapa et al, 1998).

b) LITERATURE REPORTS

1) A retrospective chart review of 2428 nursing home residents treated with antidepressants assessed the incidence of falls before and after the initiation of antidepressant therapy. Results were then compared to those not treated (n=847). Antidepressant treatment included tricyclic antidepressants (TCAs; n=665), selective serotonin reuptake inhibitors (SSRIs) (n=612), and trazodone (n=304). The rate of falls for treated patients was higher than that for patients who were not treated, both before and after the initiation of antidepressant therapy. This suggests that nursing home patients with depression or related conditions are at a greater risk of falls than those without such conditions Patients on TCAs had the highest rate of falls, with an adjusted rate ratio of 2 (95% confidence interval (CI), 1.8 to 2.2). Next were the SSRIs with an adjusted rate ratio of 1.8 (1.6 to 2, p=0.001) and trazodone with a ratio of 1.2 (1 to 1.4, p less than 0.001). No significant differences in incidence were seen within different medications of the same class. It was, however, noted that patients receiving a dose of 20 milligrams (mg) daily of fluoxetine, or an equivalent dose of another SSRI, had a statistically significant increase in the incidence of falls than those receiving lower doses (Thapa et al, 1998).

3.3.9.B.12 Paresthesia

a) Summary

1) Paresthesia were reported in 4% of patients during clinical trials with paroxetine (Prod Info Paxil (R), 2002e); (Prod Info Paxil CR(TM), 2002)(Dunbar, 1989; Rickels et al, 1989).

b) LITERATURE REPORTS

1) Three women 22 to 29 years of age reported electric shock-like paresthesias of the face and head shortly after taking the first several doses of paroxetine 20 milligrams (mg). Each paroxysm lasted 5 to 15 seconds and occurred repeatedly for up to 5 minutes. The paresthesias ceased after 5 days; 2 of 3 patients continued taking paroxetine. Paroxetine was the only medication used by each patient; none of the women had other medical or neurologic diseases which may have caused

the paresthesias. Another author reported similar shock-like paresthesias which radiated from one region to another often ending in the limbs; these cases were reported in young males when paroxetine was stopped. This report is intended to alert health care providers that paroxetine may cause shock-like paresthesias upon initiation or discontinuation of therapy (Berigan et al, 1997).

3.3.9.B.13 Parkinson's disease

a) Summary

1) Paroxetine 10 to 20 milligrams/day did not aggravate parkinsonian symptoms in most of the Parkinson's disease patients treated for depression in a small prospective study. Thirteen of 65 patients stopped paroxetine treatment within 1 to 30 days because of adverse reactions, but only 2 patients experienced exacerbation of parkinsonian tremor (Tesei et al, 2000).

b) LITERATURE REPORTS

1) A case report indicates that paroxetine exacerbated a 35- year-old woman's parkinsonism (Jimenez-Jimenez et al, 1994). Following one month of therapy with paroxetine 20 milligrams/day, the patient experienced increased tremor, mild rigidity and postural instability. Upon discontinuation of paroxetine, the patient experienced marked improvement in her Parkinson's disease symptoms.

3.3.9.B.14 Restless legs syndrome

a) In a prospective, naturalistic study of patients (median age, 46 years; range, 18 to 87 years) treated with antidepressants, 24 of 271 (9%) subjects experienced new-onset restless leg syndrome (RLS) or worsening of preexisting RLS as a side effect related to treatment. Antidepressants included fluoxetine, paroxetine, citalopram, sertraline, escitalopram, venlafaxine, duloxetine, reboxetine, and mirtazapine. Mirtazapine led to a marked decline of RLS in 28% of subjects compared with reboxetine which had none. The other antidepressants showed RLS symptoms (newly occurred or deteriorated) at the rate of 5% to 10%. Subjects stated symptoms occurred early in treatment (median of 2.5 days, range 1 to 23 days) (Rottach et al, 2008).

b) CASE REPORT - A 48-year-old woman with a history of major depressive disorder developed restless legs syndrome (RLS) immediately after receiving paroxetine. Paroxetine 20 milligrams (mg) daily was initiated after discontinuing clomipramine 60 mg daily (taken for 5 years). At that time, she began to experience an unpleasant sensation in her legs during the night which was relieved by movement. After 3 weeks of therapy, paroxetine was replaced by citalopram 20 mg daily (progressively increased to 60 mg daily in 1 week). At that time, the unpleasant sensation in the legs dramatically worsened with symptoms occurring during each period of inactivity, extending to the arms after 1 week. At a psychiatric emergency unit, she presented with motor restlessness, nocturnal worsening of symptoms, association between the desire to move the limbs and paresthesia or dysesthesia, and worsening of symptoms during rest and partial relief with activity. A diagnosis of RLS induced by paroxetine and citalopram was made; the International Restless Leg Syndrome Study Group (IRLSSG) rating scale score was 30 (the maximum score is 40). After the discontinuation of citalopram, her RLS symptoms started to diminish after 3 days of therapy with bupropion 150 mg daily and sertraline 50 mg daily. She recovered completely after 3 weeks of therapy. The authors suggested that RLS could be a possible "dopamine-dependent side effect" of selective serotonin reuptake inhibitors (SSRIs). Amongst SSRIs, sertraline may provide the least risk of RLS by blocking dopamine reuptake and bupropion may correct dopaminergic dysfunction in RLS (Nader et al, 2007).

3.3.9.B.15 Seizure

a) Summary

1) The occurrence of STATUS EPILEPTICUS has been documented in paroxetine postmarketing reports (Prod Info Paxil(R), 2002e); (Prod Info Paxil CR(TM), 2002).

b) Incidence: rare

3.3.9.B.16 Sleep walking disorder

a) Summary

1) A 34-year-old HIV-positive woman developed somnambulism while being treated with paroxetine, and later with sertraline, for anxiety and depression. The initial 10-milligram (mg) daily dose of paroxetine was gradually increased over 2 weeks to 20 mg daily. Three days after achieving 20 mg/day, the woman began to sleepwalk up to 3 times per night, according to witnesses. The somnambulism disappeared completely 1 week after the daily dose was reduced to 10 mg. However, at 10 mg/day, she had a relapse of depression. Upon again increasing the dose to 20 mg/day, the sleepwalking reappeared. Paroxetine was discontinued and sertraline 50 mg/day was substituted. Four days after the sertraline dose was increased to 100 mg/day, she again began to sleepwalk. Her symptoms of depression and anxiety improved at that dose. She therefore continued sertraline 100 mg/day despite continuing somnambulism (Alao et al, 1999).

3.3.9.B.17 Somnolence

a) Summary

1) Somnolence (19% to 24%) was reported during clinical trials with paroxetine (Prod Info Paxil(R), 2002e); (Prod Info Paxil CR(TM), 2002)(Dunbar, 1989; Rickels et al, 1989).

b) LITERATURE REPORTS

1) A 38-year-old woman developed NARCOLEPSY 4 weeks after beginning paroxetine 20 milligrams/day. Symptoms resolved after paroxetine was discontinued and returned when it was resumed at 10 milligrams/day (Owley & Flaherty, 1994).

3.3.9.B.18 Summary

a) Akathisia, chorea, extrapyramidal reactions, paresthesias, psychomotor impairments, confusion, lethargy, central nervous system depression, headache, dizziness, mild electroencephalogram changes, sleep disorders, somnolence, tetany, tremors, and seizure activity have been reported with paroxetine therapy (Prod Info Paxil(R), 2002e); (Prod Info Paxil CR(TM), 2002)(Dunbar, 1989; Rickels et al, 1989).

3.3.9.B.19 Tetany

a) Incidence: rare (Prod Info Paxil(R), 2002e)

b) Tetany was reported rarely during premarketing evaluation of paroxetine (Prod Info Paxil(R), 2002e).

3.3.9.B.20 Tremor

a) Summary

1) Tremor is a commonly reported side effect (8% to 11%) in patients during therapeutic paroxetine use (Prod Info Paxil(R), 2002e; Dunbar et al, 1993a); (Feighner et al, 1993; Ohrberg et al, 1992)(Claghorn et al, 1992a; Dunbar, 1989); (Laurson et al, 1985). In clinical trials with Paxil(R) CR(TM), tremor (7%) was reported at an incidence higher than placebo (Prod Info Paxil CR(TM), 2002).

3.3.10 Ophthalmic Effects

3.3.10.A Paroxetine Hydrochloride

Anisocoria

Eye / vision finding

Glaucoma

Optic neuritis

3.3.10.A.1 Anisocoria

a) Summary

1) CASE REPORT - Unevenly dilated pupils (anisocoria) was reported in a 33-year-old woman who had been taking paroxetine 50 milligrams/day for 4 weeks (Barrett, 1994). The patient's outcome was not disclosed.

3.3.10.A.2 Eye / vision finding

a) Summary

1) BLURRED VISION has occurred in 5% of patients treated with paroxetine (Dunbar, 1989). MYDRIASIS has been observed in some studies (Raptopoulos et al, 1989b).

b) Glaucoma, optic neuritis, anisocoria, blurred vision and mydriasis have occurred with paroxetine therapy.

3.3.10.A.3 Glaucoma

a) Summary

1) Several cases of glaucoma have been reported with therapeutic paroxetine use. The proposed mechanism is a direct effect on the iris or ciliary body muscle via serotonergic or anticholinergic effects. Careful monitoring of older patients for anticholinergic side effects may be prudent even when the newer antidepressants are used (Bennett & Wyllie, 1999; Eke & Bates, 1997; Kirwan et al, 1997).

b) LITERATURE REPORTS

1) On 2 different occasions, acute angle-closure glaucoma developed 1 to 3 days after starting paroxetine. With the first episode, paroxetine 20 milligrams (mg) daily was started 3 days before glaucoma developed; this episode resolved spontaneously after the patient stopped taking paroxetine. Ocular pain, browache, and blurred vision began 1 day after paroxetine was restarted. Ocular examination revealed conjunctival congestion, a mid-dilated pupil, and an intraocular pressure of 61 millimeters mercury. She was admitted to the hospital for medical therapy, and she underwent laser peripheral iridotomy. Her recovery was uneventful, and she required no topical treatment (Bennett & Wyllie, 1999).

2) A 91-year-old woman developed eye pain, blurred vision, and a dry mouth after taking the first dose of paroxetine (dose not specified) for depression. Evaluation in the ophthalmology clinic revealed similar symptoms, dilated pupils, and an intraocular pressure (IOP) of 70 millimeters of mercury (mmHg) in each eye. Treatment consisted of acetazolamide 500 milligrams (mg) intravenously, pilocarpine 4% every 15 minutes, and timoptic 0.5% twice daily. The IOP decreased over 5 hours. After performing bilateral laser peripheral iridotomies, the IOP was 14 mmHg in each eye. No previous eye diseases or symptoms had been reported. This patient had mild congestive heart failure and osteoarthritis which were treated with a diuretic and acetaminophen. The authors suggest careful monitoring of older patients for anticholinergic side effects even when the newer antidepressants are used (Kirwan et al, 1997).

3) Glaucoma occurred 13 days after paroxetine 10 milligrams (mg) increased to 20 mg was started in an 84-year-old woman with depression. Her presenting symptoms included eye pain and redness with blurring of vision; ophthalmic examination revealed an intraocular pressure (IOP) of 40 millimeters of mercury. Paroxetine was stopped, and the IOP responded to standard medical therapy followed by laser iridotomy. The proposed mechanism is a direct effect on the iris or ciliary body muscle via serotonergic or anticholinergic effects (Eke & Bates, 1997).

3.3.10.A.4 Optic neuritis

a) Summary

1) The occurrence of optic neuritis has been documented in post marketing paroxetine reports (Prod Info Paxil(R), 2002e); (Prod Info Paxil CR(TM), 2002).

3.3.12 Psychiatric Effects

3.3.12.A Paroxetine Hydrochloride

Delirium

Depression, exacerbation

Hallucinations

Hypomania

Inappropriate laughter

Mania

Psychiatric sign or symptom

Sleep disorder

Suicidal thoughts

3.3.12.A.1 Delirium

a) Summary

1) CASE REPORT - A 39-year-old male treated for severe depression with paroxetine 20 milligrams daily and phenothiazines (promethazine 250 milligrams daily and perazine 200 milligrams daily) developed a delirium syndrome on the second day of treatment, possibly due to the combination of a serotonin reuptake inhibitor and phenothiazine derivative. The delirium cleared after discontinuation of the phenothiazines and addition of diazepam 10 milligrams daily to the paroxetine (Koenig et al, 1993).

3.3.12.A.2 Depression, exacerbation

a) Adult and pediatric patients who experience symptoms of anxiety, agitation, panic attacks, insomnia, irritability, hostility (aggressiveness), impulsivity, akathisia (psychomotor restlessness), hypomania, or mania may be at risk of worsening of their depression. This same concern applies to treating patients with other psychiatric and nonpsychiatric disorders. If these symptoms are observed, therapy should be reevaluated and it may be necessary to discontinue medications when symptoms are severe, sudden in onset, or were not part of the patient's initial symptoms (Anon, 2004).

3.3.12.A.3 Hallucinations

a) Incidence: infrequent (Prod Info PAXIL(R) oral tablets, oral suspension, 2006)
b) Hallucinations have been reported in 22 of 9,089 patients receiving immediate-release paroxetine compared with 4 of 3,187 receiving placebo in pooled clinical trials (Prod Info PAXIL(R) oral tablets, oral suspension, 2006).

3.3.12.A.4 Hypomania
a) Incidence: 0.3 to 2.2% (Prod Info PAXIL(R) oral tablets, oral suspension, 2006)
b) Hypomania or mania occurred in approximately 1% unipolar patients receiving paroxetine compared with 0.3% unipolar patients receiving placebo during premarketing testing. In a subset of patients classified as bipolar, the rate of manic episodes was 2.2% for paroxetine and 11.6% for the combined active control groups (Prod Info PAXIL(R) oral tablets, oral suspension, 2006).

3.3.12.A.5 Inappropriate laughter
a) Summary
1) A 52-year-old woman manifested unmotivated compulsive laughing 3 days after starting paroxetine 20 milligrams (mg) per day to treat anxiety and depression. The woman had schizoaffective disorder, which was being treated with clozapine 200 mg/day, lithium 1320 mg/day, and lorazepam 1 mg/day. She also had type 2 diabetes, which was controlled with metformin and glimepiride. Toxic plasma levels of lithium were corrected by lowering the lithium dose, but depression symptoms continued for 3 weeks after the correction and were therefore treated with paroxetine. The pathologic laughing that began after initiation of paroxetine treatment could be induced at any time of day. On day 5, paroxetine was withdrawn, and the laughter was no longer inducible the next day (Zullino et al, 2002).

3.3.12.A.6 Mania
a) Incidence: rare
b) Hypomania or mania occurred in approximately 1% unipolar patients receiving paroxetine compared with 0.3% unipolar patients receiving placebo during premarketing testing. In a subset of patients classified as bipolar, the rate of manic episodes was 2.2% for paroxetine and 11.6% for the combined active control groups (Prod Info PAXIL(R) oral tablets, oral suspension, 2006).

3.3.12.A.7 Psychiatric sign or symptom
a) Summary
1) NERVOUSNESS (5% to 9%) and ANXIETY (5%) were reported during clinical trials with paroxetine (Prod Info Paxil(R), 2002e); (Prod Info Paxil CR(TM), 2002)(Dunbar, 1989; Rickels et al, 1989).
b) Paroxetine therapy has been associated with anxiety, nervousness, delirium and suicidal ideation.

3.3.12.A.8 Sleep disorder
a) Summary
1) Sleep disturbance is common with therapeutic paroxetine doses (Ohrberg et al, 1992)(Claghorn et al, 1992a; Laursen et al, 1985b). In clinical trials with Paxil CR(TM), INSOMNIA (17%) were reported at an incidence higher than placebo (Prod Info Paxil CR(TM), 2002).
b) LITERATURE REPORTS
1) In 12 volunteers paroxetine increased the time required to achieve rapid eye movement (REM) sleep, decreased the proportion of sleep spent as REM sleep, increased the number of awakenings and reduced total sleep (Oswald & Adam, 1986).

3.3.12.A.9 Suicidal thoughts
a) Summary
1) Adult and pediatric patients being treated with antidepressants for major depressive disorder who experience symptoms of anxiety, agitation, panic attacks, insomnia, irritability, hostility (aggressiveness), impulsivity, akathisia (psychomotor restlessness), hypomania, or mania may be at risk of suicidal ideation and behavior (suicidality). This same concern applies to treating patients with other psychiatric and nonpsychiatric disorders. If these symptoms are observed, therapy should be reevaluated and it may be necessary to discontinue medications when symptoms are severe, sudden in onset, or were not part of the patient's initial symptoms. Patients and their caregivers should be provided with the Medication Guide that is available for this drug (Anon, 2004; Anon, 2004).
2) A causal role for antidepressants in inducing suicidality has been established in pediatric patients. Anyone considering the use of antidepressants in a child or adolescent must balance this risk with the clinical need. In pooled analyses of 24 short-term, placebo-controlled trials of nine antidepressants (citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, bupropion, mirtazapine, nefazodone, and venlafaxine extended-release) including over 4400 pediatric patients with major depressive disorder, obsessive compulsive disorder, or other psychiatric disorders, a greater risk of suicidal behavior or ideation during the first few months of therapy was demonstrated in patients receiving antidepressants as compared with placebo (4% vs 2%, respectively). The risk of suicidality was most consistently observed in the trials that included patients with major depressive

disorder, but there were signs of risk emerging from trials in other psychiatric indications, such as obsessive compulsive disorder and social anxiety disorder. No suicides occurred in these trials. The risk of suicidality during longer-term use (ie, beyond several months) in pediatric patients is not known. It is also unknown whether this risk extends to adult patients (Anon, 2004).

b) Incidence: rare

3.3.13 Renal Effects

3.3.13.A Paroxetine Hydrochloride

Kidney finding

Renal failure

Urogenital finding

3.3.13.A.1 Kidney finding

a) Summary

1) URINARY HESITANCY (3%), URINARY FREQUENCY (3%), and URINARY TRACT INFECTION (2%) were reported during clinical trials (Prod Info Paxil(R), 2002e); (Prod Info Paxil CR(TM), 2002; Feighner et al, 1993; Ohrberg et al, 1992).

3.3.13.A.2 Renal failure

a) Summary

1) The occurrence of ACUTE RENAL FAILURE has been documented in postmarketing paroxetine reports (Prod Info Paxil(R), 2002e); (Prod Info Paxil CR(TM), 2002).

3.3.13.A.3 Urogenital finding

a) Urinary infections, frequency, hesitancy, sexual dysfunction, priapism and eclampsia have been noted with therapeutic paroxetine use. Acute renal failure has also been reported.

3.3.14 Reproductive Effects

Paroxetine

Paroxetine Hydrochloride

3.3.14.A Paroxetine

3.3.14.A.1 Sexual dysfunction

See Drug Consult reference: DRUG-INDUCED SEXUAL DYSFUNCTION
See Drug Consult reference: SELECTIVE SEROTONIN REUPTAKE INHIBITOR-INDUCED SEXUAL DYSFUNCTION

3.3.14.B Paroxetine Hydrochloride

Eclampsia

Priapism

Sexual dysfunction

3.3.14.B.1 Eclampsia

a) Summary

1) The occurrence of eclampsia has been documented in paroxetine postmarketing reports (Prod Info Paxil(R), 2002e); (Prod Info Paxil CR(TM), 2002).

3.3.14.B.2 Priapism

a) Summary

1) CASE REPORT - Priapism was reported in a 58-year-old man after receiving paroxetine 20

milligrams/day for depression. The length of therapy was not disclosed. The patient presented with a painful erection which lasted for 42 hours. Paroxetine was discontinued and the patient experienced complete recovery over the next 8 hours; rechallenge was not attempted (Ahmad, 1995).

3.3.14.B.3 Sexual dysfunction

a) Summary

1) EJACULATORY DISTURBANCES (13% to 28%) or ANORGASMIA (10%), ERECTILE DIFFICULTIES (10%), DELAYED ORGASM (10%), and IMPOTENCE (5% to 10%) were reported in males during clinical trials. Anorgasmia and difficulty reaching climax/orgasm were reported in 2% of women treated with paroxetine. Decreased libido was also reported in 3% to 12% of patients (Prod Info Paxil(R), 2002e); (Feighner et al, 1993)(Anon, 1993; Claghorn et al, 1992a). Abnormal ejaculation (26%), anorgasmia or delayed orgasm (in women; 10%), and decreased libido (7%) occurred at a higher incidence than placebo in clinical trials of Paxil CR(TM) (Prod Info Paxil CR (TM), 2002).

3.3.15 Respiratory Effects

3.3.15.A Paroxetine Hydrochloride

Lung finding

Pharyngitis

Respiratory finding

Yawning

3.3.15.A.1 Lung finding

a) Summary

1) The occurrence of PULMONARY HYPERTENSION and ALLERGIC ALVEOLITIS have been documented in postmarketing paroxetine reports (Prod Info Paxil(R), 2002e); (Prod Info Paxil CR (TM), 2002).

3.3.15.A.2 Pharyngitis

a) Summary

1) In data from the manufacturer involving 2683 paroxetine patients, pharyngitis and RHINITIS were each reported in 2% of patients treated (Dunbar, 1989).

3.3.15.A.3 Respiratory finding

a) Pharyngitis, rhinitis, pulmonary hypertension and allergic alveolitis have been noted with paroxetine therapy.

3.3.15.A.4 Yawning

a) Incidence: 4% (Prod Info Paxil(R), 2002e)

b) Yawning (4%) was reported during clinical trials with paroxetine (Prod Info Paxil(R), 2002e; Dunbar, 1989; Rickels et al, 1989).

1) Excessive daytime yawning, not associated with sedation or drowsiness, occurred in 2 women after starting paroxetine for panic disorder. In both cases they were well rested, the frequency was greatest in the morning, and the yawning completely resolved with a dose reduction or discontinuation of paroxetine. In the first case, a 21-year-old woman experienced excessive yawning, despite adequate sleep, 1 day after starting paroxetine 10 mg/day. The frequency of yawning decreased when the dose was reduced to 5 mg/day and completely resolved when paroxetine was discontinued. In the second case, a 43-year-old woman started on 10 mg/day and the dose was increased 2 weeks later to 20 mg/day. Within 1 day of increasing the dose the excessive yawning commenced. After 7 days, the dose was reduced to 10 mg/day and the yawning completely resolved (Harada, 2006)

3.3.16 Other

Paroxetine

Paroxetine Hydrochloride

3.3.16.A Paroxetine

3.3.16.A.1 Drug withdrawal

See Drug Consult reference: WITHDRAWAL SYNDROME OF SELECTIVE SEROTONIN REUPTAKE INHIBITORS

3.3.16.B Paroxetine Hydrochloride

Serotonin syndrome

Withdrawal sign or symptom

3.3.16.B.1 Serotonin syndrome

a) Summary

1) Serotonin syndrome, including life-threatening cases, or neuroleptic malignant syndrome (NMS)-like reactions have been reported with the use of paroxetine alone. Signs and symptoms of serotonin syndrome include mental status changes (eg, agitation, hallucination, coma), autonomic instability (eg, tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (eg, hyperreflexia, incoordination) and/or gastrointestinal symptoms (eg, nausea, vomiting, diarrhea). Severe serotonin syndrome can resemble NMS with symptoms including hyperthermia, muscle rigidity, autonomic instability with possible rapid fluctuation of vital signs, and mental status changes. Serotonin syndrome occurs most commonly with the concomitant use of serotonergic drugs, including triptans, with drugs that impair metabolism of serotonin, including MAOIs, or with antipsychotics or other dopamine antagonists (Prod Info PEXEVA(R) oral tablets, 2009; Prod Info PAXIL(R) oral tablets, suspension, 2009; Prod Info PAXIL CR(R) controlled-release oral tablets, 2009). Serotonin syndrome is produced most often following the concurrent use of paroxetine (an SSRI) with another drug that enhances central nervous system serotonin activity. This syndrome is characterized by alterations in cognition, behavior, autonomic nervous system function, and neuromuscular activity. The difference between serotonin syndrome and the occurrence of adverse effects due to paroxetine alone is the clustering of the signs and symptoms, their severity, and duration (Lane & Baldwin, 1997). Some drugs that may enhance central nervous system serotonin activity include: moclobemide, selegiline, tramadol, nefazodone, trazodone, dextromethorphan, phentermine, fenfluramine, lithium, tryptophan, and irreversible monoamine oxidase inhibitors. Any of these drugs taken in combination with paroxetine may result in serotonin syndrome (Mitchell, 1997).

b) LITERATURE REPORTS

1) A patient with psychotic depression who received concomitant risperidone and paroxetine developed serotonin syndrome. Within 2 hours of increasing the dosage of paroxetine to 40 mg per day and risperidone to 6 mg per day, the patient developed ataxia, tremor, shivering, and bilateral jerking movements. He presented to the emergency department and was admitted to the hospital; he was difficult to arouse and had a depressed mood with prominent psychomotor agitation. He reported auditory hallucinations; he was oriented only to year and location. On neurologic examination, he was hyperreflexic and had involuntary jerking movements but had no muscular rigidity. Within 2 days of stopping both medicines, his sensorium was clear. After appropriate laboratory and diagnostic tests for neuromuscular malignant syndrome, recurrent psychotic depression, and drug overdose, the authors believed this case represented serotonin syndrome and was due to the combination of risperidone and paroxetine. The patient responded well to the combination of nortriptyline, haloperidol, and diphenhydramine and had no adverse effects (Hamilton & Malone, 2000a).

2) A 51-year-old woman with bipolar affective disorder developed a serotonin syndrome 2 days after a 6-month course of nefazodone was stopped and 1 day after paroxetine 20 mg was started. The patient became agitated and incoherent; family members found her unresponsive with shaking movements of her arms and legs. Upon admission to the hospital, the patient was in a coma and required mechanical ventilation; her temperature rose to 102.2 degrees F; muscle rigidity was present with an elevated creatine kinase value of 20,520 units/L. Treatment consisted of a cooling blanket, sedation with propofol up to 1.5 mg/kg/hour, and dantrolene 1.5 mg/kg. Symptoms resolved, and she was extubated on day 3. Medications started 1 day before this reaction included paroxetine 20 mg daily, valproic acid 250 mg three times a day, and zopiclone 7.5 mg daily, a short-acting sedative. Rechallenge 7 days after stopping nefazodone with paroxetine 20 mg daily did NOT result in recurrence of symptoms (John et al, 1997b).

3) A 29-year-old woman developed agitation, difficulty concentrating, hyperreflexia, tremor, choreiform movements, diaphoresis, shivering, and loose stools 24 hours after paroxetine 20 mg/day was added to her regimen of trazodone 50 mg at night (Reeves & Bullen, 1995b).

4) A 51-year-old man taking diltiazem, nitroglycerin, ticlopidine, piroxicam, ranitidine, diazepam

and paroxetine developed serotonin syndrome two days after beginning a cold medication containing acetaminophen, doxylamine succinate, pseudoephedrine and dextromethorphan. Effects included hypertension, headache, confusion, tachycardia, tachypnea, shortness of breath, vomiting, increased muscle tone, rigidity, clonus, and a metabolic acidosis. Clinical presentation was felt to be due to serotonin syndrome which was most likely induced by the combination of paroxetine and dextromethorphan (Skop et al, 1994b).

3.3.16.B.2 Withdrawal sign or symptom

a) Summary

1) It is recommended that paroxetine dosage be reduced gradually when treatment is going to be discontinued. In some clinical trials paroxetine was decreased by 10 milligrams (mg) per day at weekly intervals. When a daily dose of 20 mg/day was reached, patients were continued on this dose for 1 week before treatment was stopped. If intolerable symptoms occur following a reduction in dose or upon discontinuation of treatment, then resuming the previously prescribed dose maybe be considered. Decreasing the dose at a more gradual rate is then recommended (Prod Info Paxil (R), 2002e); (Prod Info Paxil CR(TM), 2002).

2) A hyposerotonergic state has been suggested to explain selective serotonin reuptake inhibitor (SSRI) withdrawal symptoms. These symptoms typically occur two days after the last dose taken and continue for an average of 10 days. The symptoms are nonspecific and include dizziness, paresthesia, tremor, anxiety, nausea, and emesis (Stiskal et al, 2001; Price et al, 1996)

3) Sweating, dizziness, insomnia, headache, anxiety, fatigue, delirium tremor, confusion and sensory disturbance have been reported after abrupt withdrawal of paroxetine (Hayakawa et al, 2004; Anon, 1993; Zajecka et al, 1997). Children may experience withdrawal symptoms within a shorter time after abruptly stopping paroxetine due to their higher rate of drug metabolism (Diler et al, 2000). Vertigo, nausea, vomiting, diarrhea, fatigue and gait instability have been reported in patients whose paroxetine dose was tapered over 7 to 10 days (Barr et al, 1994). Other effects reported after paroxetine withdrawal include anorexia, nausea, vomiting, diarrhea, shaking chills, agitation, abdominal discomfort, and sensations like electric shocks (Frost & Lal, 1995; Phillips, 1995; Pyke, 1995).

b) LITERATURE REPORTS

1) ADULT

a) A 73-year-old woman developed delirium following the abrupt cessation of paroxetine therapy. The patient had been taking paroxetine for 2 months at a daily dose of 40 milligrams (mg) when she abruptly stopped the medication prior to undergoing left-side donor nephrectomy. Two hours following surgery, the patient suddenly developed symptoms of thirst and dizziness and then gradually exhibited symptoms of disorderly behavior. Etizolam (1 mg) and alprazolam (0.8 mg) were administered; however, the patient remained agitated and reported visual hallucinations. The woman was referred to a psychiatrist the next morning and was unable to follow verbal commands and was not fully oriented. Psychotic symptoms resolved on postoperative day 2 following the administration of tiapride hydrochloride (75 mg) and chlorpromazine (15 mg). While the authors do not attribute this reaction to the preoperative (diazepam, ranitidine) or anesthetic (thiopental, sevoflurane) medications, it is possible that these agents contributed to the patient's symptoms (Hayakawa et al, 2004).

2) PEDIATRIC

a) Twenty-four hours following the abrupt discontinuation of paroxetine (20 milligrams (mg) per day), a 9-year-old boy developed emesis, dizziness, drowsiness, headache, and fatigue. Paroxetine was restarted at the former dose and the patient's discontinuation symptoms resolved within 24 hours. An 11-year-old boy experienced discontinuation symptoms of headache, poor concentration, nausea, dizziness, drowsiness, and fatigue, 30 hours after stopping paroxetine 10 mg/day. Reinstitution of paroxetine at 10 mg/day resulted in resolution of withdrawal symptoms within 12 hours. A 10-year-old girl who was taking paroxetine 15 mg twice daily developed mild discontinuation symptoms 48 hours after stopping her morning dose. Once the paroxetine morning dose was restarted her withdrawal symptoms lessened in 12 hours and resolved completely within 48 hours (Diler & Avci, 2002)

b) Signs of withdrawal in a healthy, premature infant on day 3 after birth were attributed to the paroxetine (40 milligrams per day) taken by her mother before and throughout pregnancy. Finnegan scores (a behavior scale for neonatal withdrawal reactions) from day 1 to day 10 were 0, 0, 2, 2, 9, 9, 6, 6, 7, and 7. The baby was lethargic, irritable, hypertonic, and jittery. There were no signs of infection, and screenings for opiates were negative. Cerebral ultrasound and electroencephalogram were normal. The baby improved spontaneously, with a Finnegan score of 0 at day 13. Follow-up at 4.5 months showed normal neurological maturity (Nijhuis et al, 2001).

c) Paroxetine exposure in utero, with maternal doses ranging from 20 to 120 milligrams per day, has resulted in a neonatal withdrawal syndrome. Effects included jitteriness, vomiting, irritability, hypoglycemia, and necrotizing enterocolitis. It was speculated that paroxetine, which causes inhibition of muscarinic-type cholinergic receptors, when withdrawn may result in cholinergic rebound in neonates (Stiskal et al, 2001).

d) Some investigators have speculated that neonates actually experience serotonin

syndrome, due to time course and symptoms, as opposed to a neonatal paroxetine withdrawal syndrome Ibister et al 2001.

3.4 Teratogenicity/Effects in Pregnancy/Breastfeeding

A) Teratogenicity/Effects in Pregnancy

1) U.S. Food and Drug Administration's Pregnancy Category: Category D (Prod Info PAXIL(R) oral tablets, suspension, 2008) (All Trimesters)

a) There is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (e.g., if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective).

2) Australian Drug Evaluation Committee's (ADEC) Category: D(Australian Government Department of Health and Ageing Therapeutic Goods Administration, 2006)

a) Drugs which have caused, are suspected to have caused, or may be expected to cause an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details.

See Drug Consult reference: PREGNANCY RISK CATEGORIES

3) Crosses Placenta: Yes

4) Clinical Management

a) When used in the third trimester, the incidence of complications, primarily respiratory distress, was significantly higher when compared to women who took paroxetine in early pregnancy and women who took nonteratogenic medications (Costei et al, 2002). The use of SSRIs, including paroxetine, after 20 weeks of gestation has been associated with an increased risk of persistent pulmonary hypertension of the newborn (Chambers et al, 2006). A study of prospectively collected data suggests antenatal use of selective serotonin-reuptake inhibitor (SSRI) antidepressants is associated with QTc interval prolongation in exposed neonates (Dubnov-Raz et al, 2008). A significantly greater risk of congenital malformations were observed in infants exposed to paroxetine compared to other antidepressants (Cole et al, 2007). There was no significant association between the use of SSRIs in early pregnancy and the risks of birth defects, including congenital heart defects, according to a later population-based case-control study (Alwan et al, 2007). One study found that first trimester paroxetine exposure was associated with major congenital and cardiac malformations in newborns only at doses greater than 25 mg/day (Berard et al, 2007). There is also evidence that paroxetine use during pregnancy is associated with neonatal withdrawal syndrome and convulsions in the neonate (Sanz et al, 2005). The manufacturer recommends either discontinuing paroxetine therapy or switching to another antidepressant unless the benefits of paroxetine to the mother justify continuing treatment. For women intending to become pregnant or those already in their first trimester, paroxetine should be initiated only after other treatment options have been given thorough consideration (Prod Info PAXIL(R) oral tablets, suspension, 2008; Prod Info PAXIL CR(R) controlled-release oral tablets, 2008).

5) Literature Reports

a) A study of prospectively collected data suggests antenatal use of selective serotonin-reuptake inhibitor (SSRI) antidepressants is associated with QTc interval prolongation in exposed neonates. Between January 2000 and December 2005, researchers compared 52 neonates exposed to SSRI antidepressants (paroxetine (n=25), citalopram (n=13), fluoxetine (n=12), fluvoxamine (n=1), and venlafaxine (n=1)) in the immediate antenatal period to 52 matched neonates with no exposure. Prolonged QTc is defined as an interval of greater than 460 milliseconds (msec) (the widely used upper limit cited by authorities in both pediatric cardiology and neonatology). A pediatric cardiologist blinded to drug exposure, interpreted all electrocardiograms (ECGs) using standard statistical analyses. ECG recordings revealed markedly prolonged mean QTc intervals in exposed neonates compared to unexposed neonates (mean; 409 +/- 42 msec versus 392 +/- 29 msec, p=0.02). The mean uncorrected QT interval was 7.5% longer among exposed neonates (mean; 280 +/- 31 msec versus 261 +/- 25 msec, p less than 0.001). Ten percent (n=5) of exposed neonates had a notable increase in QTc interval prolongation (greater than 460 msec) compared to none of the unexposed neonates. The longest QTc interval observed was 543 msec (Dubnov-Raz et al, 2008).

b) Data from the case-controlled National Birth Defects Prevention Study (NBDPS), which included data from 13,714 infants born between 1997 and 2002, indicated that early maternal exposure (defined as treatment with any SSRI from 1 month before to 3 months after conception) to SSRIs was associated with anencephaly in 9 exposed infants out of 214 (adjusted odds ratio (OR), 2.4; 95% confidence interval (CI), 1.1 to 5.1; P=0.02), craniosynostosis in 24 exposed infants out of 432 (adjusted OR 2.5; 95% CI, 1.5 to 4.0; P less than 0.001), and omphalocele in 11 exposed infants out of 181 (adjusted OR 2.8; 95% CI, 1.3 to 5.7; P=0.005). However, early exposure did not significantly increase the risks of congenital heart defects or most other birth defects. The most commonly used SSRIs reported by control mothers were sertraline, fluoxetine, paroxetine, and citalopram (Alwan et al, 2007).

c) First-trimester paroxetine exposure is not associated with an increase in infant cardiovascular defects, according to an international retrospective epidemiological study. In unpublished studies, cardiovascular malformations were reported in 0.7% of 1174 infants exposed to paroxetine and in 0.7% of 1174 infants with no exposure to antidepressants or teratogenic agents (95% confidence interval (CI), 0.36 to 2.78). In an analysis of 5 published database studies including 2061 cases, the rate of cardiovascular malformations in paroxetine-exposed infants was 1.5%. When combined, the mean cardiovascular malformation rate in paroxetine-exposed infants was 1.2% (95% CI, 1.1 to 2.1) (Einarson et al, 2008).

d) Paroxetine doses above 25 mg/day are associated with major congenital and cardiac malformations in

infants exposed during the first trimester of pregnancy, according to a population-based registry analysis including 1403 women. Based on results from 2 nested case-control studies of 101 infants with major congenital malformations (including 24 with cardiac malformations), exposure to paroxetine (95% confidence interval (CI), 0.49 to 3.92) or other SSRIs (95% CI, 0.28 to 2.84) did not increase the risk of malformations compared to non-SSRI antidepressants when given at doses less than 25 mg/day. Adjusted analysis showed that infants exposed to paroxetine during the first trimester at doses greater than 25 mg/day had a 3-fold greater risk of major cardiac malformations (95% CI, 1 to 9.42) and more than 2-fold greater risk of major congenital malformations (95% CI, 1.19 to 4.17) (Berard et al, 2007).

e) Fetal exposure to paroxetine during the first trimester resulted in a higher incidence of malformations compared with exposure to other antidepressants, according to a population-based cohort study including 815 infants among 791 women exposed to paroxetine monotherapy, 1020 infants among 989 women exposed to paroxetine mono- or polytherapy, 4198 infants among 4072 women exposed to other antidepressant monotherapy, and 4936 infants among 4767 women exposed to other antidepressant mono- or polytherapy. A significantly increased risk of all congenital malformations and a nonsignificantly increased risk of cardiovascular malformations were observed in infants exposed to paroxetine compared with other antidepressants in monotherapy (89% and 46%, respectively) and mono- or polytherapy groups (76% and 68%, respectively) (Cole et al, 2007).

f) A case-control study found that the use of SSRIs after 20 weeks of gestation was associated with an increased risk of persistent pulmonary hypertension of the newborn (PPHN). Fluoxetine, paroxetine, and sertraline were the specific SSRIs studied to carry this increased risk. A total of 377 women who had infants with PPHN were matched to 836 women and their infants. Assessment of exposure was determined by telephone interview within 6 months of birth. After adjusting for other covariates, SSRI use after 20 weeks of gestation was associated with an odds ratio of 6.1 (95% CI 2.2 to 16.8; p=0.001) of delivering an infant with PPHN relative to no use during the pregnancy. SSRI use before 20 weeks of gestation and non-SSRI antidepressants use at any gestation time was not associated with increased risk of PPHN development. The incidence of PPHN in the general population is about 0.1 to 0.2%. According to this study, infants exposed to SSRIs after 20 weeks of gestation have a PPHN incidence of 0.6 to 1.2% (Chambers et al, 2006).

g) A population-based study of 1782 pregnant women exposed to SSRIs found no increased risk of adverse perinatal outcome except for treatment in the neonatal intensive or special care unit, particularly with third trimester exposure. Using 1996 to 2001 data derived from a government project involving 4 birth or medication registries in Finland, women who had at least one purchase (a 3-months supply) of an SSRI during the period of one month before pregnancy and the day pregnancy ended were compared to 1782 controls with no reimbursed drug purchases during the same peripartum period. The mean age of both cohorts was 30 years (+/-7). There were more than twice as many smokers and 6 times as many pregnancies induced by artificial reproductive techniques in the SSRI group compared to controls (p less than 0.001), and mean length of gestation and birth weight were lower (p less than 0.001) in the SSRI group. Malformations, however, were not more common in the SSRI group (p=0.4). Purchases of SSRIs (citalopram, fluoxetine, paroxetine, sertraline and fluvoxamine) were more common in the first trimester than later in pregnancy, with 152 women purchasing paroxetine during the first trimester, 54 during the second trimester, 64 during the third, and 28 throughout pregnancy. When compared to first trimester exposure, treatment in a special or intensive care unit was more common for the infants exposed during the third trimester (11.2% and 15.7%, respectively; p=0.009). Even after adjusting for confounding variables, this difference remained statistically significant (OR 1.6; 95% CI 1.1 to 2.2) (Malm et al, 2005).

h) Data recorded through the Swedish national registry included infants of 6896 women treated with antidepressants in early pregnancy, 5123 of whom were exposed to SSRIs. Paroxetine exposure occurred in 815, and these infants had an increased risk of cardiovascular malformations (primarily ventral and atrial septal defects) compared to the aggregate registry population (OR 1.8; 95% CI: 1.1 to 2.8). The corresponding rate of cardiovascular complications in these infants was 2%, compared to 1% in the aggregate registry population. Using data supplied by the US United Healthcare, a separate retrospective study evaluated 5956 infants of women dispensed paroxetine (n=815) or other antidepressants during the first trimester. Compared to other antidepressants, the data trended towards an increased risk for cardiovascular malformations for paroxetine (OR 1.5; 95% CI: 0.8 to 2.9). Following first trimester dispensing, the prevalence of cardiovascular malformations was 1.5% for paroxetine (9 of 12 infants with ventral septal defects) compared to 1% for the other antidepressants. Compared to other antidepressants, there appeared to be an increased risk of overall major congenital malformations, including cardiovascular defects, for paroxetine (OR 1.8; 95% CI: 1.2 to 2.8). With first trimester exposure, the prevalence of all congenital malformations was 4% for paroxetine and 2% for other antidepressants (Prod Info PAXIL(R) oral tablets, suspension, 2008; Prod Info PAXIL CR(R) controlled-release oral tablets, 2008).

i) Third-trimester paroxetine exposure is associated with neonatal distress, according to a prospective, controlled cohort study including 55 neonates. The pregnant women studied were taking between 10 mg and 60 mg of paroxetine daily. Data showed that 12 of 55 neonates exposed to paroxetine in late gestation had complications necessitating intensive treatment and prolonged hospitalization. A comparison group of 27 women treated with paroxetine (10 mg to 40 mg/day) in their first or second trimester and 27 women exposed to nonteratogenic agents (eg, acetaminophen or dental x-rays) were matched for maternal age, gravity, parity, social drug use, and nonteratogenic drug use. Of the 12 infants experiencing complications, 9 had respiratory distress, 2 had hypoglycemia, and 1 had jaundice. Only 3 infants in the comparison group experienced complications, 2 with respiratory distress and 1 with jaundice (Costei et al, 2002).

B) Breastfeeding

1) American Academy of Pediatrics Rating: Drugs for which the effect on nursing infants is unknown but may be of concern. (American Academy of Pediatrics Committee on Drugs, 2001)

2) Thomson Lactation Rating: Infant risk is minimal.

a) The weight of an adequate body of evidence and/or expert consensus suggests this drug poses minimal risk to the infant when used during breastfeeding.

3) Clinical Management

a) Paroxetine is excreted into the breast milk of lactating women. Case reports suggest that the dose available to the infant through breast milk may be low and not of clinical significance (Hendrick et al, 2001; Begg et al, 1999; Ohman et al, 1999). However, the long-term effects on neuro behavior and development from exposure to paroxetine during a period of rapid CNS development have not been evaluated.

4) Literature Reports

a) Paroxetine is excreted in human milk. Caution is advised when administering paroxetine to a nursing woman (Prod Info PAXIL(R) oral tablets, suspension, 2008; Prod Info PAXIL CR(R) controlled-release oral tablets, 2008).

b) From a study of 75 lactating women exposed to antidepressants, 108 samples of paroxetine in breast milk were obtained and analyzed with a new assay system for determining antidepressant concentrations in breast milk. Concentrations of paroxetine ranged from less than 5 to 101 nanograms/mL; the assay system had a 2 nanograms/mL limit of detection (LOD) for paroxetine. The assay system used in this study is reported to be more accurate than existing systems because it minimizes the intra- and inter-sample variability in the composition of human breast milk (Hostetter et al, 2004).

c) Normal infant weight gain was reported in a study of 78 breast-feeding mothers treated with venlafaxine or SSRIs, 15 of whom took paroxetine doses of approximately 20 mg/day. The mean weight gain reported with paroxetine did not significantly differ from that of other SSRIs used in the study (data not reported) or from normative growth data. Infants of mothers who relapsed to a major depressive episode, defined as an episode lasting 2 months or more despite antidepressant treatment, weighed significantly less at 6 months (p=0.002) when compared to infants of mothers who relapsed to a brief episode and to infants of mothers who did not relapse to depression. The absence of a control group and the maternal use of other medications (56 women used antidepressants during pregnancy and 6 women took psychotropics such as benzodiazepines or tricyclic antidepressants during the study) potentially confound the results of this study (Hendrick et al, 2003).

d) A study of 16 breast-feeding women taking paroxetine at a mean dose of 23.1 mg/day reported paroxetine concentrations ranging from 2 to 101 nanograms/mL in 108 breast milk samples. Samples were obtained from both fore and hind milk for all women. Hind milk had greater paroxetine concentrations than fore milk. A sub-sample of 8 women who gave more than 3 samples over 24 hours was used in an attempt to determine the time course of paroxetine excretion into milk. No time course relationship was observed, although a relationship between maternal daily paroxetine dose and breast milk peak and trough paroxetine concentrations was evident. Mothers did not report any observable adverse effects on the infants (Stowe et al, 2000).

e) Using data from 2 studies, the mean infant dose of paroxetine was 1.13% and 1.25% of the weight adjusted maternal dose. Based on the 10% rule (infant concentrations less than 10% of maternal concentrations), data from these studies suggest that paroxetine may be safe during breast-feeding. In the first study (n=6), milk and plasma concentrations were measured during a 24-hour period; whereas, in the second study (n=4), single prefeed and postfeed milk and plasma concentrations were obtained. Plasma paroxetine concentrations were undetectable in 7 of 8 infants, and 1 infant had a concentration below the level of quantification. Blood samples were not allowed in the remaining infants. No adverse behavioral or physical effects were noted in the infants (Begg et al, 1999).

f) In a study of 7 breast-feeding women, the mean relative dose to the infant ranged from 0.7% to 2.9% of the weight-adjusted maternal dose. In 6 women, serum and breast milk samples were obtained immediately before the morning dose and 4 to 7 hours after the morning dose (time corresponding to the maximum concentration). In the remaining woman, 8 serum and milk samples were drawn. The milk and serum paroxetine concentrations ranged from 18 to 92 nanograms/mL and 17 to 164 nanograms/mL, respectively. No samples were obtained from the infants although there were no changes in infant behavior or adverse effects (Ohman et al, 1999).

g) One study determined that paroxetine was not detectable in infant serum following exposure through breast milk. Samples were obtained from 16 infants whose mothers were treated with 5 mg to 30 mg per day of paroxetine. The infants were 2 to 26 weeks of age at the time of sampling and weighed an average of 5.5 kg (Hendrick et al, 2001). Similarly, paroxetine was not detectable in the serum of 6 nursing infants whose mothers were treated with the drug. There was no evidence of adverse effects in the infants as reported by the mothers. The authors suggest that breast-feeding should generally not be discouraged in mothers treated with serotonin reuptake inhibitor antidepressants (Berle et al, 2004).

3.5 Drug Interactions

Drug-Drug Combinations

Drug-Food Combinations

3.5.1 Drug-Drug Combinations

Abciximab

Aceclofenac

Acemetacin

Acenocoumarol

Alclofenac

Almotriptan

Amitriptyline

Amoxapine

Anagrelide

Ancrod

Anisindione

Antithrombin III Human

Aprepitant

Ardeparin

Aripiprazole

Aspirin

Atomoxetine

Benoxaprofen

Bivalirudin

Bromfenac

Bufexamac

Bupropion

Cannabis

Carprofen

Celecoxib

Certoparin

Cilostazol

Cimetidine

Clarithromycin

Clomipramine

Clonixin

Clopidogrel

Clorgyline

Clozapine

Cyproheptadine

Dalteparin

Danaparoid

Darunavir

Defibrotide

Dehydroepiandrosterone

Dermatan Sulfate

Desipramine

Desirudin

Desvenlafaxine

Dexfenfluramine

Dexketoprofen

Dextromethorphan

Diclofenac

Dicumarol

Diflunisal

Dipyridamole

Dipyrone

Dothiepin

Doxepin

Droperidol

Droxicam

Duloxetine

Eletriptan

Encainide

Enoxaparin

Epoprostenol

Eptifibatide

Etodolac

Etofenamate

Etoricoxib

Felbinac

Fenbufen

Fenfluramine

Fenoprofen

Fentiazac

Flecainide

Floctafenine

Flufenamic Acid

Fluoxetine

Fluphenazine

Flurbiprofen

Fondaparinux

Fosamprenavir

Fosaprepitant

Fosphenytoin

Frovatriptan

Furazolidone

Galantamine

Ginkgo

Heparin

Hydroxytryptophan

Ibuprofen

Iloperidone

Iloprost

Imipramine

Indomethacin

Indoprofen

Iproniazid

Isocarboxazid

Isoxicam

Ketoprofen

Ketorolac

Lamifiban

Lexipafant

Linezolid

Lithium

Lofepramine

Lornoxicam

Meclofenamate

Mefenamic Acid

Meloxicam

Methylphenidate

Metoprolol

Milnacipran

Moclobemide

Morniflumate

Nabumetone

Nadroparin

Naproxen

Naratriptan

Nebivolol

Nefazodone

Nialamide

Niflumic Acid

Nimesulide

Nortriptyline

Oxaprozin

Paliperidone

Parecoxib

Pargyline

Parnaparin

Pentosan Polysulfate Sodium

Perhexiline

Perphenazine

Phenelzine

Phenindione

Phenobarbital

Phenprocoumon

Phenylbutazone

Phenytoin

Pimozide

Pirazolac

Piroxicam

Pirprofen

Procarbazine

Procyclidine

Propafenone

Propyphenazone

Proquazone

Protriptyline

Quinidine

Ranolazine

Rasagiline

Reviparin

Risperidone

Ritonavir

Rizatriptan

Rofecoxib

Selegiline

Sibrafiban

Sibutramine

St John's Wort

Sulfinpyrazone

Sulindac

Sulodexide

Sumatriptan

Suprofen

Tamoxifen

Tapentadol

Tenidap

Tenoxicam

Tetrabenazine

Theophylline

Thioridazine

Tiaprofenic Acid

Ticlopidine

Tinzaparin

Tipranavir

Tirofiban

Tolmetin

Toloxatone

Tramadol

Tranylcypromine

Trazodone

Trimipramine

Tryptophan

Valdecoxib

Warfarin

Xemilofiban

Zolmitriptan

Zomepirac

3.5.1.A Abciximab

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and antiplatelet agents has been associated with an increased risk of bleeding. Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an antiplatelet agent are given concurrently, monitor patient for signs of increased bleeding (Prod Info PAXIL(R) oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008)
7) Probable Mechanism: unknown

3.5.1.B Aceclofenac

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM),

2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.C Acemetacin
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.D Acenocoumarol
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info PAXIL(R) oral tablets, suspension, 2008). Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with warfarin (Schalekamp et al, 2008; Prod Info PAXIL(R) oral tablets, suspension, 2008).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When paroxetine and an anticoagulant are given concurrently, monitor patients for signs of increased bleeding. Patients who are taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, when paroxetine therapy is initiated or discontinued (Prod Info PAXIL(R) oral tablets, suspension, 2008).
7) Probable Mechanism: unknown
8) Literature Reports
a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bleeding (hospital admission due to bleeding) in patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patients with a mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected

patients who received warfarin only (n=117). SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients experienced 11 bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experiencing bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model (Wallerstedt et al, 2009).

b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5), however, the rate of gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).

c) Preliminary data suggest that there may be a pharmacodynamic interaction (that causes an increased bleeding diathesis with unaltered prothrombin time) between paroxetine and warfarin. The concomitant use of paroxetine and warfarin should be undertaken with caution (Prod Info PAXIL(R) oral tablets, suspension, 2008).

d) In a multiple-dose study, several days of combined therapy with warfarin and paroxetine resulted in mild but clinically significant bleeding in 5 of 27 subjects. This effect occurred in the absence of a significant enhancement in warfarin-induced hypoprothrombinemia or changes in either paroxetine or warfarin disposition (Bannister et al, 1989b).

3.5.1.E Alclofenac

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).

b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.F Almotriptan

1) Interaction Effect: an increased risk of serotonin syndrome

2) Summary: Concomitant use of almotriptan and selective serotonin reuptake inhibitors (SSRI's) has been reported to cause weakness, hyperreflexia, and incoordination (Prod Info Axert(TM), 2001). Concurrent use of a triptan and an SSRI may result in serotonin syndrome which may be life-threatening. Symptoms of serotonin syndrome may include restlessness, hallucinations, loss of coordination, fast heart beat, rapid changes in blood pressure, increased body temperature, overreactive reflexes, nausea, vomiting, and diarrhea. Clinicians should be aware that triptans may be commonly used intermittently and that either the triptan or the SSRI may be prescribed by a different physician. Discuss the risks of serotonin syndrome with patients who are prescribed this combination and monitor them closely for symptoms of serotonin syndrome (US Food and Drug Administration, 2006).

3) Severity: major

4) Onset: delayed

5) Substantiation: theoretical
6) Clinical Management: Coadministration of a triptan, such as almotriptan, and an SSRI may result in a life-threatening condition called serotonin syndrome. Be aware that triptans may be commonly used intermittently and that either the triptan or the SSRI may be prescribed by a different physician. If these agents are used together, discuss the risks of serotonin syndrome with the patient and monitor closely for symptoms of serotonin syndrome (restlessness, hyperthermia, hyperreflexia, incoordination).
7) Probable Mechanism: additive pharmacologic effects resulting in excessive serotonergic stimulation
8) Literature Reports
a) Concomitant administration of fluoxetine and almotriptan is well tolerated and fluoxetine has only a modest effect on almotriptan maximum plasma concentration (Cmax). Other almotriptan pharmacokinetics are not significantly affected. A randomized, open-label, two-way crossover study involving 14 healthy volunteers has been conducted. Subjects received each of the following treatments with a minimum 3-week washout between periods: (1) three 20 mg fluoxetine capsules on day 1 to 8 and one dose almotriptan 12.5 mg on day 8, (2) one dose of almotriptan 12.5 mg on day 8 with no treatment on days 1 through 7. Peak almotriptan concentrations were 18% higher following concomitant administration of fluoxetine than after almotriptan administration alone. This difference was statistically significant (p equal 0.023). Mean almotriptan area under the concentration-time curve (AUC) and oral clearance were borderline statistically different between treatment groups. Mean half-life was not statistically different between the treatment groups. During fluoxetine coadministration, Tmax was shorter, suggesting that the absorption rate of almotriptan may have been increased by fluoxetine. The author concludes that based on the results of this study and the lack of effect of fluoxetine on almotriptan pharmacokinetics, almotriptan and fluoxetine can be safely used concomitantly in migraine management (Fleishaker et al, 2001).

3.5.1.G Amitriptyline

1) Interaction Effect: amitriptyline toxicity (dry mouth, sedation, urinary retention)
2) Summary: Paroxetine coadministered with desipramine or imipramine produced higher serum concentrations of the tricyclic antidepressant (TCA) in some patients (Brosen et al, 1993r). Although not reported specifically with amitriptyline, a similar interaction could be expected to occur. Paroxetine's effect on tricyclic antidepressants may resemble that of fluoxetine (another selective serotonin reuptake inhibitor), which is known to inhibit TCA metabolism (Aranow et al, 1989g; Vaughan, 1988g; Goodnick, 1989g). With coadministration, monitor patients for amitriptyline toxicity (Prod Info Paxil(R), 2002c). Amitriptyline doses may need to be reduced.
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When paroxetine is coadministered with amitriptyline, monitor patients for signs and symptoms of amitriptyline toxicity (dry mouth, sedation, urinary retention, blurred vision). Amitriptyline doses may need to be reduced.
7) Probable Mechanism: decreased cytochrome P450 2D6-mediated amitriptyline metabolism
8) Literature Reports
a) The effect of paroxetine on desipramine metabolism was studied in 9 extensive metabolizers (EM) and 8 poor metabolizers (PM) of desipramine (Brosen et al, 1993q). Subjects took a single oral dose of desipramine before starting paroxetine and a second dose after 11 days of paroxetine use. After the addition of paroxetine, extensive metabolizers experienced a 5-fold decrease in clearance of desipramine, indicating that paroxetine inhibits oxidation reactions catalyzed by CYP2D6. Poor metabolizers had a slight increase in clearance of desipramine with paroxetine. With concurrent administration of desipramine and paroxetine, interaction of the two drugs may result in a need for dosage adjustments, especially in extensive metabolizers of desipramine.

3.5.1.H Amoxapine

1) Interaction Effect: amoxapine toxicity (dry mouth, sedation, urinary retention)
2) Summary: Paroxetine coadministered with desipramine or imipramine produced higher serum concentrations of the tricyclic antidepressant (TCA) in some patients (Hartter et al, 1994b; Brosen et al, 1993g). Although not reported specifically with amoxapine, a similar interaction could be expected to occur. Paroxetine's effect on TCAs may resemble that of fluoxetine (another selective serotonin reuptake inhibitor), which is known to inhibit TCA metabolism (Aranow et al, 1989b; Vaughan, 1988b; Goodnick, 1989b). With coadministration, monitor patients for amoxapine toxicity. Amoxapine doses may need to be reduced (Prod Info Paxil CR(TM), 2003f).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When paroxetine is coadministered with amoxapine, monitor patients for signs and symptoms of amoxapine toxicity (dry mouth, sedation, urinary retention, blurred vision). Amoxapine doses may need to be reduced.
7) Probable Mechanism: decreased amoxapine metabolism
8) Literature Reports
a) The effect of paroxetine on desipramine metabolism was studied in 9 extensive metabolizers (EM)

and 8 poor metabolizers (PM) of desipramine (Brosen et al, 1993f). Subjects took a single oral dose of desipramine before starting paroxetine and a second dose after 11 days of paroxetine use. After the addition of paroxetine, EMs experienced a 5-fold decrease in clearance of desipramine, indicating that paroxetine inhibits oxidation reactions catalyzed by CYP2D6. PMs had a slight increase in clearance of desipramine with paroxetine. With concurrent administration of desipramine and paroxetine, interaction of the two drugs may result in a need for dosage adjustments, especially in extensive metabolizers of desipramine.

3.5.1.I Anagrelide

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and antiplatelet agents has been associated with an increased risk of bleeding. Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an antiplatelet agent are given concurrently, monitor patient for signs of increased bleeding (Prod Info PAXIL(R) oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008)
7) Probable Mechanism: unknown

3.5.1.J Ancrod

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info PAXIL(R) oral tablets, suspension, 2008). Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with warfarin (Schalekamp et al, 2008; Prod Info PAXIL(R) oral tablets, suspension, 2008).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When paroxetine and an anticoagulant are given concurrently, monitor patients for signs of increased bleeding. Patients who are taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, when paroxetine therapy is initiated or discontinued (Prod Info PAXIL(R) oral tablets, suspension, 2008).
7) Probable Mechanism: unknown
8) Literature Reports

a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bleeding (hospital admission due to bleeding) in patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patients with a mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients experienced 11 bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experiencing bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model (Wallerstedt et al, 2009).

b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5), however, the rate of gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).

c) Preliminary data suggest that there may be a pharmacodynamic interaction (that causes an increased bleeding diathesis with unaltered prothrombin time) between paroxetine and warfarin. The concomitant use of paroxetine and warfarin should be undertaken with caution (Prod Info PAXIL(R) oral

tablets, suspension, 2008).

d) In a multiple-dose study, several days of combined therapy with warfarin and paroxetine resulted in mild but clinically significant bleeding in 5 of 27 subjects. This effect occurred in the absence of a significant enhancement in warfarin-induced hypoprothrombinemia or changes in either paroxetine or warfarin disposition (Bannister et al, 1989b).

3.5.1.K Anisindione

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info PAXIL(R) oral tablets, suspension, 2008). Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with warfarin (Schalekamp et al, 2008; Prod Info PAXIL(R) oral tablets, suspension, 2008).

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: When paroxetine and an anticoagulant are given concurrently, monitor patients for signs of increased bleeding. Patients who are taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, when paroxetine therapy is initiated or discontinued (Prod Info PAXIL(R) oral tablets, suspension, 2008).

7) Probable Mechanism: unknown

8) Literature Reports

a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bleeding (hospital admission due to bleeding) in patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patients with a mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients experienced 11 bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experiencing bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model (Wallerstedt et al, 2009).

b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5), however, the rate of gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).

c) Preliminary data suggest that there may be a pharmacodynamic interaction (that causes an increased bleeding diathesis with unaltered prothrombin time) between paroxetine and warfarin. The concomitant use of paroxetine and warfarin should be undertaken with caution (Prod Info PAXIL(R) oral tablets, suspension, 2008).

d) In a multiple-dose study, several days of combined therapy with warfarin and paroxetine resulted in mild but clinically significant bleeding in 5 of 27 subjects. This effect occurred in the absence of a significant enhancement in warfarin-induced hypoprothrombinemia or changes in either paroxetine or warfarin disposition (Bannister et al, 1989b).

3.5.1.L Antithrombin III Human

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info PAXIL(R) oral tablets, suspension, 2008). Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with warfarin (Schalekamp et al, 2008; Prod Info PAXIL(R) oral tablets, suspension, 2008).

3) Severity: major

4) Onset: delayed

5) Substantiation: probable
6) Clinical Management: When paroxetine and an anticoagulant are given concurrently, monitor patients for signs of increased bleeding. Patients who are taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, when paroxetine therapy is initiated or discontinued (Prod Info PAXIL(R) oral tablets, suspension, 2008).
7) Probable Mechanism: unknown
8) Literature Reports
a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bleeding (hospital admission due to bleeding) in patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patients with a mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients experienced 11 bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experiencing bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model (Wallerstedt et al, 2009).
b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5), however, the rate of gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).
c) Preliminary data suggest that there may be a pharmacodynamic interaction (that causes an increased bleeding diathesis with unaltered prothrombin time) between paroxetine and warfarin. The concomitant use of paroxetine and warfarin should be undertaken with caution (Prod Info PAXIL(R) oral tablets, suspension, 2008).
d) In a multiple-dose study, several days of combined therapy with warfarin and paroxetine resulted in mild but clinically significant bleeding in 5 of 27 subjects. This effect occurred in the absence of a significant enhancement in warfarin-induced hypoprothrombinemia or changes in either paroxetine or warfarin disposition (Bannister et al, 1989b).

3.5.1.M Aprepitant

1) Interaction Effect: decreased AUC and Cmax of aprepitant and paroxetine
2) Summary: Once daily doses of aprepitant, as a tablet formulation comparable to 85 mg or 170 mg of the capsule formulation, co-administered with paroxetine 20 mg once daily, resulted in a decrease in AUC by approximately 25% and Cmax by approximately 20% of both aprepitant and paroxetine (Prod Info EMEND (R) oral capsules, 2008).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Coadministration of aprepitant and paroxetine may result in a decrease in AUC and Cmax of aprepitant and paroxetine (Prod Info EMEND(R) oral capsules, 2008).
7) Probable Mechanism: unknown

3.5.1.N Ardeparin

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info PAXIL(R) oral tablets, suspension, 2008). Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with warfarin (Schalekamp et al, 2008; Prod Info PAXIL(R) oral tablets, suspension, 2008).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When paroxetine and an anticoagulant are given concurrently, monitor patients for signs of increased bleeding. Patients who are taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, when paroxetine therapy is initiated or discontinued

(Prod Info PAXIL(R) oral tablets, suspension, 2008).
7) Probable Mechanism: unknown
8) Literature Reports
a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bleeding (hospital admission due to bleeding) in patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patients with a mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients experienced 11 bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experiencing bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model (Wallerstedt et al, 2009).
b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5), however, the rate of gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).
c) Preliminary data suggest that there may be a pharmacodynamic interaction (that causes an increased bleeding diathesis with unaltered prothrombin time) between paroxetine and warfarin. The concomitant use of paroxetine and warfarin should be undertaken with caution (Prod Info PAXIL(R) oral tablets, suspension, 2008).
d) In a multiple-dose study, several days of combined therapy with warfarin and paroxetine resulted in mild but clinically significant bleeding in 5 of 27 subjects. This effect occurred in the absence of a significant enhancement in warfarin-induced hypoprothrombinemia or changes in either paroxetine or warfarin disposition (Bannister et al, 1989b).

3.5.1.O Aripiprazole
1) Interaction Effect: increased aripiprazole levels
2) Summary: Aripiprazole is partly metabolized by cytochrome P450 2D6 (CYP2D6) enzymes. Coadministration with CYP2D6 inhibitors, such as paroxetine, may inhibit aripiprazole elimination causing increased blood concentrations. Consider a dosage reduction for aripiprazole when these agents are coadministered. If therapy with paroxetine is discontinued, the dose of aripiprazole should then be increased (Prod Info ABILIFY(R) oral tablets, oral solution, 2005).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Increased aripiprazole plasma levels may result if used concomitantly with paroxetine. Consider a dosage reduction for aripiprazole when these agents are coadministered. If therapy with paroxetine is discontinued, the dose of aripiprazole should then be increased.
7) Probable Mechanism: inhibition of cytochrome P450 2D6-mediated metabolism of aripiprazole

3.5.1.P Aspirin
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and antiplatelet agents has been associated with an increased risk of bleeding. Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an antiplatelet agent are given concurrently, monitor patient for signs of increased bleeding (Prod Info PAXIL(R) oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008)
7) Probable Mechanism: unknown

3.5.1.Q Atomoxetine
1) Interaction Effect: an increase in atomoxetine steady-state plasma concentrations

2) Summary: Atomoxetine is primarily metabolized by the cytochrome P450 2D6 (CYP 2D6) pathway to 4-hydroxyatomoxetine. In extensive metabolizers, atomoxetine steady-state plasma concentrations are increased with selective inhibitors of CYP2D6, such as paroxetine. The exposure is similar to that observed in poor metabolizers. In extensive metabolizers treated with paroxetine, the area under the concentration-time curve of atomoxetine is approximately 6- to 8-fold greater, and maximum plasma concentration at steady-state is about 3- to 4-fold greater than atomoxetine alone (Prod Info Strattera(TM), 2002).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Dosage adjustment of atomoxetine may be necessary when coadministered with paroxetine.
7) Probable Mechanism: inhibition of cytochrome P450 2D6-mediated metabolism of atomoxetine by paroxetine

3.5.1.R Benoxaprofen

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.S Bivalirudin

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info PAXIL(R) oral tablets, suspension, 2008). Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with warfarin (Schalekamp et al, 2008; Prod Info PAXIL(R) oral tablets, suspension, 2008).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When paroxetine and an anticoagulant are given concurrently, monitor patients for signs of increased bleeding. Patients who are taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, when paroxetine therapy is initiated or discontinued (Prod Info PAXIL(R) oral tablets, suspension, 2008).
7) Probable Mechanism: unknown
8) Literature Reports
a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bleeding (hospital admission due to bleeding) in patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patients with a mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients experienced 11 bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The

SSRI implicated in patients experiencing bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model (Wallerstedt et al, 2009).

b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5), however, the rate of gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).

c) Preliminary data suggest that there may be a pharmacodynamic interaction (that causes an increased bleeding diathesis with unaltered prothrombin time) between paroxetine and warfarin. The concomitant use of paroxetine and warfarin should be undertaken with caution (Prod Info PAXIL(R) oral tablets, suspension, 2008).

d) In a multiple-dose study, several days of combined therapy with warfarin and paroxetine resulted in mild but clinically significant bleeding in 5 of 27 subjects. This effect occurred in the absence of a significant enhancement in warfarin-induced hypoprothrombinemia or changes in either paroxetine or warfarin disposition (Bannister et al, 1989b).

3.5.1.T Bromfenac

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).

b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.U Bufexamac

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined

use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).

b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.V Bupropion

1) Interaction Effect: increased plasma levels of paroxetine

2) Summary: It is recommended that paroxetine, an antidepressant metabolized by the cytochrome P450 2D6 isoenzyme, be initiated at the lower end of the dose range when administered concomitantly with bupropion (Prod Info Zyban(R), 2000).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Coadministration of bupropion and paroxetine should be approached with caution and should be initiated at the lower end of the dose range of paroxetine. If bupropion is added to the treatment regimen of a patient already receiving paroxetine, consider decreasing the dose of paroxetine.

7) Probable Mechanism: inhibition of cytochrome P450 2D6-mediated paroxetine metabolism

3.5.1.W Cannabis

1) Interaction Effect: manic symptoms

2) Summary: One case of mania following use of marijuana with fluoxetine therapy has been reported (Stoll et al, 1991a). Although an interaction is proposed, the authors also state the manic symptoms could have resulted from the fluoxetine or marijuana alone. Caution is advised for patients using marijuana and taking fluoxetine or other serotonin reuptake inhibitors.

3) Severity: moderate

4) Onset: rapid

5) Substantiation: theoretical

6) Clinical Management: Caution patients taking selective serotonin reuptake inhibitors to avoid concomitant use of marijuana.

7) Probable Mechanism: additive serotonergic stimulation

8) Literature Reports

a) A 21-year-old female presented with mania, agitation, and grandiose delusions following use of marijuana with fluoxetine therapy. She had been taking fluoxetine 20 mg daily for 4 weeks and reported smoking 2 "joints" during a 36-hour period. Over the next 24 hours, she developed increased energy, hypersexuality, pressured speech, and grandiose delusions. Lorazepam and perphenazine were given for agitation and excitement which gradually resolved over 4 days. She remained hospitalized for 36 days. Fluoxetine 20 mg every other day was reintroduced one week prior to discharge. One week after discharge, she discontinued fluoxetine due to insomnia and feeling "hyper". These symptoms resolved rapidly upon discontinuation of fluoxetine. Due to the rapid switch to mania after smoking marijuana with fluoxetine, the manic symptoms were associated with the concomitant use of fluoxetine and marijuana, though mania could have developed from either fluoxetine or marijuana alone (Stoll et al, 1991).

3.5.1.X Carprofen

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).

b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with

hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.Y Celecoxib

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).

b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.Z Certoparin

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info PAXIL(R) oral tablets, suspension, 2008). Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with warfarin (Schalekamp et al, 2008; Prod Info PAXIL(R) oral tablets, suspension, 2008).

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: When paroxetine and an anticoagulant are given concurrently, monitor patients for signs of increased bleeding. Patients who are taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, when paroxetine therapy is initiated or discontinued (Prod Info PAXIL(R) oral tablets, suspension, 2008).

7) Probable Mechanism: unknown

8) Literature Reports

a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bleeding (hospital admission due to bleeding) in patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patients with a mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients experienced 11 bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experiencing bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model (Wallerstedt et al, 2009).

b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval

(CI), 1.1 to 2.5), however, the rate of gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).
c) Preliminary data suggest that there may be a pharmacodynamic interaction (that causes an increased bleeding diathesis with unaltered prothrombin time) between paroxetine and warfarin. The concomitant use of paroxetine and warfarin should be undertaken with caution (Prod Info PAXIL(R) oral tablets, suspension, 2008).
d) In a multiple-dose study, several days of combined therapy with warfarin and paroxetine resulted in mild but clinically significant bleeding in 5 of 27 subjects. This effect occurred in the absence of a significant enhancement in warfarin-induced hypoprothrombinemia or changes in either paroxetine or warfarin disposition (Bannister et al, 1989b).

3.5.1.AA Cilostazol
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and antiplatelet agents has been associated with an increased risk of bleeding. Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an antiplatelet agent are given concurrently, monitor patient for signs of increased bleeding (Prod Info PAXIL(R) oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008)
7) Probable Mechanism: unknown

3.5.1.AB Cimetidine
1) Interaction Effect: increased paroxetine serum concentrations and possibly paroxetine toxicity (dizziness, somnolence, nausea, headache)
2) Summary: Coadministered cimetidine may increase serum concentrations of paroxetine by as much as 50% to 80% in some patients (Greb et al, 1989a; Bannister et al, 1989a). The clinical significance of this interaction is unclear. In one study, no adverse clinical effects were reported. In another study, tiredness, dizziness, headache, muscle tension, and GI distress were observed; these effects were also reported with paroxetine alone, but to a lesser extent. The mechanism of this interaction is thought to be inhibition by cimetidine of P450 isoenzymes responsible for paroxetine metabolism. Dosage adjustment of paroxetine after the 20 mg starting dose should be guided by clinical effect. The effect of paroxetine on cimetidine's pharmacokinetics has not been studied (Prod Info Paxil CR(TM), 2004).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: If cimetidine and paroxetine are coadministered, observe the patient for signs and symptoms of paroxetine toxicity (dizziness, somnolence, nausea, headache). Lower doses of paroxetine may be required. An alternative H-2 blocker that has less impact on hepatic isoenzymes (such as famotidine or ranitidine) might be considered.
7) Probable Mechanism: inhibition of paroxetine cytochrome P450 metabolism by cimetidine
8) Literature Reports
a) In a multiple-dose study in 11 healthy volunteers, concurrent administration of oral cimetidine and paroxetine resulted in a mean increase of 51% in the area under the concentration-time curve (AUC) for paroxetine. Maximum concentration (Cmax) of paroxetine increased by 45%. Volunteers received paroxetine 30 mg once a day for 28 days, with cimetidine 300 mg three times daily given during the last 7 days. No changes in half-life or elimination rate constant occurred. The increases in the paroxetine AUC and maximum concentration were attributed to inhibition of first-pass metabolism of paroxetine by cimetidine. No adverse clinical effects were observed during the study (Bannister et al, 1989).
b) Effects of cimetidine on a single dose of paroxetine were studied in 10 healthy male subjects (Greb et al, 1989). Subjects received 8 days of cimetidine 200 mg four times daily followed by a 30 mg dose of paroxetine. Pharmacokinetic values were compared with those of the same dose of paroxetine given before initiation of the H-2 blocker. The mean AUC of paroxetine increased from 195.98 to 308.36 ng-h/mL (a 57% increase), but, due to high interindividual variation, this increase did not attain statistical significance. In two subjects, the increases were 55% and 81%, respectively.

3.5.1.AC Clarithromycin
1) Interaction Effect: an increased risk of serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)
2) Summary: Concurrent use of clarithromycin and paroxetine may increase the risk of serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes) (Jaber et al, 2006).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable

6) Clinical Management: Concurrent use of clarithromycin and paroxetine may result in serotonin syndrome. Monitor patients for serotonin syndrome effects including restlessness, tremors, blushing, diaphoresis, and hyperpyrexia. Consider reducing the dose of paroxetine.
7) Probable Mechanism: unknown
8) Literature Reports
a) A 36-year-old-woman experienced acute ocular clonus, akathisia, and fever after 2 days of clarithromycin 500 milligrams twice daily despite stopping paroxetine 3 days prior to starting clarithromycin. She was on paroxetine 10 milligrams daily for 3 months prior to stopping it. Clarithromycin was discontinued. She was treated with intravenous fluids and lorazepam and within 24 hours symptoms resolved (Jaber et al, 2006).

3.5.1.AD Clomipramine
1) Interaction Effect: clomipramine toxicity (dry mouth, sedation, urinary retention)
2) Summary: Concurrent use of paroxetine with drugs that are metabolized by cytochrome P450 2D6, such as clomipramine, should be approached with caution (Prod Info Paxil(R), 2003i).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When paroxetine is coadministered with clomipramine, monitor patients for signs and symptoms of clomipramine toxicity (dry mouth, sedation, urinary retention, blurred vision). Clomipramine doses may need to be reduced.
7) Probable Mechanism: decreased cytochrome P450 2D6-mediated clomipramine metabolism

3.5.1.AE Clonixin
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.AF Clopidogrel
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and antiplatelet agents has been associated with an increased risk of bleeding. Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an antiplatelet agent are given concurrently, monitor patient for signs of increased bleeding (Prod Info PAXIL(R) oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008)
7) Probable Mechanism: unknown

3.5.1.AG Clorgyline
1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)
2) Summary: Concurrent administration or overlapping therapy with paroxetine and a monoamine oxidase

(MAO) inhibitor may result in CNS toxicity or serotonin syndrome, a hyperserotonergic state characterized by symptoms such as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. Serious, even fatal, reactions have been reported with concomitant use of serotonin specific reuptake inhibitors and MAO inhibitors (Prod Info Paxil(R), 2003c; Lappin & Auchincloss, 1994g; Graber et al, 1994g; Suchowersky & de Vries, 1990g). Concomitant use is contraindicated.
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Concurrent use of paroxetine and an MAO inhibitor is contraindicated. Wait at least two weeks after discontinuing an MAO inhibitor before initiating paroxetine, and at least two weeks after discontinuing paroxetine before initiating therapy with an MAOI.
7) Probable Mechanism: inhibition of serotonin metabolism by monoamine oxidase
8) Literature Reports
a) Concomitant use of SSRIs and monoamine oxidase inhibitors can produce a toxic reaction known as serotonin syndrome (Sternbach, 1991h). Serotonin syndrome is a condition of serotonergic hyperstimulation and manifests as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor (Sternbach, 1991h). If the syndrome is not recognized and correctly treated, fatality can result.
b) A 26-year old woman who had been taking isocarboxazid for eight weeks stopped taking the drug for 11 days before beginning therapy with sertraline. After a single 100 mg sertraline dose, the patient became restless and developed leg twitches. The patients was later admitted to the emergency room with diaphoresis, tachycardia, hyperreflexia, and various neuromuscular disturbances. After treatment with diazepam and propranolol the patient did not improve. The patient was then given two 4 mg doses of cyproheptadine an hour apart, with notable improvement in symptoms after the second dose (Lappin & Auchincloss, 1994f).
c) A drug interaction was reported in a 61-year old woman in which sertraline 100 mg twice daily added to a regimen of lithium, phenelzine, thioridazine, and doxepin. Three hours after taking the first sertraline dose, the patient was found in a semicomatose state, with elevated body temperature, increased pulse, increased respiration rate, and a blood pressure of 140/110 mm Hg. After transportation to the hospital, the patient was misdiagnosed as having neuroleptic malignant syndrome (NMS) which was later changed to serotonin syndrome due to a reaction between sertraline and phenelzine. The authors suggest that monoamine oxidase inhibitor (MAOI) therapy should be discontinued for at least two weeks before initiation of therapy with a selective serotonin reuptake inhibitor (SSRI) and that before starting a MAOI, SSRI therapy should be discontinued for at least five half-lives of the parent drug and any active metabolites (Graber et al, 1994f).
d) Two cases reports suggested a possible interaction between fluoxetine and selegiline (Suchowersky & de Vries, 1990f). One case involved a first episode of mania being observed approximately one month after adding selegiline to fluoxetine. The patient improved two months after both drugs were discontinued, and no further details were provided. The second case involved diaphoresis, vasoconstriction, and cyanosis of the hands which occurred in close temporal relationship to adding fluoxetine to selegiline. Both drugs were discontinued, with relatively quick resolution of symptoms. Rechallenge with fluoxetine alone occurred without incident.

3.5.1.AH Clozapine
1) Interaction Effect: an increased risk of clozapine toxicity (sedation, seizures, hypotension)
2) Summary: Increased serum concentrations of clozapine and its metabolites have been observed when it is given with serotonin reuptake inhibitors; however, other published reports describe paroxetine having no effect on serum concentrations of clozapine or its metabolites (Prod Info Clozaril(R), 2002; Centorrino et al, 1996a; Wetzel et al, 1998a).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor for signs of clozapine toxicity or serum concentrations when paroxetine is given concomitantly.
7) Probable Mechanism: decreased clozapine metabolism
8) Literature Reports
a) Paroxetine had no significant effect on serum levels of clozapine in 14 patients with schizophrenia. Clozapine 2.5 to 3 mg/kg/day was given for 14 days, then paroxetine 20 mg daily was added for 14 days. Serum concentrations of clozapine and two metabolites were measured on days 1, 7, and 14. Over the course of this study there was no significant difference in serum concentrations of clozapine or its metabolites (Wetzel et al, 1998).
b) Serum concentrations of clozapine and norclozapine, the major metabolite, were evaluated when given in combination with the selective serotonin reuptake inhibitors (SSRIs) fluoxetine, paroxetine, and sertraline. Eighty outpatients receiving clozapine all had been diagnosed with schizophrenia or major affective disorder, and 40 of these patients were receiving an SSRI in combination with clozapine. Of these 40 patients, 14 were receiving fluoxetine, 10 were receiving sertraline, and 16 were receiving paroxetine therapy. Among the patients on SSRI therapy, serum concentrations of clozapine and norclozapine were 41.1% and 44.8% higher, respectively, than in matched patients who were not

receiving an SSRI. The ratio of clozapine plus norclozapine concentration to dose was also 37.7% higher in patients receiving SSRIs, indicating clozapine impaired clearance. The differences between the three SSRIs were minor, and the study groups were too limited for an accurate statistical comparison between the individual SSRIs (Centorrino et al, 1996).

3.5.1.AI Cyproheptadine

1) Interaction Effect: reduced paroxetine efficacy

2) Summary: Coadministration of cyproheptadine with paroxetine may result in reduced paroxetine effectiveness (Christensen, 1995a). Cyproheptadine acts to antagonize postsynaptic serotonin. Concomitant use of cyproheptadine with drugs that possess serotonin-enhancing properties (such as the selective serotonin reuptake inhibitors) might be expected to result in a pharmacodynamic interaction. Lack of antidepressant efficacy was also reported when cyproheptadine was given concomitantly with fluoxetine (Katz & Rosenthal, 1994; Feder, 1991; Goldbloom & Kennedy, 1991).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Monitor patients for reduced paroxetine efficacy. When cyproheptadine is coadministered with paroxetine, paroxetine doses may need to be adjusted upward. In some cases, it may be necessary to withdraw cyproheptadine therapy.

7) Probable Mechanism: unknown; because cyproheptadine is a serotonin antagonist, it may oppose effects of agents that inhibit serotonin uptake

8) Literature Reports

a) A 54-year-old woman was using paroxetine 20 mg per day for the treatment of nonpsychotic major depression. Cyproheptadine 2 mg twice a day was added to her therapy. Two days later, her depression worsened and she experienced confusion and paranoid delusions. Her psychotic symptoms resolved two days after cyproheptadine was discontinued. She declined to be rechallenged (Christensen, 1995).

3.5.1.AJ Dalteparin

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info PAXIL(R) oral tablets, suspension, 2008). Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with warfarin (Schalekamp et al, 2008; Prod Info PAXIL(R) oral tablets, suspension, 2008).

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: When paroxetine and an anticoagulant are given concurrently, monitor patients for signs of increased bleeding. Patients who are taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, when paroxetine therapy is initiated or discontinued (Prod Info PAXIL(R) oral tablets, suspension, 2008).

7) Probable Mechanism: unknown

8) Literature Reports

a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bleeding (hospital admission due to bleeding) in patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patients with a mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients experienced 11 bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experiencing bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model (Wallerstedt et al, 2009).

b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval

(CI), 1.1 to 2.5), however, the rate of gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).

c) Preliminary data suggest that there may be a pharmacodynamic interaction (that causes an increased bleeding diathesis with unaltered prothrombin time) between paroxetine and warfarin. The concomitant use of paroxetine and warfarin should be undertaken with caution (Prod Info PAXIL(R) oral tablets, suspension, 2008).

d) In a multiple-dose study, several days of combined therapy with warfarin and paroxetine resulted in mild but clinically significant bleeding in 5 of 27 subjects. This effect occurred in the absence of a significant enhancement in warfarin-induced hypoprothrombinemia or changes in either paroxetine or warfarin disposition (Bannister et al, 1989b).

3.5.1.AK Danaparoid

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info PAXIL(R) oral tablets, suspension, 2008). Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with warfarin (Schalekamp et al, 2008; Prod Info PAXIL(R) oral tablets, suspension, 2008).

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: When paroxetine and an anticoagulant are given concurrently, monitor patients for signs of increased bleeding. Patients who are taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, when paroxetine therapy is initiated or discontinued (Prod Info PAXIL(R) oral tablets, suspension, 2008).

7) Probable Mechanism: unknown

8) Literature Reports

a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bleeding (hospital admission due to bleeding) in patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patients with a mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients experienced 11 bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experiencing bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model (Wallerstedt et al, 2009).

b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5), however, the rate of gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).

c) Preliminary data suggest that there may be a pharmacodynamic interaction (that causes an increased bleeding diathesis with unaltered prothrombin time) between paroxetine and warfarin. The concomitant use of paroxetine and warfarin should be undertaken with caution (Prod Info PAXIL(R) oral tablets, suspension, 2008).

d) In a multiple-dose study, several days of combined therapy with warfarin and paroxetine resulted in mild but clinically significant bleeding in 5 of 27 subjects. This effect occurred in the absence of a significant enhancement in warfarin-induced hypoprothrombinemia or changes in either paroxetine or warfarin disposition (Bannister et al, 1989b).

3.5.1.AL Darunavir

1) Interaction Effect: decreased paroxetine exposure and plasma concentrations

2) Summary: Coadministration of darunavir/ritonavir with paroxetine has resulted in significantly decreased paroxetine exposure and plasma concentrations. If these agents are coadministered, the paroxetine dose should be carefully titrated based on clinical response. When darunavir/ritonavir is initiated in patients who are on a stable dose of paroxetine, monitor antidepressant response to paroxetine (Prod Info PREZISTA

(TM) oral tablets, 2006).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: established
6) Clinical Management: Concurrent administration of paroxetine with darunavir/ritonavir decreased paroxetine exposure and plasma concentrations. If these agents are coadministered, carefully titrate the paroxetine dose based on clinical response. When darunavir/ritonavir is initiated in patients who are on a stable dose of paroxetine, monitor antidepressant response to paroxetine.
7) Probable Mechanism: unknown
8) Literature Reports
a) In a pharmacokinetics study, concurrent administration of paroxetine and darunavir/ritonavir decreased paroxetine exposure and plasma concentrations. Subjects (n=16) were administered paroxetine 20 mg orally once daily concurrently with darunavir 400 mg/ritonavir 100 mg orally twice daily. Results indicated a 36% decrease in paroxetine Cmax (least squares (LS) mean ratio % 0.64; 90% confidence interval (CI), 0.59 to 0.71), a 39% decreased in paroxetine AUC (LS mean ratio % 0.61; 90% CI, 0.56 to 0.66), and a 37% decrease in paroxetine Cmin (LS mean ratio % 0.63; 90% CI, 0.55 to 0.73). Darunavir pharmacokinetics were not significantly altered (Prod Info PREZISTA(TM) oral tablets, 2006).

3.5.1.AM Defibrotide
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info PAXIL(R) oral tablets, suspension, 2008). Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with warfarin (Schalekamp et al, 2008; Prod Info PAXIL(R) oral tablets, suspension, 2008).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When paroxetine and an anticoagulant are given concurrently, monitor patients for signs of increased bleeding. Patients who are taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, when paroxetine therapy is initiated or discontinued (Prod Info PAXIL(R) oral tablets, suspension, 2008).
7) Probable Mechanism: unknown
8) Literature Reports
a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bleeding (hospital admission due to bleeding) in patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patients with a mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients experienced 11 bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experiencing bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model (Wallerstedt et al, 2009).
b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5), however, the rate of gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).
c) Preliminary data suggest that there may be a pharmacodynamic interaction (that causes an increased bleeding diathesis with unaltered prothrombin time) between paroxetine and warfarin. The concomitant use of paroxetine and warfarin should be undertaken with caution (Prod Info PAXIL(R) oral tablets, suspension, 2008).
d) In a multiple-dose study, several days of combined therapy with warfarin and paroxetine resulted in mild but clinically significant bleeding in 5 of 27 subjects. This effect occurred in the absence of a significant enhancement in warfarin-induced hypoprothrombinemia or changes in either paroxetine or

warfarin disposition (Bannister et al, 1989b).

3.5.1.AN Dehydroepiandrosterone

1) Interaction Effect: development of manic symptoms

2) Summary: A case has been reported in which concomitant dehydroepiandrosterone (DHEA) and sertraline use was suggested to precipitate a manic episode in a patient with a history of bipolar disorder (Dean, 2000a). DHEA was also noted to cause mania in a patient with no previous personal or family history of bipolar disorder (Markowitz et al, 1999). Elevated DHEA levels have been found in patients with mental disorders; DHEA suppression has lead to improvement in psychotic symptoms (Howard, 1992). DHEA possesses proserotonergic activity which may predispose patients to manic episodes (Majewska, 1995). DHEA is a precursor to androgenic steroids, which in high doses may precipitate mania (Markowitz et al, 1999). Patients taking medication for bipolar disorder or patients with a personal and/or family history of bipolar disorder should not take DHEA until further data is available to characterize this drug-herb interaction. Concomitant use of DHEA with selective serotonin reuptake inhibitors (SSRIs) should be avoided due to the potential additive precipitation of mania.

3) Severity: moderate

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: Avoid concomitant use of dehydroepiandrosterone (DHEA) and selective serotonin reuptake inhibitors. If patients present with manic symptoms (i.e. agitation, anger, irritability, aggressive behavior), determine if the patient is using DHEA and discontinue DHEA.

7) Probable Mechanism: serotonergic activity of dehydroepiandrosterone, possibly increased androgen levels

8) Literature Reports

a) A 31-year-old male was admitted following threats to commit suicide and injure family members. He had self-initiated sertraline 100 milligrams (mg) daily for the previous 2 to 3 weeks for depression. Sertraline had been prescribed 3 years prior when he was diagnosed with bipolar disorder, which he discontinued after 2 weeks. He had also taken dehydroepiandrosterone (DHEA) 300 mg to 500 mg daily for the previous 2 months apparently for weight training. Following use of DHEA for a short time, he became more irritable, was not sleeping well, and began threatening a female friend and family members. He also drank alcohol occasionally and reportedly had difficulty controlling his anger when intoxicated. Sertraline was stopped and the patient was treated with valproic acid with the dose titrated to 500 mg twice daily. The combination of DHEA, sertraline, and alcohol was suggested responsible for the developing of the manic episode (Dean, 2000).

3.5.1.AO Dermatan Sulfate

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info PAXIL(R) oral tablets, suspension, 2008). Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with warfarin (Schalekamp et al, 2008; Prod Info PAXIL(R) oral tablets, suspension, 2008).

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: When paroxetine and an anticoagulant are given concurrently, monitor patients for signs of increased bleeding. Patients who are taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, when paroxetine therapy is initiated or discontinued (Prod Info PAXIL(R) oral tablets, suspension, 2008).

7) Probable Mechanism: unknown

8) Literature Reports

a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bleeding (hospital admission due to bleeding) in patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patients with a mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients experienced 11 bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experiencing bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model (Wallerstedt et al, 2009).

b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5), however, the rate of gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).
c) Preliminary data suggest that there may be a pharmacodynamic interaction (that causes an increased bleeding diathesis with unaltered prothrombin time) between paroxetine and warfarin. The concomitant use of paroxetine and warfarin should be undertaken with caution (Prod Info PAXIL(R) oral tablets, suspension, 2008).
d) In a multiple-dose study, several days of combined therapy with warfarin and paroxetine resulted in mild but clinically significant bleeding in 5 of 27 subjects. This effect occurred in the absence of a significant enhancement in warfarin-induced hypoprothrombinemia or changes in either paroxetine or warfarin disposition (Bannister et al, 1989b).

3.5.1.AP Desipramine

1) Interaction Effect: an increase in the plasma concentrations of desipramine and in related side effects (dry mouth, sedation)
2) Summary: Paroxetine may increase desipramine exposure when the two are coadministered, and associated clinical toxicity (agitation, tremor, hyperreflexia, tachycardia) has been reported (Prod Info Paxil (R), 2002b; Chan et al, 1998a). Citalopram was successfully substituted for paroxetine when desipramine toxicity occurred with paroxetine coadministration (Ashton, 2000a). Paroxetine is metabolized by the cytochrome P450 2D6 isozyme, saturating it early during paroxetine dosing; desipramine is also metabolized by CYP2D6, and its metabolism is inhibited by the enzyme saturation caused by paroxetine (Prod Info Paxil(R), 2002b).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor desipramine concentrations when there is a change in therapy or dose of paroxetine. Monitor for evidence of increased plasma levels of desipramine, such as dry mouth and sedation, with concurrent therapy. Lower desipramine doses may be required in some clinical situations.
7) Probable Mechanism: decreased cytochrome P450 2D6-mediated desipramine metabolism
8) Literature Reports

a) The effect of paroxetine on desipramine metabolism was studied in 9 extensive metabolizers (EM) and 8 poor metabolizers (PM) of desipramine (Brosen et al, 1993p). Subjects took a single oral dose of desipramine before starting paroxetine and a second dose after 11 days of paroxetine use. After the addition of paroxetine, EMs experienced a 5-fold decrease in clearance of desipramine, indicating that paroxetine inhibits oxidation reactions catalyzed by CYP2D6. PMs had only a slight increase in clearance of desipramine with paroxetine. With concurrent administration of desipramine and paroxetine, interaction of the two drugs may result in a need for dosage adjustments, especially in extensive metabolizers of desipramine.
b) A 21 year-old man experienced agitation, hyperreflexia, tremor, and tachycardia after taking a single dose of paroxetine one day after discontinuing desipramine therapy. The authors recommend at least a two-week washout period between use of selective serotonin reuptake inhibitors (SSRIs) and other classes of antidepressants such as monoamine oxidase inhibitors (MAOIs), tricyclic antidepressants (TCAs), and selective noradrenaline reuptake inhibitors (SNRIs) (Chan et al, 1998).
c) A 45-year-old white female with major depressive disorder and dysthymia failed several trials of antidepressants from all available drug classes, as well as electroconvulsive therapy. The patient's medications included pindolol, desipramine, clonazepam, and olanzapine. Paroxetine was initiated and titration to 40 mg/day occurred over 3 months. The patient developed lightheadedness, ataxia, and increased confusion after the titration. Desipramine serum levels were 1810 ng/mL (therapeutic range 75-300 ng/mL). After decreasing the daily desipramine 200 mg, the serum desipramine level was still 1665 ng/mL. The reduction in side effects were evident when the paroxetine dose was decreased to 30 mg/day and desipramine dose was decreased to 150 mg/day. Despite the dosage reduction of both drugs the patient's serum desipramine level was 1153 ng/mL. Paroxetine was discontinued and desipramine dose was decreased to 100 mg/day in divided doses. Citalopram was initiated and titrated to 40 mg/day. Over the next two months the patient's desipramine level decreased to 195 ng/mL. Depressive symptoms also improved. Desipramine toxicity is presumed to be caused by hepatic cytochrome P450 2D6 (CYP2D6) isoenzyme blockade from paroxetine. The author concludes that the switch to citalopram likely is responsible for diminished desipramine serum levels, although alternative explanations should not be discounted (Ashton, 2000).
d) One study looked at the effects on the pharmacokinetics of single-dose desipramine and concomitant paroxetine therapy. Paroxetine given daily (20 mg/day) under steady-state conditions increased single dose desipramine (100mg) Cmax, AUC, and T1/2 by an average of approximately 2, 5, and 3-fold, respectively (Prod Info PAXIL(R) oral tablets and oral suspension, 2005).

3.5.1.AQ Desirudin

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info PAXIL(R) oral tablets, suspension, 2008). Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with warfarin (Schalekamp et al, 2008; Prod Info PAXIL(R) oral tablets, suspension, 2008).

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: When paroxetine and an anticoagulant are given concurrently, monitor patients for signs of increased bleeding. Patients who are taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, when paroxetine therapy is initiated or discontinued (Prod Info PAXIL(R) oral tablets, suspension, 2008).

7) Probable Mechanism: unknown

8) Literature Reports

a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bleeding (hospital admission due to bleeding) in patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patients with a mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients experienced 11 bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experiencing bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model (Wallerstedt et al, 2009).

b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5), however, the rate of gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).

c) Preliminary data suggest that there may be a pharmacodynamic interaction (that causes an increased bleeding diathesis with unaltered prothrombin time) between paroxetine and warfarin. The concomitant use of paroxetine and warfarin should be undertaken with caution (Prod Info PAXIL(R) oral tablets, suspension, 2008).

d) In a multiple-dose study, several days of combined therapy with warfarin and paroxetine resulted in mild but clinically significant bleeding in 5 of 27 subjects. This effect occurred in the absence of a significant enhancement in warfarin-induced hypoprothrombinemia or changes in either paroxetine or warfarin disposition (Bannister et al, 1989b).

3.5.1.AR Desvenlafaxine

1) Interaction Effect: increased risk of serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)

2) Summary: Concurrent use of desvenlafaxine and a selective serotonin reuptake inhibitor (SSRI) may result in serotonin syndrome, which may be life-threatening. Symptoms of serotonin syndrome may include restlessness, hallucinations, loss of coordination, fast heart beat, rapid changes in blood pressure, increased body temperature, overreactive reflexes, nausea, vomiting, and diarrhea (Prod Info PRISTIQ(TM) oral extended-release tablets, 2008).

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Coadministration of desvenlafaxine and an SSRI may result in a life-threatening condition called serotonin syndrome. If these agents are used together, discuss the risks of serotonin syndrome with the patient and monitor closely for symptoms of serotonin syndrome (restlessness, hyperthermia, hyperreflexia, incoordination), especially during treatment initiation and dose increases (Prod Info PRISTIQ(TM) oral extended-release tablets, 2008).

7) Probable Mechanism: additive serotonergic effect

3.5.1.AS Dexfenfluramine

1) Interaction Effect: serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)
2) Summary: Dexfenfluramine is a nonspecific serotonin agonist that both enhances the release of serotonin and inhibits serotonin reuptake. Combination therapy with dexfenfluramine and another selective serotonin reuptake inhibitor, such as paroxetine, has the potential to cause serotonin syndrome (Schenck & Mahowald, 1996). Serotonin syndrome is a hyperserotonergic state characterized by symptoms such as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. Serious, even fatal, reactions have been reported (Sternbach, 1991o). Dexfenfluramine should not be used in combination with paroxetine (Prod Info Redux(R), 1997).
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Concurrent use of dexfenfluramine and paroxetine may result in an additive increase in serotonin levels in the central nervous system, and could result in serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes). Dexfenfluramine should not be used in combination with paroxetine or other serotonin specific reuptake inhibitors.
7) Probable Mechanism: additive serotonergic effects

3.5.1.AT Dexketoprofen

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.AU Dextromethorphan

1) Interaction Effect: possible dextromethorphan toxicity (nausea, vomiting, blurred vision, hallucinations) or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)
2) Summary: Coadministration of paroxetine with dextromethorphan has been implicated in two cases of serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes) (Skop et al, 1994a; Harvey & Burke, 1995). Paroxetine is known to inhibit cytochrome P450IID6 (CYP2D6), the same enzyme which catalyzes dextromethorphan metabolism, and is itself metabolized by this enzyme (Prod Info Paxil(R), 1999e; Murray, 1992a). With concomitant administration, both agents may competitively inhibit each others metabolism. Thus, serum levels of both medications would be expected to increase.
3) Severity: major
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Caution patients taking paroxetine that an interaction could occur with dextromethorphan. A reduction in the dextromethorphan dose may be necessary.
7) Probable Mechanism: competitively inhibited metabolism of both agents
8) Literature Reports
a) A 51-year old male patient with vascular disease developed serotonin syndrome following concurrent use of dextromethorphan and paroxetine. Two days after self-medication with a dextromethorphan-containing cold product, the patient experienced shortness of breath, nausea, headache, and confusion. Upon arrival to the hospital, the patient presented with diaphoresis, tremor, confusion, abdominal pain, and severe shortness of breath. After administration of benzodiazepines and discontinuation of paroxetine, the patient's condition improved and no further complications were seen

(Skop et al, 1994).

3.5.1.AV Diclofenac

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).

b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.AW Dicumarol

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info PAXIL(R) oral tablets, suspension, 2008). Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with warfarin (Schalekamp et al, 2008; Prod Info PAXIL(R) oral tablets, suspension, 2008).

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: When paroxetine and an anticoagulant are given concurrently, monitor patients for signs of increased bleeding. Patients who are taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, when paroxetine therapy is initiated or discontinued (Prod Info PAXIL(R) oral tablets, suspension, 2008).

7) Probable Mechanism: unknown

8) Literature Reports

a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bleeding (hospital admission due to bleeding) in patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patients with a mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients experienced 11 bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experiencing bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model (Wallerstedt et al, 2009).

b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval

(CI), 1.1 to 2.5), however, the rate of gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).
c) Preliminary data suggest that there may be a pharmacodynamic interaction (that causes an increased bleeding diathesis with unaltered prothrombin time) between paroxetine and warfarin. The concomitant use of paroxetine and warfarin should be undertaken with caution (Prod Info PAXIL(R) oral tablets, suspension, 2008).
d) In a multiple-dose study, several days of combined therapy with warfarin and paroxetine resulted in mild but clinically significant bleeding in 5 of 27 subjects. This effect occurred in the absence of a significant enhancement in warfarin-induced hypoprothrombinemia or changes in either paroxetine or warfarin disposition (Bannister et al, 1989b).

3.5.1.AX Diflunisal
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.AY Dipyridamole
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and antiplatelet agents has been associated with an increased risk of bleeding. Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an antiplatelet agent are given concurrently, monitor patient for signs of increased bleeding (Prod Info PAXIL(R) oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008)
7) Probable Mechanism: unknown

3.5.1.AZ Dipyrone
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched

among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).

b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.BA Dothiepin

1) Interaction Effect: dothiepin toxicity (dry mouth, sedation, urinary retention)

2) Summary: Paroxetine coadministered with desipramine or imipramine produced higher serum concentrations of the tricyclic antidepressant (TCA) in some patients (Hartter et al, 1994c; Brosen et al, 1993i) because paroxetine may inhibit dothiepin metabolism (Prod Info Paxil CR(TM), 2003g). Although not reported specifically with dothiepin, a similar interaction could be expected to occur. The effect of paroxetine on TCA metabolism may resemble that of fluoxetine (another selective serotonin reuptake inhibitor), which is known to inhibit TCA metabolism (Aranow et al, 1989c; Vaughan, 1988c; Goodnick, 1989c).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: When paroxetine is coadministered with dothiepin, monitor patients for signs and symptoms of dothiepin toxicity (dry mouth, sedation, urinary retention, blurred vision). Dothiepin doses may need to be reduced.

7) Probable Mechanism: decreased dothiepin metabolism

8) Literature Reports

a) The effect of paroxetine on desipramine metabolism was studied in 9 extensive metabolizers (EM) and 8 poor metabolizers (PM) of desipramine. Subjects took a single oral dose of desipramine before starting paroxetine and a second dose after 11 days of paroxetine use. After the addition of paroxetine, extensive metabolizers experienced a 5-fold decrease in clearance of desipramine, indicating that paroxetine inhibits oxidation reactions catalyzed by CYP2D6. Poor metabolizers had a slight increase in clearance of desipramine during paroxetine coadministration. With concurrent administration of desipramine and paroxetine, interaction of the two drugs may result in a need for dosage adjustments, especially in extensive metabolizers of desipramine (Brosen et al, 1993h).

3.5.1.BB Doxepin

1) Interaction Effect: doxepin toxicity (dry mouth, sedation, urinary retention)

2) Summary: Paroxetine coadministered with desipramine or imipramine produced higher serum concentrations of the tricyclic antidepressant (TCA) in some patients (Hartter et al, 1994f; Brosen et al, 1993o). Although not reported specifically with doxepin, a similar interaction could be expected to occur. Paroxetine's effect on TCAs may resemble that of fluoxetine (another selective serotonin reuptake inhibitor), which is known to inhibit TCA metabolism (Aranow et al, 1989f; Vaughan, 1988f; Goodnick, 1989f). With coadministration, monitor patients for doxepin toxicity. Doxepin doses may need to be reduced (Prod Info Paxil CR(TM), 2003n).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: When doxepin is coadministered with paroxetine, monitor patients for signs and symptoms of doxepin toxicity (dry mouth, sedation, urinary retention, blurred vision). Doxepin doses may need to be reduced.

7) Probable Mechanism: decreased doxepin metabolism

8) Literature Reports

a) The effect of paroxetine on desipramine metabolism was studied in 9 extensive metabolizers (EM) and 8 poor metabolizers (PM) of desipramine. Subjects took a single oral dose of desipramine before starting paroxetine and a second dose after 11 days of paroxetine use. After the addition of paroxetine, EMs experienced a 5-fold decrease in clearance of desipramine, indicating that paroxetine inhibits oxidation reactions catalyzed by CYP2D6. PMs had a slight increase in clearance of desipramine with paroxetine. With concurrent administration of desipramine and paroxetine, interaction of the two drugs may result in a need for dosage adjustments, especially in extensive metabolizers of desipramine (Brosen et al, 1993n).

3.5.1.BC Droperidol

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Any drug known to have the potential to prolong the QT interval should not be used together with droperidol. Possible pharmacodynamic interactions can occur between droperidol and potentially arrhythmogenic agents such as antidepressants that prolong the QT interval (Prod Info Inapsine(R), 2002).

3) Severity: major

4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Droperidol should be administered with extreme caution in the presence of risk factors for development of prolonged QT syndrome, such as treatment with antidepressants.
7) Probable Mechanism: additive cardiac effects

3.5.1.BD Droxicam

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.BE Duloxetine

1) Interaction Effect: increased duloxetine serum concentrations and an increased risk of serotonin syndrome
2) Summary: Duloxetine is a selective serotonin and norepinephrine reuptake inhibitor (SNRI). The concomitant use of duloxetine with paroxetine, an SSRI, is not recommended due to the potential for serotonin syndrome. In addition, coadministration of paroxetine, a potent CYP2D6 inhibitor, at a dose of 20 mg once daily with duloxetine 40 mg once daily resulted in a 60% increase in duloxetine serum concentration (Prod Info CYMBALTA(R) delayed-release oral capsules, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: The concomitant use of duloxetine and paroxetine is not recommended due to the potential for development of serotonin syndrome. Additionally, concomitant use has resulted in significantly increased duloxetine serum levels (Prod Info CYMBALTA(R) delayed-release oral capsules, 2008).
7) Probable Mechanism: paroxetine inhibition of CYP2D6-mediated duloxetine metabolism; additive serotonergic effects

3.5.1.BF Eletriptan

1) Interaction Effect: an increased risk of serotonin syndrome
2) Summary: There have been case reports of weakness, hyperreflexia, and incoordination following concomitant use of sumatriptan, a 5-hydroxytryptamine-1 (5HT-1) agonist, and a serotonin specific reuptake inhibitor (SSRI) (Prod Info Imitrex(R) Nasal Spray, 2003). Because eletriptan is a 5HT 1B/1D agonist, a similar interaction between SSRIs and eletriptan may occur (Prod Info Relpax(R), 2003). Concurrent use of a triptan and an SSRI may result in serotonin syndrome which may be life-threatening. Symptoms of serotonin syndrome may include restlessness, hallucinations, loss of coordination, fast heart beat, rapid changes in blood pressure, increased body temperature, overreactive reflexes, nausea, vomiting, and diarrhea. Clinicians should be aware that triptans may be commonly used intermittently and that either the triptan or the SSRI may be prescribed by a different physician. Discuss the risks of serotonin syndrome with patients who are prescribed this combination and monitor them closely for symptoms of serotonin syndrome (US Food and Drug Administration, 2006).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Coadministration of a triptan, such as eletriptan, and an SSRI may result in a life-threatening condition called serotonin syndrome. Be aware that triptans may be commonly used intermittently and that either the triptan or the SSRI may be prescribed by a different physician. If these

agents are used together, discuss the risks of serotonin syndrome with the patient and monitor closely for symptoms of serotonin syndrome (restlessness, hyperthermia, hyperreflexia, incoordination).
7) Probable Mechanism: additive pharmacologic effects resulting in excessive serotonergic stimulation

3.5.1.BG Encainide

1) Interaction Effect: an increased risk of encainide toxicity (cardiac arrhythmia)
2) Summary: Coadministration of paroxetine with other drugs that are metabolized by the cytochrome P4502D6 enzyme, such as encainide, should be approached with caution (Prod Info Paxil CR(TM), 2003k).
3) Severity: moderate
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Monitor heart rate and the EKG in patients receiving concurrent paroxetine and encainide. Doses may need to be reduced. Coadministration of these agents should be approached with caution.
7) Probable Mechanism: inhibition of encainide metabolism

3.5.1.BH Enoxaparin

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info PAXIL(R) oral tablets, suspension, 2008). Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with warfarin (Schalekamp et al, 2008; Prod Info PAXIL(R) oral tablets, suspension, 2008).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When paroxetine and an anticoagulant are given concurrently, monitor patients for signs of increased bleeding. Patients who are taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, when paroxetine therapy is initiated or discontinued (Prod Info PAXIL(R) oral tablets, suspension, 2008).
7) Probable Mechanism: unknown
8) Literature Reports

a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bleeding (hospital admission due to bleeding) in patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patients with a mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients experienced 11 bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experiencing bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model (Wallerstedt et al, 2009).

b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5), however, the rate of gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).

c) Preliminary data suggest that there may be a pharmacodynamic interaction (that causes an increased bleeding diathesis with unaltered prothrombin time) between paroxetine and warfarin. The concomitant use of paroxetine and warfarin should be undertaken with caution (Prod Info PAXIL(R) oral tablets, suspension, 2008).

d) In a multiple-dose study, several days of combined therapy with warfarin and paroxetine resulted in mild but clinically significant bleeding in 5 of 27 subjects. This effect occurred in the absence of a significant enhancement in warfarin-induced hypoprothrombinemia or changes in either paroxetine or warfarin disposition (Bannister et al, 1989b).

3.5.1.BI Epoprostenol

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and antiplatelet agents has been associated with an increased risk of bleeding. Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an antiplatelet agent are given concurrently, monitor patient for signs of increased bleeding (Prod Info PAXIL(R) oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008)
7) Probable Mechanism: unknown

3.5.1.BJ Eptifibatide
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and antiplatelet agents has been associated with an increased risk of bleeding. Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an antiplatelet agent are given concurrently, monitor patient for signs of increased bleeding (Prod Info PAXIL(R) oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008)
7) Probable Mechanism: unknown

3.5.1.BK Etodolac
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.BL Etofenamate
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).

b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.BM Etoricoxib

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).

b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.BN Felbinac

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).

b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.BO Fenbufen

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control

and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.BP Fenfluramine
1) Interaction Effect: serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)
2) Summary: Fenfluramine is a nonspecific serotonin agonist that both enhances the release of serotonin and inhibits serotonin reuptake. Combination therapy with fenfluramine and another selective serotonin reuptake inhibitor, such as paroxetine, has the potential to cause serotonin syndrome (Schneck & Mahowald, 1996). Serotonin syndrome is a hyperserotonergic state characterized by symptoms such as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. Serious, even fatal, reactions have been reported (Sternbach, 1991). Until more data are available, fenfluramine should not be used in combination with paroxetine.
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Concurrent use of fenfluramine and paroxetine may result in an additive increase in serotonin levels in the central nervous system, and could result in serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes). Fenfluramine should not be used in combination with paroxetine or other serotonin specific reuptake inhibitors.
7) Probable Mechanism: additive serotonergic effects

3.5.1.BQ Fenoprofen
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.BR Fentiazac

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.BS Flecainide
1) Interaction Effect: an increased risk of flecainide toxicity (cardiac arrhythmia)
2) Summary: No data are currently available related to concomitant flecainide - paroxetine administration. Lower doses than usually prescribed for both paroxetine or flecainide may be required. Flecainide is metabolized in the liver by cytochrome P4502D6. Paroxetine is a potent inhibitor of this isoenzyme, in addition to being metabolized by cytochrome P4502D6 itself (Prod Info Paxil CR(TM), 2032; Caley & Weber, 1993).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor heart rate and the EKG in patients receiving concurrent flecainide and paroxetine. Doses may need to be reduced. Coadministration of these agents should be approached with caution.
7) Probable Mechanism: inhibition of flecainide metabolism

3.5.1.BT Floctafenine
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.BU Flufenamic Acid
1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.BV Fluoxetine
1) Interaction Effect: fluoxetine toxicity (dry mouth, sedation, urinary retention)
2) Summary: Coadministration of paroxetine with drugs that are metabolized by cytochrome P450 2D6 (CYP2D6), such as fluoxetine, should be approached with caution (Prod Info Paxil CR(TM), 2002).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When paroxetine is coadministered with fluoxetine monitor patients for signs and symptoms of fluoxetine toxicity (dry mouth, sedation, urinary retention, blurred vision). Fluoxetine doses may need to be reduced.
7) Probable Mechanism: decreased cytochrome P450 2D6-mediated fluoxetine metabolism

3.5.1.BW Fluphenazine
1) Interaction Effect: an increased risk of developing acute parkinsonism
2) Summary: The development of acute, severe parkinsonism has been observed in a patient receiving fluphenazine for Tourette's syndrome and paroxetine for depression. Upon discontinuation of paroxetine, the parkinsonism resolved. A similar interaction has been observed when fluphenazine was given in combination with fluoxetine or sertraline (Kurlan, 1998a).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor patients receiving concurrent therapy with fluphenazine and paroxetine for the development of drug-induced parkinsonism. Therapy with paroxetine may need to be discontinued.
7) Probable Mechanism: inhibition of cytochrome P450-mediated fluphenazine metabolism by paroxetine
8) Literature Reports
a) A 48-year-old male with depression and chronic, multiple motor and vocal tics was controlled with fluphenazine 2.5 mg daily and nortriptyline 100 mg daily. Because of a worsening of the depression, nortriptyline therapy was discontinued and paroxetine 20 mg daily was initiated. After three weeks, the patient developed an acute, severe parkinsonian syndrome marked by resting tremor, rigidity, bradykinesia, stooped posture, and postural imbalance. These symptoms resolved within three weeks of discontinuing both the fluphenazine and paroxetine, and therapy with risperidone and imipramine was instituted with no recurrence of parkinsonism (Kurlan, 1998).

3.5.1.BX Flurbiprofen
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of

increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.BY Fondaparinux
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info PAXIL(R) oral tablets, suspension, 2008). Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with warfarin (Schalekamp et al, 2008; Prod Info PAXIL(R) oral tablets, suspension, 2008).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When paroxetine and an anticoagulant are given concurrently, monitor patients for signs of increased bleeding. Patients who are taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, when paroxetine therapy is initiated or discontinued (Prod Info PAXIL(R) oral tablets, suspension, 2008).
7) Probable Mechanism: unknown
8) Literature Reports
a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bleeding (hospital admission due to bleeding) in patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patients with a mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients experienced 11 bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experiencing bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model (Wallerstedt et al, 2009).
b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5), however, the rate of gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).
c) Preliminary data suggest that there may be a pharmacodynamic interaction (that causes an increased bleeding diathesis with unaltered prothrombin time) between paroxetine and warfarin. The concomitant use of paroxetine and warfarin should be undertaken with caution (Prod Info PAXIL(R) oral tablets, suspension, 2008).
d) In a multiple-dose study, several days of combined therapy with warfarin and paroxetine resulted in mild but clinically significant bleeding in 5 of 27 subjects. This effect occurred in the absence of a significant enhancement in warfarin-induced hypoprothrombinemia or changes in either paroxetine or warfarin disposition (Bannister et al, 1989b).

3.5.1.BZ Fosamprenavir
1) Interaction Effect: decreased paroxetine plasma levels

2) Summary: The concurrent administration of fosamprenavir/ritonavir and paroxetine has resulted in significantly decreased paroxetine plasma levels. Caution is advised if these agents are used concurrently. Dose adjustments should be guided by clinical efficacy and tolerability (Prod Info LEXIVA(R) oral solution, oral tablets, 2009; Prod Info PAXIL(R) oral tablets, oral suspension, 2006). Patients may need to be monitored for loss of paroxetine efficacy.
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Coadministration of fosamprenavir/ritonavir and paroxetine has led to significantly decreased paroxetine plasma levels. Use caution if these agents are coadministered. Dose adjustments should be made based on clinical efficacy and tolerability (Prod Info LEXIVA(R) oral solution, oral tablets, 2009; Prod Info PAXIL(R) oral tablets, oral suspension, 2006). Monitor patients for loss of paroxetine efficacy.
7) Probable Mechanism: unknown

3.5.1.CA Fosaprepitant
1) Interaction Effect: decreased plasma concentrations of aprepitant and paroxetine
2) Summary: Once daily doses of aprepitant, as a tablet formulation comparable to 85 mg or 170 mg of the capsule formulation, coadministered with paroxetine 20 mg/day, resulted in a decrease in AUC by approximately 25% and Cmax by approximately 20% of both aprepitant and paroxetine (Prod Info EMEND (R) IV injection, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concomitant administration of fosaprepitant and paroxetine should be approached with caution as this may lead to decreased plasma concentrations of both agents (Prod Info EMEND(R) IV injection, 2008).
7) Probable Mechanism: unknown

3.5.1.CB Fosphenytoin
1) Interaction Effect: reduced paroxetine efficacy
2) Summary: Fosphenytoin is a prodrug of phenytoin and the same interactions that occur with phenytoin are expected to occur with fosphenytoin (Prod Info Cerebyx(R), 1999). Limited reports related to the effects of combined phenytoin-paroxetine are currently available. Because of its enzyme-inducing effect, coadministered phenytoin apparently reduces serum concentrations of paroxetine, possibly leading to reduced efficacy of paroxetine (Prod Info Paxil(R), 1999a; Andersen et al, 1991a; Boyer & Blumhardt, 1992). There has been one case report of an elevated phenytoin level after four weeks of concurrent paroxetine and phenytoin coadministration (Prod Info Paxil(R), 1999a).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor patients for paroxetine effectiveness. Doses of paroxetine might need to be increased when these two agents are coadministered.
7) Probable Mechanism: induction of paroxetine metabolism
8) Literature Reports
a) Concomitant administration of a single-dose of paroxetine and phenytoin (300 mg once a day for 14 days) resulted in a reduction in the area under the plasma concentration-time curve (AUC) of paroxetine by 27% to 50%, as well as a decrease of 35% in the half-life of paroxetine (Kaye et al, 1989; Prod Info Paxil(R), 1999). This interaction appears to be related to the enzyme-inducing properties of phenytoin. Alternatively, in a single-dose phenytoin study, paroxetine (30 mg once a day for 14 days) had no effect on the mean peak plasma levels or the elimination half-life of phenytoin 300 mg. However, a 12% reduction in the area under the plasma concentration-time curve (AUC) for phenytoin was observed.
b) Nineteen epilepsy patients who were well controlled on either phenytoin (n=5), carbamazepine (n=6), or valproate (n=8) took part in a single-blind, placebo-controlled, cross-over study to determine the effect of concurrent use of paroxetine and anticonvulsants. Subjects received placebo for seven days, then paroxetine 10 mg daily for three days, 20 mg daily for three days, and 30 mg daily for 10 days. There were no statistically significant changes in plasma levels and free fractions in any of the anticonvulsant drugs during any phase of the study. Mean paroxetine plasma levels were lowest with concurrent phenytoin therapy (p less than 0.005 when compared with valproate); however, there is no clear association between paroxetine plasma concentrations and efficacy. No severe adverse effects were seen with co-therapy, no seizures occurred, and no changes in protein binding were found (Andersen et al, 1991).
c) Paroxetine does not alter in vitro protein binding of phenytoin (Prod Info Paxil(R), 1999).

3.5.1.CC Frovatriptan
1) Interaction Effect: an increased risk of serotonin syndrome
2) Summary: There have been case reports of weakness, hyperreflexia, and incoordination following concomitant use of sumatriptan, a 5-hydroxytryptamine-1 (5HT-1) agonist, and a serotonin specific reuptake

inhibitor (SSRI) (Prod Info Imitrex(R) Nasal Spray, 2003). Because frovatriptan is a 5HT 1B/1D agonist, a similar interaction between SSRIs and frovatriptan may occur (Prod Info Frova(R), 2004). Concurrent use of frovatriptan and an SSRI may result in serotonin syndrome which may be life-threatening. Symptoms of serotonin syndrome may include restlessness, hallucinations, loss of coordination, fast heart beat, rapid changes in blood pressure, increased body temperature, overreactive reflexes, nausea, vomiting, and diarrhea. Clinicians should be aware that triptans may be commonly used intermittently and that either the triptan or the SSRI may be prescribed by a different physician. Discuss the risks of serotonin syndrome with patients who are prescribed this combination and monitor them closely for symptoms of serotonin syndrome (US Food and Drug Administration, 2006).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Coadministration of a triptan, such as frovatriptan, and an SSRI may result in a life-threatening condition called serotonin syndrome. Be aware that triptans may be commonly used intermittently and that either the triptan or the SSRI may be prescribed by a different physician. If these agents are used together, discuss the risks of serotonin syndrome with the patient and monitor closely for symptoms of serotonin syndrome (restlessness, hyperthermia, hyperreflexia, incoordination).
7) Probable Mechanism: additive pharmacologic effects resulting in excessive serotonergic stimulation

3.5.1.CD Furazolidone
1) Interaction Effect: weakness, hyperreflexia, and incoordination
2) Summary: Although not its primary mechanism of action, furazolidone has monoamine oxidase inhibitor activity. Cases of serious sometimes fatal reactions have been reported in patients receiving selective serotonin reuptake inhibitors (SSRI) in combination with monoamine oxidase inhibitors (MAOIs). Hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma have been reported. Furazolidone should not be used in combination with an SSRI, or within a minimum of 14 days of discontinuing therapy with a MAOI (Prod Info Furoxone(R), 1999).
3) Severity: contraindicated
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: If concurrent therapy with furazolidone and a selective serotonin reuptake inhibitor (SSRI) is deemed to be necessary, closely monitor the patient for signs of serotonergic excess (mental status changes, diaphoresis, fever, weakness, hyperreflexia, incoordination).
7) Probable Mechanism: additive pharmacologic effects resulting in excessive serotonergic stimulation

3.5.1.CE Galantamine
1) Interaction Effect: increased galantamine plasma concentrations
2) Summary: Based upon in vitro studies, the major enzymes involved in galantamine metabolism are CYP3A4 and CYP2D6. Paroxetine is a potent inhibitor of CYP2D6. When paroxetine 20 mg daily for 16 days was administered concurrently with galantamine, the galantamine oral bioavailability increased approximately 40%. Such an increase may warrant caution when coadministering these two medications. Monitor for galantamine toxicity including anorexia, nausea, vomiting, dizziness, arrhythmias or gastrointestinal bleeding (Prod Info RAZADYNE(R) ER extended release oral capsules, oral tablets, oral solution, 2007).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Increased galantamine plasma concentrations may result from paroxetine inhibition of galantamine CYP2D6-mediated metabolism. Monitor for galantamine toxicity including anorexia, nausea, vomiting, dizziness, arrhythmias, or gastrointestinal bleeding (Prod Info RAZADYNE(R) ER extended release oral capsules, oral tablets, oral solution, 2007).
7) Probable Mechanism: inhibition of cytochrome CYP2D6-mediated galantamine metabolism

3.5.1.CF Ginkgo
1) Interaction Effect: increased risk of serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)
2) Summary: The addition of Ginkgo biloba and/or St. John's Wort to therapy with buspirone and fluoxetine may have precipitated a hypomanic episode in a case report (Spinella & Eaton, 2002a). It is unclear if Ginkgo or St. John's Wort, the combination of both, or other patient factors, contributed to the effect. Theoretically, Ginkgo may increase the risk of serotonin syndrome when taken with selective serotonin reuptake inhibitors (SSRIs). Caution is advised, especially when ginkgo is taken to counteract sexual dysfunction associated with SSRIs. Ginkgo may inhibit monoamine oxidase (Sloley et al, 2000; White et al, 1996), and has demonstrated serotonergic activity in animals (Ramassamy et al, 1992) which might increase the risk of serotonin syndrome when ginkgo is combined with SSRIs. The potential MAO inhibitory activity of ginkgo is questionable. A human study did not show MAO inhibition in the brain following oral consumption (Fowler et al, 2000). Ginkgo biloba extract inhibited MAO-A/MAO-B in the rat brain in vitro (Sloley et al, 2000; White et al, 1996) and MAO-B in human platelets in vitro (White et al, 1996). No

significant MAO inhibition was found in mice following oral consumption (Porsolt et al, 2000).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor patients closely for symptoms of serotonin syndrome if ginkgo is combined with selective serotonin reuptake inhibitors (SSRIs).
7) Probable Mechanism: additive pharmacologic effects resulting in excessive serotonergic stimulation
8) Literature Reports
a) A 42-year-old female experienced symptoms consistent with a mixed hypomanic episode following concomitant use of fluoxetine, buspirone, Ginkgo biloba, and St. John's Wort. The symptoms resolved following discontinuation of Ginkgo and St. John's Wort. The patient was being treated for depression following a mild traumatic brain injury with fluoxetine 20 milligrams (mg) twice daily and buspirone 15 mg twice daily. Several weeks prior to presentation, buspirone was increased to 20 mg twice daily for persistent anxiety and the patient began taking Ginkgo biloba, melatonin, and St. John's Wort in unspecified doses. Melatonin was considered unlikely to have contributed to her symptoms. Ginkgo and St. John's Wort were considered possible contributors since they may potentiate antidepressants, and considering the temporal relationship between the use of the herbs and onset of symptoms and discontinuation of the herbs and resolution of symptoms. However, the brain injury was considered a possible contributor (Spinella & Eaton, 2002).

3.5.1.CG Heparin
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info PAXIL(R) oral tablets, suspension, 2008). Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with warfarin (Schalekamp et al, 2008; Prod Info PAXIL(R) oral tablets, suspension, 2008).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When paroxetine and an anticoagulant are given concurrently, monitor patients for signs of increased bleeding. Patients who are taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, when paroxetine therapy is initiated or discontinued (Prod Info PAXIL(R) oral tablets, suspension, 2008).
7) Probable Mechanism: unknown
8) Literature Reports
a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bleeding (hospital admission due to bleeding) in patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patients with a mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients experienced 11 bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experiencing bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model (Wallerstedt et al, 2009).
b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5), however, the rate of gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).
c) Preliminary data suggest that there may be a pharmacodynamic interaction (that causes an increased bleeding diathesis with unaltered prothrombin time) between paroxetine and warfarin. The concomitant use of paroxetine and warfarin should be undertaken with caution (Prod Info PAXIL(R) oral tablets, suspension, 2008).
d) In a multiple-dose study, several days of combined therapy with warfarin and paroxetine resulted in mild but clinically significant bleeding in 5 of 27 subjects. This effect occurred in the absence of a

significant enhancement in warfarin-induced hypoprothrombinemia or changes in either paroxetine or warfarin disposition (Bannister et al, 1989b).

3.5.1.CH Hydroxytryptophan

1) Interaction Effect: an increased risk of serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)

2) Summary: Hydroxytryptophan (5-HTP) may potentiate the serotonergic effect of selective serotonin reuptake inhibitors (SSRIs) (Meltzer et al, 1997a). Since 5-HTP increases serotonin levels, when combined with an SSRI, the serotonin level may be increased sufficiently to produce serotonin syndrome. Caution is advised with concomitant use of 5-HTP and SSRIs.

3) Severity: moderate

4) Onset: rapid

5) Substantiation: theoretical

6) Clinical Management: No cases have been reported of serotonin syndrome resulting from this combination. Caution is advised if hydroxytryptophan (5-HTP) and a selective serotonin reuptake inhibitor (SSRI) are used concomitantly. Monitor the patient for early signs of serotonin syndrome such as anxiety, confusion, and disorientation.

7) Probable Mechanism: additive serotonergic effect

8) Literature Reports

a) Hydroxytryptophan (5-HTP) (200 milligrams (mg) orally) as a single dose increased plasma cortisol and prolactin levels in both medicated and unmedicated patients with major depression or obsessive compulsive disorder (OCD). These responses were greater if the patient was also taking fluoxetine (n = 16) (p less than 0.0001). Mean fluoxetine dose for depressed patients was 44 mg/day,and for OCD patients it was 60 mg/day. Cortisol or prolactin (PRL) levels in patients taking 5-HTP with tricyclic antidepressants (n = 14) or those receiving no medication (n = 83) were not significantly different from each other. A measurement of serotonergic effects of antidepressants can be evaluated by measuring hypothalamic-pituitary-adrenal (HPA) axis or PRL response. No clinical manifestations of serotonin syndrome were reported in patients taking 5-HTP concomitantly with fluoxetine (Meltzer et al, 1997).

3.5.1.CI Ibuprofen

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).

b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.CJ Iloperidone

1) Interaction Effect: increased plasma concentrations of iloperidone

2) Summary: Coadministration of iloperidone and paroxetine results in increased plasma levels of iloperidone and therefore requires a dose reduction of iloperidone (Prod Info FANAPT(TM) oral tablets, 2009).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: If administered with paroxetine, reduce iloperidone doses by one-half. Upon withdrawal of paroxetine from the combination therapy, resume the previous iloperidone dose (Prod Info FANAPT(TM) oral tablets, 2009).

7) Probable Mechanism: inhibition of the CYP2D6-mediated metabolism of iloperidone

8) Literature Reports

a) Schizophrenic patients (ages 18 to 65 years) receiving paroxetine 20 mg/day for 5 to 8 days and multiple doses of iloperidone 8 or 12 mg twice daily experienced an increase in mean steady-state peak iloperidone concentrations by about 1.6-fold. Concentrations of the P88 metabolite were similarly increased, while the mean steady-state peak concentrations of the P95 metabolite were decreased by one-half(Prod Info FANAPT(TM) oral tablets, 2009).

3.5.1.CK Iloprost

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and antiplatelet agents has been associated with an increased risk of bleeding. Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an antiplatelet agent are given concurrently, monitor patient for signs of increased bleeding (Prod Info PAXIL(R) oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008)
7) Probable Mechanism: unknown

3.5.1.CL Imipramine

1) Interaction Effect: imipramine toxicity (dry mouth, sedation, urinary retention)
2) Summary: Paroxetine coadministered with desipramine or imipramine produced higher serum concentrations of the tricyclic antidepressant (TCA) in some patients (Prod Info Paxil CR(TM), 2003b; Hartter et al, 1994; Brosen et al, 1993a). Paroxetine's effect on TCAs may resemble that of fluoxetine (another selective serotonin reuptake inhibitor), which is known to inhibit TCA metabolism (Aranow et al, 1989; Vaughan, 1988; Goodnick, 1989). With coadministration, monitor patients for imipramine toxicity. Imipramine doses may need to be reduced.
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Coadministration of paroxetine with other drugs that are metabolized by cytochrome P450 2D6 (CYP2D6) should be approached with caution. When paroxetine is coadministered with imipramine, monitor patients for signs and symptoms of imipramine toxicity (dry mouth, sedation, urinary retention, blurred vision). Imipramine doses may need to be reduced.
7) Probable Mechanism: decreased cytochrome P450 2D6-mediated imipramine metabolism
8) Literature Reports

a) The effect of paroxetine on desipramine metabolism was studied in nine extensive metabolizers (EM) and eight poor metabolizers (PM) of desipramine. Subjects took a single oral dose of desipramine before starting paroxetine and a second dose after 11 days of paroxetine use. After the addition of paroxetine, EMs experienced a 5-fold decrease in clearance of desipramine, indicating that paroxetine inhibits oxidation reactions catalyzed by CYP2D6. PMs had a slight increase in clearance of desipramine with paroxetine. With concurrent administration of desipramine and paroxetine, interaction of the two drugs may result in a need for dosage adjustments, especially in extensive metabolizers of desipramine (Brosen et al, 1993).

3.5.1.CM Indomethacin

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate

an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).

b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.CN Indoprofen

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).

b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.CO Iproniazid

1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)

2) Summary: Concurrent administration or overlapping therapy with paroxetine and a monoamine oxidase (MAO) inhibitor may result in CNS toxicity or serotonin syndrome, a hyperserotonergic state characterized by symptoms such as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. Serious, even fatal, reactions have been reported with concomitant use of serotonin specific reuptake inhibitors and MAO inhibitors (Prod Info Paxil(R), 1999d; Lappin & Auchincloss, 1994k; Graber et al, 1994k; Suchowersky & de Vries, 1990k). Concomitant use is contraindicated.

3) Severity: contraindicated

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: Concurrent use of paroxetine and a MAO inhibitor is contraindicated. Wait at least two weeks after discontinuing a MAO inhibitor before initiating paroxetine, and at least two weeks after discontinuing paroxetine before initiating therapy with a MAO inhibitor.

7) Probable Mechanism: inhibition of serotonin metabolism by monoamine oxidase

8) Literature Reports

a) Concomitant use of SSRIs and monoamine oxidase inhibitors can produce a toxic reaction known as serotonin syndrome (Sternbach, 1991j). Serotonin syndrome is a condition of serotonergic hyperstimulation and manifests as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. If the syndrome is not recognized and correctly treated, fatality can result.

b) A 26-year old woman who had been taking isocarboxazid for eight weeks stopped taking the drug for 11 days before beginning therapy with sertraline. After a single 100 mg sertraline dose, the patient became restless and developed leg twitches. The patients was later admitted to the emergency room with diaphoresis, tachycardia, hyperreflexia, and various neuromuscular disturbances. After treatment with diazepam and propranolol the patient did not improve. The patient was then given two 4 mg doses of cyproheptadine an hour apart, with notable improvement in symptoms after the second dose (Lappin & Auchincloss, 1994j).

c) A drug interaction was reported in a 61-year old woman in which sertraline 100 mg twice daily was added to a regimen of lithium, phenelzine, thioridazine, and doxepin. Three hours after taking the first sertraline dose, the patient was found in a semicomatose state, with elevated body temperature, increased pulse, increased respiration rate, and a blood pressure of 140/110 mm Hg. After transportation to the hospital, the patient was misdiagnosed as having neuroleptic malignant syndrome (NMS) which was later changed to serotonin syndrome due to a reaction between sertraline and phenelzine. The authors suggest that monoamine oxidase inhibitor (MAOI) therapy should be discontinued for at least two weeks before initiation of therapy with a selective serotonin reuptake

inhibitor (SSRI) and that before starting a MAOI, SSRI therapy should be discontinued for at least five half-lives of the parent drug and any active metabolites (Graber et al, 1994j).

d) Two cases reports suggested a possible interaction between fluoxetine and selegiline (Suchowersky & de Vries, 1990j). One case involved a first episode of mania being observed approximately one month after adding selegiline to fluoxetine. The patient improved two months after both drugs were discontinued, and no further details were provided. The second case involved diaphoresis, vasoconstriction, and cyanosis of the hands which occurred in close temporal relationship to adding fluoxetine to selegiline. Both drugs were discontinued, with relatively quick resolution of symptoms. Rechallenge with fluoxetine alone occurred without incident.

3.5.1.CP Isocarboxazid

1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)

2) Summary: Concurrent administration or overlapping therapy with paroxetine and a monoamine oxidase (MAO) inhibitor may result in CNS toxicity or serotonin syndrome, a hyperserotonergic state characterized by symptoms such as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. Serious, even fatal, reactions have been reported with concomitant use of serotonin specific reuptake inhibitors and MAO inhibitors (Prod Info Paxil(R), 2003f; Lappin & Auchincloss, 1994m; Graber et al, 1994m; Suchowersky & de Vries, 1990m). Concomitant use is contraindicated (Prod Info Marplan(R), 1998).

3) Severity: contraindicated

4) Onset: rapid

5) Substantiation: theoretical

6) Clinical Management: Concurrent use of paroxetine and an MAO inhibitor is contraindicated. Wait at least two weeks after discontinuing an MAO inhibitor before initiating paroxetine, and at least two weeks after discontinuing paroxetine before initiating therapy with an MAOI.

7) Probable Mechanism: inhibition of serotonin metabolism by monoamine oxidase

8) Literature Reports

a) Concomitant use of SSRIs and monoamine oxidase inhibitors can produce a toxic reaction known as serotonin syndrome (Sternbach, 1991k). Serotonin syndrome is a condition of serotonergic hyperstimulation and manifests as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. If the syndrome is not recognized and correctly treated, fatality can result.

b) A 26-year old woman who had been taking isocarboxazid for eight weeks stopped taking the drug for 11 days before beginning therapy with sertraline. After a single 100 mg sertraline dose, the patient became restless and developed leg twitches. The patients was later admitted to the emergency room with diaphoresis, tachycardia, hyperreflexia, and various neuromuscular disturbances. After treatment with diazepam and propranolol the patient did not improve. The patient was then given two 4 mg doses of cyproheptadine an hour apart, with notable improvement in symptoms after the second dose (Lappin & Auchincloss, 1994l).

c) A drug interaction was reported in a 61-year old woman in which sertraline 100 mg twice daily was added to a regimen of lithium, phenelzine, thioridazine, and doxepin. Three hours after taking the first sertraline dose, the patient was found in a semicomatose state, with elevated body temperature, increased pulse, increased respiration rate, and a blood pressure of 140/110 mm Hg. After transportation to the hospital, the patient was misdiagnosed as having neuroleptic malignant syndrome (NMS) which was later changed to serotonin syndrome due to a reaction between sertraline and phenelzine. The authors suggest that monoamine oxidase inhibitor (MAOI) therapy should be discontinued for at least two weeks before initiation of therapy with a selective serotonin reuptake inhibitor (SSRI) and that before starting a MAOI, SSRI therapy should be discontinued for at least five half-lives of the parent drug and any active metabolites (Graber et al, 1994l).

d) Two cases reports suggested a possible interaction between fluoxetine and selegiline (Suchowersky & de Vries, 1990l). One case involved a first episode of mania being observed approximately one month after adding selegiline to fluoxetine. The patient improved two months after both drugs were discontinued, and no further details were provided. The second case involved diaphoresis, vasoconstriction, and cyanosis of the hands which occurred in close temporal relationship to adding fluoxetine to selegiline. Both drugs were discontinued, with relatively quick resolution of symptoms. Rechallenge with fluoxetine alone occurred without incident.

3.5.1.CQ Isoxicam

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.CR Ketoprofen
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.CS Ketorolac
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.CT Lamifiban

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and antiplatelet agents has been associated with an increased risk of bleeding. Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an antiplatelet agent are given concurrently, monitor patient for signs of increased bleeding (Prod Info PAXIL(R) oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008)

7) Probable Mechanism: unknown

3.5.1.CU Lexipafant

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and antiplatelet agents has been associated with an increased risk of bleeding. Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an antiplatelet agent are given concurrently, monitor patient for signs of increased bleeding (Prod Info PAXIL(R) oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008)

7) Probable Mechanism: unknown

3.5.1.CV Linezolid

1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)

2) Summary: Concurrent use of linezolid and paroxetine is contraindicated. A 2-week washout period should be used between the administration of linezolid and paroxetine (Prod Info PAXIL CR(R) controlled-release oral tablets, 2008; Prod Info PAXIL(R) oral tablets, suspension, 2008). Linezolid is a reversible, nonselective inhibitor of monoamine oxidase. Concurrent administration or overlapping therapy with paroxetine and a monoamine oxidase (MAO) inhibitor may result in CNS toxicity or serotonin syndrome such as neuromuscular abnormalities (including hyper-reflexia, tremor, muscle rigidity, clonus, peripheral hypertonicity, and shivering), autonomic hyperactivity (including tachycardia, mydriasis, diaphoresis, and diarrhea), and mental status changes (including agitation and delirium). Serious, even fatal, reactions have been reported (Boyer & Shannon, 2005). There have been spontaneous reports of serotonin syndrome associated with concomitant use of linezolid and serotonergic agents (Wigen & Goetz, 2002; Prod Info ZYVOX(R) IV injection, oral tablets, oral suspension, 2008).

3) Severity: contraindicated

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: Concurrent use of linezolid and paroxetine is contraindicated. Allow a minimum 2-week washout period between the administration of these drugs (Prod Info PAXIL CR(R) controlled-release oral tablets, 2008; Prod Info PAXIL(R) oral tablets, suspension, 2008).

7) Probable Mechanism: inhibition of serotonin metabolism by monoamine oxidase

8) Literature Reports

a) Linezolid may cause serotonin syndrome in patients receiving selective serotonin reuptake inhibitors. A 56-year-old female with a history of depression, chronic hepatitis C infection, hypertension, diabetes, and cervical stenosis was admitted for elective laminectomy. There was evidence of hepatic cirrhosis with an abdominal CT scan. Her medications preoperatively included paroxetine, IFN-alpha, felodipine, terazosin, lisinopril, insulin, methocarbamol, morphine sulfate, and ibuprofen. The last dose of paroxetine was administered on postoperative day 14. At that point it was discovered that the patient an infected surgical site and empiric therapy with vancomycin was initiated. The patient remained febrile, however, and linezolid was substituted for vancomycin. Within 24 hours the patient developed delirium, hypertension, hostility, anger, and tremors. Serotonin syndrome was diagnosed and linezolid therapy was discontinued. Vancomycin was reinstated and within 48 hours the patient returned to her baseline mental status. The serum half-life of paroxetine is 21 hours. It is likely that the inhibitory effect of linezolid combined with residual paroxetine activity produced serotonin syndrome in this patient. This particular patient may have been at increased risk for this syndrome because of her other medications as well as a decreased hepatic clearance. The author suggests that in high-risk patients, a 2-week washout period is advised between the discontinuation of selective serotonin reuptake inhibitors and initiation of linezolid (Wigen & Goetz, 2002).

3.5.1.CW Lithium

1) Interaction Effect: possible increased lithium concentrations and/or an increased risk of SSRI-related serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)

2) Summary: Concomitant use of lithium and various SSRIs has been associated with enhanced side effects of either or both drugs, and with or without elevated lithium levels. The combination has resulted in neurotoxicity and increased lithium levels in one case report (Salama & Shafey, 1989a). Signs and symptoms of lithium toxicity and serotonin syndrome have also been reported in patients who demonstrated therapeutic serum lithium levels while on concurrent fluoxetine and lithium (Muly et al, 1993a; Noveske et al, 1989a). Two studies have failed to identify a pharmacokinetic interaction between lithium and citalopram (Gram et al, 1993a; Baumann et al, 1996a). Combined administration of citalopram (40 mg daily for 10 days) and lithium (30 mmol/day for 5 days) had no significant effect on the pharmacokinetics of citalopram or lithium. However, plasma lithium levels should be monitored with appropriate adjustment to the lithium dose in accordance with standard clinical practice. Lithium may enhance the serotonergic effects of citalopram, therefore caution should be exercised when citalopram and lithium are coadministered (Prod Info Celexa(R), 2004). Concurrent use of fluvoxamine and lithium has led to case reports of increased lithium levels and neurotoxicity, serotonin syndrome, somnolence, and mania (Salama & Shafey, 1989a; Ohman & Spigset, 1993a; Evans & Marwick, 1990; Burrai et al, 1991a). No pharmacokinetic interference was apparent during a multiple-dose study of coadministered lithium and paroxetine (Prod Info Paxil CR(TM), 2003i). If these two agents are to be given concomitantly, the manufacturer suggests that caution be used until more clinical experience is available. Drug interactions leading to lithium toxicity have been reported when lithium was coadministered with fluoxetine and fluvoxamine (both in the same pharmacological class as paroxetine, eg, selective serotonin reuptake inhibitors) (Ohman & Spigset, 1993a; Salama & Shafey, 1989a).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: established

6) Clinical Management: Monitor patients on concurrent lithium and selective serotonin reuptake inhibitor therapy for increased plasma concentrations of lithium. In addition, monitor patients for signs and symptoms associated with serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes).

7) Probable Mechanism: unknown

8) Literature Reports

a) Concomitant administration of oral lithium carbonate and oral fluoxetine resulted in increased lithium serum levels with lithium toxicity in a 44-year-old woman with a bipolar affective disorder (Salama & Shafey, 1989). Fluoxetine 20 mg daily was added to a regimen of lithium 1200 mg daily following patient complaints of weakness, tiredness, decreased concentration, and early morning awakening. Lithium serum levels increased to 1.7 mEq/L from a range of 0.75 to 1.15 mEq/L prior to fluoxetine. Fluoxetine was discontinued and the dose of lithium decreased; this resulted in a decrease in the lithium serum level within 48 hours to 1.2 mEq/L. The neurologic symptoms subsided within seven days as the lithium serum level decreased to 0.9 mEq/L. The contribution of fluoxetine to lithium toxicity in this patient was obscured by the fact that the lithium was reduced at the time of fluoxetine withdrawal.

b) A 53-year old woman who had been taking fluoxetine 20 mg daily and lorazepam 0.5 mg four times daily for a major depressive disorder had lithium 900 mg per day added to her regimen in order to augment her response to fluoxetine. Within 48 hours, the patient became confused, ataxic, and developed a coarse tremor in her right arm. Vital signs showed a rectal temperature of 101 degrees F, and laboratory values were normal except for an elevated leukocyte count and slightly elevated bilirubin level. After discontinuation of lithium and fluoxetine, the patient's symptoms resolved over the next four days. At no point did the lithium levels reach a toxic level, suggesting that the patient's symptoms were due to a toxic reaction between fluoxetine and lithium (Noveske et al, 1989).

c) Serotonin syndrome was precipitated when lithium 300 mg twice daily was added to a three-month regimen of fluoxetine 40 mg per day. Five days later, the patient's lithium level was measured at 0.65 mEq/L and the dose was increased to 300 mg three times daily. Two days after this dosage change, the patient experienced akathisia, myoclonus, hyperreflexia, shivering, tremor, diarrhea, and incoordination. After discontinuation of lithium and initiation of cyproheptadine therapy, the patient's symptoms began to improve. The patient was discharged on a regimen of fluoxetine 40 mg per day without further symptoms of serotonin syndrome (Muly et al, 1993).

d) Eight healthy male volunteers completed three phases of an interaction study to determine the effects of coadministered lithium and citalopram. All subjects were extensive metabolizers of sparteine, indicating normal cytochrome P450 2D6 enzyme activity. Although lithium is not influenced by drug oxidation, citalopram metabolites are excreted by the kidney, as is lithium. Each subject received citalopram 40 mg alone as a single daily dose for 10 days, lithium 30 mmol (1980 mg) alone daily for five days, and lithium coadministered with citalopram on days 3-7. At least two weeks separated each treatment phase. Results showed that the concurrent administration of citalopram and lithium did not significantly alter the pharmacokinetics of lithium (Gram et al, 1993).

e) Twenty-four patients experiencing depression (DSM III criteria) were randomized under double-blind conditions to receive citalopram (40 mg to 60 mg daily) and lithium carbonate (800 mg daily) or placebo. All of the subjects had failed to respond to four weeks of citalopram monotherapy. Lithium was coadministered on days 29 to 42. No evidence of a pharmacokinetic interaction between lithium and citalopram was noted, and cotherapy was well tolerated (Baumann et al, 1996).

f) Serotonin syndrome was described in a 53-year-old patient who was stabilized on lithium 1400 mg daily (serum level 0.71 mmol/L) and was given fluvoxamine 50 mg daily. Over a 10-day period the fluvoxamine dose was increased to 200 mg daily; tremor and difficulty with fine hand movements developed. After two weeks, tremor, impaired motor function coordination, marked bilateral hyperreflexia of biceps and knee jerks, and clonus in both ankles were seen. After 12 weeks of continued therapy, during which time no further deterioration occurred, nortriptyline 100 mg daily replaced fluvoxamine, and the neuromuscular symptoms abated over a 2-week period. After four weeks the patient's neurological exam was normal (Ohman & Spigset, 1993).
g) Three cases of mania were reported in patients who were treated with lithium and fluvoxamine. The mania appeared 10 days, four weeks, and five weeks, respectively, after cotherapy was begun. Fluvoxamine was discontinued and, in two of the three patients, the mania resolved, and successful treatment of depression occurred with lithium alone. The third patient improved, but depression reappeared within a month of fluvoxamine discontinuation (Burrai et al, 1991).
h) In an open-labeled, placebo-controlled study, lithium 600 mg was administered to 16 subjects orally twice daily on days one through eight and once in the morning on day nine. In addition, oral sertraline 100 mg or placebo was given twice, ten hours and two hours prior to lithium dosing on day nine. The steady-state lithium level was only decreased by 1.4% (0.01 mEq/L) and the lithium renal clearance increased by 6.9% (0.11 L/hour) when sertraline was coadministered. Seven subjects experienced side effects, mainly tremors, after receiving lithium and sertraline, whereas no subjects who ingested placebo and lithium experienced side effects (Wilner et al, 1991).

3.5.1.CX Lofepramine

1) Interaction Effect: lofepramine toxicity (dry mouth, sedation, urinary retention)
2) Summary: Paroxetine coadministered with desipramine or imipramine produced higher serum concentrations of the tricyclic antidepressant (TCA) in some patients (Hartter et al, 1994a; Brosen et al, 1993c). Although not reported specifically with lofepramine, a similar interaction could be expected. Paroxetine's effect on TCAs may resemble that of fluoxetine (another selective serotonin reuptake inhibitor), which is known to inhibit TCA metabolism (Aranow et al, 1989a; Vaughan, 1988a; Goodnick, 1989a). With coadministration, monitor patients for lofepramine toxicity. Lofepramine doses may need to be reduced (Prod Info Paxil CR(TM), 2003c).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When lofepramine is coadministered with paroxetine, monitor patients for signs and symptoms of lofepramine toxicity (dry mouth, sedation, urinary retention, blurred vision). Lofepramine doses may need to be reduced.
7) Probable Mechanism: decreased lofepramine metabolism
8) Literature Reports
a) The effect of paroxetine on desipramine metabolism was studied in 9 extensive metabolizers (EM) and 8 poor metabolizers (PM) of desipramine. Subjects took a single oral dose of desipramine before starting paroxetine and a second dose after 11 days of paroxetine use. After the addition of paroxetine, EMs experienced a 5-fold decrease in clearance of desipramine, indicating that paroxetine inhibits oxidation reactions catalyzed by CYP2D6. PMs had a slight increase in clearance of desipramine with paroxetine. With concurrent administration of desipramine and paroxetine, interaction of the two drugs may result in a need for dosage adjustments, especially in extensive metabolizers of desipramine (Brosen et al, 1993b).

3.5.1.CY Lornoxicam

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate

an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.CZ Meclofenamate

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.DA Mefenamic Acid

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.DB Meloxicam

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of

increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.DC Methylphenidate
1) Interaction Effect: increased selective serotonin reuptake inhibitor plasma concentrations
2) Summary: Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism of selective serotonin reuptake inhibitors (SSRIs). Downward dose adjustments of the SSRI may be necessary when it is used concurrently with methylphenidate. Additionally, when initiating or discontinuing methylphenidate, the SSRI dose may need to be adjusted as needed (Prod Info METADATE CD(R) extended-release oral capsules, 2007).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Use caution when prescribing methylphenidate to patients who take an selective serotonin reuptake inhibitor (SSRI). Concomitant use of methylphenidate and an SSRI may cause elevated SSRI plasma concentrations. Consider a decrease in the dose of SSRI when these agents are coadministered. Additionally, consider adjusting the SSRI dose if necessary when initiating or discontinuing methylphenidate therapy (Prod Info METADATE CD(R) extended-release oral capsules, 2007).
7) Probable Mechanism: inhibition of selective serotonin reuptake inhibitor metabolism by methylphenidate

3.5.1.DD Metoprolol
1) Interaction Effect: an increased risk of metoprolol adverse effects (shortness of breath, bradycardia, hypotension, acute heart failure)
2) Summary: Paroxetine was shown to alter the pharmacokinetics and enhance the pharmacodynamics of metoprolol, most likely through inhibition of cytochrome P450 2D6 enzymes necessary for metoprolol metabolism. Multiple-dose intake of both paroxetine and metoprolol may require a reduction in the dose of metoprolol to prevent metoprolol adverse effects, such as bradycardia, hypotension, and bronchoconstriction due to loss of cardioselectivity (Hemeryck et al, 2000a). Consider other therapies, such as atenolol or bisoprolol, which are not metabolized through CYP2D6 mechanisms, or alternative antidepressant therapy (Onalan et al, 2008).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Patients receiving concurrent therapy with metoprolol and paroxetine should be monitored for bradycardia and loss of cardioselectivity. Dose reductions of metoprolol, a change from metoprolol to atenolol or bisoprolol, or substitution of paroxetine with an alternative antidepressant may be necessary.
7) Probable Mechanism: inhibition of cytochrome P450 2D6-mediated metoprolol metabolism
8) Literature Reports
a) Eight healthy male volunteers participated in an open-label trial to determine whether administration of multiple-dose paroxetine altered the stereoselective pharmacokinetics and pharmacodynamics of metoprolol. All participants received metoprolol 100 mg on day 1, followed on day 2 through 7 by paroxetine 10 mg twice daily. Another dose of metoprolol 100 mg was given on day 8. Paroxetine caused an 8-fold (from 169 ng/h/mL to 1340 ng/h/mL) and a 5-fold (from 279 ng/h/mL to 1418 ng/h/mL) increase in the area under the concentration-time curve (AUC) of (R)- and (S)- metoprolol, respectively. For both enantiomers of metoprolol, the maximum concentration (Cmax) and half-life were approximately doubled during therapy with paroxetine. The stereoselectivity of metoprolol was virtually eliminated following paroxetine, with the (S)/(R) AUC ratio decreasing from 1.72 to 1.07. Pharmacodynamically, the increase in (S)- metoprolol plasma concentrations was associated with a more sustained beta-blockade as demonstrated by a reduction in exercise heart rate and exercise systolic blood pressure (Hemeryck et al, 2000).
b) Fifteen days after initiating metoprolol (50 mg/day) therapy, a 63-year-old woman maintained on paroxetine 20 mg/day and alprazolam 0.5 mg/day for the previous year experienced complete atrioventricular (AV) block and syncope. Metoprolol was discontinued, and 3 days later the patient was asymptomatic with normal blood pressure and heart rate. A 12-lead electrocardiography (ECG) showed complete AV block with a narrow QRS escape rhythm of 40 beats/minute. Coronary angiogram was

unremarkable and the results of all other diagnostic tests were normal. Paroxetine was discontinued, and by day 5 the AV block had completely resolved. Subsequent similar doses of either paroxetine or metoprolol monotherapy did not induce bradyarrhythmia in this patient (Onalan et al, 2008).

3.5.1.DE Milnacipran

1) Interaction Effect: increased risk of serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)

2) Summary: Concurrent use of milnacipran and an SSRI may result in hypertension, coronary artery vasoconstriction or serotonin syndrome, which may be life-threatening. Symptoms of serotonin syndrome may include restlessness, hallucinations, loss of coordination, fast heart beat, rapid changes in blood pressure, increased body temperature, overreactive reflexes, nausea, vomiting, and diarrhea (Prod Info SAVELLA(R) oral tablets, 2009).

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Coadministration of milnacipran and an SSRI may result in hypertension and coronary artery vasoconstriction, through the additive serotonergic effects. If these agents are used together, discuss the risks of serotonin syndrome with the patient and monitor closely for symptoms of serotonin syndrome (restlessness, hyperthermia, hyperreflexia, incoordination), especially during treatment initiation and dose increases (Prod Info SAVELLA(R) oral tablets, 2009).

7) Probable Mechanism: additive serotonergic effect

3.5.1.DF Moclobemide

1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)

2) Summary: Concurrent administration or overlapping therapy with paroxetine and a monoamine oxidase (MAO) inhibitor may result in CNS toxicity or serotonin syndrome, a hyperserotonergic state characterized by symptoms such as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. Serious, even fatal, reactions have been reported with concomitant use of serotonin specific reuptake inhibitors and MAO inhibitors (Prod Info Paxil(R), 2003h; Lappin & Auchincloss, 1994s; Graber et al, 1994s; Suchowersky & de Vries, 1990s). Concomitant use is contraindicated.

3) Severity: contraindicated

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: Concurrent use of paroxetine and an MAO inhibitor is contraindicated. Wait at least two weeks after discontinuing an MAO inhibitor before initiating paroxetine, and at least two weeks after discontinuing paroxetine before initiating therapy with an MAOI.

7) Probable Mechanism: inhibition of serotonin metabolism by monoamine oxidase

8) Literature Reports

a) Concomitant use of SSRIs and monoamine oxidase inhibitors can produce a toxic reaction known as serotonin syndrome (Sternbach, 1991n). Serotonin syndrome is a condition of serotonergic hyperstimulation and manifests as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. If the syndrome is not recognized and correctly treated, fatality can result.

b) A 26-year old woman who had been taking isocarboxazid for eight weeks stopped taking the drug for 11 days before beginning therapy with sertraline. After a single 100 mg sertraline dose, the patient became restless and developed leg twitches. The patients was later admitted to the emergency room with diaphoresis, tachycardia, hyperreflexia, and various neuromuscular disturbances. After treatment with diazepam and propranolol the patient did not improve. The patient was then given two 4 mg doses of cyproheptadine an hour apart, with notable improvement in symptoms after the second dose (Lappin & Auchincloss, 1994r).

c) A drug interaction was reported in a 61-year old woman in which sertraline 100 mg twice daily was added to a regimen of lithium, phenelzine, thioridazine, and doxepin. Three hours after taking the first sertraline dose, the patient was found in a semicomatose state, with elevated body temperature, increased pulse, increased respiration rate, and a blood pressure of 140/110 mm Hg. After transportation to the hospital, the patient was misdiagnosed as having neuroleptic malignant syndrome (NMS) which was later changed to serotonin syndrome due to a reaction between sertraline and phenelzine. The authors suggest that monoamine oxidase inhibitor (MAOI) therapy should be discontinued for at least two weeks before initiation of therapy with a selective serotonin reuptake inhibitor (SSRI) and that before starting a MAOI, SSRI therapy should be discontinued for at least five half-lives of the parent drug and any active metabolites (Graber et al, 1994r).

d) Two cases reports suggested a possible interaction between fluoxetine and selegiline (Suchowersky & de Vries, 1990r). One case involved a first episode of mania being observed approximately one month after adding selegiline to fluoxetine. The patient improved two months after both drugs were discontinued, and no further details were provided. The second case involved diaphoresis, vasoconstriction, and cyanosis of the hands which occurred in close temporal relationship to adding fluoxetine to selegiline. Both drugs were discontinued, with relatively quick resolution of symptoms. Rechallenge with fluoxetine alone occurred without incident.

e) Five fatal overdose cases were reported due to serotonin syndrome. In three of the five cases, the drug combination that induced the fatal syndrome was moclobemide, a selective monoamine oxidase inhibitor, and citalopram. Of the three patients, blood concentrations of moclobemide ranged from five times the therapeutic level to 50 times the therapeutic level, and citalopram concentrations ranged from normal therapeutic levels to five times the therapeutic level (Neuvonen et al, 1993).

3.5.1.DG Morniflumate

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.DH Nabumetone

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.DI Nadroparin

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info PAXIL(R) oral tablets, suspension, 2008). Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with warfarin (Schalekamp et al, 2008; Prod Info PAXIL(R) oral tablets, suspension, 2008).
3) Severity: major

4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When paroxetine and an anticoagulant are given concurrently, monitor patients for signs of increased bleeding. Patients who are taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, when paroxetine therapy is initiated or discontinued (Prod Info PAXIL(R) oral tablets, suspension, 2008).
7) Probable Mechanism: unknown
8) Literature Reports

a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bleeding (hospital admission due to bleeding) in patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patients with a mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients experienced 11 bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experiencing bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model (Wallerstedt et al, 2009).

b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5), however, the rate of gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).

c) Preliminary data suggest that there may be a pharmacodynamic interaction (that causes an increased bleeding diathesis with unaltered prothrombin time) between paroxetine and warfarin. The concomitant use of paroxetine and warfarin should be undertaken with caution (Prod Info PAXIL(R) oral tablets, suspension, 2008).

d) In a multiple-dose study, several days of combined therapy with warfarin and paroxetine resulted in mild but clinically significant bleeding in 5 of 27 subjects. This effect occurred in the absence of a significant enhancement in warfarin-induced hypoprothrombinemia or changes in either paroxetine or warfarin disposition (Bannister et al, 1989b).

3.5.1.DJ Naproxen

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).

b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.DK Naratriptan

1) Interaction Effect: an increased risk of serotonin syndrome
2) Summary: Rare incidences of weakness, hyperreflexia, and incoordination have been reported with the concurrent use of a selective serotonin reuptake inhibitor (SSRI) and a 5-hydroxytryptamine-1 (5HT-1) agonist (Prod Info Amerge(TM), 2002). Concurrent use of a triptan and an SSRI may result in serotonin syndrome which may be life-threatening. Symptoms of serotonin syndrome may include restlessness, hallucinations, loss of coordination, fast heart beat, rapid changes in blood pressure, increased body temperature, overreactive reflexes, nausea, vomiting, and diarrhea. Clinicians should be aware that triptans may be commonly used intermittently and that either the triptan or the SSRI may be prescribed by a different physician. Discuss the risks of serotonin syndrome with patients who are prescribed this combination and monitor them closely for symptoms of serotonin syndrome (US Food and Drug Administration, 2006).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Coadministration of a triptan, such as naratriptan, and an SSRI may result in a life-threatening condition called serotonin syndrome. Be aware that triptans may be commonly used intermittently and that either the triptan or the SSRI may be prescribed by a different physician. If these agents are used together, discuss the risks of serotonin syndrome with the patient and monitor closely for symptoms of serotonin syndrome (restlessness, hyperthermia, hyperreflexia, incoordination).
7) Probable Mechanism: additive pharmacologic effects resulting in excessive serotonergic stimulation

3.5.1.DL Nebivolol

1) Interaction Effect: increased nebivolol exposure and plasma levels
2) Summary: Nebivolol is partially metabolized by the CYP2D6 isozyme. Coadministration of a single 10 mg dose of dose of nebivolol in healthy adults (n=10) receiving fluoxetine, a CYP2D6 inhibitor, at a dose of 20 mg/day for 21 days led to 8- and 3-fold increases in the AUC and Cmax, respectively, of d-nebivolol (pharmacologically active isomer). Although not studied with paroxetine, also a CYP2D6 inhibitor, a similar interaction can be expected. Closely monitor blood pressure in patients receiving nebivolol and paroxetine concomitantly. Downward dose adjustments of nebivolol may be necessary (Prod Info BYSTOLIC(TM) oral tablets, 2007).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of nebivolol with a CYP2D6 inhibitor, such as paroxetine, may result in increased exposure and plasma concentrations of nebivolol. In patients receiving these agents concomitantly, closely monitor blood pressure. Reduced doses of nebivolol may be necessary (Prod Info BYSTOLIC(TM) oral tablets, 2007).
7) Probable Mechanism: inhibition of CYP2D6-mediated nebivolol metabolism

3.5.1.DM Nefazodone

1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)
2) Summary: One case report describes the development of serotonin syndrome in a female who had stopped nefazodone after a two-week tapering period and started paroxetine therapy one day after the complete discontinuation of nefazodone. A repeat challenge with paroxetine seven days later did not result in the recurrence of symptoms (John et al, 1997a).
3) Severity: major
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Because of the long half-lives of some nefazodone active metabolites, a seven-day washout period should be observed between the discontinuation of nefazodone and the initiation of paroxetine therapy.
7) Probable Mechanism: unknown
8) Literature Reports
a) A 51-year old female with bipolar affective disorder had received nefazodone for six months and had tapered the dose to 75 mg every twelve hours over two weeks. One day after stopping nefazodone therapy, she started paroxetine 20 mg daily and valproic acid 250 mg three times daily. She was agitated and incoherent and then became unresponsive, with shaking movements in her arms and legs. Upon admission to the emergency department, she was diaphoretic, with uncoordinated body tremors, flailing arms, twitching legs, and dilated pupils. Her body temperature rose to 102.2 F, and her creatine kinase (CK) values reached 25,520 U/L by day 3. She became afebrile, and muscle rigidity dissipated by day 4. A repeat challenge with paroxetine seven days later did not result in the recurrence of symptoms. Nefazodone has a half-life of 1.9 to 2.9 hours, but several active metabolites exist, with half-lives of 18 to 33 hours. The authors postulated that in this patient, nefazodone metabolites caused serotonin syndrome when the patient ingested paroxetine. A seven day washout period is recommended after the discontinuation of nefazodone before the administration of any selective serotonin reuptake inhibitor is started (John et al, 1997).
b) Serotonin syndrome is a condition of serotonergic hyperstimulation and manifests as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. If the syndrome

is not recognized and correctly treated, fatality can result (Sternbach, 1991e).

3.5.1.DN Nialamide

1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)

2) Summary: Concurrent administration or overlapping therapy with paroxetine and a monoamine oxidase (MAO) inhibitor may result in CNS toxicity or serotonin syndrome, a hyperserotonergic state characterized by symptoms such as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. Serious, even fatal, reactions have been reported with concomitant use of serotonin specific reuptake inhibitors and MAO inhibitors (Prod Info Paxil(R), 1999g; Lappin & Auchincloss, 1994u; Graber et al, 1994u; Suchowersky & de Vries, 1990u). Concomitant use is contraindicated.

3) Severity: contraindicated

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: Concurrent use of paroxetine and a MAO inhibitor is contraindicated. Wait at least two weeks after discontinuing a MAO inhibitor before initiating paroxetine, and at least two weeks after discontinuing paroxetine before initiating therapy with a MAO inhibitor.

7) Probable Mechanism: inhibition of serotonin metabolism by monoamine oxidase

8) Literature Reports

a) Concomitant use of SSRIs and monoamine oxidase inhibitors can produce a toxic reaction known as serotonin syndrome (Sternbach, 1991p). Serotonin syndrome is a condition of serotonergic hyperstimulation and manifests as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. If the syndrome is not recognized and correctly treated, fatality can result.

b) A 26-year old woman who had been taking isocarboxazid for eight weeks stopped taking the drug for 11 days before beginning therapy with sertraline. After a single 100 mg sertraline dose, the patient became restless and developed leg twitches. The patients was later admitted to the emergency room with diaphoresis, tachycardia, hyperreflexia, and various neuromuscular disturbances. After treatment with diazepam and propranolol the patient did not improve. The patient was then given two 4 mg doses of cyproheptadine an hour apart, with notable improvement in symptoms after the second dose (Lappin & Auchincloss, 1994t).

c) A drug interaction was reported in a 61-year old woman in which sertraline 100 mg twice daily was added to a regimen of lithium, phenelzine, thioridazine, and doxepin. Three hours after taking the first sertraline dose, the patient was found in a semicomatose state, with elevated body temperature, increased pulse, increased respiration rate, and a blood pressure of 140/110 mm Hg. After transportation to the hospital, the patient was misdiagnosed as having neuroleptic malignant syndrome (NMS) which was later changed to serotonin syndrome due to a reaction between sertraline and phenelzine. The authors suggest that monoamine oxidase inhibitor (MAOI) therapy should be discontinued for at least two weeks before initiation of therapy with a selective serotonin reuptake inhibitor (SSRI) and that before starting a MAOI, SSRI therapy should be discontinued for at least five half-lives of the parent drug and any active metabolites (Graber et al, 1994t).

d) Two cases reports suggested a possible interaction between fluoxetine and selegiline (Suchowersky & de Vries, 1990t). One case involved a first episode of mania being observed approximately one month after adding selegiline to fluoxetine. The patient improved two months after both drugs were discontinued, and no further details were provided. The second case involved diaphoresis, vasoconstriction, and cyanosis of the hands which occurred in close temporal relationship to adding fluoxetine to selegiline. Both drugs were discontinued, with relatively quick resolution of symptoms. Rechallenge with fluoxetine alone occurred without incident.

3.5.1.DO Niflumic Acid

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined

use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).

b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.DP Nimesulide

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).

b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.DQ Nortriptyline

1) Interaction Effect: nortriptyline toxicity (dry mouth, sedation, urinary retention)

2) Summary: Concurrent use of paroxetine with tricyclic antidepressants (TCAs) produces increased TCA serum concentrations and may result in TCA toxicity (Prod Info Paxil CR(TM), 2003d; DeVane, 1994; Riesenman, 1995; Murray, 1992; Brosen et al, 1993e). The mechanism of this interaction involves potent inhibition by paroxetine of the cytochrome P450IID6 (CYP2D6) isoenzyme, the principal enzyme in TCA metabolism. Paroxetine may also weakly inhibit other P450 isoenzymes involved in TCA clearance. Other selective serotonin reuptake inhibitors (fluoxetine, fluvoxamine) have demonstrated similar effects on TCA metabolism.

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: When paroxetine is coadministered with nortriptyline, monitor patients for signs and symptoms of nortriptyline toxicity (dry mouth, sedation, urinary retention, blurred vision). Nortriptyline doses may need to be reduced.

7) Probable Mechanism: decreased cytochrome P450 2D6-mediated nortriptyline metabolism

8) Literature Reports

a) The effect of paroxetine on desipramine metabolism was studied in 9 extensive metabolizers (EM) and 8 poor metabolizers (PM) of desipramine (Brosen et al, 1993d). Subjects took a single oral dose of desipramine before starting paroxetine and a second dose after 11 days of paroxetine use. After the addition of paroxetine, EMs experienced a 5-fold decrease in clearance of desipramine, indicating that paroxetine inhibits oxidation reactions catalyzed by CYP2D6. PMs had a slight increase in clearance of desipramine during paroxetine coadministration. With concurrent administration of desipramine and paroxetine, an interaction of the two drugs may result in a need for dosage adjustments, especially in extensive metabolizers of desipramine.

b) A 35-year-old male began treatment with nortriptyline for his first depressive episode and obtained a steady-state serum level of 122 ng/mL (therapeutic level 50 to 150 ng/mL) at a daily dose of 150 mg. Because no improvement of his depression occurred, paroxetine 30 mg daily and thioridazine 50 mg at bedtime were added. A week later, the patient was irritable and complained of dry mouth and constipation. His nortriptyline level at this time was 337 ng/mL and his dose of nortriptyline was decreased to 75 mg daily. The most likely explanation for the increase in this patient's nortriptyline concentration was the addition of paroxetine, although thioridazine may have also played a role. Paroxetine may have inhibited the 10-hydroxylation of nortriptyline via the cytochrome P450 2D6 pathway. However, other studies have shown that thioridazine has the potential to also inhibit this metabolic pathway (Ghaemi & Kirkwood, 1998).

3.5.1.DR Oxaprozin

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).

b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.DS Paliperidone

1) Interaction Effect: increased plasma concentrations of paliperidone

2) Summary: Concurrent use of paliperidone and paroxetine may result in increased paliperidone plasma concentrations. Paliperidone (9-hydroxyrisperidone) is the major active metabolite of risperidone (Prod Info INVEGA(TM) extended-release oral tablets, 2007). Concomitant use of paroxetine and risperidone has resulted in increased plasma concentrations of both risperidone and 9-hydroxyrisperidone, particularly at higher (40 mg) paroxetine doses (Saito et al, 2005; Spina et al, 2001). Use caution when paliperidone and paroxetine are used concomitantly. Consider monitoring for increased paliperidone side effects, including neuroleptic malignant syndrome, QTc prolongation, or tardive dyskinesia.

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: Use caution when paliperidone and paroxetine are used concomitantly as this may result in increased paliperidone plasma concentrations (Prod Info INVEGA(TM) extended-release oral tablets, 2007). Consider monitoring for increased paliperidone side effects, including neuroleptic malignant syndrome, QTc prolongation, or tardive dyskinesia.

7) Probable Mechanism: inhibition of the CYP2D6-mediated metabolism of paliperidone

8) Literature Reports

a) In a drug interaction study, paliperidone exposures were a significant 16% (90% confidence interval, 4% to 30%) higher on average in CYP2D6 extensive metabolizers who were treated concomitantly with a single dose of paliperidone 3 mg and paroxetine 20 mg/day. Studies with higher paroxetine doses have not been conducted. The clinical relevance is not known (Prod Info INVEGA(TM) extended-release oral tablets, 2007).

b) Paroxetine, a potent inhibitor of cytochrome CYP2D6, may impair the elimination of risperidone, primarily by inhibiting CYP2D6-mediated alpha-hydroxylation and, to a lesser extent, by simultaneously affecting the further metabolism of 9-hydroxyrisperidone (9-OH-risperidone) or other pathways of risperidone biotransformation. In a study including 10 patients diagnosed with schizophrenia (n=7) or schizoaffective disorder depressive type (n=3), risperidone plasma concentrations increased when paroxetine was coadministered with risperidone. Patients were stabilized on risperidone therapy 4 to 8 mg/day and received adjunctive paroxetine 20 mg/day to treat negative symptoms, concomitant depression, or both. Risperidone dosage remained constant throughout the duration of the study. A significant elevation in risperidone plasma concentrations (p less than 0.01) and a slight, nonsignificant decrease in 9-OH-risperidone occurred. After 4 weeks of paroxetine treatment, the total concentration of risperidone and 9-OH-risperidone was increased by 45% (p less than 0.05). The mean plasma risperidone to 9-OH-risperidone ratio also changed significantly (p less than 0.001) with concomitant paroxetine treatment. Extrapyramidal side effects occurred in one patient during the second week of paroxetine coadministration. Total plasma levels of risperidone in this patient increased 62% over baseline values during paroxetine coadministration. The occurrence of extrapyramidal symptoms in patients after addition of SSRIs to antipsychotics might also be caused by an additive pharmacodynamic effect of paroxetine (Spina et al, 2001).

c) Risperidone plasma concentrations increased when risperidone-treated inpatients (n=12) with

schizophrenia and negative symptoms were coadministered incremental doses of paroxetine. Prior to initiating paroxetine, patients were receiving risperidone 2 mg twice daily for at least 6 weeks and steady-state plasma concentrations of risperidone and 9-hydroxyrisperidone (9-OH-risperidone) had been achieved. Paroxetine doses were administered in 3 consecutive 4-week increments of 10 mg/day, 20 mg/day, and 40 mg/day. Mean risperidone plasma concentrations during 10-, 20-, and 40-mg paroxetine treatment were 3.8- (95% confidence interval (CI), 3.2 to 5.8; p less than 0.01) , 7.1- (95% CI, 5.3 to 16.5; p less than 0.01), and 9.7-fold (95% CI, 7.8 to 22.5; p less than 0.01) higher compared with baseline. Increases in 9-OH-risperidone concentrations were not significant with paroxetine use. Mean active moiety (risperidone plus 9-OH-risperidone) plasma concentrations increased by 1.8-fold (95% CI, 1.4 to 2.7; p less than 0.05) during the 40-mg paroxetine dose; increases were not significant with 10- or 20-mg doses. Metabolic ratio was significantly increased (p less than 0.01) by 4.2-fold (95% CI, 3.4 to 6.2) with 10 mg of paroxetine, by 8.2-fold (95% CI, 6 to 16) with 20 mg, and by 12.6-fold (95% CI, 9.6 to 26.8) with 40 mg. Negative symptom scores were significantly improved during all paroxetine doses; however, extrapyramidal symptoms scores were significantly higher during 20- and 40-mg doses. The authors suggest that low-dose coadministration of paroxetine with risperidone may be safe and effective for treating schizophrenia with negative symptoms (Saito et al, 2005).

3.5.1.DT Parecoxib

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).

b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.DU Pargyline

1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)

2) Summary: Concurrent administration or overlapping therapy with paroxetine and a monoamine oxidase (MAO) inhibitor may result in CNS toxicity or serotonin syndrome, a hyperserotonergic state characterized by symptoms such as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. Serious, even fatal, reactions have been reported with concomitant use of serotonin specific reuptake inhibitors and MAO inhibitors (Prod Info Paxil(R), 1999c; Lappin & Auchincloss, 1994i; Graber et al, 1994i; Suchowersky & de Vries, 1990i). Concomitant use is contraindicated.

3) Severity: contraindicated

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: Concurrent use of paroxetine and a MAO inhibitor is contraindicated. Wait at least two weeks after discontinuing a MAO inhibitor before initiating paroxetine, and at least two weeks after discontinuing paroxetine before initiating therapy with a MAO inhibitor.

7) Probable Mechanism: inhibition of serotonin metabolism by monoamine oxidase

8) Literature Reports

a) Concomitant use of SSRIs and monoamine oxidase inhibitors can produce a toxic reaction known as serotonin syndrome (Sternbach, 1991i). Serotonin syndrome is a condition of serotonergic hyperstimulation and manifests as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. If the syndrome is not recognized and correctly treated, fatality can result.

b) A 26-year old woman who had been taking isocarboxazid for eight weeks stopped taking the drug for 11 days before beginning therapy with sertraline. After a single 100 mg sertraline dose, the patient became restless and developed leg twitches. The patients was later admitted to the emergency room

with diaphoresis, tachycardia, hyperreflexia, and various neuromuscular disturbances. After treatment with diazepam and propranolol the patient did not improve. The patient was then given two 4 mg doses of cyproheptadine an hour apart, with notable improvement in symptoms after the second dose (Lappin & Auchincloss, 1994h).

c) A drug interaction was reported in a 61-year old woman in which sertraline 100 mg twice daily was added to a regimen of lithium, phenelzine, thioridazine, and doxepin. Three hours after taking the first sertraline dose, the patient was found in a semicomatose state, with elevated body temperature, increased pulse, increased respiration rate, and a blood pressure of 140/110 mm Hg. After transportation to the hospital, the patient was misdiagnosed as having neuroleptic malignant syndrome (NMS) which was later changed to serotonin syndrome due to a reaction between sertraline and phenelzine. The authors suggest that monoamine oxidase inhibitor (MAOI) therapy should be discontinued for at least two weeks before initiation of therapy with a selective serotonin reuptake inhibitor (SSRI) and that before starting a MAOI, SSRI therapy should be discontinued for at least five half-lives of the parent drug and any active metabolites (Graber et al, 1994h).

d) Two cases reports suggested a possible interaction between fluoxetine and selegiline (Suchowersky & de Vries, 1990h). One case involved a first episode of mania being observed approximately one month after adding selegiline to fluoxetine. The patient improved two months after both drugs were discontinued, and no further details were provided. The second case involved diaphoresis, vasoconstriction, and cyanosis of the hands which occurred in close temporal relationship to adding fluoxetine to selegiline. Both drugs were discontinued, with relatively quick resolution of symptoms. Rechallenge with fluoxetine alone occurred without incident.

3.5.1.DV Parnaparin

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info PAXIL(R) oral tablets, suspension, 2008). Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with warfarin (Schalekamp et al, 2008; Prod Info PAXIL(R) oral tablets, suspension, 2008).

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: When paroxetine and an anticoagulant are given concurrently, monitor patients for signs of increased bleeding. Patients who are taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, when paroxetine therapy is initiated or discontinued (Prod Info PAXIL(R) oral tablets, suspension, 2008).

7) Probable Mechanism: unknown

8) Literature Reports

a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bleeding (hospital admission due to bleeding) in patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patients with a mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients experienced 11 bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experiencing bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model (Wallerstedt et al, 2009).

b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5), however, the rate of gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).

c) Preliminary data suggest that there may be a pharmacodynamic interaction (that causes an increased bleeding diathesis with unaltered prothrombin time) between paroxetine and warfarin. The concomitant use of paroxetine and warfarin should be undertaken with caution (Prod Info PAXIL(R) oral tablets, suspension, 2008).

d) In a multiple-dose study, several days of combined therapy with warfarin and paroxetine resulted in mild but clinically significant bleeding in 5 of 27 subjects. This effect occurred in the absence of a significant enhancement in warfarin-induced hypoprothrombinemia or changes in either paroxetine or warfarin disposition (Bannister et al, 1989b).

3.5.1.DW Pentosan Polysulfate Sodium

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info PAXIL(R) oral tablets, suspension, 2008). Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with warfarin (Schalekamp et al, 2008; Prod Info PAXIL(R) oral tablets, suspension, 2008).

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: When paroxetine and an anticoagulant are given concurrently, monitor patients for signs of increased bleeding. Patients who are taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, when paroxetine therapy is initiated or discontinued (Prod Info PAXIL(R) oral tablets, suspension, 2008).

7) Probable Mechanism: unknown

8) Literature Reports

a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bleeding (hospital admission due to bleeding) in patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patients with a mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients experienced 11 bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experiencing bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model (Wallerstedt et al, 2009).

b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5), however, the rate of gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).

c) Preliminary data suggest that there may be a pharmacodynamic interaction (that causes an increased bleeding diathesis with unaltered prothrombin time) between paroxetine and warfarin. The concomitant use of paroxetine and warfarin should be undertaken with caution (Prod Info PAXIL(R) oral tablets, suspension, 2008).

d) In a multiple-dose study, several days of combined therapy with warfarin and paroxetine resulted in mild but clinically significant bleeding in 5 of 27 subjects. This effect occurred in the absence of a significant enhancement in warfarin-induced hypoprothrombinemia or changes in either paroxetine or warfarin disposition (Bannister et al, 1989b).

3.5.1.DX Perhexiline

1) Interaction Effect: an increased risk of perhexiline toxicity (ataxia, lethargy, nausea)

2) Summary: Paroxetine therapy resulted in perhexiline toxicity in an 86-year-old female patient following five weeks of concurrent therapy. Perhexiline is metabolized by the cytochrome P450 2D6 enzyme system, and paroxetine is widely known to inhibit these same enzymes (Alderman, 1998a).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Closely monitor patients receiving concurrent therapy with perhexiline and paroxetine for signs and symptoms of perhexiline toxicity, including ataxia, lethargy, and nausea. Trough serum perhexiline levels (normal range 0.15 to 0.60 mg/L) may also be helpful in diagnosing perhexiline toxicity.

7) Probable Mechanism: inhibition by paroxetine of cytochrome P450 2D6-mediated perhexiline metabolism
8) Literature Reports
a) An elderly female patient receiving perhexiline 100 mg twice daily experienced recurrent falls, dizziness, and nausea five weeks after paroxetine 20 mg once daily was prescribed for depression. A perhexiline serum concentration one week after paroxetine was initiated was 0.67 mg/L. Four weeks later, upon admission to the hospital, her perhexiline concentration was 2.02 mg/L. Both paroxetine and perhexiline were discontinued, and a repeat perhexiline concentration 10 days later was 1.42 mg/L. Paroxetine, a cytochrome P450 2D6 inhibitor, was thought to be substantially inhibiting the metabolism of perhexiline (Alderman, 1998).

3.5.1.DY Perphenazine
1) Interaction Effect: increased plasma concentrations and side effects of perphenazine
2) Summary: Paroxetine significantly inhibited the metabolism of perphenazine in 8 healthy volunteers, resulting in increased plasma concentrations and side effects of perphenazine (Ozdemir et al, 1997a). Coadministration of paroxetine with other drugs that are metabolized by cytochrome P450 2D6, such as perphenazine, should be approached with caution (Prod Info Paxil CR(TM), 2003h).
3) Severity: moderate
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: In patients receiving paroxetine, the dose of perphenazine should be reduced and patients should be monitored closely for perphenazine side effects. The concomitant administration of paroxetine and perphenazine should be approached with caution.
7) Probable Mechanism: inhibition of cytochrome P450 2D6-mediated metabolism of perphenazine by paroxetine
8) Literature Reports
a) Paroxetine significantly inhibited the metabolism of perphenazine in 8 healthy volunteers, resulting in increased plasma concentrations and side effects of perphenazine. All subjects were extensive metabolizers in CYP2D6 isoenzyme activity as determined by a dextromethorphan metabolism study. Subjects were randomized to receive a single dose of perphenazine 0.11 mg/kg or placebo alone in a crossover design. Then subjects received paroxetine 20 mg/day for 10 days and then another dose of perphenazine or placebo on the tenth day. The average peak plasma concentration of perphenazine was significantly increased from 2.2 nmol/L when given alone, compared to 13.5 nmol/L when given with paroxetine. The average area under the plasma concentration-time curve (0 to 8 hours) was significantly increased from 9.4 mg (h)/L, with perphenazine alone, to 65.4 mg (h)/L when perphenazine was given with paroxetine. Side effects of perphenazine were significantly increased as demonstrated by oversedation, extrapyramidal side effects, and impaired performance on psychomotor tests. In patients receiving paroxetine the dose of perphenazine should be reduced and patients should be monitored for perphenazine side effects (Ozdemir et al, 1997).

3.5.1.DZ Phenelzine
1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)
2) Summary: Concurrent administration or overlapping therapy with paroxetine and a monoamine oxidase (MAO) inhibitor may result in CNS toxicity or serotonin syndrome, a hyperserotonergic state characterized by symptoms such as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. Serious, even fatal, reactions have been reported with concomitant use of serotonin specific reuptake inhibitors and MAO inhibitors (Prod Info Paxil(R), 2003g; Lappin & Auchincloss, 1994q; Graber et al, 1994q; Suchowersky & de Vries, 1990q). Concomitant use is contraindicated.
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Concurrent use of paroxetine and an MAO inhibitor is contraindicated. Wait at least two weeks after discontinuing an MAO inhibitor before initiating paroxetine, and at least two weeks after discontinuing paroxetine before initiating therapy with an MAOI.
7) Probable Mechanism: inhibition of serotonin metabolism by monoamine oxidase
8) Literature Reports
a) Concomitant use of SSRIs and monoamine oxidase inhibitors can produce a toxic reaction known as serotonin syndrome (Sternbach, 1991m). Serotonin syndrome is a condition of serotonergic hyperstimulation and manifests as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. If the syndrome is not recognized and correctly treated, fatality can result.
b) A 26-year old woman who had been taking isocarboxazid for eight weeks stopped taking the drug for 11 days before beginning therapy with sertraline. After a single 100 mg sertraline dose, the patient became restless and developed leg twitches. The patients was later admitted to the emergency room with diaphoresis, tachycardia, hyperreflexia, and various neuromuscular disturbances. After treatment with diazepam and propranolol the patient did not improve. The patient was then given two 4 mg doses of cyproheptadine an hour apart, with notable improvement in symptoms after the second dose (Lappin & Auchincloss, 1994p).

c) A drug interaction was reported in a 61-year old woman in which sertraline 100 mg twice daily was added to a regimen of lithium, phenelzine, thioridazine, and doxepin. Three hours after taking the first sertraline dose, the patient was found in a semicomatose state, with elevated body temperature, increased pulse, increased respiration rate, and a blood pressure of 140/110 mm Hg. After transportation to the hospital, the patient was misdiagnosed as having neuroleptic malignant syndrome (NMS) which was later changed to serotonin syndrome due to a reaction between sertraline and phenelzine. The authors suggest that monoamine oxidase inhibitor (MAOI) therapy should be discontinued for at least two weeks before initiation of therapy with a selective serotonin reuptake inhibitor (SSRI) and that before starting a MAOI, SSRI therapy should be discontinued for at least five half-lives of the parent drug and any active metabolites (Graber et al, 1994p).

d) Two cases reports suggested a possible interaction between fluoxetine and selegiline (Suchowersky & de Vries, 1990p). One case involved a first episode of mania being observed approximately one month after adding selegiline to fluoxetine. The patient improved two months after both drugs were discontinued, and no further details were provided. The second case involved diaphoresis, vasoconstriction, and cyanosis of the hands which occurred in close temporal relationship to adding fluoxetine to selegiline. Both drugs were discontinued, with relatively quick resolution of symptoms. Rechallenge with fluoxetine alone occurred without incident.

3.5.1.EA Phenindione

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info PAXIL(R) oral tablets, suspension, 2008). Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with warfarin (Schalekamp et al, 2008; Prod Info PAXIL(R) oral tablets, suspension, 2008).

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: When paroxetine and an anticoagulant are given concurrently, monitor patients for signs of increased bleeding. Patients who are taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, when paroxetine therapy is initiated or discontinued (Prod Info PAXIL(R) oral tablets, suspension, 2008).

7) Probable Mechanism: unknown

8) Literature Reports

a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bleeding (hospital admission due to bleeding) in patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patients with a mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients experienced 11 bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experiencing bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model (Wallerstedt et al, 2009).

b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5), however, the rate of gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).

c) Preliminary data suggest that there may be a pharmacodynamic interaction (that causes an increased bleeding diathesis with unaltered prothrombin time) between paroxetine and warfarin. The concomitant use of paroxetine and warfarin should be undertaken with caution (Prod Info PAXIL(R) oral tablets, suspension, 2008).

d) In a multiple-dose study, several days of combined therapy with warfarin and paroxetine resulted in mild but clinically significant bleeding in 5 of 27 subjects. This effect occurred in the absence of a significant enhancement in warfarin-induced hypoprothrombinemia or changes in either paroxetine or warfarin disposition (Bannister et al, 1989b).

3.5.1.EB Phenobarbital

1) Interaction Effect: reduced paroxetine effectiveness

2) Summary: Coadministration of paroxetine and phenobarbital may result in decreased serum concentrations of paroxetine (Prod Info Paxil(R), 2002a); however, considerable interindividual variation should be expected (Greb et al, 1989c). The clinical significance of individual pharmacokinetic alterations is uncertain at this time.

3) Severity: minor

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: Monitor patients for a reduced therapeutic response to paroxetine. Any adjustment of paroxetine should be guided by clinical effect.

7) Probable Mechanism: enhanced paroxetine clearance

8) Literature Reports

a) A study reported that the degree of psychomotor impairment healthy subjects experienced when receiving the barbiturate amylobarbitone with paroxetine was not greater compared with the degree of impairment associated with either drug alone (Cooper et al, 1989).

b) Concomitant administration of paroxetine and phenobarbital resulted in no significant effect on the mean pharmacokinetic parameters of paroxetine in a study involving 10 healthy subjects (Greb et al, 1989b). However, individual decreases in half-life and area under the plasma concentration-time curve (AUC) for paroxetine were observed. This effect appears to be related to the induction of hepatic isoenzymes by phenobarbital. As this study employed a single dose of paroxetine, further studies are needed to evaluate this combination during multiple-dose therapy.

c) When a single oral 30 mg dose was administered at phenobarbital steady state (100 mg daily for 14 days) paroxetine AUC and half-life were reduced by an average of 25% and 38%, respectively, when compared to paroxetine administered alone. The effect of paroxetine on phenobarbital pharmacokinetics was not studied (Prod Info Paxil(R), 2002).

3.5.1.EC Phenprocoumon

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info PAXIL(R) oral tablets, suspension, 2008). Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with warfarin (Schalekamp et al, 2008; Prod Info PAXIL(R) oral tablets, suspension, 2008).

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: When paroxetine and an anticoagulant are given concurrently, monitor patients for signs of increased bleeding. Patients who are taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, when paroxetine therapy is initiated or discontinued (Prod Info PAXIL(R) oral tablets, suspension, 2008).

7) Probable Mechanism: unknown

8) Literature Reports

a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bleeding (hospital admission due to bleeding) in patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patients with a mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients experienced 11 bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experiencing bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model (Wallerstedt et al, 2009).

b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval

(CI), 1.1 to 2.5), however, the rate of gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).

c) Preliminary data suggest that there may be a pharmacodynamic interaction (that causes an increased bleeding diathesis with unaltered prothrombin time) between paroxetine and warfarin. The concomitant use of paroxetine and warfarin should be undertaken with caution (Prod Info PAXIL(R) oral tablets, suspension, 2008).

d) In a multiple-dose study, several days of combined therapy with warfarin and paroxetine resulted in mild but clinically significant bleeding in 5 of 27 subjects. This effect occurred in the absence of a significant enhancement in warfarin-induced hypoprothrombinemia or changes in either paroxetine or warfarin disposition (Bannister et al, 1989b).

3.5.1.ED Phenylbutazone

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).

b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.EE Phenytoin

1) Interaction Effect: reduced phenytoin efficacy; reduced paroxetine efficacy

2) Summary: Limited reports related to the effects of combined phenytoin-paroxetine are currently available. Because of its enzyme-inducing effect, coadministered phenytoin apparently reduces serum concentrations of phenytoin and paroxetine, possibly leading to reduced efficacy of phenytoin and paroxetine (Prod Info Paxil(R), 2003e; Andersen et al, 1991c; Boyer & Blumhardt, 1992a). There has been one case report of an elevated phenytoin level after four weeks of concurrent paroxetine and phenytoin coadministration (Prod Info Paxil(R), 2003e).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Monitor patients for phenytoin and paroxetine effectiveness. No initial dosage adjustments are necessary when these drugs are coadministered, however, subsequent adjustments should be guided by clinical effect.

7) Probable Mechanism: induction of phenytoin and paroxetine metabolism

8) Literature Reports

a) Concomitant administration of a single-dose of paroxetine 30 mg and phenytoin (300 mg once a day for 14 days) resulted in a reduction in the area under the plasma concentration-time curve (AUC) of paroxetine by 27% to 50%, as well as a decrease of 35% in the half-life of paroxetine (Kaye et al, 1989a). This interaction appears to be related to the enzyme-inducing properties of phenytoin. Alternatively, in a single-dose phenytoin study, paroxetine (30 mg once a day for 14 days) had no effect on the mean peak plasma levels or the elimination half-life of phenytoin 300 mg. However, a 12% reduction in the area under the plasma concentration-time curve (AUC) for phenytoin was observed. No initial dose adjustments are necessary upon coadministration of these agents. Subsequent adjustments should be guided by clinical effect (Prod Info Paxil(R), 2003d).

b) Nineteen epilepsy patients who were well controlled on either phenytoin (n=5), carbamazepine (n=6), or valproate (n=8) took part in a single-blind, placebo-controlled, cross-over study to determine the effect of concurrent use of paroxetine and anticonvulsants (Andersen et al, 1991b). Subjects received placebo for seven days, then paroxetine 10 mg daily for three days, 20 mg daily for three days, and 30 mg daily for 10 days. There were no statistically significant changes in plasma levels and free fractions in any of the anticonvulsant drugs during any phase of the study. Mean paroxetine plasma

levels were lowest with concurrent phenytoin therapy (p less than 0.005 when compared with valproate); however, there is no clear association between paroxetine plasma concentrations and efficacy. No severe adverse effects were seen with cotherapy, no seizures occurred, and no changes in protein binding were found.

3.5.1.EF Pimozide

1) Interaction Effect: an increased risk of pimozide toxicity including cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Coadministration of paroxetine and pimozide is contraindicated. A controlled study involving concurrent administration of pimozide and paroxetine to healthy volunteers resulted in a mean increase in AUC and Cmax of 151% and 62%, respectively. The consequence of such an extreme increase of pimozide plasma concentrations may be pimozide toxicity, including risk of QT prolongation leading to torsades de pointes (Prod Info PAXIL CR(R) CONTROLLED-RELEASE TABLETS, 2005).
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: The concurrent administration of paroxetine and pimozide is contraindicated due to the possibility of significantly increased pimozide plasma concentrations resulting in a dangerous risk of pimozide toxicity.
7) Probable Mechanism: unknown
8) Literature Reports
a) A group of healthy volunteers in a controlled study received a single dose of 2 mg pimozide after being titrated up to a daily dose of 60 mg of immediate-release paroxetine hydrochloride. The study resulted in a mean increase of pimozide area under the concentration time-curve (AUC) and maximum concentration (Cmax) of 151% and 62%, respectively (Prod Info PAXIL CR(R) CONTROLLED-RELEASE TABLETS, 2005).

3.5.1.EG Pirazolac

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.EH Piroxicam

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent

use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).

b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.EI Pirprofen

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).

b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.EJ Procarbazine

1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)

2) Summary: Concurrent administration or overlapping therapy with paroxetine and a monoamine oxidase (MAO) inhibitor may result in CNS toxicity or serotonin syndrome, a hyperserotonergic state characterized by symptoms such as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. Serious, even fatal, reactions have been reported with concomitant use of serotonin specific reuptake inhibitors and MAO inhibitors (Prod Info Paxil(R), 1999f; Lappin & Auchincloss, 1994o; Graber et al, 1994o; Suchowersky & de Vries, 1990o). Concomitant use is contraindicated.

3) Severity: contraindicated

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: Concurrent use of paroxetine and a MAO inhibitor is contraindicated. Wait at least two weeks after discontinuing a MAO inhibitor before initiating paroxetine, and at least two weeks after discontinuing paroxetine before initiating therapy with a MAOI.

7) Probable Mechanism: inhibition of serotonin metabolism by monoamine oxidase

8) Literature Reports

a) Concomitant use of SSRIs and monoamine oxidase inhibitors can produce a toxic reaction known as serotonin syndrome (Sternbach, 1991l). Serotonin syndrome is a condition of serotonergic hyperstimulation and manifests as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. If the syndrome is not recognized and correctly treated, fatality can result.

b) A 26-year old woman who had been taking isocarboxazid for eight weeks stopped taking the drug for 11 days before beginning therapy with sertraline. After a single 100 mg sertraline dose, the patient became restless and developed leg twitches. The patients was later admitted to the emergency room with diaphoresis, tachycardia, hyperreflexia, and various neuromuscular disturbances. After treatment with diazepam and propranolol the patient did not improve. The patient was then given two 4 mg doses of cyproheptadine an hour apart, with notable improvement in symptoms after the second dose (Lappin & Auchincloss, 1994n).

c) A drug interaction was reported in a 61-year old woman in which sertraline 100 mg twice daily was added to a regimen of lithium, phenelzine, thioridazine, and doxepin. Three hours after taking the first

sertraline dose, the patient was found in a semicomatose state, with elevated body temperature, increased pulse, increased respiration rate, and a blood pressure of 140/110 mm Hg. After transportation to the hospital, the patient was misdiagnosed as having neuroleptic malignant syndrome (NMS) which was later changed to serotonin syndrome due to a reaction between sertraline and phenelzine. The authors suggest that monoamine oxidase inhibitor (MAOI) therapy should be discontinued for at least two weeks before initiation of therapy with a selective serotonin reuptake inhibitor (SSRI) and that before starting a MAOI, SSRI therapy should be discontinued for at least five half-lives of the parent drug and any active metabolites (Graber et al, 1994n).

d) Two cases reports suggested a possible interaction between fluoxetine and selegiline (Suchowersky & de Vries, 1990n). One case involved a first episode of mania being observed approximately one month after adding selegiline to fluoxetine. The patient improved two months after both drugs were discontinued, and no further details were provided. The second case involved diaphoresis, vasoconstriction, and cyanosis of the hands which occurred in close temporal relationship to adding fluoxetine to selegiline. Both drugs were discontinued, with relatively quick resolution of symptoms. Rechallenge with fluoxetine alone occurred without incident.

3.5.1.EK Procyclidine

1) Interaction Effect: an increased risk of anticholinergic effects (dry mouth, sedation, mydriasis)

2) Summary: Coadministered procyclidine and paroxetine may produce increased serum concentrations of procyclidine, accompanied by increased anticholinergic effects (Prod Info Paxil CR(TM), 2003a). If anticholinergic effects are seen, the dose of procyclidine should be reduced.

3) Severity: moderate

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: Monitor patients for anticholinergic effects. Depending on patient response, doses of procyclidine may need to be reduced.

7) Probable Mechanism: unknown

8) Literature Reports

a) In a multiple dose study of procyclidine and paroxetine, study subjects received paroxetine 30 mg once a day and procyclidine 5 mg once a day. Elevated procyclidine concentrations were seen at steady-state. Procyclidine area under the concentration-time curve (AUC), maximum concentration (Cmax), and minimum concentration (Cmin) were increased by 35%, 37%, and 67%, respectively, potentially leading to adverse anticholinergic effects (Prod Info Paxil CR(TM), 2003).

3.5.1.EL Propafenone

1) Interaction Effect: an increased risk of propafenone toxicity (cardiac arrhythmia)

2) Summary: Coadministration of paroxetine with other drugs that are metabolized by the cytochrome P450 2D6 enzyme, such as propafenone, should be approached with caution (Prod Info Paxil CR(TM), 2003e).

3) Severity: moderate

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: Monitor heart rate and the EKG in patients receiving concurrent paroxetine and propafenone. Doses may need to be reduced. Coadministration of these agents should be approached with caution.

7) Probable Mechanism: inhibition of propafenone metabolism

3.5.1.EM Propyphenazone

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or

low-dose aspirin increased the risk even further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.EN Proquazone

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.EO Protriptyline

1) Interaction Effect: protriptyline toxicity (dry mouth, sedation, urinary retention)
2) Summary: Paroxetine coadministered with desipramine or imipramine produced higher serum concentrations of the tricyclic antidepressant (TCA) in some patients (Hartter et al, 1994d; Brosen et al, 1993k). Although not reported for protriptyline, a similar interaction could occur. Paroxetine's effect on TCAs may resemble that of fluoxetine (another selective serotonin reuptake inhibitor), which is known to inhibit TCA metabolism (Aranow et al, 1989d; Vaughan, 1988d; Goodnick, 1989d). With coadministration, monitor patients for protriptyline toxicity. Protriptyline doses may need to be reduced (Prod Info Paxil CR(TM), 2003j).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When paroxetine is coadministered with protriptyline, monitor patients for signs and symptoms of protriptyline toxicity (dry mouth, sedation, urinary retention, blurred vision). Protriptyline doses may need to be reduced.
7) Probable Mechanism: decreased protriptyline metabolism
8) Literature Reports
a) The effect of paroxetine on desipramine metabolism was studied in 9 extensive metabolizers (EM) and 8 poor metabolizers (PM) of desipramine. Subjects took a single oral dose of desipramine before starting paroxetine and a second dose after 11 days of paroxetine use. After the addition of paroxetine, EMs experienced a 5-fold decrease in clearance of desipramine, indicating that paroxetine inhibits oxidation reactions catalyzed by CYP2D6. PMs had a slight increase in clearance of desipramine with paroxetine. With concurrent administration of desipramine and paroxetine, interaction of the two drugs may result in a need for dosage adjustments, especially in extensive metabolizers of desipramine (Brosen et al, 1993j).

3.5.1.EP Quinidine

1) Interaction Effect: elevated paroxetine plasma concentrations and possible paroxetine toxicity (nausea, dry mouth, somnolence, headache)
2) Summary: Paroxetine is metabolized in part by cytochrome P450IID6 (CYP2D6) (Prod Info Paxil CR (TM), 2003l). Quinidine is known to inhibit the CYP2D6 isoenzyme. Quinidine and paroxetine coadministration could result in reduced paroxetine metabolism, increased paroxetine plasma concentrations, and possibly paroxetine toxicity. Controlled studies are needed to document the clinical impact of quinidine - paroxetine administration.
3) Severity: moderate
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Monitor patients for signs of paroxetine toxicity. Doses of paroxetine may need to

be reduced.
7) Probable Mechanism: reduced paroxetine metabolism

3.5.1.EQ Ranolazine
1) Interaction Effect: an increase in ranolazine steady state plasma concentrations
2) Summary: Paroxetine is a potent inhibitor of cytochrome P450-2D6 enzyme. This inhibition increases the average steady state plasma concentrations of ranolazine by 1.2-fold. No adjustment in ranolazine dose is necessary when using ranolazine with paroxetine or other CYP2D6 inhibitors concomitantly (Prod Info RANEXA(TM) extended-release tablets, 2006).
3) Severity: minor
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: No dosage adjustment of ranolazine is required in patients treated with paroxetine.
7) Probable Mechanism: paroxetine inhibition of cytochrome P450-2D6 mediated ranolazine metabolism

3.5.1.ER Rasagiline
1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)
2) Summary: Concurrent administration or overlapping therapy with selective serotonin reuptake inhibitors, including paroxetine, and non-selective MAOIs or the selective MAO-B inhibitor selegiline, has been reported to cause serious, sometimes fatal reactions. Signs and symptoms included hyperthermia, rigidity, myoclonus, autonomic instability with rapid vital sign fluctuations, and mental status changes progressing to extreme agitation, delirium, and coma. Similar reactions have been reported with serotonin-norepinephrine reuptake inhibitors (SNRIs) and non-selective MAOIs or selegiline. Rasagiline clinical trials did allow concomitant use of paroxetine in doses less than or equal to 30 mg/day. However, the small number of patients exposed to SSRIs (n of 141) was not adequate to rule out the possibility of adverse events from the combination of rasagiline and paroxetine, and such use should be avoided. Wait at least 14 days after discontinuing rasagiline before initiating paroxetine treatment (Prod Info AZILECT(R) oral tablets, 2006).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concurrent use of paroxetine and rasagiline should be avoided. Wait at least 14 days after discontinuing rasagiline before initiating therapy with paroxetine.
7) Probable Mechanism: inhibition of serotonin metabolism by monoamine oxidase
8) Literature Reports
a) Concomitant use of serotonin specific reuptake inhibitors and monoamine oxidase inhibitors can produce a toxic reaction known as serotonin syndrome (Sternbach, 1991f). Serotonin syndrome is a condition of serotonergic hyperstimulation and manifests as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. If the syndrome is not recognized and correctly treated, death can result.

3.5.1.ES Reviparin
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info PAXIL(R) oral tablets, suspension, 2008). Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with warfarin (Schalekamp et al, 2008; Prod Info PAXIL(R) oral tablets, suspension, 2008).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When paroxetine and an anticoagulant are given concurrently, monitor patients for signs of increased bleeding. Patients who are taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, when paroxetine therapy is initiated or discontinued (Prod Info PAXIL(R) oral tablets, suspension, 2008).
7) Probable Mechanism: unknown
8) Literature Reports
a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bleeding (hospital admission due to bleeding) in patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patients with a mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients experienced 11 bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment

with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experiencing bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model (Wallerstedt et al, 2009).

b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5), however, the rate of gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).

c) Preliminary data suggest that there may be a pharmacodynamic interaction (that causes an increased bleeding diathesis with unaltered prothrombin time) between paroxetine and warfarin. The concomitant use of paroxetine and warfarin should be undertaken with caution (Prod Info PAXIL(R) oral tablets, suspension, 2008).

d) In a multiple-dose study, several days of combined therapy with warfarin and paroxetine resulted in mild but clinically significant bleeding in 5 of 27 subjects. This effect occurred in the absence of a significant enhancement in warfarin-induced hypoprothrombinemia or changes in either paroxetine or warfarin disposition (Bannister et al, 1989b).

3.5.1.ET Risperidone

1) Interaction Effect: increased plasma concentrations of risperidone

2) Summary: Concomitant use of paroxetine (potent CYP2D6 inhibitor) and risperidone (CYP2D6 substrate) has resulted in increased risperidone plasma concentrations and an increased risk of risperidone adverse effects such as serotonin syndrome, QT prolongation, and extrapyramidal effects. The postulated mechanism of action is inhibition of CYP2D6-mediated metabolism of risperidone by paroxetine. Two studies demonstrated increased risperidone levels resulting in a greater frequency of extrapyramidal symptoms in patients treated concurrently with paroxetine and risperidone (Saito et al, 2005; Spina et al, 2001). One of these studies showed an association between paroxetine dose increases and greater risperidone plasma concentrations (Spina et al, 2001). In a case report, serotonin syndrome was observed in a patient who had already been receiving risperidone and was initiated on paroxetine (Hamilton & Malone, 2000). Monitoring the patient for increased risperidone plasma levels side effects may be necessary. The risperidone dose should be reevaluated if paroxetine is initiated or discontinued. Concomitant use of a low dose of paroxetine with risperidone may be safe and effective in treating schizophrenia with negative symptoms (Prod Info RISPERDAL(R) oral tablets, oral solution, orally disintegrating tablets, 2008; Spina et al, 2001).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Concomitant use of paroxetine and risperidone has resulted in increased risperidone plasma concentrations and an increased risk of risperidone side effects (Prod Info RISPERDAL (R) oral tablets, oral solution, orally disintegrating tablets, 2008; Saito et al, 2005; Spina et al, 2001; Hamilton & Malone, 2000). Carefully monitor patients for increased plasma risperidone levels and side effects (serotonin syndrome, extrapyramidal symptoms, and cardiotoxicity) when paroxetine is coadministered with risperidone. Reevaluate the dose of risperidone when concomitant paroxetine is initiated or discontinued (Prod Info RISPERDAL(R) oral tablets, oral solution, orally disintegrating tablets, 2008). Coadministering a low dose of paroxetine with risperidone may be safe and effective in treating schizophrenia with negative symptoms (Saito et al, 2005).

7) Probable Mechanism: inhibition of CYP2D6-mediated metabolism of risperidone

8) Literature Reports

a) Paroxetine (a potent CYP2D6 inhibitor) 20 mg/day has been shown to increase the plasma concentration of risperidone (a CYP2D6 substrate) by 3- to 9- fold. Paroxetine also lowered the concentration of 9-hydroxyrisperidone by about 10%. In postmarketing surveillance of risperidone, torsade de pointes has been reported with combined overdose of risperidone and paroxetine. The dosage of risperidone should be reevaluated when paroxetine is initiated or discontinued (Prod Info RISPERDAL(R) oral tablets, oral solution, orally disintegrating tablets, 2008).

b) Risperidone plasma concentrations increased when risperidone-treated inpatients (n=12) with schizophrenia and negative symptoms were coadministered incremental doses of paroxetine. Prior to initiating paroxetine, patients were receiving risperidone 2 mg twice daily for at least 6 weeks and steady-state plasma concentrations of risperidone and 9-hydroxyrisperidone (9-OH-risperidone) had been achieved. Paroxetine doses were administered in 3 consecutive 4-week increments of 10 mg/day, 20 mg/day, and 40 mg/day. Mean risperidone plasma concentrations during 10-, 20-, and 40-mg paroxetine treatment were 3.8- (95% confidence interval (CI), 3.2 to 5.8; p less than 0.01) , 7.1- (95% CI, 5.3 to 16.5; p less than 0.01), and 9.7-fold (95% CI, 7.8 to 22.5; p less than 0.01) higher compared

with baseline. Increases in 9-OH-risperidone concentrations were not significant with paroxetine use. Mean active moiety (risperidone plus 9-OH-risperidone) plasma concentrations increased by 1.8-fold (95% CI, 1.4 to 2.7; p less than 0.05) during the 40-mg paroxetine dose; increases were not significant with 10- or 20-mg doses. Metabolic ratio was significantly increased (p less than 0.01) by 4.2-fold (95% CI, 3.4 to 6.2) with 10 mg of paroxetine, by 8.2-fold (95% CI, 6 to 16) with 20 mg, and by 12.6-fold (95% CI, 9.6 to 26.8) with 40 mg. Negative symptom scores were significantly improved during all paroxetine doses; however, extrapyramidal symptoms scores were significantly higher during 20- and 40-mg doses. The authors suggest that low-dose coadministration of paroxetine with risperidone may be safe and effective for treating schizophrenia with negative symptoms (Saito et al, 2005).

c) Paroxetine, a potent inhibitor of cytochrome CYP2D6, may impair the elimination of risperidone, primarily by inhibiting CYP2D6-mediated alpha-hydroxylation and, to a lesser extent, by simultaneously affecting the further metabolism of 9-hydroxyrisperidone (9-OH-risperidone) or other pathways of risperidone biotransformation. In a study including 10 patients diagnosed with schizophrenia (n=7) or schizoaffective disorder depressive type (n=3), risperidone plasma concentrations increased when paroxetine was coadministered with risperidone. Patients were stabilized on risperidone therapy 4 to 8 mg/day and received adjunctive paroxetine 20 mg/day to treat negative symptoms, concomitant depression, or both. Risperidone dosage remained constant throughout the duration of the study. A significant elevation in risperidone plasma concentrations (p less than 0.01) and a slight, nonsignificant decrease in 9-OH-risperidone occurred. After 4 weeks of paroxetine treatment, the total concentration of risperidone and 9-OH-risperidone was increased by 45% (p less than 0.05). The mean plasma risperidone to 9-OH-risperidone ratio also changed significantly (p less than 0.001) with concomitant paroxetine treatment. Extrapyramidal side effects occurred in one patient during the second week of paroxetine coadministration. Total plasma levels of risperidone in this patient increased 62% over baseline values during paroxetine coadministration. The occurrence of extrapyramidal symptoms in patients after addition of SSRIs to antipsychotics might also be caused by an additive pharmacodynamic effect of paroxetine (Spina et al, 2001).

d) Serotonin syndrome occurred in a patient using concomitant paroxetine and risperidone, an antipsychotic agent with potent serotonin antagonism and dopamine blocking activity . A 53-year-old male with a 7-month history of psychotic depression was being treated with risperidone 3 mg/day and paroxetine 20 mg/day for 10 weeks before presentation. Nine weeks into therapy, the patient showed decreased motivation and bilateral jerking movements of the mouth and legs. The patient discontinued his medication during the week before his admission. Upon presentation he was apathetic, confused, disorganized, and talked to himself. The doses of paroxetine and risperidone were doubled to 40 mg/day and 6 mg/day, respectively. Within 2 hours of taking his medication, he experienced bilateral jerking movements, ataxia, tremor, and shivering. He presented to the emergency room with involuntary jerking movements and lethargy. His mental status exam was notable for depression with psychomotor agitation, difficulty being aroused, and auditory hallucinations. Differential diagnosis included recurrent psychotic depression, neuroleptic malignant syndrome (NMS), drug overdose, and serotonin syndrome. Nortriptyline 100 mg at bedtime, haloperidol 10 mg twice daily and diphenhydramine 50 mg at night were initiated at discharge. The patient returned to baseline 9 months after discharge and is without symptoms of depression or psychosis (Hamilton & Malone, 2000).

3.5.1.EU Ritonavir

1) Interaction Effect: decreased paroxetine plasma levels

2) Summary: The concurrent administration of fosamprenavir/ritonavir and paroxetine has resulted in significantly decreased paroxetine plasma levels. Caution is advised if these agents are used concurrently. Dose adjustments should be guided by clinical efficacy and tolerability (Prod Info PAXIL(R) oral tablets, oral suspension, 2006). Patients may need to be monitored for loss of paroxetine efficacy.

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: Coadministration of fosamprenavir/ritonavir and paroxetine has led to significantly decreased paroxetine plasma levels. Use caution if these agents are coadministered. Dose adjustments should be made based on clinical efficacy and tolerability (Prod Info PAXIL(R) oral tablets, oral suspension, 2006). Monitor patients for loss of paroxetine efficacy.

7) Probable Mechanism: unknown

3.5.1.EV Rizatriptan

1) Interaction Effect: an increased risk of serotonin syndrome

2) Summary: There have been case reports of weakness, hyperreflexia, and incoordination following concomitant use of sumatriptan, a 5-hydroxytryptamine-1 (5HT-1) agonist, and a serotonin specific reuptake inhibitor (SSRI) (Prod Info Imitrex(R), 1998). Because rizatriptan is a 5HT 1B/1D receptor agonist, a similar interaction between SSRIs and rizatriptan may occur (Prod Info Maxalt(R), 1998a). Concurrent use of a triptan and an SSRI may result in serotonin syndrome which may be life-threatening. Symptoms of serotonin syndrome may include restlessness, hallucinations, loss of coordination, fast heart beat, rapid changes in blood pressure, increased body temperature, overreactive reflexes, nausea, vomiting, and diarrhea. Clinicians should be aware that triptans may be commonly used intermittently and that either the triptan or the SSRI may be prescribed by a different physician. Discuss the risks of serotonin syndrome with patients

who are prescribed this combination and monitor them closely for symptoms of serotonin syndrome (US Food and Drug Administration, 2006).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Coadministration of a triptan, such as rizatriptan, and an SSRI may result in a life-threatening condition called serotonin syndrome. Be aware that triptans may be commonly used intermittently and that either the triptan or the SSRI may be prescribed by a different physician. If these agents are used together, discuss the risks of serotonin syndrome with the patient and monitor closely for symptoms of serotonin syndrome (restlessness, hyperthermia, hyperreflexia, incoordination).
7) Probable Mechanism: additive pharmacologic effects resulting in excessive serotonergic stimulation
8) Literature Reports
a) Twelve healthy volunteers received paroxetine 20 mg daily for two weeks and a single dose of rizatriptan 10 mg. Plasma concentrations of rizatriptan were not altered by the administration of paroxetine (Prod Info Maxalt(R), 1998).

3.5.1.EW Rofecoxib
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.EX Selegiline
1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)
2) Summary: Concomitant administration of selegiline and paroxetine is contraindicated, and a minimum of 14 days should elapse after discontinuing selegiline before initiating therapy with paroxetine or a minimum of 7 days should elapse after discontinuing paroxetine before initiating therapy with selegiline (Prod Info EMSAM(R) transdermal patch, 2006). Concurrent administration or overlapping therapy may result in CNS toxicity or serotonin syndrome, a hyperserotonergic state characterized by symptoms such as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. Serious, even fatal, reactions have been reported with concomitant use of serotonin specific reuptake inhibitors and MAO inhibitors (Prod Info Paxil(R), 2003a; Lappin & Auchincloss, 1994c; Graber et al, 1994c; Suchowersky & de Vries, 1990c).
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Concurrent use of paroxetine and selegiline is contraindicated. Wait at least two weeks after discontinuing selegiline before initiating paroxetine, or at least 7 days after discontinuing paroxetine before initiating therapy with an selegiline.
7) Probable Mechanism: inhibition of serotonin metabolism by monoamine oxidase
8) Literature Reports
a) Concomitant use of SSRIs and monoamine oxidase inhibitors can produce a toxic reaction known as serotonin syndrome (Sternbach, 1991c). Serotonin syndrome is a condition of serotonergic hyperstimulation and manifests as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. If the syndrome is not recognized and correctly treated, fatality can result.
b) A 26-year old woman who had been taking isocarboxazid for eight weeks stopped taking the drug

for 11 days before beginning therapy with sertraline. After a single 100 mg sertraline dose, the patient became restless and developed leg twitches. The patients was later admitted to the emergency room with diaphoresis, tachycardia, hyperreflexia, and various neuromuscular disturbances. After treatment with diazepam and propranolol the patient did not improve. The patient was then given two 4 mg doses of cyproheptadine an hour apart, with notable improvement in symptoms after the second dose (Lappin & Auchincloss, 1994b).

c) A drug interaction was reported in a 61-year old woman in which sertraline 100 mg twice daily was added to a regimen of lithium, phenelzine, thioridazine, and doxepin. Three hours after taking the first sertraline dose, the patient was found in a semicomatose state, with elevated body temperature, increased pulse, increased respiration rate, and a blood pressure of 140/110 mm Hg. After transportation to the hospital, the patient was misdiagnosed as having neuroleptic malignant syndrome (NMS) which was later changed to serotonin syndrome due to a reaction between sertraline and phenelzine. The authors suggest that monoamine oxidase inhibitor (MAOI) therapy should be discontinued for at least two weeks before initiation of therapy with a selective serotonin reuptake inhibitor (SSRI) and that before starting a MAOI, SSRI therapy should be discontinued for at least five half-lives of the parent drug and any active metabolites (Graber et al, 1994b).

d) Two cases reports suggested a possible interaction between fluoxetine and selegiline (Suchowersky & de Vries, 1990b). One case involved a first episode of mania being observed approximately one month after adding selegiline to fluoxetine. The patient improved two months after both drugs were discontinued, and no further details were provided. The second case involved diaphoresis, vasoconstriction, and cyanosis of the hands which occurred in close temporal relationship to adding fluoxetine to selegiline. Both drugs were discontinued, with relatively quick resolution of symptoms. Rechallenge with fluoxetine alone occurred without incident.

3.5.1.EY Sibrafiban

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and antiplatelet agents has been associated with an increased risk of bleeding. Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an antiplatelet agent are given concurrently, monitor patient for signs of increased bleeding (Prod Info PAXIL(R) oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008)

7) Probable Mechanism: unknown

3.5.1.EZ Sibutramine

1) Interaction Effect: an increased risk of serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)

2) Summary: Sibutramine inhibits the reuptake of norepinephrine, dopamine, and serotonin. In addition, the two major metabolites of sibutramine, M1 and M2, also inhibit the reuptake of these neurotransmitters. A hyperserotonergic state, termed serotonin syndrome, may result if sibutramine is given concurrently with a selective serotonin reuptake inhibitor. Coadministration of sibutramine and selective serotonin reuptake inhibitors is not recommended (Prod Info Meridia(R), 1997).

3) Severity: major

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: Sibutramine should not be administered with serotonergic agents, including selective serotonin reuptake inhibitors, because of the increased risk of serotonin syndrome.

7) Probable Mechanism: additive pharmacologic effects resulting in excessive serotonergic stimulation

8) Literature Reports

a) Serotonin syndrome is a condition of serotonergic hyperstimulation and manifests as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. If the syndrome is not recognized and correctly treated, death can result (Sternbach, 1991b).

3.5.1.FA St John's Wort

1) Interaction Effect: an increased risk of serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)

2) Summary: Case reports describe the onset of serotonin syndrome-like symptoms, mania, and hypomania following the addition of St. John's Wort to sertraline, fluoxetine, and paroxetine therapy (Spinella & Eaton, 2002c; Barbanel et al, 2000a; Waksman et al, 2000a; Lantz et al, 1999a). A patient exhibited a syndrome resembling sedative/hypnotic intoxication after adding St. John's Wort to paroxetine therapy (Gordon, 1998a). St. John's Wort is thought to inhibit serotonin reuptake and may have mild monoamine oxidase inhibitory activity (Singer et al, 1999; Thiede & Walper, 1994), which when added to selective serotonin reuptake inhibitors may result in serotonin syndrome.

3) Severity: major
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Patients should be advised to wait two weeks after stopping St. John's Wort before restarting selective serotonin reuptake inhibitor therapy. If a patient plans to replace selective serotonin reuptake inhibitor (SSRI) therapy with St. John's Wort, the half-life of the specific SSRI should be taken into consideration, waiting at least 5 half-lives for the SSRI to be metabolized out of the body.
7) Probable Mechanism: additive serotonergic effect
8) Literature Reports

a) Five cases have been reported of serotonin syndrome in the elderly after combining prescription antidepressants and St. John's Wort. Case 1 developed dizziness, nausea, vomiting and a headache 4 days after starting St. John's Wort 300 milligrams (mg) three times daily combined with sertraline 50 mg daily. Her symptoms resolved 2 to 3 days after stopping all medications. Case 2 developed nausea, epigastric pain and anxiety 3 days after starting St. John's Wort 300 mg twice daily combined with sertraline 75 mg daily. His symptoms resolved in one week after discontinuing both medications, and he resumed sertraline use without complications. The third case developed nausea, vomiting, anxiety, and confusion 2 days after starting St. John's Wort 300 mg twice daily combined with sertraline 50 mg daily. His symptoms improved in 4 to 5 days after stopping both medications and taking cyproheptadine 4 mg three times daily. Case 4 developed nausea, anxiety, restless, and irritability 2 days after starting St. John's Wort 300 mg three times daily combined with sertraline 50 mg daily. Cyproheptadine 4 mg twice daily was administered for seven days, and his symptoms improved in 1 week after stopping the medication. Cases 1 through 4 resumed their prescriptive sertraline after symptoms subsided and had no further problems. Case 5 developed nausea, vomiting and restlessness 3 days after starting St. John's Wort 300 mg three times daily combined with nefazodone 100 mg twice daily. She continued to take St. John's Wort but discontinued the nefazodone and over 1 week her symptoms Improved. She refused to resume therapy with nefazodone, but continued therapy with St. John's Wort and mild to moderate symptoms of depression and anxiety returned (Lantz et al, 1999).

b) A 50-year-old female taking St. John's Wort 600 mg daily experienced symptoms of sedative intoxication when she ingested a single dose of paroxetine 20 mg. She was incoherent, groggy, slow-moving, and complained of nausea and weakness. Prior to starting St. John's Wort, she had been receiving paroxetine 40 mg daily for eight months without adverse effects. After a night of sleep, she returned to her baseline mental status (Gordon, 1998).

c) A 61-year-old female experienced restlessness and involuntary movements of her extremities after beginning paroxetine 20 milligrams (mg) two days after discontinuing St. John's Wort 600 mg daily. The patient reported agitation and akathisia 8 hours after taking the first dose of paroxetine. She presented with diaphoresis and involuntary movement of all extremities with hyperreflexia and rigidity. Blood pressure, heart rate, and temperature were normal. After admission, blood pressure increased to 200/116 mmHg and heart rate increased to 145 beats per minute. Creatine kinase increased from 212 units/liter (U/L) initially to 1024 U/L. The patient was managed with supportive care and lorazepam and discharged after two days (Waksman et al, 2000).

d) A 28-year-old male developed a manic syndrome following comedication with St. John's Wort and sertraline. The patient was also on testosterone replacement therapy following bilateral orchidectomy 2 years earlier, but testosterone levels were subtherapeutic. The patient was prescribed sertraline 50 milligrams daily for depression following a 2 week trial of St. John's Wort per patient preference (dose not specified). Before sertraline was started, the patient was instructed to discontinue St. John'sWort, but continued it despite this advice. The patient experienced improved mood so did not see his physician, believing that he did not need further treatment. Over 2 months, the patient had elated mood, was irritable, and overspent, buying a car he could not afford, and was ultimately arrested for stealing fuel for the car. On arrest, he was referred to psychiatric services due to irritability and disinhibition. He was observed to be over-aroused, distractible, have flight of ideas, and grandiose delusions, leading to a diagnosis of a manic episode. The authors state the possibility of the manic state resulting from sertraline therapy alone, and that St. John's Wort may have increased the risk as a result of monoamine oxidase inhibition. Since the patient's testosterone level was subnormal, the possibility of its contribution to the manic state was considered low. However, the patient had elevated gonadotropin levels (luteinizing hormone and follicle-stimulating hormone) which may have predisposed the patient to mania (Barbanel et al, 2000).

e) A 42-year-old female experienced symptoms consistent with a mixed hypomanic episode following concomitant use of fluoxetine, buspirone, Ginkgo biloba, and St. John's Wort. The symptoms resolved following discontinuation of Ginkgo and St. John's Wort. The patient was being treated for depression following a mild traumatic brain injury with fluoxetine 20 milligrams (mg) twice daily and buspirone 15 mg twice daily. Several weeks prior to presentation, buspirone was increased to 20 mg twice daily for persistent anxiety and the patient began taking Ginkgo biloba, melatonin, and St. John's Wort in unspecified doses. Melatonin was considered unlikely to have contributed to her symptoms. Ginkgo and St. John's Wort were considered possible contributors since they may potentiate antidepressants, and considering the temporal relationship between the use of the herbs and onset of symptoms and discontinuation of the herbs and resolution of symptoms. However, the brain injury was considered a possible contributor (Spinella & Eaton, 2002b).

3.5.1.FB Sulfinpyrazone

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and antiplatelet agents has been associated with an increased risk of bleeding. Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an antiplatelet agent are given concurrently, monitor patient for signs of increased bleeding (Prod Info PAXIL(R) oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008)

7) Probable Mechanism: unknown

3.5.1.FC Sulindac

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).

b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.FD Sulodexide

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and antiplatelet agents has been associated with an increased risk of bleeding. Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an antiplatelet agent are given concurrently, monitor patient for signs of increased bleeding (Prod Info PAXIL(R) oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008)

7) Probable Mechanism: unknown

3.5.1.FE Sumatriptan

1) Interaction Effect: an increased risk of serotonin syndrome

2) Summary: There have been case reports of weakness, hyperreflexia, incoordination, and persistent paroxysmal dyskinesias following concomitant use of sumatriptan and a serotonin specific reuptake inhibitor (SSRI) (Prod Info Paxil CR(TM), 2003m; Prod Info Imitrex(R), 2004; Abraham et al, 1997a). Concurrent use of a triptan and an SSRI may result in serotonin syndrome which may be life-threatening. Symptoms of serotonin syndrome may include restlessness, hallucinations, loss of coordination, fast heart beat, rapid changes in blood pressure, increased body temperature, overreactive reflexes, nausea, vomiting, and diarrhea. Clinicians should be aware that triptans may be commonly used intermittently and that either the triptan or the SSRI may be prescribed by a different physician. Discuss the risks of serotonin syndrome with patients who are prescribed this combination and monitor them closely for symptoms of serotonin syndrome (US Food and Drug Administration, 2006).

3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Coadministration of a triptan, such as sumatriptan, and an SSRI, such as paroxetine, may result in a life-threatening condition called serotonin syndrome. Be aware that triptans may be commonly used intermittently and that either the triptan or the SSRI may be prescribed by a different physician. If these agents are used together, discuss the risks of serotonin syndrome with the patient and monitor closely for symptoms of serotonin syndrome (restlessness, hyperthermia, hyperreflexia, incoordination).
7) Probable Mechanism: additive pharmacologic effects resulting in excessive serotonergic stimulation
8) Literature Reports
a) A 40-year old female with a 9-year history of a bipolar disorder was started on paroxetine therapy, with the dose being increased to 30 mg daily within one week. After seven days of paroxetine 30 mg, she received an injection of sumatriptan for a migraine headache. Within 24 hours, she developed sustained dystonic contractions of her neck muscles, dystonic arching of her back, choreaform rocking of her hips, choreaform up and down movements of her shoulders, and wavelike, athetoid movements of her abdominal muscles. These dyskinesias occurred about five times daily and lasted for 20 to 30 minutes. Following the discontinuation of paroxetine, these abnormal movements decreased in severity but worsened when paroxetine was again initiated. All medications were stopped, and clozapine at a dose of 100 mg daily caused a remission of her paroxysmal dyskinesias. The authors speculated that the combination of paroxetine and sumatriptan may have sensitized the 5-HT autoreceptors and induced postsynaptic receptor supersensitivity (Abraham et al, 1997).

3.5.1.FF Suprofen
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.FG Tamoxifen
1) Interaction Effect: decreased plasma concentrations of the active metabolites of tamoxifen
2) Summary: Tamoxifen is a prodrug metabolized to active metabolites by CYP450 enzymes (Stearns et al, 2003). Paroxetine, a potent inhibitor of CYP2D6, reduces plasma concentrations of the active metabolites. In one study of 12 patients, coadministration with tamoxifen significantly reduced plasma concentrations of the active metabolite 4-hydroxy-N-desmethyl-tamoxifen (Stearns et al, 2003). The patient's CYP2D6 genotype also influences the metabolism of tamoxifen, with the homozygous variant or heterozygous allele having lower plasma concentrations of the potent antiestrogenic metabolite endoxifen than subjects with a homozygous wild-type genotype (Jin et al, 2005). However, one small case control study found that pharmacokinetic alterations in tamoxifen metabolism did not significantly increase tumor recurrence in breast cancer patients (Lehmann et al, 2004).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: established
6) Clinical Management: Coadministration of paroxetine and tamoxifen has resulted in decreased plasma concentrations of 4-hydroxy-N-desmethyl-tamoxifen, an active metabolite of tamoxifen. If administered concurrently, monitor for decreased tamoxifen efficacy.
7) Probable Mechanism: inhibition of CYP2D6-mediated tamoxifen metabolism
8) Literature Reports

a) Concomitant use of paroxetine, a potent inhibitor of CYP2D6, and tamoxifen, which requires activation by CYP2D6 enzymes to the antiestrogenic metabolite (endoxifen), results in substantially reduced plasma concentrations of endoxifen. Eighty newly diagnosed breast cancer patients taking tamoxifen 20 mg/day were genotyped for the common alleles of the CYP2D6, CYP2C9, CYP3A5, and sulfotransferase (SULT) 1A1 genes. After 1 and 4 months of tamoxifen treatment, plasma concentrations of tamoxifen and endoxifen were measured. After 4 months of tamoxifen, plasma endoxifen concentrations were statistically significantly lower in those with a CYP2D6 homozygous variant genotype (20 nM, 95% CI = 11.1 to 28.9) or a heterozygous genotype (43.1 nM, 95% CI = 33.3 to 52.9) than those with a homozygous wild-type genotype (78 nM, 95% CI = 65.9 to 90.1) (both P = 0.003). The mean plasma endoxifen concentration for subjects with a homozygous wild-type genotype who were taking CYP2D6 inhibitors was 58% lower than those not taking such inhibitors (38.6 nM versus 91.4 nM, 95% CI of difference = -86.1 to -19.5, P = 0.0025). Concomitant use of venlafaxine, a weak inhibitor of CYP2D6, resulted in slightly reduced plasma concentrations of endoxifen, while the use of paroxetine, a potent inhibitor of CYP2D6, resulted in substantial reductions in endoxifen concentrations. Plasma concentrations of tamoxifen and metabolites were not altered significantly by genetic variations of CYP2C9, CYP3A5 or SULT1A1 (Jin et al, 2005).
b) A case control study (n = 28) designed to evaluate the effect of CYP isoform inhibitors on therapeutic outcome in women taking tamoxifen for estrogen receptor-positive breast cancer found no significant impact on breast cancer recurrence from chronic exposure (3 months or greater) to CYP2D6, 2C9, or 3A4 inhibitors or substrates. Cases (recurrences of breast cancer) and controls (patients without recurrent breast cancer) were matched by cancer stage, year of diagnosis, and CYP inhibitor or substrate exposure. Selective serotonin reuptake inhibitors, including paroxetine, are inhibitors of CYP2D6, 2C9, and 3A isoforms responsible for the metabolism of tamoxifen to the potent antiestrogen 4-hydroxy metabolite (Lehmann et al, 2004).
c) In a prospective clinical trial involving 12 women of known CYP2D6 genotype with breast cancer taking adjuvant tamoxifen, coadministration of paroxetine decreased the plasma concentration of the tamoxifen active metabolite endoxifen (4-hydroxy-N-desmethyl-tamoxifen). Each patient was maintained on tamoxifen 20 mg/day during treatment with paroxetine 10 mg/day for 4 weeks. Plasma concentrations of endoxifen clinically significantly decreased from a pre-paroxetine mean of 12.4 ng/mL to 5.5 ng/mL after paroxetine administration (difference = 6.9 ng/mL, 95% CI = 2.7 to 11.2 ng/mL; P = 0.004). When analyzed by genotype, reduced levels of endoxifen were more pronounced in women who carried the wild-type CYP2D6, while those with the variant genotype experienced no statistically significant effect of paroxetine on endoxifen levels. However, the authors caution that the results of this small study should not alter current treatment recommendations which include the use of selective serotonin reuptake inhibitors (SSRIs) and selective norepinephrine reuptake inhibitors (SNRIs) to relieve tamoxifen-associated hot flashes (Stearns et al, 2003).

3.5.1.FH Tapentadol

1) Interaction Effect: increased risk of serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)
2) Summary: Concurrent use of tapentadol and a selective serotonin reuptake inhibitor (SSRI) may result in serotonin syndrome, which may be life-threatening. Symptoms of serotonin syndrome may include restlessness, hallucinations, loss of coordination, fast heart beat, rapid changes in blood pressure, increased body temperature, overreactive reflexes, nausea, vomiting, and diarrhea (Prod Info tapentadol immediate release oral tablets, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of tapentadol and an SSRI may result in a life-threatening condition called serotonin syndrome. If these agents are used together, monitor the patient closely for symptoms of serotonin syndrome (restlessness, hyperthermia, hyperreflexia, incoordination), especially during treatment initiation and dose increases (Prod Info tapentadol immediate release oral tablets, 2008).
7) Probable Mechanism: additive serotonergic effect

3.5.1.FI Tenidap

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.FJ Tenoxicam

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.FK Tetrabenazine

1) Interaction Effect: increased exposure to tetrabenazine
2) Summary: Caution should be used when administering a strong CYP2D6 inhibitor (eg, paroxetine) to a patient taking tetrabenazine (a CYP2D6 substrate), and the daily dose of tetrabenazine should be halved if paroxetine and tetrabenazine are used concomitantly. Following a single 50 mg dose of tetrabenazine given after 10 days of daily administration of paroxetine 20 mg, an increase in tetrabenazine exposure was observed in 25 healthy volunteers. When compared with tetrabenazine alone, coadministration with paroxetine caused an approximately 30% increase in Cmax and a 3-fold increase in the AUC of the alpha-HTBZ metabolite of tetrabenazine. Subjects given paroxetine prior to tetrabenazine alone experienced a 2.4-fold increase in Cmax and a 9-fold increase in the AUC of the beta-HTBZ metabolite of tetrabenazine. The elimination half-life for both metabolites was approximately 14 hours when tetrabenazine was coadministered with paroxetine (Prod Info XENAZINE(R) oral tablets, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Use caution when prescribing paroxetine to patients who take tetrabenazine. Patients who are already receiving a stable dose of tetrabenazine should have their daily dose of tetrabenazine decreased by half if coadministration with paroxetine is necessary. Concomitant use of paroxetine and tetrabenazine may cause elevated tetrabenazine levels. Monitor for increased tetrabenazine side effects such as somnolence, fatigue, insomnia, depression, anxiety, akathisia, and nausea (Prod Info XENAZINE(R) oral tablets, 2008).
7) Probable Mechanism: inhibition of CYP2D6-mediated tetrabenazine metabolism by paroxetine

3.5.1.FL Theophylline

1) Interaction Effect: an increased risk of theophylline toxicity
2) Summary: There have been isolated reports of increased theophylline levels during coadministration with paroxetine. Until further study is conducted, monitoring of the theophylline level is recommended when paroxetine therapy is added, changed, or discontinued (Prod Info Paxil CR(TM), 2003o).
3) Severity: moderate
4) Onset: delayed

5) Substantiation: theoretical
6) Clinical Management: Monitor theophylline levels if paroxetine and theophylline are coadministered.
7) Probable Mechanism: unknown

3.5.1.FM Thioridazine

1) Interaction Effect: an increased risk of thioridazine toxicity, cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Paroxetine inhibits the metabolism of thioridazine, possibly through the inhibition of cytochrome P450 2D6 (CYP2D6) resulting in toxicity. The resulting elevated levels of thioridazine would be expected to enhance the prolongation of the QT interval and may increase the risk of serious, potentially fatal, cardiac arrhythmias, such as torsade de pointes-type arrhythmias (Prod Info Paxil(R), 2003b; Prod Info Mellaril(R), 2000a).
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Due to the potential for significant, possibly life-threatening, proarrhythmic effects, concurrent administration of thioridazine and paroxetine is contraindicated.
7) Probable Mechanism: inhibition of cytochrome P450 2D6-mediated thioridazine metabolism
8) Literature Reports
a) The metabolism of thioridazine is inhibited by drugs such as paroxetine due to reduced cytochrome P450 2D6 isozyme activity. The elevated levels of thioridazine would be expected to enhance the prolongation of the QTc interval associated with thioridazine. This, in turn, may increase the risk of serious, potentially fatal, cardiac arrhythmias, such as torsade de pointes-type arrhythmias (Prod Info Mellaril(R), 2000).

3.5.1.FN Tiaprofenic Acid

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.FO Ticlopidine

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and antiplatelet agents has been associated with an increased risk of bleeding. Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an antiplatelet agent are given concurrently, monitor patient for signs of increased bleeding (Prod Info PAXIL(R) oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008)
7) Probable Mechanism: unknown

3.5.1.FP Tinzaparin

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info PAXIL(R) oral tablets, suspension, 2008). Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with warfarin (Schalekamp et al, 2008; Prod Info PAXIL(R) oral tablets, suspension, 2008).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When paroxetine and an anticoagulant are given concurrently, monitor patients for signs of increased bleeding. Patients who are taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, when paroxetine therapy is initiated or discontinued (Prod Info PAXIL(R) oral tablets, suspension, 2008).
7) Probable Mechanism: unknown
8) Literature Reports
a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bleeding (hospital admission due to bleeding) in patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patients with a mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients experienced 11 bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experiencing bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model (Wallerstedt et al, 2009).
b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5), however, the rate of gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).
c) Preliminary data suggest that there may be a pharmacodynamic interaction (that causes an increased bleeding diathesis with unaltered prothrombin time) between paroxetine and warfarin. The concomitant use of paroxetine and warfarin should be undertaken with caution (Prod Info PAXIL(R) oral tablets, suspension, 2008).
d) In a multiple-dose study, several days of combined therapy with warfarin and paroxetine resulted in mild but clinically significant bleeding in 5 of 27 subjects. This effect occurred in the absence of a significant enhancement in warfarin-induced hypoprothrombinemia or changes in either paroxetine or warfarin disposition (Bannister et al, 1989b).

3.5.1.FQ Tipranavir
1) Interaction Effect: increased paroxetine plasma concentrations
2) Summary: Although the drug interaction between paroxetine and tipranavir/ritonavir has not been studied, coadministration of paroxetine with tipranavir/ritonavir may result in increased paroxetine plasma concentrations. Paroxetine doses may need to be adjusted when tipranavir/ritonavir therapy is initiated (Prod Info APTIVUS(R) oral capsules, solution, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concurrent administration of paroxetine and tipranavir/ritonavir may increase paroxetine plasma concentrations. Use caution when these agents are coadministered and consider adjusting the paroxetine dose as needed upon initiation of tipranavir/ritonavir (Prod Info APTIVUS(R) oral capsules, solution, 2008).
7) Probable Mechanism: unknown

3.5.1.FR Tirofiban
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and antiplatelet agents has been associated

with an increased risk of bleeding. Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an antiplatelet agent are given concurrently, monitor patient for signs of increased bleeding (Prod Info PAXIL(R) oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008)
7) Probable Mechanism: unknown

3.5.1.FS Tolmetin
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.FT Toloxatone
1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)
2) Summary: Concurrent administration or overlapping therapy with paroxetine and a monoamine oxidase (MAO) inhibitor may result in CNS toxicity or serotonin syndrome, a hyperserotonergic state characterized by symptoms such as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. Serious, even fatal, reactions have been reported with concomitant use of serotonin specific reuptake inhibitors and MAO inhibitors (Prod Info Paxil(R), 1999b; Lappin & Auchincloss, 1994e; Graber et al, 1994e; Suchowersky & de Vries, 1990e). As a reversible and selective monoamine oxidase inhibitor, toloxatone may not potentiate the effects of selective serotonin reuptake inhibitors to the same frequency, extent, and duration observed with other MAOIs. However, until further studies confirm the safety and efficacy of this combined therapy, concomitant use is contraindicated.
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Concurrent use of paroxetine and a MAO inhibitor is contraindicated. Wait at least two weeks after discontinuing a MAO inhibitor before initiating paroxetine, and at least two weeks after discontinuing paroxetine before initiating therapy with a MAO inhibitor.
7) Probable Mechanism: inhibition of serotonin metabolism by monoamine oxidase
8) Literature Reports
a) Concomitant use of SSRIs and monoamine oxidase inhibitors can produce a toxic reaction known as serotonin syndrome (Sternbach, 1991g). Serotonin syndrome is a condition of serotonergic hyperstimulation and manifests as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. If the syndrome is not recognized and correctly treated, fatality can result.
b) A 26-year old woman who had been taking isocarboxazid for eight weeks stopped taking the drug for 11 days before beginning therapy with sertraline. After a single 100 mg sertraline dose, the patient became restless and developed leg twitches. The patients was later admitted to the emergency room with diaphoresis, tachycardia, hyperreflexia, and various neuromuscular disturbances. After treatment with diazepam and propranolol the patient did not improve. The patient was then given two 4 mg doses of cyproheptadine an hour apart, with notable improvement in symptoms after the second dose (Lappin

& Auchincloss, 1994d).

c) A drug interaction was reported in a 61-year old woman in which sertraline 100 mg twice daily was added to a regimen of lithium, phenelzine, thioridazine, and doxepin. Three hours after taking the first sertraline dose, the patient was found in a semicomatose state, with elevated body temperature, increased pulse, increased respiration rate, and a blood pressure of 140/110 mm Hg. After transportation to the hospital, the patient was misdiagnosed as having neuroleptic malignant syndrome (NMS) which was later changed to serotonin syndrome due to a reaction between sertraline and phenelzine. The authors suggest that monoamine oxidase inhibitor (MAOI) therapy should be discontinued for at least two weeks before initiation of therapy with a selective serotonin reuptake inhibitor (SSRI) and that before starting a MAOI, SSRI therapy should be discontinued for at least five half-lives of the parent drug and any active metabolites (Graber et al, 1994d).

d) Two cases reports suggested a possible interaction between fluoxetine and selegiline (Suchowersky & de Vries, 1990d). One case involved a first episode of mania being observed approximately one month after adding selegiline to fluoxetine. The patient improved two months after both drugs were discontinued, and no further details were provided. The second case involved diaphoresis, vasoconstriction, and cyanosis of the hands which occurred in close temporal relationship to adding fluoxetine to selegiline. Both drugs were discontinued, with relatively quick resolution of symptoms. Rechallenge with fluoxetine alone occurred without incident.

3.5.1.FU Tramadol

1) Interaction Effect: an increased risk of seizures and serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes); a decrease in the analgesic effect of tramadol

2) Summary: Seizures and serotonin syndrome have been reported in patients using tramadol. Some medications, including paroxetine, are known to reduce the seizure threshold. The risk of seizures and serotonin syndrome may be enhanced when paroxetine and tramadol therapy are combined (Prod Info Ultram(R), 2004). Paroxetine also inhibits the metabolism of tramadol to its active metabolite M1. This reduces the analgesic effect of tramadol (Laugesen et al, 2005).

3) Severity: major

4) Onset: rapid

5) Substantiation: theoretical

6) Clinical Management: Caution should be used if tramadol is to be administered to patients receiving concomitant paroxetine therapy. If possible, avoid this combination, especially in patients with underlying conditions that might predispose to seizures. Observe the patient closely for signs and symptoms of serotonin syndrome, as well as decreased analgesic effect of tramadol.

7) Probable Mechanism: increased concentration of serotonin in the nervous system and periphery; inhibition of the CYP2D6 -mediated formation of tramadol active metabolites (-)-M1 and (+)-M1 by paroxetine

8) Literature Reports

a) The coadministration of paroxetine with tramadol reduced the analgesic effect of tramadol. In this study, 16 healthy subjects participated in a randomized, double blind, placebo-controlled, 4 way crossover design study to evaluate the effect of paroxetine on the analgesic effect of tramadol. Subjects received treatment with paroxetine 20 mg or equivalent placebo on the 3 days prior to the study days. This was followed by a single oral dose of tramadol 150 mg or the equivalent placebo. The washout period was at least 2 weeks between each treatment. All the subjects were included in one of the following treatment groups: placebo/placebo, placebo/tramadol, paroxetine/placebo, and paroxetine/tramadol. Nociceptive tests were conducted and included pressure pain tolerance threshold, electrical sural nerve stimulation, and the cold pressor test. Pretreatment with paroxetine resulted in a drop in the analgesic effect of tramadol in the cold pressor test mean pain measure (P=0.036) and a change in the discomfort modality (P=0.056). Paroxetine pretreatment did not cause a decrease in the analgesic effect of tramadol that was statistically significant in the other pain tests. The paroxetine/tramadol treatment combination maintained a statistically significant analgesic effect in the pressure pain tolerance threshold (P=0.01) and the single electrical stimulation tolerance threshold (P=0.15) compared with the placebo/placebo treatment group. In comparison with the placebo/tramadol group, the (+)- and (-)- tramadol AUC increased 37% and 32% respectively when paroxetine was administered with tramadol and the AUC of (+)- and (-)-M1 active metabolite decreased 67% and 40% respectively (Laugesen et al, 2005).

3.5.1.FV Tranylcypromine

1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)

2) Summary: Concurrent administration or overlapping therapy with paroxetine and a monoamine oxidase (MAO) inhibitor may result in CNS toxicity or serotonin syndrome, a hyperserotonergic state characterized by symptoms such as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. Serious, even fatal, reactions have been reported with concomitant use of serotonin specific reuptake inhibitors and MAO inhibitors (Prod Info Paxil(R), 2003; Lappin & Auchincloss, 1994a; Graber et al, 1994a; Suchowersky & de Vries, 1990a). Concomitant use is contraindicated.

3) Severity: contraindicated

4) Onset: rapid

5) Substantiation: theoretical
6) Clinical Management: Concurrent use of selective serotonin reuptake inhibitors, such as paroxetine, and tranylcypromine is contraindicated. Wait at least two weeks after discontinuing an MAO inhibitor before initiating paroxetine, and at least two weeks after discontinuing paroxetine before initiating therapy with an MAOI.
7) Probable Mechanism: inhibition of serotonin metabolism by monoamine oxidase
8) Literature Reports
a) Concomitant use of SSRIs and monoamine oxidase inhibitors can produce a toxic reaction known as serotonin syndrome (Sternbach, 1991a). Serotonin syndrome is a condition of serotonergic hyperstimulation and manifests as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. If the syndrome is not recognized and correctly treated, fatality can result.
b) A 26-year old woman who had been taking isocarboxazid for eight weeks stopped taking the drug for 11 days before beginning therapy with sertraline. After a single 100 mg sertraline dose, the patient became restless and developed leg twitches. The patient was later admitted to the emergency room with diaphoresis, tachycardia, hyperreflexia, and various neuromuscular disturbances. After treatment with diazepam and propranolol the patient did not improve. The patient was then given two 4 mg doses of cyproheptadine an hour apart, with notable improvement in symptoms after the second dose (Lappin & Auchincloss, 1994).
c) Sertraline 100 mg twice daily was added to a regimen of lithium, phenelzine, thioridazine, and doxepin in a 61-year old woman (Graber et al, 1994). Three hours after taking the first sertraline dose, the patient was found in a semicomatose state, with elevated body temperature, increased pulse, increased respiration rate, and a blood pressure of 140/110 mm Hg. After transportation to the hospital, the patient was misdiagnosed as having neuroleptic malignant syndrome (NMS) which was later changed to serotonin syndrome due to a reaction between sertraline and phenelzine. The authors suggest that monoamine oxidase inhibitor (MAOI) therapy should be discontinued for at least two weeks before initiation of therapy with a selective serotonin reuptake inhibitor (SSRI) and that before starting a MAOI, SSRI therapy should be discontinued for at least five half-lives of the parent drug and any active metabolites.
d) Two cases suggestive of an interaction between fluoxetine and selegiline were reported (Suchowersky & de Vries, 1990). One case involved a first episode of mania being observed approximately one month after adding selegiline to fluoxetine. The patient improved two months after both drugs were discontinued, and no further details were provided. The second case involved diaphoresis, vasoconstriction, and cyanosis of the hands which occurred in close temporal relationship to adding fluoxetine to selegiline. Both drugs were discontinued, with relatively quick resolution of symptoms. Rechallenge with fluoxetine alone occurred without incident.

3.5.1.FW Trazodone
1) Interaction Effect: serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)
2) Summary: There have been several reports of serotonin syndrome due to interactions between selective serotonin reuptake inhibitors and antidepressants, including one case report due to paroxetine and trazodone coadministration (George & Godleski, 1996a; Reeves & Bullen, 1995a; Alderman & Lee, 1996). Serotonin syndrome is a rare but potentially fatal condition of serotonergic hyperstimulation characterized by hypertension, hyperthermia, myoclonus and changes in mental status (Sternbach, 1991d). Further clinical studies or case reports are necessary to determine the incidence and implications of serotonin syndrome associated with this drug combination.
3) Severity: major
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Concurrent use of paroxetine and trazodone should be undertaken with caution. Monitor patients for signs and symptoms of serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes).
7) Probable Mechanism: additive serotonergic effects
8) Literature Reports
a) Serotonin syndrome was reported in a 29-year old woman taking trazodone and paroxetine. The patient was treated with trazodone 200 mg daily at bedtime for approximately three months for depression and insomnia. The patient's depressive symptoms were unresponsive to this treatment, so trazodone was subsequently decreased to 50 mg daily at bedtime for two weeks before paroxetine 20 mg every morning was added. Within 24 hours after the first dose of paroxetine, the patient became agitated, confused, shaky, and diaphoretic. Upon examination, the patient had impaired concentration, intermittent myoclonus in all extremities, hyperreflexia, tremor, and diaphoresis. After discontinuation of antidepressant medications, the patient's symptoms resolved (Reeves & Bullen, 1995).
b) A 44-year old man developed symptoms characteristic of serotonin syndrome due to a possible interaction between fluoxetine and trazodone. The patient had been taking fluoxetine 40 mg daily and trazodone 100 mg daily for approximately two months before symptoms occurred. The patient experienced disorientation, tremor, diaphoresis, and anxiety, followed by uncontrollable shaking and loss of consciousness. After the patient was treated with cyproheptadine 4 mg orally, symptoms resolved over the next 30 minutes. Trazodone was discontinued and the patient continued to take

fluoxetine 40 mg daily without further complications (George & Godleski, 1996).

3.5.1.FX Trimipramine

1) Interaction Effect: trimipramine toxicity (dry mouth, sedation, urinary retention)
2) Summary: Paroxetine coadministered with desipramine or imipramine produced higher serum concentrations of the tricyclic antidepressant (TCA) in some patients (Hartter et al, 1994e; Brosen et al, 1993m). Although not reported for trimipramine, a similar interaction could occur. Paroxetine's effect on TCAs may resemble that of fluoxetine (another selective serotonin reuptake inhibitor), which is known to inhibit TCA metabolism (Aranow et al, 1989e; Vaughan, 1988e; Goodnick, 1989e). With coadministration, monitor patients for trimipramine toxicity. Trimipramine doses may need to be reduced.
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When paroxetine is coadministered with trimipramine, monitor patients for signs and symptoms of trimipramine toxicity (dry mouth, sedation, urinary retention, blurred vision). Trimipramine doses may need to be reduced.
7) Probable Mechanism: decreased trimipramine metabolism
8) Literature Reports
a) The effect of paroxetine on desipramine metabolism was studied in 9 extensive metabolizers (EM) and 8 poor metabolizers (PM) of desipramine. Subjects took a single oral dose of desipramine before starting paroxetine and a second dose after 11 days of paroxetine use. After the addition of paroxetine, EMs experienced a 5-fold decrease in clearance of desipramine, indicating that paroxetine inhibits oxidation reactions catalyzed by CYP2D6. PMs had a slight increase in clearance of desipramine with paroxetine. With concurrent administration of desipramine and paroxetine, interaction of the two drugs may result in a need for dosage adjustments, especially in extensive metabolizers of desipramine (Brosen et al, 1993l).

3.5.1.FY Tryptophan

1) Interaction Effect: serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)
2) Summary: Adverse effects (headache, nausea, sweating, dizziness) have been reported when tryptophan was given concurrently to patients using paroxetine (Prod Info Paxil CR(TM), 2004a). Tryptophan can be metabolized to serotonin (Boyer & Blumhardt, 1992b), and paroxetine, a selective serotonin reuptake inhibitor, acts to increase available serotonin (Caley & Weber, 1993a). It is possible that combining these two serotonin-enhancing agents could result in excessive serotonin leading to a condition known as serotonin syndrome. Effects associated with the serotonin syndrome include confusion, restlessness, mental status changes, tremor, diaphoresis, hypertension, myoclonus, shivering, and hyperreflexia. Concomitant administration of the SSRI fluoxetine with tryptophan was reported to cause signs and symptoms associated with serotonin syndrome (Steiner & Fontaine, 1986).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Coadministration of tryptophan and paroxetine is not recommended by the manufacturer of paroxetine. Should tryptophan and paroxetine be given concomitantly, monitor patient response and watch for signs of excessive serotonergic activity. It may be necessary to reduce doses of either agent.
7) Probable Mechanism: additive adverse effects

3.5.1.FZ Valdecoxib

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate

an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.GA Warfarin

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info PAXIL(R) oral tablets, suspension, 2008). Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with warfarin (Schalekamp et al, 2008; Prod Info PAXIL(R) oral tablets, suspension, 2008).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When paroxetine and an anticoagulant are given concurrently, monitor patients for signs of increased bleeding. Patients who are taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, when paroxetine therapy is initiated or discontinued (Prod Info PAXIL(R) oral tablets, suspension, 2008).
7) Probable Mechanism: unknown
8) Literature Reports
a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bleeding (hospital admission due to bleeding) in patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patients with a mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients experienced 11 bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experiencing bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model (Wallerstedt et al, 2009).
b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5), however, the rate of gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).
c) Preliminary data suggest that there may be a pharmacodynamic interaction (that causes an increased bleeding diathesis with unaltered prothrombin time) between paroxetine and warfarin. The concomitant use of paroxetine and warfarin should be undertaken with caution (Prod Info PAXIL(R) oral tablets, suspension, 2008).
d) In a multiple-dose study, several days of combined therapy with warfarin and paroxetine resulted in mild but clinically significant bleeding in 5 of 27 subjects. This effect occurred in the absence of a significant enhancement in warfarin-induced hypoprothrombinemia or changes in either paroxetine or warfarin disposition (Bannister et al, 1989b).

3.5.1.GB Xemilofiban

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and antiplatelet agents has been associated with an increased risk of bleeding. Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an antiplatelet agent are given concurrently, monitor patient for signs of increased bleeding (Prod Info PAXIL(R) oral tablets, suspension, 2008; Prod Info PROZAC(R) oral

capsules, delayed-release capsules, solution, 2008)
7) Probable Mechanism: unknown

3.5.1.GC Zolmitriptan
1) Interaction Effect: an increased risk of serotonin syndrome
2) Summary: There have been case reports of weakness, hyperreflexia, and incoordination following concomitant use of sumatriptan, a 5-hydroxytryptamine-1 (5HT-1) agonist, and a serotonin specific reuptake inhibitor (SSRI) (Prod Info Imitrex(R), 1998a; Prod Info Zomig(TM), 1997). Because zolmitriptan is a 5HT 1B/1D agonist, a similar interaction between SSRIs and zolmitriptan may occur (Prod Info Zomig(TM), 1997). Concurrent use of zolmitriptan and an SSRI may result in serotonin syndrome which may be life-threatening. Symptoms of serotonin syndrome may include restlessness, hallucinations, loss of coordination, fast heart beat, rapid changes in blood pressure, increased body temperature, overreactive reflexes, nausea, vomiting, and diarrhea. Clinicians should be aware that triptans may be commonly used intermittently and that either the triptan or the SSRI may be prescribed by a different physician. Discuss the risks of serotonin syndrome with patients who are prescribed this combination and monitor them closely for symptoms of serotonin syndrome (US Food and Drug Administration, 2006).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Coadministration of a triptan, such as zolmitriptan, and an SSRI may result in a life-threatening condition called serotonin syndrome. Be aware that triptans may be commonly used intermittently and that either the triptan or the SSRI may be prescribed by a different physician. If these agents are used together, discuss the risks of serotonin syndrome with the patient and monitor closely for symptoms of serotonin syndrome (restlessness, hyperthermia, hyperreflexia, incoordination).
7) Probable Mechanism: additive pharmacologic effects resulting in excessive serotonergic stimulation
8) Literature Reports
a) The pharmacokinetics of a single 10 mg dose of zolmitriptan were not altered by four weeks of fluoxetine 20 mg daily pretreatment in healthy volunteers. The effects of zolmitriptan on blood pressure were also not changed by fluoxetine therapy (Prod Info Zomig(R), 2002).

3.5.1.GD Zomepirac
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.2 Drug-Food Combinations

3.5.2.A Ethanol
1) Interaction Effect: an increased risk of impairment of mental and motor skills
2) Summary: Paroxetine did not potentiate cognitive or psychomotor effects associated with ethanol consumption (Caley & Weber, 1993b). However, the manufacturer of paroxetine recommends that patients be advised to avoid alcohol while using paroxetine (Prod Info Paxil CR(TM), 2003p).
3) Severity: minor
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Patients receiving paroxetine should be advised to avoid the use of alcohol.
7) Probable Mechanism: additive central nervous system effects

4.0 Clinical Applications

Monitoring Parameters

Patient Instructions

Place In Therapy

Mechanism of Action / Pharmacology

Therapeutic Uses

Comparative Efficacy / Evaluation With Other Therapies

4.1 Monitoring Parameters

A) Paroxetine Hydrochloride

1) Therapeutic

a) Laboratory Parameters

1) Steady-state plasma levels of paroxetine have not correlated with clinical efficacy in depressed patients (Tasker et al, 1989b).

b) Physical Findings

1) A reduction in symptoms of depression is indicative of a therapeutic response to paroxetine.

2) Toxic

a) Laboratory Parameters

1) Hepatic and renal function tests, as well as blood pressure and pulse, should be monitored periodically throughout therapy.

2) Steady-state plasma levels of paroxetine have not correlated with toxic effects in depressed patients (Tasker et al, 1989b).

b) Physical Findings

1) Blood pressure and pulse should be monitored.

2) Monitor patients receiving antidepressants for worsening of depression, suicidality, or unusual changes in behavior, especially at the initiation of therapy or when the dose increases or decreases. Such monitoring should include at least weekly face-to-face contact with patients or their family members or caregivers during the initial 4 weeks of treatment, then visits every other week for the next 4 weeks, then at 12 weeks, and then as clinically indicated beyond 12 weeks. Families and caregivers should be advised of the need for close observation (i.e., daily observation) of patients and communication with the prescriber (Anon, 2004; Anon, 2004).

3) Patients who experience symptoms of anxiety, agitation, panic attacks, insomnia, irritability, hostility, impulsivity, akathisia, hypomania, or mania may be at an increased risk for worsening depression or suicidality. If these symptoms are observed, therapy should be re-evaluated and it may be necessary to discontinue medications when symptoms are severe, sudden in onset, or were not part of the patient's initial symptoms (Anon, 2004; Anon, 2004).

4) During discontinuation of treatment (especially when abrupt) patients should be monitored for withdrawal symptoms such as dysphoric mood, irritability, dizziness, agitation, sensory disturbances (i.e., paresthesias), anxiety, confusion, lethargy, headache, insomnia, emotional lability, and hypomania. If these symptoms are observed following a reduction of dose or upon cessation of treatment, the previously prescribed dose may be resumed and subsequently reduced at a more gradual rate (Prod Info Paxil(R), 2004; Prod Info Paxil CR(TM), 2004b).

4.2 Patient Instructions

A) Paroxetine (By mouth)

Paroxetine

Treats depression, obsessive-compulsive disorder (OCD), panic disorder, social anxiety disorder, premenstrual dysphoric disorder (PMDD), generalized anxiety disorder, and posttraumatic stress disorder (PTSD). This medicine is a selective serotonin reuptake inhibitor (SSRI).

When This Medicine Should Not Be Used:
You should not use this medicine if you have had an allergic reaction to paroxetine, or if you are pregnant. Do not use this medicine if you are also using pimozide (Orap®), thioridazine (Mellaril®), or have taken an MAO inhibitor (Marplan®, Eldepryl®, Parnate®, or Nardil®) within the past 2 weeks. This medicine is not for use in children.

How to Use This Medicine:
Liquid, Tablet, Long Acting Tablet

Your doctor will tell you how much of this medicine to use and how often. Do not use more medicine or use it more often than your doctor tells you to.
You may take this medicine with or without food. This medicine is usually taken in the morning.
Measure the oral liquid medicine with a marked measuring spoon, oral syringe, or medicine cup. Shake the bottle well before measuring each dose.
Swallow the tablet and extended-release tablet whole. Do not crush, break, or chew it. Do not use an extended-release tablet that is cracked or chipped.
This medicine should come with a Medication Guide. Read and follow these instructions carefully. Ask your doctor or pharmacist if you have any questions. Ask your pharmacist for the Medication Guide if you do not have one. Your doctor might ask you to sign some forms to show that you understand this information.

If a Dose is Missed:

If you miss a dose or forget to use your medicine, use it as soon as you can. If it is almost time for your next dose, wait until then to use the medicine and skip the missed dose. Do not use extra medicine to make up for a missed dose.

How to Store and Dispose of This Medicine:

Store the medicine in a closed container at room temperature, away from heat, moisture, and direct light.
Ask your pharmacist, doctor, or health caregiver about the best way to dispose of any leftover medicine after you have finished your treatment. You will also need to throw away old medicine after the expiration date has passed.
Keep all medicine away from children and never share your medicine with anyone.

Drugs and Foods to Avoid:
Ask your doctor or pharmacist before using any other medicine, including over-the-counter medicines, vitamins, and herbal products.

Make sure your doctor knows if you are using cimetidine (Tagamet®), linezolid (Zyvox®), St. John's wort, sumatriptan (Imitrex®), theophylline (Theo-Dur®), tramadol (Ultram®), tryptophan, medicine for seizures (such as phenobarbital, phenytoin, Dilantin®, Luminal®, or Solfoton®), or any other medicine for depression (such as amitriptyline, desipramine, doxepin, fluoxetine, imipramine, lithium, nortriptyline, Aventyl®, Elavil®, Eskalith®, Lithane®, Lithobid®, Norpramin®, Pamelor®, Prozac®, Sinequan®, or Tofranil®). Tell your doctor if you use a blood thinner (such as warfarin or Coumadin®), diuretics or "water pills" (such as furosemide or Lasix®), or phenothiazine medicine (such as prochlorperazine, Compazine®, Mellaril®, Phenergan®, Thorazine®, or Trilafon®).
Make sure your doctor knows if you are also using atomoxetine (Strattera®), digoxin (Lanoxin®), ketoconazole (Nizoral®), procyclidine (Kemadrin®), risperidone (Risperdal®), or terfenadine (Seldane®). Also tell your doctor if you are using medicine for heart rhythm problems (such as encainide, flecainide, propafenone, quinidine, Enkaid®, Quinaglute®, Rythmol®, or Tambocor®), medicine to treat HIV or AIDS (such as fosamprenavir, ritonavir, Lexiva®, or Norvir®), or any pain or arthritis medicines (NSAIDs) such as aspirin, ibuprofen, naproxen, Advil®, Aleve®, Bextra®, Celebrex®, Ecotrin®, or Motrin®.
Do not drink alcohol while you are using this medicine.

Warnings While Using This Medicine:

Using this medicine while you are pregnant can harm your unborn baby. Use an effective form of birth control to keep from getting pregnant. If you think you have become pregnant while using the medicine, tell your doctor right away.
Make sure your doctor knows if you are breastfeeding, or if you have a recent heart attack, heart disease, kidney disease, liver disease, bleeding problems, epilepsy or seizures, narrow angle glaucoma, or a history of mania or drug abuse.
You may need to take this medicine for up to 4 weeks before you feel better. Keep using this medicine for the full treatment time. If you feel that the medicine is not working well, do not take more than your prescribed dose. Call your doctor for instructions.
For some children, teenagers, and young adults, this medicine can increase thoughts of suicide. Tell your doctor or your child's doctor right away if you or your child start to feel more depressed and have thoughts about hurting yourselves. Report any unusual thoughts or behaviors that trouble you or your child, especially if they are new or are getting worse quickly. Make sure the doctor knows if you or your child have trouble sleeping, get upset easily, have a big increase in energy, or start to act reckless. Also tell the doctor if you or your child have sudden or strong feelings, such as feeling nervous, angry, restless, violent, or scared. Let the doctor know if you, your child, or anyone in your family has bipolar disorder (manic-depressive) or has tried to commit suicide.
Do not stop using this medicine suddenly without asking your doctor. You may need to slowly decrease your dose before stopping it completely.
Make sure any doctor or dentist who treats you knows that you are using this medicine. This medicine may affect the results of certain medical tests.
This medicine may make you dizzy or drowsy. Avoid driving, using machines, or doing anything else that could be dangerous if you are not alert.

Your doctor will need to check your progress at regular visits while you are using this medicine. Be sure to keep all appointments.

Possible Side Effects While Using This Medicine:
Call your doctor right away if you notice any of these side effects:
Allergic reaction: Itching or hives, swelling in your face or hands, swelling or tingling in your mouth or throat, chest tightness, trouble breathing.
Anxiety, agitation, restlessness, or mood or mental changes.
Change in how much or how often you urinate, or problems in urination.
Changes in behavior, or thoughts of hurting yourself or others.
Confusion, weakness, and muscle twitching.
Extreme lightheadedness, or fainting.
Fast, slow, or uneven heartbeat.
Fever, chills, or sore throat.
Numbness, tingling, or burning pain in your hands, arms, legs, or feet.
Seizures or tremors.
Trouble sleeping or unusual dreams.
Unusual bleeding or bruising.

If you notice these less serious side effects, talk with your doctor:
Blurred vision.
Drowsiness or sleepiness.
Headache.
Loss of appetite.
Menstrual cramps.
Nausea, dry mouth, diarrhea, constipation, or upset stomach.
Problems with sex.
Sweating.
Tiredness.
Vaginal pain or discharge.

If you notice other side effects that you think are caused by this medicine, tell your doctor.

4.3 Place In Therapy

A) SUMMARY

1) Paroxetine has received approval by the United States Food and Drug Administration for treating depression, generalized anxiety disorder, obsessive compulsive disorder, panic disorder, and social anxiety disorder. Paroxetine has also been evaluated in numerous other psychiatric disorders.

B) DEPRESSION

1) All of the selective serotonin reuptake inhibitors (SSRIs) are effective for treating depression although selected characteristics of each agent may offer greater benefit in some patients. Paroxetine does NOT have any major therapeutic benefits over other SSRIs; however, discontinuation symptoms may be troublesome in patients who stop taking paroxetine. Ultimately, the selection of an SSRI is dependent on clinical judgment and response of patients to previous therapy (Edwards & Anderson, 1999).

2) Paroxetine is a selective serotonin uptake inhibitor which has been effective as once daily therapy in the treatment of major depression. In comparative studies, paroxetine has been as effective as amitriptyline, clomipramine, imipramine, and mianserin. A more favorable adverse effect profile compared to tricyclic antidepressants has been observed in several studies. Paroxetine may have a faster onset of action than fluoxetine; however, both agents are equal in efficacy after six weeks of therapy.

3) Preliminary data suggest that a trial of a second serotonin reuptake inhibitor (SSRI) is a viable clinical alternative in depressed patients who have failed to respond to an adequate trial to the first SSRI used (Joffe et al, 1996). In a retrospective review of 55 patients who had failed to respond to at least five weeks of therapy with either fluoxetine, sertraline, fluvoxamine, or paroxetine (all at therapeutic dosages), 51% did respond to a trial of an alternative agent. The choice of the second agent was based on clinician preference; no difference between response rates of the different drugs was noted.

4.4 Mechanism of Action / Pharmacology

A) MECHANISM OF ACTION

1) Paroxetine is a phenylpiperidine antidepressant agent which selectively inhibits serotonin uptake (Magnussen et al, 1982; Hassan et al, 1985; Lassen, 1978). Similar to other selective inhibitors of serotonin uptake, paroxetine was developed as an alternative to tricyclic antidepressants which have effects on the reuptake of both serotonin and other neurotransmitters. More specific and more potent serotonin uptake inhibitors may result in more effective antidepressant therapy in the absence of adverse effects associated with norepinephrine uptake inhibition (Laursen et al, 1985; Raptopoulos et al, 1989a; Mertens & Pintens, 1988). Other selective serotonin reuptake inhibitors are fluoxetine, zimeldine, femoxetine, citalopram, and 2-nitro-imipramine (Mellerup et al, 1983).

2) In vitro and in vivo studies have demonstrated that paroxetine is a selective serotonin uptake inhibitor with minimal effects on uptake of norepinephrine (Lassen, 1974; Magnussen et al, 1982; Hassan et al, 1985). Potent

and long-lasting inhibition of serotonin uptake into platelets and synaptosomes, leading to depletion of blood serotonin, has been reported in man and animals, and potentiation of 5-hydroxytryptophan-induced central effects has been observed in mice (Mellerup et al, 1983; Lassen, 1978; Raptopoulos et al, 1989a; Magnussen et al, 1982). These effects are attributed to long-lasting binding of the drug to a serotonin uptake mechanism in neurons and platelets (Mellerup et al, 1983).

B) REVIEW ARTICLES

1) A comparison of selective serotonin reuptake inhibitors with a guide to selection is provided (Edwards & Anderson, 1999a).

2) Two reviews provide a discussion of the efficacy of selective serotonin reuptake inhibitors and other antidepressants for treatment of severe depression (Schatzberg, 1999; Hirschfeld, 1999).

3) The efficacy of antidepressants in reducing panic attack frequency, symptoms of depression, social avoidance, and overall impairments from panic disorder are addressed (den Boer, 1998).

4) A review article described the treatment of panic disorder, including the place of selective serotonin reuptake inhibitors for this disorder (DeVane, 1997).

5) Treatment of elderly patients with selective serotonin reuptake inhibitors is discussed with emphasis on improved tolerability compared to other antidepressants (Skerritt et al, 1997).

6) Drug-interactions of antidepressants are reviewed in German language (Zapotoczky & Simhandl, 1995).

4.5 Therapeutic Uses

4.5.A Paroxetine Hydrochloride

Bipolar disorder, depressed phase

Compulsive gambling

Diabetic neuropathy

Difficulty controlling emotions

Drug-induced depressive state

Fibromyalgia

Generalized anxiety disorder

Headache

Hot sweats

Insomnia

Kleptomania

Major depressive disorder

Myocardial infarction; Prophylaxis

Nocturnal sleep-related eating disorder

Obsessive-compulsive disorder

Panic disorder

Posttraumatic stress disorder

Premature ejaculation

Premenstrual dysphoric disorder

Pruritus, Non-dermatological

Schizophrenia, Negative symptoms

Social phobia

Somatization disorder

Trichotillomania

Vasovagal syncope

4.5.A.1 Bipolar disorder, depressed phase

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Ineffective
Recommendation: Adult, Class III
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

When given with lithium, no better than placebo unless serum lithium concentration is low

c) Adult:

1) Neither paroxetine nor imipramine was more effective than placebo in treating BIPOLAR DEPRESSION in patients stabilized on lithium if their serum lithium levels were above 0.8 milliequivalents per liter (meq/L). However, patients whose serum lithium concentration was less than 0.8 meq/L showed greater improvement with 8 weeks of antidepressant treatment than with placebo treatment (p=0.05 for paroxetine, p=0.04 for imipramine). In a double-blind study, patients were stratified according to serum lithium concentration and then randomized to receive paroxetine (n=35), imipramine (n=39), or placebo (n=43) for 10 weeks. Among all completers of the study, therapeutic response (Hamilton depression scale scores of 7 or less) was achieved by 56%, 48%, and 54% of patients receiving paroxetine, imipramine, and placebo, respectively. Adverse events accounted for study discontinuation in 1 patient in the paroxetine group (3%), 12 in the imipramine group (30%), and 5 in the placebo group (12%). No patient in the paroxetine group experienced induction to mania, whereas 3 patients treated with imipramine and 1 treated with placebo developed treatment-emergent mania (Nemeroff et al, 2001a).

4.5.A.2 Compulsive gambling

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIa
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Paroxetine was effective in the treatment of pathological gambling in patients without concomitant mood, anxiety, or substance use disorders.

c) Adult:

1) Paroxetine (mean dose 51.7 milligrams per day (mg/d)) was effective in the treatment of pathological gambling for patients without concomitant mood, anxiety, or substance use disorders. In this 8-week, double-blind, placebo- controlled study, 45 patients who fulfilled the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria for pathological gambling and scored at least 5 on the South Oaks Gambling Screen (SOGS) were randomly assigned to either a paroxetine or placebo treatment group. For the paroxetine group, an initial dosage of 20 mg/d was administered. This dose could be gradually increased, in increments of 10 mg per week, to a maximum of 60 mg/d, based on tolerability and efficacy. Patients' clinical status was assessed weekly using the Clinical Global Impressions (CGI) scale, (including the Pathological Gambling CGI), and both the total score and gambling urge subscale score of the Gambling Symptom Assessment Scale (G-SAS). By the study endpoint, there was a significant difference between the treatment groups in the reduction of the mean G-SAS scores, with a 52% decrease in the paroxetine group compared to a 23% decrease in the placebo group. Assessment using the CGI scale also showed significant differences in the degree of improvement in the two treatment groups. In the paroxetine group, 47.8% were very much improved (score of 1), 13% were much improved (score of 2), and 13% had no change; in the placebo group, the values were 4.5%, 18.2%, and 27.3%, respectively. There was not a significant difference between the paroxetine and placebo groups until patients completed at least 6 weeks of treatment. The most

common side effects of paroxetine were nausea (26.1%), headache (17.4%), and sweating (17.4%). A key limitation of these results is that patients in this study are not representative of the larger population of patients with pathological gambling; most of the study participants were women (30 women, 15 men), and did not have comorbid mood, anxiety, and substance use disorders (Kim et al, 2002).

4.5.A.3 Diabetic neuropathy

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Paroxetine 10 to 60 milligrams per day (median 40 milligrams/day) was effective in relieving symptoms of diabetic neuropathy in a single-blind, dose-escalation study in 19 diabetic patients. Patients conducted daily self-ratings on a visual analog scale for the following symptoms: pain, paresthesia, dysesthesia, nightly aggravation, and sleep disturbances. The most commonly reported adverse effects were fatigue, sweating, and nausea (Sindrup et al, 1991).

4.5.A.4 Difficulty controlling emotions

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIa
Strength of Evidence: Adult, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

In 2 case reports, paroxetine 20 milligrams daily was effective for relieving pathological crying related to a stroke.

c) Adult:

1) Pathologic crying resolved within 24 hours after beginning paroxetine 20 milligrams daily in a 55-year-old man following a left anterior choroidal artery infarct. Although the patient was NOT depressed, 5 to 8 crying episodes were reported daily; they generally occurred in response to a trivial environmental stimuli. Three episodes daily were still reported at 30 days at which time paroxetine was started. Definitive data are not available; however, serotonergic neurotransmission may be damaged during a stroke with the result of pathologic crying (Derex et al, 1997).

2) A 65-year-old man developed frequent (50 per day), uncontrolled episodes of crying which were effectively treated with paroxetine 20 milligrams daily (Tan & Dorevitch, 1996). Within a week, the episodes of crying had disappeared completely. The PATHOLOGIC CRYING episodes began after the man suffered a stroke. Interaction with the staff at the rehabilitation hospital and family or friends caused crying. Before the stroke, the man was emotionally reserved; he was not depressed after the stroke. Based on this and other cases treated with a selective serotonin reuptake inhibitor, these agents should be considered for treating emotional incontinence, a condition characterized by uncontrolled laughing or crying, which is common in stroke patients or patients with multiple sclerosis or pseudobulbar palsy.

4.5.A.5 Drug-induced depressive state

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Reduced the occurrence of depression in patients receiving high-dose interferon alfa for treatment of malignant melanoma

c) Adult:

1) Paroxetine treatment, given 2 weeks before and throughout interferon alfa treatment, resulted in a lower rate of occurrence and lower severity of depression than occurred with placebo administration. In a double-blind, randomized trial, 40 patients with resected malignant melanoma that was estimated to have a greater than 50% likelihood of recurrence were to be treated with high-dose interferon alfa, which is known to cause depression. Two weeks before starting interferon alfa treatment, half of the patients were given paroxetine and half were given placebo. The paroxetine dose increased from 10 milligrams (mg) per day in the first week to 20 mg/day in the second week. Thereafter, dose could be increased at the discretion of the study psychiatrist to a maximum of 40 mg/day. Interferon alfa-2b was given intravenously at 20 million units per square meter 5 days per week for the first 4 weeks and subcutaneously at 10 million units per square meter 3 days per week for the remaining 8 weeks. The incidence of major depression was significantly lower with paroxetine than with placebo (p=0.04; 11%

vs 45%, relative risk=0.24). Severity of depressive symptoms, anxiety, and neurotoxicity were all significantly less among patients receiving paroxetine than among those receiving placebo (p less than 0.001 for each parameter). Paroxetine also decreased the likelihood that interferon alfa therapy would need to be discontinued because of depression or neurotoxicity (p=0.03). The effect of paroxetine on the therapeutic efficacy of interferon alfa was not assessed (Musselman et al, 2001).

4.5.A.6 Fibromyalgia

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

In a 12-week, randomized, double-blind, placebo-controlled trial in adults with fibromyalgia without current mood or anxiety disorders (n=124), treatment with controlled-release paroxetine improved overall symptomatology but did not yield significant reduction in pain (Patkar et al, 2007).

c) Adult:

1) General Information

a) Treatment with paroxetine has demonstrated efficacy in the treatment of fibromyalgia in adults. In a 12-week, randomized, double-blind, placebo-controlled trial, treatment with controlled-release (CR) paroxetine led to improvement in overall fibromyalgia symptomatology in adults meeting the American College of Rheumatology diagnostic criteria for fibromyalgia (Patkar et al, 2007). The study excluded patients with mood or anxiety disorders. A higher proportion of paroxetine CR-treated patients (mean dose, 39.1 milligrams (mg)) had a 25% or greater reduction in Fibromyalgia Impact Questionnaire (FIQ) scores compared to placebo-treated patients. However, there was no significant difference from placebo for reduction in pain (based on FIQ subscale and Visual Analog Scale (VAS) scores) or tender point count. In another 12-week, randomized, single-blind study in patients with fibromyalgia syndrome (n=40), treatment with paroxetine 20 mg/day led to statistically significant improvements in overall condition as well as yielded significant improvements in pain, stiffness, and mood based on VAS scores and reductions in mean tender point scores compared to placebo (Giordano et al, 1999). Long-term studies in populations representative of fibromyalgia in the real world setting are warranted.

2) Clinical Trial

a) Treatment with controlled-release (CR) paroxetine improved overall symptomatology in adults with fibromyalgia without current mood or anxiety disorders in a 12-week, randomized, double-blind, placebo-controlled trial; however, there was no significant reduction of pain. Patients (n=124; aged, 18 to 65 years; 94% female) meeting the American College of Rheumatology diagnostic criteria for fibromyalgia were included. Prior to initiation of study drug, patients were required to have a Visual Analog Scale (VAS) pain score of 5 or higher and a Beck Depression Inventory score of 23 or less. Patients with inflammatory disease or current depressive or anxiety disorders were excluded. Randomization was preceded by a 1-week, single-blind, placebo run-in phase to identify and exclude patients displaying a 25% or greater reduction from baseline on the 10-item, self-reported Fibromyalgia Impact Questionnaire (FIQ) scores (range, 0 to 100). Study patients were randomized to receive either paroxetine CR (n=58; mean age, 47.9 years) or placebo (n=58; mean age, 49.1 years) for 12 weeks. Paroxetine was initiated at 12.5 milligrams (mg)/day and force-titrated in weekly 12.5-mg increments to the maximum tolerated dose up to 62.5 mg/day and maintained through week 12 (mean study dose, 39.1 mg/day). This was followed by a 2-week taper. The primary outcome was response, defined by a 25% or greater reduction on the FIQ total score from randomization to end of therapy. Baseline FIQ scores were 53 and 49 in the paroxetine CR and placebo groups, respectively. Approximately half of the patients had a greater than 5-year fibromyalgia duration (paroxetine CR, 28 (49%); placebo, 31 (53%)). An intention-to-treat analysis revealed significantly more responders in the paroxetine CR group compared to the placebo group (56.8% vs 32.7%; p=0.016). These results were consistent with a complete analysis (65.7% (n=25/38) vs 33.3% (n=16/48); p less than 0.01). Although a higher proportion of patients in the paroxetine CR group achieved a 50% or greater reduction in baseline FIQ scores, the difference compared to placebo was not statistically significant (25.8% vs 13.7%; p=0.08). Among secondary outcomes, paroxetine CR treatment led to a significant reduction in FIQ total score compared to placebo (F(1,113)=25.28; p=0.015). The mean treatment difference in FIQ scores was -6.4 (95% confidence interval (CI), -11.4 to +0.9; p less than 0.05) in favor of paroxetine CR. Among the FIQ subscales, paroxetine CR had better outcomes than placebo on fatigue, anxiety, and days the patient felt good (p less than 0.05 for all). However, the difference between the groups for pain (p=0.07) and depression (p=0.08) were not statistically significant. The groups did non differ significantly in the mean change in VAS pain scores (paroxetine CR -12.2 vs placebo -8.8; p=0.16). Additionally, improvements on other secondary outcomes measures, including changes in tender point count, tender point index, or the Sheehan Disability Scale scores, were not significantly different between the groups. For the paroxetine CR group, adverse events reported commonly and at a higher frequency than the placebo group included drowsiness (26% vs 7%), dry mouth

(36% vs 9%), female genital disorders (9% vs 2%), ejaculatory problems (66% vs 2%), impotence (33% vs 0%), insomnia (17% vs 9%), anxiety (14% vs 7%), and nausea (14% vs 9%) (Patkar et al, 2007).

4.5.A.7 Generalized anxiety disorder

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes ((regular-release)); Pediatric, no
Efficacy: Adult, Effective
Recommendation: Adult, Class I
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Paroxetine was found to be effective in patients without comorbid depression
Improved symptoms and social functioning in patients with generalized anxiety disorder

c) Adult:

1) Paroxetine was more effective than placebo in the treatment of generalized anxiety disorder. In a randomized, double-blind trial, 324 patients were given placebo or paroxetine 10 milligrams (mg) per day for the first week, 20 mg/day for the second, and, thereafter, up to 50 mg/day on an individual basis. Patients in both treatment groups showed improvement in scores of the Hamilton Rating Scale for Anxiety anxious mood item, but improvement was significantly greater for the paroxetine group as early as week one (p less than 0.05) and at every point thereafter (p less than 0.01). According to the Clinical Global Impressions-Severity of Illness scale, patients in the paroxetine group had a significantly greater reduction in illness severity. At the end of the trial, 40% of paroxetine patients and 27% of placebo patients were reported to be "not ill" or to have only "borderline illness" (p less than 0.01). A patient-rated anxiety scale also showed improvement in both groups but significantly greater improvement in patients receiving paroxetine (p less than 0.001 at week 8). In the intent-to-treat population, 62 percent of patients who received paroxetine were responders vs 36% of patients who received placebo. Improvement in social life and family life were significantly greater among patients treated with paroxetine (p less than 0.01). Adverse events were more frequent among patients taking paroxetine than among those taking placebo, with the most common events associated with paroxetine treatment being asthenia, constipation, abnormal ejaculation, decrease in libido, nausea, and somnolence. Approximately 80% of each group completed the study (Pollack et al, 2001).

2) In an 8-week multicenter study, paroxetine 20 milligrams (mg) daily and paroxetine 40 mg daily were significantly (p less than 0.001 and p less than 0.001, respectively) better than placebo at improving Hamilton Rating Scale for Anxiety (HAM-A) total, HAM-A anxiety item, HAM-A tension item, and Clinical Global Impression Severity of Illness and Improvement scores. Five-hundred and sixty-six patients with DSM-IV diagnosed generalized anxiety disorder WITHOUT current depression were randomized to receive either placebo, paroxetine 20 mg daily, or paroxetine 40 mg daily for 8 weeks. At study conclusion, patients receiving both doses of paroxetine had significantly improved HAM-A and CGI scores compared to patients receiving placebo. Drug related adverse events that occurred at rates greater than patients receiving placebo included asthenia, constipation, decreased appetite, dry mouth, nausea, libido decreases, somnolence, sweating and abnormal ejaculation (Bellew et al, 2000).

4.5.A.8 Headache

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Paroxetine has been effective for treating migraine and tension headaches in small studies. In a case report, it was also useful for prophylaxis of migraine headache.

c) Adult:

1) Three patients with preexisting classical migraine, who received paroxetine for depression, had total elimination of or a decrease in headaches after starting paroxetine. In 2 patients, headaches returned when the patients missed a dose or discontinued paroxetine. Although prospective clinical trials are needed to verify these reports, paroxetine may prevent migraine headache when taken routinely (Hays, 1997).

2) In a case report, paroxetine was effective for MIGRAINE PROPHYLAXIS (Black & Sheline, 1995). A 48-year-old woman with a long history of depression and migraine headaches was started on paroxetine 20 mg/day for her depression. She had been experiencing approximately 50 migraine headaches a year. Sumatriptan was being used to alleviate her migraines. After six weeks of paroxetine therapy her depression scores demonstrated marked improvement. She also indicated that she had a 2-week period with no migraine headaches, the first time in over a year; her usage of sumatriptan was also greatly reduced. Well controlled, double-blind trials are needed to further evaluate the role of paroxetine in migraine prophylaxis.

3) Paroxetine may be useful in treating chronic daily headache (Foster & Bafaloukos, 1994). In an open study involving 60 patients with mixed migraine/tension-type headache who had failed at least two other medications, paroxetine was started at 10 mg/day and titrated up to 50 mg/day in 2 to 4 week intervals. Patients were followed for 3 to 9 months. Forty-eight patients completed the study. A reduction of at least 50% in the number of headaches per month were reported in 92% of the patients. The most common adverse effects were fatigue and insomnia. Double-blind controlled trials are needed to validate these findings.

4) Headache decreased significantly compared to baseline in patients receiving paroxetine 20 to 30 milligrams per day for 8 weeks during a randomized, double-blind, cross-over study with sulpiride. Fifty patients with chronic tension headache were randomized to receive either sulpiride 200 to 400 milligrams/day or paroxetine for 8 weeks. Headache was recorded by the patients on a 5-point verbal score. Comparison between the 2 treatment groups after the first 8 weeks demonstrated no statistical differences in headache scores; however, both treatments did reduce headaches when compared to base line. Following crossover, patients switched to sulpiride demonstrated a reduction in headache scores, while those switched to paroxetine did not. It should be noted that there was no washout period between the crossover and paroxetine is known to have a relatively long half-life. More controlled, large scale clinical trials are necessary to determine paroxetine's role in the treatment of chronic tension headache (Langemark et al, 1989).

4.5.A.9 Hot sweats

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Paroxetine reduced hot flash severity and frequency in menopausal women.

c) Adult:

1) Treatment with paroxetine reduced hot flash severity and frequency in menopausal women. In a double-blind, placebo-controlled, multicenter, parallel-group study, menopausal women (n=165) experiencing at least 2 to 3 hot flashes daily or at least 14 hot flashes per week received paroxetine controlled-release (CR) 12.5 milligrams (mg)/day, paroxetine CR 25 mg/day, or placebo for 6 weeks. Patients recorded frequency and severity of hot flashes in diaries each day and hot flash composite scores (frequency x severity) were calculated from these ratings. Following six weeks of treatment, mean placebo-adjusted reductions in the daily composite hot flash scores were -4.7 (95% CI, -8.1 to -1.3; p=0.007) for paroxetine CR 12.5 mg and -3.6(95% CI, -6.8 to -0.4; p=0.03) for paroxetine CR 25 mg as compared with placebo. The median reduction from baseline in the hot flash composite score was 62.2% for patients taking paroxetine CR 12.5 mg and 64.6% for patients taking paroxetine CR 25 mg as compared with 37.8% for placebo. Headache, nausea, and insomnia were the most commonly reported adverse events (Stearns et al, 2003a).

4.5.A.10 Insomnia

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class III
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

A preliminary study suggests that paroxetine may be useful in patients with primary insomnia

c) Adult:

1) Patients with primary insomnia improved during treatment with paroxetine. In this 6-week study (n=15), patients received paroxetine 10 milligrams (mg) within 1 hour of bedtime; dose titration to 30 mg daily was allowed. For the primary outcome measure, Clinical Global Impressions-Improvement scale (CGI-I), 11 of 14 patients were much improved or very much improved. In addition, 7 patients no longer met criteria for primary insomnia. However, improvement was NOT consistent for other parameters including sleep quality, daytime well-being, daytime mental functioning that were determined from patient diaries and polysomnography. One patient left the study due to side effects. Results of this small, uncontrolled study support the need for a longer, randomized, placebo-controlled clinical trial (Nowell et al, 1999).

4.5.A.11 Kleptomania

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Effective for treating kleptomania in a single patient

c) Adult:

1) In a single patient, paroxetine was effective for treating depression and compulsive kleptomania. This patient initially presented with depression but also mentioned a long history of compulsive stealing that resulted in loss of several jobs. He typically stole items with little value about twice weekly. Treatment with paroxetine 30 milligrams daily for 3 months resulted in remission of depressive symptoms and absence of all stealing. Although he had fleeting thoughts about stealing, he easily controlled this behavior. This report suggests that paroxetine similar to other selective serotonin reuptake inhibitors may be useful for treating kleptomania (Kraus, 1999).

4.5.A.12 Major depressive disorder

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes (Regular and controlled-release formulations); Pediatric, no
Efficacy: Adult, Effective
Recommendation: Adult, Class I
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Paroxetine 10 to 50 mg daily was effective in uncontrolled (Gagiano et al, 1989) and controlled studies
Paroxetine was comparable to amitriptyline, clomipramine, imipramine, and mianserin
Paroxetine did not provide more symptomatic improvement than placebo in elderly nursing home residents with non-major depression
Paroxetine was effective in the treatment of late-life depression in non-nursing home residents with major depressive disorder

c) Adult:

1) COMBINATION THERAPY

a) The addition of PINDOLOL enhanced the antidepressant efficacy of PAROXETINE in patients with recurrent major depression, and longer-duration combination therapy appeared to be more beneficial compared with shorter-duration therapy (Zanardi et al, 1997). In a double-blind study, 63 patients who had not received psychotropic drugs in the previous two weeks were randomized to one of three groups: paroxetine plus placebo for 4 weeks (N=21), paroxetine plus pindolol for 1 week, followed by paroxetine plus placebo for 3 weeks (N=21), or paroxetine plus pindolol for 4 weeks (N=21). Paroxetine was given as 20 milligrams (mg) once daily; pindolol (2.5 mg) or placebo was given three times daily. An additional 10 patients were treated in an open-label manner with paroxetine 20 mg once daily plus metoprolol 25 mg twice daily for 4 weeks. After 1 and 2 weeks, the presence of pindolol significantly increased the effectiveness of paroxetine, based on the lower depression ratio of Hamilton Rating Scale for Depression scores obtained in the two groups receiving pindolol compared to the paroxetine plus placebo group. The response to 4 weeks of combined therapy was greater than that of paroxetine plus 1 week of pindolol, indicating the value of longer combination therapy. The response to metoprolol was similar to the paroxetine plus placebo group, which indicates that the mechanism of this additive effect is not beta blockade, but probably the ability of pindolol to block 5-HT1A.

2) COMPARATIVE DATA

a) Paroxetine has not been convincingly superior to any other antidepressant in available clinical studies. Several controlled trials lasting 6 to 7 weeks reported similar efficacy for paroxetine and amitriptyline (Byrne, 1989a; Kuhs & Rudolf, 1989b; Laursen et al, 1985c; Battegay et al, 1985b), although in some studies amitriptyline has been either superior to paroxetine, or exhibited a definite trend toward superiority, after 3 weeks of treatment (Laursen et al, 1985c; Kuhs & Rudolf, 1989b). Paroxetine has also been comparable to clomipramine (Guillibert et al, 1989a) and mianserin (Mertens & Pintens, 1988c) and at least as effective as imipramine in depression (Feighner & Boyer, 1989a). A safety advantage in favor of paroxetine, particularly with regard to anticholinergic effects, was reported in some, but not all, of these comparative studies.

3) SINGLE-AGENT THERAPY

a) Both paroxetine immediate-release (IR) and paroxetine controlled release (CR) were more effective than placebo in the treatment of late- life depression in elderly patients. In a flexible-dose, multi-center, randomized, double-blind, placebo-controlled trial (n=319), elderly patients (mean age, 70 years) with major depressive disorder and a score of at least 18 on the Hamilton Rating Scale for Depression (HAM- D) received paroxetine CR (12.5 to 50 milligrams (mg)/day; mean dose, 30.4 mg/day), paroxetine IR (10 to 40 milligrams (mg)/day; mean dose, 25.7 mg/day), or placebo for 12 weeks. From baseline to endpoint, there was a significantly greater reduction in the HAM-D total score for both paroxetine CR and paroxetine IR as compared with placebo (p=0.007 and p=0.003, respectively). Response was defined as a score of 1 ("much improved") or 2 ("very much improved") on the Clinical Global Impression-Improvement (CGI-I) scale. Seventy-two percent of paroxetine CR-treated patients (p less than 0.002) and 65% of paroxetine IR-treated patients were

rated as responders as compared with 52% of patients in the placebo group. Remission (defined as an endpoint HAM-D total score of 7 or less) was also significantly higher in the paroxetine CR (43%) and paroxetine IR (44%) groups as compared with placebo (26%) (p=0.009 and p=0.01, respectively). Paroxetine CR and paroxetine IR were well tolerated with somnolence, dry mouth, diarrhea, headache, abnormal ejaculation, nausea, dyspepsia, constipation, asthenia, and decreased appetite reported most commonly as adverse events (Rapaport et al, 2003).

b) An 8-week course of PAROXETINE did not show superiority over placebo for improvement of depression (non-major) in very old nursing home residents, according to a randomized, double-blind trial (n=24, mean age 87.9 years). Excluded from the trial were residents with major depression or psychosis, those who were suicidal, and those with scores less than 10 on the Mini Mental State Exam (MMSE). Subjects were chosen based on interviews with residents (videotaped), interviews with their primary nurses, and review of the videotapes by 2 investigators; interview questions were derived from the Hamilton Depression Rating Scale (HDRS) and the Cornell Scale for Depression (CS). Starting doses of PAROXETINE were 10 milligrams (mg) daily, with weekly titration in 10-mg increments (maximum 30 mg). Mean final dose of paroxetine was 23.3 mg. After 8 weeks of study medication, there were no significant differences between the paroxetine- and placebo- treated subjects using an intent-to-treat analysis (n=24). Comparing subjects who completed at least 6 weeks of treatment (n=20), 5 of 9 paroxetine subjects (56%) were rated by their nurses as 'much improved' or 'very much improved' (Clinical Global Impression of Change 1 or 2 points) compared with 4 of 11 (36%) of the control group (p=0.39). HDRS and CS scores from nurse and subject interviews both improved over time, with no significant differences between the paroxetine group and the placebo group. Overall placebo response rate was 45%. Two members of the paroxetine group had to be withdrawn due to development of delirium (which resolved after paroxetine was stopped). Cognitive ratings (MMSE scores) dropped significantly more often in the paroxetine group (7 of 8) compared with controls (4 of 11; p=0.03). No differences were seen in serum anticholinergic levels across the 2 groups. A sub-group analysis of the more symptomatic subjects at baseline (n=15) found that greater improvement occurred among the paroxetine-treated subjects in this sub-group (p=0.06). The investigators noted that there was not good correlation between subject-derived and nurse-derived measures of change (Burrows et al, 2002).

c) Pharmacotherapy with paroxetine decreased scores on the Hopkins Symptom Checklist Depression Scale (HSCL-D-20) an average of 0.61 points compared to a decrease of 0.40 points with placebo (p=0.004) in older primary care patients with minor depression or dysthymia (n=415). Inclusion criteria included: diagnosis of dysthymia or minor depression, 60 years of age or older, 3 or 4 symptoms for at least 4 weeks, and a score of at least 10 on the Hamilton Depression Rating Scale (HDRS). Patients were randomized to receive paroxetine at a target dose of 20 mg/day (n=137), placebo (n=140), or problem-solving treatment-primary care (PST-PC; n=138) for 11 weeks. HSCL-D-20 scores in patients receiving PST-PC decreased 0.52 points, not significantly different from either placebo (p=0.13) or paroxetine (p=0.17). Effects of paroxetine were similar in patients with dysthymia and minor depression (Williams et al, 2000).

d) Paroxetine 40 milligrams (mg) was more effective than paroxetine 20 mg daily for preventing recurrence of depression (Franchini et al, 1998). For all patients, the current depressive episode abated during treatment with paroxetine 40 mg daily which was continued for 4 months. During the maintenance phase, patients (n=68) were randomly assigned to blinded treatment with paroxetine 20 or 40 mg daily for 28 months. After 28 months, 51.5% and 23.5% of patients treated with paroxetine 20 and 40 mg, respectively, had 1 recurrence; 1 patient in paroxetine 20 mg group was excluded due to noncompliance with therapy. The Mantel-Cox survival analysis showed a significant survival advantage for paroxetine 40 mg versus 20 mg (p=0.018). Treatment was tolerated well with no new adverse effects reported during the maintenance phase. Based on this study, the maintenance dose should be individualized since lower doses than the one used in treatment may not be effective in all patients.

e) Increasing paroxetine from 20 milligrams (mg) to 40 mg did NOT result in a statistically significant improvement in depressive symptoms; however, there was a trend toward greater improvement in patients with major depression treated with paroxetine 40 mg (Benkert et al, 1997). In this randomized, double-blind, parallel-group study, patients (n=544) were assigned to receive paroxetine 20 mg or maprotiline 100 mg for 3 weeks. If, after 3 weeks, the Hamilton Depression Rating Scale (HAMD) failed to decrease by at least 50% or more, then the dosage of paroxetine was increased to 40 mg (n=50) or was continued at 20 mg (n=36) for an additional 3 weeks. When patients with major depression were analyzed separately, the response (reduction in HAMD greater than 50%) was 75% for paroxetine 40 mg versus 61% for paroxetine 20 mg; however, results were similar with both doses for patients with minor depression. New adverse effects occurred in 18% of patients when the dose of paroxetine was increased to 40 mg. Patients receiving maprotiline 100 mg initially were treated similarly if they had an inadequate response after 3 weeks. Results of this study are limited by the relatively small number of patients who were treated with higher doses, the inclusion of patients with major and minor depression, and lack of a placebo control. Larger studies which include patients with major depression are needed to better evaluate the efficacy of higher doses of paroxetine.

f) Significantly greater reductions in symptoms of depression were achieved with paroxetine

compared to placebo after 2 weeks of treatment, with improvements being even greater after 6 weeks of therapy. Paroxetine was evaluated for treating major depression (DSM-III) in a 6-week, placebo-controlled, double-blind study involving 111 outpatients (Rickels et al, 1989a). Patients were randomized to receive either placebo or paroxetine 20 milligrams once daily initially, followed by dosing adjustments over the subsequent 2 weeks based upon efficacy and adverse effects (range, 10 to 50 milligrams/day). All doses were given in the morning. Paroxetine was superior to placebo in reducing total scores on the Hamilton Depression Rating Scale (HAMD), the Montgomery-Asberg Depression Rating Scale (MADRS), the Raskin depression scale, and the Clinical Global Impression (CGI) scale of depression. Patients improving during this first 6-week period were allowed to enter a second 6-week treatment period; the clinical status of all patients treated during this second phase (18 paroxetine, 9 placebo) remained unchanged, with paroxetine remaining superior to placebo. Diaphoresis, diarrhea, somnolence, and nausea occurred to a significantly greater degree with paroxetine compared to placebo; laboratory parameters were not significantly affected during therapy.

g) Paroxetine was more effective than placebo in reducing psychic anxiety. The efficacy of paroxetine in treating symptoms of anxiety and/or agitation associated with depression were examined in 2963 patients (Sheehan et al, 1993).

4.5.A.13 Myocardial infarction; Prophylaxis

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class III
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

May confer a protective effect against first MI

c) Adult:

1) In a case-control study comprised of 653 cases of first myocardial infarction (MI) and 2990 control subjects, results indicated that selective serotonin reuptake inhibitors (SSRIs) may confer a protective effect against first MI. The subjects in this study were smokers, between the ages of 30 to 65 years, with a first MI hospitalized between September 1995 and December 1997. The four SSRIs investigated in this study were fluoxetine, fluvoxamine, paroxetine, and sertraline; doses taken by participants were not stated. The odds ratio of patients who were taking SSRIs having a first MI compared to controls (after adjustment for potential confounders) was 0.35 (95% CI 0.18, 0.68; p less than 0.01). The authors suggested that this effect was possibly attributable to an inhibitory effect on serotonin-medicated platelet activation or amelioration of other factors associated with increased risk for MI in depression (Sauer et al, 2001).

4.5.A.14 Nocturnal sleep-related eating disorder

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Resolved symptoms of nocturnal eating/drinking syndrome in three patients

c) Adult:

1) Paroxetine therapy resolved symptoms of nocturnal eating/drinking syndrome (NEDS) in three female patients. A 40-year-old, 28-year-old, and 38-year-old suffering from NEDS were treated with paroxetine 20 or 30 milligrams (mg) daily. All patients were conscious during uncontrollable nocturnal eating which sometimes occurred multiple times throughout the night. Following paroxetine administration, the number of awakenings due to NEDS was reduced within a few days and approximately 2 weeks after initiation of therapy, symptoms had completely resolved. Treatment was continued at 20 mg/day (Miyaoka et al, 2003).

4.5.A.15 Obsessive-compulsive disorder

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes ((regular-release formulation)); Pediatric, no
Efficacy: Adult, Effective
Recommendation: Adult, Class I
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Considered a first-line agent for treating obsessive-compulsive disorder (OCD)
Effective as a crossover therapy in patients with obsessive compulsive disorder non-responsive to

initial SSRI treatment
Venlafaxine extended-release (XR) and paroxetine were equally effective in the treatment of patients with OCD

c) Adult:

1) GENERAL INFORMATION

a) Venlafaxine extended-release (XR) was as effective as paroxetine in the treatment of patients with obsessive compulsive disorder (OCD). In a randomized, double-blind, comparative study, patients (n=150) with OCD and a score of at least 18 (or at least 12, if only obsessions or only compulsions were present) on the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) received either venlafaxine XR (initial, 75 milligrams (mg)/day, titrated to 300 mg/day by week 7) or paroxetine (initial, 15 milligrams (mg)/day, titrated to 60 mg/day by week 7) for 12 weeks. Both paroxetine and venlafaxine XR treatments were effective, producing mean reductions of 7.8 and 7.2 points, respectively, in the Y-BOCS score from baseline to endpoint. A significant decrease in the total Y-BOCS score from baseline was seen at week 3 for venlafaxine XR- treated patients (p=0.008) and at week 5 for patients in the paroxetine group (p=0.018). There were no significant differences in responder rates between treatment groups. In the venlafaxine XR group, 37% and 25% of patients were partial responders and full responders, respectively. Similarly, in the paroxetine group, 44% and 22% of patients were partial responders and full responders, respectively. Additionally, no significant differences were observed between the two treatments with regard to reduction of anxious or depressive symptoms (as measured by the Hamilton Anxiety Scale and the Hamilton Rating Scale for Depression, respectively). For both treatments, most adverse effects were of mild or moderate severity and included somnolence, sweating, insomnia, and nausea (Denys et al, 2003a).

2) PRIMARY THERAPY

a) Of the selective serotonin reuptake inhibitors (SSRIs) (ie, fluoxetine, sertraline, paroxetine, fluvoxamine) with U.S. Food and Drug Administration approval for treating OCD, all are effective. Limited clinical studies also suggest that the SSRIs are comparable to clomipramine; however, results of a meta-analysis found that clomipramine may be more effective than the SSRIs (Flament & Bisserbe; Leonard). Selection of initial treatment is often based on the side effect profile of the individual drug; in general, the SSRIs are tolerated better than clomipramine (Leonard). Early studies used near maximal doses of an SSRI which resulted in a high incidence of adverse effects; however, initial low doses with gradual dose adjustment result in a good response in some patients and better tolerance in most (Leonard). While the optimal duration of treatment has NOT been defined, most patients require long-term treatment. A few small studies have shown relapse rates between 65% and 90% when pharmacologic treatment was stopped (Rasmussen & Eisen). Patients who do NOT respond to 10 to 12 weeks of maximum doses of an SSRI and/or behavioral therapy are considered refractory to treatment. In about 20% of this group, a trial of a second SSRI will be effective. In the remaining patients, augmentation therapy with haloperidol or clonazepam may be beneficial (Rasmussen & Eisen).

b) In a 12-week, comparative study, paroxetine was as effective as clomipramine for treating obsessive compulsive disorder. Patients were randomly assigned to receive placebo (n=99), paroxetine 10 milligrams (mg) (n=201), or clomipramine 25 mg daily (n=99); the dose of active treatments was titrated to a maximum of 60 mg and 250 mg for paroxetine and clomipramine, respectively. No statistically significant differences were found in the primary efficacy measures, the Yale-Brown Obsessive-Compulsive Scale or the National Institute of Mental Health Obsessive-Compulsive Scale, between paroxetine or clomipramine; however, both drugs were significantly better than placebo. Adverse effects requiring treatment withdrawal occurred in fewer patients treated with paroxetine (9%; p=0.033) than clomipramine (17%). Limitations of the study are the relatively short duration, and the potential loss of blinding due to differences in adverse effects (Zohar et al, 1996).

c) Paroxetine was effective in at least two 12-week trials in patients suffering from obsessive compulsive disorder (OCD) (Anon, 1996). Patients studied had moderate to severe OCD (mean baseline scores on the Yale Brown Obsessive Compulsive Scale of between 23 and 26). Patients treated with paroxetine 40 mg or 60 mg daily significantly improved (mean reduction of 6 and 7 points, respectively) compared to those patients treated with either paroxetine 20 mg daily or placebo.

3) CROSSOVER THERAPY

a) Patients with obsessive-compulsive disorder (OCD) refractory to initial treatment with a selective serotonin reuptake inhibitor (SSRI) responded to crossover therapy with another SSRI. In a double-blind switch study, patients (n=150) with primary OCD received venlafaxine (titrated to 300 milligrams (mg)/day) or paroxetine (titrated to 60 mg/day) for 12 weeks and then non-responders (n=43) were switched to the opposite therapy (venlafaxine, n=16; paroxetine, n=27) for an additional 12 weeks following a 4-week washout period between phases. Non-response was defined as a reduction in the Yale-Brown Obsessive- Compulsive Scale (Y-BOCS) below 25%. Following crossover, the Y-BOCS total score decreased in both groups from baseline (week 16) to endpoint, however the score was significantly reduced in paroxetine- treated patients (p less than 0.000), but not in venlafaxine-treated patients (p=ns). Paroxetine was statistically superior as compared with venlafaxine (p=0.017). The response rate during phase II of the study was 42%

(18/43) overall, with a 16% (3/16) response rate in the venlafaxine group and a 56% (15/27) response rate in the paroxetine group (p=0.01). At the end of both phases 73% (109/150) of patients had responded to treatment. Adverse effects were similar between treatment groups including somnolence, sweating, headache, constipation, insomnia, nausea, change in mood, loss of libido, and dry mouth (Denys et al, 2004).

4.5.A.16 Panic disorder

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes ((regular and controlled-release formulations)); Pediatric, no
Efficacy: Adult, Effective; Pediatric, Evidence is inconclusive
Recommendation: Adult, Class IIa; Pediatric, Class IIb
Strength of Evidence: Adult, Category B; Pediatric, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

In short-term and long-term studies, effective for treating panic disorder in adults
Effective in children in one open study

c) Adult:

1) In a 12-week randomized, double-blind, placebo-controlled study of patients (n=367) with panic disorder (with or without agoraphobia), paroxetine was as effective as clomipramine in reducing the number of panic attacks; both agents were significantly more effective than placebo. The dose of each agent was titrated upwards from an initial dose of 10 milligrams (mg) daily to a maximum of 60 mg for paroxetine and 150 mg for clomipramine based on tolerance and clinical response. Paroxetine appeared to have a more rapid onset of action with a greater number of patients reporting no full attacks at weeks 6 and 9 compared to clomipramine or placebo. At the endpoint, 76.1% of paroxetine-treated patients showed a greater than 50% reduction in the total number of full panic attacks compared to 64.5% and 60% in the clomipramine- and placebo-treated groups, respectively. Significantly more patients in the clomipramine group compared to the paroxetine group experienced adverse effects; twice as many patients in the clomipramine group (18) withdrew from the study due to adverse effects (Lecrubier et al, 1997).

2) Although there was no significant difference in efficacy between paroxetine and clomipramine in the 36-week continuation study, the number of full panic attacks continued to decrease in the active treatment groups. One hundred and seventy-six patients continued long-term treatment at the same dose received in the initial 12-week study. Clinic visits and evaluations of patients' panic diaries occurred every 6 weeks. One hundred and sixteen patients completed the study with 42% of the placebo group withdrawing for lack of efficacy and 19% of the clomipramine group withdrawing due to adverse effects. A higher percentage of patients in the clomipramine group (76.2%) experienced at least 1 adverse effect during the continuation phase compared to 61.8% in the paroxetine- and 51.1% in the placebo-treated groups, respectively; these differences did not reach statistical significance. Efficacy in maintaining reduction in panic attacks and continued reduction of attacks throughout the study period suggests that treatment of panic disorder may be beneficial on a long-term basis (Lecrubier et al, 1997a).

3) In a 10-week, randomized, placebo-controlled trial, paroxetine 40 milligrams (mg) daily was significantly more effective than placebo for treating panic attacks; however, differences between paroxetine 10 and 20 mg were NOT significantly different from placebo. At 10 weeks, 86%, 65.2%, 67.4%, and 50%, respectively, of patients taking paroxetine 40 mg, 20 mg, 10 mg, or placebo had a complete response. Patients enrolled in the study met DSM-III criteria for panic disorder with or without agoraphobia and had at least 2 full panic attacks during the 2 weeks before study entry. Of the 278 patients entered into the study, 188 (67.6%) completed 10 weeks of treatment. Withdrawal was due primarily to adverse effects and lack of efficacy which decreased with increasing paroxetine dose. Paroxetine 40 mg daily is an effective treatment for panic attacks (Ballenger et al, 1998).

4) Paroxetine 20 to 60 mg/day was significantly more effective than placebo in reducing the number of panic attacks in patients with panic disorders. Patients (n=120) were randomly assigned to placebo or paroxetine after a three-week washout period; therapy was continued for a total of 12 weeks. Paroxetine was given as an initial dose of 20 mg daily and then adjusted at two-week intervals to 40 mg and then 60 mg daily, depending on efficacy and tolerability. The majority of patients (75%) required doses of 40 or 60 mg. After 12 weeks of therapy, 82% of patients treated with paroxetine had at least a 50% reduction in number of panic attacks compared to 50% of patients treated with placebo; 36% of paroxetine-treated patients became almost free of panic attacks. Paroxetine was generally well tolerated at all three dose levels (Oehrberg et al, 1995).

d) Pediatric:

1) A retrospective analysis of the records of 18 children with panic disorder who were treated with paroxetine showed favorable response in 15 children (83%). Children aged 7 to 16 years and unequivocally meeting the DSM-IV criteria for panic disorder were treated with paroxetine, beginning at an average of 8.9 milligrams (mg) per day and progressing to an average of 24 mg/day. Children were treated for 2 to 24 months (mean 12 months). With last- observation-carried-forward analysis, significant improvement was shown on the Clinical Global Impressions (CGI) Severity score: from an average initial score of 5.2 to an average final score of 1.8 (p less than 0.0001). Responders (83% of subjects)

were defined as those who had a CGI-Improvement score of 1 (marked improvement) or 2 (moderate improvement). Side effects were minimal or mild and transient, with no patient requiring a reduction in dosage due to side effects. The most common side effects were nausea (39%), tension-agitation (39%), sedation (33%), insomnia (22%), palpitations (22%), and headache (22%) (Masi et al, 2001).

4.5.A.17 Posttraumatic stress disorder

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes ((regular-release formulation)); Pediatric, no
Efficacy: Adult, Effective
Recommendation: Adult, Class IIa
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Paroxetine (20 to 50 mg/day) effectively treated all three components of posttraumatic stress disorder

c) Adult:

1) Paroxetine in doses of 20 to 50 milligrams (mg) per day effectively treated all three components of posttraumatic stress disorder (PTSD) (reexperiencing, avoidance/numbing and hyperarousal) when compared to a matched patient group receiving placebo. In this 12-week, double-blind, multi-center trial, 323 patients were divided into paroxetine and placebo treatment groups. Assessments using the Clinician- Administered PTSD Scale, part 2 (CAPS-2), at 4, 8, and 12 weeks, showed a statistically significant decrease (p less than 0.001) in PTSD symptoms that began at 4 weeks and showed the maximum fraction of improvement by week 8. Response, defined as very much improved or much improved on the Clinical Global Impressions-Global Improvement Scale (CGI-I), at 12 weeks was 60% in the paroxetine group and 40% in the placebo group. The proportion of patients achieving remission (CAPS-2 total score less than 20) was 29.4 % and 16.5% for paroxetine and placebo respectively (p = 0.008). CAPS-2 results showed, in the sub-group analysis, that both males and females experienced comparable decreases in PTSD symptoms by study endpoint and that patients whose index trauma occurred more than 5 years prior to this study had a greater decrease in symptom score (p=0.037) than other paroxetine-treated patients. There was also a greater proportion of responders in the trauma-type category of seeing someone hurt or die (p=0.019), compared to the other trauma types of physical or sexual attack, serious accident or injury, or exposure to combat. The mean paroxetine dose during the study was 27.6 +/- 6.72 mg/day with 22% taking 20 mg/day, 24% taking 30 mg/day, 28% taking 40 mg/day, and 25% taking 50 mg/day at study end. Patients treated with paroxetine experienced asthenia, abnormal ejaculation, dry mouth, nausea, and somnolence at an incidence of at least 10% (and at least twice the placebo rate) and approximately 60% of patients in both groups completed the 12-week study (Tucker et al, 2001).

2) Paroxetine in doses of 20 or 40 milligrams (mg) per day effectively treated all three components of posttraumatic stress disorder (PTSD) (reexperiencing, avoidance/numbing and hyperarousal) when compared to a matched patient group receiving placebo. In this 12-week, double-blind, multi-center trial, 551 patients were divided into three groups: paroxetine 20 mg/day, paroxetine 40 mg/day or placebo. Assessments using the Clinician-Administered PTSD Scale, part 2, at 1, 2, 4, 6, 8, and 12 weeks, showed a statistically significant decrease in PTSD symptoms that began at 4 weeks and continued through the remaining 12 weeks of the trial. Response at endpoint was 62% in the paroxetine 20 mg group, 54% in the paroxetine 40 mg group and 37% in the placebo group. There was no difference in response due to trauma type, time since trauma, severity of baseline PTSD, depressive symptoms or gender. Asthenia, diarrhea, abnormal ejaculation, impotence, nausea, and somnolence occurred with an incidence of at least 10% (and at least twice the placebo rate) in the paroxetine groups (Marshall et, al, 2001). This study confirms the results of an earlier, small open trial, where 65% of patients had a 48% decrease in PTSD symptoms and were rated as very much improved or much improved on the Clinical Global Impression Scale (Marshall et al, 1998).

4.5.A.18 Premature ejaculation

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Selective serotonin reuptake inhibitors fluoxetine, paroxetine, and sertraline have been effective in the symptomatic treatment of PREMATURE EJACULATION. Objective results are usually seen after 2 weeks treatment, with prolongation to ejaculation time ranging between 6 to 10 minutes compared to less than 1 minute at baseline. Significant subjective changes included increased sexual desire, partner satisfaction, and decreased anxiety. However, over 90% will relapse to baseline functional status within 2 to 3 weeks after discontinuing medication (Ludovico et al, 1996; Kara et al, 1996; Lee et al, 1996; Mendels et al, 1995; Waldinger et al, 1994).

c) Adult:

1) Paroxetine was effective for treatment of PREMATURE EJACULATION (McMahon & Touma, 1999). Paroxetine 20 milligrams 3 to 4 hours before planned intercourse delayed ejaculation from 0.3 minutes at baseline to 3.5 minutes at the end of study; paroxetine was superior to placebo in this single-blind, randomized crossover study of 26 men (p less than 0.001). In the second study, 42 men were randomly assigned to receive paroxetine 10 milligrams daily for 3 weeks followed by paroxetine 20 milligrams as needed 3 to 4 hours before planned intercourse or placebo in a crossover design. Ejaculatory latency increased during daily treatment with paroxetine compared to placebo at 2 weeks (p less than 0.05); however, the greatest benefit was achieved after daily followed by as needed paroxetine (baseline mean 0.5 minutes to week 7 mean 5.8 minutes; p less than 0.05). Based on the second study, daily followed by as needed treatment with paroxetine is likely more effective than as needed treatment only.
2) PAROXETINE is an effective treatment for premature ejaculation. In an open-label trial of 32 men, all of the subjects experienced a delay in ejaculation with paroxetine 20 milligrams daily at bedtime. Generally, benefit occurred after approximately two weeks of therapy. After paroxetine was discontinued, premature ejaculation resumed in 90% of patients. The most common side effects reported were sleepiness and mild sensory confusion which tended to subside after about 15 days of therapy (Ludovico et al, 1996).
3) Paroxetine 40 milligrams daily significantly improved premature ejaculation in a double-blind, placebo-controlled trial (Waldinger et al, 1994). Both patients and partners were questioned before and during the trial regarding time to ejaculation. Prior to treatment the median time to ejaculation was 30 seconds or less for both groups. Following 6 weeks of paroxetine therapy, placebo-treated patients had no change while treated patients had increased time to ejaculation to a median of 10 minutes.

4.5.A.19 Premenstrual dysphoric disorder

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes (controlled-release formulation)); Pediatric, no
Efficacy: Adult, Effective
Recommendation: Adult, Class IIa
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Reduced symptoms related to PDD in an open study and in controlled trials

c) Adult:

1) Treatment with paroxetine controlled-release (CR) tablets effectively reduced symptoms associated with premenstrual dysphoric disorder (PDD). In two placebo- controlled trials, patients (n=672) with PDD and a mean symptom history of 11 years received paroxetine CR 12.5 milligrams (mg)/day, paroxetine CR 25 mg/day, or placebo continuously throughout 3 menstrual cycles. Patients taking systemic hormonal contraceptives were excluded before the trials began. Treatment response was assessed using a patient-rated visual analog scale (VAS)-total score, which measured mood, physical symptoms and other symptoms. Patients in both paroxetine treatment groups showed significantly greater improvements on the luteal phase VAS-total score from baseline to endpoint as compared with placebo (Prod Info Paxil CR (TM), 2003).
2) In an open study (n=14), paroxetine reduced symptoms of premenstrual dysphoric disorder (PDD). Patients with a Clinical Global Impression (CGI) score greater than 3 during 1 cycle using placebo received paroxetine 10 milligrams (mg) daily with adjustment to a maximum dose of 30 mg daily during subsequent cycles; the average dose was 22 mg/day. Daily symptom scores for mood swings, anger/irritability, interpersonal difficulties, and behavioral control showed significant (p less than 0.05) decreases from baseline to the final cycle although luteal phase levels were NOT quite as low as follicular phase levels. Between 8 and 10 women were considered responders to paroxetine based on the following: (1) 50% decrease in luteal phase worsening of 5 symptoms (n=10), (2) absolute Hamilton Rating Scale for Depression (HAM-D) reduction of 50% (n=9), (3) luteal phase HAM-D score less than or equal to 8 (n=9), (4) luteal phase HAM-D less than or equal to follicular phase HAM-D score (n=9), and (5) absolute CGI less than or equal to 2 (n=8). Like other selective serotonin reuptake inhibitors, paroxetine reduces symptoms associated with PDD but additional controlled trials are needed (Yonkers et al, 1996).

4.5.A.20 Pruritus, Non-dermatological

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

In a small study, paroxetine was effective in the treatment of severe, non-dermatological pruritus

c) Adult:

1) Paroxetine therapy was effective in the treatment of severe, non- dermatological pruritus in patients with advanced cancer and other systemic diseases. In a randomized, double-blind, placebo-controlled,

crossover study, patients (n=26) with severe pruritus not associated with primary skin disease received placebo or paroxetine (20 milligrams/day) for 7 days and then switched over to the opposite treatment arm for 7 days. Patients assessed pruritus intensity via a numerical analogue scale. On the 7 days average, paroxetine-treated patients had lower mean pruritus intensity scores as compared with patients in the placebo group (mean difference, 0.78 (95% CI=0.37 to 1.19); p=0.001). This effect was even stronger when measured over the last 3 days average (mean difference, 1.35 (95% CI=0.61 to 2.08); p=0.002). A significantly higher percentage of patients treated with paroxetine exhibited clinical response (defined as a pruritus reduction of at least 50% in the last 3 days of the period as compared to the last 3 days of the run-in period) as compared with placebo (37.5% vs 4.2%, respectively; p=0.027). Paroxetine treatment was associated with a higher incidence of nausea and sleepiness as compared with placebo. Because this study population was composed mostly of patients with pruritus associated with advanced neoplastic disease, these findings cannot be extrapolated to all patients with severe pruritus. Additional studies are needed to explore the efficacy of paroxetine in the treatment of pruritus in more diverse patient populations (Zylicz et al, 2003).

4.5.A.21 Schizophrenia, Negative symptoms

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class III
Strength of Evidence: Adult, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Reduced negative symptoms of schizophrenia when added to antipsychotic therapy in small open study

c) Adult:

1) Paroxetine treatment added to antipsychotic treatment brought sustained improvement in negative symptoms of schizophrenia patients in a small, open study. Six patients with chronic schizophrenia and with a score of at least 20 on the negative subscale of the Positive and Negative Syndrome Scale (PANNS) took paroxetine 30 milligrams per day for 12 weeks and were followed up for 30 months. Patients were not depressed, as shown by a score of 8 or less on the Hamilton-Depression scale. The mean score on the PANNS negative subscale decreased significantly from 29.3 to 20.3 (p=0.043) by week 12. The most notable effects were on blunted affect and stereotyped thinking. One patient improved during the 12 weeks but deteriorated after stopping paroxetine. He improved again after restarting paroxetine and continued taking it thereafter. One patient did not respond within the 12-week study period but responded at 16 weeks and maintained that improvement through the following 30 months. The other 4 did not change medication and maintained their initial improvement throughout the follow-up period (Jockers-Scherubl et al, 2001).

4.5.A.22 Social phobia

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes ((regular and controlled-release formulations)); Pediatric, no
Efficacy: Adult, Effective
Recommendation: Adult, Class I
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Effective for treating SOCIAL PHOBIA

c) Adult:

1) Controlled-release (CR) paroxetine was more effective than placebo in improving the symptoms of social anxiety disorder. In a randomized, double-blind, placebo-controlled, multicenter study (n=370), patients with social anxiety disorder received paroxetine 12.5 to 37.5 milligrams (mg) (mean dose, 32.3 mg/day) or placebo daily for 12 weeks following a 1 week single-blind placebo run-in period. Changes in Liebowitz Social Anxiety Scale (LSAS) scores from baseline to endpoint significantly favored treatment with paroxetine CR as compared with placebo (adjusted mean difference= -13.33, 95%CI= -18.25 to -8.41; p less than 0.001). From baseline to week 12, mean LSAS scores for paroxetine CR-treated patients decreased from 78.3 to 47.1, while mean scores of patients in the placebo group were reduced from 78.6 to 60.5. A significantly higher percentage of patients treated with paroxetine CR achieved remission (defined as at least a 70% reduction in the LSAS total score) as compared with patients in the placebo group (24.3% vs 8.2%, respectively; 95%CI= 1.92 to 6.85; p less than 0.001). From baseline to endpoint, there were significantly more responders (defined as very much improved or much improved on the Clinical Global Impression-Improvement scale) in the paroxetine CR group as compared with the placebo group (57% vs 30.4%, respectively; p less than 0.001). The most commonly observed adverse events in paroxetine CR-treated patients included nausea, asthenia, abnormal ejaculation, sweating, impotence, somnolence, insomnia, and decreased libido (Lepola et al, 2004).

2) Paroxetine 20 milligrams (mg) per day was more effective than placebo in improving the symptoms of generalized social anxiety disorder; higher doses of paroxetine were not more efficacious. In a double-blind, placebo-controlled trial, 384 patients with a minimum of 4 interactional and performance

phobias were randomly assigned to receive paroxetine 20, 40, or 60 mg/day or placebo for 12 weeks. Using last-observation- carried-forward analysis, scores on the Liebowitz Social Anxiety Scale (LSAS) were reduced significantly more by paroxetine 20 mg than by placebo (p less than 0.001). Mean improvement in the LSAS total score was twice as great with paroxetine 20 mg as with placebo. The significant difference between paroxetine and placebo appeared at the beginning of week 8 and continued to the end of the study. Improvements in LSAS scores with paroxetine 40 mg and 60 mg approached statistical significance when compared to placebo. The percentage of responders (defined as a score of either 1 or 2 on the Clinical Global Impressions-Global Improvement scale) ranged from 43% to 47% in the paroxetine groups, compared to 28% in the placebo group. In comparison to placebo-treated patients, patients treated with paroxetine 20 mg showed greater improvements on the LSAS fear and avoidance subscales at endpoint (p=0.001 and p less than 0.001, respectively), on the Social Avoidance and Distress Scale, and on the Sheehan Disability Scale. Although scores for those taking higher doses of paroxetine were in some cases better than for those taking placebo, they were not generally superior to those with paroxetine 20 mg. Adverse effects were typical of those reported for selective serotonin reuptake inhibitors: insomnia, somnolence, asthenia, nausea, dizziness, decreased libido, dry mouth, nervousness. The only adverse events that showed a linear dose response were delayed ejaculation and constipation. More patients withdrew from paroxetine groups than from the placebo because of adverse events, whereas more withdrew from placebo treatment than from paroxetine treatment because of lack of efficacy. The authors acknowledged that the response rate in this study is lower than in some other studies, perhaps because of the fixed dosage regimens. Although flexible dosing may increase response rate, the authors suggested that the initial target dose of paroxetine should be 20 mg/day (Liebowitz et al, 2002).

3) Paroxetine was effective for treating social anxiety disorder in a 12-week, controlled study. Patients were randomly assigned to receive placebo (n=151) or paroxetine (n=139) 20 milligrams (mg) daily for 2 weeks followed by dosage titration to 50 mg daily, if needed. At 12 weeks, the mean dosage of paroxetine was 34.7 mg/day. Thirty-five (25%) and 42 (28%) patients withdrew from the paroxetine and placebo groups, respectively; no patient withdrew due to a serious drug-related adverse effect. The Liebowitz Social Anxiety Scale score was reduced by 29.4 and 15.6 in the paroxetine and placebo groups, respectively (p less than or equal to 0.001); 26.3% versus 9% of patients were rated as very much improved on the Clinical Global Impression (CGI) scale after receiving paroxetine versus placebo. The percentage of responders on the CGI scale was also higher after paroxetine treatment (p less than 0.001). This study confirms the short-term effectiveness of paroxetine for social phobia, and studies are underway that will assess long-term effectiveness (Baldwin et al, 1999).

4) In a smaller study with a similar design, paroxetine was effective and tolerated well during treatment of social anxiety disorder (Allgulander, 1999). After diagnosing social phobia by DSM-IV criteria, patients (n=96) were randomly assigned to receive paroxetine 20 to 50 milligrams daily or placebo for 3 months. Beginning after 4 weeks, the Clinical Global Impression (CGI) scale showed a significantly higher proportion of responders with paroxetine (70.5%) than placebo (8.3%; p less than 0.0001). The difference in total Liebowitz Social Anxiety Scale score was also significantly different between treatments beginning at 4 weeks (mean decrease 33.4 versus 8.6; p=0.0001). Eight patients treated with paroxetine withdrew from treatment due to adverse effects compared to 3 patients treated with placebo.

5) Paroxetine was effective for treating generalized social phobia in a 12-week, double-blind trial. Patients were randomly assigned to receive paroxetine 20 milligrams (mg) daily (n=91) or placebo (n=92). After 2 weeks of treatment, paroxetine treated patients not achieving a clinical response were increased to paroxetine 30 mg daily. Further dose titration upwards (to a maximum daily dose of 50 mg) and downwards were used to facilitate response and avoid adverse reactions. Fifty (55%) patients treated with paroxetine achieved a clinical response determined by mean changes from baseline in Liebowitz Social Anxiety Scale scores and by Clinical Global Improvement scores of very much improved or much improved. Twenty-two (23.9%) of those treated with placebo demonstrated a clinical response, a statistically significant difference from the paroxetine treated group. Paroxetine was tolerated well with 14 discontinuations due to adverse effects. Only 3 of the patients treated with placebo discontinued the study due to adverse effects. Although this study demonstrated the efficacy of paroxetine in the treatment of generalized social phobia, further studies addressing dose and duration of therapy are needed (Stein et al, 1998).

6) Of 30 patients with the generalized subtype of social phobia, 23 (76.7%) were rated as responders to paroxetine. During the double-blind, randomized discontinuation phase, 1 (13%) and 5 (63%) patients treated with paroxetine and placebo, respectively, relapsed; the difference was not significant. All patients (n=36) were initially treated with paroxetine 10 milligrams (mg) daily with titration to 50 mg daily during the open phase. Responding patients as determined by a Clinical Global Impressions scale score of much or very much improved were asked to participate in the discontinuation study where paroxetine was stopped over 1 week. Side effects were mild and tolerable. This study suggests that paroxetine is effective for treating generalized social phobia; however, long-term, placebo-controlled trials are needed (Stein et al, 1996).

4.5.A.23 Somatization disorder

a) Overview

FDA Approval: Adult, no; Pediatric, no

Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category C
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:
Paroxetine was an effective treatment for somatization disorder in one patient

c) Adult:
1) Somatization disorder was successfully treated with paroxetine in one female patient. A 38-year-old woman with a 16-year history of joint pain was given paroxetine (initial, 10 milligrams (mg)/day titrated to 40 mg/day over 6 weeks) after being diagnosed with somatization disorder. Her joint pain improved within 3 weeks of treatment and following 8 weeks, she was able to climb and descend stairs. She was maintained on paroxetine 30 mg/day and diazepam 4 mg/day during outpatient therapy (Okugawa et al, 2002).

4.5.A.24 Trichotillomania

a) Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Pediatric, Evidence is inconclusive
Recommendation: Pediatric, Class IIb
Strength of Evidence: Pediatric, Category C
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:
Produced major improvement in trichotillomania in adolescent

c) Pediatric:
1) A 16-year-old woman had clinically significant improvement in HAIR PULLING but not depression after treatment with paroxetine 10 milligrams (mg) daily for 2 weeks. She had a history of trichotillomania since 2 years of age. Depressive symptoms finally improved after several weeks of therapy with paroxetine 20 mg alternating with paroxetine 30 mg daily. This case is interesting due to the rapid, clinically significant decrease in trichotillomania with paroxetine 10 mg compared to the higher dose and longer duration of treatment required before depression responded. Additional study of paroxetine is needed for this use (Block et al, 1998).

4.5.A.25 Vasovagal syncope

a) Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class III
Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:
In a small study, paroxetine reduced the number of syncopal episodes

c) Adult:
1) Significantly fewer episodes of vasovagal syncope occurred in patients treated with paroxetine than placebo. Sixty-eight consecutive patients with a positive head-up tilt test and lack of response to other therapies were randomly assigned to blinded treatment with paroxetine 20 milligrams/day or placebo. One month after initiating paroxetine, a repeat tilt test revealed syncope in 38.2% and 61.8% of patients treated with paroxetine and placebo, respectively (p=0.001). During at least 24 months of follow-up, spontaneous syncope was reported by 52.9% and 17.6% of patients in the placebo and paroxetine groups, respectively (p less than 0.0001). Patients treated with paroxetine also reported a decrease in syncopal episodes from 8.1 to 5.9/year during treatment. Treatment was discontinued in 1 patient receiving paroxetine due to severe recurrent headaches. While paroxetine appears effective, larger and longer study is needed (Di Girolamo et al, 1999).

4.6 Comparative Efficacy / Evaluation With Other Therapies

Amisulpride

Amitriptyline

Aprepitant

Bupropion

Citalopram

Clomipramine

Delorazepam

Doxepin

Duloxetine

Escitalopram

Fluoxetine

Fluvoxamine

Imipramine

Maprotiline

Mianserin

Mirtazapine

Nortriptyline

Risperidone

Sertraline

Sildenafil

Sulpiride

Venlafaxine

4.6.A Amisulpride

4.6.A.1 Burning mouth syndrome

a) Amisulpride, sertraline, and paroxetine were all effective in reducing the symptoms of burning mouth syndrome (BMS), but response was achieved earlier with amisulpride than with the selective serotonin reuptake inhibitors (SSRIs). In a randomized, single-blind study, 76 patients with BMS and without major depression were given amisulpride 50 milligrams (mg) per day, paroxetine 20 mg/day, or sertraline 50 mg/day for 8 weeks. Pain scores decreased significantly in all groups, as did depression (Hamilton Rating Scale for Depression) and anxiety (Hamilton Rating Scale for Anxiety), by week 8. The only difference among treatments was the shorter latency to response in the amisulpride group (22% of patients responding at 2 weeks with amisulpride vs 0% with paroxetine and 6% with sertraline) (Maina et al, 2002a).

4.6.B Amitriptyline

4.6.B.1 Depression

a) SUMMARY: Paroxetine and amitriptyline have been comparable in the treatment of depression; adverse effects have occurred to a lesser degree with paroxetine.

b) Paroxetine and amitriptyline were equally efficacious for the treatment of depression in women with BREAST CANCER in an 8- week, double-blind, parallel-group, randomized study. After a 3 to 7 day washout period, breast cancer patients diagnosed with mild to severe depression were randomized to receive either paroxetine (n=88) 20 to 40 milligrams (mg) per day, or amitriptyline (n=87) 75 to 150 mg per day. There was no statistically significant difference in depressive symptomatology between the treatment groups, but both groups improved significantly compared to baseline by the end of the 8-week trial. At endpoint, both groups had about a 10 point reduction (paroxetine 10.5, amitriptyline 9.4) on the Montgomery Asberg Depression Rating Scale (MADRS) and this corresponded to an overall response rate (50% or

greater reduction in MADRS) of 43.7% and 37.9%, respectively Both groups showed improvement on the Clinical Global Impression (CGI) severity of illness scale (from moderately/mildly ill to borderline ill) and on the CGI improvement and Patient's Global Evaluation (PGE) rating scales (minimally to much improved). Each group also demonstrated a steady improvement in quality of life as measured by the Functional Living Index: Cancer (FLIC) scale. There was no statistically significant difference between the paroxetine- and amitriptyline-treated groups in regards to adverse drug reactions with somnolence most frequently reported in both groups and dry mouth most frequently reported in the amitriptyline group. Six patients in the amitripyline group and 6 in the paroxetine group withdrew from the study due to adverse experiences considered by the investigators to be possibly related or related to the study medications (Pezzella et al, 2001).

c) Paroxetine and amitriptyline were equally efficacious for the treatment of depression in patients with RHEUMATOID ARTHRITIS (RA); paroxetine was associated with fewer adverse effects. After a 2-week washout period, RA patients with mild to severe depression were randomized to receive either paroxetine 20 milligrams (n=94) and an amitriptyline-matched placebo or amitriptyline 75 mg (n=97) and a paroxetine-matched placebo for the first 2 weeks. At week 2 or week 4, doses could be increased to paroxetine 40 mg or amitriptyline 150 mg, depending on the patients' response. Improvements, according to a depression rating scale, were similar for the 2 groups at 4, 8 and 12 weeks (endpoint). At week 8, 65% of the paroxetine group and 56% of the amitriptyline group considered themselves "much improved" or "very much improved" (p=0.4). Improvements in RA symptom severity were similar for the 2 groups (Bird & Broggini, 2000).

d) Paroxetine and amitriptyline provided comparable benefit when added to maintenance lithium therapy for treating a major depressive episode; however, improvement was more rapid in the paroxetine-lithium than the amitriptyline-lithium group (Bauer et al, 1999). In this double-blind, parallel-group study, patients (n=42) were randomly assigned to receive paroxetine 20 milligrams (mg) daily or amitriptyline 50 mg daily increased to 75 mg on the fourth day. The study protocol permitted dose titration to paroxetine 40 mg daily and amitriptyline 150 mg daily. All patients were on a stable lithium regimen with documented serum lithium levels between 0.5 and 0.8 millimoles/liter. At 6 weeks, a statistically significant difference was NOT noted between treatments on the Hamilton Rating Scale for Depression (HAM-D) or the Clinical Global Impression Scale (CGI). As expected, adverse effects differed between paroxetine (ie, nausea, headache, increased motor activity) and amitriptyline (ie, dry mouth, blurred vision, tremor, hypotension, constipation). Serum lithium levels did NOT change significantly after addition of paroxetine or amitriptyline.

e) Several controlled trials of 6 to 7 weeks duration have reported the similar efficacy of paroxetine and amitriptyline in the treatment of major depression (Bascara, 1989; Byrne, 1989; Kuhs & Rudolf, 1989; Laursen et al, 1985a; Battegay et al, 1985; Gagiano et al, 1989). Based upon these data, paroxetine 30 mg once daily appears to be as effective as amitriptyline 150 mg once daily. However, in some of these studies, amitriptyline has been either superior to paroxetine, or exhibited a definite trend toward superiority, after 3 weeks of treatment (Laursen et al, 1985a; Kuhs & Rudolf, 1989). Due to these findings, some investigators recommend higher doses of paroxetine (30 to 50 mg daily) in future clinical comparisons with antidepressants. Anticholinergic effects, such as dry mouth and constipation, have been less with paroxetine compared to amitriptyline in some studies (Hassan et al, 1985a; Kuhs & Rudolf, 1989; Laursen et al, 1985a) but no significant difference was observed in others (Bascara, 1989; Battegay et al, 1985). Cardiovascular effects (increase in heart rate, decrease in left ventricular ejection time index) have also been less with paroxetine as compared to amitriptyline (Kuhs & Rudolf, 1989; Warrington et al, 1989a). However, in some studies, the cardiovascular adverse effects have occurred to a similar degree (Byrne, 1989).

f) The comparable efficacy of paroxetine and amitriptyline were reported in the treatment of DSM-III major depression in a randomized, double-blind study involving 53 patients (Bascara, 1989). Mean ages were 37 years in the paroxetine group and 31 years in the amitriptyline group. Paroxetine was administered in doses of 20 mg once daily for 3 days, then 30 mg once daily for the remainder of the 6-week study; amitriptyline was given in an initial dose of 50 mg once daily, with the dose being increased to 75 mg once daily after 3 days. All doses were administered in the morning. Both drugs produced similar reductions in the 21-item Hamilton Depression Rating Scale (HAMD) and physician's global assessment ratings. The incidence of adverse effects was similar with both agents, with the exception of sweating, which occurred to a greater degree with paroxetine. Among 50 evaluable patients, adverse effects accounted for 2 withdrawals in the paroxetine group (nausea, vomiting) and 3 in the amitriptyline group (sweating, chest pain, drowsiness in 2; daytime drowsiness in 1).

4.6.C Aprepitant

4.6.C.1 Depression

a) In a 6-week, placebo-controlled comparison, paroxetine 20 mg and aprepitant 300 mg, each given once daily, were similarly effective in patients with major depression (score of 22 of higher on the 17-item Hamilton Rating Scale for Depression (HAM-D17)) and moderately-high anxiety (at least 15 on the Hamilton Rating Scale for Anxiety (HAM-A)). Improvement in the 21-item HAM-D scale (primary endpoint) after 6 weeks was similar in the paroxetine and aprepitant groups; each agent was significantly superior to placebo. Complete response, defined as an HAM-D17 score of less than 10, was achieved in 33%, 43%, and 17% of patients treated with paroxetine, aprepitant, and placebo, respectively. Improvement in the HAM-A score was significantly greater with aprepitant (but not paroxetine) versus placebo. No adverse effect occurred more commonly with aprepitant compared to paroxetine (Krishnan, 2002; De Vane, 2001).

4.6.C.2 Adverse Effects

a) In one relatively large study (n=213), paroxetine 20 mg daily tended to produce a higher incidence of adverse effects than aprepitant 300 mg daily in depressed patients, including nausea, fatigue, anorexia, sweating, and sexual dysfunction; however, the only one of these effects which was statistically significantly higher in the paroxetine group was sexual dysfunction (26 versus 3%) (Krishnan, 2002).

4.6.D Bupropion

4.6.D.1 Depression, Elderly

a) Both bupropion sustained release (SR) and paroxetine were found to be safe and effective for the treatment of depression in the elderly (greater than or equal to 60 years of age). In a 6-week, multicenter, double-blind study, 100 patients were randomized to receive bupropion SR (100 to 300 milligrams/day) or paroxetine (10 to 40 milligrams/day). After 6 weeks, the patients had improved scores on all depression rating scales and both treatments were similarly effective, with no statistically significant differences between the 2 treatment groups. With the exception of headache (occurring in 25% of bupropion SR- treated patients versus 19% of paroxetine-treated patients), the occurrence of other side effects was generally higher with paroxetine compared with bupropion SR. The data suggests that bupropion SR may provide a safe and effective alternative to serotonergic agents in the treatment of depression in the elderly (Weihs et al, 2000).

4.6.E Citalopram

4.6.E.1 Late ejaculation

a) Paroxetine significantly increased the latency time of ejaculation in men with life-long premature ejaculation, whereas citalopram had very little effect. Thirty men with intravaginal ejaculation times (IELT) of less than 1 minute were given either paroxetine 20 milligrams (mg) per day or citalopram 20 mg/day for 5 weeks after receiving half-doses for a week. The geometric mean of IELT increased from 20 to 170 seconds in the paroxetine group and from 20 to 44 seconds in the citalopram group (p less than 0.001 for group differences; p less than 0.001 for change from baseline for paroxetine; and p=0.07 for change from baseline for citalopram). Neither drug had clinically relevant effects on sexual desire, arousal, erectile dysfunction, or penile rigidity, although 3 patients in the paroxetine group reported a slight decrease in sexual desire and penile rigidity. The authors suggested that paroxetine may be useful for treating premature ejaculation and that citalopram may be useful for treating patients in need of a selective serotonin reuptake inhibitor who do not want ejaculation delay (Waldinger et al, 2001).

4.6.F Clomipramine

Depression

Obsessive-compulsive disorder

4.6.F.1 Depression

a) In a large (n=1002) clinical trial, treatment with paroxetine or clomipramine produced similar decreases in anxiety and depression scores; however, adverse effects occurred in significantly (p=0.025) more patients treated with clomipramine than paroxetine (Ravindran et al, 1997). Statistically significant differences between treatments were NOT found on the Montgomery-Asberg Depresssion Rating Scale (MADRS) or Clinical Anxiety Scale (CAS), but a trend in favor of paroxetine was observed for the Clinical Global Impressions (CGI) score at 6 and 12 weeks (p=0.015). Patients entered into this trial had depression with anxiety which was treated in a primary care setting. Paroxetine 20 milligrams (mg) daily was used initially but the protocol permitted an increase to 40 mg daily, if needed, after 4 weeks. Clomipramine titration proceeded as follows: (1) 25 mg in the evening for 3 days; (2) 50 mg in the evening for 4 days; (3) 75 mg daily (25 mg in the morning and 50 mg in the evening); and (4) after 4 weeks, the dose could be increased to 150 mg/day. Based on this study, paroxetine and clomipramine have comparable efficacy but the incidence of adverse effects (AE) including serious AE is lower in patients treated with paroxetine.

b) Paroxetine 30 milligrams once daily was as effective as clomipramine 25 milligrams three times daily in the treatment of major depressive disorder in a 6-week, double-blind study involving 79 elderly patients (60 years of age or older) (Guillibert et al, 1989). Anticholinergic effects and somnolence occurred to a greater degree with clomipramine, whereas nausea and vomiting were observed more frequently with paroxetine.

c) Clomipramine demonstrated a significantly better therapeutic effect than paroxetine using categorical response measures and group averages of rating scores during a double-blind, randomized, inpatient study of 120 depressed patients (Anon, 1990). Patients were randomized to receive either paroxetine 30 milligrams/day or clomipramine 150 milligrams/day for this 6-week study. At the end of week 4, 27 patients were rated as nonresponders and were terminated from the study. Of thses 27 patients, 23 were in the paroxetine group.

4.6.F.2 Obsessive-compulsive disorder

a) In a 12-week, comparative study, paroxetine was as effective as clomipramine for treating obsessive compulsive disorder. Patients were randomly assigned to receive placebo (n=99), paroxetine 10 milligrams (mg) (n=201), or clomipramine 25 mg daily (n=99); the dose of active treatments was titrated to a maximum of 60 mg and 250 mg for paroxetine and clomipramine, respectively. No statistically significant differences were found in the primary efficacy measures, the Yale-Brown Obsessive-Compulsive Scale or the National Institute of Mental Health Obsessive-Compulsive Scale, between paroxetine or clomipramine; however, both drugs were significantly better than placebo. Adverse effects requiring treatment withdrawal occurred in fewer patients treated with paroxetine (9%; p=0.033) than clomipramine (17%). Limitations of the study are the relatively short duration, and the potential loss of blinding due to differences in adverse effects (Zohar et al, 1996).

4.6.G Delorazepam

4.6.G.1 Anxiety

a) Delorazepam was compared to imipramine and paroxetine in 81 patients with generalized anxiety disorders according to DSM-IV criteria. Approximately 70% of all patients who completed the study showed great or moderate improvement. Delorazepam produced the greatest improvement in anxiety ratings during the first two weeks of treatment, but both paroxetine and imipramine were more effective by the fourth week of treatment. Delorazepam affects predominantly somatic symptoms, whereas paroxetine and imipramine affect psychic symptoms (Rocca et al, 1997a).

4.6.H Doxepin

4.6.H.1 Depression

a) Paroxetine was at least as effective as doxepin in the treatment of major depression in 272 geriatric patients in a double-blind, randomized trial. After a washout-period of 4 to 14 days, patients over 60 years of age received either paroxetine 10 to 40 milligrams (mg) (mean 23.4 mg) as a single daily dose or doxepin (up to 200 milligrams (mg), mean 105.2 mg/day) divided in two doses. Therapy continued for 42 days. Paroxetine was as effective as doxepin by several measures and more effective by others. Doxepin caused more sedation, confusion, and anticholinergic effects, and less nausea and headache compared with paroxetine (Dunner et al, 1992).

4.6.I Duloxetine

4.6.I.1 Major depressive disorder

a) Duloxetine therapy was more effective than placebo and non-inferior to paroxetine therapy in the treatment of psychological and physical symptoms of depression. In a randomized, double-blind, placebo-controlled, multi-center study, patients (n=353) with major depressive disorder, a Hamilton Depression Rating Scale (HAM-D) total score of at least 15, and a moderate Clinical Global Impression (CGI) Severity rating (score of at least 4) received oral duloxetine 80 milligrams (mg) daily (in divided doses), duloxetine 40 mg daily (in divided doses), paroxetine 20 mg daily, or placebo for 8 weeks. Response was defined as at least a 50% reduction from baseline in the HAM-D total score and remission was defined as a HAM-D score of 7 or less. At week 8, both the 80 and 40 mg dosing regimens of duloxetine produced significantly greater reductions in HAM-D scores from baseline as compared with placebo (mean difference, 3.62 points, 95% CI 1.38, 5.86; p=0.002 and 2.34 points, 95% CI 0.19, 4.66; p=0.034, respectively). A significantly greater reduction in HAM-D total scores was also observed with duloxetine 80 mg therapy as compared with paroxetine treatment (mean difference, 2.39 points, 95% CI 0.14, 4.65; p=0.037). Paroxetine therapy was not significantly different from placebo at week 8, however at weeks 2, 4, and 6; paroxetine treatment was superior to placebo. The response rate at endpoint was significantly higher in patients treated with duloxetine 80 mg as compared with placebo (51% vs 31%, p=0.009, respectively). Additionally, the remission rate in the duloxetine 80 mg group (50%) was significantly higher at endpoint as compared with remission rates for patients in the duloxetine 40 mg group (35%; p=0.045) and the placebo group (30%; p=0.008), but was not superior to patients in the paroxetine group (37%; p=ns). Significant reductions from baseline to endpoint in overall pain severity were observed in patients treated with duloxetine 80 mg (reduction from baseline, 47%; -7.5 points on VAS scale, 95%CI -25, 1; p=0.005), as compared with placebo, however significant reductions were not seen with paroxetine or duloxetine 40 mg therapy as compared with placebo. Both duloxetine and paroxetine were generally well tolerated and only insomnia was reported significantly more often in duloxetine-treated (80 mg) patients as compared with paroxetine-treated patients (19.8% vs 8%, respectively; p=0.031) (Goldstein et al, 2004).

4.6.J Escitalopram

4.6.J.1 Generalized anxiety disorder

a) In a randomized, double-blind, multi-center trial involving patients (mean age, approximately 37 years) with moderate to severe generalized anxiety disorder (GAD), treatment with either escitalopram (10 to 20 milligrams (mg) per day), or paroxetine (20 to 50 mg per day) lead to improvements over time in all efficacy measures; however, escitalopram was better tolerated. The primary efficacy endpoint was change in Hamilton Anxiety Scale (HAMA) total score from baseline to week 24 for the intent -to-treat (ITT) population.

Mean baseline HAMA scores were 23.7 +/- 0.5 standard error of the mean (SEM) for the escitalopram-treated patients (n=60) and 23.4 +/- 0.4 SEM for the paroxetine-treated patients (n=61). Upon analysis of efficacy data, there were no statistically significant differences between treatment groups at week 8 or week 24. At week 24, mean changes in HAMA scores were -15.3 +/- 0.8 SEM and -13.3 +/- 1 SEM for the escitalopram and paroxetine groups, respectively. The proportions of patients who met the response criterion (Clinical Global Impressions of Improvement (CGI-I) of 1 or 2) at week 8 were 65% for escitalopram and 55.7% for paroxetine and at week 24 were 78.3% and 62.3%, respectively. These differences were not statistically significant. A greater proportion of patients treated with paroxetine withdrew from the study due to adverse events compared to those receiving escitalopram (22.6% vs. 6.6%, respectively; p=0.02). While no single adverse event was reported as the reason for discontinuation of escitalopram therapy by more than one patient, headache, insomnia, and nausea each lead to the discontinuation of paroxetine in 2 or more patients. Upper respiratory tract infections and diarrhea were reported more frequently with escitalopram than with paroxetine (14.8% vs. 4.8% and 21.3% vs. 8.1%, respectively). Insomnia (25.8% vs. 14.8%), constipation (14.5% vs. 1.6%), ejaculation disorder (30% vs. 14.8%), anorgasmia (26.2% vs. 5.9%) and decreased libido (22.6% vs. 4.9%) occurred more frequently in the paroxetine group compared to the escitalopram group, respectively. Overall, the incidence of treatment emergent adverse events was 88.7% for paroxetine and 77% for escitalopram (Bielski et al, 2005).

4.6.K Fluoxetine

4.6.K.1 Depression

a) Paroxetine, fluoxetine, and sertraline were equally effective for the treatment of depression and for improving quality of life in patients in a primary care setting. In a 9-month, randomized, open-label trial (the ARTIST trial), depressed patients, whose symptoms warranted antidepressant treatment, according to their primary care physicians (PCP), were given paroxetine (n=180), fluoxetine (n=184) or sertraline (n=182). Starting doses were paroxetine 20 milligrams (mg), fluoxetine hydrochloride 20 mg, and sertraline 50 mg. The PCP could adjust the dose on the basis of clinical response and could switch the treatment to one of the other study drugs. Final average doses were 23.5 mg for paroxetine, 23.4 mg for fluoxetine, and 72.8 mg for sertraline. All 3 groups showed substantial improvement in depressive symptoms and quality of life. Overall, the percentage of patients categorized as having major depression dropped from 74% at baseline to 32% at 3 months, and 26% at 9 months. No significant differences were evident among the 3 groups. When data from subgroups (patients with major depression, patients who completed the trial on the drug initially assigned) were analyzed separately, still no differences among the drug treatments was evident. Patient satisfaction did not differ for the 3 groups. Changes in sexual function were small but tended to show improvement for all drug treatments. The drugs were associated with similar incidences of adverse effects and discontinuation rates (Kroenke et al, 2001a).

b) Paroxetine and fluoxetine demonstrated similar efficacy following 6 weeks of treatment in depressed patients (De Wilde et al, 1993). However, the paroxetine-treated patients had a statistically significant difference in terms of reduction of Hamilton Rating Scale for depression after three weeks of treatment. This suggests that paroxetine may have a faster onset of activity than fluoxetine. The most commonly reported adverse effects were nausea and vomiting for both drugs.

4.6.L Fluvoxamine

4.6.L.1 Depression

a) Fluvoxamine and paroxetine produced similar improvements in depressive symptoms in patients with an initial or recurrent episode of major depression. Adverse effects occurred in 100% and 97% of patients treated with paroxetine and fluvoxamine, respectively. Fluvoxamine was associated with a higher incidence of asthenia, dry mouth, somnolence, and insomnia; whereas, paroxetine caused a higher incidence of headache, nausea, diarrhea, sweating, abnormal dreams, and sexual dysfunction. In this 7-week, randomized, double-blind study, 58 patients were assigned to receive fluvoxamine 50 milligrams(mg)/day or paroxetine 20 mg/day initially; the protocol allowed for dosage titration to fluvoxamine 150 mg/day or paroxetine 50 mg/day. An additional 10 fluvoxamine- and 8 paroxetine-treated patients dropped out of the study for various reasons, but all of the patients were included in the intent-to-treat efficacy analysis. Due to the small sample size of this study, only large differences between treatments would be detectable; therefore, larger studies are needed to detect differences in treatment effects between these drugs (Kiev & Feiger, 1997).

b) The pharmacology, pharmacokinetics, adverse effects, drug interactions, efficacy, and dosage and administration of fluvoxamine (FVX), sertraline (SRT) and paroxetine (PRX) were compared in a comprehensive review (Grimsley & Jann, 1992). All three agents have large volumes of distribution and are highly protein-bound. In contrast to fluoxetine, FVX, SRT, and PRX all have shorter elimination half-lives (approximately 24 hours) and are metabolized to clinically-inactive compounds. Nausea was the most commonly reported adverse effect for all three agents. Other reported adverse effects include sedation, headache, dry mouth, insomnia, sexual dysfucntion, and constipation. FVX has been found to be superior to placebo and equivalent to imipramine, clomipramine, desipramine, mianserin, and maprotiline in the treatment of depression and both FVX and SRT have been shown to be superior to placebo in the treatment of obsessive-compulsive disorder (OCD). PRX has been found to be superior to placebo and equivalent to amitriptyline, imipramine, clomipramine, and doxepin in the treatment of depression while SRT has been

found to be superior to placebo and equivalent to amitriptyline. Clinical experience has demonstrated all three drugs to be effective in the treatment of depression. They may be especially useful in elderly patients, in those who cannot tolerate alternate treatments, and in those who do not respond to adequate trials of other antidepressant therapies.

4.6.M Imipramine

Anxiety

Bipolar disorder, depressed phase

Depression

4.6.M.1 Anxiety

a) In an uncontrolled trial, paroxetine and imipramine were as effective as 2- chlordesmethyldiazepam, a benzodiazepine, for treating generalized anxiety disorder (Rocca et al, 1997). Patients (n=81) received paroxetine 20 milligrams(mg)/day, imipramine 50 to 100 mg/day, or 2-chlordesmethyldiazepam 3 to 6 mg/day for 8 weeks. Over the first 2 weeks, patients treated with 2-chlordesmethyldiazepam showed greater improvement; however, after 4 weeks for paroxetine and 8 weeks for imipramine, the anti-depressants were more effective. Adverse effects consisted primarily of anticholinergic effects for imipramine, nausea for paroxetine, and drowsiness for 2-chlordesmethyldiazepam. Larger, blinded, controlled clinical trials are needed to confirm the results of this study.

4.6.M.2 Bipolar disorder, depressed phase

a) Neither paroxetine nor imipramine was more effective than placebo in treating BIPOLAR DEPRESSION in patients stabilized on lithium if their serum lithium levels were above 0.8 milliequivalents per liter (meq/L). However, patients whose serum lithium concentration was less than 0.8 meq/L showed greater improvement with 8 weeks of antidepressant treatment than with placebo treatment (p=0.05 for paroxetine, p=0.04 for imipramine). In a double-blind study, patients were stratified according to serum lithium concentration and then randomized to receive paroxetine (n=35), imipramine (n=39), or placebo (n=43) for 10 weeks. Among all completers of the study, therapeutic response (Hamilton depression scale scores of 7 or less) was achieved by 56%, 48%, and 54% of patients receiving paroxetine, imipramine, and placebo, respectively. Adverse events accounted for study discontinuation in 1 patient in the paroxetine group (3%), 12 in the imipramine group (30%), and 5 in the placebo group (12%). No patient in the paroxetine group experienced induction to mania, whereas 3 patients treated with imipramine and 1 treated with placebo developed treatment-emergent mania (Nemeroff et al, 2001).

4.6.M.3 Depression

a) SUMMARY: Paroxetine, a selective serotonin reuptake inhibitor, and imipramine appear to be similarly effective in the treatment of major depression. The decision as to which drug to use should be based on patient-related characteristics (eg, anxiety disorders, sleep disturbances, cardiovascular disease), potential drug interactions, and side effects.

b) Paroxetine, imipramine, and placebo were compared in 120 outpatients with moderate-to-severe major depression (DSM-III) (Feighner & Boyer, 1989). Following a 4- to 14-day single-blind, placebo washout period, patients were assigned to receive either paroxetine, imipramine, or placebo for 6 weeks. The dose of paroxetine and imipramine could be increased to a maximum of 50 milligrams and 275 milligrams daily, respectively. Paroxetine was superior to placebo in 5 of 6 measures evaluated (HAMD scale, Raskin depression scale, MADRS, CGI scale, Covi anxiety scale); no improvement was observed as compared to placebo in the 56-item Symptom Checklist (SCL-56). Imipramine was also statistically superior to placebo on HAMD, Raskin, MADRS, and the CGI scale, but not on the Covi anxiety scale or the SCL-56. The only outcome measure that improved to a significantly greater degree with paroxetine was the HAMD total score. A high number of patients discontinued therapy (approximately 50%), which limits evaluation of efficacy. If only the patients completing the study are considered, imipramine and paroxetine appear to be equally effective. Based upon the number of dropouts due to adverse effects, paroxetine appeared to be better tolerated than imipramine: 10% versus 30%. The most common adverse effects with paroxetine were sedation and gastrointestinal effects, whereas anticholinergic adverse effects (dry mouth, constipation, urinary symptoms) were the most common with imipramine. However, a detailed incidence of all adverse effects was not provided, making it difficult to fully compare these agents.

c) Paroxetine was more effective than placebo in the short-term (6-week) treatment of depression; however, paroxetine was less effective than imipramine. The study was double-blinded and 122 patients with a major depressive disorder were randomized to receive either paroxetine (dose range 20 to 50 milligrams/day), imipramine (dose range 65 to 275 milligrams/day) or placebo. At the end of the study, the imipramine-treated patients demonstrated consistently better scores, both objective and subjective, on all depression rating scales when compared to paroxetine. Overall there was a 64% response rate to imipramine, a 48% response rate to paroxetine, and a 33% response rate to placebo (Peselow et al, 1989).

d) A multicenter, double-blind, placebo-controlled evaluation of paroxetine and imipramine in the outpatient treatment of major depression was conducted (Dunbar et al, 1991a). After a 4- to 14-day placebo run-in period, patients were randomized to their treatment groups; 240 to the paroxetine group, 237 to the imipramine group, and 240 to the placebo group. Therapy was started at 20 milligrams paroxetine and 80 milligrams imipramine. Dosage adjustment, if necessary, was done at weekly intervals over the six-week treatment phase. Drop-out rates were high for all groups; paroxetine 42.5%, imipramine 53.3%, and placebo 53.6%. Lack of efficacy (10%, 7%, and 33%, respectively) and side effects (23%, 36%, and 9%, respectively) were the most common reasons stated for dropping out of the study. Imipramine and paroxetine were equally superior to placebo and produced similar efficacy results. However, paroxetine therapy was associated with less sedation, cardiovascular, and anticholinergic side effects.
e) Newer clinical trials have continued to support the previous findings that imipramine and paroxetine are similar in effectiveness. The major differences between the two compounds are the frequency of side effects, types of side effects, and frequency of patients withdrawing from the clinical trials secondary to side effects from the study medications. In all cases paroxetine therapy is better tolerated and associated with lower withdrawal rates (Ohrberg et al, 1992; Feighner et al, 1993); (Arminen et al, 1994).
f) A 6-week, double-blind study was continued for 1 year by crossing over all patients who had failed to respond to initial treatment to the other drug (Peselow et al, 1989a). Patients first treated with placebo were crossed over to paroxetine (n=19). A total of 15 patients initially treated with paroxetine switched to imipramine, while 10 imipramine patients were switched to paroxetine. Of the patients who initially failed on paroxetine, 73% responded to imipramine, while 50% of the patients who initially failed on imipramine responded to paroxetine. Similar studies have shown paroxetine to be at least as effective as imipramine with fewer side effects (Fabre, 1992a; Cohn & Wilcox, 1992; Shrivastava et al, 1992; Feighner & Boyer, 1992).

4.6.N Maprotiline

Chronic pain

Depression

Premenstrual dysphoric disorder

4.6.N.1 Chronic pain

a) SUMMARY: MAPROTILINE proved more efficacious for relief of chronic back pain than PAROXETINE, in a double-blind, randomized trial.
b) MAPROTILINE, a noradrenergic antidepressant, provided more effective analgesia than did PAROXETINE, a serotonergic antidepressant, or DIPHENHYDRAMINE (placebo) in non-depressed adult patients with chronic low back pain, according to an 8-week, randomized, double-blind trial (n=74). Pain intensity was measured on the Descriptor Differential Scale (DDS; Gracely & Kwilosz, 1988). Pain intensity scores dropped by 45%, 26%, and 27% for maprotiline-, paroxetine-, and placebo-treated patients, respectively (p=0.013, maprotiline vs paroxetine; p=0.023, maprotiline vs placebo). Decreases in pain unpleasantness were also significantly greater for maprotiline compared with placebo (p=0.009), but were similar to the reductions for paroxetine (NS). Dosing of maprotiline was 50 milligrams (mg) per day for 3 days, followed by 100 mg for 3 days and then an increase to the target dose of 150 mg/day. Paroxetine was started at 10 mg/day for 3 days, followed by 20 mg/day for 3 days and then an increase to the target dose of 30 mg/day. The target dose (or maximum tolerable dose) was taken once daily at 2100 hours. Overall, 15 patients dropped out of the study due to adverse effects (9, maprotiline; 6, paroxetine); 1 patient in the paroxetine group discontinued due to lack of efficacy. The authors suggest that noradrenergic agents or combined noradrenergic/serotonergic agents may be preferable therapy for chronic back pain than serotonergic agents (Atkinson et al, 1999).

4.6.N.2 Depression

a) Paroxetine and maprotiline are similarly effective in the treatment of major depression. In a double-blind study involving a relatively small number of patients (n=71), treatment with either paroxetine (20 to 40 milligrams daily) or maprotiline (50 to 150 milligrams daily) resulted in comparable improvement in symptoms of depression as measured by the Hamilton Psychiatric Rating Scale for Depression (HAMD), the Montgomery-Asberg Depression Rating Scale, the Clinical Global Impression, and the Hopkins Symptoms Checklist. Patients treated with paroxetine experienced fewer side effects; however, this difference was not statistically significant (Schnyder & Koller-Leiser, 1996).

4.6.N.3 Premenstrual dysphoric disorder

a) Paroxetine was more effective than maprotiline or placebo for treating premenstrual symptoms. Following assessment of symptom severity for 2 months, patients were randomly assigned to placebo (n=22), maprotiline (n=21), or paroxetine (n=22). The initial dose of maprotiline and paroxetine was 25 milligrams (mg) and 10 mg, respectively. The maximum dose allowed by the study protocol was 150 mg for maprotiline

and 30 mg for paroxetine. Efficacy was assessed by determining the percentage reduction from baseline for 6 symptoms observed with PDD. All symptoms (ie, irritability, depressed mood, anxiety, increased appetite, bloating, and breast tenderness) were significantly reduced by paroxetine compared to maprotiline and placebo; there were no significant changes between maprotiline and placebo. While paroxetine, a selective serotonin reuptake inhibitor, was more effective than maprotiline, a noradrenaline reuptake inhibitor, the criteria for assessment were less stringent than in other similar trials (Eriksson et al, 1995).

4.6.O Mianserin

4.6.O.1 Depression

a) Paroxetine 30 mg once daily in the morning was as effective as mianserin 30 mg twice daily (morning and night) in the treatment of unipolar or bipolar depression in a controlled inpatient/outpatient study involving 70 patients (Mertens & Pintens, 1988a). Significantly greater reductions in subscales for cognitive disturbance and retardation were observed with paroxetine at some, but not all, time points during the 6-week study. Adverse effects occurred to a similar degree with each agent, with the most common being nausea and headache with paroxetine and somnolence with mianserin.

4.6.P Mirtazapine

4.6.P.1 Major depressive disorder

a) Paroxetine and mirtazapine demonstrated similar efficacy in the treatment of major depressive disorder, with mirtazapine demonstrating a potentially faster onset of action. In a double-blind study, patients with major depression randomly received mirtazapine (n=127) or paroxetine (n=123) for 6 weeks. Patients receiving mirtazapine received 15 milligrams/day (mg) for 2 days then 30 mg thereafter; an increase to 45 mg daily was allowed after 2 weeks in nonresponders. Initial paroxetine doses were 20 mg daily increased to 40 mg daily in nonresponders after 2 weeks. During the study, mean daily doses of mirtazapine and paroxetine were 32.7 mg and 22.9 mg, respectively. The percentage of patients responding to therapy after 1 week as measured by the Hamilton Depression Rating Score-17 (HAM-D-17) was significantly greater in the mirtazapine group (23.2%) as compared to the paroxetine group (8.9%, p=0.002). At endpoint, the patients achieving complete remission, defined as a score of less than 7 on the HAM-D-17, was 40.9% in the mirtazapine group and 34.1% in the paroxetine group (p not significant). Both treatments also produced decreases in anxiety as measured by the Hamilton Rating Scale for Anxiety. Dropouts due to adverse events occurred in 8.6% of mirtazapine patients and 7.4% of paroxetine patients. Adverse events in the paroxetine group included nausea, vomiting, tremor, and increased sweating. Adverse events in the mirtazapine patients included weight increase and influenza-like symptoms (Benkert et al, 2000).

4.6.Q Nortriptyline

4.6.Q.1 Depression

a) Paroxetine was as effective as nortriptyline and caused fewer adverse effects when used in depressed cardiac patients. Outpatients with moderate depression and ischemic heart disease randomly received paroxetine (n=41) or nortriptyline (n=40) for 6 weeks. Patients receiving paroxetine were initially prescribed 20 milligrams (mg) (except for those over 65 years old who received 10 mg) and increased to a maximum of 40 mg/day based on response. Patients prescribed nortriptyline received 25 mg and increased as needed to achieve a blood level between 50 and 150 nanograms/milliliter. A response was defined as a 50% or greater improvement in the Hamilton depression scale score. Mean final doses were paroxetine 22 mg/day and nortriptyline 73 mg/day. Both drugs were efficacious with responses of 73% in the paroxetine group and 92% in the nortriptyline group (p not significant). Significantly more patients assigned to nortriptyline discontinued treatment than with paroxetine (p less than 0.02). With paroxetine, adverse effects causing discontinuation in 2 patients included diarrhea and angina. With nortriptyline, adverse effects causing discontinuation in 10 patients included 4 with sinus tachycardia, 1 with severe angina associated with ST changes on electrocardiogram, 2 with an increase in ventricular ectopy, 1 with persistent myoclonic jerks, and 2 with constipation (Nelson et al, 1999).

b) In a small, 6-week study (n=80), nortriptyline and paroxetine appeared to have comparable efficacy and tolerability (Mulsant et al, 1999). In this double-blind study, elderly (mean age, 75 years) patients with DSM-IV major depression were randomly assigned to nortriptyline or paroxetine. For outpatients, the initial dosage of nortriptyline and paroxetine was 25 milligrams(mg)/day and 10 mg/day, respectively; whereas, inpatients received nortriptyline 50 mg/day and paroxetine 20 mg/day initially. Dosage titration to achieve nortriptyline plasma levels between 50 and 150 ng/mL was permitted, and an increase to paroxetine 30 mg/day was also allowed. Discontinuation of medication due to adverse effects was reported in 5 (14%) and 8 (19%) patients treated with nortriptyline and paroxetine, respectively. The Hamilton Rating Scale for Depression score decreased from 22.4 to 8.8 with nortriptyline and from 20.9 to 9.6 with paroxetine; the difference between treatments was NOT statistically significant. Using intent-to-treat analysis, a higher response rate was achieved in the nortriptyline versus paroxetine group (57% versus 44%; p=0.26).

c) In an open, preliminary study, paroxetine was useful for long-term maintenance therapy of depression in elderly patients (Walters et al, 1999). After completion of a 12-week efficacy study, 25 of 27 and 15 of 16 patients with a response to paroxetine (mean dose, 24.5 milligrams(mg)/day) and nortriptyline (mean dose, 51.3 mg/day), respectively, elected to continue treatment. During a mean follow-up of 11.9 months, relapse

occurred in 1 of 15 subjects treated with nortriptyline versus 5 of 25 subjects treated with paroxetine. A survival plot also suggested similar efficacy for the 2 agents; however, about half of the patients in each treatment group discontinued treatment for a variety of reasons. A larger, controlled clinical study is needed.

4.6.R Risperidone

4.6.R.1 Panic attack

a) In an 8-week, randomized, single-blind, comparative trial (n=56) of low-dose risperidone and paroxetine in the treatment of panic attacks, both treatments were effective in reducing the occurrence and severity of panic attacks but there was no difference in the efficacy of each to improve anxiety associated with panic disorders. Thirty-three (8 men, 25 women) subjects were randomized to risperidone and 23 (8 men, 15 women) to paroxetine. The average age of the group was 40.36 +/- 12.37 years. Risperidone was initiated at 0.25 mg/day, adjusted as necessary for lack of response or sedation (maximum dose of 16 mg/day). Paroxetine was initiated at 30 mg/day, increased to a maximum of 60 mg/day if needed. The average risperidone dose was 0.53 mg (range 0.125 mg to 1 mg). All subjects in the paroxetine group received 30 mg/day except for one who required a dose of 40 mg. Subject assessments were conducted by a clinical rater blinded to medication status, using the 17-item Hamilton Depression Rating Scales (Ham-D-17), the Hamilton Anxiety Rating Scale (Ham-A), the Panic Disorder Severity Scale (PDSS), the Sheehan Panic Anxiety Scale-Patient (SPAS-P) and the Clinical Global Impressions Scale (CGI). Twenty subjects in the risperidone group and 9 in the paroxetine group completed all study visits. A significant decrease in CGI score was demonstrated in all subjects (p less than 0.001), but there was no significant difference between the groups. The CGI score improved from 4.4 +/- 0.6 at baseline to 2.84 +/- 1.02 at final assessment in the risperidone arm. Similarly, paroxetine resulted in a CGI score improvement from 3.81 +/- 1.33 to 2.67 +/- 0.71 at final assessment. All subjects, regardless of treatment, demonstrated a significant decrease in outcome scores for the PDSS total score, PDSS item 1, PDSS item 2, Ham-A and Ham-D. There was no statistical difference between treatment groups by the end of the study, and there was no significant change in SPAS-p scores over time (Prosser et al, 2009).

4.6.S Sertraline

Burning mouth syndrome

Depression

Weight gain

4.6.S.1 Burning mouth syndrome

a) Amisulpride, sertraline, and paroxetine were all effective in reducing the symptoms of burning mouth syndrome (BMS), but response was achieved earlier with amisulpride than with the selective serotonin reuptake inhibitors (SSRIs). In a randomized, single-blind study, 76 patients with BMS and without major depression were given amisulpride 50 milligrams (mg) per day, paroxetine 20 mg/day, or sertraline 50 mg/day for 8 weeks. Pain scores decreased significantly in all groups, as did depression (Hamilton Rating Scale for Depression) and anxiety (Hamilton Rating Scale for Anxiety), by week 8. The only difference among treatments was the shorter latency to response in the amisulpride group (22% of patients responding at 2 weeks with amisulpride vs 0% with paroxetine and 6% with sertraline) (Maina et al, 2002).

4.6.S.2 Depression

a) Paroxetine, fluoxetine, and sertraline were equally effective for the treatment of depression and for improving quality of life in patients in a primary care setting. In a 9-month, randomized, open-label trial (the ARTIST trial), depressed patients, whose symptoms warranted antidepressant treatment, according to their primary care physicians (PCP), were given paroxetine (n=180), fluoxetine (n=184) or sertraline (n=182). Starting doses were paroxetine 20 milligrams (mg), fluoxetine hydrochloride 20 mg, and sertraline 50 mg. The PCP could adjust the dose on the basis of clinical response and could switch the treatment to one of the other study drugs. Final average doses were 23.5 mg for paroxetine, 23.4 mg for fluoxetine, and 72.8 mg for sertraline. All 3 groups showed substantial improvement in depressive symptoms and quality of life. Overall, the percentage of patients categorized as having major depression dropped from 74% at baseline to 32% at 3 months, and 26% at 9 months. No significant differences were evident among the 3 groups. When data from subgroups (patients with major depression, patients who completed the trial on the drug initially assigned) were analyzed separately, still no differences among the drug treatments was evident. Patient satisfaction did not differ for the 3 groups. Changes in sexual function were small but tended to show improvement for all drug treatments. The drugs were associated with similar incidences of adverse effects and discontinuation rates (Kroenke et al, 2001).

b) Sertraline and paroxetine were equally effective in treating major depression, although side effects may be less with sertraline. In a double-blind study, 353 outpatients meeting the DSM-III_R criteria for major depression and having a score of at least 21 on the Montgomery-Asberg Depression Rating Scale (MADRS)

that did not improve at least 25% during a 1-week washout period were randomized to receive 24 weeks of treatment with either sertraline 50 milligrams (mg) or paroxetine 20 mg. Dose adjustments were allowed after 2 weeks based on response to a maximum of 150 mg sertraline and 40 mg paroxetine. No significant differences were observed in the improvement of MADRS and Clinical Global Impression (CGI) scores between the sertraline and paroxetine group. Of the 176 patients taking sertraline, 64% completed 24 weeks of treatment, and 65 % of 177 treated with paroxetine completed 24 weeks. Of those who completed therapy, remission (MADRS score less than 7)was achieved in 80.2% of the sertraline and in 73.7% of the paroxetine-treated patients. Quality of life measures improved with no significant differences between the two groups. Comparable improvements also occurred for the 2 groups in measures of personality. Both treatments were well-tolerated, with diarrhea reported significantly more often with sertraline, and constipation, fatigue, decreased libido in women, and micturition problems significantly more common with paroxetine. A significantly greater weight gain was observed with paroxetine (2.9 pound) compared with sertraline (1.3 pound) (Aberg-Wistedt et al, 2000)

4.6.S.3 Weight gain

a) Weight gain is a common complaint during antidepressant therapy, and weight gain was significantly greater with paroxetine than either sertraline or fluoxetine after 32 weeks of treatment. Patients meeting DSM-IV criteria for major depressive disorder were randomized to double-blind treatment with sertraline 50 milligrams (mg) daily (n=96) fluoxetine 20 mg daily (n=20), or paroxetine 20 mg daily (n=96) for 4 weeks. Patients responding to this dose continued for an additional 6 weeks, and those not responding had their doses titrated based on response up to a dose of 200 mg sertraline, 60 mg fluoxetine, and 60 mg paroxetine, and then maintained at their optimal doses for 6 weeks. After this treatment phase, responders (Clinical Global Impressions-Improvement score of 1 or 2 for 2 consecutive weeks) continued for 16 additional weeks. The number of responders participating in the 16 additional weeks were similar for the 3 treatments: 48 sertraline, 44 fluoxetine, and 47 paroxetine. However, among these responders, the mean increase in weight in the paroxetine group (3.6%) was significant compared to the mean increase with sertraline (1.0%) and mean decrease with fluoxetine (-0.2%). A gain of 7% or greater in weight occurred in 25.5% of paroxetine patients, 4.2% of sertraline patients, and 6.8% of fluoxetine patients; this difference was significant (Fava et al, 2000).

4.6.T Sildenafil

4.6.T.1 Premature ejaculation

a) In a 6-month, prospective, randomized clinical trial (n=180), the use of sildenafil was more effective than paroxetine and squeeze technique in alleviating primary premature ejaculation . Male adults aged between 19 and 52 years (mean 33 years) with a history of primary premature ejaculation (defined as ejaculation before vaginal penetration or within 2 minutes after vaginal penetration) were randomly divided into 3 treatment groups: sildenafil 50 milligrams (mg) as needed an hour before intended intercourse, paroxetine 20 mg once daily, and squeeze technique daily. Participants and their female partners were assessed before treatment began, and followed 3 and 6 months post-treatment. Compared with pretreatment, all treatment groups resulted in marked improvement in participant- and partner-reported intravaginal ejaculation latency (IELT), premature ejaculation grade, and intercourse satisfactory scores (ISS) 3 and 6 months after treatment initiation (p=0). Patient-reported mean IELT from baseline to 6 months post-treatment was 1.09 +/- 0.32 minutes (min) to 6.21 +/- 1.86 min for the sildenafil group, 1.11 +/- 0.45 min to 4.93 +/- 1.36 min for the paroxetine group, and 1.06 +/- 0.36 min to 2.62 +/- 0.69 min for the squeeze technique group (p=0 among groups and from baseline). The magnitude of improvement was comparable at the 3- and 6-month follow-up. At the end of the study, 1.7%, 18.3%, and 36.7% patients in the sildenafil, paroxetine, and squeeze technique group, respectively, withdrew from the study secondary to lack of effect or adverse reaction (p=0). Sildenafil was associated with higher incidence of headache (11.7% vs 3.3%), nasal congestion (8.3% vs 0%), and flushing (8.3% vs 0%) compared with paroxetine. On the other hand, paroxetine was associated with more frequent nausea (10% vs 3.3%), dizziness (3.3% vs 0%), fatigue (5% vs 0%), and constipation (6.7% vs 0%) compared with sildenafil (Wang et al, 2007).

b) According to a double-blind, randomized, cross-over study (n=31), as-needed SILDENAFIL was superior in the treatment of premature ejaculation compared with CLOMIPRAMINE, PAROXETINE, SERTRALINE, and PAUSE-SQUEEZE technique. Clomipramine, paroxetine, and sertraline had generally similar efficacy and safety. Paroxetine exhibited improved efficacy and satisfaction over pause-squeeze, while efficacy and satisfaction were similar to pause-squeeze for clomipramine and sertraline. Median intravaginal ejaculation latency time (IELT) increased significantly to 4 minutes (min), 4 min, 3 min, 15 min, and 3 min from baseline 1 min for clomipramine, paroxetine, sertraline, sildenafil, and pause-squeeze, respectively (all p less than 0.0001). Paroxetine was superior to pause-squeeze with respect to IVELT (p=0.04) and sexual satisfaction (p=0.025). A significant positive correlation occurred between ejaculation latency and sexual satisfaction. No significant differences in adverse effects were found among the 4 drugs. Three patients dropped out due to side effects, including sildenafil (2) and clomipramine (1; also lack of efficacy in this patient). Three additional patients dropped out due to lack of efficacy related to clomipramine, paroxetine, sertraline, and/or pause-squeeze. Medications were administered as needed 3 to 5 hours before planned intercourse and not more than twice a week. Doses were clomipramine 25 milligrams (mg), paroxetine 20 mg, sertraline 50 mg, and sildenafil 50 mg (Abdel-Hamid et al, 2001).

4.6.U Sulpiride

4.6.U.1 Tension-type headache

a) Headache was significantly reduced compared with baseline in patients receiving paroxetine 20 to 30 milligrams per day for 8 weeks during a randomized, double-blind, crossover study with sulpiride (Langemark & Olesen, 1994). Fifty patients with chronic tension headache received either sulpiride 200 to 400 milligrams/day or paroxetine for 8 weeks. Headache was recorded by the patients on a 5-point verbal score. Comparison between the 2 treatment groups after the first 8 weeks demonstrated no statistical differences in headache scores; however, both treatments did reduce headaches when compared to baseline. Following crossover, patients switched to sulpiride demonstrated a reduction in headache scores, while those switched to paroxetine did not. It should be noted that there was no washout period between the crossover and paroxetine is known to have a relatively long half-life. More controlled, large scale clinical trials are necessary to determine sulpiride's role in the treatment of chronic tension headache.

4.6.V Venlafaxine

Bipolar disorder, depressed phase

Obsessive-compulsive disorder

4.6.V.1 Bipolar disorder, depressed phase

a) Paroxetine and venlafaxine had similar efficacy in the treatment of depression in bipolar patients taking concomitant mood stabilizers. This randomized, single-blind (rater blind), comparative, 6-week study demonstrated that paroxetine and venlafaxine produced responses in 43% and 48% of the patients, respectively. At the end of the 6-week trial, both treatment groups showed significant improvement in the Hamilton Rating Scale for Depression (HAM-D) and the Clinical Global Impressions (CGI) for severity rating scores, with a mean HAM-D change of -6.9 for the paroxetine group and -9.0 for the venlafaxine group. These responses were significantly different compared to baseline, but not among treatment groups. At baseline, patients (n=60) were assessed using CGI ratings, the HAM-D, the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV), Axis I Disorders (SCID-I), and the Young Mania Rating Scale (YMRS). All patients were being treated with 1 or more mood stabilizers for at least 6 months prior to onset of the current major depressive episode, and had not taken antidepressant or antipsychotic medication for at least 3 months prior to the start of the study. During the study, doses were adjusted for efficacy and tolerability. The starting dose of venlafaxine was 37.5 milligrams (mg) twice a day, which could be increased in increments of 75 mg per day (mg/d) every week. The starting dose of paroxetine was 20 mg/d, which could be adjusted in increments of 10 mg/d every week. The mean doses of venlafaxine and paroxetine were 179 mg/d and 32 mg/d, respectively. There were no significant differences in reported adverse events (43% for paroxetine, 50% for venlafaxine); the most common adverse events were nausea (20% of all patients), and dizziness (8.3% of all patients). One patient (3%) in the paroxetine group had a switch to hypomania during treatment, 4 patients (13%) in the venlafaxine group switched to either hypomania (2 patients) or full mania (2 patients). Limitations of the study include concomitant use of several different mood stabilizing drugs, no placebo group, a single-blind study design, and a short follow up period (Vieta et al, 2002).

4.6.V.2 Obsessive-compulsive disorder

a) Venlafaxine extended-release (XR) was as effective as paroxetine in the treatment of patients with obsessive compulsive disorder (OCD). In a randomized, double-blind, comparative study, patients (n=150) with OCD and a score of at least 18 (or at least 12, if only obsessions or only compulsions were present) on the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) received either venlafaxine XR (initial, 75 milligrams (mg)/day, titrated to 300 mg/day by week 7) or paroxetine (initial, 15 milligrams (mg)/day, titrated to 60 mg/day by week 7) for 12 weeks. Both paroxetine and venlafaxine XR treatments were effective, producing mean reductions of 7.8 and 7.2 points, respectively, in the Y-BOCS score from baseline to endpoint. A significant decrease in the total Y-BOCS score from baseline was seen at week 3 for venlafaxine XR- treated patients (p=0.008) and at week 5 for patients in the paroxetine group (p=0.018). There were no significant differences in responder rates between treatment groups. In the venlafaxine XR group, 37% and 25% of patients were partial responders and full responders, respectively. Similarly, in the paroxetine group, 44% and 22% of patients were partial responders and full responders, respectively. Additionally, no significant differences were observed between the two treatments with regard to reduction of anxious or depressive symptoms (as measured by the Hamilton Anxiety Scale and the Hamilton Rating Scale for Depression, respectively). For both treatments, most adverse effects were of mild or moderate severity and included somnolence, sweating, insomnia, and nausea (Denys et al, 2003).

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Last Modified: June 18, 2009

DRUGDEX® Evaluations

FLUOXETINE

0.0 Overview

1) Class

a) This drug is a member of the following class(es):
Antidepressant
Central Nervous System Agent
Serotonin Reuptake Inhibitor

2) Dosing Information

a) Fluoxetine Hydrochloride

1) Adult

a) Bulimia nervosa

1) 60 mg ORALLY once daily in the morning (Prod Info PROZAC(R) oral pulvule, oral solution, oral tablet, oral delayed-release capsule, 2005)

b) Major depressive disorder

1) initial, 20 mg ORALLY once daily in the morning (Prod Info PROZAC(R) oral pulvule, oral solution, oral tablet, oral delayed-release capsule, 2005)

2) maintenance, may increase daily dose after several weeks if inadequate response (maximum dose 80 mg daily) OR 90 mg ORALLY once a week (weekly capsule), starting 7 days after after the last daily dose of 20 mg (Prod Info PROZAC(R) oral pulvule, oral solution, oral tablet, oral delayed-release capsule, 2005)

c) Obsessive-compulsive disorder

1) initial, 20 mg ORALLY once daily in the morning (Prod Info PROZAC(R) oral pulvule, oral solution, oral tablet, oral delayed-release capsule, 2005)

2) maintenance, 20-60 mg ORALLY daily (single or divided doses) after several weeks if inadequate response; maximum dose 80 mg daily (Prod Info PROZAC(R) oral pulvule, oral solution, oral tablet, oral delayed-release capsule, 2005)

d) Panic disorder

1) 10 mg ORALLY once daily for 1 week, then increase to 20 mg per day; dosage increases up to 60 mg daily may be considered after several weeks if there is no clinical response (Prod Info PROZAC(R) oral pulvule, oral solution, oral tablet, oral delayed-release capsule, 2005)

e) Premenstrual dysphoric disorder

1) 20 mg ORALLY once daily continuously OR 20 mg ORALLY once daily intermittently (start 14 days prior to the anticipated onset of menstruation and continue daily through the first full day of menses); maximum dosage 80 mg daily (Prod Info SARAFEM(R) Oral Capsule, 2005)

2) Pediatric

a) safety and effectiveness in pediatric patients younger than age 8 (major depressive disorder) and younger than age 7 (obsessive compulsive disorder) have not been established (Prod Info PROZAC(R) oral pulvule, oral solution, oral tablet, oral delayed-release capsule, 2005)

1) Major depressive disorder

a) 8 years and older, 10-20 mg ORALLY once daily (Prod Info PROZAC(R) oral pulvule, oral solution, oral tablet, oral delayed-release capsule, 2005)

2) Obsessive-compulsive disorder

a) adolescents and higher weight children 7 years and older, initiate at 10 mg ORALLY once daily; may increase to 20 mg ORALLY once daily after 2 weeks; recommended dose range, 20-60 mg daily (Prod Info PROZAC(R) oral pulvule, oral solution, oral tablet, oral delayed-release capsule, 2005)

b) lower weight children 7 years and older, initiate at 10 mg ORALLY once daily; may increase dose after several weeks if inadequate response; recommended dose range, 20-30 mg daily (Prod Info PROZAC(R) oral pulvule, oral solution, oral tablet, oral delayed-release capsule, 2005)

3) Contraindications

a) Fluoxetine Hydrochloride

1) concomitant use of monoamine oxidase inhibitors (MAOIs), pimozide, or thioridazine (Prod Info PROZAC(R) delayed-release capsules, oral capsules, solution, 2009)

2) hypersensitivity to fluoxetine or any components of the product (Prod Info PROZAC(R) delayed-release capsules, oral capsules, solution, 2009)

3) use of MAOIs within 5 weeks after fluoxetine discontinuation (Prod Info PROZAC(R) delayed-release capsules, oral capsules, solution, 2009)

4) use of fluoxetine within 14 days of MAOI discontinuation (Prod Info PROZAC(R) delayed-release capsules, oral capsules, solution, 2009)

4) Serious Adverse Effects

a) Fluoxetine Hydrochloride

1) Bleeding

2) Depression, worsening
3) Hyponatremia
4) Mania
5) Prolonged QT interval
6) Seizure
7) Serotonin syndrome
8) Suicidal thoughts

5) Clinical Applications
a) Fluoxetine Hydrochloride
1) FDA Approved Indications
a) Bulimia nervosa
b) Major depressive disorder
c) Obsessive-compulsive disorder
d) Panic disorder
e) Premenstrual dysphoric disorder

1.0 Dosing Information

Drug Properties

Storage and Stability

Adult Dosage

Pediatric Dosage

1.1 Drug Properties

A) Information on specific products and dosage forms can be obtained by referring to the Tradename List (Product Index)
B) Synonyms
Fluoxetine
Fluoxetine HCl
Fluoxetine Hydrochloride
C) Orphan Drug Status
1) Fluoxetine Hydrochloride
a) Fluoxetine has been designated an orphan product for use in the treatment of autism.
D) Physicochemical Properties
1) Fluoxetine Hydrochloride
a) Molecular Weight
1) Fluoxetine: 309.33 (Canada, 1997); Fluoxetine hydrochloride: 345.79 (Canada, 1997; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008)
b) pKa
1) 9.5 (Taddio et al, 1996)
c) Solubility
1) Soluble at 14 mg per mL in water (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008)

1.2 Storage and Stability

A) Fluoxetine Hydrochloride
1) Oral route
a) Capsule/Capsule, Delayed Release/Solution
1) Store at controlled room temperature, between 15 and 30 degrees Celsius (59 to 86 degrees Fahrenheit). Protect from light (Prod Info Sarafem(TM), 2002; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).

1.3 Adult Dosage

Normal Dosage

Dosage in Renal Failure

Dosage in Hepatic Insufficiency

Dosage in Geriatric Patients

Dosage Adjustment During Dialysis

1.3.1 Normal Dosage

Important Note

Fluoxetine

Fluoxetine Hydrochloride

1.3.1.A Important Note

At least 14 days should elapse between the discontinuation of a monoamine oxidase (MAO) inhibitor and the initiation of fluoxetine, and at least 5 weeks should elapse between discontinuation of fluoxetine and initiation of treatment with MAO inhibitors. Cases of serious, sometimes fatal reactions have been reported in patients receiving fluoxetine in combination with an MAO inhibitor, and in patients who have recently discontinued fluoxetine and are then started on an MAO inhibitor. Reactions have been characterized by hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitations progressing to delirium and coma. Some reports resembled cases of neuroleptic malignant syndrome (Prod Info PROZAC(R) oral pulvule, oral solution, oral tablet, oral delayed-release capsule, 2005; Prod Info SARAFEM(R) Oral Capsule, 2005).

1.3.1.B Fluoxetine

1.3.1.B.1 Cataplexy - Narcolepsy

See Drug Consult reference: NARCOLEPSY AND CATAPLEXY - DRUG THERAPY

1.3.1.C Fluoxetine Hydrochloride

Oral route

Tinnitus

1.3.1.C.1 Oral route

Bulimia nervosa

Major depressive disorder

Obsessive-compulsive disorder

Panic disorder

Premenstrual dysphoric disorder

1.3.1.C.1.a Bulimia nervosa

1) The recommended dose for bulimia nervosa is 60 milligrams (mg) once daily, administered in the morning. For some patients, it may be appropriate to titrate up to 60 mg over several days. Studies in which lower doses (ie, 20 mg daily) were used did not demonstrate efficacy. Patients who have responded to fluoxetine 60 mg daily in an 8-week acute treatment phase continued to show benefit for up to 52 weeks in clinical trials. Patients should be periodically reassessed to determine the need for maintenance treatment (Prod Info PROZAC(R) oral pulvule, oral solution, oral tablet, oral delayed-release capsule, 2005).

2) Continued fluoxetine treatment (60 milligrams/day), relative to placebo treatment, was associated with a significant reduction of relapse in patients who had responded acutely to treatment with fluoxetine for bulimia nervosa. The fluoxetine group had fewer relapses in the first 3

months (p less than 0.04). Thereafter, the difference between the groups remained at 14% to 18% but was not statistically significant due to high attrition rates. By the end of 52 weeks, 33% of the fluoxetine group and 51% of the placebo group had relapsed (Romano et al, 2002).

1.3.1.C.1.b Major depressive disorder

1) The recommended starting dose of fluoxetine in patients with major depressive disorder is 20 milligrams (mg) orally once daily, administered in the morning. Studies suggest that doses of 20 mg daily may be sufficient to obtain a satisfactory antidepressant response. If no clinical improvement is observed after several weeks, the dosage can be increased at intervals of several weeks, not to exceed a maximum dose of 80 mg daily. The full effect may be delayed until 4 weeks of treatment or longer. Efficacy has been maintained up to 38 weeks following 12 weeks of treatment with fluoxetine 20 mg daily in clinical trials. Due to the long elimination half lives of both parent drug and metabolites, the full effect of a dosage change may not be observed for several weeks. Doses greater than 20 mg daily may be administered once or twice daily (morning and noon) (Prod Info PROZAC(R) oral pulvule, oral solution, oral tablet, oral delayed-release capsule, 2005).

2) Once weekly dosing of 90 milligrams (mg) enteric-coated capsules was shown to be safe, effective, and well tolerated for the long-term treatment of depression. After responding to 20 mg daily for acute treatment of depression, patients were successfully treated with the once weekly formulation for up to 25 weeks. The weekly dosing should be initiated 7 days after the last daily dose of fluoxetine. It is unknown if weekly dosing provides the same protection from relapse as does daily dosing. If weekly dosing with fluoxetine capsules does not maintain a satisfactory response, consider reestablishing daily dosing (Prod Info PROZAC(R) oral pulvule, oral solution, oral tablet, oral delayed-release capsule, 2005; Schmidt et al, 2000).

Weekly dosage	Daily dosage equivalent
90 mg	12.8 mg
180 mg	25.6 mg
270 mg	38.4 mg
360 mg	51.2 mg
540 mg	76.8 mg

(Buongiorno et al, 2002)

3) Results of a randomized double-blind study demonstrated that continuation phase treatments of major depressive disorder (MDD) with fluoxetine 20 milligrams (mg) per day (n=21), 60 mg/week (n=28), or placebo (n=21) did not differ in their ability to affect the Hamilton Rating Scale for Depression (HAM-D) (Burke et al, 2000). One hundred fourteen subjects with a diagnosis of unipolar MDD and a HAM-D score of greater than or equal to 18 were enrolled in an open label trial. After 7 weeks of open label therapy with fluoxetine 20 mg/day, subjects with HAM-D scores of 12 or less were enrolled in the double blind study. Seventy subjects were randomized to receive continuation phase therapy for 7 weeks. Repeat measures of HAM-D scores and blood levels of fluoxetine and norfluoxetine showed no group effects in the open label study. Similar results were demonstrated during double- blind therapy. No significant differences in drop out rates were observed across treatment groups. No significant correlations between HAM-D scores and serum concentrations of fluoxetine or norfluoxetine were demonstrated at randomization or at the end of the double-blind study. The authors suggest that weekly dosing is well tolerated and possibly as effective as daily dosing for maintenance of MDD treatment response.

4) Some clinical trials have utilized doses of fluoxetine in the treatment of depression of 60 to 80 milligrams orally daily, either as a single daily dose or in divided doses twice a day to three times a day. However, many patients respond adequately to doses of 20 or 40 milligrams daily (Stark & Hardison, 1985b; Fabre & Crismon, 1985a; Cohn & Wilcox, 1985b; Bremner, 1984c; Chouinard, 1985c). Many of the early clinical trials used protocols that required titration of the fluoxetine dose from 20 milligrams/day to 80 milligrams/day within 2 weeks. The adverse effect profile of fluoxetine suggests that a dose-dependent relationship exists. A more recent multicenter study utilized daily fluoxetine doses of 20 milligrams, 40 milligrams and 60 milligrams without titration (Wernicke et al, 1987). The 3 fixed-dose regimens were equally effective in controlling depression and the 2 lower dose regimens resulted in fewer patient withdrawals due to adverse effects. In a similar trial utilizing daily fluoxetine doses of 5 milligrams, 20 milligrams, and 40 milligrams, it was found that endpoint and weekly analyses of outcome variables resulted in a flat dose-response curve and superiority of all doses compared to placebo (Wernicke et al, 1987). There were differences seen on individual measures: the 5-milligram dose was superior in improving the HAM-D Sleep Disturbance factor; the 20-milligram dose was superior on the CGI severity scale; and the 40-milligram dose was more effective in improving the HAM-D Retardation factor. However, these latter differences appeared dose related; statistical analyses to support stronger conclusions were not presented. A later trial identified patients without significant response within three weeks of initiation of fluoxetine 20 milligrams/day (Dornseif et al, 1989); these patients were randomized to further treatment with 20 milligrams/day or 60 milligrams/day on a double-blind basis. Although the 60-milligram dose provided greater improvements on some measures, the differences were considered of little clinical significance and should be weighed against higher discontinuation rates and more frequent reports

of adverse events (diarrhea and abdominal pain). Further analyses of the dose-response relationship have been provided and suggest that 5 mg and 60 mg per day, respectively, are the lower and upper ends of the therapeutic range for fluoxetine (Beasley et al, 1990).
5) Beneficial effects have been observed in patients receiving fluoxetine 5 milligrams(mg)/day for depression or panic disorder (Louie et al, 1993). However, the majority of patients treated for depression respond to fluoxetine 20 to 30 mg/day (Altamura et al, 1988); (Fabre & Putnam, 1987). The dosage range for fluoxetine is 20 to 80 mg/day (Benfield et al, 1986). The effectiveness of fluoxetine 40, 60, or 80 mg is similar whether doses are administered once or twice daily (Rickels et al, 1985).
6) A trial addressing the optimal length of continuation therapy in depression suggested that therapy with fluoxetine should be continued at least 26 weeks to prevent relapse, after an initial 12 weeks of acute treatment with fluoxetine (Reimherr et al, 1998).

1.3.1.C.1.c Obsessive-compulsive disorder

1) The recommended starting dose of fluoxetine in patients with obsessive-compulsive disorder (OCD) is 20 milligrams (mg) orally once daily, administered in the morning. If a sufficient clinical response is not observed after several weeks, the dose may be increased. The full effect may be delayed until 5 weeks of treatment or longer. The recommended dose range of fluoxetine for treatment of OCD is 20 mg to 60 mg daily. The maximum dose of fluoxetine is 80 mg daily. Due to the long elimination half lives of both parent drug and metabolites, the full effect of a dosage change may not be observed for several weeks. Doses greater than 20 mg daily may be administered once or twice daily (morning and noon) (Prod Info PROZAC(R) oral pulvule, oral solution, oral tablet, oral delayed-release capsule, 2005).
2) Efficacy of fluoxetine after 13 weeks of therapy for obsessive-compulsive disorder has not been documented in clinical trials. Patients have been continued for up to an additional 6 months without loss of benefit. Dosage adjustments should be made to maintain the patient on the lowest effective dosage. Patients should be periodically reassessed to determine the need for treatment (Prod Info PROZAC(R) oral pulvule, oral solution, oral tablet, oral delayed-release capsule, 2005).

1.3.1.C.1.d Panic disorder

1) The recommended starting dose of fluoxetine for the treatment of panic disorder is 10 milligrams (mg) orally once per day. After 1 week the dose should be increased to 20 mg daily. Dosage increases up to 60 mg daily may be considered after several weeks if there is no clinical response. In 2 clinical trials, most patients received 20 mg daily. Doses above 60 mg per day have not been evaluated. Due to the long elimination half lives of both parent drug and metabolites, the full effect of a dosage change may not be observed for several weeks. Patients should be periodically reassessed to determine the need for continued treatment (Prod Info PROZAC(R) oral pulvule, oral solution, oral tablet, oral delayed-release capsule, 2005).
2) Fluoxetine in doses up to 80 milligrams daily was reported effective in the treatment of panic attacks in 7 of 16 patients in an open study (Gorman et al, 1987a). Mean doses in the responding patients were 27 milligrams daily (range, 10 to 70 milligrams daily).

1.3.1.C.1.e Premenstrual dysphoric disorder

1) The starting dose of fluoxetine (Sarafem(R)) in patients with premenstrual dysphoric disorder (PMDD) is 20 milligrams (mg) orally once daily given either continuously or on an intermittent schedule (initiate 14 days prior to the anticipated onset of menstruation and continue daily through first full day of menses and then repeating with each new cycle). Doses of 60 mg daily are also effective, however, no significant added benefit compared to 20 mg daily is obtained. Due to the long elimination half lives of both parent drug and metabolites, the full effect of a dosage change may not be observed for several weeks. Efficacy has been demonstrated for up to 6 months with continuous dosing and for 3 months with intermittent dosing. Reevaluate patients periodically to determine the need for continued treatment. The maximum dose should not exceed 80 mg daily (Prod Info SARAFEM(R) Oral Capsule, 2005).

1.3.1.C.2 Tinnitus

See Drug Consult reference: DRUG THERAPY OF TINNITUS

1.3.1.C.3 MAXIMUM DOSE

a) The maximum dose of fluoxetine is 80 milligrams per day (Prod Info PROZAC(R) oral pulvule, oral solution, oral tablet, oral delayed-release capsule, 2005; Prod Info SARAFEM(R) Oral Capsule, 2005).

1.3.2 Dosage in Renal Failure

A) Fluoxetine Hydrochloride

1) Dosage adjustments for renal impairment are not routinely necessary (Prod Info PROZAC(R) oral pulvule, oral solution, oral tablet, oral delayed-release capsule, 2005; Prod Info SARAFEM(R) Oral Capsule, 2005).
2) Only 2.5% to 5% of an oral dose of fluoxetine is excreted unchanged in the urine, with 10% appearing as the active metabolite (norfluoxetine). Studies have demonstrated no correlation between the degree of renal dysfunction and the rate of elimination, volume of distribution, or protein binding of fluoxetine when given in

single doses (Aronoff et al, 1984b; Lemberger et al, 1985b).

1.3.3 Dosage in Hepatic Insufficiency

A) Fluoxetine Hydrochloride

1) Fluoxetine is metabolized in the liver (Lemberger et al, 1985b) and dosing adjustments may be required in hepatic disease. A lower dose or less frequent dosage schedule is recommended with fluoxetine in patients with hepatic insufficiency (Prod Info PROZAC(R) oral pulvule, oral solution, oral tablet, oral delayed-release capsule, 2005; Prod Info SARAFEM(R) Oral Capsule, 2005).

2) A significant reduction in plasma clearance and an increase in the elimination half-life of fluoxetine were observed in stable alcoholic cirrhosis patients (Schenker et al, 1988a). The formation of norfluoxetine was also decreased, and its clearance reduced, in these patients compared to normal volunteers. It is recommended that a lower or less frequent dose of fluoxetine be given to patients with cirrhosis; in patients with compensated cirrhosis (without ascites), an approximately 50% reduction is suggested; whereas patients with decompensated cirrhosis may require greater adjustments in dosage, due to the possibility of a greater reduction in the rate of fluoxetine elimination.

1.3.4 Dosage in Geriatric Patients

A) Fluoxetine Hydrochloride

1) A lower dose or less frequent dosage schedule is recommended with fluoxetine in elderly patients (Prod Info PROZAC(R) oral pulvule, oral solution, oral tablet, oral delayed-release capsule, 2005).

1.3.5 Dosage Adjustment During Dialysis

A) Fluoxetine Hydrochloride

1) Fluoxetine 20 milligrams once daily for 2 months, administered to patients with depression and on dialysis (n=12), produced steady-state fluoxetine and norfluoxetine plasma concentrations that were comparable to those found in patients with normal renal function. While it is possible that renally excreted metabolites may accumulate in patients with severe renal dysfunction, dose reduction is usually not necessary in patients with renal impairment (Prod Info PROZAC(R) oral pulvule, oral solution, oral tablet, oral delayed-release capsule, 2005; Prod Info SARAFEM(R) Oral Capsule, 2005).

2) The large volume of distribution for fluoxetine and norfluoxetine (over 1,000 liters) and fluoxetine's high plasma protein binding (94%) suggest a low degree of clearance by extracorporeal extraction. Plasma levels of fluoxetine and its active metabolite (norfluoxetine) were not affected significantly by hemodialysis and indicated that dosing adjustments are not required in this setting (Aronoff et al, 1984b).

1.4 Pediatric Dosage

1.4.1 Normal Dosage

1.4.1.A Important Note

At least 14 days should elapse between the discontinuation of a monoamine oxidase (MAO) inhibitor and the initiation of fluoxetine, and at least 5 weeks should elapse between discontinuation of fluoxetine and initiation of treatment with MAO inhibitors. Cases of serious, sometimes fatal reactions have been reported in patients receiving fluoxetine in combination with an MAO inhibitor, and in patients who have recently discontinued fluoxetine and are then started on an MAO inhibitor. Reactions have been characterized by hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitations progressing to delirium and coma. Some reports resembled cases of neuroleptic malignant syndrome (Prod Info PROZAC(R) oral pulvule, oral solution, oral tablet, oral delayed-release capsule, 2005; Prod Info SARAFEM(R) Oral Capsule, 2005).

1.4.1.B Fluoxetine

1.4.1.B.1 Anorexia nervosa
See Drug Consult reference: ANOREXIA NERVOSA - DRUG THERAPY

1.4.1.C Fluoxetine Hydrochloride

1.4.1.C.1 Oral route

Major depressive disorder

Obsessive-compulsive disorder

1.4.1.C.1.a Major depressive disorder
1) The recommended initial dose of fluoxetine for the treatment of major depressive disorder in adolescents and children, 8 years and older, is 10 or 20 milligrams (mg) orally once daily. If starting at 10 mg daily, the dose should be increased to 20 mg daily after 1 week. For lower weight children, the starting and target dose may be 10 mg daily due to higher plasma levels. If sufficient clinical improvement is not observed after several weeks, a dose increase to 20 mg daily may be considered. The full effect may be delayed until 4 weeks of treatment or longer. Due to the long elimination half lives of both parent drug and metabolites, the full effect of a dosage change may not be observed for several weeks (Prod Info PROZAC(R) oral pulvule, oral solution, oral tablet, oral delayed-release capsule, 2005).

1.4.1.C.1.b Obsessive-compulsive disorder
1) The recommended initial dose of fluoxetine for the treatment of obsessive-compulsive disorder in adolescents and higher weight children (7 years and older) is 10 milligrams (mg) orally once daily. The dose should be increased to 20 mg daily after 2 weeks. If sufficient clinical response is not observed after several weeks, the dose may be increased further. Due to the long elimination half lives of both parent drug and metabolites, the full effect of a dosage change may not be observed for several weeks. The recommended dose range is 20 mg to 60 mg daily (Prod Info PROZAC(R) oral pulvule, oral solution, oral tablet, oral delayed-release capsule, 2005).
2) For lower weight children (7 years and older), the recommended starting dose of fluoxetine in the treatment of obsessive-compulsive disorder is 10 milligrams (mg) orally once daily. If sufficient clinical response is not observed after several weeks, the dose may be increased further. Due to the long elimination half lives of both parent drug and metabolites, the full effect of a dosage change may not be observed for several weeks. The recommended dose range is 20 mg to 30 mg daily (Prod Info PROZAC(R) oral pulvule, oral solution, oral tablet, oral delayed-release capsule, 2005).

1.4.2 Dosage in Renal Failure
A) Fluoxetine Hydrochloride
1) Dosage adjustments for renal impairment are not routinely necessary (Prod Info PROZAC(R) oral pulvule, oral solution, oral tablet, oral delayed-release capsule, 2005).

1.4.3 Dosage in Hepatic Insufficiency
A) Fluoxetine Hydrochloride
1) A lower dose or less frequent dosage schedule is recommended with fluoxetine in patients with hepatic insufficiency (Prod Info PROZAC(R) oral pulvule, oral solution, oral tablet, oral delayed-release capsule, 2005).

1.4.4 Dosage Adjustment During Dialysis
A) Fluoxetine Hydrochloride
1) Fluoxetine 20 milligrams once daily for 2 months, administered to patients with depression and on dialysis (n=12), produced steady-state fluoxetine and norfluoxetine plasma concentrations that were comparable to those found in patients with normal renal function. While it is possible that renally excreted metabolites may accumulate in patients with severe renal dysfunction, dose reduction is usually not necessary in patients with renal impairment (Prod Info PROZAC(R) oral pulvule, oral solution, oral tablet, oral delayed-release capsule, 2005).

2.0 Pharmacokinetics

Onset and Duration

Drug Concentration Levels

ADME

2.1 Onset and Duration

A) Onset

1) Initial Response

a) Depression, regular release: 1 to 2 weeks (Chouinard, 1985; Cohn & Wilcox, 1985c; Bremner, 1984).

2) Peak Response

a) Depression, regular release: 4 weeks (Prod Info Prozac(R), 2003b).

b) Obsessive compulsive disorder, regular release: 5 weeks or longer (Prod Info Prozac(R), 2003b).

2.2 Drug Concentration Levels

A) Time to Peak Concentration

1) Oral, regular release: 6 to 8 hours (Saletu & Grunberger, 1985; Lemberger et al, 1985a; Aronoff et al, 1984a; Lemberger et al, 1978).

a) Mean plasma concentrations were 477 ng/mL for fluoxetine and 393 ng/mL for the active metabolite, norfluoxetine, after fluoxetine 60 mg was taken for 5 weeks. These concentrations were associated with therapeutic benefit in depressed patients (Chouinard, 1985). Corresponding plasma concentrations in patients receiving fluoxetine 80 mg daily were 698 ng/mL and 421 ng/mL (norfluoxetine), respectively (Feighner & Cohn, 1985b).

B) PEAK AND TROUGH FLUCTUATIONS

1) Increased fluctuation of peak and trough concentrations resulted from 90 milligrams weekly dosing when compared to 20 mg daily dosing. Peak concentrations from the weekly dosing are within the average concentration range for the 20 mg dosing. Trough concentrations of fluoxetine and norfluoxetine are lower by 76% and 47%, respectively. Average steady state concentrations are 50% lower with weekly dosing than with daily dosing (Prod Info Prozac(R), 2003b).

2.3 ADME

Absorption

Distribution

Metabolism

Excretion

Elimination Half-life

Extracorporeal Elimination

2.3.1 Absorption

A) Bioavailability

1) Oral, regular release: 100% (Lemberger et al, 1985a).

2) The enteric-coated weekly formulation, pulvules, tablets, and oral solution are bioequivalent (Prod Info Prozac(R), 2003b).

3) The weekly formulation resists dissolution until the pH is greater than 5.5. Therefore, absorption is delayed 1-2 hours compared to immediate release formulations (Prod Info Prozac(R), 2003b).

B) Effects of Food

1) clinically insignificant (Lemberger et al, 1985a).

a) The absorption of fluoxetine is delayed but not decreased in the presence of food (Lemberger et al, 1985a).

2.3.2 Distribution

A) Distribution Sites

1) Protein Binding

a) 94.5% (Prod Info Prozac(R), 2003b; Lemberger et al, 1985a; Aronoff et al, 1984a).

1) Fluoxetine is bound to albumin and alpha-1-glycoprotein; protein binding is NOT altered in patients with renal failure (Prod Info Prozac(R), 2003b; Lemberger et al, 1985a; Aronoff et al, 1984a).

B) Distribution Kinetics

1) Volume of Distribution
a) 1000 to 7200 L (Aronoff et al, 1984a).
1) The corresponding volume of distribution for norfluoxetine ranged from 700 to 5,700 L. No relationship between the volume of distribution of fluoxetine or its metabolite and renal function has been observed (Aronoff et al, 1984a).

2.3.3 Metabolism

A) Metabolism Sites and Kinetics
1) Liver, extensive (Prod Info Prozac(R), 2003b; Aronoff et al, 1984a).
a) Fluoxetine is metabolized primarily via N-demethylation to the active metabolite, norfluoxetine (Lemberger et al, 1985a; Aronoff et al, 1984a). Glucuronide conjugates are also found but in small quantities (Lemberger et al, 1985a).
b) Extensive metabolizers with respect to cytochrome P450 2C19 (CYP2C19) showed lower maximum levels of fluoxetine (p less than 0.001) and higher levels of norfluoxetine (p less than 0.001) after a 40 milligram dose of fluoxetine than did poor metabolizers with the CYP2C19*2 or CYP2C19*3 mutation. Oral clearance by poor metabolizers was 55% lower than oral clearance by extensive metabolizers (p less than 0.001) (Liu et al, 2001).
B) Metabolites
1) Norfluoxetine, active (Aronoff et al, 1984a; Fuller et al, 1977).
a) Norfluoxetine has similar pharmacologic activity to the parent compound (Lemberger et al, 1985a).
2) Glucuronide metabolites (Lemberger et al, 1985a).

2.3.4 Excretion

A) Kidney
1) Renal Excretion (%)
a) 60% (Lemberger et al, 1985a).
2) Only 2.5 to 5.0% of an oral dose is recovered as unchanged drug; 10% is excreted as free norfluoxetine (Lemberger et al, 1985a; Aronoff et al, 1984a). Conjugated metabolites, fluoxetine glucuronide and norfluoxetine glucuronide, represent 5.2% and 9.5% of a dose, respectively (Lemberger et al, 1985a).
B) Other
1) OTHER EXCRETION
a) Feces, 12% (Lemberger et al, 1985a).

2.3.5 Elimination Half-life

A) Parent Compound
1) ELIMINATION HALF-LIFE
a) 4 to 6 days, chronic administration (Prod Info Sarafem(TM), 2002a; Prod Info Prozac(R), 2003b; Lemberger et al, 1985a).
1) Following acute administration, the elimination half-life of fluoxetine is 1 to 3 days (Prod Info Prozac(R), 2003b; Prod Info Sarafem(TM), 2002a).
2) The mean half-life of fluoxetine among extensive metabolizers with respect to cytochrome P450 2C19 (CYP2C19) was about 28 hours, whereas, among poor metabolizers with the CYP2C19*2 or CYP2C19*3 mutation, mean half-life was 62 hours (Liu et al, 2001).
3) A mean elimination half-life of 3.6 days was reported in normal subjects (range, 1 to 13 days) compared to 1.75 days in hemodialysis patients (Aronoff et al, 1984a).
B) Metabolites
1) Norfluoxetine, 4 to 16 days (Prod Info Prozac(R), 2003b; Lemberger et al, 1985a; Nash et al, 1982).

2.3.6 Extracorporeal Elimination

A) Hemodialysis
1) Dialyzable: No (Aronoff et al, 1984a).
a) Fluoxetine and norfluoxetine are not removed to a significant degree by hemodialysis (Aronoff et al, 1984a).

3.0 Cautions

Contraindications

Precautions

Adverse Reactions

Teratogenicity/Effects in Pregnancy/Breastfeeding

Drug Interactions

3.0.A Black Box WARNING

1) Fluoxetine Hydrochloride

a) Oral (Capsule; Capsule, Delayed Release; Solution)

1) Suicidality and Antidepressant Drugs - Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of fluoxetine hydrochloride or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Fluoxetine hydrochloride is approved for use in pediatric patients with MDD and obsessive compulsive disorder (OCD) (Prod Info PROZAC(R) delayed-release capsules, oral capsules, solution, 2009).

b) Oral (Tablet)

1) Suicidality and Antidepressant Drugs - Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of fluoxetine hydrochloride or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Patients who are started on antidepressant therapy should be observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. SARAFEM(R) is not approved for use in pediatric patients.

2) Pooled analyses of short-term (4 to 16 weeks) placebo-contolled trials of 9 antidepressant drugs (SSRIs and others) in children and adolescents with major depressive disorder (MDD), obsessive compulsive disorder (OCD), or other psychiatric disorders (a total of 24 trials involving over 4400 patients) have revealed a greater risk of adverse events representing suicidal thinking or behavior (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%. No suicides occurred in these trials (Prod Info SARAFEM(R) oral tablets, 2007).

3.1 Contraindications

A) Fluoxetine Hydrochloride

1) concomitant use of monoamine oxidase inhibitors (MAOIs), pimozide, or thioridazine (Prod Info PROZAC(R) delayed-release capsules, oral capsules, solution, 2009)

2) hypersensitivity to fluoxetine or any components of the product (Prod Info PROZAC(R) delayed-release capsules, oral capsules, solution, 2009)

3) use of MAOIs within 5 weeks after fluoxetine discontinuation (Prod Info PROZAC(R) delayed-release capsules, oral capsules, solution, 2009)

4) use of fluoxetine within 14 days of MAOI discontinuation (Prod Info PROZAC(R) delayed-release capsules, oral capsules, solution, 2009)

3.2 Precautions

A) Fluoxetine Hydrochloride

1) suicidal ideation and behavior or worsening depression; increased risk, particularly in children, adolescents, and young adults with major depressive disorder during the first few months of therapy or following changes in dosage (Prod Info PROZAC(R) delayed-release capsules, oral capsules, solution, 2009)

2) abrupt withdrawal; serious discontinuation symptoms have been reported (Prod Info PROZAC(R) delayed-release capsules, oral capsules, solution, 2009)

3) allergic reactions, including anaphylaxis, angioedema, and erythema multiforme have been reported; in the case of rash, or other possibly allergic symptoms for which an alternative etiology cannot be identified, discontinue therapy (Prod Info PROZAC(R) delayed-release capsules, oral capsules, solution, 2009)

4) bipolar disorder; increased risk of precipitation of a mixed/manic episode with antidepressant treatment only (Prod Info PROZAC(R) delayed-release capsules, oral capsules, solution, 2009)

5) concomitant use of NSAIDs, aspirin, or other drugs that affect coagulation; abnormal bleeding, particularly the gastrointestinal tract, may occur (Prod Info PROZAC(R) delayed-release capsules, oral capsules, solution, 2009)

6) concomitant serotonergic drug use (serotonin precursors (tryptophan), SSRIs, serotonin-norepinephrine reuptake inhibitors); risk of serotonin syndrome, use is not recommended(Prod Info PROZAC(R) delayed-release capsules, oral capsules, solution, 2009)

7) concomitant use of thioridazine; risk of serious ventricular arrhythmias and sudden death (Prod Info PROZAC (R) delayed-release capsules, oral capsules, solution, 2009)

8) diabetes, history of; increased risk of hypoglycemia (Prod Info PROZAC(R) delayed-release capsules, oral capsules, solution, 2009)

9) cirrhosis of the liver; risk of drug toxicity (Prod Info PROZAC(R) delayed-release capsules, oral capsules, solution, 2009)

10) seizures, history of (Prod Info PROZAC(R) delayed-release capsules, oral capsules, solution, 2009)

11) serotonin syndrome and neuroleptic malignant syndrome-like reactions (serotonin syndrome in its most severe form), have been reported with fluoxetine therapy alone (Prod Info PROZAC(R) delayed-release capsules, oral capsules, solution, 2009)
12) volume-depleted, elderly, or concurrent diuretic therapy; hyponatremia, syndrome of inappropriate antidiuretic hormone secretion (SIADH) has occurred with fluoxetine (Prod Info PROZAC(R) delayed-release capsules, oral capsules, solution, 2009)

3.3 Adverse Reactions

Cardiovascular Effects

Dermatologic Effects

Endocrine/Metabolic Effects

Gastrointestinal Effects

Hematologic Effects

Hepatic Effects

Musculoskeletal Effects

Neurologic Effects

Ophthalmic Effects

Psychiatric Effects

Renal Effects

Reproductive Effects

Respiratory Effects

Other

3.3.1 Cardiovascular Effects

3.3.1.A Fluoxetine Hydrochloride

Abnormal ECG

Bradyarrhythmia

Heart failure

Hypertension

Prolonged QT interval

Tachyarrhythmia

Vasculitis

3.3.1.A.1 Abnormal ECG

a) Cardiovascular side effects reported during treatment with fluoxetine included QT prolongation (Prod Info Prozac(R), 2003c);(Prod Info Sarafem(R), 2001)(Varriale, 2001b; Feighner, 1985a; Wernicke, 1985). ECGs of patients taking fluoxetine showed none of the prolongation of PR and QRS intervals seen with the tricyclics. Fluoxetine in therapeutic doses had no significant clinical effect on the ECG (Fisch, 1985).
b) One group of authors reported that 3 elderly female patients, with underlying life-threatening pulmonary and cardiac disorders, died of cardiac dysrhythmias within 10 days of beginning fluoxetine treatment. A clear relationship between the death of these patients and the start of fluoxetine therapy was not established (Spier & Frontera, 1991).
c) Fluoxetine 40 to 80 mg daily produced reductions in mean heart rate, as compared to significant increases in heart rate with imipramine and amitriptyline in doses of 150 to 300 mg daily. In this study, doxepin produced increases in heart rate which were not considered significant. No other significant clinical effects on the EKG were observed in this series of 312 fluoxetine-treated patients; however, significant increases in the QT and QRS interval were observed with other antidepressants. Intraventricular conduction delays were observed in 5 patients receiving imipramine and in one patient receiving amitriptyline, with 4 of these patients developing left bundle branch block. No Intraventricular conduction defects were observed in fluoxetine-treated patients (Fisch, 1985).

3.3.1.A.2 Bradyarrhythmia

a) One paper reported a case of bradycardia in an elderly woman treated with 20 mg fluoxetine per day (Buff et al, 1991). One report suggested that these effects are dose-related and therefore the fluoxetine dosage should be reduced in the elderly or patients with a history of cardiac problems (Friedman, 1991).

3.3.1.A.3 Heart failure

a) In a large cohort study including 481,744 persons and 1487 cases of sudden cardiac death occurring in a community setting, the use of SSRIs was not associated with an increased risk of sudden cardiac death (rate ratio, 0.95; 95% CI, 0.42 to 2.15). In contrast, users of tricyclic antidepressants in doses of 100 mg or higher (amitriptyline or equivalent) had a 41% increased rate of sudden cardiac death (rate ratio, 1.41; 95% CI, 1.02 to 1.95) (Ray et al, 2004).

3.3.1.A.4 Hypertension

a) Of 796 patients treated with fluoxetine 20 mg daily in an open trial, 1.7% developed sustained hypertension, and 2.2% developed treatment-emergent hypertension. Patients with controlled hypertension were included if the sitting diastolic blood pressure (BP) was less than or equal to 95 mmHg. At week 12, the change in mean sitting and standing systolic BP was -2.9 and -2.6 mmHg, respectively. Changes in mean diastolic BP were similar with a 2.3 mmHg (sitting) and 1.5 mmHg (standing) decrease at 12 weeks (Amsterdam et al, 1999).
b) In a 7-week, open study, patients treated with fluoxetine who had preexisting cardiovascular disease had fewer cardiovascular side effects than patients treated with nortriptyline. Twenty-seven (8 left the study) received fluoxetine 20 to 60 mg daily. Seven patients were treated with nortriptyline but the majority of data was retrieved from historical controls. Fluoxetine decreased heart rate by 6% and increased supine blood pressure by 2%. Patients with a baseline ejection fraction less than 50% showed a 7% increase during treatment with fluoxetine. Patients with a prolonged QRS interval or ventricular premature depolarizations were not adversely effected by fluoxetine treatment. Conversely, nortriptyline increased diastolic supine blood pressure by 4%, decreased standing systolic blood pressure by 5%, increased the orthostatic blood pressure drop by 3-fold, increased heart rate by 9%, decreased ejection fraction by 7%, and decreased the frequency of ventricular premature depolarization by 47%. Since conclusions are limited by the small sample, open design, and use of historical controls, treatment of depression in this group of patients must be undertaken with careful monitoring and slow dose titration until more data are available (Roose et al, 1998).

3.3.1.A.5 Prolonged QT interval

a) QT prolongation was observed on the electrocardiogram (ECG) of a 52-year-old man who had been taking fluoxetine (20 mg/day for 2 weeks, followed by 40 mg/day thereafter) for depression for 3 months. An ECG just before the start of fluoxetine treatment showed a normal QT interval. The QT interval returned to normal within 10 days of discontinuing fluoxetine treatment (Varriale, 2001c).
b) A 74-year-old woman developed syncope and torsade de pointes requiring cardioversion 3 weeks after being switched from amitriptyline to fluoxetine. ECG revealed QTc prolongation. Symptoms stopped when fluoxetine was discontinued but the ECG was not repeated (Appleby et al, 1995).
c) Cardiovascular side effects reported during treatment with fluoxetine included QT prolongation (Prod Info Prozac(R), 2003c);(Prod Info Sarafem(R), 2001)(Varriale, 2001b; Feighner, 1985a; Wernicke, 1985)

3.3.1.A.6 Tachyarrhythmia

a) A 55-year-old woman developed supraventricular tachycardia on her fifty-second day of taking fluoxetine 20 mg/day. She was concomitantly taking trimethoprim and sulfamethoxazole. She had a history of supraventricular tachycardia, but this episode was more pronounced and of longer duration

than previous ones. Sinus rhythm was restored with verapamil. Treatment for depression was changed to moclobemide, after which she had only one other episode of tachycardia. The authors concluded that a causal relationship could not be established; however, fluoxetine treatment seemed to exacerbate the underlying condition (Allhoff et al, 2001).
b) Supraventricular tachycardia and hypotension were associated with maintenance therapy with fluoxetine 20 mg daily in a 54-year-old woman. Cardiac symptoms and palpitations have not recurred in 25 months of follow-up. The patient received verapamil initially, which was discontinued 6 weeks later (Gardner et al, 1991).

3.3.1.A.7 Vasculitis

a) An 83-year-old woman developed pain, swelling and tenderness of her arms with malaise, lethargy, nausea, and vomiting 3 days after beginning fluoxetine therapy. Muscle biopsy showed acute myositis and extensive muscle infarction. Fluoxetine was discontinued and the patient died suddenly on the seventh hospital day of a ruptured abdominal aortic aneurysm. Postmortem muscle biopsy showed muscle necrosis and necrotizing vasculitis of the small and medium sized arteries (Fisher et al, 1999).

3.3.2 Dermatologic Effects

3.3.2.A Fluoxetine Hydrochloride

Bullous pemphigoid

Diaphoresis

Rash

3.3.2.A.1 Bullous pemphigoid

a) Bullous pemphigoid developed approximately 2 months after fluoxetine was started in a 75-year-old woman. This woman was admitted to the hospital for treatment of tense blisters located on the abdomen, thighs, and arms. The blisters were accompanied by red skin and intense pruritus. Skin biopsy confirmed the diagnosis of bullous pemphigoid. Fluoxetine was stopped, and the lesions cleared over 3 weeks without any topical or systemic corticosteroid treatment. From the case report, the patient was receiving several other medications, and it was unclear as to whether these medications were also continued (Rault et al, 1999).

3.3.2.A.2 Diaphoresis

a) Excessive sweating has been reported in association with fluoxetine in up to 30% of patients (Cohn & Wilcox, 1985a; Wernicke, 1985; Feighner & Cohn, 1985a; Rickels et al, 1985). Sweating appeared in fewer patients treated with fluoxetine than imipramine; however, fluoxetine was associated with a higher incidence of sweating than placebo (Cohn & Wilcox, 1985a; Wernicke, 1985; Stark & Hardison, 1985a).

3.3.2.A.3 Rash

a) Incidence: 7% (Prod Info Prozac(R), 2003c)
b) During clinical trials in the United States, 7% of patients developed rash and/or urticaria. Other clinical findings reported with the rash included fever, leukocytosis, arthralgias, edema, carpal tunnel syndrome, respiratory distress, lymphadenopathy, proteinuria, and mild elevations in transaminases. In about a third of the patients, fluoxetine was stopped. Most patients improved quickly although some were treated with antihistamines or steroids (Prod Info Prozac(R), 2003c; Wernicke, 1985). One case of erythema multiforme was also reported (Prod Info Prozac(R), 2003c).

3.3.3 Endocrine/Metabolic Effects

3.3.3.A Fluoxetine Hydrochloride

Galactorrhea

Hypertriglyceridemia

Hypoglycemia

Hyponatremia

Syndrome of inappropriate antidiuretic hormone secretion

Syndrome of inappropriate antidiuretic hormone secretion, and concurrent serotonin syndrome

Weight change finding

3.3.3.A.1 Galactorrhea

a) Summary

1) Before fluoxetine was commercially available, galactorrhea occurred in 4 of 5920 patients (0.07%); during postmarketing surveillance, 204 cases of galactorrhea were reported in an estimated 3.4 million patients treated with fluoxetine. The probable mechanism for SSRI-induced galactorrhea is an increase in serum prolactin. This may result from direct stimulation of postsynaptic serotonin receptors in the hypothalamus or presynaptic serotonin receptor mediated inhibition of dopamine release (Bronzo & Stahl, 1993).

b) Over a 10-year period, the Netherlands Pharmacovigilance Foundation received 38 reports of nonpuerperal lactation related to medications of which 15 cases were attributed to antidepressants primarily the SSRIs. The odds ratio for the risk of galactorrhea due to all antidepressants versus other medications was 8.3 (95% CI, 4.3 to 16.1). The odds ratio for SSRIs was 12.7 (95% CI, 6.4 to 25.4) versus 1.6 (95% CI, 0.2 to 11.6) for other antidepressants. Of the 15 reports attributed to antidepressants, 5, 4, and 4 were related to fluvoxamine, fluoxetine, and paroxetine, respectively. Women developing galactorrhea were significantly younger (mean age, 33 years) than women without galactorrhea (mean age, 51 years). Galactorrhea developed from 2 weeks to 2 years after starting the SSRI. In all cases, galactorrhea resolved with continuation of the SSRI, a reduction in the dose, or discontinuation of the SSRI. Several patients were taking other medications, which have caused galactorrhea, concurrently with the SSRI but galactorrhea only developed after adding the SSRI. While this is not a serious adverse reaction, increased awareness may prevent unnecessary diagnostic procedures (Bronzo & Stahl, 1993).

c) A case of galactorrhea with hyperprolactinemia was reported in a 17-year-old girl treated with fluoxetine. The dosage of fluoxetine was titrated to 60 mg daily. Two weeks after treatment began, she developed galactorrhea. The serum prolactin level was 50 mcg/L was noted. When the dose of fluoxetine was decreased to 40 mg daily, galactorrhea resolved and prolactin levels returned to normal. Fluoxetine was continued without further adverse events (Iancu et al, 1992).

3.3.3.A.2 Hypertriglyceridemia

a) A 42-year-old man with social phobia associated with panic attacks, agoraphobia, and depressive disorder developed hypertriglyceridemia when treated separately with fluoxetine and extended-release venlafaxine. He was given alprazolam 0.25 mg up to 3 times daily and fluoxetine, increasing over one week to 20 mg/day. Alprazolam was tapered thereafter. Five months later, he reported 80% to 90% benefit in symptoms. A nonfasting lipid panel before initiation of treatment had shown slightly elevated triglycerides (261 mg/dL), cholesterol, and cholesterol-to-HDL ratio. Therefore his lipid profile was reexamined 7 months later. At that time, triglycerides were highly elevated (over 600 mg/dL). Fluoxetine was discontinued and venlafaxine extended-release was begun 2 weeks later. One month later, the man reported symptom remission to be 85% of that with fluoxetine. The lipid profile was again measured, showing a further increase in triglycerides to more than 1000 mg/dL. Venlafaxine was discontinued over 10 days and replaced by alprazolam only. Two weeks later, his triglyceride level was reduced to 154 mg/dL; cholesterol and cholesterol-to-HDL ratio remained somewhat elevated as they had been initially. The author suggested that lipid profiles should be monitored during treatment with venlafaxine or SSRIs (Teitelbaum, 2001).

3.3.3.A.3 Hypoglycemia

a) Hypoglycemia has infrequently been associated with fluoxetine use (Prod Info Prozac(R), 2003c).

b) A 17-year-old male with a 2-year history of type 1 diabetes mellitus experienced unawareness of hypoglycemic episodes after receiving fluoxetine 40 mg/day for 1 month for treatment of depression. Prior to fluoxetine therapy, the subject experienced typical adrenergic symptoms with low blood glucose values of 70 mg/dL about once a week. The subject experienced depression and was treated with fluoxetine 20 mg/day for 2 weeks. Fluoxetine was increased to 40 mg/day with mood improvement. After 1 month of fluoxetine therapy, the subject reported hypoglycemic episodes (blood glucose less than 70 mg/dL) about 3 times a week with no change in insulin use; however, a strict diet log was not maintained. Episodes of hypoglycemia were associated with confusion rather than the usual symptoms for this subject. The subject experienced 3 grand mal seizures in 1 month with blood sugars ranging from 35 to 41 mg/dL. Glycosylated hemoglobin was not changed from baseline and the subject lost 1.4 kg during fluoxetine therapy. Hypoglycemic awareness returned when fluoxetine was decreased over 12 days to a dose of 10 mg every other day; however, hypoglycemic episodes still occurred about 3 times a week. Fluoxetine was discontinued and within weeks blood glucose levels rose and hypoglycemia did not occur. Depressive symptoms recurred and subsequent treatment with mirtazapine and bupropion did not cause hypoglycemia or weight loss (Sawka et al, 2000).

3.3.3.A.4 Hyponatremia

a) Hyponatremia may occur with the use of serotonin norepinephrine reuptake inhibitors (SNRIs) or SSRIs, including fluoxetine. Symptoms include headache, difficulty concentrating, memory impairment, confusion, weakness, and unsteadiness. More severe or acute cases may lead to hallucination, syncope, seizure, coma, respiratory arrest, and death. The hyponatremia may be the result of the SIADH. Reported cases in which the serum sodium was lower than 110 mmol/L appeared to be reversible when fluoxetine was discontinued. Patients who are older, who are taking a diuretic, or who are volume depleted may be at greater risk. If signs and symptoms of hyponatremia occur, fluoxetine should be discontinued (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).

3.3.3.A.5 Syndrome of inappropriate antidiuretic hormone secretion

a) Summary

1) Of the 63 case reports of fluoxetine-induced SIADH reported to the United States Food and Drug Administration, the majority occurred in patients over 70 years of age. Based on published reports, the onset of the SIADH was between 3 days and 4 months after starting fluoxetine therapy. Symptoms included confusion, lethargy, dizziness, fatigue, anorexia, delirium, and abdominal pain. Abnormal laboratory findings consisted of a decreased serum osmolality (median 251 milliosmoles/liter (mOsm/L); range 214 to 272 mOsm/L), decreased serum sodium concentration (median 118 mEq/L; range 98 to 130 mEq/L), and urine osmolality (median 392.5 mOsm/L; 229 to 613 mOsm/L). In all but 1 case report, the SSRI was stopped, and fluid restriction was required before hyponatremia resolved; 1 patient was also treated with sodium chloride 3%. Patients in their fifties generally recovered in 2 to 4 days versus patients in their eighties who required up to 14 days for complete recovery. Of the 6 patients rechallenged with an SSRI, 3 developed a decrease in serum sodium consistent with SIADH, and 3 tolerated rechallenge without adverse events. In many case reports, inadequate reporting of symptoms, laboratory results, and exclusion of other causes were not included making it difficult to attribute SIADH to the SSRI (Woo & Smythe, 1997).

b) Hyponatremia secondary to SIADH has been reported in patients taking therapeutic doses of fluoxetine (Jackson et al, 1995; Flint et al, 1996; Girault et al, 1997; Anon, 1994).

c) Hyponatremia occurred in 2 elderly patients also taking thiazide diuretics. The mechanism of this adverse effect is thought to be due to inappropriate secretion of antidiuretic hormone. The authors advise careful monitoring of serum sodium in this patient population (ten Holt et al, 1996).

d) Seven cases of hyponatremia associated with fluoxetine use were identified over a 4-year period of time in the New Zealand Intensive Monitoring Program. All of the patients were women who were taking fluoxetine 20 mg/day; normalization of serum sodium occurred after fluoxetine therapy was withdrawn (Pillans & Coulter, 1994).

e) Hyponatremia consistent with SIADH associated with fluoxetine has been reported. A 75-year-old woman was switched from dothiepin 75 mg daily of fluoxetine 20 mg daily because of urinary retention. Her only other medication was ranitidine. The patient was noted to be drowsy and confused 12 days after starting fluoxetine. Serum sodium had declined from 140 mmol/L to 116 mmol/L; serum and urine osmolality were 242 milliosmoles/liter (mOsmol/L) and 337 mOsmol/L, respectively; urine sodium was 91 mmol/L. Fluid restriction and discontinuation of fluoxetine resulted in a serum sodium of 130 mmol/L in 2 days; in another 4 days, this value had risen to 138 mmol/L, and serum osmolality had risen to 283 mOsmol/L. The patient experienced an acute myocardial infarction complicated by left ventricular failure and died 5 days later. The authors state that the patient had recovered from the metabolic derangement before her heart attack. The authors note that the manufacturer informed them that several cases of hyponatremia, with the possibility of SIADH for some, had occurred in their studies (Gommans & Edwards, 1990).

f) Prolonged hyponatremia was observed in a 75-year-old male with depression after receiving fluoxetine 20 mg orally each day for 15 days. Serum sodium and chloride were observed to decrease progressively over the first 14 days of fluoxetine therapy, reaching a nadir of 126 and 89 mmol/L, respectively, on day 14. On the fifteenth day of treatment, serum and urine osmolality were lower than normal (264 milliosmoles/liter (mOsmol/L) and 416 mOsmol/kg, respectively), consistent with the SIADH. After withdrawal of fluoxetine, electrolyte levels returned to normal within 10 days. The patient was not rechallenged with fluoxetine. Additional investigations are required to determine whether there is a true cause-effect relationship between fluoxetine and SIADH (Hwang & Magraw, 1989).

3.3.3.A.6 Syndrome of inappropriate antidiuretic hormone secretion, and concurrent serotonin syndrome

a) A 56-year-old man, with a history of intracerebral hemorrhagic stroke and depression, developed SIADH and serotonin syndrome concurrently following the addition of fluoxetine to his existing antidepressant regimen (olanzapine 2.5 mg/day and buspirone 10 mg twice daily). Four weeks following the initiation of fluoxetine 40 mg/day and one week following an increase in the dosage to 60 mg/day, the man presented with symptoms of SIADH (ie, serum osmolality of 240 mOsm/kg, low BUN, low sodium, normal serum glucose) and serotonin syndrome (ie, dilated pupils, restlessness, change in mental status, facial flushing, myoclonus, hyperreflexia, increased blood pressure, tachycardia). Following water restriction (1000 mL/day), an infusion of lorazepam (0.07 mg/kg/hr for 24 hours then tapered over 48 hours) and discontinuation of buspirone, olanzapine, and fluoxetine, the man's symptoms resolved over several days. Buspirone and olanzapine were reinitiated at the previous doses

with no recurrence of adverse effects and fluoxetine was eliminated from his therapeutic drug regimen. A probable relationship between the use of fluoxetine and the development of the concurrent syndromes was indicated through the use of the Naranjo probability scale. The authors speculate that patients with a history of stroke may be more susceptible to severe adverse effects that may result from combination antidepressant therapy; however, additional studies are required to clarify any association between this patient group an increased incidence or severity of antidepressant-related adverse events (Bogdanovic et al, 2005).

3.3.3.A.7 Weight change finding

a) Weight gain has not occurred with fluoxetine therapy; stabilization of weight or weight loss has occurred in most controlled studies (Stark & Hardison, 1985a; Cohn & Wilcox, 1985a; Feighner, 1985a; Young et al, 1987a; Levine et al, 1987).

3.3.4 Gastrointestinal Effects

3.3.4.A Fluoxetine Hydrochloride

Gastrointestinal hemorrhage

Gastrointestinal tract finding

Grinding teeth

Loss of appetite

Nausea and vomiting

Stomatitis

Upper gastrointestinal hemorrhage

3.3.4.A.1 Gastrointestinal hemorrhage

See Drug Consult reference: CONCOMITANT USE OF SSRIs AND NSAIDs - INCREASED RISK OF GASTROINTESTINAL BLEEDING

3.3.4.A.2 Gastrointestinal tract finding

a) Gastrointestinal side effects of fluoxetine have included dry mouth and diarrhea, occurring in 14% and 10% of patients, respectively (Wernicke, 1985). Diarrhea developed in 38% of patients receiving therapeutic doses of fluoxetine for panic attacks (Gorman et al, 1987). Dryness of the mouth generally occurs to a lesser degree with fluoxetine than with imipramine (Stark & Hardison, 1985a; Cohn & Wilcox, 1985a), doxepin (Feighner & Cohn, 1985a) and amitriptyline (Feighner, 1985a; Chouinard, 1985b). constipation, dyspepsia, abdominal pain and taste changes have also occurred less frequently with fluoxetine (Bremner, 1984b; Stark & Hardison, 1985a; Wernicke, 1985).

3.3.4.A.3 Grinding teeth

a) Onset of symptoms of nocturnal bruxism within 2 weeks after beginning fluoxetine 15 to 20 mg daily for unipolar depressive episodes or mood instability was reported in 3 women aged 28 to 43 years. Teeth clenching during sleep caused nighttime awakening with headaches, earaches, and aching jaws. Buspirone doses ranging from 5 mg at bedtime to 10 mg 3 times daily were effective in 2 (Ellison & Stanziani, 1993). One 28-year-old woman developed symptoms of both diurnal and nocturnal bruxism, with tender, bleeding gums and jaw clenching. The patient stopped taking fluoxetine abruptly, with improvement, then restarted fluoxetine therapy when symptoms of depression returned, which aggravated her bruxism. Alternative SSRI therapy with paroxetine 20 mg/day, sertraline 50 mg/day, and fluvoxamine 100 mg/day in succession failed to alleviate the bruxism. She discontinued all SSRI treatment when she became pregnant. After pregnancy she started taking oral fluoxetine again which exacerbated her tooth grinding. Oral buspirone 5 mg/day was added, temporarily alleviating her bruxism, but was eventually discontinued because of intolerable sedative effects (Fitzgerald & Healy, 1995).

3.3.4.A.4 Loss of appetite

a) Anorexia has also occurred during fluoxetine therapy, and is most likely associated with the weight loss observed in several studies. Anorexia has occurred in 9% to 15% of patients treated, and occurs more frequently with fluoxetine than with other antidepressants; however, it is rarely a cause for drug

discontinuation (Feighner & Cohn, 1985a; Wernicke, 1985; Prod Info Prozac(R), 2003c). Fluoxetine has been shown to cause anorexia with resultant weight loss in overweight, non-depressed individuals at fluoxetine dosages of 20 to 80 mg/day (Ferguson & Feighner, 1987).

b) In a double-blind, placebo-controlled study of 35 patients, improvement in depression and reduction in BMI (calculated as weight in kg divided by the square of height in meters) were not significantly correlated, suggesting different mechanisms for these effects. The reduction in patient's BMI bore a curvilinear relationship to fluoxetine dose (in mg per square meter of body surface area), with daily doses of 20 mg and 40 mg leading to greater decreases of BMI than 5 mg doses (Harto et al, 1988).

3.3.4.A.5 Nausea and vomiting

a) Summary

1) The most common side effect of fluoxetine therapy is nausea, which may occur in 25% to 30% of patients (Wernicke, 1985; Cohn & Wilcox, 1985a; Stark & Hardison, 1985a; Feighner & Cohn, 1985a; Chouinard, 1985b). Clinical trials, however, have reported that only 4% of patients discontinue treatment due to this side effect (Ayd, 1988). Vomiting occurs less frequently with fluoxetine (Bremner, 1984b; Stark & Hardison, 1985a; Wernicke, 1985).

b) The SSRIs produce nausea and vomiting in 20% to 25% and 2% to 3% of patients, respectively. In the majority of patients, nausea gradually decreases or resolves over approximately 3 weeks. However, in others, reduction of the dose or discontinuation of the drug is required. For this group, ondansetron or cisapride administered for a few weeks may facilitate continued treatment with the SSRI. Limited data suggest that ondansetron is more effective than cisapride; however, it is also more expensive. Use of cisapride with careful monitoring for arrhythmias may be more cost effective, and open therapy to a broader group of patients. The proposed mechanism for SSRI-induced nausea and vomiting is increased serotonin levels within the chemoreceptor trigger zone and area postrema in the brainstem, the primary areas within the brain associated with nausea and vomiting (McManis & Talley, 1997).

3.3.4.A.6 Stomatitis

a) Two women developed stomatitis during treatment with fluoxetine. A 24-year-old woman with anorexia nervosa had received fluoxetine 20 mg daily for 6 months. During the course of treatment, she experienced 6 episodes of stomatitis which showed a partial response to metronidazole 750 mg daily and spiramycin 4,500,000 International Units (IU) daily for 7 days. When she presented to the emergency department due to aphthae and inflammation of the oral cavity, fluoxetine was stopped, and complete healing was noted in 7 days. This patient was rechallenged with fluoxetine and developed stomatitis again. The second patient, a 41-year-old woman with depression, received fluoxetine 20 mg daily and a benzodiazepine. Since beginning treatment, the patient complained of dysgeusia, a dry mouth, and inflammation of the mouth which prevented swallowing. Both drugs were stopped but alprazolam was restarted. Her symptoms improved within 2 days but she refused rechallenge. The authors attribute the stomatitis to a hypersensitivity reaction (Palop et al, 1997).

3.3.4.A.7 Upper gastrointestinal hemorrhage

a) Upper gastrointestinal bleeding has been reported in association with psychotropic drugs that interfere with serotonin uptake such as fluoxetine. Epidemiological studies have suggested that concurrent use of an NSAID increases the risk of bleeding episodes (Prod Info Sarafem (R) pulvules, 2004).

3.3.5 Hematologic Effects

3.3.5.A Fluoxetine Hydrochloride

Aplastic anemia

Bleeding

Neutropenia

3.3.5.A.1 Aplastic anemia

a) Aplastic anemia developed in a 28-year-old man taking fluoxetine 40 mg/day for 6 weeks. He presented with a high fever, painful oral ulcers, and pleuritic chest pain. Pancytopenia was noted on the peripheral blood smear (ie, absolute granulocyte count 480 x 10(6) cells/L, platelets 34 x 10(9)/L, and mild macrocytic anemia). A bone marrow biopsy showed severe depression of megakaryocytes and myeloid cells with moderate depression of the erythroid cell line. Fluoxetine was stopped, and imipenem plus cilastatin was started. Complete recovery of the blood count was reported at 19 days. Rechallenge with fluoxetine resulted in reduction of the leukocyte and platelet count within 5 days; 12 days after stopping fluoxetine, the blood count returned to normal (Bosch & Vera, 1998).

3.3.5.A.2 Bleeding

a) Summary

1) Case reports, case-control, and cohort studies have shown an association between the use of drugs that interfere with serotonin reuptake and gastrointestinal bleeding. Bleeding events associated with SSRI and serotonin norepinephrine reuptake inhibitor (SNRI) use include ecchymoses, hematomas, epistaxis, petechiae, and life-threatening hemorrhages. There have also been postmarketing reports of vaginal bleeding after fluoxetine discontinuation. Risk of bleeding events may be increased by concomitant use of NSAIDs, aspirin, warfarin, and other anticoagulants; patients should be cautioned of this increased risk (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).

b) Incidence: up to 1% (Berk & Jacobson, 1998)

c) Increased bleeding (eg, bruising, ecchymoses, epistaxis, prolonged bleeding time, and rectal bleeding) has been reported with the use of SSRIs. SSRIs reduce uptake of serotonin by platelets; therefore, reduction in granular storage of serotonin is observed. Serotonin-mediated platelet aggregation may be decreased. The majority of cases have been reported in patients taking fluoxetine, but case reports are also available for paroxetine, sertraline, and fluvoxamine. Risk is increased with higher doses and in patients with underlying diseases; one case occurred in a patient with HIV. For minor bleeding diatheses (ie, bruising), treatment is usually unnecessary because it usually resolves with continued treatment. However, if bleeding is clinically significant, occurs with other underlying medical illnesses, or fails to improve with time, the drug should be discontinued (Berk & Jacobson, 1998).

d) A 31-year-old woman developed bruising 4 weeks after she began taking fluoxetine 20 mg daily for depression; the bruising worsened over the 5 days preceding her clinic visit. Examination revealed multiple bruises which were disproportionally large for the trauma incurred. The complete blood count, prothrombin time, and partial thromboplastin time were within normal limits. Although bruising continued, the patient did not want to stop fluoxetine since her depression was improving. During pre-marketing clinical trials, bruising was reported in 1% of fluoxetine-treated patients compared to 0.6% for placebo. Fluoxetine disrupts normal platelet aggregation by blocking uptake of serotonin into platelets; the end result is bruising or bleeding (Pai & Kelly, 1996).

e) Fluoxetine blocks 5-hydroxytryptamine reuptake in platelets and may lead to platelet dysfunction. One case described a patient with a minor history of bleeding disorder (occasional epistaxis and bruising) who developed a prolonged bleeding time and petechiae while taking fluoxetine 20 mg every other day for 2 years. Her platelet count, prothrombin time, and von Willebrand factors were normal, and she was on no medication. The patient was taken off fluoxetine, and bleeding time returned to normal. After a return to fluoxetine therapy at the same dose, prolonged bleeding time and petechiae again returned (Humphries et al, 1990).

3.3.5.A.3 Neutropenia

a) A 79-year-old man developed neutropenia associated with fluoxetine. Presenting symptoms included fatigue and weakness; a hemogram detected a leukocyte count of 2800 cells/mm(3) with granulocytopenia (0% segmented cells, 11% band cells). All drug therapies (ie, fluoxetine, warfarin, glipizide, diphenhydramine, and tobramycin/dexamethasone ophthalmic drops) were stopped after granulocytopenia was identified; the absolute neutrophil count returned to normal. First, fluoxetine 20 mg daily was restarted, and 3 days later, severe neutropenia recurred. After stopping fluoxetine, neutropenia resolved rapidly. Reinstitution of glipizide and warfarin had no effect on the neutrophil count. Serum drug-dependent neutrophil antibodies did not react with fluoxetine; however, the rapid response to rechallenge with fluoxetine suggests a drug-related antineutrophil antibody reaction (Vilinsky & Lubin, 1997).

3.3.6 Hepatic Effects

3.3.6.A Fluoxetine Hydrochloride

3.3.6.A.1 Hepatotoxicity

a) Asymptomatic increased liver enzymes have been reported in 0.5% of patients; however, only a few cases of hepatitis have been reported (Cai et al, 1999a; Friedenberg & Rothstein, 1996; Wernicke, 1985; Anon, 1996).

b) Elevations in total bilirubin, direct bilirubin, AST/SGOT, ALT/SGPT, total alkaline phosphatase, and gamma-glutamyltransferase were documented (Cai et al, 1999a).

c) A 35-year-old man developed chronic hepatitis in association with intermittent use of fluoxetine for depression. Liver enzymes increased shortly after fluoxetine was restarted at a daily dose of 40 mg. At the initial evaluation, fatigue resulting in an inability to work for 10 months and elevated liver enzymes (ie, gamma-glutamyl transferase) with a positive antibody against hepatitis C were present. He received prednisone 30 mg daily for 1 month followed by azathioprine 50 mg daily for 1 month which resulted in slight decreases in ALT. However, the ALT fell after stopping fluoxetine and was normal within 6 months. A liver biopsy supported a diagnosis of autoimmune hepatitis. Although hepatotoxicity occurred during fluoxetine use, this patient had a history IV drug abuse about 15 years earlier and admitted to binge drinking, marijuana and amphetamine abuse about 2 years ago (Johnston & Wheeler, 1997).

3.3.8 Musculoskeletal Effects

3.3.8.A Fluoxetine Hydrochloride

Fracture of bone

Fracture of bone, Nonvertebral

3.3.8.A.1 Fracture of bone

a) In a case-control study including fracture cases (n=124,655) during the year 2000 and age- and gender-matched controls (n=373,962), there was an increased risk of any fracture in participants who were using an average standard daily dose of fluoxetine (adjusted odds ratio (OR), 1.2; 95% CI, 1.09 to 1.32) compared to those who were not exposed to fluoxetine. Fluoxetine use was associated with an increased risk of hip fracture (adjusted OR, 1.33; 95% CI, 1.02 to 1.73) and forearm fracture (adjusted OR, 1.32; 95% CI, 1.04 to 1.68), but not spine fracture (adjusted OR, 0.7; CI, 0.4 to 1.22) (Vestergaard et al, 2008)

b) In a population-based, randomly selected, prospective cohort study adjusted for potential covariates, an increased risk of fragility fracture was reported at the 5-year follow-up in patients 50 years of age and older who used daily SSRIs (n=137; mean age of 65.1 years), including fluoxetine, compared with those who did not use an SSRI (n=4871; mean age of 65.7 years). Daily SSRI use was associated with a significant 2.1-fold increased risk of fragility fracture (95% CI, 1.3 to 3.4). Daily dose of SSRI use was associated with a 1.5-fold increased risk of fragility fracture (95% CI, 1.1 to 2.1). Daily SSRI users who were recurrent (ie, treated with SSRIs at baseline and at 5-year follow-up) had a significant 2.1-fold increased risk of fragility fracture (95% CI, 1.1 to 4). Fractures were reported at the following sites: forearm (40%), ankle and foot (21%), hip (13%), rib (13%), femur (9%), and back (4%). None were reported at the skull, toes, or fingers (Richards et al, 2007).

3.3.8.A.2 Fracture of bone, Nonvertebral

a) In a prospective, population-based, cohort study (n=7983) with a mean follow-up of 8.4 years, there was an increased risk of nonvertebral fracture in adult participants older than 55 years of age (mean age of 77.5 years) who were currently using an SSRI (citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline) compared to those who were not exposed to antidepressants. Current SSRI use was associated with an increased risk of nonvertebral fracture (adjusted hazard ratio (HR), 2.35; 95% CI, 1.32 to 4.18) compared with no antidepressant use. Current SSRI use was also associated with an increased risk of nonvertebral fracture (adjusted HR, 2.07; 95% CI, 1.23 to 3.5) compared with past antidepressant use (n=1217). In addition, duration of SSRI use showed a 9% increase in fracture risk per extra month on an SSRI (95% CI, 3% to 16%; p for trend=0.004). Fractures of the hip (most frequent), wrist, humerus, and pelvis were reported (Ziere et al, 2008).

3.3.9 Neurologic Effects

Fluoxetine

Fluoxetine Hydrochloride

3.3.9.A Fluoxetine

3.3.9.A.1 Seizure

See Drug Consult reference: COMPARATIVE INCIDENCE OF SEIZURES FROM ANTIDEPRESSANTS

3.3.9.B Fluoxetine Hydrochloride

Asthenia

Extrapyramidal disease

Impaired cognition

Impaired psychomotor performance

Myoclonus

Neurological finding

Paresthesia

Restless legs syndrome

Seizure

3.3.9.B.1 Asthenia

a) Incidence: 9% to 21% (Prod Info Prozac(R), 2003c)

b) Asthenia has occurred in 9% to 21% of patients treated with fluoxetine. This side effect is dose-related with higher incidences reported in patients being treated with a dosage of 60 mg/day for bulimia nervosa (Prod Info Prozac(R), 2003c). Asthenia has occurred to a greater degree with imipramine than with fluoxetine (Cohn & Wilcox, 1985a).

3.3.9.B.2 Extrapyramidal disease

a) The majority of extrapyramidal reactions (EPRs) occur within the first few days to the first month of starting treatment or increasing the dose. Therefore, careful monitoring for EPRs is recommended weekly during the first 4 weeks of fluoxetine therapy In all cases, symptoms disappeared after reducing the dose or stopping the SSRI. In a limited number of case reports, propranolol and/or benzodiazepines were used to treat akathisia; the dose of propranolol ranged from 40 to 90 mg daily, and the dose of clonazepam was 1.5 mg daily. Dystonic reactions were treated with an unspecified dose of intramuscular trihexyphenidyl or diphenhydramine 50 mg (Caley, 1997);(Gill et al, 1997).

b) Two women with dopa-responsive dystonia (DRD) noted worsening of the dystonia after starting venlafaxine or fluoxetine. The first patient had onset of DRD during childhood; DRD had been well controlled with Sinemet(R) plus which was continued during fluoxetine treatment. Five days after starting fluoxetine 20 mg/day, she developed torticollis, and 2 days later, she noted inversion of the left ankle. She described the changes as exactly the same as they were as a child. She stopped fluoxetine, and within 2 days, the dystonia improved and completely resolved at 1 week. The second patient developed dystonia 4 days after starting venlafaxine although she continued Sinemet(R) LS at the same dose. Without seeing a physician, she stopped venlafaxine, and the dystonia completely resolved after approximately 1 week (Mathen et al, 1999).

c) Choreiform movements were observed in an otherwise healthy 74-year-old woman treated with fluoxetine 20 mg/day. After taking fluoxetine for 7 months for major depression, the patient developed unsteadiness, with a tendency to fall backward, abnormal involuntary choreiform movements involving the tongue, lips, lower face, and buccal and masticatory muscles. The patient was hospitalized, fluoxetine was stopped, and clothiapine 20 mg/day was substituted. She improved rapidly over the next 3 weeks and was discharged from the hospital (Marchioni et al, 1996).

d) In a series of 5555 patients taking fluoxetine therapeutically 15 developed extrapyramidal effects. Eight of these were taking other drugs which may have contributed to these effects (Coulter & Pillans, 1995).

e) Tics developed in a 12-year-old boy after 8 months of therapy with fluoxetine 20 mg daily. This suggests the modulating effect that serotonin may have on dopaminergic neurons (Eisenhauer & Jermain, 1993).

f) Akathisia occurred within 7 days of initiation of fluoxetine therapy in 5 patients being treated for obsessive-compulsive disorder. Three of the patients, who had previously experienced neuroleptic-induced akathisia, described the effect of fluoxetine as identical, but milder. In all 5 cases, akathisia resolved with propranolol therapy and/or reduction of the fluoxetine dose. This side effect appears to be common, as it occurred in 5 patients among a study group of 51 (20 of whom were evaluated for akathisia from the start of therapy). They propose that the same pathophysiologic mechanism accounts for fluoxetine-induced "jitteriness," namely inhibition of dopamine transmission via increased serotonergic activity (Lipinski et al, 1989).

g) In an open trial of fluoxetine in patients with obsessive-compulsive disorder, 8 of 50 patients reported tremors and 2 of 50 reported involuntary movements. The mean daily dose of fluoxetine for the study group was 78 mg/day (undivided) (Fontaine & Chouinard, 1989).

3.3.9.B.3 Impaired cognition

a) Summary

1) In one study, the use of fluoxetine or paroxetine was not associated with degradation of cognitive function in depressed non-demented elderly patients, however, there have been case reports of memory loss associated with the use of fluoxetine (Joss et al, 2003; Cassano et al, 2002).

b) Severe memory loss resulting in hospitalization developed in an 87-year-old Caucasian woman following the administration of fluoxetine for the treatment of depression. Approximately 2 weeks after beginning fluoxetine therapy (initial, 10 mg/day for 2 weeks, then 20 mg/day) the woman's memory began to decline. Fluoxetine was discontinued after approximately 2 months of therapy and symptoms of memory loss peaked 5 days later. Symptoms improved within 2 weeks of fluoxetine cessation and continued to get better over the following 2 months. Fluoxetine therapy was cited as the probable cause of memory loss in this patient because the timeline correlates well with the half-life of fluoxetine and other possible causes of memory loss were ruled out (Joss et al, 2003).
c) A 1-year course of fluoxetine or paroxetine did NOT have detrimental effects on cognitive function in depressed non-demented elderly patients; in fact, tests of cognition showed improved results after 1 year of treatment compared with baseline, according to a randomized, double-blind trial (n=242; mean age 75.4 years). Both active treatments were well tolerated, and both significantly reduced symptoms of depression. Memory, learning, and attention improved over the year of therapy, and improved scores were seen on the Mini-Mental State Exam (MMSE), the Blessed Information and Memory Test (BIMT), the Cancellation Task Test (CTT), the Clifton Assessment Schedule (CLAS), and the Wechsler Paired Word Test (WPW). Some parameters on the Buschke Selective Reminding Test (BSRT) were better posttreatment. Daily doses of fluoxetine were in the range of 20 to 60 mg, and paroxetine dosages ranged from 20 to 40 mg/day (Cassano et al, 2002).

3.3.9.B.4 Impaired psychomotor performance

a) Summary

1) Fluoxetine therapy may have an effect on psychomotor function (Thapa et al, 1998; Hindmarch, 1988). Nursing home patients treated with fluoxetine and other SSRIs including paroxetine and sertraline have an increased risk of falls compared to patients who are not on antidepressants (Thapa et al, 1998).

b) Nursing home patients treated with fluoxetine and other SSRIs including paroxetine and sertraline have an increased risk of falls compared to patients who are not on antidepressants. A retrospective chart review of 2428 nursing home residents treated with antidepressants assessed the incidence of falls before and after the initiation of antidepressant therapy. Results were then compared to those not treated (n=847). Antidepressant treatment included tricyclic antidepressants (TCAs; n=665), SSRIs (n=612), and trazodone (n=304). The rate of falls for treated patients was higher than that for patients who were not treated, both before and after the initiation of antidepressant therapy. This suggests that nursing home patients with depression or related conditions are at a greater risk of falls than those without such conditions. Patients on TCAs had the highest rate of falls, with an adjusted rate ratio of 2 (95% CI, 1.8 to 2.2). Next were the SSRIs with an adjusted rate ratio of 1.8 (1.6 to 2, p=0.001) and trazodone with a ratio of 1.2 (1 to 1.4, p less than 0.001). No significant differences in incidence were seen within different medications of the same class. It was, however, noted that patients receiving a dose of 20 mg daily of fluoxetine, or an equivalent dose of another SSRI, had a statistically significant increase in the incidence of falls than those receiving lower doses (Thapa et al, 1998).
c) The effects of amitriptyline 50 mg, dothiepin 50 mg, fluoxetine 40 mg, and placebo were assessed with and without alcohol 0.5 g/kg body weight, on a battery of 7 tests of psychomotor and cognitive functions relevant to automobile driving. Eight female volunteers were studied, each acting as her own control. Subjects were trained on each test to a plateau of performance before the study in order to eliminate confounding effects of learning. Results indicated that, compared to placebo, single doses of fluoxetine 40 mg (with or without alcohol) did not result in any significant effect on performance for any of the tests. However, amitriptyline (with or without alcohol) and dothiepin (with or without alcohol) caused significantly impaired performance on several of the tests when compared to placebo. This difference may be important for outpatients who must be able to maintain skilled performance of various tasks, as well as for depressed patients for whom a decrease in psychomotor and cognitive function would be counter-therapeutic (Hindmarch, 1988).

3.3.9.B.5 Myoclonus

a) One month after starting treatment with fluoxetine 40 mg daily for depression following alcohol withdrawal, a 35-year-old woman developed spontaneous, non-rhythmical, involuntary jerks of the head, arm, or legs. Other medications included triazolam and vitamin B complex. Upon examination, proprioceptive, luminous, and auditory stimulation produced spontaneous, reflex, and induced myoclonic jerks. Other neurological and neuropsychological evaluations were normal; the electroencephalogram and laboratory tests were also normal. All symptoms resolved 2 days after fluoxetine was stopped. This case differs from others because the patient had no underlying cerebral disease (Ghika-Schmid et al, 1997).

3.3.9.B.6 Neurological finding

a) Summary

1) The most common side effects of fluoxetine therapy (excluding nausea) involve the CNS, including nervousness, insomnia, headache, tremor and drowsiness (Wernicke, 1985; Fabre & Crismon, 1985; Stark & Hardison, 1985a; Cohn & Wilcox, 1985a; Chouinard, 1985b; Rickels et al, 1985). Nervousness and insomnia occur in approximately 10% to 20% of patients, and have occurred more frequently than in patients receiving amitriptyline or imipramine (Cohn & Wilcox,

1985a; Wernicke, 1985; Prod Info Prozac(R), 2003c). Headache (20.3%), somnolence (13%), and tremor (10%) are also frequently reported (Prod Info Prozac(R), 2003c). Other rare CNS side effects with fluoxetine have included ataxia, dizziness, sensation disturbances, and a "high" feeling (Cohn & Wilcox, 1985a; Bremner, 1984b; Stark & Hardison, 1985a; Feighner, 1985a; Wernicke, 1985; Borys et al, 1990; Gorman et al, 1987). The incidence of dizziness, lightheadedness, and sensation disturbances has been greater with imipramine than with fluoxetine (Cohn & Wilcox, 1985a). Exacerbation of multiple sclerosis symptoms may occur with fluoxetine therapy (Browning, 1990).

b) Exacerbation of symptoms of multiple sclerosis (arm numbness and grogginess) developed in a 41-year-old woman 10 hours after beginning fluoxetine and progressed over the next 4 days of therapy. Symptoms returned to baseline after discontinuing fluoxetine therapy (Browning, 1990).

3.3.9.B.7 Paresthesia

a) Paresthesia is a rare side effect reported with SSRI therapy. In a case report, tingling in the lower extremities occurred with initiation of fluoxetine that worsened with an increase in dose and continued therapy. Following discontinuation of the drug, resolution of paresthesia was noted after 2 weeks. The patient was then started on sertraline with no further recurrence of symptoms (Bhatara et al, 1996).

3.3.9.B.8 Restless legs syndrome

a) In a prospective, naturalistic study of patients (median age, 46 years; range, 18 to 87 years) treated with antidepressants, 24 of 271 (9%) subjects experienced new-onset restless leg syndrome (RLS) or worsening of preexisting RLS as a side effect related to treatment. Antidepressants included fluoxetine, paroxetine, citalopram, sertraline, escitalopram, venlafaxine, duloxetine, reboxetine, and mirtazapine. Mirtazapine led to a marked decline of RLS in 28% of subjects compared with reboxetine which had none. The other antidepressants showed RLS symptoms (newly occurred or deteriorated) at the rate of 5% to 10%. Subjects stated symptoms occurred early in treatment (median of 2.5 days, range 1 to 23 days) (Rottach et al, 2008).

3.3.9.B.9 Seizure

a) Summary

1) In United States placebo-controlled studies the reported seizure incidence of 0.2% with fluoxetine is no greater than that observed with other antidepressants (Prod Info Prozac(R), 2003c). Several isolated reports of seizure activity have been reported in patients given therapeutic doses of fluoxetine; however, it is difficult to implicate the drug as the sole cause in some cases (Wernicke, 1985).

b) A 53-year-old woman with no prior history of seizures experienced an episode of generalized tonic-clonic convulsions 6 days after her daily dose of fluoxetine was raised from 40 to 60 mg. The patient had been receiving fluoxetine for 5 months for the treatment of depression. No causative factor was identified in laboratory or hematological tests, lumbar puncture, or brain MRI. Fluoxetine was initially discontinued and later restarted at 20 mg/day. At 3-month follow-up, she had experienced no other seizures (Oke et al, 2001).

c) Seizures were described in an 84-year-old woman after receiving fluoxetine 20 mg orally daily for approximately 5 days. The patient had no prior history of seizure activity and was on concurrent therapy with diltiazem and docusate. No factors were identified in the patient's history, laboratory data, or neurological examinations that would affect seizure threshold. This case report suggests a possible epileptogenic potential of fluoxetine; however, it does not establish a definite cause/effect relationship (Weber, 1989). Previously, seizures have been observed in 12 of 6000 patients receiving fluoxetine during premarketing trials (Prod Info Prozac(R), 2003c).

d) Two patients currently taking lithium and fluoxetine in therapeutic doses for depression and suicidal ideation experienced seizures following ingestion of LSD (Jackson & Hornfeldt, 1991).

e) Seizure activity was described in a 35-year-old woman with bipolar affective disorder after receiving fluoxetine 20 mg orally daily for approximately 3 days. The patient had no history of seizure activity and was not receiving other medications at the time. On the third day of treatment, the patient's roommate reported that the patient was flailing her arms; the patient was subsequently found in bed, unresponsive, and had a tongue laceration. It was felt that the patient had a major motor seizure. Following the withdrawal of fluoxetine, no recurrent seizure activity was observed. It is unclear whether seizure activity would have occurred in this patient in the absence of fluoxetine therapy (Ware & Stewart, 1989).

3.3.10 Ophthalmic Effects

3.3.10.A Fluoxetine Hydrochloride

Eye / vision finding

Raised intraocular pressure

Visual disturbance

3.3.10.A.1 Eye / vision finding

a) Blurred vision and other visual disturbances, cataracts, conjunctivitis, dry eyes, mydriasis, optic neuritis, photophobia and increased intraocular pressure have been reported with fluoxetine administration (Prod Info Prozac(R), 2003c; Prod Info Sarafem(TM), 2002).

3.3.10.A.2 Raised intraocular pressure

a) Increased intraocular pressure has been described following fluoxetine administration. In a series of depressed patients (n=20) in whom baseline intraocular pressures (IOP) were normal, oral fluoxetine 20 mg resulted in a significant increase (p less than 0.05) in IOP 2 hours after drug administration that persisted for up to 8 hours (Costagliola et al, 1996).

3.3.10.A.3 Visual disturbance

a) Visual disturbances, primarily blurred vision, have been described in patients receiving fluoxetine and have necessitated withdrawal of therapy (Wernicke, 1985; Prod Info Prozac(R), 2003c; Borys et al, 1990; Gorman et al, 1987). These disturbances tend to occur early in treatment. Approximately 3% of patients in clinical trials have noted changes in vision (Prod Info Prozac(R), 2003c).

3.3.12 Psychiatric Effects

3.3.12.A Fluoxetine Hydrochloride

Anxiety

Depression, worsening

Feeling nervous

Hallucinations

Hypomania

Mania

Nightmares

Psychotic disorder

Suicidal thoughts

3.3.12.A.1 Anxiety

a) Anxiety has been reported with fluoxetine therapy (Wernicke, 1985; Fabre & Crismon, 1985; Stark & Hardison, 1985a; Cohn & Wilcox, 1985a; Chouinard, 1985b; Rickels et al, 1985).

3.3.12.A.2 Depression, worsening

a) Incidence: rare (Anon, 2004)

b) Adult and pediatric patients who experience symptoms of anxiety, agitation, panic attacks, insomnia, irritability, hostility (aggressiveness), impulsivity, akathisia (psychomotor restlessness), hypomania, or mania may be at risk of worsening of their depression. This same concern applies to treating patients with other psychiatric and nonpsychiatric disorders. If these symptoms are observed, therapy should be reevaluated and it may be necessary to discontinue medications when symptoms are severe, sudden in onset, or were not part of the patient's initial symptoms (Anon, 2004).

3.3.12.A.3 Feeling nervous

a) Incidence: 13% (Prod Info PROZAC(R) oral capsules, oral solution, delayed-release oral capsules, 2006)

b) In pooled analysis controlled clinical trials (US major depressive disorder, obsessive compulsive disorders, bulimia) (n=4542), the incidence of nervousness is 13% in patients on fluoxetine vs 8% in patients on placebo (Prod Info PROZAC(R) oral capsules, oral solution, delayed-release oral capsules, 2006).

3.3.12.A.4 Hallucinations

a) In a case report, a 16-year-old boy developed auditory hallucinations following the administration of fluoxetine for the treatment of major depressive disorder without psychotic symptoms. Three days after beginning fluoxetine therapy at a 20-mg dose, the patient presented with auditory hallucinations telling him to kill his father, mother, sister, and himself. Fluoxetine was discontinued and the hallucinations stopped 3 days later (Webb & Cranswick, 2003).

b) A 38-year-old man developed a complex visual hallucination with both sertraline and fluoxetine therapy. The hallucination was described as a blue-green central disc that nearly filled the visual fields, with a dynamic yellow central portion and peripheral yellow regions and a red vertical bar in the left visual field of both eyes. The visual pattern was present daily on awakening and would last 30 to 40 seconds. The pattern occurred initially with sertraline therapy and recurred when fluoxetine was substituted. It gradually disappeared when both were discontinued and nefazodone was substituted (Bourgeois et al, 1998).

3.3.12.A.5 Hypomania

a) Incidence: rare (Prod Info Prozac(R), 2003c)

b) In United States placebo-controlled trials, 0.7% of 10,872 fluoxetine-treated patients reported mania or hypomania (Prod Info Prozac(R), 2003c).

c) Hypomania was described in 2 patients who ingested 120 mg/day for 7 days and 140 mg/day for 16 days, respectively (Tech Info, 1987), and in another patient who took 140 mg for 36 hours (Chouinard & Steiner, 1986).

d) A 28-year-old woman with depression developed hypomanic symptoms after receiving fluoxetine 80 mg daily for approximately 7 weeks. Reduction in the dose of fluoxetine resulted in frank mania, with symptoms including racing thoughts, markedly decreased sleep without fatigue, and distractibility. Withdrawal of fluoxetine and initiation of therapy with thiothixene was undertaken, but the mania continued for several more days. Lithium therapy was initiated 5 days after withdrawal of fluoxetine and thiothixene was discontinued, and mania resolved over a period of 2 weeks. The patient had never suffered a hypomanic or manic swing prior to fluoxetine therapy (Settle & Settle, 1984).

3.3.12.A.6 Mania

a) Summary

1) Several reports of manic episodes have occurred in fluoxetine-treated patients who received the drug for several months (Settle & Settle, 1984; Rickels et al, 1985). In United States placebo-controlled trials, 0.7% of 10,872 fluoxetine-treated patients reported mania or hypomania (Prod Info Prozac(R), 2003c).

b) Incidence: rare (Prod Info Prozac(R), 2003c)

c) In United States placebo-controlled trials, 0.7% of 10,872 fluoxetine-treated patients reported mania or hypomania (Prod Info Prozac(R), 2003c).

d) Hypomania was described in 2 patients who ingested 120 mg/day for 7 days and 140 mg/day for 16 days, respectively (Tech Info, 1987), and in another patient who took 140 mg for 36 hours (Chouinard & Steiner, 1986).

e) A 28-year-old woman with depression developed hypomanic symptoms after receiving fluoxetine 80 mg daily for approximately 7 weeks. Reduction in the dose of fluoxetine resulted in frank mania, with symptoms including racing thoughts, markedly decreased sleep without fatigue, and distractibility. Withdrawal of fluoxetine and initiation of therapy with thiothixene was undertaken, but the mania continued for several more days. Lithium therapy was initiated 5 days after withdrawal of fluoxetine and thiothixene was discontinued, and mania resolved over a period of 2 weeks. The patient had never suffered a hypomanic or manic swing prior to fluoxetine therapy (Settle & Settle, 1984).

3.3.12.A.7 Nightmares

a) Four cases of vivid nightmares (and night terrors) were reported in patients on fluoxetine monotherapy. The nightmares generally disappeared after several days of continued therapy; 2 of the patients required the addition of a sedative at bedtime (Lepkifker et al, 1995).

3.3.12.A.8 Psychotic disorder

a) One paper reported a case of psychosis in an 11-year-old girl who was given fluoxetine 20 mg for 35 days. The patient had no history of delusional psychosis, but had sustained head trauma 5 years before and had an abnormal electroencephalogram (EEG). The patient was normal 3 weeks after cessation of fluoxetine therapy (Hersh et al, 1991).

b) A 58-year-old man exhibited dose-related paranoid symptoms during treatment of depression with fluoxetine. The patient previously showed no psychotic symptoms. Initial treatment with 20 mg/day of fluoxetine yielded no improvement after 3 weeks and the dose was subsequently increased to 40 mg/day. The paranoia became evident 2 weeks after dissipation of the depressive symptoms. The dose was lowered back to 20 mg/day and the paranoia subsided within a week of the decrease. The patient was controlled on this dose with no further evidence of depression or paranoia. The delayed length of time to see the symptoms may be due to the long half-life of fluoxetine. Other pertinent factors include concurrent therapy with diltiazem, which may have led to higher than expected plasma fluoxetine levels

and discontinuation of triazolam, and possible withdrawal, prior to fluoxetine initiation (Mandalos & Szarek, 1990).

3.3.12.A.9 Suicidal thoughts

a) Summary

1) Adult and pediatric patients being treated with antidepressants for major depressive disorder who experience symptoms of anxiety, agitation, panic attacks, insomnia, irritability, hostility (aggressiveness), impulsivity, akathisia (psychomotor restlessness), hypomania, or mania may be at risk of suicidal ideation and behavior (suicidality). This same concern applies to treating patients with other psychiatric and nonpsychiatric disorders. If these symptoms are observed, therapy should be reevaluated and it may be necessary to discontinue medications when symptoms are severe, sudden in onset, or are not part of the patient's initial symptoms. Patients and their caregivers should be provided with the Medication Guide that is available for this drug (Anon, 2004).

2) A causal role for antidepressants in inducing suicidality has been established in pediatric patients. Anyone considering the use of antidepressants in a child or adolescent must balance this risk with the clinical need. In pooled analyses of 24 short-term, placebo-controlled trials of 9 antidepressants (citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, bupropion, mirtazapine, nefazodone, and venlafaxine extended-release) including over 4400 pediatric patients with major depressive disorder, obsessive compulsive disorder, or other psychiatric disorders, a greater risk of suicidal behavior or ideation during the first few months of therapy was demonstrated in patients receiving antidepressants as compared with placebo (4% vs 2%, respectively). The risk of suicidality was most consistently observed in the trials that included patients with major depressive disorder, but there were signs of risk emerging from trials in other psychiatric indications, such as obsessive compulsive disorder and social anxiety disorder. No suicides occurred in these trials. The risk of suicidality during longer-term use (ie, beyond several months) in pediatric patients is not known. It is also unknown whether this risk extends to adult patients (Anon, 2004).

3) Considerable controversy exists regarding the association of fluoxetine with suicidal ideation. Controlled and prospective trials and combined meta-analysis have both failed and supported an increased emergence or worsening of suicidal thoughts or actions with fluoxetine therapy and several case reports have been noted where there may be an association. Various theories have been proposed to explain these anecdotal reports, including development of akathisia which may represent toxicity; excessive doses; recent withdrawal from MAOI therapy; concomitant treatment with other neuroleptic agents that might potentiate the effects of fluoxetine or cause extrapyramidal effects such as akathisia; patients with a history of panic attacks; or possibly underlying worsening of depression (Perlis et al, 2007; Warshaw & Keller, 1996; Beasley et al, 1992a; Beasley et al, 1991).

b) In a 12-week, open multicenter trial of adults (18 to 65 yr) with nonpsychotic major depressive episodes (n=414), 14.3% of patients experienced treatment-emergent or worsening of suicidal ideation, usually early in therapy, during treatment with fluoxetine. Patients were given a modified 17-item Hamilton Depression (mHAMD) assessment at screening, baseline, and at each visit (weekly for 4 weeks, biweekly for 6 weeks and again weekly for up to 12 weeks). Suicidal ideation was defined as a score of at least 2 on item 3 of the mHAMD scale (HAMD-3); treatment-emergent suicidal ideation was defined only if the HAMD-3 score was less than 2 at both screening and baseline. A 10-week analysis reported that 14.3% (59 of 414) of subjects had treatment-emergent or worsening of suicidality; 79.7% (47 of 59) reported so by the fourth week. Patients experiencing treatment-emergent suicidality were also less likely to respond or remit to treatment than those who didn't (responders: 56% (33 of 59) vs. 75% (266 of 355) (p less than 0.004) and remitters: 41% (24 of 59) vs. 63% (225 of 355) (p=0.001), respectively). Female gender was more prevalent among the emergent group (80% vs. 65%, emergent vs. non-emergent, p=0.04) as was younger patient age (p=0.04). Emergence of suicidality was also associated with the emergence of activation (adjusted hazard ratio of 2.31 (95% CI, 1.21 to 4.43, p=0.011)) and worsening of mood (adjusted hazard ratio was 1.54 (95% CI, 1.37 to 1.72, p less than 0.001)) (Perlis et al, 2007).

c) A retrospective review of 6 cases of patients with refractory or chronic depression reported the development of intense, violent suicidal preoccupation after 2 to 7 weeks of therapy with fluoxetine. Four of the 6 patients had complicated psychiatric histories and were receiving multiple psychotropic medications at the time symptoms were experienced (Teicher et al, 1990). A review of these reports suggests that these patients were previously at risk for suicide and that none of these patients was demonstrating a therapeutic antidepressant response to fluoxetine.

d) Fluoxetine use was not found to increase the risk of suicidal behavior in patients with anxiety disorders. In a longitudinal study of 654 patients, there was a lower probability of suicidal gestures in patients with both anxiety and depressive disorders who received fluoxetine than those patients who did not receive the drug. This study further supports the concept that preexisting risk factors for suicidal behavior are the strongest determinant of suicidal acts, rather than use of a particular medication (Warshaw & Keller, 1996).

e) In a review of pooled data from clinical trials, fluoxetine was not associated with an increased risk of suicidal acts or emergence of suicidal thoughts in patients who were depressed or suffered from obsessive-compulsive disorder (Beasley et al, 1992a; Beasley et al, 1991). The incidence of suicidal

acts and suicidal ideation in fluoxetine-treated patients were compared to those patients treated with either tricyclic antidepressant agents or placebo. Suicidal ideation occurred marginally significantly less often with fluoxetine than with placebo and numerically less often than with tricyclic antidepressants (Beasley et al, 1991).
f) One trial studied 1017 patients receiving treatment for depression. Two hundred and thirty-one of those were treated with fluoxetine alone, and when compared with patients treated with other regimens, no significant increase in suicidal episodes was found. Association between fluoxetine and suicide is disputed (Hoover, 1991; Fava & Rosenbaum, 1991).
g) One paper reported 2 patients without previous history of suicidal ideation, gestures, mania, or hypomania who developed suicidal ideations beginning 3 days to 2 weeks following initiation of fluoxetine therapy for depression. Suicidal ideations disappeared within a week of discontinuing treatment in both patients (Masand et al, 1991).
h) One paper reported 3 cases in which the patient's suicidal thoughts while on fluoxetine seemed to stem directly from problems with akathisia. Cessation of fluoxetine treatment was associated with elimination of both akathisia and suicidal thoughts (Rothschild & Locke, 1991).

3.3.13 Renal Effects

3.3.13.A Fluoxetine Hydrochloride

3.3.13.A.1 Urogenital finding
a) Sexual dysfunction, abortion, albuminuria, amenorrhea, cystitis, dysuria, impotence, leukorrhea, menorrhagia, nocturia, ovarian disorder, priapism, impaired urination, polyuria, urethritis, urinary incontinence, urinary urgency, and vaginitis have been reported with fluoxetine therapy (Prod Info Prozac(R), 2003c).

3.3.14 Reproductive Effects

Fluoxetine

Fluoxetine Hydrochloride

3.3.14.A Fluoxetine

3.3.14.A.1 Sexual dysfunction
See Drug Consult reference: DRUG-INDUCED SEXUAL DYSFUNCTION
See Drug Consult reference: SELECTIVE SEROTONIN REUPTAKE INHIBITOR-INDUCED SEXUAL DYSFUNCTION

3.3.14.B Fluoxetine Hydrochloride

Fibrocystic disease of breast

Sexual dysfunction

3.3.14.B.1 Fibrocystic disease of breast
a) Exacerbation of fibrocystic breast disease occurred in a woman following 6 months of therapy with fluoxetine 20 mg/day. The patient experienced increased breast pain, discomfort, and enlargement of palpable cysts; her symptoms stabilized after fluoxetine was discontinued (McKenzie & Risch, 1995).

3.3.14.B.2 Sexual dysfunction
a) Summary
1) Both anorgasmia and delayed orgasm have been reported in both males and females receiving fluoxetine (Prod Info Prozac(R), 2003c; Herman et al, 1990; Kline, 1989; Fontaine & Chouinard, 1989). Paradoxically, there is at least one case report of a woman experiencing multiple orgasms and repeated yawning (Modell, 1989), as well as improvement of sexual response in a few cases of elderly men (Power-Smith, 1994; Smith & Levitte, 1993). Administration of oral cyproheptadine 4 mg or granisetron 1 mg about 1 hour before sexual intercourse increased sexual interest and increased the ability to achieve orgasm in 2 women (Nelson et al, 1997; Ellison, 1996). Sexual dysfunction may be more common with fluoxetine than with other antidepressants. In one small open study, 36% of patients reported some sexual dysfunction, which disappeared when the dose of fluoxetine was lowered (Benazzi & Mazzoli, 1994). Other accounts range from 7.8% to 75% (Balon, 1995; Silverglat, 1995; Hopkins, 1995; Hollander, 1995). It is not clear whether or not this

sexual dysfunction is reversible; in one study, fluoxetine was the only SSRI for which improvement of sexual functioning did not result after brief cessation of administration (Rothschild, 1995).

b) Induction of sexual dysfunction may be a positive effect in some persons, such as men with premature ejaculation. One open clinical trial found significant improvement of premature ejaculation with fluoxetine doses up to 60 mg/day (Lee et al, 1996). Positive results were also obtained in a double-blind placebo controlled study on 17 patients (Kara et al, 1996).

c) A 50-year-old woman reported difficulty achieving orgasm during sexual intercourse and unintended exercise-induced orgasms after her fluoxetine dosage was increased to 20 mg daily. Oral cyproheptadine 4 mg before sexual intercourse partially alleviated anorgasmia. Treatment with fluoxetine for several months resolved depressive symptoms; fluoxetine was tapered and stopped. Her sexual function returned to baseline. The exact mechanism by which fluoxetine causes sexual dysfunction is unknown (Ellison, 1996).

d) In 3 case reports of elderly men (Smith & Levitte, 1993) return of normal erections and sexual potency occurred with fluoxetine therapy. Improvement in sexual functioning was reported in 2 elderly men that ceased after drug discontinuance, but returned in both cases after reinstitution of therapy (Power-Smith, 1994).

e) Sexual dysfunction was reported in 5 of 60 patients treated on an outpatient basis with fluoxetine. Three of the patients (all male) experienced delayed orgasm while taking 20 mg/day of fluoxetine; 2 of the patients (both female) suffered anorgasmia. One of the women experienced anorgasmia on the initial regimen of 20 mg/day; the other woman experienced anorgasmia after the dosage had been titrated to 80 mg/day over 3 weeks. Interestingly, all of the men, but neither of the women, had a history of sexual dysfunction associated with previous antidepressant therapy. One patient (male) found the dysfunction to resolve despite continued fluoxetine therapy. The authors state that the 8% rate of sexual dysfunction associated with fluoxetine in this series of observations is similar to the 5% rate reported by others (Stark & Hardison, 1985a). The authors note that sexual dysfunction is likely to be more common than reported, due to embarrassment on the part of patients and lack of active questioning by clinicians. Proposed treatment strategies include lowering the fluoxetine dose, if possible, or adding the serotonin antagonist cyproheptadine, although these have not been tested (Herman et al, 1990).

f) The repeated occurrence of yawning (without drowsiness) and multiple orgasms (associated with clitoral engorgement) were reported in a 30-year-old woman with depression treated with fluoxetine. The patient was given doses of 20 mg orally once daily in the morning for 7 days, followed by an increase in dose to 40 mg every morning. Symptoms developed within 2 days following the dosage increase and subsided following dose reductions to 20 mg daily. The patient was rechallenged with successively increasing doses of fluoxetine, resulting in recurrence of symptoms on several occasions and abatement of symptoms after withdrawal of the drug. It is suggested that acute increases in serotonergic neuronal activity may have caused the adverse effects observed in this patient (Modell, 1989).

g) In an open trial of fluoxetine in patients with obsessive-compulsive disorder, 2 of 28 male patients reported inhibited ejaculation. The doses of fluoxetine taken by the subjects were not reported; for the study sample, the mean daily dose was 78 mg (undivided) (Fontaine & Chouinard, 1989).

3.3.15 Respiratory Effects

3.3.15.A Fluoxetine Hydrochloride

3.3.15.A.1 Respiratory finding

a) Both rhinitis (23%) and pharyngitis (10%) have been reported to occur at a greater rate with fluoxetine therapy than placebo (17% and 6%, respectively). A 62-year-old woman developed cough and dyspnea 4 months after beginning fluoxetine. Symptoms resolved when fluoxetine was discontinued and recurred within 5 days when it was restarted. She developed interstitial infiltrates and restrictive lung disease and bronchioalveolar lavage was suggestive of hypersensitivity pneumonitis (Gonzalez-Rothi et al, 1995).

3.3.16 Other

Fluoxetine

Fluoxetine Hydrochloride

3.3.16.A Fluoxetine

3.3.16.A.1 Drug withdrawal

See Drug Consult reference: WITHDRAWAL SYNDROME OF SELECTIVE SEROTONIN REUPTAKE INHIBITORS

3.3.16.B Fluoxetine Hydrochloride

Drug withdrawal

Fever

Serotonin syndrome

Serotonin syndrome, and concurrent syndrome of inappropriate vasopressin secretion

3.3.16.B.1 Drug withdrawal

a) A discontinuation syndrome of dizziness, light-headedness, insomnia, fatigue, anxiety, agitation, nausea, headache, and sensory disturbances has been described after abrupt discontinuation of fluoxetine therapy (Zajecka et al, 1997).

b) In 395 subjects completing 12 weeks of maintenance treatment of depression with fluoxetine 20 mg/day, abrupt discontinuation of fluoxetine was not associated with symptoms of a discontinuation syndrome over 6 weeks of follow-up. Subjects with depression and a Hamilton Rating Scale for Depression (HAM-D) score of greater than or equal to 16 (mean, 20.9 +/- 3.6) received fluoxetine 20 mg/day for 12 weeks. After acute treatment with fluoxetine, responding subjects were abruptly randomized to placebo (n=96) or fluoxetine 20 mg/day (n=299) and were followed for adverse events for 6 weeks. One week prior to randomization to placebo or fluoxetine, reports of new or worsened adverse events were similar in both groups. No significant difference between treatment groups in the number of patients reporting adverse events at baseline, at any reporting interval after randomization, or over the 6-week observation period was observed. With the exceptions of dizziness, somnolence, rhinitis, and dysmenorrhea, which occurred significantly more often in placebo patients at different time points during the follow-up period, the profile of new adverse events reported was similar for both treatment groups (Zajecka et al, 1998).

3.3.16.B.2 Fever

a) Pyrexia has infrequently been associated with fluoxetine use (Prod Info Prozac(R), 2003c).

3.3.16.B.3 Serotonin syndrome

a) Serotonin syndrome, including life-threatening cases, or neuroleptic malignant syndrome (NMS)-like reactions have been reported with the use of fluoxetine alone. Signs and symptoms of serotonin syndrome include mental status changes (eg, agitation, hallucination, coma), autonomic instability (eg, tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (eg, hyperreflexia, incoordination) and/or gastrointestinal symptoms (eg, nausea, vomiting, diarrhea). Severe serotonin syndrome can resemble NMS with symptoms including hyperthermia, muscle rigidity, autonomic instability with possible rapid fluctuation of vital signs, and mental status changes. Serotonin syndrome occurs most commonly with the concomitant use of serotonergic drugs, including triptans, with drugs that impair metabolism of serotonin, including MAOIs, or with antipsychotics or other dopamine antagonists (Prod Info PROZAC(R) delayed-release capsules, oral capsules, solution, 2009).

b) A 36-year-old woman developed serotonin syndrome on 4 separate occasions; 2 were attributable to fluoxetine treatment and 2 to citalopram treatment. Fluoxetine was first prescribed when she reported anxiety and insomnia precipitated by a stalker. She routinely took guaifenesin/pseudoephedrine for nasal allergies. Approximately 1 month after starting fluoxetine 20 mg/day, she collapsed. She had earlier had a few mixed drinks. She became flaccid in all extremities and unresponsive to verbal commands and painful stimuli. This was followed by apnea, requiring ventilation for 1 hour before recovery of spontaneous respiration. She recovered from coma in another hour and was immediately alert and could move all muscles normally. She had diffuse muscle aches afterward. A week later, she resumed fluoxetine treatment, while avoiding alcohol. About 2 weeks later, she was found unresponsive and became apneic, again requiring ventilation, this time for about 2 hours. No diagnostic tests showed any abnormalities. She was diagnosed with serotonin syndrome. She recovered completely the next day. Afterward, she had severe diffuse muscle pain, weakness, and tremors, which were alleviated by magnesium and vitamin B6 supplements over a 2-month period. Nearly 2 years later, after reporting trembling, a shaky feeling, easy fatigability, palpitations, sweating, exaggerated startle response, and insomnia, she was given alprazolam 0.25 mg if needed in the morning and zaleplon 10 mg if needed for sleep at night. Citalopram 10 mg/day was later added, with no change in the alprazolam and zaleplon dosages. Three days after starting citalopram, she had another attack of serotonin syndrome, which she anticipated when she developed tremulousness and palpitations. Her neurologic response was the same as it had been previously, except that she did not develop apnea. The coma lasted 3 hours. The psychiatrist chose not to discontinue citalopram but reduced the dose to 5 mg/day. Three days later, she had another episode. The coma lasted for 1.5 hours. Citalopram was discontinued and she had no recurrence of symptoms of serotonin syndrome (Chechani, 2002).

c) A 37-year-old male taking fluoxetine 20 mg/day developed confusion, diaphoresis, incoordination, diarrhea, and myoclonus after buspirone was added to his drug regimen (Manos, 2000).
d) A 50-year-old man developed serotonin syndrome several days after beginning nefazodone treatment for major depression. Rather than first tapering his standing treatment of fluoxetine over 4 days before starting nefazodone, he reduced the fluoxetine dose from 60 to 40 mg/day for 2 days and thereafter concurrently took fluoxetine and nefazodone 200 mg/day. He was hospitalized on day 6 with symptoms of serotonin syndrome. Although his condition worsened immediately after the discontinuation of the 2 antidepressants, he recovered completely by day 4 (Smith & Wenegrat, 2000).
e) The serotonin syndrome manifested by mental status changes, sweating, diarrhea, and slurred speech developed in a 39-year-old woman and was possibly attributed to use of several drugs (ie, fluoxetine, venlafaxine, clonazepam, trazodone, cimetidine) concurrently or in close proximity. This patient initially received fluoxetine, trazodone, clonazepam, and cimetidine; her psychiatric diagnoses included major depression and panic attacks. Due to continued symptoms, fluoxetine and clonazepam were abruptly stopped, and venlafaxine and lorazepam were started. Within 1 day, symptoms consistent with the serotonin syndrome developed but she delayed contacting her physician for 4 days. All medications except cimetidine were stopped with worsening symptoms over 2 days. On day 3, she restarted fluoxetine, trazodone, and clorazepate with resolution of symptoms over the next 3 days. This case is complicated by use of several drugs in close proximity with the potential for numerous drug interactions, pharmacodynamic interactions, and disease interference. Cimetidine and fluoxetine inhibit several cytochrome P450 enzymes which may have resulted in elevated concentrations of venlafaxine and the metabolite of trazodone. Noradrenergic effects of venlafaxine may have exacerbated panic disorder. Additionally, several drugs increased serotonergic activity. This case illustrates the importance of recognizing additive pharmacodynamic effects of drugs and potential drugs when prescribing several different drugs (Bhatara et al, 1998).

3.3.16.B.4 Serotonin syndrome, and concurrent syndrome of inappropriate vasopressin secretion
a) A 56-year-old man, with a history of intracerebral hemorrhagic stroke and depression, developed SIADH and serotonin syndrome concurrently following the addition of fluoxetine to his existing antidepressant regimen (olanzapine 2.5 mg/day and buspirone 10 mg twice daily). Four weeks following the initiation of fluoxetine 40 mg/day and one week following an increase in the dosage to 60 mg/day, the man presented with symptoms of SIADH (ie, serum osmolality of 240 milliosmoles (mOsm)/kg, low BUN, low sodium, normal serum glucose) and serotonin syndrome (ie, dilated pupils, restlessness, change in mental status, facial flushing, myoclonus, hyperreflexia, increased blood pressure, tachycardia). Following water restriction (1000 mL/day), an infusion of lorazepam (0.07 mg/kg/hr for 24 hours then tapered over 48 hours) and discontinuation of buspirone, olanzapine, and fluoxetine, the man's symptoms resolved over several days. Buspirone and olanzapine were reinitiated at the previous doses with no recurrence of adverse effects and fluoxetine was eliminated from his therapeutic drug regimen. A probable relationship between the use of fluoxetine and the development of the concurrent syndromes was indicated through the use of the Naranjo probability scale. The authors speculate that patients with a history of stroke may be more susceptible to severe adverse effects that may result from combination antidepressant therapy; however, additional studies are required to clarify any association between this patient group an increased incidence or severity of antidepressant-related adverse events (Bogdanovic et al, 2005).

3.4 Teratogenicity/Effects in Pregnancy/Breastfeeding
A) Teratogenicity/Effects in Pregnancy
1) U.S. Food and Drug Administration's Pregnancy Category: Category C (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008) (All Trimesters)
a) Either studies in animals have revealed adverse effects on the fetus (teratogenic or embryocidal or other) and there are no controlled studies in women or studies in women and animals are not available. Drugs should be given only if the potential benefit justifies the potential risk to the fetus.
2) Australian Drug Evaluation Committee's (ADEC) Category: C(Batagol, 1999)
a) Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible. Accompanying texts should be consulted for further details.
See Drug Consult reference: PREGNANCY RISK CATEGORIES
3) Crosses Placenta: Yes
4) Clinical Management
a) A large, population-based study found no increased risk of malformations in infants exposed to selective serotonin reuptake inhibitors (SSRI) , but the exposed infants were more likely to require treatment in a special or intensive care unit (Malm et al, 2005). The use of an SSRI, including fluoxetine, after 20 weeks of gestation has been associated with an increased risk of persistent pulmonary hypertension of the newborn (Chambers et al, 2006). A study of prospectively collected data suggests antenatal use of selective serotonin-reuptake inhibitor (SSRI) antidepressants is associated with QTc interval prolongation in exposed neonates (Dubnov-Raz et al, 2008). There was no significant association between the use of SSRIs in early pregnancy and the risks of birth defects, including congenital heart defects, according to a later population-based case-control study (Alwan et al, 2007). Neonates exposed to fluoxetine and other SSRI and selective serotonin and norepinephrine reuptake inhibitors (SNRI), late in the third trimester have developed signs and

symptoms of SSRI and SNRI toxicity or withdrawal syndrome (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008). However, the dangers of failing to treat major depression are obvious, and in each case, these dangers must be weighed against the potential for teratogenic effects (Nulman et al, 1997; Lamberg, 1999). In pregnant patients diagnosed with obsessive compulsive disorder, fluoxetine is recommended when behavioral therapy has proven inadequate (Anon, 2000; Altshuler et al, 1996).

5) Literature Reports

a) A study of prospectively collected data suggests antenatal use of selective serotonin-reuptake inhibitor (SSRI) antidepressants is associated with QTc interval prolongation in exposed neonates. Between January 2000 and December 2005, researchers compared 52 neonates exposed to SSRI antidepressants (paroxetine (n=25), citalopram (n=13), fluoxetine (n=12), fluvoxamine (n=1), and venlafaxine (n=1)) in the immediate antenatal period to 52 matched neonates with no exposure. Prolonged QTc is defined as an interval of greater than 460 milliseconds (msec) (the widely used upper limit cited by authorities in both pediatric cardiology and neonatology). A pediatric cardiologist blinded to drug exposure, interpreted all electrocardiograms (ECGs) using standard statistical analyses. ECG recordings revealed markedly prolonged mean QTc intervals in exposed neonates compared to unexposed neonates (mean; 409 +/- 42 msec versus 392 +/- 29 msec, p=0.02). The mean uncorrected QT interval was 7.5% longer among exposed neonates (mean; 280 +/- 31 msec versus 261 +/- 25 msec, p less than 0.001). Ten percent (n=5) of exposed neonates had a notable increase in QTc interval prolongation (greater than 460 msec) compared to none of the unexposed neonates. The longest QTc interval observed was 543 msec (Dubnov-Raz et al, 2008).

b) Data from the case-controlled National Birth Defects Prevention Study (NBDPS), which included data from 13,714 infants born between 1997 and 2002, indicated that early maternal exposure (defined as treatment with any SSRI from 1 month before to 3 months after conception) to SSRIs was associated with anencephaly in 9 exposed infants out of 214 (adjusted odds ratio (OR), 2.4; 95% confidence interval (CI), 1.1 to 5.1; P=0.02), craniosynostosis in 24 exposed infants out of 432 (adjusted OR 2.5; 95% CI, 1.5 to 4.0; P less than 0.001), and omphalocele in 11 exposed infants out of 181 (adjusted OR 2.8; 95% CI, 1.3 to 5.7; P=0.005). However, early exposure did not significantly increase the risks of congenital heart defects or most other birth defects. The most commonly used SSRIs reported by control mothers were sertraline, fluoxetine, paroxetine, and citalopram (Alwan et al, 2007).

c) In a prospective longitudinal study (n=201), discontinuation of antidepressant medication in women with a history of major depression and who were euthymic at the start of pregnancy increased the chance for relapse of major depression compared to women who continued antidepressant medication. However, neonatal exposure, particularly in the third trimester, to fluoxetine and other selective serotonin reuptake inhibitors (SSRIs) or serotonin and norepinephrine reuptake inhibitors (SNRIs) has led to complications requiring prolonged hospitalization, respiratory support, and tube feeding. Clinical findings have included cyanosis, apnea, seizures, tremor, and constant crying, and the clinical scenario is reflective of serotonin syndrome. Therefore, a careful assessments of potential risks and benefits of treatment must be conducted prior to using fluoxetine during pregnancy, particularly in the third trimester (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).

d) A case-control study found that the use of selective serotonin reuptake inhibitors (SSRIs) after 20 weeks of gestation was associated with an increased risk of persistent pulmonary hypertension of the newborn (PPHN). Fluoxetine, paroxetine, and sertraline were the specific SSRIs studied to carry this increased risk. A total of 377 women who had infants with PPHN were matched to 836 women and their infants. Assessment of exposure was determined by telephone interview within 6 months of birth. After adjusting for other covariates, SSRI use after 20 weeks of gestation was associated with an odds ratio of 6.1 (95% CI 2.2-16.8; p=0.001) of delivering an infant with PPHN relative to no use during the pregnancy. SSRI use before 20 weeks of gestation and non-SSRI antidepressants use at any gestation time was not associated with increased risk of PPHN development. The incidence of PPHN in the general population is about 0.1 to 0.2%. According to this study, infants exposed to SSRIs after 20 weeks of gestation have a PPHN incidence of 0.6 to 1.2% (Chambers et al, 2006).

e) A population-based study of 1782 pregnant women exposed to selective serotonin reuptake inhibitors (SSRIs) found no increased risk of adverse perinatal outcome except for treatment in the neonatal intensive or special care unit, particularly with third trimester exposure. Using 1996 to 2001 data derived from a government project involving 4 birth or medication registries in Finland, women who had at least one purchase (a 3-months' supply) of an SSRI during the period of one month before pregnancy and the day pregnancy ended were compared to 1782 controls with no reimbursed drug purchases during the same peripartum period. The mean age of both cohorts was 30 years (+/- 7). There were more than twice as many smokers and six times as many pregnancies induced by artificial reproductive techniques in the SSRI group compared to controls (p less than 0.001), and mean length of gestation and birth weight were lower (p less than 0.001) in the SSRI group. Malformations, however, were not more common in the SSRI group (p = 0.4). Purchases of SSRIs (citalopram, fluoxetine, paroxetine, sertraline and fluvoxamine) were more common in the first trimester than later in pregnancy, with 525 women purchasing fluoxetine during the first trimester, 232 during the second trimester, 239 during the third, and 65 throughout pregnancy. When compared to first trimester exposure, treatment in a special or intensive care unit was more common for the infants exposed during the third trimester (11.2% and 15.7%, respectively; p = 0.009). Even after adjusting for confounding variables, this difference remained statistically significant (OR 1.6; 95% CI 1.1 to 2.2) (Malm et al, 2005).

f) In a prospective clinical trial designed to evaluate the pharmacokinetics of fluoxetine and norfluoxetine during pregnancy, delivery, and lactation, pregnancy outcomes were found to be similar in both the control

and treated groups. The study compared results from 11 women taking fluoxetine 20 to 50 mg per day during pregnancy and lactation to 10 women in the control group who were not exposed to psychotropic medications. Due to increased hepatic blood flow, increased volume of distribution and decreased binding to plasma proteins, trough plasma concentrations of fluoxetine and norfluoxetine were low. At delivery, umbilical vein concentrations were 65% and 72% of the maternal concentrations, respectively. During the early postnatal period, plasma concentrations of fluoxetine and norfluoxetine were still elevated, likely due to the slow development of infant glucuronidation capacity and CYP2D6 enzyme activity. There were no fetal malformations or difference in birth weights between the two groups. However, Apgar scores at fifteen minutes were lower in the fluoxetine group (Heikkinen et al, 2003).

g) In one study assessing the direct effects of fluoxetine on infant outcome at birth (Chambers et al, 1996), the authors concluded that neonates exposed to fluoxetine in the third trimester may be at an increased risk for perinatal complications such as respiratory difficulty, cyanosis on feeding, and jitteriness. These neonates may have had difficulty clearing the drug due to its long half-life. Depending on the woman's clinical situation, the practitioner and patient may consider tapering the dose of fluoxetine to discontinue 10 to 14 days prior to delivery to minimize the fetal load at birth (Wisner et al, 1999).

h) Based on analyses of independently collected data and that obtained through the Motherisk Program, there appear to be no differences in cognitive function, temperament and general behavior in children exposed prenatally to fluoxetine as compared to controls (Nulman et al, 2002; Wisner et al, 1999; Nulman & Koren, 1996; Nulman et al, 1997). However, among infants who were exposed to either fluoxetine or tricyclic antidepressants throughout gestation, those born to mothers with uncontrolled depressive symptoms showed lower cognitive and language achievements than those born to mothers who were well-controlled (Nulman et al, 2002).

i) An increased risk for central nervous system serotonergic symptoms was observed during the first four days of life in infants of mothers taking selective serotonin reuptake inhibitors (SSRI) during the third trimester of pregnancy. In a controlled, prospective study, women taking 20 to 40 milligrams/day of either citalopram (n=10) or fluoxetine (n=10) while pregnant were compared to a control group (n=20). Exposure to SSRI therapy ranged from 7 to 41 weeks. Newborns in the SSRI group had a lower Apgar score at 15 minutes as compared with the control group (8.8 vs 9.4; p=0.02). The only significant difference observed in the vital signs of the newborns was a higher heart rate in the SSRI group at two weeks as compared with the controls (mean, 153 vs 141 beats per minute; p=0.049). Serotonergic symptom scores in the first 4 days after birth were significantly higher in the SSRI group than in the control group (total score, 121 vs 30, respectively; p=0.008). Tremor, restlessness, and rigidity were the most prominent symptoms. Myoclonus was reported in one infant exposed to fluoxetine. Significantly lower cord blood 5-hydroxyindoleacetic acid (5-HIAA) concentrations were seen in the SSRI-exposed infants as compared with the control group (mean, 63 mmol/L vs 77 mmol/L; p=0.02). Additionally, a significant inverse correlation was observed between the serotonergic symptom score and the umbilical vein 5-HIAA concentrations in the SSRI-exposed newborns, but not in the control group (p=0.007). Although not statistically significant, mean umbilical cord serum prolactin concentrations were 29% lower in SSRI- exposed infants than in control infants at the time of birth (Laine et al, 2003).

B) Breastfeeding

1) American Academy of Pediatrics Rating: Drugs for which the effect on nursing infants is unknown but may be of concern. (Anon, 2001)

2) Thomson Lactation Rating: Infant risk cannot be ruled out.

a) Available evidence and/or expert consensus is inconclusive or is inadequate for determining infant risk when used during breastfeeding. Weigh the potential benefits of drug treatment against potential risks before prescribing this drug during breastfeeding.

3) Clinical Management

a) Fluoxetine and its active metabolite, norfluoxetine, appear in breast milk and the oral dose available to the infant has been estimated at 15 to 20 mcg/kg/day for fluoxetine (Burch & Wells, 1992), and 40 mcg/kg/day for fluoxetine plus norfluoxetine (Taddio et al, 1996). Despite the manufacturer's recommendation that fluoxetine not be used by women while breastfeeding (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008), many women choose to do so. The American Academy of Pediatrics considers antidepressants to be drugs worthy of concern in the nursing infant (Anon, 2001). There is insufficient data available to safely recommend use of fluoxetine by nursing mothers. If the decision is made to use fluoxetine, the infant should be monitored for anorexia, weight loss, irritability, and insomnia. The long-term effects of exposure to selective serotonin reuptake inhibitors (SSRIs) via breast milk on the cognitive development of the infant have not been determined.

4) Literature Reports

a) A number of cases have been reported in which fluoxetine was used to treat postpartum depression in nursing mothers. No effect on milk production or composition was observed. While increased infant irritability during maternal fluoxetine treatment has been described, all infants developed normally after exposure to fluoxetine during nursing (Epperson et al, 2003; Burch & Wells, 1992; Isenberg, 1990).

b) In a study of 14 mother-infant pairs, the mean total infant exposure was estimated as 6.81% (3.36% for fluoxetine and 3.45% for norfluoxetine). Of the 9 infants with blood samples, 5 and 7 had detectable concentrations of fluoxetine and norfluoxetine, respectively. Two infants had colic, while 2 others had withdrawal symptoms described as uncontrollable crying, irritability, and poor feeding. Symptoms in the latter infants were consistent with high plasma concentrations of fluoxetine and/or norfluoxetine. One mother also used methadone, and 4 infants were exposed to fluoxetine in utero. The authors recommend caution

especially during the early neonatal period and in infants exposed in utero to fluoxetine (Kristensen et al, 1999).
c) A 1996 cohort study involved 11 infants nursed by 10 mothers. Although limited by maternal perception, no adverse effects in the breastfeeding infants were reported by the mothers (Taddio et al, 1996).
d) One study described 4 nursing mothers, taking 20 to 40 mg of fluoxetine per day, in which the Bayley Scales were used to assess the neurological development of the infants. None of the infants exhibited any neurological abnormality (Taddio et al, 1996).
e) The manufacturer reports a maternal plasma concentration of 295 nanograms/mL for fluoxetine plus norfluoxetine, with a corresponding breast milk concentration of 70.4 nanograms/mL. No adverse effects in the nursing infant were reported. In another case, a nursing infant's plasma drug levels were 340 nanograms/mL of fluoxetine and 208 nanograms/mL of norfluoxetine on the second day of breastfeeding. The mother's daily dose of fluoxetine was not reported. The infant developed crying, sleep disturbance, vomiting, and watery stools (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
f) No clinically significant changes in platelet 5-hydroxytryptamine (5-HT) transport were reported in 11 infants (mean age of 16.8 weeks at the start of the study) exposed to fluoxetine through maternal breast milk. Determinations of whole-blood 5-HT, fluoxetine, and norfluoxetine levels were made in both infants and mothers prior to initiating fluoxetine doses of 20 mg to 40 mg per day. Post-exposure levels were measured at 4 to 12 weeks later. Mean maternal plasma concentrations of fluoxetine were 125 nanograms/mL, and norfluoxetine were 142 nanograms/mL. All but one infant had plasma fluoxetine levels below 1 nanograms/mL, and the mean infant plasma concentration of norfluoxetine was 3.2 nanograms/mL. Mean maternal pre- and post-fluoxetine 5-HT levels were 157 nanograms/mL and 23 nanograms/mL, respectively. The mean infant pre- and postexposure 5-HT concentrations were 217 nanograms/mL and 230 nanograms/mL, respectively. Baley Scale scores were determined for 7 of the infants (age range 24 to 56 weeks), revealing that 6 infants were within one standard deviation of the mean on mental and motor developmental indices. The investigators concluded that most exclusively breastfed infants will not likely experience changes in platelet 5-HT levels upon maternal fluoxetine use (Epperson et al, 2003).

5) Drug Levels in Breastmilk
- **a)** Parent Drug
  - **1)** Milk to Maternal Plasma Ratio
    - **a)** 0.21-1.51 (Isenberg, 1990; Taddio & Ito, 1996)
- **b)** Active Metabolites
  - **1)** NORFLUOXETINE (Pons & Rey, 1994)

3.5 Drug Interactions

3.5.1 Drug-Drug Combinations

Abciximab

Acecainide

Aceclofenac

Acemetacin

Acenocoumarol

Ajmaline

Alclofenac

Almotriptan

Alprazolam

Amiodarone

Amisulpride

Amitriptyline

Amoxapine

Anagrelide

Ancrod

Anisindione

Antithrombin III Human

Aprindine

Ardeparin

Aripiprazole

Arsenic Trioxide

Aspirin

Astemizole

Atomoxetine

Azimilide

Benoxaprofen

Bepridil

Bivalirudin

Bretylium

Bromfenac

Bufexamac

Bupropion

Buspirone

Cannabis

Carbamazepine

Carprofen

Celecoxib

Certoparin

Chloral Hydrate

Chloroquine

Chlorpromazine

Cilostazol

Clarithromycin

Clonixin

Clopidogrel

Clopidogrel

Clorgyline

Clozapine

Cyclobenzaprine

Cyproheptadine

Dalteparin

Danaparoid

Defibrotide

Dehydroepiandrosterone

Delavirdine

Dermatan Sulfate

Desipramine

Desirudin

Desvenlafaxine

Dexfenfluramine

Dexketoprofen

Dextromethorphan

Diazepam

Dibenzepin

Diclofenac

Dicumarol

Diflunisal

Digitoxin

Digoxin

Dihydroergotamine

Dipyridamole

Dipyrone

Disopyramide

Dofetilide

Dolasetron

Doxepin

Droperidol

Droxicam

Duloxetine

Eletriptan

Enflurane

Enoxaparin

Epoprostenol

Eptifibatide

Ergoloid Mesylates

Ergonovine

Ergotamine

Erythromycin

Etodolac

Etofenamate

Etoricoxib

Felbinac

Fenbufen

Fenfluramine

Fenoprofen

Fentiazac

Flecainide

Floctafenine

Fluconazole

Flufenamic Acid

Fluphenazine

Flurbiprofen

Fondaparinux

Foscarnet

Fosphenytoin

Frovatriptan

Furazolidone

Galantamine

Gemifloxacin

Ginkgo

Halofantrine

Haloperidol

Halothane

Heparin

Hydroquinidine

Hydroxytryptophan

Ibuprofen

Ibutilide

Iloperidone

Iloprost

Imipramine

Indomethacin

Indoprofen

Insulin Aspart, Recombinant

Insulin Detemir

Insulin Glargine, Recombinant

Insulin Glulisine

Insulin Human Inhaled

Iproniazid

Isocarboxazid

Isoflurane

Isoxicam

Isradipine

Ketoprofen

Ketorolac

Lamifiban

Levomethadyl

Lexipafant

Lidoflazine

Linezolid

Lithium

Lorcainide

Lornoxicam

Meclofenamate

Mefenamic Acid

Mefloquine

Meloxicam

Meperidine

Mesoridazine

Methylergonovine

Methylphenidate

Methysergide

Metoprolol

Milnacipran

Mirtazapine

Moclobemide

Morniflumate

Nabumetone

Nadroparin

Naproxen

Naratriptan

Nebivolol

Nialamide

Niflumic Acid

Nimesulide

Nortriptyline

Octreotide

Oxaprozin

Parecoxib

Pargyline

Parnaparin

Paroxetine

Pentamidine

Pentazocine

Pentosan Polysulfate Sodium

Phenelzine

Phenindione

Phenprocoumon

Phenylbutazone

Phenytoin

Pimozide

Pirazolac

Pirmenol

Piroxicam

Pirprofen

Prajmaline

Probucol

Procainamide

Procarbazine

Prochlorperazine

Propafenone

Propranolol

Propyphenazone

Proquazone

Quetiapine

Quinidine

Rasagiline

Reviparin

Risperidone

Ritonavir

Rizatriptan

Rofecoxib

Selegiline

Sematilide

Sertindole

Sibrafiban

Sibutramine

Sotalol

Spiramycin

St John's Wort

Sulfamethoxazole

Sulfinpyrazone

Sulindac

Sulodexide

Sultopride

Sumatriptan

Suprofen

Tamoxifen

Tamsulosin

Tapentadol

Tedisamil

Telithromycin

Tenidap

Tenoxicam

Terfenadine

Tetrabenazine

Thioridazine

Tiaprofenic Acid

Ticlopidine

Tinzaparin

Tipranavir

Tirofiban

Tolmetin

Toloxatone

Tramadol

Tranylcypromine

Trazodone

Trifluoperazine

Trimethoprim

Trimipramine

Tryptophan

Valdecoxib

Vasopressin

Venlafaxine

Warfarin

Xemilofiban

Ziprasidone

Zolmitriptan

Zolpidem

Zomepirac

Zotepine

3.5.1.A Abciximab

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and antiplatelet agents has been associated with an increased risk of bleeding. Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an antiplatelet agent are given concurrently, monitor patient for signs of increased bleeding (Prod Info PAXIL(R) oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008)
7) Probable Mechanism: unknown

3.5.1.B Acecainide

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, the coadministration of Class III antiarrhythmics and other drugs known to prolong the QTc interval is not recommended (Allen et al, 2002; Prod Info Tikosyn(TM) dofetilide capsules, 1999; Prod Info Corvert(R), 1998). Fluoxetine has been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Prozac(R), 2001a).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of class III antiarrhythmic agents and agents that prolong the QT interval, such as fluoxetine, is not recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.C Aceclofenac

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.D Acemetacin

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.E Acenocoumarol

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008). Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with warfarin (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When fluoxetine and an anticoagulant are given concurrently, monitor patient for signs of increased bleeding. Patients who are taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, when fluoxetine therapy is initiated or discontinued (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
7) Probable Mechanism: unknown

8) Literature Reports

a) Fluoxetine is thought to inhibit the cytochrome P450 2C9 isoenzyme (CYP2C9). This is the enzyme by which the more potent warfarin isomer, S-warfarin, is metabolized (Riesenman, 1995). In addition, both fluoxetine and warfarin are tightly bound to albumin. In combination, the possibility for protein-binding displacement of either drug is present (Prod Info Coumadin(R), 1999).

b) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bleeding (hospital admission due to bleeding) in patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patients with a mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients experienced 11 bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experiencing bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model (Wallerstedt et al, 2009).

c) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5), however, the rate of gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).

d) In 6 reported cases, INR increased during combined fluoxetine and warfarin therapy. In a seventh case, severe bruising of the lower legs occurred in a woman initially treated with fluoxetine and, secondarily, started on warfarin (Woolfrey et al, 1993; Claire et al, 1991).

e) An 83-year-old man died from cerebral hemorrhage secondary to increased warfarin concentrations. The patient had been taking warfarin 30 mg per week for atrial fibrillation with a target INR between 2 and 3. The patient's other drugs included lisinopril, furosemide, potassium, digoxin, and acetaminophen. After being seen for symptoms of depression, anxiety, and insomnia, the patient was given fluoxetine 20 mg per day and diazepam 2.5 mg 3 to 4 times per day. Eight days later, the patient's INR increased to 4.8, and the dose of warfarin was decreased to 27.5 mg per week. The patient was later seen for symptoms of drug delirium, including confusion, incoherence, and speaking irrationally. At this point, the INR was 3.64 and fluoxetine was discontinued. The next day the patient presented to the hospital with left-sided weakness and later died from complications of a large interparenchymal hemorrhage. The authors proposed that the addition of fluoxetine to the patient's regimen resulted in increased serum levels of both warfarin and diazepam, resulting in delirium and loss of anticoagulant control (Dent & Orrock, 1997).

3.5.1.F Ajmaline

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Even though no formal drug interaction studies have been done, the coadministration of Class Ia antiarrhythmics and other drugs known to prolong the QTc interval is not recommended (Prod Info Quinaglute Dura-tabs(R), 1999). Fluoxetine has demonstrated QT prolongation at therapeutic doses (Prod Info Prozac(R), 2001z).

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of class Ia antiarrhythmic agents and agents that prolong the QT interval, such as fluoxetine, is not recommended.

7) Probable Mechanism: additive effects on QT prolongation

3.5.1.G Alclofenac

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.H Almotriptan

1) Interaction Effect: an increased risk of serotonin syndrome
2) Summary: Concomitant use of almotriptan and selective serotonin reuptake inhibitors (SSRI's) has been reported to cause weakness, hyperreflexia, and incoordination (Prod Info Axert(TM), 2001). Concurrent use of a triptan and an SSRI may result in serotonin syndrome which may be life-threatening. Symptoms of serotonin syndrome may include restlessness, hallucinations, loss of coordination, fast heart beat, rapid changes in blood pressure, increased body temperature, overreactive reflexes, nausea, vomiting, and diarrhea. Clinicians should be aware that triptans may be commonly used intermittently and that either the triptan or the SSRI may be prescribed by a different physician. Discuss the risks of serotonin syndrome with patients who are prescribed this combination and monitor them closely for symptoms of serotonin syndrome (US Food and Drug Administration, 2006).
3) Severity: major
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Coadministration of a triptan, such as almotriptan, and an SSRI may result in a life-threatening condition called serotonin syndrome. Be aware that triptans may be commonly used intermittently and that either the triptan or the SSRI may be prescribed by a different physician. If these agents are used together, discuss the risks of serotonin syndrome with the patient and monitor closely for symptoms of serotonin syndrome (restlessness, hyperthermia, hyperreflexia, incoordination).
7) Probable Mechanism: additive pharmacologic effects resulting in excessive serotonergic stimulation
8) Literature Reports
a) Concomitant administration of fluoxetine and almotriptan is well tolerated and fluoxetine has only a modest effect on almotriptan maximum plasma concentration (Cmax). Other almotriptan pharmacokinetics are not significantly affected. A randomized, open-label, two-way crossover study involving 14 healthy volunteers has been conducted. Subjects received each of the following treatments with a minimum 3-week washout between periods: (1) three 20 mg fluoxetine capsules on day 1 to 8 and one dose almotriptan 12.5 mg on day 8, (2) one dose of almotriptan 12.5 mg on day 8 with no treatment on days 1 through 7. Peak almotriptan concentrations were 18% higher following concomitant administration of fluoxetine than after almotriptan administration alone. This difference was statistically significant (p equal 0.023). Mean almotriptan area under the concentration-time curve (AUC) and oral clearance were borderline statistically different between treatment groups. Mean half-life was not statistically different between the treatment groups. During fluoxetine coadministration, Tmax was shorter, suggesting that the absorption rate of almotriptan may have been increased by fluoxetine. The author concludes that based on the results of this study and the lack of effect of fluoxetine on almotriptan pharmacokinetics, almotriptan and fluoxetine can be safely used concomitantly in migraine management (Fleishaker et al, 2001).

3.5.1.I Alprazolam

1) Interaction Effect: an increased risk of alprazolam toxicity (somnolence, dizziness, ataxia, slurred speech, hypotension, psychomotor impairment)
2) Summary: Coadministered fluoxetine increases alprazolam serum concentrations (Greenblatt et al, 1992a; Lasher et al, 1991a). The mechanism of this interaction is thought to be inhibition by fluoxetine of the cytochrome P453A4 isoenzyme (CYP3A4), which is principally responsible for alprazolam metabolism. Some benzodiazepines (lorazepam, oxazepam) are metabolized by glucuronidation rather than by the P450 system and may be the better choice for fluoxetine and benzodiazepine cotherapy.
3) Severity: moderate
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Monitor patients for signs and symptoms of alprazolam intoxication (somnolence, dizziness, ataxia, slurred speech, hypotension, psychomotor impairment). Alprazolam doses may need to be reduced. Alternatively, consider substituting a benzodiazepine (such as lorazepam or oxazepam) that has

less potential for interacting with fluoxetine.
7) Probable Mechanism: inhibition of cytochrome P450 3A-mediated alprazolam metabolism
8) Literature Reports
a) Alprazolam serum concentrations were analyzed in a double-blind, placebo-controlled study involving 80 healthy male volunteers (Lasher et al, 1991). Concurrent administration of alprazolam 1 mg four times a day and fluoxetine 60 mg each morning for four days resulted in a 30% increase in plasma alprazolam levels and a 21% decrease in the alprazolam elimination rate. The elevated alprazolam concentrations caused increased psychomotor impairment, but did not affect mood status or sedation.
b) The effect of fluoxetine on the pharmacokinetics of alprazolam was analyzed in a 31-day, double-blind, crossover, placebo-controlled study, which included a 10-day washout period (Greenblatt et al, 1992). Twelve healthy male volunteers were given fluoxetine 20 mg twice a day or placebo and a single dose of alprazolam 1 mg on days 3 and 24. Fluoxetine significantly increased the half-life of alprazolam from 17 hours to 20 hours and significantly decreased its clearance from 61 mL/min to 48 mL/min.
c) Inhibition of alprazolam metabolism by fluoxetine occurs via cytochrome P450 3A4. A randomized, double-blind, placebo-controlled with-in subject design was used to assess this potential interaction. Twenty healthy volunteers attended four study sessions: alprazolam/placebo was given in the absence of an SSRI in the first two study sessions; alprazolam/placebo while at steady-state with either citalopram 20 mg/day or fluoxetine 20 mg/day was given in the last two study sessions. At each session they received alprazolam 1 mg orally or placebo. Fluoxetine significantly prolonged the half-life of alprazolam by 16% and increased the area under the concentration-time curve by 32%. Citalopram did not affect these parameters. The effects of alprazolam were not altered by either SSRI. These findings suggest that citalopram and fluoxetine differentially alter alprazolam concentrations (Hall et al, 2002).

3.5.1.J Amiodarone
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, the coadministration of Class III antiarrhythmics and other drugs known to prolong the QTc interval is not recommended (Allen et al, 2002; Prod Info Tikosyn(TM) dofetilide capsules, 1999; Prod Info Corvert(R), 1998). Fluoxetine has been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Prozac(R), 2001a).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of class III antiarrhythmic agents and agents that prolong the QT interval, such as fluoxetine, is not recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.K Amisulpride
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Fluoxetine has been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Prozac(R), 2001l). Even though no formal drug interaction studies have been done, the coadministration of antipsychotics and other drugs known to prolong the QTc interval, including fluoxetine, is not recommended. Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999), quetiapine (Owens, 2001b), sertindole (Agelink et al, 2001), sultopride (Lande et al, 1992), and zotepine (Sweetman, 2003).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of fluoxetine and antipsychotics is not recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.L Amitriptyline
1) Interaction Effect: tricyclic antidepressant toxicity (dry mouth, urinary retention, sedation) and an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Tricyclic antidepressants (TCAs) and fluoxetine have been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Prozac(R), 2001h; Marshall & Forker, 1982). Even though no formal drug interaction studies have been done which demonstrate QT prolongation, the coadministration of tricyclic antidepressants and other drugs known to prolong the QTc interval, such as fluoxetine, is not recommended (Prod Info Elavil(R), 1999). In addition, concurrent use of fluoxetine and TCAs such as desipramine, nortriptyline, and imipramine has resulted in significant increases in TCA concentrations (Preskorn et al, 1994a; Preskorn et al, 1994a; Aranow et al, 1989a; Downs et al, 1989a; Goodnick, 1989a; Bell & Cole, 1988a).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: The concurrent administration of fluoxetine and a tricyclic antidepressant is not

recommended.
7) Probable Mechanism: decreased tricyclic antidepressant metabolism; additive effects on QT prolongation
8) Literature Reports
a) Fluoxetine increased the level of tricyclic antidepressants (nortriptyline, imipramine, desipramine) in 4 patients. After the addition of fluoxetine, the ratio of antidepressant level to dose increased by 109% to 486% in the patients. Three patients developed clinical symptoms (anticholinergic effects, constipation, urinary hesitancy, sedation, unstable gait) as a result of the increased levels (Aranow et al, 1989).
b) Fluoxetine statistically and clinically significantly increased desipramine concentrations in 18 healthy subjects. When fluoxetine (20 mg daily) was added to desipramine (50 mg daily), the mean maximum concentration of desipramine increased by 278% and the area under the concentration-time curve increased by 342%. Desipramine trough concentrations continued to be 198% above baseline three weeks after fluoxetine was discontinued. The same study compared pharmacokinetics of desipramine when combined with sertraline. The impact of sertraline was modest, resulting in small and short-term increases in desipramine plasma concentrations (Preskorn et al, 1994).
c) A 75-year-old female experienced symptomatic increases in her desipramine serum concentrations when fluoxetine was added. Desipramine serum levels ranged from 109 to 150 ng/mL with oral doses of 300 mg at bedtime prior to fluoxetine therapy. Following the addition of oral fluoxetine 20 mg daily to the regimen, the desipramine serum level increased to 212 ng/mL within five days. The fluoxetine dose was increased to 40 mg/day three days later, and the desipramine serum level was 419 ng/mL after four days. A worsening of depression and severe fatigue coincided with the increases in desipramine serum levels. Withdrawal of fluoxetine and reduction in the desipramine dose to 200 mg daily reduced the desipramine serum level to 231 ng/mL within two weeks (Bell & Cole, 1988).
d) A 33-year-old depressed male developed adverse effects of dry mouth, tinnitus, and difficulties with alertness and memory while receiving fluoxetine 40 mg daily and desipramine 150 mg daily for five weeks; fluoxetine was discontinued and the blood levels of desipramine decreased from 938 to 48 ng/mL with resolution of clinical symptoms (Goodnick, 1989).
e) A 39-year-old female experienced symptomatic increases in her desipramine levels with concomitant fluoxetine therapy. Prior to fluoxetine therapy, the patient's measured levels of desipramine had ranged from 148 to 160 ng/mL on a regimen of 300 mg daily. Five weeks after the addition of fluoxetine 20 mg daily, she reported anticholinergic symptoms, sedation, and confusion with a desipramine level of 527 ng/mL. The desipramine dose was lowered to 200 mg/day; eleven days later, the level was 244 ng/mL; the patient reported decreased energy, impaired short-term memory, and some "garbled" speech, as well as an episode of nausea, dizziness, and syncope. The desipramine dose was reduced to 50 mg/day; the adverse effects resolved in six days. Eight days later, the desipramine level was 122 ng/mL (Downs et al, 1989).
f) Concomitant administration of fluoxetine and desipramine was reported to result in an increased desipramine level and new onset of delirium in a 69-year-old male within 10 days of the addition of fluoxetine to the patient's regimen (Preskorn et al, 1990).

3.5.1.M Amoxapine
1) Interaction Effect: tricyclic antidepressant toxicity (dry mouth, urinary retention, sedation) and an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Tricyclic antidepressants (TCAs) and fluoxetine have been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Prozac(R), 2001h; Marshall & Forker, 1982). Even though no formal drug interaction studies have been done which demonstrate QT prolongation, the coadministration of tricyclic antidepressants and other drugs known to prolong the QTc interval, such as fluoxetine, is not recommended (Prod Info Elavil(R), 1999). In addition, concurrent use of fluoxetine and TCAs such as desipramine, nortriptyline, and imipramine has resulted in significant increases in TCA concentrations (Preskorn et al, 1994a; Preskorn et al, 1994a; Aranow et al, 1989a; Downs et al, 1989a; Goodnick, 1989a; Bell & Cole, 1988a).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: The concurrent administration of fluoxetine and a tricyclic antidepressant is not recommended.
7) Probable Mechanism: decreased tricyclic antidepressant metabolism; additive effects on QT prolongation
8) Literature Reports
a) Fluoxetine increased the level of tricyclic antidepressants (nortriptyline, imipramine, desipramine) in 4 patients. After the addition of fluoxetine, the ratio of antidepressant level to dose increased by 109% to 486% in the patients. Three patients developed clinical symptoms (anticholinergic effects, constipation, urinary hesitancy, sedation, unstable gait) as a result of the increased levels (Aranow et al, 1989).
b) Fluoxetine statistically and clinically significantly increased desipramine concentrations in 18 healthy subjects. When fluoxetine (20 mg daily) was added to desipramine (50 mg daily), the mean maximum concentration of desipramine increased by 278% and the area under the concentration-time curve increased by 342%. Desipramine trough concentrations continued to be 198% above baseline three weeks after fluoxetine was discontinued. The same study compared pharmacokinetics of desipramine

when combined with sertraline. The impact of sertraline was modest, resulting in small and short-term increases in desipramine plasma concentrations (Preskorn et al, 1994).
c) A 75-year-old female experienced symptomatic increases in her desipramine serum concentrations when fluoxetine was added. Desipramine serum levels ranged from 109 to 150 ng/mL with oral doses of 300 mg at bedtime prior to fluoxetine therapy. Following the addition of oral fluoxetine 20 mg daily to the regimen, the desipramine serum level increased to 212 ng/mL within five days. The fluoxetine dose was increased to 40 mg/day three days later, and the desipramine serum level was 419 ng/mL after four days. A worsening of depression and severe fatigue coincided with the increases in desipramine serum levels. Withdrawal of fluoxetine and reduction in the desipramine dose to 200 mg daily reduced the desipramine serum level to 231 ng/mL within two weeks (Bell & Cole, 1988).
d) A 33-year-old depressed male developed adverse effects of dry mouth, tinnitus, and difficulties with alertness and memory while receiving fluoxetine 40 mg daily and desipramine 150 mg daily for five weeks; fluoxetine was discontinued and the blood levels of desipramine decreased from 938 to 48 ng/mL with resolution of clinical symptoms (Goodnick, 1989).
e) A 39-year-old female experienced symptomatic increases in her desipramine levels with concomitant fluoxetine therapy. Prior to fluoxetine therapy, the patient's measured levels of desipramine had ranged from 148 to 160 ng/mL on a regimen of 300 mg daily. Five weeks after the addition of fluoxetine 20 mg daily, she reported anticholinergic symptoms, sedation, and confusion with a desipramine level of 527 ng/mL. The desipramine dose was lowered to 200 mg/day; eleven days later, the level was 244 ng/mL; the patient reported decreased energy, impaired short-term memory, and some "garbled" speech, as well as an episode of nausea, dizziness, and syncope. The desipramine dose was reduced to 50 mg/day; the adverse effects resolved in six days. Eight days later, the desipramine level was 122 ng/mL (Downs et al, 1989).
f) Concomitant administration of fluoxetine and desipramine was reported to result in an increased desipramine level and new onset of delirium in a 69-year-old male within 10 days of the addition of fluoxetine to the patient's regimen (Preskorn et al, 1990).

3.5.1.N Anagrelide

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and antiplatelet agents has been associated with an increased risk of bleeding. Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an antiplatelet agent are given concurrently, monitor patient for signs of increased bleeding (Prod Info PAXIL(R) oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008)
7) Probable Mechanism: unknown

3.5.1.O Ancrod

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008). Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with warfarin (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When fluoxetine and an anticoagulant are given concurrently, monitor patient for signs of increased bleeding. Patients who are taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, when fluoxetine therapy is initiated or discontinued (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
7) Probable Mechanism: unknown
8) Literature Reports
a) Fluoxetine is thought to inhibit the cytochrome P450 2C9 isoenzyme (CYP2C9). This is the enzyme by which the more potent warfarin isomer, S-warfarin, is metabolized (Riesenman, 1995). In addition, both fluoxetine and warfarin are tightly bound to albumin. In combination, the possibility for protein-binding displacement of either drug is present (Prod Info Coumadin(R), 1999).
b) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bleeding (hospital admission due to bleeding) in patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patients with a mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected

patients who received warfarin only (n=117). SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients experienced 11 bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experiencing bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model (Wallerstedt et al, 2009).

c) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5), however, the rate of gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).

d) In 6 reported cases, INR increased during combined fluoxetine and warfarin therapy. In a seventh case, severe bruising of the lower legs occurred in a woman initially treated with fluoxetine and, secondarily, started on warfarin (Woolfrey et al, 1993; Claire et al, 1991).

e) An 83-year-old man died from cerebral hemorrhage secondary to increased warfarin concentrations. The patient had been taking warfarin 30 mg per week for atrial fibrillation with a target INR between 2 and 3. The patient's other drugs included lisinopril, furosemide, potassium, digoxin, and acetaminophen. After being seen for symptoms of depression, anxiety, and insomnia, the patient was given fluoxetine 20 mg per day and diazepam 2.5 mg 3 to 4 times per day. Eight days later, the patient's INR increased to 4.8, and the dose of warfarin was decreased to 27.5 mg per week. The patient was later seen for symptoms of drug delirium, including confusion, incoherence, and speaking irrationally. At this point, the INR was 3.64 and fluoxetine was discontinued. The next day the patient presented to the hospital with left-sided weakness and later died from complications of a large interparenchymal hemorrhage. The authors proposed that the addition of fluoxetine to the patient's regimen resulted in increased serum levels of both warfarin and diazepam, resulting in delirium and loss of anticoagulant control (Dent & Orrock, 1997).

3.5.1.P Anisindione

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008). Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with warfarin (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: When fluoxetine and an anticoagulant are given concurrently, monitor patient for signs of increased bleeding. Patients who are taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, when fluoxetine therapy is initiated or discontinued (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).

7) Probable Mechanism: unknown

8) Literature Reports

a) Fluoxetine is thought to inhibit the cytochrome P450 2C9 isoenzyme (CYP2C9). This is the enzyme by which the more potent warfarin isomer, S-warfarin, is metabolized (Riesenman, 1995). In addition, both fluoxetine and warfarin are tightly bound to albumin. In combination, the possibility for protein-binding displacement of either drug is present (Prod Info Coumadin(R), 1999).

b) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bleeding (hospital admission due to bleeding) in patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patients with a mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients experienced 11 bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The

SSRI implicated in patients experiencing bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model (Wallerstedt et al, 2009).

c) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5), however, the rate of gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).

d) In 6 reported cases, INR increased during combined fluoxetine and warfarin therapy. In a seventh case, severe bruising of the lower legs occurred in a woman initially treated with fluoxetine and, secondarily, started on warfarin (Woolfrey et al, 1993; Claire et al, 1991).

e) An 83-year-old man died from cerebral hemorrhage secondary to increased warfarin concentrations. The patient had been taking warfarin 30 mg per week for atrial fibrillation with a target INR between 2 and 3. The patient's other drugs included lisinopril, furosemide, potassium, digoxin, and acetaminophen. After being seen for symptoms of depression, anxiety, and insomnia, the patient was given fluoxetine 20 mg per day and diazepam 2.5 mg 3 to 4 times per day. Eight days later, the patient's INR increased to 4.8, and the dose of warfarin was decreased to 27.5 mg per week. The patient was later seen for symptoms of drug delirium, including confusion, incoherence, and speaking irrationally. At this point, the INR was 3.64 and fluoxetine was discontinued. The next day the patient presented to the hospital with left-sided weakness and later died from complications of a large interparenchymal hemorrhage. The authors proposed that the addition of fluoxetine to the patient's regimen resulted in increased serum levels of both warfarin and diazepam, resulting in delirium and loss of anticoagulant control (Dent & Orrock, 1997).

3.5.1.Q Antithrombin III Human

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008). Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with warfarin (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: When fluoxetine and an anticoagulant are given concurrently, monitor patient for signs of increased bleeding. Patients who are taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, when fluoxetine therapy is initiated or discontinued (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).

7) Probable Mechanism: unknown

8) Literature Reports

a) Fluoxetine is thought to inhibit the cytochrome P450 2C9 isoenzyme (CYP2C9). This is the enzyme by which the more potent warfarin isomer, S-warfarin, is metabolized (Riesenman, 1995). In addition, both fluoxetine and warfarin are tightly bound to albumin. In combination, the possibility for protein-binding displacement of either drug is present (Prod Info Coumadin(R), 1999).

b) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bleeding (hospital admission due to bleeding) in patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patients with a mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients experienced 11 bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experiencing bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model (Wallerstedt et al, 2009).

c) A population-based, case-controlled study of new coumarin users (acenocoumarol and

phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5), however, the rate of gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).

d) In 6 reported cases, INR increased during combined fluoxetine and warfarin therapy. In a seventh case, severe bruising of the lower legs occurred in a woman initially treated with fluoxetine and, secondarily, started on warfarin (Woolfrey et al, 1993; Claire et al, 1991).

e) An 83-year-old man died from cerebral hemorrhage secondary to increased warfarin concentrations. The patient had been taking warfarin 30 mg per week for atrial fibrillation with a target INR between 2 and 3. The patient's other drugs included lisinopril, furosemide, potassium, digoxin, and acetaminophen. After being seen for symptoms of depression, anxiety, and insomnia, the patient was given fluoxetine 20 mg per day and diazepam 2.5 mg 3 to 4 times per day. Eight days later, the patient's INR increased to 4.8, and the dose of warfarin was decreased to 27.5 mg per week. The patient was later seen for symptoms of drug delirium, including confusion, incoherence, and speaking irrationally. At this point, the INR was 3.64 and fluoxetine was discontinued. The next day the patient presented to the hospital with left-sided weakness and later died from complications of a large interparenchymal hemorrhage. The authors proposed that the addition of fluoxetine to the patient's regimen resulted in increased serum levels of both warfarin and diazepam, resulting in delirium and loss of anticoagulant control (Dent & Orrock, 1997).

3.5.1.R Aprindine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Even though no formal drug interaction studies have been done, the coadministration of Class I antiarrhythmics and other drugs known to prolong the QTc interval is not recommended (Prod Info Tambocor(R) flecainide acetate, 1998). Fluoxetine has been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Prozac(R), 2001w).

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of class I antiarrhythmic agents and agents that prolong the QT interval, such as fluoxetine, is not recommended.

7) Probable Mechanism: additive effects on QT prolongation

3.5.1.S Ardeparin

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008). Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with warfarin (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: When fluoxetine and an anticoagulant are given concurrently, monitor patient for signs of increased bleeding. Patients who are taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, when fluoxetine therapy is initiated or discontinued (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).

7) Probable Mechanism: unknown

8) Literature Reports

a) Fluoxetine is thought to inhibit the cytochrome P450 2C9 isoenzyme (CYP2C9). This is the enzyme by which the more potent warfarin isomer, S-warfarin, is metabolized (Riesenman, 1995). In addition, both fluoxetine and warfarin are tightly bound to albumin. In combination, the possibility for protein-binding displacement of either drug is present (Prod Info Coumadin(R), 1999).

b) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bleeding (hospital admission due to bleeding) in patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patients with a mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients experienced 11 bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4

and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experiencing bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model (Wallerstedt et al, 2009).

c) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5), however, the rate of gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).

d) In 6 reported cases, INR increased during combined fluoxetine and warfarin therapy. In a seventh case, severe bruising of the lower legs occurred in a woman initially treated with fluoxetine and, secondarily, started on warfarin (Woolfrey et al, 1993; Claire et al, 1991).

e) An 83-year-old man died from cerebral hemorrhage secondary to increased warfarin concentrations. The patient had been taking warfarin 30 mg per week for atrial fibrillation with a target INR between 2 and 3. The patient's other drugs included lisinopril, furosemide, potassium, digoxin, and acetaminophen. After being seen for symptoms of depression, anxiety, and insomnia, the patient was given fluoxetine 20 mg per day and diazepam 2.5 mg 3 to 4 times per day. Eight days later, the patient's INR increased to 4.8, and the dose of warfarin was decreased to 27.5 mg per week. The patient was later seen for symptoms of drug delirium, including confusion, incoherence, and speaking irrationally. At this point, the INR was 3.64 and fluoxetine was discontinued. The next day the patient presented to the hospital with left-sided weakness and later died from complications of a large interparenchymal hemorrhage. The authors proposed that the addition of fluoxetine to the patient's regimen resulted in increased serum levels of both warfarin and diazepam, resulting in delirium and loss of anticoagulant control (Dent & Orrock, 1997).

3.5.1.T Aripiprazole

1) Interaction Effect: increased aripiprazole levels

2) Summary: Aripiprazole is partly metabolized by cytochrome P450 2D6 (CYP2D6) enzymes. Coadministration with CYP2D6 inhibitors, such as fluoxetine, may inhibit aripiprazole elimination causing increased blood concentrations. Consider a dosage reduction for aripiprazole when these agents are coadministered. If therapy with fluoxetine is discontinued, the dose of aripiprazole should then be increased (Prod Info ABILIFY(R) oral tablets, oral solution, 2005).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: Increased aripiprazole plasma levels may result if used concomitantly with fluoxetine. Consider a dosage reduction for aripiprazole when these agents are coadministered. If therapy with fluoxetine is discontinued, the dose of aripiprazole should then be increased.

7) Probable Mechanism: inhibition of cytochrome P450 2D6-mediated metabolism of aripiprazole

3.5.1.U Arsenic Trioxide

1) Interaction Effect: cardiotoxicity (QT interval prolongation, torsades de pointes, cardiac arrest)

2) Summary: Arsenic trioxide and fluoxetine have been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Trisenox(R), 2001a; Prod Info Prozac(R), 2001u). Even though no formal drug interaction studies have been done, arsenic trioxide should not be administered with other drugs which are also known or have the potential to prolong the QTc interval, including fluoxetine (Prod Info Trisenox(R), 2001a).

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of arsenic trioxide and fluoxetine is not recommended.

7) Probable Mechanism: additive effects on QT prolongation

8) Literature Reports

a) QT/QTc prolongation should be expected during treatment with arsenic trioxide and torsade de pointes as well as complete heart block has been reported. Over 460 ECG tracings from 40 patients with refractory or relapsed APL treated with arsenic trioxide were evaluated for QTc prolongation. Sixteen of 40 patients (40%) had at least one ECG tracing with a QTc interval greater than 500 msec. Prolongation of the QTc was observed between 1 and 5 weeks after arsenic trioxide infusion, and then returned towards baseline by the end of 8 weeks after arsenic trioxide infusion. In these ECG evaluations, women did not experience more pronounced QT prolongation than men, and there was no

correlation with age (Prod Info Trisenox(R), 2001).
b) QT Prolongation was observed on the electrocardiogram (ECG) of a 52- year-old man who had been taking fluoxetine (20 milligrams/day for 2 weeks, followed by 40 milligrams/day thereafter) for depression for 3 months. An ECG just before the start of fluoxetine treatment showed a normal QT interval. The QT interval returned to normal within 10 days of discontinuing fluoxetine treatment (Varriale, 2001).

3.5.1.V Aspirin
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and antiplatelet agents has been associated with an increased risk of bleeding. Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an antiplatelet agent are given concurrently, monitor patient for signs of increased bleeding (Prod Info PAXIL(R) oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008)
7) Probable Mechanism: unknown

3.5.1.W Astemizole
1) Interaction Effect: cardiotoxicity (QT interval prolongation, torsades de pointes, cardiac arrest)
2) Summary: It is theoretically possible that an interaction might occur between astemizole and fluoxetine because both drugs are metabolized by the cytochrome P450 system. Astemizole is metabolized by CYP3A4. Fluoxetine is known to be a potent inhibitor of CYP2D6 and is suspected of inhibiting other P450 enzymes, including CYP3A4 (Riesenman, 1995a). Coadministered fluoxetine may inhibit astemizole clearance, thereby leading to increased astemizole serum concentrations and potential astemizole toxicity. The manufacturer of astemizole recommends avoiding coadministration with fluoxetine (Prod Info Hismanal (R), 1998). In addition, fluoxetine has been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Prozac(R), 2001c).
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of astemizole and fluoxetine is not recommended.
7) Probable Mechanism: possible inhibition of astemizole P450 metabolism by fluoxetine and/or additive effects on QT prolongation
8) Literature Reports
a) Astemizole has been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Hismanal(R), 1996). Even though no formal drug interaction studies have been done, the coadministration of astemizole and other drugs known to prolong the QTc interval, including fluoxetine, is not recommended.

3.5.1.X Atomoxetine
1) Interaction Effect: an increase in atomoxetine steady-state plasma concentrations
2) Summary: Atomoxetine is primarily metabolized by the cytochrome P450 2D6 (CYP 2D6) pathway to 4-hydroxyatomoxetine. In extensive metabolizers, atomoxetine steady-state plasma concentrations are increased with selective inhibitors of CYP2D6, such as fluoxetine. The exposure is similar to that observed in poor metabolizers. In extensive metabolizers treated with fluoxetine, the area under the concentration-time curve of atomoxetine is approximately 6- to 8-fold greater, and maximum plasma concentration at steady-state is about 3- to 4-fold greater than atomoxetine alone (Prod Info Strattera(TM), 2002).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Dosage adjustment of atomoxetine may be necessary when coadministered with fluoxetine.
7) Probable Mechanism: inhibition of cytochrome P450 2D6-mediated metabolism of atomoxetine by fluoxetine

3.5.1.Y Azimilide
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, the coadministration of Class III antiarrhythmics and other drugs known to prolong the QTc interval is not recommended (Allen et al, 2002; Prod Info Tikosyn(TM) dofetilide capsules, 1999; Prod Info Corvert(R), 1998). Fluoxetine has been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Prozac(R), 2001a).
3) Severity: major

4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of class III antiarrhythmic agents and agents that prolong the QT interval, such as fluoxetine, is not recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.Z Benoxaprofen
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.AA Bepridil
1) Interaction Effect: cardiotoxicity (QT interval prolongation, torsades de pointes, cardiac arrest)
2) Summary: Both bepridil and fluoxetine have been shown to prolong the QTc interval at therapeutic doses (Prod Info Prozac(R), 2001aa; Prod Info Vascor(R), 2000). Even though no formal drug interaction studies have been done, the coadministration of bepridil and fluoxetine is contraindicated (Prod Info Vascor(R), 2000).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of bepridil and fluoxetine is contraindicated.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.AB Bivalirudin
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008). Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with warfarin (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When fluoxetine and an anticoagulant are given concurrently, monitor patient for signs of increased bleeding. Patients who are taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, when fluoxetine therapy is initiated or discontinued (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
7) Probable Mechanism: unknown
8) Literature Reports
a) Fluoxetine is thought to inhibit the cytochrome P450 2C9 isoenzyme (CYP2C9). This is the enzyme by which the more potent warfarin isomer, S-warfarin, is metabolized (Riesenman, 1995). In addition, both fluoxetine and warfarin are tightly bound to albumin. In combination, the possibility for protein-binding displacement of either drug is present (Prod Info Coumadin(R), 1999).
b) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bleeding (hospital admission due to bleeding) in patients receiving warfarin for atrial fibrillation during

concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patients with a mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients experienced 11 bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experiencing bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model (Wallerstedt et al, 2009).

c) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5), however, the rate of gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).

d) In 6 reported cases, INR increased during combined fluoxetine and warfarin therapy. In a seventh case, severe bruising of the lower legs occurred in a woman initially treated with fluoxetine and, secondarily, started on warfarin (Woolfrey et al, 1993; Claire et al, 1991).

e) An 83-year-old man died from cerebral hemorrhage secondary to increased warfarin concentrations. The patient had been taking warfarin 30 mg per week for atrial fibrillation with a target INR between 2 and 3. The patient's other drugs included lisinopril, furosemide, potassium, digoxin, and acetaminophen. After being seen for symptoms of depression, anxiety, and insomnia, the patient was given fluoxetine 20 mg per day and diazepam 2.5 mg 3 to 4 times per day. Eight days later, the patient's INR increased to 4.8, and the dose of warfarin was decreased to 27.5 mg per week. The patient was later seen for symptoms of drug delirium, including confusion, incoherence, and speaking irrationally. At this point, the INR was 3.64 and fluoxetine was discontinued. The next day the patient presented to the hospital with left-sided weakness and later died from complications of a large interparenchymal hemorrhage. The authors proposed that the addition of fluoxetine to the patient's regimen resulted in increased serum levels of both warfarin and diazepam, resulting in delirium and loss of anticoagulant control (Dent & Orrock, 1997).

3.5.1.AC Bretylium

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Even though no formal drug interaction studies have been done, the coadministration of Class III antiarrhythmics and other drugs known to prolong the QTc interval is not recommended (Allen et al, 2002; Prod Info Tikosyn(TM) dofetilide capsules, 1999; Prod Info Corvert(R), 1998). Fluoxetine has been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Prozac(R), 2001a).

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of class III antiarrhythmic agents and agents that prolong the QT interval, such as fluoxetine, is not recommended.

7) Probable Mechanism: additive effects on QT prolongation

3.5.1.AD Bromfenac

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched

among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).

b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.AE Bufexamac

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).

b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.AF Bupropion

1) Interaction Effect: increased plasma levels of fluoxetine

2) Summary: Because bupropion inhibits CYP2D6-mediated metabolism it is recommended that fluoxetine, an antidepressant metabolized by the cytochrome P450 2D6 isoenzyme, be initiated at the lower end of the dose range when administered concomitantly with bupropion (Prod Info Wellbutrin XL(TM), 2003; Prod Info Zyban(R), 2000). Increased plasma concentrations of fluoxetine may result in increased adverse effects.

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Coadministration of bupropion and fluoxetine should be approached with caution and should be initiated at the lower end of the dose range of fluoxetine. If bupropion is added to the treatment regimen of a patient already receiving fluoxetine, consider decreasing the dose of fluoxetine. Monitor for increased adverse effects including weight gain or loss, anxiety, weakness, or sleeping disturbances.

7) Probable Mechanism: inhibition of cytochrome P450 2D6-mediated fluoxetine metabolism

8) Literature Reports

a) The concomitant administration of fluoxetine and bupropion was associated with a hyperactive libido in a patient receiving treatment for major depression. The patient, a 35-year-old woman, initially received treatment with fluoxetine 40 milligrams (mg) daily after converting from clomipramine therapy due to suboptimal therapeutic effect. She experienced a diminished libido from the onset of clomipramine therapy which did not resolve after conversion to fluoxetine. Three months after the conversion to fluoxetine, bupropion 100 mg/day was added to her treatment regimen as a potential antidote for the sexual dysfunction. Sexual function appeared to normalize 1 month after the start of bupropion therapy. Approximately 5 months after beginning bupropion, the patient complained of having an exaggerated increase in libido, causing her to discontinue all medications. Her libido returned to normal within 2 months of stopping all medication, accompanied by a recurrence of depressive symptoms. Fluoxetine was reintroduced within the same time period, producing another reduction in libido yet accompanied by a full remission from depressive symptoms (Chollet & Andreatini, 2003).

3.5.1.AG Buspirone

1) Interaction Effect: worsening of psychiatric symptoms

2) Summary: In a number of case reports, the concomitant use of buspirone and fluoxetine has been

reported to result in a worsening of the patient's underlying anxiety/or obsessive-compulsive disorder (Bodkin & Teicher, 1989; Tanquary & Masand, 1990; Markovitz et al, 1990). One case report describes a patient maintained on fluoxetine who presented with symptoms of serotonin syndrome, including confusion, diaphoresis, incoordination, diarrhea, and myoclonus after buspirone was added to his drug regimen (Manos, 2000a).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: If possible, the combination of fluoxetine and buspirone should be avoided; however, if deemed clinically appropriate, monitor for worsening of psychiatric symptoms.

7) Probable Mechanism: possible inhibition of buspirone serotonergic effects

8) Literature Reports

a) One of 10 patients with obsessive-compulsive disorder experienced anorgasmia after buspirone (mean maximum dose, 54 mg daily) was added to fluoxetine therapy (mean maximum dose, 78 mg daily). The anorgasmia could not be definitely attributed to the buspirone or to an interaction between the two agents. Both fluoxetine and buspirone have reported a low incidence of sexual dysfunction when taken as monotherapy (Prod Info Prozac(R), 1999d; Prod Info Buspar(R), 1994; Jenike et al, 1991).

b) Three cases of potentiation of the antidepressant effects of fluoxetine by buspirone have been reported (Bakish, 1991). All three patients had treatment-resistant symptoms of depression, obsessional traits, anxiety, and a history of eating disorder prior to adding buspirone to the treatment regimen.

c) A case report describes a 37-year-old male patient maintained on fluoxetine 20mg per day who began combination treatment with buspirone to augment the actions of fluoxetine. The starting dose of buspirone was gradually increased from 5mg twice a day to 30mg twice a day over approximately five weeks. After five days at this dose, the patient complained of confusion, diaphoresis, incoordination, diarrhea, and myoclonus, which was thought to be serotonin syndrome. The patients symptoms resolved shortly after discontinuation of buspirone (Manos, 2000).

3.5.1.AH Cannabis

1) Interaction Effect: manic symptoms

2) Summary: One case of mania following use of marijuana with fluoxetine therapy has been reported (Stoll et al, 1991a). Although an interaction is proposed, the authors also state the manic symptoms could have resulted from the fluoxetine or marijuana alone. Caution is advised for patients using marijuana and taking fluoxetine or other serotonin reuptake inhibitors.

3) Severity: moderate

4) Onset: rapid

5) Substantiation: theoretical

6) Clinical Management: Caution patients taking selective serotonin reuptake inhibitors to avoid concomitant use of marijuana.

7) Probable Mechanism: additive serotonergic stimulation

8) Literature Reports

a) A 21-year-old female presented with mania, agitation, and grandiose delusions following use of marijuana with fluoxetine therapy. She had been taking fluoxetine 20 mg daily for 4 weeks and reported smoking 2 "joints" during a 36-hour period. Over the next 24 hours, she developed increased energy, hypersexuality, pressured speech, and grandiose delusions. Lorazepam and perphenazine were given for agitation and excitement which gradually resolved over 4 days. She remained hospitalized for 36 days. Fluoxetine 20 mg every other day was reintroduced one week prior to discharge. One week after discharge, she discontinued fluoxetine due to insomnia and feeling "hyper". These symptoms resolved rapidly upon discontinuation of fluoxetine. Due to the rapid switch to mania after smoking marijuana with fluoxetine, the manic symptoms were associated with the concomitant use of fluoxetine and marijuana, though mania could have developed from either fluoxetine or marijuana alone (Stoll et al, 1991).

3.5.1.AI Carbamazepine

1) Interaction Effect: carbamazepine toxicity (ataxia, nystagmus, diplopia, headache, vomiting, apnea, seizures, coma)

2) Summary: The addition of fluoxetine to carbamazepine therapy has increased carbamazepine concentrations and side effects, including diplopia, blurred vision, dizziness, and tremors in some reports (Grimsley et al, 1991a; Gernaat et al, 1991a; Pearson, 1990a). Conversely, no changes in steady state carbamazepine levels have been reported with the addition of fluoxetine (Spina et al, 1993a). Symptoms of serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes) have also been reported with this combination (Dursun et al, 1993a).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Due to the potential to increase carbamazepine levels, patients should be monitored for evidence of carbamazepine toxicity when fluoxetine is added to therapy. Carbamazepine levels should be considered within two to three weeks of adding or discontinuing fluoxetine, with dosage adjustments made as indicated.

7) Probable Mechanism: decreased carbamazepine metabolism
8) Literature Reports
a) An interaction between fluoxetine and carbamazepine was reported in six normal volunteers (Grimsley et al, 1991). Carbamazepine was given for 28 days, and fluoxetine was added to the regimen on day 7. The addition of fluoxetine 20 mg daily to carbamazepine 400 mg daily resulted in an increase in the area under the concentration-time curve for both carbamazepine and carbamazepine-epoxide and a decrease in clearance of carbamazepine. No significant changes were observed in absorption, volume of distribution or elimination rate constant, indicating that fluoxetine inhibits the metabolism of carbamazepine.
b) The effect of fluoxetine 20 mg daily was studied for three weeks in eight epileptic patients who were stabilized on carbamazepine therapy (Spina et al, 1993). Steady-state plasma levels of carbamazepine and its epoxide metabolite were not significantly changed with concurrent use of fluoxetine. These results differ from previous reports. The authors speculate that chronic carbamazepine administration may have resulted in enzyme induction that caused decreased levels of fluoxetine, thereby lowering the chances of a metabolic interaction. Unfortunately fluoxetine levels were not measured.
c) An interaction between fluoxetine and carbamazepine was reported in two patients receiving chronic carbamazepine dosages of 600 mg and 1000 mg daily respectively. Within 7 to 10 days of initiation of fluoxetine 20 mg daily, both patients developed symptoms of carbamazepine toxicity. Symptoms disappeared within two weeks in one patient following carbamazepine dosage reduction by 200 mg daily; in the other patient, fluoxetine was discontinued with symptom resolution within two weeks (Pearson, 1990).
d) Two cases of parkinsonism were reported after fluoxetine was added to an existing carbamazepine regimen. One patient, a 74-year old man, developed symptoms three days after fluoxetine 20 mg per day was added to an existing 12-month regimen of carbamazepine 200 mg twice daily. The patient developed cogwheel rigidity, a mask-like face, and a parkinsonian gait. After discontinuation of fluoxetine and treatment with dexetimide, the patient showed only a slight hypertonia of the arms 17 days later. The other patient, a 53-year old woman, developed parkinsonian symptoms after fluoxetine 20 mg per day was added to an existing regimen of carbamazepine 200 mg twice daily. The patient had also been taking thioridazine 275 mg per day which was stopped when fluoxetine was added. The patient developed cogwheel rigidity and a mask-like face nine days after initiation of fluoxetine therapy (Gernaat et al, 1991).
e) A female patient experienced a drug interaction 14 days after she had fluoxetine 20 mg added to a regimen of carbamazepine 200 mg daily. The patient presented with symptoms of serotonin syndrome, such as uncontrollable shivering, agitation, incoordination, myoclonus, hyperreflexia, and diaphoresis. The patient also had leukopenia and thrombocytopenia. After discontinuation of fluoxetine, all symptoms of serotonin syndrome and hematological abnormalities resolved over the next 72 hours (Dursun et al, 1993).

3.5.1.AJ Carprofen
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.AK Celecoxib
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an

increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.AL Certoparin
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008). Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with warfarin (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When fluoxetine and an anticoagulant are given concurrently, monitor patient for signs of increased bleeding. Patients who are taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, when fluoxetine therapy is initiated or discontinued (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
7) Probable Mechanism: unknown
8) Literature Reports
a) Fluoxetine is thought to inhibit the cytochrome P450 2C9 isoenzyme (CYP2C9). This is the enzyme by which the more potent warfarin isomer, S-warfarin, is metabolized (Riesenman, 1995). In addition, both fluoxetine and warfarin are tightly bound to albumin. In combination, the possibility for protein-binding displacement of either drug is present (Prod Info Coumadin(R), 1999).
b) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bleeding (hospital admission due to bleeding) in patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patients with a mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients experienced 11 bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experiencing bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model (Wallerstedt et al, 2009).
c) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5), however, the rate of gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).

d) In 6 reported cases, INR increased during combined fluoxetine and warfarin therapy. In a seventh case, severe bruising of the lower legs occurred in a woman initially treated with fluoxetine and, secondarily, started on warfarin (Woolfrey et al, 1993; Claire et al, 1991).
e) An 83-year-old man died from cerebral hemorrhage secondary to increased warfarin concentrations. The patient had been taking warfarin 30 mg per week for atrial fibrillation with a target INR between 2 and 3. The patient's other drugs included lisinopril, furosemide, potassium, digoxin, and acetaminophen. After being seen for symptoms of depression, anxiety, and insomnia, the patient was given fluoxetine 20 mg per day and diazepam 2.5 mg 3 to 4 times per day. Eight days later, the patient's INR increased to 4.8, and the dose of warfarin was decreased to 27.5 mg per week. The patient was later seen for symptoms of drug delirium, including confusion, incoherence, and speaking irrationally. At this point, the INR was 3.64 and fluoxetine was discontinued. The next day the patient presented to the hospital with left-sided weakness and later died from complications of a large interparenchymal hemorrhage. The authors proposed that the addition of fluoxetine to the patient's regimen resulted in increased serum levels of both warfarin and diazepam, resulting in delirium and loss of anticoagulant control (Dent & Orrock, 1997).

3.5.1.AM Chloral Hydrate

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Chloral hydrate and fluoxetine have been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Prozac(R), 2001ac; Young et al, 1986). Even though no formal drug interaction studies have been done, the coadministration of drugs known to prolong the QTc interval is not recommended.
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of chloral hydrate and fluoxetine is not recommended.
7) Probable Mechanism: additive effects on QT prolongation
8) Literature Reports
a) QT Prolongation was observed on the electrocardiogram (ECG) of a 52- year-old man who had been taking fluoxetine (20 milligrams/day for 2 weeks, followed by 40 milligrams/day thereafter) for depression for 3 months. An ECG just before the start of fluoxetine treatment showed a normal QT interval. The QT interval returned to normal within 10 days of discontinuing fluoxetine treatment (Varriale, 2001a).

3.5.1.AN Chloroquine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Chloroquine and fluoxetine have been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Prozac(R), 2001r; Prod Info Aralen(R), 2001). Even though no formal drug interaction studies have been done, the coadministration of drugs known to prolong the QTc interval is not recommended.
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of chloroquine and fluoxetine is not recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.AO Chlorpromazine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Although citing no data, the manufacturers of some phenothiazines state that concomitant use with other drugs which prolong the QT interval is not recommended. Q and T wave distortions have been observed in patients taking phenothiazines (Prod Info Compazine(R), 2002; Prod Info Stelazine(R), 2002; Prod Info Thorazine(R), 2002) . Other phenothiazines may have similar effects, though no reports are available. Fluoxetine has been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Prozac(R), 2003).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of fluoxetine and a phenothiazine is not recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.AP Cilostazol

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and antiplatelet agents has been associated

with an increased risk of bleeding. Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an antiplatelet agent are given concurrently, monitor patient for signs of increased bleeding (Prod Info PAXIL(R) oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008)
7) Probable Mechanism: unknown

3.5.1.AQ Clarithromycin
1) Interaction Effect: delirium and psychosis
2) Summary: Delirium and psychosis were reported in a 53-year-old male after clarithromycin was added to therapy of fluoxetine and nitrazepam. These effects are most likely due to accumulation of fluoxetine (Pollak et al, 1995a).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Clarithromycin should be avoided in patients treated with fluoxetine.
7) Probable Mechanism: fluoxetine toxicity due to decreased metabolism
8) Literature Reports
a) Delirium and psychosis were reported in a 53-year-old male after clarithromycin was added to therapy of fluoxetine and nitrazepam. These effects are most likely due to accumulation of fluoxetine, because these symptoms have been associated with fluoxetine and not with nitrazepam. In addition, the patient had previously tolerated an inadvertent overdose of nitrazepam without symptoms of delirium and psychosis (Pollak et al, 1995).

3.5.1.AR Clonixin
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.AS Clopidogrel
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and antiplatelet agents has been associated with an increased risk of bleeding. Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an antiplatelet agent are given concurrently, monitor patient for signs of increased bleeding (Prod Info PAXIL(R) oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008)
7) Probable Mechanism: unknown

3.5.1.AT Clopidogrel

1) Interaction Effect: reduction in clinical efficacy of clopidogrel

2) Summary: Clopidogrel is metabolized to its active metabolite by CYP2C19. Concomitant use of CYP2C19 inhibitors, such as fluoxetine, would be expected to result in reduced levels of the active metabolite, and therefore a reduction the clinical efficacy of clopidogrel. Concomitant use of CYP2C19 inhibitors with clopidogrel is discouraged (Prod Info PLAVIX(R) oral tablet, 2009).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concomitant use of clopidogrel and fluoxetine is discouraged (Prod Info PLAVIX (R) oral tablet, 2009).

7) Probable Mechanism: inhibition of CYP2C19- mediated clopidogrel metabolism by fluoxetine

3.5.1.AU Clorgyline

1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)

2) Summary: Concurrent administration or overlapping therapy with fluoxetine and a monoamine oxidase (MAO) inhibitor may result in CNS toxicity or serotonin syndrome, a hyperserotonergic state characterized by symptoms such as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. Serious, even fatal, reactions have been reported (Prod Info Prozac(R), 1999l; Sternbach, 1991w; Coplan & Gorman, 1993t; Feighner et al, 1990t; Kline et al, 1989u; Suchowersky & de Vries, 1990u). Concomitant use is contraindicated.

3) Severity: contraindicated

4) Onset: rapid

5) Substantiation: theoretical

6) Clinical Management: Concurrent use of fluoxetine and a MAO inhibitor is contraindicated. Wait at least two weeks after discontinuing a MAO inhibitor before initiating fluoxetine therapy. In addition, wait at least five weeks after discontinuing fluoxetine before initiating therapy with a MAO inhibitor.

7) Probable Mechanism: inhibition of serotonin metabolism by monoamine oxidase

8) Literature Reports

a) Concomitant use of serotonin specific reuptake inhibitors and monoamine oxidase inhibitors can produce a toxic reaction known as serotonin syndrome (Sternbach, 1991v). Serotonin syndrome is a condition of serotonergic hyperstimulation and manifests as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor (Sternbach, 1991v). If the syndrome is not recognized and correctly treated, death can result.

b) It has been suggested that fluoxetine therapy be discontinued for five weeks before beginning therapy with a monoamine oxidase inhibitor. However, one case report describes a 28-year old woman who had discontinued a 2-year fluoxetine regimen for six weeks before starting therapy with tranylcypromine. Over the next few days the patient developed fever, paresthesias, confusion, abdominal cramping, and various other CNS symptoms. Upon discontinuation of tranylcypromine, the patient's symptoms began to resolve. Blood samples taken three days after discontinuation of tranylcypromine revealed no presence of fluoxetine; however, the norfluoxetine level was 84 ng/mL (Coplan & Gorman, 1993s).

c) Adverse reactions reported when fluoxetine was given concomitantly with phenelzine (n=9) or tranylcypromine (n=4) include tremor (50%), agitation or restlessness (42%), mental status changes (42%), myoclonus (33%), diarrhea (33%), and blood pressure changes (25%) (Feighner et al, 1990s). All but one of the patients were taking other medications (ie, benzodiazepines, neuroleptics, anticonvulsants, antidepressants) that may have contributed to the adverse reactions.

d) Ten hours after her last dose of fluoxetine, a 45-year-old woman began tranylcypromine therapy (Kline et al, 1989t). Headache, muscle contractions, insomnia, and unsteady gait were reported on the second day. Thioridazine and tryptophan were added to her therapy. The patient experienced fever, rigidity of the arms and legs, and hyperreflexia. She died in the intensive care unit of a hospital 44 hours later.

e) Two cases suggestive of an interaction between fluoxetine and selegiline were reported (Suchowersky & de Vries, 1990t). One case involved a first episode of mania being observed approximately one month after adding selegiline to fluoxetine therapy. The patient improved two months after both drugs were discontinued, and no further details were provided. The second case involved diaphoresis, vasoconstriction, and cyanosis of the hands which occurred in close temporal relationship to adding fluoxetine and selegiline. Both drugs were discontinued, with relatively quick resolution of symptoms. Rechallenge with fluoxetine alone occurred without incident.

3.5.1.AV Clozapine

1) Interaction Effect: an increased risk of clozapine toxicity (sedation, seizures, hypotension)

2) Summary: With concurrent administration of fluoxetine, increased serum clozapine concentrations have been reported (Prod Info Clozaril(R), 2002; Centorrino et al, 1994a; Centorrino et al, 1996a; Spina et al, 1998a). Certain adverse effects associated with clozapine are dose-dependent, including sedation (Ayd, 1974) and seizures (Haller & Binder, 1990), and might be expected to occur with concurrent use of these

medications.
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor the therapeutic efficacy of clozapine and for any evidence of toxicity, particularly when the daily clozapine dose exceeds 300 mg or 3.5 mg/kg. Lower clozapine dosage may be required in some clinical situations.
7) Probable Mechanism: inhibition by fluoxetine of N-dealkylation and N-oxidation of clozapine via the cytochrome P450 2D6 enzymatic pathway
8) Literature Reports
a) Subjects receiving concurrent clozapine and fluoxetine had 76% higher serum clozapine concentrations and 61% higher metabolite concentrations on average compared with controls receiving only clozapine. The mean ratio of total drug level (clozapine plus metabolites) to dose was 60% higher and the mean ratio of concentrations to dose was 75% higher in patients receiving clozapine and fluoxetine compared with concentrations in patients receiving clozapine alone (Centorrino et al, 1994).
b) A study evaluated the serum concentrations of clozapine and norclozapine, the major metabolite, when given in combination with the selective serotonin reuptake inhibitors (SSRIs) fluoxetine, paroxetine, and sertraline. Eighty outpatients receiving clozapine all had been diagnosed with schizophrenia or major affective disorder, and 40 of these patients were receiving an SSRI in combination with clozapine. Of these 40 patients, 14 were receiving fluoxetine, 10 were receiving sertraline, and 16 were receiving paroxetine therapy. Among the patients on SSRI therapy, serum concentrations of clozapine and norclozapine were 41.1% and 44.8% higher, respectively, than in matched patients who were not receiving an SSRI. The ratio of clozapine plus norclozapine concentration to dose was also 37.7% higher in patients receiving SSRIs, indicating clozapine impaired clearance. The differences between the three SSRIs were minor, and the study groups were too limited for an accurate statistical comparison between the individual SSRIs (Centorrino et al, 1996).
c) A 44-year-old male receiving fluoxetine and clozapine was found dead in his yard. The dates of the prescriptions and the number of tablets which remained indicated that he had been taking his medications as prescribed. Autopsy results showed a high therapeutic fluoxetine concentration (0.7 mcg/mL) and also a high therapeutic norfluoxetine concentration (0.6 mcg/mL). Fluoxetine found in his gastric contents also indicated that the medication was being taken as directed. The clozapine blood concentration was in the lethal concentration range (4.9 mcg/mL), but the clozapine in the gastric contents suggested that the clozapine was being taken as prescribed and that the patient had not consumed a large overdose amount prior to his death. Other pathological findings included pulmonary edema, visceral vascular congestion, paralytic ileus, gastroenteritis, and eosinophilia, which are all consistent with clozapine toxicity. The combined central nervous system, respiratory, and cardiovascular depression caused by these two drugs was sufficient to result in the death of this patient, and his death was ruled to be a clozapine overdose due to a fatal drug interaction (Ferslew et al, 1998).
d) Ten institutionalized schizophrenic patients stabilized on clozapine therapy for at least one month participated in a prospective study to evaluate the effect of fluoxetine on clozapine pharmacokinetics. Fluoxetine 20 mg once daily was administered for eight consecutive weeks. Mean plasma clozapine concentrations increased from 348 ng/mL to 550 ng/mL (58%) at week 8. Plasma levels of norclozapine were also increased by 36% (from 280 ng/mL to 381 ng/mL). Clozapine N-oxide levels rose from 89 ng/mL at baseline to 128 ng/mL, representing a 38% increase. However, these increases in clozapine and metabolite plasma concentrations were not associated with significant changes in efficacy or safety (Spina et al, 1998).

3.5.1.AW Cyclobenzaprine
1) Interaction Effect: an increased risk of QT prolongation
2) Summary: Fluoxetine and cyclobenzaprine caused asymptomatic QT prolongation in a female patient. However, the administration of droperidol preoperatively to this patient resulted in torsades de pointes and cardiac arrest. The authors of this case report postulated that the metabolism of cyclobenzaprine, which is structurally similar to the tricyclic antidepressants, was inhibited by fluoxetine. Cytochrome P450 2D6 hepatic enzymes are inhibited by fluoxetine, and cyclobenzaprine may also be metabolized via this pathway (Michalets et al, 1998a).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Clinicians should monitor patients receiving cyclobenzaprine and fluoxetine for cardiac arrhythmias and QT prolongation. Patients who receive these two agents concurrently should avoid other drugs which are also known to prolong the QT interval.
7) Probable Mechanism: inhibition of cyclobenzaprine metabolism by fluoxetine via the cytochrome P450 hepatic enzyme system
8) Literature Reports
a) A 59-year-old female patient was receiving fluoxetine 30 mg daily, cyclobenzaprine 10 mg daily, amlodipine 5 mg daily, diclofenac 100 mg daily, and triamterene 37.5 mg/hydrochlorothiazide 25 mg daily. Five days prior to elective Achilles tendon surgery, her QTc was prolonged at 497 msec. Despite this finding, she was premedicated for surgery with intravenous droperidol 0.625 mg and

metoclopramide 10 mg. Approximately 105 minutes into the surgery, the patient developed ventricular tachycardia consistent with torsades de pointes which progressed into ventricular fibrillation and cardiac arrest. Immediately following cardioversion, the patient's QTc was 500 msec. All preadmission medications were discontinued following surgery. On postoperative day 1, the QTc was 440 msec and an electrocardiogram showed normal sinus rhythm (Michalets et al, 1998).

3.5.1.AX Cyproheptadine

1) Interaction Effect: decreased fluoxetine efficacy

2) Summary: Coadministration of cyproheptadine with fluoxetine may result in reduced fluoxetine effectiveness. Cyproheptadine acts to antagonize postsynaptic serotonin. Concomitant use of cyproheptadine with drugs that possess serotonergic activity (such as the selective serotonin reuptake inhibitors or SSRIs) might be expected to result in a pharmacodynamic interaction. Lack of antidepressant efficacy has been reported when cyproheptadine was given concomitantly with fluoxetine and paroxetine (Katz & Rosenthal, 1994a; Feder, 1991a; Goldbloom & Kennedy, 1991a; Christensen, 1995a).

3) Severity: moderate

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: Monitor patients for a reduction in fluoxetine efficacy. When cyproheptadine is coadministered with fluoxetine, fluoxetine doses might need to be adjusted upward. In some cases, it may be necessary to withdraw cyproheptadine.

7) Probable Mechanism: unknown; because cyproheptadine is a serotonin antagonist, it may oppose effects of agents that inhibit serotonin reuptake

8) Literature Reports

a) Although not consistently reported, decreased antidepressant effects were found in some patients when cyproheptadine was added to fluoxetine therapy (Katz & Rosenthal, 1994; Feder, 1991; Goldbloom & Kennedy, 1991). A 42-year-old woman using fluoxetine 40 mg once a day for episodes of depression, subsequently started cyproheptadine (4 mg per dose) for its antihistaminic properties (Katz & Rosenthal, 1994). Approximately 36 hours later and after four doses of cyproheptadine, she experienced dysphoria, irritability, and suicidal ideation. She improved after withdrawal of cyproheptadine. On rechallenge, her feelings of dysphoria returned.

b) A 54-year-old woman was using paroxetine 20 mg per day for the treatment of nonpsychotic major depression (Christensen, 1995). Cyproheptadine 2 mg twice a day was added to her therapy. Two days later, her depression worsened and she experienced confusion and paranoid delusions. Her psychotic symptoms resolved two days after cyproheptadine was discontinued. She declined to be rechallenged.

3.5.1.AY Dalteparin

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008). Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with warfarin (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: When fluoxetine and an anticoagulant are given concurrently, monitor patient for signs of increased bleeding. Patients who are taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, when fluoxetine therapy is initiated or discontinued (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).

7) Probable Mechanism: unknown

8) Literature Reports

a) Fluoxetine is thought to inhibit the cytochrome P450 2C9 isoenzyme (CYP2C9). This is the enzyme by which the more potent warfarin isomer, S-warfarin, is metabolized (Riesenman, 1995). In addition, both fluoxetine and warfarin are tightly bound to albumin. In combination, the possibility for protein-binding displacement of either drug is present (Prod Info Coumadin(R), 1999).

b) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bleeding (hospital admission due to bleeding) in patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patients with a mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients experienced 11 bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experiencing bleeding at the time of concomitant administration were

sertraline or citalopram. The addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model (Wallerstedt et al, 2009).

c) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5), however, the rate of gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).

d) In 6 reported cases, INR increased during combined fluoxetine and warfarin therapy. In a seventh case, severe bruising of the lower legs occurred in a woman initially treated with fluoxetine and, secondarily, started on warfarin (Woolfrey et al, 1993; Claire et al, 1991).

e) An 83-year-old man died from cerebral hemorrhage secondary to increased warfarin concentrations. The patient had been taking warfarin 30 mg per week for atrial fibrillation with a target INR between 2 and 3. The patient's other drugs included lisinopril, furosemide, potassium, digoxin, and acetaminophen. After being seen for symptoms of depression, anxiety, and insomnia, the patient was given fluoxetine 20 mg per day and diazepam 2.5 mg 3 to 4 times per day. Eight days later, the patient's INR increased to 4.8, and the dose of warfarin was decreased to 27.5 mg per week. The patient was later seen for symptoms of drug delirium, including confusion, incoherence, and speaking irrationally. At this point, the INR was 3.64 and fluoxetine was discontinued. The next day the patient presented to the hospital with left-sided weakness and later died from complications of a large interparenchymal hemorrhage. The authors proposed that the addition of fluoxetine to the patient's regimen resulted in increased serum levels of both warfarin and diazepam, resulting in delirium and loss of anticoagulant control (Dent & Orrock, 1997).

3.5.1.AZ Danaparoid

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008). Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with warfarin (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: When fluoxetine and an anticoagulant are given concurrently, monitor patient for signs of increased bleeding. Patients who are taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, when fluoxetine therapy is initiated or discontinued (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).

7) Probable Mechanism: unknown

8) Literature Reports

a) Fluoxetine is thought to inhibit the cytochrome P450 2C9 isoenzyme (CYP2C9). This is the enzyme by which the more potent warfarin isomer, S-warfarin, is metabolized (Riesenman, 1995). In addition, both fluoxetine and warfarin are tightly bound to albumin. In combination, the possibility for protein-binding displacement of either drug is present (Prod Info Coumadin(R), 1999).

b) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bleeding (hospital admission due to bleeding) in patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patients with a mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients experienced 11 bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experiencing bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model (Wallerstedt et al, 2009).

c) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an

increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5), however, the rate of gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).

d) In 6 reported cases, INR increased during combined fluoxetine and warfarin therapy. In a seventh case, severe bruising of the lower legs occurred in a woman initially treated with fluoxetine and, secondarily, started on warfarin (Woolfrey et al, 1993; Claire et al, 1991).

e) An 83-year-old man died from cerebral hemorrhage secondary to increased warfarin concentrations. The patient had been taking warfarin 30 mg per week for atrial fibrillation with a target INR between 2 and 3. The patient's other drugs included lisinopril, furosemide, potassium, digoxin, and acetaminophen. After being seen for symptoms of depression, anxiety, and insomnia, the patient was given fluoxetine 20 mg per day and diazepam 2.5 mg 3 to 4 times per day. Eight days later, the patient's INR increased to 4.8, and the dose of warfarin was decreased to 27.5 mg per week. The patient was later seen for symptoms of drug delirium, including confusion, incoherence, and speaking irrationally. At this point, the INR was 3.64 and fluoxetine was discontinued. The next day the patient presented to the hospital with left-sided weakness and later died from complications of a large interparenchymal hemorrhage. The authors proposed that the addition of fluoxetine to the patient's regimen resulted in increased serum levels of both warfarin and diazepam, resulting in delirium and loss of anticoagulant control (Dent & Orrock, 1997).

3.5.1.BA Defibrotide

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008). Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with warfarin (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: When fluoxetine and an anticoagulant are given concurrently, monitor patient for signs of increased bleeding. Patients who are taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, when fluoxetine therapy is initiated or discontinued (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).

7) Probable Mechanism: unknown

8) Literature Reports

a) Fluoxetine is thought to inhibit the cytochrome P450 2C9 isoenzyme (CYP2C9). This is the enzyme by which the more potent warfarin isomer, S-warfarin, is metabolized (Riesenman, 1995). In addition, both fluoxetine and warfarin are tightly bound to albumin. In combination, the possibility for protein-binding displacement of either drug is present (Prod Info Coumadin(R), 1999).

b) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bleeding (hospital admission due to bleeding) in patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patients with a mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients experienced 11 bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experiencing bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model (Wallerstedt et al, 2009).

c) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5), however, the rate of gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was

not significantly different (Schalekamp et al, 2008).
d) In 6 reported cases, INR increased during combined fluoxetine and warfarin therapy. In a seventh case, severe bruising of the lower legs occurred in a woman initially treated with fluoxetine and, secondarily, started on warfarin (Woolfrey et al, 1993; Claire et al, 1991).
e) An 83-year-old man died from cerebral hemorrhage secondary to increased warfarin concentrations. The patient had been taking warfarin 30 mg per week for atrial fibrillation with a target INR between 2 and 3. The patient's other drugs included lisinopril, furosemide, potassium, digoxin, and acetaminophen. After being seen for symptoms of depression, anxiety, and insomnia, the patient was given fluoxetine 20 mg per day and diazepam 2.5 mg 3 to 4 times per day. Eight days later, the patient's INR increased to 4.8, and the dose of warfarin was decreased to 27.5 mg per week. The patient was later seen for symptoms of drug delirium, including confusion, incoherence, and speaking irrationally. At this point, the INR was 3.64 and fluoxetine was discontinued. The next day the patient presented to the hospital with left-sided weakness and later died from complications of a large interparenchymal hemorrhage. The authors proposed that the addition of fluoxetine to the patient's regimen resulted in increased serum levels of both warfarin and diazepam, resulting in delirium and loss of anticoagulant control (Dent & Orrock, 1997).

3.5.1.BB Dehydroepiandrosterone

1) Interaction Effect: development of manic symptoms
2) Summary: A case has been reported in which concomitant dehydroepiandrosterone (DHEA) and sertraline use was suggested to precipitate a manic episode in a patient with a history of bipolar disorder (Dean, 2000a). DHEA was also noted to cause mania in a patient with no previous personal or family history of bipolar disorder (Markowitz et al, 1999). Elevated DHEA levels have been found in patients with mental disorders; DHEA suppression has lead to improvement in psychotic symptoms (Howard, 1992). DHEA possesses proserotonergic activity which may predispose patients to manic episodes (Majewska, 1995). DHEA is a precursor to androgenic steroids, which in high doses may precipitate mania (Markowitz et al, 1999). Patients taking medication for bipolar disorder or patients with a personal and/or family history of bipolar disorder should not take DHEA until further data is available to characterize this drug-herb interaction. Concomitant use of DHEA with selective serotonin reuptake inhibitors (SSRIs) should be avoided due to the potential additive precipitation of mania.
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Avoid concomitant use of dehydroepiandrosterone (DHEA) and selective serotonin reuptake inhibitors. If patients present with manic symptoms (i.e. agitation, anger, irritability, aggressive behavior), determine if the patient is using DHEA and discontinue DHEA.
7) Probable Mechanism: serotonergic activity of dehydroepiandrosterone, possibly increased androgen levels
8) Literature Reports
a) A 31-year-old male was admitted following threats to commit suicide and injure family members. He had self-initiated sertraline 100 milligrams (mg) daily for the previous 2 to 3 weeks for depression. Sertraline had been prescribed 3 years prior when he was diagnosed with bipolar disorder, which he discontinued after 2 weeks. He had also taken dehydroepiandrosterone (DHEA) 300 mg to 500 mg daily for the previous 2 months apparently for weight training. Following use of DHEA for a short time, he became more irritable, was not sleeping well, and began threatening a female friend and family members. He also drank alcohol occasionally and reportedly had difficulty controlling his anger when intoxicated. Sertraline was stopped and the patient was treated with valproic acid with the dose titrated to 500 mg twice daily. The combination of DHEA, sertraline, and alcohol was suggested responsible for the developing of the manic episode (Dean, 2000).

3.5.1.BC Delavirdine

1) Interaction Effect: increased trough delavirdine concentrations
2) Summary: Population pharmacokinetic data in 36 patients suggested that coadministration of delavirdine and fluoxetine resulted in an approximate 50% increase in trough delavirdine concentrations (Prod Info Rescriptor(R), 1999). The clinical significance of this interaction is not known.
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Concurrent use of delavirdine with fluoxetine should be coadministered with caution. Monitor patients for an increased incidence of delavirdine adverse effects.
7) Probable Mechanism: unknown

3.5.1.BD Dermatan Sulfate

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008). Bleeding events reported have included epistaxis,

ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with warfarin (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When fluoxetine and an anticoagulant are given concurrently, monitor patient for signs of increased bleeding. Patients who are taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, when fluoxetine therapy is initiated or discontinued (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
7) Probable Mechanism: unknown
8) Literature Reports
a) Fluoxetine is thought to inhibit the cytochrome P450 2C9 isoenzyme (CYP2C9). This is the enzyme by which the more potent warfarin isomer, S-warfarin, is metabolized (Riesenman, 1995). In addition, both fluoxetine and warfarin are tightly bound to albumin. In combination, the possibility for protein-binding displacement of either drug is present (Prod Info Coumadin(R), 1999).
b) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bleeding (hospital admission due to bleeding) in patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patients with a mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients experienced 11 bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experiencing bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model (Wallerstedt et al, 2009).
c) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5), however, the rate of gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).
d) In 6 reported cases, INR increased during combined fluoxetine and warfarin therapy. In a seventh case, severe bruising of the lower legs occurred in a woman initially treated with fluoxetine and, secondarily, started on warfarin (Woolfrey et al, 1993; Claire et al, 1991).
e) An 83-year-old man died from cerebral hemorrhage secondary to increased warfarin concentrations. The patient had been taking warfarin 30 mg per week for atrial fibrillation with a target INR between 2 and 3. The patient's other drugs included lisinopril, furosemide, potassium, digoxin, and acetaminophen. After being seen for symptoms of depression, anxiety, and insomnia, the patient was given fluoxetine 20 mg per day and diazepam 2.5 mg 3 to 4 times per day. Eight days later, the patient's INR increased to 4.8, and the dose of warfarin was decreased to 27.5 mg per week. The patient was later seen for symptoms of drug delirium, including confusion, incoherence, and speaking irrationally. At this point, the INR was 3.64 and fluoxetine was discontinued. The next day the patient presented to the hospital with left-sided weakness and later died from complications of a large interparenchymal hemorrhage. The authors proposed that the addition of fluoxetine to the patient's regimen resulted in increased serum levels of both warfarin and diazepam, resulting in delirium and loss of anticoagulant control (Dent & Orrock, 1997).

3.5.1.BE Desipramine

1) Interaction Effect: tricyclic antidepressant toxicity (dry mouth, urinary retention, sedation) and an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Tricyclic antidepressants (TCAs) and fluoxetine have been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Prozac(R), 2001h; Marshall & Forker, 1982). Even though no formal drug interaction studies have been done which demonstrate QT prolongation, the coadministration of tricyclic antidepressants and other drugs known to prolong the QTc interval, such as fluoxetine, is not recommended (Prod Info Elavil(R), 1999). In addition, concurrent use of fluoxetine and TCAs such as desipramine, nortriptyline, and imipramine has resulted in significant increases in TCA concentrations (Preskorn et al, 1994a; Preskorn et al, 1994a; Aranow et al, 1989a; Downs et al, 1989a; Goodnick, 1989a; Bell & Cole, 1988a).
3) Severity: major

4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: The concurrent administration of fluoxetine and a tricyclic antidepressant is not recommended.
7) Probable Mechanism: decreased tricyclic antidepressant metabolism; additive effects on QT prolongation
8) Literature Reports
a) Fluoxetine increased the level of tricyclic antidepressants (nortriptyline, imipramine, desipramine) in 4 patients. After the addition of fluoxetine, the ratio of antidepressant level to dose increased by 109% to 486% in the patients. Three patients developed clinical symptoms (anticholinergic effects, constipation, urinary hesitancy, sedation, unstable gait) as a result of the increased levels (Aranow et al, 1989).
b) Fluoxetine statistically and clinically significantly increased desipramine concentrations in 18 healthy subjects. When fluoxetine (20 mg daily) was added to desipramine (50 mg daily), the mean maximum concentration of desipramine increased by 278% and the area under the concentration-time curve increased by 342%. Desipramine trough concentrations continued to be 198% above baseline three weeks after fluoxetine was discontinued. The same study compared pharmacokinetics of desipramine when combined with sertraline. The impact of sertraline was modest, resulting in small and short-term increases in desipramine plasma concentrations (Preskorn et al, 1994).
c) A 75-year-old female experienced symptomatic increases in her desipramine serum concentrations when fluoxetine was added. Desipramine serum levels ranged from 109 to 150 ng/mL with oral doses of 300 mg at bedtime prior to fluoxetine therapy. Following the addition of oral fluoxetine 20 mg daily to the regimen, the desipramine serum level increased to 212 ng/mL within five days. The fluoxetine dose was increased to 40 mg/day three days later, and the desipramine serum level was 419 ng/mL after four days. A worsening of depression and severe fatigue coincided with the increases in desipramine serum levels. Withdrawal of fluoxetine and reduction in the desipramine dose to 200 mg daily reduced the desipramine serum level to 231 ng/mL within two weeks (Bell & Cole, 1988).
d) A 33-year-old depressed male developed adverse effects of dry mouth, tinnitus, and difficulties with alertness and memory while receiving fluoxetine 40 mg daily and desipramine 150 mg daily for five weeks; fluoxetine was discontinued and the blood levels of desipramine decreased from 938 to 48 ng/mL with resolution of clinical symptoms (Goodnick, 1989).
e) A 39-year-old female experienced symptomatic increases in her desipramine levels with concomitant fluoxetine therapy. Prior to fluoxetine therapy, the patient's measured levels of desipramine had ranged from 148 to 160 ng/mL on a regimen of 300 mg daily. Five weeks after the addition of fluoxetine 20 mg daily, she reported anticholinergic symptoms, sedation, and confusion with a desipramine level of 527 ng/mL. The desipramine dose was lowered to 200 mg/day; eleven days later, the level was 244 ng/mL; the patient reported decreased energy, impaired short-term memory, and some "garbled" speech, as well as an episode of nausea, dizziness, and syncope. The desipramine dose was reduced to 50 mg/day; the adverse effects resolved in six days. Eight days later, the desipramine level was 122 ng/mL (Downs et al, 1989).
f) Concomitant administration of fluoxetine and desipramine was reported to result in an increased desipramine level and new onset of delirium in a 69-year-old male within 10 days of the addition of fluoxetine to the patient's regimen (Preskorn et al, 1990).

3.5.1.BF Desirudin
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008). Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with warfarin (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When fluoxetine and an anticoagulant are given concurrently, monitor patient for signs of increased bleeding. Patients who are taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, when fluoxetine therapy is initiated or discontinued (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
7) Probable Mechanism: unknown
8) Literature Reports
a) Fluoxetine is thought to inhibit the cytochrome P450 2C9 isoenzyme (CYP2C9). This is the enzyme by which the more potent warfarin isomer, S-warfarin, is metabolized (Riesenman, 1995). In addition, both fluoxetine and warfarin are tightly bound to albumin. In combination, the possibility for protein-binding displacement of either drug is present (Prod Info Coumadin(R), 1999).
b) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bleeding (hospital admission due to bleeding) in patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patients with a mean

age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients experienced 11 bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experiencing bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model (Wallerstedt et al, 2009).

c) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5), however, the rate of gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).

d) In 6 reported cases, INR increased during combined fluoxetine and warfarin therapy. In a seventh case, severe bruising of the lower legs occurred in a woman initially treated with fluoxetine and, secondarily, started on warfarin (Woolfrey et al, 1993; Claire et al, 1991).

e) An 83-year-old man died from cerebral hemorrhage secondary to increased warfarin concentrations. The patient had been taking warfarin 30 mg per week for atrial fibrillation with a target INR between 2 and 3. The patient's other drugs included lisinopril, furosemide, potassium, digoxin, and acetaminophen. After being seen for symptoms of depression, anxiety, and insomnia, the patient was given fluoxetine 20 mg per day and diazepam 2.5 mg 3 to 4 times per day. Eight days later, the patient's INR increased to 4.8, and the dose of warfarin was decreased to 27.5 mg per week. The patient was later seen for symptoms of drug delirium, including confusion, incoherence, and speaking irrationally. At this point, the INR was 3.64 and fluoxetine was discontinued. The next day the patient presented to the hospital with left-sided weakness and later died from complications of a large interparenchymal hemorrhage. The authors proposed that the addition of fluoxetine to the patient's regimen resulted in increased serum levels of both warfarin and diazepam, resulting in delirium and loss of anticoagulant control (Dent & Orrock, 1997).

3.5.1.BG Desvenlafaxine

1) Interaction Effect: increased risk of serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)

2) Summary: Concurrent use of desvenlafaxine and a selective serotonin reuptake inhibitor (SSRI) may result in serotonin syndrome, which may be life-threatening. Symptoms of serotonin syndrome may include restlessness, hallucinations, loss of coordination, fast heart beat, rapid changes in blood pressure, increased body temperature, overreactive reflexes, nausea, vomiting, and diarrhea (Prod Info PRISTIQ(TM) oral extended-release tablets, 2008).

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Coadministration of desvenlafaxine and an SSRI may result in a life-threatening condition called serotonin syndrome. If these agents are used together, discuss the risks of serotonin syndrome with the patient and monitor closely for symptoms of serotonin syndrome (restlessness, hyperthermia, hyperreflexia, incoordination), especially during treatment initiation and dose increases (Prod Info PRISTIQ(TM) oral extended-release tablets, 2008).

7) Probable Mechanism: additive serotonergic effect

3.5.1.BH Dexfenfluramine

1) Interaction Effect: serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)

2) Summary: Dexfenfluramine is a nonspecific serotonin agonist that both enhances the release of serotonin and inhibits serotonin reuptake. Combination therapy with dexfenfluramine and another selective serotonin reuptake inhibitor, such as fluoxetine, has the potential to cause serotonin syndrome (Schenck & Mahowald, 1996). Serotonin syndrome is a hyperserotonergic state characterized by symptoms such as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. Serious, even fatal, reactions have been reported (Sternbach, 1991x). Dexfenfluramine should not be used in combination with fluoxetine (Prod Info Redux(R), 1997).

3) Severity: major

4) Onset: rapid

5) Substantiation: theoretical

6) Clinical Management: Concurrent use of dexfenfluramine and fluoxetine may result in an additive

increase in serotonin levels in the central nervous system, and could result in serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes). Dexfenfluramine should not be used in combination with fluoxetine or other serotonin specific reuptake inhibitors.
7) Probable Mechanism: additive serotonergic effects

3.5.1.BI Dexketoprofen
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.BJ Dextromethorphan
1) Interaction Effect: possible dextromethorphan toxicity (nausea, vomiting, blurred vision, hallucinations) or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)
2) Summary: Fluoxetine strongly inhibits hepatic cytochrome P450IID6 (CYP2D6), the isoenzyme known to catalyze dextromethorphan metabolism (Stevens & Wrighton, 1993). Fluoxetine inhibits dextromethorphan metabolism (Otton et al, 1993a). With concomitant administration, it is possible that both agents may competitively inhibit each others metabolism, increasing serum levels of both drugs. Serotonin syndrome, characterized by restlessness, myoclonus, and changes in mental status (Sternbach, 1991e), is a possibility with the combined use of dextromethorphan and serotonergic agents. There have been two case reports of serotonin syndrome associated with concurrent paroxetine and dextromethorphan therapy (Skop et al, 1994a; Skop et al, 1995).
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Caution patients taking fluoxetine that an interaction could occur with dextromethorphan. A reduction in the dextromethorphan dose may be necessary.
7) Probable Mechanism: competitively inhibited metabolism of both agents
8) Literature Reports
a) Therapeutic doses of fluoxetine were found to potently inhibit the metabolism of dextromethorphan, a marker of cytochrome P450 2D6 (CYP2D6) function (Otton et al, 1993). A 30 mg dose of dextromethorphan hydrobromide was given to 19 patients taking fluoxetine for clinical depression. In addition, dextromethorphan was given to 208 known extensive metabolizers and to 15 known poor metabolizers (those lacking CYP2D6 function). While dextromethorphan metabolism was reduced in the fluoxetine-treated patients, it was more significantly affected in the poor metabolizer controls. This indicates that patients who are slow metabolizers may be at greater risk for experiencing dextromethorphan toxicity when used in combination with fluoxetine.
b) A 32-year-old woman experienced visual hallucinations after concomitant use of fluoxetine and dextromethorphan (Achamallah, 1992). She had taken fluoxetine 20 mg daily for 18 days prior to taking two doses of dextromethorphan. After each dose of dextromethorphan she experienced distorted vision and saw bright colors. These effects continued for six to eight hours. Fluoxetine was withdrawn and she had no more hallucinations.
c) A 51-year old male patient with vascular disease following concurrent use of dextromethorphan and paroxetine developed serotonin syndrome. Two days after self-medication with a dextromethorphan-containing cold product, the patient experienced shortness of breath, nausea, headache, and confusion. Upon arrival to the hospital, the patient presented with diaphoresis, tremor, confusion, abdominal pain, and severe shortness of breath. After administration of benzodiazepines and discontinuation of paroxetine, the patient's condition improved and no further complications were seen (Skop et al, 1994).

3.5.1.BK Diazepam

1) Interaction Effect: higher serum concentrations of diazepam

2) Summary: During coadministration of fluoxetine with diazepam, the fluoxetine area under the concentration-time curve (AUC) was increased, but this was not associated with increased impairment (Lemberger et al, 1988a). Conversely, a controlled study observed significant decreases in psychomotor performance when diazepam was added to fluoxetine (Moskowitz & Burns, 1988a). The metabolism of diazepam is mediated by several P450 enzymes which may be inhibited by fluoxetine (Riesenman, 1995c; Shen, 1995a; Nemeroff et al, 1996b). Further case reports or controlled studies are necessary to appropriately define the pharmacokinetic effects as well as the degree of psychomotor impairment resulting from coadministration of these two agents.

3) Severity: minor

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Although dose adjustments are thought not to be necessary when fluoxetine and diazepam are given concomitantly, monitor patients for signs and symptoms of excessive diazepam concentrations (sedation, dizziness, ataxia, decreased cognition or motor performance). In some patients, such as the elderly, it may be safer to give a lower dose of diazepam during combination therapy.

7) Probable Mechanism: inhibition of the hepatic P450 metabolism of diazepam

8) Literature Reports

a) Coadministration of fluoxetine and diazepam resulted in prolonged half-life, reduced plasma clearance, and increased AUC for diazepam. Oral diazepam 10 mg was given alone, after a single dose of oral fluoxetine 60 mg, and after 8 daily doses of fluoxetine 60 mg. Psychometric data demonstrated no effect of fluoxetine on the psychomotor response to diazepam. Thus, although fluoxetine decreases the clearance of diazepam, this does not appear to be of clinical relevance and dosing adjustments are not required during combined therapy (Lemberger et al, 1988).

b) Combined therapy with diazepam and fluoxetine caused an increase in the half-life of the metabolite desmethyldiazepam, but this did not appear to be clinically significant. Diazepam had no effect on the disposition of fluoxetine or norfluoxetine (Lemberger et al, 1985).

c) To date, in-vitro studies have found that diazepam demethylation occurs via P450 1A2, 3A4, 2C9, and 2C19. Evidence with drugs known to be metabolized by these enzymes suggests that fluoxetine strongly inhibits 2C9, moderately inhibits 2C19 and 3A4, and has no effect on 1A2 (Riesenman, 1995b; Nemeroff et al, 1996a; Shen, 1995).

d) In a controlled study of performance of 90 healthy volunteers, the effects of fluoxetine, amitriptyline, or placebo with diazepam were studied. Volunteers received one of six treatment combinations, and were given performance tests including a critical tracking test, divided attention test, visual search task, memory test, and vigilance test. Fluoxetine alone did not affect performance, but when fluoxetine was added to diazepam, there was a significant increase in the divided attention tracking error and significant impairment on the vigilance test. For amitriptyline alone and during coadministration with diazepam, significant impairment was observed. On most tests, the combination of amitriptyline and diazepam resulted in additive effects. The authors concluded that the combination of diazepam and an antidepressant may increase an individual's risk during driving and while performing other complex tasks (Moskowitz & Burns, 1988).

e) A case was reported in which an 83-year old man developed delirium after the addition of fluoxetine and diazepam to a regimen of warfarin, lisinopril, furosemide, potassium, digoxin, and acetaminophen. The patient was given fluoxetine 20 mg per day and diazepam 2.5 mg three to four times per day for symptoms of depression, anxiety, and insomnia. The patient then developed symptoms of drug delirium, including confusion, incoherence, and irrational speaking. The patient also developed an increased international normalized ratio (INR), after which fluoxetine was discontinued. The patient presented to the hospital with left-sided weakness and later died from complications of a large interparenchymal hemorrhage. The authors proposed that the addition of fluoxetine to the patient's regimen resulted in increased serum levels of both warfarin and diazepam, resulting in drug-induced delirium and loss of anticoagulant control (Dent & Orrock, 1997a).

3.5.1.BL Dibenzepin

1) Interaction Effect: tricyclic antidepressant toxicity (dry mouth, urinary retention, sedation) and an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Tricyclic antidepressants (TCAs) and fluoxetine have been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Prozac(R), 2001h; Marshall & Forker, 1982). Even though no formal drug interaction studies have been done which demonstrate QT prolongation, the coadministration of tricyclic antidepressants and other drugs known to prolong the QTc interval, such as fluoxetine, is not recommended (Prod Info Elavil(R), 1999). In addition, concurrent use of fluoxetine and TCAs such as desipramine, nortriptyline, and imipramine has resulted in significant increases in TCA concentrations (Preskorn et al, 1994a; Preskorn et al, 1994a; Aranow et al, 1989a; Downs et al, 1989a; Goodnick, 1989a; Bell & Cole, 1988a).

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: The concurrent administration of fluoxetine and a tricyclic antidepressant is not recommended.
7) Probable Mechanism: decreased tricyclic antidepressant metabolism; additive effects on QT prolongation
8) Literature Reports
a) Fluoxetine increased the level of tricyclic antidepressants (nortriptyline, imipramine, desipramine) in 4 patients. After the addition of fluoxetine, the ratio of antidepressant level to dose increased by 109% to 486% in the patients. Three patients developed clinical symptoms (anticholinergic effects, constipation, urinary hesitancy, sedation, unstable gait) as a result of the increased levels (Aranow et al, 1989).
b) Fluoxetine statistically and clinically significantly increased desipramine concentrations in 18 healthy subjects. When fluoxetine (20 mg daily) was added to desipramine (50 mg daily), the mean maximum concentration of desipramine increased by 278% and the area under the concentration-time curve increased by 342%. Desipramine trough concentrations continued to be 198% above baseline three weeks after fluoxetine was discontinued. The same study compared pharmacokinetics of desipramine when combined with sertraline. The impact of sertraline was modest, resulting in small and short-term increases in desipramine plasma concentrations (Preskorn et al, 1994).
c) A 75-year-old female experienced symptomatic increases in her desipramine serum concentrations when fluoxetine was added. Desipramine serum levels ranged from 109 to 150 ng/mL with oral doses of 300 mg at bedtime prior to fluoxetine therapy. Following the addition of oral fluoxetine 20 mg daily to the regimen, the desipramine serum level increased to 212 ng/mL within five days. The fluoxetine dose was increased to 40 mg/day three days later, and the desipramine serum level was 419 ng/mL after four days. A worsening of depression and severe fatigue coincided with the increases in desipramine serum levels. Withdrawal of fluoxetine and reduction in the desipramine dose to 200 mg daily reduced the desipramine serum level to 231 ng/mL within two weeks (Bell & Cole, 1988).
d) A 33-year-old depressed male developed adverse effects of dry mouth, tinnitus, and difficulties with alertness and memory while receiving fluoxetine 40 mg daily and desipramine 150 mg daily for five weeks; fluoxetine was discontinued and the blood levels of desipramine decreased from 938 to 48 ng/mL with resolution of clinical symptoms (Goodnick, 1989).
e) A 39-year-old female experienced symptomatic increases in her desipramine levels with concomitant fluoxetine therapy. Prior to fluoxetine therapy, the patient's measured levels of desipramine had ranged from 148 to 160 ng/mL on a regimen of 300 mg daily. Five weeks after the addition of fluoxetine 20 mg daily, she reported anticholinergic symptoms, sedation, and confusion with a desipramine level of 527 ng/mL. The desipramine dose was lowered to 200 mg/day; eleven days later, the level was 244 ng/mL; the patient reported decreased energy, impaired short-term memory, and some "garbled" speech, as well as an episode of nausea, dizziness, and syncope. The desipramine dose was reduced to 50 mg/day; the adverse effects resolved in six days. Eight days later, the desipramine level was 122 ng/mL (Downs et al, 1989).
f) Concomitant administration of fluoxetine and desipramine was reported to result in an increased desipramine level and new onset of delirium in a 69-year-old male within 10 days of the addition of fluoxetine to the patient's regimen (Preskorn et al, 1990).

3.5.1.BM Diclofenac
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.BN Dicumarol

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008). Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with warfarin (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When fluoxetine and an anticoagulant are given concurrently, monitor patient for signs of increased bleeding. Patients who are taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, when fluoxetine therapy is initiated or discontinued (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
7) Probable Mechanism: unknown
8) Literature Reports

a) Fluoxetine is thought to inhibit the cytochrome P450 2C9 isoenzyme (CYP2C9). This is the enzyme by which the more potent warfarin isomer, S-warfarin, is metabolized (Riesenman, 1995). In addition, both fluoxetine and warfarin are tightly bound to albumin. In combination, the possibility for protein-binding displacement of either drug is present (Prod Info Coumadin(R), 1999).

b) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bleeding (hospital admission due to bleeding) in patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patients with a mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients experienced 11 bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experiencing bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model (Wallerstedt et al, 2009).

c) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5), however, the rate of gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).

d) In 6 reported cases, INR increased during combined fluoxetine and warfarin therapy. In a seventh case, severe bruising of the lower legs occurred in a woman initially treated with fluoxetine and, secondarily, started on warfarin (Woolfrey et al, 1993; Claire et al, 1991).

e) An 83-year-old man died from cerebral hemorrhage secondary to increased warfarin concentrations. The patient had been taking warfarin 30 mg per week for atrial fibrillation with a target INR between 2 and 3. The patient's other drugs included lisinopril, furosemide, potassium, digoxin, and acetaminophen. After being seen for symptoms of depression, anxiety, and insomnia, the patient was given fluoxetine 20 mg per day and diazepam 2.5 mg 3 to 4 times per day. Eight days later, the patient's INR increased to 4.8, and the dose of warfarin was decreased to 27.5 mg per week. The patient was later seen for symptoms of drug delirium, including confusion, incoherence, and speaking irrationally. At this point, the INR was 3.64 and fluoxetine was discontinued. The next day the patient presented to the hospital with left-sided weakness and later died from complications of a large interparenchymal hemorrhage. The authors proposed that the addition of fluoxetine to the patient's regimen resulted in increased serum levels of both warfarin and diazepam, resulting in delirium and loss of anticoagulant control (Dent & Orrock, 1997).

3.5.1.BO Diflunisal

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).

3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.BP Digitoxin
1) Interaction Effect: an increased risk of digitoxin toxicity (nausea, vomiting, arrhythmias)
2) Summary: The administration of fluoxetine to a patient taking digitoxin, also tightly bound to plasma protein, may cause a shift in plasma concentrations of digitoxin (Prod Info Prozac(R), 1999c).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Patients receiving fluoxetine and digitoxin therapy concomitantly should be monitored for increasing levels of digitoxin, along with signs and symptoms of digitoxin toxicity.
7) Probable Mechanism: unknown

3.5.1.BQ Digoxin
1) Interaction Effect: an increased risk of digoxin toxicity (nausea, vomiting, arrhythmias)
2) Summary: One case report describes a 93-year-old female stabilized on digoxin who experienced toxic levels of digoxin after fluoxetine had been added to her regimen for depression. Rechallenge with fluoxetine again caused her digoxin levels to increase dramatically. While the mechanism of this interaction is not clear, it could be related to displacement of digoxin from binding sites or reduced clearance of digoxin (Leibovitz et al, 1998a).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Patients receiving fluoxetine and digoxin therapy concomitantly should be monitored for increasing levels of digoxin, along with signs and symptoms of digoxin toxicity, including anorexia.
7) Probable Mechanism: unknown
8) Literature Reports
a) Digoxin 0.125 mg daily was being administered to a 93-year-old female for congestive heart failure and paroxysmal atrial fibrillation. Digoxin levels ranged from 1.0 to 1.4 nmol/L during the two months preceding the initiation of fluoxetine 10 mg daily. Within one week, the patient complained of anorexia. Her digoxin level measured 4.2 nmol/L, while renal function and potassium levels remained unchanged. Both digoxin and fluoxetine were discontinued, and her digoxin level returned to normal in five days with resolution of the anorexia. During the next three weeks her digoxin serum levels ranged from 0.9 nmol/L to 1.4 nmol/L. Because the symptoms of depression persisted, fluoxetine was again initiated at 10 mg daily and the digoxin serum level was closely monitored. After two days of fluoxetine therapy, the digoxin level increased to 2.0 nmol/L, and after four days it was 2.8 nmol/L. Renal function remained unchanged, as did serum electrolytes. The patient again experienced anorexia, and treatment with fluoxetine was discontinued (Leibovitz et al, 1998).

3.5.1.BR Dihydroergotamine
1) Interaction Effect: an increased risk of ergotism (nausea, vomiting, vasospastic ischemia)
2) Summary: Because of the potential for serious toxicity including vasospasm that can occur with increased plasma concentrations of ergot derivatives, the concurrent use of fluoxetine and ergot derivatives is contraindicated. Fluoxetine and ergot derivatives are both metabolized by cytochrome P450 3A4 enzymes, and the competition for metabolism could result in an increased plasma concentration of the ergot derivative (Prod Info Cafergot(R), 2002).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: The concurrent use of fluoxetine and ergot derivatives is contraindicated.

7) Probable Mechanism: inhibition of cytochrome P450 3A4- mediated ergot metabolism by fluoxetine

3.5.1.BS Dipyridamole

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and antiplatelet agents has been associated with an increased risk of bleeding. Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an antiplatelet agent are given concurrently, monitor patient for signs of increased bleeding (Prod Info PAXIL(R) oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008)
7) Probable Mechanism: unknown

3.5.1.BT Dipyrone

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.BU Disopyramide

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, the coadministration of Class Ia antiarrhythmics and other drugs known to prolong the QTc interval is not recommended (Prod Info Quinaglute Dura-tabs(R), 1999). Fluoxetine has demonstrated QT prolongation at therapeutic doses (Prod Info Prozac(R), 2001z).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of class Ia antiarrhythmic agents and agents that prolong the QT interval, such as fluoxetine, is not recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.BV Dofetilide

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, the coadministration of Class III antiarrhythmics and other drugs known to prolong the QTc interval is not recommended (Allen et al, 2002; Prod Info Tikosyn(TM) dofetilide capsules, 1999; Prod Info Corvert(R), 1998). Fluoxetine has been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Prozac(R), 2001a).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of class III antiarrhythmic agents and agents that

prolong the QT interval, such as fluoxetine, is not recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.BW Dolasetron

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Though citing no data, the manufacturer of dolasetron recommends caution if dolasetron is administered with another drug which can prolong the QTc interval (Prod Info Anzemet(R), 1997). Fluoxetine has been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Prozac(R), 2001y).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of fluoxetine and dolasetron is not recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.BX Doxepin

1) Interaction Effect: tricyclic antidepressant toxicity (dry mouth, urinary retention, sedation) and an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Tricyclic antidepressants (TCAs) and fluoxetine have been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Prozac(R), 2001h; Marshall & Forker, 1982). Even though no formal drug interaction studies have been done which demonstrate QT prolongation, the coadministration of tricyclic antidepressants and other drugs known to prolong the QTc interval, such as fluoxetine, is not recommended (Prod Info Elavil(R), 1999). In addition, concurrent use of fluoxetine and TCAs such as desipramine, nortriptyline, and imipramine has resulted in significant increases in TCA concentrations (Preskorn et al, 1994a; Preskorn et al, 1994a; Aranow et al, 1989a; Downs et al, 1989a; Goodnick, 1989a; Bell & Cole, 1988a).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: The concurrent administration of fluoxetine and a tricyclic antidepressant is not recommended.
7) Probable Mechanism: decreased tricyclic antidepressant metabolism; additive effects on QT prolongation
8) Literature Reports

a) Fluoxetine increased the level of tricyclic antidepressants (nortriptyline, imipramine, desipramine) in 4 patients. After the addition of fluoxetine, the ratio of antidepressant level to dose increased by 109% to 486% in the patients. Three patients developed clinical symptoms (anticholinergic effects, constipation, urinary hesitancy, sedation, unstable gait) as a result of the increased levels (Aranow et al, 1989).

b) Fluoxetine statistically and clinically significantly increased desipramine concentrations in 18 healthy subjects. When fluoxetine (20 mg daily) was added to desipramine (50 mg daily), the mean maximum concentration of desipramine increased by 278% and the area under the concentration-time curve increased by 342%. Desipramine trough concentrations continued to be 198% above baseline three weeks after fluoxetine was discontinued. The same study compared pharmacokinetics of desipramine when combined with sertraline. The impact of sertraline was modest, resulting in small and short-term increases in desipramine plasma concentrations (Preskorn et al, 1994).

c) A 75-year-old female experienced symptomatic increases in her desipramine serum concentrations when fluoxetine was added. Desipramine serum levels ranged from 109 to 150 ng/mL with oral doses of 300 mg at bedtime prior to fluoxetine therapy. Following the addition of oral fluoxetine 20 mg daily to the regimen, the desipramine serum level increased to 212 ng/mL within five days. The fluoxetine dose was increased to 40 mg/day three days later, and the desipramine serum level was 419 ng/mL after four days. A worsening of depression and severe fatigue coincided with the increases in desipramine serum levels. Withdrawal of fluoxetine and reduction in the desipramine dose to 200 mg daily reduced the desipramine serum level to 231 ng/mL within two weeks (Bell & Cole, 1988).

d) A 33-year-old depressed male developed adverse effects of dry mouth, tinnitus, and difficulties with alertness and memory while receiving fluoxetine 40 mg daily and desipramine 150 mg daily for five weeks; fluoxetine was discontinued and the blood levels of desipramine decreased from 938 to 48 ng/mL with resolution of clinical symptoms (Goodnick, 1989).

e) A 39-year-old female experienced symptomatic increases in her desipramine levels with concomitant fluoxetine therapy. Prior to fluoxetine therapy, the patient's measured levels of desipramine had ranged from 148 to 160 ng/mL on a regimen of 300 mg daily. Five weeks after the addition of fluoxetine 20 mg daily, she reported anticholinergic symptoms, sedation, and confusion with a desipramine level of 527 ng/mL. The desipramine dose was lowered to 200 mg/day; eleven days later, the level was 244 ng/mL; the patient reported decreased energy, impaired short-term memory, and some "garbled" speech, as well as an episode of nausea, dizziness, and syncope. The desipramine dose was reduced to 50 mg/day; the adverse effects resolved in six days. Eight days later, the desipramine level was 122 ng/mL (Downs et al, 1989).

f) Concomitant administration of fluoxetine and desipramine was reported to result in an increased

desipramine level and new onset of delirium in a 69-year-old male within 10 days of the addition of fluoxetine to the patient's regimen (Preskorn et al, 1990).

3.5.1.BY Droperidol

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Droperidol has been shown to prolong the QTc interval at the recommended therapeutic dose. Even though no formal drug interaction studies have been done, the coadministration of droperidol and other drugs known to prolong the QTc interval, including fluoxetine is not recommended (Prod Info Inapsine(TM), 2001; Prod Info Prozac(R), 2001ab).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of droperidol and fluoxetine is not recommended.
7) Probable Mechanism: additive cardiac effects

3.5.1.BZ Droxicam

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.CA Duloxetine

1) Interaction Effect: increased duloxetine and fluoxetine serum concentrations and an increased risk of serotonin syndrome
2) Summary: Duloxetine is a selective serotonin and norepinephrine reuptake inhibitor (SSNRI). The concomitant use of duloxetine with fluoxetine, an SSRI, is not recommended due to the potential for serotonin syndrome. In addition, the coadministration of duloxetine with fluoxetine is likely to increase the bioavailability of either drug, increasing the risk of serious adverse events. Duloxetine and fluoxetine are both substrates for, and moderately potent inhibitors of CYP2D6. Coadministration of duloxetine 40 mg once daily with another SSRI (the potent CYP2D6 inhibitor paroxetine 20 mg once daily) resulted in a 60% increase in the serum concentration of duloxetine (Prod Info CYMBALTA(R) delayed-release oral capsules, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: The concomitant use of duloxetine and fluoxetine is not recommended due to the potential for development of serotonin syndrome. Additionally, concomitant use has resulted in increased duloxetine and fluoxetine serum levels (Prod Info CYMBALTA(R) delayed-release oral capsules, 2008).
7) Probable Mechanism: fluoxetine inhibition of CYP2D6-mediated duloxetine metabolism; additive serotonergic effects

3.5.1.CB Eletriptan

1) Interaction Effect: an increased risk of serotonin syndrome
2) Summary: There have been case reports of weakness, hyperreflexia, and incoordination following concomitant use of sumatriptan, a 5-hydroxytryptamine-1 (5HT-1) agonist, and a serotonin specific reuptake inhibitor (SSRI) (Prod Info Imitrex(R) Nasal Spray, 2003). Because eletriptan is a 5HT 1B/1D agonist, a similar interaction between SSRIs and eletriptan may occur (Prod Info Relpax(R), 2003). Concurrent use of

a triptan and an SSRI may result in serotonin syndrome which may be life-threatening. Symptoms of serotonin syndrome may include restlessness, hallucinations, loss of coordination, fast heart beat, rapid changes in blood pressure, increased body temperature, overreactive reflexes, nausea, vomiting, and diarrhea. Clinicians should be aware that triptans may be commonly used intermittently and that either the triptan or the SSRI may be prescribed by a different physician. Discuss the risks of serotonin syndrome with patients who are prescribed this combination and monitor them closely for symptoms of serotonin syndrome (US Food and Drug Administration, 2006).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Coadministration of a triptan, such as eletriptan, and an SSRI may result in a life-threatening condition called serotonin syndrome. Be aware that triptans may be commonly used intermittently and that either the triptan or the SSRI may be prescribed by a different physician. If these agents are used together, discuss the risks of serotonin syndrome with the patient and monitor closely for symptoms of serotonin syndrome (restlessness, hyperthermia, hyperreflexia, incoordination).
7) Probable Mechanism: additive pharmacologic effects resulting in excessive serotonergic stimulation

3.5.1.CC Enflurane
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, enflurane should be coadministered cautiously with other drugs which are also known to prolong the QTc interval, including fluoxetine (Owens, 2001c; Prod Info Prozac(R), 2001n).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of enflurane with other agents that can prolong the QT interval, such as fluoxetine, is not recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.CD Enoxaparin
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008). Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with warfarin (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When fluoxetine and an anticoagulant are given concurrently, monitor patient for signs of increased bleeding. Patients who are taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, when fluoxetine therapy is initiated or discontinued (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
7) Probable Mechanism: unknown
8) Literature Reports
a) Fluoxetine is thought to inhibit the cytochrome P450 2C9 isoenzyme (CYP2C9). This is the enzyme by which the more potent warfarin isomer, S-warfarin, is metabolized (Riesenman, 1995). In addition, both fluoxetine and warfarin are tightly bound to albumin. In combination, the possibility for protein-binding displacement of either drug is present (Prod Info Coumadin(R), 1999).
b) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bleeding (hospital admission due to bleeding) in patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patients with a mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients experienced 11 bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experiencing bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model (Wallerstedt et al, 2009).
c) A population-based, case-controlled study of new coumarin users (acenocoumarol and

phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5), however, the rate of gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).

d) In 6 reported cases, INR increased during combined fluoxetine and warfarin therapy. In a seventh case, severe bruising of the lower legs occurred in a woman initially treated with fluoxetine and, secondarily, started on warfarin (Woolfrey et al, 1993; Claire et al, 1991).

e) An 83-year-old man died from cerebral hemorrhage secondary to increased warfarin concentrations. The patient had been taking warfarin 30 mg per week for atrial fibrillation with a target INR between 2 and 3. The patient's other drugs included lisinopril, furosemide, potassium, digoxin, and acetaminophen. After being seen for symptoms of depression, anxiety, and insomnia, the patient was given fluoxetine 20 mg per day and diazepam 2.5 mg 3 to 4 times per day. Eight days later, the patient's INR increased to 4.8, and the dose of warfarin was decreased to 27.5 mg per week. The patient was later seen for symptoms of drug delirium, including confusion, incoherence, and speaking irrationally. At this point, the INR was 3.64 and fluoxetine was discontinued. The next day the patient presented to the hospital with left-sided weakness and later died from complications of a large interparenchymal hemorrhage. The authors proposed that the addition of fluoxetine to the patient's regimen resulted in increased serum levels of both warfarin and diazepam, resulting in delirium and loss of anticoagulant control (Dent & Orrock, 1997).

3.5.1.CE Epoprostenol

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and antiplatelet agents has been associated with an increased risk of bleeding. Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an antiplatelet agent are given concurrently, monitor patient for signs of increased bleeding (Prod Info PAXIL(R) oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008)

7) Probable Mechanism: unknown

3.5.1.CF Eptifibatide

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and antiplatelet agents has been associated with an increased risk of bleeding. Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an antiplatelet agent are given concurrently, monitor patient for signs of increased bleeding (Prod Info PAXIL(R) oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008)

7) Probable Mechanism: unknown

3.5.1.CG Ergoloid Mesylates

1) Interaction Effect: an increased risk of ergotism (nausea, vomiting, vasospastic ischemia)

2) Summary: Because of the potential for serious toxicity including vasospasm that can occur with increased plasma concentrations of ergot derivatives, the concurrent use of fluoxetine and ergot derivatives is contraindicated. Fluoxetine and ergot derivatives are both metabolized by cytochrome P450 3A4 enzymes, and the competition for metabolism could result in an increased plasma concentration of the ergot derivative (Prod Info Cafergot(R), 2002).

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: The concurrent use of fluoxetine and ergot derivatives is contraindicated.

7) Probable Mechanism: inhibition of cytochrome P450 3A4- mediated ergot metabolism by fluoxetine

3.5.1.CH Ergonovine

1) Interaction Effect: an increased risk of ergotism (nausea, vomiting, vasospastic ischemia)
2) Summary: Because of the potential for serious toxicity including vasospasm that can occur with increased plasma concentrations of ergot derivatives, the concurrent use of fluoxetine and ergot derivatives is contraindicated. Fluoxetine and ergot derivatives are both metabolized by cytochrome P450 3A4 enzymes, and the competition for metabolism could result in an increased plasma concentration of the ergot derivative (Prod Info Cafergot(R), 2002).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: The concurrent use of fluoxetine and ergot derivatives is contraindicated.
7) Probable Mechanism: inhibition of cytochrome P450 3A4- mediated ergot metabolism by fluoxetine

3.5.1.CI Ergotamine
1) Interaction Effect: an increased risk of ergotism (nausea, vomiting, vasospastic ischemia)
2) Summary: Because of the potential for serious toxicity including vasospasm that can occur with increased plasma concentrations of ergot derivatives, the concurrent use of fluoxetine and ergot derivatives is contraindicated. Fluoxetine and ergot derivatives are both metabolized by cytochrome P450 3A4 enzymes, and the competition for metabolism could result in an increased plasma concentration of the ergot derivative (Prod Info Cafergot(R), 2002).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: The concurrent use of fluoxetine and ergot derivatives is contraindicated.
7) Probable Mechanism: inhibition of cytochrome P450 3A4- mediated ergot metabolism by fluoxetine

3.5.1.CJ Erythromycin
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Erythromycin significantly increased the mean QTc interval versus baseline in a retrospective study of 49 patients (Oberg & Bauman, 1995a). Erythromycin has demonstrated QTc prolongation in combination with other drugs that prolong the QT interval (Prod Info PCE(R), 1997). Fluoxetine has been associated with QT prolongation (Prod Info Prozac(R), 2003a). Caution is advised with coadministration of drugs that potentially prolong the QTc interval.
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Caution is advised if erythromycin and fluoxetine are used concomitantly. Monitor QT interval at baseline and periodically during treatment.
7) Probable Mechanism: additive effects on QT prolongation
8) Literature Reports
a) Erythromycin significantly increased the QTc interval compared with baseline in a retrospective study of 49 patients. The erythromycin dose was 500 milligrams or 1 gram four times daily, with a mean of 15 doses received. Patients (n equal to 9) who received 60 mg/kg/day or more all developed increases in QT interval of 15% or greater. For all patients, the mean QTc interval increased from 432 milliseconds (msec) at baseline to 483 msec (p less than 0.01). In patients with delayed repolarization at baseline (n equal to 9), the QTc interval increased from 473 msec to 525 msec (p less than 0.01). In patients with heart disease (n equal to 30), all experienced an increase in QTc interval (mean of 15%), compared with an increase of 8% in patients without heart disease (p less than 0.05). In 5 patients (10%), the QTc interval was severely prolonged. One patient developed torsades de pointes attributed to erythromycin. Of 16 patients receiving cotrimoxazole concomitantly, 8 developed QT prolongation of 15% or greater (Oberg & Bauman, 1995).

3.5.1.CK Etodolac
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched

among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).

b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.CL Etofenamate

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).

b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.CM Etoricoxib

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).

b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.CN Felbinac

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM),

2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.CO Fenbufen
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.CP Fenfluramine
1) Interaction Effect: serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)
2) Summary: Fenfluramine is a nonspecific serotonin agonist that both enhances the release of serotonin and inhibits serotonin reuptake. Combination therapy with fenfluramine and another selective serotonin reuptake inhibitor, such as fluoxetine, has the potential to cause serotonin syndrome (Schenck & Mahowald, 1996a). Serotonin syndrome is a hyperserotonergic state characterized by symptoms such as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. Serious, even fatal, reactions have been reported (Sternbach, 1991z). Until more data are available, fenfluramine should not be used in combination with fluoxetine.
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Concurrent use of fenfluramine and fluoxetine may result in an additive increase in serotonin levels in the central nervous system, and could result in serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes). Fenfluramine should not be used in combination with fluoxetine or other serotonin specific reuptake inhibitors.
7) Probable Mechanism: additive serotonergic effects

3.5.1.CQ Fenoprofen
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an

increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.CR Fentiazac
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.CS Flecainide
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, the coadministration of Class I antiarrhythmics and other drugs known to prolong the QTc interval is not recommended (Prod Info Tambocor(R) flecainide acetate, 1998). Fluoxetine has been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Prozac(R), 2001w).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of class I antiarrhythmic agents and agents that prolong the QT interval, such as fluoxetine, is not recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.CT Floctafenine
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM),

2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.CU Fluconazole
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Case reports have described QT prolongation and torsades de pointes associated with fluconazole (Khazan & Mathis, 2002; Wassmann et al, 1999). Fluoxetine has been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Prozac(R), 2001q). Even though no formal drug interaction studies have been done, caution is advised if drugs known to prolong the QT interval are used concomitantly.
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Caution is advised if fluconazole and fluoxetine are used concomitantly.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.CV Flufenamic Acid
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.CW Fluphenazine
1) Interaction Effect: an increased risk of developing acute parkinsonism
2) Summary: The development of acute, severe parkinsonism has been observed in a patient receiving fluphenazine for Tourette's syndrome and fluoxetine for depression. Upon discontinuation of fluoxetine, the parkinsonism resolved. A similar interaction has been observed when fluphenazine was given in combination with paroxetine or sertraline (Kurlan, 1998a).
3) Severity: moderate
4) Onset: delayed

5) Substantiation: probable
6) Clinical Management: Monitor patients receiving concurrent therapy with fluphenazine and fluoxetine for the development of drug-induced parkinsonism. Therapy with fluoxetine may need to be discontinued.
7) Probable Mechanism: inhibition of cytochrome P450-mediated fluphenazine metabolism by fluoxetine
8) Literature Reports
a) A 63-year-old female with chronic, multiple motor and vocal tics was successfully treated with fluphenazine 2.5 mg daily. When nortriptyline therapy for depression failed, the patient was started on fluoxetine 20 mg daily. After two weeks, she developed acute, severe parkinsonism manifesting as resting tremor, rigidity, bradykinesia, postural imbalance, and stooped posture. The parkinsonism resolved within three weeks of discontinuing the fluphenazine and the fluoxetine, but the tics reappeared (Kurlan, 1998).

3.5.1.CX Flurbiprofen
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.CY Fondaparinux
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008). Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with warfarin (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When fluoxetine and an anticoagulant are given concurrently, monitor patient for signs of increased bleeding. Patients who are taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, when fluoxetine therapy is initiated or discontinued (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
7) Probable Mechanism: unknown
8) Literature Reports
a) Fluoxetine is thought to inhibit the cytochrome P450 2C9 isoenzyme (CYP2C9). This is the enzyme by which the more potent warfarin isomer, S-warfarin, is metabolized (Riesenman, 1995). In addition, both fluoxetine and warfarin are tightly bound to albumin. In combination, the possibility for protein-binding displacement of either drug is present (Prod Info Coumadin(R), 1999).
b) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bleeding (hospital admission due to bleeding) in patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patients with a mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients experienced 11 bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4

and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experiencing bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model (Wallerstedt et al, 2009).

c) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5), however, the rate of gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).

d) In 6 reported cases, INR increased during combined fluoxetine and warfarin therapy. In a seventh case, severe bruising of the lower legs occurred in a woman initially treated with fluoxetine and, secondarily, started on warfarin (Woolfrey et al, 1993; Claire et al, 1991).

e) An 83-year-old man died from cerebral hemorrhage secondary to increased warfarin concentrations. The patient had been taking warfarin 30 mg per week for atrial fibrillation with a target INR between 2 and 3. The patient's other drugs included lisinopril, furosemide, potassium, digoxin, and acetaminophen. After being seen for symptoms of depression, anxiety, and insomnia, the patient was given fluoxetine 20 mg per day and diazepam 2.5 mg 3 to 4 times per day. Eight days later, the patient's INR increased to 4.8, and the dose of warfarin was decreased to 27.5 mg per week. The patient was later seen for symptoms of drug delirium, including confusion, incoherence, and speaking irrationally. At this point, the INR was 3.64 and fluoxetine was discontinued. The next day the patient presented to the hospital with left-sided weakness and later died from complications of a large interparenchymal hemorrhage. The authors proposed that the addition of fluoxetine to the patient's regimen resulted in increased serum levels of both warfarin and diazepam, resulting in delirium and loss of anticoagulant control (Dent & Orrock, 1997).

3.5.1.CZ Foscarnet

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Foscarnet can prolong the QT interval in some patients, which may result in ventricular tachycardia, ventricular fibrillation, and torsades de pointes. Because fluoxetine may also prolong the QT interval and increase the risk of arrhythmias, the concurrent administration of foscarnet and fluoxetine is not recommended (Prod Info Prozac(R), 2001t; Prod Info Foscavir(R), 1998).

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of foscarnet and fluoxetine is not recommended.

7) Probable Mechanism: additive cardiac effects

3.5.1.DA Fosphenytoin

1) Interaction Effect: an increased risk of phenytoin toxicity (ataxia, hyperreflexia, nystagmus, tremor)

2) Summary: Fosphenytoin is a prodrug of phenytoin and the same interactions that occur with phenytoin are expected to occur with fosphenytoin (Prod Info Cerebyx(R), 1999). Several case reports indicate that concurrent use of fluoxetine and phenytoin can result in significantly increased phenytoin serum levels leading to toxicity (FDA, 1994c; Jalil, 1992c; Woods et al, 1994a). Alternatively, patients who are stabilized on fluoxetine and phenytoin therapy may experience subtherapeutic concentrations of phenytoin and loss of seizure control when fluoxetine is discontinued (Shad & Preskorn, 1999c).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: established

6) Clinical Management: Monitor phenytoin serum levels with the addition of fluoxetine and periodically thereafter to assure stability; a lower fosphenytoin dosage may be required with concomitant therapy. Serum levels of phenytoin should be monitored following the discontinuation of fluoxetine; however, because of the long half-life of fluoxetine, decreases in phenytoin levels may not be clinically significant for a few weeks. Careful monitoring is required.

7) Probable Mechanism: decreased phenytoin metabolism

8) Literature Reports

a) Twenty-three reported cases of fluoxetine-phenytoin interactions that resulted in large increases in serum phenytoin levels and/or symptoms of phenytoin toxicity were evaluated. On the average, the adverse effects began within 2 weeks after fluoxetine was added to existing phenytoin therapy. The average increase in plasma levels in 9 evaluable cases was 161% (range 75 to 309%) and the maximum phenytoin serum concentration in 16 evaluable cases ranged from 22 to 53.5 mcg/mL

(therapeutic level, 10 to 20 mcg/mL) (FDA, 1994b).
b) An 84-year-old woman was stabilized on phenytoin 300 mg daily; after two months of treatment, fluoxetine 20 mg daily was added to her therapy and increased to 40 mg daily after 10 days (Jalil, 1992b). Within five days of starting fluoxetine, she developed vertigo, gait ataxia, diplopia, and altered mental status; her phenytoin serum level had increased from 15 to 35 mcg/mL. Both phenytoin and fluoxetine were gradually reduced and the signs and symptoms of toxicity abated. Four weeks later she was rechallenged with the same dose of fluoxetine without a return of toxicity.
c) In another case, a 57-year-old woman who had been stabilized on phenytoin 400 mg/d for a year (serum level, 11.5 mcg/mL) was given fluoxetine 20 mg/d (Jalil, 1992b). Ten days later she developed vomiting, vertigo, trunk ataxia, limb dysmetria, and multidirectional nystagmus, and the phenytoin serum level was 47 mcg/mL. Fluoxetine was discontinued and all signs and symptoms of toxicity disappeared over a 3 week period. At 4 weeks post-fluoxetine, the phenytoin serum level was 20 mcg/mL.
d) A 42-year-old male with a history of grand mal seizures and aggressive behavior was receiving phenytoin 200 mg daily and carbamazepine 600 mg daily without resolution of his problems. His phenytoin level was 2.0 ng/mL and his dose was subsequently increased to 400 mg daily. Fluoxetine 20 mg daily was added for aggression, and the patient experienced resolution of his behavioral problems and a cessation of his seizure activity. The phenytoin level ranged between 10.9 ng/mL and 15.7 ng/mL during fluoxetine therapy. However, the patient discontinued fluoxetine on his own and after a month experienced a recurrence of problems. Phenytoin concentration was measured at 6.6 ng/mL six weeks after the discontinuation of fluoxetine, despite no change in his phenytoin dose. This case report illustrates the need for close monitoring of phenytoin levels when fluoxetine is initiated and discontinued, since subtherapeutic levels of phenytoin may result if doses of phenytoin are not readjusted following the cessation of fluoxetine (Shad & Preskorn, 1999b).

3.5.1.DB Frovatriptan

1) Interaction Effect: an increased risk of serotonin syndrome
2) Summary: There have been case reports of weakness, hyperreflexia, and incoordination following concomitant use of sumatriptan, a 5-hydroxytryptamine-1 (5HT-1) agonist, and a serotonin specific reuptake inhibitor (SSRI) (Prod Info Imitrex(R) Nasal Spray, 2003). Because frovatriptan is a 5HT 1B/1D agonist, a similar interaction between SSRIs and frovatriptan may occur (Prod Info Frova(R), 2004). Concurrent use of frovatriptan and an SSRI may result in serotonin syndrome which may be life-threatening. Symptoms of serotonin syndrome may include restlessness, hallucinations, loss of coordination, fast heart beat, rapid changes in blood pressure, increased body temperature, overreactive reflexes, nausea, vomiting, and diarrhea. Clinicians should be aware that triptans may be commonly used intermittently and that either the triptan or the SSRI may be prescribed by a different physician. Discuss the risks of serotonin syndrome with patients who are prescribed this combination and monitor them closely for symptoms of serotonin syndrome (US Food and Drug Administration, 2006).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Coadministration of a triptan, such as frovatriptan, and an SSRI may result in a life-threatening condition called serotonin syndrome. Be aware that triptans may be commonly used intermittently and that either the triptan or the SSRI may be prescribed by a different physician. If these agents are used together, discuss the risks of serotonin syndrome with the patient and monitor closely for symptoms of serotonin syndrome (restlessness, hyperthermia, hyperreflexia, incoordination).
7) Probable Mechanism: additive pharmacologic effects resulting in excessive serotonergic stimulation

3.5.1.DC Furazolidone

1) Interaction Effect: weakness, hyperreflexia, and incoordination
2) Summary: Although not its primary mechanism of action, furazolidone has monoamine oxidase inhibitor activity. Cases of serious sometimes fatal reactions have been reported in patients receiving selective serotonin reuptake inhibitors (SSRI) in combination with monoamine oxidase inhibitors (MAOIs). Hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma have been reported. Furazolidone should not be used in combination with an SSRI, or within a minimum of 14 days of discontinuing therapy with a MAOI (Prod Info Furoxone(R), 1999).
3) Severity: contraindicated
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: If concurrent therapy with furazolidone and a selective serotonin reuptake inhibitor (SSRI) is deemed to be necessary, closely monitor the patient for signs of serotonergic excess (mental status changes, diaphoresis, fever, weakness, hyperreflexia, incoordination).
7) Probable Mechanism: additive pharmacologic effects resulting in excessive serotonergic stimulation

3.5.1.DD Galantamine

1) Interaction Effect: increased galantamine plasma concentrations
2) Summary: Based upon in vitro studies, the major enzymes involved in galantamine metabolism are CYP3A4 and CYP2D6. Fluoxetine is a known inhibitor of CYP2D6. In a population pharmacokinetic analysis

using a database of 852 Alzheimer's disease patients, several drugs which inhibit CYP2D6, including fluoxetine (N=48), demonstrated a 25-33% decrease in galantamine clearance. The resulting plasma concentration increase of galantamine may warrant caution when it is coadministered with fluoxetine. Monitor for galantamine toxicity including anorexia, nausea, vomiting, dizziness, arrhythmias or gastrointestinal bleeding (Prod Info RAZADYNE(R) ER extended release oral capsules, oral tablets, oral solution, 2007).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Increased galantamine plasma concentrations may result from fluoxetine inhibition of galantamine CYP2D6-mediated metabolism. Monitor for galantamine toxicity including anorexia, nausea, vomiting, dizziness, arrhythmias, or gastrointestinal bleeding (Prod Info RAZADYNE(R) ER extended release oral capsules, oral tablets, oral solution, 2007).
7) Probable Mechanism: inhibition of cytochrome CYP2D6-mediated galantamine metabolism

3.5.1.DE Gemifloxacin
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Gemifloxacin should be avoided in patients receiving fluoxetine. Gemifloxacin has the potential to prolong the QT interval in some patients (Prod Info Factive(R), 2003). Additive effects on QT prolongation may occur with the concomitant use of fluoxetine and gemifloxacin (Varriale, 2001b).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: The concurrent administration of two drugs that prolong the QT interval, such as gemifloxacin and fluoxetine, is not recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.DF Ginkgo
1) Interaction Effect: increased risk of serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)
2) Summary: The addition of Ginkgo biloba and/or St. John's Wort to therapy with buspirone and fluoxetine may have precipitated a hypomanic episode in a case report (Spinella & Eaton, 2002a). It is unclear if Ginkgo or St. John's Wort, the combination of both, or other patient factors, contributed to the effect. Theoretically, Ginkgo may increase the risk of serotonin syndrome when taken with selective serotonin reuptake inhibitors (SSRIs). Caution is advised, especially when ginkgo is taken to counteract sexual dysfunction associated with SSRIs. Ginkgo may inhibit monoamine oxidase (Sloley et al, 2000; White et al, 1996), and has demonstrated serotonergic activity in animals (Ramassamy et al, 1992) which might increase the risk of serotonin syndrome when ginkgo is combined with SSRIs. The potential MAO inhibitory activity of ginkgo is questionable. A human study did not show MAO inhibition in the brain following oral consumption (Fowler et al, 2000). Ginkgo biloba extract inhibited MAO-A/MAO-B in the rat brain in vitro (Sloley et al, 2000; White et al, 1996) and MAO-B in human platelets in vitro (White et al, 1996). No significant MAO inhibition was found in mice following oral consumption (Porsolt et al, 2000).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor patients closely for symptoms of serotonin syndrome if ginkgo is combined with selective serotonin reuptake inhibitors (SSRIs).
7) Probable Mechanism: additive pharmacologic effects resulting in excessive serotonergic stimulation
8) Literature Reports
a) A 42-year-old female experienced symptoms consistent with a mixed hypomanic episode following concomitant use of fluoxetine, buspirone, Ginkgo biloba, and St. John's Wort. The symptoms resolved following discontinuation of Ginkgo and St. John's Wort. The patient was being treated for depression following a mild traumatic brain injury with fluoxetine 20 milligrams (mg) twice daily and buspirone 15 mg twice daily. Several weeks prior to presentation, buspirone was increased to 20 mg twice daily for persistent anxiety and the patient began taking Ginkgo biloba, melatonin, and St. John's Wort in unspecified doses. Melatonin was considered unlikely to have contributed to her symptoms. Ginkgo and St. John's Wort were considered possible contributors since they may potentiate antidepressants, and considering the temporal relationship between the use of the herbs and onset of symptoms and discontinuation of the herbs and resolution of symptoms. However, the brain injury was considered a possible contributor (Spinella & Eaton, 2002).

3.5.1.DG Halofantrine
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Halofantrine can prolong the QT interval in some patients, which may result in ventricular tachycardia, ventricular fibrillation, and torsades de pointes. Because fluoxetine has demonstrated QT prolongation at therapeutic doses and may increase the risk of arrhythmias, the concurrent administration of

halofantrine with fluoxetine is not recommended (Prod Info Prozac(R), 2001i; Prod Info Halfan(R), 1998).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of halofantrine and fluoxetine is not recommended.
7) Probable Mechanism: additive cardiac effects

3.5.1.DH Haloperidol
1) Interaction Effect: haloperidol toxicity (pseudoparkinsonism, akathisia, tongue stiffness) and an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Haloperidol is associated with QTc prolongation and torsade de pointes (Hassaballa & Balk, 2003; Prod Info Haldol(R), 2001). Fluoxetine has been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Prozac(R), 2001x). Caution is advised with coadministration of drugs that potentially prolong the QTc interval. In addition, several case reports describe development of extrapyramidal symptoms when fluoxetine and haloperidol were taken together, possibly due to inhibition of haloperidol metabolism (Benazzi, 1996a; Goff et al, 1991a; Stein, 1991a; Tate, 1989a).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: The concurrent administration of fluoxetine and haloperidol is not recommended.
7) Probable Mechanism: inhibition of haloperidol metabolism by fluoxetine; theoretical additive effects on QT prolongation
8) Literature Reports
a) Fluoxetine increased plasma concentrations of haloperidol in 8 outpatients. Patients received fluoxetine 20 mg daily for 10 days with maintenance doses of haloperidol (average dose, 14 mg per day). After ten days, mean plasma concentrations of haloperidol had increased by 20%. Extrapyramidal symptom scores did not change appreciably after the addition of fluoxetine although one patient developed mild akathisia and another developed tremors. Extrapyramidal symptoms were expected to increase because of indirect inhibition of dopamine synthesis by fluoxetine (Goff et al, 1991).
b) A 39-year-old male experienced tardive dyskinesia with concomitant fluoxetine and haloperidol therapy. He was taking fluoxetine 20 mg daily for 2 months, then haloperidol 2 mg twice daily was started and later lowered to 1 mg per day. Five months later during a routine examination, tardive dyskinesia was diagnosed. The suggested mechanism was the down-regulation of dopamine activity (Stein, 1991).
c) A 39-year-old female developed tardive dyskinesia associated with concomitant fluoxetine and haloperidol therapy. She had been taking haloperidol 2 to 5 mg a day for two years (both with and without benztropine) with occasional mild, reversible extrapyramidal symptoms. Five days before stopping haloperidol, she started taking fluoxetine, which was increased over several days to 40 mg twice a day. After two weeks of fluoxetine she took haloperidol 5 mg each on two consecutive days (along with continuation of fluoxetine). She then experienced severe tongue stiffness, parkinsonism, and akathisia. Both fluoxetine and haloperidol were withdrawn. During the next seven days her extrapyramidal symptoms gradually disappeared (Tate, 1989).
d) A 40-year-old male developed urinary retention while taking fluoxetine and haloperidol. During a recurrence of depression, the patient was treated with fluoxetine 20 mg per day, alprazolam 1.5 mg per day, and haloperidol 1 mg per day. The patient had previously taken fluoxetine and alprazolam without incident. Approximately one week after beginning therapy, the patient developed difficulty in voiding urine, dilated pupils, dry mouth, palpitations, restlessness, hand tremors, and insomnia. After discontinuation of haloperidol and alprazolam, side effects ceased within one week. The authors postulated that the interaction was due to fluoxetine inhibition of cytochrome CYP2D6, which metabolizes haloperidol (Benazzi, 1996).

3.5.1.DI Halothane
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, halothane should be administered cautiously with other drugs which are also known to prolong the QTc interval, including fluoxetine (Owens, 2001; Prod Info Prozac(R), 2001).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of halothane with other agents that can prolong the QT interval, such as fluoxetine, is not recommended.
7) Probable Mechanism: additive effect on QT interval

3.5.1.DJ Heparin
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and anticoagulants has been associated

with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008). Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with warfarin (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: When fluoxetine and an anticoagulant are given concurrently, monitor patient for signs of increased bleeding. Patients who are taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, when fluoxetine therapy is initiated or discontinued (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).

7) Probable Mechanism: unknown

8) Literature Reports

a) Fluoxetine is thought to inhibit the cytochrome P450 2C9 isoenzyme (CYP2C9). This is the enzyme by which the more potent warfarin isomer, S-warfarin, is metabolized (Riesenman, 1995). In addition, both fluoxetine and warfarin are tightly bound to albumin. In combination, the possibility for protein-binding displacement of either drug is present (Prod Info Coumadin(R), 1999).

b) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bleeding (hospital admission due to bleeding) in patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patients with a mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients experienced 11 bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experiencing bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model (Wallerstedt et al, 2009).

c) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5), however, the rate of gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).

d) In 6 reported cases, INR increased during combined fluoxetine and warfarin therapy. In a seventh case, severe bruising of the lower legs occurred in a woman initially treated with fluoxetine and, secondarily, started on warfarin (Woolfrey et al, 1993; Claire et al, 1991).

e) An 83-year-old man died from cerebral hemorrhage secondary to increased warfarin concentrations. The patient had been taking warfarin 30 mg per week for atrial fibrillation with a target INR between 2 and 3. The patient's other drugs included lisinopril, furosemide, potassium, digoxin, and acetaminophen. After being seen for symptoms of depression, anxiety, and insomnia, the patient was given fluoxetine 20 mg per day and diazepam 2.5 mg 3 to 4 times per day. Eight days later, the patient's INR increased to 4.8, and the dose of warfarin was decreased to 27.5 mg per week. The patient was later seen for symptoms of drug delirium, including confusion, incoherence, and speaking irrationally. At this point, the INR was 3.64 and fluoxetine was discontinued. The next day the patient presented to the hospital with left-sided weakness and later died from complications of a large interparenchymal hemorrhage. The authors proposed that the addition of fluoxetine to the patient's regimen resulted in increased serum levels of both warfarin and diazepam, resulting in delirium and loss of anticoagulant control (Dent & Orrock, 1997).

3.5.1.DK Hydroquinidine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Even though no formal drug interaction studies have been done, the coadministration of Class Ia antiarrhythmics and other drugs known to prolong the QTc interval is not recommended (Prod Info Quinaglute Dura-tabs(R), 1999). Fluoxetine has demonstrated QT prolongation at therapeutic doses (Prod Info Prozac(R), 2001z).

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of class Ia antiarrhythmic agents and agents that prolong the QT interval, such as fluoxetine, is not recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.DL Hydroxytryptophan
1) Interaction Effect: an increased risk of serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)
2) Summary: Hydroxytryptophan (5-HTP) may potentiate the serotonergic effect of selective serotonin reuptake inhibitors (SSRIs) (Meltzer et al, 1997a). Since 5-HTP increases serotonin levels, when combined with an SSRI, the serotonin level may be increased sufficiently to produce serotonin syndrome. Caution is advised with concomitant use of 5-HTP and SSRIs.
3) Severity: moderate
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: No cases have been reported of serotonin syndrome resulting from this combination. Caution is advised if hydroxytryptophan (5-HTP) and a selective serotonin reuptake inhibitor (SSRI) are used concomitantly. Monitor the patient for early signs of serotonin syndrome such as anxiety, confusion, and disorientation.
7) Probable Mechanism: additive serotonergic effect
8) Literature Reports
a) Hydroxytryptophan (5-HTP) (200 milligrams (mg) orally) as a single dose increased plasma cortisol and prolactin levels in both medicated and unmedicated patients with major depression or obsessive compulsive disorder (OCD). These responses were greater if the patient was also taking fluoxetine (n = 16) (p less than 0.0001). Mean fluoxetine dose for depressed patients was 44 mg/day,and for OCD patients it was 60 mg/day. Cortisol or prolactin (PRL) levels in patients taking 5-HTP with tricyclic antidepressants (n = 14) or those receiving no medication (n = 83) were not significantly different from each other. A measurement of serotonergic effects of antidepressants can be evaluated by measuring hypothalamic-pituitary-adrenal (HPA) axis or PRL response. No clinical manifestations of serotonin syndrome were reported in patients taking 5-HTP concomitantly with fluoxetine (Meltzer et al, 1997).

3.5.1.DM Ibuprofen
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.DN Ibutilide
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, the coadministration of Class III antiarrhythmics and other drugs known to prolong the QTc interval is not recommended (Allen et al, 2002; Prod Info Tikosyn(TM) dofetilide capsules, 1999; Prod Info Corvert(R), 1998). Fluoxetine has been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Prozac(R), 2001a).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of class III antiarrhythmic agents and agents that prolong the QT interval, such as fluoxetine, is not recommended.

7) Probable Mechanism: additive effects on QT prolongation

3.5.1.DO Iloperidone

1) Interaction Effect: increased plasma concentrations of iloperidone
2) Summary: Coadministration of iloperidone and fluoxetine results in increased plasma levels of iloperidone and therefore requires a dose reduction of iloperidone (Prod Info FANAPT(TM) oral tablets, 2009).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: established
6) Clinical Management: If administered with fluoxetine, reduce iloperidone doses by one-half. Upon withdrawal of fluoxetine from the combination therapy, resume the previous iloperidone dose (Prod Info FANAPT(TM) oral tablets, 2009).
7) Probable Mechanism: inhibition of the CYP2D6-mediated metabolism of iloperidone
8) Literature Reports
a) Coadministration of fluoxetine 20 mg twice daily for 21 days and iloperidone 3 mg (single doses) in 23 healthy volunteers (ages 29 to 44 years) classified as CYP2D6 extensive metabolizers, increased the AUC of iloperidone and the P88 metabolite by 2- to 3-fold, and decreased the AUC of the P95 metabolite by one-half (Prod Info FANAPT(TM) oral tablets, 2009).

3.5.1.DP Iloprost

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and antiplatelet agents has been associated with an increased risk of bleeding. Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an antiplatelet agent are given concurrently, monitor patient for signs of increased bleeding (Prod Info PAXIL(R) oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008)
7) Probable Mechanism: unknown

3.5.1.DQ Imipramine

1) Interaction Effect: tricyclic antidepressant toxicity (dry mouth, urinary retention, sedation) and an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Tricyclic antidepressants (TCAs) and fluoxetine have been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Prozac(R), 2001h; Marshall & Forker, 1982). Even though no formal drug interaction studies have been done which demonstrate QT prolongation, the coadministration of tricyclic antidepressants and other drugs known to prolong the QTc interval, such as fluoxetine, is not recommended (Prod Info Elavil(R), 1999). In addition, concurrent use of fluoxetine and TCAs such as desipramine, nortriptyline, and imipramine has resulted in significant increases in TCA concentrations (Preskorn et al, 1994a; Preskorn et al, 1994a; Aranow et al, 1989a; Downs et al, 1989a; Goodnick, 1989a; Bell & Cole, 1988a).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: The concurrent administration of fluoxetine and a tricyclic antidepressant is not recommended.
7) Probable Mechanism: decreased tricyclic antidepressant metabolism; additive effects on QT prolongation
8) Literature Reports
a) Fluoxetine increased the level of tricyclic antidepressants (nortriptyline, imipramine, desipramine) in 4 patients. After the addition of fluoxetine, the ratio of antidepressant level to dose increased by 109% to 486% in the patients. Three patients developed clinical symptoms (anticholinergic effects, constipation, urinary hesitancy, sedation, unstable gait) as a result of the increased levels (Aranow et al, 1989).
b) Fluoxetine statistically and clinically significantly increased desipramine concentrations in 18 healthy subjects. When fluoxetine (20 mg daily) was added to desipramine (50 mg daily), the mean maximum concentration of desipramine increased by 278% and the area under the concentration-time curve increased by 342%. Desipramine trough concentrations continued to be 198% above baseline three weeks after fluoxetine was discontinued. The same study compared pharmacokinetics of desipramine when combined with sertraline. The impact of sertraline was modest, resulting in small and short-term increases in desipramine plasma concentrations (Preskorn et al, 1994).
c) A 75-year-old female experienced symptomatic increases in her desipramine serum concentrations when fluoxetine was added. Desipramine serum levels ranged from 109 to 150 ng/mL with oral doses of 300 mg at bedtime prior to fluoxetine therapy. Following the addition of oral fluoxetine 20 mg daily to the

regimen, the desipramine serum level increased to 212 ng/mL within five days. The fluoxetine dose was increased to 40 mg/day three days later, and the desipramine serum level was 419 ng/mL after four days. A worsening of depression and severe fatigue coincided with the increases in desipramine serum levels. Withdrawal of fluoxetine and reduction in the desipramine dose to 200 mg daily reduced the desipramine serum level to 231 ng/mL within two weeks (Bell & Cole, 1988).

d) A 33-year-old depressed male developed adverse effects of dry mouth, tinnitus, and difficulties with alertness and memory while receiving fluoxetine 40 mg daily and desipramine 150 mg daily for five weeks; fluoxetine was discontinued and the blood levels of desipramine decreased from 938 to 48 ng/mL with resolution of clinical symptoms (Goodnick, 1989).

e) A 39-year-old female experienced symptomatic increases in her desipramine levels with concomitant fluoxetine therapy. Prior to fluoxetine therapy, the patient's measured levels of desipramine had ranged from 148 to 160 ng/mL on a regimen of 300 mg daily. Five weeks after the addition of fluoxetine 20 mg daily, she reported anticholinergic symptoms, sedation, and confusion with a desipramine level of 527 ng/mL. The desipramine dose was lowered to 200 mg/day; eleven days later, the level was 244 ng/mL; the patient reported decreased energy, impaired short-term memory, and some "garbled" speech, as well as an episode of nausea, dizziness, and syncope. The desipramine dose was reduced to 50 mg/day; the adverse effects resolved in six days. Eight days later, the desipramine level was 122 ng/mL (Downs et al, 1989).

f) Concomitant administration of fluoxetine and desipramine was reported to result in an increased desipramine level and new onset of delirium in a 69-year-old male within 10 days of the addition of fluoxetine to the patient's regimen (Preskorn et al, 1990).

3.5.1.DR Indomethacin

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).

b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.DS Indoprofen

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1

to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.DT Insulin Aspart, Recombinant
1) Interaction Effect: hypoglycemia
2) Summary: Fluoxetine may increase the blood glucose-lowering effect of insulin and the susceptibility to hypoglycemia (Prod Info EXUBERA(R) inhalation powder inhaler, 2006; Prod Info NOVOLOG(R), 2005; Prod Info LEVEMIR(R) injection, 2005; Prod Info LANTUS(R) subcutaneous injection, 2004; Prod Info Apidra(TM), 2004).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Blood glucose levels should be closely monitored when fluoxetine is added or discontinued in a patient receiving insulin. Lower doses of insulin may be required with concomitant therapy.
7) Probable Mechanism: additive hypoglycemia

3.5.1.DU Insulin Detemir
1) Interaction Effect: hypoglycemia
2) Summary: Fluoxetine may increase the blood glucose-lowering effect of insulin and the susceptibility to hypoglycemia (Prod Info EXUBERA(R) inhalation powder inhaler, 2006; Prod Info NOVOLOG(R), 2005; Prod Info LEVEMIR(R) injection, 2005; Prod Info LANTUS(R) subcutaneous injection, 2004; Prod Info Apidra(TM), 2004).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Blood glucose levels should be closely monitored when fluoxetine is added or discontinued in a patient receiving insulin. Lower doses of insulin may be required with concomitant therapy.
7) Probable Mechanism: additive hypoglycemia

3.5.1.DV Insulin Glargine, Recombinant
1) Interaction Effect: hypoglycemia
2) Summary: Fluoxetine may increase the blood glucose-lowering effect of insulin and the susceptibility to hypoglycemia (Prod Info EXUBERA(R) inhalation powder inhaler, 2006; Prod Info NOVOLOG(R), 2005; Prod Info LEVEMIR(R) injection, 2005; Prod Info LANTUS(R) subcutaneous injection, 2004; Prod Info Apidra(TM), 2004).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Blood glucose levels should be closely monitored when fluoxetine is added or discontinued in a patient receiving insulin. Lower doses of insulin may be required with concomitant therapy.
7) Probable Mechanism: additive hypoglycemia

3.5.1.DW Insulin Glulisine
1) Interaction Effect: hypoglycemia
2) Summary: Fluoxetine may increase the blood glucose-lowering effect of insulin and the susceptibility to hypoglycemia (Prod Info EXUBERA(R) inhalation powder inhaler, 2006; Prod Info NOVOLOG(R), 2005; Prod Info LEVEMIR(R) injection, 2005; Prod Info LANTUS(R) subcutaneous injection, 2004; Prod Info Apidra(TM), 2004).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Blood glucose levels should be closely monitored when fluoxetine is added or discontinued in a patient receiving insulin. Lower doses of insulin may be required with concomitant therapy.
7) Probable Mechanism: additive hypoglycemia

3.5.1.DX Insulin Human Inhaled
1) Interaction Effect: hypoglycemia
2) Summary: Fluoxetine may increase the blood glucose-lowering effect of insulin and the susceptibility to hypoglycemia (Prod Info EXUBERA(R) inhalation powder inhaler, 2006; Prod Info NOVOLOG(R), 2005; Prod Info LEVEMIR(R) injection, 2005; Prod Info LANTUS(R) subcutaneous injection, 2004; Prod Info Apidra(TM), 2004).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Blood glucose levels should be closely monitored when fluoxetine is added or

discontinued in a patient receiving insulin. Lower doses of insulin may be required with concomitant therapy.
7) Probable Mechanism: additive hypoglycemia

3.5.1.DY Iproniazid

1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)
2) Summary: Concurrent administration or overlapping therapy with fluoxetine and a monoamine oxidase (MAO) inhibitor may result in CNS toxicity or serotonin syndrome, a hyperserotonergic state characterized by symptoms such as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. Serious, even fatal, reactions have been reported (Prod Info Prozac(R), 1999f; Sternbach, 1991k; Coplan & Gorman, 1993i; Feighner et al, 1990i; Kline et al, 1989i; Suchowersky & de Vries, 1990i). Concomitant use is contraindicated.
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Concurrent use of fluoxetine and iproniazid is contraindicated. Wait at least two weeks after discontinuing a MAO inhibitor before initiating fluoxetine therapy. In addition, wait at least five weeks after discontinuing fluoxetine before initiating therapy with a MAO inhibitor.
7) Probable Mechanism: inhibition of serotonin metabolism by monoamine oxidase
8) Literature Reports

a) Concomitant use of serotonin specific reuptake inhibitors and monoamine oxidase inhibitors can produce a toxic reaction known as serotonin syndrome (Sternbach, 1991j). Serotonin syndrome is a condition of serotonergic hyperstimulation and manifests as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor (Sternbach, 1991j). If the syndrome is not recognized and correctly treated, death can result.

b) It has been suggested that fluoxetine therapy be discontinued for at least five weeks before beginning therapy with a monoamine oxidase inhibitor. A 28-year old woman discontinued fluoxetine for six weeks before starting therapy with tranylcypromine. Over the next few days the patient developed fever, paresthesias, confusion, abdominal cramping, and various other CNS symptoms. Upon discontinuation of tranylcypromine, the patient's symptoms began to resolve. Blood samples taken three days after discontinuation of tranylcypromine revealed no presence of fluoxetine; however, the norfluoxetine level was 84 ng/mL (Coplan & Gorman, 1993h).

c) Adverse reactions reported when fluoxetine was given concomitantly with phenelzine (n=9) or tranylcypromine (n=4) include tremor (50%), agitation or restlessness (42%), mental status changes (42%), myoclonus (33%), diarrhea (33%), and blood pressure changes (25%) (Feighner et al, 1990h). All but one of the patients were taking other medications (ie, benzodiazepines, neuroleptics, anticonvulsants, antidepressants) that may have contributed to the adverse reactions.

d) Ten hours after her last dose of fluoxetine, a 45-year-old woman began tranylcypromine therapy (Kline et al, 1989h). Headache, muscle contractions, insomnia, and unsteady gait were reported on the second day. Thioridazine and tryptophan were added to her therapy. The patient experienced fever, rigidity of the arms and legs, and hyperreflexia. She died in the intensive care unit of a hospital 44 hours later.

e) Two cases suggestive of an interaction between fluoxetine and selegiline have been reported. One case involved a first episode of mania being observed approximately one month after adding selegiline to fluoxetine therapy. The patient improved two months after both drugs were discontinued, and no further details were provided. The second case involved diaphoresis, vasoconstriction, and cyanosis of the hands which occurred in close temporal relationship to adding fluoxetine and selegiline. Both drugs were discontinued, with relatively quick resolution of symptoms. Rechallenge with fluoxetine alone occurred without incident (Suchowersky & de Vries, 1990h).

3.5.1.DZ Isocarboxazid

1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)
2) Summary: Concurrent administration or overlapping therapy with fluoxetine and a monoamine oxidase (MAO) inhibitor may result in CNS toxicity or serotonin syndrome, a hyperserotonergic state characterized by symptoms such as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. Serious, even fatal, reactions have been reported (Prod Info Prozac(R), 1999i; Sternbach, 1991q; Coplan & Gorman, 1993o; Feighner et al, 1990o; Kline et al, 1989o; Suchowersky & de Vries, 1990o). Concomitant use is contraindicated (Prod Info Marplan(R), 1998).
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Concurrent use of fluoxetine and a MAO inhibitor is contraindicated. Wait at least two weeks after discontinuing a MAO inhibitor before initiating fluoxetine therapy. In addition, wait at least five weeks after discontinuing fluoxetine before initiating therapy with a MAO inhibitor.
7) Probable Mechanism: inhibition of serotonin metabolism by monoamine oxidase
8) Literature Reports

a) Concomitant use of serotonin specific reuptake inhibitors and monoamine oxidase inhibitors can

produce a toxic reaction known as serotonin syndrome (Sternbach, 1991p). Serotonin syndrome is a condition of serotonergic hyperstimulation and manifests as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor (Sternbach, 1991p). If the syndrome is not recognized and correctly treated, death can result.

b) It has been suggested that fluoxetine therapy be discontinued for five weeks before beginning therapy with a monoamine oxidase inhibitor. However, one case report describes a 28-year old woman who had discontinued a 2-year fluoxetine regimen for six weeks before starting therapy with tranylcypromine. Over the next few days the patient developed fever, paresthesias, confusion, abdominal cramping, and various other CNS symptoms. Upon discontinuation of tranylcypromine, the patient's symptoms began to resolve. Blood samples taken three days after discontinuation of tranylcypromine revealed no presence of fluoxetine; however, the norfluoxetine level was 84 ng/mL (Coplan & Gorman, 1993n).

c) Adverse reactions reported when fluoxetine was given concomitantly with phenelzine (n=9) or tranylcypromine (n=4) include tremor (50%), agitation or restlessness (42%), mental status changes (42%), myoclonus (33%), diarrhea (33%), and blood pressure changes (25%) (Feighner et al, 1990n). All but one of the patients were taking other medications (ie, benzodiazepines, neuroleptics, anticonvulsants, antidepressants) that may have contributed to the adverse reactions.

d) Ten hours after her last dose of fluoxetine, a 45-year-old woman began tranylcypromine therapy (Kline et al, 1989n). Headache, muscle contractions, insomnia, and unsteady gait were reported on the second day. Thioridazine and tryptophan were added to her therapy. The patient experienced fever, rigidity of the arms and legs, and hyperreflexia. She died in the intensive care unit of a hospital 44 hours later.

e) Interactions between fluoxetine and selegiline were suggested in two case reports (Suchowersky & de Vries, 1990n). One case involved a first episode of mania being observed approximately one month after adding selegiline to fluoxetine therapy. The patient improved two months after both drugs were discontinued, and no further details were provided. The second case involved diaphoresis, vasoconstriction, and cyanosis of the hands which occurred in close temporal relationship to adding fluoxetine and selegiline. Both drugs were discontinued, with relatively quick resolution of symptoms. Rechallenge with fluoxetine alone occurred without incident.

3.5.1.EA Isoflurane

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Even though no formal drug interaction studies have been done, isoflurane should be administered cautiously with other drugs which are also known to prolong the QTc interval, including fluoxetine (Owens, 2001a; Prod Info Prozac(R), 2001k).

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of isoflurane with other agents that can prolong the QT interval, such as fluoxetine, is not recommended.

7) Probable Mechanism: additive effect on QT interval

3.5.1.EB Isoxicam

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).

b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.EC Isradipine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Isradipine can prolong the QT interval in some patients, which may result in ventricular tachycardia, ventricular fibrillation, and torsades de pointes. Because fluoxetine may also prolong the QT interval and increase the risk of arrhythmias, the concurrent administration of isradipine with fluoxetine is not recommended (Prod Info DynaCirc(R), 2000).

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of isradipine and fluoxetine is not recommended.

7) Probable Mechanism: additive cardiac effects

3.5.1.ED Ketoprofen

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).

b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.EE Ketorolac

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).

b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.EF Lamifiban

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and antiplatelet agents has been associated with an increased risk of bleeding. Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an antiplatelet agent are given concurrently, monitor patient for signs of increased bleeding (Prod Info PAXIL(R) oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008)
7) Probable Mechanism: unknown

3.5.1.EG Levomethadyl

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Any drug known to have the potential to prolong the QT interval should not be used with levomethadyl. Possible pharmacodynamic interactions can occur between levomethadyl and potentially arrhythmogenic agents such as fluoxetine that prolong the QT interval (Prod Info Orlaam(R), 2001).
3) Severity: contraindicated
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Levomethadyl is contraindicated in patients being treated with fluoxetine as it may precipitate QT prolongation and interact with levomethadyl.
7) Probable Mechanism: unknown

3.5.1.EH Lexipafant

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and antiplatelet agents has been associated with an increased risk of bleeding. Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an antiplatelet agent are given concurrently, monitor patient for signs of increased bleeding (Prod Info PAXIL(R) oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008)
7) Probable Mechanism: unknown

3.5.1.EI Lidoflazine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Lidoflazine and fluoxetine have been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Prozac(R), 2001g; Hanley & Hampton, 1983). Even though no formal drug interaction studies have been done, the coadministration of drugs known to prolong the QTc interval is not recommended.
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of lidoflazine and fluoxetine is not recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.EJ Linezolid

1) Interaction Effect: increased risk of serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)
2) Summary: Linezolid is a reversible, nonselective monoamine oxidase inhibitor (MAOI). Concurrent administration or overlapping therapy with fluoxetine and a MAOI may result in CNS toxicity or serotonin syndrome, a hyperserotonergic state characterized by symptoms such as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. Serious, even fatal, reactions have been reported. There have been spontaneous reports of serotonin syndrome associated with concomitant use of linezolid and serotonergic agents, including fluoxetine (Thomas et al, 2004; Steinberg & Morin, 2007; Prod Info ZYVOX(R) IV injection, oral tablets, oral suspension, 2008; Prod Info PROZAC(R) oral capsules, oral solution, 2006). If these agents are used concomitantly, monitor for serotonin syndrome effects, including confusion, delirium, restlessness, tremors, blushing, diaphoresis, and hyperpyrexia. If symptoms occur, consider discontinuation of either one or both of the agents (Prod Info ZYVOX(R) IV injection, oral tablets, oral suspension, 2008). A washout period of 2 weeks is usually recommended following discontinuation of

an MAOI and initiation of fluoxetine. Following discontinuation of fluoxetine, a washout period of 5 weeks is usually recommended prior to initiation of an MAOI (Prod Info PROZAC(R) oral capsules, oral solution, 2006).

3) Severity: contraindicated

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: Unless carefully monitored for serotonin syndrome, linezolid should not be administered to patients taking fluoxetine(Prod Info ZYVOX(R) IV injection, oral tablets, oral suspension, 2008). A washout period of 2 weeks is usually recommended following discontinuation of an MAOI and initiation of fluoxetine. Following discontinuation of fluoxetine, a washout period of 5 weeks is usually recommended prior to initiation of an MAOI (Prod Info PROZAC(R) oral capsules, oral solution, 2006). If fluoxetine and linezolid are used concomitantly, monitor closely for symptoms of serotonin syndrome such as neuromuscular abnormalities (including hyper-reflexia, tremor, muscle rigidity, clonus, peripheral hypertonicity, and shivering), autonomic hyperactivity (including tachycardia, mydriasis, diaphoresis, and diarrhea), and mental status changes (including agitation and delirium). Serotonin syndrome can be life-threatening. If serotonin syndrome develops, discontinue the offending agents and provide supportive care and other therapy as necessary (Boyer & Shannon, 2005).

7) Probable Mechanism: inhibition of serotonin metabolism by monoamine oxidase

8) Literature Reports

a) A 4-year-old female patient, weighing 12.8 kg, experienced serotonin syndrome-like symptoms following concomitant use of linezolid and fluoxetine. Eleven days after receiving fluoxetine 5 mg daily for acute stress disorder in response to a burn injury, the patient received oral linezolid 140 mg every 12 hours. Two days later, she was premedicated with oral fentanyl 200 mcg prior to a wound debridement procedure. Shortly afterwards, she became agitated and had myoclonus in her arms and legs. She also had mydriasis, was unable to visually track across midline, and her gaze deviated to the lower left quadrant. Discontinuation of fluoxetine and initiation of oral diphenhydramine 25 mg led to partial improvement in symptoms. Subsequently, linezolid was discontinued and replaced with an alternate antibiotic. Symptoms of agitation, myoclonic movements, and nystagmus resolved over the next 2 days (Thomas et al, 2004).

b) The concomitant administration of fluoxetine and linezolid was associated with mild symptoms of serotonin syndrome in a 23-year-old male as described in a case report. The patient, who had recently achieved complete remission of acute myelogenous leukemia and was admitted for maintenance chemotherapy, routinely received treatment with oral fluoxetine 60 mg once daily, oral methadone 75 mg once daily, oral voriconazole 300 mg twice daily, transdermal nicotine patch 21 mg (changed daily), oral lorazepam 2 mg twice daily (with 1 mg doses as needed every 4 hours), and oral quetiapine 200 mg every evening. On day 9 of admission, the fluoxetine dose was increased to 80 mg daily for mood instability, and linezolid 600 mg every 12 hours was initiated on day 43. Within 12 hours of initiating linezolid, the patient experienced physical discomfort and severe abdominal pain (described as feeling like a "runner's cramp" and making it "difficult to breathe"). The discomfort continued following another 4 doses of linezolid over the next day. On day 47, linezolid was discontinued, after a total of 6 linezolid doses, and the pain and other symptoms resolved within 48 hours. During linezolid therapy, vital signs and laboratory results were unremarkable, except for chemotherapy-induced neutropenia, thrombocytopenia, and anemia (Steinberg & Morin, 2007).

c) A retrospective chart review identified one highly probable case of serotonin syndrome in a patient who received concomitant therapy with linezolid and venlafaxine, followed by citalopram. Charts of 72 inpatients who received linezolid and an SSRI or venlafaxine within 14 days of each other were reviewed for a diagnosis of serotonin syndrome (SS) using the Sternbach and the Hunter Serotonin Toxicity criteria. Of these patients, 52 (72%) were treated concomitantly with linezolid and an SSRI or venlafaxine. Four patients met the criteria for having either high or low probability of SS. Of these, one case involved an 81-year-old woman who was diagnosed with a high probability of having SS after receiving concomitant linezolid and venlafaxine followed by citalopram. Linezolid was given for a vancomycin-resistant Enterococcus urinary tract infection. When the patient presented, she refused to eat, was confused as to time and place, and began shouting. Although she appeared to have met 6 of the Sternbach criteria and 4 of the Hunter criteria for SS, a diagnosis of SS was not documented in her chart. Her blood pressure was 180 mm Hg with a heart rate of 120 beats/min, and a respiratory rate of 50 breaths/min. The following day, she barely spoke and could not be aroused; additional symptoms included lethargy, extremity twitching and jerking, eyes rolled back in her head, and labored breathing. Linezolid was discontinued, and she was sedated and intubated. Five days following onset of symptoms and 2 days after linezolid was stopped, she was extubated and had returned to baseline mental status with the ability to communicate (Taylor et al, 2006).

d) In one case report, a 39-year-old female experienced symptoms of serotonin syndrome after concomitant treatment with fluoxetine and linezolid. She was admitted to the emergency room after being found unresponsive at home. This patient had a history of depression, suicide attempts and alcohol dependency. Before admission, her medications consisted of disulfiram, fluoxetine, buspirone, cyclobenzaprine, and folate. All medications were discontinued upon admission. The patient was given two doses of physostigmine for anticholinergic symptoms believed to be caused by a cyclobenzaprine overdose. Two days after admission, the patient became sedated, developed tachycardia, and had sporadic agitation presumably due to alcohol withdrawal. She was given lorazepam and haloperidol for

the alcohol withdrawal and agitation. On day five, she was intubated for respiratory depression thought to be from either pneumonia or respiratory suppression from lorazepam. The patient received vancomycin for methicillin-resistant staphylococcus aureus (sputum) and on day thirteen, was extubated and her mental status improved. On day eighteen, vancomycin was changed to linezolid. Immediate changes in her mental status were apparent. She experienced convulsions, tremors, weakness, and perspiration. After two doses of linezolid, the patient had a temperature of 98 degrees, blood pressure of 140/90, a heart rate of 170, and respirations of 18. Linezolid was discontinued and the vancomycin regimen restarted. The patient was diagnosed with benzodiazepine withdrawal, neuroleptic syndrome, sepsis, meningitis, and serotonin syndrome. Serotonin syndrome was diagnosed as a likely drug interaction between linezolid and fluoxetine (Morales & Vermette, 2005).

3.5.1.EK Lithium

1) Interaction Effect: possible increased lithium concentrations and/or an increased risk of SSRI-related serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)

2) Summary: Concomitant use of lithium and various SSRIs has been associated with enhanced side effects of either or both drugs, and with or without elevated lithium levels. The combination has resulted in neurotoxicity and increased lithium levels in one case report (Salama & Shafey, 1989a). Signs and symptoms of lithium toxicity and serotonin syndrome have also been reported in patients who demonstrated therapeutic serum lithium levels while on concurrent fluoxetine and lithium (Muly et al, 1993a; Noveske et al, 1989a). Two studies have failed to identify a pharmacokinetic interaction between lithium and citalopram (Gram et al, 1993a; Baumann et al, 1996a). Combined administration of citalopram (40 mg daily for 10 days) and lithium (30 mmol/day for 5 days) had no significant effect on the pharmacokinetics of citalopram or lithium. However, plasma lithium levels should be monitored with appropriate adjustment to the lithium dose in accordance with standard clinical practice. Lithium may enhance the serotonergic effects of citalopram, therefore caution should be exercised when citalopram and lithium are coadministered (Prod Info Celexa(R), 2004). Concurrent use of fluvoxamine and lithium has led to case reports of increased lithium levels and neurotoxicity, serotonin syndrome, somnolence, and mania (Salama & Shafey, 1989a; Ohman & Spigset, 1993a; Evans & Marwick, 1990; Burrai et al, 1991a). No pharmacokinetic interference was apparent during a multiple-dose study of coadministered lithium and paroxetine (Prod Info Paxil CR(TM), 2003). If these two agents are to be given concomitantly, the manufacturer suggests that caution be used until more clinical experience is available. Drug interactions leading to lithium toxicity have been reported when lithium was coadministered with fluoxetine and fluvoxamine (both in the same pharmacological class as paroxetine, eg, selective serotonin reuptake inhibitors) (Ohman & Spigset, 1993a; Salama & Shafey, 1989a).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: established

6) Clinical Management: Monitor patients on concurrent lithium and selective serotonin reuptake inhibitor therapy for increased plasma concentrations of lithium. In addition, monitor patients for signs and symptoms associated with serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes).

7) Probable Mechanism: unknown

8) Literature Reports

a) Concomitant administration of oral lithium carbonate and oral fluoxetine resulted in increased lithium serum levels with lithium toxicity in a 44-year-old woman with a bipolar affective disorder (Salama & Shafey, 1989). Fluoxetine 20 mg daily was added to a regimen of lithium 1200 mg daily following patient complaints of weakness, tiredness, decreased concentration, and early morning awakening. Lithium serum levels increased to 1.7 mEq/L from a range of 0.75 to 1.15 mEq/L prior to fluoxetine. Fluoxetine was discontinued and the dose of lithium decreased; this resulted in a decrease in the lithium serum level within 48 hours to 1.2 mEq/L. The neurologic symptoms subsided within seven days as the lithium serum level decreased to 0.9 mEq/L. The contribution of fluoxetine to lithium toxicity in this patient was obscured by the fact that the lithium was reduced at the time of fluoxetine withdrawal.

b) A 53-year old woman who had been taking fluoxetine 20 mg daily and lorazepam 0.5 mg four times daily for a major depressive disorder had lithium 900 mg per day added to her regimen in order to augment her response to fluoxetine. Within 48 hours, the patient became confused, ataxic, and developed a coarse tremor in her right arm. Vital signs showed a rectal temperature of 101 degrees F, and laboratory values were normal except for an elevated leukocyte count and slightly elevated bilirubin level. After discontinuation of lithium and fluoxetine, the patient's symptoms resolved over the next four days. At no point did the lithium levels reach a toxic level, suggesting that the patient's symptoms were due to a toxic reaction between fluoxetine and lithium (Noveske et al, 1989).

c) Serotonin syndrome was precipitated when lithium 300 mg twice daily was added to a three-month regimen of fluoxetine 40 mg per day. Five days later, the patient's lithium level was measured at 0.65 mEq/L and the dose was increased to 300 mg three times daily. Two days after this dosage change, the patient experienced akathisia, myoclonus, hyperreflexia, shivering, tremor, diarrhea, and incoordination. After discontinuation of lithium and initiation of cyproheptadine therapy, the patient's symptoms began to improve. The patient was discharged on a regimen of fluoxetine 40 mg per day without further symptoms of serotonin syndrome (Muly et al, 1993).

d) Eight healthy male volunteers completed three phases of an interaction study to determine the effects of coadministered lithium and citalopram. All subjects were extensive metabolizers of sparteine, indicating normal cytochrome P450 2D6 enzyme activity. Although lithium is not influenced by drug

oxidation, citalopram metabolites are excreted by the kidney, as is lithium. Each subject received citalopram 40 mg alone as a single daily dose for 10 days, lithium 30 mmol (1980 mg) alone daily for five days, and lithium coadministered with citalopram on days 3-7. At least two weeks separated each treatment phase. Results showed that the concurrent administration of citalopram and lithium did not significantly alter the pharmacokinetics of lithium (Gram et al, 1993).

e) Twenty-four patients experiencing depression (DSM III criteria) were randomized under double-blind conditions to receive citalopram (40 mg to 60 mg daily) and lithium carbonate (800 mg daily) or placebo. All of the subjects had failed to respond to four weeks of citalopram monotherapy. Lithium was coadministered on days 29 to 42. No evidence of a pharmacokinetic interaction between lithium and citalopram was noted, and cotherapy was well tolerated (Baumann et al, 1996).

f) Serotonin syndrome was described in a 53-year-old patient who was stabilized on lithium 1400 mg daily (serum level 0.71 mmol/L) and was given fluvoxamine 50 mg daily. Over a 10-day period the fluvoxamine dose was increased to 200 mg daily; tremor and difficulty with fine hand movements developed. After two weeks, tremor, impaired motor function coordination, marked bilateral hyperreflexia of biceps and knee jerks, and clonus in both ankles were seen. After 12 weeks of continued therapy, during which time no further deterioration occurred, nortriptyline 100 mg daily replaced fluvoxamine, and the neuromuscular symptoms abated over a 2-week period. After four weeks the patient's neurological exam was normal (Ohman & Spigset, 1993).

g) Three cases of mania were reported in patients who were treated with lithium and fluvoxamine. The mania appeared 10 days, four weeks, and five weeks, respectively, after cotherapy was begun. Fluvoxamine was discontinued and, in two of the three patients, the mania resolved, and successful treatment of depression occurred with lithium alone. The third patient improved, but depression reappeared within a month of fluvoxamine discontinuation (Burrai et al, 1991).

h) In an open-labeled, placebo-controlled study, lithium 600 mg was administered to 16 subjects orally twice daily on days one through eight and once in the morning on day nine. In addition, oral sertraline 100 mg or placebo was given twice, ten hours and two hours prior to lithium dosing on day nine. The steady-state lithium level was only decreased by 1.4% (0.01 mEq/L) and the lithium renal clearance increased by 6.9% (0.11 L/hour) when sertraline was coadministered. Seven subjects experienced side effects, mainly tremors, after receiving lithium and sertraline, whereas no subjects who ingested placebo and lithium experienced side effects (Wilner et al, 1991).

3.5.1.EL Lorcainide

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Even though no formal drug interaction studies have been done, the coadministration of Class I antiarrhythmics and other drugs known to prolong the QTc interval is not recommended (Prod Info Tambocor(R) flecainide acetate, 1998). Fluoxetine has been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Prozac(R), 2001w).

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of class I antiarrhythmic agents and agents that prolong the QT interval, such as fluoxetine, is not recommended.

7) Probable Mechanism: additive effects on QT prolongation

3.5.1.EM Lornoxicam

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).

b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.EN Meclofenamate

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).

b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.EO Mefenamic Acid

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).

b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.EP Mefloquine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Fluoxetine has been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Prozac(R), 2001p). Even though no formal drug interaction studies have been done, caution is advised if mefloquine is used with other drugs which can prolong the QTc interval (Prod Info Lariam(R), 1999).

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of fluoxetine and mefloquine is not recommended.

7) Probable Mechanism: additive effects on QT prolongation

3.5.1.EQ Meloxicam

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).

b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.ER Meperidine

1) Interaction Effect: an increased risk of serotonin syndrome

2) Summary: A 43-year-old male on fluoxetine every other day experienced serotonin syndrome immediately after intravenous meperidine was administered (Tissot, 2003). If fluoxetine and meperidine are used concomitantly, monitor closely for symptoms of serotonin syndrome. Serotonin syndrome can be life-threatening. If serotonin syndrome develops, discontinue the offending agents and provide supportive care and other therapy as necessary (Boyer & Shannon, 2005).

3) Severity: major

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: A case of serotonin syndrome was reported with coadministration of fluoxetine and meperidine and therefore, concomitant use is discouraged (Tissot, 2003). If fluoxetine and meperidine are used concomitantly, monitor closely for symptoms of serotonin syndrome such as neuromuscular abnormalities (including hyper-reflexia, tremor, muscle rigidity, clonus, peripheral hypertonicity, and shivering), autonomic hyperactivity (including tachycardia, mydriasis, diaphoresis, the presence of bowel sounds, and diarrhea), and mental status changes (including agitation and delirium). Serotonin syndrome can be life-threatening. If serotonin syndrome develops, discontinue the offending agents and provide supportive care and other therapy as necessary (Boyer & Shannon, 2005).

7) Probable Mechanism: additive pharmacologic effects

8) Literature Reports

a) A 43-year-old male on fluoxetine every other day experienced serotonin syndrome immediately after intravenous meperidine was administered. His other medications were rosiglitazone and fenofibrate. His medical history includes type 2 diabetes, dyslipidemia, and recurrent episodes of pancreatitis. Prior to this adverse event he received meperidine and midazolam, while not on fluoxetine, without any sequela. Before an endoscopy procedure he was administered intravenous midazolam and 50 mg of intravenous meperidine. He immediately became agitated and restless. He was unable to follow verbal commands because of confusion. Blood pressure (180/100 mm Hg) and heart rate (130 bpm) increased and oxygen saturation decreased to 95%. He had diaphoresis and dilated pupils. Within 10 minutes his blood pressure started to decrease. He had an episode of diarrhea. Over the next 10 to 15 minutes, his agitation subsided, he remained sleepy and confused, and blood pressure and heart continued to decrease to baseline. His temperature was 98.4 degrees Farenheit. After 60 to 90 minutes his sensorium appeared to clear and diaphoresis resolved. The patient remained afebrile with stable vital signs over the next 24 hours. He was treated with hydromorphone for abdominal pain without any adverse reaction. Several weeks later he received fentanyl, midazolam, and propofol pre-endoscopy without any event, but had not taken fluoxetine for 2 weeks before the procedure (Tissot, 2003).

3.5.1.ES Mesoridazine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Fluoxetine has been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Prozac(R), 2001ad). Although citing no data, the manufacturer of mesoridazine states that concomitant use with other drugs which prolong the QT interval is contraindicated (Prod Info Serentil(R),

2000).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of fluoxetine and mesoridazine is contraindicated.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.ET Methylergonovine
1) Interaction Effect: an increased risk of ergotism (nausea, vomiting, vasospastic ischemia)
2) Summary: Because of the potential for serious toxicity including vasospasm that can occur with increased plasma concentrations of ergot derivatives, the concurrent use of fluoxetine and ergot derivatives is contraindicated. Fluoxetine and ergot derivatives are both metabolized by cytochrome P450 3A4 enzymes, and the competition for metabolism could result in an increased plasma concentration of the ergot derivative (Prod Info Cafergot(R), 2002).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: The concurrent use of fluoxetine and ergot derivatives is contraindicated.
7) Probable Mechanism: inhibition of cytochrome P450 3A4- mediated ergot metabolism by fluoxetine

3.5.1.EU Methylphenidate
1) Interaction Effect: increased selective serotonin reuptake inhibitor plasma concentrations
2) Summary: Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism of selective serotonin reuptake inhibitors (SSRIs). Downward dose adjustments of the SSRI may be necessary when it is used concurrently with methylphenidate. Additionally, when initiating or discontinuing methylphenidate, the SSRI dose may need to be adjusted as needed (Prod Info METADATE CD(R) extended-release oral capsules, 2007).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Use caution when prescribing methylphenidate to patients who take an selective serotonin reuptake inhibitor (SSRI). Concomitant use of methylphenidate and an SSRI may cause elevated SSRI plasma concentrations. Consider a decrease in the dose of SSRI when these agents are coadministered. Additionally, consider adjusting the SSRI dose if necessary when initiating or discontinuing methylphenidate therapy (Prod Info METADATE CD(R) extended-release oral capsules, 2007).
7) Probable Mechanism: inhibition of selective serotonin reuptake inhibitor metabolism by methylphenidate

3.5.1.EV Methysergide
1) Interaction Effect: an increased risk of ergotism (nausea, vomiting, vasospastic ischemia)
2) Summary: Because of the potential for serious toxicity including vasospasm that can occur with increased plasma concentrations of ergot derivatives, the concurrent use of fluoxetine and ergot derivatives is contraindicated. Fluoxetine and ergot derivatives are both metabolized by cytochrome P450 3A4 enzymes, and the competition for metabolism could result in an increased plasma concentration of the ergot derivative (Prod Info Cafergot(R), 2002).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: The concurrent use of fluoxetine and ergot derivatives is contraindicated.
7) Probable Mechanism: inhibition of cytochrome P450 3A4- mediated ergot metabolism by fluoxetine

3.5.1.EW Metoprolol
1) Interaction Effect: an increased risk of metoprolol adverse effects (shortness of breath, bradycardia, hypotension, acute heart failure)
2) Summary: To date, little information is available related to the effects of combined fluoxetine and metoprolol. A case report described a possible interaction between metoprolol and fluoxetine resulting in bradycardia (Walley et al, 1993a). Fluoxetine is a potent inhibitor of hepatic cytochrome P450 2D6, the isoenzyme that catalyzes metoprolol metabolism (DeVane, 1994). Additional research is needed to further assess the effect of fluoxetine on metoprolol pharmacokinetics.
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Atenolol should be considered for fluoxetine-treated patients who require a beta blocker. If metoprolol and fluoxetine are coadministered, monitor patients for metoprolol adverse effects. A reduction in the metoprolol dose may be necessary.
7) Probable Mechanism: inhibition of hepatic metabolism of metoprolol
8) Literature Reports
a) A case report described a possible interaction between metoprolol and fluoxetine resulting in bradycardia. A patient with angina that was controlled with metoprolol 100 mg daily developed lethargy

and bradycardia within two days after fluoxetine 20 mg per day was added to his therapy. Fluoxetine was discontinued and metoprolol was replaced with sotalol 80 mg twice daily. A week later fluoxetine was reinstituted without recurrence of the bradycardia. Fluoxetine is known to inhibit hepatic metabolism. Metoprolol is extensively metabolized via hepatic cytochrome P450 isoenzymes (CYP2D6 and possibly CYP3A). Sotalol does not undergo significant hepatic metabolism (Walley et al, 1993).

3.5.1.EX Milnacipran

1) Interaction Effect: increased risk of serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)
2) Summary: Concurrent use of milnacipran and an SSRI may result in hypertension, coronary artery vasoconstriction or serotonin syndrome, which may be life-threatening. Symptoms of serotonin syndrome may include restlessness, hallucinations, loss of coordination, fast heart beat, rapid changes in blood pressure, increased body temperature, overreactive reflexes, nausea, vomiting, and diarrhea (Prod Info SAVELLA(R) oral tablets, 2009).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of milnacipran and an SSRI may result in hypertension and coronary artery vasoconstriction, through the additive serotonergic effects. If these agents are used together, discuss the risks of serotonin syndrome with the patient and monitor closely for symptoms of serotonin syndrome (restlessness, hyperthermia, hyperreflexia, incoordination), especially during treatment initiation and dose increases (Prod Info SAVELLA(R) oral tablets, 2009).
7) Probable Mechanism: additive serotonergic effect

3.5.1.EY Mirtazapine

1) Interaction Effect: an increased risk of serotonin syndrome
2) Summary: Concurrent use of fluoxetine and mirtazapine resulted in serotonin syndrome in a 75-year-old woman. She experience dizziness, headache, nausea, dry mouth, intense anxiety and agitation with suicidal ideas. Other symptoms were difficulty walking, marked resting tremor of the hands, and insomnia (Benazzi, 1998). If fluoxetine and mirtazapine are used together, monitor closely for symptoms of serotonin syndrome. Serotonin syndrome can be life-threatening. If serotonin syndrome develops, discontinue the offending agents and provide supportive care and other therapy as necessary (Boyer & Shannon, 2005).
3) Severity: major
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: A case of serotonin syndrome was reported with concomitant use of fluoxetine and mirtazapine and therefore, concomitant use is discouraged (Benazzi, 1998). If fluoxetine and mirtazapine are used together, monitor closely for symptoms of serotonin syndrome such as neuromuscular abnormalities (including hyper-reflexia, tremor, muscle rigidity, clonus, peripheral hypertonicity, and shivering), autonomic hyperactivity (including tachycardia, mydriasis, diaphoresis, the presence of bowel sounds, and diarrhea), and mental status changes (including agitation and delirium). Serotonin syndrome can be life-threatening. If serotonin syndrome develops, discontinue the offending agents and provide supportive care and other therapy as necessary (Boyer & Shannon, 2005).
7) Probable Mechanism: potentially additive pharmacologic effects
8) Literature Reports
a) Within a few hours of starting mirtazapine and shortly after stopping fluoxetine, a 75-year-old woman experienced symptoms consistent with serotonin syndrome. Besides fluoxetine 20 mg/day, she was on chlorpromazine 75 mg/day, and lorazepam 2.5 mg/day for depression. Due to lack of response, fluoxetine was discontinued and soon afterward mirtazapine 30 mg/day was started and the dose of chlorpromazine was decreased to 50 mg/day. Within a few hours of starting mirtazapine, she experience dizziness, headache, nausea, dry mouth, intense anxiety and agitation with suicidal ideas. Other symptoms were difficulty walking, marked resting tremor of the hands, and insomnia. Over the next 3 days, she progressively worsened. Mirtazapine was discontinued on day 5. Her symptoms improved the following day. Fluoxetine 20 mg/day was restarted on day 7 with subsequent resolution of dizziness, nausea, headache, and agitation resolution over the following days. Over the next 10 days, tremor, anxiety, difficulty walking, dry mouth, and insomnia improved (Benazzi, 1998).

3.5.1.EZ Moclobemide

1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)
2) Summary: Concurrent administration or overlapping therapy with fluoxetine and a monoamine oxidase (MAO) inhibitor may result in CNS toxicity or serotonin syndrome, a hyperserotonergic state characterized by symptoms such as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. Serious, even fatal, reactions have been reported (Prod Info Prozac(R), 1999k; Sternbach, 1991u; Coplan & Gorman, 1993r; Feighner et al, 1990r; Kline et al, 1989s; Suchowersky & de Vries, 1990s). Although not reported specifically with moclobemide in therapeutic doses, a similar interaction may occur. Concomitant use is contraindicated.
3) Severity: contraindicated

4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Concurrent use of fluoxetine and a MAO inhibitor is contraindicated. Wait at least two weeks after discontinuing a MAO inhibitor before initiating fluoxetine therapy. In addition, wait at least five weeks after discontinuing fluoxetine before initiating therapy with a MAO inhibitor.
7) Probable Mechanism: inhibition of serotonin metabolism by monoamine oxidase
8) Literature Reports

a) Concomitant use of serotonin specific reuptake inhibitors and monoamine oxidase inhibitors can produce a toxic reaction known as serotonin syndrome (Sternbach, 1991t). Serotonin syndrome is a condition of serotonergic hyperstimulation and manifests as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. If the syndrome is not recognized and correctly treated, death can result.

b) Ten hours after her last dose of fluoxetine, a 45-year-old woman began tranylcypromine therapy (Kline et al, 1989r). Headache, muscle contractions, insomnia, and unsteady gait were reported on the second day. Thioridazine and tryptophan were added to her therapy. The patient experienced fever, rigidity of the arms and legs, and hyperreflexia. She died in the intensive care unit of a hospital 44 hours later.

c) Two cases suggestive of an interaction between fluoxetine and selegiline, a selective monoamine oxidase B inhibitor, have been reported (Suchowersky & de Vries, 1990r). One case involved a first episode of mania being observed approximately one month after adding selegiline to fluoxetine therapy. The patient improved two months after both drugs were discontinued, and no further details were provided. The second case involved diaphoresis, vasoconstriction, and cyanosis of the hands which occurred in close temporal relationship to adding fluoxetine and selegiline. Both drugs were discontinued, with relatively quick resolution of symptoms. Rechallenge with fluoxetine alone occurred without incident.

d) In three of five cases of serotonin syndrome following overdoses, the drug combination that induced the fatal syndrome included moclobemide, a selective monoamine oxidase inhibitor, and citalopram. Of these three patients, moclobemide blood concentrations ranged from 5 to 50 times the therapeutic level, and citalopram concentrations ranged from normal to 5 times the therapeutic level (Neuvonen et al, 1993).

e) Moclobemide is a selective and reversible inhibitor of monoamine oxidase A (MAO-A). Based on animal experiments, it is believed that both MAO-A and MAO-B are essential for the development of serotonin syndrome. In an effort to assess the safety and pharmacodynamics of combined treatment of fluoxetine and moclobemide, 18 healthy subjects participated in a randomized, placebo-controlled, parallel study. All participants ingested a single oral dose of moclobemide 300 mg on days 1 and 24, fluoxetine 40 mg on days 2 through 8, and fluoxetine 20 mg on days 9 through 24. On day 16, subjects were randomized to receive either placebo or moclobemide on an ascending dose schedule. Doses of moclobemide started at 100 mg daily, and increased to 200 mg on day 17, 300 mg on day 18, and 600 mg on days 19 through 23. Steady-state fluoxetine plasma concentrations had been achieved when moclobemide therapy was initiated, and did not change with the addition or increasing doses of moclobemide. No patients experienced serotonin syndrome or any kind of a pharmacodynamic interaction between these two agents. Additionally, fluoxetine reduced serotonin uptake into platelets almost completely as expected, but moclobemide had no effect on serotonin uptake during single- or multiple-dose therapy. These study results suggest that a long wash-out period between treatment with moclobemide and fluoxetine is not necessary (Dingemanse et al, 1998).

f) An 82-year-old woman developed various serotonin syndrome symptoms after changing from fluoxetine to moclobemide therapy without a washout period in between. She experienced agitation, confusion, and tremor, progressing to inability to answer questions with any answer other than yes or no. After treatment with 4 mg cyproheptadine, her condition improved significantly (Chan et al, 1998a).

3.5.1.FA Morniflumate

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI

bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).

b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.FB Nabumetone

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).

b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.FC Nadroparin

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008). Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with warfarin (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: When fluoxetine and an anticoagulant are given concurrently, monitor patient for signs of increased bleeding. Patients who are taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, when fluoxetine therapy is initiated or discontinued (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).

7) Probable Mechanism: unknown

8) Literature Reports

a) Fluoxetine is thought to inhibit the cytochrome P450 2C9 isoenzyme (CYP2C9). This is the enzyme by which the more potent warfarin isomer, S-warfarin, is metabolized (Riesenman, 1995). In addition, both fluoxetine and warfarin are tightly bound to albumin. In combination, the possibility for protein-binding displacement of either drug is present (Prod Info Coumadin(R), 1999).

b) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bleeding (hospital admission due to bleeding) in patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patients with a mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients experienced 11 bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experiencing bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI was not associated with a change in warfarin dose or

INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model (Wallerstedt et al, 2009).

c) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5), however, the rate of gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).

d) In 6 reported cases, INR increased during combined fluoxetine and warfarin therapy. In a seventh case, severe bruising of the lower legs occurred in a woman initially treated with fluoxetine and, secondarily, started on warfarin (Woolfrey et al, 1993; Claire et al, 1991).

e) An 83-year-old man died from cerebral hemorrhage secondary to increased warfarin concentrations. The patient had been taking warfarin 30 mg per week for atrial fibrillation with a target INR between 2 and 3. The patient's other drugs included lisinopril, furosemide, potassium, digoxin, and acetaminophen. After being seen for symptoms of depression, anxiety, and insomnia, the patient was given fluoxetine 20 mg per day and diazepam 2.5 mg 3 to 4 times per day. Eight days later, the patient's INR increased to 4.8, and the dose of warfarin was decreased to 27.5 mg per week. The patient was later seen for symptoms of drug delirium, including confusion, incoherence, and speaking irrationally. At this point, the INR was 3.64 and fluoxetine was discontinued. The next day the patient presented to the hospital with left-sided weakness and later died from complications of a large interparenchymal hemorrhage. The authors proposed that the addition of fluoxetine to the patient's regimen resulted in increased serum levels of both warfarin and diazepam, resulting in delirium and loss of anticoagulant control (Dent & Orrock, 1997).

3.5.1.FD Naproxen

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).

b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.FE Naratriptan

1) Interaction Effect: an increased risk of serotonin syndrome

2) Summary: Rare incidences of weakness, hyperreflexia, and incoordination have been reported with the concurrent use of a selective serotonin reuptake inhibitor (SSRI) and a 5-hydroxytryptamine-1 (5HT-1) agonist (Prod Info Amerge(TM), 2002). Concurrent use of a triptan and an SSRI may result in serotonin syndrome which may be life-threatening. Symptoms of serotonin syndrome may include restlessness, hallucinations, loss of coordination, fast heart beat, rapid changes in blood pressure, increased body temperature, overreactive reflexes, nausea, vomiting, and diarrhea. Clinicians should be aware that triptans may be commonly used intermittently and that either the triptan or the SSRI may be prescribed by a different physician. Discuss the risks of serotonin syndrome with patients who are prescribed this combination and monitor them closely for symptoms of serotonin syndrome (US Food and Drug Administration, 2006).

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Coadministration of a triptan, such as naratriptan, and an SSRI may result in a life-threatening condition called serotonin syndrome. Be aware that triptans may be commonly used intermittently and that either the triptan or the SSRI may be prescribed by a different physician. If these agents are used together, discuss the risks of serotonin syndrome with the patient and monitor closely for symptoms of serotonin syndrome (restlessness, hyperthermia, hyperreflexia, incoordination).
7) Probable Mechanism: additive pharmacologic effects resulting in excessive serotonergic stimulation

3.5.1.FF Nebivolol

1) Interaction Effect: increased nebivolol exposure and plasma levels
2) Summary: Nebivolol is partially metabolized by the CYP2D6 isozyme. Coadministration of a single 10 mg dose of nebivolol in healthy adults (n=10) receiving fluoxetine, a CYP2D6 inhibitor, at a dose of 20 mg/day for 21 days led to 8- and 3-fold increases in the AUC and Cmax, respectively, of d-nebivolol (pharmacologically active isomer). Closely monitor blood pressure in patients receiving fluoxetine and nebivolol concomitantly. Downward dose adjustments of nebivolol may be necessary (Prod Info BYSTOLIC (TM) oral tablets, 2007).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: established
6) Clinical Management: Coadministration of fluoxetine, a CYP2D6 inhibitor, and nebivolol led to increased exposure and plasma concentrations of d-nebivolol, the pharmacologically active isomer. In patients receiving these agents concomitantly, closely monitor blood pressure. Reduced doses of nebivolol may be necessary (Prod Info BYSTOLIC(TM) oral tablets, 2007).
7) Probable Mechanism: inhibition of CYP2D6-mediated nebivolol metabolism

3.5.1.FG Nialamide

1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)
2) Summary: Concurrent administration or overlapping therapy with fluoxetine and a monoamine oxidase (MAO) inhibitor may result in CNS toxicity or serotonin syndrome, a hyperserotonergic state characterized by symptoms such as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. Serious, even fatal, reactions have been reported (Prod Info Prozac(R), 1999e; Sternbach, 1991i; Coplan & Gorman, 1993g; Feighner et al, 1990g; Kline et al, 1989g; Suchowersky & de Vries, 1990g). Concomitant use is contraindicated.
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Concurrent use of fluoxetine and nialamide is contraindicated. Wait at least two weeks after discontinuing a MAO inhibitor before initiating fluoxetine therapy. In addition, wait at least five weeks after discontinuing fluoxetine before initiating therapy with a MAO inhibitor.
7) Probable Mechanism: inhibition of serotonin metabolism by monoamine oxidase
8) Literature Reports

a) Concomitant use of serotonin specific reuptake inhibitors and monoamine oxidase inhibitors can produce a toxic reaction known as serotonin syndrome (Sternbach, 1991h). Serotonin syndrome is a condition of serotonergic hyperstimulation and manifests as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor (Sternbach, 1991h). If the syndrome is not recognized and correctly treated, death can result.

b) It has been suggested that fluoxetine therapy be discontinued for at least five weeks before beginning therapy with a monoamine oxidase inhibitor. A 28-year old woman discontinued fluoxetine for six weeks before starting therapy with tranylcypromine. Over the next few days the patient developed fever, paresthesias, confusion, abdominal cramping, and various other CNS symptoms. Upon discontinuation of tranylcypromine, the patient's symptoms began to resolve. Blood samples taken three days after discontinuation of tranylcypromine revealed no presence of fluoxetine; however, the norfluoxetine level was 84 ng/mL (Coplan & Gorman, 1993f).

c) Adverse reactions reported when fluoxetine was given concomitantly with phenelzine (n=9) or tranylcypromine (n=4) include tremor (50%), agitation or restlessness (42%), mental status changes (42%), myoclonus (33%), diarrhea (33%), and blood pressure changes (25%) (Feighner et al, 1990f). All but one of the patients were taking other medications (ie, benzodiazepines, neuroleptics, anticonvulsants, antidepressants) that may have contributed to the adverse reactions.

d) Ten hours after her last dose of fluoxetine, a 45-year-old woman began tranylcypromine therapy (Kline et al, 1989f). Headache, muscle contractions, insomnia, and unsteady gait were reported on the second day. Thioridazine and tryptophan were added to her therapy. The patient experienced fever, rigidity of the arms and legs, and hyperreflexia. She died in the intensive care unit of a hospital 44 hours later.

e) Two cases reports suggested a possible interaction between fluoxetine and selegiline (Suchowersky & de Vries, 1990f). One case involved a first episode of mania being observed approximately one month after adding selegiline to fluoxetine therapy. The patient improved two months after both drugs were discontinued, and no further details were provided. The second case involved diaphoresis, vasoconstriction, and cyanosis of the hands which occurred in close temporal relationship to adding

fluoxetine and selegiline. Both drugs were discontinued, with relatively quick resolution of symptoms. Rechallenge with fluoxetine alone occurred without incident.

3.5.1.FH Niflumic Acid

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).

b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.FI Nimesulide

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).

b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.FJ Nortriptyline

1) Interaction Effect: tricyclic antidepressant toxicity (dry mouth, urinary retention, sedation) and an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Tricyclic antidepressants (TCAs) and fluoxetine have been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Prozac(R), 2001h; Marshall & Forker, 1982). Even though no formal drug interaction studies have been done which demonstrate QT prolongation, the coadministration of tricyclic antidepressants and other drugs known to prolong the QTc interval, such as fluoxetine, is not recommended (Prod Info Elavil(R), 1999). In addition, concurrent use of fluoxetine and TCAs such as desipramine, nortriptyline, and imipramine has resulted in significant increases in TCA concentrations (Preskorn et al, 1994a; Preskorn et al, 1994a; Aranow et al, 1989a; Downs et al, 1989a; Goodnick, 1989a; Bell & Cole, 1988a).

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable
6) Clinical Management: The concurrent administration of fluoxetine and a tricyclic antidepressant is not recommended.
7) Probable Mechanism: decreased tricyclic antidepressant metabolism; additive effects on QT prolongation
8) Literature Reports
a) Fluoxetine increased the level of tricyclic antidepressants (nortriptyline, imipramine, desipramine) in 4 patients. After the addition of fluoxetine, the ratio of antidepressant level to dose increased by 109% to 486% in the patients. Three patients developed clinical symptoms (anticholinergic effects, constipation, urinary hesitancy, sedation, unstable gait) as a result of the increased levels (Aranow et al, 1989).
b) Fluoxetine statistically and clinically significantly increased desipramine concentrations in 18 healthy subjects. When fluoxetine (20 mg daily) was added to desipramine (50 mg daily), the mean maximum concentration of desipramine increased by 278% and the area under the concentration-time curve increased by 342%. Desipramine trough concentrations continued to be 198% above baseline three weeks after fluoxetine was discontinued. The same study compared pharmacokinetics of desipramine when combined with sertraline. The impact of sertraline was modest, resulting in small and short-term increases in desipramine plasma concentrations (Preskorn et al, 1994).
c) A 75-year-old female experienced symptomatic increases in her desipramine serum concentrations when fluoxetine was added. Desipramine serum levels ranged from 109 to 150 ng/mL with oral doses of 300 mg at bedtime prior to fluoxetine therapy. Following the addition of oral fluoxetine 20 mg daily to the regimen, the desipramine serum level increased to 212 ng/mL within five days. The fluoxetine dose was increased to 40 mg/day three days later, and the desipramine serum level was 419 ng/mL after four days. A worsening of depression and severe fatigue coincided with the increases in desipramine serum levels. Withdrawal of fluoxetine and reduction in the desipramine dose to 200 mg daily reduced the desipramine serum level to 231 ng/mL within two weeks (Bell & Cole, 1988).
d) A 33-year-old depressed male developed adverse effects of dry mouth, tinnitus, and difficulties with alertness and memory while receiving fluoxetine 40 mg daily and desipramine 150 mg daily for five weeks; fluoxetine was discontinued and the blood levels of desipramine decreased from 938 to 48 ng/mL with resolution of clinical symptoms (Goodnick, 1989).
e) A 39-year-old female experienced symptomatic increases in her desipramine levels with concomitant fluoxetine therapy. Prior to fluoxetine therapy, the patient's measured levels of desipramine had ranged from 148 to 160 ng/mL on a regimen of 300 mg daily. Five weeks after the addition of fluoxetine 20 mg daily, she reported anticholinergic symptoms, sedation, and confusion with a desipramine level of 527 ng/mL. The desipramine dose was lowered to 200 mg/day; eleven days later, the level was 244 ng/mL; the patient reported decreased energy, impaired short-term memory, and some "garbled" speech, as well as an episode of nausea, dizziness, and syncope. The desipramine dose was reduced to 50 mg/day; the adverse effects resolved in six days. Eight days later, the desipramine level was 122 ng/mL (Downs et al, 1989).
f) Concomitant administration of fluoxetine and desipramine was reported to result in an increased desipramine level and new onset of delirium in a 69-year-old male within 10 days of the addition of fluoxetine to the patient's regimen (Preskorn et al, 1990).

3.5.1.FK Octreotide

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Octreotide and fluoxetine have been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Prozac(R), 2001m; Prod Info Sandostatin(R), 1999). Even though no formal drug interaction studies have been done, the coadministration of drugs known to prolong the QTc interval is not recommended.
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of octreotide and fluoxetine is not recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.FL Oxaprozin

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).

b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.FM Parecoxib

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).

b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.FN Pargyline

1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)

2) Summary: Concurrent administration or overlapping therapy with fluoxetine and a monoamine oxidase (MAO) inhibitor may result in CNS toxicity or serotonin syndrome, a hyperserotonergic state characterized by symptoms such as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. Serious, even fatal, reactions have been reported (Prod Info Prozac(R), 1999h; Sternbach, 1991o; Coplan & Gorman, 1993m; Feighner et al, 1990m; Kline et al, 1989m; Suchowersky & de Vries, 1990m). Concomitant use is contraindicated.

3) Severity: contraindicated

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: Concurrent use of fluoxetine and pargyline is contraindicated. Wait at least two weeks after discontinuing a MAO inhibitor before initiating fluoxetine therapy. In addition, wait at least five weeks after discontinuing fluoxetine before initiating therapy with a MAO inhibitor.

7) Probable Mechanism: inhibition of serotonin metabolism by monoamine oxidase

8) Literature Reports

a) Concomitant use of serotonin specific reuptake inhibitors and monoamine oxidase inhibitors can produce a toxic reaction known as serotonin syndrome (Sternbach, 1991n). Serotonin syndrome is a condition of serotonergic hyperstimulation and manifests as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor (Sternbach, 1991n). If the syndrome is not recognized and correctly treated, death can result.

b) It has been suggested that fluoxetine therapy be discontinued for at least five weeks before beginning therapy with a monoamine oxidase inhibitor. A 28-year old woman discontinued fluoxetine for six weeks before starting therapy with tranylcypromine. Over the next few days the patient developed fever, paresthesias, confusion, abdominal cramping, and various other CNS symptoms. Upon discontinuation of tranylcypromine, the patient's symptoms began to resolve. Blood samples taken three days after discontinuation of tranylcypromine revealed no presence of fluoxetine; however, the norfluoxetine level was 84 ng/mL (Coplan & Gorman, 1993l).

c) Adverse reactions reported when fluoxetine was given concomitantly with phenelzine (n=9) or tranylcypromine (n=4) include tremor (50%), agitation or restlessness (42%), mental status changes (42%), myoclonus (33%), diarrhea (33%), and blood pressure changes (25%) (Feighner et al, 1990l). All but one of the patients were taking other medications (ie, benzodiazepines, neuroleptics, anticonvulsants, antidepressants) that may have contributed to the adverse reactions.
d) Ten hours after her last dose of fluoxetine, a 45-year-old woman began tranylcypromine therapy (Kline et al, 1989l). Headache, muscle contractions, insomnia, and unsteady gait were reported on the second day. Thioridazine and tryptophan were added to her therapy. The patient experienced fever, rigidity of the arms and legs, and hyperreflexia. She died in the intensive care unit of a hospital 44 hours later.
e) Two cases reports suggested a possible interaction between fluoxetine and selegiline (Suchowersky & de Vries, 1990l). One case involved a first episode of mania being observed approximately one month after adding selegiline to fluoxetine therapy. The patient improved two months after both drugs were discontinued, and no further details were provided. The second case involved diaphoresis, vasoconstriction, and cyanosis of the hands which occurred in close temporal relationship to adding fluoxetine and selegiline. Both drugs were discontinued, with relatively quick resolution of symptoms. Rechallenge with fluoxetine alone occurred without incident.

3.5.1.FO Parnaparin

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008). Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with warfarin (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When fluoxetine and an anticoagulant are given concurrently, monitor patient for signs of increased bleeding. Patients who are taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, when fluoxetine therapy is initiated or discontinued (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
7) Probable Mechanism: unknown
8) Literature Reports

a) Fluoxetine is thought to inhibit the cytochrome P450 2C9 isoenzyme (CYP2C9). This is the enzyme by which the more potent warfarin isomer, S-warfarin, is metabolized (Riesenman, 1995). In addition, both fluoxetine and warfarin are tightly bound to albumin. In combination, the possibility for protein-binding displacement of either drug is present (Prod Info Coumadin(R), 1999).
b) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bleeding (hospital admission due to bleeding) in patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patients with a mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients experienced 11 bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experiencing bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model (Wallerstedt et al, 2009).
c) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5), however, the rate of gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).
d) In 6 reported cases, INR increased during combined fluoxetine and warfarin therapy. In a seventh case, severe bruising of the lower legs occurred in a woman initially treated with fluoxetine and, secondarily, started on warfarin (Woolfrey et al, 1993; Claire et al, 1991).
e) An 83-year-old man died from cerebral hemorrhage secondary to increased warfarin concentrations.

The patient had been taking warfarin 30 mg per week for atrial fibrillation with a target INR between 2 and 3. The patient's other drugs included lisinopril, furosemide, potassium, digoxin, and acetaminophen. After being seen for symptoms of depression, anxiety, and insomnia, the patient was given fluoxetine 20 mg per day and diazepam 2.5 mg 3 to 4 times per day. Eight days later, the patient's INR increased to 4.8, and the dose of warfarin was decreased to 27.5 mg per week. The patient was later seen for symptoms of drug delirium, including confusion, incoherence, and speaking irrationally. At this point, the INR was 3.64 and fluoxetine was discontinued. The next day the patient presented to the hospital with left-sided weakness and later died from complications of a large interparenchymal hemorrhage. The authors proposed that the addition of fluoxetine to the patient's regimen resulted in increased serum levels of both warfarin and diazepam, resulting in delirium and loss of anticoagulant control (Dent & Orrock, 1997).

3.5.1.FP Paroxetine

1) Interaction Effect: fluoxetine toxicity (dry mouth, sedation, urinary retention)
2) Summary: Coadministration of paroxetine with drugs that are metabolized by cytochrome P450 2D6 (CYP2D6), such as fluoxetine, should be approached with caution (Prod Info Paxil CR(TM), 2002).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When paroxetine is coadministered with fluoxetine monitor patients for signs and symptoms of fluoxetine toxicity (dry mouth, sedation, urinary retention, blurred vision). Fluoxetine doses may need to be reduced.
7) Probable Mechanism: decreased cytochrome P450 2D6-mediated fluoxetine metabolism

3.5.1.FQ Pentamidine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Pentamidine and fluoxetine have been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Prozac(R), 2001f; Lindsay et al, 1990). Even though no formal drug interaction studies have been done, the coadministration of drugs known to prolong the QTc interval is not recommended.
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of pentamidine and fluoxetine is not recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.FR Pentazocine

1) Interaction Effect: hypertension, diaphoresis, ataxia, flushing, nausea, dizziness, and anxiety
2) Summary: A case of neurologic effects associated with concomitant use of fluoxetine and pentazocine has been reported in the literature (Hansen et al, 1990a).
3) Severity: moderate
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Until more data are available, concomitant use of fluoxetine and pentazocine should be undertaken with caution.
7) Probable Mechanism: unknown
8) Literature Reports

a) One study reported a case in which coadministration of fluoxetine and pentazocine was associated with a marked neurologic reaction. A 39-year-old male taking fluoxetine 40 mg daily was administered oral pentazocine 50 mg for a severe headache. Approximately 30 minutes after receiving the pentazocine, the patient became hypertensive, diaphoretic, flushed, ataxic, paresthetic, nauseated, lightheaded, and anxious. Although an interaction between fluoxetine and pentazocine may have occurred, a hypersensitivity to pentazocine alone was not ruled out (Hansen et al, 1990).

b) Fluoxetine administered seven days before surgery had no effect on kappa-opiate pentazocine analgesia but significantly attenuated the analgesia produced by morphine (p less than 0.05), a mu-opiate. The duration of action of morphine analgesia was shortened by the addition of fluoxetine. The authors point out that the effect of chronic fluoxetine administration on mu-opiate analgesia is not clear and further studies are needed (Gordon et al, 1994).

3.5.1.FS Pentosan Polysulfate Sodium

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008). Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with warfarin (Prod

Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When fluoxetine and an anticoagulant are given concurrently, monitor patient for signs of increased bleeding. Patients who are taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, when fluoxetine therapy is initiated or discontinued (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
7) Probable Mechanism: unknown
8) Literature Reports
a) Fluoxetine is thought to inhibit the cytochrome P450 2C9 isoenzyme (CYP2C9). This is the enzyme by which the more potent warfarin isomer, S-warfarin, is metabolized (Riesenman, 1995). In addition, both fluoxetine and warfarin are tightly bound to albumin. In combination, the possibility for protein-binding displacement of either drug is present (Prod Info Coumadin(R), 1999).
b) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bleeding (hospital admission due to bleeding) in patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patients with a mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients experienced 11 bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experiencing bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model (Wallerstedt et al, 2009).
c) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5), however, the rate of gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).
d) In 6 reported cases, INR increased during combined fluoxetine and warfarin therapy. In a seventh case, severe bruising of the lower legs occurred in a woman initially treated with fluoxetine and, secondarily, started on warfarin (Woolfrey et al, 1993; Claire et al, 1991).
e) An 83-year-old man died from cerebral hemorrhage secondary to increased warfarin concentrations. The patient had been taking warfarin 30 mg per week for atrial fibrillation with a target INR between 2 and 3. The patient's other drugs included lisinopril, furosemide, potassium, digoxin, and acetaminophen. After being seen for symptoms of depression, anxiety, and insomnia, the patient was given fluoxetine 20 mg per day and diazepam 2.5 mg 3 to 4 times per day. Eight days later, the patient's INR increased to 4.8, and the dose of warfarin was decreased to 27.5 mg per week. The patient was later seen for symptoms of drug delirium, including confusion, incoherence, and speaking irrationally. At this point, the INR was 3.64 and fluoxetine was discontinued. The next day the patient presented to the hospital with left-sided weakness and later died from complications of a large interparenchymal hemorrhage. The authors proposed that the addition of fluoxetine to the patient's regimen resulted in increased serum levels of both warfarin and diazepam, resulting in delirium and loss of anticoagulant control (Dent & Orrock, 1997).

3.5.1.FT Phenelzine
1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)
2) Summary: Concurrent administration or overlapping therapy with fluoxetine and a monoamine oxidase (MAO) inhibitor may result in CNS toxicity or serotonin syndrome, a hyperserotonergic state characterized by symptoms such as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. Serious, even fatal, reactions have been reported (Prod Info Prozac(R), 1999b; Sternbach, 1991g; Coplan & Gorman, 1993e; Feighner et al, 1990e; Kline et al, 1989e; Suchowersky & de Vries, 1990e). Concomitant use of phenelzine and fluoxetine is contraindicated. Allow at least five weeks between discontinuation of fluoxetine and initiation of phenelzine and at least 10 days between discontinuation of phenelzine and initiation of fluoxetine, or other serotoninergic agents (Prod Info Nardil(R), 1995).
3) Severity: contraindicated
4) Onset: rapid

5) Substantiation: theoretical
6) Clinical Management: Concurrent use of fluoxetine and phenelzine is contraindicated. Wait at least 14 days after discontinuing phenelzine before initiating fluoxetine therapy. In addition, wait at least five weeks after discontinuing fluoxetine before initiating therapy with a MAO inhibitor.
7) Probable Mechanism: inhibition of serotonin metabolism by monoamine oxidase
8) Literature Reports
a) Concomitant use of serotonin specific reuptake inhibitors and monoamine oxidase inhibitors can produce a toxic reaction known as serotonin syndrome (Sternbach, 1991f). Serotonin syndrome is a condition of serotonergic hyperstimulation and manifests as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. If the syndrome is not recognized and correctly treated, death can result.
b) It has been suggested that fluoxetine therapy be discontinued for five weeks before beginning therapy with a monoamine oxidase inhibitor. However, one case report describes a 28-year old woman who had discontinued a 2-year fluoxetine regimen for six weeks before starting therapy with tranylcypromine. Over the next few days the patient developed fever, paresthesias, confusion, abdominal cramping, and various other CNS symptoms. Upon discontinuation of tranylcypromine, the patient's symptoms began to resolve. Blood samples taken three days after discontinuation of tranylcypromine revealed no presence of fluoxetine; however, the norfluoxetine level was 84 ng/mL (Coplan & Gorman, 1993d).
c) Adverse reactions reported when fluoxetine was given concomitantly with phenelzine (n=9) or tranylcypromine (n=4) include tremor (50%), agitation or restlessness (42%), mental status changes (42%), myoclonus (33%), diarrhea (33%), and blood pressure changes (25%) (Feighner et al, 1990d). All but one of the patients were taking other medications (ie, benzodiazepines, neuroleptics, anticonvulsants, antidepressants) that may have contributed to the adverse reactions.
d) Ten hours after her last dose of fluoxetine, a 45-year-old woman began tranylcypromine therapy (Kline et al, 1989d). Headache, muscle contractions, insomnia, and unsteady gait were reported on the second day. Thioridazine and tryptophan were added to her therapy. The patient experienced fever, rigidity of the arms and legs, and hyperreflexia. She died in the intensive care unit of a hospital 44 hours later.
e) Two cases suggestive of an interaction between fluoxetine and selegiline were reported (Suchowersky & de Vries, 1990d). One case involved a first episode of mania being observed approximately one month after adding selegiline to fluoxetine therapy. The patient improved two months after both drugs were discontinued, and no further details were provided. The second case involved diaphoresis, vasoconstriction, and cyanosis of the hands which occurred in close temporal relationship to adding fluoxetine and selegiline. Both drugs were discontinued, with relatively quick resolution of symptoms. Rechallenge with fluoxetine alone occurred without incident.

3.5.1.FU Phenindione
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008). Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with warfarin (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When fluoxetine and an anticoagulant are given concurrently, monitor patient for signs of increased bleeding. Patients who are taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, when fluoxetine therapy is initiated or discontinued (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
7) Probable Mechanism: unknown
8) Literature Reports
a) Fluoxetine is thought to inhibit the cytochrome P450 2C9 isoenzyme (CYP2C9). This is the enzyme by which the more potent warfarin isomer, S-warfarin, is metabolized (Riesenman, 1995). In addition, both fluoxetine and warfarin are tightly bound to albumin. In combination, the possibility for protein-binding displacement of either drug is present (Prod Info Coumadin(R), 1999).
b) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bleeding (hospital admission due to bleeding) in patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patients with a mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients experienced 11 bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment

with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experiencing bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model (Wallerstedt et al, 2009).

c) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5), however, the rate of gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).

d) In 6 reported cases, INR increased during combined fluoxetine and warfarin therapy. In a seventh case, severe bruising of the lower legs occurred in a woman initially treated with fluoxetine and, secondarily, started on warfarin (Woolfrey et al, 1993; Claire et al, 1991).

e) An 83-year-old man died from cerebral hemorrhage secondary to increased warfarin concentrations. The patient had been taking warfarin 30 mg per week for atrial fibrillation with a target INR between 2 and 3. The patient's other drugs included lisinopril, furosemide, potassium, digoxin, and acetaminophen. After being seen for symptoms of depression, anxiety, and insomnia, the patient was given fluoxetine 20 mg per day and diazepam 2.5 mg 3 to 4 times per day. Eight days later, the patient's INR increased to 4.8, and the dose of warfarin was decreased to 27.5 mg per week. The patient was later seen for symptoms of drug delirium, including confusion, incoherence, and speaking irrationally. At this point, the INR was 3.64 and fluoxetine was discontinued. The next day the patient presented to the hospital with left-sided weakness and later died from complications of a large interparenchymal hemorrhage. The authors proposed that the addition of fluoxetine to the patient's regimen resulted in increased serum levels of both warfarin and diazepam, resulting in delirium and loss of anticoagulant control (Dent & Orrock, 1997).

3.5.1.FV Phenprocoumon

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008). Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with warfarin (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: When fluoxetine and an anticoagulant are given concurrently, monitor patient for signs of increased bleeding. Patients who are taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, when fluoxetine therapy is initiated or discontinued (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).

7) Probable Mechanism: unknown

8) Literature Reports

a) Fluoxetine is thought to inhibit the cytochrome P450 2C9 isoenzyme (CYP2C9). This is the enzyme by which the more potent warfarin isomer, S-warfarin, is metabolized (Riesenman, 1995). In addition, both fluoxetine and warfarin are tightly bound to albumin. In combination, the possibility for protein-binding displacement of either drug is present (Prod Info Coumadin(R), 1999).

b) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bleeding (hospital admission due to bleeding) in patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patients with a mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients experienced 11 bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experiencing bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model (Wallerstedt et al, 2009).

c) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5), however, the rate of gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).
d) In 6 reported cases, INR increased during combined fluoxetine and warfarin therapy. In a seventh case, severe bruising of the lower legs occurred in a woman initially treated with fluoxetine and, secondarily, started on warfarin (Woolfrey et al, 1993; Claire et al, 1991).
e) An 83-year-old man died from cerebral hemorrhage secondary to increased warfarin concentrations. The patient had been taking warfarin 30 mg per week for atrial fibrillation with a target INR between 2 and 3. The patient's other drugs included lisinopril, furosemide, potassium, digoxin, and acetaminophen. After being seen for symptoms of depression, anxiety, and insomnia, the patient was given fluoxetine 20 mg per day and diazepam 2.5 mg 3 to 4 times per day. Eight days later, the patient's INR increased to 4.8, and the dose of warfarin was decreased to 27.5 mg per week. The patient was later seen for symptoms of drug delirium, including confusion, incoherence, and speaking irrationally. At this point, the INR was 3.64 and fluoxetine was discontinued. The next day the patient presented to the hospital with left-sided weakness and later died from complications of a large interparenchymal hemorrhage. The authors proposed that the addition of fluoxetine to the patient's regimen resulted in increased serum levels of both warfarin and diazepam, resulting in delirium and loss of anticoagulant control (Dent & Orrock, 1997).

3.5.1.FW Phenylbutazone

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.FX Phenytoin

1) Interaction Effect: an increased risk of phenytoin toxicity (ataxia, hyperreflexia, nystagmus, tremor)
2) Summary: Several case reports indicate that concurrent use of fluoxetine and phenytoin can result in significantly increased phenytoin serum levels leading to toxicity (FDA, 1994a; Jalil, 1992a; Woods et al, 1994). Alternatively, patients who are stabilized on fluoxetine and phenytoin therapy may experience subtherapeutic concentrations of phenytoin and loss of seizure control when fluoxetine is discontinued (Shad & Preskorn, 1999a). During an in vitro study, the inhibitory effects of fluoxetine on cytochrome P450 2C9 were evaluated using p-hydroxylation of phenytoin as an established index reaction reflecting CYP2C9 activity. In vivo, p-hydroxylation of phenytoin depends on the formation of 5-(p-hydroxy-phenyl)-5-phenylhydantoin (HPPH). Fluoxetine, specifically the R-component of the racemic fluoxetine mixture, impaired the formation of HPPH, which can lead to an increase in steady-state phenytoin levels (Schmider et al, 1997).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor phenytoin serum levels with the addition of fluoxetine and periodically thereafter to assure stability; lower phenytoin dosage may be required with concomitant therapy. Serum

levels of phenytoin should be monitored following the discontinuation of fluoxetine; however, because of the long half-life of fluoxetine, decreases in phenytoin levels may not be clinically significant for a few weeks. Careful monitoring is required.

7) Probable Mechanism: decreased phenytoin metabolism

8) Literature Reports

a) Twenty-three reported cases of fluoxetine-phenytoin interactions have resulted in large increases in serum phenytoin levels and/or symptoms of phenytoin toxicity. On the average, the adverse effects began within two weeks after fluoxetine was added to existing phenytoin therapy. The average increase in plasma levels in nine evaluable cases was 161% (range 75 to 309%) and the maximum phenytoin serum concentration in 16 evaluable cases ranged from 22 to 53.5 mcg/mL (therapeutic level, 10 to 20 mcg/mL) (FDA, 1994).

b) An 84-year-old woman was stabilized on phenytoin 300 mg daily. After two months of treatment, fluoxetine 20 mg daily was added to her therapy, and increased to 40 mg daily after 10 days (Jalil, 1992). Within five days of starting fluoxetine, she developed vertigo, gait ataxia, diplopia, and altered mental status; her phenytoin serum level had increased from 15 to 35 mcg/mL. Both phenytoin and fluoxetine were gradually reduced and the signs and symptoms of toxicity abated. Four weeks later she was rechallenged with the same dose of fluoxetine without a return of toxicity.

c) In another case, a 57-year-old woman who had been stabilized on phenytoin 400 mg daily for a year (serum level, 11.5 mcg/mL) was given fluoxetine 20 mg daily (Jalil, 1992). Ten days later she developed vomiting, vertigo, trunk ataxia, limb dysmetria, and multidirectional nystagmus, and the phenytoin serum level was 47 mcg/mL. Fluoxetine was discontinued and all signs and symptoms of toxicity disappeared over a three-week period. At four weeks post-fluoxetine, the phenytoin serum level was 20 mcg/mL.

d) A 42-year-old male with a history of grand mal seizures and aggressive behavior was receiving phenytoin 200 mg daily and carbamazepine 600 mg daily without resolution of his problems. His phenytoin level was 2.0 ng/mL and his dose was subsequently increased to 400 mg daily. Fluoxetine 20 mg daily was added for aggression, and the patient experienced resolution of his behavioral problems and a cessation of his seizure activity. The phenytoin level ranged between 10.9 ng/mL and 15.7 ng/mL during fluoxetine therapy. However, the patient discontinued fluoxetine on his own and after a month experienced a recurrence of problems. Phenytoin concentration was measured at 6.6 ng/mL six weeks after the discontinuation of fluoxetine, despite no change in his phenytoin dose. This case report illustrates the need for close monitoring of phenytoin levels when fluoxetine is initiated and discontinued, since subtherapeutic levels of phenytoin may result if doses of phenytoin are not readjusted following the cessation of fluoxetine (Shad & Preskorn, 1999).

3.5.1.FY Pimozide

1) Interaction Effect: bradycardia, somnolence, and potentially increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: One case of bradycardia and somnolence resulting from concomitant fluoxetine and pimozide therapy has been reported (Ahmed et al, 1993). Although a specific interaction study has not been conducted with these agents, due to the potential for additive QT prolongation effects, the concomitant use of fluoxetine and pimozide is contraindicated (Prod Info PROZAC(R) oral capsule, oral pulvule, oral solution, oral tablet, 2005).

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: Due to the possibility of additive effects on the QT interval, the concurrent administration of fluoxetine and pimozide is contraindicated.

7) Probable Mechanism: additive effects on QT prolongation

8) Literature Reports

a) One case has been reported in which concurrent use of pimozide 5 mg daily and fluoxetine 20 mg daily in an elderly patient resulted in severe bradycardia and somnolence. The pulse rate gradually returned to normal after discontinuation of pimozide; rechallenge with a lower pimozide dose and a higher fluoxetine dose also resulted in bradycardia (Ahmed et al, 1993).

3.5.1.FZ Pirazolac

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.GA Pirmenol

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, the coadministration of Class Ia antiarrhythmics and other drugs known to prolong the QTc interval is not recommended (Prod Info Quinaglute Dura-tabs(R), 1999). Fluoxetine has demonstrated QT prolongation at therapeutic doses (Prod Info Prozac(R), 2001z).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of class Ia antiarrhythmic agents and agents that prolong the QT interval, such as fluoxetine, is not recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.GB Piroxicam

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.GC Pirprofen

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched

among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.GD Prajmaline
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, the coadministration of Class Ia antiarrhythmics and other drugs known to prolong the QTc interval is not recommended (Prod Info Quinaglute Dura-tabs(R), 1999). Fluoxetine has demonstrated QT prolongation at therapeutic doses (Prod Info Prozac(R), 2001z).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of class Ia antiarrhythmic agents and agents that prolong the QT interval, such as fluoxetine, is not recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.GE Probucol
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Fluoxetine and probucol have been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Prozac(R), 2001v; Gohn & Simmons, 1992; Prod Info Lorelco(R), 1991). Even though no formal drug interaction studies have been done, the coadministration of drugs known to prolong the QTc interval is not recommended.
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of fluoxetine and probucol is not recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.GF Procainamide
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, the coadministration of Class Ia antiarrhythmics and other drugs known to prolong the QTc interval is not recommended (Prod Info Quinaglute Dura-tabs(R), 1999). Fluoxetine has demonstrated QT prolongation at therapeutic doses (Prod Info Prozac(R), 2001z).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of class Ia antiarrhythmic agents and agents that prolong the QT interval, such as fluoxetine, is not recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.GG Procarbazine
1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)
2) Summary: Concurrent administration or overlapping therapy with fluoxetine and a monoamine oxidase (MAO) inhibitor may result in CNS toxicity or serotonin syndrome, a hyperserotonergic state characterized by symptoms such as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. Serious, even fatal, reactions have been reported (Prod Info Prozac(R), 1999; Sternbach, 1991b; Coplan & Gorman, 1993a; Feighner et al, 1990a; Kline et al, 1989a; Suchowersky & de Vries, 1990a). Concomitant use is contraindicated.
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: established
6) Clinical Management: Concurrent use of fluoxetine and procarbazine is contraindicated. Wait at least two weeks after discontinuing a MAO inhibitor before initiating fluoxetine therapy. In addition, wait at least five weeks after discontinuing fluoxetine before initiating therapy with a MAO inhibitor.
7) Probable Mechanism: inhibition of serotonin metabolism by monoamine oxidase
8) Literature Reports

a) Concomitant use of serotonin specific reuptake inhibitors and monoamine oxidase inhibitors can produce a toxic reaction known as serotonin syndrome (Sternbach, 1991a). Serotonin syndrome is a condition of serotonergic hyperstimulation and manifests as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor (Sternbach, 1991a). If the syndrome is not recognized and correctly treated, death can result.
b) It has been suggested that fluoxetine therapy be discontinued for at least five weeks before beginning therapy with a monoamine oxidase inhibitor. A 28-year old woman discontinued fluoxetine for six weeks before starting therapy with tranylcypromine. Over the next few days the patient developed fever, paresthesias, confusion, abdominal cramping, and various other CNS symptoms. Upon discontinuation of tranylcypromine, the patient's symptoms began to resolve. Blood samples taken three days after discontinuation of tranylcypromine revealed no presence of fluoxetine; however, the norfluoxetine level was 84 ng/mL (Coplan & Gorman, 1993).
c) Adverse reactions reported when fluoxetine was given concomitantly with phenelzine (n=9) or tranylcypromine (n=4) include tremor (50%), agitation or restlessness (42%), mental status changes (42%), myoclonus (33%), diarrhea (33%), and blood pressure changes (25%) (Feighner et al, 1990). All but one of the patients were taking other medications (ie, benzodiazepines, neuroleptics, anticonvulsants, antidepressants) that may have contributed to the adverse reactions.
d) Ten hours after her last dose of fluoxetine, a 45-year-old woman began tranylcypromine therapy (Kline et al, 1989). Headache, muscle contractions, insomnia, and unsteady gait were reported on the second day. Thioridazine and tryptophan were added to her therapy. The patient experienced fever, rigidity of the arms and legs, and hyperreflexia. She died in the intensive care unit of a hospital 44 hours later.
e) Two cases reports suggested a possible interaction between fluoxetine and selegiline (Suchowersky & de Vries, 1990). One case involved a first episode of mania being observed approximately one month after adding selegiline to fluoxetine therapy. The patient improved two months after both drugs were discontinued, and no further details were provided. The second case involved diaphoresis, vasoconstriction, and cyanosis of the hands which occurred in close temporal relationship to adding fluoxetine and selegiline. Both drugs were discontinued, with relatively quick resolution of symptoms. Rechallenge with fluoxetine alone occurred without incident.

3.5.1.GH Prochlorperazine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Although citing no data, the manufacturers of some phenothiazines state that concomitant use with other drugs which prolong the QT interval is not recommended. Q and T wave distortions have been observed in patients taking phenothiazines (Prod Info Compazine(R), 2002; Prod Info Stelazine(R), 2002; Prod Info Thorazine(R), 2002) . Other phenothiazines may have similar effects, though no reports are available. Fluoxetine has been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Prozac(R), 2003).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of fluoxetine and a phenothiazine is not recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.GI Propafenone

1) Interaction Effect: increased serum propafenone concentrations and an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Propafenone has been shown to prolong the QTc interval (Larochelle et al, 1984). Fluoxetine has been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Prozac(R), 2001e). Even though no formal drug interaction studies have been done, caution is advised if drugs known to prolong the QT interval are used concomitantly. In addition, fluoxetine may inhibit cytochrome P450 2D6 (CYP2D6) and impair the metabolism of propafenone (Cai et al, 1999a).
3) Severity: major
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Caution is advised if fluoxetine and propafenone are used concomitantly.
7) Probable Mechanism: inhibition of cytochrome P450 2D6-mediated propafenone metabolism; theoretical additive effects on QT prolongation
8) Literature Reports
a) The metabolism of propafenone enantiomers was altered after fluoxetine treatment in 9 healthy Chinese subjects. All subjects were extensive CYP2D6 metabolizers. Subjects received a single oral dose of propafenone 400 mg both before and after fluoxetine 20 mg daily for ten days. The oral clearance of both S- and P- enantiomers of propafenone decreased from approximately 75 L/hr to 50 L/hr and 107 L/hr to 70 L/hr, respectively. Compared to baseline, the elimination half life, peak concentration, and area under the curve for both enantiomers after fluoxetine therapy were significantly increased (Cai et al, 1999).

3.5.1.GJ Propranolol

1) Interaction Effect: an increased risk of complete heart block

2) Summary: Metabolism of propranolol occurs in the liver and is thought to involve cytochrome P450IID6 (CYP2D6). Fluoxetine is a potent inhibitor of CYP2D6 (DeVane, 1994a). It is theoretically possible that coadministered fluoxetine could inhibit propranolol metabolism, leading to elevated serum concentrations of this beta blocker and possible toxicity. One case report describes a man who developed complete heart block two weeks after fluoxetine was added to propranolol therapy (Drake & Gordon, 1994a).

3) Severity: minor

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Fluoxetine should be prescribed cautiously to patients on propranolol therapy. A baseline electrocardiogram should be considered prior to the initiation of fluoxetine.

7) Probable Mechanism: impaired atrioventricular conduction

8) Literature Reports

a) A 53-year-old male experienced a loss of consciousness two weeks after fluoxetine 20 mg daily was prescribed for depression. Other medications included propranolol 40 mg twice daily for anxiety. He had no previous cardiac history. An electrocardiogram revealed a complete heart block, and fluoxetine and propranolol were both discontinued. Two days later, the patient reverted to sinus rhythm with a heart rate of 60 beats per minute. The heart block was attributed to the fluoxetine-propranolol combination, since sinus rhythm returned two days after the discontinuation of fluoxetine, and the patient had no previous complications from propranolol therapy. Because 5-hydroxytryptamine (5-HT) receptors are located in the atrium of the heart, fluoxetine may have potentiated the action of 5-HT, causing impaired atrioventricular conduction (Drake & Gordon, 1994).

3.5.1.GK Propyphenazone

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).

b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.GL Proquazone

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations

in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).

b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.GM Quetiapine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Fluoxetine has been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Prozac(R), 2001l). Even though no formal drug interaction studies have been done, the coadministration of antipsychotics and other drugs known to prolong the QTc interval, including fluoxetine, is not recommended. Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999), quetiapine (Owens, 2001b), sertindole (Agelink et al, 2001), sultopride (Lande et al, 1992), and zotepine (Sweetman, 2003).

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of fluoxetine and antipsychotics is not recommended.

7) Probable Mechanism: additive effects on QT prolongation

3.5.1.GN Quinidine

1) Interaction Effect: an increased risk of fluoxetine and quinidine toxicity and an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Even though no formal drug interaction studies have been done, the coadministration of Class IA antiarrhythmics such as quinidine and other drugs known to prolong the QTc interval is not recommended (Prod Info Quinaglute Dura-tabs(R), 1999a). Fluoxetine has demonstrated QT prolongation at therapeutic doses (Prod Info Prozac(R), 2001af). In addition, quinidine inhibits CYP2D6 which may reduce fluoxetine metabolism (Stevens & Wrighton, 1993b) and fluoxetine inhibits CYP3A4, which may reduce quinidine metabolism (Nemeroff et al, 1996).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of Class Ia antiarrhythmic agents, such as quinidine, and agents that prolong the QT interval, such as fluoxetine, is not recommended.

7) Probable Mechanism: altered fluoxetine or quinidine metabolism; additive effects on QT prolongation

8) Literature Reports

a) In vitro studies found that quinidine, a potent inhibitor of CYP2D6, inhibited fluoxetine N-demethylation by 20% (Stevens & Wrighton, 1993a). While indicating that fluoxetine is, in part, metabolized by CYP2D6, this study showed that much of fluoxetine metabolism may occur via alternate pathways.

3.5.1.GO Rasagiline

1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)

2) Summary: Concurrent administration or overlapping therapy with selective serotonin reuptake inhibitors, including fluoxetine, and non-selective MAOIs or the selective MAO-B inhibitor selegiline, has been reported to cause serious, sometimes fatal reactions. Signs and symptoms included hyperthermia, rigidity, myoclonus, autonomic instability with rapid vital sign fluctuations, and mental status changes progressing to extreme agitation, delirium, and coma. Similar reactions have been reported with serotonin-norepinephrine reuptake inhibitors (SNRIs) and non-selective MAOIs or selegiline. Rasagiline clinical trials did not allow concomitant use of fluoxetine; the combination of rasagiline and fluoxetine should be avoided. Wait at least two weeks after discontinuing rasagiline before initiating fluoxetine therapy. Wait at least five weeks or more, especially if fluoxetine has been used chronically and/or at high doses, after discontinuing fluoxetine before initiating therapy with rasagiline (Prod Info AZILECT(R) oral tablets, 2006).

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: Concurrent use of fluoxetine and rasagiline should be avoided. Wait at least two weeks after discontinuing rasagiline before initiating fluoxetine therapy. Wait at least five weeks or more, especially if fluoxetine has been used chronically and/or at high doses, after discontinuing fluoxetine before initiating therapy with rasagiline.

7) Probable Mechanism: inhibition of serotonin metabolism by monoamine oxidase

8) Literature Reports

a) Concomitant use of serotonin specific reuptake inhibitors and monoamine oxidase inhibitors can produce a toxic reaction known as serotonin syndrome (Sternbach, 1991l). Serotonin syndrome is a condition of serotonergic hyperstimulation and manifests as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor (Sternbach, 1991l). If the syndrome is not recognized and correctly treated, death can result.

3.5.1.GP Reviparin

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008). Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with warfarin (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: When fluoxetine and an anticoagulant are given concurrently, monitor patient for signs of increased bleeding. Patients who are taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, when fluoxetine therapy is initiated or discontinued (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).

7) Probable Mechanism: unknown

8) Literature Reports

a) Fluoxetine is thought to inhibit the cytochrome P450 2C9 isoenzyme (CYP2C9). This is the enzyme by which the more potent warfarin isomer, S-warfarin, is metabolized (Riesenman, 1995). In addition, both fluoxetine and warfarin are tightly bound to albumin. In combination, the possibility for protein-binding displacement of either drug is present (Prod Info Coumadin(R), 1999).

b) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bleeding (hospital admission due to bleeding) in patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patients with a mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients experienced 11 bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experiencing bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model (Wallerstedt et al, 2009).

c) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5), however, the rate of gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).

d) In 6 reported cases, INR increased during combined fluoxetine and warfarin therapy. In a seventh case, severe bruising of the lower legs occurred in a woman initially treated with fluoxetine and, secondarily, started on warfarin (Woolfrey et al, 1993; Claire et al, 1991).

e) An 83-year-old man died from cerebral hemorrhage secondary to increased warfarin concentrations. The patient had been taking warfarin 30 mg per week for atrial fibrillation with a target INR between 2 and 3. The patient's other drugs included lisinopril, furosemide, potassium, digoxin, and acetaminophen. After being seen for symptoms of depression, anxiety, and insomnia, the patient was given fluoxetine 20 mg per day and diazepam 2.5 mg 3 to 4 times per day. Eight days later, the patient's INR increased to 4.8, and the dose of warfarin was decreased to 27.5 mg per week. The patient was later seen for symptoms of drug delirium, including confusion, incoherence, and speaking irrationally. At this point, the INR was 3.64 and fluoxetine was discontinued. The next day the patient presented to the hospital with left-sided weakness and later died from complications of a large interparenchymal hemorrhage. The authors proposed that the addition of fluoxetine to the patient's regimen resulted in increased serum levels of both warfarin and diazepam, resulting in delirium and loss of anticoagulant control (Dent & Orrock, 1997).

3.5.1.GQ Risperidone

1) Interaction Effect: increased plasma concentrations of risperidone

2) Summary: Concomitant use of fluoxetine (CYP2D6 inhibitor) and risperidone (CYP2D6 substrate) has resulted in increased risperidone plasma concentrations and an increased risk of risperidone adverse effects such as serotonin syndrome, QT prolongation, and extrapyramidal effects. The postulated mechanism of action is inhibition of CYP2D6-mediated metabolism of risperidone by fluoxetine. One study demonstrated increased risperidone levels in patients treated concurrently with fluoxetine and risperidone (Prod Info RISPERDAL(R) oral tablets, oral solution, orally disintegrating tablets, 2008; Spina et al, 2002). Monitoring the patient for increased risperidone plasma levels side effects may be necessary (Spina et al, 2002). The risperidone dose should be reevaluated if fluoxetine is initiated or discontinued (Prod Info RISPERDAL(R) oral tablets, oral solution, orally disintegrating tablets, 2008) (Spina et al, 2002a).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: Concomitant use of fluoxetine and risperidone has resulted in increased risperidone plasma concentrations and an increased risk of risperidone side effects (Prod Info RISPERDAL (R) oral tablets, oral solution, orally disintegrating tablets, 2008). Carefully monitor patients for increased plasma risperidone levels and side effects (serotonin syndrome, extrapyramidal symptoms, and cardiotoxicity) when fluoxetine is coadministered with risperidone (Spina et al, 2002). Reevaluate the dose of risperidone when concomitant fluoxetine is initiated or discontinued (Prod Info RISPERDAL(R) oral tablets, oral solution, orally disintegrating tablets, 2008).

7) Probable Mechanism: inhibition of CYP2D6-mediated metabolism of risperidone

8) Literature Reports

a) Fluoxetine (a CYP2D6 inhibitor) 20 mg/day has been shown to increase the plasma concentration of risperidone (a CYP2D6 substrate) 2.5- to 2.8-fold. Fluoxetine did not affect the concentration of 9-hydroxyrisperidone. The dosage of risperidone should be reevaluated when fluoxetine is initiated or discontinued (Prod Info RISPERDAL(R) oral tablets, oral solution, orally disintegrating tablets, 2008).

b) Fluoxetine, an inhibitor of cytochrome CYP2D6, may impair the elimination of risperidone, primarily by inhibiting CYP2D6-mediated alpha-hydroxylation and, to a lesser extent, by simultaneously affecting the further metabolism of 9-hydroxyrisperidone (9-OH-risperidone) or other pathways of risperidone biotransformation. In an open, 4-week, pharmacokinetic study including 9 patients with schizophrenia or schizoaffective disorder, depressive type, risperidone concentrations increased when fluoxetine was coadministered with risperidone. Patients were stabilized on a fixed dose of risperidone 4 to 6 mg/day for at least four weeks and received adjunctive fluoxetine therapy 20 mg/day for the management of concomitant depression. Mean plasma risperidone concentrations increased from 12 ng/mL at baseline to 49 nanograms (ng)/mL (p less than 0.01) at week 2, and 56 ng/mL (p less than 0.01) at week 4. Plasma concentrations of 9-hydroxyrisperidone (9-OH-risperidone) showed no significant increase at 4 weeks compared with baseline. After 4 weeks of concurrent therapy, the active moiety (risperidone plus 9-OH-risperidone) was increased by 75% (range: 9% to 204%, p less than 0.01) compared with baseline. The mean plasma risperidone to 9-OH-risperidone ratio also increased significantly. Two patients experienced Parkinsonian symptoms during week 2 of concomitant therapy and were treated with anticholinergic medication. The authors suggest that monitoring plasma risperidone levels may be warranted in patients receiving concomitant fluoxetine and risperidone treatment (Spina et al, 2002).

3.5.1.GR Ritonavir

1) Interaction Effect: alterations in cardiac and/or neurologic function

2) Summary: Coadministration of fluoxetine 30 mg twice daily for eight days and ritonavir 600 mg as a single dose in 16 patients resulted in a 19% increase in the area under the concentration-time curve (AUC) of ritonavir but no changes in the ritonavir maximum concentration (Cmax). However, post-marketing experience has revealed reports of cardiac and neurologic events when ritonavir and fluoxetine have been coadministered (Prod Info Norvir(R), 1999).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: established

6) Clinical Management: Monitor the patient for changes in cardiac and/or neurologic function.

7) Probable Mechanism: unknown

3.5.1.GS Rizatriptan

1) Interaction Effect: an increased risk of serotonin syndrome

2) Summary: There have been case reports of weakness, hyperreflexia, and incoordination following concomitant use of sumatriptan, a 5-hydroxytryptamine-1 (5HT-1) agonist, and a serotonin specific reuptake inhibitor (SSRI) (Prod Info Imitrex(R), 1998). Because rizatriptan is a 5HT 1B/1D receptor agonist, a similar interaction between SSRIs and rizatriptan may occur (Prod Info Maxalt(R), 1998a). Concurrent use of a triptan and an SSRI may result in serotonin syndrome which may be life-threatening. Symptoms of serotonin syndrome may include restlessness, hallucinations, loss of coordination, fast heart beat, rapid changes in blood pressure, increased body temperature, overreactive reflexes, nausea, vomiting, and diarrhea. Clinicians should be aware that triptans may be commonly used intermittently and that either the triptan or the SSRI may be prescribed by a different physician. Discuss the risks of serotonin syndrome with patients

who are prescribed this combination and monitor them closely for symptoms of serotonin syndrome (US Food and Drug Administration, 2006).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Coadministration of a triptan, such as rizatriptan, and an SSRI may result in a life-threatening condition called serotonin syndrome. Be aware that triptans may be commonly used intermittently and that either the triptan or the SSRI may be prescribed by a different physician. If these agents are used together, discuss the risks of serotonin syndrome with the patient and monitor closely for symptoms of serotonin syndrome (restlessness, hyperthermia, hyperreflexia, incoordination).
7) Probable Mechanism: additive pharmacologic effects resulting in excessive serotonergic stimulation
8) Literature Reports
a) Twelve healthy volunteers received paroxetine 20 mg daily for two weeks and a single dose of rizatriptan 10 mg. Plasma concentrations of rizatriptan were not altered by the administration of paroxetine (Prod Info Maxalt(R), 1998).

3.5.1.GT Rofecoxib
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.GU Selegiline
1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)
2) Summary: Concurrent administration or overlapping therapy with fluoxetine and selegiline may result in CNS toxicity or serotonin syndrome, a hyperserotonergic state characterized by symptoms such as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. Serious, even fatal, reactions have been reported (Prod Info Prozac(R), 1999g; Sternbach, 1991m; Coplan & Gorman, 1993k; Feighner et al, 1990k; Kline et al, 1989k; Suchowersky & de Vries, 1990k). Concomitant use is contraindicated. A minimum of 14 days should elapse after discontinuing selegiline before initiating therapy with fluoxetine. At least five weeks should elapse after discontinuing fluoxetine prior to initiating of treatment with selegiline (Prod Info EMSAM(R) transdermal patch, 2006).
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Concurrent use of fluoxetine and selegiline is contraindicated. Wait at least two weeks after discontinuing selegiline before initiating fluoxetine therapy. In addition, wait at least five weeks after discontinuing fluoxetine before initiating therapy with selegiline.
7) Probable Mechanism: inhibition of serotonin metabolism by monoamine oxidase
8) Literature Reports
a) Concomitant use of serotonin specific reuptake inhibitors and monoamine oxidase inhibitors can produce a toxic reaction known as serotonin syndrome (Sternbach, 1991l). Serotonin syndrome is a condition of serotonergic hyperstimulation and manifests as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor (Sternbach, 1991l). If the syndrome is not recognized and correctly treated, death can result.
b) It has been suggested that fluoxetine therapy be discontinued for five weeks before beginning therapy with a monoamine oxidase inhibitor. However, one case report describes a 28-year old woman

who had discontinued a 2-year fluoxetine regimen for six weeks before starting therapy with tranylcypromine. Over the next few days the patient developed fever, paresthesias, confusion, abdominal cramping, and various other CNS symptoms. Upon discontinuation of tranylcypromine, the patient's symptoms began to resolve. Blood samples taken three days after discontinuation of tranylcypromine revealed no presence of fluoxetine; however, the norfluoxetine level was 84 ng/mL (Coplan & Gorman, 1993j).
c) Adverse reactions reported when fluoxetine was given concomitantly with phenelzine (n=9) or tranylcypromine (n=4) include tremor (50%), agitation or restlessness (42%), mental status changes (42%), myoclonus (33%), diarrhea (33%), and blood pressure changes (25%) (Feighner et al, 1990j). All but one of the patients were taking other medications (ie, benzodiazepines, neuroleptics, anticonvulsants, antidepressants) that may have contributed to the adverse reactions.
d) Ten hours after her last dose of fluoxetine, a 45-year-old woman began tranylcypromine therapy (Kline et al, 1989j). Headache, muscle contractions, insomnia, and unsteady gait were reported on the second day. Thioridazine and tryptophan were added to her therapy. The patient experienced fever, rigidity of the arms and legs, and hyperreflexia. She died in the intensive care unit of a hospital 44 hours later.
e) Two cases suggestive of an interaction between fluoxetine and selegiline were reported (Suchowersky & de Vries, 1990j). One case involved a first episode of mania being observed approximately one month after adding selegiline to fluoxetine therapy. The patient improved two months after both drugs were discontinued, and no further details were provided. The second case involved diaphoresis, vasoconstriction, and cyanosis of the hands which occurred in close temporal relationship to adding fluoxetine and selegiline. Both drugs were discontinued, with relatively quick resolution of symptoms. Rechallenge with fluoxetine alone occurred without incident.

3.5.1.GV Sematilide

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, the coadministration of Class III antiarrhythmics and other drugs known to prolong the QTc interval is not recommended (Allen et al, 2002; Prod Info Tikosyn(TM) dofetilide capsules, 1999; Prod Info Corvert(R), 1998). Fluoxetine has been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Prozac(R), 2001a).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of class III antiarrhythmic agents and agents that prolong the QT interval, such as fluoxetine, is not recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.GW Sertindole

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Fluoxetine has been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Prozac(R), 2001l). Even though no formal drug interaction studies have been done, the coadministration of antipsychotics and other drugs known to prolong the QTc interval, including fluoxetine, is not recommended. Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999), quetiapine (Owens, 2001b), sertindole (Agelink et al, 2001), sultopride (Lande et al, 1992), and zotepine (Sweetman, 2003).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of fluoxetine and antipsychotics is not recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.GX Sibrafiban

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and antiplatelet agents has been associated with an increased risk of bleeding. Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an antiplatelet agent are given concurrently, monitor patient for signs of increased bleeding (Prod Info PAXIL(R) oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008)
7) Probable Mechanism: unknown

3.5.1.GY Sibutramine

1) Interaction Effect: an increased risk of serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)

2) Summary: Sibutramine inhibits the reuptake of norepinephrine, dopamine, and serotonin. In addition, the two major metabolites of sibutramine, M1 and M2, also inhibit the reuptake of these neurotransmitters. A hyperserotonergic state, termed serotonin syndrome, may result if sibutramine is given concurrently with a selective serotonin reuptake inhibitor. Coadministration of sibutramine and selective serotonin reuptake inhibitors is not recommended (Prod Info Meridia(R), 1997).

3) Severity: major

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: Sibutramine should not be administered with serotonergic agents, including selective serotonin reuptake inhibitors, because of the increased risk of serotonin syndrome.

7) Probable Mechanism: additive pharmacologic effects resulting in excessive serotonergic stimulation

8) Literature Reports

a) Serotonin syndrome is a condition of serotonergic hyperstimulation and manifests as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. If the syndrome is not recognized and correctly treated, death can result (Sternbach, 1991).

3.5.1.GZ Sotalol

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Even though no formal drug interaction studies have been done, the coadministration of Class III antiarrhythmics and other drugs known to prolong the QTc interval is not recommended (Allen et al, 2002; Prod Info Tikosyn(TM) dofetilide capsules, 1999; Prod Info Corvert(R), 1998). Fluoxetine has been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Prozac(R), 2001a).

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of class III antiarrhythmic agents and agents that prolong the QT interval, such as fluoxetine, is not recommended.

7) Probable Mechanism: additive effects on QT prolongation

3.5.1.HA Spiramycin

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Spiramycin and fluoxetine have been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Prozac(R), 2001j; Stramba-Badiale et al, 1997). Even though no formal drug interaction studies have been done, the coadministration of drugs known to prolong the QTc interval is not recommended.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of spiramycin and fluoxetine is not recommended.

7) Probable Mechanism: additive effects on QT prolongation

3.5.1.HB St John's Wort

1) Interaction Effect: an increased risk of serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)

2) Summary: Case reports describe the onset of serotonin syndrome-like symptoms, mania, and hypomania following the addition of St. John's Wort to sertraline, fluoxetine, and paroxetine therapy (Spinella & Eaton, 2002c; Barbanel et al, 2000a; Waksman et al, 2000a; Lantz et al, 1999a). A patient exhibited a syndrome resembling sedative/hypnotic intoxication after adding St. John's Wort to paroxetine therapy (Gordon, 1998a). St. John's Wort is thought to inhibit serotonin reuptake and may have mild monoamine oxidase inhibitory activity (Singer et al, 1999; Thiede & Walper, 1994), which when added to selective serotonin reuptake inhibitors may result in serotonin syndrome.

3) Severity: major

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: Patients should be advised to wait two weeks after stopping St. John's Wort before restarting selective serotonin reuptake inhibitor therapy. If a patient plans to replace selective serotonin reuptake inhibitor (SSRI) therapy with St. John's Wort, the half-life of the specific SSRI should be taken into consideration, waiting at least 5 half-lives for the SSRI to be metabolized out of the body.

7) Probable Mechanism: additive serotonergic effect

8) Literature Reports

a) Five cases have been reported of serotonin syndrome in the elderly after combining prescription antidepressants and St. John's Wort. Case 1 developed dizziness, nausea, vomiting and a headache 4

days after starting St. John's Wort 300 milligrams (mg) three times daily combined with sertraline 50 mg daily. Her symptoms resolved 2 to 3 days after stopping all medications. Case 2 developed nausea, epigastric pain and anxiety 3 days after starting St. John's Wort 300 mg twice daily combined with sertraline 75 mg daily. His symptoms resolved in one week after discontinuing both medications, and he resumed sertraline use without complications. The third case developed nausea, vomiting, anxiety, and confusion 2 days after starting St. John's Wort 300 mg twice daily combined with sertraline 50 mg daily. His symptoms improved in 4 to 5 days after stopping both medications and taking cyproheptadine 4 mg three times daily. Case 4 developed nausea, anxiety, restless, and irritability 2 days after starting St. John's Wort 300 mg three times daily combined with sertraline 50 mg daily. Cyproheptadine 4 mg twice daily was administered for seven days, and his symptoms improved in 1 week after stopping the medication. Cases 1 through 4 resumed their prescriptive sertraline after symptoms subsided and had no further problems. Case 5 developed nausea, vomiting and restlessness 3 days after starting St. John's Wort 300 mg three times daily combined with nefazodone 100 mg twice daily. She continued to take St. John's Wort but discontinued the nefazodone and over 1 week her symptoms Improved. She refused to resume therapy with nefazodone, but continued therapy with St. John's Wort and mild to moderate symptoms of depression and anxiety returned (Lantz et al, 1999).

b) A 50-year-old female taking St. John's Wort 600 mg daily experienced symptoms of sedative intoxication when she ingested a single dose of paroxetine 20 mg. She was incoherent, groggy, slow-moving, and complained of nausea and weakness. Prior to starting St. John's Wort, she had been receiving paroxetine 40 mg daily for eight months without adverse effects. After a night of sleep, she returned to her baseline mental status (Gordon, 1998).

c) A 61-year-old female experienced restlessness and involuntary movements of her extremities after beginning paroxetine 20 milligrams (mg) two days after discontinuing St. John's Wort 600 mg daily. The patient reported agitation and akathisia 8 hours after taking the first dose of paroxetine. She presented with diaphoresis and involuntary movement of all extremities with hyperreflexia and rigidity. Blood pressure, heart rate, and temperature were normal. After admission, blood pressure increased to 200/116 mmHg and heart rate increased to 145 beats per minute. Creatine kinase increased from 212 units/liter (U/L) initially to 1024 U/L. The patient was managed with supportive care and lorazepam and discharged after two days (Waksman et al, 2000).

d) A 28-year-old male developed a manic syndrome following comedication with St. John's Wort and sertraline. The patient was also on testosterone replacement therapy following bilateral orchidectomy 2 years earlier, but testosterone levels were subtherapeutic. The patient was prescribed sertraline 50 milligrams daily for depression following a 2 week trial of St. John's Wort per patient preference (dose not specified). Before sertraline was started, the patient was instructed to discontinue St. John'sWort, but continued it despite this advice. The patient experienced improved mood so did not see his physician, believing that he did not need further treatment. Over 2 months, the patient had elated mood, was irritable, and overspent, buying a car he could not afford, and was ultimately arrested for stealing fuel for the car. On arrest, he was referred to psychiatric services due to irritability and disinhibition. He was observed to be over-aroused, distractible, have flight of ideas, and grandiose delusions, leading to a diagnosis of a manic episode. The authors state the possibility of the manic state resulting from sertraline therapy alone, and that St. John's Wort may have increased the risk as a result of monoamine oxidase inhibition. Since the patient's testosterone level was subnormal, the possibility of its contribution to the manic state was considered low. However, the patient had elevated gonadotropin levels (luteinizing hormone and follicle-stimulating hormone) which may have predisposed the patient to mania (Barbanel et al, 2000).

e) A 42-year-old female experienced symptoms consistent with a mixed hypomanic episode following concomitant use of fluoxetine, buspirone, Ginkgo biloba, and St. John's Wort. The symptoms resolved following discontinuation of Ginkgo and St. John's Wort. The patient was being treated for depression following a mild traumatic brain injury with fluoxetine 20 milligrams (mg) twice daily and buspirone 15 mg twice daily. Several weeks prior to presentation, buspirone was increased to 20 mg twice daily for persistent anxiety and the patient began taking Ginkgo biloba, melatonin, and St. John's Wort in unspecified doses. Melatonin was considered unlikely to have contributed to her symptoms. Ginkgo and St. John's Wort were considered possible contributors since they may potentiate antidepressants, and considering the temporal relationship between the use of the herbs and onset of symptoms and discontinuation of the herbs and resolution of symptoms. However, the brain injury was considered a possible contributor (Spinella & Eaton, 2002b).

3.5.1.HC Sulfamethoxazole

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Cotrimoxazole and fluoxetine have been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Prozac(R), 2001ah; Lopez et al, 1987). Even though no formal drug interaction studies have been done, the coadministration of drugs known to prolong the QTc interval is not recommended.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of cotrimoxazole and fluoxetine is not

recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.HD Sulfinpyrazone
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and antiplatelet agents has been associated with an increased risk of bleeding. Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an antiplatelet agent are given concurrently, monitor patient for signs of increased bleeding (Prod Info PAXIL(R) oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008)
7) Probable Mechanism: unknown

3.5.1.HE Sulindac
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.HF Sulodexide
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and antiplatelet agents has been associated with an increased risk of bleeding. Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an antiplatelet agent are given concurrently, monitor patient for signs of increased bleeding (Prod Info PAXIL(R) oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008)
7) Probable Mechanism: unknown

3.5.1.HG Sultopride
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Fluoxetine has been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Prozac(R), 2001l). Even though no formal drug interaction studies have been done, the coadministration of antipsychotics and other drugs known to prolong the QTc interval, including fluoxetine, is not recommended. Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999), quetiapine (Owens, 2001b), sertindole (Agelink et al, 2001), sultopride (Lande et al, 1992), and zotepine (Sweetman, 2003).

3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of fluoxetine and antipsychotics is not recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.HH Sumatriptan

1) Interaction Effect: an increased risk of serotonin syndrome
2) Summary: There have been case reports of weakness, hyperreflexia, and incoordination following concomitant use of sumatriptan and a serotonin specific reuptake inhibitor (SSRI) (Prod Info Imitrex(R), 2002). Concurrent use of a triptan and an SSRI may result in serotonin syndrome which may be life-threatening. Symptoms of serotonin syndrome may include restlessness, hallucinations, loss of coordination, fast heart beat, rapid changes in blood pressure, increased body temperature, overreactive reflexes, nausea, vomiting, and diarrhea. Clinicians should be aware that triptans may be commonly used intermittently and that either the triptan or the SSRI may be prescribed by a different physician. Discuss the risks of serotonin syndrome with patients who are prescribed this combination and monitor them closely for symptoms of serotonin syndrome (US Food and Drug Administration, 2006).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Coadministration of a triptan, such as sumatriptan, and an SSRI, such as fluoxetine, may result in a life-threatening condition called serotonin syndrome. Be aware that triptans may be commonly used intermittently and that either the triptan or the SSRI may be prescribed by a different physician. If these agents are used together, discuss the risks of serotonin syndrome with the patient and monitor closely for symptoms of serotonin syndrome (restlessness, hyperthermia, hyperreflexia, incoordination).
7) Probable Mechanism: additive pharmacologic effects resulting in excessive serotonergic stimulation
8) Literature Reports
a) In the Canadian post-marketing surveillance program of fluoxetine, six cases of suspected drug interactions with sumatriptan have been reported. Of these cases, two are strongly suggestive of a drug interaction. Patients demonstrated symptoms consistent with serotonin syndrome (Joffe & Sokolov, 1997).

3.5.1.HI Suprofen

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.HJ Tamoxifen

1) Interaction Effect: decreased tamoxifen efficacy
2) Summary: A retrospective analysis revealed a 1.9-fold higher breast cancer recurrence rate in patients receiving a CYP2D6 inhibitor concomitantly with tamoxifen than those receiving tamoxifen alone (Aubert, Stanek, and Yao, 2009). Coadministration of tamoxifen with a potent CYP2D6 inhibitor, such as fluoxetine, may inhibit the CYP2D6-mediated metabolism of tamoxifen to the active metabolite, endoxifen. Monitor patients receiving a CYP2D6 inhibitor concomitantly with tamoxifen closely for loss of tamoxifen efficacy.
3) Severity: moderate

4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of fluoxetine and tamoxifen may result in decreased concentrations of endoxifen (active metabolite of tamoxifen), thereby decreasing tamoxifen efficacy. If administered concurrently, monitor closely for decreased tamoxifen efficacy.
7) Probable Mechanism: inhibition of CYP2D6-mediated tamoxifen metabolism to endoxifen (active metabolite)
8) Literature Reports
a) A retrospective analysis of breast cancer patients revealed a 1.9-fold higher 2-year recurrence rate of breast cancer in patients receiving concomitant therapy with tamoxifen and a CYP2D6 inhibitor compared with those receiving tamoxifen therapy alone. Based on medical and pharmacy claims data, 1928 patients who were new to tamoxifen therapy in a 30-month period and who had follow-up data for at least 24 months were included in the analysis. Among these patients, 353 (median age, 53 years) received tamoxifen concurrently with a CYP2D6 inhibitor and 945 (median age, 52 years) received tamoxifen alone. Disease recurrence was identified by diagnosis and insurance billing codes for mastectomy, lumpectomy, lymph node dissection, or radiation therapy, occurring at least 6 months after initiation of tamoxifen therapy. The 2-year breast cancer recurrence rate was 13.9% in women receiving concomitant tamoxifen and CYP2D6 inhibitor therapy compared with 7.5% in women receiving tamoxifen alone (95% CI, 1.33 to 2.76, p=0.001; hazard ratio, 1.92). Intervention procedures in the tamoxifen/CYP2D6 inhibitor group to treat breast cancer included mastectomy (54%), lumpectomy (36%), and radiation therapy (47%); corresponding intervention rates in the tamoxifen only group were 52%, 38%, and 46%, respectively (Aubert, Stanek, and Yao, 2009).

3.5.1.HK Tamsulosin
1) Interaction Effect: an increase in tamsulosin plasma exposure
2) Summary: In vitro data have shown that tamsulosin is primarily metabolized by CYP2D6 and CYP3A4 hepatic isozymes. Coadministration with cimetidine, a mild inhibitor of CYP450 enzymes, resulted in moderate increases in tamsulosin plasma exposure. Although no pharmacokinetic studies have been conducted with moderate or strong CYP2D6 inhibitors, such as fluoxetine, use caution if these agents are coadministered with tamsulosin, particularly at tamsulosin doses exceeding 0.4 mg (Prod Info FLOMAX(R) oral capsules, 2007). Patients should be monitored for increased tamsulosin adverse effects such as postural hypotension, dizziness, and syncope.
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Due to the potential for increased tamsulosin plasma exposures, use caution when moderate or strong CYP2D6 inhibitors, such as fluoxetine, are coadministered with tamsulosin, particularly at tamsulosin doses higher than 0.4 mg (Prod Info FLOMAX(R) oral capsules, 2007). Monitor patients for increased tamsulosin adverse effects (postural hypotension, dizziness, and episodes of syncope).
7) Probable Mechanism: potential inhibition of CYP2D6-mediated tamsulosin metabolism

3.5.1.HL Tapentadol
1) Interaction Effect: increased risk of serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)
2) Summary: Concurrent use of tapentadol and a selective serotonin reuptake inhibitor (SSRI) may result in serotonin syndrome, which may be life-threatening. Symptoms of serotonin syndrome may include restlessness, hallucinations, loss of coordination, fast heart beat, rapid changes in blood pressure, increased body temperature, overreactive reflexes, nausea, vomiting, and diarrhea (Prod Info tapentadol immediate release oral tablets, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of tapentadol and an SSRI may result in a life-threatening condition called serotonin syndrome. If these agents are used together, monitor the patient closely for symptoms of serotonin syndrome (restlessness, hyperthermia, hyperreflexia, incoordination), especially during treatment initiation and dose increases (Prod Info tapentadol immediate release oral tablets, 2008).
7) Probable Mechanism: additive serotonergic effect

3.5.1.HM Tedisamil
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, the coadministration of Class III antiarrhythmics and other drugs known to prolong the QTc interval is not recommended (Allen et al, 2002; Prod Info Tikosyn(TM) dofetilide capsules, 1999; Prod Info Corvert(R), 1998). Fluoxetine has been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Prozac(R), 2001a).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of class III antiarrhythmic agents and agents that prolong the QT interval, such as fluoxetine, is not recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.HN Telithromycin
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, telithromycin should be coadministered cautiously with other drugs which are also known to prolong the QTc interval, including fluoxetine (Owens, 2001d; Prod Info Prozac(R), 2001o).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of telithromycin with other agents that can prolong the QT interval, such as fluoxetine, is not recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.HO Tenidap
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.HP Tenoxicam
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.HQ Terfenadine

1) Interaction Effect: cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Although 2 cases have been reported in which concomitant terfenadine and fluoxetine resulted in cardiac toxicity in patients with no previous heart disease, a study of 12 healthy males demonstrated no significant pharmacokinetic or pharmacodynamic interaction between fluoxetine and terfenadine (Swims, 1993a; Marchiando & Cook, 1995a; Bergstrom et al, 1997a). Terfenadine and fluoxetine have been reported to cause QT prolongation at therapeutic doses. The administration of terfenadine with any other medication that may prolong the QT interval is contraindicated (Prod Info Seldane(R), 1997).

3) Severity: contraindicated

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: The concomitant administration of fluoxetine and terfenadine is contraindicated.

7) Probable Mechanism: decreased terfenadine metabolism

8) Literature Reports

a) In a study of 12 healthy male volunteers, fluoxetine did not inhibit the metabolism of terfenadine. Fluoxetine 60 mg daily was given for nine days. Terfenadine 60 mg was given alone and after eight days of the nine-day fluoxetine regimen. A high dose of fluoxetine was given to test the probability of interaction rigorously. Subject were monitored for changes in terfenadine pharmacokinetics and adverse effects. Concomitant fluoxetine resulted in a slight decrease in terfenadine plasma concentration. In addition, the area under the plasma concentration time curve for terfenadine was significantly decreased by fluoxetine. No change in blood pressure, heart rate, or cardiac electrographic tracings (EKG) were observed. One subjected reported dizziness after taking terfenadine alone and one subject had an abnormal EKG at baseline and during all observations during the study (Bergstrom et al, 1997).

b) A 39-year old woman experienced cardiac toxicity due to a possible interaction of terfenadine and fluoxetine (Marchiando & Cook, 1995). The patient's medications included acyclovir, beclomethasone, pseudoephedrine, and ibuprofen. During hospitalization for a substance abuse treatment program, the patient was started on fluoxetine 40 mg daily, terfenadine 60 mg twice daily, and disulfiram 250 mg daily. Approximately 14 days later, the patient underwent a routine electrocardiogram (ECG) study that revealed a prolonged QT interval of 550 milliseconds. The patient was asymptomatic and had no prior history of heart disease. Terfenadine was discontinued, and an ECG taken one week later revealed a normal QT interval.

c) A case report describes a possible interaction with terfenadine and fluoxetine in a 41-year-old male who experienced irregular heartbeat, skipped beats, and shortness of breath a month after institution of fluoxetine 20 mg daily; he had no previous history of heart disease. His drug regimen included fluoxetine, terfenadine 60 mg twice daily, ibuprofen 800 mg three times daily, misoprostol 100 mcg four times daily, Midrin(R) (acetaminophen 325 mg, dichloralphenazone 100 mg, isometheptene mucate 65 mg) as needed, and ranitidine 150 mg twice daily. A 24-hour Holter monitor showed intermittent frequent sinus tachycardia, three isolated atrial premature contractions, and three couplets. Terfenadine was discontinued and his previously reported symptoms did not reoccur. Fluoxetine is a known enzyme inhibitor and may have inhibited terfenadine metabolism resulting in the cardiac abnormalities seen in this patient (Swims, 1993).

3.5.1.HR Tetrabenazine

1) Interaction Effect: increased exposure to tetrabenazine

2) Summary: Caution should be used when administering a strong CYP2D6 inhibitor (eg, fluoxetine, paroxetine) to a patient taking tetrabenazine (a CYP2D6 substrate), and the daily dose of tetrabenazine should be halved if fluoxetine and tetrabenazine are used concomitantly. Following a single 50 mg dose of tetrabenazine given after 10 days of daily administration of paroxetine 20 mg, an increase in tetrabenazine exposure was observed in 25 healthy volunteers. When compared with tetrabenazine alone, coadministration with paroxetine caused an approximately 30% increase in Cmax and a 3-fold increase in the AUC of the alpha-HTBZ metabolite of tetrabenazine. Subjects given paroxetine prior to tetrabenazine alone experienced a 2.4-fold increase in Cmax and a 9-fold increase in the AUC of the beta-HTBZ metabolite of tetrabenazine. The elimination half-life for both metabolites was approximately 14 hours when tetrabenazine was coadministered with paroxetine (Prod Info XENAZINE(R) oral tablets, 2008).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: Use caution when prescribing fluoxetine to patients who take tetrabenazine. Patients who are already receiving a stable dose of tetrabenazine should have their daily dose of tetrabenazine decreased by half if coadministration with fluoxetine is necessary. Concomitant use of fluoxetine and tetrabenazine may cause elevated tetrabenazine levels. Monitor for increased tetrabenazine side effects such as somnolence, fatigue, insomnia, depression, anxiety, akathisia, and nausea (Prod Info XENAZINE(R) oral tablets, 2008).

7) Probable Mechanism: inhibition of CYP2D6-mediated tetrabenazine metabolism by fluoxetine

3.5.1.HS Thioridazine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac

arrest)
2) Summary: Fluoxetine inhibits the metabolism of thioridazine through inhibition of CYP2D6. The resulting elevated levels of thioridazine may enhance QT prolongation (Prod Info Mellaril(R), 2000). Fluoxetine has been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Prozac(R), 2001ae). Although citing no data, the manufacturer of thioridazine states that concomitant use with other drugs which prolong the QT interval is contraindicated (Prod Info Mellaril(R), 2000).
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: The concurrent administration of fluoxetine and thioridazine is contraindicated.
7) Probable Mechanism: inhibition of cytochrome P450 2D6-mediated thioridazine metabolism; additive effects on QT prolongation

3.5.1.HT Tiaprofenic Acid
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.HU Ticlopidine
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and antiplatelet agents has been associated with an increased risk of bleeding. Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an antiplatelet agent are given concurrently, monitor patient for signs of increased bleeding (Prod Info PAXIL(R) oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008)
7) Probable Mechanism: unknown

3.5.1.HV Tinzaparin
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008). Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with warfarin (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When fluoxetine and an anticoagulant are given concurrently, monitor patient for signs of increased bleeding. Patients who are taking warfarin should be monitored closely for altered

anticoagulant effects, including increased bleeding, when fluoxetine therapy is initiated or discontinued (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
7) Probable Mechanism: unknown
8) Literature Reports
a) Fluoxetine is thought to inhibit the cytochrome P450 2C9 isoenzyme (CYP2C9). This is the enzyme by which the more potent warfarin isomer, S-warfarin, is metabolized (Riesenman, 1995). In addition, both fluoxetine and warfarin are tightly bound to albumin. In combination, the possibility for protein-binding displacement of either drug is present (Prod Info Coumadin(R), 1999).
b) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bleeding (hospital admission due to bleeding) in patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patients with a mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients experienced 11 bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experiencing bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model (Wallerstedt et al, 2009).
c) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5), however, the rate of gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).
d) In 6 reported cases, INR increased during combined fluoxetine and warfarin therapy. In a seventh case, severe bruising of the lower legs occurred in a woman initially treated with fluoxetine and, secondarily, started on warfarin (Woolfrey et al, 1993; Claire et al, 1991).
e) An 83-year-old man died from cerebral hemorrhage secondary to increased warfarin concentrations. The patient had been taking warfarin 30 mg per week for atrial fibrillation with a target INR between 2 and 3. The patient's other drugs included lisinopril, furosemide, potassium, digoxin, and acetaminophen. After being seen for symptoms of depression, anxiety, and insomnia, the patient was given fluoxetine 20 mg per day and diazepam 2.5 mg 3 to 4 times per day. Eight days later, the patient's INR increased to 4.8, and the dose of warfarin was decreased to 27.5 mg per week. The patient was later seen for symptoms of drug delirium, including confusion, incoherence, and speaking irrationally. At this point, the INR was 3.64 and fluoxetine was discontinued. The next day the patient presented to the hospital with left-sided weakness and later died from complications of a large interparenchymal hemorrhage. The authors proposed that the addition of fluoxetine to the patient's regimen resulted in increased serum levels of both warfarin and diazepam, resulting in delirium and loss of anticoagulant control (Dent & Orrock, 1997).

3.5.1.HW Tipranavir
1) Interaction Effect: increased fluoxetine plasma concentrations
2) Summary: Although the drug interaction between fluoxetine and tipranavir/ritonavir has not been studied, coadministration of fluoxetine with tipranavir/ritonavir may result in increased fluoxetine plasma concentrations. Fluoxetine doses may need to be adjusted when tipranavir/ritonavir therapy is initiated (Prod Info APTIVUS(R) oral capsules, solution, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concurrent administration of fluoxetine and tipranavir/ritonavir may increase fluoxetine plasma concentrations. Use caution when these agents are coadministered and consider adjusting the fluoxetine dose as needed upon initiation of tipranavir/ritonavir (Prod Info APTIVUS(R) oral capsules, solution, 2008).
7) Probable Mechanism: unknown

3.5.1.HX Tirofiban
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and antiplatelet agents has been associated with an increased risk of bleeding. Bleeding events reported have included epistaxis, ecchymosis,

hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an antiplatelet agent are given concurrently, monitor patient for signs of increased bleeding (Prod Info PAXIL(R) oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008)
7) Probable Mechanism: unknown

3.5.1.HY Tolmetin
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.HZ Toloxatone
1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)
2) Summary: Concurrent administration or overlapping therapy with fluoxetine and a monoamine oxidase (MAO) inhibitor may result in CNS toxicity or serotonin syndrome, a hyperserotonergic state characterized by symptoms such as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. Serious, even fatal, reactions have been reported (Prod Info Prozac(R), 1999a; Sternbach, 1991d; Coplan & Gorman, 1993c; Feighner et al, 1990c; Kline et al, 1989c; Suchowersky & de Vries, 1990c). As a reversible and selective monoamine oxidase inhibitor, toloxatone may not potentiate the effects of selective serotonin reuptake inhibitors to the same frequency, extent, and duration observed with other MAOIs. However, until further studies confirm the safety and efficacy of this combined therapy, concomitant use is contraindicated.
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Concurrent use of fluoxetine and toloxatone is contraindicated. Wait at least two weeks after discontinuing a MAO inhibitor before initiating fluoxetine therapy. In addition, wait at least five weeks after discontinuing fluoxetine before initiating therapy with a MAO inhibitor.
7) Probable Mechanism: inhibition of serotonin metabolism by monoamine oxidase
8) Literature Reports
a) Concomitant use of serotonin specific reuptake inhibitors and monoamine oxidase inhibitors can produce a toxic reaction known as serotonin syndrome (Sternbach, 1991c). Serotonin syndrome is a condition of serotonergic hyperstimulation and manifests as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor (Sternbach, 1991c). If the syndrome is not recognized and correctly treated, death can result.
b) It has been suggested that fluoxetine therapy be discontinued for at least five weeks before beginning therapy with a monoamine oxidase inhibitor. A 28-year old woman discontinued fluoxetine for six weeks before starting therapy with tranylcypromine. Over the next few days the patient developed fever, paresthesias, confusion, abdominal cramping, and various other CNS symptoms. Upon discontinuation of tranylcypromine, the patient's symptoms began to resolve. Blood samples taken three days after discontinuation of tranylcypromine revealed no presence of fluoxetine; however, the norfluoxetine level was 84 ng/mL (Coplan & Gorman, 1993b).

c) Adverse reactions reported when fluoxetine was given concomitantly with phenelzine (n=9) or tranylcypromine (n=4) include tremor (50%), agitation or restlessness (42%), mental status changes (42%), myoclonus (33%), diarrhea (33%), and blood pressure changes (25%) (Feighner et al, 1990b). All but one of the patients were taking other medications (ie, benzodiazepines, neuroleptics, anticonvulsants, antidepressants) that may have contributed to the adverse reactions.
d) Ten hours after her last dose of fluoxetine, a 45-year-old woman began tranylcypromine therapy (Kline et al, 1989b). Headache, muscle contractions, insomnia, and unsteady gait were reported on the second day. Thioridazine and tryptophan were added to her therapy. The patient experienced fever, rigidity of the arms and legs, and hyperreflexia. She died in the intensive care unit of a hospital 44 hours later.
e) Two cases reports suggested a possible interaction between fluoxetine and selegiline (Suchowersky & de Vries, 1990b). One case involved a first episode of mania being observed approximately one month after adding selegiline to fluoxetine therapy. The patient improved two months after both drugs were discontinued, and no further details were provided. The second case involved diaphoresis, vasoconstriction, and cyanosis of the hands which occurred in close temporal relationship to adding fluoxetine and selegiline. Both drugs were discontinued, with relatively quick resolution of symptoms. Rechallenge with fluoxetine alone occurred without incident.

3.5.1.IA Tramadol

1) Interaction Effect: an increased risk of seizures and serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes); increased concentrations of tramadol and decreased concentrations of tramadol active metabolite, M1
2) Summary: Seizures and serotonin syndrome have been reported in patients using tramadol. Some medications, including fluoxetine, are known to reduce the seizure threshold. The risk of seizures and serotonin syndrome may be enhanced when fluoxetine and tramadol therapy are combined (Prod Info Ultram(R), 2001). Fluoxetine is also an inhibitor of CYP2D6, and concomitant administration with tramadol may result in increases of tramadol concentrations and decreases in active metabolite, M1, concentrations. This may cause an increase in side effects or a reduction in the analgesic effect of tramadol (Prod Info ULTRAM(R)ER extended-release oral tablets, 2005).
3) Severity: major
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Caution should be used if tramadol is to be administered to patients receiving concomitant fluoxetine therapy. If possible, avoid this combination, especially in patients with underlying conditions that might predispose to seizures. Observe the patient closely for signs and symptoms of serotonin syndrome. Also, monitor patients for signs and symptoms of narcotic toxicity (extreme sedation, respiratory depression), as well as decreased analgesic effect of tramadol.
7) Probable Mechanism: increased concentration of serotonin in the nervous system and periphery; inhibition of CYP2D6 metabolism of tramadol to M1 active metabolite by quinidine
8) Literature Reports

a) The combination of tramadol and fluoxetine may result in serotonin syndrome and mania. A 72-year-old female with no cognitive deficits had been treated with fluoxetine for the past 10 years. She was prescribed tramadol 150 mg daily for articular pain. After 18 days of combination therapy the patient began to feel nervous, had a temperature of 37.2 C, piloerection, and muscular contractions. She discontinued tramadol and 21 days later her physical symptoms disappeared. She was still agitated, euphoric, hyperactive, had rapid speech, paranoid ideation, and slept less than 3 hours a day. She was hospitalized and haloperidol treatment was initiated, however, her symptoms continued. She was readmitted one week later and treatment with olanzapine was initiated. Two weeks later she became euthymic and continued olanzapine therapy after being released from the hospital. The potential for inducing mania and serotonergic syndrome when using tramadol combined with SSRIs must be considered (Gonzalez-Pinto, 2001).

3.5.1.IB Tranylcypromine

1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)
2) Summary: Concurrent administration or overlapping therapy with fluoxetine and a monoamine oxidase (MAO) inhibitor may result in CNS toxicity or serotonin syndrome, a hyperserotonergic state characterized by symptoms such as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. Serious, even fatal, reactions have been reported (Prod Info Prozac(R), 1999j; Sternbach, 1991s; Coplan & Gorman, 1993q; Feighner et al, 1990q; Kline et al, 1989q; Suchowersky & de Vries, 1990q; Sternbach, 1988a). Concomitant use is contraindicated.
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Concurrent use of fluoxetine and tranylcypromine is contraindicated. Wait at least two weeks after discontinuing a MAO inhibitor before initiating fluoxetine therapy. In addition, wait at least five weeks after discontinuing fluoxetine before initiating therapy with a MAO inhibitor.
7) Probable Mechanism: inhibition of serotonin metabolism by monoamine oxidase

8) Literature Reports

a) Concomitant use of serotonin specific reuptake inhibitors and monoamine oxidase inhibitors can produce a toxic reaction known as serotonin syndrome (Sternbach, 1991r). Serotonin syndrome is a condition of serotonergic hyperstimulation and manifests as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor (Sternbach, 1991r). If the syndrome is not recognized and correctly treated, death can result.

b) It has been suggested that fluoxetine therapy be discontinued for five weeks before beginning therapy with a monoamine oxidase inhibitor. However, one case report describes a 28-year old woman who had discontinued a 2-year fluoxetine regimen for six weeks before starting therapy with tranylcypromine. Over the next few days the patient developed fever, paresthesias, confusion, abdominal cramping, and various other CNS symptoms. Upon discontinuation of tranylcypromine, the patient's symptoms began to resolve. Blood samples taken three days after discontinuation of tranylcypromine revealed no presence of fluoxetine; however, the norfluoxetine level was 84 ng/mL (Coplan & Gorman, 1993p).

c) Adverse reactions reported when fluoxetine was given concomitantly with phenelzine (n=9) or tranylcypromine (n=4) include tremor (50%), agitation or restlessness (42%), mental status changes (42%), myoclonus (33%), diarrhea (33%), and blood pressure changes (25%) (Feighner et al, 1990p). All but one of the patients were taking other medications (ie, benzodiazepines, neuroleptics, anticonvulsants, antidepressants) that may have contributed to the adverse reactions.

d) Ten hours after her last dose of fluoxetine, a 45-year-old woman began tranylcypromine therapy (Kline et al, 1989p). Headache, muscle contractions, insomnia, and unsteady gait were reported on the second day. Thioridazine and tryptophan were added to her therapy. The patient experienced fever, rigidity of the arms and legs, and hyperreflexia. She died in the intensive care unit of a hospital 44 hours later.

e) Two cases suggestive of an interaction between fluoxetine and selegiline were reported (Suchowersky & de Vries, 1990p). One case involved a first episode of mania being observed approximately one month after adding selegiline to fluoxetine therapy. The patient improved two months after both drugs were discontinued, and no further details were provided. The second case involved diaphoresis, vasoconstriction, and cyanosis of the hands which occurred in close temporal relationship to adding fluoxetine and selegiline. Both drugs were discontinued, with relatively quick resolution of symptoms. Rechallenge with fluoxetine alone occurred without incident.

f) A 31-year-old female received fluoxetine 20 mg daily for 14 days, and was subsequently discontinued due to nausea and restlessness (Sternbach, 1988). The administration of tranylcypromine 10 mg daily commenced two days following the discontinuation of fluoxetine. Four days later, the patient increased tranylcypromine to 20 mg daily and developed a serotonin-like syndrome two to three hours later. Following the discontinuation of tranylcypromine, all signs and symptoms resolved within 24 hours.

3.5.1.IC Trazodone

1) Interaction Effect: trazodone toxicity (sedation, dry mouth, urinary retention) or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)

2) Summary: When given concurrently, trazodone and fluoxetine have been reported to be therapeutically effective with and without side effects (Metz & Shader, 1990; Swerdlow & Andia, 1989; Neirenberg et al, 1992; Maes et al, 1997a). Coadministration of trazodone and fluoxetine has been reported to result in speech dysfunction in a 43-year old man following traumatic brain injury (Patterson et al, 1997a). There have also been several reports of serotonin syndrome due to interactions between selective serotonin reuptake inhibitors and antidepressants (George & Godleski, 1996a; Reeves & Bullen, 1995a; Alderman & Lee, 1996). Serotonin syndrome is a rare but potentially fatal condition of serotonergic hyperstimulation characterized by hypertension, hyperthermia, myoclonus and changes in mental status (Sternbach, 1991y). Further clinical studies are necessary to determine the incidence and implications of serotonin syndrome associated with this drug combination.

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Due to the potential for impairment in trazodone metabolism, patients should be monitored for any signs of trazodone toxicity. Occasional dosage reductions of trazodone may be required. Serotonin syndrome, characterized by hypertension, hyperthermia, myoclonus, and mental status changes, may also occur during concomitant therapy.

7) Probable Mechanism: decreased trazodone clearance

8) Literature Reports

a) Five cases of elevated antidepressant levels, four involving tricyclic antidepressants (nortriptyline, imipramine, desipramine) and one involving trazodone, have been reported. After the addition of fluoxetine, the ratio of antidepressant level to dose increased by 109% to 486% in the patients on tricyclics and by 31% in the patient on trazodone. The trazodone-treated patient developed sedation and unstable gait (Aranow et al, 1989b).

b) A 44-year-old man developed symptoms characteristic of serotonin syndrome due to a possible interaction between fluoxetine and trazodone. The patient had been taking fluoxetine 40 mg daily and trazodone 100 mg daily for approximately two months before symptoms occurred. The patient

experienced disorientation, tremor, diaphoresis, and anxiety, followed by uncontrollable shaking and loss of consciousness. After the patient was treated with cyproheptadine 4 mg orally, symptoms resolved over the next 30 minutes. Trazodone was discontinued and the patient continued to take fluoxetine 40 mg daily without further complications (George & Godleski, 1996).
c) Serotonin syndrome was also reported in a 29-year-old woman taking trazodone and paroxetine. The patient was treated with trazodone 200 mg daily at bedtime for approximately three months for depression and insomnia. The patient's depressive symptoms were unresponsive to this treatment, so trazodone was subsequently decreased to 50 mg daily at bedtime for two weeks before paroxetine 20 mg every morning was added. Within 24 hours after the first dose of paroxetine, the patient became agitated, confused, shaky, and diaphoretic. Upon examination, the patient had impaired concentration, intermittent myoclonus in all extremities, hyperreflexia, tremor, and diaphoresis. After discontinuation of antidepressant medications, the patient's symptoms resolved (Reeves & Bullen, 1995).
d) A 43-year-old male with traumatic brain injury developed speech dysfunction during therapy with fluoxetine and trazodone. The patient was being treated with trazodone 150 mg at bedtime for chronic pain as a result of a fall. After undergoing a comprehensive psychiatric evaluation as part of rehabilitation, fluoxetine 20 mg every morning was added to the patient's regimen for treatment of symptoms of depression. Within one week of starting therapy with fluoxetine, the patient began to slur his speech and later exhibited a slow rate of speech, increased pause length, prolongation of initial phonemes, and word-finding difficulties. After discontinuation of fluoxetine and tapering of trazodone therapy, the patient had marked improvement in speech difficulty and returned to normal over the next week (Patterson et al, 1997).
e) The pharmacokinetic effect of trazodone and fluoxetine cotherapy was studied in 27 inpatients with a major depressive episode. All were treated with trazodone 100 mg daily, followed one week later with the addition of fluoxetine 20 mg daily, pindolol 7.5 mg daily, or placebo for four weeks. Pindolol and placebo had no significant effect on the plasma concentrations of trazodone or its active metabolite, meta-chlorophenylpiperazine (mCPP). However, when fluoxetine was combined with trazodone, levels of mCPP increased from a mean baseline value of 11.3 ng/mL to 38.3 ng/mL in four weeks. This increase was also associated with an improvement in the clinical response to the antidepressants (Maes et al, 1997).

3.5.1.ID Trifluoperazine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Although citing no data, the manufacturers of some phenothiazines state that concomitant use with other drugs which prolong the QT interval is not recommended. Q and T wave distortions have been observed in patients taking phenothiazines (Prod Info Compazine(R), 2002; Prod Info Stelazine(R), 2002; Prod Info Thorazine(R), 2002) . Other phenothiazines may have similar effects, though no reports are available. Fluoxetine has been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Prozac(R), 2003).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of fluoxetine and a phenothiazine is not recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.IE Trimethoprim

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Cotrimoxazole and fluoxetine have been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Prozac(R), 2001ah; Lopez et al, 1987). Even though no formal drug interaction studies have been done, the coadministration of drugs known to prolong the QTc interval is not recommended.
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of cotrimoxazole and fluoxetine is not recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.IF Trimipramine

1) Interaction Effect: tricyclic antidepressant toxicity (dry mouth, urinary retention, sedation) and an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Tricyclic antidepressants (TCAs) and fluoxetine have been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Prozac(R), 2001h; Marshall & Forker, 1982). Even though no formal drug interaction studies have been done which demonstrate QT prolongation, the coadministration of tricyclic antidepressants and other drugs known to prolong the QTc interval, such as fluoxetine, is not recommended (Prod Info Elavil(R), 1999). In addition, concurrent use of fluoxetine and TCAs such as

desipramine, nortriptyline, and imipramine has resulted in significant increases in TCA concentrations (Preskorn et al, 1994a; Preskorn et al, 1994a; Aranow et al, 1989a; Downs et al, 1989a; Goodnick, 1989a; Bell & Cole, 1988a).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: The concurrent administration of fluoxetine and a tricyclic antidepressant is not recommended.
7) Probable Mechanism: decreased tricyclic antidepressant metabolism; additive effects on QT prolongation
8) Literature Reports
a) Fluoxetine increased the level of tricyclic antidepressants (nortriptyline, imipramine, desipramine) in 4 patients. After the addition of fluoxetine, the ratio of antidepressant level to dose increased by 109% to 486% in the patients. Three patients developed clinical symptoms (anticholinergic effects, constipation, urinary hesitancy, sedation, unstable gait) as a result of the increased levels (Aranow et al, 1989).
b) Fluoxetine statistically and clinically significantly increased desipramine concentrations in 18 healthy subjects. When fluoxetine (20 mg daily) was added to desipramine (50 mg daily), the mean maximum concentration of desipramine increased by 278% and the area under the concentration-time curve increased by 342%. Desipramine trough concentrations continued to be 198% above baseline three weeks after fluoxetine was discontinued. The same study compared pharmacokinetics of desipramine when combined with sertraline. The impact of sertraline was modest, resulting in small and short-term increases in desipramine plasma concentrations (Preskorn et al, 1994).
c) A 75-year-old female experienced symptomatic increases in her desipramine serum concentrations when fluoxetine was added. Desipramine serum levels ranged from 109 to 150 ng/mL with oral doses of 300 mg at bedtime prior to fluoxetine therapy. Following the addition of oral fluoxetine 20 mg daily to the regimen, the desipramine serum level increased to 212 ng/mL within five days. The fluoxetine dose was increased to 40 mg/day three days later, and the desipramine serum level was 419 ng/mL after four days. A worsening of depression and severe fatigue coincided with the increases in desipramine serum levels. Withdrawal of fluoxetine and reduction in the desipramine dose to 200 mg daily reduced the desipramine serum level to 231 ng/mL within two weeks (Bell & Cole, 1988).
d) A 33-year-old depressed male developed adverse effects of dry mouth, tinnitus, and difficulties with alertness and memory while receiving fluoxetine 40 mg daily and desipramine 150 mg daily for five weeks; fluoxetine was discontinued and the blood levels of desipramine decreased from 938 to 48 ng/mL with resolution of clinical symptoms (Goodnick, 1989).
e) A 39-year-old female experienced symptomatic increases in her desipramine levels with concomitant fluoxetine therapy. Prior to fluoxetine therapy, the patient's measured levels of desipramine had ranged from 148 to 160 ng/mL on a regimen of 300 mg daily. Five weeks after the addition of fluoxetine 20 mg daily, she reported anticholinergic symptoms, sedation, and confusion with a desipramine level of 527 ng/mL. The desipramine dose was lowered to 200 mg/day; eleven days later, the level was 244 ng/mL; the patient reported decreased energy, impaired short-term memory, and some "garbled" speech, as well as an episode of nausea, dizziness, and syncope. The desipramine dose was reduced to 50 mg/day; the adverse effects resolved in six days. Eight days later, the desipramine level was 122 ng/mL (Downs et al, 1989).
f) Concomitant administration of fluoxetine and desipramine was reported to result in an increased desipramine level and new onset of delirium in a 69-year-old male within 10 days of the addition of fluoxetine to the patient's regimen (Preskorn et al, 1990).

3.5.1.IG Tryptophan
1) Interaction Effect: serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)
2) Summary: Tryptophan is metabolized to serotonin, and fluoxetine, a selective serotonin reuptake inhibitor (SSRI), increases serotonergic activity (Steiner & Fontaine, 1986a; Boyer & Blumhardt, 1992). It is possible that combining these agents may result in excessive serotonin leading to a condition known as "serotonin syndrome".
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: If tryptophan and fluoxetine are coadministered, monitor patients for signs of serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes). It may be necessary to reduce doses of one or both agents or to discontinue tryptophan.
7) Probable Mechanism: additive adverse effects
8) Literature Reports
a) In a case series, the concurrent use of fluoxetine 50 to 100 mg daily and L-tryptophan 1 to 4 g daily resulted in all five patients experiencing central nervous system toxicity (agitation, poor concentration, nausea, diarrhea, paresthesias, palpitations, chills, headaches, aggressive behavior, and severe insomnia) within a few days. Tryptophan was discontinued and the symptoms disappeared (Steiner & Fontaine, 1986).
b) Concurrent paroxetine (another SSRI) and tryptophan have been linked to headache, nausea, sweating, and dizziness (Prod Info Paxil(R), 1999). L-tryptophan administration increases serotonin

concentration in the central nervous system and paroxetine inhibits serotonin reuptake. Patients who receive potent serotonin reuptake inhibitors should be advised not to take L-tryptophan.

3.5.1.IH Valdecoxib

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).

b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.II Vasopressin

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Fluoxetine and vasopressin have been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Prozac(R), 2001b; Jacoby & Wiegman, 1990). Even though no formal drug interaction studies have been done, the coadministration of drugs known to prolong the QTc interval is not recommended.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of fluoxetine and vasopressin is not recommended.

7) Probable Mechanism: additive effects on QT prolongation

3.5.1.IJ Venlafaxine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest) and an increased risk of serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)

2) Summary: Venlafaxine and fluoxetine have been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Prozac(R), 2001s; Prod Info Effexor(R) XR, 2000). Even though no formal drug interaction studies have been done, the coadministration of drugs known to prolong the QTc interval is not recommended. In addition, the concurrent use of venlafaxine and fluoxetine may result in serotonin syndrome (Chan et al, 1998).

3) Severity: major

4) Onset: rapid

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of venlafaxine and fluoxetine is not recommended.

7) Probable Mechanism: additive effects on QT prolongation; additive serotonergic effect

3.5.1.IK Warfarin

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008). Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with warfarin (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).

3) Severity: major

4) Onset: delayed

5) Substantiation: probable
6) Clinical Management: When fluoxetine and an anticoagulant are given concurrently, monitor patient for signs of increased bleeding. Patients who are taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, when fluoxetine therapy is initiated or discontinued (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
7) Probable Mechanism: unknown
8) Literature Reports
a) Fluoxetine is thought to inhibit the cytochrome P450 2C9 isoenzyme (CYP2C9). This is the enzyme by which the more potent warfarin isomer, S-warfarin, is metabolized (Riesenman, 1995). In addition, both fluoxetine and warfarin are tightly bound to albumin. In combination, the possibility for protein-binding displacement of either drug is present (Prod Info Coumadin(R), 1999).
b) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bleeding (hospital admission due to bleeding) in patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patients with a mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients experienced 11 bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experiencing bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model (Wallerstedt et al, 2009).
c) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5), however, the rate of gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).
d) In 6 reported cases, INR increased during combined fluoxetine and warfarin therapy. In a seventh case, severe bruising of the lower legs occurred in a woman initially treated with fluoxetine and, secondarily, started on warfarin (Woolfrey et al, 1993; Claire et al, 1991).
e) An 83-year-old man died from cerebral hemorrhage secondary to increased warfarin concentrations. The patient had been taking warfarin 30 mg per week for atrial fibrillation with a target INR between 2 and 3. The patient's other drugs included lisinopril, furosemide, potassium, digoxin, and acetaminophen. After being seen for symptoms of depression, anxiety, and insomnia, the patient was given fluoxetine 20 mg per day and diazepam 2.5 mg 3 to 4 times per day. Eight days later, the patient's INR increased to 4.8, and the dose of warfarin was decreased to 27.5 mg per week. The patient was later seen for symptoms of drug delirium, including confusion, incoherence, and speaking irrationally. At this point, the INR was 3.64 and fluoxetine was discontinued. The next day the patient presented to the hospital with left-sided weakness and later died from complications of a large interparenchymal hemorrhage. The authors proposed that the addition of fluoxetine to the patient's regimen resulted in increased serum levels of both warfarin and diazepam, resulting in delirium and loss of anticoagulant control (Dent & Orrock, 1997).

3.5.1.IL Xemilofiban
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and antiplatelet agents has been associated with an increased risk of bleeding. Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an antiplatelet agent are given concurrently, monitor patient for signs of increased bleeding (Prod Info PAXIL(R) oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008)
7) Probable Mechanism: unknown

3.5.1.IM Ziprasidone
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac

arrest)
2) Summary: Even though no formal drug interaction studies have been done, ziprasidone should not be coadministered with other drugs which are also known to prolong the QTc interval, including fluoxetine (Prod Info Geodon(TM), 2002; Prod Info Prozac(R), 2001ag).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of ziprasidone with other agents that can prolong the QT interval, such as fluoxetine, is not recommended.
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) It has been shown that ziprasidone prolongs the QTc and that this represents a risk of potentially fatal ventricular dysrhythmias (Anon, 2000). QT prolongation is dose-related. It is not yet known whether ziprasidone will cause torsades de pointes or increase the rate of sudden death. In clinical trials ziprasidone increased the QTc interval, compared to placebo, by approximately 10 milliseconds (msec) at the highest dose (160 milligrams). Baseline QTc interval increased 9 to 14 msec more with ziprasidone than with risperidone, olanzapine, quetiapine, and haloperidol, but QTc interval was 14 msec less than that observed with thioridazine (Prod Info Geodon(R), 2002).

3.5.1.IN Zolmitriptan
1) Interaction Effect: an increased risk of serotonin syndrome and an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Zolmitriptan and fluoxetine have been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Prozac(R), 2001d; Prod Info Zomig(R), 2001). Even though no formal drug interaction studies have been done, the coadministration of drugs known to prolong the QTc interval is not recommended. Additionally, concurrent use of a triptan and an SSRI may result in serotonin syndrome which may be life-threatening. Symptoms of serotonin syndrome may include restlessness, hallucinations, loss of coordination, fast heart beat, rapid changes in blood pressure, increased body temperature, overreactive reflexes, nausea, vomiting, and diarrhea. Clinicians should be aware that triptans may be commonly used intermittently and that either the triptan or the SSRI may be prescribed by a different physician. Discuss the risks of serotonin syndrome with patients who are prescribed this combination and monitor them closely for symptoms of serotonin syndrome (US Food and Drug Administration, 2006).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of a triptan, such as zolmitriptan, and an SSRI, such as fluoxetine, may result in a life-threatening condition called serotonin syndrome. Be aware that triptans may be commonly used intermittently and that either the triptan or the SSRI may be prescribed by a different physician. If these agents are used together, discuss the risks of serotonin syndrome with the patient and monitor closely for symptoms of serotonin syndrome (restlessness, hyperthermia, hyperreflexia, incoordination). Additionally, concurrent administration of zolmitriptan and fluoxetine may result in an increased risk of cardiotoxicity due to additive QT prolongation effects.
7) Probable Mechanism: additive pharmacologic effects resulting in excessive serotonergic stimulation; additive effects on QT prolongation
8) Literature Reports
a) The pharmacokinetics of zolmitriptan were unaffected by 4 weeks of pretreatment with fluoxetine 20 mg/day (Prod Info Zomig(R), 2003).

3.5.1.IO Zolpidem
1) Interaction Effect: an increased risk of hallucinations
2) Summary: Short-term combined therapy with fluoxetine and zolpidem was determined to be safe by a study involving 29 healthy women. After a single dose of zolpidem followed by one washout day, the subjects were given a daily dose of fluoxetine on days three through 27, then zolpidem was added each evening on days 28 through 32. There were no significant changes in either fluoxetine or zolpidem plasma concentrations, and both medications were tolerated well, either individually or combined (Allard et al, 1998a). However, the publication of five case reports from the Washington Poison Center elucidates potential interactions between zolpidem and various antidepressant medications. Five patients reported hallucinations after concurrent use of zolpidem and antidepressant medication. The hallucination episodes all lasted longer than one hour, but resolved without further sequelae (Elko et al, 1998a).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Observe patients for hallucinatory activity. Alternative anti-insomnia medication may be warranted.
7) Probable Mechanism: unknown
8) Literature Reports
a) A study conducted by Lorex Pharmaceuticals and Boston Research and Science Consulting demonstrates the safety of concomitant short-term therapy with fluoxetine and zolpidem. In this study,

29 healthy female volunteers were given a single evening dose of zolpidem 10 mg, followed by one washout day. This was followed by a daily morning dose of fluoxetine 20 mg on days 3 through 27. On days 28 through 32, a daily evening dose of zolpidem was added. Steady state plasma concentrations of fluoxetine and norfluoxetine were reached on day 24 of fluoxetine dosing as determined by serial venous blood sampling. There were no significant differences in area under concentration curve (AUC), peak concentration (Cmax), or time to reach peak concentration (Tmax) after one or five consecutive doses of zolpidem in conjunction with fluoxetine administration. The following pharmacokinetic mean parameters were observed for zolpidem: AUC 917.04 ng/hr/mL on day 28, 978.77 ng/hr/mL on day 32, Cmax 167.94 ng/mL on day 28, 175.91 ng/mL on day 32, Tmax 1.67 hr on day 28, 1.54 hr on day 32. For fluoxetine the following were noted: AUC 2674.53 ng/hr/mL on day 27, 2879.63 ng/hr/mL on day 32, Cmax 133.48 ng/mL on day 27, 142.23 ng/mL on day 32, Tmax 8.28 hr on day 27, 9.04 hr on day 32. The only statistically significant difference was a higher half-life value for zolpidem on day 32, the fifth consecutive dose of zolpidem in the presence of fluoxetine (Allard et al, 1998).

b) The Washington Poison Center reports that they received five different calls from patients experiencing hallucinations after concurrent use of zolpidem and antidepressant medication. Four of the five reports came from patients taking serotonin reuptake inhibitors in addition to zolpidem. The antidepressant medications being taken were desipramine, fluoxetine, sertraline, venlafaxine, and bupropion. In each case, the hallucinatory activity lasted longer than one hour, but the patients' symptoms resolved without further sequelae. The authors concluded that the mechanism by which zolpidem might cause hallucinations has not been firmly established (Elko et al, 1998).

3.5.1.IP Zomepirac

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).

b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.IQ Zotepine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Fluoxetine has been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Prozac(R), 2001l). Even though no formal drug interaction studies have been done, the coadministration of antipsychotics and other drugs known to prolong the QTc interval, including fluoxetine, is not recommended. Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999), quetiapine (Owens, 2001b), sertindole (Agelink et al, 2001), sultopride (Lande et al, 1992), and zotepine (Sweetman, 2003).

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of fluoxetine and antipsychotics is not recommended.

7) Probable Mechanism: additive effects on QT prolongation

4.0 Clinical Applications

Monitoring Parameters

Patient Instructions

Place In Therapy

Mechanism of Action / Pharmacology

Therapeutic Uses

Comparative Efficacy / Evaluation With Other Therapies

4.1 Monitoring Parameters

A) Fluoxetine Hydrochloride

1) Therapeutic

a) ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD)

1) Reduction in 3 essential features consistent with ADHD:

a) Inappropriate inattention (manifested as inability to finish tasks, listening, easily distracted, difficulty at concentrating with schoolwork or other tasks).

b) Impulsivity (which may be manifested as acting or engaging in dangerous activities before thinking, shifting from activity to activity, difficulty in organizing work, requiring significant supervision, calling out in class frequently, difficulty awaiting a turn in games or group situations.

c) Hyperactivity (evident by excessive running about or climbing, difficulty sitting still or staying seated, excessive movement, talks excessively)

2) Improvement in cognitive performance (i.e., reading, memory and mathematical skills)

3) All children should receive a drug-free trial every year.

b) BULIMIA

1) Reduction or resolution of signs/symptoms associated with bulimia (binge eating, purging episodes, inconspicuous eating, frequent weight swings, suicide attempts, kleptomania, laxative/diuretic abuse, and associated medical complications).

c) DEPRESSION

1) Improvement in target symptoms associated with depression (depressed mood, suicidal thoughts or intent, change in appetite, lack of energy, change in sleep patterns, lack of pleasure/interest in usual activities, feeling of excessive guilt/worthlessness, psychomotor retardation or agitation, difficulties in thinking/concentration/memory).

d) NARCOLEPSY

1) Reduction in daytime sedation with sleep attacks

2) Reduction in fatigue, impaired performance

3) Improved night time sleep

4) Resolution/improvement of cataplexy (characterized by muscle weakness and/or paralysis, sleep paralysis, and hypnagogic hallucinations)

e) PANIC ATTACKS

1) Reduction or resolution of signs/symptoms consistent with panic disorder (dyspnea, palpitations, dizziness, trembling, sweating, choking, nausea, paresthesias, depersonalization, hot and/or cold flashes, chest pain or discomfort, fear of dying, or experiencing an uncontrolled feeling).

f) POSTTRAUMATIC STRESS DISORDER

1) Reduction or resolution of flashbacks, recollections, and dreams of the traumatic event.

2) Reduction or resolution of sleep disturbances, outbursts of anger, hypervigilance, emotional numbing, guilt, inability to concentrate, and the physiological reaction (e.g., sweating) upon re-exposure to the event (e.g., nightmare).

g) OBSESSIVE-COMPULSIVE DISORDER

1) Reduction or resolution of recurrent and persistent impulses, ideas or thoughts that are intrusive and senseless.

2) Reduction or resolution of repetitive and intentional behaviors performed in response to obsessive thoughts.

h) PREMENSTRUAL SYNDROME

1) Reduction or resolution of signs/symptoms associated with premenstrual syndrome (i.e., tension, irritability, dysphoria, fatigue, anxiety, crying, depression, restlessness, craving for sweet/salty foods, binge eating, headache).

i) SOCIAL PHOBIA

1) Reduction or resolution of fear (may be manifested as nervousness, nausea, sweating, headaches) surrounding social encounters

j) TRICHOTILLOMANIA

1) Reduction or resolution of alopecia and hair pulling

2) Toxic

a) Monitor patients receiving antidepressants for worsening of depression, suicidality, or unusual changes in

behavior especially at the initiation of therapy or when the dose increases or decreases. Such monitoring should include at least weekly face-to-face contact with patients or their family members or caregivers during the initial 4 weeks of treatment, then visits every other week for the next 4 weeks, then at 12 weeks, and then as clinically indicated beyond 12 weeks. Families and caregivers should be advised of the need for close observation (i.e., daily observation) of patients and communication with the prescriber (US Food and Drug Administration, 2004; Anon, 2004). .
b) Patients who experience symptoms of anxiety, agitation, panic attacks, insomnia, irritability, hostility, impulsivity, akathisia, hypomania, or mania may be at an increased risk for worsening depression or suicidality. If these symptoms are observed, therapy should be re-evaluated and it may be necessary to discontinue medications when symptoms are severe, sudden in onset, or were not part of the patient's initial symptoms (US Food and Drug Administration, 2004; Anon, 2004).
c) Psychosis, hypomania or mania, hallucinations, euphoria, akathisia or ataxia
d) Seizures
e) Suicidal ideation
f) SIADH/hyponatremia
g) Sexual dysfunction (anorgasmia/delayed orgasm, inhibited ejaculation, and impotency)
h) Visual disturbances may develop and require withdrawal of therapy

4.2 Patient Instructions

A) Fluoxetine (By mouth)

Fluoxetine

Treats depression, obsessive compulsive disorder (OCD), eating disorders, and panic disorders. Sarafem® treats premenstrual dysphoric disorder (PMDD), which is mood disorders and physical symptoms that occur 1 to 2 weeks before a woman's menstrual period. This medicine is a selective serotonin reuptake inhibitor (SSRI).

When This Medicine Should Not Be Used:
You should not use this medicine if you have had an allergic reaction to fluoxetine, or if you are also using pimozide. You should not use this medicine if you have used an MAO inhibitor (MAOI) such as Eldepryl®, Marplan®, Nardil®, or Parnate® within the past 14 days. Do not take an MAO inhibitor or thioridazine while you are using this medicine and for at least 5 weeks after you stop taking this medicine.

How to Use This Medicine:
Capsule, Delayed Release Capsule, Tablet, Liquid
Your doctor will tell you how much of this medicine to use and how often. Your dose may need to be changed several times in order to find out what works best for you. Do not use more medicine or use it more often than your doctor tells you to.Some people need to take this medicine every day, and some people need to take it only once a week. Make sure you understand your own schedule.
You may need to take this medicine for up to 4 weeks before you start feeling better.
Measure the oral liquid medicine with a marked measuring spoon, oral syringe, or medicine cup.
You may take this medicine with or without food. Take your medicine at the same time each day.
Swallow the delayed-release capsule whole. Do not crush, break, or chew it.
This medicine should come with a Medication Guide. Read and follow these instructions carefully. Ask your doctor or pharmacist if you have any questions. Ask your pharmacist for the Medication Guide if you do not have one. Your doctor might ask you to sign some forms to show that you understand this information.

If a Dose is Missed:
For people who take this medicine every day (Prozac® or Sarafem®): If you miss a dose or forget to take your medicine, take it as soon as you can. If it is almost time for your next dose, wait until then to take the medicine and skip the missed dose. Do not use extra medicine to make up for a missed dose.
For people who take this medicine once a week (Prozac® Weekly): If you miss a dose or forget to take your medicine, take it as soon as you can. Then go back to your regular schedule the next week. Do not use extra medicine to make up for a missed dose.

How to Store and Dispose of This Medicine:
Store the medicine in a closed container at room temperature, away from heat, moisture, and direct light.
Ask your pharmacist, doctor, or health caregiver about the best way to dispose of any leftover medicine after you have finished your treatment. You will also need to throw away old medicine after the expiration date has passed.
Keep all medicine away from children and never share your medicine with anyone.

Drugs and Foods to Avoid:
Ask your doctor or pharmacist before using any other medicine, including over-the-counter medicines, vitamins, and herbal products.
Make sure your doctor knows if you are using alprazolam (Xanax®), diazepam (Valium®), digoxin (Lanoxin®), flecainide (Tambocor®), linezolid (Zyvox®), St. John's wort, sumatriptan (Imitrex®), tramadol (Ultram®), tryptophan, vinblastine, medicine for seizures (such as carbamazepine, phenytoin, Dilantin®, or Tegretol®), or a blood thinner (such as warfarin or Coumadin®).

Tell your doctor if you are using other medicines to treat depression (such as amitriptyline, desipramine, doxepin, imipramine, lithium, nortriptyline, pimozide, Orap®, Pamelor®, or Sinequan®), medicine to treat mental illness (such as clozapine, haloperidol, Clozaril®, or Haldol®), or a medicine called flecainide (Tambocor®) for heart rhythm problems.
Make sure your doctor knows if you are also using any pain or arthritis medicines, sometimes called "NSAIDs" (such as aspirin, ibuprofen, naproxen, Advil®, Aleve®, Bextra®, Celebrex®, Ecotrin®, or Motrin®).
Also tell your doctor if you have used an MAO inhibitor such as Eldepryl®, Marplan®, Nardil®, or Parnate® within the past 14 days.
Tell your doctor if you are using any medicines that make you sleepy. These include sleeping pills, cold and allergy medicine, narcotic pain relievers, and sedatives.
Do not drink alcohol while you are using this medicine.

Warnings While Using This Medicine:
Make sure your doctor knows if you are pregnant, planning to become pregnant, or breastfeeding. Tell your doctor if you have seizures, diabetes, heart disease, liver disease, hyponatremia (low sodium in the blood), bleeding problems, manic disorder, or recent heart attack.
For some children, teenagers, and young adults, this medicine can increase thoughts of suicide. Tell your doctor or your child's doctor right away if you or your child start to feel more depressed and have thoughts about hurting yourselves. Report any unusual thoughts or behaviors that trouble you or your child, especially if they are new or get worse quickly. Make sure the doctor knows if you or your child have trouble sleeping, get upset easily, have a big increase in energy, or start to act reckless. Also tell the doctor if you or your child have sudden or strong feelings, such as feeling nervous, angry, restless, violent, or scared. Let the doctor know if you, your child, or anyone in your family has bipolar disorder (manic-depressive) or has tried to commit suicide.
Do not stop using this medicine suddenly without asking your doctor. You may need to slowly decrease your dose before stopping it completely.
If you develop a skin rash, even a mild one, stop taking this medicine and call your doctor right away.
This medicine may make you dizzy or drowsy. Avoid driving, using machines, or doing anything else that could be dangerous if you are not alert.
Your doctor will need to check your progress at regular visits while you are using this medicine. Be sure to keep all appointments.

Possible Side Effects While Using This Medicine:
Call your doctor right away if you notice any of these side effects:
Allergic reaction: Itching or hives, swelling in your face or hands, swelling or tingling in your mouth or throat, chest tightness, trouble breathing.
Blistering, peeling, red skin rash.
Change in how much or how often you urinate.
Chest pain, pounding or uneven heartbeat.
Confusion, weakness, and muscle twitching.
Dry mouth, increased thirst, muscle cramps, nausea, or vomiting.
Feelings of intense anxiety, agitation, or irritability.
Fever, chills, body aches, or weakness.
Painful, prolonged erection of your penis.
Unusual bleeding, bruising, or weakness.
Vomiting blood or something that looks like coffee grounds.

If you notice these less serious side effects, talk with your doctor:
Changes in appetite with weight gain or loss.
Decreased interest in sex.
Dry mouth, sore throat, or yawning more than usual.
Ear pain or ringing in your ears.
Headache.
Nausea, diarrhea, constipation, or upset stomach.
Nervousness, shakiness, or sweating.
Trouble having sex.
Trouble sleeping.

If you notice other side effects that you think are caused by this medicine, tell your doctor.

4.3 Place In Therapy

A) SUMMARY

1) Fluoxetine has received approval by the United States Food and Drug Administration for treating bulimia nervosa, depression, obsessive compulsive disorder, and premenstrual dysphoria. Fluoxetine has also been evaluated in numerous other psychiatric disorders.

B) DEPRESSION

1) All of the selective serotonin reuptake inhibitors (SSRIs) are effective for treating depression although selected characteristics of each agent may offer greater benefit in some patients. Fluoxetine differs from other

SSRIs with regard to its pharmacokinetic profile; it has a longer half-life partly due to the extremely long half-life of its active metabolite. In comparative clinical trials with other SSRIs, fluoxetine had a slower onset of antidepressant action than other agents. Compared to other SSRIs, fluoxetine does NOT appear to have a higher incidence of most adverse effects. Fluoxetine is not the first choice of an antidepressant for severely depressed patients because it has a slower onset of action than other agents. If it was used previously and was effective in these patients, a higher starting dose may be tried. Also, fluoxetine may NOT be the best agent for patients with agitation. However, fluoxetine may be especially useful in poorly compliant patients or in patients who previously experienced withdrawal reactions. Ultimately, the selection of an SSRI is dependent on clinical judgement and response of patients to previous therapy (Edwards & Anderson, 1999).

2) Fluoxetine is as effective for treating typical or endogenous depression as the tricyclic antidepressants (TCAs) and is comparable to clomipramine for obsessive-compulsive behavior. Advantages of fluoxetine over the TCAs include minimal anticholinergic effects, lack of orthostatic hypotension, minimal sedation, and no association with prolonged cardiac conduction time. The disadvantages of this agent compared to the TCAs are induction of nervousness or anxiety, insomnia, gastrointestinal disturbances, and headaches. Fluoxetine has been noted to induce weight loss, which may be an advantage or disadvantage depending on the circumstances. The drug may be especially beneficial in geriatric patients due to a low incidence of postural hypotension and a lack of cardiovascular effects. Its single or twice daily dosing may improve compliance in some patients. Seizures do not appear to be a problem with therapeutic doses.

3) Preliminary data suggest that a trial of a second serotonin reuptake inhibitor (SSRI) is a viable clinical alternative in depressed patients who have failed to respond to an adequate trial to the first SSRI used. In a retrospective review of 55 patients who had failed to respond to at least five weeks of therapy with either fluoxetine, sertraline, fluvoxamine, or paroxetine (all at therapeutic dosages), 51% did respond to a trial of an alternative agent. The choice of the second agent was based on clinician preference; no difference between response rates of the different drugs was noted (Joffe et al, 1996).

4.4 Mechanism of Action / Pharmacology

A) MECHANISM OF ACTION

1) Fluoxetine is a "second-generation" antidepressant agent which is a specific inhibitor of serotonin reuptake (Stark et al, 1985). The chemical structure of fluoxetine differs from that of tricyclic antidepressants (Chouinard, 1985); the drug is a non-tricyclic compound with the chemical name of N-methyl-3-phenyl-3(alpha, alpha, alpha-trifluoro-p-tolyl)-oxy-propylamine hydrochloride (Bremner, 1984).

2) Fluoxetine has been demonstrated to be a specific inhibitor of serotonin uptake in vitro and in vivo in man and animals (Lemberger et al, 1978; Lemberger et al, 1978a; Wong et al, 1974; Fuller et al, 1977; Stark et al, 1985; Lemberger et al, 1987) while producing little effect on the noradrenergic system (Wong et al, 1975; Lemberger et al, 1978; Wong et al, 1974; Stark et al, 1985; Fuller & Wong, 1987). The drug has been shown to have little affinity for muscarinic, histaminic H1, serotonergic 5-HT1 or 5-HT2, or noradrenergic alpha-1 or alpha-2 receptors (Stark et al, 1985; Lemberger et al, 1987). Fluoxetine is reportedly 100 times more potent as an inhibitor of serotonin uptake than norepinephrine or dopamine uptake in in vitro studies; inhibition of serotonin uptake has occurred in vivo without affecting norepinephrine uptake (Stark et al, 1985). The drug has minimal anticholinergic and antihistaminic effects.

3) The inhibition of serotonin uptake produced by fluoxetine correlates with plasma concentrations. Doses of 20 to 30 mg daily for 7 days in healthy volunteers produced a 65% inhibition of serotonin uptake into platelets, which correlated with fluoxetine plasma concentrations of 55 ng/mL; endogenous serotonin content of platelets had decreased from 100% to 70% after 7 days of treatment. With doses of 20 to 30 mg daily for 28 days, 80% inhibition of serotonin uptake into platelets was observed, corresponding to plasma levels of 80 ng/mL; corresponding endogenous serotonin content at 28 days had decreased by 80% (Lemberger et al, 1985a).

4) Evidence for serotonin deficiency in depressive disorders stems primarily from 1) measurement of decreased serotonin levels in brain samples from postmortem depressed patients, 2) measurement of a decrease in the serotonin metabolite (5-hydroxyindoleacetic acid) in CSF prior to and after probenecid in depressed patients, and 3) demonstration of benefits of administration of 5-hydroxytryptophan, or drugs that increase serotonin concentrations in the synaptic cleft (MAO inhibitors) (Stark et al, 1985; van Praag, 1983).

B) REVIEW ARTICLES

1) A comparison of selective serotonin reuptake inhibitors with a guide to selection is provided (Edwards & Anderson, 1999a).

2) Two reviews provide a discussion of the efficacy of selective serotonin reuptake inhibitors and other antidepressants for treatment of severe depression (Schatzberg, 1999; Hirschfeld, 1999).

3) The efficacy of antidepressants in reducing panic attack frequency, symptoms of depression, social avoidance, and overall impairments from panic disorder is addressed (den Boer, 1998).

4) A review article described the treatment of panic disorder, including the place of selective serotonin reuptake inhibitors for this disorder (DeVane, 1997).

5) Treatment of elderly patients with selective serotonin reuptake inhibitors is discussed with emphasis on improved tolerability compared to other antidepressants (Skerritt et al, 1997).

6) A review article discussed the rational treatment of depression and included a discussion of each class of antidepressants (Cohen, 1997).

7) Pharmacologic comparisons of the various selective serotonin reuptake inhibitors and their potential therapeutic distinctions were provided in a review (Finley, 1994).

8) Drug-interactions of antidepressants are reviewed in German language (Zapotoczky & Simhandl, 1995).

4.5 Therapeutic Uses

Fluoxetine

Fluoxetine Hydrochloride

4.5.A Fluoxetine

Anorexia nervosa

Cataplexy - Narcolepsy

4.5.A.1 Anorexia nervosa

See Drug Consult reference: ANOREXIA NERVOSA - DRUG THERAPY

4.5.A.2 Cataplexy - Narcolepsy

See Drug Consult reference: NARCOLEPSY AND CATAPLEXY - DRUG THERAPY

4.5.B Fluoxetine Hydrochloride

Alcoholism - Depression

Anorexia nervosa

Anxiety disorder of childhood

Attention deficit hyperactivity disorder

Autistic disorder

Bipolar disorder; Adjunct

Body dysmorphic disorder

Bulimia nervosa

Cancer - Depression

Cerebrovascular accident, Mortality

Cerebrovascular accident, Post

Cerebrovascular accident, Post - Depression

Chronic fatigue syndrome

Depersonalization disorder

Depression - Diabetes mellitus

Depression - HIV infection

Diabetic neuropathy

Dysthymia

Fibromyalgia

Headache

Hot sweats

Huntington's disease

Major depressive disorder

Myocardial infarction; Prophylaxis

Obesity

Obsessive-compulsive disorder

Panic disorder

Picking own skin

Postpartum depression

Posttraumatic stress disorder

Premature ejaculation

Premenstrual dysphoric disorder

Raynaud's phenomenon

Schizophrenia; Adjunct

Seasonal affective disorder

Severe major depression with psychotic features

Slow channel syndrome

Social phobia

Tinnitus

Trichotillomania

Vasovagal syncope; Prophylaxis

4.5.B.1 Alcoholism - Depression

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

In a small study, fluoxetine was significantly better than placebo for relieving symptoms of major depression associated with alcohol dependence.

c) Adult:

1) In a 12-week study of patients (n=51) with major depression and alcohol dependence, fluoxetine resulted in a significantly greater improvement in depression and a reduction in alcohol consumption compared to placebo. Fluoxetine demonstrated significant improvement on the 24-item Hamilton Rating Scale for Depression (HAM-D-24) but not the Beck Depression Inventory (BDI) compared to placebo; however, differences for the HAM-D-24 and BDI were significant from baseline to study completion for fluoxetine. All parameters of alcohol consumption showed significant improvement with fluoxetine compared to placebo. Patients were randomly assigned to placebo or fluoxetine 20 milligrams (mg) daily which could be titrated to 40 mg daily. Fluoxetine was tolerated well; no patient left the study due to adverse effects. Additional large studies are needed to assess the long-term efficacy of fluoxetine in a less severely depressed population of alcoholics (Cornelius et al, 1997).

4.5.B.2 Anorexia nervosa

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Ineffective
Recommendation: Adult, Class III
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Ineffective in the treatment of patients with anorexia nervosa (n=93) following weight restoration during a randomized, double-blind trial (Walsh et al, 2006)
Ineffective during a small (n=31), placebo-controlled trial when added to a structured psychological and behavioral program (Attia et al, 1998)

c) Adult:

1) Results from a randomized, double blind study failed to demonstrate any benefit of fluoxetine over placebo in the treatment of patients with anorexia nervosa following weight restoration. Prior to randomization, patients (mean age, 23 +/- 4.6 years; mean body mass index (BMI), 15.4 +/-1.8 kilograms/square meter (kg/m(2)); mean length of illness, 56.5 +/-44.7 months) received inpatient or intensive outpatient treatment and were eligible to participate in the study once they regained weight to a minimum BMI of 19 kg/m(2). Patients were then randomized to an initial dose of fluoxetine 20 milligrams (mg) (n=49) or placebo (n=44) orally daily. The dose of fluoxetine was increased to 60 mg daily over 1 week and could be further increased to 80 mg daily if the patient's clinical status deteriorated. Patients were treated on an outpatient basis for up to 1 year. All patients received cognitive behavioral therapy. The primary outcome measure was time-to-relapse. Approximately 57% of patients dropped out of the study early, with similar completion rates in each arm (p=0.98). The mean fluoxetine dose at the end of the study was 63.5 +/- 15.8 mg daily. In the most conservative analysis of time-to-relapse, which classified all patients who terminated early as having relapsed, there was no significant difference between fluoxetine and placebo (p=0.64). Less conservative analyses led to similar results. The percentage of patients who maintained a BMI of at least 18.5 kg/m(2) and remained in the study for 1 year was 26.5% and 31.5% for fluoxetine and placebo, respectively (p=0.57). When treatment was terminated prematurely, there were no significant differences between patients with regard to BMI or psychological state. At the end of the study, 45% and 43% of the fluoxetine and placebo groups, respectively, had not relapsed (Walsh et al, 2006).

2) In a small, placebo-controlled study (n=31), fluoxetine was no more effective than placebo for patients with anorexia nervosa who were also receiving inpatient psychological and behavioral therapy. The initial dose of fluoxetine was 20 milligrams (mg) daily which was increased over 1 week to 60 mg daily. At 7 weeks (study end-point), the mean dose of fluoxetine and placebo was 56 and 58.7 mg/day, respectively. Therapy was tolerated well. Results of this study are similar to others which used antidepressants for anorexia nervosa. All of the studies were similar with regard to small sample size, short duration, and addition to behavior therapy. None of the studies have addressed the issue of whether antidepressants are better than placebo if behavior therapy is omitted (Attia et al, 1998).

4.5.B.3 Anxiety disorder of childhood

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Pediatric, Evidence is inconclusive
Recommendation: Pediatric, Class IIb
Strength of Evidence: Pediatric, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Fluoxetine 10 to 60 milligrams/day was effective in the treatment of overanxious disorder, social phobia, or separation anxiety disorder in an analysis of twenty-one patients ages 11 to 17 years of age (Birmaher et al, 1994).

4.5.B.4 Attention deficit hyperactivity disorder

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive

Recommendation: Adult, Class III
Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:
In a single, uncontrolled, trial (n=22), fluoxetine showed some benefit in attention deficit hyperactivity disorder (ADHD) as assessed by both global clinical impressions and parent questionnaires. However, up to one-third of all patients experienced side effects during treatment. Larger studies with better patient controls will be needed to assess the usefulness of fluoxetine in this condition (Barrickman et al, 1991).

4.5.B.5 Autistic disorder

a) Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category C
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:
The efficacy of fluoxetine for treating idiopathic autism in children has been demonstrated in a long-term trial

c) Pediatric:
1) Twenty-two of 37 children with idiopathic autism experienced improvements in behavior (mood and temperament), social skills, language, cognition, and adaptive skills when treated in an open-label trial with fluoxetine. In these patients, the ideal dose of fluoxetine ranged from 0.2 milligrams/kilogram/day (mg/kg) to 1.4 mg/kg/day for a mean duration of 21 months. Improvements were measured through various tests and through the observations of those who dealt with the patient on a regular basis. Eleven children were considered to have an excellent response, 11 had a good response, and 15 had no long-term improvements. Fluoxetine was discontinued in those children not responding due to the development of hyperactivity, agitation, and lethargy. Discontinuation of fluoxetine was also attempted in responders; however, regression generally followed. A strong correlation existed between those responding positively to treatment with fluoxetine and those with a family history of major affective disorders. Those that had responded previously remained on fluoxetine for over 1 year and were still demonstrating improvements. After completion of the initial study 31 additional patients were treated with fluoxetine. An additional 4 patients had an excellent response to fluoxetine therapy (22% of the overall 68 patients), an additional 22 patients had a good response (49%), and an additional 5 patients had no long-term improvement (29%). Fluoxetine was found to be an effective treatment option for idiopathic autism in 71% of the total 68 patients studied (DeLong GR, Teague LA & Kamran MM, 1998).

4.5.B.6 Bipolar disorder; Adjunct

a) Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class III
Strength of Evidence: Adult, Category C
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:
Twice weekly dosing overcame depression without inducing mood switching in a single case

c) Adult:
1) Twice weekly dosing with fluoxetine overcame depression in a 59-year-old woman with type I bipolar disorder without causing mood switching. In a manic state and with psychotic behaviors, the woman was hospitalized and treated with lithium 600 milligrams (mg) twice daily, olanzapine 5 mg at bedtime, and clonazepam 0.5 mg twice daily. She became calmer and rational and reported that she had been depressed. On hospital day 12, she was given fluoxetine 10 mg each morning, while continuing the other medications. Twenty-two days later she was diagnosed as manic. Fluoxetine was reduced to 10 mg twice weekly. Her manic symptoms rapidly subsided. She remained euthymic thereafter. At 13 days after the reduction of fluoxetine, her fluoxetine blood concentration was less than 20 micrograms per liter; norfluoxetine was 53 micrograms per liter. At discharge 60 days after admission, her medications were oral lithium 600 mg twice daily, oral olanzapine 5 mg at bedtime, oral clonazepam 1 mg at bedtime, and oral fluoxetine 10 mg every Monday and Thursday. At 9-month follow-up, she remained euthymic (Megna & Devitt, 2001).

4.5.B.7 Body dysmorphic disorder

a) Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:
Fluoxetine was safe and more effective than placebo in the treatment of body dysmorphic disorder

c) Adult:

1) In a 12-week, double-blind, placebo controlled study, fluoxetine was more effective than placebo in the treatment of body dysmorphic disorder (BDD). After establishing the diagnosis of BDD, patients were divided into matched fluoxetine (n=34) and placebo groups (n=33). Study participants in the active treatment group received fluoxetine 20 milligrams (mg) daily for two weeks and an additional 20 mg per day every 10 days as tolerated to a maximum of 80 mg per day. At eight weeks of treatment there was a statistically significant (p less than 0.001) decrease in the Yale-Brown Obsessive Compulsive Scale modified for BDD (BDD-YBOCS) score of 35% versus 14% for the fluoxetine (54% response rate) and placebo groups, (18% response rate) respectively. Treatment outcome was not affected by the presence of personality disorder, obsessive-compulsive disorder, depression, or BDD severity or duration. There was also no difference in response between delusional and non-delusional patients to fluoxetine, but delusional patients were less likely to respond to placebo. The mean dose of fluoxetine by study end was 78 mg/day (range 20-80 mg/day) and the mean response time was 7.7 weeks (range 2 to 12 weeks). Drowsiness and stomach/abdominal discomfort were the only adverse effects that occurred significantly more frequently with fluoxetine treatment (Phillips et al, 2002).

4.5.B.8 Bulimia nervosa

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes; Pediatric, no
Efficacy: Adult, Effective; Pediatric, Evidence is inconclusive
Recommendation: Adult, Class IIa; Pediatric, Class IIb
Strength of Evidence: Adult, Category B; Pediatric, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Indicated for the treatment of binge-eating and vomiting behaviors in patients with moderate to severe bulimia nervosa (Prod Info PROZAC(R) oral pulvule, oral solution, oral tablet, oral delayed-release capsule, 2005)

Fluoxetine is effective in the treatment of bulimia; beneficial effects may be seen as early as one week after initiation of therapy

In a small, open-label study, fluoxetine therapy reduced symptoms of bulimia nervosa in pediatric patients

c) Adult:

1) Continued fluoxetine treatment, relative to placebo treatment, was associated with a significant reduction of relapse in patients who had responded acutely to treatment with fluoxetine for bulimia nervosa. Patients with DSM-IV diagnosis of bulimia nervosa, purging type, who showed a 50% or greater reduction in vomiting episodes during at least 1 of the last 2 weeks of 8 weeks of acute treatment with fluoxetine (60 milligrams (mg) per day) were regarded as responders and were entered into a 52-week randomized, double-blind study to observe relapse rates. Relapse was defined as a return to baseline frequency of vomiting for 2 consecutive weeks. Of the 150 responders (65% of the original 232 participants), 76 continued to receive fluoxetine 60 mg/day and 74 received placebo. The fluoxetine group had fewer relapses in the first 3 months (p less than 0.04). Thereafter, the difference between the groups remained at 14% to 18% but was not statistically significant due to the high attrition rates. By the end of 52 weeks, 33% of the fluoxetine group and 51% of the placebo group had relapsed. Among fluoxetine-treated patients, there was no difference in relapse rates between depressed and non-depressed patients. Statistically significant differences favoring fluoxetine were observed for vomiting episodes, binge-eating episodes, Clinical Global Impression (CGI) severity and improvement scores, and the Yale-Brown-Cornell Eating Disorder Scale total score. The rate of discontinuation because of adverse events was similar for the 2 groups. In the first 3 months, 8 patients of the fluoxetine group and 15 of the placebo group discontinued because of poorer than expected efficacy (Romano et al, 2002).

2) Addition of medication to psychological therapy resulted in greater improvement in binge eating, vomiting, and depression than psychological therapy alone (Walsh et al, 1997). In this complex study, patients (n=120) meeting criteria for bulimia nervosa and using self-induced vomiting were randomly assigned to the following treatments: (1) cognitive-behavioral therapy with placebo; (2) cognitive-behavioral therapy with medication; (3) supportive psychotherapy with placebo; (4) supportive psychotherapy with medication; or (5) medication alone. Patients receiving medication began treatment with desipramine with titration to 300 milligrams/day, if tolerated. Patients with intolerable side effects or a less than 75% decrease in binge eating were switched to fluoxetine 60 mg/day; 74% of patients received fluoxetine. Major study results were: (1) Cognitive-behavioral therapy was more effective than supportive psychotherapy; (2) Cognitive-behavioral therapy plus medication was more effective than medication alone; and (3) Use of a stepped approach to drug therapy improved the benefit of medication. Limitations of this study are a short evaluation period, inability to maintain blinding due to differences in drug side effects, and reliability of patient reporting.

3) Fluoxetine 60 to 80 milligrams/day was effective in the treatment of BULIMIA nervosa in an uncontrolled study involving 10 patients (Freeman & Hampson, 1987).

4) Among obese subjects treated with fluoxetine and behavior modification, those classified as binge-eaters lost half the weight lost by those who were not so classified at the end of the year-long trial; this difference was not statistically significant (Marcus et al, 1990).

d) Pediatric:

1) Fluoxetine therapy was effective in the treatment of pediatric patients with bulimia nervosa. In a small, prospective, open-label study, ten female patients, 12 to 18 years of age (mean age, 16.2 years), with bulimia nervosa (n=8) or eating disorder not otherwise specified (n=2) received fluoxetine 60 milligrams (mg)/day (initial, 20 mg/day, titrated to 60 mg/day by day 7) for 8 weeks with concurrent psychotherapy. From baseline to week 8, the mean number of weekly binges was significantly reduced from 4.1 to 0 (p less than 0.01) and the mean number of weekly purges decreased from 6.4 to 0.4 (p less than 0.005). Significant improvements were also observed for several other outcome measures, including the Eating Attitudes Test, Eating Disorder Inventory, and the Self-report For Childhood Anxiety Related Disorders (p less than 0.05, all values). Body mass index, body weight, and scores for the Body Shape Questionnaire and Beck Depression Inventory were not significantly changed from baseline to week 8 (p=ns). Clinical Global Impression-Improvement Scale scores were "much improved" for 2 patients, "improved" for 5 patients, and "slightly improved" for 3 patients. Fluoxetine was generally well tolerated. The most common adverse events included headache (n=4), drowsiness (n=4), difficulty falling asleep (n=5), and difficulty staying asleep (n=4) (Kotler et al, 2003).

4.5.B.9 Cancer - Depression

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Possibly effective in improving quality of life and reducing depressive symptoms in cancer patients

c) Adult:

1) The results of one study suggest that fluoxetine therapy may be effective in improving quality of life and reducing depressive symptoms in patients with advanced cancer. In a randomized, double-blind, placebo-controlled study, patients (n=163) with advanced incurable malignancies and at least minimal depressive symptoms received fluoxetine (20 milligrams once daily in the morning) or placebo for 12 weeks. Quality of life (measured via the Functional Assessment of Cancer Therapy-General (FACT-G) scale) and depression (assessed via the Brief Zung Self-rating Depression Scale (BZSDS)) were measured at baseline and every 3 to 6 weeks. Fluoxetine-treated patients showed statistically significant improvements in scores for both the FACT-G (p=0.05) and the BZSDS (p=0.0005) as compared with placebo however, clinically significant improvements (defined as a 6-point difference in best-change score) between groups were not found. Vomiting was more commonly reported by patients taking fluoxetine (33%) as compared with placebo (4.6%) (Fisch et al, 2003).

4.5.B.10 Cerebrovascular accident, Mortality

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Antidepressant treatment given during the first six months following stroke increased long-term survival in depressed and non-depressed patients

c) Adult:

1) Treatment with nortriptyline or fluoxetine during the first six months following stroke significantly increased long-term survival in depressed and non-depressed patients. In a randomized, double-blind, placebo-controlled study, patients (n=104) who had suffered a stroke within the previous 6 months received fluoxetine (initial, 10 milligrams (mg)/day, titrated to 40 mg/day over 9 weeks), nortriptyline (initial, 25 mg/day, titrated to 100 mg/day over 6 weeks), or placebo for 12 weeks. According to the intent-to-treat analysis, significantly more patients treated with an antidepressant were alive at 9 years follow-up as compared with patients who received placebo (59.2% vs 36.4%, respectively; p=0.03). Of patients who completed the full 12- week treatment period (n=81), 67.9% of antidepressant-treated patients and 35.7% of placebo-treated patients were alive at the 9-year follow- up (p=0.005). The likelihood of long-term survival was higher for patients who received antidepressant therapy as compared with placebo for both depressed and non-depressed patients (p=0.02, both values). Of the 50 patients that died during the 9-year follow-up, the percentage of deaths attributable to vascular causes (ie, cardiovascular disease and recurrent stroke) was significantly higher in patients given placebo as compared to patients who received antidepressant therapy (87.8% vs 35.3%, respectively, p=0.0005) (Jorge et al, 2003).

4.5.B.11 Cerebrovascular accident, Post

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class III
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Improved motor performance after stroke reported in a limited number of patients
In a limited number of patients, fluoxetine was effective for post-stroke emotionalism

c) Adult:

1) A single dose of fluoxetine 20 milligrams, in comparison to placebo, was associated with cerebral activation and improved motor performance in 8 patients with single ischemic lacunar infarction and resultant pure motor hemiplegia. The increase in cerebral activation was localized in the sensorimotor cortex contralateral to the paralysis. Decreases in activation occurred in other areas, including the cerebellum bilaterally and the contralesional caudate nucleus. Improvement in motor performance was evident in speed of execution of specific muscle movements and in strength. Also, improvement in task performance with practice was evident with fluoxetine and not with placebo (Pariente et al, 2001).

2) Fluoxetine reduced post-stroke emotionalism in 8 of 9 patients compared to none of the control patients (Brown et al, 1998). Twenty patients with emotionalism of greater than 4 weeks duration were randomly assigned to fluoxetine 20 milligrams daily or placebo for 10 days. One patient receiving fluoxetine stopped treatment due to a generalized rash. Ratings on the modified Lawson and MacLeod scale and patient self-rating scale were significantly lower in the fluoxetine than placebo group (p=0.011; p=0.049). By day 10, a 50% reduction in the frequency of emotional outbursts was reported by 8 of 9 fluoxetine-treated patients and 0 of 10 placebo-treated patients.

3) Within a few months of a stroke, two Chinese patients developed pathologic crying which improved rapidly after starting fluoxetine 10 or 20 milligrams (mg) daily. The first patient reported 2 months of uncontrollable crying spells which were not associated with depression. On the fifth day of fluoxetine treatment, the crying spells ceased and did not return during 4 months of therapy. The second patient also denied depression and responded to fluoxetine within 1 week. Since fluoxetine and other selective serotonin reuptake inhibitors have been effective for this disorder, an abnormality of the serotonin system or partial destruction of the serotonergic raphe nuclei in the brain stem are possibly associated with this disorder (Low & Chong, 1998).

4.5.B.12 Cerebrovascular accident, Post - Depression

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

FLUOXETINE may prevent post-stroke depression

c) Adult:

1) Based on a randomized, double-blind trial (n=48), a 12-week course of oral FLUOXETINE or NORTRIPTYLINE appeared to provide effective prophylaxis against depression in non-depressed patients within 6 months onset of acute stroke (either thromboembolic or hemorrhagic); however, there was a tendency for depression to develop after the course of fluoxetine or nortriptyline was finished, especially in nortriptyline- treated subjects. Subjects were followed for 21 months after the 3- month treatment period. FLUOXETINE-treated subjects (n=17) were given daily doses of 10 milligrams (mg) for the first 3 weeks (wk), 20 mg (wk 4 to 6), 30 mg (wk 7 to 9), and 40 mg (wk 10 to 12). NORTRIPTYLINE- treated subjects (n=15) received daily doses of 25 mg (wk 1), 50 mg (wk 2 to 3), 75 mg (wk 4 to 6), and 100 mg (wk 7 to 12). Nortriptyline- treated patients received therapeutic drug monitoring to maintain serum levels at 50 to 120 mg/milliliter. Dosages were reduced if side effects developed, which happened for 6 subjects (2 fluoxetine, 4 nortriptyline). Assessments were made using the Present State Exam (PSE) and the Hamilton Depression scale (Ham-D). During the 12-wk treatment period, no cases of major depression were reported. Minor depression occurred in 3 (20.0%) of fluoxetine-treated subjects, 1 (7.7%) nortriptyline-treated subject, and 5 (33.3%) placebo-treated subjects. Two of three depressed fluoxetine-treated subjects dropped out before completing 3 months of therapy. For those who completed 3 months of treatment, the rate of depression was significantly higher in the control group compared with a combined fluoxetine-nortriptyline group (5 of 15 versus 2 of 26; p=0.036). Six months after treatment ended, rates of depression were higher in the combined active treatment group compared with controls (p=0.047). No significant between-group differences were seen at 1 and 2 years. Using time-by-treatment analysis, Ham-D scores were lower in the active group compared with the placebo group during months 0 to 3 (p=0.026). For months 3 to 9, Ham-D scores were significantly declining in the nortriptyline group compared with controls (p=0.022) and were trending lower in the fluoxetine group (p=0.09 versus placebo). After 1 year and 2 years, no significant differences were seen across the 3 groups. The authors emphasized that patients treated

prophylactically with nortriptyline post-stroke need careful monitoring, and might be helped by a longer course of therapy or a more gradual withdrawal of the drug (Narushima et al, 2002).

4.5.B.13 Chronic fatigue syndrome

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Ineffective
Recommendation: Adult, Class III
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Despite earlier case reports of efficacy of fluoxetine in the treatment of chronic fatigue syndrome, a randomized, controlled trial of fluoxetine in both depressed and non-depressed chronic fatigue syndrome patients demonstrated no beneficial effect. Patients were treated with fluoxetine 20 mg daily for a period of 8 weeks. None of the symptoms of chronic fatigue syndrome, including fatigue, depression, functional impairment, sleep disturbances, cognitions, and physical activity, improved in either the depressed or non-depressed subgroup (Vercoulen et al, 1996).

4.5.B.14 Depersonalization disorder

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

In a case report, fluoxetine relieved chronic symptoms of depersonalization.

c) Adult:

1) A 27-year-old man with a 10-year history of depersonalization, depression, and anxiety with panic attacks noted marked improvement in symptoms 2 to 3 months after starting fluoxetine 20 milligrams (mg) daily. Alprazolam 0.5 mg 3 times daily was started a few months before fluoxetine but only decreased the frequency of panic attacks. Previous treatment with imipramine and psychotherapy was ineffective. Alprazolam 0.25 mg and fluoxetine 20 mg daily were continued for 2 years with complete remission of depersonalization and panic attacks; depression also improved (Ratliff & Kerski, 1995).

4.5.B.15 Depression - Diabetes mellitus

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Fluoxetine is effective for reducing the severity of depression in diabetic patients

c) Adult:

1) Fluoxetine was more effective than placebo for management of major depression in patients with comorbid diabetes in an 8-week, randomized, placebo-controlled, double-blind trial. Sixty patients with diabetes who were 21 to 65 years of age were randomized to placebo or fluoxetine 20 milligrams (mg) daily in the morning. Fluoxetine could be increased to a maximum of 40 mg daily depending on side effects and clinical response. The Beck Depression Inventory (BDI) and Hamilton Rating Scale for Depression (HAMD) were used to assess the severity of depression and improvement. Glycemic control was monitored by glycosylated hemoglobin (GHb). Of the 60 patients enrolled, 54 (90%) completed 8 weeks of treatment. Fluoxetine-treated patients demonstrated significantly lower mean posttreatment scores on the BDI and the HAMD compared with placebo-treated patients (BDI, 9.6 versus 13.6, respectively, p=0.03; HAMD, 9.4 versus 14.1, respectively, p=0.01). The percentage of patients with significant clinical improvement measured by the BDI was greater with fluoxetine than placebo (66.7% versus 37%, respectively, p=0.03). Although fluoxetine- treated patients demonstrated a greater reduction in mean GHb levels compared with the placebo group, the difference was not statistically significant (-0.40% versus -0.07%, respectively, p=0.13). Depression remission per HAMD was observed in 43.3% of the fluoxetine group compared with 23.3% of the placebo group, although the difference was not significant (p=0.09). Fluoxetine was generally well tolerated (Lustman et al, 2000).

4.5.B.16 Depression - HIV infection

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Depression improved in 78% of women with HIV

c) Adult:

1) In an 8-week, open trial, 14 of 18 women had a clinical response as measured by the Hamilton Rating Scale for Depression (HAM-D) and the Clinical Global Impressions Severity and Improvement scale (CGI). Thirty women began treatment but only 18 completed the trial. Treatment consisted of fluoxetine 20 milligrams (mg) per day or sertraline 50 mg per day if the patient refused fluoxetine. From baseline to week 8, the total HAM-D score (24 to 9; p less than 0.0001) and total Beck Depression Inventory (28 to 13; p less than 0.0001) decreased significantly. Five patients discontinued treatment due to side effects primarily anxiety, overstimulation, or insomnia. The response rate in this study was similar to other studies that included HIV-seropositive men or the 1 study that included HIV-seropositive women (Ferrando et al, 1999).

2) Fluoxetine was safe and effective for treating depression in men who were human immunodeficiency virus (HIV) seropositive and were treated with 1 or more antiretroviral agents primarily zidovudine. All patients (n=47) in this study received weekly supportive group psychotherapy and were randomly assigned to blinded treatment with placebo or fluoxetine 20 milligrams (mg) daily with titration to a maximum dose of 60 mg daily. Thirty-seven (79%) patients completed the 7-week study; withdrawal rates were similar between treatments. Significant reductions in the Hamilton Rating Scale for Depression (HAM-D; p less than 0.05) and Beck Depression Inventory (p less than 0.01) occurred in the fluoxetine compared to the placebo group. A 50% reduction in the HAM-D score occurred in 64% and 23% of patients treated with fluoxetine and placebo, respectively. Adverse effects were frequent in both treatment groups; however, only 1 patient in the placebo group and no patients receiving fluoxetine left the study due to an adverse effect (Zisook et al, 1998).

4.5.B.17 Diabetic neuropathy

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class III
Strength of Evidence: Adult, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

The following case report suggests that, like tricyclic antidepressants, fluoxetine may have a role in treating painful diabetic neuropathy, and that it offers a more favorable adverse effect profile for some patients

c) Adult:

1) The case of a 31-year-old woman with autonomic and peripheral neuropathy secondary to insulin-dependent diabetes mellitus and major depression is reported. Previous therapy with trazodone and tricyclic antidepressants had been unsatisfactory due to drug-induced exacerbations of orthostatic hypotension and urinary retention. Fluoxetine treatment was begun using a low dose (5 milligrams) for seven days, then titrated by 5 milligrams/day every three to four days until 20 milligrams/day was reached; after another week, titration continued in the same manner to a daily dose of 40 milligrams. The patient reported decreased pain in her extremities while on 5 milligrams/day and showed continued improvement for three weeks. During this same hospitalization, her depression improved, though not as quickly as her neuropathic symptoms. The patient complained of excessive sweating on the dose of 20 milligrams/day; this adverse effect decreased with confined use of fluoxetine. After seven months without pain on 40 milligrams fluoxetine/day, the patient's pain and depression returned, accompanying deterioration in her disease state. A dosage increase to 60 milligrams/day was quickly followed by pain relief, and later followed by improvement of her depression. More research is needed into the use of fluoxetine for analgesia (Theesen & Marsh, 1989).

4.5.B.18 Dysthymia

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIa
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Small, uncontrolled clinical studies have shown that fluoxetine improves dysthymia in adult and elderly patients. Larger, controlled clinical trials are needed for this indication.

c) Adult:

1) In a study of patients with primary dysthymia, fluoxetine resulted in significant improvement in clinical and social functioning compared to placebo; non-responders also showed improvement with an increase in fluoxetine dose. Patients showing a response at 3 months continued fluoxetine 20 milligrams (mg)/day for an additional 3 months. If a response was NOT evident, the dosage of fluoxetine was increased to 40 mg/day, and placebo-treated patients received fluoxetine 20 mg/day for the

remaining 3 months of the study. At the 6-month evaluation, initial responders were still improved; 50% of non-responders also showed improvement with the higher dose of fluoxetine or after treatment with fluoxetine. Adverse effects were similar in incidence and affected body system between the treatments. This is 1 of the few studies to include an adequate sample (n=140), blinding of treatment assessment, a reasonable duration of treatment, randomization, and a placebo control; however, maintenance of blinding was questionable during the last 3 months of the study, and the sample size was smaller due to exclusion of 37 patients from 1 center who had an exceptional response to fluoxetine. Additional longer, comparative studies are still needed to assess the efficacy of long-term fluoxetine for treating dysthymia (Vanelle et al, 1997).

2) Fluoxetine 20 to 60 milligrams/day has demonstrated efficacy in primary dysthymia (Ravindran et al, 1994). Though this was a non-controlled observation, an overall response rate of 73.1% was reported with subaffective-type dysthymia patients exhibiting a better clinical response to drug therapy than those with character spectrum dysthymia (77% versus 25%, respectively). Full efficacy of fluoxetine treatment for dysthymia may not be seen for a period of 16 weeks (Albert & Ebert, 1996).

3) FLUOXETINE (mean dose, 35.5 milligrams/day) was also effective in a group of elderly patients with dysthymic disorder. Outcome criteria were based on a 50% reduction in Hamilton Rating Scale for Depression (HAM-D) score, final HAM-D score less than 8, and a Clinical Global Impression score of 1 or 2 which was interpreted as very much or much improved. Although this was a relatively small study population (n=20), 60% of patients responded. Further controlled studies are needed to evaluate fluoxetine efficacy for this indication (Nobler et al, 1996).

4.5.B.19 Fibromyalgia

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Reduced pain and physical impairment due to fibromyalgia

c) Adult:

1) Fluoxetine reduced pain and improved physical function in women with fibromyalgia. In a randomized, double-blind, placebo- controlled trial, 60 women meeting criteria of the American College of Rheumatology for fibromyalgia were given placebo or fluoxetine in individualized doses for 12 weeks. Subjects were also allowed to continue taking non-steroidal antiinflammatory drugs (NSAIDs) and acetaminophen on their usual schedules. Fluoxetine was started at 20 milligrams/day for the first 2 weeks. If that dose was not tolerated, it was reduced to 20 mg every other day. After the first 2 weeks, the dose could be titrated to a maximum of 80 mg/day by 2-week increments of 10 to 20 mg. The average dose of subjects completing the 12-week study was 55 mg/day. Changes in total scores from baseline to end-of-study on the Fibromyalgia Impact Questionnaire (FIQ) were significantly better for the fluoxetine group than for the placebo group (p=0.005). Pain scores also improved more in the fluoxetine group than in the placebo group (p=0.002). Improvement of 25% or more on total FIQ scores or pain scores were considered clinically meaningful. Total scores were improved by 25% or more in 32% of the fluoxetine group and 15% of the placebo group (p=0.19); pain scores improved by 25% or more in 56% of the fluoxetine group and 15% of the placebo group (p=0.003). There was no significant difference between groups in change in tender-point score. The most common adverse events reported for fluoxetine were headache, insomnia, sedation, and nausea (Arnold et al, 2002).

4.5.B.20 Headache

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Fluoxetine has shown modest efficacy for treating chronic daily headache
Fluoxetine lacks efficacy for treating migraine
S-fluoxetine is more effective than placebo in the prevention of migraine headache

c) Adult:

1) In a double-blind trial, S-fluoxetine was more effective than placebo in the prophylaxis of migraine. Following a 1-month placebo period (n=49), patients were randomized to receive 40 milligrams (mg) nightly of S-fluoxetine (a dose equivalent to 80 mg of the marketed racemic fluoxetine) or placebo for 3 months. The primary outcome measure was the 28-day frequency of migraine attacks. Patients treated with active drug experienced a 52% (1.7 attacks/28 days) decline in the frequency of attacks and those receiving placebo experienced a 27% (1.1 attacks/28 days) decline in the frequency of attacks. The differences in the frequency of attacks between the 2 treatment groups were statistically significant in month 2 (n=39) and month 4 (n=33) only. An equivalent number of patients discontinued the study due

to adverse events and inadequacy of response in both treatment groups. S-fluoxetine was, therefore, well-tolerated. Due to the decrease in sample size, absolute conclusions of the efficacy of S-fluoxetine in the prophylaxis of migraine must be made with caution (Steiner et al, 1998).

2) Fluoxetine 20 to 40 mg/day was moderately effective in the treatment of chronic daily headache, but was not effective in the treatment of migraine headache. In this study, patients with chronic daily headache (n=64) and migraine headache (n=58) were randomly assigned to fluoxetine or placebo for a three month period. Fluoxetine was initially given as a dose of 20 mg/daily and advanced to 40 mg/daily after one month depending on patient response; the majority of patients required 40 mg. Overall headache status, headache-free days, and investigator judgment were the three determinants of effectiveness. Chronic daily headache sufferers did note significant improvement on the three scales which became apparent after the third month of treatment with fluoxetine. Mood improvement was a major determinant of headache improvement (Saper et al, 1994).

4.5.B.21 Hot sweats

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Modestly reduced frequency and severity of hot flashes in women with a history of breast cancer

c) Adult:

1) Fluoxetine treatment modestly reduced the frequency and severity of hot flashes in women who could not take hormones because of a history of breast cancer or perceived high risk of breast cancer. In a double-blind, randomized, cross-over trial, 68 women experiencing at least 14 hot flashes per week were given fluoxetine 20 milligrams (mg) per day orally or placebo for 4 weeks and then switched to the opposite treatment for 4 weeks. Hot flash scores (severity times frequency) were reduced at least 75% (in comparison to baseline scores) in 24% of patients taking fluoxetine in the first treatment period and in 11% of those taking placebo. Hot flash scores were increased in 27% of patients receiving fluoxetine and 23% receiving placebo. Crossover data showed a trend for greater improvement in hot flash severity with fluoxetine treatment (p=0.055). Adverse events were similar with the 2 treatments except for more mouth dryness with fluoxetine. Patients reported less trouble sleeping while taking fluoxetine (Loprinzi et al, 2002).

4.5.B.22 Huntington's disease

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class III
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Fluoxetine did NOT significantly improve total functional capacity (TFC) over 4 months in non-depressed patients with Huntington's Disease (HD).

c) Adult:

1) Thirty patients were randomly assigned to receive placebo or fluoxetine 20 milligrams/day; however, 5 fluoxetine-treated and 2 placebo-treated patients dropped out before the 2 month assessment. Baseline TFC scores were 9.2 and 9.7 (indicating high functional capacity) in the fluoxetine and placebo treatment groups, respectively. At 4 months, the TFC score improved by an average of 0.25 and 0.09 points in the fluoxetine and placebo group, respectively; this is compared to an expected decline of 0.7 over 1 year in most patients with HD. Patients with obsessive behaviors as a component of their disease showed some improvement; however, this must be tested in a controlled clinical trial. The lack of statistically significant improvement in this trial is due to the small sample size which allows only detection of large changes in TFC (Como et al, 1997).

4.5.B.23 Major depressive disorder

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes; Pediatric, yes ((8 years and older))
Efficacy: Adult, Effective; Pediatric, Effective
Recommendation: Adult, Class IIa; Pediatric, Class IIb
Strength of Evidence: Adult, Category B; Pediatric, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Indicated for the treatment of major depressive disorder (Prod Info PROZAC(R) oral pulvule, oral solution, oral tablet, oral delayed-release capsule, 2005)
Effective in placebo-controlled studies using doses from 20 to 80 mg daily (Wernicke et al, 1987;

Rickels et al, 1986; Stark & Hardison, 1985; Fabre & Crismon, 1985)
Similar onset of antidepressant effect to amitriptyline and imipramine (Chouinard, 1985; Cohn & Wilcox, 1985; Bremner, 1984)

c) Adult:

1) SINGLE-AGENT THERAPY

a) A retrospective review of 12 adult patients treated in an outpatient clinic, showed that once-weekly dosing of fluoxetine (90 milligrams (mg) was effective in the treatment of mild to severe depression. All patients were treatment-naive and had an average decrease of 4.6 points on the Hamilton Depression Rating Scale after 12 weeks of therapy (Kabinoff et al, 2002).

b) In a 3-month open label study of 39 outpatients, weekly administration of enteric-coated fluoxetine was effective and well tolerated in the short-term management of depression. Thirty-one patients stabilized on daily fluoxetine were converted to a single weekly dose of 90 milligrams (mg) to 540 mg; one patient required twice-weekly dosing. Seven previously untreated, symptomatic patients were started on fluoxetine 90 mg per week and achieved remission of symptoms before their first monthly appointment. No serious adverse events or hospitalizations were reported. The once-weekly capsule releases 291 micromoles of fluoxetine over 7 days (roughly equivalent to 13 mg released per day). Patients previously receiving fluoxetine 20 mg daily were converted to a 180 mg weekly dosage. At doses similar to usual maintenance doses, all patients remained in remission throughout the study period. The authors suggested that a delayed release, enteric-coated formulation of fluoxetine may provide a convenient alternative in patients requiring long-term treatment for depression (Boungiorno, 2002).

c) Of 106 patients with major depression, who did not respond to sertraline, 67 responded to fluoxetine suggesting that a trial of a second selective serotonin reuptake inhibitor (SSRI) is warranted in unresponsive patients (Thase et al, 1997). Fluoxetine therapy was initiated with 20 milligrams(mg)/day and increased to 60 mg/day as required. At the conclusion of the trial, 36.8%, 40.6%, and 22.6%, respectively, of patients were receiving fluoxetine 20 mg, 40 mg, or 60 mg per day. Scores for the Hamilton Rating Scale for Depression, the primary efficacy measure, showed a 50% decrease which was statistically significant (p less than 0.05). The incidence and severity of common SSRI-induced adverse effects (ie, headache, insomnia, nausea) were NOT higher than expected in patients with prior intolerance to sertraline; however, peripheral edema, myalgia, and pruritus were more common in patients intolerant to sertraline. Randomized, comparative studies are needed to further assess whether a second SSRI is warranted for treating patients who were unresponsive to the first SSRI.

2) COMBINATION THERAPY

a) The combination of clonazepam and fluoxetine was more effective than placebo and fluoxetine for initial treatment of depression. Eighty patients were randomly assigned to receive fluoxetine 20 milligrams (mg) daily plus placebo or fluoxetine 20 mg daily plus clonazepam 0.5 mg at bedtime with an increase to 1 mg at day 4, if needed. Clonazepam and placebo were gradually tapered between days 21 and 33; the dose of fluoxetine could be increased to 40 mg daily at day 42. Scores on the Hamilton depression scale were significantly (p less than 0.001) lower at day 21 for clonazepam and fluoxetine versus placebo and fluoxetine; however, 1 week after discontinuing clonazepam, there was NOT a significant difference between treatment groups. Combination therapy also resulted in more patients with a greater than 50% decrease in the Hamilton depression scale and greater overall improvement on the physician and patient Clinical Global Impression improvement score at day 21. After discontinuing clonazepam, scores on the Hamilton depression scale rose and then decreased to the lowest score by day 56 of treatment. Reasons for using clonazepam augmentation include a decrease in the anxiety and insomnia components of the illness and a possible decrease in the stimulating side effects of fluoxetine. Although combination therapy appeared safe and effective, the presence of confounding factors require careful interpretation (Smith et al, 1998).

b) The efficacy of fluoxetine in treating depression may be enhanced by coadministered pindolol, according to a 6-week randomized, double-blind study (Perez et al, 1997). Overall, 41 of 55 patients (75%) administered fluoxetine 20 milligrams/day with pindolol 7.5 milligrams/day responded to treatment compared with 33 of 56 patients (59%) given fluoxetine and placebo (p=0.04). Drug efficacy measured by decreases in Hamilton Rating Scale for Depression scores and Montgomery-Asberg Depression Rating Scale scores also favored the fluoxetine-pindolol group (p=0.04 and p=0.02, respectively). Patients administered concomitant fluoxetine and pindolol did not experience adverse side effects. The advantage of the combination therapy may relate to pindolol's action in blocking the decrease in serotonergic neural activity caused by selective serotonin reuptake inhibitors (SSRIs), thus enhancing therapeutic effects of the SSRI.

3) MAINTENANCE THERAPY

a) Once-weekly dosing of fluoxetine with the enteric-coated 90- milligram (mg) formulation was effective for maintaining response in patients who had been treated successfully with daily citalopram, paroxetine, or sertraline. In an open-label study, 246 patients who had responded to citalopram 20 to 40 mg/day (n=83), paroxetine 20 mg/day (n=77), or sertraline 50 to 100 mg/day (n=86) were switched to weekly fluoxetine for 12 weeks. Seventy-nine percent of patients successfully completed treatment; 9.3% discontinued treatment because of relapse/lack of efficacy, and 4.9% because of an adverse event. There were no significant increases in depression scores

for any previous-therapy group and there were no significant differences for efficacy among the groups. Statistically significant improvements in general mental health, role limitations due to emotional problems, and vitality were seen for all previous-therapy groups. Treatment-emergent adverse events that occurred in 10% or more of patients included rhinitis, headache, nervousness and insomnia. Diarrhea was the only adverse event showing a difference among previous-therapy groups: 6% each of citalopram group and the sertraline group and 13% of the paroxetine group experienced diarrhea. The incidence of diarrhea in the paroxetine group decreased as time progressed. At the end of the study, 85% of patients preferred the once-weekly fluoxetine treatment to daily treatment with their previous drug (Miner et al, 2002).

b) In a small, double blind, placebo-controlled trial, once weekly fluoxetine, 60 milligrams (mg), was as effective as fluoxetine 20 mg per day or placebo during the continuation phase of major depressive disorder (MDD). Patients with unipolar MDD, who responded to fluoxetine 20 mg daily for 7 weeks, were randomly enrolled into one of three groups: fluoxetine 20 mg daily, fluoxetine 60 mg weekly, or placebo. The fluoxetine groups showed less depressive symptomatology than the placebo group during the 7-week continuation phase, but the difference was not statistically significant. The authors suggest that the placebo response may be due to carry over effects from norfluoxetine following the initial 7 weeks of treatment or due to too short of a continuation phase in this study to determine actual relapse rates. Norfluoxetine serum concentrations for the 60 mg weekly group were approximately 50% of that of found in the fluoxetine 20 mg daily group, leading the authors to suggest that higher weekly doses may be needed (Burke & McArthur-Miller, 2001).

c) A once-weekly formulation of enteric-coated fluoxetine is safe, effective and well tolerated for the long term treatment of depression in patients who responded to 20 milligrams (mg) per day of fluoxetine for acute treatment. Nine hundred thirty-two patients with major depression were treated with fluoxetine 20 mg daily in a thirteen week, open-label phase trial. Patients who responded to acute treatment were randomly assigned to one of three groups in a 25-week, multicenter, placebo-controlled, double-blind, randomized continuation treatment phase. The treatment groups for the continuation phase were as follows: (1) 25 weeks of treatment with 90 mg enteric-coated fluoxetine once weekly (n=190), (2) 25 weeks of treatment with 20 mg fluoxetine daily (n=189), and (3) 25 weeks of placebo (n=122). Patients receiving fluoxetine 90 mg weekly or fluoxetine 20 mg per day showed significantly lower relapse rates than placebo. No significant difference in efficacy was shown between the two groups receiving active drug. The safety profile of the weekly dosing was similar to that of the daily dosing with nervousness and thinking abnormal (ie, impaired concentration or thought process) significantly more frequent in the former group. It was concluded that long-term treatment with once weekly dosing of enteric-coated fluoxetine is effective, safe, and well tolerated for patients responding to 20 mg per day of fluoxetine for acute treatment (Schmidt et al, 2000). The use of fluoxetine 90 milligram (mg) enteric-coated tablets once weekly was associated with increased compliance compared to 20 milligrams of regular release fluoxetine once daily (85.9% versus 79.4%, respectively) in a 12-week, open-label, randomized trial (n=109) (Claxton et al, 2000).

d) Treatment of major depression with fluoxetine for at least 38 weeks has demonstrated efficacy in preventing relapse. Eight hundred and thirty-nine patients with major depression were treated with 20 milligrams (mg) daily of fluoxetine in a 12 to 14 week open-label phase of this trial. Patients experiencing remission (ie, no longer met DSM-III-R criteria for major depression) following this phase were then randomized to one of 4 treatment groups in a 50-week, double-blind, long-term therapy phase. The treatment groups for the long-term phase were as follows: (1) 50 weeks of placebo therapy (n=96), (2) 14 weeks of fluoxetine therapy followed by 36 weeks of placebo (n=97), (3) 38 weeks of fluoxetine followed by 12 weeks of placebo (n=100), and (4) 50 weeks of fluoxetine (n=102). The primary outcome measure was the relapse rate following the 12 week open-label phase of the trial. Patients treated with fluoxetine after the open-label phase of the trial were less likely to experience relapse than those who had received placebo for 50 weeks. This difference, however, was only statistically significant for patients receiving an additional 14 weeks or 38 weeks of fluoxetine treatment. Relapse rates for those treated with a total of 38 weeks with fluoxetine were the lowest. It was, therefore, concluded that optimal therapy to prevent relapse entails 12 initial weeks, followed by at least 26 additional weeks. Due to analysis methods, researchers were uncertain whether therapy with fluoxetine beyond a total of 38 weeks may actually be of greater benefit than demonstrated here in preventing relapse (Reimherr et al, 1998).

d) Pediatric:

1) SINGLE-AGENT THERAPY

a) In an 8-week, placebo-controlled study, fluoxetine was more effective than placebo for treating major depressive disorder in children and adolescents (Emslie et al, 1997a). After a 4-week evaluation phase, patients were randomly assigned to receive placebo or fluoxetine 20 milligrams (mg) daily. Physician assessment using the Clinical Global Impression (CGI) scale and Children's Depression Rating Scale-Revised (CDRS-R) demonstrated statistically significant improvement for fluoxetine compared to placebo; 56% versus 33% of patients treated with fluoxetine and placebo improved on the CGI scale. Drop-outs occurred primarily due to lack of efficacy (19 - placebo, 7 - fluoxetine) but 4 fluoxetine- and 1 placebo-treated patient left the study due to side effects. Fluoxetine produced mania in 3 patients and a severe rash in another. In this study, fluoxetine was effective for the short-term treatment of depression in children; however, confirmation in another

study and long-term evaluation are needed.

2) COMBINATION THERAPY

a) Compared with fluoxetine alone, cognitive-behavioral therapy (CBT) alone, or placebo, fluoxetine combined with CBT improved outcome and reduced suicidal thinking in a randomized controlled trial involving 439 patients between the ages of 12 to 17 years with a primary diagnosis of major depressive disorder. Patients were randomized to fluoxetine 10 to 40 milligrams/day (mg/d), CBT alone, CBT with fluoxetine 10 to 40 mg/d, or placebo for 12 weeks. Outcomes were measured using a Children's Depression Rating Scale-Revised total score and a Clinical Global Impressions improvement score. Compared with placebo, fluoxetine with CBT was statistically significant on the Children's Depression Rating Scale-Revise (p=0.001). Fluoxetine with CBT was superior to fluoxetine alone (p=0.02) and CBT alone (p=0.01) as well. Fluoxetine alone was also superior to CBT alone (p=0.01). Response rates for fluoxetine with CBT were 71% (95% confidence (CI), 62% to 80%); fluoxetine alone, 60.6% (95% CI, 51% to 70%); CBT alone, 43.2% (95% CI 34% to 52%); and placebo, 34.8% (95% CI, 26% to 44%). Fluoxetine alone and fluoxetine with CBT were statistically superior to CBT alone and placebo on the Clinical Global Impressions improvement responder analysis. Suicidal thinking improved significantly in all 4 treatment groups. The greatest reduction occurred with fluoxetine plus CBT (p=0.02 compared to placebo) (Treatment for Adolescents With Depression Study (TADS) Team, 2004).

4.5.B.24 Myocardial infarction; Prophylaxis

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class III
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

May confer a protective effect against first MI

c) Adult:

1) In a case-control study comprised of 653 cases of first myocardial infarction (MI) and 2990 control subjects, results indicated that selective serotonin reuptake inhibitors (SSRIs) may confer a protective effect against first MI. The subjects in this study were smokers, between the ages of 30 to 65 years, with a first MI hospitalized between September 1995 and December 1997. The four SSRIs investigated in this study were fluoxetine, fluvoxamine, paroxetine, and sertraline; doses taken by participants were not stated. The odds ratio of patients who were taking SSRIs having a first MI compared to controls (after adjustment for potential confounders) was 0.35 (95% CI 0.18, 0.68; p less than 0.01). The authors suggested that this effect was possibly attributable to an inhibitory effect on serotonin-medicated platelet activation or amelioration of other factors associated with increased risk for MI in depression (Sauer et al, 2001).

4.5.B.25 Obesity

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Fluoxetine 20 to 80 milligrams/day was effective for promoting weight loss in non-depressed patients, but patients tended to regain weight after fluoxetine was stopped (Levine et al, 1987; Ferguson & Feighner, 1987). The drug has been as effective as benzphetamine (Ferguson & Feighner, 1987). Optimal doses appear to be 60 to 80 milligrams daily.

c) Adult:

1) Patients treated with fluoxetine who completed the trial lost significantly more weight than those in the placebo group. Although at year's end fluoxetine subjects who were classified as binge eaters had lost half the weight lost by the fluoxetine subjects who were not so classified, this difference was not statistically significant. Follow-up data obtained for 15 of the subjects who completed the study showed that, 3 to 6 months later, former fluoxetine subjects had regained significantly more weight than former placebo subjects. Fluoxetine and placebo were compared in a double-blind trial of 45 obese subjects (Marcus et al, 1990). Twenty-one patients completed the year-long program, which included behavior modification instruction (provided primarily during the first 20 weeks) and treatment with placebo or 60 mg of fluoxetine daily. Compliance was assessed by means of pill counts at each of 13 clinic visits and by determination of plasma levels of fluoxetine and norfluoxetine at 3 of the visits. Larger studies are needed to confirm and elucidate the differential effects of fluoxetine on binge- and non-binge-eaters.

2) Therapy with fluoxetine resulted in statistically significant weight loss to week 28; however, at the end of the study period, there was no difference between fluoxetine and placebo. The efficacy of fluoxetine 60 milligrams/day versus placebo in promoting weight loss was evaluated in a 52 week multicenter trial (Goldstein et al, 1994). Study sites that demonstrated the greatest benefit with

fluoxetine also utilized nutrition and behavior counseling.

4.5.B.26 Obsessive-compulsive disorder

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes; Pediatric, yes ((7 years and older))
Efficacy: Adult, Effective; Pediatric, Effective
Recommendation: Adult, Class IIa; Pediatric, Class IIa
Strength of Evidence: Adult, Category B; Pediatric, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Indicated for the treatment of obsessions and compulsions in patients with obsessive-compulsive disorder (OCD), defined as obsessions or compulsions that cause marked distress, are time-consuming, or significantly interfere with social or occupational functioning (Prod Info PROZAC(R) oral pulvule, oral solution, oral tablet, oral delayed-release capsule, 2005).

c) Adult:

1) Of the selective serotonin reuptake inhibitors (SSRIs) (ie, fluoxetine, sertraline, paroxetine, fluvoxamine) with U.S. Food and Drug Administration approval for treating OCD, all are effective. Limited clinical studies also suggest that the SSRIs are comparable to clomipramine; however, results of a meta-analysis found that clomipramine may be more effective than the SSRIs (Flament & Bisserbe, 1997; Leonard, 1997). Selection of initial treatment is often based on the side effect profile of the individual drug; in general, the SSRIs are tolerated better than clomipramine (Leonard, 1997). Early studies used near maximal doses of an SSRI which resulted in a high incidence of adverse effects; however, initial low doses with gradual dose adjustment result in a good response in some patients and better tolerance in most (Leonard, 1997). While the optimal duration of treatment has NOT been defined, most patients require long-term treatment. A few small studies have shown relapse rates between 65% and 90% when pharmacologic treatment was stopped (Rasmussen & Eisen, 1997). Patients who do NOT respond to 10 to 12 weeks of maximum doses of an SSRI and/or behavioral therapy are considered refractory to treatment. In about 20% of this group, a trial of a second SSRI will be effective. In the remaining patients, augmentation therapy with haloperidol or clonazepam may be beneficial (Rasmussen & Eisen, 1997).

2) Fluoxetine produced beneficial effects on the time spent obsessing, time spent ritualizing, the SCL-5 obsessive-compulsive disorder subscale, and therapists' global ratings; obsessive thought frequency and compulsive rituals improved slightly, but not to a significant degree. Improvement in overall distress, depression, and anxiety was also observed. In a single-blind trial, 10 patients meeting the DSM-III criteria for obsessive-compulsive disorder were treated with fluoxetine 20 to 80 milligrams daily (Turner et al, 1985). Patients with psychosis, organic brain pathology or primary depression were excluded from the trial.

3) There are at least four cases where combined therapy with clomipramine and fluoxetine was effective in the treatment of obsessive-compulsive disorder where patients were previously unresponsive to singular therapy, in most cases to both agents (Browne et al, 1993). None of the cases mentioned showed evidence of excess serotonin stimulation, despite both agents having potent effects on serotonin.

4) In a report of 72 patients in an ongoing study of over 150 outpatients with obsessive-compulsive disorder, depressed and non-depressed subgroups experienced significant improvements on at least one of two assessments of obsessive-compulsive disorder at 4, 8, and 12 weeks of fluoxetine therapy, compared to baseline (Jenike et al, 1989). Although baseline depression scores were found not to predict the improvements in these scales, overall scores on the depression inventory used did decline significantly at 8 and 12 weeks. The favorable results need to be considered in light of the uncontrolled nature of the study and the fact that 11 patients from an original group of 72 dropped out, primarily due to adverse effects or noncompliance. This study used initial doses of fluoxetine 20 milligrams/day, titrated upward as tolerated to a maximum of 80 milligrams/day; the mean maximal dose was 75 milligrams/day. Doses above 20 milligrams/day were divided (not necessarily evenly) into morning and afternoon allotments.

5) In a one-year open study using 50 patients with obsessive-compulsive disorder unresponsive to, or intolerant of, other antidepressants, 86% of subjects experienced significant improvements on a variety of psychiatric assessment scales. Although the authors stated that subjects had shown no evidence of spontaneous remissions before the trial, they noted that only 23% of fluoxetine-responsive patients who discontinued therapy after the trial relapsed with the same symptoms. The favorable results should be interpreted in light of the fact that fluoxetine doses were rapidly escalated from 20 milligrams/day to 60 to 100 milligrams/day (undivided) over approximately one week, and outcomes were reported only for assessments made after 12 months. Also, 7 patients of an original group of 57 dropped out of the study but were not counted as treatment failures (Fontaine & Chouinard, 1989a).

6) Fluoxetine-treated patients experienced significant improvements (compared to baseline) on a variety of assessments made at 5 monthly intervals after study entry. Weight also decreased significantly for 4 months. An open trial of fluoxetine was performed in 75 outpatients with obsessive-compulsive disorder (Levine et al, 1989). Fluoxetine was titrated from an initial daily dose of 20 milligrams/day to 80 milligrams/day by the end of the second month in most patients. This study may be

criticized for using successively smaller numbers of patients in analyses of results after 2 months, since patients entered the 5-month study at different times. Also, 11 subjects dropped out of the study by the end of their first month, and dropouts continued at a rate of up to 10% per month thereafter.

d) Pediatric:

1) In a retrospective evaluation of 20 children and 18 adolescents with obsessive compulsive disorder (OCD), fluoxetine 1 mg/kg/day (mean dose, 50 mg) effectively improved symptoms of OCD in 74% of patients. Prepubertal and postpubertal subjects responded similarly and a clinical response was maintained over a follow up period averaging 19 months (Geller et al, 1995).

2) In a group of 11 children (ages 10 to 18 years) with obsessive-compulsive symptoms in association with Tourette's syndrome, fluoxetine at a dosage of 20 to 40 milligrams/day was associated with decreased tic severity, and improvement in attention abilities and social functioning (Kurlan et al, 1993). Scores on measures of obsessive-compulsive symptoms, however, showed some improvement, but were not statistically different from placebo.

3) Fluoxetine produced a therapeutic response in 50% of subjects (2 of 4 with primary obsessive compulsive disorder, and 3 of 6 with Tourette's syndrome in addition). Fluoxetine was used for 4 to 20 weeks in an open-label study of 10 children and adolescents with obsessive compulsive disorder (with or without Tourette's syndrome) (Riddle et al, 1990). All responders were receiving 20 mg fluoxetine each day. The subjects ranged in age from 8 to 15 years. Nine subjects were started on a regimen of 20 mg fluoxetine each day; one received 20 mg every other day (reason not stated). One subject's dose was increased after 3 weeks to 40 mg each day.

4.5.B.27 Panic disorder

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes; Pediatric, no
Efficacy: Adult, Effective
Recommendation: Adult, Class IIa
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Fluoxetine is indicated for the treatment of panic disorder, with or without agoraphobia (Prod Info PROZAC(R) oral pulvule, oral solution, oral tablet, oral delayed-release capsule, 2005)

c) Adult:

1) Fluoxetine (20 to 60 milligrams daily) was shown to be effective in the treatment of panic disorder, with or without agoraphobia, in two 12-week, randomized trials. At study endpoint, the fluoxetine-treated groups had a statistically significantly greater percentage of patients who were free from panic attacks as compared to the placebo groups. Response rates were 42% vs 28% and 62% vs 44% for the fluoxetine and placebo groups, respectively for the first and second studies (Prod Info PROZAC(R) oral pulvule, oral solution, oral tablet, oral delayed-release capsule, 2005).

2) Fluoxetine was useful for treating panic disorder in a 10-week study (Michelson et al, 1998). In a double-blind study, 243 patients with confirmed panic disorder were randomly assigned to placebo, fluoxetine 10 milligrams (mg) daily, or fluoxetine 20 mg daily for 10 weeks with the option for continuing therapy for an additional 24 weeks. Fluoxetine 20 mg compared to placebo resulted in a significant reduction in the Clinical Global Impression improvement scores as assessed by physicians (p=0.02) and patients (p=0.006). Patients treated with fluoxetine 10 mg but not 20 mg daily experienced a significant reduction in total panic attack frequency compared to placebo. Other assessment parameters including the Phobia rating scale score (p=0.01), Hamilton depression scale (p=0.007), Hamilton anxiety scale (p=0.002), Phobic avoidance (p=0.002), anticipatory anxiety (patient-rated, p=0.002), and overall functioning (p=0.08) also showed significant improvement primarily with fluoxetine 20 mg but for some assessments, improvement also occurred with fluoxetine 10 mg. Discontinuation due to adverse effects was similar for all treatment groups. Fluoxetine was effective and tolerated well for treatment of panic disorder.

3) Weekly fluoxetine prevented recurrence of panic attacks in 9 of 10 patients. Ten patients who met DSM-III-R criteria for panic disorder were treated with daily fluoxetine 10 to 40 milligrams/day until control was achieved. Patients were then switched to fluoxetine weekly at the same dose as was used daily with titration to a higher dose if needed. Six of 10 patients required a higher weekly than daily dose (range, 10 to 60 milligrams/week). Only 1 patient had a recurrence of panic disorder 18 months after the switch to weekly therapy. The remaining patients have remained panic attack free for periods of 1 to 26 months. Based on results of this open trial, a controlled clinical trial is needed to further evaluate weekly fluoxetine for panic disorder (Emmanuel et al, 1999).

4) Fluoxetine up to 80 milligrams daily was effective in the treatment of panic attacks in 7 of 16 patients in an open study (Gorman et al, 1987a). Mean doses in the responding patients were 27 mg daily (range, 10 to 70 mg daily). Response was observed after the 6th week of treatment, with the mean time to achieve a complete panic-free state for 4 successive weeks being 10.8 weeks. Side effects were minimal in responding patients; however, 8 of 9 nonresponders developed intolerable side effects (jitteriness, restlessness, diarrhea, and insomnia); these side effects occurred with doses as low as 10 milligrams daily, suggesting idiosyncrasy. Controlled studies are required to allow full evaluation of the efficacy of fluoxetine in panic attacks.

4.5.B.28 Picking own skin

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Reduced skin-picking behavior in some subjects

c) Adult:

1) Pathological skin-picking behavior was reduced by fluoxetine treatment in about half of the subjects in a small study. Skin- picking behavior returned after discontinuation of the drug. Fifteen women, of mean age 40.7 years and mean duration of symptoms 25 years, took fluoxetine for 6 weeks, starting at 20 milligrams (mg) per day. Doses were increased, as tolerated, to as high as 60 mg/day in nonresponders. Eight patients showed a response of a 30% or more decrease in their score on the Yale- Brown Obsessive Compulsive Scale. Those 8 were then randomized to continue fluoxetine at their successful dose or to receive placebo, in a double-blind manner, for 6 more weeks. Those taking fluoxetine maintained their response, whereas, those taking placebo all experienced symptom worsening. At follow-up 21 to 30 months later, one patient from the fluoxetine group remained in remission while continuing to take fluoxetine. One discontinued fluoxetine because of sexual side effects and relapsed. Two from that group were lost to follow-up. One patient from the placebo group restarted fluoxetine and remained in remission at 21 months. The other 3 from the placebo group did not resume fluoxetine treatment because of side effects and continued their skin-picking behaviors (Bloch et al, 2001).

4.5.B.29 Postpartum depression

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Fluoxetine or 6 counseling sessions produced similar improvement in women with postpartum depression at 4 and 12 weeks. Six to 8 weeks after delivery, 87 women who had a score of 12 or greater on the revised clinical interview schedule and satisfied diagnostic criteria for depression were randomly assigned to receive fluoxetine with 1 or 6 counseling sessions or placebo with 1 or 6 counseling sessions. The investigators and patients were blinded to treatment allocation. Additional benefit was NOT derived from combining fluoxetine with counseling; however, 6 counseling sessions were better than 1. Treatment with fluoxetine or 6 counseling sessions is effective and may be chosen depending on patient preference (Appleby et al, 1997).

4.5.B.30 Posttraumatic stress disorder

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Effective in treating PTSD in civilians and combat veterans

c) Adult:

1) Fluoxetine was more effective than placebo in treating posttraumatic stress disorder (PTSD) in a population composed mostly of men (81%), many of whom were exposed to multiple traumas of combat (48%) and/or were victims of war or witnesses of a war event (47%). In a randomized, double- blind, placebo-controlled trial, patients were treated with fluoxetine (n=226), beginning at 20 milligrams (mg) per day and increasing to a maximum of 80 mg/day, or placebo (n=75) for 12 weeks. Mean dose at the end of the study was 57 mg/day. Fluoxetine-treated patients showed significantly greater improvement in the total score of the Treatment Outcome PTSD scale (TOP-8) in comparison to placebo-treated patients (fluoxetine, -10.3; placebo, -8; p=0.006). Improvement was significant beginning at 6 weeks. Response rates (a 50% or greater decrease in the TOP-8 total score and a Clinical Global Impressions-Severity of Illness scale (CGI- S) score of 1 or 2) were 60% for the fluoxetine group and 44% for the placebo group (p=0.02). Significantly greater improvements compared with placebo treatment were seen in those with combat-related trauma (p less than 0.01) and those with no dissociative symptoms (p less than 0.001). In contrast to other studies that have reported little effect of fluoxetine in combat veterans, the patients in this study were comparatively young and had recently experienced trauma. Dissociative symptoms at baseline may be a predictor of a high placebo effect. Adverse effects were

similar for fluoxetine and placebo (Martenyi et al, 2002).
2) Fluoxetine was more effective than placebo for treating post-traumatic stress disorder (PTSD) (Connor et al, 1999). In a 12-week, double-blind study, 54 patients were randomly assigned to placebo or fluoxetine 10 milligrams (mg) daily with titration to 60 mg daily, if needed. Seventeen patients withdrew from treatment of whom 11 and 6 were in the placebo and fluoxetine group, respectively. For the primary efficacy measure, the Duke Global Rating (Duke) for PTSD, significantly more patients reached a score of 1 (no symptoms) during treatment with fluoxetine than placebo (59% versus 19%; p less than 0.0005). The Davidson Trauma Scale (DTS) total scores were also significantly lower in patients treated with fluoxetine compared to placebo. The onset of beneficial effects was observed at 2 weeks on the Duke scale and at 4 weeks on the DTS. This study included only civilians, primarily women, who fulfilled DSM-IV criteria for PTSD.

4.5.B.31 Premature ejaculation

a) Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class III
Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:
Fluoxetine was useful in the treatment of premature ejaculation by increasing time to ejaculation

c) Adult:
1) Treatment with either 20 milligram (mg) daily or 90 mg weekly fluoxetine effectively increased ejaculatory latency time in men with premature ejaculation. In a prospective, randomized study, patients (n=80) with premature ejaculation received fluoxetine 90 mg once weekly or fluoxetine 20 mg once daily for 3 months. Mean latency time to ejaculation increased in both treatment groups, however, there were no significant differences between groups. From baseline to 4 weeks after the end of treatment, mean ejaculatory latency time increased from 0.48 minute to 3.57 minutes and from 0.50 minute to 3.37 minutes in patients given 90 mg and 20 mg fluoxetine, respectively (p less than 0.01, both values). Partner sexual satisfaction was 27% in the 90 mg treatment group and 26% in the 20 mg treatment group. Adverse events were similar between groups, including, headache, nausea, and insomnia, (Manasia et al, 2003).
2) Latency time to ejaculation increased from slightly less than 1 minute to nearly 10 minutes during 8-weeks open-label treatment of 11 men with fluoxetine 40 milligrams (mg) daily (maximum 60 mg), with confirmation in a placebo-controlled trial of 17 men (Lee et al, 1996a; Kara et al, 1996a). Significant subjective changes included increased sexual desire, partner satisfaction, and decreased anxiety concerning premature ejaculation (Lee et al, 1996a).

4.5.B.32 Premenstrual dysphoric disorder

FDA Labeled Indication

a) Overview
FDA Approval: Adult, yes; Pediatric, no
Efficacy: Adult, Effective
Recommendation: Adult, Class IIa
Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:
Indicated for the treatment of premenstrual dysphoric disorder (PMDD) (Prod Info SARAFEM(R) Oral Capsule, 2005)

c) Adult:
1) Fluoxetine was significantly superior to placebo in reducing symptoms of tension, irritability, and dysphoria, as measured by visual-analogue scales. Benefit was noted as early as the first menstrual cycle. The authors concluded that fluoxetine administered once daily at a dosage of 20 milligrams was optimum in providing therapeutic efficacy and a side effect profile similar to the placebo group. Fluoxetine treatment was studied in a randomized, double-blind, placebo-controlled trial involving a large group of women (180 women completed the study) with PREMENSTRUAL DYSPHORIA, or premenstrual syndrome (Steiner et al, 1995). The study included women who had at least a one-year history of five or more symptoms of premenstrual dysphoria defined as being severe enough to impair activities of daily living. After a washout period of two menstrual cycles, patients were randomized to receive placebo, fluoxetine 20 milligrams/daily, or fluoxetine 60 milligrams/daily for six menstrual cycles. Further analysis of this study showed that fluoxetine was superior to placebo in relieving physical symptoms (including specifically bloating, breast tenderness) other than headache (Steiner et al, 2001). Fluoxetine 60 mg was not better than fluoxetine 20 mg. Further study is needed to define whether fluoxetine is required on a daily basis throughout the menstrual cycle.
2) Patients treated with fluoxetine had significantly lower overall premenstrual scores for affective but not somatic symptoms. The effect of fluoxetine was examined in 10 women with premenstrual syndrome (PMS) or late luteal phase dysphoric disorder in an open-label trial (Rickels et al, 1990). After initial evaluations and a one-month placebo period, patients were to take fluoxetine (20 mg/day) for two

months. Patients recorded the daily severity of 17 affective and somatic symptoms of PMS. The means of the premenstrual total scores (sum for the 7 worst days of days 20 to 28) and postmenstrual total scores (sum for days 6 to 12) for the second month of fluoxetine therapy were compared to scores for the same patients during the placebo period.

4.5.B.33 Raynaud's phenomenon

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Decreased attack frequency and severity in patients with primary Raynaud's phenomenon
More effective in women than in men

c) Adult:

1) Fluoxetine reduced the severity and frequency of attacks of Raynaud's phenomenon and was more effective than nifedipine. After a 2-week washout period, patients with primary (n=26) or secondary (n=27) Raynaud's phenomenon were given fluoxetine 20 milligrams (mg) daily or nifedipine 40 mg daily for 6 weeks. After another 2-week washout period, patients were crossed over to the alternate treatment for 6 weeks. Attack severity was significantly reduced by fluoxetine (p=0.0002) but not by nifedipine (p=0.14). Likewise, attack frequency was significantly reduced by fluoxetine (p=0.003) and not by nifedipine (p=0.22). Subgroup analysis showed significant reductions in attack severity and frequency with fluoxetine in females (p less than 0.0002 and p=0.0004, respectively), whereas the reduction in males was not statistically significant. Reductions in attack severity with fluoxetine were statistically significant in patients with primary Raynaud's phenomenon (p=0.009) and in those with secondary Raynaud's phenomenon (p=0.01). Reductions in attack frequency were significant for patients with primary Raynaud's phenomenon (p=0.03) but not for those with secondary Raynaud's phenomenon . Reductions with nifedipine were not statistically significant for those subgroups (Coleiro et al, 2001a).

4.5.B.34 Schizophrenia; Adjunct

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class III
Strength of Evidence: Adult, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Fluoxetine improved positive symptom scores in one study and negative symptom scores in another
Fluoxetine reduced the effectiveness of olanzapine treatment
Fluoxetine did not reduce olanzapaine-induced weight gain

c) Adult:

1) Addition of fluoxetine to olanzapine treatment of first- episode schizophrenia did not reduce OLANZAPINE-INDUCED WEIGHT GAIN, and, furthermore, fluoxetine reduced the effectiveness of olanzapine on positive symptoms and disorganized behavior. In a randomized, double-blind, placebo-controlled trial, 30 patients with first-episode DSM-IV schizophrenia were given olanzapine 10 milligrams (mg) per day and either fluoxetine 20 mg/day (n=15) or placebo (n=15) for 8 weeks. Mean weight gain in the 11 completers in the fluoxetine group was 7.9 kilograms (kg) and in the 13 completers of the placebo group 6 kg (p=0.44). Patients in the placebo group had significantly greater reductions in scores on the positive and disorganized subscales of the psychometric instruments used (p=0.001 and p=0.02, respectively). Scores on the negative symptom subscale or the Hamilton depression scale were not significantly different for the 2 groups. Two patients (both in the fluoxetine group) withdrew from the study because of lack of response and 2 from each group because of psychotic exacerbation (Poyurovsky et al, 2002).

2) Fluoxetine-treated patients showed statistically significant improvement of negative symptoms as measured by change on the Scale for the Assessment of Negative Symptoms at the end point (12 weeks) compared to the baseline value (p less than 0.001). Furthermore, fluoxetine decreased depressive symptoms as measured by the Hamilton Rating Scale for Depression and Anxiety (HAMD) (p less than 0.05). The effect of adjunctive fluoxetine on negative schizophrenic symptoms was evaluated in 34 inpatients with chronic schizophrenia. Fluoxetine 20 milligrams/day or placebo was administered for 12 weeks in a randomized, double-blind study. Adverse effects were more common with fluoxetine than placebo; they included nausea, headache, nervousness, anxiety, and insomnia. However, these effects were mild and transient (Spina et al, 1994).

4.5.B.35 Seasonal affective disorder

a) Overview

FDA Approval: Adult, no; Pediatric, no

Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:
In a short-term, small study, fluoxetine was effective in the treatment of seasonal affective disorder

c) Adult:
1) Fluoxetine was comparable to bright light therapy in the treatment of seasonal affective disorder/winter type. Forty patients with seasonal affective disorder/winter type were randomized to receive 5 weeks of treatment with fluoxetine 20 milligrams (mg) once in the morning (n=20) or bright light (3000 lux) therapy (n=20) in a parallel design, single-blind study. Those receiving bright light therapy did so for either 2 hours in the morning (n=12), 2 hours in the evening (n=5), or 1 hour in the morning and 1 hour in the evening (n=3). Responders were those experiencing reductions in both the Hamilton Depression Rating Scale scores and Hamilton Depression Rating Scale supplement scores from baseline. Thirteen (65%) patients were responders in the fluoxetine treated group, and 14 (70%) were responders in the bright light group; differences were not statistically significant. Five (25%) of those in the fluoxetine group and 10 (50%) of those in the bright light group met criteria for remission, differences were not statistically significant. Both treatments were found to be very well tolerated. Although fluoxetine was relatively effective in the treatment of seasonal affective disorder, further studies involving a larger patient population are necessary to establish significance (Ruhrmann et al, 1998).

4.5.B.36 Severe major depression with psychotic features

See Drug Consult reference: PSYCHOTIC DEPRESSION - DRUG THERAPY

4.5.B.37 Slow channel syndrome

a) Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category C
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:
Improved symptoms of slow-channel myasthenic syndrome in two female patients

c) Adult:
1) Two female patients with slow-channel myasthenic syndrome reported improved muscle strength and endurance following fluoxetine treatment. The first patient, a 22-year-old woman carrying the epsilon-T264P slow- channel mutation received fluoxetine treatment at an initial dose of 40 milligrams (mg) daily, titrated over 18 months to 120 mg/day. She was confined to a wheelchair, required nocturnal respiratory support and had a Neuropathy Impairment Score (NIS) of 78/176. The second patient, a 34-year-old woman carrying the epsilon-L269F slow-channel mutation received fluoxetine 80 mg daily and had a NIS of 42/176. After 3 years of fluoxetine therapy, both patients reported ongoing improvements in muscle strength, endurance, and daily activities. The NIS scores were reduced by 77% and 81% for the first and second patient, respectively (Harper et al, 2003).

4.5.B.38 Social phobia

a) Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:
In 1 trial, FLUOXETINE, comprehensive cognitive behavioral group therapy (CCBGT) and their combination significantly improved symptoms of social phobia compared with placebo; however, fluoxetine plus CCBGT was not superior to fluoxetine monotherapy and symptoms remained in many patients after 14 weeks of treatment
Another trial found no significant difference between placebo and fluoxetine related to improvement of social phobia
Fluoxetine may be effective in ameliorating social phobic symptoms during clozapine treatment in schizophrenic patients

c) Adult:
1) A randomized, double-blind trial suggests that FLUOXETINE or comprehensive cognitive behavioral group therapy (CCBGT) may improve symptoms of GENERALIZED SOCIAL PHOBIA (GSP), and that combining fluoxetine with CCBGT was NOT significantly better than either monotherapy. The 14-week trial enrolled subjects with GSP according to DSM-IV criteria (n=295, intent-to-treat; n=211, completers). Randomization was to 5 groups treated with fluoxetine (n=57), CCBGT (n=60), fluoxetine and CCBGT (n=59), CCBGT and placebo (n=59), or placebo (n=60). Fluoxetine was initiated as a daily dose of 10

milligrams (mg), followed by 20 mg at day 8, 30 mg at day 15, and 40 mg at day 29; increases could be made to 50 or 60 mg/day, if tolerated and therapeutically warranted (doses at final visit averaged 43.6 mg). At the end of 14 weeks, response rates on the Clinical Global Impressions scale by group (based on ITT data) were 50.9% for fluoxetine, 51.7% for CCBGT, 54.2% for fluoxetine/CCBGT, 50.8% for CCBGT/placebo, and 31.7% for placebo (p less than 0.05, pair-wise each active treatment versus placebo; p=0.09 overall active treatment vs placebo). According to both the Brief Social Phobia Scale and the Social Phobia and Anxiety Inventory, all active treatments conferred significantly better results than did placebo (p less than 0.05). In linear mixed-effects models analysis, all active treatments were superior to placebo, although there were no significant differences between one active treatment group and another (also no significant differences between combination therapy and monotherapy). All treatments were well tolerated. The investigators noted that substantial GSP symptoms remained after 14 weeks of treatment, and that longer-term may be necessary (Davidson et al, 2004).

2) A 14-week course of oral FLUOXETINE (n=30) failed to provide greater improvement in symptoms of SOCIAL PHOBIA than placebo (n=30), based on a randomized, double-blind trial. During a placebo run-in period, potential enrollees were excluded if they scored less than 50 on the Liebowitz Social Anxiety Scale (LSAS) or if their LSAS score dropped by more than 20% during the 2 weeks of placebo treatment. All subjects had a primary diagnosis of generalized social phobia (DSM-IV) over a duration of at least 6 months. Fluoxetine dosing started at 20 milligrams (mg)/day, which could be reduced to 10 mg/day if an adverse event occurred. After 8 weeks at the 10- or 20-mg/day level, fluoxetine could be increased every 2 weeks in 20 mg/day increments to a maximum of 60 mg/day. Mean daily doses of fluoxetine were 34.23, 46.92, and 50.00 mg at weeks 10, 12, and 14, respectively (mode was 40 mg and 60 mg at weeks 12 and 14). After 14 weeks of treatment, both the fluoxetine and placebo group showed a significant improvement from baseline on the LSAS (mean change: fluoxetine, 22.6, p less than 0.001; placebo, 23.4, p less than 0.001). No significant difference on the LSAS was found between fluoxetine- and placebo-treated subjects (p=0.901). On the Clinical Global Impressions - Improvement scale, proportions rated as 'much improved' or 'very much improved' were 40% and 30% for the fluoxetine and placebo groups, respectively (p=0.417). Hamilton Rating Scale for Depression (HAM-D) scores showed no significant changes between baseline and post-treatment for either fluoxetine or control. Although there were significant changes from baseline on many secondary outcome measures, no significant between-group differences were found, except for a rating of bodily pain. The short form health survey (SF-36) showed a significantly greater decrease in bodily pain after treatment with fluoxetine compared with placebo (p=0.05). Drop-outs for adverse side effects were 1 and 3 for the fluoxetine and placebo groups, respectively. Fluoxetine-related adverse events were headache (53%), insomnia (47%), asthenia (30%), and nervousness (30%); placebo-related adverse reactions included headache (40%), insomnia (30%), nervousness (23%), and myalgia (20%) (Kobak et al, 2002).

3) Fluoxetine was effective for ameliorating social phobia that emerged during clozapine treatment. Twelve patients (5 women and 7 men, aged 19 to 28 years) with paranoid schizophrenia based on DSM-III-R criteria who developed social phobia 9 to 20 weeks after beginning clozapine were included in the study. The mean daily dose of clozapine and fluoxetine was 325 milligrams (mg) (range, 250 to 400 mg) and 35.83 mg, respectively, at 12 weeks. Patients were evaluated using the Scale for the Assessment of Negative Symptoms (SANS), Scale for the Assessment of Positive Symptoms (SAPS), the Brief Psychiatric Rating Scale (BPRS), the Liebowitz Social Phobia Scale (LSPS), the Frankfurter Beschwerde Fragebogen Scale (FBF), and the Brief Psychiatric Rating Scale. Following 8 weeks of treatment with fluoxetine, no significant differences were observed in the mean BPRS and SAPS scores while a significant decrease was found in SANS anhedonia (p less than 0.05) and avolition (p less than 0.05). After 8 weeks of fluoxetine treatment, 8 of 12 patients demonstrated amelioration of social phobic symptoms of 35% or greater on the LSPS total score, and 3 patients showed a greater than 50% reduction. Four of 12 patients demonstrated less than 25% reduction in LSPS total score. The LSPS mean anxiety/fear subscore (range of scale 0 to 72) and mean withdrawal subscore (range of scale 0 to 72) were reduced from 38.5 and 44.7, respectively, to 24.81 and 35.67, respectively, following 12 weeks of fluoxetine treatment (p less than 0.05) (Pallanti et al, 1999).

4.5.B.39 Tinnitus

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Relieved intractable tinnitus in 3 patients
See Drug Consult reference: DRUG THERAPY OF TINNITUS

c) Adult:

1) In 3 patients, fluoxetine 10 milligrams daily abolished tinnitus within 1 week. All 3 patients had high-tone sensorineural hearing loss with intractable tinnitus which interfered with sleep. Vitamins and stress relief produced no improvement so fluoxetine was tried. Further study of fluoxetine for this indication is warranted (Shemen, 1998).

4.5.B.40 Trichotillomania

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class III
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Fluoxetine has been effective in several case reports; however, it was ineffective in a small clinical trial which evaluated fluoxetine for treating trichotillomania. Larger, placebo-controlled clinical trials are needed.

c) Adult:

1) Fluoxetine up to 80 mg/day was NOT effective in a group of patients with trichotillomania. In this placebo-controlled trial, 23 adult patients were treated for a period of 12 weeks. No significant differences were noted between fluoxetine and placebo (Streichenwein & Thornby, 1995).

2) Case reports of trichotillomania and other forms of self-injurious behaviors have noted some benefit with fluoxetine therapy (Ricketts et al, 1993; Sheika et al, 1993; Sovner et al, 1993). These behaviors are often associated with depression or obsessive-compulsive disorder which may account for the efficacy of fluoxetine.

4.5.B.41 Vasovagal syncope; Prophylaxis

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Ineffective; Pediatric, Ineffective
Recommendation: Adult, Class III; Pediatric, Class III
Strength of Evidence: Adult, Category B; Pediatric, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

In a prospective, randomized study, fluoxetine was not superior to propranolol or placebo in the prophylaxis of vasovagal syncope (VVS) in patients, aged 15 to 70 years, with a history of untreated VVS (Theodorakis et al, 2006)

c) Adult:

1) Results of a prospective, randomized study showed that fluoxetine was not superior to propranolol or placebo in preventing the recurrence of vasovagal syncope (VVS) in patients with untreated VVS. Patients (n=96; mean age 42 years; range, 15 to 70 years) who had experienced at least 5 syncopes in their lifetime, not less than 2 syncopal attacks during the prior year, and whose last syncopal attack occurred at least 1 month prior to study enrollment were randomized to receive either oral fluoxetine (n=32), oral propranolol (n=32), or placebo (n=32) for 6 months. The fluoxetine dose was 20 milligrams (mg) per day and the propranolol dose ranged from 10 to 40 mg three times daily, depending on the subject's resting heart rate and tolerance of treatment. The primary endpoint was the time to the first recurrence of syncope or presyncope. Secondary endpoints included the number of patients with recurrence of syncope/presyncope and total vasovagal episodes (sum of syncopal and presyncopal episodes), and patient's well-being. Excluding 2 patients who refused follow-up, no difference was noted between the 3 groups with regards to the occurrence of syncopal, presyncopal, and total vasovagal episodes during the 6-month follow-up period (p greater than 0.05). Overall, a syncopal or presyncopal episode occurred in 38% (n=36/94) of the patients, with rates of 22% (n=7/32) in the fluoxetine group, 41% (n=13/31) in the placebo group, and 51% (n=16/31) in the propranolol group. Additionally, no difference was noted between the 3 groups when syncopal and presyncopal episodes were assessed separately. However, an on-treatment analysis that further excluded 18 patients who discontinued therapy revealed significantly longer mean time to a syncopal or presyncopal episode for the fluoxetine group (5.4 +/- 0.3 months) compared to the placebo group (4.2 +/- 0.5 months; p=0.05) and the propranolol group (4.1 +/- 0.4 months; p=0.046). Although the difference in mean times to a syncopal episode between the 3 groups was not statistically significant, the mean time to a presyncopal episode was significantly longer for the fluoxetine group (5.5 +/- 0.2 months) compared to the placebo group (4.6 +/- 0.4 months; p=0.048) and the propranolol group (4.5 +/- 0.4 months; p=0.008). Additionally, after 6 months of treatment, improvements in well-being scores (assessed by patient-filled questionnaires) were observed only for the fluoxetine group (p less than 0.01) (Theodorakis et al, 2006).

d) Pediatric:

1) Results of a prospective, randomized study showed that fluoxetine was not superior to propranolol or placebo in preventing the recurrence of vasovagal syncope (VVS) in patients with untreated VVS. Patients (n=96; mean age 42 years; range, 15 to 70 years) who had experienced at least 5 syncopes in their lifetime, not less than 2 syncopal attacks during the prior year, and whose last syncopal attack occurred at least 1 month prior to study enrollment were randomized to receive either oral fluoxetine (n=32), oral propranolol (n=32), or placebo (n=32) for 6 months. The fluoxetine dose was 20 milligrams (mg) per day and the propranolol dose ranged from 10 to 40 mg three times daily, depending on the subject's resting heart rate and tolerance of treatment. The primary endpoint was the time to the first recurrence of syncope or presyncope. Secondary endpoints included the number of patients with recurrence of syncope/presyncope and total vasovagal episodes (sum of syncopal and presyncopal

episodes), and patient's well-being. Excluding 2 patients who refused follow-up, no difference was noted between the 3 groups with regards to the occurrence of syncopal, presyncopal, and total vasovagal episodes during the 6-month follow-up period (p greater than 0.05). Overall, a syncopal or presyncopal episode occurred in 38% (n=36/94) of the patients, with rates of 22% (n=7/32) in the fluoxetine group, 41% (n=13/31) in the placebo group, and 51% (n=16/31) in the propranolol group. Additionally, no difference was noted between the 3 groups when syncopal and presyncopal episodes were assessed separately. However, an on-treatment analysis that further excluded 18 patients who discontinued therapy revealed significantly longer mean time to a syncopal or presyncopal episode for the fluoxetine group (5.4 +/- 0.3 months) compared to the placebo group (4.2 +/- 0.5 months; p=0.05) and the propranolol group (4.1 +/- 0.4 months; p=0.046). Although the difference in mean times to a syncopal episode between the 3 groups was not statistically significant, the mean time to a presyncopal episode was significantly longer for the fluoxetine group (5.5 +/- 0.2 months) compared to the placebo group (4.6 +/- 0.4 months; p=0.048) and the propranolol group (4.5 +/- 0.4 months; p=0.008). Additionally, after 6 months of treatment, improvements in well-being scores (assessed by patient-filled questionnaires) were observed only for the fluoxetine group (p less than 0.01) (Theodorakis et al, 2006).

4.6 Comparative Efficacy / Evaluation With Other Therapies

Amineptine

Amisulpride

Amitriptyline

Aprepitant

Bupropion

Clomipramine

Desipramine

Dothiepin

Doxepin

Fluvoxamine

Imipramine

Maprotiline

Mianserin

Milnacipran

Mirtazapine

Moclobemide

Nefazodone

Nifedipine

Nortriptyline

Olanzapine/Fluoxetine Hydrochloride

Paroxetine

Phenelzine

Protriptyline

Reboxetine

Sertraline

St John's Wort

Trazodone

Venlafaxine

4.6.A Amineptine

4.6.A.1 Depression

a) A multicenter study of 169 patients compared the efficacy and the tolerability of amineptine 200 milligrams (mg)/day and fluoxetine 20 mg/day for 90 days in major depressive episodes. The patients were selected according to the Diagnostic and Statistical Manual, third edition revised, (DSM-III-R) criteria of major depressive disorders. Use of tranquilizers was permitted during the study. The efficacy for each drug began as soon as day 7 and lasted throughout the study (p less than 0.01). Clinical evaluation using Montgomery and Asberg Depression Rating Scales (MADRS), Humeur Angoisse Ralentissement Danger scale (HARDS) , Widlocher Retardation Rating Scale and Hopkins Symptoms Check-List (HSCL) showed significant improvement (p less than 0.01 on day 7 for fluoxetine; p less than 0.05 on day 7 and less than 0.01 on day 21 for amineptine). It appeared that the effect of amineptine began earlier than fluoxetine, but in general no statistical differences were noted between the two drugs at any time of the study. The tolerability was judged to be good. The most common adverse effects in the amineptine group included excitement and insomnia, whereas tachycardia, nausea and vomiting were most frequently reported in the fluoxetine group (Dalery et al, 1992).

4.6.B Amisulpride

4.6.B.1 Dysthymia

a) The efficacy and safety of low doses of amisulpride (50 milligrams (mg) daily) and of fluoxetine (20 mg daily) were evaluated in a randomized, double-blind, parallel-group comparison. One hundred forty-two patients with dysthymia received amisulpride and 139 received fluoxetine. No statistically significant difference between the two groups was found in the number of responders at study-end according to the Montgomery and Asberg Depressive Rating Scale. In addition, amisulpride was well tolerated (Smeraldi et al, 1996).

b) Another double-blind, randomized trial reported that amisulpride 50 milligrams (mg) daily (139 patients) was at least as effective as fluoxetine 20 mg daily (129 patients) in medium-term treatment (three months) of dysthymia, in spite of 72 withdrawals (Biondi et al, 1996). These preliminary results should be confirmed in further trials.

4.6.C Amitriptyline

Depression

Diabetic neuropathy - Pain

Headache

Mixed anxiety and depressive disorder

Musculoskeletal pain

4.6.C.1 Depression

a) SUMMARY: In clinical studies (n=64, n=44, n=51, n=130), fluoxetine (20 to 80 mg/day) showed comparable antidepressant efficacy to amitriptyline (50 to 300 mg/day). The study periods were 5 to 6

weeks. Fluoxetine has been reported to be better tolerated than amitriptyline with weight gain occurring in amitriptyline-treated patients and weight loss occurring in fluoxetine-treated patients (Chouinard, 1985a; Feighner, 1985; Young et al, 1987; Laakmann et al, 1988; Fawcett et al, 1989); (Altamura et al, 1989). In addition, anticholinergic effects associated with amitriptyline have been bothersome (Altamura et al, 1989).
b) Amitriptyline and fluoxetine provided similar efficacy in elderly patients with Alzheimer's Disease and major depression (Taragano et al, 1997). Thirty-seven patients were randomly assigned to receive amitriptyline 25 milligrams (mg) or fluoxetine 10 mg daily for 6 weeks. At 6 weeks, scores on the Hamilton Rating Scale for Depression decreased from 25.9 to 16.5 (p less than 0.0001); the Mini-Mental State Exam also decreased by 2.4 points. In the amitriptyline group, 58% of patients left the study due to adverse effects which included confusion, disorientation, and constipation. In the fluoxetine group, 22% of patients dropped out due to nausea and loose stools. Limitations of this study are the small size, lack of a placebo-control, and differences in the side effect profile which may have prevented effective blinding. While both agents are effective, fluoxetine was tolerated better than amitriptyline.
c) In 51 outpatients with primary major depressive disorder, amitriptyline and fluoxetine showed comparable antidepressant efficacy with amitriptyline showing some possible superiority over fluoxetine with respect to Hamilton Psychiatric Rating Scale for Depression (HAM-D) anxiety/somatization and sleep disturbance factors. Fluoxetine had a significantly better efficacy/side effect index and significantly fewer autonomic adverse effects than amitriptyline. However, there was a trend for fluoxetine to have greater effects than amitriptyline on HAM-D cognitive disturbance factors. Patients received fluoxetine 20 to 80 mg/day or amitriptyline 75 to 300 mg/day (Chouinard, 1985a). Similar results were reported in another study (n=40) (Fawcett et al, 1989).
d) Fluoxetine 20 mg/day and amitriptyline 75 mg/day were effective in treating 28 elderly patients with major depressive episodes. This was a 5-week randomized, double-blind study. The difference in response to biological symptoms such as early morning awakening, weight loss, sexual dysfunction, guilt and suicidal thoughts was not statistically significant between treatment groups. However, amitriptyline provided a significantly better response than fluoxetine on anxious symptoms. More severe side effects, mainly anticholinergic, were seen with amitriptyline and weight gain was only seen in amitriptyline-treated patients (Altamura et al, 1989).

4.6.C.2 Diabetic neuropathy - Pain

a) Treatment with amitriptyline and desipramine showed no significant difference in pain relief, in either depressed or non-depressed patients with diabetic neuropathy and fluoxetine was no better than placebo in this patient population. There was no significant difference in any groups relative to adverse effects (Max et al, 1992). Thirty-eight patients received either amitriptyline 12.5 to 150 mg (mean 105 mg) once daily or desipramine 12.5 to 150 mg (mean 111 mg) once daily and 46 patients received either fluoxetine 20 to 40 mg (mean 40 mg) once daily or placebo (benztropine 0.125 to 1.5 mg) once daily. Pain intensity was rated by patient daily diary and global rating scales and mood was assessed by a psychiatrist at the beginning and end of each six-week treatment period. This was a randomized, double-blind, two-period crossover study.

4.6.C.3 Headache

a) In a small, unblinded, 12-week study, patients found that both fluoxetine and amitriptyline were beneficial for chronic tension-type headache and episodic tension-type headache while neither was very effective for migraine headache (Oguzhanoglu et al, 1999). Patients with a variety of headaches were assigned to receive either amitriptyline titrated up to 50 milligrams (mg) nightly or fluoxetine 20 mg every morning. In the group with migraine headaches, neither the amitriptyline group (n=8) nor the fluoxetine group (n=7) experienced a decrease in number of headaches or pain intensity. Fluoxetine reduced duration of pain as compared to baseline at 4, 8, and 12 weeks (p=0.01, p=0.0146, p=0.013, respectively). In patients with chronic tension-type headache, amitriptyline-treated patients (n=5) experienced reduced numbers of days of pain per month at 4, 8, and 12 weeks (p=0.0187, p=0.03, p=0.009, respectively). Fluoxetine-treated patients (n=8) experienced reduced days of pain only at 4 and 8 weeks (p=0.0157, p=0.004, respectively). Neither drug was very effective against pain intensity. In the episodic tension-type headache, amitriptyline patients (n=9) experienced a decrease in the number of days with pain at 4 and 8 weeks only (p=0.0012, p=0.0002, respectively) while fluoxetine patients (n=10) experienced this at 4, 8, and 12 weeks (p=0.0018, p=0.0148, p=0.0179, respectively). Reduction in pain intensity occurred only with fluoxetine during weeks 4 and 8 (p=0.0156, p=0.0313, respectively).

4.6.C.4 Mixed anxiety and depressive disorder

a) Fluoxetine and amitriptyline had comparable effectiveness in patients with depression and associated anxiety (Versiani et al, 1999). Patients (n=157) were randomly assigned to blinded treatment with fluoxetine 20 milligrams (mg) per day or amitriptyline 50 mg per day titrated to a maximum dose of 250 mg if needed; all patients received capsules in the morning (fluoxetine) and evening (amitriptyline). No statistically significant differences were detected between treatments for efficacy measures including the Hamilton Rating Scale for Depression (HAM-D), the HAM for Anxiety (HAM-A), the Raskin-Covi Depression and Anxiety Scale, the Clinical Global Impression-Improvement, and the Patient Global Impression. The only difference between treatments was a single factor, the HAM-D sleep factor which favored amitriptyline (p less than 0.001). The response rate for both treatments was 74%. Greater than 80% of patients completed the study. Fluoxetine is comparable to amitriptyline for treating patients with anxious depression.

4.6.C.5 Musculoskeletal pain

a) Fluoxetine was superior (p less than 0.001) to amitriptyline and placebo in decreasing pain intensity and providing pain relief in 59 patients with rheumatic pain conditions. Amitriptyline was also superior (p less than 0.05) to placebo in decreasing pain intensity and providing pain relief. Rheumatic pain conditions consisted of low back pain, fibromyalgia, osteoarthritis, and rheumatoid arthritis. Patients received fluoxetine 20 mg/day, amitriptyline 25 mg/day or placebo once daily for 4 weeks (Rani et al, 1996).

4.6.D Aprepitant

4.6.D.1 Depression

a) In a large dose-finding study (n=approximately 800) involving patients with major depression and anxiety, neither aprepitant (10 to 300 milligrams (mg) once daily) nor fluoxetine (20 mg once daily) were superior to placebo (Krishnan, 2002). Lack of benefit in this study has shed doubt on the efficacy of aprepitant in depression. However, poorly controlled patient selection may have contributed to negative results. Post hoc analysis of this study did suggest a trend toward benefit of aprepitant in severely depressed patients (Lieb et al, 2002; Krishnan, 2002), and a further confirmatory study in a well-defined population is required to confirm the efficacy of aprepitant and/or its usefulness in certain depressed subgroups.

4.6.E Bupropion

4.6.E.1 Depression

a) Bupropion and fluoxetine were found to be equally effective for the treatment of DSM-III-R major depressive disorder, with no significant difference in the incidence of adverse effects. Weekly assessments of therapeutic response (HAM-A, HAM-D, CGI) and presence of adverse effects were carried over a 6-week period. Mean daily dosage was 382 milligrams for bupropion and 38 milligrams for fluoxetine (Feighner et al, 1991).

4.6.E.2 Adverse Effects

a) Fluoxetine was more frequently associated with sexual dysfunction than was sustained release (SR) bupropion or placebo in patients being treated for moderate to severe depression. In a double-blind, double-dummy, 8-week trial, patients experiencing an episode of recurrent major depression were randomized to receive bupropion SR 150 to 400 milligrams (mg) per day (n=150), fluoxetine 20 to 60 mg/day (n=154), or placebo (n=152). Bupropion and fluoxetine showed similar efficacy for the treatment of depressive symptoms. However, significantly more patients receiving fluoxetine experienced orgasm dysfunction (p less than 0.001) and sexual arousal disorder (p less than 0.05) than did patients receiving bupropion or placebo. The difference between fluoxetine and bupropion was maintained when only patients with remission of depression were analyzed. There were no significant differences between bupropion and placebo for either orgasm dysfunction or sexual arousal disorder at any treatment week. Relative to baseline values, sexual desire disorder decreased in the bupropion group but was unchanged in the placebo and fluoxetine groups over the 8-week study. Of the patients who were satisfied with their sexual functioning at baseline, more in the fluoxetine group than in the bupropion group became dissatisfied during treatment (p less than 0.05) (Coleman et al, 2001).

4.6.F Clomipramine

4.6.F.1 Obsessive-compulsive disorder

a) Treatment with fluoxetine (FLX) was compared with treatment with clomipramine (CMI) in two groups of patients with obsessive compulsive disorder (OCD) using two different experimental designs. In the first group of 11 patients with OCD studied using a randomized, double-blind, crossover design, treatment with FLX (20 to 80 milligrams/d) for 10 weeks was found to produce therapeutic effects similar to that obtained with CMI (50 to 250 milligrams/d) for 10 weeks. There were significantly fewer total side effects reported during FLX than CMI treatment. Drug tapering and placebo substitution in the 4-week crossover interval phase led to substantial relapses in OCD symptoms and depression. In addition, response to the second drug took as long as response to the first drug, despite a putative common mechanism of action of serotonin uptake inhibition. A second group of 21 patients with OCD that had been previously stabilized on CMI with at least partial benefit were crossed over to FLX in double blind fashion. After 10 weeks of FLX, most patients manifested behavioral rating scores of OCD and depressive symptoms that were comparable with pre-crossover ratings completed during CMI treatment. A significant exacerbation in OCD and depression ratings as well as a similar lag in therapeutic efficacy were also noted in this second cohort of patients with OCD. Platelet serotonin concentrations were reduced 95% during both CMI and FLX treatment periods. These results suggest that FLX may represent a viable alternative to CMI in the treatment of OCD, although more studies with larger sample sizes are needed (Pigott et al, 1990).

b) Clomipramine (CMI) and fluoxetine (FLX) were shown to be equally effective in the treatment of 120 patients with DSM-III major unipolar depressive disorder over a 6-week period. Adverse effects were more frequent with CMI. Those that did occur with FLX tended to disappear during the course of the study (Noguera et al, 1991).

4.6.G Desipramine

4.6.G.1 Depression

a) Fluoxetine and desipramine had similar efficacy in a double-blind, randomized, 6-week study (n=55). The 46 patients completing the study (desipramine = 20, fluoxetine = 26) showed improvement in Hamilton Depression rating and Clinical Global Impression Scales vs placebo with no statistically significant differences between drugs. Fewer side effects of lesser intensity were noted with fluoxetine (Remick et al, 1993).

b) For the initial treatment of depression, desipramine and fluoxetine are equivalent in terms of overall treatment costs, efficacy, and quality of life. In a randomized, controlled trial, patients with newly diagnosed depression (n=536) were prescribed either fluoxetine or a tricyclic antidepressant (imipramine or desipramine) and assessed at 1, 3, and 6 months for both efficacy of the antidepressant regimen as measured by the Hamilton Depression Rating Scale and the Hopkins Symptom Checklist and quality of life. Drug cost and total health care costs were also measured. Clinical efficacy and quality of life were similar between the two groups; however, patients treated with fluoxetine had fewer adverse effects, were less likely to require a change in their medication, and had less outpatients visits. Although drug costs were higher, total treatment costs were slightly lower for the fluoxetine group; however, this difference was not statistically significant (Simon et al, 1996a).

4.6.H Dothiepin

1) Efficacy

a) Dothiepin and fluoxetine were shown to have similar limited effects on psychomotor and driving performance in a double-blind, placebo controlled, crossover, 3 week study involving 18 healthy volunteers (Ramaekers et al, 1995). At the doses used in this study, neither dothiepin nor fluoxetine would be expected to impair driving performance. Placebo, fluoxetine 20 mg, and dothiepin 75 mg (increased to 150 mg on day 8) were administered for 22 days. Sustained attention was reduced by 6.7% on day 1 by dothiepin and by 7.4% (day 1), 6.7% (day 8), and 6.5% (day 22) by fluoxetine. Critical fusion frequency was significantly reduced by day 22 by 1.13 Hz (dothiepin) and 1.24 Hz (fluoxetine). There was no significant effect with either drug in two tests of actual highway driving. Similar incidence of side effects was reported for each drug.

b) Dothiepin and fluoxetine were shown to have similar limited effects on psychomotor and driving performance in a double-blind, placebo controlled, crossover, 3 week study involving 18 healthy volunteers (Ramaekers et al, 1995a). At the doses used in this study, neither dothiepin nor fluoxetine would be expected to impair driving performance. Placebo, fluoxetine 20 mg, and dothiepin 75 mg (increased to 150 mg on day 8) were administered for 22 days. Sustained attention was reduced by 6.7% on day 1 by dothiepin and by 7.4% (day 1), 6.7% (day 8), and 6.5% (day 22) by fluoxetine. Critical fusion frequency was significantly reduced by day 22 by 1.13 Hz (dothiepin) and 1.24 Hz (fluoxetine). There was no significant effect with either drug in two tests of actual highway driving. Similar incidence of side effects was reported for each drug.

4.6.I Doxepin

4.6.I.1 Depression

a) Doxepin and fluoxetine had similar efficacy in a comparative study involving 80 depressed patients (61 outpatients, 19 inpatients) diagnosed as having major depressive disorder. The patients received either fluoxetine 20 to 60 milligrams/day (mean, 28.9 mg/day) or doxepin 100 to 200 milligrams/day (mean, 146.8 mg/day). Both treatment groups showed improvement over time, with no difference between fluoxetine and doxepin at study termination. The most common side effects of fluoxetine (headache, nausea, and insomnia) were in contrast to the pronounced anticholinergic side effects of doxepin (dry mouth, fatigue, constipation). Moreover, the significant weight gain associated with doxepin therapy was not seen with fluoxetine treatment (Remick et al, 1989).

b) Fluoxetine 20 to 80 milligrams daily (once daily or divided twice a day) and doxepin 50 to 200 milligrams daily (once daily or divided twice a day or three times a day) had comparable efficacy in the treatment of depression in geriatric patients (at least 64 years of age). Each drug was administered in increasing doses over the first two weeks of the study, with maintenance doses (up to 80 mg daily of fluoxetine and 200 mg daily of doxepin) being determined by the third week; this maintenance dose was given for three more weeks (total, six weeks). Both drugs were considered equally effective using the following parameters: Hamilton Psychiatric Rating Scale for Depression (HAM-D), Raskin Severity of Depression Scale, Covi Anxiety Scale, Clinical Global Impressions severity and improvement, Patient Global Improvement, and SCL-58 scales. Both drugs produced significant improvement compared to baseline scores. Fluoxetine was associated with a lower degree of drowsiness/sedation, dry mouth, constipation and vision disturbances. However, nervousness/anxiety, insomnia, sweating, dyspepsia, and nausea occurred to a greater degree with fluoxetine. Body weight decreased with fluoxetine and increased with doxepin (Feighner & Cohn, 1985).

c) In one study comparing fluoxetine and doxepin, both drugs were effective in major depressive disorder in geriatric patients, with a lower incidence of side effects being observed with fluoxetine (Feighner & Cohn, 1985). Weight loss occurred with fluoxetine, as compared to weight gain with doxepin, which was statistically significant. Heart rate was shown to increase in doxepin-treated patients as compared to decreases in fluoxetine-treated patients; this was also a statistically significant difference. Significant improvement in depressive symptoms was further demonstrated in a group (n=33) of geropsychiatric patients. Although this study only followed patients for a period of one month, significant side effects such as nausea, weight loss,

and agitation were not noted. Doses of fluoxetine used were 20 mg every other day to 20 mg daily (Orengo et al, 1996).

4.6.J Fluvoxamine

4.6.J.1 Depression

a) In a randomized, double-blind study (n=100), fluvoxamine and fluoxetine demonstrated comparable efficacy and side effects in out-patients with major depression. After randomization, patients were treated initially with fluvoxamine 50 milligrams (mg) daily adjusted to a maximum of 150 mg daily or fluoxetine 20 mg daily adjusted to a maximum of 80 mg daily. Throughout the study, significant differences in efficacy were NOT detected on several depression scales including the Hamilton depression scale and clinical global impressions scale. Adverse effects were common with both drugs but the severity was mild in the majority of patients. Even though this study included 100 patients, it may NOT have detected subtle differences between the 2 treatments (Rapaport et al, 1996).

4.6.K Imipramine

4.6.K.1 Depression

a) SUMMARY: Fluoxetine has been as effective as imipramine in the treatment of depression, while producing a lower incidence of side effects. Overall cost of therapy, clinical efficacy, and patient quality of life have been shown to be equivalent after six months of treatment.

b) In a double-blind, randomized, parallel group study, fluoxetine was better tolerated although not more effective than imipramine in the treatment of major depression with atypical features. A total of 154 patients (age 18 to 65 years) who met DSM-IV criteria for major depression for at least 1 month and also met the Columbia criteria for atypical depression were randomized to receive fluoxetine, imipramine, or placebo for 10 weeks. Fluoxetine was administered as 20 milligrams (mg) daily for 4 weeks, 40 mg daily for week 5, and 60 mg daily for the remaining weeks. Imipramine was administered as 50 mg daily for the first week, increasing by 50 mg/day each week until a maximum of 300 mg daily was reached. Mean daily doses at the end of the study were 51.4 mg/day for fluoxetine and 204.9 mg/day for imipramine. Fluoxetine and imipramine did not differ from one another based on the Clinical Global Impression (CGI) scale improvement scores following 10 weeks of treatment. Fluoxetine and imipramine were significantly more effective than placebo in the intention-to-treat (p less than 0.007 and 0.003, respectively) and completer groups (p less than 0.03 and 0.001, respectively). Imipramine-treated patients demonstrated a significantly higher dropout rate than fluoxetine-treated patients (p=0.04). In the intention-to-treat group, depression outcome measures including the 17-item and 28-item Hamilton Depression Rating Scale and Patient Global Improvement demonstrated no differences between fluoxetine and imipramine and a consistent clinical benefit of both treatment groups compared with placebo. Adverse effects significantly more common for imipramine than for fluoxetine included dry mouth (81% versus 28%, respectively), somnolence (42% versus 24%, respectively), and dizziness (44% versus 25%, respectively); cough and back pain occurred at a significantly higher incidence in fluoxetine- versus imipramine-treated patients (McGrath et al, 2000).

c) For the initial treatment of depression, imipramine and fluoxetine are equivalent in terms of overall treatment costs, efficacy, and quality of life. In a randomized, controlled trial, patients with newly diagnosed depression (n=536) were prescribed either fluoxetine or a tricyclic antidepressant (imipramine or desipramine) and assessed at 1, 3, and 6 months for both efficacy of the antidepressant regimen as measured by the Hamilton Depression Rating Scale and the Hopkins Symptom Checklist and quality of life. Drug cost and total health care costs were also measured. Clinical efficacy and quality of life were similar between the two groups; however, patients treated with fluoxetine had fewer adverse effects, were less likely to require a change in their medication, and had less outpatients visits. Although drug costs were higher, total treatment costs were slightly lower for the fluoxetine group; however, this difference was not statistically significant (Simon et al, 1996).

d) Controlled studies have demonstrated that oral fluoxetine in doses of 40 to 80 milligrams daily is as effective as imipramine 150 to 250 milligrams daily in the treatment of major depression (Cohn & Wilcox, 1985; Stark & Hardison, 1985; Levine et al, 1987a). Fluoxetine was as effective as imipramine doses of 150 to 300 milligrams/day (Byerly et al, 1988). However, in one report (Bremner, 1984a), fluoxetine was reported superior to imipramine in several depression scales in a 5-week controlled study involving 40 depressed outpatients. In all studies, the incidence of side effects (anticholinergic effects, dizziness, drowsiness, dry mouth, cardiovascular effects) was less with fluoxetine as compared with imipramine; fluoxetine was associated with a greater incidence of anxiety or nervousness, insomnia, and excessive sweating. In another study, excessive sweating (as well as nausea) was higher with fluoxetine than imipramine (Stark & Hardison, 1985). Of significance, weight loss has occurred during fluoxetine therapy, as compared to generally no change in body weight or increases in weight with imipramine. The onset of antidepressant action of each drug has been similar, generally within one week.

e) Imipramine and fluoxetine had similar efficacy in multicenter, double-blind, placebo-controlled, outpatient studies comparing the treatment of major depressive disorder (Stark & Hardison, 1985). Five hundred forty patients were randomly assigned to receive either fluoxetine 60 to 80 milligrams daily, imipramine 150 to 300 milligrams daily (the majority of patients), or placebo. Patients were treated for up to 6 weeks in double-blind fashion. Imipramine and fluoxetine were both superior to placebo on all measures (Hamilton Psychiatric Rating Scale for Depression total, Raskin Severity of Depression Scale, Clinical Global

Impressions Severity of Illness Scale, Global Improvement and secondary symptom measures). Fluoxetine and imipramine were similarly effective on all general measures of improvement. Anorexia and nausea occurred to a significantly higher degree in fluoxetine-treated patients; constipation, dizziness, drowsiness, dry mouth, somatosensory disturbances, and excessive sweating were reported more frequently with imipramine.

f) The efficacy and safety of fluoxetine and imipramine was compared in 40 depressed outpatients in a double-blind, 5-week parallel trial (Bremner, 1984a). Fluoxetine was given in doses increasing from 20 to 40 milligrams daily, then to 60 milligrams daily, during the first week; imipramine doses were increased from 75 to 100 milligrams daily, then to 125 milligrams daily. During the second and third weeks, the maintenance dose of each drug was determined, with fluoxetine being given in doses up to 80 milligrams daily and imipramine up to 300 milligrams daily. During the fourth and fifth weeks of the study, the maintenance dose was achieved; the maintenance dose for most fluoxetine patients was 60 milligrams daily, and 175 or 200 milligrams daily for imipramine. Fluoxetine was reported superior to imipramine in the total Hamilton Psychiatric Rating Scale for Depression, as well as the HAM-D scales for anxiety/somatization, retardation and sleep disturbance. Fluoxetine was also reported more beneficial than imipramine in the Raskin Severity of Depression Scale and Covi Anxiety Scale. However, for the HAM-D total score, and the Raskin and Covi scales, fluoxetine was statistically superior to imipramine only during the last week of the study (week 5). The Clinical Global Impressions demonstrated the superiority of fluoxetine over imipramine for severity of depression but not global improvement. Weight loss (average, 3.8 pounds) occurred with fluoxetine during treatment, with an increase in weight being seen with imipramine (average, 0.7 pounds). Heart rate increased significantly with imipramine, as compared to slight decreases with fluoxetine. Blood pressure decreased with fluoxetine as compared with increases with imipramine, and fluoxetine was associated with a lesser degree of gastrointestinal disturbances, dizziness, and drowsiness. Dry mouth occurred in one of 20 fluoxetine patients and in 9 of 20 imipramine-treated patients, with nervousness occurring in three fluoxetine-treated patients and in two imipramine-treated patients.

4.6.L Maprotiline

4.6.L.1 Cerebral hemiplegia - Cerebrovascular accident

a) A randomized, placebo-controlled trial analyzed the effects of maprotiline and fluoxetine on the motor/functional capacities of poststroke patients undergoing physical therapy. Fifty-two severely disabled hemiplegic subjects after unilateral ischemic stroke in the territory of the middle cerebral artery were randomly assigned to three treatment groups - placebo, maprotiline (150 mg/day), or fluoxetine (20 mg/day) - during 3 months of physical therapy. The greatest improvement in walking and activity of daily living capacity was observed in the fluoxetine treatment group and the lowest in the maprotiline group. Furthermore, fluoxetine yielded a significantly larger number of patients with good recovery compared to maprotiline or placebo. These effects of the drugs were not related to their efficacy in treating depressive symptoms (Dam et al, 1996). Further investigation is needed to assess the efficacy of fluoxetine in facilitating recovery in stroke survivors undergoing physical therapy.

4.6.M Mianserin

4.6.M.1 Depression

a) Both mianserin- and fluoxetine-treated groups showed significant improvement in depressive symptoms at 3 and 6 weeks in a comparative study of the treatment of elderly depressed patients (Pia et al, 1992). Forty patients were randomly assigned to receive fluoxetine 20 milligrams/day or mianserin 40 milligrams/day. Fluoxetine showed a greater effect on Hamilton Rating Scale for Depression subgroup analyses. Mianserin was associated with a greater number of side effects requiring discontinuation of therapy.

b) In a placebo-controlled, double-blind trial in depressed outpatients, clinical improvement occurred in significantly more of the patients receiving fluoxetine (55%) than in those receiving placebo (23%); there was no significant difference between the results for mianserin (50%) and the results for fluoxetine or placebo. Although the authors counted subjects who withdrew within 2 weeks of the start of the 6-week trial as treatment failure, the results may still be considered equivocal due to the high overall dropout rates (46% for fluoxetine, 48% for mainserin, and 43% for placebo). The incidence of side effects was high, 92%, 88%, and 44% for fluoxetine, mianserin, and placebo, respectively (Muijen et al, 1988).

4.6.N Milnacipran

4.6.N.1 Depression

a) Several comparative trials (mainly unpublished) have indicated no significant difference in efficacy between milnacipran 50 to 150 mg twice daily and fluvoxamine 100 mg twice daily or fluoxetine 20 mg once daily in major depression (Guelfi et al, 1998; Anon, 1997). One study reported the superiority of fluoxetine 20 mg once daily (statistically significant for most parameters) over milnacipran 100 mg once daily in major depressive outpatients (Ansseau et al, 1994); however, this study suffered from methodological problems, the most significant being once-daily dosing of milnacipran, which may not achieve therapeutic levels.

b) Meta-analyses of studies comparing milnacipran and fluoxetine/fluvoxamine have been performed by the manufacturer; greater improvements (eg, Hamilton, Montgomery-Asberg) were described for milnacipran,

which were usually statistically significant (Lopez-Ibor et al, 1996; Anon, 1997; Elwood, 1997). However, only a few trials were selected for analysis, and not all patients in these trials were evaluated; the superiority of milnacipran was demonstrated only after results were subjected to multiple reanalysis (Anon, 1997).
c) Comparisons with other similar agents (eg, sertraline) are lacking.

4.6.O Mirtazapine

4.6.O.1 Depression

a) In a multicenter, double-blind, 6-week study, mirtazapine was as effective as fluoxetine but mirtazapine may have had an earlier onset of action (Wheatley et al, 1998). Patients with major depression were randomly selected to receive mirtazapine titrated up to 15 to 60 milligrams (mg) daily (n=66) or fluoxetine titrated up to 20 to 40 mg daily (n=67). The major endpoint was improvement on the 17-item Hamilton Rating Scale for Depression (17-HAM-D). The mean daily dosage was mirtazapine 39.8 mg/day and fluoxetine 23.8 mg/day. Both groups had improved 17-HAM-D scores throughout the study. Mirtazapine-treated patients had significantly better scores than the fluoxetine group on days 21 (p =0.16) and 28 (p=0.009). However, the magnitude of change between the 2 groups was not significantly different at the end of the study. At the endpoint, 23.3% of mirtazapine-treated and 25.4% of fluoxetine-treated patients had 17-HAM-D scores less than or equal to 7. The incidence of adverse events was low in both groups at 10% or less.

4.6.P Moclobemide

4.6.P.1 Depression

a) Moclobemide and fluoxetine were at least equally effective in the short-term treatment of depression with dysthymia. In a 6 week, double-blind study, patients were randomized to receive either moclobemide 150 milligrams (mg) twice daily (n=21) or fluoxetine 20 mg daily (n=21) for 6 weeks. At 6 weeks, the Hamilton depression rating scale (HDRS) scores showed similar decreases from baseline on both drugs. However, more patients achieved a greater than 50% decrease in the HDRS score on moclobemide (71%) than on fluoxetine (38%)(p less than 0.05). The clinical global impression scale also trended towards a better response with moclobemide but the difference was not significant. A larger study with a placebo group is needed to provide evidence of the possible superiority of moclobemide over fluoxetine (Duarte et al, 1996).
b) A study suggested a tendency for patients with atypical depression (using the MADRS and GCI scores) to respond more favorably to moclobemide than to fluoxetine (Lonnqvist et al, 1994). This needs to be substantiated by other studies. In one study, elderly patients with major depression associated with cognitive impairment or dementia showed significant improvement in orientation and memory recall ability with moclobemide compared with placebo (Fitton et al, 1992).

4.6.Q Nefazodone

Depression - Parkinson's disease

Depression - Sleep disorder

4.6.Q.1 Depression - Parkinson's disease

a) Nefazodone was more effective than fluoxetine in reducing extrapyramidal symptoms in patients with Parkinson's disease and comorbid depression, while both therapies were equally effective as antidepressants. In a prospective, randomized, single-blind study, depressed patients with Parkinson's disease (n=16) received nefazodone (100 to 300 milligrams (mg)/day; final mean dose 200 mg/day) or fluoxetine (20 to 50 mg/day; final mean dose, 25 mg/day) for 3 months. Antiparkinsonian medications remained stable from 4 weeks prior to initiation of nefazodone or fluoxetine therapy and throughout the study. A neurologist made blinded assessments and a psychiatrist made non-blinded assessments at baseline, and on days 15, 30, 60 and 90. The total Unified Parkinson Disease Rating Scale (UPDRS) score and the UPDRS part III score improved significantly over time in nefazodone- treated patients (time effect: p=0.004 and p=0.003, respectively). Fluoxetine-treated patients did not show a significant improvement in these scores over time. From baseline to endpoint, the nefazodone group showed a mean difference in total UPDRS scores of -12 as compared with 1.1 for the fluoxetine group. Scores for the Beck Depression Inventory and Clinical Global Impressions-Severity of Illness Scale improved significantly from baseline to endpoint in both treatment groups, with no significant difference between groups. Three patients in the nefazodone group discontinued treatment due to increased tremor or diarrhea. Other adverse events associated with either treatment were asthenia, anxiety, orthostatic dizziness, and constipation. Larger, well-controlled studies are needed to support the preferred use of nefazodone for the treatment of depression and comorbid Parkinson's disease (Avila et al, 2003).

4.6.Q.2 Depression - Sleep disorder

a) Nefazodone and fluoxetine were similarly effective for treating depression; however, nefazodone produced greater improvement in sleep disturbances than fluoxetine (Gillin et al, 1997). Patients (n=44) with

depression confirmed by the Hamilton Rating Scale for Depression (HAM-D) were randomly assigned to receive nefazodone 100 milligrams (mg) twice daily increased to 200 mg twice daily or fluoxetine 20 mg/day; the double dummy technique was used to maintain blinding. Nefazodone decreased the percentage of awake and movement time and the number of awakenings without altering rapid eye movement (REM) sleep or REM latency; whereas, fluoxetine decreased sleep efficiency, REM sleep, and increased the number of awakenings per night. While results of this study suggest that nefazodone improves sleep in depressed patients, larger, placebo controlled studies are needed to confirm the present findings.

4.6.R Nifedipine

4.6.R.1 Raynaud's phenomenon

a) Fluoxetine reduced the severity and frequency of attacks of Raynaud's phenomenon and was more effective than nifedipine. After a 2-week washout period, patients with primary (n=26) or secondary (n=27) Raynaud's phenomenon were given fluoxetine 20 milligrams (mg) daily or nifedipine 40 mg daily for 6 weeks. After another 2-week washout period, patients were crossed over to the alternate treatment for 6 weeks. Attack severity was significantly reduced by fluoxetine (p=0.0002) but not by nifedipine (p=0.14). Likewise, attack frequency was significantly reduced by fluoxetine (p=0.003) and not by nifedipine (p=0.22). Subgroup analysis showed significant reductions in attack severity and frequency with fluoxetine in females (p less than 0.0002 and p=0.0004, respectively), whereas the reduction in males was not statistically significant. Reductions in attack severity with fluoxetine were statistically significant in patients with primary Raynaud's phenomenon (p=0.009) and in those with secondary Raynaud's phenomenon (p=0.01). Reductions in attack frequency were significant for patients with primary Raynaud's phenomenon (p=003) but not for those with secondary Raynaud's phenomenon . Reductions with nifedipine were not statistically significant for those subgroups (Coleiro et al, 2001).

4.6.S Nortriptyline

Cerebrovascular accident - Depression

Depression

4.6.S.1 Cerebrovascular accident - Depression

a) Nortriptyline was superior to fluoxetine in the treatment of post-stroke depression; neither had an effect on improving recovery in depressed or non- depressed patients. Depressed patients who had suffered a stroke in the last 6 months randomly received either nortriptyline (n=16) or fluoxetine (n=23) for 12 weeks. Some patients also entered a 12-week crossover phase to placebo (n=17). Non-depressed stroke patients randomly received 12 weeks of nortriptyline (n=15), fluoxetine (n=17), or placebo (n=16). Initial nortriptyline doses of 25 milligrams (mg) were titrated to 100 mg over 6 weeks and fluoxetine 10 mg was titrated to 40 mg over 9 weeks. Outcome measures included the Hamilton Rating Scale for Depression (HAM-D) and the recovery of activities of daily living as measured by the Functional Independence Measures. After 12 weeks, the depressed patients in the nortriptyline group had a significantly lower mean HAM-D score as compared to those in the fluoxetine or placebo groups (p less than 0.05). The successful treatment rate of depression was 63% for nortriptyline, 9% for fluoxetine, and 24% for placebo. All patients showed significant (p less than 0.006) improvements in the Functional Independence measures with no differences seen between the depressed or non-depressed patients (Robinson et al, 2000).

4.6.S.2 Depression

a) In a double-blind, randomized, comparative study involving 156 patients, nortriptyline and fluoxetine were found to be equally efficacious in the treatment of acute major depression of moderate severity. Patients received either nortriptyline 100 mg/day or fluoxetine 40 mg/day in 2 divided doses for a total of 5 weeks. By the end of 5 weeks, the percentages of patients much or very much improved were 71% for nortriptyline and 65% for fluoxetine. The average total scores on the Hamilton Rating Scale for Depression, for patients in both treatment groups, declined by approximately 50%. Analysis of the side effect profiles revealed statistically significant differences for only 2 symptoms; nausea was more common among patients treated with fluoxetine, while dry mouth was more frequently associated with nortriptyline (Fabre et al, 1991).

4.6.T Olanzapine/Fluoxetine Hydrochloride

4.6.T.1 Depression - Schizophrenia

a) Results of an 8-week, double-blind trial demonstrated that patients receiving both olanzapine and fluoxetine in combination demonstrated greater improvement in Montgomery-Asberg Depression Rating Scale (MADRS) and Clinical Global Impression (CGI) total scores than patients receiving either medication alone. Twenty-eight patients with nonpsychotic treatment-refractory depression received olanzapine (5 to 20 milligrams/day) and/or fluoxetine (20 to 60 milligrams/day). In addition, there were no significant differences in adverse events among the 3 different treatment groups (Keck et al, 2000).

4.6.U Paroxetine

4.6.U.1 Depression

a) Paroxetine, fluoxetine, and sertraline were equally effective for the treatment of depression and for improving quality of life in patients in a primary care setting. In a 9-month, randomized, open-label trial (the ARTIST trial), depressed patients, whose symptoms warranted antidepressant treatment, according to their primary care physicians (PCP), were given paroxetine (n=180), fluoxetine (n=184) or sertraline (n=182). Starting doses were paroxetine 20 milligrams (mg), fluoxetine hydrochloride 20 mg, and sertraline 50 mg. The PCP could adjust the dose on the basis of clinical response and could switch the treatment to one of the other study drugs. Final average doses were 23.5 mg for paroxetine, 23.4 mg for fluoxetine, and 72.8 mg for sertraline. All 3 groups showed substantial improvement in depressive symptoms and quality of life. Overall, the percentage of patients categorized as having major depression dropped from 74% at baseline to 32% at 3 months, and 26% at 9 months. No significant differences were evident among the 3 groups. When data from subgroups (patients with major depression, patients who completed the trial on the drug initially assigned) were analyzed separately, still no differences among the drug treatments was evident. Patient satisfaction did not differ for the 3 groups. Changes in sexual function were small but tended to show improvement for all drug treatments. The drugs were associated with similar incidences of adverse effects and discontinuation rates (Kroenke et al, 2001).

b) Paroxetine and fluoxetine demonstrated similar efficacy following 6 weeks of treatment in depressed patients (De Wilde et al, 1993). However, the paroxetine-treated patients had a statistically significant difference in terms of reduction of Hamilton Rating Scale for depression after three weeks of treatment. This suggests that paroxetine may have a faster onset of activity than fluoxetine. The most commonly reported adverse effects were nausea and vomiting for both drugs.

4.6.V Phenelzine

4.6.V.1 Obsessive-compulsive disorder

a) In a small study (n=54), fluoxetine was superior (p less than 0.05) to phenelzine and placebo based on the Yale-Brown Obsessive Compulsive scale but not 3 other rating scales. Changes in score from baseline to week 10 were generally less than 1 point on the National Institute of Mental Health Global Obsessive Compulsive scale, the Clinical Global Impression scale, and the obsessive compulsive scale. Patients were randomly assigned to receive placebo, fluoxetine adjusted to a maximum of 80 milligrams (mg) daily, or phenelzine adjusted to a maximum of 60 mg daily. No serious adverse effects occurred in any of the treatment groups. The small sample size and relatively small changes limit the power of this study to detect differences between treatments.

4.6.W Protriptyline

4.6.W.1 Obstructive sleep apnea

a) Fluoxetine was better tolerated and equally effective as protriptyline in the treatment of obstructive sleep apnea. Six of 12 subjects with obstructive sleep apnea had a good response to either protriptyline (10 mg) or fluoxetine (20 mg) per day. The proportion of time spent in REM sleep and the number of apneas or hypopneas during NREM sleep were significantly reduced in both treatment groups. There was however, no significant improvement in the number of arterial oxygen desaturation events, the level of arterial oxygen desaturation, or the number of arousals with either treatment for the group as a whole (Hanzel et al, 1991).

4.6.X Reboxetine

4.6.X.1 Depression

a) SUMMARY: Reboxetine appears to be at least as effective and well-tolerated as fluoxetine.

b) In an 8-week double-blind comparison, oral REBOXETINE (4 milligrams (mg) twice daily; n=79) and oral FLUOXETINE (20 mg once daily; n=89) were equally efficacious and well tolerated in the treatment of patients with acute major depressive disorder (DSM-III-R). Decreases in scores on the Hamilton Rating Scale for Depression (HAM-D) were similar between groups (19.2 and 16.8 points, respectively, reboxetine and fluoxetine); the percentages for responders (at least 50% decrease in HAM-D score) and for those achieving remission (HAM-D score of 10 or less) were not significantly different in the 2 groups. No significant differences occurred between reboxetine- and fluoxetine-treated patients with respect to improvement in ratings on the Clinical Global Impression scale, the Montgomery-Asberg Depression Rating Scale, and the Social Adaptation Self-evaluation Scale. Most adverse effects were mild or moderate, with at least 1 adverse event occurring in 67.1% and 67.4%, respectively, of the reboxetine and fluoxetine groups. The authors suggested that reboxetine was more effective than fluoxetine in patients with the most severe depression based on a subgroup analysis involving those rated most severely ill at baseline (Massana et al, 1999).

c) In a placebo-controlled comparative trial employing a 21-item self- rating scale, the Social Adaptation Self-evaluation Scale (SASS), reboxetine was superior to placebo (p less than 0.05) and fluoxetine (p less than 0.05). Using the Hamilton Depression rating scale (HAM-D), both active treatments were superior to placebo in efficacy, but little difference in efficacy was observed between the 2 active treatments. Total

HAM-D scores at last assessment demonstrated average improvements of 13.3, 13.4 and 8.6 points, respectively, with reboxetine, fluoxetine, and placebo. Patients (n=302) were randomized to treatment with reboxetine 8 milligrams (mg) per day (n=103), fluoxetine 20 mg/day (n=100), or placebo (n=99) for an 8-week study period, with dosage increases to 10 mg/day reboxetine or 40 mg/day fluoxetine possible after 4 weeks of treatment. The mean total SASS scores were significantly higher for patients treated with either active treatment than those treated with placebo and significantly higher for reboxetine-treated patients than for the fluoxetine-treated group. An analysis of individual SASS items (point-biserial correlation analysis), reboxetine treatment demonstrated a significant correlation to improvement in individual item score for 20 of the 21 items compared with placebo; fluoxetine demonstrated significant correlation for 12 items compared with placebo. In direct comparison of SASS scores for groups treated with reboxetine and fluoxetine, 9 of the 21 items were significantly correlated with reboxetine, but none were significantly correlated with fluoxetine. A subset of patients classified as "in remission" (HAM-D total score of 10 or lower) at last assessment, 14 SASS items were significantly associated with reboxetine treatment. Both active treatments positively affected social motivation and behavior, but reboxetine also demonstrated efficacy in improving negative self- perception and motivation towards action (Dubini et al, 1997; Dubini et al, 1997a).

4.6.Y Sertraline

Depression

Obsessive-compulsive disorder

Weight gain

4.6.Y.1 Depression

a) Paroxetine, fluoxetine, and sertraline were equally effective for the treatment of depression and for improving quality of life in patients in a primary care setting. In a 9-month, randomized, open-label trial (the ARTIST trial), depressed patients, whose symptoms warranted antidepressant treatment, according to their primary care physicians (PCP), were given paroxetine (n=180), fluoxetine (n=184) or sertraline (n=182). Starting doses were paroxetine 20 milligrams (mg), fluoxetine hydrochloride 20 mg, and sertraline 50 mg. The PCP could adjust the dose on the basis of clinical response and could switch the treatment to one of the other study drugs. Final average doses were 23.5 mg for paroxetine, 23.4 mg for fluoxetine, and 72.8 mg for sertraline. All 3 groups showed substantial improvement in depressive symptoms and quality of life. Overall, the percentage of patients categorized as having major depression dropped from 74% at baseline to 32% at 3 months, and 26% at 9 months. No significant differences were evident among the 3 groups. When data from subgroups (patients with major depression, patients who completed the trial on the drug initially assigned) were analyzed separately, still no differences among the drug treatments was evident. Patient satisfaction did not differ for the 3 groups. Changes in sexual function were small but tended to show improvement for all drug treatments. The drugs were associated with similar incidences of adverse effects and discontinuation rates (Kroenke et al, 2001a).

b) An eight-week, double-blind, randomized study evaluated the efficacy and safety of fluoxetine vs sertraline in the treatment of major depression (DSM-III-R). One-hundred and eight out-patients with major depression entered into the study, but only 88 (48 sertraline and 40 fluoxetine) were evaluable. The final mean daily dose of fluoxetine was 28 milligrams (mg) and for sertraline 72 mg. Both treatment groups showed a statistically significant improvement from baseline at one week, and this was maintained until the end of treatment. No statistically significant differences were observed between the two treatment groups on the primary efficacy variables measured by Hamilton Rating Scale for Depression and Anxiety (HAMD), Clinical Global Impression Scale (CGI), Montgomery Asberg Depression Rating Scale (MADRS), Leeds Sleep Score scale and Zung Anxiety Rating Scale. The incidence of adverse events was similar: 39.3% for fluoxetine and 40.4% for sertraline. Most common were gastrointestinal (nausea and abdominal pain) and central nervous system (irritability, headache, somnolence, anorexia, agitation, anxiety and insomnia) effects. Sertraline was better tolerated than fluoxetine overall; 9.6% of sertraline-treated patients discontinued treatment, compared with 19.6% in the fluoxetine-treated group (Aguaglia et al, 1993). Investigation in a larger population is warranted to definitively establish the comparative efficacy and safety of the two drugs (Aguaglia et al, 1993).

4.6.Y.2 Obsessive-compulsive disorder

a) Both fluoxetine and sertraline were effective and well tolerated in the treatment of patients with obsessive- compulsive disorder (OCD). Patients received either sertraline, 50 to 200 milligrams (mg) per day (mean 139.5 +/- 58.5 mg; N=76), or fluoxetine, 20 to 80 mg/day (mean 56.7 +/- 23.0 mg; N=72), in a double-blind manner for 24 weeks. Group assignment was random and resulted in matched patient populations. Safety and efficacy measures were taken at the end of study weeks 1, 2, 4, 6, 8, 12, 16, 20, and 24 weeks or at the last assessment period if patients failed to complete the study. Primary efficacy measures included the Yale-Brown Obsessive- Compulsive Scale (Y-BOCS), the National Institute of Mental Health Global Obsessive-Compulsive Rating (NIHM-OC), and the Clinical Global Impression Severity and Improvement

scales (CGI-S and CGI-I). Secondary measures included the Hamilton Rating Scale for Depression (HAM-D 21 item version) and the Clinical Anxiety Scale (CAS). By the end of the 24 week study, both medications were effective and there were no significant treatment differences between the two groups. All primary and secondary measures showed similar amounts of improvement. The time-course of improvement was also similar for both groups, with sertraline showing a statistically significant greater improvement, on some measures (Y-BOCS change score and global severity of illness score) during some of the early assessments (weeks 4, 8, 12), however this study was not sufficiently powered to reliably detect differences between the drug treatments during this time period. Adverse drug effects were described as mild to moderate for both drugs with no significant difference in incidence reported for sertraline or fluoxetine (Bergeron et al, 2002).

4.6.Y.3 Weight gain

a) Weight gain is a common complaint during antidepressant therapy, and weight gain was significantly greater with paroxetine than either sertraline or fluoxetine after 32 weeks of treatment. Patients meeting DSM-IV criteria for major depressive disorder were randomized to double-blind treatment with sertraline 50 milligrams (mg) daily (n=96) fluoxetine 20 mg daily (n=20), or paroxetine 20 mg daily (n=96) for 4 weeks. Patients responding to this dose continued for an additional 6 weeks, and those not responding had their doses titrated based on response up to a dose of 200 mg sertraline, 60 mg fluoxetine, and 60 mg paroxetine, and then maintained at their optimal doses for 6 weeks. After this treatment phase, responders (Clinical Global Impressions-Improvement score of 1 or 2 for 2 consecutive weeks) continued for 16 additional weeks. The number of responders participating in the 16 additional weeks were similar for the 3 treatments: 48 sertraline, 44 fluoxetine, and 47 paroxetine. However, among these responders, the mean increase in weight in the paroxetine group (3.6%) was significant compared to the mean increase with sertraline (1.0%) and mean decrease with fluoxetine (-0.2%). A gain of 7% or greater in weight occurred in 25.5% of paroxetine patients, 4.2% of sertraline patients, and 6.8% of fluoxetine patients; this difference was significant(Fava et al, 2000).

4.6.Z St John's Wort

4.6.Z.1 Depression

a) St. John's Wort and fluoxetine significantly decreased symptoms of depression, with no difference found between groups in a randomized, double-blind, multicenter trial. Seventy patients diagnosed with mild to moderate depression by International Classification of Diseases (ICD)-10 criteria and having a Hamilton Rating Scale for Depression (HAMD) score between 16 and 24 were given either a Hypericum preparation (Calmigen(R)) 150 milligrams (mg) twice daily (n=35) or fluoxetine (Prozac(R)) 20 mg twice daily (n=35) for 6 weeks. The Hypericum perforatum extract contained 0.45 to 0.495 mg hypericin per 150 mg. Mean HAMD scores decreased significantly (p less than 0.001) for both groups: by 50% for the St. John's Wort group and 58% for the fluoxetine group. The changes for the 2 groups were not significantly different. Response rates (responder = a subject with 50% or greater decrease in HAMD score) were 55% for St. John's Wort and 66% for fluoxetine (p=0.41). Two patients in each group dropped out because of adverse effects: anxiety and nausea in the St. John's wort group and headache/dry mouth and nausea/diarrhea in the fluoxetine group (Behnke et al, 2002).

4.6.AA Trazodone

Depression

Mania

4.6.AA.1 Depression

a) Fluoxetine was as effective as trazodone in the treatment of major depression in a 6-week, double-blind, outpatient study involving 43 patients (Debus et al, 1988). The mean final doses of oral trazodone and fluoxetine in the responding patients were 284 and 29 mg daily, respectively. In nonresponders, the corresponding doses were 327 and 33 mg, respectively. HAM-D scores were lower at weeks 1 and 2 with fluoxetine when compared to trazodone and sleep was improved to a greater degree with trazodone. Adverse effects occurred to a similar degree with each agent with the exception of weight loss (more frequent with fluoxetine) and dizziness (more frequent with trazodone).

b) A six-week, double-blind trial compared fluoxetine (21 patients) with trazodone (19 patients) in the treatment of major depression (Perry et al, 1989). Although trazodone appeared to provide significantly greater improvement in HAM-D and Clinical Global Impressions scores at 3 weeks, the differences were not statistically significant at 4, 5, and 6 weeks. The authors surmise that the early difference may have been due to: an insufficient fluoxetine dose early in the trial (mean daily doses of fluoxetine and trazodone during week 3 were 21 mg and 241 mg, respectively), which was mitigated by larger subsequent increases in fluoxetine doses compared to trazodone doses; a slower onset of antidepressant action for fluoxetine, compared to trazodone; or a higher incidence of depressive illness lasting longer than one year in the

fluoxetine group (67%) than in the trazodone group (37%, reported incorrectly as 35%). Although the authors cite the statistically significant fluoxetine-associated weight loss seen in this trial (mean 1.98 lb/patient) as a clinically significant advantage for this agent, trazodone was also associated with weight loss in this study (mean 0.13 lb/patient), and the weight losses exhibited by the treatment groups were not significantly different.

4.6.AA.2 Mania

a) In literature reports of drug-induced mania caused by fluoxetine or trazadone, fluoxetine-treated patients manifested symptoms of mania more slowly than trazodone-treated patients (Terao, 1993). Mean time to onset of mania in fluoxetine-treated patients was significantly longer than trazodone-treated patients; 59 days (range = 10 to 154 days) versus 16 days (range =4 to 70 days) respectively.

4.6.AB Venlafaxine

Depression

Mixed anxiety and depressive disorder

4.6.AB.1 Depression

a) Analysis of pooled data from 8 randomized, double-blind studies (n=2045) showed a remission rate of depression of 45% with venlafaxine treatment, 35% with serotonin reuptake inhibitors (SSRIs), and 25% with placebo. Remission was defined as a total score of 7 or less on the 17-item Hamilton Rating Scale for Depression. Venlafaxine was significantly (p less than 0.001) more effective than SSRIs from 2 weeks onward and from placebo from 3 weeks onward. The end-of-therapy remission rate with SSRIs was significantly better than that with placebo (p=0.001). The odds ratio for remission was 1.5, in favor of venlafaxine over SSRIs (Thase et al, 2001).

b) Venlafaxine and fluoxetine had similar efficacy in the treatment of major depression in an 8 week, double-blind study. One-hundred and ninety-six patients were randomized to receive venlafaxine 37.5 milligrams (mg) twice daily, and 186 patients were randomized to receive fluoxetine 20 mg daily. If patients did not demonstrate an adequate response to therapy, venlafaxine was increased to 75 mg twice daily and fluoxetine to 20 mg twice daily. Primary outcome measures were scores on the Hamilton Rating Scale for Depression (HAM-D), the Montgomery-Asberg Depression Rating Scale (MADRS), the Clinical Global Impressions Severity of Illness Score (CGI-S), and the Clinical Global Impressions Improvement Score (CGI-I). In both treatment groups, HAM-D and MADRS scores improved significantly after 8 weeks of therapy. CGI-I scores were also improved, 80.6% of patients scored 1 (very much improved) or 2 (much improved) with venlafaxine and 83.9% with fluoxetine. Remission rates were equivalent in both groups, 60.2%, as determined by scores of 8 or less on the HAM-D scale. The only significant difference between treatment groups was the number of patients that required a dosage increase, fluoxetine (n=54) and venlafaxine (n=43). After treatment with higher doses, the number of patients scoring 1 on the CGI-I were significantly greater in the venlafaxine group than the fluoxetine group. The frequency of adverse events associated with both medications were comparable. Overall, there were very few differences in efficacy and tolerability between venlafaxine and fluoxetine (Cost e Silva, 1998).

c) Venlafaxine was effective in the treatment of major depression in an 8-week, open-label, comparative trial with fluoxetine. At the initiation of the study, 55 patients received venlafaxine 37.5 milligrams (mg) twice daily; 55 received fluoxetine 20 mg daily. If after 15 days of treatment response was inadequate, doses were increased to venlafaxine 75 mg twice daily and fluoxetine 40 mg daily. Both medications were significantly effective in treating major depression, as determined by improvements in patient scores on the Hamilton Depression Rating Scale (HAM-D), Montgomery-Asberg Depression Rating Scale (MADRS), and the Clinical Global Impressions Scale (CGI). There were no significant differences between the 2 medications. A trend towards greater improvement existed in patients requiring higher doses of venlafaxine than fluoxetine. Patients treated with venlafaxine were significantly more likely to experience constipation, dizziness, dry mouth, and vomiting (Diaz-Martinez et al, 1998).

d) Venlafaxine 200 mg/day for 4 weeks tended to be more effective than fluoxetine 40 mg/day in the treatment of 68 inpatients with major depression; however, the difference was not statistically significant by the end of the 6-week study period (Holliday & Benfield, 1995). Patients were assessed using the Hamilton Depression Rating Scale, Montgomery-Asberg Depression Rating Scale, and the Clinical Global Impressions scale. The incidence of adverse effects was similar for both groups.

4.6.AB.2 Mixed anxiety and depressive disorder

a) Extended release (XR) venlafaxine was more effective than placebo for improving the symptoms of depression and anxiety in patients with major depressive disorder and comorbid generalized anxiety disorder (GAD). However, time to response was greater in patients with comorbidity than in patients with major depressive disorder only. Fluoxetine, on the other hand, was not significantly better than placebo in patients with comorbidity. From the data of all the patients meeting DSM-IV criteria for major depressive disorder in a double-blind, randomized trial (n=368), results from the subset of patients who had comorbid

GAD (n=92) were analyzed separately and compared to results of the noncomorbid patients. Patients took once-daily doses of venlafaxine XR 75 milligrams (mg), fluoxetine 20 mg, or placebo for 12 weeks. Doses could be increased to a maximum of 225 mg for venlafaxine and 60 mg for fluoxetine. According to the criteria of more than 50% reduction (from baseline) in the Hamilton-Depression (HAM-D) and Hamilton-Anxiety (HAM-A) scores, improvement with venlafaxine was significantly greater (p less than 0.05) than with placebo by 12 weeks of treatment. There was a similar trend with fluoxetine, but at no time was fluoxetine statistically superior to placebo. About one third of patients with comorbidity showed response at 4 weeks; however, overall, there was no evident trend for a placebo- drug difference until after the eighth week of treatment. Among patients without comorbidity, the placebo-venlafaxine difference was evident as early as week 2. By week 12, response rate was 66% on HAM-D and 59% on HAM-A for those taking venlafaxine, 52% and 45% for those taking fluoxetine, and 36% and 24% for those taking placebo (Silverstone & Salinas, 2001).

4.6.AB.3 Adverse Effects

a) During a randomized, double-blind trial of elderly patients with major depression, the rate of study discontinuation as a result of adverse events was significantly greater for patients receiving venlafaxine (27%) compared with patients receiving placebo (9%; p=0.0017) but there were no significant differences when the fluoxetine group (19%) was compared with the placebo group (p=0.0666) or when fluoxetine was compared to venlafaxine (p=0.1838). Elderly patients (mean age, 71 years) with major depression were randomized to venlafaxine immediate-release (n=104), fluoxetine (n=100), or placebo (n=96) for 8 weeks. The dose of venlafaxine was titrated from 37.5 to 225 milligrams (mg) per day, and fluoxetine doses were titrated from 20 to 60 mg per day over a 29-day period. The most frequently reported adverse events in the venlafaxine and fluoxetine groups were nausea (45% and 23%, respectively) and headache (26% and 18%, respectively). The adverse events most frequently reported in the placebo group were headache (22%) and dry mouth (15%) (Schatzberg & Roose, 2006).

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Last Modified: June 26, 2009

DRUGDEX® Evaluations

RISPERIDONE

0.0 Overview

1) Class

a) This drug is a member of the following class(es):
Antipsychotic
Benzisoxazole

2) Dosing Information

a) Adult

1) if overlapping of antipsychotics is necessary, in all cases, the period of overlapping should be minimized; if swi antipsychotics and if medically appropriate, initiate risperidone therapy in place of the next scheduled injection (Pr RISPERDAL M-TAB(R) tablets, oral solution, orally disintegrating tablets, 2005)

2) previous oral antipsychotics should be continued for 3 weeks following the initiation of therapy with risperidone that adequate therapeutic concentrations are maintained until the main release phase of risperidone from the inje RISPERDAL(R) CONSTA(R) long acting injection, 2009)

a) Bipolar I disorder

1) (oral, monotherapy or in combination with lithium or valproate) initial, 2 to 3 mg ORALLY once a day (tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDA

2) (oral, monotherapy or in combination with lithium or valproate) maintenance, dosage adjustments sho mg/day at intervals of at least 24 hours; doses higher than 6 mg/day have not been evaluated in clinical t oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPEF

3) (intramuscular, monotherapy or in combination with lithium or valproate) initiation of therapy, recomm oral risperidone prior to initiation of treatment with the risperidone long-acting IM injection; oral risperidon medication should be given with the initial injection and should be continued for 3 weeks and then discor (R) CONSTA(R) long acting injection, 2009)

4) initial, 25 mg IM every 2 weeks (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009)

5) (intramuscular, monotherapy or in combination with lithium or valproate) maintenance, dose may be i at intervals of at least 4 weeks; clinical effects of dose adjustment should not be expected earlier than 3 higher dose; MAX 50 mg IM every 2 weeks (Prod Info RISPERDAL(R) CONSTA(R) long acting injection

b) Schizophrenia

1) (oral) initial, 1 mg ORALLY twice daily, with increases in increments of 1 mg twice daily on the secon target dose of 3 mg twice daily on the third day OR 1 mg ORALLY once daily, with increases to 2 mg dai dose of 4 mg once daily on the third day (Prod Info RISPERDAL(R), RISPERDAL M-TAB(R) tablets, ora tablets, 2005)

2) (oral) maintenance, small, ORAL dose increments/decrements of 1 to 2 mg are recommended at inte Maximal effect is usually seen within a range of 4 to 8 mg/day. Doses above 6 mg/day for twice-daily dos efficacious than lower doses; the safety of doses above 16 mg/day has not been evaluated in clinical tria RISPERDAL M-TAB(R) tablets, oral solution, orally disintegrating tablets, 2005)

3) (intramuscular) initiation of therapy, recommended to establish tolerability to oral risperidone prior to i risperidone long-acting IM injection; oral risperidone or another antipsychotic medication should be giver should be continued for 3 weeks and then discontinued (Prod Info RISPERDAL(R) CONSTA(R) long act

4) initial, 25 mg IM every 2 weeks (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009)

5) (intramuscular) maintenance, dose may be increased to 37.5 mg or 50 mg IM at intervals of at least 4 adjustment should not be expected earlier than 3 weeks after the injection of the higher dose; MAX 50 m RISPERDAL(R) CONSTA(R) long acting injection, 2009)

b) Pediatric

1) safety and effectiveness of long-acting risperidone injection has not been established in pediatric patients und RISPERDAL(R) CONSTA(R) long acting injection, 2009)

2) safety and effectiveness of oral risperidone in pediatric patients less than 13 years of age with schizophrenia o mania have not been established (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB 2007; Prod Info RISPERDAL(R) oral solution, 2007)

3) safety and effectiveness or oral risperidone in pediatric patients less than 5 years of age with autistic disorder Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod solution, 2007)

a) Autistic disorder - Irritability

1) dosing individualized according to the response and tolerability (Prod Info RISPERDAL(R) oral tablets disintegrating tablets, 2006)

2) (weight less than 20 kg) initial, 0.25 mg ORALLY once a day or half the total daily dose given twice da minimum of 4 days to 0.5 mg/day (Prod Info RISPERDAL(R) oral tablets, oral solution, orally-disintegrati

3) (weight less than 20 kg) maintenance, 0.5 mg ORALLY once a day or half the total daily dose given t a minimum of 14 days and may increase doses at 2-week intervals or longer, in increments of 0.25 mg p clinical response; use with caution in children weighing less than 15 kg (Prod Info RISPERDAL(R) oral ta disintegrating tablets, 2006)

4) (weight 20 kg or greater) initial, 0.5 mg ORALLY once a day or half the total daily dose given twice da
minimum of 4 days to 1 mg/day (Prod Info RISPERDAL(R) oral tablets, oral solution, orally-disintegrating
5) (weight 20 kg or greater) maintenance, 1 mg ORALLY once a day or half the total daily dose given tw
minimum of 14 days; may increase doses at 2-week intervals or longer, in increments of 0.5 mg per day
response (Prod Info RISPERDAL(R) oral tablets, oral solution, orally-disintegrating tablets, 2006)
6) in patients with persistent somnolence, a once-daily dose at bedtime or half the daily dose twice daily
be considered (Prod Info RISPERDAL(R) oral tablets, oral solution, orally-disintegrating tablets, 2006)

b) Bipolar I disorder
1) (10 years and older) initial, 0.5 mg ORALLY once daily as a single dose in the morning or evening; ad
than 24 hours and in increments of 0.5 to 1 mg/day up to a maximum recommended dose of 2.5 mg/day
tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDA

c) Schizophrenia
1) (13 years and older) initial, 0.5 mg ORALLY once daily as a single dose in the morning or evening; ad
than 24 hours and in increments of 0.5 to 1 mg/day up to a recommended dose of 3 mg/day (Prod Info R
Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solut

3) Contraindications
a) hypersensitivity to risperidone or to any product component (Prod Info RISPERDAL(R) CONSTA(R) long acting inje
RISPERDAL(R) oral tablets, solution, RISPERDAL(R) M-TAB(R) orally disintegrating tablets, 2008)

4) Serious Adverse Effects
a) Agranulocytosis
b) Death
c) Diabetic ketoacidosis
d) Hypothermia
e) Leukopenia
f) Neuroleptic malignant syndrome
g) Neutropenia
h) Pancreatitis
i) Priapism
j) Purpura
k) Seizure
l) Sudden cardiac death
m) Syncope
n) Tardive dyskinesia
o) Thrombocytopenia
p) Thrombotic thrombocytopenic purpura

5) Clinical Applications
a) FDA Approved Indications
1) Autistic disorder - Irritability
2) Bipolar I disorder
3) Schizophrenia

1.0 Dosing Information

Drug Properties

Storage and Stability

Adult Dosage

Pediatric Dosage

1.1 Drug Properties

A) Information on specific products and dosage forms can be obtained by referring to the Tradename List (Product In
B) Synonyms
Risperidone
C) Physicochemical Properties
1) Molecular Weight
a) 410.49 (Canada, 1997)
2) pKa
a) pKa1: 8.24 ; pKa2: 3.11 (Prod Info Risperdal, 93)

1.2 Storage and Stability

A) Preparation
1) Intramuscular route

a) Preparation

1) Risperidone long-acting injection must only be suspended in the diluent supplied by the manufacturer and diluent to come to room temperature prior to reconstitution. After injecting the diluent into the vial, sh minimum of 10 seconds. The suspension should appear uniform, thick, and milky in color. The particles v particle should remain. It should be used immediately after suspension and must be used within 6 hours pass before injection, resuspend by shaking vigorously, as settling will occur over time once the product RISPERDAL(R) CONSTA(R) long acting injection, 2009).

b) Administration

1) Do NOT inject intravenously. Administer by deep intramuscular injection into the deltoid or gluteal mu arms or two buttocks. Use a 1-inch 21 gauge needle for deltoid injection and a 2-inch 20 gauge needle fo combine different dosage strengths in a single administration (Prod Info RISPERDAL(R) CONSTA(R) lon

2) Oral route

a) Orally Disintegrating Tablets

1) Oral disintegrating tablets are supplied in blister packs and should not be opened until ready for use. do NOT push the tablet through the foil backing because this could damage the tablet. Use dry hands to unit and immediately place the entire tablet on the tongue. The tablet should be consumed immediately o unit. Tablets disintegrate in the mouth within seconds and can be swallowed subsequently with or withou tablet (Prod Info RISPERDAL(R), RISPERDAL M-TAB(R) tablets, oral solution, orally disintegrating table

b) Oral Solution

1) Calibrated dispensing-pipettes are provided with risperidone oral solution. The oral solution is compat juice, and low-fat milk. However, it is not compatible with cola or tea (Prod Info RISPERDAL(R), RISPER solution, orally disintegrating tablets, 2005)

B) Intramuscular route

1) The long-acting injection should be stored in the refrigerator between 36 and 46 degrees Fahrenheit (F) (2 and refrigeration is not available, it may be stored at temperatures not exceeding 77 degrees F (25 degrees C) for no l administration; protect from light (Prod Info Risperdal(R) Consta(TM), 2003h).

C) Oral route

1) Solution

a) Store the oral solution at room temperature 59 to 77 degrees Fahrenheit (15 to 25 degrees Celsius); prote Info Risperdal(R), 2004).

2) Tablet

a) Tablets should be stored at room temperature 59 to 77 degrees Fahrenheit (15 to 25 degrees Celsius); pr (Prod Info Risperdal(R), 2004).

1.3 Adult Dosage

Normal Dosage

Dosage in Renal Failure

Dosage in Hepatic Insufficiency

Dosage in Geriatric Patients

Dosage in Other Disease States

1.3.1 Normal Dosage

Intramuscular route

Intramuscular route/Oral route

Oral route

1.3.1.A Intramuscular route

Bipolar I disorder

Schizophrenia

1.3.1.A.1 Bipolar I disorder

a) For patients who have not previously taken oral risperidone, it is recommended that tolerability be est prior to initiation of treatment with the long-acting risperidone intramuscular injection (Prod Info RISPERD injection, 2009).

b) The recommended dose of risperidone long-acting injection is 25 milligrams (mg) intramuscularly eve responding to a lower dose, the dose may be increased to 37.5 mg or 50 mg at intervals of at least 4 we dosage adjustment should not be expected earlier than 3 weeks following the first injection of the higher not exceed 50 mg every 2 weeks. Patients should be maintained on the lowest effective dose and shoul determine the necessity of continued treatment. Risperidone long-acting injection should be administere into the deltoid or gluteal muscles, alternating between the two arms or two buttocks; should be administ professional using the enclosed safety needle and should NOT be administered intravenously (Prod Info long acting injection, 2009).

c) Oral risperidone or another antipsychotic medication should be administered with the initial injection o should be continued for 3 weeks (and then discontinued) so that adequate therapeutic plasma concentra main release phase of risperidone from the injection site (Prod Info RISPERDAL(R) CONSTA(R) long ac

d) Do NOT combine different dosage strengths of risperidone long-acting injection in a single administra CONSTA(R) long acting injection, 2009).

e) Supplementation with oral risperidone or another antipsychotic should accompany reinitiation of treat discontinued from risperidone long-acting injection (Prod Info RISPERDAL(R) CONSTA(R) long acting in

1.3.1.A.2 Schizophrenia

a) For patients who have not previously taken oral risperidone, it is recommended that tolerability be est prior to initiation of treatment with the long-acting risperidone intramuscular injection (Prod Info RISPERD injection, 2009).

b) The recommended dose of risperidone long-acting injection is 25 milligrams (mg) intramuscularly eve responding to a lower dose, the dose may be increased to 37.5 mg or 50 mg at intervals of at least 4 we dosage adjustment should not be expected earlier than 3 weeks following the first injection of the higher not exceed 50 mg every 2 weeks. Patients should be maintained on the lowest effective dose and shoul determine the necessity of continued treatment. Risperidone long-acting injection should be administere into the deltoid or gluteal muscles, alternating between the two arms or two buttocks; should be administ professional using the enclosed safety needle and should NOT be administered intravenously (Prod Info long acting injection, 2009).

c) Oral risperidone or another antipsychotic medication should be administered with the initial injection o should be continued for 3 weeks (and then discontinued) so that adequate therapeutic plasma concentra main release phase of risperidone from the injection site (Prod Info RISPERDAL(R) CONSTA(R) long ac

d) Do NOT combine different dosage strengths of risperidone long-acting injection in a single administra CONSTA(R) long acting injection, 2009).

e) Supplementation with oral risperidone or another antipsychotic should accompany reinitiation of treat discontinued from risperidone long-acting injection (Prod Info RISPERDAL(R) CONSTA(R) long acting in

1.3.1.B Intramuscular route/Oral route

1) Switching Antipsychotics

a) If overlapping of antipsychotics is necessary, in all cases, the period of overlapping should be minimiz previous antipsychotic treatment may be acceptable for some patients while gradual discontinuation may switching patients from depot antipsychotics and if medically appropriate, initiate risperidone therapy in p injection (Prod Info RISPERDAL(R), RISPERDAL M-TAB(R) tablets, oral solution, orally disintegrating ta

b) Previous oral antipsychotics should be continued for 3 weeks following the initiation of therapy with ris ensure that adequate therapeutic concentrations are maintained until the main release phase of risperido begun (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).

1.3.1.C Oral route

Bipolar I disorder

Schizophrenia

1.3.1.C.1 Bipolar I disorder

a) Risperidone is approved for use as monotherapy or in combination with lithium or valproate in the trea Risperidone should be administered once daily at an initial dose of 2 to 3 milligrams (mg) per day. If nee be made at intervals of at least 24 hours in increments/decrements of 1 mg/day. In clinical trials, doses r used; doses higher than 6 mg/day have not been studied (Prod Info RISPERDAL(R) oral tablets, 2007; R orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007).

b) The effectiveness of risperidone for maintenance therapy beyond 3 weeks has not been evaluated. W treatment in a responding patient is generally desirable for maintenance of the initial response and for pr

there are no data from clinical trials to support the use of risperidone in long-term treatment (Prod Info RI
Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solut

1.3.1.C.2 Schizophrenia

a) Low doses, 1 milligram (mg) twice daily, should be generally used initially to avoid the typical first-dos
adrenoreceptor antagonists. Doses may be increased by 1 mg twice daily until a target dose of 6 mg per
on day 3. Controlled trials have demonstrated that total daily doses of up to 8 mg on a once-daily regime
some patients, slower titration may be indicated. Further increases/decreases in dose, if indicated, shoul
weekly intervals since steady state for the active metabolite would not be attained for one week in the typ
maximal antipsychotic efficacy was seen with doses between 4 and 8 mg/day while effective oral doses
However, doses above 6 mg/day at a twice-daily dosing regimen are not generally recommended as the
extrapyramidal and other adverse effects, with no additional treatment benefit than lower doses (Prod Inf
M-TAB(R) tablets, oral solution, orally disintegrating tablets, 2005; Borison et al, 1992b; Anon, 1991a; M

b) If risperidone is discontinued, reinitiate with the initial titration schedule (Prod Info RISPERDAL(R), RI
oral solution, orally disintegrating tablets, 2005).

c) In a controlled, clinical trial, risperidone given at once-daily doses of 2 to 8 milligrams was effective in
had been clinically stable for 4 weeks or longer. However, patients should be periodically re-assessed to
maintenance treatment (Prod Info RISPERDAL(R), RISPERDAL M-TAB(R) tablets, oral solution, orally d

d) The Consensus Study Group on Risperidone Dosing reports their empiric clinical experience has res
titration strategy for many patients. They target a goal of 2 to 4 milligrams (mg) daily during the first week
response occurs, the dose is increased to 6 to 8 mg/day during the second week of treatment. If there is
the next 2 weeks, then a higher dose may be warranted, usually increases of 2 mg/week up to a maximu
attempted. Any further dosage adjustments, if indicated, should be made at intervals of no less than 1 w

e) In a small study (n=11) rapid oral-loading risperidone was well tolerated within 24 hours. Seven patie
milligrams (mg) twice daily in 16 hours; 3 patients achieved the maintenance dose in 24 hours and 1 pati
three times daily (Feifel et al, 2000).

f) In dose comparison studies chiefly utilizing chronic schizophrenic patients, the most consistently posit
were seen for the 6 milligram (mg) dose group (Marder & Meibach, 1994a; Chouinard et al, 1993b; Mard
in one study (Muller-Spahn, 1992a). In a review of 12 double-blind studies (n=2099), symptom improvem
mg/day (Lemmens et al, 1999). There was no suggestion of increased benefit from larger doses. Anothe
naive patients found a superior outcome in the 2 to 4 mg group versus a 5 to 8 mg dose group (Kopala e

1.3.1.C.3 Bioequivalence

a) Risperdal(R) orally disintegrating tablets are bioequivalent to Risperdal(R) tablets (Prod Info RISPER
tablets, oral solution, orally disintegrating tablets, 2005; van Schaick et al, 2003).

1.3.2 Dosage in Renal Failure

A) Oral

1) The recommended initial dosage in patients with severe renal impairment is 0.5 milligrams twice daily. Do
milligrams twice daily until a dose of 3 milligrams per day (1.5 milligrams twice daily) is reached. Further incre
be limited to 0.5 milligrams twice daily at weekly intervals. Slower titration may be necessary in some patients
RISPERDAL M-TAB(R) tablets, oral solution, orally disintegrating tablets, 2005). In Germany, a maximum do
recommended for patients in renal failure and caution is advised for overall use in this patient population until
(Fachinfo Risperdal(R), 1997).

B) Intramuscular

1) Patients with renal impairment should receive titrated doses of oral risperidone prior to initiating treatment
intramuscular injection. For titration, the recommended initial dosage is 0.5 milligram (mg) of oral risperidone
the dosage may be increased to 1 mg twice daily or 2 mg once daily during the second week. If a dose of 2 m
risperidone long-acting injection can be given intramuscularly every 2 weeks. Although the efficacy has not b
12.5 mg of risperidone long-acting injection may be given to patients with renal impairment. Continue oral sup
following the first injection until the main release of risperidone from the injection site has begun. Slower titrat
patients (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).

1.3.3 Dosage in Hepatic Insufficiency

A) Oral

1) The recommended initial dosage in patients with severe hepatic impairment is 0.5 milligrams (mg) twice a
0.5 mg twice daily until a dose of 3 mg per day (1.5 mg twice daily) is reached. Further increases in dose, if ir
mg twice daily at weekly intervals. Slower titration may be necessary in some patients (Prod Info RISPERDAL
tablets, oral solution, orally disintegrating tablets, 2005). In Germany, a maximum dose of 2 mg twice daily is
hepatic insufficiency and caution is advised for overall use in this patient population until further research is a
2000).

B) Intramuscular

1) Patients with hepatic impairment should receive titrated doses of oral risperidone prior to initiating treatme
acting intramuscular (IM) injection. For titration, the recommended initial dosage is 0.5 milligram (mg) of oral
week; then the dosage may be increased to 1 mg twice daily or 2 mg once daily during the second week. If a
mg of risperidone long-acting injection can be given IM every 2 weeks. Although the efficacy has not been co
of risperidone long-acting injection may be given to patients with hepatic impairment. Continue oral suppleme
first injection until the main release of risperidone from the injection site has begun. Slower titration may be n
Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).

1.3.4 Dosage in Geriatric Patients

A) Oral

1) The initial dosage should be 0.5 milligrams (mg) orally twice a day. Doses may be increased by 0.5 mg tw day (1.5 mg twice daily) is reached. Further increases in dose, if indicated, should be limited to 0.5 mg twice titration may be necessary in some patients. If once-daily dosing is desired, initiate and titrate patient on a twi to achieve target dose and switch to once-daily dosing thereafter (Prod Info RISPERDAL(R), RISPERDAL M- orally disintegrating tablets, 2005). In Germany, a maximum dose of 2 mg twice daily is recommended for ge advised for overall use in this patient population until further research is available (Fachinfo Risperdal(R), 200

B) Intramuscular

1) The recommended dosage of risperidone long-acting injection for elderly patients is 25 milligrams intramu risperidone or another antipsychotic medication should be administered with the initial injection of long-acting continued for 3 weeks (and then discontinued) so that adequate therapeutic plasma concentrations are maint phase of risperidone from the injection site (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 200

1.3.6 Dosage in Other Disease States

A) Debilitated Patients

1) Debilitated patients may have less ability to eliminate risperidone than normal patients. The initial dosage twice daily. Doses may be increased by 0.5 mg twice daily until a dose of 3 mg per day (1.5 mg twice daily) is dose, if indicated, should be limited to 0.5 mg twice daily at weekly intervals. Slower titration may be necessa dosing is desired, initiate and titrate patient on a twice-daily regimen for 2 to 3 days to achieve target dose an thereafter (Prod Info RISPERDAL(R), RISPERDAL M-TAB(R) tablets, oral solution, orally disintegrating table

B) Hypotension Predisposition

1) Patients with a predisposition to hypotension or for whom hypotension may pose a risk should receive a r dosage should be 0.5 milligrams (mg) twice a day. Doses may be increased by 0.5 mg twice daily until a dos daily) is reached. Further increases in dose, if indicated, should be limited to 0.5 mg twice daily at weekly inte necessary in some patients (Prod Info RISPERDAL(R), RISPERDAL M-TAB(R) tablets, oral solution, orally d

C) Concomitant Medications

1) For patients on CYP2D6 inhibitors (eg, fluoxetine, paroxetine), risperidone long-acting intramuscular injec 12.5 milligrams (mg) or 25 mg. For patients already on 25 mg of long-acting risperidone injection and initiatin continue the 25 mg dose. However, if clinical judgement warrants, the dose of risperidone may be decreased acting intramuscular injection may be discontinued. Although, the efficacy of 12.5 mg has not been confirmed RISPERDAL(R) CONSTA(R) long acting injection, 2009).

2) For patients on CYP3A4 inducers (eg, carbamazepine, phenytoin, rifampin, phenobarbital), the dose of ris intramuscular injection will need to be titrated accordingly, especially during initiation or discontinuation of the CYP3A4 inducers are discontinued, continue with the 25 milligram (mg) dose. However, if clinical judgement may be decreased to 12.5 mg or risperidone long-acting intramuscular injection may be discontinued. Althou not been confirmed in clinical trials (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).

D) Poor Tolerability to Psychotropic Medications

1) Although the efficacy has not been confirmed in clinical trials, 12.5 milligrams intramuscularly may be give poor tolerability to psychotropic medications (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 20

1.4 Pediatric Dosage

1.4.1 Normal Dosage

Intramuscular route

Oral route

1.4.1.A Intramuscular route

1) The safety and effectiveness of long-acting risperidone injection has not been established in pediatric pati Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).

1.4.1.B Oral route

Autistic disorder - Irritability

Bipolar I disorder

Schizophrenia

1.4.1.B.1 Autistic disorder - Irritability

a) Dosing should be individualized according to the response and tolerability. Doses are administered o dose twice daily. In patients with persistent somnolence, a once-daily dose at bedtime or half the daily d the dose may be considered (Prod Info RISPERDAL(R) oral tablets, oral solution, orally-disintegrating ta
b) For children weighing less than 20 kilograms (kg), the recommended initial dose is 0.25 milligram (m increased after a minimum of 4 days to 0.5 mg per day. Doses should be maintained for at least 14 days week intervals or longer, in increments of 0.25 mg per day if the patient has not achieved sufficient clinic clinical response has been achieved and maintained, doses may be lowered gradually to obtain the optir safety. Risperidone should be used with caution in children weighing less than 15 kg (Prod Info RISPER orally-disintegrating tablets, 2006).
c) For children weighing 20 kilograms (kg) or greater, the recommended initial dose is 0.5 milligram (mg increased after at least 4 days to 1 mg per day. Doses should be maintained for at least 14 days. They n intervals or longer, in increments of 0.5 mg per day if the patient has not achieved sufficient clinical respo response has been achieved and maintained, doses may be lowered gradually to obtain the optimal bala Info RISPERDAL(R) oral tablets, oral solution, orally-disintegrating tablets, 2006).
d) In clinical trials, a response (based on at least 25% improvement on ABC-I) was achieved in 90% of p risperidone between 0.5 mg and 2.5 mg per day. In one of the pivotal trials, the maximum daily dose of r weighing less than 20 kg, 2.5 mg in patients weighing 20 kg or greater, or 3 mg in patients weighing grea therapeutic effect reached plateau (Prod Info RISPERDAL(R) oral tablets, oral solution, orally-disintegrat

1.4.1.B.2 Bipolar I disorder

a) For the short-term treatment of bipolar mania, initiate treatment at 0.5 milligrams (mg) orally once dail either in the morning or evening. Dose adjustments should occur at intervals not less than 24 hours and as indicated and tolerated. The maximum recommended daily dose is 2.5 mg/day. If somnolence occurs into 2 equal doses. Data are unavailable to support use of risperidone beyond 3 weeks for the treatment therapy is required for extended periods, periodically reevaluate the long-term usefulness for the individu (R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RIS

1.4.1.B.3 Schizophrenia

a) In children 13 years of age and older, initiate treatment at 0.5 milligrams (mg) orally once daily, given the morning or evening. Dose adjustments should occur at intervals not less than 24 hours and in increm indicated and tolerated. The maximum recommended daily dose is 3 mg/day. If somnolence occurs, the equal doses. Data are unavailable to support use of risperidone beyond 8 weeks in adolescents with sch is required for extended periods, periodically reevaluate the long-term usefulness for the individual patier reinitiate with the initial titration schedule. When switching schizophrenic patients from depot antipsychot place of the next scheduled injection (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDA tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007).

4) The safety and effectiveness in children less than 13 years of age with schizophrenia or less than 10 year associated with bipolar I disorder have not been established (Prod Info RISPERDAL(R) oral tablets, 2007; Pr orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007).
5) The safety and effectiveness in pediatric patients with autistic disorder less than 5 years of age have not b RISPERDAL(R) oral tablets, oral solution, orally-disintegrating tablets, 2006).
6) Risperidone was beneficial in children and adolescents with pervasive developmental disorder. Starting d twice daily and increased in 0.25 mg/day increments every 5 to 7 days have been used (Fisman & Steele, 19 0.75 to 6 mg daily (Perry et al, 1997; Fisman & Steele, 1996).

2.0 Pharmacokinetics

Onset and Duration

Drug Concentration Levels

ADME

2.1 Onset and Duration

A) Onset
1) Initial Response
a) Psychotic symptoms, oral: 1 to 2 weeks (Vanden Borre et al, 1993; Borison et al, 1992a; Mesotten et al, 1
b) Psychotic symptoms, intramuscular: 3 weeks (Prod Info Risperdal(R) Consta(TM), 2003i).
1) Following a single intramuscular injection of long-acting risperidone, a small initial release of the drug 1% of the dose), followed by a lag time of 3 weeks. The main release of the drug occurs from 3 weeks o weeks, and subsides by 7 weeks following the injection (Prod Info Risperdal(R) Consta(TM), 2003i).
B) Duration
1) Single Dose
a) Psychotic symptoms, intramuscular: 7 weeks (Prod Info Risperdal(R) Consta(TM), 2003i).
1) Following a single intramuscular injection of long-acting risperidone, a small initial release of the drug

1% of the dose), followed by a lag time of 3 weeks. The main release of the drug occurs from 3 weeks o
weeks, and subsides by 7 weeks following the injection (Prod Info Risperdal(R) Consta(TM), 2003i).

2) Multiple Dose

a) Psychotic symptoms, oral: 1 year (Addington et al, 1993; Carman & Wyatt-Knowles, 1993; Bressa et al, 1
(Mertens, 1991).

1) Clinical improvement in positive and negative symptoms has been observed for up to 7 months (Addi
Wyatt-Knowles, 1993; Bressa et al, 1991; De Wilde & Dierick, 1991); (Mertens, 1991).

2.2 Drug Concentration Levels

A) Therapeutic Drug Concentration

1) Oral

a) A therapeutic range has not been established. A dose of 6 mg/day produces a risperidone serum level of
patients (Olesen et al, 1998).

b) Plasma concentrations are dose proportional over the dosing range of 1 to 16 mg daily (Prod Info Risperd
1993a).

B) Time to Peak Concentration

1) Oral, solution: 1 hour (Prod Info Risperdal(R), 2004).

2.3 ADME

Absorption

Distribution

Metabolism

Excretion

Elimination Half-life

2.3.1 Absorption

A) Bioavailability

1) Oral: 70% (CV=25%) (Prod Info Risperdal(R), 2004)(Nyberg et al, 1993a; Anon, 1991; Vanden Bussche e

a) The relative oral bioavailability from a tablet was 94% (CV=10%) when compared to a solution (Prod
et al, 1993a; Anon, 1991; Vanden Bussche et al, 1988).

B) Effects of Food

1) None (Prod Info Risperdal(R), 2004)(Anon, 1991; Vanden Bussche et al, 1988).

2.3.2 Distribution

A) Distribution Sites

1) Protein Binding

a) Risperidone: approximately 90% (Prod Info Risperdal(R), 2004)(Prod Info Risperdal(R) Consta(TM),

b) 9-hydroxyrisperidone: 77% (Prod Info Risperdal(R), 2004)(Prod Info Risperdal(R) Consta(TM), 2003i)

B) Distribution Kinetics

1) Volume of Distribution

a) 1 to 2 liters/kilogram (Prod Info Risperdal(R), 2004)(Prod Info Risperdal(R) Consta(TM), 2003i).

2.3.3 Metabolism

A) Metabolism Sites and Kinetics

1) Liver, extensive (Prod Info Risperdal(R) Consta(TM), 2003i); (Prod Info Risperdal(R), 2004)(Nyberg et al,

a) Risperidone is extensively metabolized in the liver. The main metabolic pathway is through hydroxyla
hydroxyrisperidone by the enzyme, CYP2D6 (debrisoquin hydroxylase) with a second minor pathway of
Risperdal(R) Consta(TM), 2003i); (Prod Info Risperdal(R), 2004)(Nyberg et al, 1993a).

b) Metabolism is sensitive to the debrisoquine hydroxylation type genetic polymorphism (Prod Info Risp
1993a).

B) Metabolites

1) 9-hydroxyrisperidone, active (Prod Info Risperdal(R), 2004)(Nyberg et al, 1993a).

a) Metabolite is approximately equi-effective to the parent compound in terms of receptor binding activity
(Nyberg et al, 1993a).

2.3.4 Excretion

A) Total Body Clearance

1) 3.2 to 13.7 liters/hour (L/hr) (Prod Info Risperdal(R) Consta(TM), 2003i).

a) The clearance of risperidone and risperidone plus 9-hydroxyrisperidone is 13.7 L/h and 5 L/h in exten

3.3 L/h and 3.2 L/h in poor metabolizers, respectively (Prod Info Risperdal(R) Consta(TM), 2003i).

2.3.5 Elimination Half-life

A) Parent Compound

1) ELIMINATION HALF-LIFE

a) oral: 20 to 30 hours (Prod Info Risperdal(R), 2004)(Anon, 1991; Vanden Bussche et al, 1988).

1) The apparent half-life of risperidone was 3 hours in extensive metabolizers and 20 hours in poor Risperdal(R), 2004).

2) ELIMINATION HALF-LIFE

a) intramuscular: 3 to 6 days (Prod Info Risperdal(R) Consta(TM), 2003i).

1) The half-life of intramuscular risperidone is related to the erosion of the microspheres and subse (Prod Info Risperdal(R) Consta(TM), 2003i).

B) Metabolites

1) 9-hydroxyrisperidone, 21 to 30 hours (Prod Info Risperdal(R), 2004).

a) The apparent half-life of 9-hydroxyrisperidone was 21 hours in extensive metabolizers and 30 hours i Risperdal(R), 2004).

3.0 Cautions

Contraindications

Precautions

Adverse Reactions

Teratogenicity/Effects in Pregnancy/Breastfeeding

Drug Interactions

3.0.A Black Box WARNING

1) Intramuscular (Powder for Suspension, Extended Release)

a) Increased Mortality in Elderly Patients with Dementia Related Psychosis: Elderly patients with dementia-relate antipsychotic drugs are at an increased risk of death. Analyses of 17 placebo-controlled trials (modal duration of 1 taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of between 1.6 times to 1.7 tir treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients wa rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared heart failure, sudden death) or infectious (eg, pneumonia) in nature. Observational studies suggest that, similar to treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increa studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clea for the treatment of patients with dementia-related psychosis (Prod Info RISPERDAL(R) CONSTA(R) long acting

2) Oral (Tablet; Tablet, Disintegrating; Solution)

a) Increased Mortality in Elderly Patients with Dementia Related Psychosis - Elderly patients with dementia-relate antipsychotic drugs are at an increased risk of death. Analyses of 17 placebo controlled trials (modal duration of 1 taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of between 1.6 times to 1.7 tir treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients wa rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared heart failure, sudden death) or infectious (eg, pneumonia) in nature. Observational studies suggest that, similar to treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increa studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clea for the treatment of patients with dementia-related psychosis (Prod Info RISPERDAL(R) CONSTA(R) long acting

3.1 Contraindications

A) hypersensitivity to risperidone or to any product component (Prod Info RISPERDAL(R) CONSTA(R) long acting inj RISPERDAL(R) oral tablets, solution, RISPERDAL(R) M-TAB(R) orally disintegrating tablets, 2008)

3.2 Precautions

A) elderly patients with dementia-related psychosis (unapproved use); increased risk of death; most deaths were attri (eg, heart failure or sudden death) or infections (eg, pneumonia) (Prod Info RISPERDAL(R) CONSTA(R) long acting ir RISPERDAL(R) oral tablets, solution, RISPERDAL(R) M-TAB(R) orally disintegrating tablets, 2008)

B) agranulocytosis; potentially fatal; has been reported; risk factors include history of low WBC, leukopenia and neutr (R) CONSTA(R) long acting injection, 2009)

C) cardiovascular or cerebrovascular disease or conditions that predispose patients to hypotension (eg, dehydration, medications); increased risk of orthostatic hypotension (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2 oral tablets, solution, RISPERDAL(R) M-TAB(R) orally disintegrating tablets, 2008)

D) cerebrovascular adverse events (stroke, transient ischemic attack), including fatalities, have been reported in elde

psychosis (unapproved use) (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009; Prod Info RISPERDA
RISPERDAL(R) M-TAB(R) orally disintegrating tablets, 2008)
E) conditions that may contribute to elevated body temperature; may disrupt body temperature regulation (Prod Info F
acting injection, 2009; Prod Info RISPERDAL(R) oral tablets, solution, RISPERDAL(R) M-TAB(R) orally disintegrating
F) diabetes mellitus or risk factors for diabetes mellitus; increased risk of severe hyperglycemia (Prod Info RISPERDA
injection, 2009; Prod Info RISPERDAL(R) oral tablets, solution, RISPERDAL(R) M-TAB(R) orally disintegrating tablets
G) diseases or conditions that could affect metabolism or hemodynamic responses (Prod Info RISPERDAL(R) CONS
Prod Info RISPERDAL(R) oral tablets, solution, RISPERDAL(R) M-TAB(R) orally disintegrating tablets, 2008)
H) elderly patients; increased risk of tardive dyskinesia, especially among elderly women (Prod Info RISPERDAL(R) C
2009; Prod Info RISPERDAL(R) oral tablets, solution, RISPERDAL(R) M-TAB(R) orally disintegrating tablets, 2008)
I) elderly patients; increased risk of orthostatic hypotension, especially during the initial dose-titration period (oral) (Pr
tablets, solution, RISPERDAL(R) M-TAB(R) orally disintegrating tablets, 2008)
J) esophageal dysmotility and aspiration may occur; use cautiously in patients at risk for aspiration pneumonia (Prod
long acting injection, 2009; Prod Info RISPERDAL(R) oral tablets, solution, RISPERDAL(R) M-TAB(R) orally disintegra
K) hepatic impairment, severe; increased risperidone exposure and side effects have been reported; dosage adjustm
RISPERDAL(R) CONSTA(R) long acting injection, 2009; Prod Info RISPERDAL(R) oral tablets, solution, RISPERDAL
disintegrating tablets, 2008)
L) hyperglycemia has been reported, some may lead to ketoacidosis, hyperosmolar coma, or death (Prod Info RISPE
acting injection, 2009; Prod Info RISPERDAL(R) oral tablets, solution, RISPERDAL(R) M-TAB(R) orally disintegrating
M) hyperprolactinemia; may result in galactorrhea, amenorrhea, gynecomastia, impotence, hypogonadism and decre
hyperprolactinemia appears to be higher with risperidone relative to other antipsychotic agents (Prod Info RISPERDAL
injection, 2009; Prod Info RISPERDAL(R) oral tablets, solution, RISPERDAL(R) M-TAB(R) orally disintegrating tablets
N) increased duration of therapy and/or higher cumulative doses; increased risk of tardive dyskinesia (Prod Info RISP
acting injection, 2009; Prod Info RISPERDAL(R) oral tablets, solution, RISPERDAL(R) M-TAB(R) orally disintegrating
O) neuroleptic malignant syndrome, potentially fatal, has been reported in association with antipsychotic drugs; imme
Info RISPERDAL(R) CONSTA(R) long acting injection, 2009; Prod Info RISPERDAL(R) oral tablets, solution, RISPER
disintegrating tablets, 2008)
P) Parkinson's disease or dementia with Lewy bodies; increased sensitivity to antipsychotic medications (Prod Info RI
acting injection, 2009; Prod Info RISPERDAL(R) oral tablets, solution, RISPERDAL(R) M-TAB(R) orally disintegrating
Q) priapism has been reported; severe cases may require surgical intervention (Prod Info RISPERDAL(R) CONSTA(R
Prod Info RISPERDAL(R) oral tablets, solution, RISPERDAL(R) M-TAB(R) orally disintegrating tablets, 2008)
R) renal impairment, severe; increase in free fraction of risperidone and side effects have been reported; dosage adju
RISPERDAL(R) CONSTA(R) long acting injection, 2009; Prod Info RISPERDAL(R) oral tablets, solution, RISPERDAL
disintegrating tablets, 2008)
S) seizure disorder, history, or conditions which lower seizure threshold (Prod Info RISPERDAL(R) CONSTA(R) long
RISPERDAL(R) oral tablets, solution, RISPERDAL(R) M-TAB(R) orally disintegrating tablets, 2008)
T) suicide risk; close monitoring of high-risk patients recommended (Prod Info RISPERDAL(R) CONSTA(R) long actir
RISPERDAL(R) oral tablets, solution, RISPERDAL(R) M-TAB(R) orally disintegrating tablets, 2008)
U) tardive dyskinesia, potentially irreversible; discontinue treatment if appropriate (Prod Info RISPERDAL(R) CONSTA
Prod Info RISPERDAL(R) oral tablets, solution, RISPERDAL(R) M-TAB(R) orally disintegrating tablets, 2008)

3.3 Adverse Reactions

Cardiovascular Effects

Dermatologic Effects

Endocrine/Metabolic Effects

Gastrointestinal Effects

Hematologic Effects

Hepatic Effects

Musculoskeletal Effects

Neurologic Effects

Ophthalmic Effects

Psychiatric Effects

Renal Effects

Reproductive Effects

Respiratory Effects

Other

3.3.1 Cardiovascular Effects

Cardiac dysrhythmia

Hypertension

Orthostatic hypotension

Palpitations

Peripheral edema

Sudden cardiac death

Summary

Syncope

Tachycardia

3.3.1.A Cardiac dysrhythmia

1) During clinical trials of schizophrenic and bipolar I disorder patients, there was no significant difference in patients receiving risperidone long-acting injection at recommended doses and patients receiving placebo (P CONSTA(R) long acting injection, 2009).

2) The manufacturer reports that intergroup comparisons for pooled, placebo-controlled studies did not reve differences between oral risperidone and placebo in mean changes from baseline in ECG parameters, includ and heart rate. There was a mean increase in heart rate of 1 beat per minute when all risperidone doses wer controlled studies in several indications, as compared with no change for patients who received placebo. In s schizophrenia, higher doses of risperidone (8 to 16 milligrams/day) were associated with a higher mean incre per minute) as compared with placebo (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007).

3) QRS prolongation and QTc prolongation, sometimes resulting in death, have been reported in patients ta (Duenas-Laita et al, 1999ak; Ravin & Levenson, 1997p; Gesell & Stephen, 1997h; Lo Vecchio et al, 1996h; E

4) A 40-year-old man experienced symptomatic bradyarrhythmia 1 day following an increase in his risperido (mg)/day to 6 mg/day. The patient developed sinus bradycardia (38 beats per minute) and had several episo seconds. During this time, the QTc interval was 410 milliseconds. Risperidone was discontinued and the sym following 48 hours (Goyal & Goyal, 2003).

5) A 7-year-old boy developed sinus dysrhythmia and a QTc interval of 0.46 seconds after a single dose of r attention deficit hyperactivity disorder (Gesell & Stephen, 1997h).

6) A 34-year-old woman with no history of cardiac disease developed fatal pulseless electrical activity followi day 3, she developed postural hypotension and was then maintained on 2 milligrams (mg) twice daily. On da and was treated for pulseless electrical activity with a prolonged QRS interval and an abnormal QTc interval Despite resuscitative efforts, the patient expired (Ravin & Levenson, 1997p).

3.3.1.B Hypertension

1) Incidence: 3% (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009)

2) In a 24-month, double-blind, placebo-controlled trial of adult bipolar I disorder patients, hypertension was receiving risperidone intramuscular (n=154) as monotherapy compared with 1% in placebo (n=149) (Prod Inf long acting injection, 2009).

3.3.1.C Orthostatic hypotension

1) Incidence: intramuscular, schizophrenia, less than 2%; bipolar I disorder, less than 4% (Prod Info RISPER

injection, 2009)
2) Orthostatic hypotension was reported in less than 2% of schizophrenic patients and in less than 4% of bip premarketing trials of various design types in patients receiving long-acting intramuscular risperidone for schi (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).
3) Orthostatic hypotension associated with dizziness, tachycardia, and in some patients, syncope (0.2% of p receiving oral risperidone, and 0.8% of patients receiving intramuscular risperidone in multiple-dose studies) clinical trial revealed a positive dose-related trend for orthostatic dizziness. A dose reduction should be consi risperidone cautiously in patients with known cardiovascular or cerebrovascular disease and conditions which hypotension (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrat RISPERDAL(R) oral solution, 2007; Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).

3.3.1.D Palpitations
1) Incidence: oral, adults, 2% (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB 2007; Prod Info RISPERDAL(R) oral solution, 2007); intramuscular, schizophrenia, less than 2%; bipolar I dis RISPERDAL(R) CONSTA(R) long acting injection, 2009)
2) Palpitations were reported in less than 2% of schizophrenic patients and in less than 4% of bipolar disorde trials of various design types in patients receiving long-acting intramuscular risperidone for schizophrenia and RISPERDAL(R) CONSTA(R) long acting injection, 2009).
3) In two 3-week, double-blind, placebo-controlled studies of adjuvant oral risperidone therapy in adults, palp patients receiving risperidone (n=127) compared to 0% for placebo (n=126) (Prod Info RISPERDAL(R) oral ta RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007).
4) During premarketing (n=2607) evaluation of oral risperidone, palpitations were reported. Data from a large of risperidone (1, 4, 8, 12, and 16 mg/day) revealed a positive dose-related trend (p less than 0.05) for palpita oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL

3.3.1.E Peripheral edema
1) Incidence: adults, up to 3%; children, less than 5% (Prod Info RISPERDAL(R) CONSTA(R) long acting inj RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod solution, 2007)
2) In a 12-week placebo-controlled trial of adult schizophrenic patients , peripheral edema was reported in 2% 25 mg (n=99) and 50 mg (n=103) of risperidone intramuscular therapy, respectively, compared with 1% in pla RISPERDAL(R) CONSTA(R) long acting injection, 2009).
3) During premarketing risperidone studies of various design types, peripheral edema was reported in less th oral therapy, and in less than 5% of pediatric patients receiving oral therapy (Prod Info RISPERDAL(R) oral ta RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007).
4) In a study of 110 elderly Chinese patients (age 65 or greater), 16% experienced peripheral edema. Leg-pi complaint leading to discontinuation of treatment (Hwang et al, 2001).
5) A 27-year-old woman developed pitting edema in the legs and moderate periorbital and facial edema duri (4 milligrams per day (mg/day)) treatment for schizophrenia. She experienced a 5 kilogram (kg) weight gain d received diphenhydramine during the first 3 weeks for the management of mild dystonia and restlessness; thi after week 3. Resolution of edema occurred within 1 week when the dose of risperidone was reduced to 3 mg was reported during an 8-month follow-up period (Tamam et al, 2002).
6) A 35-year-old male experienced edema with a 15 pound weight gain after 2 1/2 weeks of risperidone thera included divalproex sodium and clorazepate. Diuretic therapy with hydrochlorothiazide 25 milligrams (mg)/day resolved the edema within 1 week. The authors note that although edema is associated with divalproex, it did was added. They suggest that both of these medications when used together may be more likely to cause ed mechanism (Baldassano & Ghaemi, 1996).

3.3.1.F Sudden cardiac death
1) In a large, retrospective, cohort study that included a primary cohort of 93,300 users of antipsychotic drug antipsychotic drugs, there was an increased risk of sudden cardiac death in adult participants 30 to 74 years who were using risperidone compared to those who were not using antipsychotic drugs (incidence-rate ratio, (CI), 2.26 to 3.76; p less than 0.001). In participants being treated with atypical antidepressants (clozapine, ol risperidone), the incidence-rate ratio for sudden cardiac death increased from 1.59 (95% CI, 1.03 to 2.46) for (95% CI, 2.25 to 3.65) for those using high doses (p=0.01) (Ray et al, 2009).

3.3.1.G Summary
1) AV block, myocardial infarction, palpitations, hypertension, hypotension, pulmonary embolism, T-wave inv prolonged QRS interval, abnormal QTc interval, tachycardia, bradyarrhythmia, and edema have all been repo administration. Stroke and transient ischemic attack have been reported in the elderly (mean age 85 years ol CONSTA(R) long acting injection, 2009; Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007).

3.3.1.H Syncope
1) Incidence: adults, up to 2%(Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB 2007; Prod Info RISPERDAL(R) oral solution, 2007; Prod Info RISPERDAL(R) CONSTA(R) long acting inject
2) Syncope was reported in 0.2% (6/2607) of patients receiving oral risperidone in Phase 2 and 3 clinical tria tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R)

3) During a 12-week clinical trial, syncope was observed in 2% of patients receiving risperidone 25 mg long-
patients receiving risperidone 50 mg long-acting injection (n=103), compared with 0% of patients receiving pl
studies, syncope occurred in 0.8% (12/1499) of patients receiving long-acting injections (Prod Info RISPERD
injection, 2009).

3.3.1.I Tachycardia

1) Incidence: oral, adults, up to 5%; children, up to 7% (Prod Info RISPERDAL(R) oral tablets, 2007; Prod In
disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007); intramuscular, schizophrenia, less
than 4% (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009)

2) Tachycardia was reported in less than 2% of schizophrenic patients and in less than 4% of bipolar disorde
trials of various design types in patients receiving long-acting intramuscular risperidone for schizophrenia and
RISPERDAL(R) CONSTA(R) long acting injection, 2009), and in up to 5% of adult patients receiving oral ther
patients receiving oral therapy. Tachycardia was responsible for 0.3% and 0.5% of discontinuation of therapy
patients receiving 2 to 8 mg/day (n=366) and in 8 to 16 mg/day or greater (n=198), respectively, compared w
Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; F
solution, 2007).

3) A compensatory increased heart rate (7 to 8 beats/minute) may develop at therapeutic doses of risperidor

3.3.2 Dermatologic Effects

Acne

Discoloration of skin

Dry skin

Injection site reaction

Peeling of skin

Rash

Summary

3.3.2.A Acne

1) Incidence: adults, 1% to 2% (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TA
2007; Prod Info RISPERDAL(R) oral solution, 2007)

2) During risperidone clinical trials, acne was reported in 2% of adult patients receiving intramuscular therapy
patients receiving oral therapy (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TA
2007; Prod Info RISPERDAL(R) oral solution, 2007; Prod Info RISPERDAL(R) CONSTA(R) long acting inject

3.3.2.B Discoloration of skin

1) Incidence: oral, adults, less than 1%; children, less than 5% (Prod Info RISPERDAL(R) oral tablets, 2007;
TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007)

2) During risperidone clinical trials, skin discoloration was reported in less than 1% of adult patients receiving
of pediatric patients receiving oral therapy (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDA
tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007).

3.3.2.C Dry skin

1) Incidence: intramuscular, adults, up to 2% (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2

2) In a 12-week placebo-controlled trial of adult schizophrenic patients, dry skin was reported in 2% and 0%
(n=99) and 50 mg (n=103) of risperidone intramuscular therapy, respectively, compared with 0% in placebo (
CONSTA(R) long acting injection, 2009).

3.3.2.D Injection site reaction

1) Incidence: intramuscular, 1% (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009)

2) During the 10th week of a 12-week clinical trial, injection site reaction (including redness, swelling, or indu
patients receiving risperidone 25 mg or 50 mg long-acting injection (n=202). Between the first and last injectio
mean injection pain intensity scores (0=no pain to 100=unbearable pain) in the placebo group (16.7 to 12.6) a
injection groups (25 mg: 12 to 9; 50 mg: 18.2 to 11.8). In a separate study in which long-acting risperidone inj
muscle every 2 weeks over 8 weeks period, only mild injection site events were observed in patients receivin
hours after the injection (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).

3.3.2.E Peeling of skin

1) A 37-year-old male with DSM-IV bipolar I disorder experienced rash and desquamation following oral risp
presented to an inpatient clinic as euphoric and irritable with rapid speech, sleep and appetite disturbances. T
consisted of several manic episodes since the age of 23. Treatment with oral risperidone solution 2 mg at be
lithium (900 mg/day), diazepam (15 mg/day), zolpidem (10 mg at bedtime), and procyclidine hydrochloride (5
and rash under the patient's eyes were seen on day 3 of treatment. Risperidone and lithium were both increa
mg/day, respectively, on day 4, due to persisting manic symptoms. By day 5, the rash had spread over the er
desquamation developing over areas of his face. Risperidone was discontinued on day 6 and switched to que
was increased to 600 mg/day to manage the patient's manic symptoms. Lithium dosing was maintained. Two
discontinuation, the patient's skin lesions had completely cleared (Chae & Kang, 2008).

3.3.2.F Rash

1) Incidence: oral, adults, 2% to 4%; children, up to 11% (Prod Info RISPERDAL(R) oral tablets, 2007; Prod
orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007); intramuscular, schizophreni
disorder, less than 4% (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009)

2) Rash was reported in less than 2% of schizophrenic patients and in less than 4% of bipolar disorder patie
various design types in patients receiving long-acting intramuscular risperidone for schizophrenia and bipolar
(R) CONSTA(R) long acting injection, 2009).

3) During risperidone clinical trials, rash was reported in 2% to 4% of adult patients receiving oral therapy, ar
patients receiving oral therapy (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TA
2007; Prod Info RISPERDAL(R) oral solution, 2007).

4) A 37-year-old male with DSM-IV bipolar I disorder experienced rash and desquamation following oral risp
presented to an inpatient clinic as euphoric and irritable with rapid speech, sleep and appetite disturbances. T
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mg/day, respectively, on day 4, due to persisting manic symptoms. By day 5, the rash had spread over the er
desquamation developing over areas of his face. Risperidone was discontinued on day 6 and switched to que
was increased to 600 mg/day to manage the patient's manic symptoms. Lithium dosing was maintained. Two
discontinuation, the patient's skin lesions had completely cleared (Chae & Kang, 2008).

3.3.2.G Summary

1) Rash, dry skin, seborrhea, skin discoloration, injection site reaction, photosensitivity, skin exfoliation, pruri
sweating, skin ulceration, and dermatitis were reported with risperidone therapy (Prod Info RISPERDAL(R) o
RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007; Proc
(R) long acting injection, 2009).

3.3.3 Endocrine/Metabolic Effects

Body temperature above normal

Diabetes mellitus

Diabetic ketoacidosis

Excessive thirst

Hyperglycemia

Hyperprolactinemia

Hypothermia

Metabolic syndrome

Weight gain

Weight loss

3.3.3.A Body temperature above normal

1) Hyperthermia has been associated with the use of antipsychotic agents, including oral risperidone (Prod I
2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral sol

RISPERDAL(R) CONSTA(R) long acting injection, 2009).

3.3.3.B Diabetes mellitus

See Drug Consult reference: ATYPICAL ANTIPSYCHOTIC AGENTS - EFFECT ON GLUCOSE AND RISK C

3.3.3.C Diabetic ketoacidosis

1) Incidence: rare (Lu & Yan, 2009)

2) Diabetic ketoacidosis in patients with impaired glucose metabolism has been reported during the risperidc Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).

3) A 27-year-old schizophrenic male was hospitalized with fever and severe diabetic ketoacidosis (DKA) resu of risperidone treatment. The patient had no history of diabetes. On admission his serum glucose was 1297 r metabolic acidosis were positive, and his glycosylated hemoglobin was 13%. Risperidone was immediately d insulin treatment and fluid replacement, the patient died within 12 hours due to the rapid progression of DKA. risperidone-induced hyperglycemia resulting in fatal diabetic ketoacidosis (Lu & Yan, 2009).

3.3.3.D Excessive thirst

1) Incidence: adults, less than 1%; children, less than 5% (Prod Info RISPERDAL(R) oral tablets, 2007; Proc orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007)

2) During the double-blind, placebo-controlled trials for oral risperidone, less than 1% of adults and less than experiencing thirst (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disi Info RISPERDAL(R) oral solution, 2007).

3) Risperidone was suspected of causing polydipsia in a 28-year-old male receiving the drug for treatment of type). His schizophrenia had been refractory to various oral and injectable antipsychotics and electroconvulsi risperidone 8 mg/day (which improved his psychotic symptoms). Within 2 weeks, he started drinking water ex variable period of a few minutes to 8 hours. His polydipsia episodes initially occurred intermittently at 10- to 1 became more frequent (ie, every 3 to 4 days, sometimes twice daily), especially after his risperidone was incı to polydipsia, the patient experienced polyuria and, occasionally, nausea, vomiting, marked lassitude, slurring an episode. Staring and unresponsiveness would sometimes precede an episode. Later risperidone was dec decrease in frequency of polydipsia episodes occurred. Then risperidone was withdrawn. Polydipsia disappe period. The patient was started on clozapine, and had no return of polydipsia. The authors noted that during t excessive amounts of water, he never developed hyponatremia or water intoxication. Diabetes mellitus or ins inappropriate secretion of antidiuretic hormone (SIADH), had been ruled out, and he was taking no other mec et al, 2002).

3.3.3.E Hyperglycemia

1) Incidence: oral, adults, less than 1%; children, less than 5% (Prod Info RISPERDAL(R) oral tablets, 2007; TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007); intramuscular, schizop disorder, less than 4% (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009)

2) Hyperglycemia, including cases associated with ketoacidosis, hyperosmolar coma, or death, has been rep atypical antipsychotics, including risperidone. Hyperglycemia has resolved in some cases after discontinuatio cases, continuation of antidiabetic treatment was required after drug discontinuation (Prod Info RISPERDAL(RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007; Proc (R) long acting injection, 2009).

3) Hyperglycemia was reported in less than 2% of schizophrenic patients and in less than 4% of bipolar diso trials of various design types in patients receiving long-acting intramuscular risperidone for schizophrenia anc RISPERDAL(R) CONSTA(R) long acting injection, 2009). Hyperglycemia was reported in less than 1% of adı and in less than 5% of pediatric patients receiving oral therapy (Prod Info RISPERDAL(R) oral tablets, 2007; orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007).

3.3.3.F Hyperprolactinemia

1) Summary

a) Hyperprolactinemia was reported in less than 2% of schizophrenic patients and in less than 4% of bip premarketing trials of various design types in patients receiving long-acting intramuscular risperidone for disorder (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).

b) Antipsychotic-induced hyperprolactinemia was reported in 65.6%, 45.1%, and 42.4% of women of ch postmenopausal women, and men, respectively, in an open-label, clinical trial of patients treated with firs risperidone at average doses of 4.2 to 5.2 mg/day. Compared to baseline, prolactin levels were significar following use of first-generation antipsychotics (ie, chlorpromazine, droperidol, flupenthixol, fluphenazine perazine, perphenazine, pimozide, trifluoperazine, and zuclopenthixol) or risperidone in several clinical tr schizophrenia. Younger patients and women of childbearing potential have a greater risk for hyperprolac higher doses of these antipsychotics. Hyperprolactinemia may potentially result in menstrual disturbance bone mineral density (ie, osteopenia and osteoporosis), and breast and pituitary tumors (Bostwick et al,

c) Elevated prolactin levels associated with risperidone use appear to be dose-dependent and greater ir elevations are higher with risperidone use compared to elevations associated with other antipsychotic ag oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPEF

d) Adverse events associated with hyperprolactinemia include inhibited reproductive function, galactorrh and impotence. Hypogonadism associated with chronic hyperprolactinemia may lead to reduced bone de (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating table

(R) oral solution, 2007).

2) Incidence: oral, adults, less than 1%; children, 49% to 87% (Prod Info RISPERDAL(R) oral tablets, 2007; orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007); intramuscular, schizophreni disorder, less than 4% (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009)

3) Adult

a) Hyperprolactinemia was reported in less than 2% of schizophrenic patients and in less than 4% of bip premarketing trials of various design types in patients receiving long-acting intramuscular risperidone for disorder (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009). Hyperprolactinemia was re receiving oral therapy (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB or Prod Info RISPERDAL(R) oral solution, 2007).

b) Risperidone is associated with increased prolactin which persists with chronic therapy (Prod Info RIS acting injection, 2009; Hellings et al, 2005; Kleinberg et al, 1999; Caracci & Ananthamoorthy, 1999). Mal hypothyroidism may be particularly sensitive to a neuroleptic-induced elevation of prolactin levels and clo within the first 3 months of initiating risperidone therapy (Mabini et al, 2000).

c) Prolactin concentrations increased and remained elevated for at least 26 weeks in males and females experiencing a significantly greater increase. During a double-blind, placebo-controlled trial, serum prola during the acute and maintenance phases in a subset of 10 children and adolescents and 11 adults with developmental disorders. For children and adolescents (mean age of 12.5 years), the mean acute and m were 0.92 milligrams/day (mg/day) (range, 0.25 to 1.36 mg/day) and 1.25 mg per day (0.25 to 2 mg/day) age of 35.3 years), the mean acute and maintenance doses of risperidone were 2 mg/day and 1.36 mg/d respectively. Normal prolactin concentrations were 1.6 to 18.8 nanograms/mL for males and 1.4 to 24.2 n children and adolescents, the mean baseline serum prolactin of 13.2 +/- 8.6 nanograms/milliliter (ng/mL) nanograms/mL (p=0.01) in the acute phase and 37.9 +/- 10.4 nanograms/mL (p=0.02) in the maintenanc weeks from baseline. In adults, the mean baseline serum prolactin of 11.6 +/- 7.4 nanograms/mL increas nanograms/mL (p=0.001) in the acute phase and 67.8 +/- 62.9 nanograms/mL (p=0.02) in the maintenar weeks from baseline. With similar mean baseline prolactin levels in adult females and males (11.7 nanog nanograms/mL; p=0.86), the prolactin elevation was 2.2 greater in adult females compared with adult ma versus 57.8 nanograms/mL; p=0.01) and 3.7 times greater in the maintenance phase (98.5 nanograms/m (Hellings et al, 2005).

d) In a small study of 20 women, risperidone produced prolactin levels twice as high as in women receiv (Caracci & Ananthamoorthy, 1999). Another author reviewed the results of 4 clinical trials and found sign levels with risperidone versus haloperidol. In women, risperidone increased prolactin levels significantly l receiving haloperidol 10 milligrams/day (mg/day) (p less than 0.001). Women receiving haloperidol 20 m to women receiving risperidone. In men, risperidone 4 to 6 mg/day produced significantly higher prolactin mg/day (p=0.01) but not 20 mg/day. With doses of risperidone 6 mg/day and greater, prolactin levels wer haloperidol doses (p less than 0.01). Elevated prolactin levels are associated with amenorrhea, galactorr osteoporosis. Amenorrhea or galactorrhea has been reported in 10% of female patients receiving risperi

4) Pediatric

a) In double-blind clinical trials lasting 8 weeks in children and adolescents (5 to 17 years) with autistic d other than autistic disorder, bipolar mania, or schizophrenia, elevated prolactin levels were reported in 4 compared to 2% of patients receiving placebo (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RI disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007).

b) In placebo-controlled clinical trials in adolescents (13 to 17 years) with schizophrenia and children an with bipolar disorder, elevated prolactin levels were reported in 82% to 87% of patients receiving risperid placebo (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegra RISPERDAL(R) oral solution, 2007).

c) Prolactin concentrations increased and remained elevated for at least 26 weeks in males and females experiencing a significantly greater increase. During a double-blind, placebo-controlled trial, serum prola during the acute and maintenance phases in a subset of 10 children and adolescents and 11 adults with developmental disorders. For children and adolescents (mean age of 12.5 years), the mean acute and m were 0.92 milligrams/day (mg/day) (range, 0.25 to 1.36 mg/day) and 1.25 mg per day (0.25 to 2 mg/day) age of 35.3 years), the mean acute and maintenance doses of risperidone were 2 mg/day and 1.36 mg/d respectively. Normal prolactin concentrations were 1.6 to 18.8 nanograms/mL for males and 1.4 to 24.2 n children and adolescents, the mean baseline serum prolactin of 13.2 +/- 8.6 nanograms/milliliter (ng/mL) nanograms/mL (p=0.01) in the acute phase and 37.9 +/- 10.4 nanograms/mL (p=0.02) in the maintenanc weeks from baseline. In adults, the mean baseline serum prolactin of 11.6 +/- 7.4 nanograms/mL increas nanograms/mL (p=0.001) in the acute phase and 67.8 +/- 62.9 nanograms/mL (p=0.02) in the maintenar weeks from baseline. With similar mean baseline prolactin levels in adult females and males (11.7 nanog nanograms/mL; p=0.86), the prolactin elevation was 2.2 greater in adult females compared with adult ma versus 57.8 nanograms/mL; p=0.01) and 3.7 times greater in the maintenance phase (98.5 nanograms/m (Hellings et al, 2005).

5) Management

a) Appropriate drug selection, monitoring and management are all important when prescribing antipsych inducing hyperprolactinemia. Prior to treatment with an antipsychotic, question patients regarding change Female patients should be assessed for menstrual abnormalities and male patients, for erectile or ejacul that any of these symptoms are present, consider obtaining baseline prolactin levels. Patients should be sexual dysfunction with antipsychotic use. Several weeks after an antipsychotic is initiated, obtain a prola cases where the patient experiences troublesome adverse effects related to elevated prolactin levels and

is not an option, treatment with a dopamine agonist (eg, bromocriptine or cabergoline) should be conside

3.3.3.G Hypothermia

1) Hypothermia has been associated with the use of antipsychotic agents, including oral risperidone (Prod In 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral sol RISPERDAL(R) CONSTA(R) long acting injection, 2009).

2) A 37-year-old woman with psychosis in association with Prader-Willi syndrome suffered hypothermia with risperidone therapy. Her rectal temperature was 30 degrees Celsius. She had experienced 2 previous episod month after starting risperidone treatment. Withdrawal of risperidone resulted in normalization of temperature with olanzapine therapy. Hypothyroidism was excluded. The authors hypothesized that hypothermia may res the serotonin 5-HT(2) receptor (Phan et al, 1998).

3.3.3.H Metabolic syndrome

See Drug Consult reference: ANTIPSYCHOTIC AGENTS - METABOLIC SYNDROME

3.3.3.I Weight gain

1) Summary

a) In adult clinical trials, up to 18% of patients receiving oral risperidone reported weight gains of at leas 9% reported for placebo. (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB 2007; Prod Info RISPERDAL(R) oral solution, 2007).

b) Weight gain was reported in up to 14% of adolescent and pediatric patients (5 to 16 years) receiving (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating table (R) oral solution, 2007).

c) During clinical trial of schizophrenic patients, weight gain was reported in 5% and 4% of patients rece acting injection and risperidone 50 mg long-acting injection, respectively. In 2 clinical trials of adult bipola was reported in 5% to 7% of patients receiving long-acting risperidone injection (Prod Info RISPERDAL(injection, 2009).

d) An adverse event analysis from a large study comparing five fixed doses of oral risperidone (1, 4, 8, 1 demonstrated a dose-related effect for reports of weight gain (p less than 0.05) (Prod Info RISPERDAL(RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007)

2) Incidence: oral, adults, up to 18%; children, up to 14%(Prod Info RISPERDAL(R) oral tablets, 2007; Prod orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007); intramuscular, schizophreni 5% to 7% (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009)

3) Adult

a) Statistically significant weight gains of at least 7% of body weight were reported in 18% of patients re 9% reported for placebo in a pooled analysis of 6- to 8-week placebo-controlled trials of adults with schiz (R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RIS

b) During a 12-week, double-blind, placebo-control trial of schizophrenic patients, weight gain was repor risperidone 25 mg long-acting injection (n=99) and 4% of patients receiving risperidone 50 mg long-actin with 2% of patients receiving placebo (n=98). In a 24-month, double-blind, placebo-controlled trial of adu weight gain was reported in 5% of patients receiving long-acting risperidone injection (n=154) as monoth placebo (n=149). In a 52-week, double-blind, placebo-controlled trial of bipolar I disorder patients, weigh patients receiving long-acting risperidone injection (n=72) compared with 0% in placebo (n=67)(Prod Info long acting injection, 2009).

c) An adverse event analysis from a large study comparing five fixed doses of oral risperidone (1, 4, 8, 1 demonstrated a dose-related effect for reports of weight gain (p less than 0.05) (Prod Info RISPERDAL(RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007)

d) Mean weight gain in patients treated with atypical neuroleptics included zotepine 4.3 kilograms (kg), and risperidone 1.5 kg, according to a retrospective chart review. The weight gain was significantly more neuroleptics compared with patients receiving classic neuroleptics, such as haloperidol, flupenthixol, or p risk of weight gain was seen in patients who were young and had not been previously treated with neuro Mussigbrodt, 1999).

e) A controlled study of risperidone treatment in children, adolescents, and adults with mental retardatio weight gain in the group treated with risperidone over a year period (children aged 8 to 12 (n=5) gained a (n=6) a mean of 8.4 kg; adults aged 21 to 51 (n=8) a mean of 5.4 kg (Hellings et al, 2001).

4) Pediatric

a) In two pooled 8-week, double-blind, placebo-controlled trials of adolescent and pediatric patients (5 to associated with autistic disorder, increases in weight were reported in 5% of patients receiving oral rispe for placebo (n=80) (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally Prod Info RISPERDAL(R) oral solution, 2007).

b) Treatment-emergent weight gain (mean increases of 9 kg) was reported in 14% of adolescents (n=10 extension study of oral risperidone. Most increases were observed within the first months of the study (P tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDA

c) A controlled study of risperidone treatment in children, adolescents, and adults with mental retardatio weight gain in the group treated with risperidone over a year period (children aged 8 to 12 (n=5) gained a (n=6) a mean of 8.4 kg; adults aged 21 to 51 (n=8) a mean of 5.4 kg (Hellings et al, 2001).

d) Risperidone-treated adolescents had significantly higher weight gains and increases in body mass in treated with conventional neuroleptic agents (p=0.0141 and p=0.0011, respectively). Adolescent inpatien

center being treated with risperidone (n=18), conventional antipsychotics (n=23), or no antipsychotic me
and BMI followed for 6 months. In the risperidone group mean changes were a gain of 8.64 kilograms (k
(2)), for conventional antipsychotics changes were a gain of 3.03 kg and 0.31 kg/m(2), and for the no an
loss of 1.04 kg and 1.01 kg/m(2). The average daily dose of risperidone was 2.83 milligrams (mg) and ga
(Kelly et al, 1998).

3.3.3.J Weight loss

1) Incidence: adults, 1% to 4% (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009)

2) During a 12-week, placebo-controlled trial of intramuscular risperidone, weight decreases were reported i
risperidone 25 mg (n=99), and 1% receiving risperidone 50 mg (n=103), compared to 1% receiving placebo (
CONSTA(R) long acting injection, 2009).

3.3.4 Gastrointestinal Effects

Abdominal pain

Constipation

Decrease in appetite

Diarrhea

Excessive salivation

Increased appetite

Indigestion

Nausea

Pancreatitis

Summary

Toothache

Vomiting

Xerostomia

3.3.4.A Abdominal pain

1) Incidence: oral, adults, 2% to 4%; children, 15% to 18% (Prod Info RISPERDAL(R) M-TAB orally disintegr
RISPERDAL(R) oral solution, 2007; Prod Info RISPERDAL(R) CONSTA(R) long-acting IM injection, 2007); ir
than 2%; bipolar I disorder, less than 4% (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009)

2) Adult

a) Abdominal pain was reported in less than 2% of schizophrenic patients and in less than 4% of bipolar
premarketing trials of various design types in patients receiving long-acting intramuscular risperidone for
disorder (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).

b) During risperidone clinical trials, abdominal pain was reported in 2% to 4% of adult patients receiving
RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; I
solution, 2007).

3) Pediatric

a) In a 3-week double-blind, placebo-controlled trial in pediatric patients with bipolar mania, abdominal p
treated with risperidone 0.5 to 2.5 mg daily (n=50), 15% in patients treated with 3 to 6 mg daily (n=61), c
(n=58) (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrati
RISPERDAL(R) oral solution, 2007).

3.3.4.B Constipation

1) Incidence: oral, adults, 5% to 9%; children, 21% (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info R
disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007); intramuscular, schizophrenia, 5%
CONSTA(R) long acting injection, 2009)

2) Adult

a) In a 12-week placebo-controlled trial of adult schizophrenic patients, constipation was reported in 5% mg (n=99) and 50 mg (n=103) of long-acting risperidone intramuscular therapy, respectively, compared v Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).

b) During risperidone clinical trials, constipation was reported in 8% to 9% of adult patients receiving ora (R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RIS

3) Pediatric

a) In two 8-week double-blind, placebo-controlled trials in pediatric patients treated for irritability associa incidence of constipation was 21% in patients treated with oral risperidone 0.5 to 4 mg daily (n=76), com (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating table (R) oral solution, 2007).

3.3.4.C Decrease in appetite

1) Incidence: adult, bipolar disorder, 6% (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009)

2) In a 52-week, double-blind, placebo-controlled trial of bipolar I disorder patients, decreased appetite was r receiving long-acting risperidone injection (n=72) compared with 1% in placebo (n=67) (Prod Info RISPERDA injection, 2009).

3.3.4.D Diarrhea

1) Incidence: oral, adults, up to 6%; children, 7% to 8% (Prod Info RISPERDAL(R) oral tablets, 2007; Prod In disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007); intramuscular, schizophrenia, less than 4% (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009)

2) Adult

a) Diarrhea was reported in less than 2% of schizophrenic patients and in less than 4% of bipolar disord trials of various design types in patients receiving long-acting intramuscular risperidone for schizophrenia RISPERDAL(R) CONSTA(R) long acting injection, 2009). Diarrhea was reported up to 6% of adult patien Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 20 oral solution, 2007).

3) Pediatric

a) In a 3-week double-blind, placebo-controlled trial in pediatric patients with bipolar mania, diarrhea occ with risperidone 0.5 to 2.5 mg daily (n=50), 7% in patients treated with 3 to 6 mg daily (n=61), compared Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 20 oral solution, 2007).

3.3.4.E Excessive salivation

1) Incidence: oral, adults, 1% to 4%; children, up to 22% (Prod Info RISPERDAL(R) oral tablets, 2007; Prod orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007); intramuscular, schizophreni RISPERDAL(R) CONSTA(R) long acting injection, 2009)

2) Adult

a) During a 12-week, double-blind, placebo-control trial of schizophrenic patients, salivary hypersecretio receiving risperidone 25 mg long-acting injection (n=99) and 1% of patients receiving risperidone 50 mg compared with 0% of patients receiving placebo (n=98) (Prod Info RISPERDAL(R) CONSTA(R) long act risperidone clinical trials, increased salivation was reported in 1% to 4% of adult patients receiving oral th oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPER

3) Pediatric

a) In a 6-week double-blind, placebo-controlled trial in pediatric patients with schizophrenia, increased s patients treated with risperidone 1 to 3 mg daily (n=55), 10% treated with 4 to 6 mg daily (n=51), compar (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating table (R) oral solution, 2007).

b) In two 8-week double-blind, placebo-controlled trials in pediatric patients treated for irritability associa incidence of increased salivation was 22% in patients treated with oral risperidone 0.5 to 4 mg daily (n=7 (n=80) (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrati RISPERDAL(R) oral solution, 2007).

3.3.4.F Increased appetite

1) Incidence: oral, children, 4 to 49% (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007); intramuscular, bipolar I disorder, 4% (Prod Info long acting injection, 2009)

2) Adult

a) In a 52-week, double-blind, placebo-controlled trial of bipolar I disorder patients, increased appetite w receiving long-acting risperidone injection (n=72) compared with 0% in placebo (n=67) (Prod Info RISPE acting injection, 2009; Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB ora Prod Info RISPERDAL(R) oral solution, 2007).

3) Pediatric

a) In a 3-week double-blind, placebo-controlled trial in pediatric patients with bipolar mania, increased a treated with risperidone 0.5 to 2.5 mg daily (n=50), 7% in patients treated with 3 to 6 mg daily (n=61), co (n=58) (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrati RISPERDAL(R) oral solution, 2007).

b) In two 8-week double-blind, placebo-controlled trials in pediatric patients treated for irritability associa incidence of increased appetite was 49% in patients treated with oral risperidone 0.5 to 4 mg daily (n=76 (n=80) (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrati RISPERDAL(R) oral solution, 2007).

3.3.4.G Indigestion

1) Incidence: oral, adults, 4% to 10%; children, 5% to 16% (Prod Info RISPERDAL(R) oral tablets, 2007; Pro orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007); intramuscular, schizophreni CONSTA(R) long acting injection, 2009)

2) In a 12-week placebo-controlled trial of adult schizophrenic patients, dyspepsia was reported in 6% and 6 (n=99) and 50 mg (n=103) of long-acting risperidone intramuscular therapy, respectively, compared with 0% RISPERDAL(R) CONSTA(R) long acting injection, 2009). During risperidone clinical trials, dyspepsia was rep patients receiving oral therapy (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TA 2007; Prod Info RISPERDAL(R) oral solution, 2007).

3) Pediatric

a) In a 3-week double-blind, placebo-controlled trial in pediatric patients with bipolar mania, dyspepsia o treated with risperidone 0.5 to 2.5 mg daily (n=50), 5% in patients treated with 3 to 6 mg daily (n=61), co (n=58) (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrati RISPERDAL(R) oral solution, 2007).

3.3.4.H Nausea

1) Incidence: oral, adults, 4% to 9%; children, 8% to 16% (Prod Info RISPERDAL(R) oral tablets, 2007; Prod orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007); intramuscular, schizophreni RISPERDAL(R) CONSTA(R) long acting injection, 2009)

2) Adult

a) In a 12-week placebo-controlled trial of adult schizophrenic patients, nausea was reported in 3% and (n=99) and 50 mg (n=103) of long-acting risperidone intramuscular therapy, respectively, compared with RISPERDAL(R) CONSTA(R) long acting injection, 2009).

b) During risperidone clinical trials, nausea was reported in 4% to 9% of adult patients receiving oral the for 1.4% of discontinuation of therapy in schizophrenic adult trials in patients receiving oral therapy with 2 with 0% in patients receiving risperidone 8 to 16 mg/day (n=198), or in placebo (n=225) (Prod Info RISPE Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solut

3) Pediatric

a) In a 3-week double-blind, placebo-controlled trial in pediatric patients with bipolar mania, nausea occ with risperidone 0.5 to 2.5 mg daily (n=50), 13% in patients treated with 3 to 6 mg daily (n=61), compare (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating table (R) oral solution, 2007).

3.3.4.I Pancreatitis

1) During postmarketing risperidone use, pancreatitis has been reported (Prod Info RISPERDAL(R) oral tabl (R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007; Prod Info RISPE acting injection, 2009).

2) In one study of reported cases (n=192) of antipsychotic-induced pancreatitis, 16% of the cases were asso at a mean daily dose of 4 milligrams. In most patients, time to onset of pancreatitis was within 6 months after al, 2003c).

3) A 32-year-old, male, chronic, paranoid schizophrenic, patient developed cholestatic hepatitis and pancrea risperidone 2 milligrams (mg) daily. He had a sudden onset of nausea, anorexia, vomiting, abdominal pain, ja colored stools. He had no history of abdominal trauma, alcohol, or drug abuse and tests for autoimmune dise A, B, and C were all negative. Initial laboratory results were: amylase, 1,617 international units/L; AST, 179 ir international units/L; GGT, 448 international units/L; AP, 367 international units/L; TB, 2.8 mg/dL; CB, 1.9 mg risperidone, the patient improved clinically and his laboratory results were: amylase, 113 international units/L ALT, 118 international units/L; GGT, 292 international units/L; AP, 284 international units/L; TB, 0.7 internatio units/L (Cordeiro & Ikis, 2001).

4) A 32-year-old male was diagnosed with pancreatitis after he complained of diffuse abdominal pain, nause after starting risperidone therapy. His initial amylase level was 1087 international units (international units)/lite slight glycemic elevation, but no other changes in liver function tests. His risperidone was tapered off over 2 v 147 international units/L (Berent et al, 1997).

3.3.4.J Summary

1) Hypersalivation, pancreatitis, constipation, diarrhea, nausea, dyspepsia, vomiting, abdominal pain, toothac dysphagia, melena, flatulence, fecal incontinence, rectal hemorrhage, gingivitis, and gastroesophageal reflux risperidone therapy (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally dis Info RISPERDAL(R) oral solution, 2007; Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).

3.3.4.K Toothache

1) Incidence: intramuscular, 1% to 3% (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009)

2) In a 12-week placebo-controlled trial of adult schizophrenic patients, toothache was reported in 1% and 3 (n=99) and 50 mg (n=103) of risperidone intramuscular therapy, respectively, compared with 0% in placebo (

CONSTA(R) long acting injection, 2009).

3.3.4.L Vomiting

1) Incidence: oral, children, 10% to 12% (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007); intramuscular, schizophrenia, less than 2%; bipo (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009)

2) Adult

a) Vomiting was reported in less than 2% of schizophrenic patients and in less than 4% of bipolar disord trials of various design types in patients receiving long-acting intramuscular risperidone for schizophrenia RISPERDAL(R) CONSTA(R) long acting injection, 2009).

3) Pediatric

a) In a 3-week double-blind, placebo-controlled trial in pediatric patients with bipolar mania, vomiting occ with risperidone 0.5 to 2.5 mg daily (n=50), 10% in patients treated with 3 to 6 mg daily (n=61), compared (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablet (R) oral solution, 2007).

3.3.4.M Xerostomia

1) Incidence: oral, adults, up to 4%; children, up to 13% (Prod Info RISPERDAL(R) oral tablets, 2007; Prod I disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007); intramuscular, schizophrenia, 0% CONSTA(R) long acting injection, 2009)

2) Adult

a) During a 12-week, double-blind, placebo-control trial of schizophrenic patients, dry mouth was reporte risperidone 25 mg long-acting injection (n=99) and 7% of patients receiving risperidone 50 mg long-actin with 1% of patients receiving placebo (n=98) (Prod Info RISPERDAL(R) CONSTA(R) long acting injectio clinical trials, dry mouth was reported up to 4% of adult patients receiving oral therapy (Prod Info RISPER Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2

3) Pediatric

a) In two 8-week double-blind, placebo-controlled trials in pediatric patients treated for irritability associa incidence of dry mouth was 13% in patients treated with oral risperidone 0.5 to 4 mg daily (n=76), compa (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablet (R) oral solution, 2007).

3.3.5 Hematologic Effects

Agranulocytosis

Anemia

Leukopenia

Neutropenia

Purpura

Thrombocytopenia

Thrombotic thrombocytopenic purpura

3.3.5.A Agranulocytosis

1) Agranulocytosis, including fatal cases, has been reported during postmarketing use of risperidone (Prod I long acting injection, 2009; Prod Info RISPERDAL(R) oral tablets, solution, orally disintegrating tablets, 2008)

2) A case report described agranulocytosis in a 40-year-old woman after 2 weeks of risperidone treatment. S agranulocytosis with other antipsychotic therapies: chlorpromazine with carbamazepine (WBC count, 2500/m haloperidol (WBC count, 2200/mm(3); neutrophil rate, 52%), and zuclopenthixol (WBC count, 2700/mm(3); n risperidone 4 mg/day, her WBC count was 2400/mm(3) and her neutrophil count was 32% (Finkel et al, 1998

3.3.5.B Anemia

1) Incidence: oral, adults, up to 1% (Prod Info RISPERDAL(R) oral tablets, solution, orally disintegrating tabl schizophrenia, less than 2%; bipolar I disorder, less than 4% (Prod Info RISPERDAL(R) CONSTA(R) long ac

2) Anemia was reported in less than 1% of adult patients treated with oral risperidone 2 to 8 mg per day (n=3 risperidone greater than 8 to 16 mg/day (n=198), and 0% of those treated with placebo in three double-blind, weeks duration including adult patients being treated for schizophrenia (Prod Info RISPERDAL(R) oral tablets tablets, 2008).

3) Anemia was reported in less than 2% of schizophrenic patients and in less than 4% of bipolar disorder pat of various design types in patients receiving long-acting intramuscular risperidone for schizophrenia and bipo RISPERDAL(R) CONSTA(R) long acting injection, 2009).

3.3.5.C Leukopenia

1) Leukopenia has been reported during postmarketing use of risperidone. The potential risk factors include induced leukopenia and neutropenia. These patients should have frequent monitoring of CBC during the first Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).

2) A case report described leukopenia in a 32-year-old man following treatment with risperidone and aripipra history of paranoid schizophrenia, had been initiated on risperidone 2 mg/day a few years earlier. Although h results of his annual physical exam were normal, laboratory assessment showed a WBC and absolute neutro and 1.27 x 10(9), respectively. Risperidone-induced leukopenia was suspected and the patient agreed to red mg/day. A few weeks later, a lab workup showed WBC count and ANC at 2.7 x 10(9) and 1.22 x 10(9), respe risperidone was discontinued and the patient was initiated on aripiprazole 10 mg daily. He was evaluated eve adverse effects. Six months later, his WBC count and ANC were 2.4 x 10(9) and 0.85 x 10(9), respectively, a Two weeks later, he experienced paranoid delusions, irritable mood, and auditory hallucinations for which he admission, his WBC count and ANC were 6.4 x 10(9) and 1.29 x 10(9), respectively. He was discharged afte 10 mg/day. At a follow-up appointment, his WBC count and ANC were again low (2.9 x 10(9) and 1.29 x 10(9 discontinue aripiprazole and treat the patient with paliperidone 6 mg and lithium 300 mg. Subsequent to the n count and ANC increased to 3.3 x 10(9) and 1.42 x 10(9). A full hematologic workup was pending at the time Rubin, 2008).

3) A 63-year-old man developed leukopenia and neutropenia 1 week after beginning risperidone 2 mg twice reaction was confirmed upon rechallenge. He had experienced a similar reaction with clozapine (Dernovsek &

4) A case of leukopenia, possibly related to risperidone, was reported following 7 days of therapy (2 to 6 mg/ count decreased from 5100/mm(3) to 3500/mm(3) over 7 days, and the neutrophil count decreased from 343 9, the neutrophil count had further decreased to 980/mm(3). The patient also had influenza during this same confounded the circumstances (Meylan et al, 1995).

3.3.5.D Neutropenia

1) Neutropenia has been reported during postmarketing use of risperidone. The potential risk factors include induced leukopenia and neutropenia. These patients should be evaluated for signs of infection, and frequent few months of treatment is recommended. Patients with severe neutropenia (absolute neutrophil count less t discontinue risperidone and have their WBC followed at discontinuation of treatment until recovery (Prod Info long acting injection, 2009).

3.3.5.E Purpura

1) Incidence: adults, less than 1%; children, less than 5% (Prod Info RISPERDAL(R) oral tablets, solution, o

2) During premarketing risperidone studies of various design types, purpura was reported in less than 1% of therapy, and in less than 5% of pediatric patients receiving oral therapy (Prod Info RISPERDAL(R) oral tablet tablets, 2008).

3) During premarketing trials of approximately 1300 patients receiving oral risperidone, a 28-year-old female thrombotic thrombocytopenic purpura, which included fever, jaundice and bruising. The patient recovered foll RISPERDAL(R) CONSTA(R) long acting injection, 2009).

3.3.5.F Thrombocytopenia

1) Thrombocytopenia has been reported during postmarketing use of risperidone (Prod Info RISPERDAL(R) injection, 2009; Prod Info RISPERDAL(R) oral tablets, solution, orally disintegrating tablets, 2008).

2) A case report described thrombocytopenia in a 48-year-old man following risperidone use. The patient, wh hematological disorders, presented to the emergency room with sudden right hemiplegia, aphasia, and disori hypertension but was not receiving medication for it. According to a brain CT scan, there was hemorrhaging i Upon admission, his platelet count was 160,000/microliter and he was treated fairly conservatively. On day 3, brain edema and underwent emergency surgery. His postoperative regimen included carbamazepine 600 mg nizatidine 300 mg/day to prevent gastric ulcer, and nifedipine 40 mg/day for hypertension. At 2 days post-ope agitation, emotional lability, and sensory aphasia and would not remain on bedrest. A diagnosis of postoperat the patient was initiated on risperidone 1 mg twice daily resulting in an improvement in symptoms. Two week 38,000/microliter. Because thrombocytopenia was suspected and his delirium had improved, risperidone was risperidone discontinuation, platelet count increased to 112,000/microliter. He continued to receive carbamaz discharge, but nizatidine was discontinued 3 days after risperidone was discontinued. Upon discharge on pos count was 158,000/microliter with WBC and RBC counts within normal limits. Two months later, his platelet c (Semba & Okui, 2009).

3.3.5.G Thrombotic thrombocytopenic purpura

1) In a large open-marketing trial of approximately 1300 patients receiving oral risperidone therapy, a 28-yea thrombotic thrombocytopenic purpura (TTP), which included fever, jaundice and bruising. The patient recover The relationship of the TTP to risperidone is not known (Prod Info RISPERDAL(R) CONSTA(R) long acting ir

3.3.6 Hepatic Effects

gamma-Glutamyltransferase deficiency

Increased liver function test

3.3.6.A gamma-Glutamyltransferase deficiency

1) Reductions in plasma gamma-glutamyl transferase have been reported with risperidone therapy (Anon, 19

3.3.6.B Increased liver function test

1) Incidence: oral, adults, up to 1%; children, up to 5% (Prod Info RISPERDAL(R) oral tablets, 2007; Prod In disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007); intramuscular, schizophrenia, less than 4% (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009)

2) Increased hepatic enzymes were reported in less than 2% of schizophrenic patients and in less than 4% o premarketing trials of various design types in patients receiving long-acting intramuscular risperidone for schi (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).

3) During risperidone clinical trials, increased hepatic enzymes were reported in up to 1% of adult patients re than 5% of pediatric patients receiving oral therapy (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info R disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007).

4) A 32-year-old male patient with chronic paranoid schizophrenia developed cholestatic hepatitis and pancr risperidone 2 milligrams (mg) daily. He had a sudden onset of nausea, anorexia, vomiting, abdominal pain, ja colored stools. He had no history of abdominal trauma, alcohol, or drug abuse, and tests for autoimmune dise A, B, and C were all negative. Initial laboratory results were: amylase, 1,617 international units/L; AST, 179 ir international units/L; GGT, 448 international units/L; AP, 367 international units/L; TB, 2.8 mg/dL; and CB, 1.9 discontinuing risperidone, the patient improved clinically and his laboratory results were: amylase, 113 interna international units/L; ALT, 118 international units/L; GGT, 292 international units/L; AP, 284 international units and CB, 0.5 international units/L (Cordeiro & Ikis, 2001).

5) Two patients developed moderate increases of liver function tests within the first 1 or 2 weeks of risperido normalized spontaneously with only a slight decrease of 1 milligram in one patient and an unchanged dose ir to check liver function tests in the early phase of risperidone treatment (Whitworth et al, 1999).

6) An 81-year-old man with paranoid delusions, Parkinson's disease, dementia, and depression developed h of risperidone 0.5 milligrams (mg). Other medications included aspirin, diltiazem, sublingual nitroglycerin, levo liver functions tests had been normal before beginning risperidone. After 2 doses, he was noted to be jaundic aminotransferase (AST) 434 units/liter (L), alanine aminotransferase (ALT) 101 units/L, total bilirubin 3.6 milli alkaline phosphatase 244 units/L. Ultrasound showed mild splenomegaly and small gallstones. Two weeks a risperidone, liver function tests were normal (Phillips et al, 1998).

3.3.8 Musculoskeletal Effects

Abnormal gait

Arthralgia

Decreased bone mineral density

Myalgia

Pain, in Extremity

Summary

3.3.8.A Abnormal gait

1) Incidence: intramuscular, bipolar disorder, 4% (Prod Info RISPERDAL(R) CONSTA(R) long acting injectio

2) In a 52-week, double-blind, placebo-controlled trial of bipolar I disorder patients, gait abnormality was repo long-acting risperidone injection (n=72) compared with 0% in placebo (n=67) (Prod Info RISPERDAL(R) CON 2009).

3.3.8.B Arthralgia

1) Incidence: oral, schizophrenia, 2% to 3% (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPER disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007); intramuscular, bipolar I disorder, 4 CONSTA(R) long acting injection, 2009)

2) In a 52-week, double-blind, placebo-controlled trial of bipolar I disorder patients, arthralgia was reported ir acting risperidone injection (n=72) compared with 3% in placebo (n=67) (Prod Info RISPERDAL(R) CONSTA

3) During risperidone clinical trials, arthralgia was reported in 2% to 3% of adult schizophrenic patients recei

RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod solution, 2007).

3.3.8.C Decreased bone mineral density

1) In a small study, decreased bone mineral density was observed in female, premenopausal schizophrenia (n=12; 3 to 6 milligrams (mg)/day for at least 24 months), but not in those receiving olanzapine (n=14; 15 to 2 Age-adjusted bone speed of sound was significantly lower in women treated with risperidone as compared w when determined at the radius and phalanx (p less than 0.05), but not the tibia. This effect is most likely due t hyperprolactinemia (Becker et al, 2003).

3.3.8.D Myalgia

1) Incidence: oral, adults, 0% to 2% (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007); intramuscular, schizophrenia, less than 2%; bipo (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009)

2) Myalgia was reported in less than 2% of schizophrenic patients and in less than 4% of bipolar disorder pa of various design types in patients receiving long-acting intramuscular risperidone for schizophrenia and bipo RISPERDAL(R) CONSTA(R) long acting injection, 2009).

3) During risperidone clinical trials, myalgia was reported in 0% to 2% of adult patients receiving oral therapy tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R)

3.3.8.E Pain, in Extremity

1) Incidence: intramuscular, schizophrenia, 2% to 6% (Prod Info RISPERDAL(R) CONSTA(R) long acting inj

2) During a 12-week, double-blind, placebo-control trial of schizophrenic patients, pain in extremity was repo risperidone 25 mg long-acting injection (n=99) and 2% of patients receiving risperidone 50 mg long-acting inj 1% of patients receiving placebo (n=98) (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).

3.3.8.F Summary

1) Arthralgia, myalgia, arthrosis, synostosis, skeletal pain, abnormal gait, and decreases in bone mineral den risperidone therapy (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009; Prod Info RISPERDA RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007).

3.3.9 Neurologic Effects

Akathisia

Cerebrovascular accident

Chorea

Confusion

Disturbance of attention

Dizziness

Dystonia

EEG abnormality

Extrapyramidal disease

Headache

Insomnia

Paresthesia

Parkinsonism

Reduced sensation of skin

Seizure

Somnolence

Stuttering

Summary

Tardive dyskinesia

Transient ischemic attack

Tremor

3.3.9.A Akathisia

1) Incidence: oral, adults, 5% to 9%; children, up to 10% (Prod Info RISPERDAL(R) oral tablets, 2007; Prod
orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007); intramuscular, schizophreni
RISPERDAL(R) CONSTA(R) long acting injection, 2009)

2) Adult

a) In a 12-week placebo-controlled trial of adult schizophrenic patients, akathisia, including restlessness
patients receiving 25 mg (n=99) and 50 mg (n=103) of risperidone intramuscular therapy, respectively, c
(n=98) (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009). During premarketing risperid
types, akathisia, which includes akathisia and hyperkinesia, was reported in 5% to 9% of adult patients r
RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; P
solution, 2007).

b) A 69-year-old woman suffered protracted akathisia after risperidone withdrawal. The akathisia and pa
with haloperidol therapy, but due to lack of efficacy she was switched to risperidone 1.5 milligrams (mg) t
persisted for 4 months and risperidone was discontinued. Her restlessness became worse during the firs
lorazepam. Five weeks later, propranolol therapy resulted in a gradual resolution of the akathisia (Roseb

3) Pediatric

a) In a 6-week double-blind, placebo-controlled trial in pediatric patients with schizophrenia, akathisia oc
with risperidone 1 to 3 mg daily (n=55), 10% treated with 4 to 6 mg daily (n=51), compared with 6% in pla
RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; P
solution, 2007).

b) In a 3-week double-blind, placebo-controlled trial in pediatric patients with bipolar mania, akathisia oc
with risperidone 0.5 to 2.5 mg daily (n=50), 7% in patients treated with 3 to 6 mg daily (n=61), compared
Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 20
oral solution, 2007).

3.3.9.B Cerebrovascular accident

1) Incidence: adults, less than 1%, children, less than 5% (Prod Info RISPERDAL(R) oral tablets, 2007; Proc
orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007)

2) In premarketing oral risperidone clinical trials, cerebrovascular disorder was reported in less than 1% of ac
pediatric patients receiving risperidone therapy. During postmarketing period, cerebrovascular accidents have
of long-acting risperidone injection (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M
2007; Prod Info RISPERDAL(R) oral solution, 2007; Prod Info RISPERDAL(R) CONSTA(R) long acting inject

3) Cerebrovascular adverse events (stroke, transient ischemic attack) occurred at a significantly higher rate i
85 years of age) who received risperidone compared to those given placebo. Individuals in these 4 placebo-c
97 years of age and were being treated for dementia-related psychosis (Prod Info RISPERDAL(R) oral tablet
(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007).

3.3.9.C Chorea

1) In a case report, chorea and tardive dyskinesia were reported in a 13 1/2 year-old female receiving risperi
initiation of risperidone and dose decrease, chorea-like movements were evident. Risperidone was discontinu
were decreased and at month 16, the movement disorder was resolved (Carroll et al, 1999).

3.3.9.D Confusion

1) Incidence: children, 5% (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB or
Prod Info RISPERDAL(R) oral solution, 2007)

2) In two 8-week double-blind, placebo-controlled trials in pediatric patients treated for irritability associated w
incidence of confusion was 5% in patients treated with oral risperidone 0.5 to 4 mg daily (n=76), compared wi
Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; P
solution, 2007).

3.3.9.E Disturbance of attention

1) Incidence: adults, 4% (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009)

2) In a 52-week, double-blind, placebo-controlled trial of bipolar I disorder patients, disturbance in attention w receiving long-acting risperidone intramuscular (n=72) compared with 0% in placebo (n=67) (Prod Info RISPE acting injection, 2009).

3.3.9.F Dizziness

1) Incidence: oral, adults, 4% to 11%; children, 7% to 16% (Prod Info RISPERDAL(R) oral tablets, 2007; Pro orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007); intramuscular, schizophreni 3% (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009)

2) Adult

a) During a 12-week clinical trial in schizophrenic patients, dizziness was observed in 7% of patients rec acting injection (n=99) and 11% of patients receiving risperidone 50 mg long-acting injection (n=103), co receiving placebo (n=98). In a 24-month, double-blind, placebo-controlled trial of adult bipolar I disorder p in 3% of patients receiving risperidone intramuscular (n=154) as monotherapy compared with 1% in plac RISPERDAL(R) CONSTA(R) long acting injection, 2009). Dizziness was responsible for 1.4% and 1% of schizophrenic adult trials in patients receiving oral therapy with 2 to 8 mg/day (n=366) and in 8 to 16 mg/ respectively, compared with 0% in placebo (n=225).

b) During premarketing risperidone studies of various design types, dizziness was reported in 4% to 10% therapy (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrat RISPERDAL(R) oral solution, 2007).

3) Pediatric

a) In a 6-week double-blind, placebo-controlled trial in pediatric patients with schizophrenia, dizziness oc with risperidone 1 to 3 mg daily (n=55), 14% treated with 4 to 6 mg daily (n=51), compared with 2% in pla responsible for 2% of discontinuation of therapy in schizophrenic trials including pediatric patients treated Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 20 oral solution, 2007).

b) In a 3-week double-blind, placebo-controlled trial in pediatric patients with bipolar mania, dizziness oc with risperidone 0.5 to 2.5 mg daily (n=50), 13% in patients treated with 3 to 6 mg daily (n=61), compared (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating table (R) oral solution, 2007).

c) In two 8-week double-blind, placebo-controlled trials in pediatric patients treated for irritability associa incidence of dizziness was 9% in patients treated with oral risperidone 0.5 to 4 mg daily (n=76), compare (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating table (R) oral solution, 2007).

3.3.9.G Dystonia

1) Incidence: oral, adults, less than 5% to 11%; children, 8% to 18% (Prod Info RISPERDAL(R) oral tablets, M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007); intramuscular, schiz disorder, less than 4% (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009)

2) Dystonia, which includes spasm of the neck muscles, sometimes progressing to tightness of the throat, sw and/or protrusion of the tongue, was reported in less than 2% of schizophrenic patients and in less than 4% o premarketing trials of various design types in patients receiving long-acting intramuscular risperidone for schi (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009). Dystonia was reported in 5% to 11% of a therapy, and in 8% to 18% of pediatric patients receiving oral therapy (Prod Info RISPERDAL(R) oral tablets, M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007).

3.3.9.H EEG abnormality

1) In a case report, fifteen days after initiation of risperidone 2 milligrams (mg) per day, a 55-year-old man de symptoms, with EEG (electroencephalogram) revealing bifrontal slow-wave abnormalities (De Leon et al, 199

3.3.9.I Extrapyramidal disease

1) Summary

a) Extrapyramidal symptoms were reported in 7% to 31% of adult patients receiving oral risperidone the risperidone, extrapyramidal symptoms were found to be dose-related (Prod Info RISPERDAL(R) oral tab RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007) extrapyramidal symptoms in patients treated with 25 mg long-acting risperidone injection was comparabl higher in patients receiving 50 mg long-acting risperidone injection (Prod Info RISPERDAL(R) CONSTA(

2) Incidence: adults, 7% to 31% (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-T 2007; Prod Info RISPERDAL(R) oral solution, 2007)

3) Adult

a) In a 12-week, double-blind, placebo-controlled trial comparing 3 doses of long-acting risperidone (25 placebo in patients with schizophrenia, the overall incidence of extrapyramidal symptoms in patients trea risperidone injection was comparable to that of placebo but was higher in patients receiving 50 mg long-a Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).

b) In two 8-week, fixed-dose trials of adult schizophrenia patients, extrapyramidal symptoms increased i risperidone dose increased 7% to 31% in 1 mg to 16 mg treatment groups (Prod Info RISPERDAL(R) ora RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007)

c) A 43-year-old male treated with risperidone 6 milligrams per day presented with episodic blepharospa occurred spontaneously or were brought on by stress requiring him to discontinue driving. The more he t tightly they closed (Ananth et al, 2000).

d) In a review of risperidone studies, factors associated with the development of extrapyramidal sympto increase in severity with higher doses, especially above 8 milligrams (mg)/day (p less than 0.001). Also, extrapyramidal symptom rating scale (ESRS) was associated with a reduction in the severity of EPS (p l noted that worse scores on the ESRS scale correspond with an increased time since diagnosis, especial 1999).

e) A 79-year-old woman treated with risperidone 1 milligram (mg) twice daily for behavior problems asso severe extrapyramidal symptoms when donepezil 10 mg daily was added to her regimen. Risperidone w decreased to 5 mg. There was a complete resolution of symptoms. The authors hypothesize that extrapy to an excess in central acetylcholine while dopamine receptors were blocked (Magnuson et al, 1998).

f) Data from a multicenter comparative study of risperidone, placebo, and haloperidol revealed that rispe extrapyramidal symptoms. Mean changes in Extrapyramidal Symptom Rating Scale (ESRS) scores from significantly lower in each risperidone group than the haloperidol group (P less than 0.001). At 6 milligrar change score was not significantly different from that of the placebo group (Simpson & Lindenmayer, 19

g) A 26-year-old man developed extrapyramidal symptoms the day after starting risperidone 4 milligram breathing which his physician characterized as possible laryngospasm. This resolved after the medicatio later, the patient requested that the risperidone be restarted. Risperidone 2 mg was restarted and after 2 and very distressing tongue movements. The risperidone was decreased to 1 mg and these symptoms s 1997).

h) A 55-year-old man with a left acoustic neurinoma (a manifestation of his neurofibromatosis) develope reaction to risperidone. Over a period of 10 years, he had experienced a gradual deterioration with perio ideation. He was started on risperidone 2 milligrams daily. Fifteen days later, he experienced multiple sy cogwheeling, and slowness. Risperidone was discontinued and he returned to baseline (De Leon et al, 1

i) Acute dystonia with an oculogyric crisis occurred in a 33-year-old male with paranoid schizophrenia d treatment after a period of noncompliance. Following a 2-month period of noncompliance, he restarted ri milligrams (mg) twice daily by the third day of treatment; the next day he experienced intermittent retroc both eyes for 2 hours. The only other medication at the time of this dystonic reaction was clonazepam 3 with benztropine 2 mg IM (intramuscular) and all signs resolved; a second dose was given when he com which resolved 30 minutes after treatment. He continued risperidone, clonazepam, and benztropine 1 m which he discontinued the benztropine. At a 1-month follow-up, there was no further indication of dystoni reaction occurred in a 34-year-old schizophrenic male who was titrated in 3 days up to risperidone 3 milli noncompliant period in which he used crack cocaine. He experienced rigid extremities, mild torticollis, to laryngospasm and was cyanotic. He was treated with diphenhydramine 50 milligrams intravenously with symptoms within 10 minutes. Risperidone dose was decreased to 1 mg twice daily and titrated more slo (Brody, 1996).

j) Acute dystonia occurred in a 17-year-old male with new onset schizophrenia who had been administe twice daily. After 3 doses, he experienced throat restriction, thickening of the tongue, increased salivatio minutes, mild cogwheel rigidity, and stiffness. Risperidone was reduced to 2 mg at bedtime and benztrop Benztropine 2 mg IM was given. Risperidone 2 mg at bedtime and benztropine 2 mg twice daily were giv he showed increased mental and autonomic instability; risperidone was reduced to 2 mg at bedtime, ben and two doses of lorazepam 1 mg were given. All medications were then discontinued and all symptoms Manchanda, 1996).

4) Pediatric

a) A 12-year-old boy, with attention-deficit hyperactivity disorder and psychotic symptoms, developed ex treatment with risperidone and several other drugs. On the day before a laser treatment to remove a birth risperidone 1 milligram (mg) twice daily in addition to sertraline 25 mg per day and methylphenidate 10 m premedications for the procedure included morphine, ketorolac, and tropisetron. Eight hours after the pro of breath, stiffness, difficulty talking and moving, had slurred speech, and was unable to close his mouth. shoulders, neck, and head and progressed to jerking movements of his jaw and arms. He was treated wi for these acute dystonic reactions and his symptoms gradually improved. His risperidone dose was decr ketorolac and tropisetron were eliminated from the premedication regimen (due to potential synergism fo reactions). There was no recurrence of dystonic symptoms during the remaining five laser procedures (T

b) A 7-year-old boy developed hypertonicity of the extremities, confusion, lethargy, and limited tongue m risperidone 1 milligram (mg) for attention deficit hyperactivity disorder. Two doses of diphenhydramine di child recovered the following day (Gesell & Stephen, 1997h).

See Drug Consult reference: NEUROLEPTIC-INDUCED EXTRAPYRAMIDAL REACTIONS

3.3.9.J Headache

1) Incidence: intramuscular, 15% to 21% (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009)

2) During a 12-week, double-blind, placebo-control trial of schizophrenic patients, headache was reported in risperidone 25 mg long-acting injection (n=99) and 21% of patients receiving risperidone 50 mg long-acting ir 12% of patients receiving placebo (n=98) (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009)

3.3.9.K Insomnia

1) Incidence: oral, adults, less than 1%; children, less than 5% (Prod Info RISPERDAL(R) oral tablets, 2007; TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007); intramuscular, schizop

disorder, less than 4% (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009)
2) Insomnia was reported in less than 2% of schizophrenic patients and in less than 4% of bipolar disorder p of various design types in patients receiving long-acting intramuscular risperidone for schizophrenia and bipo RISPERDAL(R) CONSTA(R) long acting injection, 2009). Insomnia was reported in less than 1% of adult pat in less than 5% of pediatric patients receiving oral therapy (Prod Info RISPERDAL(R) oral tablets, 2007; Proc orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007).

3.3.9.L Paresthesia

1) Incidence: intramuscular, schizophrenia, less than 2%; bipolar I disorder, less than 4% (Prod Info RISPER injection, 2009)
2) Paresthesia was reported in less than 2% of schizophrenic patients and in less than 4% of bipolar disorde trials of various design types in patients receiving long-acting intramuscular risperidone for schizophrenia and RISPERDAL(R) CONSTA(R) long acting injection, 2009).
3) Six patients (aged 37 to 65 years old) developed burning paresthesias while on risperidone therapy. The l feet, lower body, back, face, arms, throat, and chest. The burning resolved with continued therapy in two cas discontinued in the other 4 cases (Heimberg & Yearian, 1996).

3.3.9.M Parkinsonism

1) Incidence: oral, adults, 0.6% to 20%; children, 2% to 16% (Prod Info RISPERDAL(R) oral tablets, 2007; P orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007); intramuscular, schizophreni 15% (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009)
2) During risperidone clinical trials, parkinsonism, which includes extrapyramidal disorder, musculoskeletal s bradykinesia, was reported in 8% to 15% of adult patients receiving intramuscular therapy for schizophrenia. muscle rigidity, hypokinesia, cogwheel rigidity, and bradykinesia, was reported in 15% of patients receiving in disorder (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009). Adult patients receiving oral the in 2% to 16% of pediatric patients receiving oral therapy. Parkinsonism was responsible for 0.4% of discontin adult trials in patients receiving oral therapy with 1 to 6 mg/day (n=448) compared with 0% in placebo (n=424 tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R)
3) The results of a cohort study indicate that high-dose atypical antipsychotic therapy carries a similar risk fo parkinsonism as does typical antipsychotic therapy. In a population-based, retrospective cohort study, adults evidence of dementia were followed for up to 1 year for the development of parkinsonism symptoms associat antipsychotic use. As compared with older adults receiving atypical antipsychotic therapy (ie, olanzapine, risp parkinsonism was 30% more likely to occur in those taking typical antipsychotics (ie, chlorpromazine, haloper HR, 1.3; 95% CI, 1.04 to 1.58), and 60% less likely to occur in patients who did not receive either therapy (HF Older adults using higher potency typical antipsychotics had almost a 50% greater risk of experiencing parkin patients prescribed atypical antipsychotics (all were considered lower potency) (HR, 1.44; 95% CI, 1.13 to 1.8 receiving lower potency typical antipsychotics, the risk of developing parkinsonism was no different from that antipsychotics (HR, 0.75; 95% CI. 0.48 to 1.15). In addition, a positive dose-related relationship was observe incident parkinsonism and the use of atypical antipsychotics. The risk for developing parkinsonism was more using a high-dose atypical antipsychotic agent as compared with those prescribed a low-dose atypical antips 1.42 to 3.02). Furthermore, patients taking a typical antipsychotic were found to have a similar risk for the dev patients receiving high-dose atypical antipsychotic therapy (p=ns). The authors conclude that atypical antipsy typical antipsychotics when dose and potency are considered (Rochon et al, 2005).

3.3.9.N Reduced sensation of skin

1) Incidence: intramuscular, schizophrenia, 2% (Prod Info RISPERDAL(R) CONSTA(R) long acting injection
2) During a 12-week, double-blind, placebo-control trial of schizophrenic patients, hypoesthesia was reported risperidone 25 mg long-acting injection (n=99) and 0% of patients receiving risperidone 50 mg long-acting inj 0% of patients receiving placebo (n=98) (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).

3.3.9.O Seizure

1) Incidence: 0.3% (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally dis Info RISPERDAL(R) oral solution, 2007; Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009)
2) During premarketing trials, seizures occurred in 0.3% of patients receiving oral risperidone (9/2607) (Prod 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral sol patients receiving intramuscular risperidone (5/1499) (Prod Info RISPERDAL(R) CONSTA(R) long acting inje with oral therapy were associated with hyponatremia. Risperidone should be used cautiously in patients with RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod solution, 2007; Diaz, 1996).
3) A 64-year-old woman experienced a seizure 2 days after beginning risperidone therapy. She received two 2 mg doses before having a 1-minute generalized tonic-clonic seizure with a 5-minute postictal confusion per risperidone therapy, she also received trimethoprim-sulfamethoxazole for a urinary tract infection and astemiz risperidone was restarted at 0.5 mg/day and increased to 0.5 mg twice daily with control of her psychotic sym (Lane et al, 1998).

3.3.9.P Somnolence

1) Incidence: oral, adults, 5% to 14%; children, 12% to 67% (Prod Info RISPERDAL(R) oral tablets, 2007; Pr orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007); intramuscular, schizophreni

7% (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009)

2) Adult

a) During risperidone clinical trials of various design types, somnolence was reported in 5% to 6% of adu intramuscular therapy for schizophrenia and 7% in patients with bipolar disorder (Prod Info RISPERDAL(injection, 2009), and in 5% to 14% of adult patients receiving oral therapy. Somnolence was responsible discontinuation of therapy in schizophrenic adult trials in patients receiving oral therapy with 2 to 8 mg/da or greater (n=198), respectively, compared with 0% in placebo (n=225) (Prod Info RISPERDAL(R) oral ta RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007)

3) Pediatric

a) In a 6-week double-blind, placebo-controlled trial in pediatric patients with schizophrenia, somnolence treated with risperidone 1 to 3 mg daily (n=55), 12% treated with 4 to 6 mg daily (n=51), compared with 4 Somnolence was responsible for 2% of discontinuation of therapy in schizophrenic trials including pediat risperidone (n=106) (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orall Prod Info RISPERDAL(R) oral solution, 2007).

b) In a 3-week double-blind, placebo-controlled trial in pediatric patients with bipolar mania, somnolence treated with risperidone 0.5 to 2.5 mg daily (n=50), 56% in patients treated with 3 to 6 mg daily (n=61), c (n=58). Somnolence was responsible for 5% of discontinuation of therapy in bipolar mania trials including risperidone (n=111) (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orall Prod Info RISPERDAL(R) oral solution, 2007).

c) In two 8-week double-blind, placebo-controlled trials in pediatric patients treated for irritability associa incidence of somnolence was 67% in patients treated with oral risperidone 0.5 to 4 mg daily (n=76), com (n=80) (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrati RISPERDAL(R) oral solution, 2007).

3.3.9.Q Stuttering

1) A 32-year-old Korean patient with a prior history of stuttering demonstrated a recurrence of stuttering with day 5 of hospitalization. The dosage was increased to 8 milligrams daily on day 25 and the stuttering was mo auditory hallucinations and idea of reference, the dosage was maintained. On day 48, the stuttering was less

3.3.9.R Summary

1) Stutter, chorea, EEG (electroencephalogram) abnormalities, extrapyramidal symptoms, catatonia, tardive seizures, somnolence, dizziness, insomnia, headache, amnesia, vertigo, stupor, confusion, impaired concent paralysis, torticollis, coma, migraine, withdrawal syndrome, sleep-related eating disorder, and yawning have l administration (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegr RISPERDAL(R) oral solution, 2007; Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).

3.3.9.S Tardive dyskinesia

1) Incidence: oral, adults, less than 1%; children, less than 5% (Prod Info RISPERDAL(R) oral tablets, 2007; TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007); intramuscular, schizop disorder, up to 6% (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009)

2) Tardive dyskinsia was reported in less than 2% of schizophrenic patients and in less than 4% of bipolar di premarketing trials of various design types in patients receiving long-acting intramuscular risperidone for schi (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).

3) During premarketing risperidone studies of various design types, tardive dyskinesia was reported in less t receiving oral therapy, and in less than 5% of pediatric patients receiving oral therapy (Prod Info RISPERDAL RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007).

4) In a 52-week, double-blind, placebo-controlled trial in patients with bipolar disorder, dyskinesia was report long-acting risperidone injection (n=72) compared with 3% receiving placebo (n=67) (Prod Info RISPERDAL(injection, 2009).

5) A potentially irreversible tardive dyskinesia may develop in patients receiving antipsychotic drugs; this ma treatment and the cumulative dose. Less commonly, the syndrome can develop after brief treatment periods mask the underlying process by suppressing the signs and symptoms of the syndrome. The prevalence of th highest among the elderly, especially elderly women; however, it is impossible to rely upon prevalence to esti develop the syndrome. The syndrome may remit partially or completely upon discontinuation of the antipsych RISPERDAL(R) CONSTA(R) long acting injection, 2009; Prod Info RISPERDAL(R) oral tablets, oral solution, 2006; Carroll et al, 1999; Saran, 1998; Sakkas et al, 1998; Campbell, 1999; Gwinn & Caviness, 1997; Meco e

6) The use of long-acting risperidone in schizophrenic patients has been associated with a low incidence of e well as improvement in existing dyskinesia. In an open label trial (n=725), patients with stable schizophrenia received long-acting risperidone in 25 mg, 50 mg, or 75 mg intramuscular doses every 2 weeks for up to 50 v via the Extrapyramidal Symptom Rating Scale (ESRS) at months 1, 2, 3, 6, 9, and 12; tardive dyskinesia was "mild" scores or 1 or more "moderate" scores on the ESRS dyskinesia 7-item subscale over at least a 4-week whom ESRS data were available, 530 (80.1%) had no dyskinesia and 132 (19.2%) has existing dyskinesia at tardive dyskinesia was observed in 0.94% (5/530) of patients without dyskinesia at baseline. This represents when adjusted for study drug exposure or when assessed by Kaplan-Meier survival analysis (95% confidence incidence of tardive dyskinesia was similar among all doses, with no observation of a dose-dependent effect. existing at baseline, mean ESRS scores were significantly improved from baseline to endpoint (6.9 vs 4.6, re (Gharabawi et al, 2005).

7) Case Reports

a) Tardive dyskinesia (TD) has been reported in a 24-year-old male following risperidone treatment for T
15, the patient developed repetitive twisting movements of his head and neck. Nine years following the o
diagnosed with TS. He experienced motor and phonic tics, along with obsessional thoughts. Sertraline (5
mg/day) was initiated. No follow-up was available. The patient returned for treatment with identical sympt
and fluoxetine (40 mg/day) were initiated and maintained. His tics were mild, but the patient developed o
movements of the lower jaw after 4 months of treatment. Treatment with risperidone was discontinued ar
was initiated. The patient experienced a significant improvement in dyskinetic symptoms within about 45
significantly worsened causing severe distress (Thomas et al, 2009).

b) Tardive dyskinesia (TD) has been reported in a 44-year-old female following risperidone treatment fo
The patient suffered for 4 years with delusions, hallucinations, alogia, and had minimal contact with reali
episode, she was hospitalized and risperidone 4 mg/day was initiated. Symptoms improved, but without
discharge, the patient maintained her risperidone dose without issue for approximately 4 years. Her rispe
mg/day following a worsening of positive psychotic symptoms. Within 2 weeks, she experienced partial r
significant reduction of aggression, hostility and auditory hallucinations. However, the patient reported ab
lips, mouth, tongue, and lower extremities 4 months following the increased risperidone dose. With no fa
disorders and testing results were normal, the patient was diagnosed with neuroleptic-induced TD. Rispe
aripiprazole 15 mg/day, and was gradually discontinued. Her severity of TD started to subside within 2 w
aripiprazole with no reoccurrence of TD or other involuntary movements or psychotic symptoms (Caykoy

c) In a substudy (n=21) of a randomized double-blind, placebo-controlled trial, a 51-year-old female dev
manifested by involuntary tongue movements during maintenance. For the substudy, the mean risperido
first 10 weeks (acute) and 1.36 mg per day (maintenance). During the acute phase, prolactin level was 2
maintenance after 41 weeks from initial risperidone dose, prolactin was 199.6 nanograms/mL. Prolactin r
nanograms/mL after 5.1 years (Hellings et al, 2005).

d) In case reports, risperidone has caused tardive dyskinesias with doses as low as 1 milligrams (mg) d
course of therapy as short as 8 months (Sakkas et al, 1998). In patients with a history of tardive dyskines
their dyskinesia or made it reappear within 1 week of therapy (Sherr & Thaker, 1998). Several more case
risperidone have been reported in the literature (Campbell, 1999).

e) A 69-year-old man with a long history of bipolar disorder developed involuntary oral-buccal-lingual dy
treated with risperidone. A few months after being treated with valproic acid, lorazepam, bupropion, trihe
milligrams (mg) twice daily, he developed involuntary mouth movements, tremor, slowness, and difficulty
risperidone and trihexyphenidyl were discontinued. Three weeks later the movements and parkinsonism
was no rigidity present but the dyskinesia persisted. The patient was then lost to follow-up. The authors b
and parkinsonism was induced by risperidone and that the bupropion may have contributed. However, si
after discontinuation of risperidone, they believe that the risperidone was mostly responsible for these ex
Caviness, 1997).

3.3.9.T Transient ischemic attack

1) Cerebrovascular adverse events (eg, stroke, transient ischemic attack) occurred at a significantly higher ra
age 85 years of age) who received oral risperidone compared to those given placebo. Individuals in these 4 p
from 73 to 97 years of age and were being treated for dementia-related psychosis, which is not an approved
RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod
solution, 2007; Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).

3.3.9.U Tremor

1) Incidence: oral, adults, up to 5% to 6%; children, 10% to 12% (Prod Info RISPERDAL(R) oral tablets, 200
TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007); intramuscular, schizop
disorder, 24% (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009)

2) Adult

a) During a 12-week, double-blind, placebo-control trial of schizophrenic patients, tremor was reported in
risperidone 25 mg long-acting injection (n=99) and 3% of patients receiving risperidone 50 mg long-actin
with 0% of patients receiving placebo (n=98). In a 52-week, double-blind, placebo-controlled trial of bipol
reported in 24% of patients receiving long-acting risperidone intramuscular (n=72) compared with 16% in
RISPERDAL(R) CONSTA(R) long acting injection, 2009). Adult patients receiving oral therapy reported t
(Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating table
(R) oral solution, 2007).

3) Pediatric

a) In a 6-week double-blind, placebo-controlled trial in pediatric patients with schizophrenia, tremor occu
with risperidone 1 to 3 mg daily (n=55), 10% treated with 4 to 6 mg daily (n=51), compared with 6% in pla
RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; P
solution, 2007).

b) In two 8-week double-blind, placebo-controlled trials in pediatric patients treated for irritability associa
incidence of tremor was 12% in patients treated with oral risperidone 0.5 to 4 mg daily (n=76), compared
Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 20
oral solution, 2007).

3.3.10 Ophthalmic Effects

3.3.10.A Abnormal vision

1) Incidence: oral, adults, 1% to 3%; children, 4% to 7% (Prod Info RISPERDAL(R) oral tablets, 2007; Prod I disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007); intramuscular, schizophrenia, 2% CONSTA(R) long acting injection, 2009)
2) During a 12-week, double-blind, placebo-control trial of schizophrenic patients, blurred vision was reporte risperidone 25 mg long-acting injection (n=99) and 3% of patients receiving risperidone 50 mg long-acting inj 0% of patients receiving placebo (n=98) (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).
3) During risperidone clinical trials, abnormal vision was reported in 1% to 3% of adult patients receiving oral pediatric patients receiving oral therapy (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007).

3.3.12 Psychiatric Effects

Agitation

Anxiety

Catatonia

Delirium

Fatigue

Mania

Nocturnal sleep-related eating disorder

Obsessive-compulsive disorder

Summary

3.3.12.A Agitation

1) Incidence: oral, adults, less than 1%; children, less than 5% (Prod Info RISPERDAL(R) oral tablets, 2007; TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007); intramuscular, schizop disorder, less than 4% (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009)
2) Agitation was reported in less than 2% of schizophrenic patients and in less than 4% of bipolar disorder pa of various design types in patients receiving long-acting intramuscular risperidone for schizophrenia and bipo RISPERDAL(R) CONSTA(R) long acting injection, 2009).
3) During risperidone clinical trials, agitation was reported in less than 1% of adult patients receiving oral the pediatric patients receiving oral therapy. Agitation was responsible for 1.1% and 1% of discontinuation of ther in patients receiving oral therapy with 2 to 8 mg/day (n=366) and in 8 to 16 mg/day or greater (n=198), respec placebo (n=225) (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disinte RISPERDAL(R) oral solution, 2007).
4) Agitation and aggressive reaction occurred in 1% or more (and were at least as frequent among) risperidc mg/day or less) than among placebo-treated patients (Diaz, 1996).

3.3.12.B Anxiety

1) Incidence: oral, adults, 2% to 16%; children, up to 16% (Prod Info RISPERDAL(R) oral tablets, 2007; Proc orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007); intramuscular, schizophreni disorder, less than 4% (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009)
2) Adult
a) Anxiety was reported in less than 2% of schizophrenic patients and in less than 4% of bipolar disorde trials of various design types in patients receiving long-acting intramuscular risperidone for schizophrenia RISPERDAL(R) CONSTA(R) long acting injection, 2009).
b) During risperidone clinical trials, anxiety was reported in 2% to 16% of adult patients receiving oral th M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007).
3) Pediatric
a) In a 6-week double-blind, placebo-controlled trial in pediatric patients with schizophrenia, anxiety occ with risperidone 1 to 3 mg daily (n=55), 6% treated with 4 to 6 mg daily (n=51), compared with 0% in pla responsible for 1% of discontinuation of therapy in schizophrenic trials including pediatric patients treate Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 20 oral solution, 2007).
b) In a 3-week double-blind, placebo-controlled trial in pediatric patients with bipolar mania, anxiety occu

with risperidone 0.5 to 2.5 mg daily (n=50), 8% in patients treated with 3 to 6 mg daily (n=61), compared
Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 20
oral solution, 2007).

c) In two 8-week double-blind, placebo-controlled trials in pediatric patients treated for irritability associa
incidence of anxiety was 16% in patients treated with oral risperidone 0.5 to 4 mg daily (n=76), compare
(Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating table
(R) oral solution, 2007).

3.3.12.C Catatonia

1) A 61-year-old schizophrenic woman developed catatonia after beginning risperidone 2 milligrams (mg) da
frontal lobotomy 36 years previously. She had been receiving fluphenazine decanoate 25 mg intramuscularly
her last dose, she began risperidone which was increased to 5 mg. Catatonic symptoms worsened and she v
placed on clozapine. Her catatonia subsided within 5 days (Bahro et al, 1999).

3.3.12.D Delirium

1) Three cases of possible risperidone-induced delirium were reported in patients aged 71, 83, and 83 years
being treated for major depression with psychotic features. In each case, the mania abated after risperidone
acknowledge that the delirium may have been multifactorial in etiology, however, risperidone use appeared t
Springer et al, 1998).

2) An 85-year-old woman with schizophreniform disorder was treated with risperidone 1 milligrams (mg) dail
twice daily after 4 days with resultant delirium. The woman was restless, disoriented, and hallucinating. Rispe
recovered after 18 hours (Tavcar & Dernovsek, 1998).

3.3.12.E Fatigue

1) Incidence: oral, adults, 1% to 3%; children, 18% to 42% .(Prod Info RISPERDAL(R) oral tablets, 2007; Pr
orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007); intramuscular, schizophreni
RISPERDAL(R) CONSTA(R) long acting injection, 2009)

2) Adults

a) During a 12-week, double-blind, placebo-control trial of schizophrenic patients, fatigue, which include
patients receiving risperidone 25 mg long-acting injection (n=99) and 9% of patients receiving risperidon
(n=103), compared with 0% of patients receiving placebo (n=98) (Prod Info RISPERDAL(R) CONSTA(R)

b) During risperidone clinical trials, fatigue was reported in 1% to 3% of adult patients receiving oral ther
oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPER

3) Pediatrics

a) In a 3-week double-blind, placebo-controlled trial in pediatric patients with bipolar mania, fatigue occu
with risperidone 0.5 to 2.5 mg daily (n=50), 30% in patients treated with 3 to 6 mg daily (n=61), compare
(Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating table
(R) oral solution, 2007).

b) In two 8-week double-blind, placebo-controlled trials in pediatric patients treated for irritability associa
incidence of fatigue was 42% in patients treated with oral risperidone 0.5 to 4 mg daily (n=76), compare
(Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating table
(R) oral solution, 2007).

3.3.12.F Mania

1) Mania has been reported during postmarketing use of risperidone (Prod Info RISPERDAL(R) oral tablets,
M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007; Prod Info RISPERDA
injection, 2009).

2) A review of the literature identified 16 cases of mania related to risperidone therapy. Patients were treated
schizoaffective, bipolar type, mixed (n=2); schizoaffective, bipolar type, depressed (n=4); schizophrenia (n=5
(n=2); recurrent depression, psychotic (n=1); and bipolar type I, manic (n=2). The onset of development of ma
40 days. Five of 16 patients were receiving no other medications and in 6 cases it wasn't determined if there
Two patients received valproate, 1 lithium, and 1 haloperidol concomitantly, which makes causality difficult to
was continued and manic symptoms resolved without treatment. On 7 occasions, risperidone was discontinu
instances, risperidone was either continued with antimanic medications or reduced in dosage, or both. Remis
occurred within 2 to 14 days, although there was one case where it took 60 days for manic symptoms to reso

3) Four cases of mania developing after beginning risperidone therapy were presented. Two patients were tr
risperidone 5 and 6 milligrams (mg) while 1 patient was treated for schizoaffective disorder with risperidone 2
of the most predominant symptoms. In 1 patient, only risperidone discontinuation was needed to resolve the
patient, carbamazepine, benzodiazepines, and neuroleptics were required for control. In the schizoaffective p
(Zolezzi & Badr, 1999).

4) Mania occurred in a 50-year-old male with chronic schizophrenia and mild mental retardation. He had bee
risperidone was started and titrated to 9 milligrams/day (mg/day) within 12 days. Forty days later he exhibited
was reduced to 6 mg/day and clonazepam 2 mg was initiated. A week later the patient was hospitalized and,
treated with lithium, valproic acid, and haloperidol until the mania resolved (Diaz, 1996).

5) Three cases of mania developing within days of starting risperidone therapy were reported. The patient's
schizoaffective disorder, one with schizophrenia, and one with bipolar I disorder. Risperidone was discontinu
decreased in the last 2 patients with resolution of symptoms (Schnierow & Graeber, 1996).

3.3.12.G Nocturnal sleep-related eating disorder

1) Risperidone-induced sleep-related eating disorder was observed in a 68-year-old man following the admir treatment of vascular dementia. The patient's psychotic symptoms resolved after his daily dose of risperidone (mg) to 2 mg; however, he began experiencing sleep disturbances almost nightly, including episodes during v quantities of food while asleep. These episodes persisted for 2 months and then quickly resolved when the d (Lu & Shen, 2004).

3.3.12.H Obsessive-compulsive disorder

1) A schizophrenic man developed obsessive imagery after being treated with risperidone 4 milligrams/day (also receiving valproate, trihexyphenidyl, and zuclopenthixol. He repeatedly saw the image of a person's face This disappeared after the dosage of risperidone was decreased to 3 mg/day (Mahendran, 1999).

2) A 26-year-old woman with schizophrenia developed obsessive-compulsive symptoms after 2 weeks of risp receiving risperidone 4 milligrams (mg) daily when she experienced excessive thoughts about playing mahjor mg without success. Clomipramine 25 mg was added and the ruminations disappeared. The clomipramine w weeks and she was maintained on risperidone 1 mg daily (Mahendran, 1998).

3.3.12.I Summary

1) Nervousness, depression, psychosis, apathy, delusion, euphoria, emotional lability, and delirium have bee risperidone therapy (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally dis Info RISPERDAL(R) oral solution, 2007; Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).

3.3.13 Renal Effects

Hemorrhagic cystitis

Urinary incontinence

3.3.13.A Hemorrhagic cystitis

1) An 11-year-old boy with significant behavioral problems developed hemorrhagic cystitis 1 week after begi medications included fluoxetine, valproic acid, benztropine, haloperidol, clonidine, trazodone, and nasal desm acute onset of dysuria and increased frequency with gross hematuria. There were no signs of viral illness and Ultrasonography showed a thickened bladder wall and mild hydronephrosis. Symptoms were not relieved wit sulfamethoxazole. Risperidone was withdrawn and symptoms resolved within a week. At a 1-month follow-up and ultrasonography showed a normal thin-walled bladder (Hudson & Cain, 1998).

3.3.13.B Urinary incontinence

1) Incidence: oral, adults, 2%; children, up to 22% (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RI disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007); intramuscular, schizophrenia, less than 4% (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009)

2) Adult

a) Urinary incontinence was reported in less than 2% of schizophrenic patients and in less than 4% of bi premarketing trials of various design types in patients receiving long-acting intramuscular risperidone for disorder (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).

b) During risperidone clinical trials, urinary incontinence was reported in 2% of adult patients receiving o RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; F solution, 2007).

c) There was a temporal correlation with risperidone therapy and urinary incontinence in 2 case reports. incontinence with risperidone 4 milligrams daily. Upon discontinuation of risperidone, urinary incontinenc

3) Pediatric

a) In a 3-week double-blind, placebo-controlled trial in pediatric patients with bipolar mania, urinary inco patients treated with risperidone 0.5 to 2.5 mg daily (n=50), 5% in patients treated with 3 to 6 mg daily (n placebo (n=58) (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally dis Info RISPERDAL(R) oral solution, 2007).

b) In two 8-week double-blind, placebo-controlled trials in pediatric patients treated for irritability associa incidence of urinary incontinence was 22% in patients treated with oral risperidone 0.5 to 4 mg daily (n=7 placebo (n=80) (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally dis Info RISPERDAL(R) oral solution, 2007).

3.3.14 Reproductive Effects

Abnormal ejaculation

Absence of ejaculation

Amenorrhea

Erectile dysfunction

Priapism

Summary

3.3.14.A Abnormal ejaculation

1) Incidence: oral, adults, less than 1%; children, less than 5% (Prod Info RISPERDAL(R) oral tablets, 2007; TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007); intramuscular, schizop disorder, less than 4% (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009)

2) Ejaculation disorder was reported in less than 2% of schizophrenic patients and in less than 4% of bipolar premarketing trials of various design types in patients receiving long-acting intramuscular risperidone for schi (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).

3) During risperidone clinical trials, ejaculation disorder was reported in less than 1% of adult patients receivi 5% of pediatric patients receiving oral therapy (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPE disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007).

4) A large study comparing 5 fixed-doses of oral risperidone revealed a positive dose-related trend (p less th dysfunction among patients receiving oral risperidone therapy (Prod Info RISPERDAL(R) oral tablets, 2007; F orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007).

5) Two cases of probable retrograde ejaculation were attributed to risperidone treatment. A 36-year-old Afric old Caucasian man, being treated with risperidone 6 milligrams (mg) and 3 mg per day, respectively, were pc was later determined that their poor compliance was due to concern over an absence of semen with ejaculati

6) The absence of ejaculation was reported in 2 male patients treated with risperidone. In one patient, ejacul spontaneously after 4 weeks of risperidone treatment. In the other patient, absence of ejaculation was still pr of risperidone (Raga, 1999).

7) A 38-year-old man experienced ejaculatory dysfunction and dysuria one week after starting risperidone. H genitourinary problems. On day 12 of treatment, risperidone was discontinued with symptoms resolving 2 day rechallenge with risperidone and symptoms recurred in 2 days. (Madhusoodanan & Brenner, 1996).

3.3.14.B Absence of ejaculation

1) Incidence: adults, 0.1% to 1% (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M- 2007; Prod Info RISPERDAL(R) oral solution, 2007)

2) During risperidone clinical trials, ejaculation failure was reported in up to 1% of adult patients receiving ora (R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPER

3.3.14.C Amenorrhea

1) Incidence: oral, adults, less than 1%; children, less than 5% (Prod Info RISPERDAL(R) oral tablets, 2007; TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007); intramuscular, bipolar (RISPERDAL(R) CONSTA(R) long acting injection, 2009)

2) In a 52-week, double-blind, placebo-controlled trial of bipolar I disorder patients, amenorrhea was reporte acting risperidone injection (n=72) compared with 1% in placebo (n=67) (Prod Info RISPERDAL(R) CONSTA During risperidone clinical trials, amenorrhea was reported in less than 1% of adult patients receiving oral the pediatric patients receiving oral therapy (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007).

3) Five psychiatric patients developed amenorrhea with elevated serum prolactin levels on risperidone 1 to 8 menstruation resumed upon discontinuation; menstruation resumed in case 5 after tapering risperidone (Kim

3.3.14.D Erectile dysfunction

1) Incidence: intramuscular, schizophrenia, less than 2%; bipolar I disorder, less than 4% (Prod Info RISPER injection, 2009)

2) Erectile dysfunction was reported in less than 2% of schizophrenic patients and in less than 4% of bipolar premarketing trials of various design types in patients receiving long-acting intramuscular risperidone for schi (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).

3) A large study comparing 5 fixed-doses of oral risperidone revealed a positive dose-related trend (p less th among patients receiving oral risperidone therapy (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RIS disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007).

3.3.14.E Priapism

1) Incidence: adults, less than 1%; children, less than 5% (Prod Info RISPERDAL(R) oral tablets, 2007; Proc orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007)

2) During risperidone clinical trials, priapism was reported in less than 1% of adult patients receiving oral the pediatric patients receiving oral therapy. Also, there have been reports of priapism with the use of risperidone postmarketing period (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally d

Info RISPERDAL(R) oral solution, 2007; Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).
3) An African American male developed priapism on two occasions after receiving risperidone and again afte
treatment of schizophrenia. Following risperidone treatment (4 milligrams (mg) twice daily), the man develope
which resolved upon irrigation of the corpora with phenylephrine 200 micrograms. Following discontinuation c
developed another unwanted erection after an increase in his ziprasidone dose from 20 mg twice daily to 40 r
lasted 2 hours and resolved upon urination. He experienced several more unwanted erections until the zipras
priapism quickly resolved (Reeves & Mack, 2002).
4) A 47-year-old African American man developed priapism after taking risperidone 2 milligrams twice daily f
prolonged painful erections multiple times in the past few weeks. Physical and laboratory examinations revea
the erect penis. Penile irrigation with normal saline and phenylephrine injection caused detumescence. Rispe
other antipsychotic treatment was started. One month later, he reported spontaneous, partial rigid erection (A
5) A 26-year-old Hispanic man had a 5-day episode of persistent erection, dysuria, and urinary incontinence.
been receiving for one year, included risperidone, 3 milligrams (mg)/day and divalproex sodium 1500 mg/day
mood and psychotic symptoms. His erection persisted despite two corpora cavernosa irrigations with phenyle
venous blood gas analysis was consistent with a diagnosis of low-flow priapism. A cavernosal glandular shun
cavernosum/corpus spongiosum shunt were performed. As there have not been any previously reported insta
divalproex use, the authors assumed that risperidone was the likely cause of the condition (Bourgeois and Mu

3.3.14.F Summary

1) Amenorrhea, dysmenorrhea, erectile dysfunction, priapism, and ejaculation failure have been reported in p
therapy (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating t
RISPERDAL(R) oral solution, 2007; Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).

3.3.15 Respiratory Effects

Cough

Dyspnea

Pharyngitis

Pulmonary embolism

Rhinitis

Sinusitis

Summary

Upper respiratory infection

3.3.15.A Cough

1) Incidence: oral, adults, 3%; children, 24% (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERI
disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007); intramuscular, schizophrenia, 2%
(Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009)
2) During a 12-week, double-blind, placebo-control trial of schizophrenic patients, cough was reported in 4%
25 mg long-acting injection (n=99) and 2% of patients receiving risperidone 50 mg long-acting injection (n=10
receiving placebo (n=98). In a 52-week, double-blind, placebo-controlled trial of bipolar I disorder patients, co
patients receiving long-acting risperidone injection (n=72) compared with 1% in placebo (n=67) (Prod Info RIS
acting injection, 2009).
3) During risperidone clinical trials, coughing was reported in 3% of adult patients receiving oral therapy, and
receiving oral therapy (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally d
Info RISPERDAL(R) oral solution, 2007).

3.3.15.B Dyspnea

1) Incidence: oral, adults, 2%; children, 2% to 5% (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RIS
disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007); intramuscular, schizophrenia, less
than 4% (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009)
2) Dyspnea was reported in less than 2% of schizophrenic patients and in less than 4% of bipolar disorder pa
of various design types in patients receiving long-acting intramuscular risperidone for schizophrenia and bipo
RISPERDAL(R) CONSTA(R) long acting injection, 2009).
3) During risperidone clinical trials, dyspnea was reported in 2% of adult patients receiving oral therapy, and
receiving oral therapy (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally d

Info RISPERDAL(R) oral solution, 2007).

3.3.15.C Pharyngitis

1) Incidence: oral, adults, 5% (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB 2007; Prod Info RISPERDAL(R) oral solution, 2007); intramuscular, schizophrenia, less than 2%; bipolar I dis RISPERDAL(R) CONSTA(R) long acting injection, 2009)

2) Pharyngitis was reported in less than 2% of schizophrenic patients and in less than 4% of bipolar disorder trials of various design types in patients receiving long-acting intramuscular risperidone for schizophrenia and RISPERDAL(R) CONSTA(R) long acting injection, 2009).

3) During clinical trials, pharyngitis was reported in 5% of adult patients receiving risperidone oral therapy co (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2 oral solution, 2007).

3.3.15.D Pulmonary embolism

1) A case report described 3 episodes of pulmonary embolism in a 25-year-old man after treatment with olan early-onset schizoaffective disorder. His physical health was generally good and there was no personal or fa overweight nor had his weight or physical activity level changed under neuroleptic medication. Smoking a pa only known cardiovascular risk factor. His antipsychotic therapy included olanzapine 20 mg/day, paroxetine 2 2000 mg/day for his psychotic symptoms. After 12 weeks of treatment, the patient presented with a complain the left front part of his thorax. Over the next few hours, he became short of breath and experienced an episo revealed bilateral pulmonary embolism. Ultrasound of the lower extremities showed no signs of DVT. His coa demonstrate any abnormalities. Olanzapine was discontinued and oral warfarin treatment with a target INR o initiated and maintained for 6 months. Twelve weeks after olanzapine was discontinued, he was initiated on r recurrence of psychotic symptoms. After 3 weeks of risperidone treatment, the patient presented with chest p hemoptysis. Multiple peripheral pulmonary emboli were observed on a chest spiral CT scan. Concomitant DV out. Nonadherence to warfarin treatment (evidenced by low INR) appeared to be the cause of this second ep Therefore, warfarin was reinitiated under close supervision to confirm adherence. Sixteen weeks later, the pa and dyspnea. Spiral chest CT scan and Doppler ultrasound of the lower limbs indicated bilateral pulmonary e lower limbs. Because antipsychotic agents appeared to be the causal factor of the pulmonary emboli, the pat anticoagulant therapy and amisulpride 400 mg/day which resulted in improvement in his condition. Paroxetin mg/day therapy was continued after being maintained throughout the 3 episodes of pulmonary embolism (Bo

3.3.15.E Rhinitis

1) Incidence: oral, adults, 2% to 11%; children, 13% to 36% (Prod Info RISPERDAL(R) oral tablets, 2007; Pr orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007); intramuscular, schizophreni disorder, less than 4% (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009)

2) Rhinitis was reported in less than 2% of schizophrenic patients and in less than 4% of bipolar disorder pat various design types in patients receiving long-acting intramuscular risperidone for schizophrenia and bipolar (R) CONSTA(R) long acting injection, 2009).

3) During risperidone clinical trials, rhinitis was reported in 2% to 11% of adult patients receiving oral therapy patients receiving oral therapy (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TA 2007; Prod Info RISPERDAL(R) oral solution, 2007).

3.3.15.F Sinusitis

1) Incidence: intramuscular, schizophrenia, less than 2%; bipolar I disorder, less than 4% (Prod Info RISPER injection, 2009)

2) Sinusitis was reported in less than 2% of schizophrenic patients and in less than 4% of bipolar disorder pa of various design types in patients receiving long-acting intramuscular risperidone for schizophrenia and bipo RISPERDAL(R) CONSTA(R) long acting injection, 2009).

3.3.15.G Summary

1) Rhinitis, coughing, sinusitis, pharyngitis, dyspnea, stridor, pneumonia, and aspiration have been reported Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; F solution, 2007; Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009). A case report described t embolism in a 25-year-old man following oral risperidone therapy. The patient experienced improvement afte and anticoagulation therapy was initiated (Borras et al, 2008).

3.3.15.H Upper respiratory infection

1) Incidence: oral, adults, 2% to 3%; children, 34% (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info R disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007); intramuscular, schizophrenia, 0% (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009)

2) Adult

a) During a 12-week, double-blind, placebo-control trial of schizophrenic patients, upper respiratory tract patients receiving risperidone 25 mg long-acting injection (n=99) and 0% of patients receiving risperidon (n=103), compared with 1% of patients receiving placebo (n=98). In a 52-week, double-blind, placebo-co patients, upper respiratory tract infection was reported in 6% of patients receiving long-acting risperidone 3% in placebo (n=67) (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009). Upper respira in 2% to 3% of adult patients receiving oral therapy (Prod Info RISPERDAL(R) oral tablets, 2007; Prod In

disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007).

3) Pediatric

a) In two 8-week double-blind, placebo-controlled trials in pediatric patients treated for irritability associa incidence of upper respiratory tract infection was 34% in patients treated with oral risperidone 0.5 to 4 m 15% in placebo (n=80) (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB c Prod Info RISPERDAL(R) oral solution, 2007).

3.3.16 Other

Angioedema

Death

Drug withdrawal

Extrapyramidal disease

Fever

Neuroleptic malignant syndrome

Opioid withdrawal

Pain, General

3.3.16.A Angioedema

1) Angioedema has been reported during postmarketing use of risperidone (Prod Info RISPERDAL(R) oral ta RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007; Proc (R) long acting injection, 2009).

2) A 63-year-old woman, who had been hospitalized for 36 years with paranoid schizophrenia, developed pe occasions when risperidone was added to her continuing therapy. In all instances, the edema disappeared w discontinuation of risperidone. The first time, risperidone 2 milligrams (mg) daily, titrated to 6 mg/day over 2 w regimen of fluphenazine, biperiden, and bromazepam. Periorbital edema occurred after 1 month and faded 1 risperidone, with all other medications maintained. A year later, risperidone 6 mg/day was again introduced, a promethazine, biperiden, clonazepam, and nitrazepam; after 45 days moderate periorbital and orbital edema promethazine did not alter the edema. Discontinuation of risperidone resulted in disappearance of the edema risperidone was reintroduced at 3 mg/day. After 3 weeks, angioedema occurred, affecting the lips, face, neck difficult. She was given intensive anti-allergenic therapy and risperidone was discontinued. The edema dimini completely in 4 days (Plesnicar et al, 2001).

3.3.16.B Death

1) Sudden death has been reported in postmarketing use of oral risperidone (Prod Info RISPERDAL(R) oral RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007).

2) Results of a population-based, retrospective cohort study demonstrated that the use of conventional antip even greater risk for death than atypical antipsychotics when administered to elderly patients (aged 66 years Atypical versus no antipsychotic use and conventional versus atypical antipsychotic use pair-wise comparisor matched pairs were identified and the dementia cohort was stratified based on place of residence (community In order to adjust for difference in baseline health status, propensity score matching was used. The primary o cause mortality. The risk for death was evaluated at 30, 60, 120, and 180 days after the antipsychotic medica There was a statistically significant increase in the risk for death at 30 days associated with new use of atypic compared with nonuse in both the community-dwelling cohort (adjusted hazard ratio (HR), 1.31 (95% confide absolute risk difference, 0.2 percentage point) and long-term care cohort (adjusted HR, 1.55 (95% CI, 1.15 to 1.2 percentage points). For both cohorts, the risk associated with atypical antipsychotics appeared to persist associated with conventional antipsychotics was even greater than the risk identified with atypical antipsycho for the community-dwelling cohort was 1.55 (95% CI, 1.19 to 2.02) and 1.26 (95% CI, 1.04 to 1.53) for the lor difference for both was 1.1 percentage points). The risk appeared to persist to 180 days for both groups. Son study include unknown or unmeasured confounders may influence the results and cause of death could not b

3) Results of a population-based, retrospective cohort study demonstrated comparable to possibly greater ris use of conventional antipsychotic medications in the elderly (aged 65 years and older) compared with atypica analysis excluded patients with cancer and included only new users of antipsychotic medications. The primar all-cause mortality. A set of potential confounders was measured based on healthcare utilization data within 6 antipsychotic medications. Of the 37,241 elderly patients identified, 12,882 and 24,359 received conventional medications, respectively. The risk of death in the conventional drug group within the first 180 days was 14.1

atypical drug group (unadjusted mortality ratio, 1.47; 95% confidence interval (CI), 1.39 to 1.56). In the multi-v
for potential confounders, the adjusted mortality ratio for the risk of death within 180 days for conventional ve
1.32 (95% CI, 1.23 to 1.42). When the most frequently prescribed conventional antipsychotic drugs were com
mortality ratio associated with haloperidol was 2.14 (95% CI, 1.86 to 2.45) and loxapine was 1.29 (95% CI, 1.
difference associated with olanzapine. The increased mortality risk for conventional versus atypical drug thera
higher (above median) doses were used (mortality ratio 1.67; 95% CI, 1.5 to 1.86) and also during the first 40
1.6; 95% CI, 1.42 to 1.8). Confirmatory analyses consisting of multi-variable Cox regression, propensity score
estimation confirmed the results of the study (Schneeweiss et al, 2007).
4) The findings of one meta-analysis suggest that there may be a small increased risk of death associated w
antipsychotic agents for the treatment of dementia in elderly patients. The study analysis (n=5110), including
placebo-controlled, parallel group trials of antipsychotic use (ie, aripiprazole (n=3), olanzapine (n=5), quetiapi
elderly patients (weighted mean age, 81.2 years) with dementia, found that death occurred more often in pati
antipsychotic therapy as compared with placebo (118 (3.5%) vs 40 (2.3%), respectively). The overall odds ra
analysis, for death in elderly patients receiving atypical antipsychotics as compared with placebo was 1.54 (9
to 2.23; p=0.02), and the risk difference was 0.01 (95% CI, 0.004 to 0.02; p=0.01). Overall, the relative risk as
antipsychotic use was 1.65 (95% CI, 1.19 to 2.29; p=0.003); however this increased risk was only identified w
analysis; meta-analyses of individual drugs did not show a statistically significant increased risk. A similar dro
antipsychotic- and placebo-treated patients (32.2% vs 31.4%, respectively), with no significant difference in d
(Schneider et al, 2005).
5) The results of a retrospective cohort study indicate that conventional antipsychotic agents are at least as l
agents to increase the risk of death among elderly patients 65 years of age or older. The study included 9,14
agents (mean age, 83.2 years) and 13,748 new users of atypical agents (mean age, 83.5 years). A higher ad
associated with the use of conventional antipsychotics as compared with atypical antipsychotics at all time pc
therapy (within 180 days: relative risk (RR), 1.37; 95% confidence interval (CI), 1.27 to 1.49; less than 40 day
1.78; 40 to 79 days: RR, 1.37; 95% CI, 1.19 to 1.59; 80 to 180 days: RR, 1.27; 95% CI, 1.14 to 1.41). In addit
observed in patients with dementia (RR, 1.29; 95% CI, 1.15 to 1.45), without dementia (RR, 1.45; 95% CI, 1.3
(RR, 1.26; 95% CI, 1.08 to 1.47), or not in a nursing home (RR, 1.42; 95% CI, 1.29 to 1.56) were also higher
antipsychotic therapy as compared with atypical antipsychotic use. This risk appeared to be dose-related and
higher dose (ie, greater than the median) conventional antipsychotics (RR, 1.73; 95% CI, 1.57 to 1.90). Addit
investigate the optimum care of elderly patients requiring antipsychotic therapy are needed so that appropriat
intervention can be provided (Wang et al, 2005).

3.3.16.C Drug withdrawal

1) A 38-year-old man with long-standing schizophrenia unresponsive to conventional therapy received an un
which resulted in mania when the drug was withdrawn. He had been increased to risperidone 2 milligrams (m
tachycardia, tremor, and akathisia. After a taper, his hallucinations and delusions reoccurred but with manic s
Risperidone 1 mg twice daily was reinitiated with resolution of his psychotic symptoms and his mania (Lane &

3.3.16.D Extrapyramidal disease

See Drug Consult reference: NEUROLEPTIC-INDUCED EXTRAPYRAMIDAL REACTIONS

3.3.16.E Fever

1) Incidence: oral, adults, 1% to 2%; children, 20% .(Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info R
disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007); intramuscular, schizophrenia, less
than 4% (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009)
2) Adult
a) During a 12-week, double-blind, placebo-control trial of schizophrenic patients, pyrexia was reported
risperidone 25 mg long-acting injection (n=99) and 1% of patients receiving risperidone 50 mg long-actin
with 0% of patients receiving placebo (n=98) (Prod Info RISPERDAL(R) CONSTA(R) long acting injectio
b) During risperidone clinical trials, fever was reported in 1% to 2% of adult patients receiving oral thera
tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDA
3) Pediatric
a) In two 8-week double-blind, placebo-controlled trials in pediatric patients treated for irritability associa
incidence of fever was 20% in patients treated with oral risperidone 0.5 to 4 mg daily (n=76), compared v
Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 20
oral solution, 2007).

3.3.16.F Neuroleptic malignant syndrome

1) Incidence: adults, less than 1%; children, less than 5%(Prod Info RISPERDAL(R) oral tablets, 2007; Prod
orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007)
2) Neuroleptic malignant syndrome has been reported in patients receiving long-acting risperidone injection
CONSTA(R) long acting injection, 2009)
3) During premarketing risperidone studies of various design types, neuroleptic malignant syndrome was rep
patients receiving oral therapy, and in less than 5% of pediatric patients receiving oral therapy (Prod Info RIS
Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2
4) Neuroleptic malignant syndrome (NMS), with hyperpyrexia, muscle rigidity, autonomic instability, altered n
levels, myoglobinuria, and acute renal failure cannot be excluded as a side effect of risperidone therapy. If ne
does occur, all antipsychotic medications and other drugs not essential to concurrent therapy should be disco

and medical monitoring should be initiated, and treatment of any concomitant serious medical problems shou
reintroduction of antipsychotics after a patient has experienced NMS should be taken; recurrences have beer
RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod
solution, 2007; Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).

5) Adult

a) A 27-year-old male developed neuromuscular malignant syndrome 21 months after being treated with
daily (Lee et al, 2000).

b) A 47-year-old man developed neuroleptic malignant syndrome after the administration of risperidone
(diazepam) withdrawal period. Symptoms abated over the next 9 days after discontinuation of risperidon
bromocriptine, and diazepam (Bobolakis, 2000).

c) A 73-year-old woman developed neuroleptic malignant syndrome while on monotherapy with risperid
daily for multiinfarct dementia. Symptoms resolved after discontinuation (Gleason & Conigliaro, 1997).

d) Two cases of neuroleptic malignant syndrome (NMS) were reported in which each patient developed
beginning risperidone 6 milligrams/day (mg/day). The drug was discontinued and both patients were trea
symptoms resolved in 7 and 10 days, respectively. One of these patients was restarted on risperidone 1
returned within 24 to 36 hours. The drug was again discontinued and the symptoms resolved within 72 h
1996). Five previously reported cases of risperidone-associated NMS had histories of extrapyramidal sid
various antipsychotic drugs; two of the patients had experienced a previous episode of NMS (Meterissiar

6) Pediatric

a) Neuroleptic malignant syndrome (NMS) has been reported in a 13-year-old male following risperidone
(JS). The patient was admitted for agitation, fever, diaphoresis, and extremity spasms, including his neck
risperidone 0.5 mg/day and clonazepam 0.1 mg/kg/day for subsequent dystonia. Due to fever, rigidity, ar
elevated CPK levels (1200 units/L), he was diagnosed with risperidone-associated NMS. Risperidone wa
intravenous hydration, biperidene lactate, cold compresses, and paracetamol treatment. His agitation, sv
CPK (390 units/L) improved, and he was discharged normalized biochemical results on the fourth day (V

3.3.16.G Opioid withdrawal

1) Two patients receiving stable doses of opioids experienced withdrawal symptoms 3 days after beginning r
over 2 days following discontinuation of risperidone (Wines & Weiss, 1999d).

3.3.16.H Pain, General

1) Incidence: oral, adults, less than 1%; children, less than 5% (Prod Info RISPERDAL(R) oral tablets, 2007;
TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007); intramuscular, schizop
RISPERDAL(R) CONSTA(R) long acting injection, 2009)

2) During a 12-week, double-blind, placebo-control trial of schizophrenic patients, generalized pain was repo
risperidone 25 mg long-acting injection (n=99) and 1% of patients receiving risperidone 50 mg long-acting inj
0% of patients receiving placebo (n=98) (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).

3) During risperidone clinical trials, generalized pain was reported in less than 1% of adult patients receiving
of pediatric patients receiving oral therapy (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDA
tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007).

3.4 Teratogenicity/Effects in Pregnancy/Breastfeeding

A) Teratogenicity/Effects in Pregnancy

1) U.S. Food and Drug Administration's Pregnancy Category: Category C (Prod Info RISPERDAL(R) oral tablets,
(R) orally disintegrating tablets, 2008) (All Trimesters)

a) Either studies in animals have revealed adverse effects on the fetus (teratogenic or embryocidal or other)
studies in women or studies in women and animals are not available. Drugs should be given only if the poten
risk to the fetus.

2) Australian Drug Evaluation Committee's (ADEC) Category: B3(Australian Drug Evaluation Committee, 1999)

a) Drugs which have been taken by only a limited number of pregnant women and women of childbearing ag
frequency of malformation or other direct or indirect harmful effects on the human fetus having been observe
evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in hu

See Drug Consult reference: PREGNANCY RISK CATEGORIES

3) Crosses Placenta: Yes

4) Clinical Management

a) Risperidone should be used during pregnancy only after consideration is given to the potential benefit to t
to the fetus. It is recommended that patients notify their physician if they become pregnant or intend to becom
treatment (Prod Info RISPERDAL(R) oral tablets, solution, RISPERDAL(R) M-TAB(R) orally disintegrating tab

5) Literature Reports

a) A prospective, observational study of 54 women (mean age, 30.7 years) recruited from the Emory Womer
exposed to antipsychotic medication during pregnant showed permeability of the placental barrier. Outcomes
and umbilical cord blood samples taken at delivery and through data collected from maternal reports and me
showed a significant difference between antipsychotic medications, olanzapine 72.1% (95% CI, 46.8%-97.5%
haloperidol 65.5% (95% CI, 40.3%-90.7%), risperidone 49.2% (95% CI, 13.6%-84.8%), and quetiapine 24.1%
showing the lowest placental passage. In the risperidone group, there were no reports of preterm labor or infa
care admission. Of the 6 infants with maternal risperidone exposure, one infant weighed less than 2500 g (Ne

b) A review of pooled data from the Benefit Risk Management Worldwide Safety database found no increase
abortions, structural malformations, or fetal teratogenic risk from in utero exposure to risperidone. The volunta

197 retrospective) of drug exposure during pregnancy identified 713 pregnancies in women with psychiatric il during pregnancy. Of the 68 prospective pregnancies reported with known outcome, organ malformations (3. (16.9%) were documented (non-medically induced abortions excluded). Third-trimester exposure to risperido withdrawal, or possible withdrawal-emergent syndrome (WES) in 13 retrospectively reported cases. The stud neurodevelopmental outcomes in the neonate and developing child. In addition, many of the reports were co medications, several of which are known teratogens (Coppola et al, 2007).

c) A case report described two successive, normal pregnancies in a 23-year-old woman receiving risperidon unplanned yet uneventful pregnancy 6 months after starting risperidone 3 mg/day for treatment of schizophre at 39 weeks gestation and delivered a healthy baby girl weighing 3.2 kg. There were no postnatal complicatic risperidone dose was decreased to 2 mg/day due to mental stability. Nine months later, she became pregnar the 2 mg/day dose of risperidone without prenatal complications. Following spontaneous labor at 39 weeks, s weighing 3 kg. Both of the infants were breastfed for 6 months. The children did not show any signs of neuro behavioral problems at 36 and 18 months of age, respectively (Mendhekar & Lohia, 2008).

d) A case report described a normal pregnancy and healthy baby born to a middle-aged woman with schizo risperidone prior to and throughout her pregnancy. Successfully maintained for 7 years on risperidone, her do from 3 mg/day to 1 mg/day at 6 months' gestation, then to 0.5 mg/day a few days prior to delivery. The baby remained healthy over the first 3 months of life (Rodriguez-Salgado, 2008).

e) One case report of agenesis of the corpus callosum in an infant exposed in utero to risperidone has been risperidone has not been established. In postmarketing surveillance, following use of risperidone in the last tr extrapyramidal symptoms have been observed in the neonate (Prod Info RISPERDAL(R) oral tablets, solutio orally disintegrating tablets, 2008).

B) Breastfeeding

1) Thomson Lactation Rating: Infant risk cannot be ruled out.

a) Available evidence and/or expert consensus is inconclusive or is inadequate for determining infant risk wh Weigh the potential benefits of drug treatment against potential risks before prescribing this drug during breas

2) Clinical Management

a) In animal and human lactation studies, risperidone and its active 9-hydroxy metabolite are excreted into b (R) oral tablets, solution, RISPERDAL(R) M-TAB(R) orally disintegrating tablets, 2008). It is estimated that a 0.84% of the maternal dose as risperidone and an additional 3.46% from 9-hydroxyrisperidone (as risperidon amount is not likely to result in sedation or extrapyramidal side effects in a full-term or older infant, the possib effects, such as neuroleptic malignant syndrome, should not be overlooked (Hill et al, 2000). Because risperi women should not breastfeed during treatment with risperidone (Prod Info RISPERDAL(R) oral tablets, soluti orally disintegrating tablets, 2008).

3) Literature Reports

a) One case report described a 21-year-old woman who was treated postpartum with risperidone. She was a infant. After a gradual increase in maternal dose to 6 mg/day, she agreed to provide serial samples (over 24 so that risperidone and 9-hydroxyrisperidone could be measured. The milk to plasma ratios calculated from t risperidone and the active metabolite, respectively (Hill et al, 2000).

4) Drug Levels in Breastmilk

a) Parent Drug

1) Milk to Maternal Plasma Ratio

a) 0.42 (Hill et al, 2000)

b) Active Metabolites

1) 9-hydroxyrisperidone (Prod Info Risperdal(R), 1999)

a) Milk to Maternal Plasma Ratio

1) 0.24 (Hill et al, 2000)

3.5 Drug Interactions

3.5.1 Drug-Drug Combinations

Acecainide

Ajmaline

Amiodarone

Amisulpride

Amitriptyline

Amoxapine

Aprindine

Arsenic Trioxide

Astemizole

Azimilide

Bepridil

Bretylium

Bupropion

Carbamazepine

Chloral Hydrate

Chloroquine

Chlorpromazine

Cimetidine

Cisapride

Clarithromycin

Clozapine

Darunavir

Dehydroepiandrosterone

Desipramine

Dibenzepin

Disopyramide

Dofetilide

Dolasetron

Doxepin

Droperidol

Encainide

Enflurane

Erythromycin

Flecainide

Fluconazole

Fluoxetine

Foscarnet

Gemifloxacin

Ginkgo Biloba

Halofantrine

Haloperidol

Halothane

Hydroquinidine

Ibutilide

Imipramine

Isoflurane

Isradipine

Itraconazole

Lamotrigine

Levodopa

Levomethadyl

Levorphanol

Lidoflazine

Linezolid

Lithium

Lorcainide

Mefloquine

Mesoridazine

Methadone

Midodrine

Nortriptyline

Octreotide

Paroxetine

Pentamidine

Phenobarbital

Phenylalanine

Phenytoin

Pimozide

Pirmenol

Prajmaline

Probucol

Procainamide

Prochlorperazine

Propafenone

Protriptyline

Quetiapine

Ranitidine

Rifampin

Ritonavir

Ropinirole

Sematilide

Sertindole

Simvastatin

Sotalol

Spiramycin

Sulfamethoxazole

Sultopride

Tedisamil

Telithromycin

Terfenadine

Tetrabenazine

Thioridazine

Topiramate

Tramadol

Trifluoperazine

Trimethoprim

Trimipramine

Valproic Acid

Vasopressin

Zolmitriptan

Zotepine

3.5.1.A Acecainide

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Concurrent use of acecainide and risperidone is not recommended due to the risk of additive e concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised (Yamreudeewong et
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of acecainide and risperidone is not recommended d life-threatening arrhythmias. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring i
7) Probable Mechanism: additive QT prolongation
8) Literature Reports
a) Class III antiarrhythmics have been shown to prolong the QT interval, which may result in ventricular fibrillation, and torsades de pointes. Several antipsychotic agents have demonstrated QT prolongation in Laita et al, 1999a). Concomitant use of Class III antiarrhythmic agents such as acecainide and risperidor the QT interval and is not recommended (Yamreudeewong et al, 2003).

3.5.1.B Ajmaline

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Several antipsychotic agents have demonstrated QT prolongation including amisulpride, halop quetiapine, risperidone, sertindole, sultopride, ziprasidone, and zotepine (Prod Info FANAPT(TM) oral tablets 1999z; O'Brien et al, 1999q; Prod Info INVEGA(TM) extended-release oral tablets, 2006; Owens, 2001ab; Du et al, 2001v; Lande et al, 1992z; Prod Info GEODON(R) intramuscular injection, oral capsule, 2005; Sweetma antiarrhythmic agents may also prolong the QT interval and increase the risk of arrhythmias, the concurrent a with a drug from this class is not recommended (Prod Info FANAPT(TM) oral tablets, 2009; Prod Info Quinag
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: The concurrent administration of a Class IA antiarrhythmic and an antipsychotic is r
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) In an open-label QTc study of patients with schizophrenia or schizoaffective disorder (n=160), iloperic associated with QTc prolongation of 9 msec (Prod Info FANAPT(TM) oral tablets, 2009).
b) QRS widening, QTc interval prolongation, and torsades de pointes may occur with disopyramide ther 1997).
c) The effects of combined therapy with quinidine (Class IA antiarrhythmic agent) and haloperidol (antip giving 12 healthy volunteers haloperidol 5 mg alone and with 250 mg of quinidine bisulfate. The study de in the plasma concentrations of haloperidol when given concurrently with quinidine versus haloperidol tre under the concentration curve (AUC) was increased from 54.3 ng/h/mL on haloperidol alone to 103.2 ng/ peak concentration (Cmax) also showed an increase from 1.9 ng/mL on haloperidol to 3.8 ng/mL on com and time to peak concentration (Tmax) were not significantly changed, thereby suggesting to the authors is more likely responsible for the plasma level changes than an elimination alteration (Young et al, 1993)

3.5.1.C Amiodarone

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Concurrent use of amiodarone and risperidone is not recommended due to the risk of additive concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised (Yamreudeewong et
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of amiodarone and risperidone is not recommended life-threatening arrhythmias. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring i
7) Probable Mechanism: additive QT prolongation
8) Literature Reports
a) Class III antiarrhythmics have been shown to prolong the QT interval, which may result in ventricular fibrillation, and torsades de pointes. Several antipsychotic agents have demonstrated QT prolongation in Laita et al, 1999a). Concomitant use of Class III antiarrhythmic agents such as amiodarone and risperidc the QT interval and is not recommended (Yamreudeewong et al, 2003).

3.5.1.D Amisulpride

1) Interaction Effect: cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Coadministration of amisulpride with other drugs that potentiallly prolong the QTc interval, such approached with caution (Prod Info Solian(R), 1999n; Prod Info Risperdal(R), 2002b).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of agents that prolong the QT interval, such as amisu recommended.
7) Probable Mechanism: additive effects on QT prolongation
8) Literature Reports
a) Sometimes fatal QRS prolongation and QTc prolongation have been reported in patients taking rispe Laita et al, 1999r; Ravin & Levenson, 1997f; Gesell & Stephen, 1997b; Lo Vecchio et al, 1996b; Brown e

3.5.1.E Amitriptyline

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod haloperidol (O'Brien et al, 1999a), risperidone (Duenas-Laita et al, 1999d), sertindole (Agelink et al, 2001a), c sultopride (Lande et al, 1992a), and zotepine (Sweetman, 2003). Even though no formal drug interaction stuc coadministration of a tricyclic antidepressant and an antipsychotic is not recommended (Prod Info Pamelor(R 1982).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of a tricyclic antidepressant and an antipsychotic is n
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) Electrocardiographic changes that have occurred during clinical trials with pimozide have included pr interval, flattening, notching, and inversion of the T wave and the appearance of U waves. In experiment deaths have occurred while patients were receiving pimozide doses of 1 mg/kg. The proposed mechanis prolongation of the QT interval predisposing patients to ventricular arrhythmias (Prod Info Orap(R), 1999

3.5.1.F Amoxapine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod haloperidol (O'Brien et al, 1999a), risperidone (Duenas-Laita et al, 1999d), sertindole (Agelink et al, 2001a), c sultopride (Lande et al, 1992a), and zotepine (Sweetman, 2003). Even though no formal drug interaction stuc coadministration of a tricyclic antidepressant and an antipsychotic is not recommended (Prod Info Pamelor(R 1982).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of a tricyclic antidepressant and an antipsychotic is n
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) Electrocardiographic changes that have occurred during clinical trials with pimozide have included pr interval, flattening, notching, and inversion of the T wave and the appearance of U waves. In experiment deaths have occurred while patients were receiving pimozide doses of 1 mg/kg. The proposed mechanis prolongation of the QT interval predisposing patients to ventricular arrhythmias (Prod Info Orap(R), 1999

3.5.1.G Aprindine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Coadministration of risperidone with other drugs that potentially prolong the QTc interval, such approached with caution. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is a Larochelle et al, 1984).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of aprindine and risperidone is not recommended du threatening arrhythmias. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is ac
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.H Arsenic Trioxide
1) Interaction Effect: prolongation of the QTc interval and/or torsades de pointes
2) Summary: Arsenic trioxide can prolong the QT interval in some patients, which may result in ventricular ta and torsades de pointes and should not be administered with other drugs that may prolong the QT interval (P Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), al, 1999i), paliperidone (Prod Info INVEGA(TM) extended-release oral tablets, 2006), risperidone (Duenas-La (Agelink et al, 2001m), quetiapine (Owens, 2001r), sultopride (Lande et al, 1992o), ziprasidone (Prod Info GE injection, oral capsule, 2005), and zotepine (Sweetman, 2003).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of arsenic trioxide and antipsychotics is not recomme
7) Probable Mechanism: additive effects on QTc prolongation
8) Literature Reports
a) QT/QTc prolongation should be expected during treatment with arsenic trioxide and torsade de pointe block has been reported. Over 460 ECG tracings from 40 patients with refractory or relapsed APL treate evaluated for QTc prolongation. Sixteen of 40 patients (40%) had at least one ECG tracing with a QTc in Prolongation of the QTc was observed between 1 and 5 weeks after arsenic trioxide infusion, and then re end of 8 weeks after arsenic trioxide infusion. In these ECG evaluations, women did not experience more than men, and there was no correlation with age (Prod Info Trisenox(R), 2001).

3.5.1.I Astemizole
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod I haloperidol (O'Brien et al, 1999h), quetiapine (Owens, 2001p), risperidone (Duenas-Laita et al, 1999q; Prod I 2002a), sertindole (Agelink et al, 2001l), sultopride (Lande et al, 1992n), and zotepine (Sweetman, 2003). Ev interaction studies have been done, the coadministration of astemizole and other drugs known to prolong the antipsychotics, is not recommended (Prod Info Hismanal(R), 1996).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of astemizole and agents that prolong the QT interva recommended.
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) A total of 7 patients developed torsade de pointes after therapeutic use of haloperidol in high doses (I et al, 1993c). Three patients developed the dysrhythmia after administration of 211 to 825 mg haloperidc delirium. These 3 patients recovered from the initial episodes, but 1 patient subsequently died of cardiac haloperidol. Four patients developed the dysrhythmia after administration of 170 to 580 mg over 1 to 4 d bacterial meningitis (1), status asthmaticus (2) or respiratory insufficiency (1). All 4 patients recovered wi

3.5.1.J Azimilide
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Concurrent use of azimilide and risperidone is not recommended due to the risk of additive effe concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised (Yamreudeewong et
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of azimilide and risperidone is not recommended due threatening arrhythmias. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is ac
7) Probable Mechanism: additive QT prolongation
8) Literature Reports
a) Class III antiarrhythmics have been shown to prolong the QT interval, which may result in ventricular fibrillation, and torsades de pointes. Several antipsychotic agents have demonstrated QT prolongation in Laita et al, 1999a). Concomitant use of Class III antiarrhythmic agents such as azimilide and risperidone QT interval and is not recommended (Yamreudeewong et al, 2003).

3.5.1.K Bepridil

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Some antipsychotic agents prolong the QT interval and an additive effect would be anticipated which lengthen the QT interval (Prod Info Geodon(TM), 2002a; Agelink et al, 2001c; Owens, 2001e; Prod Info Haldol(R), 1998a). In U.S. clinical trials, bepridil increased QT and QTc intervals which was associated with t approximately 1% of patients. Other drugs that increase the QT interval may exaggerate the prolongation of t bepridil (Prod Info Vascor(R), 1997). Pimozide is contraindicated in patients taking other drugs which may pro Orap(R), 1999d).
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of antipsychotics and agents that prolong the QT inte contraindicated. In particular, pimozide is contraindicated in individuals with congenital QT syndrome, patient arrhythmias, or patients taking other drugs which may prolong the QT interval.
7) Probable Mechanism: additive effects on QT prolongation
8) Literature Reports
a) Electrocardiographic changes that have occurred during clinical trials with pimozide have included pro interval, flattening, notching, and inversion of the T wave and the appearance of U waves. In experiment deaths have occurred while patients were receiving pimozide doses of 1 mg/kg. The proposed mechanis prolongation of the QT interval predisposing patients to ventricular arrhythmias (Prod Info Orap(R), 1999
b) Sometimes fatal QRS prolongation and QTc prolongation have been reported in patients taking rispe Laita et al, 1999e; Ravin & Levenson, 1997a).

3.5.1.L Bretylium

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Concurrent use of bretylium and risperidone is not recommended due to the risk of additive effe concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised (Yamreudeewong et
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of bretylium and risperidone is not recommended du threatening arrhythmias. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is ac
7) Probable Mechanism: additive QT prolongation
8) Literature Reports
a) Class III antiarrhythmics have been shown to prolong the QT interval, which may result in ventricular fibrillation, and torsades de pointes. Several antipsychotic agents have demonstrated QT prolongation in Laita et al, 1999a). Concomitant use of Class III antiarrhythmic agents such as bretylium and risperidone QT interval and is not recommended (Yamreudeewong et al, 2003).

3.5.1.M Bupropion

1) Interaction Effect: increased plasma levels of risperidone
2) Summary: It is recommended that risperidone, an antipsychotic metabolized by the cytochrome P450 2D6 lower end of the dose range when administered concomitantly with bupropion (Prod Info Wellbutrin XL(TM), 2
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Coadministration of bupropion and risperidone should be approached with caution a lower end of the dose range of risperidone. If bupropion is added to the treatment regimen of a patient alread decreasing the dose of risperidone.
7) Probable Mechanism: inhibition of cytochrome P450 2D6-mediated risperidone metabolism

3.5.1.N Carbamazepine

1) Interaction Effect: increased risperidone clearance
2) Summary: The manufacturer reports that carbamazepine may increase risperidone clearance with chronic be closely monitored. Patients may be placed on a lower dose of risperidone between 2 to 4 weeks before th carbamazepine therapy to adjust for the expected increase in plasma concentrations of risperidone plus 9-hy subjects received risperidone titrated to 6 mg/day orally for 3 weeks, followed by coadministration of carbama Plasma concentrations of risperidone and 9-hydroxyrisperidone were decreased by 50%. The plasma concer unaffected (Prod Info Risperdal(R) Consta(TM), 2003a). One published case report describes a patient who h less than expected during carbamazepine therapy, along with decreased risperidone efficacy. The risperidon when carbamazepine was discontinued (de Leon & Bork, 1997a). Carbamazepine is an inducer of cytochrom while risperidone is primarily metabolized by CYP2D6. Whether carbamazepine is also inducing CYP2D6 or partly metabolized by CYP3A is uncertain (Lane & Chang, 1998; de Leon & Bork, 1998). The marked decrea by carbamazepine may result in decreased therapeutic efficacy. When risperidone is used in combination wit risperidone may be required to achieve or maintain a desired antipsychotic effect (Spina et al, 2000a).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor therapeutic efficacy of risperidone following the addition of carbamazepine

therapy; higher risperidone doses may be needed. Patients may be placed on a lower dose of risperidone be
discontinuation of carbamazepine therapy to adjust for the expected increase in plasma concentrations of risp
hydroxyrisperidone.
7) Probable Mechanism: induction of cytochrome P450-mediated metabolism of risperidone by carbamazepi
8) Literature Reports
a) Carbamazepine was reported to induce the metabolism of risperidone in a 22-year-old male with chro
low risperidone levels and lack of effectiveness. The patient was started on carbamazepine 600 mg daily
plasma concentration of 9-hydroxyrisperidone was less than half the expected concentration when the d
8 mg daily. After achieving a therapeutic plasma concentration of 9-hydroxyrisperidone (19 mcg/L), the d
tapered and stopped. Plasma levels of 9-hydroxyrisperidone increased to 49 mcg/L, necessitating a decr
(de Leon & Bork, 1997).
b) Plasma concentrations of risperidone and 9-OH risperidone decreased when carbamazepine was ad
discontinued. One study evaluated the pharmacokinetic interactions between risperidone and carbamaze
DSM-IV diagnosis of schizophrenia, schizoaffective disorder, or bipolar disorder participated in the study
risperidone alone or in combination with carbamazepine for at least four weeks. Steady-state plasma cor
hydroxyrisperidone (9-OH risperidone) were compared in patients treated with risperidone alone and pat
carbamazepine. The plasma concentrations of both 9-OH risperidone and the sum of risperidone and 9-(
differed significantly among groups. In five patients evaluated with and without comedication, the plasma
and 9-OH risperidone decreased when carbamazepine was added or increased when it was discontinue
in patients receiving risperidone alone, the concentration of the active moiety (risperidone plus its active
was reduced by approximately 70% when carbamazepine was given concomitantly (Spina et al, 2000).
c) The concomitant use of carbamazepine and risperidone leads to a marked decrease in the steady-sta
risperidone and 9-hydroxyrisperidone through stimulation of an inducible cytochrome as well as the influe
2D6 genotype. A 50-year-old male with chronic schizophrenia and deficient CYP2D6 activity was given c
risperidone therapy. Carbamazepine 800 mg/day for 5 days was added to his medication regimens as a
carbamazepine treatment, the patient exhibited psychotic symptoms including hallucinations, paranoid d
mild excitement. Plasma concentrations of risperidone and its active metabolite 9-hydroxyrisperidone, ha
ng/mL, respectively. Carbamazepine concentration was 8.2 mcg/mL. The risperidone dose was increase
was discontinued, and lorazepam 5 mg/day was added. Psychotic symptoms improved over the followin
risperidone and 9-hydroxyrisperidone increased to 40 and 57 ng/mL, respectively. A resultant decrease i
risperidone and 9-hydroxyrisperidone suggest that the CYP2D6 genotype may influence susceptibility to
with risperidone and carbamazepine (Spina et al, 2001).
d) Eleven schizophrenic patients in a drug interaction study received oral risperidone titrated to 6 mg/da
concurrent administration of carbamazepine for an additional 3 weeks. The plasma concentrations of risp
pharmacologically active metabolite, 9-hydroxyrisperidone, were decreased by about 50%. At the initiatio
carbamazepine, patients should be closely monitored during the first 4-8 weeks, since the dose of risperi
dose increase or additional risperidone may need to be considered. If carbamazepine is discontinued, th
be re-evaluated and, if necessary, decreased. A lower dose of risperidone may be required between 2 to
discontinuation of carbamazepine therapy to adjust for the expected increase in plasma concentrations o
hydroxyrisperidone (Prod Info Risperdal(R) Consta(TM), 2003).

3.5.1.O Chloral Hydrate

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Chloral hydrate has been shown to prolong the QTc interval at the recommended therapeutic d
though no formal drug interaction studies have been done, the administration of drugs known to prolong the Q
antipsychotics and chloral hydrate is not recommended. Several antipsychotic agents have demonstrated QT
amisulpride (Prod Info Solian(R), 1999l), haloperidol (O'Brien et al, 1999g), quetiapine (Owens, 2001o), rispe
1999o), sertindole (Agelink et al, 2001k), sultopride (Lande et al, 1992k), and zotepine (Sweetman, 2003).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of chloral hydrate and antipsychotics is not recomme
7) Probable Mechanism: additive effects on QT prolongation
8) Literature Reports
a) The overall incidence of QT interval prolongation with sertindole is estimated at 1.9% to 4%, and the
torsades de pointes has been estimated at 0.13% to 0.21% (Brown & Levin, 1998b). Periodic electrocard
in the United Kingdom per sertindole's official labeling (Cardoni & Myer, 1997).
b) A total of 7 patients developed torsade de pointes after therapeutic use of haloperidol in high doses (
et al, 1993b). Three patients developed the dysrhythmia after administration of 211 to 825 mg haloperido
delirium. These 3 patients recovered from the initial episodes, but 1 patient subsequently died of cardiac
haloperidol.

3.5.1.P Chloroquine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Chloroquine has been shown to prolong the QTc interval at the recommended therapeutic dos
anticipated if administered with other agents which lengthen the QT interval (Prod Info Aralen(R), 2001). Sev
demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999w), haloperidol (O'Brien et al,
2001z), risperidone (Duenas-Laita et al, 1999ad), sertindole (Agelink et al, 2001s), sultopride (Lande et al, 19

2004).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of antipsychotics and agents that prolong the QT inte
recommended.
7) Probable Mechanism: additive effect on QT prolongation
8) Literature Reports
a) Sometimes fatal QRS prolongation and QTc prolongation have been reported in patients taking rispe
Laita et al, 1999ac; Ravin & Levenson, 1997k).

3.5.1.Q Chlorpromazine
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest
2) Summary: Concomitant use of phenothiazines and antipsychotic agents may cause additive effects on the
recommended. Q and T wave distortions have been observed in patients taking phenothiazines (Prod Info Co
Stelazine(R), 2002; Prod Info Thorazine(R), 2002). Other phenothiazines may have similar effects, though no
antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999j),
paliperidone (Prod Info INVEGA(TM) extended-release oral tablets, 2006), quetiapine (Owens, 2001n), risper
1999n), sertindole (Agelink et al, 2001j), sultopride (Lande et al, 1992i), ziprasidone (Prod Info GEODON(R) i
capsule, 2005), and zotepine (Sweetman, 2003).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of agents that prolong the QT interval, such as phen
not recommended.
7) Probable Mechanism: additive QT prolongation

3.5.1.R Cimetidine
1) Interaction Effect: increased risperidone bioavailability
2) Summary: Concurrent use of risperidone and cimetidine resulted in a 64% increase in the bioavailability o
active metabolite, 9-hydroxyrisperidone, was not affected (Prod Info RISPERDAL(R) CONSTA(R) long-acting
if these agents are used concomitantly. Monitor patients for increased risperidone adverse events (sedation,
dyspepsia, tachycardia, constipation, or dry mouth).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Concurrent treatment with cimetidine and risperidone has resulted in a 64% increas
The AUC of the active metabolite, 9-hydroxyrisperidone, was not affected (Prod Info RISPERDAL(R) CONST
2007). Caution is advised if these agents are used concomitantly. Consider monitoring for increased risperido
sedation, akathisia, parkinsonism, dyspepsia, tachycardia, constipation, or dry mouth.
7) Probable Mechanism: unknown

3.5.1.S Cisapride
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest
2) Summary: Some antipsychotic agents prolong the QT interval and an additive effect would be anticipated
which lengthen the QT interval (Prod Info Geodon(TM), 2002; Owens, 2001a; Prod Info Orap(R), 1999a). Tor
prolongation have been reported with cisapride (Prod Info Propulsid(R), 2000).
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of antipsychotics and agents that prolong the QT inte
contraindicated. In particular, pimozide is contraindicated in individuals with congenital QT syndrome, patient
arrhythmias, or patients taking other drugs which may prolong the QT interval.
7) Probable Mechanism: additive effects on QT prolongation
8) Literature Reports
a) Electrocardiographic changes that have occurred during clinical trials with pimozide have included pro
interval, flattening, notching, and inversion of the T wave and the appearance of U waves. In experiment
deaths have occurred while patients were receiving pimozide doses of 1 mg/kg. The proposed mechanis
prolongation of the QT interval predisposing patients to ventricular arrhythmias (Prod Info Orap(R), 1999
b) Fatal QRS prolongation and QTc prolongation have been reported in patients taking risperidone (Due
Levenson, 1997).

3.5.1.T Clarithromycin
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest
2) Summary: Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod I
haloperidol (O'Brien et al, 1999b), quetiapine (Owens, 2001f), risperidone (Duenas-Laita et al, 1999f), sertind
sultopride (Lande et al, 1992c), and zotepine (Sweetman, 2004). Even though no formal drug interaction stud
use of clarithromycin and antipsychotic agents may cause additive effects on the QT interval and is not recon

2002).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of clarithromycin and agents that prolong the QT inte
not recommended.
7) Probable Mechanism: additive effects on QT prolongation
8) Literature Reports
a) A 32-year-old male with schizoaffective disorder and metabolic syndrome experienced a significant in
following administration of quetiapine. The patient, hospitalized for acute psychotic symptoms was treate
with a gradual increase in dosage to 700 mg over 10 days. Psychotic symptoms dissipated within 3 weel
developed a lower airway infection, and was orally treated with 750 mg sultamicillin, 500 mg clarithromyc
quetiapine 400 mg. The following morning, 750 mg sultamicillin, 500 mg clarithromycin, and the morning
given. Within hours the patient became somnolent, and plasma sample testing resulted in 826.8 microgr
microgram/L). The patient developed severe impaired consciousness and respiratory depression. Quetia
and treatment was discontinued. Plasma levels were continually measured over the course of a week un
achieved (Schulz-Du Bois et al, 2008).
b) A total of 7 patients developed torsade de pointes after therapeutic use of haloperidol in high doses (
et al, 1993). Three patients developed the dysrhythmia after administration of 211 to 825 mg haloperidol
delirium. These 3 patients recovered from the initial episodes, but 1 patient subsequently died of cardiac
haloperidol. Four patients developed the dysrhythmia after administration of 170 to 580 mg over 1 to 4 d
bacterial meningitis (1), status asthmaticus (2) or respiratory insufficiency (1). All 4 patients recovered wi
c) Prolongation of the QTc interval was reported in 8 patients receiving risperidone (Prod Info Risperdal

3.5.1.U Clozapine
1) Interaction Effect: decreased risperidone clearance
2) Summary: The manufacturer reports that clozapine may decrease risperidone clearance with chronic com
(R) Consta(TM), 2003g).
3) Severity: minor
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Monitor patients for increased adverse effects of risperidone when these drugs are
7) Probable Mechanism: unknown

3.5.1.V Darunavir
1) Interaction Effect: increased risperidone plasma concentrations
2) Summary: Coadministration of ritonavir-boosted darunavir, a CYP2D6 inhibitor, and risperidone, a CYP2D
increased plasma concentrations of risperidone, possibly due to inhibition of CYP2D6-mediated risperidone m
As this may result in risperidone adverse effects, a lower dose of risperidone should be considered with conc
Info PREZISTA(R) film coated oral tablets, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concurrent administration of ritonavir-boosted darunavir and risperidone may increa
concentrations. Consider using a lower risperidone dose when these agents are coadministered (Prod Info P
tablets, 2008).
7) Probable Mechanism: inhibition of CYP2D6-mediated risperidone metabolism by darunavir/ritonavir

3.5.1.W Dehydroepiandrosterone
1) Interaction Effect: reduced effectiveness of risperidone
2) Summary: Dehydroepiandrosterone (DHEA) levels within the normal range of 100 to 400 microgram/decil
optimal treatment of patients with psychosis (Howard, 1992a). In case reports, patients have been resistant t
levels were elevated (Howard, 1992a). Patients being treated with risperidone should avoid DHEA supplemer
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Avoid concomitant use of dehydroepiandrosterone (DHEA) and risperidone. If DHE
dexamethasone 1 mg orally per day may be used to normalize DHEA levels.
7) Probable Mechanism: elevated dehydroepiandrosterone (DHEA) blood levels may reduce responsiveness
8) Literature Reports
a) A 24-year-old female diagnosed with schizophrenia was resistant to daily doses of haloperidol 20 mill
mg, lithium carbonate 1200 mg, and lithium carbonate 900 mg plus thioridazine 300 mg. The patient app
acne, facial hair, abdominal hair, and a 40 pound weight gain in the previous 8 months. Dehydroepiandro
part of an endocrine panel was 725 micrograms/deciliter (mcg/dL) (normal: 100 to 400 mcg/dL). Dexame
resulted in substantial improvement within one week. The patient appeared calmer, more alert with impro
ability to concentrate. At two weeks, a repeated DHEA level was within normal range (328 mcg/dL). The
DHEA levels were associated with severe psychosis resistant to conventional antipsychotic therapy (Hov
b) A 13-year-old male decompensated with a subsequent two-year period of emotional problems accom

hashish, barbiturates, and alcohol. His mental status included bizarre, disorganized, delusional thinking, hallucinations, paranoia, lack of attention to personal hygiene, agitation, and combativeness. He was dia schizophrenia; schizophrenia, chronic undifferentiated type, and schizoaffective disorder, excited type. H trifluoperazine 40 mg, chlorpromazine 400 mg, and imipramine 100 mg. He was also resistant to combin chlorpromazine 400 mg with thiothixene 80 mg, thioridazine 1000 mg, perphenazine 48 mg with lithium c 4 mg, and carbamazepine 1200 mg daily. Baseline DHEA level exceeded 900 mcg/dL. A seven-day sup dexamethasone 1 mg orally at bedtime resulted in a normal DHEA level of 200 mcg/dL. By day 5, psych was well-oriented, conversational, and was making good eye contact. Once dexamethasone was discon and florid psychosis ensued despite "substantial amounts of psychotropic medications". DHEA increased concluded that elevated DHEA levels were associated with florid psychosis resistant to conventional anti 1992).

3.5.1.X Desipramine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod I haloperidol (O'Brien et al, 1999a), risperidone (Duenas-Laita et al, 1999d), sertindole (Agelink et al, 2001a), c sultopride (Lande et al, 1992a), and zotepine (Sweetman, 2003). Even though no formal drug interaction stud coadministration of a tricyclic antidepressant and an antipsychotic is not recommended (Prod Info Pamelor(R 1982).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of a tricyclic antidepressant and an antipsychotic is n
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) Electrocardiographic changes that have occurred during clinical trials with pimozide have included pr interval, flattening, notching, and inversion of the T wave and the appearance of U waves. In experiment deaths have occurred while patients were receiving pimozide doses of 1 mg/kg. The proposed mechanis prolongation of the QT interval predisposing patients to ventricular arrhythmias (Prod Info Orap(R), 1999

3.5.1.Y Dibenzepin

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod I haloperidol (O'Brien et al, 1999a), risperidone (Duenas-Laita et al, 1999d), sertindole (Agelink et al, 2001a), c sultopride (Lande et al, 1992a), and zotepine (Sweetman, 2003). Even though no formal drug interaction stud coadministration of a tricyclic antidepressant and an antipsychotic is not recommended (Prod Info Pamelor(R 1982).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of a tricyclic antidepressant and an antipsychotic is n
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) Electrocardiographic changes that have occurred during clinical trials with pimozide have included pr interval, flattening, notching, and inversion of the T wave and the appearance of U waves. In experiment deaths have occurred while patients were receiving pimozide doses of 1 mg/kg. The proposed mechanis prolongation of the QT interval predisposing patients to ventricular arrhythmias (Prod Info Orap(R), 1999

3.5.1.Z Disopyramide

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Several antipsychotic agents have demonstrated QT prolongation including amisulpride, halop quetiapine, risperidone, sertindole, sultopride, ziprasidone, and zotepine (Prod Info FANAPT(TM) oral tablets 1999z; O'Brien et al, 1999q; Prod Info INVEGA(TM) extended-release oral tablets, 2006; Owens, 2001ab; Du et al, 2001v; Lande et al, 1992z; Prod Info GEODON(R) intramuscular injection, oral capsule, 2005; Sweetma antiarrhythmic agents may also prolong the QT interval and increase the risk of arrhythmias, the concurrent a with a drug from this class is not recommended (Prod Info FANAPT(TM) oral tablets, 2009; Prod Info Quinag
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: The concurrent administration of a Class IA antiarrhythmic and an antipsychotic is r
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) In an open-label QTc study of patients with schizophrenia or schizoaffective disorder (n=160), iloperic associated with QTc prolongation of 9 msec (Prod Info FANAPT(TM) oral tablets, 2009).
b) QRS widening, QTc interval prolongation, and torsades de pointes may occur with disopyramide ther 1997).
c) The effects of combined therapy with quinidine (Class IA antiarrhythmic agent) and haloperidol (antip giving 12 healthy volunteers haloperidol 5 mg alone and with 250 mg of quinidine bisulfate. The study de

in the plasma concentrations of haloperidol when given concurrently with quinidine versus haloperidol tre
under the concentration curve (AUC) was increased from 54.3 ng/h/mL on haloperidol alone to 103.2 ng/
peak concentration (Cmax) also showed an increase from 1.9 ng/mL on haloperidol to 3.8 ng/mL on com
and time to peak concentration (Tmax) were not significantly changed, thereby suggesting to the authors
is more likely responsible for the plasma level changes than an elimination alteration (Young et al, 1993)

3.5.1.AA Dofetilide

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Concurrent use of dofetilide and risperidone is not recommended due to the risk of additive effe
concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised. Dofetilide should be
before any interacting drug is initiated (Yamreudeewong et al, 2003a).
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of dofetilide and risperidone is not recommended due
threatening arrhythmias. Dofetilide should be stopped for at least 2 days before any interacting drug is initiate
avoided, cautious dosing and telemetric monitoring is advised.
7) Probable Mechanism: additive QT prolongation
8) Literature Reports
a) Class III antiarrhythmics have been shown to prolong the QT interval, which may result in ventricular
fibrillation, and torsades de pointes. Several antipsychotic agents have also demonstrated QT prolongati
(Duenas-Laita et al, 1999a). Concomitant use of Class III antiarrhythmic agents such as dofetilide and ris
effects on the QT interval and is not recommended (Yamreudeewong et al, 2003).

3.5.1.AB Dolasetron

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod I
haloperidol (O'Brien et al, 1999e), quetiapine (Owens, 2001l), risperidone (Duenas-Laita et al, 1999k), sertinc
sultopride (Lande et al, 1992g), and zotepine (Sweetman, 2003). Even though no formal drug interaction stuc
coadministration of dolasetron and other drugs known to prolong the QTc interval, including antipsychotics, is
Anzemet(R), 1997a).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of dolasetron and agents that prolong the QT interva
recommended.
7) Probable Mechanism: additive effects on QT prolongation
8) Literature Reports
a) In several studies, dolasetron resulted in significant, dose-related increases in mean PR, QRS, and Q
baseline values. Measured changes in ECG parameters were transient, reversible, and asymptomatic. In
intervals may be due to prolongation of maximum upstroke velocity (Vmax) due to binding of dolasetron t
cause of QTc interval prolongation appears to be due to prolongation of the QRS interval, increases in h
Anzemet(R), 1997; Hunt et al, 1995; Kris et al, 1994).
b) A total of 7 patients developed torsade de pointes after therapeutic use of haloperidol in high doses (I
et al, 1993a). Three patients developed the dysrhythmia after administration of 211 to 825 mg haloperidc
delirium. These 3 patients recovered from the initial episodes, but 1 patient subsequently died of cardiac
haloperidol. Four patients developed the dysrhythmia after administration of 170 to 580 mg over 1 to 4 da
bacterial meningitis (1), status asthmaticus (2) or respiratory insufficiency (1). All 4 patients recovered wi
c) Prolongation of the QTc interval was reported in 8 patients receiving risperidone (Prod Info Risperdal(

3.5.1.AC Doxepin

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod I
haloperidol (O'Brien et al, 1999a), risperidone (Duenas-Laita et al, 1999d), sertindole (Agelink et al, 2001a), c
sultopride (Lande et al, 1992a), and zotepine (Sweetman, 2003). Even though no formal drug interaction stuc
coadministration of a tricyclic antidepressant and an antipsychotic is not recommended (Prod Info Pamelor(R
1982).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of a tricyclic antidepressant and an antipsychotic is n
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) Electrocardiographic changes that have occurred during clinical trials with pimozide have included pro
interval, flattening, notching, and inversion of the T wave and the appearance of U waves. In experiment
deaths have occurred while patients were receiving pimozide doses of 1 mg/kg. The proposed mechanis
prolongation of the QT interval predisposing patients to ventricular arrhythmias (Prod Info Orap(R), 1999

3.5.1.AD Droperidol

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod
(O'Brien et al, 1999l), quetiapine (Owens, 2001w), risperidone (Duenas-Laita et al, 1999z), sertindole (Agelin
et al, 1992t), and zotepine (Sweetman, 2003). Droperidol has been shown to prolong the QTc interval at the
Even though no formal drug interaction studies have been done, the coadministration of droperidol and other
interval, including antipsychotics is not recommended (Prod Info Inapsine(R), 2002).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of droperidol and antipsychotics is not recommended
7) Probable Mechanism: additive cardiac effects

3.5.1.AE Encainide

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Coadministration of risperidone with other drugs that potentially prolong the QTc interval, such
approached with caution. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is a
Larochelle et al, 1984).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of encainide and risperidone is not recommended du
threatening arrhythmias. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is ac
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.AF Enflurane

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Some antipsychotic agents prolong the QT interval and an additive effect would be anticipated
which lengthen the QT interval (Agelink et al, 2001y; Owens, 2001af; Prod Info Haldol(R), 1998i; Lande et al,
drug interaction studies have been done, antipsychotic agents should not be coadministered with other drugs
the QTc interval, including enflurane (Owens, 2001af).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of enflurane and agents that prolong the QT interval,
recommended.
7) Probable Mechanism: additive effects on QT prolongation
8) Literature Reports
a) Sometimes fatal QRS prolongation and QTc prolongation have been reported in patients taking rispe
Laita et al, 1999ai; Ravin & Levenson, 1997n).

3.5.1.AG Erythromycin

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Erythromycin significantly increased the mean QTc interval versus baseline in a retrospective s
Bauman, 1995a). Erythromycin has demonstrated QTc prolongation in combination with other drugs that prol
PCE(R), 1997). Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Pro
haloperidol (O'Brien et al, 1999p), risperidone (Duenas-Laita et al, 1999ae), sertindole (Agelink et al, 2001t),
and zotepine (Sweetman, 2003). Caution is advised with coadministration of drugs that potentially prolong th
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Caution is advised if erythromycin and antipsychotics are used concomitantly. Moni
periodically during treatment.
7) Probable Mechanism: additive effects on QT prolongation
8) Literature Reports
a) Erythromycin significantly increased the QTc interval compared with baseline in a retrospective study
dose was 500 milligrams or 1 gram four times daily, with a mean of 15 doses received. Patients (n equal
or more all developed increases in QT interval of 15% or greater. For all patients, the mean QTc interval
(msec) at baseline to 483 msec (p less than 0.01). In patients with delayed repolarization at baseline (n e
increased from 473 msec to 525 msec (p less than 0.01). In patients with heart disease (n equal to 30), a
QTc interval (mean of 15%), compared with an increase of 8% in patients without heart disease (p less t
the QTc interval was severely prolonged. One patient developed torsades de pointes attributed to erythr
cotrimoxazole concomitantly, 8 developed QT prolongation of 15% or greater (Oberg & Bauman, 1995).

3.5.1.AH Flecainide

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Coadministration of risperidone with other drugs that potentially prolong the QTc interval, such
approached with caution. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is a

Tambocor(R), 1998; Larochelle et al, 1984).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of flecainide and risperidone is not recommended du threatening arrhythmias. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is ac
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.AI Fluconazole
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Case reports have described QT prolongation and torsades de points associated with fluconaz Wassmann et al, 1999). Haloperidol (Prod Info Haldol(R), 1998d), risperidone (Prod Info Risperdal(R) risperic Info Solian(R), 1999k), sertindole (Brown & Levin, 1998a); sultopride (Lande et al, 1992j), and zotepine (Swe to prolong the QT interval at therapeutic doses. Even though no formal drug interaction studies have been do known to prolong the QT interval are used concomitantly.
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Caution is advised if fluconazole and antipsychotics are used concomitantly.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.AJ Fluoxetine
1) Interaction Effect: increased plasma concentrations of risperidone
2) Summary: Concomitant use of fluoxetine (CYP2D6 inhibitor) and risperidone (CYP2D6 substrate) has res plasma concentrations and an increased risk of risperidone adverse effects such as serotonin syndrome, QT effects. The postulated mechanism of action is inhibition of CYP2D6-mediated metabolism of risperidone by f demonstrated increased risperidone levels in patients treated concurrently with fluoxetine and risperidone (Pr tablets, oral solution, orally disintegrating tablets, 2008; Spina et al, 2002). Monitoring the patient for increase effects may be necessary (Spina et al, 2002). The risperidone dose should be reevaluated if fluoxetine is initi RISPERDAL(R) oral tablets, oral solution, orally disintegrating tablets, 2008) (Spina et al, 2002a).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Concomitant use of fluoxetine and risperidone has resulted in increased risperidone increased risk of risperidone side effects (Prod Info RISPERDAL(R) oral tablets, oral solution, orally disintegr monitor patients for increased plasma risperidone levels and side effects (serotonin syndrome, extrapyramida when fluoxetine is coadministered with risperidone (Spina et al, 2002). Reevaluate the dose of risperidone wh initiated or discontinued (Prod Info RISPERDAL(R) oral tablets, oral solution, orally disintegrating tablets, 200
7) Probable Mechanism: inhibition of CYP2D6-mediated metabolism of risperidone
8) Literature Reports
a) Fluoxetine (a CYP2D6 inhibitor) 20 mg/day has been shown to increase the plasma concentration of substrate) 2.5- to 2.8-fold. Fluoxetine did not affect the concentration of 9-hydroxyrisperidone. The dosag reevaluated when fluoxetine is initiated or discontinued (Prod Info RISPERDAL(R) oral tablets, oral solut 2008).
b) Fluoxetine, an inhibitor of cytochrome CYP2D6, may impair the elimination of risperidone, primarily b alpha-hydroxylation and, to a lesser extent, by simultaneously affecting the further metabolism of 9-hydr risperidone) or other pathways of risperidone biotransformation. In an open, 4-week, pharmacokinetic stu schizophrenia or schizoaffective disorder, depressive type, risperidone concentrations increased when fl with risperidone. Patients were stabilized on a fixed dose of risperidone 4 to 6 mg/day for at least four we fluoxetine therapy 20 mg/day for the management of concomitant depression. Mean plasma risperidone ng/mL at baseline to 49 nanograms (ng)/mL (p less than 0.01) at week 2, and 56 ng/mL (p less than 0.01 concentrations of 9-hydroxyrisperidone (9-OH-risperidone) showed no significant increase at 4 weeks co weeks of concurrent therapy, the active moiety (risperidone plus 9-OH-risperidone) was increased by 75 than 0.01) compared with baseline. The mean plasma risperidone to 9-OH-risperidone ratio also increas experienced Parkinsonian symptoms during week 2 of concomitant therapy and were treated with antich suggest that monitoring plasma risperidone levels may be warranted in patients receiving concomitant flu treatment (Spina et al, 2002).

3.5.1.AK Foscarnet
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Foscarnet can prolong the QT interval in some patients, which may result in ventricular tachyca torsades de pointes. Several antipsychotic agents have demonstrated QT prolongation including amisulpride haloperidol (O'Brien et al, 1999r), quetiapine (Owens, 2001ae), risperidone (Duenas-Laita et al, 1999ah), ser sultopride (Lande et al, 1992ab), and zotepine (Sweetman, 2003). Because antipsychotics may also prolong risk of arrhythmias, the concurrent administration of foscarnet and antipsychotics is not recommended (Prod Levenson, 1997m).
3) Severity: major
4) Onset: unspecified

5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of foscarnet and antipsychotics is not recommended
7) Probable Mechanism: additive cardiac effects

3.5.1.AL Gemifloxacin
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Although pharmacokinetic studies between gemifloxacin and drugs that prolong the QT interva not been performed, gemifloxacin should be used cautiously in patients receiving antipsychotic medications (
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of two drugs that prolong the QT interval, such as ge not recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.AM Ginkgo Biloba
1) Interaction Effect: increased risk of risperidone adverse effects
2) Summary: Concomitant use of risperidone and ginkgo biloba may have precipitated priapism in one case cytochrome P450 isoforms 3A4 and 2C9, both of which are responsible for risperidone metabolism. Increase risperidone may lead to an increased risk of side effects, including priapism, as in this case report (Lin et al, 2
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Caution patients taking risperidone to discuss the use of nonprescription medicines with their doctor or pharmacist. If a patient presents with symptoms consistent with excessive risperidone, inc nonprescription medicines, herbs, and dietary supplements. It is recommended to avoid ginkgo in patients tal
7) Probable Mechanism: unknown
8) Literature Reports
a) Priapism occurred in a 26-year-old patient treated with risperidone 3 mg/day for 3 years who began g emergency department admission. He reported no other recent trauma, illness, or use of drugs or medic adverse effects related to risperidone therapy. He was treating occasional tinnitus with ginkgo biloba 160

3.5.1.AN Halofantrine
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Halofantrine can prolong the QT interval in some patients, which may result in ventricular tachy torsades de pointes. Some antipsychotic agents prolong the QT interval and an additive effect would be antic agents which lengthen the QT interval (Agelink et al, 2001b; Owens, 2001d; Prod Info Solian(R), 1999c; Proc al, 1992b). The concurrent administration of halofantrine with antipsychotics is not recommended (Prod Info H
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of halofantrine and an antipsychotic is not recommer
7) Probable Mechanism: additive cardiac effects

3.5.1.AO Haloperidol
1) Interaction Effect: cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Haloperidol is associated with QTc prolongation and torsade de pointes (Hassaballa & Balk, 20 2001a). Sometimes fatal QRS prolongation and QTc prolongation have been reported in patients taking rispe Laita et al, 1999t; Ravin & Levenson, 1997h; Gesell & Stephen, 1997d) and in overdose situations (Lo Vecch 1993d). Caution is advised with coadministration of drugs that potentially prolong the QTc interval.
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Caution is advised if haloperidol and risperidone are used concomitantly. Screen pa predispose to QT prolongation and torsade de pointes (i.e. cardiomyopathy, alcohol abuse, hypothyroidism). at baseline and throughout therapy.
7) Probable Mechanism: additive effects on QT prolongation
8) Literature Reports
a) Sometimes fatal QRS prolongation and QTc prolongation have been reported in patients taking rispe Laita et al, 1999s; Ravin & Levenson, 1997g; Gesell & Stephen, 1997c) and in overdose situations (Lo V 1993c).
b) Numerous case reports have described significant QTc prolongation and torsades de pointes (TdP) a Hemodynamically significant ventricular tachyarrhythmias, ventricular fibrillation, asystole, and death hav appears to be greater with intravenous haloperidol, but has occurred with oral and intramuscular use. Th greater than 35 milligrams (mg) over 24 hours, although TdP has been associated with a dose as low as intravenously over 4 hours. To prevent haloperidol-induced TdP, screen patients for a history of dilated c testing for hypothyroidism before therapy, obtaining an electrocardiogram at baseline and throughout the magnesium, and calcium. In patients with a baseline QTc greater than 450 milliseconds (msec), haloperi

an alternative agent should be used. Discontinue haloperidol if the QTc increases more than 25% from b or development of U-waves occurs (Hassaballa & Balk, 2003).

3.5.1.AP Halothane

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Some antipsychotic agents prolong the QT interval and an additive effect would be anticipated which lengthen the QT interval (Agelink et al, 2001i; Owens, 2001m; Prod Info Solian(R), 1999i; Prod Info Ha 1992h). Even though no formal drug interaction studies have been done, antipsychotic agents should not be which may also prolong the QTc interval, including halothane (Owens, 2001m).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of halothane and agents that prolong the QT interval recommended.
7) Probable Mechanism: additive effect on QT interval
8) Literature Reports
a) Sometimes fatal QRS prolongation and QTc prolongation have been reported in patients taking rispe Laita et al, 1999m; Ravin & Levenson, 1997d).

3.5.1.AQ Hydroquinidine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Several antipsychotic agents have demonstrated QT prolongation including amisulpride, halop quetiapine, risperidone, sertindole, sultopride, ziprasidone, and zotepine (Prod Info FANAPT(TM) oral tablets 1999z; O'Brien et al, 1999q; Prod Info INVEGA(TM) extended-release oral tablets, 2006; Owens, 2001ab; Du et al, 2001v; Lande et al, 1992z; Prod Info GEODON(R) intramuscular injection, oral capsule, 2005; Sweetma antiarrhythmic agents may also prolong the QT interval and increase the risk of arrhythmias, the concurrent a with a drug from this class is not recommended (Prod Info FANAPT(TM) oral tablets, 2009; Prod Info Quinag
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: The concurrent administration of a Class IA antiarrhythmic and an antipsychotic is r
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) In an open-label QTc study of patients with schizophrenia or schizoaffective disorder (n=160), iloperic associated with QTc prolongation of 9 msec (Prod Info FANAPT(TM) oral tablets, 2009).
b) QRS widening, QTc interval prolongation, and torsades de pointes may occur with disopyramide ther 1997).
c) The effects of combined therapy with quinidine (Class IA antiarrhythmic agent) and haloperidol (antip giving 12 healthy volunteers haloperidol 5 mg alone and with 250 mg of quinidine bisulfate. The study de in the plasma concentrations of haloperidol when given concurrently with quinidine versus haloperidol tre under the concentration curve (AUC) was increased from 54.3 ng/h/mL on haloperidol alone to 103.2 ng/ peak concentration (Cmax) also showed an increase from 1.9 ng/mL on haloperidol to 3.8 ng/mL on com and time to peak concentration (Tmax) were not significantly changed, thereby suggesting to the authors is more likely responsible for the plasma level changes than an elimination alteration (Young et al, 1993)

3.5.1.AR Ibutilide

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Concurrent use of ibutilide and risperidone is not recommended due to the risk of additive effec concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised (Yamreudeewong et
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of ibutilide and risperidone is not recommended due threatening arrhythmias. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is ac
7) Probable Mechanism: additive QT prolongation
8) Literature Reports
a) Class III antiarrhythmics have been shown to prolong the QT interval, which may result in ventricular fibrillation, and torsades de pointes. Several antipsychotic agents have demonstrated QT prolongation in Laita et al, 1999a). Concomitant use of Class III antiarrhythmic agents such as ibutilide and risperidone r QT interval and is not recommended (Yamreudeewong et al, 2003).

3.5.1.AS Imipramine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod haloperidol (O'Brien et al, 1999a), risperidone (Duenas-Laita et al, 1999d), sertindole (Agelink et al, 2001a), c sultopride (Lande et al, 1992a), and zotepine (Sweetman, 2003). Even though no formal drug interaction stuc coadministration of a tricyclic antidepressant and an antipsychotic is not recommended (Prod Info Pamelor(R 1982).

3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of a tricyclic antidepressant and an antipsychotic is n
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) Electrocardiographic changes that have occurred during clinical trials with pimozide have included pr interval, flattening, notching, and inversion of the T wave and the appearance of U waves. In experiment deaths have occurred while patients were receiving pimozide doses of 1 mg/kg. The proposed mechanis prolongation of the QT interval predisposing patients to ventricular arrhythmias (Prod Info Orap(R), 1999

3.5.1.AT Isoflurane
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest
2) Summary: Some antipsychotic agents prolong the QT interval and an additive effect would be anticipated which lengthen the QT interval (Agelink et al, 2001w; Owens, 2001ac; Prod Info Solian(R), 1999aa; Prod Info 1992aa). Even though no formal drug interaction studies have been done, antipsychotic agents should not be which are also known to prolong the QTc interval, including isoflurane (Owens, 2001ac).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of isoflurane and agents that prolong the QT interval recommended.
7) Probable Mechanism: additive effect on QT interval
8) Literature Reports
a) Sometimes fatal QRS prolongation and QTc prolongation have been reported in patients taking rispe Laita et al, 1999ag; Ravin & Levenson, 1997l).

3.5.1.AU Isradipine
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest
2) Summary: Isradipine can prolong the QT interval in some patients, which may result in ventricular tachyca torsades de pointes, and its use with other drugs known to cause QT prolongation is not recommended (Proc Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), al, 1999c), quetiapine (Owens, 2001h), risperidone (Duenas-Laita et al, 1999h), sertindole (Agelink et al, 200 2004).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of isradipine and an antipsychotic is not recommend
7) Probable Mechanism: additive cardiac effects

3.5.1.AV Itraconazole
1) Interaction Effect: increased risperidone concentrations
2) Summary: In an open-label study, coadministration of itraconazole and risperidone in 19 schizophrenic pa serum concentrations of both risperidone and its active metabolite, 9-hydroxyrisperidone. It has been postula P450 2D6 enzymes, risperidone may also be metabolized by cytochrome P450 3A (CYP3A) enzymes. Inhibit mediated metabolism by itraconazole, a potent CYP3A inhibitor, may result in increased serum risperidone c affect clinical symptoms and side effects of risperidone (Jung et al, 2005). If these two agents are coadminist patients for clinical symptoms of risperidone efficacy and potentially, increased risperidone side effects (hypo side effects, arrhythmias).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: established
6) Clinical Management: Coadministration of itraconazole and risperidone can result in increased serum con and its active metabolite, 9-hydroxyrisperidone. If these two agents are coadministered, consider monitoring risperidone efficacy and potentially, increased risperidone side effects (hypotension, sedation, extrapyramida
7) Probable Mechanism: inhibition of cytochrome P450 3A-mediated risperidone metabolism
8) Literature Reports
a) Concurrent administration of itraconazole with risperidone resulted in increased serum risperidone co patients (n=19, mean age 41.4 years) who were being treated with 2 to 8 milligrams (mg) of risperidone pm) for at least 2 months were administered itraconazole 200 mg per day (dosed at 8 pm) for 1 week an open-label study indicated that the dose-normalized, steady-state plasma concentrations of both risperid hydroxyrisperidone, were significantly increased by 82% and 70%, respectively (p less than 0.01). Upon both concentrations returned to the levels prior to itraconazole administration. Scores on the Brief Psych improvement in clinical symptoms, decreased by 6% (p=0.017). However, there was no increase in adve Udvalg for Kliniske Undersogelser (UKU) Side Effect Rating scale. It has been postulated that in addition enzymes, risperidone may also be metabolized by cytochrome P450 3A (CYP3A) enzymes. The propose is inhibition of risperidone's CYP3A-mediated metabolism by itraconazole, a potent CYP3A inhibitor (Jun

3.5.1.AW Lamotrigine

1) Interaction Effect: increased risperidone plasma concentrations and risk of adverse effects

2) Summary: Increased risperidone plasma concentrations, with signs of toxicity, developed in a patient adm to a stable dose-regimen of risperidone and clozapine (Bienentreu & Kronmuller, 2005).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Clinicians should be aware of the increased risk of risperidone adverse effects in pa together with risperidone. When concomitant lamotrigine is initiated, discontinued, or the dose of lamotrigine of risperidone.

7) Probable Mechanism: unknown

8) Literature Reports

a) Increased risperidone plasma concentrations and subsequent toxicity were reported in a patient recei stable dose-regimen of risperidone and clozapine. The patient, a 26-year-old woman diagnosed with sch partial response to her established regimen of clozapine 550 milligrams (mg) daily and risperidone 8 mg concentrations of risperidone and clozapine were 55-70 nanograms/milliliter (ng/mL) and 800-1100 ng/m initiated, with the dose incrementally titrated up to 200 mg daily. Clozapine and risperidone plasma conc ng/mL and 263 ng/mL, respectively; no symptoms of intoxication were observed. Lamotrigine was furthe daily, after which risperidone plasma concentration increased to 412 ng/mL, accompanied by symptoms risperidone dose was reduced to 2 mg daily and completely withdrawn shortly thereafter (Bienentreu & K

3.5.1.AX Levodopa

1) Interaction Effect: loss of levodopa efficacy

2) Summary: Because risperidone is an antagonist with a high affinity for dopamine type 2 receptors, it is exp of levodopa (Prod Info Stalevo(TM), 2003; Prod Info Risperdal(R) Consta(TM), 2003d).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concurrent use of risperidone in patients with parkinsonism should be avoided. If c monitor the patient for loss of levodopa therapeutic efficacy.

7) Probable Mechanism: pharmacologic antagonism

3.5.1.AY Levomethadyl

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Any drug known to have the potential to prolong the QT interval should not be used with levom pharmacodynamic interactions can occur between levomethadyl and potentially arrhythmogenic agents such QT interval (Prod Info Orlaam(R), 2001).

3) Severity: contraindicated

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: Levomethadyl is contraindicated in patients being treated with risperidone as it may interact with levomethadyl.

7) Probable Mechanism: additive cardiac effects

3.5.1.AZ Levorphanol

1) Interaction Effect: precipitation of opioid withdrawal symptoms in opioid-dependent patients

2) Summary: A patient stabilized on levorphanol 14 mg daily for neck pain experienced opioid cravings and d risperidone therapy. Discontinuing risperidone resolved her symptoms of withdrawal. Possible mechanisms fo accelerating opioid metabolism via the cytochrome P450 system, interference with the gastrointestinal absorp altered opioid distribution, or opioid displacement from plasma protein binding sites (Wines & Weiss, 1999a).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Opioid-dependent patients should be monitored for signs of opioid withdrawal if risp prescribed.

7) Probable Mechanism: unknown

8) Literature Reports

a) A 31-year-old female with a lengthy history of drug dependency, including opioids, was being treated depression and levorphanol 14 mg daily for chronic severe neck pain. Because of recurring nightmares a mg daily was initiated and increased to 1.5 mg daily within two days. While her dissociative symptoms im cramps, gooseflesh, and opioid cravings. Risperidone was decreased to 1 mg daily but her dissociative s risperidone was again increased to 2 mg daily, but she experienced an increase in her withdrawal sympt Risperidone therapy was eventually discontinued (Wines & Weiss, 1999).

3.5.1.BA Lidoflazine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Lidoflazine has been shown to prolong the QTc interval at the recommended therapeutic dose though no formal drug interaction studies have been done, the coadministration of antipsychotics and other d

interval is not recommended. Several antipsychotic agents have demonstrated QT prolongation including am
1999), haloperidol (O'Brien et al, 1999), quetiapine (Owens, 2001), risperidone (Duenas-Laita et al, 1999), se
sultopride (Lande et al, 1992), and zotepine (Sweetman, 2003).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of lidoflazine and antipsychotics is not recommended
7) Probable Mechanism: additive cardiac effects

3.5.1.BB Linezolid

1) Interaction Effect: increased risk of serotonin syndrome
2) Summary: In a review of post-marketing data, 1 case of serotonin toxicity was reported with the concurrer
which was coadministered with other serotonergic agents (Lawrence et al, 2006) . Risperidone, in combinatio
has been associated with the serotonin syndrome (Springuel & McMorran, 2003). There have been spontane
syndrome associated with concomitant use of linezolid and serotonergic agents (Wigen & Goetz, 2002; Prod
tablets, oral suspension, 2008). Although coadministration of linezolid and serotonergic agents did not result
1, 2, or 3 clinical trials, linezolid is a reversible, non-selective MAOI and can potentially interact with serotone
serotonin syndrome. If concurrent use of linezolid and a serotonergic agent is clinically warranted, monitor pa
symptoms of serotonin syndrome. Consider discontinuing either one or both agents if these symptoms occur,
discontinuation of the concomitant serotonergic agent may result in associated discontinuation symptoms (Pr
oral tablets, oral suspension, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Serotonin toxicity has been reported in 1 individual with the concurrent use of linezo
coadministered with other serotonergic agents (Lawrence et al, 2006). If concurrent use of linezolid and rispe
serotonergic agents, is clinically necessary, monitor patients closely for signs and symptoms of serotonin syn
abnormalities (including hyper-reflexia, tremor, muscle rigidity, clonus, peripheral hypertonicity, and shivering
(including tachycardia, mydriasis, diaphoresis, and diarrhea), and mental status changes (including agitation
syndrome can be life-threatening. If serotonin syndrome develops, discontinue the offending agents and prov
therapy as necessary (Boyer & Shannon, 2005). Keep in mind that discontinuation of the concomitant serotor
associated discontinuation symptoms (Prod Info ZYVOX(R) IV injection, oral tablets, oral suspension, 2008).
7) Probable Mechanism: inhibition of serotonin metabolism by monoamine oxidase
8) Literature Reports
a) In a review of post-marketing data, one case of serotonin toxicity was reported in the concurrent use
which was coadministered with other serotonergic agents. A review was conducted of post-marketing ad
Food and Drug Administration's Adverse Event Reporting System (AERS) database between November
regarding serotonin toxicity with linezolid use. A serotonin toxicity case was defined as having: (a) linezo
(b) concomitant administration of 1 or more secondary suspect drug with CNS serotonergic activity, and
by the modified Hunter Serotonin Toxicity Criteria or by the reporter of the adverse event. A total of 29 ca
17 to 83 years), where linezolid was used concomitantly with 1 drug (n=20), with 2 drugs (n=6), and with
SSRIs were the most common class of drugs received concomitantly with linezolid (n=26), other drug cla
antidepressants (n=6), and atypical antidepressants (n=4). Additionally, drugs used concurrently include
dextromethorphan (n=1), lithium (n=1), metoclopramide (n=1), risperidone (n=1), and tramadol (n=1). Sy
included tremor, fever, seizure, clonus, sweating, agitation, akathesia, rigors, twitching, and muscle rigidi
hospitalization was required in 13 patients, and 3 deaths were reported with concurrent SSRI use. For th
concurrent use linezolid and risperidone, additional coadministered serotonergic drugs included bupropio
(Lawrence et al, 2006).

3.5.1.BC Lithium

1) Interaction Effect: weakness, dyskinesias, increased extrapyramidal symptoms, encephalopathy, and brai
2) Summary: An encephalopathic syndrome followed by irreversible brain damage has occurred in a few pat
dopamine-2 antagonist, particularly haloperidol. A causal relationship between these events and the concomi
dopamine-2 antagonist and lithium has not been established (Prod Info LITHOBID(R) slow-release oral tablet
lithium and a number of antipsychotic drugs has caused a wide variety of encephalopathic symptoms, brain d
symptoms, and dyskinesias in isolated case reports. In most cases, these effects have occurred with therape
1982; Prakash, 1982; Addonizio et al, 1988a). However, many series and trials have reported using such con
adverse consequences (Goldney & Spence, 1986). The mechanism is not fully understood, but chronic lithiur
neostriatal dopaminergic activity, probably through a direct action on the G protein and the capacity of the G p
stimulate adenyl cyclase (Carli et al, 1994). Hyperglycemic reactions have also occurred during combined ph
et al, 1968).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor patients closely for any signs of toxicity or extrapyramidal symptoms, espec
antagonists, particularly haloperidol, and lithium are used. Serum lithium levels should be monitored periodica
maintaining levels in the low therapeutic range.
7) Probable Mechanism: unknown

8) Literature Reports

a) Concomitant haloperidol and lithium therapy has resulted in symptoms of encephalopathy, confusion, fever in several patients with mania (Cohen & Cohen, 1974; Loudon & Waring, 1976; Thomas, 1979). Irr have been reported (Sandyk & Hurwitz, 1983; Keitner & Rahman, 1984).

b) Seizures, encephalopathy, delirium, and abnormal EEG occurred in four patients during combined lith (Spring, 1979). Serum lithium levels were below 1 mEq/L at the time of the toxic reaction in all cases. All lithium in combination with another phenothiazine. Three of these patients developed symptoms within e therapy.

c) The addition of lithium to neuroleptic therapy exacerbated extrapyramidal symptoms (EPS) in a small The patients had received at least five days of treatment with either oral thiothixene, haloperidol, or fluph chlorpromazine equivalents prior to initiation of the lithium and were experiencing drug-induced extrapyra was added when clinically indicated in sufficient doses to achieve a therapeutic serum concentration. Th 0.65 to 1.27 mEq/L. The EPS ratings increased in all ten patients following the addition of lithium. Howev marked symptoms and no patient developed lithium toxicity. Significantly increased symptoms included g rigidity, and tremor.

d) Ten patients treated with clozapine and lithium were studied (Blake et al, 1992). Of the ten patients, f neurologic effects, including jerking of limbs, facial spasms and tics, tremor of hands and arms, tongue tv of these also experienced delirium. These effects reversed when lithium was discontinued or given at a l of two patients suffered recurrence of symptoms. By keeping serum lithium no greater than 0.5 mEq/L, c coadministered.

e) Chlorpromazine serum levels can be significantly reduced in the presence of lithium treatment. If use of lithium may result in rebound elevation of chlorpromazine levels, resulting in chlorpromazine toxicity. I chlorpromazine combination, abrupt withdrawal of the lithium may precipitate chlorpromazine cardiotoxic was manifested as sudden ventricular fibrillation associated with prolongation of the QTc interval. Hypote in this situation (Stevenson et al, 1989).

f) However, other data do not support that such adverse events are frequent or indeed causally related Combination of dopamine antagonist antipsychotic drugs and lithium have been used successfully in ma depressive illness. It has been proposed that the interaction may only become significant with very high with failure to discontinue dosing in the presence of toxic symptoms (Miller & Menninger, 1987).

g) A 69-year-old patient with oxygen-dependent chronic obstructive pulmonary disorder and a 25-year h started on risperidone 3 mg for the treatment of new-onset auditory and visual hallucinations. She had al regimen of lithium (450 mg daily) for more than 10 years. In addition, she was given amantadine (100 mg weeks after the start of risperidone, the patient experienced a decline in mental status in addition to dizzi and vomiting, polyuria, depression, and visual and auditory hallucinations. She was then admitted to the serum level was 1.36 mEq/L at the time of the admission. All medications were discontinued. Although h mEq/L, she continued to experience profound delirium, tremors, lethargy, and hallucinations for almost o respond to commands, she was restarted on lithium (300 mg at bedtime) because of the onset of mild hy was discharged with a regimen of lithium and low-dose lorazepam for treatment of insomnia. It is sugges caused by the concurrent use of lithium and risperidone. Other factors could also have caused delirium, lithium level and the underlying pulmonary pathology. In addition, amantadine, which facilitates the relea has a mild anticholinergic effect, may have contributed (Chen & Cardasis, 1996).

3.5.1.BD Lorcainide

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Coadministration of risperidone with other drugs that potentially prolong the QTc interval, such approached with caution. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is a Larochelle et al, 1984).

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of lorcainide and risperidone is not recommended du threatening arrhythmias. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is ac

7) Probable Mechanism: additive effects on QT prolongation

3.5.1.BE Mefloquine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Even though no formal drug interaction studies have been done, caution is advised if mefloquir can prolong the QTc interval (Prod Info Lariam(R), 1999). Mefloquine was associated with significant QT prol subjects (Davis et al, 1996). Antipsychotics including haloperidol (Prod Info Haldol(R), 1998f), quetiapine (Ow Info Risperdal(R) risperidone, 2000b), amisulpride (Prod Info Solian(R), 1999r), sertindole (Agelink et al, 200 1992r), and zotepine (Sweetman, 2004) have been shown to prolong the QT interval at therapeutic doses.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Caution is advised if mefloquine and antipsychotics are used concomitantly.

7) Probable Mechanism: additive effect on QT interval

3.5.1.BF Mesoridazine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Although citing no data, the manufacturer of mesoridazine states that concomitant use with oth interval is contraindicated (Prod Info Serentil(R), 2001). Several antipsychotic agents have demonstrated QT amisulpride (Prod Info Solian(R), 1999s), haloperidol (O'Brien et al, 1999k), paliperidone (Prod Info INVEGA(tablets, 2006), quetiapine (Owens, 2001v), risperidone (Duenas-Laita et al, 1999y), sertindole (Agelink et al, 1992s), ziprasidone (Prod Info GEODON(R) intramuscular injection, oral capsule, 2005), and zotepine (Swee
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of agents that prolong the QT interval, such as antips contraindicated.
7) Probable Mechanism: additive QT prolongation

3.5.1.BG Methadone

1) Interaction Effect: precipitation of opioid withdrawal symptoms in opioid-dependent patients
2) Summary: A patient stabilized on methadone 50 mg daily experienced aches, nasal congestion, and irrital risperidone therapy. Discontinuing risperidone resolved his symptoms of withdrawal. Possible mechanisms fo accelerating opioid metabolism via the cytochrome P450 system, interference with the gastrointestinal absorp altered opioid distribution, or opioid displacement from plasma protein binding sites (Wines & Weiss, 1999c).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Opioid-dependent patients should be monitored for signs of opioid withdrawal if risp prescribed.
7) Probable Mechanism: unknown
8) Literature Reports
a) A 26-year-old male with a long history of chemical dependency was receiving a methadone maintena was hospitalized for an exacerbation of paranoia and agitation. Risperidone 0.5 mg twice daily was initia patient complained of feeling "dope sick", with symptoms of aches, nasal congestion, and irritability. The risperidone was increased to 2 mg daily and dissipated when risperidone was discontinued. His paranoia chlorpromazine with no further signs of opioid withdrawal (Wines & Weiss, 1999b).

3.5.1.BH Midodrine

1) Interaction Effect: an increased risk of acute dystonia
2) Summary: A case report described development of acute dystonia in a 33-year-old female following concc midodrine and risperidone (Takahashi, 2000). Patients receiving this combination may need to be monitored events, including signs and symptoms of acute dystonia.
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Use caution if midodrine and risperidone are prescribed concurrently. Monitor for si dystonia or other risperidone adverse events.
7) Probable Mechanism: unknown
8) Literature Reports
a) A 33-year-old female developed acute dystonia after addition of midodrine to treat orthostatic hypoter therapy. The patient had a 12-year history of catatonic schizophrenia, which was adequately controlled v mg/day. Two days after addition of midodrine 4 mg/day to treat complaints of orthostatic hypotension, the of acute dystonia, including tongue protrusion, retrocollis, and oculogyric crisis. Intramuscular injection of resolved all symptoms. Midodrine was discontinued and risperidone 6 mg/day monotherapy was continu dystonic symptoms, midodrine 4 mg/day was added again to therapy to treat continuing complaints of or acute dystonic reaction recurred one day later and was successfully treated with one intramuscular injec midodrine was discontinued and the patient remained on risperidone 6 mg/day without dystonic sympton risperidone dose was decreased to 3 mg/day due to persistent orthostatic hypotension, and the patient w symptoms at a 3-month follow-up. Increased risperidone-associated central noradrenergic activity due to activity of midodrine was a postulated mechanism for this interaction (Takahashi, 2000).

3.5.1.BI Nortriptyline

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod I haloperidol (O'Brien et al, 1999a), risperidone (Duenas-Laita et al, 1999d), sertindole (Agelink et al, 2001a), c sultopride (Lande et al, 1992a), and zotepine (Sweetman, 2003). Even though no formal drug interaction stuc coadministration of a tricyclic antidepressant and an antipsychotic is not recommended (Prod Info Pamelor(R 1982).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of a tricyclic antidepressant and an antipsychotic is n
7) Probable Mechanism: additive cardiac effects

8) Literature Reports

a) Electrocardiographic changes that have occurred during clinical trials with pimozide have included pr interval, flattening, notching, and inversion of the T wave and the appearance of U waves. In experiment deaths have occurred while patients were receiving pimozide doses of 1 mg/kg. The proposed mechanis prolongation of the QT interval predisposing patients to ventricular arrhythmias (Prod Info Orap(R), 1999

3.5.1.BJ Octreotide

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Octreotide has been shown to prolong the QTc interval at the recommended therapeutic dose (Even though no formal drug interaction studies have been done, the coadministration of antipsychotics and o QTc interval, including octreotide, is not recommended. Several antipsychotic agents have demonstrated QT amisulpride (Prod Info Solian(R), 1999u), haloperidol (O'Brien et al, 1999m), risperidone (Duenas-Laita et al, al, 2001q), quetiapine (Owens, 2001x), sultopride (Lande et al, 1992u), and zotepine (Sweetman, 2003).

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of octreotide and antipsychotics is not recommended

7) Probable Mechanism: additive effects on QT prolongation

3.5.1.BK Paroxetine

1) Interaction Effect: increased plasma concentrations of risperidone

2) Summary: Concomitant use of paroxetine (potent CYP2D6 inhibitor) and risperidone (CYP2D6 substrate) risperidone plasma concentrations and an increased risk of risperidone adverse effects such as serotonin syn extrapyramidal effects. The postulated mechanism of action is inhibition of CYP2D6-mediated metabolism of studies demonstrated increased risperidone levels resulting in a greater frequency of extrapyramidal symptom concurrently with paroxetine and risperidone (Saito et al, 2005; Spina et al, 2001a). One of these studies sho paroxetine dose increases and greater risperidone plasma concentrations (Spina et al, 2001a). In a case rep observed in a patient who had already been receiving risperidone and was initiated on paroxetine (Hamilton & patient for increased risperidone plasma levels side effects may be necessary. The risperidone dose should b initiated or discontinued. Concomitant use of a low dose of paroxetine with risperidone may be safe and effec with negative symptoms (Prod Info RISPERDAL(R) oral tablets, oral solution, orally disintegrating tablets, 20

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Concomitant use of paroxetine and risperidone has resulted in increased risperidon increased risk of risperidone side effects (Prod Info RISPERDAL(R) oral tablets, oral solution, orally disintegr 2005; Spina et al, 2001a; Hamilton & Malone, 2000). Carefully monitor patients for increased plasma risperid (serotonin syndrome, extrapyramidal symptoms, and cardiotoxicity) when paroxetine is coadministered with r of risperidone when concomitant paroxetine is initiated or discontinued (Prod Info RISPERDAL(R) oral tablets disintegrating tablets, 2008). Coadministering a low dose of paroxetine with risperidone may be safe and effe with negative symptoms (Saito et al, 2005).

7) Probable Mechanism: inhibition of CYP2D6-mediated metabolism of risperidone

8) Literature Reports

a) Paroxetine (a potent CYP2D6 inhibitor) 20 mg/day has been shown to increase the plasma concentra substrate) by 3- to 9- fold. Paroxetine also lowered the concentration of 9-hydroxyrisperidone by about 1 surveillance of risperidone, torsade de pointes has been reported with combined overdose of risperidone risperidone should be reevaluated when paroxetine is initiated or discontinued (Prod Info RISPERDAL(R disintegrating tablets, 2008).

b) Risperidone plasma concentrations increased when risperidone-treated inpatients (n=12) with schizo were coadministered incremental doses of paroxetine. Prior to initiating paroxetine, patients were receivi for at least 6 weeks and steady-state plasma concentrations of risperidone and 9-hydroxyrisperidone (9- achieved. Paroxetine doses were administered in 3 consecutive 4-week increments of 10 mg/day, 20 mg risperidone plasma concentrations during 10-, 20-, and 40-mg paroxetine treatment were 3.8- (95% conf less than 0.01) , 7.1- (95% CI, 5.3 to 16.5; p less than 0.01), and 9.7-fold (95% CI, 7.8 to 22.5; p less tha baseline. Increases in 9-OH-risperidone concentrations were not significant with paroxetine use. Mean a OH-risperidone) plasma concentrations increased by 1.8-fold (95% CI, 1.4 to 2.7; p less than 0.05) durin increases were not significant with 10- or 20-mg doses. Metabolic ratio was significantly increased (p les 3.4 to 6.2) with 10 mg of paroxetine, by 8.2-fold (95% CI, 6 to 16) with 20 mg, and by 12.6-fold (95% CI, symptom scores were significantly improved during all paroxetine doses; however, extrapyramidal sympt higher during 20- and 40-mg doses. The authors suggest that low-dose coadministration of paroxetine w effective for treating schizophrenia with negative symptoms (Saito et al, 2005).

c) Paroxetine, a potent inhibitor of cytochrome CYP2D6, may impair the elimination of risperidone, prim mediated alpha-hydroxylation and, to a lesser extent, by simultaneously affecting the further metabolism risperidone) or other pathways of risperidone biotransformation. In a study including 10 patients diagnos schizoaffective disorder depressive type (n=3), risperidone plasma concentrations increased when parox risperidone. Patients were stabilized on risperidone therapy 4 to 8 mg/day and received adjunctive parox symptoms, concomitant depression, or both. Risperidone dosage remained constant throughout the dura elevation in risperidone plasma concentrations (p less than 0.01) and a slight, nonsignificant decrease in

4 weeks of paroxetine treatment, the total concentration of risperidone and 9-OH-risperidone was increa
The mean plasma risperidone to 9-OH-risperidone ratio also changed significantly (p less than 0.001) wi
treatment. Extrapyramidal side effects occurred in one patient during the second week of paroxetine coa
of risperidone in this patient increased 62% over baseline values during paroxetine coadministration. The
symptoms in patients after addition of SSRIs to antipsychotics might also be caused by an additive pharr
(Spina et al, 2001a).

d) Serotonin syndrome occurred in a patient using concomitant paroxetine and risperidone, an antipsycl
antagonism and dopamine blocking activity . A 53-year-old male with a 7-month history of psychotic depr
risperidone 3 mg/day and paroxetine 20 mg/day for 10 weeks before presentation. Nine weeks into thera
decreased motivation and bilateral jerking movements of the mouth and legs. The patient discontinued h
before his admission. Upon presentation he was apathetic, confused, disorganized, and talked to himsel
risperidone were doubled to 40 mg/day and 6 mg/day, respectively. Within 2 hours of taking his medicati
jerking movements, ataxia, tremor, and shivering. He presented to the emergency room with involuntary
His mental status exam was notable for depression with psychomotor agitation, difficulty being aroused,
Differential diagnosis included recurrent psychotic depression, neuroleptic malignant syndrome (NMS), c
syndrome. Nortriptyline 100 mg at bedtime, haloperidol 10 mg twice daily and diphenhydramine 50 mg a
discharge. The patient returned to baseline 9 months after discharge and is without symptoms of depres
Malone, 2000).

3.5.1.BL Pentamidine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Pentamidine has been shown to prolong the QTc interval at the recommended therapeutic dos
though no formal drug interaction studies have been done, the coadministration of antipsychotics and other d
interval, including pentamidine, is not recommended (Agelink et al, 2001e; Owens, 2001g; Prod Info Haldol(R
1999e; Duenas-Laita et al, 1999g; Duenas-Laita et al, 1999g; Prod Info Nipolept(R), 1996a; Metzger & Friedr
3) Severity: major
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of pentamidine and antipsychotics is not recommend
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.BM Phenobarbital

1) Interaction Effect: decreased plasma concentrations of risperidone and the active metabolite 9-hydroxyris
2) Summary: Concomitant use of phenobarbital may reduce plasma concentrations of risperidone. Patients s
Patients may be placed on a lower dose of risperidone between 2 to 4 weeks before the planned discontinua
adjust for the expected increase in plasma concentrations of risperidone plus 9-hydroxyrisperidone (Prod Info
2003e).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor therapeutic efficacy of risperidone following the addition of phenobarbital du
therapy; higher risperidone doses may be needed. Patients may be placed on a lower dose of risperidone be
discontinuation of phenobarbital therapy to adjust for the expected increase in plasma concentrations of rispe
hydroxyrisperidone. For patients currently maintained on the lowest available dose (25 mg) risperidone, it is r
that dose unless an interruption of treatment is necessary.
7) Probable Mechanism: induction of cytochrome P450-mediated metabolism of risperidone by phenobarbita

3.5.1.BN Phenylalanine

1) Interaction Effect: increased incidence of tardive dyskinesia
2) Summary: Taking phenylalanine concomitantly with certain neuroleptic drugs may exacerbate tardive dysl
Abnormal phenylalanine metabolism in certain patients may lead to phenylalanine accumulation in the brain a
availability of other large neutral amino acids. This may interfere with the synthesis of catecholamines (Gardo
3) Severity: moderate
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Caution is advised if phenylalanine is administered with a neuroleptic agent. Monito
tardive dyskinesia.
7) Probable Mechanism: reduced brain availability of other large neutral amino acids and interference with ca
8) Literature Reports

a) Phenylalanine tended to increase the incidence of tardive dyskinesia in patients taking neuroleptics ir
patients were studied: (1) patients with unipolar depression with tardive dyskinesia (n=11), (2) patients w
current or past exposure to greater than or equal to 100 milligrams (mg) of a chlorpromazine equivalent f
(3) patients with no tardive dyskinesia not previously exposed to a neuroleptic drug (n=10). Neuroleptic a
study by 6 patients in group 1, and 5 patients in group 2. Patients received powdered phenylalanine 100
juice after an overnight fast. Blood samples were obtained just prior to phenylalanine administration and
Three patients in group 1 (with tardive dyskinesia) had the highest postloading phenylalanine plasma lev
higher (though nonsignificant) mean phenylalanine levels than the other groups. Tardive dyskinesia scor
Involuntary Movements Scale (AIMS)) nonsignificantly increased in group 1. Postloading phenylalanine l

scores were significantly positively correlated in group 1 (rs=0.347, p less than 0.05; Spearman correlatic 0.05). Postloading phenylalanine level and baseline AIMS scores demonstrated a trend toward correlatic correlation coefficient 0.679, p less than 0.05). In all patients, phenylalanine loading increased plasma pl eight-fold, and plasma tyrosine increased 2.5 times as a result of conversion of phenylalanine to tyrosine large neutral amino acids such as tryptophan decreased slightly (Gardos et al, 1992).

3.5.1.BO Phenytoin

1) Interaction Effect: decreased plasma concentrations of risperidone and the active metabolite 9-hydroxyris
2) Summary: Concomitant use of phenytoin may reduce plasma concentrations of risperidone. Upon initiatio patients should be closely monitored during the first 4-8 weeks, since the dose of risperidone may need to be placed on a lower dose of risperidone between 2 to 4 weeks before the planned discontinuation of phenytoin expected increase in plasma concentrations of risperidone plus 9-hydroxyrisperidone (Prod Info Risperdal(R)
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor therapeutic efficacy of risperidone following the addition of phenytoin highe needed. Monitor patients during the first 4-8 weeks of coadministration with phenytoin and risperidone; highe needed. Patients may be placed on a lower dose of risperidone between 2 to 4 weeks before the discontinua adjust for the expected increase in plasma concentrations of risperidone plus 9-hydroxyrisperidone. For patie lowest available dose (25 mg) risperidone, it is recommended to continue with that dose unless an interruptio
7) Probable Mechanism: induction of risperidone metabolism through cytochrome P450 enzymes by phenyto

3.5.1.BP Pimozide

1) Interaction Effect: cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Although no drug interaction studies have been performed, the manufacturer of pimozide state pimozide with drugs known to prolong the QTc interval should be approached with caution (Prod Info Orap(R has been reported to prolong the QTc interval (Prod Info Risperdal(R), 2002).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of agents that prolong the QT interval, such as pimoz contraindicated.
7) Probable Mechanism: additive effects on QT prolongation
8) Literature Reports
a) In experimental studies of conditions other than Tourette's Disorder, sudden, unexpected deaths hav receiving pimozide dosages of approximately 1 mg per kg. One possible mechanism for such deaths is p predisposing patients to ventricular arrhythmia. The manufacturer recommends that an electrocardiograr treatment is initiated and periodically thereafter, especially during the period of dose adjustment (Prod In
b) Sometimes fatal QRS prolongation and QTc prolongation have been reported in patients taking rispe Laita et al, 1999l; Ravin & Levenson, 1997c; Gesell & Stephen, 1997; Lo Vecchio et al, 1996; Brown et a

3.5.1.BQ Pirmenol

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Several antipsychotic agents have demonstrated QT prolongation including amisulpride, halop quetiapine, risperidone, sertindole, sultopride, ziprasidone, and zotepine (Prod Info FANAPT(TM) oral tablets 1999z; O'Brien et al, 1999q; Prod Info INVEGA(TM) extended-release oral tablets, 2006; Owens, 2001ab; Du et al, 2001v; Lande et al, 1992z; Prod Info GEODON(R) intramuscular injection, oral capsule, 2005; Sweetma antiarrhythmic agents may also prolong the QT interval and increase the risk of arrhythmias, the concurrent a with a drug from this class is not recommended (Prod Info FANAPT(TM) oral tablets, 2009; Prod Info Quinag
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: The concurrent administration of a Class IA antiarrhythmic and an antipsychotic is r
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) In an open-label QTc study of patients with schizophrenia or schizoaffective disorder (n=160), iloperic associated with QTc prolongation of 9 msec (Prod Info FANAPT(TM) oral tablets, 2009).
b) QRS widening, QTc interval prolongation, and torsades de pointes may occur with disopyramide ther 1997).
c) The effects of combined therapy with quinidine (Class IA antiarrhythmic agent) and haloperidol (antip giving 12 healthy volunteers haloperidol 5 mg alone and with 250 mg of quinidine bisulfate. The study de in the plasma concentrations of haloperidol when given concurrently with quinidine versus haloperidol tre under the concentration curve (AUC) was increased from 54.3 ng/h/mL on haloperidol alone to 103.2 ng/ peak concentration (Cmax) also showed an increase from 1.9 ng/mL on haloperidol to 3.8 ng/mL on com and time to peak concentration (Tmax) were not significantly changed, thereby suggesting to the authors is more likely responsible for the plasma level changes than an elimination alteration (Young et al, 1993)

3.5.1.BR Prajmaline

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Several antipsychotic agents have demonstrated QT prolongation including amisulpride, haloperi quetiapine, risperidone, sertindole, sultopride, ziprasidone, and zotepine (Prod Info FANAPT(TM) oral tablets 1999z; O'Brien et al, 1999q; Prod Info INVEGA(TM) extended-release oral tablets, 2006; Owens, 2001ab; Du et al, 2001v; Lande et al, 1992z; Prod Info GEODON(R) intramuscular injection, oral capsule, 2005; Sweetma antiarrhythmic agents may also prolong the QT interval and increase the risk of arrhythmias, the concurrent a with a drug from this class is not recommended (Prod Info FANAPT(TM) oral tablets, 2009; Prod Info Quinag
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: The concurrent administration of a Class IA antiarrhythmic and an antipsychotic is r
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) In an open-label QTc study of patients with schizophrenia or schizoaffective disorder (n=160), iloperic associated with QTc prolongation of 9 msec (Prod Info FANAPT(TM) oral tablets, 2009).
b) QRS widening, QTc interval prolongation, and torsades de pointes may occur with disopyramide ther 1997).
c) The effects of combined therapy with quinidine (Class IA antiarrhythmic agent) and haloperidol (antip giving 12 healthy volunteers haloperidol 5 mg alone and with 250 mg of quinidine bisulfate. The study de in the plasma concentrations of haloperidol when given concurrently with quinidine versus haloperidol tre under the concentration curve (AUC) was increased from 54.3 ng/h/mL on haloperidol alone to 103.2 ng/ peak concentration (Cmax) also showed an increase from 1.9 ng/mL on haloperidol to 3.8 ng/mL on com and time to peak concentration (Tmax) were not significantly changed, thereby suggesting to the authors is more likely responsible for the plasma level changes than an elimination alteration (Young et al, 1993)

3.5.1.BS Probucol

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, the coadministration of drugs interval is not recommended. Probucol has been shown to prolong the QTc interval (Gohn & Simmons, 1992 Antipsychotics including haloperidol (Prod Info Haldol(R), 1998e), quetiapine (Owens, 2001s), risperidone (Pr 2000a), amisulpride (Prod Info Solian(R), 1999p), sertindole (Brown & Levin, 1998c); sultopride (Lande et al, (Sweetman, 2004) have been shown to prolong the QT interval at therapeutic doses.
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Caution is advised if probucol and antipsychotics are used concomitantly.
7) Probable Mechanism: additive effect on QT interval

3.5.1.BT Procainamide

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Several antipsychotic agents have demonstrated QT prolongation including amisulpride, haloperi quetiapine, risperidone, sertindole, sultopride, ziprasidone, and zotepine (Prod Info FANAPT(TM) oral tablets 1999z; O'Brien et al, 1999q; Prod Info INVEGA(TM) extended-release oral tablets, 2006; Owens, 2001ab; Du et al, 2001v; Lande et al, 1992z; Prod Info GEODON(R) intramuscular injection, oral capsule, 2005; Sweetma antiarrhythmic agents may also prolong the QT interval and increase the risk of arrhythmias, the concurrent a with a drug from this class is not recommended (Prod Info FANAPT(TM) oral tablets, 2009; Prod Info Quinag
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: The concurrent administration of a Class IA antiarrhythmic and an antipsychotic is r
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) In an open-label QTc study of patients with schizophrenia or schizoaffective disorder (n=160), iloperic associated with QTc prolongation of 9 msec (Prod Info FANAPT(TM) oral tablets, 2009).
b) QRS widening, QTc interval prolongation, and torsades de pointes may occur with disopyramide ther 1997).
c) The effects of combined therapy with quinidine (Class IA antiarrhythmic agent) and haloperidol (antip giving 12 healthy volunteers haloperidol 5 mg alone and with 250 mg of quinidine bisulfate. The study de in the plasma concentrations of haloperidol when given concurrently with quinidine versus haloperidol tre under the concentration curve (AUC) was increased from 54.3 ng/h/mL on haloperidol alone to 103.2 ng/ peak concentration (Cmax) also showed an increase from 1.9 ng/mL on haloperidol to 3.8 ng/mL on com and time to peak concentration (Tmax) were not significantly changed, thereby suggesting to the authors is more likely responsible for the plasma level changes than an elimination alteration (Young et al, 1993)

3.5.1.BU Prochlorperazine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Concomitant use of phenothiazines and antipsychotic agents may cause additive effects on the recommended. Q and T wave distortions have been observed in patients taking phenothiazines (Prod Info Co

Stelazine(R), 2002; Prod Info Thorazine(R), 2002). Other phenothiazines may have similar effects, though nc antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999j), paliperidone (Prod Info INVEGA(TM) extended-release oral tablets, 2006), quetiapine (Owens, 2001n), risper 1999n), sertindole (Agelink et al, 2001j), sultopride (Lande et al, 1992i), ziprasidone (Prod Info GEODON(R) i capsule, 2005), and zotepine (Sweetman, 2003).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of agents that prolong the QT interval, such as phen not recommended.
7) Probable Mechanism: additive QT prolongation

3.5.1.BV Propafenone
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Coadministration of risperidone with other drugs that potentially prolong the QTc interval, such approached with caution. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is a Larochelle et al, 1984).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of propafenone and risperidone is not recommended life-threatening arrhythmias. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring i
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.BW Protriptyline
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod haloperidol (O'Brien et al, 1999a), risperidone (Duenas-Laita et al, 1999d), sertindole (Agelink et al, 2001a), c sultopride (Lande et al, 1992a), and zotepine (Sweetman, 2003). Even though no formal drug interaction stuc coadministration of a tricyclic antidepressant and an antipsychotic is not recommended (Prod Info Pamelor(R 1982).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of a tricyclic antidepressant and an antipsychotic is n
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) Electrocardiographic changes that have occurred during clinical trials with pimozide have included pr interval, flattening, notching, and inversion of the T wave and the appearance of U waves. In experiment deaths have occurred while patients were receiving pimozide doses of 1 mg/kg. The proposed mechanis prolongation of the QT interval predisposing patients to ventricular arrhythmias (Prod Info Orap(R), 1999

3.5.1.BX Quetiapine
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Risperidone can prolong the QT interval in some patients, which may result in ventricular tachy torsades de pointes, and its use with other agents that may prolong the QT interval, such as quetiapine, is no Risperdal(R), 2002c; Owens, 2001q). Coadministration of risperidone 3 mg twice daily with quetiapine 300 m steady-state pharmacokinetics of quetiapine (Prod Info Seroquel(R), 2003).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Because of the potential additive effects on the QT interval, the concurrent administ risperidone is not recommended.
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) Sometimes fatal QRS prolongation and QTc prolongation have been reported in patients taking risper Laita et al, 1999u; Ravin & Levenson, 1997i; Gesell & Stephen, 1997e; Lo Vecchio et al, 1996e; Brown e

3.5.1.BY Ranitidine
1) Interaction Effect: increased risperidone bioavailability
2) Summary: Concurrent use of risperidone and ranitidine resulted in a 26% increase in the bioavailability of active metabolite, 9-hydroxyrisperidone, and risperidone combined was increased by 20% (Prod Info RISPER IM injection, 2009). Use caution if these agents are used concomitantly. Monitor patients for increased risperi akathisia, parkinsonism, dyspepsia, tachycardia, constipation, or dry mouth).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Concurrent treatment with ranitidine and risperidone has resulted in increased rispe

RISPERDAL(R) CONSTA(R) long-acting IM injection, 2009). Caution is advised if these agents are used con
for increased risperidone adverse events, including sedation, akathisia, parkinsonism, dyspepsia, tachycardia
7) Probable Mechanism: unknown

3.5.1.BZ Rifampin

1) Interaction Effect: decreased plasma concentrations of risperidone and the active metabolite 9-hydroxyris
2) Summary: Concomitant use of rifampin may reduce plasma concentrations of risperidone (Prod Info RISP
RISPERDAL(R) M-TAB(R) orally disintegrating tablets, 2008). Patients should be closely monitored if concon
may be placed on a lower dose of risperidone between 2 to 4 weeks before the planned discontinuation of rif
expected increase in plasma concentrations of risperidone plus 9-hydroxyrisperidone (Prod Info RISPERDAL
injection, 2008).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Monitor therapeutic efficacy of risperidone following the addition of rifampin during t
higher risperidone doses may be needed. Patients may be placed on a lower dose of risperidone 2 to 4 week
rifampin therapy to adjust for the expected increase in plasma concentrations of risperidone plus 9-hydroxyris
maintained on the lowest available dose of risperidone long-acting injection (25 mg), it is recommended to co
interruption of treatment is necessary (Prod Info RISPERDAL(R) CONSTA(R) long-acting IM injection, 2008).
7) Probable Mechanism: induction of cytochrome P450-mediated metabolism of risperidone by rifampin

3.5.1.CA Ritonavir

1) Interaction Effect: increased risperidone serum concentrations and potential toxicity (hypotension, sedatio
arrhythmias)
2) Summary: Coadministered ritonavir may increase serum concentrations of risperidone, resulting in risperi
Kelly et al, 2002a)A risperdal dose decrease may be required when coadministered with ritonavir (Prod Info N
3) Severity: moderate
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Monitor patients for signs and symptoms of neuroleptic toxicity (hypotension, sedati
arrhythmias). Reduce doses of risperidone as required.
7) Probable Mechanism: decreased risperidone metabolism
8) Literature Reports

a) Increases in risperidone serum concentration occurred in a patient taking concomitant ritonavir. A 48-
diagnosed with acquired immunodeficiency syndrome (AIDS) was admitted to a psychiatric hospital for n
medications included zidovudine 250 mg twice daily, didanosine 300 mg once daily, indinavir 400 mg twi
twice daily. He was given risperidone 3 mg twice daily upon admission. After receiving two doses of rispe
progressively drowsy and disoriented. He then became lethargic and comatose. Physical exam revealed
points with miotic pupils. Laboratory tests were normal. A toxic or metabolic etiology was suspected to be
medication was discontinued. Twenty-four hours later, his neurologic status returned to baseline and pro
reappeared. The author suggests that an interaction between risperidone, indinavir and ritonavir may hav
coma (Jover et al, 2002).

b) Extrapyramidal symptoms (EPS) occurred in a patient initiated on ritonavir and indinavir while taking
35-year-old white male with AIDS received risperidone 2 mg twice daily for treatment of Tourette's-like tic
month history of hand tremor, twitching and jerky involuntary movements of the face, shoulders, arms, an
were dapsone, pyrimethamine, azithromycin, and hydroxyzine. Risperidone was initiated at 1 mg twice d
increased to 2 mg twice daily. Indinavir 800 mg twice daily and ritonavir 200 mg twice daily was initiated
dosage was increased. One week later he experienced significantly impaired swallowing, speaking, and
existing tremors. Ritonavir and indinavir were discontinued. One month later the patient agreed to try ind
the same time he increased the risperidone dose to 3 mg twice daily. Symptoms worsened over the next
parameters were unremarkable and vital signs were stable. Risperidone was discontinued and clonazep
patients symptoms improved. Caution is warranted when risperidone is prescribed with ritonavir/indinavi

3.5.1.CB Ropinirole

1) Interaction Effect: diminished effectiveness of ropinirole
2) Summary: Theoretically, risperidone may oppose the dopaminergic effect of dopamine agonists, such as r
(R) oral tablets, 2007; Prod Info REQUIP(R) oral tablets, 2006). If concurrent use of ropinirole and a dopamin
warranted, monitor patients closely for loss of ropinirole efficacy.
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Use caution with the concurrent use of risperidone and ropinirole as this may result
ropinirole due to the antagonistic dopaminergic effect of risperidone (Prod Info REQUIP(R) oral tablets, 2006)
and a dopamine antagonist is clinically warranted, monitor patients closely for signs and symptoms of diminis
such as worsening of extrapyramidal movements, rigidity, tremor, or gait disturbances.
7) Probable Mechanism: pharmacological antagonism

3.5.1.CC Sematilide

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Concurrent use of sematilide and risperidone is not recommended due to the risk of additive ef concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised (Yamreudeewong et
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of sematilide and risperidone is not recommended du life-threatening arrhythmias. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring i
7) Probable Mechanism: additive QT prolongation
8) Literature Reports
a) Class III antiarrhythmics have been shown to prolong the QT interval, which may result in ventricular fibrillation, and torsades de pointes. Several antipsychotic agents have demonstrated QT prolongation in Laita et al, 1999a). Concomitant use of Class III antiarrhythmic agents such as sematilide and risperidon the QT interval and is not recommended (Yamreudeewong et al, 2003).

3.5.1.CD Sertindole

1) Interaction Effect: cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Coadministration of sertindole with other drugs that potentiallly prolong the QTc interval, such a approached with caution (Brown & Levin, 1998e; Prod Info Risperdal(R), 2002e).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of agents that prolong the QT interval, such as risper recommended.
7) Probable Mechanism: additive effects on QT prolongation
8) Literature Reports
a) Sometimes fatal QRS prolongation and QTc prolongation have been reported in patients taking rispe Laita et al, 1999aj; Ravin & Levenson, 1997o; Gesell & Stephen, 1997g; Lo Vecchio et al, 1996g; Brown
b) Thirty, otherwise healthy, schizophrenic patients participated in an open, dose titration (4 to 16 mg/da cardiovascular effects of sertindole. At the end of the 3-week study it was concluded that resting heart ra times increased in a dose-related manner, while there was no change in PQ-conduction times, autonomi pressure. Conduction times increased an average 3.5% to 6.5% over the dosing range (Agelink et al, 20
c) The overall incidence of QT interval prolongation with sertindole is estimated at 1.9% to 4%, and the torsades de pointes has been estimated at 0.13% to 0.21% (Brown & Levin, 1998d). Periodic electrocard in the United Kingdom per sertindole's official labeling (Cardoni & Myer, 1997a).

3.5.1.CE Simvastatin

1) Interaction Effect: increased simvastatin serum concentrations with an increased risk of myopathy or rhab
2) Summary: Concomitant use of risperidone and simvastatin may increase the bioavailability of simvastatin. are both metabolized by cytochrome P450-3A4 (CYP3A4). Although risperidone is predominantly metabolize a slow metabolizer phenotype due to possession of a CYP2D6 polymorphic genotype may convert to CYP3A risperidone metabolism. As a result, risperidone may competitively inhibit simvastatin metabolism, thereby in rhabdomyolysis. In a case report, a patient developed rhabdomyolysis complicated by acute compartment sy simvastatin concomitantly with risperidone (Webber et al, 2004).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Concomitant use of risperidone with simvastatin is not recommended. If concurrent patient for signs and symptoms of myopathy or rhabdomyolysis (muscle pain, tenderness, or weakness). Mo and discontinue use if CK levels show a marked increase, or if myopathy or rhabdomyolysis is diagnosed or
7) Probable Mechanism: competitive inhibition of cytochrome P450-3A4-mediated simvastatin metabolism
8) Literature Reports
a) Rhabdomyolysis occurred in a 22-year-old man after simvastatin 10 milligrams (mg) daily was added comprising clonazepam 2 mg and risperidone 4 mg daily. Approximately 5 days after beginning simvasta presented with right ankle and heel pain. Over the next 24 hours, the pain advanced proximally and incre extremity showing signs of warmth, erythema, rash, and pronounced tenseness of the distal muscle com kinase (CK), aspartate and alanine aminotransferase concentrations were 12, 408 units/liter (L), 296 Inte IU/L, respectively. CK concentrations peaked at 25, 498 units/L. Simvastatin was withdrawn and the pati decompression fasciotomies due to acute compartment syndrome of the right lower extremity. Risperido continued without incident (Webber et al, 2004).

3.5.1.CF Sotalol

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Concurrent use of sotalol and risperidone is not recommended due to the risk of additive effect use cannot be avoided, cautious dosing and telemetric monitoring is advised (Yamreudeewong et al, 2003a).
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of sotalol and risperidone is not recommended due t threatening arrhythmias. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is ac
7) Probable Mechanism: additive QT prolongation
8) Literature Reports
a) Class III antiarrhythmics have been shown to prolong the QT interval, which may result in ventricular fibrillation, and torsades de pointes. Several antipsychotic agents have demonstrated QT prolongation in Laita et al, 1999a). Concomitant use of Class III antiarrhythmic agents such as sotalol and risperidone m QT interval and is not recommended (Yamreudeewong et al, 2003).

3.5.1.CG Spiramycin
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Spiramycin has been shown to prolong the QTc interval at the recommended therapeutic dose Even though no formal drug interaction studies have been done, the coadministration of antipsychotics and o QTc interval, including spiramycin, is not recommended. Several antipsychotic agents have demonstrated QT amisulpride (Prod Info Solian(R), 1999v), haloperidol (O'Brien et al, 1999n), quetiapine (Owens, 2001y), rispe 1999ab), sertindole (Agelink et al, 2001r), sultopride (Lande et al, 1992v), and zotepine (Sweetman, 2003).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of spiramycin and antipsychotics is not recommende
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.CH Sulfamethoxazole
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Cotrimoxazole has been shown to prolong the QTc interval at the recommended therapeutic do though no formal drug interaction studies have been done, the coadministration of antipsychotics and other d interval, including cotrimoxazole, is not recommended. Several antipsychotic agents have demonstrated QT p amisulpride (Prod Info Solian(R), 1999g), haloperidol (O'Brien et al, 1999d), quetiapine (Owens, 2001i), rispe 1999i), sertindole (Agelink et al, 2001f), sultopride (Lande et al, 1992e), and zotepine (Sweetman, 2003).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of cotrimoxazole and antipsychotics is not recommer
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.CI Sultopride
1) Interaction Effect: cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Coadministration of sultopride with other drugs that potentiallly prolong the QTc interval, such a approached with caution (Lande et al, 1992m; Montaz et al, 1992a; Harry, 1997b; Prod Info Risperdal(R), 20
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of agents that prolong the QT interval, such as risper recommended.
7) Probable Mechanism: additive effects on QT prolongation
8) Literature Reports
a) Fatal QRS prolongation and QTc prolongation have been reported in patients taking risperidone thera 1999p; Ravin & Levenson, 1997e; Gesell & Stephen, 1997a; Lo Vecchio et al, 1996a; Brown et al, 1993a
b) Sultopride may induce prolongation of the QT interval and ventricular arrhythmias including torsades or toxic doses (Lande et al, 1992l; Montaz et al, 1992; Harry, 1997a).

3.5.1.CJ Tedisamil
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Concurrent use of tedisamil and risperidone is not recommended due to the risk of additive effe concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised (Yamreudeewong et
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of tedisamil and risperidone is not recommended due threatening arrhythmias. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is ac
7) Probable Mechanism: additive QT prolongation
8) Literature Reports
a) Class III antiarrhythmics have been shown to prolong the QT interval, which may result in ventricular fibrillation, and torsades de pointes. Several antipsychotic agents have demonstrated QT prolongation in Laita et al, 1999a). Concomitant use of Class III antiarrhythmic agents such as tedisamil and risperidone QT interval and is not recommended (Yamreudeewong et al, 2003).

3.5.1.CK Telithromycin

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Some antipsychotic agents prolong the QT interval and an additive effect would be anticipated which lengthen the QT interval (Agelink et al, 2001g; Owens, 2001j; Prod Info Haldol(R), 1998b; Lande et al, drug interaction studies have been done, antipsychotic agents should not be coadministered with other drugs the QTc interval, including telithromycin (Owens, 2001j).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Due to the potential for additive effects on the QT interval, the concurrent administra antipsychotic is not recommended.
7) Probable Mechanism: additive effect on QT interval
8) Literature Reports
a) Fatal QRS prolongation and QTc prolongation have been reported in patients taking risperidone thera 1999j; Ravin & Levenson, 1997b).

3.5.1.CL Terfenadine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Some antipsychotics have been shown to prolong the QTc interval at the recommended therap (TM), 2002b; Owens, 2001ad; Prod Info Orap(R), 1999g). Even though no formal drug interaction studies hav coadministration of terfenadine and other drugs known to prolong the QTc interval, including antipsychotics, i
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of terfenadine with any drug that prolongs the QT int agents, is contraindicated.
7) Probable Mechanism: additive effect on QT interval
8) Literature Reports
a) Electrocardiographic changes that have occurred during clinical trials with pimozide have included pr interval, flattening, notching, and inversion of the T wave and the appearance of U waves. In experiment deaths have occurred while patients were receiving pimozide doses of 1 mg/kg. The proposed mechanis prolongation of the QT interval predisposing patients to ventricular arrhythmias (Prod Info Orap(R), 1999

3.5.1.CM Tetrabenazine

1) Interaction Effect: increased risk of QT interval prolongation, neuroleptic malignant syndrome, extrapyram
2) Summary: Tetrabenazine causes a small increase in the correct QT interval. As the degree of prolongatio develop into torsade de pointes-type VT. The concomitant use of tetrabenazine with other drugs known for Q should be avoided. In a randomized, double-blind, placebo controlled crossover study of healthy subjects, the mg dose of tetrabenazine on the QT interval was studied with moxifloxacin as a positive control. The 50 mg d approximate 8 millisecond mean increase in QT (Prod Info XENAZINE(R) oral tablets, 2008) In addition to QT may also cause adverse reactions such as neuroleptic malignant syndrome and extrapyramidal disorders, wh coadministered with neuroleptic drugs (eg, risperidone) (Prod Info XENAZINE(R) oral tablets, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of tetrabenazine with risperidone or other neuroleptic drugs may i reactions, such as QT interval prolongation and increased risk of torsade de pointes. Other adverse reactions syndrome and extrapyramidal disorders may be enhanced when given with a dopamine agonist such as rispe oral tablets, 2008).
7) Probable Mechanism: increased dopamine levels; additive effects on QT interval prolongation

3.5.1.CN Thioridazine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Although citing no data, the manufacturer of thioridazine states that concomitant use with other interval is contraindicated (Prod Info Mellaril(R), 2001). Several antipsychotic agents have demonstrated QT amisulpride (Prod Info Solian(R), 1999q), haloperidol (O'Brien et al, 1999j), pimozide (Prod Info Orap(R), 200 paliperidone (Prod Info INVEGA(TM) extended-release oral tablets, 2006), risperidone (Duenas-Laita et al, 1 2001n), sultopride (Lande et al, 1992q), ziprasidone (Prod Info GEODON(R) intramuscular injection, oral cap (Sweetman, 2004).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of agents that prolong the QT interval, such as antips contraindicated.
7) Probable Mechanism: additive QT prolongation

3.5.1.CO Topiramate

1) Interaction Effect: decreased risperidone exposure
2) Summary: Concurrent administration of topiramate (200 mg/day) with a single, 2 mg dose of risperidone i

in a 25% decrease in risperidone exposure. Patients receiving risperidone and topiramate together should be response to risperidone (Prod Info TOPAMAX(R) oral tablets, oral sprinkle capsules, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: established
6) Clinical Management: If risperidone and topiramate are administered concurrently, monitor patients closel risperidone (Prod Info TOPAMAX(R) oral tablets, oral sprinkle capsules, 2008).
7) Probable Mechanism: unknown

3.5.1.CP Tramadol
1) Interaction Effect: an increased risk of seizures
2) Summary: Seizures have been reported in patients using tramadol. The manufacturer of tramadol states t medications with tramadol may enhance the risk of seizures (Prod Info Ultram(R), 1998).
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Caution should be used if tramadol is to be administered to patients receiving neuro this combination, especially in patients with underlying conditions that might predispose to seizures.
7) Probable Mechanism: unknown

3.5.1.CQ Trifluoperazine
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Concomitant use of phenothiazines and antipsychotic agents may cause additive effects on the recommended. Q and T wave distortions have been observed in patients taking phenothiazines (Prod Info Co Stelazine(R), 2002; Prod Info Thorazine(R), 2002). Other phenothiazines may have similar effects, though no antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999j), paliperidone (Prod Info INVEGA(TM) extended-release oral tablets, 2006), quetiapine (Owens, 2001n), risper 1999n), sertindole (Agelink et al, 2001j), sultopride (Lande et al, 1992i), ziprasidone (Prod Info GEODON(R) i capsule, 2005), and zotepine (Sweetman, 2003).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of agents that prolong the QT interval, such as phen not recommended.
7) Probable Mechanism: additive QT prolongation

3.5.1.CR Trimethoprim
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Cotrimoxazole has been shown to prolong the QTc interval at the recommended therapeutic do though no formal drug interaction studies have been done, the coadministration of antipsychotics and other d interval, including cotrimoxazole, is not recommended. Several antipsychotic agents have demonstrated QT p amisulpride (Prod Info Solian(R), 1999g), haloperidol (O'Brien et al, 1999d), quetiapine (Owens, 2001i), rispe 1999i), sertindole (Agelink et al, 2001f), sultopride (Lande et al, 1992e), and zotepine (Sweetman, 2003).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of cotrimoxazole and antipsychotics is not recommer
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.CS Trimipramine
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod haloperidol (O'Brien et al, 1999a), risperidone (Duenas-Laita et al, 1999d), sertindole (Agelink et al, 2001a), o sultopride (Lande et al, 1992a), and zotepine (Sweetman, 2003). Even though no formal drug interaction stud coadministration of a tricyclic antidepressant and an antipsychotic is not recommended (Prod Info Pamelor(R 1982).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of a tricyclic antidepressant and an antipsychotic is n
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) Electrocardiographic changes that have occurred during clinical trials with pimozide have included pr interval, flattening, notching, and inversion of the T wave and the appearance of U waves. In experiment deaths have occurred while patients were receiving pimozide doses of 1 mg/kg. The proposed mechanis prolongation of the QT interval predisposing patients to ventricular arrhythmias (Prod Info Orap(R), 1999

3.5.1.CT Valproic Acid

1) Interaction Effect: increased plasma valproic acid concentrations
2) Summary: The addition of risperidone to valproic acid produces a significant increase in the peak plasma acid (Prod Info Risperdal(R) Consta(TM), 2003c) as well as marked increases in ammonia levels (Carlson et capacity of risperidone could lead to a competition for protein-binding with the high protein-binding capacity o displacement of valproic acid from plasma protein-binding sites (van Wattum, 2001). However, Valproic acid treatment regimen consisting of risperidone (Spina et al, 2000c). Monitoring of ammonia levels may be warra new or increased manic behavior when taking valproic acid and risperidone, especially in patients vulnerable hyperammonemia, including the young, on valproate polytherapy, severely handicapped, or suffering from m decreased free serum carnitine (Carlson et al, 2007). In patients prescribed this combination of drugs, monitc OH-risperidone concentrations does not appear to be warranted.
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Monitor for increased ammonia levels and plasma valproic acid concentrations with drug therapy or changes in risperidone dose.
7) Probable Mechanism: unknown
8) Literature Reports
a) In 2 case reports of 11 year-old boys, there were marked exacerbations in manic behavior and a 2 to ammonia levels when risperidone and valproic acid were concomitantly administered. The first patient, w disorder, attention-deficit/hyperactivity disorder (ADHD), psychosis, and manic symptoms, was admitted behavior. Chlorpromazine was added as needed and risperidone was added to replace his aripiprazole. acid 250 mg twice daily, the patient experienced a qualitative exacerbation of manic behavior. The risper adjusted to 2 mg/day and valproic acid to 625 mg/day. The patient's valproate level ranged from 87 to 9C When valproic acid was discontinued, and the ammonia level fell to 55, his manic behavior stopped. The absence epilepsy and ADHD, was on stable doses of valproic acid. Because of his psychotic symptoms, increased to 1.125 mg/day over 5 weeks. The patients exhibited markedly pronounced manic behavior a 113, despite a normal valproic acid level of 71. Upon discontinuation of risperidone and valproic acid, the and the manic behavior resolved. One month later when the patient was rechallenged with risperidone (i there was no return of either mania or hyperammonemia (Carlson et al, 2007).
b) A study was performed to evaluate the pharmacokinetic interaction between risperidone and valproic concentrations of risperidone and 9-hydroxyrisperidone (9-OH risperidone) were compared in patients tre patients comedicated with valproic acid. Thirty-three patients with a DSM-IV diagnosis of schizophrenia, bipolar disorder, were stabilized with risperidone alone or in combination with valproic acid. The results c given at doses up to 1200-1500 mg/day had clinically insignificant effects on plasma concentrations of ris metabolite. Valproic acid can be added safely to a treatment regimen consisting of risperidone. In patient drugs, monitoring of plasma risperidone or 9-OH-risperidone concentrations does not appear to be warra
c) The combination of valproic acid and risperidone led to significantly increased levels of valproic acid i suffered from mood swings and increasingly aggressive behavior. Valproic acid treatment was initiated a Valproate serum levels were in the therapeutic range. After 10 days of treatment, risperidone 2 mg/day w to 3 mg/day on day 4. On day 5 after risperidone was started, the patients symptoms improved but valpr therapeutic range at 191 mg/L. Valproic acid was decreased to 1000 mg/day and the level normalized to subsequently stabilized. The author concludes that the high-protein-binding capacity of risperidone coulc binding with the high protein-binding capacity of valproic acid, leading to displacement of valproic acid fr (Van Wattum, 2001).
d) In 21 patients, repeated oral doses of risperidone 4 mg daily did not affect the pre-dose or average pl (area under the concentration-time curve) of valproate 1000 mg daily compared to placebo. There was, h valproate maximum plasma concentration (Cmax) after risperidone coadministration (Prod Info Risperda

3.5.1.CU Vasopressin
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Antipsychotics and vasopressin have been shown to prolong the QTc interval at the recommen 2001b; Prod Info Solian(R), 1999a; Duenas-Laita et al, 1999c; Brown & Levin, 1998; Harry, 1997; Prod Info N Friedman, 1993; Mauro et al, 1988). Even though no formal drug interaction studies have been done, the coa prolong the QTc interval is not recommended.
3) Severity: major
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of drugs that prolong the QT interval, such as antipsy recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.CV Zolmitriptan
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Zolmitriptan has been shown to prolong the QTc interval at the recommended therapeutic dose Antipsychotics including haloperidol (Prod Info Haldol(R), 1998g), quetiapine (Owens, 2001aa), risperidone (I risperidone, 2000c), amisulpride (Prod Info Solian(R), 1999y), sertindole (Agelink et al, 2001u); sultopride (La (Sweetman, 2004) have been shown to prolong the QT interval at therapeutic doses. Even though no formal been done, the coadministration of drugs known to prolong the QT interval is not recommended.

3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of zolmitriptan and antipsychotics is not recommende
7) Probable Mechanism: additive effect on QT interval

3.5.1.CW Zotepine
1) Interaction Effect: increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Zotepine used concurrently with neuroleptics may increase the risk of seizures (Hori et al, 1992 drugs that potentiallly prolong the QTc interval, such as zotepine and risperidone, should be approached with Info Risperdal(R), 2002d).
3) Severity: major
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Monitoring for seizures is particularly important in those patients who: (1) are taking have a history of seizure disorders; (3) are of young age; or (4) have a past history of brain injury. The concu prolong the QT interval, such as zotepine and risperdone, is not recommended.
7) Probable Mechanism: additive effects on QT prolongation
8) Literature Reports
a) Since zotepine can prolong the QT interval it is recommended that an ECG is performed before starti existing prolongation of the QT interval should not be given zotepine (Sweetman, 2004).
b) Fatal QRS prolongation and QTc prolongation have been reported in patients taking risperidone thera 1999w; Ravin & Levenson, 1997j; Gesell & Stephen, 1997f; Lo Vecchio et al, 1996f; Brown et al, 1993f).

4.0 Clinical Applications

Monitoring Parameters

Patient Instructions

Place In Therapy

Mechanism of Action / Pharmacology

Therapeutic Uses

Comparative Efficacy / Evaluation With Other Therapies

4.1 Monitoring Parameters
A) Therapeutic
1) Physical Findings
a) Bipolar Disorder
1) A prolonged time to relapse to any mood episode (depression, mania, hypomania, or mixed) is indica risperidone (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).
2) Closely monitor effectiveness during the first 4 to 8 weeks of starting carbamazepine or other known inducers. The dose of risperidone may need to be titrated upward (Prod Info RISPERDAL(R) CONSTA(R
b) Schizophrenia
1) Positive and Negative Syndrome Scale (PANSS), which measures positive symptoms, negative symp uncontrolled hostility/excitement, and anxiety/depression, evaluates response to therapy (Prod Info RISP acting injection, 2009).
a) Positive psychotic symptoms (delusions, auditory hallucinations, racing thoughts)
b) Negative psychotic symptoms (anhedonia, apathy, amotivation, ambivalence).
2) Closely monitor effectiveness during the first 4 to 8 weeks of starting carbamazepine or other known inducers. The dose of risperidone may need to be titrated upward (Prod Info RISPERDAL(R) CONSTA(R
B) Toxic
1) Laboratory Parameters
a) Fasting blood glucose testing should be measured prior treatment and periodically during treatment in pat obesity, family history of diabetes) for diabetes mellitus. Patients with known diabetes mellitus should be regu glucose control during risperidone treatment. When symptoms of hyperglycemia develop, fasting blood gluco (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).
b) Complete blood count should be monitored frequently during the first few months of risperidone. If there a a decrease in CBC, then risperidone should be discontinued at the first sign of decline in WBC. For absolute 1000/mm(3), discontinue risperidone and perform follow-up WBC until recovery. Patients with preexisting low induced leukopenia/neutropenia are potentially at greatest risk for leukopenia, neutropenia, and agranulocyto

CONSTA(R) long acting injection, 2009).

2) Physical Findings

a) Tardive dyskinesia should be observed for in patients on risperidone particularly the elderly (elderly wome patients on chronic risperidone (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).

b) Hyperglycemia symptoms including polydipsia, polyuria, polyphagia, and weakness should be monitored f (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).

c) Monitor ECG at baseline and periodically during treatment (Pacher & Kecskemeti, 2004).

d) Cerebrovascular events (eg, stroke, transient ischemic attack) should be observed for in elderly patients v (not an indication) because of the higher incidence of cerebrovascular events observed with oral risperidone

e) Neuroleptic malignant syndrome (NMS) (hyperpyrexia, muscle rigidity, altered mental status, and evidenc (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia) should be monitored fc should be immediately discontinued in the presence of NMS. Carefully monitor for NMS recurrence if risperid RISPERDAL(R) CONSTA(R) long acting injection, 2009).

f) Orthostatic hypotension symptoms including heart rate and blood pressure should be monitored for in all p during the initial dose-titration phase of oral risperidone. A dose reduction may be necessary if hypotension o predisposed to hypotension include those with known cardiovascular disease (history of myocardial infarction conduction abnormalities), cerebrovascular disease, who are dehydrated and hypovolemic, and in the elderly hepatic impairment (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).

g) Fever and other symptoms or signs of infection should be monitored for in patients on risperidone becaus neutropenia or agranulocytosis (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).

h) Patients at high-risk for suicide should be closely supervised during therapy because of the increased risk with schizophrenia or bipolar disorder (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).

i) Confusion, obtundation, postural instability with frequent falls, extrapyramidal symptoms, and clinical featu neuroleptic malignant syndrome are manifestation of increased sensitivity in patients with Parkinson's Diseas

4.2 Patient Instructions

A) Risperidone (By mouth)

Risperidone

Treats schizophrenia and certain problems caused by bipolar disorder.

When This Medicine Should Not Be Used:
You should not use this medicine if you have had an allergic reaction to risperidone.

How to Use This Medicine:
Tablet, Liquid, Dissolving Tablet

Your doctor will tell you how much of this medicine to use and how often. Your dose may need to be changed what works best for you. Do not use more medicine or use it more often than your doctor tells you to.

Measure the oral liquid medicine with a marked measuring spoon, oral syringe, or medicine cup. You may mi milk, coffee, or orange juice. Do not mix with cola or tea.

If you are using the disintegrating tablet, make sure your hands are dry before you handle the tablet. Do not c contains the tablet until you are ready to take it. Remove the tablet from the blister pack by peeling back the f not push the tablet through the foil. Place the tablet in your mouth. It should melt quickly. After the tablet has water.

If a Dose is Missed:

If you miss a dose or forget to use your medicine, use it as soon as you can. If it is almost time for your next c medicine and skip the missed dose. Do not use extra medicine to make up for a missed dose.

How to Store and Dispose of This Medicine:

Store the medicine in a closed container at room temperature, away from heat, moisture, and direct light. Do Ask your pharmacist, doctor, or health caregiver about the best way to dispose of any leftover medicine after treatment. You will also need to throw away old medicine after the expiration date has passed.

Keep all medicine away from children and never share your medicine with anyone.

Drugs and Foods to Avoid:

Ask your doctor or pharmacist before using any other medicine, including over-the-counter medicines, vitamins, a

There are many other medicines that you should not use while you are taking risperidone. Taking risperidone may be dangerous, even life-threatening. Make sure your doctor and your pharmacist knows about all other r

Make sure your doctor knows if you are taking carbamazepine (Tegretol®), cimetidine, furosemide (Lasix®), paroxetine (Paxil®), phenobarbital, ranitidine, or valproate (Depakene®, Depakote®). Tell your doctor if you a quinidine, phenytoin (Dilantin®), or rifampin (Rifadin®). Make sure your doctor knows if you are also using m

Some blood pressure medicines are atenolol, hydrochlorothiazide (HCTZ), lisinopril, metoprolol, quinapril, Ac Lotrel®, Norvasc®, Toprol®, and Zestril®.

Tell your doctor if you are using any medicines that make you sleepy. These include sleeping pills, cold and a relievers, and sedatives.

Do not drink alcohol while you are using this medicine.

Warnings While Using This Medicine:

Make sure your doctor knows if you are pregnant, plan to become pregnant, or if you are breast feeding. Tell
of liver disease, kidney disease, stroke, or breast cancer. Make sure your doctor knows if you have heart prol
seizures, or trouble swallowing.
Make sure your doctor knows if you have a family history of a heart condition called congenital long QT syndı
ever had Neuroleptic Malignant Syndrome (NMS) caused by other antipsychotic medicines.
This medicine may cause an increase in your blood sugar. If you have diabetes, you may need to check your
are using medicine for diabetes, your doctor may need to change your dose.
This medicine is not approved to treat behavior disorders in older people who have dementia. Using this med
increase the risk of death. This risk has not been shown for the approved uses of this medicine.
Some side effects are more likely to happen in elderly people who have memory problems or other reduced r
doctor knows if the person who will be using this medicine has Alzheimer's disease or similar problems (ofter
This medicine may make you dizzy or drowsy. Avoid driving, using machines, or doing anything else that cou
alert.
This medicine might reduce how much you sweat. Your body could get too hot if you do not sweat enough. If
might feel dizzy, weak, tired, or confused. You might vomit or have an upset stomach. Do not get too hot whil
places that are very hot. Call your doctor if you are too hot and cannot cool down.
This medicine may make your skin more sensitive to sunlight. Use a sunscreen when you are outdoors. Avoi
Risperdal® M-Tab® contains aspartame (phenylalanine). If you have phenylketonuria (PKU), talk to your doc

Possible Side Effects While Using This Medicine:
Call your doctor right away if you notice any of these side effects:

Allergic reaction: Itching or hives, swelling in your face or hands, swelling or tingling in your mouth or throat, c
Change in how much or how often you urinate.
Confusion, weakness, and muscle twitching.
Constant muscle movement that you cannot control (often in your lips, tongue, arms, or legs).
Dry mouth, increased thirst, muscle cramps, nausea or vomiting.
Fast, slow, irregular (uneven), or pounding heartbeat.
Fever, sweating, muscle stiffness.
In males: Painful, prolonged erection of your penis.
Lightheadedness, fainting, or seizures.
Severe diarrhea, vomiting, or stomach pain.
Skin rash.
Sudden or severe headache, problems with vision, speech, or walking.
Twitching or muscle movements you cannot control (often in your eyes, jaw, neck or upper body).
Unusual bleeding, bruising, or weakness.
Yellowing of your skin or the whites of your eyes.

If you notice these less serious side effects, talk with your doctor:

Anxiety, trouble sleeping, increased dreaming.
Constipation, diarrhea, nausea, or upset stomach.
Darkening of your skin.
Drooling, or stuffy nose.
In women: Unusually heavy bleeding during your menstrual period.
Severe tiredness.
Trouble having sex.
Weight gain.

If you notice other side effects that you think are caused by this medicine, tell your doctor.

B) Risperidone (Injection)

Risperidone

Treats schizophrenia and certain problems caused by bipolar disorder.

When This Medicine Should Not Be Used:
You should not receive this medicine if you have had an allergic reaction to risperidone.

How to Use This Medicine:
Injectable

Your doctor will prescribe your exact dose and tell you how often it should be given. This medicine is given as
A nurse or other trained health professional will give you this medicine. This medicine is usually given every 2

If a Dose is Missed:

This medicine needs to be given on a fixed schedule. If you miss a dose or forget to use your medicine, call y
instructions.

Drugs and Foods to Avoid:
Ask your doctor or pharmacist before using any other medicine, including over-the-counter medicines, vitamins, a

There are many other medicines that you should not use while you are taking risperidone. Taking risperidone may be dangerous, even life-threatening. Make sure your doctor and your pharmacist knows about all other m
Make sure your doctor knows if you are taking carbamazepine (Tegretol®), cimetidine (Tagamet®), furosemi (Larodopa®), fluoxetine (Prozac®), paroxetine (Paxil®), phenobarbital (Luminal®), ranitidine (Zantac®), or va Depakote®). Tell your doctor if you are using clozapine (Clozaril®), quinidine, phenytoin (Dilantin®), or rifamp doctor knows if you are also using medicine to lower blood pressure (such as atenolol, hydrochlorothiazide (H quinapril, Accupril®, Cozaar®, Diovan®, Lotrel®, Norvasc®, Toprol®, or Zestril®).
Tell your doctor if you are using any medicines that make you sleepy. These include sleeping pills, cold and a relievers, and sedatives.
Do not drink alcohol while you are using this medicine.

Warnings While Using This Medicine:

Make sure your doctor knows if you are pregnant or if you plan to become pregnant while you are using this m after you stop using it. Do not breastfeed while you are using this medicine and for at least 12 weeks after yo
Make sure your doctor knows if you have kidney disease, liver disease, diabetes, breast cancer, bone proble Reye's syndrome, Parkinson's disease, trouble with swallowing, or a history of seizures or neuroleptic malign doctor if you have any kind of blood vessel or heart problems, including low blood pressure, heart failure, a lo problems, or a history of a heart attack or stroke.
This medicine may cause an increase in your blood sugar. If you have diabetes, you may need to check your are using a medicine for diabetes, your doctor may need to change your dose.
This medicine is not approved to treat behavior disorders in older people who have dementia. Using this med increase the risk of death. This risk has not been shown for the approved uses of this medicine.
Some side effects are more likely to happen in elderly people who have memory problems or other reduced m doctor knows if the person who will be using this medicine has forgetfulness or confusion related to aging (su dementia).
Stop taking this medicine and check with your doctor right away if you have any of the following symptoms wh convulsions (seizures), difficulty with breathing, a fast heartbeat, a high fever, high or low blood pressure, inc control, severe muscle stiffness, unusually pale skin, or tiredness. These could be symptoms of a serious cor malignant syndrome (NMS).
Tardive dyskinesia (a movement disorder) may occur and may not go away after you stop using the medicine away if you have any of the following symptoms while taking this medicine: lip smacking or puckering, puffing movements of the tongue, uncontrolled chewing movements, or uncontrolled movements of the arms and leg
This medicine may make you dizzy, lightheaded, or drowsy. Avoid driving, using machines, or doing anything you are not alert. Change positions slowly when getting up from a lying or sitting position.
This medicine lowers the number of some types of blood cells in your body. Because of this, you may bleed o help with these problems, avoid being near people who are sick or have infections. Wash your hands often. S other situations where you could be bruised, cut, or injured. Brush and floss your teeth gently. Be careful whe razors and fingernail clippers.
This medicine might reduce how much you sweat. Your body could get too hot if you do not sweat enough. If might feel dizzy, weak, tired, or confused. You might vomit or have an upset stomach. Do not get too hot whil places that are very hot. Call your doctor if you are too hot and cannot cool down.
This medicine may cause some people to be agitated, irritable, or display other abnormal behaviors. It may a suicidal thoughts and tendencies or to become more depressed. If you or your caregiver notice any of these a right away.
This medicine may increase your weight. Your doctor may need to check your weight regularly during treatme
Your doctor will need to check your blood at regular visits while you are using this medicine. Be sure to keep
Your doctor will need to check your progress at regular visits while you are using this medicine. Be sure to ke

Possible Side Effects While Using This Medicine:

Call your doctor right away if you notice any of these side effects:

Allergic reaction: Itching or hives, swelling in your face or hands, swelling or tingling in your mouth or throat, o
Change in how much or how often you urinate.
Chills, cough, sore throat, and body aches.
Dry mouth, increased hunger or thirst, or muscle cramps.
Fast, slow, pounding, or uneven heartbeat.
Feeling depressed, agitated, or nervous.
Fever, sweating, confusion, or muscle stiffness.
Lightheadedness, dizziness, or fainting.
Mood or behavioral changes, or thoughts of hurting yourself or others.
Numbness or weakness in your arm or leg, or on one side of your body.
Painful, prolonged erection of your penis (in males).
Problems with balance or walking.
Seizures or tremors.
Swelling in your hands, ankles, or feet.
Trouble with speaking or swallowing.
Twitching or muscle movements you cannot control (often in your eyes, jaw, neck or upper body).
Unusual bleeding, bruising, or weakness.
Yellowing of your skin or the whites of your eyes.

If you notice these less serious side effects, talk with your doctor:
Blurred vision or change in vision.
Constipation, diarrhea, nausea, vomiting, or stomach pain or upset.
Dry mouth or drooling.
Headache.
Pain, swelling, or a lump under your skin where the shot is given.
Rash or itching skin.
Stuffy or runny nose.
Weight gain.

If you notice other side effects that you think are caused by this medicine, tell your doctor.

4.3 Place In Therapy

A) Current users of atypical antipsychotic drugs (including risperidone) and typical antipsychotic drugs had a similar d cardiac death, according to a retrospective cohort of 93,300 adult users of antipsychotic drugs and 186,600 matched c patients age 30 to 74 years (mean 45.7 +/- 11.8 years) with similar cardiovascular risk at baseline who had at least on outpatient visit in each of the 2 preceding years. Sudden cardiac death was defined as occurring in the community and admitted to the hospital, non-sudden deaths, deaths due to extrinsic causes, or causes not related to ventricular tachy defined as the interval between the time the prescription was filled and the end of the day's supply. Low and high dose less than 100 milligrams (mg) of chlorpromazine, and doses comparable to chlorpromazine 300 mg or greater, respec sudden cardiac death (incidence-rate ratio) in current users of atypical antipsychotic drugs in 79,589 person-years was less than 0.001) which was similar to the risk in current users of typical antipsychotic drugs in 86,735 person-years wh 2.34, p less than 0.001). The risk of sudden cardiac death in current risperidone users in 24,589 person-years was 2.9 than 0.001). The risk of sudden cardiac death significantly increased with increasing dose in both the typical and atypi atypical antipsychotic use, the incidence rate ratio increased from 1.59 (95% CI, 1.03 to 2.46) in low-dose use to 2.86 dose use. To limit the effects of confounding of the study results, there was a secondary analysis performed in a coho propensity score, which resulted in a similar risk of sudden death as the primary cohort analysis (Ray et al, 2009). In a Journal of Medicine, it has been suggested that antipsychotic drugs continue to be used in patients with clear evidence populations with cardiac risk profiles (eg, elderly patients), there should an age-dependent justification required prior to suggested (although not formally tested) that ECGs be performed before and shortly after initiation of antipsychotic the emergent QT interval prolongation (Schneeweiss & Avorn, 2009).

B) Schizophrenia

1) Risperidone is a benzisoxazole derivative. It is approved for the treatment of schizophrenia. It blocks both serc (2) receptors. It is effective in chronic schizophrenia for positive and negative symptoms with a response rate of 5 Rossi et al, 1997; Smith et al, 1996). At doses of 8 milligrams or less risperidone is associated with a lower risk of conventional antipsychotics (Foster & Goa, 1998). Comparative efficacy with haloperidol and other conventional n shown that risperidone has a significantly higher clinical response rate and allows for significantly less prescribing (Davies et al, 1998; Bech et al, 1998; Luebbe, 1996). Risperidone has also shown some efficacy in psychotic disc HIV, levodopa, and other medical conditions. Refractory obsessive-compulsive disorder and refractory depressior risperidone in select cases.

C) Bipolar Mania

1) Long-acting injection risperidone alone or in combination with lithium or valproate is approved for the maintena disorder (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009). Oral risperidone alone or in combina approved for the short-term treatment of acute manic or mixed episodes associated with Bipolar I Disorder (Prod I oral solution, orally-disintegrating tablets, 2006).

D) Irritability associated with Autistic Disorder

1) Risperidone is approved for the treatment of irritability associated with autistic disorder in children and adolesc aggression towards others, deliberate self-injuriousness, temper tantrums, and quickly changing moods (Prod Info oral solution, orally-disintegrating tablets, 2006).

See Drug Consult reference: FIRST- VS SECOND-GENERATION ANTIPSYCHOTIC AGENTS FOR SCHIZOPHREN

4.4 Mechanism of Action / Pharmacology

A) MECHANISM OF ACTION

1) In vitro studies have shown that risperidone acts primarily as a serotonin (5-HT2) and dopamine (D2) antagoni serotonergic receptors. Risperidone also binds to alpha-1 and alpha-2 adrenergic and histamine H1 receptors, alt Dissociation from 5-HT2 and H1 receptors is slow; however, the drug rapidly dissociates from dopaminergic and a potency of risperidone as a dopamine D2 antagonist is less than that of haloperidol, and its 5-HT2 antagonist pote ritanserin. Risperidone interacts weakly or not at all with other receptor and neurotransmitter systems, including cl Anon, 1993a; Gerlach, 1991; Leysen et al, 1988; Niemegeers et al, 1988).

2) Studies have shown that there is an exponential dose-response relationship between the daily dose of risperid receptor occupancy (Dresel et al, 1998; Remington et al, 1998). The slope of the curve is between that of haloper closely resembles haloperidol. One study did find that extrapyramidal effects were linked to D(2) occupancy with t symptoms having the highest percentage of binding (Remington et al, 1998). The other study found no clear relati D(2) occupancy. They hypothesized that the decreased incidence of extrapyramidal effects seen with risperidone the D(2) receptor but to risperidone's high 5-HT(2) affinity providing a relative protection from symptoms (Dresel e

3) Animal studies have shown that risperidone inhibits tryptamine- and serotonin-induced cyanosis and 5-hydroxy twitching; it also blocks central and peripheral manifestations of dopaminergic stimulation, including apomorphine-

apomorphine- or amphetamine-induced stereotypy or hypermotility (Anon, 1991; Megens et al, 1988). Risperidon
than haloperidol in the inhibition of locomotion and induction of catalepsy; in addition, risperidone causes a signifi
corresponding to the effect of ritanserin (Gerlach, 1991).
4) Potent alpha-2 adrenoceptor blockade has been demonstrated with risperidone, as it reverses clonidine inhibit
norepinephrine release in occipital cortex. It also exhibits complete and potent lysergic acid diethylamide (LSD) a
1991; Leysen et al, 1988; Niemegeers et al, 1988).

B) REVIEW ARTICLES

1) The use of atypical antipsychotic medications in adults (Markowitz et al, 1999)(Brown et al, 1993h), and childre
1998; Toren et al, 1998) has been reviewed.
2) A pharmacoeconomic review of risperidone's use in schizophrenia has been published (Foster & Goa, 1998a).
3) Meta-analyses of risperidone versus haldoperidol's efficacy and safety (Davies et al, 1998) and cost-effectiven
been published.
4) Risperidone's role in the treatment of schizophrenia has been reviewed by the American Psychiatric Associati
5) Risperidone controlled trials, clinical observations, and reports of side effects have been reviewed (Marder, 19
6) The Consensus Study Group on Risperidone Dosing has published guidelines on transitioning patients to rispe
7) A review of new neuroleptics with emphasis on risperidone as a new prototype is published in the German liter
8) New generation neuroleptics in the treatment of patients with negative symptomology are reviewed in the Gerr
9) Risperidone is examined with respect to its clinical profile and its place in therapy; in the German literature (Ta
10) A literary review rating the therapeutic actions of risperidone with a focus on negative symptomology, cognitiv
aspects is published in the German literature (Franz & Gallhofer, 1997).

4.5 Therapeutic Uses

Agitation, acute - Psychotic disorder

Anorexia nervosa

Autistic disorder - Irritability

Behavioral syndrome - Dementia

Behavioral syndrome - Mental retardation

Bipolar I disorder

Borderline personality disorder

Catatonia

Cocaine dependence

Cognitive function finding

Delusional disorder

Dementia

Dementia - Psychotic disorder

Depression, Refractory; Adjunct

Drug-induced psychosis - Levodopa adverse reaction

Gilles de la Tourette's syndrome

Huntington's disease

Inhalant abuse

Obsessive-compulsive disorder, Refractory

Organic psychotic condition

Parkinson's disease - Psychotic disorder

Pervasive developmental disorder

Pick's disease

Posttraumatic stress disorder

Schizophrenia

Schizotypal personality disorder

Stuttering

Tardive dyskinesia

Trichotillomania

Water intoxication syndrome

4.5.A Agitation, acute - Psychotic disorder

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Olanzapine orally disintegrating tablets and risperidone oral solution yielded similar improvements on the and Negative Syndrome Scale and the Clinical Global Impression scale in 87 patients treated for acute p emergency setting, according to an open-label, flexible-dose study(Hatta et al, 2008)

3) Adult:

a) Olanzapine orally disintegrating tablets (ODT) and risperidone oral solution (OS) yielded similar improvem for Positive and Negative Syndrome Scale (PANSS-EC) and the Clinical Global Impression (CGI) scale in 87 psychotic agitation in a psychiatric emergency setting, according to an open-label, flexible-dose study. Patien score of 15 or higher who accepted oral medication were assigned to receive initial doses of either olanzapin or risperidone OS 3 mg (n=53). Treatment group assignments were based on previous effective treatments, olanzapine or risperidone according to the time of study trial entry. Patients who experienced continued agita time, and after 1 hour could receive adjunctive drug therapy. PANSS-EC scores in both groups decreased ov from baseline was similar between the olanzapine and risperidone group (2.8 vs 3.2; p=0.22). Repeated mea score over time ANOVA (at baseline and every 15 minutes for 1 hour) revealed no significant main effect of t treatment over time (p=0.09 and p=0.41, respectively). There was a significant mean change in heart rate in t compared with risperidone OS group (-9.2 vs 1.1 beats/minute, p=0.03). There were no significant differences for adverse effects including extrapyramidal symptoms (Hatta et al, 2008).

4.5.B Anorexia nervosa

See Drug Consult reference: ANOREXIA NERVOSA - DRUG THERAPY

4.5.C Autistic disorder - Irritability

FDA Labeled Indication

1) Overview

FDA Approval: Adult, no; Pediatric, yes (5 years and older)
Efficacy: Pediatric, Effective
Recommendation: Pediatric, Class IIa
Strength of Evidence: Pediatric, Category A

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Risperidone was more effective than placebo in improving the emotional and behavioral symptoms of au towards others, deliberate self-injuriousness, temper tantrums, and quickly changing moods in short-ter studies (Prod Info RISPERDAL(R) oral tablets, oral solution, orally-disintegrating tablets, 2006; McCrack

continued risperidone therapy maintained efficacy up to 6 months and led to lower relapse rates compar
2002).
Treatment with oral risperidone was well tolerated and more effective in improving autism symptoms con
randomized, double-blind study (n=40) (Nagaraj et al, 2006).

3) Pediatric:

a) Risperidone was more effective than placebo for the short-term treatment of severe behavioral problems i
randomized, double-blind, placebo-controlled study (n=101). Patients (ages 5 to 17 years) with autism accom
problems (tantrums, aggression, or self-injurious behavior) received placebo (n=49) or risperidone 0.5 to 3.5
dose during last week, 1.8 mg/day) for 8 weeks. Primary efficacy measures were the score at eight weeks on
Aberrant Behavior Checklist and the rating on the Clinical Global Impressions-Improvement (CGI-I) scale. A p
a 25% or greater reduction in the Irritability score and a rating of much improved or very much improved on th
Irritability score for the risperidone group decreased by 56.9% following 8 weeks of treatment as compared w
placebo group (p less than 0.001). The rate of positive response was significantly higher in risperidone-treate
placebo (69% vs 12%, respectively; p less than 0.001). Risperidone was generally well tolerated and most ac
transient. Due to the uncertainty of a clear benefit with regard to the core symptoms of autism the authors rec
reserved for the treatment of moderate-to-severe behavioral problems accompanying autism (McCracken et a
endpoints, risperidone significantly decreased the overall score on the Ritvo-Freeman scale, which was modi
measure to a parent rating scale and included subscales for assessing sensory motor behaviors, social relate
sensory responses, and language (subscales I, II, III, IV, and IV, respectively). Specifically, significant treatm
noted for subscales I (effect size, 0.45; p=0.002), III (effect size, 1.1; p less than 0.001), and IV (effect size, 0
statistically significant effect on the subscales scores for social relatedness (subscale II) or language (subsca
deviation Children's Yale-Brown Obsessive Compulsive scale score (modified to only assess the compulsion
20) decreased from a baseline score of 15.51 +/- 2.73 to 11.65 +/- 4.02 in the risperidone group compared to
14.21 +/- 4.81 in the placebo group. For the total Maladaptive Behavior Domain (measured using the Vinelan
there was a significant treatment and time interaction during the 8-week trial (effect size, 1.03; p less than 0.0
baseline scores of 33.26 and 33.51 to 7.93 and 8.87 for the risperidone and placebo groups, respectively (Mc

1) Long-Term Extension

a) In a 24-week extension of the aforementioned study that included a 4-month, open-label extensio
placebo-controlled discontinuation phase, continued risperidone therapy maintained efficacy for auti
compared to the placebo group. Following 8 weeks of double-blind therapy in 101 patients, a total of
years) from both the risperidone and placebo groups received open-label risperidone for another 16
adjustments were allowed up to a maximum total daily dose of 3.5 milligrams (mg)/day in children w
and up to 4.5 mg/day for children weighing over 45 kg. Response was defined as at least 25% reduc
the Aberrant Behavior Checklist (ABC) and a rating of much improved or very much improved on the
Improvement (CGI-I) scale). Responders to the 4-month open-label extension therapy were random
either to continue risperidone at the same dose or to gradual placebo substitution (risperidone dose
weeks and assessed for relapse (defined as a 25% increase in the ABC-Irritability (ABC-I) subscale
much worse or very much worse for at least 2 consecutive weeks). At the end of the 4-month, open-
treat analysis revealed a minor but clinically insignificant increase in ABC-I score, going from a base
therapy) mean +/- standard deviation (SD) score of 9.5 +/- 6.8 to 10.8 +/- 7.1. There was a significar
at the end of the 4-month extension phase (p=0.02), Additionally, among 51 patients who completec
a much improved or very much improved rating on the CGI-I scale. A preplanned interim analysis du
revealed higher relapse rates in the placebo group compared to the risperidone group (62.5% (n=10
median time to relapse was 34 days and 57 days, respectively. This prompted early termination of th
Pediatric Psychopharmacology Autism Network, 2005). For secondary outcomes, improvements see
scores of the modified Ritvo-Freeman scale, the Children's Yale-Brown Obsessive Compulsive scale
the Maladaptive Behavior Domain of the Vineland Adaptive Behavior Scales, after 8 weeks of initial
the 4-month extension phase (McDougle et al, 2005).

b) Risperidone was more effective than placebo in improving the irritability symptoms of autism in an 8-week
children and adolescents with autistic disorder. Children (n=55; 5 to 12 years of age) with autistic disorder rec
0.02 to 0.06 mg/kg/day once or twice daily, starting at 0.01 mg/kg/day (mean modal dose of 0.05 mg/kg/day,
Efficacy was evaluated using the Aberrant Behavior Checklist (ABC). The change from baseline to endpoint i
ABC (ABC-I) was the primary outcome measure. This subscale evaluated the emotional and behavioral symp
aggression towards others, deliberate self-injuriousness, temper tantrums, and quickly changing moods. Risp
scores on the ABC-I subscale compared with placebo (Prod Info RISPERDAL(R) oral tablets, oral solution, o

c) Treatment with oral risperidone was more effective in improving autism symptoms compared to placebo ir
double-blind study (n=40). Consecutive children up to 12 years of age diagnosed with autism according to the
symptoms that included hyperactivity, aggression, stereotypies, and language difficulties were randomized to
either risperidone (initiated at 0.5 milligrams (mg)/day, increased to 1 mg/day 2 weeks later; n=19; mean age
(n=20; mean age, 63 months) for 6 months. The primary efficacy measures were changes from baseline in th
Rating Scale (CARS) and the mean Children's Global Assessment Scale (CGAS) scores at end of treatment.
irritability was the most common autism symptom (92%). At endpoint, 63% (n=12/19) of children in the risperi
improvement of at least 20% from baseline CARS scores compared to none in the placebo group. Median CA
(range, 32.5 to 46) at baseline to 32 (range, 24.5-40.5) at the end of treatment for the risperidone group comp
(range, 31.5-43 at baseline to 37.5 (30-42.5) at end of treatment for the placebo group (p less than 0.001). O
patients in the risperidone group had improvements (ie, increase in CGAS score of at least 20% from baselin
group (n=17 vs n=2). Mean CGAS scores increased from 29.79 and 32.65 at baseline in the risperidone and
40.94 and 35.2, respectively, at the end of treatment (p =0.035). Among secondary endpoints, based on an ir

questionnaire, risperidone improved functioning in domains of social responsiveness (n=7/19; p=0.014), nonv
p=0.008), decreased hyperactivity symptoms (n=7/19; p=0.002), and aggression and irritability (n=5/19; p=0.(
significant improvements in the domains of restricted interests, emotional interaction, or verbal communicatio
was well tolerated. Mild and transient dyskinesias occurred in 3 children. There was a nonstatistically significa
increase from baseline among risperidone-treated children (2.81 kilograms (kg; 17%) vs 1.71 kg (9.3%)) (Nag

4.5.D Behavioral syndrome - Dementia

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class III
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Improved target symptoms of agitation, aggression, hallucinations, and delusions in demented elderly
Cerebrovascular adverse events (stroke, transient ischemic attack) have occurred in elderly individuals (
received risperidone for treatment of dementia-related psychosis (Prod Info Risperdal(R), 2004)
Improved management of behavioral and psychological symptoms in elderly patients with dementia (De

3) Adult:

a) Risperidone and haloperidol produced similar reductions in severity of behavioral symptoms, especially ag
patients (DeDeyn et al, 1999). In a double-blind, 12-week study, agitated patients (55 years and older) with A
dementia, or a mixed dementia were randomized to receive risperidone (n=115), haloperidol (n=115), or plac
assessed using the Behavior Pathology in Alzheimer's Disease Rating Scale (BEHAVE-AD). Both medicatior
milligrams (mg) daily and increased by 0.25 mg every 4 days up to 1 mg twice daily. If indicated, the patient's
to a maximum of 2 mg twice daily. At the end of 12 weeks mean doses were risperidone 1.1 mg/day and halo
patients having at least a 30% improvement at 12 weeks was similar at 72% for risperidone, 69% for haloperi
significant). However, risperidone showed significantly greater improvements in mean BEHAVE-AD total scor
(p=0.05). Risperidone also had a significantly greater improvement than placebo and haloperidol in the BEHA
(p=0.002; p=0.05). Somnolence occurred in 18% of haloperidol patients, 12% of risperidone, and 4% of place
b) In a retrospective chart review, demented patients treated with risperidone were shown to benefit from the
al, 1999). Charts of patients with Alzheimer's disease, Lewy body dementia, or a mixed dementia who had re
problems were reviewed. The average dose of risperidone used was 1.8 milligrams for a mean duration of 4 r
occurred in 15% of patients treated, 41% had a partial response, and 44% had no response. Approximately h
adverse effects including extrapyramidal symptoms in 32%, sedation in 17%, or worsening agitation in 7%.
c) In a case series of 22 patients with dementia and behavioral disturbances, risperidone in doses ranging fr
other day to 3 mg twice daily resulted in substantially improved behavior in 11 patients (50%). All patients me
14 patients with dementia of the Alzheimer's type, 6 with vascular dementia, and 2 with Lewy body dementia.
target symptoms were agitation, aggression, hallucinations, and delusions. The mean dose of risperidone use
Clinical Global Impression scale, 6 patients (27%) were rated as very much improved, 5 patients (23%) were
patients (27%) were rated as minimally improved. Eleven patients (50%) experienced extrapyramidal sympto
therapy within the first two weeks due to side effects (Herrmann et al, 1998).
d) In a pooled analysis, risperidone therapy was superior compared to placebo in managing behavioral and p
dementia in elderly nursing home residents. The pooled data was from three randomized, placebo-controlled
parallel group, Phase III trials. The efficacy analysis was preceded by a one week single-blind washout perio
psychotropic medications were discontinued. Patients were then randomized to receive risperidone (n=722) o
at a dose range of 0.25 to 1 milligram (mg) twice daily. Overall, the demographics and baseline characteristic
patients being women, Caucasian, and suffering from dementia for an average of 5 or more years. Agitation a
assessed using the Cohen-Mansfield agitation inventory (CMAI) scores. Risperidone produced significantly g
to placebo in CMAI total scores from week 4 through week 12 (mean change from baseline to end point: -11.
than 0.001). Decreases in the total aggression and total non-aggression scores were also both statistically sig
less than 0.001). The severity of behavioral and psychological symptoms associated with dementia were ass
behavioral pathology in Alzheimer's disease (BEHAVE-AD). At all evaluation points, scores on the BEHAVE-
more improved with risperidone versus placebo (mean change from baseline to end point: -6.1 versus -3.6, re
The psychotic symptoms subscale of the BEHAVE-AD found that risperidone produced significantly greater in
patients with psychosis at baseline (mean change from baseline: -3.5 +/- 0.21 (n=434) versus -2.5 +/- 0.32 (n
The paranoid and delusional symptoms were significantly improved in the risperidone group compared to pla
0.002). However, there was no significant difference between the groups regarding improvement in hallucinat
0.3; p=0.191). The clinical global impression (CGI) scores were also significantly improved in the risperidone
A subgroup analysis on dementia type (Alzheimer's disease, vascular dementia and mixed dementia) found t
total scores were significantly improved in the risperidone group in both Alzheimer's disease and vascular de
dementia subjects. Treatment-emergent adverse events were comparable between risperidone (84.3%) and
number of patients who discontinued therapy due to treatment-emergent adverse events was higher in the ris
versus placebo (11.2%). Common adverse events leading to discontinuation in the risperidone group were sc
extrapyramidal disorders, aggressive reaction, pneumonia, injury, cerebrovascular disorder, and fall (De Deyn

4.5.E Behavioral syndrome - Mental retardation

1) Overview

FDA Approval: Adult, no; Pediatric, no

Efficacy: Adult, Evidence favors efficacy; Pediatric, Evidence favors efficacy
Recommendation: Adult, Class IIb; Pediatric, Class IIb
Strength of Evidence: Adult, Category B; Pediatric, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:
Useful for the adjunctive therapy of behavioral disturbances in patients with mental retardation
Effectively reduced severe behavior problems in children with below average intelligence

3) Adult:

a) Seven patients with Prader-Willi Syndrome and behavioral disturbances responded favorably to risperidor average dose was 1.64 milligrams daily). Six patients were adults and 1 was an adolescent. The patients hac antipsychotic medications (Durst et al, 2000).

b) In one double-blind, placebo-controlled crossover study, 37 patients with behavioral abnormalities such as irritability, agitation, hyperactivity, automutilation, and autism despite current therapy improved on risperidone medications were given orally for 3 weeks, followed by 3 weeks of crossover treatment. Doses of risperidone day; at weekly evaluations, daily dosage was increased by 4 mg/day up to a maximum total dose of 12 mg/da Global Impression (CGI) scores occurred. Risperidone caused significant improvement in CGI parameters thr study; placebo was not effective. No extrapyramidal symptoms occurred. No significant cardiovascular, bioch were reported (Vanden Borre et al, 1993a).

4) Pediatric:

a) Risperidone was safe and effective as a short- and long-term therapy for the reduction of severe behavior moderate intellectual disabilities. In a 6-week, randomized, double- blind, placebo controlled study, patients (average intelligence (IQ, 36 to 84) and a diagnosis of conduct disorder, oppositional defiant disorder, or disru otherwise specified received placebo (n=63) or risperidone (n=55) 0.02 to 0.06 milligrams (mg)/kilogram/day Efficacy of risperidone was assessed according to the change in score from baseline to endpoint on the cond Nisonger Child Behavior Rating Form. Patients treated with risperidone showed a significantly larger reductio subscale scores from baseline to endpoint as compared with placebo (-15.2 vs -6.2, respectively; p less than patients also showed significantly better improvements than did placebo-treated patients on all other subscal Rating Form. Risperidone was generally well tolerated and most adverse effects were mild to moderate, inclu headache (29%). As a long-term, open-label extension, 107 patients from this controlled study received rispe titrated up to maximum of 0.06 mg/kg/day; mean dose 1.51 mg/day) for 48 weeks. Throughout the 48-week e was maintained in patients treated with risperidone during the controlled trial and significant symptom improv who had received placebo during the controlled trial. Risperidone was generally well tolerated throughout the Adverse events included headache (32.7%), somnolence (32.7%), rhinitis (28%), increased appetite (9.3%), increase from baseline, 5.5 kilograms), and transient, mild elevations in prolactin levels (mean maximum leve (ng/mL) in boys; 23.9 ng/mL in girls). Additional studies are needed to investigate the safety and efficacy of ri for the treatment of severe, disruptive behavior in pediatric patients (Findling et al, 2004; Aman et al, 2002).

4.5.F Bipolar I disorder

FDA Labeled Indication

1) Overview
FDA Approval: Adult, yes (oral and intramuscular); Pediatric, yes (10 years and older, oral only)
Efficacy: Adult, Effective; Pediatric, Evidence favors efficacy
Recommendation: Adult, Class IIa; Pediatric, Class IIb
Strength of Evidence: Adult, Category B; Pediatric, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:
Intramuscular long-acting risperidone is indicated as monotherapy or in combination with lithium or valpr treatment of bipolar I disorder in adults (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 200
Oral risperidone is indicated for the short-term treatment of acute manic or mixed episodes associated w aged 10 years of age and older and adults (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPI disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007).
Oral risperidone, at doses ranging from 0.5 to 6 milligrams per day for 3 weeks, was effective in the treat episodes of bipolar I disorder in children aged 10 to 17 years in a multicenter, randomized, double-blind, Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 20 oral solution, 2007).

3) Adult:

a) Monotherapy

1) Intramuscular

a) In a multicenter, randomized, double-blind, placebo-controlled study of adult patients who met DS bipolar disorder type I and who were stable on medications or experiencing an acute manic or mixed intramuscular (IM) risperidone was effective for the maintenance treatment of bipolar I disorder. Dur a total of 501 patients were treated with IM risperidone at the starting dose of 25 mg and titrated up in patients not tolerating the starting dose). Of the 501 treated patients, 303 (60%) were deemed to h to double-blind treatment with either the same dose of IM risperidone or placebo. The results of the s compared to placebo, patients receiving monotherapy IM risperidone were delayed to reaching the s was the time to relapse to any mood episode (depression, mania, hypomania, or mixed). The majori rather than depressive symptoms and based on their history of bipolar disorder, these patients had, episodes than depressive episodes (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 20

2) Oral

a) Risperidone monotherapy was effective in the acute and continuation treatment of mania in patie
open- label, multicenter study, patients with acute mania and a score of at least 20 on the Young Ma
received six months of risperidone monotherapy at a mean dose of 4.2 milligrams (mg) daily (range
improvements in the YMRS score were observed from baseline to weeks 1, 2, 4, 6, 12, and 24 (p les
improvements in Clinical Global Impression and Positive and Negative Syndrome Scale scores were
as compared with baseline (p less than 0.0001). Extrapyramidal symptoms (ie, dystonia, hypokinesi
week 4 (p=0.015) (correlating with the highest mean doses of risperidone), but then decreased signi
(p=0.027). Other adverse events included impotence, drowsiness, weight gain (mean increase, 3.2 l
dizziness, hypotension, incontinence, and galactorrhea. Within the initial 4 weeks of treatment, incre
symptoms was seen in four patients (4.2%) and the appearance of a depressive episode was obser
Randomized, controlled studies are needed to confirm the safety and efficacy of risperidone monoth
of bipolar mania (Vieta et al, 2004).

b) In two placebo-controlled trials, risperidone monotherapy was more effective than placebo in red
patients with bipolar disorder. Patients meeting DSM-IV criteria for bipolar I disorder with manic or m
without psychotic features received risperidone (1 to 6 milligrams (mg)/day; mean modal dose, 4.1 t
weeks (n=246; n=286). In both trials, risperidone was more effective than placebo in the reduction o
(YMRS) scores of these patients (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDA
tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007).

b) Combination Therapy

1) Intramuscular

a) In a multicenter, randomized, double-blind, placebo-controlled study of adult patients who met DS
bipolar disorder type I and who experienced at least 4 episodes of mood disorder requiring psychiat
previous 12 months and at least 2 episodes in the 6 months prior to starting the trial, long-acting intr
effective for bipolar I disorder when used as combination therapy with lithium or valproate. During a
total of 240 patients were treated with IM risperidone at the starting dose of 25 mg and titrated up if
patients not tolerating the starting dose) in addition to continuing their usual bipolar disorder therapy
discontinued after the first 3 weeks of the initial injection of IM risperidone. Of the 240 treated patien
be stable for at least the last 4 weeks and were randomized to double-blind treatment with either the
placebo in addition to their usual bipolar disorder therapy for 52 weeks. The results of the 52-week s
compared to placebo, patients receiving IM risperidone as combination therapy were delayed to rea
which was the time to relapse to any new mood episode (depression, mania, hypomania, or mixed)
RISPERDAL(R) CONSTA(R) long acting injection, 2009).

2) Oral

a) The efficacy of risperidone as a combination therapy for the treatment of manic or mixed episode
disorder was established in one controlled trial, while a second controlled trial failed to show efficacy
combination trial, patients (n=148) on lithium or valproate therapy (therapeutic range, 0.6 to 1.4 mEq
respectively) with bipolar I disorder with or without psychotic features and with inadequately controlle
received risperidone (1 to 6 mg/day; mean modal dose, 3.8 mg/day), an active comparator, or place
original therapy. Combination therapy with adjunctive risperidone was more effective than lithium or
of the YMRS total score. However, in a second combination trial in 142 patients on lithium, valproate
inadequately controlled manic or mixed symptoms, the addition of risperidone (1 to 6 mg/day; mean
not superior to lithium, valproate, or carbamazepine (therapeutic range, 0.6 to 1.4 mEq/L, 50 to 125
respectively) alone in the reduction of the YMRS total score. The failure of this trial could be due to i
hydroxyrisperidone clearance by carbamazepine, leading to subtherapeutic levels of risperidone and
RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 20
oral solution, 2007).

b) Risperidone (median modal dose of 4 milligrams) may be more effective in the treatment of mani
bipolar disorder than placebo when combined with mood stabilizing drugs. Bipolar patients, aged 18
with a manic or mixed episode and a score of at least 20 on the Young Mania Rating Scale (YMRS)
double-blind, placebo-controlled study. To be eligible for this study the patient also had to be taking
divalproex or carbamazepine) for a minimum of 2 weeks prior to randomized assignment into treatm
measure was the change in YMRS score from baseline to endpoint. There was a decrease of 14.5 a
score for the risperidone and placebo groups, respectively, at the end of the 3 weeks (p=0.089). Ris
patients with or without psychotic features. When combined with carbamazepine, risperidone media
concentrations decreased by 40%. Due to a high number of dropouts in both groups the study was i
determine the true treatment effects. Additional studies are ongoing (Yatham et al, 2003).

c) Risperidone was associated with significantly greater improvement compared with placebo. A mu
group study investigated adding risperidone, haloperidol, or placebo to a mood stabilizer (lithium or
acute mania. After completing the 3 week, double-blind phase of the study, patients were offered op
an additional 10 weeks of follow-up. Improvement on the Young Mania Rating Scale and the Clinica
Improvement scale was greater with risperidone at 3 weeks. The investigators concluded that risper
addition to lithium or valproate for the treatment of bipolar mania (Ghaemi & Sachs, 1997).

d) An improvement was seen in all patients who completed another small, 6-week, open label study
(mean dose, 3 mg per day) and concurrent mood-stabilizing drugs in the treatment of acute psychot
enrolled and by week 6, all of the completers had a 50% improvement as assessed by the Young M
1996).

e) As an add-on therapy, risperidone brought significant improvement to patients with bipolar disorc

bipolar type. In a 6-month, open study, patients with a diagnosis of bipolar or schizoaffective disorde hypomanic, depressive, or mixed episode (n=541; 430 completed the study) were given risperidone anticonvulsants, and antidepressants to clinical response and tolerability. The average dose of rispe was 4 milligrams (mg) per day and at the end of the study, 3.9 mg/day. For all patients, scores on th (YMRS) were significantly reduced at week 1 and at every point thereafter (p less than 0.001 for all patients, for whom p was less than 0.05). Mean scores on the YMRS decreased from 25.6 at baseli scores on the Hamilton Rating Scale for Depression (HAM-D) were significantly reduced from baseli than 0.0001), with scores declining from 12.8 at baseline to 4.1 at 6 months. Scores on the Positive (PANSS) declined from 72 at baseline to 40 at 6 months (p less than 0.0001). According to the Clini (CGI), no patients were free from symptoms at baseline and only 5% were rated as "mildly ill." At st showed no symptoms of mania or depression and a further 30% were "mildly ill." During the study, 2 relapses into a mood state different from that at the start of the trial. Scores for extrapyramidal symp study than at baseline (p less than 0.0001). There were significant reductions in dystonia, rigidity, hy dyskinesia, tremor, and akathisia subscores. There were no cases of new-emergent tardive dyskine reactions included increase in weight (2.4% of patients), drowsiness (1.3%), impotence (0.7%), and very low incidence of exacerbation mania in the first 6 weeks (1.8%) (Vieta et al, 2001).

f) Long-term use of adjunctive risperidone for breakthrough episodes of mania or depression was re study. A group of outpatients (n=12) with bipolar disorder type I, who experienced breakthrough epis maintenance medication, were treated with a mean dose of 2.75 mg per day of risperidone. Scores Functioning scale improved from 10 to 25 points in 4 of the 8 patients who completed 6 months of tr worsening of mania (Sachs G, 1999).

g) In an open study, 10 patients with rapid cycling bipolar disorder (type I or type II) improved with r 1998). Patients were allowed to continue thyroid medications and benzodiazepines but had all antid discontinued. Risperidone was started at 1 milligram twice daily and titrated as needed. After 6 mon 5.5 affective episodes during the previous 6 months to 2 episodes while receiving risperidone (p less Rating Scale for Depression scores also decreased from 14 to 6.

h) Open studies using risperidone 1 to 6 milligrams as adjunct therapy in the treatment of refractory some efficacy. In one study, 9 out of 14 patients were rated as much improved on the Clinical Globa Among the other 5 patients, 3 stopped due to ataxia and dizziness or weight gain and 2 experienced al, 1997). In another study, 4 of 7 patients had a mild to moderate improvement on the CGI rating sc change after therapy (McIntyre et al, 1997). A controlled trial is needed to establish the benefits of ri

4) Pediatric:

a) Monotherapy

1) In a multicenter, randomized, double-blind, placebo-controlled trial, oral risperidone, at doses ranging day, was effective in the treatment of mania in children aged 10 to 17 years. Patients who were experien bipolar I disorder were randomized to receive either risperidone 0.5 to 2.5 mg/day (n=50; mean modal do mg/day (n=61; mean modal dose, 4.7 mg), or placebo (n=58) for 3 weeks. Risperidone was initiated at 0 target dose by day 7, with further increases to the maximum tolerated dose by day 10. Compared to plac groups showed a significant reduction from baseline in the total Young Mania Rating Scale (YMRS) scor seen in the 3 to 6 mg/day dose group were comparable to those seen in the 0.5 to 2.5 mg/day dose grou evident at doses higher than 2.5 mg/day. Adverse events reported at a higher incidence than placebo in fatigue (18%-30%), dizziness (13%-16%), dystonia (8%-13%), abdominal pain (15%-18%), nausea (13% somnolence (42%-56%), and abnormal vision (4%-7%) (Prod Info RISPERDAL(R) oral tablets, 2007; Pr orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007).

b) Combination Therapy

1) In a case series including 11 children and adolescents aged 5 to 16 years with difficult to manage mo bipolar disorder) and aggressive behavior, 8 had therapeutic responses to risperidone 0.75 to 2.5 milligra symptoms were clinically very diverse and most were taking concurrent medications, such as mood stab psychometric instruments were used for assessment, so improvement was purely subjective. Seven pati marked improvement and one patient was considered moderately improved. Side effects reported includ anxiety (Schreier, 1998).

4.5.G Borderline personality disorder

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Has reduced aggressive behavior and hostility in patients with borderline personality disorder

3) Adult:

a) Treatment with risperidone was associated with improvement in aggression, mood, and anergy in 13 patie disorder. In an 8-week open label study, patients were given risperidone, starting at 1 milligram (mg) per day basis to a maximum of 4 mg/day. The average final dose was 3.27 mg/day. Scores on the Brief Psychiatric R reduced by an average of 21% (p=0.003), with improvements specifically on the anergia scale (p=0.0033) an (p=0.0144). Depression was reduced (p=0.0025) and, according to the self-rated Aggression Questionnaire, by 18% (p=0.0057). Four patients experienced insomnia and 3 experienced agitation. Somnolence, anxiety,

reported by 2 patients (Rocca et al, 2002).

b) A 31-year-old woman with comorbid borderline personality disorder and dysthymia was successfully treat
(Szigethy & Schulz, 1997). She had been hospitalized 5 times and had failed therapy with fluoxetine, sertralir
perphenazine. She had been maintained on fluvoxamine but after an exacerbation of symptoms, risperidone
sustained improvement over the next 3 months. Risperidone was increased and a fluvoxamine taper was uns
resumption of fluvoxamine she was again able to return to her full-time job.

c) A 31-year-old woman was successfully treated with risperidone for her extreme impulsivity associated witl
personality disorder (Khouzam & Donnelly, 1997). After being refractory to multiple antipsychotics, antidepres
carbamazepine and valproate, she went into remission on risperidone 4 milligrams daily.

4.5.H Catatonia

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

One case report documents the successful use of risperidone for catatonia

3) Adult:

a) A 47-year-old man with persistent organic catatonia responded to risperidone 4 milligrams twice daily ther
with psychotherapy and pharmacologic therapy that included antidepressants, lithium carbonate, and various
1996).

4.5.I Cocaine dependence

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Risperidone is not effective in reducing cocaine use
Risperidone reduced craving and relapses in cocaine-dependent patients with schizophrenia

3) Adult:

a) Cocaine Dependence Only

1) There was no reduction in cocaine use associated with risperidone. A 12-week, randomized, double-l
evaluated using risperidone for the treatment of cocaine dependence. Cocaine-dependent subjects (n=1
or 8 mg of risperidone, with a subsequent change to active doses of 2 mg and 4 mg. Subjects attended t
provided urine samples, obtained medication, and underwent one behavioral therapy session per week.
interim analysis. Retention was worse for the 4 and 8 mg medication groups. Side effects were primarily
although neither the 2 nor 4 mg dose was well accepted by subjects. Risperidone is unlikely to find broa
cocaine dependence (Grabowski et al, 2000).

b) Schizophrenia With Concomitant Cocaine Dependence

1) The results of a pilot study suggest that risperidone therapy reduced craving and relapses in cocaine-
schizophrenia. In this 6-week, open label trial, patients with a dual diagnosis of schizophrenia and cocair
of cocaine/month) received risperidone (n=8; initial, 2 milligrams (mg)/day, titrated to maximum dose of 6
neuroleptic medication treatment (n=10; haloperidol, fluphenazine, or chlorpromazine). Patients in the ris
less cue reactivity in regard to the intensity (p=0.005) and depression (p=0.031) dimensions of craving a
therapy, but there was no statistical difference on the energy and feeling sick dimensions. Risperidone-tr
significantly lower rate of relapse (defined as any substance abuse) than did patients on typical neurolep
respectively; p=0.025). Although not significant, a tendency toward a greater reduction in negative and g
was seen in risperidone-treated patients. Larger, double-blind studies are needed to substantiate these f

4.5.J Cognitive function finding

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Risperidone-treated patients have shown some positive results in their neurocognitive abilities

3) Adult:

a) In a small randomized study (n=13), risperidone demonstrated an advantage over haloperidol for improvir
(Addington & Addington, 1997). Patients received either risperidone or haloperidol over a 6 week period. The
risperidone subjects on executive functioning (Wisconsin Card Sorting Test), on a measure of sustained atter
test), and on delayed verbal recall.

b) Risperidone therapy appeared to exert a more favorable effect on verbal working memory in treatment-res than did haloperidol therapy (Green et al, 1997a). In a randomized, double-blind comparison of treatment witl haloperidol (n=29), verbal working memory was measured at baseline and after 4 weeks of both a fixed dose Risperidone patients showed a significant improvement in memory using a Digit Span Distractibility Test from the fixed-dose (p less than 0.0001) and the flexible dose (p less than 0.0003) phases. The haloperidol-treated significantly. Results suggest that treatment of schizophrenia could be broadened to include the impact on ne
c) Risperidone improved neuropsychological impairment in withdrawn cocaine-dependent patients (Smelson patients received either risperidone 2 to 4 milligrams or no drug. Neuropsychological testing was done before group receiving risperidone showed improvement in the Digit Symbol test (p less than 0.01), the Trails Part A Grooved Peg Board dominant (p less than 0.003) and nondominant tests (p less than 0.06). No difference wa

4.5.K Delusional disorder

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Risperidone has been effective in the treatment of delusional disorder in case reports and open trials
Risperidone was effective treatment of monosymptomatic hypochondriacal psychosis

3) Adult:

a) Risperidone reduced most delusional parameters in a 50-year-old female with persecutory delusions (Fea treatment with sulpiride, 200 to 800 milligrams (mg) daily, produced side effects and resulted in patient noncc patient was originally part of a 24-week, double-blind, randomized, placebo-controlled, crossover trial (1 to 4 placebo) with 4 participants; all other participants dropped out of the study. A collaborative approach was use in the study. In this approach the delusions are not challenged from the outset. The certainty with which the p change, but these beliefs were qualitatively different; the persecution had happened in the past, but was not tools used were the Brief Psychiatric Rating Scale (BPRS), Positive and Negative Syndrome Scale (PANSS) of Delusions Schedule (MADS). During the placebo phase (weeks 0 to 11) there was no change in delusiona (weeks 12 to 24), the patient received 2 weeks of 1 mg risperidone, which was then titrated to 2 mg accordin trial crossover, MADS results indicated improvement in delusional condition had begun; substantial improvem risperidone treatment. The final trial dose was 2 mg of risperidone at night. By the end of the 24-week trial, ef marked reduction or absence of delusions, suspicions, anxiety, tension, and depression.
b) Risperidone eliminated or reduced delusions of theft in 17 of 18 patients treated for 12 weeks in an open- burden on the caretaker was evaluated for 16 of the responding patients. The mean daily risperidone dose fo milligrams. There were significant reductions in Neuropsychiatric Inventory (NPI) scores for delusion (p less t (p=0.002), anxiety (p=0.017), irritability/lability (p=0.023), and aberrant motor behavior (p=0.011) with risperid Zarit Caregiver Burden Interview (ZBI) dropped from 41 at the start of the study to 23 at 12 weeks (p less tha
c) An 81-year-old male presented with tactile hallucinations and DELUSIONS OF INFESTATION at which tir initiated and started gradually. The patient was asymptomatic 3 months later. After 9 months he returned with haloperidol that had been prescribed by another physician. Haloperidol was discontinued and low dose risper later his symptoms recurred and the risperidone dose was increased. At the time of publication he was sympt
d) A 23-year-old male presented with ocular complaints. He was suffering from continuous pain and the feeli down his face. Risperidone 2 milligrams per day was started and increased to 4 milligrams per day 3 days lat after 2 weeks and discharged at 4 weeks (Cetin et al, 1999).

4.5.L Dementia

See Drug Consult reference: BEHAVIORAL AND PSYCHOLOGICAL SYMPTOMS OF DEMENTIA

4.5.M Dementia - Psychotic disorder

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class III
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Reduces frequency and severity of delusions and agitation
Cerebrovascular adverse events (stroke, transient ischemic attack) have occurred in elderly individuals (received risperidone for treatment of dementia-related psychosis (Prod Info RISPERDAL(R), RISPERDA solution, orally disintegrating tablets, 2005)

3) Adult:

a) Low-dose risperidone was efficacious in the treatment of behavioral and psychological symptoms of deme 8-week study included 34 patients, ranging in age from 53 through 89 years (35% between 70 and 79 years; exhibiting dementia and at least one of the following symptoms: delusions, hallucinations, agitation/aggressio primary diagnosis of 59% of the patients was Alzheimer's type dementia. At baseline, the illness of 71% of pa "severe" or "very severe." By the end of the study, the mean dose of risperidone was 1.1 milligram (mg) per d

received 1 mg/day, 18% received 0.5 mg/day, and 32% more than 1 mg/day. Both frequency and severity of
were significantly reduced by week 8 (p=0.0002 and p=0.0033, respectively for the product of frequency and
was also significantly reduced (p=0.0452). Fifty-nine percent of patients were rated as "much" or "very much
some degree of improvement, according to the Clinical Global Impression of Change scale. Cognition was ur
The mean increase in the Extrapyramidal Symptom Rating Scale (ESRS) score was 0.8 (p less than 0.01). O
sedation, and vertigo occurred in a few patients. No patient withdrew because of extrapyramidal symptoms o
al, 2001).

b) Risperidone was effective and well-tolerated for the treatment of psychotic symptoms and behavioral distu
comorbid medical illnesses and medications (Zarate et al, 1997). In a review of medical records, 122 hospital
newly treated with risperidone were assessed. Patients received risperidone for agitation or psychosis associ
major mood disorder (29%), or other disorder (18%). Most were also medically ill and received other psychot
drugs (70%). Risperidone appeared to be effective in 85% of cases. In the demented group of patients with a
82% were rated as improved. Patients starting on low doses and undergoing slow dosage increases, were le
drug events (p=0.002). Risperidone was discontinued in 11% due to side effects and in 7% due to lack of effi

c) Two cases of patients with psychotic symptoms secondary to Lewy-Body dementia responsive to risperid
& Hussain, 1998; Geizer & Ancill, 1998). The first was a 59-year-old man with depressive illness, anxiety, agg
hallucinations, and hallucinations (Hussain & Hussain, 1998). He had some relief of symptoms with trifluoper
Risperidone 2 milligrams twice daily increased to 3 mg twice daily made the visual hallucinations disappear a
74-year-old male with visual hallucinations, persecutory delusions, and agitation. He was started on risperido
psychotic experiences. He then had donepezil added and within 2 weeks had complete resolution of psychos

4.5.N Depression, Refractory; Adjunct

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Improvement was demonstrated with risperidone compared with placebo augmentation of antidepressan
depression in a double-blind, 4-week, placebo-controlled, study (n=97); however, the treatment effect wa
(Keitner et al, 2009).

There were modest but statistically significant improvements in treatment-resistant depression with 6 we
to antidepressant drugs compared with placebo in a multicenter, double-blind, randomized trial in adults

Short-term benefit of risperidone augmentation in patients with treatment-resistant depression was not su
months) in a multinational, double-blind, placebo-controlled study (n=243) (Rapaport et al, 2006).

3) Adult:

a) General Information

1) Risperidone, as augmentation to antidepressant medication, has provided some benefit in the short-t
with treatment-resistant or difficult-to-treat depression (Mahmoud et al, 2007), (Keitner et al, 2009); howe
augmentation for 24 weeks failed to prevent relapse of depression (Rapaport et al, 2006). There were m
improvements with 6 weeks of risperidone augmentation compared with placebo in a multicenter, double
randomized trial (n=274) (Mahmoud et al, 2007). In another double-blind, 4-week, placebo-controlled, stu
demonstrated with risperidone compared with placebo augmentation diminished around 4 weeks (Keitne
augmentation did not prevent relapse in the long-term (9 months) in a multinational, double-blind, placeb
(Rapaport et al, 2006).

b) Clinical Trials

1) Improvement was demonstrated with risperidone compared with placebo augmentation of antidepres
depression in a double-blind, 4-week, placebo-controlled study (n=97); however, the treatment effect wa
Patients (n=147) with unipolar, nonpsychotic major depression were enrolled in an open-label treatment
monotherapy for 5 weeks if they were currently not on antidepressant drugs, if they were not currently re
an adequate dose and duration, or if they had poorly documented antidepressant therapy. At the end of t
responders and non-responders with a Montgomery-Asberg Depression Rating Scale (MADRS) rating of
double-blind, randomized phase (n=43). Additionally, patients (n=54) with well documented failure of cur
adequate dose and duration were enrolled in the double-blind phase directly, without going through the o
bipolar I, bipolar II, or psychotic features were among those excluded. During the double-blind phase, pa
dose of their antidepressant drug and were randomized to additionally receive either risperidone (n=62) o
Risperidone was initiated at 0.5 milligrams (mg) per day, and the dose was increased, if necessary, to 2
thereafter (mean dose at end of 4 weeks, 1.6 mg/day). Based on Clinical Global Impression (CGI) scores
moderately ill at baseline (risperidone, 68.8%; placebo, 69.7%) and mean baseline MADRS scores were
the risperidone and placebo groups, respectively. In the modified intent-to-treat population (received at le
competed at least 1 set of assessments), the primary outcome of remission (MADRS rating of 10 or less)
(n=32/62) and 24.2% (n=8/33) of patients in the risperidone- and placebo-treated groups, respectively, a
The corresponding rates of remission for those who completed all 4 weeks of treatment (n=82) were 52.
(p=0.052). Treatment difference was evident after 2 weeks, with remission rates of 37.3% and 15.6% in t
groups, respectively. Notably, while both treatments demonstrated improvement over time, the difference
significant at week 4. The odds ratio for remission with risperidone compared with placebo was 3.33 (95
Among other outcomes, rates of response (50% decrease from baseline MADRS rating) at 4 weeks were

risperidone and placebo groups, respectively (p=0.049), with significant differences seen after 1 week of respectively; p=0.031). When remission and response were evaluated on the Hamilton Depression Scale between risperidone and placebo were not statistically significant. Patient ratings of overall life satisfactio significantly better in the risperidone group compared with the placebo group (from 1.3 to 2.5 and 1.2 to differences apparent by 2 weeks of treatment. The overall frequency of side effects was similar in the risp (81.8%) groups (Keitner et al, 2009).

2) There were modest but statistically significant improvements in treatment-resistant depression with 6 augmentation to antidepressant drugs compared with placebo in a multicenter, double-blind, randomized label, 4-week, run-in period identified 274 patients (age range, 18 to 65 years) with unremitting major dep Impression-Severity of Illness (CGI-S) score of 4 or more, and a Carroll Depression Scale score of 20 or antidepressant monotherapy at the recommended dosage. These patients were then randomized to 6 w with either oral risperidone (n=141) or placebo (n=133). The risperidone dose was 0.25 milligrams (mg) e every day for days 4 to 15, followed by 1 mg every day for days 16 to 28. At the investigator's determinat day 29, risperidone was either continued at 1 mg/day or the dose was increased to 2 mg/day, or double- At the start of randomization, the mean time since diagnosis of depression was 16.7 +/- 12.3 years, and Depression 17-item (HRSD-17) scores for the risperidone- and placebo-treated patients were 24.3 and 2 patients continued on their baseline antidepressant regimen, which consisted of a selective serotonin reu group, 59.1%; placebo group, 59.5%), a serotonin-norepinephrine reuptake inhibitor (22.6% and 19.8%, such as bupropion and trazodone (17.6% and 19.9%, respectively). The primary outcome was the chang HRSD-17 total score; response was defined as a 50% or more reduction in score and remission was def The final risperidone dose was 1 mg for 65.7% and 59.5% of risperidone- and placebo-treated patients, r primary outcome are listed in the table below (Mahmoud et al, 2007).

Outcome	Risperidone	Placebo	Difference (95% CI)
Mean (+/- SE) HRSD-17			
Week 4*	15.4 +/- 0.52	17.3 +/- 0.52	-1.9 +/- 0.69 (95% CI, -3.3 t
Week 6**	13.4 +/- 0.54	16.2 +/- 0.53	-2.8 +/- 0.72 (95% CI, -4.2 t
Remission Rates			
Week 4*	13.6%	6%	--
Week 6**	24.5%	10.7%	--
Response Rates			
Week 4*	35.6%	18.8%	--
Week 6**	46.2%	29.5%	--

KEY: SE = standard error; CI = confidence interval; HRSD-17 = Hamilton Rating Scale for Depress
*risperidone: n=118; placebo: n=117
** risperidone: n=106; placebo: n=112.

Secondary outcomes, which included clinician-rated measures (measured by CGI-S) and patient-rat Quality of Life Enjoyment and Satisfaction Questionnaire, Patient Global Improvement Scale, Sheeh significantly more with risperidone compared with placebo at week 6. The number needed to treat w augmentation to achieve 50% baseline symptom improvement in treatment-resistant depression wa tolerated, with premature study discontinuation due to adverse effects occurring in 5.8% of risperido placebo-treated patients. Frequency of motor events was similar between the risperidone and place 0%, respectively; dystonia, 0% and 0.8%; tremor, 0.7% and 0.8%) and did not require use of benztr

3) Short-term benefit of risperidone augmentation in patients with treatment-resistant depression was nc months) in a multinational, double-blind, placebo-controlled study (n=243). The study design consisted o weeks of open-label citalopram monotherapy (initial dose, 20 milligrams (mg); target dose range, 40 mg label risperidone augmentation, and a 24-week double-blind, placebo-controlled continuation of the rispe enrolled in the open-label citalopram monotherapy phase had major depressive disorder, single or recur psychotic features, a score of 20 or more on the Hamilton Rating Scale for Depression (HAMD-17), and to respond to at least 1 but not more than 3 antidepressant trials of at least 6 weeks' duration at the labe failed to respond (less than 50% reduction in HAMD-17 total score) after 6 weeks or were unchanged or citalopram were augmented with open-label, oral risperidone (n=390). For patients aged 18 to 54 years, mg/day and increased up to 2 mg/day (goal, 1 mg/day); patients aged 55 to 85 years old received 0.25 n increases permitted up to 1 mg/day (goal, 0.5 mg/day). Patients achieving a HAMD-17 score of 7 or less (CGI)-Severity score of 1 or 2 during the risperidone augmentation (n=243, 63% of the open-label risperi randomized to receive either placebo (n=120; mean age, 48.4 years) or to continue on risperidone (n=12 weeks. Time to relapse, the primary outcome, was defined as 1 or more of the following: 6 (much worse) CGI-Change score, 16 or higher on the HAMD-17 score, lack of efficacy leading to discontinuation, or int ideation. There were more women than men in the double-blind continuation phase (71.3% vs 56.3%). T risperidone and placebo groups at baseline was 17.9 +/- 12.3 years and 17.6 +/- 13.9 years, respectively double-blind phase, 63.1% were complete non-responders (less than 25% reduction in HAMD-17 score) responders (25% to 49% reduction in HAMD-17) to open-label citalopram. Based on Kaplan-Meier analy was 102 days and 85 days (p=0.52) for the risperidone augmentation group and placebo augmentation g

rates of 53.3% and 54.6%, respectively. The HAMD-17 baseline scores worsened by 7.6 +/- 8.8 points fr
blind phase) score of 6 +/- 3 in the risperidone group and by 7.9 +/- 8.1 points from a baseline score of 6
(for both, p less than 0.001 compared with baseline). The Montgomery-Asberg Depression Rating Scale
12.6 points from a baseline score of 6.8 +/- 4.7 in the risperidone group and 10.4 +/- 11.2 points from a b
both, p less than 0.001 compared with baseline) in the placebo group. The mean prolactin concentration
nanograms/milliliters (ng/mL) and 6.6 +/- 21 ng/mL (p less than 0.001) in the risperidone and placebo gro
occurred in 2.5% and 0%, respectively. During the double-blind phase, the mean weight increase was 1.
risperidone group compared with a mean loss of 0.5 +/- 2.9 kg in the placebo group (Rapaport et al, 200
4) Adjunctive risperidone therapy was effective in the treatment of nonpsychotic depressive disorders in
a case series, five female patients (ages 48 to 61 years) with treatment-resistant depression and suicida
(maximum dose, 1 milligram/day) in addition to their current antidepressant medication for at least 5 mor
Impressions-Severity of illness scores were reported as "markedly ill" or "among the most extremely ill" a
adjunctive therapy, all patients were rated as "very much improved" on the Clinical Global Impressions-Ir
patients did not report further suicidal ideation. Risperidone was well tolerated. Larger, controlled studies
these findings (Viner et al, 2003).
5) Eight cases were described of risperidone therapy augmenting selective serotonin reuptake inhibitor
major depressive episodes without psychotic features (Ostroff & Nelson, 1999). All patients had incomple
therapy with Hamilton Rating Scale for Depression (HAM-D) scores of 16 to 27. Risperidone 0.5 to 1 mill
and HAM-D scores decreased to a range of 0 to 6 within 1 to 7 days.

4.5.O Drug-induced psychosis - Levodopa adverse reaction

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Effective for levodopa-induced psychotic symptoms

3) Adult:

a) In an open-label trial in 10 patients, low dose risperidone was useful for levodopa-induced psychotic symp
with advanced Parkinson's disease and cognitive decline (Meco et al, 1997b). Nine patients improved signific
Rating Scale and the Hallucinosis Questionnaire after 2 weeks and peaked after 6 weeks (p less than 0.01).
risperidone due to worsening Parkinson's disease.
b) In a 26 week-trial, 23 of 39 parkinsonism patients treated with risperidone demonstrated complete or near
hallucinations and delusions and an approximately 50% to 75% reduction was seen in another 4 patients. Six
improvement and an additional 6 had rapid and pronounced deterioration of parkinsonism which required risp
mean dose of risperidone was 1.10 milligrams (mg) with a mean duration of treatment of 16.2 weeks. Sixteen
trial (Leopold, 2000). Similar results were found in a 12-week open pilot study involving 17 patients receiving
day (Mohr et al, 2000).

4.5.P Gilles de la Tourette's syndrome

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy; Pediatric, Evidence favors efficacy
Recommendation: Adult, Class IIa; Pediatric, Class IIb
Strength of Evidence: Adult, Category B; Pediatric, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

May be an effective alternative for treatment of Tourette's syndrome

3) Adult:

a) Risperidone was effective in treating patients with Tourette's Syndrome (TS). In a randomized, double-blir
patients with moderate to severe TS received either risperidone 0.5 to 6 milligrams/day or placebo for 8 week
0.25 mg once daily and increased to 0.5 mg twice daily. Thereafter, the dose could be altered for an individua
exceed 6 mg/day. Sixty-one percent of patients in the risperidone group and 26% in the placebo group impro
Tourette's Syndrome Severity Scale (TSSS) by 8 weeks (p=0.04). The severity of disease at baseline did not
risperidone group also showed significantly greater improvement in functioning than did the placebo group (p
occurring in patients with greater impairment in functioning at baseline. Patients treated with risperidone shov
parkinsonism than did patients treated with placebo (p=0.004. An increase in parkinsonism occurred only in p
average parkinsonism at baseline. Risperidone caused a greater incidence of fatigue than did placebo (57%
(35% vs 4%, p=0.02). Depression also occurred more frequently with risperidone, resulting in discontinuation
group (Dion et al, 2001).
b) Risperidone treatment resulted in improvement in the severity of Tourette's syndrome tics in an open trial
1996). All subjects (age range 8 to 53 years) had been treated with clonidine and neuroleptics and had exper
unacceptable side effects. The mean risperidone dose was 2.7 milligrams/day (range 0.5 to 9 mg/d). Twenty-
took neuroleptics during the study period. Eight patients dropped out because of side effects; of the original 3
experienced improvement. Reported side effects included sedation (18% of patients), akathisia/agitation (10%
weakness, insomnia, depression, anxiety, and aggressive behavior (3% each). Risperidone dose, other medi

diagnoses did not significantly affect response, and there was no correlation between those factors and the ty

4) Pediatric:

a) Tourette syndrome patients demonstrated a reduction in aggression in 78.5% of 28 patients and a decrea of tics in 61.7% of 28 patients. The average daily dose of risperidone was 2 milligrams daily. The tics and agg at baseline and 2 weeks to 4 months later (average 2 months) (Sandor & Stephens, 2000).

4.5.Q Huntington's disease

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Effective for the involuntary movements per case reports

3) Adult:

a) Four patients with involuntary movements secondary to Huntington Chorea (and no psychotic symptoms) therapy (Dallocchio et al, 1999). Patients received an initial dose of risperidone 1 milligram (mg) every 8 hour were increased in 0.5-mg increments per day to 3 mg every 8 hours. There was no significant improvement s higher doses produced a significant reduction in choreic disturbances as seen on the Marsden and Quinn Sc Symptoms worsened again as the patients were withdrawn from risperidone. Another patient with genetically but only with psychosis and no movement disorder also received risperidone 3 mg/day. Her psychiatric condi any side effects.

4.5.R Inhalant abuse

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Risperidone was effective in the treatment of inhalant abuse

3) Adult:

a) A 25-year-old male had a 5-year history of inhalant (gasoline and carburetor cleaning fluid) abuse. Risperi daily was started which effectively reduced hallucinations and paranoia and eliminated aggressive behavior c After an increase to 1 mg twice daily paranoid thoughts ceased and craving for inhalants was reduced. He ha follow-up (Misra et al, 1999).

4.5.S Obsessive-compulsive disorder, Refractory

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Adjunctive therapy may be effective for obsessive-compulsive disorder refractory to serotonin reuptake i 2008; McDougle et al, 2000; Agid & Lerer, 1999; Stein et al, 1997; Saxena et al, 1996).

3) Adult:

a) Adjunctive therapy of risperidone or olanzapine with serotonin-reuptake inhibitors (SRI) were equally effec compulsive symptoms in SRI monotherapy-resistant outpatients, according to an 8-week, single-blind, rando conclusion may be limited by the lack of a placebo arm, single-arm design, and underpowered nature of the t prospective, open-label phase of SRI monotherapy (n=96), patients who were treatment-resistant (defined as the total score of Yale-Brown Obsessive Compulsive Scale (Y-BOCS) and a Clinical Global Impression Seve entered an 8-week single-blind phase (n=50). Patients in the single-blind phase received SRI daily doses of c citalopram 50 to 80 mg, fluoxetine 60 mg, fluvoxamine 200 to 300 mg, paroxetine 50 to 60 mg, or sertraline 2 receive either risperidone 1 to 3 mg/day (n=25), or olanzapine 2.5 to 10 mg/day (n=25) in addition to the SRI personnel and assessor-blinding constituted the single-blind study design; patients were not blinded. In an int carried forward analysis of the primary endpoints, both treatments significantly improved Y-BOCS and CGI-S The magnitude of change in mean Y-BOCS total scores, CGI-S scores, and responder rates (35% or greater versus baseline, and a CGI-I score of 2 or less) was similar between groups.

Primary Efficacy Endpoints at 8 Weeks		
	Risperidone (n=25)	Olanzapine (n=25)

Responder rates*	44% (11/25)	48% (12/25)
Mean end-point Y-BOCS score	22.6 +/- 7.2	22.2 +/- 7.4
Change in mean Y-BOCS score from baseline	-7.5; p less than 0.001	-8.4; p less than 0.0
Mean end-point CGI-S score	3.2 +/- 1.7	3.1 +/- 1.8
Change in mean CGI-S score from baseline	-1.7; p less than 0.001	-1.9; p less than 0.0
* p=1; Y-BOCS=Yale-Brown Obsessive Compulsive Scale; CGI-S=Clinical Global Impression Severity s		

b) Adverse effects of risperidone compared with olanzapine-treated patients included tension/inner unrest (2 (16% vs 52%, p=0.016), and amenorrhea (66.7% vs 10%, p=0.02), respectively. The small sample size and t calculation may have contributed to the limitations of this study (Maina et al, 2008).
c) Obsessive compulsive disorder (OCD) patients with and without comorbid chronic tic disorders or schizoty respond to the addition of low-dose risperidone to ongoing serotonin reuptake inhibitor (SRI) therapy. A doub was designed to determine the short-term efficacy and tolerability of potent SRIs in combination with risperid refractory to SRIs alone. Seventy adult patients with a primary diagnosis of OCD received 12 weeks of treatm patients were refractory to 6 weeks of risperidone (n=20) or placebo (n=16) addition. Behavioral ratings, inclu Compulsive Scale, were obtained at baseline and throughout the trial. Placebo-treated patients subsequently trial of risperidone addition. For study completers, 9 (50%) of 18 risperidone-treated patients were responder mg per day) compared to 0 of 15 in the placebo addition (p less than 0.005). Seven (50%) of 14 patients who addition responded. Risperidone addition was superior to placebo in reducing OCD (p less than 0.001), depre anxiety (p=0.003) symptoms. Other than mild, transient sedation, risperidone was well tolerated (McDougle e
d) Risperidone (initial dose of 2 milligrams/day) was effective in a 24-year-old patient with methamphetamine compulsive disorder-like symptoms (Iyo et al, 1999).
e) Fourteen of 16 patients with obsessive-compulsive disorder had substantial reductions in obsessive-comp within 3 weeks of initiating risperidone. Result were usually seen within the first few days. Before the addition received a serotonin reuptake inhibitor (SRI) for at least 12 weeks either alone or in combination with mood s anxiolytics. In addition to the OCD, patients had horrific mental imagery, comorbid schizophrenia, schizoaffec disorder (Saxena et al, 1996).
f) In a case series, 3 of 8 patients with obsessive- compulsive disorder (DSM-IV criteria) showed significant i Global Impression Change Scale after receiving augmentation with risperidone 1 to 2 milligrams/day. Of the noted minimal to much improvement, 3 patients had no change in symptoms and 1 patient was unable to tole 1997).
g) A 25-year-old man with obsessive compulsive disorder refractory to multiple medications improved with ri paroxetine (Agid & Lerer, 1999). Risperidone 1.5 milligrams (mg)/day was added to paroxetine 60 mg/day. Hi Obsessive Compulsive Scale for obsessions went from 14 to 4 and for compulsions went from 20 to 2. After The depressed symptoms responded to a decreased dose of risperidone of 0.5 mg/day.

4.5.T Organic psychotic condition

1) Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category C
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:
Has reduced symptoms of psychosis caused by medical conditions

3) Adult:
a) A case series reports the successful use of risperidone in five patients who fulfilled DSM-IV criteria for psy condition and two who met the criteria for mood disorder due to a general medical condition with severe psyc 1997). All seven responded to treatment including four patients who had previously failed initial treatment wit antipsychotic agent.
b) In a case series of 21 patients with HIV-related psychotic disorders, 20 patients treated with risperidone h (Singh et al, 1997). Most responded to low doses (mean 3.3 milligrams) and required only a short course (me adverse effects were reported and no hematological effects were observed.

4.5.U Parkinson's disease - Psychotic disorder

See Drug Consult reference: THERAPY OF PSYCHOTIC DISTURBANCES IN PARKINSONIAN PATIENTS

4.5.V Pervasive developmental disorder

1) Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive; Pediatric, Evidence favors efficacy
Recommendation: Adult, Class IIb; Pediatric, Class IIb
Strength of Evidence: Adult, Category B; Pediatric, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Effective for the treatment of symptoms related to pervasive developmental disorders and autism in adul
In children with autism spectrum disorder, responders to 24 weeks of open-label therapy with oral risperi
rates when randomized to continue additional 8 weeks of double-blind treatment with risperidone versus
Treatment with oral risperidone relieved several behavioral symptoms associated with pervasive develop
to 12 years in an 8-week, multicenter, randomized, double-blind, placebo-controlled study (n=79) (Shea

3) Adult:

a) Risperidone therapy was effective in 3 autistic disorder patients. All 3 patients tolerated risperidone well a
effects. Effective doses in each patient were 5 milligrams daily, 4 milligrams daily, and 1 milligram daily, resp
2 of the patients and both showed no increase in seizure frequency. Improved social relations and reduced a
observed in all patients and decreased repetitive behavior in 1 patient (McCartney et al, 1999).

b) In a double-blind, placebo controlled trial including adults with autistic disorder (n=17) or pervasive develo
patients treated with risperidone (mean dose 2.9 milligrams per day) were considered responsive to therapy
recipients (p less than 0.002). At the end of the 12 week trial, patients initially randomized to placebo were tre
During open-label treatment, 60% of patients were considered responders. Repetitive behaviors were evalua
the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) and aggression was evaluated with the Self-injurious
Q). The Clinical Global Impression (CGI) Scale and the Rivto-Freeman Real-life Rating Scale were also used
the CGI, Y-BOCS, SIB-Q, and overall Rivto-Freeman Scale were significantly improved with risperidone com
0.05 for all analyses). Improvements became evident at 4 weeks and continued throughout the 12-week stud
effect was transient sedation. Other than one patient who developed gait abnormalities, extrapyramidal side e
(McDougle et al, 1998).

4) Pediatric:

a) In a double-blind extension phase, continued treatment with risperidone was more effective than placebo
spectrum disorder symptoms among responders to 24 weeks of open-label risperidone therapy. Children age
the DSM-IV (Third Revision) criteria for a pervasive development disorder (PDD) and who demonstrated clini
aggression, self-injurious behavior, or a combination of these problems were enrolled in the open-label phase
children weighing under 45 kilograms (kg), risperidone was initiated at 0.5 milligrams (mg) at bedtime, increas
later, and subsequently increased in 0.5-mg increments to a maximum dose of 2.5 mg/day by day 29. Doses
mg/day by day 29 in children weighing more than 45 kg. Patients with an at least 25% reduction from the bas
(ABC) Irritability score (baseline mean score, 23) and a rating of much improved or very much improved on th
(CGI) of Severity scale after 8 weeks were classified as responders (26/36) and allowed to continue taking ris
At 24 weeks of open-label treatment, 69% (18/26) of patients were rated as much improved or very much imp
Change (CGI-SC) scale, with significant decreases in ABC Irritability subscores as well; most improvements
Completers of the additional 16 weeks of therapy were randomized in a double-blind fashion to either continu
placebo (gradual withdrawal for 3 weeks and placebo only for 5 weeks; n=12) for 8 weeks. Relapse was defir
Symptom Change (CGI-SC) scores of much worse or very much worse for at least 2 consecutive weeks and
the last ABC Irritability score. An intention-to-treat analysis revealed relapses (primary endpoint) in 3 and 8 pa
placebo groups, respectively (p=0.049), with a longer mean time to relapse in patients maintained on risperid
Compared to mean +/- standard deviation (SD) ABC Irritability subscale scores of 11.1 +/- 8.1 and 12.7 +/- 7.
groups, respectively, at week 24, scores at the end of the study (week 32) were 12.6 +/- 9.8 (14% increase) a
p=0.043), respectively. Improvements noted at week 24 among other ABC subscales, such as social withdra
inappropriate speech, were fairly well maintained until the end of the study in the risperidone, there were no s
between the groups at study end. Treatment-emergent adverse events were mild to moderate and included i
(39%), fatigue (35%), and increased thirst (26%). At week 24, the mean weight gain from baseline was 5.7 +/
less than 0.0001). It should be noted that the majority (75%; n=18/24) of the study population had a form of P
and 63% (n=15/24) had average or above-average intelligence (Troost et al, 2005).

In an 8-week, multicenter, randomized, double-blind, placebo-controlled study (n=79) in children, treatme
several behavioral symptoms associated with pervasive development disorder (PDD). Pediatric outpatie
age, 7.5 years; greater than 75% male) with a DSM-IV Axis I diagnosis of PDD and a total score of 30 or
Rating Scale (CARS), with or without mental retardation were randomized to receive either an oral soluti
placebo (n=39) in 1 or 2 divided doses for 8 weeks. Risperidone was initiated at 0.01 milligram/kilogram/
0.02 mg/kg/day on day 3. At day 8, the dose was further increased at a maximal increment of 0.02 mg/kg
increments or decrements were allowed up to a maximum daily dose of 0.06 mg/kg/day. Using the Aberr
efficacy was primarily assessed for change in irritability from baseline to endpoint on the irritability subsc
assessments included scores on the other 4 ABC subscales (hyperactivity/noncompliance, inappropriate
withdrawal, and stereotypic behavior), the parent-rated Nisonger Child Behavior Rating Form (N-CBRF),
Impression-Change (CGI-C; 7-point scale ranging from very much improved to very much worse). At bas
most common form of PDD (risperidone, 67.5%; placebo, 71.8%), and 57.5% and 53.8% of patients in th
groups, respectively, were diagnosed with severe autism. At endpoint, patients in the risperidone group h
daily dose was 0.05 mg/kg/day (mean daily dose, 1.48 mg) for a mean duration of 52.7 days (range, 2 to
analysis (included all patients receiving at least 1 study dose and with at least 1 postbaseline assessmer
decreases from baseline irritability scores in the risperidone group (64% improvement) compared to plac
Based on CGI-C scores, global improvements occurred in 87.2% and 39.5% of risperidone- and placebo
with 54% and 18% of patients, respectively, reporting a rating of much improved or very much improved
there was a greater decrease in the Visual Analog Scale score of aggression (most frequently reported t
the risperidone-treated patients compared to placebo (mean score decrease, 38.4 vs 26.2, respectively;
Results of the primary and key secondary endpoints are listed in the table below. Treatment-emergent a
severity, with somnolence (72.5% vs 7.7%), upper respiratory tract infection (37.5% vs 15.4%), rhinitis (2

appetite (22.5% vs 10.3%) being the most commonly reported among risperidone-treated patients (Shea

Efficacy measure	Risperidone (n=39)		Placebo (n=38)
	Baseline	Endpoint (change from baseline)	Baseline
ABC subscale (mean +/- SD)			
Irritability	18.9 +/- 8.8	-12.1 +/- 5.8*	21.2 +/- 9.7
Hyperactivity/noncompliance	27.3 +/- 9.7	-14.9 +/- 6.7*	30.9 +/- 8.8
Inappropriate speech	4.6 +/- 3.4	-2.6 +/- 2.6**	4.8 +/- 3.7
Lethargy/social withdrawal	13.7 +/- 7	-8.6 +/- 5.9***	14.3 +/- 8.2
Stereotypic behavior	7.9 +/- 5	-4.3 +/- 3.8**	8.1 +/- 5.6
N-CBRF (parent version) subscale (mean +/- SD)			
Conduct problem	16.8 +/- 9.4	-10.4 +/- 7.4*	23.3 +/- 12
Hyperactive	17.2 +/- 5.8	-8.1 +/- 4.6**	18.9 +/- 5.3
Self-Isolated/ritualistic	7.5 +/- 4.1	-4.8 +/- 3.9	8.2 +/- 4.5
Insecure/anxious	8.7 +/- 8.1	-4.6 +/- 6.5**	10.6 +/- 7.6
Overly sensitive	6.9 +/- 3.4	-3.8 +/- 2.8**	7.4 +/- 3.5
Self-injurious/sterotypic	4.2 +/- 4.2	-2.6 +/-3.3	3.5 +/- 4.2

Key: n=number of subjects; ABC=Aberrant Behavior Checklist ; N-CBRF=Nisonger Child Behavior Rati
deviation
*p less than or equal to 0.001 vs placebo
**p less than or equal to 0.05 vs placebo
***p less than or equal to 0.01 vs placebo

b) Risperidone improved functionality on the Children's Global Assessment Scale in 13 out of 14 cases in an adolescents (ages 9 to 17 years) treated for pervasive developmental disorders. Starting doses of 0.25 milligi increased in 0.25 mg/day increments every 5 to 7 days to optimal doses ranging from 0.75 to 1.5 mg daily in occurred in attention, lessening of obsessional behaviors, decrease in agitation and anxiety and improvemen Steele, 1996).

c) Behavioral symptoms improved in a series of 6 children (ages 7 to 15) with pervasive developmental diso treatment for 5 months (range 1-8 months) at a mean optimal dose of 2.7 milligrams (mg) daily (range 1 to 6 patient rating scores decreased, which reflected improvements in aggression, temper tantrums, and mood ins followed for more than 2 years, of whom one discontinued risperidone due to increased liver enzymes; one p new agent, and the third patient continued risperidone with good response (Perry et al, 1997)

4.5.W Pick's disease

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Effective in one case report

3) Adult:

a) A 42-year-old woman with a presumptive diagnosis of Picks Disease was treated with risperidone (titrated demonstrated significant improvements and cognitive stabilization. The author suggested that controlled trials antipsychotics in treating Picks Disease need to be performed and might produce promising results (Curtis &

4.5.X Posttraumatic stress disorder

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Possibly effective in treating patients with irritable aggression in posttraumatic stress disorder
Possibly effective in treating intrusive thoughts associated with posttraumatic stress disorder

3) Adult:

a) Risperidone was effective in a 48-year-old male war veteran demonstrating increased irritability and anger stress disorder. Fluoxetine and diazepam were ineffective. With the addition of risperidone 1 milligram daily t reported less intensity in his anger and more confidence in his ability not to act on it (Monnelly & Ciraulo, 199
b) Two patients with posttraumatic stress disorder responded favorably to risperidone 6 milligrams daily and Other agents were ineffective (Krashin & Oates, 1999).

4.5.Y Schizophrenia

FDA Labeled Indication

1) Overview

FDA Approval: Adult, yes (oral and intramuscular); Pediatric, yes (13 years and older, oral only)
Efficacy: Adult, Effective; Pediatric, Evidence favors efficacy
Recommendation: Adult, Class IIa; Pediatric, Class IIb
Strength of Evidence: Adult, Category B; Pediatric, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Risperidone is indicated for the treatment of schizophrenia in adults (Prod Info RISPERDAL(R) CONSTA Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating table (R) oral solution, 2007)and pediatric patients 13 years of age and older (Prod Info RISPERDAL(R) oral ta RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007) Approved for maintenance treatment of schizophrenia in adults (Prod Info RISPERDAL(R) oral tablets, 2 M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007; Prod Info RISPE acting injection, 2009)
Oral risperidone, at doses ranging from 1 to 6 milligrams per day, was effective in the treatment of schizo to 17 years in 2 short-term (6 and 8 weeks), double-blind, controlled trials (Prod Info RISPERDAL(R) ora RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007)

3) Adult:

a) General Information

1) Risperidone is effective for the positive and negative symptoms associated with chronic schizophreni 75% (Foster & Goa, 1998b; Rossi et al, 1997a; Smith et al, 1996a). Dose ranges of risperidone 4 to 16 m greater improvement than placebo in Clinical Global Impression (CGI) and total Positive and Negative Sy The 4 to 6 milligram dose appears to be the most effective (Marder & Meibach, 1994a; Chouinard et al, 1 Spahn, 1992a). At doses of 8 milligrams or less risperidone is associated with a lower risk of extrapyram antipsychotics (Foster & Goa, 1998b). Comparative efficacy with haloperidol and other conventional neu risperidone has a significantly higher clinical response rate and allows for significantly less prescribing of (Davies et al, 1998)(Bech et al, 1998a; Luebbe, 1996a). Patients treated with risperidone have a lower re with haloperidol (Csernansky et al, 2002a). Patients have also been successfully switched from depot an et al, 1999).

b) Monotherapy

1) Intramuscular

a) Long-acting injectable risperidone was significantly more effective than placebo in the treatment a randomized, double-blind, placebo-controlled, multicenter study, patients (n=400) with schizophre injections of long-acting risperidone (25 milligrams (mg), 50 mg, or 75 mg) or placebo every two wee week run-in period, patients received oral risperidone (titrated to a dose of 4 mg/day) for at least 3 d risperidone (2 mg/day, 4 mg/day, or 6 mg/day) or placebo for the first three weeks of the double-blin Positive and Negative Syndrome Scale (PANSS) total scores were significantly more improved in pa risperidone 25 mg, 50 mg, or 75 mg as compared with those who received placebo (p=0.002, p less respectively). Improvements in positive and negative symptoms were also significantly greater in all groups as compared with the placebo group (p less then or equal to 0.05, all values). Clinical improv 20% reduction in PANSS total scores and was observed in only 17% of placebo patients as compar patients in the 25 mg, 50 mg and 75 mg long-acting risperidone groups, respectively (p less then 0.0 long-acting risperidone was efficacious, it offered no additional benefit over the 25 mg and 50 mg do well tolerated and extrapyramidal adverse events were mild throughout the study period. Small incre baseline to endpoint were observed in risperidone-treated patients and these changes appeared to 2003).

2) Oral

a) Olanzapine and risperidone were equally safe and effective therapies in the treatment of schizop international, multicenter, double-blind study, 175 elderly patients (mean age, 71 years) were rando risperidone (mean dose, 1.9 milligrams (mg)/day) or olanzapine (mean dose, 11.1 mg/day) for 8 wee period of all psychotropic medications. Mean duration of illness was 36.5 years and Positive and Ne scores were between 50 and 120 at baseline. Clinical improvement was defined as a decrease of at score. Both treatment groups showed significant reductions from baseline in the total PANSS score 0.005) and significant differences were not observed between groups. Fifty-eight percent of risperido olanzapine-treated patients achieved clinical improvement as defined by the study. Both groups also improvement in four of the five PANSS factor scores (p less than 0.001). The greatest mean change occurred in the 93 patients who had received conventional antipsychotic medications in the thirty da less than 0.001). The rate of extrapyramidal symptoms (EPS) was similar between the risperidone a (9.2% vs 15.9%, respectively, p=nonsignificant). The severity of EPS symptoms was reduced in both endpoint with no significant difference between groups. A 7% or higher increase in weight occurred

treated patients as compared with those who received risperidone (14.8% vs 5.1%, p=0.043). No ne
observed in this patient population and mean QTc changes were not considered clinically relevant (
b) Risperidone treatment resulted in mild to substantial improvement in psychotic symptoms in appr
elderly Chinese patients (age 65 years or greater) participating in an open, 4-week study. Doses of r
basis of clinical responses and adverse effects and ranged from 0.25 to 7 milligrams (mg) per day (r
dose for functional psychoses was greater than that for organic mental disorders (2.8 mg/day vs 1.6
schizophrenia received the highest mean dose (4.1 mg/day). With improvement defined as a reducti
scores on various rating instruments, improvement occurred in 61% to 78% of patients. Patients witl
better than Alzheimer's patients. Of the 110 patients, 81 had one or more adverse effects. Weaknes
dizziness, and peripheral edema were the most common side effects (Hwang et al, 2001a).
c) Risperidone is beneficial in the treatment of patients with chronic schizophrenia, compared with c
and these benefits may appear only after longer-term treatment. A randomized, open, parallel, multi
term (12 months) effectiveness of risperidone with that of CNs. One hundred eighty-four subjects we
risperidone or CN and 165 of them completed the follow-up. Outcome measures were taken at 3, 6,
the Positive and Negative Syndrome Scale (PANSS) and the Extrapyramidal Symptom Rating Scale
risperidone was found to be superior to CNs in terms of both the average change in score from base
and the proportion of good responders (as defined by a 20% decrease in total PANSS scores; p=0.0
effectiveness of the risperidone treatment tended to increase over time and at 12 months, the perce
risperidone group was twice as large as that in the CN group (30% vs 15%; p=0.03). A worsening of
subjects receiving risperidone than in those receiving CNs (p=0.02) (Bouchard et al, 2000).
d) In an open, multicenter trial, risperidone was found to be effective in outpatients (Chouinard et al
subchronic or chronic schizophrenia treated on an outpatient basis were screened initially while on t
Their current therapy was discontinued and risperidone started at 2 milligrams (mg) daily and increa
After 2 weeks the dose could be titrated to a maximum of 10 mg or a minimum of 4 mg. At the end o
risperidone dose was 6.1 mg daily in 244 patients completing the study. The mean total Positive and
(PANSS) for schizophrenia decreased significantly from 86.3 to 63.6 (p=0.0001). Clinical improveme
baseline in total PANSS score) was seen in 85% of patients. The most frequent adverse events repo
headache, somnolence, dizziness, fatigue, anxiety, vomiting, and ejaculation failure/disorder.
e) In an open multicenter trial, risperidone was viewed as an efficacious and well tolerated medicati
overall antipsychotic action and above standard improvement in negative symptomology in 254 chro
and without exacerbation who were treated with risperidone 1 to 5 milligrams twice daily for 8 weeks
discontinuation of previous psychotropic medications; significant improvement in the overall Brief Ps
observed at every evaluation time (p less than 0.0001); 73% of patients showed improvement in neg
significant improvement was noted in the extrapyramidal symptom scores in all patients, including th
early (p less than 0.0001); the Clinical Global Impression scores significantly improved for those finis
0.0001); 98% of those finishing the study tolerated risperidone very well or well; 32% of patients disc
which 51% dropped out within the first 2 weeks, probably due to adverse reactions stemming from tl
previous psychotropics; the research team now recommends initial overlapping of therapies, especia
medicated with sedatives (Phillip, 1997).

c) Combination Therapy

1) Addition of celecoxib to risperidone therapy for patients with an acute exacerbation of schizophrenia r
than did risperidone therapy alone. In a randomized, double-blind study, 25 patients were given risperido
plus celecoxib 400 mg/day and 25 patients were given risperidone plus placebo. Both groups showed im
over the 5- week study, mainly with reductions in scores on the positive symptoms subscale of the Positi
(PANSS) (p=0.006) and on the general psychopathology subscale (p=0.01). Negative symptoms were n
Celecoxib therapy resulted in an improvement in total PANSS score relative to that of the placebo group
significant effects of celecoxib on the group-by-time interaction on any of the subscales, although a trend
on all subscales. The main influence of celecoxib occurred in weeks 2 to 4, resulting in earlier improvem
treating side effects of risperidone was not significantly different for the 2 groups. The use of benzodiaze
agitation appeared less in the celecoxib group, but the difference for the 2 groups was not statistically sig
were not observed (Muller et al, 2002).
2) In an open trial, risperidone added to clozapine was well tolerated and produced significant reduction
measured by the Brief Psychiatric Rating Scale (42.2 to 30.3, p=0.0002). Patients enrolled had either pe
symptoms despite optimal doses of clozapine (n=10) or a maximal clozapine dose limited by significant s
doses were kept constant while risperidone doses were increased to a maximum of 6 milligrams (mg) pe
tolerated, however, complaints included mild akathisia, hypersalivation, and worsening fatigue (Henderso
cases of refractory schizophrenic patients responding to combination therapy have been reported (More
clozapine 300 mg with risperidone 4.5 mg, and clozapine 400 mg with risperidone 6 mg.
3) As an add-on therapy, risperidone brought significant improvement to patients with bipolar disorder a
bipolar type. In a 6-month, open study, patients with a diagnosis of bipolar or schizoaffective disorder wh
depressive, or mixed episode (n=541; 430 completed the study) were given risperidone in combination w
antidepressants to clinical response and tolerability. The average dose of risperidone at the start of the s
day and at the end of the study, 3.9 mg/day. For all patients, scores on the Young Mania Rating Scale (Y
at week 1 and at every point thereafter (p less than 0.001 for all but the subgroup of depressed patients,
Mean scores on the YMRS decreased from 25.6 at baseline to 2.4 at 6 months. Likewise, scores on the
Depression (HAM-D) were significantly reduced from baseline at all evaluation times (p less than 0.0001
at baseline to 4.1 at 6 months. Scores on the Positive and Negative Syndrome Scale (PANSS) declined
months (p less than 0.0001). According to the Clinical Global Impressions scale (CGI), no patients were

and only 5% were rated as "mildly ill." At study endpoint, 44% of patients showed no symptoms of mania were "mildly ill." During the study, 25% of the patients experienced relapses into a mood state different fr Scores for extrapyramidal symptoms were lower at the end of study than at baseline (p less than 0.0001 reductions in dystonia, rigidity, hypokinesia, hyperkinesia, dyskinesia, tremor, and akathisia subscores. T emergent tardive dyskinesia. Nonextrapyramidal adverse reactions included increase in weight (2.4% of impotence (0.7%), and dysarthria (0.7%). There was a very low incidence of exacerbation mania in the fi 2001).

d) Refractory

1) Among patients who had been hospitalized for schizophrenia for longer than 5 years and who were c approximately 45% showed sufficient clinical improvement after 3 months of treatment with olanzapine o from the hospital. The 79 patients were not suited to treatment with clozapine either because of medical unwillingness to submit to the weekly blood drawings. Patients were given olanzapine 10 to 30 milligram 10 mg/day. Treatments were titrated quickly to the maximum tolerated dose and continued for 3 months. Psychiatric Rating Scale decreased from 67 to 53 for the olanzapine group (n=32) and from 63 to 52 for less than 0.001 for both groups). Of the 34 patients who were discharged from the hospital, only 3 requir 90-day follow-up. No significant side effects (such as weight change) were observed during the 3 months

e) Schizophrenia With Concomitant Cocaine Dependence

1) The results of a pilot study suggest that risperidone therapy reduced craving and relapses in cocaine- schizophrenia. In this 6-week, open label trial, patients with a dual diagnosis of schizophrenia and cocair of cocaine/month) received risperidone (n=8; initial, 2 milligrams (mg)/day, titrated to maximum dose of 6 neuroleptic medication treatment (n=10; haloperidol, fluphenazine, or chlorpromazine). Patients in the ris less cue reactivity in regard to the intensity (p=0.005) and depression (p=0.031) dimensions of craving a therapy, but there was no statistical difference on the energy and feeling sick dimensions. Risperidone-tr significantly lower rate of relapse (defined as any substance abuse) than did patients on typical neurolep respectively; p=0.025). Although not significant, a tendency toward a greater reduction in negative and g was seen in risperidone-treated patients. Larger, double-blind studies are needed to substantiate these f

4) Pediatric:

a) In 2 short-term (6 and 8 weeks), double-blind, controlled trials, oral risperidone, at doses ranging from 1 to effective in the treatment of schizophrenia in adolescents aged 13 to 17 years. Patients met the DSM-IV diag and were experiencing an acute episode at the time of enrollment. In the first trial (trial 1), patients were rand risperidone 1 to 3 mg/day (n=55; mean modal dose, 2.6 mg), risperidone 4 to 6 mg/day (n=51; mean modal d for 6 weeks. In the second trial (trial 2), patients were randomized to receive either risperidone 0.15 to 0.6 mg 0.5 mg) or risperidone 1.5 to 6 mg/day (n=125; mean modal dose, 4 mg). In both studies, risperidone was init up to the target dose range by approximately day 7 (except for the risperidone 0.15 to 0.6 mg/day group in tri initiated at 0.05 mg/day). Eventually, the dosage was increased to the maximum tolerated dose by day 14. C reduction occurred in the Positive and Negative Syndrome Scale (PANSS) score in all risperidone dose group (primary efficacy endpoint). Reductions in the PANSS scores in the 1 to 3 mg/day group were comparable to and to the 1.5 to 6 mg/day group in trial 2. The 1.5 to 6 mg/day group showed statistically significantly greater mg/day group in trial 2, with no additional benefit evident beyond the 3 mg/day dose. Adverse events reported placebo in both the risperidone 1 to 3 mg/day and 4 to 6 mg/day dose groups in trial 1 included parkinsonism dystonia (9%-18%), dizziness (7%-14%), akathisia (7%-10%), somnolence (12%-24%), and anxiety (6%-7%) tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R)

b) The results of a small study suggest that risperidone may be effective in the treatment of schizophrenia in prospective, open-label trial, eleven patients (mean age, 17.27 years) with first-episode, early-onset schizoph 0.5 milligrams (mg)/day, titrated based on clinical response and adverse effects; mean dose, 3.14 mg/day) fo Positive and Negative Syndrome Scale (PANSS) total score and positive symptoms score were significantly r than 0.01 and p less than 0.0001, respectively), however, a significant reduction was not observed for the ne PANSS (p=ns). Total scores for the Brief Psychotic Rating Scale were significantly reduced from baseline to baseline to endpoint, Clinical Global Impression-Severity (CGI-S) scores decreased by 31.6% (p less than 0.(scores decreased by 45.5% (p less than 0.0001). The most common adverse events observed were weight g depression (63%), orthostatic hypertension (45%), emotional indifference (45%), akathisia (36%). Because th improved significantly at a dose of only 1 mg/day, the authors suggest that lower initial doses of risperidone s as compared with adults, in order to minimize the risk of extrapyramidal side effects. Larger, controlled studie the safety and efficacy of risperidone for the treatment of schizophrenia in pediatric patients (Zalsman et al, 2

c) A 15-year old boy, with a diagnosis of simple deteriorative disorder (DSM-IV criteria or simple schizophrer improvement following risperidone therapy. He was started on 2 mg daily and this dosage was increased to 3 He did not report any significant side effects and showed clinical improvement. The author advocates the furt risperidone in the treatment of simple schizophrenia (Hirose, 2000).

4.5.Z Schizotypal personality disorder

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Appeared to effective in the treatment of schizotypal personality disorder

3) Adult:

a) Risperidone treatment was more effective than placebo in reducing the symptoms of schizotypal personal randomized, double-blind, placebo-controlled study, patients (n=25) with schizotypal personality disorder rece (0.25 milligrams (mg)/day for 1 week, then titrated by 0.5 mg/day every 2 weeks for 8 weeks; final dose, 2 mg comorbid borderline personality disorder. Weekly measurements of symptoms were taken using the Positive (PANSS), the Hamilton Rating Scale for Depression (HAM-D), and the Clinical Global Impressions Scale (CG Questionnaire (SPQ) was administered biweekly. Total PANSS scores were significantly lower in risperidone with placebo at weeks 3, 5, 7, and 9 (p=0.021, p=0.003, p=0.003, and p=0.013, respectively). PANSS negativ patients in the risperidone group than in the placebo group at all time points, with the difference reaching sign (p=0.027, p=0.006, and p=0.01, respectively). Patients in the risperidone group had significantly lower PANS patients in the placebo group at weeks 3, 5, 7, and 9 (p=0.042, p=0.007, p=0.005, and p=0.013, respectively) had significantly lower PANSS positive symptom scores at weeks 7 and 9 as compared with placebo (p=0.02 the end of treatment, SPQ and CGI scores showed greater reductions in the risperidone group than in the pla difference was not significant. The change in HAM-D scores was non- significant in both groups. Adverse eve decreased sexual arousal, delayed ejaculation, mild dystonic reaction and dry mouth. Larger studies are nee (Koenigsberg et al, 2003).

4.5.AA Stuttering

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Risperidone may be beneficial

3) Adult:

a) Risperidone may be effective in the treatment of developmental stuttering. A small, randomized, double- b was conducted to assess the efficacy of risperidone in the treatment of developmental stuttering in 16 adults. and eight received risperidone at 0.5 mg once daily at night, increased to a maximum of 2 mg per day. After 6 in all measures of stuttering severity were greater in the risperidone group than in the placebo group; the betw significant (p less than 0.05) on the most important measure, the percentage of syllables stuttered. In the risp baseline in scores for the percentage of syllables stuttered, time stuttering as a percentage of total time spea severity were significant (p less than 0.01); changes in scores on the fourth measure of stuttering, duration, w differences occurred in the placebo group. Five of the eight patients in the risperidone group responded best stuttering recurring at higher doses. Risperidone was generally well-tolerated (Maguire et al, 2000).

b) In one small study (n=21), patients were randomized to receive risperidone (n=10) up to 2 milligrams daily Every 2 weeks stuttering severity, adverse events, compliance, and tolerability were assessed. Risperidone t the mean stuttering severity compared to placebo (3.93 and 5.23, respectively (p less than 0.05). However, e social alienation-personal disorganization did not (Maguire et al, 1999).

4.5.AB Tardive dyskinesia

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Effective in reducing tardive dyskinesia in some patients when substituted for conventional antipsychotic

See Drug Consult reference: TARDIVE DYSKINESIA - DRUG THERAPY

3) Adult:

a) Risperidone treatment was more effective than withdrawal of antipsychotic therapy in reducing symptoms randomized, double-blind, placebo-controlled study (n=42), schizophrenic patients with persistent, severe tar risperidone (initial, 2 milligrams (mg)/day titrated in 2 mg increments to 6 mg/day over 6 weeks) or placebo fo washout period from all original conventional antipsychotic medications. Response was defined as a decreas Involuntary Movement Scale (AIMS) total score. Risperidone- treated patients showed a significantly greater score from baseline to endpoint, as compared with placebo (5.5 vs 1.1, respectively; p=0.001). This significar AIMS score between groups was observed from week 8 to endpoint, and grew more distinct over time. In adc significantly higher in the risperidone group as compared with the placebo group (68%(15) vs 30%(6), respec dyskinesia improvement in the risperidone group was noted mainly in the buccolinguomasticatory area rather movement of the extremities. Additional studies are needed to evaluate the long-term efficacy of risperidone t dyskinesia and whether symptoms reemerge when the risperidone dosage is withdrawn or reduced (Bai et al

b) Five of nine patients with tardive dyskinesia showed a lessening of severity of tardive dyskinesia when ris conventional antipsychotic drug they had been taking. After a tapering of the previous antipsychotic and antip patients were prescribed risperidone 2 milligrams (mg) per day. The dose was gradually increased over 4 we adjusted to maintain the least severity of tardive dyskinesia. Over the year-long study, 5 patients showed imp in score on the Abnormal Involuntary Movement Scale (AIMS) (responders). The dose for maximum effect in

improvement in AIMS score was 7 for responders and 0.5 for nonresponders (Chen et al, 2001).
c) Tardive movements were resolved with the addition of risperidone and a reduction in doses of trihexypher
old schizophrenic patient (Chong et al, 1999).
d) Tardive dyskinesia was diminished in a 54-year-old schizophrenic woman after switching to risperidone th
Risperidone 2 milligrams daily resolved her schizophrenic symptoms. At 8 months, her tardive dyskinesia wa
months, her parkinsonism had also resolved.

4.5.AC Trichotillomania

1) Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category C
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS
2) Summary:
Augmented therapy in patients with trichotillomania
3) Adult:
a) In a case series, 3 of 5 patients with trichotillomania disorder (DSM-IV criteria) showed significant improve
Impression Change Scale after receiving augmentation with risperidone 1 milligram/day (Stein et al, 1997).

4.5.AD Water intoxication syndrome

1) Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Ineffective
Recommendation: Adult, Class III
Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS
2) Summary:
No effect on self-induced water intoxication
3) Adult:
a) Risperidone had no significant effect in treating self-induced water intoxication. In a prospective, 11 month
in 8 men with chronic schizophrenia and a history of polydipsia and episodic water intoxication, fluid intake wa
4 times daily weights. Risperidone was increased in doses up to 16 milligrams per day. Though there was a t
intake, there was no significant change in body weight over the study period (Milson et al, 1996).

4.6 Comparative Efficacy / Evaluation With Other Therapies

Amisulpride

Chlorpromazine

Clozapine

Haloperidol

Lithium

Olanzapine

Paroxetine

Perphenazine

Quetiapine

Ziprasidone

4.6.A Amisulpride

4.6.A.1 Schizophrenia

a) Amisulpride and risperidone therapies were equally effective in the treatment of positive and negative sym
with schizophrenia. In a randomized, double-blind, multi-center study, schizophrenic patients with productive

amisulpride 400 to 800 milligrams (mg) per day (mean dose, 630 mg/day) or risperidone 4 to 8 mg per day (n
weeks following a 3-to-6-day washout period. At 6 weeks, patients in both treatment groups showed significa
and Negative Symptom Scale (PANSS) total score and the three PANSS sub- scale scores, but no significan
treatment groups. The occurrence of adverse events was also similar between groups. Akathisia (16%), trem
were most commonly reported with risperidone administration while insomnia (17.3%) and constipation (17.3
in the amisulpride group (Hwang et al, 2003).

4.6.B Chlorpromazine

4.6.B.1 Schizophrenia

a) Based upon comparisons of minimum effective dosages identified in placebo- controlled, fixed-dose and f
development trials, the minimum effective dose of risperidone was 4 milligrams/day (equivalent to chlorproma
SW, 2003).

4.6.C Clozapine

Bipolar disorder

Hostile behavior

Parkinson's disease - Psychotic disorder

Schizophrenia

4.6.C.1 Bipolar disorder

a) In a retrospective study of 50 consecutive patients treated for bipolar disorder with atypical antipsychotic r
olanzapine (n=20), and risperidone (n=25), along with standard mood stabilizers, showed similar efficacy. Ov
improvement of at least 1 point in their Clinical Global Impressions assessment over the 12-week study. Mea
(mg) per day for clozapine, 11.7 mg/day for olanzapine, and 1.7 mg day for risperidone. The only serious adv
study was a seizure in a patient taking clozapine. Extrapyramidal symptoms (EPS) were reported in 12 of 42
occurred in 4 of 25 patients taking risperidone, 1 of 20 taking olanzapine, and 1 of 5 taking clozapine. Weight
patients taking clozapine and olanzapine than in those taking risperidone. Weight gain, which was greater tha
have been affected by concurrent mood enhancing medications (Guille et al, 2000a).

4.6.C.2 Hostile behavior

a) Clozapine reduced hostility in patients with schizophrenia and was superior to haloperidol and risperidone
seven patients with a diagnosis of schizophrenia or schizoaffective disorder and a history of poor response to
assigned to receive clozapine, olanzapine, risperidone, or haloperidol in cross-titration with the antipsychotic
study. Concomitant mood stabilizers and antidepressants had been phased out earlier. Daily doses of olanza
haloperidol were escalated within the first week to the target doses of 20, 8, and 20 milligrams (mg), respecti
were scheduled to achieve the target daily dose of 500 mg on day 24. Doses remained fixed for the remainde
second (6-week) period, doses were allowed to vary: 200 to 800 mg for clozapine, 10 to 40 mg for olanzapine
10 to 30 mg for haloperidol. Hostility, measured by the hostility item of the Positive and Negative Syndrome S
significantly (in comparison to baseline) in the clozapine group only (p=0.019). This effect was independent o
(delusional thinking, hallucinations) or on sedation. The effect of clozapine on hostility was superior to that of
risperidone (p=0.012) but not to that of olanzapine (Citrome et al, 2001).

4.6.C.3 Parkinson's disease - Psychotic disorder

a) In subjects with Parkinson's Disease (PD), risperidone may be considered as an alternative to clozapine h
extrapyramidal symptoms more than clozapine and therefore must be used with caution. A small (n=10) doub
efficacy and safety of risperidone and clozapine for the treatment of psychosis in patients with PD. Five patie
clozapine and five patients received risperidone. Clozapine was started at 12.5 mg at bedtime and risperidon
and both were titrated to symptomatic improvement was achieved or intolerable side effects emerged. Each s
months and was assessed prior to initiation of treatment and after 2, 4, 8, and 12 weeks of treatment. Assess
the Brief Psychiatric Rating Scale and the Unified Parkinson's Disease Rating Scale. Mean improvement in th
psychosis score was similar in the clozapine and the risperidone groups (p=0.23). Although the mean motor U
Rating Scale scores worsened in the risperidone group and improved in the clozapine group, this difference d
significance. Risperidone may be a reasonable alternative to clozapine in the treatment of psychosis in patien
used with caution since it may worsen extrapyramidal side effects (Ellis et al, 2000).

4.6.C.4 Schizophrenia

a) Olanzapine and risperidone improved neurocognitive deficits more than did haloperidol or clozapine in pat
schizoaffective disorder that was refractory to treatment with typical antipsychotics. In a randomized, double-
clozapine (n=24) 200 to 800 milligrams (mg) per day, olanzapine (n=26) 10 to 40 mg/day, risperidone (n=26)

(n=25) 10 to 30 mg/day. Dose escalation and fixed-dose treatment (target doses: olanzapine 20 mg/day, risp
mg/day, clozapine 500 mg/day) occurred during the first 8 weeks of the 14-week study; during the last 6 wee
individually (generally increased if response was insufficient, but sometimes reduced because of adverse effe
global neurocognitive score was seen for olanzapine and risperidone. In general executive and perceptual or
speed and attention, improvement was seen with olanzapine. In simple motor function, there was improveme
global neurocognitive performance with olanzapine and risperidone were of medium magnitude (approximate
large enough to be clinically significant. Beneficial changes with clozapine were modest. Despite cognitive ga
impairments of cognitive ability and social/vocational functioning. Improvements in neurocognitive deficits we
in negative symptoms (Bilder et al, 2002b).

b) Clozapine was superior to risperidone for improving positive and negative symptoms of schizophrenia in p
response to treatment. In a prospective, double-blind study, patients meeting DSM-IV criteria for schizophren
to previous treatment underwent a single-blind placebo run-in period when all psychotropic and anticholinergi
They were then randomly assigned to treatment with clozapine (n=138) or risperidone (n=135). Starting with
milligrams (mg) and risperidone 1 mg, dosages were titrated over a period of 4 weeks to a minimum of 300 m
respectively, and possibly to 600 mg/day and 6 mg/day. Patients unable to tolerate the minimum dose were v
the next 8 weeks, doses were adjusted at 2-week intervals within the range of 200 to 900 mg/day for clozapir
risperidone. For patients who completed the 12-week study (n=201), median final daily doses were 600 mg fo
risperidone. Changes in the Positive and Negative Syndrome Scale of the BPRS (Brief Psychiatric Rating Sc
Impression (CBI) scale were significantly greater in the clozapine group than in the risperidone group for the i
who received at least one dose of treatment medication and had one post-dose BPRS evaluation) and in the
who completed the 28-day dose-setting period) (p less than 0.008 for all comparisons). Eighty-six percent of
protocol population and 70% in the risperidone per-protocol population showed 20% or more improvement in
between groups, p less than 0.01). By the end of the study, 94 (76%) patients in the clozapine group and 81
longer met the severity of psychopathology inclusion criteria (p less than 0.05). Extrapyramidal symptoms oc
in the clozapine group than in the risperidone group (13% vs 28%, p=0.008). However, convulsions, dizziness
somnolence occurred significantly more frequently among those receiving clozapine. No case of agranulocyt
study. Granulocytopenia occurred with low incidence in both groups (1% clozapine, 2% risperidone). Low neu
more frequent among risperidone-treated patients (3% vs 11%, p less than 0.01). Hypotension occurred more
treated patients (p less than 0.01). Weight gain was significantly greater for the clozapine group (2.4 kilogram
0.002) (Azorin et al, 2001).

c) In the treatment of refractory schizophrenia, giving a risperidone trial before clozapine was more beneficia
profile. A retrospective review study compared the relative efficacy profiles of clozapine and risperidone in a g
chronically institutionalized patients. The specific goal was to identify superiority (or lack thereof) of either age
well as on specific symptom domains, including positive symptoms, negative symptoms, and aggressive beha
of conventional antipsychotic treatment in a total of 24 patients. Information obtained from systematic retrosp
rated by 2 psychiatrists using the 7-point Clinical Global Impressions Improvement (CGI-I) scale on overall cli
symptom domains as above. The mean dose was 520 +/- 94 mg daily for clozapine and 7.5 +/- 2.2 mg daily f
(58%) were classified as responders to clozapine, while 6 (25%) responded to risperidone. On specific sympt
clozapine were 38% (9/24) on positive symptoms, 29% (7/24) on negative symptoms, and 71% (12/17) on ag
risperidone, response rates were 17% (4/24) on positive symptoms, 8% (2/24) on negative symptoms, and 4
behavior. The results of this study would support the utility of first giving a risperidone trial in patients with trea
because of its better side effect profile compared with clozapine (Sharif et al, 2000).

d) Risperidone and clozapine had similar antipsychotic effects in 59 patients with paranoid schizophrenia. In
study, patients were divided in three groups receiving either 4 milligrams risperidone, 8 milligrams risperidone
daily for 28 days. The antipsychotic effect was highly significant for both risperidone and clozapine. Patients
better tolerated therapy than those patients receiving clozapine. Withdrawals from clozapine treatment were
whereas withdrawals from risperidone treatment occurred from lack of therapeutic response (Heinrich et al, 1

e) Similar effectiveness of risperidone and clozapine was also observed in an 8-week, double-blind trial that
on response in 86 patients with treatment-resistant chronic schizophrenia. The mean effective dose was 6.4
and 291 mg for clozapine. The larger proportion of patients with clinical improvement after 7 and 14 days' trea
suggested earlier onset of effect compared to clozapine treatment (Bondolfi et al, 1998)

f) In a prospective, open-label, 12-week trial, risperidone was found to be a poor substitute for clozapine in th
schizophrenia. Six patients with schizophrenia and 4 with schizoaffective disorder were switched from a mea
milligrams(mg)/day to a mean dose of risperidone 8 mg/day at 12 weeks. No subjects improved after being s
were switched from clozapine tended to worsen when taking risperidone. Statistically significant increases ov
the Positive and Negative Syndrome Scale occurred at 9 and 12 weeks (P less than 0.05). The Brief Psychia
increased significantly over baseline at weeks 6, 9, and 12 (P less than 0.05). Five subjects failed to complete
patients that completed the 12 weeks, the Clinical Global Impressions Scale indicated that 2 patients were ur
worse, and 2 were much worse. The authors concluded that this study does not support replacing clozapine v
treatment-resistant schizophrenia (Still et al, 1996).

4.6.C.5 Adverse Effects

a) Adverse effects and death were more commonly reported as the reasons for the discontinuation of clozap
more often reported as the reason for discontinuation of risperidone (long-acting injection) in a retrospective,
with a diagnosis of schizophrenia, schizoaffective disorder, bipolar disorder or other psychotic disorders who
had mean duration of therapy of 12.3 +/- 18.6 months (range, 0.25 to 100 months; median, 3 months) were m
12.6 years (yr); range, 18 to 83 yr) and gender at discontinuation to patients who discontinued risperidone lon
risperidone patients (mean age, 39.9 +/- 13.1 yr , range 18 to 83 yr) were matched without knowledge of the
therapy (mean duration of therapy of 5.9 +/- 8.7 months; range, 0.5 to 46 months; median, 3 months). The re

significantly between clozapine and risperidone injection; additionally, death as reason for discontinuation wa
clozapine (13%) vs risperidone injection (1.9%) (Taylor et al, 2009).

Reasons for Discontinuation: Clozapine vs Risperidone

Reason	Clozapine (n=161) n (%)	Risperidone (n=161) n (%)	OR (95% CI)	p value
Patient's decision	77 (47.8)	64 (39.7)	1.41 (0.89 to 2.21)	0.139
Adverse effects	57 (35.4)	32 (19.9)	2.19 (1.31 to 3.67)	0.0023
Ineffectiveness	3 (1.9)	59 (36.6)	0.034 (0.01 to 0.14)	less than 0.0001
Death	21 (13)	3 (1.9)	7 (2.09 to 23.5)	0.0003
Other	3 (1.9)	3 (1.9)	-	-

The cause of death reported in clozapine patients (mean age, 49.2 +/- 14.5 yr, range 30 to 83 yr) include
carcinoma (n=3), other carcinoma (n=2), myocardial infarction (n=2), cerebrovascular accident (n=2), clo
gastrointestinal hemorrhage (n=1), cardiac arrest (n=1), left ventricular failure (n=1), asphyxia during rest
There was no incidence of neutropenia or agranulocytosis at the time of death in any of the patients. The
risperidone patients included: myocardial infarction (n=1), left ventricular failure (n=1) and sudden unexp
rate for clozapine patients was 8.5 per 1000 patient-years (95% CI, 5.53 to 13.07) vs 5.3 per 1000 patier
(Taylor et al, 2009).

b) The results of one study suggest that patients receiving atypical antipsychotics have a higher incidence of
receiving a conventional antipsychotic medication. In a retrospective, pharmacovigilance study, 192 cases of
patients taking clozapine (mean dose, 306.7 milligrams (mg)/day), olanzapine (mean dose, 15 mg/day), rispe
or haloperidol (mean dose, 8.2 mg/day). Of the identified cases, 40%, 33%, and 16% were related to treatme
medications clozapine, olanzapine, or risperidone, respectively, as compared with 12% of the cases which w
neuroleptic, haloperidol. In most patients, time to onset of pancreatitis was within 6 months after initiation of t

c) Clozapine was associated with fewer extrapyramidal side effects (EPS) than was risperidone (Miller et al,
stable doses of clozapine (n=41), risperidone (n=23), or conventional antipsychotics (n=42) were screened fo
Akathisia Scale, akathisia was noted in 7.3% of clozapine patients, 13% of risperidone patients, and 23.8% o
users. From the Simpson-Angus scale, rigidity and cogwheeling were noted in 4.9% and 2.4% of clozapine p
risperidone patients, and 35.7% and 26.2% of conventional antipsychotic users, respectively. However, saliva
clozapine patients, 8.7% of risperidone patients, and 4.8% of conventional antipsychotic users.

d) Insomnia and extrapyramidal side effects were more common with risperidone, and sedation and weight g
clozapine in a single-blind, crossover pilot study of the side effect profiles of the 2 drugs (Daniel et al, 1996).
schizophrenia or schizoaffective disorder were randomized to each drug for 6 weeks separated by a 1-week
crossover. The mean doses at week 6 were 6.1 milligrams/day (range 1 to 10 mg/d) of risperidone and 375 m
mg/d) of clozapine. Three patients dropped out of the study; there was no significant difference in therapeutic
groups. Mean body weight was greater (p less than 0.005) and sleepiness and lack of alertness were reporte
treatment phase. Restlessness and insomnia were more frequent complaints after the risperidone phase. A l
large sample of patients is needed to further elucidate the therapeutic differences and side effect profiles of t

4.6.D Haloperidol

Cognitive function finding

Dementia

Extrapyramidal disease

Mania

Schizophrenia

4.6.D.1 Cognitive function finding

a) Results of a multicenter, randomized, double blind trial assessing cognitive function in patients experienci
episode or a related psychosis demonstrated that overall improvement in cognitive functioning was superior v
haloperidol. Patients (n=533) were randomized to receive either risperidone or haloperidol on a one-to-one ra
2 years or more. There were no significant differences in sex, race or ethnicity, age, diagnosis, or previous ne
group. Dosing strategies were equivalent in both groups where patients were started on 1 milligram per day (
titrated up to 4 mg/day, or in some cases, to a maximum of 8 mg/day. Patients in the risperidone group recei

modal total dose 3.3 mg/day) for an average of 192 days while patients in the haloperidol group received trea
2.9 mg/day) for an average of 218 days. Cognitive assessments, performed at several different follow-up inte
verbal and visuospatial episodic memory, vigilance, executive functioning, processing speed, and verbal fluer
conducted with a focus on the 3-month assessment revealed that there was significant improvement from bas
(n=169) for all measures except category verbal fluency and letter verbal fluency (p less than 0.05). In the ha
statistically significant improvements from baseline were noted in episodic memory, vigilance, and visuomoto
functioning and verbal fluency. Comparison between the two groups showed that, after 3 months of treatmen
significantly more beneficial than the haloperidol group on the composite measure of cognitive functioning. In
as a result of treatment with risperidone was not affected by changes in symptoms. Risperidone therapy also
haloperidol in relapse prevention and extrapyramidal side effects (Harvey et al, 2005).

b) Risperidone therapy appeared to exert a more favorable effect on verbal working memory in treatment-res
than did haloperidol therapy (Green et al, 1997). In a randomized, double-blind comparison of treatment with
haloperidol (n = 29), verbal working memory was measured at baseline and after 4 weeks of both a fixed dos
Risperidone patients showed a significant improvement in memory using a Digit Span Distractibility Test from
the fixed-dose (p less than 0.0001) and the flexible dose (p less than 0.0003) phases. The haloperidol-treated
significantly. Results suggest that treatment of schizophrenia could be broadened to include the impact on ne

4.6.D.2 Dementia

a) Some Chinese patients with dementia, who were non-responders to haloperidol, responded to risperidone
disturbances and improved mood. Thirty-five Chinese patients who had shown insufficient response to an 8-
having a total score of more than 10 on the Brief Psychiatric Rating Scale (BPRS) at the end of 8 weeks) (typ
switched abruptly from haloperidol to risperidone 0.5 milligrams (mg) at bedtime for weeks 1 to 4 and then (if
weeks 5 to 12. At week 13, the regimen was shifted again to haloperidol at the dose used in the earlier trial. T
the trial. Sixteen patients responded by the end of the risperidone trial (response = a decrease of 25% in the
resumption, the mean BPRS score stayed the same, but the number of responders decreased to 15. Patients
almost 6 times more likely to respond to risperidone than patients with Alzheimer's disease. Mean scores on
Alzheimer's Disease Rating Scale decreased (6.1 at baseline to 1.9 at 12 weeks of risperidone treatment) an
to haloperidol (to 2.4 after 4 weeks of haloperidol). Thirty- four of the 35 patients tolerated both doses of rispe
One patient experienced moderate rigidity with risperidone 1 mg/day, which was relieved by reduction of the
experienced fewer extrapyramidal symptoms with risperidone than with haloperidol (Lane et al, 2002).

b) Both risperidone and haloperidol in low doses reduced the severity and frequency of behavioral and psycl
Chinese patients with dementia. Risperidone was associated with less severe exacerbation of extrapyramida
randomized, double-blind trial, 55 elderly Chinese patients (mean age 80 years) with Alzheimer's dementia o
behavioral disturbance, were given either risperidone or haloperidol for 12 weeks after a 2-week washout per
psychotropic and antiparkinsonian drugs. The starting dose for both treatment drugs was 0.5 milligrams (mg)
individually in increments of 0.5 mg no faster than every other day, to a maximum of 2 mg/day. At 12 weeks,
haloperidol was 0.9 mg, and that of risperidone, 0.85 mg. Significant improvements on the Cohen- Mansfield
evident in both groups (haloperidol, p less than 0.001; risperidone, p=0.002). Significant reduction was seen
group and at 4 weeks in the haloperidol group. With risperidone, there were significant improvements in score
disturbances, aggressiveness and diurnal rhythm disturbances, whereas with haloperidol, improvement in on
reached statistical significance. However, none of the measures showed a significant difference between the
haloperidol, there was a significant worsening of EPS (p less than 0.001), whereas, with risperidone, EPS sc
worsened. Final EPS scores were significantly higher for haloperidol (p=0.001) (Chan et al, 2001).

4.6.D.3 Extrapyramidal disease

a) Data from a multicenter comparative study of risperidone, placebo, and haloperidol revealed that risperidc
extrapyramidal symptoms (Simpson & Lindenmayer, 1997). Mean changes in Extrapyramidal Symptom Ratir
baseline to worst score were significantly lower in each risperidone group than the haloperidol group (P less t

4.6.D.4 Mania

a) A small, controlled study, compared the efficacy and safety of risperidone versus lithium and haloperidol i
results with risperidone. Patients (n=45) were assigned to take risperidone (as monotherapy), dosed at 6 mg
day, or 800 to 1000 mg daily of lithium. All 3 groups showed a similar improvement on Brief Psychiatric Ratin
Scale scores. The EPS of risperidone and haloperidol were not significantly different and mania did not worse
treated patients (Segal et al, 1998).

4.6.D.5 Schizophrenia

a) Olanzapine and risperidone improved neurocognitive deficits more than did haloperidol or clozapine in pat
schizoaffective disorder that was refractory to treatment with typical antipsychotics. In a randomized, double-
clozapine (n=24) 200 to 800 milligrams (mg) per day, olanzapine (n=26) 10 to 40 mg/day, risperidone (n=26)
(n=25) 10 to 30 mg/day. Dose escalation and fixed-dose treatment (target doses: olanzapine 20 mg/day, risp
mg/day, clozapine 500 mg/day) occurred during the first 8 weeks of the 14-week study; during the last 6 weel
individually (generally increased if response was insufficient, but sometimes reduced because of adverse effe
global neurocognitive score was seen for olanzapine and risperidone. In general executive and perceptual or
speed and attention, improvement was seen with olanzapine. In simple motor function, there was improveme
global neurocognitive performance with olanzapine and risperidone were of medium magnitude (approximate
large enough to be clinically significant. Beneficial changes with clozapine were modest. Despite cognitive ga
impairments of cognitive ability and social/vocational functioning. Improvements in neurocognitive deficits we

in negative symptoms (Bilder et al, 2002a).

b) The risk of relapse of schizophrenia was significantly less with long-term treatment with risperidone than v
double-blind study, 365 patients meeting DSM-IV criteria for schizophrenia or schizoaffective disorder and in
flexible doses of either risperidone or haloperidol. The trial was continued until the last enrolled patient had c
Means of modal daily doses were 4.9 milligrams (mg) for risperidone and 11.7 mg for haloperidol. At the end
risperidone group and 40% of the haloperidol group had relapsed. The risk of relapse was significantly higher
haloperidol (risk ratio 1.93, p less than 0.001). The risk of premature discontinuation was greater for the halop
risperidone group (risk ratio 1.52), mainly because of relapse. Median duration of treatment for the risperidon
haloperidol group, 238 days (p=0.02). The subtypes of relapse (psychiatric hospitalization, clinical deteriorati
suicidal or homicidal ideation) were similar in the 2 groups. In the risperidone group, there were improvement
negative symptoms, disorganized thoughts, and anxiety- depression, whereas symptoms were not improved
extrapyramidal symptoms was reduced from baseline in the risperidone group and increased in the haloperid
the groups were significant (p less than 0.02 for total score on the Extrapyramidal Symptom Rating Scale). Th
were somnolence (14% with risperidone and 25% with haloperidol), agitation (10% and 18% respectively), ar
respectively). Those taking risperidone had a mean increase in body weight of 2.3 kilograms (kg) and those t
decrease of 0.73 kg (p less than 0.001) (Csernansky et al, 2002).

c) Risperidone was more efficacious and had fewer adverse effects than haloperidol when used to treat refra
patients. Chinese patients, meeting DSM-III-R criteria for schizophrenia and having a history of treatment fail
neuroleptics given at least 3 months at full dose, were randomly assigned to receive risperidone (n=41) or ha
double-blind trial. The dose of risperidone was increased during the first week to 6 milligrams (mg) per day, a
mg/day. By the end of the study, the average score on the Positive and Negative Syndrome Scale (PANSS) I
risperidone group and by 28.3% for the haloperidol group (p=0.03). The general psychopathology and negati
showed greater improvement with risperidone, but there was no difference between treatments in the positive
patients rated as responders was higher in the risperidone group (31 of 41 vs 20 of 37, p=0.046). Total score
Symptoms Scale (TESS) were significantly lower with risperidone than with haloperidol (2.9 vs 6.9, p=0.01). I
favoring risperidone were those showing symptoms of the nervous system (rigidity, tremor, dystonia, and aka
system (hypotension, dizziness, tachycardia, hypertension and electrocardiogram abnormalities) (p=0.02 and
in the risperidone group required less medication for extrapyramidal symptoms during the study than did patie
authors mentioned that the dose of haloperidol was higher than the dose recommended in the United States
accounted for some of the difference between treatments in efficacy and adverse effects (Zhang et al, 2001).

d) Results of a subanalysis of data from the multinational risperidone trial (double-blind, randomized, paralle
reduction in negative symptoms was significantly better in patients receiving risperidone 16 mg/day than halo
0.05) (Moller et al, 1997). Patients with chronic schizophrenia (n=169) were treated with risperidone 1 mg, 4 r
haloperidol 10 mg/day for 8 weeks. Improvement was noted in each group. Risperidone onset was faster tha
Positive and Negative Syndrome Scale cluster scores revealed significantly greater improvement in the rispe
the haloperidol group on 2 clusters: activity and anxiety/depression (p less than 0.05).

e) Risperidone was significantly better than haloperidol in the treatment of chronic schizophrenia using comb
(Chouinard et al, 1993a; Marder & Meibach, 1994) to evaluate five factors of the Positive and Negative Syndr
Data from 513 patients showed that after 6 to 8 weeks of therapy, patients receiving risperidone 6 to 16 millig
adjusted mean changes in total Positive and Negative Syndrome Scale than patients treated with haloperidol
symptom areas that risperidone was significantly superior to haloperidol included: negative symptoms (p less
less than 0.05), disorganized thought (p less than 0.05), uncontrolled hostility/excitement (p less than 0.01), a
than 0.01). One author, however, noted some positive symptoms that reemerged after an initial response to r
1997).

f) In a meta-analysis, risperidone (4 to 8 milligrams(mg)/day) was found to be more effective and produce fe
haloperidol (4 to 20 mg/day). Seven studies done in a double-blind, randomized fashion were included. The p
clinical improvement defined as a 20% reduction in the total scores on the Brief Psychiatric Rating Scale or th
Syndrome Scale. Results showed that patients identified as treatment failures were 50% of those taking rispe
83% on placebo. There was a highly significant need for anticholinergic medication in the haloperidol-treated
risperidone (P less than 0.00001) (de Oliveira et al, 1996).

g) Risperidone was more effective than haloperidol in a double-blind, placebo-controlled, multicenter study (
schizophrenic patients were randomly assigned to receive 4 fixed doses of risperidone (2, 6, 10, and 16 millig
haloperidol 20 milligrams daily or placebo for 8-weeks (Marder and Meibach, 1994). Patients receiving risperi
statistically greater improvement than placebo or haloperidol in Clinical Global Impression (CGI) and total Pos
Scale (PANSS) scores. Of the four doses studied, the 6, 10, and 16 milligram doses were all effective with th
most effective. Similar results have been reported (Chouinard et al, 1993a; Marder, 1992).

h) In an 8-week, double-blind study, 1362 schizophrenic patients were randomly assigned to receive either r
milligrams/day, on a BID schedule, or haloperidol 10 milligrams daily (Muller-Spahn, 1992). Significantly grea
Negative Syndrome Scale (PANSS) and Brief Psychiatric Rating Scale (BPRS) total score, the PANSS Gene
the BPRS Activity and Anxiety/Depression cluster, was observed in the risperidone 4 milligram and 8 milligra
treated patients. In addition, a greater percentage of patients treated with risperidone 4 and 8 milligrams achi
PANSS and BPRS as compared with the haloperidol group.

i) Risperidone was faster acting, more effective, and had fewer side effects than haloperidol in a study to det
negative symptoms of schizophrenia (Claus et al, 1992a). The multicenter double-blind study that took place
included a two-week run-in period and a one-week washout period. The patients (n=42) took one to 5 mg bid
weeks. The Positive and Negative Syndrome Scale for Schizophrenia was the key efficacy parameter. The S
and Schizophrenia Change Conversion was used as a diagnostic aid and symptom severity measure. The Cl
was complete as a global rating. In addition, the occurrence of extrapyramidal side effects was also monitore

was approximately three times greater in the risperidone group, both at week six and at endpoint. In addition, was quicker in the risperidone group. Finally, the risperidone group needed 10 times less anticholinergic med extrapyramidal side effects than did the haloperidol group. According to this study, risperidone showed a grea schizophrenic symptoms than haloperidol.

j) Risperidone was less effective as monotherapy when compared to combination therapy of haloperidol and coexisting psychotic and depressive disorders. In this double-blind multicenter study, 123 patients were rand risperidone (dose titrated to 8 milligrams (mg) by the end of week 1) or the combination of haloperidol and an mg and 200 mg by the end of week 1). For all patients, doses were then adjusted under double blind conditio on response. At endpoint, the mean effective daily dose was 6.9 mg risperidone, and 9 mg haloperidol in con amitriptyline. In the 98 patients who completed at least 3 weeks of treatment, Brief Psychiatric Rating Scale (treatment groups, but the reduction in the combination treatment group was significantly greater than the risp The proportion of patients achieving at least 50% improvement in BPRS scores was also significantly higher 0.002). Greater benefit by combination therapy was still observed in an intent-to-treat analyses of the 123 pat medication for extrapyramidal symptoms was higher in the risperidone group (Muller-Siecheneder et al, 1998

4.6.D.6 Adverse Effects

a) The results of one study suggest that patients receiving atypical antipsychotics have a higher incidence of receiving a conventional antipsychotic medication. In a retrospective, pharmacovigilance study, 192 cases of patients taking clozapine (mean dose, 306.7 milligrams (mg)/day), olanzapine (mean dose, 15 mg/day), rispe or haloperidol (mean dose, 8.2 mg/day). Of the identified cases, 40%, 33%, and 16% were related to treatme medications clozapine, olanzapine, or risperidone, respectively, as compared with 12% of the cases which w neuroleptic, haloperidol. In most patients, time to onset of pancreatitis was within 6 months after initiation of t

4.6.E Lithium

4.6.E.1 Mania

a) A small, controlled study, compared the efficacy and safety of risperidone versus lithium and haloperidol i results with risperidone. Patients (n=45) were assigned to take risperidone (as monotherapy), dosed at 6 mg day, or 800 to 1000 mg daily of lithium. All 3 groups showed a similar improvement on Brief Psychiatric Ratin Scale scores. The EPS of risperidone and haloperidol were not significantly different and mania did not worse treated patients (Segal et al, 1998a).

4.6.F Olanzapine

Agitation, acute - Psychotic disorder

Bipolar disorder

Chronic schizophrenia

Dementia - Problem behavior

Extrapyramidal disease

Obsessive-compulsive disorder, Refractory

Schizophrenia

4.6.F.1 Agitation, acute - Psychotic disorder

a) Olanzapine orally disintegrating tablets (ODT) and risperidone oral solution (OS) yielded similar improvem for Positive and Negative Syndrome Scale (PANSS-EC) and the Clinical Global Impression (CGI) scale in 87 psychotic agitation in a psychiatric emergency setting, according to an open-label, flexible-dose study. Patien score of 15 or higher who accepted oral medication were assigned to receive initial doses of either olanzapin or risperidone OS 3 mg (n=53). Treatment group assignments were based on previous effective treatments, olanzapine or risperidone according to the time of study trial entry. Patients who experienced continued agita time, and after 1 hour could receive adjunctive drug therapy. PANSS-EC scores in both groups decreased ov from baseline was similar between the olanzapine and risperidone group (2.8 vs 3.2; p=0.22). Repeated mea score over time ANOVA (at baseline and every 15 minutes for 1 hour) revealed no significant main effect of t treatment over time (F=2.94, p=0.09 and F=0.88, p=0.41, respectively). There was a significant mean change ODT group compared with risperidone OS group (-9.2 vs 1.1 beats/minute, p=0.03). There were no significar treatment groups for adverse effects including extrapyramidal symptoms (Hatta et al, 2008).

4.6.F.2 Bipolar disorder

a) In a retrospective study of 50 consecutive patients treated for bipolar disorder with atypical antipsychotic r

improvement of at least 1 point in their Clinical Global Impressions assessment over the 12-week study. Mea
(mg) per day for clozapine, 11.7 mg/day for olanzapine, and 1.7 mg day for risperidone. The only serious adv
study was a seizure in a patient taking clozapine. Extrapyramidal symptoms (EPS) were reported in 12 of 42
occurred in 4 of 25 patients taking risperidone, 1 of 20 taking olanzapine, and 1 of 5 taking clozapine. Weight
patients taking clozapine and olanzapine than in those taking risperidone. Weight gain, which was greater tha
have been affected by concurrent mood enhancing medications (Guille et al, 2000).

4.6.F.3 Chronic schizophrenia

a) When newer antipsychotic medications (olanzapine, quetiapine, risperidone, and ziprasidone) were comp
antipsychotic, perphenazine, the majority of patients in each group discontinued their antipsychotic study me
Patients (n=1493) with chronic schizophrenia were randomized to receive olanzapine 7.5 to 30 milligrams/da
mg/day, quetiapine 200 to 800 mg/day, risperidone 1.5 to 6.0 mg/day, or ziprasidone 40 to 160 mg/day for up
patients discontinued treatment for any cause before 18 months; discontinuation rates ranged from 64 to 82%
from 3.5 months for ziprasidone to 9.2 months with olanzapine. The time to discontinuation was significantly l
compared with the quetiapine (hazard ratio (HR), 0.63; 95% confidence interval (CI), 0.52 to 0.76; p less than
(HR, 0.75; 95% CI, 0.62 to 0.90; p=0.002). Time to discontinuation due to adverse events were similar betwe
ranged from 10% for risperidone to 19% for olanzapine (p=0.04). More patients discontinued olanzapine due
of 0.9 kilograms/month) and greater increases in glycosylated hemoglobin, total cholesterol, and triglycerides

4.6.F.4 Dementia - Problem behavior

a) Risperidone and olanzapine were equally effective in the treatment of dementia-related behavioral disturb
term care facilities. In a double-blind, parallel study, patients (mean age, 83 years) with dementia received or
2.5 milligrams (mg)/day, titrated to maximum dose of 10 mg/day) or risperidone (n=19, initial dose 0.5 mg/da
mg/day) at bedtime for two weeks following a 3-day washout period of psychotropic drugs. Antidepressants a
at stable doses and lorazepam was used as a rescue medication at doses of 0.5 to 1 mg as needed for acute
for olanzapine and risperidone were 6.65 mg (range, 2.5 to 10 mg) and 1.47 mg (range, 0.5 to 2 mg), respect
median of 3.5 days (range 1-12 days) and the median dose was 2 mg (range, 0.2 to 21 mg). Primary outcom
Neuropsychiatric Inventory (NPI) and the Clinical Global Impressions Scale (CGI). Both treatments significant
NPI scores from baseline to endpoint (p less than 0.0001, both values), however, there was no difference be
events were frequent in this elderly population, with the most common including drowsiness, falls, and extrap
at, 2003).

4.6.F.5 Extrapyramidal disease

a) Results of a retrospective analysis showed that olanzapine treatment was associated with a lower rate of
than haloperidol, but was similar to rates occurring with risperidone and clozapine therapy. In a pooled analys
clinical trials in 4611 patients with schizophrenia, frequency and severity of EPS associated with olanzapine t
(mg)/day) was compared with that of haloperidol (1 to 20 mg/day), risperidone (4 to 12 mg/day), clozapine (2
Dystonic events (ie, dystonia, oculogyric crisis, opisthotonos, torticollis) occurred in significantly fewer patient
compared with haloperidol (0.5% vs 5.6%, respectively; p less than 0.001) or risperidone (1% vs 3.2%, respe
no significant difference was found between olanzapine- and clozapine-treated patients. As compared with ol
significantly higher percentage of haloperidol-treated patients experienced parkinsonian events (ie, akinesia,
syndrome, hypertonia, hypokinesia, masked facies, and tremor) (9.3% vs 28.3%, respectively; p less than 0.0
akathisia, hyperkinesia) (6.7% vs 20.4%, respectively; p less than 0.001) during therapy. However, no signific
between the olanzapine group as compared with the placebo, risperidone, or clozapine groups in regard to th
akathisia events. Overall, EPS occurred in significantly more patients treated with haloperidol as compared w
respectively; p less than 0.001) and in fewer patients treated with clozapine as compared with olanzapine (2.
p=0.047). The overall rate of EPS was similar between the placebo and risperidone groups as compared with
patients received anticholinergic medications in the olanzapine group as compared with the haloperidol (p les
(p=0.018) groups. No difference was found between olanzapine-treated patients as compared with placebo o
percentage of patients given anticholinergic drugs during therapy (Carlson et al, 2003).

4.6.F.6 Obsessive-compulsive disorder, Refractory

a) Adjunctive therapy of risperidone or olanzapine with serotonin-reuptake inhibitors (SRI) were equally effec
compulsive symptoms in SRI monotherapy-resistant outpatients, according to an 8-week, single-blind, randor
conclusion may be limited by the lack of a placebo arm, single-arm design, and underpowered nature of the t
prospective, open-label phase of SRI monotherapy (n=96), patients who were treatment-resistant (defined as
the total score of Yale-Brown Obsessive Compulsive Scale (Y-BOCS) and a Clinical Global Impression Seve
entered an 8-week single-blind phase (n=50). Patients in the single-blind phase received SRI daily doses of c
citalopram 50 to 80 mg, fluoxetine 60 mg, fluvoxamine 200 to 300 mg, paroxetine 50 to 60 mg, or sertraline 2
receive either risperidone 1 to 3 mg/day (n=25), or olanzapine 2.5 to 10 mg/day (n=25) in addition to the SRI
personnel and assessor-blinding constituted the single-blind study design; patients were not blinded. In an int
carried forward analysis of the primary endpoints, both treatments significantly improved Y-BOCS and CGI-S
The magnitude of change in mean Y-BOCS total scores, CGI-S scores, and responder rates (35% or greater
versus baseline, and a CGI-I score of 2 or less) was similar between groups.

Primary Efficacy Endpoints at 8 Weeks		

	Risperidone (n=25)	Olanzapine (n=25)
Responder rates*	44% (11/25)	48% (12/25)
Mean end-point Y-BOCS score	22.6 +/- 7.2	22.2 +/- 7.4
Change in mean Y-BOCS score from baseline	-7.5; t=7.588, df=21, p less than 0.001	-8.4; t=7.456, df=20 0.001
Mean end-point CGI-S score	3.2 +/- 1.7	3.1 +/- 1.8
Change in mean CGI-S score from baseline	-1.7; t=7.022, df=21, p less than 0.001	-1.9; t=7.707, df=20 0.001
* p=1; Y-BOCS=Yale-Brown Obsessive Compulsive Scale; CGI-S=Clinical Global Impression Severity s		

b) Adverse effects of risperidone compared with olanzapine-treated patients included tension/inner unrest (2 (16% vs 52%, p=0.016), and amenorrhea (66.7% vs 10%, p=0.02), respectively. The small sample size and t calculation may have contributed to the limitations of this study (Maina et al, 2008).

4.6.F.7 Schizophrenia

a) Olanzapine and risperidone were equally safe and effective therapies in the treatment of schizophrenia in international, multicenter, double-blind study, 175 elderly patients (mean age, 71 years) were randomized to dose, 1.9 milligrams (mg)/day) or olanzapine (mean dose, 11.1 mg/day) for 8 weeks following a 1 week wash medications. Mean duration of illness was 36.5 years and Positive and Negative Syndrome Scale (PANSS) s at baseline. Clinical improvement was defined as a decrease of at least 20% in the total PANSS score. Both significant reductions from baseline in the total PANSS score at all time points (p less than 0.005) and signific observed between groups. Fifty-eight percent of risperidone-treated patients and 59% of olanzapine-treated improvement as defined by the study. Both groups also exhibited significant improvement in four of the five P 0.001). The greatest mean change in the total PANSS score occurred in the 93 patients who had received co medications in the thirty days prior to entering the study (p less than 0.001). The rate of extrapyramidal symp the risperidone and olanzapine treatment groups (9.2% vs 15.9%, respectively, p=ns). The severity of EPS sy groups from baseline to endpoint with no significant difference between groups. A 7% or higher increase in w more olanzapine-treated patients as compared with those who received risperidone (14.8% vs 5.1%, p=0.043 were observed in this patient population and mean QT-c changes were not considered clinically relevant (Jes

b) Olanzapine and risperidone improved neurocognitive deficits more than did haloperidol or clozapine in pa schizoaffective disorder that was refractory to treatment with typical antipsychotics. In a randomized, double- clozapine (n=24) 200 to 800 milligrams (mg) per day, olanzapine (n=26) 10 to 40 mg/day, risperidone (n=26) (n=25) 10 to 30 mg/day. Dose escalation and fixed-dose treatment (target doses: olanzapine 20 mg/day, risp mg/day, clozapine 500 mg/day) occurred during the first 8 weeks of the 14-week study; during the last 6 wee individually (generally increased if response was insufficient, but sometimes reduced because of adverse effe global neurocognitive score was seen for olanzapine and risperidone. In general executive and perceptual or speed and attention, improvement was seen with olanzapine. In simple motor function, there was improveme global neurocognitive performance with olanzapine and risperidone were of medium magnitude (approximate large enough to be clinically significant. Beneficial changes with clozapine were modest. Despite cognitive ga impairments of cognitive ability and social/vocational functioning. Improvements in neurocognitive deficits we in negative symptoms (Bilder et al, 2002).

c) In a prospective, multicenter, double-blind trial, olanzapine was more cost-effective than risperidone in pa schizoaffective disorder, or schizophreniform disorder. One hundred fifty patients were randomized to either per day (mg/d) (n=75) or risperidone (4 to 12 mg/d) (n=75) treatment for a period of 28 weeks. During the stu were significantly more likely to maintain a therapeutic response throughout the course of therapy than risper However, the proportion of patients who responded to treatment was not significantly different between group effects was similar between groups, but significantly more risperidone-treated patients required an anticholine emergent extrapyramidal effects than did those receiving olanzapine (45% versus 25%, p=0.016). Medicatior for olanzapine-treated patients than those treated with risperidone ($2513 versus $1581 US), but this differer in inpatient and outpatient service costs ($3516 vs $7291 US) (Edgell et al, 2000).

d) In an open-label study of patients with DSM-IV schizophrenia, olanzapine (n=21) was shown to be as effe acute treatments. At 6 months, risperidone was more effective for treatment of psychotic symptoms. Howeve less akathisia at the end of 6 months. At discharge the average doses of olanzapine and risperidone were 14 respectively. The reduction of psychotic symptoms with risperidone was significantly greater than with olanaz uncontrolled and adjusted by the treating psychiatrist based on the patient's response, tolerability of side effe recommendations. Measures of effectiveness included the SANS, SAPS, Brief Psychiatric Rating Scale (BPF (GAS) and quality of life measures. (Ho et al, 1999). Larger studies are needed comparing olanzapine and ris

e) Olanzapine (10 to 20 milligrams (mg) daily) was superior to risperidone (4 to 12 mg daily) in the treatment In an international, multicenter, double-blind, parallel-group 28-week prospective study of 339 patients with D schizophreniform disorder, or schizoaffective disorder, the olanzapine group had a significantly better overall decrease in the Positive and Negative syndrome Scale) and was significantly superior to risperidone in the tr

symptomatology. Based on the Kaplan-Meier survival curves, a significantly greater number of the olanzapine response at 28 weeks compared to the risperidone group. Overall adverse reactions were significantly less w extrapyramidal side effects, hyperprolactinemia and sexual dysfunction, with the exception of weight gain; su significantly less in the olanzapine group (Tran et al, 1997). The use of possibly unequivalent doses in this st criticized (Schooler, 1998; Gheuens & Grebb, 1998).

4.6.F.8 Adverse Effects

a) The results of one study suggest that patients receiving atypical antipsychotics have a higher incidence of receiving a conventional antipsychotic medication. In a retrospective, pharmacovigilance study, 192 cases of patients taking clozapine (mean dose, 306.7 milligrams (mg)/day), olanzapine (mean dose, 15 mg/day), rispe or haloperidol (mean dose, 8.2 mg/day). Of the identified cases, 40%, 33%, and 16% were related to treatme medications clozapine, olanzapine, or risperidone, respectively, as compared with 12% of the cases which w neuroleptic, haloperidol. In most patients, time to onset of pancreatitis was within 6 months after initiation of t

4.6.G Paroxetine

4.6.G.1 Panic attack

a) In an 8-week, randomized, single-blind, comparative trial (n=56) of low-dose risperidone and paroxetine ir both treatments were effective in reducing the occurrence and severity of panic attacks but there was no diffe improve anxiety associated with panic disorders. Thirty-three (8 men, 25 women) subjects were randomized t women) to paroxetine. The average age of the group was 40.36 +/- 12.37 years. Risperidone was initiated at necessary for lack of response or sedation (maximum dose of 16 mg/day). Paroxetine was initiated at 30 mg/ 60 mg/day if needed. The average risperidone dose was 0.53 mg (range 0.125 mg to 1 mg). All subjects in th mg/day except for one who required a dose of 40 mg. Subject assessments were conducted by a clinical rate using the 17-item Hamilton Depression Rating Scales (Ham-D-17), the Hamilton Anxiety Rating Scale (Ham- Scale (PDSS), the Sheehan Panic Anxiety Scale-Patient (SPAS-P) and the Clinical Global Impressions Scale risperidone group and 9 in the paroxetine group completed all study visits. A significant decrease in CGI scor subjects (p less than 0.001), but there was no significant difference between the groups. The CGI score impr to 2.84 +/- 1.02 at final assessment in the risperidone arm. Similarly, paroxetine resulted in a CGI score impr 2.67 +/- 0.71 at final assessment. All subjects, regardless of treatment, demonstrated a significant decrease i total score, PDSS item 1, PDSS item 2, Ham-A and Ham-D. There was no statistical difference between trea study, and there was no significant change in SPAS-p scores over time (Prosser et al, 2009).

4.6.H Perphenazine

Chronic schizophrenia

Schizophrenia

4.6.H.1 Chronic schizophrenia

a) When newer antipsychotic medications (olanzapine, quetiapine, risperidone, and ziprasidone) were comp antipsychotic, perphenazine, the majority of patients in each group discontinued their antipsychotic study me Patients (n=1493) with chronic schizophrenia were randomized to receive olanzapine 7.5 to 30 milligrams/da mg/day, quetiapine 200 to 800 mg/day, risperidone 1.5 to 6.0 mg/day, or ziprasidone 40 to 160 mg/day for up patients discontinued treatment for any cause before 18 months; discontinuation rates ranged from 64 to 82% from 3.5 months for ziprasidone to 9.2 months with olanzapine. The time to discontinuation was significantly l compared with the quetiapine (hazard ratio (HR), 0.63; 95% confidence interval (CI), 0.52 to 0.76; p less than (HR, 0.75; 95% CI, 0.62 to 0.90; p=0.002). Time to discontinuation due to adverse events were similar betwe ranged from 10% for risperidone to 19% for olanzapine (p=0.04). More patients discontinued olanzapine due of 0.9 kilograms/month) and greater increases in glycosylated hemoglobin, total cholesterol, and triglycerides

4.6.H.2 Schizophrenia

a) Risperidone and perphenazine were equally efficacious in a double-blind, multicenter, parallel-group study schizophrenics with acute exacerbation were enrolled (Hoyberg et al, 1993a). No statistically significant differ (defined as a 20% reduction in total Positive and Negative Syndrome Scale score at endpoint) were found be Clinical Global Impression severity scores were also comparable. Patients with predominantly negative symp significantly lower Brief Psychiatric Rating Scale hostility scores compared to patients taking perphenazine.

4.6.I Quetiapine

Chronic schizophrenia

Psychotic disorder

4.6.I.1 Chronic schizophrenia

a) When newer antipsychotic medications (olanzapine, quetiapine, risperidone, and ziprasidone) were comp
antipsychotic, perphenazine, the majority of patients in each group discontinued their antipsychotic study me
Patients (n=1493) with chronic schizophrenia were randomized to receive olanzapine 7.5 to 30 milligrams/da
mg/day, quetiapine 200 to 800 mg/day, risperidone 1.5 to 6.0 mg/day, or ziprasidone 40 to 160 mg/day for up
patients discontinued treatment for any cause before 18 months; discontinuation rates ranged from 64 to 82%
from 3.5 months for ziprasidone to 9.2 months with olanzapine. The time to discontinuation was significantly l
compared with the quetiapine (hazard ratio (HR), 0.63; 95% confidence interval (CI), 0.52 to 0.76; p less than
(HR, 0.75; 95% CI, 0.62 to 0.90; p=0.002). Time to discontinuation due to adverse events were similar betwe
ranged from 10% for risperidone to 19% for olanzapine (p=0.04). More patients discontinued olanzapine due
of 0.9 kilograms/month) and greater increases in glycosylated hemoglobin, total cholesterol, and triglycerides

4.6.I.2 Psychotic disorder

a) Quetiapine and risperidone were similarly efficacious in treating psychotic symptoms and had similar over
treatment resulted in fewer extrapyramidal symptoms (EPS) and was more effective in reducing depression.
patients with schizophrenia, schizoaffective disorder, or other psychotic disorders (including bipolar disorder,
various forms of dementia) were randomized in a ratio of 3:1 to receive quetiapine (n=553) or risperidone (n=
quetiapine was 50 milligrams/day (mg/day), which was increased in 50- or 100- mg increments every 1 to 2 d
mg/day, given in divided doses. Risperidone was started at 1 mg twice daily, with upward titration to a target
3. Dosages were individually titrated to maximize efficacy while minimizing adverse reactions (mean prescrib
risperidone 4.4 mg). At the beginning of the study, approximately half of each group had EPS. There was a s
patients reporting EPS in both groups as the study progressed. The incidence of EPS in the quetiapine group
risperidone group at one month (41.1 vs 47.3) but not at the end of the study (38.6 vs 39.2). The percentage
treatment due to EPS or requiring anti-EPS medication was lower in the quetiapine group than in the risperid
Approximately one third of patients in each group withdrew before completion of the study. A higher percenta
treatment for lack of efficacy (10.3% vs 5.8%) and a higher percentage withdrew from quetiapine treatment b
vs 5.1%). Somnolence was the most common adverse event in both groups, followed by dry mouth and dizzi
significantly more often with quetiapine treatment (p less than 0.05). Occurrence of weight gain was low in bo

4.6.J Ziprasidone

4.6.J.1 Chronic schizophrenia

a) When newer antipsychotic medications (olanzapine, quetiapine, risperidone, and ziprasidone) were comp
antipsychotic, perphenazine, the majority of patients in each group discontinued their antipsychotic study me
Patients (n=1493) with chronic schizophrenia were randomized to receive olanzapine 7.5 to 30 milligrams/da
mg/day, quetiapine 200 to 800 mg/day, risperidone 1.5 to 6.0 mg/day, or ziprasidone 40 to 160 mg/day for up
patients discontinued treatment for any cause before 18 months; discontinuation rates ranged from 64 to 82%
from 3.5 months for ziprasidone to 9.2 months with olanzapine. The time to discontinuation was significantly l
compared with the quetiapine (hazard ratio (HR), 0.63; 95% confidence interval (CI), 0.52 to 0.76; p less than
(HR, 0.75; 95% CI, 0.62 to 0.90; p=0.002). Time to discontinuation due to adverse events were similar betwe
ranged from 10% for risperidone to 19% for olanzapine (p=0.04). More patients discontinued olanzapine due
of 0.9 kilograms/month) and greater increases in glycosylated hemoglobin, total cholesterol, and triglycerides

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Last Modified: June 26, 2009

DRUGDEX® Evaluations

QUETIAPINE

0.0 Overview

1) Class

a) This drug is a member of the following class(es):
Antipsychotic
Dibenzothiazepine

2) Dosing Information

a) Quetiapine Fumarate

1) Adult

a) Bipolar disorder, depressed phase

1) regular-release tablets, 50 mg ORALLY once a day on day 1, then 100 mg once daily on day 2, then day 3, then 300 mg once daily on day 4 (all doses given at bedtime); patients requiring higher doses sho day 5, increased to 600 mg on day 8 (week 1) (Prod Info SEROQUEL(R) oral tablets, 2008a)

2) re-initiation of therapy: if less than 1 week off of quetiapine, titration of dose is not required and maint re-initiated; if greater than 1 week off of quetiapine, initial titration schedule should be followed (Prod Info tablets, 2008a)

b) Bipolar disorder, Maintenance

1) regular-release tablets, 400 mg to 800 mg per day ORALLY divided twice daily; generally continuatio or lowest dose to maintain remission; periodically reassess for need and appropriate dose for maintenan Info SEROQUEL(R) oral tablets, 2008a)

c) Manic bipolar I disorder

1) regular-release tablets, initial, 50 mg ORALLY twice daily, may increase dosage by increments up to the second and third day, to a target dose 400 mg per day by the fourth day given in 2 divided doses (Pr (R) oral tablets, 2007b)

2) regular-release tablets, maintenance, dosage adjustments in increments of not more than 200 mg/da day 6; usual effective dosage range is 400 to 800 mg/day; MAX dosage 800 mg/day (Prod Info SEROQU 2007b)

3) re-initiation of therapy: if less than 1 week off of quetiapine, titration of dose is not required and maint re-initiated; if greater than 1 week off of quetiapine, initial titration schedule should be followed (Prod Info tablets, 2007b)

d) Schizophrenia

1) regular-release tablets, initial, 25 mg ORALLY twice daily, may increase dosage by 25 to 50 mg 2 to second and third day, as tolerated, to a target dose range of 300 to 400 mg daily by the fourth day, given doses (Prod Info SEROQUEL(R) oral tablets, 2007b)

2) regular-release tablets, maintenance, dosage adjustments, if indicated, should generally occur at inte days in dose increments/decrements of 25 to 50 mg twice a day; usual effective dosage range is 150 to divided doses), MAX dosage 800 mg/day (Prod Info SEROQUEL(R) oral tablets, 2007b)

3) extended-release tablets, initial, 300 mg ORALLY once daily, preferably in the evening; titrate to a tar to 800 mg daily; dose increases may occur at intervals of at least 1 day in increments of up to 300 mg/da mg/day (Prod Info SEROQUEL XR(TM) extended-release oral tablets, 2007)

4) re-initiation of therapy: if less than 1 week off of quetiapine, titration of dose is not required and maint re-initiated; if greater than 1 week off of quetiapine, initial titration schedule should be followed (Prod Info extended-release oral tablets, 2007; Prod Info SEROQUEL(R) oral tablets, 2007b)

e) Schizophrenia, Maintenance

1) extended-release tablets, 400 to 800 mg ORALLY once daily, preferable in the evening; periodically r appropriate dose for maintenance treatment (Prod Info SEROQUEL(R)XR extended-release oral tablets,

2) Pediatric

a) safety and effectiveness in pediatric patients have not been established (Prod Info SEROQUEL XR(TM) e tablets, 2007; Prod Info SEROQUEL(R) oral tablets, 2008a)

3) Contraindications

a) Quetiapine Fumarate

1) hypersensitivity to quetiapine fumarate or any component of the product (Prod Info SEROQUEL(R) oral tablets

4) Serious Adverse Effects

a) Quetiapine Fumarate

1) Agranulocytosis
2) Anaphylaxis
3) Death
4) Leukopenia
5) Neuroleptic malignant syndrome
6) Neutropenia
7) Priapism
8) Seizure

9) Sudden cardiac death
10) Suicidal thoughts
11) Syncope
12) Tardive dyskinesia

5) Clinical Applications
a) Quetiapine Fumarate
1) FDA Approved Indications
a) Bipolar disorder, depressed phase
b) Bipolar disorder, Maintenance
c) Manic bipolar I disorder
d) Schizophrenia
e) Schizophrenia, Maintenance

1.0 Dosing Information

Drug Properties

Storage and Stability

Adult Dosage

Pediatric Dosage

1.1 Drug Properties

A) Information on specific products and dosage forms can be obtained by referring to the Tradename List (Product In
B) Synonyms
Quetiapine
Quetiapine Fum
Quetiapine Fumarate
C) Physicochemical Properties
1) Molecular Weight
a) Quetiapine fumarate: 883.11 (Prod Info Seroquel, 97)
2) Solubility
a) Systemic: Quetiapine fumarate is moderately soluble in water (Prod Info Seroquel, 97).

1.2 Storage and Stability

A) Quetiapine Fumarate
1) Preparation
a) Oral route
1) Administration
a) Quetiapine extended-release tablets should not be chewed, crushed or split and should be swall
SEROQUEL XR(TM) extended-release oral tablets, 2007).
b) The absorption of extended-release quetiapine tablets is affected by food; give without food or w
approximately 300 calories (Prod Info SEROQUEL XR(TM) extended-release oral tablets, 2007). Re
are only marginally affected by food, and may be given without regards to food (Prod Info SEROQU
2008a).
B) Quetiapine Fumarate
1) Oral route
a) Tablet/Tablet, Extended Release
1) Store at 25 degrees C (77 degrees F), with excursions permitted between 15 and 30 degrees C (59 a
(Prod Info SEROQUEL(R) oral tablets, 2008; Prod Info SEROQUEL XR(R) extended-release oral tablets

1.3 Adult Dosage

Normal Dosage

Dosage in Renal Failure

Dosage in Hepatic Insufficiency

Dosage in Geriatric Patients

Dosage in Other Disease States

1.3.1 Normal Dosage

1.3.1.A Quetiapine Fumarate

1.3.1.A.1 Oral route

Bipolar disorder, depressed phase

Manic bipolar I disorder

Schizophrenia

Schizophrenia, Maintenance

1.3.1.A.1.a Bipolar disorder, depressed phase

1) The recommended quetiapine dosing schedule for the treatment of depressive episodes associa disorder is 50 milligrams (mg), 100 mg, 200 mg, and 300 mg given once a day at bedtime on days 1 respectively. If a higher dose is required, the dose may be increased to 400 mg on day 5 and 600 m In clinical trials, both 300 mg and 600 mg doses demonstrated antidepressant efficacy; however, no seen in the 600 mg group (Prod Info SEROQUEL(R) oral tablets, 2008a).

2) When restarting treatment in patients who have had an interval of less than 1 week off of quetiap dose is not required and the maintenance dose may be re-initiated. The initial titration schedule sho re-initiating therapy in patients who have not taken quetiapine for more than 1 week (Prod Info SER tablets, 2008a).

1.3.1.A.1.b Manic bipolar I disorder

1) As monotherapy or adjunct therapy (with lithium or divalproex) in the treatment of acute bipolar m recommended initial dose of quetiapine is 100 milligrams per day (mg/day) (in two divided doses) or 400 mg/day on day 4 in increments of up to 100 mg/day (in two divided doses). Additional dosage a mg/day by day 6 should be in increments of no more than 200 mg/day. Most patients respond to dos 800 mg/day. The safety of doses greater than 800 mg/day has not been evaluated (Prod Info SERO 2007b).

2) When restarting treatment in patients who have had an interval of less than 1 week off of quetiap dose is not required and the maintenance dose may be re-initiated. The initial titration schedule sho re-initiating therapy in patients who have not taken quetiapine for more than 1 week (Prod Info SER tablets, 2007b).

1.3.1.A.1.c Schizophrenia

1) Regular-Release Tablets

a) For the treatment of schizophrenia, the recommended initial dose of quetiapine regular-relea milligrams (mg) twice daily. On the second or third day, the dose may be increased in incremen or three times daily. By the fourth day a target dose of 300 to 400 mg daily divided in two or thre recommended. Further increases can be made in increments of 25 to 50 mg twice daily at inter days. Antipsychotic efficacy has been demonstrated in the range of 150 to 750 mg usually given The safety of doses greater than 800 mg has not been determined (Prod Info SEROQUEL(R) o

b) For the treatment of schizophrenia, average effective doses of quetiapine in clinical trials ha and 400 milligrams daily, with the dose given in 2 or 3 divided doses; maximum doses have bee (Goren & Levin, 1998; Fulton & Goa, 1995b; Anon, 1995b; Borison et al, 1996b).

c) When restarting treatment in patients who have had an interval of less than 1 week off of qu dose is not required and the maintenance dose may be re-initiated. The initial titration schedule when re-initiating therapy in patients who have not taken quetiapine for more than 1 week (Proc oral tablets, 2008a).

2) Extended-Release Tablets

a) For the treatment of schizophrenia, the recommended initial dose of quetiapine extended-rel milligrams (mg) once daily, preferably given in the evening. Titrate the dose based upon patient tolerance within a range of 400 to 800 mg/day. Doses may be increased in increments of up to intervals as short as 1 day. Doses greater than 800 mg/day have not been evaluated for safety Info SEROQUEL XR(TM) extended-release oral tablets, 2007).

b) When restarting treatment in patients who have had an interval of less than 1 week off of qu the dose is not required and the maintenance dose may be re-initiated. The initial titration sched followed when re-initiating therapy in patients who have not taken quetiapine for more than 1 we

SEROQUEL XR(TM) extended-release oral tablets, 2007).

3) Switching from Regular-Release to Extended-Release

a) Schizophrenic patients currently receiving 2 to 3 divided doses of oral quetiapine fumarate (i formulation) may be switched to the extended-release formulation at the equivalent total daily d orally once daily (Prod Info SEROQUEL(R)XR extended-release oral tablets, 2007).

1.3.1.A.1.d Schizophrenia, Maintenance

1) Doses of 400 to 800 milligrams (mg) per day of extended-release quetiapine were successful in compared to placebo in the double-blind extension phase of a clinical trial in schizophrenic patients open-label treatment for 16 weeks. The dose should be administered once daily in the evening eithe a light meal. The maximum dose evaluated in clinical trials was 800 mg. Periodic reassessments are evaluate the need and appropriate dose for maintenance treatment (Prod Info SEROQUEL(R)XR ex tablets, 2007).

2) When restarting treatment in patients who have had an interval of less than 1 week off of quetiap dose is not required and the maintenance dose may be re-initiated. The initial titration schedule for a be followed when re-initiating therapy in patients who have not taken quetiapine for more than 1 wee SEROQUEL(R)XR extended-release oral tablets, 2007).

1.3.1.A.1.e IMPORTANT NOTE

1) The FDA Safety Information and Adverse Event Reporting Program has reported that there have errors due to the similarity of the names, dosage forms, strengths, and dosing intervals for Seroquel (Anon, 2002).

1.3.2 Dosage in Renal Failure

A) Quetiapine Fumarate

1) Dosage adjustment does not appear necessary in patients with renal insufficiency (Prod Info SEROQUEL release oral tablets, 2007; Prod Info SEROQUEL(R) oral tablets, 2008a).

1.3.3 Dosage in Hepatic Insufficiency

A) Quetiapine Fumarate

1) Patients with hepatic impairment should be started on quetiapine therapy using the regular-release tablets (mg)/day then increased daily in increments of 25 to 50 mg/day to an effective dose. In these patients, the me quetiapine is 30% lower than subjects with normal hepatic clearance (Prod Info SEROQUEL XR(TM) extende 2007; Prod Info SEROQUEL(R) oral tablets, 2008a; Green, 1999a).

2) Patients may be switched to an equivalent total daily dose using extended-release tablets once an effectiv reached with the regular-release tablets (Prod Info SEROQUEL XR(TM) extended-release oral tablets, 2007)

1.3.4 Dosage in Geriatric Patients

A) Quetiapine Fumarate

1) Elderly patients should be started on quetiapine therapy using the regular-release tablets at 25 milligrams increased daily in increments of 25 to 50 mg/day to an effective dose. Oral clearance of quetiapine was reduc older than 65 years (Prod Info SEROQUEL XR(TM) extended-release oral tablets, 2007).

2) Patients may be switched to an equivalent total daily dose using extended-release tablets once an effectiv reached with the regular-release tablets (Prod Info SEROQUEL XR(TM) extended-release oral tablets, 2007)

1.3.6 Dosage in Other Disease States

A) Quetiapine Fumarate

1) Debilitated Patients

a) The manufacturer recommends that patients who are debilitated or have a predisposition to hypotens slower dose escalation and lower target dose (Prod Info SEROQUEL(R) oral tablets, 2008a; Prod Info S extended-release oral tablets, 2007).

1.4 Pediatric Dosage

1.4.1 Normal Dosage

1.4.1.A Quetiapine Fumarate

1.4.1.A.1 Oral route

a) Safety and effectiveness for use in pediatric patients have not been established (Prod Info SEROQUI release oral tablets, 2007; Prod Info SEROQUEL(R) oral tablets, 2008a).

b) In a small trial (n=10) of adolescents (mean age of 13.6 years) with selected psychotic disorders, que in a dosage range of 50 to 800 milligrams daily led to satisfactory clinical results and similar pharmacoki profiles to that of adults (McConville et al, 2000).

2.0 Pharmacokinetics

Onset and Duration

Drug Concentration Levels

ADME

2.1 Onset and Duration
A) Onset
1) Quetiapine Fumarate
a) Initial Response
1) Schizophrenia, oral: 7 to 14 days (Borison et al, 1996; Fulton & Goa, 1995)

2.2 Drug Concentration Levels
A) Quetiapine Fumarate
1) Therapeutic Drug Concentration
a) Schizophrenia, undefined (Fabre et al, 1995)
2) Time to Peak Concentration
a) Oral, regular-release tablets: 1.5 hours (Prod Info SEROQUEL(R) oral tablets, 2007; Fabre et al, 1995; Sh
1) Steady-state concentrations of quetiapine fumarate regular-release tablets occur within 2 days of dos
SEROQUEL(R) oral tablets, 2007).
2) A mean peak level of 278 ng/mL (range, 140 to 365 ng/mL) was observed after a 75-mg oral midday
quetiapine therapy; at this time, patients were receiving total daily doses of up to 250 mg. After a single d
quetiapine in schizophrenic patients, peak serum levels ranged from 18 to 136 ng/mL (mean, 60 ng/mL)
b) Oral, extended-release tablets: 6 h (Prod Info SEROQUEL(R)XR extended-release oral tablets, 2007)
1) Steady-state concentrations of quetiapine fumarate extended-release tablets occur within 2 days of d
SEROQUEL(R)XR extended-release oral tablets, 2007).

2.3 ADME

Absorption

Distribution

Metabolism

Excretion

Elimination Half-life

2.3.1 Absorption
A) Quetiapine Fumarate
1) Bioavailability
a) Oral: 9% (Goren & Levin, 1998).
1) The bioavailability of the extended-release quetiapine fumarate tablets, dosed once daily at stea
comparable to an equivalent dose of the regular-release tablets, dosed twice daily (Prod Info SERO
extended-release oral tablets, 2007).
2) Effects of Food
a) Regular-release tablets: marginally affected (Prod Info SEROQUEL(R) oral tablets, 2007)
1) When regular-release quetiapine fumarate tablets were administered with food, the Cmax and AU
and 15%, respectively (Prod Info SEROQUEL(R) oral tablets, 2007b).
2) Food increases the absorption of quetiapine (Goren & Levin, 1998). In healthy volunteers, admin
with food resulted in an increase in the peak serum concentration and area under the time-concentra
(each by approximately 1.5-fold) compared to the fasting state (Shimada et al, 1994).
b) Extended-release tablets: significant (Prod Info SEROQUEL(R)XR extended-release oral tablets, 200
1) Statistically significant increases in the Cmax and AUC of 44% to 52% and 20% to 22%, respecti
the 50-mg and 300-mg quetiapine fumarate extended-release tablets when given with a high-fat me
to 1000 calories). There was no significant effect on the Cmax or AUC when given with a light meal
calories) (Prod Info SEROQUEL(R)XR extended-release oral tablets, 2007; Prod Info SEROQUEL(R

2.3.2 Distribution
A) Distribution Sites
1) Quetiapine Fumarate
a) Protein Binding
1) 83% (Prod Info SEROQUEL(R) oral tablets, 2007; Prod Info SEROQUEL(R)XR extended-releas

B) Distribution Kinetics
1) Quetiapine Fumarate
a) Volume of Distribution
1) 10 L/kg +/- 4 L/kg (Prod Info SEROQUEL(R) oral tablets, 2007; Prod Info SEROQUEL(R)XR ext tablets, 2007)

2.3.3 Metabolism
A) Metabolism Sites and Kinetics
1) Quetiapine Fumarate
a) LIVER, extensive (Goren & Levin, 1998; Green, 1999)
1) Extensive first-pass metabolism occurs with quetiapine (Wetzel et al, 1995a).
2) Quetiapine fumarate is primarily metabolized by sulfoxidation and oxidation via the P450 CYP3A Info SEROQUEL(R) oral tablets, 2007; Prod Info SEROQUEL(R)XR extended-release oral tablets, 2
3) After a single oral dose, less than 1% of quetiapine is excreted unchanged (Prod Info SEROQUE 2007; Prod Info SEROQUEL(R)XR extended-release oral tablets, 2007).
B) Metabolites
1) Quetiapine Fumarate
a) N-desalkyl quetiapine, (active) (Prod Info SEROQUEL(R)XR extended-release oral tablets, 2007)
1) Twenty metabolites of quetiapine have been identified; the 7-hydroxylated metabolite and the N- are pharmacologically active (Goren & Levin, 1998).

2.3.4 Excretion
A) Kidney
1) Quetiapine Fumarate
a) Renal Excretion (%)
1) 70% to 73% (Prod Info SEROQUEL(R) oral tablets, 2007; Prod Info SEROQUEL(R)XR extended 2007; Green, 1999; Fulton & Goa, 1995)
a) Following administration of a single oral dose of carbon-labeled quetiapine, approximately 7 recovered in the urine (Prod Info SEROQUEL(R) oral tablets, 2007; Prod Info SEROQUEL(R)X oral tablets, 2007).
B) Feces
1) Quetiapine Fumarate
a) approximately 20% (Prod Info SEROQUEL(R) oral tablets, 2007; Prod Info SEROQUEL(R)XR extend tablets, 2007)
1) Following administration of a single oral dose of carbon-labeled quetiapine, approximately 20% c recovered in the feces (Prod Info SEROQUEL(R) oral tablets, 2007; Prod Info SEROQUEL(R)XR ex tablets, 2007).

2.3.5 Elimination Half-life
A) Parent Compound
1) Quetiapine Fumarate
a) Regular-release tablet, 6 hours (Prod Info SEROQUEL(R) oral tablets, 2007)
b) Extended-release tablet, 7 hours (Prod Info SEROQUEL(R)XR extended-release oral tablets, 2007)

3.0 Cautions

Contraindications

Precautions

Adverse Reactions

Teratogenicity/Effects in Pregnancy/Breastfeeding

Drug Interactions

3.0.A Black Box WARNING
1) Quetiapine Fumarate
a) Oral (Tablet)
Increased Mortality in Elderly Patients with Dementia-Related Psychosis
Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk seventeen placebo-controlled trials (modal duration of 10 weeks) largely in patients taking atypical antips revealed a risk of death in drug-treated patients of between 1.6 times to 1.7 times the risk of death in pla Over the course of a typical 10 week controlled trial, the rate of death in drug-treated patients was about rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths a

cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Observationa similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mo which the findings of increased mortality in observational studies may be attributed to the antipsychotic d some characteristic(s) of the patients is not clear. Quetiapine fumarate is not approved for the treatment dementia-related psychosis (Prod Info SEROQUEL(R) oral tablets, 2008).

Suicidality and Antidepressant Drugs

Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorde considering the use of quetiapine fumarate or any other antidepressant in a child, adolescent, or young a risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antid to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to place and older. Depression and certain other psychiatric disorders are themselves associated with increases Patients of all ages who are started on antidepressant therapy should be monitored appropriately and ob clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advise observation and communication with the prescriber. Quetiapine fumarate is not approved for use in pedia Info SEROQUEL(R) oral tablets, 2008).

b) Oral (Tablet, Extended Release)

Increased Mortality in Elderly Patients with Dementia-related Psychosis

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk seventeen placebo-controlled trials (modal duration of 10 weeks) largely in patients taking atypical antips revealed a risk of death in the drug-treated patients of between 1.6 times to 1.7 times the risk of death in patients. Over the course of a typical 10 week controlled trial, the rate of death in drug-treated patients w compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in studies suggest that, similar to atypical antipsychotic drugs may increase mortality. The extent to which t increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to so the patients is not clear. Quetiapine fumarate extended-release is not approved for the treatment of patie related psychosis (Prod Info SEROQUEL XR(R) extended-release oral tablets, 2008).

Suicidality and Antidepressant Drugs

Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorde considering the use of quetiapine fumarate or any other antidepressant in a child, adolescent, or young a risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antid to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to place and older. Depression and certain other psychiatric disorders are themselves associated with increases Patients of all ages who are started on antidepressant therapy should be monitored appropriately and ob clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advise observation and communication with the prescriber. Quetiapine fumarate extended-release tablets are n pediatric patients. Quetiapine fumarate is not approved for use in the treatment of depression, however, form of quetiapine fumarate is approved for the treatment of bipolar depression (Prod Info SEROQUEL X release oral tablets, 2008).

3.1 Contraindications

A) Quetiapine Fumarate

1) hypersensitivity to quetiapine fumarate or any component of the product (Prod Info SEROQUEL(R) oral tablets

3.2 Precautions

A) Quetiapine Fumarate

1) elderly patients with dementia-related psychosis (unapproved use); increased risk of death reported when atyp were used to treat behavorial disorders associated with dementia (Prod Info SEROQUEL XR(R) extended-release Prod Info SEROQUEL(R) oral tablets, 2008)

2) suicidal ideation and behavior or worsening depression; increased risk, particularly in children and adolescents first few months of therapy or during changes in dosing (decreases or increases) (Prod Info SEROQUEL XR(R) e tablets, 2008; Prod Info SEROQUEL(R) oral tablets, 2008)

3) agranulocytosis, including fatal cases, has been reported (Prod Info SEROQUEL(R)XR extended-release oral Info SEROQUEL(R) oral tablets, 2007)

4) aspiration pneumonia, patients at risk for; may cause esophageal dysmotility and aspiration (Prod Info SEROQ release oral tablets, 2007; Prod Info SEROQUEL(R) oral tablets, 2007)

5) cardiovascular disease, known; risk of orthostatic hypotension (Prod Info SEROQUEL(R)XR extended-release Prod Info SEROQUEL(R) oral tablets, 2007)

6) cerebrovascular disease; risk of orthostatic hypotension (Prod Info SEROQUEL(R)XR extended-release oral ta SEROQUEL(R) oral tablets, 2007)

7) concomitant use of antihypertensive medications; risk of orthostatic hypotension (Prod Info SEROQUEL(R)XR tablets, 2007; Prod Info SEROQUEL(R) oral tablets, 2007)

8) dehydration; risk of orthostatic hypotension (Prod Info SEROQUEL(R) oral tablets, 2007; Prod Info SEROQUE 2007)

9) diabetes mellitus or at risk of diabetes mellitus; occurrence of hyperglycemia, some cases associated with keto hyperosmolar coma or death (Prod Info SEROQUEL(R)XR extended-release oral tablets, 2007; Prod Info SEROQ

2007)
10) elderly patients (especially elderly women); increased risk of tardive dyskinesia (Prod Info SEROQUEL(R)XR tablets, 2007; Prod Info SEROQUEL(R) oral tablets, 2007)
11) elevated cholesterol and triglyceride levels have been reported (Prod Info SEROQUEL(R)XR extended-relea Prod Info SEROQUEL(R) oral tablets, 2007a)
12) elevated serum transaminases (asymptomatic, transient and reversible) have been reported(Prod Info SERO extended-release oral tablets, 2007; Prod Info SEROQUEL(R) oral tablets, 2007)
13) hypovolemia; risk of orthostatic hypotension (Prod Info SEROQUEL(R)XR extended-release oral tablets, 200 SEROQUEL(R) oral tablets, 2007)
14) leukopenia/neutropenia has been reported; increased risk with history of drug-induced leukopenia/neutropeni WBC; if develops, discontinue therapy (Prod Info SEROQUEL(R)XR extended-release oral tablets, 2007; Prod In tablets, 2007)
15) neuroleptic malignant syndrome (NMS) has occurred (Prod Info SEROQUEL(R)XR extended-release oral tab SEROQUEL(R) oral tablets, 2007)
16) orthostatic hypotension, with or without syncope, may occur; increased risk during initial dose-titration period, titration, return to previous dose (Prod Info SEROQUEL(R)XR extended-release oral tablets, 2007; Prod Info SER tablets, 2007)
17) seizures, history of or predisposing factors for developing (Prod Info SEROQUEL(R)XR extended-release ora Info SEROQUEL(R) oral tablets, 2007)
18) tardive dyskinesia may occur; increased risk with increased duration of treatment and increased total cumula SEROQUEL(R)XR extended-release oral tablets, 2007; Prod Info SEROQUEL(R) oral tablets, 2007)

3.3 Adverse Reactions

Cardiovascular Effects

Dermatologic Effects

Endocrine/Metabolic Effects

Gastrointestinal Effects

Hematologic Effects

Hepatic Effects

Immunologic Effects

Musculoskeletal Effects

Neurologic Effects

Ophthalmic Effects

Psychiatric Effects

Reproductive Effects

Respiratory Effects

Other

3.3.1 Cardiovascular Effects

3.3.1.A Quetiapine Fumarate

Orthostatic hypotension

Sudden cardiac death

Syncope

Tachycardia

3.3.1.A.1 Orthostatic hypotension

a) Incidence: 4% to 7% (Prod Info SEROQUEL(R)XR extended-release oral tablets, 2007; Prod Info SE tablets, 2007)

b) In monotherapy, placebo-controlled clinical trials for the treatment of schizophrenia (up to 6 weeks) a to 12 weeks) in adults, orthostatic hypotension was reported in 4% of patients receiving quetiapine fuma compared to 1% for placebo (n=404); doses ranged from 75 to 800 milligrams/day (Prod Info SEROQUE 2007).

c) In placebo-controlled clinical trials for the adjunct treatment of acute mania (up to 3 weeks) in adults, hypotension was reported in 7% of patients receiving quetiapine fumarate tablets (n=196) compared to 2 (n=203); doses ranged from 100 to 800 milligrams/day (Prod Info SEROQUEL(R) oral tablets, 2007).

d) During acute therapy (up to 6 weeks) placebo-controlled clinical trials of adult patients with schizophr hypotension was reported in 7% of patients receiving quetiapine fumarate extended-release tablets (n=9 for placebo (n=319). Use quetiapine fumarate cautiously in patients with cerebrovascular disease, cardio conditions that predispose them to hypotension (i.e., hypovolemia, dehydration, and concomitant antihyp (Prod Info SEROQUEL(R)XR extended-release oral tablets, 2007).

e) The risk of hypotension is greater during dose-titration periods. Should hypotension develop during tit pre-titration dose is appropriate (Prod Info SEROQUEL(R) oral tablets, 2007; Prod Info SEROQUEL(R)X oral tablets, 2007).

3.3.1.A.2 Sudden cardiac death

a) In a large, retrospective, cohort study that included a primary cohort of 93,300 users of antipsychotic non-users of antipsychotic drugs, there was an increased risk of sudden cardiac death in adult participan age (mean age of 45.7 years) who were using quetiapine compared to those who were not using antipsy (incidence-rate ratio, 1.88; 95% confidence interval (CI), 1.3 to 2.71; p less than 0.001). In participants be atypical antidepressants (clozapine, olanzapine, quetiapine, risperidone), the incidence-rate ratio for sud increased from 1.59 (95% CI, 1.03 to 2.46) for those using low doses to 2.86 (95% CI, 2.25 to 3.65) for th (p=0.01) (Ray et al, 2009).

3.3.1.A.3 Syncope

a) Incidence: tablets, 1% (Prod Info SEROQUEL(R) oral tablets, 2007); extended-release tablets, 0.3% SEROQUEL(R)XR extended-release oral tablets, 2007)

b) During clinical trials, syncope was reported in 1% of patients receiving quetiapine fumarate tablets (n= 0.2% for placebo (n=954) and 0.4% for active control (n=527) (Prod Info SEROQUEL(R) oral tablets, 20

c) During clinical trials, syncope was reported in 0.3% of patients receiving quetiapine fumarate extende (n=951) and in 0.3% receiving placebo (n=319) (Prod Info SEROQUEL(R)XR extended-release oral tabl

3.3.1.A.4 Tachycardia

a) Incidence: 0.5% to 6% (Prod Info SEROQUEL(R)XR extended-release oral tablets, 2007; Prod Info S tablets, 2007)

b) In placebo-controlled clinical trials for the treatment (monotherapy) of schizophrenia (up to 6 weeks) a to 12 weeks) in adults, tachycardia was reported in 6% of patients receiving quetiapine fumarate tablets 4% for placebo (n=404); doses ranged from 75 to 800 milligrams/day (Prod Info SEROQUEL(R) oral tabl

c) During clinical trials, tachycardia was reported in 3% of patients receiving quetiapine fumarate extend compared to 1% for placebo. Tachycardia (greater than 120 bpm) was reported in 0.8% of patients recei compared to 0% for placebo at any time during the clinical trials for quetiapine fumarate extended-releas SEROQUEL(R)XR extended-release oral tablets, 2007).

d) In four pooled, placebo controlled clinical trials for the treatment of schizophrenia (3 to 6 weeks in dur tachycardia was reported in 1% of patients receiving quetiapine fumarate tablets (n=399) compared to 0. (n=156) (Prod Info SEROQUEL(R) oral tablets, 2007).

e) In pooled, placebo-controlled clinical trials for the treatment (monotherapy) of acute bipolar mania in a was reported in 0.5% of patients receiving quetiapine fumarate tablets (n=192) compared to 0% for place SEROQUEL(R) oral tablets, 2007).

f) In pooled, placebo-controlled clinical trials for the adjunctive treatment of acute bipolar mania in adults reported in 0.6% of patients receiving quetiapine fumarate tablets (n=166) compared to 0% for placebo (SEROQUEL(R) oral tablets, 2007).

g) Evaluation of ECG's associated a mean increase in heart rate of 7 beats per minute (bpm) for quetiap compared to a mean increase of 1 bpm for placebo (Prod Info SEROQUEL(R) oral tablets, 2007; Prod In extended-release oral tablets, 2007).

h) An increase in heart rate (approximately 9 beats/minute) has been detected during 6 weeks of therap 1996a). Greater than 20 percent of patients receiving 100 to 200 milligrams daily have shown an increas beats per minute or greater or have experienced a decrease in systolic blood pressure of 30 millimeters (Garver, 2000a). The drug has not induced clinically significant arrhythmias in placebo-controlled studies

3.3.2 Dermatologic Effects

3.3.2.A Quetiapine Fumarate

3.3.2.A.1 Rash

a) Incidence: tablets, 4% (Prod Info SEROQUEL(R) oral tablets, 2007); extended-release tablets, less th
SEROQUEL(R)XR extended-release oral tablets, 2007)

b) In placebo-controlled clinical trials for the treatment (monotherapy) of schizophrenia (up to 6 weeks) a
to 12 weeks) in adults, rash was reported in 4% of patients receiving quetiapine fumarate tablets (n=719
placebo (n=404); doses ranged from 75 to 800 milligrams/day (Prod Info SEROQUEL(R) oral tablets, 20

c) During clinical trials for the treatment of schizophrenia in adults, rash was reported in less than 5% of
quetiapine fumarate extended-release tablets (Prod Info SEROQUEL(R)XR extended-release oral tablet

3.3.3 Endocrine/Metabolic Effects

Quetiapine

Quetiapine Fumarate

3.3.3.A Quetiapine

Diabetes mellitus

Metabolic syndrome

3.3.3.A.1 Diabetes mellitus

See Drug Consult reference: ATYPICAL ANTIPSYCHOTIC AGENTS - EFFECT ON GLUCOSE AND RI

3.3.3.A.2 Metabolic syndrome

See Drug Consult reference: ANTIPSYCHOTIC AGENTS - METABOLIC SYNDROME

3.3.3.B Quetiapine Fumarate

Decreased prolactin level

Hyperglycemia

Hypothyroidism

Serum cholesterol raised

Serum triglycerides raised

Weight gain

3.3.3.B.1 Decreased prolactin level

a) In studies of patients with high prolactin levels, serum prolactin was reduced further in patients treate
in those receiving chlorpromazine. Prolactin levels were similar with placebo and quetiapine after 21 and
Quetiapine has minimal effect on the serum prolactin levels of schizophrenic patients. Decreases in prola
cases, were most likely related to discontinuation of the patient's antipsychotic therapy (Borison et al, 19
Fulton & Goa, 1995b).

3.3.3.B.2 Hyperglycemia

a) Incidence: 0.1% to 1% (Prod Info SEROQUEL(R) oral tablets, 2007)

b) Hyperglycemia, including cases associated with ketoacidosis, hyperosmolar coma, or death, has bee
receiving atypical antipsychotics, including quetiapine fumarate. Hyperglycemia has resolved in some ca
discontinuation of the drug, while in other cases, continuation of antidiabetic treatment was required afte
(Prod Info SEROQUEL(R) oral tablets, 2007; Prod Info SEROQUEL(R)XR extended-release oral tablets

c) In two long-term, placebo-controlled clinical trials, blood glucose increases of 126 mg/dL or greater fo than 8 hours since a meal were reported in 10.7% of patients taking quetiapine fumarate tablets (n=646; exposure, 213 days) compared to 4.6% for placebo (n=680; mean duration of exposure, 152 days) (Proc oral tablets, 2007).
d) In placebo-controlled clinical trials of up to 12 weeks, fasting blood glucose levels of 126 mg/dL or gre blood glucose levels of 200 mg/dL or greater were reported for 3.5% of patients taking quetiapine fumara compared to 2.1% for placebo (n=1490) (Prod Info SEROQUEL(R) oral tablets, 2007).
e) In a 24-week trial (n=115), a fasting blood glucose of 126 mg/dL or greater was reported in 2.6% of p nonfasting blood glucose of 200 mg/dL or greater was reported in 1.7% of patients taking quetiapine fum Info SEROQUEL(R) oral tablets, 2007).
f) A 42-year-old man, after one month of quetiapine use, was diagnosed with new-onset diabetes mellitu admitted to the hospital after several days of nausea, vomiting, polyuria, and confusion. His blood glucos admission was 607 milligram/deciliter (mg/dL). Random blood glucose concentrations 4 months prior to t were 126 and 107 mg/dL. He had no prior history of glucose intolerance, hyperglycemia, and no familial The patient's history of bipolar disorder was concurrently treated with lithium carbonate, gabapentin, clor venlafaxine in addition to his quetiapine titration of 200 milligrams at night. He was eventually discharged regimen, and quetiapine was discontinued over the course of 9 days. The patient's insulin dose was wea 5 months after admission (Sobel et al, 1999).

3.3.3.B.3 Hypothyroidism

a) Summary

1) Cases of hypothyroidism have been reported with quetiapine use. Thyroid monitoring is recomm therapy, at least in patients with a history of or a propensity for thyroid disease (Liappas et al, 2006;

b) In placebo-controlled clinical trials, 0.5% and 2.7% of patients receiving quetiapine fumarate extende experienced decreased free thyroxine and increased TSH, respectively, compared to 0% and 1.2% for p (Prod Info SEROQUEL(R)XR extended-release oral tablets, 2007).
c) In clinical trials using quetiapine fumarate tablets as monotherapy treatment, 0.7% of patients receivi experienced increased TSH levels with six patients requiring thyroid replacement therapy (Prod Info SEF tablets, 2007).
d) In placebo-controlled clinical trials for the adjunctive treatment of mania in adults, elevated TSH level 12% of patients receiving quetiapine fumarate tablets (n=196) compared to 7% for placebo (n=203). Thr treated patients also had concurrent low free T4 levels (Prod Info SEROQUEL(R) oral tablets, 2007).
e) In clinical trials, decreases in total and free thyroxine (T4) appear to be dose-related, with levels drop 20% at the higher end of the therapeutic dose range; maximal decreases were seen during the first two t therapy (Prod Info SEROQUEL(R) oral tablets, 2007).
f) A case of quetiapine-induced hypothyroidism was described in a 49-year-old woman. The patient had dysthymia, with 2 major depressive episodes in the past 14 years, and had been treated over the years v antidepressant and anxiolytic medications to varying degrees of success. Over the last 4 years, she was taking up to 150 mg/day. Six months prior to current presentation, in an attempt to discontinue zolpidem mood, treatment with venlafaxine (300 mg/day), paroxetine (30 mg/day), and quetiapine (800 mg/day) w significant improvement. A routine thyroid screening at the time of current presentation revealed decreas (4.17 mcg/dL; normal range, 6.09 to 12.23 mcg/dL) and free T4 values (0.53 ng/dL; normal range, 0.58 t elevated TSH level (6.78 micro-International Units/mL; normal range, 0.34 to 5.6 micro-International Unit symptoms included a modest weight gain, decrease in appetite, hoarseness of voice, slowing of motor a constipation. Although the patient's past medical record was negative for a thyroid disorder, she had a p for hypothyroidism. Subsequently, quetiapine was tapered and discontinued over a week, while the rest were continued at the same doses. Within the next 2 months, laboratory thyroid tests were within normal displayed a steady mood improvement. It is believed that thyroid autoimmunity may be responsible for th function monitoring is recommended in quetiapine-treated patients with a history of or a propensity for th et al, 2006).
g) A 46-year-old woman developed hypothyroidism 2 months after the addition of quetiapine to her exist Reaching a final titrated total dose of 425 milligrams of quetiapine daily, the patient developed an elevate hormone concentration of 8.45 microunits per liter. Prior medical history included successful radioactive hyperthyroidism but without detection of thyroid abnormalities until 4 years later when quetiapine was init function monitoring is recommended during quetiapine therapy (Feret & Caley, 2000).
h) Decreases in mean total thyroxine and occasionally decreased triiodothyronine levels have occurred schizophrenia with quetiapine (Anon, 1995a; Borison et al, 1996a).

3.3.3.B.4 Serum cholesterol raised

a) Incidence: tablets, 9% to 16% (Prod Info SEROQUEL(R) oral tablets, 2007)
b) During clinical trials for the treatment of schizophrenia in adults, elevations in cholesterol to levels of were reported in 16% of patients receiving quetiapine fumarate tablets compared to 7% for placebo (Pro oral tablets, 2007).
c) During adult bipolar depression clinical trials, elevations in cholesterol to levels of 240 mg/dL or great of patients receiving quetiapine fumarate tablets compared to 6% for placebo (Prod Info SEROQUEL(R)
d) During clinical trials for the treatment of schizophrenia in adults, an increase in mean cholesterol leve were reported in patients receiving quetiapine fumarate extended-release tablets compared to a decreas for placebo (Prod Info SEROQUEL(R)XR extended-release oral tablets, 2007).

3.3.3.B.5 Serum triglycerides raised

a) Incidence: tablets, 14% to 23% (Prod Info SEROQUEL(R) oral tablets, 2007)

b) During clinical trials for the treatment of schizophrenia in adults, elevations in triglycerides to levels of were reported in 23% of patients receiving quetiapine fumarate tablets compared to 16% for placebo (Pr (R) oral tablets, 2007).

c) During adult bipolar depression clinical trials, elevations in triglycerides to levels of 200 mg/dL or grea 14% of patients receiving quetiapine fumarate tablets compared to 9% for placebo (Prod Info SEROQUE 2007).

d) During clinical trials for the treatment of schizophrenia in adults, an increase in mean triglyceride leve 15% was reported in patients receiving quetiapine fumarate extended-release tablets compared to a dec 6% for placebo (Prod Info SEROQUEL(R)XR extended-release oral tablets, 2007).

3.3.3.B.6 Weight gain

a) Incidence: 5% to 23% (Prod Info SEROQUEL(R) oral tablets, 2007; Prod Info SEROQUEL(R)XR exte tablets, 2007)

b) Patients receiving quetiapine fumarate tablets demonstrated a greater incidence of weight increase (weight) than placebo in placebo-controlled schizophrenia trials (23% and 6%, respectively); in mania mo and 7%, respectively); in mania adjunct therapy trials (13% and 4%, respectively); and in bipolar depress respectively) (Prod Info SEROQUEL(R) oral tablets, 2007).

c) During adult schizophrenia clinical trials, weight gain of 7% or greater of body weight was reported in receiving quetiapine fumarate extended-release tablets compared to 5% for placebo (Prod Info SEROQU release oral tablets, 2007).

d) In placebo-controlled clinical trials for the treatment (monotherapy) of schizophrenia (up to 6 weeks) a to 12 weeks) in adults, weight gain was reported in 5% of patients receiving quetiapine fumarate tablets 1% for placebo (n=404); doses ranged from 75 to 800 milligrams/day (Prod Info SEROQUEL(R) oral tabl

e) In placebo-controlled clinical trials for the adjunct treatment of acute mania (up to 3 weeks) in adults, reported in 6% of patients receiving quetiapine fumarate tablets (n=196) compared to 3% for placebo (n= from 100 to 800 milligrams/day (Prod Info SEROQUEL(R) oral tablets, 2007).

f) A logistic regression analysis of placebo-controlled clinical study of five fixed-doses of quetiapine fuma patients with schizophrenia revealed a positive correlation between dose and the occurrence of weight g Doses included in these studies included 75 milligrams (mg)/day, 150 mg/day, 300 mg/day, 600 mg/day, (Prod Info SEROQUEL(R) oral tablets, 2007).

g) Adolescent patients taking olanzapine experienced greater weight gain and increased in body mass i patients taking quetiapine in a retrospective study involving 103 patients younger than 18 years of age. F olanzapine (n=50, mean daily dose 13.9 milligrams (mg)) or quetiapine (n=53, mean daily dose 510.9 mg Weight and height were measured at baseline and 14 or more days after baseline. Average weight gain olanzapine group was 3.8 kilograms (kg) (p less than 0.001) compared to 0.03 kg in the quetiapine group and quetiapine groups showed slight, but significant, increases in height from baseline (0.006 meters, p= meters, p less than 0.001, respectively). After controlling for baseline differences, the mean weight chang was significant (3.4 kg, p less than 0.001). BMI increased by an average of 1.3 kg per square meter (m(2 group (p less than 0.001) compared to a decreased of 0.2 kg/m(2) in the quetiapine group. After controlli differences, the mean difference in change in BMI was significant (0.9 kg/m(2), p=0.008) (Patel et al, 200

3.3.4 Gastrointestinal Effects

3.3.4.A Quetiapine Fumarate

Abdominal pain

Constipation

Increased appetite

Indigestion

Vomiting

Xerostomia

3.3.4.A.1 Abdominal pain

a) Incidence: 4% to 7% (Prod Info SEROQUEL(R) oral tablets, 2007)

b) In placebo-controlled clinical trials for the treatment (monotherapy) of schizophrenia (up to 6 weeks) a to 12 weeks) in adults, abdominal pain was reported in 4% of patients receiving quetiapine fumarate tabl

to 1% for placebo (n=404); doses ranged from 75 to 800 milligrams/day (Prod Info SEROQUEL(R) oral t
c) In placebo-controlled clinical trials for the adjunct treatment of acute mania (up to 3 weeks) in adults, reported in 7% of patients receiving quetiapine fumarate tablets (n=196) compared to 3% for placebo (n= from 100 to 800 milligrams/day (Prod Info SEROQUEL(R) oral tablets, 2007).
d) A logistic regression analysis of placebo-controlled clinical study of five fixed-doses of quetiapine fum patients with schizophrenia revealed a positive correlation between dose and the occurrence of abdomin 0.05). Doses included in these studies included 75 milligrams (mg)/day, 150 mg/day, 300 mg/day, 600 m mg/day (Prod Info SEROQUEL(R) oral tablets, 2007).
e) Anticholinergic adverse effects of quetiapine therapy are dose-related. Dry mouth occurred in 8% to 1 patients in clinical trials. Constipation was also reported. Abdominal pain, dyspepsia, and anorexia occur (Borison et al, 1996a; Wetzel et al, 1995; Fulton & Goa, 1995b).

3.3.4.A.2 Constipation
a) Incidence: tablets, 8% to 10% (Prod Info SEROQUEL(R) oral tablets, 2007); extended-release tablets SEROQUEL(R)XR extended-release oral tablets, 2007)
b) In placebo-controlled clinical trials for the treatment (monotherapy) of schizophrenia (up to 6 weeks) a to 12 weeks) in adults, constipation was reported in 8% of patients receiving quetiapine fumarate tablets 3% for placebo (n=404); doses ranged from 75 to 800 milligrams/day (Prod Info SEROQUEL(R) oral tab
c) In placebo-controlled clinical trials for the adjunct treatment of acute mania (up to 3 weeks) in adults, reported in 10% of patients receiving quetiapine fumarate tablets (n=196) compared to 5% for placebo (r from 100 to 800 milligrams/day (Prod Info SEROQUEL(R) oral tablets, 2007).
d) In placebo-controlled clinical trials for the treatment of bipolar depression (up to 8 weeks) in adults, co reported in 10% of patients receiving quetiapine fumarate tablets (n=698) compared to 4% for placebo (r from 300 to 600 milligrams/day (Prod Info SEROQUEL(R) oral tablets, 2007).
e) In placebo-controlled clinical trials for the treatment of schizophrenia (up to 6 weeks) in adults, constip 6% of patients receiving quetiapine fumarate extended-release tablets (n=951) compared to 5% for place ranged from 300 to 800 mg (Prod Info SEROQUEL(R)XR extended-release oral tablets, 2007).
f) Anticholinergic adverse effects of quetiapine therapy are dose-related. Dry mouth occurred in 8% to 1 patients in clinical trials. Constipation was also reported. Abdominal pain, dyspepsia, and anorexia occur (Borison et al, 1996a; Wetzel et al, 1995; Fulton & Goa, 1995b).

3.3.4.A.3 Increased appetite
a) Incidence: tablets, 5% (Prod Info SEROQUEL(R) oral tablets, 2007); extended-release tablets, less th SEROQUEL(R)XR extended-release oral tablets, 2007)
b) In placebo-controlled clinical trials for the treatment of bipolar depression (up to 8 weeks) in adults, in reported in 5% of patients receiving quetiapine fumarate tablets (n=698) compared to 3% for placebo (n= from 300 to 600 milligrams/day (Prod Info SEROQUEL(R) oral tablets, 2007).
c) During clinical trials for the treatment of schizophrenia in adults, increased appetite was reported in le taking quetiapine fumarate extended-release tablets (Prod Info SEROQUEL(R)XR extended-release ora

3.3.4.A.4 Indigestion
a) Incidence: 5% to 7% (Prod Info SEROQUEL(R) oral tablets, 2007; Prod Info SEROQUEL(R)XR exter tablets, 2007)
b) In placebo-controlled clinical trials for the treatment (monotherapy) of schizophrenia (up to 6 weeks) a to 12 weeks) in adults, dyspepsia was reported in 5% of patients receiving quetiapine fumarate tablets (r 1% for placebo (n=404); doses ranged from 75 to 800 milligrams/day (Prod Info SEROQUEL(R) oral tabl
c) In placebo-controlled clinical trials for the treatment of bipolar depression (up to 8 weeks) in adults, dy in 7% of patients receiving quetiapine fumarate tablets (n=698) compared to 4% for placebo (n=347); do to 600 milligrams/day (Prod Info SEROQUEL(R) oral tablets, 2007).
d) In placebo-controlled clinical trials for the treatment of schizophrenia (up to 6 weeks) in adults, dyspe 5% of patients receiving quetiapine fumarate extended-release tablets (n=951) compared to 2% for place ranged from 300 to 800 mg (Prod Info SEROQUEL(R)XR extended-release oral tablets, 2007).
e) A logistic regression analysis of placebo-controlled clinical study of five fixed-doses of quetiapine fum patients with schizophrenia revealed a positive correlation between dose and the occurrence of dyspeps Doses included in these studies included 75 milligrams (mg)/day, 150 mg/day, 300 mg/day, 600 mg/day, (Prod Info SEROQUEL(R) oral tablets, 2007).
f) Anticholinergic adverse effects of quetiapine therapy are dose-related. Dry mouth occurred in 8% to 1 patients in clinical trials. Constipation was also reported. Abdominal pain, dyspepsia, and anorexia occur (Borison et al, 1996a; Wetzel et al, 1995; Fulton & Goa, 1995b).

3.3.4.A.5 Vomiting
a) Incidence: 5% to 6% (Prod Info SEROQUEL(R) oral tablets, 2007)
b) In placebo-controlled clinical trials for the treatment (monotherapy) of schizophrenia (up to 6 weeks) a to 12 weeks) in adults, vomiting was reported in 6% of patients receiving quetiapine fumarate tablets (n= for placebo (n=404); doses ranged from 75 to 800 milligrams/day (Prod Info SEROQUEL(R) oral tablets,
c) In placebo-controlled clinical trials for the treatment of bipolar depression (up to 8 weeks) in adults, vo 5% of patients receiving quetiapine fumarate tablets (n=698) compared to 4% for placebo (n=347); dose 600 milligrams/day (Prod Info SEROQUEL(R) oral tablets, 2007).

3.3.4.A.6 Xerostomia

a) Incidence: 9% to 44% (Prod Info SEROQUEL(R) oral tablets, 2007; Prod Info SEROQUEL(R)XR exte tablets, 2007)

b) In placebo-controlled clinical trials for the treatment (monotherapy) of schizophrenia (up to 6 weeks) a to 12 weeks) in adults, dry mouth was reported in 9% of patients receiving quetiapine fumarate tablets (r 3% for placebo (n=404); doses ranged from 75 to 800 milligrams/day (Prod Info SEROQUEL(R) oral tabl

c) In placebo-controlled clinical trials for the adjunct treatment of acute mania (up to 3 weeks) in adults, reported in 19% of patients receiving quetiapine fumarate tablets (n=196) compared to 3% for placebo (r from 100 to 800 milligrams/day (Prod Info SEROQUEL(R) oral tablets, 2007).

d) In placebo-controlled clinical trials for the treatment of bipolar depression (up to 8 weeks) in adults, dı in 44% of patients receiving quetiapine fumarate tablets (n=698) compared to 13% for placebo (n=347); 300 to 600 milligrams/day (Prod Info SEROQUEL(R) oral tablets, 2007).

e) In placebo-controlled clinical trials for the treatment of schizophrenia (up to 6 weeks) in adults, dry mo 12% of patients receiving quetiapine fumarate extended-release tablets (n=951) compared to 1% for pla ranged from 300 to 800 mg (Prod Info SEROQUEL(R)XR extended-release oral tablets, 2007).

f) Anticholinergic adverse effects of quetiapine therapy are dose-related. Dry mouth occurred in 8% to 1 patients in clinical trials. Constipation was also reported. Abdominal pain, dyspepsia, and anorexia occur (Borison et al, 1996a; Wetzel et al, 1995; Fulton & Goa, 1995b).

3.3.5 Hematologic Effects

3.3.5.A Quetiapine Fumarate

Agranulocytosis

Leukopenia

Neutropenia

Pancytopenia

3.3.5.A.1 Agranulocytosis

a) Agranulocytosis, including fatal incidences, has been reported during clinical trials and post-marketing fumarate (Prod Info SEROQUEL(R) oral tablets, 2008; Prod Info SEROQUEL XR(R) extended-release o

3.3.5.A.2 Leukopenia

a) Incidence: tablets, at least 1% (Prod Info SEROQUEL(R) oral tablets, 2008); extended-release tablet Info SEROQUEL XR(R) extended-release oral tablets, 2008; Prod Info SEROQUEL(R) oral tablets, 200

b) During quetiapine fumarate clinical trials, leukopenia was reported in at least 1% of patients receiving less than 5% of patients receiving extended-release tablets. Leukopenia has also been reported during p quetiapine fumarate. Patients possibly at risk for developing leukopenia include those with a preexisting of drug-induced leukopenia. Should leukopenia develop during quetiapine fumarate therapy, discontinue SEROQUEL(R) oral tablets, 2008; Prod Info SEROQUEL(R) oral tablets, 2008).

3.3.5.A.3 Neutropenia

a) Incidence: 0.3% (Prod Info SEROQUEL(R) oral tablets, 2008; Prod Info SEROQUEL XR(R) extended 2008)

b) During placebo-controlled clinical trials with quetiapine fumarate, neutropenia was reported in 0.3% o quetiapine fumarate monotherapy (n=2967) compared to 0.1% for placebo (n=1349). Neutropenia has al during post-marketing use of quetiapine fumarate. Patients possibly at risk for developing neutropenia in preexisting low WBC or a history of drug-induced neutropenia. Should neutropenia develop, discontinue SEROQUEL(R) oral tablets, 2008; Prod Info SEROQUEL XR(R) extended-release oral tablets, 2008).

3.3.5.A.4 Pancytopenia

a) Pancytopenia developed in a 71-year-old Caucasian male with a history of Parkinson's disease 3 wee quetiapine therapy at a dose of 25 milligrams twice daily for the treatment of drug-induced hallucinations counts improved within 48 hours of withdrawal of the drug and returned to normal in 7 days (Iraqi, 2003).

3.3.6 Hepatic Effects

3.3.6.A Quetiapine Fumarate

3.3.6.A.1 Increased liver enzymes

a) Incidence: tablets, 6% (Prod Info SEROQUEL(R) oral tablets, 2007); extended-release tablets, 1% (P
(R)XR extended-release oral tablets, 2007)
b) Transient, asymptomatic and reversible elevations in serum transaminase, primarily alanine aminotra
been reported. Peak elevations are usually seen within the first three weeks of treatment and most retur
with continued therapy (Prod Info SEROQUEL(R) oral tablets, 2007; Prod Info SEROQUEL(R)XR extenc
tablets, 2007).
c) In pooled, placebo-controlled clinical trials for the treatment of schizophrenia (3 to 6 weeks in duratior
in serum transaminases of greater than 3 times the upper limits of normal was reported in 6% of patients
fumarate tablets compared to 1% for placebo (Prod Info SEROQUEL(R) oral tablets, 2007).
d) In pooled, placebo-controlled 6-week clinical trials for the treatment of schizophrenia in adults, elevati
transaminases of greater than 3 times the upper limits of normal was reported in 1% of patients receiving
extended-release tablets compared to 2% for placebo (Prod Info SEROQUEL(R)XR extended-release or

3.3.7 Immunologic Effects

3.3.7.A Quetiapine Fumarate

3.3.7.A.1 Anaphylaxis
a) Anaphylactic reactions, temporally related to quetiapine therapy, have been reported during post-mar
SEROQUEL(R) oral tablets, 2008a).

3.3.8 Musculoskeletal Effects

3.3.8.A Quetiapine Fumarate

3.3.8.A.1 Backache
a) Incidence: 3% to 5% (Prod Info SEROQUEL(R) oral tablets, 2007)
b) In placebo-controlled clinical trials for the treatment (monotherapy) of schizophrenia (up to 6 weeks) a
to 12 weeks) in adults, back pain was reported in 3% of patients receiving quetiapine fumarate tablets (n
1% for placebo (n=404); doses ranged from 75 to 800 milligrams/day (Prod Info SEROQUEL(R) oral tabl
c) In placebo-controlled clinical trials for the adjunct treatment of acute mania (up to 3 weeks) in adults,
reported in 5% of patients receiving quetiapine fumarate tablets (n=196) compared to 3% for placebo (n=
from 100 to 800 milligrams/day (Prod Info SEROQUEL(R) oral tablets, 2007).

3.3.9 Neurologic Effects

3.3.9.A Quetiapine Fumarate

Akathisia

Altered mental status

Asthenia

Dizziness

Dystonia

Extrapyramidal disease

Headache

Insomnia

Lethargy

Parkinsonism

Restless legs syndrome

Sedated

Seizure

Somnolence

Tardive dyskinesia

Tremor

3.3.9.A.1 Akathisia

a) Incidence: less than 5% (Prod Info SEROQUEL(R)XR extended-release oral tablets, 2007)

b) During clinical trials for the treatment of schizophrenia in adults, akathisia was reported in less than 5 quetiapine fumarate extended-release tablets (Prod Info SEROQUEL(R)XR extended-release oral tablet

c) Akathisia developed in a male patient with Parkinson's disease following the administration of quetiap of dopamimetic psychosis. The 62-year-old man was taking levodopa at a daily dose of 400 milligrams (r a dose of 12.5 to 25 mg daily for approximately 5 days, when he developed severe motor restlessness, a pacing. His score on the Barnes Akathisia Scale (range, 0= no symptoms to 14=severe akathisia) reache withdrawn and symptoms of akathisia completely resolved within 2 days (Prueter et al, 2003).

3.3.9.A.2 Altered mental status

a) A 62-year-old man experienced acute mental status changes within 3 days of increasing his quetiapir milligrams daily while symptoms resolved within 48 hours of discontinuing quetiapine. There was no clini serotonin syndrome, or alcohol intoxication or withdrawal. Quetiapine is believed to be associated with th changes due to the close temporal relationship between the onset and resolution of symptoms (Sim et al

3.3.9.A.3 Asthenia

a) Incidence: 5% to 10% (Prod Info SEROQUEL(R) oral tablets, 2007)

b) In placebo-controlled clinical trials for the treatment (monotherapy) of schizophrenia (up to 6 weeks) a to 12 weeks) in adults, asthenia was reported in 5% of patients receiving quetiapine fumarate tablets (n= for placebo (n=404); doses ranged from 75 to 800 milligrams/day (Prod Info SEROQUEL(R) oral tablets,

c) In placebo-controlled clinical trials for the adjunct treatment of acute mania (up to 3 weeks) in adults, in 10% of patients receiving quetiapine fumarate tablets (n=196) compared to 4% for placebo (n=203); d to 800 milligrams/day (Prod Info SEROQUEL(R) oral tablets, 2007).

3.3.9.A.4 Dizziness

a) Incidence: 9% to 18% (Prod Info SEROQUEL(R) oral tablets, 2007; Prod Info SEROQUEL(R)XR exte tablets, 2007)

b) In placebo-controlled clinical trials for the treatment (monotherapy) of schizophrenia (up to 6 weeks) a to 12 weeks) in adults, dizziness was reported in 11% of patients receiving quetiapine fumarate tablets (r 5% for placebo (n=404); doses ranged from 75 to 800 milligrams/day (Prod Info SEROQUEL(R) oral tabl

c) In placebo-controlled clinical trials for the adjunct treatment of acute mania (up to 3 weeks) in adults, reported in 9% of patients receiving quetiapine fumarate tablets (n=196) compared to 6% for placebo (n= from 100 to 800 milligrams/day (Prod Info SEROQUEL(R) oral tablets, 2007).

d) In placebo-controlled clinical trials for the treatment of bipolar depression (up to 8 weeks) in adults, di in 18% of patients receiving quetiapine fumarate tablets (n=698) compared to 7% for placebo (n=347); d to 600 milligrams/day (Prod Info SEROQUEL(R) oral tablets, 2007).

e) In placebo-controlled clinical trials for the treatment of schizophrenia (up to 6 weeks) in adults, dizzine 10% of patients receiving quetiapine fumarate extended-release tablets (n=951) compared to 4% for pla ranged from 300 to 800 mg (Prod Info SEROQUEL(R)XR extended-release oral tablets, 2007).

3.3.9.A.5 Dystonia

a) Incidence: less than 5% (Prod Info SEROQUEL(R)XR extended-release oral tablets, 2007)

b) During the first few days after initiating treatment with an antipsychotic medication, symptoms of dyst susceptible individuals. Symptoms may include spasm of neck muscles, which may progress to tightenin swallowing difficulty, breathing difficulty, and/or protrusion of the tongue. These symptoms can occur at l often occur (and occur with a greater severity) with high potency and at higher doses of first generation a medications. Males and younger age groups appear to be at greater risk for developing acute dystonia (I (R) oral tablets, 2008a).

c) During clinical trials for the treatment of schizophrenia in adults, dystonia was reported in less than 5% quetiapine fumarate extended-release tablets (Prod Info SEROQUEL(R)XR extended-release oral tablet

d) A 43-year-old Caucasian woman developed acute dystonia after receiving four weeks of quetiapine tl dose of 400 milligrams (mg) daily. The woman experienced slow movement of her head to the right side, increased incidence of involuntary movement when under stress. Dystonic movement of her head to the observed. The patient was cross-tapered to ziprasidone (80 mg/day) and symptoms of dystonia resolved dose was reduced to 100 mg/day (Kropp et al, 2004).

3.3.9.A.6 Extrapyramidal disease

a) Incidence: 4% to 12% (Prod Info SEROQUEL(R) oral tablets, 2007; Prod Info SEROQUEL(R)XR exte tablets, 2007)

b) In two placebo-controlled clinical trials of adult bipolar depression patients, extrapyramidal symptoms included akathisia, tremor, dyskinesia, dystonia, extrapyramidal disorder, involuntary muscle contraction muscle rigidity and psychomotor hyperactivity) were reported in 12% of patients receiving quetiapine fum or 600 mg) compared to 6% for placebo. Individual adverse events in these studies did not exceed 4% fo (Prod Info SEROQUEL(R) oral tablets, 2007).

c) There were no differences in the incidence of extrapyramidal symptoms between groups receiving qu tablets and placebo in three adult acute mania and three adult schizophrenia placebo-controlled clinical t SEROQUEL(R) oral tablets, 2007)

d) In a 6-week, fixed-dose clinical trial of adult schizophrenia patients, extrapyramidal symptoms (which akathisia, akinesia, extrapyramidal syndrome, hypertonia, neck rigidity, hypokinesia, tremor and cogwhe reported in 6%, 6%, 4%, 8% and 6% of patients receiving quetiapine fumarate tablets (75 milligrams (mg 300 mg/day, 600 mg/day, and 750 mg/day, respectively) compared to 16% for placebo (Prod Info SERO 2007).

e) In placebo-controlled clinical trials of adult schizophrenic patients, adverse reactions potentially relate symptoms (akathisia, extrapyramidal disorder, dyskinesia, restlessness, dystonia, muscle rigidity, and tre for 8% of patients receiving quetiapine fumarate extended-release tablets, 8% for patients receiving quet tablets, and 5% for placebo; quetiapine doses ranged from 300 to 800 milligrams. Individual adverse eve did not exceed 3% for any treatment group (Prod Info SEROQUEL(R)XR extended-release oral tablets,

f) The severity of extrapyramidal symptoms (EPS) with quetiapine therapy has not differed from that of p trials (Garver, 2000a; Green, 1999a; Borison et al, 1996a; Fulton & Goa, 1995b; Anon, 1995a; Fabre et a

3.3.9.A.7 Headache

a) Incidence: tablets, 17% to 21% (Prod Info SEROQUEL(R) oral tablets, 2007); extended-release table SEROQUEL(R)XR extended-release oral tablets, 2007)

b) In placebo-controlled clinical trials for the treatment (monotherapy) of schizophrenia (up to 6 weeks) a to 12 weeks) in adults, headache was reported in 21% of patients receiving quetiapine fumarate tablets (14% for placebo (n=404); doses ranged from 75 to 800 milligrams/day (Prod Info SEROQUEL(R) oral tal

c) In placebo-controlled clinical trials for the adjunct treatment of acute mania (up to 3 weeks) in adults, reported in 17% of patients receiving quetiapine fumarate tablets (n=196) compared to 13% for placebo from 100 to 800 milligrams/day (Prod Info SEROQUEL(R) oral tablets, 2007).

d) Headache was reported 7.4% of adult schizophrenic patients taking quetiapine fumarate extended-re a randomized, placebo-controlled, long-term trial (up to 12 months). After completion of an initial open la with quetiapine fumarate extended-release tablets, stabilized patients were randomized to either continu or switch to placebo (n=103) to determine the possibility of relapse (Prod Info SEROQUEL(R)XR extend tablets, 2007).

3.3.9.A.8 Insomnia

a) Incidence: tablets, 12% (Masand, 2000a; Green, 1999a; Borison et al, 1996a; Anon, 1995a; Fulton & al, 1995a); extended-release tablets, 8.5% (Prod Info SEROQUEL(R)XR extended-release oral tablets,

b) Insomnia was reported 8.5% of adult schizophrenic patients taking quetiapine fumarate extended-rel a randomized, placebo-controlled, long-term trial (up to 12 months). At the completion of the initial open patients who were stabilized on quetiapine fumarate extended-release tablets were randomized to either therapy or switch to placebo (n=103) to determine the possibility of relapse (Prod Info SEROQUEL(R)XR oral tablets, 2007).

c) The adverse effect of insomnia has a 12% frequency with quetiapine use (Masand, 2000a; Green, 19 1996a; Anon, 1995a; Fulton & Goa, 1995b; Fabre et al, 1995a).

3.3.9.A.9 Lethargy

a) Incidence: 5% (Prod Info SEROQUEL(R) oral tablets, 2007)

b) In placebo-controlled clinical trials for the treatment of bipolar depression (up to 8 weeks) in adults, le 5% of patients receiving quetiapine fumarate tablets (n=698) compared to 2% for placebo (n=347); dose 600 milligrams/day (Prod Info SEROQUEL(R) oral tablets, 2007).

3.3.9.A.10 Parkinsonism

a) The results of a cohort study indicate that high-dose atypical antipsychotic therapy carries a similar ris of parkinsonism as does typical antipsychotic therapy. In a population-based, retrospective cohort study, and older) with evidence of dementia were followed for up to 1 year for the development of parkinsonism with typical or atypical antipsychotic use. As compared with older adults receiving atypical antipsychotic olanzapine, risperidone, quetiapine), incident parkinsonism was 30% more likely to occur in those taking (i.e., chlorpromazine, haloperidol, perphenazine) (adjusted HR, 1.3; 95% CI, 1.04 to 1.58), and 60% less patient who did not receive either therapy (HR, 0.4; 95% CI, 0.29 to 0.43). Older adults using higher pote antipsychotics had almost a 50% greater risk of experiencing parkinsonism as compared with patients pr antipsychotics (all were considered lower potency) (HR, 1.44; 95% CI, 1.13 to 1.84); however, in patients potency typical antipsychotics, the risk of developing parkinsonism was no different from that in adults ta antipsychotics (HR, 0.75; 95% CI. 0.48 to 1.15). In addition, a positive dose-related relationship was obs

occurrence of incident parkinsonism and the use of atypical antipsychotics. The risk for developing parki
than twice as great in patients using a high-dose atypical antipsychotic agent as compared with those pr
atypical antipsychotic agent (HR, 2.07; 95% CI, 1.42 to 3.02). Furthermore, patients taking a typical antip
to have a similar risk for the development of parkinsonism as patients receiving high-dose atypical antips
(p=ns). The authors conclude that atypical antipsychotics may not be safer than typical antipsychotics wh
are considered (Rochon et al, 2005).

3.3.9.A.11 Restless legs syndrome

a) Restless legs, temporally related to quetiapine therapy, have been reported during post-marketing us
SEROQUEL(R) oral tablets, 2008a).

3.3.9.A.12 Sedated

a) Incidence: tablets, 30% (Prod Info SEROQUEL(R) oral tablets, 2007); extended-release tablets, 13%
SEROQUEL(R)XR extended-release oral tablets, 2007)

b) In placebo-controlled clinical trials for the treatment of bipolar depression (up to 8 weeks) in adults, se
in 30% of patients receiving quetiapine fumarate tablets (n=698) compared to 8% for placebo (n=347); d
to 600 milligrams/day (Prod Info SEROQUEL(R) oral tablets, 2007).

c) In placebo-controlled clinical trials for the treatment of schizophrenia (up to 6 weeks) in adults, sedati
13% of patients receiving quetiapine fumarate extended-release tablets (n=951) compared to 7% for pla
ranged from 300 to 800 mg (Prod Info SEROQUEL(R)XR extended-release oral tablets, 2007).

3.3.9.A.13 Seizure

a) Incidence: tablets, 0.5% (Prod Info SEROQUEL(R) oral tablets, 2007); extended-release tablets, 0.1%
SEROQUEL(R)XR extended-release oral tablets, 2007)

b) Seizures were reported in 0.5% of patients treated with quetiapine fumarate tablets (n=3490) compar
with active control drugs (n=527) and 0.2% for placebo (n=954) in clinical trials (Prod Info SEROQUEL(R

c) During clinical trials, seizures were reported in 0.1% of patients treated with quetiapine fumarate exte
(n=951) compared to 0.9% for placebo (n=319) (Prod Info SEROQUEL(R)XR extended-release oral tabl

d) Quetiapine fumarate should be used cautiously in patients with a history of seizures (Prod Info SERO
2007; Prod Info SEROQUEL(R)XR extended-release oral tablets, 2007).

3.3.9.A.14 Somnolence

a) Summary

1) Somnolence was commonly reported during quetiapine fumarate clinical trials, especially during
periods (Prod Info SEROQUEL(R) oral tablets, 2007; Prod Info SEROQUEL(R)XR extended-release

b) Incidence: tablets, 16% to 34% (Prod Info SEROQUEL(R) oral tablets, 2007); extended-release table
SEROQUEL(R)XR extended-release oral tablets, 2007)

c) In placebo-controlled clinical trials for the adjunct treatment of acute mania (up to 3 weeks) in adults,
reported in 34% of patients receiving quetiapine fumarate tablets (n=196) compared to 9% for placebo (r
from 100 to 800 milligrams/day (Prod Info SEROQUEL(R) oral tablets, 2007).

d) In placebo-controlled clinical trials for the treatment of bipolar depression (up to 8 weeks) in adults, so
reported in 28% of patients receiving quetiapine fumarate tablets (n=698) compared to 7% for placebo (r
from 300 to 600 milligrams/day (Prod Info SEROQUEL(R) oral tablets, 2007).

e) Somnolence was reported in 18% of patients treated with quetiapine fumarate tablets compared to 11
schizophrenia trials (Prod Info SEROQUEL(R) oral tablets, 2007).

f) In clinical trials for the treatment of acute bipolar mania using quetiapine fumarate as monotherapy, so
reported in 16% of patients taking quetiapine fumarate tablets compared to 4% for placebo (Prod Info SE
tablets, 2007).

g) In placebo-controlled clinical trials for the treatment of schizophrenia (up to 6 weeks) in adults, somno
12% of patients receiving quetiapine fumarate extended-release tablets (n=951) compared to 4% for pla
ranged from 300 to 800 mg (Prod Info SEROQUEL(R)XR extended-release oral tablets, 2007).

3.3.9.A.15 Tardive dyskinesia

a) Incidence: tablets, 0.1% to 1% (Prod Info SEROQUEL(R) oral tablets, 2007); extended-release tablet
Info SEROQUEL(R)XR extended-release oral tablets, 2007)

b) A potentially irreversible tardive dyskinesia may develop in patients receiving antipsychotic drugs; this
duration of treatment and the cumulative dose. Less commonly, the syndrome can develop after brief tre
doses. Antipsychotics may mask the underlying process by suppressing the signs and symptoms of the s
prevalence of the syndrome appears to be highest among the elderly, especially elderly women; howeve
rely upon prevalence to estimate which patients are likely to develop the syndrome. The syndrome may
completely upon discontinuation of the antipsychotic medication (Prod Info SEROQUEL(R) oral tablets, 2
SEROQUEL(R)XR extended-release oral tablets, 2007).

c) During clinical trials for the treatment of schizophrenia in adults, tardive dyskinesia was reported 0.1%
taking quetiapine fumarate tablets (Prod Info SEROQUEL(R) oral tablets, 2007).

d) During clinical trials for the treatment of schizophrenia in adults, tardive dyskinesia was reported in le
taking quetiapine fumarate extended-release tablets (Prod Info SEROQUEL(R)XR extended-release ora

e) A 44-year-old woman with schizophrenia resistant to typical neuroleptic agents developed tardive dys
of quetiapine therapy. While receiving 150 milligrams of quetiapine daily she developed involuntary chor

the tongue and jaw. Later, she also developed finger involvement. Quetiapine was discontinued and she therapy which improved the tardive dyskinesia symptoms (Ghelber & Belmaker, 1999).

3.3.9.A.16 Tremor

a) Incidence: tablets, 8% (Prod Info SEROQUEL(R) oral tablets, 2007); extended-release tablets, less th SEROQUEL(R)XR extended-release oral tablets, 2007)

b) In placebo-controlled clinical trials for the adjunct treatment of acute mania (up to 3 weeks) in adults, 8% of patients receiving quetiapine fumarate tablets (n=196) compared to 7% for placebo (n=203); dose 800 milligrams/day (Prod Info SEROQUEL(R) oral tablets, 2007).

c) During clinical trials for the treatment of schizophrenia in adults, tremor was reported in less than 5% quetiapine fumarate extended-release tablets (Prod Info SEROQUEL(R)XR extended-release oral tablet

3.3.10 Ophthalmic Effects

3.3.10.A Quetiapine Fumarate

Amblyopia

Disorder of lens

3.3.10.A.1 Amblyopia

a) Incidence: 2% (Prod Info SEROQUEL(R) oral tablets, 2007)

b) In placebo-controlled clinical trials for the treatment (monotherapy) of schizophrenia (up to 6 weeks) a to 12 weeks) in adults, amblyopia was reported in 2% of patients receiving quetiapine fumarate tablets (r 1% for placebo (n=404); doses ranged from 75 to 800 milligrams/day (Prod Info SEROQUEL(R) oral tabl

3.3.10.A.2 Disorder of lens

a) Although a causal relationship has not been substantiated, lens changes in patients during long-term fumarate have been reported. Examination to detect cataract formation is recommended at initiation of tr after beginning treatment, and every 6 months during the course of treatment (Prod Info SEROQUEL(R) Prod Info SEROQUEL(R)XR extended-release oral tablets, 2007).

3.3.12 Psychiatric Effects

3.3.12.A Quetiapine Fumarate

Agitation

Anxiety

Suicidal thoughts

3.3.12.A.1 Agitation

a) Incidence: 6% to 20% (Prod Info SEROQUEL(R) oral tablets, 2007)

b) In placebo-controlled clinical trials for the treatment (monotherapy) of schizophrenia (up to 6 weeks) a to 12 weeks) in adults, agitation was reported in 20% of patients receiving quetiapine fumarate tablets (n 17% for placebo (n=404); doses ranged from 75 to 800 milligrams/day (Prod Info SEROQUEL(R) oral tal

c) In placebo-controlled clinical trials for the adjunct treatment of acute mania (up to 3 weeks) in adults, in 6% of patients receiving quetiapine fumarate tablets (n=196) compared to 4% for placebo (n=203); do to 800 milligrams/day (Prod Info SEROQUEL(R) oral tablets, 2007).

3.3.12.A.2 Anxiety

a) Incidence: 4% (Prod Info SEROQUEL(R) oral tablets, 2007)

b) In placebo-controlled clinical trials for the treatment (monotherapy) of schizophrenia (up to 6 weeks) a to 12 weeks) in adults, anxiety was reported in 4% of patients receiving quetiapine fumarate tablets (n=7 for placebo (n=404); doses ranged from 75 to 800 milligrams/day (Prod Info SEROQUEL(R) oral tablets,

3.3.12.A.3 Suicidal thoughts

a) In two clinical studies involving patients with bipolar depression, the incidence of treatment emergent attempt during eight weeks of treatment was 1.7% and 2.6% in patients treated with quetiapine fumarate (mg)/day (n=350) and 600 mg/day (n=348), respectively, and 2.0% in patients receiving placebo (Prod Ir oral tablets, 2007).

3.3.14 Reproductive Effects

3.3.14.A Quetiapine Fumarate

3.3.14.A.1 Priapism

a) Priapism was reported in one patient taking quetiapine fumarate tablets; a causal relationship has not (Prod Info SEROQUEL(R) oral tablets, 2007).

3.3.15 Respiratory Effects

3.3.15.A Quetiapine Fumarate

Cough

Hyperventilation

Nasal congestion

Pharyngitis

Rhinitis

3.3.15.A.1 Cough

a) Incidence: at least 1% (Prod Info SEROQUEL(R) oral tablets, 2007)

b) During clinical trials for the treatment of schizophrenia in adults, increased cough was reported in at l taking quetiapine fumarate tablets (Prod Info SEROQUEL(R) oral tablets, 2007).

3.3.15.A.2 Hyperventilation

a) A 69-year-old African-American female, admitted for major depression with psychotic features, develo acute respiratory alkalosis 3 days after being discharged from the hospital. At the time of the occurrence dose of quetiapine was 50 milligrams twice daily with concurrent treatments with metronidazole and micc etiologies include a comorbid hypersensitivity to quetiapine or to the concomitant administration of metro inhibit metabolism of quetiapine. Symptoms improved after discontinuation of quetiapine (Shelton et al, 2

3.3.15.A.3 Nasal congestion

a) Incidence: 5% (Prod Info SEROQUEL(R) oral tablets, 2007)

b) In placebo-controlled clinical trials for the treatment of bipolar depression (up to 8 weeks) in adults, na reported in 5% of patients receiving quetiapine fumarate tablets (n=698) compared to 3% for placebo (n= from 300 to 600 milligrams/day (Prod Info SEROQUEL(R) oral tablets, 2007).

3.3.15.A.4 Pharyngitis

a) Incidence: 4% to 6% (Prod Info SEROQUEL(R) oral tablets, 2007)

b) In placebo-controlled clinical trials for the treatment (monotherapy) of schizophrenia (up to 6 weeks) a to 12 weeks) in adults, pharyngitis was reported in 4% of patients receiving quetiapine fumarate tablets (3% for placebo (n=404); doses ranged from 75 to 800 milligrams/day (Prod Info SEROQUEL(R) oral tabl

c) In placebo-controlled clinical trials for the adjunct treatment of acute mania (up to 3 weeks) in adults, reported in 6% of patients receiving quetiapine fumarate tablets (n=196) compared to 3% for placebo (n= from 100 to 800 milligrams/day (Prod Info SEROQUEL(R) oral tablets, 2007).

3.3.15.A.5 Rhinitis

a) Incidence: 3% (Prod Info SEROQUEL(R) oral tablets, 2007)

b) In placebo-controlled clinical trials for the treatment (monotherapy) of schizophrenia (up to 6 weeks) a to 12 weeks) in adults, rhinitis was reported in 3% of patients receiving quetiapine fumarate tablets (n=71 for placebo (n=404); doses ranged from 75 to 800 milligrams/day (Prod Info SEROQUEL(R) oral tablets,

3.3.16 Other

Quetiapine

Quetiapine Fumarate

3.3.16.A Quetiapine

3.3.16.A.1 Extrapyramidal disease

See Drug Consult reference: NEUROLEPTIC-INDUCED EXTRAPYRAMIDAL REACTIONS

3.3.16.B Quetiapine Fumarate

Death

Fatigue

Fever

Neuroleptic malignant syndrome

Pain

3.3.16.B.1 Death

a) Results of a population-based, retrospective cohort study demonstrated that the use of conventional a
associated with an even greater risk for death than atypical antipsychotics when administered to elderly p
years and older) with dementia. Atypical versus no antipsychotic use and conventional versus atypical ar
wise comparisons were made. A total of 27,259 matched pairs were identified and the dementia cohort w
place of residence (community versus long-term care facilities). In order to adjust for difference in baselir
propensity score matching was used. The primary outcome of the study was all-cause mortality. The risk
evaluated at 30, 60, 120, and 180 days after the antipsychotic medications were initially dispensed. Ther
significant increase in the risk for death at 30 days associated with new use of atypical antipsychotic med
with nonuse in both the community-dwelling cohort (adjusted hazard ratio (HR), 1.31 (95% confidence in
1.70); absolute risk difference, 0.2 percentage point) and long-term care cohort (adjusted HR, 1.55 (95%
absolute risk difference, 1.2 percentage points). For both cohorts, the risk associated with atypical antips
persist to 180 days. The risk for death associated with conventional antipsychotics was even greater thar
with atypical antipsychotics. At 30 days, the adjusted HR for the community-dwelling cohort was 1.55 (95
and 1.26 (95% CI, 1.04 to 1.53) for the long-term care cohort (adjusted risk difference for both was 1.1 p
risk appeared to persist to 180 days for both groups. Some important limitations to the study include unk
confounders may influence the results and cause of death could not be examined (Gill et al, 2007).

b) Results of a population-based, retrospective cohort study demonstrated comparable to possibly great
associated with the use of conventional antipsychotic medications in the elderly (aged 65 years and olde
atypical antipsychotic medications. The analysis excluded patients with cancer and included only new us
medications. The primary study outcome was 180-day all-cause mortality. A set of potential confounders
on healthcare utilization data within 6 months before the initiation of antipsychotic medications. Of the 37
identified, 12,882 and 24,359 received conventional and atypical antipsychotic medications, respectively
the conventional drug group within the first 180 days was 14.1% compared with 9.6% in the atypical drug
mortality ratio, 1.47; 95% confidence interval (CI), 1.39 to 1.56). In the multi-variable analysis which cont
confounders, the adjusted mortality ratio for the risk of death within 180 days for conventional versus aty
1.32 (95% CI, 1.23 to 1.42). When the most frequently prescribed conventional antipsychotic drugs were
risperidone, the mortality ratio associated with haloperidol was 2.14 (95% CI, 1.86 to 2.45) and loxapine
1.19 to 1.40), while there was no difference associated with olanzapine. The increased mortality risk for c
atypical drug therapy was greatest when doses higher (above median) doses were used (mortality ratio 1
1.86) and also during the first 40 days of therapy (mortality ratio 1.6; 95% CI, 1.42 to 1.8). Confirmatory a
multi-variable Cox regression, propensity score, and instrumental variable estimation confirmed the resu
(Schneeweiss et al, 2007).

c) The findings of one meta-analysis suggest that there may be a small increased risk of death associat
atypical antipsychotic agents for the treatment of dementia in elderly patients. The study analysis (n=511
randomized, double-blind, placebo-controlled, parallel group trials of antipsychotic use (i.e., aripiprazole
(n=5), quetiapine (n=3), risperidone (n=5)) in elderly patients (weighted mean age, 81.2 years) with dem
occurred more often in patients receiving atypical antipsychotic therapy as compared with placebo (118 (
respectively). The overall odds ratio, as assessed by meta-analysis, for death in elderly patients receivin
antipsychotics as compared with placebo was 1.54 (95% CI, 1.06 to 2.23; p=0.02), and the risk differenc
0.004 to 0.02; p=0.01). Overall, the relative risk associated with atypical antipsychotic use was 1.65 (95%
p=0.003); however this increased risk was only identified when all drugs were pooled for analysis; meta-
drugs did not show a statistically significant increased risk. A similar dropout rate was observed between
placebo-treated patients (32.2% vs 31.4%, respectively), with no significant difference in dropouts found
(Schneider et al, 2005).

d) The results of a retrospective cohort study indicate that conventional antipsychotic agents are at leas
antipsychotic agents to increase the risk of death among elderly patients 65 years of age or older. The st
new users of conventional agents (mean age, 83.2 years) and 13,748 new users of atypical agents (mea

higher adjusted relative risk of death was associated with the use of conventional antipsychotics as comp
antipsychotics at all time points studied after beginning therapy (within 180 days: RR, 1.37; 95% CI, 1.27
days: RR, 1.56; 95% CI, 1.37 to 1.78; 40 to 79 days: RR, 1.37; 95% CI, 1.19 to 1.59; 80 to 180 days: RR
1.41). In addition, the adjusted risks of death observed in patients with dementia (RR, 1.29; 95% CI, 1.15
dementia (RR, 1.45; 95% CI, 1.30 to 1.63), in a nursing home (RR, 1.26; 95% CI, 1.08 to 1.47), or not in
1.42; 95% CI, 1.29 to 1.56) were also higher with the use of conventional antipsychotic therapy as comp
antipsychotic use. This risk appeared to be dose-related and was greater with the use of higher dose (i.e
median) conventional antipsychotics (RR, 1.73; 95% CI, 1.57 to 1.90). Additional studies which specifica
optimum care of elderly patients requiring antipsychotic therapy are needed so that appropriate guidance
intervention can be provided (Wang et al, 2005).

3.3.16.B.2 Fatigue

a) Incidence: 10% (Prod Info SEROQUEL(R) oral tablets, 2007)

b) In placebo-controlled clinical trials for the treatment of bipolar depression (up to 8 weeks) in adults, fa
10% of patients receiving quetiapine fumarate tablets (n=698) compared to 8% for placebo (n=347); dos
600 milligrams/day (Prod Info SEROQUEL(R) oral tablets, 2007).

3.3.16.B.3 Fever

a) Incidence: 2% (Prod Info SEROQUEL(R) oral tablets, 2007)

b) In placebo-controlled clinical trials for the treatment (monotherapy) of schizophrenia (up to 6 weeks) a
to 12 weeks) in adults, fever was reported in 2% of patients receiving quetiapine fumarate tablets (n=719
placebo (n=404); doses ranged from 75 to 800 milligrams/day (Prod Info SEROQUEL(R) oral tablets, 20

3.3.16.B.4 Neuroleptic malignant syndrome

a) Incidence: rare (Prod Info SEROQUEL(R) oral tablets, 2007; Prod Info SEROQUEL(R)XR extended-r
2007)

b) A 20-year-old man developed neuroleptic malignant syndrome (NMS) within 8 to 9 weeks of starting
treatment of unprovoked aggression. The patient's medical history included severe mental retardation (IQ
of frequent unprovoked episodes of aggression, and treatment with haloperidol 5 mg/day for 14 months
symptoms. Quetiapine (100 mg/day) was added to the haloperidol therapy to help control the aggression
developed increased salivation, profuse perspiration, daytime drowsiness, decreased psychomotor activ
emotional reactivity within 4 to 5 days of starting the quetiapine. The symptoms persisted for 5 weeks an
haloperidol was decreased to 2.5 mg/day and the quetiapine was increased to 200 mg/day. Additionally,
started on lorazepam up to 5 mg/day. Within 3 weeks, the symptoms worsened and the patient develope
grade fever and later developed difficulty in walking with stiffness of the entire body, coarse tremors, high
sensorium, and difficulty in swallowing with regurgitation of both liquids and solids. Upon physical examir
muscular rigidity, profuse perspiration and elevated blood pressure. Laboratory analyses revealed leuko
creatinine phosphokinase (greater than ten fold increase), myoglobinuria, and mild renal impairment. The
a recent history of strenuous physical exercise, exposure to high ambient temperatures or any concomita
counter medications. Computed tomography of the brain and cerebrospinal fluid analysis did not reveal a
patient was diagnosed with NMS and all psychotropic medications were discontinued. Bromocriptine 7.5
consequently started along with supportive management. Within 48 hours the patient experienced a dec
perspiration, and his blood pressure stabilized. By the 4th day of treatment with bromocriptine his muscu
however, he developed patchy pneumonitis and was treated with antibiotics. Despite the treatment with a
respiratory status continued to decline and he died on the 10th day. Authors concluded a temporal relatio
initiation of quetiapine and the onset of NMS symptoms (Dan et al, 2009).

c) Based on a retrospective medication review, quetiapine was a probable cause of neuroleptic maligna
a 34-year-old male. His past medical history included a childhood accident resulting in severe brain dam
mental retardation, and seizures was hospitalized for mental status changes, tremors, temperature of 39
(C), and was subsequently diagnosed with (NMS) accompanied by extrapyramidal effects (EPS). During
patient experienced lead pipe rigidity, tachycardia, and high creatine kinase (CK) level. His medications i
200 mg three times per day, guanfacine 2 mg/day, carbamazepine 400 mg every 12 hours, valproic acid
and lorazepam 2 mg (frequency unknown). Quetiapine was discontinued on hospital day 2, and the patie
traditional treatment for NMS, which included bromocriptine 2.5 mg via a gastric feeding tube every 8 ho
dantrolene 1 mg/kg. On day 3, the patient continues to have high fever (41 degrees C), became hypoxic
intubated. Midazolam drip was started and titrated per hospital protocol to sedate the patient, bromocript
mg every 8 hours, and an infusion of 0.45% NaCl with sodium bicarbonate was started due to a high CK
international units per liter (L) and serum creatine levels up to 1.4 mcg/mL. Further, IV norepinephrine dr
because the patient was not hemodynamically stable. On day 6, his blood cell counts remained stable, t
NaCl with sodium bicarbonate was discontinued and bromocriptine was decreased to 2.5 mg every 6 ho
level and temperature have decreased (4450 international units/L and 39.3 degrees C, respectively). On
of NMS had resolved. The Naranjo probability scale suggested that quetiapine was the probable cause o
is not common for atypical antipsychotic drugs to cause NMS with associated EPS as reported in this ca
cases of NMS due to quetiapine identified in the literature and 75% of these cases had reactions that inc
et al, 2009).

d) Neuroleptic malignant syndrome (NMS), which can manifest clinically with hyperpyrexia, muscle rigid
instability, altered mental status, elevated CPK levels, myoglobinuria, and acute renal failure has been re
antipsychotic substances, including quetiapine fumarate. If neuroleptic malignant syndrome does occur,

medications and other drugs not essential to concurrent therapy should be discontinued, intensive sympt
monitoring should be initiated, and treatment of any concomitant serious medical problems should occur
of reintroduction of antipsychotics after a patient has experienced NMS should be taken; recurrences ha
(Prod Info SEROQUEL(R) oral tablets, 2007; Prod Info SEROQUEL(R)XR extended-release oral tablets
e) A 44-year-old woman with a history of schizoaffective disorder and 3 earlier episodes of neuroleptic n
(NMS) presented with fever, decreased level of consciousness, rigidity, and urinary incontinence. Her me
quetiapine 200 milligrams/day (mg/day), clozapine 400 mg/day, divalproex sodium 750 mg/day, lamotrig
clonazepam 4 mg/day. She was found to have bilateral pneumonia and highly elevated creatine phospho
Antibiotics and oral bromocriptine 1.25 mg twice daily were started; antipsychotics were withheld. When
day 3, she showed paranoid delusions. Clozapine, divalproex sodium, lamotrigine, and clonazepam were
hospital day 4, her temperature was normal and her CPK level reduced. Ten days later her CPK level wa
returned to her baseline mental status. Although some of the findings could be attributable to pneumonia
symptoms and the previous history of NMS supported the diagnosis of NMS in this instance (Bourgeois e

3.3.16.B.5 Pain

a) Incidence: 7% (Prod Info SEROQUEL(R) oral tablets, 2007)

b) In placebo-controlled clinical trials for the treatment (monotherapy) of schizophrenia (up to 6 weeks) a
to 12 weeks) in adults, pain was reported in 7% of patients receiving quetiapine fumarate tablets (n=719)
placebo (n=404); doses ranged from 75 to 800 milligrams/day (Prod Info SEROQUEL(R) oral tablets, 20

3.4 Teratogenicity/Effects in Pregnancy/Breastfeeding

A) Teratogenicity/Effects in Pregnancy

1) U.S. Food and Drug Administration's Pregnancy Category: Category C (Prod Info SEROQUEL(R) oral tablets,

a) Either studies in animals have revealed adverse effects on the fetus (teratogenic or embryocidal or other)
controlled studies in women or studies in women and animals are not available. Drugs should be given only if
justifies the potential risk to the fetus.

2) Australian Drug Evaluation Committee's (ADEC) Category: B3(Australian Government Department of Health a
Therapeutic Goods Administration, 2006)

a) Drugs which have been taken by only a limited number of pregnant women and women of childbearing ag
in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been ob
animals have shown evidence of an increased occurrence of fetal damage, the significance of which is consi
humans.

See Drug Consult reference: PREGNANCY RISK CATEGORIES

3) Crosses Placenta: Unknown

4) Clinical Management

a) There are no adequate and well-controlled studies in pregnant women. Two cases of quetiapine use durin
produced no abnormalities in the infants (Gentile, 2006; Tenyi et al, 2003). Until more information is available
quetiapine during pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus (P
(R) oral tablets, 2007).

5) Literature Reports

a) A prospective, observational study of 54 women (mean age, 30.7 years) recruited from the Emory Women
program exposed to antipsychotic medication during pregnant showed permeability of the placental barrier. C
determined by maternal and umbilical cord blood samples taken at delivery and though data collected from m
medical records. Placental passage showed a significant difference between antipsychotic medications, olan
CI, 46.8%-97.5%) being the highest, followed by haloperidol 65.5% (95% CI, 40.3%-90.7%), risperidone 49.2
84.8%), and quetiapine 24.1% (95% CI, 18.7%-29.5%), showing the lowest placental passage. In the quetiap
there was one case of preterm labor (< less than 37 weeks gestation) and 2 infants that required neonatal int
admission. Seven neonates developed respiratory complications and 2 developed cardiovascular events. Lo
2500 g) occurred in one infant (Newport et al, 2007).

b) Treatment of a 33-year-old woman with fluvoxamine 200 mg/day and quetiapine 400 mg/day during her s
resulted in an uneventful pregnancy and the birth of a healthy female infant. The patient was being treated wi
quetiapine when she was diagnosed with a severe postpartum psychotic depression after the birth of her first
attempts at reducing her medication led to relapse. After being informed of the risk-benefit of fluvoxamine/que
during pregnancy, the patient decided to go forward with a second pregnancy while maintaining her drug regi
and quetiapine with the addition of folate 5 mg/day throughout the pregnancy. The patient gained 9 kg with no
psychiatric instability. Routine biochemical tests were within the normal range and 5 echographic reports four
abnormalities. The presence of an intrauterine myoma led to an elective caesarean-section. A healthy female
g and measuring 49 cm in length was delivered, with Apgar scores of 9 and 10 at 1 minute and 5 minutes, re
2006).

c) One case report describes the maternal use of quetiapine 300 to 400 mg throughout gestation, and the su
healthy male infant without abnormality. At 6 months of age, the infant was developing normally (Tenyi et al,

d) In pregnant rats and rabbits treated with quetiapine 0.3 to 2.4 times the maximum recommended human d
to 2.4 times the MRHD, no teratogenicity was observed. However, embryo/fetal toxicity was observed in rats
0.6 to 2.4 times the MRHD and 1.2 to 2.4 times the MRHD, respectively. The high quetiapine dose in rats and
produced maternal toxicity. In a perio/postnatal reproductive study in rats, no quetiapine-related effects were
0.12, and 0.24 the MRHD. There were, however, increased fetal and pup death and decreased mean litter we
MRHD (Prod Info SEROQUEL(R) oral tablets, 2007).

B) Breastfeeding

1) Thomson Lactation Rating: Infant risk cannot be ruled out.
a) Available evidence and/or expert consensus is inconclusive or is inadequate for determining infant risk wh breastfeeding. Weigh the potential benefits of drug treatment against potential risks before prescribing this dr breastfeeding.
2) Clinical Management
a) Limited data on the safety of quetiapine in nursing infants demonstrates no evidence of toxicity (Rampono 2006). It is recommended that nursing woman who are receiving quetiapine should not breast-feed (Prod Info tablets, 2007). If quetiapine treatment is required in a nursing mother, monitor infant progress and periodically in the infant's plasma (Rampono et al, 2007).
3) Literature Reports
a) A case report of a 26-year-old woman prescribed quetiapine while breast-feeding her 3-month-old infant d plasma (M:P) ratio of 0.29 (an estimated relative infant dose of 0.09% of the maternal weight-adjusted dose) of exposure generally acceptable for breast-feeding. The woman was prescribed quetiapine 400 mg at night f treatment of nonresponsive depression with concomitant chronic pain. At 16 months prior to the study, she w quetiapine 300 mg with an increase to 400 mg during month 4 of her pregnancy and continuing to the study d treated with oxycodone 20 mg 3 times daily and fluoxetine 40 mg daily during gestation and up to the study d weighing 3.4 kg (50th percentile) was delivered at week 37. On the study day, the 3-month-old infant weighed percentile). During the study, the infant was receiving oral morphine 120 mcg 3 times daily for opioid depende fed 6 to 7 times daily. Blood samples were collected immediately prior to the mother's quetiapine dose and 5 elimination phase (between 12.8 and 23.1 hours after the dose). Due to limited plasma concentration measur quetiapine dosing, the M:P ratio, calculated using the milk and average plasma concentration during the elim 0.29 (0.09% of the maternal weight-adjusted dose). The infant's plasma contained quetiapine 1.4 mcg/L equi maternal plasma concentration. Upon clinical examination, the infant was healthy and his Denver age was th chronological age (Rampono et al, 2007).
b) Treatment with fluvoxamine 200 mg/day and quetiapine 400 mg/day in a 33-year-old woman during her se resulted in an uneventful pregnancy and the birth of a healthy female infant weighing 2600 g and measuring 4 Apgar scores of 9 and 10 at 1 minute and 5 minutes, respectively. The patient chose to breast-feed; however to supplement her breast milk due to insufficient milk production. In the 3 months that the infant received brea with formula, no adverse effects were detected and the infant continues to develop normally (Gentile, 2006).

3.5 Drug Interactions

Drug-Drug Combinations

Drug-Food Combinations

Drug-Lab Modifications

3.5.1 Drug-Drug Combinations

Acecainide

Ajmaline

Amiodarone

Amitriptyline

Amobarbital

Amoxapine

Amprenavir

Aprindine

Aprobarbital

Arsenic Trioxide

Astemizole

Atazanavir

Azimilide

Bepridil

Betamethasone

Bretylium

Butabarbital

Butalbital

Carbamazepine

Chloral Hydrate

Chloroquine

Chlorpromazine

Cisapride

Clarithromycin

Cortisone

Darunavir

Deflazacort

Dehydroepiandrosterone

Desipramine

Dexamethasone

Dibenzepin

Disopyramide

Dofetilide

Dolasetron

Doxepin

Droperidol

Encainide

Enflurane

Erythromycin

Eterobarb

Flecainide

Fluconazole

Fluoxetine

Fosamprenavir

Foscarnet

Fosphenytoin

Gemifloxacin

Halofantrine

Haloperidol

Halothane

Hydrocortisone

Hydroquinidine

Ibutilide

Imipramine

Indinavir

Isoflurane

Isradipine

Itraconazole

Ketoconazole

Lidoflazine

Lopinavir

Lorcainide

Mefloquine

Mephobarbital

Mesoridazine

Methohexital

Methylprednisolone

Nelfinavir

Nortriptyline

Octreotide

Paramethasone

Pentamidine

Pentobarbital

Phenobarbital

Phenylalanine

Phenytoin

Pirmenol

Prajmaline

Prednisolone

Prednisone

Primidone

Probucol

Procainamide

Prochlorperazine

Propafenone

Protriptyline

Rifampin

Risperidone

Ritonavir

Saquinavir

Secobarbital

Sematilide

Sotalol

Spiramycin

Sulfamethoxazole

Tedisamil

Telithromycin

Terfenadine

Thiopental

Thioridazine

Tipranavir

Triamcinolone

Trifluoperazine

Trimethoprim

Trimipramine

Vasopressin

Warfarin

Zolmitriptan

3.5.1.A Acecainide

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Concurrent use of acecainide and quetiapine is not recommended due to the risk of additive ef interval. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised (Yamreud
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of acecainide and quetiapine is not recommended du inducing life-threatening arrhythmias. If concurrent use cannot be avoided, cautious dosing and telemetric mo
7) Probable Mechanism: additive QT prolongation
8) Literature Reports
a) Class III antiarrhythmics have been shown to prolong the QT interval, which may result in ventricular ventricular fibrillation, and torsades de pointes. Several antipsychotic agents have demonstrated QT prol quetiapine (Owens, 2001c). Concomitant use of Class III antiarrhythmic agents such as acecainide and additive effects on the QT interval and is not recommended (Yamreudeewong et al, 2003).

3.5.1.B Ajmaline

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Several antipsychotic agents have demonstrated QT prolongation including amisulpride, halop paliperidone, quetiapine, risperidone, sertindole, sultopride, ziprasidone, and zotepine (Prod Info FANAPT(TM Prod Info Solian(R), 1999x; O'Brien et al, 1999p; Prod Info INVEGA(TM) extended-release oral tablets, 2006; Duenas-Laita et al, 1999x; Agelink et al, 2001v; Lande et al, 1992w; Prod Info GEODON(R) intramuscular inj 2005; Sweetman, 2003). Because Class IA antiarrhythmic agents may also prolong the QT interval and incre arrhythmias, the concurrent administration of antipsychotics with a drug from this class is not recommended ((TM) oral tablets, 2009; Prod Info Quinaglute(R), 1999).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: The concurrent administration of a Class IA antiarrhythmic and an antipsychotic is r
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) In an open-label QTc study of patients with schizophrenia or schizoaffective disorder (n=160), iloperic day was associated with QTc prolongation of 9 msec (Prod Info FANAPT(TM) oral tablets, 2009).

b) QRS widening, QTc interval prolongation, and torsades de pointes may occur with disopyramide ther
Norpace(R), 1997).
c) The effects of combined therapy with quinidine (Class IA antiarrhythmic agent) and haloperidol (antip
studied by giving 12 healthy volunteers haloperidol 5 mg alone and with 250 mg of quinidine bisulfate. Th
significant increases in the plasma concentrations of haloperidol when given concurrently with quinidine
treatment alone. The mean area under the concentration curve (AUC) was increased from 54.3 ng/h/mL
to 103.2 ng/h/mL on combined therapy. The peak concentration (Cmax) also showed an increase from 1
haloperidol to 3.8 ng/mL on combined therapy. Half-life (T1/2) and time to peak concentration (Tmax) we
changed, thereby suggesting to the authors that a tissue binding mechanism is more likely responsible fo
changes than an elimination alteration (Young et al, 1993).

3.5.1.C Amiodarone

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Concurrent use of amiodarone and quetiapine is not recommended due to the risk of additive e
interval. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised (Yamreud
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of amiodarone and quetiapine is not recommended c
inducing life-threatening arrhythmias. If concurrent use cannot be avoided, cautious dosing and telemetric mo
7) Probable Mechanism: additive QT prolongation
8) Literature Reports
a) Class III antiarrhythmics have been shown to prolong the QT interval, which may result in ventricular
ventricular fibrillation, and torsades de pointes. Several antipsychotic agents have demonstrated QT prol
quetiapine (Owens, 2001c). Concomitant use of Class III antiarrhythmic agents such as amiodarone and
additive effects on the QT interval and is not recommended (Yamreudeewong et al, 2003).

3.5.1.D Amitriptyline

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod
haloperidol (O'Brien et al, 1999a), risperidone (Duenas-Laita et al, 1999c), sertindole (Agelink et al, 2001b), c
2001e), sultopride (Lande et al, 1992b), and zotepine (Sweetman, 2003). Even though no formal drug interac
been done, the coadministration of a tricyclic antidepressant and an antipsychotic is not recommended (Prod
2001; Marshall & Forker, 1982).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of a tricyclic antidepressant and an antipsychotic is n
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) Electrocardiographic changes that have occurred during clinical trials with pimozide have included pr
corrected QT interval, flattening, notching, and inversion of the T wave and the appearance of U waves.
studies, sudden, unexpected deaths have occurred while patients were receiving pimozide doses of 1 m
mechanism for these deaths is prolongation of the QT interval predisposing patients to ventricular arrhytl
(R), 1999b).

3.5.1.E Amobarbital

1) Interaction Effect: decreased serum quetiapine concentrations
2) Summary: Increased doses of quetiapine may be required to maintain control of symptoms of schizophrer
receiving a barbiturate, a hepatic enzyme inducer (Prod Info Seroquel(R), 2001c).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Caution is indicated when quetiapine is administered with barbiturates or other indu
P450 3A. Increased doses of quetiapine may be required to maintain control of psychotic symptoms in patien
and barbiturates.
7) Probable Mechanism: induction of cytochrome P450-mediated metabolism of quetiapine by barbiturates

3.5.1.F Amoxapine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod
haloperidol (O'Brien et al, 1999a), risperidone (Duenas-Laita et al, 1999c), sertindole (Agelink et al, 2001b), c
2001e), sultopride (Lande et al, 1992b), and zotepine (Sweetman, 2003). Even though no formal drug interac
been done, the coadministration of a tricyclic antidepressant and an antipsychotic is not recommended (Prod
2001; Marshall & Forker, 1982).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of a tricyclic antidepressant and an antipsychotic is n
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) Electrocardiographic changes that have occurred during clinical trials with pimozide have included pr corrected QT interval, flattening, notching, and inversion of the T wave and the appearance of U waves. studies, sudden, unexpected deaths have occurred while patients were receiving pimozide doses of 1 m mechanism for these deaths is prolongation of the QT interval predisposing patients to ventricular arrhytl (R), 1999b).

3.5.1.G Amprenavir
1) Interaction Effect: increased quetiapine plasma concentrations
2) Summary: In vitro studies indicated that quetiapine is metabolized by the CYP3A4 isozyme in the liver. Co ketoconazole (200 mg once daily for 4 days), a potent CYP3A inhibitor, reduced oral clearance of quetiapine 335% increase in maximum plasma concentration of quetiapine. Although not studied, a similar interaction co other CYP3A inhibitors such as protease inhibitors. Therefore, caution and a reduced quetiapine dosage are quetiapine is administered to patients receiving protease inhibitors concomitantly (Prod Info SEROQUEL(R) c
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Use caution when prescribing quetiapine to patients who take protease inhibitors as elevated quetiapine plasma concentrations. A reduced quetiapine dosage is recommended when administeri protease inhibitors (Prod Info SEROQUEL(R) oral tablets, 2008a).
7) Probable Mechanism: inhibition of CYP3A-mediated quetiapine metabolism

3.5.1.H Aprindine
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Coadministration of quetiapine with other drugs that potentially prolong the QTc interval, such a be approached with caution. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring 2001o; Larochelle et al, 1984).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of aprindine and quetiapine is not recommended due inducing life-threatening arrhythmias. If concurrent use cannot be avoided, cautious dosing and telemetric mo
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.I Aprobarbital
1) Interaction Effect: decreased serum quetiapine concentrations
2) Summary: Increased doses of quetiapine may be required to maintain control of symptoms of schizophrer receiving a barbiturate, a hepatic enzyme inducer (Prod Info Seroquel(R), 2001c).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Caution is indicated when quetiapine is administered with barbiturates or other indu P450 3A. Increased doses of quetiapine may be required to maintain control of psychotic symptoms in patien and barbiturates.
7) Probable Mechanism: induction of cytochrome P450-mediated metabolism of quetiapine by barbiturates

3.5.1.J Arsenic Trioxide
1) Interaction Effect: prolongation of the QTc interval and/or torsades de pointes
2) Summary: Arsenic trioxide can prolong the QT interval in some patients, which may result in ventricular ta fibrillation, and torsades de pointes and should not be administered with other drugs that may prolong the QT Trisenox(R), 2001a). Several antipsychotic agents have demonstrated QT prolongation including amisulpride 1999m), haloperidol (O'Brien et al, 1999i), paliperidone (Prod Info INVEGA(TM) extended-release oral tablets (Duenas-Laita et al, 1999p), sertindole (Agelink et al, 2001m), quetiapine (Owens, 2001s), sultopride (Lande ziprasidone (Prod Info GEODON(R) intramuscular injection, oral capsule, 2005), and zotepine (Sweetman, 2
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of arsenic trioxide and antipsychotics is not recomme
7) Probable Mechanism: additive effects on QTc prolongation
8) Literature Reports
a) QT/QTc prolongation should be expected during treatment with arsenic trioxide and torsade de pointe heart block has been reported. Over 460 ECG tracings from 40 patients with refractory or relapsed APL t trioxide were evaluated for QTc prolongation. Sixteen of 40 patients (40%) had at least one ECG tracing greater than 500 msec. Prolongation of the QTc was observed between 1 and 5 weeks after arsenic triox returned towards baseline by the end of 8 weeks after arsenic trioxide infusion. In these ECG evaluations experience more pronounced QT prolongation than men, and there was no correlation with age (Prod Int

3.5.1.K Astemizole

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod I haloperidol (O'Brien et al, 1999h), quetiapine (Owens, 2001q), risperidone (Duenas-Laita et al, 1999n; Prod I risperidone, 2002a), sertindole (Agelink et al, 2001l), sultopride (Lande et al, 1992k), and zotepine (Sweetma no formal drug interaction studies have been done, the coadministration of astemizole and other drugs known interval, including antipsychotics, is not recommended (Prod Info Hismanal(R), 1996).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of astemizole and agents that prolong the QT interva antipsychotics, is not recommended.
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) A total of 7 patients developed torsade de pointes after therapeutic use of haloperidol in high doses (I 1993e; Wilt et al, 1993c). Three patients developed the dysrhythmia after administration of 211 to 825 m 2 days for agitated delirium. These 3 patients recovered from the initial episodes, but 1 patient subseque arrest upon readministration of haloperidol. Four patients developed the dysrhythmia after administration over 1 to 4 days for delirium associated with bacterial meningitis (1), status asthmaticus (2) or respirator patients recovered with no adverse sequelae.

3.5.1.L Atazanavir

1) Interaction Effect: increased quetiapine plasma concentrations
2) Summary: In vitro studies indicated that quetiapine is metabolized by the CYP3A4 isozyme in the liver. Co ketoconazole (200 mg once daily for 4 days), a potent CYP3A inhibitor, reduced oral clearance of quetiapine 335% increase in maximum plasma concentration of quetiapine. Although not studied, a similar interaction co other CYP3A inhibitors such as protease inhibitors. Therefore, caution and a reduced quetiapine dosage are quetiapine is administered to patients receiving protease inhibitors concomitantly (Prod Info SEROQUEL(R) c
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Use caution when prescribing quetiapine to patients who take protease inhibitors as elevated quetiapine plasma concentrations. A reduced quetiapine dosage is recommended when administeri protease inhibitors (Prod Info SEROQUEL(R) oral tablets, 2008a).
7) Probable Mechanism: inhibition of CYP3A-mediated quetiapine metabolism

3.5.1.M Azimilide

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Concurrent use of azimilide and quetiapine is not recommended due to the risk of additive effe If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised (Yamreudeewong
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of azimilide and quetiapine is not recommended due inducing life-threatening arrhythmias. If concurrent use cannot be avoided, cautious dosing and telemetric mo
7) Probable Mechanism: additive QT prolongation
8) Literature Reports
a) Class III antiarrhythmics have been shown to prolong the QT interval, which may result in ventricular ventricular fibrillation, and torsades de pointes. Several antipsychotic agents have demonstrated QT prol quetiapine (Owens, 2001c). Concomitant use of Class III antiarrhythmic agents such as azimilide and qu additive effects on the QT interval and is not recommended (Yamreudeewong et al, 2003).

3.5.1.N Bepridil

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Some antipsychotic agents prolong the QT interval and an additive effect would be anticipated other agents which lengthen the QT interval (Prod Info Geodon(TM), 2002a; Agelink et al, 2001c; Owens, 20 1999d; Prod Info Haldol(R), 1998a). In U.S. clinical trials, bepridil increased QT and QTc intervals which was torsades de pointes in approximately 1% of patients. Other drugs that increase the QT interval may exaggera the QT interval observed with bepridil (Prod Info Vascor(R), 1997). Pimozide is contraindicated in patients tak may prolong the QT interval (Prod Info Orap(R), 1999d).
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of antipsychotics and agents that prolong the QT inte is contraindicated. In particular, pimozide is contraindicated in individuals with congenital QT syndrome, patie cardiac arrhythmias, or patients taking other drugs which may prolong the QT interval.
7) Probable Mechanism: additive effects on QT prolongation

8) Literature Reports

a) Electrocardiographic changes that have occurred during clinical trials with pimozide have included pr corrected QT interval, flattening, notching, and inversion of the T wave and the appearance of U waves. studies, sudden, unexpected deaths have occurred while patients were receiving pimozide doses of 1 m mechanism for these deaths is prolongation of the QT interval predisposing patients to ventricular arrhytl (R), 1999c).

b) Sometimes fatal QRS prolongation and QTc prolongation have been reported in patients taking rispe (Duenas-Laita et al, 1999d; Ravin & Levenson, 1997a).

3.5.1.O Betamethasone

1) Interaction Effect: decreased serum quetiapine concentrations

2) Summary: Increased doses of quetiapine may be required to maintain control of symptoms of schizophrer receiving a glucocorticoid, a hepatic enzyme inducer (Prod Info Seroquel(R), 2001b).

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: Caution is indicated when quetiapine is administered with glucocorticoids or other ir P450 3A.

7) Probable Mechanism: induction of cytochrome P450-mediated metabolism of quetiapine by glucocorticoid

3.5.1.P Bretylium

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Concurrent use of bretylium and quetiapine is not recommended due to the risk of additive effe If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised (Yamreudeewong

3) Severity: major

4) Onset: rapid

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of bretylium and quetiapine is not recommended due inducing life-threatening arrhythmias. If concurrent use cannot be avoided, cautious dosing and telemetric mo

7) Probable Mechanism: additive QT prolongation

8) Literature Reports

a) Class III antiarrhythmics have been shown to prolong the QT interval, which may result in ventricular ventricular fibrillation, and torsades de pointes. Several antipsychotic agents have demonstrated QT prol quetiapine (Owens, 2001c). Concomitant use of Class III antiarrhythmic agents such as bretylium and qu additive effects on the QT interval and is not recommended (Yamreudeewong et al, 2003).

3.5.1.Q Butabarbital

1) Interaction Effect: decreased serum quetiapine concentrations

2) Summary: Increased doses of quetiapine may be required to maintain control of symptoms of schizophrer receiving a barbiturate, a hepatic enzyme inducer (Prod Info Seroquel(R), 2001c).

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: Caution is indicated when quetiapine is administered with barbiturates or other indu P450 3A. Increased doses of quetiapine may be required to maintain control of psychotic symptoms in patien and barbiturates.

7) Probable Mechanism: induction of cytochrome P450-mediated metabolism of quetiapine by barbiturates

3.5.1.R Butalbital

1) Interaction Effect: decreased serum quetiapine concentrations

2) Summary: Increased doses of quetiapine may be required to maintain control of symptoms of schizophrer receiving a barbiturate, a hepatic enzyme inducer (Prod Info Seroquel(R), 2001c).

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: Caution is indicated when quetiapine is administered with barbiturates or other indu P450 3A. Increased doses of quetiapine may be required to maintain control of psychotic symptoms in patien and barbiturates.

7) Probable Mechanism: induction of cytochrome P450-mediated metabolism of quetiapine by barbiturates

3.5.1.S Carbamazepine

1) Interaction Effect: decreased serum quetiapine concentrations

2) Summary: Increased doses of quetiapine may be required to maintain control of symptoms of schizophrer receiving carbamazepine, a hepatic enzyme inducer (Prod Info Seroquel(R), 2001a).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Caution is indicated when quetiapine is administered with carbamazepine or other i

cytochrome P450 3A. Increased doses of quetiapine may be required to maintain control of psychotic sympto
receiving quetiapine and carbamazepine.
7) Probable Mechanism: unknown

3.5.1.T Chloral Hydrate
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Chloral hydrate has been shown to prolong the QTc interval at the recommended therapeutic d
1986). Even though no formal drug interaction studies have been done, the administration of drugs known to
interval, such as antipsychotics and chloral hydrate is not recommended. Several antipsychotic agents have
prolongation including amisulpride (Prod Info Solian(R), 1999k), haloperidol (O'Brien et al, 1999g), quetiapine
risperidone (Duenas-Laita et al, 1999m), sertindole (Agelink et al, 2001k), sultopride (Lande et al, 1992j), and
2003).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of chloral hydrate and antipsychotics is not recomme
7) Probable Mechanism: additive effects on QT prolongation
8) Literature Reports
a) The overall incidence of QT interval prolongation with sertindole is estimated at 1.9% to 4%, and the
developing torsades de pointes has been estimated at 0.13% to 0.21% (Brown & Levin, 1998a). Periodic
monitoring is required in the United Kingdom per sertindole's official labeling (Cardoni & Myer, 1997).
b) A total of 7 patients developed torsade de pointes after therapeutic use of haloperidol in high doses (
1993d; Wilt et al, 1993b). Three patients developed the dysrhythmia after administration of 211 to 825 m
2 days for agitated delirium. These 3 patients recovered from the initial episodes, but 1 patient subseque
arrest upon readministration of haloperidol.

3.5.1.U Chloroquine
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Chloroquine has been shown to prolong the QTc interval at the recommended therapeutic dos
effect would be anticipated if administered with other agents which lengthen the QT interval (Prod Info Aralen
antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999v),
et al, 1999o), quetiapine (Owens, 2001ab), risperidone (Duenas-Laita et al, 1999w), sertindole (Agelink et al,
(Lande et al, 1992u), and zotepine (Sweetman, 2004).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of antipsychotics and agents that prolong the QT inte
chloroquine is not recommended.
7) Probable Mechanism: additive effect on QT prolongation
8) Literature Reports
a) Sometimes fatal QRS prolongation and QTc prolongation have been reported in patients taking rispe
(Duenas-Laita et al, 1999v; Ravin & Levenson, 1997e).

3.5.1.V Chlorpromazine
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Concomitant use of phenothiazines and antipsychotic agents may cause additive effects on the
recommended. Q and T wave distortions have been observed in patients taking phenothiazines (Prod Info Co
Prod Info Stelazine(R), 2002; Prod Info Thorazine(R), 2002). Other phenothiazines may have similar effects,
available. Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info
haloperidol (O'Brien et al, 1999f), paliperidone (Prod Info INVEGA(TM) extended-release oral tablets, 2006),
2001n), risperidone (Duenas-Laita et al, 1999l), sertindole (Agelink et al, 2001j), sultopride (Lande et al, 1992
Info GEODON(R) intramuscular injection, oral capsule, 2005), and zotepine (Sweetman, 2003).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of agents that prolong the QT interval, such as phen
antipsychotics, is not recommended.
7) Probable Mechanism: additive QT prolongation

3.5.1.W Cisapride
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Some antipsychotic agents prolong the QT interval and an additive effect would be anticipated
other agents which lengthen the QT interval (Prod Info Geodon(TM), 2002; Owens, 2001a; Prod Info Orap(R)
pointes and QT prolongation have been reported with cisapride (Prod Info Propulsid(R), 2000).
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of antipsychotics and agents that prolong the QT inte

cisapride, is contraindicated. In particular, pimozide is contraindicated in individuals with congenital QT syndr history of cardiac arrhythmias, or patients taking other drugs which may prolong the QT interval.
7) Probable Mechanism: additive effects on QT prolongation
8) Literature Reports
a) Electrocardiographic changes that have occurred during clinical trials with pimozide have included pr corrected QT interval, flattening, notching, and inversion of the T wave and the appearance of U waves. studies, sudden, unexpected deaths have occurred while patients were receiving pimozide doses of 1 m mechanism for these deaths is prolongation of the QT interval predisposing patients to ventricular arrhytl (R), 1999).
b) Fatal QRS prolongation and QTc prolongation have been reported in patients taking risperidone (Due 1999a; Ravin & Levenson, 1997).

3.5.1.X Clarithromycin
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod haloperidol (O'Brien et al, 1999b), quetiapine (Owens, 2001g), risperidone (Duenas-Laita et al, 1999e), sertin 2001d), sultopride (Lande et al, 1992c), and zotepine (Sweetman, 2004). Even though no formal drug interac been done, concomitant use of clarithromycin and antipsychotic agents may cause additive effects on the QT recommended (Prod Info Biaxin(R), 2002).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of clarithromycin and agents that prolong the QT inte antipsychotics, is not recommended.
7) Probable Mechanism: additive effects on QT prolongation
8) Literature Reports
a) A 32-year-old male with schizoaffective disorder and metabolic syndrome experienced a significant in concentration following administration of quetiapine. The patient, hospitalized for acute psychotic sympto 50 mg quetiapine daily, with a gradual increase in dosage to 700 mg over 10 days. Psychotic symptoms weeks. On day 28, the patient developed a lower airway infection, and was orally treated with 750 mg su clarithromycin along with his evening dose of quetiapine 400 mg. The following morning, 750 mg sultami clarithromycin, and the morning 300-mg quetiapine dose were given. Within hours the patient became so sample testing resulted in 826.8 microgram/L (normal range, 70 to 170 microgram/L). The patient develo consciousness and respiratory depression. Quetiapine overdose was suspected and treatment was disc levels were continually measured over the course of a week until complete recovery was achieved (Schu 2008).
b) A total of 7 patients developed torsade de pointes after therapeutic use of haloperidol in high doses (1993a; Wilt et al, 1993). Three patients developed the dysrhythmia after administration of 211 to 825 mg 2 days for agitated delirium. These 3 patients recovered from the initial episodes, but 1 patient subseque arrest upon readministration of haloperidol. Four patients developed the dysrhythmia after administration over 1 to 4 days for delirium associated with bacterial meningitis (1), status asthmaticus (2) or respirator patients recovered with no adverse sequelae.
c) Prolongation of the QTc interval was reported in 8 patients receiving risperidone (Prod Info Risperdal

3.5.1.Y Cortisone
1) Interaction Effect: decreased serum quetiapine concentrations
2) Summary: Increased doses of quetiapine may be required to maintain control of symptoms of schizophrer receiving a glucocorticoid, a hepatic enzyme inducer (Prod Info Seroquel(R), 2001b).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Caution is indicated when quetiapine is administered with glucocorticoids or other i P450 3A.
7) Probable Mechanism: induction of cytochrome P450-mediated metabolism of quetiapine by glucocorticoid

3.5.1.Z Darunavir
1) Interaction Effect: increased quetiapine plasma concentrations
2) Summary: In vitro studies indicated that quetiapine is metabolized by the CYP3A4 isozyme in the liver. Co ketoconazole (200 mg once daily for 4 days), a potent CYP3A inhibitor, reduced oral clearance of quetiapine 335% increase in maximum plasma concentration of quetiapine. Although not studied, a similar interaction co other CYP3A inhibitors such as protease inhibitors. Therefore, caution and a reduced quetiapine dosage are quetiapine is administered to patients receiving protease inhibitors concomitantly (Prod Info SEROQUEL(R) c
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Use caution when prescribing quetiapine to patients who take protease inhibitors as elevated quetiapine plasma concentrations. A reduced quetiapine dosage is recommended when administeri

protease inhibitors (Prod Info SEROQUEL(R) oral tablets, 2008a).
7) Probable Mechanism: inhibition of CYP3A-mediated quetiapine metabolism

3.5.1.AA Deflazacort
1) Interaction Effect: decreased serum quetiapine concentrations
2) Summary: Increased doses of quetiapine may be required to maintain control of symptoms of schizophrer receiving a glucocorticoid, a hepatic enzyme inducer (Prod Info Seroquel(R), 2001b).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Caution is indicated when quetiapine is administered with glucocorticoids or other ir P450 3A.
7) Probable Mechanism: induction of cytochrome P450-mediated metabolism of quetiapine by glucocorticoid

3.5.1.AB Dehydroepiandrosterone
1) Interaction Effect: reduced effectiveness of quetiapine
2) Summary: Dehydroepiandrosterone (DHEA) levels within the normal range of 100 to 400 microgram/decil conducive for optimal treatment of patients with psychosis (Howard, 1992a). In case reports, patients have be antipsychotics when DHEA levels were elevated (Howard, 1992a). Patients being treated with quetiapine sho supplementation.
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Avoid concomitant use of dehydroepiandrosterone (DHEA) and quetiapine. If DHEA treatment with dexamethasone 1 mg orally per day may be used to normalize DHEA levels.
7) Probable Mechanism: elevated dehydroepiandrosterone (DHEA) blood levels may reduce responsiveness
8) Literature Reports
a) A 24-year-old female diagnosed with schizophrenia was resistant to daily doses of haloperidol 20 mill fluphenazine 40 mg, lithium carbonate 1200 mg, and lithium carbonate 900 mg plus thioridazine 300 mg Cushinoid with moon face, acne, facial hair, abdominal hair, and a 40 pound weight gain in the previous Dehydroepiandrosterone (DHEA) measured as part of an endocrine panel was 725 micrograms/deciliter to 400 mcg/dL). Dexamethasone 1 mg orally at bedtime resulted in substantial improvement within one w appeared calmer, more alert with improved psychotic symptoms and ability to concentrate. At two weeks level was within normal range (328 mcg/dL). The author concluded that elevated DHEA levels were assc psychosis resistant to conventional antipsychotic therapy (Howard, 1992).
b) A 13-year-old male decompensated with a subsequent two-year period of emotional problems accom of LSD, hashish, barbiturates, and alcohol. His mental status included bizarre, disorganized, delusional t visual hallucinations, paranoia, lack of attention to personal hygiene, agitation, and combativeness. He w chronic paranoid schizophrenia; schizophrenia, chronic undifferentiated type, and schizoaffective disorde was resistant to daily doses of trifluoperazine 40 mg, chlorpromazine 400 mg, and imipramine 100 mg. H to combination therapy with chlorpromazine 400 mg with thiothixene 80 mg, thioridazine 1000 mg, perph lithium carbonate 1200 mg, clonazepam 4 mg, and carbamazepine 1200 mg daily. Baseline DHEA level mcg/dL. A seven-day suppression test with dexamethasone 1 mg orally at bedtime resulted in a normal l mcg/dL. By day 5, psychosis improved and the patient was well-oriented, conversational, and was makir Once dexamethasone was discontinued, rapid decompensation and florid psychosis ensued despite "sul psychotropic medications". DHEA increased to 536 mcg/dL. The author concluded that elevated DHEA l with florid psychosis resistant to conventional antipsychotic therapy (Howard, 1992).

3.5.1.AC Desipramine
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod haloperidol (O'Brien et al, 1999a), risperidone (Duenas-Laita et al, 1999c), sertindole (Agelink et al, 2001b), c 2001e), sultopride (Lande et al, 1992b), and zotepine (Sweetman, 2003). Even though no formal drug interac been done, the coadministration of a tricyclic antidepressant and an antipsychotic is not recommended (Prod 2001; Marshall & Forker, 1982).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of a tricyclic antidepressant and an antipsychotic is n
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) Electrocardiographic changes that have occurred during clinical trials with pimozide have included pr corrected QT interval, flattening, notching, and inversion of the T wave and the appearance of U waves. studies, sudden, unexpected deaths have occurred while patients were receiving pimozide doses of 1 m mechanism for these deaths is prolongation of the QT interval predisposing patients to ventricular arrhyt (R), 1999b).

3.5.1.AD Dexamethasone

1) Interaction Effect: decreased serum quetiapine concentrations
2) Summary: Increased doses of quetiapine may be required to maintain control of symptoms of schizophrer receiving a glucocorticoid, a hepatic enzyme inducer (Prod Info Seroquel(R), 2001b).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Caution is indicated when quetiapine is administered with glucocorticoids or other ir P450 3A.
7) Probable Mechanism: induction of cytochrome P450-mediated metabolism of quetiapine by glucocorticoid

3.5.1.AE Dibenzepin

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod haloperidol (O'Brien et al, 1999a), risperidone (Duenas-Laita et al, 1999c), sertindole (Agelink et al, 2001b), c 2001e), sultopride (Lande et al, 1992b), and zotepine (Sweetman, 2003). Even though no formal drug interac been done, the coadministration of a tricyclic antidepressant and an antipsychotic is not recommended (Prod 2001; Marshall & Forker, 1982).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of a tricyclic antidepressant and an antipsychotic is n
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) Electrocardiographic changes that have occurred during clinical trials with pimozide have included pr corrected QT interval, flattening, notching, and inversion of the T wave and the appearance of U waves. studies, sudden, unexpected deaths have occurred while patients were receiving pimozide doses of 1 m mechanism for these deaths is prolongation of the QT interval predisposing patients to ventricular arrhyt (R), 1999b).

3.5.1.AF Disopyramide

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Several antipsychotic agents have demonstrated QT prolongation including amisulpride, halop paliperidone, quetiapine, risperidone, sertindole, sultopride, ziprasidone, and zotepine (Prod Info FANAPT(TM Prod Info Solian(R), 1999x; O'Brien et al, 1999p; Prod Info INVEGA(TM) extended-release oral tablets, 2006; Duenas-Laita et al, 1999x; Agelink et al, 2001v; Lande et al, 1992w; Prod Info GEODON(R) intramuscular inj 2005; Sweetman, 2003). Because Class IA antiarrhythmic agents may also prolong the QT interval and incre arrhythmias, the concurrent administration of antipsychotics with a drug from this class is not recommended ((TM) oral tablets, 2009; Prod Info Quinaglute(R), 1999).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: The concurrent administration of a Class IA antiarrhythmic and an antipsychotic is r
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) In an open-label QTc study of patients with schizophrenia or schizoaffective disorder (n=160), iloperic day was associated with QTc prolongation of 9 msec (Prod Info FANAPT(TM) oral tablets, 2009).
b) QRS widening, QTc interval prolongation, and torsades de pointes may occur with disopyramide ther Norpace(R), 1997).
c) The effects of combined therapy with quinidine (Class IA antiarrhythmic agent) and haloperidol (antip studied by giving 12 healthy volunteers haloperidol 5 mg alone and with 250 mg of quinidine bisulfate. Th significant increases in the plasma concentrations of haloperidol when given concurrently with quinidine treatment alone. The mean area under the concentration curve (AUC) was increased from 54.3 ng/h/mL to 103.2 ng/h/mL on combined therapy. The peak concentration (Cmax) also showed an increase from 1 haloperidol to 3.8 ng/mL on combined therapy. Half-life (T1/2) and time to peak concentration (Tmax) we changed, thereby suggesting to the authors that a tissue binding mechanism is more likely responsible fo changes than an elimination alteration (Young et al, 1993).

3.5.1.AG Dofetilide

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Concurrent use of dofetilide and quetiapine is not recommended due to the risk of additive effe If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised. Dofetilide should l 2 days before any interacting drug is initiated (Yamreudeewong et al, 2003a).
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of dofetilide and quetiapine is not recommended due inducing life-threatening arrhythmias. Dofetilide should be stopped for at least 2 days before any interacting d concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised.

7) Probable Mechanism: additive QT prolongation
8) Literature Reports
a) Class III antiarrhythmics have been shown to prolong the QT interval, which may result in ventricular ventricular fibrillation, and torsades de pointes. Several antipsychotic agents have also demonstrated QT including quetiapine (Owens, 2001c). Concomitant use of Class III antiarrhythmic agents such as dofetili have additive effects on the QT interval and is not recommended (Yamreudeewong et al, 2003).

3.5.1.AH Dolasetron
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod haloperidol (O'Brien et al, 1999e), quetiapine (Owens, 2001l), risperidone (Duenas-Laita et al, 1999j), sertind 2001h), sultopride (Lande et al, 1992g), and zotepine (Sweetman, 2003). Even though no formal drug interac been done, the coadministration of dolasetron and other drugs known to prolong the QTc interval, including a recommended (Prod Info Anzemet(R), 1997a).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of dolasetron and agents that prolong the QT interva antipsychotics, is not recommended.
7) Probable Mechanism: additive effects on QT prolongation
8) Literature Reports
a) In several studies, dolasetron resulted in significant, dose-related increases in mean PR, QRS, and Q to baseline values. Measured changes in ECG parameters were transient, reversible, and asymptomatic QRS intervals may be due to prolongation of maximum upstroke velocity (Vmax) due to binding of dolase channels. The cause of QTc interval prolongation appears to be due to prolongation of the QRS interval, rate, or both (Prod Info Anzemet(R), 1997; Hunt et al, 1995; Kris et al, 1994).
b) A total of 7 patients developed torsade de pointes after therapeutic use of haloperidol in high doses (1993c; Wilt et al, 1993a). Three patients developed the dysrhythmia after administration of 211 to 825 m 2 days for agitated delirium. These 3 patients recovered from the initial episodes, but 1 patient subseque arrest upon readministration of haloperidol. Four patients developed the dysrhythmia after administration over 1 to 4 days for delirium associated with bacterial meningitis (1), status asthmaticus (2) or respirator patients recovered with no adverse sequelae.
c) Prolongation of the QTc interval was reported in 8 patients receiving risperidone (Prod Info Risperdal

3.5.1.AI Doxepin
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod haloperidol (O'Brien et al, 1999a), risperidone (Duenas-Laita et al, 1999c), sertindole (Agelink et al, 2001b), c 2001e), sultopride (Lande et al, 1992b), and zotepine (Sweetman, 2003). Even though no formal drug interac been done, the coadministration of a tricyclic antidepressant and an antipsychotic is not recommended (Prod 2001; Marshall & Forker, 1982).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of a tricyclic antidepressant and an antipsychotic is n
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) Electrocardiographic changes that have occurred during clinical trials with pimozide have included pr corrected QT interval, flattening, notching, and inversion of the T wave and the appearance of U waves. studies, sudden, unexpected deaths have occurred while patients were receiving pimozide doses of 1 m mechanism for these deaths is prolongation of the QT interval predisposing patients to ventricular arrhytl (R), 1999b).

3.5.1.AJ Droperidol
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod haloperidol (O'Brien et al, 1999l), quetiapine (Owens, 2001y), risperidone (Duenas-Laita et al, 1999s), sertinc 2001q), sultopride (Lande et al, 1992r), and zotepine (Sweetman, 2003). Droperidol has been shown to prolo the recommended therapeutic dose. Even though no formal drug interaction studies have been done, the coa droperidol and other drugs known to prolong the QTc interval, including antipsychotics is not recommended (2002).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of droperidol and antipsychotics is not recommendec
7) Probable Mechanism: additive cardiac effects

3.5.1.AK Encainide

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Coadministration of quetiapine with other drugs that potentially prolong the QTc interval, such a be approached with caution. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring 2001o; Larochelle et al, 1984).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of encainide and quetiapine is not recommended due inducing life-threatening arrhythmias. If concurrent use cannot be avoided, cautious dosing and telemetric mo
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.AL Enflurane

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Some antipsychotic agents prolong the QT interval and an additive effect would be anticipated other agents which lengthen the QT interval (Agelink et al, 2001y; Owens, 2001ah; Prod Info Haldol(R), 1998 1992z). Even though no formal drug interaction studies have been done, antipsychotic agents should not be other drugs which are also known to prolong the QTc interval, including enflurane (Owens, 2001ah).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of enflurane and agents that prolong the QT interval, antispychotics, is not recommended.
7) Probable Mechanism: additive effects on QT prolongation
8) Literature Reports
a) Sometimes fatal QRS prolongation and QTc prolongation have been reported in patients taking rispe (Duenas-Laita et al, 1999aa; Ravin & Levenson, 1997h).

3.5.1.AM Erythromycin

1) Interaction Effect: increased quetiapine serum concentrations
2) Summary: Coadministration of ketoconazole (200 mg once daily for 4 days), a potent inhibitor of CYP3A, clearance of quetiapine by 84%, resulting in a 335% increase in maximum plasma concentration of quetiapin studied, a similar interaction could be expected with other inhibitors of CYP3A (e.g., itraconazole, fluconazole Therefore, use caution and a reduced quetiapine dosage when it is administered concomitantly with a potent including erythromycin (Prod Info SEROQUEL(R) oral tablets, 2008a). There may also be some potential for prolongation with the concomitant administration of erythromycin and quetiapine. Erythromycin significantly ir QTc interval versus baseline in a retrospective study of 49 patients (Oberg & Bauman, 1995). Erythromycin h prolongation in combination with other drugs that prolong the QT interval (Prod Info PCE(R), 2000). Although QT interval prolongation has been reported with quetiapine during postmarketing use (Prod Info SEROQUEL 2008a).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Use caution and a reduced quetiapine dose if it is administered concomitantly with Info SEROQUEL(R) oral tablets, 2008a). Monitor the patient for quetiapine adverse events (tardive dyskinesi hypotension) as well as for QTc interval prolongation.
7) Probable Mechanism: inhibition of CYP3A-mediated quetiapine metabolism by erythromycin

3.5.1.AN Eterobarb

1) Interaction Effect: decreased serum quetiapine concentrations
2) Summary: Increased doses of quetiapine may be required to maintain control of symptoms of schizophrer receiving a barbiturate, a hepatic enzyme inducer (Prod Info Seroquel(R), 2001c).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Caution is indicated when quetiapine is administered with barbiturates or other indu P450 3A. Increased doses of quetiapine may be required to maintain control of psychotic symptoms in patien and barbiturates.
7) Probable Mechanism: induction of cytochrome P450-mediated metabolism of quetiapine by barbiturates

3.5.1.AO Flecainide

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Coadministration of quetiapine with other drugs that potentially prolong the QTc interval, such a be approached with caution. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring 2001o; Prod Info Tambocor(R), 1998; Larochelle et al, 1984).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of flecainide and quetiapine is not recommended due inducing life-threatening arrhythmias. If concurrent use cannot be avoided, cautious dosing and telemetric mo
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.AP Fluconazole
1) Interaction Effect: increased quetiapine serum concentrations
2) Summary: Coadministration of ketoconazole (200 mg once daily for 4 days), a potent inhibitor of CYP3A, clearance of quetiapine by 84%, resulting in a 335% increase in maximum plasma concentration of quetiapin studied, a similar interaction could be expected with other inhibitors of CYP3A (e.g., itraconazole, fluconazole Therefore, use caution and a reduced quetiapine dosage when it is administered concomitantly with a potent including fluconazole (Prod Info SEROQUEL(R) oral tablets, 2008a). There may also be some potential for a prolongation with the concomitant administration of fluconazole and quetiapine. Case reports have described prolongation and torsades de points associated with fluconazole (Khazan & Mathis, 2002; Wassmann et al, 1 result in ventricular tachycardia, ventricular fibrillation, and torsades de pointes. Although data are conflicting, prolongation has been reported with quetiapine during postmarketing use (Prod Info SEROQUEL(R) oral tabl
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Use caution and a reduced quetiapine dose if it is administered concomitantly with SEROQUEL(R) oral tablets, 2008a). Monitor the patient for quetiapine adverse events (tardive dyskinesia, sc hypotension) as well as for QTc interval prolongation.
7) Probable Mechanism: inhibition of CYP3A-mediated quetiapine metabolism by fluconazole

3.5.1.AQ Fluoxetine
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest
2) Summary: Fluoxetine has been shown to prolong the QTc interval at the recommended therapeutic dose 2001). Even though no formal drug interaction studies have been done, the coadministration of antipsychotics known to prolong the QTc interval, including fluoxetine, is not recommended. Several antipsychotic agents ha prolongation including amisulpride (Prod Info Solian(R), 1999o), quetiapine (Owens, 2001u), sertindole (Agel sultopride (Lande et al, 1992n), and zotepine (Sweetman, 2003).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of fluoxetine and antipsychotics is not recommended
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.AR Fosamprenavir
1) Interaction Effect: increased quetiapine plasma concentrations
2) Summary: In vitro studies indicated that quetiapine is metabolized by the CYP3A4 isozyme in the liver. Co ketoconazole (200 mg once daily for 4 days), a potent CYP3A inhibitor, reduced oral clearance of quetiapine 335% increase in maximum plasma concentration of quetiapine. Although not studied, a similar interaction co other CYP3A inhibitors such as protease inhibitors. Therefore, caution and a reduced quetiapine dosage are quetiapine is administered to patients receiving protease inhibitors concomitantly (Prod Info SEROQUEL(R) o
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Use caution when prescribing quetiapine to patients who take protease inhibitors as elevated quetiapine plasma concentrations. A reduced quetiapine dosage is recommended when administeri protease inhibitors (Prod Info SEROQUEL(R) oral tablets, 2008a).
7) Probable Mechanism: inhibition of CYP3A-mediated quetiapine metabolism

3.5.1.AS Foscarnet
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest
2) Summary: Foscarnet can prolong the QT interval in some patients, which may result in ventricular tachyca fibrillation, and torsades de pointes. Several antipsychotic agents have demonstrated QT prolongation includi Info Solian(R), 1999z), haloperidol (O'Brien et al, 1999q), quetiapine (Owens, 2001ag), risperidone (Duenas- sertindole (Agelink et al, 2001x), sultopride (Lande et al, 1992y), and zotepine (Sweetman, 2003). Because a prolong the QT interval and increase the risk of arrhythmias, the concurrent administration of foscarnet and a recommended (Prod Info Foscavir(R), 1998; Ravin & Levenson, 1997g).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of foscarnet and antipsychotics is not recommended
7) Probable Mechanism: additive cardiac effects

3.5.1.AT Fosphenytoin
1) Interaction Effect: decreased quetiapine efficacy
2) Summary: Fosphenytoin is a prodrug of phenytoin and the same interactions that occur with phenytoin are

with fosphenytoin (Prod Info Cerebyx(R), 1999). Coadministration of quetiapine 250 mg three times daily and three times daily increased the mean oral clearance of quetiapine by 5-fold. Quetiapine is metabolized by cyt isoenzymes, which are induced by the administration of phenytoin (Prod Info Seroquel(R), 1997).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Increased doses of quetiapine may be required to maintain control of psychotic sym receiving quetiapine and fosphenytoin. Caution should be taken if fosphenytoin is withdrawn from therapy or inducing anticonvulsant.
7) Probable Mechanism: induction of quetiapine metabolism by phenytoin

3.5.1.AU Gemifloxacin
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Although pharmacokinetic studies between gemifloxacin and drugs that prolong the QT interva antipsychotics, have not been performed, gemifloxacin should be used cautiously in patients receiving antips (Prod Info Factive(R), 2003).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of two drugs that prolong the QT interval, such as ge antipsychotics, is not recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.AV Halofantrine
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Halofantrine can prolong the QT interval in some patients, which may result in ventricular tachy fibrillation, and torsades de pointes. Some antipsychotic agents prolong the QT interval and an additive effec if administered with other agents which lengthen the QT interval (Agelink et al, 2001a; Owens, 2001d; Prod In Prod Info Haldol(R), 1998; Lande et al, 1992a). The concurrent administration of halofantrine with antipsycho recommended (Prod Info Halfan(R), 1998).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of halofantrine and an antipsychotic is not recommer
7) Probable Mechanism: additive cardiac effects

3.5.1.AW Haloperidol
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Haloperidol is associated with QTc prolongation and torsade de pointes (Hassaballa & Balk, 20 (R), 2001a). Quetiapine may prolong the QT interval at therapeutic and toxic doses. Coadministration of halo daily with quetiapine 300 mg twice daily did not alter the steady-state pharmacokinetics of quetiapine (Prod In 2003). Caution is advised with coadministration of drugs that potentially prolong the QTc interval.
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Caution is advised if haloperidol and quetiapine are used concomitantly. Screen pa that may predispose to QT prolongation and torsade de pointes (i.e. cardiomyopathy, alcohol abuse, hypothy ECG and electrolytes at baseline and throughout therapy.
7) Probable Mechanism: additive effects on QT prolongation
8) Literature Reports
a) Numerous case reports have described significant QTc prolongation and torsades de pointes (TdP) a haloperidol. Hemodynamically significant ventricular tachyarrhythmias, ventricular fibrillation, asystole, a reported. The risk of TdP appears to be greater with intravenous haloperidol, but has occurred with oral a The risk increases with doses greater than 35 milligrams (mg) over 24 hours, though TdP has been assc low as 10 mg administered intravenously over 4 hours. To prevent haloperidol-induced TdP, screen patie dilated cardiomyopathy or alcohol abuse, testing for hypothyroidism before therapy, obtaining an electro and throughout therapy, and monitoring potassium, magnesium, and calcium. In patients with a baseline milliseconds (msec), haloperidol should be used cautiously or an alternative agent should be used. Disc the QTc increases more than 25% from baseline or if flattening of T-waves or development of U-waves c Balk, 2003).

3.5.1.AX Halothane
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Some antipsychotic agents prolong the QT interval and an additive effect would be anticipated other agents which lengthen the QT interval (Agelink et al, 2001i; Owens, 2001m; Prod Info Solian(R), 1999i; 1998c; Lande et al, 1992h). Even though no formal drug interaction studies have been done, antipsychotic ag coadministered with other drugs which may also prolong the QTc interval, including halothane (Owens, 2001
3) Severity: major

4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of halothane and agents that prolong the QT interval antispsychotics, is not recommended.
7) Probable Mechanism: additive effect on QT interval
8) Literature Reports
a) Sometimes fatal QRS prolongation and QTc prolongation have been reported in patients taking rispe (Duenas-Laita et al, 1999k; Ravin & Levenson, 1997c).

3.5.1.AY Hydrocortisone
1) Interaction Effect: decreased serum quetiapine concentrations
2) Summary: Increased doses of quetiapine may be required to maintain control of symptoms of schizophrer receiving a glucocorticoid, a hepatic enzyme inducer (Prod Info Seroquel(R), 2001b).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Caution is indicated when quetiapine is administered with glucocorticoids or other i P450 3A.
7) Probable Mechanism: induction of cytochrome P450-mediated metabolism of quetiapine by glucocorticoid

3.5.1.AZ Hydroquinidine
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Several antipsychotic agents have demonstrated QT prolongation including amisulpride, halop paliperidone, quetiapine, risperidone, sertindole, sultopride, ziprasidone, and zotepine (Prod Info FANAPT(TM Prod Info Solian(R), 1999x; O'Brien et al, 1999p; Prod Info INVEGA(TM) extended-release oral tablets, 2006; Duenas-Laita et al, 1999x; Agelink et al, 2001v; Lande et al, 1992w; Prod Info GEODON(R) intramuscular inj 2005; Sweetman, 2003). Because Class IA antiarrhythmic agents may also prolong the QT interval and incre arrhythmias, the concurrent administration of antipsychotics with a drug from this class is not recommended ((TM) oral tablets, 2009; Prod Info Quinaglute(R), 1999).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: The concurrent administration of a Class IA antiarrhythmic and an antipsychotic is r
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) In an open-label QTc study of patients with schizophrenia or schizoaffective disorder (n=160), iloperic day was associated with QTc prolongation of 9 msec (Prod Info FANAPT(TM) oral tablets, 2009).
b) QRS widening, QTc interval prolongation, and torsades de pointes may occur with disopyramide ther Norpace(R), 1997).
c) The effects of combined therapy with quinidine (Class IA antiarrhythmic agent) and haloperidol (antip studied by giving 12 healthy volunteers haloperidol 5 mg alone and with 250 mg of quinidine bisulfate. Th significant increases in the plasma concentrations of haloperidol when given concurrently with quinidine treatment alone. The mean area under the concentration curve (AUC) was increased from 54.3 ng/h/mL to 103.2 ng/h/mL on combined therapy. The peak concentration (Cmax) also showed an increase from 1 haloperidol to 3.8 ng/mL on combined therapy. Half-life (T1/2) and time to peak concentration (Tmax) we changed, thereby suggesting to the authors that a tissue binding mechanism is more likely responsible fo changes than an elimination alteration (Young et al, 1993).

3.5.1.BA Ibutilide
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Concurrent use of ibutilide and quetiapine is not recommended due to the risk of additive effect concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised (Yamreudeewong et
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of ibutilide and quetiapine is not recommended due t inducing life-threatening arrhythmias. If concurrent use cannot be avoided, cautious dosing and telemetric mo
7) Probable Mechanism: additive QT prolongation
8) Literature Reports
a) Class III antiarrhythmics have been shown to prolong the QT interval, which may result in ventricular ventricular fibrillation, and torsades de pointes. Several antipsychotic agents have demonstrated QT prol quetiapine (Owens, 2001c). Concomitant use of Class III antiarrhythmic agents such as ibutilide and que additive effects on the QT interval and is not recommended (Yamreudeewong et al, 2003).

3.5.1.BB Imipramine
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod haloperidol (O'Brien et al, 1999a), risperidone (Duenas-Laita et al, 1999c), sertindole (Agelink et al, 2001b), c

2001e), sultopride (Lande et al, 1992b), and zotepine (Sweetman, 2003). Even though no formal drug interac
been done, the coadministration of a tricyclic antidepressant and an antipsychotic is not recommended (Prod
2001; Marshall & Forker, 1982).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of a tricyclic antidepressant and an antipsychotic is n
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) Electrocardiographic changes that have occurred during clinical trials with pimozide have included pr
corrected QT interval, flattening, notching, and inversion of the T wave and the appearance of U waves.
studies, sudden, unexpected deaths have occurred while patients were receiving pimozide doses of 1 m
mechanism for these deaths is prolongation of the QT interval predisposing patients to ventricular arrhytl
(R), 1999b).

3.5.1.BC Indinavir
1) Interaction Effect: increased quetiapine plasma concentrations
2) Summary: In vitro studies indicated that quetiapine is metabolized by the CYP3A4 isozyme in the liver. Co
ketoconazole (200 mg once daily for 4 days), a potent CYP3A inhibitor, reduced oral clearance of quetiapine
335% increase in maximum plasma concentration of quetiapine. Although not studied, a similar interaction co
other CYP3A inhibitors such as protease inhibitors. Therefore, caution and a reduced quetiapine dosage are
quetiapine is administered to patients receiving protease inhibitors concomitantly (Prod Info SEROQUEL(R) o
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Use caution when prescribing quetiapine to patients who take protease inhibitors as
elevated quetiapine plasma concentrations. A reduced quetiapine dosage is recommended when administeri
protease inhibitors (Prod Info SEROQUEL(R) oral tablets, 2008a).
7) Probable Mechanism: inhibition of CYP3A-mediated quetiapine metabolism

3.5.1.BD Isoflurane
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Some antipsychotic agents prolong the QT interval and an additive effect would be anticipated
other agents which lengthen the QT interval (Agelink et al, 2001w; Owens, 2001ae; Prod Info Solian(R), 1999
(R), 1998g; Lande et al, 1992x). Even though no formal drug interaction studies have been done, antipsychot
be coadministered with other drugs which are also known to prolong the QTc interval, including isoflurane (O
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of isoflurane and agents that prolong the QT interval,
antipsychotics, is not recommended.
7) Probable Mechanism: additive effect on QT interval
8) Literature Reports
a) Sometimes fatal QRS prolongation and QTc prolongation have been reported in patients taking risper
(Duenas-Laita et al, 1999y; Ravin & Levenson, 1997f).

3.5.1.BE Isradipine
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Isradipine can prolong the QT interval in some patients, which may result in ventricular tachyca
fibrillation, and torsades de pointes, and its use with other drugs known to cause QT prolongation is not recor
DynaCirc(R), 2000). Several antipsychotic agents have demonstrated QT prolongation including amisulpride
1999f), haloperidol (O'Brien et al, 1999c), quetiapine (Owens, 2001i), risperidone (Duenas-Laita et al, 1999g)
al, 2001a), and zotepine (Sweetman, 2004).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of isradipine and an antipsychotic is not recommende
7) Probable Mechanism: additive cardiac effects

3.5.1.BF Itraconazole
1) Interaction Effect: increased quetiapine serum concentrations
2) Summary: In vitro studies indicated that quetiapine is metabolized by the CYP3A4 isozyme in the liver. Co
ketoconazole (200 mg once daily for 4 days), a potent CYP3A inhibitor, reduced oral clearance of quetiapine
335% increase in maximum plasma concentration of quetiapine. Although not studied, a similar interaction co
other CYP3A inhibitors such as itraconazole. Therefore, caution and a reduced quetiapine dosage are recom
quetiapine is administered to patients receiving itraconazole concomitantly (Prod Info SEROQUEL(R) oral tab
3) Severity: moderate
4) Onset: unspecified

5) Substantiation: theoretical
6) Clinical Management: Use caution when prescribing quetiapine to patients who take itraconazole as this r quetiapine plasma concentrations. A reduced quetiapine dosage is recommended when administering conco itraconazole (Prod Info SEROQUEL(R) oral tablets, 2008a).
7) Probable Mechanism: inhibition of CYP3A4-mediated quetiapine metabolism

3.5.1.BG Ketoconazole
1) Interaction Effect: increased quetiapine serum concentrations
2) Summary: In vitro studies indicated that quetiapine is metabolized by the CYP3A4 isozyme in the liver. Co ketoconazole (200 mg once daily for 4 days), a potent inhibitor of CYP3A, reduced oral clearance of quetiapi a 335% increase in maximum plasma concentration of quetiapine. Therefore, caution and a reduced quetiapi recommended when quetiapine is administered to patients receiving ketoconazole concomitantly (Prod Info S tablets, 2008a).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor patients for an increased incidence of quetiapine adverse effects and toxici somnolence, hypotension). A reduced quetiapine dosage is recommended when administering concomitantly (Prod Info SEROQUEL(R) oral tablets, 2008a).
7) Probable Mechanism: inhibition of CYP3A4-mediated quetiapine metabolism by ketoconazole

3.5.1.BH Lidoflazine
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Lidoflazine has been shown to prolong the QTc interval at the recommended therapeutic dose 1983). Even though no formal drug interaction studies have been done, the coadministration of antipsychotics known to prolong the QTc interval is not recommended. Several antipsychotic agents have demonstrated QT amisulpride (Prod Info Solian(R), 1999), haloperidol (O'Brien et al, 1999), quetiapine (Owens, 2001), risperid al, 1999), sertindole (Agelink et al, 2001), sultopride (Lande et al, 1992), and zotepine (Sweetman, 2003).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of lidoflazine and antipsychotics is not recommended
7) Probable Mechanism: additive cardiac effects

3.5.1.BI Lopinavir
1) Interaction Effect: increased quetiapine plasma concentrations
2) Summary: In vitro studies indicated that quetiapine is metabolized by the CYP3A4 isozyme in the liver. Co ketoconazole (200 mg once daily for 4 days), a potent CYP3A inhibitor, reduced oral clearance of quetiapine 335% increase in maximum plasma concentration of quetiapine. Although not studied, a similar interaction co other CYP3A inhibitors such as protease inhibitors. Therefore, caution and a reduced quetiapine dosage are quetiapine is administered to patients receiving protease inhibitors concomitantly (Prod Info SEROQUEL(R) c
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Use caution when prescribing quetiapine to patients who take protease inhibitors as elevated quetiapine plasma concentrations. A reduced quetiapine dosage is recommended when administeri protease inhibitors (Prod Info SEROQUEL(R) oral tablets, 2008a).
7) Probable Mechanism: inhibition of CYP3A-mediated quetiapine metabolism

3.5.1.BJ Lorcainide
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Coadministration of quetiapine with other drugs that potentially prolong the QTc interval, such a be approached with caution. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring 2001o; Larochelle et al, 1984).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of lorcainide and quetiapine is not recommended due inducing life-threatening arrhythmias. If concurrent use cannot be avoided, cautious dosing and telemetric mo
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.BK Mefloquine
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, caution is advised if mefloquin drugs which can prolong the QTc interval (Prod Info Lariam(R), 1999). Mefloquine was associated with signifi in a study of 46 healthy subjects (Davis et al, 1996). Antipsychotics including haloperidol (Prod Info Haldol(R) (Owens, 2001w), risperidone (Prod Info Risperdal(R) risperidone, 2000a), amisulpride (Prod Info Solian(R), 1 (Agelink et al, 2001p); sultopride (Lande et al, 1992p), and zotepine (Sweetman, 2004) have been shown to p

at therapeutic doses.
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Caution is advised if mefloquine and antipsychotics are used concomitantly.
7) Probable Mechanism: additive effect on QT interval

3.5.1.BL Mephobarbital
1) Interaction Effect: decreased serum quetiapine concentrations
2) Summary: Increased doses of quetiapine may be required to maintain control of symptoms of schizophrer receiving a barbiturate, a hepatic enzyme inducer (Prod Info Seroquel(R), 2001c).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Caution is indicated when quetiapine is administered with barbiturates or other indu P450 3A. Increased doses of quetiapine may be required to maintain control of psychotic symptoms in patien and barbiturates.
7) Probable Mechanism: induction of cytochrome P450-mediated metabolism of quetiapine by barbiturates

3.5.1.BM Mesoridazine
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Although citing no data, the manufacturer of mesoridazine states that concomitant use with oth prolong the QT interval is contraindicated (Prod Info Serentil(R), 2001). Several antipsychotic agents have de prolongation including amisulpride (Prod Info Solian(R), 1999r), haloperidol (O'Brien et al, 1999k), paliperidor (TM) extended-release oral tablets, 2006), quetiapine (Owens, 2001x), risperidone (Duenas-Laita et al, 1999 et al, 2001o), sultopride (Lande et al, 1992q), ziprasidone (Prod Info GEODON(R) intramuscular injection, ora zotepine (Sweetman, 2004).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of agents that prolong the QT interval, such as antips mesoridazine, is contraindicated.
7) Probable Mechanism: additive QT prolongation

3.5.1.BN Methohexital
1) Interaction Effect: decreased serum quetiapine concentrations
2) Summary: Increased doses of quetiapine may be required to maintain control of symptoms of schizophrer receiving a barbiturate, a hepatic enzyme inducer (Prod Info Seroquel(R), 2001c).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Caution is indicated when quetiapine is administered with barbiturates or other indu P450 3A. Increased doses of quetiapine may be required to maintain control of psychotic symptoms in patien and barbiturates.
7) Probable Mechanism: induction of cytochrome P450-mediated metabolism of quetiapine by barbiturates

3.5.1.BO Methylprednisolone
1) Interaction Effect: decreased serum quetiapine concentrations
2) Summary: Increased doses of quetiapine may be required to maintain control of symptoms of schizophrer receiving a glucocorticoid, a hepatic enzyme inducer (Prod Info Seroquel(R), 2001b).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Caution is indicated when quetiapine is administered with glucocorticoids or other ir P450 3A.
7) Probable Mechanism: induction of cytochrome P450-mediated metabolism of quetiapine by glucocorticoid

3.5.1.BP Nelfinavir
1) Interaction Effect: increased quetiapine plasma concentrations
2) Summary: In vitro studies indicated that quetiapine is metabolized by the CYP3A4 isozyme in the liver. Co ketoconazole (200 mg once daily for 4 days), a potent CYP3A inhibitor, reduced oral clearance of quetiapine 335% increase in maximum plasma concentration of quetiapine. Although not studied, a similar interaction co other CYP3A inhibitors such as protease inhibitors. Therefore, caution and a reduced quetiapine dosage are quetiapine is administered to patients receiving protease inhibitors concomitantly (Prod Info SEROQUEL(R) c
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Use caution when prescribing quetiapine to patients who take protease inhibitors as

elevated quetiapine plasma concentrations. A reduced quetiapine dosage is recommended when administeri
protease inhibitors (Prod Info SEROQUEL(R) oral tablets, 2008a).
7) Probable Mechanism: inhibition of CYP3A-mediated quetiapine metabolism

3.5.1.BQ Nortriptyline
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod I
haloperidol (O'Brien et al, 1999a), risperidone (Duenas-Laita et al, 1999c), sertindole (Agelink et al, 2001b), c
2001e), sultopride (Lande et al, 1992b), and zotepine (Sweetman, 2003). Even though no formal drug interac
been done, the coadministration of a tricyclic antidepressant and an antipsychotic is not recommended (Prod
2001; Marshall & Forker, 1982).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of a tricyclic antidepressant and an antipsychotic is n
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) Electrocardiographic changes that have occurred during clinical trials with pimozide have included pr
corrected QT interval, flattening, notching, and inversion of the T wave and the appearance of U waves.
studies, sudden, unexpected deaths have occurred while patients were receiving pimozide doses of 1 m
mechanism for these deaths is prolongation of the QT interval predisposing patients to ventricular arrhyt
(R), 1999b).

3.5.1.BR Octreotide
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Octreotide has been shown to prolong the QTc interval at the recommended therapeutic dose
(R), 1999). Even though no formal drug interaction studies have been done, the coadministration of antipsych
known to prolong the QTc interval, including octreotide, is not recommended. Several antipsychotic agents ha
prolongation including amisulpride (Prod Info Solian(R), 1999t), haloperidol (O'Brien et al, 1999m), risperidon
1999t), sertindole (Agelink et al, 2001r), quetiapine (Owens, 2001z), sultopride (Lande et al, 1992s), and zote
2003).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of octreotide and antipsychotics is not recommended
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.BS Paramethasone
1) Interaction Effect: decreased serum quetiapine concentrations
2) Summary: Increased doses of quetiapine may be required to maintain control of symptoms of schizophrer
receiving a glucocorticoid, a hepatic enzyme inducer (Prod Info Seroquel(R), 2001b).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Caution is indicated when quetiapine is administered with glucocorticoids or other ir
P450 3A.
7) Probable Mechanism: induction of cytochrome P450-mediated metabolism of quetiapine by glucocorticoid

3.5.1.BT Pentamidine
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Pentamidine has been shown to prolong the QTc interval at the recommended therapeutic dos
1990). Even though no formal drug interaction studies have been done, the coadministration of antipsychotics
known to prolong the QTc interval, including pentamidine, is not recommended (Agelink et al, 2001e; Owens,
Haldol(R), 2001; Prod Info Solian(R), 1999e; Duenas-Laita et al, 1999f; Duenas-Laita et al, 1999f; Prod Info M
Metzger & Friedman, 1993b; Lande et al, 1992d).
3) Severity: major
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of pentamidine and antipsychotics is not recommend
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.BU Pentobarbital
1) Interaction Effect: decreased serum quetiapine concentrations
2) Summary: Increased doses of quetiapine may be required to maintain control of symptoms of schizophrer
receiving a barbiturate, a hepatic enzyme inducer (Prod Info Seroquel(R), 2001c).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable

6) Clinical Management: Caution is indicated when quetiapine is administered with barbiturates or other indu
P450 3A. Increased doses of quetiapine may be required to maintain control of psychotic symptoms in patien
and barbiturates.
7) Probable Mechanism: induction of cytochrome P450-mediated metabolism of quetiapine by barbiturates

3.5.1.BV Phenobarbital
1) Interaction Effect: decreased serum quetiapine concentrations
2) Summary: Increased doses of quetiapine may be required to maintain control of symptoms of schizophrer
receiving a barbiturate, a hepatic enzyme inducer (Prod Info Seroquel(R), 2001c).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Caution is indicated when quetiapine is administered with barbiturates or other indu
P450 3A. Increased doses of quetiapine may be required to maintain control of psychotic symptoms in patien
and barbiturates.
7) Probable Mechanism: induction of cytochrome P450-mediated metabolism of quetiapine by barbiturates

3.5.1.BW Phenylalanine
1) Interaction Effect: increased incidence of tardive dyskinesia
2) Summary: Taking phenylalanine concomitantly with certain neuroleptic drugs may exacerbate tardive dysl
1992a). Abnormal phenylalanine metabolism in certain patients may lead to phenylalanine accumulation in th
reduced brain availability of other large neutral amino acids. This may interfere with the synthesis of catechol
1992a).
3) Severity: moderate
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Caution is advised if phenylalanine is administered with a neuroleptic agent. Monito
for signs of tardive dyskinesia.
7) Probable Mechanism: reduced brain availability of other large neutral amino acids and interference with ca
synthesis
8) Literature Reports
a) Phenylalanine tended to increase the incidence of tardive dyskinesia in patients taking neuroleptics ir
groups of patients were studied: (1) patients with unipolar depression with tardive dyskinesia (n=11), (2)
tardive dyskinesia with current or past exposure to greater than or equal to 100 milligrams (mg) of a chlo
for at least 3 months (n=10), and (3) patients with no tardive dyskinesia not previously exposed to a neur
Neuroleptic agents were taken during the study by 6 patients in group 1, and 5 patients in group 2. Patie
phenylalanine 100 mg/kilogram dissolved in orange juice after an overnight fast. Blood samples were ob
phenylalanine administration and 2 hours after administration. Three patients in group 1 (with tardive dys
highest postloading phenylalanine plasma levels, this group as a whole had higher (though nonsignificar
levels than the other groups. Tardive dyskinesia score (measured using the Abnormal Involuntary Mover
nonsignificantly increased in group 1. Postloading phenylalanine level and postloading AIMS scores were
positively correlated in group 1 (rs=0.347, p less than 0.05; Spearman correlation coefficient 0.543, p les
Postloading phenylalanine level and baseline AIMS scores demonstrated a trend toward correlation (rs=
Spearman correlation coefficient 0.679, p less than 0.05). In all patients, phenylalanine loading increased
phenylalanine levels approximately eight-fold, and plasma tyrosine increased 2.5 times as a result of cor
phenylalanine to tyrosine. Plasma levels of competing large neutral amino acids such as tryptophan decr
(Gardos et al, 1992).

3.5.1.BX Phenytoin
1) Interaction Effect: decreased quetiapine efficacy
2) Summary: Coadministration of quetiapine 250 mg three times daily and phenytoin 100 mg three times dai
oral clearance of quetiapine by 5-fold. Quetiapine is metabolized by cytochrome P450 3A4 isoenzymes, whic
administration of phenytoin (Prod Info Seroquel(R), 2003b; Wong et al, 2001a).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: established
6) Clinical Management: Increased doses of quetiapine may be required to maintain control of psychotic sym
receiving quetiapine and phenytoin. Caution should be taken if phenytoin is withdrawn from therapy or replac
anticonvulsant.
7) Probable Mechanism: induction of quetiapine metabolism by phenytoin
8) Literature Reports
a) Coadministration of phenytoin with quetiapine significantly decreased the plasma concentration-time
resulting in a 5-fold increase in oral clearance in patients with DSM-IV-diagnosed schizophrenia, schizoa
bipolar disorder. Seventeen patients participated in an open-label, nonrandomized, multiple-dose study t
pharmacokinetics and tolerability of quetiapine when administered alone or in combination with phenytoi
escalating doses of quetiapine from 25 to 250 mg three times daily on days 3 to 10. Maintenance doses
administered on days 11 to 22. Phenytoin 100 mg three times daily was administered between days 13 a
under the concentration-time curve (AUC) from 0 to 8 hours after dosing at steady-state with quetiapine

phenytoin was 3642 ng hr/mL and 728 ng hr/mL , respectively (P equal 0.0001). The maximum plasma c
steady-state (Cmax, ss) for quetiapine versus quetiapine plus phenytoin was 1,048 ng/mL and 359 ng/m
Clearance over bioavailability (CL/F) for quetiapine alone versus quetiapine plus phenytoin was 80.3 L/h
respectively. The induction of cytochrome P450 3A4 by phenytoin is the most likely mechanism for the a
quetiapine metabolism (Wong et al, 2001).

3.5.1.BY Pirmenol

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Several antipsychotic agents have demonstrated QT prolongation including amisulpride, halop
paliperidone, quetiapine, risperidone, sertindole, sultopride, ziprasidone, and zotepine (Prod Info FANAPT(TM
Prod Info Solian(R), 1999x; O'Brien et al, 1999p; Prod Info INVEGA(TM) extended-release oral tablets, 2006;
Duenas-Laita et al, 1999x; Agelink et al, 2001v; Lande et al, 1992w; Prod Info GEODON(R) intramuscular inj
2005; Sweetman, 2003). Because Class IA antiarrhythmic agents may also prolong the QT interval and incre
arrhythmias, the concurrent administration of antipsychotics with a drug from this class is not recommended (
(TM) oral tablets, 2009; Prod Info Quinaglute(R), 1999).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: The concurrent administration of a Class IA antiarrhythmic and an antipsychotic is r
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) In an open-label QTc study of patients with schizophrenia or schizoaffective disorder (n=160), iloperic
day was associated with QTc prolongation of 9 msec (Prod Info FANAPT(TM) oral tablets, 2009).
b) QRS widening, QTc interval prolongation, and torsades de pointes may occur with disopyramide ther
Norpace(R), 1997).
c) The effects of combined therapy with quinidine (Class IA antiarrhythmic agent) and haloperidol (antip
studied by giving 12 healthy volunteers haloperidol 5 mg alone and with 250 mg of quinidine bisulfate. Th
significant increases in the plasma concentrations of haloperidol when given concurrently with quinidine
treatment alone. The mean area under the concentration curve (AUC) was increased from 54.3 ng/h/mL
to 103.2 ng/h/mL on combined therapy. The peak concentration (Cmax) also showed an increase from 1
haloperidol to 3.8 ng/mL on combined therapy. Half-life (T1/2) and time to peak concentration (Tmax) we
changed, thereby suggesting to the authors that a tissue binding mechanism is more likely responsible fo
changes than an elimination alteration (Young et al, 1993).

3.5.1.BZ Prajmaline

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Several antipsychotic agents have demonstrated QT prolongation including amisulpride, halop
paliperidone, quetiapine, risperidone, sertindole, sultopride, ziprasidone, and zotepine (Prod Info FANAPT(TM
Prod Info Solian(R), 1999x; O'Brien et al, 1999p; Prod Info INVEGA(TM) extended-release oral tablets, 2006;
Duenas-Laita et al, 1999x; Agelink et al, 2001v; Lande et al, 1992w; Prod Info GEODON(R) intramuscular inj
2005; Sweetman, 2003). Because Class IA antiarrhythmic agents may also prolong the QT interval and incre
arrhythmias, the concurrent administration of antipsychotics with a drug from this class is not recommended (
(TM) oral tablets, 2009; Prod Info Quinaglute(R), 1999).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: The concurrent administration of a Class IA antiarrhythmic and an antipsychotic is r
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) In an open-label QTc study of patients with schizophrenia or schizoaffective disorder (n=160), iloperic
day was associated with QTc prolongation of 9 msec (Prod Info FANAPT(TM) oral tablets, 2009).
b) QRS widening, QTc interval prolongation, and torsades de pointes may occur with disopyramide ther
Norpace(R), 1997).
c) The effects of combined therapy with quinidine (Class IA antiarrhythmic agent) and haloperidol (antip
studied by giving 12 healthy volunteers haloperidol 5 mg alone and with 250 mg of quinidine bisulfate. Th
significant increases in the plasma concentrations of haloperidol when given concurrently with quinidine
treatment alone. The mean area under the concentration curve (AUC) was increased from 54.3 ng/h/mL
to 103.2 ng/h/mL on combined therapy. The peak concentration (Cmax) also showed an increase from 1
haloperidol to 3.8 ng/mL on combined therapy. Half-life (T1/2) and time to peak concentration (Tmax) we
changed, thereby suggesting to the authors that a tissue binding mechanism is more likely responsible fo
changes than an elimination alteration (Young et al, 1993).

3.5.1.CA Prednisolone

1) Interaction Effect: decreased serum quetiapine concentrations
2) Summary: Increased doses of quetiapine may be required to maintain control of symptoms of schizophrer
receiving a glucocorticoid, a hepatic enzyme inducer (Prod Info Seroquel(R), 2001b).
3) Severity: major
4) Onset: unspecified

5) Substantiation: probable
6) Clinical Management: Caution is indicated when quetiapine is administered with glucocorticoids or other ir
P450 3A.
7) Probable Mechanism: induction of cytochrome P450-mediated metabolism of quetiapine by glucocorticoid

3.5.1.CB Prednisone
1) Interaction Effect: decreased serum quetiapine concentrations
2) Summary: Increased doses of quetiapine may be required to maintain control of symptoms of schizophrer
receiving a glucocorticoid, a hepatic enzyme inducer (Prod Info Seroquel(R), 2001b).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Caution is indicated when quetiapine is administered with glucocorticoids or other ir
P450 3A.
7) Probable Mechanism: induction of cytochrome P450-mediated metabolism of quetiapine by glucocorticoid

3.5.1.CC Primidone
1) Interaction Effect: decreased serum quetiapine concentrations
2) Summary: Increased doses of quetiapine may be required to maintain control of symptoms of schizophrer
receiving a barbiturate, a hepatic enzyme inducer (Prod Info Seroquel(R), 2001c).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Caution is indicated when quetiapine is administered with barbiturates or other indu
P450 3A. Increased doses of quetiapine may be required to maintain control of psychotic symptoms in patien
and barbiturates.
7) Probable Mechanism: induction of cytochrome P450-mediated metabolism of quetiapine by barbiturates

3.5.1.CD Probucol
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, the coadministration of drugs
QTc interval is not recommended. Probucol has been shown to prolong the QTc interval (Gohn & Simmons, 1
Lorelco(R), 1991). Antipsychotics including haloperidol (Prod Info Haldol(R), 1998d), quetiapine (Owens, 200
Info Risperdal(R) risperidone, 2000), amisulpride (Prod Info Solian(R), 1999n), sertindole (Brown & Levin, 19
(Lande et al, 1992m), and zotepine (Sweetman, 2004) have been shown to prolong the QT interval at therape
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Caution is advised if probucol and antipsychotics are used concomitantly.
7) Probable Mechanism: additive effect on QT interval

3.5.1.CE Procainamide
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Several antipsychotic agents have demonstrated QT prolongation including amisulpride, halop
paliperidone, quetiapine, risperidone, sertindole, sultopride, ziprasidone, and zotepine (Prod Info FANAPT(TM
Prod Info Solian(R), 1999x; O'Brien et al, 1999p; Prod Info INVEGA(TM) extended-release oral tablets, 2006;
Duenas-Laita et al, 1999x; Agelink et al, 2001v; Lande et al, 1992w; Prod Info GEODON(R) intramuscular inj
2005; Sweetman, 2003). Because Class IA antiarrhythmic agents may also prolong the QT interval and incre
arrhythmias, the concurrent administration of antipsychotics with a drug from this class is not recommended (
(TM) oral tablets, 2009; Prod Info Quinaglute(R), 1999).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: The concurrent administration of a Class IA antiarrhythmic and an antipsychotic is r
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) In an open-label QTc study of patients with schizophrenia or schizoaffective disorder (n=160), iloperic
day was associated with QTc prolongation of 9 msec (Prod Info FANAPT(TM) oral tablets, 2009).
b) QRS widening, QTc interval prolongation, and torsades de pointes may occur with disopyramide ther
Norpace(R), 1997).
c) The effects of combined therapy with quinidine (Class IA antiarrhythmic agent) and haloperidol (antip
studied by giving 12 healthy volunteers haloperidol 5 mg alone and with 250 mg of quinidine bisulfate. Th
significant increases in the plasma concentrations of haloperidol when given concurrently with quinidine
treatment alone. The mean area under the concentration curve (AUC) was increased from 54.3 ng/h/mL
to 103.2 ng/h/mL on combined therapy. The peak concentration (Cmax) also showed an increase from 1
haloperidol to 3.8 ng/mL on combined therapy. Half-life (T1/2) and time to peak concentration (Tmax) we
changed, thereby suggesting to the authors that a tissue binding mechanism is more likely responsible fo
changes than an elimination alteration (Young et al, 1993).

3.5.1.CF Prochlorperazine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Concomitant use of phenothiazines and antipsychotic agents may cause additive effects on the recommended. Q and T wave distortions have been observed in patients taking phenothiazines (Prod Info Co Prod Info Stelazine(R), 2002; Prod Info Thorazine(R), 2002). Other phenothiazines may have similar effects, available. Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info haloperidol (O'Brien et al, 1999f), paliperidone (Prod Info INVEGA(TM) extended-release oral tablets, 2006), 2001n), risperidone (Duenas-Laita et al, 1999l), sertindole (Agelink et al, 2001j), sultopride (Lande et al, 1992 Info GEODON(R) intramuscular injection, oral capsule, 2005), and zotepine (Sweetman, 2003).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of agents that prolong the QT interval, such as phen antipsychotics, is not recommended.
7) Probable Mechanism: additive QT prolongation

3.5.1.CG Propafenone

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Coadministration of quetiapine with other drugs that potentially prolong the QTc interval, such a should be approached with caution. If concurrent use cannot be avoided, cautious dosing and telemetric mon (Owens, 2001o; Larochelle et al, 1984).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of propafenone and quetiapine is not recommended inducing life-threatening arrhythmias. If concurrent use cannot be avoided, cautious dosing and telemetric mo
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.CH Protriptyline

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod haloperidol (O'Brien et al, 1999a), risperidone (Duenas-Laita et al, 1999c), sertindole (Agelink et al, 2001b), c 2001e), sultopride (Lande et al, 1992b), and zotepine (Sweetman, 2003). Even though no formal drug interac been done, the coadministration of a tricyclic antidepressant and an antipsychotic is not recommended (Prod 2001; Marshall & Forker, 1982).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of a tricyclic antidepressant and an antipsychotic is n
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) Electrocardiographic changes that have occurred during clinical trials with pimozide have included pro corrected QT interval, flattening, notching, and inversion of the T wave and the appearance of U waves. studies, sudden, unexpected deaths have occurred while patients were receiving pimozide doses of 1 m mechanism for these deaths is prolongation of the QT interval predisposing patients to ventricular arrhyth (R), 1999b).

3.5.1.CI Rifampin

1) Interaction Effect: decreased serum quetiapine concentrations
2) Summary: Increased doses of quetiapine may be required to maintain control of symptoms of schizophrer receiving rifampin, a hepatic enzyme inducer (Prod Info Seroquel(R), 2001).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Caution is indicated when quetiapine is administered with rifampin or other inducers 3A.
7) Probable Mechanism: induction of cytochrome P450-mediated metabolism of quetiapine by rifampin

3.5.1.CJ Risperidone

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Risperidone can prolong the QT interval in some patients, which may result in ventricular tachy fibrillation, and torsades de pointes, and its use with other agents that may prolong the QT interval, such as q recommended (Prod Info Risperdal(R), 2002; Owens, 2001r). Coadministration of risperidone 3 mg twice dail mg twice daily did not alter the steady-state pharmacokinetics of quetiapine (Prod Info Seroquel(R), 2003a).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable

6) Clinical Management: Because of the potential additive effects on the QT interval, the concurrent administ
and risperidone is not recommended.
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) Sometimes fatal QRS prolongation and QTc prolongation have been reported in patients taking rispe
(Duenas-Laita et al, 1999o; Ravin & Levenson, 1997d; Gesell & Stephen, 1997; Lo Vecchio et al, 1996;

3.5.1.CK Ritonavir
1) Interaction Effect: increased quetiapine plasma concentrations
2) Summary: In vitro studies indicated that quetiapine is metabolized by the CYP3A4 isozyme in the liver. Co
ketoconazole (200 mg once daily for 4 days), a potent CYP3A inhibitor, reduced oral clearance of quetiapine
335% increase in maximum plasma concentration of quetiapine. Although not studied, a similar interaction co
other CYP3A inhibitors such as protease inhibitors. Therefore, caution and a reduced quetiapine dosage are
quetiapine is administered to patients receiving protease inhibitors concomitantly (Prod Info SEROQUEL(R) o
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Use caution when prescribing quetiapine to patients who take protease inhibitors as
elevated quetiapine plasma concentrations. A reduced quetiapine dosage is recommended when administeri
protease inhibitors (Prod Info SEROQUEL(R) oral tablets, 2008a).
7) Probable Mechanism: inhibition of CYP3A-mediated quetiapine metabolism

3.5.1.CL Saquinavir
1) Interaction Effect: increased quetiapine plasma concentrations
2) Summary: In vitro studies indicated that quetiapine is metabolized by the CYP3A4 isozyme in the liver. Co
ketoconazole (200 mg once daily for 4 days), a potent CYP3A inhibitor, reduced oral clearance of quetiapine
335% increase in maximum plasma concentration of quetiapine. Although not studied, a similar interaction co
other CYP3A inhibitors such as protease inhibitors. Therefore, caution and a reduced quetiapine dosage are
quetiapine is administered to patients receiving protease inhibitors concomitantly (Prod Info SEROQUEL(R) o
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Use caution when prescribing quetiapine to patients who take protease inhibitors as
elevated quetiapine plasma concentrations. A reduced quetiapine dosage is recommended when administeri
protease inhibitors (Prod Info SEROQUEL(R) oral tablets, 2008a).
7) Probable Mechanism: inhibition of CYP3A-mediated quetiapine metabolism

3.5.1.CM Secobarbital
1) Interaction Effect: decreased serum quetiapine concentrations
2) Summary: Increased doses of quetiapine may be required to maintain control of symptoms of schizophrer
receiving a barbiturate, a hepatic enzyme inducer (Prod Info Seroquel(R), 2001c).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Caution is indicated when quetiapine is administered with barbiturates or other indu
P450 3A. Increased doses of quetiapine may be required to maintain control of psychotic symptoms in patien
and barbiturates.
7) Probable Mechanism: induction of cytochrome P450-mediated metabolism of quetiapine by barbiturates

3.5.1.CN Sematilide
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Concurrent use of sematilide and quetiapine is not recommended due to the risk of additive eff
interval. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised (Yamreud
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of sematilide and quetiapine is not recommended du
inducing life-threatening arrhythmias. If concurrent use cannot be avoided, cautious dosing and telemetric mo
7) Probable Mechanism: additive QT prolongation
8) Literature Reports
a) Class III antiarrhythmics have been shown to prolong the QT interval, which may result in ventricular
ventricular fibrillation, and torsades de pointes. Several antipsychotic agents have demonstrated QT prol
quetiapine (Owens, 2001c). Concomitant use of Class III antiarrhythmic agents such as sematilide and q
additive effects on the QT interval and is not recommended (Yamreudeewong et al, 2003).

3.5.1.CO Sotalol
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Concurrent use of sotalol and quetiapine is not recommended due to the risk of additive effects

concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised (Yamreudeewong et
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of sotalol and quetiapine is not recommended due to inducing life-threatening arrhythmias. If concurrent use cannot be avoided, cautious dosing and telemetric mo
7) Probable Mechanism: additive QT prolongation
8) Literature Reports
a) Class III antiarrhythmics have been shown to prolong the QT interval, which may result in ventricular ventricular fibrillation, and torsades de pointes. Several antipsychotic agents have demonstrated QT prol quetiapine (Owens, 2001c). Concomitant use of Class III antiarrhythmic agents such as sotalol and queti additive effects on the QT interval and is not recommended (Yamreudeewong et al, 2003).

3.5.1.CP Spiramycin
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Spiramycin has been shown to prolong the QTc interval at the recommended therapeutic dose al, 1997). Even though no formal drug interaction studies have been done, the coadministration of antipsycho known to prolong the QTc interval, including spiramycin, is not recommended. Several antipsychotic agents h prolongation including amisulpride (Prod Info Solian(R), 1999u), haloperidol (O'Brien et al, 1999n), quetiapine risperidone (Duenas-Laita et al, 1999u), sertindole (Agelink et al, 2001s), sultopride (Lande et al, 1992t), and 2003).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of spiramycin and antipsychotics is not recommende
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.CQ Sulfamethoxazole
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Cotrimoxazole has been shown to prolong the QTc interval at the recommended therapeutic do 1987). Even though no formal drug interaction studies have been done, the coadministration of antipsychotics known to prolong the QTc interval, including cotrimoxazole, is not recommended. Several antipsychotic agen QT prolongation including amisulpride (Prod Info Solian(R), 1999g), haloperidol (O'Brien et al, 1999d), quetia risperidone (Duenas-Laita et al, 1999h), sertindole (Agelink et al, 2001f), sultopride (Lande et al, 1992e), and 2003).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of cotrimoxazole and antipsychotics is not recommer
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.CR Tedisamil
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Concurrent use of tedisamil and quetiapine is not recommended due to the risk of additive effe If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised (Yamreudeewong
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of tedisamil and quetiapine is not recommended due inducing life-threatening arrhythmias. If concurrent use cannot be avoided, cautious dosing and telemetric mo
7) Probable Mechanism: additive QT prolongation
8) Literature Reports
a) Class III antiarrhythmics have been shown to prolong the QT interval, which may result in ventricular ventricular fibrillation, and torsades de pointes. Several antipsychotic agents have demonstrated QT prol quetiapine (Owens, 2001c). Concomitant use of Class III antiarrhythmic agents such as tedisamil and qu additive effects on the QT interval and is not recommended (Yamreudeewong et al, 2003).

3.5.1.CS Telithromycin
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Some antipsychotic agents prolong the QT interval and an additive effect would be anticipated other agents which lengthen the QT interval (Agelink et al, 2001g; Owens, 2001k; Prod Info Haldol(R), 1998b Even though no formal drug interaction studies have been done, antipsychotic agents should not be coadmin drugs which are also known to prolong the QTc interval, including telithromycin (Owens, 2001k).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Due to the potential for additive effects on the QT interval, the concurrent administra and an antipsychotic is not recommended.

7) Probable Mechanism: additive effect on QT interval
8) Literature Reports
a) Fatal QRS prolongation and QTc prolongation have been reported in patients taking risperidone thera Laita et al, 1999i; Ravin & Levenson, 1997b).

3.5.1.CT Terfenadine
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Some antipsychotics have been shown to prolong the QTc interval at the recommended therap Geodon(TM), 2002b; Owens, 2001af; Prod Info Orap(R), 1999f). Even though no formal drug interaction stud the coadministration of terfenadine and other drugs known to prolong the QTc interval, including antipsychoti (Anon, 1997).
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of terfenadine with any drug that prolongs the QT int antipsychotic agents, is contraindicated.
7) Probable Mechanism: additive effect on QT interval
8) Literature Reports
a) Electrocardiographic changes that have occurred during clinical trials with pimozide have included pr corrected QT interval, flattening, notching, and inversion of the T wave and the appearance of U waves. studies, sudden, unexpected deaths have occurred while patients were receiving pimozide doses of 1 m mechanism for these deaths is prolongation of the QT interval predisposing patients to ventricular arrhyt (R), 1999e).

3.5.1.CU Thiopental
1) Interaction Effect: decreased serum quetiapine concentrations
2) Summary: Increased doses of quetiapine may be required to maintain control of symptoms of schizophrer receiving a barbiturate, a hepatic enzyme inducer (Prod Info Seroquel(R), 2001c).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Caution is indicated when quetiapine is administered with barbiturates or other indu P450 3A. Increased doses of quetiapine may be required to maintain control of psychotic symptoms in patien and barbiturates.
7) Probable Mechanism: induction of cytochrome P450-mediated metabolism of quetiapine by barbiturates

3.5.1.CV Thioridazine
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Although citing no data, the manufacturer of thioridazine states that concomitant use with other the QT interval is contraindicated (Prod Info Mellaril(R), 2001). Several antipsychotic agents have demonstra including amisulpride (Prod Info Solian(R), 1999p), haloperidol (O'Brien et al, 1999j), pimozide (Prod Info Ora quetiapine (Owens, 2001v), paliperidone (Prod Info INVEGA(TM) extended-release oral tablets, 2006), risper et al, 1999q), sertindole (Agelink et al, 2001o), sultopride (Lande et al, 1992o), ziprasidone (Prod Info GEOD injection, oral capsule, 2005), and zotepine (Sweetman, 2004).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of agents that prolong the QT interval, such as antips thioridazine, is contraindicated.
7) Probable Mechanism: additive QT prolongation

3.5.1.CW Tipranavir
1) Interaction Effect: increased quetiapine plasma concentrations
2) Summary: In vitro studies indicated that quetiapine is metabolized by the CYP3A4 isozyme in the liver. Co ketoconazole (200 mg once daily for 4 days), a potent CYP3A inhibitor, reduced oral clearance of quetiapine 335% increase in maximum plasma concentration of quetiapine. Although not studied, a similar interaction co other CYP3A inhibitors such as protease inhibitors. Therefore, caution and a reduced quetiapine dosage are quetiapine is administered to patients receiving protease inhibitors concomitantly (Prod Info SEROQUEL(R) c
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Use caution when prescribing quetiapine to patients who take protease inhibitors as elevated quetiapine plasma concentrations. A reduced quetiapine dosage is recommended when administeri protease inhibitors (Prod Info SEROQUEL(R) oral tablets, 2008a).
7) Probable Mechanism: inhibition of CYP3A-mediated quetiapine metabolism

3.5.1.CX Triamcinolone
1) Interaction Effect: decreased serum quetiapine concentrations

2) Summary: Increased doses of quetiapine may be required to maintain control of symptoms of schizophrer receiving a glucocorticoid, a hepatic enzyme inducer (Prod Info Seroquel(R), 2001b).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Caution is indicated when quetiapine is administered with glucocorticoids or other ir P450 3A.
7) Probable Mechanism: induction of cytochrome P450-mediated metabolism of quetiapine by glucocorticoid

3.5.1.CY Trifluoperazine
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Concomitant use of phenothiazines and antipsychotic agents may cause additive effects on the recommended. Q and T wave distortions have been observed in patients taking phenothiazines (Prod Info Co Prod Info Stelazine(R), 2002; Prod Info Thorazine(R), 2002). Other phenothiazines may have similar effects, available. Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info haloperidol (O'Brien et al, 1999f), paliperidone (Prod Info INVEGA(TM) extended-release oral tablets, 2006), 2001n), risperidone (Duenas-Laita et al, 1999l), sertindole (Agelink et al, 2001j), sultopride (Lande et al, 1992 Info GEODON(R) intramuscular injection, oral capsule, 2005), and zotepine (Sweetman, 2003).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of agents that prolong the QT interval, such as phen antipsychotics, is not recommended.
7) Probable Mechanism: additive QT prolongation

3.5.1.CZ Trimethoprim
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Cotrimoxazole has been shown to prolong the QTc interval at the recommended therapeutic do 1987). Even though no formal drug interaction studies have been done, the coadministration of antipsychotics known to prolong the QTc interval, including cotrimoxazole, is not recommended. Several antipsychotic agen QT prolongation including amisulpride (Prod Info Solian(R), 1999g), haloperidol (O'Brien et al, 1999d), quetia risperidone (Duenas-Laita et al, 1999h), sertindole (Agelink et al, 2001f), sultopride (Lande et al, 1992e), and 2003).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of cotrimoxazole and antipsychotics is not recommer
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.DA Trimipramine
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod haloperidol (O'Brien et al, 1999a), risperidone (Duenas-Laita et al, 1999c), sertindole (Agelink et al, 2001b), c 2001e), sultopride (Lande et al, 1992b), and zotepine (Sweetman, 2003). Even though no formal drug interac been done, the coadministration of a tricyclic antidepressant and an antipsychotic is not recommended (Prod 2001; Marshall & Forker, 1982).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of a tricyclic antidepressant and an antipsychotic is n
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) Electrocardiographic changes that have occurred during clinical trials with pimozide have included pr corrected QT interval, flattening, notching, and inversion of the T wave and the appearance of U waves. studies, sudden, unexpected deaths have occurred while patients were receiving pimozide doses of 1 m mechanism for these deaths is prolongation of the QT interval predisposing patients to ventricular arrhytl (R), 1999b).

3.5.1.DB Vasopressin
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Antipsychotics and vasopressin have been shown to prolong the QTc interval at the recommen (Owens, 2001b; Prod Info Solian(R), 1999a; Duenas-Laita et al, 1999b; Brown & Levin, 1998; Harry, 1997; P 1996; Metzger & Friedman, 1993; Mauro et al, 1988). Even though no formal drug interaction studies have be coadministration of drugs known to prolong the QTc interval is not recommended.
3) Severity: major
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of drugs that prolong the QT interval, such as antipsy

vasopressin, is not recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.DC Warfarin
1) Interaction Effect: potentiation of anticoagulant effects
2) Summary: A 71-year-old female experienced enhanced anticoagulant effects from warfarin when quetiapi drug regimen. Her medications included phenytoin 300 mg daily with a serum concentration of 9.87 mg/L, wa with an international normalized ratio (INR) of 2.6, benztropine 0.5 mg daily, and olanzapine 20 mg daily. Ola discontinued, and quetiapine therapy was initiated at 200 mg daily. Five days later, the INR was 2.7. After tw treatment, the INR increased to 9.2. Quetiapine was discontinued and two doses of vitamin K 10 mg were ad clinical signs observed in the patient were a small amount of bleeding at the site of the vitamin K injection an The INR decreased back to baseline with the discontinuation of quetiapine (Rogers et al, 1999).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Closely monitor the international normalized ratio (INR) in patients receiving concur quetiapine therapy.
7) Probable Mechanism: competitive inhibition of cytochrome P450 3A4 and 2C9 by quetiapine

3.5.1.DD Zolmitriptan
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest
2) Summary: Zolmitriptan has been shown to prolong the QTc interval at the recommended therapeutic dose 2001). Antipsychotics including haloperidol (Prod Info Haldol(R), 1998f), quetiapine (Owens, 2001ac), risperi Risperdal(R) risperidone, 2000b), amisulpride (Prod Info Solian(R), 1999w), sertindole (Agelink et al, 2001u); al, 1992v), and zotepine (Sweetman, 2004) have been shown to prolong the QT interval at therapeutic doses formal drug interaction studies have been done, the coadministration of drugs known to prolong the QT interv recommended.
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of zolmitriptan and antipsychotics is not recommende
7) Probable Mechanism: additive effect on QT interval

3.5.2 Drug-Food Combinations

3.5.2.A Ethanol
1) Interaction Effect: potentiation of the cognitive and motor effects of alcohol
2) Summary: Quetiapine potentiated the cognitive and motor effects of alcohol in a clinical trial in subjects wi disorders. Alcoholic beverages should be avoided while taking quetiapine (Prod Info Seroquel(R), 2001d).
3) Severity: moderate
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Patients should be instructed to avoid ethanol ingestion while taking quetiapine.
7) Probable Mechanism: additive CNS depression

3.5.3 Drug-Lab Modifications

Methadone measurement, urine

Tricyclic antidepressant measurement

3.5.3.A Methadone measurement, urine
1) Interaction Effect: false-positive urine drug screen for methadone
2) Summary: There have been cases of false-positive methadone urine drug screens with the use of assays Methadone II testkit(R) in patients treated with quetiapine. Clinicians should consider confirming positive met more specific methods, such as gas chromatography/mass spectrometry, or other quantitative methods parti whose results do not coincide with medical history, or current behaviors and observations (Cherwinski et al, 2 et al, 2007).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Clinicians should be aware that there have been cases of false-positive urine meth patients receiving quetiapine. Consider confirming a positive urine methadone screen with more specific met chromatography/mass spectrometry, or other quantitative methods, particularly in patients whose results do r medical history, or current behaviors and observations (Cherwinski et al, 2007; Widschwendter et al, 2007).

7) Probable Mechanism: mechanism unknown
8) Literature Reports
a) In a retrospective chart review, 12 pediatric patients (mean age of 15.5 years) admitted to a behavior treated with quetiapine from 125 to 160 mg daily had false methadone-positive urine drug screens with t (R) by Roche. Although 5 of these patients had positive substance abuse history, none were admitted fo issues. All patients denied current methadone use, and final clinical impressions were that they had not u substances. Results of confirmatory testing using gas chromatography/mass spectroscopy, performed in were negative for methadone (Cherwinski et al, 2007).
b) Three schizophrenic patients, being treated with quetiapine monotherapy, had false-positive urinalysi methadone using the Cobas Integra Methadone II testkit(R) by Roche. This method, used for semiquanti detection of methadone in urine, has a threshold of 300 ng/mL for methadone positivity. Blood samples t day after quetiapine administration ended also tested positive for methadone with mass spectrometry. H medical histories of the patients, these results were unexpected. Further screening of the patient's plasm quantitative assay did not reveal methadone positivity (Widschwendter et al, 2007).

3.5.3.B Tricyclic antidepressant measurement
1) Interaction Effect: a false-positive urine tricyclic antidepressant assay
2) Summary: A 34-year-old male patient receiving quetiapine 600 mg daily showed a positive toxicology scre antidepressants despite his denial of tricyclic use. Quetiapine is structurally similar to tricyclic antidepressants as the cause of this assay abnormality. A laboratory test confirmed that quetiapine is capable of causing a fal screen for tricyclic antidepressants (Sloan et al, 2000).
3) Severity: minor
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Clinicians should be aware that quetiapine may cause false-positive test results in a tricyclic antidepressants. This possibility should be considered in patients receiving quetiapine who deny tricy use but have a positive urine screen for tricyclics.
7) Probable Mechanism: assay interference

4.0 Clinical Applications

Monitoring Parameters

Patient Instructions

Place In Therapy

Mechanism of Action / Pharmacology

Therapeutic Uses

Comparative Efficacy / Evaluation With Other Therapies

4.1 Monitoring Parameters
A) Quetiapine Fumarate
1) Therapeutic
a) Physical Findings
1) In schizophrenic patients, improvements of positive symptoms (eg, delusions, hallucinations, paranoi negative symptoms (eg, blunted affect, poverty of speech, amotivation) are indicative of a therapeutic res
2) Reassess the need for maintenance treatment and appropriate dose periodically (Prod Info SEROQU release oral tablets, 2007).
2) Toxic
a) Laboratory Parameters
1) Quetiapine use has been associated with exacerbation of pre-existing diabetes, hyperglycemia, diabe diabetic coma, and death. For patients with diabetes mellitus risk factors (eg, obesity, family history), per glucose testing at the beginning of and periodically during quetiapine therapy. For patients with pre-exist monitor fasting blood glucose regularly during quetiapine therapy to detect worsening of glucose control. SEROQUEL(R) oral tablets, 2007; Prod Info SEROQUEL(R)XR extended-release oral tablets, 2007).
2) Quetiapine use has been associated with leukopenia, neutropenia, and agranulocytosis, which has in Perform CBC frequently during the first few months of therapy in patients with a pre-existing low WBC or induced leukopenia/neutropenia. Monitor patients for severe neutropenia (absolute neutrophil count less which will necessitate discontinuing quetiapine therapy (Prod Info SEROQUEL(R) oral tablets, 2007; Pro XR extended-release oral tablets, 2007).
b) Physical Findings

1) Patients should be carefully monitored for clinical worsening of depression, suicidality, and unusual cl which make be precursors to suicidality, especially if symptoms are severe, abrupt or unusual. This is es the initial few months of antidepressant therapy or during dose changes. Adult and pediatric patients with disorder may experience unusual changes in behavior and onset of suicidal behavior (suicidality). Antide be associated with the emergence of suicidality and inducing worsening of depression in patients, espec treatment phase and in children, adolescents, and young adults ages 18 to 24 years. It is important that to patients with major depressive disorder or other psychiatric and nonpsychiatric disorders be vigilant in emergent anxiety, agitation, hostility, aggressiveness, impulsivity, akathisia, hypomania, mania, irritability changes in behavior (Prod Info SEROQUEL(R) oral tablets, 2007; Prod Info SEROQUEL(R)XR extended 2007).

2) In patients with neutropenia, carefully monitor for fever or other signs or symptoms of infection (Prod oral tablets, 2007; Prod Info SEROQUEL(R)XR extended-release oral tablets, 2007).

3) Quetiapine use has been associated with exacerbation of pre-existing diabetes, hyperglycemia, diabe diabetic coma, and death. Monitor all patients receiving quetiapine for symptoms of hyperglycemia (eg, p polyphagia, weakness). For patients with diabetes mellitus risk factors (eg, obesity, family history), perfo glucose testing at the beginning of and periodically during quetiapine therapy. Patients with pre-existing regularly monitor fasting blood glucose during quetiapine therapy to detect worsening of glucose control SEROQUEL(R) oral tablets, 2007; Prod Info SEROQUEL(R)XR extended-release oral tablets, 2007).

4) Quetiapine use has been rarely associated with the development of neuroleptic malignant syndrome should be monitored for signs and symptoms of NMS, such as hyperpyrexia, muscle rigidity, altered mer autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythm SEROQUEL(R) oral tablets, 2007; Prod Info SEROQUEL(R)XR extended-release oral tablets, 2007).

5) Due to the risk of developing irreversible, involuntary, dyskinetic movements, patients should be obse symptoms of extrapyramidal effects and tardive dyskinesia. Monitoring is especially critical in elderly pati longer duration of treatment, and higher total cumulative doses, but has occurred after relatively brief du (Prod Info SEROQUEL(R) oral tablets, 2007; Prod Info SEROQUEL(R)XR extended-release oral tablets

6) Although a causal relationship has not been established, long-term quetiapine therapy has been impl changes. Ocular examination (eg, slit lamp exam) to detect cataract formation is recommended at treatm every 6 months during chronic quetiapine treatment (Prod Info SEROQUEL(R) oral tablets, 2007; Prod I extended-release oral tablets, 2007).

7) Quetiapine use may induce postural hypotension, dizziness, tachycardia, and syncope has been repo (Prod Info SEROQUEL(R) oral tablets, 2007; Prod Info SEROQUEL(R)XR extended-release oral tablets pressure and heart rate during quetiapine therapy. Perform ECG at baseline and periodically during ther Kecskemeti, 2004).

4.2 Patient Instructions

A) Quetiapine (By mouth)

Quetiapine

Treats schizophrenia and symptoms of bipolar disorder (manic-depressive illness).

When This Medicine Should Not Be Used:
You should not use this medicine if you have had an allergic reaction to quetiapine.

How to Use This Medicine:
Long Acting Tablet, Tablet

Your doctor will tell you how much of this medicine to use and how often. Your dose may need to be changed order to find out what works best for you. Do not use more medicine or use it more often than your doctor tell start with a low dose, even if you have used this medicine before.
Your doctor may tell you to take the medicine at bedtime, because quetiapine can make you sleepy.
This medicine should come with a Medication Guide. Read and follow these instructions carefully. Ask your d you have any questions. Ask your pharmacist for the Medication Guide if you do not have one. Your doctor m some forms to show that you understand this information.

If a Dose is Missed:

If you miss a dose or forget to use your medicine, use it as soon as you can. If it is almost time for your next d use the medicine and skip the missed dose. Do not use extra medicine to make up for a missed dose.

How to Store and Dispose of This Medicine:

Store the medicine in a closed container at room temperature, away from heat, moisture, and direct light.
Ask your pharmacist, doctor, or health caregiver about the best way to dispose of any leftover medicine after your treatment. You will also need to throw away old medicine after the expiration date has passed.
Keep all medicine away from children and never share your medicine with anyone.

Drugs and Foods to Avoid:
Ask your doctor or pharmacist before using any other medicine, including over-the-counter medicines, vitamins, a

Make sure your doctor knows if you are also using levodopa, Sinemet®, erythromycin (Ery-Tab®), lorazepam (Rifadin®, Rifamate®), or a steroid medicine (such as dexamethasone, prednisolone, prednisone, or Medrol®

Tell your doctor if you are also using medicine for seizures (such as carbamazepine, divalproex, phenytoin, p
Depakote®, Dilantin®, Luminal®, or Tegretol®), medicine to treat a fungus infection (such as fluconazole, itra
ketoconazole, Diflucan®, Nizoral®, or Sporanox®), or other antipsychotic medicine such as thioridazine (Mell
Make sure your doctor knows if you are also using medicine to lower blood pressure. Some blood pressure m
hydrochlorothiazide (HCTZ), lisinopril, metoprolol, quinapril, Accupril®, Cozaar®, Diovan®, Lotrel®, Norvasc®
Zestril®.
Tell your doctor if you are using any medicines that make you sleepy. These include sleeping pills, cold and a
narcotic pain relievers, and sedatives.
Do not drink alcohol while you are using this medicine.

Warnings While Using This Medicine:
Make sure your doctor knows if you are pregnant or breastfeeding, or if you have liver disease, Alzheimer's d
problems, or a history of seizures or breast cancer. Tell your doctor if you have diabetes or a family history of
Make sure your doctor knows if you have heart disease or circulation problems, such as heart failure, low blo
problems, blood problems, high cholesterol, or a history of heart attack or stroke. Also tell your doctor if you h
condition called neuroleptic malignant syndrome (NMS) in the past.
For some children, teenagers, and young adults, this medicine can increase thoughts of suicide. Tell your do
doctor right away if you or your child start to feel more depressed and have thoughts about hurting yourselves
thoughts or behaviors that trouble you or your child, especially if they are new or are getting worse quickly. M
knows if you or your child have trouble sleeping, get upset easily, have a big increase in energy, or start to ac
the doctor if you or your child have sudden or strong feelings, such as feeling nervous, angry, restless, violen
doctor know if you, your child, or anyone in your family has bipolar disorder (manic-depressive) or has tried to
This medicine is not approved to treat behavior disorders in older people who have dementia. Using this med
problem could increase the risk of death. This risk has not been shown for the approved uses of this medicine
Tardive dyskinesia (a movement disorder) may occur and may not go away after you stop using the medicine
you are having signs of tardive dyskinesia such as rapid, worm-like movements of the tongue, or other uncon
the mouth, tongue, cheeks, jaw, or arms and legs.
This medicine may make you dizzy or drowsy. Avoid driving, using machines, or doing anything else that cou
are not alert. You may also feel lightheaded when getting up suddenly from a lying or sitting position, so get u
Your doctor will need to check your progress at regular visits while you are using this medicine. Be sure to ke
appointments.You may also need to have your eyes tested on a regular basis.
Tell your doctor about any other medicine you have used to treat a mental disorder, especially if the medicine
You might get overheated more easily while using this medicine. Be aware of this if you are exercising or the
Drinking water might help. If you get too hot and feel dizzy, weak, tired, confused, or sick to your stomach, yo

Possible Side Effects While Using This Medicine:
Call your doctor right away if you notice any of these side effects:
Allergic reaction: Itching or hives, swelling in your face or hands, swelling or tingling in your mouth or throat, o
breathing.
Agitation, anxiety, or restlessness.
Changes in behavior, or thoughts of hurting yourself or others.
Constant muscle movement that you cannot control (often in your lips, tongue, jaw, arms, or legs).
Decrease in how much or how often you urinate, increased thirst, increased hunger, or weakness.
Fast heartbeat.
Fever, sweating, confusion, uneven heartbeat, muscle stiffness.
Lightheadedness or fainting (more common at the beginning or when changing doses).
Painful, prolonged erection of the penis.
Seizures or tremors.
Severe drowsiness, dizziness, or sleepiness.
Trouble seeing, or bright light bothering your eyes.
Trouble swallowing.
Unusual tiredness.

If you notice these less serious side effects, talk with your doctor:
Back pain.
Changes in menstrual periods.
Headache, sore throat.
Increased appetite.
Nausea, vomiting, constipation, dry mouth, upset stomach, or stomach pain.
Stuffy or runny nose.
Weight gain.

If you notice other side effects that you think are caused by this medicine, tell your doctor.

4.3 Place In Therapy

A) Current users of atypical antipsychotic drugs (including quetiapine) and typical antipsychotic drugs had a similar do
sudden cardiac death, according to a retrospective cohort of 93,300 adult users of antipsychotic drugs and 186,600 m
study included patients age 30 to 74 years (mean 45.7 +/- 11.8 years) with similar cardiovascular risk at baseline who

prescription and had 1 outpatient visit in each of the 2 preceding years. Sudden cardiac death was defined as occurrin and excluded deaths of patients admitted to the hospital, non-sudden deaths, deaths due to extrinsic causes, or cause ventricular tachyarrhythmia. Current use was defined as the interval between the time the prescription was filled and th supply. Low and high doses was defined as comparable to less than 100 milligrams (mg) of chlorpromazine, and dose chlorpromazine 300 mg or greater, respectively. The adjusted rate of sudden cardiac death (incidence-rate ratio) in cu antipsychotic drugs in 79,589 person-years was 2.26 (95% CI, 1.88 to 2.72, p less than 0.001) which was similar to the of typical antipsychotic drugs in 86,735 person-years which was 1.99 (95% CI, 1.68 to 2.34, p less than 0.001). The ris death in current quetiapine users in 17,355 person-years was 1.88 (95% CI, 1.3 to 2.71, p less than 0.001). The risk o death significantly increased with increasing dose in both the typical and atypical antipsychotic drug groups. In atypica the incidence rate ratio increased from 1.59 (95% CI, 1.03 to 2.46) in low-dose use to 2.86 (95% CI, 2.25 to 3.65) in hi the effects of confounding of the study results, there was a secondary analysis performed in a cohort of patients matc score, which resulted in a similar risk of sudden death as the primary cohort analysis (Ray et al, 2009). In an editorial i Journal of Medicine, it has been suggested that antipsychotic drugs continue to be used in patients with clear evidence vulnerable populations with cardiac risk profiles (eg, elderly patients), there should be an age-dependent justification r administration. It has also been suggested (although not formally tested) that ECGs be performed before and shortly a antipsychotic therapy to screen for existing or emergent QT interval prolongation (Schneeweiss & Avorn, 2009).
B) Quetiapine is indicated for the treatment of depressive episodes associated with bipolar disorder and acute manic with bipolar I disorder as either monotherapy or adjunct therapy to lithium or divalproex. Quetiapine is also indicated fo schizophrenia (Prod Info SEROQUEL(R) oral tablets, 2006).
See Drug Consult reference: FIRST- VS SECOND-GENERATION ANTIPSYCHOTIC AGENTS FOR SCHIZOPHREN

4.4 Mechanism of Action / Pharmacology

A) Quetiapine Fumarate

1) PHARMACOLOGY

a) Quetiapine is a dibenzothiazepine antipsychotic agent bearing structural similarity to clozapine and olanza 1998; Fabre et al, 1995; Anon, 1995; Green, 1999).

b) Quetiapine has been shown to have affinity for multiple neurotransmitter receptors in in vitro binding studi high affinity for serotonergic type 2 (5-HT2) receptors and moderate affinity for dopamine type 2 (D2) recepto antagonism of D1 and 5-HT1A receptors is relatively weak. Appreciable affinity for alpha-1 adrenergic, alpha- histamine H1 receptors has also been observed (Saller & Salama, 1993; Fulton & Goa, 1995; Anon, 1995). C clozapine, affinities of quetiapine for all receptor types are lower; notably, the binding affinities of quetiapine f adrenergic receptors are 11 times and 7 times lower, respectively, than affinities for clozapine (Saller & Salar clozapine, quetiapine has essentially no affinity for benzodiazepine receptors; unlike clozapine, quetiapine de affinity for muscarinic receptor types (Anon, 1995; Saller & Salama, 1993; Fulton & Goa, 1995). Despite relat receptor binding, these collectively suggest the similarity of clozapine and quetiapine with respect to mixed 5- (which may contribute to lower EPS potential), and that quetiapine may be less likely than clozapine to induc antiadrenergic effects.

c) Quetiapine's D2/5-HT2a affinity profile has not yet been established with certainty. Affinity for 5-HT2 recep reported as greater than for D2 receptors with both quetiapine and risperidone, another atypical agent, althou the D2 receptor is relatively weak with quetiapine and very high with risperidone (similar to haloperidol) (Boris However, others report higher D2-receptor affinity for quetiapine (Caley & Rosenbaum, 1998). Atypical antips generally share higher affinity for 5-HT2 receptors.

d) Platelet serotonin-2 (5-HT(2)) receptor density in schizophrenic patients appears to have increased with s quetiapine therapy in a small (n=9), double-blind, placebo-controlled study, (Faustman et al, 1996). Two patie maximum dose of 250 milligrams/day; one of these patients dropped out after 2 weeks. Two patients receive mg/d and one patient received 750 mg/d for the final 12 days before he dropped out at day 38 of the study. T platelet 5-HT(2) receptor density increased over the mean baseline value for the quetiapine-treated patients b group (n=4). Similar increases have been seen during clozapine therapy. The clinical significance of these re addressed by the authors.

2) REVIEW ARTICLES

a) The use of atypical antipsychotics for the treatment of drug- induced psychosis in Parkinson's disease has (Friedman & Factor, 2000).

b) The pharmacology and clinical efficacy of quetiapine have been reviewed (Green, 1999; Goren & Levin, 1 1995).

c) The new antipsychotic medications including quetiapine have been reviewed (Keck et al, 2000; Glazer, 20

d) The use of atypical antipsychotic medications in adults (Markowitz et al, 1999; Brown et al, 1999), older a 1999), and children (Malone et al, 1999; Lewis, 1998; Toren et al, 1998) has been reviewed.

e) The side effects of antipsychotics, including quetiapine, in adults and the elderly were reviewed (Garver, 2

4.5 Therapeutic Uses

Quetiapine

Quetiapine Fumarate

4.5.A Quetiapine

4.5.A.1 Dementia

See Drug Consult reference: BEHAVIORAL AND PSYCHOLOGICAL SYMPTOMS OF DEMENTIA

4.5.B Quetiapine Fumarate

Bipolar disorder

Bipolar disorder, depressed phase

Bipolar disorder, Maintenance

Bipolar disorder - Cocaine dependence

Delirium

Delirium, Refractory

Dementia

Gilles de la Tourette's syndrome

Manic bipolar I disorder

Obsessive-compulsive disorder, Refractory

Parkinson's disease - Psychotic disorder

Posttraumatic stress disorder

Schizophrenia

Schizophrenia, Maintenance

Tardive dyskinesia

4.5.B.1 Bipolar disorder

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Add-on quetiapine therapy may be effective for patients with rapid cycling bipolar disorder, as demo
open-label study (n=14; average treatment cycle=112 days) (Vieta et al, 2002)

c) Adult:

1) The results of a small, open-label study suggest that add-on quetiapine therapy may be an effective t
with rapid cycling bipolar disorder. In this prospective study, fourteen patients with rapid cycling bipolar d
quetiapine (initial, 50 milligrams (mg)/day, then titrated according to clinical response and tolerability) in a
ongoing psychotropic treatment for an average of 112 days. Response was evaluated using the Global C
Bipolar Disorder Scale (CGI-BP), the Young Mania Rating Scale (YMRS), and the Hamilton Depression
The general and manic sub-scales of the CGI-BP showed significant score reductions following the addit
therapy (p=0.013 and p=0.016, respectively). A significant reduction in manic symptoms was also seen v
YMRS scores (p=0.025). While there were reductions in depressive symptoms, they were not significant
during the first fifteen days of quetiapine treatment varied according to the initial episode treated (manic,
depressive, 183 mg/day). Additionally, there were significant reductions in maximum average dose as co
dose for the entire sample group (443 mg/day vs 268 mg/day, respectively; p=0.008). Quetiapine was ge
with drowsiness (43%) and weight gain (29%) as the most commonly reported side effects (Vieta et al, 2

4.5.B.2 Bipolar disorder, depressed phase

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIa
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Quetiapine is indicated for the treatment of depressive episodes associated with bipolar disorder (Pr
(R) oral tablets, 2008a)

Quetiapine monotherapy was well-tolerated and more effective than placebo in the treatment of bipo
(Calabrese et al, 2005)

c) Adult:

1) Quetiapine was more effective than placebo in the treatment of depressive episodes associated with
identical 8-week, randomized, double-blind, placebo-controlled studies (n=1045), patients with either bip
those with or without a rapid cycling course received quetiapine fixed doses of either 300 milligrams (mg
daily. The change from baseline in Montgomery-Asberg Depression Rating Scale (MADRS) score at wee
endpoint for both studies. Quetiapine was superior to placebo in reducing the MADRS score. In both stu
symptoms as measured by the change in MADRS score relative to placebo was observed on day 8 (We
The Quality of Life Satisfaction Scale Questionnaire (Q-LES-Q(SF)) measurement showed statistically si
improvements in overall quality of life and satisfaction, related to various areas of functioning, for the 300
the placebo; however, no additional benefit was observed with the 600 mg dose (Prod Info SEROQUEL(
2007b).

2) Quetiapine monotherapy was well-tolerated and more effective than placebo in the treatment of bipol
a double-blind, randomized, fixed-dose, placebo-controlled, parallel-group study, patients with bipolar I (
with a major depressive episode (DSM-IV) were assigned to 8 weeks of quetiapine 600 (n=180) or 300 n
(n=181) or placebo (n=181). An initial dose of 50 mg was given on day 1 and titrated up to 300 mg by da
8, and all doses were given at bedtime. In this study, effects of treatment were evaluated by Montgomery
Rating Scale (MADRS) total score (primary end-point, mean change from baseline to week 8), Clinical G
severity and improvement, Hamilton Anxiety Rating Scale, Pittsburgh Sleep Quality Index, and Quality of
Satisfaction Questionnaire. Statistically significant improvement in MADRS total score from week 1 onwa
both quetiapine groups compared with placebo. The mean change in MADRS total score from baseline t
(intent-to-treat) was -16.73, -16.39, and -10.26 for the 600 mg, 300 mg and placebo groups, respectively
both quetiapine doses vs placebo). At the final assessment, both quetiapine groups had significantly high
(defined as at least 50% MADRS score improvement) when compared with placebo (58.2% in 600 mg/da
300 mg/day group vs 36.1% in placebo; p less than 0.001). In addition, 52.9% of patients in both quetiap
remission criteria (MADRS score of 12 or less) compared to 28.4% of patients in the placebo group (p les
Significant improvements from baseline were observed in 9 of 10 and 8 of 10 MADRS items in the quetia
mg/day groups, respectively, compared with placebo (p less than 0.05). Quetiapine and placebo groups
rates of treatment-emergent mania (3.2% and 3.9%, respectively). The rates of serious adverse events w
different across treatment groups, and none were treatment related (5% in the 600 mg/day group and 3.4
group compared with 8.9% in the placebo group). The overall rates of study discontinuation due to adver
(n=47), 16% (n=29), and 8.8% (n=16) for the 600 mg/day group, 300 mg/day group, and placebo group,
(Calabrese et al, 2005).

4.5.B.3 Bipolar disorder, Maintenance

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIa
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Indicated for the maintenance treatment of bipolar I disorder as adjunctive therapy to lithium or dival
SEROQUEL(R) oral tablets, 2008a)

As adjunct therapy to lithium or divalproex, quetiapine was more effective than placebo in maintenar
bipolar I disorder in 2 double-blind, randomized, placebo-controlled studies (n=1326) (Prod Info SEF
tablets, 2008a)

c) Adult:

1) As adjunct therapy to either lithium or divalproex, quetiapine was more effective than placebo in main
bipolar I disorder. Two identical, randomized, double-blind studies evaluated patients (n=1326), with bipo
defined by the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV). Patients m
could be manic, depressed, or mixed, with or without psychotic characteristics. Once in the open-label pl
required to be stabilized on quetiapine plus lithium or divalproex for a minimum of 12 weeks, (mean was
were to continue either lithium or divalproex, and were randomized to quetiapine twice daily for a total da

milligrams (mg) to 800 mg or to placebo. The primary outcome was time to recurrence of a mood event. defined as medication intervention, or requirement of hospitalization for a mood occurrence, a Young Ma (YMRS) score, or a Montgomery-Asberg Depression Rating Scale (MADRS) score greater than or equal discontinuation of study due to a mood event. During the double-blind phase, by day 280, approximately quetiapine group discontinued, and by day 117, approximately 50% of patients in the placebo group disc revealed quetiapine as superior to placebo at improving length of time before recurrence of any mood ev was independent of subgroup specifics, such as concomitant mood stabilizers, gender, age, race, or mo episode, or rapid cycling episode (Prod Info SEROQUEL(R) oral tablets, 2008a)

4.5.B.4 Bipolar disorder - Cocaine dependence

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

A small, 12-week, open-label, add-on study (n=17) demonstrated that quetiapine may be effective ir symptoms and drug cravings in patients with bipolar disorder and comorbid cocaine dependence (B

c) Adult:

1) The results of an open-label study indicate that quetiapine therapy may be effective in decreasing psy and drug cravings in patients with bipolar disorder and cocaine dependence. In this small, 12-week, ope patients with bipolar I or II disorder with comorbid cocaine dependence received quetiapine at initial dose milligrams (mg) daily with weekly titrations as indicated for symptoms (mean dose at exit, 229 mg/day)(n was an add-on therapy, patients continued to take their current psychiatric medications and those enrolle treatment programs continued with that therapy as well. Psychiatric symptoms were measured at baselir intervals using the Hamilton Depression Rating Scale (HDRS), and Young Mania Rating Scale (YMRS). were assessed at baseline and at weekly intervals using a version of the Cocaine Craving Questionnaire report of dollar amount spent on cocaine was used to assess weekly drug use. In the intent to treat grou HDRS, YMRS, and BPRS were significantly decreased from baseline to exit (p less than 0.01). In additic significantly reduced from baseline to exit in this group (p=0.05). Money spent on cocaine, days of drug u positive urine drug screens were reduced; however, this change was not significant (Brown et al, 2002).

4.5.B.5 Delirium

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Effective in the treatment of delirium in two small, prospective, open-label studies (Pae et al, 2004; Sasa

c) Adult:

1) Low-dose quetiapine therapy may be effective in the treatment of delirium. In a prospective, open-lab Korean patients (mean age, 69 years; age range, 48 to 85 years) with delirium secondary to a medical c lung cancer, intra- cranial hemorrhage, cerebrovascular attack, femur neck fracture, or acquired immune received quetiapine for the treatment of delirious symptoms. Patients received quetiapine at a mean dail milligrams (mg) (initial mean dose, 37.5 mg/day; maximum mean dose, 177.3 mg/day) for an average of reductions in the mean severity scores for the Delirium Rating Scale-revised-98 (DRS-R-98) and Clinical Severity (CGI-S) scale were observed from baseline to post-treatment (21.8 vs 9.3 and 4.9 vs 2.1, respe 0.0001, both values). A reduction in the DRS-R-98 and CGI-S scores of at least 50% was observed in 19 (77.3%) patients, respectively. Sedation was the most common adverse event and no extrapyramidal sy observed. Controlled trials are needed to confirm these findings (Pae et al, 2004).

2) Symptoms of delirium resolved in twelve patients (mean age 67.3 years) following treatment with que prospective, open-label study, patients with delirium received oral quetiapine (mean dose, 44.9 milligram mean dose, 63.5 mg/day) at flexible dosing schedules for a time period lasting at least until remission of was defined as a Delirium Rating Scale-Japanese version (DRS-J) score of less than 12 points in additic assessment that symptoms of delirium had remitted clinically. Remission of delirium was achieved in all following a mean treatment duration of 4.8 days. From baseline to time of remission, the mean DRS-J sc 18.1 to 9.3. In an assessment of 8 of the 12 patients, the mean score for the Mini Mental Health State Ex version significantly improved from 19.6 at baseline to 24 after remission (p=0.0256). No adverse events quetiapine was generally well tolerated. Randomized, controlled studies are needed to substantiate thes al, 2003).

4.5.B.6 Delirium, Refractory

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive

Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category C
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:
Improved symptoms of treatment-refractory delirium in two hospitalized patients (52-year-old male and 5
Samarrai et al, 2003)

c) Adult:
1) Quetiapine therapy improved symptoms of agitation and aggression in two hospitalized patients with
delirium. A 52 year-old male and a 50-year-old female patient with delirium refractory to treatment with ri
haloperidol responded to quetiapine therapy. Trials of quetiapine in the male and female patient (initial 5
titrated to 400 mg/day and 200 mg/day, respectively) effectively controlled aggression and agitation in bo
improved cognitive ability (Al-Samarrai et al, 2003).

4.5.B.7 Dementia
See Drug Consult reference: BEHAVIORAL AND PSYCHOLOGICAL SYMPTOMS OF DEMENTIA

4.5.B.8 Gilles de la Tourette's syndrome

a) Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Pediatric, Evidence favors efficacy
Recommendation: Pediatric, Class IIb
Strength of Evidence: Pediatric, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:
In a small, 8-week, prospective, open-label study (n=12) of pediatric patients with Tourette's disorder, pa
reduction in motor and phonic tics with quetiapine therapy (Mukaddes & Abali, 2003)

c) Pediatric:
1) Quetiapine therapy was effective in the reduction of motor and phonic tics in pediatric patients with To
prospective, open-label study (n=12) patients 8 to 16 years of age (11 boys, 1 girl) with Tourette's disord
quetiapine therapy at an initial dose of 25 milligrams (mg) daily, titrated to maximum doses of 75 mg/day
100 mg/day (12 years and older). The mean dose of quetiapine was 72.9 mg/day with a range of 50 to 1
total tic score of the Yale Global Tic Severity Scale was significantly reduced from baseline to 4 weeks (6
respectively; p less than 0.01), and from baseline to 8 weeks (61.17 vs 24.17, respectively; p less than 0
patients demonstrated a 30% to 100% improvement in tic severity (mean change, 61.91; 95% CI=50.03
Mild, transient sedation was reported in three patients; however, extrapyramidal adverse effects and stat
weight gain were not observed. Larger, randomized, controlled studies are needed to confirm the safety
quetiapine for the treatment of Tourette's disorder in children (Mukaddes & Abali, 2003).

4.5.B.9 Manic bipolar I disorder
FDA Labeled Indication

a) Overview
FDA Approval: Adult, yes (regular-release oral tablets); Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIa
Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:
Indicated for the treatment of acute manic episodes associated with bipolar I disorder as either mon
therapy to lithium or divalproex (Prod Info SEROQUEL(R) oral tablets, 2008a)
As monotherapy, two studies revealed that quetiapine was more effective than placebo in the treatm
patients with bipolar I disorder (McIntyre et al, 2005; Bowden et al, 2005)
As adjunct therapy, quetiapine was more effective than placebo in the treatment of acute manic sym
bipolar I mania(Sachs et al, 2004; Yatham et al, 2004)

c) Adult:
1) Monotherapy
a) Quetiapine monotherapy was more effective than placebo in the treatment of acute mania in pati
disorder. This international, 12 week, multicenter, double-blind, parallel-group study randomized pat
quetiapine (n=107), lithium (n=98), or placebo (n=95). Primary inclusion criteria allowed for adult pat
hospitalized for less than 3 weeks, with diagnosis of bipolar I disorder, and who were presently expe
manic episode based on the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (
were required to have at least 1 previously, well documented manic or mixed episode, however, pat
and mixed episodes, based on DSM-IV criteria were excluded. Patients required a score of at least
Young Mania Rating Scale (YMRS), items of irritability, speech, content, and disruptive/aggressive b
baseline YMRS scores for the quetiapine group was (32.7) and (34) for the placebo group. Quetiapi
as a flexible, twice daily dose, starting at 100 milligrams (mg) on day 1, 200 mg on day 2, 300 mg or
on day 4. By day 5, the patients' dose could be increased to 600 mg/day, and up to 800 mg/day from
84. The average dose of quetiapine in the responders was 586 mg/day in the week prior to day 21.
was the change from baseline of the YMRS score at day 21. The parallel group evaluated lithium ve

and secondary outcomes were analyzed on the intent to treat (ITT) groups and included all randomi
at least 1 dose of study treatment and who had at least 1 set of post-baseline YMRS scores. The av
was 38 years and 56.1% of them were male. At day 21, change in YMRS score from baseline was s
in the quetiapine groups versus placebo (-14.62 vs -6.71; p less than 0.001). Change in YMRS scor
versus placebo group was also statistically significant (-15.20 vs -6.71; p less than 0.001); however,
between quetiapine and lithium groups was not significant. Secondary outcomes of note include sig
in the change in YRMS score from baseline through treatment day 84 (-20.28 vs -9; p less than 0.0
defined as 50% or greater reduction in YMRS score from baseline at day 21 were significant (53.3%
0.001). YMRS remission rates, defined as a YMRS score of 12 or less at day 21 were also significar
less than 0.001). Adverse effects were considered mild to moderate. The most common, occurring a
included dry mouth, somnolence, weight gain, dizziness, insomnia, headache, asthenia, depression
(Bowden et al, 2005).

b) Quetiapine monotherapy was more effective than placebo in the treatment of acute mania in pati
disorder. This international, 12 week, multicenter, double-blind, parallel-group study randomized pat
quetiapine (n=101), haloperidol (n=98), or placebo (n=100). Primary inclusion criteria allowed for ad
age of 42.8 years, 36.6% male, who were hospitalized for less than 3 weeks, with diagnosis of bipol
without psychotic characteristics, and who were presently experiencing an acute manic episode bas
and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV). Patients were required to have
well documented manic or mixed episode, however, patients with rapid cycling and mixed episodes
criteria were excluded. Patients required a score of at least 4, on 2 of the core Young Mania Rating
of irritability, speech, content, and disruptive/aggressive behavior. Mean baseline YMRS scores for t
was (34) and (33.1) for the placebo group. Quetiapine was administered twice daily, starting at 100 r
1, 200 mg on day 2, 300 mg on day 3, and 400 mg on day 4. By day 5, the patients' dose could be i
mg/day based on efficacy and tolerability, and up to 800 mg/day thereafter from treatment days 6 to
recommended target dose was 600 mg/day. The average dose of quetiapine in the responders was
primary outcome was the change from baseline of the YMRS score at day 21. The parallel group ev
versus placebo. Primary and secondary outcomes were analyzed on the intent to treat (ITT) groups
randomized patients who took at least 1 dose of study treatment and who had at least 1 set of post-
scores. At day 21, change in YMRS score from baseline was statistically significant in the quetiapine
placebo (-12.29 vs -8.32; p less than 0.01). Change in YMRS scores for the haloperidol versus plac
statistically significant (-15.71 vs -8.32; p less than 0.001). Secondary outcome of change from base
day 84 revealed quetiapine and haloperidol treated patients continued to experience statistically sig
17.52 and -18.92 vs -9.48, respectively; p less than 0.001 for both comparisons to placebo). The mo
effects occurring greater than 10% included insomnia, somnolence, and extrapyramidal-related effe
and extrapyramidal syndromes were significantly more frequent with haloperidol compared to quetia
less than 0.001) (McIntyre et al, 2005).

2) Adjunct Therapy

a) Quetiapine with lithium or divalproex was more effective than lithium or divalproex monotherapy
acute mania in patients with bipolar I disorder. This 3-week, double blind, placebo controlled, paralle
patients to receive quetiapine (n=81) as add on therapy to lithium or divalproex versus placebo (n=8
divalproex. Inclusion criteria allowed for adult patients, average age of 39.6 years, 49 patients were
of bipolar I disorder based on the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edit
required hospitalization for less than 3 weeks for a current manic episode and treatment with lithium
least 7 days of the immediately preceding 28 days prior to randomization. Patients were also require
previously, well documented manic or mixed episode prior to the current episode, and a score of at l
core YMRS items of irritability, speech, content, and disruptive/aggressive behavior. Patients with ra
were excluded. Eligible patients either began or continued lithium or divalproex on day 1 of study. Q
administered twice daily, morning and evening, starting at 100 milligram (mg) on day 1, 200 mg on d
3, and 400 mg on day 4. By day 5, the patients' dose could range from 200 milligram per day (mg/da
based on efficacy and tolerability, and up to 800 mg/day on days 6 to 21. Study guidelines encourag
quetiapine dosage to at least 600 mg/day prior to patients withdrawing from the study due to lack of
last-week quetiapine dose among the responders was 584 mg/day. The primary outcome was the ch
the YMRS score at final assessment. Mean baseline YMRS scores for the quetiapine with lithium or
(31.5) and (31.1) for the placebo group. Outcomes were analyzed on the intent to treat (ITT) groups
YMRS score from baseline was statistically significant in the quetiapine group versus placebo (-13.7
Secondary outcomes, also statistically significant were YRMS response rates, defined as 50% or gr
YMRS score from baseline at day 21, (54.3% vs 32.6%; p=0.005). As well as, YMRS remission rate
score of 12 or less at day 21, (45.7% vs 25.8%; p=0.007). The most common adverse effects occur
were somnolence, headache, dry mouth, asthenia, postural hypotension, and dizziness (Sachs et al

b) Quetiapine with lithium or divalproex was more effective than lithium or divalproex monotherapy
acute mania in patients with bipolar I disorder. This double blind, placebo controlled study randomiz
quetiapine (n=185) as add on therapy to lithium or divalproex versus placebo (n=185) with lithium or
weeks or 6 weeks duration. Eligible patients were adult patients, average age of 39.2 years, 54.1% r
bipolar I disorder, with or without psychotic features, based on the Diagnostic and Statistical Manual
Fourth Edition (DSM-IV). Patients required hospitalization for less than 3 weeks for a current manic
with lithium or divalproex for at least 7 days prior to randomization, and a history of at least 1 manic
the last 5 years. Patients with rapidly cycling or mixed episodes were excluded. Patients required a
on 2 of the core Young Mania Rating Scale (YMRS) items of irritability, speech, content, and disrupt

behavior, and a score of 4 or greater on the Clinical Global Impression-Bipolar (CGI-BP) Severity of
randomization, patients were to continue lithium or divalproex treatment. Clinicians could adjust lithi
doses for efficacy, for reduction of adverse effects, and for established, therapeutic range (0.7 to 1.0
liter, (mEq/L) lithium, or 50 to 100 microgram per milliliter (mcg/mL) divalproex). Quetiapine was adn
starting at 100 milligram per day (mg/day) on day 1, 200 mg/day on day 2, 300 mg/day on day 3, an
4. By day 5, quetiapine could be administered up to 600 mg/day, and up to 800 mg/day from day 6 t
treatment. By day 21, the average dose of quetiapine in the responders was 492 mg/day. The prima
change from baseline of the YMRS score at day 21. Because the protocol was identical for the 3 we
treatment group, the results were combined for analysis to increase the power of the study to identif
important effects. Mean baseline YMRS scores for the quetiapine with lithium or divalproex group wa
the placebo group. Outcomes were analyzed on the intent to treat (ITT) groups. At day 21, change i
baseline was statistically significant in the quetiapine group versus placebo (-15.29 vs -12.19; p less
statistically significant secondary outcomes were change in response rate, defined as 50% or greate
score from baseline at day 21, (55.7% vs 41.6%; p less than 0.01). YMRS remission rates, defined a
or less at day 21, was statistically significant (48.7% vs 33%; p less than 0.01). Common adverse ef
or greater, and at least twice that of placebo were somnolence, dry mouth, asthenia, postural hypote
and pharyngitis (Yatham et al, 2004).

4.5.B.10 Obsessive-compulsive disorder, Refractory

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Obsessive-compulsive disorder (OCD) symptoms were reduced when quetiapine was added to SSRI (se
reuptake inhibitor) treatment (Denys et al, 2002; Mohr et al, 2002)

c) Adult:

1) The addition of quetiapine to selective serotonin reuptake inhibitor (SSRI) therapy was effective in pro
of symptom activity in patients with treatment-refractory obsessive-compulsive disorder (OCD). In a sma
patients with at least a 5-year history of OCD symptoms who failed a minimum of 3 adequate treatments
scored at least 18 on the Yale-Brown Obsessive Compulsive Scale (YBOCS) received quetiapine for 8 w
their current SSRI (n=10). Using a fixed dosing schedule, quetiapine was given at an initial dose of 75 m
titrated to 200 mg/day (100 mg/day in week 2, 150 mg/day in week 3, 200 mg/day in week 4). Overall, th
reduction (35.4%) in patients' mean YBOCS score from baseline to endpoint (p=0.002). Quetiapine was
sedation being the most common adverse event (Denys et al, 2002).

2) Symptoms of obsessive-compulsive disorder (OCD) were reduced by treatment with quetiapine, in co
selective serotonin reuptake inhibitor (SSRI). The charts of 8 patients who had been treated for OCD by
tolerated dose of an SSRI for at least 12 weeks and who were then given add- on treatment of quetiapin
Quetiapine doses were started at 25 milligrams (mg) daily and increased to a maximum of 300 mg daily.
Brown Obsessive-Compulsive Scale improved for 4 of the patients, at doses of 50, 75 (2 patients), and 3
patient was unable to tolerate quetiapine (Mohr et al, 2002).

4.5.B.11 Parkinson's disease - Psychotic disorder

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

In several studies and case reports, quetiapine therapy controlled psychotic symptoms in patients with P
(Fernandez et al, 2000; Weiner et al, 2000; Fernandez et al, 1999; Friedman & Factor, 2000a)(Parsa & E

c) Adult:

1) A study designed to measure the effectiveness of clozapine replacement by quetiapine in 15 patients
induced psychosis in Parkinson's disease concluded that quetiapine is an effective alternative to clozapi
assessed at baseline, and 4 and 8 weeks after discontinuation of clozapine. At baseline, the starting cloz
reduced by 6.25 milligrams (mg) per week for 2 weeks, 12.5 mg per week for 2 weeks, and 25 mg per w
was discontinued. The baseline initiation dose of quetiapine was 12.5 mg daily for 1 week and was incre
mg per day until the patient was no longer receiving clozapine. Quetiapine dosage adjustments were per
titration period, which ranged from 1 to 10 weeks. The average quetiapine ending dose was 62.5 mg. An
standardized weekly telephone interview was performed on all patients and their caregivers. Twelve of th
transition without a worsening of cognition or loss of antipsychotic effect at the 4 and 8-week visits. All 12
quetiapine. Side-effects noted were mild and transient. Only 1 patient had increased dyskinesia and 4 pa
transient worsening of tremor. At the end of 12 months, 9 of 12 patients were stable on quetiapine. Two
experienced a decline in motor function switched back to clozapine (Fernandez et al, 2000).

2) An 81-year-old man with a 14-year history of Parkinson's disease who developed levodopa-induced p

successfully treated with quetiapine after olanzapine was discontinued due to worsened parkinsonism. Q
6 weeks after the discontinuation of olanzapine and was titrated to a dose of 25 milligrams at bedtime. T
complete resolution of hallucinations, complete resolution of belligerent behavior, and no worsening of pa
al, 2000).
3) Quetiapine was shown to be beneficial and well tolerated in the treatment of drug-induced psychosis
Parkinson's disease (PD) (Fernandez et al, 1999). Thirty-five patients received a mean daily dose of que
milligrams. Of 24 neuroleptic-naive patients, 20 reported marked improvement of psychosis without a co
motor function. There was a clinically and statistically significant (p=0.024) improvement in Brief Psychia
(BPRS) in the patients that had a baseline and 4-week follow-up assessment. Five patients were able to
a transition from clozapine or olanzapine to quetiapine, while 6 could not due to confusion, erratic behavi
hallucinations. The data suggests quetiapine may be beneficial to treat DIP in PD but it should be used v
replacing other atypical antipsychotic drugs.
4) In a review of several smaller studies (n= 10 to 40), quetiapine (25 to 300 milligrams/day) was succes
Psychiatric Rating Scale (BPRS) scores and improving or not worsening motor functions (Friedman & Fa
5) A 52-week open-label pilot study reported successful use of quetiapine in treating psychosis in two ne
patients with Parkinson's disease (1 with and 1 without dementia) (Parsa & Bastani, 1998). For each pati
introduced at 25 milligrams (mg) per day; it was increased to a maximum dose of 200 mg/day over 16 we
without dementia (a 74-year-old man) and 400 mg/day over 12 weeks for the patient with dementia (a 74
Severity of psychiatric symptoms was measured by the Brief Psychiatric Rating Scale and a Clinical Glob
Severity of Illness scale. Treatment successfully controlled psychotic symptoms without worsening motor
patients, although improvement was not as pronounced in the patient with dementia.

4.5.B.12 Posttraumatic stress disorder

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Adjunctive quetiapine therapy reduced the posttraumatic stress disorder (PTSD) symptoms of a 49-year-
with severe PTSD (Sattar et al, 2002)

c) Adult:

1) Adjunctive quetiapine therapy reduced symptoms in one patient suffering from posttraumatic stress d
year-old Caucasian male with severe PTSD received adjunctive treatment with quetiapine after therapy w
of paroxetine (titrated to 40 milligrams (mg)/day) failed to control his symptoms. Initially, he received que
bedtime for 2 days, but continued to be irritable and anxious. The dose was then increased to 100 mg at
following 3 days his symptoms eased, however periodic episodes of severe anxiety persisted during the
dose was increased to 25 mg twice daily and 100 mg at bedtime and he showed continued improvement
His scores on the Hamilton-D rating scale for Depression (HAM-D) and clinician-administered PTSD scre
from 40 and 98 (on admission) to 11 and 60, respectively. His symptoms remained controlled at this dos
months. No adverse events were reported (Sattar et al, 2002).

4.5.B.13 Schizophrenia

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes; Pediatric, no
Efficacy: Adult, Evidence favors efficacy; Pediatric, Evidence favors efficacy
Recommendation: Adult, Class IIa; Pediatric, Class IIb
Strength of Evidence: Adult, Category B; Pediatric, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Quetiapine is indicated for the treatment of schizophrenia (Prod Info SEROQUEL(R) oral tablets, 20
SEROQUEL XR(TM) extended-release oral tablets, 2007)
In 3 short-term (6-week) controlled-trials of patients with schizophrenia who met DSM III-R criteria fo
higher quetiapine doses were generally more effective than lower doses in treating patients with sch
DSM III-R criteria for schizophrenia (Prod Info SEROQUEL(R) oral tablets, 2007b)
Moderate degree of efficacy for treating positive and negative symptoms in schizophrenic patients ir
studies (Wetzel et al, 1995b; Fulton & Goa, 1995b; Fabre et al, 1995b; Borison et al, 1996b; Anon, 1
In one 6-week placebo-controlled trial (n=109), the efficacy of quetiapine was not sustained beyond
(Borison et al, 1996b)
In an open-label, 12-week, prospective study (n=56), oral quetiapine, at doses ranging from 200 to 8
was well tolerated and yielded clinical benefit in symptoms of early-onset schizopreniform-spectrum
adolescents (Schimmelmann et al, 2007)
In a small, open-label study (n=10) of adolescents, quetiapine was well tolerated and effective in the
schizoaffective disorder or bipolar disorder with psychotic features (McConville et al, 2000; McConvi

c) Adult:

1) In 3 short-term (6-week) controlled-trials of patients with schizophrenia who met DSM III-R criteria for

quetiapine doses were generally more effective than lower doses in treating patients with schizophrenia
criteria for schizophrenia. One of the trials used a single fixed dose haloperidol arm as a comparative tre
single group was inadequate to provide a reliable and valid comparison of quetiapine and haloperidol (Pr
(R) oral tablets, 2007b).

a) A placebo-controlled trial (n=361) that involved 5 fixed doses of quetiapine 75, 150, 300, 600 and
day (mg/day) in 3 divided doses reported that the 4 highest doses were superior to placebo on the B
Scale (BPRS) total score, the BPRS psychosis cluster and the Clinical Global Impression (CGI) sev
maximal effect was observed at 300 mg/day, and this dose was superior to placebo on the Scale for
Symptoms (SANS). The observed effects of 150 to 750 mg/day were generally identical (Prod Info S
tablets, 2007b).

b) Another placebo-controlled trial (n=286) that involved the titration of quetiapine in high (up to 750
(mg/day) in 3 divided doses) and low (up to 250 mg/day in 3 divided doses) doses reported that only
quetiapine group was superior to placebo on the Brief Psychiatric Rating Scale (BPRS) total score, t
cluster, the Clinical Global Impression (CGI) severity score, and the Scale for Assessing Negative S
(Prod Info SEROQUEL(R) oral tablets, 2007b).

c) A dose regimen comparison trial (n=618) that compared two fixed doses of quetiapine (450 millig
3 divided doses and 50 mg/day in 2 divided doses) reported that only the 450 mg/day (225 mg twice
was superior to the 50 mg/day (25 mg twice daily) quetiapine dose group on the Brief Psychiatric Ra
total score, the BPRS psychosis cluster, the Clinical Global Impression (CGI) severity score, and on
Assessing Negative Symptoms (SANS) (Prod Info SEROQUEL(R) oral tablets, 2007b).

2) A 6-week, fixed-dose, placebo-controlled trial of patients who met DSM IV criteria for schizophrenia (r
that 400 milligram (mg), 600 mg, and 800 mg once daily doses of extended-release quetiapine were sup
Therapy was initiated with extended-release tablets at 300 mg/day (once daily) on Day 1. The dose was
400 mg or 600 mg on Day 2 or to 800 mg by Day 3. Change between baseline and endpoint (Day 42) fo
Negative Syndrome Scall (PANSS) was used as the primary efficacy measure. Analysis of PANSS total
quetiapine extended-release doses of 400 mg, 600 mg and 800 mg were all superior to placebo (Prod In
(TM) extended-release oral tablets, 2007).

3) Several open (Wetzel et al, 1995b; Fulton & Goa, 1995b) and placebo-controlled studies (Fabre et al,
1996b; Anon, 1995b; Fulton & Goa, 1995b) of short duration (6 weeks or less) have suggested the effica
for treating both positive and negative symptoms of schizophrenia (mostly patients with acute exacerbati
chronic illness). In these trials, effects of treatment were mainly evaluated by the Brief Psychiatric Rating
Clinical Global Impression (CGI) Severity of Illness score, and the modified Scale for Assessment of Neg
(SANS). Clinical responses were observed within 2 weeks of starting quetiapine therapy and were best v
300 milligrams daily; in one study, doses of up to 750 milligrams daily (mean, 360 milligrams daily) were
to lower doses (up to 250 milligrams daily; mean, 209 milligrams daily) and placebo at week 6 of treatme
and SANS (Anon, 1995b). The severity of extrapyramidal symptoms (EPS) was similar in patients treate
quetiapine.

4) Quetiapine therapy in 145 patients diagnosed with psychotic mood disorders was reviewed. All patier
with quetiapine, and 20% received quetiapine alone while 80% received other psychoactive drugs with q
was associated with more substantial clinical effects in patients with affective psychoses and in patients
chronically ill. The response rate for the majority of psychiatric diagnoses studied was equal or superior t
schizophrenia. These preliminary findings suggest that quetiapine may be useful as an alternative or adj
patients with affective psychosis when used with mood stabilizers. Controlled studies are needed (Zarate

5) An uncontrolled trial in elderly patients with psychotic disorders found quetiapine to be associated wit
improvement and to be well tolerated (McManus et al, 1999). An interim statistical analysis was performe
week 12. The median total daily dose of quetiapine was 100 milligrams/day. The most common adverse
the central nervous system (somnolence, dizziness, agitation) and cardiovascular system (postural hypo
Extrapyramidal symptoms occurred in 6% of patients. Mean Simpson-Angus Scale total score showed si
(p less than 0.0001) at endpoint. In addition, Brief Psychiatric Rating Scale (BPRS) and Clinical Global Ir
scores showed significant (p less than 0.0001 and p less than 0.01, respectively) improvement. This non
supports the need for further controlled clinical trials of quetiapine use in the elderly.

6) Considerable interindividual differences in the response to quetiapine have been reported (Wetzel et
Goa, 1995b), and in larger placebo-controlled trials, differences in favor of quetiapine have not always re
significance or were marginally significant and beneficial changes from baseline scores were at times sm
questionable clinical significance; up to one-third of patients receiving quetiapine have dropped out of tre
efficacy (Fulton & Goa, 1995b; Borison et al, 1996b; Anon, 1995b). One 6-week placebo-controlled trial (
1996b) reported a significant reduction in BPRS and CGI scores with oral quetiapine for three of the first
there was no significant difference in scores between placebo and quetiapine at week 6. Improvement in
sustained with quetiapine on days 21 to 42, although statistical significance was barely achieved. Thirty
treated patients discontinued therapy due to lack of benefit in this study.

d) Pediatric:

1) In an open-label, 12-week, prospective study (n=56), treatment with oral quetiapine, at doses ranging
milligrams (mg) per day, was well tolerated and led to significant improvement in symptoms of early-onse
spectrum disorders in adolescents. Following a 1- to 9-day washout period of prior psychoactive medicat
age, 15.9 years; range, 12-17.9 years; 67.9% male) meeting the DSM-IV criteria for schizophrenia, schiz
schizophreniform disorder and had a Positive and Negative Syndrome Scale (PANSS) total score of 60 o
with quetiapine for 12 weeks. Following a fixed titration protocol during week 1 (50 mg at day 1 increased
7), the quetiapine dose was adjusted based on clinical response and tolerability to a range of 200 to 800

dose, 605.6 mg/day (week 6) and 584.2 mg/day (week 12)). The use of benztropine (1 to 6 mg/day) to tr
symptoms (EPS) and benzodiazepines (diazepam or lorazepam; up to 40 mg/day of diazepam equivaler
agitation, or sleep disturbances were allowed during the study. Assessments occurred at weekly visits ur
visits every other week during weeks 6-12. The majority of study patients (76.8%) were antipsychotic-nai
week 12, 51.8% (n=25/52) of study participants had dropped out, with 30.4% discontinuing due to lack o
modified intent-to-treat (ie, patients with at least 1 post-baseline efficacy measurement) revealed a signif
mean +/- standard deviation PANSS total score (primary endpoint) from baseline (91.5 +/- 17.2) to week
less than 0.0001), yielding a difference of 24.9 points (95% confidence interval (CI), 17.3 to 32.4; effect s
difference was evident as early as week 1 and was maintained throughout the study. A 50% reduction in
occurred in 34.6% (n=18/52) at a median of 85 days while 51.9% (n=27/52) had a 40% reduction in PAN
median of 57 days. Among the PANSS sub-scales, the effect size at week 12 was greater for the positive
5.2 at baseline to 14.9 +/- 6.9; 95% CI, 4.8 to 9.1; effect size=0.91) than the negative sub-scale (22.8 +/-
18.2 +/- 8.7; 95% CI, 2 to 7.1; effect size=0.5). Additionally, significant improvements occurred among th
impulsivity/hostility, and anxiety/depression sub-scales of the PANSS, along with the Clinical Global Impr
Illness scale (5.2 +/- 0.9 at baseline to 3.7 +/- 1.8 at week 12) and the Subjective Well-being under Neuro
Scale (75.5 +/- 17.6 at baseline to 7.5 +/- 17.1 at week 12). Adverse events occurred in 78.6% of patient
(21.4%), fatigue (17.9%), and headache (17.9%) being the most common. Five (8.9%) and 2 (3.6%) pati
least 1 moderate EPS (at doses of 400 to 600 mg/day) and mild-to-moderate akithisia (at doses of 500 to
respectively; however, none required treatment or resulted in study discontinuation. Compared to baselir
significant increase in weight and BMI at week 12 (mean increase, 6.2 kilograms (weight), 2.1 kilograms/
with 60.7% of patients gaining more than 7% of their baseline weight (Schimmelmann et al, 2007).

2) A small study (n=10) of adolescents ranging in age from 12.3 through 15.9 years concluded quetiapir
and effective in the treatment of schizoaffective disorder or bipolar disorder with psychotic features. Quet
open-label, rising-dose trial was initiated at 25 milligrams (mg) twice daily and reached 400 mg twice dail
concluded on day 23. Quetiapine improved both positive and negative symptoms significantly (p less tha
and endpoint symptoms were compared and there were no unexpected side effects (McConville et al, 20
of this trial, all ten patients continued open-label treatment with quetiapine (initial, 800 mg/day titrated ov
optimal dose; mean dose, 600 mg/day) for up to 88 weeks. Significant improvements in mean scores fro
were seen at all time points through week 64 for the Brief Psychiatric Rating Scale (BPRS) and Clinical G
(CGI) Severity of Illness scale (p less than 0.05). Improvements in mean scores on the Scale for Assessi
Symptoms (SANS) were significant through week 52 (p less than 0.05). Quetiapine was well tolerated ar
were mild to moderate, with somnolence (60%), headache (50%), and pharyngitis (40%) being reported
Extrapyramidal symptoms were not observed during the trial, however, 30% of patients reported increas
body mass index as a "mild" adverse event. Larger, controlled studies are needed to further establish lor
efficacy and safety in this patient population (McConville et al, 2003).

4.5.B.14 Schizophrenia, Maintenance

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes (extended release only); Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIa
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

The extended-release formulation of quetiapine fumarate is indicated for the maintenance treatment
(Prod Info SEROQUEL(R)XR extended-release oral tablets, 2007)
In a randomized, double-blind, extension study (n=171), continued treatment with extended-release
400 to 800 milligrams per day led to a longer time to relapse compared to placebo in adult patients v
stabilized during 16 weeks of an open-label trial (Prod Info SEROQUEL(R)XR extended-release ora

c) Adult:

1) Maintenance treatment with extended-release quetiapine fumarate (quetiapine XR), at doses of 400 t
per day, led to a statistically significant delay in relapse compared to placebo in the double-blind, random
of an open-label trial. Clinically stable adult outpatients (n=171) who met the Diagnostic and Statistical M
Disorders (4th edition) criteria for schizophrenia and who remained stable following 16 weeks of open-lal
quetiapine XR 400 to 800 mg/day were included. Patients who had a Clinical Global Impression (CGI)-S
less and a Positive and Negative Syndrome Scale (PANSS) total score of 60 or less beginning to end of
(not exceeding a 10- or greater point increase in PANSS total score) were considered to be stabilized. In
extension phase, patients were randomized to continue receiving quetiapine XR at their current dose or
observed for possible relapse, which was defined as a 30% or greater increase in the PANSS total score
score of 6 or greater, hospitalization due to worsening of schizophrenia, or need for any other antipsycho
Treatment with quetiapine XR led to a significantly longer time to relapse than placebo (Prod Info SERO
release oral tablets, 2007).

4.5.B.15 Tardive dyskinesia

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy

Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category C
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:
Quetiapine treatment improved symptoms in three women with tardive dyskinesia (Chari et al, 2002)

c) Adult:
1) Treatment with quetiapine reduced persistent symptoms of tardive dyskinesia in three women receivi therapy. A 42-year-old Caucasian woman with a 25-year history of schizophrenia and scoring a 22 on th Involuntary Movement Scale (AIMS) was prescribed quetiapine for tardive dyskinesia. Within a year and treatment she no longer scored on the scale. The tardive dyskinesia symptoms of a 63-year-old Caucasi year history of schizoaffective disorder were also successfully treated with quetiapine. After a year of the was reduced from 19 to 3. In addition, a 52-year-old Asian woman with a 5-year history of psychotic illne quetiapine for tardive dyskinesia and after 24 weeks of treatment her AIMS score dropped from 17 to 10 are needed to substantiate these findings (Chari et al, 2002).

4.6 Comparative Efficacy / Evaluation With Other Therapies

Chlorpromazine

Haloperidol

Olanzapine

Paliperidone

Perphenazine

Risperidone

Ziprasidone

4.6.A Chlorpromazine

4.6.A.1 Schizophrenia

a) Based upon comparisons of minimum effective dosages identified in placebo- controlled, fixed-dose and f drug development trials, the minimum effective dose of quetiapine was 150 milligrams/day (equivalent to chlo milligrams/day) (Woods SW, 2003).

b) Quetiapine 75 to 750 milligrams daily (mean, 407 mg daily) offered no significant advantage over chlorpro milligrams daily (mean, 384 mg daily) in a double-blind, parallel-group trial involving patients with acute exace subchronic schizophrenia, or schizophreniform disorder (n=201). Both drugs were associated with similar red Psychiatric Rating Scale (BPRS) scores, Clinical Global Impression (CGI) scores, and negative scale scores Negative Syndrome Scale (PANSS) (negative symptom assessment). The severity of extrapyramidal sympto comparable (assessed by Simpson scale) (Fulton & Goa, 1995a).

4.6.B Haloperidol

4.6.B.1 Schizophrenia

a) In a study involving 361 patients, quetiapine (across 5 fixed doses) was found to be superior to placebo in symptoms in schizophrenic patients, while haloperidol (12 milligrams/day) was not. Additionally, depressive s improved in a greater proportion of patients treated with quetiapine versus haloperidol or placebo. None of th withdrew from the study due to extrapyramidal symptoms, while 4 haloperidol and 1 placebo patient withdrew Glazer, 2000).

b) A 6-week, multicenter, double-blind trial comparing quetiapine and haloperidol (mean total daily doses of milligrams, respectively) in the treatment of acute exacerbation of schizophrenia concluded that quetiapine in better tolerated than haloperidol. Both agents produced clear reductions in the Positive and Negative Syndro Clinical Global Impression Severity of Illness and Global Improvement scores. Quetiapine was better tolerate extrapyramidal symptoms. In addition, mean serum prolactin concentration decreased in quetiapine patients haloperidol patients (Copolov et al, 2000).

4.6.C Olanzapine

4.6.C.1 Chronic schizophrenia

a) When newer antipsychotic medications (olanzapine, quetiapine, risperidone, and ziprasidone) were comp

generation antipsychotic, perphenazine, the majority of patients in each group discontinued their antipsychoti
before 18 months. Patients (n=1493) with chronic schizophrenia were randomized to receive olanzapine 7.5 t
(mg/day), perphenazine 8 to 32 mg/day, quetiapine 200 to 800 mg/day, risperidone 1.5 to 6.0 mg/day, or zipr
mg/day for up to 19 months. Overall, 74% of patients discontinued treatment for any cause before 18 months
ranged from 64 to 82%. Time to discontinuation ranged from 3.5 months for ziprasidone to 9.2 months with o
discontinuation was significantly longer in the olanzapine group as compared with the quetiapine (hazard rati
confidence interval (CI), 0.52 to 0.76; p less than 0.001) or risperidone groups (HR, 0.75; 95% CI, 0.62 to 0.9
discontinuation due to adverse events were similar between all groups, but the rates ranged from 10% for risp
olanzapine (p=0.04). More patients discontinued olanzapine due to greater weight gain (average of 0.9 kilogr
greater increases in glycosylated hemoglobin, total cholesterol, and triglycerides (Lieberman et al, 2005).

4.6.D Paliperidone

4.6.D.1 Schizophrenia, Recent exacerbation, in hospitalized patients

a) In a randomized, double-blind, placebo- and active-controlled clinical trial (n=394), treatment with paliperic
(ER) produced significantly improved Positive and Negative Syndrome Scale (PANSS) total scores compared
hospitalized patients with a recent exacerbation of schizophrenia. Hospitalized patients 18 to 65 years of age
(defined as lasting less than 4 weeks but more than 4 days) of schizophrenia (paranoid, disorganized, or und
diagnosed using Diagnostic and Statistical Manual of Mental Disorders Fourth edition (DSM-IV)), a Clinical G
Severity (CGI-S) scale score of 5 or greater, and symptom scores of 4 or greater on 2 or more of the following
hostility, excitement, tension, uncooperativeness, and poor impulse control (with a combined score of these it
were eligible for enrollment. Following the discontinuation of all psychotropic agents, patients were randomize
paliperidone ER (n=157; baseline mean PANSS total score, 102.8 +/- 13.1 points), quetiapine (n=157; baseli
score, 101.3 +/- 13.3 points), or placebo (n=80; baseline mean PANSS total score, 103.8 +/- 15.7 points). In a
phase, paliperidone ER was initiated at 6 milligrams (mg)/day on days 1 to 3 and then increased to 9 mg/day
an optional dose increase to 12 mg/day starting on day 8 if necessary (mean dose, 10.4 +/- 1.7 mg/day) and
at 50 mg/day on day 1, 100 mg/day on day 2, 200 mg/day on day 3, 400 mg/day on day 4, 600 mg/day on da
dose increase to 800 mg/day on day 8 (mean dose, 690.9 +/- 134.3 mg/day). Psychotropic medications (excl
additional paliperidone ER or quetiapine) could be added following the 14-day monotherapy phase (one or m
agents: paliperidone ER, 52.9%; quetiapine, 55.4%; placebo, 66.7%). The least-squares mean PANSS total s
baseline to day 14 was significantly decreased in the paliperidone ER arm (-23.4 +/- 1.8 (standard error (SE))
with the quetiapine arm (-17.1 +/- 1.8 (SE) points; p less than 0.001) (primary endpoint) and the placebo arm
between group analyses (using a least-squares mean differences in change scores with the last observation
patients in the paliperidone ER arm had significantly improved PANSS total score, PANSS scale negative sy
PANSS scale disorganized thoughts scores, PANSS scale uncontrolled hostility/excitement scores, and CGI-
with patients in the quetiapine and placebo arms at day 14 and at the end of 6 weeks of treatment (day 42) (T
the PANSS scale positive symptoms score (PANSS-P) and Clinical Global Impression of Change (CGI-C) sc
improved in the paliperidone ER arm compared with the quetiapine and placebo arms at day 14 and paliperic
improved PANSS-P and CGI-C compared with placebo at day 42 (Table 1). Serious adverse events were rep
and 2.5% of patients in the paliperidone ER, quetiapine, and placebo arms, respectively. Extrapyramidal sym
significantly (p less than 0.001) higher in the paliperidone ER arm following the 14-day monotherapy phase c
quetiapine using the Simpson-Angus Rating Scale (total score). The incidence of movement disorders at day
significantly different between the 3 arms using the Barnes Akathisia Rating Scale and the Abnormal Involunt
(Canuso et al, 2009).

Table 1: Between Group Analyses

Outcome measures	Day 14			Day 42	
PANSS score Mean (SE)	Paliperidone ER versus Quetiapine	Paliperidone ER versus Placebo	Quetiapine versus Placebo	Paliperidone ER versus Quetiapine	Paliperido ER versus Placebo
Total	-6.3* (1.8)	-8.4* (2.2)	-2.1 (2.2)	-4.7* (2)	-7.8* (2.
Positive symptoms	-1.6* (0.6)	-2.1* (0.7)	-0.5 (0.7)	-1.1 (0.6)	-1.9* (0.
Negative symptoms	-1.3* (0.5)	-2.2* (0.6)	-0.9 (0.6)	-1.2* (0.5)	-2.1* (0.
Anxiety/depression	-0.5 (0.3)	-0.6 (0.4)	-0.1 (0.4)	-0.4 (0.3)	-0.5 (0.4
Disorganized thoughts	-1.3* (0.4)	-2.1* (0.5)	-0.8 (0.5)	-1* (0.5)	-2* (0.6
Uncontrolled hostility/excitement	-1.5* (0.4)	-1.6* (0.5)	-0.1 (0.5)	-1* (0.4)	-1.3* (0.
CGI-S (Mean SE)	-0.3* (0.1)	-0.4* (0.1)	-0.1 (0.1)	-0.3* (0.1)	-0.5* (0.
CGI-C (Mean SE)	-0.4* (0.1)	-0.5* (0.1)	-0.2 (0.1)	-0.1 (0.1)	-0.4* (0.

*p less than 0.05
PANSS, Positive and Negative Syndrome Scale; SE, standard error; CGI-S, Clinical Global Impression Clinical Global Impression of Change

4.6.E Perphenazine

4.6.E.1 Chronic schizophrenia

a) When newer antipsychotic medications (olanzapine, quetiapine, risperidone, and ziprasidone) were comp generation antipsychotic, perphenazine, the majority of patients in each group discontinued their antipsychoti before 18 months. Patients (n=1493) with chronic schizophrenia were randomized to receive olanzapine 7.5 t (mg/day), perphenazine 8 to 32 mg/day, quetiapine 200 to 800 mg/day, risperidone 1.5 to 6.0 mg/day, or zipr mg/day for up to 19 months. Overall, 74% of patients discontinued treatment for any cause before 18 months ranged from 64 to 82%. Time to discontinuation ranged from 3.5 months for ziprasidone to 9.2 months with o discontinuation was significantly longer in the olanzapine group as compared with the quetiapine (hazard rati confidence interval (CI), 0.52 to 0.76; p less than 0.001) or risperidone groups (HR, 0.75; 95% CI, 0.62 to 0.9 discontinuation due to adverse events were similar between all groups, but the rates ranged from 10% for risp olanzapine (p=0.04). More patients discontinued olanzapine due to greater weight gain (average of 0.9 kilogr greater increases in glycosylated hemoglobin, total cholesterol, and triglycerides (Lieberman et al, 2005).

4.6.F Risperidone

Chronic schizophrenia

Psychotic disorder

4.6.F.1 Chronic schizophrenia

a) When newer antipsychotic medications (olanzapine, quetiapine, risperidone, and ziprasidone) were comp generation antipsychotic, perphenazine, the majority of patients in each group discontinued their antipsychoti before 18 months. Patients (n=1493) with chronic schizophrenia were randomized to receive olanzapine 7.5 t (mg/day), perphenazine 8 to 32 mg/day, quetiapine 200 to 800 mg/day, risperidone 1.5 to 6.0 mg/day, or zipr mg/day for up to 19 months. Overall, 74% of patients discontinued treatment for any cause before 18 months ranged from 64 to 82%. Time to discontinuation ranged from 3.5 months for ziprasidone to 9.2 months with o discontinuation was significantly longer in the olanzapine group as compared with the quetiapine (hazard rati confidence interval (CI), 0.52 to 0.76; p less than 0.001) or risperidone groups (HR, 0.75; 95% CI, 0.62 to 0.9 discontinuation due to adverse events were similar between all groups, but the rates ranged from 10% for risp olanzapine (p=0.04). More patients discontinued olanzapine due to greater weight gain (average of 0.9 kilogr greater increases in glycosylated hemoglobin, total cholesterol, and triglycerides (Lieberman et al, 2005).

4.6.F.2 Psychotic disorder

a) Quetiapine and risperidone were similarly efficacious in treating psychotic symptoms and had similar over quetiapine treatment resulted in fewer extrapyramidal symptoms (EPS) and was more effective in reducing d month, open-label study, patients with schizophrenia, schizoaffective disorder, or other psychotic disorders (i disorder, major depressive disorder and various forms of dementia) were randomized in a ratio of 3:1 to recei or risperidone (n=175). The starting dosage of quetiapine was 50 milligrams/day (mg/day), which was increas increments every 1 to 2 days, to a maximum of 800 mg/day, given in divided doses. Risperidone was started with upward titration to a target dose of 3 mg twice daily by day 3. Dosages were individually titrated to maxin minimizing adverse reactions (mean prescribed dose: quetiapine 253.9 mg, risperidone 4.4 mg). At the begin approximately half of each group had EPS. There was a steady decline in the number of patients reporting EI the study progressed. The incidence of EPS in the quetiapine group was lower than in the risperidone group 47.3) but not at the end of the study (38.6 vs 39.2). The percentage of patients requiring a change of treatme requiring anti-EPS medication was lower in the quetiapine group than in the risperidone group (7% vs 20.5%) third of patients in each group withdrew before completion of the study. A higher percentage withdrew from ri for lack of efficacy (10.3% vs 5.8%) and a higher percentage withdrew from quetiapine treatment because of vs 5.1%). Somnolence was the most common adverse event in both groups, followed by dry mouth and dizzi occurred significantly more often with quetiapine treatment (p less than 0.05). Occurrence of weight gain was (Mullen et al, 2001).

4.6.G Ziprasidone

4.6.G.1 Chronic schizophrenia

a) When newer antipsychotic medications (olanzapine, quetiapine, risperidone, and ziprasidone) were comp generation antipsychotic, perphenazine, the majority of patients in each group discontinued their antipsychoti before 18 months. Patients (n=1493) with chronic schizophrenia were randomized to receive olanzapine 7.5 t

(mg/day), perphenazine 8 to 32 mg/day, quetiapine 200 to 800 mg/day, risperidone 1.5 to 6.0 mg/day, or zipr
mg/day for up to 19 months. Overall, 74% of patients discontinued treatment for any cause before 18 months
ranged from 64 to 82%. Time to discontinuation ranged from 3.5 months for ziprasidone to 9.2 months with o
discontinuation was significantly longer in the olanzapine group as compared with the quetiapine (hazard rati
confidence interval (CI), 0.52 to 0.76; p less than 0.001) or risperidone groups (HR, 0.75; 95% CI, 0.62 to 0.9
discontinuation due to adverse events were similar between all groups, but the rates ranged from 10% for ris
olanzapine (p=0.04). More patients discontinued olanzapine due to greater weight gain (average of 0.9 kilogr
greater increases in glycosylated hemoglobin, total cholesterol, and triglycerides (Lieberman et al, 2005).

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Last Modified: June 25, 2009

DRUGDEX® Evaluations

DOXEPIN

0.0 Overview

1) Class

a) This drug is a member of the following class(es):

Antianxiety
Antidepressant
Antidepressant, Tricyclic
Antiulcer
Dermatological Agent

2) Dosing Information

a) Doxepin Hydrochloride

1) Adult

a) Alcoholism - Anxiety - Depression

1) very mild, 25 to 50 mg/day ORALLY initially, gradually increase as needed (max, 300 mg/day) (Prod Info SINEQUAN(R) capsule, oral concentrate, 2005)

2) mild to moderate, 75 mg ORALLY per day in single or divided doses, increase as needed; usual range is 75 to 150 mg/day (max, 300 mg/day) (Prod Info SINEQUAN(R) capsule, oral concentrate, 2005)

b) Anxiety - Depression

1) very mild, 25 to 50 mg/day ORALLY initially, gradually increase as needed (max, 300 mg/day) (Prod Info SINEQUAN(R) capsule, oral concentrate, 2005)

2) mild to moderate, 75 mg ORALLY per day in single or divided doses, increase as needed; usual range is 75 to 150 mg/day (max, 300 mg/day) (Prod Info SINEQUAN(R) capsule, oral concentrate, 2005)

c) Anxiety - Depression - Psychoneurotic personality disorder

1) outpatients: 75 mg/day ORALLY (divided into 1-3 doses); may increase up to a MAX of 150 mg/day

2) inpatients: 150 mg/day ORALLY (divided into 1-3 doses); may increase up to a MAX of 300 mg/day

d) Pruritus (Moderate), Due to atopic dermatitis or lichen simplex chronicus

1) 10 mg ORALLY at bedtime; may gradually increase to 25 mg ORALLY at bedtime

2) apply a thin film TOPICALLY to skin 4 times a day (3-4 hr between applications) for a MAX of 8 days

2) Pediatric

a) safety and effectiveness in children below the age of 12 years have not been established

1) Alcoholism - Anxiety - Depression

a) (12 years and older) very mild, 25 to 50 mg/day ORALLY initially, gradually increase as needed (max, 300 mg/day) (Prod Info SINEQUAN(R) capsule, oral concentrate, 2005)

b) (12 years and older) mild to moderate, 75 mg ORALLY per day in single or divided doses, increase as needed; usual range is 75 to 150 mg/day (max, 300 mg/day) (Prod Info SINEQUAN(R) capsule, oral concentrate, 2005)

2) Anxiety - Depression

a) (12 years and older) very mild, 25 to 50 mg/day ORALLY initially, gradually increase as needed (max, 300 mg/day) (Prod Info SINEQUAN(R) capsule, oral concentrate, 2005)

b) (12 years and older) mild to moderate, 75 mg ORALLY per day in single or divided doses, increase as needed; usual range is 75 to 150 mg/day (max, 300 mg/day) (Prod Info SINEQUAN(R) capsule, oral concentrate, 2005)

3) Contraindications

a) Doxepin Hydrochloride

1) glaucoma (Prod Info SINEQUAN(R) oral capsules, 2007)

2) hypersensitivity to doxepin, other dibenzoxepines, or any component of the product (Prod Info SINEQUAN(R) oral capsules, 2007)

3) urinary retention (Prod Info SINEQUAN(R) oral capsules, 2007)

4) Serious Adverse Effects

a) Doxepin Hydrochloride

1) Agranulocytosis
2) Depression, worsening
3) Hypertension
4) Hypotension
5) Leukopenia
6) Pancytopenia
7) Purpuric disorder
8) Suicidal thoughts
9) Suicide
10) Tachyarrhythmia

11) Thrombocytopenia

5) Clinical Applications
a) Doxepin Hydrochloride
1) FDA Approved Indications
a) Alcoholism - Anxiety - Depression
b) Anxiety - Depression
c) Anxiety - Depression - Psychoneurotic personality disorder
d) Pruritus (Moderate), Due to atopic dermatitis or lichen simplex chronicus

1.0 Dosing Information

Drug Properties

Storage and Stability

Adult Dosage

Pediatric Dosage

1.1 Drug Properties

A) Information on specific products and dosage forms can be obtained by referring to the Tradename List (Product Index)
B) Synonyms
Doxepin
Doxepin HCl
Doxepin Hydrochloride
C) Physicochemical Properties
1) Molecular Weight
a) 316 (Prod Info Zonalon, 94)

1.2 Storage and Stability

A) Oral route
1) Preparation and storage of bulk dilutions of the concentrate is not recommended (Prod Info Sinequan(R), 2004).
2) Store capsules at a controlled room temperature of 15 to 30 degrees Celsius (59 to 86 degrees Fahrenheit). Dispense in a tight, light-resistant container with a child-resistant closure (Prod Info Adapin(R), 1995).
3) Store doxepin topical cream at or below 27 degrees C (80 degrees F) (Prod Info Zonalon(R), 2004).

1.3 Adult Dosage

Normal Dosage

Dosage in Renal Failure

Dosage in Hepatic Insufficiency

Dosage in Geriatric Patients

Dosage Adjustment During Dialysis

1.3.1 Normal Dosage

1.3.1.A Doxepin Hydrochloride

Oral route

Rectal route

Topical application route

1.3.1.A.1 Oral route

Anxiety - Depression

Urticaria

1.3.1.A.1.a Anxiety - Depression

1) Dosage ranges of 75 to 150 milligrams daily have been shown effective in anxiety associated with depression (Goldberg & Finnerty, 1972; Smith, 1971); (Goldstein, 1973)(Goldstein & Pinosky, 1969).

2) Doxepin in doses of 200 milligrams daily also have been shown effective and well tolerated in the elderly for anxiety-depression states (Bohlau et al, 1972).

3) Anxiety patients with psychotic symptoms may require higher doses than with neurotic illness (Pinder et al, 1977e).

4) DEPRESSION

a) Dosage must be individualized. Usual dosage range for outpatients is 75 to 150 milligrams daily and for hospitalized patients 150 to 300 milligrams daily (Grof et al, 1974; Bianchi et al, 1971a; Kiev, 1974; Gillmer, 1970). Additional therapeutic benefit is rarely obtained by using more than 300 milligrams/day (Prod Info Sinequan(R), 2004)(Prod Info Adapin(R), 1995a). However, initial and maintenance doses of 500 milligrams daily have been used (Krakowski, 1968).

b) Pulse dosing of doxepin (250 milligrams every 6 days) has not been found to be more effective than conventional dosing (Deuschle et al, 1997).

c) For patients on once-a-day dosing, the maximum recommended dose is 150 milligrams/day, usually given at bedtime (Prod Info Sinequan(R), 2004).

1.3.1.A.1.b Urticaria

1) Doxepin in doses of 10 to 30 milligrams orally daily has been effective in the treatment of IDIOPATHIC COLD URTICARIA (Neittaanmaki et al, 1984a).

2) Doxepin 5 milligrams orally twice daily was reported effective in the treatment of chronic idiopathic URTICARIA in a controlled study (Harto et al, 1985; Ledo et al, 1985).

3) Doxepin 25 milligrams orally three times daily was effective in the treatment of CHRONIC IDIOPATHIC URTICARIA in a placebo-controlled trial involving 16 adult patients (Goldsobel et al, 1986).

1.3.1.A.2 Rectal route

1.3.1.A.2.a Cancer pain; Adjunct

1) Doxepin capsules were administered rectally in four severely debilitated cancer patients with clinical neuropathic pain (Storey & Trumble, 1992). Commercially available capsules without modification were inserted rectally. Serum concentrations of N-desmethyldoxepin after two to five days of treatment with a constant dose of doxepin were 573 micrograms/milliliter and 403 micrograms/milliliter (with 50 milligrams three times daily), 204 micrograms/milliliter (with 50 milligrams twice daily) and less than 25 micrograms/milliliter (with 25 milligrams daily).

1.3.1.A.3 Topical application route

1.3.1.A.3.a Pruritus (Moderate), Due to atopic dermatitis or lichen simplex chronicus

1) Doxepin cream (5%), applied four times a day, with at least 3 to 4 hour intervals between applications, provides effective short-term (up to 8 days) management of moderate pruritus in adults with atopic dermatitis and lichen simplex chronicus (Prod Info Zonalon(R), 2004). Occlusive dressings should not be used with doxepin cream as it may increase dermal absorption.

1.3.1.A.4 MUCOSAL LOCAL

a) ORAL MUCOSAL PAIN

1) Five milliliters of a solution of doxepin 5 milligrams/milliliter, held in the mouth for 5 minutes and spat out, relieved mucosal pain in patients (n=41) with mucosal damage caused by cancer or cancer treatment. Relief lasted for more than 3 hours (Epstein et al, 2001).

1.3.1.A.5 LONG-TERM THERAPY

a) Long-term maintenance therapy with doxepin is safe and effective (Ayd, 1975a). Forty patients (31 to 73 years of age) were treated with doxepin 50 to 300 milligrams daily over a period of 57 to 93 months (total dose 194, 100 to 508, 500 milligrams) for recurrent depression. All patients experienced mood elevation, improved sleep and appetite, and increased energy and interest. Laboratory values revealed no serious toxicity and blood pressure was not significantly affected throughout therapy. Transient tachycardia with doses greater than 200 milligrams daily occurred in several patients and

weight gain in the first 6 months in a few other patients. Otherwise, adverse reactions were minimal.
b) Doxepin therapy has been used continuously for up to 15 years in the treatment of chronic depressive illness, with maintenance of efficacy and a low order of toxicity. Continuous therapy for 5 to 15 years in 52 patients did not reveal any changes in hematologic, renal or hepatic function tests, and the drug was well tolerated in patients with concomitant cardiovascular disorders (Ayd, 1984).

1.3.1.A.6 ONCE DAILY DOSING

a) The major portion or total daily dose of doxepin administered at bedtime is effective and may be of benefit in decreasing the incidence of daytime drowsiness. SINGLE BEDTIME DOSE is also of benefit in patients with mixed anxiety-depression with resultant sleep disturbances (Goldberg et al, 1974; Mendels & Schless, 1975). If the once-a-day schedule is used, the maximum daily dose is 150 milligrams/day (Prod Info Adapin(R), 1995a).

1.3.1.A.7 ORAL CONCENTRATE DILUTION

a) Doxepin oral concentrate should be diluted just prior to administration, with 120 milliliters water, skim milk, whole milk, orange juice, grapefruit juice, tomato juice, prune juice, or pineapple juice (Prod Info Sinequan(R), 2004).
b) Doxepin oral concentrate is not compatible in many carbonated beverages (Prod Info Sinequan(R), 2004).
c) Patients who are on methadone maintenance and require doxepin concentrate can mix the methadone and doxepin together and then dilute the mixture in Gatorade(R), lemonade, orange juice, sugar water, Tang(R), or water. Grape juice should not be used (Prod Info Sinequan(R), 2004).

1.3.1.A.8 WITHDRAWAL SCHEDULE

a) Delirium upon abrupt withdrawal of doxepin has been reported in a single case (Santos and McCurdy, 1980). After 2 weeks of therapy for depression, doxepin was abruptly discontinued because of lack of response and undue sedation. Two days later, the patient exhibited impaired attention, concentration, and short-term memory. He was agitated and moderately diaphoretic. Two days later, an abnormal EEG was recorded. Symptoms disappeared and the EEG returned to normal in 2 weeks. The patient had also been taking disulfiram, which could have contributed to the reaction.
b) Gradual reduction in dosage will prevent development of withdrawal symptoms (Prod Info Adapin (R), 1995a).

1.3.2 Dosage in Renal Failure

A) Doxepin Hydrochloride

1) Based upon the small amount of doxepin excreted unchanged in the urine, no dosage adjustment would appear to be necessary (Bennett et al, 1994a).

1.3.3 Dosage in Hepatic Insufficiency

A) Doxepin Hydrochloride

1) Data for other tricyclic antidepressants suggests the use of doxepin in patients with liver disease may result in increases in the incidence of adverse reactions. Dosage should be reduced and adjusted gradually.

1.3.4 Dosage in Geriatric Patients

A) Doxepin Hydrochloride

1) Caution should be taken when selecting a dosage schedule in an elderly patient. Therapy should be initiated on the low end of the dosing range to account for decreased hepatic, renal, or cardiac function or concomitant diseases/drug regimens that may be present in this patient population (Prod Info Sinequan(R), 2004)(FDA, 2000).
2) Dosage should be individualized with adjustments based upon patient response. Initial dosage should be 25 to 50 milligrams with adjustments made gradually (Pinder et al, 1977e).
3) Clinical guidelines for utilizing antidepressants in the treatment of depression in geriatric patients have been reviewed (Salzman, 1985).

1.3.5 Dosage Adjustment During Dialysis

A) Doxepin Hydrochloride

1) No dosage supplement is required in patients following hemodialysis or peritoneal dialysis (Bennett et al, 1994a).

1.4 Pediatric Dosage

1.4.1 Normal Dosage

1.4.1.A Doxepin Hydrochloride

1.4.1.A.1 Oral route

a) DOXEPIN is not recommended for use in children under 12 years of age (Prod Info Sinequan(R), 2004).

2.0 Pharmacokinetics

Onset and Duration

Drug Concentration Levels

ADME

2.1 Onset and Duration

A) Onset

1) Initial Response

a) Depression, oral: 2 to 3 weeks (Gilman et al, 1985b).

1) DOXEPIN may have an onset sooner than other tricyclic antidepressants (Barranco et al, 1979).

b) Anxiety, oral: 5 to 6 days (Pereira & Lipke, 1970)(DuBois, 1969).

2.2 Drug Concentration Levels

A) Therapeutic Drug Concentration

1) Depression, greater than 100 ng/mL (parent compound with active metabolite, desmethyldoxepin) (Amsterdam et al, 1980).

a) Other studies have found no correlation between serum concentration and therapeutic response (Ward et al, 1982; Brunswick et al, 1983; Norman et al, 1980).

b) Therapeutic response has been associated with 20 ng/mL or above of the active metabolite desmethyldoxepin (Pinder et al, 1977b).

B) Time to Peak Concentration

1) Oral: 30 minutes to 1 hour (Pinder et al, 1977b).

2) TOPICAL: 1.32 hours (Drake et al, 1999).

a) Time to peak concentration was 1.32 hours with a maximum concentration of 0.41 mcg/L in 12 subjects with pruritic atopic dermatitis who applied topical DOXEPIN 4 times daily every 4 hours for 7 days (Drake et al, 1999).

2.3 ADME

Absorption

Distribution

Metabolism

Excretion

Elimination Half-life

Extracorporeal Elimination

2.3.1 Absorption

A) Bioavailability

1) Oral: well-absorbed (Pinder et al, 1977b).

2) Topical, percutaneous absorption may occur (Prod Info Zonalon(R), 1999).

a) Plasma DOXEPIN concentrations ranged from undetectable to 46 ng/mL in 19 eczema patients using topical doxepin (Prod Info Zonalon(R), 1999).

2.3.2 Distribution

A) Distribution Sites

1) Protein Binding

a) 79% to 84% (Virtanen et al, 1982)

2) OTHER DISTRIBUTION SITES

a) Tissues, initially high in the liver, kidney, spleen and lung. Large amounts of the active metabolite (desmethyldoxepin) also found in tissues (Hobbs, 1969).

B) Distribution Kinetics

1) Volume of Distribution

a) 9 to 33 L/kg (Bennett et al, 1994).

2.3.3 Metabolism

A) Metabolism Sites and Kinetics
1) LIVER
a) DOXEPIN undergoes hepatic metabolism to the active metabolite desmethyldoxepin (Prod Info Zonalon(R), 1999).
B) Metabolites
1) Desmethyldoxepin, active (Pinder et al, 1977b).
2) Doxepin-N-oxide, hydroxydoxepin and hydroxydoxepin glucuronide (Hobbs, 1969).

2.3.4 Excretion
A) Kidney
1) Renal Excretion (%)
a) 0.5% (Kimura, 1972a).
B) Other
1) OTHER EXCRETION
a) Bile, small amounts (Kimura, 1972).

2.3.5 Elimination Half-life
A) Parent Compound
1) ELIMINATION HALF-LIFE
a) 16.8 hours (range: 8 to 25 hours) (Bennett et al, 1994; Faulkner et al, 1983; Amsterdam et al, 1980).
B) Metabolites
1) Desmethyldoxepin, 51.3 hours (range: 33.2 to 80.7 hours) (Amsterdam et al, 1980).
a) Desmethyldoxepin half-life ranges from 28 to 52 hours (Prod Info Zonalon(R), 1999).

2.3.6 Extracorporeal Elimination
A) Hemodialysis
1) Dialyzable: No (Anderson et al, 1976).
a) Only 7.6% of DOXEPIN and 13.9% of desmethyldoxepin is extracted by hemodialysis (Faulkner et al, 1984).
B) Peritoneal
1) Dialyzable: No (Anderson et al, 1976).

3.0 Cautions

Contraindications

Precautions

Adverse Reactions

Teratogenicity/Effects in Pregnancy/Breastfeeding

Drug Interactions

3.0.A Black Box WARNING
1) Doxepin Hydrochloride
a) Oral (Capsule; Solution)
Suicidality and Antidepressant Drugs
Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of doxepin hydrochloride or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Doxepin hydrochloride is not approved for use in pediatric patients (Prod Info SINEQUAN(R) oral capsules, 2007).

3.1 Contraindications
A) Doxepin Hydrochloride
1) glaucoma (Prod Info SINEQUAN(R) oral capsules, 2007)
2) hypersensitivity to doxepin, other dibenzoxepines, or any component of the product (Prod Info SINEQUAN(R)

oral capsules, 2007)
3) urinary retention (Prod Info SINEQUAN(R) oral capsules, 2007)

3.2 Precautions

A) Doxepin Hydrochloride

1) suicidal ideation and behavior or worsening depression; increased risk, particularly in children, adolescents, and young adults during the first few months of therapy or following changes in dosage (Prod Info SINEQUAN(R) oral capsules, 2007)
2) alcohol, excessive use; increased danger of intentional or unintentional doxepin overdose (Prod Info SINEQUAN(R) oral capsules, 2007)
3) bipolar disorder; increased risk of precipitation of a mixed/manic episode(Prod Info SINEQUAN(R) oral capsules, 2007)
4) concomitant use of monoamine oxidase inhibitors (MAOIs) or use of doxepin within 14 days of MAOI discontinuation (Prod Info SINEQUAN(R) oral capsules, 2007)
5) elderly; increased risk of confusion and oversedation (Prod Info SINEQUAN(R) oral capsules, 2007)

3.3 Adverse Reactions

Cardiovascular Effects

Dermatologic Effects

Endocrine/Metabolic Effects

Gastrointestinal Effects

Hematologic Effects

Hepatic Effects

Immunologic Effects

Musculoskeletal Effects

Neurologic Effects

Ophthalmic Effects

Otic Effects

Psychiatric Effects

Renal Effects

Reproductive Effects

Other

3.3.1 Cardiovascular Effects

3.3.1.A Doxepin Hydrochloride

Abnormal ECG

Cardiovascular finding

Hypotension

3.3.1.A.1 Abnormal ECG

a) ELECTROCARDIOGRAPHIC CHANGES have been reported with doxepin and manifest as INCREASED PR INTERVAL and PROLONGATION OF QRS COMPLEX. Some studies suggest doxepin has a relatively lesser influence on intracardiac conduction than other tricyclic antidepressants (Pinder et al, 1977f).

b) Available evidence does not support the contention that DOXEPIN is the antidepressant of choice for the treatment of depression in cardiac patients or the elderly. The incidence of toxicity of the drug in therapeutic and toxic doses appears to be similar to that of other tricyclic antidepressants. In therapeutic doses, doxepin is capable of producing prolongations of the PR, QRS, and QTc intervals, ST-T changes, sinus tachycardia, bundle branch block, arrhythmias, orthostatic hypotension, and rarely congestive heart failure. Additionally, in higher doses (overdose), the drug is capable of producing second or third degree AV block, atrial or ventricular arrhythmias, supine hypotension, and decreases in myocardial contractility (Marshall & Forker, 1982ah). However, therapeutic doses of doxepin in healthy adult patients are generally free of clinically important adverse cardiovascular effects, except for orthostatic hypotension (Mahapatra et al, 1986; Cassem, 1982; Glassman, 1984; Glassman & Bigger, 1981). Patients at highest risk are those with preexisting bundle branch block; these patients are at greater risk of developing potentially serious conduction abnormalities during tricyclic antidepressant therapy as compared to patients with normal pretreatment EKG's (Roose et al, 1987; Glassman & Bigger, 1981).

c) Tricyclic antidepressants are thought to resemble quinidine with respect to certain effects on cardiac rhythm (Glassman, 1984; Glassman & Bigger, 1981). Doxepin may be associated with the improvement of ventricular arrhythmias when used in the treatment of depression in some patients. The efficacy of doxepin as an antiarrhythmic agent was studied in 10 cardiac patients with symptoms of frequent ventricular premature depolarizations in a dose-ranging study. Suppression of ventricular premature depolarizations (equal to or greater than 80%) was observed in 4 patients (40%) with doxepin administration; 4 of 8 patients with pairs arrhythmia and 4 of 6 with ventricular tachycardia had 90% or greater suppression. Mean maximal doxepin doses were 115 mg daily, with mean nadir total doxepin concentrations being 61 ng/mL (mean nadir total desmethyldoxepin concentrations, 51 ng/mL). Increases in heart rate and PR, QRS and QTc intervals were also observed. No significant change in resting mean left ventricular ejection fraction was observed with doxepin, even in patients with moderate to severely diminished left ventricular performance. However, sedation and other side effects (dry mouth, weight gain, light-headedness, constipation, hypotension) limited dose ranging in this study, precluding complete evaluation of the antiarrhythmic efficacy of doxepin (Giardina et al, 1987a). More studies are required in larger patient populations, possibly using lower doses, to more fully evaluate antiarrhythmic effects of doxepin.

3.3.1.A.2 Cardiovascular finding

a) According to one study, the use of higher-dose tricyclic antidepressants (TCAs) was associated with an increased risk of SUDDEN CARDIAC DEATH, while lower doses did not increase this risk. In a cohort study including 481,744 persons and 1487 cases of sudden cardiac death occurring in a community setting, researchers found that compared to non-use, the current use of TCAs was associated with a dose-related increase in the risk of sudden cardiac death. For doses lower than 100 milligrams (mg) (amitriptyline or its equivalent), the rate ratio was 0.97 (95% CI, 0.72 to 1.29), however this increased to 2.53 (95% CI, 1.04 to 6.12) for doses of 300 mg or more (p=0.03, test for dose-response). In the entire cohort, users of TCAs in doses of 100 mg or higher (amitriptyline or its equivalent) had a 41% increased rate of sudden cardiac death (rate ratio, 1.41; 95% CI, 1.02 to 1.95). However, TCAs taken in doses of less than 100 mg (amitriptyline or its equivalent) were not associated with an increased risk of sudden cardiac death in the entire cohort or in any subgroups, including persons with treated cardiovascular disease. Use of selective serotonin reuptake inhibitors was not associated with an increased risk of sudden cardiac death (rate ratio, 0.95; 95% CI, 0.42 to 2.15) (Ray et al, 2004).

b) A systematic study of the cardiovascular effects of doxepin was conducted in depressed patients with preexisting cardiovascular disease. Doxepin had little effect on heart rate and did not adversely affect left ventricular function, but did have a significant antiarrhythmic effect, slowed cardiac conduction, and caused a significant increase in orthostatic hypotension. Five (16%) of the 32 patients dropped out of the study due to cardiovascular effects. The authors concluded that doxepin provided no more cardiovascular safety than imipramine or nortriptyline (Roose et al, 1991).

c) In a comparison of the cardiovascular effects of maprotiline (75 to 225 mg/day) with doxepin (50 to 200 mg/day) in 49 elderly depressed patients, there were no significant differences in orthostatic hypotension. Maprotiline caused fewer premature ventricular contractions (PVCs) and a longer PRS interval. Both drugs had a small but significant effect on heart rate and PR interval (Ahles et al, 1984).

d) VENTRICULAR ARRHYTHMIAS associated with doxepin and amitriptyline occurred in a 57-year-old man with preexisting heart disease. The patient was treated with a total doxepin dose of 250 mg/day, and after discontinuation of the cardiac medications, he developed a quadrigeminy pattern of ventricular premature depolarizations (VPDs) without atrioventricular or intraventricular conduction defects. Upon discontinuation of doxepin, progressive decrease of the VPDs were seen. Subsequent challenge with amitriptyline again resulted in VPDs which also ceased upon discontinuation of the drug. For this

patient, doxepin had no advantage over amitriptyline in terms of relative cardiotoxicity. A significant correlation was found between the occurrence of premature ventricular depolarization and serum levels of both antidepressants (Todd & Faber, 1983).
e) Since an overdose of tricyclic antidepressants has been associated with cardiotoxicity, it has been assumed that tricyclic antidepressants should not be used in cardiac patients. This theory has been evaluated in a double-blind, randomized trial involving 24 depressed patients with heart disease treated with imipramine, doxepin, or placebo for 4 weeks (Veith et al, 1982). Many patients were also receiving cardiac medications throughout the trial period. Patients were administered imipramine or doxepin 50 milligrams (mg) at bedtime or placebo. Doses were gradually increased every 3 days until side effects or a dose of 150 mg given at bedtime was achieved. After examination revealed that there was no evidence of cardiovascular adverse effects in patients receiving tricyclic antidepressants, dosages were allowed to be increased over 150 mg. Two patients required doses less than 50 mg/day due to severe nausea, ataxia, and sedation. As measured by radionuclide ventriculograms, tricyclic antidepressants had no effect on left ventricular ejection fraction at rest or during maximal exercise. The incidence of premature ventricular contractions was reduced in patients treated with imipramine; however, no consistent change was observed in patients receiving doxepin or placebo. Imipramine- and doxepin-treated patients showed a significant improvement (p less than 0.001) in depression when compared with placebo-treated patients. This study would indicate that in the absence of severe impairment of myocardial performance, depressed patients with preexisting heart disease can be treated effectively with imipramine or doxepin without an adverse effect on ventricular rhythm or hemodynamic function. However, further evaluation of the tricyclics and their effect on cardiovascular function is required.
f) The literature was reviewed to ascertain the validity of suggestions that doxepin caused fewer cardiovascular effects than other antidepressants (Luchins, 1983). After reviewing the studies comparing antidepressant effects on cardiac conduction, cardiac rhythm, heart rate, blood pressure, and mechanical function of the heart, the author concluded that there is little evidence that doxepin has fewer cardiovascular effects than other antidepressants.

3.3.1.A.3 Hypotension

a) Incidence: rare
b) POSTURAL HYPOTENSION and TACHYCARDIA have been reported during doxepin therapy at an incidence of 3% to 4% (Pitts, 1969).

3.3.2 Dermatologic Effects

3.3.2.A Doxepin Hydrochloride

Contact dermatitis

Skin irritation

3.3.2.A.1 Contact dermatitis

a) Severe allergic contact dermatitis was reported in 6 patients after they used doxepin 5% cream for 2 weeks to 7 months (Shelley et al, 1996). Even though dosage recommendations limit its use to 8 days, many patients use it for a much longer period. Angioedema-like swelling, photodermatitis, and generalized weeping dermatitis were some of the reactions described. All patients were patch tested to rule out a reaction to the vehicle ingredients in the cream. The authors suggest that doxepin's histamine blocking activity may augment cell-mediated hypersensitivity.
b) A 40-year-old man developed vesicular eczema on his arms and legs within 2 weeks of initiation of DOXEPIN 5% cream for pruritic epidermolysis bullosa pruriginosa. The eczema cleared after withdrawal of doxepin. He had not previously used the oral form of this drug (Wakelin & Rycroft, 1999).

3.3.2.A.2 Skin irritation

a) The manufacturer reports that 23% of patients treated with doxepin 5% cream experienced stinging and/or burning at the site of application. Although mild in most instances, 25% of the patients who experienced this reaction categorized it as severe (Prod Info Zonalon(R), 2004).

3.3.3 Endocrine/Metabolic Effects

3.3.3.A Doxepin Hydrochloride

Body temperature above normal

Endocrine finding

Syndrome of inappropriate antidiuretic hormone secretion

Weight gain

3.3.3.A.1 Body temperature above normal

a) Drug fever associated with antidepressant use was reported in a 47-year-old woman with a history of major depression who was treated with a variety of antidepressants including doxepin, amitriptyline, trazodone, imipramine, maprotiline, and fluoxetine. Each time the remission of depression coincided with a low-grade fever, malaise, and sore throat. Upon discontinuation of the drug, the symptoms resolved and depression reappeared. The authors postulated this may be due to the action of serotonin on thermoregulation and this was a particularly sensitive individual to this mechanism (Zajecka et al, 1991).

b) A NEUROLEPTIC MALIGNANT SYNDROME (NMS)-like condition occurred with the use of lithium and doxepin in a 64-year-old male with a history of depression with psychotic features. Previously, he had been successfully treated with lithium and haloperidol or electroconvulsive therapy (ECT); he was then treated with lithium 300 mg twice a day and doxepin 100 mg at bedtime for recurrent depression. In two weeks, he began having periods of confusion and disorientation and in another two weeks was admitted for urinary retention. His symptoms worsened after discontinuing the lithium and doxepin with gradual improvement shown on days 5 to 8. He demonstrated classic NMS symptoms in the absence of neuroleptic exposure (fever, muscle rigidity, changes in levels of consciousness, autonomic dysfunction). He later showed improvement with ECT (Rosenberg & Pearlman, 1991).

3.3.3.A.2 Endocrine finding

a) Changes in libido, GYNECOMASTIA, GALACTORRHEA, changes in blood sugar levels, and weight gain have also been reported with doxepin (Prod Info Adapin(R), 1995).

3.3.3.A.3 Syndrome of inappropriate antidiuretic hormone secretion

a) SIADH-induced hyponatremia has been reported rarely with tricyclic antidepressant use.

3.3.3.A.4 Weight gain

a) Weight gain has occurred during doxepin therapy (Forsen, 1975).

3.3.4 Gastrointestinal Effects

3.3.4.A Doxepin Hydrochloride

Dental caries

Disorder of taste

Gastroesophageal reflux disease

Gastrointestinal tract finding

Increased appetite

Stomatitis

3.3.4.A.1 Dental caries

a) Doxepin has moderate anticholinergic properties which may lead to decreased salivation resulting in the development of dental caries (Kastrup, 1987; Winer & Bahn, 1967).

3.3.4.A.2 Disorder of taste

a) Decreased taste sensitivity has been reported with doxepin use.

3.3.4.A.3 Gastroesophageal reflux disease

a) Gastroesophageal reflux has been reported rarely with tricyclic antidepressant use.

3.3.4.A.4 Gastrointestinal tract finding

a) NAUSEA and sometimes VOMITING has been associated with doxepin (Sterlin, 1970)(Pinder et al, 1977f).

b) DRY MOUTH has been reported to occur in up to 15% of patients treated with doxepin (Pinder et al,

1977f).
c) CONSTIPATION has been reported to occur in approximately 4% of patients receiving therapeutic doses of doxepin (Pinder et al, 1977f).

3.3.4.A.5 Increased appetite
a) An increased appetite and craving for sweets was reported in geriatric outpatients receiving doxepin and other antidepressants for depressive disorders or other psychiatric illnesses. Of 93 patients, 34% were taking doxepin (average daily dose 119 mg) and this group showed the highest positive relationship to excessive appetite, craving for sweets, and weight gain (Stein et al, 1985).

3.3.4.A.6 Stomatitis
a) A 34-year-old depressed, asthmatic patient was placed on doxepin (50 mg at bedtime) and suffered severe anticholinergic effects manifested as dry mouth, blurred vision, and constipation. During the second week of therapy, the dose was increased to 100 mg at bedtime and 5 days later the patient developed stomatitis. The symptoms completely resolved 4 days after discontinuation of doxepin (Salem et al, 1981).
b) Approximately 7 days after beginning ampicillin and doxepin 25 mg three times/day plus 100 mg at bedtime, a 48-year-old female developed painful papular lesions on the dorsal surface of her tongue. The lesions resolved over a 3-week period following discontinuation of both medications. Because doxepin was relieving her depression, she began 25 mg three times/day and 50 mg at bedtime for a second time. Eight days later, generalized pain and erythema of the tongue developed and subsided over a 2-week period following doxepin discontinuation (Ives & Stewart, 1980).

3.3.5 Hematologic Effects

3.3.5.A Doxepin Hydrochloride

Hematology finding

Thrombocytopenia

3.3.5.A.1 Hematology finding
a) Isolated cases of ANEMIA, LEUKOPENIA, LYMPHOPENIA, AGRANULOCYTOSIS, and NEUTROPHILIA have occurred during doxepin therapy (Prod Info Adapin(R), 1995; Swanson & Cook, 1977).
b) Surveying the literature, the hematological effects of doxepin (Sinequan(R)) seem infrequent and limited to rare cases of transient neutrophilia (Voina et al, 1971)(Glick, 1973). Only one case of thrombocytopenia has been attributed to doxepin, within our knowledge (Nixon, 1972). A 73-year-old female was given 75 mg/day for depression, prior to admission into a hospital. Initiation of symptoms occurred 6 days afterwards with bone marrow aspirations revealing megakaryocytic hyperplasia. The author did not rule out other concurrent antidepressants administered, such as amitriptyline, not the rapid discontinuation of prednisone therapy for bleeding diathesis, as the possible cause. However, the time relationship between doxepin dosing and subsequent adverse effects and doxepin structural similarity to amitriptyline, which is known to cause blood dyscrasias, did not rule out its chance as the source.
c) Coombs-positive HEMOLYTIC ANEMIA and thrombocytopenia with acute renal failure occurred after a patient received doxepin for approximately 5 weeks (50 to 100 mg orally daily). The patient recovered following withdrawal of doxepin, exchange transfusion, and repeated hemodialysis. Doxepin was the only medication taken by the patient (Wolf et al, 1989).
d) Four patients who were receiving tricyclic antidepressants developed severe unexpected postsurgical bleeding and loss of local anesthetic effect after undergoing nasal surgery. The authors suggested that this resulted from vasodilation resulting from chronic tricyclic antidepressant administration leading to increased blood supply as well as enhanced removal of cocaine from its site of action (Schechter et al, 1982).

3.3.5.A.2 Thrombocytopenia
a) Incidence: rare
b) Thrombocytopenia has been reported secondary to doxepin (Nixon, 1972). A 73-year-old female received doxepin 75 mg daily over a period of 6 days for severe depressive reaction. On the sixth day of therapy, the patient developed SUBCONJUNCTIVAL HEMORRHAGES, generalized oozing from the mouth, and showers of PETECHIAE over the extremities and trunk. Lab data at this time revealed platelet count 1200/cubic mm, prothrombin time 15/13 seconds, and normal PTT and Lee white clotting time. Immunoelectrophoresis was normal. Bone marrow aspirations revealed MEGAKARYOCYTIC-HYPERPLASIA with many young megakaryocytes and decreased iron stores. Doxepin was discontinued and the patient was treated with prednisone 60 mg daily. The platelet count increased to

103,000/cubic mm within 3 days. Prednisone dose was tapered and the patient was started on imipramine. This had no effect on platelet count and was ineffective in the treatment of her depression. Amitriptyline was started resulting in the development of thrombocytopenia which was unresponsive to prednisone. Amitriptyline was discontinued and the platelet count returned to normal.

3.3.6 Hepatic Effects

3.3.6.A Doxepin Hydrochloride

3.3.6.A.1 Hepatotoxicity

a) A previously well, 50-year-old man, experienced 3 separate episodes of acute hepatitis one week after taking small doses of doxepin (25 to 50 mg). Due to the patient's complete recovery between doxepin doses, the absence of other possible causes for recurrent hepatitis, and the temporal relationship between doxepin dose and icteric symptoms, a causal relationship was assumed (Keegan, 1993).

b) Liver function tests have been reported as abnormal in several studies with doxepin (Pinder et al, 1977f).

3.3.7 Immunologic Effects

3.3.7.A Doxepin Hydrochloride

3.3.7.A.1 Cross sensitivity reaction

a) Two patients developed a skin rash during therapy with desipramine (Norpramin(R)) and amitriptyline (Elavil(R)). Discontinuation of these medications in each patient resulted in subsidence of the skin rash. Doxepin was substituted in the patient receiving desipramine and imipramine was substituted in the patient receiving amitriptyline. On both occasions, recurrence of the rash did not occur. These data would suggest that substitution of a structurally dissimilar antidepressant agent is a viable alternative in patients developing allergic skin reactions (Salem et al, 1982).

b) In a double-blind, single dose, noncrossover study, 33 healthy adult volunteers (32 males, 1 female) received a single 25-mg dose of oral desipramine or doxepin. The duration of H1-receptor blockade by these two tricyclic antidepressants, doxepin (the most potent antihistamine) and desipramine (the least potent) were compared. Results showed significant differences in the suppression of the weal-and-flare responses to histamine between the two drugs (Rao et al, 1988a). Desipramine suppressed the wheal for 2 days and flare for one day, whereas doxepin suppressed the wheal for 4 days and flare for 6 days. These results suggest that doxepin should be withheld for at least 7 days before allergy skin testing.

3.3.8 Musculoskeletal Effects

3.3.8.A Doxepin Hydrochloride

Fracture of bone, Nonvertebral

Hip fracture

3.3.8.A.1 Fracture of bone, Nonvertebral

a) In a prospective, population-based, cohort study (n=7983) with a mean follow-up of 8.4 years, there was an increased risk of nonvertebral fracture in adult participants older than 55 years of age (mean age of 77.5 years) who were currently using an tricyclic antidepressant (TCA), including amitriptyline, clomipramine, dosulepine, doxepine, imipramine, maprotiline, nortriptyline, and opipramol, compared to those who were not exposed to antidepressants. Current TCA use was associated with an increased risk of nonvertebral fracture (hazard ratio (HR), 1.6; 95% confidence interval (CI), 1.08 to 2.38) compared with no antidepressant use. Current TCA use was also associated with an increased risk of nonvertebral fracture (HR, 1.6; 95% CI, 1.02 to 2.5) compared with past antidepressant use (n=1217). Duration of TCA use of greater than 6 months was not associated with an increased risk of fractures when compared with no antidepressant use and with past antidepressant use. Fractures of the hip (most frequent), wrist, humerus, and pelvis were reported (Ziere et al, 2008).

3.3.8.A.2 Hip fracture

a) An increased incidence of hip fracture was reported in elderly patients receiving psychotropic agents. This study was a case-control evaluation of 1021 patients with hip fractures and 5606 controls. An increased risk of hip fracture was observed with the use of hypnotic/anxiolytic agents with a long elimination half-life (greater than 24 hours), tricyclic antidepressants, and antipsychotic agents. Current users were defined as subjects who had received a prescription in the 30-day period prior to the admission date for initial hospitalization. The long half-life hypnotic/anxiolytic agents studied were

lorazepam, diazepam, chlordiazepoxide, and barbiturates (excluding phenobarbital). The tricyclic antidepressants included amitriptyline, doxepin, and imipramine; antipsychotic agents evaluated were thioridazine, haloperidol, chlorpromazine, and perphenazine-amitriptyline. In contrast, shorter-acting hypnotic-anxiolytic agents (half-life of 24 hours or less) were not associated with an increased risk of hip fracture in these patients. The most frequently used agents in this category were diphenhydramine, hydroxyzine, and chloral hydrate. The increased risk of hip fracture observed in this study was directly related to the doses of the drugs. Analysis for confounding by dementia did not alter the results. Additional studies are needed to confirm these results in this and other populations and to evaluate the effects of other psychotropic drugs that have less pronounced sedative effects (Ray et al, 1987).

3.3.9 Neurologic Effects

Doxepin

Doxepin Hydrochloride

3.3.9.A Doxepin

3.3.9.A.1 Seizure

See Drug Consult reference: COMPARATIVE INCIDENCE OF SEIZURES FROM ANTIDEPRESSANTS

3.3.9.B Doxepin Hydrochloride

Central nervous system finding

Extrapyramidal sign

Myoclonus

Seizure

Tardive dyskinesia

3.3.9.B.1 Central nervous system finding

a) DROWSINESS is the most frequently reported side effect of doxepin and appears to be dose related (Sterlin et al, 1970; Toru et al, 1972a; Goldstein & Pinosky, 1969). Even topically applied doxepin cream (5%) has caused drowsiness in greater than 20% of patients who used it, particularly when applied to greater than 10% of total body surface area (Prod Info Zonalon(R), 2004).
b) Euphoria does not appear to occur with doxepin therapy and there are no cases of PHYSICAL DEPENDENCE associated with the drug (Pinder et al, 1977f).
c) In a case report, topical administration of doxepin 5% cream resulted in altered mental status in a 5-year-old female. Due to a generalized eczematous rash over approximately 50% of the body surface, the patient was prescribed doxepin 5% cream to alleviate itching. Over the course of 24 hours, 30 grams of cream was applied to the rash and the following day the patient was difficult to arouse and responded only to noxious stimuli. Physical examination revealed 3 millimeter bilaterally active pupils, a temperature of 37.2 degrees Celsius, blood pressure of 102/62, sinus tachycardia (heart rate = 120 beats per minute), and a respiratory rate of 24 breaths per minute. Serum concentrations of doxepin and desmethyldoxepin (major active metabolite) were 11.95 nanograms per milliliter (ng/mL) and 17.71 ng/mL, respectively. Eighteen hours following skin decontamination with soap and water, a full recovery was made and the patient was discharged (Zell-Kanter et al, 2000).
d) Confusion, dizziness disorientation, headache, fatigue, weakness, numbness, paresthesias, and ataxia have also been reported with doxepin (Prod Info Adapin(R), 1995).

3.3.9.B.2 Extrapyramidal sign

a) Extrapyramidal side effects including TREMOR, AKATHISIA and GAIT DISTURBANCES have been reported (Pinder et al, 1977f).
b) Extrapyramidal symptoms were seen in 109 of 1116 patients receiving doxepin less than 75 mg to greater than 300 mg daily for periods of 4 to 52 weeks (Pitts, 1969).
c) A dystonic reaction occurred in a 30-year-old female who had been on antidepressant (amitriptyline 100 mg at bedtime) therapy for 3 years before discontinuing for a pregnancy. After giving birth, she took a 75-mg dose for insomnia and immediately developed dystonic symptoms. Treatment with doxepin

was started and titrated up to 300 mg at bedtime. After the third 300-mg dose, she had another dystonic reaction. Later she took a single 150-mg dose for insomnia with another reaction. All symptoms resolved within 24 hours after discontinuing the medication (Lee, 1988).

3.3.9.B.3 Myoclonus

a) A high incidence of myoclonus during cyclic antidepressant therapy was reported with imipramine, desipramine, amitriptyline, doxepin, trazodone, nortriptyline, and maprotiline (Garvey & Tollefson, 1987). Ninety-eight patients with major depression (93) or panic disorder were treated with these agents in initial doses of 50 mg daily of imipramine or its equivalent increasing to a maximum of 300 mg daily after several weeks. Of these patients, 39 (40%) developed myoclonus that was clinically significant in 9 (9%) and resulted in withdrawal of the antidepressant or a medication change. Myoclonus occurred within 1 month of therapy in 81% of the 39 patients, with 46% of patients developing myoclonus within 2 weeks. The mean dose of antidepressant being administered at the time of myoclonus was 169 mg daily in imipramine equivalents, which was similar to the mean dose utilized by the patients not developing myoclonus (164 mg daily). Myoclonus was reversible upon withdrawal of the antidepressant but persisted if medication changes were not initiated; however, spontaneous remission of myoclonus was observed in 9 patients. No predictors for the development of myoclonus were observed.

3.3.9.B.4 Seizure

a) A retrospective review of 47 patients treated with doxepin for anxious or agitated depression revealed a seizure disorder in 19 patients. In these 19 patients, 15 exhibited improved seizure control during therapy with doxepin, while 2 exhibited no change and 2 exhibited decreased control. The authors concluded that doxepin reduced seizure frequency, and postulated 1 or a combination of 3 mechanisms: a direct antiepileptic effect; an indirect effect caused by improved affective state; or, a drug interaction with other anticonvulsants (Ojemann et al, 1983).

b) Seizures are a potential complication of doxepin overdosage, but the clinical data is quite limited with few case reports. In depressed patients, doxepin produces EEG changes that are similar to other tricyclic antidepressants (Pinder et al, 1977f).

3.3.9.B.5 Tardive dyskinesia

a) A prevalence study of tardive dyskinesia (TD) in the course of antidepressant therapy was conducted in 50 patients (Yassa et al, 1987). Of the 23 patients treated with doxepin, 2 men receiving doxepin 100 milligrams daily developed TD. The first was a 74-year-old man suffering from a major depressive disorder. He developed marked buccolingual chewing, lip smacking, and choreoathetoid movements of the body and extremities forty-five days after the start of antidepressant therapy. Seven months after the onset of TD the patient still had occasional lip smacking. The second man who developed TD was 64 years old. He had been started on doxepin 75 milligrams and increased to 100 milligrams daily after one month. Two days after the increase, chewing movements and lateral tongue movements of moderate intensity were noted without any signs of extrapyramidal symptoms. These movements persisted three months later despite a decrease in his dose to 50 milligrams daily.

3.3.10 Ophthalmic Effects

3.3.10.A Doxepin Hydrochloride

3.3.10.A.1 Eye / vision finding

a) BLURRED VISION is an autonomic (anticholinergic) side effect and has been reported to occur in approximately 3% of patients receiving therapeutic doses of doxepin (Pinder et al, 1977f).

b) OCULOGYRIC CRISIS has been reported following the use of doxepin 300 milligrams (Lee, 1988).

3.3.11 Otic Effects

3.3.11.A Doxepin Hydrochloride

3.3.11.A.1 Ototoxicity

a) Tinnitus has been reported during treatment of depression with doxepin in therapeutic doses in a 66-year-old female. The tinnitus recurred upon rechallenge (Golden et al, 1983).

3.3.12 Psychiatric Effects

3.3.12.A Doxepin Hydrochloride

Aggressive behavior

Suicidal thoughts

3.3.12.A.1 Aggressive behavior

a) Aggressiveness has been reported rarely with tricyclic antidepressant use.

3.3.12.A.2 Suicidal thoughts

a) Adult and pediatric patients being treated with antidepressants for major depressive disorder who experience symptoms of anxiety, agitation, panic attacks, insomnia, irritability, hostility (aggressiveness), impulsivity, akathisia (psychomotor restlessness), hypomania, or mania may be at risk of suicidal ideation and behavior (SUICIDALITY). This same concern applies to treating patients with other psychiatric and nonpsychiatric disorders. If these symptoms are observed, therapy should be reevaluated and it may be necessary to discontinue medications when symptoms are severe, sudden in onset, or were not part of the patient's initial symptoms. Patients and their caregivers should be provided with the Medication Guide that is available for this drug (Anon, 2004).

b) A causal role for antidepressants in inducing suicidality has been established in pediatric patients. Anyone considering the use of antidepressants in a child or adolescent must balance this risk with the clinical need. In pooled analyses of 24 short-term, placebo-controlled trials of nine antidepressants (citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, bupropion, mirtazapine, nefazodone, and venlafaxine extended-release) including over 4400 pediatric patients with major depressive disorder, obsessive compulsive disorder, or other psychiatric disorders, a greater risk of suicidal behavior or ideation during the first few months of therapy was demonstrated in patients receiving antidepressants as compared with placebo (4% vs 2%, respectively). The risk of suicidality was most consistently observed in the trials that included patients with major depressive disorder, but there were signs of risk emerging from trials in other psychiatric indications, such as obsessive compulsive disorder and social anxiety disorder. No suicides occurred in these trials. The risk of suicidality during longer-term use (ie, beyond several months) in pediatric patients is not known. It is also unknown whether this risk extends to adult patients (Anon, 2004).

3.3.13 Renal Effects

3.3.13.A Doxepin Hydrochloride

Nephrotoxicity

Urinary incontinence

3.3.13.A.1 Nephrotoxicity

a) Coombs-positive hemolytic anemia and thrombocytopenia with acute renal failure occurred in a patient who received doxepin for approximately 5 weeks (50 to 100 mg orally daily). The patient recovered following withdrawal of doxepin, exchange transfusion, and repeated hemodialysis. Doxepin was the only medication taken by the patient (Wolf et al, 1989).

3.3.13.A.2 Urinary incontinence

a) Urinary incontinence was described as a side effect of doxepin. An elderly patient received 25 mg doxepin four times a day over a period of 1 year for depression. The patient began voiding every hour and continued to have frequent urinary tract infections. In addition, he commonly had an itching rash which appeared on the thighs and buttocks. The rash did not respond to soothing lotions and doxepin was discontinued resulting in continuation of rash and disappearance of incontinence (Kimbrough, 1972).

3.3.14 Reproductive Effects

3.3.14.A Doxepin Hydrochloride

Priapism

Sexual dysfunction

3.3.14.A.1 Priapism

a) One case of priapism is reported in a patient receiving doxepin 20 mg at bedtime. Symptoms of testicular swelling and tingling resolved upon discontinuation (Mitchell & Popkin, 1983).

3.3.14.A.2 Sexual dysfunction

a) EJACULATORY DYSFUNCTION has been reported in patients taking doxepin, which resolves on

discontinuation. Decreased libido has also been reported (Mitchell & Popkin, 1983).
b) Improved sexual functioning has been noted in depressed patients with sexual dysfunction after 4 weeks of doxepin therapy in a mean dose of 122.2 mg (Renshaw, 1975).

3.3.16 Other

3.3.16.A Doxepin Hydrochloride

Adverse reaction to drug, General

Drug tolerance - finding

3.3.16.A.1 Adverse reaction to drug, General

a) Doxepin therapy has been used continuously for up to 15 years in the treatment of chronic depressive illness, with maintenance of efficacy and a low order of toxicity. Continuous therapy for 5 to 15 years in 52 patients did not reveal any changes in hematologic, renal or hepatic function tests, and the drug was well tolerated in patients with concomitant cardiovascular disorders (Ayd, 1984).

3.3.16.A.2 Drug tolerance - finding

a) Oral doxepin has not been shown to produce physical tolerance or psychological dependence (Prod Info Sinequan(R), 2004).

3.4 Teratogenicity/Effects in Pregnancy/Breastfeeding

A) Teratogenicity/Effects in Pregnancy

1) U.S. Food and Drug Administration's Pregnancy Category: Category B (Prod Info Zonalon(R) cream, 1997) (All Trimesters)

a) Either animal-reproduction studies have not demonstrated a fetal risk but there are no controlled studies in pregnant women or animal-reproduction studies have shown adverse effect (other than a decrease in fertility) that was not confirmed in controlled studies in women in the first trimester (and there is no evidence of a risk in later trimesters).

2) Australian Drug Evaluation Committee's (ADEC) Category: C (Batagol, 1996)

a) Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible. Accompanying texts should be consulted for further details.

See Drug Consult reference: PREGNANCY RISK CATEGORIES

3) Crosses Placenta: Unknown

4) Clinical Management

a) Due to reported teratogenic effects with other tricyclic antidepressants, use of doxepin during pregnancy should be avoided if possible, especially during the first trimester. The dangers of failure to treat major depression, however, are obvious, and in each case these dangers must be weighed against the potential for teratogenic effects.

5) Literature Reports

a) Based on data collected through the Motherisk Program for a very small number of patients, there appear to be no differences in cognitive function, temperament and general behavior in children exposed to doxepin throughout gestation as compared to controls (Nulman et al, 2002). However, among infants who were exposed to either fluoxetine or tricyclic antidepressants thoughout gestation, those born to mothers with uncontrolled depressive symptoms showed lower cognitive and language achievements than those born to mothers who were well-controlled (Nulman et al, 2002).

b) Poor sucking and swallowing, muscle hypotonia, drowsiness, vomiting, and jaundice occurred in a neonate whose mother used doxepin in her third trimester and during the postpartum period. The doxepin dose had been 75 mg/day, but was tapered in the last weeks of pregnancy and was 35 mg/day at parturition (Frey et al, 1999).

B) Breastfeeding

1) American Academy of Pediatrics Rating: Drugs for which the effect on nursing infants is unknown but may be of concern. (Anon, 2001)

2) Thomson Lactation Rating: Infant risk has been demonstrated.

a) Evidence and/or expert consensus has demonstrated harmful infant effects when used during breastfeeding. An alternative to this drug should be prescribed or patients should be advised to discontinue breastfeeding.

3) Clinical Management

a) Both doxepin and its active metabolite have been found in breast milk, and the active metabolite has been found in infant serum at a concentration similar to therapeutic concentrations in adults. Sedation and respiratory depression has been reported in a breastfeeding infant (Matheson et al, 1985), therefore breastfeeding is not recommended during maternal doxepin therapy. Alternatively, available data suggest that clomipramine is a safer agent for use during breastfeeding, and clomipramine is considered compatible

with breastfeeding by the American Academy of Pediatrics.

4) Literature Reports

a) Doxepin and desmethyldoxepin levels were measured in the milk of a mother being treated with doxepin 150 mg daily for major depressive disorder (Kemp et al, 1985). The milk to plasma ratio averaged 1.46 for both doxepin and desmethyldoxepin. With an average maternal serum level of 46 mcg/L for doxepin and 90 mcg/L for desmethyldoxepin, a nursing infant would consume a dose of 237 mcg in 1.2 L of milk per day.

b) Respiratory depression occurred in an 8-week-old breastfed girl whose mother was receiving doxepin 25 mg TID. In the infant's serum, the level of doxepin was almost undetectable (3 mcg/mL); therefore, the respiratory depression was attributed to the high concentrations of N-desmethyldoxepin (58 and 66 mcg/mL) which were similar to the levels in the mother (Matheson et al, 1985). After discontinuing breastfeeding, the infant's respiration normalized within 24 hours.

c) Poor sucking and swallowing, muscle hypotonia, drowsiness, vomiting, and jaundice occurred in a neonate whose mother used doxepin in her third trimester and during the postpartum period. The doxepin dose had been 75 mg/day, but was tapered in the last weeks of pregnancy and was 35 mg/day at parturition. The amount of doxepin and desmethyldoxepin (active metabolite) ingested by the nursing infant was estimated at 10 to 20 mcg/kg/day (2.5% of the weight-adjusted dose of the mother) (Frey et al, 1999a).

5) Drug Levels in Breastmilk

a) Parent Drug

1) Milk to Maternal Plasma Ratio

a) 1.08-1.66 (Kemp et al, 1985)

b) Active Metabolites

1) DESMETHYLDOXEPIN (Bennett, 1996)

a) Milk to Maternal Plasma Ratio

1) 1.02-1.53 (Kemp et al, 1985)

3.5 Drug Interactions

Drug-Drug Combinations

Drug-Food Combinations

3.5.1 Drug-Drug Combinations

Acecainide

Acenocoumarol

Ajmaline

Amiodarone

Amisulpride

Amobarbital

Amphetamine

Amprenavir

Anisindione

Aprobarbital

Arbutamine

Arformoterol

Arsenic Trioxide

Astemizole

Atomoxetine

Azimilide

Baclofen

Belladonna

Belladonna Alkaloids

Bepridil

Bethanidine

Bretylium

Butabarbital

Butalbital

Cannabis

Carbamazepine

Chloroquine

Chlorotrianisene

Cimetidine

Cisapride

Clarithromycin

Clonidine

Clorgyline

Conjugated Estrogens

Dexfenfluramine

Dexmethylphenidate

Dextroamphetamine

Dicumarol

Dienestrol

Diethylpropion

Diethylstilbestrol

Disopyramide

Dofetilide

Dolasetron

Droperidol

Duloxetine

Enflurane

Epinephrine

Erythromycin

Esterified Estrogens

Estradiol

Estriol

Estrone

Estropipate

Eterobarb

Ethinyl Estradiol

Etilefrine

Fenfluramine

Fluconazole

Fluoxetine

Formoterol

Fosamprenavir

Foscarnet

Fosphenytoin

Gatifloxacin

Gemifloxacin

Grepafloxacin

Guanadrel

Guanethidine

Halofantrine

Haloperidol

Halothane

Heptabarbital

Hexobarbital

Hydroquinidine

Ibutilide

Iproniazid

Isocarboxazid

Isoflurane

Isradipine

Levomethadyl

Linezolid

Lisdexamfetamine

Mazindol

Mephentermine

Mephobarbital

Mesoridazine

Mestranol

Methamphetamine

Methohexital

Methoxamine

Methylphenidate

Midodrine

Moclobemide

Moxifloxacin

Nefopam

Nialamide

Norepinephrine

Octreotide

Oxilofrine

Pargyline

Paroxetine

Pemoline

Pentamidine

Pentobarbital

Phendimetrazine

Phenelzine

Phenindione

Phenmetrazine

Phenobarbital

Phenprocoumon

Phentermine

Phenylephrine

Phenytoin

Pimozide

Pirmenol

Prajmaline

Primidone

Procainamide

Procarbazine

Prochlorperazine

Propafenone

Propoxyphene

Propylhexedrine

Quetiapine

Quinestrol

Quinidine

Quinidine

Rasagiline

Risperidone

S-Adenosylmethionine

Salmeterol

Secobarbital

Selegiline

Sematilide

Sertindole

Sertraline

Sotalol

Sparfloxacin

Spiramycin

St John's Wort

Sulfamethoxazole

Sultopride

Tapentadol

Tedisamil

Telithromycin

Terfenadine

Thiopental

Thioridazine

Tibolone

Toloxatone

Tramadol

Tranylcypromine

Trifluoperazine

Trimethoprim

Vasopressin

Venlafaxine

Warfarin

Ziprasidone

Zolmitriptan

Zotepine

3.5.1.A Acecainide

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Cases of QTc prolongation and/or torsades de pointes have been reported with all Class III antiarrhythmic agents, including acecainide (Chow et al, 1984), amiodarone (Faggiano et al, 1996), azimilide (Corey et al, 1999), bretylium (Gilman et al, 1985a), ibutilide (Rodriguez et al, 2001), sematilide (Singh, 1996), dofetilide (Allen et al, 2002), and sotalol (Marill & Runge, 2001). Even though no formal drug interaction studies have been done, the coadministration of Class III antiarrhythmics and other drugs known to prolong the QTc interval, including tricyclic antidepressants, is not recommended (Yamreudeewong et al, 2003a; Prod Info Corvert(R), 2000).
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of a Class III antiarrhythmic and a tricyclic antidepressant (TCA) is not recommended.
7) Probable Mechanism: additive QT prolongation
8) Literature Reports
a) EKG effects reported in patients receiving therapeutic doses of tricyclic antidepressants include increased heart rate, prolonged PR interval, intraventricular conduction delays, increased corrected QT interval (QTc) and flattened T waves (Marshall & Forker, 1982y).
b) Concurrent use of Class III antiarrhythmic agents, and other drugs that can prolong the QT interval, such as tricyclic antidepressants, is not recommended. Dofetilide should be stopped for at least 2 days before any interacting drug is initiated. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised (Yamreudeewong et al, 2003).

3.5.1.B Acenocoumarol

1) Interaction Effect: increased risk of bleeding
2) Summary: Tricyclic antidepressants (TCAs) may increase the half-life and bioavailability of oral anticoagulants (Vesell et al, 1970i; Williams et al, 1976i). Considerable interindividual differences may be found (Pond et al, 1975i).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: In patients receiving tricyclic antidepressants and oral anticoagulant therapy, the prothrombin time ratio or INR (international normalized ratio) should be closely monitored with the addition and withdrawal of the antidepressant, and should be periodically reassessed during concurrent therapy. Achieving a stable drug regimen which produces the desired level of anticoagulation may be difficult in patients on this combination, and frequent adjustments of the anticoagulant dose may be required.
7) Probable Mechanism: decreased acenocoumarol metabolism; increased acenocoumarol absorption
8) Literature Reports
a) In a study of healthy volunteers, the concurrent use of nortriptyline or amitriptyline resulted in an increase of dicumarol levels and an increase in the plasma half-life of dicumarol, although the effect was not consistent in all subjects (Pond et al, 1975h). This effect was not observed with warfarin.
b) A single oral dose of bishydroxycoumarin after 8 days of nortriptyline resulted in a significantly prolonged half-life and decreased volume of distribution of the coumarin anticoagulant in 6 healthy volunteers (Vesell et al, 1970h). The mechanism of action was suggested to be reduced bishydroxycoumarin metabolism and/or altered coumarin absorption.

c) Drug dosing was studied in 16 patients on long-term anticoagulant therapy who used concurrent TCAs (Williams et al, 1976h). TCAs affected the stability of anticoagulant control leading to frequent changes in the doses of anticoagulants. Inhibition of coumarin metabolism was the postulated mechanism.

3.5.1.C Ajmaline

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Class Ia antiarrhythmics and tricyclic antidepressants have been shown to prolong the QTc interval at the recommended therapeutic dose. Even though no formal drug interaction studies have been done, the coadministration of Class Ia antiarrhythmics and other drugs known to prolong the QTc interval, including tricyclic antidepressants, is not recommended (Prod Info Elavil(R), 1999g; Prod Info Quinaglute(R), 1999; Marshall & Forker, 1982m).

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: The concurrent administration of a Class IA antiarrhythmic agent and a tricyclic antidepressant is not recommended.

7) Probable Mechanism: additive cardiac effects

8) Literature Reports

a) Quinidine is an inhibitor of the cytochrome P450 isoenzyme responsible for the 2-hydroxylation of imipramine and desipramine (Brosen & Gram, 1989). Inhibition of this enzyme system can result in a 35% decrease in imipramine clearance and 85% decrease in desipramine clearance. Demethylation of imipramine by the cytochrome P450 system is unaffected by this interaction. Until more information is available all patients having quinidine added to drug regimen containing imipramine or desipramine should be monitored for increased antidepressant serum concentrations and potential toxicity.

b) An increased incidence in sudden death was observed in six out of 53 patients with cardiac disease receiving amitriptyline, compared to 0 out of 53 in the control group. It was recommended that amitriptyline be avoided in patients with underlying cardiac disease except when depression was debilitating and no other drugs were helpful (Moir et al, 1972; Coull et al, 1970).

c) In a placebo controlled study, imipramine 3.5 mg/kg was administered daily for seven patients with severe depression and titrated doses to obtain therapeutic plasma concentrations. Two patients displayed premature atrial depolarizations and premature ventricular depolarizations before therapy. On patient had 33 premature atrial depolarizations (PAD) and 30 premature ventricular depolarizations (PVD) per hour, which decreased to 0.4 PAC and zero PVC per hour on imipramine. The other patient had 12 PAD and 169 PVD per hour before treatment and 1.8 PAD and 28.1 PVD per hour on imipramine. The authors also cautioned that the incidence of cardiotoxicity may increase if tricyclic antidepressants are administered with Type I antiarrhythmics. It was also recommended that quinidine and procainamide not be used to treat the arrhythmias of a tricyclic overdose. The similarities between these agents may exacerbate the cardiotoxicity (Kantor et al, 1978).

3.5.1.D Amiodarone

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Cases of QTc prolongation and/or torsades de pointes have been reported with all Class III antiarrhythmic agents, including acecainide (Chow et al, 1984), amiodarone (Faggiano et al, 1996), azimilide (Corey et al, 1999), bretylium (Gilman et al, 1985a), ibutilide (Rodriguez et al, 2001), sematilide (Singh, 1996), dofetilide (Allen et al, 2002), and sotalol (Marill & Runge, 2001). Even though no formal drug interaction studies have been done, the coadministration of Class III antiarrhythmics and other drugs known to prolong the QTc interval, including tricyclic antidepressants, is not recommended (Yamreudeewong et al, 2003a; Prod Info Corvert(R), 2000).

3) Severity: major

4) Onset: rapid

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of a Class III antiarrhythmic and a tricyclic antidepressant (TCA) is not recommended.

7) Probable Mechanism: additive QT prolongation

8) Literature Reports

a) EKG effects reported in patients receiving therapeutic doses of tricyclic antidepressants include increased heart rate, prolonged PR interval, intraventricular conduction delays, increased corrected QT interval (QTc) and flattened T waves (Marshall & Forker, 1982y).

b) Concurrent use of Class III antiarrhythmic agents, and other drugs that can prolong the QT interval, such as tricyclic antidepressants, is not recommended. Dofetilide should be stopped for at least 2 days before any interacting drug is initiated. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised (Yamreudeewong et al, 2003).

3.5.1.E Amisulpride

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac

arrest)
2) Summary: Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999), haloperidol (O'Brien et al, 1999), risperidone (Duenas-Laita et al, 1999), sertindole (Agelink et al, 2001), quetiapine (Owens, 2001b), sultopride (Lande et al, 1992), and zotepine (Sweetman, 2003). Even though no formal drug interaction studies have been done, the coadministration of a tricyclic antidepressant and an antipsychotic is not recommended (Prod Info Pamelor(R), 2001; Marshall & Forker, 1982p).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of a tricyclic antidepressant and an antipsychotic is not recommended.
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) Electrocardiographic changes that have occurred during clinical trials with pimozide have included prolongation of the corrected QT interval, flattening, notching, and inversion of the T wave and the appearance of U waves. In experimental studies, sudden, unexpected deaths have occurred while patients were receiving pimozide doses of 1 mg/kg. The proposed mechanism for these deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmias (Prod Info Orap(R), 1999).

3.5.1.F Amobarbital
1) Interaction Effect: possible decreased tricyclic antidepressant serum concentrations and possible additive adverse effects
2) Summary: Concomitant barbiturate and tricyclic antidepressant (TCA) therapy may result in increased metabolism of the TCA. There have been scattered reports of individuals with decreased serum levels of TCAs in the presence of a barbiturate (Moody et al, 1977; Silverman & Braithwaite, 1972; Burrows & Davies, 1971). In addition, TCAs can worsen seizure control by reducing the seizure threshold (Brodie, 1992). These drugs also have additive CNS and respiratory depressant effects.
3) Severity: minor
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor for efficacy of antidepressant effect. Increases in tricyclic antidepressant dosages may be required. Additionally, monitor for toxicity when either drug is added to or withdrawn from therapy. Serum concentrations may be of value in determining appropriate dosage.
7) Probable Mechanism: increased tricyclic antidepressant metabolism
8) Literature Reports
a) The pharmacokinetics of a single oral dose of desipramine (100 mg) were studied in eight epileptic patients chronically treated with phenobarbital and in eight drug-free healthy controls (Spina et al, 1996). All subjects were extensive metabolizers with respect to the genetically determined CYP2D6-related metabolic polymorphism. Compared with controls, epileptic patients exhibited lower peak plasma desipramine concentrations (74 nmol/L vs. 107 nmol/L), smaller desipramine area under the concentration-time curve values (1943 nmol/L/h vs. 3234 nmol/L/h), and shorter desipramine elimination half-lives (15.1 h vs. 20.6 h). All barbiturates are believed to have similar effects leading to induction of hepatic enzymes and the 2D6 isozyme is believed to be important in the metabolism of most or all TCAs. Thus, similar effects should be expected with any combination of TCA and barbiturate.

3.5.1.G Amphetamine
1) Interaction Effect: hypertension, other cardiac effects, and CNS stimulation
2) Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been reported to result in enhanced amphetamine effects from the release of norepinephrine (Beaumont, 1973d; Raisfeld, 1972). A similar reaction might also occur with all drugs that have amphetamine-like effects. Acute elevations in blood pressure have been noted (Flemenbaum, 1971a). Some amphetamine-like drugs may inhibit the metabolism of TCAs, although most combinations have not been studied. When amphetamine analogs are being used to treat obesity, it should be noted that TCAs frequently lead to moderate weight gain (Russ & Ackerman, 1988). False positive urine tests for amphetamines have been reported during therapy with some TCAs (Merigian & Browning, 1993). Caution is advised when concurrent administration of amphetamine-like agents and TCAs is warranted. The patient should be closely monitored for increased cardiovascular effects (hypertension and dysrhythmias).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other sympathomimetic agents could lead to hypertension, increased cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006; Flemenbaum, 1972). Use caution if such therapy is warranted. Monitor the patient closely for hypertension and dysrhythmias.
7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission

8) Literature Reports

a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agents. Additionally, coadministration of d-amphetamine with TCAs such as desipramine or protriptyline results in sustained increases in d-amphetamine concentration in the brain (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006).

b) Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism of some tricyclic antidepressants, such as imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transdermal system, 2006).

c) Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases in blood pressure such that the hypotensive effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of combined therapy. Discontinuation of the methylphenidate usually results in the blood pressure returning to normotensive levels; reinstitution of the methylphenidate resulted in further blood pressure elevation (Flemenbaum, 1971; Flemenbaum, 1972).

d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine given for at least four weeks, were given fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical improvement. However, fenfluramine more than doubled steady-state plasma levels of desipramine (Price et al, 1990).

e) There have been claims based on uncontrolled studies that a better antidepressant response may occur with combined therapy (Garrettson et al, 1969). However, a systemic review of stimulants in the treatment of depression concluded that although uncontrolled studies were generally positive, the ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated little advantage of drug over placebo and did not appear to be as effective as the conventional antidepressants in primary depression (Satel & Nelson, 1989).

3.5.1.H Amprenavir

1) Interaction Effect: increased tricyclic serum concentrations and potential toxicity (anticholinergic effects, sedation, confusion, cardiac arrhythmias)

2) Summary: Coadministered amprenavir may increase serum concentrations of tricyclic antidepressants, causing a potential risk of arrhythmias or other serious adverse effects. Currently no interaction study has been conducted. Amprenavir is metabolized by cytochrome P450 3A4 enzymes in addition to being a CYP3A4 inhibitor, and tricyclics may partially depend on this pathway for metabolism. Plasma concentrations of the tricyclic should be closely monitored and dose adjustments made accordingly in patients also receiving amprenavir (Prod Info Agenerase(R), 2000).

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: If concomitant therapy with amprenavir and a tricyclic antidepressant is unavoidable, plasma concentrations of the tricyclic should be closely monitored and dose adjustments made accordingly. Also monitor patients for signs and symptoms of tricyclic toxicity (anticholinergic effects, sedation, confusion, cardiac arrhythmias).

7) Probable Mechanism: inhibition of cytochrome P450-mediated tricyclic metabolism

3.5.1.I Anisindione

1) Interaction Effect: increased risk of bleeding

2) Summary: Tricyclic antidepressants (TCAs) may increase the half-life and bioavailability of oral anticoagulants (Vesell et al, 1970c; Williams et al, 1976c). Considerable interindividual differences may be found (Pond et al, 1975c).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: In patients receiving tricyclic antidepressants and oral anticoagulant therapy, the prothrombin time ratio or INR (international normalized ratio) should be closely monitored with the addition and withdrawal of the antidepressant, and should be periodically reassessed during concurrent therapy. Achieving a stable drug regimen which produces the desired level of anticoagulation may be difficult in patients on this combination, and frequent adjustments of the anticoagulant dose may be required.

7) Probable Mechanism: decreased anisindione metabolism; increased anisindione absorption

8) Literature Reports

a) In a study of healthy volunteers, the concurrent use of nortriptyline or amitriptyline resulted in an increase of dicumarol levels and an increase in the plasma half-life of dicumarol, although the effect was not consistent in all subjects (Pond et al, 1975b). This effect was not observed with warfarin.

b) A single oral dose of bishydroxycoumarin after 8 days of nortriptyline resulted in a significantly prolonged half-life and decreased volume of distribution of the coumarin anticoagulant in 6 healthy volunteers (Vesell et al, 1970b). The mechanism of action was suggested to be reduced bishydroxycoumarin metabolism and/or altered coumarin absorption.

c) Drug dosing was studied in 16 patients on long-term anticoagulant therapy who used concurrent TCAs (Williams et al, 1976b). TCAs affected the stability of anticoagulant control leading to frequent changes in the doses of anticoagulants. Inhibition of coumarin metabolism was the postulated

mechanism.

3.5.1.J Aprobarbital

1) Interaction Effect: possible decreased tricyclic antidepressant serum concentrations and possible additive adverse effects

2) Summary: Concomitant barbiturate and tricyclic antidepressant (TCA) therapy may result in increased metabolism of the TCA. There have been scattered reports of individuals with decreased serum levels of TCAs in the presence of a barbiturate (Moody et al, 1977; Silverman & Braithwaite, 1972; Burrows & Davies, 1971). In addition, TCAs can worsen seizure control by reducing the seizure threshold (Brodie, 1992). These drugs also have additive CNS and respiratory depressant effects.

3) Severity: minor

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Monitor for efficacy of antidepressant effect. Increases in tricyclic antidepressant dosages may be required. Additionally, monitor for toxicity when either drug is added to or withdrawn from therapy. Serum concentrations may be of value in determining appropriate dosage.

7) Probable Mechanism: increased tricyclic antidepressant metabolism

8) Literature Reports

a) The pharmacokinetics of a single oral dose of desipramine (100 mg) were studied in eight epileptic patients chronically treated with phenobarbital and in eight drug-free healthy controls (Spina et al, 1996). All subjects were extensive metabolizers with respect to the genetically determined CYP2D6-related metabolic polymorphism. Compared with controls, epileptic patients exhibited lower peak plasma desipramine concentrations (74 nmol/L vs. 107 nmol/L), smaller desipramine area under the concentration-time curve values (1943 nmol/L/h vs. 3234 nmol/L/h), and shorter desipramine elimination half-lives (15.1 h vs. 20.6 h). All barbiturates are believed to have similar effects leading to induction of hepatic enzymes and the 2D6 isozyme is believed to be important in the metabolism of most or all TCAs. Thus, similar effects should be expected with any combination of TCA and barbiturate.

3.5.1.K Arbutamine

1) Interaction Effect: unreliable arbutamine test results

2) Summary: Because tricyclic antidepressants may affect heart rate, arbutamine should not be administered to a patient receiving a tricyclic antidepressant, since arbutamine test results may be unreliable (Prod Info GenESA(R), 1997).

3) Severity: moderate

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: Arbutamine should not be administered to a patient receiving tricyclic antidepressant therapy.

7) Probable Mechanism: alteration of heart rate by the tricyclic antidepressant

3.5.1.L Arformoterol

1) Interaction Effect: an increased risk of cardiovascular excitation

2) Summary: Concurrent administration of arformoterol with a tricyclic antidepressant (TCA) may lead to potentiation of arformoterol's adrenergic effects on the cardiovascular system. Therefore, extreme caution is advised if arformoterol is administered to patients who are being treated with a TCA (Prod Info BROVANA (TM) inhalation solution, 2006). Monitor patients closely for adverse cardiovascular effects.

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Extreme caution and close observation for adverse cardiovascular effects are warranted when arformoterol is administered concurrently with a tricyclic antidepressant (TCA) as the cardiovascular effects of arformoterol can be potentiated by TCAs (Prod Info BROVANA(TM) inhalation solution, 2006).

7) Probable Mechanism: potentiation of cardiovascular effects

3.5.1.M Arsenic Trioxide

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Any drug known to have the potential to prolong the QT interval should not be used with arsenic trioxide. Possible pharmacodynamic interactions can occur between arsenic trioxide and potentially arrhythmogenic agents such as tricyclic antidepressants that prolong the QT interval (Prod Info Trisenox(R), 2000a). Even though no formal drug interaction studies have been done, the coadministration of arsenic trioxide and other drugs known to prolong the QTc interval, including tricyclic antidepressants, is not recommended (Prod Info Elavil(R), 1999k; Marshall & Forker, 1982af).

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of arsenic trioxide and other drugs that may prolong

the QTc interval, such as tricyclic antidepressants is not recommended.
7) Probable Mechanism: additive effects on QT prolongation
8) Literature Reports
a) An increased incidence in sudden death was observed in six out of 53 patients with cardiac disease receiving amitriptyline, compared to zero out of 53 in the control group using a hospital based information system. The authors recommended that amitriptyline not be used in patients with underlying cardiac disease except when depression was debilitating and no other drugs were helpful (Moir et al, 1972a; Coull et al, 1970a).
b) QT/QTc prolongation should be expected during treatment with arsenic trioxide and torsade de pointes as well as complete heart block has been reported. Over 460 ECG tracings from 40 patients with refractory or relapsed APL treated with arsenic trioxide were evaluated for QTc prolongation. Sixteen of 40 patients (40%) had at least one ECG tracing with a QTc interval greater than 500 msec. Prolongation of the QTc was observed between 1 and 5 weeks after arsenic trioxide infusion, and then returned towards baseline by the end of 8 weeks after arsenic trioxide infusion. In these ECG evaluations, women did not experience more pronounced QT prolongation than men, and there was no correlation with age (Prod Info Trisenox(R), 2000).

3.5.1.N Astemizole
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Tricyclic antidepressants have been shown to prolong the QTc interval at the recommended therapeutic dose. Even though no formal drug interaction studies have been done, the coadministration of astemizole and other drugs known to prolong the QTc interval, including tricyclic antidepressants, is not recommended (Prod Info Elavil(R), 1999l; Prod Info Hismanal(R), 1996).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of astemizole and agents that prolong the QT interval, such as tricyclic antidepressants, is not recommended.
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) A comprehensive discussion of the cardiovascular effects of tricyclic antidepressants has been presented (Marshall & Forker, 1982ag). Electrocardiogram effects reported in patients receiving therapeutic doses of tricyclic antidepressants include increased heart rate, prolonged PR interval, intraventricular conduction delays, increased corrected QT interval (QTc) and flattened T waves.

3.5.1.O Atomoxetine
1) Interaction Effect: an increase in atomoxetine steady-state plasma concentrations
2) Summary: Atomoxetine is primarily metabolized by the cytochrome P450 2D6 (CYP 2D6) pathway to 4-hydroxyatomoxetine. In extensive metabolizers, atomoxetine steady-state plasma concentrations are increased with selective inhibitors of CYP2D6, such as doxepin. The exposure is similar to that observed in poor metabolizers. In extensive metabolizers treated with doxepin, the area under the concentration-time curve of atomoxetine is approximately 6- to 8-fold greater, and maximum plasma concentration at steady-state is about 3- to 4-fold greater than atomoxetine alone (Prod Info Strattera(TM), 2002).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Dosage adjustment of atomoxetine may be necessary when coadministered with doxepin.
7) Probable Mechanism: inhibition of cytochrome P450 2D6-mediated metabolism of atomoxetine by doxepin

3.5.1.P Azimilide
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Cases of QTc prolongation and/or torsades de pointes have been reported with all Class III antiarrhythmic agents, including acecainide (Chow et al, 1984), amiodarone (Faggiano et al, 1996), azimilide (Corey et al, 1999), bretylium (Gilman et al, 1985a), ibutilide (Rodriguez et al, 2001), sematilide (Singh, 1996), dofetilide (Allen et al, 2002), and sotalol (Marill & Runge, 2001). Even though no formal drug interaction studies have been done, the coadministration of Class III antiarrhythmics and other drugs known to prolong the QTc interval, including tricyclic antidepressants, is not recommended (Yamreudeewong et al, 2003a; Prod Info Corvert(R), 2000).
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of a Class III antiarrhythmic and a tricyclic antidepressant (TCA) is not recommended.
7) Probable Mechanism: additive QT prolongation

8) Literature Reports

a) EKG effects reported in patients receiving therapeutic doses of tricyclic antidepressants include increased heart rate, prolonged PR interval, intraventricular conduction delays, increased corrected QT interval (QTc) and flattened T waves (Marshall & Forker, 1982y).

b) Concurrent use of Class III antiarrhythmic agents, and other drugs that can prolong the QT interval, such as tricyclic antidepressants, is not recommended. Dofetilide should be stopped for at least 2 days before any interacting drug is initiated. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised (Yamreudeewong et al, 2003).

3.5.1.Q Baclofen

1) Interaction Effect: memory loss, loss of muscle tone

2) Summary: Baclofen when administered with antidepressants, specifically imipramine, amitriptyline, and clomipramine, has induced short term memory loss (Sandyk & Gillman, 1985a). In addition, concomitant imipramine and baclofen may result in additive muscle relaxant effects (Silverglat, 1981a).

3) Severity: minor

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Due to the additive effects of both drugs, monitor for excess anticholinergic activity and muscle relaxant effects with concomitant therapy.

7) Probable Mechanism: unknown

8) Literature Reports

a) Baclofen when administered with antidepressants, specifically imipramine, amitriptyline, and clomipramine, has induced short-term memory loss in three patients. Specifically, the patients could not remember names of persons or places familiar to them. The interaction is believed to be caused by baclofen enhancing the anticholinergic effects of antidepressants, which may be partially reversed by piracetam (Sandyk & Gillman, 1985).

b) Concomitant imipramine and baclofen therapy has been reported to result in an additive muscle relaxant effect. A 54-year-old male with a 12-year history of multiple sclerosis and a two-year history of depression was maintained on baclofen 10 mg four times daily. The patient experienced good relief of spasticity with this regimen and maintained sufficient muscle tone to stand. Nortriptyline 50 mg nightly was added to relieve depression. On the sixth day of therapy, the patient was no longer able to stand. Nortriptyline was withdrawn and muscle tone returned within 48 hours. Two weeks later, imipramine 75 mg daily was given to the patient for treatment of depression, however, the patient again experienced loss of muscle tone. Muscle tone returned within two days of imipramine discontinuation. The additive effect between baclofen and the tricyclic antidepressants is attributed to an interaction affecting the neurotransmitters at the presynaptic membrane (Silverglat, 1981).

3.5.1.R Belladonna

1) Interaction Effect: excessive anticholinergic activity (severe dry mouth, constipation, decreased urination, excessive sedation, blurred vision)

2) Summary: The anticholinergic activity of the active alkaloids present in belladonna may predispose the patient to excessive anticholinergic activity if taken with tricyclic antidepressants. Belladonna contains L-hyoscyamine, atropine, and scopolamine with a total alkaloid content of at least 0.3% in the leaves and 0.5% in the roots (Blumenthal et al, 1998). Because belladonna is typically available as a homeopathic preparation, the clinical severity of the interaction with tricyclic antidepressants is unknown. Caution is advised.

3) Severity: minor

4) Onset: rapid

5) Substantiation: theoretical

6) Clinical Management: Excessive anticholinergic activity may be manifested by dry mouth, constipation, urinary retention, tachycardia, decreased sweating, mydriasis, blurred vision, elevated temperature, muscular weakness, and sedation. If such effects are noted, belladonna should be discontinued immediately. In severe cases, paralytic ileus, confusion, psychoses, agitation, delusions, delirium, and paranoia may be encountered as well as tachycardia, dysrhythmia, and hypertension. In severe cases, immediate medical attention should be obtained.

7) Probable Mechanism: additive anticholinergic effect

3.5.1.S Belladonna Alkaloids

1) Interaction Effect: excessive anticholinergic activity (severe dry mouth, constipation, decreased urination, excessive sedation, blurred vision)

2) Summary: The anticholinergic activity of the active alkaloids present in belladonna may predispose the patient to excessive anticholinergic activity if taken with tricyclic antidepressants. Belladonna contains L-hyoscyamine, atropine, and scopolamine with a total alkaloid content of at least 0.3% in the leaves and 0.5% in the roots (Blumenthal et al, 1998). Because belladonna is typically available as a homeopathic preparation, the clinical severity of the interaction with tricyclic antidepressants is unknown. Caution is advised.

3) Severity: minor

4) Onset: rapid

5) Substantiation: theoretical
6) Clinical Management: Excessive anticholinergic activity may be manifested by dry mouth, constipation, urinary retention, tachycardia, decreased sweating, mydriasis, blurred vision, elevated temperature, muscular weakness, and sedation. If such effects are noted, belladonna should be discontinued immediately. In severe cases, paralytic ileus, confusion, psychoses, agitation, delusions, delirium, and paranoia may be encountered as well as tachycardia, dysrhythmia, and hypertension. In severe cases, immediate medical attention should be obtained.
7) Probable Mechanism: additive anticholinergic effect

3.5.1.T Bepridil

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: In US clinical trials, the QT and QTc intervals were commonly prolonged by bepridil in a dose-related fashion (Prod Info Vascor(R), 2000). Tricyclic antidepressants (TCAs) have been shown to prolong the QTc interval at the recommended therapeutic dose (Marshall & Forker, 1982t).
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Concurrent use of bepridil and other drugs which may prolong the QTc interval, including tricyclic antidepressants, is contraindicated.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.U Bethanidine

1) Interaction Effect: decreased antihypertensive effectiveness
2) Summary: Tricyclic antidepressants inhibit the uptake of bethanidine at its site of action in the adrenergic neuron. The antagonism may last for several days after discontinuation of the antidepressant. The interaction with doxepin is dose related (Oates et al, 1969; Fann et al, 1971); doxepin in doses less than 150 mg daily may be used with bethanidine, but the antidepressant effect may be insufficient at such a low dose (Skinner et al, 1969a; Avery, 1973; Feagin et al, 1969).
3) Severity: moderate
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: The combination of bethanidine and doxepin, as well as other tricyclic antidepressant agents, should be avoided. An alternative antihypertensive should be considered.
7) Probable Mechanism: decreased uptake of bethanidine into adrenergic neurons
8) Literature Reports
a) Adequate control of hypertension was reported in only two of eight adult hypertensive patients who received bethanidine or debrisoquine concurrently with a tricyclic antidepressant. In 24 control patients given the same drugs without antidepressants, blood pressure control was achieved in 18. Withdrawal of hypotension that necessitated a reduction in dosage of bethanidine or debrisoquine (Skinner et al, 1969).

3.5.1.V Bretylium

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Cases of QTc prolongation and/or torsades de pointes have been reported with all Class III antiarrhythmic agents, including acecainide (Chow et al, 1984), amiodarone (Faggiano et al, 1996), azimilide (Corey et al, 1999), bretylium (Gilman et al, 1985a), ibutilide (Rodriguez et al, 2001), sematilide (Singh, 1996), dofetilide (Allen et al, 2002), and sotalol (Marill & Runge, 2001). Even though no formal drug interaction studies have been done, the coadministration of Class III antiarrhythmics and other drugs known to prolong the QTc interval, including tricyclic antidepressants, is not recommended (Yamreudeewong et al, 2003a; Prod Info Corvert(R), 2000).
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of a Class III antiarrhythmic and a tricyclic antidepressant (TCA) is not recommended.
7) Probable Mechanism: additive QT prolongation
8) Literature Reports
a) EKG effects reported in patients receiving therapeutic doses of tricyclic antidepressants include increased heart rate, prolonged PR interval, intraventricular conduction delays, increased corrected QT interval (QTc) and flattened T waves (Marshall & Forker, 1982y).
b) Concurrent use of Class III antiarrhythmic agents, and other drugs that can prolong the QT interval, such as tricyclic antidepressants, is not recommended. Dofetilide should be stopped for at least 2 days before any interacting drug is initiated. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised (Yamreudeewong et al, 2003).

3.5.1.W Butabarbital

1) Interaction Effect: possible decreased tricyclic antidepressant serum concentrations and possible additive adverse effects
2) Summary: Concomitant barbiturate and tricyclic antidepressant (TCA) therapy may result in increased metabolism of the TCA. There have been scattered reports of individuals with decreased serum levels of TCAs in the presence of a barbiturate (Moody et al, 1977; Silverman & Braithwaite, 1972; Burrows & Davies, 1971). In addition, TCAs can worsen seizure control by reducing the seizure threshold (Brodie, 1992). These drugs also have additive CNS and respiratory depressant effects.
3) Severity: minor
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor for efficacy of antidepressant effect. Increases in tricyclic antidepressant dosages may be required. Additionally, monitor for toxicity when either drug is added to or withdrawn from therapy. Serum concentrations may be of value in determining appropriate dosage.
7) Probable Mechanism: increased tricyclic antidepressant metabolism
8) Literature Reports
a) The pharmacokinetics of a single oral dose of desipramine (100 mg) were studied in eight epileptic patients chronically treated with phenobarbital and in eight drug-free healthy controls (Spina et al, 1996). All subjects were extensive metabolizers with respect to the genetically determined CYP2D6-related metabolic polymorphism. Compared with controls, epileptic patients exhibited lower peak plasma desipramine concentrations (74 nmol/L vs. 107 nmol/L), smaller desipramine area under the concentration-time curve values (1943 nmol/L/h vs. 3234 nmol/L/h), and shorter desipramine elimination half-lives (15.1 h vs. 20.6 h). All barbiturates are believed to have similar effects leading to induction of hepatic enzymes and the 2D6 isozyme is believed to be important in the metabolism of most or all TCAs. Thus, similar effects should be expected with any combination of TCA and barbiturate.

3.5.1.X Butalbital

1) Interaction Effect: possible decreased tricyclic antidepressant serum concentrations and possible additive adverse effects
2) Summary: Concomitant barbiturate and tricyclic antidepressant (TCA) therapy may result in increased metabolism of the TCA. There have been scattered reports of individuals with decreased serum levels of TCAs in the presence of a barbiturate (Moody et al, 1977; Silverman & Braithwaite, 1972; Burrows & Davies, 1971). In addition, TCAs can worsen seizure control by reducing the seizure threshold (Brodie, 1992). These drugs also have additive CNS and respiratory depressant effects.
3) Severity: minor
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor for efficacy of antidepressant effect. Increases in tricyclic antidepressant dosages may be required. Additionally, monitor for toxicity when either drug is added to or withdrawn from therapy. Serum concentrations may be of value in determining appropriate dosage.
7) Probable Mechanism: increased tricyclic antidepressant metabolism
8) Literature Reports
a) The pharmacokinetics of a single oral dose of desipramine (100 mg) were studied in eight epileptic patients chronically treated with phenobarbital and in eight drug-free healthy controls (Spina et al, 1996). All subjects were extensive metabolizers with respect to the genetically determined CYP2D6-related metabolic polymorphism. Compared with controls, epileptic patients exhibited lower peak plasma desipramine concentrations (74 nmol/L vs. 107 nmol/L), smaller desipramine area under the concentration-time curve values (1943 nmol/L/h vs. 3234 nmol/L/h), and shorter desipramine elimination half-lives (15.1 h vs. 20.6 h). All barbiturates are believed to have similar effects leading to induction of hepatic enzymes and the 2D6 isozyme is believed to be important in the metabolism of most or all TCAs. Thus, similar effects should be expected with any combination of TCA and barbiturate.

3.5.1.Y Cannabis

1) Interaction Effect: tachycardia and delirium
2) Summary: Concomitant tetrahydrocannabinol and tricyclic antidepressant therapy has increased the heart rate and cause delirium beyond that expected with either drug alone (Wilens et al, 1997a; Hillard & Vieweg, 1983a).
3) Severity: moderate
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Caution is advised if patients use cannabis with a tricyclic antidepressant. Monitor heart rate changes closely.
7) Probable Mechanism: possibly due to beta-adrenergic effect of cannabis coupled with the anticholinergic effect of tricyclic antidepressants
8) Literature Reports
a) A 21-year-old female receiving oral nortriptyline 30 milligrams at bedtime for 9 months developed marked sinus tachycardia (160 beats/minute) within 30 minutes of smoking a cannabis cigarette. The patient's heart rate was about 90 beats/minute before smoking the cannabis. She had used cannabis many times before starting the nortriptyline without ill effects (Hillard & Vieweg, 1983).

b) Four cases of tachycardia, cognitive changes, and delirium have been reported in adolescent males treated with tricyclic antidepressants who smoked marijuana. One of the four cases was evaluated by a physician, the others were later accounts of the event. The toxic effects were considered by the reporters to have resulted from a drug interaction because they occurred with lower doses of marijuana than are common in other reports of marijuana toxicity (usually greater than 20 mg). In case 1, a 16-year-old male taking nortriptyline 75 mg/day presented with tachycardia (130 beats/minute), delirium, confusion, and short-term memory loss 30 minutes after smoking one marijuana cigarette. Symptoms resolved spontaneously after 24 hours. In case 2, and 18-year-old male taking desipramine 200 mg/day presented 12 hours after smoking marijuana with symptoms of edginess, severe dry mouth, lightheadedness, confusion, short-term memory impairment, and tachycardia (110 beats/minute). Symptoms resolved within 48 hours. Case 3, a 15-year-old male taking desipramine 150 mg/day and sertraline 50 mg/day, reported mood lability, irritability, and a racing heart after smoking 2 marijuana cigarettes which resolved after 16 hours. Case 4, a 16-year-old male taking desipramine and clonidine reported hallucinations, confusion, mild shortness of breath, and elevated heart rate after smoking marijuana. This was different than the effect he experienced prior to taking desipramine (Wilens et al, 1997).

3.5.1.Z Carbamazepine

1) Interaction Effect: decreased doxepin effectiveness and possibly increased carbamazepine toxicity (diplopia, blurred vision, dizziness, tremor)
2) Summary: The concomitant use of carbamazepine and antidepressants has been reported to decrease doxepin levels (Leinonen et al, 1991a).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor for clinical efficacy of the doxepin therapy and for any signs of toxicity of carbamazepine. Serum levels of both agents should be considered when either agent is added or discontinued, with appropriate dosage adjustments made accordingly.
7) Probable Mechanism: increased doxepin metabolism
8) Literature Reports
a) The effect of carbamazepine on doxepin levels were examined in 17 psychiatric inpatients who were stabilized for a minimum of 7 days prior to measurement of baseline antidepressant concentrations. The average daily doxepin dosage was 201.5 mg. Carbamazepine was added in a mean dose of 593 mg and continued over a 4-week period. Serum doxepin concentrations were decreased to 46% in patients receiving combination therapy compared to patients receiving doxepin alone (Leinonen et al, 1991).

3.5.1.AA Chloroquine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Chloroquine can prolong the QT interval in some patients, which may result in ventricular tachycardia, ventricular fibrillation, and torsades de pointes. Because tricyclic antidepressants may also prolong the QT interval and increase the risk of arrhythmias, the concurrent administration of chloroquine and tricyclic antidepressants is not recommended (Prod Info Aralen(R), 1999; Marshall & Forker, 1982v).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of chloroquine and a tricyclic antidepressant is not recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.AB Chlorotrianisene

1) Interaction Effect: attenuation of antidepressant effectiveness; tricyclic toxicity (drowsiness, hypotension, akathisia)
2) Summary: In isolated cases, the pharmacologic effects of tricyclic antidepressants may be increased or decreased by estrogens (Somani & Khurana, 1973i), with paradoxical loss of antidepressant effect yet tricyclic toxicity being manifested simultaneously (Prange, 1972i). The effects of the interaction appear to be estrogen dose-related (Khurana, 1972i) and may be of clinical importance primarily in patients previously stabilized on tricyclic therapy who are being started on estrogen therapy (Krishnan et al, 1984i).
3) Severity: minor
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: If signs or symptoms of altered tricyclic response are noted, dose adjustment downward of either the estrogen or tricyclic component may be successful in restoring effectiveness or resolving toxicity. However, drug withdrawal may be required.
7) Probable Mechanism: possible estrogen-enhanced hepatic metabolism of the tricyclic
8) Literature Reports
a) Some studies evaluated the qualitative effects of concomitant administration of estrogen and TCAs. In one trial, 30 depressed female prisoners were randomly assigned to four treatment groups. Ten

patients received placebo, 10 received imipramine (150 mg daily) and placebo, five patients received imipramine (150 mg daily) and ethinyl estradiol (50 mcg daily), while five patients received imipramine (150 mg daily) and ethinyl estradiol (25 mcg daily). The 10 patients that received placebo did not improve over the six weeks of the study. The 10 patients taking estrogen and imipramine demonstrated a significantly greater improvement in symptoms than did the 10 patients taking imipramine alone. However, after two weeks, the five patients that received imipramine and high-dose estrogen had not improved as much as the patients receiving imipramine and low-dose estrogen. The only side-effect reported was drowsiness, which only affected the patients taking imipramine. Following the discontinuation of ethinyl estradiol, a time period of two weeks was required for the high-dose estrogen group to do as well as the low-dose group. This effect was attributed to the presence of residual estrogen in the high-dose group. In another group, five women received imipramine 150 mg and ethinyl estradiol 50 mcg daily did not improve as much as 10 patients receiving only imipramine. Also, the patients on the combination had severe side-effects including lethargy, coarse tremor and systolic hypotension (Prange, 1972h).

b) A case reported demonstrated an interaction in a 32-year-old female taking conjugated estrogens 2.5 mg and imipramine 100 mg (Khurana, 1972h). The patient developed lethargy, tremors, and signs of depersonalization. After two years of therapy, the patient increased her estrogen dose to 5 mg and then 7.5 mg daily. The patient became nauseated, had constant headaches, and low normal blood pressure. All lab work was normal. Upon discontinuing the estrogen, the side-effects abated. Some investigators have proposed that the side effects resulted from enhanced TCA effects secondary to estrogen inhibition of hepatic microsomal enzymes (Somani & Khurana, 1973h).

c) In a study women received clomipramine and oral contraceptives or clomipramine alone. At the beginning of the study there were 30 women taking the combination, but 12 subsequently dropped out. The 18 patients on the combination were matched with 18 patients taking clomipramine alone. No significant difference was noted in the patients' responses to clomipramine. It was proposed that there was no significant difference in side-effects between the groups; however, the groups were matched after patients had dropped out of the study. Had the patients been matched prior to the study, different conclusions may have been drawn (Beaumont, 1973e).

d) The effects of oral contraceptives on clomipramine were studied in 42 women between the ages of 18 and 40. Twenty-three women took clomipramine 25 mg at bedtime while 19 took clomipramine 25 mg at bedtime with oral contraceptives. Over the four-week study, three control patients (two due to side-effects) and five in the experimental group (two due to side-effects) dropped out. Venous blood samples were drawn at weekly intervals for measurement of serum clomipramine concentrations. No difference in serum concentrations was noted between the groups. However, this result may be partially due to the low dose of clomipramine given (Luscombe & John, 1980d).

e) The onset of akathisia was reported in 3 patients receiving conjugated estrogens and tricyclic antidepressants concurrently. A 24-year-old patient receiving clomipramine 120 mg daily for anorexia nervosa and conjugated estrogens 1.25 mg daily for amenorrhea developed restless legs and a constant desire to move continuously. Estrogen was discontinued and benztropine 2 mg was administered, resulting in marked reduction and resolution within 48 hours. Akathisia and disorientation developed in a 55-year-old patient on conjugated estrogen 1.25 mg daily who was prescribed amitriptyline 50 mg daily for depression. Within hours of amitriptyline, the patient was confused, restless, and possessed an inner desire to move continuously. Symptoms disappeared after discontinuing amitriptyline. A third case of akathisia was reported in a 35-year-old patient who received conjugated estrogen 1.25 mg daily and amitriptyline 50 mg daily. Akathisia developed within a few hours after taking the first dose of amitriptyline and resolved within 48 hours following discontinuation of the antidepressant (Krishnan et al, 1984h).

f) The absolute bioavailability of imipramine increased in women who received low-dose oral contraceptives (50 mcg or less of ethinyl estradiol) from 27% to 44% (p less than 0.05) as evident by an increase in the area under the plasma concentration time curve (Abernethy et al, 1984d).

g) Estrogens may inhibit the oxidation of TCAs by affecting hepatic microsomal enzymes (John et al, 1980d). Many TCAs are metabolized via oxidation and conjugation pathways. Inhibition of the oxidation of TCAs could result in accumulation and toxicity due to decreased clearance. Estrogens are suspected of possessing other effects on the central nervous system resulting in an antidepressant effect (Oppenheim, 1983d).

3.5.1.AC Cimetidine

1) Interaction Effect: doxepin toxicity (dry mouth, blurred vision, urinary retention)

2) Summary: Concomitant administration of doxepin 50 mg daily and cimetidine 600 mg twice daily was reported to result in significant increases in doxepin concentration and elimination half-life (Sutherland et al, 1987; Curry et al, 1987; Wells et al, 1986).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Monitor serum tricyclic antidepressant levels within the first few days of starting or discontinuing cimetidine. An H2 blocker that does not impair the metabolism of the tricyclic agents, such as ranitidine or famotidine, may be an alternative.

7) Probable Mechanism: decreased doxepin metabolism

3.5.1.AD Cisapride

1) Interaction Effect: cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Cisapride therapy has resulted in serious cardiac arrhythmias, including ventricular tachycardia, ventricular fibrillation, torsades de pointes, and QT prolongation. Because tricyclic antidepressant agents also may prolong the QT interval and increase the risk of arrhythmias, the concurrent administration of cisapride with a drug from this class is contraindicated (Prod Info Propulsid(R), 2000).
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent use of cisapride and tricyclic antidepressants is contraindicated.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.AE Clarithromycin

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Tricyclic antidepressants (TCAs) and clarithromycin have been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Biaxin(R), 2002; Marshall & Forker, 1982n). Even though no formal drug interaction studies have been done, the coadministration of tricyclic antidepressants and other drugs known to prolong the QTc interval, such as clarithromycin, is not recommended (Prod Info Elavil(R), 1999h).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of tricyclic antidepressants and agents that prolong the QT interval, such as clarithromycin, is not recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.AF Clonidine

1) Interaction Effect: decreased antihypertensive effectiveness
2) Summary: Concomitant clonidine and tricyclic antidepressant (TCA) therapy may impair the antihypertensive effects of clonidine (Prod Info Catapres(R), 1996). Tricyclic antidepressants increase the release of noradrenaline, presumably through re-uptake blockade. Clonidine reduces the release of noradrenaline by stimulating pre-synaptic alpha-2 adrenoreceptors, whose function is to inhibit noradrenaline release (Briant et al, 1973a; Hicks et al, 1981; Hui, 1983; Glass et al, 1982a). Mianserin, a tetracyclic antidepressant, was not shown to exhibit the impairment of clonidine's antihypertensive effects seen with tricyclic antidepressants (Elliott et al, 1981; Elliott et al, 1983).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Blood pressure should be monitored for an appropriate clinical response. Higher doses of clonidine may be required. An alternative class of antihypertensive agents or an alternative class of antidepressants might be considered.
7) Probable Mechanism: pharmacological antagonism at central alpha-2 receptors
8) Literature Reports

a) The interaction between clonidine and desipramine was studied in five hypertensive patients. The results of this double-blind placebo controlled study showed that the introduction of the tricyclic antidepressant led to the loss of blood pressure control in four of the five subjects within two weeks. The rise in the arterial pressure was more prominent in the supine position than in the erect. The average blood pressure increase in the desipramine period compared to the placebo period was 22/15 mm Hg in the lying position and 12/11 mm Hg standing (Briant et al, 1973).

b) Eleven drug-free patients who met the Research Diagnostic Criteria for Major Depressive Disorder enrolled in a study to determine the effects of desipramine on central adrenergic function. Patients were given a clonidine infusion after 0, 1 and 3 weeks of treatment with desipramine. Results showed that the sedative and hypotensive effects of clonidine were significantly inhibited after three weeks of treatment with desipramine. This interaction was also seen at one week, but did not reach clinical significance. The authors concluded that the effects that were observed during the study were due to an acute drug effect, rather than to a chronic adaptive change (Glass et al, 1982).

c) One case report describes a 65-year-old man who was experiencing perineal pain following the excision of a carcinoma. Pain management of amitriptyline 75 mg nightly and sodium valproate 500 mg three times daily was initiated after slow-release morphine only had a limited effect. A clonidine spinal intrathecal injection of 75 micrograms was given when it was felt that the patient had become tolerant to opioid treatment. Within five minutes, the patient was found to be in severe pain, which resolved within 30 minutes after diamorphine was given. Two mechanisms for this interaction were postulated. In the first, the pain could have been the result of a clonidine-cholinergic interaction. In the second, the tricyclic augmentation of serotoninergic transmission may have unmasked an effect of clonidine at central receptors to enhance nociception (Hardy & Wells, 1988).

3.5.1.AG Clorgyline

1) Interaction Effect: neurotoxicity, seizures, or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)

2) Summary: Concomitant TCA and MAOI use has resulted in hyperpyrexia, convulsions, and death. Concurrent use of MAOIs and TCAs has also been reported to result in a condition termed serotonin syndrome (Insel et al, 1982e; Spigset et al, 1993f; Brodribb et al, 1994e; Neuvonen et al, 1993b). Serotonin syndrome is a rare but potentially fatal condition of serotonergic hyperstimulation characterized by hypertension, hyperthermia, myoclonus, and changes in mental status (Sternbach, 1991c). If TCAs and MAOIs must be used concurrently, avoid large doses, use only oral TCAs, avoid imipramine, clomipramine, desipramine, and tranylcypromine, and monitor patients closely (Schuckit et al, 1971g; White & Simpson, 1984e).

3) Severity: major

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: Concomitant use of a tricyclic antidepressant, such as doxepin, and a monoamine oxidase inhibitor (MAOI), such as clorgyline, should be done only with close monitoring and where the clinical benefit outweighs the potential risk. Other antidepressant therapy should first be considered. If deemed clinically necessary, avoid large doses and use agents other than imipramine, clomipramine, desipramine, and tranylcypromine. If doxepin is replacing treatment with clorgyline, a minimum of 14 days should elapse after clorgyline is discontinued before doxepin therapy begins (Prod Info SINEQUAN(R) capsule, oral concentrate, 2005). There is no specific washout period for replacing doxepin treatment with clorgyline. However, it is advisable to gradually taper the tricyclic antidepressant dosage before starting treatment with the MAOI (Remick, 2002).

7) Probable Mechanism: altered catecholamine uptake and metabolism

8) Literature Reports

a) Concomitant administration of monoamine oxidase inhibitors (MAOIs) with tricyclic antidepressants (TCAs) has been considered an absolute contraindication in the past and still is listed as such by the manufacturers. Reports of excitation, hyperpyrexia, convulsions, and possible death have been attributed to the combination (Lockett & Milner, 1965c; Brachfeld et al, 1963b; Winston, 1971c; Schuckit et al, 1971f; Sargent, 1965b; Spiker & Pugh, 1976c). The mechanism may relate to the combined inhibition of catecholamine reuptake into the central nervous system and inhibition of catecholamine metabolism (Sjoqvist, 1965c).

b) Administration of a TCA after MAOI therapy may result in the development of serotonin syndrome. In a double-blind, crossover study examining the effects of clorgyline and clomipramine for the treatment of obsessive-compulsive disorder, two subjects developed severe reactions characteristic of serotonin syndrome. During the study, patients had received clorgyline therapy, followed by a washout period of approximately four weeks and subsequent clomipramine therapy. After taking the first 100 mg dose of clomipramine, one patient developed coarse myoclonic jerking in both legs, hyperreflexia, diaphoresis, and arrhythmia. Another patient developed a similar reaction after the first dose, with upper motor neuron symptoms, myoclonic movements, and cardiac irritability. Both patient's symptoms resolved several hours later, and both patients were later treated successfully with clomipramine without adverse effects (Insel et al, 1982d).

c) A drug interaction occurred in a 76-year old woman who had been taking clomipramine 50 mg daily for several months prior to switching to moclobemide 300 mg daily. The patient experienced somnolence, confusion, and fever which then progressed to further mental impairment, muscle stiffness, myoclonus, and convulsive attacks. The patient's symptoms were described as fulfilling the diagnostic criteria for serotonin syndrome and were resolved a few days later after discontinuing all antidepressant medications (Spigset et al, 1993e).

d) A 39-year old woman with bipolar disorder developed serotonin syndrome after imipramine was added to moclobemide. The patient was taking moclobemide 300 mg twice daily when imipramine was started at 50 mg daily, followed by two dosage increases of imipramine to 200 mg and a reduction of moclobemide dosage to 150 mg twice daily. Five days after the increase in imipramine to 200 mg per day, the patient developed symptoms of serotonin syndrome, including sweating, shivering, confusion, fever, and spasms in the extremities. The patient was treated with chlorpromazine and symptoms resolved over the next few days without further complications (Brodribb et al, 1994d).

e) Three patients with bipolar disorder developed manic symptoms while undergoing concurrent therapy with isocarboxazid and amitriptyline. In all three cases the patients had been given MAOIs and TCAs alone without complications. It was only when the drugs were used in combination that symptoms of mania emerged, suggesting a synergistic effect (de la Fuente et al, 1986a).

f) In one case, clomipramine 10 mg twice daily was added to a stable regimen of tranylcypromine in a physically healthy 34-year old man. After taking several doses, the patients developed symptoms of nausea and profuse sweating, followed by pyrexia, dyspnea, and agitation. The hyperpyrexical state led to disseminated intravascular coagulation and eventual death (Tackley & Tregaskis, 1987c).

g) There is evidence that MAOIs and TCAs can be given concomitantly in patients previously unresponsive to the MAOI or TCA alone. A few precautions must be followed including: a) avoidance of large doses (no more than 150 mg amitriptyline or its equivalent, 45 mg phenelzine, or 60 mg isocarboxazid) b) oral administration c) avoidance of clomipramine, imipramine, desipramine, and tranylcypromine in any combination, and d) close monitoring of patients (Kline, 1974a; Winston, 1971c;

Schuckit et al, 1971f; White & Simpson, 1984d; Rom & Benner, 1972a). The combination may be utilized in one of two ways. Most frequently, the recommendation is to stop all previous antidepressants (five to ten days for TCAs and 14 days for MAOIs); the combination is then simultaneously started (Perry et al, 1991b). Alternatively, in a patient previously receiving a TCA, small doses of the MAOI may be slowly added (Schoonover, 1983). Some sources suggest that the combination of amitriptyline and isocarboxazid is preferred (Perry et al, 1991b). Numerous studies in patients with refractory depression or phobic anxiety states have successfully used the combination of MAOIs and TCAs (Ponto et al, 1977c; Schuckit et al, 1971f; Ashcroft, 1975b).

3.5.1.AH Conjugated Estrogens

1) Interaction Effect: possible attenuation of antidepressant effectiveness; tricyclic toxicity (drowsiness, hypotension, akathisia)

2) Summary: In isolated cases, the pharmacologic effects of tricyclic antidepressants may be increased or decreased by estrogens (Somani & Khurana, 1973a), with paradoxical loss of antidepressant effect yet tricyclic toxicity being manifested simultaneously (Prange, 1972a). The effects of the interaction appear to be estrogen dose-related (Khurana, 1972a) and may be of clinical importance primarily in patients previously stabilized on tricyclic therapy who are being started on estrogen therapy (Krishnan et al, 1984a).

3) Severity: minor

4) Onset: delayed

5) Substantiation: established

6) Clinical Management: If signs or symptoms of altered tricyclic response are noted, dose adjustment downward of either the estrogen or tricyclic component may be successful in restoring effectiveness or resolving toxicity. However, drug withdrawal may be required.

7) Probable Mechanism: possible inhibition of hepatic metabolism of the tricyclic antidepressant

8) Literature Reports

a) Some studies evaluated the qualitative effects of concomitant administration of estrogen and TCAs. In one trial, 30 depressed female prisoners were randomly assigned to four treatment groups. Ten patients received placebo, 10 received imipramine (150 mg daily) and placebo, five patients received imipramine (150 mg daily) and ethinyl estradiol (50 mcg daily), while five patients received imipramine (150 mg daily) and ethinyl estradiol (25 mcg daily). The 10 patients that received placebo did not improve over the six weeks of the study. The 10 patients taking estrogen and imipramine demonstrated a significantly greater improvement in symptoms than did the 10 patients taking imipramine alone. However, after two weeks, the five patients that received imipramine and high-dose estrogen had not improved as much as the patients receiving imipramine and low-dose estrogen. The only side-effect reported was drowsiness, which only affected the patients taking imipramine. Following the discontinuation of ethinyl estradiol, a time period of two weeks was required for the high-dose estrogen group to do as well as the low-dose group. This effect was attributed to the presence of residual estrogen in the high-dose group. In another group, five women received imipramine 150 mg and ethinyl estradiol 50 mrg daily did not improve as much as 10 patients receiving only imipramine. Also, the patients on the combination had severe side-effects including lethargy, coarse tremor and systolic hypotension (Prange, 1972).

b) A 32-year-old female taking conjugated estrogens 2.5 mg and imipramine 100 mg developed lethargy, tremors, and signs of depersonalization. After two years of therapy, the patient increased her estrogen dose to 5 mg and then 7.5 mg daily. The patient became nauseated, had constant headaches, and low normal blood pressure. All lab work was normal. Upon discontinuing the estrogen, the side effects abated. Some investigators have proposed that the side effects resulted from enhanced TCA effects secondary to estrogen inhibition of hepatic microsomal enzymes (Somani & Khurana, 1973; Khurana, 1972).

c) In a study women received clomipramine and oral contraceptives or clomipramine alone. At the beginning of the study there were 30 women taking the combination, but 12 subsequently dropped out. The 18 patients on the combination were matched with 18 patients taking clomipramine alone. No significant difference was noted in the patients' responses to clomipramine. It was proposed that there was no significant difference in side-effects between the groups; however, the groups were matched after patients had dropped out of the study. Had the patients been matched prior to the study, different conclusions may have been drawn (Beaumont, 1973).

d) The effects of oral contraceptives on clomipramine was studied in 42 women between the ages of 18 and 40. Twenty-three women took clomipramine 25 mg at bedtime while 19 took clomipramine 25 mg at bedtime with oral contraceptives. Over the four-week study, three control patients (two due to side-effects) and five in the experimental group (two due to side-effects) dropped out. Venous blood samples were drawn at weekly intervals for measurement of serum clomipramine concentrations. No difference in serum concentrations was noted between the groups. However, this result may be partially due to the low dose of clomipramine given (Luscombe & John, 1980).

e) The onset of akathisia was reported in 3 patients receiving conjugated estrogens and tricyclic antidepressants concurrently. A 24-year-old patient receiving clomipramine 120 mg daily for anorexia nervosa and conjugated estrogens 1.25 mg daily for amenorrhea developed restless legs and a constant desire to move continuously. Estrogen was discontinued and benztropine 2 mg was administered, resulting in marked reduction and resolution within 48 hours. Akathisia and disorientation developed in a 55-year-old patient on conjugated estrogen 1.25 mg daily who was prescribed

amitriptyline 50 mg daily for depression. Within hours of amitriptyline, the patient was confused, restless, and possessed an inner desire to move continuously. Symptoms disappeared after discontinuing amitriptyline. A third case of akathisia was reported in a 35-year-old patient who received conjugated estrogen 1.25 mg daily and amitriptyline 50 mg daily. Akathisia developed within a few hours after taking the first dose of amitriptyline and resolved within 48 hours following discontinuation of the antidepressant (Krishnan et al, 1984).

f) The absolute bioavailability of imipramine increased in women who received low-dose oral contraceptives (50 mcg or less of ethinyl estradiol) from 27% to 44% (p less than 0.05) as evident by an increase in the area under the plasma concentration time curve (Abernethy et al, 1984).

g) Estrogens may inhibit the oxidation of TCAs by affecting hepatic microsomal enzymes (John et al, 1980). Many TCAs are metabolized via oxidation and conjugation pathways. Inhibition of the oxidation of TCAs could result in accumulation and toxicity due to decreased clearance. Estrogens are suspected of possessing other effects on the central nervous system resulting in an antidepressant effect (Oppenheim, 1983).

3.5.1.AI Dexfenfluramine

1) Interaction Effect: hypertension, other cardiac effects, and CNS stimulation

2) Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been reported to result in enhanced amphetamine effects from the release of norepinephrine (Beaumont, 1973d; Raisfeld, 1972). A similar reaction might also occur with all drugs that have amphetamine-like effects. Acute elevations in blood pressure have been noted (Flemenbaum, 1971a). Some amphetamine-like drugs may inhibit the metabolism of TCAs, although most combinations have not been studied. When amphetamine analogs are being used to treat obesity, it should be noted that TCAs frequently lead to moderate weight gain (Russ & Ackerman, 1988). False positive urine tests for amphetamines have been reported during therapy with some TCAs (Merigian & Browning, 1993). Caution is advised when concurrent administration of amphetamine-like agents and TCAs is warranted. The patient should be closely monitored for increased cardiovascular effects (hypertension and dysrhythmias).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other sympathomimetic agents could lead to hypertension, increased cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006; Flemenbaum, 1972). Use caution if such therapy is warranted. Monitor the patient closely for hypertension and dysrhythmias.

7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission

8) Literature Reports

a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agents. Additionally, coadministration of d-amphetamine with TCAs such as desipramine or protriptyline results in sustained increases in d-amphetamine concentration in the brain (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006).

b) Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism of some tricyclic antidepressants, such as imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transdermal system, 2006).

c) Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases in blood pressure such that the hypotensive effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of combined therapy. Discontinuation of the methylphenidate usually results in the blood pressure returning to normotensive levels; reinstitution of the methylphenidate resulted in further blood pressure elevation (Flemenbaum, 1971; Flemenbaum, 1972).

d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine given for at least four weeks, were given fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical improvement. However, fenfluramine more than doubled steady-state plasma levels of desipramine (Price et al, 1990).

e) There have been claims based on uncontrolled studies that a better antidepressant response may occur with combined therapy (Garrettson et al, 1969). However, a systemic review of stimulants in the treatment of depression concluded that although uncontrolled studies were generally positive, the ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated little advantage of drug over placebo and did not appear to be as effective as the conventional antidepressants in primary depression (Satel & Nelson, 1989).

3.5.1.AJ Dexmethylphenidate

1) Interaction Effect: hypertension, other cardiac effects, and CNS stimulation

2) Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been reported to result in enhanced amphetamine effects from the release of norepinephrine (Beaumont, 1973d; Raisfeld, 1972). A similar reaction might also occur with all drugs that have amphetamine-like effects. Acute elevations in blood pressure have been noted (Flemenbaum, 1971a). Some amphetamine-like drugs may inhibit the metabolism of TCAs, although most combinations have not been studied. When amphetamine

analogs are being used to treat obesity, it should be noted that TCAs frequently lead to moderate weight gain (Russ & Ackerman, 1988). False positive urine tests for amphetamines have been reported during therapy with some TCAs (Merigian & Browning, 1993). Caution is advised when concurrent administration of amphetamine-like agents and TCAs is warranted. The patient should be closely monitored for increased cardiovascular effects (hypertension and dysrhythmias).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other sympathomimetic agents could lead to hypertension, increased cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006; Flemenbaum, 1972). Use caution if such therapy is warranted. Monitor the patient closely for hypertension and dysrhythmias.
7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission
8) Literature Reports
a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agents. Additionally, coadministration of d-amphetamine with TCAs such as desipramine or protriptyline results in sustained increases in d-amphetamine concentration in the brain (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006).
b) Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism of some tricyclic antidepressants, such as imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transdermal system, 2006).
c) Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases in blood pressure such that the hypotensive effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of combined therapy. Discontinuation of the methylphenidate usually results in the blood pressure returning to normotensive levels; reinstitution of the methylphenidate resulted in further blood pressure elevation (Flemenbaum, 1971; Flemenbaum, 1972).
d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine given for at least four weeks, were given fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical improvement. However, fenfluramine more than doubled steady-state plasma levels of desipramine (Price et al, 1990).
e) There have been claims based on uncontrolled studies that a better antidepressant response may occur with combined therapy (Garrettson et al, 1969). However, a systemic review of stimulants in the treatment of depression concluded that although uncontrolled studies were generally positive, the ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated little advantage of drug over placebo and did not appear to be as effective as the conventional antidepressants in primary depression (Satel & Nelson, 1989).

3.5.1.AK Dextroamphetamine
1) Interaction Effect: hypertension, other cardiac effects, and CNS stimulation
2) Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been reported to result in enhanced amphetamine effects from the release of norepinephrine (Beaumont, 1973d; Raisfeld, 1972). A similar reaction might also occur with all drugs that have amphetamine-like effects. Acute elevations in blood pressure have been noted (Flemenbaum, 1971a). Some amphetamine-like drugs may inhibit the metabolism of TCAs, although most combinations have not been studied. When amphetamine analogs are being used to treat obesity, it should be noted that TCAs frequently lead to moderate weight gain (Russ & Ackerman, 1988). False positive urine tests for amphetamines have been reported during therapy with some TCAs (Merigian & Browning, 1993). Caution is advised when concurrent administration of amphetamine-like agents and TCAs is warranted. The patient should be closely monitored for increased cardiovascular effects (hypertension and dysrhythmias).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other sympathomimetic agents could lead to hypertension, increased cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006; Flemenbaum, 1972). Use caution if such therapy is warranted. Monitor the patient closely for hypertension and dysrhythmias.
7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission
8) Literature Reports
a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agents. Additionally, coadministration of d-amphetamine with TCAs such as desipramine or protriptyline results in sustained increases in d-amphetamine concentration in the brain (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006).
b) Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism of some tricyclic antidepressants, such as imipramine, clomipramine, or desipramine (Prod Info

DAYTRANA(TM) transdermal system, 2006).
c) Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases in blood pressure such that the hypotensive effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of combined therapy. Discontinuation of the methylphenidate usually results in the blood pressure returning to normotensive levels; reinstitution of the methylphenidate resulted in further blood pressure elevation (Flemenbaum, 1971; Flemenbaum, 1972).
d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine given for at least four weeks, were given fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical improvement. However, fenfluramine more than doubled steady-state plasma levels of desipramine (Price et al, 1990).
e) There have been claims based on uncontrolled studies that a better antidepressant response may occur with combined therapy (Garrettson et al, 1969). However, a systemic review of stimulants in the treatment of depression concluded that although uncontrolled studies were generally positive, the ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated little advantage of drug over placebo and did not appear to be as effective as the conventional antidepressants in primary depression (Satel & Nelson, 1989).

3.5.1.AL Dicumarol

1) Interaction Effect: increased risk of bleeding
2) Summary: Tricyclic antidepressants (TCAs) may increase the half-life and bioavailability of oral anticoagulants (Vesell et al, 1970k; Williams et al, 1976k). Considerable interindividual differences may be found (Pond et al, 1975k).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: In patients receiving oral anticoagulant therapy, the prothrombin time ratio or international normalized ratio (INR) should be closely monitored with the addition and withdrawal of treatment with doxepin, and should be reassessed periodically during concurrent therapy. Adjustments of the dicumarol dose may be necessary in order to maintain the desired level of anticoagulation.
7) Probable Mechanism: decreased dicumarol metabolism; increased dicumarol absorption
8) Literature Reports
a) In a study of healthy volunteers, the concurrent use of nortriptyline or amitriptyline resulted in an increase of dicumarol levels and an increase in the plasma half-life of dicumarol, although the effect was not consistent in all subjects (Pond et al, 1975j). This effect was not observed with warfarin.
b) A single oral dose of bishydroxycoumarin after eight days of nortriptyline resulted in a significantly prolonged half-life and decreased volume of distribution of the coumarin anticoagulant in six healthy volunteers (Vesell et al, 1970j). The mechanism of action was suggested to be reduced bishydroxycoumarin metabolism and/or altered coumarin absorption.
c) Drug dosing was studied in 16 patients on long-term anticoagulant therapy who used concurrent TCAs (Williams et al, 1976j). TCAs affected the stability of anticoagulant control leading to frequent changes in the doses of anticoagulants. Inhibition of coumarin metabolism was the postulated mechanism.

3.5.1.AM Dienestrol

1) Interaction Effect: attenuation of antidepressant effectiveness; tricyclic toxicity (drowsiness, hypotension, akathisia)
2) Summary: In isolated cases, the pharmacologic effects of tricyclic antidepressants may be increased or decreased by estrogens (Somani & Khurana, 1973g), with paradoxical loss of antidepressant effect yet tricyclic toxicity being manifested simultaneously (Prange, 1972g). The effects of the interaction appear to be estrogen dose-related (Khurana, 1972g) and may be of clinical importance primarily in patients previously stabilized on tricyclic therapy who are being started on estrogen therapy (Krishnan et al, 1984g).
3) Severity: minor
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: If signs or symptoms of altered tricyclic response are noted, dose adjustment downward of either the estrogen or tricyclic component may be successful in restoring effectiveness or resolving toxicity. However, drug withdrawal may be required.
7) Probable Mechanism: possible estrogen-enhanced hepatic metabolism of the tricyclic
8) Literature Reports
a) Some studies evaluated the qualitative effects of concomitant administration of estrogen and TCAs. In one trial, 30 depressed female prisoners were randomly assigned to 4 treatment groups. Ten patients received placebo, 10 received imipramine (150 milligrams/day) and placebo, 5 patients received imipramine (150 milligrams/day) and ethinyl estradiol (50 micrograms/day), while 5 patients received imipramine (150 milligrams/day) and ethinyl estradiol (25 micrograms/day). The 10 patients that received placebo did not improve over the 6 weeks of the study. The 10 patients taking estrogen and imipramine demonstrated a significantly greater improvement in symptoms than did the 10 patients taking imipramine alone. However, after 2 weeks, the 5 patients that received imipramine and high-dose estrogen had not improved as much as the patients receiving imipramine and low-dose estrogen. The

only side-effect reported was drowsiness, which only affected the patients taking imipramine. Following the discontinuation of ethinyl estradiol, a time period of 2 weeks was required for the high-dose estrogen group to do as well as the low-dose group. This effect was attributed to the presence of residual estrogen in the high-dose group. In another group, 5 women received imipramine 150 milligrams and ethinyl estradiol 50 micrograms daily did not improve as much as 10 patients receiving only imipramine. Also, the patients on the combination had severe side-effects including lethargy, coarse tremor and systolic hypotension (Prange, 1972f).

b) A case reported by (Khurana, 1972f) demonstrated an interaction in a 32-year-old female taking conjugated estrogens 2.5 milligrams and imipramine 100 milligrams. The patient developed lethargy, tremors, and signs of depersonalization. After 2 years of therapy, the patient increased her estrogen dose to 5 milligrams and then 7.5 milligrams daily. The patient became nauseated, had constant headaches, and low normal blood pressure. All lab work was normal. Upon discontinuing the estrogen, the side-effects abated. Some investigators have proposed that the side effects resulted from enhanced TCA effects secondary to estrogen inhibition of hepatic microsomal enzymes (Somani & Khurana, 1973f).

c) In a study women received clomipramine and oral contraceptives or clomipramine alone. At the beginning of the study there were 30 women taking the combination, but 12 subsequently dropped out. The 18 patients on the combination were matched with 18 patients taking clomipramine alone. No significant difference was noted in the patients' responses to clomipramine. It was proposed that there was no significant difference in side-effects between the groups; however, the groups were matched after patients had dropped out of the study. Had the patients been matched prior to the study, different conclusions may have been drawn (Beaumont, 1973c).

d) The effect of oral contraceptives on clomipramine was studied in 42 women between the ages of 18 and 40. Twenty-three women took clomipramine 25 milligrams at bedtime while 19 took clomipramine 25 milligrams at bedtime with oral contraceptives. Over the 4-week study, 3 control patients (2 due to side-effects) and 5 in the experimental group (2 due to side-effects) dropped out. Venous blood samples were drawn at weekly intervals for measurement of serum clomipramine concentrations. No difference in serum concentrations was noted between the groups. However, this result may be partially due to the low dose of clomipramine given (Luscombe & John, 1980c).

e) The onset of akathisia was reported in 3 patients receiving conjugated estrogens and tricyclic antidepressants concurrently. A 24-year-old patient receiving clomipramine 120 milligrams/day for anorexia nervosa and conjugated estrogens 1.25 milligrams/day for amenorrhea developed restless legs and a constant desire to move continuously. Estrogen was discontinued and benztropine 2 milligrams was administered, resulting in marked reduction and resolution within 48 hours. Akathisia and disorientation developed in a 55-year-old patient on conjugated estrogens 1.25 milligrams/day who was prescribed amitriptyline 50 milligrams/day for depression. Within hours of amitriptyline, the patient was confused, restless, and possessed an inner desire to move continuously. Symptoms disappeared after discontinuing amitriptyline. Positive rechallenge at one week with doxepin 100 milligrams, with resolution following discontinuation of doxepin. A third case of akathisia was reported in a 35-year-old patient who received conjugated estrogens 1.25 milligrams/day and amitriptyline 50 milligrams/day. Akathisia developed within a few hours after taking the first dose of amitriptyline and resolved within 48 hours following discontinuation of the antidepressant (Krishnan et al, 1984f).

f) The absolute bioavailability of imipramine increased in women who received low-dose oral contraceptives (50 micrograms or less of ethinyl estradiol) from 27 to 44% (p less than 0.05) as evident by an increase in the area under the plasma concentration time curve (Abernethy et al, 1984c).

g) Estrogens may inhibit the oxidation of TCAs by affecting hepatic microsomal enzymes (John et al, 1980c). Many TCAs are metabolized via oxidation and conjugation pathways. Inhibition of the oxidation of TCAs could result in accumulation and toxicity due to decreased clearance. Estrogens are suspected of possessing other effects on the central nervous system resulting in an antidepressant effect (Oppenheim, 1983c).

3.5.1.AN Diethylpropion

1) Interaction Effect: hypertension, other cardiac effects, and CNS stimulation

2) Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been reported to result in enhanced amphetamine effects from the release of norepinephrine (Beaumont, 1973d; Raisfeld, 1972). A similar reaction might also occur with all drugs that have amphetamine-like effects. Acute elevations in blood pressure have been noted (Flemenbaum, 1971a). Some amphetamine-like drugs may inhibit the metabolism of TCAs, although most combinations have not been studied. When amphetamine analogs are being used to treat obesity, it should be noted that TCAs frequently lead to moderate weight gain (Russ & Ackerman, 1988). False positive urine tests for amphetamines have been reported during therapy with some TCAs (Merigian & Browning, 1993). Caution is advised when concurrent administration of amphetamine-like agents and TCAs is warranted. The patient should be closely monitored for increased cardiovascular effects (hypertension and dysrhythmias).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other sympathomimetic agents could lead to hypertension, increased cardiovascular effects, or CNS stimulation

(Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006; Flemenbaum, 1972). Use caution if such therapy is warranted. Monitor the patient closely for hypertension and dysrhythmias.

7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission

8) Literature Reports

a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agents. Additionally, coadministration of d-amphetamine with TCAs such as desipramine or protriptyline results in sustained increases in d-amphetamine concentration in the brain (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006).

b) Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism of some tricyclic antidepressants, such as imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transdermal system, 2006).

c) Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases in blood pressure such that the hypotensive effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of combined therapy. Discontinuation of the methylphenidate usually results in the blood pressure returning to normotensive levels; reinstitution of the methylphenidate resulted in further blood pressure elevation (Flemenbaum, 1971; Flemenbaum, 1972).

d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine given for at least four weeks, were given fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical improvement. However, fenfluramine more than doubled steady-state plasma levels of desipramine (Price et al, 1990).

e) There have been claims based on uncontrolled studies that a better antidepressant response may occur with combined therapy (Garrettson et al, 1969). However, a systemic review of stimulants in the treatment of depression concluded that although uncontrolled studies were generally positive, the ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated little advantage of drug over placebo and did not appear to be as effective as the conventional antidepressants in primary depression (Satel & Nelson, 1989).

3.5.1.AO Diethylstilbestrol

1) Interaction Effect: attenuation of antidepressant effectiveness; tricyclic toxicity (drowsiness, hypotension, akathisia)

2) Summary: In isolated cases, the pharmacologic effects of tricyclic antidepressants may be increased or decreased by estrogens (Somani & Khurana, 1973e), with paradoxical loss of antidepressant effect yet tricyclic toxicity being manifested simultaneously (Prange, 1972e). The effects of the interaction appear to be estrogen dose-related (Khurana, 1972e) and may be of clinical importance primarily in patients previously stabilized on tricyclic therapy who are being started on estrogen therapy (Krishnan et al, 1984e).

3) Severity: minor

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: If signs or symptoms of altered tricyclic response are noted, dose adjustment downward of either the estrogen or tricyclic component may be successful in restoring effectiveness or resolving toxicity. However, drug withdrawal may be required.

7) Probable Mechanism: possible estrogen-enhanced hepatic metabolism of the tricyclic

8) Literature Reports

a) Some studies evaluated the qualitative effects of concomitant administration of estrogen and TCAs. In one trial, 30 depressed female prisoners were randomly assigned to 4 treatment groups. Ten patients received placebo, 10 received imipramine (150 milligrams/day) and placebo, 5 patients received imipramine (150 milligrams/day) and ethinyl estradiol (50 micrograms/day), while 5 patients received imipramine (150 milligrams/day) and ethinyl estradiol (25 micrograms/day). The 10 patients that received placebo did not improve over the 6 weeks of the study. The 10 patients taking estrogen and imipramine demonstrated a significantly greater improvement in symptoms than did the 10 patients taking imipramine alone. However, after 2 weeks, the 5 patients that received imipramine and high-dose estrogen had not improved as much as the patients receiving imipramine and low-dose estrogen. The only side-effect reported was drowsiness, which only affected the patients taking imipramine. Following the discontinuation of ethinyl estradiol, a time period of 2 weeks was required for the high-dose estrogen group to do as well as the low-dose group. This effect was attributed to the presence of residual estrogen in the high-dose group. In another group, 5 women received imipramine 150 milligrams and ethinyl estradiol 50 micrograms daily did not improve as much as 10 patients receiving only imipramine. Also, the patients on the combination had severe side-effects including lethargy, coarse tremor and systolic hypotension (Prange, 1972d).

b) A case reported by (Khurana, 1972d) demonstrated an interaction in a 32-year-old female taking conjugated estrogens 2.5 milligrams and imipramine 100 milligrams. The patient developed lethargy, tremors, and signs of depersonalization. After 2 years of therapy, the patient increased her estrogen dose to 5 milligrams and then 7.5 milligrams daily. The patient became nauseated, had constant headaches, and low normal blood pressure. All lab work was normal. Upon discontinuing the estrogen, the side-effects abated. Some investigators have proposed that the side effects resulted from enhanced TCA effects secondary to estrogen inhibition of hepatic microsomal enzymes (Somani & Khurana,

1973d).
c) In a study women received clomipramine and oral contraceptives or clomipramine alone. At the beginning of the study there were 30 women taking the combination, but 12 subsequently dropped out. The 18 patients on the combination were matched with 18 patients taking clomipramine alone. No significant difference was noted in the patients' responses to clomipramine. It was proposed that there was no significant difference in side-effects between the groups; however, the groups were matched after patients had dropped out of the study. Had the patients been matched prior to the study, different conclusions may have been drawn (Beaumont, 1973b).
d) The effect of oral contraceptives on clomipramine was studied in 42 women between the ages of 18 and 40. Twenty-three women took clomipramine 25 milligrams at bedtime while 19 took clomipramine 25 milligrams at bedtime with oral contraceptives. Over the 4-week study, 3 control patients (2 due to side-effects) and 5 in the experimental group (2 due to side-effects) dropped out. Venous blood samples were drawn at weekly intervals for measurement of serum clomipramine concentrations. No difference in serum concentrations was noted between the groups. However, this result may be partially due to the low dose of clomipramine given (Luscombe & John, 1980b).
e) The onset of akathisia was reported in 3 patients receiving conjugated estrogens and tricyclic antidepressants concurrently. A 24-year-old patient receiving clomipramine 120 milligrams/day for anorexia nervosa and conjugated estrogens 1.25 milligrams/day for amenorrhea developed restless legs and a constant desire to move continuously. Estrogen was discontinued and benztropine 2 milligrams was administered, resulting in marked reduction and resolution within 48 hours. Akathisia and disorientation developed in a 55-year-old patient on conjugated estrogens 1.25 milligrams/day who was prescribed amitriptyline 50 milligrams/day for depression. Within hours of amitriptyline, the patient was confused, restless, and possessed an inner desire to move continuously. Symptoms disappeared after discontinuing amitriptyline. Positive rechallenge at one week with doxepin 100 milligrams, with resolution following discontinuation of doxepin. A third case of akathisia was reported in a 35-year-old patient who received conjugated estrogens 1.25 milligrams/day and amitriptyline 50 milligrams/day. Akathisia developed within a few hours after taking the first dose of amitriptyline and resolved within 48 hours following discontinuation of the antidepressant (Krishnan et al, 1984d).
f) The absolute bioavailability of imipramine increased in women who received low-dose oral contraceptives (50 micrograms or less of ethinyl estradiol) from 27 to 44% (p less than 0.05) as evident by an increase in the area under the plasma concentration time curve (Abernethy et al, 1984b).
g) Estrogens may inhibit the oxidation of TCAs by affecting hepatic microsomal enzymes (John et al, 1980b). Many TCAs are metabolized via oxidation and conjugation pathways. Inhibition of the oxidation of TCAs could result in accumulation and toxicity due to decreased clearance. Estrogens are suspected of possessing other effects on the central nervous system resulting in an antidepressant effect (Oppenheim, 1983b).

3.5.1.AP Disopyramide
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Class Ia antiarrhythmics and tricyclic antidepressants have been shown to prolong the QTc interval at the recommended therapeutic dose. Even though no formal drug interaction studies have been done, the coadministration of Class Ia antiarrhythmics and other drugs known to prolong the QTc interval, including tricyclic antidepressants, is not recommended (Prod Info Elavil(R), 1999g; Prod Info Quinaglute(R), 1999; Marshall & Forker, 1982m).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: The concurrent administration of a Class IA antiarrhythmic agent and a tricyclic antidepressant is not recommended.
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) Quinidine is an inhibitor of the cytochrome P450 isoenzyme responsible for the 2-hydroxylation of imipramine and desipramine (Brosen & Gram, 1989). Inhibition of this enzyme system can result in a 35% decrease in imipramine clearance and 85% decrease in desipramine clearance. Demethylation of imipramine by the cytochrome P450 system is unaffected by this interaction. Until more information is available all patients having quinidine added to drug regimen containing imipramine or desipramine should be monitored for increased antidepressant serum concentrations and potential toxicity.
b) An increased incidence in sudden death was observed in six out of 53 patients with cardiac disease receiving amitriptyline, compared to 0 out of 53 in the control group. It was recommended that amitriptyline be avoided in patients with underlying cardiac disease except when depression was debilitating and no other drugs were helpful (Moir et al, 1972; Coull et al, 1970).
c) In a placebo controlled study, imipramine 3.5 mg/kg was administered daily for seven patients with severe depression and titrated doses to obtain therapeutic plasma concentrations. Two patients displayed premature atrial depolarizations and premature ventricular depolarizations before therapy. On patient had 33 premature atrial depolarizations (PAD) and 30 premature ventricular depolarizations (PVD) per hour, which decreased to 0.4 PAC and zero PVC per hour on imipramine. The other patient had 12 PAD and 169 PVD per hour before treatment and 1.8 PAD and 28.1 PVD per hour on

imipramine. The authors also cautioned that the incidence of cardiotoxicity may increase if tricyclic antidepressants are administered with Type I antiarrhythmics. It was also recommended that quinidine and procainamide not be used to treat the arrhythmias of a tricyclic overdose. The similarities between these agents may exacerbate the cardiotoxicity (Kantor et al, 1978).

3.5.1.AQ Dofetilide

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Cases of QTc prolongation and/or torsades de pointes have been reported with all Class III antiarrhythmic agents, including acecainide (Chow et al, 1984), amiodarone (Faggiano et al, 1996), azimilide (Corey et al, 1999), bretylium (Gilman et al, 1985a), ibutilide (Rodriguez et al, 2001), sematilide (Singh, 1996), dofetilide (Allen et al, 2002), and sotalol (Marill & Runge, 2001). Even though no formal drug interaction studies have been done, the coadministration of Class III antiarrhythmics and other drugs known to prolong the QTc interval, including tricyclic antidepressants, is not recommended (Yamreudeewong et al, 2003a; Prod Info Corvert(R), 2000).
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of a Class III antiarrhythmic and a tricyclic antidepressant (TCA) is not recommended.
7) Probable Mechanism: additive QT prolongation
8) Literature Reports
a) EKG effects reported in patients receiving therapeutic doses of tricyclic antidepressants include increased heart rate, prolonged PR interval, intraventricular conduction delays, increased corrected QT interval (QTc) and flattened T waves (Marshall & Forker, 1982y).
b) Concurrent use of Class III antiarrhythmic agents, and other drugs that can prolong the QT interval, such as tricyclic antidepressants, is not recommended. Dofetilide should be stopped for at least 2 days before any interacting drug is initiated. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised (Yamreudeewong et al, 2003).

3.5.1.AR Dolasetron

1) Interaction Effect: cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Tricyclic antidepressants (TCAs) and dolasetron have been shown to prolong the QTc interval at the recommended therapeutic dose (Marshall & Forker, 1982c). Even though no formal drug interaction studies have been done, the coadministration of tricyclic antidepressants and other drugs known to prolong the QTc interval, such as dolasetron, is not recommended (Prod Info Elavil(R), 1999b; Prod Info Anzemet (R), 1997).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of dolasetron with other agents that may prolong the QTc interval, such as tricyclic antidepressants, is not recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.AS Droperidol

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Droperidol has been shown to prolong the QTc interval at the recommended therapeutic dose. Even though no formal drug interaction studies have been done, the coadministration of droperidol and other drugs known to prolong the QTc interval, including tricylclic antidepressants is not recommended (Prod Info Inapsine(R), 2002; Marshall & Forker, 1982aa).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of droperidol and tricyclic antidepressants is not recommended.
7) Probable Mechanism: additive cardiac effects

3.5.1.AT Duloxetine

1) Interaction Effect: increased tricyclic antidepressant serum concentrations and potential toxicity (anticholinergic effects, sedation, confusion, cardiac arrhythmias)
2) Summary: The coadministration of duloxetine with a tricyclic antidepressant is likely to increase bioavailability of the tricyclic agent, increasing the risk of adverse events. Duloxetine is a moderately potent inhibitor of CYP2D6. When a single dose of the CYP2D6 substrate desipramine 50 mg and duloxetine 60 mg twice daily were coadministered, the desipramine AUC increased 3-fold over baseline (Prod Info CYMBALTA(R) delayed-release oral capsules, 2008).
3) Severity: moderate
4) Onset: unspecified

5) Substantiation: theoretical
6) Clinical Management: Use caution with the combined use of duloxetine with tricyclic antidepressants (TCAs). If concomitant therapy with duloxetine and a TCA is unavoidable, plasma concentrations of the tricyclic should be closely monitored and dose adjustments made accordingly (Prod Info CYMBALTA(R) delayed-release oral capsules, 2008). Also, monitor patients for signs and symptoms of TCA toxicity (anticholinergic effects, sedation, confusion, and cardiac arrhythmias).
7) Probable Mechanism: duloxetine inhibition of CYP2D6-mediated tricyclic agent metabolism

3.5.1.AU Enflurane
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest) and an increased risk of seizure activity
2) Summary: Enflurane may prolong the QT interval in some patients (Owens, 2001). Because tricyclic antidepressants may also prolong the QT interval and increase the risk of arrhythmias, the concurrent administration of enflurane and tricyclic antidepressants is not recommended (Marshall & Forker, 1982a). Concomitant administration of amitriptyline and enflurane anesthesia has been reported to result in seizures in two cases (Sprague & Wolf, 1982a).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Avoid concurrent use of enflurane and tricyclic antidepressants, particularly in patients with a history of seizure activity or when hyperventilation or high concentrations of enflurane will be required.
7) Probable Mechanism: additive effects on QT prolongation
8) Literature Reports
a) Two case reports of patients on amitriptyline therapy who experienced seizure activity while receiving enflurane anesthesia have been documented (Sprague & Wolf, 1982). The first patient, a 42-year old female, was taking amitriptyline 100 mg daily. Anesthesia was induced with fentanyl, enflurane, and nitrous oxide. Approximately three hours after anesthesia was induced, clonic movements of the patient's right hand and forearm were noted. Enflurane concentration was 1% at the time. Changes in ventilation did not affect the involuntary movements, so enflurane was discontinued and replaced with halothane 1%. The movements decreased in frequency and amplitude and subsequently disappeared in approximately one minute. The second case report involved a 39-year old male who was taking amitriptyline 150 mg daily. Anesthesia was maintained with enflurane 1% to 2%, and intermittent clonic movements started in the right arm and leg approximately one hour into the surgery. Enflurane was discontinued and halothane was instituted, which caused the involuntary movements to disappear in approximately two minutes. No further movements were seen during the remaining three hours of anesthesia.

3.5.1.AV Epinephrine
1) Interaction Effect: hypertension, cardiac arrhythmias, and tachycardia
2) Summary: Clinical trials have demonstrated a 2- to 8-fold increase in the effects of intravenous infusions of alpha adrenergic drugs to volunteers on tricyclic antidepressants. Arrhythmias and other severe adverse effects have also been reported (Ghose, 1980; Avery, 1973a; Boakes et al, 1973a; Boakes, 1973; Mitchell et al, 1970; Stone et al, 1964). Local use (e.g., dental anesthesia) of epinephrine in concentrations of 1:100,000 or less is less likely to precipitate clinically significant hemodynamic changes (Steinberg & Block, 1971).
3) Severity: major
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: The vasoconstriction and other alpha-adrenergic effects of sympathomimetic drugs are substantially enhanced in the presence of tricyclic antidepressants (TCAs). Concomitant use should be avoided. If these drugs are given together, careful monitoring and a dose reduction of the sympathomimetic is required. Patients should be instructed to inform their doctor or dentist that they are taking a tricyclic antidepressant prior to any surgery or procedure.
7) Probable Mechanism: inhibition of norepinephrine reuptake
8) Literature Reports
a) Four healthy volunteers received intravenous infusions of various sympathomimetic amines (epinephrine, norepinephrine, phenylephrine, and isoproterenol) before and after imipramine (25 mg three times daily for five days). They showed an increased pressor response to epinephrine (2- to 4-fold), norepinephrine (4- to 8-fold), and phenylephrine (2- to 3-fold) after imipramine, but no difference was observed in the response to isoproterenol. Thus, the increased pressor response appeared to occur only for alpha adrenergic effects. All four subjects demonstrated changes in cardiac rhythm with epinephrine and imipramine consisting of sinus arrhythmia in three subjects and multiple ectopic beats and a nodal rhythm in the fourth subject (Boakes et al, 1973).
b) A review of spontaneous reports of adverse reactions to vasoconstrictors in local anesthetics found that 15 patients receiving a local anesthetic with norepinephrine (1:25,000) had severe reactions (severe headaches, chest tightness, subarachnoid hemorrhage). The drug history was incomplete, but at least three had been taking a tricyclic antidepressant at the time (Anon, 1972).

3.5.1.AW Erythromycin

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Erythromycin significantly increased the mean QTc interval versus baseline in a retrospective study of 49 patients (Oberg & Bauman, 1995a). Erythromycin has demonstrated QTc prolongation in combination with other drugs that prolong the QT interval (Prod Info PCE(R), 1997). Tricyclic antidepressants have been shown to prolong the QTc interval at the recommended therapeutic dose (Marshall & Forker, 1982g). Caution is advised with coadministration of drugs that potentially prolong the QTc interval.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Caution is advised if erythromycin and tricyclic antidepressants are used concomitantly. Monitor QT interval at baseline and periodically during treatment.

7) Probable Mechanism: additive effects on QT prolongation

8) Literature Reports

a) Erythromycin did not significantly affect the metabolism of tricyclic antidepressants in a study of 8 patients. Patients were maintained on desipramine (n equal to 5), imipramine (n equal to 1), doxepin (n equal to 1), or doxepin (n equal to 1). All patients received erythromycin stearate 250 mg four times daily for six days while maintaining their usual tricyclic regimen. No change in the antidepressant or active metabolite concentrations was seen during coadministration with erythromycin (Amsterdam & Maislin, 1991).

b) Tricyclic antidepressants have been shown to prolong the QTc interval at the recommended therapeutic dose (Marshall & Forker, 1982f).

c) Erythromycin significantly increased the QTc interval compared with baseline in a retrospective study of 49 patients. The erythromycin dose was 500 milligrams or 1 gram four times daily, with a mean of 15 doses received. Patients (n equal to 9) who received 60 mg/kg/day or more all developed increases in QT interval of 15% or greater. For all patients, the mean QTc interval increased from 432 milliseconds (msec) at baseline to 483 msec (p less than 0.01). In patients with delayed repolarization at baseline (n equal to 9), the QTc interval increased from 473 msec to 525 msec (p less than 0.01). In patients with heart disease (n equal to 30), all experienced an increase in QTc interval (mean of 15%), compared with an increase of 8% in patients without heart disease (p less than 0.05). In 5 patients (10%), the QTc interval was severely prolonged. One patient developed torsades de pointes attributed to erythromycin. Of 16 patients receiving cotrimoxazole concomitantly, 8 developed QT prolongation of 15% or greater (Oberg & Bauman, 1995).

3.5.1.AX Esterified Estrogens

1) Interaction Effect: possible attenuation of antidepressant effectiveness; tricyclic toxicity (drowsiness, hypotension, akathisia)

2) Summary: In isolated cases, the pharmacologic effects of tricyclic antidepressants may be increased or decreased by estrogens (Somani & Khurana, 1973a), with paradoxical loss of antidepressant effect yet tricyclic toxicity being manifested simultaneously (Prange, 1972a). The effects of the interaction appear to be estrogen dose-related (Khurana, 1972a) and may be of clinical importance primarily in patients previously stabilized on tricyclic therapy who are being started on estrogen therapy (Krishnan et al, 1984a).

3) Severity: minor

4) Onset: delayed

5) Substantiation: established

6) Clinical Management: If signs or symptoms of altered tricyclic response are noted, dose adjustment downward of either the estrogen or tricyclic component may be successful in restoring effectiveness or resolving toxicity. However, drug withdrawal may be required.

7) Probable Mechanism: possible inhibition of hepatic metabolism of the tricyclic antidepressant

8) Literature Reports

a) Some studies evaluated the qualitative effects of concomitant administration of estrogen and TCAs. In one trial, 30 depressed female prisoners were randomly assigned to four treatment groups. Ten patients received placebo, 10 received imipramine (150 mg daily) and placebo, five patients received imipramine (150 mg daily) and ethinyl estradiol (50 mcg daily), while five patients received imipramine (150 mg daily) and ethinyl estradiol (25 mcg daily). The 10 patients that received placebo did not improve over the six weeks of the study. The 10 patients taking estrogen and imipramine demonstrated a significantly greater improvement in symptoms than did the 10 patients taking imipramine alone. However, after two weeks, the five patients that received imipramine and high-dose estrogen had not improved as much as the patients receiving imipramine and low-dose estrogen. The only side-effect reported was drowsiness, which only affected the patients taking imipramine. Following the discontinuation of ethinyl estradiol, a time period of two weeks was required for the high-dose estrogen group to do as well as the low-dose group. This effect was attributed to the presence of residual estrogen in the high-dose group. In another group, five women received imipramine 150 mg and ethinyl estradiol 50 mrg daily did not improve as much as 10 patients receiving only imipramine. Also, the patients on the combination had severe side-effects including lethargy, coarse tremor and systolic

hypotension (Prange, 1972).
b) A 32-year-old female taking conjugated estrogens 2.5 mg and imipramine 100 mg developed lethargy, tremors, and signs of depersonalization. After two years of therapy, the patient increased her estrogen dose to 5 mg and then 7.5 mg daily. The patient became nauseated, had constant headaches, and low normal blood pressure. All lab work was normal. Upon discontinuing the estrogen, the side effects abated. Some investigators have proposed that the side effects resulted from enhanced TCA effects secondary to estrogen inhibition of hepatic microsomal enzymes (Somani & Khurana, 1973; Khurana, 1972).
c) In a study women received clomipramine and oral contraceptives or clomipramine alone. At the beginning of the study there were 30 women taking the combination, but 12 subsequently dropped out. The 18 patients on the combination were matched with 18 patients taking clomipramine alone. No significant difference was noted in the patients' responses to clomipramine. It was proposed that there was no significant difference in side-effects between the groups; however, the groups were matched after patients had dropped out of the study. Had the patients been matched prior to the study, different conclusions may have been drawn (Beaumont, 1973).
d) The effects of oral contraceptives on clomipramine was studied in 42 women between the ages of 18 and 40. Twenty-three women took clomipramine 25 mg at bedtime while 19 took clomipramine 25 mg at bedtime with oral contraceptives. Over the four-week study, three control patients (two due to side-effects) and five in the experimental group (two due to side-effects) dropped out. Venous blood samples were drawn at weekly intervals for measurement of serum clomipramine concentrations. No difference in serum concentrations was noted between the groups. However, this result may be partially due to the low dose of clomipramine given (Luscombe & John, 1980).
e) The onset of akathisia was reported in 3 patients receiving conjugated estrogens and tricyclic antidepressants concurrently. A 24-year-old patient receiving clomipramine 120 mg daily for anorexia nervosa and conjugated estrogens 1.25 mg daily for amenorrhea developed restless legs and a constant desire to move continuously. Estrogen was discontinued and benztropine 2 mg was administered, resulting in marked reduction and resolution within 48 hours. Akathisia and disorientation developed in a 55-year-old patient on conjugated estrogen 1.25 mg daily who was prescribed amitriptyline 50 mg daily for depression. Within hours of amitriptyline, the patient was confused, restless, and possessed an inner desire to move continuously. Symptoms disappeared after discontinuing amitriptyline. A third case of akathisia was reported in a 35-year-old patient who received conjugated estrogen 1.25 mg daily and amitriptyline 50 mg daily. Akathisia developed within a few hours after taking the first dose of amitriptyline and resolved within 48 hours following discontinuation of the antidepressant (Krishnan et al, 1984).
f) The absolute bioavailability of imipramine increased in women who received low-dose oral contraceptives (50 mcg or less of ethinyl estradiol) from 27% to 44% (p less than 0.05) as evident by an increase in the area under the plasma concentration time curve (Abernethy et al, 1984).
g) Estrogens may inhibit the oxidation of TCAs by affecting hepatic microsomal enzymes (John et al, 1980). Many TCAs are metabolized via oxidation and conjugation pathways. Inhibition of the oxidation of TCAs could result in accumulation and toxicity due to decreased clearance. Estrogens are suspected of possessing other effects on the central nervous system resulting in an antidepressant effect (Oppenheim, 1983).

3.5.1.AY Estradiol

1) Interaction Effect: possible attenuation of antidepressant effectiveness; tricyclic toxicity (drowsiness, hypotension, akathisia)
2) Summary: In isolated cases, the pharmacologic effects of tricyclic antidepressants may be increased or decreased by estrogens (Somani & Khurana, 1973a), with paradoxical loss of antidepressant effect yet tricyclic toxicity being manifested simultaneously (Prange, 1972a). The effects of the interaction appear to be estrogen dose-related (Khurana, 1972a) and may be of clinical importance primarily in patients previously stabilized on tricyclic therapy who are being started on estrogen therapy (Krishnan et al, 1984a).
3) Severity: minor
4) Onset: delayed
5) Substantiation: established
6) Clinical Management: If signs or symptoms of altered tricyclic response are noted, dose adjustment downward of either the estrogen or tricyclic component may be successful in restoring effectiveness or resolving toxicity. However, drug withdrawal may be required.
7) Probable Mechanism: possible inhibition of hepatic metabolism of the tricyclic antidepressant
8) Literature Reports
a) Some studies evaluated the qualitative effects of concomitant administration of estrogen and TCAs. In one trial, 30 depressed female prisoners were randomly assigned to four treatment groups. Ten patients received placebo, 10 received imipramine (150 mg daily) and placebo, five patients received imipramine (150 mg daily) and ethinyl estradiol (50 mcg daily), while five patients received imipramine (150 mg daily) and ethinyl estradiol (25 mcg daily). The 10 patients that received placebo did not improve over the six weeks of the study. The 10 patients taking estrogen and imipramine demonstrated a significantly greater improvement in symptoms than did the 10 patients taking imipramine alone. However, after two weeks, the five patients that received imipramine and high-dose estrogen had not improved as much as the patients receiving imipramine and low-dose estrogen. The only side-effect

reported was drowsiness, which only affected the patients taking imipramine. Following the discontinuation of ethinyl estradiol, a time period of two weeks was required for the high-dose estrogen group to do as well as the low-dose group. This effect was attributed to the presence of residual estrogen in the high-dose group. In another group, five women received imipramine 150 mg and ethinyl estradiol 50 mrg daily did not improve as much as 10 patients receiving only imipramine. Also, the patients on the combination had severe side-effects including lethargy, coarse tremor and systolic hypotension (Prange, 1972).

b) A 32-year-old female taking conjugated estrogens 2.5 mg and imipramine 100 mg developed lethargy, tremors, and signs of depersonalization. After two years of therapy, the patient increased her estrogen dose to 5 mg and then 7.5 mg daily. The patient became nauseated, had constant headaches, and low normal blood pressure. All lab work was normal. Upon discontinuing the estrogen, the side effects abated. Some investigators have proposed that the side effects resulted from enhanced TCA effects secondary to estrogen inhibition of hepatic microsomal enzymes (Somani & Khurana, 1973; Khurana, 1972).

c) In a study women received clomipramine and oral contraceptives or clomipramine alone. At the beginning of the study there were 30 women taking the combination, but 12 subsequently dropped out. The 18 patients on the combination were matched with 18 patients taking clomipramine alone. No significant difference was noted in the patients' responses to clomipramine. It was proposed that there was no significant difference in side-effects between the groups; however, the groups were matched after patients had dropped out of the study. Had the patients been matched prior to the study, different conclusions may have been drawn (Beaumont, 1973).

d) The effects of oral contraceptives on clomipramine was studied in 42 women between the ages of 18 and 40. Twenty-three women took clomipramine 25 mg at bedtime while 19 took clomipramine 25 mg at bedtime with oral contraceptives. Over the four-week study, three control patients (two due to side-effects) and five in the experimental group (two due to side-effects) dropped out. Venous blood samples were drawn at weekly intervals for measurement of serum clomipramine concentrations. No difference in serum concentrations was noted between the groups. However, this result may be partially due to the low dose of clomipramine given (Luscombe & John, 1980).

e) The onset of akathisia was reported in 3 patients receiving conjugated estrogens and tricyclic antidepressants concurrently. A 24-year-old patient receiving clomipramine 120 mg daily for anorexia nervosa and conjugated estrogens 1.25 mg daily for amenorrhea developed restless legs and a constant desire to move continuously. Estrogen was discontinued and benztropine 2 mg was administered, resulting in marked reduction and resolution within 48 hours. Akathisia and disorientation developed in a 55-year-old patient on conjugated estrogen 1.25 mg daily who was prescribed amitriptyline 50 mg daily for depression. Within hours of amitriptyline, the patient was confused, restless, and possessed an inner desire to move continuously. Symptoms disappeared after discontinuing amitriptyline. A third case of akathisia was reported in a 35-year-old patient who received conjugated estrogen 1.25 mg daily and amitriptyline 50 mg daily. Akathisia developed within a few hours after taking the first dose of amitriptyline and resolved within 48 hours following discontinuation of the antidepressant (Krishnan et al, 1984).

f) The absolute bioavailability of imipramine increased in women who received low-dose oral contraceptives (50 mcg or less of ethinyl estradiol) from 27% to 44% (p less than 0.05) as evident by an increase in the area under the plasma concentration time curve (Abernethy et al, 1984).

g) Estrogens may inhibit the oxidation of TCAs by affecting hepatic microsomal enzymes (John et al, 1980). Many TCAs are metabolized via oxidation and conjugation pathways. Inhibition of the oxidation of TCAs could result in accumulation and toxicity due to decreased clearance. Estrogens are suspected of possessing other effects on the central nervous system resulting in an antidepressant effect (Oppenheim, 1983).

3.5.1.AZ Estriol

1) Interaction Effect: possible attenuation of antidepressant effectiveness; tricyclic toxicity (drowsiness, hypotension, akathisia)

2) Summary: In isolated cases, the pharmacologic effects of tricyclic antidepressants may be increased or decreased by estrogens (Somani & Khurana, 1973a), with paradoxical loss of antidepressant effect yet tricyclic toxicity being manifested simultaneously (Prange, 1972a). The effects of the interaction appear to be estrogen dose-related (Khurana, 1972a) and may be of clinical importance primarily in patients previously stabilized on tricyclic therapy who are being started on estrogen therapy (Krishnan et al, 1984a).

3) Severity: minor

4) Onset: delayed

5) Substantiation: established

6) Clinical Management: If signs or symptoms of altered tricyclic response are noted, dose adjustment downward of either the estrogen or tricyclic component may be successful in restoring effectiveness or resolving toxicity. However, drug withdrawal may be required.

7) Probable Mechanism: possible inhibition of hepatic metabolism of the tricyclic antidepressant

8) Literature Reports

a) Some studies evaluated the qualitative effects of concomitant administration of estrogen and TCAs. In one trial, 30 depressed female prisoners were randomly assigned to four treatment groups. Ten patients received placebo, 10 received imipramine (150 mg daily) and placebo, five patients received

imipramine (150 mg daily) and ethinyl estradiol (50 mcg daily), while five patients received imipramine (150 mg daily) and ethinyl estradiol (25 mcg daily). The 10 patients that received placebo did not improve over the six weeks of the study. The 10 patients taking estrogen and imipramine demonstrated a significantly greater improvement in symptoms than did the 10 patients taking imipramine alone. However, after two weeks, the five patients that received imipramine and high-dose estrogen had not improved as much as the patients receiving imipramine and low-dose estrogen. The only side-effect reported was drowsiness, which only affected the patients taking imipramine. Following the discontinuation of ethinyl estradiol, a time period of two weeks was required for the high-dose estrogen group to do as well as the low-dose group. This effect was attributed to the presence of residual estrogen in the high-dose group. In another group, five women received imipramine 150 mg and ethinyl estradiol 50 mrg daily did not improve as much as 10 patients receiving only imipramine. Also, the patients on the combination had severe side-effects including lethargy, coarse tremor and systolic hypotension (Prange, 1972).

b) A 32-year-old female taking conjugated estrogens 2.5 mg and imipramine 100 mg developed lethargy, tremors, and signs of depersonalization. After two years of therapy, the patient increased her estrogen dose to 5 mg and then 7.5 mg daily. The patient became nauseated, had constant headaches, and low normal blood pressure. All lab work was normal. Upon discontinuing the estrogen, the side effects abated. Some investigators have proposed that the side effects resulted from enhanced TCA effects secondary to estrogen inhibition of hepatic microsomal enzymes (Somani & Khurana, 1973; Khurana, 1972).

c) In a study women received clomipramine and oral contraceptives or clomipramine alone. At the beginning of the study there were 30 women taking the combination, but 12 subsequently dropped out. The 18 patients on the combination were matched with 18 patients taking clomipramine alone. No significant difference was noted in the patients' responses to clomipramine. It was proposed that there was no significant difference in side-effects between the groups; however, the groups were matched after patients had dropped out of the study. Had the patients been matched prior to the study, different conclusions may have been drawn (Beaumont, 1973).

d) The effects of oral contraceptives on clomipramine was studied in 42 women between the ages of 18 and 40. Twenty-three women took clomipramine 25 mg at bedtime while 19 took clomipramine 25 mg at bedtime with oral contraceptives. Over the four-week study, three control patients (two due to side-effects) and five in the experimental group (two due to side-effects) dropped out. Venous blood samples were drawn at weekly intervals for measurement of serum clomipramine concentrations. No difference in serum concentrations was noted between the groups. However, this result may be partially due to the low dose of clomipramine given (Luscombe & John, 1980).

e) The onset of akathisia was reported in 3 patients receiving conjugated estrogens and tricyclic antidepressants concurrently. A 24-year-old patient receiving clomipramine 120 mg daily for anorexia nervosa and conjugated estrogens 1.25 mg daily for amenorrhea developed restless legs and a constant desire to move continuously. Estrogen was discontinued and benztropine 2 mg was administered, resulting in marked reduction and resolution within 48 hours. Akathisia and disorientation developed in a 55-year-old patient on conjugated estrogen 1.25 mg daily who was prescribed amitriptyline 50 mg daily for depression. Within hours of amitriptyline, the patient was confused, restless, and possessed an inner desire to move continuously. Symptoms disappeared after discontinuing amitriptyline. A third case of akathisia was reported in a 35-year-old patient who received conjugated estrogen 1.25 mg daily and amitriptyline 50 mg daily. Akathisia developed within a few hours after taking the first dose of amitriptyline and resolved within 48 hours following discontinuation of the antidepressant (Krishnan et al, 1984).

f) The absolute bioavailability of imipramine increased in women who received low-dose oral contraceptives (50 mcg or less of ethinyl estradiol) from 27% to 44% (p less than 0.05) as evident by an increase in the area under the plasma concentration time curve (Abernethy et al, 1984).

g) Estrogens may inhibit the oxidation of TCAs by affecting hepatic microsomal enzymes (John et al, 1980). Many TCAs are metabolized via oxidation and conjugation pathways. Inhibition of the oxidation of TCAs could result in accumulation and toxicity due to decreased clearance. Estrogens are suspected of possessing other effects on the central nervous system resulting in an antidepressant effect (Oppenheim, 1983).

3.5.1.BA Estrone

1) Interaction Effect: possible attenuation of antidepressant effectiveness; tricyclic toxicity (drowsiness, hypotension, akathisia)

2) Summary: In isolated cases, the pharmacologic effects of tricyclic antidepressants may be increased or decreased by estrogens (Somani & Khurana, 1973a), with paradoxical loss of antidepressant effect yet tricyclic toxicity being manifested simultaneously (Prange, 1972a). The effects of the interaction appear to be estrogen dose-related (Khurana, 1972a) and may be of clinical importance primarily in patients previously stabilized on tricyclic therapy who are being started on estrogen therapy (Krishnan et al, 1984a).

3) Severity: minor

4) Onset: delayed

5) Substantiation: established

6) Clinical Management: If signs or symptoms of altered tricyclic response are noted, dose adjustment downward of either the estrogen or tricyclic component may be successful in restoring effectiveness or

resolving toxicity. However, drug withdrawal may be required.
7) Probable Mechanism: possible inhibition of hepatic metabolism of the tricyclic antidepressant
8) Literature Reports
a) Some studies evaluated the qualitative effects of concomitant administration of estrogen and TCAs. In one trial, 30 depressed female prisoners were randomly assigned to four treatment groups. Ten patients received placebo, 10 received imipramine (150 mg daily) and placebo, five patients received imipramine (150 mg daily) and ethinyl estradiol (50 mcg daily), while five patients received imipramine (150 mg daily) and ethinyl estradiol (25 mcg daily). The 10 patients that received placebo did not improve over the six weeks of the study. The 10 patients taking estrogen and imipramine demonstrated a significantly greater improvement in symptoms than did the 10 patients taking imipramine alone. However, after two weeks, the five patients that received imipramine and high-dose estrogen had not improved as much as the patients receiving imipramine and low-dose estrogen. The only side-effect reported was drowsiness, which only affected the patients taking imipramine. Following the discontinuation of ethinyl estradiol, a time period of two weeks was required for the high-dose estrogen group to do as well as the low-dose group. This effect was attributed to the presence of residual estrogen in the high-dose group. In another group, five women received imipramine 150 mg and ethinyl estradiol 50 mrg daily did not improve as much as 10 patients receiving only imipramine. Also, the patients on the combination had severe side-effects including lethargy, coarse tremor and systolic hypotension (Prange, 1972).
b) A 32-year-old female taking conjugated estrogens 2.5 mg and imipramine 100 mg developed lethargy, tremors, and signs of depersonalization. After two years of therapy, the patient increased her estrogen dose to 5 mg and then 7.5 mg daily. The patient became nauseated, had constant headaches, and low normal blood pressure. All lab work was normal. Upon discontinuing the estrogen, the side effects abated. Some investigators have proposed that the side effects resulted from enhanced TCA effects secondary to estrogen inhibition of hepatic microsomal enzymes (Somani & Khurana, 1973; Khurana, 1972).
c) In a study women received clomipramine and oral contraceptives or clomipramine alone. At the beginning of the study there were 30 women taking the combination, but 12 subsequently dropped out. The 18 patients on the combination were matched with 18 patients taking clomipramine alone. No significant difference was noted in the patients' responses to clomipramine. It was proposed that there was no significant difference in side-effects between the groups; however, the groups were matched after patients had dropped out of the study. Had the patients been matched prior to the study, different conclusions may have been drawn (Beaumont, 1973).
d) The effects of oral contraceptives on clomipramine was studied in 42 women between the ages of 18 and 40. Twenty-three women took clomipramine 25 mg at bedtime while 19 took clomipramine 25 mg at bedtime with oral contraceptives. Over the four-week study, three control patients (two due to side-effects) and five in the experimental group (two due to side-effects) dropped out. Venous blood samples were drawn at weekly intervals for measurement of serum clomipramine concentrations. No difference in serum concentrations was noted between the groups. However, this result may be partially due to the low dose of clomipramine given (Luscombe & John, 1980).
e) The onset of akathisia was reported in 3 patients receiving conjugated estrogens and tricyclic antidepressants concurrently. A 24-year-old patient receiving clomipramine 120 mg daily for anorexia nervosa and conjugated estrogens 1.25 mg daily for amenorrhea developed restless legs and a constant desire to move continuously. Estrogen was discontinued and benztropine 2 mg was administered, resulting in marked reduction and resolution within 48 hours. Akathisia and disorientation developed in a 55-year-old patient on conjugated estrogen 1.25 mg daily who was prescribed amitriptyline 50 mg daily for depression. Within hours of amitriptyline, the patient was confused, restless, and possessed an inner desire to move continuously. Symptoms disappeared after discontinuing amitriptyline. A third case of akathisia was reported in a 35-year-old patient who received conjugated estrogen 1.25 mg daily and amitriptyline 50 mg daily. Akathisia developed within a few hours after taking the first dose of amitriptyline and resolved within 48 hours following discontinuation of the antidepressant (Krishnan et al, 1984).
f) The absolute bioavailability of imipramine increased in women who received low-dose oral contraceptives (50 mcg or less of ethinyl estradiol) from 27% to 44% (p less than 0.05) as evident by an increase in the area under the plasma concentration time curve (Abernethy et al, 1984).
g) Estrogens may inhibit the oxidation of TCAs by affecting hepatic microsomal enzymes (John et al, 1980). Many TCAs are metabolized via oxidation and conjugation pathways. Inhibition of the oxidation of TCAs could result in accumulation and toxicity due to decreased clearance. Estrogens are suspected of possessing other effects on the central nervous system resulting in an antidepressant effect (Oppenheim, 1983).

3.5.1.BB Estropipate
1) Interaction Effect: possible attenuation of antidepressant effectiveness; tricyclic toxicity (drowsiness, hypotension, akathisia)
2) Summary: In isolated cases, the pharmacologic effects of tricyclic antidepressants may be increased or decreased by estrogens (Somani & Khurana, 1973a), with paradoxical loss of antidepressant effect yet tricyclic toxicity being manifested simultaneously (Prange, 1972a). The effects of the interaction appear to be estrogen dose-related (Khurana, 1972a) and may be of clinical importance primarily in patients previously

stabilized on tricyclic therapy who are being started on estrogen therapy (Krishnan et al, 1984a).
3) Severity: minor
4) Onset: delayed
5) Substantiation: established
6) Clinical Management: If signs or symptoms of altered tricyclic response are noted, dose adjustment downward of either the estrogen or tricyclic component may be successful in restoring effectiveness or resolving toxicity. However, drug withdrawal may be required.
7) Probable Mechanism: possible inhibition of hepatic metabolism of the tricyclic antidepressant
8) Literature Reports

a) Some studies evaluated the qualitative effects of concomitant administration of estrogen and TCAs. In one trial, 30 depressed female prisoners were randomly assigned to four treatment groups. Ten patients received placebo, 10 received imipramine (150 mg daily) and placebo, five patients received imipramine (150 mg daily) and ethinyl estradiol (50 mcg daily), while five patients received imipramine (150 mg daily) and ethinyl estradiol (25 mcg daily). The 10 patients that received placebo did not improve over the six weeks of the study. The 10 patients taking estrogen and imipramine demonstrated a significantly greater improvement in symptoms than did the 10 patients taking imipramine alone. However, after two weeks, the five patients that received imipramine and high-dose estrogen had not improved as much as the patients receiving imipramine and low-dose estrogen. The only side-effect reported was drowsiness, which only affected the patients taking imipramine. Following the discontinuation of ethinyl estradiol, a time period of two weeks was required for the high-dose estrogen group to do as well as the low-dose group. This effect was attributed to the presence of residual estrogen in the high-dose group. In another group, five women received imipramine 150 mg and ethinyl estradiol 50 mrg daily did not improve as much as 10 patients receiving only imipramine. Also, the patients on the combination had severe side-effects including lethargy, coarse tremor and systolic hypotension (Prange, 1972).

b) A 32-year-old female taking conjugated estrogens 2.5 mg and imipramine 100 mg developed lethargy, tremors, and signs of depersonalization. After two years of therapy, the patient increased her estrogen dose to 5 mg and then 7.5 mg daily. The patient became nauseated, had constant headaches, and low normal blood pressure. All lab work was normal. Upon discontinuing the estrogen, the side effects abated. Some investigators have proposed that the side effects resulted from enhanced TCA effects secondary to estrogen inhibition of hepatic microsomal enzymes (Somani & Khurana, 1973; Khurana, 1972).

c) In a study women received clomipramine and oral contraceptives or clomipramine alone. At the beginning of the study there were 30 women taking the combination, but 12 subsequently dropped out. The 18 patients on the combination were matched with 18 patients taking clomipramine alone. No significant difference was noted in the patients' responses to clomipramine. It was proposed that there was no significant difference in side-effects between the groups; however, the groups were matched after patients had dropped out of the study. Had the patients been matched prior to the study, different conclusions may have been drawn (Beaumont, 1973).

d) The effects of oral contraceptives on clomipramine was studied in 42 women between the ages of 18 and 40. Twenty-three women took clomipramine 25 mg at bedtime while 19 took clomipramine 25 mg at bedtime with oral contraceptives. Over the four-week study, three control patients (two due to side-effects) and five in the experimental group (two due to side-effects) dropped out. Venous blood samples were drawn at weekly intervals for measurement of serum clomipramine concentrations. No difference in serum concentrations was noted between the groups. However, this result may be partially due to the low dose of clomipramine given (Luscombe & John, 1980).

e) The onset of akathisia was reported in 3 patients receiving conjugated estrogens and tricyclic antidepressants concurrently. A 24-year-old patient receiving clomipramine 120 mg daily for anorexia nervosa and conjugated estrogens 1.25 mg daily for amenorrhea developed restless legs and a constant desire to move continuously. Estrogen was discontinued and benztropine 2 mg was administered, resulting in marked reduction and resolution within 48 hours. Akathisia and disorientation developed in a 55-year-old patient on conjugated estrogen 1.25 mg daily who was prescribed amitriptyline 50 mg daily for depression. Within hours of amitriptyline, the patient was confused, restless, and possessed an inner desire to move continuously. Symptoms disappeared after discontinuing amitriptyline. A third case of akathisia was reported in a 35-year-old patient who received conjugated estrogen 1.25 mg daily and amitriptyline 50 mg daily. Akathisia developed within a few hours after taking the first dose of amitriptyline and resolved within 48 hours following discontinuation of the antidepressant (Krishnan et al, 1984).

f) The absolute bioavailability of imipramine increased in women who received low-dose oral contraceptives (50 mcg or less of ethinyl estradiol) from 27% to 44% (p less than 0.05) as evident by an increase in the area under the plasma concentration time curve (Abernethy et al, 1984).

g) Estrogens may inhibit the oxidation of TCAs by affecting hepatic microsomal enzymes (John et al, 1980). Many TCAs are metabolized via oxidation and conjugation pathways. Inhibition of the oxidation of TCAs could result in accumulation and toxicity due to decreased clearance. Estrogens are suspected of possessing other effects on the central nervous system resulting in an antidepressant effect (Oppenheim, 1983).

3.5.1.BC Eterobarb

1) Interaction Effect: possible decreased tricyclic antidepressant serum concentrations and possible additive adverse effects
2) Summary: Concomitant barbiturate and tricyclic antidepressant (TCA) therapy may result in increased metabolism of the TCA. There have been scattered reports of individuals with decreased serum levels of TCAs in the presence of a barbiturate (Moody et al, 1977; Silverman & Braithwaite, 1972; Burrows & Davies, 1971). In addition, TCAs can worsen seizure control by reducing the seizure threshold (Brodie, 1992). These drugs also have additive CNS and respiratory depressant effects.
3) Severity: minor
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor for efficacy of antidepressant effect. Increases in tricyclic antidepressant dosages may be required. Additionally, monitor for toxicity when either drug is added to or withdrawn from therapy. Serum concentrations may be of value in determining appropriate dosage.
7) Probable Mechanism: increased tricyclic antidepressant metabolism
8) Literature Reports
a) The pharmacokinetics of a single oral dose of desipramine (100 mg) were studied in eight epileptic patients chronically treated with phenobarbital and in eight drug-free healthy controls (Spina et al, 1996). All subjects were extensive metabolizers with respect to the genetically determined CYP2D6-related metabolic polymorphism. Compared with controls, epileptic patients exhibited lower peak plasma desipramine concentrations (74 nmol/L vs. 107 nmol/L), smaller desipramine area under the concentration-time curve values (1943 nmol/L/h vs. 3234 nmol/L/h), and shorter desipramine elimination half-lives (15.1 h vs. 20.6 h). All barbiturates are believed to have similar effects leading to induction of hepatic enzymes and the 2D6 isozyme is believed to be important in the metabolism of most or all TCAs. Thus, similar effects should be expected with any combination of TCA and barbiturate.

3.5.1.BD Ethinyl Estradiol
1) Interaction Effect: attenuation of antidepressant effectiveness; tricyclic toxicity (drowsiness, hypotension, akathisia)
2) Summary: In isolated cases, the pharmacologic effects of tricyclic antidepressants may be increased or decreased by estrogens (Somani & Khurana, 1973k), with paradoxical loss of antidepressant effect yet tricyclic toxicity being manifested simultaneously (Prange, 1972k). The effects of the interaction appear to be estrogen dose-related (Khurana, 1972k) and may be of clinical importance primarily in patients previously stabilized on tricyclic therapy who are being started on estrogen therapy (Krishnan et al, 1984k).
3) Severity: minor
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: If signs or symptoms of altered tricyclic response are noted, dose adjustment downward of either the estrogen or tricyclic component may be successful in restoring effectiveness or resolving toxicity. However, drug withdrawal may be required.
7) Probable Mechanism: possible estrogen-enhanced hepatic metabolism of the tricyclic
8) Literature Reports
a) Some studies evaluated the qualitative effects of concomitant administration of estrogen and TCAs. In one trial, 30 depressed female prisoners were randomly assigned to 4 treatment groups. Ten patients received placebo, 10 received imipramine (150 milligrams/day) and placebo, 5 patients received imipramine (150 milligrams/day) and ethinyl estradiol (50 micrograms/day), while 5 patients received imipramine (150 milligrams/day) and ethinyl estradiol (25 micrograms/day). The 10 patients that received placebo did not improve over the 6 weeks of the study. The 10 patients taking estrogen and imipramine demonstrated a significantly greater improvement in symptoms than did the 10 patients taking imipramine alone. However, after 2 weeks, the 5 patients that received imipramine and high-dose estrogen had not improved as much as the patients receiving imipramine and low-dose estrogen. The only side-effect reported was drowsiness, which only affected the patients taking imipramine. Following the discontinuation of ethinyl estradiol, a time period of 2 weeks was required for the high-dose estrogen group to do as well as the low-dose group. This effect was attributed to the presence of residual estrogen in the high-dose group. In another group, 5 women received imipramine 150 milligrams and ethinyl estradiol 50 micrograms daily did not improve as much as 10 patients receiving only imipramine. Also, the patients on the combination had severe side-effects including lethargy, coarse tremor and systolic hypotension (Prange, 1972j).
b) A case reported by (Khurana, 1972j) demonstrated an interaction in a 32-year-old female taking conjugated estrogens 2.5 milligrams and imipramine 100 milligrams. The patient developed lethargy, tremors, and signs of depersonalization. After 2 years of therapy, the patient increased her estrogen dose to 5 milligrams and then 7.5 milligrams daily. The patient became nauseated, had constant headaches, and low normal blood pressure. All lab work was normal. Upon discontinuing the estrogen, the side-effects abated. Some investigators have proposed that the side effects resulted from enhanced TCA effects secondary to estrogen inhibition of hepatic microsomal enzymes (Somani & Khurana, 1973j).
c) In a study women received clomipramine and oral contraceptives or clomipramine alone. At the beginning of the study there were 30 women taking the combination, but 12 subsequently dropped out. The 18 patients on the combination were matched with 18 patients taking clomipramine alone. No

significant difference was noted in the patients' responses to clomipramine. It was proposed that there was no significant difference in side-effects between the groups; however, the groups were matched after patients had dropped out of the study. Had the patients been matched prior to the study, different conclusions may have been drawn (Beaumont, 1973f).

d) The effect of oral contraceptives on clomipramine was studied in 42 women between the ages of 18 and 40. Twenty-three women took clomipramine 25 milligrams at bedtime while 19 took clomipramine 25 milligrams at bedtime with oral contraceptives. Over the 4-week study, 3 control patients (2 due to side-effects) and 5 in the experimental group (2 due to side-effects) dropped out. Venous blood samples were drawn at weekly intervals for measurement of serum clomipramine concentrations. No difference in serum concentrations was noted between the groups. However, this result may be partially due to the low dose of clomipramine given (Luscombe & John, 1980e).

e) The onset of akathisia was reported in 3 patients receiving conjugated estrogens and tricyclic antidepressants concurrently. A 24-year-old patient receiving clomipramine 120 milligrams/day for anorexia nervosa and conjugated estrogens 1.25 milligrams/day for amenorrhea developed restless legs and a constant desire to move continuously. Estrogen was discontinued and benztropine 2 milligrams was administered, resulting in marked reduction and resolution within 48 hours. Akathisia and disorientation developed in a 55-year-old patient on conjugated estrogens 1.25 milligrams/day who was prescribed amitriptyline 50 milligrams/day for depression. Within hours of amitriptyline, the patient was confused, restless, and possessed an inner desire to move continuously. Symptoms disappeared after discontinuing amitriptyline. Positive rechallenge at one week with doxepin 100 milligrams, with resolution following discontinuation of doxepin. A third case of akathisia was reported in a 35-year-old patient who received conjugated estrogens 1.25 milligrams/day and amitriptyline 50 milligrams/day. Akathisia developed within a few hours after taking the first dose of amitriptyline and resolved within 48 hours following discontinuation of the antidepressant (Krishnan et al, 1984j).

f) The absolute bioavailability of imipramine increased in women who received low-dose oral contraceptives (50 micrograms or less of ethinyl estradiol) from 27 to 44% (p less than 0.05) as evident by an increase in the area under the plasma concentration time curve (Abernethy et al, 1984e).

g) Estrogens may inhibit the oxidation of TCAs by affecting hepatic microsomal enzymes (John et al, 1980e). Many TCAs are metabolized via oxidation and conjugation pathways. Inhibition of the oxidation of TCAs could result in accumulation and toxicity due to decreased clearance. Estrogens are suspected of possessing other effects on the central nervous system resulting in an antidepressant effect (Oppenheim, 1983e).

3.5.1.BE Etilefrine

1) Interaction Effect: hypertension, cardiac arrhythmias, and tachycardia

2) Summary: Clinical trials have demonstrated a 2- to 8-fold increase in the effects of intravenous infusions of alpha adrenergic drugs to volunteers on tricyclic antidepressants. Arrhythmias and other severe adverse effects have also been reported (Ghose, 1980; Avery, 1973a; Boakes et al, 1973a; Boakes, 1973; Mitchell et al, 1970; Stone et al, 1964). Local use (e.g., dental anesthesia) of epinephrine in concentrations of 1:100,000 or less is less likely to precipitate clinically significant hemodynamic changes (Steinberg & Block, 1971).

3) Severity: major

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: The vasoconstriction and other alpha-adrenergic effects of sympathomimetic drugs are substantially enhanced in the presence of tricyclic antidepressants (TCAs). Concomitant use should be avoided. If these drugs are given together, careful monitoring and a dose reduction of the sympathomimetic is required. Patients should be instructed to inform their doctor or dentist that they are taking a tricyclic antidepressant prior to any surgery or procedure.

7) Probable Mechanism: inhibition of norepinephrine reuptake

8) Literature Reports

a) Four healthy volunteers received intravenous infusions of various sympathomimetic amines (epinephrine, norepinephrine, phenylephrine, and isoproterenol) before and after imipramine (25 mg three times daily for five days). They showed an increased pressor response to epinephrine (2- to 4-fold), norepinephrine (4- to 8-fold), and phenylephrine (2- to 3-fold) after imipramine, but no difference was observed in the response to isoproterenol. Thus, the increased pressor response appeared to occur only for alpha adrenergic effects. All four subjects demonstrated changes in cardiac rhythm with epinephrine and imipramine consisting of sinus arrhythmia in three subjects and multiple ectopic beats and a nodal rhythm in the fourth subject (Boakes et al, 1973).

b) A review of spontaneous reports of adverse reactions to vasoconstrictors in local anesthetics found that 15 patients receiving a local anesthetic with norepinephrine (1:25,000) had severe reactions (severe headaches, chest tightness, subarachnoid hemorrhage). The drug history was incomplete, but at least three had been taking a tricyclic antidepressant at the time (Anon, 1972).

3.5.1.BF Fenfluramine

1) Interaction Effect: hypertension, other cardiac effects, and CNS stimulation

2) Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been reported to result in enhanced amphetamine effects from the release of norepinephrine (Beaumont, 1973d;

Raisfeld, 1972). A similar reaction might also occur with all drugs that have amphetamine-like effects. Acute elevations in blood pressure have been noted (Flemenbaum, 1971a). Some amphetamine-like drugs may inhibit the metabolism of TCAs, although most combinations have not been studied. When amphetamine analogs are being used to treat obesity, it should be noted that TCAs frequently lead to moderate weight gain (Russ & Ackerman, 1988). False positive urine tests for amphetamines have been reported during therapy with some TCAs (Merigian & Browning, 1993). Caution is advised when concurrent administration of amphetamine-like agents and TCAs is warranted. The patient should be closely monitored for increased cardiovascular effects (hypertension and dysrhythmias).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other sympathomimetic agents could lead to hypertension, increased cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006; Flemenbaum, 1972). Use caution if such therapy is warranted. Monitor the patient closely for hypertension and dysrhythmias.

7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission

8) Literature Reports

a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agents. Additionally, coadministration of d-amphetamine with TCAs such as desipramine or protriptyline results in sustained increases in d-amphetamine concentration in the brain (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006).

b) Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism of some tricyclic antidepressants, such as imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transdermal system, 2006).

c) Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases in blood pressure such that the hypotensive effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of combined therapy. Discontinuation of the methylphenidate usually results in the blood pressure returning to normotensive levels; reinstitution of the methylphenidate resulted in further blood pressure elevation (Flemenbaum, 1971; Flemenbaum, 1972).

d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine given for at least four weeks, were given fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical improvement. However, fenfluramine more than doubled steady-state plasma levels of desipramine (Price et al, 1990).

e) There have been claims based on uncontrolled studies that a better antidepressant response may occur with combined therapy (Garrettson et al, 1969). However, a systemic review of stimulants in the treatment of depression concluded that although uncontrolled studies were generally positive, the ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated little advantage of drug over placebo and did not appear to be as effective as the conventional antidepressants in primary depression (Satel & Nelson, 1989).

3.5.1.BG Fluconazole

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Case reports have described QT prolongation and torsades de points associated with fluconazole (Wassmann et al, 1999). Several tricyclic antidepressants (TCAs) have been shown to prolong the QTc interval at the recommended therapeutic dose (Marshall & Forker, 1982u). Even though no formal drug interaction studies have been done, the coadministration of drugs known to prolong the QTc interval is not recommended.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of fluconazole and a tricyclic antidepressant is not recommended.

7) Probable Mechanism: additive effects on QT prolongation

3.5.1.BH Fluoxetine

1) Interaction Effect: tricyclic antidepressant toxicity (dry mouth, urinary retention, sedation) and an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Tricyclic antidepressants (TCAs) and fluoxetine have been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Prozac(R), 2001; Marshall & Forker, 1982h). Even though no formal drug interaction studies have been done which demonstrate QT prolongation, the coadministration of tricyclic antidepressants and other drugs known to prolong the QTc interval, such as fluoxetine, is not recommended (Prod Info Elavil(R), 1999d). In addition, concurrent use of fluoxetine and TCAs such as desipramine, nortriptyline, and imipramine has resulted in significant increases in TCA concentrations (Preskorn et al, 1994a; Preskorn et al, 1994a; Aranow et al, 1989a; Downs et al, 1989a; Goodnick, 1989a; Bell & Cole, 1988a).

3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: The concurrent administration of fluoxetine and a tricyclic antidepressant is not recommended.
7) Probable Mechanism: decreased tricyclic antidepressant metabolism; additive effects on QT prolongation
8) Literature Reports
a) Fluoxetine increased the level of tricyclic antidepressants (nortriptyline, imipramine, desipramine) in 4 patients. After the addition of fluoxetine, the ratio of antidepressant level to dose increased by 109% to 486% in the patients. Three patients developed clinical symptoms (anticholinergic effects, constipation, urinary hesitancy, sedation, unstable gait) as a result of the increased levels (Aranow et al, 1989).
b) Fluoxetine statistically and clinically significantly increased desipramine concentrations in 18 healthy subjects. When fluoxetine (20 mg daily) was added to desipramine (50 mg daily), the mean maximum concentration of desipramine increased by 278% and the area under the concentration-time curve increased by 342%. Desipramine trough concentrations continued to be 198% above baseline three weeks after fluoxetine was discontinued. The same study compared pharmacokinetics of desipramine when combined with sertraline. The impact of sertraline was modest, resulting in small and short-term increases in desipramine plasma concentrations (Preskorn et al, 1994).
c) A 75-year-old female experienced symptomatic increases in her desipramine serum concentrations when fluoxetine was added. Desipramine serum levels ranged from 109 to 150 ng/mL with oral doses of 300 mg at bedtime prior to fluoxetine therapy. Following the addition of oral fluoxetine 20 mg daily to the regimen, the desipramine serum level increased to 212 ng/mL within five days. The fluoxetine dose was increased to 40 mg/day three days later, and the desipramine serum level was 419 ng/mL after four days. A worsening of depression and severe fatigue coincided with the increases in desipramine serum levels. Withdrawal of fluoxetine and reduction in the desipramine dose to 200 mg daily reduced the desipramine serum level to 231 ng/mL within two weeks (Bell & Cole, 1988).
d) A 33-year-old depressed male developed adverse effects of dry mouth, tinnitus, and difficulties with alertness and memory while receiving fluoxetine 40 mg daily and desipramine 150 mg daily for five weeks; fluoxetine was discontinued and the blood levels of desipramine decreased from 938 to 48 ng/mL with resolution of clinical symptoms (Goodnick, 1989).
e) A 39-year-old female experienced symptomatic increases in her desipramine levels with concomitant fluoxetine therapy. Prior to fluoxetine therapy, the patient's measured levels of desipramine had ranged from 148 to 160 ng/mL on a regimen of 300 mg daily. Five weeks after the addition of fluoxetine 20 mg daily, she reported anticholinergic symptoms, sedation, and confusion with a desipramine level of 527 ng/mL. The desipramine dose was lowered to 200 mg/day; eleven days later, the level was 244 ng/mL; the patient reported decreased energy, impaired short-term memory, and some "garbled" speech, as well as an episode of nausea, dizziness, and syncope. The desipramine dose was reduced to 50 mg/day; the adverse effects resolved in six days. Eight days later, the desipramine level was 122 ng/mL (Downs et al, 1989).
f) Concomitant administration of fluoxetine and desipramine was reported to result in an increased desipramine level and new onset of delirium in a 69-year-old male within 10 days of the addition of fluoxetine to the patient's regimen (Preskorn et al, 1990).

3.5.1.BI Formoterol

1) Interaction Effect: an increased risk of cardiovascular excitation
2) Summary: Concurrent administration of formoterol with a tricyclic antidepressant (TCA) may lead to potentiation of formoterol's adrenergic effects on the cardiovascular system. Therefore, extreme caution is advised if formoterol is administered to patients who are being treated with a TCA (Prod Info FORADIL(R) AEROLIZER(R) inhalation powder, 2006). Monitor patients closely for adverse cardiovascular effects.
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Extreme caution and close observation for adverse cardiovascular effects are warranted when formoterol is administered concurrently with a tricyclic antidepressant (TCA) as the cardiovascular effects of formoterol can be potentiated by TCAs (Prod Info FORADIL(R) AEROLIZER(R) inhalation powder, 2006).
7) Probable Mechanism: potentiation of cardiovascular effects

3.5.1.BJ Fosamprenavir

1) Interaction Effect: increased tricyclic agent serum concentrations and potential toxicity (anticholinergic effects, sedation, confusion, cardiac arrhythmias)
2) Summary: Coadministration of fosamprenavir with a tricyclic antidepressant may provoke increased serum concentrations of the tricyclic antidepressant, causing a potential risk of arrhythmias or other serious adverse effects. Fosamprenavir is a prodrug of amprenavir, an inhibitor of the CYP3A4 isoenzyme in addition to being a CYP3A4 substrate. Tricyclic agents may partially depend on the CYP3A4 pathway for metabolism. Plasma concentrations of the tricyclic agent should be closely monitored in patients also receiving fosamprenavir (Prod Info LEXIVA(R) oral solution, oral tablets, 2009).

3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: If concomitant therapy with fosamprenavir and a tricyclic antidepressant is unavoidable, plasma concentrations of the tricyclic agent should be closely monitored. Also monitor patients for signs and symptoms of tricyclic toxicity (anticholinergic effects, sedation, confusion, cardiac arrhythmias) (Prod Info LEXIVA(R) oral solution, oral tablets, 2009).
7) Probable Mechanism: inhibition of CYP3A4-mediated tricyclic agent metabolism

3.5.1.BK Foscarnet
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Foscarnet can prolong the QT interval in some patients, which may result in ventricular tachycardia, ventricular fibrillation, and torsades de pointes. Because tricyclic antidepressants may also prolong the QT interval and increase the risk of arrhythmias, the concurrent administration of foscarnet and tricyclic antidepressants is not recommended (Prod Info Foscavir(R), 1998; Marshall & Forker, 1982r).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of foscarnet and tricyclic antidepressants is not recommended.
7) Probable Mechanism: additive cardiac effects

3.5.1.BL Fosphenytoin
1) Interaction Effect: an increased risk of phenytoin toxicity (ataxia, hyperreflexia, nystagmus, tremor)
2) Summary: Fosphenytoin is a prodrug of phenytoin and the same interactions that occur with phenytoin are expected to occur with fosphenytoin (Prod Info Cerebyx(R), 1999). A few case reports have indicated that imipramine inhibits phenytoin metabolism resulting in increased serum phenytoin concentration (Petti & Campbell, 1975; Perucca & Richens, 1977). Tricyclic antidepressants (TCAs) may lower the seizure threshold in epileptic patients stabilized on anticonvulsants. Theoretically, because phenytoin is an enzyme inducer, the metabolism of antidepressants may be increased resulting in reduced TCA serum levels.
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Consider monitoring phenytoin serum levels if a tricyclic antidepressant is added to therapy or if the patient begins to exhibit signs of toxicity (tremor, nystagmus, ataxia, hyperreflexia); lower doses of phenytoin may be required. If phenytoin is added to tricyclic antidepressant therapy, monitor for clinical efficacy of the tricyclic agent.
7) Probable Mechanism: inhibition of phenytoin metabolism

3.5.1.BM Gatifloxacin
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Gatifloxacin may prolong the QT interval in some patients, which may result in ventricular tachycardia, ventricular fibrillation, and torsades de pointes. Although pharmacokinetic studies between gatifloxacin and other drugs which prolong the QT interval have not been performed, an additive effect cannot be excluded. Therefore, the concurrent administration of gatifloxacin and a tricyclic antidepressant is not recommended (Prod Info Tequin(TM), 1999).
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of gatifloxacin and a tricyclic antidepressant is not recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.BN Gemifloxacin
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Although pharmacokinetic studies between gemifloxacin and drugs that prolong the QT interval, such as tricyclic antidepressants, have not been performed, gemifloxacin should be used cautiously when given concurrently with tricyclic antidepressants (Prod Info Factive(R), 2003).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of two drugs that prolong the QT interval, such as gemifloxacin and tricyclic antidepressants, is not recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.BO Grepafloxacin

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Healthy volunteers who received grepafloxacin during a Phase I study experienced prolongation of the QTc interval. On an outpatient basis, grepafloxacin is contraindicated with other drugs that are known to also prolong the QTc interval or cause torsades de pointes, including tricyclic antidepressants. When appropriate cardiac monitoring can be assured, such as in the hospitalized patient, these two agents should be coadministered with caution (Prod Info Raxar(R), 1999).
3) Severity: contraindicated
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: The concurrent use of grepafloxacin and tricyclic antidepressants is contraindicated unless appropriate cardiac monitoring can be assured, such as in the hospitalized patient.
7) Probable Mechanism: additive cardiac effects

3.5.1.BP Guanadrel

1) Interaction Effect: decreased antihypertensive effectiveness
2) Summary: Tricyclic antidepressants inhibit the uptake of guanethidine, and possibly guanadrel into the adrenergic neuron, resulting in an inhibition of its antihypertensive effect (Mitchell et al, 1967; Ober & Wang, 1973). When a patient is on concomitant tricyclic antidepressant and guanadrel therapy, caution should be exercised when the tricyclic antidepressant is discontinued, since an exaggerated effect of guanadrel may be seen (Prod Info Hylorel(R), 1995).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Blood pressure should be monitored for an appropriate clinical response; higher doses of guanadrel may be required. An alternative class of antihypertensive agents, such as an angiotensin-converting enzyme inhibitor might be considered.
7) Probable Mechanism: decreased uptake of guanadrel into adrenergic neurons

3.5.1.BQ Guanethidine

1) Interaction Effect: decreased antihypertensive effectiveness
2) Summary: Tricyclic antidepressants inhibit the uptake of guanethidine, and possibly guanadrel, into the adrenergic neuron, resulting in a inhibition of the antihypertensive effect (Meyer et al, 1970; Pinder et al, 1977).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Blood pressure should be monitored for an appropriate clinical response; higher doses of guanethidine may be required. An alternative class of antihypertensive agents, such as an angiotensin-converting enzyme inhibitor, might be considered.
7) Probable Mechanism: decreased uptake of guanethidine into adrenergic neurons
8) Literature Reports
a) Doses of doxepin of 200 mg daily or more progressively produce blockade of the effects of guanethidine (Fann et al, 1971a; Oates et al, 1969a). Antagonism of the effects of guanethidine developed slowly in one patient (over two to four days), even when given in a dose of 300 mg daily doxepin. Two other patients experienced reversal of the hypotensive effects of guanethidine at doses of doxepin 200 to 300 mg daily. In all cases, the antagonism of antihypertensive effects was less than that of desipramine (Fann et al, 1971a).
b) No antagonism of guanethidine was reported in two patients receiving doxepin 200 mg (Ayd, 1975). However, antagonism was observed at 300 mg doses (Ayd, 1971). A single case report describes a hypertensive crisis in a patient receiving guanethidine and chlorpromazine upon initiation of doxepin therapy less than 200 mg (Poe et al, 1979). Doses of 300 mg a day or more will usually completely reverse the hypotensive effects of guanethidine (Ayd, 1973).

3.5.1.BR Halofantrine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Halofantrine can prolong the QT interval in some patients, which may result in ventricular tachycardia, ventricular fibrillation, and torsades de pointes. Because tricyclic antidepressants may also prolong the QT interval and increase the risk of arrhythmias, the concurrent administration of halofantrine and tricyclic antidepressants is not recommended (Prod Info Halfan(R), 1998; Marshall & Forker, 1982x).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: The concurrent administration of halofantrine and a tricyclic antidepressant is not recommended.
7) Probable Mechanism: additive cardiac effects

3.5.1.BS Haloperidol

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999), haloperidol (O'Brien et al, 1999), risperidone (Duenas-Laita et al, 1999), sertindole (Agelink et al, 2001), quetiapine (Owens, 2001b), sultopride (Lande et al, 1992), and zotepine (Sweetman, 2003). Even though no formal drug interaction studies have been done, the coadministration of a tricyclic antidepressant and an antipsychotic is not recommended (Prod Info Pamelor(R), 2001; Marshall & Forker, 1982p).

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of a tricyclic antidepressant and an antipsychotic is not recommended.

7) Probable Mechanism: additive cardiac effects

8) Literature Reports

a) Electrocardiographic changes that have occurred during clinical trials with pimozide have included prolongation of the corrected QT interval, flattening, notching, and inversion of the T wave and the appearance of U waves. In experimental studies, sudden, unexpected deaths have occurred while patients were receiving pimozide doses of 1 mg/kg. The proposed mechanism for these deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmias (Prod Info Orap(R), 1999).

3.5.1.BT Halothane

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Halothane may prolong the QT interval in some patients (Owens, 2001a). Because tricyclic antidepressants may also prolong the QT interval and increase the risk of arrhythmias, the concurrent administration of halothane and tricyclic antidepressants is not recommended (Marshall & Forker, 1982o).

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Because of the potential for additive QT interval prolongation, the concurrent administration of halothane and tricyclic antidepressants is not recommended.

7) Probable Mechanism: additive effects on QT prolongation

3.5.1.BU Heptabarbital

1) Interaction Effect: possible decreased tricyclic antidepressant serum concentrations and possible additive adverse effects

2) Summary: Concomitant barbiturate and tricyclic antidepressant (TCA) therapy may result in increased metabolism of the TCA. There have been scattered reports of individuals with decreased serum levels of TCAs in the presence of a barbiturate (Moody et al, 1977; Silverman & Braithwaite, 1972; Burrows & Davies, 1971). In addition, TCAs can worsen seizure control by reducing the seizure threshold (Brodie, 1992). These drugs also have additive CNS and respiratory depressant effects.

3) Severity: minor

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Monitor for efficacy of antidepressant effect. Increases in tricyclic antidepressant dosages may be required. Additionally, monitor for toxicity when either drug is added to or withdrawn from therapy. Serum concentrations may be of value in determining appropriate dosage.

7) Probable Mechanism: increased tricyclic antidepressant metabolism

8) Literature Reports

a) The pharmacokinetics of a single oral dose of desipramine (100 mg) were studied in eight epileptic patients chronically treated with phenobarbital and in eight drug-free healthy controls (Spina et al, 1996). All subjects were extensive metabolizers with respect to the genetically determined CYP2D6-related metabolic polymorphism. Compared with controls, epileptic patients exhibited lower peak plasma desipramine concentrations (74 nmol/L vs. 107 nmol/L), smaller desipramine area under the concentration-time curve values (1943 nmol/L/h vs. 3234 nmol/L/h), and shorter desipramine elimination half-lives (15.1 h vs. 20.6 h). All barbiturates are believed to have similar effects leading to induction of hepatic enzymes and the 2D6 isozyme is believed to be important in the metabolism of most or all TCAs. Thus, similar effects should be expected with any combination of TCA and barbiturate.

3.5.1.BV Hexobarbital

1) Interaction Effect: possible decreased tricyclic antidepressant serum concentrations and possible additive adverse effects

2) Summary: Concomitant barbiturate and tricyclic antidepressant (TCA) therapy may result in increased metabolism of the TCA. There have been scattered reports of individuals with decreased serum levels of

TCAs in the presence of a barbiturate (Moody et al, 1977; Silverman & Braithwaite, 1972; Burrows & Davies, 1971). In addition, TCAs can worsen seizure control by reducing the seizure threshold (Brodie, 1992). These drugs also have additive CNS and respiratory depressant effects.
3) Severity: minor
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor for efficacy of antidepressant effect. Increases in tricyclic antidepressant dosages may be required. Additionally, monitor for toxicity when either drug is added to or withdrawn from therapy. Serum concentrations may be of value in determining appropriate dosage.
7) Probable Mechanism: increased tricyclic antidepressant metabolism
8) Literature Reports
a) The pharmacokinetics of a single oral dose of desipramine (100 mg) were studied in eight epileptic patients chronically treated with phenobarbital and in eight drug-free healthy controls (Spina et al, 1996). All subjects were extensive metabolizers with respect to the genetically determined CYP2D6-related metabolic polymorphism. Compared with controls, epileptic patients exhibited lower peak plasma desipramine concentrations (74 nmol/L vs. 107 nmol/L), smaller desipramine area under the concentration-time curve values (1943 nmol/L/h vs. 3234 nmol/L/h), and shorter desipramine elimination half-lives (15.1 h vs. 20.6 h). All barbiturates are believed to have similar effects leading to induction of hepatic enzymes and the 2D6 isozyme is believed to be important in the metabolism of most or all TCAs. Thus, similar effects should be expected with any combination of TCA and barbiturate.

3.5.1.BW Hydroquinidine
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Class Ia antiarrhythmics and tricyclic antidepressants have been shown to prolong the QTc interval at the recommended therapeutic dose. Even though no formal drug interaction studies have been done, the coadministration of Class Ia antiarrhythmics and other drugs known to prolong the QTc interval, including tricyclic antidepressants, is not recommended (Prod Info Elavil(R), 1999g; Prod Info Quinaglute(R), 1999; Marshall & Forker, 1982m).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: The concurrent administration of a Class IA antiarrhythmic agent and a tricyclic antidepressant is not recommended.
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) Quinidine is an inhibitor of the cytochrome P450 isoenzyme responsible for the 2-hydroxylation of imipramine and desipramine (Brosen & Gram, 1989). Inhibition of this enzyme system can result in a 35% decrease in imipramine clearance and 85% decrease in desipramine clearance. Demethylation of imipramine by the cytochrome P450 system is unaffected by this interaction. Until more information is available all patients having quinidine added to drug regimen containing imipramine or desipramine should be monitored for increased antidepressant serum concentrations and potential toxicity.
b) An increased incidence in sudden death was observed in six out of 53 patients with cardiac disease receiving amitriptyline, compared to 0 out of 53 in the control group. It was recommended that amitriptyline be avoided in patients with underlying cardiac disease except when depression was debilitating and no other drugs were helpful (Moir et al, 1972; Coull et al, 1970).
c) In a placebo controlled study, imipramine 3.5 mg/kg was administered daily for seven patients with severe depression and titrated doses to obtain therapeutic plasma concentrations. Two patients displayed premature atrial depolarizations and premature ventricular depolarizations before therapy. On patient had 33 premature atrial depolarizations (PAD) and 30 premature ventricular depolarizations (PVD) per hour, which decreased to 0.4 PAC and zero PVC per hour on imipramine. The other patient had 12 PAD and 169 PVD per hour before treatment and 1.8 PAD and 28.1 PVD per hour on imipramine. The authors also cautioned that the incidence of cardiotoxicity may increase if tricyclic antidepressants are administered with Type I antiarrhythmics. It was also recommended that quinidine and procainamide not be used to treat the arrhythmias of a tricyclic overdose. The similarities between these agents may exacerbate the cardiotoxicity (Kantor et al, 1978).

3.5.1.BX Ibutilide
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Cases of QTc prolongation and/or torsades de pointes have been reported with all Class III antiarrhythmic agents, including acecainide (Chow et al, 1984), amiodarone (Faggiano et al, 1996), azimilide (Corey et al, 1999), bretylium (Gilman et al, 1985a), ibutilide (Rodriguez et al, 2001), sematilide (Singh, 1996), dofetilide (Allen et al, 2002), and sotalol (Marill & Runge, 2001). Even though no formal drug interaction studies have been done, the coadministration of Class III antiarrhythmics and other drugs known to prolong the QTc interval, including tricyclic antidepressants, is not recommended (Yamreudeewong et al, 2003a; Prod Info Corvert(R), 2000).
3) Severity: major

4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of a Class III antiarrhythmic and a tricyclic antidepressant (TCA) is not recommended.
7) Probable Mechanism: additive QT prolongation
8) Literature Reports
a) EKG effects reported in patients receiving therapeutic doses of tricyclic antidepressants include increased heart rate, prolonged PR interval, intraventricular conduction delays, increased corrected QT interval (QTc) and flattened T waves (Marshall & Forker, 1982y).
b) Concurrent use of Class III antiarrhythmic agents, and other drugs that can prolong the QT interval, such as tricyclic antidepressants, is not recommended. Dofetilide should be stopped for at least 2 days before any interacting drug is initiated. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised (Yamreudeewong et al, 2003).

3.5.1.BY Iproniazid
1) Interaction Effect: neurotoxicity, seizures, or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)
2) Summary: Concomitant TCA and MAOI use has resulted in hyperpyrexia, convulsions, and death. Concurrent use of MAOIs and TCAs has also been reported to result in a condition termed serotonin syndrome (Insel et al, 1982o; Spigset et al, 1993p; Brodribb et al, 1994m; Neuvonen et al, 1993g). Serotonin syndrome is a rare but potentially fatal condition of serotonergic hyperstimulation characterized by hypertension, hyperthermia, myoclonus, and changes in mental status (Sternbach, 1991h). If TCAs and MAOIs must be used concurrently, avoid large doses, use only oral TCAs, avoid imipramine, clomipramine, desipramine, and tranylcypromine, and monitor patients closely (Schuckit et al, 1971q; White & Simpson, 1984m).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Concomitant use of a tricyclic antidepressant (TCA) and a monoamine oxidase inhibitor (MAOI) should be done only with close monitoring and where the clinical benefit outweighs the potential risk. Other antidepressant therapy should first be considered. Consider using a 14 day washout period between treatment with both medicines. If deemed clinically necessary, avoid large doses and use agents other than imipramine, clomipramine, desipramine, and tranylcypromine.
7) Probable Mechanism: altered catecholamine uptake and metabolism
8) Literature Reports
a) Concomitant administration of monoamine oxidase inhibitors (MAOIs) with tricyclic antidepressants (TCAs) has been considered an absolute contraindication in the past. Reports of excitation, hyperpyrexia, convulsions, and possible death have been attributed to the combination (Lockett & Milner, 1965h; Winston, 1971h; Schuckit et al, 1971p; Spiker & Pugh, 1976h). The mechanism may relate to the combined inhibition of catecholamine reuptake into the central nervous system and inhibition of catecholamine metabolism (Sjoqvist, 1965h).
b) Administration of a TCA after MAOI therapy may result in the development of serotonin syndrome. In a double-blind, crossover study examining the effects of clorgyline and clomipramine for the treatment of obsessive-compulsive disorder, two subjects developed severe reactions characteristic of serotonin syndrome. During the study, patients had received clorgyline therapy, followed by a washout period of approximately four weeks and subsequent clomipramine therapy. After taking the first 100 mg dose of clomipramine, one patient developed coarse myoclonic jerking in both legs, hyperreflexia, diaphoresis, and arrhythmia. Another patient developed a similar reaction after the first dose, with upper motor neuron symptoms, myoclonic movements, and cardiac irritability. Both patient's symptoms resolved several hours later, and both patients were later treated successfully with clomipramine without adverse effects (Insel et al, 1982n).
c) A drug interaction occurred in a 76-year old woman who had been taking clomipramine 50 mg daily for several months prior to switching to moclobemide 300 mg daily. The patient experienced somnolescence, confusion, and fever which then progressed to further mental impairment, muscle stiffness, myoclonus, and convulsive attacks. The patient's symptoms were described as fulfilling the diagnostic criteria for serotonin syndrome and were resolved a few days later after discontinuing all antidepressant medications (Spigset et al, 1993o).
d) In one case, clomipramine 10 mg twice daily was added to a stable regimen of tranylcypromine in a physically healthy 34-year old man. After taking several doses, the patients developed symptoms of nausea and profuse sweating, followed by pyrexia, dyspnea, and agitation. The hyperpyrexical state led to disseminated intravascular coagulation and eventual death (Tackley & Tregaskis, 1987h).
e) There is evidence that MAOIs and TCAs can be given concomitantly in patients previously unresponsive to the MAOI or TCA alone. The combination may be utilized in one of two ways. Most frequently, the recommendation is to stop all previous antidepressants (five to ten days for TCAs and 14 days for MAOIs); the combination is then simultaneously started (Perry et al, 1991g). Alternatively, in a patient previously receiving a TCA, small doses of the MAOI may be slowly added (Schoonover, 1983). Numerous studies in patients with refractory depression or phobic anxiety states have successfully used the combination of MAOIs and TCAs (Ponto et al, 1977h; Schuckit et al, 1971p; Ashcroft, 1975g).

3.5.1.BZ Isocarboxazid

1) Interaction Effect: neurotoxicity, seizures, or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)

2) Summary: The concurrent administration of isocarboxazid and doxepin is contraindicated (Prod Info Marplan(R), 1998). Concomitant TCA and MAOI use has resulted in hyperpyrexia, convulsions, and death. Concurrent use of MAOIs and TCAs has also been reported to result in a condition termed serotonin syndrome (Insel et al, 1982r; Spigset et al, 1993s; Brodribb et al, 1994q; Neuvonen et al, 1993i). Serotonin syndrome is a rare but potentially fatal condition of serotonergic hyperstimulation characterized by hypertension, hyperthermia, myoclonus, and changes in mental status (Sternbach, 1991j). If TCAs and MAOIs must be used concurrently, avoid large doses, use only oral TCAs, avoid imipramine, clomipramine, desipramine, and tranylcypromine, and monitor patients closely (Schuckit et al, 1971u; White & Simpson, 1984p).

3) Severity: contraindicated

4) Onset: delayed

5) Substantiation: established

6) Clinical Management: The concurrent use of doxepin and isocarboxazid is contraindicated. In patients being transferred to isocarboxazid therapy from a dibenzazepine-related entity, allow at least a one-week medication-free interval and then initiate isocarboxazid at one-half of the normal dose for at least the first week of therapy. Also allow one week to elapse between the discontinuation of isocarboxazid and the administration of another MAO inhibitor or dibenzazepine-related entity.

7) Probable Mechanism: altered catecholamine uptake and metabolism

8) Literature Reports

a) Concomitant administration of monoamine oxidase inhibitors (MAOI) with tricyclic antidepressants (TCAs) has been considered an absolute contraindication in the past and still is listed as such by the manufacturers. Reports of excitation, hyperpyrexia, convulsions, and possible death have been attributed to the combination (Lockett & Milner, 1965j; Brachfeld et al, 1963f; Winston, 1971j; Schuckit et al, 1971t; Sargent, 1965f; Spiker & Pugh, 1976j). The mechanism may relate to the combined inhibition of catecholamine reuptake into the central nervous system and inhibition of catecholamine metabolism (Sjoqvist, 1965j).

b) The development of serotonin syndrome was first reported due to administration of a TCA after MAOI therapy. In a double-blind, crossover study examining the effects of clorgyline and clomipramine for the treatment of obsessive-compulsive disorder, two subjects developed severe reactions characteristic of serotonin syndrome. During the study, patients had received clorgyline therapy, followed by a washout period of approximately four weeks and subsequent clomipramine therapy. After taking the first 100 mg dose of clomipramine, one patient developed coarse myoclonic jerking in both legs, hyperreflexia, diaphoresis, and arrhythmia. Another patient developed a similar reaction after the first dose, with upper motor neuron symptoms, myoclonic movements, and cardiac irritability. Both patient's symptoms resolved several hours later, and both patients were later treated successfully with clomipramine without adverse effects (Insel et al, 1982q).

c) A drug interaction was reported when a 76-year old woman who had been taking clomipramine 50 mg daily for several months was switched to moclobemide 300 mg daily. The patient experienced somnolescence, confusion, and fever which then progressed to further mental impairment, muscle stiffness, myoclonus, and convulsive attacks. The patient's symptoms were described as fulfilling the diagnostic criteria for serotonin syndrome and were resolved a few days later after discontinuing all antidepressant medications (Spigset et al, 1993r).

d) A 39-year old woman with bipolar disorder developed serotonin syndrome after imipramine was added to moclobemide. The patient was taking moclobemide 300 mg twice daily when imipramine was started at 50 mg daily, followed by two dosage increases of imipramine to 200 mg and a reduction of moclobemide dosage to 150 mg twice daily. Five days after the increase in imipramine to 200 mg per day, the patient developed symptoms of serotonin syndrome, including sweating, shivering, confusion, fever, and spasms in the extremities. The patient was treated with chlorpromazine and symptoms resolved over the next few days without further complications (Brodribb et al, 1994p).

e) Three patients with bipolar disorder developed manic symptoms while undergoing concurrent therapy with isocarboxazid and amitriptyline. In all three cases the patients had been given MAOIs and TCAs alone without complications. It was only when the drugs were used in combination that symptoms of mania emerged, suggesting a synergistic effect (de la Fuente et al, 1986e).

f) In one case, clomipramine 10 mg twice daily was added to a stable regimen of tranylcypromine in a physically healthy 34-year old man. After taking several doses, the patients developed symptoms of nausea and profuse sweating, followed by pyrexia, dyspnea, and agitation. The hyperpyrexical state led to disseminated intravascular coagulation and eventual death (Tackley & Tregaskis, 1987i).

g) There is evidence that MAOIs and TCAs can be given concomitantly in patients previously unresponsive to the MAOI or TCA alone. A few precautions must be followed including: a) avoidance of large doses (no more than 150 mg amitriptyline or its equivalent, 45 mg phenelzine, or 60 mg isocarboxazid) b) oral administration c) avoidance of clomipramine, imipramine, desipramine, and tranylcypromine in any combination, and d) close monitoring of patients (Kline, 1974e; Winston, 1971j; Schuckit et al, 1971t; White & Simpson, 1984o; Rom & Benner, 1972e). The combination may be utilized in one of two ways. Most frequently, the recommendation is to stop all previous antidepressants

(five to ten days for TCAs and 14 days for MAOIs); the combination is then simultaneously started (Perry et al, 1991i). Alternatively, in a patient previously receiving a TCA, small doses of the MAOI may be slowly added (Schoonover, 1983). Some sources suggest that the combination of amitriptyline and isocarboxazid is preferred (Perry et al, 1991i). Numerous studies in patients with refractory depression or phobic anxiety states have successfully used the combination of MAOIs and TCAs (Ponto et al, 1977j; Schuckit et al, 1971t; Ashcroft, 1975i).

3.5.1.CA Isoflurane

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Isoflurane may prolong the QT interval in some patients (Owens, 2001c). Because tricyclic antidepressants may also prolong the QT interval and increase the risk of arrhythmias, the concurrent administration of isoflurane and tricyclic antidepressants is not recommended (Marshall & Forker, 1982s).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Because of the potential for additive QT interval prolongation, the concurrent administration of isoflurane and a tricyclic antidepressants is not recommended.
7) Probable Mechanism: additive effect on QT prolongation

3.5.1.CB Isradipine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Isradipine can prolong the QT interval in some patients, which may result in ventricular tachycardia, ventricular fibrillation, and torsades de pointes. Because tricyclic antidepressants may also prolong the QT interval and increase the risk of arrhythmias, the concurrent administration of isradipine with a tricyclic antidepressant is not recommended (Prod Info DynaCirc(R), 2000; Marshall & Forker, 1982w).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of isradipine and a tricyclic antidepressant is not recommended.
7) Probable Mechanism: additive cardiac effects

3.5.1.CC Levomethadyl

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Levomethadyl can prolong the QT interval in some patients, which may result in ventricular tachycardia, ventricular fibrillation, and torsades de pointes. Because doxepin may also prolong the QT interval and increase the risk of arrhythmias, the concurrent administration of levomethadyl with doxepin is contraindicated (Prod Info Orlaam(R), 2001; Giardina et al, 1987).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of levomethadyl and doxepin is contraindicated.
7) Probable Mechanism: additive cardiac effects

3.5.1.CD Linezolid

1) Interaction Effect: increased risk of serotonin syndrome (hyperthermia, hyperreflexia, myoclonus, mental status changes)
2) Summary: Concomitant use of linezolid and a tricyclic antidepressant, such as doxepin, is contraindicated in the absence of monitoring for serotonin syndrome. If symptoms occur, consider discontinuation of either one or both of the drugs. Linezolid is a reversible, nonselective inhibitor of monoamine oxidase and may therefore interact with tricyclic antidepressants. Spontaneous reports of serotonin syndrome associated with the co-administration of linezolid and serotonergic agents have been reported (Prod Info ZYVOX(R) IV injection, oral tablets, oral suspension, 2008).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concurrent use of linezolid and tricyclic antidepressants, such as doxepin, is contraindicated unless patient is closely observed for signs and/or symptoms of serotonin syndrome. If concomitant use is clinically warranted, monitor for signs and symptoms of serotonin syndrome, such as neuromuscular abnormalities (including hyper-reflexia, tremor, muscle rigidity, clonus, peripheral hypertonicity, and shivering), autonomic hyperactivity (including tachycardia, mydriasis, diaphoresis, the presence of bowel sounds, and diarrhea), and mental status changes (including agitation and delirium). Serotonin syndrome can be life-threatening. If serotonin syndrome develops, discontinue the offending agents and provide supportive care and other therapy as necessary (Boyer & Shannon, 2005; Prod Info ZYVOX(R) IV injection, oral tablets, oral suspension, 2008).

7) Probable Mechanism: linezolid inhibition of monoamine oxidase resulting in an increased concentration of serotonin

3.5.1.CE Lisdexamfetamine

1) Interaction Effect: hypertension, other cardiac effects, and CNS stimulation

2) Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been reported to result in enhanced amphetamine effects from the release of norepinephrine (Beaumont, 1973d; Raisfeld, 1972). A similar reaction might also occur with all drugs that have amphetamine-like effects. Acute elevations in blood pressure have been noted (Flemenbaum, 1971a). Some amphetamine-like drugs may inhibit the metabolism of TCAs, although most combinations have not been studied. When amphetamine analogs are being used to treat obesity, it should be noted that TCAs frequently lead to moderate weight gain (Russ & Ackerman, 1988). False positive urine tests for amphetamines have been reported during therapy with some TCAs (Merigian & Browning, 1993). Caution is advised when concurrent administration of amphetamine-like agents and TCAs is warranted. The patient should be closely monitored for increased cardiovascular effects (hypertension and dysrhythmias).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other sympathomimetic agents could lead to hypertension, increased cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006; Flemenbaum, 1972). Use caution if such therapy is warranted. Monitor the patient closely for hypertension and dysrhythmias.

7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission

8) Literature Reports

a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agents. Additionally, coadministration of d-amphetamine with TCAs such as desipramine or protriptyline results in sustained increases in d-amphetamine concentration in the brain (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006).

b) Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism of some tricyclic antidepressants, such as imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transdermal system, 2006).

c) Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases in blood pressure such that the hypotensive effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of combined therapy. Discontinuation of the methylphenidate usually results in the blood pressure returning to normotensive levels; reinstitution of the methylphenidate resulted in further blood pressure elevation (Flemenbaum, 1971; Flemenbaum, 1972).

d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine given for at least four weeks, were given fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical improvement. However, fenfluramine more than doubled steady-state plasma levels of desipramine (Price et al, 1990).

e) There have been claims based on uncontrolled studies that a better antidepressant response may occur with combined therapy (Garrettson et al, 1969). However, a systemic review of stimulants in the treatment of depression concluded that although uncontrolled studies were generally positive, the ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated little advantage of drug over placebo and did not appear to be as effective as the conventional antidepressants in primary depression (Satel & Nelson, 1989).

3.5.1.CF Mazindol

1) Interaction Effect: hypertension, other cardiac effects, and CNS stimulation

2) Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been reported to result in enhanced amphetamine effects from the release of norepinephrine (Beaumont, 1973d; Raisfeld, 1972). A similar reaction might also occur with all drugs that have amphetamine-like effects. Acute elevations in blood pressure have been noted (Flemenbaum, 1971a). Some amphetamine-like drugs may inhibit the metabolism of TCAs, although most combinations have not been studied. When amphetamine analogs are being used to treat obesity, it should be noted that TCAs frequently lead to moderate weight gain (Russ & Ackerman, 1988). False positive urine tests for amphetamines have been reported during therapy with some TCAs (Merigian & Browning, 1993). Caution is advised when concurrent administration of amphetamine-like agents and TCAs is warranted. The patient should be closely monitored for increased cardiovascular effects (hypertension and dysrhythmias).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other sympathomimetic agents could lead to hypertension, increased cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006; Flemenbaum, 1972). Use caution if such

therapy is warranted. Monitor the patient closely for hypertension and dysrhythmias.
7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission
8) Literature Reports
a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agents. Additionally, coadministration of d-amphetamine with TCAs such as desipramine or protriptyline results in sustained increases in d-amphetamine concentration in the brain (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006).
b) Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism of some tricyclic antidepressants, such as imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transdermal system, 2006).
c) Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases in blood pressure such that the hypotensive effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of combined therapy. Discontinuation of the methylphenidate usually results in the blood pressure returning to normotensive levels; reinstitution of the methylphenidate resulted in further blood pressure elevation (Flemenbaum, 1971; Flemenbaum, 1972).
d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine given for at least four weeks, were given fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical improvement. However, fenfluramine more than doubled steady-state plasma levels of desipramine (Price et al, 1990).
e) There have been claims based on uncontrolled studies that a better antidepressant response may occur with combined therapy (Garrettson et al, 1969). However, a systemic review of stimulants in the treatment of depression concluded that although uncontrolled studies were generally positive, the ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated little advantage of drug over placebo and did not appear to be as effective as the conventional antidepressants in primary depression (Satel & Nelson, 1989).

3.5.1.CG Mephentermine
1) Interaction Effect: hypertension, other cardiac effects, and CNS stimulation
2) Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been reported to result in enhanced amphetamine effects from the release of norepinephrine (Beaumont, 1973d; Raisfeld, 1972). A similar reaction might also occur with all drugs that have amphetamine-like effects. Acute elevations in blood pressure have been noted (Flemenbaum, 1971a). Some amphetamine-like drugs may inhibit the metabolism of TCAs, although most combinations have not been studied. When amphetamine analogs are being used to treat obesity, it should be noted that TCAs frequently lead to moderate weight gain (Russ & Ackerman, 1988). False positive urine tests for amphetamines have been reported during therapy with some TCAs (Merigian & Browning, 1993). Caution is advised when concurrent administration of amphetamine-like agents and TCAs is warranted. The patient should be closely monitored for increased cardiovascular effects (hypertension and dysrhythmias).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other sympathomimetic agents could lead to hypertension, increased cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006; Flemenbaum, 1972). Use caution if such therapy is warranted. Monitor the patient closely for hypertension and dysrhythmias.
7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission
8) Literature Reports
a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agents. Additionally, coadministration of d-amphetamine with TCAs such as desipramine or protriptyline results in sustained increases in d-amphetamine concentration in the brain (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006).
b) Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism of some tricyclic antidepressants, such as imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transdermal system, 2006).
c) Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases in blood pressure such that the hypotensive effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of combined therapy. Discontinuation of the methylphenidate usually results in the blood pressure returning to normotensive levels; reinstitution of the methylphenidate resulted in further blood pressure elevation (Flemenbaum, 1971; Flemenbaum, 1972).
d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine given for at least four weeks, were given fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical improvement. However, fenfluramine more than doubled steady-state plasma levels of desipramine (Price et al, 1990).
e) There have been claims based on uncontrolled studies that a better antidepressant response may occur with combined therapy (Garrettson et al, 1969). However, a systemic review of stimulants in the

treatment of depression concluded that although uncontrolled studies were generally positive, the ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated little advantage of drug over placebo and did not appear to be as effective as the conventional antidepressants in primary depression (Satel & Nelson, 1989).

3.5.1.CH Mephobarbital

1) Interaction Effect: possible decreased tricyclic antidepressant serum concentrations and possible additive adverse effects

2) Summary: Concomitant barbiturate and tricyclic antidepressant (TCA) therapy may result in increased metabolism of the TCA. There have been scattered reports of individuals with decreased serum levels of TCAs in the presence of a barbiturate (Moody et al, 1977; Silverman & Braithwaite, 1972; Burrows & Davies, 1971). In addition, TCAs can worsen seizure control by reducing the seizure threshold (Brodie, 1992). These drugs also have additive CNS and respiratory depressant effects.

3) Severity: minor

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Monitor for efficacy of antidepressant effect. Increases in tricyclic antidepressant dosages may be required. Additionally, monitor for toxicity when either drug is added to or withdrawn from therapy. Serum concentrations may be of value in determining appropriate dosage.

7) Probable Mechanism: increased tricyclic antidepressant metabolism

8) Literature Reports

a) The pharmacokinetics of a single oral dose of desipramine (100 mg) were studied in eight epileptic patients chronically treated with phenobarbital and in eight drug-free healthy controls (Spina et al, 1996). All subjects were extensive metabolizers with respect to the genetically determined CYP2D6-related metabolic polymorphism. Compared with controls, epileptic patients exhibited lower peak plasma desipramine concentrations (74 nmol/L vs. 107 nmol/L), smaller desipramine area under the concentration-time curve values (1943 nmol/L/h vs. 3234 nmol/L/h), and shorter desipramine elimination half-lives (15.1 h vs. 20.6 h). All barbiturates are believed to have similar effects leading to induction of hepatic enzymes and the 2D6 isozyme is believed to be important in the metabolism of most or all TCAs. Thus, similar effects should be expected with any combination of TCA and barbiturate.

3.5.1.CI Mesoridazine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Although citing no data, the manufacturer of mesoridazine states that concomitant use with other drugs which prolong the QT interval is contraindicated (Prod Info Serentil(R), 2001). Tricyclic antidepressants (TCAs) at therapeutic doses can cause QT prolongation (Marshall & Forker, 1982e).

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concurrent administration of a tricyclic antidepressant and mesoridazine is contraindicated.

7) Probable Mechanism: additive effect on QT interval

3.5.1.CJ Mestranol

1) Interaction Effect: attenuation of antidepressant effectiveness; tricyclic toxicity (drowsiness, hypotension, akathisia)

2) Summary: In isolated cases, the pharmacologic effects of tricyclic antidepressants may be increased or decreased by estrogens (Somani & Khurana, 1973k), with paradoxical loss of antidepressant effect yet tricyclic toxicity being manifested simultaneously (Prange, 1972k). The effects of the interaction appear to be estrogen dose-related (Khurana, 1972k) and may be of clinical importance primarily in patients previously stabilized on tricyclic therapy who are being started on estrogen therapy (Krishnan et al, 1984k).

3) Severity: minor

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: If signs or symptoms of altered tricyclic response are noted, dose adjustment downward of either the estrogen or tricyclic component may be successful in restoring effectiveness or resolving toxicity. However, drug withdrawal may be required.

7) Probable Mechanism: possible estrogen-enhanced hepatic metabolism of the tricyclic

8) Literature Reports

a) Some studies evaluated the qualitative effects of concomitant administration of estrogen and TCAs. In one trial, 30 depressed female prisoners were randomly assigned to 4 treatment groups. Ten patients received placebo, 10 received imipramine (150 milligrams/day) and placebo, 5 patients received imipramine (150 milligrams/day) and ethinyl estradiol (50 micrograms/day), while 5 patients received imipramine (150 milligrams/day) and ethinyl estradiol (25 micrograms/day). The 10 patients that received placebo did not improve over the 6 weeks of the study. The 10 patients taking estrogen and imipramine demonstrated a significantly greater improvement in symptoms than did the 10 patients taking imipramine alone. However, after 2 weeks, the 5 patients that received imipramine and high-dose

estrogen had not improved as much as the patients receiving imipramine and low-dose estrogen. The only side-effect reported was drowsiness, which only affected the patients taking imipramine. Following the discontinuation of ethinyl estradiol, a time period of 2 weeks was required for the high-dose estrogen group to do as well as the low-dose group. This effect was attributed to the presence of residual estrogen in the high-dose group. In another group, 5 women received imipramine 150 milligrams and ethinyl estradiol 50 micrograms daily did not improve as much as 10 patients receiving only imipramine. Also, the patients on the combination had severe side-effects including lethargy, coarse tremor and systolic hypotension (Prange, 1972j).

b) A case reported by (Khurana, 1972j) demonstrated an interaction in a 32-year-old female taking conjugated estrogens 2.5 milligrams and imipramine 100 milligrams. The patient developed lethargy, tremors, and signs of depersonalization. After 2 years of therapy, the patient increased her estrogen dose to 5 milligrams and then 7.5 milligrams daily. The patient became nauseated, had constant headaches, and low normal blood pressure. All lab work was normal. Upon discontinuing the estrogen, the side-effects abated. Some investigators have proposed that the side effects resulted from enhanced TCA effects secondary to estrogen inhibition of hepatic microsomal enzymes (Somani & Khurana, 1973j).

c) In a study women received clomipramine and oral contraceptives or clomipramine alone. At the beginning of the study there were 30 women taking the combination, but 12 subsequently dropped out. The 18 patients on the combination were matched with 18 patients taking clomipramine alone. No significant difference was noted in the patients' responses to clomipramine. It was proposed that there was no significant difference in side-effects between the groups; however, the groups were matched after patients had dropped out of the study. Had the patients been matched prior to the study, different conclusions may have been drawn (Beaumont, 1973f).

d) The effect of oral contraceptives on clomipramine was studied in 42 women between the ages of 18 and 40. Twenty-three women took clomipramine 25 milligrams at bedtime while 19 took clomipramine 25 milligrams at bedtime with oral contraceptives. Over the 4-week study, 3 control patients (2 due to side-effects) and 5 in the experimental group (2 due to side-effects) dropped out. Venous blood samples were drawn at weekly intervals for measurement of serum clomipramine concentrations. No difference in serum concentrations was noted between the groups. However, this result may be partially due to the low dose of clomipramine given (Luscombe & John, 1980e).

e) The onset of akathisia was reported in 3 patients receiving conjugated estrogens and tricyclic antidepressants concurrently. A 24-year-old patient receiving clomipramine 120 milligrams/day for anorexia nervosa and conjugated estrogens 1.25 milligrams/day for amenorrhea developed restless legs and a constant desire to move continuously. Estrogen was discontinued and benztropine 2 milligrams was administered, resulting in marked reduction and resolution within 48 hours. Akathisia and disorientation developed in a 55-year-old patient on conjugated estrogens 1.25 milligrams/day who was prescribed amitriptyline 50 milligrams/day for depression. Within hours of amitriptyline, the patient was confused, restless, and possessed an inner desire to move continuously. Symptoms disappeared after discontinuing amitriptyline. Positive rechallenge at one week with doxepin 100 milligrams, with resolution following discontinuation of doxepin. A third case of akathisia was reported in a 35-year-old patient who received conjugated estrogens 1.25 milligrams/day and amitriptyline 50 milligrams/day. Akathisia developed within a few hours after taking the first dose of amitriptyline and resolved within 48 hours following discontinuation of the antidepressant (Krishnan et al, 1984j).

f) The absolute bioavailability of imipramine increased in women who received low-dose oral contraceptives (50 micrograms or less of ethinyl estradiol) from 27 to 44% (p less than 0.05) as evident by an increase in the area under the plasma concentration time curve (Abernethy et al, 1984e).

g) Estrogens may inhibit the oxidation of TCAs by affecting hepatic microsomal enzymes (John et al, 1980e). Many TCAs are metabolized via oxidation and conjugation pathways. Inhibition of the oxidation of TCAs could result in accumulation and toxicity due to decreased clearance. Estrogens are suspected of possessing other effects on the central nervous system resulting in an antidepressant effect (Oppenheim, 1983e).

3.5.1.CK Methamphetamine

1) Interaction Effect: hypertension, other cardiac effects, and CNS stimulation

2) Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been reported to result in enhanced amphetamine effects from the release of norepinephrine (Beaumont, 1973d; Raisfeld, 1972). A similar reaction might also occur with all drugs that have amphetamine-like effects. Acute elevations in blood pressure have been noted (Flemenbaum, 1971a). Some amphetamine-like drugs may inhibit the metabolism of TCAs, although most combinations have not been studied. When amphetamine analogs are being used to treat obesity, it should be noted that TCAs frequently lead to moderate weight gain (Russ & Ackerman, 1988). False positive urine tests for amphetamines have been reported during therapy with some TCAs (Merigian & Browning, 1993). Caution is advised when concurrent administration of amphetamine-like agents and TCAs is warranted. The patient should be closely monitored for increased cardiovascular effects (hypertension and dysrhythmias).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other

sympathomimetic agents could lead to hypertension, increased cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006; Flemenbaum, 1972). Use caution if such therapy is warranted. Monitor the patient closely for hypertension and dysrhythmias.
7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission
8) Literature Reports
a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agents. Additionally, coadministration of d-amphetamine with TCAs such as desipramine or protriptyline results in sustained increases in d-amphetamine concentration in the brain (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006).
b) Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism of some tricyclic antidepressants, such as imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transdermal system, 2006).
c) Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases in blood pressure such that the hypotensive effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of combined therapy. Discontinuation of the methylphenidate usually results in the blood pressure returning to normotensive levels; reinstitution of the methylphenidate resulted in further blood pressure elevation (Flemenbaum, 1971; Flemenbaum, 1972).
d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine given for at least four weeks, were given fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical improvement. However, fenfluramine more than doubled steady-state plasma levels of desipramine (Price et al, 1990).
e) There have been claims based on uncontrolled studies that a better antidepressant response may occur with combined therapy (Garrettson et al, 1969). However, a systemic review of stimulants in the treatment of depression concluded that although uncontrolled studies were generally positive, the ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated little advantage of drug over placebo and did not appear to be as effective as the conventional antidepressants in primary depression (Satel & Nelson, 1989).

3.5.1.CL Methohexital

1) Interaction Effect: possible decreased tricyclic antidepressant serum concentrations and possible additive adverse effects
2) Summary: Concomitant barbiturate and tricyclic antidepressant (TCA) therapy may result in increased metabolism of the TCA. There have been scattered reports of individuals with decreased serum levels of TCAs in the presence of a barbiturate (Moody et al, 1977; Silverman & Braithwaite, 1972; Burrows & Davies, 1971). In addition, TCAs can worsen seizure control by reducing the seizure threshold (Brodie, 1992). These drugs also have additive CNS and respiratory depressant effects.
3) Severity: minor
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor for efficacy of antidepressant effect. Increases in tricyclic antidepressant dosages may be required. Additionally, monitor for toxicity when either drug is added to or withdrawn from therapy. Serum concentrations may be of value in determining appropriate dosage.
7) Probable Mechanism: increased tricyclic antidepressant metabolism
8) Literature Reports
a) The pharmacokinetics of a single oral dose of desipramine (100 mg) were studied in eight epileptic patients chronically treated with phenobarbital and in eight drug-free healthy controls (Spina et al, 1996). All subjects were extensive metabolizers with respect to the genetically determined CYP2D6-related metabolic polymorphism. Compared with controls, epileptic patients exhibited lower peak plasma desipramine concentrations (74 nmol/L vs. 107 nmol/L), smaller desipramine area under the concentration-time curve values (1943 nmol/L/h vs. 3234 nmol/L/h), and shorter desipramine elimination half-lives (15.1 h vs. 20.6 h). All barbiturates are believed to have similar effects leading to induction of hepatic enzymes and the 2D6 isozyme is believed to be important in the metabolism of most or all TCAs. Thus, similar effects should be expected with any combination of TCA and barbiturate.

3.5.1.CM Methoxamine

1) Interaction Effect: hypertension, cardiac arrhythmias, and tachycardia
2) Summary: Clinical trials have demonstrated a 2- to 8-fold increase in the effects of intravenous infusions of alpha adrenergic drugs to volunteers on tricyclic antidepressants. Arrhythmias and other severe adverse effects have also been reported (Ghose, 1980; Avery, 1973a; Boakes et al, 1973a; Boakes, 1973; Mitchell et al, 1970; Stone et al, 1964). Local use (e.g., dental anesthesia) of epinephrine in concentrations of 1:100,000 or less is less likely to precipitate clinically significant hemodynamic changes (Steinberg & Block, 1971).
3) Severity: major
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: The vasoconstriction and other alpha-adrenergic effects of sympathomimetic drugs

are substantially enhanced in the presence of tricyclic antidepressants (TCAs). Concomitant use should be avoided. If these drugs are given together, careful monitoring and a dose reduction of the sympathomimetic is required. Patients should be instructed to inform their doctor or dentist that they are taking a tricyclic antidepressant prior to any surgery or procedure.

7) Probable Mechanism: inhibition of norepinephrine reuptake

8) Literature Reports

a) Four healthy volunteers received intravenous infusions of various sympathomimetic amines (epinephrine, norepinephrine, phenylephrine, and isoproterenol) before and after imipramine (25 mg three times daily for five days). They showed an increased pressor response to epinephrine (2- to 4-fold), norepinephrine (4- to 8-fold), and phenylephrine (2- to 3-fold) after imipramine, but no difference was observed in the response to isoproterenol. Thus, the increased pressor response appeared to occur only for alpha adrenergic effects. All four subjects demonstrated changes in cardiac rhythm with epinephrine and imipramine consisting of sinus arrhythmia in three subjects and multiple ectopic beats and a nodal rhythm in the fourth subject (Boakes et al, 1973).

b) A review of spontaneous reports of adverse reactions to vasoconstrictors in local anesthetics found that 15 patients receiving a local anesthetic with norepinephrine (1:25,000) had severe reactions (severe headaches, chest tightness, subarachnoid hemorrhage). The drug history was incomplete, but at least three had been taking a tricyclic antidepressant at the time (Anon, 1972).

3.5.1.CN Methylphenidate

1) Interaction Effect: hypertension, other cardiac effects, and CNS stimulation

2) Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been reported to result in enhanced amphetamine effects from the release of norepinephrine (Beaumont, 1973d; Raisfeld, 1972). A similar reaction might also occur with all drugs that have amphetamine-like effects. Acute elevations in blood pressure have been noted (Flemenbaum, 1971a). Some amphetamine-like drugs may inhibit the metabolism of TCAs, although most combinations have not been studied. When amphetamine analogs are being used to treat obesity, it should be noted that TCAs frequently lead to moderate weight gain (Russ & Ackerman, 1988). False positive urine tests for amphetamines have been reported during therapy with some TCAs (Merigian & Browning, 1993). Caution is advised when concurrent administration of amphetamine-like agents and TCAs is warranted. The patient should be closely monitored for increased cardiovascular effects (hypertension and dysrhythmias).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other sympathomimetic agents could lead to hypertension, increased cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006; Flemenbaum, 1972). Use caution if such therapy is warranted. Monitor the patient closely for hypertension and dysrhythmias.

7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission

8) Literature Reports

a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agents. Additionally, coadministration of d-amphetamine with TCAs such as desipramine or protriptyline results in sustained increases in d-amphetamine concentration in the brain (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006).

b) Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism of some tricyclic antidepressants, such as imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transdermal system, 2006).

c) Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases in blood pressure such that the hypotensive effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of combined therapy. Discontinuation of the methylphenidate usually results in the blood pressure returning to normotensive levels; reinstitution of the methylphenidate resulted in further blood pressure elevation (Flemenbaum, 1971; Flemenbaum, 1972).

d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine given for at least four weeks, were given fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical improvement. However, fenfluramine more than doubled steady-state plasma levels of desipramine (Price et al, 1990).

e) There have been claims based on uncontrolled studies that a better antidepressant response may occur with combined therapy (Garrettson et al, 1969). However, a systemic review of stimulants in the treatment of depression concluded that although uncontrolled studies were generally positive, the ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated little advantage of drug over placebo and did not appear to be as effective as the conventional antidepressants in primary depression (Satel & Nelson, 1989).

3.5.1.CO Midodrine

1) Interaction Effect: hypertension, cardiac arrhythmias, and tachycardia

2) Summary: Clinical trials have demonstrated a 2- to 8-fold increase in the effects of intravenous infusions

of alpha adrenergic drugs to volunteers on tricyclic antidepressants. Arrhythmias and other severe adverse effects have also been reported (Ghose, 1980; Avery, 1973a; Boakes et al, 1973a; Boakes, 1973; Mitchell et al, 1970; Stone et al, 1964). Local use (e.g., dental anesthesia) of epinephrine in concentrations of 1:100,000 or less is less likely to precipitate clinically significant hemodynamic changes (Steinberg & Block, 1971).

3) Severity: major

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: The vasoconstriction and other alpha-adrenergic effects of sympathomimetic drugs are substantially enhanced in the presence of tricyclic antidepressants (TCAs). Concomitant use should be avoided. If these drugs are given together, careful monitoring and a dose reduction of the sympathomimetic is required. Patients should be instructed to inform their doctor or dentist that they are taking a tricyclic antidepressant prior to any surgery or procedure.

7) Probable Mechanism: inhibition of norepinephrine reuptake

8) Literature Reports

a) Four healthy volunteers received intravenous infusions of various sympathomimetic amines (epinephrine, norepinephrine, phenylephrine, and isoproterenol) before and after imipramine (25 mg three times daily for five days). They showed an increased pressor response to epinephrine (2- to 4-fold), norepinephrine (4- to 8-fold), and phenylephrine (2- to 3-fold) after imipramine, but no difference was observed in the response to isoproterenol. Thus, the increased pressor response appeared to occur only for alpha adrenergic effects. All four subjects demonstrated changes in cardiac rhythm with epinephrine and imipramine consisting of sinus arrhythmia in three subjects and multiple ectopic beats and a nodal rhythm in the fourth subject (Boakes et al, 1973).

b) A review of spontaneous reports of adverse reactions to vasoconstrictors in local anesthetics found that 15 patients receiving a local anesthetic with norepinephrine (1:25,000) had severe reactions (severe headaches, chest tightness, subarachnoid hemorrhage). The drug history was incomplete, but at least three had been taking a tricyclic antidepressant at the time (Anon, 1972).

3.5.1.CP Moclobemide

1) Interaction Effect: neurotoxicity, seizures, or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)

2) Summary: Concomitant TCA and MAOI use has resulted in hyperpyrexia, convulsions, and death. Concurrent use of MAOIs and TCAs has also been reported to result in a condition termed serotonin syndrome (Insel et al, 1982c; Spigset et al, 1993c; Brodribb et al, 1994b; Neuvonen et al, 1993a). Serotonin syndrome is a rare but potentially fatal condition of serotonergic hyperstimulation characterized by hypertension, hyperthermia, myoclonus, and changes in mental status (Sternbach, 1991b). Consequently, coadministration of TCAs and MAOIs is contraindicated in most cases. If TCAs and MAOIs must be used concurrently, avoid large doses, use only oral TCAs, avoid imipramine, clomipramine, desipramine, and tranylcypromine, and monitor patients closely (Schuckit et al, 1971e; White & Simpson, 1984c).

3) Severity: contraindicated

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: Concomitant use of moclobemide and a tricyclic antidepressant, such as doxepin, is contraindicated. If doxepin is replacing treatment with moclobemide, a minimum of two days should elapse after moclobemide is discontinued and doxepin therapy is begun (Prod Info Manerix(R), 2001). However, the manufacturer of doxepin recommends that the monoamine oxidase inhibitor (MAOI) be discontinued for at least 14 days before treatment with doxepin is initiated (Prod Info SINEQUAN(R) oral capsule, 2005). There is no specific washout period for replacing doxepin treatment with moclobemide. However, it is advisable to gradually taper the tricyclic antidepressant dosage before starting treatment with and MAOI (Remick, 2002).

7) Probable Mechanism: altered catecholamine uptake and metabolism

8) Literature Reports

a) Concomitant administration of monoamine oxidase inhibitors (MAOIs) with tricyclic antidepressants (TCAs) has been considered an absolute contraindication in the past and still is listed as such by the manufacturers (Prod Info Manerix(R), 2001). Reports of excitation, hyperpyrexia, convulsions, and possible death have been attributed to the combination (Lockett & Milner, 1965b; Brachfeld et al, 1963a; Winston, 1971b; Schuckit et al, 1971d; Sargent, 1965a; Spiker & Pugh, 1976b). The mechanism may relate to the combined inhibition of catecholamine reuptake into the central nervous system and inhibition of catecholamine metabolism (Sjoqvist, 1965b).

b) A clinical study designed to detect an interaction between moclobemide and a tricyclic antidepressant (clomipramine) resulted in severe adverse effects, and the study was terminated. Information about interactions with moclobemide and other tricyclic antidepressants is limited (Prod Info Manerix(R), 2001).

c) A drug interaction occurred in which a 76-year old woman who had been taking clomipramine 50 mg daily for several months prior to switching to moclobemide 300 mg daily. The patient experienced somnolence, confusion, and fever which then progressed to further mental impairment, muscle stiffness, myoclonus, and convulsive attacks. The patient's symptoms were described as fulfilling the diagnostic criteria for serotonin syndrome and were resolved a few days later after discontinuing all

antidepressant medications (Spigset et al, 1993b).
d) Administration of a TCA after MAOI therapy may result in the development of serotonin syndrome. In a double-blind, crossover study examining the effects of clorgyline and clomipramine for the treatment of obsessive-compulsive disorder, two subjects developed severe reactions characteristic of serotonin syndrome. During the study, patients had received clorgyline therapy, followed by a washout period of approximately four weeks and subsequent clomipramine therapy. After taking the first 100 mg dose of clomipramine, one patient developed coarse myoclonic jerking in both legs, hyperreflexia, diaphoresis, and arrhythmia. Another patient developed a similar reaction after the first dose, with upper motor neuron symptoms, myoclonic movements, and cardiac irritability. Both patient's symptoms resolved several hours later, and both patients were later treated successfully with clomipramine without adverse effects (Insel et al, 1982b).
e) A 39-year old woman with bipolar disorder developed serotonin syndrome after imipramine was added to moclobemide. The patient was taking moclobemide 300 mg twice daily when imipramine was started at 50 mg daily, followed by two dosage increases of imipramine to 200 mg and a reduction of moclobemide dosage to 150 mg twice daily. Five days after the increase in imipramine to 200 mg per day, the patient developed symptoms of serotonin syndrome, including sweating, shivering, confusion, fever, and spasms in the extremities. The patient was treated with chlorpromazine and symptoms resolved over the next few days without further complications (Brodribb et al, 1994a).
f) Three patients with bipolar disorder developed manic symptoms while undergoing concurrent therapy with isocarboxazid and amitriptyline. In all three cases the patients had been given MAOIs and TCAs alone without complications. It was only when the drugs were used in combination that symptoms of mania emerged, suggesting a synergistic effect (de la Fuente et al, 1986).
g) In one case, clomipramine 10 mg twice daily was added to a stable regimen of tranylcypromine in a physically healthy 34-year old man. After taking several doses, the patients developed symptoms of nausea and profuse sweating, followed by pyrexia, dyspnea, and agitation. The hyperpyrexical state led to disseminated intravascular coagulation and eventual death (Tackley & Tregaskis, 1987a).
h) There is evidence that MAOIs and TCAs can be given concomitantly in patients previously unresponsive to the MAOI or TCA alone. A few precautions must be followed including: a) avoidance of large doses (no more than 150 mg amitriptyline or its equivalent, 45 mg phenelzine, or 60 mg isocarboxazid) b) oral administration c) avoidance of clomipramine, imipramine, desipramine, and tranylcypromine in any combination, and d) close monitoring of patients (Kline, 1974; Winston, 1971b; Schuckit et al, 1971d; White & Simpson, 1984b; Rom & Benner, 1972). The combination may be utilized in one of two ways. Most frequently, the recommendation is to stop all previous antidepressants (five to ten days for TCAs and 14 days for MAOIs); the combination is then simultaneously started (Perry et al, 1991a). Alternatively, in a patient previously receiving a TCA, small doses of the MAOI may be slowly added (Schoonover, 1983). Some sources suggest that the combination of amitriptyline and isocarboxazid is preferred (Perry et al, 1991a). Numerous studies in patients with refractory depression or phobic anxiety states have successfully used the combination of MAOIs and TCAs (Ponto et al, 1977b; Schuckit et al, 1971d; Ashcroft, 1975a).

3.5.1.CQ Moxifloxacin
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Moxifloxacin has been shown to prolong the QT interval in some patients and should be avoided in those patients receiving agents that also prolong the QT interval, such as tricyclic antidepressants. Although pharmacokinetic studies between moxifloxacin and other drugs which prolong the QT interval have not been performed, an additive effect cannot be excluded. Therefore, moxifloxacin should be used with caution when given concurrently with a tricyclic antidepressant (Prod Info Avelox(TM), 2000).
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Moxifloxacin should be used with caution when given concurrently with a tricyclic antidepressant.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.CR Nefopam
1) Interaction Effect: an increased risk of seizures
2) Summary: Nefopam inhibits the neuronal uptake of norepinephrine and serotonin and increases the risk of seizures, especially in patients with a history of a convulsive disorder. Tricyclic antidepressants also lower the seizure threshold. Therefore, the manufacturer of nefopam advises caution in patients on concurrent tricyclic antidepressant therapy (Pillans & Woods, 1995).
3) Severity: major
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Because of the increased risk of seizures, extreme caution should be exercised in patients receiving nefopam and a tricyclic antidepressant. An alternative analgesic may be considered.
7) Probable Mechanism: additive lowering of seizure threshold

3.5.1.CS Nialamide

1) Interaction Effect: neurotoxicity, seizures, or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)

2) Summary: Concomitant TCA and MAOI use has resulted in hyperpyrexia, convulsions, and death. Concurrent use of MAOIs and TCAs has also been reported to result in a condition termed serotonin syndrome (Insel et al, 1982m; Spigset et al, 1993n; Brodribb et al, 1994l; Neuvonen et al, 1993f). Serotonin syndrome is a rare but potentially fatal condition of serotonergic hyperstimulation characterized by hypertension, hyperthermia, myoclonus, and changes in mental status (Sternbach, 1991g). If TCAs and MAOIs must be used concurrently, avoid large doses, use only oral TCAs, avoid imipramine, clomipramine, desipramine, and tranylcypromine, and monitor patients closely (Schuckit et al, 1971o; White & Simpson, 1984l).

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Concomitant use of a tricyclic antidepressant (TCA) and a monoamine oxidase inhibitor (MAOI) should be done only with close monitoring and where the clinical benefit outweighs the potential risk. Other antidepressant therapy should first be considered. If deemed clinically necessary, avoid large doses and use agents other than imipramine, clomipramine, desipramine, and tranylcypromine.

7) Probable Mechanism: altered catecholamine uptake and metabolism

8) Literature Reports

a) Concomitant administration of monoamine oxidase inhibitors (MAOIs) with tricyclic antidepressants (TCAs) has been considered an absolute contraindication in the past. Reports of excitation, hyperpyrexia, convulsions, and possible death have been attributed to the combination (Lockett & Milner, 1965g; Winston, 1971g; Schuckit et al, 1971n; Spiker & Pugh, 1976g). The mechanism may relate to the combined inhibition of catecholamine reuptake into the central nervous system and inhibition of catecholamine metabolism (Sjoqvist, 1965g).

b) In a double-blind, crossover study examining the effects of clorgyline and clomipramine for the treatment of obsessive-compulsive disorder, two subjects developed severe reactions characteristic of serotonin syndrome. During the study, patients had received clorgyline therapy, followed by a washout period of approximately four weeks and subsequent clomipramine therapy. After taking the first 100 mg dose of clomipramine, one patient developed coarse myoclonic jerking in both legs, hyperreflexia, diaphoresis, and arrhythmia. Another patient developed a similar reaction after the first dose, with upper motor neuron symptoms, myoclonic movements, and cardiac irritability. Both patient's symptoms resolved several hours later, and both patients were later treated successfully with clomipramine without adverse effects (Insel et al, 1982l).

c) A drug interaction occurred in a 76-year old woman who had been taking clomipramine 50 mg daily for several months prior to switching to moclobemide 300 mg daily. The patient experienced somnolescence, confusion, and fever which then progressed to further mental impairment, muscle stiffness, myoclonus, and convulsive attacks. The patient's symptoms were described as fulfilling the diagnostic criteria for serotonin syndrome and were resolved a few days later after discontinuing all antidepressant medications (Spigset et al, 1993m).

d) In one case, clomipramine 10 mg twice daily was added to a stable regimen of tranylcypromine in a physically healthy 34-year old man. After taking several doses, the patients developed symptoms of nausea and profuse sweating, followed by pyrexia, dyspnea, and agitation. The hyperpyrexical state led to disseminated intravascular coagulation and eventual death (Tackley & Tregaskis, 1987g).

e) There is evidence that MAOIs and TCAs can be given concomitantly in patients previously unresponsive to the MAOI or TCA alone. The combination may be utilized in one of two ways. Most frequently, the recommendation is to stop all previous antidepressants (five to ten days for TCAs and 14 days for MAOIs); the combination is then simultaneously started (Perry et al, 1991f). Alternatively, in a patient previously receiving a TCA, small doses of the MAOI may be slowly added (Schoonover, 1983). Numerous studies in patients with refractory depression or phobic anxiety states have successfully used the combination of MAOIs and TCAs (Ponto et al, 1977g; Schuckit et al, 1971n; Ashcroft, 1975f).

3.5.1.CT Norepinephrine

1) Interaction Effect: hypertension, cardiac arrhythmias, and tachycardia

2) Summary: Clinical trials have demonstrated a 2- to 8-fold increase in the effects of intravenous infusions of alpha adrenergic drugs to volunteers on tricyclic antidepressants. Arrhythmias and other severe adverse effects have also been reported (Ghose, 1980; Avery, 1973a; Boakes et al, 1973a; Boakes, 1973; Mitchell et al, 1970; Stone et al, 1964). Local use (e.g., dental anesthesia) of epinephrine in concentrations of 1:100,000 or less is less likely to precipitate clinically significant hemodynamic changes (Steinberg & Block, 1971).

3) Severity: major

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: The vasoconstriction and other alpha-adrenergic effects of sympathomimetic drugs are substantially enhanced in the presence of tricyclic antidepressants (TCAs). Concomitant use should be avoided. If these drugs are given together, careful monitoring and a dose reduction of the sympathomimetic is required. Patients should be instructed to inform their doctor or dentist that they are taking a tricyclic

antidepressant prior to any surgery or procedure.
7) Probable Mechanism: inhibition of norepinephrine reuptake
8) Literature Reports
a) Four healthy volunteers received intravenous infusions of various sympathomimetic amines (epinephrine, norepinephrine, phenylephrine, and isoproterenol) before and after imipramine (25 mg three times daily for five days). They showed an increased pressor response to epinephrine (2- to 4-fold), norepinephrine (4- to 8-fold), and phenylephrine (2- to 3-fold) after imipramine, but no difference was observed in the response to isoproterenol. Thus, the increased pressor response appeared to occur only for alpha adrenergic effects. All four subjects demonstrated changes in cardiac rhythm with epinephrine and imipramine consisting of sinus arrhythmia in three subjects and multiple ectopic beats and a nodal rhythm in the fourth subject (Boakes et al, 1973).
b) A review of spontaneous reports of adverse reactions to vasoconstrictors in local anesthetics found that 15 patients receiving a local anesthetic with norepinephrine (1:25,000) had severe reactions (severe headaches, chest tightness, subarachnoid hemorrhage). The drug history was incomplete, but at least three had been taking a tricyclic antidepressant at the time (Anon, 1972).

3.5.1.CU Octreotide
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Tricyclic antidepressants (TCAs) and octreotide have been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Sandostatin(R), 1999; Marshall & Forker, 1982). Even though no formal drug interaction studies have been done, the coadministration of tricyclic antidepressants and other drugs known to prolong the QTc interval, such as octreotide, is not recommended (Prod Info Elavil (R), 1999).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of octreotide and tricyclic antidepressants is not recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.CV Oxilofrine
1) Interaction Effect: hypertension, cardiac arrhythmias, and tachycardia
2) Summary: Clinical trials have demonstrated a 2- to 8-fold increase in the effects of intravenous infusions of alpha adrenergic drugs to volunteers on tricyclic antidepressants. Arrhythmias and other severe adverse effects have also been reported (Ghose, 1980; Avery, 1973a; Boakes et al, 1973a; Boakes, 1973; Mitchell et al, 1970; Stone et al, 1964). Local use (e.g., dental anesthesia) of epinephrine in concentrations of 1:100,000 or less is less likely to precipitate clinically significant hemodynamic changes (Steinberg & Block, 1971).
3) Severity: major
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: The vasoconstriction and other alpha-adrenergic effects of sympathomimetic drugs are substantially enhanced in the presence of tricyclic antidepressants (TCAs). Concomitant use should be avoided. If these drugs are given together, careful monitoring and a dose reduction of the sympathomimetic is required. Patients should be instructed to inform their doctor or dentist that they are taking a tricyclic antidepressant prior to any surgery or procedure.
7) Probable Mechanism: inhibition of norepinephrine reuptake
8) Literature Reports
a) Four healthy volunteers received intravenous infusions of various sympathomimetic amines (epinephrine, norepinephrine, phenylephrine, and isoproterenol) before and after imipramine (25 mg three times daily for five days). They showed an increased pressor response to epinephrine (2- to 4-fold), norepinephrine (4- to 8-fold), and phenylephrine (2- to 3-fold) after imipramine, but no difference was observed in the response to isoproterenol. Thus, the increased pressor response appeared to occur only for alpha adrenergic effects. All four subjects demonstrated changes in cardiac rhythm with epinephrine and imipramine consisting of sinus arrhythmia in three subjects and multiple ectopic beats and a nodal rhythm in the fourth subject (Boakes et al, 1973).
b) A review of spontaneous reports of adverse reactions to vasoconstrictors in local anesthetics found that 15 patients receiving a local anesthetic with norepinephrine (1:25,000) had severe reactions (severe headaches, chest tightness, subarachnoid hemorrhage). The drug history was incomplete, but at least three had been taking a tricyclic antidepressant at the time (Anon, 1972).

3.5.1.CW Pargyline
1) Interaction Effect: neurotoxicity, seizures, or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)
2) Summary: Concomitant TCA and MAOI use has resulted in hyperpyrexia, convulsions, and death. Concurrent use of MAOIs and TCAs has also been reported to result in a condition termed serotonin syndrome (Insel et al, 1982a; Spigset et al, 1993a; Brodribb et al, 1994; Neuvonen et al, 1993). Serotonin

syndrome is a rare but potentially fatal condition of serotonergic hyperstimulation characterized by hypertension, hyperthermia, myoclonus, and changes in mental status (Sternbach, 1991a). If TCAs and MAOIs must be used concurrently, avoid large doses, use only oral TCAs, avoid imipramine, clomipramine, desipramine, and tranylcypromine, and monitor patients closely (Schuckit et al, 1971a; White & Simpson, 1984).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Concomitant use of a tricyclic antidepressant (TCA) and a monoamine oxidase inhibitor (MAOI) should be done only with close monitoring and where the clinical benefit outweighs the potential risk. Other antidepressant therapy should first be considered. If deemed clinically necessary, avoid large doses and use agents other than imipramine, clomipramine, desipramine, and tranylcypromine.
7) Probable Mechanism: altered catecholamine uptake and metabolism
8) Literature Reports
a) Concomitant administration of monoamine oxidase inhibitors (MAOIs) with tricyclic antidepressants (TCAs) has been considered an absolute contraindication in the past. Reports of excitation, hyperpyrexia, convulsions, and possible death have been attributed to the combination (Lockett & Milner, 1965; Winston, 1971; Schuckit et al, 1971; Spiker & Pugh, 1976). The mechanism may relate to the combined inhibition of catecholamine reuptake into the central nervous system and inhibition of catecholamine metabolism (Sjoqvist, 1965).
b) Administration of a TCA after MAOI therapy may result in the development of serotonin syndrome. In a double-blind, crossover study examining the effects of clorgyline and clomipramine for the treatment of obsessive-compulsive disorder, two subjects developed severe reactions characteristic of serotonin syndrome. During the study, patients had received clorgyline therapy, followed by a washout period of approximately four weeks and subsequent clomipramine therapy. After taking the first 100 mg dose of clomipramine, one patient developed coarse myoclonic jerking in both legs, hyperreflexia, diaphoresis, and arrhythmia. Another patient developed a similar reaction after the first dose, with upper motor neuron symptoms, myoclonic movements, and cardiac irritability. Both patient's symptoms resolved several hours later, and both patients were later treated successfully with clomipramine without adverse effects (Insel et al, 1982).
c) A drug interaction occurred in a 76-year old woman who had been taking clomipramine 50 mg daily for several months prior to switching to moclobemide 300 mg daily. The patient experienced somnolescence, confusion, and fever which then progressed to further mental impairment, muscle stiffness, myoclonus, and convulsive attacks. The patient's symptoms were described as fulfilling the diagnostic criteria for serotonin syndrome and were resolved a few days later after discontinuing all antidepressant medications (Spigset et al, 1993).
d) In one case, clomipramine 10 mg twice daily was added to a stable regimen of tranylcypromine in a physically healthy 34-year old man. After taking several doses, the patients developed symptoms of nausea and profuse sweating, followed by pyrexia, dyspnea, and agitation. The hyperpyrexical state led to disseminated intravascular coagulation and eventual death (Tackley & Tregaskis, 1987).
e) There is evidence that MAOIs and TCAs can be given concomitantly in patients previously unresponsive to the MAOI or TCA alone. The combination may be utilized in one of two ways. Most frequently, the recommendation is to stop all previous antidepressants (five to ten days for TCAs and 14 days for MAOIs); the combination is then simultaneously started (Perry et al, 1991). Alternatively, in a patient previously receiving a TCA, small doses of the MAOI may be slowly added (Schoonover, 1983). Numerous studies in patients with refractory depression or phobic anxiety states have successfully used the combination of MAOIs and TCAs (Ponto et al, 1977; Schuckit et al, 1971; Ashcroft, 1975).

3.5.1.CX Paroxetine
1) Interaction Effect: doxepin toxicity (dry mouth, sedation, urinary retention)
2) Summary: Paroxetine coadministered with desipramine or imipramine produced higher serum concentrations of the tricyclic antidepressant (TCA) in some patients (Hartter et al, 1994; Brosen et al, 1993a). Although not reported specifically with doxepin, a similar interaction could be expected to occur. Paroxetine's effect on TCAs may resemble that of fluoxetine (another selective serotonin reuptake inhibitor), which is known to inhibit TCA metabolism (Aranow et al, 1989b; Vaughan, 1988; Goodnick, 1989b). With coadministration, monitor patients for doxepin toxicity. Doxepin doses may need to be reduced (Prod Info Paxil CR(TM), 2003).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When doxepin is coadministered with paroxetine, monitor patients for signs and symptoms of doxepin toxicity (dry mouth, sedation, urinary retention, blurred vision). Doxepin doses may need to be reduced.
7) Probable Mechanism: decreased doxepin metabolism
8) Literature Reports
a) The effect of paroxetine on desipramine metabolism was studied in 9 extensive metabolizers (EM) and 8 poor metabolizers (PM) of desipramine. Subjects took a single oral dose of desipramine before starting paroxetine and a second dose after 11 days of paroxetine use. After the addition of paroxetine,

EMs experienced a 5-fold decrease in clearance of desipramine, indicating that paroxetine inhibits oxidation reactions catalyzed by CYP2D6. PMs had a slight increase in clearance of desipramine with paroxetine. With concurrent administration of desipramine and paroxetine, interaction of the two drugs may result in a need for dosage adjustments, especially in extensive metabolizers of desipramine (Brosen et al, 1993).

3.5.1.CY Pemoline

1) Interaction Effect: hypertension, other cardiac effects, and CNS stimulation
2) Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been reported to result in enhanced amphetamine effects from the release of norepinephrine (Beaumont, 1973d; Raisfeld, 1972). A similar reaction might also occur with all drugs that have amphetamine-like effects. Acute elevations in blood pressure have been noted (Flemenbaum, 1971a). Some amphetamine-like drugs may inhibit the metabolism of TCAs, although most combinations have not been studied. When amphetamine analogs are being used to treat obesity, it should be noted that TCAs frequently lead to moderate weight gain (Russ & Ackerman, 1988). False positive urine tests for amphetamines have been reported during therapy with some TCAs (Merigian & Browning, 1993). Caution is advised when concurrent administration of amphetamine-like agents and TCAs is warranted. The patient should be closely monitored for increased cardiovascular effects (hypertension and dysrhythmias).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other sympathomimetic agents could lead to hypertension, increased cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006; Flemenbaum, 1972). Use caution if such therapy is warranted. Monitor the patient closely for hypertension and dysrhythmias.
7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission
8) Literature Reports

a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agents. Additionally, coadministration of d-amphetamine with TCAs such as desipramine or protriptyline results in sustained increases in d-amphetamine concentration in the brain (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006).

b) Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism of some tricyclic antidepressants, such as imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transdermal system, 2006).

c) Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases in blood pressure such that the hypotensive effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of combined therapy. Discontinuation of the methylphenidate usually results in the blood pressure returning to normotensive levels; reinstitution of the methylphenidate resulted in further blood pressure elevation (Flemenbaum, 1971; Flemenbaum, 1972).

d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine given for at least four weeks, were given fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical improvement. However, fenfluramine more than doubled steady-state plasma levels of desipramine (Price et al, 1990).

e) There have been claims based on uncontrolled studies that a better antidepressant response may occur with combined therapy (Garrettson et al, 1969). However, a systemic review of stimulants in the treatment of depression concluded that although uncontrolled studies were generally positive, the ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated little advantage of drug over placebo and did not appear to be as effective as the conventional antidepressants in primary depression (Satel & Nelson, 1989).

3.5.1.CZ Pentamidine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Tricyclic antidepressants (TCAs) and pentamidine have been shown to prolong the QTc interval at the recommended therapeutic dose (Lindsay et al, 1990; Marshall & Forker, 1982i). Even though no formal drug interaction studies have been done, the coadministration of tricyclic antidepressants and other drugs known to prolong the QTc interval, such as pentamidine, is not recommended (Prod Info Elavil (R), 1999e).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of pentamidine and tricyclic antidepressants is not recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.DA Pentobarbital

1) Interaction Effect: possible decreased tricyclic antidepressant serum concentrations and possible additive adverse effects
2) Summary: Concomitant barbiturate and tricyclic antidepressant (TCA) therapy may result in increased metabolism of the TCA. There have been scattered reports of individuals with decreased serum levels of TCAs in the presence of a barbiturate (Moody et al, 1977; Silverman & Braithwaite, 1972; Burrows & Davies, 1971). In addition, TCAs can worsen seizure control by reducing the seizure threshold (Brodie, 1992). These drugs also have additive CNS and respiratory depressant effects.
3) Severity: minor
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor for efficacy of antidepressant effect. Increases in tricyclic antidepressant dosages may be required. Additionally, monitor for toxicity when either drug is added to or withdrawn from therapy. Serum concentrations may be of value in determining appropriate dosage.
7) Probable Mechanism: increased tricyclic antidepressant metabolism
8) Literature Reports
a) The pharmacokinetics of a single oral dose of desipramine (100 mg) were studied in eight epileptic patients chronically treated with phenobarbital and in eight drug-free healthy controls (Spina et al, 1996). All subjects were extensive metabolizers with respect to the genetically determined CYP2D6-related metabolic polymorphism. Compared with controls, epileptic patients exhibited lower peak plasma desipramine concentrations (74 nmol/L vs. 107 nmol/L), smaller desipramine area under the concentration-time curve values (1943 nmol/L/h vs. 3234 nmol/L/h), and shorter desipramine elimination half-lives (15.1 h vs. 20.6 h). All barbiturates are believed to have similar effects leading to induction of hepatic enzymes and the 2D6 isozyme is believed to be important in the metabolism of most or all TCAs. Thus, similar effects should be expected with any combination of TCA and barbiturate.

3.5.1.DB Phendimetrazine
1) Interaction Effect: hypertension, other cardiac effects, and CNS stimulation
2) Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been reported to result in enhanced amphetamine effects from the release of norepinephrine (Beaumont, 1973d; Raisfeld, 1972). A similar reaction might also occur with all drugs that have amphetamine-like effects. Acute elevations in blood pressure have been noted (Flemenbaum, 1971a). Some amphetamine-like drugs may inhibit the metabolism of TCAs, although most combinations have not been studied. When amphetamine analogs are being used to treat obesity, it should be noted that TCAs frequently lead to moderate weight gain (Russ & Ackerman, 1988). False positive urine tests for amphetamines have been reported during therapy with some TCAs (Merigian & Browning, 1993). Caution is advised when concurrent administration of amphetamine-like agents and TCAs is warranted. The patient should be closely monitored for increased cardiovascular effects (hypertension and dysrhythmias).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other sympathomimetic agents could lead to hypertension, increased cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006; Flemenbaum, 1972). Use caution if such therapy is warranted. Monitor the patient closely for hypertension and dysrhythmias.
7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission
8) Literature Reports
a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agents. Additionally, coadministration of d-amphetamine with TCAs such as desipramine or protriptyline results in sustained increases in d-amphetamine concentration in the brain (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006).
b) Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism of some tricyclic antidepressants, such as imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transdermal system, 2006).
c) Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases in blood pressure such that the hypotensive effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of combined therapy. Discontinuation of the methylphenidate usually results in the blood pressure returning to normotensive levels; reinstitution of the methylphenidate resulted in further blood pressure elevation (Flemenbaum, 1971; Flemenbaum, 1972).
d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine given for at least four weeks, were given fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical improvement. However, fenfluramine more than doubled steady-state plasma levels of desipramine (Price et al, 1990).
e) There have been claims based on uncontrolled studies that a better antidepressant response may occur with combined therapy (Garrettson et al, 1969). However, a systemic review of stimulants in the treatment of depression concluded that although uncontrolled studies were generally positive, the ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated little

advantage of drug over placebo and did not appear to be as effective as the conventional antidepressants in primary depression (Satel & Nelson, 1989).

3.5.1.DC Phenelzine

1) Interaction Effect: neurotoxicity, seizures, or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)

2) Summary: Concomitant TCA and MAOI use has resulted in hyperpyrexia, convulsions, and death. Concurrent use of MAOIs and TCAs has also been reported to result in a condition termed serotonin syndrome (Insel et al, 1982k; Spigset et al, 1993l; Brodribb et al, 1994k; Neuvonen et al, 1993e). Serotonin syndrome is a rare but potentially fatal condition of serotonergic hyperstimulation characterized by hypertension, hyperthermia, myoclonus, and changes in mental status (Sternbach, 1991f). If TCAs and MAOIs must be used concurrently, avoid large doses, use only oral TCAs, avoid imipramine, clomipramine, desipramine, and tranylcypromine, and monitor patients closely (Schuckit et al, 1971m; White & Simpson, 1984k).

3) Severity: major

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: Concomitant use of a tricyclic antidepressant, such as doxepin, and a monoamine oxidase inhibitor (MAOI), such as phenelzine, should be done only with close monitoring and where the clinical benefit outweighs the potential risk. Other antidepressant therapy should first be considered. If deemed clinically necessary, avoid large doses and use agents other than imipramine, clomipramine, desipramine, and tranylcypromine. If doxepin is replacing treatment with phenelzine, a minimum of 14 days should elapse after phenelzine is discontinued before doxepin therapy begins (Prod Info SINEQUAN(R) capsule, oral concentrate, 2005). The manufacturer of phenelzine recommends a minimum of 10 days should elapse between discontinuing the tricyclic antidepressant therapy and initiating treatment with phenelzine (Prod Info NARDIL(R) Tablets, USP, 2005).

7) Probable Mechanism: altered catecholamine uptake and metabolism

8) Literature Reports

a) Concomitant administration of monoamine oxidase inhibitors (MAOIs) with tricyclic antidepressants (TCAs) has been considered an absolute contraindication in the past and still is listed as such by the manufacturers. Reports of excitation, hyperpyrexia, convulsions, and possible death have been attributed to the combination (Lockett & Milner, 1965f; Brachfeld et al, 1963e; Winston, 1971f; Schuckit et al, 1971l; Sargent, 1965e; Spiker & Pugh, 1976f). The mechanism may relate to the combined inhibition of catecholamine reuptake into the central nervous system and inhibition of catecholamine metabolism (Sjoqvist, 1965f).

b) Administration of a TCA after MAOI therapy may result in the development of serotonin syndrome. In a double-blind, crossover study examining the effects of clorgyline and clomipramine for the treatment of obsessive-compulsive disorder, two subjects developed severe reactions characteristic of serotonin syndrome. During the study, patients had received clorgyline therapy, followed by a washout period of approximately four weeks and subsequent clomipramine therapy. After taking the first 100 mg dose of clomipramine, one patient developed coarse myoclonic jerking in both legs, hyperreflexia, diaphoresis, and arrhythmia. Another patient developed a similar reaction after the first dose, with upper motor neuron symptoms, myoclonic movements, and cardiac irritability. Both patient's symptoms resolved several hours later, and both patients were later treated successfully with clomipramine without adverse effects (Insel et al, 1982j).

c) A drug interaction occurred in a 76-year old woman who had been taking clomipramine 50 mg daily for several months prior to switching to moclobemide 300 mg daily. The patient experienced somnolence, confusion, and fever which then progressed to further mental impairment, muscle stiffness, myoclonus, and convulsive attacks. The patient's symptoms were described as fulfilling the diagnostic criteria for serotonin syndrome and were resolved a few days later after discontinuing all antidepressant medications (Spigset et al, 1993k).

d) A 39-year old woman with bipolar disorder developed serotonin syndrome after imipramine was added to moclobemide. The patient was taking moclobemide 300 mg twice daily when imipramine was started at 50 mg daily, followed by two dosage increases of imipramine to 200 mg and a reduction of moclobemide dosage to 150 mg twice daily. Five days after the increase in imipramine to 200 mg per day, the patient developed symptoms of serotonin syndrome, including sweating, shivering, confusion, fever, and spasms in the extremities. The patient was treated with chlorpromazine and symptoms resolved over the next few days without further complications (Brodribb et al, 1994j).

e) Three patients with bipolar disorder developed manic symptoms while undergoing concurrent therapy with isocarboxazid and amitriptyline. In all three cases the patients had been given MAOIs and TCAs alone without complications. It was only when the drugs were used in combination that symptoms of mania emerged, suggesting a synergistic effect (de la Fuente et al, 1986d).

f) In one case, clomipramine 10 mg twice daily was added to a stable regimen of tranylcypromine in a physically healthy 34-year old man. After taking several doses, the patient developed symptoms of nausea and profuse sweating, followed by pyrexia, dyspnea, and agitation. The hyperpyrexical state led to disseminated intravascular coagulation and eventual death (Tackley & Tregaskis, 1987f).

g) There is evidence that MAOIs and TCAs can be given concomitantly in patients previously unresponsive to the MAOI or TCA alone. A few precautions must be followed including: a) avoidance of

large doses (no more than 150 mg amitriptyline or its equivalent, 45 mg phenelzine, or 60 mg isocarboxazid) b) oral administration c) avoidance of clomipramine, imipramine, desipramine, and tranylcypromine in any combination, and d) close monitoring of patients (Kline, 1974d; Winston, 1971f; Schuckit et al, 1971l; White & Simpson, 1984j; Rom & Benner, 1972d). The combination may be utilized in one of two ways. Most frequently, the recommendation is to stop all previous antidepressants (five to ten days for TCAs and 14 days for MAOIs); the combination is then simultaneously started (Perry et al, 1991e). Alternatively, in a patient previously receiving a TCA, small doses of the MAOI may be slowly added (Schoonover, 1983). Some sources suggest that the combination of amitriptyline and isocarboxazid is preferred (Perry et al, 1991e). Numerous studies in patients with refractory depression or phobic anxiety states have successfully used the combination of MAOIs and TCAs (Ponto et al, 1977f; Schuckit et al, 1971l; Ashcroft, 1975e).

3.5.1.DD Phenindione

1) Interaction Effect: increased risk of bleeding
2) Summary: Tricyclic antidepressants (TCAs) may increase the half-life and bioavailability of oral anticoagulants (Vesell et al, 1970e; Williams et al, 1976e). Considerable interindividual differences may be found (Pond et al, 1975e).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: In patients receiving tricyclic antidepressants and oral anticoagulant therapy, the prothrombin time ratio or INR (international normalized ratio) should be closely monitored with the addition and withdrawal of the antidepressant, and should be periodically reassessed during concurrent therapy. Achieving a stable drug regimen which produces the desired level of anticoagulation may be difficult in patients on this combination, and frequent adjustments of the anticoagulant dose may be required.
7) Probable Mechanism: decreased phenindione metabolism; increased phenindione absorption
8) Literature Reports

a) In a study of healthy volunteers, the concurrent use of nortriptyline or amitriptyline resulted in an increase of dicumarol levels and an increase in the plasma half-life of dicumarol, although the effect was not consistent in all subjects (Pond et al, 1975d). This effect was not observed with warfarin.
b) A single oral dose of bishydroxycoumarin after 8 days of nortriptyline resulted in a significantly prolonged half-life and decreased volume of distribution of the coumarin anticoagulant in 6 healthy volunteers (Vesell et al, 1970d). The mechanism of action was suggested to be reduced bishydroxycoumarin metabolism and/or altered coumarin absorption.
c) Drug dosing was studied in 16 patients on long-term anticoagulant therapy who used concurrent TCAs (Williams et al, 1976d). TCAs affected the stability of anticoagulant control leading to frequent changes in the doses of anticoagulants. Inhibition of coumarin metabolism was the postulated mechanism.

3.5.1.DE Phenmetrazine

1) Interaction Effect: hypertension, other cardiac effects, and CNS stimulation
2) Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been reported to result in enhanced amphetamine effects from the release of norepinephrine (Beaumont, 1973d; Raisfeld, 1972). A similar reaction might also occur with all drugs that have amphetamine-like effects. Acute elevations in blood pressure have been noted (Flemenbaum, 1971a). Some amphetamine-like drugs may inhibit the metabolism of TCAs, although most combinations have not been studied. When amphetamine analogs are being used to treat obesity, it should be noted that TCAs frequently lead to moderate weight gain (Russ & Ackerman, 1988). False positive urine tests for amphetamines have been reported during therapy with some TCAs (Merigian & Browning, 1993). Caution is advised when concurrent administration of amphetamine-like agents and TCAs is warranted. The patient should be closely monitored for increased cardiovascular effects (hypertension and dysrhythmias).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other sympathomimetic agents could lead to hypertension, increased cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006; Flemenbaum, 1972). Use caution if such therapy is warranted. Monitor the patient closely for hypertension and dysrhythmias.
7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission
8) Literature Reports

a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agents. Additionally, coadministration of d-amphetamine with TCAs such as desipramine or protriptyline results in sustained increases in d-amphetamine concentration in the brain (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006).
b) Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism of some tricyclic antidepressants, such as imipramine, clomipramine, or desipramine (Prod Info

DAYTRANA(TM) transdermal system, 2006).
c) Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases in blood pressure such that the hypotensive effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of combined therapy. Discontinuation of the methylphenidate usually results in the blood pressure returning to normotensive levels; reinstitution of the methylphenidate resulted in further blood pressure elevation (Flemenbaum, 1971; Flemenbaum, 1972).
d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine given for at least four weeks, were given fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical improvement. However, fenfluramine more than doubled steady-state plasma levels of desipramine (Price et al, 1990).
e) There have been claims based on uncontrolled studies that a better antidepressant response may occur with combined therapy (Garrettson et al, 1969). However, a systemic review of stimulants in the treatment of depression concluded that although uncontrolled studies were generally positive, the ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated little advantage of drug over placebo and did not appear to be as effective as the conventional antidepressants in primary depression (Satel & Nelson, 1989).

3.5.1.DF Phenobarbital
1) Interaction Effect: possible decreased tricyclic antidepressant serum concentrations and possible additive adverse effects
2) Summary: Concomitant barbiturate and tricyclic antidepressant (TCA) therapy may result in increased metabolism of the TCA. There have been scattered reports of individuals with decreased serum levels of TCAs in the presence of a barbiturate (Moody et al, 1977; Silverman & Braithwaite, 1972; Burrows & Davies, 1971). In addition, TCAs can worsen seizure control by reducing the seizure threshold (Brodie, 1992). These drugs also have additive CNS and respiratory depressant effects.
3) Severity: minor
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor for efficacy of antidepressant effect. Increases in tricyclic antidepressant dosages may be required. Additionally, monitor for toxicity when either drug is added to or withdrawn from therapy. Serum concentrations may be of value in determining appropriate dosage.
7) Probable Mechanism: increased tricyclic antidepressant metabolism
8) Literature Reports
a) The pharmacokinetics of a single oral dose of desipramine (100 mg) were studied in eight epileptic patients chronically treated with phenobarbital and in eight drug-free healthy controls (Spina et al, 1996). All subjects were extensive metabolizers with respect to the genetically determined CYP2D6-related metabolic polymorphism. Compared with controls, epileptic patients exhibited lower peak plasma desipramine concentrations (74 nmol/L vs. 107 nmol/L), smaller desipramine area under the concentration-time curve values (1943 nmol/L/h vs. 3234 nmol/L/h), and shorter desipramine elimination half-lives (15.1 h vs. 20.6 h). All barbiturates are believed to have similar effects leading to induction of hepatic enzymes and the 2D6 isozyme is believed to be important in the metabolism of most or all TCAs. Thus, similar effects should be expected with any combination of TCA and barbiturate.

3.5.1.DG Phenprocoumon
1) Interaction Effect: increased risk of bleeding
2) Summary: Tricyclic antidepressants (TCAs) may increase the half-life and bioavailability of oral anticoagulants (Vesell et al, 1970g; Williams et al, 1976g). Considerable interindividual differences may be found (Pond et al, 1975g).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: In patients receiving tricyclic antidepressants and oral anticoagulant therapy, the prothrombin time ratio or INR (international normalized ratio) should be closely monitored with the addition and withdrawal of the antidepressant, and should be periodically reassessed during concurrent therapy. Achieving a stable drug regimen which produces the desired level of anticoagulation may be difficult in patients on this combination, and frequent adjustments of the anticoagulant dose may be required.
7) Probable Mechanism: decreased phenprocoumon metabolism; increased phenprocoumon absorption
8) Literature Reports
a) In a study of healthy volunteers, the concurrent use of nortriptyline or amitriptyline resulted in an increase of dicumarol levels and an increase in the plasma half-life of dicumarol, although the effect was not consistent in all subjects (Pond et al, 1975f). This effect was not observed with warfarin.
b) A single oral dose of bishydroxycoumarin after 8 days of nortriptyline resulted in a significantly prolonged half-life and decreased volume of distribution of the coumarin anticoagulant in 6 healthy volunteers (Vesell et al, 1970f). The mechanism of action was suggested to be reduced bishydroxycoumarin metabolism and/or altered coumarin absorption.
c) Drug dosing was studied in 16 patients on long-term anticoagulant therapy who used concurrent TCAs (Williams et al, 1976f). TCAs affected the stability of anticoagulant control leading to frequent changes in the doses of anticoagulants. Inhibition of coumarin metabolism was the postulated

mechanism.

3.5.1.DH Phentermine

1) Interaction Effect: hypertension, other cardiac effects, and CNS stimulation

2) Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been reported to result in enhanced amphetamine effects from the release of norepinephrine (Beaumont, 1973d; Raisfeld, 1972). A similar reaction might also occur with all drugs that have amphetamine-like effects. Acute elevations in blood pressure have been noted (Flemenbaum, 1971a). Some amphetamine-like drugs may inhibit the metabolism of TCAs, although most combinations have not been studied. When amphetamine analogs are being used to treat obesity, it should be noted that TCAs frequently lead to moderate weight gain (Russ & Ackerman, 1988). False positive urine tests for amphetamines have been reported during therapy with some TCAs (Merigian & Browning, 1993). Caution is advised when concurrent administration of amphetamine-like agents and TCAs is warranted. The patient should be closely monitored for increased cardiovascular effects (hypertension and dysrhythmias).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other sympathomimetic agents could lead to hypertension, increased cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006; Flemenbaum, 1972). Use caution if such therapy is warranted. Monitor the patient closely for hypertension and dysrhythmias.

7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission

8) Literature Reports

a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agents. Additionally, coadministration of d-amphetamine with TCAs such as desipramine or protriptyline results in sustained increases in d-amphetamine concentration in the brain (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006).

b) Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism of some tricyclic antidepressants, such as imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transdermal system, 2006).

c) Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases in blood pressure such that the hypotensive effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of combined therapy. Discontinuation of the methylphenidate usually results in the blood pressure returning to normotensive levels; reinstitution of the methylphenidate resulted in further blood pressure elevation (Flemenbaum, 1971; Flemenbaum, 1972).

d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine given for at least four weeks, were given fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical improvement. However, fenfluramine more than doubled steady-state plasma levels of desipramine (Price et al, 1990).

e) There have been claims based on uncontrolled studies that a better antidepressant response may occur with combined therapy (Garrettson et al, 1969). However, a systemic review of stimulants in the treatment of depression concluded that although uncontrolled studies were generally positive, the ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated little advantage of drug over placebo and did not appear to be as effective as the conventional antidepressants in primary depression (Satel & Nelson, 1989).

3.5.1.DI Phenylephrine

1) Interaction Effect: hypertension, cardiac arrhythmias, and tachycardia

2) Summary: Clinical trials have demonstrated a 2- to 8-fold increase in the effects of intravenous infusions of alpha adrenergic drugs to volunteers on tricyclic antidepressants. Arrhythmias and other severe adverse effects have also been reported (Ghose, 1980; Avery, 1973a; Boakes et al, 1973a; Boakes, 1973; Mitchell et al, 1970; Stone et al, 1964). Local use (e.g., dental anesthesia) of epinephrine in concentrations of 1:100,000 or less is less likely to precipitate clinically significant hemodynamic changes (Steinberg & Block, 1971).

3) Severity: major

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: The vasoconstriction and other alpha-adrenergic effects of sympathomimetic drugs are substantially enhanced in the presence of tricyclic antidepressants (TCAs). Concomitant use should be avoided. If these drugs are given together, careful monitoring and a dose reduction of the sympathomimetic is required. Patients should be instructed to inform their doctor or dentist that they are taking a tricyclic antidepressant prior to any surgery or procedure.

7) Probable Mechanism: inhibition of norepinephrine reuptake

8) Literature Reports

a) Four healthy volunteers received intravenous infusions of various sympathomimetic amines (epinephrine, norepinephrine, phenylephrine, and isoproterenol) before and after imipramine (25 mg

three times daily for five days). They showed an increased pressor response to epinephrine (2- to 4-fold), norepinephrine (4- to 8-fold), and phenylephrine (2- to 3-fold) after imipramine, but no difference was observed in the response to isoproterenol. Thus, the increased pressor response appeared to occur only for alpha adrenergic effects. All four subjects demonstrated changes in cardiac rhythm with epinephrine and imipramine consisting of sinus arrhythmia in three subjects and multiple ectopic beats and a nodal rhythm in the fourth subject (Boakes et al, 1973).
b) A review of spontaneous reports of adverse reactions to vasoconstrictors in local anesthetics found that 15 patients receiving a local anesthetic with norepinephrine (1:25,000) had severe reactions (severe headaches, chest tightness, subarachnoid hemorrhage). The drug history was incomplete, but at least three had been taking a tricyclic antidepressant at the time (Anon, 1972).

3.5.1.DJ Phenytoin
1) Interaction Effect: an increased risk of phenytoin toxicity (ataxia, hyperreflexia, nystagmus, tremor)
2) Summary: A few case reports have indicated that imipramine inhibits phenytoin metabolism resulting in increased serum phenytoin. Tricyclic antidepressants (TCAs) may lower the seizure threshold in epileptic patients stabilized on anticonvulsants. Theoretically, because phenytoin is an enzyme inducer, the metabolism of antidepressants may be increased resulting in reduced TCA serum levels (Petti & Campbell, 1975a; Perucca & Richens, 1977a).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor therapeutic efficacy of doxepin; an increased dose may be required. Serum phenytoin levels should be obtained when tricyclic antidepressant agents are added to therapy due to the potential for impaired phenytoin metabolism.
7) Probable Mechanism: inhibition of phenytoin metabolism

3.5.1.DK Pimozide
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Although citing no data, the manufacturer of pimozide states that concomitant use with other drugs which prolong the QT interval is contraindicated (Prod Info Orap(R), 1999a). Tricyclic antidepressants (TCAs) at therapeutic doses can cause QT prolongation (Prod Info Norpramin(R), 2000; Marshall & Forker, 1982z).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Because of the potential to prolong the QT interval, concurrent administration of a tricyclic antidepressant and pimozide is contraindicated.
7) Probable Mechanism: additive effects on QT interval
8) Literature Reports
a) Electrocardiogram (ECG) changes seen during clinical trials of pimozide in Tourette's syndrome and schizophrenia patients include prolongation of the QT interval, flattening, notching, and inversion of the T wave, and the appearance of U waves. Sudden, unexpected deaths have occurred at doses greater than 20 milligrams/day (Prod Info Orap(R) pimozide, 1999).

3.5.1.DL Pirmenol
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Class Ia antiarrhythmics and tricyclic antidepressants have been shown to prolong the QTc interval at the recommended therapeutic dose. Even though no formal drug interaction studies have been done, the coadministration of Class Ia antiarrhythmics and other drugs known to prolong the QTc interval, including tricyclic antidepressants, is not recommended (Prod Info Elavil(R), 1999g; Prod Info Quinaglute(R), 1999; Marshall & Forker, 1982m).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: The concurrent administration of a Class IA antiarrhythmic agent and a tricyclic antidepressant is not recommended.
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) Quinidine is an inhibitor of the cytochrome P450 isoenzyme responsible for the 2-hydroxylation of imipramine and desipramine (Brosen & Gram, 1989). Inhibition of this enzyme system can result in a 35% decrease in imipramine clearance and 85% decrease in desipramine clearance. Demethylation of imipramine by the cytochrome P450 system is unaffected by this interaction. Until more information is available all patients having quinidine added to drug regimen containing imipramine or desipramine should be monitored for increased antidepressant serum concentrations and potential toxicity.
b) An increased incidence in sudden death was observed in six out of 53 patients with cardiac disease receiving amitriptyline, compared to 0 out of 53 in the control group. It was recommended that

amitriptyline be avoided in patients with underlying cardiac disease except when depression was debilitating and no other drugs were helpful (Moir et al, 1972; Coull et al, 1970).
c) In a placebo controlled study, imipramine 3.5 mg/kg was administered daily for seven patients with severe depression and titrated doses to obtain therapeutic plasma concentrations. Two patients displayed premature atrial depolarizations and premature ventricular depolarizations before therapy. On patient had 33 premature atrial depolarizations (PAD) and 30 premature ventricular depolarizations (PVD) per hour, which decreased to 0.4 PAC and zero PVC per hour on imipramine. The other patient had 12 PAD and 169 PVD per hour before treatment and 1.8 PAD and 28.1 PVD per hour on imipramine. The authors also cautioned that the incidence of cardiotoxicity may increase if tricyclic antidepressants are administered with Type I antiarrhythmics. It was also recommended that quinidine and procainamide not be used to treat the arrhythmias of a tricyclic overdose. The similarities between these agents may exacerbate the cardiotoxicity (Kantor et al, 1978).

3.5.1.DM Prajmaline

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Class Ia antiarrhythmics and tricyclic antidepressants have been shown to prolong the QTc interval at the recommended therapeutic dose. Even though no formal drug interaction studies have been done, the coadministration of Class Ia antiarrhythmics and other drugs known to prolong the QTc interval, including tricyclic antidepressants, is not recommended (Prod Info Elavil(R), 1999g; Prod Info Quinaglute(R), 1999; Marshall & Forker, 1982m).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: The concurrent administration of a Class IA antiarrhythmic agent and a tricyclic antidepressant is not recommended.
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) Quinidine is an inhibitor of the cytochrome P450 isoenzyme responsible for the 2-hydroxylation of imipramine and desipramine (Brosen & Gram, 1989). Inhibition of this enzyme system can result in a 35% decrease in imipramine clearance and 85% decrease in desipramine clearance. Demethylation of imipramine by the cytochrome P450 system is unaffected by this interaction. Until more information is available all patients having quinidine added to drug regimen containing imipramine or desipramine should be monitored for increased antidepressant serum concentrations and potential toxicity.
b) An increased incidence in sudden death was observed in six out of 53 patients with cardiac disease receiving amitriptyline, compared to 0 out of 53 in the control group. It was recommended that amitriptyline be avoided in patients with underlying cardiac disease except when depression was debilitating and no other drugs were helpful (Moir et al, 1972; Coull et al, 1970).
c) In a placebo controlled study, imipramine 3.5 mg/kg was administered daily for seven patients with severe depression and titrated doses to obtain therapeutic plasma concentrations. Two patients displayed premature atrial depolarizations and premature ventricular depolarizations before therapy. On patient had 33 premature atrial depolarizations (PAD) and 30 premature ventricular depolarizations (PVD) per hour, which decreased to 0.4 PAC and zero PVC per hour on imipramine. The other patient had 12 PAD and 169 PVD per hour before treatment and 1.8 PAD and 28.1 PVD per hour on imipramine. The authors also cautioned that the incidence of cardiotoxicity may increase if tricyclic antidepressants are administered with Type I antiarrhythmics. It was also recommended that quinidine and procainamide not be used to treat the arrhythmias of a tricyclic overdose. The similarities between these agents may exacerbate the cardiotoxicity (Kantor et al, 1978).

3.5.1.DN Primidone

1) Interaction Effect: possible decreased tricyclic antidepressant serum concentrations and possible additive adverse effects
2) Summary: Concomitant barbiturate and tricyclic antidepressant (TCA) therapy may result in increased metabolism of the TCA. There have been scattered reports of individuals with decreased serum levels of TCAs in the presence of a barbiturate (Moody et al, 1977; Silverman & Braithwaite, 1972; Burrows & Davies, 1971). In addition, TCAs can worsen seizure control by reducing the seizure threshold (Brodie, 1992). These drugs also have additive CNS and respiratory depressant effects.
3) Severity: minor
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor for efficacy of antidepressant effect. Increases in tricyclic antidepressant dosages may be required. Additionally, monitor for toxicity when either drug is added to or withdrawn from therapy. Serum concentrations may be of value in determining appropriate dosage.
7) Probable Mechanism: increased tricyclic antidepressant metabolism
8) Literature Reports
a) The pharmacokinetics of a single oral dose of desipramine (100 mg) were studied in eight epileptic patients chronically treated with phenobarbital and in eight drug-free healthy controls (Spina et al, 1996). All subjects were extensive metabolizers with respect to the genetically determined CYP2D6-

related metabolic polymorphism. Compared with controls, epileptic patients exhibited lower peak plasma desipramine concentrations (74 nmol/L vs. 107 nmol/L), smaller desipramine area under the concentration-time curve values (1943 nmol/L/h vs. 3234 nmol/L/h), and shorter desipramine elimination half-lives (15.1 h vs. 20.6 h). All barbiturates are believed to have similar effects leading to induction of hepatic enzymes and the 2D6 isozyme is believed to be important in the metabolism of most or all TCAs. Thus, similar effects should be expected with any combination of TCA and barbiturate.

3.5.1.DO Procainamide

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Class Ia antiarrhythmics and tricyclic antidepressants have been shown to prolong the QTc interval at the recommended therapeutic dose. Even though no formal drug interaction studies have been done, the coadministration of Class Ia antiarrhythmics and other drugs known to prolong the QTc interval, including tricyclic antidepressants, is not recommended (Prod Info Elavil(R), 1999g; Prod Info Quinaglute(R), 1999; Marshall & Forker, 1982m).

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: The concurrent administration of a Class IA antiarrhythmic agent and a tricyclic antidepressant is not recommended.

7) Probable Mechanism: additive cardiac effects

8) Literature Reports

a) Quinidine is an inhibitor of the cytochrome P450 isoenzyme responsible for the 2-hydroxylation of imipramine and desipramine (Brosen & Gram, 1989). Inhibition of this enzyme system can result in a 35% decrease in imipramine clearance and 85% decrease in desipramine clearance. Demethylation of imipramine by the cytochrome P450 system is unaffected by this interaction. Until more information is available all patients having quinidine added to drug regimen containing imipramine or desipramine should be monitored for increased antidepressant serum concentrations and potential toxicity.

b) An increased incidence in sudden death was observed in six out of 53 patients with cardiac disease receiving amitriptyline, compared to 0 out of 53 in the control group. It was recommended that amitriptyline be avoided in patients with underlying cardiac disease except when depression was debilitating and no other drugs were helpful (Moir et al, 1972; Coull et al, 1970).

c) In a placebo controlled study, imipramine 3.5 mg/kg was administered daily for seven patients with severe depression and titrated doses to obtain therapeutic plasma concentrations. Two patients displayed premature atrial depolarizations and premature ventricular depolarizations before therapy. On patient had 33 premature atrial depolarizations (PAD) and 30 premature ventricular depolarizations (PVD) per hour, which decreased to 0.4 PAC and zero PVC per hour on imipramine. The other patient had 12 PAD and 169 PVD per hour before treatment and 1.8 PAD and 28.1 PVD per hour on imipramine. The authors also cautioned that the incidence of cardiotoxicity may increase if tricyclic antidepressants are administered with Type I antiarrhythmics. It was also recommended that quinidine and procainamide not be used to treat the arrhythmias of a tricyclic overdose. The similarities between these agents may exacerbate the cardiotoxicity (Kantor et al, 1978).

3.5.1.DP Procarbazine

1) Interaction Effect: neurotoxicity, seizures

2) Summary: Concomitant tricyclic antidepressant and more potent MAOI use has resulted in hyperpyrexia, convulsions, and death. Procarbazine has relatively weak MAOI actions, so while the potential for drug interactions between tricyclic antidepressants and procarbazine exists, clinical data are lacking at this time (Schuckit et al, 1971c; White & Simpson, 1984a). Concurrent use is not recommended (Prod Info Matulane (R), 1997).

3) Severity: major

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: Concomitant use is not recommended and should probably be initiated only under close medical supervision, and then only if other antidepressant class agents have proven unsuccessful. With more potent MAOIs, recommendations for concurrent use of TCAs have included avoiding large doses of the TCA, using only oral tricyclics, and avoiding imipramine, clomipramine, and desipramine. Procarbazine therapy should not begin until seven days following discontinuation of tricyclic antidepressants and 14 days following the discontinuation of other MAO inhibitors.

7) Probable Mechanism: altered catecholamine uptake and metabolism

8) Literature Reports

a) Procarbazine is primarily used as an antineoplastic agent, but was originally investigated as a monoamine oxidase inhibitor (Gilman et al, 1985). Animal studies have indicated that procarbazine is a monoamine oxidase inhibitor (MAOI) (DeVita et al, 1965) but appears to be a relatively weak MAOI in man (Gilman et al, 1985). Hypertensive reactions may still result from concomitant administration of tricyclic antidepressants, sympathomimetics, and tyramine containing foods (Gilman et al, 1985; Ponto et al, 1977a).

b) Concomitant administration of monoamine oxidase (MAO) inhibitors with tricyclic antidepressants

has been considered an absolute contraindication in the past and still is listed as such by the manufacturers. Reports of excitation, hyperpyrexia, convulsions, and possible death have been attributed to the combination (Lockett & Milner, 1965a; Brachfeld et al, 1963; Winston, 1971a; Schuckit et al, 1971b; Sargent, 1965; Spiker & Pugh, 1976a). Careful examination of such reports indicate unusual circumstances in most cases such as parenteral administration of a tricyclic. The mechanism may relate to the combined inhibition of catecholamine reuptake into the central nervous system and inhibition of catecholamine metabolism (Sjoqvist, 1965a).
c) Procarbazine therapy should not begin until 7 days following discontinuation of tricyclic antidepressants and 14 days following the discontinuation of other MAO inhibitors (AMA Department of Drugs, 1992; Gilman et al, 1985).

3.5.1.DQ Prochlorperazine
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Q and T wave distortions have been observed in patients taking phenothiazines (Prod Info Compazine(R), 2002; Prod Info Stelazine(R), 2002; Prod Info Thorazine(R), 2002). Other phenothiazines may have similar effects, though no reports are available. Tricyclic antidepressants (TCAs) at therapeutic doses can cause QT prolongation (Marshall & Forker, 1982ad). Case reports have described increased plasma levels and adverse effects when phenothiazines and tricyclic antidepressants were taken together, likely due to inhibition of their metabolism (Ghaemi & Kirkwood, 1998; Geller et al, 1985; Siris et al, 1982; Loga et al, 1981).
3) Severity: major
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Concurrent administration of a phenothiazine and a tricyclic antidepressant is not recommended.
7) Probable Mechanism: additive effect on QT interval

3.5.1.DR Propafenone
1) Interaction Effect: doxepin toxicity (sedation, dry mouth)
2) Summary: A single case was reported in which coadministration of propafenone and desipramine in an elderly patient resulted in desipramine toxicity at a desipramine dosage which had previously produced levels in the therapeutic range (Katz, 1991a). Although not reported for doxepin, caution should be used with concomitant use of propafenone.
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Monitor for symptoms of tricyclic antidepressant toxicity.
7) Probable Mechanism: decreased doxepin metabolism
8) Literature Reports
a) A 68-year-old man suffering from agitated major depression was started on a dose of desipramine 125 mg daily which produced a subtherapeutic serum level of 442 nmol/L (therapeutic range 500 to 1000 nmol/L). An increased dose of 175 mg daily produced excellent clinical response with no side effects. He developed atrial fibrillation and flutter. Digoxin 0.25 mg daily was added to his therapy, and desipramine was discontinued. His arrhythmia was suppressed with the addition of propafenone 150 mg twice daily and 300 mg at bedtime. Desipramine 150 mg daily was again begun, at which point he experienced dry mouth, sedation, and shakiness; the desipramine serum level was measured at 2092 nmol/L. The desipramine was discontinued for five days, the side effects ceased, and desipramine therapy was resumed at 75 mg daily. The desipramine serum level was measured at 1130 nmol/L (Katz, 1991).

3.5.1.DS Propoxyphene
1) Interaction Effect: doxepin toxicity (sedation, lethargy, dry mouth, urinary retention)
2) Summary: Concomitant therapy with propoxyphene and doxepin has been reported to double steady state doxepin and desmethyldoxepin plasma concentrations and decrease cognitive function. This interaction is most likely related to inhibition of hepatic microsomal enzymes by propoxyphene (Abernethy et al, 1982).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor for symptoms of tricyclic antidepressant toxicity such as sedation, dry mouth, and urinary retention. Serum doxepin levels may also be of value in predicting toxicity. An alternative analgesic agent such as acetaminophen with codeine might be considered if clinically appropriate.
7) Probable Mechanism: decreased doxepin metabolism

3.5.1.DT Propylhexedrine
1) Interaction Effect: hypertension, other cardiac effects, and CNS stimulation
2) Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been

reported to result in enhanced amphetamine effects from the release of norepinephrine (Beaumont, 1973d; Raisfeld, 1972). A similar reaction might also occur with all drugs that have amphetamine-like effects. Acute elevations in blood pressure have been noted (Flemenbaum, 1971a). Some amphetamine-like drugs may inhibit the metabolism of TCAs, although most combinations have not been studied. When amphetamine analogs are being used to treat obesity, it should be noted that TCAs frequently lead to moderate weight gain (Russ & Ackerman, 1988). False positive urine tests for amphetamines have been reported during therapy with some TCAs (Merigian & Browning, 1993). Caution is advised when concurrent administration of amphetamine-like agents and TCAs is warranted. The patient should be closely monitored for increased cardiovascular effects (hypertension and dysrhythmias).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other sympathomimetic agents could lead to hypertension, increased cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006; Flemenbaum, 1972). Use caution if such therapy is warranted. Monitor the patient closely for hypertension and dysrhythmias.

7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission

8) Literature Reports

a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agents. Additionally, coadministration of d-amphetamine with TCAs such as desipramine or protriptyline results in sustained increases in d-amphetamine concentration in the brain (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006).

b) Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism of some tricyclic antidepressants, such as imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transdermal system, 2006).

c) Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases in blood pressure such that the hypotensive effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of combined therapy. Discontinuation of the methylphenidate usually results in the blood pressure returning to normotensive levels; reinstitution of the methylphenidate resulted in further blood pressure elevation (Flemenbaum, 1971; Flemenbaum, 1972).

d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine given for at least four weeks, were given fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical improvement. However, fenfluramine more than doubled steady-state plasma levels of desipramine (Price et al, 1990).

e) There have been claims based on uncontrolled studies that a better antidepressant response may occur with combined therapy (Garrettson et al, 1969). However, a systemic review of stimulants in the treatment of depression concluded that although uncontrolled studies were generally positive, the ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated little advantage of drug over placebo and did not appear to be as effective as the conventional antidepressants in primary depression (Satel & Nelson, 1989).

3.5.1.DU Quetiapine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999), haloperidol (O'Brien et al, 1999), risperidone (Duenas-Laita et al, 1999), sertindole (Agelink et al, 2001), quetiapine (Owens, 2001b), sultopride (Lande et al, 1992), and zotepine (Sweetman, 2003). Even though no formal drug interaction studies have been done, the coadministration of a tricyclic antidepressant and an antipsychotic is not recommended (Prod Info Pamelor(R), 2001; Marshall & Forker, 1982p).

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of a tricyclic antidepressant and an antipsychotic is not recommended.

7) Probable Mechanism: additive cardiac effects

8) Literature Reports

a) Electrocardiographic changes that have occurred during clinical trials with pimozide have included prolongation of the corrected QT interval, flattening, notching, and inversion of the T wave and the appearance of U waves. In experimental studies, sudden, unexpected deaths have occurred while patients were receiving pimozide doses of 1 mg/kg. The proposed mechanism for these deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmias (Prod Info Orap(R), 1999).

3.5.1.DV Quinestrol

1) Interaction Effect: attenuation of antidepressant effectiveness; tricyclic toxicity (drowsiness, hypotension,

akathisia)
2) Summary: In isolated cases, the pharmacologic effects of tricyclic antidepressants may be increased or decreased by estrogens (Somani & Khurana, 1973c), with paradoxical loss of antidepressant effect yet tricyclic toxicity being manifested simultaneously (Prange, 1972c). The effects of the interaction appear to be estrogen dose-related (Khurana, 1972c) and may be of clinical importance primarily in patients previously stabilized on tricyclic therapy who are being started on estrogen therapy (Krishnan et al, 1984c).
3) Severity: minor
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: If signs or symptoms of altered tricyclic response are noted, dose adjustment downward of either the estrogen or tricyclic component may be successful in restoring effectiveness or resolving toxicity. However, drug withdrawal may be required.
7) Probable Mechanism: possible estrogen-enhanced hepatic metabolism of the tricyclic
8) Literature Reports
a) Some studies evaluated the qualitative effects of concomitant administration of estrogen and TCAs. In one trial, 30 depressed female prisoners were randomly assigned to four treatment groups. Ten patients received placebo, 10 received imipramine (150 mg daily) and placebo, five patients received imipramine (150 mg daily) and ethinyl estradiol (50 mcg daily), while five patients received imipramine (150 mg daily) and ethinyl estradiol (25 mcg daily). The 10 patients that received placebo did not improve over the six weeks of the study. The 10 patients taking estrogen and imipramine demonstrated a significantly greater improvement in symptoms than did the 10 patients taking imipramine alone. However, after two weeks, the five patients that received imipramine and high-dose estrogen had not improved as much as the patients receiving imipramine and low-dose estrogen. The only side-effect reported was drowsiness, which only affected the patients taking imipramine. Following the discontinuation of ethinyl estradiol, a time period of two weeks was required for the high-dose estrogen group to do as well as the low-dose group. This effect was attributed to the presence of residual estrogen in the high-dose group. In another group, five women received imipramine 150 mg and ethinyl estradiol 50 mcg daily did not improve as much as 10 patients receiving only imipramine. Also, the patients on the combination had severe side-effects including lethargy, coarse tremor, and systolic hypotension (Prange, 1972b).
b) A case reported by (Khurana, 1972b) demonstrated an interaction in a 32-year-old female taking conjugated estrogens 2.5 mg and imipramine 100 mg. The patient developed lethargy, tremors, and signs of depersonalization. After two years of therapy, the patient increased her estrogen dose to 5 mg and then 7.5 mg daily. The patient became nauseated, had constant headaches, and low normal blood pressure. All lab work was normal. Upon discontinuing the estrogen, the side-effects abated. Some investigators have proposed that the side effects resulted from enhanced TCA effects secondary to estrogen inhibition of hepatic microsomal enzymes (Somani & Khurana, 1973b).
c) In a study women received clomipramine and oral contraceptives or clomipramine alone. At the beginning of the study there were 30 women taking the combination, but 12 subsequently dropped out. The 18 patients on the combination were matched with 18 patients taking clomipramine alone. No significant difference was noted in the patients' responses to clomipramine. It was proposed that there was no significant difference in side-effects between the groups; however, the groups were matched after patients had dropped out of the study. Had the patients been matched prior to the study, different conclusions may have been drawn (Beaumont, 1973a).
d) The effect of oral contraceptives on clomipramine was studied in 42 women between the ages of 18 and 40. Twenty-three women took clomipramine 25 mg at bedtime while 19 took clomipramine 25 mg at bedtime with oral contraceptives. Over the four-week study, three control patients (two due to side-effects) and five in the experimental group (two due to side-effects) dropped out. Venous blood samples were drawn at weekly intervals for measurement of serum clomipramine concentrations. No difference in serum concentrations was noted between the groups. However, this result may be partially due to the low dose of clomipramine given (Luscombe & John, 1980a).
e) The onset of akathisia was reported in 3 patients receiving conjugated estrogens and tricyclic antidepressants concurrently. A 24-year-old patient receiving clomipramine 120 mg daily for anorexia nervosa and conjugated estrogens 1.25 mg daily for amenorrhea developed restless legs and a constant desire to move continuously. Estrogen was discontinued and benztropine 2 mg was administered, resulting in marked reduction and resolution within 48 hours. Akathisia and disorientation developed in a 55-year-old patient on conjugated estrogen 1.25 mg daily who was prescribed amitriptyline 50 mg daily for depression. Within hours of amitriptyline, the patient was confused, restless, and possessed an inner desire to move continuously. Symptoms disappeared after discontinuing amitriptyline. A third case of akathisia was reported in a 35-year-old patient who received conjugated estrogen 1.25 mg daily and amitriptyline 50 mg daily. Akathisia developed within a few hours after taking the first dose of amitriptyline and resolved within 48 hours following discontinuation of the antidepressant (Krishnan et al, 1984b).
f) The absolute bioavailability of imipramine increased in women who received low-dose oral contraceptives (50 mcg or less of ethinyl estradiol) from 27% to 44% (p less than 0.05) as evident by an increase in the area under the plasma concentration time curve (Abernethy et al, 1984a).
g) Estrogens may inhibit the oxidation of TCAs by affecting hepatic microsomal enzymes (John et al, 1980a). Many TCAs are metabolized via oxidation and conjugation pathways. Inhibition of the oxidation

of TCAs could result in accumulation and toxicity due to decreased clearance. Estrogens are suspected of possessing other effects on the central nervous system resulting in an antidepressant effect (Oppenheim, 1983a).

3.5.1.DW Quinidine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Class Ia antiarrhythmics and tricyclic antidepressants have been shown to prolong the QTc interval at the recommended therapeutic dose. Even though no formal drug interaction studies have been done, the coadministration of Class Ia antiarrhythmics and other drugs known to prolong the QTc interval, including tricyclic antidepressants, is not recommended (Prod Info Elavil(R), 1999g; Prod Info Quinaglute(R), 1999; Marshall & Forker, 1982m).

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: The concurrent administration of a Class IA antiarrhythmic agent and a tricyclic antidepressant is not recommended.

7) Probable Mechanism: additive cardiac effects

8) Literature Reports

a) Quinidine is an inhibitor of the cytochrome P450 isoenzyme responsible for the 2-hydroxylation of imipramine and desipramine (Brosen & Gram, 1989). Inhibition of this enzyme system can result in a 35% decrease in imipramine clearance and 85% decrease in desipramine clearance. Demethylation of imipramine by the cytochrome P450 system is unaffected by this interaction. Until more information is available all patients having quinidine added to drug regimen containing imipramine or desipramine should be monitored for increased antidepressant serum concentrations and potential toxicity.

b) An increased incidence in sudden death was observed in six out of 53 patients with cardiac disease receiving amitriptyline, compared to 0 out of 53 in the control group. It was recommended that amitriptyline be avoided in patients with underlying cardiac disease except when depression was debilitating and no other drugs were helpful (Moir et al, 1972; Coull et al, 1970).

c) In a placebo controlled study, imipramine 3.5 mg/kg was administered daily for seven patients with severe depression and titrated doses to obtain therapeutic plasma concentrations. Two patients displayed premature atrial depolarizations and premature ventricular depolarizations before therapy. On patient had 33 premature atrial depolarizations (PAD) and 30 premature ventricular depolarizations (PVD) per hour, which decreased to 0.4 PAC and zero PVC per hour on imipramine. The other patient had 12 PAD and 169 PVD per hour before treatment and 1.8 PAD and 28.1 PVD per hour on imipramine. The authors also cautioned that the incidence of cardiotoxicity may increase if tricyclic antidepressants are administered with Type I antiarrhythmics. It was also recommended that quinidine and procainamide not be used to treat the arrhythmias of a tricyclic overdose. The similarities between these agents may exacerbate the cardiotoxicity (Kantor et al, 1978).

3.5.1.DX Quinidine

1) Interaction Effect: doxepin toxicity (sedation, dry mouth, urinary retention) and an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Two studies have demonstrated that concomitant use of quinidine and imipramine or desipramine results in increased serum concentrations of these antidepressants (Brosen & Gram, 1989b; Steiner et al, 1987). A similar interaction may occur with other tricyclic antidepressants including doxepin. Due to their similar cardiac effects, the incidence of cardiotoxicity (increased PR interval, QRS complex, and QTc interval) may also be increased if tricyclic antidepressants are administered with Type I antiarrhythmics (Kantor et al, 1978b; Bigger et al, 1977).

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Concurrent use of quinidine and doxepin is not recommended. Monitor for symptoms of tricyclic antidepressant toxicity; a decrease in doxepin dosage may be required. Also monitor the patient for signs and symptoms of additive cardiac effects, including any changes in the EKG.

7) Probable Mechanism: decreased doxepin metabolism, additive cardiac effects

8) Literature Reports

a) Quinidine is an inhibitor of the cytochrome P450 isoenzyme responsible for the 2-hydroxylation of imipramine and desipramine (Brosen & Gram, 1989a). Inhibition of this enzyme system can result in a 35% decrease in imipramine clearance and 85% decrease in desipramine clearance. Demethylation of imipramine by the cytochrome P450 system is unaffected by this interaction. Until more information is available, all patients having quinidine added to drug regimen containing imipramine or desipramine should be monitored for increased antidepressant serum concentrations and potential toxicity.

b) In a placebo controlled study, (Kantor et al, 1978a) administered imipramine 3.5 mg/kg daily for seven patients with severe depression and titrated doses to obtain therapeutic plasma concentrations. Two patients displayed premature atrial depolarizations and premature ventricular depolarizations before therapy. On patient had 33 premature atrial depolarizations (PAD) and 30 premature ventricular depolarizations (PVD) per hour, which decreased to 0.4 PAC and zero PVC per hour on imipramine.

The other patient had 12 PAD and 169 PVD per hour before treatment and 1.8 PAD and 28.1 PVD per hour on imipramine. The authors also cautioned that the incidence of cardiotoxicity may increase if tricyclic antidepressants are administered with Type I antiarrhythmics. It was also recommended that quinidine and procainamide not be used to treat the arrhythmias of a tricyclic overdose. The similarities between these agents may exacerbate the cardiotoxicity.

3.5.1.DY Rasagiline

1) Interaction Effect: severe CNS toxicity
2) Summary: Concomitant use of rasagiline and tricyclic antidepressants should be avoided. Concurrent administration or overlapping therapy with tricyclic antidepressants and non-selective MAOIs has been reported to cause serious, sometimes fatal, reactions; the mechanisms of these reactions are not fully understood. Signs and symptoms include severe CNS toxicity (behavioral and mental status changes, diaphoresis, muscular rigidity, hypertension, and syncope) associated with hyperpyrexia and death. Data from clinical studies, where rasagiline-treated patients (n=115) were concomitantly exposed to tricyclic antidepressants, are insufficient to rule out an interaction. At least 14 days should elapse after discontinuing rasagiline before initiating therapy with a tricyclic antidepressant (Prod Info AZILECT(R) oral tablets, 2006).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concurrent use of rasagiline and a tricyclic antidepressant is not recommended. Wait at least 14 days after discontinuing rasagiline before initiating therapy with a tricyclic antidepressant (Prod Info AZILECT(R) oral tablets, 2006).
7) Probable Mechanism: unknown

3.5.1.DZ Risperidone

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999), haloperidol (O'Brien et al, 1999), risperidone (Duenas-Laita et al, 1999), sertindole (Agelink et al, 2001), quetiapine (Owens, 2001b), sultopride (Lande et al, 1992), and zotepine (Sweetman, 2003). Even though no formal drug interaction studies have been done, the coadministration of a tricyclic antidepressant and an antipsychotic is not recommended (Prod Info Pamelor(R), 2001; Marshall & Forker, 1982p).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of a tricyclic antidepressant and an antipsychotic is not recommended.
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) Electrocardiographic changes that have occurred during clinical trials with pimozide have included prolongation of the corrected QT interval, flattening, notching, and inversion of the T wave and the appearance of U waves. In experimental studies, sudden, unexpected deaths have occurred while patients were receiving pimozide doses of 1 mg/kg. The proposed mechanism for these deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmias (Prod Info Orap(R), 1999).

3.5.1.EA S-Adenosylmethionine

1) Interaction Effect: an increased risk of serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)
2) Summary: A single case has been reported of serotonin syndrome likely resulting from the combination of S-adenosylmethionine (SAMe) and clomipramine (Iruela et al, 1993a). SAMe was shown to hasten the onset of therapeutic response of imipramine in a clinical trial involving 40 patients, without serotonergic side effects (Berlanga et al, 1992). If therapy is initiated with SAMe and a tricyclic antidepressant, the patient should be monitored closely for early signs of serotonin syndrome. Serotonin syndrome is a condition of serotonergic hyperstimulation and manifests as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. If the syndrome is not recognized and correctly treated, death can result (Sternbach, 1991).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: S-adenosylmethionine (SAMe) used concomitantly with imipramine was found to decrease depressive symptoms sooner than imipramine alone (Berlanga et al, 1992). One case has been reported of serotonin syndrome likely resulting from concomitant use of SAMe and clomipramine (Iruela et al, 1993). If SAMe and a tricyclic antidepressant are used together, use low doses of each and titrate upward slowly, while monitoring closely for early signs of serotonin syndrome such as increasing anxiety, confusion, and disorientation.
7) Probable Mechanism: additive pharmacologic effects resulting in excessive serotonergic stimulation

8) Literature Reports

a) A 71 year-old female was hospitalized with anxiety, agitation, confusion, and symptoms of serotonin syndrome. She had been taking S-adenosylmethionine 100 milligrams (mg) intramuscularly daily and clomipramine 25 mg daily for 10 days, which was then increased to 75 mg/day. Within 48-72 hours of the increased clomipramine dosage, she became progressively anxious, agitated, and confused. On admission she was verbally unresponsive and stuporous, with heart rate 130 beats/minute, respiratory rate 30 breaths/minute, temperature 40.5 degrees Celsius, diarrhea, myoclonus, generalized tremors, rigidity, hyperreflexia, shivering, diaphoresis, and dehydration. Temperature increased to 43 degrees Celsius during her hospital stay, with no documented infection. White blood cell count (WBC) was 13,040 mm3, lactic dehydrogenase was 662 units/liter (U/L), creatine phosphokinase was 8920 U/L, serum potassium 2.7 milliequivalents/liter (mEq/L), creatinine 1.1 mg/100 milliliter (mL) (laboratory reference values were not provided). A cranial computed tomography (CT) scan was normal. The patient was not taking neuroleptics. Serum benzodiazepine and tricyclic antidepressant levels were normal. Symptoms resolved gradually with 4 days of hydration and supportive care. The interaction was proposed to be a result of synergistic activity of S-adenosylmethionine and clomipramine (Iruela et al, 1993).

3.5.1.EB Salmeterol

1) Interaction Effect: an increased risk of cardiovascular excitation

2) Summary: Salmeterol should be administered with extreme caution to patients who are being treated with a tricyclic antidepressant, or within two weeks of the discontinuation of a tricyclic antidepressant (Prod Info SEREVENT(R) DISKUS(R) inhalation powder, 2006). Clinically significant changes in systolic and diastolic blood pressure, pulse rate, and electrocardiograms have been seen with the use of salmeterol, and these changes may be exacerbated by the use of a tricyclic antidepressant.

3) Severity: moderate

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: Close observation for adverse cardiovascular effects is warranted when these agents are administered concurrently or if salmeterol is given within two weeks of discontinuation of a tricyclic antidepressant.

7) Probable Mechanism: potentiation of vascular effects

3.5.1.EC Secobarbital

1) Interaction Effect: possible decreased tricyclic antidepressant serum concentrations and possible additive adverse effects

2) Summary: Concomitant barbiturate and tricyclic antidepressant (TCA) therapy may result in increased metabolism of the TCA. There have been scattered reports of individuals with decreased serum levels of TCAs in the presence of a barbiturate (Moody et al, 1977; Silverman & Braithwaite, 1972; Burrows & Davies, 1971). In addition, TCAs can worsen seizure control by reducing the seizure threshold (Brodie, 1992). These drugs also have additive CNS and respiratory depressant effects.

3) Severity: minor

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Monitor for efficacy of antidepressant effect. Increases in tricyclic antidepressant dosages may be required. Additionally, monitor for toxicity when either drug is added to or withdrawn from therapy. Serum concentrations may be of value in determining appropriate dosage.

7) Probable Mechanism: increased tricyclic antidepressant metabolism

8) Literature Reports

a) The pharmacokinetics of a single oral dose of desipramine (100 mg) were studied in eight epileptic patients chronically treated with phenobarbital and in eight drug-free healthy controls (Spina et al, 1996). All subjects were extensive metabolizers with respect to the genetically determined CYP2D6-related metabolic polymorphism. Compared with controls, epileptic patients exhibited lower peak plasma desipramine concentrations (74 nmol/L vs. 107 nmol/L), smaller desipramine area under the concentration-time curve values (1943 nmol/L/h vs. 3234 nmol/L/h), and shorter desipramine elimination half-lives (15.1 h vs. 20.6 h). All barbiturates are believed to have similar effects leading to induction of hepatic enzymes and the 2D6 isozyme is believed to be important in the metabolism of most or all TCAs. Thus, similar effects should be expected with any combination of TCA and barbiturate.

3.5.1.ED Selegiline

1) Interaction Effect: neurotoxicity, seizures, or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)

2) Summary: Concomitant TCA and MAOI use has resulted in hyperpyrexia, convulsions, and death. Concurrent use of MAOIs and TCAs has also been reported to result in a condition termed serotonin syndrome (Insel et al, 1982i; Spigset et al, 1993j; Brodribb et al, 1994i; Neuvonen et al, 1993d). Serotonin syndrome is a rare but potentially fatal condition of serotonergic hyperstimulation characterized by hypertension, hyperthermia, myoclonus, and changes in mental status (Sternbach, 1991e). If TCAs and MAOIs must be used concurrently, avoid large doses, use only oral TCAs, avoid imipramine, clomipramine, desipramine, and tranylcypromine, and monitor patients closely (Schuckit et al, 1971k; White & Simpson,

1984i).
3) Severity: major
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of a tricyclic antidepressant, such as doxepin, and a monoamine oxidase inhibitor (MAOI), such as selegiline, should be done only with close monitoring and where the clinical benefit outweighs the potential risk. Other antidepressant therapy should first be considered. If deemed clinically necessary, avoid large doses and use agents other than imipramine, clomipramine, desipramine, and tranylcypromine. A minimum of 14 days should elapse after selegiline is discontinued before doxepin therapy begins (Prod Info SINEQUAN(R) capsule, oral concentrate, 2005). There is no specific washout period for doxepin when beginning treatment with selegiline. However, it is advisable to gradually taper the tricyclic antidepressant dosage before starting treatment with the MAOI (Remick, 2002).
7) Probable Mechanism: altered catecholamine uptake and metabolism
8) Literature Reports
a) Concomitant administration of monoamine oxidase inhibitors (MAOIs) with tricyclic antidepressants (TCAs) has been considered an absolute contraindication in the past and still is listed as such by the manufacturers. Reports of excitation, hyperpyrexia, convulsions, and possible death have been attributed to the combination (Lockett & Milner, 1965e; Brachfeld et al, 1963d; Winston, 1971e; Schuckit et al, 1971j; Sargent, 1965d; Spiker & Pugh, 1976e). The mechanism may relate to the combined inhibition of catecholamine reuptake into the central nervous system and inhibition of catecholamine metabolism (Sjoqvist, 1965e).
b) Administration of a TCA after MAOI therapy may result in the development of serotonin syndrome. In a double-blind, crossover study examining the effects of clorgyline and clomipramine for the treatment of obsessive-compulsive disorder, two subjects developed severe reactions characteristic of serotonin syndrome. During the study, patients had received clorgyline therapy, followed by a washout period of approximately four weeks and subsequent clomipramine therapy. After taking the first 100 mg dose of clomipramine, one patient developed coarse myoclonic jerking in both legs, hyperreflexia, diaphoresis, and arrhythmia. Another patient developed a similar reaction after the first dose, with upper motor neuron symptoms, myoclonic movements, and cardiac irritability. Both patient's symptoms resolved several hours later, and both patients were later treated successfully with clomipramine without adverse effects (Insel et al, 1982h).
c) A drug interaction occurred in a 76-year old woman who had been taking clomipramine 50 mg daily for several months prior to switching to moclobemide 300 mg daily. The patient experienced somnolence, confusion, and fever which then progressed to further mental impairment, muscle stiffness, myoclonus, and convulsive attacks. The patient's symptoms were described as fulfilling the diagnostic criteria for serotonin syndrome and were resolved a few days later after discontinuing all antidepressant medications (Spigset et al, 1993i).
d) A 39-year old woman with bipolar disorder developed serotonin syndrome after imipramine was added to moclobemide. The patient was taking moclobemide 300 mg twice daily when imipramine was started at 50 mg daily, followed by two dosage increases of imipramine to 200 mg and a reduction of moclobemide dosage to 150 mg twice daily. Five days after the increase in imipramine to 200 mg per day, the patient developed symptoms of serotonin syndrome, including sweating, shivering, confusion, fever, and spasms in the extremities. The patient was treated with chlorpromazine and symptoms resolved over the next few days without further complications (Brodribb et al, 1994h).
e) Three patients with bipolar disorder developed manic symptoms while undergoing concurrent therapy with isocarboxazid and amitriptyline. In all three cases the patients had been given MAOIs and TCAs alone without complications. It was only when the drugs were used in combination that symptoms of mania emerged, suggesting a synergistic effect (de la Fuente et al, 1986c).
f) In one case, clomipramine 10 mg twice daily was added to a stable regimen of tranylcypromine in a physically healthy 34-year old man. After taking several doses, the patient developed symptoms of nausea and profuse sweating, followed by pyrexia, dyspnea, and agitation. The hyperpyrexical state led to disseminated intravascular coagulation and eventual death (Tackley & Tregaskis, 1987e).
g) There is evidence that MAOIs and TCAs can be given concomitantly in patients previously unresponsive to the MAOI or TCA alone. A few precautions must be followed including: a) avoidance of large doses (no more than 150 mg amitriptyline or its equivalent, 45 mg phenelzine, or 60 mg isocarboxazid) b) oral administration c) avoidance of clomipramine, imipramine, desipramine, and tranylcypromine in any combination, and d) close monitoring of patients (Kline, 1974c; Winston, 1971e; Schuckit et al, 1971j; White & Simpson, 1984h; Rom & Benner, 1972c). The combination may be utilized in one of two ways. Most frequently, the recommendation is to stop all previous antidepressants (five to ten days for TCAs and 14 days for MAOIs); the combination is then simultaneously started (Perry et al, 1991d). Alternatively, in a patient previously receiving a TCA, small doses of the MAOI may be slowly added (Schoonover, 1983). Some sources suggest that the combination of amitriptyline and isocarboxazid is preferred (Perry et al, 1991d). Numerous studies in patients with refractory depression or phobic anxiety states have successfully used the combination of MAOIs and TCAs (Ponto et al, 1977e; Schuckit et al, 1971j; Ashcroft, 1975d).

3.5.1.EE Sematilide
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac

arrest)
2) Summary: Cases of QTc prolongation and/or torsades de pointes have been reported with all Class III antiarrhythmic agents, including acecainide (Chow et al, 1984), amiodarone (Faggiano et al, 1996), azimilide (Corey et al, 1999), bretylium (Gilman et al, 1985a), ibutilide (Rodriguez et al, 2001), sematilide (Singh, 1996), dofetilide (Allen et al, 2002), and sotalol (Marill & Runge, 2001). Even though no formal drug interaction studies have been done, the coadministration of Class III antiarrhythmics and other drugs known to prolong the QTc interval, including tricyclic antidepressants, is not recommended (Yamreudeewong et al, 2003a; Prod Info Corvert(R), 2000).
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of a Class III antiarrhythmic and a tricyclic antidepressant (TCA) is not recommended.
7) Probable Mechanism: additive QT prolongation
8) Literature Reports
a) EKG effects reported in patients receiving therapeutic doses of tricyclic antidepressants include increased heart rate, prolonged PR interval, intraventricular conduction delays, increased corrected QT interval (QTc) and flattened T waves (Marshall & Forker, 1982y).
b) Concurrent use of Class III antiarrhythmic agents, and other drugs that can prolong the QT interval, such as tricyclic antidepressants, is not recommended. Dofetilide should be stopped for at least 2 days before any interacting drug is initiated. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised (Yamreudeewong et al, 2003).

3.5.1.EF Sertindole
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999), haloperidol (O'Brien et al, 1999), risperidone (Duenas-Laita et al, 1999), sertindole (Agelink et al, 2001), quetiapine (Owens, 2001b), sultopride (Lande et al, 1992), and zotepine (Sweetman, 2003). Even though no formal drug interaction studies have been done, the coadministration of a tricyclic antidepressant and an antipsychotic is not recommended (Prod Info Pamelor(R), 2001; Marshall & Forker, 1982p).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of a tricyclic antidepressant and an antipsychotic is not recommended.
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) Electrocardiographic changes that have occurred during clinical trials with pimozide have included prolongation of the corrected QT interval, flattening, notching, and inversion of the T wave and the appearance of U waves. In experimental studies, sudden, unexpected deaths have occurred while patients were receiving pimozide doses of 1 mg/kg. The proposed mechanism for these deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmias (Prod Info Orap(R), 1999).

3.5.1.EG Sertraline
1) Interaction Effect: modest elevations in doxepin serum levels or possible serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)
2) Summary: There is limited evidence suggesting that sertraline may inhibit tricyclic antidepressant (TCA) metabolism resulting in higher TCA serum concentrations. Sertraline inhibits cytochrome P450 2D6 enzyme activity and may increase the plasma concentrations of coadministered drugs that are metabolized by this pathway, including the tricyclic antidepressants (Prod Info Zoloft(R), 2002; Preskorn et al, 1994c; Lydiard et al, 1993). Effects of the interaction may have little or no clinical impact, however. Increases in TCA serum levels associated with sertraline coadministration were modest compared with those found when fluoxetine (another selective serotonin reuptake inhibitor) was combined with desipramine (von Moltke et al, 1994). Monitor patients on doxepin-sertraline therapy for TCA toxicity (dry mouth, urinary retention, CNS depression). Doxepin doses may need to be reduced.
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: The combined use of tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs) may result in the inhibition of the TCA metabolism. A few cases of serotonin syndrome have also been reported with concurrent TCA and SSRI therapy. Caution should be observed when drugs in these two classes are used together.
7) Probable Mechanism: inhibition of doxepin metabolism
8) Literature Reports
a) Desipramine pharmacokinetics was studied in 18 healthy male volunteers. Study subjects received

only desipramine (50 mg daily) for 7 days followed by desipramine with sertraline (50 mg daily) for 21 days. When sertraline was added to desipramine therapy, the mean maximum concentration of desipramine increased by 34% and the area under the concentration-time curve increased by 26%. Trough concentrations of desipramine were close to baseline one week after sertraline was discontinued. The changes in desipramine concentrations were modest and the interaction may not be clinically significant (Preskorn et al, 1994b).

3.5.1.EH Sotalol

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Cases of QTc prolongation and/or torsades de pointes have been reported with all Class III antiarrhythmic agents, including acecainide (Chow et al, 1984), amiodarone (Faggiano et al, 1996), azimilide (Corey et al, 1999), bretylium (Gilman et al, 1985a), ibutilide (Rodriguez et al, 2001), sematilide (Singh, 1996), dofetilide (Allen et al, 2002), and sotalol (Marill & Runge, 2001). Even though no formal drug interaction studies have been done, the coadministration of Class III antiarrhythmics and other drugs known to prolong the QTc interval, including tricyclic antidepressants, is not recommended (Yamreudeewong et al, 2003a; Prod Info Corvert(R), 2000).

3) Severity: major

4) Onset: rapid

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of a Class III antiarrhythmic and a tricyclic antidepressant (TCA) is not recommended.

7) Probable Mechanism: additive QT prolongation

8) Literature Reports

a) EKG effects reported in patients receiving therapeutic doses of tricyclic antidepressants include increased heart rate, prolonged PR interval, intraventricular conduction delays, increased corrected QT interval (QTc) and flattened T waves (Marshall & Forker, 1982y).

b) Concurrent use of Class III antiarrhythmic agents, and other drugs that can prolong the QT interval, such as tricyclic antidepressants, is not recommended. Dofetilide should be stopped for at least 2 days before any interacting drug is initiated. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised (Yamreudeewong et al, 2003).

3.5.1.EI Sparfloxacin

1) Interaction Effect: prolongation of the QTc interval and/or torsades de pointes

2) Summary: Torsades de pointes has been reported in patients receiving sparfloxacin concomitantly with disopyramide and amiodarone. The use of sparfloxacin is contraindicated with drugs which produce an increase in the QTc interval and/or torsades de pointes, including tricyclic antidepressants. Sparfloxacin is also contraindicated in persons with known QTc prolongation (Prod Info Zagam(R), 1998a).

3) Severity: contraindicated

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: Sparfloxacin is contraindicated in individuals with known QTc prolongation or in patients being treated concurrently with drugs that are known to increase the QTc interval and/or cause torsades de pointes.

7) Probable Mechanism: additive effects on QTc prolongation

8) Literature Reports

a) In clinical trials involving 1489 patients with a baseline QTc measurement, the mean prolongation of the QTc interval at sparfloxacin steady-state was 10 msec (2.5%). Of these subjects, 0.7% had a QTc interval greater than 500 msec at steady-state. However, no arrhythmic effects were seen in any of the patients. The magnitude of the QTc effect does not increase with repeated administration of sparfloxacin, and the QTc interval returns to baseline within 48 hours after discontinuation of sparfloxacin (Prod Info Zagam(R), 1998).

b) A case of sparfloxacin-induced torsades de pointes is described (Dupont et al, 1996). A 47-year old woman hospitalized for suppurative otitis media and mastoiditis was treated with sparfloxacin due to an allergy to betalactam antibiotics. On day six of treatment she felt dizzy and lost consciousness. This was attributed to torsades de pointes on the cardioscope and was followed by cardiac arrest which required cardiopulmonary resuscitation. Her pre-treatment electrocardiogram showed QT and QTc intervals of 0.34 and 0.46 seconds, respectively. An electrocardiogram post-arrest revealed QT and QTc intervals of 0.35 and 0.60 seconds, respectively. A 24-hour continuous electrocardiography confirmed numerous episodes of torsades de pointes occurring after episodes of sino-auricular block. Sparfloxacin was discontinued and the QTc returned to baseline within a week. Upon further testing, it was determined that the patient suffered from a mild idiopathic long QT syndrome. Due to the onset of symptoms with administration of sparfloxacin and the relief of symptoms following discontinuation of the drug, it is highly probable that sparfloxacin contributed to the torsades de pointes.

3.5.1.EJ Spiramycin

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Tricyclic antidepressants (TCAs) and spiramycin have been shown to prolong the QTc interval at the recommended therapeutic dose (Stramba-Badiale et al, 1997; Marshall & Forker, 1982b). Even though no formal drug interaction studies have been done, the coadministration of tricyclic antidepressants and other drugs known to prolong the QTc interval, such as spiramycin, is not recommended (Prod Info Elavil(R), 1999a).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of spiramycin and tricyclic antidepressants is not recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.EK St John's Wort
1) Interaction Effect: an increased risk of serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)
2) Summary: Theoretically, since St. John's Wort is thought to inhibit serotonin reuptake and may have mild monoamine oxidase inhibitory activity (Singer et al, 1999; Thiede & Walper, 1994), serotonin syndrome could result when St. John's Wort is taken along with a tricyclic antidepressant. This theoretical risk of serotonin syndrome is also based on case reports of serotonin syndrome resulting from concomitant use of selective serotonin reuptake inhibitors with tricyclic antidepressants (Alderman & Lee, 1996), as well as concomitant use of monoamine oxidase inhibitors with tricyclic antidepressants (Brodribb et al, 1994c; Spigset et al, 1993d; Tackley & Tregaskis, 1987b). Coadministration of amitriptyline and St. John's Wort decreased the area under the concentration-time curve of amitriptyline and its metabolite nortriptyline (Roots et al, 2000); if other tricyclic antidepressants are similarly affected by St. John's Wort, the risk of serotonin syndrome may be reduced, yet effectiveness of the tricyclic antidepressant may also be reduced. To maintain maximal effectiveness of the tricyclic antidepressant, as well as avoid any potential risk of serotonin syndrome, avoid concomitant use of St. John's Wort and tricyclic antidepressants.
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Avoid concomitant use of St. John's Wort with tricyclic antidepressants.
7) Probable Mechanism: additive pharmacologic effects resulting in excessive serotonergic stimulation

3.5.1.EL Sulfamethoxazole
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Tricyclic antidepressants (TCAs) and cotrimoxazole have been shown to prolong the QTc interval at the recommended therapeutic dose (Lopez et al, 1987; Marshall & Forker, 1982q). Even though no formal drug interaction studies have been done, the coadministration of tricyclic antidepressants and other drugs known to prolong the QTc interval, such as cotrimoxazole, is not recommended (Prod Info Elavil (R), 1999i).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: The concurrent administration of cotrimoxazole and tricyclic antidepressants is not recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.EM Sultopride
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999), haloperidol (O'Brien et al, 1999), risperidone (Duenas-Laita et al, 1999), sertindole (Agelink et al, 2001), quetiapine (Owens, 2001b), sultopride (Lande et al, 1992), and zotepine (Sweetman, 2003). Even though no formal drug interaction studies have been done, the coadministration of a tricyclic antidepressant and an antipsychotic is not recommended (Prod Info Pamelor(R), 2001; Marshall & Forker, 1982p).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of a tricyclic antidepressant and an antipsychotic is not recommended.
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) Electrocardiographic changes that have occurred during clinical trials with pimozide have included prolongation of the corrected QT interval, flattening, notching, and inversion of the T wave and the appearance of U waves. In experimental studies, sudden, unexpected deaths have occurred while patients were receiving pimozide doses of 1 mg/kg. The proposed mechanism for these deaths is

prolongation of the QT interval predisposing patients to ventricular arrhythmias (Prod Info Orap(R), 1999).

3.5.1.EN Tapentadol

1) Interaction Effect: increased risk of serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)
2) Summary: Concurrent use of tapentadol and a tricyclic antidepressant may result in serotonin syndrome, which may be life-threatening. Symptoms of serotonin syndrome may include restlessness, hallucinations, loss of coordination, fast heart beat, rapid changes in blood pressure, increased body temperature, overreactive reflexes, nausea, vomiting, and diarrhea (Prod Info tapentadol immediate release oral tablets, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of tapentadol and a tricyclic antidepressant may result in a life-threatening condition called serotonin syndrome. If these agents are used together, monitor the patient closely for symptoms of serotonin syndrome (restlessness, hyperthermia, hyperreflexia, incoordination), especially during treatment initiation and dose increases (Prod Info tapentadol immediate release oral tablets, 2008).
7) Probable Mechanism: additive serotonergic effect

3.5.1.EO Tedisamil

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Cases of QTc prolongation and/or torsades de pointes have been reported with all Class III antiarrhythmic agents, including acecainide (Chow et al, 1984), amiodarone (Faggiano et al, 1996), azimilide (Corey et al, 1999), bretylium (Gilman et al, 1985a), ibutilide (Rodriguez et al, 2001), sematilide (Singh, 1996), dofetilide (Allen et al, 2002), and sotalol (Marill & Runge, 2001). Even though no formal drug interaction studies have been done, the coadministration of Class III antiarrhythmics and other drugs known to prolong the QTc interval, including tricyclic antidepressants, is not recommended (Yamreudeewong et al, 2003a; Prod Info Corvert(R), 2000).
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of a Class III antiarrhythmic and a tricyclic antidepressant (TCA) is not recommended.
7) Probable Mechanism: additive QT prolongation
8) Literature Reports
a) EKG effects reported in patients receiving therapeutic doses of tricyclic antidepressants include increased heart rate, prolonged PR interval, intraventricular conduction delays, increased corrected QT interval (QTc) and flattened T waves (Marshall & Forker, 1982y).
b) Concurrent use of Class III antiarrhythmic agents, and other drugs that can prolong the QT interval, such as tricyclic antidepressants, is not recommended. Dofetilide should be stopped for at least 2 days before any interacting drug is initiated. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised (Yamreudeewong et al, 2003).

3.5.1.EP Telithromycin

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Telithromycin may prolong the QT interval in some patients (Owens, 2001d). Because tricyclic antidepressants may also prolong the QT interval and increase the risk of arrhythmias, the concurrent administration of telithromycin and tricyclic antidepressants is not recommended (Marshall & Forker, 1982ac).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Because of the potential for additive QT interval prolongation, the concurrent administration of telithromycin and a tricyclic antidepressants is not recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.EQ Terfenadine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Tricyclic antidepressants (TCAs) have been shown to prolong the QTc interval at the recommended therapeutic dose (Marshall & Forker, 1982ab). Even though no formal drug interaction studies have been done, the coadministration of terfenadine and other drugs known to prolong the QTc interval, including tricyclic antidepressants, is contraindicated (Prod Info Elavil(R), 1999j; Anon, 1997).
3) Severity: contraindicated

4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of terfenadine with any drug that prolongs the QT interval, such as tricyclic antidepressants, is contraindicated.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.ER Thiopental

1) Interaction Effect: possible decreased tricyclic antidepressant serum concentrations and possible additive adverse effects
2) Summary: Concomitant barbiturate and tricyclic antidepressant (TCA) therapy may result in increased metabolism of the TCA. There have been scattered reports of individuals with decreased serum levels of TCAs in the presence of a barbiturate (Moody et al, 1977; Silverman & Braithwaite, 1972; Burrows & Davies, 1971). In addition, TCAs can worsen seizure control by reducing the seizure threshold (Brodie, 1992). These drugs also have additive CNS and respiratory depressant effects.
3) Severity: minor
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor for efficacy of antidepressant effect. Increases in tricyclic antidepressant dosages may be required. Additionally, monitor for toxicity when either drug is added to or withdrawn from therapy. Serum concentrations may be of value in determining appropriate dosage.
7) Probable Mechanism: increased tricyclic antidepressant metabolism
8) Literature Reports
a) The pharmacokinetics of a single oral dose of desipramine (100 mg) were studied in eight epileptic patients chronically treated with phenobarbital and in eight drug-free healthy controls (Spina et al, 1996). All subjects were extensive metabolizers with respect to the genetically determined CYP2D6-related metabolic polymorphism. Compared with controls, epileptic patients exhibited lower peak plasma desipramine concentrations (74 nmol/L vs. 107 nmol/L), smaller desipramine area under the concentration-time curve values (1943 nmol/L/h vs. 3234 nmol/L/h), and shorter desipramine elimination half-lives (15.1 h vs. 20.6 h). All barbiturates are believed to have similar effects leading to induction of hepatic enzymes and the 2D6 isozyme is believed to be important in the metabolism of most or all TCAs. Thus, similar effects should be expected with any combination of TCA and barbiturate.

3.5.1.ES Thioridazine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Although citing no data, the manufacturer of thioridazine states that concomitant use with other drugs which prolong the QT interval is contraindicated (Prod Info Mellaril(R), 2001). Tricyclic antidepressants (TCAs) at therapeutic doses can cause QT prolongation (Marshall & Forker, 1982k).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concurrent administration of a tricyclic antidepressant and thioridazine is contraindicated.
7) Probable Mechanism: additive effect on QT interval

3.5.1.ET Tibolone

1) Interaction Effect: attenuation of antidepressant effectiveness; tricyclic toxicity (drowsiness, hypotension, akathisia)
2) Summary: In isolated cases, the pharmacologic effects of tricyclic antidepressants may be increased or decreased by estrogens (Somani & Khurana, 1973m), with paradoxical loss of antidepressant effect yet tricyclic toxicity being manifested simultaneously (Prange, 1972m). The effects of the interaction appear to be estrogen dose-related (Khurana, 1972m) and may be of clinical importance primarily in patients previously stabilized on tricyclic therapy who are being started on estrogen therapy (Krishnan et al, 1984m).
3) Severity: minor
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: If signs or symptoms of altered tricyclic response are noted, dose adjustment downward of either the estrogen or tricyclic component may be successful in restoring effectiveness or resolving toxicity. However, drug withdrawal may be required.
7) Probable Mechanism: possible estrogen-enhanced hepatic metabolism of the tricyclic
8) Literature Reports
a) Some studies evaluated the qualitative effects of concomitant administration of estrogen and TCAs. In one trial, 30 depressed female prisoners were randomly assigned to 4 treatment groups. Ten patients received placebo, 10 received imipramine (150 milligrams/day) and placebo, 5 patients received imipramine (150 milligrams/day) and ethinyl estradiol (50 micrograms/day), while 5 patients received imipramine (150 milligrams/day) and ethinyl estradiol (25 micrograms/day). The 10 patients that received placebo did not improve over the 6 weeks of the study. The 10 patients taking estrogen and imipramine demonstrated a significantly greater improvement in symptoms than did the 10 patients

taking imipramine alone. However, after 2 weeks, the 5 patients that received imipramine and high-dose estrogen had not improved as much as the patients receiving imipramine and low-dose estrogen. The only side-effect reported was drowsiness, which only affected the patients taking imipramine. Following the discontinuation of ethinyl estradiol, a time period of 2 weeks was required for the high-dose estrogen group to do as well as the low-dose group. This effect was attributed to the presence of residual estrogen in the high-dose group. In another group, 5 women received imipramine 150 milligrams and ethinyl estradiol 50 micrograms daily did not improve as much as 10 patients receiving only imipramine. Also, the patients on the combination had severe side-effects including lethargy, coarse tremor and systolic hypotension (Prange, 1972l).

b) A case reported by (Khurana, 1972l) demonstrated an interaction in a 32-year-old female taking conjugated estrogens 2.5 milligrams and imipramine 100 milligrams. The patient developed lethargy, tremors, and signs of depersonalization. After 2 years of therapy, the patient increased her estrogen dose to 5 milligrams and then 7.5 milligrams daily. The patient became nauseated, had constant headaches, and low normal blood pressure. All lab work was normal. Upon discontinuing the estrogen, the side-effects abated. Some investigators have proposed that the side effects resulted from enhanced TCA effects secondary to estrogen inhibition of hepatic microsomal enzymes (Somani & Khurana, 1973l).

c) In a study women received clomipramine and oral contraceptives or clomipramine alone. At the beginning of the study there were 30 women taking the combination, but 12 subsequently dropped out. The 18 patients on the combination were matched with 18 patients taking clomipramine alone. No significant difference was noted in the patients' responses to clomipramine. It was proposed that there was no significant difference in side-effects between the groups; however, the groups were matched after patients had dropped out of the study. Had the patients been matched prior to the study, different conclusions may have been drawn (Beaumont, 1973g).

d) The effect of oral contraceptives on clomipramine was studied in 42 women between the ages of 18 and 40. Twenty-three women took clomipramine 25 milligrams at bedtime while 19 took clomipramine 25 milligrams at bedtime with oral contraceptives. Over the 4-week study, 3 control patients (2 due to side-effects) and 5 in the experimental group (2 due to side-effects) dropped out. Venous blood samples were drawn at weekly intervals for measurement of serum clomipramine concentrations. No difference in serum concentrations was noted between the groups. However, this result may be partially due to the low dose of clomipramine given (Luscombe & John, 1980f).

e) The onset of akathisia was reported in 3 patients receiving conjugated estrogens and tricyclic antidepressants concurrently. A 24-year-old patient receiving clomipramine 120 milligrams/day for anorexia nervosa and conjugated estrogens 1.25 milligrams/day for amenorrhea developed restless legs and a constant desire to move continuously. Estrogen was discontinued and benztropine 2 milligrams was administered, resulting in marked reduction and resolution within 48 hours. Akathisia and disorientation developed in a 55-year-old patient on conjugated estrogens 1.25 milligrams/day who was prescribed amitriptyline 50 milligrams/day for depression. Within hours of amitriptyline, the patient was confused, restless, and possessed an inner desire to move continuously. Symptoms disappeared after discontinuing amitriptyline. Positive rechallenge at one week with doxepin 100 milligrams, with resolution following discontinuation of doxepin. A third case of akathisia was reported in a 35-year-old patient who received conjugated estrogens 1.25 milligrams/day and amitriptyline 50 milligrams/day. Akathisia developed within a few hours after taking the first dose of amitriptyline and resolved within 48 hours following discontinuation of the antidepressant (Krishnan et al, 1984l).

f) The absolute bioavailability of imipramine increased in women who received low-dose oral contraceptives (50 micrograms or less of ethinyl estradiol) from 27 to 44% (p less than 0.05) as evident by an increase in the area under the plasma concentration time curve (Abernethy et al, 1984f).

g) Estrogens may inhibit the oxidation of TCAs by affecting hepatic microsomal enzymes (John et al, 1980f). Many TCAs are metabolized via oxidation and conjugation pathways. Inhibition of the oxidation of TCAs could result in accumulation and toxicity due to decreased clearance. Estrogens are suspected of possessing other effects on the central nervous system resulting in an antidepressant effect (Oppenheim, 1983f).

3.5.1.EU Toloxatone

1) Interaction Effect: neurotoxicity, seizures, or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)

2) Summary: Concomitant TCA and MAOI use has resulted in hyperpyrexia, convulsions, and death. Concurrent use of MAOIs and TCAs has also been reported to result in a condition termed serotonin syndrome (Insel et al, 1982p; Spigset et al, 1993q; Brodribb et al, 1994o; Neuvonen et al, 1993h). Serotonin syndrome is a rare but potentially fatal condition of serotonergic hyperstimulation characterized by hypertension, hyperthermia, myoclonus, and changes in mental status (Sternbach, 1991i). If TCAs and MAOIs must be used concurrently, avoid large doses, use only oral TCAs, avoid imipramine, clomipramine, desipramine, and tranylcypromine, and monitor patients closely (Schuckit et al, 1971s; White & Simpson, 1984n).

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Concomitant use of a tricyclic antidepressant (TCA) and a monoamine oxidase

inhibitor (MAOI) should be done only with close monitoring and where the clinical benefit outweighs the potential risk. Other antidepressant therapy should first be considered. If deemed clinically necessary, avoid large doses and use agents other than imipramine, clomipramine, desipramine, and tranylcypromine.
7) Probable Mechanism: altered catecholamine uptake and metabolism
8) Literature Reports
a) Concomitant administration of monoamine oxidase inhibitors (MAOIs) with tricyclic antidepressants (TCAs) has been considered an absolute contraindication in the past. Reports of excitation, hyperpyrexia, convulsions, and possible death have been attributed to the combination (Lockett & Milner, 1965i; Winston, 1971i; Schuckit et al, 1971r; Spiker & Pugh, 1976i). The mechanism may relate to the combined inhibition of catecholamine reuptake into the central nervous system and inhibition of catecholamine metabolism (Sjoqvist, 1965i).
b) There is minimal risk of a clinically significant pharmacokinetic interaction between amitriptyline and toloxatone, a MAOI-A (Vandel et al, 1993). Seventeen inpatients being treated for major depressive illness were administered amitriptyline 125 mg once daily for two weeks, and the following two weeks they received amitriptyline 125 mg daily and toloxatone 600 mg daily. With combined therapy there was a small, nonsignificant increase in amitriptyline plasma levels. The availability and urinary excretion of amitriptyline and its metabolites were not significantly affected.
c) There is evidence that MAOIs and TCAs can be given concomitantly in patients previously unresponsive to the MAOI or TCA alone. The combination may be utilized in one of two ways. Most frequently, the recommendation is to stop all previous antidepressants (five to ten days for TCAs and 14 days for MAOIs); the combination is then simultaneously started (Perry et al, 1991h). Alternatively, in a patient previously receiving a TCA, small doses of the MAOI may be slowly added (Schoonover, 1983). Numerous studies in patients with refractory depression or phobic anxiety states have successfully used the combination of MAOIs and TCAs (Ponto et al, 1977i; Schuckit et al, 1971r; Ashcroft, 1975h).
d) Serotonin syndrome has been reported with the use of moclobemide, a reversible inhibitor of monoamine oxidase, and a TCA. A 39-year old woman with bipolar disorder developed serotonin syndrome after imipramine was added to moclobemide. The patient was taking moclobemide 300 mg twice daily when imipramine was started at 50 mg daily, followed by two dosage increases of imipramine to 200 mg and a reduction of moclobemide dosage to 150 mg twice daily. Five days after the increase in imipramine to 200 mg per day, the patient developed symptoms of serotonin syndrome, including sweating, shivering, confusion, fever, and spasms in the extremities. The patient was treated with chlorpromazine and symptoms resolved over the next few days without further complications (Brodribb et al, 1994n).

3.5.1.EV Tramadol
1) Interaction Effect: an increased risk of seizures
2) Summary: Seizures have been reported in patients using tramadol. Some medications, including tricyclic antidepressants (TCAs), are known to reduce the seizure threshold. The risk of seizures may be enhanced when doxepin and tramadol therapy are combined (Prod Info Ultram(R), 1998).
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Caution should be used if tramadol is to be administered to patients receiving concomitant TCA therapy. If possible, avoid this combination, especially in patients with underlying conditions that might predispose to seizures.
7) Probable Mechanism: unknown

3.5.1.EW Tranylcypromine
1) Interaction Effect: neurotoxicity, seizures, or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)
2) Summary: Concomitant TCA and MAOI use has resulted in hyperpyrexia, convulsions, and death. Concurrent use of MAOIs and TCAs has also been reported to result in a condition termed serotonin syndrome (Insel et al, 1982g; Spigset et al, 1993h; Brodribb et al, 1994g; Neuvonen et al, 1993c). Serotonin syndrome is a rare but potentially fatal condition of serotonergic hyperstimulation characterized by hypertension, hyperthermia, myoclonus, and changes in mental status (Sternbach, 1991d). Consequently, coadministration of TCAs and MAOIs is contraindicated in most cases. If TCAs and MAOIs must be used concurrently, avoid large doses, use only oral TCAs, avoid imipramine, clomipramine, desipramine, and tranylcypromine, and monitor patients closely (Schuckit et al, 1971i; White & Simpson, 1984g).
3) Severity: contraindicated
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of doxepin with a monoamine oxidase inhibitor (MAOI), such as tranylcypromine is contraindicated (Prod Info Parnate(R), 2001). If doxepin is replacing treatment with tranylcypromine, a minimum of 14 days should elapse after tranylcypromine is discontinued before therapy with doxepin begins (Prod Info SINEQUAN(R) capsule, oral concentrate, 2005). The manufacturer of tranylcypromine recommends that at least 7 days should elapse before tranylcypromine therapy is replaced by doxepin. Similarly, if doxepin therapy is substituted by tranylcypromine, there should be a 7 day washout period. Tranylcypromine should then be given using half the normal starting dosage for, minimally, the first

week of therapy (Prod Info Parnate(R), 2001).
7) Probable Mechanism: altered catecholamine uptake and metabolism
8) Literature Reports
a) Concomitant administration of monoamine oxidase inhibitors (MAOIs) with tricyclic antidepressants (TCAs) has been considered an absolute contraindication in the past and still is listed as such by the manufacturers (Prod Info Parnate(R), 2001). Reports of excitation, hyperpyrexia, convulsions, and possible death have been attributed to the combination (Lockett & Milner, 1965d; Brachfeld et al, 1963c; Winston, 1971d; Schuckit et al, 1971h; Sargent, 1965c; Spiker & Pugh, 1976d). The mechanism may relate to the combined inhibition of catecholamine reuptake into the central nervous system and inhibition of catecholamine metabolism (Sjoqvist, 1965d).
b) Administration of a TCA after MAOI therapy may result in the development of serotonin syndrome. In a double-blind, crossover study examining the effects of clorgyline and clomipramine for the treatment of obsessive-compulsive disorder, two subjects developed severe reactions characteristic of serotonin syndrome. During the study, patients had received clorgyline therapy, followed by a washout period of approximately four weeks and subsequent clomipramine therapy. After taking the first 100 mg dose of clomipramine, one patient developed coarse myoclonic jerking in both legs, hyperreflexia, diaphoresis, and arrhythmia. Another patient developed a similar reaction after the first dose, with upper motor neuron symptoms, myoclonic movements, and cardiac irritability. Both patient's symptoms resolved several hours later, and both patients were later treated successfully with clomipramine without adverse effects (Insel et al, 1982f).
c) A drug interaction occurred in a 76-year old woman who had been taking clomipramine 50 mg daily for several months prior to switching to moclobemide 300 mg daily. The patient experienced somnolence, confusion, and fever which then progressed to further mental impairment, muscle stiffness, myoclonus, and convulsive attacks. The patient's symptoms were described as fulfilling the diagnostic criteria for serotonin syndrome and were resolved a few days later after discontinuing all antidepressant medications (Spigset et al, 1993g).
d) A 39-year old woman with bipolar disorder developed serotonin syndrome after imipramine was added to moclobemide. The patient was taking moclobemide 300 mg twice daily when imipramine was started at 50 mg daily, followed by two dosage increases of imipramine to 200 mg and a reduction of moclobemide dosage to 150 mg twice daily. Five days after the increase in imipramine to 200 mg per day, the patient developed symptoms of serotonin syndrome, including sweating, shivering, confusion, fever, and spasms in the extremities. The patient was treated with chlorpromazine and symptoms resolved over the next few days without further complications (Brodribb et al, 1994f).
e) Three patients with bipolar disorder developed manic symptoms while undergoing concurrent therapy with isocarboxazid and amitriptyline. In all three cases the patients had been given MAOIs and TCAs alone without complications. It was only when the drugs were used in combination that symptoms of mania emerged, suggesting a synergistic effect (de la Fuente et al, 1986b).
f) In one case, clomipramine 10 mg twice daily was added to a stable regimen of tranylcypromine in a physically healthy 34-year old man. After taking several doses, the patient developed symptoms of nausea and profuse sweating, followed by pyrexia, dyspnea, and agitation. The hyperpyrexical state led to disseminated intravascular coagulation and eventual death (Tackley & Tregaskis, 1987d).
g) There is evidence that MAOIs and TCAs can be given concomitantly in patients previously unresponsive to the MAOI or TCA alone. A few precautions must be followed including: a) avoidance of large doses (no more than 150 mg amitriptyline or its equivalent, 45 mg phenelzine, or 60 mg isocarboxazid) b) oral administration c) avoidance of clomipramine, imipramine, desipramine, and tranylcypromine in any combination, and d) close monitoring of patients (Kline, 1974b; Winston, 1971d; Schuckit et al, 1971h; White & Simpson, 1984f; Rom & Benner, 1972b). The combination may be utilized in one of two ways. Most frequently, the recommendation is to stop all previous antidepressants (five to ten days for TCAs and 14 days for MAOIs); the combination is then simultaneously started (Perry et al, 1991c). Alternatively, in a patient previously receiving a TCA, small doses of the MAOI may be slowly added (Schoonover, 1983). Some sources suggest that the combination of amitriptyline and isocarboxazid is preferred (Perry et al, 1991c). Numerous studies in patients with refractory depression or phobic anxiety states have successfully used the combination of MAOIs and TCAs (Ponto et al, 1977d; Schuckit et al, 1971h; Ashcroft, 1975c).

3.5.1.EX Trifluoperazine
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Q and T wave distortions have been observed in patients taking phenothiazines (Prod Info Compazine(R), 2002; Prod Info Stelazine(R), 2002; Prod Info Thorazine(R), 2002). Other phenothiazines may have similar effects, though no reports are available. Tricyclic antidepressants (TCAs) at therapeutic doses can cause QT prolongation (Marshall & Forker, 1982ad). Case reports have described increased plasma levels and adverse effects when phenothiazines and tricyclic antidepressants were taken together, likely due to inhibition of their metabolism (Ghaemi & Kirkwood, 1998; Geller et al, 1985; Siris et al, 1982; Loga et al, 1981).
3) Severity: major
4) Onset: rapid
5) Substantiation: probable

6) Clinical Management: Concurrent administration of a phenothiazine and a tricyclic antidepressant is not recommended.
7) Probable Mechanism: additive effect on QT interval

3.5.1.EY Trimethoprim
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Tricyclic antidepressants (TCAs) and cotrimoxazole have been shown to prolong the QTc interval at the recommended therapeutic dose (Lopez et al, 1987; Marshall & Forker, 1982q). Even though no formal drug interaction studies have been done, the coadministration of tricyclic antidepressants and other drugs known to prolong the QTc interval, such as cotrimoxazole, is not recommended (Prod Info Elavil (R), 1999i).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: The concurrent administration of cotrimoxazole and tricyclic antidepressants is not recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.EZ Vasopressin
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Tricyclic antidepressants and vasopressin have been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Vivactil(R), 1999; McCue et al, 1989; Munger & Effron, 1988; Mauro et al, 1988; Marshall & Forker, 1982j; Goldstein & Claghorn, 1980; Buckhardt et al, 1978; Pinder et al, 1977a; Thorstrand, 1976; Singh, 1972). Even though no formal drug interaction studies have been done, the coadministration of drugs known to prolong the QTc interval is not recommended.
3) Severity: major
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of drugs that prolong the QT interval, such as tricyclic antidepressants and vasopressin, is not recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.FA Venlafaxine
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest) and adverse effects of both drugs
2) Summary: Tricyclic antidepressants (TCAs) and venlafaxine have been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Effexor(R) XR, 2003; Marshall & Forker, 1982d). Even though no formal drug interaction studies have been done, the coadministration of tricyclic antidepressants and other drugs known to prolong the QTc interval, such as venlafaxine, is not recommended (Prod Info Elavil(R), 1999c). In addition, venlafaxine and tricyclic antidepressants (TCAs) may competitively inhibit each other's metabolism which may increase side effects of both drugs (Perry, 2000; Prod Info Effexor(R) XR, 2003; Ellingrod & Perry, 1994). Venlafaxine increased the AUC, Cmax, and Cmin of desipramine by approximately 35%. The AUCs of 2-OH-desipramine increased by 2.5 and 4.5 fold when administered with venlafaxine 37.5 mg and 75 mg every 12 hours, respectively. The pharmacokinetics of imipramine and the 2-hydroxy metabolite were not affected (Prod Info venlafaxine extended release oral tablets, 2008).
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Due to the potential for additive effects on the QT interval, the concurrent administration of venlafaxine and tricyclic antidepressants is not recommended.
7) Probable Mechanism: decreased TCA and venlafaxine metabolism; additive effects on QT prolongation
8) Literature Reports
a) When administered with imipramine, the pharmacokinetics of imipramine and the 2-hydroxy metabolite were not affected. Venlafaxine increased the area under the concentration-time curve (AUC), maximum concentration (Cmax), and minimum concentration (Cmin) of desipramine by approximately 35%. The 2-OH-desipramine AUCs increased by 2.5-fold (venlafaxine 37.5 mg every 12 hours) and by 4.5-fold (venlafaxine 75 mg every 12 hours). The clinical significance of this finding is unknown (Prod Info venlafaxine extended release oral tablets, 2008).

3.5.1.FB Warfarin
1) Interaction Effect: an increased risk of bleeding
2) Summary: Tricyclic antidepressants (TCAs) may increase the half-life and bioavailability of oral anticoagulants (Vesell et al, 1970a; Williams et al, 1976a). Considerable interindividual differences may be found (Pond et al, 1975a).
3) Severity: moderate

4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: In patients receiving doxepin and warfarin concurrently, the prothrombin time ratio or international normalized ratio (INR) should be closely monitored for stability of the anticoagulant response. Adjustment of the warfarin dosage may be required to maintain the desired level of anticoagulation.
7) Probable Mechanism: decreased warfarin metabolism; increased warfarin absorption
8) Literature Reports
a) In a study of healthy volunteers, the concurrent use of nortriptyline or amitriptyline resulted in an increase of dicumarol levels and an increase in the plasma half-life of dicumarol, although the effect was not consistent in all subjects (Pond et al, 1975). This effect was not observed with warfarin.
b) A single oral dose of bishydroxycoumarin after eight days of nortriptyline resulted in a significantly prolonged half-life and decreased volume of distribution of the coumarin anticoagulant in six healthy volunteers (Vesell et al, 1970). The mechanism of action was suggested to be reduced bishydroxycoumarin metabolism and/or altered coumarin absorption.
c) Drug dosing was studied in 16 patients on long-term anticoagulant therapy who used concurrent TCAs (Williams et al, 1976). TCAs affected the stability of anticoagulant control leading to frequent changes in the doses of anticoagulants. Inhibition of coumarin metabolism was the postulated mechanism.

3.5.1.FC Ziprasidone
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Ziprasidone use is associated with dose-related prolongation of the QTc interval. Even though no formal drug interaction studies have been done, it is recommended that concurrent use with other agents that may prolong QTc interval be avoided (Prod Info GEODON(R) oral capsules, IM injection, 2007; Marshall & Forker, 1982ae).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Due to the potential for additive QTc interval prolongation, avoid the concurrent administration of ziprasidone and agents that can prolong the QTc interval (Prod Info GEODON(R) oral capsules, IM injection, 2007).
7) Probable Mechanism: additive cardiac effects

3.5.1.FD Zolmitriptan
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Tricyclic antidepressants (TCAs) and zolmitriptan have been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Zomig(R), 2001; Marshall & Forker, 1982l). Even though no formal drug interaction studies have been done, the coadministration of tricyclic antidepressants and other drugs known to prolong the QTc interval, such as zolmitriptan, is not recommended (Prod Info Elavil(R), 1999f).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of zolmitriptan and tricyclic antidepressants is not recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.FE Zotepine
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999), haloperidol (O'Brien et al, 1999), risperidone (Duenas-Laita et al, 1999), sertindole (Agelink et al, 2001), quetiapine (Owens, 2001b), sultopride (Lande et al, 1992), and zotepine (Sweetman, 2003). Even though no formal drug interaction studies have been done, the coadministration of a tricyclic antidepressant and an antipsychotic is not recommended (Prod Info Pamelor(R), 2001; Marshall & Forker, 1982p).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of a tricyclic antidepressant and an antipsychotic is not recommended.
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) Electrocardiographic changes that have occurred during clinical trials with pimozide have included prolongation of the corrected QT interval, flattening, notching, and inversion of the T wave and the

appearance of U waves. In experimental studies, sudden, unexpected deaths have occurred while patients were receiving pimozide doses of 1 mg/kg. The proposed mechanism for these deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmias (Prod Info Orap(R), 1999).

3.5.2 Drug-Food Combinations

3.5.2.A Ethanol

1) Interaction Effect: enhanced drowsiness; impairment of motor skills
2) Summary: Ethanol in combination with antidepressants may alter behavior, with the predominant effect being enhanced impairment in psychomotor performance. Almost all studies to date have evaluated the effects of the combination on motor skills, driving behavior and psychomotor skills (Landauer et al, 1969; Patman et al, 1969; Milner & Landauer, 1973a; Seppala et al, 1975; Seppala, 1977). There are no studies evaluating respiratory response with the combination.
3) Severity: moderate
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Encourage abstention from alcohol during at least the first few weeks of tricyclic administration to allow patient accommodation to potential CNS depressant effects of the tricyclic.
7) Probable Mechanism: additive CNS depressant activity; impaired hepatic metabolism of the tricyclic antidepressant
8) Literature Reports
a) The studies available indicate that the interaction between amitriptyline (and other antidepressants) in combination with ethanol is unpredictable. They indicate that antidepressants may enhance, prevent, or not affect the CNS depressant actions of ethanol. The most significant effect reported is enhanced CNS depression. However, there are reports that tricyclic antidepressants may actually antagonize the sedative effects of ethanol (Milner & Landauer, 1973).
b) The propensity for interaction may be related to the inherent CNS depressant action of the tricyclic antidepressant, listed in one series in descending order as amitriptyline, doxepin, imipramine, nortriptyline, desipramine, and protriptyline (Marco & Randels, 1981).
c) Imipramine and amitriptyline are the best documented examples of disruptions of metabolism. Clearance of imipramine was 3-fold higher in alcoholics compared with healthy volunteers (Ciraulo et al, 1988).
d) Individual case reports have documented "blackouts" following modest amounts of alcohol in combination with either amitriptyline or imipramine (Hudson, 1981), and reversible extrapyramidal effects (parkinsonian effects, akathisia) with amoxapine (Shen, 1984).

4.0 Clinical Applications

Monitoring Parameters

Patient Instructions

Place In Therapy

Mechanism of Action / Pharmacology

Therapeutic Uses

Comparative Efficacy / Evaluation With Other Therapies

4.1 Monitoring Parameters

A) Doxepin Hydrochloride
1) Therapeutic
a) Laboratory Parameters
1) Urinary MHPG
a) Elevations of urinary MHPG (3-methoxy-4-hydroxyphenethylene glycol) before treatment were reported to correlate with pain relief with doxepin treatment, but not improvement in depression (Ward et al, 1983).
b) Physical Findings
1) Relief of symptoms of depression
2) Improvement of mood
3) Relief of anxiety
a) ANXIETY AND DEPRESSION ASSOCIATED WITH ALCOHOLISM

1) Reduction or resolution of palpitations, tachycardia, chest pain or tightness, shortness of breath, hyperventilation, or depressed mood.

b) ANOREXIA NERVOSA

1) Reduction and resolution of signs/symptoms associated with anorexia nervosa (ie, calorie restriction, excess energy or exercise, disturbed sleep, sense of personal ineffectiveness, amenorrhea, social withdrawal, emaciated appearance, dry-cracked skin, fine downy hair, vomiting, malnutrition, and associated medical complications.

c) DEPRESSION

1) The following target symptoms should be monitored (depressed mood, suicidal thoughts or intent, change in appetite (increased/decreased), lack of energy, change in sleep patterns (hypersomnia/insomnia), lack of pleasure/interest in usual activities, feeling of excessive guilt/worthlessness, psychomotor retardation or agitation, difficulties in thinking/concentration/memory).

d) DETRUSOR OVERACTIVITY

1) Reduction or resolution of nocturnal micturition and incontinence.

e) INSOMNIA

1) Patients should be monitored for improvement in the signs/symptoms consistent with insomnia (delay in sleep onset, frequent nocturnal awakenings, the subjective feeling of not feeling rested, and disturbances in daytime functioning, such as decreased concentration, fatigue, myalgias).

f) CHRONIC PAIN

1) Reduction or resolution of pain perception, depression, sleep disturbances, anxiety, and irritability.

2) Improve or maintain patient's level of functioning, decreasing the rate of physical deterioration, improve sense of well being, improve family and social relationships.

g) PREMENSTRUAL SYNDROME

1) Reduction or resolution of signs/symptoms associated with premenstrual syndrome (ie, tension, irritability, dysphoria, fatigue, anxiety, crying, depression, restlessness, cravings for sweet/salty foods, binge eating, headache).

h) POSTTRAUMATIC STRESS DISORDER

1) Reduction or resolution of flashbacks, recollections, and dreams associated with a traumatic event.

2) Reduction or resolution of sleep disturbances, outbursts of anger, hypervigilance, emotional numbing, guilt, inability to concentrate, and the physiological reaction (ie, sweating) upon re-exposure to the event (ie, nightmare).

i) TOBACCO CESSATION

1) Reduction or resolution of irritability, craving, anxiety/nervousness, difficulty with concentration, restlessness, headaches, drowsiness, changes in sleep patterns, increase in appetite and weight, and gastrointestinal upset.

j) URTICARIA

1) Reduction or resolution of erythema, wheal, swelling, angioedema, itching, and lesions.

2) Toxic

a) Laboratory Parameters

1) Complete blood cell count

2) Liver function tests

b) Physical Findings

1) Blood pressure for hypotension and pulse

2) Seizures have developed during therapy

3) Sexual dysfunction (ejaculatory dysfunction) or priapism

4) Monitor patients receiving antidepressants for worsening of depression, suicidality, or unusual changes in behavior, especially at the initiation of therapy or when the dose increases or decreases. Such monitoring should include at least weekly face-to-face contact with patients or their family members or caregivers during the initial 4 weeks of treatment, then visits every other week for the next 4 weeks, then at 12 weeks, and then as clinically indicated beyond 12 weeks. Families and caregivers should be advised of the need for close observation (ie, daily observation) of patients and communication with the prescriber (Anon, 2004).

5) Patients who experience symptoms of anxiety, agitation, panic attacks, insomnia, irritability, hostility, impulsivity, akathisia, hypomania, or mania may be at an increased risk for worsening depression or suicidality. If these symptoms are observed, therapy should be re-evaluated and it may be necessary to discontinue medications when symptoms are severe, sudden in onset, or were not part of the patient's initial symptoms (Anon, 2004).

4.2 Patient Instructions

A) Doxepin (By mouth)

Doxepin

Treats depression, anxiety, and sleep disorders. This medicine is a tricyclic antidepressant.

When This Medicine Should Not Be Used:
You should not use this medicine if you have ever had an allergic reaction to doxepin or other tricyclic antidepressants (such as Elavil® or Tofranil®), maprotiline (Ludiomil®), or trazodone (Desyrel®). Do not use this medicine if you have glaucoma or if you are unable to pass urine.

How to Use This Medicine:
Capsule, Liquid, Tablet
- Your doctor will tell you how much of this medicine to use and how often. Do not use more medicine or use it more often than your doctor tells you to.
- You may take this medicine with or without food.
- Measure the oral liquid with a marked dropper that comes with the medicine.
- The oral liquid must be mixed with one-half glass of water, milk, or fruit juice before you drink it. Do not use grape juice or carbonated beverages (soda pop). Mix the medicine just before taking the dose. Do not prepare ahead of time.
- If you are using this medicine once a day, you may take it at bedtime.
- This medicine should come with a Medication Guide. Read and follow these instructions carefully. Ask your doctor or pharmacist if you have any questions. Ask your pharmacist for the Medication Guide if you do not have one. Your doctor might ask you to sign some forms to show that you understand this information.

If a Dose is Missed:
- If you miss a dose or forget to use your medicine, use it as soon as you can. If it is almost time for your next dose, wait until then to use the medicine and skip the missed dose. Do not use extra medicine to make up for a missed dose.
- If you use only one dose at bedtime, skip the missed dose. Wait until the next night. You should not use two doses at the same time.

How to Store and Dispose of This Medicine:
- Store the medicine in a closed container at room temperature, away from heat, moisture, and direct light.
- Ask your pharmacist, doctor, or health caregiver about the best way to dispose of any leftover medicine after you have finished your treatment. You will also need to throw away old medicine after the expiration date has passed.
- Keep all medicine away from children and never share your medicine with anyone.

Drugs and Foods to Avoid:
Ask your doctor or pharmacist before using any other medicine, including over-the-counter medicines, vitamins, and herbal products.
- Make sure your doctor knows if you are using disulfiram (Antabuse®), cimetidine (Tagamet®), tolazamide (Tolinase®), or certain medicine for heart rhythm problems (such as flecainide, propafenone, quinidine, Cardioquin®, Quinaglute®, Rythmol®, or Tambocor®).
- You must wait at least 5 weeks between using this medicine and other medicine to treat depression (such as citalopram, escitalopram, fluoxetine, paroxetine, sertraline, Celexa®, Lexapro™, Paxil®, Prozac®, or Zoloft®). Do not use this medicine if you have used an MAO inhibitor (MAOI) such as Eldepryl®, Marplan®, Nardil®, or Parnate® within the past 14 days.
- Do not drink alcohol while you are using this medicine.
- Tell your doctor if you are using any medicines that make you sleepy. These include sleeping pills, cold and allergy medicine, narcotic pain relievers, and sedatives.

Warnings While Using This Medicine:
- Make sure your doctor knows if you are pregnant or breastfeeding, or if you have heart disease, epilepsy, or stomach problems.
- For some children, teenagers, and young adults, this medicine can increase thoughts of suicide. Tell your doctor or your child's doctor right away if you or your child start to feel more depressed and have thoughts about hurting yourselves. Report any unusual thoughts or behaviors that trouble you or your child, especially if they are new or are getting worse quickly. Make sure the doctor knows if you or your child have trouble sleeping, get upset easily, have a big increase in energy, or start to act reckless. Also tell the doctor if you or your child have sudden or strong feelings, such as feeling nervous, angry, restless, violent, or scared. Let the doctor know if you, your child, or anyone in your family has bipolar disorder (manic-depressive) or has tried to commit suicide.
- If you are using this medicine for depression, it may take 2 to 3 weeks before you start to feel better.
- Do not stop using this medicine suddenly without asking your doctor. You may need to slowly decrease your dose before stopping it completely.
- This medicine may make you drowsy. Avoid driving, using machines, or doing anything else that could be dangerous if you are not alert.

Possible Side Effects While Using This Medicine:
Call your doctor right away if you notice any of these side effects:
- Allergic reaction: Itching or hives, swelling in your face or hands, swelling or tingling in your mouth or throat, chest tightness, trouble breathing.

Changes in behavior, or thoughts of hurting yourself or others.
Fast or uneven heartbeat.
Feeling nervous, restless, anxious, agitated, or excited for no reason.
Jerky muscle movement you cannot control (often in your face, tongue, or jaw).
Lightheadedness or fainting.
Numbness, tingling, or burning pain in your hands, arms, legs, or feet.
Problems with balance or walking.
Problems with urination.
Ringing, buzzing, or other unexplained noise in ears.
Seizures or tremors.
Severe confusion, or seeing or hearing things that are not there.
Swelling in your hands, ankles, or feet.
Trouble sleeping.
Twitching or muscle movements you cannot control.
Unexplained fever, chills, or sweating.
Unusual bleeding or bruising.
Unusual tiredness or weakness.
Yellowing of your skin or the whites of your eyes.

If you notice these less serious side effects, talk with your doctor:
Blurred vision.
Change in taste.
Constipation, diarrhea, nausea, vomiting, or upset stomach.
Drowsiness or dizziness.
Dry mouth or mouth sores.
Hair loss.
Headache.
Problems having sex.
Sensitivity to sunlight.
Skin rash or itching.
Swelling in scrotum or testicles.
Swelling of the breasts or breast soreness in both females and males.
Warmth or redness in your face, neck, arms, or upper chest.

If you notice other side effects that you think are caused by this medicine, tell your doctor.

B) Doxepin (On the skin)

Doxepin

Reduces itching caused by skin diseases such as atopic dermatitis or lichen simplex chronicus.

When This Medicine Should Not Be Used:
You should not use this medicine if you have had an allergic reaction to doxepin, or if you have glaucoma or problems urinating.

How to Use This Medicine:
Cream
Apply a thin layer to the affected area. Rub it in gently.
Apply a thin layer of this medicine each time you use it.
Wash your hands with soap and water before and after using this medicine.
Do not cover the treated area with a bandage unless your doctor has told you to.

If a Dose is Missed:
If you miss a dose or forget to use your medicine, apply it as soon as you can. If it is almost time for your next dose, wait until then to apply the medicine and skip the missed dose. Do not apply extra medicine to make up for a missed dose.

How to Store and Dispose of This Medicine:
Store the medicine in a closed container at room temperature, away from heat, moisture, and direct light.
Ask your pharmacist, doctor, or health caregiver about the best way to dispose of the used medicine container and any leftover medicine after you have finished your treatment. You will also need to throw away old medicine after the expiration date has passed.
Keep all medicine away from children and never share your medicine with anyone.

Drugs and Foods to Avoid:
Ask your doctor or pharmacist before using any other medicine, including over-the-counter medicines, vitamins, and herbal products.
Make sure your doctor knows if you are using MAO inhibitors such as Eldepryl®, Marplan®, Nardil®, or Parnate®, or allergy medicines.

Make sure your doctor knows if you are using medicine for depression such as trazadone, Clexa®, Prozac®, Paxil®, or Zoloft®, or amitriptyline, Norpramin®, or Vivactil®.
There are many other drugs that can interact with doxepin. Make sure your doctor knows about all other medicines you are using.
Tell your doctor if you are using any medicines that make you sleepy. These include sleeping pills, cold and allergy medicine, narcotic pain relievers, and sedatives.
Do not drink alcohol while you are using this medicine.

Warnings While Using This Medicine:
Make sure your doctor knows if you are pregnant or breast feeding.
This medicine may make you dizzy or drowsy. Avoid driving, using machines, or doing anything else that could be dangerous if you are not alert.

Possible Side Effects While Using This Medicine:
Call your doctor right away if you notice any of these side effects:
Allergic reaction: Itching or hives, swelling in your face or hands, swelling or tingling in your mouth or throat, chest tightness, trouble breathing.
Confusion, hallucinations, severe weakness, vomiting, muscle stiffness.
Drowsiness or lightheadedness or fainting.
Irregular heartbeat
Swelling in your feet, arms, or body.

If you notice these less serious side effects, talk with your doctor:
Burning or stinging of your skin where the medicine in applied.
Change in taste or dryness of your mouth.
Headache or tiredness.
Nervousness, anxiety.
Numbness in your tongue.
Redness, pain, swelling, or itching on site of cream application.
Worsening of you skin condition.

If you notice other side effects that you think are caused by this medicine, tell your doctor.

4.3 Place In Therapy

A) Depression is a complicated disorder and consequently treatment regimens are diverse. The two most prevalent diagnostic syndromes among affective disorders are major depression and bipolar disorders. The tricyclic antidepressants (TCAs) serotonin reuptake inhibitors (SSRIs) and the monoamine oxidase inhibitors (MAOIs) are considered the most effective agents for treating major depression. For treating bipolar disorders, lithium is considered the standard of therapy over TCAs, MAOIs, SSRIs, and other agents such as carbamazepine or levothyroxine.

B) Doxepin is effective for the treatment of endogenous or typical depression. Doxepin has similar efficacy and adverse effects as the other TCAs, but possesses some distinguishing characteristics. Doxepin inhibits histamine release and has been used topically to treat pruritus and systemically for peptic ulcer disease. Doxepin has also been used for treating anxiety-depression states and depression-induced insomnia. Cardiac effects of doxepin are considered mild compared to those of the other TCAs.

C) Doxepin does have a place in therapy for the treatment of unipolar depression, but should be considered secondary to imipramine and amitriptyline. Because of anxiolytic properties, antihistamine action, sedative effects and fewer cardiac effects, doxepin may be useful for treating depressed patients with coanxiety, peptic ulcer disease, associated insomnia, or who are elderly. Doxepin should be considered an alternative agent and formulary considerations should be based primarily on cost.

4.4 Mechanism of Action / Pharmacology

A) MECHANISM OF ACTION

1) Doxepin has similar pharmacologic properties to other tricyclic antidepressants (amitriptyline and imipramine). Doxepin has a pronounced sedative effect similar to amitriptyline but probably less than that of imipramine. Doxepin is particularly effective in depression associated with anxiety or in mixed anxiety depression syndromes (Pinder et al, 1977b).

2) Doxepin may be more effective than imipramine in patients with depression associated with sleep disturbances but it is not superior to other tricyclic antidepressants for severe endogenous depression (Pinder et al, 1977b).

3) Doxepin has been shown to exert a significant antihistamine effect. In 8 subjects administered a dose of 25 mg, the amount of histamine required to cause an urticarial reaction increased 82-fold (Sullivan, 1982).

B) REVIEW ARTICLES

1) A review of the other uses of antidepressant agents, including enuresis, bulimia, anorexia nervosa, panic disorder, chronic pain, migraine headache, and peptic ulcer disease is available (Orsulak & Waller, 1989).

2) Drug-interactions of antidepressants are reviewed in German language (Zapotoczky & Simhandl, 1995).

4.5 Therapeutic Uses

Doxepin

Doxepin Hydrochloride

4.5.A Doxepin

4.5.A.1 Anorexia nervosa
See Drug Consult reference: ANOREXIA NERVOSA - DRUG THERAPY

4.5.B Doxepin Hydrochloride

Alcoholism - Anxiety - Depression

Anxiety - Depression

Anxiety - Depression - Psychoneurotic personality disorder

Cancer pain; Adjunct

Chronic pain

Cocaine-induced anxiety disorder

Complex regional pain syndrome

Cyclical vomiting syndrome

Depression - Opioid dependence

Detrusor instability of bladder

Disorder of gastrointestinal tract

Disorder of oral mucous membrane - Pain

Insomnia

Nicotine dependence

Peptic ulcer disease

Post-prandial hypoglycemia

Posttraumatic stress disorder

Pruritus (Moderate), Due to atopic dermatitis or lichen simplex chronicus

Psychogenic headache

Urticaria

4.5.B.1 Alcoholism - Anxiety - Depression
FDA Labeled Indication
a) Overview
FDA Approval: Adult, yes; Pediatric, yes (12 years and older)
Efficacy: Adult, Effective

Recommendation: Adult, Class IIa
Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:
Indicated for controlling the anxiety and/or depression associated with alcoholism

c) Adult:

1) GENERAL INFORMATION

a) The most effective dose of DOXEPIN for mild-to-moderate anxiety or depression ranges between 75 and 150 milligrams/day. A starting dose of DOXEPIN 25 milligrams 3 times daily is recommended, but the entire daily dose up to 150 milligrams may be administered at bedtime without altering efficacy. For more severe anxiety and depression, DOXEPIN 50 milligrams 3 times daily may be administered and the dose increased to a maximum of 300 milligrams/day. The antidepressant effect of DOXEPIN may take 2 or 3 weeks to achieve, but the antianxiety effect usually occurs rapidly (Prod Info Adapin(R), 1995a).

4.5.B.2 Anxiety - Depression

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes; Pediatric, yes (12 years and older)
Efficacy: Adult, Effective; Pediatric, Effective
Recommendation: Adult, Class IIa; Pediatric, Class IIa
Strength of Evidence: Adult, Category B; Pediatric, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:
Indicated for the treatment of depression and/or anxiety associated with organic disease
Also indicated for PSYCHOTIC DEPRESSIVE DISORDERS with associated anxiety including involutional depression and manic-depressive disorders

c) Adult:

1) GENERAL INFORMATION

a) DOXEPIN is an effective agent in the treatment of ENDOGENOUS DEPRESSION (Grof et al, 1974; Burrows et al, 1972; Bianchi et al, 1971a) and NEUROTIC DEPRESSION (Mendels & Schless, 1975; Solis et al, 1970a). Clinical trials have shown that DOXEPIN has less marked mood elevating activities than IMIPRAMINE but similar to that of AMITRIPTYLINE. DOXEPIN has been shown to be most effective in agitated depressed patients and less effective in retarded depressive patients. In addition, DOXEPIN is shown to be more effective than IMIPRAMINE in neurotic-type depression and less effective than IMIPRAMINE in endogenous depression (Pinder et al, 1977e).

2) In the absence of severe impairment of myocardial performance, depressed patients with pre-existing heart disease were treated effectively with IMIPRAMINE or DOXEPIN without an adverse effect on ventricular rhythm or hemodynamic function (Veith et al, 1982a). In a double-blind, randomized trial involving 24 depressed patients with heart disease treated with IMIPRAMINE or DOXEPIN 50 milligrams (mg) at bedtime or placebo. Doses were gradually increased every 3 days until side effects or a dose of 150 mg given at bedtime was achieved. No evidence of cardiovascular adverse effects were seen. As measured by radionuclide ventriculograms, tricyclic antidepressants had no effect on left ventricular ejection fraction at rest or during maximal exercise. The incidence of premature ventricular contractions was reduced in patients treated with IMIPRAMINE; however, no consistent change was observed in patients receiving DOXEPIN or placebo. IMIPRAMINE- and DOXEPIN-treated patients showed a significant improvement (p less than 0.001) in depression when compared with placebo-treated patients. Further evaluation of the tricyclics and their effect on cardiovascular function is required.

3) DOXEPIN has produced a more favorable response than AMITRIPTYLINE in patients with depression associated with anxiety or the MIXED DEPRESSION ANXIETY syndrome, and it is possible that DOXEPIN may have more prominent sedative effects than AMITRIPTYLINE (Pinder et al, 1977e).

4) Several studies have reported the benefits of doxepin in patients with mixed ANXIETY and depression (Goldberg et al, 1974; Goldstein et al, 1973).

5) Doxepin titrated in a conventional manor (beginning with 50 milligrams daily and titrating upwards to 250 mg daily over 1 week) was more effective than using pulse dosing (250 mg every 6 days) (Deuschle et al, 1997). Depressed patients were randomly assigned to receive either conventional dosing (n=10) or pulse dosing (n=9) over 39 days. In the pulse dosing group, scores on the Hamilton Depression Rating (HAM-D) scale differed from baseline after day 36 (p less than 0.03) while in the conventional dosing group, they differed after only 2 days (p less than 0.02). Starting on day 25, significantly lower HAM-D scores were seen in the conventional dosing group versus the pulse dosing group (p less than 0.05) and this continued through day 39 (p less than 0.01).

4.5.B.3 Anxiety - Depression - Psychoneurotic personality disorder

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes; Pediatric, yes (12 years and older)
Efficacy: Adult, Evidence favors efficacy

Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:
Indicated for the treatment of psychoneurotic patients with depression and/or anxiety (Prod Info SINEQUAN(R) capsule, oral concentrate, 2005)

4.5.B.4 Cancer pain; Adjunct

a) Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category C
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:
Case reports have described the use of doxepin in terminal cancer patients who are unresponsive to narcotic analgesics

c) Adult:
1) Four severely debilitated cancer patients with neuropathic pain were reported to be more comfortable following rectal administration of unmodified DOXEPIN capsules. Serum concentrations of N-desmethyldoxepin after two to five days of treatment with a constant dose of DOXEPIN were 573 micrograms/milliliter (mcg/mL) and 403 mcg/mL (with 50 milligrams (mg) three times/day), 204 mcg/mL (with 50 mg twice a day), and less than 25 mcg/mL (with 25 mg every day) (Storey & Trumble, 1992).
2) The combination of PIROXICAM (60 to 120 milligrams orally daily, given with SUCRALFATE 1 to 2 g daily) plus DOXEPIN (25 to 225 mg daily) was reported effective in the treatment of advanced cancer pain (Cohn et al, 1988). SUCRALFATE given concurrently with PIROXICAM was effective in preventing severe gastrointestinal (GI) toxicity. However, several patients did not administer sucralfate concurrently with PIROXICAM and developed GI symptoms (GI hemorrhage, gastric ulcer or perforation). It is recommended that PIROXICAM and DOXEPIN therapy (with adjunctive SUCRALFATE administration) be considered in patients with terminal cancer who are unresponsive to narcotic analgesics.

4.5.B.5 Chronic pain

a) Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:
Patients with chronic pain have experienced some relief with doxepin therapy
A review of doxepin as adjunctive therapy for chronic pain has been published by the Boston Pain Center (Aronoff & Evans, 1982)

c) Adult:
1) DOXEPIN (up to 3 milligrams/kilogram/day (mg/kg)) for pain relief was better than placebo in 60 patients with chronic low back or cervical pain and depression (Hameroff et al, 1984). Relative to the percent of time the pain was felt, effect of pain on sleep, and muscle tension, DOXEPIN was slightly better than placebo at 1 week, and significantly better at 6 weeks. Benefit was most consistently derived when the daily dose was at least 2.5 mg/kg, and the combined DOXEPIN/desmethyldoxepin plasma level exceeded 70 ng/mL. The proposed mechanism, as demonstrated by the laboratory, was enhanced enkephalin activity.

4.5.B.6 Cocaine-induced anxiety disorder

a) Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Ineffective
Recommendation: Adult, Class III
Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:
Not effective in the treatment of panic attacks associated with cocaine abuse

c) Adult:
1) The use of tricyclic antidepressant therapy in 10 patients with cocaine-induced panic attacks resulted in extreme anxiety and had to be discontinued (Louie et al, 1989). One patient improved after doxepin 50 milligrams/day (mg/day) but, at higher doses, became severely confused and panicky and had to be hospitalized. Another patient had a partial response to trazodone 150 mg/day and did not want to be switched to another agent. Other agents used in this patient population included amitriptyline, desipramine, and nortriptyline. Thus, heterocyclic antidepressants were not well tolerated except for trazodone and low doses of doxepin, two medications with relatively high serotonergic re-uptake

blockade.

4.5.B.7 Complex regional pain syndrome

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Topical doxepin reduced the symptoms of complex regional pain syndrome CRPS, including pain, discoloration, and thermal and mechanical allodynia

c) Adult:

1) A 32-year-old woman attained relief of symptoms of complex regional pain syndrome (CRPS) with topical application of doxepin 5% cream (Xepin(R)). After a fall on her left wrist, the woman developed the symptoms of CRPS, although the wrist was not broken. In addition to burning dermatomal pain, she showed blue discoloration, hyperhidrosis, and mechanical and thermal allodynia. A stellate ganglion block on the left side gave significant reduction in symptoms for 4 weeks. A second block provided similar relief. Topical application of doxepin cream twice daily reduced her symptoms significantly after 2 weeks. Each time she omitted using the cream for more than 5 days, her symptoms returned. In addition to reducing the pain, it decreased the thermal and mechanical allodynia and the discoloration (McCleane, 2002).

4.5.B.8 Cyclical vomiting syndrome

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Tricyclic antidepressant therapy, including DOXEPIN, may be beneficial in treating CYCLIC VOMITING SYNDROME

c) Adult:

1) In a retrospective case series (n=17), adults with CYCLIC VOMITING SYNDROME (CVS) were shown to derive benefit from treatment with low-dose tricyclic antidepressants (open-label), including DOXEPIN (median dose 50 milligrams (mg) daily; range 25 to 150 mg). However, a comparison group of 37 patients with usual functional nausea and vomiting had superior results from tricyclic-antidepressant therapy compared with those with CVS. Of the 17 patients with CVS, 3 (17.6%) achieved complete remission, and 10 (58.8%) attained partial response (decreased intensity of symptoms, decreased cycle frequency, or shortening of cycles). Of 7 patients who used doxepin, 6 experienced remission or improvement -- the same response as 7 patients given amitriptyline. No patient responded to desipramine (0 of 3) or imipramine (0 of 1), with 4 of 4 responding to nortriptyline. Of the patients with functional nausea and vomiting treated with tricyclic antidepressants, 19 of 37 (51.4%) achieved complete remission and 12 (32.4%) showed partial response. The authors suggest that the pathophysiology of CVS might be similar to that of migraine headache (Prakash & Clouse, 1999).

4.5.B.9 Depression - Opioid dependence

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

DOXEPIN reduced the craving for HEROIN, nervousness, and the use of amphetamines

c) Adult:

1) Doxepin was superior in the treatment of depression when compared with placebo in a 5-week trial as adjunctive treatment in a methadone maintenance program. Only 46 of 76 patients completed the study. Relative to several depression parameters, doxepin was shown better than placebo. Doxepin did not significantly increase the incidence or severity of adverse effects to methadone (Titievsky et al, 1982)

2) DOXEPIN was efficacious in HEROIN addicts with associated anxiety and depression. Doses of 100 to 150 mg daily for periods of longer than 4 weeks significantly decreased symptoms of anxiety and depression as measured by the Hamilton depression rating scale (Woody et al, 1975).

4.5.B.10 Detrusor instability of bladder

a) Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class III
Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:
Effective in the treatment of detrusor overactivity in women

c) Adult:
1) DOXEPIN caused a significant decrease in the nighttime micturition frequency and the nighttime incontinence episodes. Cystometric parameters improved significantly during treatment with DOXEPIN. The authors concluded that DOXEPIN seems to offer a new alternative in the pharmacological treatment of detrusor overactivity and associated symptoms (Lose et al, 1989).
2) In this randomized, double-blind, placebo-controlled study of DOXEPIN, 19 females with detrusor overactivity and associated symptoms who had failed to respond to conventional pharmacotherapy, obtained relief ascribed to the ability of DOXEPIN to improve storage failure by decreasing bladder contractility and/or decreasing sensory input (Lose et al, 1989). DOXEPIN caused a significant decrease in the nighttime micturition frequency and the nighttime incontinence episodes (p less than 0.05). Cystometric parameters improved significantly during treatment with DOXEPIN. The authors concluded that DOXEPIN seems to offer a new alternative in the pharmacological treatment of detrusor overactivity and associated symptoms.

4.5.B.11 Disorder of gastrointestinal tract

a) Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category A
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:
An effective alternative in treating IRRITABLE BOWEL SYNDROME
Other types of epigastric distress have also reportedly responded to therapy

c) Adult:
1) A meta-analysis of controlled clinical trials related to the use of antidepressants for the treatment of functional gastrointestinal (GI) disorders concluded that this type of therapy (primarily tricyclic antidepressants) is efficacious in some patients. Included were 11 trials published between 1978 and 1998 focused on antidepressant therapy in irritable bowel syndrome (8) and dyspepsia (non-ulcer) (2); one study included patients with either disorder. Among the medications studied were amitriptyline (3), trimipramine (3), desipramine (2), DOXEPIN (1), mianserin (1), and either clomipramine or mianserin (1). All of the trials compared the treatment drug against placebo. In 8 studies using a dichotomous outcome measure, ie, response to treatment, the odds ratio for improvement with therapy was 4.2. In 7 studies using a continuous variable of pain scores, the standardized mean improvement in pain averaged 0.9 standard deviation (SD) (means for the treatment and control groups divided by the SD). Pooling of the risk difference indicated that 3.2 patients needed to be treated for 1 to experience symptom improvement. The authors were uncertain if the improvement in GI symptoms was an independent action of the drugs or if the improvement reflected the effects of the drugs on the psychological outlook of the recipients (Jackson et al, 2000).
2) A nondepressed patient obtained relief from irritable bowel syndrome, resistant to other therapies, while receiving DOXEPIN 150 milligrams/day (Gartrell & Mosbacher, 1982). Another similar case with similar results was reported (Pies, 1983).
3) Doxepin relieved 2 cases of epigastric distress (Shen et al, 1983). A 77-year-old man with an 8-year history of severe, unremitting epigastric distress experienced significant relief on DOXEPIN 100 milligrams/day. Similar results were observed in a 55-year-old man after initiation of DOXEPIN 125 milligrams/day.

4.5.B.12 Disorder of oral mucous membrane - Pain

a) Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:
Mucosal local doxepin rinse relieved mucosal pain caused by cancer or cancer treatment for more than 3 hours

c) Adult:
1) An oral rinse of doxepin solution gave relief of pain to patients with oral mucosal damage. In an single-dose, open trial, 41 patients with oral mucosal pain resulting from cancer or cancer treatment

rinsed their mouths for 1 minute with 5 milliliters (mL) of doxepin suspension 5 milligrams/mL. At 15 minutes post- rinsing, mean pain reduction was 60% (p less than 0.01), and at 3 hours, 25% (p less than 0.05). By 24 hours, pain had returned to pre-rinse levels. Thirty-five percent of patients reported absence of fatigue, 13% mild fatigue, 20% moderate, 16% moderate-to-severe, and 16% severe (Epstein et al, 2001).

4.5.B.13 Insomnia

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Used as a sedative-hypnotic, however, benzodiazepines are usually recommended for patients with sleep disturbances

c) Adult:

1) GENERAL INFORMATION

a) Doxepin has been promoted as a sedative-hypnotic for all patients, whether they have underlying symptoms of anxiety and depression or not. One manufacturer has indicated that doxepin is recommended for sleep disturbances that accompany anxiety neurosis and depression, but not for patients with INSOMNIA as the only disorder (Prod Info Sinequan(R), 1989). Doxepin does have marked sedative effects, similar to those of amitriptyline (Hollister, 1972; Ayd, 1969), and studies have shown that somnolence occurs in up to 19% of those on chronic treatment (Pitts, 1969a); (Belsasso, 1969; Gallant, 1969). These studies have most likely prompted the use of the drug as a sedative hypnotic. Indeed, some have recommended the drug be administered at bedtime because of its noticeable sedative and hypnotic properties, but this advice was referred to patients with emotional disorders or depression (Belasso et al, 1969). Doxepin also has been reported to produce insomnia, excitement, restlessness, agitation, euphoria, and anxiety which are certainly not the most desirable effects of a sedative (Pitts, 1969a).

2) In a randomized, double-blind, placebo-controlled trial, doxepin improved sleep and working ability in patients with chronic primary insomnia more than did placebo but was associated with more rebound insomnia upon discontinuation. Patients with DSM-IV primary insomnia (mean duration 11 years) were treated either with placebo (n=20) or doxepin 25 to 50 milligrams/night for 4 weeks. Polysomnographic measures showed improved sleep efficiency, increased total sleep time, and decreased time of wake-after- sleep-onset (WASO) with doxepin (relative to baseline and to values of placebo-treated patients, p less than 0.01 or better for all comparisons) at the first night of treatment. Improvements persisted at day 28 of treatment. Sleep efficiency with doxepin was 89% at day 1 and throughout treatment (compared to 78% at baseline). Average total sleep time with doxepin at day 28 was 7.1 hours (vs 6.3 hours at baseline). With discontinuation of treatment, the number of doxepin-treated patients experiencing rebound on 3 or more sleep parameters was significantly greater than the number of placebo-treated patients experiencing rebound (p less than 0.05) for the 3 nights of acute withdrawal. At night 42 (2 weeks without treatment), some sleep parameters in the doxepin group were better than at baseline (sleep efficiency, p less than 0.05; WASO, p less than 0.01), and none was worse. Frequency of adverse events did not differ significantly for the 2 groups. Dry mouth, dizziness, and somnolence tended to be more pronounced in the doxepin group, and diarrhea, dyspepsia, anorexia, sweating, and common colds more frequent in the placebo group. Sleep improvements with doxepin were rated slight or moderate by the authors (Hajak et al, 2001).

3) In June, 1971, three separate studies concerning the treatment of nondepressed insomniacs with doxepin were presented at the First International Congress, The Association for Psychophysiological Study of Sleep. Baseline sleep patterns, established while the patients received a placebo, were compared with sleep patterns recorded while receiving doxepin 25 or 50 milligrams at bedtime for 2 weeks. Each investigator reported a decrease in all the patient's REM sleep and awake time while receiving doxepin. During the placebo withdrawal administration, each patient experienced REM rebound. The authors did note a slight decrease of doxepin's effectiveness as the trials continued, however, they concluded that tolerance to drowsiness did not develop (Pers Comm, 1989). Because drug exposure lasted only 14 days, surmising that tolerance does not develop to doxepin therapy seems premature. No studies could be found indicating that tolerance occurs to the sedative effects. Tolerance to the drowsiness has been reported by Roerig, one manufacturer of doxepin, thus until proven otherwise tolerance to the sedative effects is assumed to occur (Prod Info Sinequan(R), 1999).

4) DOXEPIN had a positive effect on sleep disturbances in 9 patients with depression accompanied by disorders of sleep. DOXEPIN 75 and 150 milligrams/day improved sleep efficiency as evidenced by decreased sleep latency and increased total sleep time (Roth et al, 1982).

5) One study reported using doxepin 100 milligrams for treating insomnia in heroin addicts receiving clonidine to alleviate withdrawal symptoms. The investigators did not report the success rate for treating insomnia, however, doxepin seem to be beneficial for inhibiting the peripheral hypotensive actions of clonidine (Schanda et al, 1983).

6) Long-term side effects of doxepin were assessed in 1706 patients who received the drug for periods

of a few weeks to 22 months (mean 3.3 months) in doses ranging from 25 to 600 milligrams daily. The most common side effects (greater than 2%) consisted of: drowsiness (17.4%), anticholinergic effects, mostly dry mouth (22.9%), extrapyramidal symptoms, usually in high doses (6.3%), dizziness (5.9%), hypotension (2.8%), tachycardia (2.6%), gastrointestinal effects (3.7%), and insomnia (2.1%). No abnormalities in WBC, Hgb, Hct or evidence of BLOOD DYSCRASIAS were reported in the more than 800 patients for whom blood tests were done. AST, ALT, and ALKALINE PHOSPHATASE values were abnormal in only a few of the patients tested (less than 1%) (Pitts, 1969a).

4.5.B.14 Nicotine dependence

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Doxepin may be a useful adjunct in smoking cessation

c) Adult:

1) DOXEPIN was efficacious in the treatment of NICOTINE WITHDRAWAL (Edwards et al, 1990). DOXEPIN was given to 8 patients prior to smoking cessation with the following regimen: 25 milligrams at bedtime initially and titrated in increments of 25 milligrams every third day to reach a target dose of 150 milligrams. When 150 milligrams/day was maintained for 1 week, patients were instructed to terminate smoking. Twenty-one patients were instructed to begin smoking cessation after the initial visit. Dropouts were more frequent in the patients that did not receive DOXEPIN (72% compared with 50% in the DOXEPIN patients). DOXEPIN significantly suppressed symptom frequency during the first and second week as compared with the patients who did not receive DOXEPIN.

2) A 5-week pilot study revealed that DOXEPIN therapy was useful in nicotine withdrawal (Whelan & Davis, 1990). Of the original 8 subjects treated with DOXEPIN and 21 controls, only 4 of the DOXEPIN group and 6 controls finished the study. DOXEPIN reduced the severity of symptoms during the first 2 weeks but there was no significant difference in the last 3 weeks.

3) DOXEPIN was reported effective in achieving smoking cessation in a small double-blind study involving 19 adults (Murphy et al, 1990; Edwards et al, 1989). Prior to smoking cessation, the DOXEPIN (or placebo) was given in doses of 50 milligrams daily for 3 days, then 100 milligrams daily on days 4 through 6, followed by 150 milligrams daily from day 7 to 21. On day 22, subjects stopped smoking and DOXEPIN 150 milligrams daily or placebo was continued for an additional 4 weeks. The study medication was given at bedtime. Smoking cessation was achieved in all of the 9 subjects treated with DOXEPIN 7 days after stopping smoking and was maintained in 7 of the subjects at 9 weeks; only 1 of 10 placebo subjects reported cessation. A precessation DOXEPIN serum level higher than 10 ng/mL was associated with cessation of smoking in this study. In the 2 DOXEPIN subjects reporting relapse, DOXEPIN levels were less than 10 ng/mL. DOXEPIN appeared to reduce the intensity of cigarette craving (2.8 +/- 1.7 for DOXEPIN users versus 5.1 +/- 0.8 for placebo). Substantial weight gain was observed in subjects treated with DOXEPIN who were able to stop smoking (mean, 11.7 pounds). It is suggested that the weight gain attributable to cessation of smoking was most likely compounded by weight gain secondary to DOXEPIN use. This small study suggests that DOXEPIN may have a role in assisting smoking cessation.

4.5.B.15 Peptic ulcer disease

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class III
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Effective in the treatment of peptic ulcer disease due to its histamine blocking activity

c) Adult:

1) Tricyclic antidepressants have anti-histamine blocking properties, however, standard H2 antagonists are recommended for the treatment of peptic ulcer disease. For peptic ulcer disease, doxepin has been as effective as cimetidine (Shrivastava et al, 1985a; Ruud et al, 1982; Hoff et al, 1981) and doxepin was effective in patients who had failed cimetidine (Shrivastava et al, 1985a; Mangla & Pereira, 1982).

2) Doxepin was superior to placebo in a study of the effect of doxepin on gastric acid and salivary secretion in patients with asymptomatic, chronic duodenal ulcer disease. Seven patients received either 50 or 100 milligrams doxepin or placebo, and were evaluated at 3.5, 5.5, 7.5, and 9.5 hours after drug administration. Both gastric acid and salivary secretion were decreased significantly more by doxepin than placebo, but no statistically significant differences were seen between the 2 doses of doxepin (Brown-Cartwright et al, 1986).

4.5.B.16 Post-prandial hypoglycemia

a) Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class III
Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:
Has reduced symptoms of postprandial symptomatic hypoglycemic.

c) Adult:
1) DOXEPIN reduced symptoms of postprandial symptomatic hypoglycemic in 32 subjects (Lechin et al, 1991). There was a 4-week baseline period followed by an 8-week study with DOXEPIN 25 milligrams being substituted for placebo. During the placebo period, all patients showed hypoglycemia, hyperinsulinemia, and disorders of plasma neurotransmitters during the oral glucose tolerance test when compared with control subjects. The subjects were divided into 3 separate groups according to different blood levels of neurotransmitters. Groups I and II showed low basal noradrenalin/adrenalin ratios and low serotonin levels. Group III had a high noradrenalin/adrenalin ratio with a raised serotonin level and all subjects showed severe dysthymic depression. The symptoms of postprandial hypoglycemia did not correlate with a low glucose level but rather an imbalance in the neurotransmitter levels. Serotonin and noradrenalin stimulate hypothalamic activity which reduces pituitary-adrenocortical functioning. This in turn reduces the adrenaline level and causes hypoglycemia. All 32 subjects showed pituitary-adrenocortical hyperactivity before treatment. After treatment with DOXEPIN they were all asymptomatic.

4.5.B.17 Posttraumatic stress disorder

a) Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category C
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:
Tricyclic antidepressant therapy including doxepin has been reported beneficial in the treatment of posttraumatic stress disorder in COMBAT VETERANS (Falcon et al, 1985)

c) Adult:
1) Posttraumatic stress disorder due to trauma, burns, rape, and other noncombat physical insults have been treated with antidepressants. A 36-year-old male suffered posttraumatic stress disorder several months after receiving second and third degree burns in a truck fire. The patient responded well to DOXEPIN (daily doses of 50 milligrams (mg) to start, increasing to 300 mg, then tapering to 50 mg) over a period of 1 year (Blake, 1986).

4.5.B.18 Pruritus (Moderate), Due to atopic dermatitis or lichen simplex chronicus

FDA Labeled Indication

a) Overview
FDA Approval: Adult, yes (5% cream); Pediatric, no
Efficacy: Adult, Effective; Pediatric, Evidence favors efficacy
Recommendation: Adult, Class IIa; Pediatric, Class IIb
Strength of Evidence: Adult, Category B; Pediatric, Category C
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:
DOXEPIN cream reduces the pruritus associated with atopic dermatitis and lichen simplex chronicus
Topical DOXEPIN combined with corticosteroids improves treatment results
Topical doxepin reduced erythema and itching in chronically pruritic burn wounds
Eliminated recalcitrant lichen simplex in a child (Thomson & Highet, 2001)

c) Adult:
1) GENERAL INFORMATION
a) Doxepin cream 5% is indicated for the short-term treatment (up to 8 days) of moderate pruritus in adult patients with atopic dermatitis or lichen simplex chronicus. The use of doxepin cream in children is not recommended (Prod Info Zonalon(R), 2004). In two multi-center, double-blind, placebo-controlled studies, atopic dermatitis, lichen simplex chronicus, and other eczemas were successfully treated with doxepin cream in 559 adults (Tech Info Zonalon(R), 1994).
2) MONOTHERAPY
a) Topical doxepin therapy effectively reduced erythema and itching in chronically pruritic burn wounds. In a prospective, randomized study, thirty-one patients reporting itch in healed burns 4 to 12 months of age (mean, 7 months) received either ongoing standard care with oral antihistamines (ie, diphenhydramine, hydroxyzine) or topical 5% doxepin cream applied 4 times daily to affected area(s) for 3 months. Both groups used a skin moisturizer two to three times daily during the study. Patients rated itch and erythema daily using a visual analog scale. Patients in the doxepin

treatment group had significantly greater reductions in itching and erythema at 1, 8, and 12 weeks as compared with the standard care group. Itching completely stopped in 75% of doxepin-treated patients compared to only 20% of standard care patients. Mild to moderate somnolence was reported in both groups (Demling & DeSanti, 2003).

b) Doxepin cream 5% was superior to placebo (ie, vehicle only) in 270 patients with moderate to severe atopic dermatitis with pruritus in a double-blind, randomized, vehicle-controlled trial lasting seven days. Eighty-five percent of patients receiving the active cream reported relief of pruritus, compared with 57% using the vehicle only. Localized stinging and burning requiring discontinuation in 37 doxepin and 3 placebo patients, were the only significant side effects (Drake et al, 1994).

c) In two multicenter, double-blind, placebo-controlled studies, atopic dermatitis, lichen simplex chronicus, and other eczemas, were successfully treated by DOXEPIN cream in 559 adults (Tech Info Zonalon(R), 1994).

d) Oral DOXEPIN has been effectively used to treat chronic urticaria in numerous clinical trials (Gupta et al, 1987; Goldsobel et al, 1986; Harto et al, 1985); (Greene et al, 1985)(Neittaanmaki et al, 1984a), however, few trials using topical preparations have been published. In one double-blind study, 40 subjects were injected with 8 different dilutions of histamine. Sixty-eight percent showed relief from itching with a 5% topical solution of DOXEPIN, compared to 53% with DIPHENHYDRAMINE and 25% with vehicle alone (Bernstein et al, 1981).

3) COMBINATION THERAPY

a) Patients with pruritic atopic dermatitis responded more promptly and their symptoms improved to a significantly greater extent when topical DOXEPIN was added to HYDROCORTISONE or TRIAMCINOLONE therapy compared with topical corticosteroid monotherapy. In a randomized, double-blind, multi-center trial, cream was applied 4 times daily for 8 days: hydrocortisone 2.5% (HC, n=83); triamcinolone 0.1% (TR, n=90); doxepin 5% plus HC 2.5% (n=86); and doxepin 5% plus TR 0.1% (n=90). Patient-rated visual analog scores for pruritus severity had declined by 8% and 10.7% for HC- and TR-treated patients at 12 hours after initiation of therapy. At the same time, mean reductions in the doxepin-HC and doxepin-TR groups were 31.6% and 22.4%, respectively (p less than 0.001; p=0.07). On day 2, pruritus relief was noted in 46.7%, 66.7%, 70.4%, and 79.1%, respectively, for groups receiving HC, TR, doxepin-HC, and doxepin-TR, according to physician ratings (p=0.01 doxepin-HC vs monotherapy; p=0.027, doxepin-TR vs monotherapy). Common side effects of the corticosteroids were local stinging or burning (not improved by doxepin). Mild and transient drowsiness occurred in 38% and 10% of patients using doxepin plus HC or TR, respectively; rates were 9% and 5% with single-agent corticosteroid therapy (Berberian et al, 1999).

d) Pediatric:

1) Recalcitrant lichen simplex in a 3-year-old boy was resolved by application of 5% doxepin cream. At age 1 year, the boy had intense pruritus of the lower left leg. With persistent scratching, the area developed lichen simplex, which was effectively treated with emollients. At 2 years of age, he had a recurrence, which did not respond to potent topical preparations and occlusive wraps, including mometasone ointment, hydrocolloid dressings, tar bandages, and clobetasol propionate, because the child would remove the dressings. At age 3 years, the boy was treated with 5% doxepin cream in an attempt to break the "itch- scratch cycle." Within 24 hours of doxepin application, scratching stopped, and at 14 days, there was complete resolution. No side effects were observed. In particular, there was no sedation (the principal side effect observed with topical doxepin) (Thomson & Highet, 2001).

4.5.B.19 Psychogenic headache

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Beneficial results of DOXEPIN have been reported in patients with PSYCHOGENIC HEADACHE

c) Adult:

1) Beneficial results of DOXEPIN were reported in patients with PSYCHOGENIC HEADACHE following anxiety/depressive illnesses (Okasha et al, 1973). Doses of 10 milligrams three times/day were administered and dosage increased when required by 2 mg daily after 2 weeks at weekly intervals. The study lasted 8 weeks, and by the fourth week the majority of patients noticed marked improvement. When compared with AMITRIPTYLINE and DIAZEPAM, DOXEPIN was the only drug with a highly significant effect on headache, anxiety, and depression. The investigators speculate that superiority of DOXEPIN may be attributed to its effect as an antianxiety agent, antidepressant, and central muscle relaxant.

4.5.B.20 Urticaria

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy

Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:
Effective in the treatment of urticaria

c) Adult:
1) Oral DOXEPIN 10 to 30 milligrams daily has been effective in the treatment of IDIOPATHIC COLD URTICARIA, effectively suppressing the wheal and itching responses and shortening the duration of the wheal response in the ice cube test (Neittaanmaki et al, 1984a).
2) Oral DOXEPIN 5 milligrams twice a day was effective in the treatment of chronic idiopathic URTICARIA in a controlled study. Oral MEQUITAZINE (a phenothiazine antihistamine) 5 mg twice a day was equally effective (Harto et al, 1985; Ledo et al, 1985).
3) Oral DOXEPIN 25 milligrams three times a day was effective in the treatment of CHRONIC IDIOPATHIC URTICARIA in a placebo-controlled trial involving 16 adult patients (Goldsobel et al, 1986). Patients were randomly assigned to receive either DOXEPIN or placebo for 4 weeks; each group was then crossed over for the next 4 weeks. DOXEPIN was associated with fewer waking hours with lesions, and less angioedema and swelling as compared to placebo-treated patients. Daily antihistamine use was less in patients treated with DOXEPIN. Lethargy was observed during DOXEPIN therapy but decreased with continued use of the drug; dry mouth and constipation were also reported.

4.6 Comparative Efficacy / Evaluation With Other Therapies

Amitriptyline

Amitriptylinoxide

Amoxapine

Bupropion

Capsaicin

Chlordiazepoxide

Cimetidine

Cinnarizine

Clomipramine

Clovoxamine

Desipramine

Diazepam

Diphenhydramine

Dothiepin

Fluoxetine

Imipramine

Loxapine

Maprotiline

Mianserin

Nomifensine

Opipramol

Paroxetine

Perphenazine/Amitriptyline Hydrochloride

Trazodone

Trimipramine

4.6.A Amitriptyline

4.6.A.1 Depression

a) Clinical studies have shown that doxepin and amitriptyline are of comparable efficacy in depression; side effects have occurred with greater frequency in patients receiving amitriptyline (Toru et al, 1972; Bianchi et al, 1971; Solis et al, 1970).

b) In one study, amitriptyline-perphenazine produced significantly greater improvement than doxepin on several measures of psychiatric tests. The combination also produced a greater incidence of sedation and anticholinergic side effects (Rickels et al, 1982a). Doxepin 100 to 150 milligrams/day was compared with a combination of amitriptyline 100 to 150 milligrams/day plus perphenazine 8 to 12 milligrams/day in 130 depressed, nonpsychotic outpatients over a period of 4 weeks.

c) Four antidepressants were used in a group of 116 private practice patients suffering from depression associated with chronic or recurrent pain. Dosage range was 150 to 300 milligrams/day, and the antidepressant was changed if necessary to get an adequate response. The response to the 4 antidepressants was not statistically significantly different: doxepin 17 of 22 (77%); imipramine 33 of 44 (75%); amitriptyline 21 of 25 (84%); and desipramine 34 of 44 (75%). A significant response was a 50% reduction in pain judged subjectively (Lindsay & Wyckoff, 1981).

d) Doxepin was compared with amitriptyline in acutely depressed patients using cortical evoked potentials as the measurement of success (Friedman et al, 1980). Many depressed patients have a magnified perception of intervisity to a stimulus; thus, often they complain of pain which to others might be described as discomfort. In 33 patients, baseline potentials were measured after 1 week of placebo therapy, then they received 150 milligrams/day of either doxepin or amitriptyline. Five visual and 5 auditory evoked potentials were recorded. Doxepin reduced the amplitudes of the evoked potentials significantly. Amitriptyline had a similar, but insignificant effect.

e) One author reported that doxepin showed faster pharmacologic activity and greater antidepressive and anxiolytic effects than amitriptyline (Solis et al, 1970).

4.6.B Amitriptylinoxide

4.6.B.1 Depression

a) Doxepin and amitriptylinoxide, in doses of 180 to 360 milligrams/day, had a similar efficacy in a four-week study involving 44 inpatients with severe depression. Efficacy was judged on several rating scales. The two drugs showed comparable efficacy and there were no significant differences in adverse effects (Konig et al, 1994).

4.6.C Amoxapine

4.6.C.1 Mixed anxiety and depressive disorder

a) Amoxapine 160 milligrams/day (maximum dose) was compared with doxepin 130 milligrams/day (maximum dose) in the treatment of mixed anxiety/depression in 142 patients. Twenty-four to 31 of amoxapine-treated subjects (n=71) and 16 to 24 of doxepin-treated subjects (n=71) receiving doxepin were identified as improved after 4 weeks. Amoxapine achieved a more rapid response. Side effects between the 2 treatments were comparable; however, doxepin caused more constipation (Hekimian et al, 1983).

4.6.D Bupropion

4.6.D.1 Depression

a) Bupropion 300 to 450 milligrams daily was reported similar in efficacy to doxepin 100 to 225 milligrams daily in the treatment of major depressive disorder in a double-blind study involving 147 outpatients (Feighner et al, 1986). Doxepin, however, improved sleep better than bupropion; anticholinergic side effects were more frequent with doxepin as compared with bupropion, as was increased appetite and weight gain.

4.6.E Capsaicin

4.6.E.1 Chronic pain - Neuropathic pain

a) Topical doxepin hydrochloride, topical capsaicin, or the combination of the 2 all provided analgesia in chronic human neuropathic pain (CNP), in contrast to placebo. In a randomized, double-blind, placebo-controlled trial, 200 patients with CNP were given placebo cream, 3.3% doxepin hydrochloride cream, 0.25% capsaicin cream, or a cream containing 3.3% doxepin and 0.25% capsaicin. Patients were to apply a volume of cream approximately equal in size to a grain of rice 3 times daily to the painful area for 4 weeks. Overall pain was unchanged in the placebo group. In the other 3 groups, overall pain decreased from approximately 7 to approximately 6 on a pain scale ranging from 0 to 10 (p less than 0.001 for all drug groups). Scores for burning pain were unchanged in the placebo group but increased in all 3 drug groups at week 1 and, though diminishing somewhat thereafter, remained significantly above that of the placebo group. Sensitivity was unchanged by placebo and doxepin but declined significantly, beginning in the first week, with both capsaicin (p less than 0.001) and doxepin/capsaicin (p less than 0.01) treatments. Shooting pain was reduced by the capsaicin treatments but not by doxepin or placebo. Ten percent of patients in the doxepin group and 5% in the doxepin/capsaicin group complained of drowsiness, suggesting the systemic absorption of doxepin. A burning sensation was reported by 81% of those in the capsaicin and by 61% of those in the doxepin/capsaicin group (McCleane, 2000).

4.6.F Chlordiazepoxide

4.6.F.1 Anxiety

a) Most clinical studies to date have indicated that doxepin has proven as useful as chlordiazepoxide in patients with anxiety neurosis (Simeon et al, 1970; Kingstone et al, 1970; Johnstone & Claghorn, 1968). At this point doxepin can not be recommended over chlordiazepoxide or other benzodiazepines in neurotic anxiety but is recommended as the drug of choice in patients with mixed anxiety-depression states (Pinder et al, 1977c).

4.6.G Cimetidine

4.6.G.1 Duodenal ulcer disease

a) In a double-blind randomized study of 21 patients, doxepin (50 milligrams at bedtime for 1 week, followed by 100 milligrams at bedtime) was comparable with cimetidine 300 milligrams four times a day for the treatment of duodenal ulcers (Shrivastava et al, 1985). After 6 weeks, the average ulcer size decreased by 97% in both groups. Interestingly, doxepin was significantly more effective in women than in men, while cimetidine was more effective in men than in women. Further large studies are needed to confirm whether there truly exists a sex-related difference in ulcer healing, especially with doxepin.

4.6.H Cinnarizine

4.6.H.1 Urticaria

a) A randomized, double-blind, crossover trial in 10 patients with primary acquired idiopathic cold urticaria compared the effects of cinnarizine 10 milligrams (mg) three times daily with doxepin 10 mg three times daily and placebo. Each arm of therapy lasted two weeks. Eight patients considered doxepin superior to cinnarizine. Cinnarizine provided some symptom relief in five patients, and was ineffective in four. One patient discontinued cinnarizine therapy due to excessive fatigue. Placebo produced no symptom relief (Neittaanmaki et al, 1984).

4.6.I Clomipramine

4.6.I.1 Dysthymia

a) Results were equivocal in a study that compared clomipramine and doxepin (75 milligrams/day of either) in a group of 66 patients with neurotic depression. Patient-rated measures did not show a superior agent. Clomipramine was rated better by physician-rated measures. There were no significant differences in side effects (Kornhaber & Horwitz, 1984).

b) Doxepin (25 milligrams three times a day) and clomipramine (25 milligrams three times a day), were more effective than L-tryptophan (500 mg three times a day) in 42 neurotically-depressed patients. The findings of the study were that doxepin and clomipramine resulted in more responses than L-tryptophan, therapeutic blood levels of clomipramine and doxepin were much smaller than those found in endogenously depressed patients, that responders had a significantly higher blood level of the two than non-responders at 21 days, and that the response to clomipramine, but not doxepin, parallelled its accumulation in the blood. (Linnoila et al, 1980).

4.6.J Clovoxamine

4.6.J.1 Depression

a) SUMMARY: Clovoxamine offered no clinical advantage over doxepin in the treatment of major depression in one small double-blind study.

b) In a small, double-blind study (n=34), clovoxamine 150 to 300 milligrams daily was generally comparable in efficacy with doxepin 75 to 150 milligrams daily in the treatment of major depression (Lodge & Freeman, 1986). However, doxepin was statistically superior to clovoxamine with regard to improvement of the anxiety/somatization component of Hamilton Rating Scale for Depression (HAM-D) during the first week of treatment. In addition, patient assessments of the response to treatment were highly in favor of doxepin; 97% of doxepin-treated patients indicated they had improved significantly compared to only 50% in the clovoxamine group. Adverse effects were similar in each group, although headache, sweating, and anticholinergic symptoms tended to occur more frequently with clovoxamine. Analysis of pretreatment data in this study indicated more severe depression in the clovoxamine group, which may have influenced results reported. However, several patients with severe psychotic depression were also treated effectively with clovoxamine, suggesting efficacy of the drug in this subgroup. A larger and placebo-controlled study comparing these agents is needed.

4.6.K Desipramine

Chronic pain

Endogenous depression

4.6.K.1 Chronic pain

a) Desipramine and doxepin had similar efficacy in treating depression and doxepin was more effective than desipramine in the treatment of pain severity in one study (Ward et al, 1984). Desipramine (mean dose 173 milligrams/day) was compared with doxepin (mean dose 188 milligrams/day) in 36 patients with depression and chronic back pain. Both drugs produced equal responses in depression ratings. Pain severity showed a better response to doxepin.

b) Four antidepressants had similar efficacy in a group of 116 private practice patients suffering from depression associated with chronic or recurrent pain. Dosage range was 150 to 300 milligrams/day, and the antidepressant was changed if necessary to get an adequate response. The response to the 4 antidepressants was not significantly different: doxepin 17 of 22 (77%); imipramine 33 of 44 (75%); amitriptyline 21 of 25 (84%); and desipramine 34 of 44 (75%). A significant response was a 50% reduction in pain subjectively judged (Lindsay & Wyckoff, 1981a).

4.6.K.2 Endogenous depression

a) Doxepin and desipramine were equally effective in a group of 38 patients with a diagnosis of primary affective disorder, endogenous depression. Both drugs had equal efficacy, but doxepin had a more rapid onset (Amsterdam et al, 1982).

4.6.K.3 Efficacy

a) A prospective study compared oral doses and corresponding plasma levels of doxepin with desipramine (as standard reference compound) for 31 patients (19 females, 12 males), mean age 76 (range, 66 to 86). The results in eight doxepin-treated patients (25 to 100 milligrams/day) showed zero levels of doxepin or its metabolite, desmethyldoxepin, in their plasma. The authors believed that doxepin's reputation for having fewer side effects may reflect the low plasma levels achieved at commonly prescribed doses and that at more appropriate doses, the side-effect profile may be more in line with standard tricyclics. The authors recommend routine monitoring of doxepin levels in the elderly and question poor bioavailability or absorption of this tricyclic antidepressant in some patients (Gosselin et al, 1989).

b) Desipramine suppressed wheal response for 2 days and flare for one day, whereas doxepin suppressed the wheal for 4 days and flare for 6 days in a double-blind, single dose, noncrossover study. Thirty-three healthy adult volunteers (32 males, 1 female) received a single, oral 25-milligram dose of desipramine or doxepin. The duration of H1-receptor blockade by these two tricyclic antidepressants were compared. Results showed significant differences in the suppression of the wheal-and-flare responses to histamine between the two drugs (Rao et al, 1988). These results suggest that doxepin should be withheld for at least 7 days before allergy skin testing.

4.6.L Diazepam

4.6.L.1 Anxiety

a) No significant difference has been observed in clinical trials in patients with anxiety (with or without depression) between doxepin and diazepam (d'Elia et al, 1974; Fielding et al, 1969; Kasich, 1969).

b) A double-blind, placebo-controlled study of 61 outpatients compared doxepin and diazepam in the treatment of anxious and anxious-depressive syndromes (Haskell et al, 1978). After the first week, an enhanced sense of well-being was associated with diazepam. By the end of 6 weeks, there was no significant difference for altering mood and symptomatology with either drug. Objective evaluation rated diazepam more effective than doxepin among anxious patients. Drowsiness was the most common side effect. Significant weight gain occurred with doxepin. Possible biases may have been induced by the sampling technique, population characteristics, and consequent drop-out rate.

4.6.M Diphenhydramine

4.6.M.1 Urticaria

a) Oral doxepin 10 milligrams three times a day was reported significantly superior to oral diphenhydramine 25 milligrams three times a day in the treatment chronic idiopathic urticaria in a controlled study involving 50 patients (Greene et al, 1985). Clearing of pruritus and urticarial lesions was observed in 5% and 43% of diphenhydramine and doxepin-treated patients, respectively; partial or total control pruritus and hives occurred in 10% and 74% of patients, respectively. Doxepin was also associated with significantly less sedation than diphenhydramine.

4.6.N Dothiepin

4.6.N.1 Depression

a) Dothiepin and doxepin were similarly effective when administered in single daily doses of 150 milligrams in a ten-week, placebo-controlled, double-blind study of 579 outpatients with major depressive disorder with psychotic features. Efficacy was judged by several rating scales. Only 341 patients completed the trial. Both drug groups were significantly superior to placebo and there were no significant differences between the two groups. Dothiepin was superior to doxepin relative to the incidence and severity of adverse events (Ferguson et al, 1994).

4.6.O Fluoxetine

4.6.O.1 Depression

a) Doxepin and fluoxetine had similar efficacy in a comparative study involving 80 depressed patients (61 outpatients, 19 inpatients) diagnosed as having major depressive disorder. The patients received either fluoxetine 20 to 60 milligrams/day (mean, 28.9 mg/day) or doxepin 100 to 200 milligrams/day (mean, 146.8 mg/day). Both treatment groups showed improvement over time, with no difference between fluoxetine and doxepin at study termination. The most common side effects of fluoxetine (headache, nausea, and insomnia) were in contrast to the pronounced anticholinergic side effects of doxepin (dry mouth, fatigue, constipation). Moreover, the significant weight gain associated with doxepin therapy was not seen with fluoxetine treatment (Remick et al, 1989).

b) Fluoxetine 20 to 80 milligrams daily (once daily or divided twice a day) and doxepin 50 to 200 milligrams daily (once daily or divided twice a day or three times a day) had comparable efficacy in the treatment of depression in geriatric patients (at least 64 years of age). Each drug was administered in increasing doses over the first two weeks of the study, with maintenance doses (up to 80 mg daily of fluoxetine and 200 mg daily of doxepin) being determined by the third week; this maintenance dose was given for three more weeks (total, six weeks). Both drugs were considered equally effective using the following parameters: Hamilton Psychiatric Rating Scale for Depression (HAM-D), Raskin Severity of Depression Scale, Covi Anxiety Scale, Clinical Global Impressions severity and improvement, Patient Global Improvement, and SCL-58 scales. Both drugs produced significant improvement compared to baseline scores. Fluoxetine was associated with a lower degree of drowsiness/sedation, dry mouth, constipation and vision disturbances. However, nervousness/anxiety, insomnia, sweating, dyspepsia, and nausea occurred to a greater degree with fluoxetine. Body weight decreased with fluoxetine and increased with doxepin (Feighner & Cohn, 1985).

c) In one study comparing fluoxetine and doxepin, both drugs were effective in major depressive disorder in geriatric patients, with a lower incidence of side effects being observed with fluoxetine (Feighner & Cohn, 1985). Weight loss occurred with fluoxetine, as compared to weight gain with doxepin, which was statistically significant. Heart rate was shown to increase in doxepin-treated patients as compared to decreases in fluoxetine-treated patients; this was also a statistically significant difference. Significant improvement in depressive symptoms was further demonstrated in a group (n=33) of geropsychiatric patients. Although this study only followed patients for a period of one month, significant side effects such as nausea, weight loss, and agitation were not noted. Doses of fluoxetine used were 20 mg every other day to 20 mg daily (Orengo et al, 1996).

4.6.P Imipramine

4.6.P.1 Depression

a) Imipramine may be slightly more effective than doxepin in the treatment of depression. Ninety-nine patients with neurotic depression received imipramine 100 to 200 milligrams/day or doxepin 100 to 200 milligrams/day for 4 weeks in a double-blind study. Imipramine was superior in 24 of 27 parameters. Imipramine was shown to be superior to doxepin in improving the symptoms of anxiety/depression; global evaluations showed improvement in 39 of 48 (81%) of imipramine patients and 34 and 49 (69%) of doxepin patients (Finnerty et al, 1978).

b) In a study involving 79 patients, a higher socioeconomic status and shorter duration of illness were indicative of a favorable response to imipramine, whereas a higher response rate to doxepin was found in male patients (Finnerty & Goldberg, 1981).

c) Amitriptyline was superior to imipramine and doxepin in relation to their effects on interpersonal learning in 50 depressed inpatients (Gillis, 1981). All subjects performed better, according to quantitative indices of

learning tasks, than patients who received antipsychotic or neuroleptic drugs but no antidepressants. Amitriptyline patients scored significantly higher than either imipramine or doxepin patients.
d) No significant differences in overall efficacy of the 2 drugs was reported in one study (Kimura, 1972), but doxepin 30 to 150 mg daily was superior to imipramine 150 mg daily in neurotic depression, whereas imipramine appeared to be superior to doxepin in endogenous depression (Pinder et al, 1977d).
e) Similar antidepressant effects of doxepin and imipramine were reported; however, imipramine had a more rapid onset of action. Doxepin appeared to have more sustained effects (Hasan & Akhtar, 1971).

4.6.P.2 Efficacy

a) In elderly patients doxepin produces less orthostatic effects than imipramine (10.5 mmHg vs 25.9 mmHg). The orthostatic effect observed with imipramine was weakly related to dose and did not correlate with pretreatment orthostatic hypotension or with duration of treatment (Neshkes et al, 1985).

4.6.Q Loxapine

4.6.Q.1 Anxiety

a) No significant differences were reported between doxepin and loxapine succinate in patients with anxiety neurosis (Charlalampous et al, 1974).

4.6.R Maprotiline

4.6.R.1 Depression

a) Single nightly doses of doxepin and maprotiline, 75 to 150 milligrams orally for 6 weeks produced moderate to marked improvement in depression in a majority of 47 depressed patients. Both drugs were rated equally effective in this double-blind study. Side effects were not significantly different (Anon, 1978).
b) Maprotiline and doxepin were equally effective in a double-blind, multicenter trial in 95 depressed (neurotic and psychotic) inpatients/outpatients who were randomized into 2 equal groups (Vaisanen et al, 1978). A dose of 75 milligrams daily of either maprotiline or doxepin was given initially; the dose was doubled if needed. Seventy-eight patients completed the three-to-four week trial. The dropout group included six due to unwanted effects (2 maprotiline, 4 doxepin), one from each group due to lack of efficacy and nine for other reasons (non-cooperation/noncompliance). Almost one-half of the patients in the study received additional psychoactive medication including sedatives, neuroleptics, and tranquilizers which were not thought to influence the trial. Overall assessment using a five point scale of target symptoms and a visual analogue scale showed no statistically significant difference between the two treatment groups. The most common side effects in both groups were dry mouth and fatigue. Fourteen patients continued treatment with maprotiline after the trial for a mean of 13 weeks (five received maprotiline for 30 weeks) with no pathological changes in laboratory values except for a slight rise in liver enzyme levels in two patients during initial therapy.

4.6.S Mianserin

4.6.S.1 Mixed anxiety and depressive disorder

a) Mianserin 60 milligrams/day and doxepin 150 milligrams/day had similar efficacy in 60 patients with mixed anxiety/depression. After 4 weeks of treatment, there was no consistent difference in efficacy, but a higher incidence of side effects occurred in the doxepin group (Khan et al, 1983).

4.6.T Nomifensine

4.6.T.1 Depression

a) Doxepin 186 mg daily was more effective than nomifensine 196 mg daily in treatment of endogenous and neurotic depression (Anderson, 1977). Fatigue and dizziness occurred more often with doxepin than nomifensine.

4.6.U Opipramol

4.6.U.1 Depression

a) In a randomized double-blind 5-week trial, doxepin was found to be more effective overall than opipramol. Patients were diagnosed with one of the following types of depression: neurotic depression, psychotic depression, involutional melancholia and senile depression. Eighteen patients were in the opipramol group and 22 in the doxepin group. The average dose of doxepin was between 10 and 20 milligrams (mg)/day and opipramol was between 50 and 100 mg/day. Effects of the drugs were viewed from three standpoints: nosologic classification, syndrome classification and individual symptoms. From the nosological standpoint, doxepin was significantly more effective; although opipramol was very effective in treating patients with involutional melancholia. From the syndrome classification standpoint, doxepin was once again better overall. From the individual symptoms standpoint, doxepin was more effective in relieving depressive mood, fear, suicidal thoughts, feeling of insufficiency, guilt, insomnia, vegetative symptoms and psychomotor disturbances than was opipramol. Drowsiness was the only adverse effect reported with either drug (Terzani, 1972).

4.6.V Paroxetine

4.6.V.1 Depression

a) Paroxetine was at least as effective as doxepin in the treatment of major depression in 272 geriatric patients in a double-blind, randomized trial. After a washout-period of 4 to 14 days, patients over 60 years of age received either paroxetine 10 to 40 milligrams (mg) (mean 23.4 mg) as a single daily dose or doxepin (up to 200 milligrams (mg), mean 105.2 mg/day) divided in two doses. Therapy continued for 42 days. Paroxetine was as effective as doxepin by several measures and more effective by others. Doxepin caused more sedation, confusion, and anticholinergic effects, and less nausea and headache compared with paroxetine (Dunner et al, 1992).

4.6.W Perphenazine/Amitriptyline Hydrochloride

4.6.W.1 Depression

a) Doxepin (100 to 150 milligrams/day) was not as effective as amitriptyline/perphenazine (100/8 to 150/12 milligrams/day) in 130 nonpsychotic depressed outpatients over 4 weeks. Amitriptyline/perphenazine produced greater improvement based on several rating scales. The combination also showed a greater incidence of anticholinergic and sedative side effects (Rickels et al, 1982).

4.6.X Trazodone

4.6.X.1 Depression

a) No significant difference in safety or efficacy was seen in a comparison of trazodone (mean daily dose during weeks 1, 3, and 6 was 125 milligrams (mg), 221 mg, and 246 mg) with doxepin (mean daily dose during weeks 1, 3, and 6 was 58 mg, 105 mg, and 127 mg) in 30 outpatients with major depressive disorder in a 6-week, double-blind, parallel study (Himmelhoch, 1986).

b) No significant difference was reported in a double-blind study of 101 patients, on the efficacy of trazodone and doxepin in the treatment of depression (Murphy & Ankier, 1980).

4.6.Y Trimipramine

4.6.Y.1 Depression

a) The therapeutic efficacy and cardiac safety of trimipramine and doxepin were comparable in 37 patients with major depressive disorder. Patients received one week of placebo followed by five weeks of either trimipramine or doxepin in doses up to 200 milligrams/day. Based on ECG and psychiatric and cognitive function tests, the drugs were concluded to be equally safe and efficacious in this group of patients (Nair et al, 1993).

b) Trimipramine was superior to doxepin in safety and efficacy in a 4-week study. Trimipramine and doxepin (150 milligrams/day of each) were compared in 25 depressed hospitalized patients. Comparisons of efficacy favored trimipramine over doxepin. Doxepin had a higher incidence of side effects (Assalian et al, 1985).

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Last Modified: May 18, 2009

DRUGDEX® Evaluations

ATOMOXETINE

0.0 Overview

1) Class
- **a)** This drug is a member of the following class(es):
  - Central Nervous System Agent
  - Norepinephrine Reuptake Inhibitor

2) Dosing Information
- **a)** Atomoxetine Hydrochloride
  - **1)** Adult
    - **a)** Attention deficit hyperactivity disorder
      - **1)** 40 mg/day ORALLY; increase after a minimum of 3 days to a target dose of approximately 80 mg/day; MAX dosage of 100 mg/day may be considered after 2 to 4 additional weeks in patients who have not achieved adequate response on lower doses (Prod Info STRATTERA(R) oral capsules, 2008)
  - **2)** Pediatric
    - **a)** safety and effectiveness not established in children less than 6 years of age (Prod Info STRATTERA(R) oral capsules, 2008)
      - **1)** Attention deficit hyperactivity disorder
        - **a)** acute treatment: (weight of 70 kg or less) 0.5 mg/kg/day ORALLY; increase after a minimum of 3 days to a target dose of 1.2 mg/kg/day; MAX dosage is 1.4 mg/kg/day or 100 mg/day (whichever is less) (Prod Info STRATTERA(R) oral capsules, 2008)
        - **b)** acute treatment: (weight greater than 70 kg) 40 mg/day ORALLY; increase after a minimum of 3 days to a target dose of approximately 80 mg/day; MAX dosage of 100 mg/day may be considered after 2 to 4 additional weeks in patients who have not achieved adequate response on lower doses (Prod Info STRATTERA(R) oral capsules, 2008)
        - **c)** maintenance: 1.2 to 1.8 mg/kg/day ORALLY has been studied in 1 clinical trial; MAX dosage is 1.4 mg/kg/day or 100 mg/day, whichever is less (weight of 70 kg or less) OR 100 mg/day (weight greater than 70 kg) (Prod Info STRATTERA(R) oral capsules, 2008)

3) Contraindications
- **a)** Atomoxetine Hydrochloride
  - **1)** hypersensitivity to atomoxetine or to other components of the product (Prod Info STRATTERA(R) oral capsules, 2009)
  - **2)** MAO inhibitor use; do not administer atomoxetine during therapy with or within 2 weeks of discontinuing an MAO inhibitor (Prod Info STRATTERA(R) oral capsules, 2009)
  - **3)** narrow angle glaucoma; increased risk of mydriasis (Prod Info STRATTERA(R) oral capsules, 2009)

4) Serious Adverse Effects
- **a)** Atomoxetine Hydrochloride
  - **1)** Angioedema
  - **2)** Cerebrovascular accident
  - **3)** Dyskinesia
  - **4)** Injury of liver (Severe)
  - **5)** Mania
  - **6)** Myocardial infarction
  - **7)** Priapism
  - **8)** Prolonged QT interval
  - **9)** Psychotic disorder
  - **10)** Seizure
  - **11)** Sudden cardiac death
  - **12)** Suicidal thoughts

5) Clinical Applications
- **a)** Atomoxetine Hydrochloride
  - **1)** FDA Approved Indications
    - **a)** Attention deficit hyperactivity disorder

1.0 Dosing Information

Drug Properties

Storage and Stability

Adult Dosage

Pediatric Dosage

1.1 Drug Properties

A) Information on specific products and dosage forms can be obtained by referring to the Tradename List (Product Index)

B) Synonyms

Atomoxetine
Atomoxetine HCl
Atomoxetine Hydrochloride
Tomoxetine

C) Physicochemical Properties

1) Molecular Weight

a) 291.82 (Prod Info Strattera(R), 2004)

2) Solubility

a) 27.8 mg/mL in water (Prod Info Strattera(R), 2004)

1.2 Storage and Stability

A) Atomoxetine Hydrochloride

1) Preparation

a) Oral route

1) Atomoxetine hydrochloride (HCl) may be taken with or without food. Swallow capsules whole, and do not open (Prod Info STRATTERA(R) oral capsules, 2008).

1.3 Adult Dosage

Normal Dosage

Dosage in Renal Failure

Dosage in Hepatic Insufficiency

Dosage in Other Disease States

1.3.1 Normal Dosage

1.3.1.A Atomoxetine Hydrochloride

1.3.1.A.1 Oral route

1.3.1.A.1.a Attention deficit hyperactivity disorder

1) The recommended starting dose of atomoxetine hydrochloride (HCl) in adult patients with attention-deficit hyperactivity disorder is 40 milligrams (mg)/day orally. The dose may be increased after a minimum of 3 days to a target dose of approximately 80 mg/day, given as a single daily dose (in the morning) or as 2 divided doses (in the morning and late afternoon/early evening). The maximum dose of atomoxetine 100 mg/day may be given after 2 to 4 additional weeks in patients who have not achieved an adequate response on lower doses. Tapering of the dose is not required upon therapy discontinuation (Prod Info STRATTERA(R) oral capsules, 2008).

2) Concomitant CYP2D6 Inhibitors

a) Atomoxetine hydrochloride should be initiated at 40 milligrams (mg)/day in adult patients receiving concomitant strong CYP2D6 inhibitors, such as paroxetine, fluoxetine, or quinidine. Patients should only be titrated to the maximum dose of 80 mg/day after 4 weeks if they have tolerated the initial dose but did not achieve an adequate response on lower doses (Prod Info STRATTERA(R) oral capsules, 2008).

1.3.2 Dosage in Renal Failure

A) Atomoxetine Hydrochloride

1) No dose adjustment of atomoxetine hydrochloride is necessary in patients with renal insufficiency (Prod Info STRATTERA(R) oral capsules, 2008).

1.3.3 Dosage in Hepatic Insufficiency

A) Atomoxetine Hydrochloride

1) Atomoxetine hydrochloride (HCl) is metabolized in the liver, and dose adjustments are necessary in patients with hepatic impairment. Starting and target doses of atomoxetine HCl should be reduced by 50%

of the normal dose in patients with moderate hepatic insufficiency (Child-Pugh Class B) and reduced to 25% of the normal dose in patients with severe hepatic insufficiency (Child-Pugh Class C) (Prod Info STRATTERA(R) oral capsules, 2008).

1.3.6 Dosage in Other Disease States

A) Atomoxetine Hydrochloride

1) CYP2D6 Poor Metabolizers

a) In patients who are known poor metabolizers of CYP2D6, atomoxetine hydrochloride should be initiated at 40 milligrams/day (mg/day). Patients should only be titrated to the target dose of 80 mg/day after 4 weeks if they have tolerated the initial dose but did not achieve an adequate response on lower doses (Prod Info STRATTERA(R) oral capsules, 2008).

1.4 Pediatric Dosage

Normal Dosage

Dosage in Renal Failure

Dosage in Hepatic Insufficiency

Dosage in Other Disease States

1.4.1 Normal Dosage

1.4.1.A Atomoxetine Hydrochloride

1.4.1.A.1 Oral route

1.4.1.A.1.a Attention deficit hyperactivity disorder

1) Acute Therapy

a) Patients Weighing 70 Kilograms or Less

1) The recommended starting dose of atomoxetine hydrochloride (HCl) in children and adolescent patients with attention-deficit hyperactivity disorder who weigh 70 kilograms (kg) or less is approximately 0.5 milligrams (mg)/kg/day orally. The dose may be increased after a minimum of 3 days to a target dose of approximately 1.2 mg/kg/day, given as a single daily dose (in the morning) or as 2 divided doses (in the morning and late afternoon/early evening). Although no additional benefits were observed in clinical studies with doses higher than 1.2 mg/kg/day, the maximum dose in children and adolescents is atomoxetine 1.4 mg/kg/day or 100 mg/day, whichever is less. Tapering of the dose is not required upon therapy discontinuation (Prod Info STRATTERA(R) oral capsules, 2008).

2) Concomitant CYP2D6 Inhibitors

a) Atomoxetine hydrochloride should be initiated at 0.5 milligrams/kilogram/day (mg/kg/day) in patients receiving concomitant strong CYP2D6 inhibitors, such as paroxetine, fluoxetine, or quinidine. Patients should only be titrated to the maximum dose of 1.2 mg/kg/day after 4 weeks if they have tolerated the initial dose but did not achieve an adequate response on lower doses (Prod Info STRATTERA(R) oral capsules, 2008).

b) Patients Weighing Greater than 70 Kilograms

1) The recommended starting dose of atomoxetine hydrochloride (HCl) in children and adolescent patients with attention-deficit hyperactivity disorder who weigh greater than 70 kilograms is 40 milligrams (mg)/day orally. The dose may be increased after a minimum of 3 days to a target dose of approximately 80 mg/day, given as a single daily dose (in the morning) or as 2 divided doses (in the morning and late afternoon/early evening). The maximum dose of atomoxetine 100 mg/day may be given after 2 to 4 additional weeks in patients who have not achieved an adequate response on lower doses. Tapering of the dose is not required upon therapy discontinuation (Prod Info STRATTERA(R) oral capsules, 2008).

2) Concomitant CYP2D6 Inhibitors

a) Atomoxetine hydrochloride should be initiated at 40 milligrams (mg)/day in patients receiving concomitant strong CYP2D6 inhibitors, such as paroxetine, fluoxetine, or quinidine. Patients should only be titrated to the maximum dose of 80 mg/day after 4 weeks if they have tolerated the initial dose but did not achieve an adequate response on lower doses (Prod Info STRATTERA(R) oral capsules, 2008).

c) The safety of single doses exceeding 120 mg or total daily doses exceeding 150 mg has not been evaluated (Prod Info STRATTERA(R) oral capsules, 2008).

2) Maintenance Therapy

a) In one study, pediatric patients (ages 6 to 15 years) with attention-deficit hyperactivity disorder continued on atomoxetine hydrochloride (HCl) 1.2 to 1.8 milligrams (mg)/kilogram (kg)/day after achieving a continuous response during an initial 10-week, open-label treatment phase. The maximum recommended total daily dose is 1.4 mg/kg/day or 100 mg/day (whichever is less) in patients weighing 70 kg or less, and 100 milligrams/day in patients weighing over 70 kg. Tapering of the dose is not required upon therapy discontinuation. Patients who receive atomoxetine HCl for extended time periods should be periodically reassessed to verify drug effectiveness (Prod Info STRATTERA(R) oral capsules, 2008).

b) The safety of single doses exceeding 120 mg or total daily doses exceeding 150 mg has not been evaluated (Prod Info STRATTERA(R) oral capsules, 2008).

2) The safety and effectiveness of atomoxetine hydrochloride have not been evaluated in pediatric patients less than 6 years of age (Prod Info STRATTERA(R) oral capsules, 2008).

1.4.2 Dosage in Renal Failure

A) Atomoxetine Hydrochloride

1) No dose adjustment of atomoxetine hydrochloride is necessary in patients with renal insufficiency (Prod Info STRATTERA(R) oral capsules, 2008).

1.4.3 Dosage in Hepatic Insufficiency

A) Atomoxetine Hydrochloride

1) Atomoxetine hydrochloride (HCl) is metabolized in the liver, and dose adjustments are necessary in patients with hepatic impairment. Starting and target doses of atomoxetine HCl should be reduced by 50% of the normal dose in patients with moderate hepatic insufficiency (Child-Pugh Class B) and reduced to 25% of the normal dose in patients with severe hepatic insufficiency (Child-Pugh Class C) (Prod Info STRATTERA(R) oral capsules, 2008).

1.4.5 Dosage in Other Disease States

A) Atomoxetine Hydrochloride

1) CYP2D6 Poor Metabolizers

a) In patients who are known poor metabolizers of CYP2D6, atomoxetine hydrochloride should be initiated at 0.5 milligrams/kilogram/day (mg/kg/day). Patients should only be titrated to the target dose of 1.2 mg/kg/day after 4 weeks if they have tolerated the initial dose but did not achieve an adequate response on lower doses (Prod Info STRATTERA(R) oral capsules, 2008).

2.0 Pharmacokinetics

Onset and Duration

Drug Concentration Levels

ADME

2.1 Onset and Duration

A) Onset

1) Initial Response

a) ATTENTION-DEFICIT/HYPERACTIVITY DISORDER, ORAL: 1 week (Spencer et al, 2001).

1) Based on data from children with ADHD in an open study (twice-daily dosing).

2) In adults with ADHD, a significant reduction in symptoms versus placebo was seen after 2 weeks of treatment (Spencer et al, 1998).

b) MAJOR DEPRESSION, ORAL: within one week (Chouinard et al, 1985).

1) Based on limited patient data from an open study.

2.2 Drug Concentration Levels

A) Therapeutic Drug Concentration

1) Not established in any indication.

B) Time to Peak Concentration

1) ORAL: 1 to 2 hours (Farid et al, 1985); (Prod Info Strattera(R), 2002).

a) In children ages 7 to 14 years with attention deficit hyperactivity disorder and classified as extensive metabolizers, maximal concentration was achieved in 2 hours after either a single dose of atomoxetine 10 milligrams (mg) or steady-state dosing (20 to 45 mg twice daily) (Witcher et al, 2003).

b) Following single 90-mg oral doses in healthy subjects (extensive metabolizers), peak plasma levels of atomoxetine varied considerably, ranging from 315 to 1231 ng/mL. Plasma levels fell to undetectable levels

at 36 hours postdosing. In poor metabolizers, peak levels tended to be higher, and occurred later (based on two subjects) (Farid et al, 1985).

c) With administration of 20 and 40 mg twice daily for 7 days in extensive metabolizers (healthy subjects), peak levels on day 1 were approximately 100 and 250 ng/mL, respectively; there was no significant accumulation on days 2 through 7. Plasma concentrations of the metabolite, noratomoxetine, were low in these subjects (less than 10 ng/mL). In subjects who were poor metabolizers in this study (n=2), significant accumulation of both atomoxetine and noratomoxetine was observed during repeat dosing (Farid et al, 1985).

C) Area Under the Curve

1) mean 2766 ng x hr/mL after 90-mg single dose (extensive metabolizers) (Farid et al, 1985).

a) In children ages 7 to 14 years with attention deficit disorder and classified as extensive metabolizers, plasma concentrations of the active metabolite 4-hydroxyatomoxetine were 26 to 35 times less than those for atomoxetine (Witcher et al, 2003).

b) During repeat dosing in extensive metabolizers (healthy subjects), AUC data indicated no significant accumulation of atomoxetine; in subjects receiving 20 mg and 40 mg twice daily for one week, AUC(0-24) values at steady-state (last dose) were 975 to 1126 ng x hr/mL and 2460 to 3710 ng x hr/mL, respectively. In poor metabolizers receiving these doses, accumulation was significant, with corresponding values of 10,490 ng x hr/mL and 29,330 ng x hr/mL (based on data from two subjects) (Farid et al, 1985).

2.3 ADME

Absorption

Distribution

Metabolism

Excretion

Elimination Half-life

2.3.1 Absorption

A) Bioavailability

1) ORAL: 63% in extensive metabolizers; 94% in poor metabolizers (Prod Info Strattera(TM), 2002t).

B) Effects of Food

1) extent of absorption unaffected (Prod Info Strattera(TM), 2002t).

a) The rate of absorption is reduced when given with food in adults (by 37%) and time to peak levels prolonged (by about 3 hours); however, AUC is unaffected (Prod Info Strattera(TM), 2002t).

2.3.2 Distribution

A) Distribution Sites

1) Protein Binding

a) 98% (albumin) (Prod Info Strattera(TM), 2002t).

B) Distribution Kinetics

1) Volume of Distribution

a) Approximately 74 to 250 liters (extensive metabolizers) (Witcher et al, 2003; Farid et al, 1985).

1) Volume of distribution was similar (74 to 328 liters) between single oral doses (10 to 90 milligrams (mg)), and repeat dosing (20 to 45 mg twice daily) in extensive metabolizers (healthy subjects). In poor metabolizers (data limited), a slightly lower volume of distribution was reported (about 90 L) (Witcher et al, 2003; Farid et al, 1985).

2.3.3 Metabolism

A) Metabolism Sites and Kinetics

1) LIVER, extensive (Michelson et al, 2001; Farid et al, 1985).

a) Cytochrome P450 (CYP)-2D6 is involved in the metabolism of atomoxetine (Michelson et al, 2001). An active metabolite, 4-hydroxyatomoxetine, undergoes significant glucuronidation and renal excretion (Michelson et al, 2001).

b) Some patients are poor metabolizers of atomoxetine and will have significantly higher AUC values (10-fold) and plasma levels compared to extensive metabolizers; lab tests are available to identify poor metabolizers (Prod Info Strattera(TM), 2002t).

B) Metabolites

1) 4-Hydroxyatomoxetine (active) (Michelson et al, 2001; Farid et al, 1985).

a) Equipotent to the parent compound as a norepinephrine transporter inhibitor; however, it is present in low concentrations in plasma relative to the parent compound (about 1%) (Prod Info Strattera(TM),

2002t). Its contribution to clinical effects is unknown.
2) Noratomoxetine (inactive) (Farid et al, 1985).
3) N-desmethylatomoxetine (inactive) (Witcher et al, 2003).

2.3.4 Excretion
A) Kidney
1) Renal Excretion (%)
a) less than 3% unchanged (Prod Info Strattera(TM), 2002t).
1) Most of an oral dose of atomoxetine is excreted in the urine as 4-hydroxyatomoxetine-O-glucuronide (80%) (Prod Info Strattera(TM), 2002t; Michelson et al, 2001).
B) Total Body Clearance
1) 0.3 to 0.5 L/hr/kg (extensive metabolizers) (Farid et al, 1985; Prod Info Strattera(TM), 2002t).
a) Clearance is about 10-fold lower in poor metabolizers (0.03 to 0.04 L/hr/kg) (Farid et al, 1985; Prod Info Strattera(TM), 2002t).
b) Plasma clearance was similar (17 to 62 liters/hour; average, 36 to 40 liters/ hour) between single oral doses (10 to 90 mg) and repeat dosing (20 to 45 mg twice daily) in extensive metabolizers (healthy subjects); there was no evidence of dose-dependency. In poor metabolizers receiving repeat doses, a substantially lower clearance was observed (about 3 L/hr) (Witcher et al, 2003; Farid et al, 1985).
C) Other
1) OTHER EXCRETION
a) FECES
1) Less than 17% of a dose is excreted in feces as 4-hydroxyatomoxetine-O-glucuronide (Prod Info Strattera(TM), 2002t).

2.3.5 Elimination Half-life
A) Parent Compound
1) ELIMINATION HALF-LIFE
a) 4 to 5 hours (in extensive metabolizers; 22 hours in poor metabolizers (Farid et al, 1985; Michelson et al, 2001; Prod Info Strattera(TM), 2002).
1) Half-life was similar (3 to 6 hours) between single oral doses (10 to 90 milligrams (mg)), and repeat dosing (20 to 45 mg twice daily) in extensive metabolizers (healthy subjects); there was no evidence of dose-dependency. In poor metabolizers receiving the same repeat doses, a substantially longer half-life was observed (17 to 21 hours) (Witcher et al, 2003; Farid et al, 1985).

3.0 Cautions

Contraindications

Precautions

Adverse Reactions

Teratogenicity/Effects in Pregnancy/Breastfeeding

Drug Interactions

3.0.A Black Box WARNING
1) Atomoxetine Hydrochloride
a) Oral (Capsule)
Suicidal Ideation in Children and Adolescents:
Atomoxetine increased the risk of suicidal ideation in short-term studies in children or adolescents with Attention-Deficit/Hyperactivity Disorder (ADHD). Anyone considering the use of atomoxetine in a child or adolescent must balance this risk with the clinical need. Co-morbidities occurring with ADHD may be associated with an increase in the risk of suicidal ideation and/or behavior. Patients who are started on therapy should be monitored closely for suicidality (suicidal thinking and behavior), clinical worsening, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Atomoxetine is approved for ADHD in pediatric and adult patients. Atomoxetine is not approved for major depressive disorder.
Pooled analyses of short-term (6 to 18 weeks) placebo-controlled trials of atomoxetine in children and adolescents (a total of 12 trials involving over 2200 patients, including 11 trials in ADHD and 1 trial in enuresis) have revealed a greater risk of suicidal ideation early during treatment in those receiving atomoxetine compared to placebo. The average risk of suicidal ideation in patients receiving atomoxetine was 0.4% (5/1357 patients), compared to none in placebo-treated patients (851 patients). No suicides occurred in these trials (Prod Info STRATTERA(R) oral capsules, 2009).

3.1 Contraindications

A) Atomoxetine Hydrochloride

1) hypersensitivity to atomoxetine or to other components of the product (Prod Info STRATTERA(R) oral capsules, 2009)

2) MAO inhibitor use; do not administer atomoxetine during therapy with or within 2 weeks of discontinuing an MAO inhibitor (Prod Info STRATTERA(R) oral capsules, 2009)

3) narrow angle glaucoma; increased risk of mydriasis (Prod Info STRATTERA(R) oral capsules, 2009)

3.2 Precautions

A) Atomoxetine Hydrochloride

1) suicidal ideation has occurred; increased risk in children and adolescents during the first few months of therapy or following a dosage adjustment; monitoring for signs of suicidality, clinical worsening, and unusual changes in behavior (eg, agitation, irritability) recommended; discontinuation may be necessary (Prod Info STRATTERA(R) oral capsules, 2009; US Food and Drug Administration, 2005)

2) bipolar disorder; mixed/manic episode may be induced; screening recommended prior to therapy for patients with comorbid depressive symptoms (Prod Info STRATTERA(R) oral capsules, 2009)

3) cardiovascular disease, cerebrovascular disease, hypertension, tachycardia; risk of increased blood pressure and heart rate; monitoring recommended (Prod Info STRATTERA(R) oral capsules, 2009)

4) liver injury has been reported rarely; if signs of liver injury occur (eg, elevated liver enzymes, jaundice, pruritus, dark urine, right upper quadrant tenderness), discontinue use and do not restart (Prod Info STRATTERA (R) oral capsules, 2009)

5) orthostatic hypotension and syncope have been reported; use cautiously in conditions predisposing to hypotension or associated with abrupt heart rate or blood pressure changes (Prod Info STRATTERA(R) oral capsules, 2009)

6) priapism has been reported rarely in children and adults; seek prompt medical attention (Prod Info STRATTERA(R) oral capsules, 2009)

7) psychotic or manic symptoms, hallucinations, delusional thinking or mania may occur in children and adolescents without a prior history of psychotic illness or mania at usual doses; discontinuation may be necessary (Prod Info STRATTERA(R) oral capsules, 2009)

8) structural cardiac abnormalities; risk of sudden death at usual doses; should not be used in adult or pediatric patients with known structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, coronary artery disease, or other serious heart problems (Prod Info STRATTERA(R) oral capsules, 2009)

3.3 Adverse Reactions

Cardiovascular Effects

Dermatologic Effects

Endocrine/Metabolic Effects

Gastrointestinal Effects

Hepatic Effects

Immunologic Effects

Neurologic Effects

Psychiatric Effects

Renal Effects

Reproductive Effects

Other

3.3.1 Cardiovascular Effects

3.3.1.A Atomoxetine Hydrochloride

Increased diastolic arterial pressure

Increased systolic arterial pressure

Myocardial infarction

Orthostatic hypotension

Palpitations

Prolonged QT interval

Raynaud's phenomenon

Sudden cardiac death

Syncope

Tachycardia

3.3.1.A.1 Increased diastolic arterial pressure

a) Incidence: pediatrics, 3.5% to 4% (Prod Info STRATTERA(R) oral capsules, 2008)

b) In clinical studies, increased diastolic blood pressure (mean increase of 1 and 2.4 mmHg in adults and pediatric patients, respectively, compared to placebo) has been reported in atomoxetine-treated patients with attention-deficit hyperactivity disorder (ADHD). Use caution in patients receiving atomoxetine who have preexisting hypertension, tachycardia, or cardiovascular or cerebrovascular disease due to the risk of heart rate and blood pressure elevation in these patients. Pulse and blood pressure monitoring is recommended at baseline, following dose increases, and periodically during therapy (Prod Info STRATTERA(R) oral capsules, 2008). In addition, greater increases in heart rate and systolic pressure have been reported among cytochrome P450 2D6 poor metabolizers (Michelson et al, 2001a; Chouinard et al, 1985a).

c) In placebo-controlled trials in adult patients with attention-deficit hyperactivity disorder (ADHD), diastolic blood pressures of 105 mm Hg or greater were reported in 0% of patients who received atomoxetine (n=0 of 510) compared to 0.3% of patients who received placebo (n=1 of 393). No patients had a high diastolic blood pressure documented on more than one occasion (Prod Info STRATTERA(R) oral capsules, 2008).

d) In pediatric placebo-controlled trials, high diastolic blood pressures were reported in 4% of atomoxetine-treated patients (n=50 of 1262) compared to 1.1% of placebo-treated patients (n=8 of 759) at the final study visit. Additionally, high systolic blood pressures were reported on 2 or more occasions in 3.5% (n=44 of 1262) of pediatric patients treated with atomoxetine and 0.5% (n=4 of 759) treated with placebo during the study (Prod Info STRATTERA(R) oral capsules, 2008).

3.3.1.A.2 Increased systolic arterial pressure

a) Incidence: pediatrics, 4.4% to 4.8% (Prod Info STRATTERA(R) oral capsules, 2008)

b) In clinical studies, increased systolic blood pressure (mean increase of 2 and 1.6 mmHg in adults and pediatric patients, respectively, compared to placebo) has been reported in atomoxetine-treated patients with attention-deficit hyperactivity disorder (ADHD). Use caution in patients receiving atomoxetine who have preexisting hypertension, tachycardia, or cardiovascular or cerebrovascular disease due to the risk of heart rate and blood pressure elevation in these patients. Pulse and blood pressure monitoring is recommended at baseline, following dose increases, and periodically during therapy (Prod Info STRATTERA(R) oral capsules, 2008). In addition, greater increases in heart rate and systolic pressure have been reported among cytochrome P450 2D6 poor metabolizers (Michelson et al, 2001a; Chouinard et al, 1985a).

c) In placebo-controlled trials in adult patients with attention-deficit hyperactivity disorder (ADHD), systolic blood pressures of 180 mm Hg or greater were not reported in patients taking atomoxetine (n=510) or placebo (n=393). No patients had a high systolic blood pressure documented on more than one occasion (Prod Info STRATTERA(R) oral capsules, 2008).

d) In pediatric placebo-controlled trials, high systolic blood pressures were reported in 4.8% of atomoxetine-treated patients (n=59 of 1226) compared to 3.5% of placebo-treated patients (n=26 of 748) at the final study visit. Additionally, high systolic blood pressures were reported on 2 or more occasions in 4.4% (n=54 of 1226) of pediatric patients treated with atomoxetine and 1.9% (n=14 of 748) treated with placebo during the study (Prod Info STRATTERA(R) oral capsules, 2008).

3.3.1.A.3 Myocardial infarction

a) Myocardial infarction has occurred in adult patients receiving atomoxetine at usual doses. Consider not using atomoxetine in adult patients with clinically significant cardiac abnormalities (eg, coronary artery disease, serious structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, other serious cardiac problems) (Prod Info STRATTERA(R) oral capsules, 2008).

3.3.1.A.4 Orthostatic hypotension

a) Incidence: pediatric, up to 1.8% (Prod Info STRATTERA(R) oral capsules, 2008)

b) Orthostatic hypotension has been reported in 0.2% of atomoxetine-treated child and adolescent patients (n=12 of 5596). Additionally, in child and adolescent patients with attention-deficit hyperactivity disorder (ADHD), orthostatic hypotension occurred in 1.8% of patients who received atomoxetine (n=6 of 340) compared to 0.5% of patients who received placebo (n=1 of 207) in short-term, placebo-controlled studies. Patients with any condition that may predispose them to hypotension should use atomoxetine with caution (Prod Info STRATTERA(R) oral capsules, 2008).

3.3.1.A.5 Palpitations

a) Incidence: adults, 3% (Prod Info STRATTERA(R) oral capsules, 2008)

b) In acute (up to 25 weeks), placebo-controlled trials in adult patients with attention-deficit hyperactivity disorder (ADHD), palpitations were reported in 3% of patients who received atomoxetine (n=540) compared to 1% of patients who received placebo (n=402) (Prod Info STRATTERA(R) oral capsules, 2008).

3.3.1.A.6 Prolonged QT interval

a) There have been spontaneous postmarketing reports of QT prolongation with atomoxetine use (Prod Info STRATTERA(R) oral capsules, 2008).

3.3.1.A.7 Raynaud's phenomenon

a) New onset and exacerbation of preexisting Raynaud's phenomenon have been reported in spontaneous postmarketing accounts (Prod Info STRATTERA(R) oral capsules, 2008).

3.3.1.A.8 Sudden cardiac death

a) Sudden death has occurred in adult patients receiving atomoxetine at usual doses and in children and adolescent patients with structural cardiac abnormalities or other serious heart problems who were receiving atomoxetine at usual doses. Therefore, consider not using atomoxetine in adult patients with clinically significant cardiac abnormalities (eg, coronary artery disease, serious structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, other serious cardiac problems). Additionally, use of atomoxetine is not recommended in pediatric patients with known serious structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, or other serious cardiac problems. Patients should be assessed prior to starting atomoxetine therapy for a family history of sudden death or ventricular arrhythmia and should receive a physical exam to look for signs of cardiac disease. Furthermore, a prompt cardiac evaluation should be performed in patients who develop symptoms suggesting cardiac disease (eg, exertional chest pain, unexplained syncope) during atomoxetine therapy (Prod Info STRATTERA(R) oral capsules, 2008).

3.3.1.A.9 Syncope

a) Incidence: pediatric, 0.8% (Prod Info STRATTERA(R) oral capsules, 2008)

b) Syncope has been reported in 0.8% of atomoxetine-treated child and adolescent patients (n=46 of 5596) and there have been spontaneous postmarketing reports of syncope; however, syncope has not been reported with atomoxetine use in child and adolescent patients with attention-deficit hyperactivity disorder (ADHD) during short-term, placebo-controlled studies. Patients with any condition that may predispose them to hypotension should use atomoxetine with caution (Prod Info STRATTERA(R) oral capsules, 2008).

c) Reports of syncope were significantly higher in patients classified as poor metabolizers of CYP2D6 drugs than those classified as extensive metabolizers (3% and 1%, respectively) (Prod Info STRATTERA(R) oral capsules, 2008).

3.3.1.A.10 Tachycardia

a) Incidence: adults, 1.5%; pediatrics, 0.3% (Prod Info STRATTERA(R) oral capsules, 2008)

b) In clinical studies, tachycardia has been reported in atomoxetine-treated patients with attention-deficit hyperactivity disorder (ADHD). Use caution in patients receiving atomoxetine who have preexisting hypertension, tachycardia, or cardiovascular or cerebrovascular disease due to the risk of heart rate and blood pressure elevation in these patients. Pulse and blood pressure monitoring is recommended at baseline, following dose increases, and periodically during therapy (Prod Info STRATTERA(R) oral capsules, 2008). In addition, greater increases in heart rate and systolic pressure have been reported among cytochrome P450 2D6 poor metabolizers (Michelson et al, 2001a; Chouinard et al, 1985a).

c) In placebo-controlled trials in adult patients with attention-deficit hyperactivity disorder (ADHD),

tachycardia was reported more frequently in patients taking atomoxetine (1.5%; n=8 of 540) than placebo (0.5%; n=2 of 402). Compared to placebo, mean increases in heart rate of 5 beats/minute were reported for atomoxetine-treated patients (Prod Info STRATTERA(R) oral capsules, 2008).
d) In pediatric placebo-controlled trials, tachycardia was reported in 0.3% of atomoxetine-treated patients (n=5 of 1597) compared to 0% of placebo-treated patients (n=0 of 934). At the final study visit, heart rates greater than or equal to 110 beats/minute with increases of at least 25 beats/minute were reported for 2.5% of patients taking atomoxetine (n=36 of 1434) compared to 0.2% receiving placebo (n=2 of 850). Heart rates of at least 110 beats/minute with increases of at least 25 beats/minute were reported on more than one occasion in 1.1% (n=15 of 1417) of pediatric patients treated with atomoxetine during the study. Additionally, patients identified as extensive metabolizers had reported increases in mean heart rate of 5 beats/minute while poor metabolizers had increases of 9.4 beats/minute (Prod Info STRATTERA(R) oral capsules, 2008).

3.3.2 Dermatologic Effects

3.3.2.A Atomoxetine Hydrochloride

Rash

Urticaria

3.3.2.A.1 Rash
a) Incidence: adults, 2%; pediatrics, 2% (Prod Info STRATTERA(R) oral capsules, 2008)
b) Allergic reactions, including rash, have been reported with atomoxetine use (Prod Info STRATTERA (R) oral capsules, 2008).
c) In acute (up to 25 weeks), placebo-controlled trials in adult patients with attention-deficit hyperactivity disorder (ADHD), rash was reported in 2% of patients who received atomoxetine (n=540) compared to 1% of patients who received placebo (n=402) (Prod Info STRATTERA(R) oral capsules, 2008).
d) In acute (up to 18 weeks), placebo-controlled trials in pediatric patients with attention-deficit hyperactivity disorder (ADHD), rash was reported in 2% of atomoxetine-treated patients (n=1597) compared to 1% of placebo-treated patients (n=934) (Prod Info STRATTERA(R) oral capsules, 2008).

3.3.2.A.2 Urticaria
a) Allergic reactions, including urticaria, have been reported with atomoxetine use (Prod Info STRATTERA(R) oral capsules, 2008).

3.3.3 Endocrine/Metabolic Effects

3.3.3.A Atomoxetine Hydrochloride

Abnormal height in relation to growth / age standard

Hyponatremia

Weight loss

3.3.3.A.1 Abnormal height in relation to growth / age standard
a) The weight and height gains in atomoxetine-treated pediatric patients lags behind the normative population for the first 9 to 12 months of therapy and rebounds at about 3 years of treatment regardless of pubertal status at the time of treatment initiation. After approximately 12 months of atomoxetine therapy, gain in height stabilizes and at 3 years pediatric patients gain 19.4 cm on average, which is 0.4 cm less than predicted by baseline data. Poor metabolizers of CYP2D6 treated for at least 2 years gained an average of 1.1 cm less than predicted and extensive metabolizers of CYP2D6 gained an average of 0.4 cm less than predicted. In short-term controlled 9 week studies atomoxetine-treated patients gained an average of 0.9 cm compared to 1.1 cm in placebo (Prod Info STRATTERA(R) oral capsules, 2008).

3.3.3.A.2 Hyponatremia
a) A 32-year-old man receiving atomoxetine hydrochloride (HCl) for attention deficit hyperactivity disorder (ADHD) experienced hyponatremia which resolved upon drug withdrawal. After taking atomoxetine 60 milligrams daily for 2 months with good results, the patient presented to his outpatient psychiatrist with a few week history of nausea and fatigue. He reported no psychiatric symptoms or

other medical problems and was not taking any other medications. A laboratory workup revealed a low serum sodium level of 122 millimole/liter (mmol/L), which was decreased from a sodium level of 141 mmol/L obtained 1-year previously. All other laboratory results were reported as normal. Hyponatremia due to medication-induced syndrome of inappropriate antidiuretic hormone (SIADH) was suspected by the patient's primary care physician who did not find any other cause for the low sodium level; therefore, atomoxetine HCl was discontinued. Sodium levels obtained 1 and 2 weeks later were 130 mmol/L and 140 mmol/L, respectively. Two weeks after discontinuing atomoxetine HCl, the patient initiated amphetamine/dextroamphetamine (Adderall XR(R)) for the treatment of his ADHD. Consider monitoring serum sodium and other signs and symptoms of hyponatremia and SIADH in patients receiving atomoxetine HCl (Singh, 2007).

3.3.3.A.3 Weight loss

a) Incidence: pediatrics, 7.1% to 29.1% (Prod Info STRATTERA(R) oral capsules, 2008)
b) The weight and height gains in atomoxetine-treated pediatric patients lags behind the normative population for the first 9 to 12 months of therapy and rebounds at about 3 years (17.9 kg on average, 0.5 kg more than predicted from baseline data) of treatment regardless of pubertal status at the time of treatment initiation. In short-term controlled 9 week studies atomoxetine-treated patients lost an average of 0.4 kg compared to a gain of 1.5 kg in the placebo group. Poor metabolizers of CYP2D6 treated for at least 2 years gained an average 2.4 kg less than predicted and extensive metabolizers of CYP2D6 gained an average of 0.2 kg less than predicted. Additionally, in a fixed-dose controlled trial patients lost at least 3.5% of their body weight in the atomoxetine-treated patients in 7.1% (0.5 mg/kg day dose), 19.3% (1.2 mg/kg day dose), and 29.1% (1.8 mg/kg day dose) of patients compared with 1.3% in the placebo group (Prod Info STRATTERA(R) oral capsules, 2008).
c) Weight loss and anorexia have been reported more often with atomoxetine than placebo in limited controlled studies (Michelson et al, 2001a; Zerbe et al, 1985a; Spencer et al, 1998a). Both effects are dose-related, and were also observed in open studies. The magnitude of weight loss was similar to that observed during methylphenidate therapy in ADHD patients in an unpublished study (Michelson et al, 2001a).

3.3.4 Gastrointestinal Effects

3.3.4.A Atomoxetine Hydrochloride

Abdominal pain

Constipation

Decrease in appetite

Indigestion

Loss of appetite

Nausea

Sialolithiasis

Vomiting

Xerostomia

3.3.4.A.1 Abdominal pain

a) Incidence: adults, 7%; pediatrics, 17% to 18% (Prod Info STRATTERA(R) oral capsules, 2008)
b) In acute (up to 25 weeks), placebo-controlled trials in adult patients with attention-deficit hyperactivity disorder (ADHD), abdominal pain was reported in 7% of patients who received atomoxetine (n=540) compared to 5% of patients who received placebo (n=402) (Prod Info STRATTERA(R) oral capsules, 2008).
c) In acute (up to 18 weeks), placebo-controlled trials in pediatric patients with attention-deficit hyperactivity disorder (ADHD), abdominal pain was reported in 18% of atomoxetine-treated patients (n=1597) compared to 10% of placebo-treated patients (n=934) (Prod Info STRATTERA(R) oral capsules, 2008).
d) In acute (up to 18 weeks), placebo-controlled trials in pediatric patients with attention-deficit

hyperactivity disorder (ADHD), abdominal pain was reported in 18% and 17% of patients treated with atomoxetine once (n=882) and twice (n=715) daily, respectively, compared to 7% and 13% of patients treated with placebo once (n=500) and twice (n=434) daily, respectively (Prod Info STRATTERA(R) oral capsules, 2008).

3.3.4.A.2 Constipation

a) Incidence: adults, 9%; pediatric, 1% to 2%(Prod Info STRATTERA(R) oral capsules, 2008)

b) In acute (up to 25 weeks), placebo-controlled trials in adult patients with attention-deficit hyperactivity disorder (ADHD), constipation was reported in 9% of patients who received atomoxetine (n=540) compared to 3% of patients who received placebo (n=402) (Prod Info STRATTERA(R) oral capsules, 2008).

c) In acute (up to 18 weeks), placebo-controlled trials in pediatric patients with attention-deficit hyperactivity disorder (ADHD), constipation was reported in 1% and 2% of patients treated with atomoxetine once (n=882) and twice (n=715) daily, respectively, compared to 0% and 1% of patients treated with placebo once (n=500) and twice (n=434) daily, respectively. Reports of constipation were significantly higher in patients classified as poor metabolizers of CYP2D6 drugs than those classified as extensive metabolizers (7% and 4%, respectively) (Prod Info STRATTERA(R) oral capsules, 2008).

3.3.4.A.3 Decrease in appetite

a) Incidence: adult, 11%; pediatrics, 16% (Prod Info STRATTERA(R) oral capsules, 2008),

b) In acute (up to 25 weeks), placebo-controlled trials in adult patients with attention-deficit hyperactivity disorder (ADHD), decreased appetite was reported in 11% of patients who received atomoxetine (n=540) compared to 2% of patients who received placebo (n=402) (Prod Info STRATTERA(R) oral capsules, 2008).

c) In acute (up to 18 weeks), placebo-controlled trials in pediatric patients with attention-deficit hyperactivity disorder (ADHD), anorexia was reported in 16% of atomoxetine-treated patients (n=1597) compared to 4% of placebo-treated patients (n=934) (Prod Info STRATTERA(R) oral capsules, 2008).

3.3.4.A.4 Indigestion

a) Incidence: adults, 4% (Prod Info STRATTERA(R) oral capsules, 2008)

b) In acute (up to 25 weeks), placebo-controlled trials in adult patients with attention-deficit hyperactivity disorder (ADHD), dyspepsia was reported in 4% of patients who received atomoxetine (n=540) compared to 2% of patients who received placebo (n=402) (Prod Info STRATTERA(R) oral capsules, 2008).

3.3.4.A.5 Loss of appetite

a) Incidence: pediatrics, 3% (Prod Info STRATTERA(R) oral capsules, 2008),

b) In acute (up to 18 weeks), placebo-controlled trials in pediatric patients with attention-deficit hyperactivity disorder (ADHD), anorexia was reported in 3% of atomoxetine-treated patients (n=1597) compared to 1% of placebo-treated patients (n=934) (Prod Info STRATTERA(R) oral capsules, 2008).

3.3.4.A.6 Nausea

a) Incidence: adults, 21%; pediatrics, 7% to 13% (Prod Info STRATTERA(R) oral capsules, 2008)

b) In acute (up to 25 weeks), placebo-controlled trials in adult patients with attention-deficit hyperactivity disorder (ADHD), nausea was reported in 21% of patients who received atomoxetine (n=540) compared to 5% of patients who received placebo (n=402) (Prod Info STRATTERA(R) oral capsules, 2008).

c) In acute (up to 18 weeks), placebo-controlled trials in pediatric patients with attention-deficit hyperactivity disorder (ADHD), nausea was reported in 10% of atomoxetine-treated patients (n=1597) compared to 5% of placebo-treated patients (n=934) (Prod Info STRATTERA(R) oral capsules, 2008).

d) In acute (up to 18 weeks), placebo-controlled trials in pediatric patients with attention-deficit hyperactivity disorder (ADHD), nausea was reported in 13% and 7% of patients treated with atomoxetine once (n=882) and twice (n=715) daily, respectively, compared to 4% and 6% of patients treated with placebo once (n=500) and twice (n=434) daily, respectively (Prod Info STRATTERA(R) oral capsules, 2008).

3.3.4.A.7 Sialolithiasis

a) Sialolithiasis developed and then recurred each time atomoxetine was restarted in a 36-year-old male. Initially, he was on dextroamphetamine spansules 20 mg/day for 16 weeks for attention deficit hyperactivity disorder prior to adding atomoxetine 18 mg/day. An extruded, left submandibular sialolith in the salivary gland developed within 10 days of starting atomoxetine, with a second recurrence 10 days later. Subsequently, atomoxetine was discontinued and the stone passed. Within 4 to 5 days of restarting atomoxetine 2 weeks later, the sialolithiasis recurred with 3 subsequent episodes each time atomoxetine was discontinued and restarted. The time to onset was quicker for each recurrence. The stone was passed by massaging the gland. Pain and swelling of the gland was evident and at no time did he experience dry mouth. At a 6-month follow-up after permanently discontinuing atomoxetine, no further stones developed. Significant medical history included 3 events of sialolithiasis, all occurring within a few months of each other and 18 months prior to starting atomoxetine. The first of these 3

episodes was identified by computed tomography scan, and each time the stone was passed by massaging the gland (Jerome et al, 2007).

3.3.4.A.8 Vomiting

a) Incidence: adults, 3%; pediatrics, 11%(Prod Info STRATTERA(R) oral capsules, 2008)
b) In acute (up to 25 weeks), placebo-controlled trials in adult patients with attention-deficit hyperactivity disorder (ADHD), vomiting was reported in 3% of patients who received atomoxetine (n=540) compared to 2% of patients who received placebo (n=402) (Prod Info STRATTERA(R) oral capsules, 2008).
c) In acute (up to 18 weeks), placebo-controlled trials in pediatric patients with attention-deficit hyperactivity disorder (ADHD), vomiting was reported in 11% of atomoxetine-treated patients (n=1597) compared to 6% of placebo-treated patients (n=934) (Prod Info STRATTERA(R) oral capsules, 2008).
d) In acute (up to 18 weeks), placebo-controlled trials in pediatric patients with attention-deficit hyperactivity disorder (ADHD), vomiting was reported in 11% of patients treated with either atomoxetine once (n=882) or twice (n=715) daily compared to 4% and 8% of patients treated with placebo once (n=500) and twice (n=434) daily, respectively (Prod Info STRATTERA(R) oral capsules, 2008).

3.3.4.A.9 Xerostomia

a) Incidence: adults, 21% (Prod Info STRATTERA(R) oral capsules, 2008)
b) In acute (up to 25 weeks), placebo-controlled trials in adult patients with attention-deficit hyperactivity disorder (ADHD), dry mouth was reported in 21% of patients who received atomoxetine (n=540) compared to 7% of patients who received placebo (n=402) (Prod Info STRATTERA(R) oral capsules, 2008).

3.3.6 Hepatic Effects

3.3.6.A Atomoxetine Hydrochloride

3.3.6.A.1 Injury of liver (Severe)

a) Incidence: rare (Prod Info STRATTERA(R) oral capsules, 2008)
b) During postmarketing surveillance severe liver injury has occurred in rare instances including hepatic enzymes elevated by up to 40 times the upper limit of normal (ULN) and jaundice with a bilirubin up to 12 times ULN recurring upon rechallenge and recovering upon discontinuation of atomoxetine. Severe liver injury may occur several months after therapy initiation and may worsen for several weeks upon discontinuation with the potential to progress to acute liver failure and death or the need for a liver transplant. In patients with laboratory evidence of liver injury or jaundice, atomoxetine should be discontinued and not reinstituted. Additionally, at the first sign or symptom of liver dysfunction (eg, pruritus, dark urine, jaundice, right upper quadrant tenderness, unexplained flu-like symptoms), liver enzyme levels should be obtained (Prod Info STRATTERA(R) oral capsules, 2008).
c) Liver injury has been reported in clinical trials and postmarketing reports in patients with attention-deficit hyperactivity disorder (ADHD) treated with atomoxetine. Of 7961 pediatric or adult patients with ADHD who received treatment with atomoxetine in 45 clinical trials, 41 cases of liver injury were possibly related to atomoxetine therapy and included mild to moderate increases in total bilirubin consistent with Gilbert's syndrome (n=18) and elevated ALT, AST, alkaline phosphatase (ALP) and CPK levels. When laboratory data from 14 pediatric and 2 adult placebo-controlled trials were reviewed, no significant differences in treatment-related elevations in AST, ALT, ALP, CPK, or total bilirubin levels were found between patients who received atomoxetine and placebo. Additionally, out of 351 postmarketing case reports (calculated reported liver injury rate of less than 0.01%), 133 and 3 cases, respectively, were possibly and probably related to atomoxetine therapy. All 3 probable cases were reversible: (Bangs et al, 2008).

1) A male adolescent patient developed lethargy and abdominal pain after receiving atomoxetine 40 mg twice daily for 3 to 4 months. Atomoxetine and sertraline were discontinued and liver enzyme elevations were noted the following day (ALT, 33 x ULN; AST, 15 x ULN; total bilirubin, 1.5 x ULN). Liver enzymes returned to normal within 2 months; however, upon rechallenge with atomoxetine 40 mg/day, liver enzymes and bilirubin were elevated within approximately 5 weeks of therapy and a liver biopsy revealed hepatitis with focal hepatocellular necrosis. A subsequent liver biopsy 2 months later revealed hepatitis with cholestasis, primarily lymphocytic inflammatory infiltrate. Liver enzymes returned to normal within 4.5 months (Bangs et al, 2008).
2) The second patient was a female adolescent who was hospitalized with jaundice, abdominal pain, diarrhea, vomiting, conjunctival icterus, and right upper quadrant tenderness after receiving atomoxetine 40 mg/day for almost one year. On admission, liver enzyme elevations were present (ALT, 65 x ULN; AST, 67 x ULN; total bilirubin, 9.1 x ULN). Liver biopsy showed moderate, mixed portal inflammatory infiltrate (mainly lymphoid with some eosinophils) and normal interlobular ducts and central veins. After discontinuing atomoxetine, liver enzymes returned to normal and symptoms resolved over the next 4 weeks (Bangs et al, 2008).
3) The third patient was a female child who was receiving atomoxetine 25 mg/day (1.03 mg/kg/day) presented with a 2-day history of emesis after 37 days of therapy, and was admitted to the hospital. The patient had elevated liver enzymes (ALT, 80 x ULN; AST, 115 x ULN; total

bilirubin, 10.8 x ULN; alkaline phosphatase, 3.5 x ULN), and symptoms of jaundice and hepatomegaly. A liver biopsy demonstrated mixed portal inflammation with lymphocytes, neutrophils and eosinophils in the lobule with moderate piecemeal necrosis. Improvement of signs and symptoms was observed and the patient was discharged from the hospital after 13 days (Bangs et al, 2008).

3.3.7 Immunologic Effects

3.3.7.A Atomoxetine Hydrochloride

3.3.7.A.1 Immune hypersensitivity reaction

a) Allergic reactions, including angioneurotic edema, urticaria, and rash, have been reported with atomoxetine use (Prod Info STRATTERA(R) oral capsules, 2008).

3.3.9 Neurologic Effects

3.3.9.A Atomoxetine Hydrochloride

Akathisia

Cerebrovascular accident

Dizziness

Dyskinesia

Headache

Insomnia

Seizure

Sinus headache

Somnolence

Tic

3.3.9.A.1 Akathisia

a) Anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia, hypomania, and mania have been reported with atomoxetine use and may be precursors to emerging suicidality. It is recommended that pediatric patients receiving atomoxetine be monitored for clinical worsening, suicidal ideation, suicidal behavior, irritability, agitation, or unusual changes in behavior, particularly during the first few months of therapy or following a dosage adjustment. Monitoring should be daily by family members or caregivers and by healthcare providers weekly for the first 4 weeks, then every other week for 4 weeks, then every 12 weeks and as clinically indicated thereafter. Consider changing the therapeutic regimen and possibly discontinuing atomoxetine therapy if patients experience suicidality or precursors to emerging suicidality, particularly if symptoms are severe or present with an abrupt onset and were not part of original presenting symptoms (Prod Info STRATTERA(R) oral capsules, 2008).

3.3.9.A.2 Cerebrovascular accident

a) Stroke has occurred in adult patients receiving atomoxetine at usual doses. Consider not using atomoxetine in adult patients with clinically significant cardiac abnormalities (eg, coronary artery disease, serious structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, other serious cardiac problems) (Prod Info STRATTERA(R) oral capsules, 2008).

3.3.9.A.3 Dizziness

a) Incidence: adult, 6%; pediatric, 5% (Prod Info STRATTERA(R) oral capsules, 2008)
b) In acute (up to 25 weeks), placebo-controlled trials in adult patients with attention-deficit hyperactivity disorder (ADHD), dizziness was reported in 6% of patients who received atomoxetine (n=540) compared to 4% of patients who received placebo (n=402) (Prod Info STRATTERA(R) oral

capsules, 2008).
c) In acute (up to 18 weeks), placebo-controlled trials in pediatric patients with attention-deficit hyperactivity disorder (ADHD), dizziness was reported in 5% of atomoxetine-treated patients (n=1597) compared to 2% of placebo-treated patients (n=934) (Prod Info STRATTERA(R) oral capsules, 2008).

3.3.9.A.4 Dyskinesia
a) Dyskinesias with other neurological abnormalities developed in 2 pediatric patients with attention deficit hyperactivity disorder after starting atomoxetine. Both patients required hospitalization due to severity of tremors and psychiatric disturbances. The events resolved after discontinuation of atomoxetine in 1 patient and atomoxetine and venlafaxine in the other patient (Bond et al, 2007).
1) A 9-year-old boy on amphetamine/dextroamphetamine extended-release and clonidine for attention deficit hyperactivity disorder developed insomnia and involuntary hand and mouth movements within 14 days of starting atomoxetine 25 mg every day. He initially developed anorexia a few days after starting atomoxetine with subsequent signs of disturbed sleep, compulsive lip licking, seeing things ("bugs") that caused fear. All signs progressively worsened. Vital signs were a temperature of 36.9 degrees Celsius, heart rate of 89 beats per minute, respiration rate of 24 breaths/minute, and blood pressure of 145/93 mmHg, which was slightly above his baseline diastolic blood pressure. He was alert and oriented to person and place. Neurologic examination revealed involuntary, continuous twitching movements of his perioral area and writhing fingers and restless legs, which moved continuously as he lay on the bed. Intravenous diphenhydramine 50 mg failed to provide any improvement in symptoms. He was admitted for observation. Amphetamine/dextroamphetamine and atomoxetine were discontinued. Although he did not sleep that night, the abnormal movements resolved the next day. At a 5-month follow-up visit, there was no evidence of movement disorder while on amphetamine/dextroamphetamine, clonidine, and sertraline (Bond et al, 2007).
2) An 18-year-old female with attention deficit hyperactivity disorder and generalized anxiety disorder with panic attacks on venlafaxine developed severe tremors and abnormal facial movements after starting atomoxetine. Approximately 2 months prior to the event she started paroxetine, which was subsequently replaced with venlafaxine 37.5 mg daily. Atomoxetine 18 mg every day was started about 3 weeks prior to the event. The dose of venlafaxine and atomoxetine were gradually increased. Approximately 5 days after attaining maximum doses of venlafaxine 225 mg every day and atomoxetine 40 mg every day, she developed fine hand tremors present only at rest. The dose of venlafaxine was reduced to 150 mg every day and atomoxetine was discontinued. Within 3 days the following evolved: the tremors worsened in her upper extremities and progressed to her lower extremities (intentional movements did not improve the tremors); she developed abnormal facial movements with muscular twitching and uncontrollable movements of her lips and tongue, which rendered her unable to vocalize; and the tremors progressively worsened rendering her unable to ambulate. Vital signs were a temperature of 36.5 degrees Celsius, heart rate of 110 beats per minute, respiration rate of 18 breaths/minute, and blood pressure of 108/67 mmHg. Neurologic examination revealed intact cranial nerves II-XII, no nystagmus, intact sensations, and slightly increased deep tendon reflexes (DTR) of the lower and normal DTR of the upper extremities. She was admitted and administered diphenhydramine 50 mg intramuscularly and intravenous (IV) normal saline. The tremors improved slightly. An additional diphenhydramine 12.5 mg IV was of no benefit. She was discharged 24 hours later with moderate improvement in tremors. Complete resolution of the event was reported at follow-up day 7, while off venlafaxine and atomoxetine (Bond et al, 2007).

3.3.9.A.5 Headache
a) Incidence: pediatrics, 19% (Prod Info STRATTERA(R) oral capsules, 2008)
b) In acute (up to 18 weeks), placebo-controlled trials in pediatric patients with attention-deficit hyperactivity disorder (ADHD), headache was reported in 19% of atomoxetine-treated patients (n=1597) compared to 15% of placebo-treated patients (n=934) (Prod Info STRATTERA(R) oral capsules, 2008).

3.3.9.A.6 Insomnia
a) Incidence: adults, 16%; pediatrics, at least 2%; (Prod Info STRATTERA(R) oral capsules, 2008)
b) Insomnia has been commonly reported in adult patients with attention-deficit hyperactivity disorder (ADHD) who were receiving atomoxetine in clinical trials. However, anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia, hypomania, and mania may be precursors to emerging suicidality. It is recommended that pediatric patients receiving atomoxetine be monitored for clinical worsening, suicidal ideation, suicidal behavior, irritability, agitation, or unusual changes in behavior, especially during the first few months of therapy or following a dosage adjustment. Monitoring should be daily by family members or caregivers and by healthcare providers weekly for the first 4 weeks, then every other week for 4 weeks, then every 12 weeks and as clinically indicated thereafter. Consider changing the therapeutic regimen and possibly discontinuing atomoxetine therapy if patients experience suicidality or precursors to emerging suicidality, particularly if symptoms are severe or with an abrupt onset and were not part of original presenting symptoms (Prod Info STRATTERA(R) oral capsules, 2008).
c) In acute (up to 25 weeks), placebo-controlled trials in adult patients with attention-deficit

hyperactivity disorder (ADHD), insomnia was reported in 15% of patients who received atomoxetine (n=540) compared to 7% of patients who received placebo (n=402) (Prod Info STRATTERA(R) oral capsules, 2008).
d) In acute (up to 18 weeks), placebo-controlled trials in pediatric patients with attention-deficit hyperactivity disorder (ADHD), insomnia was reported in at least 2% of atomoxetine-treated patients (n=1597) compared to 2% or less of placebo-treated patients (n=934). Reports of insomnia were significantly higher in patients classified as poor metabolizers of CYP2D6 drugs than those classified as extensive metabolizers (15% and 10%, respectively) (Prod Info STRATTERA(R) oral capsules, 2008).

3.3.9.A.7 Seizure
a) Incidence: adults, 0.1%; pediatrics, 0.2% (Prod Info STRATTERA(R) oral capsules, 2008)
b) Clinical studies did not systematically evaluate adult or pediatric patients with seizure disorders. However, in clinical development program, seizures were reported in children (average age 10 years, range 6 to 16 years) with an incidence of 0.2% (12/5073). In clinical trials among poor metabolizers of CYP2D6 the incidence of seizure in pediatrics was 0.3% (1/293) and was 0.2% (11/4741) for extensive metabolizers of CYP2D6 (Prod Info STRATTERA(R) oral capsules, 2008).
c) In adults, the incidence of seizures was 0.1% (1/748) and was 0.1% (1/705) of adult extensive metabolizers of CYP2D6. There have also been postmarketing reports of seizures, which have included patients both with and without a history of seizure disorders or identified risk factors for developing seizures (Prod Info STRATTERA(R) oral capsules, 2008).

3.3.9.A.8 Sinus headache
a) Incidence: adults, 3% (Prod Info STRATTERA(R) oral capsules, 2008)
b) In acute (up to 25 weeks), placebo-controlled trials in adult patients with attention-deficit hyperactivity disorder (ADHD), sinus headache was reported in 3% of patients who received atomoxetine (n=540) compared to 1% of patients who received placebo (n=402) (Prod Info STRATTERA(R) oral capsules, 2008).

3.3.9.A.9 Somnolence
a) Incidence: adult, 4%; pediatrics, 11% (Prod Info STRATTERA(R) oral capsules, 2008)
b) In acute (up to 25 weeks), placebo-controlled trials in adult patients with attention-deficit hyperactivity disorder (ADHD), somnolence was reported in 4% of patients who received atomoxetine (n=540) compared to 3% of patients who received placebo (n=402) (Prod Info STRATTERA(R) oral capsules, 2008).
c) In acute (up to 18 weeks), placebo-controlled trials in pediatric patients with attention-deficit hyperactivity disorder (ADHD), somnolence was reported in 11% of atomoxetine-treated patients (n=1597) compared to 4% of placebo-treated patients (n=934) (Prod Info STRATTERA(R) oral capsules, 2008).

3.3.9.A.10 Tic
a) Tics reoccurred or were exacerbated in 4 pediatric patients within approximately 5 to 30 days of starting atomoxetine for attention deficit hyperactivity disorder (ADHD). Three of the 4 patients had experienced tics on stimulants such as amphetamine/dextroamphetamine and 1 patient had a comorbid condition of Tourette's syndrome. Significant improvement or resolution resulted when atomoxetine was discontinued. Two of the patients subsequently tolerated guanfacine for ADHD (Lee et al, 2004).
1) A 9-year-old boy with combined type attention deficit hyperactivity disorder developed motor tics with the stimulants methylphenidate, amphetamine/dextroamphetamine, and dextroamphetamine. The tics resolved after discontinuation of the stimulants. After a 6-month washout, atomoxetine was started at 10 mg every day for 7 days then 20 mg every day. Within a few days of starting 20 mg, he developed motor tics described as rapid, severe eye blinking. This event was similar to the event with previous stimulants. Vocal tics were absent. Within 1 to 2 days of stopping atomoxetine, the tics resolved. There was no recurrence of tics after 1 year on guanfacine (Lee et al, 2004).
2) A 14-year-old boy with attention deficit hyperactivity disorder developed eye-blinking motor tic on methylphenidate. Methylphenidate was discontinued and atomoxetine 20 mg every day was started. The eye blinking worsened, and he subsequently developed a vocal tic of severe episodes of throat clearing. The vocal tics stopped and the eye-blinking improved following discontinuation of atomoxetine. Mild eye blinking persisted with no other signs of tics while on guanfacine (Lee et al, 2004).
3) A 9-year-old boy with attention deficit hyperactivity disorder and chronic tic disorders experienced tic exacerbations on stimulants. Prior to starting atomoxetine, facial tics were the sole symptoms. He started atomoxetine 18 mg every day and within 30 days developed dramatic vocal tics and increased motor tics. Associated adverse effects were irritability, anxiety, dysphoria, compulsive finger picking, and obsessional ruminations. The event improved after discontinuation of atomoxetine (Lee et al, 2004).
4) A 15-year-old boy with attention deficit hyperactivity disorder and Tourette's syndrome experienced tic exacerbations on stimulants. Significant increase in tics, impulsivity, and fatigue occurred within 5 days of starting atomoxetine 10 mg every day. The event improved after discontinuation of atomoxetine(Lee et al, 2004).

3.3.12 Psychiatric Effects

3.3.12.A Atomoxetine Hydrochloride

Aggressive behavior

Agitation

Anxiety

Hostile behavior

Hypomania

Impulsive character

Irritability

Mania

Panic attack

Psychotic disorder

Suicidal thoughts

3.3.12.A.1 Aggressive behavior

a) Anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia, hypomania, and mania have been reported with atomoxetine use and may be precursors to emerging suicidality. It is recommended that pediatric patients receiving atomoxetine be monitored for clinical worsening, suicidal ideation, suicidal behavior, irritability, agitation, or unusual changes in behavior, particularly during the first few months of therapy or following a dosage adjustment. Monitoring should be daily by family members or caregivers and by healthcare providers weekly for the first 4 weeks, then every other week for 4 weeks, then every 12 weeks and as clinically indicated thereafter. Consider changing the therapeutic regimen and possibly discontinuing atomoxetine therapy if patients experience suicidality or precursors to emerging suicidality, particularly if symptoms are severe or present with an abrupt onset and were not part of original presenting symptoms (Prod Info STRATTERA(R) oral capsules, 2008).

b) Although not statistically significant, short-term placebo-controlled clinical trials of children and adolescents with attention-deficit hyperactivity disorder reported observations of aggressive behavior or hostility more frequently in atomoxetine-treated patients (1.6%; n=21 of 1308) than placebo-treated patients (1.1%; n=9 of 806) (overall risk ratio of 1.33; 95% confidence interval, 0.67-2.64; p=nonsignificant). Monitor patients for the appearance or worsening of aggressive behavior or hostility (Prod Info STRATTERA(R) oral capsules, 2008).

3.3.12.A.2 Agitation

a) An 11-year-old boy on atomoxetine for attention deficit hyperactivity disorder developed acute agitation and suicidal ideation within 17 days of starting atomoxetine. He also had anxiety, obsessive compulsive disorder and oppositional defiant behaviors. Atomoxetine 25 mg was administered every day for 14 days, with the medication scheduled to increase to 60 mg every day thereafter. He initially showed a marked reduction in anxiety and obsessive symptoms; however, the family noted increased emotional liability, cycling of his mood and agitation, and that his handwriting had changed from neat script to messy and 'tiny.' After the dose increase as planned on day 14, the boy developed increased agitation, greater mood swings with more rapid cycling, increased crying, and he threatened suicide. The family discontinued the medication, and the patient’s agitation calmed after a few days and he was described as back to his normal self (Paxton & Cranswick, 2008).

b) Anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia, hypomania, and mania have been reported with atomoxetine use and may be precursors to emerging suicidality. It is recommended that pediatric patients receiving atomoxetine be monitored for clinical worsening, suicidal ideation, suicidal behavior, irritability, agitation, or unusual changes in behavior, particularly during the first few months of therapy or following a dosage adjustment. Monitoring should

be daily by family members or caregivers and by healthcare providers weekly for the first 4 weeks, then every other week for 4 weeks, then every 12 weeks and as clinically indicated thereafter. Consider changing the therapeutic regimen and possibly discontinuing atomoxetine therapy if patients experience suicidality or precursors to emerging suicidality, particularly if symptoms are severe or present with an abrupt onset and were not part of original presenting symptoms (Prod Info STRATTERA(R) oral capsules, 2008).

3.3.12.A.3 Anxiety

a) Anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia, hypomania, and mania have been reported with atomoxetine use and may be precursors to emerging suicidality. It is recommended that pediatric patients receiving atomoxetine be monitored for clinical worsening, suicidal ideation, suicidal behavior, irritability, agitation, or unusual changes in behavior, particularly during the first few months of therapy or following a dosage adjustment. Monitoring should be daily by family members or caregivers and by healthcare providers weekly for the first 4 weeks, then every other week for 4 weeks, then every 12 weeks and as clinically indicated thereafter. Consider changing the therapeutic regimen and possibly discontinuing atomoxetine therapy if patients experience suicidality or precursors to emerging suicidality, particularly if symptoms are severe or present with an abrupt onset and were not part of original presenting symptoms (Prod Info STRATTERA(R) oral capsules, 2008).

3.3.12.A.4 Hostile behavior

a) Anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia, hypomania, and mania have been reported with atomoxetine use and may be precursors to emerging suicidality. It is recommended that pediatric patients receiving atomoxetine be monitored for clinical worsening, suicidal ideation, suicidal behavior, irritability, agitation, or unusual changes in behavior, particularly during the first few months of therapy or following a dosage adjustment. Monitoring should be daily by family members or caregivers and by healthcare providers weekly for the first 4 weeks, then every other week for 4 weeks, then every 12 weeks and as clinically indicated thereafter. Consider changing the therapeutic regimen and possibly discontinuing atomoxetine therapy if patients experience suicidality or precursors to emerging suicidality, particularly if symptoms are severe or present with an abrupt onset and were not part of original presenting symptoms (Prod Info STRATTERA(R) oral capsules, 2008).

b) Although not statistically significant, short-term placebo-controlled clinical trials of children and adolescents with attention-deficit hyperactivity disorder reported observations of aggressive behavior or hostility more frequently in atomoxetine-treated patients (1.6%; n=21 of 1308) than placebo-treated patients (1.1%; n=9 of 806) (overall risk ratio of 1.33; 95% confidence interval, 0.67-2.64; p=nonsignificant). Monitor patients for the appearance or worsening of aggressive behavior or hostility (Prod Info STRATTERA(R) oral capsules, 2008).

3.3.12.A.5 Hypomania

a) Anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia, hypomania, and mania have been reported with atomoxetine use and may be precursors to emerging suicidality. It is recommended that pediatric patients receiving atomoxetine be monitored for clinical worsening, suicidal ideation, suicidal behavior, irritability, agitation, or unusual changes in behavior, particularly during the first few months of therapy or following a dosage adjustment. Monitoring should be daily by family members or caregivers and by healthcare providers weekly for the first 4 weeks, then every other week for 4 weeks, then every 12 weeks and as clinically indicated thereafter. Consider changing the therapeutic regimen and possibly discontinuing atomoxetine therapy if patients experience suicidality or precursors to emerging suicidality, particularly if symptoms are severe or present with an abrupt onset and were not part of original presenting symptoms (Prod Info STRATTERA(R) oral capsules, 2008).

3.3.12.A.6 Impulsive character

a) Anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia, hypomania, and mania have been reported with atomoxetine use and may be precursors to emerging suicidality. It is recommended that pediatric patients receiving atomoxetine be monitored for clinical worsening, suicidal ideation, suicidal behavior, irritability, agitation, or unusual changes in behavior, particularly during the first few months of therapy or following a dosage adjustment. Monitoring should be daily by family members or caregivers and by healthcare providers weekly for the first 4 weeks, then every other week for 4 weeks, then every 12 weeks and as clinically indicated thereafter. Consider changing the therapeutic regimen and possibly discontinuing atomoxetine therapy if patients experience suicidality or precursors to emerging suicidality, particularly if symptoms are severe or present with an abrupt onset and were not part of original presenting symptoms (Prod Info STRATTERA(R) oral capsules, 2008).

3.3.12.A.7 Irritability

a) Anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia, hypomania, and mania have been reported with atomoxetine use and may be precursors to emerging

suicidality. It is recommended that pediatric patients receiving atomoxetine be monitored for clinical worsening, suicidal ideation, suicidal behavior, irritability, agitation, or unusual changes in behavior, particularly during the first few months of therapy or following a dosage adjustment. Monitoring should be daily by family members or caregivers and by healthcare providers weekly for the first 4 weeks, then every other week for 4 weeks, then every 12 weeks and as clinically indicated thereafter. Consider changing the therapeutic regimen and possibly discontinuing atomoxetine therapy if patients experience suicidality or precursors to emerging suicidality, particularly if symptoms are severe or present with an abrupt onset and were not part of original presenting symptoms (Prod Info STRATTERA(R) oral capsules, 2008).

3.3.12.A.8 Mania

a) In a review of 49 randomized, controlled pediatric ADHD clinical trials involving pscyhostimulant medications (atomoxetine hydrochloride, methylphenidate hydrochloride, modafinil and dextromethylphenidate hydrochloride), the rate of psychosis/mania events in pediatric subjects receiving active drug was 1.48 (95% CI, 0.74 to 2.65) per 100 person-years, with no comparable adverse events recorded in the placebo group. A request from the US Food and Drug Administration to manufacturers of marketed ADHD drugs for submission of postmarketing case reports of psychosis or mania events between 2000 and 2005, yielded a total of 865 reports (pediatrics and adults) in which signs and/or symptoms of psychoses or mania were reported. The majority of reports involved pediatric subjects, with almost half of the reports in children 10 years-old or younger, and approximately 90% of cases involving no prior history of similar psychiatric conditions. Visual and/or tactile sensations of insects, snakes, or worms were commonly reported. Positive rechallenge was reported for each of the psychostimulant medications (methylphenidate hydrochloride, atomoxetine hydrochloride, and mixed salts of a single entity amphetamine product) included in the analysis; and in many cases a strong temporal association was identified. The onset of psychiatric symptoms ranged from days to weeks, but in some cases it was months or years from the start of ADHD treatment and symptom onset (Mosholder et al, 2009).

b) Anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia, hypomania, and mania have been reported with atomoxetine use and may be precursors to emerging suicidality. It is recommended that pediatric patients receiving atomoxetine be monitored for clinical worsening, suicidal ideation, suicidal behavior, irritability, agitation, or unusual changes in behavior, particularly during the first few months of therapy or following a dosage adjustment. Monitoring should be daily by family members or caregivers and by healthcare providers weekly for the first 4 weeks, then every other week for 4 weeks, then every 12 weeks and as clinically indicated thereafter. Consider changing the therapeutic regimen and possibly discontinuing atomoxetine therapy if patients experience suicidality or precursors to emerging suicidality, particularly if symptoms are severe or present with an abrupt onset and were not part of original presenting symptoms (Prod Info STRATTERA(R) oral capsules, 2008).

c) A pooled analysis of multiple short-term, placebo-controlled studies in children and adolescents without a prior history of psychotic illness or mania demonstrated that about 0.2% of atomoxetine-treated patients (n=4 of 1939) exhibited treatment emergent psychotic or manic symptoms (eg, hallucinations, mania, delusional thinking) compared to 0% of placebo-treated patients (n=0 of 1056). Discontinuation of treatment should be considered if such symptoms develop during atomoxetine therapy (Prod Info STRATTERA(R) oral capsules, 2008).

d) Mania was described in one patient with major depression after more than a year of atomoxetine therapy (up to 80 mg daily). However, a causal relationship to the drug was not established; numerous other factors may have contributed to the manic episode (Steinberg & Chouinard, 1985).

3.3.12.A.9 Panic attack

a) Anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia, hypomania, and mania have been reported with atomoxetine use and may be precursors to emerging suicidality. It is recommended that pediatric patients receiving atomoxetine be monitored for clinical worsening, suicidal ideation, suicidal behavior, irritability, agitation, or unusual changes in behavior, particularly during the first few months of therapy or following a dosage adjustment. Monitoring should be daily by family members or caregivers and by healthcare providers weekly for the first 4 weeks, then every other week for 4 weeks, then every 12 weeks and as clinically indicated thereafter. Consider changing the therapeutic regimen and possibly discontinuing atomoxetine therapy if patients experience suicidality or precursors to emerging suicidality, particularly if symptoms are severe or present with an abrupt onset and were not part of original presenting symptoms (Prod Info STRATTERA(R) oral capsules, 2008).

3.3.12.A.10 Psychotic disorder

a) In a review of 49 randomized, controlled pediatric ADHD clinical trials involving pscyhostimulant medications (atomoxetine hydrochloride, methylphenidate hydrochloride, modafinil and dextromethylphenidate hydrochloride), the rate of psychosis/mania events in pediatric subjects receiving active drug was 1.48 (95% CI, 0.74 to 2.65) per 100 person-years, with no comparable adverse events recorded in the placebo group. A request from the US Food and Drug Administration to manufacturers of marketed ADHD drugs for submission of postmarketing case reports of psychosis or

mania events between 2000 and 2005, yielded a total of 865 reports (pediatrics and adults) in which signs and/or symptoms of psychoses or mania were reported. The majority of reports involved pediatric subjects, with almost half of the reports in children 10 years-old or younger, and approximately 90% of cases involving no prior history of similar psychiatric conditions. Visual and/or tactile sensations of insects, snakes, or worms were commonly reported. Positive rechallenge was reported for each of the psychostimulant medications (methylphenidate hydrochloride, atomoxetine hydrochloride, and mixed salts of a single entity amphetamine product) included in the analysis; and in many cases a strong temporal association was identified. The onset of psychiatric symptoms ranged from days to weeks, but in some cases it was months or years from the start of ADHD treatment and symptom onset (Mosholder et al, 2009).

3.3.12.A.11 Suicidal thoughts

a) Incidence: pediatrics, 0.4% (Prod Info STRATTERA(R) oral capsules, 2008)

b) An 11-year-old boy on atomoxetine for attention deficit hyperactivity disorder developed acute agitation and suicidal ideation within 17 days of starting atomoxetine. He also had anxiety, obsessive compulsive disorder and oppositional defiant behaviors. Atomoxetine 25 mg was administered every day for 14 days, with the medication scheduled to increase to 60 mg every day thereafter. He initially showed a marked reduction in anxiety and obsessive symptoms; however, the family noted increased emotional liability, cycling of his mood and agitation, and that his handwriting had changed from neat script to messy and 'tiny.' After the dose increase as planned on day 14, the boy developed increased agitation, greater mood swings with more rapid cycling, increased crying, and he threatened suicide. The family discontinued the medication, and the patient's agitation calmed after a few days and he was described as back to his normal self (Paxton & Cranswick, 2008).

c) An association has been reported between the use of atomoxetine and the development of suicidal ideation in children and adolescents. A pooled analysis of 12 short-term (6 to 18 weeks) clinical trials conducted in pediatric patients with attention-deficit hyperactivity disorder (11 trials) or enuresis (1 trial) demonstrated that 0.4% of patients (n=5 of 1357) who received atomoxetine therapy experienced suicidal ideation compared to no patients who received placebo (n=0 of 851). Although no suicides were reported in these trials (one suicide attempt), it is recommended that pediatric patients receiving atomoxetine be monitored for clinical worsening, suicidal ideation, suicidal behavior, irritability, agitation, or unusual changes in behavior, particularly during the first few months of therapy or following a dosage adjustment. Monitoring should be daily by family members or caregivers and by healthcare providers weekly for the first 4 weeks, then every other week for 4 weeks, then every 12 weeks and as clinically indicated thereafter. Consider changing the therapeutic regimen and possibly discontinuing atomoxetine therapy if patients experience suicidality or possible precursors to emerging suicidality (eg, anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia, hypomania, mania) (Prod Info STRATTERA(R) oral capsules, 2008).

3.3.13 Renal Effects

3.3.13.A Atomoxetine Hydrochloride

Delay when starting to pass urine

Urinary retention

3.3.13.A.1 Delay when starting to pass urine

a) Incidence: adults, 5.6% (Prod Info STRATTERA(R) oral capsules, 2008)

b) In controlled trials in adult patients with attention-deficit hyperactivity disorder (ADHD), urinary hesitation has been reported in 5.6% of atomoxetine-treated patients (n=30 of 540) compared to 0.5% of placebo-treated patients (n=4 of 402). Additionally, urinary hesitation and/or urinary retention were reported in 7% of patients who received atomoxetine compared to 1% of patients who received placebo (Prod Info STRATTERA(R) oral capsules, 2008).

3.3.13.A.2 Urinary retention

a) Incidence: adults, 1.7% (Prod Info STRATTERA(R) oral capsules, 2008)

b) In controlled trials in adult patients with attention-deficit hyperactivity disorder (ADHD), urinary retention has been reported in 1.7% of atomoxetine-treated patients (n=9 of 540) compared to 0% of placebo-treated patients (n=0 of 402). Additionally, urinary hesitation and/or urinary retention were reported in 7% of patients who received atomoxetine compared to 1% of patients who received placebo (Prod Info STRATTERA(R) oral capsules, 2008).

3.3.14 Reproductive Effects

3.3.14.A Atomoxetine Hydrochloride

Disorder of ejaculation

Dysmenorrhea

Erectile dysfunction

Priapism

Sexual dysfunction

3.3.14.A.1 Disorder of ejaculation

a) In acute (up to 25 weeks), placebo-controlled trials in adult patients with attention-deficit hyperactivity disorder (ADHD), ejaculation delayed and/or ejaculation disorder were reported in 3% of patients who received atomoxetine (n=326) compared to 1% of patients who received placebo (n=260) (Prod Info STRATTERA(R) oral capsules, 2008).

3.3.14.A.2 Dysmenorrhea

a) Incidence: adults, 6% (Prod Info STRATTERA(R) oral capsules, 2008)

b) In acute (up to 25 weeks), placebo-controlled trials in adult patients with attention-deficit hyperactivity disorder (ADHD), dysmenorrhea was reported in 6% of patients who received atomoxetine (n=214) compared to 2% of patients who received placebo (n=142) (Prod Info STRATTERA(R) oral capsules, 2008).

3.3.14.A.3 Erectile dysfunction

a) Incidence: adults, 9% (Prod Info STRATTERA(R) oral capsules, 2008)

b) In acute (up to 25 weeks), placebo-controlled trials in adult patients with attention-deficit hyperactivity disorder (ADHD), erectile dysfunction was reported in 9% of patients who received atomoxetine (n=326) compared to 1% of patients who received placebo (n=260) (Prod Info STRATTERA(R) oral capsules, 2008).

3.3.14.A.4 Priapism

a) Incidence: rare (Prod Info STRATTERA(R) oral capsules, 2008)

b) There have been rare postmarketing reports of priapism lasting more than 4 hours in pediatric and adult patients receiving atomoxetine. If priapism occurs during atomoxetine therapy, patients should seek prompt medical attention (Prod Info STRATTERA(R) oral capsules, 2008).

3.3.14.A.5 Sexual dysfunction

a) While changes in sexual desire, sexual performance, and sexual satisfaction have not been assessed in clinical trials, atomoxetine appears to impair sexual function in some male and female patients. Patients receiving atomoxetine should be routinely asked about sexual side effects (Prod Info STRATTERA(R) oral capsules, 2008).

3.3.16 Other

3.3.16.A Atomoxetine Hydrochloride

Angioedema

Fatigue

Menopausal flushing

3.3.16.A.1 Angioedema

a) Allergic reactions, including angioneurotic edema, have been reported with atomoxetine use (Prod Info STRATTERA(R) oral capsules, 2008).

3.3.16.A.2 Fatigue

a) Incidence: adults, 9%; pediatrics, 6% to 9% (Prod Info STRATTERA(R) oral capsules, 2008)

b) In acute (up to 25 weeks), placebo-controlled trials in adult patients with attention-deficit hyperactivity disorder (ADHD), fatigue was reported in 9% of patients who received atomoxetine (n=540) compared to 4% of patients who received placebo (n=402) (Prod Info STRATTERA(R) oral capsules, 2008).

c) In acute (up to 18 weeks), placebo-controlled trials in pediatric patients with attention-deficit hyperactivity disorder (ADHD), fatigue was reported in 8% of atomoxetine-treated patients (n=1597) compared to 3% of placebo-treated patients (n=934) (Prod Info STRATTERA(R) oral capsules, 2008).
d) In acute (up to 18 weeks), placebo-controlled trials in pediatric patients with attention-deficit hyperactivity disorder (ADHD), fatigue was reported in 9% and 6% of patients treated with atomoxetine once (n=882) and twice (n=715) daily, respectively, compared to 2% and 4% of patients treated with placebo once (n=500) and twice (n=434) daily, respectively (Prod Info STRATTERA(R) oral capsules, 2008).

3.3.16.A.3 Menopausal flushing

a) Incidence: adults, 8% (Prod Info STRATTERA(R) oral capsules, 2008)
b) In acute (up to 25 weeks), placebo-controlled trials in adult patients with attention-deficit hyperactivity disorder (ADHD), hot flushes were reported in 8% of patients who received atomoxetine (n=214) compared to 1% of patients who received placebo (n=142) (Prod Info STRATTERA(R) oral capsules, 2008).

3.4 Teratogenicity/Effects in Pregnancy/Breastfeeding

A) Teratogenicity/Effects in Pregnancy
1) U.S. Food and Drug Administration's Pregnancy Category: Category C (Prod Info Strattera(TM), 2002s) (All Trimesters)
a) Either studies in animals have revealed adverse effects on the fetus (teratogenic or embryocidal or other) and there are no controlled studies in women or studies in women and animals are not available. Drugs should be given only if the potential benefit justifies the potential risk to the fetus.
See Drug Consult reference: PREGNANCY RISK CATEGORIES
2) Crosses Placenta: Unknown
3) Clinical Management
a) There is insufficient clinical experience with the use of atomoxetine in pregnancy to confirm its safety in that patient population. Until additional data are available, caution should be exercised with the use of atomoxetine in pregnant women.
4) Literature Reports
a) Adverse fetal effects and some evidence of teratogenicity was reported with relatively high doses of atomoxetine in animal studies (Prod Info Strattera(TM), 2002s).
B) Breastfeeding
1) Thomson Lactation Rating: Infant risk cannot be ruled out.
a) Available evidence and/or expert consensus is inconclusive or is inadequate for determining infant risk when used during breastfeeding. Weigh the potential benefits of drug treatment against potential risks before prescribing this drug during breastfeeding.
2) Clinical Management
a) It is not known whether atomoxetine is excreted into human breast milk and the potential for adverse effects in the nursing infant from exposure to the drug are unknown. It is not known if atomoxetine affects the quantity or composition of breastmilk. According to the manufacturer, atomoxetine and/or its metabolites were excreted into the milk of lactating rats (Prod Info STRATTERA(TM) Oral Capsule, 2002).
3) Literature Reports
a) No reports describing the use of atomoxetine during human lactation or measuring the amount, if any, of the drug excreted into milk have been located.

3.5 Drug Interactions

3.5.1 Drug-Drug Combinations

Albuterol

Amitriptyline

Amoxapine

Brofaromine

Clomipramine

Clorgyline

Desipramine

Dibenzepin

Dothiepin

Doxepin

Fluoxetine

Furazolidone

Imipramine

Iproniazid

Isocarboxazid

Lazabemide

Linezolid

Lofepramine

Moclobemide

Nialamide

Nortriptyline

Opipramol

Pargyline

Paroxetine

Phenelzine

Procarbazine

Protriptyline

Quinidine

Rasagiline

Selegiline

Tianeptine

Toloxatone

Tranylcypromine

Trimipramine

3.5.1.A Albuterol

1) Interaction Effect: an increase in heart rate and blood pressure
2) Summary: Albuterol (600 mcg intravenously over 2 hours) induced increases in heart rate and blood pressure. The effects were potentiated by atomoxetine (60 mg BID for 5 days) and were most marked after the initial coadministration of albuterol and atomoxetine (Prod Info Strattera(TM), 2002h).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Close monitoring of blood pressure and heart rate is indicated during combined therapy with atomoxetine and albuterol or other beta-2 agonists, particularly in patients with cardiovascular disease.
7) Probable Mechanism: unknown

3.5.1.B Amitriptyline
1) Interaction Effect: an increase in atomoxetine steady-state plasma concentrations
2) Summary: Atomoxetine is primarily metabolized by the cytochrome P450 2D6 (CYP 2D6) pathway to 4-hydroxyatomoxetine. In extensive metabolizers, atomoxetine steady-state plasma concentrations are increased with selective inhibitors of CYP2D6, such as amitriptyline. The exposure is similar to that observed in poor metabolizers. In extensive metabolizers treated with amitriptyline, the area under the concentration-time curve of atomoxetine is approximately 6- to 8-fold greater, and maximum plasma concentration at steady-state is about 3- to 4-fold greater than atomoxetine alone (Prod Info Strattera(TM), 2002n).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Dosage adjustment of atomoxetine may be necessary when coadministered with amitriptyline.
7) Probable Mechanism: inhibition of cytochrome P450 2D6-mediated metabolism of atomoxetine by amitriptyline

3.5.1.C Amoxapine
1) Interaction Effect: an increase in atomoxetine steady-state plasma concentrations
2) Summary: Atomoxetine is primarily metabolized by the cytochrome P450 2D6 (CYP 2D6) pathway to 4-hydroxyatomoxetine. In extensive metabolizers, atomoxetine steady-state plasma concentrations are increased with selective inhibitors of CYP2D6, such as amoxapine. The exposure is similar to that observed in poor metabolizers. In extensive metabolizers treated with amoxapine, the area under the concentration-time curve of atomoxetine is approximately 6- to 8-fold greater, and maximum plasma concentration at steady-state is about 3- to 4-fold greater than atomoxetine alone (Prod Info Strattera(TM), 2002j).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Dosage adjustment of atomoxetine may be necessary when coadministered with amoxapine.
7) Probable Mechanism: inhibition of cytochrome P450 2D6-mediated metabolism of atomoxetine by amoxapine

3.5.1.D Brofaromine
1) Interaction Effect: an increased risk of serotonin syndrome (hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delerium and coma)
2) Summary: The combination of atomoxetine and a monoamine oxidase inhibitor (MAOI) may increase the risk of serotonin syndrome. There have been reports of serious, sometimes fatal, reactions (including hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma) when atomoxetine is coadministered with an MAOI. Some case presented with signs and symptoms similar to neuroleptic malignant syndrome (Prod Info Strattera(TM), 2002).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Atomoxetine should not be taken with a monoamine oxidase inhibitor (MAOI), or within 2 weeks after discontinuing an MAOI. Treatment with an MAOI should not be initiated within 2 weeks after discontinuing atomoxetine. Observe the patient closely for signs and symptoms of serotonin syndrome or neuroleptic malignant syndrome.
7) Probable Mechanism: additive serotonergic effect

3.5.1.E Clomipramine
1) Interaction Effect: an increase in atomoxetine steady-state plasma concentrations
2) Summary: Atomoxetine is primarily metabolized by the cytochrome P450 2D6 (CYP 2D6) pathway to 4-hydroxyatomoxetine. In extensive metabolizers, atomoxetine steady-state plasma concentrations are

increased with selective inhibitors of CYP2D6, such as clomipramine. The exposure is similar to that observed in poor metabolizers. In extensive metabolizers treated with clomipramine, the area under the concentration-time curve of atomoxetine is approximately 6- to 8-fold greater, and maximum plasma concentration at steady-state is about 3- to 4-fold greater than atomoxetine alone (Prod Info Strattera(TM), 2002m).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Dosage adjustment of atomoxetine may be necessary when coadministered with clomipramine.
7) Probable Mechanism: inhibition of cytochrome P450 2D6-mediated metabolism of atomoxetine by clomipramine

3.5.1.F Clorgyline
1) Interaction Effect: an increased risk of serotonin syndrome (hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delerium and coma)
2) Summary: The combination of atomoxetine and a monoamine oxidase inhibitor (MAOI) may increase the risk of serotonin syndrome. There have been reports of serious, sometimes fatal, reactions (including hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma) when atomoxetine is coadministered with an MAOI. Some case presented with signs and symptoms similar to neuroleptic malignant syndrome (Prod Info Strattera(TM), 2002).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Atomoxetine should not be taken with a monoamine oxidase inhibitor (MAOI), or within 2 weeks after discontinuing an MAOI. Treatment with an MAOI should not be initiated within 2 weeks after discontinuing atomoxetine. Observe the patient closely for signs and symptoms of serotonin syndrome or neuroleptic malignant syndrome.
7) Probable Mechanism: additive serotonergic effect

3.5.1.G Desipramine
1) Interaction Effect: an increase in atomoxetine steady-state plasma concentrations
2) Summary: Atomoxetine is primarily metabolized by the cytochrome P450 2D6 (CYP 2D6) pathway to 4-hydroxyatomoxetine. In extensive metabolizers, atomoxetine steady-state plasma concentrations are increased with selective inhibitors of CYP2D6, such as desipramine. The exposure is similar to that observed in poor metabolizers. In extensive metabolizers treated with desipramine, the area under the concentration-time curve of atomoxetine is approximately 6- to 8-fold greater, and maximum plasma concentration at steady-state is about 3- to 4-fold greater than atomoxetine alone (Prod Info Strattera(TM), 2002r).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Dosage adjustment of atomoxetine may be necessary when coadministered with desipramine.
7) Probable Mechanism: inhibition of cytochrome P450 2D6-mediated metabolism of atomoxetine by desipramine

3.5.1.H Dibenzepin
1) Interaction Effect: an increase in atomoxetine steady-state plasma concentrations
2) Summary: Atomoxetine is primarily metabolized by the cytochrome P450 2D6 (CYP 2D6) pathway to 4-hydroxyatomoxetine. In extensive metabolizers, atomoxetine steady-state plasma concentrations are increased with selective inhibitors of CYP2D6, such as dibenzepin. The exposure is similar to that observed in poor metabolizers. In extensive metabolizers treated with dibenzepin, the area under the concentration-time curve of atomoxetine is approximately 6- to 8-fold greater, and maximum plasma concentration at steady-state is about 3- to 4-fold greater than atomoxetine alone (Prod Info Strattera(TM), 2002e).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Dosage adjustment of atomoxetine may be necessary when coadministered with dibenzepin.
7) Probable Mechanism: inhibition of cytochrome P450 2D6-mediated metabolism of atomoxetine by dibenzepin

3.5.1.I Dothiepin
1) Interaction Effect: an increase in atomoxetine steady-state plasma concentrations
2) Summary: Atomoxetine is primarily metabolized by the cytochrome P450 2D6 (CYP 2D6) pathway to 4-

hydroxyatomoxetine. In extensive metabolizers, atomoxetine steady-state plasma concentrations are increased with selective inhibitors of CYP2D6, such as dothiepin. The exposure is similar to that observed in poor metabolizers. In extensive metabolizers treated with dothiepin, the area under the concentration-time curve of atomoxetine is approximately 6- to 8-fold greater, and maximum plasma concentration at steady-state is about 3- to 4-fold greater than atomoxetine alone (Prod Info Strattera(TM), 2002d).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Dosage adjustment of atomoxetine may be necessary when coadministered with dothiepin.
7) Probable Mechanism: inhibition of cytochrome P450 2D6-mediated metabolism of atomoxetine by dothiepin

3.5.1.J Doxepin
1) Interaction Effect: an increase in atomoxetine steady-state plasma concentrations
2) Summary: Atomoxetine is primarily metabolized by the cytochrome P450 2D6 (CYP 2D6) pathway to 4-hydroxyatomoxetine. In extensive metabolizers, atomoxetine steady-state plasma concentrations are increased with selective inhibitors of CYP2D6, such as doxepin. The exposure is similar to that observed in poor metabolizers. In extensive metabolizers treated with doxepin, the area under the concentration-time curve of atomoxetine is approximately 6- to 8-fold greater, and maximum plasma concentration at steady-state is about 3- to 4-fold greater than atomoxetine alone (Prod Info Strattera(TM), 2002g).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Dosage adjustment of atomoxetine may be necessary when coadministered with doxepin.
7) Probable Mechanism: inhibition of cytochrome P450 2D6-mediated metabolism of atomoxetine by doxepin

3.5.1.K Fluoxetine
1) Interaction Effect: an increase in atomoxetine steady-state plasma concentrations
2) Summary: Atomoxetine is primarily metabolized by the cytochrome P450 2D6 (CYP 2D6) pathway to 4-hydroxyatomoxetine. In extensive metabolizers, atomoxetine steady-state plasma concentrations are increased with selective inhibitors of CYP2D6, such as fluoxetine. The exposure is similar to that observed in poor metabolizers. In extensive metabolizers treated with fluoxetine, the area under the concentration-time curve of atomoxetine is approximately 6- to 8-fold greater, and maximum plasma concentration at steady-state is about 3- to 4-fold greater than atomoxetine alone (Prod Info Strattera(TM), 2002c).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Dosage adjustment of atomoxetine may be necessary when coadministered with fluoxetine.
7) Probable Mechanism: inhibition of cytochrome P450 2D6-mediated metabolism of atomoxetine by fluoxetine

3.5.1.L Furazolidone
1) Interaction Effect: an increased risk of serotonin syndrome (hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delerium and coma)
2) Summary: The combination of atomoxetine and a monoamine oxidase inhibitor (MAOI) may increase the risk of serotonin syndrome. There have been reports of serious, sometimes fatal, reactions (including hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma) when atomoxetine is coadministered with an MAOI. Some case presented with signs and symptoms similar to neuroleptic malignant syndrome (Prod Info Strattera(TM), 2002).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Atomoxetine should not be taken with a monoamine oxidase inhibitor (MAOI), or within 2 weeks after discontinuing an MAOI. Treatment with an MAOI should not be initiated within 2 weeks after discontinuing atomoxetine. Observe the patient closely for signs and symptoms of serotonin syndrome or neuroleptic malignant syndrome.
7) Probable Mechanism: additive serotonergic effect

3.5.1.M Imipramine
1) Interaction Effect: an increase in atomoxetine steady-state plasma concentrations
2) Summary: Atomoxetine is primarily metabolized by the cytochrome P450 2D6 (CYP 2D6) pathway to 4-hydroxyatomoxetine. In extensive metabolizers, atomoxetine steady-state plasma concentrations are

increased with selective inhibitors of CYP2D6, such as imipramine. The exposure is similar to that observed in poor metabolizers. In extensive metabolizers treated with imipramine, the area under the concentration-time curve of atomoxetine is approximately 6- to 8-fold greater, and maximum plasma concentration at steady-state is about 3- to 4-fold greater than atomoxetine alone (Prod Info Strattera(TM), 2002a).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Dosage adjustment of atomoxetine may be necessary when coadministered with imipramine.
7) Probable Mechanism: inhibition of cytochrome P450 2D6-mediated metabolism of atomoxetine by imipramine

3.5.1.N Iproniazid
1) Interaction Effect: an increased risk of serotonin syndrome (hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delerium and coma)
2) Summary: The combination of atomoxetine and a monoamine oxidase inhibitor (MAOI) may increase the risk of serotonin syndrome. There have been reports of serious, sometimes fatal, reactions (including hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma) when atomoxetine is coadministered with an MAOI. Some case presented with signs and symptoms similar to neuroleptic malignant syndrome (Prod Info Strattera(TM), 2002).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Atomoxetine should not be taken with a monoamine oxidase inhibitor (MAOI), or within 2 weeks after discontinuing an MAOI. Treatment with an MAOI should not be initiated within 2 weeks after discontinuing atomoxetine. Observe the patient closely for signs and symptoms of serotonin syndrome or neuroleptic malignant syndrome.
7) Probable Mechanism: additive serotonergic effect

3.5.1.O Isocarboxazid
1) Interaction Effect: an increased risk of serotonin syndrome (hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delerium and coma)
2) Summary: The combination of atomoxetine and a monoamine oxidase inhibitor (MAOI) may increase the risk of serotonin syndrome. There have been reports of serious, sometimes fatal, reactions (including hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma) when atomoxetine is coadministered with an MAOI. Some case presented with signs and symptoms similar to neuroleptic malignant syndrome (Prod Info Strattera(TM), 2002).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Atomoxetine should not be taken with a monoamine oxidase inhibitor (MAOI), or within 2 weeks after discontinuing an MAOI. Treatment with an MAOI should not be initiated within 2 weeks after discontinuing atomoxetine. Observe the patient closely for signs and symptoms of serotonin syndrome or neuroleptic malignant syndrome.
7) Probable Mechanism: additive serotonergic effect

3.5.1.P Lazabemide
1) Interaction Effect: an increased risk of serotonin syndrome (hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delerium and coma)
2) Summary: The combination of atomoxetine and a monoamine oxidase inhibitor (MAOI) may increase the risk of serotonin syndrome. There have been reports of serious, sometimes fatal, reactions (including hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma) when atomoxetine is coadministered with an MAOI. Some case presented with signs and symptoms similar to neuroleptic malignant syndrome (Prod Info Strattera(TM), 2002).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Atomoxetine should not be taken with a monoamine oxidase inhibitor (MAOI), or within 2 weeks after discontinuing an MAOI. Treatment with an MAOI should not be initiated within 2 weeks after discontinuing atomoxetine. Observe the patient closely for signs and symptoms of serotonin syndrome or neuroleptic malignant syndrome.
7) Probable Mechanism: additive serotonergic effect

3.5.1.Q Linezolid

1) Interaction Effect: an increased risk of serotonin syndrome (hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delerium and coma)
2) Summary: The combination of atomoxetine and a monoamine oxidase inhibitor (MAOI) may increase the risk of serotonin syndrome. There have been reports of serious, sometimes fatal, reactions (including hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma) when atomoxetine is coadministered with an MAOI. Some case presented with signs and symptoms similar to neuroleptic malignant syndrome (Prod Info Strattera(TM), 2002).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Atomoxetine should not be taken with a monoamine oxidase inhibitor (MAOI), or within 2 weeks after discontinuing an MAOI. Treatment with an MAOI should not be initiated within 2 weeks after discontinuing atomoxetine. Observe the patient closely for signs and symptoms of serotonin syndrome or neuroleptic malignant syndrome.
7) Probable Mechanism: additive serotonergic effect

3.5.1.R Lofepramine

1) Interaction Effect: an increase in atomoxetine steady-state plasma concentrations
2) Summary: Atomoxetine is primarily metabolized by the cytochrome P450 2D6 (CYP 2D6) pathway to 4-hydroxyatomoxetine. In extensive metabolizers, atomoxetine steady-state plasma concentrations are increased with selective inhibitors of CYP2D6, such as lofepramine. The exposure is similar to that observed in poor metabolizers. In extensive metabolizers treated with lofepramine, the area under the concentration-time curve of atomoxetine is approximately 6- to 8-fold greater, and maximum plasma concentration at steady-state is about 3- to 4-fold greater than atomoxetine alone (Prod Info Strattera(TM), 2002o).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Dosage adjustment of atomoxetine may be necessary when coadministered with lofepramine.
7) Probable Mechanism: inhibition of cytochrome P450 2D6-mediated metabolism of atomoxetine by lofepramine

3.5.1.S Moclobemide

1) Interaction Effect: an increased risk of serotonin syndrome (hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delerium and coma)
2) Summary: The combination of atomoxetine and a monoamine oxidase inhibitor (MAOI) may increase the risk of serotonin syndrome. There have been reports of serious, sometimes fatal, reactions (including hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma) when atomoxetine is coadministered with an MAOI. Some case presented with signs and symptoms similar to neuroleptic malignant syndrome (Prod Info Strattera(TM), 2002).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Atomoxetine should not be taken with a monoamine oxidase inhibitor (MAOI), or within 2 weeks after discontinuing an MAOI. Treatment with an MAOI should not be initiated within 2 weeks after discontinuing atomoxetine. Observe the patient closely for signs and symptoms of serotonin syndrome or neuroleptic malignant syndrome.
7) Probable Mechanism: additive serotonergic effect

3.5.1.T Nialamide

1) Interaction Effect: an increased risk of serotonin syndrome (hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delerium and coma)
2) Summary: The combination of atomoxetine and a monoamine oxidase inhibitor (MAOI) may increase the risk of serotonin syndrome. There have been reports of serious, sometimes fatal, reactions (including hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma) when atomoxetine is coadministered with an MAOI. Some case presented with signs and symptoms similar to neuroleptic malignant syndrome (Prod Info Strattera(TM), 2002).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical

6) Clinical Management: Atomoxetine should not be taken with a monoamine oxidase inhibitor (MAOI), or within 2 weeks after discontinuing an MAOI. Treatment with an MAOI should not be initiated within 2 weeks after discontinuing atomoxetine. Observe the patient closely for signs and symptoms of serotonin syndrome or neuroleptic malignant syndrome.
7) Probable Mechanism: additive serotonergic effect

3.5.1.U Nortriptyline
1) Interaction Effect: an increase in atomoxetine steady-state plasma concentrations
2) Summary: Atomoxetine is primarily metabolized by the cytochrome P450 2D6 (CYP 2D6) pathway to 4-hydroxyatomoxetine. In extensive metabolizers, atomoxetine steady-state plasma concentrations are increased with selective inhibitors of CYP2D6, such as nortriptyline. The exposure is similar to that observed in poor metabolizers. In extensive metabolizers treated with nortriptyline, the area under the concentration-time curve of atomoxetine is approximately 6- to 8-fold greater, and maximum plasma concentration at steady-state is about 3- to 4-fold greater than atomoxetine alone (Prod Info Strattera(TM), 2002l).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Dosage adjustment of atomoxetine may be necessary when coadministered with nortriptyline.
7) Probable Mechanism: inhibition of cytochrome P450 2D6-mediated metabolism of atomoxetine by nortriptyline

3.5.1.V Opipramol
1) Interaction Effect: an increase in atomoxetine steady-state plasma concentrations
2) Summary: Atomoxetine is primarily metabolized by the cytochrome P450 2D6 (CYP 2D6) pathway to 4-hydroxyatomoxetine. In extensive metabolizers, atomoxetine steady-state plasma concentrations are increased with selective inhibitors of CYP2D6, such as opipramol. The exposure is similar to that observed in poor metabolizers. In extensive metabolizers treated with opipramol, the area under the concentration-time curve of atomoxetine is approximately 6- to 8-fold greater, and maximum plasma concentration at steady-state is about 3- to 4-fold greater than atomoxetine alone (Prod Info Strattera(TM), 2002f).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Dosage adjustment of atomoxetine may be necessary when coadministered with opipramol.
7) Probable Mechanism: inhibition of cytochrome P450 2D6-mediated metabolism of atomoxetine by opipramol

3.5.1.W Pargyline
1) Interaction Effect: an increased risk of serotonin syndrome (hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delerium and coma)
2) Summary: The combination of atomoxetine and a monoamine oxidase inhibitor (MAOI) may increase the risk of serotonin syndrome. There have been reports of serious, sometimes fatal, reactions (including hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma) when atomoxetine is coadministered with an MAOI. Some case presented with signs and symptoms similar to neuroleptic malignant syndrome (Prod Info Strattera(TM), 2002).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Atomoxetine should not be taken with a monoamine oxidase inhibitor (MAOI), or within 2 weeks after discontinuing an MAOI. Treatment with an MAOI should not be initiated within 2 weeks after discontinuing atomoxetine. Observe the patient closely for signs and symptoms of serotonin syndrome or neuroleptic malignant syndrome.
7) Probable Mechanism: additive serotonergic effect

3.5.1.X Paroxetine
1) Interaction Effect: an increase in atomoxetine steady-state plasma concentrations
2) Summary: Atomoxetine is primarily metabolized by the cytochrome P450 2D6 (CYP 2D6) pathway to 4-hydroxyatomoxetine. In extensive metabolizers, atomoxetine steady-state plasma concentrations are increased with selective inhibitors of CYP2D6, such as paroxetine. The exposure is similar to that observed in poor metabolizers. In extensive metabolizers treated with paroxetine, the area under the concentration-time curve of atomoxetine is approximately 6- to 8-fold greater, and maximum plasma concentration at steady-state is about 3- to 4-fold greater than atomoxetine alone (Prod Info Strattera(TM), 2002i).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical

6) Clinical Management: Dosage adjustment of atomoxetine may be necessary when coadministered with paroxetine.
7) Probable Mechanism: inhibition of cytochrome P450 2D6-mediated metabolism of atomoxetine by paroxetine

3.5.1.Y Phenelzine
1) Interaction Effect: an increased risk of serotonin syndrome (hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delerium and coma)
2) Summary: The combination of atomoxetine and a monoamine oxidase inhibitor (MAOI) may increase the risk of serotonin syndrome. There have been reports of serious, sometimes fatal, reactions (including hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma) when atomoxetine is coadministered with an MAOI. Some case presented with signs and symptoms similar to neuroleptic malignant syndrome (Prod Info Strattera(TM), 2002).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Atomoxetine should not be taken with a monoamine oxidase inhibitor (MAOI), or within 2 weeks after discontinuing an MAOI. Treatment with an MAOI should not be initiated within 2 weeks after discontinuing atomoxetine. Observe the patient closely for signs and symptoms of serotonin syndrome or neuroleptic malignant syndrome.
7) Probable Mechanism: additive serotonergic effect

3.5.1.Z Procarbazine
1) Interaction Effect: an increased risk of serotonin syndrome (hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delerium and coma)
2) Summary: The combination of atomoxetine and a monoamine oxidase inhibitor (MAOI) may increase the risk of serotonin syndrome. There have been reports of serious, sometimes fatal, reactions (including hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma) when atomoxetine is coadministered with an MAOI. Some case presented with signs and symptoms similar to neuroleptic malignant syndrome (Prod Info Strattera(TM), 2002).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Atomoxetine should not be taken with a monoamine oxidase inhibitor (MAOI), or within 2 weeks after discontinuing an MAOI. Treatment with an MAOI should not be initiated within 2 weeks after discontinuing atomoxetine. Observe the patient closely for signs and symptoms of serotonin syndrome or neuroleptic malignant syndrome.
7) Probable Mechanism: additive serotonergic effect

3.5.1.AA Protriptyline
1) Interaction Effect: an increase in atomoxetine steady-state plasma concentrations
2) Summary: Atomoxetine is primarily metabolized by the cytochrome P450 2D6 (CYP 2D6) pathway to 4-hydroxyatomoxetine. In extensive metabolizers, atomoxetine steady-state plasma concentrations are increased with selective inhibitors of CYP2D6, such as protriptyline. The exposure is similar to that observed in poor metabolizers. In extensive metabolizers treated with protriptyline, the area under the concentration-time curve of atomoxetine is approximately 6- to 8-fold greater, and maximum plasma concentration at steady-state is about 3- to 4-fold greater than atomoxetine alone (Prod Info Strattera(TM), 2002q).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Dosage adjustment of atomoxetine may be necessary when coadministered with protriptyline.
7) Probable Mechanism: inhibition of cytochrome P450 2D6-mediated metabolism of atomoxetine

3.5.1.AB Quinidine
1) Interaction Effect: an increase in atomoxetine steady-state plasma concentrations
2) Summary: Atomoxetine is primarily metabolized by the cytochrome P450 2D6 (CYP 2D6) pathway to 4-hydroxyatomoxetine. In extensive metabolizers, atomoxetine steady-state plasma concentrations are increased with selective inhibitors of CYP2D6, such as quinidine. The exposure is similar to that observed in poor metabolizers (Prod Info Strattera(TM), 2002p).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Dosage adjustment of atomoxetine may be necessary when coadministered with

quinidine.
7) Probable Mechanism: inhibition of cytochrome P450 2D6-mediated metabolism of atomoxetine by quinidine

3.5.1.AC Rasagiline
1) Interaction Effect: an increased risk of serotonin syndrome (hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delerium and coma)
2) Summary: The combination of atomoxetine and a monoamine oxidase inhibitor (MAOI) may increase the risk of serotonin syndrome. There have been reports of serious, sometimes fatal, reactions (including hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma) when atomoxetine is coadministered with an MAOI. Some case presented with signs and symptoms similar to neuroleptic malignant syndrome (Prod Info Strattera(TM), 2002).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Atomoxetine should not be taken with a monoamine oxidase inhibitor (MAOI), or within 2 weeks after discontinuing an MAOI. Treatment with an MAOI should not be initiated within 2 weeks after discontinuing atomoxetine. Observe the patient closely for signs and symptoms of serotonin syndrome or neuroleptic malignant syndrome.
7) Probable Mechanism: additive serotonergic effect

3.5.1.AD Selegiline
1) Interaction Effect: an increased risk of serotonin syndrome (hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delerium and coma)
2) Summary: The combination of atomoxetine and a monoamine oxidase inhibitor (MAOI) may increase the risk of serotonin syndrome. There have been reports of serious, sometimes fatal, reactions (including hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma) when atomoxetine is coadministered with an MAOI. Some case presented with signs and symptoms similar to neuroleptic malignant syndrome (Prod Info Strattera(TM), 2002).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Atomoxetine should not be taken with a monoamine oxidase inhibitor (MAOI), or within 2 weeks after discontinuing an MAOI. Treatment with an MAOI should not be initiated within 2 weeks after discontinuing atomoxetine. Observe the patient closely for signs and symptoms of serotonin syndrome or neuroleptic malignant syndrome.
7) Probable Mechanism: additive serotonergic effect

3.5.1.AE Tianeptine
1) Interaction Effect: an increase in atomoxetine steady-state plasma concentrations
2) Summary: Atomoxetine is primarily metabolized by the cytochrome P450 2D6 (CYP 2D6) pathway to 4-hydroxyatomoxetine. In extensive metabolizers, atomoxetine steady-state plasma concentrations are increased with selective inhibitors of CYP2D6, such as tianeptine. The exposure is similar to that observed in poor metabolizers. In extensive metabolizers treated with tianeptine, the area under the concentration-time curve of atomoxetine is approximately 6- to 8-fold greater, and maximum plasma concentration at steady-state is about 3- to 4-fold greater than atomoxetine alone (Prod Info Strattera(TM), 2002k).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Dosage adjustment of atomoxetine may be necessary when coadministered with tianeptine.
7) Probable Mechanism: inhibition of cytochrome P450 2D6-mediated metabolism of atomoxetine by tianeptine

3.5.1.AF Toloxatone
1) Interaction Effect: an increased risk of serotonin syndrome (hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delerium and coma)
2) Summary: The combination of atomoxetine and a monoamine oxidase inhibitor (MAOI) may increase the risk of serotonin syndrome. There have been reports of serious, sometimes fatal, reactions (including hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma) when atomoxetine is coadministered with an MAOI. Some case presented with signs and symptoms similar to neuroleptic malignant syndrome (Prod Info Strattera(TM), 2002).

3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Atomoxetine should not be taken with a monoamine oxidase inhibitor (MAOI), or within 2 weeks after discontinuing an MAOI. Treatment with an MAOI should not be initiated within 2 weeks after discontinuing atomoxetine. Observe the patient closely for signs and symptoms of serotonin syndrome or neuroleptic malignant syndrome.
7) Probable Mechanism: additive serotonergic effect

3.5.1.AG Tranylcypromine

1) Interaction Effect: an increased risk of serotonin syndrome (hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delerium and coma)
2) Summary: The combination of atomoxetine and a monoamine oxidase inhibitor (MAOI) may increase the risk of serotonin syndrome. There have been reports of serious, sometimes fatal, reactions (including hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma) when atomoxetine is coadministered with an MAOI. Some case presented with signs and symptoms similar to neuroleptic malignant syndrome (Prod Info Strattera(TM), 2002).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Atomoxetine should not be taken with a monoamine oxidase inhibitor (MAOI), or within 2 weeks after discontinuing an MAOI. Treatment with an MAOI should not be initiated within 2 weeks after discontinuing atomoxetine. Observe the patient closely for signs and symptoms of serotonin syndrome or neuroleptic malignant syndrome.
7) Probable Mechanism: additive serotonergic effect

3.5.1.AH Trimipramine

1) Interaction Effect: an increase in atomoxetine steady-state plasma concentrations
2) Summary: Atomoxetine is primarily metabolized by the cytochrome P450 2D6 (CYP 2D6) pathway to 4-hydroxyatomoxetine. In extensive metabolizers, atomoxetine steady-state plasma concentrations are increased with selective inhibitors of CYP2D6, such as trimipramine. The exposure is similar to that observed in poor metabolizers. In extensive metabolizers treated with trimipramine, the area under the concentration-time curve of atomoxetine is approximately 6- to 8-fold greater, and maximum plasma concentration at steady-state is about 3- to 4-fold greater than atomoxetine alone (Prod Info Strattera(TM), 2002b).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Dosage adjustment of atomoxetine may be necessary when coadministered with trimipramine.
7) Probable Mechanism: inhibition of cytochrome P450 2D6-mediated metabolism of atomoxetine by trimipramine

4.0 Clinical Applications

Monitoring Parameters

Patient Instructions

Place In Therapy

Mechanism of Action / Pharmacology

Therapeutic Uses

4.1 Monitoring Parameters

A) Atomoxetine Hydrochloride
1) Therapeutic
a) Physical Findings
1) Improvement in mental and behavioral symptoms of ADHD, including inappropriate inattention, impulsivity, hyperactivity, and cognitive performance.
2) Toxic

a) Laboratory Parameters

1) Monitor hepatic function tests if signs of liver dysfunction are present including pruritus, dark urine, jaundice, right upper quadrant tenderness, or unexplained flu-like symptoms (Prod Info STRATTERA(R) oral capsules, 2009).

b) Physical Findings

1) The American Academy of Pediatrics (AAP) does not recommend the routine use of electrocardiograms (ECGS) or routine subspecialty cardiology evaluations (which were previously recommended by the American Heart Association (AHA) scientific statement to detect cardiac conditions that might place the child at risk for sudden cardiac death) before initiating stimulant therapy to treat attention-deficit/hyperactivity disorder ADHD in most children. The APA cited specific reasons for changing the recommendation including: lack of evidence establishing a relationship between stimulant drugs used to treat ADHD and sudden cardiac death (SCD), the frequency of sudden unexpected deaths among patients taking stimulant drugs is not higher than that in the general population of children, and lack of cost-effective analysis to support ECG screening or special evaluation by pediatric cardiologist (Perrin et al, 2008).

2) Based on the American Academy of Pediatrics (AAP) and the American Heart Association (AHA) consensus statements, the following cardiac monitoring recommendations have been established to assist clinicians in the evaluation of children treated with stimulant drugs, including atomoxetine, for ADHD (Perrin et al, 2008; Vetter et al, 2008):

- Conduct a thorough examination prior to initiating atomoxetine therapy for a diagnosis of ADHD. Special attention should be given to symptoms indicative of a cardiac condition, including palpitations, near syncope, or syncope. Palpitations have been reported with atomoxetine use in adults.
- Obtain a complete family and patient history for conditions associated with SCD, and determine current use of any other prescription or over-the-counter medications.
- Conduct a complete physical evaluation of the patient for hypertension, cardiac murmurs, physical findings associated with Marfan syndrome, and signs of irregular cardiac rhythms.
- Perform further evaluation if family history, patient history or physical exam is suggestive of cardiac disease during initial visit or at follow up visits, and if indicated, consult pediatric cardiologist .
- Continue to assess the patient for cardiac symptoms and any changes in family history at follow up visits.
- Blood pressure and heart rate should be evaluated at baseline, during routine follow-up within 1 to 3 months, and at follow up visits every 6 to 12 months. Increases in blood pressure and heart rate have been reported with the use of certain ADHD drugs.

3) Monitor children and adolescents receiving atomoxetine for signs of clinical worsening, suicidal thinking or behaviors, and unusual changes in behavior at the start of therapy and during the first few months of therapy or when the dose is increased or decreased. Symptoms of clinical worsening may include anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia, hypomania, and mania (Prod Info STRATTERA(R) oral capsules, 2009; US Food and Drug Administration, 2005).

4) Monitor for signs of liver dysfunction including pruritus, dark urine, jaundice, right upper quadrant tenderness, or unexplained flu-like symptoms (Prod Info STRATTERA(R) oral capsules, 2009).

5) Monitor growth in pediatric patients (Prod Info STRATTERA(R) oral capsules, 2006).

6) Monitor for signs of hypersensitivity including angioneurotic edema, urticaria, and rash.

4.2 Patient Instructions

A) Atomoxetine (By mouth)

Atomoxetine

Treats attention-deficit/hyperactivity disorder (ADHD).

When This Medicine Should Not Be Used:
You should not use this medicine if you or your child have had an allergic reaction to atomoxetine, if you or your child have narrow angle glaucoma, or have used an MAO inhibitor such as Eldepryl®, Marplan®, Nardil®, or Parnate® in the past 14 days. After you or your child stop using atomoxetine, do not use an MAO inhibitor for at least 14 days.

How to Use This Medicine:
Capsule

Your doctor will tell you how much of this medicine to use and how often. Do not use more medicine or use it more often than your doctor tells you to.
This medicine should come with a Medication Guide. Read and follow these instructions carefully. Ask your doctor or pharmacist if you have any questions. Ask your pharmacist for the Medication Guide if you do not have one. Your doctor might ask you to sign some forms to show that you understand this information.
For children or teenagers, the dose may need to be changed several times in order to find out what works best for them. Pay close attention to any changes in behavior that might happen.
Swallow the capsule whole. Do not crush, break, chew, or open it.

You may take this medicine with or without food.

If a Dose is Missed:
If you miss a dose or forget to use your medicine, use it as soon as you can. If it is almost time for your next dose, wait until then to use the medicine and skip the missed dose. Do not use extra medicine to make up for a missed dose.

How to Store and Dispose of This Medicine:
Store the medicine in a closed container at room temperature, away from heat, moisture, and direct light.
Ask your pharmacist, doctor, or health caregiver about the best way to dispose of any leftover medicine after you have finished your treatment. You will also need to throw away old medicine after the expiration date has passed.
Keep all medicine away from children and never share your medicine with anyone.

Drugs and Foods to Avoid:
Ask your doctor or pharmacist before using any other medicine, including over-the-counter medicines, vitamins, and herbal products.
Make sure your doctor knows if you are using dopamine (Intropin®), dobutamine (Dobutrex®), an asthma medicine (such as albuterol), or a heart rhythm medicine (such as disopyramide, procainamide, quinidine, Norpace®, or Procanbid®). Tell your doctor if you are also using a medicine for depression, such as fluoxetine, paroxetine, Luvox®, Paxil®, Prozac®, or Sarafem®.

Warnings While Using This Medicine:
Make sure your doctor knows if you or your child are pregnant or breastfeeding, or if you or your child have high or low blood pressure, liver disease, heart disease, heart rhythm problems, blood vessel disease, or problems with urination.
This medicine may make you or your child dizzy or drowsy. Avoid driving, using machines, or doing anything else that could be dangerous if you are not alert.
This medicine may cause slow growth. If your child is using this medicine, the doctor will need to keep track of your child's height and weight to make sure that your child is growing properly.
For some children and teenagers, this medicine can increase thoughts of suicide. All of the warnings in this leaflet are true for a child or teenager who is using this medicine.Tell your doctor right away if you start to feel more depressed. Also tell your doctor right away if you have thoughts about hurting yourself. Report any unusual thoughts or behaviors that trouble you, especially if they are new or get worse quickly.Make sure your caregiver knows if you have trouble sleeping, get upset easily, have a big increase in energy, or start to act reckless. Also tell your doctor if you have sudden or strong feelings, such as feeling nervous, angry, restless, violent, or scared.Let your doctor know if you or anyone in your family has bipolar disorder (manic-depressive) or has tried to commit suicide.
Your doctor will need to check your progress at regular visits while you are using this medicine. Be sure to keep all appointments.

Possible Side Effects While Using This Medicine:
Call your doctor right away if you notice any of these side effects:
Allergic reaction: Itching or hives, swelling in your face or hands, swelling or tingling in your mouth or throat, chest tightness, trouble breathing.
Change in how much or how often you urinate.
Chest pain or shortness of breath.
Dark-colored urine or pale stools.
Fast, pounding, or irregular heartbeat.
Flu-like symptoms.
Headache, lightheadedness, dizziness, or fainting.
Mood changes, aggressiveness, irritability, or depression.
Nausea, vomiting, loss of appetite, constipation, upset stomach, or pain in your upper stomach.
Painful, prolonged erection of the penis.
Seeing, hearing, or feeling things that are not there.
Seizures or tremors.
Yellowing of your skin or the whites of your eyes.

If you notice these less serious side effects, talk with your doctor:
Changes in your menstrual cycle (periods), or menstrual cramps.
Dry mouth.
Loss of interest in sex, or trouble having sex.
Tiredness.
Trouble sleeping.
Warmth or redness in your face, neck, arms, or upper chest.

If you notice other side effects that you think are caused by this medicine, tell your doctor.

4.3 Place In Therapy

A) ADHD

1) Atomoxetine is promoted as an equally efficacious form of ADHD therapy as conventional agents (eg, methylphenidate, dextroamphetamine, pemoline, bupropion, tricyclic antidepressants). Controlled studies, essential for evaluation of this agent, have shown evidence of efficacy; direct comparisons are lacking. Unpublished data suggest that the frequency and severity of some adverse effects are similar to those of methylphenidate (eg, cardiovascular effects, weight loss).

2) At the very least, prospective comparisons with short- and long-acting forms of methylphenidate (usual agent of choice) are indicated before the place in therapy of atomoxetine can be addressed.

3) Until additional data for atomoxetine are made available, it should not be considered over conventional therapy.

B) DEPRESSION

1) Clinical data for atomoxetine in major depression are limited to small, uncontrolled studies. Placebo-controlled studies are required to confirm efficacy; comparisons with selective serotonin reuptake inhibitors (SSRIs)/other antidepressants are needed to assess its role in therapy.

4.4 Mechanism of Action / Pharmacology

A) MECHANISM OF ACTION

1) Atomoxetine is a methylphenoxy-benzene propanamine derivative with antidepressant activity (Zerbe et al, 1985; Chouinard et al, 1985); its structure is unlike that of other antidepressants. The drug is under investigation as a "nonstimulant" treatment of attention-deficit/hyperactivity disorder (ADHD) in both adults and children, and for treatment of adult depression.

2) Atomoxetine purportedly enhances noradrenergic function via selective inhibition of the presynaptic norepinephrine transporter (Ki of 4.5 nanomols (nM)) (Michelson et al, 2001; Kratochvil et al, 2001). It has minimal-to-no affinity for other neuronal transporters or neurotransmitter receptor sites (eg, muscarinic, histaminic, dopaminergic, serotonergic, alpha-adrenergic) (Zerbe et al, 1985; Cusack et al, 1994; Spencer et al, 1998a; Chouinard et al, 1985; Spencer et al, 1998).

3) Animal and human studies suggest a low propensity for anticholinergic and adverse cardiovascular effects with atomoxetine (Zerbe et al, 1985; Kratochvil et al, 2001; Spencer et al, 2001). No significant hypertensive effects were seen in healthy subjects given single doses of 20 or 40 mg twice daily for one week in one study (Zerbe et al, 1985).

B) REVIEW ARTICLES

1) Drug treatment of attention-deficit/hyperactivity disorder (ADHD) (Popper, 2000).

2) Diagnostic dilemmas in ADHD and treatment modalities (Spencer et al, 1998a).

3) Use of nonstimulant agents in ADHD (Biederman & Spencer, 2000).

4.5 Therapeutic Uses

4.5.A Atomoxetine Hydrochloride

Attention deficit hyperactivity disorder

Attention deficit hyperactivity disorder - Social phobia

Nocturnal enuresis

4.5.A.1 Attention deficit hyperactivity disorder

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes; Pediatric, yes (6 years and older)
Efficacy: Adult, Evidence favors efficacy; Pediatric, Evidence favors efficacy
Recommendation: Adult, Class IIb; Pediatric, Class IIb
Strength of Evidence: Adult, Category B; Pediatric, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Atomoxetine hydrochloride (HCl) is indicated for the acute treatment of attention-deficit hyperactivity disorder (ADHD) in pediatric (ages 6 years and older) and adult patients and as maintenance/extended therapy in pediatric patients (aged 6 to 15 years) (Prod Info STRATTERA (R) oral capsules, 2008).

Atomoxetine is used as an integral part of a total treatment program for (ADHD) that may include other psychological, educational, and/or social measures (Prod Info STRATTERA(R) oral capsules, 2008).

In two 10-week, randomized, placebo-controlled studies (n=536), atomoxetine hydrochloride produced significant improvement in symptoms in adult patients with attention-deficit/hyperactivity disorder (Prod Info STRATTERA(R) oral capsules, 2008).

Oral atomoxetine has shown short-term efficacy for treating attention-deficit hyperactivity disorder (ADHD) in over 600 children/adolescents (6 to 18 years of age) in open and placebo-controlled trials (Spencer et al, 2002; Kratochvil et al, 2001a; Michelson et al, 2001b; Spencer et al, 2001a). Pediatric patients (ages 6 to 15 years) with attention-deficit hyperactivity disorder who received maintenance treatment with atomoxetine hydrochloride had significantly longer times to relapse compared to patients who received placebo (Prod Info STRATTERA(R) oral capsules, 2008).

c) Adult:

1) In two 10-week, randomized, placebo-controlled studies in adult patients with attention-deficit hyperactivity disorder (n=536), atomoxetine hydrochloride (HCl) produced significant improvement in symptoms as assessed on the ADHD symptom score from the Conners Adult ADHD Rating Scale Screening Version (CAARS). Atomoxetine HCl was titrated to 60 to 120 mg/day given in 2 daily divided doses (mean daily dose, 95 mg). Efficacy was similar regardless of gender and age (older or younger than 42 years) (Prod Info STRATTERA(R) oral capsules, 2008).

2) Oral atomoxetine 40 to 80 milligrams (mg) daily for three weeks was effective in adult attention-deficit/hyperactivity disorder (ADHD). In a small placebo-controlled crossover study (n=21), improvements in the ADHD Rating Scale significantly favored atomoxetine after the second week of treatment; the average dose at week three was 76 mg daily. A 30% or greater decrease in ADHD symptoms was observed in 52% of patients during treatment (10% response with placebo) (Spencer et al, 1998b). However, several aspects of the study design were not included, and this response rate is less than that observed with methylphenidate or desipramine in some other studies.

d) Pediatric:

1) Acute Treatment

a) Oral atomoxetine has shown short-term efficacy for treating Attention- Deficit/Hyperactivity Disorder (ADHD) in over 600 children/adolescents (6 to 18 years of age) in open and placebo-controlled trials. The primary efficacy measure was ADHD Rating Scale-IV-Parent Version (ADHD RS), which has demonstrated validity in prior studies. Compared to placebo, oral atomoxetine in doses ranging from 1.2 to 1.8 milligrams/kilogram/day resulted in a significantly greater mean reduction in ADHD RS total score (p less than 0.05 for all studies); smaller doses failed to show consistent efficacy. Therapeutic doses of atomoxetine also generally but less consistently produced significant improvements on select subscales of the ADHD RS, namely scores of inattentiveness and hyperactivity/impulsivity. Other secondary measures showing improvements with atomoxetine included the Clinical Global Impressions-ADHD- Severity (CGI-ADHD-S) score (p less than 0.05 for all studies) and the Conners' Parent Rating Scale-Revised: Short Form (CPRS-R:S) (p less than or equal to 0.05 for all studies). Similar efficacy was reported in a subset analysis in school- age girls. Furthermore, no differences were reported between patients with and without previous psychostimulant treatment or among age groups (Biderman et al, 2002)(Spencer et al, 2002; Kratochvil et al, 2001a; Michelson et al, 2001b; Spencer et al, 2001a).

2) Maintenance Treatment

a) Pediatric patients with attention-deficit hyperactivity disorder (ADHD) who received maintenance treatment with atomoxetine hydrochloride (HCl) had significantly longer times to relapse compared to patients who received placebo. Patients (aged 6 to 15 years) who had a continuous response (defined as a Clinical Global Impressions of Severity of ADHD (CGI-ADHD-S) score of 2 or less and 25% or greater decrease from baseline in the ADHD rating scale-IV Parent Version with the hyperactivity/impulsive and inattentive subscales (ADHDRS-IV-Parent:Inv) total score) for approximately 4 weeks during an initial 10-week, open-label treatment phase were randomized to either their current atomoxetine HCl dose (n=292) of 1.2 to 1.8 milligrams/kilogram/day or placebo (n=124). Patients who experienced a continuous response for approximately 8 months with atomoxetine HCl therapy were randomized again to either their current atomoxetine HCl dose (n=81) or placebo (n=82). In both randomized, double-blind maintenance treatment phases, time to relapse (defined as the time to a CGI-ADHD-S score increase of 2 or more and a ADHDRS-IV-Parent:Inv total score of 90% or greater from baseline for 2 consecutive visits) was significantly longer in patients who received atomoxetine HCl compared to placebo (Prod Info STRATTERA(R) oral capsules, 2008).

b) Maintenance treatment with low-dose atomoxetine did not lead to a statistically significant difference in relapse rates compared to the higher, acute treatment dose in a randomized, double-blind, dose-response study in patients with Attention-Deficit/Hyperactivity Disorder (ADHD). Patients aged 6 to 16 years (n=229), who had a robust response to initial 7- to 9-week treatment with oral atomoxetine for ADHD, were randomized to either continue atomoxetine at the same dose (mean dose, 1.43 +/- 0.28 milligrams/kilogram (mg/kg) per day; n=116) or at a low dose of 0.5 mg/kg per day (n=113) for up to 8 months. Symptom severity was low and similar in both groups at randomization. The primary efficacy measure was relapse, which was determined using the investigator-administered and investigator-scored version of the ADHD Rating Scale (ADHD-RS) and was defined as a total ADHD-RS score of 90% of more of the original baseline value (prior to acute treatment) for 2 consecutive visits. At study conclusion, relapse rates did not differ significantly between the 2 groups (p=0.924), and were 2.6% (3/116) and 2.7% (3/113) for the continued same-dose and the low-dose groups, respectively. The mean change in the ADHD-RS total scores was similar for both groups (p=0.237), with a mean change of 1.1 +/- 10.8 (p=0.751) for the continued same-dose group and 3.1 +/- 10.4 (p=0.017) for the low-dose group. Among

secondary measures, there were no statistically significant differences between the 2 groups in mean changes in the Clinical Global Impressions-ADHD-Severity scores (p=0.078) and in the Child Health Questionnaire psychosocial summary scores (p=0.205). However, scores on the role emotion/behavior subscale were significantly lower (worsening) for patients in the low-dose group (-1.13 +/- 33.9) compared to patients in the continued same-dose group (5.75 +/- 29.9) (p=0.017). Among treatment-emergent adverse events, reports of affective lability were higher in the low-dose group (5/112 versus 0/116; p=0.027) while increases in heart rate (HR) were higher in the continued same-dose group (mean change in HR, 9 +/- 12.5 versus 5.2 +/- 13.9; p=0.013) (Newcorn et al, 2006).

4.5.A.2 Attention deficit hyperactivity disorder - Social phobia

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy; Pediatric, Evidence favors efficacy
Recommendation: Adult, Class IIb; Pediatric, Class IIb
Strength of Evidence: Adult, Category B; Pediatric, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Atomoxetine was superior to placebo for the treatment of attention deficit hyperactivity disorder (ADHD) in adults with comorbid social anxiety disorder in a randomized, double-blind, placebo-controlled trial demonstrated (n=442) (Adler et al, 2009).
Atomoxetine was superior to placebo for the treatment of attention deficit hyperactivity disorder (ADHD) in pediatric and adolescent patients with comorbid generalized anxiety disorder (GAD) in a randomized, double-blind, placebo-controlled trial (n=176) (Geller et al, 2007).

c) Adult:

1) A multicenter, randomized, double-blind, placebo-controlled, parallel-group study demonstrated that atomoxetine was superior to placebo for the treatment of attention deficit hyperactivity disorder (ADHD) in adults with comorbid social anxiety disorder (SAD) (n=442). Adult patients, aged 18 to 65 years, with Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) diagnosis for ADHD and SAD were enrolled. Patients were randomized to receive either placebo (n=218) or atomoxetine (n=224) 40 milligrams (mg) daily in 2 divided doses for a minimum of 7 days, then 80 mg total daily dose (target dose) for a minimum of 7 days. After randomization, all patients entered a 2-week placebo lead-in period. At week 10, atomoxetine may be increased to 100 mg/day if significant residual symptoms remained. The study duration was 16 weeks. The primary outcome was the mean change from baseline to endpoint in the Conners' Adult ADHD Rating Scale: Investigator-Rates: Screening Version (CAARS:Inv:SV) Total ADHD symptoms score. The statistical analysis for the primary outcome was performed on the per protocol population of qualified patients (n=342). Qualified patients included those who had 25% or less improvement in social anxiety symptoms during the placebo lead-in phase. At baseline, the mean CAARS:Inv:SV total ADHD score was 29.6 +/- 10.4 and 31.2 +/- 9.4 in the atomoxetine and placebo group, respectively. The per protocol analysis revealed that atomoxetine was significantly superior to placebo in the mean CAARS:Inv:SV total ADHD score improvement from baseline (-8.7 +/- 10 vs -5.6 +/- 10.2; p less than 0.001). Similarly, the mean change in Liebowitz Social Anxiety Scale total score (LSAS) from baseline to endpoint was -22.9 +/- 25.3 and -14.4 +/-20.3 (p less than 0.001) in the atomoxetine and placebo groups, respectively. Common adverse effects included insomnia (17% vs 9%), nausea (16% vs 7.6%), dry mouth (15.6% vs 4.3%) and dizziness (7.5% vs 2.4%) in the atomoxetine vs placebo groups, respectively (Adler et al, 2009).

d) Pediatric:

1) Atomoxetine was superior to placebo for the treatment of attention deficit hyperactivity disorder (ADHD) in pediatric and adolescent patients with comorbid generalized anxiety disorder (GAD) in a multicenter, randomized, double-blind, parallel-design, placebo-controlled trial, with an optional, open-label extension period (n=176). Patients aged 8 to 17 years (yr), who met the DSM-IV criteria for ADHD and at least 1 of the following anxiety disorders (separation anxiety, generalized anxiety or social phobia) were enrolled. Study period I included a medication washout period for approximately 2 weeks. Study period II included a 2-week, placebo lead-in period to identify high placebo responders. After the placebo lead-in period, patients were randomized to receive atomoxetine (n=87; mean age 12.2 +/- 2.8 yr; 62.1% male) or placebo (n=89; age 11.8 +/- 2.5 yr; 67.4% male) twice daily for 12 weeks. The atomoxetine group received an initial dose of 0.8 milligrams/kilogram (mg/kg) daily, in 2 divided doses for 3 days, then a target dose of 1.2 mg/kg/day. At visit 6, atomoxetine could be increased to a maximum dose of 1.8 mg/kg/day for significant residual ADHD symptoms. The primary outcome was reduction of ADHD and GAD symptoms assessed by the mean change from baseline to endpoint in the Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version: Investigator Administered and Scored (ADHDRS-IV-PI) and the Pediatric Anxiety Rating Scale (PARS) total scores. Statistical analysis for the primary outcome was performed on the per protocol population of eligible patients (n=133) who had a baseline and at least 1 post baseline measurement and 25% or less reduction on the PARS total score during the blinded placebo lead-in period. The per protocol analysis revealed that atomoxetine was significantly superior to placebo for improvement of both the ADHDRS-IV-PI and PARS total scores. The mean change from baseline in the ADHDRS-IV-PI scale improvement was -10.5 vs -1.4 (95% CI for difference, -12.56 to -5.58; p less than 0.001) in the atomoxetine group compared with the

placebo group. The corresponding mean change in the PARS score was -5.5 and -3.2, respectively (95% CI for difference, -4.01 to -0.52; p less than 0.012). Subjects in the atomoxetine group had a higher response rate compared with cohorts in the placebo group (61.8% vs 12.1%; p less than 0.001). Atomoxetine was associated with higher incidence of decreased appetite (14.3% vs 3.8%), headache (14.3% vs 8.8%), upper abdominal pain (11.7% vs 5%) and vomiting (10.4% vs 5%) relative to placebo (Geller et al, 2007).

4.5.A.3 Nocturnal enuresis

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Efficacy is limited to case report; a controlled trial is needed

c) Pediatric:

1) Atomoxetine shows efficacy in treatment of nocturnal enuresis. In a multicenter, randomized, double-blind, placebo-controlled, intent-to-treat (ITT) trial in which 87 patients (aged 6 to 18 years) received atomoxetine (n=44) or placebo (n=43) for 12 weeks. Atomoxetine was dosed at 0.5 milligrams/kilogram (mg/kg) daily for 3 days, followed by 1 mg/kg/day for the next 3 days and then increased to 1.5 mg/kg/day for the rest of the study. Doses were given twice daily, in the morning and late afternoon. The primary outcome measure was change from baseline in the number of dry nights as recorded on the Day Night Log-Parent Report. At baseline, the mean number of dry nights was 1.51 for the atomoxetine group and 1.01 for the placebo group (statistical difference not provided). Results were reported for 42 atomoxetine-treated and 41 placebo- treated patients. Patients treated with atomoxetine had an average increase of 1.47 dry nights per week compared with 0.60 for the placebo-treated patients (p=0.02). Headache was the most common adverse event occurring in 9 atomoxetine-treated patients and 4 placebo-treated patients (Sumner et al, 2003; Sumner et al, 2003a); (Anon, 2003; Anon, 2003a).

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Last Modified: June 22, 2009

DRUGDEX® Evaluations

CARBAMAZEPINE

0.0 Overview

1) Class

a) This drug is a member of the following class(es):

Anticonvulsant
Antimanic
Dibenzazepine Carboxamide
Neuropathic Pain Agent

2) Dosing Information

a) Adult

1) Bipolar I disorder, acute manic and mixed episodes

a) ORAL; (extended-release capsules) initial, 400 mg/day ORALLY in 2 divided doses, may increase dosage 200 mg/day up to a max of 1600 mg/day as needed (Prod Info EQUETRO(TM) oral extended release capsul

2) Epilepsy, Partial, generalized, and mixed types

a) ORAL; (suspension) initial, 1 teaspoon (100 mg) ORALLY 4 times a day for the first week, may increase d mg/day at weekly intervals (usual max dosage 1000 mg/day in children 12-15 years of age, 1200 mg/day in p years of age, and up to 1600 mg/day in adults) (Prod Info TEGRETOL(R) chewable oral tablets, oral tablets, TEGRETOL(R) XR extended-release oral tablets, 2003)

b) ORAL; (regular-release tablet) initial, 200 mg orally twice daily for the first week, may increase dose by 20 weekly intervals (usual max dosage 1000 mg/day in children 12-15 years of age, 1200 mg/day in patients ab age, and up to 1600 mg/day in adults) (Prod Info TEGRETOL(R) chewable oral tablets, oral tablets, oral susp TEGRETOL(R) XR extended-release oral tablets, 2003)

c) ORAL; (extended-release tablet) initial, 200 mg ORALLY twice daily for the first week, may increase dosa at weekly intervals until optimal response is obtained (usual max dosage 1000 mg/day in children 12-15 year mg/day in patients above 15 years of age, and up to 1600 mg/day in adults) (Prod Info TEGRETOL(R) chewa oral tablets, oral suspension, TEGRETOL(R) XR extended-release oral tablets, 2003)

d) ORAL; maintenance, adjust dosage to the minimum effective level, usually 800-1200 mg/day ORALLY (P TEGRETOL(R) chewable oral tablets, oral tablets, oral suspension, TEGRETOL(R) XR extended-release ora

3) Glossopharyngeal neuralgia

a) ORAL; (suspension) initial, 50 mg ORALLY 4 times a day on the first day, may increase dosage by 200 m doses/day) as needed for pain control, do not exceed 1200 mg/day (Prod Info TEGRETOL(R) chewable oral tablets, oral suspension, TEGRETOL(R) XR extended-release oral tablets, 2003)

b) ORAL; (regular-release tablets) initial, 100 mg ORALLY every 12 hr, may increase by 200 mg/day (divide needed for pain control (max dose 1200 mg/day) (Prod Info TEGRETOL(R) chewable oral tablets, oral tablet TEGRETOL(R) XR extended-release oral tablets, 2003)

c) ORAL; (extended-release tablets) initial, 100 mg ORALLY every 12 hr, may increase by 200 mg/day (divi as needed for pain control (max dose 1200 mg/day) (Prod Info TEGRETOL(R) chewable oral tablets, oral tab suspension, TEGRETOL(R) XR extended-release oral tablets, 2003)

d) maintenance, 400-800 mg/day ORALLY (range 200-1200 mg/day); at least once every 3 months throughc period, attempts should be made to reduce the dose to the minimum effective level or even to discontinue the TEGRETOL(R) chewable oral tablets, oral tablets, oral suspension, TEGRETOL(R) XR extended-release ora

4) Psychotic disorder

a) 200 to 400 mg/day ORALLY in 3 to 4 divided doses, may increase dosage gradually at weekly intervals u mg/day as needed

5) Trigeminal neuralgia

a) ORAL; (suspension) initial, 50 mg ORALLY 4 times a day on the first day, may increase dosage by 200 m doses/day) as needed for pain control, do not exceed 1200 mg/day (Prod Info TEGRETOL(R) chewable oral tablets, oral suspension, TEGRETOL(R) XR extended-release oral tablets, 2003)

b) ORAL; (regular-release tablets) initial, 100 mg ORALLY every 12 hr, may increase by 200 mg/day (divide needed for pain control (max dose 1200 mg/day) (Prod Info TEGRETOL(R) chewable oral tablets, oral tablet TEGRETOL(R) XR extended-release oral tablets, 2003)

c) ORAL; (extended-release tablets) initial, 100 mg ORALLY every 12 hr, may increase by 200 mg/day (divi as needed for pain control (max dose 1200 mg/day) (Prod Info TEGRETOL(R) chewable oral tablets, oral tab suspension, TEGRETOL(R) XR extended-release oral tablets, 2003)

d) maintenance, 400-800 mg/day ORALLY (range 200-1200 mg/day); at least once every 3 months throughc period, attempts should be made to reduce the dose to the minimum effective level or even to discontinue the TEGRETOL(R) chewable oral tablets, oral tablets, oral suspension, TEGRETOL(R) XR extended-release ora

b) Pediatric

1) Epilepsy, Partial, generalized, and mixed types

a) ORAL; children up to 6 years of age (suspension), initial, 10-20 mg/kg/day ORALLY in 4 divided doses, m dosage by 100 mg/day at weekly intervals as needed, do not exceed 35 mg/kg/day (Prod Info TEGRETOL(R tablets, oral tablets, oral suspension, TEGRETOL(R) XR extended-release oral tablets, 2003)

b) ORAL; children up to 6 years of age (regular-release tablet), initial, 10-20 mg/kg/day ORALLY in 2 or 3 div increase dosage by 100 mg/day at weekly intervals as needed, do not exceed 35 mg/kg/day (Prod Info TEGR chewable oral tablets, oral tablets, oral suspension, TEGRETOL(R) XR extended-release oral tablets, 2003)
c) ORAL; children up to 6 years of age, maintenance, adjust to the minimum effective dosage, usually 250-3 max 400 mg/day or 35 mg/kg/day) (Prod Info TEGRETOL(R) chewable oral tablets, oral tablets, oral suspens (R) XR extended-release oral tablets, 2003)
d) ORAL; children 6-12 years of age (suspension), initial, 0.5 teaspoon (50 mg) ORALLY 4 times daily (total mg), may increase dosage by 100 mg/day at weekly intervals as needed, do not exceed 1000 mg/day (Prod (R) chewable oral tablets, oral tablets, oral suspension, TEGRETOL(R) XR extended-release oral tablets, 20
e) ORAL; children 6-12 years of age (regular-release tablet), initial, 100 mg twice daily, may increase dosage weekly intervals as needed, doses greater than 200 mg/day should be given in 3 to 4 divided doses, do not e mg/day (Prod Info TEGRETOL(R) chewable oral tablets, oral tablets, oral suspension, TEGRETOL(R) XR ex oral tablets, 2003)
f) ORAL; children 6-12 years of age (extended-release tablet), initial, 100 mg twice daily, may increase dosa at weekly intervals as needed, doses greater than 200 mg/day may continue to be given twice daily, do not e mg/day (Prod Info TEGRETOL(R) chewable oral tablets, oral tablets, oral suspension, TEGRETOL(R) XR ex oral tablets, 2003)
g) ORAL; children 6-12 years of age, maintenance, adjust to the minimum effective dosage, usually 400-800 TEGRETOL(R) chewable oral tablets, oral tablets, oral suspension, TEGRETOL(R) XR extended-release ora

3) Contraindications
a) bone marrow depression, history of previous (Prod Info TEGRETOL(R) oral chewable tablets, tablets, suspension, TEGRETOL(R)-XR extended-release oral tablets, 2007)
b) concomitant use of an MAOI, or use within 14 days of discontinuing an MAOI (Prod Info TEGRETOL(R) oral chewa tablets, suspension, 2007; Prod Info TEGRETOL(R)-XR extended-release oral tablets, 2007)
c) concomitant use of nefazodone; decreased nefazodone plasma levels may reduce drug effectiveness (Prod Info TE chewable tablets, tablets, suspension, 2007; Prod Info TEGRETOL(R)-XR extended-release oral tablets, 2007)
d) hypersensitivity to carbamazepine or tricyclic compounds (Prod Info TEGRETOL(R) oral chewable tablets, tablets, Prod Info TEGRETOL(R)-XR extended-release oral tablets, 2007)

4) Serious Adverse Effects
a) Acute intermittent porphyria
b) Acute renal failure
c) Agranulocytosis
d) Angioedema
e) Aplastic anemia
f) Atrioventricular block
g) Bone marrow depression
h) Cardiac dysrhythmia
i) Congestive heart failure
j) Drug-induced eosinophilia
k) Hepatitis
l) Hypocalcemia
m) Hyponatremia
n) Leukocytosis
o) Leukopenia
p) Nephrotoxicity
q) Pancytopenia
r) Stevens-Johnson syndrome
s) Syncope
t) Thrombocytopenia
u) Toxic epidermal necrolysis

5) Clinical Applications
a) FDA Approved Indications
1) Bipolar I disorder, acute manic and mixed episodes
2) Epilepsy, Partial, generalized, and mixed types
3) Glossopharyngeal neuralgia
4) Trigeminal neuralgia
b) Non-FDA Approved Indications
1) Psychotic disorder

1.0 Dosing Information

Drug Properties

Storage and Stability

Adult Dosage

Pediatric Dosage

1.1 Drug Properties

A) Information on specific products and dosage forms can be obtained by referring to the Tradename List (Product In

B) Synonyms

Carbamazepine

C) Physicochemical Properties

1) Molecular Weight

a) 236.27 (Fleegler & Carolyn A., 1986)

2) pKa

a) 7 (Anon, 1980) (Goodman and Gilman, 1980)

1.2 Storage and Stability

A) Suspension

1) Do not store in temperatures above 86 degrees F (30 degrees C) and dispense in a tight, light-resistant contai Tegretol(R), 2002b). Shake well before using. CARBAMAZEPINE suspension (commercially available) repackage mL aliquots in amber glass vials, polypropylene vials, amber polypropylene syringes and in 2-mL aliquots in ambe syringes were found to be stable for 8 weeks at room temperature under constant fluorescent lighting. These repa suspensions retained at least 86% of the initial carbamazepine concentration (Lowe et al, 1989).

2) Tegretol suspension(R) (carbamazepine) should not be administered simultaneously with other liquid medicati (Prod Info Tegretol(R), 2002b). In a case report, a man passed an orange rubbery mass after ingesting Tegretol S immediately followed by Thorazine(R) solution (chlorpromazine). The manufacturer reports that mixing Tegretol s chlorpromazine solution (generic and brand name) results in the precipitation of a rubbery orange mass.

B) Tablet

1) Do not store tablets above 86 degrees F (30 degrees C). Protect from moisture and dispense in tight containe Tegretol(R), 2002b).

2) The Food and Drug Administration (FDA) found that carbamazepine, in both its generic and brand-name forms third or more of its potency if stored in humid conditions. Tablets exposed continuously to 97% humidity at room t weeks hardened and dissolved poorly. Patients should be instructed to keep their carbamazepine supply in a tigh prescription container and in a dry location, away from showers, bathrooms, and humidifiers (Anon, 1990).

C) Tablet, Chewable

1) Do not store above 86 degrees F (30 degrees C). Protect from light and moisture; do not keep medicine in the chewable tablets should be dispensed in a tight, light-resistant container (Prod Info Tegretol(R), 2002b).

D) Tablet, Extended Release

1) EXTENDED RELEASE TABLETS

a) Tegretol(R) extended-release tablets should be stored at controlled room temperature between 15 and 30 (59 to 86 degrees Fahrenheit) and protected from moisture. Dispense in a tight container (Prod Info Tegretol(

b) Carbatrol(R) extended-release capsules should be stored at controlled room temperature between 15 and Celsius (59 to 77 degrees Fahrenheit) and protected from moisture. Dispense in a tight, light-resistant contai Carbatrol(R), 2002).

c) Equetro(TM) extended-release capsules should be stored at controlled room temperature between 15 and Celsius (59 to 86 degrees Fahrenheit) and protected from light. (Prod Info Equetro(TM) extended release cap

E) Extemporaneous Formulation - Oral route

1) Carbamazepine oral suspension 200 mg/5 mL was stable for 90 days when prepared with the following vehicle degrees C in amber bottles:

Sucrose	95 g
Sorbitol 70%	49 mL
Glycerin	8.5 mL
Saccharin sodium	170 mg
Methylparaben	340 mg
Methylcellulose 400	4.7 g
Methylcellulose 4000	2.1 g
FD&C Yellow	510 mg
Lemon Lime Flavor	1 mL
Purified Water	QS 500 mL

2) This formulation is easier to pour and produces less foam than simple syrup formulations (Burkart et al, 1981).

3) A carbamazepine 40 mg/mL suspension, 120 mL, may be prepared using 24 carbamazepine 200 mg tablets (and a sufficient quantity of simple syrup to bring the volume to 120 mL. This suspension should be labeled "shake "refrigerate" and is stable for 90 days (Burkart et al, 1981).

4) A carbamazepine 50 mg/mL suspension, 120 mL, may be prepared using 30 carbamazepine 200 mg tablets (Basel), distilled water to levigate, Cologel(R) (methylcellulose; Lilly) 40 mL, and a sufficient quantity of a 2:1 simpl syrup mixture to bring the volume to 120 mL. This suspension should be labeled "shake well" and "refrigerate" an days (Anon, 1987).

5) The palatability of an extemporaneously prepared oral suspension of carbamazepine was reported (Bloomer e suspension was prepared by combining fifty 200 mg carbamazepine tablets (Tegretol(R)) with HSC suspending v syrup 300 mL/L, methylcellulose 1% gel 700 mL/L, and sodium benzoate 0.14%) to yield a volume of 500 mL of s was flavored with banana, tutti-frutti, or grape. A cherry-mint suspension was prepared by using Tegretol(R) in ch The final suspension consisted of 20 mg/mL of carbamazepine. The cherry-mint formulation was judged least pal volunteers, with no trend in preference between the unflavored suspension and other flavors (banana, tutti-frutti, g

F) Extemporaneous Formulation - Rectal route

1) Carbamazepine has also been formulated into a gel for rectal administration without the addition of sorbitol to the associated premature defecation. The preparation consisted of:

2) 200 milligrams (mg) of carbamazepine powder dissolved in 5 milliliters of 20% alcohol and then incorporated w methylhydroxyethylcellulose 250 mg

3) This mixture may be dispensed in syringes as 200 mg doses for rectal administration. The syringes should be degrees Centigrade prior to administration to maintain adequate gelation and discourage microbial growth (Broua

4) The total absorption of a carbamazepine suspension following rectal and oral administration was similar in a a volunteers (Neuvonen PJ & Tokola O, 1987); however, slower absorption was associated with the rectal route. Th mixture consisted of:

5) Carbamazepine 20 milligrams/mL, Sorbitol 300 milligrams/mL, and Water.

1.3 Adult Dosage

Normal Dosage

Dosage in Renal Failure

Dosage in Hepatic Insufficiency

Dosage in Geriatric Patients

Dosage Adjustment During Dialysis

Dosage in Other Disease States

1.3.1 Normal Dosage

Oral route

Restless legs syndrome

Tinnitus

1.3.1.A Oral route

Bipolar I disorder, acute manic and mixed episodes

Epilepsy, Partial, generalized, and mixed types

Trigeminal neuralgia

1.3.1.A.1 Bipolar I disorder, acute manic and mixed episodes

a) The recommended initial dose for the treatment of acute manic and mixed episodes associated with b 200 milligrams (mg) twice daily (400 mg/day), and may be taken with or without food. The dose should b increments of 200 mg/day to achieve the optimum clinical response; doses above 1600 mg/day have no Equetro(TM) capsules may be opened and the beads sprinkled over applesauce or other similar food pr Do not crush or chew capsules (Prod Info Equetro(TM) extended release capsules, 2004).

b) The longer-term or prophylactic use of Equetro(TM) capsules for the treatment of bipolar mania has r Physicians who choose to prescribe this medication for extended periods of time should re-evaluate the benefits of the drug for the individual patient at regular intervals (Prod Info Equetro(TM) extended releas

c) Most patients with bipolar disorder have responded to carbamazepine 600 to 1600 milligrams (mg)/da

divided doses, although some patients have required doses as high as 2000 to 3000 mg/day (Ballenger, cycling patients usually require higher doses of 1000 to 2000 mg daily (Perry et al, 1991).

1.3.1.A.2 Epilepsy, Partial, generalized, and mixed types

a) The initial recommended dosage is 200 milligrams (mg) twice a day (tablets or sustained-release tabl four times a day (suspension). The dosage is then increased by adding 200 mg per day in weekly interva daily regimen for sustained-release tablets or a 3 or 4 times a day regimen for conventional tablets or su desired clinical response is obtained (Prod Info Tegretol(R), 2002c). Usual average dose ranges are 17 t mg/kilogram/day (Anon, 1975a). Usual effective maintenance doses reported by the manufacturer are 8((Prod Info Carbatrol(R), 20029)(Prod Info Tegretol(R), 2002c). This medication should be taken with fooc

b) Dosage should generally not exceed 1200 milligrams (mg)/day in adults, although doses of up to 160 been used in rare instances (Prod Info Tegretol(R), 2002c). Serum drug levels should guide dosage requ

1.3.1.A.3 Trigeminal neuralgia

a) The recommended initial dose is 100 milligrams (mg) twice a day of carbamazepine tablets or extend (Prod Info Tegretol(R), 2002c) or one carbamazepine 200 mg extended-release capsule per day (Prod In 2002) or 1/2 teaspoonful 4 times daily of carbamazepine suspension (Prod Info Tegretol(R), 2002c). This increased by up to 200 mg a day using increments of 100 mg every 12 hours for tablets or sustained-rele Info Tegretol(R), 2002c) or by a single 200 mg extended-release capsule (Prod Info Carbatrol(R), 2002) teaspoonsful of carbamazepine suspension administered in divided doses 4 times a day (Prod Info Tegr Effective maintenance doses for most patients have been 400 to 800 mg/day. Do not exceed 1200 mg/d Carbatrol(R), 2002; Prod Info Tegretol(R), 2002c).

b) At 3-month intervals attempts should be made to reduce the dose of the drug to the minimum effectiv discontinue the drug (Prod Info Tegretol(R), 2002c).

1.3.1.B Restless legs syndrome

See Drug Consult reference: RESTLESS LEG SYNDROME - DRUGS OF CHOICE

1.3.1.C Tinnitus

See Drug Consult reference: DRUG THERAPY OF TINNITUS

1.3.1.D IMPORTANT NOTE

1) The dosage of carbamazepine should be adjusted to meet the needs of the individual patient based upon and monitoring of blood levels (Prod Info Tegretol(R), 2002c).

2) To convert patients from regular carbamazepine to the sustained-release formulation (Tegretol(R)-XR or C same total daily milligram dose should be given (Mirza et al, 1998; Prod Info Carbatrol(R), 2002; Prod Info Te When using other formulations besides the Tegretol(R)-XR or Carbatrol(R), please consult the manufacturer's recommendations. The carbamazepine extended release tablets should never be crushed or chewed and sh whole. Damaged tablets or tablets without a release portal should not be consumed (Prod Info Tegretol(R), 2

3) Tegretol suspension(R) (carbamazepine) should not be administered simultaneously with other liquid mec diluents (Prod Info Tegretol(R), 2002c).

4) The suspension will produce higher peak levels than the same dose given as a tablet; therefore, patients the same number of milligrams/day in smaller, more frequent doses (Prod Info Tegretol(R), 2002c).

1.3.1.E SINGLE DAILY DOSE

1) Single daily carbamazepine doses (mean, 13.7 milligrams/kilogram/day) for 4 weeks maintained carbama epoxide metabolite levels in the therapeutic range, but higher fluctuations of serum carbamazepine levels occ compared to divided dose regimens twice a day, three times daily). Adverse effects or loss of efficacy were n once daily dosing; however, the authors suggest further long-term studies (Ghose et al, 1983; Ghose et al, 19

1.3.1.F Oral loading doses of carbamazepine 8 milligrams (mg)/kilogram given as the suspension or as tablets h (Cohen et al, 1998). Therapeutic concentrations (range=7.1 to 9.9 mg/liter) were reached within 2 hours with the s within 5 hours with the tablets. The 6 patients in this study tolerated it well.

1) WITHDRAWAL OF THERAPY

a) SUMMARY

1) The length of time for and method of anticonvulsant withdrawal is not considered to be a prime fa determining the prognosis of the patient. However, sudden withdrawal of medication may precipitate therefore medication should be withdrawn gradually over a period of at least 3 months. Excellent res achieved by withdrawing each anticonvulsant over a period of 9 months, with downward increments month intervals.

b) The risk factors associated with withdrawal of anticonvulsants in 92 patients who had been free of se with single agent therapy were evaluated (Callaghan et al, 1988). The dose of each anticonvulsant was r at intervals of 2 weeks (1 unit equivalent to 200 milligrams of carbamazepine or valproic acid, or 100 mill phenytoin), with a mean follow-up period of 26 months (range, 6 to 62 months). Relapse occurred in 31 p patients remaining free of seizures (relapse rate 33.7%).

1.3.2 Dosage in Renal Failure

A) No dosage reduction is required in patients with renal failure (Bennett et al, 1994).

1.3.3 Dosage in Hepatic Insufficiency

A) Carbamazepine should not be used in cases of aggravated liver dysfunction or active liver disease (Prod Info

2002c).

1.3.4 Dosage in Geriatric Patients

A) The pharmacokinetics of a single 400-milligram carbamazepine dose in 6 young and 5 elderly patients were c (Hockings et al, 1986). No age-related changes in pharmacokinetics or psychomotor function were noted. Dosage not recommended.

1.3.5 Dosage Adjustment During Dialysis

A) No dosage supplementation is required in patients following hemodialysis (Bennett et al, 1994).

B) The half life and apparent clearance of carbamazepine were not changed during hemodialysis in one woman carbamazepine 200 milligrams twice daily. No dosage adjustments are required (Kandrotas et al, 1989).

1.3.6 Dosage in Other Disease States

A) MYOCARDIAL INFARCTION

1) A case of carbamazepine toxicity (carbamazepine levels 18.2 to 21.5 micrograms/milliliter) was reported i two days after cardiothoracic surgery and intraoperative myocardial infarction; levels normalized 10 days afte dosage adjustment (Wright et al, 1990). The authors postulate that the change in levels may relate to change binding and decreased hepatic clearance resulting from both cardiopulmonary bypass surgery and myocardia specific dosage adjustment was recommended.

1.4 Pediatric Dosage

Normal Dosage

Dosage in Renal Failure

Dosage in Hepatic Insufficiency

Dosage Adjustment During Dialysis

1.4.1 Normal Dosage

Oral route

Migraine; Prophylaxis

1.4.1.A Oral route

1.4.1.A.1 Epilepsy, Partial, generalized, and mixed types

a) For children under the age of 6 years, the initial recommended dosage is 10 to 20 milligrams/kilogram administered in divided doses 2 or 3 times a day (chewable or conventional tablets) or 4 times a day (su dose may then be increased in weekly intervals to obtain the desired clinical response; maintenance dos either 3 or 4 times a day for both tablets and suspension. The maximum recommended dose is 35 mg/kg Tegretol(R), 2002c).

b) For children ages 6 to 12 years, the initial recommended dosage is 100 milligrams (mg) twice a day (sustained-release tablets) or 50 mg (one-half teaspoonful) 4 times a day (suspension). The dosage is the adding 100 mg per day in weekly intervals using a twice daily regimen for sustained-release tablets or a regimen for conventional tablets or suspension until the desired clinical response is obtained. The usual dosage is 400 to 800 mg a day; the maximum daily dosage is generally 1000 mg/day or less (Prod Info T 2002c).

c) For children over 12 years of age, the initial recommended dosage is 200 milligrams (mg) twice a day sustained-release tablets) or 100 mg (one teaspoonful) four times a day (suspension). The dosage is the adding 200 mg per day in weekly intervals using a twice daily regimen for sustained-release tablets or a regimen for conventional tablets or suspension until the desired clinical response is obtained (Prod Info T 2002c). Usual effective maintenance doses reported by the manufacturer are 800 to 1000 mg/day in chil years and up to 1200 mg in patients over 15 years old (Prod Info Tegretol(R), 2002c). This medication sh food.

d) In a review of dose-plasma concentration relationships in 196 children, usual pediatric dosage recom to 30 milligrams/kilogram/day were insufficient to achieve therapeutic serum concentrations in many pati on monotherapy. Use of higher dosages requires careful evaluation of efficacy and potential toxicity (Suz

e) Carbamazepine oral suspension was adequately absorbed from the GI tract of newborn infants with a disorders (MacKintosh et al, 1987). All infants were receiving other anticonvulsant agents in addition to c

Maintenance therapy with carbamazepine doses of 5 to 8 milligrams/kilogram orally twice a day resulted carbamazepine serum concentrations in the therapeutic range (10 to 40 micromoles/liter). An elimination from 7.2 to 15.2 hours was observed; carbamazepine oral suspension may be useful for the treatment of SEIZURES, and further study is required to evaluate its efficacy in this age group.

1.4.1.B Migraine; Prophylaxis

1) Carbamazepine 10 to 20 milligrams/kilogram/day divided into 2 daily doses has been used for migraine he prophylaxis (Hamalainen, 1998). Doses should be increased slowly.

1.4.1.C IMPORTANT NOTE

1) The dosage of carbamazepine should be adjusted to meet the needs of the individual patient based upon and monitoring of blood levels (Prod Info Tegretol(R), 2002c).

2) Loss of efficacy has been reported when carbamazepine tablets were exposed to humid conditions (Anon

3) Tegretol suspension(R) (carbamazepine) should not be administered simultaneously with other liquid mec diluents (Prod Info Tegretol(R), 2002c). The suspension will produce higher peak levels than the same dose therefore, patients should be started on lower doses of the suspension and increased slowly (Prod Info Tegre

1.4.1.D MAXIMUM DOSE

1) Dosage of tablets should not exceed 1000 milligrams daily in children 6 to 15 years and 1200 milligrams c or older (Prod Info Tegretol(R), 2002c).

2) The recommended maximum dose of carbamazepine suspension is 1000 milligrams/day in children 6 to 1 1200 milligrams/day in children over 15 years (Prod Info Tegretol(R), 2002c).

1.4.1.E WITHDRAWAL OF THERAPY

1) Withdrawal of anticonvulsant medication in children free of seizures for 2 to 4 years appears to be safe, w children remaining free of seizures after medication withdrawal (Shinnar et al, 1985). In a prospective study, a medications were discontinued in 88 epileptic children who had not had a seizure for 2 to 4 years. Anticonvul withdrawn gradually over 2 to 3 months. The mean age at the time of the first seizure was 5 years (0 to 16 ye mean age at the time of the last seizure being 8.7 years (0 to 22 years). The mean duration of seizures was 3 to 17.4 years). Sixty-six (75%) patients remained free of seizures after withdrawal of anticonvulsants, and the of remaining seizure-free was 79% at 12 months, 77% at 24 months, and 74% at 30 months. The risk of recu was highest within the first few months of initiation of withdrawal. Of 22 patients with recurrence of seizures, 9 the first 3 months, 13 in the first 6 months and 18 (82%) within the first year of withdrawal. The type of seizure and EEG characteristics were considered important in predicting the outcome of anticonvulsant withdrawal. It that anticonvulsants be discontinued in children with good prognostic factors after a 2- year period without se

1.4.2 Dosage in Renal Failure

A) No dosage reduction is required in patients with renal impairment (Bennett et al, 1994).

1.4.3 Dosage in Hepatic Insufficiency

A) DOSAGE IN HEPATIC INSUFFICIENCY

1) Carbamazepine should not be used in cases of aggravated liver dysfunction or active liver disease (Prod 2002c).

1.4.4 Dosage Adjustment During Dialysis

A) No dose supplementation is required in patients following hemodialysis (Bennett et al, 1994).

B) The half life and apparent clearance of carbamazepine were not changed during hemodialysis in one woman carbamazepine 200 milligrams twice daily. No dosage adjustments are required (Kandrotas et al, 1989).

2.0 Pharmacokinetics

Drug Concentration Levels

ADME

2.2 Drug Concentration Levels

A) Therapeutic Drug Concentration

1) Seizure disorder, 4 to 12 mcg/mL (16 to 50 mmol/L) (Prod Info Tegretol(R), 2002a; Rapeport, 1985).

a) Monitoring of free CARBAMAZEPINE concentrations is indicated in conditions associated with altered bin (Perucca, 1984).

b) Saliva and plasma carbamazepine, total and free levels, have a strong and highly significant correlation (r respectively) (Gorodischer et al, 1997).

c) According to plasma levels, no dosage adjustments are needed during the gestational period (Tomson et al, 1985).

d) Urine levels correlate closely with free plasma levels (Elmquist et al, 1991).

e) Extended-release capsules taken every 12 hours provide steady state plasma levels comparable to imme tablets taken every 6 hours at the same milligram dose (Prod Info Carbatrol(R), 2002a).

f) Some researchers advocate the need for monitoring the carbamazepine-10, 11-epoxide metabolite (Potter

1998).
2) Antidepressant/Antimania, no correlation (Post et al, 1983).
B) Time to Peak Concentration
1) Oral, immediate release: 4 to 5 hours (Prod Info Tegretol(R), 2002a; Sillanpaa, 1981).
2) Oral, chew tablets: 6 hours (Prod Info Tegretol(R), 1990).
3) Oral, extended release: 3 to 12 hours (Prod Info Tegretol(R), 2002a; Prod Info Carbatrol(R), 2002a).
4) Oral, suspension: 1.5 hours (Prod Info Tegretol(R), 2002a).

2.3 ADME

Absorption

Distribution

Metabolism

Excretion

Elimination Half-life

Extracorporeal Elimination

2.3.1 Absorption
A) Bioavailability
1) Oral, tablet: 70% to 79% (Hvidberg & Dam, 1976; Levy et al, 1975).
2) Oral, solution: 95.9% (Levy et al, 1975).
3) Oral, extemporaneously formulated suspension: 94.5% (Bloomer et al, 1987).
a) An extemporaneously prepared oral suspension of carbamazepine had a mean bioavailability of 94.5 tablet formulation. However, peak serum concentrations occurred earlier and were higher as compared t formulation; peak serum concentrations occurred in 3.8 hours and 11.8 hours following administration of tablet, respectively. These data suggest that more frequent administration of lower doses of the suspens indicated to avoid toxicity, as compared to the tablet formulation (Bloomer et al, 1987).
B) Effects of Food
1) increases bioavailability (Levy et al, 1975).

2.3.2 Distribution
A) Distribution Sites
1) Protein Binding
a) 76% (Prod Info Carbatrol(R), 2002a; Prod Info Tegretol(R), 2002a).
1) Unbound drug decreases with increasing total concentrations (Hooper et al, 1975).
2) Tissues and Fluids
a) Cerebrospinal fluid (CSF), the CSF/serum ratio 0.22 (Prod Info Tegretol(R), 2002a).
B) Distribution Kinetics
1) Volume of Distribution
a) 0.8 to 2 L/kg (Graves et al, 1985; Hvidberg & Dam, 1976; Rawlins et al, 1975).

2.3.3 Metabolism
A) Metabolism Sites and Kinetics
1) Liver, 98% (Levy et al, 1975)
a) Carbamazepine induces its own metabolism during prolonged treatment, and is complete in 3 to 5 we dosing regimen (Prod Info Tegretol(R), 2002a).
b) With increasing carbamazepine doses in children, a dose-dependent autoinduction process was seer al, 1997).
c) Metabolism occurs via cytochrome P450 3A4 (Prod Info Tegretol(R), 2002a).
B) Metabolites
1) Carbamazepine-10,11-epoxide, active (Bertilsson, 1978; Tomson et al, 1983)
a) Carbamazepine-10,11-epoxide/CARBAMAZEPINE ratios are higher in infants and preschool children 1985a).
b) Epoxide metabolite exists in a 0.1 to 0.2 ratio to CARBAMAZEPINE 120 hours after administration (E 1975). In 1 study, the carbamazepine epoxide to carbamazepine ratio in serum was 0.12 during monothe et al, 1998). This ratio rose to 0.14 when phenobarbital was added, to 0.18 when phenytoin was added, both phenobarbital and and phenytoin were added. These increased ratios were seen as carbamazepine declined.
c) The epoxide metabolite is partly responsible for CARBAMAZEPINE intoxication (Hvidberg & Dam, 19

d) Higher epoxide levels are seen in patients receiving concomitant valproate or lamotrigine therapy (Pc 1998).

2) 9 hydroxymethyl-10-carbamoyl acridan, active (Wad et al, 1997).

2.3.4 Excretion

A) Kidney

1) Renal Excretion (%)

a) 72% (Prod Info Tegretol(R), 2002a)

B) Total Body Clearance

1) 3.85 L/hr (Graves et al, 1985).

a) Clearance in children was reported to be 2.37 liters/hour (Iribarnegaray et al, 1997). Clearance increa increasing doses. Clearance decreases with increasing age (Gray et al, 1998).

b) Patients 70 years and older had a decreased clearance by approximately 70% (Graves et al, 1985).

C) Other

1) Feces, 28% (Prod Info Tegretol(R), 2002a; Hvidberg & Dam, 1976).

2.3.5 Elimination Half-life

A) Parent Compound

1) ELIMINATION HALF-LIFE

a) 12 to 17 hours (Prod Info Carbatrol(R), 2002a; Prod Info Tegretol(R), 2002a; Hvidberg & Dam, 1976)

1) The half-life is 25 to 65 hours with single doses (Prod Info Tegretol(R), 2002a; Hvidberg & Dam,

2) Newborn infants, receiving the drug transplacentally, have half-life values within the same range multiple doses (Rane et al, 1975).

B) Metabolites

1) 10,11-epoxide metabolite, 6.1 hours (Tomson et al, 1983; Bertilsson & Tomson, 1986).

2.3.6 Extracorporeal Elimination

A) Hemodialysis

1) Dialyzable: Yes, 53.6 mL/min (Lee et al, 1980)

a) Clearance ranges from 40 to 64 mL/min (mean 53.6 mL/min). Calculated total drug removed over a 4 period ranges from 40.5 to 53.1 mg (Lee et al, 1980).

B) Peritoneal

1) Dialyzable: No (Bradley et al, 1984)

a) Carbamazepine is minimally dialyzable during peritoneal dialysis (Bradley et al, 1984).

3.0 Cautions

Contraindications

Precautions

Adverse Reactions

Teratogenicity/Effects in Pregnancy/Breastfeeding

Drug Interactions

3.0.A Black Box WARNING

1) Oral (Tablet; Tablet, Chewable; Suspension; Tablet, Extended Release; Capsule, Extended Release)

Serious Dermatologic Reactions and HLA-B*1502 Allele

Serious and sometimes fatal dermatologic reactions, including toxic epidermal necrolysis (TEN) and Stevens syndrome (SJS), have been reported during treatment with carbamazepine. These reactions are estimated to per 10,000 new users in countries with mainly Caucasian populations, but the risk in some Asian countries is about 10 times higher. Studies in patients of Chinese ancestry have found a strong association between the r SJS/TEN and the presence of HLA-B*1502, an inherited allelic variant of the HLA-B gene. HLA-B*1502 is fou exclusively in patients with ancestry across broad areas of Asia. Patients with ancestry in genetically at-risk p be screened for the presence of HLA-B*1502 prior to initiating treatment with carbamazepine. Patients testing allele should not be treated with carbamazepine unless the benefit clearly outweighs the risk.

Aplastic Anemia and Agranulocytosis

Aplastic anemia and agranulocytosis have been reported in association with the use of carbamazepine. Data based case control study demonstrate that the risk of developing these reactions is 5-8 times greater than in population. However, the overall risk of these reactions in the untreated general population is low, approxima per one million population per year for agranulocytosis and two patients per one million population per year fo Although reports of transient or persistent decreased platelet or white blood cell counts are not uncommon in the use of carbamazepine, data are not available to estimate accurately their incidence or outcome. However

of the cases of leukopenia have not progressed to the more serious conditions of aplastic anemia or agranulc
Because of the very low incidence of agranulocytosis and aplastic anemia, the vast majority of minor hemato
observed in monitoring of patients on carbamazepine are unlikely to signal the occurrence of either abnormal
complete pretreatment hematological testing should be obtained as a baseline. If a patient in the course of tre
low or decreased white blood cell or platelet counts, the patient should be monitored closely. Discontinuation
be considered if any evidence of significant bone marrow depression develops (Prod Info TEGRETOL(R) ora
tablets, suspension, 2007; Prod Info TEGRETOL(R)-XR extended-release oral tablets, 2007).

3.1 Contraindications

A) bone marrow depression, history of previous (Prod Info TEGRETOL(R) oral chewable tablets, tablets, suspension, TEGRETOL(R)-XR extended-release oral tablets, 2007)

B) concomitant use of an MAOI, or use within 14 days of discontinuing an MAOI (Prod Info TEGRETOL(R) oral chew tablets, suspension, 2007; Prod Info TEGRETOL(R)-XR extended-release oral tablets, 2007)

C) concomitant use of nefazodone; decreased nefazodone plasma levels may reduce drug effectiveness (Prod Info T chewable tablets, tablets, suspension, 2007; Prod Info TEGRETOL(R)-XR extended-release oral tablets, 2007)

D) hypersensitivity to carbamazepine or tricyclic compounds (Prod Info TEGRETOL(R) oral chewable tablets, tablets, Prod Info TEGRETOL(R)-XR extended-release oral tablets, 2007)

3.2 Precautions

A) dermatologic reactions, serious and sometimes fatal (eg, Stevens-Johnson syndrome, toxic epidermal necrolysis) reported; discontinue drug if signs or symptoms develop (Prod Info TEGRETOL(R) oral chewable tablets, tablets, susp Prod Info TEGRETOL(R)-XR extended-release oral tablets, 2007)

B) HLA-B*1502-positive (most common in Asians including South Asian Indians); increased risk of Stevens-Johnson toxic epidermal necrolysis; test for HLA-B*1502 and if positive do not initiate carbamazepine (Prod Info TEGRETOL(R tablets, tablets, suspension, 2007; Prod Info TEGRETOL(R)-XR extended-release oral tablets, 2007)

C) adverse hematologic drug reaction, history of; increased risk of bone marrow suppression (Prod Info TEGRETOL(tablets, tablets, suspension, 2007; Prod Info TEGRETOL(R)-XR extended-release oral tablets, 2007)

D) (Prod Info TEGRETOL(R) chewable oral tablets, oral tablets, suspension, 2007; Prod Info TEGRETOL(R)-XR exte tablets, 2007a)

E) atypical absence seizures or other mixed seizure disorders, history of; may increase generalized convulsion freque TEGRETOL(R) oral chewable tablets, tablets, suspension, 2007; Prod Info TEGRETOL(R)-XR extended-release oral

F) cardiac conduction disturbance, history; increased risk of atrioventricular heart block (Prod Info TEGRETOL(R) ora tablets, suspension, 2007; Prod Info TEGRETOL(R)-XR extended-release oral tablets, 2007)

G) cardiac damage (Prod Info TEGRETOL(R) oral chewable tablets, tablets, suspension, 2007; Prod Info TEGRETOL release oral tablets, 2007)

H) elderly patients; may cause confusion or agitation (Prod Info TEGRETOL(R) oral chewable tablets, tablets, susper Info TEGRETOL(R)-XR extended-release oral tablets, 2007)

I) electrocardiogram abnormalities; increased risk of atrioventricular heart block (Prod Info TEGRETOL(R) oral chewa suspension, 2007; Prod Info TEGRETOL(R)-XR extended-release oral tablets, 2007)

J) hypersensitivity drug reactions, history of; risk of cross-sensitivity (Prod Info TEGRETOL(R) oral chewable tablets, suspension, 2007; Prod Info TEGRETOL(R)-XR extended-release oral tablets, 2007)

K) hepatic damage (Prod Info TEGRETOL(R) oral chewable tablets, tablets, suspension, 2007; Prod Info TEGRETOL release oral tablets, 2007)

L) hepatic porphyria; acute attacks have been reported and use should be avoided (Prod Info TEGRETOL(R) oral che tablets, suspension, 2007; Prod Info TEGRETOL(R)-XR extended-release oral tablets, 2007)

M) interrupted courses of carbamazepine therapy, history of (Prod Info TEGRETOL(R) oral chewable tablets, tablets, Prod Info TEGRETOL(R)-XR extended-release oral tablets, 2007)

N) increased intraocular pressure; exacerbation of condition due to cholinergic antagonism (Prod Info TEGRETOL(R) tablets, tablets, suspension, 2007; Prod Info TEGRETOL(R)-XR extended-release oral tablets, 2007)

O) mental illness, history; risk of latent psychosis activation (Prod Info TEGRETOL(R) oral chewable tablets, tablets, Prod Info TEGRETOL(R)-XR extended-release oral tablets, 2007)

P) renal damage (Prod Info TEGRETOL(R) oral chewable tablets, tablets, suspension, 2007; Prod Info TEGRETOL(R release oral tablets, 2007)

Q) suicidality, increased risk of; based on data analysis of 199 placebo-controlled studies of 11 antiepileptic drugs, sm occurred as early as 1 week after starting therapy and continued to at least 24 weeks (US Food and Drug Administrati

R) women of childbearing potential; teratogenic effects have been reported and efficacy of oral contraceptives may be Info TEGRETOL(R) oral chewable tablets, tablets, suspension, 2007; Prod Info TEGRETOL(R)-XR extended-release

3.3 Adverse Reactions

Cardiovascular Effects

Dermatologic Effects

Endocrine/Metabolic Effects

Gastrointestinal Effects

Hematologic Effects

Hepatic Effects

Immunologic Effects

Musculoskeletal Effects

Neurologic Effects

Ophthalmic Effects

Otic Effects

Psychiatric Effects

Renal Effects

Reproductive Effects

Respiratory Effects

Other

3.3.1 Cardiovascular Effects

Cardiac dysrhythmia

Cardiovascular finding

Congestive heart failure

Heart disease

Vasculitis

3.3.1.A Cardiac dysrhythmia

1) Summary

a) Carbamazepine may suppress both atrioventricular conduction and ventricular automaticity shortly af
administration. bradyarrhythmia and av block occur at therapeutic or mildly elevated carbamazepine bloc
most frequently reported in elderly women. sinus tachycardia has also been reported in overdose situatic
Tegretol(R), 2002b; Kasarskis et al, 1992).

2) Literature Reports

a) Three cases of stokes-adams attacks caused by intermittent AV block, SA block with junctional escap
intermittent asystole secondary to carbamazepine were described (Boesen et al, 1983). Conduction distu
after withdrawal of therapy and recurrence of symptoms was noted after resumption of treatment in 2 pa
pacemaker insertion. Since epileptic seizures and Stokes-Adams attacks are at times difficult to different
suggested that if syncope or changes in seizure patterns occur in patients treated

b) Cardiac conduction abnormalities were reported in an isolated case involving a 13-month-old child, d
serum levels of both carbamazepine and 10,11-epoxide metabolite (Weig & Pollack, 1993). The patient h
tuberous sclerosis and cardiac rhabdomyoma. After two weeks of therapy with carbamazepine, the child
irregular heart rate; EKG and Holter monitor showed intermittent periods of Mobitz type II second-degree
block and occasional premature ventricular beats. Carbamazepine was discontinued with resolution of ca
irregularities.

3.3.1.B Cardiovascular finding

1) Cardiovascular effects reported in patients receiving carbamazepine include AV block, arrhythmias, conge aggravation of hypertension, hypotension, syncope and collapse, edema, vasculitis, aggravation of coronary primary thrombophlebitis, and recurrence of thrombophlebitis. Some of these cardiovascular effects have res

3.3.1.C Congestive heart failure

1) Summary

a) One case of congestive heart failure associated with carbamazepine therapy was reported (Prod Info 2002b; Terrence & Fromm, 1980).

2) Literature Reports

a) A 33-year-old black man with a 12-year history of complex partial and left-sided sensory seizures hac 200 mg added to his anticonvulsant regimen. The dose was subsequently increased to 400 and 600 milli hospital days 4 and 6, respectively. On day 13 the patient complained of pedal edema, shortness of brea Over the next 48 hours the patient received 100 mg furosemide orally and carbamazepine was discontin of diuresis, the patient was asymptomatic and follow-up for 15 months was uneventful with no recurrence symptoms of congestive heart failure (Terrence & Fromm, 1980).

3.3.1.D Heart disease

1) Summary

a) Cardiovascular effects reported in patients receiving carbamazepine include aggravation of hypertens syncope and collapse, edema, aggravation of coronary artery disease, primary thrombophlebitis, and rec thrombophlebitis. Some of these cardiovascular effects have resulted in death (Prod Info Tegretol(R), 20

3.3.1.E Vasculitis

1) Summary

a) A case of leukocytoclastic vasculitis was reported in a 66-year-old male using carbamazepine therap Shant, 1987).

2) Literature Reports

a) Nonthrombocytopenic purpura with histological features of leukocytoclastic vasculitis was described i male with trigeminal neuralgia following carbamazepine 200 milligrams by mouth, three times daily (PO approximately 3 weeks. Withdrawal of carbamazepine and therapy with hydrocortisone IV resulted in gra purpura resolved within 3 months. Rechallenge was not undertaken in this patient (Harats & Shant, 1987

3.3.2 Dermatologic Effects

Acne

Alopecia

Dermatitis

Diaphoresis

Disorder of skin pigmentation

Drug-induced toxic pustuloderma

Eosinophilic pustular folliculitis

Erythema

Erythema multiforme

Fixed drug eruption

Hirsutism

Lichenoid dermatitis

Mycosis fungoides

Onychomadesis

Photosensitivity

Pruritic rash

Rash

Stevens-Johnson syndrome

Summary

Toxic epidermal necrolysis

Urticaria

3.3.2.A Acne

1) Summary

a) The prevalence of acne in patients on anticonvulsant medication compared to those in a control popu different (Greenwood et al, 1983; Harman, 1967; Simpson, 1966).

2) Literature Reports

a) One long-term study has evaluated the incidence of acne in 243 patients with epilepsy receiving varic on a long- term basis. Results were compared with matched controls from a normal population of 2,176 i prevalence of acne or sebum excretion rate was not different in anticonvulsant treated patients as compa group, or in patients taking phenytoin as compared to those who were not taking phenytoin. However, pr regarding length of anticonvulsant treatment, types of drugs administered and doses were not presented 1983; Harman, 1967; Simpson, 1966).

3.3.2.B Alopecia

1) Summary

a) Alopecia has been reported with carbamazepine therapy (Prod Info TEGRETOL(R) oral chewable tab suspension, 2007; Prod Info TEGRETOL(R)-XR extended-release oral tablets, 2007; Ikeda et al, 1997).

2) Literature Reports

a) Two young women developed alopecia after being treated with carbamazepine for partial seizures. O also experienced alopecia with valproic acid. Alopecia began after 2 to 3 months of therapy. The hair los was described as becoming sparse mostly in the front of her head. Hair loss stopped after one woman's decreased and the other woman was switched to phenobarbital (Ikeda et al, 1997).

3.3.2.C Dermatitis

1) Summary

a) Exfoliative dermatitis induced by carbamazepine has been reported in the literature (Prod Info TEGRI chewable tablets, tablets, suspension, 2007; Prod Info TEGRETOL(R)-XR extended-release oral tablets, Bieder, 1968; Reed et al, 1982). These reactions usually resolve upon withdrawal of carbamazepine.

3.3.2.D Diaphoresis

1) Diaphoresis has been reported with carbamazepine therapy. Discontinuation of therapy may be necessar (Prod Info TEGRETOL(R) oral chewable tablets, tablets, suspension, 2007; Prod Info TEGRETOL(R)-XR ext tablets, 2007).

3.3.2.E Disorder of skin pigmentation

1) Alterations in skin pigmentation have been reported with carbamazepine therapy. Discontinuation of thera necessary in some cases (Prod Info TEGRETOL(R) oral chewable tablets, tablets, suspension, 2007; Prod Ir (R)-XR extended-release oral tablets, 2007).

3.3.2.F Drug-induced toxic pustuloderma

1) Toxic pustuloderma was described in a 24-year-old woman, in association with erythema multiforme, follo carbamazepine therapy 200 milligrams daily for approximately 2 weeks. The patient improved following 4 da wet packs and hydrocortisone topical cream; however, there was a residual post inflammatory hyperpigmenta Fischer, 1988). These data suggest that carbamazepine is capable of producing pustular drug reactions.

3.3.2.G Eosinophilic pustular folliculitis

1) Summary

a) A 58-year-old male developed eosinophilic pustular folliculitis (Ofuji's disease) after taking acetamino carbamazepine for headache and fever (Mizoguchi et al, 1998).

2) Literature Reports

a) A 58-year-old male developed eosinophilic pustular folliculitis (Ofuji's disease) after taking acetamino

carbamazepine for headache and fever (Mizoguchi et al, 1998). Patch testing revealed carbamazepine a drug. Initially, he experienced stomatitis and edematous erythema with papules and pustules. Two montl edema of the upper eyelids, erythema with follicular papules and pustules on the face, neck, chest and u Eosinophil-rich folliculitis with mononuclear cells and neutrophil infiltration was seen on biopsy. He also h and elevated IgE. The eruptions subsided over 2 months with prednisolone 30 milligrams/day.

3.3.2.H Erythema

1) Although prudence suggests the withdrawal of carbamazepine following the occurrence of dermatologic re reactions necessitate permanent carbamazepine (CBZ) withdrawal. Three patients developed an erythemato their face and neck, accompanied by slight fever. Symptoms resolved within 5 to 6 days following CBZ withdr rechallenge with the drug several months later was uneventful (Livingston et al, 1974).

3.3.2.I Erythema multiforme

1) Summary

a) Several cases of erythema multiforme have been noted with carbamazepine therapy. Erythema nodo reported (Prod Info TEGRETOL(R) oral chewable tablets, tablets, suspension, 2007; Prod Info TEGRET extended-release oral tablets, 2007; Ward, 1987; Green, 1986; Meisel & North, 1984; Reed et al, 1982; I 1968).

2) Literature Reports

a) Product selection may have a bearing on the occurrence of dermatological reactions secondary to ca 38-year-old woman who had been treated with carbamazepine for several years without incident, develo multiforme a week after receiving a generic version of the drug. Symptoms resolved spontaneously one discontinuation of the drug. Because of her continuing pain from trigeminal neuralgia, carbamazepine (T restarted and there was no recurrence of symptoms (Busch, 1989).

b) A 36-year-old woman receiving chronic carbamazepine therapy experienced facial erythema and ede photocopier for 2 hours. Superficial corneal burns were present one month later (Ward, 1987).

c) Erythema multiforme was described twice in the same patient (43-year-old woman): first in associatio and then with carbamazepine (Green, 1986). The patient developed a seizure disorder secondary to an i malignant neoplasm considered inoperable, and was given phenytoin 300 milligrams by mouth at bedtim betamethasone. A maculopapular rash developed 3 weeks later, which extended to much of the skin sur multiforme was diagnosed and phenytoin was discontinued resulting in improvement despite replacemer carbamazepine 100 milligrams by mouth 3 times a day (PO TID). Approximately one year later, the patie with a severe dull red maculopapular rash covering most of the body surface. Withdrawal of carbamazep subsidence of symptoms, and the patient was treated with valproic acid (and betamethasone) without fu sequelae. It is suggested that concurrent betamethasone therapy in this patient may have prevented a m reaction from occurring. However, based upon data provided in this report, it is unclear if either phenytoi carbamazepine were the sole cause of the erythema multiforme episodes in this patient.

d) Severe erythema multiforme with extreme eosinophilia was described in a 57-year-old Navajo Indian carbamazepine therapy 200 milligrams by mouth 3 times a day (PO TID) for 2 months for partial seizure reaction occurred upon inadvertent reinstitution of drug therapy by the patient (Meisel & North, 1984).

3.3.2.J Fixed drug eruption

1) A case of a fixed drug eruption due to carbamazepine has also been reported (Shuttleworth & Graham-Br

3.3.2.K Hirsutism

1) Isolated cases of hirsutism have been reported although a causal relationship has not been established (F TEGRETOL(R) oral chewable tablets, tablets, suspension, 2007; Prod Info TEGRETOL(R)-XR extended-rele 2007)

3.3.2.L Lichenoid dermatitis

1) A 75-year-old male developed a lichenoid reaction (biopsy specimens confirming lichen planus) within 2 w of carbamazepine therapy. The rash resolved 7 days after discontinuation of the drug. On rechallenge with ca lichenoid rash reappeared (Thompson & Skaehill, 1994).

3.3.2.M Mycosis fungoides

1) Summary

a) Mycosis fungoides-like lesions have been reported in association with carbamazepine therapy. Cases several months of therapy and skin lesions were present without evidence of systemic symptoms. Skin b revealed lymphoid infiltrates. Patients responded promptly to discontinuation of the drug and treatment w (Welykyj et al, 1990; Rijlaarsdam et al, 1991).

b) Several different types of skin reactions have been associated with carbamazepine (CBZ), including r pruritic rash, erythema multiforme, light sensitive dermatitis, lichenoid eruptions and mycosis fungoides (Rijlaarsdam et al, 1991).

3.3.2.N Onychomadesis

1) Summary

a) A possible case of onychomadesis induced by carbamazepine in a 31-year-old man with complex-pa reported (Mishra et al, 1989).

2) Literature Reports

a) A possible case of onychomadesis induced by carbamazepine in a 31-year-old man with complex-pa reported (Mishra et al, 1989). Nail detachment and pale color were first reported following 4 months of th discontinuation of carbamazepine, fingernails eventually grew back but had a mild bluish hue.

3.3.2.O Photosensitivity

1) Photosensitivity reactions have been reported with carbamazepine therapy. Discontinuation of therapy ma some cases (Prod Info TEGRETOL(R) oral chewable tablets, tablets, suspension, 2007; Prod Info TEGRETC extended-release oral tablets, 2007).

3.3.2.P Pruritic rash

1) Purpura has been reported with carbamazepine therapy. Discontinuation of therapy may be necessary in Info TEGRETOL(R) oral chewable tablets, tablets, suspension, 2007; Prod Info TEGRETOL(R)-XR extended tablets, 2007).

3.3.2.Q Rash

1) Summary

a) Reactions including erythematous and pruritic rashes have occurred. Concomitant rashes and blood also been reported associated with carbamazepine therapy (Prod Info TEGRETOL(R) oral chewable tab suspension, 2007; Prod Info TEGRETOL(R)-XR extended-release oral tablets, 2007; Cates & Powers, 1

2) Literature Reports

a) Thirty-three out of 335 (9.9%) children with epilepsy, who were treated with carbamazepine develope Rash was more frequent in children over 6 years old, and appeared on the average, within 2 weeks of in (Konishi et al, 1993).

b) A case of a generalized, pruritic, erythematous rash, which developed after 3 months of carbamazepi been reported. Over the course of a month, this rash developed into florid lichenoid lesions. Biopsy revea hyperkeratosis, localized acanthosis and the presence of eosinophilic infiltrates. Gradual resolution of th following discontinuation of the drug and treatment with betamethasone cream (Atkin et al, 1990).

c) Prednisone 40 milligrams daily was effective in treating carbamazepine-induced skin rash in 3 patient unresponsive to other anticonvulsants. Gradual tapering of prednisone followed by discontinuation succe carbamazepine to be continued in 2 patients. The third patient again experienced a rash after prednison had a permanent response to another course of prednisone therapy after 6 weeks of tapering (Vick, 198

d) Rashes were described in 3 patients who received treatment with carbamazepine. A 75-year-old mar receiving carbamazepine 800 milligrams (mg) daily for 2 weeks for treatment of trigeminal neuralgia dev rash, which rapidly became widespread and involved the limbs. Lichenoid papules were present on his w dorsal surfaces of his feet. Carbamazepine therapy was discontinued with notable improvement in the ra within 7 days. The patient was rechallenged with 800 mg/day of carbamazepine and within 24 hours pru days later, a red, scaly, itchy rash appeared, which was most prominent in light-exposed areas. Two oth developed an exfoliative eczema, which subsequently disappeared when carbamazepine therapy was di (Roberts & Marx, 1981).

e) A skin reaction occurred in a 63-year-old male with a previous history of dermatological disease. Duri therapy, an eruption developed which was identical to his previous eczema. In 3 months, a non-irritant ra different nature developed in his right scapular region and was associated with pain and malaise. The pa developed an eruption of heliotrope color affecting the eyelids, eyebrows, elbows, and wrists. The clinica suggestive of either lupus erythematosus or dermatomyositis. Upon discontinuation of the drug the patie spontaneously. There was prompt recurrence of the skin reaction when therapy was restarted (Simpson,

3.3.2.R Stevens-Johnson syndrome

1) Summary

a) Carbamazepine therapy has been associated with serious and sometimes fatal dermatologic reactior Stevens-Johnson Syndrome (SJS). Over 90% of the patients experience these reactions within the first f carbamazepine therapy. These reactions occurred at an estimated rate of 1 to 6 per 10,000 new users w Caucasian populations, but the risk in some Asian countries is estimated to be about 10 times higher. Th correlation between the risk of developing these reactions and the presence of human leukocyte antigen B*1502) allele, an inherited allelic variant of the HLA-B gene, among patients of Asian ancestry, particula ancestry. Based on a case control study, there is an absolute risk of 5% for TEN/Stevens Johnson Syndr B*1502 positive patients on carbamazepine. Individuals not of Asian origin (eg, Caucasians, African-Ame and Native Americans) generally are not HLA-B*1502 positive, yet, are still at risk for fatal dermatologic r Genetically at-risk patients should be screened prior to receiving carbamazepine. Careful assessment of should be conducted among patients tested positive for the allele prior to initiation of carbamazepine. Pa been taking carbamazepine for more than a few months (including HLA-B*1502 positive Asians) are at lo (Prod Info TEGRETOL(R) oral chewable tablets, tablets, suspension, 2007; Prod Info TEGRETOL(R)-XR oral tablets, 2007; US Food and Drug Administration, 2007).

2) Human Leukocyte Antigen-B*1502 (HLA-B*1502) Positive

a) Human leukocyte antigen-B*1502 (HLA-B*1502) allele is common in Asians including South Asian In prevalence of HLA-B*1502 is not known for all regions of Asia. The following are known HLA-B*1502 pos rates in some regions of Asia: greater than 15% in Hong Kong, Thailand, Malaysia, and parts of the Phili in Taiwan; 4% in North China; 2% to 4% in South Asians, including Indians but may be higher in some gr

than 1% in Japan and Korea. Individuals not of Asian origin (eg, Caucasians, African-Americans, Hispan Americans) generally are not HLA-B*1502 positive (Prod Info TEGRETOL(R) oral chewable tablets, tabl 2007; Prod Info TEGRETOL(R)-XR extended-release oral tablets, 2007).

3) Literature Reports

a) Short-term therapy with carbamazepine has been associated with Stevens Johnson Syndrome (SJS) epidermal necrolysis (TEN) in a case-control study and appears to be a risk factor. Twenty- one cases w either SJS or TEN following a range of therapy of 2 to 4 weeks. The risk is largely confined to the start of therapy (Rzany et al, 1999).

b) Stevens-Johnson syndrome (erythema multiforme major) was described in a 22-year-old male followi 4 weeks of carbamazepine therapy (200 milligrams by mouth 3 times a day). At that time, the patient pre rash, fever, chills, and sore throat of three days duration; carbamazepine as well as previous (lithium and discontinued; however, the rash progressed to multiple confluent bullous lesions about the face, shoulde mucosa. A maculopapular rash extended over the rest of the thorax, anteriorly and posteriorly, and to the Stevens-Johnson syndrome was diagnosed and the patient was eventually treated intensively with IV flu The patient recovered following several months of hospitalization. However, based upon data presented ascertain if carbamazepine was the cause of this patient's skin reaction (Fawcett, 1987).

c) Cases of exfoliative dermatitis, including Steven's-Johnson syndrome, have been reported in patients carbamazepine (CBZ). Generally these patients have been successfully treated with steroids and discon with recovery occurring within 3 weeks (Hoang-Xuan et al, 1990); (Vaillant et al, 1989)(Pagliaro & Paglia

3.3.2.S Summary

1) Various dermatologic reactions have been associated with carbamazepine use in an estimated 4% of trea onset generally occurs at approximately 1 month (range 2 weeks to 5 months) after starting therapy. Reactio erythematous and pruritic rashes, urticaria, toxic epidermal necrolysis, Stevens-Johnson syndrome, photoser alterations in skin pigmentation, exfoliative dermatitis, erythema multiforme and nodosum, purpura, alopecia, Hirsutism has been reported in isolated cases. In addition, toxic pustuloderma and onychomadesis were eac case. Cases of exfoliative dermatitis induced by carbamazepine have been reported in the literature. These r resolve upon withdrawal of carbamazepine. Other reactions such as mild erythema may resolve even with co

3.3.2.T Toxic epidermal necrolysis

1) Summary

a) Carbamazepine therapy has been associated with serious and sometimes fatal dermatologic reactior epidermal necrolysis (TEN). Over 90% of the patients experience these reactions within the first few mor carbamazepine therapy. These reactions occurred at an estimated rate of 1 to 6 per 10,000 new users w Caucasian populations, but the risk in some Asian countries is estimated to be about 10 times higher. Th correlation between the risk of developing these reactions and the presence of human leukocyte antigen B*1502) allele, an inherited allelic variant of the HLA-B gene, among patients of Asian ancestry, particula ancestry. Based on a case control study, there is an absolute risk of 5% for TEN/Stevens Johnson Syndr B*1502 positive patients on carbamazepine. Individuals not of Asian origin (eg, Caucasians, African-Ame and Native Americans) generally are not HLA-B*1502 positive, yet, are still at risk for fatal dermatologic r Genetically at-risk patients should be screened prior to receiving carbamazepine. Careful assessment of should be conducted among patients tested positive for the allele prior to initiation of carbamazepine. Pa been taking carbamazepine for more than a few months (including HLA-B*1502 positive Asians) are at lo (Prod Info TEGRETOL(R) oral chewable tablets, tablets, suspension, 2007; Prod Info TEGRETOL(R)-XR oral tablets, 2007; US Food and Drug Administration, 2007).

2) Literature Reports

a) Toxic epidermal necrolysis was reported in a 5 year-old male following treatment with carbamazepine a history of epileptic seizures treated with carbamazepine 100 mg/day. Titration of carbamazepine was b 100 mg weekly. Three weeks later, (1 day after the last increment) the patient was admitted to the hospit of malaise, fever, and erythematous rash on his face and neck. Carbamazepine was immediately discon antihistamine with methylprednisolone 2 mg/kg/day was initiated. His rash and bullae continued to sprea his body within 24 hours and the patient was transferred to the pediatric ICU. Both the antihistamine and methylprednisolone were discontinued. IV immunoglobulin 1 g/kg/day was given for 2 days along with ag replacement, enteral and parenteral nutrition , and appropriate infection and wound management. On da cultures were positive for Escherichia coli, which was treated with cefotaxime and amikacin. A 3-day cou colony-stimulating factor was initiated. From day 10, no new lesions occurred. On day 37 of hospitalizatio epithelialized and the patient was discharged (Sevketoglu et al, 2009).

b) A suspected case of Lyell's syndrome was reported in a 52-year-old male treated with carbamazepin neuralgia. The patient received 200 milligrams (mg) 3 times daily for 15 days and developed a pruritic ra dryness of the oral mucosa. After a 2 day interval, a single 200 mg dose was administered resulting in ge headache and fever with a general exudative erythema. The patient then developed icterus, hepatomega hemorrhage. Tachycardia, hypotension, and respiratory difficulty ensued. Complete epidermal necrolysis followed. Laboratory findings were consistent with those of Lyell's syndrome. The patient also developed septicemia. He was treated with corticosteroids, antihistamines and antibiotics with complete recovery (M Khramtsova, 1976).

3) Human Leukocyte Antigen-B*1502 (HLA-B*1502) Positive

a) Human leukocyte antigen-B*1502 (HLA-B*1502) allele is common in Asians including South Asian In prevalence of HLA-B*1502 is not known for all regions of Asia. The following are known HLA-B*1502 pos

rates in some regions of Asia: greater than 15% in Hong Kong, Thailand, Malaysia, and parts of the Phili in Taiwan; 4% in North China; 2% to 4% in South Asians, including Indians but may be higher in some g than 1% in Japan and Korea. Individuals not of Asian origin (eg, Caucasians, African-Americans, Hispan Americans) generally are not HLA-B*1502 positive (Prod Info TEGRETOL(R) oral chewable tablets, tabl 2007; Prod Info TEGRETOL(R)-XR extended-release oral tablets, 2007).

3.3.2.U Urticaria

1) Urticaria has been reported with carbamazepine therapy. Discontinuation of therapy may be necessary in Info TEGRETOL(R) oral chewable tablets, tablets, suspension, 2007; Prod Info TEGRETOL(R)-XR extended tablets, 2007).

3.3.3 Endocrine/Metabolic Effects

Acute intermittent porphyria

Body temperature above normal

Hyperhomocysteinemia

Hypocalcemia

Hyponatremia

Hypophosphatemia

Hypothyroidism due to drugs

Lipids abnormal

Male sex hormones - serum level - finding

Porphyria

Summary

Syndrome of inappropriate antidiuretic hormone secretion

Vitamin D deficiency

Weight gain

3.3.3.A Acute intermittent porphyria

See Drug Consult reference: DRUGS CONSIDERED UNSAFE- ACUTE PORPHYRIAS

3.3.3.B Body temperature above normal

1) A case of recurrent fever was reported in a 62-year-old woman who was receiving carbamazepine 800 mi control of epilepsy. The patient's fever began 2 days after the first dose of carbamazepine and spiked to 40 d daily. Carbamazepine therapy was discontinued and the fever ceased. Carbamazepine was reintroduced at a fever recurred; however, they were not as high as before. The patient's dose was again raised to 800 milligra fever returned to 40 degrees C twice daily. When the medication was discontinued the second time the fever (Stewart et al, 1980).

3.3.3.C Hyperhomocysteinemia

1) In a study of 60 adolescent epileptic patients (aged 14 to 18 years), a one-year course of carbamazepine therapy was found to produce significantly higher plasma concentrations of homocysteine. this was compare levels prior to therapy and compared with levels in a healthy age- and sex-matched control group (n=63; p les comparisons). the finding of hyperhomocysteinemia held true with both fasting and post- methionine homocys measurements. For the patients taking carbamazepine or valproate, serum concentrations of folate and plasr phosphate (PLP) were significantly decreased with respect to pre- treatment values and to values in the cont than 0.01, folate; p less than 0.001, PLP). Levels of vitamin B12 and erythrocyte folate remained in the norma

al, 2000a).

3.3.3.D Hypocalcemia

1) In a study of 21 epileptic patients, hypocalcemia, hypophosphatemia, and elevated serum alkaline phosph noted (Hoikka et al, 1984).

3.3.3.E Hyponatremia

1) Summary

a) The significant antidiuretic actions of carbamazepine have resulted in water intoxication and hyponatr children. Hyponatremia was demonstrated in 4% to 21.7% of patients receiving carbamazepine. Hypona likely to occur in older patients (Dong et al, 2005; Prod Info Tegretol(R), 2002b; Kamiyama et al, 1993; L O'Griofa & Voris, 1991; Rajantie et al, 1984; Hoikka et al, 1984; Kalff et al, 1984; Yeung Laiwah et al, 19 Valikangas, 1983; Uhde & Post, 1983; Byrne et al, 1979; Ashton et al, 1977; Stephens et al, 1977; Henry incidence of hyponatremia appears to be lower with carbamazepine use as compared with the use oxca al, 2005). In a case report, a woman experienced tonic-clonic seizures secondary to carbamazepine-indu (Kuz & Manssourian, 2005).

2) Incidence: 4% to 21.7% (Dong et al, 2005; Lahr, 1985; Kalff et al, 1984)

3) The results of one study indicate that oxcarbazepine use is associated with a greater incidence of hypona compared with the use of carbamazepine. In a cross-sectional study, the sodium levels of patients receiving t either oxcarbazepine (n=97; mean age, 36.3 years) or carbamazepine (n=451; mean age, 38.2 years) were e presence of hyponatremia. Hyponatremia was defined as a sodium level less than or equal to 134 milliequiva severe hyponatremia was defined as a sodium level less than or equal to 128 mEq/L. Hyponatremia was obs significantly greater number of oxcarbazepine-treated patients, as compared with those receiving carbamaze (29.9% (29/97) vs 13.5% (61/451), respectively; p less than 0.0001). The incidence of severe hyponatremia v the oxcarbazepine group as compared with the carbamazepine group (12.4% (12/97) vs 2.8%(13/451), respe hyponatremia accounted for 41% (12/29) of all hyponatremia cases in oxcarbazepine-treated patients, while 21.3% (13/61) of all hyponatremia cases reported in patients receiving carbamazepine therapy (p less than 0 investigators also found that, for both groups, hyponatremia was more likely to occur in older patients. Hypon observed in 62.2% and 20.6% of oxcarbazepine- and carbamazepine-treated patients 40 years of age or olde with 10% and 7.9% of oxcarbazepine- and carbamazepine-treated patients less than 40 years of age, respec 0.0001, both values) (Dong et al, 2005).

4) In a case report, a 44-year-old woman experienced new-onset, tonic-clonic seizures secondary to hypona a larger than her usual dose of carbamazepine. Concomitant medications include paroxetine, risperidone, bu and hydroxyzine. The night before the seizures she took double the bedtime dose of carbamazepine (1200 m instead of 600 mg). The next day, symptoms experienced were faintness, dizziness, light-headedness, and th blood rushing to her head and immediately prior to seizures were vision "began narrowing" and loss of consc emergency room, serum sodium concentration was 122 milliequivalent/liter and serum carbamazepine was 1 microgram/milliliter. Past medical history includes a similar event after she took a large dose of carbamazepir Manssourian, 2005).

5) Sixty patients receiving carbamazepine and 61 age-matched controls were studied to determine the preva hyponatremia. There was a significant difference between the mean serum sodium levels of the subjects (138 milliequivalents/liter) and the controls (141.7+/-0.4 milliequivalents/liter). Thirteen (21.7%) of the subjects, but controls, had sodium levels less than 135 milliequivalents/liter. The risk of hyponatremia increased with age a serum level (Lahr, 1985).

6) In 1 study, hyponatremia was demonstrated in 28 of 674 (4%) of patients receiving carbamazepine for sei patients, 113 were on carbamazepine monotherapy and 460 were receiving carbamazepine in combination w anticonvulsant medications. Of the 23 patients available for long-term follow- up, 10 were consistently hypona remainder were intermittently hyponatremic. All patients who developed hyponatremia were receiving carbam these were on monotherapy. In all patients, the hyponatremia was slight and did not cause clinical symptoms

3.3.3.F Hypophosphatemia

1) In a study of 21 epileptic patients, hypocalcemia, hypophosphatemia, and elevated serum alkaline phosph noted (Hoikka et al, 1984)

3.3.3.G Hypothyroidism due to drugs

1) One study found that carbamazepine and oxcarbazepine both decrease serum thyroxine (T4) and free thy girls with epilepsy. These effects were reversible upon discontinuation of therapy. Patients, between the ages years, were compared to 54 age-matched controls. Mean T4 and FT4 levels in patients receiving carbamaze 11.5 nM and 70.2 nM compared to 14.4 nM and 96.6 nM in the control group (p less than 0.01 and 0.001, res T4 and FT4 in patients receiving oxcarbazepine (n=18) were 11.3 nM and 74.9 nM (p less than 0.001 for both compared control). Thyrotropin and free triiodothyronine levels were not significantly different. A second evalu mean of 5.8 years later, was performed. Thyroid hormone levels in patients who had discontinued therapy (1 patients and 10 oxcarbazepine patients) did not significantly differ from the controls. Patients had been off the 5 and 4.8 years, respectively (Vainionpaa et al, 2004).

2) Carbamazepine may increase the hepatic clearance of thyroid hormones as well as having an inhibitory e hypothalamic level. The effect of carbamazepine on thyroid function was examined in 40 epileptic patients. A levels of thyroxine, free thyroxine and thyroxine binding globulin were decreased at both 2 and 12 months foll therapy; low serum thyroxine and free thyroxine concentrations were also found after long-term therapy. No p

demonstrated clinical signs of hypothyroidism. Thyrotropin levels were not changed although the response to releasing hormone increased slightly. The decreased thyroid function tests did not correlate with serum carba (Prod Info Tegretol(R), 2002b; Isojarvi et al, 1989).

3.3.3.H Lipids abnormal

1) Significant increases in atherogenic lipids (total cholesterol, very-low-density lipoprotein (VLDL), LDL, and noted after 3 months of carbamazepine therapy in a prospective study of children with partial epilepsy. Over a 29 children (mean age 7.3 years (yr); range 3 to 12 yr; 16 male) were enrolled within 48 hours of presentation seizures, placed on carbamazepine monotherapy, and followed up monthly for 3 months to study the effect o therapy on serum lipids. Family histories, weight, height, and body mass index were recorded. Participants w carbamazepine at a dose of 10 mg/kg per day, with doses increased by 5 mg/kg per day if required, up to a m 30 mg/kg/day. Participants were advised against dietary changes. After 12 hours of fasting, venous blood sam lipid levels were taken. Participants were monitored monthly and compliance was noted. Blood samples were months for lipid profiles and carbamazepine levels. Correlation of lipid levels with carbamazepine was determ of correlation. A p-value of less than 0.05 was taken as significant. Results for the study participants were an liver function tests and lipid levels. Baseline lipid and liver function levels were compared with 3-month finding increased 10% during the study period with mean total cholesterol at baseline 130.6 +/- 27.4 mg/dL and 144. 3 months (p=0.018). Significant increases were also noted in LDL, VLDL, total cholesterol/HDL ratio, and LDL There was no significant change in HDL levels, alkaline phosphate or serum glutamine transaminase. At 3 m the mean dose of carbamazepine was 10.3 +/- 1.1 mg/kg per day, and the mean carbamazepine levels were mcg/dL. There was no correlation of carbamazepine level with lipid levels at 3 months, and no correlation wa the change in lipids and carbamazepine levels. Lipid monitoring should be advised for high-risk patients on ca therapy. Long-term implications of increased risk of atherosclerosis needs further study (Aggarwal et al, 2009

2) In a study evaluating lipids in children and adolescents receiving carbamazepine (n=14), valproic acid (n= phenobarbital (n=20), serum lipid and lipoprotein levels returned completely to normal at 1 to 1.5 years after t discontinued (Verrotti et al, 1998). During therapy patients receiving carbamazepine demonstrated increased cholesterol, triglycerides, low-density lipoprotein cholesterol, and high-density lipoprotein as compared to a co (n=110) (all p less than 0.01). Children receiving valproic acid had low triglycerides (p less than 0.05) and low lipoproteins (p less than 0.05) and high levels of high-density lipoproteins (p less than 0.01) as compared to t Children receiving phenobarbital had high concentrations of total cholesterol and low-density lipoprotein chole concentrations of triglycerides as compared to the control group (all p less than 0.01).

3) Carbamazepine was shown to adversely affect serum lipids in a study comparing 57 healthy children to 2 treated children (Sozuer et al, 1997). The carbamazepine-treated children had significantly higher levels of m cholesterol (p less than 0.01), mean low-density lipoprotein (p less than 0.005), and mean total cholesterol/hi lipoprotein (p less than 0.05).

4) High-density lipoprotein cholesterol levels were significantly elevated in epileptic children receiving carban as phenobarbital and valproic acid (Heldenberg et al, 1983); however, this effect may be protective against th heart disease.

5) The effects of valproic acid, carbamazepine or phenobarbital on serum lipids, lipoproteins and apolipoprot examined in 101 epileptic patients and 75 age-matched controls (Calandre et al, 1991). Patients treated with demonstrated significantly higher high-density lipoprotein and apolipoprotein A concentrations. The total chol cholesterol ratio was also significantly lower in patients receiving carbamazepine. The change in serum lipid p correlate with drug concentrations or with duration of therapy.

3.3.3.I Male sex hormones - serum level - finding

1) Antiepileptic agents have been associated with changes in serum concentrations of male reproductive hor compared to healthy controls (n=41), carbamazepine treated men with partial epilepsy (n=15) had lower seru dehydroepiandrosterone sulfate concentrations (3068 ng/mL for controls versus 1952 ng/mL for carbamazep 0.001). No statistically significant differences in dehydroepiandrosterone levels were detected between contro oxcarbazepine treated (n=18) or valproic acid treated (n=27) men with generalized epilepsy. It was also found valproic acid group had higher androstenedione levels (5.9 ng/mL) when compared to the control group (2.2 0.001) whereas the other arms did not. Serum testosterone, sex hormone binding globulin, free androgen inc hormone, follicle stimulating hormone, prolactin and inhibin B measurements were not statistically significantl all 4 groups. Whether the differences in reproductive hormones are epilepsy-induced changes or antiepileptic changes remains to be determined (Isojarvi et al, 2004).

2) Reproductive hormone levels in men with epilepsy may be affected by use of valproic acid or carbamazep effect shown by oxcarbazepine at high doses. In valproate-treated men (n=21), androstenedione levels were increased compared with controls (n=25) (p less than 0.001), and more than half of the cohort taking valproat serum concentrations of testosterone, androstenedione, or dehydroepiandrosterone (DHEA) above the refere than 0.001). Follicle stimulating hormone levels were abnormally low in valproate- treated men (p less than 0. carbamazepine-treated men (n=40), serum concentrations of DHEA were low (p less than 0.001) and sex hor globulin (SHBG) levels were high (p less than 0.05). In men taking high doses of oxcarbazepine (900 mg/day concentrations of testosterone, luteinizing hormone, and SHBG were high (p=0.008, p=0.02, p=0.005, respec authors noted that serum insulin levels were high across all groups (Rattya et al, 2001).

3) Carbamazepine and (to a lesser extent) valproic acid were found to alter serum concentrations of sex hor male epileptic patients (aged 15 to 18 years; n=48) treated at least 2 years with these drugs; however, serum permanently changed and soon after the drugs were withdrawn, hormone levels normalized (Verrotti et al, 20 with concentrations in normal healthy male controls, subjects treated with carbamazepine monotherapy (n=2

levels of free testosterone (FT) (p less than 0.05) and dehydro- epiandrosterone sulphate (DHEAS) (p less th concentrations of sex hormone-binding globulin were significantly increased (p less than 0.01). Subjects treat acid monotherapy (n=18) had insignificantly decreased levels of FT and DHEAS. Subjects on combination ca valproic acid (n=10) had the same significant alterations as those on carbamazepine monotherapy. At least fo withdrawal of these drugs, all values had returned to normal. Levels of testosterone, luteinizing hormone, folli hormone, and prolactin were normal throughout the study.

3.3.3.J Porphyria

1) Carbamazepine has been associated with the development of nonhereditary acute porphyria, similar to ac porphyria, in a 38-year-old male during treatment of epilepsy. Carbamazepine reportedly produces direct sup on the enzyme uroporphyrinogen I synthase. Decreases in this enzyme are also present in hereditary acute i porphyria (Yeung Laiwah et al, 1983).

3.3.3.K Summary

1) The significant antidiuretic actions of carbamazepine have resulted in water intoxication and hyponatremia children. Hyponatremia was demonstrated in 4% to 21.7% of patients receiving carbamazepine. Hyponatrem to occur in older patients (Dong et al, 2005; Prod Info Tegretol(R), 2002b; Kamiyama et al, 1993; Lampl et al, Voris, 1991; Rajantie et al, 1984; Hoikka et al, 1984; Kalff et al, 1984; Yeung Laiwah et al, 1983; Koivikko & V Uhde & Post, 1983; Byrne et al, 1979; Ashton et al, 1977; Stephens et al, 1977; Henry et al, 1977). In a study epileptic patients, hyperhomocystinemia was reported (Verrotti et al, 2000a). Reproductive hormone levels in may be affected by carbamazepine use (Rattya et al, 2001). Soon after the drug is withdrawn, the hormone le normal (Verrotti et al, 2000). Serum calcium concentrations and 25-hydroxyvitamin D levels were found to be in mentally retarded patients and patients on chronic carbamazepine monotherapy (Rajantie et al, 1984). In a epileptic patients, hypocalcemia, hypophosphatemia, and elevated serum alkaline phosphatase levels were r 1984). Carbamazepine may increase the hepatic clearance of thyroid hormones as well as having an inhibito hypothalamic level(Prod Info Tegretol(R), 2002b; Isojarvi et al, 1989). Carbamazepine has been shown to ad serum lipids and lipoprotein levels in children (Prod Info Tegretol(R), 2002b; Verrotti et al, 1998) (Souzuer et et al, 2009). Syndrome of inappropriate antidiuretic hormone secretion has been reported (Prod Info Tegretol
2) There have been case reports of recurrent fever (Stewart et al, 1980), nonhereditary acute porphyria, simi intermittent porphyria (Yeung Laiwah et al, 1983), and weight gain (Lampl et al, 1991).

3.3.3.L Syndrome of inappropriate antidiuretic hormone secretion

1) Syndrome of inappropriate antidiuretic hormone secretion has been reported (Prod Info Tegretol(R), 2002

3.3.3.M Vitamin D deficiency

1) A 2-year cross-sectional and retrospective study reported lower 25-hydroxy vitamin D serum levels in prep treated with carbamazepine when compared to children treated with valproic acid and controls. Sixty-six childc antiepileptics (carbamazepine: 20 boys, 13 girls; mean age 9.7 +/-1.6 years; valproic acid: 17 boys, 16 girls; r years) were compared to age- and sex-matched controls (13 boys, 9 girls; mean age 8.9 +/- 2.3 years). Mear treatment was 35.52 +/- 12.84 months for carbamazepine and 33.72 +/- 15 months for valproic acid. Serum 2 D levels in patients treated with carbamazepine were significantly lower than those of patients treated with va controls (9.8 +/- 3.6 micrograms per liter (mcg/L), 15.1 +/- 3.5 mcg/L, and 16.6 +/- 4.7 mcg/L, respectively; p< carbamazepine) (Kumandas et al, 2006).
2) Serum calcium concentrations and 25-hydroxyvitamin D levels were reported to decrease in mentally reta receiving carbamazepine, as compared to a control group. Alkaline phosphatase levels were higher in patien carbamazepine and administration of vitamin D in the diet abolished the syndrome. It is suggested that hypov occur during long-term carbamazepine treatment especially if other risks for vitamin D deficiency exist (Rajan
3) Bone mineral metabolism was studied in 21 epileptic patients on chronic carbamazepine monotherapy at of 505 milligrams. In 3 cases, hypocalcemia was identified; hypophosphatemia was noted in 1 patient and 4 p demonstrated elevated serum alkaline phosphatase levels. Serum 25-hydroxyvitamin D levels were significar controls. No significant difference was noted in bone mineral density or in the amount of trabecular bone betv controls. Two patients were found to have histological evidence of osteomalacia (Hoikka et al, 1984).

3.3.3.N Weight gain

1) Weight gain induced by carbamazepine has been reported in 4 adolescent patients taking the drug at usu doses for control of seizures. Over a 2-month period, all patients developed an increase in appetite with conc increased food intake; body weight increased by 7 to 15 kilograms. Dietary restriction was ineffective in achie while the patients remained on the drug; a return to original body weight was achieved 2 to 3 months followin of the drug (Lampl et al, 1991).

3.3.4 Gastrointestinal Effects

Diarrhea

Disease of mouth

Disorder of gastrointestinal tract

Gastrointestinal tract finding

Nausea and vomiting

Pancreatitis

3.3.4.A Diarrhea

1) Summary

a) Several cases of intractable diarrhea have been reported with therapeutic carbamazepine therapy (P
(R), 2002b; Mahajan et al, 1997; Iyer et al, 1992).

2) Literature Reports

a) An 8-year-old boy with Lennox-Gastaut syndrome developed protracted watery diarrhea while receivi
(Mahajan et al, 1997). The diarrhea started approximately 3 weeks after beginning carbamazepine. A ra
biopsy was consistent with the diagnosis of LYMPHOCYTIC COLITIS. No improvement was noted after
of sulfasalazine. The diarrhea gradually resolved over a 2-month period while the carbamazepine was ta

b) Three cases of intractable diarrhea were reported following initiation of carbamazepine therapy (Iyer
three cases, the patients experienced frequent loose stools approximately one week after starting carba
abdominal pain or discomfort were noted, and antidiarrheal medications were ineffective. The diarrhea c
carbamazepine was discontinued.

3.3.4.B Disease of mouth

1) Summary

a) Dryness of the mouth and pharynx, glossitis, stomatitis, and loss of taste have been reported in patie
carbamazepine therapy (Prod Info Tegretol(R), 2002b).

3.3.4.C Disorder of gastrointestinal tract

1) Summary

a) Constipation, abdominal cramps, and anorexia have been reported in patients receiving carbamazepi
Info Tegretol(R), 2002b).

3.3.4.D Gastrointestinal tract finding

1) Nausea and vomiting are two of the most frequent adverse effects associated with carbamazepine therap
usually occur during the initiation of therapy. Diarrhea, constipation, abdominal cramps, anorexia, and drynes
pharynx, glossitis, stomatitis, pancreatitis, and loss of taste have been reported in patients receiving carbama

3.3.4.E Nausea and vomiting

1) Summary

a) Nausea and vomiting are two of the most frequent adverse effects associated with carbamazepine th
effects usually occur during the initiation of therapy (Prod Info Tegretol(R), 2002b).

3.3.4.F Pancreatitis

1) Summary

a) Pancreatitis has been reported in one case during carbamazepine therapy (Soman & Swenson, 1985

2) Literature Reports

a) A 73-year-old female receiving carbamazepine 200 mg twice a day for partial seizures developed nau
anorexia, malaise, headache, and increased thirst 4 weeks after starting therapy. Her symptoms continu
the addition of lower abdominal pain. Her serum amylase rose to 429 units/dL (normal 60 to 160). The ca
discontinued with an immediate decrease in symptoms. Ten days after stopping the carbamazepine, the
was 172 units/dL and the patient was free of symptoms (Soman & Swenson, 1985).

3.3.5 Hematologic Effects

Agranulocytosis

Aplastic anemia

Disorder of hematopoietic structure

Drug-induced eosinophilia

Hematology finding

Hemolytic anemia

Leukemoid reaction

Leukopenia

Malignant lymphoma

Pancytopenia

Pure red cell aplasia

Thrombocytopenia

3.3.5.A Agranulocytosis

1) Summary

a) Agranulocytosis is one of the most severe hematologic effects. It is reported to occur 5 to 8 times mo patients treated with carbamazepine than in the general population. While agranulocytosis is a low risk e untreated general population (6 patients/1 million population/year), a fatal case has been associated with therapy (Prod Info Tegretol(R), 2002b; Luchins, 1984; Owens et al, 1980; Hawson et al, 1980; Murphy e Agranulocytosis can occur after different periods of exposure and is not clearly related to the total dose c cases over 12 years have been reported during chronic therapy. It appears to be an idiosyncratic respon 1995; Pellock, 1998a; Owens et al, 1980).

2) Literature Reports

a) A 49-year-old asthmatic epileptic woman began receiving carbamazepine 200 milligrams three times epilepsy, and within a week she developed an erythematous non-itchy rash which resolved spontaneous recurred and was itchy 3-1/2 weeks later. Twenty days after commencing therapy, routine blood count sh 1.8 x 10(9)/liter with neutrophil count of 0.4 x 10(9)/liter. Three days later the patient became febrile and (9)/liter with 1% myelocytes but no neutrophils was seen. Carbamazepine was discontinued and a bone examination two days later showed normal cellularity with 3% promyelocytes, 25% myelocytes and 34% and band cells and virtually no mature neutrophils. The patient made an uneventful recovery (Hawson et

b) A case of fatal agranulocytosis was reported in a 48-year-old chronic schizophrenic patient after carb milligrams twice daily for 1 month for aggression (Luchins, 1984). Routine hematological monitoring was prior to or during carbamazepine therapy.

3.3.5.B Aplastic anemia

1) Summary

a) Aplastic anemia is one of the most severe hematological effects and it occurs rarely during carbamaz (Gerson et al, 1983; Donaldson & Graham, 1965). Aplastic anemia is reported to occur 5 to 8 times more patients treated with carbamazepine than in the general population. It has also been reported during chr cases over 12 years) (Prod Info Tegretol(R), 2002b; Tohen et al, 1995; Pellock, 1998a).

2) Literature Reports

a) Aplastic anemia is one of the most severe hematologic effects. Aplastic anemia is reported to occur 5 frequently in patients treated with carbamazepine than in the general population. The risk of aplastic ane low with approximately 2 persons per 1,000,000 population per year likely to develop the disorder (Prod 2002b).

b) Clinically significant hematological toxicity with carbamazepine is uncommon in adults (Hart & Easton review indicated the occurrence of aplastic anemia in 20 patients since 1964, with leukopenia and throm occurring in about 2% of patients treated.

1) Monitoring - The authors suggested a conservative approach to hematological monitoring during complete blood and platelet count performed prior to therapy; 2) CBC performed every 2 weeks for t (if no abnormalities are present, CBC should be obtained quarterly or with the appearance of signs c bone marrow depression); 3) if leukopenia develops, white blood cell count should be monitored at 2 seeking the expected return to baseline (withdrawal is indicated in the presence of WBC less than 3 millimeters) (Hart & Easton, 1982).

c) A low incidence of hematologic toxicity with carbamazepine in children has been reported (Silverstein

1) Monitoring - The authors recommend the following monitoring guidelines: 1) hemoglobin, hemato platelet count prior to therapy, monthly for 6 months, then every 3 months; 2) obtain neutrophil, plate reticulocyte count if WBC falls less than 4000; 3) if neutrophil count decreases to 1000 to 1500/cubi in 2 weeks, and consider withdrawal of therapy if remains in this range (neutrophil counts below 100 decreased dosage or drug withdrawal); 4) request hematologic consultation if depression in platelet count occurs in addition to neutropenia (Silverstein et al, 1983).

3.3.5.C Disorder of hematopoietic structure

1) Summary

a) Rates of blood dyscrasias per 100,000 anticonvulsant prescriptions have been reported as 2.8 for ne thrombocytopenia, and 0.5 for hemolytic anemia. These were determined using the United Kingdom Dep Health's General Practice Research Database with 5-year records of 16,686 carbamazepine recipients. differ between phenytoin, phenobarbital, carbamazepine, or valproate throughout all age groups (Blackb

3.3.5.D Drug-induced eosinophilia

1) Summary

a) A slight increase of eosinophilia was reported in patients taking carbamazepine (De Marco & Melchio

2) Literature Reports

a) A 5% increase of eosinophilia with normal leukocyte counts was reported in 653 patients taking carba 48 months. Blood levels ranged from 3 to 12 milligrams/milliliter (Prod Info Tegretol(R), 2002b; Perry et a & Melchiori, 1986; Killian & Fromm, 1968).

b) A 13-year-old boy developed fever, rash, and eosinophilia (white blood cell count of 20,400 cells/cubi eosinophils) weeks after starting carbamazepine therapy. He developed chest pain and died from uncon dysrhythmias. Autopsy revealed severe eosinophilic myocarditis Salzman & Valderrama, 1997).

3.3.5.E Hematology finding

1) Hematopoietic toxicity (neutropenia, thrombocytopenia, and aplastic anemia) has been reported following but not acute overdose. Pancytopenia, thrombocytopenia, leukopenia, leukocytosis, eosinophilia, agranulocy dyscrasia, hemolytic anemia, and pure red cell aplasia have also been reported in patients receiving carbama

3.3.5.F Hemolytic anemia

1) Summary

a) CASE REPORT - Hemolytic anemia was reported in a 63-year-old male following carbamazepine ad milligrams daily for approximately 20 days). Withdrawal of the drug resulted in

3.3.5.G Leukemoid reaction

1) Summary

a) CASE REPORT - A case of leukocytosis induced by carbamazepine has been reported. A 26-year-ol receiving carbamazepine for the treatment of epilepsy had a white blood cell count of 21.2 x 10(3)/cubic patient's medication was changed from carbamazepine 600 milligrams/day to phenytoin 400 milligrams/c phenobarbital 120 milligrams/day and her white count decreased to a normal range. The patient experie ataxia and the phenytoin and phenobarbital were replaced with carbamazepine 600 milligrams/day. Whit performed 11 and 13 days later were significantly elevated (Murphy et al, 1980).

3.3.5.H Leukopenia

1) Summary

a) Carbamazepine may produce leukopenia in 10% of patients for whom it is prescribed. Usually the rea transient although a few cases of persistent neutropenia have been described. In some patients, the rea dose-related (Prod Info Tegretol(R), 2002b; Perry et al, 1991); (de Marco & Melchiori, 1986)(Killian & Fro

b) Transient leukopenia is not an absolute indication to stop the drug although it is an indication to moni Upon continuation of therapy, the WBC has returned to normal in some patients, while in others it has flu normal and low values. Where the drug is discontinued, the WBC returns to normal within a period of 1 v Cook, 1977).

c) In an evaluation of chronic leukopenia resulting from antiepileptic drug use, it was demonstrated that antiepileptic drug regimen was safe to continue despite asymptomatic leukopenia when the percentage polymorphonuclear leukocytes (PMN) remained normal. If the absolute PMN count dropped to less than cells/microliter, a bone marrow aspirate should be obtained and the ratio of myeloid to erythroid precurso ratio is reduced, or the absolute PMN count remains less than 500, the antiepileptic agent should be disc (O'Connor et al, 1994). Several authors have suggested that carbamazepine be discontinued when the t count is less than 3000/cubic millimeter or neutrophils are less than 1500/cubic millimeter (Hart & Easter al, 1985).

2) Literature Reports

a) A 66-year-old woman with bipolar disorder developed an initial drop in white blood cell count to a leve millimeter. The drug was discontinued for a 2-week period and then gradually titrated from a dose of 100 carbamazepine daily to 800 mg daily. Although leukopenia occurred, the dosage of carbamazepine was time the white blood cell count reached 3000/cubic millimeter. Her hematologic indices remained normal to the therapeutic dosage (Regan, 1987).

b) Leukopenia and neutropenia occurred in a 27-year-old female who received carbamazepine for at lea time of presentation, the carbamazepine dosage was 1200 milligrams (mg)/day. A reduction in dose to 1 an increase in white cell count. The patient's dose was further reduced to 900 mg/day 21 days later, but carbamazepine serum level rose and white cell count fell again. Approximately 3 months later, the patier carbamazepine and her white cell count rose when the serum concentration of carbamazepine fell to 11 patient's white cell counts showed a relationship to serum concentrations of the drug. The authors sugge important to determine if the hematologic side effects of carbamazepine are dose-related or idiosyncratic particular patient. If it is dose-related, carbamazepine can be continued provided the patient is closely m Beran, 1984).

3.3.5.I Malignant lymphoma

1) Summary

a) An 81-year-old man experienced lymphoma after 50 days of carbamazepine therapy (Lombardi et al, pseudolymphoma induced by carbamazepine in a 78-year-old woman was reported (Sinnige et al, 1990)

2) Literature Reports

a) CD30+ primary cutaneous anaplastic large-cell lymphoma was associated with carbamazepine thera girl. the patient started on carbamazepine, titrated to a dose of 600 mg/day, for lipothymic episodes durir Eight months later she was admitted for an erythematous macular eruption diagnosed as pityriasis rosea regressing, until 1 month later, the patient suddenly developed multiple painless reddish skin nodules on and arms. The nodules were 0.5 to 6 cm, and quickly grew and ulcerated. Histologic examination reveale pseudoepitheliomatous hyperplasia overlying a diffuse lymphoid infiltrate of large anaplastic cells, scatte cohesive clusters. Most of the anaplastic cells expressed the CD30/Ki-1 antigen, the TIA-1 antigen, and antigens. Carbamazepine was tapered and withdrawn. Lesions regressed with radiotherapy; some untre regressed after 4 months, though prominent scarring remained. After 3 years, the patient was healthy, w in remission (Di Lernia et al, 2001).

b) An 81-year-old man experienced lymphoma after 50 days of carbamazepine therapy (Lombardi et al, presented with fever, morbilliform pruritic rash, and jaundice with dark urine and acholic feces. He also h liver and mildly enlarged spleen. Carbamazepine was discontinued. The maculopapular rash progressec erythroderma. The patient also developed oliguria. Leukocyte count fell to 2400/cubic millimeter and hen grams/decaliter. The bone marrow aspirate showed anemia associated with bone marrow hypercellularit dyserythropoietic changes. Lab values improved but a repeat bone marrow aspirate confirmed a low-gra (non-Hodgkin's) and the absence of myelodysplastic changes.

c) A 44-year-old woman, who was allergic to phenytoin, developed anticonvulsant hypersensitivity syndi pseudolymphoma after 1 month of carbamazepine therapy (Nathan & Belsito, 1998). Her symptoms inclu lymphadenopathy, pneumonitis, hepatitis, and a morbilliform eruption. The skin biopsy showed atypical l dermis that were CD-3(+), CD-30(+), and L26(-). Her symptoms resolved 3 weeks after carbamazepine

d) A case of pseudolymphoma induced by carbamazepine in a 78-year-old woman was reported (Sinnig condition was characterized by generalized lymphadenopathy, hepatosplenomegaly, an abnormal differe cell count, hypergammaglobulinemia and anemia with evidence of severe immune dysregulation. Withdr carbamazepine resulted in resolution of all symptoms within a few days.

3.3.5.J Pancytopenia

1) Summary

a) Neutropenia (75 to 100 cases over 12 years) and pancytopenia (8 cases over 12 years), have been r chronic carbamazepine therapy (Tohen et al, 1995; Pellock, 1998a; Prod Info Tegretol(R), 2002b; Perry Marco & Melchiori, 1986)(Killian & Fromm, 1968). (Cates & Powers, 1998) reported concomitant rashes, thrombocytopenia associated with carbamazepine therapy, in 2 geriatric patients.

3.3.5.K Pure red cell aplasia

1) Summary

a) Two cases of pure red cell aplasia were reported in young girls taking carbamazepine for seizures (T Buitendag, 1990).

2) Literature Reports

a) A case of pure red cell aplasia was reported in a 3-year-old girl taking carbamazepine 150 milligrams control. Recovery followed drug discontinuation (Buitendag, 1990). A 7-year-old girl developed pure red months of carbamazepine monotherapy (Tagawa et al, 1997). She began to recover within 1 week of ca discontinuation.

3.3.5.L Thrombocytopenia

1) Summary

a) Thrombocytopenia is an infrequent but potentially serious side effect of carbamazepine and its occur discontinuation of the drug. The mechanism of this effect is unknown, but has been postulated to be imm due to the identification of carbamazepine-dependent antiplatelet antibodies (Tohen et al, 1991). Thromb often develops 2 weeks after initiating carbamazepine treatment, but there have also been cases reporte therapy (Tohen et al, 1995; Pellock, 1998a; Ishikita et al, 1999; Prod Info Tegretol(R), 2002b); (Tohen et al, 1991); (de Marco & Melchiori, 1986)(Killian & Fromm, 1968). Some cases are asymptomatic while oth fever, skin rash, arthralgia or swollen joints. Recovery usually occurs within 1 week of carbamazepine dis (Ishikita et al, 1999). There have been 31 cases reported to the manufacturer over a 12-year span (Pello incidence rate for thrombocytopenia of 0.5 per 100,000 prescriptions was reported by the United Kingdo Health's General Practice Research Database (Blackburn et al, 1998).

2) Literature Reports

a) ADULT

1) A 67-year-old woman, with Lennox-Gasteau syndrome, developed severe, isolated thrombocyto placed on a combination of carbamazepine and valproate for the treatment of generalized tonic-clon patient received carbamazepine 150 milligrams (mg) per day for 7 days, 600 mg/day on day eight, a mg/day by day nine. On day 10, valproate 300 mg/day was added because of nonconvulsive status valproate was discontinued 5 days later because the patient developed urticaria and a maculopapul

The thrombocyte count was 262 GIGA/L (normal: 150-360 GIGA/L) on day 5 and had dropped to 5 G at which time carbamazepine was also discontinued. The patient received two thrombocyte transfus thrombocyte count was within normal limits 3 days after the carbamazepine was discontinued. It cou determine whether it was carbamazepine alone or the combination of carbamazepine and valproate responsible for the severe thrombocytopenia (Finsterer et al, 2001).

2) Four cases of thrombocytopenia were reported in patients taking carbamazepine for bipolar diso the drop in platelet count occurred 14 to 16 days following the initiation of therapy and resolved with discontinuation. Carbamazepine doses in all patients were 400 to 600 milligrams daily. These cases somewhat by the presence of concomitant drug therapy including antipsychotics, lithium and benzoc et al, 1991).

3) A 31-year-old epileptic, female developed thrombocytopenia after receiving carbamazepine thera The patient was admitted with diffuse purpura and ecchymoses and her platelet count was 5000/ cu (3)). A migration inhibition factor test for carbamazepine was positive. Following withdrawal of the dr with phenytoin, her platelet count rose to 210,000/mm(3) (Schoenfeld et al, 1982).

4) In one study, 1 patient out of a total of 79 (1.5%) was reported with a platelet count of less than 8 millimeter and no evidence of bruising. The average doses given in the study were 600 to 800 millig although the specific dose and duration of treatment was not mentioned for this patient. After discon drug, a normal platelet count was measured within 1 week (Davis, 1969).

5) Thrombocytopenia was reported a patient receiving carbamazepine 800 milligrams daily for trige over a 10 month period. The platelet count was 50,000/cubic millimeter and a sternal biopsy reveale megakaryocytes with decreased platelet production. The patient's platelet count returned to normal carbamazepine discontinuation (Pearce & Ron, 1968).

b) PEDIATRIC

1) A 12-year-old boy developed thrombocytopenia 10,000/cubic millimeter with petechial rash after carbamazepine therapy. His platelet count recovered 7 days after withdrawal of carbamazepine and prednisone therapy. The boy was subsequently rechallenged with a single oral dose of carbamazep milligrams/kilogram. After 4 hours he developed fever, flushing, and conjunctival hyperemia. Leukoc increased with a left shift in the neutrophilic series. On the second day, platelet counts decreased ar increased. Levels of platelet glycoprotein IIb/IIIa or Ib were detected in plasma (Ishikita et al, 1999).

2) A 12-year-old girl developed thrombocytopenia and petechiae 2 weeks after starting carbamazep milligrams/kilogram/day. Her platelet count was noted to have decreased from 300,000/cubic millime 100,000/mm(3). Carbamazepine was discontinued with resolution of petechiae and an increase in p days (Ueda et al, 1998).

3) A case of carbamazepine-induced thrombocytopenia was reported in a young child. The child wa hospital with a diagnosis of scattered petechiae, 2 weeks after starting carbamazepine 100 milligram All of the patient's laboratory values were within normal limits except for a platelet count of 14,000/ c (mm(3)). Carbamazepine was withdrawn and the patient's platelet count rose to 239,000/mm(3) by c was not rechallenged (Bradley et al, 1985).

3.3.6 Hepatic Effects

Cholangitis

Hepatotoxicity

Injury of bile duct

Liver finding

3.3.6.A Cholangitis

1) Summary

a) Cholangitis has been reported in patients receiving carbamazepine (La Spina et al, 1994)(Larrey et a

2) Literature Reports

a) Cholangitis was described in a 79-year-old woman following carbamazepine 200 mg daily for approxi the treatment of facial neuralgia. A marked hypereosinophilia (54%) was associated with the hepatic lesi cholestasis was observed in the centrilobular areas on liver biopsy. However, granuloma or hepatocellul observed. Withdrawal of carbamazepine resulted in resolution of symptoms over a period of 2 weeks wit tests and eosinophils returning to normal over 3 months (Larrey et al, 1987). This patient had also been vincamine and clonazepam at the time of acute cholangitis, and these drugs were also discontinued with however, readministration of these 2 latter agents did not result in recurrence of symptoms. A second ca has been reported (La Spina et al, 1994).

3.3.6.B Hepatotoxicity

1) Summary

a) Hepatitis, cholestatic and hepatocellular jaundice, abnormal liver function tests and hepatic failure (ve have been reported in patients receiving carbamazepine. Several cases of hepatotoxicity were reported carbamazepine therapy. Symptoms were alleviated with the discontinuation of the drug (Prod Info Tegre Morales-Diaz et al, 1999; Horowitz et al, 1988; Larrey et al, 1987; Luke et al, 1986).

2) Literature Reports

a) A 9-year-old girl developed hepatotoxicity after 5 months of carbamazepine 500 milligrams per day (M 1999). She presented with persistent vomiting, fever, headache, jaundice and dark urine. Her aspartate a was level 550 International units/liter, alanine aminotransferase 570 International units/liter, alkaline phos International units/liter, and ammonia 148 micrograms/decaliter. She also had hypoprothrombinemia not intravenous vitamin K. Her carbamazepine was discontinued and she received prednisone 50 mg/day wi over the next 8 days.

b) Dose-related carbamazepine hepatotoxicity was reported in a 2-year-old child treated with carbamaz disorder (Luke et al, 1986). In one instance, she received an excessive dose of medication with a resulti blood level of 28 micrograms/milliliter; the concentration of the 10,11-epoxide metabolite was also signifi the second situation, the patient had been maintained on carbamazepine 150 milligrams twice daily for a months. In each situation, the patient developed severe neurological symptoms, significant elevations in (100 to 200 times baseline values) and elevated serum ammonia levels. All evidence of hepatotoxicity di discontinuation of the drug.

c) A 6-year-old, 13-kilogram boy with cerebral palsy suffered hepatorenal failure secondary to carbamaz milligrams/kilogram/day. He presented with fever, flaccidness, lethargy, and seizures. His blood urea nitr milligrams/decaliter, serum creatinine 3 milligrams/decaliter, aspartate aminotransferase 5168 Internatio alanine aminotransferase 6166 International units/liter, and lactate dehydrogenase 7378 International un carbamazepine level was elevated at 17.7 micrograms/milliliter after missing 2 doses. Carbamazepine w and fluid challenges were initiated. Serum creatinine peaked at 5.3 milligrams/decaliter on day 6, and dia on days 3 through 5. He slowly recovered during the next 13 days (Haase, 1999).

3.3.6.C Injury of bile duct

1) Summary

a) Severe bile duct injury and vanishing bile-duct syndrome have been reported with carbamazepine us Johnston, 1999)(de Galoscy et al, 1994; Forbes et al, 1992).

2) Literature Reports

a) A 52-year-old woman developed severe bile duct injury 4 weeks after starting carbamazepine 600 mg Johnston, 1999). She presented with fever and jaundice. Her aspartate aminotransferase level was 166 aminotransferase 122 units/L, alkaline phosphatase 2906 units/L, gamma-glutamyl transferase 4026 uni total/direct serum bilirubin 4.2/4. Histology from a percutaneous liver biopsy showed intact lobular archite few severely damaged bile ductules. Carbamazepine was discontinued and liver enzymes gradually dec next month.

b) Two cases of vanishing bile duct-syndrome occurred following carbamazepine administration (de Gal Forbes et al, 1992). Both patients presented with fever, skin rash, eosinophilia, and disappearance of int on liver biopsy.

3.3.6.D Liver finding

1) Hepatitis, cholangitis, cholestatic and hepatocellular jaundice, hepatorenal failure, abnormal liver function failure (very rare cases) have been reported in patients receiving carbamazepine. The hepatotoxic reaction to generally appears within the first month of therapy and usually improves upon withdrawal of the drug; the me presumed to be an idiosyncratic hypersensitivity reaction. Symptoms occur with usual therapeutic doses and the therapeutic range.

3.3.7 Immunologic Effects

Cross sensitivity reaction

Drug hypersensitivity syndrome

Hypogammaglobulinemia

Immune hypersensitivity reaction

Lymphadenopathy

Summary

Systemic lupus erythematosus

3.3.7.A Cross sensitivity reaction

1) Cross-sensitivity is reported in an 18-year-old male treated with carbamazepine for generalized tonic-clon
treatment with phenytoin resulted in an anticonvulsant hypersensitivity syndrome consisting of fever, rash, my
neck glands. Treatment with switched to carbamazepine 200 milligrams (mg) twice daily (BID), but the patien
following day with worsening symptoms. Physical examination revealed a maculopapular rash and painful lyn
Laboratory tests demonstrated an elevated white blood cell count (17,000 per cubic millimeter) with 9% eosir
elevated hepatic enzymes. Valproic acid 500 mg BID was started, as was intravenous methylprednisolone. T
patient's symptoms resolved and hepatic enzymes began to normalize. The patient was discharged; follow-up
recurrence of symptoms on valproic acid therapy. Cross-sensitivity with phenytoin, carbamazepine, and pher
explained by metabolism of the aromatic ring compounds to a toxic arene oxide intermediate, which stimulate
response. Valproic acid and benzodiazepines, structurally and metabolically different, are suitable alternative
seizures who experience the anticonvulsant hypersensitivity syndrome. Treatment involves discontinuation of
anticonvulsant, supportive care, and corticosteroids (Moss, et al, 1999). Cross sensitivity has been reported b
carbamazepine and phenytoin. Although the drugs are chemically dissimilar, they share the formation of arer
intermediate metabolites which may be responsible for toxicity, including hypersensitivity (Nathan & Balsito, 1
et al, 1991; Reents et al, 1989).

3.3.7.B Drug hypersensitivity syndrome

1) Carbamazepine treatment is suspected to be the cause of Drug Reaction with Eosinophilia and Systemic
(DRESS) syndrome in this 35-year-old male patient who presented with a 1-week history of jaundice, dark-co
lethargy, rash, vomiting, and high-fever. He had been taking phenytoin 200 mg twice daily for 14 months to tr
carbamazepine had been added 8 weeks prior to admission for uncontrolled seizures. The patient had no oth
relevance. Examination revealed a temperature of 104 degrees, jaundice, some facial edema, and a diffuse r
rash on his trunk, limbs, and face. Over the next few days, the rash became exfoliative, and the patients conc
He was screened for infection and started on benzylpenicillin and doxycycline for suspected leptospiral and ri
infections. Blood cultures, serology, cytomegalovirus, and herpes virus 6 screenings were negative. Total wh
was 4.2 X10(9)/L with a normal differential, and eosinophil count was normal. Echocardiogram and CT scan c
were normal. Despite adequate carbamazepine and phenytoin levels, the patient had a grand mal seizure du
A carbamazepine-induced reaction was suspected, therefore carbamazepine was stopped and a high-dose c
was started. Fever lowered, liver function tests that had been 10 times the upper limit of normal improved, an
discharged on a tapering dose of steroids. Follow-up indicated that the jaundice had gradually resolved and h
continued to demonstrate a downward trend. Study authors suspect that phenytoin may have sensitized the p
carbamazepine, and that carbamazepine was likely the causative agent of the clinical manifestation of DRES
2008).

3.3.7.C Hypogammaglobulinemia

1) A 49-year-old woman developed bronchiolitis obliterans organizing pneumonia (BOOP) secondary to carb
induced hypogammaglobulinemia after two years of carbamazepine therapy for epilepsy. The woman presen
progressive exertional dyspnea and prolonged productive cough. BOOP was diagnosed via computerize tom
and transbronchial biopsy. Laboratory analysis revealed severe hypogammaglobulinemia including immunog
milligrams/deciliter (mg/dL), Ig A 20 mg/dL, and Ig M 51 mg/dL. After carbamazepine withdrawal, gammaglob
and roentgenogram findings improved (Tamada et al, 2007).

3.3.7.D Immune hypersensitivity reaction

1) A 62-year-old woman developed a hypersensitivity syndrome associated with carbamazepine therapy. Sh
her first epileptic seizure in a neurological emergency unit. No intracranial pathology was found after an EEG
Cerebral spinal fluid and serum tested negative for parasitic, fungal, viral, or bacterial pathogens, and blood a
fluids were unremarkable. Epilepsy was suspected to cause the seizure; therefore, the patient was started or
carbamazepine 200 mg twice daily. Ten days after starting carbamazepine, she developed a fever, watery di
reddish, pruritic, maculopapulous rash on her entire body except her face and legs. Diarrhea improved, temp
normalized, and skin lesions disappeared after decreasing carbamazepine to 200 mg once daily and institutir
and antipyretic drugs; however, her condition dramatically worsened 20 days later. The patient experienced g
exanthema, watery diarrhea, and an increased temperature. Carbamazepine was discontinued and valproic a
admission, lab tests indicated a normal white blood cell count with relative eosinophilia and elevated transam
reactive protein level of 2.2 mg/dL, elevated serum creatinine of 1.3 mg/dl, and elevated serum potassium wa
ECG indicated terminal negative T waves in I, II, aVL, V(5), and V(6) with normalizing tendency after strain. M
scintigraphy, negative angina history, and normal troponine T and creatinine kinase ruled out an ischemic cai
condition improved, fever and diarrhea stopped, and the ECG normalized after treatment with IV methylpredr
for 1 week and antihistamines. Antiepileptic drug-induced hypersensitivity syndrome (AEDHS) was the plausi
the patient had no previous history of drug related side effects, cardiac, gastrointestinal, or dermatologic diso
apparent acute infection (Aigner et al, 2008).

2) A 5-year-old boy developed a hypersensitivity to carbamazepine after 3 weeks of therapy (Brown et al, 19
with fever, lethargy, diarrhea, abdominal pain, and macular rash. Lab tests showed hyponatremia and elevate
Carbamazepine was discontinued. Over the next few days, he developed edema and right-sided pleural effus
intubation. He improved over a 2-week period during which he required 12 days of ventilation. He also had 5
parenteral nutrition. The patient's peripheral blood monocyte proliferation response in vitro to carbamazepine
diagnosis of carbamazepine hypersensitivity.

3) A patient who had developed fever, headache, and a maculopapular rash while receiving carbamazepine from therapy and her symptoms resolved. Two years later, carbamazepine was reinstituted along with predni milligrams/day. After 10 days of carbamazepine therapy, the patient experienced fever, headache, photophol elevations of transamidase levels, and EEG findings consistent with toxic or metabolic encephalopathy. Altho occurred, no rash developed. All symptoms resolved within 72 hours of discontinuing the carbamazepine. Alt suppressed the rash associated with carbamazepine, the other manifestations of carbamazepine hypersensit prevented (Hampton et al, 1985).
4) A hypersensitivity reaction to carbamazepine, characterized by generalized erythroderma, a severe leuke hyponatremia, marked eosinophilia, and renal failure, was described in a 35-year-old woman with late-onset receiving carbamazepine therapy for approximately 3 weeks (Ray-Chaudhuri et al, 1989). The patient improv of carbamazepine and steroid therapy; however, introduction of sodium valproate resulted in development of leukocytosis, and eosinophilia; valproate was discontinued. The patient was not treated further with anticonvu seizures did not recur. A multisystemic hypersensitivity reaction after 50 days of chronic carbamazepine thera a 81-year-old man. His reaction was characterized by generalized erythroderma and renal, hepatic and bone (dyserythropoietic anemia)(Lombardi et al, 1999). A positive proactive test implicated carbamazepine as the

3.3.7.E Lymphadenopathy

1) A 17-year-old male with seizures secondary to a right parietal abscess developed cervical lymphadenopat of carbamazepine therapy titrated up to 600 milligrams per day (Ganga et al, 1998). He developed fever, mac and painful lymph nodes that were 1 to 2 centimeters, solid and round. Biopsies revealed kikuchi disease witl immunohistochemistry positive for CD68 and CD43. Liver transaminases were elevated with normal leukocyt lymphopenia, monocytosis and eosinophilia. Antibiotics were unsuccessful. Symptoms resolved 1 week after withdrawal.

3.3.7.F Summary

1) Multisystemic hypersensitivity and cross sensitivity has transpired in a variety of carbamazepine treated p al, 1999; Lombardi et al, 1999; Ray-Chaudhuri et al, 1989; Hampton et al, 1985; Moss et al, 1999); (Nathan & (Pirmohamed et al, 1991; Reents et al, 1989). Carbamazepine is suspected to be the most likely cause of a D Eosinophilia and Systemic Symptoms (DRESS) syndrome in a 35-year-old male patient (Fsadni et al, 2008). erythematosus (SLE) has been reported in several cases with varying length of carbamazepine therapy (Toe (Reiffers-Mettelock et al, 1997; Jain, 1991; Drory et al, 1989; Bateman, 1985)

3.3.7.G Systemic lupus erythematosus

1) Systemic lupus erythematosus (SLE) occurred in a 34-year-old male after 8 years of carbamazepine thera occurs after only months of therapy, however, this patient exhibited all of the clinical symptoms (rash, enlarge joint involvement, myalgia, fever, leukopenia, and positive antinuclear antibody titer) associated with SLE (To
2) A syndrome resembling systemic Lupus erythematosus (SLE) was induced by carbamazepine in a 40-yea a paralyzed left arm following an aneurysm. After one year of carbamazepine therapy, she developed red fac Raynaud's phenomenon of the extremities, the left-paralyzed arm being more affected. Her ANA was positive Later she developed a lichen-planus- like eruption with an increased ANA titer of 1/1280. Valproate was subs carbamazepine and after 6 months, the ANA titer was unchanged but anti-DNA antibodies and antihistone ar negative. The cutaneous lichenoid lesions improved (Reiffers-Mettelock et al, 1997).
3) Lupus erythematosus was described in a 30-year-old woman with complex partial seizures following carba daily (plus phenobarbital 120 milligrams daily) for approximately 1 year. At that time, the patient developed st the joints, a blotchy rash on her hands and feet, and eye symptoms (soreness and pruritus). Pleuritic chest pa leukopenia, as well as a positive ANA titer, were observed and the drug was withdrawn with continuance of p therapy and the addition of prednisolone 30 mg daily. Improvement occurred rapidly; however, the ANA titer r at 1:160 (Bateman, 1985).
4) Systemic lupus erythematosus (SLE) was described in an 18- year-old male after receiving carbamazepin each day for approximately 5 months in the treatment of complex partial seizures and secondary generalizati developed severe migrating arthralgia 5 months after initiation of therapy; low-grade fever and profuse sweat weeks later. Antinuclear factor was positive at that time, and anti-DNA was 74% (normal, 14%); a few LE cell Withdrawal of carbamazepine and institution of prednisone therapy (60 milligrams daily) resulted in abatemer However, seizure activity recurred and phenytoin was initiated, resulting in a severe relapse of SLE symptom despite continued steroid therapy. Substitution of phenytoin with sodium valproate, with continued steroid the recovery within 3 weeks. The patient was treated subsequently with sodium valproate and primidone without systemic manifestations. This case report suggests that carbamazepine may be associated with SLE, and tha phenytoin therapy can induce relapse in these patients. Based upon this case report, Ciba-Geigy has include potential adverse effect of carbamazepine in the product data (Drory et al, 1989). However, in the absence of impossible to establish a definite cause-effect relationship between carbamazepine and SLE in this patient. A cases of systemic lupus erythematosus induced by carbamazepine was provided (Jain, 1991).
5) (Verma et al, 2000) report a carbamazepine-induced systemic lupus erythematosus syndrome presenting tamponade after 8 months of therapy in a 45-year-old male. Blood serologic studies revealed a positive ANA Pericardicenteses was performed with immediate relief and carbamazepine was discontinued. The patient ful
See Drug Consult reference: DRUG-INDUCED SYSTEMIC LUPUS ERYTHEMATOSUS

3.3.8 Musculoskeletal Effects

Disorder of connective tissue

Musculoskeletal finding

Myasthenia gravis

Osteomalacia

3.3.8.A Disorder of connective tissue

1) Summary

a) The occurrence of connective tissue disorders is 6% of patients who were treated with a single barbit monotherapy (Mattson et al, 1989). It is suggested that switching to an alternative antiepileptic should be patients presenting with symptoms of musculoskeletal problems who are receiving barbiturates.

2) Literature Reports

a) The occurrence of connective tissue disorders in 10 of 178 patients (6%) who were treated with a sin (phenobarbital or primidone) as monotherapy for 6 months or longer were reported in a prospective stud 1989). The disorders occurred in 7 of the 10 patients during the first year of treatment. The connective tis associated with primidone in these patients were frozen shoulder, arthralgias, Dupuytren's contractures; shoulder pain, Dupuytren's contractures, Peyronie's disease were observed. In this study, no associatior between new-onset connective tissue disorders and carbamazepine or phenytoin therapy (for 6 months data support the association between barbiturate use and the development of connective tissue disorder that switching to an alternative antiepileptic (carbamazepine, phenytoin, valproic acid) should be conside presenting with symptoms of musculoskeletal problems who are receiving barbiturates.

3.3.8.B Musculoskeletal finding

1) Summary

a) Aching joints, sore muscles and leg cramps have been reported in patients receiving carbamazepine (R), 2002b).

2) Aching joints and muscles, leg cramps and general connective tissue disorders have been reported in pat carbamazepine. The data is conflicting with regard the propensity of carbamazepine to induce osteomalacia . systemic lupus erythematosus have also been reported.

3.3.8.C Myasthenia gravis

See Drug Consult reference: DRUG-INDUCED MYASTHENIA GRAVIS

3.3.8.D Osteomalacia

1) Summary

a) There are conflicting data regarding the effects of carbamazepine on bone mineral density in children identified reduced bone mineral density in children treated with carbamazepine for an average of approx (Kumandas et al, 2006). Another showed an association between carbamazepine use and increased bor collagen metabolism in young male patients (Verotti et al, 2000). However, earlier studies differed by cor mineral density in the lumbar region of children receiving carbamazepine was not significantly different fr group (Akin et al, 1998; Hoikka et al, 1984; Tjellesen et al, 1983; Zerwekh et al, 1982).

2) A 2-year cross sectional and retrospective study concluded that lumbar spine bone mineral density values reduced in prepubertal children treated with carbamazepine and valproic acid compared to controls. Sixty-six with antiepileptics (carbamazepine: 20 boys, 13 girls; mean age 9.7 +/-1.6 years; valproic acid: 17 boys, 16 g +/- 2 years) were compared to age- and sex-matched controls (13 boys, 9 girls; mean age 8.9 +/- 2.3 years). ambulatory with normal activity and had adequate nutritional intake, which excluded factors that could reduce biochemical markers of bone turnover. Mean length of treatment was 35.52 +/- 12.84 months for carbamazep 15 months for valproic acid. Mean BMD z-scores at lumbar spine were -1.69 +/- 0.85 for carbamazepine, -1.2 valproic acid, and -0.23 +/- 0.87 for the control group. Differences in serum insulin-like growth factor (IGF)-I a protein (IGFBP)-3 levels, which affect bone metabolism and BMD, between children receiving antiepileptics c controls were not significant. It is thought that the mechanism of carbamazepine-associated reduction in BMD altered hepatic conversion of vitamin D or excessive enzymatic degradation of vitamin D (Kumandas et al, 20

3) Carbamazepine has been associated with increased bone turnover and collagen metabolism in young ma et al, 2000). Bone mineral density in the lumbar region in children receiving carbamazepine was not significar the control group (Akin et al, 1998; Hoikka et al, 1984; Tjellesen et al, 1983; Zerwekh et al, 1982).

4) A prospective evaluation demonstrated that carbamazepine therapy was associated with increased bone collagen metabolism in young male patients receiving the drug for idiopathic partial epilepsy. Markers of bone (alkaline phosphatase, Osteocalcin, and propeptides of type I and III procollagen) were significantly higher at carbamazepine-treated patients as compared to those in 15 healthy, age-matched volunteers. Similarly, mark resorption (serum telopeptide of type I collagen and urinary N- telopeptides of type I collagen) were significar patients. Serum levels of calcium, phosphate, magnesium, parathyroid hormone, and vitamin D metabolites v normal range before and after carbamazepine treatment. Carbamazepine-treated patients received usual dos milligrams per kilogram per day and had therapeutic serum concentrations (Verotti et al, 2000).

5) Bone mineral density at L2-L4 levels of lumbar vertebrae in children receiving carbamazepine (n=28, aver micrograms/milliliter (mcg/mL)) for an average of 2.6 years were not significantly different from a control grou than 0.05). Bone mineral density measured by dual-energy x-ray absorptiometry was 0.611 grams per centim the carbamazepine group and 0.568 grams per centimeter squared in the control group (Akin et al, 1998).
6) Bone mineral metabolism was studied in 21 epileptic patients on chronic carbamazepine monotherapy at of 505 milligrams. In 3 cases, hypocalcemia was identified; hypophosphatemia was noted in 1 patient and 4 p demonstrated elevated serum alkaline phosphatase levels. Serum 25-hydroxy vitamin D levels were significa controls in all patients. No significant difference was noted in bone mineral density or in the amount of trabec patients and controls. Two patients were found to have histological evidence of osteomalacia (Hoikka et al, 1
7) Data are conflicting with regard to the propensity of carbamazepine to induce osteomalacia to a similar de Reductions in 24,25-dihydroxycholecalciferol concentrations during carbamazepine, phenytoin and phenobar been reported (Zerwekh et al, 1982). This deficiency may play an important role in the pathogenesis of anticc osteomalacia induced by carbamazepine. Reduction in 25-hydroxycholecalciferol occurred only in patients tre phenobarbital. Calcium metabolism was evaluated in 30 adult epileptic patients receiving carbamazepine as therapy for 1 to 10 years (serum levels, 3 to 11 micrograms/milliliter) (Tjellesen et al, 1983). Their examinatio normal bone mass in these patients as well as normal serum concentrations of 25-hydroxycholecalciferol. Se were decreased and alkaline phosphatase levels were increased. The authors suggest that single agent ther carbamazepine is not associated with adverse effects on bone metabolism (anticonvulsant osteomalacia). In 25- hydroxycholecalciferol levels were decreased significantly only in patients treated with phenobarbital, anc receiving carbamazepine, suggesting that this deficiency is not the abnormality in anticonvulsant osteomalaci reductions in 24,25- dihydroxycholecalciferol may be implicated (Zerwekh et al, 1982). Serum levels of 24,25,dihydroxycholecalciferol were not performed in the other study (Tjellesen et al, 1983).

3.3.9 Neurologic Effects

Aseptic meningitis

Finding related to coordination / incoordination

Impaired cognition

Motor dysfunction

Movement disorder

Myoclonus

Neuroleptic malignant syndrome

Neurological finding

Nystagmus

Seizure

Somnolence

3.3.9.A Aseptic meningitis

1) Summary
a) Aseptic meningitis has been associated with the use of carbamazepine in 2 cases (Simon et al, 1990 1989).
2) Literature Reports
a) Aseptic meningitis, confirmed on rechallenge, has been described in a 45-year-old female during carb therapy (Hilton & Stroh, 1989). Three days after beginning therapy with carbamazepine 100 milligrams tv patient developed a fever, sore throat, and rhinorrhea. Carbamazepine was discontinued and therapy wi milligrams 3 times a day was initiated. The patient's symptoms resolved over 5 days and carbamazepine restarted. Within 1 day, the patient developed perioral numbness, which progressed over 2 days to perip paresthesias. Fever developed and a malar rash was noted. The patient was diagnosed wish aseptic me basis of physical examination and laboratory findings. Symptoms again resolved over 7 to 10 days follow discontinuation of carbamazepine. A similar case without rechallenge has been reported (Simon et al, 19

3.3.9.B Finding related to coordination / incoordination

1) Summary

a) Vertigo, unsteadiness and dizziness are relatively common side effects of carbamazepine therapy, ge with the initiation of therapy (Prod Info Tegretol(R), 2002b).

3.3.9.C Impaired cognition

1) Summary

a) Carbamazepine did not impair the elderly patient's reflexes while driving (Etminan et al, 2004). Cogni memory tests performed in 7 children during carbamazepine therapy demonstrated that therapeutic dose associated with adverse neurologic effects (Riva & Devoti, 1999).

2) Literature Reports

a) Elderly users of lithium (but not carbamazepine) are at increased risk of having an injurious car accid than age-matched controls. A case-control study nested within a cohort was conducted. The cohort cons drivers between the age of 67 and 84 years living in Quebec providence for at least two years. Cohort su followed until they reached 85 years of age, left the providence, or the end of study date, May 31, 1993. vehicle crash was defined as one person in the car sustaining a physical injury. Drug exposure was defir prescription dispensed within the 60 days before the date of car accident. Of the 5579 subjects that had during the study period, 20 were prescribed lithium and 18 carbamazepine. A random sample of 6% (13, subjects within the cohort showed 27 and 48 were prescribed lithium and carbamazepine, respectively. I accidents were more likely to occur with elderly drivers who were prescribed lithium (rate ratio 2.08 (95% interval (CI), 1.11 to 3.9)). The rate of injurious car accidents with drivers prescribed carbamazepine, wa different from controls (rate ratio 0.83 (95% CI, 0.48 to 1.44)) (Etminan et al, 2004).

b) Cognitive function and memory tests performed in 7 children during carbamazepine therapy demonst therapeutic doses were not associated with adverse neurologic effects. Patients with symptomatic partia carbamazepine for 4 to 15 years, with measured serum concentrations consistently within the therapeuti Withdrawal of treatment was allowed if patients were seizure- free for 2 years and demonstrated no electroencephalographic abnormalities for 1 year. At a mean of 17 months following carbamazepine with testing showed improvement in all scores, but significant improvement occurred only in tests assessing f more complete tasks. This potentially suggests that the effects of carbamazepine on decreasing neuron excitability may impair information circuitry in the front areas of the brain. However, in patients' studies, c testing scores never fell below the normal range (Riva & Devoti, 1999).

3.3.9.D Motor dysfunction

1) Summary

a) Carbamazepine has been associated with episodes of dystonia possibly due to its antagonism of dop Tegretol(R), 2002b); (Bradbury & Bentick, 1982; Larazo, 1982)(Crosley & Swender, 1979; Jacome, 1979

2) Literature Reports

a) Four episodes of dystonia in 3 children with generalized tonic-clonic seizures occurred in association carbamazepine use. Carbamazepine dosage was increased to a maximum of 25 milligrams/kilogram/da symptoms beginning 2 to 3 weeks after start of therapy. Symptoms subsided within 3 weeks following di second course of carbamazepine in 1 child resulted in dystonia (Crosley & Swender, 1979).

b) Carbamazepine produces dyskinesias similar to those induced by neuroleptic agents (Chadwick et al asterixis and cerebellar syndrome is reported in a 66-year-old patient receiving doses of 800 to 1200 mil decreasing the dose to 800 milligrams daily, the asterixis improved markedly and only minor nystagmus discontinuation of therapy, asterixis and nystagmus subsided completely.

c) Treatment with carbamazepine in ordinary doses can cause motor impairment in children (Braathen e Nineteen children were tested while receiving carbamazepine and 6 months later without treatment. Sign improvements were found in response speed (p less than 0.05), composite fine-motor tests (p less than test battery (p less than 0.05).

3.3.9.E Movement disorder

1) Summary

a) The appearance or worsening of tics has been reported in 9 cases. With the withdrawal of carbamaze patients with a previous history, the tics did not resolve, suggesting the drug may trigger the onset of Tou Tics did subside in patients without a history of movement disorders after discontinuation of carbamazep (Robertson et al, 1993; Kurlan et al, 1989; Neglia et al, 1984).

2) Literature Reports

a) The appearance or worsening of tics was reported in 3 patients with underlying movement disorders chorea, tardive dyskinesia and tourette's syndrome) following initiation of low doses of carbamazepine (K The tics included vocalizations, facial tics and generalized motor tics; these disappeared or returned to b discontinuation of the drug.

b) Three similar cases of a syndrome like Tourette's associated with carbamazepine for control of seizu reported (Neglia et al, 1984). Tics and vocalizations did not resolve upon discontinuation of the carbama that the drug might trigger the onset of Tourette's syndrome in susceptible patients.

c) Transient facial tics were reported in 3 children with no previous history of involuntary movements (R 1993). The tics, characterized by abnormal movements of the eyes and mouth, began about two weeks carbamazepine and despite therapeutic serum levels. In 2 of the cases the tics gradually subsided after continuous therapy; in the third case, carbamazepine was discontinued with resolution of symptoms.

3.3.9.F Myoclonus

1) Summary

a) Myoclonus was reported secondary to carbamazepine. Withdrawal of therapeutic levels of carbamaz involuntary movements (Nanba & Maegaki, 1999; Aguglia et al, 1987).

2) Literature Reports

a) A case of epileptic negative myoclonus is reported in a 7- year-old child treated with carbamazepine f childhood epilepsy with centrotemporal spikes. Carbamazepine was increased to 300 milligrams per day frequency did not decrease. In addition, several weeks after beginning carbamazepine treatment, the pa brief episodes of loss of tone in one or both arms, accompanied by eye blinking. Electroencephalograms spike and wave discharges that tended to spread diffusely. This activity ceased when carbamazepine wa (Nanba & Maegaki, 1999).

b) A further report of myoclonus secondary to carbamazepine was described in a 11-year-old boy with b epilepsy (Aguglia et al, 1987). Nonepileptic myoclonus and tic-like movements were observed after 2 we carbamazepine therapy (15 milligrams/kilogram/day). Withdrawal of the drug resulted in resolution of inv movements within several days; rechallenge with carbamazepine again produced myoclonic symptoms. occurred in the presence of therapeutic serum levels of carbamazepine.

3.3.9.G Neuroleptic malignant syndrome

1) Summary

a) A case of neuroleptic malignant syndrome (NMS) induced by carbamazepine was reported in a schiz a history of classic NMS secondary to antipsychotics (O'Griofa & Voris, 1991).

2) Literature Reports

a) A case of neuroleptic malignant syndrome (NMS) induced by carbamazepine was reported in a schiz a history of classic NMS secondary to antipsychotics (O'Griofa & Voris, 1991). Following 3 weeks of carb milligrams 3 times daily (serum level 10.8 micrograms/milliliter), the patient developed fever, increased c phosphokinase, tachycardia, hypertension, diaphoresis and leukocytosis; there was no evidence of musc Symptoms of NMS resolved within 10 days following discontinuation of the carbamazepine despite conti intramuscular lorazepam and amobarbital.

3.3.9.H Neurological finding

1) Summary

a) Other central nervous system effects that have been reported carbamazepine therapy include headac disturbances, confusion, peripheral neuritis, and paresthesias, (Bradbury & Bentick, 1982)(Lazaro, 1982 O'Donnell, 1984)(Aguglia et al, 1987; Silverstein et al, 1982; Shields & Saslow, 1983; Kurlan et al, 1989; (R), 2002b).

2) Symptoms of vertigo, drowsiness, unsteadiness and dizziness are relatively common side effects of carba Other central nervous system effects that have been reported include aseptic meningitis, headache, speech confusion, depression with agitation, psychosis, mania, nystagmus, visual hallucinations, peripheral neuritis, worsening of tics, dystonic reactions such as dyskinesias and myoclonus, and neuroleptic malignant syndrom seizures in children has also occurred. Patients with chronic focal epilepsy who exhibited cerebellar atrophy c resonance imaging were at increased risk of cerebellar adverse effects of carbamazepine.

3.3.9.I Nystagmus

1) Summary

a) Nystagmus occurs often with therapeutic levels of carbamazepine (Prod Info Tegretol(R), 2002b; Rar (Weeler et al, 1982).

2) Literature Reports

a) In a controlled trial, nystagmus occurred in 52% of 35 adult epileptic patients treated with carbamaze sufficient to maintain therapeutic serum concentrations (Ramsay et al, 1983a). Nystagmus was consider effect and did not interfere with daily functioning and in some cases was transient. Nystagmus did not ne discontinuation in any patient. Nystagmus may also occur in overdosage or acute toxic reactions (Fraunf 1982).

b) DOWNBEAT NYSTAGMUS was reported following several weeks of carbamazepine therapy in a 23- (Wheeler et al, 1982). The occurrence of nystagmus was associated with a high unbound concentration (2.6 micrograms/milliliter). Downbeat nystagmus with oscillopsia and reduced visual acuity has also beer patients taking carbamazepine with blood levels of 9 to 12 micrograms/milliliter. Symptoms reversed upo reduction (Chrousos et al, 1987).

c) Patients with chronic focal epilepsy who exhibited cerebellar atrophy on magnetic resonance imaging increased risk of cerebellar adverse effects of carbamazepine. These patients exhibited gaze-evoked ny than 0.001), dizziness (p less than 0.008), and ataxia of stance (p less than 0.02) at significantly lower se concentrations as compared to patients without cerebellar atrophy (Specht et al, 1997).

3.3.9.J Seizure

1) Summary

a) Carbamazepine increases the risk of exacerbation of seizures in children and adolescents (Prasad et al, 1986; Snead & Hosey, 1985). Patients developing uncontrolled, generalized seizures during carbama should be examined for possible carbamazepine exacerbation of epilepsy (Dhuna et al, 1991).

2) Literature Reports

a) Exacerbation of seizures may occur in children receiving carbamazepine monotherapy (Prasad et al, 1998; Shields & Saslow, 1983). Exacerbations occur when children with absence seizures are erroneous carbamazepine. Patients have experienced increased absences or myoclonic jerking. One study noted t children (28.5%) beginning carbamazepine therapy experienced a clinical or electroencephalographic de seizure disorder regardless of type (Prasad et al, 1998).
b) Fifteen children were evaluated with complex partial seizures where 1 or more seizure type was exac carbamazepine therapy (Snead & Hosey, 1985). The most common seizure type exacerbated by the dru atypical absence seizures in 11 children. in 4 patients, more frequent and severe generalized convulsive the use of video-electroencephalographic monitoring enabled evaluation of risk factors for seizures induc carbamazepine. a bilaterally synchronous spike and wave discharge of 2.5 to 3 cycles/second was consi an increase in atypical absence seizures with carbamazepine. generalized bursts of spikes and slow wav cycles/second were suggestive of a risk of increased generalized convulsive seizures. A generalized par wave discharge was observed in all children who had exacerbated seizures induced by carbamazepine.
c) It is suggested that carbamazepine be used cautiously to treat a complex partial component of mixed in children, as the risk of seizure exacerbation was approximately 12% in this series of patients. Children of generalized absence or atypical absence seizures appear to be at a particularly high risk. The drug sh when generalized, synchronous, spike and wave discharges of 2.5 to 3 cycles/second are observed rega clinical manifestation. Prolonged video-EEG monitoring is suggested prior to carbamazepine therapy in c seizure disorders to identify patients at risk of developing seizure exacerbation during treatment. The occ worsening of atypical absence or generalized convulsive seizures following the addition of carbamazepir be an indication that seizure activity may be a result of carbamazepine rather than the natural history of Hosey, 1985).
d) Myoclonic, atypical absence and/or atonic (minor motor) seizures were reported within a few days of carbamazepine treatment for epilepsy in 5 children (3 to 11 years of age) (Shields & Saslow, 1983). With resulted in resolution of symptoms in 2 children, whereas in 2 others, minor motor seizures resolved in 3 the remaining child, seizures persisted, and this child was later found to have ceroid lipofuscinosis. The a that carbamazepine can in some cases precipitate or exacerbate minor motor seizures and their occurre days of initiation of therapy requires withdrawal of the drug.
e) Exacerbation of epilepsy was reported in 26 adolescents and children receiving carbamazepine (Horr epileptic syndromes were affected by carbamazepine: childhood absence seizures; focal symptomatic, fi epilepsy; Lennox-Gastaut syndrome; and severe myoclonic epilepsy of infancy. New-onset absence seiz of the 26 patients, and 3 patients with established absence seizures experienced absence status. It is su caution be exercised when carbamazepine is administered to children or adolescents with absence or m Patients developing uncontrolled, generalized seizures during carbamazepine therapy should be examin carbamazepine exacerbation of epilepsy. Withdrawal of the drug in these patients may result in marked i
f) Seizure exacerbation was attributed to high levels of carbamazepine-10,11-epoxide in a series of 6 pa condition unexpectedly deteriorated (So et al, 1994). In all 6 cases, the patients were taking other drugs serum carbamazepine- epoxide levels. Status epilepticus did not respond to intravenous phenytoin, and after withholding carbamazepine. While routine monitoring of serum carbamazepine-epoxide levels is no the authors suggest obtaining a level when the cause of seizure exacerbation or drug toxicity is not appa
g) The development of frequent complex partial seizures and nonepileptic multifocal myoclonus was rep month-old child started on carbamazepine therapy for generalized tonic-clonic seizures previously unres phenobarbital and valproic acid. Carbamazepine blood levels reached 8.2 micrograms/milliliter and carba epoxide levels were 8.9 micrograms/milliliter. Within 24 hours of carbamazepine discontinuation, seizure myoclonus disappeared within 5 days. The authors postulate that symptoms may have related to toxic co the epoxide metabolite (Dhuna et al, 1991).

3.3.9.K Somnolence

1) Summary

a) Marked drowsiness is a common adverse effect of carbamazepine therapy (Prod Info Tegretol(R), 20 1997; Smith, 1991; Levy et al, 1985).

2) Literature Reports

a) Daytime sleepiness was worse in carbamazepine patients as compared with controls (Bonanni et al, carbamazepine monotherapy (n=26) and controls (n=12) were tested for sleepiness using the multiple sl Compared with controls, the carbamazepine group showed statistically significant shorter sleep latencies 0.001).
b) Profound drowsiness was reported in a 19-month-old boy receiving carbamazepine for seizure activit receiving carbamazepine 100 milligrams 4 times a day (35 milligrams/kilogram/day) which produced sev 17 days. Serum levels of carbamazepine were within therapeutic range upon admission. Further investig normal behavior when serum levels of carbamazepine had decreased to 4 micrograms/milliliter (10 hours dose) and severe drowsiness occurred immediately following a test dose of 100 mg carbamazepine (Lev
c) Carbamazepine 800 mg daily in combination with phenytoin 500 mg daily was prescribed for symptor neuralgia in a 66-year-old woman. Maximum blood levels were 2.6 micrograms/milliliter and 16.5 microg respectively. After 2 weeks of combined therapy, the patient developed drowsiness, confusion, staggerin disorientation and confusion. The EEG indicated diffuse cerebral dysfunction. Within 48 hours of drug dis encephalomyelopathy disappeared and facial pain returned. A retrial of carbamazepine resulted in hyper spasticity without evidence of mental status change. Discontinuation resulted in complete resolution of sy 1991).

3.3.10 Ophthalmic Effects

Disorder of oculomotor system

Eye / vision finding

Oculogyric crisis

Retinopathy

3.3.10.A Disorder of oculomotor system

1) Summary

a) Oculomotor disturbances have been reported with carbamazepine therapy (Prod Info Tegretol(R), 20

3.3.10.B Eye / vision finding

1) Summary

a) Diplopia, esotropia, blurred vision and impaired visual contrast sensitivity occasionally occur with carb therapy (Fukuo et al, 1998; Tomson et al, 1988; Fraunfelder & Meyer, 1982; Livingston et al, 1974). In ac opacities and conjunctivitis have been reported; a direct causal relationship has not been established (Pr (R), 2002b)

2) The following ocular effects have been reported during carbamazepine therapy: blurred vision, transient d oculomotor disturbances. In addition, lens opacities and conjunctivitis have been reported; a direct causal rel been established. An oculogyric crisis has been reported in 1 case and ophthalmoplegia was reported in 2 pa elevated carbamazepine blood levels. Visual disturbances are reversible and may clear without reduction of c however, such problems are most common with high doses and typically respond to dosage decreases.

3) Literature Reports

a) An 11-year-old boy with head trauma and postsurgical convulsions developed diplopia associated wit his carbamazepine had been increased to 700 milligrams per day and his level was 12.5 micrograms/mil examination he was also noted to have esotropia and lateral gaze nystagmus. Carbamazepine was decr milligrams and the symptoms disappeared (Fukuo et al, 1998).

b) Blurred vision, most often manifested as diplopia, occurs occasionally during therapy with carbamaze figures have varied from 0% of patients in 1 series (n=280) (Andersen et al, 1983) to as many as 17% wi another 5.5% with transient blurred vision in another series (n=255) (Livingston et al, 1974). Visual distur reversible and may clear without reduction of drug dosage although such problems are most common wi typically respond to dosage decreases. Vision changes generally are not serious; a small number of lens resembling cataracts have been reported, but an association with carbamazepine is unproved (Fraunfelc 1982).

c) Impaired visual contrast sensitivity has been reported in a study of 27 epileptic patients receiving carb monotherapy. These patients had no subjective complaints of visual disturbance and critical flicker-fusion not affected. The effect upon visual contrast sensitivity appeared to be dose-related, with higher blood le greater impairment (Tomson et al, 1988).

3.3.10.C Oculogyric crisis

1) Summary

a) A case report of an oculogyric crisis in an 8-year-old girl was also reported with carbamazepine thera 1979).

2) Literature Reports

a) One case of oculogyric crisis in a 8-year-old girl was reported (Fallat & Norris, 1979). Oculogyric crisis carbamazepine was added to her regimen of phenytoin and phenobarbital. There was temporary cessati when treated with 25 milligrams of oral diphenhydramine and permanent cessation when the carbamaze completely withdrawn. The highest serum level of carbamazepine recorded was 4.3 micrograms/milliliter

3.3.10.D Retinopathy

1) Summary

a) Two cases of retinopathy in patients treated with long-term carbamazepine therapy have been report Syversen, 1986).

2) Literature Reports

a) Two cases of retinopathy in patients treated with long-term carbamazepine therapy have been report Syversen, 1986). Despite the absence of systemic toxicity, both patients developed decreases in visual a disturbances. Examination revealed lesions of the retinal pigment epithelium, which partially resolved in discontinuation of the drug.

3.3.11 Otic Effects

Auditory dysfunction

Ear and auditory finding

3.3.11.A Auditory dysfunction

1) Summary

a) Several case reports of a lowered pitch perception shift have been identified following the administrat carbamazepine (Kobayaski et al, 2001)(Kashihara et al, 1998).

2) Literature Reports

a) In two separate case reports, a 17-year-old girl and a 10-year-old boy experienced a downwards pitcl of one semitone after receiving carbamazepine 400 milligrams per day. In addition to carbamazepine, th receiving sulpiride and bromazepam, and the boy was taking imipramine and bromazepam. The girl noti two days following the carbamazepine, and the boy noticed the pitch perception change 3 to 4 hours afte drug. Neither patient demonstrated any other signs of carbamazepine toxicity. The girl's pitch perception one week after discontinuing carbamazepine, and the boy stopped complaining of the pitch perception c remaining on carbamazepine (Kobayashi et al, 2001).

b) Within 3 days of beginning carbamazepine 200 milligrams (mg)/day, an 18-year-old woman with gene noticed a false lowering of perceived pitch (Kashihara et al, 1998). She noted false pitches of the telepho sounds, and mechanical noises. After 2 weeks, her carbamazepine dose was increased to 300 mg and s TINNITUS (noted in approximately 0.2% of carbamazepine patients). Carbamazepine was subsequently auditory symptoms disappearing in 2 days.

3.3.11.B Ear and auditory finding

1) Several cases of lowered pitch perception shift have been reported in association with carbamazepine the

3.3.12 Psychiatric Effects

Mania

Psychiatric sign or symptom

Psychotic disorder

Suicidal thoughts

3.3.12.A Mania

1) Summary

a) Carbamazepine has been associated with mania in a few cases (Prod Info Tegretol(R), 2002b; Kurla Aguglia et al, 1987; Drake & Peruzzi, 1986; Reiss & O'Donnell, 1984; Reiss & O'Donnell, 1984); (Shields 1983; Bradbury & Bentick, 1982)(Lazaro, 1982; Silverstein et al, 1982).

2) Literature Reports

a) Mania attributable to carbamazepine was described in 2 children (Reiss & O'Donnell, 1984). In 1 chil had also developed after receiving imipramine and dextroamphetamine. The authors suggest that, due t similarities between carbamazepine and tricyclic antidepressants, this reaction may be similar to that ind antidepressants.

b) Carbamazepine was associated with the occurrence of an acute manic state in a 40-year-old seizure days of therapy for complex partial seizures (200 milligrams 4 times a day). Withdrawal of the drug result of psychiatric symptoms within the ensuing 24 hours. Inadvertent readministration of carbamazepine 200 times a day reproduced acute manic symptoms, which again subsided upon withdrawal of the drug. It is carbamazepine may have produced a paradoxical effect; the patient recalled brief euphoric episodes foll occurrence of seizures, at which time carbamazepine was administered, and exacerbation or prolongatic cerebral dysfunction may have occurred (Drake & Peruzzi, 1986).

3.3.12.B Psychiatric sign or symptom

1) Psychiatric effects that have been reported with carbamazepine therapy include depression with agitation and visual hallucinations.

3.3.12.C Psychotic disorder

1) Summary

a) Acute adverse behavioral changes were noted with both the initiation and withdrawal of carbamazepi Depression with agitation has also been reported (Heh et al, 1988); (Reiss &O'Donnell, 1984)(Silverstein Berger, 1971).

2) Literature Reports

a) Acute adverse behavioral changes were reported in 7 children following initiation of carbamazepine th
et al, 1982). Symptoms of irritability, agitation, insomnia, aggressive outbursts, delirium, confusion, and h
appeared within 4 days to several weeks after initiation of therapy. Serum concentrations at the time of th
ranged from 5.8 to 11.8 micrograms/milliliter. The 3 most severe reactions occurred in children who were
retarded, suggesting that prior psychopathological problems may predispose to adverse reactions. In all
behavior changes resolved upon drug discontinuation, and 5 of the 7 patients were eventually able to tol
when lower doses were used.
b) Abrupt discontinuation of carbamazepine 600 to 800 mg daily resulted in exacerbations of psychotic s
including paranoia, hostility and agitation in 2 of 20 schizophrenic patients treated with carbamazepine in
an antipsychotic. The authors postulate the possibility of a withdrawal syndrome caused by carbamazepi
rebound or a hyperdopaminergic state (Heh et al, 1988).
c) At least 1 case of visual hallucinations has been reported secondary to carbamazepine therapy (Berg
year-old female developed visual hallucinations after 2 weeks of carbamazepine 100 milligrams 4 times a
neuralgia. Specifically, she complained of strangers in her apartment and insects on walls. The patient w
hospital and all drugs were discontinued including pentazocine, corticosteroids, carisoprodol, and analge
Hallucinations disappeared gradually and the neuralgia did not occur. A test dose of carbamazepine 60 m
a day was administered and visual hallucinations recurred within 2 days. They again subsided when the
withdrawn.

3.3.12.D Suicidal thoughts

1) Data reviewed by the US Food and Drug Administration suggest an increased risk of suicidal behavior or
in patients receiving therapy with antiepileptic drugs (AEDs). The analysis included 199 placebo-controlled cli
covering 11 different AEDs used for several different indications such as epilepsy, selected psychiatric illness
conditions, including migraine and neuropathic pain syndromes. The analysis included 27,863 patients treate
16,029 patients who received placebo, and patients were aged 5 years and older. There were 4 completed su
patients in the AED treatment groups versus (vs) none in the placebo groups. Suicidal behavior or ideation oc
patients in the AED treatment groups compared to 0.22% of patients in the placebo groups. This corresponde
2.1 per 1000 (95% confidence interval, 0.7 to 4.2) more patients in the AED treatment groups having suicidal
ideation than the placebo groups. The increased risk of suicidality was noted at 1 week after starting an AED
at least 24 weeks. When compared to placebo, results were generally consistent among the drugs and were
demographic subgroups. Patients treated for epilepsy, psychiatric disorders, or other conditions were all at ar
suicidality compared to placebo. Closely monitor patients treated with AEDs for emergence or worsening of d
suicidality and other unusual changes in behavior, which may include symptoms such as anxiety, agitation, h
hypomania (US Food and Drug Administration, 2008).

3.3.13 Renal Effects

Drug-induced tubulointerstitial nephritis, acute

Kidney finding

Necrotizing arteritis, Granulomatous

Renal failure

Urogenital finding

3.3.13.A Drug-induced tubulointerstitial nephritis, acute

1) Summary

a) Infrequent cases of tubulointerstitial nephritis and tubular necrosis have occurred with therapeutic car
(Hogg et al, 1981; Jubert et al, 1994).

2) Literature Reports

a) A case of acute renal failure secondary to tubulointerstitial nephritis in a 7-year-old boy receiving carb
reported (Hogg et al, 1981). Because of worsening control of grand mal seizures, carbamazepine 200 m
milligrams/kilogram/day) was initiated, phenobarbital was discontinued, and the dosage of phenytoin was
25 days treatment with carbamazepine, he developed a fever and patchy erythematous rash. Relevant la
included bilirubin 0.9 nanograms/decaliter, SGOT 89 International units/liter, alkaline phosphatase 393 In
units/liter, and a white blood cell count of 3500/cubic millimeter with a normal differential. His carbamaze
decreased, but 3 days later, spiking fevers occurred with development of a generalized swelling and eryt
over his entire body. Over the next 7 days, urinalysis revealed 1+ proteinuria with coarse granular casts.
increased to 3.4 nanograms/decaliter. Urine output decreased and the patient became anuric over the ne
Peritoneal dialysis was begun. Sonography revealed enlarged kidneys and renal biopsy showed tubular
infiltration of lymphocytes and plasma cells. High dose parenteral methylprednisolone was begun and co
with gradual improvement leading to a return of renal function to normal over the following 4 weeks.

3.3.13.B Kidney finding

1) Summary

a) Urinary frequency, acute urinary retention, oliguria, azotemia, albuminuria, glycosuria, elevated bun, a in the urine have been reported in patients receiving carbamazepine (Prod Info Tegretol(R), 2002b).

3.3.13.C Necrotizing arteritis, Granulomatous

1) Summary

a) CASE REPORT- Granulomatous necrotizing angiitis accompanying acute renal failure was describec male with schizophrenia following carbamazepine therapy (150 milligrams daily) for approximately 3 mor 1989). The patient developed a skin eruption initially, followed by acute renal failure. On admission, signi and eosinophilia were observed, suggesting an allergic reaction. Renal biopsy demonstrated granulomat angiitis, differing from classic periarteritis nodosa and hypersensitivity angiitis. The patient was also rece zometapine and profenamine. After withdrawal of all drugs and with conservative therapy renal function i gradually. A carefully performed provocation test identified carbamazepine as the causative agent.

3.3.13.D Renal failure

1) Summary

a) Renal failure has been reported in patients. Acute renal failure was described in a 59-year-old male w carbamazepine 200 to 400 milligrams four times daily for 8 weeks for trigeminal neuralgia. Also, a case c hypersensitivity reaction to carbamazepine was described in a 35-year-old woman with late-onset epilep Tegretol(R), 2002b; Nicholls & Yasin, 1972); (Ray- Chaudhuri et al, 1989).

2) Literature Reports

a) A 79-year-old man developed kidney failure within 4 weeks of starting carbamazepine therapy for cor seizures. He first manifested a rash (within 2 weeks), which led to discontinuation of all other medication his carbamazepine dose to 200 milligrams (mg) twice daily. Two weeks later, his rash had worsened anc hospitalized. Carbamazepine was replaced by sodium valproate and he was given topical hydrocortisone rash. Laboratory results showed liver dysfunction, which improved over the next 6 days. However, he wa acute renal failure. Biopsy showed a giant cell granuloma. He became anuric and was treated with hemc steroids. He was discharged 15 days after admission with normal liver function, normal renal function, re rash, and on prednisone 60 mg, which was eventually reduced and withdrawn (Hegarty et al, 2002).

b) Acute renal failure was described in a 59-year-old male who had received carbamazepine 200 to 400 times daily for 8 weeks for trigeminal neuralgia (Nicholls & Yasin, 1972). The patient developed symptom sweating, and passing of dark urine. The eyes and face became swollen, and the patient passed large v urine. BUN was 285 milligrams/100 milliliters and serum creatinine was 6.5 milligrams/100 milliliters. Urir trace of protein and some hyaline casts. The drug was withdrawn and the patient rapidly improved, not r and BUN levels fell to 60 milligrams/100 milliliters in the next 2 weeks and serum electrolytes normalized revealed a non-specific tubular damage. A similar case has been reported (Prod Info Tegretol(R), 2002b 1993).

c) A hypersensitivity reaction to carbamazepine, characterized by generalized erythroderma, a severe le hyponatremia, marked eosinophilia, and renal failure, was described in a 35-year-old woman with late-or receiving carbamazepine therapy for approximately 3 weeks (Ray-Chaudhuri et al, 1989). The patient im withdrawal of carbamazepine and steroid therapy; however, introduction of sodium valproate resulted in new skin rash, leukocytosis, and eosinophilia; valproate was discontinued. The patient was not treated fu anticonvulsants, and seizures did not recur. This appears to be the first report of this type of reaction to c

3.3.13.E Urogenital finding

1) Renal failure, urinary frequency, acute urinary retention, oliguria, azotemia, albuminuria, glycosuria, eleva deposits in the urine, and impotence have been reported in patients receiving carbamazepine. Ejaculatory fai granulomatous necrotizing angitis has also been reported. Infrequent cases of tubulointerstitial nephritis and have occurred.

2) When compared to healthy controls (n=41), valproic acid treated men with generalized epilepsy (n=27) ha volumes (p=0.01). Within the same study however, the testicular volumes of carbamazepine treated men with (n=15) or oxcarbazepine treated men with generalized epilepsy (n=18) did not differ from controls. When furtl valproic acid treated men with abnormal sperm morphology had smaller testicular volumes than control wher volumes of valproic acid treated men with normal sperm were similar to controls (Isojarvi et al, 2004).

3.3.14 Reproductive Effects

Impotence

Semen finding

3.3.14.A Impotence

1) Summary

a) Sexual dysfunction has been reported in patients receiving carbamazepine (Prod Info Tegretol(R), 20

2) Literature Reports

a) A 61-year-old man developed ejaculatory failure and associated loss of sensation of orgasm shortly a taking carbamazepine (Leris et al, 1997). His symptoms returned to normal after discontinuation of carba returned upon rechallenge.

3.3.14.B Semen finding

1) Antiepileptic agents have been associated with changes in sperm morphology and motility. A lower freque morphologically normal sperm was found in carbamazepine treated men with partial epilepsy (n=15), in valpr men with generalized epilepsy and in oxcarbazepine treated men with partial epilepsy (n=18) (p less than 0.0 carbamazepine and valproic acid and p less than 0.05 for oxcarbazepine) compared to healthy controls (n=4 significant decrease in the frequency of motile sperm was also found with all treatment groups combined whe healthy controls (p less than 0.05). Within the various treatment groups, valproic acid treated patients had a s significant decrease in the frequency of motile sperm than in the control group (p less than 0.05). Carbamaze had high frequencies of abnormally low sperm concentration (p less than 0.001) and poorly motile sperm (p l when compared to controls (Isojarvi et al, 2004).

3.3.15 Respiratory Effects

Cryptogenic organizing pneumonia

Pulmonary eosinophilia

Pulmonary hypersensitivity

3.3.15.A Cryptogenic organizing pneumonia

1) A 49-year-old woman developed bronchiolitis obliterans organizing pneumonia (BOOP) secondary to carb induced hypogammaglobulinemia after two years of carbamazepine therapy for epilepsy. The woman presen progressive exertional dyspnea and prolonged productive cough. BOOP was diagnosed via computerize tom and transbronchial biopsy. Laboratory analysis revealed severe hypogammaglobulinemia including immunog milligrams/deciliter (mg/dL), Ig A 20 mg/dL, and Ig M 51 mg/dL. After carbamazepine withdrawal, gammaglob and roentgenogram findings improved (Tamada et al, 2007).

2) A 52-year-old woman developed Bronchiolitis obliterans organizing pneumonia (BOOP) and lupus while ta carbamazepine (Milesi-Lecat et al, 1997). Her symptoms included facial erythema, arthralgia, dyspnea and m rounded masses and nodules. BOOP was diagnosed via pulmonary histologic examination. Antinuclear antib antihistone antibodies were present without antibodies to double-stranded DNA. All symptoms disappeared 1 carbamazepine withdrawal.

3.3.15.B Pulmonary eosinophilia

1) Summary

a) A few cases of pulmonary eosinophilia have been described following carbamazepine therapy (Tolmi Lewis & Rosenbloom, 1982).

2) Literature Reports

a) Pulmonary eosinophilia was described in an 8-year-old girl following carbamazepine (elixir) 300 millig approximately 12 weeks. The patient presented with eczema and wheezing; a chest X-ray revealed colla of the right middle lobe accompanied by a diffuse increase in bronchovascular markings. The absolute e was 11 x 10(9)/liter. valproic acid was substituted for carbamazepine, and the eosinophil count dropped later; the patient recovered in 1 month. Rechallenge with 20 mg of oral carbamazepine elixir resulted in a expiratory flow rate, wheezing, and pruritus (Tolmie et al, 1983).

b) A hypersensitivity reaction to carbamazepine was described in an 8-year-old boy who received carba milligrams orally, twice daily for approximately 5 weeks. The child developed symptoms of both pulmona asthma and fever, rash, lymphadenopathy, and hepatosplenomegaly. Symptoms improved within 3 days carbamazepine (Lewis & Rosenbloom, 1982).

3.3.15.C Pulmonary hypersensitivity

1) Summary

a) Acute pulmonary hypersensitivity was reported in patients receiving carbamazepine (Prod Info Tegret et al, 1994; Tolmie et al, 1983; Lewis & Rosenbloom, 1982; Cullinan & Bower, 1975).

2) Literature Reports

a) A case of acute pulmonary hypersensitivity was reported in a 55-year-old woman receiving carbamaz milligrams (mg) twice daily for trigeminal neuralgia (Cullinan & Bower, 1975). After 5 weeks of drug thera developed symptoms of shortness of breath, cough, and skin rash on the forearms, thighs and trunk. Exa chest disclosed crackling RALES throughout both lungs associated with a white blood cell count of 17,40 millimeter (mm(3)) with 58% eosinophils. Carbamazepine was discontinued and the patient was treated corticosteroids and diphenhydramine 25 mg every 6 hours. Within 1 to 2 weeks, the patient improved an

with a white blood cell count of 8,100 per mm(3) (8% eosinophils). Three months after discharge, the pat and blood studies were normal.

3.3.16 Other

Summary

Angioedema

Desensitization therapy

Drug withdrawal

Toxic shock syndrome

3.3.16.A Summary

1) OTHER EFFECTS

a) Withdrawal of carbamazepine was found to increase the risk of rebound seizures.

3.3.16.B Angioedema

1) Carbamazepine-associated angioedema and maculopapular eruptions occurred in a 27 year-old Indian w history of postpartum psychosis. The patient presented with symptoms of mania and aggressive behavior an carbamazepine 400 milligrams each day after failing to adequately respond to lithium and valproic acid. Carb discontinued on the second day after she developed mild palpebral edema, itching, and discoloration of the s giddiness, syncope, vomiting, and fever. Her palpebral edema became worse on the third day. Her blood cou white blood cells of 13,800 cells/cubic millimeter, with 70% neutrophils, 27% lymphocytes, 3% eosinophils, 0 0% basophils. Her serum chemistry was essentially normal with the exception of serum sodium (133 milliequ A dermatological examination indicated she had angioedema and maculopapular rash. The angioedema resp treatment with pheniramine and oral hydroxyzine hydrchloride, and her skin rash resolved gradually. The autl subsidence of angioedema with carbamazepine cessation and continued use of her other drugs suggests tha did not account or contribute to this adverse reaction (Elias et al, 2006).

3.3.16.C Desensitization therapy

1) Summary

a) The use of desensitization to carbamazepine was described in a 12-year-old epileptic boy with multip allergies (Smith & Newton, 1985).

2) Literature Reports

a) The use of desensitization to carbamazepine was described in a 12-year-old epileptic boy with multip allergies. Desensitization was accomplished by initiating 0.1 milligrams (mg) carbamazepine daily and do every 2 days until the patient had reached a therapeutic dosage of 200 milligrams twice daily (Smith & N

3.3.16.D Drug withdrawal

1) Summary

a) Withdrawal of carbamazepine was found to increase the risk of rebound seizures in patients with refra epilepsies who had incompletely controlled seizures compared to rebound seizure occurrence rates in pa from other antiepileptic drugs (DeToledo et al, 2000).

2) Literature Reports

a) Withdrawal of carbamazepine was found to increase the risk of rebound seizures in patients with refra epilepsies who had incompletely controlled seizures compared to rebound seizure occurrence rates in pa from other antiepileptic drugs (AEDs); patients who had NOT had seizures for several years on carbama seemed not to have a higher risk of recurring seizures than patients who had used other AEDs. The stud seizure occurrence rates in patients with epilepsy who had all AEDs discontinued during an 8-week perio converted to gabapentin monotherapy and observed on gabapentin for 26 weeks (n=275). Seizure rates the first 2 weeks after discontinuation of CBZ, and the state of activation of seizures was found to possib 10 weeks. Patients discontinuing CBZ had more seizures and earlier seizures than patients tapered from VALPROATE. When CBZ was part of combination treatment, the sequence in which CBZ was withdrawn inconsequential (ie, CBZ withdrawn first versus CBZ withdrawn second). No new types of seizures were CBZ withdrawal (DeToledo et al, 2000).

3.3.16.E Toxic shock syndrome

1) Summary

a) A case of pseudo-toxic shock syndrome was attributed to carbamazepine in a 13-year-old girl after 1 for temporal lobe seizures (Burnstein et al, 1983).

2) Literature Reports

a) A case of pseudo-toxic shock syndrome was attributed to carbamazepine in a 13-year-old girl after 1 for temporal lobe seizures (Burnstein et al, 1983). One week prior to admission, the patient experienced malaise, vomiting, anorexia and a facial rash had progressed to the entire body. Diarrhea, elevations in h tests and white blood cells in the urine were observed. S aureus was recovered from the patient's blood Leukopenia was also present. The patient was treated with methicillin IV and became afebrile within 48 h with oral carbamazepine resulted in recurrence of original symptoms including a spiking fever. The mech development of the S aureus bacteremia is unclear. The authors ruled out the possibility of staphylococc

3.4 Teratogenicity/Effects in Pregnancy/Breastfeeding

A) Teratogenicity/Effects in Pregnancy

1) U.S. Food and Drug Administration's Pregnancy Category: Category D (Prod Info TEGRETOL(R)-XR extende tablets, 2007) (All Trimesters)

a) There is positive evidence of human fetal risk, but the benefits from use in pregnant women may be accep risk (e.g., if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs car ineffective).

2) Australian Drug Evaluation Committee's (ADEC) Category: D(Australian Drug Evaluation Committee, 1999)

a) Drugs which have caused, are suspected to have caused, or may be expected to cause an increased inci fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Ac should be consulted for further details.

See Drug Consult reference: PREGNANCY RISK CATEGORIES

3) Crosses Placenta: Yes

4) Clinical Management

a) Retrospective reviews suggest that teratogenic effects are associated with the use of anticonvulsants in c therapy. If therapy is to be continued, monotherapy is preferred for pregnant women (Prod Info TEGRETOL(R release oral tablets, 2007). Carbamazepine can cause fetal harm when administered to a pregnant woman. W childbearing potential should be counseled to weigh the benefits of therapy against the risks. Antiepileptic dru discontinued abruptly in patients taking the drug to prevent major seizures due to the strong possibility of pre epilepticus with the danger of hypoxia and threat to life. Standard prenatal care of childbearing women taking should include currently accepted tests including a fetal echocardiograph during the first trimester to detect p defects (Diav-Citrin et al, 2001).

5) Literature Reports

a) Reports indicate an increased risk of neural-tube defects, cardiovascular defects, and urinary tract defects hypoplasia of the nose, anal atresia, meningomyelocele, ambiguous genitalia, congenital heart disease, hype hypoplasia of the nails, congenital hip dislocation, spina bifida, and inguinal hernia have also been reported (A possible risk of birth defects with the folic acid antagonist, carbamazepine, has been found when used duri trimester of pregnancy (Hernandez-Diaz et al, 2000). A negative relationship between serum folate and serur concentrations has been found, suggesting that folate deficiency may play a role in carbamazepine teratoger 1998).

b) If phenytoin or carbamazepine (or any prodrugs) are used in pregnant women, there is a substantially incr teratogenicity with many combinations of other anticonvulsants. The teratogenicity of these drugs is largely o the levels of the reactive epoxide metabolites (Finnell et al, 1992g; Van Dyke et al, 1991g; Buehler et al, 199 epoxide/parent drug ratio is generally increased when phenytoin or carbamazepine is combined with each otl other drugs that induce cytochrome P450 enzymes (3A4, 2C9, 2C19), or drugs which inhibit epoxide hydrola valproic acid, progabide, and lamotrigine. Such combinations increase the risk of major birth defects 3- to 4-f monotherapy and about 10-fold over background rates.(Spina et al, 1996f; Ramsay et al, 1990g; Bianchetti e

c) In a large retrospective cohort study (n=1411), an increased risk of major congenital abnormalities was ob offspring of women treated with carbamazepine (relative risk (RR) 2.6) or valproate (RR 4.1) monotherapy du trimester of pregnancy. Risk was unaffected by the type of seizure disorder, but in the case of valproate and was dependent upon the dose used. The risk for phenobarbital was significantly increased when other antiep or caffeine were added (RR 2.5) or when all were combined (RR 5.1). Significant associations were observed tube defects and valproate alone (RR 4.0, p=0.03) and when combined with other antiepileptic medications (I specifically with carbamazepine (RR 8.1, p=0.01). In addition, the risk of hypospadia was higher with valproat p=0.05) or combined with other antiepileptic drugs (RR 4.8, p=0.03) (Samren et al, 1999).

d) The results of a prospective study involving 210 pregnant women suggest that carbamazepine treatment the risk of major congenital abnormalities when used in the first trimester of pregnancy. The data was gathere Teratogen Information Service between January 1989 and March 1999. The 210 carbamazepine-exposed pr compared with 629 controls. Sixty-eight percent of the women in the carbamazepine group were treated throu The relative risk (RR) of major congenital anomalies was 2.24 for women in the carbamazepine group (p= 0.0 birth weights were also noted (mean 3046 grams versus 3277 grams; p= 0.000). The prevalence of congenita was 2.9% in the treatment group, compared with 0.7% in the control group. As a result, the investigators recc echocardiography in women treated with carbamazepine in the first trimester (Diav-Citrin et al, 2001).

e) A case of radial microbrain form of microencephaly in a 35-week-old premature infant exposed to carbam was reported. The mother had a history of seizures for which she was receiving carbamazepine 600 mg/day pregnancy. The last carbamazepine level, measured 18 months prior to delivery, was within the therapeutic r mcg/mL). No other levels were obtained and no seizures were recorded during the pregnancy. At birth, facial were observed in the infant. An echocardiogram showed normal cardiac structure, but reduced contractility. C revealed a grossly undersized but histologically normal brain. Due to an extremely poor prognosis, life suppo The absence of trauma, infection, or vascular disease suggests that the disorder was related to impaired neu

Although causality cannot be definitively determined, the occurrence of multiple birth defects associated with raises the possibility that carbamazepine exposure may have contributed to the pathogenesis in this infant (H 1999).

f) A pregnant, 44-year-old woman ingested 24 carbamazepine 200 mg tablets and developed mild clinical to 28.5 mcg/mL). Last menstrual period, pelvic exam and sonography indicated she was 3 to 4 weeks postconc of ingestion, which correlated with the time period of the neural tube closure. Maternal alpha-fetoprotein level 16 weeks gestation and sonography at 20 weeks suggested spina bifida. The pregnancy was electively termi showed a fetus with a large open myeloschisis from T 11 to L 5 and a hypoplastic left cerebral hemisphere (L

B) Breastfeeding

1) American Academy of Pediatrics Rating: Maternal medication usually compatible with breastfeeding. (Anon, 2(

2) World Health Organization Rating: Compatible with breastfeeding. Monitor infant for side effects. (Anon, 2002)

3) Thomson Lactation Rating: Infant risk cannot be ruled out.

a) Available evidence and/or expert consensus is inconclusive or is inadequate for determining infant risk wh breastfeeding. Weigh the potential benefits of drug treatment against potential risks before prescribing this dr breastfeeding.

4) Clinical Management

a) The World Health Organization considers carbamazepine compatible with breast-feeding, but recommenc infant for jaundice, drowsiness, poor suckling, vomiting, and poor weight gain (Anon, 2002). Carbamazepine for use during the breast-feeding period (Froescher et al, 1984).

5) Literature Reports

a) Carbamazepine and the epoxide metabolite transfers to breast milk. The concentration ratio of breast milk plasma is nearly 0.4 for carbamazepine and 0.5 for the epoxide. Estimated doses transferred to the newborn feeding range from 2 to 5 mg/day for carbamazepine and 1 to 2 mg/day for the epoxide. Due to the potential adverse reactions in nursing infants from carbamazepine, a decision should be made regarding discontinuing discontinuing the medication, taking into account the importance for the use of the medication for the mother TEGRETOL(R)-XR extended-release oral tablets, 2007).

b) A lower milk:maternal plasma ratio was reported in women treated with multiple, unspecified anticonvulsa 1979). Carbamazepine levels in milk were equal to 39.4% of maternal serum concentration (milk equal to 1.9 equal to 4.3 mcg/mL; n= 3). These amounts were considered pharmacologically insignificant. No adverse effe the nursing infants in any of these reports (Kaneko et al, 1979; Niebyl et al, 1979; Pynnonen et al, 1977; Pynı 1975); however, such effects were not systematically sought.

c) In four women treated with carbamazepine and phenytoin the approximate milk to serum ratio of carbama (Wilson et al, 1980; Pynnonen et al, 1977; Pynnonen & Sillanpaa, 1975). The metabolite 10,11-epoxy carban measured. Milk levels of the epoxide were approximately equal to serum levels, but the epoxide was not dete nursing infants' serum for undetermined reasons. Maternal plasma concentrations assayed at 0.5 to 3.2 mcg/ lower than the therapeutic range of 6 to 8 mcg/mL (Gilman et al, 1980).

d) One case of cholestatic hepatitis in a breast-fed infant has been reported in association with maternal use carbamazepine. Symptoms resolved following cessation of breast-feeding (Anon, 2001; Frey et al, 1990; Cha nursing infant is expected to ingest between 2% to 7.2% of the lowest weight-adjusted therapeutic dose (Iqba another report, breast-fed newborns developed serum carbamazepine levels between 15% to 65% of matern Perel, 1998) Breast milk concentrations are reported to be approximately 24% to 69% of that found in matern usual infant serum levels of 0.4 mcg/mL (Pynnonen et al, 1977).

6) Drug Levels in Breastmilk

a) Parent Drug

1) Milk to Maternal Plasma Ratio

a) 0.24-0.69 (Kok et al, 1982; Nau et al, 1982; Neibly et al, 1979; Pynnonen & Sillanpaa, 1975; Pyn

3.5 Drug Interactions

Drug-Drug Combinations

Drug-Food Combinations

Drug-Lab Modifications

3.5.1 Drug-Drug Combinations

Acetaminophen

Acetylcysteine

Activated Charcoal

Adenosine

Alprazolam

Amitriptyline

Amoxapine

Amprenavir

Anisindione

Aprepitant

Aripiprazole

Armodafinil

Atracurium

Azithromycin

Betamethasone

Bortezomib

Bromperidol

Buprenorphine

Bupropion

Caspofungin

Cimetidine

Cisatracurium

Cisplatin

Clarithromycin

Clobazam

Clomipramine

Clonazepam

Clorgyline

Clozapine

Cortisone

Cyclosporine

Dalfopristin

Danazol

Darunavir

Dasatinib

Dehydroepiandrosterone

Delavirdine

Desipramine

Dexamethasone

Dicumarol

Diltiazem

Dothiepin

Doxacurium

Doxepin

Doxorubicin Hydrochloride

Doxorubicin Hydrochloride Liposome

Doxycycline

Efavirenz

Ergocalciferol

Erlotinib

Erythromycin

Estazolam

Ethinyl Estradiol

Ethosuximide

Etonogestrel

Etravirine

Etretinate

Evening Primrose

Everolimus

Felbamate

Felodipine

Fentanyl

Fluconazole

Flunarizine

Fluoxetine

Fluvoxamine

Fosamprenavir

Fosaprepitant

Fosphenytoin

Ginkgo

Haloperidol

Hydrochlorothiazide

Hydrocortisone

Imatinib

Imipramine

Indinavir

Influenza Virus Vaccine

Iproniazid

Irinotecan

Isocarboxazid

Isoniazid

Itraconazole

Ixabepilone

Ketoconazole

Lamotrigine

Lapatinib

Levetiracetam

Levonorgestrel

Levothyroxine

Lithium

L-Methylfolate

Lopinavir

Loxapine

Maraviroc

Mebendazole

Mefloquine

Mestranol

Methadone

Methylphenidate

Methylprednisolone

Metronidazole

Mianserin

Midazolam

Mifepristone

Milnacipran

Miokamycin

Moclobemide

Modafinil

Nafimidone

Nefazodone

Nelfinavir

Nevirapine

Niacinamide

Nialamide

Nifedipine

Nilotinib

Nimodipine

Norelgestromin

Norethindrone

Norgestrel

Nortriptyline

Olanzapine

Omeprazole

Oxcarbazepine

Paliperidone

Pancuronium

Pargyline

Pentobarbital

Phenelzine

Phenobarbital

Phenprocoumon

Phenytoin

Pipecuronium

Praziquantel

Prednisolone

Prednisone

Primidone

Procarbazine

Propoxyphene

Protriptyline

Psyllium

Quetiapine

Quinupristin

Ranolazine

Rapacuronium

Remacemide

Repaglinide

Rifampin

Rifapentine

Risperidone

Ritonavir

Rocuronium

Rufinamide

Sabeluzole

Saquinavir

Selegiline

Sertraline

Simvastatin

Sirolimus

Sorafenib

St John's Wort

Sunitinib

Tacrolimus

Tadalafil

Telithromycin

Temsirolimus

Terfenadine

Theophylline

Tiagabine

Ticlopidine

Tipranavir

Toloxatone

Topiramate

Tramadol

Tranylcypromine

Trazodone

Trimipramine

Troleandomycin

Valnoctamide

Valproic Acid

Vecuronium

Verapamil

Vigabatrin

Viloxazine

Voriconazole

Warfarin

Yohimbine

Zaleplon

Ziprasidone

Zotepine

3.5.1.A Acetaminophen

1) Interaction Effect: an increased risk of acetaminophen hepatotoxicity

2) Summary: The hepatotoxicity of acetaminophen may be related to the formation of toxic metabolites in the carbamazepine, an enzyme inducer, is given concurrently with high and frequent doses of acetaminophen, th metabolism of acetaminophen may result in an increased level of hepatotoxic metabolites. In support of this t observed that patients who receive enzyme-inducing agents do not recover as well from an acetaminophen o patients who are not taking enzyme-inducing drugs. The significance of this interaction at therapeutic doses o administered intermittently appears low. In addition, acetaminophen has been shown to have lower bioavailal patients receiving enzyme-inducing agents (Perucca & Richens, 1979).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: At usual therapeutic oral doses of acetaminophen and carbamazepine, no special r required.

7) Probable Mechanism: increased metabolism of acetaminophen resulting in abnormally high levels of hepa metabolites

8) Literature Reports

a) A 17-year-old female with a history of anorexia nervosa and who was receiving carbamazepine 300 r stabilization ingested acetaminophen 7800 mg in a suicide attempt. Upon admission to the hospital, her were significantly elevated and her serum acetaminophen level was 15 mcg/mL. Treatment with acetylcy initiated and her acetaminophen level decreased in the expected manner. However, eight days later, she

transplant because of fulminant hepatic failure that was believed to be due to a combination of low body malnutrition, and carbamazepine therapy. A small portion of acetaminophen is metabolized by the cytoch system to toxic metabolites which are then detoxified by glutathione. Carbamazepine is known to induce P450 system, and her malnutrition status depleted her glutathione concentrations. These two factors res concentration of acetaminophen toxic metabolites, resulting in liver failure (Young & Mazure, 1998).

3.5.1.B Acetylcysteine

1) Interaction Effect: subtherapeutic carbamazepine levels
2) Summary: One woman experienced decreased carbamazepine trough levels three days after starting N-a therapy, which led to three consecutive tonic-clonic seizures. It was proposed that high doses of N-acetylcyst the clearance of carbamazepine and its metabolites to inactive derivatives, leaving the patient at an increase activity (Simonart et al, 1998a). Closely monitor carbamazepine levels in patients also receiving N-acetylcyste
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Use caution when prescribing N-acetylcysteine to patients who take carbamazepine of N-acetylcysteine and carbamazepine may cause decreased carbamazepine plasma concentrations resulti risk of seizures. Closely monitor carbamazepine levels in patients also receiving N-acetylcysteine.
7) Probable Mechanism: increased clearance of carbamazepine
8) Literature Reports
a) A 59-year-old female being treated for two years with carbamazepine 800 mg daily had serum trough mcg/mL. Lamotrigine was added to her therapeutic regimen to allow a slow withdrawal of carbamazepine lamotrigine increased to 75 mg daily, the patient developed fever, lymphadenopathy, conjunctivitis, and r eruptions on the face and upper torso. Carbamazepine trough level at this time was 11.1 mcg/mL. The p diagnosed with lamotrigine-induced hypersensitivity, and N-acetylcysteine 2 g every six hours was initiat clinical improvement. However, on the third day of N-acetylcysteine therapy, the patient had three tonic-c within five hours. Although her carbamazepine dose had not changed, the trough level was 8.1 mcg/mL. that the high doses of N-acetylcysteine increased the clearance of carbamazepine and its metabolites to derivatives, leaving the patient at an increased risk for seizure activity (Simonart et al, 1998).

3.5.1.C Activated Charcoal

1) Interaction Effect: decreased carbamazepine exposure
2) Summary: In a cross-over study involving six healthy volunteers, activated charcoal 8 g administered imm carbamazepine 400 mg resulted in a decrease in the carbamazepine absorption by 90%. Maximum concentr decreased from 2.7 mg/L to 0.28 mg/L, and the area under the concentration-time curve (AUC) of carbamaze mg/L/h to 11 mg/L/h (Neuvonen et al, 1988). This drug interaction may make activated charcoal useful in cas carbamazepine overdose, but should be kept in mind when using activated charcoal in therapy concurrently v carbamazepine.
3) Severity: moderate
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Since activated charcoal binds carbamazepine in the gastrointestinal tract, administ two hours before or four to six hours after activated charcoal. If this is not possible, separate administration ti possible. During concurrent therapy, monitor carbamazepine serum levels closely and observe the patient for response to carbamazepine.
7) Probable Mechanism: reduced carbamazepine absorption

3.5.1.D Adenosine

1) Interaction Effect: a higher degree of heart block
2) Summary: Carbamazepine has been reported to increase the degree of heart block that may be produced Adenosine exerts its effect by decreasing conduction through the AV node, and may cause a short-lasting firs third-degree block. Therefore, higher degrees of heart block induced by adenosine may occur in the presence carbamazepine (Prod Info Adenocard(R), 2002).
3) Severity: major
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: If possible, carbamazepine should be withheld for at least five half-lives (approxima prior to the use of adenosine.
7) Probable Mechanism: additive effects

3.5.1.E Alprazolam

1) Interaction Effect: decreased alprazolam effectiveness
2) Summary: The addition of carbamazepine 600 mg daily to a patient stabilized on alprazolam resulted in a decrease in alprazolam concentration (43 ng/mL vs 20 ng/mL) (Arana et al, 1988a).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor for signs of benzodiazepine clinical effectiveness. Concurrent use of carbar

alprazolam may require higher doses of alprazolam. The dose of alprazolam should be decreased if carbama discontinued.
7) Probable Mechanism: increased hepatic metabolism
8) Literature Reports
a) Combined therapy with alprazolam and carbamazepine was reported to result in significant reduction plasma levels, corresponding with clinical deterioration, in a 32-year-old male with atypical bipolar disord attacks (Arana et al, 1988). The patient was receiving oral lithium carbonate 1200 mg daily with oral alpr daily prior to the initiation of carbamazepine. Carbamazepine 300 to 600 mg daily orally was used to con impulsivity and psychosis; the lithium was discontinued. It is speculated that carbamazepine reduced alp levels by induction of hepatic microsomal enzymes. More studies are required to evaluate this interactior mechanisms.

3.5.1.F Amitriptyline
1) Interaction Effect: decreased amitriptyline effectiveness
2) Summary: The concomitant use of carbamazepine and antidepressants has been reported to decrease ar levels (Leinonen et al, 1991h; Brown et al, 1988b).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor for clinical efficacy of the amitriptyline therapy and for any signs of toxicity c Serum levels of both agents should be considered when either agent is added or discontinued, with appropria adjustments made accordingly.
7) Probable Mechanism: increased amitriptyline metabolism
8) Literature Reports
a) A study examined the effect of carbamazepine on amitriptyline levels in 8 psychiatric inpatients treate amitriptyline dosage of 137.5 mg daily. All patients were treated for a minimum of 7 days prior to measur antidepressant concentrations. Carbamazepine was added in a mean dose of 593 mg continued over a patients receiving combination therapy, serum amitriptyline and nortriptyline concentrations were signific and 40% respectively) than in patients receiving amitriptyline alone, although the ratio of amitriptyline to remained relatively unchanged (Leinonen et al, 1991g).

3.5.1.G Amoxapine
1) Interaction Effect: decreased amoxapine concentration
2) Summary: The concomitant use of carbamazepine and antidepressants has been reported to decrease ar levels (Leinonen et al, 1991e; Brown et al, 1990c). Although not reported for amoxapine, a similar interaction
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor for clinical efficacy of the amoxapine therapy and for any signs of toxicity of Serum levels of both agents should be considered when either agent is added or discontinued, with appropria adjustments made accordingly.
7) Probable Mechanism: increased amoxapine metabolism
8) Literature Reports
a) Concomitant administration of imipramine and carbamazepine to children with attention deficit disorde reported to result in a 50% decrease in the total plasma concentration of imipramine plus desipramine (E Carbamazepine probably enhances the hepatic microsomal metabolism of imipramine and other tricyclic by inducing hepatic enzymes (Moody et al, 1977a). Although not reported specifically for amoxapine, be potential for a similar interaction exists. Patients on chronic Carbamazepine therapy may require increas tricyclic antidepressants.

3.5.1.H Amprenavir
1) Interaction Effect: reduced amprenavir efficacy due to reduced amprenavir serum concentrations
2) Summary: Coadministration of carbamazepine and amprenavir may result in reduced amprenavir serum c Dose adjustments of amprenavir may be necessary to maintain antiviral efficacy of amprenavir (Prod Info Ag
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Clinicians may want to consider using alternative medication to carbamazepine in p amprenavir therapy. However, if it becomes necessary to give these agents concurrently, upward adjustment dosing may be needed to maintain antiviral effectiveness.
7) Probable Mechanism: induction of cytochrome P450 3A4-mediated amprenavir metabolism

3.5.1.I Anisindione
1) Interaction Effect: decreased anticoagulant effectiveness
2) Summary: Concomitant carbamazepine and warfarin therapy has been reported to result in a decreased a effect, secondary to the induction of hepatic metabolism of the anticoagulant (Massey, 1983a; Cohen & Arms Koch-Weser & Koch-Weser, 1975a; Kendall & Boivin, 1981a; Hansen et al, 1971b). A similar effect may occu
3) Severity: moderate

4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: In patients receiving oral anticoagulant therapy, the prothrombin time ratio or INR (i normalized ratio) should be closely monitored with the addition and withdrawal of treatment with carbamazep reassessed periodically during concurrent therapy. Adjustments of the anisindione dose may be necessary in the desired level of anticoagulation.
7) Probable Mechanism: increased anisindione metabolism

3.5.1.J Aprepitant

1) Interaction Effect: reduced plasma aprepitant concentrations and decreased aprepitant efficacy
2) Summary: Coadministration of aprepitant with drugs that strongly induce cytochrome P450 3A4 activity, s carbamazepine, may result in reduced plasma concentrations of aprepitant and decreased efficacy of aprepit EMEND(R) oral capsules, 2008).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Concomitant administration of aprepitant and carbamazepine may result in reducec concentrations of aprepitant and may decrease the efficacy of aprepitant (Prod Info EMEND(R) oral capsules
7) Probable Mechanism: induction of cytochrome P450 3A4-mediated metabolism of aprepitant by carbamaz

3.5.1.K Aripiprazole

1) Interaction Effect: decreased aripiprazole concentrations
2) Summary: Coadministration of carbamazepine 200 milligrams (mg) twice daily with aripiprazole 30 mg on the maximum concentration (Cmax) and the area under the concentration-time curve (AUC) values of both a active metabolite, dehydro-aripiprazole, by approximately 70%. Aripiprazole is partly metabolized by cytochro (CYP3A4) enzymes. Coadministration with carbamazepine, a potent CYP3A4 inducer, could increase aripipr causing decreased blood concentrations. The dose of aripiprazole should be doubled when it is administered carbamazepine. If therapy with carbamazepine is discontinued, the dose of aripiprazole should then be decre ABILIFY(R) oral tablets, oral solution, 2005).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Coadministration of aripiprazole and carbamazepine has resulted in decreased arip concentrations. The dose of aripiprazole should be doubled when it is administered concurrently with carbam with carbamazepine is discontinued, the dose of aripiprazole should then be decreased.
7) Probable Mechanism: induction of CYP3A4-mediated aripiprazole metabolism

3.5.1.L Armodafinil

1) Interaction Effect: decreased armodafinil exposure or plasma levels
2) Summary: Armodafinil is partially metabolized by the CYP3A enzyme system. Use caution with the coadm armodafinil with other drugs that are potent inducers of CYP3A4, such as carbamazepine, as this could resul exposure or plasma levels of armodafinil (Prod Info NUVIGIL(TM) oral tablets, 2007). Also, monitor patient's armodafinil if these 2 agents are used concurrently.
3) Severity: minor
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Use caution with the coadministration of armodafinil and carbamazepine as this ma decreased armodafinil exposure or levels (Prod Info NUVIGIL(TM) oral tablets, 2007). Monitor patient respon these 2 agents are used concurrently.
7) Probable Mechanism: induction of CYP3A-mediated armodafinil metabolism

3.5.1.M Atracurium

1) Interaction Effect: decreased atracurium duration of action
2) Summary: The effects of carbamazepine on the neuromuscular blocking effects of atracurium have been well-controlled studies. The effect of atracurium was significantly shortened in patients taking carbamazepine phenytoin or valproic acid, compared to patients not taking anticonvulsants (Tempelhoff et al, 1990a). Other reported that carbamazepine had no effect on the onset time or duration of atracurium (Spacek et al, 1997a).
3) Severity: moderate
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Monitor patients for an appropriate clinical response to the neuromuscular blocker. intervals or higher doses of atracurium may be needed in patients receiving carbamazepine.
7) Probable Mechanism: increased atracurium metabolism
8) Literature Reports
a) Researchers studied the effect of carbamazepine on the onset and duration of neuromuscular blocka atracurium. Three groups of patients were studied; 21 nonepileptic patients, 14 epileptic patients treated carbamazepine alone, and 18 epileptic patients receiving carbamazepine and either phenytoin or valproi receiving carbamazepine had been maintained for many years. All patients were treated with atracurium

intravenously following standard induction of anesthesia. The time to onset of neuromuscular blockade w different for the three groups of patients. However, time to recovery of baseline and train-of-four respons shorter for the two groups receiving carbamazepine (Tempelhoff et al, 1990).

b) Carbamazepine had no effect on the neuromuscular blockade induced by atracurium in one study. Af induction of anesthesia, 0.5 mg/kg of atracurium was administered in two groups of patients, with eight p carbamazepine and ten patients not receiving carbamazepine. The average duration of carbamazepine t weeks. There was no significant difference between the two groups in lag time, onset time, or time to rec neuromuscular blockade induced by atracurium (Spacek et al, 1997).

3.5.1.N Azithromycin

1) Interaction Effect: increased serum carbamazepine levels

2) Summary: Although some macrolide antibiotics interfere with hepatic metabolism of carbamazepine, azith the semisynthetic macrolides that does not inactivate cytochrome P450, and, therefore, does not interact with (Periti et al, 1992a; Hopkins, 1991a). It is suggested, however, that elevations of serum carbamazepine level the concomitant use of azithromycin, and that careful monitoring of patients is advised by the manufacturer (P Zithromax(R), 2001).

3) Severity: minor

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Until further data are available regarding drug interactions with azithromycin and ca careful monitoring of patients is advised.

7) Probable Mechanism: unknown

8) Literature Reports

a) Although quite variable in their ability to produce enzyme inhibition, the macrolide antibiotics have be significant drug interactions. They can be classified into three groups: 1) erythromycins and troleandomy nitrosoalkanes leading to inactive cytochrome P450- metabolite complexes, 2) clarithromycin, flurithromy midecamycin, miocamycin, and roxithromycin form complexes to a smaller degree and seldom cause dr and 3) azithromycin, dirithromycin, rokitamycin, and spiramycin do not affect cytochrome P450 and, ther produce drug interactions (Periti et al, 1992).

b) In a toleration and safety profile of azithromycin assessing 3995 patients, no pharmacokinetic interac observed with carbamazepine, cimetidine, methylprednisolone, theophylline, or warfarin (Hopkins, 1991)

3.5.1.O Betamethasone

1) Interaction Effect: decreased betamethasone effectiveness

2) Summary: Carbamazepine has been demonstrated to increase the metabolism of corticosteroids (Olivesi, al, 1982b). Although not specifically reported for betamethasone, a similar interaction could be expected.

3) Severity: moderate

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: Monitor therapeutic efficacy of betamethasone. An increase in the steroid dosage m after three to five days of concurrent carbamazepine therapy.

7) Probable Mechanism: increased betamethasone metabolism

3.5.1.P Bortezomib

1) Interaction Effect: reduced efficacy of bortezomib

2) Summary: Carbamazepine may induce the metabolism of bortezomib. Monitor patients closely for reduce CYP3A4 inducers (ie, carbamazepine) are coadministered with bortezomib (Prod Info VELCADE(R) injection

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concomitant use of bortezomib and CYP3A4 inducers (ie, carbamazepine) may bortezomib efficacy. Monitor patients if bortezomib and carbamazepine are coadministered (Prod Info VELCA 2008).

7) Probable Mechanism: induction of CYP3A4-mediated bortezomib metabolism by carbamazepine

3.5.1.Q Bromperidol

1) Interaction Effect: decreased bromperidol efficacy

2) Summary: Concurrent administration of carbamazepine and bromperidol may decrease plasma concentra bromperidol and its reduced metabolite by inducing their metabolism. However, when carbamazepine and br coadministered in schizophrenic patients, clinical improvement was seen. This indicates that these two agent some pharmacodynamic synergism (Otani et al, 1997a).

3) Severity: minor

4) Onset: delayed

5) Substantiation: established

6) Clinical Management: Monitor patients for bromperidol efficacy. When given concomitantly with carbamaz bromperidol may need to be increased.

7) Probable Mechanism: induction of bromperidol metabolism by carbamazepine

8) Literature Reports

a) In one study, 13 schizophrenic patients were given bromperidol 12 mg to 24 mg daily for 1 to 20 weel addition of carbamazepine 400 mg daily for 4 weeks. Carbamazepine reduced plasma concentrations of and reduced bromperidol by 37% and 23%, respectively, at four weeks. It appeared that the induction by was fastest during the first week of cotherapy, but maximal effects were seen at four weeks. The authors cytochrome P450 3A4 isoenzymes may be involved in this process, since carbamazepine is known to in CYP 3A4. Although carbamazepine and bromperidol coadministration resulted in decreased plasma con bromperidol, the Clinical Global Impression scores were decreased significantly, indicating that some ph synergism exists between carbamazepine and bromperidol which results in clinical improvement (Otani e

3.5.1.R Buprenorphine

1) Interaction Effect: decreased buprenorphine plasma concentrations
2) Summary: Buprenorphine is primarily metabolized by the CYP3A4 isoenzyme system. Coadministration o inducer, such as carbamazepine, may result in increased clearance and reduced plasma concentrations of b concomitant use of buprenorphine and carbamazepine is warranted, dosage adjustment may be necessary (buprenorphine hcl injection, 2004) along with increased monitoring for buprenorphine withdrawal signs and s et al, 2003).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Use caution when prescribing buprenorphine to patients who take carbamazepine. of buprenorphine and carbamazepine may cause reduced buprenorphine plasma concentrations. If concurre dosage adjustments should be considered (Prod Info buprenorphine hcl injection, 2004). Increased monitorin signs and symptoms is also recommended when buprenorphine is coadministered with carbamazepine (Brid
7) Probable Mechanism: induction of CYP3A4-mediated buprenorphine metabolism by carbamazepine

3.5.1.S Bupropion

1) Interaction Effect: decreased bupropion effectiveness
2) Summary: Since bupropion is extensively metabolized by the cytochrome P450 enzyme system, the coad bupropion with other drugs that are inducers of the CYP450 system may affect its clinical activity. Carbamaze the metabolism of bupropion, resulting in decreased efficacy of bupropion (Prod Info Wellbutrin XL(TM), 2003
3) Severity: minor
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Care should be taken when administering bupropion with carbamazepine. Monitor t bupropion efficacy.
7) Probable Mechanism: induction of bupropion metabolism by carbamazepine

3.5.1.T Caspofungin

1) Interaction Effect: reduced caspofungin plasma levels
2) Summary: Enhanced clearance of caspofungin may occur during concomitant therapy with carbamazepin drug clearance. Patients may require an increase in dose to 70 mg caspofungin daily (Prod Info CANCIDAS(2008).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When caspofungin is coadministered with inducers of drug clearance, such as carb consider using a daily dose of 70 mg of caspofungin (Prod Info CANCIDAS(R) IV infusion, 2008).
7) Probable Mechanism: enzyme induction by carbamazepine
8) Literature Reports

a) Combined use of carbamazepine and caspofungin, an inducer of drug clearance, may result in a sign caspofungin plasma levels. This is based on regression analyses of pharmacokinetic data. It is not know clearance mechanism involved in caspofungin disposition may be inducible (Prod Info CANCIDAS(R) IV

3.5.1.U Cimetidine

1) Interaction Effect: carbamazepine toxicity (ataxia, nystagmus, diplopia, headache, vomiting, apnea, seizur
2) Summary: The effects of cimetidine on carbamazepine plasma concentration may be temporary. Possible limitation of carbamazepine auto-induction may occur (Macphee et al, 1984; Dalton et al, 1985a; Dalton et al, 1985a).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Consider obtaining plasma carbamazepine levels two to four days after starting or c cimetidine. Usual therapeutic levels are 6 mg/L to 12 mg/L; however, the relationship between plasma levels variable. Patients should also be cautioned that transient signs of carbamazepine toxicity may occur during th cimetidine therapy. An alternative H-2 blocker that has not been reported to cause this interaction, such as ra famotidine, might be considered.
7) Probable Mechanism: decreased carbamazepine metabolism
8) Literature Reports

a) In a single dose study, cimetidine pretreatment increased the carbamazepine area under the curve by elimination half-life by 18% (Dalton et al, 1985). It is possible that this is due to decreased metabolism se inhibition of hepatic microsomal enzymes by cimetidine (Telerman-Toppet et al, 1981); however, others l significant alterations in steady-state plasma concentrations of carbamazepine or its metabolite with con administration of cimetidine (Sonne et al, 1983; Levine et al, 1985).
b) Cimetidine 400 mg three times daily significantly increased steady-state carbamazepine plasma level days. However, carbamazepine levels decreased to pretreatment levels by the seventh day of cimetidine Carbamazepine side effects appeared in most patients within 24 hours following cimetidine initiation, but next 48 to 72 hours. The investigators concluded that dosage adjustments appear unnecessary, but that warned of the appearance of carbamazepine side effects for the first 3 to 5 days after beginning cimetidi 1986).
c) A case of carbamazepine toxicity was reported in an elderly man receiving carbamazepine 200 mg th isoniazid 300 mg daily, and cimetidine 400 mg twice daily. Two days after initiating this drug combinatior developed nausea, vomiting, dizziness, and epigastric pain. Carbamazepine serum concentrations were receiving this combination of therapy should have close monitoring of carbamazepine concentrations (Ga

3.5.1.V Cisatracurium

1) Interaction Effect: resistance to neuromuscular blocking action
2) Summary: Some medications, including carbamazepine, may enhance resistance to the neuromuscular b nondepolarizing agents such as cisatracurium (Prod Info Nimbex(R), 1999). Dose adjustments of cisatracuriu when these agents are being used concurrently.
3) Severity: minor
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The dose of cisatracurium may need to be adjusted upward in patients receiving co carbamazepine.
7) Probable Mechanism: unknown

3.5.1.W Cisplatin

1) Interaction Effect: decreased carbamazepine plasma concentrations
2) Summary: A 36-year old epileptic female undergoing antineoplastic therapy with doxorubicin and cisplatin subtherapeutic carbamazepine and valproic acid concentrations which resulted in tonic-clonic seizures. Altho mechanism is unknown, possible causes include decreased absorption or accelerated elimination of carbama Voogd-van der Straaten, 1988c).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Anticonvulsant levels should be closely monitored in patients receiving antineoplast doxorubicin or cisplatin. Doses of carbamazepine may need to be increased.
7) Probable Mechanism: decreased absorption or accelerated elimination of carbamazepine
8) Literature Reports
a) A 36-year old female epileptic patient requiring cisplatin and doxorubicin therapy for papillary adenoc experienced tonic-clonic seizures after two days of antineoplastic treatment. Plasma concentrations of ca valproic acid, and phenytoin were all determined to be subtherapeutic (0.5 mg/L, 24.3 mg/L, and 0.3 mg/ One month later, she was controlled on phenytoin 450 mg daily, carbamazepine 1200 mg daily, and valp daily. During her second course of cisplatin and doxorubicin, she again suffered a tonic-clonic seizure. P concentrations of her anticonvulsants were phenytoin 0.2 mg/L, carbamazepine 3.5 mg/L, and valproic a Three days following her chemotherapy, plasma concentrations of the anticonvulsants had returned to th values. During her sixth and final chemotherapy course, carbamazepine levels remained low (1.4 mg/L) all 15 days of the course (Neef & de Voogd-van der Straaten, 1988b).

3.5.1.X Clarithromycin

1) Interaction Effect: an increased risk of carbamazepine toxicity (ataxia, nystagmus, diplopia, headache, vo seizures, coma)
2) Summary: Clarithromycin has been reported to elevate the serum levels of carbamazepine (Prod Info Biax resulting in the clinical symptoms of lethargy, fatigue, blurred vision, nausea, confusion, and ataxia (Tatum & Albani et al, 1993a).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Decreasing the carbamazepine dose by approximately 25% is advised at the initiati clarithromycin therapy with further modification according to clinical symptoms and serum carbamazepine tro concentrations. Consider monitoring carbamazepine plasma levels.
7) Probable Mechanism: decreased carbamazepine metabolism
8) Literature Reports
a) Carbamazepine toxicity with an increase in serum level associated with the addition of clarithromycin 35-year-old female diagnosed with complex partial seizures (Tatum & Gonzalez, 1994). She was mainta carbamazepine 200 mg three times daily with an approximate steady-state level of 8.3 mcg/mL. With dev

upper respiratory infection, clarithromycin 500 mg two times daily was initiated. Symptoms of lethargy, fa vision, nausea, "muddled thoughts", and ataxia occurred within a few hours of the first dose. A carbamaz of 15.5 mcg/mL was obtained 26 hours after the first clarithromycin dose. The symptoms of toxicity resol level returned to baseline within 36 hours of discontinuing carbamazepine and clarithromycin.

b) A 29 year-old male was diagnosed with simple partial seizures since the age of 11 years and was ma carbamazepine 400 mg two times daily with an approximate steady-state level of 8 mcg/mL (Albani et al addition of clarithromycin increased the serum level to 12.7 mcg/mL, measured at the end of the clarithro despite decreasing carbamazepine (300 mg two times daily); yet, he did not notice any adverse symptor elevated serum level. Upon completion of the therapy, he was placed on the previous carbamazepine do the level returned to baseline.

c) Clarithromycin 500 mg was given concurrently with either oral carbamazepine 400 mg or placebo twi healthy volunteers in a randomized, double-blind study. The mean area under the concentration-time cu carbamazepine was increased and the formation of the 10,11-epoxide metabolite was significantly reduc significant change in carbamazepine pharmacokinetics (Sturgill & Rapp, 1992). Whether this would lead significant effect is unknown.

d) Macrolide antibiotics have been implicated in severe drug interactions, but there are differences amo not all are responsible for drug interactions. They can be classified into 3 groups: 1) erythromycins and t form nitrosoalkanes leading to inactive cytochrome P450-metabolite complexes, 2) clarithromycin, flurith josamycin, midecamycin, miocamycin, and roxithromycin form complexes to a smaller degree and are le drug interactions, and 3) azithromycin, dirithromycin, rokitamycin, and spiramycin do not affect cytochron therefore, would not be expected to interfere with drugs metabolized by this enzyme system (Periti et al,

3.5.1.Y Clobazam

1) Interaction Effect: decreased carbamazepine parent drug and/or increased active metabolite concentratio

2) Summary: Studies that investigated the effect of clobazam on carbamazepine have shown variable effects and active metabolite concentrations, including increases in carbamazepine levels (Franceschi et al, 1983), c et al, 1986a), and no significant change (Sennoune et al, 1992; Munoz et al, 1990a). Carbamazepine effects been shown to include decreased plasma levels and area under the concentration-time curve (AUC) of cloba levels and AUC of norclobazam (the active metabolite) (Bun et al, 1990; Jawad et al, 1984; Levy et al, 1983; 1992).

3) Severity: minor

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Monitor carbamazepine serum concentrations and seizure control.

7) Probable Mechanism: increased hepatic metabolism

8) Literature Reports

a) Concomitant administration of clobazam and carbamazepine has been reported to result in a 14% re parent drug carbamazepine plasma concentrations; changes to active metabolites were not noted (Schm

b) Metabolite/parent drug plasma ratios were studied in 15 patients with seizure disorders on carbamaz and five patients receiving both clobazam and carbamazepine. Carbamazepine plasma concentrations w groups, but clobazam-treated patients demonstrated higher concentrations of metabolites, particularly th metabolite. This suggested induction of carbamazepine metabolism, probably by induction of cytochrom resulting increases in carbamazepine epoxidation (Munoz et al, 1990).

3.5.1.Z Clomipramine

1) Interaction Effect: decreased clomipramine effectiveness

2) Summary: The concomitant use of carbamazepine and antidepressants has been reported to decrease ar levels (Leinonen et al, 1991f; Brown et al, 1990d). Although not reported for clomipramine, a similar interactic

3) Severity: moderate

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: Monitor for clinical efficacy of the clomipramine therapy and for any signs of toxicity carbamazepine. Serum levels of both agents should be considered when either agent is added or discontinue appropriate dosage adjustments made accordingly.

7) Probable Mechanism: increased clomipramine metabolism

8) Literature Reports

a) Concomitant administration of imipramine and carbamazepine to children with attention deficit disord reported to result in a 50% decrease in the total plasma concentration of imipramine plus desipramine (E Carbamazepine enhances the hepatic microsomal metabolism of imipramine and other tricyclic antidepr inducing hepatic enzymes (Moody et al, 1977b). Although not reported specifically for clomipramine, be a potential for a similar interaction exists. Patients on chronic carbamazepine therapy may require increase tricyclic antidepressants.

3.5.1.AA Clonazepam

1) Interaction Effect: reduced plasma levels of clonazepam

2) Summary: Clonazepam and carbamazepine cotherapy has resulted in decreased clonazepam serum con may be a result of carbamazepine enzyme induction (Sunaoshi et al, 1988a; Lai et al, 1978a). One study invo administration to epileptic patients maintained on carbamazepine either alone or in combination with other an

determined that clonazepam administration did not influence serum concentrations of carbamazepine (Johan 1977a).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Clonazepam levels should be monitored whenever carbamazepine is added or with therapy, or when the carbamazepine dose is changed. Also monitor the patient for seizure control.
7) Probable Mechanism: induction of clonazepam hepatic metabolism
8) Literature Reports
a) The effect of carbamazepine on clonazepam plasma levels during chronic administration were evalua healthy volunteers (Lai et al, 1978). Subjects were given clonazepam 1 mg once daily for 29 consecutive carbamazepine 200 mg was coadministered on days 8 to 29. Clonazepam plasma levels reached a stea to the initiation of carbamazepine therapy. After the addition of carbamazepine, plasma clonazepam leve 5 to 15 days to a level 19% to 37% less than their prior steady-state concentrations. Carbamazepine als clonazepam half-life. The proposed mechanism for this drug interaction is enzyme induction caused by c
b) The effects of clonazepam on serum levels of phenytoin, phenobarbital, and carbamazepine were stu epileptic patients who were receiving one or two of these drugs (Johannessen et al, 1977). Clonazepam was added to their therapeutic regimens and anticonvulsant levels were determined weekly for at least s nine patients receiving carbamazepine either as monotherapy or combined with another anticonvulsant, plasma concentrations averaged 8.1 mcg/mL prior to clonazepam and 8.3 mcg/mL after clonazepam the concluded that clonazepam has an insignificant effect on plasma concentrations of carbamazepine.
c) Concurrently administered clonazepam and carbamazepine were investigated in epileptic children (S 1988). The steady-state plasma concentration of clonazepam was determined in 66 epileptic children wh both carbamazepine and clonazepam. These levels were compared to the plasma levels of clonazepam children who were receiving clonazepam as monotherapy. In another group of 12 children, some of whor the previous groups, carbamazepine was added to their pre-existing regimen of clonazepam. Another gr was maintained on clonazepam and carbamazepine, and their therapeutic regimen was changed to clon plasma levels were determined four or more weeks after maintaining the same dose and regimen. When plasma levels of clonazepam, children who received clonazepam monotherapy had a mean level of 30.9 children who were receiving therapy with clonazepam and carbamazepine had a mean level of 26.2 ng/r carbamazepine was added to clonazepam monotherapy, steady-state plasma concentrations of clonaze from 47.5 ng/mL to 35.1 ng/mL. Conversely, when children who were receiving clonazepam and carbam switched to clonazepam monotherapy, plasma levels of clonazepam increased from 28.6 ng/mL to 34.4

3.5.1.AB Clorgyline

1) Interaction Effect: hypertensive urgency, hyperpyrexia, and seizures
2) Summary: Concomitant MAO inhibitor and carbamazepine therapy is contraindicated (Prod Info Tegretol(Simultaneous use may theoretically result in hyperpyrexia, excitation, and seizure activity (Prod Info Parnate(Info Tegretol(R), 1998e; Thweatt, 1986e). However, there is preliminary evidence that the combination of car an MAOI may be safe and efficacious, even in some refractory cases (Ketter et al, 1995k; Barker & Ecclestor controlled studies are needed.
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of carbamazepine and monoamine oxidase inhibitors contraindicated by the manufacturer. Monoamine oxidase inhibitors should be discontinued for a minimum of if the clinical situation permits, before carbamazepine therapy is initiated.
7) Probable Mechanism: unknown
8) Literature Reports
a) A double-blind study was conducted in ten inpatients with depression that had proved refractory to m therapies (electroconvulsive therapy, tricyclic antidepressants, monoamine oxidase inhibitors, lithium, ca benzodiazepines, and antipsychotics) (Ketter et al, 1995j). In addition to their regular carbamazepine and four patients received phenelzine (mean maximum dose 67.5 mg daily) and six patients received tranylc maximum dose 55 mg daily) for a mean duration combination therapy of 52.2 days. During MAOI coadm concentrations of carbamazepine and lithium did not change significantly from baseline values. Self-rate not substantially different. Four patients (three on phenelzine and one on tranylcypromine) responded to were subsequently discharged.
b) A 60-year-old woman who had an atypical endogenous, depressive illness of psychotic intensity was intermittently with cyclic antidepressants and intermittent electroconvulsive therapy. Following an acute v illness, she was treated successfully with a combination of phenelzine and L-tryptophan. Following a few improvement, her situation worsened and she was subsequently treated with zimelidine and lithium. Faili placed on a regimen of tranylcypromine with doses increasing progressively up to 30 mg daily in conjunc and tryptophan. Subsequently, carbamazepine was added in small doses with increments to achieve a p approximately 5 mg/L. This regimen proved successful, and she was discharged home and had remaine two months of follow up at the time of publication (Barker & Eccleston, 1984j).
c) Addition of tranylcypromine to carbamazepine therapy did not significantly affect carbamazepine seru case (Joffe et al, 1985e). Conversely, five patients on tranylcypromine needed a mean daily dose of carb mg to achieve a carbamazepine blood level of 8.0-11.1 mcg/mL (Barklage et al, 1992e). Four other patie

phenelzine only required a mean daily dose of carbamazepine 450 mg to attain a blood level of 8.7-10.9

3.5.1.AC Clozapine

1) Interaction Effect: an increased risk of bone marrow suppression, asterixis, or decreased serum clozapine
2) Summary: Clozapine and carbamazepine both have the potential to cause bone marrow suppression, incl agranulocytosis (Prod Info Clozaril(R), 2002). Asterixis (flapping tremor) has also been reported in patients u concurrent therapy with carbamazepine and clozapine (Rittmannsberger, 1996c). In addition, a therapeutic d study revealed significantly lower clozapine concentrations when carbamazepine was added to therapy (Jerli The mechanism may be due to carbamazepine induction of clozapine metabolism through cytochrome P450 studies are needed to further evaluate the pharmacokinetic and clinical effects of combining these agents.
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Avoid concurrent use; an alternative anticonvulsant agent should be considered. If these agents is necessary, monitor patients for decreased response to clozapine and agranulocytosis. Lower clozapine or carbamazepine may be required.
7) Probable Mechanism: additive bone marrow-suppressive effects and neurotoxicity; induction of clozapine
8) Literature Reports

a) One agranulocytosis fatality has been reported in association with the use of a multi-drug regimen wh clozapine, carbamazepine, clonazepam, benztropine, and lithium (Gerson & Lieberman JA Friedenberg, exhibited pancytopenia which is not characteristic of clozapine-induced agranulocytosis.

b) Over a three-year period, some drug combinations caused a greater risk of asterixis (flapping tremor) regimen of multiple psychopharmacologic agents (Rittmannsberger, 1996b). With regard to the agents c clozapine, and lithium, incidence of asterixis was greatest in those patients that were on at least two of t Out of ten patients developing asterixis, five patients received carbamazepine and clozapine as part of m and in two cases carbamazepine and clozapine were the sole psychopharmacologic agents. In all cases the drugs were within normal therapeutic ranges, suggesting an additive effect of combination therapy ra of a single agent.

c) Therapeutic drug monitoring data showed a 50% lower clozapine concentration/dose (C/D) ratio whe carbamazepine was taken compared to clozapine alone. The clozapine C/D ratio was inversely correlate carbamazepine. An additional analysis of eight patients confirmed that upon addition of carbamazepine t regimen, clozapine concentrations decreased significantly. The mean C/D ratio during monotherapy was cotherapy with carbamazepine fell to 0.30. The change in clozapine metabolism was suggested to be du carbamazepine induction of cytochrome P450 3A4 (Jerling et al, 1994).

3.5.1.AD Cortisone

1) Interaction Effect: decreased cortisone effectiveness
2) Summary: Carbamazepine has been demonstrated to increase the metabolism of corticosteroids (Olivesi, al, 1982a). Although not specifically reported for cortisone, a similar interaction could be expected.
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Monitor therapeutic efficacy of the corticosteroid. An increase in the steroid dosage after three to five days of concurrent carbamazepine therapy.
7) Probable Mechanism: increased cortisone metabolism

3.5.1.AE Cyclosporine

1) Interaction Effect: reduced cyclosporine serum levels and potentially increased risk for organ rejection
2) Summary: In a number of case reports, the concomitant use of cyclosporine and carbamazepine resulted cyclosporine levels (Soto Alvarez et al, 1991; Yee & McGuire, 1990a).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Within the first two to three weeks of initiating or discontinuing carbamazepine thera cyclosporine levels and adjust cyclosporine dosage as necessary; therapeutic trough levels range from 150 transplant, to 50 to 100 mcg/L thereafter; also monitor for signs of organ rejection.
7) Probable Mechanism: increased cyclosporine metabolism

3.5.1.AF Dalfopristin

1) Interaction Effect: an increased risk of carbamazepine toxicity (ataxia, nystagmus, diplopia, headache, vo seizures, coma)
2) Summary: Quinupristin/dalfopristin is a potent inhibitor of cytochrome P450 3A4 enzymes and may cause carbamazepine concentrations when administered concurrently. Because carbamazepine possesses a narro window, carbamazepine concentrations should be closely monitored during therapy with quinupristin/dalfopri carbamazepine should be adjusted accordingly (Prod Info Synercid(R) I.V., 1999).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable

6) Clinical Management: Monitor the trough carbamazepine concentrations when therapy with quinupristin/d administered concurrently. Dose reductions of carbamazepine may be required. Also monitor the patient for e carbamazepine toxicity.
7) Probable Mechanism: inhibition of cytochrome P450 3A4-mediated carbamazepine metabolism

3.5.1.AG Danazol
1) Interaction Effect: carbamazepine toxicity (ataxia, nystagmus, diplopia, headache, vomiting, apnea, seizur
2) Summary: Concomitant use of danazol and carbamazepine has led to significant increases in carbamaze resulted in toxicity (Kramer et al, 1986a; Zielinski et al, 1987; Hayden & Buchanan, 1991).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor for symptoms of carbamazepine toxicity when danazol is added to therapy. carbamazepine levels should also be considered with the addition or discontinuation of danazol and dosage a accordingly.
7) Probable Mechanism: decreased carbamazepine metabolism
8) Literature Reports
a) In a case report of a patient on carbamazepine 600 mg daily, the concurrent use of danazol 600 mg c carbamazepine level 60%, the area under the concentration-time curve (AUC) 148%, half-life 120%, and clearance approximately 60% within a month. Evaluation of the interaction by stable isotope technique re danazol inhibits carbamazepine metabolism, specifically the epoxide-trans-diol pathway (Kramer et al, 19

3.5.1.AH Darunavir
1) Interaction Effect: increased carbamazepine plasma concentrations and potential toxicity
2) Summary: Coadministration of carbamazepine with darunavir/ritonavir, an inhibitor of CYP450 enzymes, r inhibition of CYP3A-mediated carbamazepine metabolism, resulting in significantly increased carbamazepine concentrations and potential toxicity. In a pharmacokinetic drug interaction study, concurrent administration o and darunavir/ritonavir significantly increased plasma concentrations of carbamazepine. No significant chang pharmacokinetic parameters were noted. If coadministration of carbamazepine and darunavir/ritonavir is nec monitoring of carbamazepine concentrations and dose titration is recommended to attain the desired clinical initiating coadministration of darunavir/ritonavir and carbamazepine, no dose adjustment of either darunavir/ri carbamazepine is required (Prod Info PREZISTA(R) film coated oral tablets, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: established
6) Clinical Management: Coadministration of carbamazepine and darunavir/ritonavir may result in significant carbamazepine plasma concentrations due to inhibition of CYP3A-mediated carbamazepine metabolism by c coadministration of carbamazepine and darunavir/ritonavir is necessary, clinical monitoring of carbamazepine and dose titration is recommended to attain the desired clinical response. When initiating coadministration of and carbamazepine, no dose adjustment of either darunavir/ritonavir or carbamazepine is required (Prod Info film coated oral tablets, 2008).
7) Probable Mechanism: inhibition of CYP3A-mediated carbamazepine metabolism
8) Literature Reports
a) In a pharmacokinetic drug interaction study, concurrent administration of carbamazepine and darunav significantly increased plasma concentrations of carbamazepine. Subjects (n=16) were administered car mg twice daily concurrently with darunavir 600 mg/ritonavir 100 mg twice daily. Carbamazepine Cmax w (Least squares (LS) mean ratio 1.43; 90% confidence interval (CI), 1.34 to 1.53), AUC was increased 45 1.45; 90% CI, 1.35 to 1.57), and Cmin was increased 54% (LS mean ratio 1.54; 90% CI, 1.41 to 1.68). N changes in darunavir pharmacokinetic parameters were noted (Prod Info PREZISTA(R) film coated oral

3.5.1.AI Dasatinib
1) Interaction Effect: decreased dasatinib plasma concentrations
2) Summary: Dasatinib is a CYP3A4 substrate. Coadministration of a strong CYP3A4 inducer, such as carba dasatinib should be avoided as this may result in decreased dasatinib plasma concentrations leading to subth dasatinib levels. Consider using alternative therapeutic agents with low enzyme induction potential for coadm dasatinib. If concomitant use of dasatinib and carbamazepine is clinically warranted, a dasatinib dose increas considered and the patient should be monitored carefully for signs/symptoms of dasatinib toxicity (myelosupp retention, diarrhea, hemorrhage, or skin rash) (Prod Info SPRYCEL(R) oral tablets, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Avoid concomitant administration of carbamazepine, a strong CYP3A4 inducer, and CYP3A4 substrate, as this may result in decreased dasatinib plasma concentrations and consequently, subth Consider using alternative therapeutic agents with low enzyme induction potential for coadministration with d if concomitant use with carbamazepine is clinically warranted, consider increasing the dasatinib dose and mo closely for dasatinib toxicity (myelosuppression, fluid retention, diarrhea, hemorrhage, or skin rash) (Prod Info oral tablets, 2008).
7) Probable Mechanism: induction of CYP3A4-mediated dasatinib metabolism

3.5.1.AJ Dehydroepiandrosterone

1) Interaction Effect: reduced effectiveness of carbamazepine

2) Summary: Dehydroepiandrosterone (DHEA) in a single case report was noted to cause mania in a patient personal or family history of bipolar disorder (Markowitz et al, 1999a). Elevated DHEA levels have been found mental disorders; DHEA suppression has lead to improvement in psychotic symptoms (Howard, 1992a). Pati medication for bipolar disorder or patients with a personal and/or family history of bipolar disorder should not further data is available to characterize this drug-herb interaction.

3) Severity: moderate

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: If carbamazepine is being used for manic symptoms, concomitant use of dehydroep (DHEA) may cause a return of symptoms. Patients with a personal or family history of bipolar disorder should avoid DHEA use.

7) Probable Mechanism: proserotonergic activity of dehydroepiandrosterone may predispose patients to mar dehydroepiandrosterone is a precursor to androgenic steroids, which in high doses may precipitate mania

8) Literature Reports

a) A 68-year-old male with no documented psychiatric history initiated dehydroepiandrosterone (DHEA) (mg) daily and increased the dose to 200 to 300 mg daily for 6 months. Within 3 months, family members of odd behavior with prominent symptoms of agitation, delusional thinking, decreased sleep and appetite sprees. The patient was not taking any prescribed medication but did ingest alcohol in amounts up to 1 c Another 3 months elapsed, leading to involuntary inpatient admission secondary to rapid, loud, pressured grandiose thoughts. At admission, the patient reported that he had decreased alcohol intake to 2 beers c concerns about his behavior changes. There was no family history of bipolar disorder. Urinary drug scree Over the seven-day hospital stay, with the institution of valproic acid 500 mg twice daily, the patient's beh patterns improved, and the patient believed DHEA led to his symptoms. There were no ethanol withdraw patient was discharged with follow-up care from his primary care physician with a diagnosis of substance disorder (Markowitz et al, 1999).

b) A 13-year-old male decompensated with a subsequent two-year period of emotional problems accom use of LSD, hashish, barbiturates, and alcohol. His mental status included bizarre, disorganized, delusio auditory and visual hallucinations, paranoia, lack of attention to personal hygiene, agitation, and combati diagnosed with chronic paranoid schizophrenia; schizophrenia, chronic undifferentiated type, and schizo excited type. He was resistant to daily doses of trifluoperazine 40 mg, chlorpromazine 400 mg, and imipr was also resistant to combination therapy with chlorpromazine 400 mg with thiothixene 80 mg, thioridazi perphenazine 48 mg with lithium carbonate 1200 mg, clonazepam 4 mg, and carbamazepine 1200 mg d DHEA level exceeded 900 mcg/dL. A seven-day suppression test with dexamethasone 1 mg orally at be normal DHEA level of 200 mcg/dL. By day 5, psychosis improved and the patient was well-oriented, con was making good eye contact. Once dexamethasone was discontinued, rapid decompensation and floric despite "substantial amounts of psychotropic medications." DHEA increased to 536 mcg/dL. The author elevated DHEA levels were associated with florid psychosis resistant to conventional antipsychotic thera 1992).

3.5.1.AK Delavirdine

1) Interaction Effect: decreased trough plasma delavirdine concentrations

2) Summary: Pharmacokinetic data on eight patients suggested that coadministration of phenytoin, phenoba carbamazepine with delavirdine results in substantial reductions in trough plasma delavirdine concentrations 90%). Coadministration of delavirdine with any of these drugs is not recommended (Prod Info RESCRIPTOR 2006).

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Coadministration of delavirdine and carbamazepine is not recommended, due to th reduction in plasma delavirdine concentrations seen with concurrent use.

7) Probable Mechanism: induction of delavirdine metabolism

3.5.1.AL Desipramine

1) Interaction Effect: increased carbamazepine toxicity, decreased desipramine effectiveness

2) Summary: The concomitant use of carbamazepine and desipramine has been reported to increase carbar concentrations and decrease desipramine concentrations (Lesser, 1984; Brown et al, 1990a).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Monitor for clinical efficacy of the desipramine therapy and for any signs of toxicity c Serum levels of both agents should be considered when either agent is added or discontinued, with appropria adjustments made accordingly.

7) Probable Mechanism: increased desipramine metabolism, decreased carbamazepine metabolism

3.5.1.AM Dexamethasone

1) Interaction Effect: decreased dexamethasone effectiveness
2) Summary: Carbamazepine has been demonstrated to increase the metabolism of corticosteroids (Olivesi, Carbamazepine does interfere with the dexamethasone suppression test (Privitera et al, 1982c).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Monitor therapeutic efficacy of the corticosteroid. An increase in the steroid dosage after three to five days of concurrent carbamazepine therapy.
7) Probable Mechanism: increased dexamethasone metabolism

3.5.1.AN Dicumarol
1) Interaction Effect: decreased anticoagulant effectiveness
2) Summary: Concomitant carbamazepine and warfarin therapy has been reported to result in a decreased a effect, secondary to the induction of hepatic metabolism of the anticoagulant (Massey, 1983c; Cohen & Arms Koch-Weser & Koch-Weser, 1975c; Kendall & Boivin, 1981c; Hansen et al, 1971e). A similar effect may occu
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: In patients receiving oral anticoagulant therapy, the prothrombin time ratio or INR (i normalized ratio) should be closely monitored with the addition and withdrawal of treatment with carbamazep reassessed periodically during concurrent therapy. Adjustments of the dicumarol dose may be necessary in c the desired level of anticoagulation.
7) Probable Mechanism: increased dicumarol metabolism

3.5.1.AO Diltiazem
1) Interaction Effect: carbamazepine toxicity (ataxia, nystagmus, diplopia, headache, vomiting, apnea, seizur
2) Summary: Concomitant administration of carbamazepine and diltiazem may increase carbamazepine leve 72%, resulting in toxicity (Prod Info Tiazac(TM), 1996; Shaughnessy & Mosley, 1992a; Brodie & Macphee, 19 al, 1986; Eimer & Carter, 1987a; Bahls et al, 1991).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor carbamazepine serum levels and clinical signs of carbamazepine toxicity. U levels are 6-12 mg/L; adjust dose accordingly. Nifedipine does not appear to interact with carbamazepine and considered as an alternative to diltiazem.
7) Probable Mechanism: decreased carbamazepine metabolism
8) Literature Reports
a) Concomitant carbamazepine and diltiazem administration may produce elevated serum carbamazepi in neurotoxicity (Brodie & Macphee, 1986; Eimer & Carter, 1987; Ahmad, 1990; Shaughnessy & Mosley, case report, diltiazem 60 mg three times daily elevated the carbamazepine level by 40% higher than bas clinical signs of carbamazepine toxicity. Nifedipine 20 mg three times daily did not produce any adverse Macphee, 1986). In another case report, a patient with a stable carbamazepine dose (800 mg daily) and concentration (8.5 to 10.1 mg/L) was started on diltiazem 30 mg three times a day for atrial fibrillation. Ap weeks later, the patient was admitted to the hospital with mental slowing and speech difficulties. The ser level the next day was 15.5 mg/L. Carbamazepine was consequently reduced to 300 mg daily, which pro level of 8.3 mg/L and resolution of the mental disturbances (Eimer & Carter, 1987). Competitive inhibitior system by diltiazem may be the most likely cause of the elevated carbamazepine serum concentrations.

3.5.1.AP Dothiepin
1) Interaction Effect: decreased dothiepin effectiveness
2) Summary: The concomitant use of carbamazepine and antidepressants has been reported to decrease se antidepressant levels (Leinonen et al, 1991l; Brown et al, 1990i). Although not reported for dothiepin, a simila occur.
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Monitor for clinical efficacy of the dothiepin therapy and for any signs of toxicity of c Serum levels of both agents should be considered when either agent is added or discontinued, with appropria adjustments made accordingly.
7) Probable Mechanism: increased dothiepin metabolism
8) Literature Reports
a) Concomitant administration of imipramine and carbamazepine to children with attention deficit disorde reported to result in a 50% decrease in the total plasma concentration of imipramine plus desipramine (E Carbamazepine probably enhances the hepatic microsomal metabolism of imipramine and other tricyclic by inducing hepatic enzymes (Moody et al, 1977d). Although not reported specifically for dothiepin, be av potential for a similar interaction exits. Patients on chronic carbamazepine therapy may require increase antidepressants.

3.5.1.AQ Doxacurium

1) Interaction Effect: decreased doxacurium duration of action

2) Summary: It has been demonstrated that in patients taking carbamazepine for at least one month prior to neuromuscular blockers, the recovery time after being given neuromuscular blockers was about 65% faster w control patients (Ornstein et al, 1991a; Prod Info Nuromax(R), 1994).

3) Severity: moderate

4) Onset: rapid

5) Substantiation: theoretical

6) Clinical Management: Monitor patients for an appropriate clinical response to the neuromuscular blocker. intervals or higher doses of doxacurium may be needed in patients receiving carbamazepine.

7) Probable Mechanism: unknown

8) Literature Reports

a) Twenty-seven adult neurosurgical patients participated in a study to determine the effects of doxacuri neuromuscular blockade. Patients were divided into three equal groups, with nine patients having been c therapy for at least one week, nine patients having been on carbamazepine therapy for at least one weel patients serving as controls. All subjects received a bolus intravenous dose of doxacurium 60 mcg/kg du with nitrous oxide, fentanyl, and droperidol. The onset of paralysis was prolonged by 49% in the phenyto not altered in the carbamazepine group. Recovery times were significantly shortened in both anticonvuls recovering approximately twice as fast as the controls. Times from doxacurium administration to 75% rec follows: control group, 203 minutes; phenytoin group, 97 minutes; carbamazepine group, 80 minutes. Sir recovery times were seen for 5%, 25%, 50%, and 90% recovery. Once the recovery from paralysis starte more quickly in the anticonvulsant groups. The 25% to 75% recovery index was increased by 67% in the group and 53% in the phenytoin group when compared to controls (Ornstein et al, 1991).

3.5.1.AR Doxepin

1) Interaction Effect: decreased doxepin effectiveness and possibly increased carbamazepine toxicity (diplop dizziness, tremor)

2) Summary: The concomitant use of carbamazepine and antidepressants has been reported to decrease do (Leinonen et al, 1991d).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Monitor for clinical efficacy of the doxepin therapy and for any signs of toxicity of ca Serum levels of both agents should be considered when either agent is added or discontinued, with appropria adjustments made accordingly.

7) Probable Mechanism: increased doxepin metabolism

8) Literature Reports

a) The effect of carbamazepine on doxepin levels were examined in 17 psychiatric inpatients who were minimum of 7 days prior to measurement of baseline antidepressant concentrations. The average daily d was 201.5 mg. Carbamazepine was added in a mean dose of 593 mg and continued over a 4-week perio concentrations were decreased to 46% in patients receiving combination therapy compared to patients r alone (Leinonen et al, 1991c).

3.5.1.AS Doxorubicin Hydrochloride

1) Interaction Effect: decreased carbamazepine plasma concentrations

2) Summary: A 36-year old epileptic female undergoing antineoplastic therapy with doxorubicin and cisplatin subtherapeutic carbamazepine, phenytoin, and valproic acid concentrations which resulted in tonic-clonic sei the exact mechanism is unknown, possible causes include decreased absorption or accelerated elimination o (Neef & de Voogd-van der Straaten, 1988e).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: Anticonvulsant levels should be closely monitored in patients receiving antineoplast doxorubicin or cisplatin. Doses of carbamazepine may need to be increased.

7) Probable Mechanism: decreased absorption or accelerated elimination of carbamazepine

8) Literature Reports

a) A 36-year old female epileptic patient requiring cisplatin and doxorubicin therapy for papillary adenoc experienced tonic-clonic seizures after two days of antineoplastic treatment. Plasma concentrations of ca valproic acid, and phenytoin were all determined to be subtherapeutic (0.5 mg/L, 24.3 mg/L, and 0.3 mg/ One month later, she was controlled on phenytoin 450 mg daily, carbamazepine 1200 mg daily, and valp daily. During her second course of cisplatin and doxorubicin, she again suffered a tonic-clonic seizure. P concentrations of her anticonvulsants were phenytoin 0.2 mg/L, carbamazepine 3.5 mg/L, and valproic a Three days following her chemotherapy, plasma concentrations of the anticonvulsants had returned to th values. During her sixth and final chemotherapy course, carbamazepine levels remained low (1.4 mg/L) all 15 days of the course (Neef & de Voogd-van der Straaten, 1988d).

3.5.1.AT Doxorubicin Hydrochloride Liposome

1) Interaction Effect: decreased carbamazepine plasma concentrations

2) Summary: Although no formal drug interaction studies have been done with doxorubicin hydrochloride lipo may interact with drugs known to interact with the conventional formulation of doxorubicin (Prod Info Doxil(R) old epileptic female undergoing antineoplastic therapy with doxorubicin and cisplatin experienced subtherape carbamazepine, phenytoin, and valproic acid concentrations which resulted in tonic-clonic seizures. Although mechanism is unknown, possible causes include decreased absorption or accelerated elimination of carbama Voogd-van der Straaten, 1988a).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Anticonvulsant levels should be closely monitored in patients receiving antineoplast doxorubicin or cisplatin. Doses of carbamazepine may need to be increased.
7) Probable Mechanism: decreased absorption or accelerated elimination of carbamazepine
8) Literature Reports
a) A 36-year old female epileptic patient requiring cisplatin and doxorubicin therapy for papillary adenoc experienced tonic-clonic seizures after two days of antineoplastic treatment. Plasma concentrations of ca valproic acid, and phenytoin were all determined to be subtherapeutic (0.5 mg/L, 24.3 mg/L, and 0.3 mg/ One month later, she was controlled on phenytoin 450 mg daily, carbamazepine 1200 mg daily, and valp daily. During her second course of cisplatin and doxorubicin, she again suffered a tonic-clonic seizure. P concentrations of her anticonvulsants were phenytoin 0.2 mg/L, carbamazepine 3.5 mg/L, and valproic a Three days following her chemotherapy, plasma concentrations of the anticonvulsants had returned to th values. During her sixth and final chemotherapy course, carbamazepine levels remained low (1.4 mg/L) all 15 days of the course (Neef & de Voogd-van der Straaten, 1988).

3.5.1.AU Doxycycline

1) Interaction Effect: decreased doxycycline effectiveness
2) Summary: Chronic carbamazepine therapy may decrease the half-life of doxycycline by 50% (Neuvonen e et al, 1974).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Monitor clinical effectiveness of doxycycline therapy in patients concurrently receivi increased doxycycline dosage might be considered.
7) Probable Mechanism: may increase metabolism doxycycline

3.5.1.AV Efavirenz

1) Interaction Effect: decreased efavirenz plasma concentrations and/or carbamazepine plasma concentratio
2) Summary: Coadministration of carbamazepine and efavirenz resulted in lowered exposures and plasma c both carbamazepine and efavirenz. However, as no dosing recommendations can be made, use of an alterna anticonvulsant should be considered in patients receiving efavirenz (Prod Info SUSTIVA(R) oral capsules, tab
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: established
6) Clinical Management: The concomitant use of carbamazepine and efavirenz has resulted in reduced plas of carbamazepine and efavirenz. An alternative anticonvulsant should be considered in patients receiving efa adjusted dosing recommendations are available for carbamazepine (Prod Info SUSTIVA(R) oral capsules, tal
7) Probable Mechanism: unknown
8) Literature Reports
a) Coadministration of carbamazepine and efavirenz resulted in decreased exposure and plasma conce carbamazepine in pharmacokinetic studies. In 12 subjects, efavirenz (600 mg orally daily for 14 days) de plasma Cmax, AUC, and Cmin of carbamazepine (200 mg/day for 3 days, 200 mg twice daily for 3 days, for 29 days) by an average of 20% (90% confidence interval (CI), 15 to 24%), 27% (90% CI, 20 to 33%), 24 to 44%), respectively. In 14 subjects, carbamazepine (200 mg/day for 3 days, 200 mg twice daily for 3 mg/day for 15 days) decreased the plasma Cmax, AUC, and Cmin of efavirenz (600 mg orally daily for 3 average of 21% (90% confidence interval (CI), 15 to 26%), 36% (90% CI, 32 to 40%), and 47% (90% CI, respectively. (Prod Info SUSTIVA(R) oral capsules, tablets, 2008).

3.5.1.AW Ergocalciferol

1) Interaction Effect: decreased systemic ergocalciferol (vitamin D) exposure
2) Summary: Coadministration of carbamazepine and vitamin D may reduce exposure to vitamin D and may events related to vitamin D deficiency, including hypocalcemia and secondary hyperparathyroidism. If carban vitamin D are used concomitantly, additional vitamin D supplementation may be necessary (Prod Info FOSAM oral tablets, 2008). Monitoring the patient for signs and symptoms of vitamin D deficiency (ie, hypocalcemia a hyperparathyroidism) may be warranted.
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Concomitant administration of carbamazepine and vitamin D may reduce exposure to increased ergocalciferol clearance. Consider additional vitamin D supplementation if these agents are used

(Prod Info FOSAMAX PLUS D(TM) oral tablets, 2008). Monitor the patient for adverse events related to vitam including signs and symptoms of hypocalcemia and secondary hyperparathyroidism.
7) Probable Mechanism: increased catabolism of vitamin D

3.5.1.AX Erlotinib
1) Interaction Effect: increased erlotinib clearance and reduced erlotinib exposure
2) Summary: Erlotinib is primarily metabolized by the CYP3A4 isozyme. Coadministration of erlotinib and rifa inducer, decreased the erlotinib AUC by approximately 67% to 80%, which is equivalent to an erlotinib dose c mg in non-small cell lung cancer patients; it also significantly increased erlotinib clearance. Although not direc concomitant use of erlotinib and carbamazepine, also a CYP3A4 inducer, could result in a similar interaction therefore be avoided. If concomitant use is clinically warranted, an increase in erlotinib dose as tolerated at 2 should be considered, while monitoring patient safety. If the erlotinib dose is increased, the dose should be re immediately to the indicated starting dose upon discontinuation of carbamazepine (Prod Info TARCEVA(R) o
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Avoid concomitant use of erlotinib and carbamazepine as this may result in decreas exposure and efficacy. However, if concomitant use is clinically warranted, consider an increase in erlotinib d 2 week intervals and monitor patient's safety. If the erlotinib dose is increased, reduce it immediately to the in dose upon discontinuation of carbamazepine (Prod Info TARCEVA(R) oral tablets, 2007).
7) Probable Mechanism: induction of CYP3A4-mediated erlotinib metabolism by carbamazepine

3.5.1.AY Erythromycin
1) Interaction Effect: carbamazepine toxicity (ataxia, nystagmus, diplopia, headache, vomiting, apnea, seizur
2) Summary: Erythromycin decreases the hepatic clearance of carbamazepine causing elevated carbamaze concentrations and possible toxicity (Hendrick et al, 1983a; MacNab et al, 1987a; Miles & Tennison, 1989a; V 1987a; Wroblewski et al, 1986).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: established
6) Clinical Management: The combination of carbamazepine and macrolide antibiotics should be avoided an given to an alternative antibiotic. If the combination is necessary, carbamazepine levels should be obtained w adding or discontinuing erythromycin and dosage adjustments made accordingly.
7) Probable Mechanism: decreased carbamazepine metabolism
8) Literature Reports
a) Toxicity following concomitant administration of carbamazepine and erythromycin was reported in six (Goulden et al, 1986). Toxicity occurred in less than two days with erythromycin therapy in five patients; the interaction was not observed until the eighth day of erythromycin therapy when the dose was double mg/kg/day. Carbamazepine serum concentrations decreased to baseline levels within 8 to 12 hours of di erythromycin, suggesting that normalization of carbamazepine metabolism occurs rapidly.
b) It is suggested that erythromycin inhibits the metabolism of carbamazepine in liver (cytochrome P450 al, 1983). Concomitant administration of erythromycin and carbamazepine in healthy volunteers resulted increases in carbamazepine half-life and 24-hour postdose serum concentrations, as well as decreases i oral clearance (Miles & Tennison, 1989). Decreases in maximum carbamazepine-10,11-epoxide serum c area under concentration-time curve (AUC), and the carbamazepine-10,11-epoxide to carbamazepine ra observed during combined therapy. In this study, carbamazepine was given in daily doses of 300 mg to 4 17 consecutive days; subjects were given placebo erythromycin every six hours on days 12, 13 and 14, t base 250 mg every six hours for the final three days. It is suggested that erythromycin significantly inhibi metabolic pathway required for transformation of carbamazepine to carbamazepine-10,11-epoxide. Wide variability was seen in this study; individual changes in oral clearance ranged from plus 23% to minus 41 unpredictability of this interaction. Close patient monitoring is advised when these two agents are given c when one agent is discontinued.
c) Increases in carbamazepine serum concentrations were observed in four children during concurrent e carbamazepine therapy. All children developed signs of toxicity (nausea, vomiting, ataxia, dizziness) with initiation of erythromycin therapy, which subsided after erythromycin was discontinued and was associat in carbamazepine serum concentrations. The authors suggest that erythromycin inhibits the metabolism The onset of the interaction generally occurred three to four days after addition of erythromycin to the ca regimen (Hendrick et al, 1983).
d) Concomitant carbamazepine and erythromycin stearate therapy was reported to result in carbamazep SIADH in a 41-year-old epileptic woman (Carranco et al, 1985).
e) A further report of the interaction between erythromycin ethylsuccinate and carbamazepine was desc old girl with tonic-clonic seizures (Zitelli et al, 1987). The patient had been maintained on carbamazepine (serum level 12 mcg/mL) and developed symptoms of carbamazepine toxicity (vomiting, lethargy, ataxia, cogwheeling movements) after five days of erythromycin ethylsuccinate therapy (250 mg four times daily increases in carbamazepine serum levels to 26 mcg/mL. Following withdrawal of erythromycin, serum co carbamazepine returned to normal levels, with resolution of symptoms. This article also provides a brief r clinically-relevant erythromycin drug interactions.
f) Two cases describing the interaction of carbamazepine and erythromycin in children resulting in carba

were reported by (Woody et al, 1987). The authors suggest that parents should be advised of the interac
medications are frequently prescribed independently by pediatrician and neurologist.
g) Concomitant administration of erythromycin and carbamazepine was reported to result in sinus arrest
10-year-old boy secondary to carbamazepine toxicity (MacNab et al, 1987). The patient recovered follow
therapy and the EKG normalized when carbamazepine serum levels returned to the therapeutic range. T
preexisting cardiac symptoms.

3.5.1.AZ Estazolam

1) Interaction Effect: decreased estazolam plasma concentrations and reduced effectiveness
2) Summary: Carbamazepine is a potent inducer of cytochrome P450-3A4 and estazolam metabolism is cata
coadministration of carbamazepine and estazolam would therefore be expected to reduce estazolam plasma
levels (Prod Info ProSom(TM), 2004).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Monitor for signs of benzodiazepine clinical ineffectiveness. Concurrent use of carb
estazolam may require higher doses of estazolam. The dose of estazolam should be decreased if carbamaze
discontinued.
7) Probable Mechanism: carbamazepine induction of CYP3A-isoform mediated estazolam metabolism

3.5.1.BA Ethinyl Estradiol

1) Interaction Effect: a decrease in plasma concentrations of estrogens and in estrogen effectiveness
2) Summary: Breakthrough bleeding, spotting, and pregnancy have been reported in women on anticonvulsa
contraceptives (Prod Info Ortho Evra(TM), 2001; Mattson et al, 1986a; Crawford et al, 1986; Haukkamaa, 198
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: In some women the use of higher estrogen content in the contraceptive may be suf
use of alternate methods of birth control may be necessary.
7) Probable Mechanism: increased metabolism of contraceptive steroids
8) Literature Reports
a) Concomitant administration of oral contraceptives with enzyme-inducing anticonvulsant agents, prima
phenytoin, carbamazepine, or primidone, has been reported to result in an increased failure rate of contr
et al, 1986). The benzodiazepines and valproic acid have not been associated with increased failure rate
receiving oral contraceptives. Increasing the dose of ethinyl estradiol or mestranol in oral contraceptives
breakthrough bleeding and decrease the risk of conception. However, higher doses of estrogens may als
of vascular side effects, primarily in patients where enzyme induction does not occur. It is recommended
estrogen and progestin be given initially in patients receiving an enzyme inducing anticonvulsant; howev
pregnancy is a special concern, a moderate dose formulation (50 mcg ethinyl estradiol) should be consid
breakthrough bleeding occurs with low-dose contraception, progressive increases in the dose of mestran
(up to 80 mcg) should be considered. If spotting occurs, it is suggested that the contraceptive not be disc
rather that a traditional method of barrier contraception be initiated during the remainder of that cycle. Sv
dose oral contraceptive is recommended if enzyme inducing anticonvulsants are discontinued in women
moderate or high-dose contraceptives.
b) Carbamazepine reduced the area under the plasma concentration time curve (AUC) of ethinyl estrad
4 women taking carbamazepine 300 to 600 mg daily within 8 to 12 weeks of initiation of therapy. Norges
also significantly reduced to 29% to 57% of baseline. The authors suggest that breakthrough bleeding ca
most women with use of oral contraceptives containing 80 to 100 mcg ethinyl estradiol (Crawford et al, 1
c) Accidental pregnancy occurred in a 20-year-old epileptic who was using phenytoin 400 mg daily plus
400 mg daily (Haukkamaa, 1986). The plasma concentration of levonorgestrel in this patient was very lo
pg/mL) when compared to controls (325 +/- 135 pg/mL). Carbamazepine appears to decrease plasma le
concentrations by enhancing the hepatic metabolism of the steroid via enzyme induction. Levonorgestrel
relied upon as the sole means of contraception in patients on anticonvulsant therapy.

3.5.1.BB Ethosuximide

1) Interaction Effect: decreased ethosuximide serum concentrations
2) Summary: Two studies have documented that ethosuximide disposition is altered during carbamazepine t
decreased steady-state plasma concentrations, decreased half-life, and increased clearance of ethosuximide
1996a; Warren et al, 1980a).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Patients receiving concurrent therapy with carbamazepine and ethosuximide may a
serum ethosuximide concentrations compared to patients not taking carbamazepine, leading to a decreased
If these two agents are used together, careful evaluation of clinical response and serum drug level monitoring
7) Probable Mechanism: carbamazepine induction of cytochrome P450 enzymes
8) Literature Reports
a) In a study of 22 volunteers, the effects of chronic epileptic medication on the pharmacokinetics of eth

evaluated. The study consisted of 10 epileptic patients undergoing chronic treatment with carbamazepin phenobarbital, and 12 healthy control subjects taking no chronic medications. Each subject received a si dose of ethosuximide after an overnight fast. Patients on chronic epileptic therapy had a decreased mea half-life of 29.0 +/- 7.8 hours compared to 53.7 +/- 14.3 hours for control subjects. Patients on chronic ep had higher oral clearance values and slightly decreased apparent volume of distribution values compare patients. The authors postulate that the mechanism of action was due to antiepileptic medication inductic CYP3A (Giaccone et al, 1996).

b) The disposition of ethosuximide was demonstrated to be altered by carbamazepine therapy (Warren Concomitant therapy with carbamazepine 200 mg daily and ethosuximide 250 mg twice daily resulted in ethosuximide steady-state plasma concentrations. The clearance of ethosuximide was shown to increas concomitant decrease in serum half-life. Thus carbamazepine induced the metabolism of ethosuximide a adjustments may be required during concomitant therapy.

3.5.1.BC Etonogestrel

1) Interaction Effect: a decrease in plasma concentrations of estrogens and in estrogen effectiveness

2) Summary: Breakthrough bleeding, spotting, and pregnancy have been reported in women on anticonvulsa contraceptives (Prod Info Ortho Evra(TM), 2001; Mattson et al, 1986a; Crawford et al, 1986; Haukkamaa, 198

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: In some women the use of higher estrogen content in the contraceptive may be suf use of alternate methods of birth control may be necessary.

7) Probable Mechanism: increased metabolism of contraceptive steroids

8) Literature Reports

a) Concomitant administration of oral contraceptives with enzyme-inducing anticonvulsant agents, prima phenytoin, carbamazepine, or primidone, has been reported to result in an increased failure rate of contr et al, 1986). The benzodiazepines and valproic acid have not been associated with increased failure rate receiving oral contraceptives. Increasing the dose of ethinyl estradiol or mestranol in oral contraceptives breakthrough bleeding and decrease the risk of conception. However, higher doses of estrogens may als of vascular side effects, primarily in patients where enzyme induction does not occur. It is recommended estrogen and progestin be given initially in patients receiving an enzyme inducing anticonvulsant; howev pregnancy is a special concern, a moderate dose formulation (50 mcg ethinyl estradiol) should be consic breakthrough bleeding occurs with low-dose contraception, progressive increases in the dose of mestrar (up to 80 mcg) should be considered. If spotting occurs, it is suggested that the contraceptive not be disc rather that a traditional method of barrier contraception be initiated during the remainder of that cycle. Sv dose oral contraceptive is recommended if enzyme inducing anticonvulsants are discontinued in women moderate or high-dose contraceptives.

b) Carbamazepine reduced the area under the plasma concentration time curve (AUC) of ethinyl estrad 4 women taking carbamazepine 300 to 600 mg daily within 8 to 12 weeks of initiation of therapy. Norges also significantly reduced to 29% to 57% of baseline. The authors suggest that breakthrough bleeding ca most women with use of oral contraceptives containing 80 to 100 mcg ethinyl estradiol (Crawford et al, 1

c) Accidental pregnancy occurred in a 20-year-old epileptic who was using phenytoin 400 mg daily plus 400 mg daily (Haukkamaa, 1986). The plasma concentration of levonorgestrel in this patient was very lo pg/mL) when compared to controls (325 +/- 135 pg/mL). Carbamazepine appears to decrease plasma le concentrations by enhancing the hepatic metabolism of the steroid via enzyme induction. Levonorgestrel relied upon as the sole means of contraception in patients on anticonvulsant therapy.

3.5.1.BD Etravirine

1) Interaction Effect: decreased etravirine plasma concentrations

2) Summary: Carbamazepine and etravirine should not be coadministered. The combination of carbamazepi may result in significant decreases in etravirine plasma concentrations due to CYP3A4-mediated induction of carbamazepine (Prod Info INTELENCE(TM) oral tablets, 2008).

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Carbamazepine and etravirine should not be coadministered. Concomitant use of c etravirine may result in decreased etravirine plasma concentrations and loss of therapeutic effect of etravirine CYP3A4-mediated induction of etravirine by carbamazepine (Prod Info INTELENCE(TM) oral tablets, 2008).

7) Probable Mechanism: induction of CYP3A4-mediated metabolism of etravirine by carbamazepine

3.5.1.BE Etretinate

1) Interaction Effect: decreased etretinate effectiveness

2) Summary: A case report described a possible interaction between carbamazepine and etretinate (Moham Concurrent use resulted in the lack of etretinate efficacy; withdrawal of carbamazepine was followed by the e response to etretinate.

3) Severity: moderate

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: Monitor for therapeutic efficacy of etretinate. If no clinical response is seen, and etr necessary, consideration might be given to changing to an alternative anticonvulsant regimen.
7) Probable Mechanism: induction of etretinate metabolism
8) Literature Reports
a) A 15-year-old girl with epilepsy and pityriasis rubra pilaris was being treated with carbamazepine 200 acid 100 mg/d when etretinate 30 mg/d was added to her therapy. After 2 months of therapy no clinical ir seen, and none of the usual cutaneous side effects of etretinate were noted. Etretinate was discontinued was gradually withdrawn and the valproic acid dose increased to 350 mg/d. Etretinate 30 mg/d was resta weeks a good clinical response and dry lips and mouth, a common side effect, were seen. No etretinate concentrations were reported, and rechallenge was not attempted (Mohammed, 1992).

3.5.1.BF Evening Primrose

1) Interaction Effect: reduced anticonvulsant effectiveness
2) Summary: Theoretically, evening primrose oil may reduce the effectiveness of anticonvulsants by lowering threshold. Evening primrose oil is contraindicated in patients with epilepsy (Barber, 1998; Newall et al, 1996).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Avoid concomitant use of evening primrose oil with anticonvulsants.
7) Probable Mechanism: evening primrose oil may reduce the seizure threshold

3.5.1.BG Everolimus

1) Interaction Effect: loss of everolimus efficacy
2) Summary: Drugs such as carbamazepine, which is a cytochrome CYP3A4 inducer, may increase the met everolimus, causing decreased everolimus plasma concentrations. Caution should be used when these two a concomitantly. Dosage increase of everolimus is recommended (Prod Info AFINITOR(R) oral tablets, 2009).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Monitor the patient closely or perform additional tests to determine effectiveness of Dosage increase of everolimus is recommended (Prod Info AFINITOR(R) oral tablets, 2009).
7) Probable Mechanism: induction of cytochrome CYP3A4-mediated everolimus metabolism

3.5.1.BH Felbamate

1) Interaction Effect: decreased carbamazepine or felbamate effectiveness
2) Summary: Felbamate reduces carbamazepine levels (Albani et al, 1991a; Graves et al, 1989a; Wilensky e carbamazepine decreases felbamate levels (Prod Info Felbatol(R), 2000a).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Consider monitoring carbamazepine levels following the addition of felbamate thera carbamazepine concentrations may be reduced, there is an increase in the active metabolite (carbamazepine concentration, such that the overall effectiveness of carbamazepine may not change.
7) Probable Mechanism: increased carbamazepine or felbamate metabolism
8) Literature Reports
a) The manufacturer reports that a 50% increase in felbamate clearance and a 40% decrease in felbam trough concentration occurs when carbamazepine is added to felbamate therapy. Additionally, felbamate decrease in the steady-state plasma concentrations of carbamazepine and an increase in the steady-sta epoxide plasma concentration (Prod Info Felbatol(R), 2000).
b) Four patients who were receiving carbamazepine, phenytoin, and felbamate have been described. Fo discontinuation of phenytoin, felbamate clearance decreased 21%. Carbamazepine dosage was reduced additional felbamate clearance of 16.5% (Wagner et al, 1991).
c) Felbamate has been reported to increase carbamazepine metabolism. The effect of felbamate 3000 r carbamazepine levels in four patients on monotherapy was studied. Carbamazepine levels had previous at 4 to 12 mcg/mL with dosages of 800 to 1800 mg carbamazepine daily. Carbamazepine levels were re of 25% with concurrent use; this effect was evident within one week of initiation of felbamate and plateau weeks. Felbamate appeared to reduce carbamazepine concentrations and increase carbamazepine-epo concentrations without affecting free fraction (Albani et al, 1991). Similar results were reported in anothe al, 1989).
d) If phenytoin or carbamazepine (or any prodrugs) is used in pregnant women, there is a substantially i teratogenicity with many combinations of other anticonvulsants. The teratogenicity of these drugs is large related to the levels of the reactive epoxide metabolites (Buehler et al, 1990d; Van Dyke et al, 1991d; Fir The epoxide/parent drug ratio is generally increased when phenytoin or carbamazepine is combined with other drugs that induce cytochrome P450 enzymes (3A4, 2C9, 2C19), or drugs which inhibit epoxide hyc valproic acid, progabide, and lamotrigine (Bianchetti et al, 1987d; Ramsay et al, 1990d; Spina et al, 1996 combinations increase the risk of major birth defects 3- to 4-fold over monotherapy and about 10-fold ove rates.

3.5.1.BI Felodipine

1) Interaction Effect: decreased felodipine effectiveness

2) Summary: Several studies have shown that concurrent use carbamazepine with some but not all calcium (nimodipine, felodipine) has resulted in decreased levels of the calcium channel blocker (Capewell et al, 1987 1988a; Woodcock et al, 1991; Tartara et al, 1991a).

3) Severity: minor

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Monitor clinical response to felodipine with dose adjustments as needed to achieve cardiovascular response. Nifedipine does not appear to interact with carbamazepine and may be considered to felodipine.

7) Probable Mechanism: increased felodipine metabolism

8) Literature Reports

a) Three groups of eight subjects were studied (Tartara et al, 1991). Group 1 was comprised of healthy had epileptic patients treated at least four months with carbamazepine, phenobarbital, phenytoin (all enz a combination, and group 3 included epileptic patients treated for at least four months with sodium valpro the control group, nimodipine AUCs averaged a 7-fold decrease in the enzyme inducer group, probably d first-pass metabolism. The nimodipine AUCs were increased by 50% in the valproate-treated group.

b) Maximum plasma concentrations of felodipine were considerably lower in 10 epileptic patients (1.6 nr anticonvulsant therapy (phenytoin, carbamazepine, phenobarbital) than in 12 healthy volunteers (8.7 nm administration of oral felodipine 5 mg twice daily for four days to both groups (Capewell et al, 1987). The the felodipine plasma concentration-time curve at 12 hours postdose was reduced from 33 nmol/L/hr in t nmol/L/hr in epileptics on anticonvulsant medications (Saltiel et al, 1988).

3.5.1.BJ Fentanyl

1) Interaction Effect: decreased plasma concentrations of fentanyl

2) Summary: Induction of fentanyl metabolism by carbamazepine, a cytochrome P450 inducer, may cause ir of fentanyl (Prod Info Duragesic(R), 2001).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Caution is advised when administering fentanyl to patients receiving carbamazepin adjustments should be considered if necessary.

7) Probable Mechanism: induction of cytochrome P450-mediated metabolism of fentanyl

3.5.1.BK Fluconazole

1) Interaction Effect: an increased risk of carbamazepine toxicity (ataxia, nystagmus, diplopia, headache, vor seizures, coma)

2) Summary: Several cases of carbamazepine toxicity attributed to the coadministration of fluconazole have (Finch et al, 2002a; Nair & Morris, 1999a; Ulivelli et al, 2004). Fluconazole inhibits cytochrome P450 3A4 enz for carbamazepine metabolism. A similar interaction has also been reported between fluconazole and phenyt

3) Severity: moderate

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: Consider monitoring carbamazepine levels and symptoms of carbamazepine toxicit addition of fluconazole.

7) Probable Mechanism: fluconazole inhibition of cytochrome P450 3A4-mediated carbamazepine metabolis

8) Literature Reports

a) A 33-year-old male with mental retardation and a history of seizures had been taking carbamazepine times daily for more than five years. His last carbamazepine concentration before the initiation of flucona 11.1 mcg/mL, which was consistent with his past levels. Fluconazole 150 mg daily, ciprofloxacin 250 mg oral steroid taper were prescribed for a skin eruption which was thought to be candidiasis. Ciprofloxacin after two days since no clinical improvement was noted. By the end of the third day of fluconazole therap lethargic and unarousable to painful stimuli. A carbamazepine concentration was measured at 24.5 mcg/ was discontinued and carbamazepine was held for 24 hours. By the next day, the carbamazepine conce mcg/mL and his symptoms had resolved. He was restarted on his prior dose of carbamazepine and four level of 11.7 mcg/mL (Nair & Morris, 1999).

b) Fluconazole, an inhibitor of the cytochrome P450 enzyme system (CYP450), inhibits the metabolism but undergoes metabolism itself via the CYP3A4 isoenzyme. A 38-year-old mentally retarded male was hospital because of coffee ground emesis. His medications included lansoprazole, ranitidine, carbamaze three times a day and 400 mg at bedtime), cisapride, clonazepam, docusate, lactulose, dantrolene, and tablet. The serum carbamazepine level on admission was 6 mcg/mL. The patient seized and when seizu carbamazepine dose increased to 1000 mg/day with no further seizure activity. On hospital day 24, fluco initiated at 200 mg/day for severe tinea cruris. Three days later fluconazole was increased to 400 mg/da culture was positive for candida albicans. After 10 days of fluconazole therapy the carbamazepine level The patient showed no signs of toxicity. Carbamazepine was decreased to 200 mg four times daily which therapeutic carbamazepine levels. He was discharged on day 45 of hospitalization. This case report sug elevations in carbamazepine serum concentrations can occur with concomitant fluconazole therapy (Finc

c) Addition of fluconazole to a stable drug regimen containing carbamazepine resulted in an increased c plasma level with associated symptoms of carbamazepine toxicity (ataxia, nystagmus, diplopia, nausea, year-old female with a history of partial epilepsy had been taking carbamazepine 1600 mg/day, lamotrigi and barbexaclone 100 mg/day for many years without incident. The carbamazepine plasma level drawn to initiation of fluconazole was approximately 7.5 mcg/mL. Fluconazole was initiated at 150 mg/day for tr corporis. On the first day of fluconazole administration the patient noted episodes of blurred vision and d head movements. After 11 days of fluconazole therapy the patient complained of severe diplopia, oscillo vomiting and gait instability. Lamotrigine and barbexaclone plasma levels remained mostly unchanged, b carbamazepine plasma level increased to approximately 18.5 mcg/mL. Neurological exam revealed a ga nystagmus and smooth pursuit impairment. Twenty four hours after fluconazole withdrawal, carbamazep decreased to approximately 8 mcg/mL and neurological symptoms improved (Ulivelli et al, 2004).

3.5.1.BL Flunarizine

1) Interaction Effect: increased carbamazepine serum levels and possible toxicity (ataxia, nystagmus, diplop vomiting, apnea, seizures, coma)
2) Summary: Among patients comedicated with flunarizine and carbamazepine, a mean increase of 0.22 mc carbamazepine serum levels was noted (Pledger et al, 1994a).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Continue routine monitoring of carbamazepine serum levels. Some dose adjustmer both clinical symptoms and laboratory findings suggest carbamazepine toxicity.
7) Probable Mechanism: unknown
8) Literature Reports

a) During a 24-week trial of adjunctive flunarizine added to regimens consisting of either carbamazepine both, only patients in the group receiving carbamazepine-flunarizine showed a modest increase in mean serum levels of 0.22 mcg/mL compared to baseline. A parallel placebo-carbamazepine group showed a 0.57 mcg/mL (Pledger et al, 1994).

3.5.1.BM Fluoxetine

1) Interaction Effect: carbamazepine toxicity (ataxia, nystagmus, diplopia, headache, vomiting, apnea, seizur
2) Summary: The addition of fluoxetine to carbamazepine therapy has increased carbamazepine concentrati effects, including diplopia, blurred vision, dizziness, and tremors in some reports (Grimsley et al, 1991a; Gerr Pearson, 1990b). Conversely, no changes in steady state carbamazepine levels have been reported with the fluoxetine (Spina et al, 1993c). Symptoms of serotonin syndrome (hypertension, hyperthermia, myoclonus, m changes) have also been reported with this combination (Dursun et al, 1993a).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Due to the potential to increase carbamazepine levels, patients should be monitore carbamazepine toxicity when fluoxetine is added to therapy. Carbamazepine levels should be considered wit weeks of adding or discontinuing fluoxetine, with dosage adjustments made as indicated.
7) Probable Mechanism: decreased carbamazepine metabolism
8) Literature Reports

a) An interaction between fluoxetine and carbamazepine was reported in six normal volunteers (Grimsle Carbamazepine was given for 28 days, and fluoxetine was added to the regimen on day 7. The addition daily to carbamazepine 400 mg daily resulted in an increase in the area under the concentration-time cu carbamazepine and carbamazepine-epoxide and a decrease in clearance of carbamazepine. No signific observed in absorption, volume of distribution or elimination rate constant, indicating that fluoxetine inhib of carbamazepine.

b) The effect of fluoxetine 20 mg daily was studied for three weeks in eight epileptic patients who were s carbamazepine therapy (Spina et al, 1993b). Steady-state plasma levels of carbamazepine and its epoxi were not significantly changed with concurrent use of fluoxetine. These results differ from previous repor speculate that chronic carbamazepine administration may have resulted in enzyme induction that caused of fluoxetine, thereby lowering the chances of a metabolic interaction. Unfortunately fluoxetine levels wer

c) An interaction between fluoxetine and carbamazepine was reported in two patients receiving chronic dosages of 600 mg and 1000 mg daily respectively. Within 7 to 10 days of initiation of fluoxetine 20 mg c developed symptoms of carbamazepine toxicity. Symptoms disappeared within two weeks in one patient carbamazepine dosage reduction by 200 mg daily; in the other patient, fluoxetine was discontinued with resolution within two weeks (Pearson, 1990a).

d) Two cases of parkinsonism were reported after fluoxetine was added to an existing carbamazepine r patient, a 74-year old man, developed symptoms three days after fluoxetine 20 mg per day was added t month regimen of carbamazepine 200 mg twice daily. The patient developed cogwheel rigidity, a mask-li parkinsonian gait. After discontinuation of fluoxetine and treatment with dexetimide, the patient showed c hypertonia of the arms 17 days later. The other patient, a 53-year old woman, developed parkinsonian s fluoxetine 20 mg per day was added to an existing regimen of carbamazepine 200 mg twice daily. The p been taking thioridazine 275 mg per day which was stopped when fluoxetine was added. The patient dev rigidity and a mask-like face nine days after initiation of fluoxetine therapy (Gernaat et al, 1991).

e) A female patient experienced a drug interaction 14 days after she had fluoxetine 20 mg added to a re carbamazepine 200 mg daily. The patient presented with symptoms of serotonin syndrome, such as unc shivering, agitation, incoordination, myoclonus, hyperreflexia, and diaphoresis. The patient also had leuk thrombocytopenia. After discontinuation of fluoxetine, all symptoms of serotonin syndrome and hematolo resolved over the next 72 hours (Dursun et al, 1993).

3.5.1.BN Fluvoxamine

1) Interaction Effect: carbamazepine toxicity (ataxia, nystagmus, diplopia, headache, vomiting, apnea, seizur
2) Summary: Several cases have been reported in which fluvoxamine appeared to cause increased carbama symptoms of carbamazepine toxicity (Martinelli et al, 1993; Fritze et al, 1991b). However, one study of eight e found no such increase in carbamazepine levels with three weeks of concurrent use (Spina et al, 1993a).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Due to the potential to increase carbamazepine levels, patients should be monitore carbamazepine toxicity when fluvoxamine is added to therapy. Carbamazepine levels should be considered v discontinuing fluvoxamine, with dosage adjustments made as indicated.
7) Probable Mechanism: decreased carbamazepine metabolism
8) Literature Reports

a) The addition of fluvoxamine to a constant dosage of carbamazepine in three patients caused an incre carbamazepine levels resulting in symptoms of toxicity (Fritze et al, 1991a). The authors concluded that inhibition of carbamazepine metabolism. However, (Spina et al, 1993) found no increase in carbamazepi epileptic patients who were given fluvoxamine 100 mg daily or fluoxetine 20 mg daily with carbamazepin

3.5.1.BO Fosamprenavir

1) Interaction Effect: reduced effectiveness of fosamprenavir due to reduced serum concentrations
2) Summary: Fosamprenavir is a prodrug of amprenavir and is susceptible to amprenavir-associated drug in Coadministration of carbamazepine and fosamprenavir may result in reduced amprenavir serum concentratio LEXIVA(R) oral solution, oral tablets, 2009).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Use caution when prescribing carbamazepine to patients who take fosamprenavir. of carbamazepine and fosamprenavir may cause reduced amprenavir plasma concentrations (Prod Info LEX solution, oral tablets, 2009).
7) Probable Mechanism: induction of CYP3A4-mediated amprenavir metabolism

3.5.1.BP Fosaprepitant

1) Interaction Effect: decreased plasma concentrations and efficacy of aprepitant
2) Summary: Fosaprepitant is a prodrug of aprepitant, which is a CYP3A4 substrate. Coadministration of wit inducer, such as carbamazepine, should be approached with caution as this may lead to decreased aprepita concentrations and efficacy (Prod Info EMEND(R) IV injection, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Use caution if carbamazepine and fosaprepitant are coadministered as this may lea aprepitant levels and decreased efficacy (Prod Info EMEND(R) IV injection, 2008).
7) Probable Mechanism: induction of CYP3A4-mediated aprepitant metabolism

3.5.1.BQ Fosphenytoin

1) Interaction Effect: decreased/increased phenytoin concentrations, decreased carbamazepine concentratio
2) Summary: Fosphenytoin is a prodrug of phenytoin and the same interactions that occur with phenytoin are occur with fosphenytoin (Prod Info Cerebyx(R), 1999). Concurrent use of phenytoin and carbamazepine may carbamazepine levels (Zielinski & Haidukewych, 1987b; Randall & Tett, 1993a). The addition of carbamazepi therapy may decrease (Hansen et al, 1971d) or increase (Browne et al, 1988a) phenytoin levels.
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Serum levels of both phenytoin and carbamazepine should be measured after initia discontinuation of either agent, with appropriate dosage adjustment made accordingly. Serum levels should a following dosage adjustments and periodically thereafter.
7) Probable Mechanism: altered metabolism
8) Literature Reports

a) Twenty-four epileptic patients who were stabilized on phenytoin (PHT) and had carbamazepine (CBZ drug regimen were studied (Zielinski et al, 1985). The mean phenytoin level increased from 13.89 +/- 4.6 (35.9% increase). The effect of carbamazepine on phenytoin in an individual is unpredictable; 12 of the s change in phenytoin levels while the other 12 patients showed an average increase of 81.3% in phenyto Five of the patients with increased levels had symptoms of acute phenytoin toxicity.

b) Concomitant administration of carbamazepine and phenytoin has been reported to result in a dual int simultaneous effects of inhibition of phenytoin metabolism by carbamazepine and induction of carbamaz by phenytoin. The result is potential phenytoin intoxication and significant reductions of carbamazepine p concentrations to subtherapeutic levels. These dual effects appear to be especially significant when phe levels approach a change from linear to saturation kinetics. It is suggested that the interaction may be av minimized by adjusting phenytoin plasma levels to approximately 13 mcg/mL prior to the addition of carb regimen or increasing carbamazepine doses (Zielinski & Haidukewych, 1987).
c) Factors influencing simultaneous plasma concentrations of carbamazepine and its epoxide metabolite (McKauge et al, 1981) and it was found that plasma carbamazepine concentrations were significantly lov taking carbamazepine and phenytoin than those taking carbamazepine alone. In contrast to another stuc epoxide levels were unaltered (Pynnonen et al, 1980). Other researchers studied carbamazepine plasma four groups of epileptic patients on a variety of anticonvulsants (Christiansen & Dam, 1973). Their results administration of phenytoin or phenobarbital to patients receiving carbamazepine results in a significant carbamazepine plasma concentration when compared to patients receiving carbamazepine alone. It sho however, that some subjects in the trial were treated with carbamazepine for only one week prior to the i phenytoin. Carbamazepine has been shown to induce its own metabolism for up to 30 days after the initi thus lowering carbamazepine plasma concentration (Pynnonen et al, 1980). This may account for some carbamazepine plasma concentration in subjects also receiving phenytoin.
d) A prospective controlled study of the effects of reduction and discontinuation of phenytoin and carbar levels of concomitant antiepileptic drugs was conducted (Duncan et al, 1991). Phenytoin discontinuation 48% increase in total carbamazepine concentration and a 30% increase in free carbamazepine concentr change in carbamazepine epoxide concentrations. The authors suggest that phenytoin is a strong induce enzymes metabolizing carbamazepine to carbamazepine epoxide, but has less of an effect on the epoxi enzyme. This results in elevations in carbamazepine-epoxide/carbamazepine ratios in patients on conco Conversely, when carbamazepine was discontinued, phenytoin concentrations decreased by a mean of change in free fraction. The authors propose that this may result from inhibition of phenytoin metabolism carbamazepine. There appeared to be no impact on protein binding of either drug. Similar results were r researchers in 49 patients on concomitant phenytoin and carbamazepine therapy (Ramsay et al, 1990a)
e) If phenytoin or carbamazepine (or any prodrugs) is used in pregnant women, there is a substantially i teratogenicity with many combinations of other anticonvulsants. The teratogenicity of these drugs is large related to the levels of the reactive epoxide metabolites (Buehler et al, 1990f; Van Dyke et al, 1991f; Finr The epoxide/parent drug ratio is generally increased when phenytoin or carbamazepine is combined with other drugs that induce cytochrome P450 enzymes (3A4, 2C9, 2C19), or drugs which inhibit epoxide hyc valproic acid, progabide, and lamotrigine (Bianchetti et al, 1987f; Ramsay et al, 1990f; Spina et al, 1996e combinations increase the risk of major birth defects 3- to 4-fold over monotherapy and about 10-fold ove rates.

3.5.1.BR Ginkgo

1) Interaction Effect: decreased anticonvulsant effectiveness
2) Summary: In a case report, 2 patients with epilepsy previously well controlled by valproate sodium develo of seizures after ingesting ginkgo extract. Seizure control was regained after ginkgo was withdrawn (Granger developed seizures after exposure to 4'-O-methylpyridoxine arising from ingestion of ginkgo seeds (Yagi et a compound 4'-O-methylpyridoxine, a neurotoxin, is found in ginkgo seeds (used as food in Japan) as well as i ginkgo component from which commercially available extracts are derived (Arenz et al, 1996a). The majority products should not contain sufficient amounts of 4'-O-methylpyridoxine to cause seizures. However, ginkgo commonly assayed to assure that 4'-O-methylpyridixone is not contained in the commercial product. Of conc instances where, depending on the harvest season and the potential introduction of contamination, 4'-O-meth be present in sufficient amounts to be problematic in vulnerable populations (eg, infants or those with known
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Avoid concomitant use of ginkgo and anticonvulsants in patients with epilepsy. If se the first time or recur in patients previously controlled by anticonvulsant medication, inquire about the use of g extract. If possible, an assay should be conducted on the specific product to ascertain if 4'-O-methylpyridoxin
7) Probable Mechanism: neurotoxin 4'-O-methylpyridoxine (found in leaves and seeds of ginkgo biloba) may
8) Literature Reports

a) The serum of a 21-month-old patient with gin-nan food poisoning was assayed for 4'-O-methylpyridox serum concentration was 0.9 micrograms/milliliter (mcg/mL) at 8.5 hours after ingesting ginkgo seeds, de mcg/mL at 15.5 hours. The authors concluded that the 4'-O-methylpyridoxine content was responsible fo convulsions and loss of consciousness observed. They further observed that infants are particularly vuln 1993).

b) Four to six milligrams of the neurotoxin 4'-O-methylpyridoxine have been isolated from 2 kilograms of leaves which is the source of commercially-available products. Highest amounts were found in seeds (85 (mcg)/seed) and leaves (5 mcg/leaf) derived from the tree at the end of July and beginning of August. Th seed can contain 105.15 mcg/gram dry weight, but this is reduced to 0.75-1.32 mcg/gram dry weight wh unprocessed seed coats contain from 5.44-7.15 mcg/gram dry weight. The neurotoxin in ginkgo leaf was medications and it was even detectable in homeopathic preparations. Specifically, 8.13 mcg/mL of 4'-O-r was found in Tebonin Forte(R), 9.77 mcg/mL in Rokan(R), 3.80 mcg/mL in Kaveri Forte(R), and 7.18 mc

(R). Based on recommended daily intake, this translates into a maximum daily intake of 4'-O-methylpyrid
mcg, 58.62 mcg, 11.40 mcg, and 43.08 mcg for Tebonin Forte(R), Rokan(R), Kaveri Forte(R), and Gingi
respectively. Among the homeopathic products, Ginkgo biloba Urtinktur Hanosan(R) and Ginkgo biloba
contained 0.301 mcg/mL and 0.589 mcg/mL of 4'-O-methylpyridoxine, respectively. However, the author
amount contained in medicinal extracts of ginkgo leaves may be too low to be of clinical significance. Co
the variance in 4'-O-methylpyridoxine content depending on the season during which the ginkgo was har
al, 1996).

c) Seizures recurred in 2 patients, both with epilepsy that was well controlled prior to ingesting ginkgo bi
patients (an 84-year-old woman and a 78-year-old man) had been free of seizures for at least 18 months
therapy with Gb 120 milligrams daily to treat cognitive decline. Both patients developed seizures within 2
beginning Gb therapy, and both remained seizure-free (without changing anticonvulsant therapy) after di
(Granger, 2001).

3.5.1.BS Haloperidol

1) Interaction Effect: decreased haloperidol effectiveness

2) Summary: In a case report, the addition of carbamazepine to patients stabilized with haloperidol resulted i
of haloperidol levels by 60%. Two other case reports and a clinical study supported this finding, while a third
(Kahn et al, 1990a; Arana et al, 1986a; Fast et al, 1986; Klein et al, 1984; Hesslinger et al, 1999a).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Monitor for the therapeutic efficacy of haloperidol following the addition of carbama
haloperidol dosage may be required in some clinical situations.

7) Probable Mechanism: increased cytochrome P450 2D6 and 3A4-mediated haloperidol metabolism

8) Literature Reports

a) Serum haloperidol levels of 14 schizophrenic patients dropped an average of 50% when carbamazep
their therapy. Haloperidol doses ranged from 2 mg to 20 mg daily and the carbamazepine dose was adju
of 8 to 12 mcg/mL. The drop in haloperidol levels resulted in the worsening of one patient's condition. Tw
significant symptom reduction while on carbamazepine, despite the decrease in the haloperidol levels. T
may have been due to direct effects of the carbamazepine, or as a secondary effect due to the lowering
levels. The authors recommend monitoring serum medication levels when administering haloperidol in c
carbamazepine (Kahn et al, 1990).

b) Serum haloperidol levels of seven patients treated for psychosis fell when carbamazepine was addec
Haloperidol doses ranged from 10 mg to 40 mg daily and carbamazepine doses ranged from 400 mg to
After carbamazepine was added, haloperidol levels decreased by 19% to 100%. The two patients whose
undetectable levels had a marked worsening of symptoms. Careful monitoring should take place if carba
to haloperidol therapy (Arana et al, 1986).

c) Concomitant administration of haloperidol and carbamazepine as reported to result in neurotoxicity (c
speech, concentration difficulties) in a 37-year-old woman with cerebral palsy and dipolar disorder (Brayl
1987). Withdrawal of carbamazepine resulted in subsidence of symptoms on this second occasion. It is s
interaction occurred at the level of the CNS, as opposed to toxic effects of either drug alone, as carbama
levels were subtherapeutic during the toxic episodes and due to the fact that carbamazepine is reported
haloperidol metabolism. In addition, the patient received higher doses of carbamazepine following withdr
without the occurrence of toxic effects. Cerebral palsy may have been a predisposing factor to the intera

d) Twenty-seven schizophrenic patients enrolled in a study to determine the effects of carbamazepine a
the plasma levels of haloperidol and the psychopathologic outcome. Following a four-day washout perioc
assigned to receive treatment for four weeks with haloperidol monotherapy, haloperidol with carbamazep
with valproic acid. Doses of haloperidol remained stable throughout the study, and the doses of carbama
valproic acid were titrated to a plasma level of 6 to 12 mg/L and 50 to 100 mg/L, respectively. When adm
carbamazepine, haloperidol plasma levels decreased by 45% (from 7.6 ng/mL to 4.6 ng/mL) over the 28
Decreases in the rating scores on the Positive subscale of the Positive and Negative Syndrome Scale (p
significant during the carbamazepine phase of the study, indicating that the coadministration of carbama
haloperidol may worsen the clinical outcome compared to haloperidol monotherapy (Hesslinger et al, 19

3.5.1.BT Hydrochlorothiazide

1) Interaction Effect: hyponatremia

2) Summary: Concomitant administration of carbamazepine and diuretics (hydrochlorothiazide or furosemide
reported to result in symptomatic hyponatremia in epileptic patients (Yassa et al, 1987). It is felt that a synerg
diuretics and carbamazepine is responsible for occurrence of the hyponatremia, and that epileptic patients m
to developing this complication than are patients with affective disorders, due to the higher doses of carbama
in epilepsy.

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Monitor electrolytes during concurrent therapy. Consider discontinuing the diuretic
alternative anticonvulsant if appropriate.

7) Probable Mechanism: additive hyponatremic effects

3.5.1.BU Hydrocortisone

1) Interaction Effect: decreased hydrocortisone effectiveness
2) Summary: Carbamazepine has been demonstrated to increase the metabolism of corticosteroids (Olivesi, al, 1982). Although not specifically reported for hydrocortisone, a similar interaction could be expected.
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Monitor therapeutic efficacy of the corticosteroid. An increase in the steroid dosage after three to five days of concurrent carbamazepine therapy.
7) Probable Mechanism: increased hydrocortisone metabolism

3.5.1.BV Imatinib

1) Interaction Effect: decreased plasma levels of imatinib
2) Summary: Concurrent administration of imatinib and carbamazepine may result in a significant decrease i imatinib due to induction of CYP3A4-mediated imatinib metabolism. Caution is advised when these two agen coadministered. Alternatives to carbamazepine, with less enzyme induction potential, should be considered. ' used concurrently with carbamazepine, consider an increase in imatinib dose by at least 50% to maintain the and monitor clinical response closely (Prod Info GLEEVEC(R) oral tablets, 2005).
3) Severity: major
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Coadministration of imatinib and carbamazepine, a CYP3A4 inducer, may result in reduction in exposure to imatinib. Caution is advised when these two agents are coadministered. Consider us carbamazepine with less enzyme induction potential. However, if imatinib is used concurrently with carbamaz increase in imatinib dose by at least 50% to maintain therapeutic efficacy and monitor clinical response close
7) Probable Mechanism: induction of cytochrome P450 3A4-mediated metabolism of imatinib by carbamaze

3.5.1.BW Imipramine

1) Interaction Effect: decreased imipramine effectiveness
2) Summary: In a retrospective study of 36 children suffering from hyperactivity secondary to attention deficit antidepressant levels (imipramine and its metabolite desipramine) were decreased by 50% in children receivi compared to levels obtained with imipramine alone (Brown et al, 1990h).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor for clinical efficacy of the imipramine therapy and for any signs of toxicity of Serum levels of both agents should be considered when either agent is added or discontinued, with appropria adjustments made accordingly.
7) Probable Mechanism: increased imipramine metabolism
8) Literature Reports
a) In a retrospective study, of 36 children with attention deficit hyperactivity disorder, the average plasm imipramine was significantly lower in patients treated with carbamazepine concurrently. The average dos was 1.3 mg/kg in patients receiving imipramine alone, compared to an imipramine dose of 1.8 mg/kg in p both imipramine and carbamazepine. The plasma level of imipramine, desipramine, and total tricyclic ant plasma levels were significantly lower in patients treated with carbamazepine concurrently. The dose of i need to be increased if carbamazepine is added to therapy and the dose of imipramine may need to be carbamazepine is stopped (Brown et al, 1990g).
b) Combination therapy with carbamazepine decreases steady-state total serum concentrations of imipr concentrations of desipramine. Thirteen patients were treated with imipramine 2 mg/kg/day for 3 weeks, carbamazepine 400 mg/day was added. The ratios of total concentrations of imipramine to desipramine and two weeks after carbamazepine intake (0.7 +/- 0.41 versus 0.63 +/- 0.36; p greater than 0.05). Free imipramine and desipramine were elevated after the addition of carbamazepine. Despite lowever imiprar desipramine total concentrations, the combination treatment with carbamazepine in depressed patients i tolerated. Dosage increase of imipramine does not appear to be necessary in the depressed patients inc (Szymura-Oleksiak et al, 2001).

3.5.1.BX Indinavir

1) Interaction Effect: decreased indinavir plasma concentrations and an increased risk of antiretroviral therap
2) Summary: Inducers of cytochrome P450 3A4 enzymes, including carbamazepine, may decrease the plasi of indinavir during concurrent therapy. Decreased plasma concentrations of indinavir may cause antiretrovira Caution should be observed when these two drugs are given together. If alternative therapy is not possible, c adjustments, therapeutic drug monitoring, and close clinical observation should be utilized to reduce adverse consequences (Prod Info Crixivan(R), 2004; Hugen et al, 2000a).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Concurrent treatment with indinavir and carbamazepine should be undertaken caut patient for an adequate response to indinavir therapy. Alternatives to carbamazepine therapy should be cons

7) Probable Mechanism: induction of cytochrome P450 3A4-mediated indinavir metabolism
8) Literature Reports
a) A 48-year-old HIV-positive male was started on triple therapy consisting of indinavir 800 mg every eig lamivudine 150 mg twice daily, and zidovudine 200 mg three times daily with a resulting undetectable HI later. Because of the development of postherpetic neuralgia, carbamazepine 200 mg daily was initiated a approximately 10 weeks. His indinavir concentrations drawn during carbamazepine therapy were 25% ar population values, whereas before carbamazepine was started, they were slightly below the lower limit o population curve. Two weeks following the discontinuation of carbamazepine, the HIV-RNA was detectal to lamivudine therapy was observed in a blood sample. A further increase in HIV-RNA prompted his anti to be switched to nevirapine, didanosine, and zidovudine. Carbamazepine is an inducer of the cytochrom enzyme system, while indinavir is a substrate of this pathway. Decreased indinavir concentrations cause between indinavir and carbamazepine is the most likely explanation for the increased HIV-RNA and the c lamivudine resistance in this patient (Hugen et al, 2000).

3.5.1.BY Influenza Virus Vaccine

1) Interaction Effect: increased carbamazepine serum concentrations
2) Summary: Influenza vaccine has been reported to cause a decrease in the elimination and an increase in carbamazepine, resulting in an increase in the carbamazepine plasma concentration (Jann & Fidone, 1986a; 1990). It has been proposed that the immune response after influenza vaccination may cause a depression o P450 isoenzymes responsible for oxidation of carbamazepine (Robertson, 2002a).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: The majority of patients might experience only a transient and slight increase in car levels. No routine monitoring appears necessary.
7) Probable Mechanism: decreased cytochrome P450-mediated metabolism of carbamazepine
8) Literature Reports
a) In a study conducted on mentally retarded residents who were receiving single-drug anticonvulsant th vaccine resulted in increased levels of phenytoin, phenobarbital, and carbamazepine. Prior to vaccinatio carbamazepine concentration was 6.17 mcg/mL. Serum carbamazepine concentrations were measured to vaccination (day 0), and on days 7, 14, and 28. On day 7, the mean carbamazepine concentration hac 6.89 mcg/mL. By day 14 and 28, concentrations had increased and decreased to 9.04 mcg/mL and 8.65 respectively. Similar increases in plasma concentrations were observed in patients receiving phenobarbi The proposed mechanism for the increased carbamazepine concentration is that influenza vaccine decre of hepatic enzymes which are responsible for carbamazepine metabolism (Jann & Fidone, 1986).
b) Influenza vaccination may significantly increase carbamazepine blood levels. A report describes a ca carbamazepine toxicity that developed 13 days after administration of the influenza vaccine. A female 14 old complained of ataxia and increased lethargy. Her drug regimen included carbamazepine for partial c and gabapentin. Thirteen days prior to her complaints the patient received the inactivated influenza vacc manufactured by Aventis Pasteur, Inc (Swiftwater, PA). Thirteen days later the child complained of naus subsequently vomited. She was dizzy, had slurred speech, became lethargic and poorly responsive. In th department her CBZ level was 27.5 mcg/mL and a urine drug screen was positive for TCAs and cocaine intubated, received IV fluids and activated charcoal. Four days after admission her CBZ level was 9.1 mc recovered and remains seizure free on her former dose of CBZ (400 mg am and 600 mg pm) and gabap TID). The author concludes that the patients immune response after influenza vaccination caused a depr isoenzymes responsible for oxidation of CBZ. This resulted in a rise in CBZ levels and observed CBZ tox instances of CBZ toxicity may be secondary to inhibition of hepatic clearance by interferon production (R

3.5.1.BZ Iproniazid

1) Interaction Effect: hypertensive urgency, hyperpyrexia, and seizures
2) Summary: Concomitant MAO inhibitor and carbamazepine therapy is contraindicated (Prod Info Tegretol(Simultaneous use may theoretically result in hyperpyrexia, excitation, and seizure activity (Prod Info Parnate(Info Tegretol(R), 1998b; Thweatt, 1986b). However, there is preliminary evidence that the combination of car an MAOI may be safe and efficacious, even in some refractory cases (Ketter et al, 1995e; Barker & Eccleston controlled studies are needed.
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of carbamazepine and monoamine oxidase inhibitors contraindicated by the manufacturer. Monoamine oxidase inhibitors should be discontinued for a minimum of if the clinical situation permits, before carbamazepine therapy is initiated.
7) Probable Mechanism: unknown
8) Literature Reports
a) A double-blind study was conducted in ten inpatients with depression that had proven refractory to mu therapies (electroconvulsive therapy, tricyclic antidepressants, monoamine oxidase inhibitors, lithium, ca benzodiazepines, and antipsychotics). In addition to their regular carbamazepine and lithium doses, four phenelzine (mean maximum dose 67.5 mg daily) and six patients received tranylcypromine (mean maxir daily) for a mean duration combination therapy of 52.2 days. During MAOI coadministration, serum conc

carbamazepine and lithium did not change significantly from baseline values. Self-rated side effects were different. Four patients (three on phenelzine and one on tranylcypromine) responded to this therapy and discharged (Ketter et al, 1995d).

b) A 60-year-old woman who had an atypical endogenous, depressive illness of psychotic intensity was intermittently with cyclic antidepressants and intermittent electroconvulsive therapy. Following an acute v illness, she was treated successfully with a combination of phenelzine and L-tryptophan. Following a few improvement, her situation worsened and she was subsequently treated with zimelidine and lithium. Faili placed on a regimen of tranylcypromine with doses increasing progressively up to 30 mg daily in conjunc and tryptophan. Subsequently, carbamazepine was added in small doses with increments to achieve a p approximately 5 mg/L. This regimen proved successful, and she was discharged home and had remaine two months of follow up at the time of publication (Barker & Eccleston, 1984d).

c) Addition of tranylcypromine to carbamazepine therapy did not significantly affect carbamazepine seru presented (Joffe et al, 1985b). Conversely, five patients on tranylcypromine were reported to need a mea carbamazepine 1040 mg to achieve a carbamazepine blood level of 8.0-11.1 mcg/mL. Four other patient phenelzine only required a mean daily dose of carbamazepine 450 mg to attain a blood level of 8.7-10.9 et al, 1992b).

3.5.1.CA Irinotecan

1) Interaction Effect: substantially decreased exposure to irinotecan and its active metabolite SN-38 and may irinotecan efficacy

2) Summary: Concomitant use of carbamazepine and irinotecan has resulted in a substantially decreased ex irinotecan and its active metabolite SN-38 in both adult and pediatric patients. This decreased exposure is du carbamazepine induction of CYP3A4-mediated metabolism of irinotecan and may decrease the efficacy of iri An alternative non-enzyme inducing anticonvulsant should be considered. Substitution should be implemente weeks prior to initiation of irinotecan therapy (Prod Info Camptosar(R) Injection, 2004).

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: Consider a non-enzyme inducing anticonvulsant alternative for those patients requi therapy. Begin substitution at least 2 weeks prior to initiation of irinotecan therapy. The appropriate starting d for patients on CYP3A4 inducing anticonvulsants has not yet been established.

7) Probable Mechanism: induction of CYP3A4-mediated irinotecan metabolism

3.5.1.CB Isocarboxazid

1) Interaction Effect: hypertensive urgency, hyperpyrexia, and seizures

2) Summary: Concomitant MAO inhibitor and carbamazepine therapy is contraindicated (Prod Info Tegretol(Info Marplan(R), 1998). Simultaneous use may theoretically result in hyperpyrexia, excitation, and seizure ac Parnate(R), 1995h; Prod Info Tegretol(R), 1998i; Thweatt, 1986i). However, there is preliminary evidence tha of carbamazepine and an MAOI may be safe and efficacious, even in some refractory cases (Ketter et al, 19 Eccleston, 1984s). Further controlled studies are needed.

3) Severity: contraindicated

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of carbamazepine and monoamine oxidase inhibitors contraindicated by the manufacturer. Monoamine oxidase inhibitors should be discontinued for a minimum of if the clinical situation permits, before carbamazepine therapy is initiated.

7) Probable Mechanism: unknown

8) Literature Reports

a) A double-blind study was conducted in ten inpatients with depression who had proved refractory to m therapies (electroconvulsive therapy, tricyclic antidepressants, monoamine oxidase inhibitors, lithium, ca benzodiazepines, and antipsychotics). In addition to their regular carbamazepine and lithium doses, four phenelzine (mean maximum dose 67.5 mg daily) and six patients received tranylcypromine (mean maxir daily) for a mean duration combination therapy of 52.2 days. During MAOI coadministration, serum conc carbamazepine and lithium did not change significantly from baseline values. Self-rated side effects were different. Four patients (three on phenelzine and one on tranylcypromine) responded to this therapy and discharged (Ketter et al, 1995r).

b) A 60-year-old woman who had an atypical endogenous, depressive illness of psychotic intensity was intermittently with cyclic antidepressants and intermittent electroconvulsive therapy. Following an acute v illness, she was treated successfully with a combination of phenelzine and L-tryptophan. Following a few improvement, her situation worsened and she was subsequently treated with zimelidine and lithium. Faili placed on a regimen of tranylcypromine with doses increasing progressively up to 30 mg daily in conjunc and tryptophan. Subsequently, carbamazepine was added in small doses with increments to achieve a p approximately 5 mg/L. This regimen proved successful, and she was discharged home and had remaine two months of follow up at the time of publication (Barker & Eccleston, 1984r).

c) Addition of tranylcypromine to carbamazepine therapy did not significantly affect carbamazepine seru case (Joffe et al, 1985i). Conversely, five patients on tranylcypromine needed a mean daily dose of carb mg to achieve a carbamazepine blood level of 8.0-11.1 mcg/mL (Barklage et al, 1992i). Four other patier phenelzine only required a mean daily dose of carbamazepine 450 mg to attain a blood level of 8.7-10.9

3.5.1.CC Isoniazid

1) Interaction Effect: elevated carbamazepine levels and toxicity (ataxia, nystagmus, diplopia, headache, vor seizures, coma)

2) Summary: Concomitant carbamazepine and isoniazid therapy has been reported to produce increases in serum concentrations and toxicity at isoniazid doses of 200 mg daily or more (Block, 1982a; Wright et al, 198 changes were noted in 10 of 13 epileptics following the addition of isoniazid 200 mg daily to their maintenanc therapy (Valsalan & Cooper, 1982). Carbamazepine may increase isoniazid liver toxicity (Wright et al, 1982a)

3) Severity: moderate

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: Watch for signs of carbamazepine toxicity such as nausea, vomiting, drowsiness ar consider monitoring serum carbamazepine levels following the addition of isoniazid; lower carbamazepine do required. Conversely, if isoniazid is discontinued or the dosage reduced, carbamazepine levels should be mo dose adjusted accordingly. Usual anticonvulsant levels are 6-12 mg/L.

7) Probable Mechanism: decreased carbamazepine metabolism

8) Literature Reports

a) Five days after concurrent use of carbamazepine with isoniazid 300 mg daily, a patient presented wit headache, vomiting, drowsiness, and confusion. Carbamazepine serum levels had increased from 5 mcg mcg/mL. The patient was also receiving phenytoin, with levels increasing from 13 to 18 mcg/mL; this was in the therapeutic range and not related to an interaction with carbamazepine. Upon withdrawal of the iso carbamazepine level decreased to 6 mcg/mL within seven days, and the phenytoin level remained at 18 patient's symptoms disappeared at day 2. However, it is difficult to rule out the effects of phenytoin as a p toxicity, since some patients may present with toxic symptoms at these serum concentrations (Block, 198

b) Administration of isoniazid to a patient receiving chronic carbamazepine therapy resulted in significar carbamazepine clearance as well as delayed isoniazid-induced hepatotoxicity. This was presumably rela carbamazepine's microsomal enzyme metabolism by isoniazid and increased metabolism of isoniazid to metabolite (acetylhydrazine) by carbamazepine (Wright et al, 1982).

c) One study reported a case of carbamazepine toxicity following the addition of antituberculosis medica anticonvulsant medication. Carbamazepine levels had previously been 8.5 to 9.5 mcg/mL without eviden Isoniazid 300 mg daily was well tolerated for three days prior to the introduction of rifampin 600 mg daily. of initiation of rifampin, the patient developed nausea, ataxia, confusion and drowsiness. The carbamaze noted to be 16.9 mcg/mL. The authors suggest that rifampin may have augmented the enzyme inhibiting isoniazid, resulting in carbamazepine toxicity (Fleenor et al, 1991).

3.5.1.CD Itraconazole

1) Interaction Effect: loss of itraconazole efficacy

2) Summary: Concomitant administration of itraconazole and carbamazepine has resulted in subtherapeutic concentrations and therapeutic failure (Hay et al, 1988; Tucker et al, 1992a). Itraconazole is a known inhibito P450 3A4 enzyme system, which is the major isoform responsible for the metabolism of carbamazepine. Bas metabolic pathways, it seems possible that itraconazole could inhibit the metabolism of carbamazepine, resu plasma concentrations of carbamazepine (Prod Info Sporonox(R), 2002; Prod Info Tegretol(R), 1997). Howev not been reported to date.

3) Severity: moderate

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: Monitor antifungal therapy for clinical efficacy; larger itraconazole doses may be rec situations.

7) Probable Mechanism: induction by carbamazepine of cytochrome P450 3A4-mediated itraconazole metab

8) Literature Reports

a) Interactions between azole antifungals and rifampin, phenytoin, and carbamazepine have been descr 1992). Twelve patients receiving a combination of these agents for systemic mycoses experienced drug resulted in substantial decreases in the azole serum concentrations. All four of the patients who received concurrent phenytoin or carbamazepine failed to respond to the antifungal therapy or suffered a relapse These four patients had undetectable or substantially lower serum concentrations of the azole compared measured during therapy with the azole alone.

3.5.1.CE Ixabepilone

1) Interaction Effect: decreased ixabepilone plasma concentrations

2) Summary: Ixabepilone is a CYP3A4 substrate. Coadministration of a strong CYP3A4 inducer, such as car ixabepilone may result in decreased ixabepilone plasma concentrations leading to subtherapeutic ixabepilone using alternative therapeutic agents with low enzyme induction potential for coadministration with ixabepilone IXEMPRA(TM) IV injection, 2007).

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concomitant administration of carbamazepine, a strong CYP3A4 inducer, and ixabe substrate, may result in decreased ixabepilone plasma concentrations and consequently, subtherapeutic leve

alternative therapeutic agents with low enzyme induction potential for coadministration with ixabepilone (Proc (TM) IV injection, 2007).
7) Probable Mechanism: induction of CYP3A4-mediated ixabepilone metabolism

3.5.1.CF Ketoconazole
1) Interaction Effect: increased carbamazepine serum levels
2) Summary: Ketoconazole, a CYP 3A4 enzyme system inhibitor, can inhibit the metabolism of carbamazepi plasma carbamazepine levels would be expected (Prod Info Tegretol(R), 2002).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: If carbamazepine and ketoconazole are administered together, carefully monitor se carbamazepine levels and monitor the patient for signs and symptoms of toxicity.
7) Probable Mechanism: inhibition of CYP 3A4 mediated metabolism of carbamazepine

3.5.1.CG Lamotrigine
1) Interaction Effect: reduced lamotrigine efficacy, loss of seizure control, and a potential risk of neurotoxicity nystagmus, ataxia)
2) Summary: The clearance of lamotrigine may double during concomitant therapy with carbamazepine (Goa Rambeck & Wolf, 1993; Ramsay et al, 1991a; Mikati et al, 1989a; Jawad et al, 1987a). In addition, increased concentrations of carbamazepine-10,11-epoxide (an active metabolite of carbamazepine) and neurotoxicity h during concomitant administration of carbamazepine and lamotrigine (Wolf, 1992; Warner et al, 1992). Other found that lamotrigine had no effect on either carbamazepine or its metabolite (Schapel et al, 1991; Pisani et & Boreus, 1997a). While lamotrigine has no appreciable effect on the steady-state carbamazepine concentra carbamazepine decreases the lamotrigine steady-state level by 40% (Prod Info Lamictal(R), 2003).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor seizure control and follow patients for signs of neurotoxicity (nausea, vertig ataxia). Anticipate a possible need to increase lamotrigine doses and/or reduce carbamazepine doses. It may to monitor the serum concentration of both carbamazepine and its metabolite, carbamazepine-10,11-epoxide effects have been associated with carbamazepine-10,11- epoxide serum levels above 9 micromoles/liter. Wh combination with an enzyme-inducing antiepileptic agent, the manufacturer recommends an initial lamotrigine once daily for the first two weeks for adult patients, followed by 50 mg twice daily for the third and fourth weel 100 mg daily every two weeks to a total daily dose of 300 mg to 500 mg administered in two divided doses.
7) Probable Mechanism: hepatic induction by carbamazepine of lamotrigine metabolism; possible alteration elimination by lamotrigine
8) Literature Reports
a) While lamotrigine alone has a steady-state elimination half-life of between 25 to 37 hours, coadminist carbamazepine reduces the half-life to approximately 14 or 15 hours (Binnie et al, 1986; Jawad et al, 198 Lamotrigine clearance ranged from 0.021 to 0.035 L/h/kg (0.35 to 0.59 mL/min/kg) in healthy volunteers alone (Cohen et al, 1987; Posner et al, 1989; Posner et al, 1991). Comparable values during combinatio from 0.044 to 0.084 L/h/kg (0.73 to 1.4 mL/min/kg) (Jawad et al, 1987; Mikati et al, 1989; Ramsay et al, Carbamazepine was found to decrease incrementally the half-life of lamotrigine by 1.7 hours for every 1 carbamazepine within the dosing range of 800 to 1600 mg daily (Jawad et al, 1987).
b) If phenytoin or carbamazepine (or any prodrugs) is used in pregnant women, there is a substantially i teratogenicity with many combinations of other anticonvulsants. The teratogenicity of these drugs is large related to the levels of the reactive epoxide metabolites (Buehler et al, 1990g; Van Dyke et al, 1991g; Fir The epoxide/parent drug ratio is generally increased when phenytoin or carbamazepine is combined with other drugs that induce cytochrome P450 enzymes (3A4, 2C9, 2C19), or drugs which inhibit epoxide hyc valproic acid, progabide, and lamotrigine (Bianchetti et al, 1987g; Ramsay et al, 1990g; Spina et al, 1996 combinations increase the risk of major birth defects 3- to 4-fold over monotherapy and about 10-fold ov rates.
c) No pharmacokinetic interaction between carbamazepine and lamotrigine was found in children. Three eleven children with intractable generalized epilepsy who had been treated with carbamazepine for longe started lamotrigine 1 mg/kg/day divided into two daily dosages. The lamotrigine dose was increased by 1 other week until clinical response or side effects occurred. The mean carbamazepine levels did not chan from baseline when lamotrigine was coadministered (29.9 mmol/L vs. 28.8 mmol/L). In addition, the plas of the active metabolite of carbamazepine, carbamazepine-10,11-epoxide, significantly decreased from 6 mmol/L with lamotrigine therapy (Eriksson & Boreus, 1997).
d) Carbamazepine reduces the plasma levels of lamotrigine. A 65-year-old male suffering from complex for 40 years was receiving carbamazepine (400 mg three times daily) and lamotrigine (200 mg three time occurred at least twice a week. Steroids, ipratropium bromide and a beta-agonist were used for an obstru disease. A current pneumonia was being treated with an oral amoxicillin preparation. A trough lamotrigin mcmol/mL and a trough carbamazepine was 11 mcmol/mL. The patient continued to suffer from seizures was gradually replaced by levitiracetam (1500 mg twice daily) within 4 weeks. After 4 weeks of levitiracet patient's carbamazepine plasma levels were 1.3 mcmol/mL and lamotrigine plasma levels were 12.1 mc Lamotrigine levels increased rapidly after reductions in the carbamazepine dose. Levetiracetam and lam

combination was well tolerated and seizures stopped completely after 4 weeks. A drug interaction should when carbamazepine and lamotrigine result in ineffective antiepileptic therapy (Koch et al, 2003).

3.5.1.CH Lapatinib

1) Interaction Effect: decreased lapatinib exposure or plasma concentrations

2) Summary: In healthy participants, concurrent administration of lapatinib with carbamazepine, a CYP3A4-in 100 mg twice daily for 3 days and 200 mg twice daily for 17 days led to a 72% decrease in lapatinib AUC. Th recommended that concurrent use of carbamazepine with lapatinib be avoided. However, if these agents mus concurrently, then depending on tolerability, a gradual titration of lapatinib dose from 1250 mg/day up to 4500 considered. This adjustment is recommended based on pharmacokinetic data and would be expected to adju the therapeutic ranges achieved without CYP3A4 inducers. However, no clinical data is currently available wi adjustments. If carbamazepine is discontinued, the increased lapatinib dose should be reduced to the indicat TYKERB(R) oral tablets, 2007).

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: Coadministration of lapatinib with carbamazepine, a CYP3A4-inducer, resulted in si decreased lapatinib AUC and should be avoided. However, if concurrent use is warranted, then consider titra lapatinib gradually from 1250 mg/day up to 4500 mg/day, depending on tolerability. Once carbamazepine is d reduce the increased lapatinib dose to the indicated dose (Prod Info TYKERB(R) oral tablets, 2007).

7) Probable Mechanism: induction of CYP3A4-mediated lapatinib metabolism

3.5.1.CI Levetiracetam

1) Interaction Effect: symptoms of carbamazepine toxicity (nystagmus, ataxia, dizziness, double vision)

2) Summary: In pharmacokinetic and clinical studies, concurrent administration of carbamazepine and levetir affect serum levels of either drug (Prod Info KEPPRA(R) oral solution, tablets, 2006). However, in post-marke coadministration of these agents resulted in symptoms consistent with carbamazepine toxicity in 4 individuals refractory epilepsy. While the exact mechanism for this interaction is unknown, it is postulated to be pharmac pharmacokinetic, in origin. Caution is advised when these agents are prescribed together. Patients may neec closely for symptoms of carbamazepine toxicity (nystagmus, ataxia, dizziness, double vision). Reduction of c dosage may be necessary to resolve the symptoms (Sisodiya et al, 2002).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Although in pharmacokinetic and clinical studies, coadministration of carbamazepin levetiracetam did not significantly affect serum levels of either drug (Prod Info KEPPRA(R) oral solution, table marketing experience, coadministration of these agents resulted in symptoms consistent with carbamazepine individuals with severe refractory epilepsy. Therefore, use caution when these agents are prescribed togethe need to be monitored closely for symptoms of carbamazepine toxicity (nystagmus, ataxia, dizziness, double v of carbamazepine dosage may be necessary to resolve the symptoms (Sisodiya et al, 2002).

7) Probable Mechanism: unknown

8) Literature Reports

a) Symptoms of carbamazepine toxicity occurred with coadministration of carbamazepine and levetiracet severe refractory epilepsy. The patients, aged 31 to 57 years old, received levetiracetam as add-on thera anti-epileptic drug (AED) therapy, which included monotherapy with carbamazepine 600 mg twice daily i polytherapy in the other 3 cases, with medications including carbamazepine 600 to 1600 mg/day (regula release), sodium valproate, lamotrigine, primidone, or phenobarbital. Levetiracetam was initiated at 500 daily and slowly titrated up to either 500 mg twice daily (in 2 cases), 1000 mg twice daily (in 1 case), or 1 case). Following introduction of levetiracetam, serum blood levels in 3 of the cases were within the norm ranges for all the AEDs. However, in all 4 cases, upward titration of levetiracetam led to symptoms consi carbamazepine toxicity, which included unsteadiness of gait, nystagmus, double vision, dizziness, nause 1 patient, symptoms worsened upon further increase in levetiracetam dose from 500 mg twice daily to 25 Symptoms resolved with a reduction in carbamazepine dosage from 600 mg once daily or twice daily to twice daily, respectively (in 2 cases), and from 800 mg twice daily to 600 mg twice daily (in 1 case). One discontinued levetiracetam on her own accord following symptom onset and data are not available with r symptom resolution. While the exact mechanism for this interaction is unknown, based on serum levels, interactions or altered compliance were ruled out. It was postulated that this interaction may be pharmac (Sisodiya et al, 2002).

3.5.1.CJ Levonorgestrel

1) Interaction Effect: a decrease in plasma concentrations of estrogens and in estrogen effectiveness

2) Summary: Breakthrough bleeding, spotting, and pregnancy have been reported in women on anticonvulsa contraceptives (Prod Info Ortho Evra(TM), 2001; Mattson et al, 1986a; Crawford et al, 1986; Haukkamaa, 198

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: In some women the use of higher estrogen content in the contraceptive may be suf use of alternate methods of birth control may be necessary.

7) Probable Mechanism: increased metabolism of contraceptive steroids
8) Literature Reports
a) Concomitant administration of oral contraceptives with enzyme-inducing anticonvulsant agents, prima phenytoin, carbamazepine, or primidone, has been reported to result in an increased failure rate of contr et al, 1986). The benzodiazepines and valproic acid have not been associated with increased failure rate receiving oral contraceptives. Increasing the dose of ethinyl estradiol or mestranol in oral contraceptives breakthrough bleeding and decrease the risk of conception. However, higher doses of estrogens may als of vascular side effects, primarily in patients where enzyme induction does not occur. It is recommended estrogen and progestin be given initially in patients receiving an enzyme inducing anticonvulsant; howev pregnancy is a special concern, a moderate dose formulation (50 mcg ethinyl estradiol) should be consic breakthrough bleeding occurs with low-dose contraception, progressive increases in the dose of mestrar (up to 80 mcg) should be considered. If spotting occurs, it is suggested that the contraceptive not be disc rather that a traditional method of barrier contraception be initiated during the remainder of that cycle. Sv dose oral contraceptive is recommended if enzyme inducing anticonvulsants are discontinued in women moderate or high-dose contraceptives.
b) Carbamazepine reduced the area under the plasma concentration time curve (AUC) of ethinyl estrad 4 women taking carbamazepine 300 to 600 mg daily within 8 to 12 weeks of initiation of therapy. Norges also significantly reduced to 29% to 57% of baseline. The authors suggest that breakthrough bleeding ca most women with use of oral contraceptives containing 80 to 100 mcg ethinyl estradiol (Crawford et al, 1
c) Accidental pregnancy occurred in a 20-year-old epileptic who was using phenytoin 400 mg daily plus 400 mg daily (Haukkamaa, 1986). The plasma concentration of levonorgestrel in this patient was very lo pg/mL) when compared to controls (325 +/- 135 pg/mL). Carbamazepine appears to decrease plasma le concentrations by enhancing the hepatic metabolism of the steroid via enzyme induction. Levonorgestrel relied upon as the sole means of contraception in patients on anticonvulsant therapy.

3.5.1.CK Levothyroxine

1) Interaction Effect: decreased levothyroxine effectiveness
2) Summary: Concomitant use of carbamazepine and levothyroxine may decrease levothyroxine efficacy by metabolism potentially resulting in hypothyroidism. Carbamazepine may also reduce serum protein binding o total- and free- T4 by 20% to 40%. If concurrent use of carbamazepine and levothyroxine is required, an incre levothyroxine dose may be necessary (Prod Info SYNTHROID(R) oral tablets, 2008; Prod Info LEVOTHYRO oral tablet, 2007).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of carbamazepine and levothyroxine may result in reduced levoth As a result, an increase in the levothyroxine dose may be required (Prod Info SYNTHROID(R) oral tablets, 2(LEVOTHYROXINE SODIUM(R) oral tablet, 2007). Consider monitoring TSH levels and/or other measures of when carbamazepine is initiated or discontinued during levothyroxine treatment.
7) Probable Mechanism: increased hepatic metabolism of levothyroxine

3.5.1.CL Lithium

1) Interaction Effect: additive neurotoxicity (weakness, tremor, nystagmus, asterixis)
2) Summary: Case reports have described the development of neurotoxicity during concurrent administratior carbamazepine despite normal therapeutic levels of either drug (Rittmannsberger, 1996a; Chaudhry & Water & Richens, 1980).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor for signs of neurotoxicity with concomitant therapy; serum levels have not b predicting this adverse effect. If neurotoxicity occurs, one or both of the agents may need to be discontinued.
7) Probable Mechanism: unknown
8) Literature Reports
a) A potential interaction between lithium and carbamazepine has been reported (Chaudhry & Waters, 1 a 22-year-old woman with bipolar affective disorder, developed neurotoxicity despite therapeutic plasma drugs. Previous reports of neurotoxicity due to either of these agents have occurred when recommendec were exceeded. Toxicity due to carbamazepine was not observed in this case when the plasma level wa (therapeutic: 8 to 12 mcg/mL). Similarly, no neurotoxicity occurred with plasma lithium levels of 0.9 mEq/ to 1.4 Eq/L). However, when the drugs were administered concurrently, neurotoxicity, characterized by u truncal tremors, ataxia, horizontal nystagmus, hyperflexia of all four limbs, and occasional muscle fascicu within three days. Plasma levels of lithium and carbamazepine were 0.9 mEq/L and 7.6 mcg/mL, respect discontinuation of carbamazepine, neurologic symptoms subsided within three days. Therapeutic plasma two drugs administered concomitantly may lead to acute neurotoxicity.
b) Neurotoxic syndromes developed in five manic patients treated with a combination of lithium and carb although all five had therapeutic plasma levels of both drugs (Shukla et al, 1984). The clinical picture of t consisted of symptoms of confusion, drowsiness, generalized weakness, lethargy, coarse tremor, hyperr cerebellar signs. Patients with previous lithium-induced neurotoxicity and those with underlying CNS dise disease appeared to be at greater risk for developing the neurotoxicity when the combination of the two

c) The laboratory effects of adding lithium to carbamazepine were examined in 23 patients with affective (Kramlinger & Post, 1990). The combination produced additive antithyroid effects, particularly on T4 and addition of lithium resulted in prompt reversal of carbamazepine-induced leukopenia.
d) An analysis of the data from other researchers (Chaudhry & Waters, 1983; Shukla et al, 1984) was p (McGinness et al, 1990). The analysis demonstrated no synergistic toxicity between the two drugs, but n hypothetical plot of blood levels of both drugs that lithium appears to contribute more significantly to the t The authors further concluded that usually used therapeutic ranges cannot be used in monitoring for toxi drugs are used together and a two-dimensional plot of serum levels may be of assistance in ascertaining serum levels with combinations of drugs.
e) Over a three-year period, some drug combinations were observed to cause a greater risk of asterixis in patients on a regimen of multiple psychopharmacologic agents (Rittmannsberger, 1996). With regard t clozapine, and lithium, the incidence of asterixis was greatest in those patients that were on at least two agents. Serum levels of all three drugs were within normal therapeutic ranges, suggesting an additive eff therapy rather than the effect of a single agent.
f) Lithium intoxication occurred in a patient following carbamazepine-induced renal failure. A 33-year-old with bipolar manic-depressive disorder was treated with lithium for the last 18 months. Carbamazepine 6 to his drug regimen. Serum lithium levels were 1.08 mEq/L and serum carbamazepine concentration was weeks later. Upon admission he was stuporous but arousable. His serum creatinine was 6.5 mg/dL, and carbamazepine concentration was 11mcg/mL and serum lithium concentration was 3.5 mEq/L. After 2 L was administered, this patient developed pulmonary edema. After one session of hemodialysis, serum lit concentrations decreased to 1.3 mEq/d, and serum creatinine decreased to 3.5 mg/dL. Three weeks late was 1.0 mg/dL and lithium concentrations were within the therapeutic range. Renal failure was most likel carbamazepine induced interstitial nephritis. Patients who are treated with lithium and carbamazepine sh carefully to prevent carbamazepine-induced interstitial nephritis. The presence of fever, eosinophiluria, u casts, and the patients improvement after withdrawal of carbamazepine support the diagnosis of interstit Patients who are treated with lithium and carbamazepine should be followed carefully to prevent carbam interstitial nephritis (Mayan et al, 2001).

3.5.1.CM L-Methylfolate

1) Interaction Effect: decreased carbamazepine serum levels
2) Summary: Concomitant administration of first-generation anticonvulsants, including carbamazepine, with l folate may lead to decreased serum levels of the anticonvulsant, thereby decreasing carbamazepine efficacy risk of seizures. Although there have been no such reports with the use of carbamazepine and l-methylfolate, if these agents are used concomitantly (Prod Info DEPLIN(R) oral tablets, 2006; Prod Info Zervalx(R) oral tab Monitor patients for loss of carbamazepine efficacy.
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Caution is advised if l-methylfolate is prescribed to patients receiving carbamazepir folate may theoretically result in decreased serum carbamazepine levels, thereby reducing carbamazepine e increasing the frequency of seizures (Prod Info DEPLIN(R) oral tablets, 2006; Prod Info Zervalx(R) oral tablet agents are used concomitantly, monitor patients for loss of carbamazepine efficacy.
7) Probable Mechanism: unknown

3.5.1.CN Lopinavir

1) Interaction Effect: decreased lopinavir exposure; increased serum carbamazepine levels and toxicity
2) Summary: Coadministration of carbamazepine and lopinavir/ritonavir may result in reduced lopinavir seru resulting from carbamazepine induction of CYP3A metabolism. The effectiveness of lopinavir/ritonavir is likely in patients receiving concurrent carbamazepine therapy due to reduced lopinavir bioavailability. The once dai for lopinavir/ritonavir should not be used when a patient is also taking carbamazepine (Prod Info KALETRA(F solution, 2005). Carbamazepine toxicity has been reported in an HIV-positive patient upon concomitant treatr lopinavir/ritonavir, as part of a highly active antiretroviral regimen. This may be a result of inhibition of CYP3A carbamazepine metabolism by the protease inhibitors. If used concurrently with lopinavir/ritonavir, consider re carbamazepine dose by 25 to 50%. Additionally, monitor patients for serum carbamazepine levels, 3 to 5 day lopinavir/ritonavir (Bates & Herman, 2006).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Use caution with the coadministration of carbamazepine and lopinavir/ritonavir due lopinavir metabolism. Do not use a once daily dosing regimen of lopinavir/ritonavir concurrently with carbama Additionally, coadministration of carbamazepine with a lopinavir/ritonavir-containing highly active antiretrovira resulted in increased serum carbamazepine levels and toxicity. If used concurrently with lopinavir/ritonavir, co the carbamazepine dose by 25 to 50%. Additionally, monitor patients for serum carbamazepine levels, 3 to 5 initiating the protease inhibitor.
7) Probable Mechanism: carbamazepine induction of CYP3A-mediated lopinavir metabolism; inhibition of CY carbamazepine metabolism by lopinavir/ritonavir
8) Literature Reports
a) Symptoms of carbamazepine toxicity developed in a 50-year-old HIV-positive male upon addition of l

his highly active antiretroviral therapy (HAART). The patient had been stabilized on carbamazepine 400 for 7 months, with a serum concentration within reference range (10.3 mg/L) 1 week prior to starting the tenofovir 300 mg daily; lamivudine 150 mg twice daily; and lopinavir 133 mg/ritonavir 33 mg, 3 capsules 9 of the new HAART regimen, the patient experienced excessive drowsiness, and the carbamazepine se increased by 46% to 15 mg/L. Decreasing the carbamazepine dose to 400 mg twice daily improved drow repeat serum level on day 11 was 7.4 mg/L. On day 12, the patient developed fatigue, difficulty swallowi hemorrhagic lesions over the extremities. The HAART regimen was stopped and carbamazepine dose w 400 mg 3 times daily. The patient was hospitalized 10 days later for evaluation of the rash. Blood tests a marrow toxicity. Subsequently, a neurology consult resulted in tapering of carbamazepine (over 2 to 4 we topiramate 25 mg twice daily and titrating to a target dose of 200 mg twice daily. On day 17 of hospitaliza regimen was re-initiated, replacing lopinavir/ritonavir with nelfinavir 1250 mg twice daily. On day 20, the p feeling tired and unsteady on his feet and the carbamazepine serum level had increased to 15 mg/L. Dec carbamazepine dose as before prompted resolution of symptoms within 24 hours. This interaction betwe as probable by the Naranjo probability scale and inhibition of CYP3A4-mediated carbamazepine metabo lopinavir/ritonavir or nelfinavir was postulated as the probable mechanism (Bates & Herman, 2006).

3.5.1.CO Loxapine

1) Interaction Effect: an increased risk of carbamazepine toxicity (ataxia, nystagmus, diplopia, headache, vo seizures, coma)

2) Summary: The concurrent use of carbamazepine and loxapine has resulted in neurotoxicity in one case re 1993a). Also, the use of carbamazepine in pregnant women has been reported to increase the risk of birth de al, 1990j; Van Dyke et al, 1991j; Finnell et al, 1992j).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: For patients receiving concurrent carbamazepine and loxapine therapy, monitor for carbamazepine toxicity and adjust doses accordingly.

7) Probable Mechanism: unknown

8) Literature Reports

a) A patient experienced neurotoxicity (visual disturbances, lethargy, ataxia, and falling) 10 days after ca mg three times a day was added to a regimen including loxapine 350 mg daily (Collins et al, 1993). His s with a reduction of carbamazepine to 100 mg twice daily. Subsequently loxapine was discontinued, and carbamazepine epoxide (an active metabolite) to carbamazepine decreased from 0.76 to 0.18. A retrosp four other cases in which carbamazepine and loxapine had been coadministered showed a greater than carbamazepine epoxide to carbamazepine ratio. Loxapine appeared to interact with carbamazepine to in carbamazepine epoxide plasma concentrations. The mode of action may be induction of carbamazepine epoxide metabolite and/or inhibition of carbamazepine epoxide metabolism to an inactive metabolite.

b) If phenytoin or carbamazepine (or any prodrugs) is used in pregnant women, there is a substantially i teratogenicity with many combinations of other anticonvulsants. The teratogenicity of these drugs is large related to the levels of the reactive epoxide metabolites (Buehler et al, 1990i; Van Dyke et al, 1991i; Finn The epoxide/parent drug ratio is generally increased when phenytoin or carbamazepine is combined with other drugs that induce cytochrome P450 enzymes (3A4, 2C9, 2C19), or drugs which inhibit epoxide hyc valproic acid, progabide, and lamotrigine (Bianchetti et al, 1987i; Ramsay et al, 1990i; Spina et al, 1996h combinations increase the risk of major birth defects 3- to 4-fold over monotherapy and about 10-fold ove rates.

3.5.1.CP Maraviroc

1) Interaction Effect: decreased maraviroc concentrations

2) Summary: Maraviroc is a substrate of CYP3A4. Concomitant administration of a CYP3A4 isoenzyme indu carbamazepine, may increase maraviroc metabolism, leading to loss of virologic response, and possible resis maraviroc. Use caution if maraviroc and carbamazepine are used concomitantly (without a strong CYP3A inh increase the dose of maraviroc to 600 mg twice daily (Prod Info SELZENTRY(R) oral tablets, 2007).

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Use caution when carbamazepine is co-administered with maraviroc as the combin loss of virologic response and possible resistance to maraviroc. If maraviroc and carbamazepine are used co (without a strong CYP3A inhibitor), monitor carefully for maraviroc effectiveness and increase the dose of ma twice daily (Prod Info SELZENTRY(R) oral tablets, 2007).

7) Probable Mechanism: induction of CYP3A4-mediated maraviroc metabolism

3.5.1.CQ Mebendazole

1) Interaction Effect: decreased mebendazole effectiveness

2) Summary: In patients with prior or current use of carbamazepine or phenytoin, the use of mebendazole fo resulted in therapeutic failure. This is thought to be due to the lower concentration of mebendazole in the pati anticonvulsants. For treatment of whipworms or hookworms, this interaction is not significant (Luder et al, 198 1986).

3) Severity: moderate

4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Monitor therapeutic efficacy of mebendazole. Depending on the reason for use of m higher doses may be required for some therapeutic uses.
7) Probable Mechanism: increased mebendazole metabolism

3.5.1.CR Mefloquine
1) Interaction Effect: loss of seizure control
2) Summary: In patients taking an anticonvulsant, such as carbamazepine, the concomitant use of mefloquir seizure control by lowering the anticonvulsant plasma levels (Prod Info Lariam(R), 2003).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: If mefloquine and carbamazepine must be administered concurrently, monitor the le carbamazepine. Adjustments of the carbamazepine dose may be required. Also monitor the patient for seizu
7) Probable Mechanism: unknown

3.5.1.CS Mestranol
1) Interaction Effect: a decrease in plasma concentrations of estrogens and in estrogen effectiveness
2) Summary: Breakthrough bleeding, spotting, and pregnancy have been reported in women on anticonvulsa contraceptives (Prod Info Ortho Evra(TM), 2001; Mattson et al, 1986a; Crawford et al, 1986; Haukkamaa, 19
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: In some women the use of higher estrogen content in the contraceptive may be suf use of alternate methods of birth control may be necessary.
7) Probable Mechanism: increased metabolism of contraceptive steroids
8) Literature Reports
a) Concomitant administration of oral contraceptives with enzyme-inducing anticonvulsant agents, prima phenytoin, carbamazepine, or primidone, has been reported to result in an increased failure rate of contr et al, 1986). The benzodiazepines and valproic acid have not been associated with increased failure rate receiving oral contraceptives. Increasing the dose of ethinyl estradiol or mestranol in oral contraceptives breakthrough bleeding and decrease the risk of conception. However, higher doses of estrogens may als of vascular side effects, primarily in patients where enzyme induction does not occur. It is recommended estrogen and progestin be given initially in patients receiving an enzyme inducing anticonvulsant; howev pregnancy is a special concern, a moderate dose formulation (50 mcg ethinyl estradiol) should be consic breakthrough bleeding occurs with low-dose contraception, progressive increases in the dose of mestrar (up to 80 mcg) should be considered. If spotting occurs, it is suggested that the contraceptive not be disc rather that a traditional method of barrier contraception be initiated during the remainder of that cycle. Sv dose oral contraceptive is recommended if enzyme inducing anticonvulsants are discontinued in women moderate or high-dose contraceptives.
b) Carbamazepine reduced the area under the plasma concentration time curve (AUC) of ethinyl estrad 4 women taking carbamazepine 300 to 600 mg daily within 8 to 12 weeks of initiation of therapy. Norges also significantly reduced to 29% to 57% of baseline. The authors suggest that breakthrough bleeding ca most women with use of oral contraceptives containing 80 to 100 mcg ethinyl estradiol (Crawford et al, 1
c) Accidental pregnancy occurred in a 20-year-old epileptic who was using phenytoin 400 mg daily plus 400 mg daily (Haukkamaa, 1986). The plasma concentration of levonorgestrel in this patient was very lo pg/mL) when compared to controls (325 +/- 135 pg/mL). Carbamazepine appears to decrease plasma le concentrations by enhancing the hepatic metabolism of the steroid via enzyme induction. Levonorgestrel relied upon as the sole means of contraception in patients on anticonvulsant therapy.

3.5.1.CT Methadone
1) Interaction Effect: decreased methadone effectiveness
2) Summary: The concurrent use of anticonvulsants and methadone resulted in lower methadone levels (eg, ng/mL) (Bell et al, 1988; Ketter et al, 1991).
3) Severity: minor
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Higher methadone doses may be required in patients taking enzyme-inducing medi carbamazepine.
7) Probable Mechanism: increased hepatic metabolism

3.5.1.CU Methylphenidate
1) Interaction Effect: loss of methylphenidate efficacy
2) Summary: Two case reports describe the loss of methylphenidate efficacy after carbamazepine therapy w Carbamazepine is an inducer of cytochrome P450 enzymes, a pathway involved in methylphenidate metabol methylphenidate plasma concentrations are not routinely measured, they may be helpful in patients receiving who are showing no benefits or side effects from methylphenidate (Behar et al, 1998a; Schaller & Behar, 199

3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Clinicians should monitor patient response to methylphenidate therapy when carba initiated. Monitoring of plasma methylphenidate levels may also be helpful. Doses of methylphenidate may ne increased to maintain efficacy.
7) Probable Mechanism: induction by carbamazepine of cytochrome P450 3A4-mediated methylphenidate m
8) Literature Reports
a) A 7-year-old male with severe mental retardation and attention deficit disorder was failing to respond methylphenidate 20 mg every four hours and thiothixene 10 mg daily. Other drug therapy included carba mg daily to control grand mal epilepsy. After five days of confirmed medication compliance, plasma level methylphenidate were measured two hours after the morning dose. No trace of either psychotropic agen metabolites could be found. Doses were increased to methylphenidate 30 mg every four hours and thioth with no evidence of efficacy or side effects. Both agents were then discontinued (Behar et al, 1998).
b) Attention deficit/hyperactivity disorder (ADHD) was being treated with methylphenidate 20 mg three ti year-old female. Because of mood lability and significant impulsivity, carbamazepine was introduced at 2 strict two-hour peak methylphenidate and ritalinic acid serum level was 5.3 ng/mL (normal range 5 to 20 time. ADHD symptoms began to worsen as the carbamazepine dose was increased to 800 mg daily. Six start of combination therapy, the patient's methylphenidate and ritalinic acid strict two-hour peak blood le to 4.2 ng/mL. A month later, the carbamazepine dose was increased to 1000 mg daily with a steady-stat 11.2 mcg/mL. Despite an increase in her methylphenidate dose to 35 mg three times daily, her methylph ritalinic acid peak level had further decreased to 2.4 ng/mL. After another two months, her carbamazepir mg daily with a steady-state blood level of 11.5 mcg/mL, and methylphenidate was increased to 60 mg th regain the benefit from the drug that she had experienced before the initiation of carbamazepine (Schalle

3.5.1.CV Methylprednisolone

1) Interaction Effect: decreased methylprednisolone effectiveness
2) Summary: Carbamazepine has been demonstrated to increase the metabolism of corticosteroids (Olivesi, al, 1982e), possibly by inducing the cytochrome P450 3A4 enzymes which are responsible for methylpredniso (Feldweg & Leddy, 1999a).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor therapeutic efficacy of the corticosteroid. An increase in the steroid dosage after three to five days of concurrent carbamazepine therapy.
7) Probable Mechanism: increased cytochrome P450 3A4-mediated methylprednisolone metabolism
8) Literature Reports
a) A 54-year-old male who developed progressive distal sensory and motor impairment during a four we diagnosed with Churg-Strauss vasculitis. He was treated with methylprednisolone 40 mg intravenously tw rapidly resolved his eosinophilia. Because of nocturnal neuropathic pain, carbamazepine was initiated at Within 24 hours of starting carbamazepine, new motor weakness developed in the patient's fingers, and eosinophils increased from a baseline of 160/mcgL to 1330/mcgL. Carbamazepine therapy was stopped methylprednisolone was replaced with dexamethasone. Intravenous immunoglobulin therapy was also in eosinophils disappeared within 48 hours. The patient was subsequently maintained on oral cyclophosph prednisone, with substantial recovery of motor and sensory function (Feldweg & Leddy, 1999).

3.5.1.CW Metronidazole

1) Interaction Effect: increased carbamazepine serum concentrations and potential carbamazepine toxicity
2) Summary: Significantly increased carbamazepine serum concentrations and CNS toxicity have been repo receiving concurrent metronidazole (Patterson, 1994a). The mechanism was thought to be inhibition by metro cytochrome P450 aromatic oxidative metabolism of carbamazepine. Further study is needed to validate this i
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When metronidazole and carbamazepine are coadministered, monitor carbamazep concentrations and observe patients for signs and symptoms of carbamazepine toxicity (nausea, dizziness, d effects). Doses of carbamazepine may need to be adjusted when metronidazole is added to or withdrawn fro
7) Probable Mechanism: unknown but may involve inhibition of carbamazepine metabolism by metronidazole
8) Literature Reports
a) A 49-year-old woman was seen in the ER with left quadrant pain thought to be caused by diverticulitis carbamazepine 1000 mg daily for bipolar disorder. Her other medications included conjugated estrogens Her carbamazepine serum concentration at 12 hours was 9 mcg/mL. She was then started on metronida times a day and trimethoprim/sulfamethoxazole double strength twice a day. Two days later she was adr worsening symptoms. Her metronidazole was increased to 500 mg intravenously every eight hours. Cefa and trimethoprim/sulfamethoxazole withdrawn. Two days later she reported nausea, dizziness, and diplo her 10-hour carbamazepine serum concentration was 14.3 mcg/mL, a 60% increase over the previous 9 mechanism of this interaction was thought to be inhibition of the hepatic cytochrome P-450 enzyme syste metronidazole (Patterson, 1994).

3.5.1.CX Mianserin

1) Interaction Effect: decreased mianserin serum concentrations

2) Summary: Serum mianserin levels were reported to be decreased in patients treated with carbamazepine (Leinonen et al, 1991a).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Serum levels and clinical response to mianserin should be carefully monitored if ca added to therapy or discontinued.

7) Probable Mechanism: increased metabolism of mianserin

8) Literature Reports

a) The effect of carbamazepine on mianserin levels was examined in 4 psychiatric inpatients stabilized f days prior to measurement of baseline antidepressant concentrations. The average daily mianserin dos Carbamazepine was added in a mean dose of 593 mg and continued over a 4-week period. Serum mian concentrations were decreased an average of 46% in patients receiving combination therapy compared with mianserin alone (Leinonen et al, 1991).

3.5.1.CY Midazolam

1) Interaction Effect: decreased efficacy of midazolam

2) Summary: Carbamazepine and phenytoin have been shown to greatly reduce the bioavailability of a singl midazolam. Carbamazepine is known to induce the cytochrome P450 3A enzymes, the same pathway that m midazolam during its first-pass and elimination phases. Patients receiving both carbamazepine and midazola have a hypnotic response to midazolam due to the induction of its metabolism caused by carbamazepine (Ba 1996a).

3) Severity: moderate

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: In a patient receiving carbamazepine therapy, larger doses of midazolam may be re a hypnotic response. Because of patient intervariability, a hypnotic other than midazolam may be preferable.

7) Probable Mechanism: induction of cytochrome P450 3A enzymes by carbamazepine

8) Literature Reports

a) Six patients with epilepsy and seven healthy control subjects were studied to determine the effects of and phenytoin on an oral dose of midazolam. Epileptic patients had been receiving either carbamazepin mg to 900 mg daily), phenytoin (dose range 150 mg to 300 mg daily), or both drugs twice daily for at leas control subjects were not receiving any enzyme-inducing agents. All study participants were administere dose of midazolam 15 mg. In the patient group, the mean area under the concentration-time curve of mi 5.7% (0.60 mcg/min/mL vs. 10.5 mcg/min/mL) and the maximum concentration was 7.4% (5.2 ng/mL vs. the control values. In one patient, only traces of midazolam (less than 0.1 ng/mL) were detectable in the elimination half-life of midazolam was reduced to 1.3 hours in the patient group compared to 3.1 hours in There was no difference in the time to maximum concentration (1 hour) between the two groups. As exp reduced serum concentrations of midazolam, the majority of the patient group did not report any sedatio subjects from the control group experienced sedative effects which lasted from two to four hours. The lo plasma concentrations, decreased elimination half-life, and lack of sedative effects are most likely the re P450 3A enzyme induction by carbamazepine and phenytoin, since midazolam is extensively metabolize enzymes during first-pass and elimination phases (Backman et al, 1996).

3.5.1.CZ Mifepristone

1) Interaction Effect: decreased serum levels of mifepristone and potentially decreased efficacy

2) Summary: Although formal interaction studies have not been conducted, carbamazepine may induce the metabolism of mifepristone, thereby decreasing serum levels of mifepristone (Prod Info MIFEPREX(R) oral ta

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Clinicians should be aware that carbamazepine may induce mifepristone metabolis resulting in decreased mifepristone efficacy.

7) Probable Mechanism: induction of CYP3A4-mediated metabolism of mifepristone by carbamazepine

3.5.1.DA Milnacipran

1) Interaction Effect: slight reductions in milnacipran plasma levels

2) Summary: In a multiple-dose study involving healthy subjects (provided by the manufacturer), a moderate milnacipran plasma levels (20%) was observed when the drug was given in combination with carbamazepine accompanied by an increase in plasma levels of the N-dealkylated metabolite of milnacipran (inactive). Carba active metabolite were unaffected (Puozzo & Leonard, 1996). The reduced concentration of milnacipran is of significance, and dose adjustment is not indicated during initiation of combined therapy. However, baseline a therapy plasma levels of milnacipran are suggested if prolonged treatment is expected (where assays are av

3) Severity: minor

4) Onset: delayed

5) Substantiation: probable
6) Clinical Management: Dose adjustment is not indicated during initiation of combined therapy with carbama milnacipran. However, baseline and combination-therapy plasma levels of milnacipran are suggested if prolo expected.
7) Probable Mechanism: hepatic enzyme induction by carbamazepine

3.5.1.DB Miokamycin
1) Interaction Effect: an increase in carbamazepine plasma levels
2) Summary: Miokamycin has been reported to increase half-life and area under the concentration-time curv decrease the clearance of carbamazepine in 14 healthy volunteers (Couet et al, 1990a; Prod Info Miokacin(R
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Caution is advised when using miokamycin in combination with carbamazepine. Mo carbamazepine plasma concentrations and adjust the carbamazepine dose as necessary.
7) Probable Mechanism: inhibition of carbamazepine metabolism
8) Literature Reports
a) The effect of miokamycin 800 mg twice daily for 12 days on the pharmacokinetics of carbamazepine single oral dose of 200 mg was assessed in a crossover study involving 14 healthy volunteers. The study statistically significant increase (13%) in half-life and area under the concentration-time curve (AUC) of c decrease in its clearance. The authors also demonstrated that the maximum concentration (Cmax) and A epoxycarbamazepine, a major active metabolite of carbamazepine, were significantly decreased during t miokamycin (Couet et al, 1990; Prod Info Miokacin(R), 1996).

3.5.1.DC Moclobemide
1) Interaction Effect: hypertensive urgency, hyperpyrexia, and seizures
2) Summary: Concomitant MAO inhibitor and carbamazepine therapy is contraindicated (Prod Info Tegretol(Simultaneous use may theoretically result in hyperpyrexia, excitation, and seizure activity (Prod Info Parnate(Info Tegretol(R), 1998d; Thweatt, 1986d). However, there is preliminary evidence that the combination of car an MAOI may be safe and efficacious, even in some refractory cases (Ketter et al, 1995i; Barker & Eccleston controlled studies are needed.
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of carbamazepine and monoamine oxidase inhibitors contraindicated by the manufacturer. Monoamine oxidase inhibitors should be discontinued for a minimum of if the clinical situation permits, before carbamazepine therapy is initiated.
7) Probable Mechanism: unknown
8) Literature Reports
a) A double-blind study was conducted in ten inpatients with depression that had proved refractory to m therapies (electroconvulsive therapy, tricyclic antidepressants, monoamine oxidase inhibitors, lithium, ca benzodiazepines, and antipsychotics) (Ketter et al, 1995h). In addition to their regular carbamazepine an four patients received phenelzine (mean maximum dose 67.5 mg daily) and six patients received tranylc maximum dose 55 mg daily) for a mean duration combination therapy of 52.2 days. During MAOI coadm concentrations of carbamazepine and lithium did not change significantly from baseline values. Self-rate not substantially different. Four patients (three on phenelzine and one on tranylcypromine) responded to were subsequently discharged.
b) A 60-year-old woman who had an atypical endogenous, depressive illness of psychotic intensity was intermittently with cyclic antidepressants and intermittent electroconvulsive therapy. Following an acute v illness, she was treated successfully with a combination of phenelzine and L-tryptophan. Following a few improvement, her situation worsened and she was subsequently treated with zimelidine and lithium. Faili placed on a regimen of tranylcypromine with doses increasing progressively up to 30 mg daily in conjunc and tryptophan. Subsequently, carbamazepine was added in small doses with increments to achieve a p approximately 5 mg/L. This regimen proved successful, and she was discharged home and had remaine two months of follow up at the time of publication (Barker & Eccleston, 1984h).
c) Addition of tranylcypromine to carbamazepine therapy did not significantly affect carbamazepine seru case (Joffe et al, 1985d). Conversely, five patients on tranylcypromine needed a mean daily dose of carb mg to achieve a carbamazepine blood level of 8.0-11.1 mcg/mL (Barklage et al, 1992d). Four other patie phenelzine only required a mean daily dose of carbamazepine 450 mg to attain a blood level of 8.7-10.9

3.5.1.DD Modafinil
1) Interaction Effect: decreased modafinil efficacy
2) Summary: Coadministration of modafinil with other drugs that are potent inducers of CYP3A4, such as ca could result in decreased efficacy of modafinil which is partially metabolized by the CYP3A4 isoenzyme (Proc modafinil, 2004).
3) Severity: minor
4) Onset: unspecified
5) Substantiation: theoretical

6) Clinical Management: Clinicians should monitor patient response to modafinil therapy when carbamazepir
7) Probable Mechanism: induction by carbamazepine of cytochrome P450 3A4-mediated modafinil metaboli

3.5.1.DE Nafimidone

1) Interaction Effect: carbamazepine toxicity (ataxia, nystagmus, diplopia, headache, vomiting, apnea, seizur
2) Summary: Concurrent use of nafimidone in 6 patients with intractable seizures taking carbamazepine and in a reduction in carbamazepine elimination by 76 to 87% and a reduction in phenytoin elimination by 38 to 7 showed symptoms characteristic of carbamazepine toxicity by the second day of nafimidone treatment. Effec were apparent within 24 hours of initiation of nafimidone and began to decline within 12 hours of discontinuat Ben-Menachem, 1987a).
3) Severity: moderate
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Monitor carbamazepine concentrations closely when adding or discontinuing nafimi adjust carbamazepine dose accordingly.
7) Probable Mechanism: decreased carbamazepine metabolism
8) Literature Reports
a) Addition of nafimidone to the anticonvulsant regimens of 6 patients with intractable seizures taking ca phenytoin resulted in a reduction in carbamazepine elimination by 76% to 87% and a reduction in phenyt 38% to 77%. This effect was apparent within 24 hours of initiation of nafimidone and began to decline wi nafimidone discontinuation. The effect on carbamazepine elimination persisted over the course of 1 year elected to continue therapy beyond the trial period. Two patients showed symptoms characteristic of carl toxicity by the second day of nafimidone treatment. The degree of toxicity was greatly reduced for 4 addi reducing both the phenytoin and carbamazepine doses during the titration of nafimidone. Although the p of this interaction is unknown, the authors postulate that nafimidone may inhibit the cytochrome P-450-m function oxidase system (Treiman & Ben-Menachem, 1987).

3.5.1.DF Nefazodone

1) Interaction Effect: reduced plasma concentrations and efficacy of nefazodone and its active metabolite, ar risk of carbamazepine toxicity (ataxia, nystagmus, diplopia, headache, vomiting, apnea, seizures, coma)
2) Summary: Coadministration of nefazodone and carbamazepine is contraindicated. Concomitant use may reduce plasma concentrations of nefazodone and its active metabolite, resulting in reduced therapeutic effica (Prod Info TEGRETOL(R) chewable oral tablets, oral tablets, suspension, 2007; Prod Info SERZONE(R) oral a study conducted on 12 healthy volunteers, the coadministration of nefazodone with carbamazepine at steac a reduction in the mean AUC of nefazodone and hydroxynefazodone by 93% and 94%, respectively. Additior increase in carbamazepine plasma levels and a 21% decrease in carbamazepine-10,11 epoxide levels were findings suggest that nefazodone inhibits carbamazepine metabolism through the CYP3A4 system, and carb induces nefazodone metabolism through the same pathway (Laroudie et al, 2000a). Two other cases of nefa carbamazepine toxicity have been reported in the literature (Ashton & Wolin, 1996).
3) Severity: contraindicated
4) Onset: delayed
5) Substantiation: established
6) Clinical Management: Concomitant use of carbamazepine and nefazodone is contraindicated due to redu nefazodone and its active metabolite (Prod Info TEGRETOL(R) chewable oral tablets, oral tablets, suspensio SERZONE(R) oral tablets, 2005). In addition, concomitant use may also result in increased toxicity of carbam Wolin, 1996).
7) Probable Mechanism: induction of CYP3A4-mediated nefazodone metabolism; inhibition of CYP3A4-med carbamazepine metabolism
8) Literature Reports
a) Twelve healthy male volunteers participated in an open-label multiple-dose study to explore the poter interaction between carbamazepine and nefazodone. Each subject received nefazodone 200 mg twice d through 5. A four-day washout period followed. On days 10 to 12, carbamazepine 200 mg daily was give was increased to 200 mg twice daily from days 14 to 39. From days 40 to 44, nefazodone 200 mg twice carbamazepine 200 mg twice daily were coadministered. Carbamazepine mean steady-state area under time curve (AUC) increased from 60.77 mcg/hr/mL to 74.98 mcg/hr/mL in the presence of nefazodone, w the metabolite carbamazepine-10,11-epoxide decreased from 7.1 mcg/hr/mL to 5.71 mcg/hr/mL. The ma concentration (Cmax) of carbamazepine increased from 5794 mg/L to 7133.2 mg/L and the Cmax for ca 10,11-epoxide decreased from 680.5 mg/L to 535.2 mg/L. Nefazodone mean steady-state AUC was dec ng/hr/mL to 542 ng/hr/mL in the presence of carbamazepine, although the clinical significance of carbam on nefazodone metabolism has not yet been studied (Laroudie et al, 2000).
b) A 35-year-old female with bipolar disorder developed carbamazepine toxicity following the addition of to 150 mg twice daily) to an existing drug regimen of carbamazepine (1000 mg daily) and risperidone (3 Prior to nefazodone therapy, her carbamazepine serum concentrations ranged from 7.0 mcg/mL to 8.3 m days after her nefazodone dose was increased to 300 mg daily, she presented with lightheadedness and carbamazepine serum concentration was 10.8 mcg/mL (Ashton & Wolin, 1996a).
c) In a second case, a 39-year-old female with bipolar disorder developed carbamazepine toxicity after r 150 mg twice daily) was added to an existing regimen of carbamazepine (1000 mg daily). During concon serum carbamazepine levels increased to 15.1 mcg/mL from a previous range of 5.2 mcg/mL to 6.2 mcg

carbamazepine alone (Ashton & Wolin, 1996a).

3.5.1.DG Nelfinavir

1) Interaction Effect: decreased nelfinavir plasma concentrations; increased serum carbamazepine levels an
2) Summary: The concurrent use of carbamazepine and nelfinavir may result in decreased nelfinavir plasma potentially reducing the efficacy of nelfinavir (Prod Info Viracept(R), 1999). Carbamazepine toxicity has been HIV-positive patient upon concomitant treatment with nelfinavir, as part of a highly active antiretroviral regime result of inhibition of CYP3A4-mediated carbamazepine metabolism by nelfinavir. If used concurrently with ne reducing the carbamazepine dose by 25 to 50%. Additionally, monitor patients for serum carbamazepine leve after initiating nelfinavir (Bates & Herman, 2006).
3) Severity: major
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Monitor patients for signs of reduced efficacy of nelfinavir. Dosing adjustments of ne necessary. Additionally, coadministration of carbamazepine with a nelfinavir, as part of a highly active antiretr has resulted in increased serum carbamazepine levels and toxicity. If used concurrently with nelfinavir, consi carbamazepine dose by 25 to 50% and monitor patients for serum carbamazepine levels, 3 to 5 days after in
7) Probable Mechanism: induction of cytochrome P450 3A-mediated metabolism of nelfinavir; inhibition of C carbamazepine metabolism by nelfinavir
8) Literature Reports
a) Symptoms of carbamazepine toxicity developed in a 50-year-old HIV-positive male upon addition of lo his highly active antiretroviral therapy (HAART). The patient had been stabilized on carbamazepine 400 for 7 months, with a serum concentration within reference range (10.3 mg/L) 1 week prior to starting the tenofovir 300 mg daily; lamivudine 150 mg twice daily; and lopinavir 133 mg/ritonavir 33 mg, 3 capsules 9 of the new HAART regimen, the patient experienced excessive drowsiness, and the carbamazepine se increased by 46% to 15 mg/L. Decreasing the carbamazepine dose to 400 mg twice daily improved drow repeat serum level on day 11 was 7.4 mg/L. On day 12, the patient developed fatigue, difficulty swallowi hemorrhagic lesions over the extremities. The HAART regimen was stopped and carbamazepine dose w 400 mg 3 times daily. The patient was hospitalized 10 days later for evaluation of the rash. Blood tests a marrow toxicity. Subsequently, a neurology consult resulted in tapering of carbamazepine (over 2 to 4 we topiramate 25 mg twice daily and titrating to a target dose of 200 mg twice daily. On day 17 of hospitaliza regimen was re-initiated, replacing lopinavir/ritonavir with nelfinavir 1250 mg twice daily. On day 20, the p feeling tired and unsteady on his feet and the carbamazepine serum level had increased to 15 mg/L. Dec carbamazepine dose as before prompted resolution of symptoms within 24 hours. This interaction betwe as probable by the Naranjo probability scale and inhibition of CYP3A4-mediated carbamazepine metabo lopinavir/ritonavir or nelfinavir was postulated as the probable mechanism (Bates & Herman, 2006).

3.5.1.DH Nevirapine

1) Interaction Effect: decreased plasma concentrations of carbamazepine
2) Summary: Nevirapine is an inducer of cytochrome P450 3A4 enzymes, which are also involved in the met carbamazepine. Although studies involving nevirapine and carbamazepine have not been conducted, nevirap shown to induce the metabolism of carbamazepine, significantly decreasing carbamazepine bioavailability (P (R), 2004).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Dose adjustment of carbamazepine may be needed due to possible decrease in cli
7) Probable Mechanism: induction of cytochrome P450 3A4-mediated metabolism of carbamazepine by nevi

3.5.1.DI Niacinamide

1) Interaction Effect: an increased risk of carbamazepine toxicity (ataxia, nystagmus, diplopia, headache, vo seizures, coma)
2) Summary: Two case reports describe a decrease in carbamazepine clearance when niacinamide was ad decrease seen in the carbamazepine clearance correlated highly with increasing niacinamide doses (Bourge
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor carbamazepine plasma levels in patients receiving niacinamide concomitar carbamazepine doses accordingly.
7) Probable Mechanism: inhibition of cytochrome P450 enzymes by niacinamide
8) Literature Reports
a) Carbamazepine concentration increased in two epileptic patients after the addition of niacinamide. Bo also receiving primidone therapy, and niacinamide was added to decrease the conversion of primidone t Patient 1, a 23-month old male receiving carbamazepine 72.7 mg/kg/day, had a carbamazepine clearanc prior to niacinamide treatment, and the carbamazepine clearance decreased to 2.16 L/kg/day by the time dose had been titrated up to 178 mg/kg/day. In patient 2, a 10-year old male, the carbamazepine clearar from 8.0 L/kg/day before niacinamide therapy to 3.37 L/kg/day when the niacinamide dose was 60 mg/kg suspected that niacinamide inhibited the cytochrome P450 metabolism of carbamazepine (Bourgeois et

3.5.1.DJ Nialamide

1) Interaction Effect: hypertensive urgency, hyperpyrexia, and seizures

2) Summary: Concomitant MAO inhibitor and carbamazepine therapy is contraindicated (Prod Info Tegretol(Simultaneous use may theoretically result in hyperpyrexia, excitation, and seizure activity (Prod Info Parnate(Info Tegretol(R), 1998f; Thweatt, 1986f). However, there is preliminary evidence that the combination of carb MAOI may be safe and efficacious, even in some refractory cases (Ketter et al, 1995m; Barker & Eccleston, controlled studies are needed.

3) Severity: contraindicated

4) Onset: rapid

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of carbamazepine and monoamine oxidase inhibitors contraindicated by the manufacturer. Monoamine oxidase inhibitors should be discontinued for a minimum of if the clinical situation permits, before carbamazepine therapy is initiated.

7) Probable Mechanism: unknown

8) Literature Reports

a) A double-blind study was conducted in ten inpatients with depression that had proved refractory to m therapies (electroconvulsive therapy, tricyclic antidepressants, monoamine oxidase inhibitors, lithium, ca benzodiazepines, and antipsychotics). In addition to their regular carbamazepine and lithium doses, four phenelzine (mean maximum dose 67.5 mg daily) and six patients received tranylcypromine (mean maxir daily) for a mean duration combination therapy of 52.2 days. During MAOI coadministration, serum conc carbamazepine and lithium did not change significantly from baseline values. Self-rated side effects were different. Four patients (three on phenelzine and one on tranylcypromine) responded to this therapy and discharged (Ketter et al, 1995l).

b) A 60-year-old woman who had an atypical endogenous, depressive illness of psychotic intensity was intermittently with cyclic antidepressants and intermittent electroconvulsive therapy. Following an acute v illness, she was treated successfully with a combination of phenelzine and L-tryptophan. Following a few improvement, her situation worsened and she was subsequently treated with zimelidine and lithium. Faili placed on a regimen of tranylcypromine with doses increasing progressively up to 30 mg daily in conjunc and tryptophan. Subsequently, carbamazepine was added in small doses with increments to achieve a p approximately 5 mg/L. This regimen proved successful, and she was discharged home and had remaine two months of follow up at the time of publication (Barker & Eccleston, 1984l).

c) Addition of tranylcypromine to carbamazepine therapy did not significantly affect carbamazepine seru (Joffe et al, 1985f). Conversely, five patients on tranylcypromine need a mean daily dose of carbamazep achieve a carbamazepine blood level of 8.0-11.1 mcg/mL. Four other patients receiving phenelzine only daily dose of carbamazepine 450 mg to attain a blood level of 8.7-10.9 mcg/mL (Barklage et al, 1992f).

3.5.1.DK Nifedipine

1) Interaction Effect: decreased nifedipine exposure and may decrease nifedipine efficacy

2) Summary: Concurrent administration of nifedipine and carbamazepine may induce CYP3A4-mediated nife and decrease exposure to nifedipine, which may increase the risk of hypertension or angina (Prod Info Adala Release Tablets, 2004).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: Concomitant administration of nifedipine and carbamazepine may decrease exposu Monitor patient for loss of calcium channel blocker effects, including clinical signs or symptoms of hypertensio Consider a dose adjustment of nifedipine.

7) Probable Mechanism: induction of CYP3A4-mediated nifedipine metabolism

3.5.1.DL Nilotinib

1) Interaction Effect: decreased nilotinib plasma concentrations

2) Summary: Nilotinib is a CYP3A4 substrate. Coadministration of rifampin, a strong CYP3A4 inducer, at a d for 12 days decreased nilotinib AUC by approximately 80% in healthy subjects. Although not studied with car a strong CYP3A4 inducer, a similar interaction would be expected. Concomitant use of carbamazepine and n therefore be avoided. However, if concomitant use is required, nilotinib dose may need to be increased depe tolerability. Upon discontinuation of carbamazepine, reduce the nilotinib dose to the indicated dose (Prod Info capsules, 2007).

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Avoid concomitant administration of carbamazepine, a strong CYP3A4 inducer, and CYP3A4 substrate, as this may result in decreased nilotinib plasma concentrations and consequently, subthe concomitant administration is warranted, consider increasing nilotinib dose depending on patient tolerability. discontinuation of the strong CYP3A4 inducer, reduce the nilotinib dose to the indicated dose (Prod Info TAS capsules, 2007).

7) Probable Mechanism: induction of CYP3A4-mediated nilotinib metabolism

3.5.1.DM Nimodipine

1) Interaction Effect: decreased nimodipine effectiveness

2) Summary: A single study has shown that concurrent use of enzyme inducing antiepileptic agents (phenyto and carbamazepine) with nimodipine has resulted in decreased nimodipine levels (Tartara et al, 1991b).

3) Severity: minor

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Monitor clinical response to nimodipine, with dose adjustments as needed to achiev cardiovascular response.

7) Probable Mechanism: increased nimodipine metabolism

8) Literature Reports

a) Three groups of eight subjects were studied (Tartara et al, 1991). Group 1 was comprised of healthy had epileptic patients treated at least four months with carbamazepine, phenobarbital, phenytoin (all enz a combination, and group 3 included epileptic patients treated for at least four months with sodium valpro the control group, nimodipine AUCs averaged a 7-fold decrease in the enzyme inducer group, probably d first-pass metabolism. The nimodipine AUCs were increased by 50% in the valproate-treated group.

3.5.1.DN Norelgestromin

1) Interaction Effect: a decrease in plasma concentrations of estrogens and in estrogen effectiveness

2) Summary: Breakthrough bleeding, spotting, and pregnancy have been reported in women on anticonvulsa contraceptives (Prod Info Ortho Evra(TM), 2001; Mattson et al, 1986a; Crawford et al, 1986; Haukkamaa, 198

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: In some women the use of higher estrogen content in the contraceptive may be suf use of alternate methods of birth control may be necessary.

7) Probable Mechanism: increased metabolism of contraceptive steroids

8) Literature Reports

a) Concomitant administration of oral contraceptives with enzyme-inducing anticonvulsant agents, prima phenytoin, carbamazepine, or primidone, has been reported to result in an increased failure rate of contr et al, 1986). The benzodiazepines and valproic acid have not been associated with increased failure rate receiving oral contraceptives. Increasing the dose of ethinyl estradiol or mestranol in oral contraceptives breakthrough bleeding and decrease the risk of conception. However, higher doses of estrogens may als of vascular side effects, primarily in patients where enzyme induction does not occur. It is recommended estrogen and progestin be given initially in patients receiving an enzyme inducing anticonvulsant; howev pregnancy is a special concern, a moderate dose formulation (50 mcg ethinyl estradiol) should be consid breakthrough bleeding occurs with low-dose contraception, progressive increases in the dose of mestrar (up to 80 mcg) should be considered. If spotting occurs, it is suggested that the contraceptive not be disc rather that a traditional method of barrier contraception be initiated during the remainder of that cycle. Sv dose oral contraceptive is recommended if enzyme inducing anticonvulsants are discontinued in women moderate or high-dose contraceptives.

b) Carbamazepine reduced the area under the plasma concentration time curve (AUC) of ethinyl estrad 4 women taking carbamazepine 300 to 600 mg daily within 8 to 12 weeks of initiation of therapy. Norges also significantly reduced to 29% to 57% of baseline. The authors suggest that breakthrough bleeding ca most women with use of oral contraceptives containing 80 to 100 mcg ethinyl estradiol (Crawford et al, 1

c) Accidental pregnancy occurred in a 20-year-old epileptic who was using phenytoin 400 mg daily plus 400 mg daily (Haukkamaa, 1986). The plasma concentration of levonorgestrel in this patient was very lo pg/mL) when compared to controls (325 +/- 135 pg/mL). Carbamazepine appears to decrease plasma le concentrations by enhancing the hepatic metabolism of the steroid via enzyme induction. Levonorgestrel relied upon as the sole means of contraception in patients on anticonvulsant therapy.

3.5.1.DO Norethindrone

1) Interaction Effect: a decrease in plasma concentrations of estrogens and in estrogen effectiveness

2) Summary: Breakthrough bleeding, spotting, and pregnancy have been reported in women on anticonvulsa contraceptives (Prod Info Ortho Evra(TM), 2001; Mattson et al, 1986a; Crawford et al, 1986; Haukkamaa, 198

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: In some women the use of higher estrogen content in the contraceptive may be suf use of alternate methods of birth control may be necessary.

7) Probable Mechanism: increased metabolism of contraceptive steroids

8) Literature Reports

a) Concomitant administration of oral contraceptives with enzyme-inducing anticonvulsant agents, prima phenytoin, carbamazepine, or primidone, has been reported to result in an increased failure rate of contr et al, 1986). The benzodiazepines and valproic acid have not been associated with increased failure rate receiving oral contraceptives. Increasing the dose of ethinyl estradiol or mestranol in oral contraceptives breakthrough bleeding and decrease the risk of conception. However, higher doses of estrogens may als of vascular side effects, primarily in patients where enzyme induction does not occur. It is recommended

estrogen and progestin be given initially in patients receiving an enzyme inducing anticonvulsant; howev
pregnancy is a special concern, a moderate dose formulation (50 mcg ethinyl estradiol) should be consic
breakthrough bleeding occurs with low-dose contraception, progressive increases in the dose of mestrar
(up to 80 mcg) should be considered. If spotting occurs, it is suggested that the contraceptive not be disc
rather that a traditional method of barrier contraception be initiated during the remainder of that cycle. Sv
dose oral contraceptive is recommended if enzyme inducing anticonvulsants are discontinued in women
moderate or high-dose contraceptives.

b) Carbamazepine reduced the area under the plasma concentration time curve (AUC) of ethinyl estrad
4 women taking carbamazepine 300 to 600 mg daily within 8 to 12 weeks of initiation of therapy. Norges
also significantly reduced to 29% to 57% of baseline. The authors suggest that breakthrough bleeding ca
most women with use of oral contraceptives containing 80 to 100 mcg ethinyl estradiol (Crawford et al, 1

c) Accidental pregnancy occurred in a 20-year-old epileptic who was using phenytoin 400 mg daily plus
400 mg daily (Haukkamaa, 1986). The plasma concentration of levonorgestrel in this patient was very lo
pg/mL) when compared to controls (325 +/- 135 pg/mL). Carbamazepine appears to decrease plasma le
concentrations by enhancing the hepatic metabolism of the steroid via enzyme induction. Levonorgestrel
relied upon as the sole means of contraception in patients on anticonvulsant therapy.

3.5.1.DP Norgestrel

1) Interaction Effect: a decrease in plasma concentrations of estrogens and in estrogen effectiveness

2) Summary: Breakthrough bleeding, spotting, and pregnancy have been reported in women on anticonvulsa
contraceptives (Prod Info Ortho Evra(TM), 2001; Mattson et al, 1986a; Crawford et al, 1986; Haukkamaa, 198

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: In some women the use of higher estrogen content in the contraceptive may be suf
use of alternate methods of birth control may be necessary.

7) Probable Mechanism: increased metabolism of contraceptive steroids

8) Literature Reports

a) Concomitant administration of oral contraceptives with enzyme-inducing anticonvulsant agents, prima
phenytoin, carbamazepine, or primidone, has been reported to result in an increased failure rate of contr
et al, 1986). The benzodiazepines and valproic acid have not been associated with increased failure rate
receiving oral contraceptives. Increasing the dose of ethinyl estradiol or mestranol in oral contraceptives
breakthrough bleeding and decrease the risk of conception. However, higher doses of estrogens may als
of vascular side effects, primarily in patients where enzyme induction does not occur. It is recommended
estrogen and progestin be given initially in patients receiving an enzyme inducing anticonvulsant; howev
pregnancy is a special concern, a moderate dose formulation (50 mcg ethinyl estradiol) should be consic
breakthrough bleeding occurs with low-dose contraception, progressive increases in the dose of mestrar
(up to 80 mcg) should be considered. If spotting occurs, it is suggested that the contraceptive not be disc
rather that a traditional method of barrier contraception be initiated during the remainder of that cycle. Sv
dose oral contraceptive is recommended if enzyme inducing anticonvulsants are discontinued in women
moderate or high-dose contraceptives.

b) Carbamazepine reduced the area under the plasma concentration time curve (AUC) of ethinyl estrad
4 women taking carbamazepine 300 to 600 mg daily within 8 to 12 weeks of initiation of therapy. Norges
also significantly reduced to 29% to 57% of baseline. The authors suggest that breakthrough bleeding ca
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c) Accidental pregnancy occurred in a 20-year-old epileptic who was using phenytoin 400 mg daily plus
400 mg daily (Haukkamaa, 1986). The plasma concentration of levonorgestrel in this patient was very lo
pg/mL) when compared to controls (325 +/- 135 pg/mL). Carbamazepine appears to decrease plasma le
concentrations by enhancing the hepatic metabolism of the steroid via enzyme induction. Levonorgestrel
relied upon as the sole means of contraception in patients on anticonvulsant therapy.

3.5.1.DQ Nortriptyline

1) Interaction Effect: decreased nortriptyline effectiveness

2) Summary: One case has been reported in which nortriptyline levels dropped by more than half after carba
added (Brosen & Kragh-Sorensen, 1993b). Similar effects have been observed with other tricyclic antidepres
al, 1991k; Brown et al, 1988c; Moody et al, 1977c).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Monitor for clinical efficacy of the nortriptyline therapy and for any signs of toxicity o
Serum levels of both agents should be considered when either agent is added or discontinued, with appropria
adjustments made accordingly.

7) Probable Mechanism: increased nortriptyline metabolism

3.5.1.DR Olanzapine

1) Interaction Effect: reduced olanzapine efficacy

2) Summary: Carbamazepine induces CYP1A2 mediated oxidation. Concomitant administration of olanzapir
carbamazepine 200 mg twice daily increased the clearance of olanzapine by 50% (Prod Info Zyprexa(R), 199

doses of carbamazepine may cause an even greater effect on olanzapine clearance. In a study of 11 healthy concurrent administration of olanzapine and carbamazepine resulted in a 46% increase in olanzapine clearar 1998). Because patients respond to a relatively wide range of olanzapine serum concentrations, close clinica symptom patterns and changes is necessary whenever carbamazepine is added to or withdrawn from olanza need for olanzapine dose adjustments will most likely be highly patient specific (Licht et al, 2000a).
3) Severity: moderate
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Monitor patients for olanzapine efficacy. Doses of olanzapine may need to be adjus concomitantly with carbamazepine.
7) Probable Mechanism: induction of cytochrome P450 1A2-mediated olanzapine metabolism
8) Literature Reports
a) A 23-year-old paranoid schizophrenic female was admitted to the hospital for treatment of hallucinatic Her only medication on admission was perphenazine 12 mg daily, but carbamazepine 600 mg daily was aggressive outbursts. Perphenazine was replaced by risperidone 6 mg daily due to akathisia, rigidity, an risperidone was also discontinued due to extrapyramidal side effects. Olanzapine 15 mg daily was starte psychiatric symptoms improved over the next three weeks. Because her aggressive outbursts were still carbamazepine was discontinued due to lack of efficacy. She had received cotherapy with olanzapine 15 carbamazepine 600 mg daily for three consecutive weeks. The day prior to carbamazepine discontinuati olanzapine serum concentration was measured at 21 ng/mL. Over the next few weeks, her olanzapine c increased by 114% to 45 ng/mL. The dose of olanzapine was decreased to 10 mg daily and a correspon olanzapine level occurred. This case report suggests that carbamazepine induces the metabolism of ola likely through the cytochrome P450 1A2 enzyme system (Licht et al, 2000).

3.5.1.DS Omeprazole
1) Interaction Effect: an increased risk of carbamazepine toxicity
2) Summary: Omeprazole has been reported to increase the elimination half-life, increase the area under the time curve (AUC), and decrease the clearance of a single-dose of carbamazepine (Dammann, 1996a). Conv Getz, 1995a) described a patient who had no alteration in the carbamazepine plasma level during concurrent omeprazole for helicobacter pylori gastritis. One of the reasons for the conflicting results may be that carbam own metabolism, thereby possibly causing different interactions between single-dose and multiple-dose thera carbamazepine.
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor patients receiving concurrent carbamazepine and omeprazole therapy for s carbamazepine toxicity (ataxia, nystagmus, diplopia, headache, vomiting, apnea, seizures, coma). Also moni serum levels. Doses of carbamazepine may need to be reduced.
7) Probable Mechanism: inhibition of carbamazepine metabolism
8) Literature Reports
a) The administration of a single dose of carbamazepine to nine patients receiving omeprazole therapy prolongation of the carbamazepine half-life (17.2 hours vs. 37.3 hours) and an increase in the AUC from 668 mcg/hr/mL. The clearance of carbamazepine decreased from 20.7 mL/hr/kg to 12.5 mL/hr/kg. These any adjuvant therapy of omeprazole has the potential to interact with carbamazepine concentrations, and administered with close monitoring of the carbamazepine serum levels (Dammann, 1996).
b) An epileptic patient stabilized on carbamazepine (900 mg daily) therapy, had a serum level of 7.5 mg the addition of clarithromycin (500 mg three times daily) and omeprazole (20 mg twice daily), the carbam risen to 14 mg/L. Despite carbamazepine dose reductions of 200 mg daily, the plasma level reached 20. clarithromycin was then discontinued, and metronidazole and bismuth subsalicylate were substituted. Th carbamazepine returned to normal, even though therapy with omeprazole was continued. Omeprazole is hepatic microsomal cytochrome P450 2C enzymes, whereas carbamazepine is metabolized by and indu different metabolic pathways between omeprazole and carbamazepine suggest that in this patient, claritl solely responsible for the increased carbamazepine serum levels and no drug interaction exists between carbamazepine (Metz & Getz, 1995).

3.5.1.DT Oxcarbazepine
1) Interaction Effect: decreased plasma concentration of the active 10-monohydroxy metabolite of oxcarbaze
2) Summary: Concurrent administration of oxcarbazepine and carbamazepine (CBZ) has resulted in a 40% d plasma concentration of the active 10-monohydroxy derivative (MHD) of oxcarbazepine (Prod Info TRILEPTA oral suspension, 2005). Although the exact mechanism for this decrease is unknown, it is believed to be parti potential induction of oxcarbazepine's metabolism by CBZ, which is strong inducer of cytochrome P450 enzy 1994). Although, the clinical significance of this interaction is unknown, decreased plasma MHD concentratio potential loss of oxcarbazepine efficacy. If oxcarbazepine and carbamazepine are administered concurrently, to oxcarbazepine may need to be monitored.
3) Severity: moderate
4) Onset: delayed
5) Substantiation: established
6) Clinical Management: Coadministration of oxcarbazepine and carbamazepine may result in a decreased d

the active 10-monohydroxy metabolite of oxcarbazepine. Monitor patients for clinical response to oxcarbazep
7) Probable Mechanism: potential induction of cytochrome P450-mediated oxcarbazepine metabolism
8) Literature Reports
a) In a randomized, double-blind, placebo-controlled trial in adults, coadministration of carbamazepine (
oxcarbazepine resulted in decreased levels of the pharmacologically active 10-monohydroxy derivative (
oxcarbazepine. Patients (n=12) being treated with a mean CBZ dose of 1025 milligrams (mg) (range 40
administered a single 600 mg oral dose of oxcarbazepine and were randomized, a week later, to receive
oxcarbazepine three times daily or matched placebo for 3 weeks. Active controls (n=7) were untreated p
received the single 600 mg oxcarbazepine dose and 3 weeks active treatment. Study results showed tha
the concentration-time curve (AUC) for MHD at steady state was reduced by 40% (90% confidence inter
57% decrease) in the CBZ-treated group compared to the active controls (p less than 0.05) while AUC fo
significantly. Although the exact mechanism for this decrease is unknown, it was partially attributed to a p
of oxcarbazepine metabolism by carbamazepine, a strong inducer of cytochrome P450 enzymes (McKee
Info TRILEPTAL(R) oral tablets, oral suspension, 2005).

3.5.1.DU Paliperidone
1) Interaction Effect: decreased paliperidone concentration
2) Summary: Concomitant use of paliperidone and carbamazepine decreased the maximum concentration (C
area under the concentration-time curve (AUC) values of paliperidone by 37%. Coadministration with carbam
CYP3A4 inducer, could increase paliperidone renal clearance by 35%. The dose of paliperidone should be ev
administered concurrently with carbamazepine. If therapy with carbamazepine is discontinued, the dose of pa
be decreased if necessary (Prod Info INVEGA(TM) extended-release oral tablets, 2007).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of paliperidone and carbamazepine resulted in decreased paliperi
concentrations. Dosing of paliperidone should be evaluated when it is administered concurrently with carbam
with carbamazepine is discontinued, the dose of paliperidone should be decreased if necessary(Prod Info IN
extended-release oral tablets, 2007).
7) Probable Mechanism: induction of paliperidone metabolism
8) Literature Reports
a) Coadministration of paliperidone 6 mg daily and carbamazepine 200 mg twice daily decreased the pa
steady-state maximum concentration (Cmax) and area under the concentration-time curve (AUC) by app
This decrease is caused by a 35% increase in renal clearance of paliperidone. There is little effect on the
bioavailability of paliperidone when coadministered with carbamazepine. Carefully evaluate paliperidone
initiation or discontinuation of carbamazepine (Prod Info INVEGA(TM) extended-release oral tablets, 200

3.5.1.DV Pancuronium
1) Interaction Effect: decreased pancuronium duration of action
2) Summary: It has been demonstrated that, in patients taking carbamazepine for at least one month prior to
pancuronium, the recovery time after being given pancuronium was about 65% faster when compared to con
& Ebrahim, 1987a).
3) Severity: moderate
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Monitor patients for an appropriate clinical response to the neuromuscular blocker.
intervals or higher doses of pancuronium may be needed in patients receiving carbamazepine.
7) Probable Mechanism: unknown
8) Literature Reports
a) Nine patients on chronic carbamazepine therapy undergoing craniotomy for tumors or cerebrovascula
pancuronium 0.1 mg/kg intravenously to facilitate endotracheal intubation. As compared with controls, th
from neuromuscular blockade was significantly (65%) reduced. Times to percent recovery of baseline tw
controls and the carbamazepine group are as follows: 25%, 85 vs 30 minutes; 50%, 106 vs 39 minutes;
minutes; 90%, 149 vs 57 minutes. Carbamazepine and pancuronium may compete for binding sites at th
junction or carbamazepine may increase the rate of pancuronium metabolism (Roth & Ebrahim, 1987).

3.5.1.DW Pargyline
1) Interaction Effect: hypertensive urgency, hyperpyrexia, and seizures
2) Summary: Concomitant MAO inhibitor and carbamazepine therapy is contraindicated (Prod Info Tegretol(
Simultaneous use may theoretically result in hyperpyrexia, excitation, and seizure activity (Prod Info Parnate(
Info Tegretol(R), 1998j; Thweatt, 1986j). However, there is preliminary evidence that the combination of carba
MAOI may be safe and efficacious, even in some refractory cases (Ketter et al, 1995u; Barker & Eccleston, 1
controlled studies are needed.
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of carbamazepine and monoamine oxidase inhibitors
contraindicated by the manufacturer. Monoamine oxidase inhibitors should be discontinued for a minimum of

if the clinical situation permits, before carbamazepine therapy is initiated.
7) Probable Mechanism: unknown
8) Literature Reports
a) A double-blind study was conducted in ten inpatients with depression that had proved refractory to m therapies (electroconvulsive therapy, tricyclic antidepressants, monoamine oxidase inhibitors, lithium, ca benzodiazepines, and antipsychotics). In addition to their regular carbamazepine and lithium doses, four phenelzine (mean maximum dose 67.5 mg daily) and six patients received tranylcypromine (mean maxir daily) for a mean duration combination therapy of 52.2 days. During MAOI coadministration, serum conc carbamazepine and lithium did not change significantly from baseline values. Self-rated side effects were different. Four patients (three on phenelzine and one on tranylcypromine) responded to this therapy and discharged (Ketter et al, 1995t).
b) A 60-year-old woman who had an atypical endogenous, depressive illness of psychotic intensity was intermittently with cyclic antidepressants and intermittent electroconvulsive therapy. Following an acute v illness, she was treated successfully with a combination of phenelzine and L-tryptophan. Following a few improvement, her situation worsened and she was subsequently treated with zimelidine and lithium. Faili placed on a regimen of tranylcypromine with doses increasing progressively up to 30 mg daily in conjunc and tryptophan. Subsequently, carbamazepine was added in small doses with increments to achieve a p approximately 5 mg/L. This regimen proved successful, and she was discharged home and had remaine two months of follow up at the time of publication (Barker & Eccleston, 1984t).
c) Addition of tranylcypromine to carbamazepine therapy did not significantly affect carbamazepine seru (Joffe et al, 1985j). Conversely, five patients on tranylcypromine need a mean daily dose of carbamazep achieve a carbamazepine blood level of 8.0-11.1 mcg/mL. Four other patients receiving phenelzine only daily dose of carbamazepine 450 mg to attain a blood level of 8.7-10.9 mcg/mL (Barklage et al, 1992j).

3.5.1.DX Pentobarbital
1) Interaction Effect: decreased carbamazepine effectiveness with loss of seizure control
2) Summary: Concomitant use of carbamazepine and primidone (a prodrug of phenobarbital) has been sugg primidone concentration/dose ratio, while increasing the phenobarbital concentration to primidone concentrat al, 1983e). Concurrent therapy has also been reported to lower carbamazepine concentrations (Benetello & F with the barbiturate decreasing the level of carbamazepine while increasing the level of 10, 11-epoxide metab carbamazepine (McKauge et al, 1981c; Eichelbaum et al, 1985b). Evidence from these studies indicates that effects may be more pronounced in children.
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: With combined carbamazepine-pentobarbital therapy, monitor patients for seizure a pediatric patients, and adjust doses accordingly.
7) Probable Mechanism: microsomal enzyme induction with altered metabolism of either drug
8) Literature Reports
a) Concomitant administration of primidone and carbamazepine has been reported to result in lack of se low levels of carbamazepine in a 15 year-old male with partial complex seizures. Withdrawal of the primi significant increases in carbamazepine serum levels with decreases in carbamazepine-10, 11-epoxide le reduction (60%) in carbamazepine clearance (Benetello & Furlanut, 1987d).
b) A study of primidone levels and metabolism related to age and coadministration of other anticonvulsa children metabolize primidone more extensively than older persons and that coadministration of carbama primidone causes lower primidone to dose ratios and higher derived phenobarbital to primidone levels co primidone monotherapy (Battino et al, 1983d).
c) Decreased levels of primidone, which is converted to phenobarbital and PEMA in vivo, have been rep taking carbamazepine. A retrospective study statistically analyzed routine determinations of serum conce anticonvulsant medications in patients on combination regimens. A phenobarbital-carbamazepine interac specifically examined. A lowering of primidone levels during combination therapy with carbamazepine wa difference was not statistically significant. It was unknown how long patients were on primidone therapy i before the levels were taken, so auto-induction of primidone could not be ruled out (Windofer & Saver, 1
d) One study prospectively examined carbamazepine in patients already on other anticonvulsants. Eigh studied. Four patients were on phenytoin and phenobarbital, and four were on phenytoin, phenobarbital Although the authors concluded that serum phenobarbital and primidone levels appeared to actually incr patients after nine days of carbamazepine therapy, numerical data were not given. The increased levels and primidone could reflect only the incremental changes typical of rises to steady state levels (Cereghir
e) One study examined 14 patients on concomitant carbamazepine and phenobarbital therapy. A mean carbamazepine levels was noted with an increase in levels of carbamazepine epoxide and free carbama The carbamazepine epoxide to carbamazepine ratio was also increased in these patients. No effect on p phenobarbital metabolite levels was observed (Ramsay et al, 1990h). Similarly, a prospective, controlled carbamazepine reduction and discontinuation produced no change in phenobarbital levels in patients on therapy (Duncan et al, 1991c).
f) If phenytoin or carbamazepine (or any prodrugs) is used in pregnant women, there is a substantially ir teratogenicity with many combinations of other anticonvulsants. The teratogenicity of these drugs is large related to the levels of the reactive epoxide metabolites (Buehler et al, 1990h; Van Dyke et al, 1991h; Fir The epoxide/parent drug ratio is generally increased when phenytoin or carbamazepine is combined with

other drugs that induce cytochrome P450 enzymes (3A4, 2C9, 2C19) (barbiturates, felbamate), or drugs epoxide hydrolase, such as valproic acid, progabide, and lamotrigine (Bianchetti et al, 1987h; Ramsay et et al, 1996g). Such combinations increase the risk of major birth defects 3- to 4-fold over monotherapy a over background rates.

3.5.1.DY Phenelzine

1) Interaction Effect: hypertensive urgency, hyperpyrexia, and seizures

2) Summary: Concomitant MAO inhibitor and carbamazepine therapy is contraindicated (Prod Info Tegretol(Simultaneous use may theoretically result in hyperpyrexia, excitation, and seizure activity (Prod Info Parnate(Info Tegretol(R), 1998a; Thweatt, 1986a). However, there is preliminary evidence that the combination of car an MAOI may be safe and efficacious, even in some refractory cases (Ketter et al, 1995c; Barker & Ecclestor controlled studies are needed.

3) Severity: contraindicated

4) Onset: rapid

5) Substantiation: theoretical

6) Clinical Management: Avoid concurrent administration of carbamazepine and monoamine oxidase inhibitc monoamine oxidase inhibitors 14 days or longer before starting carbamazepine therapy. Successful concomi reported; monitor carbamazepine levels and adjust doses accordingly.

7) Probable Mechanism: unknown

8) Literature Reports

a) A double-blind study was conducted in ten inpatients with depression that had proved refractory to m therapies (electroconvulsive therapy, tricyclic antidepressants, monoamine oxidase inhibitors, lithium, ca benzodiazepines, and antipsychotics). In addition to their regular carbamazepine and lithium doses, four phenelzine (mean maximum dose 67.5 mg daily) and six patients received tranylcypromine (mean maxir daily) for a mean duration combination therapy of 52.2 days. During MAOI coadministration, serum conc carbamazepine and lithium did not change significantly from baseline values. Self-rated side effects were different. Four patients (three on phenelzine and one on tranylcypromine) responded to this therapy and discharged (Ketter et al, 1995b).

b) A 60-year-old woman who had an atypical endogenous, depressive illness of psychotic intensity was intermittently with cyclic antidepressants and intermittent electroconvulsive therapy. Following an acute v illness, she was treated successfully with a combination of phenelzine and L-tryptophan. Following a few improvement, her situation worsened and she was subsequently treated with zimelidine and lithium. Faili placed on a regimen of tranylcypromine with doses increasing progressively up to 30 mg daily in conjunc and tryptophan. Subsequently, carbamazepine was added in small doses with increments to achieve a p approximately 5 mg/L. This regimen proved successful, and she was discharged home and had remaine two months of follow up at the time of publication (Barker & Eccleston, 1984b).

c) Addition of tranylcypromine to carbamazepine therapy did not significantly affect carbamazepine seru (Joffe et al, 1985a). Conversely, five patients on tranylcypromine need a mean daily dose of carbamazep achieve a carbamazepine blood level of 8.0 to 11.1 mcg/mL. Four other patients receiving phenelzine on daily dose of carbamazepine 450 mg to attain a blood level of 8.7 to 10.9 mcg/mL (Barklage et al, 1992a

3.5.1.DZ Phenobarbital

1) Interaction Effect: decreased carbamazepine effectiveness with loss of seizure control

2) Summary: Concomitant use of carbamazepine and primidone (a prodrug of phenobarbital) has been sugg primidone concentration/dose ratio, while increasing the phenobarbital concentration to primidone concentrat al, 1983a). Concurrent therapy has also been reported to lower carbamazepine concentrations (Benetello & F with the barbiturate decreasing the level of carbamazepine while increasing the level of carbamazepine meta al, 1981a; Eichelbaum et al, 1985). Evidence from these studies indicates that the metabolic effects may be r in children.

3) Severity: moderate

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: With combined carbamazepine-phenobarbital therapy, monitor patients for seizure pediatric patients, and adjust doses accordingly.

7) Probable Mechanism: microsomal enzyme induction with altered metabolism of either drug

8) Literature Reports

a) Concomitant administration of primidone and carbamazepine has been reported to result in lack of se low levels of carbamazepine in a 15 year-old male with partial complex seizures. Withdrawal of the primi significant increases in carbamazepine serum levels with decreases in carbamazepine-10, 11-epoxide le reduction (60%) in carbamazepine clearance (Benetello & Furlanut, 1987).

b) A study of primidone plasma levels and metabolism related to age and coadministration of other antic that children metabolize primidone more extensively than older persons and that coadministration of carb primidone causes lower primidone to dose ratios and higher derived phenobarbital to primidone levels cc primidone monotherapy (Battino et al, 1983).

c) Decreased levels of primidone, which is converted to phenobarbital and PEMA in vivo, have been rep taking carbamazepine. A retrospective study statistically analyzed routine determinations of serum conce anticonvulsant medications in patients on combination regimens. A phenobarbital-carbamazepine interac specifically examined. A lowering of primidone levels during combination therapy with carbamazepine wa

difference was not statistically significant. It was unknown how long patients were on primidone therapy i
before the levels were taken, so auto-induction of primidone could not be ruled out (Windofer & Saver, 1
d) A study prospectively examined carbamazepine in patients already on other anticonvulsants. Eight pa
studied. Four patients were on phenytoin and phenobarbital, and four were on phenytoin, phenobarbital
Although the authors concluded that serum phenobarbital and primidone levels appeared to actually incr
patients after nine days of carbamazepine therapy, numerical data were not given. The increased levels
and primidone could reflect only the incremental changes typical of rises to steady-state levels (Cereghir
e) A study was done on 14 patients on concomitant carbamazepine and phenobarbital therapy. A mean
carbamazepine levels was noted with an increase in levels of carbamazepine epoxide and free carbama
The carbamazepine epoxide to carbamazepine ratio was also increased in these patients. No effect on p
phenobarbital metabolite levels was observed (Ramsay et al, 1990b). Similarly, a prospective, controlled
carbamazepine reduction and discontinuation produced no change in phenobarbital levels in patients on
therapy (Duncan et al, 1991a).
f) If phenytoin or carbamazepine (or any prodrugs) is used in pregnant women, there is a substantially ir
teratogenicity with many combinations of other anticonvulsants. The teratogenicity of these drugs is large
related to the levels of the reactive epoxide metabolites (Buehler et al, 1990b; Van Dyke et al, 1991b; Fir
The epoxide/parent drug ratio is generally increased when phenytoin or carbamazepine is combined with
other drugs that induce cytochrome P450 enzymes (3A4, 2C9, 2C19) (barbiturates, felbamate), or drugs
epoxide hydrolase, such as valproic acid, progabide, and lamotrigine (Bianchetti et al, 1987b; Ramsay et
et al, 1996b). Such combinations increase the risk of major birth defects 3- to 4-fold over monotherapy a
over background rates.

3.5.1.EA Phenprocoumon

1) Interaction Effect: decreased anticoagulant effectiveness
2) Summary: Concomitant carbamazepine and warfarin therapy has been reported to result in a decreased a
effect, secondary to the induction of hepatic metabolism of the anticoagulant (Massey, 1983b; Cohen & Arms
Koch-Weser & Koch-Weser, 1975b; Kendall & Boivin, 1981b; Hansen et al, 1971c).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: In patients receiving oral anticoagulant therapy, the prothrombin time ratio or INR (i
normalized ratio) should be closely monitored with the addition and withdrawal of treatment with carbamazep
reassessed periodically during concurrent therapy. Adjustments of the phenprocoumon dose may be necessa
maintain the desired level of anticoagulation.
7) Probable Mechanism: increased phenprocoumon metabolism

3.5.1.EB Phenytoin

1) Interaction Effect: increased phenytoin concentrations and decreased carbamazepine concentrations
2) Summary: Concurrent use of phenytoin and carbamazepine may decrease carbamazepine levels (Zielinsk
1987a; Randall & Tett, 1993). The addition of carbamazepine to phenytoin therapy may decrease (Hansen et
increase (Browne et al, 1988) phenytoin levels.
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Serum levels of both phenytoin and carbamazepine should be measured after initia
discontinuation of either agent, with appropriate dosage adjustment made accordingly. Serum levels should a
following dosage adjustments and periodically thereafter.
7) Probable Mechanism: inhibition of cytochrome P450 2C19-mediated metabolism of phenytoin by carbama
8) Literature Reports
a) Twenty-four epileptic patients who were stabilized on phenytoin (PHT) and had carbamazepine (CBZ
drug regimen were studied. The mean phenytoin level increased from 13.89 +/- 4.68 to 19 +/- 4.75 (35.9
effect of carbamazepine on phenytoin in an individual is unpredictable; 12 of the subjects showed no cha
levels while the other 12 patients showed an average increase of 81.3% in phenytoin concentration. Five
with increased levels had symptoms of acute phenytoin toxicity (Zielinski et al, 1985).
b) Concomitant administration of carbamazepine and phenytoin has been reported to result in a dual int
simultaneous effects of inhibition of phenytoin metabolism by carbamazepine and induction of carbamaz
by phenytoin. The result is potential phenytoin intoxication and significant reductions of carbamazepine p
concentrations to subtherapeutic levels. These dual effects appear to be especially significant when phe
levels approach a change from linear to saturation kinetics. It is suggested that the interaction may be av
minimized by adjusting phenytoin plasma levels to approximately 13 mcg/mL prior to the addition of carb
regimen or increasing carbamazepine doses (Zielinski & Haidukewych, 1987).
c) Factors influencing simultaneous plasma concentrations of carbamazepine and its epoxide metabolite
(McKauge et al, 1981) and it was found that plasma carbamazepine concentrations were significantly lov
taking carbamazepine and phenytoin than those taking carbamazepine alone. In contrast to another stud
epoxide levels were unaltered (Pynnonen et al, 1980). Other researchers studied carbamazepine plasma
four groups of epileptic patients on a variety of anticonvulsants (Christiansen & Dam, 1973). Their results
administration of phenytoin or phenobarbital to patients receiving carbamazepine results in a significant
carbamazepine plasma concentration when compared to patients receiving carbamazepine alone. It sho

however, that some subjects in the trial were treated with carbamazepine for only one week prior to the i phenytoin. Carbamazepine has been shown to induce its own metabolism for up to 30 days after the initi thus lowering carbamazepine plasma concentration (Pynnonen et al, 1980). This may account for some carbamazepine plasma concentration in subjects also receiving phenytoin.

d) A prospective controlled study of the effects of reduction and discontinuation of phenytoin and carbar levels of concomitant antiepileptic drugs was conducted (Duncan et al, 1991). Phenytoin discontinuation 48% increase in total carbamazepine concentration and a 30% increase in free carbamazepine concentr change in carbamazepine epoxide concentrations. The authors suggest that phenytoin is a strong induce enzymes metabolizing carbamazepine to carbamazepine epoxide, but has less of an effect on the epoxi enzyme. This results in elevations in carbamazepine-epoxide/carbamazepine ratios in patients on conco Conversely, when carbamazepine was discontinued, phenytoin concentrations decreased by a mean of change in free fraction. The authors propose that this may result from inhibition of phenytoin metabolism carbamazepine. There appeared to be no impact on protein binding of either drug. Similar results were n researchers in 49 patients on concomitant phenytoin and carbamazepine therapy (Ramsay et al, 1990a)

e) If phenytoin or carbamazepine is used in pregnant women, there is a substantially increased risk of te many combinations of other anticonvulsants. The teratogenicity of these drugs is largely or wholly relatec the reactive epoxide metabolites (Buehler et al, 1990a; Van Dyke et al, 1991a; Finnell et al, 1992a). The drug ratio is generally increased when phenytoin or carbamazepine is combined with each other, any oth induce cytochrome P450 enzymes (3A4, 2C9, 2C19), or drugs which inhibit epoxide hydrolase, such as progabide and lamotrigine (Bianchetti et al, 1987a; Ramsay et al, 1990a). Such combinations increase th birth defects three- to four-fold over monotherapy and about 10-fold over background rates.

3.5.1.EC Pipecuronium

1) Interaction Effect: resistance to neuromuscular blockade

2) Summary: Phenytoin and carbamazepine have been reported to cause some resistance to neuromuscula patients treated with pipecuronium. A prolonged onset time of action was observed in patients with therapeut levels, but the accelerated recovery from paralysis was seen in all patients treated with anticonvulsants, rega plasma level (Hans et al, 1995a; Jellish et al, 1993a).

3) Severity: moderate

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: In patients on chronic carbamazepine therapy, higher doses of pipecuronium may b the depth of neuromuscular blockade and adjust the dose of pipecuronium accordingly.

7) Probable Mechanism: unknown

8) Literature Reports

a) Twenty adults scheduled for neurosurgery were enrolled in a study. The patients were then divided in group 1 (n=10) was not on anticonvulsant therapy, and group 2 (n=10) was being treated with either phe carbamazepine (n=5). All patients achieved muscle relaxation by a single intravenous dose of pipecuron The onset time was prolonged in patients receiving anticonvulsants when compared to controls (230.5 s seconds). Of the patients who had therapeutic anticonvulsant levels (n=6), the onset time was more prol seconds) than the patients (n=4) who had subtherapeutic levels (181.8 seconds). The recovery index wa shortened in patients who were receiving anticonvulsant therapy when compared to controls (35 min vs. plasma anticonvulsant level was not a discriminant factor for recovery from the neuromuscular blockade

b) An accelerated recovery rate from pipecuronium-induced neuromuscular blockade in patients receivi alone and in combination with other anticonvulsants was observed. Nineteen adult patients were divided six healthy patients who had never received any anticonvulsant medications, and 13 epileptic patients wi seizures who had been treated for years with anticonvulsants. Of these 13 epileptic patients, they were f a group who received carbamazepine as monotherapy (n=6) and a group who was treated with carbama phenytoin or valproic acid (n=7). Anesthesia was induced with thiopental sodium and fentanyl prior to a s bolus dose of pipecuronium 0.08 mg/kg. No statistical significance was reached when comparing the tim (T-1 25%), T-1 50%, and T-1 75%, although there was a trend suggesting that patients on carbamazepir the effects of pipecuronium more quickly than controls. However, the train-of-four recovery times were si shortened in the carbamazepine monotherapy group and the multiple anticonvulsant group when compa Results were as follows when comparing controls with the carbamazepine monotherapy and carbamaze anticonvulsant groups: train-of-four recovery to 10% (TR 10%), 142 vs. 101 vs. 78 minutes; TR 20%, 16 minutes; and TR 25%, 172 vs. 130 vs. 101 minutes (Jellish et al, 1993).

3.5.1.ED Praziquantel

1) Interaction Effect: decreased praziquantel effectiveness

2) Summary: A controlled study demonstrated that carbamazepine reduced the AUC of praziquantel by 90% plasma level by 92% (Bittencourt et al, 1992). Phenytoin also significantly reduced praziquantel AUC and pea concentration in the same study. Because seizure disorders commonly accompany neurocysticercosis, comb these agents may frequently be necessary. Cimetidine (an enzyme inhibitor) has been successfully employed counteract the enzyme induction caused by phenytoin and phenobarbital, however these results have not be controlled prospective study (Dachman et al, 1994).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable
6) Clinical Management: If concomitant use is necessary, an increased dose of praziquantel may be required effective.
7) Probable Mechanism: increased praziquantel metabolism

3.5.1.EE Prednisolone
1) Interaction Effect: decreased prednisolone effectiveness
2) Summary: Carbamazepine has been demonstrated to increase the metabolism of prednisolone (Privitera Olivesi, 1986f).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Monitor therapeutic efficacy of prednisolone. An increase in prednisolone dosage m after three to five days of concurrent carbamazepine therapy.
7) Probable Mechanism: increased prednisolone metabolism

3.5.1.EF Prednisone
1) Interaction Effect: decreased prednisone effectiveness
2) Summary: Carbamazepine has been demonstrated to increase the metabolism of corticosteroids (Olivesi, al, 1982d). Although not specifically reported for prednisone, a similar interaction could be expected.
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Monitor therapeutic efficacy of the corticosteroid. An increase in the steroid dosage after three to five days of concurrent carbamazepine therapy.
7) Probable Mechanism: increased prednisone metabolism

3.5.1.EG Primidone
1) Interaction Effect: decreased carbamazepine effectiveness with loss of seizure control
2) Summary: Concomitant use of carbamazepine and primidone (a prodrug of phenobarbital) may lower the concentration/dose ratio, while increasing the phenobarbital concentration to primidone concentration ratio (E 1983c). Concurrent therapy has also been reported to lower carbamazepine concentrations (Benetello & Furl the barbiturate decreasing the level of carbamazepine while increasing the level of carbamazepine metabolite 1981b; Eichelbaum et al, 1985a). Evidence from these studies indicates that the metabolic effects may be mo children.
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: With combined carbamazepine-primidone therapy, monitor patients for seizure activ pediatric patients, and adjust doses accordingly.
7) Probable Mechanism: microsomal enzyme induction with altered metabolism of either drug
8) Literature Reports
a) Concomitant administration of primidone and carbamazepine has been reported to result in lack of se low levels of carbamazepine in a 15-year-old male with partial complex seizures. Withdrawal of the primi significant increases in carbamazepine serum levels with decreases in carbamazepine-10,11-epoxide le reduction (60%) in carbamazepine clearance (Benetello & Furlanut, 1987b).
b) A study of primidone plasma levels and metabolism related to age and coadministration of other antic done. This study found that children metabolize primidone more extensively than older persons and that of carbamazepine with primidone causes lower primidone to dose ratios and higher derived phenobarbita levels compared with primidone monotherapy (Battino et al, 1983b).
c) Decreased levels of primidone, which is converted to phenobarbital and PEMA in vivo, have been rep taking carbamazepine. A retrospective study statistically analyzed routine determinations of serum conce anticonvulsant medications in patients on combination regimens. A phenobarbital-carbamazepine interac specifically examined. A lowering of primidone levels during combination therapy with carbamazepine wa difference was not statistically significant. It was unknown how long patients were on primidone therapy i before the levels were taken, so auto-induction of primidone could not be ruled out (Windofer & Saver, 1
d) One study analyzed 14 patients on concomitant carbamazepine and phenobarbital therapy. A mean c carbamazepine levels were noted with an increase in levels of carbamazepine epoxide and free carbama No effect on phenobarbital or phenobarbital metabolite levels was observed (Ramsay et al, 1990c). Simi prospective, controlled study of carbamazepine reduction and discontinuation produced no change in ph in patients on concomitant therapy (Duncan et al, 1991b).
e) If phenytoin or carbamazepine is used in pregnant women, there is a substantially increased risk of te many combinations of other anticonvulsants. The teratogenicity of these drugs is largely or wholly related the reactive epoxide metabolites (Buehler et al, 1990c; Van Dyke et al, 1991c; Finnell et al, 1992c). The drug ratio is generally increased when phenytoin or carbamazepine is combined with each other, any oth induce cytochrome P450 enzymes (3A4, 2C9, 2C19), or drugs which inhibit epoxide hydrolase, such as progabide and lamotrigine (Bianchetti et al, 1987c; Ramsay et al, 1990c). Such combinations increase th birth defects three- to four-fold over monotherapy and about 10-fold over background rates.

3.5.1.EH Procarbazine

1) Interaction Effect: hypertensive urgency, hyperpyrexia, and seizures

2) Summary: Concomitant MAO inhibitor and carbamazepine therapy is contraindicated (Prod Info Tegretol(
Simultaneous use may theoretically result in hyperpyrexia, excitation, and seizure activity (Prod Info Parnate(
Info Tegretol(R), 1998g; Thweatt, 1986g). However, there is preliminary evidence that the combination of car
an MAOI may be safe and efficacious, even in some refractory cases (Ketter et al, 1995o; Barker & Eccleston
controlled studies are needed.

3) Severity: contraindicated

4) Onset: rapid

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of carbamazepine and monoamine oxidase inhibitors
contraindicated by the manufacturer. Monoamine oxidase inhibitors should be discontinued for a minimum of
if the clinical situation permits, before carbamazepine therapy is initiated.

7) Probable Mechanism: unknown

8) Literature Reports

a) A double-blind study was conducted in ten inpatients with depression that had proved refractory to m
therapies (electroconvulsive therapy, tricyclic antidepressants, monoamine oxidase inhibitors, lithium, ca
benzodiazepines, and antipsychotics). In addition to their regular carbamazepine and lithium doses, four
phenelzine (mean maximum dose 67.5 mg daily) and six patients received tranylcypromine (mean maxir
daily) for a mean duration combination therapy of 52.2 days. During MAOI coadministration, serum conc
carbamazepine and lithium did not change significantly from baseline values. Self-rated side effects were
different. Four patients (three on phenelzine and one on tranylcypromine) responded to this therapy and
discharged (Ketter et al, 1995n).

b) A 60-year-old woman who had an atypical endogenous, depressive illness of psychotic intensity was
intermittently with cyclic antidepressants and intermittent electroconvulsive therapy. Following an acute v
illness, she was treated successfully with a combination of phenelzine and L-tryptophan. Following a few
improvement, her situation worsened and she was subsequently treated with zimelidine and lithium. Faili
placed on a regimen of tranylcypromine with doses increasing progressively up to 30 mg daily in conjunc
and tryptophan. Subsequently, carbamazepine was added in small doses with increments to achieve a p
approximately 5 mg/L. This regimen proved successful, and she was discharged home and had remaine
two months of follow up at the time of publication (Barker & Eccleston, 1984n).

c) Addition of tranylcypromine to carbamazepine therapy did not significantly affect carbamazepine seru
(Joffe et al, 1985g). Conversely, five patients on tranylcypromine need a mean daily dose of carbamazep
achieve a carbamazepine blood level of 8.0-11.1 mcg/mL. Four other patients receiving phenelzine only
daily dose of carbamazepine 450 mg to attain a blood level of 8.7-10.9 mcg/mL (Barklage et al, 1992g).

3.5.1.EI Propoxyphene

1) Interaction Effect: an increased risk of carbamazepine toxicity (ataxia, nystagmus, diplopia, headache, vo
seizures, coma)

2) Summary: Concurrent propoxyphene therapy significantly increases carbamazepine concentrations and n
moderate to severe neurotoxicity (Allen, 1994a; Oles et al, 1989; Yu et al, 1986a; Kubacka & Ferrante, 1983;
1997a).

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Concurrent use of propoxyphene and carbamazepine should be avoided. Use of ar
analgesic, such as a codeine or hydrocodone, should be considered. If concomitant therapy with propoxyphe
carbamazepine is required, closely monitor carbamazepine serum concentrations. Dosage reductions are like
necessary.

7) Probable Mechanism: decreased hepatic metabolism

8) Literature Reports

a) In an observational study of elderly patients, carbamazepine serum concentrations were significantly
carbamazepine side effects were significantly more common when propoxyphene was taken concomitar
used both carbamazepine and propoxyphene were compared to patients who took either carbamazepine
and to patients who took neither of these drugs. The patients were matched for gender, age, and concor
In patients who took propoxyphene and carbamazepine the average dose of carbamazepine was lower (
compared to 378.6 mg) and the average serum level of carbamazepine was higher (28.2 mcmol/L compa
mcmol/L), than in those that took carbamazepine, but not propoxyphene; serum concentrations of carba
metabolites were also higher. In addition, side effects related to carbamazepine occurred significantly mo
patients taking both carbamazepine and propoxyphene, including depression, sedation, sleep disturbanc
restlessness (Bergendal et al, 1997).

b) Seven outpatients (6 with epilepsy and 1 with trigeminal neuralgia) were receiving carbamazepine alo
combination with phenobarbital, clonazepam, or ethosuximide (Dam & Christiansen, 1977). Study subjec
coadministered propoxyphene 65 mg 3 times a day. In 5 patients, carbamazepine clearance decreased
carbamazepine plasma levels increased 44% to 77%. The other 2 patients discontinued the propoxyphe
due to severe side effects.

c) Six epileptic patients who had taken carbamazepine (600 to 800 mg/day) for more than 6 months we

dextropropoxyphene 65 mg 3 times/day (Hansen et al, 1980). A 66% mean increase in carbamazepine s concentrations was observed 6 days after initiation of propoxyphene dosing.

d) Three elderly patients were administered carbamazepine 200 mg 3 times a day (one patient only rec a day) and dextropropoxyphene 32 mg every 4 hours or 64 mg every 6 hours (Yu et al, 1986). All 3 deve carbamazepine toxicity and 2 became comatose.

e) A 24-year-old epileptic man on maintenance carbamazepine therapy was given dextropropoxyphene ear infection (Allen, 1994). He experienced acute onset ataxia, marked intention tremor, slurred speech, multidirectional nystagmus. On presentation, he was hardly able to stand. During the preceding 24 hours coproxaml tablets (propoxyphene 32.5 mg, acetaminophen 325 mg). A fourfold increase in his carbamaz concentration was found. Carbamazepine was withheld for 48 hours, by which time his serum concentra normal. His symptoms rapidly resolved.

3.5.1.EJ Protriptyline

1) Interaction Effect: decreased protriptyline plasma concentrations and increased carbamazepine plasma c possible toxicity (ataxia, nystagmus, apnea, seizures, coma)

2) Summary: The concomitant use of carbamazepine and tricyclic antidepressants has been reported to dec antidepressant plasma concentrations and raise carbamazepine levels (Leinonen et al, 1991j; Brown et al, 19 Kragh-Sorensen, 1993a). Although not reported specifically for protriptyline, a similar interaction would be ex Carbamazepine is known to induce enzyme action. Tricyclic antidepressants can lower the seizure threshold stabilized on anticonvulsants.

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Monitor patients for antidepressant efficacy and carbamazepine toxicity (nausea, vo tremor, blurred vision) with concurrent use. Doses of protriptyline may need to be increased and carbamazep reduced. Serum carbamazepine levels might be considered when a tricyclic antidepressant is added to or dis therapy.

7) Probable Mechanism: alterations in hepatic metabolism

8) Literature Reports

a) The effect of carbamazepine on doxepin levels was studied in 17 psychiatric inpatients stabilized for a days prior to measurement of baseline antidepressant concentrations. The average daily doxepin dosag Carbamazepine was added in a mean dose of 593 mg and continued over a 4-week period. In patients r combination therapy, serum doxepin concentrations were decreased an average of 46% (Leinonen et al,

b) Concomitant administration of imipramine and carbamazepine to children with attention deficit disord reported to result in a 50% decrease in the total plasma concentration of imipramine plus desipramine (E

c) One case was reported in which nortriptyline levels dropped by more than half after carbamazepine w & Kragh-Sorensen, 1993).

3.5.1.EK Psyllium

1) Interaction Effect: decreased absorption and effectiveness of carbamazepine

2) Summary: In healthy volunteers, carbamazepine bioavailability was reduced when psyllium was administe (Etman, 1995a). If patients are treated with carbamazepine and psyllium, their administration times of should far as possible, and plasma levels of carbamazepine should be monitored (Etman, 1995a).

3) Severity: moderate

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: If patients are treated with carbamazepine and psyllium, their administration times s separated as far as possible, and plasma levels of carbamazepine should be monitored.

7) Probable Mechanism: reduced dissolution rate and slowed diffusion of carbamazepine

8) Literature Reports

a) Decreased absorption, a decreased maximum concentration, and reduced area under the curve (AU carbamazepine were noted after administration with a psyllium product to 4 healthy volunteers. Voluntee other medications one week prior to and during the study. Carbamazepine 200 mg orally was administer husk (psyllium) suspended in 200 milliliters (mL) of water. Cmax with carbamazepine alone was 2.33 mi (mcg/hour), which was reduced to 1.11 mcg/hour when psyllium was added. AUC with carbamazepine a micrograms/milliliter/hour (mcg/mL/hour), when psyllium was added AUC was reduced to 25.03 mcg/mL increased from 5.52 hours to 24.14 hours with psyllium cotreatment. Bioavailability was reduced to 55% carbamazepine alone. Statistical significance values were not provided. The mechanism of interaction w due to a decrease in the amount of biological fluid available in the gastrointestinal tract as a result of wat psyllium, which would reduce the dissolution rate of the drug from the tablet. Diffusion of the drug may b result of gel formation by psyllium. Administration times of carbamazepine and psyllium should be separ possible, and plasma levels of carbamazepine should be monitored (Etman, 1995).

3.5.1.EL Quetiapine

1) Interaction Effect: decreased serum quetiapine concentrations

2) Summary: Increased doses of quetiapine may be required to maintain control of symptoms of schizophrer receiving carbamazepine, a hepatic enzyme inducer (Prod Info Seroquel(R), 2001).

3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Caution is indicated when quetiapine is administered with carbamazepine or other i cytochrome P450 3A. Increased doses of quetiapine may be required to maintain control of psychotic sympto receiving quetiapine and carbamazepine.
7) Probable Mechanism: unknown

3.5.1.EM Quinupristin
1) Interaction Effect: an increased risk of carbamazepine toxicity (ataxia, nystagmus, diplopia, headache, vo seizures, coma)
2) Summary: Quinupristin/dalfopristin is a potent inhibitor of cytochrome P450 3A4 enzymes and may cause carbamazepine concentrations when administered concurrently. Because carbamazepine possesses a narro window, carbamazepine concentrations should be closely monitored during therapy with quinupristin/dalfopris carbamazepine should be adjusted accordingly (Prod Info Synercid(R) I.V., 1999).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor the trough carbamazepine concentrations when therapy with quinupristin/d administered concurrently. Dose reductions of carbamazepine may be required. Also monitor the patient for e carbamazepine toxicity.
7) Probable Mechanism: inhibition of cytochrome P450 3A4-mediated carbamazepine metabolism

3.5.1.EN Ranolazine
1) Interaction Effect: decreased ranolazine plasma concentrations
2) Summary: The concomitant use of carbamazepine and ranolazine is contraindicated. Ranolazine is a sub glycoprotein and is primarily metabolized by CYP3A. In pharmacokinetic studies, coadministration of 600 mg CYP3A and P-glycoprotein inducer) with ranolazine 1000 mg twice daily resulted in a 95% decrease in ranol concentration. Although not evaluated, concomitant use of ranolazine and other CYP3A and P-glycoprotein i carbamazepine, could result in a similar interaction (Prod Info RANEXA(R) extended-release oral tablets, 200
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concomitant use of ranolazine and CYP3A inducers, such as carbamazepine, i (Prod Info RANEXA(R) extended-release oral tablets, 2008).
7) Probable Mechanism: induction of P-glycoprotein- and CYP3A-mediated ranolazine metabolism

3.5.1.EO Rapacuronium
1) Interaction Effect: resistance to neuromuscular blocking action
2) Summary: Some medications, including carbamazepine, may enhance resistance to the neuromuscular b nondepolarizing agents such as rapacuronium (Prod Info Raplon(TM), 1999). Dose adjustments of rapacuror needed when these agents are being used concurrently.
3) Severity: minor
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The dose of rapacuronium may need to be adjusted upward in patients receiving cc carbamazepine.
7) Probable Mechanism: receptor up-regulation

3.5.1.EP Remacemide
1) Interaction Effect: reduced remacemide exposure and increased carbamazepine exposure
2) Summary: Coadministration of carbamazepine with remacemide may significantly decrease serum levels and its active metabolite. A remacemide-induced increase in serum levels of carbamazepine may also occur 1991; Walker & Patsalos, 1995a; Bialer, 1993a).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor the patient for reduced remacemide effectiveness. Higher doses of remace necessary during concomitant therapy with carbamazepine. However, until target therapeutic serum levels/op remacemide are known (as well as its potential for interaction with other anticonvulsants), it will be difficult to with this agent in refractory epilepsy. In addition, because carbamazepine serum concentrations may be mod during concomitant therapy, monitor the patient for signs and symptoms of carbamazepine toxicity.
7) Probable Mechanism: induction by carbamazepine of remacemide metabolism
8) Literature Reports
a) Preliminary studies in epileptic patients receiving either carbamazepine or phenytoin (monotherapy) h significantly lower steady-state serum concentrations of both remacemide and its desglycinated (active) compared to values achieved in healthy volunteers receiving remacemide alone (Muir & Palmer, 1991; V 1995; Bialer, 1993). Serum level reductions of both parent compound and active metabolite have been 5

many patients (Bialer, 1993).
b) In addition, serum concentrations of both carbamazepine and phenytoin have been increased by up t combined remacemide therapy (Walker & Patsalos, 1995). Interaction data for remacemide and other ar unavailable.

3.5.1.EQ Repaglinide
1) Interaction Effect: decreased repaglinide plasma concentrations
2) Summary: Repaglinide is metabolized by the CYP2C8 and CYP3A4 enzyme systems. Coadministration w carbamazepine, an inducer of CYP2C8 and CYP3A4 enzyme systems, may result in decreased repaglinide p concentrations. Use caution if carbamazepine and repaglinide are coadministered (Prod Info PRANDIN(R) or Dosage adjustments to repaglinide may be necessary and blood glucose concentrations should be carefully m
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Caution is advised if carbamazepine and repaglinide are coadministered as this ma induction of repaglinide metabolism, thereby decreasing repaglinide plasma concentrations (Prod Info PRANI 2006). Dosage adjustments to repaglinide may be necessary and blood glucose concentrations should be ca
7) Probable Mechanism: induction of CYP2C8- and CYP3A4-mediated repaglinide metabolism

3.5.1.ER Rifampin
1) Interaction Effect: elevated carbamazepine levels and toxicity (ataxia, nystagmus, diplopia, headache, vor seizures, coma)
2) Summary: Carbamazepine toxicity following the addition of antituberculosis medication to chronic anticonv has been reported (Fleenor et al, 1991a). Carbamazepine levels had previously been 8.5 to 9.5 mcg/mL with toxicity. Isoniazid 300 mg daily was well tolerated for three days prior to the introduction of rifampin 600 mg d hours of initiation of rifampin, the patient developed nausea, ataxia, confusion and drowsiness. The carbama noted to be 16.9 mcg/mL. The authors suggest that rifampin may have augmented the enzyme inhibiting effe
3) Severity: moderate
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Monitor the patient for signs of carbamazepine toxicity, including ataxia, nystagmus headache, vomiting, apnea, seizures, and coma. A carbamazepine plasma concentration may be helpful in d carbamazepine toxicity.
7) Probable Mechanism: inhibition of carbamazepine metabolism

3.5.1.ES Rifapentine
1) Interaction Effect: decreased anticonvulsant effectiveness
2) Summary: The efficacy of anticonvulsants may be impaired with concomitant use of rifapentine. Rifapentin the metabolism of other coadministered drugs that are metabolized by cytochrome P450 3A4 or 2C8/9. Dosa anticonvulsants may be necessary if given concurrently with rifapentine (Prod Info Priftin(R), 2000).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor serum anticonvulsant levels and with concomitant use and adjust doses ac
7) Probable Mechanism: increased hepatic metabolism

3.5.1.ET Risperidone
1) Interaction Effect: increased risperidone clearance
2) Summary: The manufacturer reports that carbamazepine may increase risperidone clearance with chronic Patients should be closely monitored. Patients may be placed on a lower dose of risperidone between 2 to 4 planned discontinuation of carbamazepine therapy to adjust for the expected increase in plasma concentratio plus 9-hydroxyrisperidone. Eleven subjects received risperidone titrated to 6 mg/day orally for 3 weeks, follow coadministration of carbamazepine for an additional 3 weeks. Plasma concentrations of risperidone and 9-hy were decreased by 50%. The plasma concentrations of carbamazepine were unaffected (Prod Info Risperdal 2003a). One published case report describes a patient who had risperidone levels which were less than expe carbamazepine therapy, along with decreased risperidone efficacy. The risperidone level dramatically increas carbamazepine was discontinued (de Leon & Bork, 1997a). Carbamazepine is an inducer of cytochrome P45 enzymes, while risperidone is primarily metabolized by CYP2D6. Whether carbamazepine is also inducing C risperidone may be partly metabolized by CYP3A is uncertain (Lane & Chang, 1998; de Leon & Bork, 1998). decrease in risperidone levels caused by carbamazepine may result in decreased therapeutic efficacy. When used in combination with carbamazepine larger doses of risperidone may be required to achieve or maintain antipsychotic effect (Spina et al, 2000a).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor therapeutic efficacy of risperidone following the addition of carbamazepine weeks of therapy; higher risperidone doses may be needed. Patients may be placed on a lower dose of rispe to 4 weeks before the discontinuation of carbamazepine therapy to adjust for the expected increase in plasm

risperidone plus 9-hydroxyrisperidone.
7) Probable Mechanism: induction of cytochrome P450-mediated metabolism of risperidone by carbamazepi
8) Literature Reports
a) Carbamazepine was reported to induce the metabolism of risperidone in a 22-year-old male with chro resulting in low risperidone levels and lack of effectiveness. The patient was started on carbamazepine 6 risperidone 4 mg daily. The plasma concentration of 9-hydroxyrisperidone was less than half the expecte when the dose of risperidone was doubled to 8 mg daily. After achieving a therapeutic plasma concentra hydroxyrisperidone (19 mcg/L), the dose of carbamazepine was tapered and stopped. Plasma levels of 9 hydroxyrisperidone increased to 49 mcg/L, necessitating a decrease in the dose of risperidone (de Leon
b) Plasma concentrations of risperidone and 9-OH risperidone decreased when carbamazepine was ad when it was discontinued. One study evaluated the pharmacokinetic interactions between risperidone an Thirty-four patients with a DSM-IV diagnosis of schizophrenia, schizoaffective disorder, or bipolar disorde the study. All patients were stabilized on risperidone alone or in combination with carbamazepine for at le Steady-state plasma concentrations of risperidone and 9-hydroxyrisperidone (9-OH risperidone) were co treated with risperidone alone and patients comedicated with carbamazepine. The plasma concentration risperidone and the sum of risperidone and 9-OH risperidone (active moiety) differed significantly among patients evaluated with and without comedication, the plasma concentrations of risperidone and 9-OH ris decreased when carbamazepine was added or increased when it was discontinued. The results demons patients receiving risperidone alone, the concentration of the active moiety (risperidone plus its active me risperidone) was reduced by approximately 70% when carbamazepine was given concomitantly (Spina e
c) The concomitant use of carbamazepine and risperidone leads to a marked decrease in the steady-sta concentrations of risperidone and 9-hydroxyrisperidone through stimulation of an inducible cytochrome a influence of the cytochrome P450 2D6 genotype. A 50-year-old male with chronic schizophrenia and def activity was given carbamazepine with his existing risperidone therapy. Carbamazepine 800 mg/day for 5 to his medication regimens as a mood stabilizer. After 4 weeks of carbamazepine treatment, the patient symptoms including hallucinations, paranoid delusions, ideas of reference, and mild excitement. Plasma risperidone and its active metabolite 9-hydroxyrisperidone, had decreased from 22 and 30 ng/mL, respec Carbamazepine concentration was 8.2 mcg/mL. The risperidone dose was increased to 9 mg/day, carba discontinued, and lorazepam 5 mg/day was added. Psychotic symptoms improved over the following 3 w concentrations of risperidone and 9-hydroxyrisperidone increased to 40 and 57 ng/mL, respectively. A re in the plasma concentrations of risperidone and 9-hydroxyrisperidone suggest that the CYP2D6 genotyp susceptibility to a clinically important interaction with risperidone and carbamazepine (Spina et al, 2001).
d) Eleven schizophrenic patients in a drug interaction study received oral risperidone titrated to 6 mg/da followed by concurrent administration of carbamazepine for an additional 3 weeks. The plasma concentr risperidone and its pharmacologically active metabolite, 9-hydroxyrisperidone, were decreased by about initiation of therapy with carbamazepine, patients should be closely monitored during the first 4-8 weeks, risperidone may need to be adjusted. A dose increase or additional risperidone may need to be consider carbamazepine is discontinued, the dosage of risperidone should be re-evaluated and, if necessary, dec dose of risperidone may be required between 2 to 4 weeks before the planned discontinuation of carbam adjust for the expected increase in plasma concentrations of risperidone plus 9-hydroxyrisperidone (Proc Consta(TM), 2003).

3.5.1.EU Ritonavir
1) Interaction Effect: increased carbamazepine serum concentrations and potential toxicity
2) Summary: Coadministered ritonavir may significantly increase serum concentrations of carbamazepine du inhibition of cytochrome P450 3A enzymes, resulting in carbamazepine toxicity (Prod Info NORVIR(R), 2005; 2000a).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor carbamazepine serum levels and follow patients for signs and symptoms of toxicity (nausea, drowsiness, dizziness, weakness, headache). Reduce doses of carbamazepine as required
7) Probable Mechanism: decreased carbamazepine metabolism
8) Literature Reports
a) A 36-year-old HIV-positive patient maintained on carbamazepine and phenytoin to control seizures ex dizziness and progressive gait disorder after the addition of ritonavir to his antiretroviral treatment. The p managed for over a year when his antiretroviral therapy, consisting of lamivudine, didanosine and saquir augmented with ritonavir 600mg twice a day. At that time, serum phenytoin and carbamazepine levels w 16.5mcg/mL and 6.5mcg/mL, respectively. Approximately two months later, the patient presented with di impaired gait. Carbamazepine serum levels were measured at 18mcg/mL while phenytoin levels remaine (14.7mcg/mL). Carbamazepine was discontinued and replaced with primidone, resulting in resolution of and continued seizure control. Viral load remained undetectable (Garcia et al, 2000).
b) A case report demonstrates a severe interaction between ritonavir and carbamazepine resulting in ca toxicity. A 36-year-old AIDS patient with a history of alcoholism, intravenous drug use, hepatitis B and C tuberculosis, and seizures developed elevated plasma carbamazepine levels leading to CNS disorders v concomitant treatment with ritonavir. His anticonvulsant medication regimen consisted of carbamazepine times daily, phenytoin 200 mg in the morning and 100 mg at night. Two days after initiation of the new ar schedule (after 4 ritonavir doses), he presented with diplopia, disorientation, drowsiness, vertigo, and se

Carbamazepine plasma levels were increased by 99.4% to 16.6 mg/L (4-12), and his phenytoin concentı by 32.7% to 7 mg/L (10-20). Carbamazepine concentration returned to the therapeutic range two days a dosage was reduced to 200 mg three times daily, ritonavir was discontinued and nelfinavir 1000 mg twic initiated. Symptoms of toxicity disappeared as well. The author concludes that blood concentrations of a be monitored during the first 24-48 hours when ritonavir is added to carbamazepine and phenytoin treatr Reduction of the carbamazepine dose may prevent toxicity (Mateu-de Antonio et al, 2001).

3.5.1.EV Rocuronium

1) Interaction Effect: decreased duration of rocuronium-induced neuromuscular blockade
2) Summary: One case report has described a resistance to rocuronium in a patient maintained on chronic c therapy. This resistance is similar to that seen during therapy with other neuromuscular blockers and carbam precise mechanism of this interaction is not known, but may involve both pharmacodynamic and pharmacoki (Baraka & Idriss, 1996a). A study involving 22 healthy individuals undergoing neurosurgical procedures also duration of the rocuronium-induced neuromuscular block is significantly shortened by chronic carbamazepine et al, 1999a).
3) Severity: moderate
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Monitor patients for an appropriate clinical response to the neuromuscular blocker. intervals or higher doses of rocuronium may be needed in patients receiving carbamazepine.
7) Probable Mechanism: induction of rocuronium metabolism via cytochrome P450 enzyme system
8) Literature Reports

a) A 61-year old epileptic male who had been maintained on oral carbamazepine 200 mg three times da underwent cataract surgery. Anesthesia was induced with thiopental and fentanyl prior to the administrat intravenous bolus dose of rocuronium 0.6 mg/kg. This dose of rocuronium is twice the 95% effective dos Rocuronium caused a partial neuromuscular block and was followed by rapid recovery to T1 to 25% of th within five minutes. This response suggests that long-term therapy with carbamazepine causes a resista nondepolarizing neuromuscular blocking effects of rocuronium (Baraka & Idriss, 1996).

b) Twenty-two healthy individuals scheduled for neurosurgical procedures were studied to determine the carbamazepine therapy on the duration of rocuronium-induced neuromuscular blockade. Eleven patients treated with carbamazepine for a minimum of four weeks prior to surgery, while the other eleven patients controls. All patients received oral diazepam one hour prior to surgery, and anesthesia was induced with thiopental. A single bolus dose of rocuronium 0.6 mg/kg, which is two times the ED95, was given intrave the two groups, the lag time and the onset time did not differ significantly. However, when comparing the carbamazepine groups, the time to 10% recovery was 29.2 min vs. 19.8 min, 25% recovery was 36.1 mi 50% recovery was 43.5 min vs. 30.4 min, and 75% recovery was 57.0 min vs. 36.5 min, respectively. Th calculated as the time required for the response to the first stimulus to recover from 25% to 75% of base decreased from 20.8 min in the control group to 10.9 min in the carbamazepine group (Spacek et al, 199

3.5.1.EW Rufinamide

1) Interaction Effect: decreased carbamazepine and rufinamide plasma concentrations
2) Summary: Concomitant administration of carbamazepine and rufinamide may result in rufinamide concen of 19% to 26% (dependent on the carbamazepine dose) and carbamazepine concentration decreases of 7% Carbamazepine decreases are dependent on the concentration of rufinamide, so maximum changes will mos children and other patients who achieve significantly higher levels of rufinamide (Prod Info BANZEL(TM) oral
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Caution is advised if carbamazepine and rufinamide are coadministered as this ma decreased carbamazepine or rufinamide plasma concentrations. Risk of carbamazepine concentration reduc children and in other patients who achieve significantly higher levels of rufinamide (Prod Info BANZEL(TM) o
7) Probable Mechanism: induction of carboxylesterase-mediated rufinamide metabolism by carbamazepine

3.5.1.EX Sabeluzole

1) Interaction Effect: reduced sabeluzole efficacy
2) Summary: In epileptic patients receiving a variety of anticonvulsants (primarily carbamazepine or phenyto combinations), sabeluzole plasma concentrations have been reduced compared to data from healthy subject al, 1995a).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Higher doses of sabeluzole may be required during combined therapy with carbam therapeutic plasma levels of sabeluzole are unknown, dose titration is necessarily empirical.
7) Probable Mechanism: induction by carbamazepine of sabeluzole metabolism
8) Literature Reports

a) In one study, a target minimal trough sabeluzole concentration of 50 ng/mL was not achieved in most receiving anticonvulsants (primarily carbamazepine and/or phenytoin) and sabeluzole in doses of up to 6 (Aldenkamp et al, 1995). In contrast, prior sabeluzole pharmacokinetic studies have consistently demons

levels of 40 to 50 ng/mL with 10-mg twice daily doses (De Deyn et al, 1992). Unpublished data from the (Janssen) also provide evidence of enhanced elimination of sabeluzole when combined with antiepileptic levels of anticonvulsants were unaffected by sabeluzole (Aldenkamp et al, 1995). However, these data n preliminary and are based predominantly on indirect observations; a formal kinetic study in epileptic patie ascertain the magnitude of the interaction with specific anticonvulsants.

3.5.1.EY Saquinavir

1) Interaction Effect: reduced saquinavir effectiveness
2) Summary: Coadministration of carbamazepine and saquinavir may result in reduced saquinavir serum cor Info Invirase(R), 2003). The mechanism of action is thought to be induction by carbamazepine of the cytochro isoenzyme, the enzyme primarily responsible for saquinavir metabolism. The effectiveness of saquinavir is lik decreased in patients receiving carbamazepine-saquinavir therapy due to reduced saquinavir bioavailability.
3) Severity: moderate
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Clinicians may want to consider using alternative medication to carbamazepine in p saquinavir therapy. However, if it becomes necessary to give these agents concurrently, upward adjustments dosing may be needed to maintain antiviral effectiveness.
7) Probable Mechanism: P450 induction of saquinavir metabolism

3.5.1.EZ Selegiline

1) Interaction Effect: an increase in selegiline concentrations
2) Summary: Concomitant administration of carbamazepine and MAO inhibitors, such as selegiline, is contra Info EMSAM(R) transdermal patch, 2006; Prod Info Tegretol(R), 1998). Simultaneous use may theoretically r hyperpyrexia, excitation, and seizure activity (Prod Info Parnate(R), 1995; Prod Info Tegretol(R), 1998; Thwe minimum of 14 days should elapse after discontinuing selegiline before initiating therapy with carbamazepine EMSAM(R) transdermal patch, 2006). However, there is preliminary evidence that the combination of carbam MAOI may be safe and efficacious, even in some refractory cases (Ketter et al, 1995a; Barker & Eccleston, 1 controlled studies are needed.
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of carbamazepine and monoamine oxidase inhibitors contraindicated. Selegiline should be discontinued for a minimum of 14 days, or longer if the clinical situation carbamazepine therapy is initiated.
7) Probable Mechanism: unknown
8) Literature Reports

a) A double-blind study was conducted in ten inpatients with depression that had proved refractory to m therapies (electroconvulsive therapy, tricyclic antidepressants, monoamine oxidase inhibitors, lithium, ca benzodiazepines, and antipsychotics) (Ketter et al, 1995). In addition to their regular carbamazepine and four patients received phenelzine (mean maximum dose 67.5 mg daily) and six patients received tranylc maximum dose 55 mg daily) for a mean duration combination therapy of 52.2 days. During MAOI coadm concentrations of carbamazepine and lithium did not change significantly from baseline values. Self-rate not substantially different. Four patients (three on phenelzine and one on tranylcypromine) responded to were subsequently discharged.

b) A 60-year-old woman who had an atypical endogenous, depressive illness of psychotic intensity was intermittently with cyclic antidepressants and intermittent electroconvulsive therapy. Following an acute v illness, she was treated successfully with a combination of phenelzine and L-tryptophan. Following a few improvement, her situation worsened and she was subsequently treated with zimelidine and lithium. Faili placed on a regimen of tranylcypromine with doses increasing progressively up to 30 mg daily in conjunc and tryptophan. Subsequently, carbamazepine was added in small doses with increments to achieve a p approximately 5 mg/L. This regimen proved successful, and she was discharged home and had remaine two months of follow up at the time of publication (Barker & Eccleston, 1984).

c) Addition of tranylcypromine to carbamazepine therapy did not significantly affect carbamazepine seru case (Joffe et al, 1985). Conversely, five patients on tranylcypromine needed a mean daily dose of carba mg to achieve a carbamazepine blood level of 8.0-11.1 mcg/mL (Barklage et al, 1992). Four other patien phenelzine only required a mean daily dose of carbamazepine 450 mg to attain a blood level of 8.7-10.9

d) In subjects who had received carbamazepine (400 mg/day) for 14 days, slightly increased levels of s metabolites were seen after a single application of selegiline transdermal patch, Emsam (R), 6 mg/24 ho the selegiline plasma levels were nearly 2 fold and variable across the subject population (Prod Info EMS transdermal patch, 2006).

3.5.1.FA Sertraline

1) Interaction Effect: an increased risk of carbamazepine toxicity (ataxia, nystagmus, diplopia, headache, vo seizures, coma)
2) Summary: Coadministration of sertraline and carbamazepine may cause reduced carbamazepine clearan carbamazepine toxicity manifesting in blurred vision, dizziness, tremor, and possibly blood dyscrasias (Joblin Similar interactions have been reported between carbamazepine and two other selective serotonin reuptake i

fluoxetine and fluvoxamine (Pearson, 1990; Fritze et al, 1991). However, in two separate in vivo studies, coad sertraline and carbamazepine under steady-state conditions did not increase the plasma concentrations of ca (Prod Info Zoloft(R), 2002). Two case reports of coadministration of carbamazepine and sertraline resulted in expected levels as well as lack of efficacy of sertraline (Khan et al, 2000).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Due to the potential for elevated carbamazepine levels, patients should be closely f evidence of carbamazepine toxicity when sertraline is added to therapy. Consider measuring carbamazepine concentrations within two to three weeks of adding or discontinuing sertraline, with dosage adjustments as ne cytochrome P450 3A4-mediated metabolism of sertraline, sertraline levels may be lower than expected, whic lack of efficacy of sertraline when carbamazepine is coadministered.

7) Probable Mechanism: inhibition of carbamazepine metabolism, increase in sertraline CYP3A4-mediated n

8) Literature Reports

a) A 24-year-old woman received maintenance carbamazepine 600 mg daily and flecainide 100 mg dail beginning sertraline 100 mg daily, her carbamazepine trough level increased from 4.7 to 8.5 mg/L (norm mg/L), and her blood counts were normal. Two months later, in routine testing before elective surgery, he platelet, and red and white blood cell counts were abnormally low. Postoperatively her blood counts rem blood transfusions, and on day 3 her trough carbamazepine was 11.9 mg/L, although she had missed or On bone marrow examination, erythroid hyperplasia with megaloblastic characteristics and reduced meg numbers were observed. Her hematologic counts began to improve five days after withdrawal of sertralir carbamazepine; she was not rechallenged. Suggested mechanisms of action were reduced carbamazep due to inhibition of cytochrome P450 isoenzymes and carbamazepine protein binding displacement (Job 1994).

b) Sertraline is suspected of inhibiting cytochrome P450IIIA4 (CYP3A4) enzyme activity (DeVane, 1994 carbamazepine is known to be a CYP3A4 substrate, carbamazepine might have a potentially significant sertraline. Conversely, carbamazepine is also a known potent inducer of CYP3A4 and may stimulate the sertraline, resulting in decreased sertraline concentrations (Spina et al, 1996).

c) Two cases have been reported in which concomitant use of sertraline and carbamazepine resulted in efficacy. The first such case describes a 33-year-old female with schizoaffective disorder who had been treated with haloperidol and carbamazepine for 3 years. After a depressive episode, sertraline had been titrated slowly to 300 mg/day. A plasma level for carbamazepine and sertraline was obtained after sertral Sertraline was undetectable with levels below 10 ng/ml. Another case describes a 25-year-old male diag posttraumatic stress disorder who had been successfully treated with carbamazepine for 13 years. Sertr after the patient developed major depressive disorder. Plasma levels were obtained for sertraline and ca during therapy. Sertraline levels were undetectable with carbamazepine doses of 400 mg/day and sertra mg/day (Kahn et al, 2000).

3.5.1.FB Simvastatin

1) Interaction Effect: reduced simvastatin exposure

2) Summary: Concurrent administration of carbamazepine with simvastatin significantly reduced maximum s concentration, serum half-life, and area under the concentration-time curve for both simvastatin and its active simvastatin acid (Ucar et al, 2004).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Monitor cholesterol levels in patients receiving concomitant therapy with carbamaze simvastatin. Simvastatin dose may need to be adjusted.

7) Probable Mechanism: induction of CYP3A4-mediated first-pass metabolism of simvastatin by carbamazep

8) Literature Reports

a) Concurrent administration of carbamazepine with simvastatin significantly reduced simvastatin expos randomized, crossover study with a 2-week wash out period, healthy subjects (n=12) received either no carbamazepine 200 milligrams (mg) once daily for 2 days, after which the active drug group received car mg twice daily for the next 12 days. On day 15 (12 hours after the last carbamazepine dose), subjects fa prior to receiving a single dose of simvastatin 80 mg. Serial blood samples were obtained immediately pr hours after simvastatin administration. Carbamazepine co-administration significantly reduced the mean concentration for both simvastatin and its active metabolite simvastatin acid (from 18.7 nanograms/millili ng/mL and from 3.5 ng/mL to 1.1 ng/mL, respectively; p less than 0.01, both values). Simvastatin and sir mean areas under the concentration-time curves (AUC, 0-infinity) declined from 88.8 ng/mL x hour to 22 and from 33.5 ng/mL x hour to 6.8 ng/mL x hour, respectively (p less than 0.001, both values). Concurre with carbamazepine also significantly reduced simvastatin acid serum mean half-life (from 5.9 hours to 3 than 0.01) (Ucar et al, 2004).

3.5.1.FC Sirolimus

1) Interaction Effect: decreased plasma sirolimus concentration

2) Summary: Sirolimus is extensively metabolized by cytochrome P450 3A4 (CYP3A4) enzymes in the gut w such as carbamazepine, which are cytochrome P450 3A4 inducers, may increase the metabolism of sirolimu decreased sirolimus plasma concentrations. Caution should be used when these two agents are used concor

Rapamune(R), 2005).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Monitor sirolimus levels and adjust sirolimus dosage accordingly. Monitor the patier perform additional tests to determine effectiveness of sirolimus.
7) Probable Mechanism: induction of cytochrome P450-mediated sirolimus metabolism

3.5.1.FD Sorafenib
1) Interaction Effect: decreased sorafenib concentrations
2) Summary: Sorafenib is primarily metabolized by the cytochrome P450 3A4 (CYP3A4) enzymes in the live carbamazepine, which are inducers of CYP3A4, may increase the metabolism of sorafenib, thus decreasing concentrations. Although no drug studies have been conducted between carbamazepine and sorafenib, cauti when these two agents are coadministered (Prod Info NEXAVAR(R) oral tablets, 2005).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Coadministration of carbamazepine and sorafenib may result in decreased sorafeni due to induction of cytochrome P450-mediated sorafenib metabolism by carbamazepine. Use caution if carba sorafenib are administered concurrently. Monitor patients for clinical response to sorafenib.
7) Probable Mechanism: induction of cytochrome P450-mediated sorafenib metabolism

3.5.1.FE St John's Wort
1) Interaction Effect: altered carbamazepine blood concentrations
2) Summary: An open trial involving 8 healthy volunteers taking St. John's Wort (300 milligrams (mg) three ti carbamazepine (400 mg once daily) concomitantly for 14 days demonstrated no alterations of mean carbama (Burstein et al, 2000a). This trial found some individual variability in carbamazepine clearance, indicating that have differing sensitivity to enzyme induction, which may be clinically significant. It is unknown if longer thera days as used in this trial) with St. John's Wort may affect carbamazepine levels due to a more slowly accumu which may induce cytochrome P450 enzymes. Carbamazepine is metabolized by the cytochrome P450 syste CYP3A4, and is capable of autoinduction of its own metabolism by these enzymes. St. John's Wort has been CYP3A4 in human subjects (Durr et al, 2000a; Moore et al, 2000a; Roby et al, 2000a), which suggests that a between St. John's Wort and drugs metabolized by CYP3A4 such as carbamazepine is possible. St. John's W significantly alter the cytochrome P450 system once it has already been induced by carbamazepine, which m of effect in this trial (Burstein et al, 2000a). Carbamazepine may also be capable of inducing the clearance of and its metabolites, specifically hyperforin which has been found to induce CYP3A4 transcription and expres activation of pregnane X receptors (Burstein et al, 2000a; Moore et al, 2000a).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Caution is advised if St. John's Wort and carbamazepine are taken concomitantly. a consistent dose of St. John's Wort with a reputable product containing a consistent amount of active ingred Wort. Carbamazepine concentrations should be monitored if patients report the loss of seizure control or new taking St. John's Wort concomitantly. When patients discontinue St. John's Wort, carbamazepine levels and carbamazepine toxicity (e.g. drowsiness, ataxia, slurred speech, nystagmus, dystonic reactions, hallucination should be monitored.
7) Probable Mechanism: induction of cytochrome P450 3A4 by St. John's Wort
8) Literature Reports
a) St. John's Wort had no effect on steady state carbamazepine and carbamazepine-10,11-epoxide pha Eight volunteers participated in an unblinded study in which subjects received immediate release carbam days. A dose titration upward from carbamazepine 200 mg daily to carbamazepine 400 mg daily occurre therapy. From days 22 through 35 subjects received 1 tablet of St. John's Wort (300 mg reagent grade ta hypericin) 3 times daily with food concomitantly with the once daily dose of carbamazepine 400 mg. No c carbamazepine or the carbamazepine-10,11-epoxide concentration-time profiles before and after St. Joh noted. None of the pharmacokinetic parameters for carbamazepine and carbamazepine-10,11-epoxide w concomitant administration of St. John's Wort. The data in this study suggest that the potential for a phar interaction is minimal and that the two agents can be given safely in combination. However, interindividu enzyme induction may be clinically important. Carbamazepine concentrations should be monitored if pat loss of seizure control or new side effects while taking St. John's Wort concomitantly (Burstein et al, 200
b) In 8 healthy male volunteers, St. John's Wort significantly induced intestinal P-glycoprotein/MDR1 an cytochrome P450 3A4. Subjects were nonsmokers, aged 23-35 years, and abstained from caffeine, alco and medications for 5 days prior to and during the study. Biopsy specimens of the duodenal intestinal mu obtained to determine P-gycoprotein/MDR1, CYP3A4 expression, and villin content at baseline and on d Erythromycin breath test was performed on days 2, 15 and 16 to determine effect on CYP3A4 function. D milligrams (mg) was given orally on day 2 for pharmacokinetic analysis. St. John's Wort extract (LI 160, L AG, Berlin) was given as 300 mg three times daily for 14 days, digoxin 0.5 mg was given again on day 1 bioavailability was increased by 18% after St. John's Wort administration. Mean intestinal P-glycoprotein increased 1.37 +/- 0.31 times following St. John's Wort (p = 0.025). One subject demonstrated a decreas

glycoprotein/villin ratio, indicating that interindividual variability is possible. Mean CYP3A4/villin ratios inc
0.17 times following St. John's Wort (p = 0.012). Induction of CYP3A4 was further evidenced by increase
erythromycin, 1.44 +/- 0.28 times over baseline, by the erythromycin breath test (Durr et al, 2000).
c) St. John's Wort has been reported to induce cytochrome P450 isoenzyme 3A4 as measured by urina
hydroxycortisol to cortisol ratios in a study of 13 healthy volunteers treated with St. John's Wort for 2 wee
baseline, mean urinary 6-beta hydroxycortisol to cortisol ratios increased from 7.1 to 13.0 (p=0.003). One
experienced an unexplained 25% decrease in urinary 6-beta hydroxycortisol to cortisol ratio. The results
recommended doses of St. John's Wort induce CYP3A4 activity (Roby et al, 2000).
d) Hyperforin was shown to activate the pregnane X receptor (PXR), which regulates expression of CYP
human hepatocytes. Levels of hyperforin in humans taking standard doses of St. John's Wort (300 mg th
are well above those required for hyperforin to activate PXR. All three St. John's Wort extracts tested act
extent comparable to that of rifampicin, which is a known activator of PXR and CYP3A4 expression (Moo

3.5.1.FF Sunitinib

1) Interaction Effect: decreased plasma concentrations of sunitinib and its active metabolite
2) Summary: Sunitinib is primarily metabolized by the cytochrome P450 3A4 (CYP3A4) enzyme to its active
is also further metabolized by CYP3A4. Coadministration of sunitinib with a CYP3A4 inducer, such as carban
result in decreased plasma concentrations of sunitinib and its active metabolite. Selection of an alternative to
with no or minimal enzyme induction potential is advised. However, if carbamazepine is used concurrently, a
sunitinib is recommended. The dose may be increased in 12.5 milligrams (mg) increments, depending on ind
tolerability, to a maximum daily dose of 87.5 mg (Prod Info SUTENT(R) oral capsules, 2006).
3) Severity: major
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Due to induction of the cytochrome P450-mediated sunitinib metabolism, concomita
of sunitinib and carbamazepine may result in decreased plasma concentrations of sunitinib and its active met
of an alternative to carbamazepine, with no or minimal enzyme induction potential is advised. However, if car
used concurrently, consider increasing sunitinib dose in increments of 12.5 milligrams (mg), based on individ
tolerability, to a maximum daily dose of 87.5 mg.
7) Probable Mechanism: induction of cytochrome P450-mediated sunitinib metabolism

3.5.1.FG Tacrolimus

1) Interaction Effect: decreased tacrolimus efficacy
2) Summary: Tacrolimus, an immunosuppressant agent, is principally metabolized by the CYP3A hepatic en
Coadministered drugs known to induce this enzyme system could be expected to reduce plasma concentrati
Carbamazepine is one of the agents known to induce the cytochrome P-450 system. Patients receiving carba
concomitantly with tacrolimus may exhibit decreased plasma and whole blood levels of tacrolimus. When the
concurrently, monitor patients for reduced tacrolimus plasma concentrations and reduced tacrolimus efficacy.
tacrolimus doses may need to be increased (Prod Info PROGRAF(R) oral capsules, IV injection, 2006).
3) Severity: major
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: If carbamazepine and tacrolimus are used concurrently, monitor patient for reduced
plasma concentrations and reduced tacrolimus efficacy. Additionally, tacrolimus doses may need to be increa
7) Probable Mechanism: increased CYP3A-mediated tacrolimus metabolism

3.5.1.FH Tadalafil

1) Interaction Effect: decreased tadalafil plasma concentrations
2) Summary: Although the carbamazepine/tadalafil interaction has not been studied, concomitant use of rifar
CYP3A4 inducer) 600 mg/day, and tadalafil (a CYP3A4 substrate) as a 10-mg single dose resulted in decrea
Cmax and AUC by 88% and 46% compared with tadalafil 10 mg alone. Therefore, tadalafil use should be avo
chronically treated with potent inducers of CYP3A4, such as carbamazepine (Prod Info ADCIRCA (TM) oral t
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of carbamazepine, a CYP3A4 inducer, and tadalafil, a CYP3A4 su
resulted in significantly decreased tadalafil bioavailability. Therefore, tadalafil use should be avoided in patier
chronic treatment with a potent CYP3A4 inducer, such as carbamazepine (Prod Info ADCIRCA (TM) oral tabl
7) Probable Mechanism: induction of CYP3A4-mediated metabolism of tadalafil by carbamazepine

3.5.1.FI Telithromycin

1) Interaction Effect: subtherapeutic telithromycin concentrations and/or elevated serum levels of carbamaze
2) Summary: Concomitant administration of carbamazepine, a cytochrome P450 3A4 inducer, is likely to res
subtherapeutic levels of telithromycin and loss of effect. Elevation of serum levels of drugs metabolized by th
P450 system, such as carbamazepine, may be observed when coadministered with telithromycin, a cytochro
inhibitor. As a result, increases or prolongation of the therapeutic and/or adverse effects of carbamazepine m
(Prod Info Ketek(TM), 2004).
3) Severity: moderate

4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Concomitant treatment of telithromycin and carbamazepine is not recommended. W and carbamazepine are coadministered, monitor carbamazepine concentrations and monitor for telithromycin
7) Probable Mechanism: induction of cytochrome P450 3A4-mediated metabolism of telithromycin by carban of cytochrome P450-mediated phenytoin metabolism by telithromycin

3.5.1.FJ Temsirolimus

1) Interaction Effect: decreased maximum concentration of sirolimus, the active metabolite of temsirolimus
2) Summary: Temsirolimus is primarily metabolized by the CYP3A4 isozyme into 5 metabolites, of which sirc principal active metabolite. Sirolimus is also primarily metabolized by CYP3A4 (Prod Info RAPAMUNE(R) ora tablets, 2007). Although not studied with carbamazepine, coadministration of rifampin, a potent CYP3A4 indu intravenous temsirolimus decreased the Cmax and AUC of sirolimus by 65% and 56%, respectively, compare alone. Therefore, avoid using carbamazepine and temsirolimus concurrently. If concurrent use of temsirolimu CYP3A4 inducer is clinically warranted, the temsirolimus dose may be increased from 25 mg/week up to 50 r discontinuation of the inducer, the temsirolimus dose should be returned to its original dose used prior to initia (Prod Info TORISEL(TM) KIT IV injection, 2007).
3) Severity: major
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Avoid using carbamazepine and temsirolimus concurrently as coadministration may substantially decreased exposure and maximum concentration of sirolimus (active metabolite of temsirolimus of temsirolimus with a strong CYP3A4 inducer, such as carbamazepine, is clinically warranted, consider increa temsirolimus dose from 25 mg/week up to 50 mg/week. Upon discontinuation of the inducer, reduce the tems to its original dose used prior to initiation of the inducer (Prod Info TORISEL(TM) KIT IV injection, 2007).
7) Probable Mechanism: induction of CYP3A4-mediated metabolism of sirolimus (active metabolite of temsir

3.5.1.FK Terfenadine

1) Interaction Effect: carbamazepine toxicity (ataxia, nystagmus, diplopia, headache, vomiting, apnea, seizur
2) Summary: A case report indicates that terfenadine may displace carbamazepine from protein binding sites free carbamazepine levels and toxicity when terfenadine is added to carbamazepine therapy (Hirschfeld & Ja
3) Severity: moderate
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Monitor serum concentrations of carbamazepine when terfenadine is added or disc therapy. Patients should be followed for any symptoms of carbamazepine toxicity.
7) Probable Mechanism: carbamazepine displacement from protein binding sites by terfenadine
8) Literature Reports
a) An 18-year-old female displayed confusion, disorientation, visual hallucinations, nausea, and ataxia. began shortly after terfenadine 60 mg twice daily was added to her regular regimen of carbamazepine (d unspecified) which resulted in an excess of free (unbound) carbamazepine (6 mg/L). The free carbamaz returned to 2.1 mg/L (normal, 1.6 to 2.2 mg/L) and the symptoms resolved after terfenadine was disconti may have displaced carbamazepine from protein binding sites, leading to the high free carbamazepine le Jarosinski, 1993).

3.5.1.FL Theophylline

1) Interaction Effect: decreased theophylline effectiveness
2) Summary: The concurrent use of theophylline and carbamazepine could lead to decreased theophylline le et al, 1983a). Carbamazepine induces hepatic cytochrome P450 activity and would be expected to affect theo metabolized in the liver (Prod Info Tegretol(R) carbamazepine chewable tablets, 2002). An increase in theopl be necessary with concomitant use. One report of decreased carbamazepine levels and efficacy suggests tha both drugs is necessary (Mitchell et al, 1986a).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Carbamazepine and theophylline serum concentrations should be closely monitored carbamazepine is added, discontinued, or when dosing changes of either drug occur. Dosing adjustments of be necessary.
7) Probable Mechanism: increased theophylline metabolism
8) Literature Reports
a) A single case was reported in which a short course of theophylline appeared to cause a mild reductio of carbamazepine in close temporal relationship to a brief generalized tonic-clonic seizure. During hospit trough serum carbamazepine levels were reduced by about 50% after six doses of theophylline every 6 l seizure occurred shortly after the seventh dose (Mitchell et al, 1986).
b) An asthmatic child was receiving theophylline 10 mg/kg/day and phenobarbital. The phenobarbital wa carbamazepine, resulting in subtherapeutic theophylline levels and markedly decreased half-life after 3 w concurrent use. Within 3 weeks of changing carbamazepine to ethotoin, the half-life of theophylline had i asthma controlled (Rosenberry et al, 1983).

3.5.1.FM Tiagabine

1) Interaction Effect: decreased tiagabine efficacy

2) Summary: Concurrent use of tiagabine and carbamazepine had no effect on the steady-state plasma conc carbamazepine or its epoxide metabolite in epileptic patients. However, it has been shown in population phar studies that tiagabine clearance is 60% greater in patients taking carbamazepine than in patients not receivin inducing agents. Tiagabine is metabolized primarily by the cytochrome P450 3A isoform subfamily of enzyme is known to induce these enzymes, therefore causing an increase in the metabolism of tiagabine (Prod Info G

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Monitor patients for tiagabine efficacy. It may be useful to obtain tiagabine plasma l after the addition or withdrawal of carbamazepine.

7) Probable Mechanism: induction of tiagabine metabolism by carbamazepine

3.5.1.FN Ticlopidine

1) Interaction Effect: an increased risk of carbamazepine toxicity (ataxia, nystagmus, diplopia, headache, vor seizures, coma)

2) Summary: Carbamazepine toxicity developed in a patient one week after ticlopidine therapy was initiated. carbamazepine is mediated through the cytochrome P450 3A4 enzyme system, and ticlopidine appears to be pathway (Brown & Cooper, 1997a).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Monitor patients for signs of carbamazepine toxicity if ticlopidine is added to their th A carbamazepine plasma level may be useful if toxicity is suspected and downward dosing adjustments may carbamazepine dose may need to be increased when ticlopidine is discontinued.

7) Probable Mechanism: inhibition of cytochrome P450-mediated carbamazepine metabolism by ticlopidine

8) Literature Reports

a) A 67-year-old male scheduled to undergo elective coronary stenting was started on ticlopidine 250 m week prior to the procedure. Other medications included aspirin , diltiazem 180 mg daily, a nitroglycerin p carbamazepine 600 mg twice daily. Shortly after ticlopidine therapy was initiated, the patient experienced ataxia that resulted in his inability to walk. These symptoms would resolve five to six hours after his ticlop Although the patient's carbamazepine level had been 43 mol/L (therapeutic range 25 to 50 mol/L) five we carbamazepine was 75 mol/L on admission to the hospital. The carbamazepine dose was decreased to and his symptoms resolved. One week after the dose decrease, the carbamazepine level was 53 mol/L. the discontinuation of ticlopidine, the carbamazepine level had fallen to 42 mol/L (Brown & Cooper, 1997

3.5.1.FO Tipranavir

1) Interaction Effect: decreased tipranavir concentrations

2) Summary: Tipranavir is a CYP3A substrate. Concomitant use of tipranavir and carbamazepine, a CYP3A cause decreased tipranavir plasma concentrations (Prod Info APTIVUS(R) oral capsules, solution, 2008).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Use caution when prescribing carbamazepine to patients who are taking tipranavir decreased tipranavir plasma concentrations (Prod Info APTIVUS(R) oral capsules, solution, 2008).

7) Probable Mechanism: induction of CYP3A-mediated tipranavir metabolism

3.5.1.FP Toloxatone

1) Interaction Effect: hypertensive urgency, hyperpyrexia, and seizures

2) Summary: Concomitant MAO inhibitor and carbamazepine therapy is contraindicated (Prod Info Tegretol(Simultaneous use may theoretically result in hyperpyrexia, excitation, and seizure activity (Prod Info Parnate(Info Tegretol(R), 1998h; Thweatt, 1986h). However, there is preliminary evidence that the combination of car an MAOI may be safe and efficacious, even in some refractory cases (Ketter et al, 1995q; Barker & Ecclestor controlled studies are needed.

3) Severity: contraindicated

4) Onset: rapid

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of carbamazepine and monoamine oxidase inhibitors contraindicated by the manufacturer. Monoamine oxidase inhibitors should be discontinued for a minimum of if the clinical situation permits, before carbamazepine therapy is initiated.

7) Probable Mechanism: unknown

8) Literature Reports

a) A double-blind study was conducted in ten inpatients with depression that had proved refractory to m therapies (electroconvulsive therapy, tricyclic antidepressants, monoamine oxidase inhibitors, lithium, ca benzodiazepines, and antipsychotics). In addition to their regular carbamazepine and lithium doses, four phenelzine (mean maximum dose 67.5 mg daily) and six patients received tranylcypromine (mean maxir

daily) for a mean duration combination therapy of 52.2 days. During MAOI coadministration, serum conc carbamazepine and lithium did not change significantly from baseline values. Self-rated side effects were different. Four patients (three on phenelzine and one on tranylcypromine) responded to this therapy and discharged (Ketter et al, 1995p).

b) A 60-year-old woman who had an atypical endogenous, depressive illness of psychotic intensity was intermittently with cyclic antidepressants and intermittent electroconvulsive therapy. Following an acute v illness, she was treated successfully with a combination of phenelzine and L-tryptophan. Following a few improvement, her situation worsened and she was subsequently treated with zimelidine and lithium. Faili placed on a regimen of tranylcypromine with doses increasing progressively up to 30 mg daily in conjunc and tryptophan. Subsequently, carbamazepine was added in small doses with increments to achieve a p approximately 5 mg/L. This regimen proved successful, and she was discharged home and had remaine two months of follow up at the time of publication (Barker & Eccleston, 1984p).

c) Addition of tranylcypromine to carbamazepine therapy did not significantly affect carbamazepine seru (Joffe et al, 1985h). Conversely, five patients on tranylcypromine need a mean daily dose of carbamazep achieve a carbamazepine blood level of 8.0-11.1 mcg/mL. Four other patients receiving phenelzine only daily dose of carbamazepine 450 mg to attain a blood level of 8.7-10.9 mcg/mL (Barklage et al, 1992h).

3.5.1.FQ Topiramate

1) Interaction Effect: decreased topiramate concentrations

2) Summary: In controlled, clinical pharmacokinetic studies, patients with epilepsy showed a 40% decrease i concentrations when carbamazepine was added to topiramate therapy (Prod Info TOPAMAX(R) oral tablets, capsules, 2008). Topiramate oral and nonrenal clearance is twofold to threefold higher during concurrent carl therapy. The renal clearance of topiramate, however, is not affected by concomitant carbamazepine therapy. changes in carbamazepine pharmacokinetic parameters were evident upon coadministration with topiramate 1996a). In another study, addition of topiramate to existing carbamazepine regimens in epileptic patients resu significant pharmacokinetic changes in either drug (Wilensky et al, 1989a).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Upon the addition of carbamazepine to a drug regimen involving topiramate, the do may need to be increased to accommodate for the decreased concentration of topiramate that occurs with co (Prod Info TOPAMAX(R) oral tablets, oral sprinkle capsules, 2008).

7) Probable Mechanism: unknown

8) Literature Reports

a) Twelve patients with partial epilepsy receiving chronic stable doses of carbamazepine were enrolled i determine the steady-state pharmacokinetic profile of topiramate and the effects of comedication with ca subjects were receiving carbamazepine in doses of 300 mg to 800 mg every eight hours. Topiramate wa doses were increased at approximately two week intervals until the highest tolerated dose was reached. was then tapered off over the next four weeks, and topiramate was maintained as monotherapy for two r Results showed that the mean topiramate area under the concentration-time curve (AUC), Cmax, Cmin, were all approximately 40% lower during carbamazepine treatment as compared to topiramate monother suggest that the metabolic clearance of topiramate increases when carbamazepine is coadministered. T significant changes in the carbamazepine pharmacokinetic profile during topiramate administration (Sach

b) The interaction between carbamazepine and topiramate was assessed in eight epileptic patients. Pha profiles were evaluated after a single dose of topiramate, after two weeks at three different doses of topir each subject had taken topiramate at its highest tolerated dose for two months. No significant changes ir carbamazepine, or carbamazepine metabolite pharmacokinetics were observed at any dose level (Wilen

3.5.1.FR Tramadol

1) Interaction Effect: decreased tramadol efficacy and increased seizure risk

2) Summary: Chronic carbamazepine therapy increases the metabolism of tramadol by the cytochrome P45(which may significantly reduce the analgesic effect of tramadol. Due to the seizure risk involved with tramadc administration of tramadol and carbamazepine is not recommended (Prod Info ULTRAM(R)ER extended-rele 2005).

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: Concomitant administration of carbamazepine and tramadol is not recommended, a may reduce tramadol efficacy and tramadol may increase the risk of seizure.

7) Probable Mechanism: induction of CYP3A4 metabolism of tramadol by carbamazepine

3.5.1.FS Tranylcypromine

1) Interaction Effect: hypertensive urgency, hyperpyrexia, and seizures

2) Summary: Concomitant tranylcypromine and carbamazepine therapy is contraindicated (Prod Info Tegretc Simultaneous use may theoretically result in hyperpyrexia, excitation, and seizure activity (Prod Info Parnate(Info Tegretol(R), 1998c; Thweatt, 1986c). However, there is preliminary evidence that the combination of carl an MAOI may be safe and efficacious, even in some refractory cases (Ketter et al, 1995g; Barker & Eccleston controlled studies are needed.

3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of carbamazepine and monoamine oxidase inhibitors contraindicated by the manufacturer. Monoamine oxidase inhibitors should be discontinued for a minimum of if the clinical situation permits, before carbamazepine therapy is initiated.
7) Probable Mechanism: unknown
8) Literature Reports
a) A double-blind study was conducted on ten inpatients with depression that had proved refractory to m therapies (electroconvulsive therapy, tricyclic antidepressants, monoamine oxidase inhibitors, lithium, ca benzodiazepines, and antipsychotics). In addition to their regular carbamazepine and lithium doses, four phenelzine (mean maximum dose 67.5 mg daily) and six patients received tranylcypromine (mean maxir daily) for a mean duration combination therapy of 52.2 days. During MAOI coadministration, serum conc carbamazepine and lithium did not change significantly from baseline values. Self-rated side effects were different. Four patients (three on phenelzine and one on tranylcypromine) responded to this therapy and discharged (Ketter et al, 1995f).
b) A 60-year-old woman who had an atypical endogenous, depressive illness of psychotic intensity was intermittently with cyclic antidepressants and intermittent electroconvulsive therapy. Following an acute v illness, she was treated successfully with a combination of phenelzine and L-tryptophan. Following a few improvement, her situation worsened and she was subsequently treated with zimeldine and lithium. Faili placed on a regimen of tranylcypromine with doses increasing progressively up to 30 mg daily in conjunc and tryptophan. Subsequently, carbamazepine was added in small doses with increments to achieve a p approximately 5 mg/L. This regimen proved successful, and she was discharged home and had remaine two months of follow up at the time of publication (Barker & Eccleston, 1984f).
c) Addition of tranylcypromine to carbamazepine therapy did not significantly affect carbamazepine seru (Joffe et al, 1985c). Conversely, five patients on tranylcypromine needed a mean daily dose of carbamaz achieve a carbamazepine blood level of 8.0-11.1 mcg/mL. Four other patients receiving phenelzine only daily dose of carbamazepine 450 mg to attain a blood level of 8.7-10.9 mcg/mL (Barklage et al, 1992c).

3.5.1.FT Trazodone

1) Interaction Effect: decreased trazodone plasma concentrations
2) Summary: An increase in carbamazepine concentration/dose ratio was reported when trazodone was add although the patient did not exhibit any signs of carbamazepine toxicity (Romero et al, 1999a). Trazodone se have been decreased during coadministration with carbamazepine. Patients should be closely monitored to s need for an increased dose of trazodone when taking both drugs (Prod Info Desyrel(R), 2003).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When given concurrently with carbamazepine, trazodone serum concentrations sho monitored and trazodone dose adjustments made as needed.
7) Probable Mechanism: induction of trazodone CYP3A4-mediated metabolism
8) Literature Reports
a) A 53-year-old male diagnosed with generalized partial epilepsy was receiving carbamazepine 700 mg corresponding serum concentration of 7.9 mg/L. The concentration/dose ratio, calculated by dividing the concentration (mg/L) by the dose (mg/kg), was 0.89. Trazodone therapy was initiated for depression, and the carbamazepine serum concentration had increased to 10.0 mg/L with a corresponding concentration The serum concentration of the main pharmacologically active metabolite of carbamazepine, carbamaze epoxide, was not measured. Although this patient did not show any signs or symptoms of carbamazepin interaction may be clinically significant in patients stabilized at a higher carbamazepine steady-state con et al, 1999).

3.5.1.FU Trimipramine

1) Interaction Effect: decreased trimipramine effectiveness
2) Summary: The concomitant use of carbamazepine and antidepressants has been reported to decrease se antidepressant levels (Leinonen et al, 1991b; Brown et al, 1990). Although not reported for trimipramine, a sir could occur.
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Monitor for clinical efficacy of the trimipramine therapy and for any signs of toxicity Serum levels of both agents should be considered when either agent is added or discontinued, with appropria adjustments made accordingly.
7) Probable Mechanism: increased trimipramine metabolism
8) Literature Reports
a) Concomitant administration of imipramine and carbamazepine to children with attention deficit disorde reported to result in a 50% decrease in the total plasma concentration of imipramine plus desipramine (E Carbamazepine probably enhances the hepatic microsomal metabolism of imipramine and other tricyclic by inducing hepatic enzymes (Moody et al, 1977). Although not reported specifically for trimipramine, be

potential for a similar interaction exists. Patients on chronic carbamazepine therapy may require increase tricyclic antidepressants.

3.5.1.FV Troleandomycin

1) Interaction Effect: carbamazepine toxicity (ataxia, nystagmus, diplopia, headache, vomiting, apnea, seizur
2) Summary: Concurrent administration of carbamazepine and troleandomycin has resulted in increased pla carbamazepine levels and signs of toxicity (Dravet et al, 1977; Mesdjian et al, 1980a).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: established
6) Clinical Management: The combination of carbamazepine and macrolide antibiotics should be avoided an given to an alternative antibiotic. If the combination is necessary, carbamazepine levels should be obtained w adding or discontinuing troleandomycin and dosage adjustments made accordingly.
7) Probable Mechanism: decreased carbamazepine metabolism
8) Literature Reports

a) Seventeen epileptic patients receiving troleandomycin concurrently with carbamazepine alone or in c other anticonvulsants experienced symptoms of acute intoxication (dizziness, drowsiness, nausea, vomi Troleandomycin was given a second time to 3 patients who experienced similar symptoms. Six patients increase in carbamazepine plasma levels after administration of troleandomycin; when the antibiotic was carbamazepine levels returned to normal (Mesdjian et al, 1980).

3.5.1.FW Valnoctamide

1) Interaction Effect: carbamazepine toxicity (ataxia, nystagmus, diplopia, headache, vomiting, apnea, seizur
2) Summary: One study in six epileptic patients demonstrated that concurrent administration of valnoctamide carbamazepine (CBZ) resulted in a significant increase in carbamazepine epoxide serum concentrations. Fou experienced clinical symptoms of carbamazepine intoxication. Carbamazepine epoxide serum levels returned discontinuation of valnoctamide, and all signs of toxicity abated (Pisani et al, 1993).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Concurrent use of carbamazepine and valnoctamide is best avoided; however, if th necessary, careful monitoring for signs of carbamazepine toxicity is needed with dosage adjustments made a
7) Probable Mechanism: inhibition of carbamazepine metabolism
8) Literature Reports

a) If phenytoin or carbamazepine (or any prodrugs) is used in pregnant women, there is a substantially i teratogenicity with many combinations of other anticonvulsants. The teratogenicity of these drugs is large related to the levels of the reactive epoxide metabolites (Buehler et al, 1990e; Van Dyke et al, 1991e; Fir The epoxide/parent drug ratio is generally increased when phenytoin or carbamazepine is combined with other drugs that induce cytochrome P450 enzymes (3A4, 2C9, 2C19), or drugs which inhibit epoxide hyc valproic acid, progabide, and lamotrigine (Bianchetti et al, 1987e; Ramsay et al, 1990e; Spina et al, 1996 combinations increase the risk of major birth defects 3- to 4-fold over monotherapy and about 10-fold ov rates.

3.5.1.FX Valproic Acid

1) Interaction Effect: carbamazepine toxicity (ataxia, nystagmus, diplopia, headache, vomiting, apnea, seizur decreased valproic acid effectiveness
2) Summary: The literature contains conflicting data regarding the effects of combined carbamazepine and v Carbamazepine may decrease valproic acid levels by 15% to 25% while increasing clearance by up to 30% (1979a; Rimmer & Richens, 1985a; Mahaly et al, 1979a; Jann et al, 1988a). Furthermore, the conversion of va ene-VPA (thought to be the most toxic metabolite with potential for hepatotoxicity and teratogenicity) is signifi with coadministration of carbamazepine (Kondo et al, 1990a). Valproic acid may increase, decrease, or caus carbamazepine concentrations (Mattson et al, 1982a; Levy et al, 1984a; Pisani et al, 1990a; Anderson et al,
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor patients for signs of carbamazepine toxicity such as nausea, vomiting, drov when valproic acid is added. Serum carbamazepine concentrations should also be measured, though clinicia aware of the increase in the concentration of the active metabolite, carbamazepine-epoxide, which is not rout but does contribute to the efficacy and toxicity of the drug. If carbamazepine is added to valproic acid therapy acid levels; increased valproic acid dosage may be required.
7) Probable Mechanism: increased valproic acid clearance; variable effects on carbamazepine metabolism
8) Literature Reports

a) Significant increases (59%) in valproic acid serum concentrations have been reported following the w carbamazepine in six epileptic patients. A new plateau for the valproic acid serum level was observed at weeks after withdrawal of the carbamazepine (Jann et al, 1988).

b) Several reports have indicated conflicting effects of valproic acid on carbamazepine serum levels (Ri 1985; Flachs et al, 1979; Adams et al, 1978). In an in vitro study of protein binding, valproic acid compet carbamazepine plasma protein binding sites, resulting in significant increases in free carbamazepine (Ma

Concurrent therapy of valproic acid and carbamazepine in seven patients was found to decrease levels c by 3% to 59% and protein binding decreased. The plasma concentration ratio of carbamazepine-10,11-e carbamazepine increased in all patients by 11% to 500% (Levy et al, 1984; Pisani et al, 1990) probably c epoxide hydroxylase by valproic acid (Robbins et al, 1990). In addition, carbamazepine may cause a red valproic acid half-life with increased clearance secondary to enzyme induction and increased hepatic me et al, 1979; Rimmer & Richens, 1985; Mahaly et al, 1979). Infrequent reports have indicated symptoms c nausea, or confusion when valproic acid was added to carbamazepine therapy (Lhermitte et al, 1978; Ha A single case of psychosis following the addition of carbamazepine to valproic acid has been reported in refractory epilepsy (McKee et al, 1989).

c) Select patients with suspected genetic deficiencies may tolerate poorly the effects of valproic acid on certain amino and fatty acids, which may impact anticonvulsant therapy based on carbamazepine-valpro these individuals (Anderson et al, 1994).

d) The pharmacokinetics of valproic acid and its metabolites when coadministered with carbamazepine epileptic patients. The ratio of valproic acid concentration to dose was significantly lower in those patient acid with carbamazepine compared with those receiving only valproic acid. Additionally, the ratio of 4-en concentration to valproic acid concentration was significantly higher in those receiving combined carbam acid compared with those on valproic acid monotherapy. 4-ene-VPA, reported to be the most toxic of val metabolites, may manifest as hepatotoxicity and teratogenicity (Kondo et al, 1990).

e) If phenytoin or carbamazepine (or any prodrug) is used in pregnant women, there is a substantially in teratogenicity with many combinations of other anticonvulsants. The teratogenicity of these drugs is large related to the levels of the reactive epoxide metabolites (Buehler et al, 1990; Van Dyke et al, 1991; Finne epoxide/parent drug ratio is generally increased when phenytoin or carbamazepine is combined with eac drugs that induce cytochrome P450 enzymes (3A4, 2C9, 2C19), or drugs which inhibit epoxide hydrolase acid, progabide, and lamotrigine (Bianchetti et al, 1987; Ramsay et al, 1990; Spina et al, 1996a). Such c increase the risk of major birth defects 3- to 4-fold over monotherapy and about 10-fold over background

3.5.1.FY Vecuronium

1) Interaction Effect: decreased vecuronium duration of action

2) Summary: Patients on carbamazepine maintenance therapy required significantly higher doses of vecuror similar neuromuscular blocking effects as controls (Whalley & Ebrahim, 1994a; Norman, 1993a). This may be pharmacokinetic interaction between carbamazepine and vecuronium, although a pharmacodynamic interact ruled out (Alloul et al, 1996a).

3) Severity: moderate

4) Onset: rapid

5) Substantiation: established

6) Clinical Management: Monitor patients for an appropriate clinical response to the neuromuscular blocker. intervals or higher doses of vecuronium may be needed in patients receiving carbamazepine.

7) Probable Mechanism: increased clearance of vecuronium

8) Literature Reports

a) Twenty-four surgical patients were evaluated, of which eight were receiving carbamazepine (along wi other drugs) and 16 were using several different drugs but not carbamazepine (Whalley & Ebrahim, 199 vecuronium required for 50%, 90%, and 95% depression of first twitch were 29, 52, and 64 mcg/kg, resp carbamazepine group, compared with 21, 36, and 44 mcg/kg, respectively, for the non-carbamazepine g 40% higher dose of vecuronium was required in study subjects using carbamazepine.

b) A case report describes a 19-year old epileptic female who underwent a sigmoid colectomy (Norman, patient had been maintained on carbamazepine 700 mg daily. The first bolus dose of vecuronium 6 mg p for only 18 minutes. A continuous infusion of vecuronium at an average of 6.67 mg/hr was needed to sus neuromuscular block. This is higher than the average of vecuronium 4 mg/hr that is needed to produce b patients not treated with carbamazepine.

c) The pharmacokinetic and pharmacodynamic effects of a bolus intravenous dose of vecuronium were carbamazepine-treated subjects and in ten control subjects (Alloul et al, 1996). No changes in onset time distribution at steady-state were observed. However, the carbamazepine group had a shorter mean reco (T1 25%) compared to controls (28.1 minutes vs. 47.3 minutes). The T1 25% to T1 75% recovery index v the carbamazepine group compared to 21.9 minutes in controls. Clearance of vecuronium was 9.0 mL/kg carbamazepine group and only 3.8 mL/kg/min in the control group. This two-fold increase in the clearanc provides evidence of a pharmacokinetic origin to the interaction with carbamazepine, although the possib concurrent pharmacodynamic interaction cannot be ruled out.

d) Long-term phenytoin or carbamazepine therapy accelerates recovery from vecuronium-induced paral The patients were assigned to one of 3 groups: control (n=10; no history of epilepsy and not receiving ch affecting neurotransmission), children receiving phenytoin (n=10) or carbamazepine (n=10). The eliminat significantly shorter for the phenytoin and carbamazepine groups compared with control. A statistically si in clearance of vecuronium occurred in the carbamazepine groups compared with control. Increased clea vecuronium in the phenytoin group also occurred but was not statistically significant. The recovery indice vecuronium-induced block for the children on antiepileptic drugs were significantly faster than those for th The author concludes that resistance to vecuronium in children on chronic anticonvulsant therapy is part increased metabolism. The contribution of altered pharmacodynamics to the resistance to vecuronium co determined in this study (Soriano et al, 2001).

3.5.1.FZ Verapamil

1) Interaction Effect: increased carbamazepine plasma concentrations and risk of toxicity (ataxia, nystagmus headache, vomiting, apnea, seizures, coma)

2) Summary: Concomitant administration of carbamazepine and verapamil has resulted in increased carbam increasing the risk of toxicity (Summers et al, 2004; Prod Info Covera HS(R), 2003; Brodie & Macphee, 1986l 1986a; Eimer & Carter, 1987b; Bahls et al, 1991a).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Monitor for clinical signs of carbamazepine toxicity along with carbamazepine serur dose accordingly. Nifedipine does not appear to interact with carbamazepine and may be considered as an a verapamil.

7) Probable Mechanism: decreased carbamazepine metabolism and inhibition of p-glycoprotein-mediated ef

8) Literature Reports

a) Concomitant administration of verapamil 120 mg orally 3 times a day in patients receiving carbamaze partial epilepsy was reported to result in carbamazepine neurotoxicity in all of 6 patients treated (MacPhe Increase in free and total carbamazepine levels were observed in 5 patients (mean increases of 33 and associated with a concurrent decrease by 36% in the ratio of carbamazepine-10,11 epoxide to carbamaz resolved after several days following withdrawal of verapamil in all patients. Rechallenge in 2 patients re neurotoxic symptoms. These data suggest that verapamil inhibits carbamazepine metabolism. Reductior carbamazepine may be required when verapamil is administered, and increased when verapamil is witho exacerbation of epileptic seizures. Seizure aggravation occurred in one patient in this series following ab verapamil.

b) The concurrent use of verapamil with carbamazepine was effective in suppressing p-glycoprotein-me carbamazepine transport and clearance in a 24-year-old woman with intractable epilepsy. The patient's c seizures had been refractory to multiple anticonvulsants, partial temporal lobectomy, and vagal nerve sti resulted in intermittent hospitalization a mean of every 55 days for management of complex partial status Verapamil 180 milligrams (mg)/day was added to an anticonvulsant regimen comprising carbamazepine in addition to levetiracetam, topiramate, and clonazepam. Baseline carbamazepine plasma concentratior low end of the therapeutic range (4.2 mg/milliliter (mL). At 1-month follow up, carbamazepine plasma cor mg/L, and the patient reported subjective improvement in seizure control. Verapamil dose was titrated in 480 mg daily, resulting in an increase in carbamazepine plasma concentration to 13.3 mg/L, without repo effects, and with an extension of between-hospitalization time to approximately 4 months between admis et al, 2004).

3.5.1.GA Vigabatrin

1) Interaction Effect: carbamazepine toxicity (ataxia, nystagmus, diplopia, headache, vomiting, apnea, seizur

2) Summary: In a study of sixty-six epileptic patients, when vigabatrin was added to carbamazepine therapy carbamazepine serum concentrations increased 24.2%. A strong negative correlation between the value of th the initial level of carbamazepine concentration after vigabatrin addition also was revealed in this study (Jedrz 2000a).

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: When vigabatrin is added to carbamazepine therapy, concentration of carbamazepi monitored and the dose of carbamazepine should be adjusted accordingly.

7) Probable Mechanism: decreased carbamazepine metabolism

8) Literature Reports

a) Sixty-six epileptic patients were evaluated for the changes in carbamazepine concentration following All patients had simple or complex partial seizures, and all were drug-resistant. Vigabatrin was added as after long-term (at least 3 months) carbamazepine monotherapy and was administered in increasing dos Carbamazepine concentrations prior to vigabatrin addition was 9.41 mcg/ml (range 4.33 to 13.05 mcg/m vigabatrin the mean carbamazepine concentration increased to 11.31 mcg/ml (range 6.88 to 18.57 mcg/ increase in carbamazepine concentration was 24.2%. An increase in carbamazepine concentration by at occurred in 46 out of 66 patients, i.e. 69.7%, after vigabatrin therapy. Twenty-four patients (36.4%) respo carbamazepine level of at least 12 mcg/ml. Carbamazepine concentration in this group ranged from 11.9 whereas the carbamazepine concentration before vigabatrin therapy was 10.57 mcg/ml (range 6.59 to 1 significant relationship was found between vigabatrin dosage and the percentile change in carbamazepir after the addition of vigabatrin. There was a strong negative correlation between the percentile increase concentration and initial carbamazepine concentration (Jedrzejczak et al, 2000).

b) Vigabatrin produces a statistically significant increase in the plasma clearance of carbamazepine (CE drugs are given simultaneously. Fifteen patients with refractory partial epilepsy and receiving vigabatrin a were studied. Treatment 1 consisted of an initial period with CBZ monotherapy. Treatment 2 consisted o combination with vigabatrin. CBZ monotherapy was given for 3-12 months with monitoring of CBZ plasm After an initial period, patients received open add-on treatment with vigabatrin 1500 mg/day in two divide 1500 mg daily dose of vigabatrin was increased up to a maximum of 4000 mg. The final daily dose of vig 2150+/-900 mg, with a range of 1500-4000 mg. The steady-state trough plasma concentration of CBZ w the presence of vigabatrin, with a mean value of 7.9+/-1.4 vs 6.5+/-2.0 mcg/mL (p less than 0.03), respe

ratio of CBZ was significantly decreased from 0.59 +/- 0.20 in monotherapy to 0.45+/-0.15 in combinatior less than 0.05). CBZ plasma clearances in monotherapy ranged from 40 to 128 mL/h/kg, with a mean va mL/h/kg. When CBZ was combined with vigabatrin there was a marked increase in the plasma clearance mL/h/kg) with a mean value of 105.8 +/- 38.9 mL/h/kg (P less than 0.01). The plasma clearance of CBZ i 35% in the presence of vigabatrin. Dosing of CBZ and vigabatrin in combination is best adjusted by indiv drug monitoring (Sanchez-Alcaraz et al, 2002).

3.5.1.GB Viloxazine

1) Interaction Effect: carbamazepine toxicity (ataxia, nystagmus, diplopia, headache, vomiting, apnea, seizur
2) Summary: Viloxazine administered concurrently with carbamazepine increased carbamazepine steady-sta significantly (Pisani et al, 1984a; Pisani et al, 1986aa). These increased serum levels were associated with sy carbamazepine toxicity (dizziness, ataxia, fatigue, drowsiness) in five of seven patients and four of seven pat aformentioned studies, respectively. The concentration of the active metabolite, carbamazepine-10,11-epoxic increased (Pisani et al, 1986aa). In another study by (Pisani et al, 1986ba), viloxazine pharmacokinetics were the administration of carbamazepine.
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Downward adjustment of carbamazepine dosage may be necessary when adding v therapy. Monitor serum carbamazepine concentrations closely.
7) Probable Mechanism: inhibition of carbamazepine hepatic metabolism by viloxazine
8) Literature Reports

a) The possibility of a drug interaction between viloxazine and carbamazepine was studied in seven epil stabilized on carbamazepine therapy. Viloxazine 100 mg three times daily was added to drug therapy for significantly increased steady-state carbamazepine serum levels from an average of 8.1 mcg/mL before to an average of 12.1 mcg/mL during the second and third weeks of viloxazine therapy (p less than 0.005 increased levels were associated with mild symptoms of carbamazepine toxicity (dizziness, ataxia, fatigu five patients. Serum carbamazepine levels returned to normal and symptoms abated after discontinuing et al, 1984).

b) Significant increases in serum carbamazepine and carbamazepine-10,11-epoxide levels during viloxa investigated. The study was performed in six epileptic patients stabilized on carbamazepine. After three viloxazine administration, steady-state plasma carbamazepine levels increased by 55% (p less than 0.00 carbamazepine-10,11-epoxide levels increased by 16% (p less than 0.001). Three of the six patients suf symptoms of carbamazepine intoxication. In a seventh patient, viloxazine had to be discontinued after tw severe carbamazepine intoxication (Pisani et al, 1986a).

c) The pharmacokinetics of viloxazine and whether chronic anticonvulsant therapy has any affect on vilo pharmacokinetics were studied in six epileptic patients taking one or two anticonvulsants (carbamazepin or phenytoin) and six drug-free control subjects. One oral viloxazine 200 mg dose followed by a single in of viloxazine 200 mg at least one week later were administered to each patient and control subject. Term not affected by anticonvulsant therapy (4.3 +/- 1.5 hours for the patients and 4.3 +/- 1.8 hours for the cor Absolute oral availability was 85% +/- 14%. Clearance and volume of distribution calculated from the intr the patients were 124 +/- 11 mL/kg/hr and 0.73 +/-0.28 L/kg, respectively. The authors concluded that vil pharmacokinetics did not appear to be significantly altered by carbamazepine, phenobarbital, or phenyto 1986b).

3.5.1.GC Voriconazole

1) Interaction Effect: reduced systemic exposure to voriconazole
2) Summary: Although not studied clinically, plasma voriconazole concentrations may be significantly reduce administration of carbamazepine (Prod Info VFEND(R) IV injection, oral tablets, suspension, 2008).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of voriconazole and carbamazepine is contraindicated (Prod Info injection, oral tablets, suspension, 2008).
7) Probable Mechanism: induction by carbamazepine of cytochrome P450-mediated voriconazole metabolis

3.5.1.GD Warfarin

1) Interaction Effect: decreased anticoagulant effectiveness
2) Summary: Concomitant carbamazepine and warfarin therapy has been reported to result in a decreased a effect, secondary to the induction of hepatic metabolism of the anticoagulant (Massey, 1983; Cohen & Armstr Weser & Koch-Weser, 1975; Kendall & Boivin, 1981; Hansen et al, 1971).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When carbamazepine is added or deleted from oral anticoagulant therapy with warf coumarin anticoagulant, intensified monitoring of the prothrombin time ratio or international normalized ratio (undertaken. It is often necessary to increase the dose of warfarin with the addition of carbamazepine, while a warfarin dose is frequently required upon the discontinuation of carbamazepine. Stabilization of the warfarin d

anticoagulant effect may require four to six weeks after the addition or deletion of carbamazepine.
7) Probable Mechanism: increased warfarin metabolism
8) Literature Reports
a) A patient taking carbamazepine 300 mg to 600 mg daily and warfarin 6 mg daily was stable at 2 to 3 i experienced a PT increase to 5 times the control value within four weeks of discontinuation of carbamaz dosage was reduced to 4 mg daily. Carbamazepine was reinstituted, and five weeks were required for re steady-state warfarin level at a dose of 5.5 mg daily (Ross & Beeley, 1980).

3.5.1.GE Yohimbine
1) Interaction Effect: increased risk of manic episodes in patients taking carbamazepine for bipolar disorder
2) Summary: Yohimbine may exacerbate bipolar disorder by precipitating manic episodes. This effect has be reports, generally within one to two hours of yohimbine administration. The authors concluded that patients w diathesis are predisposed to the psychogenic effect of yohimbine (Price et al, 1984a). Yohimbine appears to alpha2-adrenergic receptors on sympathetic nerve endings, increasing noradrenergic output through negative Alpha2-adrenoceptors may be involved in the pathogenesis of psychiatric disorders (Price et al, 1984a). Theo taking carbamazepine for bipolar disorder may experience a return of manic symptoms if they take yohimbine
3) Severity: moderate
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Avoid yohimbine use in patients taking carbamazepine for treatment of bipolar diso
7) Probable Mechanism: increased norepinephrine release by yohimbine
8) Literature Reports
a) Yohimbine challenges were administered to 55 patients with major depression, 39 patients with agora disorder, and 20 normal control subjects. Three patients developed manic-like symptoms, 2 of which hac bipolar disorder and one with manic symptoms which developed on withdrawal of desipramine. Normal s experienced either mild anxiety or no effect after yohimbine. Yohimbine increases anxiety in patients with disorder (Price et al, 1984).
b) A 41-year-old male with a 3 year history of bipolar disorder presented with depressive symptoms of 1 unresponsive to a 6 month trial of desipramine 250 mg/day and lithium 2100 mg/day. Lithium was discor given a 10 mg yohimbine challenge upon hospital admission. One hour after receiving yohimbine, the pa tremulousness, restlessness, giddiness, pressured speech, and feelings of increased energy and eupho after receiving yohimbine, he began to return to his baseline state. He continued to experienced increase decreased hopelessness, and decreased depression 4 hours after the yohimbine challenge. His full depr returned by the next morning. Following a 4 week period during which desipramine was discontinued and given, the patient's depression resolved. A second challenge of yohimbine 10 mg led to chills within 60 m 90 minutes he reported feeling euphoric. After 2 hours he returned to his baseline state (Price et al, 1984
c) A 20-year-old female with melancholic major depression with mood-congruent psychosis during her s was treated with desipramine 250 mg and perphenazine 40 mg daily with partial response. Perphenazine 6 weeks postpartum and desipramine was tapered off and discontinued 5 days prior to hospital admissio placebo washout period, she reported hearing voices telling her to kill herself. She was given a 20 mg yo challenge. Within one hour she experienced tremor, lacrimation, rhinorrhea, and became talkative. In the her affect brightened, her speech became increasingly clear and loud, and her hallucinations stopped. D symptoms gradually returned over the next several hours. Bupropion was initiated at doses up to 600 mg depression and intermittent hallucinations continued. A second challenge of yohimbine 20 mg led to mild tremulousness within 30 minutes, which resolved over an hour. Her affect improved and remained bright after which she returned to her baseline state (Price et al, 1984).
d) A 43-year-old woman with a 26-year history of bipolar disorder was discontinued from all medications admission (thioridazine, lithium, l-triiodothyronine, methylphenidate, and lorazepam) with the exception o was tapered off over 5 days following admission. One hour after receiving yohimbine 20 mg orally, she b voluble, and expansive. She experienced diaphoresis, palpitations, and tremors. Her elation progressed loud hysterical, inappropriate laughter. The intense manic symptoms persisted for 40 minutes. Her affect for the remainder of the day (Price et al, 1984).

3.5.1.GF Zaleplon
1) Interaction Effect: reduced zaleplon plasma concentrations
2) Summary: Zaleplon is partially metabolized by the CYP3A4 isozyme. Concomitant use of rifampin, a poter inducer, and zaleplon reduced zaleplon exposure and plasma concentrations by approximately 80%. Althoug carbamazepine, also a potent CYP3A4 inducer, a similar interaction can be expected. An alternative hypnotic substrate of CYP3A4 should be considered in patients receiving rifampin (Prod Info SONATA(R) oral capsule
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of carbamazepine, a potent CYP3A4 inducer, and zaleplon may r zaleplon levels and efficacy. Consider using an alternative hypnotic agent that is not a substrate of CYP3A4 i receiving rifampin (Prod Info SONATA(R) oral capsules, 2007).
7) Probable Mechanism: induction of CYP3A4-mediated zaleplon metabolism by carbamazepine

3.5.1.GG Ziprasidone

1) Interaction Effect: decreased ziprasidone plasma concentrations
2) Summary: Ziprasidone is metabolized primarily by CYP3A4. The concomitant use of carbamazepine (a C
200 mg twice daily for 21 days decreased the ziprasidone AUC by approximately 35%. Therefore, caution sh
carbamazepine and ziprasidone are coadministered due to the potential for reduced ziprasidone plasma con
Info GEODON(R) oral capsules, IM injection, 2008).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Use caution when prescribing carbamazepine to a patient who takes ziprasidone. C
carbamazepine and ziprasidone has resulted in decreased ziprasidone plasma concentrations (Prod Info GE
capsules, IM injection, 2008).
7) Probable Mechanism: induction of CYP3A4-mediated ziprasidone metabolism by carbamazepine

3.5.1.GH Zotepine

1) Interaction Effect: decreased zotepine plasma concentrations
2) Summary: Carbamazepine enhances the metabolism of zotepine by induction of the hepatic microsomal e
This may result in lower plasma levels of zotepine (Prod Info Nipolept(R), 1994).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Monitor the patient carefully and increase the dose of zotepine if necessary.
7) Probable Mechanism: hepatic microsomal enzyme induction

3.5.2 Drug-Food Combinations

3.5.2.A Grapefruit Juice

1) Interaction Effect: increased carbamazepine bioavailability
2) Summary: Grapefruit juice increased the peak concentration, trough concentration, and area under the co
curve of carbamazepine by 40.4%, 39.2%, and 40.8%, respectively, during a randomized crossover study. C
metabolized in the liver to the active metabolite 10,11-epoxide by cytochrome P450 3A4 enzymes. Grapefruit
metabolic pathway, causing an increase in the bioavailability of carbamazepine. Because of the narrow thera
carbamazepine, patients should be advised to avoid the consumption of grapefruit juice (Garg et al, 1998a).
3) Severity: moderate
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Patients receiving carbamazepine therapy should be instructed to avoid grapefruit j
7) Probable Mechanism: inhibition by grapefruit juice of cytochrome P450 3A-mediated carbamazepine meta
8) Literature Reports
a) Ten hospitalized epileptic patients who had been receiving carbamazepine 200 mg three times daily f
three to four weeks received 300 mL of grapefruit juice or water with their morning dose of carbamazepir
maximum concentration (Cmax) and minimum concentration (Cmin) values of carbamazepine increased
to 9.2 mcg/mL and from 4.51 mcg/mL to 6.28 mcg/mL, respectively, in the presence of grapefruit juice. T
concentration-time curve (AUC) from 0 to 8 hours also increased from 43.99 mcg/h/mL to 61.95 mcg/h/m
indicate that grapefruit juice does inhibit the metabolism of carbamazepine in epileptic patients (Garg et a

3.5.3 Drug-Lab Modifications

Perphenazine measurement

Tricyclic antidepressant measurement

3.5.3.A Perphenazine measurement

1) Interaction Effect: false increases in perphenazine levels
2) Summary: Carbamazepine was reported to cause false increases in perphenazine levels when measured
Beckman Ultrasphere ODS 3 mcm particle, 4.6 x 75 mm column using the method of Larson (with modificatic
patient (Spigset et al, 1994). Retention times were indistinguishable for the two drugs, resulting in a greater th
overestimation of the perphenazine concentration. Serendipitous changing of the column to a Nucelosil C18 5
x 150 mm column adequately resolved the two peaks. All HPLC perphenazine assay methods should be eva
carbamazepine interference.
3) Severity: minor
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: All HPLC perphenazine assay methods should be evaluated for carbamazepine int
7) Probable Mechanism: perphenazine assay interference

3.5.3.B Tricyclic antidepressant measurement

1) Interaction Effect: false positive tricyclic antidepressant assay results with serum fluorescence-polarized ir
2) Summary: Because carbamazepine is structurally similar to tricyclic antidepressants (TCAs), it can interfe fluorescence-polarized immunoassays for TCAs, causing falsely positive results. Carbamazepine does not in enzyme-linked immunoassays for TCAs, as they are much less sensitive than the serum assays. In the event assay with no history of TCA use, gas chromatography/mass spectrometry (GC/MS) should be considered to TCA toxicity (Saidinejad et al, 2007).
3) Severity: moderate
4) Onset: rapid
5) Substantiation: established
6) Clinical Management: The molecular structural similarity of carbamazepine to tricyclic antidepressants (TC falsely positive results with the serum fluorescence-polarized immunoassay but not the less sensitive urine er immunoassay. When an assay is positive for TCAs and there is no history of TCA use, gas chromatography/r (GC/MS) should be considered, as they are specific enough to differentiate between TCAs and structurally si (Saidinejad et al, 2007).
7) Probable Mechanism: molecular structural similarity of carbamazepine to the tricyclic antidepressant class
8) Literature Reports

a) A cross-sectional study of pediatric patients (n=52) taking carbamazepine or oxcarbazepine showed carbamazepine significantly interferes with the serum fluorescence-polarized immunoassay for tricyclic a (TCAs), but does not interfere with the urine enzyme-linked immunoassay for TCAs. Patients aged 3 to 1 been prescribed carbamazepine or oxcarbazepine and needed routine laboratory testing were enrolled ir were also excluded if they had used TCAs or a structurally similar compound other than the medications week prior to the study. The investigators used the TCA screening serum and urine assays, measured s carbamazepine or oxcarbazepine metabolite levels, and then performed gas chromatography/mass spec to confirm or rule out the presence of TCAs in the serum. Thirteen of 33 patients on carbamazepine had the serum assay, which had a positive cutoff of 50 micrograms per liter (mcg/L). All of the patients had a level within therapeutic range (4 to 12 mcg/L), but 12 of the 13 patients with carbamazepine levels of 8 m positive serum assay results. Linear regression showed a significant dose-dependent relationship betwe carbamazepine levels and the quantity of TCAs detected (p less than 0.0001). The investigators estimate mcg/L of carbamazepine present in the serum, the assay detected 4.2 mcg/L of TCAs. Urine assays had 150 mcg/L, as recommended by the manufacturer, and there were no positive results in patients taking e carbamazepine or oxcarbazepine.(Saidinejad et al, 2007).

4.0 Clinical Applications

Monitoring Parameters

Patient Instructions

Place In Therapy

Mechanism of Action / Pharmacology

Therapeutic Uses

Comparative Efficacy / Evaluation With Other Therapies

4.1 Monitoring Parameters

A) Therapeutic

1) Laboratory Parameters

a) Monitor blood concentrations of carbamazepine is recommended to optimize therapeutic effect and reduc (Prod Info TEGRETOL(R) oral chewable tablets, tablets, suspension, 2007; Prod Info TEGRETOL(R)-XR ext tablets, 2007).
b) The usual adult therapeutic levels are between 4 and 12 micrograms/milliliter (Warner et al, 1998; Yukawa
c) Levels drawn during the first few weeks of therapy should be cautiously interpreted, due to induction of en
d) Routine monitoring of the epoxide metabolite may also be required during carbamazepine therapy, as ser carbamazepine levels alone may not be adequate to detect toxicity in some patients. Total serum carbamaze epoxide serum levels above 9 micromol/L are associated with greater side effects than lower levels (Patsalos
e) Therapeutic levels for therapy of neuralgias have been reported to be 2 to 7 micrograms/milliliter (HPLC) (1993).

2) Physical Findings

a) EPILEPSY

1) Monitor patients for reduction in seizure frequency.

b) NEUROLOGICAL PAIN SYNDROMES

1) Monitor patients for improvement in pain of trigeminal neuralgia and other neurological syndromes.

B) Toxic

1) Laboratory Parameters

a) High-resolution human leukocyte antigen-B*1502 (HLA-B*1502) typing in Asian patients including South A should be performed due to a strong correlation between the risk of developing serious and sometimes fatal c reactions (including Stevens-Johnson syndrome and toxic epidermal necrolysis) and the presence of HLA-B* Info TEGRETOL(R) oral chewable tablets, tablets, suspension, 2007; Prod Info TEGRETOL(R)-XR extended tablets, 2007; US Food and Drug Administration, 2007).

1) Prevalence of HLA-B*1502 allele

a) Human leukocyte antigen-B*1502 (HLA-B*1502) allele is common in Asians including South Asia prevalence of HLA-B*1502 is not known for all regions of Asia. The following are known HLA-B*150 prevalence rates in some regions of Asia: greater than 15% in Hong Kong, Thailand, Malaysia, and Philippines; about 10% in Taiwan; 4% in North China; 2% to 4% in South Asians, including Indians b in some groups; and less than 1% in Japan and Korea. Individuals not of Asian origin (eg, Caucasia Americans, Hispanics, and Native Americans) generally are not HLA-B*1502 positive (Prod Info TE chewable tablets, tablets, suspension, 2007; Prod Info TEGRETOL(R)-XR extended-release oral tab Food and Drug Administration, 2007).

b) Perform complete blood counts including platelets, and possibly reticulocytes and serum iron before thera periodically (Prod Info TEGRETOL(R) oral chewable tablets, tablets, suspension, 2007; Prod Info TEGRETO release oral tablets, 2007).

1) If significant bone marrow depression develops, the manufacturer recommends the following (Prod In oral chewable tablets, tablets, suspension, 2007; Prod Info TEGRETOL(R)-XR extended-release oral tab

a) Stop drug

b) Perform daily CBC, platelet, and reticulocyte counts

c) Do bone marrow aspiration and trephine biopsy and repeat as necessary to monitor recovery

d) Other specific studies that might help include: white cell and platelet antibodies, (59)Fe-ferrokine peripheral blood cell typing, cytogenetic studies on marrow and peripheral blood, bone marrow cultu colony-forming units, hemoglobin electrophoresis for A(2) and F hemoglobin, and serum folic acid a

c) Hepatic function tests (AST, alkaline phosphatase) should be conducted prior to and periodically during th TEGRETOL(R) oral chewable tablets, tablets, suspension, 2007; Prod Info TEGRETOL(R)-XR extended-rele 2007).

d) Baseline and periodic monitoring of renal function tests (complete urinalysis and BUN) is recommended d renal dysfunction (Prod Info TEGRETOL(R) oral chewable tablets, tablets, suspension, 2007; Prod Info TEGI extended-release oral tablets, 2007).

e) Monitor serum sodium due to the risk of hyponatremia (Prod Info TEGRETOL(R) oral chewable tablets, ta 2007).

f) Conduct periodic thyroid function tests at the physician's discretion during therapy as thyroid levels may be Info TEGRETOL(R) oral chewable tablets, tablets, suspension, 2007; Prod Info TEGRETOL(R)-XR extended tablets, 2007)

2) Physical Findings

a) Observe patients for hypersensitivity reactions who previously experienced this reaction to anticonvulsant phenytoin and phenobarbital (Prod Info TEGRETOL(R) oral chewable tablets, tablets, suspension, 2007; Pro (R)-XR extended-release oral tablets, 2007).

b) Due to the potential of serious and sometimes fatal dermatologic reactions, carefully observe patients for symptoms of Stevens-Johnson syndrome and toxic epidermal necrolysis (Prod Info TEGRETOL(R) oral chew tablets, suspension, 2007; Prod Info TEGRETOL(R)-XR extended-release oral tablets, 2007).

c) Baseline and periodic eye examinations, including slit-lamp, funduscopy, and tonometry, are recommende phenothiazines and related drugs have been shown to cause eye changes (Prod Info TEGRETOL(R) oral ch tablets, suspension, 2007; Prod Info TEGRETOL(R)-XR extended-release oral tablets, 2007).

d) Monitor patients with a mixed seizure disorder, including atypical absence seizures, for the potential incre generalized convulsion (Prod Info TEGRETOL(R) oral chewable tablets, tablets, suspension, 2007; Prod Info XR extended-release oral tablets, 2007).

e) Activation of latent psychosis is a possibility due to the relationship between carbamazepine and tricyclic c Info TEGRETOL(R) oral chewable tablets, tablets, suspension, 2007).

f) Confusion or agitation in the elderly is a possibility due to the relationship between carbamazepine and tric (Prod Info TEGRETOL(R) oral chewable tablets, tablets, suspension, 2007).

g) Data reviewed by the US Food and Drug Administration suggest an increased risk of suicidal behavior or in patients receiving therapy with antiepileptic drugs (AEDs). The increased risk of suicidality was noted at 1 an AED and continued to at least 24 weeks. Patients treated for epilepsy, psychiatric disorders, or other conc an increased risk for suicidality compared to placebo. Closely monitor patients treated with AEDs for emerge of depression, suicidality, and other unusual changes in behavior, which may include symptoms such as anxi hostility, mania, and hypomania (US Food and Drug Administration, 2008).

4.2 Patient Instructions

A) Carbamazepine (By mouth)

Carbamazepine

Treats different types of seizures. Also used to treat nerve pain and bipolar disorder, also known as manic-depres

When This Medicine Should Not Be Used:
You should not use this medicine if you have had an allergic reaction to carbamazepine or to certain medicines fo
as amitriptyline, desipramine, imipramine, protriptyline, and nortriptyline. You should not use this medicine if you h
bone marrow depression (low blood counts). Do not use this medicine if you are using nefazodone (Serzone®) or
MAO inhibitor (MAOI) such as selegiline (Eldepryl®), isocarboxazid (Marplan®), phenylzine (Nardil®), or tranylcyp
(Parnate®) within the past 14 days. Do not use this medicine if you are pregnant.

How to Use This Medicine:
Long Acting Capsule, Liquid, Tablet, Chewable Tablet, Long Acting Tablet
Your doctor will tell you how much of this medicine to use and how often. Do not use more medicine or use it
your doctor tells you to.
It is best to take this medicine with food or milk.
Swallow the extended-release tablet or extended-release capsule whole. Do not crush, break, or chew it. Do
extended-release tablet that is cracked or chipped.
If you cannot swallow the extended-release capsule, you may open it and pour the medicine into a small amo
such as pudding, yogurt, or applesauce. Stir this mixture well and swallow it without chewing.
The chewable tablet must be chewed before you swallow it.
Measure the oral liquid medicine with a marked measuring spoon, oral syringe, or medicine cup.

If a Dose is Missed:
If you miss a dose or forget to use your medicine, use it as soon as you can. If it is almost time for your next d
then to use the medicine and skip the missed dose. Do not use extra medicine to make up for a missed dose

How to Store and Dispose of This Medicine:
Store the medicine in a closed container at room temperature, away from heat, moisture, and direct light.
Ask your pharmacist, doctor, or health caregiver about the best way to dispose of any leftover medicine after
your treatment. You will also need to throw away old medicine after the expiration date has passed.
Keep all medicine away from children and never share your medicine with anyone.

Drugs and Foods to Avoid:
Ask your doctor or pharmacist before using any other medicine, including over-the-counter medicines, vitamins, a
products.
There are many other drugs that can interact with carbamazepine. Make sure your doctor knows about all oth
are using. Some medicines that can interact include heart medicines, blood pressure medicines, seizure mec
antidepressants, pain medicines, cancer medicines, steroids, and medicines to treat infections, including HIV
medicines. Also tell your doctor if you are using cimetidine (Tagamet®), haloperidol (Haldol®), levothyroxine
nicotinamide, praziquantel (Biltricide®), risperidone (Risperdal®), theophylline (Theo-Dur®), ziprasidone (Ge
thinner such as warfarin (Coumadin®).
Birth control pills, implants, or shots will not work while you are using this medicine. To keep from getting pre
form of birth control such as condoms or a diaphragm with contraceptive foam or jelly.
Do not eat grapefruit or drink grapefruit juice while you are using this medicine.
Tell your doctor if you are using any medicines that make you sleepy. These include sleeping pills, cold and a
narcotic pain relievers, and sedatives.
Do not drink alcohol while you are using this medicine.

Warnings While Using This Medicine:
Using this medicine while you are pregnant can harm your unborn baby. Use an effective form of birth contro
getting pregnant. If you think you have become pregnant while using the medicine, tell your doctor right away
Make sure your doctor knows if you are breastfeeding, or if you have glaucoma, liver disease, kidney disease
heart or heart rhythm problems, or if you have ever had a mental illness or an inherited disease such as porp
doctor if you have had an allergic reaction to any other medicines (especially seizure medicines).
Do not stop using this medicine suddenly without asking your doctor. You may need to slowly decrease your
stopping it completely.
Your doctor will need to check your blood or urine at regular visits while you are using this medicine. Be sure
appointments.
Make sure any doctor or dentist who treats you knows that you are using this medicine. This medicine may a
certain medical tests.
This medicine may make you dizzy or drowsy. Avoid driving, using machines, or doing anything else that cou
you are not alert.

Possible Side Effects While Using This Medicine:
Call your doctor right away if you notice any of these side effects:
Allergic reaction: Itching or hives, swelling in your face or hands, swelling or tingling in your mouth or throat, d
trouble breathing.
Blistering, peeling, red skin rash.
Change in how much or how often you urinate.
Chest pain, fast or uneven heartbeat.

Dark-colored urine or pale stools.
Fever, sore throat, or sores in your mouth.
Lightheadedness or fainting.
Nausea, vomiting, loss of appetite, or pain in your upper stomach.
Problems with balance, walking, or speech.
Shortness of breath, cold sweat, and bluish-colored skin.
Swelling in your hands, ankles, or feet.
Unusual bleeding, bruising, or weakness.
Yellowing of your skin or the whites of your eyes.

If you notice these less serious side effects, talk with your doctor:
Anxiety, confusion, depression, restlessness, or agitation.
Diarrhea, constipation, or upset stomach.
Dizziness, drowsiness or unsteady on your feet.
Dry mouth.
Headache or back pain.
Vision changes.

If you notice other side effects that you think are caused by this medicine, tell your doctor.

4.3 Place In Therapy

A) Carbamazepine is considered the drug of first choice with the least toxicity for treating partial seizures with or witho generalization (Herman & Pedley, 1998). Carbamazepine should not be used for absence seizure since an exacerbati occur (Parker et al, 1998).
B) In comparison with phenobarbital, phenytoin, and primidone, carbamazepine appears to have the least effect on c and behavioral disturbances (Trimble, 1988).
C) Carbamazepine is the drug of choice for trigeminal neuralgia and is considered a drug of choice for bipolar disorde
D) Carbamazepine should be included on the hospital formulary.

4.4 Mechanism of Action / Pharmacology

A) MECHANISM OF ACTION
1) SUMMARY
a) Carbamazepine is an anticonvulsant chemically related to imipramine; its mechanism of action in preventi remains unclear but may involve reduction of polysynaptic responses and blocking the post-tetanic potentiati models, carbamazepine reduces pain by stimulation of the infraorbital nerve. In addition, the drug may depre potential and bulbar and polysynaptic reflexes (Prod Info Tegretol(R), 2002a).
2) Carbamazepine is a dibenzoazepine iminostilbene derivative, which has shown to be an effective anticonvulsa patients not responding to other anticonvulsant therapy. Carbamazepine has been shown effective in <GENERAL CLONIC SEIZURES>, COMPLEX PARTIAL SEIZURES, and SIMPLE PARTIAL SEIZURES, as well as those rep secondary generalization (Troupin et al, 1974; Penovich & Morgan, 1976; Anon, 1975). True ABSENCE SEIZURE SPASMS have not responded well although atypical absence seizures have been more responsive (Troupin et al
3) Carbamazepine possesses psychotropic effects. Carbamazepine is less sedating than most anticonvulsants (1974). The drug elevates mood in some depressed patients with epilepsy and is considered a drug of choice for b
4) Although effective in psychiatric disorders, carbamazepine does not have a neurochemical profile resembling t antipsychotics. Data suggest, however, that carbamazepine may decrease dopamine turnover without directly blo receptors (Post et al, 1986).
B) REVIEW ARTICLES
1) The treatment of seizures have been reviewed; these include treatment of first seizure and status epilepticus (treatment of the elderly (Rowan, 1998), and management of epilepsy in adults (Feely, 1999; Mattson, 1998). Pedi management has also been reviewed (Wolf et al, 1998; Pellock, 1998).
2) With the addition of the newer antiepileptic drugs, polypharmacy in epilepsy is being revisited (Schneiderman, 1998).
3) Carbamazepine prophylaxis for bipolar disorder has been reviewed (Keck et al, 1998; Post et al, 1997).
4) A review of the metabolism of carbamazepine is presented (Eichelbaum et al, 1985c).
5) Reviews of the use of carbamazepine in children are available (Gilman, 1991; Seetharam & Pellock, 1991).
6) The treatment and prophylaxis of facial neuralgias has been reviewed (Diener et al, 1994).
7) Drug-interactions of antidepressants are reviewed in German language (Zapotoczky & Simhandl, 1995).

4.5 Therapeutic Uses

Aggressive behavior

Agitation - Brain injury

Agitation - Dementia

Alcohol withdrawal syndrome

Apraxia

Behavioral syndrome - Mental retardation

Benzodiazepine withdrawal

Bipolar I disorder, acute manic and mixed episodes

Chorea

Chronic paroxysmal hemicrania - Tic disorder

Cocaine dependence

Dementia

Depression

Diabetes insipidus

Diaphragmatic tic

Dystonia

Encephalitis due to human herpes simplex virus; Adjunct

Epilepsy, Partial, generalized, and mixed types

Erythrodermic psoriasis

Facial spasm

Glossopharyngeal neuralgia

Hiccoughs, Intractable

Huntington's disease

Migraine; Prophylaxis

Multiple sclerosis, Sensory symptoms

Myoclonus

Myokymia

Neuralgia

Neurogenic pain

Neuropathy, General

Obsessive-compulsive disorder

Obsessive compulsive personality disorder

Pain

Panic disorder

Phantom limb syndrome

Polyradiculoneuropathy

Postherpetic neuralgia

Posttraumatic stress disorder

Psychotic disorder

Restless legs syndrome

Schwartz-Jampel syndrome

Subacute sclerosing panencephalitis

Tabes dorsalis

Temporal lobectomy behavior syndrome

Tinnitus

Trigeminal neuralgia

Trigeminal trophic syndrome

Uremic neuropathy

4.5.A Aggressive behavior

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Possibly effective for aggression (Coons, 1992; Yatham & McHale, 1988)

3) Adult:

a) Case reports of CARBAMAZEPINE 300 to 800 milligrams daily were reported effective in the treatment of BEHAVIOR (Coons, 1992; Yatham & McHale, 1988).

4.5.B Agitation - Brain injury

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

May be safe and effective for the treatment of post-traumatic agitation, but the response is inconsistent (

3) Adult:

a) Post-traumatic agitated behaviors, particularly irritability and disinhibition, were effectively treated with car patients severe CLOSED-HEAD INJURY. In this prospective, open trial, patients (mean age 34 years) receiv

200 milligrams (mg) per day, increased by 200 mg increments until 600 to 1200 mg/day was reached. Behav including the Neurobehavioral Rating Scale-revised (NRS-R) and the Agitated Behavior Scale (ABS) were pe baseline and every 2 weeks during treatment. Significant improvement in scores of both tools was observed a assessment (p=0.02 for both), but considerable interindividual variability was observed. Five patients demons than 50% improvement in NRS- R score, while 3 showed a 25% to 43% improvement, and 2 patients showed during the study period. Adverse effects consisted of drowsiness, for which the dose was reduced, and 1 cas allergic cutaneous reaction requiring drug withdrawal (Azouvi et al, 1999).

4.5.C Agitation - Dementia

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIa
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Effective in the treatment of hyperactivity, psychomotor restlessness, and agitation associated with deme

3) Adult:

a) In a 6-week, randomized, parallel-group study, carbamazepine was more effective than placebo in patient and aggression associated with dementia (Tariot et al, 1998); however following DRUG WITHDRAWAL, agita aggressive behavior returned to baseline levels (Tariot et al, 1999). At multiple nursing home sites, patients r carbamazepine (n=27) or placebo (n=24). The modal carbamazepine dose at 6 weeks was 300 milligrams/da serum level of 5.3 micrograms/milliliter was achieved. Mean total Brief Psychiatric Rating Scale decreased by carbamazepine group and 0.9 for the placebo group. The Clinical Global Impression ratings showed improve patients taking carbamazepine and 21% of those taking placebo. Staff perception of the extra time required t behavioral problems also significantly decreased in the carbamazepine group as compared to placebo. The s terminated after a planned interim analysis showed that carbamazepine provided more benefit than placebo (An additional open treatment period of 12 weeks was undertaken to examine long-term efficacy and safety a patterns of behavioral response. Behaviors were assessed at 6, 9, 15, and 21 weeks. Evaluations performed washout period demonstrated that scores for agitation and aggression were no different from untreated basel those assessing anxiety, depression, psychosis, and cognitive function were similar to those following 6 week carbamazepine treatment. Longer treatment with carbamazepine produced similar benefits regarding aggres behaviors, as well as improvements in other psychopathologic behaviors. Over the 21 weeks of study, 26 pat from participation for the following reasons: adverse effects (11), administrative reasons (12), lack of efficacy oral medications (1). Only 1 adverse effect, ataxia, was possibly related to carbamazepine treatment. Ongoin generally well tolerated (Tariot et al, 1999).

b) CARBAMAZEPINE 200 to 1000 milligrams daily was useful in the treatment of agitation in 6 of 9 patients disease (Gleason & Schneider, 1990). Corresponding serum concentrations ranged from 2.3 to 9.6 micrograi Overall improvement was greatest in agitation and hostility; some improvement was also seen in tension and uncooperativeness. Clinical improvement was generally seen within 2 to 4 weeks following the start of treatm

c) CARBAMAZEPINE was reported effective in the treatment of assaultive and aggressive behavior in patier DEMENTIA in a small study involving 8 ambulatory male patients (Patterson, 1987). The drug was given in d milligrams (mg) 3 times daily for 1 day, followed by 200 mg orally 4 times daily for the second day; subseque administered to achieve serum levels of 8 to 12 micrograms/milliliter. The number of assaults decreased sign CARBAMAZEPINE therapy (by more than 50%); assaultive behavior was also considered to be less intense duration.

4.5.D Alcohol withdrawal syndrome

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

May prove useful in the treatment of anxiety, dysphoria, somatization, and other signs of alcohol abstine (Flygenring et al, 1984; Agricola et al, 1982; Wilbur & Kulik, 1981).

See Drug Consult reference: DRUG THERAPY OF ETHANOL WITHDRAWAL

3) Adult:

a) In an open trial of approximately 100 patients, CARBAMAZEPINE was found to be effective in relieving ar associated with acute alcohol withdrawal syndromes (Poutanen, 1979).

4.5.E Apraxia

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Apraxia may respond to carbamazepine therapy (Naqvi et al, 1998)

3) Pediatric:

a) In a case series, carbamazepine was useful in treating 3 patients with apraxia and new-onset partial seizu 1998). Seven children (2 to 12 years old) with either oral motor apraxia or ocular motor apraxia received carb milligrams/kilogram/day. Responders had interictal epileptiform discharges on EEG while non-responders (n= seizures and had non-epileptiform EEG findings.

4.5.F Behavioral syndrome - Mental retardation

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Effective in the treatment of overactive, severely mentally handicapped patients (Reid et al, 1981)

3) Adult:

a) CARBAMAZEPINE was used for behavioral disorders including aggression, self-injurious behavior, hyper tantrums in 76 chronically institutionalized mentally retarded individuals previously unresponsive to other mec patients demonstrated nearly complete resolution of symptoms and 10 showed some improvement. Previous seizure disorders or underlying electroencephalogram abnormalities were noted in 27 of the 30 responders. T study is limited due to the lack of psychiatric diagnosis and the failure to distinguish among "behavior disorde 1989).

4.5.G Benzodiazepine withdrawal

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Possibly useful in the treatment of benzodiazepine withdrawal (Ries et al, 1989; Klein et al, 1986)

3) Adult:

a) CARBAMAZEPINE in doses of 400 to 800 milligrams daily was reported effective in treating withdrawal fr benzodiazepines (CHLORDIAZEPOXIDE, ALPRAZOLAM, DIAZEPAM, CLONAZEPAM) in a small open stuc 1989; Klein et al, 1986). Controlled studies are required to confirm these findings.

4.5.H Bipolar I disorder, acute manic and mixed episodes

FDA Labeled Indication

1) Overview

FDA Approval: Adult, yes (Extended release formulation); Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Indicated for the treatment of acute manic and mixed episodes associated with bipolar I disorder (Prod Ir extended release capsules, 2004)
Effective in the acute and prophylactic treatment of bipolar affective disorder
Effective in bipolar patients who have shown no response to LITHIUM therapy
In combination with LITHIUM may be effective when either or both agents alone have failed

3) Adult:

a) Therapy with carbamazepine extended-release (ER) capsules was more effective than placebo in the trea manic and mixed episodes in patients with bipolar disorder. In two randomized, double-blind, multicenter, flex patients diagnosed with bipolar I disorder with manic or mixed episodes received carbamazepine ER (titrated of 400 to 1600 milligrams (mg)/day, given twice daily in divided doses) or placebo for 3 weeks. The mean car dose during the last week of treatment was 952 mg/day in the first study and 726 mg/day in the second study Young Mania Rating Scale scores from baseline to endpoint were significantly more reduced in carbamazepi patients as compared with those who received placebo (Prod Info Equetro(TM) extended release capsules, 2

b) In a double-blind study in 52 bipolar patients, lithium and carbamazepine had a roughly equal but less tha prophylactic efficacy in overall bipolar illness (Denicoff et al, 1997a). Patients were randomly assigned to 1 ye with lithium or carbamazepine, and then crossed over to the other drug in the second year. During a third yea received a combination of the 2 drugs. A marked or moderate improvement occurred in 33% of patients recei 31% of patients receiving carbamazepine and 55% of those receiving the combination. Lithium, however, wa prophylaxis of mania (no mania experienced by 11% on lithium, 4% on carbamazepine, and 33% on combina

less than 0.01). The combination of lithium and carbamazepine was better than monotherapy in rapid cyclers
c) The addition of LITHIUM CARBONATE (plasma levels, 0.7 to 1.2 milliequivalents/liter) to CARBAMAZEPI
to 1500 milligrams daily) was reported effective in improving MANIA in 6 of 7 patients previously refractory to
alone. These patients were also refractory to several weeks of CARBAMAZEPINE therapy (Kramlinger & Pos
data support previous studies suggesting that some manic patients may respond to a combination of LITHIU
CARBAMAZEPINE, but not to each agent alone (Woods, 1986).
d) CARBAMAZEPINE was effective as an adjunctive medication in the treatment of 11 of 13 patients with tre
affective disorders including LITHIUM nonresponders. CARBAMAZEPINE was used in combination with neu
as well as with LITHIUM CARBONATE. Four patients were judged to have had markedly effective responses
effective response and in 4 there was a slightly effective response. The mean daily dose varied from 300 to 1
(Kwamie et al, 1984).

4.5.I Chorea

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy; Pediatric, Evidence favors efficacy
Recommendation: Adult, Class IIb; Pediatric, Class IIb
Strength of Evidence: Adult, Category C; Pediatric, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Effective in the treatment of chorea

3) Adult:

a) CARBAMAZEPINE 15 to 24 milligrams/kilogram/day orally (plasma levels, 6.5 to 8.8 micrograms/milliliter)
be effective in the treatment of NONHEREDITARY CHOREA in 5 patients (Roig et al, 1988). Chorea was ca
streptococcal infection in 2 patients and head injury in 1 other; the cause in the remaining 2 patients could no
Clinical improvement was observed within 4 to 15 days after initiation of CARBAMAZEPINE treatment. Side e
observed in 4 patients during 3 months to 36 months therapy. In one patient, withdrawal of the drug was requ
an allergic cutaneous reaction after 17 days. More studies are required to evaluate the efficacy of CARBAMA
b) CARBAMAZEPINE has been reported to be effective in the treatment of benign dominant hereditary chor
mother and daughter). Both showed decreased involuntary movements and functional improvement and felt s
quieter. Doses of CARBAMAZEPINE were 250 milligrams (mg) (3.5 mg/kilogram) daily in the child and 400 m
mother (Roulet & Deonna, 1989).

4) Pediatric:

a) Carbamazepine was found to be safe and effective in the treatment of choreic movements in 17 pediatric
female; 10.9 +/- 2.4 years-old) with SYDENHAM'S CHOREA in an open-label trial. The children received 15 m
kilogram per day of carbamazepine. Onset of clinical improvement was 7.4 +/- 8.2 days; time to complete rem
movements was 6.7 +/- 6.3 weeks; and the duration of treatment was 5.0 +/- 2.4 months. There was a recurr
and no adverse drug events were reported during the trial (Genel et al, 2002).
b) A prospective case series of 10 children with RHEUMATIC CHOREA found low-dose CARBAMAZEPINE
effective (Harel et al, 2000). Ages of the children ranged from 7 to 16 years; 9 children in the cohort had Syde
with concomitant carditis and 1 child had antiphospholipid antibody syndrome that evolved to systemic lupus
Dosing of carbamazepine was 4 to 10 milligrams/kilogram daily (associated plasma concentrations were 2.8
micrograms/milliliter). Initial improvement was observed within 2 to 14 days. Chorea disappeared in 7 childre
and in all patients within 12 weeks. Treatment duration was 1 to 15 months. Symptoms recurred in 3 patients
retreatment. One patient experienced a treatment-related side effect, a maculopapular rash that responded to

4.5.J Chronic paroxysmal hemicrania - Tic disorder

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category C
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

INDOMETHACIN and CARBAMAZEPINE may be beneficial for treatment of chronic paroxysmal hemicra
based on anecdotal evidence (Martinez-Salio et al, 2000)

3) Adult:

a) A 52-year-old man suffering from chronic paroxysmal hemicrania- tic syndrome (CPS-tic) was successfull
INDOMETHACIN and CARBAMAZEPINE . The patient initially presented with a 2-month history of headache
severe, sharp, or stabbing pain behind the right eye and temporal area, with attacks occurring 5 to 8 times a
to 15 minutes. During the attacks, he also experienced ipsilateral lacrimation, nasal congestion, and rhinorrhe
PAROXYSMAL HEMICRANIA (CPH) was diagnosed. Indomethacin 25 milligrams (mg) 3 times a day brough
complete relief. Some months later (indomethacin had been terminated after 6 months), he developed brief e
pains spreading from his right jaw to his right ear, that were triggered by talking, chewing, or touching the affe
shock-like pains were diagnosed as TRIGEMINAL NEURALGIA. Indomethacin was tried unsuccessfully. CA
200 mg 3 times a day brought complete relief in 24 hours. Two months later (with continuing use of carbama
type of headache (CPH) returned. Again indomethacin provided complete response. One month later, he suc
discontinued indomethacin, and carbamazepine was slowly tapered off. At 3-months follow-up, the patient wa

(Martinez-Salio et al, 2000).

4.5.K Cocaine dependence

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Effective in reducing cocaine craving and assisting in maintaining cocaine abstinence

3) Adult:

a) In a 12-week, randomized, double-blind, placebo-controlled study, carbamazepine reduced the duration a craving episodes but had little impact on frequency of urges (Halikas et al, 1997). Patients (n=183) were ranc placebo, carbamazepine 400 milligrams (mg), or 800 mg daily (31% of patients randomized completed the st carbamazepine levels were associated with lower rates of positive cocaine urinalysis (p=0.004), fewer days c cocaine use (p=0.014), shorter craving duration (p less than 0.001), and greater overall therapeutic effect (p=

b) CARBAMAZEPINE 200 to 400 milligrams daily was reported to be effective in reducing COCAINE craving maintaining COCAINE abstinence in 1 small study (Halikas et al, 1989). Similar results were reported in place crossover studies for the treatment of crack cocaine use (Halikas et al, 1992; Halikas et al, 1991). CARBAMA more than 4 micrograms/milliliter were associated with greater improvement.

4.5.L Dementia

See Drug Consult reference: BEHAVIORAL AND PSYCHOLOGICAL SYMPTOMS OF DEMENTIA

4.5.M Depression

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Carbamazepine was effective in unipolar depressed patients who had not previously been treated with a other psychotherapeutic treatments in a double-blind, randomized, placebo-controlled study (n=89) (Zha
Carbamazepine was effective in the prophylaxis of unipolar depression in an open-label study involving
(Stuppaeck et al, 1994)
Carbamazepine was effective in patients with depression resistant to other treatment, but the high rate o may limit its utility (Cullen et al, 1991)

3) Adult:

a) Carbamazepine was effective in unipolar depressed patients who had not previously been treated with an other psychotherapeutic treatments in a double-blind, randomized, placebo-controlled study (n=89). Patients with a history 2 or more episodes of major depression, no history of mania or hypomania, and currently exper episode of depression with a duration of at least 2 weeks, were randomized to immediate release carbamaze placebo (n=38) for 12 weeks. Carbamazepine was started at 300 milligrams/day (mg/day) in 2 divided doses (within 2 weeks) to a maximum of 800 mg/day based on patient response and tolerability. The mean final car was 461.6 +/- 87.7 mg/day. The primary efficacy analysis was based on a modified-intention-to-treat (MITT) p as all patients who completed at least one post baseline evaluation utilizing the last observation carried forwa method. Measures of primary efficacy included the Hamilton Rating Scale for Depression (HAMD), the Montg Depression Rating Scale (MADRS), and the Clinical Global Impression-Severity (CGI-S). Clinical response w greater than or equal to a 50% reduction in score on the HAMD from baseline to endpoint. Patients in both ar symptomatic improvements by week 8 (p less than 0.05 vs baseline), but significant separation in HAMD, MA results occurred between treatment groups (p less than 0.05). Mean HAMD score improved from 25 at baseli 8 in the carbamazepine arm compared with an improvement from 24 to 13.1 in the placebo arm (p less than (endpoint clinical response rate of carbamazepine-treated patients was 73.9% (34/46) compared to 45.9% (17 patients (p=0.018). The most frequently reported adverse event was benign leucopenia (30.4%) in the carbar Four carbamazepine patients discontinued treatment due to intolerable adverse events (3 rash, 1 blurred visi 2008).

b) Carbamazepine was effective in the prophylaxis of unipolar depression in an open-label study involving 15 study, patients received an initial dose of carbamazepine of 200 milligrams/day (mg/day), slowly increasing to final dose was adjusted to maintain a serum level in the lower end of the therapeutic range of 5 to 12 microgr Patients were followed for a period of 5 years. Carbamazepine was beneficial in 11 of 15 (73%) treated patie patients were completely free of depressive episodes (Stuppaeck et al, 1994).

c) Carbamazepine was effective in patients with depression resistant to other treatment, but the high rate of may limit its utility. In a retrospective study, 7 of 16 patients. demonstrated moderate to marked improvement included those with both psychotic and nonpsychotic depression as well as patients with organic brain diseas responders discontinued medication because of rash, hyponatremia, or hepatotoxicity (Cullen et al, 1991).

d) Relapse of depression was prevented with carbamazepine prophylaxis in a single patient. Recurrence of

appeared within 2 to 4 months of carbamazepine discontinuation. No significant side effects were noted durir (Kobayashi et al, 1988).

4.5.N Diabetes insipidus

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Induces antidiuresis by releasing antidiuretic hormone

3) Adult:

a) Seven of 9 patients with diabetes insipidus (1 to 23 years' duration) were successfully treated with CARBA to 1200 milligrams daily in divided doses for 7 to 10 days in a controlled study. In 7 patients, there was satisfa urine output and fluid intake. Plasma osmolality significantly decreased after 7 days. Upon substituting placeb symptoms of diabetes insipidus recurred (Wales, 1975).

b) Carbamazepine therapy successfully treated a patient's NEPHROGENIC DIABETES INSIPIDUS induced drug was also effective in the treatment of the patient's affective psychosis (Brook & Lessin, 1983).

c) Successful use of CARBAMAZEPINE was described in a 19-year-old black pituitary dwarf with diabetes ir age of 6 (Dindar & Cooper, 1974). Doses of 100 milligrams (mg) twice daily to 200 mg three times daily resul urinary output from 3 to 4 liters/day (L/day) to 1.5 L/day. Upon discontinuing therapy, urinary volume increase successfully maintained at 100 mg twice daily. The patient had previously failed to respond to pituitary snuff, and CHLORPROPAMIDE.

d) One study investigating the mechanism of ANTIDIURETIC ACTION showed that CARBAMAZEPINE in dc milligrams orally increased plasma ADH from 0.4 micrograms/milliliter (mcg/mL) to 3.8 mcg/mL and increasec from 0.4 to 1.7. Water loading did not inhibit the effects of CARBAMAZEPINE (Kimura et al, 1974).

4.5.O Diaphragmatic tic

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Successfully treated with carbamazepine in 3 patients (Vantrappen et al, 1992)

3) Adult:

a) High frequency diaphragmatic flutter characterized by esophageal belching, hiccups, and retching was tre CARBAMAZEPINE 200 to 400 milligrams 3 times daily in 3 patients with long-standing symptoms. All patient complete remission or significant improvement in symptoms and reductions in flutter as demonstrated by elec (Vantrappen et al, 1992).

4.5.P Dystonia

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Limited data suggests efficacy of CARBAMAZEPINE in dystonia (Geller et al, 1976)

3) Adult:

a) Successful use of CARBAMAZEPINE in 8 of 8 patients with dystonic symptoms (hereditary torsion dyston dystonia, 4) has been reported. The drug was given in doses of 300 to 1200 milligrams daily for a period of 4 was noted that brief episodes of dystonia responded most dramatically and completely, but returned the soor discontinuation of the drug. More sustained tension in dystonia responded more slowly to CARBAMAZEPINE completely, and required higher doses than brief dystonic episodes. Effectiveness of the dystonias was maint for periods of 4 to 12 months. Although symptoms remained improved for some time after withdrawal in 2 pat eventually relapsed following discontinuation of therapy or when placebo was substituted (Geller et al, 1976).

4.5.Q Encephalitis due to human herpes simplex virus; Adjunct

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:
Stabilized psychiatric sequelae of herpes simplex encephalitis (Vallini & Burns, 1987)
3) Adult:
a) In 1 case report, carbamazepine 200 milligrams 3 to 4 times daily was effective in stabilizing psychiatric se simplex ENCEPHALITIS in a 62-year-old male. It is unclear if beneficial effects observed were secondary to s mesial temporal seizure activity observed in this patient, or to mood-stabilizing effects of the drug (Vallini & B

4.5.R Epilepsy, Partial, generalized, and mixed types
FDA Labeled Indication
1) Overview
FDA Approval: Adult, yes; Pediatric, yes
Efficacy: Adult, Effective; Pediatric, Effective
Recommendation: Adult, Class IIa; Pediatric, Class IIa
Strength of Evidence: Adult, Category B; Pediatric, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS
2) Summary:
Indicated for the following seizure types (Prod Info Tegretol(R), 2002):
Partial seizures with complex symptomatology (psychomotor, temporal lobe)
Generalized tonic-clonic seizures (grand mal)
Mixed seizure patterns which include the above or other partial or generalized seizures
Not effective against absence seizures (petit mal)
3) Adult:
a) GENERAL INFORMATION
1) Carbamazepine is the drug of choice for the initial treatment of partial seizures with or without seconc (Herman & Pedley, 1998a). The drug is ineffective for absence seizures (may actually exacerbate these only minimally effective for atonic and myoclonic seizures (Parker et al, 1998a; Troupin et al, 1974a). CA as single-agent therapy has been effective in controlling seizures in over 75% of outpatients, reducing se more than 75% (Dodson, 1987; Andersen et al, 1983a). Other studies report that CARBAMAZEPINE is a PHENYTOIN as initial seizure therapy in adults with partial and generalized seizures (Mattson et al, 198 1983b). The sustained-release formulation of carbamazepine provides less peak-related adverse effects control, and greater compliance (Herman & Pedley, 1998a).
b) Following temporal lobectomy for treatment of medically intractable temporal lobe epilepsy, carbamazepir has been shown to be as effective as multidrug therapy (Kuzniecky et al, 1992). In this study, patients were r either carbamazepine or continued on their same multidrug antiepileptic regimen that they were on prior to su to monotherapy was achieved by discontinuing other antiepileptic drugs postoperatively. Carbamazepine ser maintained in the range of 6 to 10 micrograms/milliliter.
4) Pediatric:
a) CARBAMAZEPINE was effective in the treatment of grand mal seizures and psychomotor seizures, and w against absence seizures. Carbamazepine therapy was evaluated in 106 children and adolescents with vario disorders (Fischel & Heyer, 1970). Average doses of 15 to 20 milligrams/kilogram/day (mg/kg/d) (100 to 120(administered for an average of 45 months. In 40 patients with grand mal seizures alone, good to excellent re in 21 patients with no response in 14 patients and worsening of seizure control in 5. In 20 patients with psych alone, good to excellent results were obtained in 16 patients. The drug was not effective in absence seizures patients treated, 71 exhibited good to excellent results. Only 6 patients worsened during therapy with CARBA this group, 44 patients received other anticonvulsants concurrently with CARBAMAZEPINE. The main side e were initial fatigue, headache, and abdominal pains.
b) In 45 patients with chronic complex partial seizures or secondarily generalized tonic-clonic seizures, CAR monotherapy significantly improved complex-partial seizures regardless of the site of the EEG focus. In patie secondarily generalized seizures, seizures were better controlled in patients with a left-sided vs right-sided E et al, 1991).
c) Although CARBAMAZEPINE has generally been considered ineffective in absence seizures, one study re of CARBAMAZEPINE in a case of absence seizures unresponsive to ETHOSUXIMIDE or VALPROIC ACID (1988).
d) The successful use of a combination of benzodiazepines and CARBAMAZEPINE in controlling refractory myoclonic-astatic seizures in 24 children was reported (Tatzer et al, 1987). During the 5-year follow-up perioc infantile spasms and 4 children with myoclonic seizures became seizure-free; 6 additional children demonstra reduction in seizure frequency. Further controlled studies are required in this area.
e) In one study, carbamazepine controlled seizures in 22 of 58 children not adequately controlled on other m (Gamstorp, 1970). An additional 8 children experienced a 75% reduction in seizure frequency. After follow-up 19 of the 22 complete responders still remained seizure-free and 5 of the 8 patients maintained a 75% reduct frequency. Follow-up after 2 to 6.5 years revealed that 13 of 22 patients remained seizure-free, and in 3 of 22 carbamazepine was successfully withdrawn after 5 years.

4.5.S Erythrodermic psoriasis
1) Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category C
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:
Effective in one case of psoriatic erythroderma (Smith & Skelton, 1996)

3) Adult:
a) A 29-year-old HIV-1-positive man with a CD4+ T-cell count below 10 cells per cubic millimeter was succes carbamazepine for psoriatic erythroderma. This patient's skin disease had become progressively more difficu EXFOLIATIVE ERYTHRODERMA developed. He has continued to take carbamazepine for 1 year without re disease and with no changes in his laboratory values (Smith & Skelton, 1996). Other practitioners have been duplicate this response (Redondo & Vazquez-Doral, 1998).

4.5.T Facial spasm

1) Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category C
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:
Effective in the treatment of HEMIFACIAL SPASM in uncontrolled studies (Alexander & Moses, 1982)

3) Adult:
a) Efficacy of CARBAMAZEPINE in hemifacial spasm was reported in 3 patients receiving doses of 600 to 1 daily. These authors reviewed previous reports indicating the efficacy of the drug in over 50% of patients trea controlled trials are required to establish the efficacy of the drug as compared to surgical therapies or other m (Alexander & Moses, 1982).

4.5.U Glossopharyngeal neuralgia

FDA Labeled Indication

1) Overview
FDA Approval: Adult, yes; Pediatric, no
Efficacy: Adult, Effective
Recommendation: Adult, Class IIa
Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:
Indicated for glossopharyngeal neuralgia (Prod Info Tegretol(R), 1998)

3) Adult:
a) CARBAMAZEPINE 600 milligrams daily was effective in the treatment of paroxysms of pain and associate symptoms in an 83-year-old woman with glossopharyngeal neuralgia (Saviolo & Fiasconaro, 1987). It is sugg CARBAMAZEPINE may be an alternative to surgical resection of the glossopharyngeal nerve in these patien studies are required to fully evaluate the efficacy of CARBAMAZEPINE in glossopharyngeal neuralgia.
b) The efficacy of CARBAMAZEPINE 1200 milligrams daily in controlling paroxysmal pain associated with gl neuralgia in a 53-year-old man was reported (Johnston & Redding, 1990).

4.5.V Hiccoughs, Intractable

1) Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category C
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:
Effective in 1 patient with INTRACTABLE HICCUPS due to multiple sclerosis (McFarling & Susac, 1974)

4.5.W Huntington's disease

1) Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category C
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:
May alleviate micturitional disturbances in some patients with Huntington's disease (Cochen et al, 2000)

3) Adult:
a) CARBAMAZEPINE 200 milligrams (mg)/day resolved PRECIPITATE MICTURITIONS and DIURNAL or N INCONTINENCE in 3 male patients (aged 42 to 50 years) with genetically confirmed Huntington's disease (H patients with severe HD, dementia, and incontinence not characterized as precipitate micturition were not hel carbamazepine therapy. For those benefiting from carbamazepine, micturition difficulties ceased within 2 to 7

carbamazepine 200 mg/day. Two of these 3 patients failed on 100 mg/day, but were successful when the dos
to 200 mg/day. None of the patients who responded to carbamazepine had demonstrated seizures. The auth
that carbamazepine may have a direct action on the control center of micturition and defecation (Cochen et a

4.5.X Migraine; Prophylaxis

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy; Pediatric, Evidence is inconclusive
Recommendation: Adult, Class IIb; Pediatric, Class IIb
Strength of Evidence: Adult, Category C; Pediatric, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Carbamazepine has been used for migraine headache prophylaxis
Studies on the effectiveness of carbamazepine for migraine prophylaxis have produced mixed results

3) Adult:

a) Carbamazepine was moderately effective in the prophylactic treatment of 51 adult patients with symptoms
(Anthony et al, 1972). Carbamazepine 600 milligrams/day was effective in reducing the frequency of migraine
patients. Fifty-three percent of patients experienced side effects (giddiness, ataxia, drowsiness, nausea) and
discontinued in 24% of these patients.

b) CARBAMAZEPINE was more effective than placebo in a double-blind study of 48 patients with migraine h
CARBAMAZEPINE treatment resulted in improvement in 84.4% of patients as compared to 27.1% of patients
placebo. Doses of CARBAMAZEPINE were not specified (Rompel & Bauermeister, 1970).

4) Pediatric:

a) Carbamazepine 10 to 20 milligrams/kilogram/day divided into 2 doses has been used in children for migra
prophylaxis (Hamalainen, 1998). The dosage should be increased slowly and the patient monitored every 3 r
monitoring the usual lab values, height and body weight should also be monitored.

4.5.Y Multiple sclerosis, Sensory symptoms

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Effective in a few patients with PAROXYSMAL DYSARTHRIA and ATAXIA associated with multiple scle

3) Adult:

a) CARBAMAZEPINE was effective 100 milligrams three times daily in a 41-year-old male with multiple scler
loss of control of right arm and leg with burning sensations around the left eye and dysarthria. These attacks
following administration of the drug and recurred when the drug was discontinued. Three other patients with r
(including 1 PHENYTOIN failure) experienced suppression of attacks when CARBAMAZEPINE was administ
Walker, 1967).

b) Two patients with multiple sclerosis and paroxysmal dysarthria and ataxia were treated with CARBAMAZE
milligrams twice daily (Miley & Forster, 1974). Paroxysmal episodes decreased in both patients within 2 days
patient, the drug was discontinued after 1 month of therapy with no recurrences seen at a 5 month follow-up.

c) CARBAMAZEPINE 400 milligrams daily was effective in alleviating both spontaneous and TONIC SPASM
hyperventilation and pain in a 31-year-old man with multiple sclerosis (Honig et al, 1991).

4.5.Z Myoclonus

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

ACTION MYOCLONUS secondary to acute hypoxia has responded to CARBAMAZEPINE therapy (Hiros

4.5.AA Myokymia

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Pediatric, Evidence favors efficacy
Recommendation: Pediatric, Class IIb
Strength of Evidence: Pediatric, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Effective for the treatment of myokymia based on 1 case report (Kinnett & Keebler, 2001)

3) Pediatric:

a) Oral CARBAMAZEPINE successfully prevented painful cramping of the anterior thigh muscles in a 12-yea diagnosed with HEREDITARY MYOKYMIA. Her condition received medical attention when she declined to pa physical education classes due to recurrent cramping. The patient was started on carbamazepine 200 milligra daily. Compared with test results before carbamazepine, endurance time on a treadmill without cramping was after she began receiving carbamazepine. Strength testing showed improvement in only the hamstring muscl reports of sedation, the dose of carbamazepine was reduced to 100 mg twice a day and gradually increased twice a day. After 2 years, she was slowly weaned off of carbamazepine over 8 weeks, without symptom recu later, she was using prednisone for an exacerbation of asthma and the cramping returned. Reintroduction of brought relief. She received a 2-week course of carbamazepine 100 mg twice daily while being weaned off pr patient continued to do well without carbamazepine (Kinnett & Keebler, 2001).

4.5.AB Neuralgia

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Effective in treating a variety of neuralgias

3) Adult:

a) Two patients with SUNCT SYNDROME (short-lasting, unilateral, neuralgi-form, headache attacks with cor and tearing) received relief with carbamazepine therapy (Raimondi & Gardella, 1997). The first patient was a whose moderately painful episodes in the medial right supraciliary area lasted between 15 and 20 seconds a times per day. Treatment with carbamazepine 600 milligrams (mg) provided a decrease in intervals between months. After 3 months the medication was discontinued with only 2 attacks per week. The second patient wa woman with 6 or 7 attacks of right orbitofrontal area pain which peaked in intensity after 30 seconds followed lesser pain for 35 to 120 minutes. She was treated with prednisolone 60 mg for 6 days and then 20 mg for 10 carbamazepine 800 mg/day for 11 weeks. She eventually received complete relief from this regimen.

b) CARBAMAZEPINE 200 milligrams (mg) at bedtime was effective in treating the pain associated with MOR NEURALGIA in a 79-year-old woman. Similarly, 200 mg 3 to 4 times daily effectively controlled pain in a 46-y (Guiloff, 1979).

4.5.AC Neurogenic pain

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIa
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Effective in some types of neurogenic pain

3) Adult:

a) Carbamazepine effectively reduced NEURITIC PAIN and OPIOID REQUIREMENTS in 12 patients recove GUILLAIN-BARRE SYNDROME. In a prospective, double-blind, crossover study, mechanically ventilated pat 54 years with moderate to severe body and back aches requiring increasing doses of opioids were randomize placebo or carbamazepine 100 milligrams via a nasogastric feeding tube every 8 hours for 3 days. Carbamaz associated with significantly reduced pain scores, meperidine requirements, and less sedation (p less than 0. groups). It is suggested that these effects may benefit patients with Guillain-Barre syndrome who are candida weaning (Tripathi & Kaushik, 2000).

b) CARBAMAZEPINE 400 milligrams (mg) to 1200 mg daily was effective in the treatment of intractable neu 7 patients (Rapeport et el, 1984). However, of 16 patients entering the study, 9 withdrew due to side effects o the 7 patients completing the protocol were used for efficacy evaluation. Controlled studies are required to de the drug in neurogenic pain.

c) CARBAMAZEPINE 200 milligrams 3 times daily was effectively used in combination with HYDROMORPH old patient with PANCOAST SYNDROME who had suffered severe, unrelieved pain for approximately 10 mo combination therapy, the patient was able to remain pain-free until the time of death (Tanelian & Cousins, 19

4.5.AD Neuropathy, General

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy; Pediatric, Evidence favors efficacy
Recommendation: Adult, Class IIb; Pediatric, Class IIb
Strength of Evidence: Adult, Category C; Pediatric, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Effective in some types of neuropathic pain

3) Adult:

a) Reduced pain was noted in patients (n=12) with THIAMINE-DEFICIENCY NEUROPATHY treated with PH milligrams (mg) at bedtime or CARBAMAZEPINE 200 mg at bedtime (Skelton & Skelton, 1991). Two patients were unable to tolerate the side effects of these medications. Of the remaining patients, similar effects were r treatment groups with significant reductions in pain noted in all patients. Two patients treated with PHENYTC treated with CARBAMAZEPINE reported complete relief.

4) Pediatric:

a) Two 14-year-old boys experienced relief of their painful neuropathy secondary to MERCURY POISONING carbamazepine 20 milligrams/kilogram/day (Karagol et al, 1997). Both had distal extremity pain with severe a along with, excessive sweating, weight loss, fatigue, photophobia and diarrhea. Urine mercury levels were 70 micrograms/liter (mcg/L) (normal 2 to 26 mcg/L). Both experience continued pain after 2 days of N-acetyl-D,L therapy. After 2 days of carbamazepine and pyridoxine therapy the pain subsided.

4.5.AE Obsessive-compulsive disorder

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category C
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Mixed results have been obtained when assessing carbamazepine in the use of obsessive-compulsive d

3) Adult:

a) The addition of carbamazepine to clomipramine therapy was effective in the treatment of refractory obses disorder (OCD) in a 27-year-old woman. The patient had been unresponsive to clomipramine treatment since Coadministration of numerous medications (haloperidol, thioridazine, bromazepam, sulpiride, oxazepam, diaz risperidone) with clomipramine failed to improve her condition. After adding carbamazepine 500 milligrams (m (plasma level=6.1 mg/milliliter) to clomipramine 200 mg/day, her OCD symptoms dramatically improved withi improvement was sustained for at least 5 months (Iwata et al, 2000).

b) CARBAMAZEPINE in mean doses of 1088 mg daily was ineffective in the treatment of obsessive-compuls uncontrolled study involving 9 patients (Joffe & Swinson, 1987). No effects on mood or behavior were observ of treatment.

c) A small population of patients with obsessive-compulsive symptoms might respond to CARBAMAZEPINE anticonvulsant effects. The use of CARBAMAZEPINE 600 to 1000 milligrams daily in 7 patients meeting diag obsessive-compulsive disorder was reported (Khanna, 1988). Blood levels were maintained in the range of 8 micrograms/milliliter during the 12-week study. Only 2 patients reported a greater than 50% reduction in obse symptoms; in both cases, there was a history of a seizure disorder likely to respond to CARBAMAZEPINE.

4.5.AF Obsessive compulsive personality disorder

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category C
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Improved symptoms in one case (Greve & Adams, 2002)

3) Adult:

a) Carbamazepine reduced irritable and agitated behavior of a 61- year-old man with Obsessive-Compulsive Disorder (OCPD). The man presented with mild cognitive impairment, including reduced attention, concentrat motivation, which had been worsening over the preceding 3 years. He had a life-long rigid, perfectionistic, an personality style and became easily irritated and agitated. He was diagnosed with OCPD with features of Obs Compulsive Disorder. One month after starting carbamazepine 100 milligrams (mg) twice daily, he reported f less prone to excessive reactions. The dosage was raised to 200 mg twice daily, and he developed a rash. T discontinued. Eight months later he reported some return of symptoms, including problems with self- regulatc & Adams, 2002).

4.5.AG Pain

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Possibly effective for pain associated with depression (Kudoh et al, 1998)

3) Adult:

a) Carbamazepine demonstrated both analgesic and antidepressant effects in depressed patients who had f adequate pain relief with tricyclic or tetracyclic antidepressants or nonsteroidal analgesics. After a central me

a clinically significant organic disorder were ruled out, carbamazepine 450 milligrams/day was started. Doses every 2 weeks until satisfactory pain relief and then maintained for 3 weeks. Thereafter, placebo was adminis followed by an additional 3 weeks of carbamazepine at the same dose that previously produced satisfactory p of 15 patients completed the study, 3 patients were unable to tolerate the initial dose. On a visual analog scal significantly improved from 8.2 to 4.0 on the first round of carbamazepine therapy (p less than 0.05), increase during placebo, and decreased to 4.1 with the second carbamazepine trial (p less than 0.05). Hamilton depre improved from 27.4 to 20.2 with carbamazepine therapy (Kudoh et al, 1998).

4.5.AH Panic disorder

1) Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:
Results were mixed in the treatment of panic disorder (Uhde et al, 1988)

3) Adult:
a) Mixed results were obtained when 14 patients with panic disorder were treated with CARBAMAZEPINE 2(milligrams daily (median 800 milligrams) during a 3-week, placebo-controlled trial. Although a statistically sign overall anxiety was noted on several rating scales, only 1 patient demonstrated sustained clinical improveme panic attacks was noted in 40% of patients as compared with an increase in 50% of patients (Uhde et al, 198

4.5.AI Phantom limb syndrome

1) Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category C
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:
Total abatement of phantom limb pain has been achieved (Patterson, 1988)

3) Adult:
a) The successful use of CARBAMAZEPINE 200 milligrams four times a day in the treatment of phantom lim year-old male was reported. The drug was given in increasing doses to achieve serum levels of 8 to 12 micro resulted in total abatement of pain. Controlled studies are required to more fully evaluate the efficacy of CARI phantom limb pain (Patterson, 1988).

4.5.AJ Polyradiculoneuropathy

1) Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category C
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:
Effective in one case report (Winspur, 1970)

3) Adult:
a) A case of POLYRADICULONEUROPATHY with severe shooting pains in both legs was successfully treat CARBAMAZEPINE 400 milligrams (mg) at bedtime initially, followed by 200 mg three times daily in combinat PREDNISONE 60 mg daily. Further investigations are required to determine the efficacy of CARBAMAZEPIN polyradiculoneuropathy (Winspur, 1970).

4.5.AK Postherpetic neuralgia

1) Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:
Variable results in POSTHERPETIC NEURALGIA (Thompson & Bones, 1985)

3) Adult:
a) Limited response was seen with carbamazepine 400 to 1200 milligrams/day in 4 patients with intractable (associated with post-herpetic neuralgia. A favorable response (greater than 50% reduction in subjective pain attained in 1 patient. The response was limited by side effects, especially neurotoxicity (drowsiness, diplopia, ataxia), as only 7 of a total of 16 patients in the study were able to complete the entire 6-week protocol (Rape
b) Carbamazepine has been reported to be ineffective for preventing post-hepatic neuralgia. Forty otherwise

over 50 years of age with early, severe painful herpes zoster were randomly grouped to receive either predni daily for 10 days with gradual reduction over 3 weeks or carbamazepine 400 milligrams daily. Thirteen (65%) given carbamazepine developed post-herpetic neuralgia lasting up to 2 years whereas three (15%) of 20 pre patients had post-herpetic neuralgia lasting up to 5 months only (Keczkes & Basheer, 1980).

4.5.AL Posttraumatic stress disorder

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Symptomatic improvement has been seen with the use of carbamazepine for posttraumatic stress disorc 1986)

3) Adult:

a) In a preliminary study of CARBAMAZEPINE in 10 patients with post-traumatic stress disorder, 7 patients marked to moderate improvement as measured by the Clinical Global Impression Scale. Symptomatic impro in reduced frequency and intensity of flashbacks, intrusive memories and nightmares. CARBAMAZEPINE do to maintain levels at 5 to 10 micrograms/milliliter (Lipper et al, 1986).

4.5.AM Psychotic disorder

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

May augment neuroleptic therapy in psychotic patients with aggression (Neppe et al, 1991)
In case reports, provides neuroleptic-augmentation of CANNABIS-INDUCED PSYCHOTIC DISORDER
In case reports, relieves sensory-induced psychotic symptoms

3) Adult:

a) Two patients with cannabis-induced psychotic symptoms benefited from adding carbamazepine to their n (Leweke & Emrich, 1999). These young patients (19 and 22 years old) developed a schizophrenia-like psych term cannabis use. They were both treated with perazine up to 400 milligrams. One patient had also failed h risperidone trials. Symptoms improved over the next 2 weeks as measured on the Brief Psychiatric Rating Sc

b) Eight women with violent episodic outbursts ranging from murder to serious assaults, with EEGs revealin were successfully treated with CARBAMAZEPINE 400 to 800 milligrams/day (mg/day). Patients were also re doses of neuroleptics (mean 2040 mg/day in CHLORPROMAZINE equivalents). CARBAMAZEPINE therapy 2 months to 11 years (mean 2.7 years). Violent behavior disappeared almost completely in all 8 patients and schizophrenic symptoms decreased markedly. By the end of the trial, the neuroleptic dosage had been reduc of 1310 mg/day in CHLORPROMAZINE equivalents. It appears that the combination of CARBAMAZEPINE a therapy successfully controls violent schizophrenia and allows reduced doses of the neuroleptics (Hakola & L

c) One study reported CARBAMAZEPINE efficacy in 9 schizophrenic patients with episodic hostility and agg suggested that the presence of these target features may be predictive of CARBAMAZEPINE responsivenes 1991).

d) The combination of CARBAMAZEPINE plus HALOPERIDOL was superior to haloperidol plus placebo in involving 43 patients with EXCITED PSYCHOSES. Combination therapy was reported superior to HALOPER clinical benefits being as apparent in excited SCHIZOPHRENIA as in mania (Klein et al, 1984a).

e) Carbamazepine therapy was effective for MUSICAL HALLUCINATIONS with temporal lobe abnormalities woman (Terao & Tani, 1998). The woman's musical hallucinations had lasted for at least 2 years. Alpha wave predominately in the occipital area were evident on electroencephalography (EEG). Carbamazepine 300 milli softened, slowed and decreased the duration of the music. The mild spike activity on EEG disappeared.

f) A 40-year-old man with PALINOPSIA (the recurrence of visual images after the stimulus is removed) was treated with carbamazepine. This man's diagnoses included DSM-IV diagnostic criteria for psychosis not othe anxiety disorder not otherwise specified, and some of the symptoms of post-traumatic stress disorder. He des abnormalities as unrelated to his combat experiences and as perseverations of images or objects he had pre He was treated with imipramine 200 milligrams (mg) and trifluoperazine 10 mg daily. This decreased his flash and insomnia; however, the palinopsia continued. Carbamazepine 400 mg/day was started and within 48 hou had decreased. After 6 days of carbamazepine 800 mg, his palinoptic experiences disappeared (Silva et al, 1

4.5.AN Restless legs syndrome

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Short-term efficacy for restless legs syndrome

See Drug Consult reference: RESTLESS LEG SYNDROME - DRUGS OF CHOICE

3) Adult:

a) CARBAMAZEPINE in doses of 200 milligrams at bedtime initially, increasing to maximum doses of 200 m morning and 400 milligrams at bedtime, was effective in reducing the number of attacks of restless legs (EKE SYNDROME) in a placebo-controlled study (Lundvall et al, 1983).

b) An additional report of the efficacy of CARBAMAZEPINE in restless legs (Ekbom's syndrome) was reporte 1984). In this study, the placebo response was remarkable, although response to CARBAMAZEPINE was su daily dose was 236 milligrams CARBAMAZEPINE.

4.5.AO Schwartz-Jampel syndrome

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Pediatric, Evidence favors efficacy
Recommendation: Pediatric, Class IIb
Strength of Evidence: Pediatric, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Possibly beneficial for Schwartz-Jampel syndrome (Topaloglu et al, 1993)

3) Pediatric:

a) Three cases of MYOTONIC CHONDRODYSTROPHY (Schwartz-Jampel syndrome) were reported to ber with carbamazepine. The three children were placed on carbamazepine 20 milligrams/kilogram/day. Symptor gradually improved over several months (Topaloglu et al, 1993).

4.5.AP Subacute sclerosing panencephalitis

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Effective in 1 case report (Kertesz et al, 1970)

3) Adult:

a) CARBAMAZEPINE effectively reduced the number and intensity of akinetic attacks secondary to subacute PANENCEPHALITIS in 1 patient with doses of 200 milligrams three times daily. Symptoms were ameliorated initiation of therapy (Kertesz et al, 1970).

4.5.AQ Tabes dorsalis

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Effective for lightning pains of tabes dorsalis (Ekbom, 1972; Alarcon-Segovia & Lazcano, 1968; Ekbom,

3) Adult:

a) Three uncontrolled studies have revealed the beneficial effects of carbamazepine in 10 of 10 patients with tabes dorsalis (Ekbom, 1972; Alarcon-Segovia & Lazcano, 1968; Ekbom, 1966). In all patients, pain symptom 1 to 3 days and attempts to withdraw medication led to reappearance of pain. During long-term therapy, mild sporadic pain was usually exacerbated by infections with fever or by consumption of ETHANOL. Also, during larger doses were required in some patients to maintain adequate analgesia.

4.5.AR Temporal lobectomy behavior syndrome

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Effective in one case of posttraumatic Kluver-Bucy syndrome (Stewart, 1985)

3) Adult:

a) In one case, CARBAMAZEPINE blood levels of 8 to 11 micrograms/milliliter were effective in controlling ra affective blunting, hypersexuality, hyperorality and hypermetamorphosis in a 20-year-old man with post-traun

syndrome. His bulimia was unaffected by drug therapy (Stewart, 1985).

4.5.AS Tinnitus

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Ineffective in the general treatment of tinnitus (Hulshof & Vermeij, 1985)
Effective in case reports of ear clicking and HYPERACUSIS

See Drug Consult reference: DRUG THERAPY OF TINNITUS

3) Adult:

a) Two women with hyperacusis due to Lyme disease benefited from carbamazepine therapy (Nields et al, 1 had other central nervous system effects which remitted after treatment with cefotaxime. After cefotaxime, bo remained so sensitive to sound that they wore ear plugs, rifle range headphones, or airport headphones to pr kindling-like phenomenon occurred in each woman where repeated subthreshold sound lowered their toleran hours or days. This led to a trial of carbamazepine titrated to a blood level of 4 to 6 micrograms/milliliter. Both experienced an increase in baseline sound tolerance. Symptoms again worsened in each patient after a trial

b) Although an early study (Rahko & Akkinen, 1979) demonstrated CARBAMAZEPINE to have considerable treatment of clicking tinnitus (clicks almost totally disappeared in 3 patients, with symptoms reappearing whe discontinued), a double-blind study involving 78 patients failed to show a statistically significant difference in t patient's tinnitus when taking CARBAMAZEPINE or placebo (Donaldson, 1981a).

c) In an anecdotal report, benefits were reported with CARBAMAZEPINE 200 milligrams orally three times a treatment of ear-clicking tinnitus. Withdrawal of CARBAMAZEPINE resulted in return of tinnitus and reinstituti again produced symptom resolution. In this case report, a caffeine-free diet was also reported helpful in allev when the patient was not receiving CARBAMAZEPINE. More studies are required to fully evaluate the efficac CARBAMAZEPINE in this form of tinnitus (Mardini, 1987).

4.5.AT Trigeminal neuralgia

FDA Labeled Indication

1) Overview

FDA Approval: Adult, yes; Pediatric, no
Efficacy: Adult, Effective
Recommendation: Adult, Class I
Strength of Evidence: Adult, Category A

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Indicated for pain associated with trigeminal neuralgia
Drug of choice

3) Adult:

a) CARBAMAZEPINE has been used effectively in patients with trigeminal neuralgia for many years and is n drug of choice (Voorhies & Patterson, 1981; Tomson et al, 1980; Daly & Sajor, 1973; Lewis, 1969; Killian, 19 Sachdev, 1969; Marotta, 1969; Sturman & O'Brien, 1969; Killian & Fromm, 1968a; Walsh & Smith, 1968). Eff these studies range from 100 to 800 milligrams daily resulting in blood levels of 6 to 12 micrograms/milliliter. can be used over long periods of time for the treatment of trigeminal neuralgia without loss of efficacy.

b) The results of 143 patients with trigeminal neuralgia who had received CARBAMAZEPINE over a 16-year reviewed (Taylor et al, 1981). Fifty-six males and 87 female patients received a starting dose of CARBAMAZ 200 milligrams (mg) 3 or 4 times daily. The dose was increased until the pain was controlled or side effects d then continued to receive the minimum dose needed to prevent pain and were instructed to stop the drug dur Forty-six (32%) of the patients were completely or well-controlled by CARBAMAZEPINE and 53 (37%) were p acceptably, controlled. Ten patients experienced mild side effects, but did not stop treatment. Of these 99 pa good initial response, 19 developed a late resistance in that pain recurred and did not respond to CARBAMA Resistance developed anywhere from 2 months to 10 years after treatment began. Sixty-three of the original required alternate treatment. Thirty-six of the patients failed to respond to CARBAMAZEPINE initially, eight p intolerant and 9 responded initially, but developed resistance.

c) A synergistic effect between BACLOFEN and CARBAMAZEPINE was shown in the treatment of trigemina 57-year-old patient. The patient had a history of paroxysmal jaw pain unresponsive to CARBAMAZEPINE alo eventually controlled with BACLOFEN 60 milligrams (mg) per day plus CARBAMAZEPINE 800 mg per day (E

4.5.AU Trigeminal trophic syndrome

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:
Successfully treated a case of trigeminal trophic syndrome (Bhushan et al, 1999)
3) Adult:
a) Carbamazepine was effective in the treatment of trigeminal trophic syndrome in a 58-year-old male. This i
caused by damage to the trigeminal nerve and is associated with facial dysesthesias and ulceration. Carbam
milligrams twice daily effectively reduced the patient's sensory symptoms within 48 hours of initiation (Bhusha

4.5.AV Uremic neuropathy
1) Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category C
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS
2) Summary:
Antidepressant actions may contribute to analgesic effectiveness
Further data is needed to evaluate this mode of therapy
3) Adult:
a) CARBAMAZEPINE was effective in relieving pain in 5 patients with severe UREMIC NEUROPATHY (Zar
1976). Doses of 100 milligrams (mg) twice daily were given initially, followed by maintenance doses of 200 to
daily for several weeks. In all patients, pain relief was noted within 1 to 2 weeks. However, motor weakness,
other symptoms remained unchanged in all patients.

4.6 Comparative Efficacy / Evaluation With Other Therapies

Amitriptyline

Baclofen

Clonazepam

Haloperidol

Lamotrigine

Lithium

Lorazepam

Oxazepam

Oxcarbazepine

Phenobarbital

Phenytoin

Primidone

Progabide

Propranolol

Tiapride

Topiramate

Valproic Acid

Vigabatrin

Zonisamide

4.6.A Amitriptyline

4.6.A.1 Neurogenic pain

a) Carbamazepine 800 mg daily was compared with amitriptyline 75 mg daily in a 4-week, randomized, doub over trial in 15 patients with central post-stroke pain. Amitriptyline produced a statistically significant reductior weeks of the start of treatment. Five of the patients treated with carbamazepine obtained pain relief but it was significant as compared with placebo. Carbamazepine produced a greater number of side effects which requi reduction in 4 patients (Leijon & Boivie, 1989).

4.6.B Baclofen

4.6.B.1 Trigeminal neuralgia

a) Baclofen reduced the number of trigeminal neuralgic attacks in patients resistant to carbamazepine but ef significant when the drug was combined with carbamazepine. This was a double-blind trial (Parekh et al, 198

4.6.C Clonazepam

4.6.C.1 Psychomotor epilepsy

a) Clonazepam and carbamazepine were equally effective in the treatment of newly diagnosed and previous psychomotor epilepsy. In a double-blind, randomized study, 36 patients were maintained on either clonazepa or carbamazepine 900 milligrams/day for a period of 6 months. Plasma levels for each drug remained within t range throughout treatment. Both drugs were equally effective in controlling epilepsy. Side effects were simila (Mikkelsen et al, 1981).

4.6.D Haloperidol

4.6.D.1 Drug-induced psychosis, Inhalant

a) Carbamazepine demonstrated comparable efficacy to haloperidol in the treatment of inhalant-induced psy (Hernandez- Avila et al, 1998). Patients received either 1 capsule of carbamazepine 200 milligrams (mg) 3 tir 1 capsule of haloperidol 5 mg 3 times daily (n=20) for 5 weeks. Doses were increased at weekly intervals by patient failed to show a 25% decrease in the Brief Psychiatric Rating Scale (BPRS). At the end of the study, r were carbamazepine 920 mg (serum level of 10.8 micrograms/liter) and haloperidol 21.7 mg. Similar improve in both groups with 48.3% improvement in the carbamazepine group and 52.7% improvement in the haloperi

4.6.E Lamotrigine

4.6.E.1 Seizure

a) Carbamazepine and lamotrigine are equally effective as monotherapy in patients with newly diagnosed ep double-blind manner, patients were randomly assigned to a fixed dosage titration of either carbamazepine or four weeks, all patients were receiving either 150 milligrams/day (mg) of lamotrigine or 600 mg/day of carbam next 24 weeks, doses were adjusted according to efficacy, tolerance, and drug serum levels. The percentage were seizure-free for the last 6 months of the study were 39% and 38% for lamotrigine and carbamazepine g respectively. However, lamotrigine was better tolerated, and more patients were able to complete the study p treated with carbamazepine. Sleepiness was significantly more common with carbamazepine than lamotrigin 12%, respectively) (Brodie et al, 1995).

b) As initial monotherapy in elderly patients newly diagnosed with epilepsy, lamotrigine demonstrated a supe tolerability profile compared to carbamazepine. Subjects (n=150) were randomized in a double-blinded 2:1 ra 25 milligrams/day (mg/day) or carbamazepine 100 mg/day. Both medications were titrated slowly upward ove mg twice daily and 200 mg twice daily, respectively, with adjustments as needed over the 24-week study dura doses of lamotrigine and carbamazepine in study completers were 100 mg/day and 400 mg/day, respectively serum concentrations at week 24 were 2.3 mg/liter (L) and 6.9 mg/L, respectively. Somnolence (29% versus (25% versus 9%) occurred significantly more often in the carbamazepine versus lamotrigine groups, respecti corresponding withdrawal rates were 58% and 29%, with adverse events accounting for 42% and 18% of dis respectively. The hazard ratio for withdrawal with carbamazepine compared to lamotrigine was 2.4 (95% con 1.4 to 4). Efficacy measures were considered secondary endpoints in this trial. While no between-group differ respect to time to first seizure, significantly more lamotrigine recipients remained seizure-free over the last 16 study (39% versus 21%, p=0.03) (Brodie et al, 1999).

4.6.F Lithium

Bipolar disorder

Depression

Mania

4.6.F.1 Bipolar disorder

a) SUMMARY: Comparisons of prophylactic use of lithium and carbamazepine for bipolar disorder have proc results for superiority of one agent over the other, with both agents showing only modest efficacy rates.

b) In treatment-naive bipolar patients, lithium was superior to carbamazepine for preventing recurrence of m depressive episodes. Based upon analyses of 94 patients who had been randomized to blinded treatment eit blood levels 0.6 to 1.0 millimoles/liter) or carbamazepine (target blood levels 6 to 10 milligrams/liter), 27% an on lithium and carbamazepine, respectively, experienced relapse within the 2-year study period. Among relap almost all on lithium had initially experienced a hypomanic episode, and had recurrent episodes within the firs therapy. In contrast, patients relapsing during carbamazepine had episodes that were more evenly distributed entire study period. Notably, patients randomized during an acute episode showed different results from thos during the prophylactic treatment phase; the authors speculated that differences may be attributed to the dise which randomization occurred or to characteristics of bipolar disease. Post hoc analysis of subgroup characte to clarify these differences (Hartong et al, 2003).

c) In an open, randomized, controlled clinical trial, lithium was superior to carbamazepine for maintenance th with bipolar disorder. Patients received lithium (n=86) and carbamazepine (n=85) in average doses of 26.8 m per day (serum concentration 0.61 +/- 0.12 mmol/liter) and 635 milligrams per day (serum concentration 6.12 micrograms per milliliter), respectively, for 2.5 years. Outcomes measured included inter-episodic morbidity, a average severity of affective symptoms during outpatient treatment, as well as drop-out rate, and rate of reho Although rates of rehospitalization were similar for both treatment groups, more patients demonstrated a goo (low inter-episodic morbidity without rehospitalization or drop-out) with lithium than during carbamazepine tre versus 24%; p=0.03). This difference was largely due to a difference in drop-out rate in patients without rehos versus 42%). Drop-outs were primarily related to the development of adverse effects. Overall, inter-episodic r similar. However, in lithium-treated patients, average inter-episodic morbidity declined by about 50% during th months and remained at this level for the rest of the observation period, while in those treated with carbamaz was not observed (Kleindienst et al, 2002)

d) Lithium appeared superior to carbamazepine in the treatment of classic bipolar symptoms (Bipolar Type I) carbamazepine may have been more useful in patients with nonclassic symptoms (Greil et al, 1998). Patients depressive symptoms or schizoaffective disorder requiring prophylactic therapy were categorized as having e symptoms (bipolar type I) or nonclassic symptoms, and randomized to receive either lithium or carbamazepir during the 2.5-year study were lithium 26.8 millimoles (mmol)/day with a serum level of 0.61 mmol/liter (L) an 190 milligrams/day with a level of 6.12 micrograms/milliliter. Prevention of hospitalization was the primary out with classic symptoms (n=67), lithium use was associated with significantly fewer hospitalizations than carba (p=0.005). In the non- classic bipolar patients (n=104), there was a trend favoring carbamazepine (p=0.075). group, hospitalizations correlated significantly with the number of nonclassic features (p=0.035). In the carba negative association was found between hospitalization rate and number of nonclassic features (p=0.033). D in both groups with fewer occurrences in the lithium group (p=0.004).

e) In a retrospective chart review, younger patients with rapid cycling affective disorder had their manic symp controlled with carbamazepine while older-onset patients had their symptoms better controlled with lithium (F 1998). Early-onset cases were defined as affective disorder beginning at 25 years of age or younger (n=14) v disorder was defined as beginning after the age of 25 (n=21). Further controlled studies are needed.

f) In a double-blind study of 52 bipolar patients, lithium and carbamazepine had a roughly equal but less thar prophylactic efficacy in overall bipolar illness (Denicoff et al, 1997). Patients were randomly assigned to 1 yea lithium or carbamazepine, and then crossed over to the other drug in the second year. During a third year, pa combination of the 2 drugs. A marked or moderate improvement occurred in 33%, 31%, and 55% of patients carbamazepine, and the combination, respectively. Lithium, however, was superior in the prophylaxis of man experienced by 11% on lithium, 4% on carbamazepine, and 33% on combination therapy; p less than 0.01). T lithium and carbamazepine was better than monotherapy in rapid cyclers (p less than 0.05).

4.6.F.2 Depression

a) In an controlled study, 15 depressed patients who did not respond to treatment with carbamazepine were Eight of the 15 patients responded to the addition of lithium therapy (0.8 +/= 0.2 mmol/L) within 4.1 +/- 2.4 da responders tended to be more rapid cyclers (ie, 6.9 +/- 4.1 affective episodes/year versus 3.4 +/- 2.4 year) (K 1989a). A controlled study comparing the two drugs in patients unresponsive to lithium may be useful in disce characteristics of patients most likely to respond to carbamazepine.

4.6.F.3 Mania

a) Lithium and carbamazepine were similarly effective in the treatment of manic patients in a controlled study 1987). However, results suggested that lithium is more effective than carbamazepine in a heterogenous popu patients. A more consistent beneficial effect was observed in lithium-treated patients with regard to Clinical G the Brief Psychiatric Rating Scale and the Beigel- Murphy Manic State Rating Scale. It is suggested that carb antimanic potential in specific types of bipolar patients whose characteristics must be defined in further clinica in this study suggested that carbamazepine may be useful in the "brittle" lithium non- responsive bipolar patie affective relapses.

b) The combination of lithium plus carbamazepine was more effective than lithium alone in reducing depress

episodes in patients with bipolar disorder. Lithium concentrations were maintained between 0.6 and 1 milliequ
those taking carbamazepine concurrently maintained carbamazepine concentrations 4.6 to 8.8 milligrams/mil
was limited in that there were only 8 patients per group (Di Costanzo & Schifano, 1991).
c) Efficacy of carbamazepine and lithium carbonate was compared in a randomized trial of 52 patients with r
previously failed other courses of treatment (Small et al, 1991). Following a two-week drug withdrawal period
assessments were performed for 8 weeks with long term follow-up in responders for up to 2 years. Dosages
titrated to obtain therapeutic plasma levels. One third of the patients showed a positive response with no stati
differences noted between the two treatment groups. Carbamazepine-treated patients demonstrated better c
during the first 3 weeks of therapy although the drop-out rate was higher in this group.

4.6.F.4 Adverse Effects

a) In a comparative efficacy trial for bipolar disorder, adverse effects occurred more often with lithium than w
despite therapeutic blood levels in the majority of each group. Effects that occurred more often with lithium in
vision, difficulties concentrating, feeling thirsty, decreased appetite, hand tremor, muscle weakness. Increase
occurred more often with carbamazepine, however (Hartong et al, 2003).

4.6.G Lorazepam

4.6.G.1 Alcohol withdrawal syndrome

a) Carbamazepine and lorazepam were equally efficacious for the treatment of symptoms associated with al
but carbamazepine was superior for preventing rebound withdrawal symptoms and for reducing post-treatme
especially in those patients with a history of multiple withdrawals. In a randomized, double-blind trial, 136 trea
patients with alcohol dependence were stratified according to number of previous withdrawal experiences (2
than 2) prior to randomization to treatment with carbamazepine on a 5-day fixed dose taper, starting with 600
(mg) on day 1 and tapering to 200 mg as a single dose on day 5, or lorazepam, 6 to 8 mg on day 1 and taper
mg dose on day 5. Prior research had determined the equivalency of the dosages of carbamazepine and lora
with 2 or more previous detoxifications had significantly higher scores on the CIWA-Ar (Clinical Institute Withd
Assessment for Alcohol-Revised) throughout treatment and during the post-treatment follow-up (days 7 to 12
with fewer than 2 previous detoxifications. The mean number of drinks per day during post-treatment was sim
carbamazepine-treated and lorazepam-treated patients who had 0 or 1 prior detoxifications, whereas, among
than 2 prior detoxifications, the average daily consumption was 5 drinks for the lorazepam group and 1 for the
group (p=0.004). The relative risk of having a first drink was 3 times higher for the lorazepam group than for t
group. Twenty percent of carbamazepine-treated patients and 1.3% of lorazepam-treated patients complaine
not with rash). Seven percent of the carbamazepine group and 23% of the lorazepam group showed signs of
incoordination, light-headedness, and drowiness, which they themselves did not recognize (Malcolm et al, 20

4.6.H Oxazepam

4.6.H.1 Alcohol withdrawal syndrome

a) Carbamazepine (CBZ) and oxazepam were equally effective in the treatment of alcohol withdrawal in a 7-
study in 60 inpatients (Stuppaeck et al, 1992). Oxazepam 120 milligrams (n=30) or CBZ 800 milligrams (n=30
days 1 to 3; on days 4 through 7, the doses were reduced to 90 milligrams and 600 milligrams, respectively; a
the 7-day trial, all patients received CBZ 200 milligrams twice a day on day 8 and 200 milligrams/d on day 9.
Institute Withdrawal Scale-Alcohol (CIWA-A), Clinical Global Impression Scale (CGI), and self-rating scores s
improvement of symptom severity throughout the trial. CBZ was superior to oxazepam on days 6 and 7 as m
A (p less than 0.05) and on day 7 as measured by CGI (p less than 0.05). Three patients from each group dr
of side effects, and 1 patient in each group withdrew consent and left treatment. The authors conclude that C
treatment in non-delirious patients with alcohol withdrawal syndrome.
b) Carbamazepine 200 milligrams orally 4 times daily was as effective as oxazepam 30 milligrams orally 4 ti
treatment of severe alcohol withdrawal during a 7-day, double-blind study involving 86 alcoholic men (Malcol
Both drugs were equally effective in reducing alcohol withdrawal symptoms, and adverse effects were also si
carbamazepine was more effective with regard to improving psychiatric symptoms and is therefore recomme
rehabilitation phase of alcoholism therapy.

4.6.I Oxcarbazepine

Epilepsy

Trigeminal neuralgia

4.6.I.1 Epilepsy

a) SUMMARY: Oxcarbazepine appears to be as effective as carbamazepine in the treatment of epilepsy; se
effects have occurred to a lesser degree with oxcarbazepine in some studies. Further studies are needed to i
enzyme-inducing effects, particularly at higher doses.
b) Oxcarbazepine is similar in efficacy to carbamazepine as monotherapy or add-on therapy in epileptic pati
1989; Reinikainen et al, 1987); (Bulau et al, 1987)(Houtkooper et al, 1987; Houtkooper et al, 1984; Dam, 199

1986; Anon, 1990; Jensen, 1990). There is some evidence of efficacy in patients unresponsive to carbamaze associated with therapeutic equivalency in some studies have been 200 mg carbamazepine and 300 to 400 r (Houtkooper et al, 1987), however the ratio has been closer to 1:1 in others (Bulau et al, 1987).

c) Oxcarbazepine is at least as effective as carbamazepine in patients receiving polytherapy, and oxcarbaze tolerated in some patients. The efficacy of oxcarbazepine and carbamazepine was compared in 48 epileptic i controlled on polytherapy, including carbamazepine, in a double- blind, crossover study (Houtkooper et al, 19 seizures were generalized (9 patients), partial (10 patients), or both generalized and partial (29 patients); all p least 2 seizures/week despite therapy with 2 to 4 antiepileptic agents. Patients were randomly allocated to ox mg/day or carbamazepine 200 mg/day. Following a titration period, where the dose of each was increased to seizure control, therapy was continued for 12 weeks (steady- state) in each trial period. As compared to carb therapy with oxcarbazepine reduced the total number of seizures by 9%; tonic-clonic and tonic seizures were 20% and 31%, respectively. In 5 patients, a shift from complex partial to simple partial seizures or atypical ab was observed during oxcarbazepine therapy. Other differences reported during oxcarbazepine therapy were alertness and greater ability to concentrate in 5 patients and remission of carbamazepine related allergic skin Serum levels of valproic acid and phenytoin were higher in oxcarbazepine treated patients, and serum sodiur were lower. Other adverse effects were similar with each agent.

d) In a double-blind study, the efficacy of oxcarbazepine and carbamazepine in 16 epileptic patients inadequ at least 1 anticonvulsant (other than carbamazepine) was evaluated (Bulau et al, 1987). Each patient had exp 1 tonic-clonic or complex partial seizure per month. Oxcarbazepine or carbamazepine were added sequentia fashion during a 1 month titration period; therapy was continued for an additional 3 months. Mean doses were mg daily for oxcarbazepine and carbamazepine, respectively. Concomitant anticonvulsants were continued th frequency was reduced by 90% during therapy with both agents, with 28% of all patients becoming seizure-fr effects were less in oxcarbazepine treated patients. Increases in serum levels of valproic acid, phenytoin, and observed in the oxcarbazepine group, presumably secondary to a lesser degree of enzyme induction as com carbamazepine.

4.6.I.2 Trigeminal neuralgia

a) Oxcarbazepine and its 10-hydroxy-metabolite (10-hydroxy-carbazepine; 10,11-dihydro-10-hydroxy carbar compared with carbamazepine in 24 patients with trigeminal neuralgia (Farago, 1987). All patients had either trigeminal neuralgia or other idiopathic facial neuralgias for at least 2 weeks. Fourteen patients had been trea carbamazepine. Oxcarbazepine was administered to 13 of the 24 patients for a mean of 11 months (mean m 1100 milligrams daily), resulting in an adequate clinical response in 10 and a moderate response in 3. Sympt however, was seen in 1 patient after 6 months of treatment. Eleven patients were treated with the 10-hydroxy oxcarbazepine (GP 47779) for a mean of 3.5 months (mean maximal dose, 1100 milligrams daily), with 7 ach of symptoms and 4 noticing definite improvement. However, recurrence of symptoms occurred in 2 patients a months of treatment, respectively. In the 14 patients treated previously with carbamazepine, therapy with eith or its metabolite was reported to be more effective than carbamazepine in 12; efficacy was considered equiva worse in another. These overall results suggest the potential superiority of oxcarbazepine over carbamazepir neuralgia. However, placebo-controlled trials are required to confirm these findings.

4.6.I.3 Efficacy

a) The primary difference between oxcarbazepine and carbamazepine is in regard to pharmacokinetic prope affect the propensity of these agents to elicit adverse effects. Following absorption, oxcarbazepine is rapidly converted via reduction to 10-hydroxy-carbazepine, the active metabolite, which is excreted in the urine as th conjugate. A portion of the 10-hydroxy-metabolite is hydroxylated to isomeric 10,11-diols, the trans-diol predo (Theisohn & Heimann, 1982; Schutz et al, 1986; Anon, 1989).

b) In contrast, carbamazepine is oxidized to the active carbamazepine-10,11-epoxide; a portion of this metal converted to the inactive 10,11-diol (Eichelbaum et al, 1985d; Anon, 1989; Anon, 1990). The 10,11-epoxide r carbamazepine is responsible for dose-dependent adverse effects (Anon, 1990; Anon, 1989). Because an ep produced during oxcarbazepine metabolism, this drug is expected to be better tolerated than carbamazepine

4.6.I.4 Adverse Effects

a) A trend toward a lower incidence of severe adverse effects has been observed with oxcarbazepine as cor carbamazepine in some studies (Bulau et al, 1987)(Dam, 1990; Houtkooper et al, 1987), which at times reach significance (Dam, 1990).

b) Oxcarbazepine appears less likely than carbamazepine to influence oxidative processes, as the metabolis oxcarbazepine is facilitated primarily by reduction. Studies have reported that oxcarbazepine lacks autoinduc unlike carbamazepine, a feature which may decrease the incidence of breakthrough seizures (Anon, 1989; B Anon, 1990).

c) In some studies, oxcarbazepine has not influenced antipyrine kinetics, suggesting an advantage with rega interactions (Anon, 1989). However, dose-dependent enzyme induction has been reported by other investiga doses producing effects similar to carbamazepine (Patsalos et al, 1990). As the optimal dose of oxcarbazepir undefined, further studies will be needed to determine if the drug will offer a significant advantage in regard to and autoinduction.

4.6.J Phenobarbital

Epilepsy

Epilepsy, Children

4.6.J.1 Epilepsy

a) Phenobarbital in doses of 4 to 5 mg/kg/day proved to be more effective than carbamazepine 20 mg/kg/da day doses) in the treatment of recurrent febrile convulsions in a double-blind study. Nine of 19 carbamazepin (47%) had recurrent seizures despite therapeutic blood levels, however only two of the phenobarbital treated had recurrent seizures (Antony & Hawke, 1983).

b) The efficacy and toxicity of carbamazepine, phenobarbital, phenytoin and primidone were compared in 62 simple partial, complex partial and secondarily generalized seizures in a multicenter, randomized, double blin were treated with monotherapy and if treatment failure occurred, patients were randomly switched to an alter There was no significant difference among the drugs in the treatment of tonic-clonic seizures. Conversely, ca significantly more effective in controlling simple partial and complex partial seizures than were any of the othe rather than seizure control appeared to be the greatest differentiating factor among the four study drugs with primidone manifesting the highest incidence of side effects early in therapy with no significant differences afte Patient tolerance of the drugs as measured by retention rates were significantly better among carbamazepine treated patients. In studies of behavioral toxicity, carbamazepine-treated patients showed the least deteriorat of patients were successfully managed for 1 year on monotherapy, regardless of the drug chosen. The autho based on anticonvulsant activity and side effect profile, carbamazepine may be the preferred drug for initiatio adults with either generalized tonic-clonic, simple partial or complex partial seizures (Smith et al, 1987).

4.6.J.2 Epilepsy, Children

a) The efficacy and tolerability of phenobarbital, phenytoin, carbamazepine, and sodium valproate in the trea epilepsy were compared in a long-term, prospective, randomized trial (de Silva et al, 1996). Children aged 3 (n=167) with at least two previously untreated tonic-clonic or partial seizures were eligible for participation in drugs were equally efficacious with 20% of the patients remaining seizure-free and 73% achieving a 1-year re years. However, randomization to phenobarbital was discontinued early in the study period due to unaccepta Carbamazepine and sodium valproate were the best tolerated with only 4% of children discontinuing treatme 9% of children treated with phenytoin.

4.6.K Phenytoin

Epilepsy

Epilepsy, Children

Impaired cognition

Myotonia

4.6.K.1 Epilepsy

a) Carbamazepine is as effective an anticonvulsant as phenytoin (Simonsen et al, 1975; Ramsay et al, 1983 1975).

b) In a controlled study, carbamazepine was reported as effective as phenytoin as initial seizure therapy in 7 with either simple seizures, complex seizures, partial evolving to generalized seizures and generalized convu (Ramsay et al, 1983). Thirty-five patients were treated with each drug. Complete control of seizures was achi patients in each treatment group. Mean serum levels during weeks 8 to 24 of treatment were 9.1 to 11 mcg/m and 4.7 to 6.5 mcg/mL for carbamazepine. The incidence of side effects was similar in both groups. Carbama recommended as a major anticonvulsant to be given initially as single agent therapy in the management of th

c) The efficacy and toxicity of carbamazepine, phenobarbital, phenytoin and primidone were compared in 62 simple partial, complex partial and secondarily generalized seizures in a multicenter, randomized, double blin were treated with monotherapy with doses titrated to produce blood levels in the therapeutic range. If treatme (inadequate seizure control with the initial drug or unacceptable toxicity from the initial drug), patients were ra to an alternate study drug. Combined results with all four drugs suggested that full seizure control was signifi patients with generalized tonic-clonic seizures than for those with partial seizure disorders (56% vs 39%). Th significant difference among the drugs in treatment of tonic- clonic seizures. Conversely, carbamazepine was effective in controlling simple partial and complex partial seizures than were any of the other drugs. Toxicity a greatest differentiating factor among the 4 study drugs. Patients taking primidone exhibited the highest incide early in therapy, although there were no significant differences with chronic therapy. Patient tolerance of the d by retention rates were significantly better among carbamazepine- and phenytoin-treated patients. In studies toxicity, carbamazepine-treated patients showed the least deterioration. Overall, 80% of patients were succes 1 year on monotherapy, regardless of the drug chosen. The authors concluded that based on anticonvulsant carbamazepine may be the preferred drug for initiation of therapy in adults with either generalized tonic-clonic complex partial seizures (Smith et al, 1987a).

d) One hundred eighty-one patients with previously untreated epilepsy were randomized to receive valproic a carbamazepine as monotherapy and followed for 14 to 24 months (Callaghan et al, 1985). The oral drug dose phenytoin 300 milligrams/day (mg/day) (adults) and 5 to 10 milligrams/kilogram/day (children), carbamazepin (adults) and 5 to 10 mg/kg/day (children), and valproic acid 600 mg/day (adults) and 5 to 10 mg/kg/day (child were highly effective in the control of generalized seizures but less effective for partial seizures. There was no difference between the overall incidence of side effects between the 3 drugs.

4.6.K.2 Epilepsy, Children

a) The efficacy and tolerability of phenobarbital, phenytoin, carbamazepine, and sodium valproate in the trea epilepsy were compared in a long-term, prospective, randomized trial (de Silva et al, 1996a). Children aged 3 (n=167) with at least two previously untreated tonic-clonic or partial seizures were eligible for participation in t drugs were equally efficacious with 20% of the patients remaining seizure free and 73% achieving 1-year rem However, randomization to phenobarbital was discontinued early in the study period due to unacceptable side Carbamazepine and sodium valproate were the best tolerated with only 4% of children discontinuing treatmen 9% of children treated with phenytoin.

4.6.K.3 Impaired cognition

a) Most studies have found phenytoin to cause more cognitive impairment than carbamazepine, but there wa didn't find any clinically significant differences in cognitive adverse effects between phenytoin and carbamaze similar kinds of neuropsychological evaluations (Meador et al, 1991).

b) A study was conducted to compare the cognitive effects of phenytoin and carbamazepine during monothe controlled withdrawal in two groups of chronic epileptic patients who were seizure-free for at least two years. (mean age 28.5 +/- 7 years) who took phenytoin for a mean duration of 32.08 +/- 17.8 months and 13 patient +/- 8.9 years) receiving carbamazepine for a mean duration of 28.07 +/- 16.1 months were compared with 26 age 23.57 +/- 8.3 years). Neuropsychological baseline assessment included tests of intelligence, vigilance, at and visuomotor performance. The effects of drug withdrawal were assessed by further neuropsychological re months after a fifty percent dosage reduction and three months and one year following complete withdrawal o carbamazepine. Results of neuropsychological testing at baseline showed that patients taking phenytoin suffe impairments in attention, visuomotor, and intellectual abilities as well as in global performance. Patients who carbamazepine performed markedly worse only on tasks requiring attention. After discontinuation of phenytoi markedly worse performances on verbal digits span, three months after a fifty percent dosage reduction and performances on verbal learning three months after discontinuation of phenytoin. Following discontinuation of patients suffered no further impairments on neuropsychological testing. One year after complete withdrawal o carbamazepine, both groups were no different than controls on the neuropsychological exam, thus demonstra reversibility of cognitive effects (Gallassi et al, 1988).

c) The cognitive effects of phenytoin and carbamazepine during monotherapy were compared in two groups referrals with epilepsy and with an untreated control group of epileptic patients. Twenty-one patients were in e seizure activity well-controlled in the majority of patients for 2 to 3.5 years. Patients in the phenytoin-treated g phenytoin plasma concentrations of 9.5 microgram/milliliter (mcg/mL) (range 1 to 21 mcg/mL) and had been t duration of 5.8 years. Patients in the carbamazepine-treated group had mean carbamazepine plasma concer mcg/mL (range 0.5 to 10.6 mcg/mL) and had been treated for a mean duration of 3.6 years. Assessments of included tests of memory scanning, word list learning, memory (immediate recall and with a one-hour delay), (three subtasks of graduated difficulty), and the tracking task. The phenytoin group performed significantly wo two groups on the most demanding subtest of short-term memory scanning (p less than 0.05). Performance o memory tasks were significantly worse in the phenytoin-treated group (p less than 0.05). The phenytoin-treat demonstrated greater impairment on the prose recall test than the carbamazepine-treated group. Patients tre carbamazepine showed a trend to learn more rapidly than the phenytoin-treated patients. After a one-hour de carbamazepine-treated patients forgot significantly more than the phenytoin-treated patients (p less than 0.05 next list-learning task, the carbamazepine group relearned significantly more than the phenytoin group (p less significant difference was observed between the two treatment groups for the decision-making task or trackin et al, 1986).

d) In another clinical trial, patients receiving carbamazepine performed better than those receiving phenytoin tasks. The phenytoin group performed significantly worse (p less than 0.05) on short-term memory scanning t short-term memory task became more complex, the phenytoin group made more errors as compared with the treated group (p less than 0.06). Patients on carbamazepine performed significantly better than the phenytoin the tracking task (p less than 0.05) (Andrewes et al, 1984).

e) A randomized, double-blind, 10-month study, in 56 adult patients with chronic epilepsy was conducted to c cognitive effects of phenytoin and carbamazepine. Following a two-month stabilization period, patients were r to continue phenytoin or begin carbamazepine and then continue treatment for four months. All patients were to receive treatment for an additional four months. Mean phenytoin plasma concentrations were 31.2 +/- 2.13 microgram/milliliter (mcg/mL) for the entire study population, and the mean dose of phenytoin administered w milligrams/kilogram (mg/kg). Mean carbamazepine plasma concentrations were reported to be 9.3 +/- 0.55 m patients on mean doses of carbamazepine of 18.4 mg/kg. Twenty patients from each treatment group were ra from 47 patients who completed the 10 month study. No significant differences were reported on Halstead's r battery or the Weschler adult intelligence scale regardless of treatment; however, even though patients solve the same number of problems when receiving either phenytoin or carbamazepine, fewer errors were made on high cognitive component while taking carbamazepine. Patients reported feeling more alert during carbamaze than while taking phenytoin (Troupin et al, 1977).

f) A double-blind, crossover study compared the cognitive effects of four month trials of phenytoin and carba adult patients with chronic epilepsy. No significant differences were reported between phenytoin or carbamaz the Halstead battery or the Weschsler intelligence scale. Other neuropsychological tests showed significant i patients taking phenytoin on tasks requiring concentration and mental manipulation such as receptive aphasi 0.05), constructional dyspraxia (p less than 0.01), Stroop attention tasks (p less than 0.05), and Wonderlic pr tasks (p less than 0.05). Differences in performances on tasks requiring greater mental manipulation were mo patients being treated with phenytoin. As the task increased in complexity, the cognitive impairment effects o became more apparent as compared to carbamazepine. The investigators suggested that the impact of phen abilities may not be readily detectable when testing performance on routine tasks, but may require testing tas complexity to detect subtle cognitive impairment. The patients in this study reported feeling more alert when t treatment with carbamazepine compared to phenytoin (Dodrill & Troupin, 1977).

4.6.K.4 Myotonia

a) One study reported that phenytoin in doses of 200 to 300 milligrams (mg) daily and carbamazepine 600 to were similarly effective in the treatment of myotonia (Sechi et al, 1983). Carbamazepine is indicated as the a myotonia and Steinert's disease by virtue of its lesser long-term side effects.

4.6.L Primidone

4.6.L.1 Seizure

a) The efficacy and toxicity of carbamazepine, phenobarbital, phenytoin and primidone were compared in 62 simple partial, complex partial and secondarily generalized seizures in a multicenter, randomized, double blin were treated with monotherapy with doses titrated to produce blood levels in the therapeutic range. If treatme (inadequate seizure control with the initial drug or unacceptable toxicity from the initial drug), patients were ra to an alternate study drug. Combined results with all four drugs suggested that full seizure control was signifi patients with generalized tonic-clonic seizures than for those with partial seizure disorders (56% vs 39%). The significant difference among the drugs in treatment of tonic-clonic seizures. Conversely, carbamazepine was effective in controlling simple partial and complex partial seizures than were any of the other drugs. Toxicity r control appeared to be the greatest differentiating factor among the four study drugs with patients taking prim the highest incidence of side effects early in therapy although there were no significant differences with chron tolerance of the drugs as measured by retention rates were significantly better among carbamazepine- and p patients . In studies of behavioral toxicity, carbamazepine-treated patients showed the least deterioration. Ov patients were successfully managed for 1 year on monotherapy, regardless of the drug chosen. The authors based on anticonvulsant activity and side effect profile, carbamazepine may be the preferred drug for initiatio adults with either generalized tonic-clonic, simple partial or complex partial seizures (Smith et al, 1987b).

4.6.M Progabide

4.6.M.1 Epilepsy

a) There are no direct comparisons of progabide with carbamazepine in the treatment of any form of epilepsy comparisons of clinical studies suggest that adjunctive therapy with progabide in therapy-resistant partial seiz effective as other primary anticonvulsants such as phenytoin, phenobarbital, primidone, or carbamazepine wh adjunctive therapy to patients who have failed previous therapy (Schmidt, 1984; Schmidt, 1982).

4.6.N Propranolol

4.6.N.1 Intermittent explosive disorder

a) One study (Mattes, 1990) compared the efficacy of propranolol and carbamazepine in a randomized trial i diagnosed with intermittent explosive disorder. An additional 29 patients with rage outbursts secondary to res deficit disorder, alcohol or drug abuse, antisocial personality disorder, unsocialized conduct disorder and bord disorder; 27 of these patients received carbamazepine. Mean daily dosages were 486 mg and 860 mg for pro carbamazepine respectively. Both medications were equally well tolerated and were effective in reducing targ However, the absence of a placebo-control group makes the efficacy of either drug difficult to evaluate. Two f predict a differential benefit between the two drugs; these were diagnosis of attention deficit disorder, residua more effective) and age of onset of symptoms (again, propranolol more effective). Carbamazepine appeared patients with intermittent explosive disorder.

4.6.O Tiapride

4.6.O.1 Alcohol withdrawal syndrome, acute

a) Tiapride was as effective as carbamazepine in the treatment of acute alcohol withdrawal. Sixty patients w receive either tiapride 200 milligrams (mg) 3 times daily (n=30) or carbamazepine 200 mg 3 times daily (n=30 Withdrawal symptoms improved significantly in both groups. Symptoms such as frequent awakening, nightma palpitations decreased more quickly in the carbamazepine group while aggression and gastrointestinal disco more quickly in the tiapride group. Carbamazepine was more effective against fear and hallucinations, while t vertigo. No seizures occurred and both drugs were well tolerated. Overall, tiapride and carbamazepine demo efficacy for the treatment of acute alcohol withdrawal (Agricola et al, 1982).

4.6.P Topiramate

4.6.P.1 Epilepsy

a) In a double-blinded, randomized study, topiramate, carbamazepine and valproate monotherapy demonstr to study exit, times to first seizure and proportions of patients who were seizure-free during the final 6 months Newly diagnosed epilepsy patients were randomized to receive topiramate 100 milligrams (mg) daily (n=210) mg daily (n=199), or traditional therapy (n=204). Patients in the traditional therapy arm were prescribed either 600 mg/day or valproate 1250 mg/day depending on the prescribing physician's treatment choice. Patients w months after the final patient was enrolled. Of the total 285 patients, 46% completed the study. Adverse even 19% and 23% of discontinuations in the topiramate and traditional therapy arms, respectively. Ineffective trea for 11% and 12% of discontinuations in the topiramate and traditional therapy arms, respectively. The time to to first seizure between the arms did not differ (p=0.53 and 0.35, respectively). The proportion of patients who experience a seizure during the last 6 months of the study was 49% of topiramate-100 mg patients and 44% other arms. Dose related paresthesia (25 to 33%), difficulty with concentration or attention (4 to 11%), langua 7%), confusion (3 to 6%), nausea (7 to 14%) and abdominal pain (3 to 7%) were reported with topiramate. Ca valproate were associated with concentration and attention difficulty (4% and 1%), and language problems (6 Carbamazepine was also associated with confusion (3%) (Privitera et al, 2003a).

4.6.Q Valproic Acid

Epilepsy

Epilepsy, Children

Rheumatic chorea

4.6.Q.1 Epilepsy

a) One hundred eighty-one patients with previously untreated epilepsy were randomized to valproic acid, phe carbamazepine as monotherapy and followed for 14 to 24 months. All 3 drugs were highly effective in the cor seizures but less effective for partial seizures. There was no significant difference between the overall incider between the 3 drugs (Callaghan et al, 1985a).

b) Carbamazepine and sodium valproate were shown to be equally effective in controlling seizures in patient diagnosed primary generalized or partial seizures (Richens et al, 1994). In this large multicenter study patient randomized to either carbamazepine or valproate and followed for a period of three years. Although long-term similar in the two groups, significantly more patients in the carbamazepine group (15% vs 5%) discontinued t first six months due to adverse reactions (predominantly rash). Headache and dizziness were also reported n the carbamazepine group; weight gain was reported more often in patients receiving sodium valproate.

c) Results from a large multicenter trial comparing valproate with carbamazepine in the treatment of complex secondarily generalized tonic-clonic seizures indicate similar effectiveness of both drugs for control of seconc tonic-clonic seizures. However, for complex partial seizures, carbamazepine was more effective and was ass adverse reactions (Mattson et al, 1992). Long-term side effects associated with valproate therapy included w loss or change in texture, and tremor. Hypersensitivity, characterized by rash, occurred more frequently in tho carbamazepine.

d) Patients switched to high dose valproic acid (target serum level 80 to 150 micrograms/milliliter) demonstra improved seizure control versus treatment with their baseline antiepileptic drug. Participating patients had pa history of at least 2 complex partial seizures per month with or without secondarily generalized tonic-clonic se maintained on therapeutic levels of either carbamazepine, phenytoin, phenobarbital or primidone. A 30% mec complex partial seizures and a 70% median reduction for secondarily generalized tonic-clonic seizures over p occurred. The authors conclude that valproic acid is efficacious as monotherapy for partial-onset seizures an considered as first-line therapy (Beydoun et al, 1997).

e) In a double-blinded, randomized study, topiramate, carbamazepine and valproate monotherapy demonstr to study exit, times to first seizure and proportions of patients who were seizure-free during the final 6 months Newly diagnosed epilepsy patients were randomized to receive topiramate 100 milligrams (mg) daily (n=210) mg daily (n=199), or traditional therapy (n=204). Patients in the traditional therapy arm were prescribed either 600 mg/day or valproate 1250 mg/day depending on the prescribing physician's treatment choice. Patients w months after the final patient was enrolled. Of the total 285 patients, 46% completed the study. Adverse even 19% and 23% of discontinuations in the topiramate and traditional therapy arms, respectively. Ineffective trea for 11% and 12% of discontinuations in the topiramate and traditional therapy arms, respectively. The time to to first seizure between the arms did not differ (p=0.53 and 0.35, respectively). The proportion of patients who experience a seizure during the last 6 months of the study was 49% of topiramate-100 mg patients and 44% other arms. Dose related paresthesia (25 to 33%), difficulty with concentration or attention (4 to 11%), langua 7%), confusion (3 to 6%), nausea (7 to 14%) and abdominal pain (3 to 7%) were reported with topiramate. Ca valproate were associated with concentration and attention difficulty (4% and 1%), and language problems (6 Carbamazepine was also associated with confusion (3%) (Privitera et al, 2003).

4.6.Q.2 Epilepsy, Children

a) The efficacy and tolerability of phenobarbital, phenytoin, carbamazepine, and sodium valproate in the trea epilepsy were compared in a long-term, prospective, randomized trial (de Silva et al, 1996b). Children aged 3 (n=167) with at least two previously untreated tonic-clonic or partial seizures were eligible for participation in t drugs were equally efficacious with 20% of the patients remaining seizure free and 73% achieving 1-year rem However, randomization to phenobarbital was discontinued early in the study period due to unacceptable sid Carbamazepine and sodium valproate were the best tolerated with only 4% of children discontinuing treatme 9% of children treated with phenytoin.

4.6.Q.3 Rheumatic chorea

a) Carbamazepine and valproic acid were found to be safe and equally effective in the treatment of choreic r of clinical improvement, time to complete remission, duration of treatment, and recurrence rates in a group of patients with Sydenham's chorea. In this open-label trial, 7 children received 20 to 25 milligrams per kilogram sodium valproate and a matched group of 17 children received 15 mg/kg/day of carbamazepine. No adverse reported by either group.

Demographics and Response to Treatment

	Sodium valproate	Carbamazepine	P
Female sex (%)	71.4	58.8	0.56
Age (years)	12.4 +/- 1.5	10.9 +/- 2.4	0.13
Onset of improvement (days)	8.0 +/- 4.0	7.4 +/- 8.2	0.88
Time to remission (weeks)	10.1 +/- 8.5	6.7 +/- 6.3	0.36
Duration of treatment (months)	4.3 +/- 2.8	5.0 +/- 2.4	0.56
Recurrences (%)	14.3	17.6	0.84
Generalized chorea (%)	71.4	64.7	0.75

(Genel et al, 2002)

4.6.R Vigabatrin

4.6.R.1 Seizure

a) Time to withdrawal for lack of efficacy or adverse events did not differ in newly diagnosed epileptic patient carbamazepine (n=226) or vigabatrin (n=220) in a double-blind, randomized, monotherapy study (p=0.318) (However, patients treated with carbamazepine were more likely to withdraw sooner than vigabatrin patients, first 4 to 6 months of therapy. The total daily dose of vigabatrin was 1 gram (g) during the first 6 weeks after r Vigabatrin dose was increased to 2 g as an initial maintenance dose with a dose range from 1.5 g to 4 g daily dose of carbamazepine was 200 milligrams (mg) followed by an increase to 600 mg after 6 weeks. Maintena carbamazepine ranged from 400 mg to 1600 mg per day. No treatment differences between treatment groups throughout the study. After 12 months of double-blind therapy, 107 vigabatrin and 116 carbamazepine patien months of remission. The time to first seizure was significantly less for vigabatrin patients compared to carba (p=0.0003). Twenty-three vigabatrin and 9 carbamazepine patients withdrew from the study solely due to lac effect (p=0.0298). Drowsiness, fatigue, and headache were reported by more than 20% of patients with no di the two treatment groups observed.. Adverse events in the psychiatric system were reported significantly mo vigabatrin patients (25%) compared to carbamazepine patients (15%; p less than 0.05). Likewise, more patie vigabatrin experienced weight gain (11%) compared to those treated with carbamazepine (5%; p less than 0. Carbamazepine patients experienced significantly more adverse events in the skin and appendages system vigabatrin patients (14%; p less than 0.05). A decrease in white-cell counts, uric acid and bilirubin and an inc phosphatase were observed in carbamazepine patients.

b) Preliminary results from an open-label comparative trial (n=34) suggested the potential superiority of carb monotherapy over vigabatrin monotherapy in patients with newly diagnosed epilepsy (Grant & Heel, 1991). In patients treated with vigabatrin 50 milligrams/kilogram/day were considered non- responders; 1 of these patie failed to respond to carbamazepine. None of the patients treated with carbamazepine (plasma levels of 35 m considered non-responders. However, 3 carbamazepine-treated patients discontinued therapy due to hypers

c) Carbamazepine monotherapy was compared to vigabatrin monotherapy in patients with newly-diagnosed

generalized tonic-clonic seizures (Kalviainen et al, 1995). Sixty percent of patients (n=50) were considered su in both groups; however, significantly more patients were totally seizure free while receiving carbamazepine. resulted in fewer side effects that resulted in discontinuation of therapy. Vigabatrin monotherapy may be an a carbamazepine or other standard antiepileptic drugs in cases where patients are intolerant of toxic or cognitiv

4.6.S Zonisamide

4.6.S.1 Epilepsy

a) In a small study, zonisamide was as effective as carbamazepine in the treatment of refractory partial seizu week run-in period, 8 patient with a poor response to phenytoin (more than 4 seizures/month) received either zonisamide for 12 weeks, and then were switched to the other drug for an additional 12 weeks. Patients rece carbamazepine and zonisamide adjusted to maximal therapeutic response and minimal toxicity; phenytoin wa the 4 patients completing the study, 2 had the best response to carbamazepine, an intermediate response to poor response to phenytoin. Two patients responded best to zonisamide. Optimal seizure control and minima seen with serum zonisamide concentrations of 20 to 30 micrograms/milliliter (mcg/mL), and a high incidence were seen with serum levels exceeding 30 mcg/mL (Wilensky et al, 1985a).

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Last Modified: June 24, 2009

DRUGDEX® Evaluations

IMIPRAMINE

0.0 Overview

1) Class

a) This drug is a member of the following class(es):
Antidepressant
Antidepressant, Tricyclic
Urinary Enuresis Agent

2) Dosing Information

a) Imipramine Hydrochloride

1) Adult

a) Depression

1) (hospitalized patients) 100 mg ORALLY per day in divided doses; may increase up to a MAX of 300 r TOFRANIL(R) tablets, 2005)

2) (outpatients) 75 mg ORALLY per day; may increase up to a MAX of 200 mg/day; usual maintenance mg/day (Prod Info TOFRANIL(R) tablets, 2005).

b) Panic disorder

1) 100-200 mg ORALLY in divided doses (1-3 doses per day), higher doses may be required if agoraph

c) Urinary incontinence

1) 25 mg ORALLY at bedtime, may increase in 25 mg increments to max dose of 150mg at bedtime

2) Pediatric

a) safety and effectiveness in children with nocturnal enuresis below the age of 6 years have not been estab effectiveness in pediatric patients for any other condition has not been established (Prod Info TOFRANIL(R) t

1) Nocturnal enuresis

a) (children 6 to 12 y) initial, 25 mg ORALLY 1 h before bedtime, may increase in 25 mg increments 50 mg/d or 2.5 mg/kg/d (Prod Info TOFRANIL(R) tablets, 2005)

b) (children over 12 y) initial, 25 mg ORALLY 1 h before bedtime, may increase in 25 mg increment 75 mg/d or 2.5 mg/kg/d (Prod Info TOFRANIL(R) tablets, 2005)

b) Imipramine Pamoate

1) Adult

a) Depression

1) (hospitalized patients) initial, 100 to 150 mg ORALLY once daily at bedtime; may increase up to MAX usual maintenance dose, 75 to 150 mg ORALLY once daily at bedtime (Prod Info TOFRANIL-PM(R) cap

2) (outpatients) 75 mg ORALLY once daily at bedtime; may increase up to a max of 200 mg/day; usual 75 to 150 mg ORALLY once daily at bedtime (Prod Info TOFRANIL-PM(R) capsules, 2005)

b) Panic disorder

1) 100-200 mg/day ORALLY in divided doses (1-3 doses per day), higher doses may be required if agor

2) Pediatric

a) safety and effectiveness have not been established in children (Prod Info TOFRANIL-PM(R) capsules, 20

3) Contraindications

a) Imipramine Hydrochloride

1) coadministration with a MAOI or use within 14 days of discontinuing a MAOI; may cause serious reactions (eg crisis, convulsive seizures, death) (Prod Info imipramine hcl oral tablets, 2007)

2) hypersensitivity to dibenzazepines; risk of cross-sensitivity reactions (Prod Info imipramine hcl oral tablets, 20

3) hypersensitivity to imipramine hydrochloride (Prod Info imipramine hcl oral tablets, 2007)

4) myocardial infarction, during the acute recovery period (Prod Info imipramine hcl oral tablets, 2007)

b) Imipramine Pamoate

1) coadministration with an MAOI or use within 14 days of discontinuing an MAOI; may cause serious reactions (crisis, severe convulsive seizures, death) (Prod Info TOFRANIL-PM(R) oral capsules, 2007)

2) hypersensitivity to dibenzazepines; risk of cross-sensitivity reactions (Prod Info TOFRANIL-PM(R) oral capsule

3) hypersensitivity to imipramine pamoate (Prod Info TOFRANIL-PM(R) oral capsules, 2007)

4) myocardial infarction, during the acute recovery period (Prod Info TOFRANIL-PM(R) oral capsules, 2007)

4) Serious Adverse Effects

a) Imipramine Hydrochloride

1) Agranulocytosis
2) Atrioventricular conduction pattern - finding
3) Cardiac dysrhythmia
4) Cerebrovascular accident
5) Decreased liver function
6) Depression, worsening
7) Heart block
8) Hypertension
9) Jaundice

10) Myocardial infarction
11) Orthostatic hypotension
12) Palpitations
13) Psychotic disorder
14) Seizure
15) Suicidal thoughts
16) Suicide
17) Syncope

b) Imipramine Pamoate
1) Agranulocytosis
2) Atrioventricular conduction pattern - finding
3) Cardiac dysrhythmia
4) Cardiac dysrhythmia
5) Cerebrovascular accident
6) Decreased liver function
7) Depression, worsening
8) Hypertension
9) Jaundice
10) Myocardial infarction
11) Orthostatic hypotension
12) Seizure
13) Suicidal thoughts
14) Suicide
15) Syncope

5) Clinical Applications
a) Imipramine Hydrochloride
1) FDA Approved Indications
a) Depression
b) Nocturnal enuresis
2) Non-FDA Approved Indications
a) Panic disorder
b) Urinary incontinence

b) Imipramine Pamoate
1) FDA Approved Indications
a) Depression
2) Non-FDA Approved Indications
a) Panic disorder

1.0 Dosing Information

Drug Properties

Storage and Stability

Adult Dosage

Pediatric Dosage

1.1 Drug Properties

A) Information on specific products and dosage forms can be obtained by referring to the Tradename List (Product In

B) Synonyms
Imipramine
Imipramine HCl
Imipramine Hydrochloride
Imipramine Pamoate

1.2 Storage and Stability

A) Oral route
1) Store between 59 and 86 degrees F (15 to 30 degrees C) (Prod Info Tofranil(R), 1995).

B) Parenteral route
1) Store between 59 to 86 degrees F (15 to 30 degrees C). Upon storing, minute crystals may form; this has no ir drug's therapeutic efficacy. Crystals will dissolve when the ampul is immersed in hot water (Prod Info Tofranil(R), al, 1994; Trissel, 1994).

1.3 Adult Dosage

Normal Dosage

Dosage in Renal Failure

Dosage in Geriatric Patients

Dosage Adjustment During Dialysis

Dosage in Other Disease States

1.3.1 Normal Dosage

Imipramine

Imipramine Hydrochloride

Imipramine Pamoate

1.3.1.A Imipramine

1.3.1.A.1 Cataplexy - Narcolepsy

See Drug Consult reference: NARCOLEPSY AND CATAPLEXY - DRUG THERAPY

1.3.1.B Imipramine Hydrochloride

Intramuscular route

Oral route

1.3.1.B.1 Intramuscular route

1.3.1.B.1.a Depression

1) Initial intramuscular dose of up to 100 milligrams/day in divided doses. Lower dosages are recom
adolescents and for outpatients (Prod Info Tofranil(R), 1995b; Anon, 1983a; Trissel, 1994).

1.3.1.B.2 Oral route

Agoraphobia

Bulimia nervosa

Depression

Diabetic neuropathy

Panic disorder

Urinary incontinence

1.3.1.B.2.a Agoraphobia

1) Efficacy is dose related and may require doses of 150 milligrams/day or greater (Cohen et al, 19
(Mavissaakalian & Perel, 1985a)(Mavissakalian & Perel, 1994; Mavissakalian & Michelson, 1986).

1.3.1.B.2.b Bulimia nervosa

1) The doses used in the treatment of bulimia have ranged from the doses commonly used in the tr depression (75 to 275 milligrams/day) (Pope et al, 1983a; Pope et al, 1983; Rothschild et al, 1994).

1.3.1.B.2.c Depression

1) HOSPITALIZED PATIENTS

a) The recommended initial dose for hospitalized patients is 100 milligrams (mg) orally per day and gradually increased to 200 mg/day as required. If no response is seen after 2 weeks, then t increased up to 250 to 300 mg ORALLY per day in divided doses (Prod Info TOFRANIL(R) tabl as high as 750 milligrams/day maintenance in divided doses have been reported (Schuckit & Fe are not recommended.

2) OUTPATIENTS

a) The recommended initial dose for outpatients is 75 milligrams (mg) orally per day, increased day. Usual maintenance dose ranges from 50 to 150 mg daily. The recommended maximum do (Prod Info TOFRANIL(R) tablets, 2005).

b) Maintenance doses greater than 150 milligrams/day have been well tolerated and may be re patients to prevent relapses, but are associated with a higher incidence of persistent side effect headache, nausea, and vomiting) (Kupfer et al, 1989). The best method, other than experience, the optimal maintenance dose for a particular individual has not been established.

c) Patients with chronic depression that respond to imipramine may benefit from long-term mai (Kocsis et al, 1991).

1.3.1.B.2.d Diabetic neuropathy

1) Standard doses of 100 milligrams/day of imipramine may not be high enough to produce therape some patients with diabetic neuropathy. In one study, the therapeutic dose range was 125 milligram milligrams/day. The maximum therapeutic effect in neuropathy is reached within a week. Dosage titr started with a dose corresponding to a plasma level of 100 to 200 nmol/L for imipramine plus desipra should then be increased in a stepwise fashion (Sindrup et al, 1990a).

1.3.1.B.2.e Panic disorder

1) Based upon a dose-response study in patients with panic disorder with agoraphobia, IMIPRAMIN doses of 1.5 milligrams/kilogram/day (approximately 100 milligrams daily) may be effective in the tre some patients, whereas higher doses (3 milligrams/kilogram/day, approximately 200 milligrams daily for the agoraphobic dimension of this disorder (Mavissakalian & Perel, 1989); (Mavissakalian & Pera 1989a).

2) The suggested target dose is 2.25 milligrams/kilogram/day or a total (imipramine and N-desmeth plasma concentration of 110 to 140 nanograms/milliliter in the acute treatment of patients with panic agoraphobia. Higher doses were associated with good clinical response but a greater dropout rate s effects (Mavissakalian & Peral, 1995).

1.3.1.B.2.f Urinary incontinence

1) The dose used in the treatment of urinary incontinence is 75 to 150 milligrams/day. The dose car milligrams per day and titrated to clinical effect. Some patients may require the dose to be administe doses throughout the day instead of single dose administration (Rabey et al, 1979; Gilja et al, 1984) 1981)(Jarvis, 1981).

2) Imipramine 25 milligrams three times daily has been used in the treatment of females with urinar to detrusor instability (Jarvis, 1981).

1.3.1.C Imipramine Pamoate

1.3.1.C.1 Oral route

Agoraphobia

Bulimia nervosa

Depression

Diabetic neuropathy

Panic disorder

1.3.1.C.1.a Agoraphobia

1) Efficacy is dose related and may require doses of 150 milligrams/day or greater (Cohen et al, 19

(Mavissaakalian & Perel, 1985a)(Mavissakalian & Perel, 1994; Mavissakalian & Michelson, 1986).

1.3.1.C.1.b Bulimia nervosa

1) The doses used in the treatment of bulimia have ranged from the doses commonly used in the tr depression (75 to 275 milligrams/day) (Pope et al, 1983a; Pope et al, 1983; Rothschild et al, 1994).

1.3.1.C.1.c Depression

1) HOSPITALIZED PATIENTS

a) The initial oral dose for hospitalized patients is usually 100 to 150 milligrams (mg) once daily may be increased to 200 mg/day as required. If no response is seen after 2 weeks, then the dos increased up to 250 to 300 mg/day. Doses greater than 150 mg daily may be administered once optimum dosage and tolerance have been determined. The usual maintenance dose ranges fro once daily at bedtime (Prod Info TOFRANIL-PM(R) capsules, 2005). Doses as high as 750 milli maintenance in divided doses have been reported (Schuckit & Feighner, 1972) but are not reco

2) OUTPATIENTS

a) The usual initial oral dose for outpatients is 75 milligrams (mg) once daily at bedtime and ma to 200 mg/day. Doses greater than 75 mg daily may be administered once a day after the optim tolerance have been determined. The usual maintenance dose ranges from 75 to 150 mg once (Prod Info TOFRANIL-PM(R) capsules, 2005).

b) Maintenance doses greater than 150 milligrams/day have been well tolerated and may be re patients to prevent relapses, but are associated with a higher incidence of persistent side effect headache, nausea, and vomiting) (Kupfer et al, 1989). The best method, other than experience the optimal maintenance dose for a particular individual has not been established.

c) Patients with chronic depression that respond to imipramine may benefit from long-term mai (Kocsis et al, 1991).

1.3.1.C.1.d Diabetic neuropathy

1) Standard doses of 100 milligrams/day of imipramine may not be high enough to produce therape some patients with diabetic neuropathy. In one study, the therapeutic dose range was 125 milligram milligrams/day. The maximum therapeutic effect in neuropathy is reached within a week. Dosage titr started with a dose corresponding to a plasma level of 100 to 200 nmol/L for imipramine plus desipra should then be increased in a stepwise fashion (Sindrup et al, 1990a).

1.3.1.C.1.e Panic disorder

1) Based upon a dose-response study in patients with panic disorder with agoraphobia, IMIPRAMIN doses of 1.5 milligrams/kilogram/day (approximately 100 milligrams daily) may be effective in the tre some patients, whereas higher doses (3 milligrams/kilogram/day, approximately 200 milligrams daily for the agoraphobic dimension of this disorder (Mavissakalian & Perel, 1989); (Mavissakalian & Pera 1989a).

2) The suggested target dose is 2.25 milligrams/kilogram/day or a total (imipramine and N-desmeth plasma concentration of 110 to 140 nanograms/milliliter in the acute treatment of patients with panic agoraphobia. Higher doses were associated with good clinical response but a greater dropout rate s effects (Mavissakalian & Peral, 1995).

1.3.2 Dosage in Renal Failure

A) Imipramine Hydrochloride

1) No specific dosage adjustment is necessary (Bennett et al, 1994).

B) Imipramine Pamoate

1) No specific dosage adjustment is necessary (Bennett et al, 1994).

1.3.4 Dosage in Geriatric Patients

A) Imipramine Hydrochloride

1) GENERAL INFORMATION

a) Dosage reduction is recommended in elderly patients since this patient population is reported to have incidence of confusional-type reactions and other central nervous system symptoms while on tricyclic an therapy (Davies et al, 1971). A one-third to one-half reduction in tricyclic antidepressant dosage is sugge An increase in age is correlated with elevated steady-state serum levels of imipramine, desipramine and (Hicks et al, 1981a; Benetello et al, 1990).

2) DEPRESSION

a) The initial recommended dose for depression in geriatric patients is 30 to 40 milligrams orally daily; it necessary to exceed 100 milligrams/day (Prod Info TOFRANIL(R) tablets, 2005).

3) URINARY INCONTINENCE

a) In elderly patients with urinary incontinence associated with spontaneous unstable detrusor contractio imipramine is started at 25 milligrams at bedtime and increased by 25 milligrams, until the patient is cont side effects, or reaches 150 milligrams/day (Castleden et al, 1981).

b) A review for utilizing antidepressants in the treatment of depression in geriatric patients has been pub 1985).

B) Imipramine Pamoate

1) GENERAL INFORMATION

a) Dosage reduction is recommended in elderly patients since this patient population is reported to have incidence of confusional-type reactions and other central nervous system symptoms while on tricyclic an therapy (Davies et al, 1971). A one-third to one-half reduction in tricyclic antidepressant dosage is sugge An increase in age is correlated with elevated steady-state serum levels of imipramine, desipramine and (Hicks et al, 1981a; Benetello et al, 1990).

b) It is recommended that therapy in geriatric patients is initiated with imipramine hydrochloride tablets (orally per day (Prod Info TOFRANIL(R) tablets, 2005)) since lower dosages should be used. Imipramine may be used once a total daily dosage of 75 mg or higher is established (Prod Info TOFRANIL-PM(R) ca

1.3.5 Dosage Adjustment During Dialysis

A) Imipramine Hydrochloride

1) HEMODIALYSIS

a) No dosage supplementation is required following hemodialysis or peritoneal dialysis (Bennett et al, 19

2) PERITONEAL DIALYSIS

a) No dosage supplementation is required following hemodialysis or peritoneal dialysis (Bennett et al, 19

B) Imipramine Pamoate

1) HEMODIALYSIS

a) No dosage supplementation is required following hemodialysis or peritoneal dialysis (Bennett et al, 19

2) PERITONEAL DIALYSIS

a) No dosage supplementation is required following hemodialysis or peritoneal dialysis (Bennett et al, 19

1.3.6 Dosage in Other Disease States

A) Imipramine Hydrochloride

1) DIABETES

a) Studies in mice have shown that imipramine stimulates insulin secretion in the presence of low glucos whereas it inhibits insulin secretion in the presence of high glucose levels. Imipramine should be adminis to type II diabetic patients (El-Dakhakhny et al, 1996).

B) Imipramine Pamoate

1) DIABETES

a) Studies in mice have shown that imipramine stimulates insulin secretion in the presence of low glucos whereas it inhibits insulin secretion in the presence of high glucose levels. Imipramine should be adminis to type II diabetic patients (El-Dakhakhny et al, 1996).

1.4 Pediatric Dosage

Normal Dosage

Dosage in Renal Failure

Dosage Adjustment During Dialysis

1.4.1 Normal Dosage

Imipramine

Imipramine Hydrochloride

Imipramine Pamoate

1.4.1.A Imipramine

1.4.1.A.1 Anorexia nervosa

See Drug Consult reference: ANOREXIA NERVOSA - DRUG THERAPY

1.4.1.B Imipramine Hydrochloride

1.4.1.B.1 Oral route

Attention deficit hyperactivity disorder, predominantly inattentive type

Depression

Nocturnal enuresis

1.4.1.B.1.a Attention deficit hyperactivity disorder, predominantly inattentive type

1) The dose used ranges from 25 to 100 milligrams/day and tends to be lower than those needed tc Children tend to respond within 24 hours after initiating therapy. The monitoring of serum imipramine levels may be useful. The serum levels associated with reported responses have been 10 to 54 nan imipramine and 10 to 65 nanograms/milliliter of desipramine (Hussey & Wright, 1970)(Linnoila et al, 1985; Winsberg et al, 1980).

1.4.1.B.1.b Depression

1) For the treatment of depression in children the initial starting dose of imipramine is 1.5 milligrams given in 1 to 4 divided doses with dosage increased 1 milligram/kilogram every 3 to 4 days. The dail imipramine should not exceed 5 milligrams/kilogram/day, and children receiving doses of 3.5 milligra or more should be closely monitored (Taketomo et al, 1992).

2) Adolescents should initially receive 30 to 40 milligrams/day. Dosages exceeding 100 mg/day are necessary (Prod Info TOFRANIL(R) tablets, 2005).

1.4.1.B.1.c Nocturnal enuresis

1) Children, aged 6 and over, should initially receive 25 milligrams orally, 1 hour before bedtime. If s response does not occur within 1 week, the dose may be increased by 25 milligrams/day: children u receive a maximum daily dose of 50 milligrams and children over 12 may receive 75 milligrams (Pro 1995b; Taketomo et al, 1992).

2) In early-night bedwetters, it is more effective to give the drug earlier and in divided doses, ie, 25 afternoon and then at bedtime (Prod Info Tofranil(R), 1995b).

3) The daily dose of imipramine should not exceed 2.5 milligrams/kilogram, or 50 milligrams at bedt years of age, or 75 milligrams at bedtime if 12 years of age or older (Prod Info Tofranil(R), 1995b; Ta 1992; Denniston et al, 1994).

4) The optimization of imipramine dose in the treatment of enuresis should be guided by clinical res imipramine/desipramine levels. The use of serum imipramine/desipramine levels may help determin with the drug regimen and outliers. The use of a Bayesian dosing method offers no major advantage method used in combination using serum level data. However, the Bayesian method may be useful possible analytical errors, noncompliance, and non-steady state serum concentrations (Tamayo et a

1.4.1.C Imipramine Pamoate

1.4.1.C.1 Oral route

1.4.1.C.1.a Depression

1) Tofranil-PM(R) should not be used in children because of the increased potential for overdose du capsule potency (75 mg, 100 mg, 125 mg and 150 mg capsule) (Prod Info TOFRANIL-PM(R) capsu

1.4.2 Dosage in Renal Failure

A) Imipramine Hydrochloride

1) No specific dosage adjustment is necessary (Bennett et al, 1994).

B) Imipramine Pamoate

1) No specific dosage adjustment is necessary (Bennett et al, 1994).

1.4.4 Dosage Adjustment During Dialysis

A) Imipramine Hydrochloride

1) HEMODIALYSIS

a) No dosage supplementation is required following hemodialysis or peritoneal dialysis (Bennett et al, 19

2) PERITONEAL DIALYSIS

a) No dosage supplementation is required following hemodialysis or peritoneal dialysis (Bennett et al, 19

B) Imipramine Pamoate

1) HEMODIALYSIS

a) No dosage supplementation is required following hemodialysis or peritoneal dialysis (Bennett et al, 19

2) PERITONEAL DIALYSIS

a) No dosage supplementation is required following hemodialysis or peritoneal dialysis (Bennett et al, 19

2.0 Pharmacokinetics

Onset and Duration

Drug Concentration Levels

ADME

2.1 Onset and Duration

A) Onset

1) Initial Response

a) Depression, oral: 7 to 21 days (Prod Info Tofranil(R), 1995a); (Greenblatt & Shader, 1975).

2) Peak Response

a) Depression, oral: 4 to 6 weeks (Eisenberg & Asnis, 1986).

2.2 Drug Concentration Levels

A) Therapeutic Drug Concentration

1) Endogenous depression, greater than 200 ng/mL (IMIPRAMINE plus DESIPRAMINE) (Peselow et al, 1983; G 1977).

2) Prepubertal depressive symptoms, 200 to 225 ng/mL (IMIPRAMINE plus DESIPRAMINE), minimum level of 1 (Preskorn et al, 1983).

3) Hyperactivity, 10 to 54 ng/mL (imipramine only) (Linnoila et al, 1979).

4) Enuresis in children, no correlation (Fritz et al, 1994; Manglick & Buchanan, 1992; DeVane et al, 1984).

a) Some studies have shown levels of 80 to 150 ng/mL (IMIPRAMINE plus DESIPRAMINE) to be effective (I 1980a; Fernandez de Gatta et al, 1984).

5) Ventricular premature depolarizations, 74 to 385 ng/mL (IMIPRAMINE plus desipramine) (Giardina et al, 1983)

6) Diabetic neuropathy, less than 100 nmol/L (IMIPRAMINE plus DESIPRAMINE); 400 to 500 nmol/L required in (Sindrup et al, 1990).

B) Time to Peak Concentration

1) Oral: 1 hour (Gram & Christiansen, 1975).

2.3 ADME

Absorption

Distribution

Metabolism

Excretion

Elimination Half-life

Extracorporeal Elimination

2.3.1 Absorption

A) Bioavailability

1) Oral, tablet: 94% to 96% (Heck et al, 1979).

a) The bioavailability of IMIPRAMINE from tablet and syrup form is equivalent (Gagnon et al, 1980).

B) Effects of Food

1) None (Abernethy et al, 1984h).

2.3.2 Distribution

A) Distribution Sites

1) Protein Binding

a) 89% (Kristensen, 1983).

1) Patients with severe burns (35% to 85% BSA) exhibit increased binding during the initial convale 20 days) (Martyn et al, 1984).

2) The free fraction is reduced in cancer patients (Schulz & Luttrell, 1982).

3) The free fraction in rheumatoid arthritis patients is slightly lower than in healthy control subjects ((Kristensen, 1985).

2) OTHER DISTRIBUTION SITES

a) Tissue

1) At steady-state, tissue concentrations are greatest in the lung followed by the brain, the adipose (Sallee & Pollock, 1990a).

B) Distribution Kinetics

1) Volume of Distribution
a) 10 to 20 L/kg (Bennett et al, 1994a; Sallee & Pollock, 1990a).

2.3.3 Metabolism
A) Metabolism Sites and Kinetics
1) Liver, extensive (Gram & Christensen, 1975)(Olivier-Martin et al, 1975).
a) First-pass metabolism occurs with extensive metabolism to conjugated and non-conjugated metaboli
et al, 1975).
b) N-demethylation of imipramine is under pharmacogenic control of CYP2C19 (Morinobu et al, 1997).
c) Hydroxylation may become saturated resulting in drug accumulation (Brosen et al, 1986).
B) Metabolites
1) N-desmethyl metabolite (DESIPRAMINE), active (Drayer, 1976).
a) Patients with recurrent episodes of depression have a significantly lower IMIPRAMINE/DESIPRAMIN
those who do not experience recurrences (1.73) (Tollefson et al, 1985).
b) DESIPRAMINE exists in a 0.3 to 15.0 ratio to IMIPRAMINE in plasma (Nagy & Treiber, 1973).
2) 2-hydroxy IMIPRAMINE, active (Buckley, 1975).
a) Reported to depress cardiac contractility in dogs (Buckley, 1975).
3) 2-hydroxydesipramine, active (DeVane & Jusko, 1981).
a) Serum concentration of the hydroxy metabolites may have some relationship to the drug's toxicity (De
DeVane & Jusko, 1981a).

2.3.4 Excretion
A) Kidney
1) Renal Excretion (%)
a) 0.05 to 0.1% (DESIPRAMINE only) (Gram & Christiansen, 1975).
2) IMIPRAMINE metabolites are excreted in urine (Gram et al, 1971; Crammer et al, 1969).

2.3.5 Elimination Half-life
A) Parent Compound
1) ELIMINATION HALF-LIFE
a) 6 to 18 hours (Benetello et al, 1990a; Sutfin et al, 1984).
1) The half-life of IMIPRAMINE in children ranges from 6 to 15 hours (Rancurello, 1985).
2) In elderly patients the serum half-life ranges from 25 to 30 hours (Benetello et al, 1990a; Abernet
3) The terminal half-life of IMIPRAMINE and the active metabolites is 1.5 to 2.0 times longer followi
administration than that observed following oral administration (Sutfin et al, 1984).
B) Metabolites
1) DESIPRAMINE, 12 to 36 hours (Sutfin et al, 1984).
2) 2-hydroxyimipramine, 6 to 18 hours (Sutfin et al, 1984).
3) 2-hydroxydesipramine, 12 to 36 hours (Sutfin et al, 1984).

2.3.6 Extracorporeal Elimination
A) Hemodialysis
1) Dialyzable: No (Prod Info Tofranil(R), 1995a; Asbach & Schuler, 1974; Bailey et al, 1974; Wright & Cooke
B) Peritoneal
1) Dialyzable: No (Prod Info Tofranil(R), 1995a; Asbach & Schuler, 1974; Bailey et al, 1974; Wright & Cooke

3.0 Cautions

Contraindications

Precautions

Adverse Reactions

Teratogenicity/Effects in Pregnancy/Breastfeeding

Drug Interactions

3.0.A Black Box WARNING
1) Imipramine Hydrochloride
a) Oral (Tablet)
Suicidality and Antidepressant Drugs
Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in child
and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. A
the use of imipramine hydrochloride or any other antidepressant in a child, adolescent, or young adult must b

with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressar placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in a older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observ clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of observation and communication with the prescriber. Imipramine hydrochloride is not approved for use in pedi Info imipramine hcl oral tablets, 2007).

2) Imipramine Pamoate

a) Oral (Capsule)

Suicidality and Antidepressant Drugs

Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in child and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. A the use of imipramine pamoate or any other antidepressant in a child, adolescent, or young adult must balanc clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants comp adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged Depression and certain other psychiatric disorders are themselves associated with increases in the risk of su all ages who are started on antidepressant therapy should be monitored appropriately and observed closely f worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the nee observation and communication with the prescriber. Imipramine pamoate is not approved for use in pediatric TOFRANIL-PM(R) oral capsules, 2007).

3.1 Contraindications

A) Imipramine Hydrochloride

1) coadministration with a MAOI or use within 14 days of discontinuing a MAOI; may cause serious reactions (eg crisis, convulsive seizures, death) (Prod Info imipramine hcl oral tablets, 2007)

2) hypersensitivity to dibenzazepines; risk of cross-sensitivity reactions (Prod Info imipramine hcl oral tablets, 200

3) hypersensitivity to imipramine hydrochloride (Prod Info imipramine hcl oral tablets, 2007)

4) myocardial infarction, during the acute recovery period (Prod Info imipramine hcl oral tablets, 2007)

B) Imipramine Pamoate

1) coadministration with an MAOI or use within 14 days of discontinuing an MAOI; may cause serious reactions (crisis, severe convulsive seizures, death) (Prod Info TOFRANIL-PM(R) oral capsules, 2007)

2) hypersensitivity to dibenzazepines; risk of cross-sensitivity reactions (Prod Info TOFRANIL-PM(R) oral capsule

3) hypersensitivity to imipramine pamoate (Prod Info TOFRANIL-PM(R) oral capsules, 2007)

4) myocardial infarction, during the acute recovery period (Prod Info TOFRANIL-PM(R) oral capsules, 2007)

3.2 Precautions

A) Imipramine Hydrochloride

1) suicidal ideation and behavior or worsening depression, increased risk, particularly in children, adolescents, ar during the first few months of therapy or following changes in dosage (Prod Info imipramine hcl oral tablets, 2007)

2) alcohol, excessive use; increased danger of intentional or unintentional imipramine overdose (Prod Info imipra tablets, 2007)

3) bipolar disorder, in patients at risk; increased risk of precipitation of a mixed/manic episode with only antidepre (Prod Info imipramine hcl oral tablets, 2007)

4) cardiovascular disease, current or history; may cause cardiac conduction defects, arrhythmias, congestive hea myocardial infarction, stoke, and tachycardia (Prod Info imipramine hcl oral tablets, 2007)

5) concurrent use with electroshock therapy; may increase hazards of electroshock therapy (Prod Info imipramine 2007)

6) cyclic-type psychiatric disorders, history; may cause mania or hypomania (Prod Info imipramine hcl oral tablets

7) elderly patients; increased risk of developing cardiac abnormalities (Prod Info imipramine hcl oral tablets, 2007

8) excessive exposure to sunlight; may cause photosensitization (Prod Info imipramine hcl oral tablets, 2007)

9) glaucoma, narrow-angle, history of; due to anticholinergic effects of imipramine hydrochloride (Prod Info imipra tablets, 2007)

10) hepatic function, significantly impaired (Prod Info imipramine hcl oral tablets, 2007)

11) hyperthyroidism or concurrent use of thyroid medications; may increase risk of cardiovascular toxicity (Prod I oral tablets, 2007)

12) intraocular pressure, increased; exacerbation of condition due to cholinergic antagonism (Prod Info imipramir 2007)

13) neutrophil depression, pathological, may occur (Prod Info imipramine hcl oral tablets, 2007)

14) renal function, significantly impaired (Prod Info imipramine hcl oral tablets, 2007)

15) schizophrenia; may activate psychosis (Prod Info imipramine hcl oral tablets, 2007)

16) seizure disorder, history; may lower the convulsive threshold (Prod Info imipramine hcl oral tablets, 2007)

17) surgery, elective (Prod Info imipramine hcl oral tablets, 2007)

18) urinary retention, history of; due to anticholinergic effects of imipramine hydrochloride (Prod Info imipramine h 2007)

B) Imipramine Pamoate

1) suicidal ideation and behavior or worsening depression; increased risk, particularly in children, adolescents, ar during the first few months of therapy or following changes in dosage (Prod Info TOFRANIL-PM(R) oral capsules,

2) alcohol, excessive use; increased danger of intentional or unintentional imipramine overdose (Prod Info TOFR

capsules, 2007)
3) bipolar disorder; increased risk of precipitation of a mixed/manic episode with only antidepressant treatment (F
TOFRANIL-PM(R) oral capsules, 2007)
4) cardiovascular disease, current or history; may increase risk of tachycardia, congestive heart failure, cardiac c
arrhythmias, myocardial infarction (MI), and stroke (Prod Info TOFRANIL-PM(R) oral capsules, 2007)
5) concurrent use with electroshock therapy; may increase hazards of electroshock therapy (Prod Info TOFRANI
capsules, 2007)
6) elderly patients; may increase risk of ECG changes (Prod Info TOFRANIL-PM(R) oral capsules, 2007)
7) glaucoma, history of narrow-angle; exacerbation of condition due to cholinergic antagonism (Prod Info TOFRA
capsules, 2007)
8) hyperthyroidism or concurrent use of thyroid medications; may cause cardiac toxicity (Prod Info TOFRANIL-PM
2007)
9) intraocular pressure, increased; exacerbation of condition due to cholinergic antagonism (Prod Info TOFRANI
capsules, 2007)
10) mania/hypomania; risk of disease activation (Prod Info TOFRANIL-PM(R) oral capsules, 2007)
11) schizophrenia; may activate psychosis (Prod Info TOFRANIL-PM(R) oral capsules, 2007)
12) seizure disorder, history; may lower the convulsive threshold (Prod Info TOFRANIL-PM(R) oral capsules, 200
13) surgery, elective (Prod Info TOFRANIL-PM(R) oral capsules, 2007)
14) urinary retention, history of; exacerbation of condition due to cholinergic antagonism (Prod Info TOFRANIL-P
capsules, 2007)

3.3 Adverse Reactions

Cardiovascular Effects

Dermatologic Effects

Endocrine/Metabolic Effects

Gastrointestinal Effects

Hematologic Effects

Hepatic Effects

Immunologic Effects

Musculoskeletal Effects

Neurologic Effects

Otic Effects

Psychiatric Effects

Renal Effects

Reproductive Effects

Respiratory Effects

Other

3.3.1 Cardiovascular Effects

Abnormal ECG

Cardiac dysrhythmia

Cardiogenic shock

Cardiomyopathy

Cardiovascular finding

Dead - sudden death

Hypertension

Hypotension

Myocarditis

Vasoconstriction

3.3.1.A Abnormal ECG

1) Summary

a) ECG effects reported in patients receiving therapeutic doses of tricyclic antidepressants include INCF RATE, PROLONGED PR INTERVAL, INTRAVENTRICULAR CONDUCTION DELAYS, INCREASED CC INTERVAL (QTc), and FLATTENED T WAVES (Marshall & Forker, 1982ak).

2) In one comparative study, phenelzine and mianserin were less likely than imipramine or amitriptyline to pr cardiac conduction, in patients without cardiac disease. Prolongation of the PR interval was observed with im amitriptyline but not with phenelzine or mianserin. There was a trend towards prolongation of the QRS compl tricyclics, as well as the QTc interval; no QRS changes were observed with phenelzine or mianserin and ther phenelzine to decrease the QTc interval, whereas mianserin produced no effect on the QTc interval. These d mianserin and phenelzine are less likely than imipramine or amitriptyline to produce heart block in patients wi mianserin appeared to be the least likely of the four agents to induce cardiac conduction abnormalities (McGı

3) Forty-four depressed patients receiving imipramine 3.5 mg/kg/day for 4 weeks demonstrated prolonged P intervals, lowered T-wave amplitude, and increased heart rate compared to a 2 week drug-free period. None developed severe intraventricular conduction abnormalities nor high-grade AV block (Giardina et al, 1979).

4) IMIPRAMINE therapy in the elderly has been associated with increased heart rate and isolated ECG comp (shortening of the QT interval, changes in ST segments, and T waves) (Hayes et al, 1983). Two elderly, depr with preexisting cardiac arrhythmias, had significant increases in PR interval, QRS segment, and QTc interva treatment with oral imipramine 3.5 mg/kg/day. Both patients also had a reduction in atrial and ventricular prer depolarizations during therapy (Bigger et al, 1977b).

3.3.1.B Cardiac dysrhythmia

1) Summary

a) Production and suppression of atrial and ventricular arrhythmias have been reported in patients recei (Marshall & Forker, 1982ak; Raskind et al, 1982; Levin et al, 1985; Williams & Sherter, 1971). Multifocal ventricular contractions occurred in a 62-year-old woman following withdrawal of IMIPRAMINE. The depı preexisting nonspecific intraventricular conduction delay (Regan et al, 1989).

2) ARRHYTHMIAS ADULT

a) A 25-year-old quadriplegic patient receiving oral imipramine 200 mg at bedtime developed a life-threa arrhythmia shortly after achieving therapeutic levels (Levin et al, 1985). This may have occurred because patients frequently have autonomic supersensitivity. Thus the autonomic effects of imipramine may have cardiac arrhythmia.

b) A 37-year-old black male, who was receiving antihypertensive therapy (guanethidine, hydralazine, an experienced cardiac stand still and died following treatment with 25 mg of imipramine TID for 5 days, des discontinuation of all drugs (Williams & Sherter, 1971). In other reports, discontinuation of imipramine us improvement of cardiac arrhythmias although in some cases of AV block, a pacemaker was required (Ra Moorehead & Knox, 1965; Kantor et al, 1975). Arrhythmias, usually supraventricular or VENTRICULAR T have also been reported following acute overdose of imipramine (Brown et al, 1972; Lund-Larsen & Sive

c) The cardiovascular effects associated with imipramine therapy were evaluated in 12 men with stable disease who had become depressed following a myocardial infarction or coronary artery bypass-graft su al, 1982). All other drug regimens were kept constant during the course of the study. The mean maximur was 125 mg/day with a mean plasma level (imipramine plus desmethylimipramine) of 194 ng/mL. During imipramine therapy some patients experienced an antiarrhythmic effect from the imipramine, observed a premature ventricular contractions. Other cardiovascular side effects observed in this study included a m PR interval, QT interval, and heart rate, and orthostatic blood pressure changes.

3) ARRHYTHMIAS - PEDIATRIC

a) The cardiovascular status of 23 pediatric patients (ages 5 to 17 years), who were candidates for imipı

(eg, oppositional behavior, conduct disorders, and depression), were evaluated before and after the initia therapy. Each patient was started on 1.5 mg/kg/day which could be increased to a maximum of 5 mg/kg/ divided doses. The follow-up cardiovascular evaluation was conducted 10 to 14 days after clinical improv condition or steady-state serum concentration of between 150 ng/mL and 250 ng/mL. Resting heart rate PR interval lengthened (average 21.2 msec) in all 23 children (p less than 0.001). One child developed M while on imipramine, but this child had a resting PR interval of 176 msec before the initiation of imipramir on these findings the authors support the recommendation that baseline electrocardiogram should be co patients. In addition, patients with a family history of sudden death, a baseline PR interval greater than th for age, or any alterations in intraventricular conduction are candidates for ambulatory Holter monitor wh imipramine therapy (Fletcher et al, 1993).

3.3.1.C Cardiogenic shock

1) An imipramine-provoked paradoxical pheochromocytoma crisis occurred in a 35-year-old male who prese with severe cardiogenic shock after taking two unknown doses of imipramine for headaches. The hypotensio unresponsive to fluids and anatropes (Ferguson, 1994). Subsequent CT scan revealed a pheochromocytoma confirmed with other diagnostic tests. Previous cases reports of the adverse effects of imipramine in patients pheochromocytoma have resulted in hypertensive crises. It appears that imipramine should be avoided or us patients with known or suspected pheochromocytoma.

3.3.1.D Cardiomyopathy

1) CONGESTIVE CARDIOMYOPATHY was reported in a 50-year-old male after receiving tricyclic antidepre period (amitriptyline/perphenazine for 6 months, then imipramine 150 mg/day for 4 years). The patient experi onset of weakness, shortness of breath, and pedal edema over 2 months prior to admission. Evaluation reve and interstitial edema on chest X-ray and EKG revealed bilateral enlargement. The patient improved somewh furosemide and hydralazine but remained severely disabled (functional class 3) (Howland et al, 1983). A caus relationship was not definitely established in this case.

3.3.1.E Cardiovascular finding

1) Summary

a) Some of the following adverse effects have not been associated with imipramine but have occurred w antidepressants. These include MYOCARDIAL INFARCTION, STROKE, HEART BLOCK, precipitation o HEART FAILURE, ECG CHANGES, ORTHOSTATIC HYPOTENSION, HYPERTENSION, and TACHYC Tofranil(R), 1995). ECG effects reported in patients receiving therapeutic doses of tricyclic antidepressar INCREASED HEART RATE, PROLONGED PR INTERVAL, INTRAVENTRICULAR CONDUCTION DEL INCREASED CORRECTED QT INTERVAL (QTc), and FLATTENED T WAVES (Marshall & Forker, 198 shock, vasoconstriction, vasospasm of the hands and feet (ACROCYANOSIS), and myocarditis have ea in 1 to 2 patients (Appelbaum & Kapoor, 1983; Anderson & Morris, 1988; Ferguson, 1994; Morrow et al,

2) Two authors reported that tricyclic antidepressants when given in therapeutic doses are essentially free of cardiovascular effects in patients without cardiovascular disease and may improve the status of patients with arrhythmias (Glassman & Bigger, 1981; Roose et al, 1987a). The development of second degree atrioventric significantly greater in patients with preexisting bundle-branch block than in patients with normal electrocardio hypotension occurred more frequently in patients with conduction abnormalities (Roose et al, 1987a).

3.3.1.F Dead - sudden death

1) According to one study, the use of higher-dose tricyclic antidepressants (TCAs) was associated with an in SUDDEN CARDIAC DEATH, while lower doses did not increase this risk. In a cohort study including 481,744 cases of sudden cardiac death occurring in a community setting, researchers found that compared to non-us of TCAs was associated with a dose-related increase in the risk of sudden cardiac death. For doses lower tha (mg) (amitriptyline or its equivalent), the rate ratio was 0.97 (95% CI, 0.72 to 1.29), however this increased to 1.04 to 6.12) for doses of 300 mg or more (p=0.03, test for dose-response). In the entire cohort, users of TCA mg or higher (amitriptyline or its equivalent) had a 41% increased rate of sudden cardiac death (rate ratio, 1.4 1.95). However, TCAs taken in doses of less than 100 mg (amitriptyline or its equivalent) were not associated risk of sudden cardiac death in the entire cohort or in any subgroups, including persons with treated cardiova Use of selective serotonin reuptake inhibitors was not associated with an increased risk of sudden cardiac de 0.95; 95% CI, 0.42 to 2.15) (Ray et al, 2004).

2) An 8-year-old boy died of cardiac arrest that was attributed to imipramine toxicity. Although there were no taken more than the prescribed dose, the dose at time of death (6.9 milligrams/kilogram/day (mg/kg/day)) wa excess of the recommended dose of 5 mg/kg/day. One month after his dose had been raised to 100 mg twice (approximately a year after starting treatment), he complained of his heart hurting and of being dizzy. Two mo dextroamphetamine 5 mg/day was added to his regimen and was raised to 10 mg/day one month later. Two initial cardiac episode, he again complained of his heart hurting. One month later, while playing basketball, he arrest. On autopsy (20 hours after death), highly elevated venous and ventricular levels of imipramine and its desipramine, were the only abnormalities found (Varley, 2000).

3.3.1.G Hypertension

1) A 57-year-old female treated with 150 mg/day of imipramine for 12 days developed hypertension (Hessov pressure before therapy was noted to be 140/90 mmHg and 3 days after initiating imipramine for endogenous blood pressure rose to 150/110 mmHg. Nine days after initiating therapy the blood pressure had risen to 175/

no associated changes in the EKG. Twenty-four hour urinary excretion of noradrenaline-adrenaline and vanill
was normal. Dosage reduction failed to lower blood pressure and so the drug was discontinued. After 3 week
pressure was close to or at controlled levels.
2) Imipramine, 75 mg at bedtime, produced a rise in diastolic blood pressure in 18 enuretic boys (mean age
diastolic pressure increased by 8 +/- 6 mmHG and standing by 10 +/- 12 mmHG (Lake et al, 1979).

3.3.1.H Hypotension

1) Summary: ORTHOSTATIC HYPOTENSION has been reported in patients receiving imipramine (Glassma
Koehl & Wenzel, 1971; Glassman et al, 1979). Elderly depressed patients (n=45) may be at an increased risk
ORTHOSTATIC HYPOTENSION if they have preexisting severe heart disease, impaired left ventricular funct
concurrent cardiovascular medications. Another factor, that requires further assessment, was increased forea
Individuals with increased forearm resistance had a greater frequency of imipramine-induced orthostatic hypo
with normal or low forearm resistance. Patients were receiving therapeutic doses of imipramine (Glassman et
2) A 9-year-old white female treated with imipramine 25 mg twice daily for 9 days developed POSTURAL HY
the fifth day of therapy, the child developed decreased appetite, dry mouth, and constipation. During the sixth
therapy, she developed WEAKNESS, and DIZZINESS upon standing, pallor, diaphoresis, vomiting when pro
rapid heart rate. Physical exam revealed a supine pulse rate of 120/min with supine blood pressure of 100/70
pressure was noted to fall to 80/50 mmHg and pulse rate increased to 170/min, and the patient also became
sweated profusely. Upon standing, blood pressure dropped to 60/0 mmHg with pulse increasing to greater th
association with a SYNCOPAL ATTACK. An ECG revealed a FIRST DEGREE AV BLOCK. Discontinuation o
resulted in improvement of the patient's condition over the 7 day hospital course with subsequent normalizati
& Wenzel, 1971).
3) A study of 44 depressed adults receiving therapeutic doses of imipramine (average 245 mg/day in males,
females) demonstrated a significant decrease in blood pressure upon standing; average decrease during imi
was 26.1 mmHg during therapy and 10.9 mmHg prior to therapy. This decrease was independent of age, pla
preexisting heart rate (Glassman et al, 1979).
4) Forty-five elderly patients (mean age 63.6) were initially treated with 25 mg/day imipramine with dose bein
mg/day (Branconnier et al, 1983). Cardiovascular function was assessed 3 times during the course of the stu
day 7 and day 28). On day 7 and day 28 the patient exhibited a significant orthostatic change in diastolic bloo
increase in heart rate compared to pretreatment.
5) The cardiovascular effects of imipramine, doxepin, and placebo were compared in 24 depressed patients
The tricyclic antidepressants had no effects on left ventricular ejection fraction but did cause orthostatic chan
pressure. The imipramine therapy was associated with a reduction in premature ventricular contractions, whi
consistently seen in the placebo and doxepin treated patients. Based on the results of this study it would app
patients with preexisting heart disease, without any severe impairment of myocardial performance, can be tre
imipramine or doxepin without an adverse effect on ventricular rhythm or hemodynamic function (Veith et al,

3.3.1.I Myocarditis

1) A 54-year-old female developed myocarditis and hepatitis after restarting imipramine therapy. The patient
later secondary to the myocarditis. It could not be determined if this rare hypersensitivity reaction was directly
imipramine, its desipramine metabolite, or the combination of imipramine and desipramine (Morrow et al, 198

3.3.1.J Vasoconstriction

1) A 37-year-old female, developed severe and prolonged episodes of vasospasm of the hands within 10 da
discontinuation of her amitriptyline therapy and the initiation of 150 mg/day imipramine. Vasospasm reoccurre
rechallenge (Appelbaum & Kapoor, 1983).
2) ACROCYANOSIS of the hands and feet occurred in an 11-year-old girl following imipramine therapy (25 r
approximately 10 weeks) for nocturnal enuresis (Anderson & Morris, 1988). The patient developed initial sym
after initiation of treatment (painful swelling of metacarpophalangeal joints of the feet). Examination after 10 v
revealed cold, blue and moist hands and feet which blanched on pressure. LIVEDO RETICULARIS was obse
forearms. Withdrawal of imipramine resulted in resolution of symptoms in 3 days.

3.3.2 Dermatologic Effects

3.3.2.A Discoloration of skin

1) HYPERPIGMENTATION was described in 4 women (53 to 75 years old) receiving imipramine 150 to 375
years (Ming et al, 1999). Hyperpigmentation began after 2 to 11 years of use. Coloration was described as sl
women and as dark brown or golden brown in the other 2. The site of the reaction was in the face, chest, arm
woman also had a darkening of her iris. The pigmentation disappeared over 6 to 12 months in 2 of the wome
discontinue imipramine.
2) A 46-year-old male was treated with imipramine 75 to 100 mg three times/day for 9 years and developed
pigmentation of his face, neck, and fingers (Hare, 1970). Characteristically the skin of the nose and ears was
the patient had normal skin folds with no ophthalmological disturbances.
3) A 48-year-old white female developed a slate-gray discoloration in sun-exposed areas, predominately her
both hands, and eyes, after receiving imipramine 150 mg/day for five years (Hashimoto et al, 1991). These di
became lighter after discontinuation of the imipramine therapy and returned to normal within one year.

3.3.3 Endocrine/Metabolic Effects

Acute intermittent porphyria

Anticholinergic adverse reaction

Galactorrhea

Hyperthyroidism

Hypoglycemia

Syndrome of inappropriate antidiuretic hormone secretion

3.3.3.A Acute intermittent porphyria

See Drug Consult reference: DRUGS CONSIDERED UNSAFE- ACUTE PORPHYRIAS

3.3.3.B Anticholinergic adverse reaction

1) IMIPRAMINE HYDROCHLORIDE may produce a slightly higher incidence of anticholinergic side effects t
salt due to higher peak concentrations with this salt form; however, this has not been proven. Any dissimilarit
when changed from one salt form to the other is most likely psychological, and is probably due to changes in
between the two products (ie hydrochloride salt - tablet, pamoate salt - capsule (Prod Info Tofranil PM(R), 19
Tofranil(R), 1990; Pers Comm, 1982a).

3.3.3.C Galactorrhea

1) A 34-year-old female treated with imipramine 75 to 100 mg/day for 6 months developed spontaneous gala
Discontinuation of imipramine resulted in subsiding of the LACTATION which recurred when therapy with imi
resumed. During imipramine therapy, it was noted that the patient had low levels of serum serotonin and urin
The author postulated that the mechanism for the galactorrhea was similar to that seen with reserpine which
of the normal hypothalamic inhibition of pituitary prolactin secretion (Klein, 1964).

3.3.3.D Hyperthyroidism

1) A case of a 9.5-year-old female was treated with 25 mg/day oral imipramine for enuresis and also receive
thyroid therapy; the patient demonstrated increased restlessness, hyperkineticism, nervousness, easy fatigab
and warm skin. Physical exam revealed a resting heart rate of 120 beats/min with deep tendon reflexes noted
without clonus. Lab values revealed a thyroxine level of 9.2 mg/dL and a triiodothyronine uptake of 31.9%. EI
sinus tachycardia with ST-T wave changes and basal metabolic rate was elevated by 33%. Discontinuing imi
continuing the same dose of thyroid resulted in the child becoming euthyroid (Colantonio & Orson, 1974).

3.3.3.E Hypoglycemia

1) A 50-year-old male treated with 200 mg/d of imipramine developed severe hypoglycemia (Shrivastava & E
Six days after starting imipramine therapy the patient complained of fatigue, dizziness, loss of weight, and inc
On laboratory examination, he was found to have a nonfasting serum glucose of 57 mg/dL with all other lab v
normal limits. Imipramine therapy was discontinued and his serum glucose returned to 79 mg/dL and sympto
Following an unintentional rechallenge the man began complaining of weakness and dizziness one week late
serum glucose was 34 mg/dL. Following discontinuation of the imipramine therapy his serum glucose returne
2) Imipramine may increase an individual's sensitivity to insulin-induced hypoglycemia, but does not affect th
regulatory response of ACTH and cortisol (Kathol et al, 1991).

3.3.3.F Syndrome of inappropriate antidiuretic hormone secretion

1) Imipramine was associated with SIADH in a 78-year-old woman during therapy for major depression. The
imipramine 25 to 50 mg orally daily for approximately 3 months prior to admission. HYPONATREMIA was ob
admission and subsided during a 9 day interval without imipramine therapy. The patient subsequently develo
bupropion and upon rechallenge with imipramine (Liskin et al, 1984).
2) A 73-year-old thin and frail white female was admitted to a psychiatric unit for evaluation after deliberate ir
cleaning fluid (Colgate, 1993). She was diagnosed with severe depression and started on paroxetine therapy
the paroxetine was discontinued because the depression was getting worse. A single session of electroconvu
tried and then she was started on imipramine syrup, 25 mg twice daily. The dose was increased to 125 mg pe
divided doses, and diazepam was used in doses up to 10 mg/day to control her agitation. Over the next few v
condition improved, but she did fall and sustained a fractured left femur neck. Her mental condition continued
her mobility deteriorated and she suffered several more falls. Physical examination revealed a profound orthc
blood pressure (40 mmHg) and she had hyponatremia (124 mmol/l) and a low serum osmolality (266 mOsm/
intoxication was ruled out and a diagnosis of inappropriate secretion of antidiuretic hormone was made. The i
was then held. Over the next ten days her serum sodium levels returned to the normal range.

3.3.4 Gastrointestinal Effects

Colitis

Xerostomia

3.3.4.A Colitis

1) ISCHEMIC COLITIS, requiring surgical intervention, has been reported in one patient following the ingesti quantity of imipramine (Patel et al, 1992). The individual was a 38-year-old female with a past medical history hospitalized following an ingestion of unspecified quantity of imipramine. Her serum imipramine level was 1,0 micrograms/milliliter. Over the next few days her abdomen became increasingly distended with rebound tend absence of bowel sounds. Laparotomy revealed a necrotic ascending and transverse colon which was subse and the patient's condition improved.

3.3.4.B Xerostomia

1) XEROSTOMIA is frequently associated with imipramine therapy in usual therapeutic doses (150 mg/day). mouth is often associated with gum shrinkage, inflammation of the oral cavity, stomatitis, cracking of the lips mouth, pseudomembrane formation, hairy tongue with white or black or bald beefy red tongue, ill-fitting dentu and oral moniliasis. Discontinuation of the drug and/or treatment with pilocarpine (5 mg four times/day) usuall increase of salivation (Pollack, 1964; Winer & Bahn, 1967).

2) Imipramine, 75 mg every day, given to 12 volunteers in a placebo controlled study caused a significant re secretion rate (Sheth et al, 1979a).

3) A comparison of 5 different antidepressants on salivary flow reveals that amitriptyline and doxepin had the salivation and desipramine the least (Blackwell et al, 1980). Imipramine and nortriptyline were intermediate a in their effects.

3.3.5 Hematologic Effects

3.3.5.A Hematology finding

1) Summary

a) Some of the following adverse effects have not been associated with imipramine but have occurred w antidepressants. These include BONE MARROW DEPRESSION including AGRANULOCYTOSIS, EOS PURPURA, and THROMBOCYTOPENIA (Prod Info Tofranil(R), 1995). IMIPRAMINE-induced agranuloc about 10 cases have been reported (Gravenor et al, 1986).

2) A 59-year-old white female treated with imipramine 50 mg three times per day for 2 months developed ag which was fatal. The patient died 2 weeks after discontinuing imipramine (Hnatko, 1965).

3) A 55-year-old male treated with 25 mg/day of IMIPRAMINE developed asymptomatic eosinophilia. The pa cell count was noted to be 19,650 which gradually decreased in association with an eosinophil count of 693 (300). All through the course the patient remained asymptomatic and well. Following discontinuation of the dru recovered with the eosinophilia subsiding (Penick & Carrier, 1967).

3.3.6 Hepatic Effects

3.3.6.A Hepatotoxicity

1) Summary

a) Hepatotoxicity induced by imipramine (hepatic necrosis) occurs infrequently. The mechanism by whic reaction occurs in unknown, but may be a hypersensitivity reaction. Elevations in bilirubin, alkaline phosp transaminases, and other liver function tests can occur within one to two weeks of the start of therapy. C include pruritus, jaundice, icterus, rashes (erythematous maculopapular, desquamation, xanthelasma an and splenomegaly. Most cases improve following discontinuation of therapy. However, a few patients co severe that they either died or required a liver transplant (Hynes, 1965; Powell et al, 1968; Grace, 1970; 1982; Morrow et al, 1989; Schaefer et al, 1990).

2) High, single-daily dosing of imipramine may be more hazardous to the liver than divided doses. A 33-year receiving 300 mg (6 mg/kg) of imipramine at bedtime along with thiothixene 10 mg and developed an elevatic (Moskovitz et al, 1982). Prior to the hospitalization for worsening mental status she had been receiving 200 to imipramine in divided doses. On day 26 of the single daily dosage of imipramine therapy, liver function tests following subjective complaints by the patient. The test revealed an elevation in liver enzymes. No baseline li were obtained at the time of hospitalization, but a previous liver function test taken one month after the initiati therapy was normal. Antihepatitis A and B antibodies and HAA tests were negative. The imipramine therapy and the thiothixene therapy was continued. Two weeks following the discontinuation of the imipramine therap returned to normal.

3) A 11-year-old boy developed fulminant HEPATIC FAILURE seven days after being started on imipramine for enuresis (Schaefer et al, 1990). Histologically, the liver showed massive HEPATOCELLULAR NECROSIS proliferation and loss of parenchymal volume. Mild amounts of acute and chronic inflammation were found in Hepatocellular necrosis occurred predominantly in the pericentral areas with focal hemorrhage encircling the damage was so extensive a liver transplant was required.

4) A rare hypersensitivity reaction to imipramine is the development of myocarditis and HEPATITIS (Morrow

3.3.7 Immunologic Effects

3.3.7.A Cross sensitivity reaction

1) Two patients developed a skin rash during therapy with desipramine (Norpramin(R)) and amitriptyline (Ela al, 1982). Discontinuation of these medications in each patient resulted in subsidence of the skin rash. Doxep in the patient receiving desipramine and imipramine was substituted in the patient receiving amitriptyline. On recurrence of the rash did not occur. These data would suggest that substitution of a structurally dissimilar an is a viable alternative in patients developing allergic skin reactions.

3.3.8 Musculoskeletal Effects

Fracture of bone, Nonvertebral

Hip fracture

Myasthenia gravis

3.3.8.A Fracture of bone, Nonvertebral

1) In a prospective, population-based, cohort study (n=7983) with a mean follow-up of 8.4 years, there was a nonvertebral fracture in adult participants older than 55 years of age (mean age of 77.5 years) who were curr tricyclic antidepressant (TCA), including amitriptyline, clomipramine, dosulepine, doxepine, imipramine, mapr nortriptyline, and opipramol, compared to those who were not exposed to antidepressants. Current TCA use with an increased risk of nonvertebral fracture (hazard ratio (HR), 1.6; 95% confidence interval (CI), 1.08 to 2 with no antidepressant use. Current TCA use was also associated with an increased risk of nonvertebral frac CI, 1.02 to 2.5) compared with past antidepressant use (n=1217). Duration of TCA use of greater than 6 mon associated with an increased risk of fractures when compared with no antidepressant use and with past antid Fractures of the hip (most frequent), wrist, humerus, and pelvis were reported (Ziere et al, 2008).

3.3.8.B Hip fracture

1) An increased incidence of hip fracture was reported in elderly patients receiving psychotropic agents. This control evaluation of 1021 patients with hip fractures and 5606 control patients. An increased risk of hip fractu with the use of hypnotic/anxiolytic agents with a long elimination half-life (greater than 24 hours), tricyclic anti antipsychotic agents. Current users were defined as subjects who had received a prescription in the 30 day p admission date for the initial hospitalization. The long half-life hypnotic/anxiolytic agents studied were lorazep chlordiazepoxide, and barbiturates (excluding phenobarbital). The tricyclic antidepressants included amitripty imipramine; antipsychotic agents evaluated were thioridazine, haloperidol, chlorpromazine, and perphenazine contrast, shorter-acting hypnotic/anxiolytic agents (half-life of 24 hours or less) were not associated with an in fracture in these patients. The most frequently used agents in this category were diphenhydramine, hydroxyz hydrate. The increased risk of hip fracture observed in this study was directly related to the doses of the drug confounding by dementia did not alter the results. Additional studies are needed to confirm these results in th populations and to evaluate the effects of other psychotropic drugs that have less pronounced sedative effect 1987).

3.3.8.C Myasthenia gravis

See Drug Consult reference: DRUG-INDUCED MYASTHENIA GRAVIS

3.3.9 Neurologic Effects

Akathisia

Central nervous system finding

Cerebral ischemia

Gilles de la Tourette's syndrome

Impaired psychomotor performance

Myoclonus

Seizure

Suicidal thoughts

Tremor

3.3.9.A Akathisia

1) One patient developed akathisia while receiving imipramine therapy and 4 others developed the same wh desipramine, trazodone, or tranylcypromine. The imipramine patient was a 54-year-old female who was treat and imipramine for depression. After titrating the dose of imipramine to 150 mg/day, the patient complained o feeling in her legs and the inability to remain still. Propranolol 10 mg three times daily was started, and the sy completely within several hours of the first dose. Discontinuation of the propranolol resulted in a recurrence o within 24 hours (Zubenko et al, 1987).

3.3.9.B Central nervous system finding

1) Summary

a) Some of the following adverse effects have not been associated with imipramine but have occurred w antidepressants. These include NUMBNESS, TINGLING, PARESTHESIAS of the extremities, ATAXIA, T EXTRAPYRAMIDAL SYMPTOMS, PERIPHERAL NEUROPATHY, SEIZURES, EEG CHANGES, CONF STATES with HALLUCINATIONS especially in the elderly, DISORIENTATION, DELUSIONS, FORGETF ANXIETY, RESTLESSNESS, AGITATION, INSOMNIA, NIGHTMARES, HYPOMANIA, and exacerbation (Prod Info Tofranil(R), 1995; Davies et al, 1971). PARANOIA, AGGRESSIVE BEHAVIOR (Rampling, 19 Petti, 1979), psychomotor impairment (Clayton et al, 1977a), delirium (Godwin, 1983), myoclonus (Garve 1987), akathisia (Zubenko et al, 1987), and Tourette's syndrome (Parraga & Cochran, 1992) have been use of imipramine; SUICIDAL IDEATION is a potential side effect of imipramine (Prod Info Tofranil(R), 19 1992). LEARNING IMPAIRMENT in a social context is NOT seen with tricyclic antidepressants (Gillis, 19

3.3.9.C Cerebral ischemia

1) A 59-year-old male treated with usual therapeutic doses of imipramine for mild depression developed cere attacks (Brechter, 1968). Two weeks after starting drug therapy PARESTHESIA over the entire left side of his with short attacks of SPEECH DISTURBANCES. The drug was discontinued but PARESIS continued to prog involvement and total stenosis of the medial cerebral artery. Although no definite cause and effect relationshi the author postulated that tricyclic antidepressants may cause recurrent ischemic attacks in persons with par the cerebral arteries.

3.3.9.D Gilles de la Tourette's syndrome

1) Two children experienced tics or Tourette's syndrome that may have been precipitated by imipramine (Pa 1992). Motor (throat clearing, head shaking) and vocal tics (stuttering, echolalia, palilalia, profane utterances) boys two weeks after treatment with imipramine (75 to 100 mg/day) for attention deficit hyperactivity disorder concurrent depression. The tics remained despite discontinuation of the imipramine. Remission of the tics wa through the use of haloperidol and thioridazine.

3.3.9.E Impaired psychomotor performance

1) A placebo-controlled study of healthy male volunteers demonstrated DETERIORATION OF DRIVING SKI received 25 mg imipramine three times a day compared with 10 who received placebo and 10 who were cont 1977a).

3.3.9.F Myoclonus

1) A high incidence of myoclonus was reported during cyclic antidepressant therapy with imipramine, desipra amitriptyline, doxepin, trazodone, nortriptyline, and maprotiline (Garvey & Tollefson, 1987). Ninety-eight patie depression (93) or panic disorder were treated with these agents in initial doses of 50 mg daily of imipramine increasing to a maximum of 300 mg daily after several weeks. Of these patients, 39 (40%) developed myoclo of therapy, with the myoclonus being clinically significant in 9 (9%) and resulting in withdrawal of the antidepr medication change. Myoclonus occurred within one month of initiation of therapy in 81% of the 39 patients, w developing myoclonus within 2 weeks; the mean dose of antidepressant administered at the time of myoclonu daily in imipramine equivalents, which was similar to the mean dose utilized by the patients not developing m daily). Myoclonus was reversible upon withdrawal of the antidepressant but persisted if medication changes v however, spontaneous remission of myoclonus was observed in 9 patients. No predictors for the developmer were observed.

3.3.9.G Seizure

1) Summary

a) Imipramine has been shown to decrease the convulsive threshold (Misurec & Nahunek, 1969) and ha documented to cause seizure disorders including the occurrence of GRAND MAL TONIC-CLONIC SEIZ with or without seizure histories. Three reports have cited cases in pediatric patients (Fromm et al, 1972; Petti & Campbell, 1975b). However, cases of grand mal seizures occurring in younger adults (30 years o reported (Fromm et al, 1972; Kaufmann, 1974). Discontinuation of the tricyclic antidepressant and/or inst anticonvulsant therapy usually results in control of seizures.

2) A 25-year-old female that had been treated with 4 weeks therapy of imipramine (150 mg/day) and cloraze developed a seizure following the abrupt discontinuation of clorazepate therapy (Simons, 1983). Since the se solely contributed to the abrupt discontinuation of the clorazepate therapy, the author feels that all patients re prescriptions for antidepressant and benzodiazepines should avoid the abrupt discontinuation of the benzodi See Drug Consult reference: COMPARATIVE INCIDENCE OF SEIZURES FROM ANTIDEPRESSANTS

3.3.9.H Suicidal thoughts

1) Adult and pediatric patients being treated with antidepressants for major depressive disorder who experie anxiety, agitation, panic attacks, insomnia, irritability, hostility (aggressiveness), impulsivity, akathisia (psycho restlessness), hypomania, or mania may be at risk of suicidal ideation and behavior (SUICIDALITY). This sar to treating patients with other psychiatric and nonpsychiatric disorders. If these symptoms are observed, ther reevaluated and it may be necessary to discontinue medications when symptoms are severe, sudden in onse of the patient's initial symptoms. Patients and their caregivers should be provided with the Medication Guide f this drug (Anon, 2004).

2) A causal role for antidepressants in inducing suicidality has been established in pediatric patients. Anyone use of antidepressants in a child or adolescent must balance this risk with the clinical need. In pooled analyse placebo-controlled trials of nine antidepressants (citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, b mirtazapine, nefazodone, and venlafaxine extended-release) including over 4400 pediatric patients with majo disorder, obsessive compulsive disorder, or other psychiatric disorders, a greater risk of suicidal behavior or i first few months of therapy was demonstrated in patients receiving antidepressants as compared with placeb respectively). The risk of suicidality was most consistently observed in the trials that included patients with ma disorder, but there were signs of risk emerging from trials in other psychiatric indications, such as obsessive c disorder and social anxiety disorder. No suicides occurred in these trials. The risk of suicidality during longer- beyond several months) in pediatric patients is not known. It is also unknown whether this risk extends to adu 2004).

3.3.9.I Tremor

1) Imipramine-induced TREMOR occurred in a 61-year-old male. Following doses of 75 mg daily for 3 days, developed a marked action tremor of the upper extremities which was smooth and rhythmic (6 to 9 cycles pe interfered with routine activities. The tremor did not worsen when the dose of imipramine was increased to 15 Propranolol (20 mg twice a day) produced attenuation of the tremor within 25 to 48 hours (Kronfol et al, 1983

2) Some patients with panic disorder imipramine therapy may develop a jitteriness syndrome (Yeragani et al condition is characterized by jitteriness, restlessness, trouble sitting still, insomnia, increased energy, increas possible decreased serum iron level. Whether iron supplementation will prevent or treat this syndrome remai

3.3.11 Otic Effects

3.3.11.A Ototoxicity

1) TINNITUS has been reported in 4 patients: a 37-year-old female, a 30-year-old fem old male, all receiving 50 to 150 mg imipramine daily. Tinnitus disappeared when the imipramine dose was re females and the male required a change in therapy (Racy & Ward-Racy, 1980).

2) Five additional reports of tinnitus secondary to imipramine therapy have been published (Tandon et al, 19 had no history of tinnitus or other otologic abnormalities. All patients developed tinnitus during the second or treatment, with doses of 150 to 250 mg daily of imipramine (combined plasma imipramine-desipramine levels 450 ng/mL). The tinnitus subsided spontaneously within 2 to 4 weeks without any specific treatment in all pat imipramine was maintained in 3 patients and increased in 2). Based upon a chart review of 475 patients treat University of Michigan Medical Center, the authors indicate that approximately 1% of patients receiving tricyc develop tinnitus.

3) A 38 year-old depressed female develop ringing in her ears one week after the dose of imipramine was in mg/day (Laird & Lydiard, 1989). She had no history of ear problems and denied using aspirin or other salicyla medication was continued since the tinnitus was only mildly bothersome and no abnormalities could be found physical examination. The dose of imipramine was increased to 150 mg/day during the second week. The tin approximately six weeks and then diminished without any changes in drug therapy.

3.3.12 Psychiatric Effects

Aggressive behavior

Delirium

Psychotic disorder

Sleep disorder

3.3.12.A Aggressive behavior

1) A 26-year-old male treated with a single oral dose of imipramine for cataplexy developed a feeling of aggr increased intensely over the next half hour with the patient struggling to keep control. The patient was noted staggering, and feelings of drunkenness. It was noted that the patient had previously received diazepam and (Rampling, 1976). In addition, increased aggression was reported in 2 depressed boys, ages 12 and 6 years, therapy (Pallmeyer & Petti, 1979).

2) Four cases of rapid onset untoward aggressiveness was associated with the use of tricyclic antidepressar cases the aggressive behavior coincided with the reintroduction of the tricyclic antidepressant. The mechanis paradoxical response of rapid onset and qualitative characteristics of their reaction are consistent with a prob in the reticular formation which is the rational for their usefulness in cataplexy (Rampling, 1978).

3.3.12.B Delirium

1) Summary

a) Risk factors for the development of tricyclic-induced delirium include high tricyclic serum concentratio organic brain disease, and concomitant neuroleptic therapy (Godwin, 1983).

2) A 31-year-old hospitalized female developed delirium during imipramine therapy; the patient had no know (Godwin, 1983). Initially she presented with a hypomanic reaction (characterized by restlessness, hyperactivi lability of mood, and insomnia) that later developed into the delirium reaction (disorientation to time and place speech, periods of blank stares, periods of unresponsiveness, visual distortions, hallucinations) while on stan imipramine therapy. Plasma imipramine concentrations were in the low end of the therapeutic range. Thus, in delirium may occur in some patients as an idiosyncratic reaction unrelated to imipramine serum concentratior

3.3.12.C Psychotic disorder

1) Summary

a) Psychotic reactions following doses of imipramine ranging from 75 to 600 mg/day have been reportec included DISORIENTATION, AGITATION, CONFUSION, RESTLESSNESS, INSOMNIA, tremor, ATAXI HALLUCINATIONS, PARANOIA and other abnormal manifestations. Some data suggests that these effe more frequently in elderly patients and/or those receiving higher doses. Discontinuation of the drug resul and disappearance of the symptoms (Kane & Keeler, 1964; Ananth, 1973; Wilson et al, 1974; Schulterbr Prod Info Tofranil(R), 1995).

2) A high number of geriatric patients on tricyclic antidepressant therapy have developed confusional reactio as restlessness, sleep disturbances, FORGETFULNESS, agitation, disorientation, and DELUSIONS. This rea appear to be dose-related and is possibly due to the central anticholinergic effects of these drugs. These epis reported to develop within the first 2 weeks of drug therapy and are usually self-limiting, lasting from 3 to 20 d reduction of dosage or discontinuation of the drug appears to result in resolution of these confusional reactior (Davies et al, 1971).

3.3.12.D Sleep disorder

1) Imipramine can markedly suppress REM sleep (REM time, REM activity, and number of REM periods) in adults (Shain et al, 1990).

3.3.13 Renal Effects

3.3.13.A Nephrotoxicity

1) A 65-year-old white male was treated with doses of up to 100 mg three times/day of imipramine for 24 day developed RENAL DAMAGE (Sathananthan & Gershon, 1973c). The patient developed symptoms of anorex confusion, disorientation, and tremulousness in association with elevated BUN (80 mg/dL) and creatinine (2.5 Urine output fell to 725 mL/day despite a fluid intake of approximately 2.5 L. Discontinuation of imipramine re improvement of this clinical condition and abnormal laboratory values returning to normal by the third day.

3.3.14 Reproductive Effects

3.3.14.A Sexual dysfunction

1) ERECTILE DYSFUNCTION and EJACULATORY DELAY or loss has been reported in depressed and nor minimum daily dose of 75 mg. Pain on ejaculation (Couper-Smartt & Rodham, 1973; Simpson et al, 1965; Gr Aizenberg et al, 1991) and loss of libido (Jenkins et al, 1976) as well as increased libido has been reported (S 1965).

2) The occurrence of sexual dysfunction associated with antidepressant therapy is frequent. Decreases in se occurs in 8% of males and 16% of females treated with placebo, 80% of males and 57% of females treated w and 50% of males and 27% of females treated with imipramine (Harrison et al, 1985). Sexual dysfunctions re DECREASE IN LIBIDO, excitement, and orgasm and a delay in ejaculation. Similar results have been reporte by the same group of investigators (Harrison et al, 1986).

3) Other investigators feel that long-term treatment with imipramine has no negative effect on sexual functior 1994). Instead they feel that the presence of depressive symptoms is associated with diminished libido or dec pleasure. An evaluation of 90 patients with a major depressive disorder treated with imipramine found no rela imipramine and sexual function in the total group or the females alone. The number of males included in the s inadequate to draw any conclusions regarding population.

4) A 51-year-old male was treated with an initial dose of 75 mg/day which was reduced to oral imipramine 25

weeks and developed erectile IMPOTENCE at the higher dose. Potency rapidly returned upon decreasing the
25 mg/day (Greenberg, 1965).
5) ANORGASMIA has been reported in a woman treated with imipramine therapy and disappeared when de
was substituted for the imipramine (Sovner, 1983).
See Drug Consult reference: DRUG-INDUCED SEXUAL DYSFUNCTION

3.3.15 Respiratory Effects

3.3.15.A Acute respiratory distress syndrome

1) A 15-year-old was admitted to the emergency department following the ingestion of 5 grams (150 mg/kg)
approximately 45 minutes prior to arrival (Flaherty et al, 1986). Within 5 hours of ingestion the patient develop
hypoxemia, increased QS/QT, and decreased lung compliance. At that time a diagnosis of adult respiratory d
(ARDS) was made. Positive end-expiratory pressure (PEEP) resulted in an improvement in lung compliance,
shunting. Whether or not the development of adult respiratory distress syndrome ARDS was a direct result of
overdose or the development of bradycardia, hypoxemia, metabolic acidosis, hypotension or physostigmine t
unknown.

3.3.16 Other

Drug tolerance - finding

Withdrawal sign or symptom

3.3.16.A Drug tolerance - finding

1) Tolerance to the therapeutic effects of IMIPRAMINE therapy has been reported in a small number of patie
Baldessarini, 1985). Usually these patients initially respond to therapy and then weeks to months later they re
continued antidepressant therapy. Remission can usually be regained by increasing the dose of the medicati
medication. The exact mechanism for the development of this tolerance is not known.

3.3.16.B Withdrawal sign or symptom

1) Withdrawal symptoms have been associated with the discontinuation of tricyclic antidepressant therapy a
to 55% of the patients. These symptoms frequently occur within the first 24 to 48 hours after cessation of ther
withdrawal period is characterized by general somatic malaise (muscle aches, coryza, excessive sweating), g
(nausea, vomiting, diarrhea, and abdominal pain), motor restlessness, and/or neuropsychiatric symptoms (dr
irritability, agitation, and recurrence of depressed mood). Restarting imipramine therapy generally improves th
prevent the occurrence of this withdrawal reaction, the imipramine therapy should be withdrawn gradually, wh
(Sathananthan & Gershon, 1973a; Stern & Mendels, 1980; Petti & Law, 1981; Shrivastava & Itil, 1985; Prod I
1995).
2) Children withdrawn from high-dose imipramine therapy over 3 to 10 days may develop a withdrawal syndr
1981). The syndrome is characterized by nausea, vomiting, decreased appetite, tearfulness, headaches, agit
It is thought that this withdrawal syndrome may be the result of a cholinergic rebound following the discontinu
anticholinergic medications. Extending the duration of the tapering period may be helpful in avoiding the occu
syndrome, but there is no clinical evidence to support this theory.
3) A 53-year-old woman, with a 25-year history of unipolar depression but no evidence of bipolar illness, dev
cycling bipolar disorder following abrupt discontinuation of her long-term tricyclic antidepressant therapy (Jon
The bipolar illness presented as hypomania 2 days after stopping drug therapy. The hypomanic period was fo
depression and subsequent fluctuation between mania and depression, each lasting from 2 to 8 weeks.
4) Multifocal premature ventricular contractions (PVCs) occurred in a 62-year-old woman following withdrawa
The depressed women had preexisting nonspecific intraventricular conduction delay (Regan et al, 1989). Imip
daily) was tapered over a 4-day period, and then doxepin was initiated at a dose of 50 mg at bedtime. PVCs a
observed the day following discontinuance of imipramine. Reinitiation of imipramine therapy (100 mg daily) pr
sinus rhythm with only occasional uniform PVCs, and no couplets, multiforms, runs, or pauses. It was felt that
drug resulted in rebound irritability with resultant aberrant rhythms. Tricyclic antidepressants should be withdr
with frequent EKG monitoring, in patients with a preexisting conduction defects. In patients with no suspected
defect, monitoring for signs of ectopy should be undertaken during withdrawal.
5) Withdrawal of imipramine therapy used to treat postpsychotic depression after six months in six schizophr
resulted in DEPRESSIVE RELAPSES (Siris et al, 1989). All six patients had benefit from the initial addition of
their fluphenazine decanoate and benztropine therapy. After six months the dose of imipramine was decreas
weekly intervals without the patient knowledge until it was discontinued. All six patients had experienced recu
depressive-like state and three manifested a coincident exacerbation of psychotic symptoms. While only one
maintained on all three drugs experienced a depressive-like relapse.

3.4 Teratogenicity/Effects in Pregnancy/Breastfeeding

A) Teratogenicity/Effects in Pregnancy
1) Australian Drug Evaluation Committee's (ADEC) Category: C (Batagol, 1996)

a) Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing harmfu human fetus or neonate without causing malformations. These effects may be reversible. Accompanying text consulted for further details.

See Drug Consult reference: PREGNANCY RISK CATEGORIES

2) Crosses Placenta: Yes

3) Clinical Management

a) Due to reported teratogenic effects, use of imipramine during pregnancy should be avoided if possible, es first trimester. The dangers of failure to treat major depression, however, are obvious, and in each case these weighed against the potential for teratogenic effects. If pregnancy occurs during treatment, the patient should possible consequences to the fetus.

4) Literature Reports

a) Imipramine has been associated with teratogenic effects, however, a clear causal relationship has not bee the large cohort study (Heinonen et al, 1977), of 19 mother-child pairs exposed to imipramine in the first trime malformations were reported, suggesting an increased risk of teratogenic effects.

b) A review of the Finnish register of congenital malformations for 1964 to 1972 revealed 3 possible cases of effects (2 cleft lips, 1 CNS anomaly) that were related to the use of an imipramine/chloropyramine combinatio Heikkila & Saxen, 1973).

c) Neonatal intoxication and withdrawal symptoms may be observed with maternal use of imipramine. Sympt the neonate include cyanosis, respiratory distress, vasomotor instability, irritability, hypokinesia, convulsions, increased respiratory rate, autonomic dysfunction, hypoactivity, and belly dance movements of the abdomen (Anon, 1983; Shrand, 1982).

d) Several infants have been described who developed transient respiratory and neurological symptoms sho possibly in relation to maternal imipramine. Of 3 infants whose mothers had used imipramine throughout the infants developed postnatal symptoms of irritability, restlessness, inconsolable crying, tachypnea, cyanosis, h fasciculations, and tremors. One infant developed signs of heart failure despite a normal electrocardiogram, a to 180 per minute, and absence of a congenital cardiac malformation. One infant experienced laryngeal spas difficulties (Eggermont et al, 1972).

e) Based on data collected through the Motherisk Program, there appear to be no differences in cognitive fu temperament and general behavior in children exposed to imipramine throughout gestation when compared t et al, 2002). However, among infants who were exposed to either fluoxetine or tricyclic antidepressants thoug those born to mothers with uncontrolled depressive symptoms showed lower cognitive and language achieve born to mothers who were well-controlled (Nulman et al, 2002).

B) Breastfeeding

1) American Academy of Pediatrics Rating: Drugs for which the effect on nursing infants is unknown but may be 2001)

2) Thomson Lactation Rating: Infant risk cannot be ruled out.

a) Available evidence and/or expert consensus is inconclusive or is inadequate for determining infant risk wh breastfeeding. Weigh the potential benefits of drug treatment against potential risks before prescribing this dr breastfeeding.

3) Clinical Management

a) Imipramine and its metabolite, desipramine, appear in breast milk in low concentrations. The potential for the nursing infant has not been evaluated. When the maternal dose is high, exposure of the infant to the drug minimized by limiting the number of feeds per day (Bennett, 1996).

4) Literature Reports

a) The amount of imipramine and desipramine available to an infant is small. The amount of imipramine mea milk was 4 to 29 ng/mL and desipramine was 17 to 35 ng/mL; a milk:plasma ratio of 1 has been suggested (S 1979).

5) Drug Levels in Breastmilk

a) Parent Drug

1) Milk to Maternal Plasma Ratio

a) 1 (Briggs et al, 1998)

b) Active Metabolites

1) desipramine (Sallee & Pollock, 1990)

3.5 Drug Interactions

Drug-Drug Combinations

Drug-Food Combinations

Drug-Tobacco Combinations

Intravenous Admixtures

3.5.1 Drug-Drug Combinations

Acecainide

Acenocoumarol

Ajmaline

Alprazolam

Amiodarone

Amisulpride

Amobarbital

Amphetamine

Amprenavir

Anisindione

Aprindine

Aprobarbital

Arbutamine

Arformoterol

Arsenic Trioxide

Astemizole

Atazanavir

Atomoxetine

Azimilide

Belladonna

Belladonna Alkaloids

Bepridil

Bethanidine

Bretylium

Bupropion

Butabarbital

Butalbital

Butalbital

Cannabis

Carbamazepine

Chloral Hydrate

Chloroquine

Chlorotrianisene

Cimetidine

Cisapride

Citalopram

Clarithromycin

Clonidine

Clorgyline

Conjugated Estrogens

Darifenacin

Dexfenfluramine

Dexmethylphenidate

Dextroamphetamine

Dicumarol

Dienestrol

Diethylpropion

Diethylstilbestrol

Diltiazem

Disopyramide

Disulfiram

Dofetilide

Dolasetron

Droperidol

Duloxetine

Enflurane

Epinephrine

Erythromycin

Esterified Estrogens

Estradiol

Estriol

Estrone

Estropipate

Eterobarb

Ethinyl Estradiol

Etilefrine

Fenfluramine

Fenfluramine

Flecainide

Fluconazole

Fluoxetine

Fluvoxamine

Formoterol

Fosamprenavir

Foscarnet

Fosphenytoin

Gatifloxacin

Gemifloxacin

Grepafloxacin

Guanadrel

Guanethidine

Guanfacine

Halofantrine

Haloperidol

Halothane

Heptabarbital

Hexobarbital

Hydroquinidine

Ibutilide

Iobenguane I 131

Iproniazid

Isocarboxazid

Isoflurane

Isradipine

Ketoconazole

Labetalol

Levomethadyl

Lidoflazine

Linezolid

Lisdexamfetamine

Lorcainide

Lumefantrine

Mazindol

Mephentermine

Mephobarbital

Mesoridazine

Mestranol

Methamphetamine

Methohexital

Methoxamine

Methylphenidate

Mibefradil

Midodrine

Moclobemide

Moxifloxacin

Nefopam

Nialamide

Norepinephrine

Octreotide

Oxilofrine

Pargyline

Paroxetine

Pemoline

Pentamidine

Pentobarbital

Phendimetrazine

Phenelzine

Phenindione

Phenmetrazine

Phenobarbital

Phenprocoumon

Phentermine

Phenylephrine

Phenytoin

Pimozide

Pirmenol

Prajmaline

Primidone

Procainamide

Procarbazine

Prochlorperazine

Propafenone

Propranolol

Propylhexedrine

Quetiapine

Quinestrol

Quinidine

Quinidine

Rasagiline

Risperidone

Ritonavir

Ropivacaine

S-Adenosylmethionine

Salmeterol

Secobarbital

Selegiline

Sematilide

Sertindole

Sertraline

Sotalol

Sparfloxacin

Spiramycin

St John's Wort

Sulfamethoxazole

Sultopride

Tapentadol

Tedisamil

Telithromycin

Terfenadine

Thiopental

Thioridazine

Tibolone

Toloxatone

Tramadol

Tranylcypromine

Trifluoperazine

Trimethoprim

Vasopressin

Venlafaxine

Verapamil

Warfarin

Ziprasidone

Zolmitriptan

Zotepine

3.5.1.A Acecainide

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Cases of QTc prolongation and/or torsades de pointes have been reported with all Class III ant agents, including acecainide (Chow et al, 1984), amiodarone (Faggiano et al, 1996), azimilide (Corey et al, 1 (Gilman et al, 1985), ibutilide (Rodriguez et al, 2001), sematilide (Singh, 1996), dofetilide (Allen et al, 2002), a & Runge, 2001). Even though no formal drug interaction studies have been done, the coadministration of Cla antiarrhythmics and other drugs known to prolong the QTc interval, including tricyclic antidepressants, is not (Yamreudeewong et al, 2003a; Prod Info Corvert(R), 2000).

3) Severity: major

4) Onset: rapid

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of a Class III antiarrhythmic and a tricyclic antidepres recommended.

7) Probable Mechanism: additive QT prolongation

8) Literature Reports

a) EKG effects reported in patients receiving therapeutic doses of tricyclic antidepressants include incre prolonged PR interval, intraventricular conduction delays, increased corrected QT interval (QTc) and flat (Marshall & Forker, 1982ab).

b) Concurrent use of Class III antiarrhythmic agents, and other drugs that can prolong the QT interval, s antidepressants, is not recommended. Dofetilide should be stopped for at least 2 days before any interac initiated. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised (Yam 2003).

3.5.1.B Acenocoumarol

1) Interaction Effect: increased risk of bleeding

2) Summary: Tricyclic antidepressants (TCAs) may increase the half-life and bioavailability of oral anticoagul 1970c; Williams et al, 1976c). Considerable interindividual differences may be found (Pond et al, 1975c).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: In patients receiving tricyclic antidepressants and oral anticoagulant therapy, the pr ratio or INR (international normalized ratio) should be closely monitored with the addition and withdrawal of th and should be periodically reassessed during concurrent therapy. Achieving a stable drug regimen which pro level of anticoagulation may be difficult in patients on this combination, and frequent adjustments of the antic be required.
7) Probable Mechanism: decreased acenocoumarol metabolism; increased acenocoumarol absorption
8) Literature Reports
a) In a study of healthy volunteers, the concurrent use of nortriptyline or amitriptyline resulted in an incre levels and an increase in the plasma half-life of dicumarol, although the effect was not consistent in all su 1975b). This effect was not observed with warfarin.
b) A single oral dose of bishydroxycoumarin after 8 days of nortriptyline resulted in a significantly prolon decreased volume of distribution of the coumarin anticoagulant in 6 healthy volunteers (Vesell et al, 197(mechanism of action was suggested to be reduced bishydroxycoumarin metabolism and/or altered coum
c) Drug dosing was studied in 16 patients on long-term anticoagulant therapy who used concurrent TCA 1976b). TCAs affected the stability of anticoagulant control leading to frequent changes in the doses of a Inhibition of coumarin metabolism was the postulated mechanism.

3.5.1.C Ajmaline

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Class Ia antiarrhythmics and tricyclic antidepressants have been shown to prolong the QTc inte recommended therapeutic dose. Even though no formal drug interaction studies have been done, the coadm Ia antiarrhythmics and other drugs known to prolong the QTc interval, including tricyclic antidepressants, is n (Prod Info Elavil(R), 1999g; Prod Info Quinaglute(R), 1999; Marshall & Forker, 1982n).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: The concurrent administration of a Class IA antiarrhythmic agent and a tricyclic anti recommended.
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) Quinidine is an inhibitor of the cytochrome P450 isoenzyme responsible for the 2-hydroxylation of imi desipramine (Brosen & Gram, 1989). Inhibition of this enzyme system can result in a 35% decrease in im clearance and 85% decrease in desipramine clearance. Demethylation of imipramine by the cytochrome unaffected by this interaction. Until more information is available all patients having quinidine added to dr containing imipramine or desipramine should be monitored for increased antidepressant serum concentr potential toxicity.
b) An increased incidence in sudden death was observed in six out of 53 patients with cardiac disease r amitriptyline, compared to 0 out of 53 in the control group. It was recommended that amitriptyline be avo with underlying cardiac disease except when depression was debilitating and no other drugs were helpfu Coull et al, 1970).
c) In a placebo controlled study, imipramine 3.5 mg/kg was administered daily for seven patients with se and titrated doses to obtain therapeutic plasma concentrations. Two patients displayed premature atrial c and premature ventricular depolarizations before therapy. On patient had 33 premature atrial depolarizat premature ventricular depolarizations (PVD) per hour, which decreased to 0.4 PAC and zero PVC per ho The other patient had 12 PAD and 169 PVD per hour before treatment and 1.8 PAD and 28.1 PVD per h The authors also cautioned that the incidence of cardiotoxicity may increase if tricyclic antidepressants a with Type I antiarrhythmics. It was also recommended that quinidine and procainamide not be used to tre of a tricyclic overdose. The similarities between these agents may exacerbate the cardiotoxicity (Kantor e

3.5.1.D Alprazolam

1) Interaction Effect: increased imipramine plasma concentrations
2) Summary: Imipramine steady state plasma concentrations increased an average of 31% when used conc alprazolam at doses up to 4 mg/day. The clinical significance of this increase is unknown. A decrease in the i should be considered for patients who are being treated with alprazolam and imipramine concurrently and wh increase in side effects such as dry eyes and mouth, constipation, decreased urination, or arrhythmias (Prod (TM) orally disintegrating tablet, 2003).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Concomitant use of alprazolam and imipramine may increase the plasma concentra imipramine. The clinical significance of this increase is unknown. If signs or symptoms of increased imipramir as blurred vision, dry mouth, constipation, urinary retention, or arrhythmias are noticed, a downward dosage imipramine should be considered.

7) Probable Mechanism: unknown

3.5.1.E Amiodarone

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Cases of QTc prolongation and/or torsades de pointes have been reported with all Class III ant agents, including acecainide (Chow et al, 1984), amiodarone (Faggiano et al, 1996), azimilide (Corey et al, 1 (Gilman et al, 1985), ibutilide (Rodriguez et al, 2001), sematilide (Singh, 1996), dofetilide (Allen et al, 2002), a & Runge, 2001). Even though no formal drug interaction studies have been done, the coadministration of Cla antiarrhythmics and other drugs known to prolong the QTc interval, including tricyclic antidepressants, is not (Yamreudeewong et al, 2003a; Prod Info Corvert(R), 2000).

3) Severity: major

4) Onset: rapid

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of a Class III antiarrhythmic and a tricyclic antidepres recommended.

7) Probable Mechanism: additive QT prolongation

8) Literature Reports

a) EKG effects reported in patients receiving therapeutic doses of tricyclic antidepressants include incre prolonged PR interval, intraventricular conduction delays, increased corrected QT interval (QTc) and flat (Marshall & Forker, 1982ab).

b) Concurrent use of Class III antiarrhythmic agents, and other drugs that can prolong the QT interval, s antidepressants, is not recommended. Dofetilide should be stopped for at least 2 days before any intera initiated. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised (Yam 2003).

3.5.1.F Amisulpride

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod 1999), haloperidol (O'Brien et al, 1999), risperidone (Duenas-Laita et al, 1999), sertindole (Agelink et al, 2001 (Owens, 2001b), sultopride (Lande et al, 1992), and zotepine (Sweetman, 2003). Even though no formal drug studies have been done, the coadministration of a tricyclic antidepressant and an antipsychotic is not recomm Pamelor(R), 2001; Marshall & Forker, 1982t).

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of a tricyclic antidepressant and an antipsychotic is n

7) Probable Mechanism: additive cardiac effects

8) Literature Reports

a) Electrocardiographic changes that have occurred during clinical trials with pimozide have included pr corrected QT interval, flattening, notching, and inversion of the T wave and the appearance of U waves. studies, sudden, unexpected deaths have occurred while patients were receiving pimozide doses of 1 m proposed mechanism for these deaths is prolongation of the QT interval predisposing patients to ventricu (Prod Info Orap(R), 1999).

3.5.1.G Amobarbital

1) Interaction Effect: possible decreased tricyclic antidepressant serum concentrations and possible additive

2) Summary: Concomitant barbiturate and tricyclic antidepressant (TCA) therapy may result in increased me TCA. There have been scattered reports of individuals with decreased serum levels of TCAs in the presence (Moody et al, 1977; Silverman & Braithwaite, 1972; Burrows & Davies, 1971). In addition, TCAs can worsen s reducing the seizure threshold (Brodie, 1992). These drugs also have additive CNS and respiratory depressa

3) Severity: minor

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Monitor for efficacy of antidepressant effect. Increases in tricyclic antidepressant do required. Additionally, monitor for toxicity when either drug is added to or withdrawn from therapy. Serum con be of value in determining appropriate dosage.

7) Probable Mechanism: increased tricyclic antidepressant metabolism

8) Literature Reports

a) The pharmacokinetics of a single oral dose of desipramine (100 mg) were studied in eight epileptic pa treated with phenobarbital and in eight drug-free healthy controls (Spina et al, 1996). All subjects were e metabolizers with respect to the genetically determined CYP2D6-related metabolic polymorphism. Comp epileptic patients exhibited lower peak plasma desipramine concentrations (74 nmol/L vs. 107 nmol/L), s area under the concentration-time curve values (1943 nmol/L/h vs. 3234 nmol/L/h), and shorter desipran half-lives (15.1 h vs. 20.6 h). All barbiturates are believed to have similar effects leading to induction of h and the 2D6 isozyme is believed to be important in the metabolism of most or all TCAs. Thus, similar eff expected with any combination of TCA and barbiturate.

3.5.1.H Amphetamine

1) Interaction Effect: hypertension, other cardiac effects, and CNS stimulation
2) Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been reporte enhanced amphetamine effects from the release of norepinephrine (Beaumont, 1973d; Raisfeld, 1972). A sin also occur with all drugs that have amphetamine-like effects. Acute elevations in blood pressure have been n (Flemenbaum, 1971a). Some amphetamine-like drugs may inhibit the metabolism of TCAs, although most co not been studied. When amphetamine analogs are being used to treat obesity, it should be noted that TCAs f moderate weight gain (Russ & Ackerman, 1988). False positive urine tests for amphetamines have been repo therapy with some TCAs (Merigian & Browning, 1993). Caution is advised when concurrent administration of agents and TCAs is warranted. The patient should be closely monitored for increased cardiovascular effects dysrhythmias).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other sympatho could lead to hypertension, increased cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) o Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral t Flemenbaum, 1972). Use caution if such therapy is warranted. Monitor the patient closely for hypertension ar
7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission
8) Literature Reports
a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agen coadministration of d-amphetamine with TCAs such as desipramine or protriptyline results in sustained i amphetamine concentration in the brain (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info DEXE sustained-release oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006).
b) Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism o antidepressants, such as imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transde 2006).
c) Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases i such that the hypotensive effects induced by TCAs may lead to blood pressures as high as 170/120 mm of combined therapy. Discontinuation of the methylphenidate usually results in the blood pressure return normotensive levels; reinstitution of the methylphenidate resulted in further blood pressure elevation (Fle Flemenbaum, 1972).
d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine g four weeks, were given fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transie clinical improvement. However, fenfluramine more than doubled steady-state plasma levels of desiprami 1990).
e) There have been claims based on uncontrolled studies that a better antidepressant response may oc therapy (Garrettson et al, 1969). However, a systemic review of stimulants in the treatment of depressior although uncontrolled studies were generally positive, the ten placebo-controlled studies of stimulant dru depression, with one exception, indicated little advantage of drug over placebo and did not appear to be conventional antidepressants in primary depression (Satel & Nelson, 1989).

3.5.1.I Amprenavir

1) Interaction Effect: increased tricyclic serum concentrations and potential toxicity (anticholinergic effects, se cardiac arrhythmias)
2) Summary: Coadministered amprenavir may increase serum concentrations of tricyclic antidepressants, ca risk of arrhythmias or other serious adverse effects. Currently no interaction study has been conducted. Ampr metabolized by cytochrome P450 3A4 enzymes in addition to being a CYP3A4 inhibitor, and tricyclics may pa this pathway for metabolism. Plasma concentrations of the tricyclic should be closely monitored and dose adj accordingly in patients also receiving amprenavir (Prod Info Agenerase(R), 2000).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: If concomitant therapy with amprenavir and a tricyclic antidepressant is unavoidable concentrations of the tricyclic should be closely monitored and dose adjustments made accordingly. Also mon signs and symptoms of tricyclic toxicity (anticholinergic effects, sedation, confusion, cardiac arrhythmias).
7) Probable Mechanism: inhibition of cytochrome P450-mediated tricyclic metabolism

3.5.1.J Anisindione

1) Interaction Effect: increased risk of bleeding
2) Summary: Tricyclic antidepressants (TCAs) may increase the half-life and bioavailability of oral anticoagul 1970k; Williams et al, 1976k). Considerable interindividual differences may be found (Pond et al, 1975k).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: In patients receiving tricyclic antidepressants and oral anticoagulant therapy, the pr ratio or INR (international normalized ratio) should be closely monitored with the addition and withdrawal of th and should be periodically reassessed during concurrent therapy. Achieving a stable drug regimen which pro level of anticoagulation may be difficult in patients on this combination, and frequent adjustments of the antic

be required.
7) Probable Mechanism: decreased anisindione metabolism; increased anisindione absorption
8) Literature Reports
a) In a study of healthy volunteers, the concurrent use of nortriptyline or amitriptyline resulted in an incre levels and an increase in the plasma half-life of dicumarol, although the effect was not consistent in all su 1975j). This effect was not observed with warfarin.
b) A single oral dose of bishydroxycoumarin after 8 days of nortriptyline resulted in a significantly prolon decreased volume of distribution of the coumarin anticoagulant in 6 healthy volunteers (Vesell et al, 197(mechanism of action was suggested to be reduced bishydroxycoumarin metabolism and/or altered coum
c) Drug dosing was studied in 16 patients on long-term anticoagulant therapy who used concurrent TCA 1976j). TCAs affected the stability of anticoagulant control leading to frequent changes in the doses of ar Inhibition of coumarin metabolism was the postulated mechanism.

3.5.1.K Aprindine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Class I antiarrhythmics have been shown to prolong the QTc interval at the recommended ther Even though no formal drug interaction studies have been done, the coadministration of Class I antiarrhythmi known to prolong the QTc interval, including tricyclic antidepressants, is not recommended (Prod Info Tambo acetate, 1998; Larochelle et al, 1984; Scagliotti et al, 1982).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of a Class I antiarrhythmic and a tricyclic antidepress recommended.
7) Probable Mechanism: additive effects on QT prolongation
8) Literature Reports
a) EKG effects reported in patients receiving therapeutic doses of tricyclic antidepressants include incre prolonged PR interval, intraventricular conduction delays, increased corrected QT interval (QTc) and flat (Marshall & Forker, 1982q).
b) A 68-year-old man suffering from agitated major depression was begun on a dose of desipramine 12 produced a subtherapeutic serum level of 442 nmol/L (therapeutic range = 500 to 1000 nmol/L). An incre mg daily produced excellent clinical response with no side effects. He developed atrial fibrillation and flut mg daily was added to his therapy, and desipramine was discontinued. His arrhythmia was suppressed v propafenone 150 mg twice daily and 300 mg at bedtime. Desipramine 150 mg daily was again begun, at experienced dry mouth, sedation, and shakiness; the desipramine serum level was measured at 2092 nr desipramine was discontinued for five days, the side effects ceased, and desipramine therapy was resur The desipramine serum level was measured at 1130 nmol/L (Katz, 1991).

3.5.1.L Aprobarbital

1) Interaction Effect: possible decreased tricyclic antidepressant serum concentrations and possible additive
2) Summary: Concomitant barbiturate and tricyclic antidepressant (TCA) therapy may result in increased me TCA. There have been scattered reports of individuals with decreased serum levels of TCAs in the presence (Moody et al, 1977; Silverman & Braithwaite, 1972; Burrows & Davies, 1971). In addition, TCAs can worsen s reducing the seizure threshold (Brodie, 1992). These drugs also have additive CNS and respiratory depressa
3) Severity: minor
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor for efficacy of antidepressant effect. Increases in tricyclic antidepressant do required. Additionally, monitor for toxicity when either drug is added to or withdrawn from therapy. Serum con be of value in determining appropriate dosage.
7) Probable Mechanism: increased tricyclic antidepressant metabolism
8) Literature Reports
a) The pharmacokinetics of a single oral dose of desipramine (100 mg) were studied in eight epileptic pa treated with phenobarbital and in eight drug-free healthy controls (Spina et al, 1996). All subjects were e metabolizers with respect to the genetically determined CYP2D6-related metabolic polymorphism. Comp epileptic patients exhibited lower peak plasma desipramine concentrations (74 nmol/L vs. 107 nmol/L), s area under the concentration-time curve values (1943 nmol/L/h vs. 3234 nmol/L/h), and shorter desipran half-lives (15.1 h vs. 20.6 h). All barbiturates are believed to have similar effects leading to induction of h and the 2D6 isozyme is believed to be important in the metabolism of most or all TCAs. Thus, similar effe expected with any combination of TCA and barbiturate.

3.5.1.M Arbutamine

1) Interaction Effect: unreliable arbutamine test results
2) Summary: Because tricyclic antidepressants may affect heart rate, arbutamine should not be administered receiving a tricyclic antidepressant, since arbutamine test results may be unreliable (Prod Info GenESA(R), 1
3) Severity: moderate
4) Onset: rapid
5) Substantiation: probable

6) Clinical Management: Arbutamine should not be administered to a patient receiving tricyclic antidepressar
7) Probable Mechanism: alteration of heart rate by the tricyclic antidepressant

3.5.1.N Arformoterol

1) Interaction Effect: an increased risk of cardiovascular excitation
2) Summary: Concurrent administration of arformoterol with a tricyclic antidepressant (TCA) may lead to pote arformoterol's adrenergic effects on the cardiovascular system. Therefore, extreme caution is advised if arfor administered to patients who are being treated with a TCA (Prod Info BROVANA(TM) inhalation solution, 200 patients closely for adverse cardiovascular effects.
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Extreme caution and close observation for adverse cardiovascular effects are warra arformoterol is administered concurrently with a tricyclic antidepressant (TCA) as the cardiovascular effects o be potentiated by TCAs (Prod Info BROVANA(TM) inhalation solution, 2006).
7) Probable Mechanism: potentiation of cardiovascular effects

3.5.1.O Arsenic Trioxide

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Any drug known to have the potential to prolong the QT interval should not be used with arseni pharmacodynamic interactions can occur between arsenic trioxide and potentially arrhythmogenic agents suc antidepressants that prolong the QT interval (Prod Info Trisenox(R), 2000a). Even though no formal drug inte have been done, the coadministration of arsenic trioxide and other drugs known to prolong the QTc interval, i antidepressants, is not recommended (Prod Info Elavil(R), 1999l; Marshall & Forker, 1982ai).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of arsenic trioxide and other drugs that may prolong such as tricyclic antidepressants is not recommended.
7) Probable Mechanism: additive effects on QT prolongation
8) Literature Reports
a) An increased incidence in sudden death was observed in six out of 53 patients with cardiac disease r amitriptyline, compared to zero out of 53 in the control group using a hospital based information system. recommended that amitriptyline not be used in patients with underlying cardiac disease except when dep debilitating and no other drugs were helpful (Moir et al, 1972a; Coull et al, 1970a).
b) QT/QTc prolongation should be expected during treatment with arsenic trioxide and torsade de pointe complete heart block has been reported. Over 460 ECG tracings from 40 patients with refractory or relap with arsenic trioxide were evaluated for QTc prolongation. Sixteen of 40 patients (40%) had at least one QTc interval greater than 500 msec. Prolongation of the QTc was observed between 1 and 5 weeks afte infusion, and then returned towards baseline by the end of 8 weeks after arsenic trioxide infusion. In thes evaluations, women did not experience more pronounced QT prolongation than men, and there was no (Prod Info Trisenox(R), 2000).

3.5.1.P Astemizole

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Tricyclic antidepressants have been shown to prolong the QTc interval at the recommended th Even though no formal drug interaction studies have been done, the coadministration of astemizole and othe prolong the QTc interval, including tricyclic antidepressants, is not recommended (Prod Info Elavil(R), 1999m Hismanal(R), 1996).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of astemizole and agents that prolong the QT interva antidepressants, is not recommended.
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) A comprehensive discussion of the cardiovascular effects of tricyclic antidepressants has been prese Forker, 1982aj). Electrocardiogram effects reported in patients receiving therapeutic doses of tricyclic an include increased heart rate, prolonged PR interval, intraventricular conduction delays, increased correct (QTc) and flattened T waves.

3.5.1.Q Atazanavir

1) Interaction Effect: increased plasma concentrations of tricyclic antidepressants (drowsiness, hypotension,
2) Summary: Coadministration of atazanavir and tricyclic antidepressants has not been studied. However, th of atazanavir and tricyclic antidepressants has the potential to produce serious and/or life-threatening advers Reyataz(TM), 2003).
3) Severity: major
4) Onset: unspecified

5) Substantiation: theoretical
6) Clinical Management: If atazanavir and tricyclic antidepressants are used concomitantly, monitor patient f and symptoms of tricyclic antidepressant toxicity (hypotenstion, akathisia, anticholinergic effects, sedation, cc arrhythmias).
7) Probable Mechanism: unknown

3.5.1.R Atomoxetine

1) Interaction Effect: an increase in atomoxetine steady-state plasma concentrations
2) Summary: Atomoxetine is primarily metabolized by the cytochrome P450 2D6 (CYP 2D6) pathway to 4-hy In extensive metabolizers, atomoxetine steady-state plasma concentrations are increased with selective inhib such as imipramine. The exposure is similar to that observed in poor metabolizers. In extensive metabolizers imipramine, the area under the concentration-time curve of atomoxetine is approximately 6- to 8-fold greater, plasma concentration at steady-state is about 3- to 4-fold greater than atomoxetine alone (Prod Info Strattera
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Dosage adjustment of atomoxetine may be necessary when coadministered with im
7) Probable Mechanism: inhibition of cytochrome P450 2D6-mediated metabolism of atomoxetine by imipran

3.5.1.S Azimilide

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Cases of QTc prolongation and/or torsades de pointes have been reported with all Class III ant agents, including acecainide (Chow et al, 1984), amiodarone (Faggiano et al, 1996), azimilide (Corey et al, 1 (Gilman et al, 1985), ibutilide (Rodriguez et al, 2001), sematilide (Singh, 1996), dofetilide (Allen et al, 2002), a & Runge, 2001). Even though no formal drug interaction studies have been done, the coadministration of Cla antiarrhythmics and other drugs known to prolong the QTc interval, including tricyclic antidepressants, is not (Yamreudeewong et al, 2003a; Prod Info Corvert(R), 2000).
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of a Class III antiarrhythmic and a tricyclic antidepres recommended.
7) Probable Mechanism: additive QT prolongation
8) Literature Reports
a) EKG effects reported in patients receiving therapeutic doses of tricyclic antidepressants include incre prolonged PR interval, intraventricular conduction delays, increased corrected QT interval (QTc) and flat (Marshall & Forker, 1982ab).
b) Concurrent use of Class III antiarrhythmic agents, and other drugs that can prolong the QT interval, s antidepressants, is not recommended. Dofetilide should be stopped for at least 2 days before any intera initiated. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised (Yam 2003).

3.5.1.T Belladonna

1) Interaction Effect: excessive anticholinergic activity (severe dry mouth, constipation, decreased urination, sedation, blurred vision)
2) Summary: The anticholinergic activity of the active alkaloids present in belladonna may predispose the pa anticholinergic activity if taken with tricyclic antidepressants. Belladonna contains L-hyoscyamine, atropine, a with a total alkaloid content of at least 0.3% in the leaves and 0.5% in the roots (Blumenthal et al, 1998). Bec typically available as a homeopathic preparation, the clinical severity of the interaction with tricyclic antidepre Caution is advised.
3) Severity: minor
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Excessive anticholinergic activity may be manifested by dry mouth, constipation, ur tachycardia, decreased sweating, mydriasis, blurred vision, elevated temperature, muscular weakness, and s effects are noted, belladonna should be discontinued immediately. In severe cases, paralytic ileus, confusion agitation, delusions, delirium, and paranoia may be encountered as well as tachycardia, dysrhythmia, and hy severe cases, immediate medical attention should be obtained.
7) Probable Mechanism: additive anticholinergic effect

3.5.1.U Belladonna Alkaloids

1) Interaction Effect: excessive anticholinergic activity (severe dry mouth, constipation, decreased urination, sedation, blurred vision)
2) Summary: The anticholinergic activity of the active alkaloids present in belladonna may predispose the pa anticholinergic activity if taken with tricyclic antidepressants. Belladonna contains L-hyoscyamine, atropine, a with a total alkaloid content of at least 0.3% in the leaves and 0.5% in the roots (Blumenthal et al, 1998). Bec typically available as a homeopathic preparation, the clinical severity of the interaction with tricyclic antidepre Caution is advised.

3) Severity: minor
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Excessive anticholinergic activity may be manifested by dry mouth, constipation, ur tachycardia, decreased sweating, mydriasis, blurred vision, elevated temperature, muscular weakness, and s effects are noted, belladonna should be discontinued immediately. In severe cases, paralytic ileus, confusion agitation, delusions, delirium, and paranoia may be encountered as well as tachycardia, dysrhythmia, and hy severe cases, immediate medical attention should be obtained.
7) Probable Mechanism: additive anticholinergic effect

3.5.1.V Bepridil
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: In US clinical trials, the QT and QTc intervals were commonly prolonged by bepridil in a dose-r (Prod Info Vascor(R), 2000). Tricyclic antidepressants (TCAs) have been shown to prolong the QTc interval a recommended therapeutic dose (Marshall & Forker, 1982w).
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Concurrent use of bepridil and other drugs which may prolong the QTc interval, incl antidepressants, is contraindicated.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.W Bethanidine
1) Interaction Effect: decreased antihypertensive effectiveness
2) Summary: Antidepressants inhibit the uptake of bethanidine at its site of action in the adrenergic neuron. T may last for several days after discontinuation of the antidepressant (Skinner et al, 1969a; Avery, 1973; Feag
3) Severity: moderate
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The combination of bethanidine and imipramine, as well as other tricyclic antidepres should be avoided. An alternative antihypertensive agent should be considered.
7) Probable Mechanism: decreased uptake of bethanidine into adrenergic neurons
8) Literature Reports
a) Adequate control of hypertension was reported in only 2 of 8 adult hypertensive patients who receive debrisoquine concurrently with a tricyclic antidepressant. In 24 control patients given the same drugs wit antidepressants, blood pressure control was achieved in 18. Withdrawal of antidepressant therapy in sev resulted in postural hypotension that necessitated a reduction in dosage of bethanidine or debrisoquine (1969).

3.5.1.X Bretylium
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Cases of QTc prolongation and/or torsades de pointes have been reported with all Class III ant agents, including acecainide (Chow et al, 1984), amiodarone (Faggiano et al, 1996), azimilide (Corey et al, 1 (Gilman et al, 1985), ibutilide (Rodriguez et al, 2001), sematilide (Singh, 1996), dofetilide (Allen et al, 2002), a & Runge, 2001). Even though no formal drug interaction studies have been done, the coadministration of Cla antiarrhythmics and other drugs known to prolong the QTc interval, including tricyclic antidepressants, is not (Yamreudeewong et al, 2003a; Prod Info Corvert(R), 2000).
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of a Class III antiarrhythmic and a tricyclic antidepres recommended.
7) Probable Mechanism: additive QT prolongation
8) Literature Reports
a) EKG effects reported in patients receiving therapeutic doses of tricyclic antidepressants include incre prolonged PR interval, intraventricular conduction delays, increased corrected QT interval (QTc) and flat (Marshall & Forker, 1982ab).
b) Concurrent use of Class III antiarrhythmic agents, and other drugs that can prolong the QT interval, s antidepressants, is not recommended. Dofetilide should be stopped for at least 2 days before any interac initiated. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised (Yam 2003).

3.5.1.Y Bupropion
1) Interaction Effect: increased imipramine plasma level
2) Summary: Bupropion was reported to decrease clearance and increase plasma levels of imipramine and i metabolite desipramine in a 64-year-old woman (Shad & Preskorn, 1997a). Coadministration of bupropion wi metabolized by the cytochrome P450 2D6 isoenzyme, such as imipramine, should be approached with cautic initiated at the lower end of the dose range of imipramine. If bupropion is added to the treatment regimen of a

receiving imipramine, a decrease in the dose of imipramine should be considered (Prod Info Wellbutrin XL(TM Zyban(R), 2000).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: When imipramine is given with bupropion, monitor for signs of imipramine toxicity o imipramine plasma concentrations. Coadministration of imipramine with bupropion should be approached wit should be initiated at the lower end of the dose range of imipramine. If bupropion is added to the treatment re already receiving imipramine, consider decreasing the dose of imipramine.
7) Probable Mechanism: inhibition of cytochrome P450 2D6-mediated imipramine metabolism
8) Literature Reports
a) Bupropion was reported to decrease clearance and increase plasma levels of imipramine and its prim desipramine in a 64-year-old woman. This patient was treated with imipramine for 8 years prior to additio therapy. Estimated imipramine clearance decreased from 1.7 mL/min without bupropion to 0.73 mL/min Additional studies are needed to confirm this observation (Shad & Preskorn, 1997).

3.5.1.Z Butabarbital
1) Interaction Effect: possible decreased tricyclic antidepressant serum concentrations and possible additive
2) Summary: Concomitant barbiturate and tricyclic antidepressant (TCA) therapy may result in increased me TCA. There have been scattered reports of individuals with decreased serum levels of TCAs in the presence (Moody et al, 1977; Silverman & Braithwaite, 1972; Burrows & Davies, 1971). In addition, TCAs can worsen s reducing the seizure threshold (Brodie, 1992). These drugs also have additive CNS and respiratory depressa
3) Severity: minor
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor for efficacy of antidepressant effect. Increases in tricyclic antidepressant do required. Additionally, monitor for toxicity when either drug is added to or withdrawn from therapy. Serum con be of value in determining appropriate dosage.
7) Probable Mechanism: increased tricyclic antidepressant metabolism
8) Literature Reports
a) The pharmacokinetics of a single oral dose of desipramine (100 mg) were studied in eight epileptic pa treated with phenobarbital and in eight drug-free healthy controls (Spina et al, 1996). All subjects were ex metabolizers with respect to the genetically determined CYP2D6-related metabolic polymorphism. Comp epileptic patients exhibited lower peak plasma desipramine concentrations (74 nmol/L vs. 107 nmol/L), s area under the concentration-time curve values (1943 nmol/L/h vs. 3234 nmol/L/h), and shorter desipram half-lives (15.1 h vs. 20.6 h). All barbiturates are believed to have similar effects leading to induction of h and the 2D6 isozyme is believed to be important in the metabolism of most or all TCAs. Thus, similar effe expected with any combination of TCA and barbiturate.

3.5.1.AA Butalbital
1) Interaction Effect: decreased efficacy of imipramine
2) Summary: A 44-year old female on imipramine therapy experienced a relapse of her depressive disorder a butalbital-containing product for headaches. Her imipramine concentration decreased by approximately 50% attributed to an induction of cytochrome P450 1A2 enzymes caused by butalbital (Garey et al, 1997a).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Imipramine serum levels should be measured one week after the addition of butalbi dosage adjustments should be based on the results of the imipramine level and on the patient's response.
7) Probable Mechanism: induction of imipramine metabolism by butalbital
8) Literature Reports
a) A 44-year old woman was admitted to a psychiatric unit for an exacerbation of her depression. At the antidepressant regimen included imipramine 300 mg daily, with an imipramine concentration of 174 ng/m desipramine concentration of 134 ng/mL. These levels were considered within the normal range, and we her past concentrations. Because of recurring headaches, she was prescribed a product containing buta required 8 tablets (butalbital 400 mg) daily to control her headaches. The patient progressed well until tw hospital stay, when she again experienced a relapse of her depressive disorder. Concentrations at this ti imipramine 48 ng/mL and desipramine 122 ng/mL. Butalbital was the most reasonable explanation for th imipramine levels, so it was discontinued and imipramine was increased to 325 mg daily. However, furth documenting a return to normal imipramine concentrations were futile, since the patient restarted the but product from her stockpile at home (Garey et al, 1997).

3.5.1.AB Butalbital
1) Interaction Effect: possible decreased tricyclic antidepressant serum concentrations and possible additive
2) Summary: Concomitant barbiturate and tricyclic antidepressant (TCA) therapy may result in increased me TCA. There have been scattered reports of individuals with decreased serum levels of TCAs in the presence (Moody et al, 1977; Silverman & Braithwaite, 1972; Burrows & Davies, 1971). In addition, TCAs can worsen s reducing the seizure threshold (Brodie, 1992). These drugs also have additive CNS and respiratory depressa

3) Severity: minor
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor for efficacy of antidepressant effect. Increases in tricyclic antidepressant do required. Additionally, monitor for toxicity when either drug is added to or withdrawn from therapy. Serum con be of value in determining appropriate dosage.
7) Probable Mechanism: increased tricyclic antidepressant metabolism
8) Literature Reports
a) The pharmacokinetics of a single oral dose of desipramine (100 mg) were studied in eight epileptic pa treated with phenobarbital and in eight drug-free healthy controls (Spina et al, 1996). All subjects were ex metabolizers with respect to the genetically determined CYP2D6-related metabolic polymorphism. Comp epileptic patients exhibited lower peak plasma desipramine concentrations (74 nmol/L vs. 107 nmol/L), s area under the concentration-time curve values (1943 nmol/L/h vs. 3234 nmol/L/h), and shorter desipran half-lives (15.1 h vs. 20.6 h). All barbiturates are believed to have similar effects leading to induction of h and the 2D6 isozyme is believed to be important in the metabolism of most or all TCAs. Thus, similar effe expected with any combination of TCA and barbiturate.

3.5.1.AC Cannabis

1) Interaction Effect: tachycardia and delirium
2) Summary: Concomitant tetrahydrocannabinol and tricyclic antidepressant therapy has increased the hear delirium beyond that expected with either drug alone (Wilens et al, 1997a; Hillard & Vieweg, 1983a).
3) Severity: moderate
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Caution is advised if patients use cannabis with a tricyclic antidepressant. Monitor h closely.
7) Probable Mechanism: possibly due to beta-adrenergic effect of cannabis coupled with the anticholinergic antidepressants
8) Literature Reports
a) A 21-year-old female receiving oral nortriptyline 30 milligrams at bedtime for 9 months developed ma tachycardia (160 beats/minute) within 30 minutes of smoking a cannabis cigarette. The patient's heart ra beats/minute before smoking the cannabis. She had used cannabis many times before starting the nortri effects (Hillard & Vieweg, 1983).
b) Four cases of tachycardia, cognitive changes, and delirium have been reported in adolescent males t tricyclic antidepressants who smoked marijuana. One of the four cases was evaluated by a physician, th accounts of the event. The toxic effects were considered by the reporters to have resulted from a drug in they occurred with lower doses of marijuana than are common in other reports of marijuana toxicity (usu mg). In case 1, a 16-year-old male taking nortriptyline 75 mg/day presented with tachycardia (130 beats/ confusion, and short-term memory loss 30 minutes after smoking one marijuana cigarette. Symptoms re spontaneously after 24 hours. In case 2, and 18-year-old male taking desipramine 200 mg/day presente smoking marijuana with symptoms of edginess, severe dry mouth, lightheadedness, confusion, short-ter impairment, and tachycardia (110 beats/minute). Symptoms resolved within 48 hours. Case 3, a 15-year desipramine 150 mg/day and sertraline 50 mg/day, reported mood lability, irritability, and a racing heart a marijuana cigarettes which resolved after 16 hours. Case 4, a 16-year-old male taking desipramine and hallucinations, confusion, mild shortness of breath, and elevated heart rate after smoking marijuana. This than the effect he experienced prior to taking desipramine (Wilens et al, 1997).

3.5.1.AD Carbamazepine

1) Interaction Effect: decreased imipramine effectiveness
2) Summary: In a retrospective study of 36 children suffering from hyperactivity secondary to attention deficit antidepressant levels (imipramine and its metabolite desipramine) were decreased by 50% in children receivi compared to levels obtained with imipramine alone (Brown et al, 1990a).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor for clinical efficacy of the imipramine therapy and for any signs of toxicity of Serum levels of both agents should be considered when either agent is added or discontinued, with appropria adjustments made accordingly.
7) Probable Mechanism: increased imipramine metabolism
8) Literature Reports
a) In a retrospective study, of 36 children with attention deficit hyperactivity disorder, the average plasma imipramine was significantly lower in patients treated with carbamazepine concurrently. The average dos was 1.3 mg/kg in patients receiving imipramine alone, compared to an imipramine dose of 1.8 mg/kg in p both imipramine and carbamazepine. The plasma level of imipramine, desipramine, and total tricyclic ant plasma levels were significantly lower in patients treated with carbamazepine concurrently. The dose of i need to be increased if carbamazepine is added to therapy and the dose of imipramine may need to be carbamazepine is stopped (Brown et al, 1990).
b) Combination therapy with carbamazepine decreases steady-state total serum concentrations of imipr

concentrations of desipramine. Thirteen patients were treated with imipramine 2 mg/kg/day for 3 weeks, carbamazepine 400 mg/day was added. The ratios of total concentrations of imipramine to desipramine and two weeks after carbamazepine intake (0.7 +/- 0.41 versus 0.63 +/- 0.36; p greater than 0.05). Free imipramine and desipramine were elevated after the addition of carbamazepine. Despite lowever imipran desipramine total concentrations, the combination treatment with carbamazepine in depressed patients i tolerated. Dosage increase of imipramine does not appear to be necessary in the depressed patients inc (Szymura-Oleksiak et al, 2001).

3.5.1.AE Chloral Hydrate

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Chloral hydrate and tricyclic antidepressants have been shown to prolong the QTc interval at th therapeutic dose (Young et al, 1986; Marshall & Forker, 1982m). Even though no formal drug interaction stud done, the coadministration of drugs known to prolong the QTc interval is not recommended.
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of chloral hydrate and a tricyclic antidepressant is no
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.AF Chloroquine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Chloroquine can prolong the QT interval in some patients, which may result in ventricular tachy fibrillation, and torsades de pointes. Because tricyclic antidepressants may also prolong the QT interval and i arrhythmias, the concurrent administration of chloroquine and tricyclic antidepressants is not recommended ((R), 1999; Marshall & Forker, 1982y).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of chloroquine and a tricyclic antidepressant is not re
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.AG Chlorotrianisene

1) Interaction Effect: attenuation of antidepressant effectiveness; tricyclic toxicity (drowsiness, hypotension, a
2) Summary: In isolated cases, the pharmacologic effects of tricyclic antidepressants may be increased or de estrogens (Somani & Khurana, 1973e), with paradoxical loss of antidepressant effect yet tricyclic toxicity beir simultaneously (Prange, 1972e). The effects of the interaction appear to be estrogen dose-related (Khurana, be of clinical importance primarily in patients previously stabilized on tricyclic therapy who are being started o (Krishnan et al, 1984e).
3) Severity: minor
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: If signs or symptoms of altered tricyclic response are noted, dose adjustment down estrogen or tricyclic component may be successful in restoring effectiveness or resolving toxicity. However, d may be required.
7) Probable Mechanism: unknown
8) Literature Reports

a) Some studies evaluated the qualitative effects of concomitant administration of estrogen and TCAs. I depressed female prisoners were randomly assigned to 4 treatment groups. Ten patients received place imipramine (150 mg daily) and placebo, five patients received imipramine (150 mg daily) and ethinyl estr daily), while five patients received imipramine (150 mg daily) and ethinyl estradiol (25 mcg daily). The ter received placebo did not improve over the six weeks of the study. The ten patients taking estrogen and i demonstrated a significantly greater improvement in symptoms than did the ten patients taking imipramir after two weeks, the five patients who received imipramine and high-dose estrogen had not improved as patients receiving imipramine and low-dose estrogen. The only side effect reported was drowsiness, whi the patients taking imipramine. Following the discontinuation of ethinyl estradiol, a time period of two wee for the high-dose estrogen group to do as well as the low-dose group. This effect was attributed to the pr estrogen in the high-dose group. In another group, five women received imipramine 150 mg and ethinyl e daily did not improve as much as ten patients receiving only imipramine. Also, the patients on the combi side-effects including lethargy, coarse tremor and systolic hypotension (Prange, 1972d).

b) A case reported demonstrated an interaction in a 32-year-old female taking conjugated estrogens 2.5 imipramine 100 mg (Khurana, 1972d). The patient developed lethargy, tremors, and signs of depersonal years of therapy, the patient increased her estrogen dose to 5 mg and then 7.5 mg daily. The patient bec had constant headaches, and low normal blood pressure. All lab work was normal. Upon discontinuing th side-effects abated. Some investigators have proposed that the side effects resulted from enhanced TCA secondary to estrogen inhibition of hepatic microsomal enzymes (Somani & Khurana, 1973d).

c) In a study women received clomipramine and oral contraceptives or clomipramine alone. At the begin there were 30 women taking the combination, but 12 subsequently dropped out. The 18 patients on the matched with 18 patients taking clomipramine alone. No significant difference was noted in the patients'

clomipramine. It was proposed that there was no significant difference in side-effects between the groups groups were matched after patients had dropped out of the study. Had the patients been matched prior t different conclusions may have been drawn (Beaumont, 1973b).

d) The effects of oral contraceptives on clomipramine were studied in 42 women between the ages of 18 three women took clomipramine 25 mg at bedtime while 19 took clomipramine 25 mg at bedtime with ora Over the four-week study, three control patients (two due to side-effects) and five in the experimental gro side-effects) dropped out. Venous blood samples were drawn at weekly intervals for measurement of ser concentrations. No difference in serum concentrations was noted between the groups. However, this res due to the low dose of clomipramine given (Luscombe & John, 1980b).

e) The onset of akathisia was reported in 3 patients receiving conjugated estrogens and tricyclic antidep concurrently. A 24-year-old patient receiving clomipramine 120 mg daily for anorexia nervosa and conjug 1.25 mg daily for amenorrhea developed restless legs and a constant desire to move continuously. Estro discontinued and benztropine 2 mg was administered, resulting in marked reduction and resolution withi Akathisia and disorientation developed in a 55-year-old patient on conjugated estrogen 1.25 mg daily wh amitriptyline 50 mg daily for depression. Within hours of amitriptyline, the patient was confused, restless, inner desire to move continuously. Symptoms disappeared after discontinuing amitriptyline. A third case reported in a 35-year-old patient who received conjugated estrogen 1.25 mg daily and amitriptyline 50 m developed within a few hours after taking the first dose of amitriptyline and resolved within 48 hours follo discontinuation of the antidepressant (Krishnan et al, 1984d).

f) The absolute bioavailability of imipramine increased in women who received low-dose oral contracept less of ethinyl estradiol) from 27% to 44% (p less than 0.05) as evident by an increase in the area under concentration time curve (Abernethy et al, 1984c).

g) Estrogens may inhibit the oxidation of TCAs by affecting hepatic microsomal enzymes (John et al, 19 are metabolized via oxidation and conjugation pathways. Inhibition of the oxidation of TCAs could result and toxicity due to decreased clearance. Estrogens are suspected of possessing other effects on the cer system resulting in an antidepressant effect (Oppenheim, 1983b).

3.5.1.AH Cimetidine

1) Interaction Effect: imipramine toxicity (dry mouth, urinary retention, blurred vision)

2) Summary: Concomitant cimetidine and imipramine therapy has resulted in inhibition of the metabolism of leading to prolonged half-life and elevated serum concentrations (Miller & Macklin, 1983a; Wells et al, 1986a; 1984b) and adverse effects (Miller & Macklin, 1983a; Sutherland et al, 1987; Wells et al, 1986a).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Imipramine levels should be considered within the first few days of starting or disco cimetidine. An alternative H2 blocker that does not appear to impair the metabolism of imipramine, such as ra famotidine, might be considered.

7) Probable Mechanism: decreased imipramine metabolism

8) Literature Reports

a) In a case report, a 32-year-old woman concurrently on cimetidine 300 mg four times daily for abdomi exhibited severe anticholinergic side effects and orthostatic hypotension with the addition of imipramine, (Miller & Macklin, 1983). Upon rechallenge, imipramine pharmacokinetics with and without cimetidine we concurrent administration of cimetidine 300 mg four times daily and imipramine 100 mg daily, steady stat life for imipramine was 44 hours and plasma clearance 210 mL/minute. The ratio of imipramine to desipr calculated to be 2.6 (normal ratio 1 to 1.2). Upon discontinuation of cimetidine the elimination half-life of i decreased to 23 hours and the plasma clearance increased to 355 mL/minute. The patient was able to c without complaints of anticholinergic side effects without cimetidine. Cimetidine also was reported to incr bioavailability of oral imipramine doses in six healthy volunteers, in addition to impairing imipramine clea increasing the desipramine area under the curve (Abernethy et al, 1984a).

b) Six healthy young (24 to 25 year-old) volunteers participated in four randomly sequenced clinical trial effects of cimetidine administration on the pharmacokinetics of imipramine. Each clinical trial was separa week. Trial 1: 12.5 mg of imipramine was infused over 30 minutes. Trial 2: 300 mg of cimetidine was adm every six hours, starting 12 hours prior to the imipramine dose (12.5 mg intravenously infused over 30 m continued for 96 hours after the imipramine dose. Trial 3: 50 mg of imipramine was administered orally fo overnight fast, with the fast continued for three hours following administration of the drug. Trial 4: Cimetic administered as described in trial 2 and 50 mg imipramine was administered oral as described in trial 3. half-life for imipramine was significantly increased (15.5 hours to 22.1 hours) during cimetidine therapy ir administration group and increased (15.3 hours to 20.7 hours), but not significantly, in the oral administra Absolute bioavailability for orally administered imipramine nearly doubled (40% to 75%) during cimetidine on these results patients receiving concurrent cimetidine and imipramine therapy should have a 50% to 6 imipramine dose in order to avoid potential imipramine toxicity or should have their plasma imipramine/d monitored closely (Abernethy & Kerzner, 1984b).

c) Concomitant administration of cimetidine and imipramine was reported to result in psychosis (in the p sensorium) in a 38-year-old woman with major depression. Discontinuation of both drugs resulted in reso and depression within 72 hours. However, it is unclear if this patient's psychotic features were induced s combination of these two agents (Miller et al, 1987).

d) The impaired elimination of these tricyclic antidepressants is rather rapid and new steady state serum

would be expected to be achieved in three to five days after initiation of cimetidine therapy. It is suggeste doses be adjusted downward by 50% when cimetidine is given concurrently with further adjustments in c determined by plasma level monitoring (Wells et al, 1986).

e) Using microsomes from 4 human livers, cimetidine was shown to inhibit the demethylation of imipram hydroxylation of desmethylimipramine (Spina & Koike, 1986).

3.5.1.AI Cisapride

1) Interaction Effect: cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Cisapride therapy has resulted in serious cardiac arrhythmias, including ventricular tachycardia fibrillation, torsades de pointes, and QT prolongation. Because tricyclic antidepressant agents also may prolo and increase the risk of arrhythmias, the concurrent administration of cisapride with a drug from this class is c (Prod Info Propulsid(R), 2000).

3) Severity: contraindicated

4) Onset: rapid

5) Substantiation: theoretical

6) Clinical Management: The concurrent use of cisapride and tricyclic antidepressants is contraindicated.

7) Probable Mechanism: additive effects on QT prolongation

3.5.1.AJ Citalopram

1) Interaction Effect: an increase in the bioavailability and half-life of desipramine, the major metabolite of im

2) Summary: Imipramine pharmacokinetics were not influenced by citalopram when the two were coadminist Celexa(TM), 2002; Gram et al, 1993a). However, citalopram may increase exposure to desipramine, the majo imipramine. Clinical events have not been reported and, in an isolated report, citalopram was successfully su paroxetine in a patient who had experienced elevated tricyclic antidepressant levels during paroxetine treatm an inhibitor of cytochrome P450 2D6 enzymes, and imipramine, a tertiary amine, is converted to a secondary (desipramine) by N-demethylation. The secondary amine then undergoes hydroxylation, a process which is c oxidative enzymes of the CYP2D6 system (Taylor, 1995).

3) Severity: moderate

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: Caution is indicated in the coadministration of tricyclic antidepressants and citalopra monitoring tricyclic antidepressant concentration and/or dose adjustment when there is a change in therapy c citalopram. However, citalopram may be preferred over paroxetine when tricyclic antidepressants are coadmi

7) Probable Mechanism: inhibition of desipramine metabolism, the major metabolite of imipramine

8) Literature Reports

a) Eight healthy male volunteers completed three phases of an interaction study to determine the effects imipramine and citalopram. All subjects were extensive metabolizers of sparteine, indicating normal cyto enzyme activity. Each subject received citalopram 40 mg alone as a single daily dose for 10 days, imipra single oral dose, and a single oral dose of imipramine 100 mg coadministered on day 7 of citalopram the weeks separated each treatment phase. Results showed that the concurrent administration of citalopram resulted in a 50% increase in the desipramine area under the concentration-time curve (AUC) and a simi 2-hydroxy-desipramine AUC. Also, the desipramine half-life was approximately seven hours longer wher citalopram (27 hours vs. 20 hours). The AUC and half-life of imipramine were not affected by citalopram These results showed that citalopram is an inhibitor of cytochrome P450 2D6 hepatic enzymes, since mo antidepressants rely on this system for metabolism (Gram et al, 1993).

b) A case report describes a 45-year-old white female with major depressive disorder and dysthymia. Th several trials of antidepressants from all available drug classes, as well as electroconvulsive therapy. Th medications included pindolol, desipramine, clonazepam, and olanzapine. Paroxetine was initiated and t mg/day occurred over 3 months. The patient developed light-headedness, ataxia, and increased confusi titration. Desipramine serum levels were 1810 ng/mL (therapeutic range 75-300 ng/mL). After decreasing desipramine 200 mg, the serum desipramine level was still 1665 ng/mL. The reduction in side effects we the paroxetine dose was decreased to 30 mg/day and desipramine dose was decreased to 150 mg/day. dosage reduction of both drugs the patient's serum desipramine level was 1153 ng/mL. Paroxetine was d desipramine dose was decreased to 100 mg/day in divided doses. Citalopram was initiated and titrated t the next two months the patient's desipramine level decreased to 195 ng/mL. Depressive symptoms also Desipramine toxicity is presumed to be caused by hepatic cytochrome P450 2D6 (CYP2D6) isoenzyme I paroxetine. The author concludes that the switch to citalopram likely is responsible for diminished desipra levels, although alternative explanations should not be discounted (Ashton, 2000).

3.5.1.AK Clarithromycin

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Tricyclic antidepressants (TCAs) and clarithromycin have been shown to prolong the QTc inter recommended therapeutic dose (Prod Info Biaxin(R), 2002; Marshall & Forker, 1982o). Even though no forma studies have been done, the coadministration of tricyclic antidepressants and other drugs known to prolong th such as clarithromycin, is not recommended (Prod Info Elavil(R), 1999h).

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of tricyclic antidepressants and agents that prolong t
such as clarithromycin, is not recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.AL Clonidine

1) Interaction Effect: decreased antihypertensive effectiveness
2) Summary: Concomitant clonidine and tricyclic antidepressant (TCA) therapy may impair the antihypertens
clonidine (Prod Info Catapres(R), 1996). Tricyclic antidepressants increase the release of noradrenaline, pres
re-uptake blockade. Clonidine reduces the release of noradrenaline by stimulating pre-synaptic alpha-2 adrer
whose function is to inhibit noradrenaline release (Briant et al, 1973a; Hicks et al, 1981; Hui, 1983; Glass et a
Mianserin, a tetracyclic antidepressant, was not shown to exhibit the impairment of clonidine's antihypertensi
with tricyclic antidepressants (Elliott et al, 1981; Elliott et al, 1983).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Blood pressure should be monitored for an appropriate clinical response. Higher do
may be required. An alternative class of antihypertensive agents or an alternative class of antidepressants m
7) Probable Mechanism: pharmacological antagonism at central alpha-2 receptors
8) Literature Reports

a) The interaction between clonidine and desipramine was studied in five hypertensive patients. The res
blind placebo controlled study showed that the introduction of the tricyclic antidepressant led to the loss
control in four of the five subjects within two weeks. The rise in the arterial pressure was more prominent
position than in the erect. The average blood pressure increase in the desipramine period compared to t
was 22/15 mm Hg in the lying position and 12/11 mm Hg standing (Briant et al, 1973).

b) Eleven drug-free patients who met the Research Diagnostic Criteria for Major Depressive Disorder er
determine the effects of desipramine on central adrenergic function. Patients were given a clonidine infus
3 weeks of treatment with desipramine. Results showed that the sedative and hypotensive effects of clor
significantly inhibited after three weeks of treatment with desipramine. This interaction was also seen at
not reach clinical significance. The authors concluded that the effects that were observed during the stuc
acute drug effect, rather than to a chronic adaptive change (Glass et al, 1982).

c) One case report describes a 65-year-old man who was experiencing perineal pain following the excis
carcinoma. Pain management of amitriptyline 75 mg nightly and sodium valproate 500 mg three times da
after slow-release morphine only had a limited effect. A clonidine spinal intrathecal injection of 75 microg
when it was felt that the patient had become tolerant to opioid treatment. Within five minutes, the patient
severe pain, which resolved within 30 minutes after diamorphine was given. Two mechanisms for this int
postulated. In the first, the pain could have been the result of a clonidine-cholinergic interaction. In the se
augmentation of serotoninergic transmission may have unmasked an effect of clonidine at central recept
nociception (Hardy & Wells, 1988).

3.5.1.AM Clorgyline

1) Interaction Effect: neurotoxicity, seizures, or serotonin syndrome (hypertension, hyperthermia, myoclonus
changes)
2) Summary: Concomitant TCA and MAOI use has resulted in hyperpyrexia, convulsions, and death. Concur
and TCAs has also been reported to result in a condition termed serotonin syndrome (Insel et al, 1982e; Spig
Brodribb et al, 1994e; Neuvonen et al, 1993b). Serotonin syndrome is a rare but potentially fatal condition of
hyperstimulation characterized by hypertension, hyperthermia, myoclonus, and changes in mental status (Ste
Consequently, coadministration of TCAs and MAOIs is contraindicated in most cases. If TCAs and MAOIs mu
concurrently, avoid large doses, use only oral TCAs, avoid imipramine, clomipramine, desipramine, and trany
monitor patients closely (Schuckit et al, 1971e; White & Simpson, 1984d).
3) Severity: contraindicated
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of a tricyclic antidepressant, such as imipramine with an monoam
inhibitor (MAOI), such as clorgyline is contraindicated. If imipramine is replacing treatment with clorgyline, a m
weeks should elapse after clorgyline is discontinued before therapy with imipramine begins (Prod Info imipran
oral tablet, 2003). There is no specific washout period for replacing imipramine treatment with clorgyline. How
advisable to gradually taper the tricyclic antidepressant dosage before starting treatment with the MAOI (Rem
7) Probable Mechanism: altered catecholamine uptake and metabolism
8) Literature Reports

a) Concomitant administration of monoamine oxidase inhibitors (MAOIs) with tricyclic antidepressants (T
considered an absolute contraindication in the past and still is listed as such by the manufacturers (Prod
hydrochloride oral tablet, 2003). Reports of excitation, hyperpyrexia, convulsions, and possible death hav
to the combination (Lockett & Milner, 1965b; Brachfeld et al, 1963a; Winston, 1971b; Schuckit et al, 197
1965a; Spiker & Pugh, 1976b). The mechanism may relate to the combined inhibition of catecholamine r
central nervous system and inhibition of catecholamine metabolism (Sjoqvist, 1965b).

b) The development of serotonin syndrome due to administration of a TCA after MAOI therapy has beer
double-blind, crossover study examining the effects of clorgyline and clomipramine for the treatment of o
compulsive disorder, two subjects developed severe reactions characteristic of serotonin syndrome. Dur

patients had received clorgyline therapy, followed by a washout period of approximately four weeks and clomipramine therapy. After taking the first 100 mg dose of clomipramine, one patient developed coarse in both legs, hyperreflexia, diaphoresis, and arrhythmia. Another patient developed a similar reaction afte with upper motor neuron symptoms, myoclonic movements, and cardiac irritability. Both patient's sympto several hours later, and both patients were later treated successfully with clomipramine without adverse 1982d).

c) A 76-year old woman who had been taking clomipramine 50 mg daily for several months was switche 300 mg daily. The patient experienced somnolence, confusion, and fever which then progressed to furth impairment, muscle stiffness, myoclonus, and convulsive attacks. The patient's symptoms were describe diagnostic criteria for serotonin syndrome and were resolved a few days later after discontinuing all antid medications (Spigset et al, 1993e).

d) A 39-year old woman with bipolar disorder developed serotonin syndrome after imipramine was adde The patient was taking moclobemide 300 mg twice daily when imipramine was started at 50 mg daily, fol dosage increases of imipramine to 200 mg and a reduction of moclobemide dosage to 150 mg twice dail the increase in imipramine to 200 mg per day, the patient developed symptoms of serotonin syndrome, i shivering, confusion, fever, and spasms in the extremities. The patient was treated with chlorpromazine a resolved over the next few days without further complications (Brodribb et al, 1994d).

e) Three patients with bipolar disorder developed manic symptoms while undergoing concurrent therapy isocarboxazid and amitriptyline. In all three cases the patients had been given MAOIs and TCAs alone w complications. It was only when the drugs were used in combination that symptoms of mania emerged, s synergistic effect (de la Fuente et al, 1986a).

f) In one case, clomipramine 10 mg twice daily was added to a stable regimen of tranylcypromine in a pl 34-year old man. After taking several doses, the patients developed symptoms of nausea and profuse sw by pyrexia, dyspnea, and agitation. The hyperpyrexical state led to disseminated intravascular coagulatio death (Tackley & Tregaskis, 1987c).

g) There is evidence that MAOIs and TCAs can be given concomitantly in patients previously unrespons TCA alone. A few precautions must be followed including: a) avoidance of large doses (no more than 15 or its equivalent, 45 mg phenelzine, or 60 mg isocarboxazid) b) oral administration c) avoidance of clomi imipramine, desipramine, and tranylcypromine in any combination, and d) close monitoring of patients (K Winston, 1971b; Schuckit et al, 1971d; White & Simpson, 1984c; Rom & Benner, 1972a). The combinati in one of two ways. Most frequently, the recommendation is to stop all previous antidepressants (five to t and 14 days for MAOIs); the combination is then simultaneously started (Perry et al, 1991b). Alternativel previously receiving a TCA, small doses of the MAOI may be slowly added (Schoonover, 1983). Some s that the combination of amitriptyline and isocarboxazid is preferred (Perry et al, 1991b). Numerous studie refractory depression or phobic anxiety states have successfully used the combination of MAOIs and TC 1977b; Schuckit et al, 1971d; Ashcroft, 1975b).

3.5.1.AN Conjugated Estrogens

1) Interaction Effect: possible attenuation of antidepressant effectiveness; tricyclic toxicity (drowsiness, hypo

2) Summary: In isolated cases, the pharmacologic effects of tricyclic antidepressants may be increased or de estrogens (Somani & Khurana, 1973c), with paradoxical loss of antidepressant effect yet tricyclic toxicity bein simultaneously (Prange, 1972c). The effects of the interaction appear to be estrogen dose-related (Khurana, be of clinical importance primarily in patients previously stabilized on tricyclic therapy who are being started o (Krishnan et al, 1984c).

3) Severity: minor

4) Onset: delayed

5) Substantiation: established

6) Clinical Management: If signs or symptoms of altered tricyclic response are noted, dose adjustment down estrogen or tricyclic component may be successful in restoring effectiveness or resolving toxicity. However, d may be required.

7) Probable Mechanism: possible inhibition of hepatic metabolism of the tricyclic antidepressant

8) Literature Reports

a) Some studies evaluated the qualitative effects of concomitant administration of estrogen and TCAs. I depressed female prisoners were randomly assigned to four treatment groups. Ten patients received pla imipramine (150 mg daily) and placebo, five patients received imipramine (150 mg daily) and ethinyl estr daily), while five patients received imipramine (150 mg daily) and ethinyl estradiol (25 mcg daily). The 10 received placebo did not improve over the six weeks of the study. The 10 patients taking estrogen and in demonstrated a significantly greater improvement in symptoms than did the 10 patients taking imipramin after two weeks, the five patients that received imipramine and high-dose estrogen had not improved as patients receiving imipramine and low-dose estrogen. The only side-effect reported was drowsiness, whi the patients taking imipramine. Following the discontinuation of ethinyl estradiol, a time period of two wee for the high-dose estrogen group to do as well as the low-dose group. This effect was attributed to the pr estrogen in the high-dose group. In another group, five women received imipramine 150 mg and ethinyl e daily did not improve as much as 10 patients receiving only imipramine. Also, the patients on the combin side-effects including lethargy, coarse tremor and systolic hypotension (Prange, 1972b).

b) A 32-year-old female taking conjugated estrogens 2.5 mg and imipramine 100 mg developed lethargy signs of depersonalization. After two years of therapy, the patient increased her estrogen dose to 5 mg a daily. The patient became nauseated, had constant headaches, and low normal blood pressure. All lab v

Upon discontinuing the estrogen, the side effects abated. Some investigators have proposed that the sid from enhanced TCA effects secondary to estrogen inhibition of hepatic microsomal enzymes (Somani & Khurana, 1972b).

c) In a study women received clomipramine and oral contraceptives or clomipramine alone. At the begir there were 30 women taking the combination, but 12 subsequently dropped out. The 18 patients on the c matched with 18 patients taking clomipramine alone. No significant difference was noted in the patients' clomipramine. It was proposed that there was no significant difference in side-effects between the groups groups were matched after patients had dropped out of the study. Had the patients been matched prior t different conclusions may have been drawn (Beaumont, 1973a).

d) The effects of oral contraceptives on clomipramine was studied in 42 women between the ages of 18 three women took clomipramine 25 mg at bedtime while 19 took clomipramine 25 mg at bedtime with ora Over the four-week study, three control patients (two due to side-effects) and five in the experimental gro side-effects) dropped out. Venous blood samples were drawn at weekly intervals for measurement of se concentrations. No difference in serum concentrations was noted between the groups. However, this res due to the low dose of clomipramine given (Luscombe & John, 1980a).

e) The onset of akathisia was reported in 3 patients receiving conjugated estrogens and tricyclic antidep concurrently. A 24-year-old patient receiving clomipramine 120 mg daily for anorexia nervosa and conjug 1.25 mg daily for amenorrhea developed restless legs and a constant desire to move continuously. Estro discontinued and benztropine 2 mg was administered, resulting in marked reduction and resolution withi Akathisia and disorientation developed in a 55-year-old patient on conjugated estrogen 1.25 mg daily wh amitriptyline 50 mg daily for depression. Within hours of amitriptyline, the patient was confused, restless, inner desire to move continuously. Symptoms disappeared after discontinuing amitriptyline. A third case reported in a 35-year-old patient who received conjugated estrogen 1.25 mg daily and amitriptyline 50 m developed within a few hours after taking the first dose of amitriptyline and resolved within 48 hours follo discontinuation of the antidepressant (Krishnan et al, 1984b).

f) The absolute bioavailability of imipramine increased in women who received low-dose oral contracept less of ethinyl estradiol) from 27% to 44% (p less than 0.05) as evident by an increase in the area under concentration time curve (Abernethy et al, 1984a).

g) Estrogens may inhibit the oxidation of TCAs by affecting hepatic microsomal enzymes (John et al, 19 are metabolized via oxidation and conjugation pathways. Inhibition of the oxidation of TCAs could result and toxicity due to decreased clearance. Estrogens are suspected of possessing other effects on the cer system resulting in an antidepressant effect (Oppenheim, 1983a).

3.5.1.AO Darifenacin

1) Interaction Effect: increased imipramine exposure and potentially increased adverse effects

2) Summary: Concomitant use of darifenacin and imipramine may result in substantially increased exposure its active metabolite desipramine. The mean maximum concentration (Cmax) and area under the concentrati (AUC) of imipramine increased 57% and 70%, respectively, when used together with darifenacin 30 mg once state. Note: The recommended dose of darifenacin is 7.5 or 15 mg once daily. The AUC of desipramine, the a of imipramine, increased 3.6-fold. Caution should be used with the coadministration of darifenacin and CYP2 a narrow therapeutic window, such as tricyclic antidepressants, including imipramine (Prod Info Enablex, 200

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Use caution with the coadministration of darifenacin and other CYP2D6 substrates therapeutic window, such as imipramine. Monitor for imipramine toxicity.

7) Probable Mechanism: competitive inhibition of CYP2D6-mediated imipramine metabolism

3.5.1.AP Dexfenfluramine

1) Interaction Effect: hypertension, other cardiac effects, and CNS stimulation

2) Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been reporte enhanced amphetamine effects from the release of norepinephrine (Beaumont, 1973d; Raisfeld, 1972). A sim also occur with all drugs that have amphetamine-like effects. Acute elevations in blood pressure have been n (Flemenbaum, 1971a). Some amphetamine-like drugs may inhibit the metabolism of TCAs, although most co not been studied. When amphetamine analogs are being used to treat obesity, it should be noted that TCAs f moderate weight gain (Russ & Ackerman, 1988). False positive urine tests for amphetamines have been repo therapy with some TCAs (Merigian & Browning, 1993). Caution is advised when concurrent administration of agents and TCAs is warranted. The patient should be closely monitored for increased cardiovascular effects dysrhythmias).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other sympatho could lead to hypertension, increased cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) o Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral t Flemenbaum, 1972). Use caution if such therapy is warranted. Monitor the patient closely for hypertension ar

7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission

8) Literature Reports

a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agen
coadministration of d-amphetamine with TCAs such as desipramine or protriptyline results in sustained i
amphetamine concentration in the brain (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info DEXE
sustained-release oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006).
b) Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism o
antidepressants, such as imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transde
2006).
c) Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases i
such that the hypotensive effects induced by TCAs may lead to blood pressures as high as 170/120 mm
of combined therapy. Discontinuation of the methylphenidate usually results in the blood pressure return
normotensive levels; reinstitution of the methylphenidate resulted in further blood pressure elevation (Fle
Flemenbaum, 1972).
d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine g
four weeks, were given fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transie
clinical improvement. However, fenfluramine more than doubled steady-state plasma levels of desiprami
1990).
e) There have been claims based on uncontrolled studies that a better antidepressant response may oc
therapy (Garrettson et al, 1969). However, a systemic review of stimulants in the treatment of depressior
although uncontrolled studies were generally positive, the ten placebo-controlled studies of stimulant dru
depression, with one exception, indicated little advantage of drug over placebo and did not appear to be
conventional antidepressants in primary depression (Satel & Nelson, 1989).

3.5.1.AQ Dexmethylphenidate

1) Interaction Effect: hypertension, other cardiac effects, and CNS stimulation
2) Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been reporte
enhanced amphetamine effects from the release of norepinephrine (Beaumont, 1973d; Raisfeld, 1972). A sin
also occur with all drugs that have amphetamine-like effects. Acute elevations in blood pressure have been n
(Flemenbaum, 1971a). Some amphetamine-like drugs may inhibit the metabolism of TCAs, although most co
not been studied. When amphetamine analogs are being used to treat obesity, it should be noted that TCAs f
moderate weight gain (Russ & Ackerman, 1988). False positive urine tests for amphetamines have been repo
therapy with some TCAs (Merigian & Browning, 1993). Caution is advised when concurrent administration of
agents and TCAs is warranted. The patient should be closely monitored for increased cardiovascular effects
dysrhythmias).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other sympatho
could lead to hypertension, increased cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) o
Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral t
Flemenbaum, 1972). Use caution if such therapy is warranted. Monitor the patient closely for hypertension ar
7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission
8) Literature Reports

a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agen
coadministration of d-amphetamine with TCAs such as desipramine or protriptyline results in sustained i
amphetamine concentration in the brain (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info DEXE
sustained-release oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006).
b) Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism o
antidepressants, such as imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transde
2006).
c) Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases i
such that the hypotensive effects induced by TCAs may lead to blood pressures as high as 170/120 mm
of combined therapy. Discontinuation of the methylphenidate usually results in the blood pressure return
normotensive levels; reinstitution of the methylphenidate resulted in further blood pressure elevation (Fle
Flemenbaum, 1972).
d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine g
four weeks, were given fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transie
clinical improvement. However, fenfluramine more than doubled steady-state plasma levels of desiprami
1990).
e) There have been claims based on uncontrolled studies that a better antidepressant response may oc
therapy (Garrettson et al, 1969). However, a systemic review of stimulants in the treatment of depressior
although uncontrolled studies were generally positive, the ten placebo-controlled studies of stimulant dru
depression, with one exception, indicated little advantage of drug over placebo and did not appear to be
conventional antidepressants in primary depression (Satel & Nelson, 1989).

3.5.1.AR Dextroamphetamine

1) Interaction Effect: hypertension, other cardiac effects, and CNS stimulation
2) Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been reporte
enhanced amphetamine effects from the release of norepinephrine (Beaumont, 1973d; Raisfeld, 1972). A sin

also occur with all drugs that have amphetamine-like effects. Acute elevations in blood pressure have been n
(Flemenbaum, 1971a). Some amphetamine-like drugs may inhibit the metabolism of TCAs, although most co
not been studied. When amphetamine analogs are being used to treat obesity, it should be noted that TCAs f
moderate weight gain (Russ & Ackerman, 1988). False positive urine tests for amphetamines have been repo
therapy with some TCAs (Merigian & Browning, 1993). Caution is advised when concurrent administration of
agents and TCAs is warranted. The patient should be closely monitored for increased cardiovascular effects
dysrhythmias).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other sympatho
could lead to hypertension, increased cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) o
Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral t
Flemenbaum, 1972). Use caution if such therapy is warranted. Monitor the patient closely for hypertension ar
7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission
8) Literature Reports
a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agen
coadministration of d-amphetamine with TCAs such as desipramine or protriptyline results in sustained in
amphetamine concentration in the brain (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info DEXE
sustained-release oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006).
b) Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism o
antidepressants, such as imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transde
2006).
c) Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases in
such that the hypotensive effects induced by TCAs may lead to blood pressures as high as 170/120 mm
of combined therapy. Discontinuation of the methylphenidate usually results in the blood pressure return
normotensive levels; reinstitution of the methylphenidate resulted in further blood pressure elevation (Fle
Flemenbaum, 1972).
d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine g
four weeks, were given fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transie
clinical improvement. However, fenfluramine more than doubled steady-state plasma levels of desiprami
1990).
e) There have been claims based on uncontrolled studies that a better antidepressant response may oc
therapy (Garrettson et al, 1969). However, a systemic review of stimulants in the treatment of depressior
although uncontrolled studies were generally positive, the ten placebo-controlled studies of stimulant dru
depression, with one exception, indicated little advantage of drug over placebo and did not appear to be
conventional antidepressants in primary depression (Satel & Nelson, 1989).

3.5.1.AS Dicumarol
1) Interaction Effect: increased risk of bleeding
2) Summary: Tricyclic antidepressants (TCAs) may increase the half-life and bioavailability of oral anticoagul
1970e; Williams et al, 1976e). Considerable interindividual differences may be found (Pond et al, 1975e).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: In patients receiving oral anticoagulant therapy, the prothrombin time ratio or INR (i
normalized ratio) should be closely monitored with the addition and withdrawal of treatment with imipramine,
reassessed periodically during concurrent therapy. Adjustments of the dicumarol dose may be necessary in o
the desired level of anticoagulation.
7) Probable Mechanism: decreased dicumarol metabolism; increased dicumarol absorption
8) Literature Reports
a) In a study of healthy volunteers, the concurrent use of nortriptyline or amitriptyline resulted in an incre
levels and an increase in the plasma half-life of dicumarol, although the effect was not consistent in all su
1975d). This effect was not observed with warfarin.
b) A single oral dose of bishydroxycoumarin after eight days of nortriptyline resulted in a significantly pro
and decreased volume of distribution of the coumarin anticoagulant in six healthy volunteers (Vesell et a
mechanism of action was suggested to be reduced bishydroxycoumarin metabolism and/or altered coum
c) Drug dosing was studied in 16 patients on long-term anticoagulant therapy who used concurrent TCA
1976d). TCAs affected the stability of anticoagulant control leading to frequent changes in the doses of a
Inhibition of coumarin metabolism was the postulated mechanism.

3.5.1.AT Dienestrol
1) Interaction Effect: attenuation of antidepressant effectiveness; tricyclic toxicity (drowsiness, hypotension, a
2) Summary: In isolated cases, the pharmacologic effects of tricyclic antidepressants may be increased or de
estrogens (Somani & Khurana, 1973g), with paradoxical loss of antidepressant effect yet tricyclic toxicity beir
simultaneously (Prange, 1972g). The effects of the interaction appear to be estrogen dose-related (Khurana,
be of clinical importance primarily in patients previously stabilized on tricyclic therapy who are being started o
(Krishnan et al, 1984g).

3) Severity: minor
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: If signs or symptoms of altered tricyclic response are noted, dose adjustment down estrogen or tricyclic component may be successful in restoring effectiveness or resolving toxicity. However, d may be required.
7) Probable Mechanism: possible estrogen-enhanced hepatic metabolism of the tricyclic
8) Literature Reports

a) Some studies evaluated the qualitative effects of concomitant administration of estrogen and TCAs. I depressed female prisoners were randomly assigned to 4 treatment groups. Ten patients received place imipramine (150 milligrams/day) and placebo, 5 patients received imipramine (150 milligrams/day) and e micrograms/day), while 5 patients received imipramine (150 milligrams/day) and ethinyl estradiol (25 mic 10 patients that received placebo did not improve over the 6 weeks of the study. The 10 patients taking e imipramine demonstrated a significantly greater improvement in symptoms than did the 10 patients takin alone. However, after 2 weeks, the 5 patients that received imipramine and high-dose estrogen had not i as the patients receiving imipramine and low-dose estrogen. The only side-effect reported was drowsine affected the patients taking imipramine. Following the discontinuation of ethinyl estradiol, a time period o required for the high-dose estrogen group to do as well as the low-dose group. This effect was attributed residual estrogen in the high-dose group. In another group, 5 women received imipramine 150 milligrams estradiol 50 micrograms daily did not improve as much as 10 patients receiving only imipramine. Also, th combination had severe side-effects including lethargy, coarse tremor and systolic hypotension (Prange,

b) A case reported by (Khurana, 1972f) demonstrated an interaction in a 32-year-old female taking conj 2.5 milligrams and imipramine 100 milligrams. The patient developed lethargy, tremors, and signs of dep After 2 years of therapy, the patient increased her estrogen dose to 5 milligrams and then 7.5 milligrams became nauseated, had constant headaches, and low normal blood pressure. All lab work was normal. the estrogen, the side-effects abated. Some investigators have proposed that the side effects resulted fr effects secondary to estrogen inhibition of hepatic microsomal enzymes (Somani & Khurana, 1973f).

c) In a study women received clomipramine and oral contraceptives or clomipramine alone. At the begin there were 30 women taking the combination, but 12 subsequently dropped out. The 18 patients on the matched with 18 patients taking clomipramine alone. No significant difference was noted in the patients' clomipramine. It was proposed that there was no significant difference in side-effects between the groups groups were matched after patients had dropped out of the study. Had the patients been matched prior t different conclusions may have been drawn (Beaumont, 1973c).

d) The effect of oral contraceptives on clomipramine was studied in 42 women between the ages of 18 a three women took clomipramine 25 milligrams at bedtime while 19 took clomipramine 25 milligrams at be contraceptives. Over the 4-week study, 3 control patients (2 due to side-effects) and 5 in the experimenta side-effects) dropped out. Venous blood samples were drawn at weekly intervals for measurement of se concentrations. No difference in serum concentrations was noted between the groups. However, this res due to the low dose of clomipramine given (Luscombe & John, 1980c).

e) The onset of akathisia was reported in 3 patients receiving conjugated estrogens and tricyclic antidep concurrently. A 24-year-old patient receiving clomipramine 120 milligrams/day for anorexia nervosa and estrogens 1.25 milligrams/day for amenorrhea developed restless legs and a constant desire to move co Estrogen was discontinued and benztropine 2 milligrams was administered, resulting in marked reductio within 48 hours. Akathisia and disorientation developed in a 55-year-old patient on conjugated estrogens milligrams/day who was prescribed amitriptyline 50 milligrams/day for depression. Within hours of amitrip was confused, restless, and possessed an inner desire to move continuously. Symptoms disappeared af amitriptyline. Positive rechallenge at one week with doxepin 100 milligrams, with resolution following disc doxepin. A third case of akathisia was reported in a 35-year-old patient who received conjugated estroge milligrams/day and amitriptyline 50 milligrams/day. Akathisia developed within a few hours after taking th amitriptyline and resolved within 48 hours following discontinuation of the antidepressant (Krishnan et al,

f) The absolute bioavailability of imipramine increased in women who received low-dose oral contracept micrograms or less of ethinyl estradiol) from 27 to 44% (p less than 0.05) as evident by an increase in th plasma concentration time curve (Abernethy et al, 1984d).

g) Estrogens may inhibit the oxidation of TCAs by affecting hepatic microsomal enzymes (John et al, 19 are metabolized via oxidation and conjugation pathways. Inhibition of the oxidation of TCAs could result and toxicity due to decreased clearance. Estrogens are suspected of possessing other effects on the cer system resulting in an antidepressant effect (Oppenheim, 1983c).

3.5.1.AU Diethylpropion

1) Interaction Effect: hypertension, other cardiac effects, and CNS stimulation
2) Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been reporte enhanced amphetamine effects from the release of norepinephrine (Beaumont, 1973d; Raisfeld, 1972). A sin also occur with all drugs that have amphetamine-like effects. Acute elevations in blood pressure have been n (Flemenbaum, 1971a). Some amphetamine-like drugs may inhibit the metabolism of TCAs, although most co not been studied. When amphetamine analogs are being used to treat obesity, it should be noted that TCAs f moderate weight gain (Russ & Ackerman, 1988). False positive urine tests for amphetamines have been repo therapy with some TCAs (Merigian & Browning, 1993). Caution is advised when concurrent administration of agents and TCAs is warranted. The patient should be closely monitored for increased cardiovascular effects

dysrhythmias).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other sympatho could lead to hypertension, increased cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) o Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral t Flemenbaum, 1972). Use caution if such therapy is warranted. Monitor the patient closely for hypertension ar
7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission
8) Literature Reports
a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agen coadministration of d-amphetamine with TCAs such as desipramine or protriptyline results in sustained i amphetamine concentration in the brain (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info DEXE sustained-release oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006).
b) Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism c antidepressants, such as imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transde 2006).
c) Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases i such that the hypotensive effects induced by TCAs may lead to blood pressures as high as 170/120 mm of combined therapy. Discontinuation of the methylphenidate usually results in the blood pressure return normotensive levels; reinstitution of the methylphenidate resulted in further blood pressure elevation (Fle Flemenbaum, 1972).
d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine g four weeks, were given fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transie clinical improvement. However, fenfluramine more than doubled steady-state plasma levels of desiprami 1990).
e) There have been claims based on uncontrolled studies that a better antidepressant response may oc therapy (Garrettson et al, 1969). However, a systemic review of stimulants in the treatment of depressior although uncontrolled studies were generally positive, the ten placebo-controlled studies of stimulant dru depression, with one exception, indicated little advantage of drug over placebo and did not appear to be conventional antidepressants in primary depression (Satel & Nelson, 1989).

3.5.1.AV Diethylstilbestrol
1) Interaction Effect: attenuation of antidepressant effectiveness; tricyclic toxicity (drowsiness, hypotension, a
2) Summary: In isolated cases, the pharmacologic effects of tricyclic antidepressants may be increased or de estrogens (Somani & Khurana, 1973k), with paradoxical loss of antidepressant effect yet tricyclic toxicity bein simultaneously (Prange, 1972k). The effects of the interaction appear to be estrogen dose-related (Khurana, be of clinical importance primarily in patients previously stabilized on tricyclic therapy who are being started o (Krishnan et al, 1984k).
3) Severity: minor
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: If signs or symptoms of altered tricyclic response are noted, dose adjustment down estrogen or tricyclic component may be successful in restoring effectiveness or resolving toxicity. However, d may be required.
7) Probable Mechanism: possible estrogen-enhanced hepatic metabolism of the tricyclic
8) Literature Reports
a) Some studies evaluated the qualitative effects of concomitant administration of estrogen and TCAs. I depressed female prisoners were randomly assigned to 4 treatment groups. Ten patients received place imipramine (150 milligrams/day) and placebo, 5 patients received imipramine (150 milligrams/day) and e micrograms/day), while 5 patients received imipramine (150 milligrams/day) and ethinyl estradiol (25 mic 10 patients that received placebo did not improve over the 6 weeks of the study. The 10 patients taking e imipramine demonstrated a significantly greater improvement in symptoms than did the 10 patients takin alone. However, after 2 weeks, the 5 patients that received imipramine and high-dose estrogen had not i as the patients receiving imipramine and low-dose estrogen. The only side-effect reported was drowsine affected the patients taking imipramine. Following the discontinuation of ethinyl estradiol, a time period o required for the high-dose estrogen group to do as well as the low-dose group. This effect was attributed residual estrogen in the high-dose group. In another group, 5 women received imipramine 150 milligrams estradiol 50 micrograms daily did not improve as much as 10 patients receiving only imipramine. Also, th combination had severe side-effects including lethargy, coarse tremor and systolic hypotension (Prange,
b) A case reported by (Khurana, 1972j) demonstrated an interaction in a 32-year-old female taking conju 2.5 milligrams and imipramine 100 milligrams. The patient developed lethargy, tremors, and signs of dep After 2 years of therapy, the patient increased her estrogen dose to 5 milligrams and then 7.5 milligrams became nauseated, had constant headaches, and low normal blood pressure. All lab work was normal. U the estrogen, the side-effects abated. Some investigators have proposed that the side effects resulted fr effects secondary to estrogen inhibition of hepatic microsomal enzymes (Somani & Khurana, 1973j).
c) In a study women received clomipramine and oral contraceptives or clomipramine alone. At the begin there were 30 women taking the combination, but 12 subsequently dropped out. The 18 patients on the c

matched with 18 patients taking clomipramine alone. No significant difference was noted in the patients' clomipramine. It was proposed that there was no significant difference in side-effects between the groups groups were matched after patients had dropped out of the study. Had the patients been matched prior t different conclusions may have been drawn (Beaumont, 1973f).

d) The effect of oral contraceptives on clomipramine was studied in 42 women between the ages of 18 a three women took clomipramine 25 milligrams at bedtime while 19 took clomipramine 25 milligrams at be contraceptives. Over the 4-week study, 3 control patients (2 due to side-effects) and 5 in the experimenta side-effects) dropped out. Venous blood samples were drawn at weekly intervals for measurement of ser concentrations. No difference in serum concentrations was noted between the groups. However, this res due to the low dose of clomipramine given (Luscombe & John, 1980e).

e) The onset of akathisia was reported in 3 patients receiving conjugated estrogens and tricyclic antidep concurrently. A 24-year-old patient receiving clomipramine 120 milligrams/day for anorexia nervosa and estrogens 1.25 milligrams/day for amenorrhea developed restless legs and a constant desire to move co Estrogen was discontinued and benztropine 2 milligrams was administered, resulting in marked reductio within 48 hours. Akathisia and disorientation developed in a 55-year-old patient on conjugated estrogens milligrams/day who was prescribed amitriptyline 50 milligrams/day for depression. Within hours of amitrip was confused, restless, and possessed an inner desire to move continuously. Symptoms disappeared af amitriptyline. Positive rechallenge at one week with doxepin 100 milligrams, with resolution following disc doxepin. A third case of akathisia was reported in a 35-year-old patient who received conjugated estroge milligrams/day and amitriptyline 50 milligrams/day. Akathisia developed within a few hours after taking th amitriptyline and resolved within 48 hours following discontinuation of the antidepressant (Krishnan et al,

f) The absolute bioavailability of imipramine increased in women who received low-dose oral contracept micrograms or less of ethinyl estradiol) from 27 to 44% (p less than 0.05) as evident by an increase in th plasma concentration time curve (Abernethy et al, 1984f).

g) Estrogens may inhibit the oxidation of TCAs by affecting hepatic microsomal enzymes (John et al, 19 are metabolized via oxidation and conjugation pathways. Inhibition of the oxidation of TCAs could result and toxicity due to decreased clearance. Estrogens are suspected of possessing other effects on the cer system resulting in an antidepressant effect (Oppenheim, 1983e).

3.5.1.AW Diltiazem

1) Interaction Effect: imipramine toxicity (dry mouth, sedation)

2) Summary: Diltiazem decreased imipramine oral clearance by 35% (statistically significant) compared to pl randomized, crossover study in 12 healthy subjects (Hermann et al, 1992c). Diltiazem increased imipramine l 30% compared to placebo which was also significant; the clinical significance of this is not known.

3) Severity: minor

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: Monitor for anticholinergic side effects of imipramine if diltiazem is added to therapy imipramine may be appropriate. Conversely, if diltiazem is discontinued, monitor continued clinical efficacy of adjust dosage accordingly.

7) Probable Mechanism: decreased imipramine clearance

8) Literature Reports

a) Imipramine serum concentrations may be altered if administered concomitantly with diltiazem. Follow imipramine 100 mg/day on day 4 of a 7 day course of diltiazem 90 mg/q8h during a controlled study, the imipramine decreased by 35% resulting in a significant increase (35%) in the peak serum concentration. failed to occur when the drug was given to those receiving placebo. Monitor drug levels for effectiveness when adding or decreasing diltiazem dosages (Hermann et al, 1992b).

3.5.1.AX Disopyramide

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Class Ia antiarrhythmics and tricyclic antidepressants have been shown to prolong the QTc inte recommended therapeutic dose. Even though no formal drug interaction studies have been done, the coadm Ia antiarrhythmics and other drugs known to prolong the QTc interval, including tricyclic antidepressants, is n (Prod Info Elavil(R), 1999g; Prod Info Quinaglute(R), 1999; Marshall & Forker, 1982n).

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: The concurrent administration of a Class IA antiarrhythmic agent and a tricyclic anti recommended.

7) Probable Mechanism: additive cardiac effects

8) Literature Reports

a) Quinidine is an inhibitor of the cytochrome P450 isoenzyme responsible for the 2-hydroxylation of imi desipramine (Brosen & Gram, 1989). Inhibition of this enzyme system can result in a 35% decrease in im clearance and 85% decrease in desipramine clearance. Demethylation of imipramine by the cytochrome unaffected by this interaction. Until more information is available all patients having quinidine added to dr containing imipramine or desipramine should be monitored for increased antidepressant serum concentr potential toxicity.

b) An increased incidence in sudden death was observed in six out of 53 patients with cardiac disease r

amitriptyline, compared to 0 out of 53 in the control group. It was recommended that amitriptyline be avo with underlying cardiac disease except when depression was debilitating and no other drugs were helpfu Coull et al, 1970).

c) In a placebo controlled study, imipramine 3.5 mg/kg was administered daily for seven patients with se and titrated doses to obtain therapeutic plasma concentrations. Two patients displayed premature atrial and premature ventricular depolarizations before therapy. On patient had 33 premature atrial depolarizat premature ventricular depolarizations (PVD) per hour, which decreased to 0.4 PAC and zero PVC per ho The other patient had 12 PAD and 169 PVD per hour before treatment and 1.8 PAD and 28.1 PVD per h The authors also cautioned that the incidence of cardiotoxicity may increase if tricyclic antidepressants a with Type I antiarrhythmics. It was also recommended that quinidine and procainamide not be used to tre of a tricyclic overdose. The similarities between these agents may exacerbate the cardiotoxicity (Kantor

3.5.1.AY Disulfiram

1) Interaction Effect: increased bioavailability of imipramine

2) Summary: Increased elimination half-life, higher peak plasma levels, and decreased total body clearance when administered during disulfiram therapy have been demonstrated (Ciraulo et al, 1985). The clinical signif finding is unknown.

3) Severity: minor

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Monitor the patient for excessive adverse effects to imipramine.

7) Probable Mechanism: disulfiram-induced inhibition of imipramine hepatic metabolism

8) Literature Reports

a) Two healthy men who had been detoxified for 14 days participated in a study to determine the effect pharmacokinetics of imipramine and desipramine. Doses of imipramine 12.5 mg were administered intra to disulfiram 500 mg daily therapy and after 14 days of therapy with disulfiram. The protocol for desipram same but was performed only in one subject. For imipramine, the area under the concentration-time curv by 32.5% and 26.8% after disulfiram administration in patient 1 and patient 2, respectively. The eliminati also increased by 18.3% and 13.6%, respectively, while the total body imipramine clearance decreased respectively. Desipramine showed a 32.3% increase in the AUC when administered with disulfiram. The also increased by 19.8% and the total body clearance decreased 24.3% (Ciraulo et al, 1985).

3.5.1.AZ Dofetilide

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Cases of QTc prolongation and/or torsades de pointes have been reported with all Class III ant agents, including acecainide (Chow et al, 1984), amiodarone (Faggiano et al, 1996), azimilide (Corey et al, 1 (Gilman et al, 1985), ibutilide (Rodriguez et al, 2001), sematilide (Singh, 1996), dofetilide (Allen et al, 2002), a & Runge, 2001). Even though no formal drug interaction studies have been done, the coadministration of Cla antiarrhythmics and other drugs known to prolong the QTc interval, including tricyclic antidepressants, is not (Yamreudeewong et al, 2003a; Prod Info Corvert(R), 2000).

3) Severity: major

4) Onset: rapid

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of a Class III antiarrhythmic and a tricyclic antidepres recommended.

7) Probable Mechanism: additive QT prolongation

8) Literature Reports

a) EKG effects reported in patients receiving therapeutic doses of tricyclic antidepressants include incre prolonged PR interval, intraventricular conduction delays, increased corrected QT interval (QTc) and flat (Marshall & Forker, 1982ab).

b) Concurrent use of Class III antiarrhythmic agents, and other drugs that can prolong the QT interval, s antidepressants, is not recommended. Dofetilide should be stopped for at least 2 days before any interac initiated. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised (Yam 2003).

3.5.1.BA Dolasetron

1) Interaction Effect: cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Tricyclic antidepressants (TCAs) and dolasetron have been shown to prolong the QTc interval recommended therapeutic dose (Marshall & Forker, 1982b). Even though no formal drug interaction studies h the coadministration of tricyclic antidepressants and other drugs known to prolong the QTc interval, such as c recommended (Prod Info Elavil(R), 1999a; Prod Info Anzemet(R), 1997).

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of dolasetron with other agents that may prolong the as tricyclic antidepressants, is not recommended.

7) Probable Mechanism: additive effects on QT prolongation

3.5.1.BB Droperidol

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Droperidol has been shown to prolong the QTc interval at the recommended therapeutic dose. formal drug interaction studies have been done, the coadministration of droperidol and other drugs known to interval, including tricylclic antidepressants is not recommended (Prod Info Inapsine(R), 2002; Marshall & For

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of droperidol and tricyclic antidepressants is not reco

7) Probable Mechanism: additive cardiac effects

3.5.1.BC Duloxetine

1) Interaction Effect: increased tricyclic antidepressant serum concentrations and potential toxicity (anticholir sedation, confusion, cardiac arrhythmias)

2) Summary: The coadministration of duloxetine with a tricyclic antidepressant is likely to increase bioavailab agent, increasing the risk of adverse events. Duloxetine is a moderately potent inhibitor of CYP2D6. When a CYP2D6 substrate desipramine 50 mg and duloxetine 60 mg twice daily were coadministered, the desipramir 3-fold over baseline (Prod Info CYMBALTA(R) delayed-release oral capsules, 2008).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Use caution with the combined use of duloxetine with tricyclic antidepressants (TCA therapy with duloxetine and a TCA is unavoidable, plasma concentrations of the tricyclic should be closely m adjustments made accordingly (Prod Info CYMBALTA(R) delayed-release oral capsules, 2008). Also, monito and symptoms of TCA toxicity (anticholinergic effects, sedation, confusion, and cardiac arrhythmias).

7) Probable Mechanism: duloxetine inhibition of CYP2D6-mediated tricyclic agent metabolism

3.5.1.BD Enflurane

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest) risk of seizure activity

2) Summary: Enflurane may prolong the QT interval in some patients (Owens, 2001). Because tricyclic antid also prolong the QT interval and increase the risk of arrhythmias, the concurrent administration of enflurane a antidepressants is not recommended (Marshall & Forker, 1982a). Concomitant administration of amitriptyline anesthesia has been reported to result in seizures in two cases (Sprague & Wolf, 1982a).

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: Avoid concurrent use of enflurane and tricyclic antidepressants, particularly in patie of seizure activity or when hyperventilation or high concentrations of enflurane will be required.

7) Probable Mechanism: additive effects on QT prolongation

8) Literature Reports

a) Two case reports of patients on amitriptyline therapy who experienced seizure activity while receiving anesthesia have been documented (Sprague & Wolf, 1982). The first patient, a 42-year old female, was 100 mg daily. Anesthesia was induced with fentanyl, enflurane, and nitrous oxide. Approximately three h anesthesia was induced, clonic movements of the patient's right hand and forearm were noted. Enflurane was 1% at the time. Changes in ventilation did not affect the involuntary movements, so enflurane was d replaced with halothane 1%. The movements decreased in frequency and amplitude and subsequently c approximately one minute. The second case report involved a 39-year old male who was taking amitripty Anesthesia was maintained with enflurane 1% to 2%, and intermittent clonic movements started in the ri approximately one hour into the surgery. Enflurane was discontinued and halothane was instituted, whic involuntary movements to disappear in approximately two minutes. No further movements were seen du three hours of anesthesia.

3.5.1.BE Epinephrine

1) Interaction Effect: hypertension, cardiac arrhythmias, and tachycardia

2) Summary: Clinical trials have demonstrated a 2- to 8-fold increase in the effects of intravenous infusions c drugs to volunteers on tricyclic antidepressants. Arrhythmias and other severe adverse effects have also bee 1980; Avery, 1973a; Boakes et al, 1973a; Boakes, 1973; Mitchell et al, 1970; Stone et al, 1964a). Local use (anesthesia) of epinephrine in concentrations of 1:100,000 or less is less likely to precipitate clinically significa changes (Steinberg & Block, 1971).

3) Severity: major

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: The vasoconstriction and other alpha-adrenergic effects of sympathomimetic drugs enhanced in the presence of tricyclic antidepressants (TCAs). Concomitant use should be avoided. If these d together, careful monitoring and a dose reduction of the sympathomimetic is required. Patients should be inst their doctor or dentist that they are taking a tricyclic antidepressant prior to any surgery or procedure.

7) Probable Mechanism: inhibition of norepinephrine reuptake

8) Literature Reports

a) Four healthy volunteers received intravenous infusions of various sympathomimetic amines (epineph norepinephrine, phenylephrine, and isoproterenol) before and after imipramine (25 mg three times daily f showed an increased pressor response to epinephrine (2- to 4-fold), norepinephrine (4- to 8-fold), and ph 3-fold) after imipramine, but no difference was observed in the response to isoproterenol. Thus, the incre response appeared to occur only for alpha adrenergic effects. All four subjects demonstrated changes in with epinephrine and imipramine consisting of sinus arrhythmia in three subjects and multiple ectopic be rhythm in the fourth subject (Boakes et al, 1973).

b) A review of spontaneous reports of adverse reactions to vasoconstrictors in local anesthetics found th receiving a local anesthetic with norepinephrine (1:25,000) had severe reactions (severe headaches, che subarachnoid hemorrhage). The drug history was incomplete, but at least three had been taking a tricycl at the time (Anon, 1972).

3.5.1.BF Erythromycin

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Erythromycin significantly increased the mean QTc interval versus baseline in a retrospective s (Oberg & Bauman, 1995a). Erythromycin has demonstrated QTc prolongation in combination with other drug QT interval (Prod Info PCE(R), 1997). Tricyclic antidepressants have been shown to prolong the QTc interval recommended therapeutic dose (Marshall & Forker, 1982g). Caution is advised with coadministration of drug prolong the QTc interval.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Caution is advised if erythromycin and tricyclic antidepressants are used concomita interval at baseline and periodically during treatment.

7) Probable Mechanism: additive effects on QT prolongation

8) Literature Reports

a) Erythromycin did not significantly affect the metabolism of tricyclic antidepressants in a study of 8 pat were maintained on desipramine (n equal to 5), imipramine (n equal to 1), doxepin (n equal to 1), or doxe All patients received erythromycin stearate 250 mg four times daily for six days while maintaining their us regimen. No change in the antidepressant or active metabolite concentrations was seen during coadmini erythromycin (Amsterdam & Maislin, 1991).

b) Tricyclic antidepressants have been shown to prolong the QTc interval at the recommended therapeu & Forker, 1982f).

c) Erythromycin significantly increased the QTc interval compared with baseline in a retrospective study The erythromycin dose was 500 milligrams or 1 gram four times daily, with a mean of 15 doses received to 9) who received 60 mg/kg/day or more all developed increases in QT interval of 15% or greater. For a mean QTc interval increased from 432 milliseconds (msec) at baseline to 483 msec (p less than 0.01). In delayed repolarization at baseline (n equal to 9), the QTc interval increased from 473 msec to 525 msec In patients with heart disease (n equal to 30), all experienced an increase in QTc interval (mean of 15%) increase of 8% in patients without heart disease (p less than 0.05). In 5 patients (10%), the QTc interval prolonged. One patient developed torsades de pointes attributed to erythromycin. Of 16 patients receivin concomitantly, 8 developed QT prolongation of 15% or greater (Oberg & Bauman, 1995).

3.5.1.BG Esterified Estrogens

1) Interaction Effect: possible attenuation of antidepressant effectiveness; tricyclic toxicity (drowsiness, hypo

2) Summary: In isolated cases, the pharmacologic effects of tricyclic antidepressants may be increased or de estrogens (Somani & Khurana, 1973c), with paradoxical loss of antidepressant effect yet tricyclic toxicity bein simultaneously (Prange, 1972c). The effects of the interaction appear to be estrogen dose-related (Khurana, be of clinical importance primarily in patients previously stabilized on tricyclic therapy who are being started o (Krishnan et al, 1984c).

3) Severity: minor

4) Onset: delayed

5) Substantiation: established

6) Clinical Management: If signs or symptoms of altered tricyclic response are noted, dose adjustment down estrogen or tricyclic component may be successful in restoring effectiveness or resolving toxicity. However, d may be required.

7) Probable Mechanism: possible inhibition of hepatic metabolism of the tricyclic antidepressant

8) Literature Reports

a) Some studies evaluated the qualitative effects of concomitant administration of estrogen and TCAs. I depressed female prisoners were randomly assigned to four treatment groups. Ten patients received pla imipramine (150 mg daily) and placebo, five patients received imipramine (150 mg daily) and ethinyl estr daily), while five patients received imipramine (150 mg daily) and ethinyl estradiol (25 mcg daily). The 10 received placebo did not improve over the six weeks of the study. The 10 patients taking estrogen and in demonstrated a significantly greater improvement in symptoms than did the 10 patients taking imipramin after two weeks, the five patients that received imipramine and high-dose estrogen had not improved as patients receiving imipramine and low-dose estrogen. The only side-effect reported was drowsiness, whi the patients taking imipramine. Following the discontinuation of ethinyl estradiol, a time period of two wee

for the high-dose estrogen group to do as well as the low-dose group. This effect was attributed to the pr
estrogen in the high-dose group. In another group, five women received imipramine 150 mg and ethinyl e
daily did not improve as much as 10 patients receiving only imipramine. Also, the patients on the combin
side-effects including lethargy, coarse tremor and systolic hypotension (Prange, 1972b).

b) A 32-year-old female taking conjugated estrogens 2.5 mg and imipramine 100 mg developed lethargy
signs of depersonalization. After two years of therapy, the patient increased her estrogen dose to 5 mg a
daily. The patient became nauseated, had constant headaches, and low normal blood pressure. All lab v
Upon discontinuing the estrogen, the side effects abated. Some investigators have proposed that the sid
from enhanced TCA effects secondary to estrogen inhibition of hepatic microsomal enzymes (Somani &
Khurana, 1972b).

c) In a study women received clomipramine and oral contraceptives or clomipramine alone. At the begir
there were 30 women taking the combination, but 12 subsequently dropped out. The 18 patients on the c
matched with 18 patients taking clomipramine alone. No significant difference was noted in the patients'
clomipramine. It was proposed that there was no significant difference in side-effects between the groups
groups were matched after patients had dropped out of the study. Had the patients been matched prior t
different conclusions may have been drawn (Beaumont, 1973a).

d) The effects of oral contraceptives on clomipramine was studied in 42 women between the ages of 18
three women took clomipramine 25 mg at bedtime while 19 took clomipramine 25 mg at bedtime with ora
Over the four-week study, three control patients (two due to side-effects) and five in the experimental gro
side-effects) dropped out. Venous blood samples were drawn at weekly intervals for measurement of ser
concentrations. No difference in serum concentrations was noted between the groups. However, this res
due to the low dose of clomipramine given (Luscombe & John, 1980a).

e) The onset of akathisia was reported in 3 patients receiving conjugated estrogens and tricyclic antidep
concurrently. A 24-year-old patient receiving clomipramine 120 mg daily for anorexia nervosa and conjug
1.25 mg daily for amenorrhea developed restless legs and a constant desire to move continuously. Estro
discontinued and benztropine 2 mg was administered, resulting in marked reduction and resolution withi
Akathisia and disorientation developed in a 55-year-old patient on conjugated estrogen 1.25 mg daily wh
amitriptyline 50 mg daily for depression. Within hours of amitriptyline, the patient was confused, restless,
inner desire to move continuously. Symptoms disappeared after discontinuing amitriptyline. A third case
reported in a 35-year-old patient who received conjugated estrogen 1.25 mg daily and amitriptyline 50 m
developed within a few hours after taking the first dose of amitriptyline and resolved within 48 hours follo
discontinuation of the antidepressant (Krishnan et al, 1984b).

f) The absolute bioavailability of imipramine increased in women who received low-dose oral contracept
less of ethinyl estradiol) from 27% to 44% (p less than 0.05) as evident by an increase in the area under
concentration time curve (Abernethy et al, 1984a).

g) Estrogens may inhibit the oxidation of TCAs by affecting hepatic microsomal enzymes (John et al, 19
are metabolized via oxidation and conjugation pathways. Inhibition of the oxidation of TCAs could result
and toxicity due to decreased clearance. Estrogens are suspected of possessing other effects on the cer
system resulting in an antidepressant effect (Oppenheim, 1983a).

3.5.1.BH Estradiol

1) Interaction Effect: possible attenuation of antidepressant effectiveness; tricyclic toxicity (drowsiness, hypo

2) Summary: In isolated cases, the pharmacologic effects of tricyclic antidepressants may be increased or de
estrogens (Somani & Khurana, 1973c), with paradoxical loss of antidepressant effect yet tricyclic toxicity bein
simultaneously (Prange, 1972c). The effects of the interaction appear to be estrogen dose-related (Khurana,
be of clinical importance primarily in patients previously stabilized on tricyclic therapy who are being started o
(Krishnan et al, 1984c).

3) Severity: minor

4) Onset: delayed

5) Substantiation: established

6) Clinical Management: If signs or symptoms of altered tricyclic response are noted, dose adjustment down
estrogen or tricyclic component may be successful in restoring effectiveness or resolving toxicity. However, d
may be required.

7) Probable Mechanism: possible inhibition of hepatic metabolism of the tricyclic antidepressant

8) Literature Reports

a) Some studies evaluated the qualitative effects of concomitant administration of estrogen and TCAs. I
depressed female prisoners were randomly assigned to four treatment groups. Ten patients received pla
imipramine (150 mg daily) and placebo, five patients received imipramine (150 mg daily) and ethinyl estr
daily), while five patients received imipramine (150 mg daily) and ethinyl estradiol (25 mcg daily). The 10
received placebo did not improve over the six weeks of the study. The 10 patients taking estrogen and in
demonstrated a significantly greater improvement in symptoms than did the 10 patients taking imipramin
after two weeks, the five patients that received imipramine and high-dose estrogen had not improved as
patients receiving imipramine and low-dose estrogen. The only side-effect reported was drowsiness, whi
the patients taking imipramine. Following the discontinuation of ethinyl estradiol, a time period of two wee
for the high-dose estrogen group to do as well as the low-dose group. This effect was attributed to the pr
estrogen in the high-dose group. In another group, five women received imipramine 150 mg and ethinyl e
daily did not improve as much as 10 patients receiving only imipramine. Also, the patients on the combin
side-effects including lethargy, coarse tremor and systolic hypotension (Prange, 1972b).

b) A 32-year-old female taking conjugated estrogens 2.5 mg and imipramine 100 mg developed lethargy signs of depersonalization. After two years of therapy, the patient increased her estrogen dose to 5 mg a daily. The patient became nauseated, had constant headaches, and low normal blood pressure. All lab v Upon discontinuing the estrogen, the side effects abated. Some investigators have proposed that the sid from enhanced TCA effects secondary to estrogen inhibition of hepatic microsomal enzymes (Somani & Khurana, 1972b).

c) In a study women received clomipramine and oral contraceptives or clomipramine alone. At the begin there were 30 women taking the combination, but 12 subsequently dropped out. The 18 patients on the c matched with 18 patients taking clomipramine alone. No significant difference was noted in the patients' clomipramine. It was proposed that there was no significant difference in side-effects between the groups groups were matched after patients had dropped out of the study. Had the patients been matched prior t different conclusions may have been drawn (Beaumont, 1973a).

d) The effects of oral contraceptives on clomipramine was studied in 42 women between the ages of 18 three women took clomipramine 25 mg at bedtime while 19 took clomipramine 25 mg at bedtime with ora Over the four-week study, three control patients (two due to side-effects) and five in the experimental gro side-effects) dropped out. Venous blood samples were drawn at weekly intervals for measurement of se concentrations. No difference in serum concentrations was noted between the groups. However, this res due to the low dose of clomipramine given (Luscombe & John, 1980a).

e) The onset of akathisia was reported in 3 patients receiving conjugated estrogens and tricyclic antidep concurrently. A 24-year-old patient receiving clomipramine 120 mg daily for anorexia nervosa and conjug 1.25 mg daily for amenorrhea developed restless legs and a constant desire to move continuously. Estro discontinued and benztropine 2 mg was administered, resulting in marked reduction and resolution withi Akathisia and disorientation developed in a 55-year-old patient on conjugated estrogen 1.25 mg daily wh amitriptyline 50 mg daily for depression. Within hours of amitriptyline, the patient was confused, restless, inner desire to move continuously. Symptoms disappeared after discontinuing amitriptyline. A third case reported in a 35-year-old patient who received conjugated estrogen 1.25 mg daily and amitriptyline 50 m developed within a few hours after taking the first dose of amitriptyline and resolved within 48 hours follo discontinuation of the antidepressant (Krishnan et al, 1984b).

f) The absolute bioavailability of imipramine increased in women who received low-dose oral contracept less of ethinyl estradiol) from 27% to 44% (p less than 0.05) as evident by an increase in the area under concentration time curve (Abernethy et al, 1984a).

g) Estrogens may inhibit the oxidation of TCAs by affecting hepatic microsomal enzymes (John et al, 19 are metabolized via oxidation and conjugation pathways. Inhibition of the oxidation of TCAs could result and toxicity due to decreased clearance. Estrogens are suspected of possessing other effects on the cer system resulting in an antidepressant effect (Oppenheim, 1983a).

3.5.1.BI Estriol

1) Interaction Effect: possible attenuation of antidepressant effectiveness; tricyclic toxicity (drowsiness, hypo

2) Summary: In isolated cases, the pharmacologic effects of tricyclic antidepressants may be increased or de estrogens (Somani & Khurana, 1973c), with paradoxical loss of antidepressant effect yet tricyclic toxicity bein simultaneously (Prange, 1972c). The effects of the interaction appear to be estrogen dose-related (Khurana, be of clinical importance primarily in patients previously stabilized on tricyclic therapy who are being started o (Krishnan et al, 1984c).

3) Severity: minor

4) Onset: delayed

5) Substantiation: established

6) Clinical Management: If signs or symptoms of altered tricyclic response are noted, dose adjustment down estrogen or tricyclic component may be successful in restoring effectiveness or resolving toxicity. However, d may be required.

7) Probable Mechanism: possible inhibition of hepatic metabolism of the tricyclic antidepressant

8) Literature Reports

a) Some studies evaluated the qualitative effects of concomitant administration of estrogen and TCAs. I depressed female prisoners were randomly assigned to four treatment groups. Ten patients received pla imipramine (150 mg daily) and placebo, five patients received imipramine (150 mg daily) and ethinyl estr daily), while five patients received imipramine (150 mg daily) and ethinyl estradiol (25 mcg daily). The 10 received placebo did not improve over the six weeks of the study. The 10 patients taking estrogen and in demonstrated a significantly greater improvement in symptoms than did the 10 patients taking imipramin after two weeks, the five patients that received imipramine and high-dose estrogen had not improved as patients receiving imipramine and low-dose estrogen. The only side-effect reported was drowsiness, whi the patients taking imipramine. Following the discontinuation of ethinyl estradiol, a time period of two wee for the high-dose estrogen group to do as well as the low-dose group. This effect was attributed to the pr estrogen in the high-dose group. In another group, five women received imipramine 150 mg and ethinyl e daily did not improve as much as 10 patients receiving only imipramine. Also, the patients on the combin side-effects including lethargy, coarse tremor and systolic hypotension (Prange, 1972b).

b) A 32-year-old female taking conjugated estrogens 2.5 mg and imipramine 100 mg developed lethargy signs of depersonalization. After two years of therapy, the patient increased her estrogen dose to 5 mg a daily. The patient became nauseated, had constant headaches, and low normal blood pressure. All lab v Upon discontinuing the estrogen, the side effects abated. Some investigators have proposed that the sid

from enhanced TCA effects secondary to estrogen inhibition of hepatic microsomal enzymes (Somani & Khurana, 1972b).

c) In a study women received clomipramine and oral contraceptives or clomipramine alone. At the begin there were 30 women taking the combination, but 12 subsequently dropped out. The 18 patients on the matched with 18 patients taking clomipramine alone. No significant difference was noted in the patients' clomipramine. It was proposed that there was no significant difference in side-effects between the groups groups were matched after patients had dropped out of the study. Had the patients been matched prior t different conclusions may have been drawn (Beaumont, 1973a).

d) The effects of oral contraceptives on clomipramine was studied in 42 women between the ages of 18 three women took clomipramine 25 mg at bedtime while 19 took clomipramine 25 mg at bedtime with ora Over the four-week study, three control patients (two due to side-effects) and five in the experimental gro side-effects) dropped out. Venous blood samples were drawn at weekly intervals for measurement of se concentrations. No difference in serum concentrations was noted between the groups. However, this res due to the low dose of clomipramine given (Luscombe & John, 1980a).

e) The onset of akathisia was reported in 3 patients receiving conjugated estrogens and tricyclic antidep concurrently. A 24-year-old patient receiving clomipramine 120 mg daily for anorexia nervosa and conjug 1.25 mg daily for amenorrhea developed restless legs and a constant desire to move continuously. Estro discontinued and benztropine 2 mg was administered, resulting in marked reduction and resolution withi Akathisia and disorientation developed in a 55-year-old patient on conjugated estrogen 1.25 mg daily wh amitriptyline 50 mg daily for depression. Within hours of amitriptyline, the patient was confused, restless, inner desire to move continuously. Symptoms disappeared after discontinuing amitriptyline. A third case reported in a 35-year-old patient who received conjugated estrogen 1.25 mg daily and amitriptyline 50 m developed within a few hours after taking the first dose of amitriptyline and resolved within 48 hours follo discontinuation of the antidepressant (Krishnan et al, 1984b).

f) The absolute bioavailability of imipramine increased in women who received low-dose oral contracept less of ethinyl estradiol) from 27% to 44% (p less than 0.05) as evident by an increase in the area under concentration time curve (Abernethy et al, 1984a).

g) Estrogens may inhibit the oxidation of TCAs by affecting hepatic microsomal enzymes (John et al, 19 are metabolized via oxidation and conjugation pathways. Inhibition of the oxidation of TCAs could result and toxicity due to decreased clearance. Estrogens are suspected of possessing other effects on the cer system resulting in an antidepressant effect (Oppenheim, 1983a).

3.5.1.BJ Estrone

1) Interaction Effect: possible attenuation of antidepressant effectiveness; tricyclic toxicity (drowsiness, hypo

2) Summary: In isolated cases, the pharmacologic effects of tricyclic antidepressants may be increased or d estrogens (Somani & Khurana, 1973c), with paradoxical loss of antidepressant effect yet tricyclic toxicity bein simultaneously (Prange, 1972c). The effects of the interaction appear to be estrogen dose-related (Khurana, be of clinical importance primarily in patients previously stabilized on tricyclic therapy who are being started o (Krishnan et al, 1984c).

3) Severity: minor

4) Onset: delayed

5) Substantiation: established

6) Clinical Management: If signs or symptoms of altered tricyclic response are noted, dose adjustment down estrogen or tricyclic component may be successful in restoring effectiveness or resolving toxicity. However, d may be required.

7) Probable Mechanism: possible inhibition of hepatic metabolism of the tricyclic antidepressant

8) Literature Reports

a) Some studies evaluated the qualitative effects of concomitant administration of estrogen and TCAs. I depressed female prisoners were randomly assigned to four treatment groups. Ten patients received pla imipramine (150 mg daily) and placebo, five patients received imipramine (150 mg daily) and ethinyl estr daily), while five patients received imipramine (150 mg daily) and ethinyl estradiol (25 mcg daily). The 10 received placebo did not improve over the six weeks of the study. The 10 patients taking estrogen and in demonstrated a significantly greater improvement in symptoms than did the 10 patients taking imipramin after two weeks, the five patients that received imipramine and high-dose estrogen had not improved as patients receiving imipramine and low-dose estrogen. The only side-effect reported was drowsiness, whi the patients taking imipramine. Following the discontinuation of ethinyl estradiol, a time period of two we for the high-dose estrogen group to do as well as the low-dose group. This effect was attributed to the pr estrogen in the high-dose group. In another group, five women received imipramine 150 mg and ethinyl daily did not improve as much as 10 patients receiving only imipramine. Also, the patients on the combin side-effects including lethargy, coarse tremor and systolic hypotension (Prange, 1972b).

b) A 32-year-old female taking conjugated estrogens 2.5 mg and imipramine 100 mg developed lethargy signs of depersonalization. After two years of therapy, the patient increased her estrogen dose to 5 mg a daily. The patient became nauseated, had constant headaches, and low normal blood pressure. All lab v Upon discontinuing the estrogen, the side effects abated. Some investigators have proposed that the sid from enhanced TCA effects secondary to estrogen inhibition of hepatic microsomal enzymes (Somani & Khurana, 1972b).

c) In a study women received clomipramine and oral contraceptives or clomipramine alone. At the begin there were 30 women taking the combination, but 12 subsequently dropped out. The 18 patients on the

matched with 18 patients taking clomipramine alone. No significant difference was noted in the patients' clomipramine. It was proposed that there was no significant difference in side-effects between the groups groups were matched after patients had dropped out of the study. Had the patients been matched prior t different conclusions may have been drawn (Beaumont, 1973a).

d) The effects of oral contraceptives on clomipramine was studied in 42 women between the ages of 18 three women took clomipramine 25 mg at bedtime while 19 took clomipramine 25 mg at bedtime with ora Over the four-week study, three control patients (two due to side-effects) and five in the experimental gro side-effects) dropped out. Venous blood samples were drawn at weekly intervals for measurement of se concentrations. No difference in serum concentrations was noted between the groups. However, this res due to the low dose of clomipramine given (Luscombe & John, 1980a).

e) The onset of akathisia was reported in 3 patients receiving conjugated estrogens and tricyclic antidep concurrently. A 24-year-old patient receiving clomipramine 120 mg daily for anorexia nervosa and conjug 1.25 mg daily for amenorrhea developed restless legs and a constant desire to move continuously. Estro discontinued and benztropine 2 mg was administered, resulting in marked reduction and resolution withi Akathisia and disorientation developed in a 55-year-old patient on conjugated estrogen 1.25 mg daily wh amitriptyline 50 mg daily for depression. Within hours of amitriptyline, the patient was confused, restless, inner desire to move continuously. Symptoms disappeared after discontinuing amitriptyline. A third case reported in a 35-year-old patient who received conjugated estrogen 1.25 mg daily and amitriptyline 50 m developed within a few hours after taking the first dose of amitriptyline and resolved within 48 hours follo discontinuation of the antidepressant (Krishnan et al, 1984b).

f) The absolute bioavailability of imipramine increased in women who received low-dose oral contracept less of ethinyl estradiol) from 27% to 44% (p less than 0.05) as evident by an increase in the area under concentration time curve (Abernethy et al, 1984a).

g) Estrogens may inhibit the oxidation of TCAs by affecting hepatic microsomal enzymes (John et al, 19 are metabolized via oxidation and conjugation pathways. Inhibition of the oxidation of TCAs could result and toxicity due to decreased clearance. Estrogens are suspected of possessing other effects on the cer system resulting in an antidepressant effect (Oppenheim, 1983a).

3.5.1.BK Estropipate

1) Interaction Effect: possible attenuation of antidepressant effectiveness; tricyclic toxicity (drowsiness, hypo

2) Summary: In isolated cases, the pharmacologic effects of tricyclic antidepressants may be increased or de estrogens (Somani & Khurana, 1973c), with paradoxical loss of antidepressant effect yet tricyclic toxicity bein simultaneously (Prange, 1972c). The effects of the interaction appear to be estrogen dose-related (Khurana, be of clinical importance primarily in patients previously stabilized on tricyclic therapy who are being started o (Krishnan et al, 1984c).

3) Severity: minor

4) Onset: delayed

5) Substantiation: established

6) Clinical Management: If signs or symptoms of altered tricyclic response are noted, dose adjustment down estrogen or tricyclic component may be successful in restoring effectiveness or resolving toxicity. However, d may be required.

7) Probable Mechanism: possible inhibition of hepatic metabolism of the tricyclic antidepressant

8) Literature Reports

a) Some studies evaluated the qualitative effects of concomitant administration of estrogen and TCAs. I depressed female prisoners were randomly assigned to four treatment groups. Ten patients received pla imipramine (150 mg daily) and placebo, five patients received imipramine (150 mg daily) and ethinyl estr daily), while five patients received imipramine (150 mg daily) and ethinyl estradiol (25 mcg daily). The 10 received placebo did not improve over the six weeks of the study. The 10 patients taking estrogen and in demonstrated a significantly greater improvement in symptoms than did the 10 patients taking imipramin after two weeks, the five patients that received imipramine and high-dose estrogen had not improved as patients receiving imipramine and low-dose estrogen. The only side-effect reported was drowsiness, whi the patients taking imipramine. Following the discontinuation of ethinyl estradiol, a time period of two we for the high-dose estrogen group to do as well as the low-dose group. This effect was attributed to the pr estrogen in the high-dose group. In another group, five women received imipramine 150 mg and ethinyl daily did not improve as much as 10 patients receiving only imipramine. Also, the patients on the combin side-effects including lethargy, coarse tremor and systolic hypotension (Prange, 1972b).

b) A 32-year-old female taking conjugated estrogens 2.5 mg and imipramine 100 mg developed lethargy signs of depersonalization. After two years of therapy, the patient increased her estrogen dose to 5 mg a daily. The patient became nauseated, had constant headaches, and low normal blood pressure. All lab v Upon discontinuing the estrogen, the side effects abated. Some investigators have proposed that the sid from enhanced TCA effects secondary to estrogen inhibition of hepatic microsomal enzymes (Somani & Khurana, 1972b).

c) In a study women received clomipramine and oral contraceptives or clomipramine alone. At the begin there were 30 women taking the combination, but 12 subsequently dropped out. The 18 patients on the matched with 18 patients taking clomipramine alone. No significant difference was noted in the patients' clomipramine. It was proposed that there was no significant difference in side-effects between the groups groups were matched after patients had dropped out of the study. Had the patients been matched prior t different conclusions may have been drawn (Beaumont, 1973a).

d) The effects of oral contraceptives on clomipramine was studied in 42 women between the ages of 18 three women took clomipramine 25 mg at bedtime while 19 took clomipramine 25 mg at bedtime with ora Over the four-week study, three control patients (two due to side-effects) and five in the experimental gro side-effects) dropped out. Venous blood samples were drawn at weekly intervals for measurement of se concentrations. No difference in serum concentrations was noted between the groups. However, this res due to the low dose of clomipramine given (Luscombe & John, 1980a).

e) The onset of akathisia was reported in 3 patients receiving conjugated estrogens and tricyclic antidep concurrently. A 24-year-old patient receiving clomipramine 120 mg daily for anorexia nervosa and conjug 1.25 mg daily for amenorrhea developed restless legs and a constant desire to move continuously. Estro discontinued and benztropine 2 mg was administered, resulting in marked reduction and resolution withi Akathisia and disorientation developed in a 55-year-old patient on conjugated estrogen 1.25 mg daily wh amitriptyline 50 mg daily for depression. Within hours of amitriptyline, the patient was confused, restless, inner desire to move continuously. Symptoms disappeared after discontinuing amitriptyline. A third case reported in a 35-year-old patient who received conjugated estrogen 1.25 mg daily and amitriptyline 50 m developed within a few hours after taking the first dose of amitriptyline and resolved within 48 hours follo discontinuation of the antidepressant (Krishnan et al, 1984b).

f) The absolute bioavailability of imipramine increased in women who received low-dose oral contracept less of ethinyl estradiol) from 27% to 44% (p less than 0.05) as evident by an increase in the area under concentration time curve (Abernethy et al, 1984a).

g) Estrogens may inhibit the oxidation of TCAs by affecting hepatic microsomal enzymes (John et al, 19 are metabolized via oxidation and conjugation pathways. Inhibition of the oxidation of TCAs could result and toxicity due to decreased clearance. Estrogens are suspected of possessing other effects on the cer system resulting in an antidepressant effect (Oppenheim, 1983a).

3.5.1.BL Eterobarb

1) Interaction Effect: possible decreased tricyclic antidepressant serum concentrations and possible additive

2) Summary: Concomitant barbiturate and tricyclic antidepressant (TCA) therapy may result in increased me TCA. There have been scattered reports of individuals with decreased serum levels of TCAs in the presence (Moody et al, 1977; Silverman & Braithwaite, 1972; Burrows & Davies, 1971). In addition, TCAs can worsen s reducing the seizure threshold (Brodie, 1992). These drugs also have additive CNS and respiratory depressa

3) Severity: minor

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Monitor for efficacy of antidepressant effect. Increases in tricyclic antidepressant do required. Additionally, monitor for toxicity when either drug is added to or withdrawn from therapy. Serum con be of value in determining appropriate dosage.

7) Probable Mechanism: increased tricyclic antidepressant metabolism

8) Literature Reports

a) The pharmacokinetics of a single oral dose of desipramine (100 mg) were studied in eight epileptic pa treated with phenobarbital and in eight drug-free healthy controls (Spina et al, 1996). All subjects were e metabolizers with respect to the genetically determined CYP2D6-related metabolic polymorphism. Comp epileptic patients exhibited lower peak plasma desipramine concentrations (74 nmol/L vs. 107 nmol/L), s area under the concentration-time curve values (1943 nmol/L/h vs. 3234 nmol/L/h), and shorter desipram half-lives (15.1 h vs. 20.6 h). All barbiturates are believed to have similar effects leading to induction of h and the 2D6 isozyme is believed to be important in the metabolism of most or all TCAs. Thus, similar eff expected with any combination of TCA and barbiturate.

3.5.1.BM Ethinyl Estradiol

1) Interaction Effect: possible attenuation of antidepressant effectiveness; tricyclic toxicity (drowsiness, hypo

2) Summary: In isolated cases, the pharmacologic effects of tricyclic antidepressants may be increased or d estrogens (Somani & Khurana, 1973i), with paradoxical loss of antidepressant effect yet tricyclic toxicity being simultaneously (Prange, 1972i). The effects of the interaction appear to be estrogen dose-related (Khurana, 1 of clinical importance primarily in patients previously stabilized on tricyclic therapy who are being started on e (Krishnan et al, 1984i).

3) Severity: minor

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: If signs or symptoms of altered tricyclic response are noted, dose adjustment down estrogen or tricyclic component may be successful in restoring effectiveness or resolving toxicity. However, d may be required.

7) Probable Mechanism: possible inhibition of hepatic metabolism of the tricyclic antidepressant

8) Literature Reports

a) Some studies evaluated the qualitative effects of concomitant administration of estrogen and TCAs. I depressed female prisoners were randomly assigned to 4 treatment groups. Ten patients received place imipramine (150 milligrams/day) and placebo, 5 patients received imipramine (150 milligrams/day) and e micrograms/day), while 5 patients received imipramine (150 milligrams/day) and ethinyl estradiol (25 mic 10 patients that received placebo did not improve over the 6 weeks of the study. The 10 patients taking e imipramine demonstrated a significantly greater improvement in symptoms than did the 10 patients takin

alone. However, after 2 weeks, the 5 patients that received imipramine and high-dose estrogen had not i
as the patients receiving imipramine and low-dose estrogen. The only side-effect reported was drowsine
affected the patients taking imipramine. Following the discontinuation of ethinyl estradiol, a time period o
required for the high-dose estrogen group to do as well as the low-dose group. This effect was attributed
residual estrogen in the high-dose group. In another group, 5 women received imipramine 150 milligram
estradiol 50 micrograms daily did not improve as much as 10 patients receiving only imipramine. Also, th
combination had severe side-effects including lethargy, coarse tremor and systolic hypotension (Prange,
b) A case report demonstrated an interaction in a 32-year-old female taking conjugated estrogens 2.5 m
imipramine 100 milligrams (Khurana, 1972h). The patient developed lethargy, tremors, and signs of depe
After 2 years of therapy, the patient increased her estrogen dose to 5 milligrams and then 7.5 milligrams
became nauseated, had constant headaches, and low normal blood pressure. All lab work was normal. U
the estrogen, the side-effects abated. Some investigators have proposed that the side effects resulted fr
effects secondary to estrogen inhibition of hepatic microsomal enzymes (Somani & Khurana, 1973h).
c) In a study women received clomipramine and oral contraceptives or clomipramine alone. At the begir
there were 30 women taking the combination, but 12 subsequently dropped out. The 18 patients on the
matched with 18 patients taking clomipramine alone. No significant difference was noted in the patients'
clomipramine. It was proposed that there was no significant difference in side-effects between the groups
groups were matched after patients had dropped out of the study. Had the patients been matched prior t
different conclusions may have been drawn (Beaumont, 1973e).
d) The effects of oral contraceptives on clomipramine was studied in 42 women between the ages of 18
three women took clomipramine 25 milligrams at bedtime while 19 took clomipramine 25 milligrams at be
contraceptives. Over the 4-week study, 3 control patients (2 due to side-effects) and 5 in the experimenta
side-effects) dropped out. Venous blood samples were drawn at weekly intervals for measurement of se
concentrations. No difference in serum concentrations was noted between the groups. However, this res
due to the low dose of clomipramine given (Luscombe & John, 1980d).
e) The onset of akathisia was reported in 3 patients receiving conjugated estrogens and tricyclic antidep
concurrently. A 24-year-old patient receiving clomipramine 120 milligrams/day for anorexia nervosa and
estrogens 1.25 milligrams/day for amenorrhea developed restless legs and a constant desire to move co
Estrogen was discontinued and benztropine 2 milligrams was administered, resulting in marked reductio
within 48 hours. Akathisia and disorientation developed in a 55-year-old patient on conjugated estrogens
milligrams/day who was prescribed amitriptyline 50 milligrams/day for depression. Within hours of amitrip
was confused, restless, and possessed an inner desire to move continuously. Symptoms disappeared af
amitriptyline. Positive rechallenge at one week with doxepin 100 milligrams, with resolution following disc
doxepin. A third case of akathisia was reported in a 35-year-old patient who received conjugated estroge
milligrams/day and amitriptyline 50 milligrams/day. Akathisia developed within a few hours after taking th
amitriptyline and resolved within 48 hours following discontinuation of the antidepressant (Krishnan et al,
f) The absolute bioavailability of imipramine increased in women who received low-dose oral contracept
micrograms or less of ethinyl estradiol) from 27 to 44% (p less than 0.05) as evident by an increase in th
plasma concentration time curve (Abernethy et al, 1984e).
g) Estrogens may inhibit the oxidation of TCAs by affecting hepatic microsomal enzymes (John et al, 19
are metabolized via oxidation and conjugation pathways. Inhibition of the oxidation of TCAs could result
and toxicity due to decreased clearance. Estrogens are suspected of possessing other effects on the cer
system resulting in an antidepressant effect (Oppenheim, 1983d).

3.5.1.BN Etilefrine

1) Interaction Effect: hypertension, cardiac arrhythmias, and tachycardia
2) Summary: Clinical trials have demonstrated a 2- to 8-fold increase in the effects of intravenous infusions o
drugs to volunteers on tricyclic antidepressants. Arrhythmias and other severe adverse effects have also bee
1980; Avery, 1973a; Boakes et al, 1973a; Boakes, 1973; Mitchell et al, 1970; Stone et al, 1964a). Local use (
anesthesia) of epinephrine in concentrations of 1:100,000 or less is less likely to precipitate clinically significa
changes (Steinberg & Block, 1971).
3) Severity: major
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: The vasoconstriction and other alpha-adrenergic effects of sympathomimetic drugs
enhanced in the presence of tricyclic antidepressants (TCAs). Concomitant use should be avoided. If these d
together, careful monitoring and a dose reduction of the sympathomimetic is required. Patients should be inst
their doctor or dentist that they are taking a tricyclic antidepressant prior to any surgery or procedure.
7) Probable Mechanism: inhibition of norepinephrine reuptake
8) Literature Reports
a) Four healthy volunteers received intravenous infusions of various sympathomimetic amines (epineph
norepinephrine, phenylephrine, and isoproterenol) before and after imipramine (25 mg three times daily f
showed an increased pressor response to epinephrine (2- to 4-fold), norepinephrine (4- to 8-fold), and ph
3-fold) after imipramine, but no difference was observed in the response to isoproterenol. Thus, the incre
response appeared to occur only for alpha adrenergic effects. All four subjects demonstrated changes in
with epinephrine and imipramine consisting of sinus arrhythmia in three subjects and multiple ectopic be
rhythm in the fourth subject (Boakes et al, 1973).
b) A review of spontaneous reports of adverse reactions to vasoconstrictors in local anesthetics found th

receiving a local anesthetic with norepinephrine (1:25,000) had severe reactions (severe headaches, che subarachnoid hemorrhage). The drug history was incomplete, but at least three had been taking a tricycl at the time (Anon, 1972).

3.5.1.BO Fenfluramine

1) Interaction Effect: hypertension, other cardiac effects, and CNS stimulation

2) Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been reporte enhanced amphetamine effects from the release of norepinephrine (Beaumont, 1973d; Raisfeld, 1972). A sim also occur with all drugs that have amphetamine-like effects. Acute elevations in blood pressure have been n (Flemenbaum, 1971a). Some amphetamine-like drugs may inhibit the metabolism of TCAs, although most co not been studied. When amphetamine analogs are being used to treat obesity, it should be noted that TCAs f moderate weight gain (Russ & Ackerman, 1988). False positive urine tests for amphetamines have been repo therapy with some TCAs (Merigian & Browning, 1993). Caution is advised when concurrent administration of agents and TCAs is warranted. The patient should be closely monitored for increased cardiovascular effects dysrhythmias).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other sympatho could lead to hypertension, increased cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) o Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral t Flemenbaum, 1972). Use caution if such therapy is warranted. Monitor the patient closely for hypertension ar

7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission

8) Literature Reports

a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agen coadministration of d-amphetamine with TCAs such as desipramine or protriptyline results in sustained i amphetamine concentration in the brain (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info DEXE sustained-release oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006).

b) Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism c antidepressants, such as imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transde 2006).

c) Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases i such that the hypotensive effects induced by TCAs may lead to blood pressures as high as 170/120 mm of combined therapy. Discontinuation of the methylphenidate usually results in the blood pressure return normotensive levels; reinstitution of the methylphenidate resulted in further blood pressure elevation (Fle Flemenbaum, 1972).

d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine g four weeks, were given fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transi clinical improvement. However, fenfluramine more than doubled steady-state plasma levels of desiprami 1990).

e) There have been claims based on uncontrolled studies that a better antidepressant response may oc therapy (Garrettson et al, 1969). However, a systemic review of stimulants in the treatment of depressior although uncontrolled studies were generally positive, the ten placebo-controlled studies of stimulant dru depression, with one exception, indicated little advantage of drug over placebo and did not appear to be conventional antidepressants in primary depression (Satel & Nelson, 1989).

3.5.1.BP Fenfluramine

1) Interaction Effect: an increased risk of imipramine toxicity (sedation)

2) Summary: When fenfluramine was added to imipramine therapy, the blood concentration of imipramine pl was dramatically increased in a 55-year old female. The increased blood levels caused the patient to fall asle (Fogelson, 1997a).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: If fenfluramine is used in combination with imipramine, the patient should be monitc sedation, hypertension and dysrhythmias.

7) Probable Mechanism: inhibition of imipramine metabolism

8) Literature Reports

a) A 55-year old female patient was maintained on imipramine 350 mg daily for several years, with imipr desipramine blood levels ranging from 218 mcg/L to 145 mcg/L. After four weeks of treatment with fenflu three times daily, the patient fell asleep while driving. The imipramine plus desipramine level was 704 mc may have inhibited the cytochrome p450 isoenzyme responsible for metabolizing imipramine (Fogelson,

b) A study was conducted in 15 patients with DSM-III major depression who failed to respond to treatme desipramine given for at least four weeks. Fenfluramine 40 mg to 120 mg daily for two weeks was then a transient or sustained clinical improvement. However, fenfluramine more than doubled steady-state plas desipramine (Price et al, 1990a).

3.5.1.BQ Flecainide

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Class I antiarrhythmics have been shown to prolong the QTc interval at the recommended ther Even though no formal drug interaction studies have been done, the coadministration of Class I antiarrhythmi known to prolong the QTc interval, including tricyclic antidepressants, is not recommended (Prod Info Tambo acetate, 1998; Larochelle et al, 1984; Scagliotti et al, 1982).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of a Class I antiarrhythmic and a tricyclic antidepress recommended.
7) Probable Mechanism: additive effects on QT prolongation
8) Literature Reports
a) EKG effects reported in patients receiving therapeutic doses of tricyclic antidepressants include incre prolonged PR interval, intraventricular conduction delays, increased corrected QT interval (QTc) and flat (Marshall & Forker, 1982q).
b) A 68-year-old man suffering from agitated major depression was begun on a dose of desipramine 12 produced a subtherapeutic serum level of 442 nmol/L (therapeutic range = 500 to 1000 nmol/L). An incre mg daily produced excellent clinical response with no side effects. He developed atrial fibrillation and flut mg daily was added to his therapy, and desipramine was discontinued. His arrhythmia was suppressed v propafenone 150 mg twice daily and 300 mg at bedtime. Desipramine 150 mg daily was again begun, at experienced dry mouth, sedation, and shakiness; the desipramine serum level was measured at 2092 nr desipramine was discontinued for five days, the side effects ceased, and desipramine therapy was resur The desipramine serum level was measured at 1130 nmol/L (Katz, 1991).

3.5.1.BR Fluconazole

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Case reports have described QT prolongation and torsades de points associated with fluconaz al, 1999). Several tricyclic antidepressants (TCAs) have been shown to prolong the QTc interval at the recom therapeutic dose (Marshall & Forker, 1982x). Even though no formal drug interaction studies have been done coadministration of drugs known to prolong the QTc interval is not recommended.
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of fluconazole and a tricyclic antidepressant is not re
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.BS Fluoxetine

1) Interaction Effect: tricyclic antidepressant toxicity (dry mouth, urinary retention, sedation) and an increase cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Tricyclic antidepressants (TCAs) and fluoxetine have been shown to prolong the QTc interval a recommended therapeutic dose (Prod Info Prozac(R), 2001; Marshall & Forker, 1982h). Even though no form studies have been done which demonstrate QT prolongation, the coadministration of tricyclic antidepressants known to prolong the QTc interval, such as fluoxetine, is not recommended (Prod Info Elavil(R), 1999d). In ac use of fluoxetine and TCAs such as desipramine, nortriptyline, and imipramine has resulted in significant incr concentrations (Preskorn et al, 1994a; Preskorn et al, 1994a; Aranow et al, 1989a; Downs et al, 1989a; Gooc & Cole, 1988a).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: The concurrent administration of fluoxetine and a tricyclic antidepressant is not rec
7) Probable Mechanism: decreased tricyclic antidepressant metabolism; additive effects on QT prolongation
8) Literature Reports
a) Fluoxetine increased the level of tricyclic antidepressants (nortriptyline, imipramine, desipramine) in 4 addition of fluoxetine, the ratio of antidepressant level to dose increased by 109% to 486% in the patient developed clinical symptoms (anticholinergic effects, constipation, urinary hesitancy, sedation, unstable the increased levels (Aranow et al, 1989).
b) Fluoxetine statistically and clinically significantly increased desipramine concentrations in 18 healthy fluoxetine (20 mg daily) was added to desipramine (50 mg daily), the mean maximum concentration of d increased by 278% and the area under the concentration-time curve increased by 342%. Desipramine tr concentrations continued to be 198% above baseline three weeks after fluoxetine was discontinued. The compared pharmacokinetics of desipramine when combined with sertraline. The impact of sertraline was in small and short-term increases in desipramine plasma concentrations (Preskorn et al, 1994).
c) A 75-year-old female experienced symptomatic increases in her desipramine serum concentrations w was added. Desipramine serum levels ranged from 109 to 150 ng/mL with oral doses of 300 mg at bedti fluoxetine therapy. Following the addition of oral fluoxetine 20 mg daily to the regimen, the desipramine s increased to 212 ng/mL within five days. The fluoxetine dose was increased to 40 mg/day three days late desipramine serum level was 419 ng/mL after four days. A worsening of depression and severe fatigue c increases in desipramine serum levels. Withdrawal of fluoxetine and reduction in the desipramine dose t

reduced the desipramine serum level to 231 ng/mL within two weeks (Bell & Cole, 1988).
d) A 33-year-old depressed male developed adverse effects of dry mouth, tinnitus, and difficulties with a memory while receiving fluoxetine 40 mg daily and desipramine 150 mg daily for five weeks; fluoxetine w and the blood levels of desipramine decreased from 938 to 48 ng/mL with resolution of clinical symptoms 1989).
e) A 39-year-old female experienced symptomatic increases in her desipramine levels with concomitant Prior to fluoxetine therapy, the patient's measured levels of desipramine had ranged from 148 to 160 ng/ of 300 mg daily. Five weeks after the addition of fluoxetine 20 mg daily, she reported anticholinergic sym and confusion with a desipramine level of 527 ng/mL. The desipramine dose was lowered to 200 mg/day later, the level was 244 ng/mL; the patient reported decreased energy, impaired short-term memory, and speech, as well as an episode of nausea, dizziness, and syncope. The desipramine dose was reduced to adverse effects resolved in six days. Eight days later, the desipramine level was 122 ng/mL (Downs et al
f) Concomitant administration of fluoxetine and desipramine was reported to result in an increased desip new onset of delirium in a 69-year-old male within 10 days of the addition of fluoxetine to the patient's reg al, 1990).

3.5.1.BT Fluvoxamine

1) Interaction Effect: imipramine toxicity (dry mouth, urinary retention, sedation)
2) Summary: Addition of fluvoxamine to imipramine or desipramine therapy can result in significantly increas antidepressant plasma levels and signs of tricyclic toxicity (Spina et al, 1992a; Spina et al, 1993aa; Spina et a Fluvoxamine significantly increases imipramine half-life and reduces clearance (Spina et al, 1993a). The add fluvoxamine to imipramine or desipramine therapy may result in greatly increased tricyclic antidepressant pla tricyclic toxicity (Spina et al, 1992a; Spina et al, 1993aa). A bidirectional effect is suggested, in which fluvoxa imipramine concentrations (by interfering with N-demethylation), and imipramine increases fluvoxamine level 1993a).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor patients for signs of imipramine and fluvoxamine toxicity; lower doses of on may be required with concomitant therapy.
7) Probable Mechanism: decreased imipramine metabolism
8) Literature Reports
a) The pharmacokinetics of combined imipramine and fluvoxamine were studied in healthy volunteers (S After a 7-day course of fluvoxamine, imipramine half-life was significantly increased (from 23 to 41 hours decreased (from 1.02 to 0.28 L/h/kg).
b) The addition of fluvoxamine to imipramine or desipramine in four patients was reported to result in gre tricyclic antidepressant plasma levels (Spina et al, 1992). Three of four patients showed signs of tricyclic of fluvoxamine 100 mg daily for 10 days on plasma concentrations of imipramine was studied in seven d on maintenance therapy (Spina et al, 1993a). Imipramine plasma levels were three to four times higher d coadministration. One patient complained of anticholinergic effects, along with tremor and confusion. The this drug interaction was inhibition of demethylation of imipramine. A pharmacokinetic study in healthy vo demonstrated a significantly increased imipramine half-life and reduced clearance (Spina et al, 1993).
c) Metabolism of tricyclic antidepressants coadministered with fluvoxamine was studied in eight depress patients received imipramine) (Hartter et al, 1993). Fluvoxamine was found to interfere with N-demethyla The combination of fluvoxamine and imipramine led to increased plasma levels of imipramine and decrea concentrations of the N-demethylated imipramine metabolite desimipramine. In addition, TCA-fluvoxamin apparently raised plasma levels of fluvoxamine.

3.5.1.BU Formoterol

1) Interaction Effect: an increased risk of cardiovascular excitation
2) Summary: Concurrent administration of formoterol with a tricyclic antidepressant (TCA) may lead to poten formoterol's adrenergic effects on the cardiovascular system. Therefore, extreme caution is advised if formote to patients who are being treated with a TCA (Prod Info FORADIL(R) AEROLIZER(R) inhalation powder, 200 patients closely for adverse cardiovascular effects.
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Extreme caution and close observation for adverse cardiovascular effects are warra formoterol is administered concurrently with a tricyclic antidepressant (TCA) as the cardiovascular effects of f potentiated by TCAs (Prod Info FORADIL(R) AEROLIZER(R) inhalation powder, 2006).
7) Probable Mechanism: potentiation of cardiovascular effects

3.5.1.BV Fosamprenavir

1) Interaction Effect: increased tricyclic agent serum concentrations and potential toxicity (anticholinergic effe confusion, cardiac arrhythmias)
2) Summary: Coadministration of fosamprenavir with a tricyclic antidepressant may provoke increased serum the tricyclic antidepressant, causing a potential risk of arrhythmias or other serious adverse effects. Fosampr of amprenavir, an inhibitor of the CYP3A4 isoenzyme in addition to being a CYP3A4 substrate. Tricyclic agen

depend on the CYP3A4 pathway for metabolism. Plasma concentrations of the tricyclic agent should be close patients also receiving fosamprenavir (Prod Info LEXIVA(R) oral solution, oral tablets, 2009).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: If concomitant therapy with fosamprenavir and a tricyclic antidepressant is unavoida concentrations of the tricyclic agent should be closely monitored. Also monitor patients for signs and symptor toxicity (anticholinergic effects, sedation, confusion, cardiac arrhythmias) (Prod Info LEXIVA(R) oral solution,
7) Probable Mechanism: inhibition of CYP3A4-mediated tricyclic agent metabolism

3.5.1.BW Foscarnet
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Foscarnet can prolong the QT interval in some patients, which may result in ventricular tachyca fibrillation, and torsades de pointes. Because tricyclic antidepressants may also prolong the QT interval and i arrhythmias, the concurrent administration of foscarnet and tricyclic antidepressants is not recommended (Pr (R), 1998; Marshall & Forker, 1982u).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of foscarnet and tricyclic antidepressants is not recor
7) Probable Mechanism: additive cardiac effects

3.5.1.BX Fosphenytoin
1) Interaction Effect: an increased risk of phenytoin toxicity (ataxia, hyperreflexia, nystagmus, tremor)
2) Summary: Fosphenytoin is a prodrug of phenytoin and the same interactions that occur with phenytoin are occur with fosphenytoin (Prod Info Cerebyx(R), 1999). A few case reports have indicated that imipramine inhi metabolism resulting in increased serum phenytoin concentration (Petti & Campbell, 1975; Perucca & Richer antidepressants (TCAs) may lower the seizure threshold in epileptic patients stabilized on anticonvulsants. Tl because phenytoin is an enzyme inducer, the metabolism of antidepressants may be increased resulting in re levels.
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Consider monitoring phenytoin serum levels if a tricyclic antidepressant is added to patient begins to exhibit signs of toxicity (tremor, nystagmus, ataxia, hyperreflexia); lower doses of phenytoin If phenytoin is added to tricyclic antidepressant therapy, monitor for clinical efficacy of the tricyclic agent.
7) Probable Mechanism: inhibition of phenytoin metabolism

3.5.1.BY Gatifloxacin
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Gatifloxacin may prolong the QT interval in some patients, which may result in ventricular tachy fibrillation, and torsades de pointes. Although pharmacokinetic studies between gatifloxacin and other drugs v QT interval have not been performed, an additive effect cannot be excluded. Therefore, the concurrent admir gatifloxacin and a tricyclic antidepressant is not recommended (Prod Info Tequin(TM), 1999).
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of gatifloxacin and a tricyclic antidepressant is not re
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.BZ Gemifloxacin
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Although pharmacokinetic studies between gemifloxacin and drugs that prolong the QT interva antidepressants, have not been performed, gemifloxacin should be used cautiously when given concurrently antidepressants (Prod Info Factive(R), 2003).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of two drugs that prolong the QT interval, such as ge tricyclic antidepressants, is not recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.CA Grepafloxacin
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Healthy volunteers who received grepafloxacin during a Phase I study experienced prolongatio interval. On an outpatient basis, grepafloxacin is contraindicated with other drugs that are known to also prolo interval or cause torsades de pointes, including tricyclic antidepressants. When appropriate cardiac monitorin such as in the hospitalized patient, these two agents should be coadministered with caution (Prod Info Raxar

3) Severity: contraindicated
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: The concurrent use of grepafloxacin and tricyclic antidepressants is contraindicated appropriate cardiac monitoring can be assured, such as in the hospitalized patient.
7) Probable Mechanism: additive cardiac effects

3.5.1.CB Guanadrel
1) Interaction Effect: decreased antihypertensive effectiveness
2) Summary: Tricyclic antidepressants inhibit the uptake of guanethidine and possibly guanadrel into the adr resulting in an inhibition of its antihypertensive effect (Mitchell et al, 1967; Ober & Wang, 1973). When a patie concomitant tricyclic antidepressant and guanadrel therapy, caution should be exercised when the tricyclic ar discontinued, since an exaggerated effect of guanadrel may be seen (Prod Info Hylorel(R), 1995).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Blood pressure should be monitored for an appropriate clinical response; higher do may be required. An alternative class of antihypertensive agents such as angiotensin-converting enzyme inhi considered.
7) Probable Mechanism: decreased uptake of guanadrel into adrenergic neurons

3.5.1.CC Guanethidine
1) Interaction Effect: decreased antihypertensive effectiveness
2) Summary: Tricyclic antidepressants inhibit the uptake of guanethidine, and possibly guanadrel, into the ac resulting in an inhibition of the antihypertensive effect (Gulati et al, 1966; Mitchell et al, 1967a; Ober & Wang, al, 1964).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Blood pressure should be monitored for an appropriate clinical response; higher do guanethidine may be required. An alternative class of antihypertensive agents, such as angiotensin-convertir might be considered.
7) Probable Mechanism: decrease uptake of guanethidine into adrenergic neurons

3.5.1.CD Guanfacine
1) Interaction Effect: decreased antihypertensive effectiveness
2) Summary: Concomitant clonidine and tricyclic antidepressant (TCA) therapy may impair the antihypertens clonidine. Since the mechanism of action of guanfacine is similar to clonidine, patients stabilized on guanfaci monitored for a hypertensive response when TCA (i.e. desipramine or imipramine) therapy is started (Briant e 1983b). A case has been reported of a patient maintained on guanfacine who developed an increase in blooc imipramine was added to therapy. When imipramine was discontinued, her blood pressure returned to baseli Feely, 1991a).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Blood pressure should be monitored for an appropriate clinical response; higher do may be required. An alternative class of antihypertensive agents, such as an angiotensin-converting enzyme considered.
7) Probable Mechanism: unknown
8) Literature Reports
a) A case of a hypertensive female who was maintained on guanfacine 2 mg daily with mean blood pres mm Hg was reported (Buckley & Feely, 1991). After amitriptyline 75 mg daily was begun, her mean bloo 150/100 mm Hg; upon discontinuation of the amitriptyline, the blood pressure returned to 136/91 mm Hg was given imipramine 50 mg daily and experienced similar changes in loss of blood pressure control; up of imipramine, the blood pressure again returned to 137/90 mm Hg.
b) Concomitant clonidine and tricyclic antidepressant therapy may impair the antihypertensive effects of the mechanism of action of guanfacine is similar to clonidine, patients stabilized on guanfacine should be hypertensive response when desipramine therapy is started (Briant et al, 1973b; Hui, 1983a).

3.5.1.CE Halofantrine
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Halofantrine can prolong the QT interval in some patients, which may result in ventricular tachy fibrillation, and torsades de pointes. Because tricyclic antidepressants may also prolong the QT interval and i arrhythmias, the concurrent administration of halofantrine and tricyclic antidepressants is not recommended ((R), 1998; Marshall & Forker, 1982aa).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable

6) Clinical Management: The concurrent administration of halofantrine and a tricyclic antidepressant is not re
7) Probable Mechanism: additive cardiac effects

3.5.1.CF Haloperidol

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod I 1999), haloperidol (O'Brien et al, 1999), risperidone (Duenas-Laita et al, 1999), sertindole (Agelink et al, 2001 (Owens, 2001b), sultopride (Lande et al, 1992), and zotepine (Sweetman, 2003). Even though no formal drug studies have been done, the coadministration of a tricyclic antidepressant and an antipsychotic is not recomm Pamelor(R), 2001; Marshall & Forker, 1982t).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of a tricyclic antidepressant and an antipsychotic is n
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) Electrocardiographic changes that have occurred during clinical trials with pimozide have included pr corrected QT interval, flattening, notching, and inversion of the T wave and the appearance of U waves. studies, sudden, unexpected deaths have occurred while patients were receiving pimozide doses of 1 m proposed mechanism for these deaths is prolongation of the QT interval predisposing patients to ventricu (Prod Info Orap(R), 1999).

3.5.1.CG Halothane

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Halothane may prolong the QT interval in some patients (Owens, 2001a). Because tricyclic ant also prolong the QT interval and increase the risk of arrhythmias, the concurrent administration of halothane a antidepressants is not recommended (Marshall & Forker, 1982p).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Because of the potential for additive QT interval prolongation, the concurrent admin halothane and tricyclic antidepressants is not recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.CH Heptabarbital

1) Interaction Effect: possible decreased tricyclic antidepressant serum concentrations and possible additive
2) Summary: Concomitant barbiturate and tricyclic antidepressant (TCA) therapy may result in increased me TCA. There have been scattered reports of individuals with decreased serum levels of TCAs in the presence (Moody et al, 1977; Silverman & Braithwaite, 1972; Burrows & Davies, 1971). In addition, TCAs can worsen s reducing the seizure threshold (Brodie, 1992). These drugs also have additive CNS and respiratory depressa
3) Severity: minor
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor for efficacy of antidepressant effect. Increases in tricyclic antidepressant do required. Additionally, monitor for toxicity when either drug is added to or withdrawn from therapy. Serum con be of value in determining appropriate dosage.
7) Probable Mechanism: increased tricyclic antidepressant metabolism
8) Literature Reports
a) The pharmacokinetics of a single oral dose of desipramine (100 mg) were studied in eight epileptic pa treated with phenobarbital and in eight drug-free healthy controls (Spina et al, 1996). All subjects were ex metabolizers with respect to the genetically determined CYP2D6-related metabolic polymorphism. Comp epileptic patients exhibited lower peak plasma desipramine concentrations (74 nmol/L vs. 107 nmol/L), s area under the concentration-time curve values (1943 nmol/L/h vs. 3234 nmol/L/h), and shorter desipram half-lives (15.1 h vs. 20.6 h). All barbiturates are believed to have similar effects leading to induction of h and the 2D6 isozyme is believed to be important in the metabolism of most or all TCAs. Thus, similar effe expected with any combination of TCA and barbiturate.

3.5.1.CI Hexobarbital

1) Interaction Effect: possible decreased tricyclic antidepressant serum concentrations and possible additive
2) Summary: Concomitant barbiturate and tricyclic antidepressant (TCA) therapy may result in increased me TCA. There have been scattered reports of individuals with decreased serum levels of TCAs in the presence (Moody et al, 1977; Silverman & Braithwaite, 1972; Burrows & Davies, 1971). In addition, TCAs can worsen s reducing the seizure threshold (Brodie, 1992). These drugs also have additive CNS and respiratory depressa
3) Severity: minor
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor for efficacy of antidepressant effect. Increases in tricyclic antidepressant do required. Additionally, monitor for toxicity when either drug is added to or withdrawn from therapy. Serum con

be of value in determining appropriate dosage.
7) Probable Mechanism: increased tricyclic antidepressant metabolism
8) Literature Reports
a) The pharmacokinetics of a single oral dose of desipramine (100 mg) were studied in eight epileptic pa treated with phenobarbital and in eight drug-free healthy controls (Spina et al, 1996). All subjects were ex metabolizers with respect to the genetically determined CYP2D6-related metabolic polymorphism. Comp epileptic patients exhibited lower peak plasma desipramine concentrations (74 nmol/L vs. 107 nmol/L), s area under the concentration-time curve values (1943 nmol/L/h vs. 3234 nmol/L/h), and shorter desipram half-lives (15.1 h vs. 20.6 h). All barbiturates are believed to have similar effects leading to induction of h and the 2D6 isozyme is believed to be important in the metabolism of most or all TCAs. Thus, similar effe expected with any combination of TCA and barbiturate.

3.5.1.CJ Hydroquinidine
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Class Ia antiarrhythmics and tricyclic antidepressants have been shown to prolong the QTc inte recommended therapeutic dose. Even though no formal drug interaction studies have been done, the coadm Ia antiarrhythmics and other drugs known to prolong the QTc interval, including tricyclic antidepressants, is n (Prod Info Elavil(R), 1999g; Prod Info Quinaglute(R), 1999; Marshall & Forker, 1982n).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: The concurrent administration of a Class IA antiarrhythmic agent and a tricyclic anti recommended.
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) Quinidine is an inhibitor of the cytochrome P450 isoenzyme responsible for the 2-hydroxylation of imi desipramine (Brosen & Gram, 1989). Inhibition of this enzyme system can result in a 35% decrease in im clearance and 85% decrease in desipramine clearance. Demethylation of imipramine by the cytochrome unaffected by this interaction. Until more information is available all patients having quinidine added to di containing imipramine or desipramine should be monitored for increased antidepressant serum concentr potential toxicity.
b) An increased incidence in sudden death was observed in six out of 53 patients with cardiac disease r amitriptyline, compared to 0 out of 53 in the control group. It was recommended that amitriptyline be avo with underlying cardiac disease except when depression was debilitating and no other drugs were helpfu Coull et al, 1970).
c) In a placebo controlled study, imipramine 3.5 mg/kg was administered daily for seven patients with se and titrated doses to obtain therapeutic plasma concentrations. Two patients displayed premature atrial c and premature ventricular depolarizations before therapy. On patient had 33 premature atrial depolarizat premature ventricular depolarizations (PVD) per hour, which decreased to 0.4 PAC and zero PVC per ho The other patient had 12 PAD and 169 PVD per hour before treatment and 1.8 PAD and 28.1 PVD per h The authors also cautioned that the incidence of cardiotoxicity may increase if tricyclic antidepressants a with Type I antiarrhythmics. It was also recommended that quinidine and procainamide not be used to tre of a tricyclic overdose. The similarities between these agents may exacerbate the cardiotoxicity (Kantor e

3.5.1.CK Ibutilide
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Cases of QTc prolongation and/or torsades de pointes have been reported with all Class III ant agents, including acecainide (Chow et al, 1984), amiodarone (Faggiano et al, 1996), azimilide (Corey et al, 1 (Gilman et al, 1985), ibutilide (Rodriguez et al, 2001), sematilide (Singh, 1996), dofetilide (Allen et al, 2002), a & Runge, 2001). Even though no formal drug interaction studies have been done, the coadministration of Cla antiarrhythmics and other drugs known to prolong the QTc interval, including tricyclic antidepressants, is not (Yamreudeewong et al, 2003a; Prod Info Corvert(R), 2000).
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of a Class III antiarrhythmic and a tricyclic antidepres recommended.
7) Probable Mechanism: additive QT prolongation
8) Literature Reports
a) EKG effects reported in patients receiving therapeutic doses of tricyclic antidepressants include incre prolonged PR interval, intraventricular conduction delays, increased corrected QT interval (QTc) and flat (Marshall & Forker, 1982ab).
b) Concurrent use of Class III antiarrhythmic agents, and other drugs that can prolong the QT interval, s antidepressants, is not recommended. Dofetilide should be stopped for at least 2 days before any interac initiated. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised (Yam 2003).

3.5.1.CL Iobenguane I 131

1) Interaction Effect: false-negative results of scintigraphy
2) Summary: Imipramine, which selectively blocks the active transport of catecholamines into storage vesicle myocardial uptake of iobenguane I-131 and increases the rate of loss of iobenguane I-131 from the liver, thus scintigraphy (Sisson et al, 1987).
3) Severity: moderate
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Imipramine should be discontinued prior to any procedure using iobenguane I-131.
7) Probable Mechanism: reduction of iobenguane I-131 uptake

3.5.1.CM Iproniazid

1) Interaction Effect: neurotoxicity, seizures, or serotonin syndrome (hypertension, hyperthermia, myoclonus changes)
2) Summary: Concomitant TCA and MAOI use has resulted in hyperpyrexia, convulsions, and death. Concu and TCAs has also been reported to result in a condition termed serotonin syndrome (Insel et al, 1982o; Spig Brodribb et al, 1994m; Neuvonen et al, 1993g). Serotonin syndrome is a rare but potentially fatal condition of hyperstimulation characterized by hypertension, hyperthermia, myoclonus, and changes in mental status (Ste TCAs and MAOIs must be used concurrently, avoid large doses, use only oral TCAs, avoid imipramine, clom desipramine, and tranylcypromine, and monitor patients closely (Schuckit et al, 1971n; White & Simpson, 198
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Concomitant use of a tricyclic antidepressant (TCA) and a monoamine oxidase inhi should be done only with close monitoring and where the clinical benefit outweighs the potential risk. Other a therapy should first be considered. Consider using a 14 day washout period between treatment with both me clinically necessary, avoid large doses and use agents other than imipramine, clomipramine, desipramine, ar
7) Probable Mechanism: altered catecholamine uptake and metabolism
8) Literature Reports

a) Concomitant administration of monoamine oxidase inhibitors (MAOIs) with tricyclic antidepressants (T considered an absolute contraindication in the past. Reports of excitation, hyperpyrexia, convulsions, an have been attributed to the combination (Lockett & Milner, 1965g; Winston, 1971g; Schuckit et al, 1971m 1976g). The mechanism may relate to the combined inhibition of catecholamine reuptake into the centra and inhibition of catecholamine metabolism (Sjoqvist, 1965g).

b) Administration of a TCA after MAOI therapy may result in the development of serotonin syndrome. In crossover study examining the effects of clorgyline and clomipramine for the treatment of obsessive-com two subjects developed severe reactions characteristic of serotonin syndrome. During the study, patients clorgyline therapy, followed by a washout period of approximately four weeks and subsequent clomipram taking the first 100 mg dose of clomipramine, one patient developed coarse myoclonic jerking in both leg diaphoresis, and arrhythmia. Another patient developed a similar reaction after the first dose, with upper symptoms, myoclonic movements, and cardiac irritability. Both patient's symptoms resolved several hou patients were later treated successfully with clomipramine without adverse effects (Insel et al, 1982n).

c) A drug interaction occurred in a 76-year old woman who had been taking clomipramine 50 mg daily fo prior to switching to moclobemide 300 mg daily. The patient experienced somnolescence, confusion, an progressed to further mental impairment, muscle stiffness, myoclonus, and convulsive attacks. The patie were described as fulfilling the diagnostic criteria for serotonin syndrome and were resolved a few days l discontinuing all antidepressant medications (Spigset et al, 1993o).

d) In one case, clomipramine 10 mg twice daily was added to a stable regimen of tranylcypromine in a p 34-year old man. After taking several doses, the patients developed symptoms of nausea and profuse sw by pyrexia, dyspnea, and agitation. The hyperpyrexical state led to disseminated intravascular coagulatio death (Tackley & Tregaskis, 1987h).

e) There is evidence that MAOIs and TCAs can be given concomitantly in patients previously unrespons TCA alone. The combination may be utilized in one of two ways. Most frequently, the recommendation is previous antidepressants (five to ten days for TCAs and 14 days for MAOIs); the combination is then sim started (Perry et al, 1991g). Alternatively, in a patient previously receiving a TCA, small doses of the MA added (Schoonover, 1983). Numerous studies in patients with refractory depression or phobic anxiety st successfully used the combination of MAOIs and TCAs (Ponto et al, 1977g; Schuckit et al, 1971m; Ashc

3.5.1.CN Isocarboxazid

1) Interaction Effect: neurotoxicity, seizures, or serotonin syndrome (hypertension, hyperthermia, myoclonus changes)
2) Summary: The concurrent administration of isocarboxazid and imipramine is contraindicated (Prod Info M Concomitant TCA and MAOI use has resulted in hyperpyrexia, convulsions, and death. Concurrent use of MA has also been reported to result in a condition termed serotonin syndrome (Insel et al, 1982g; Spigset et al, 1 al, 1994g; Neuvonen et al, 1993c). Serotonin syndrome is a rare but potentially fatal condition of serotonergic characterized by hypertension, hyperthermia, myoclonus, and changes in mental status (Sternbach, 1991d). MAOIs must be used concurrently, avoid large doses, use only oral TCAs, avoid imipramine, clomipramine, d tranylcypromine, and monitor patients closely (Schuckit et al, 1971g; White & Simpson, 1984f).
3) Severity: contraindicated

4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: The concurrent use of imipramine and isocarboxazid is contraindicated. In patients to isocarboxazid therapy from a dibenzazepine-related entity, allow at least a one-week medication-free inter initiate isocarboxazid at one-half of the normal dose for at least the first week of therapy. Also allow one week between the discontinuation of isocarboxazid and the administration of another MAO inhibitor or dibenzazepi
7) Probable Mechanism: altered catecholamine uptake and metabolism
8) Literature Reports

a) Concomitant administration of monoamine oxidase inhibitors (MAOI) with tricyclic antidepressants (TC considered an absolute contraindication in the past and still is listed as such by the manufacturers. Repo hyperpyrexia, convulsions, and possible death have been attributed to the combination (Lockett & Milner et al, 1963b; Winston, 1971c; Schuckit et al, 1971f; Sargent, 1965b; Spiker & Pugh, 1976c). The mechar the combined inhibition of catecholamine reuptake into the central nervous system and inhibition of catec metabolism (Sjoqvist, 1965c).

b) The development of serotonin syndrome was reported due to administration of a TCA after MAOI the blind, crossover study examining the effects of clorgyline and clomipramine for the treatment of obsessiv disorder, two subjects developed severe reactions characteristic of serotonin syndrome. During the study received clorgyline therapy, followed by a washout period of approximately four weeks and subsequent c therapy. After taking the first 100 mg dose of clomipramine, one patient developed coarse myoclonic jerk hyperreflexia, diaphoresis, and arrhythmia. Another patient developed a similar reaction after the first do motor neuron symptoms, myoclonic movements, and cardiac irritability. Both patient's symptoms resolve later, and both patients were later treated successfully with clomipramine without adverse effects (Insel e

c) A drug interaction was reported when a 76-year old woman who had been taking clomipramine 50 mg months was switched to moclobemide 300 mg daily. The patient experienced somnolescence, confusion then progressed to further mental impairment, muscle stiffness, myoclonus, and convulsive attacks. The symptoms were described as fulfilling the diagnostic criteria for serotonin syndrome and were resolved a after discontinuing all antidepressant medications (Spigset et al, 1993g).

d) A 39-year old woman with bipolar disorder developed serotonin syndrome after imipramine was adde The patient was taking moclobemide 300 mg twice daily when imipramine was started at 50 mg daily, fol dosage increases of imipramine to 200 mg and a reduction of moclobemide dosage to 150 mg twice dail the increase in imipramine to 200 mg per day, the patient developed symptoms of serotonin syndrome, i shivering, confusion, fever, and spasms in the extremities. The patient was treated with chlorpromazine a resolved over the next few days without further complications (Brodribb et al, 1994f).

e) Three patients with bipolar disorder developed manic symptoms while undergoing concurrent therapy isocarboxazid and amitriptyline. In all three cases the patients had been given MAOIs and TCAs alone w complications. It was only when the drugs were used in combination that symptoms of mania emerged, s synergistic effect (de la Fuente et al, 1986b).

f) In one case, clomipramine 10 mg twice daily was added to a stable regimen of tranylcypromine in a pl 34-year old man. After taking several doses, the patients developed symptoms of nausea and profuse sw by pyrexia, dyspnea, and agitation. The hyperpyrexical state led to disseminated intravascular coagulatio death (Tackley & Tregaskis, 1987d).

g) There is evidence that MAOIs and TCAs can be given concomitantly in patients previously unresponsi TCA alone. A few precautions must be followed including: a) avoidance of large doses (no more than 15 or its equivalent, 45 mg phenelzine, or 60 mg isocarboxazid) b) oral administration c) avoidance of clomi imipramine, desipramine, and tranylcypromine in any combination, and d) close monitoring of patients (K Winston, 1971c; Schuckit et al, 1971f; White & Simpson, 1984e; Rom & Benner, 1972b). The combinatio in one of two ways. Most frequently, the recommendation is to stop all previous antidepressants (five to t and 14 days for MAOIs); the combination is then simultaneously started (Perry et al, 1991c). Alternatively previously receiving a TCA, small doses of the MAOI may be slowly added (Schoonover, 1983). Some s that the combination of amitriptyline and isocarboxazid is preferred (Perry et al, 1991c). Numerous studie refractory depression or phobic anxiety states have successfully used the combination of MAOIs and TC 1977c; Schuckit et al, 1971f; Ashcroft, 1975c).

3.5.1.CO Isoflurane

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Isoflurane may prolong the QT interval in some patients (Owens, 2001c). Because tricyclic anti also prolong the QT interval and increase the risk of arrhythmias, the concurrent administration of isoflurane a antidepressants is not recommended (Marshall & Forker, 1982v).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Because of the potential for additive QT interval prolongation, the concurrent admin isoflurane and a tricyclic antidepressants is not recommended.
7) Probable Mechanism: additive effect on QT prolongation

3.5.1.CP Isradipine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Isradipine can prolong the QT interval in some patients, which may result in ventricular tachyca

fibrillation, and torsades de pointes. Because tricyclic antidepressants may also prolong the QT interval and i arrhythmias, the concurrent administration of isradipine with a tricyclic antidepressant is not recommended (F (R), 2000; Marshall & Forker, 1982z).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of isradipine and a tricyclic antidepressant is not rec
7) Probable Mechanism: additive cardiac effects

3.5.1.CQ Ketoconazole
1) Interaction Effect: decreased clearance and prolonged half-life of imipramine
2) Summary: In a controlled study of six healthy volunteers, coadministration of ketoconazole with a single d resulted in an increase in imipramine area under the concentration-time curve (AUC) and imipramine half-life decrease in imipramine clearance. The changes were minor, however, and deemed to be likely clinically insig considering the wide therapeutic range of imipramine (Spina et al, 1997a).
3) Severity: minor
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: If signs or symptoms of altered tricyclic response are noted, downward dosage adju imipramine may be necessary.
7) Probable Mechanism: inhibition of imipramine hepatic metabolism
8) Literature Reports
a) A controlled study evaluated oral ketoconazole and the pharmacokinetic effects on oral imipramine a 12 healthy male volunteers. The subjects were divided into two groups and received either a single dose mg or desipramine 100 mg, both alone and after 10 days of a 14-day regimen of oral ketoconazole 200 r Coadministration of ketoconazole resulted in significantly increased imipramine area under the concentra (AUC) values (from 3795 +/- 918 nmol h/L to 4567 +/- 1076 nmol h/L) and significantly decreased imipra clearance (from 1.16 +/- 0.21 L/hr/kg to 0.96 +/- 0.20 L/hr/kg). Imipramine half-life was also significantly i coadministration with ketoconazole, from 16.7 +/- 3.3 hours to 19.2 +/- 5.4 hours. The changes in imipra pharmacokinetics were deemed to be minor considering the therapeutic range of the drug. During coadm ketoconazole with desipramine, no significant pharmacokinetic changes were observed. The authors cor ketoconazole inhibits the N-demethylation of imipramine by cytochrome P450 3A4, without affecting the imipramine and desipramine, which is thought to be mediated through the cytochrome P450 2D6 pathwa 1997).

3.5.1.CR Labetalol
1) Interaction Effect: imipramine toxicity (dry mouth, urinary retention, sedation)
2) Summary: Labetalol decreased imipramine clearance by 38% (statistically significant) compared to placeb crossover study in 12 healthy subjects (Hermann et al, 1992). Labetalol increased imipramine area under the time curve (AUC) by 53% compared to placebo, which was also significant. The clinical significance of the ph interaction is undetermined.
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Monitor for anticholinergic side effects of imipramine if labetalol is added to therapy imipramine may be appropriate. Conversely, if labetalol is discontinued, monitor continued clinical efficacy of adjust dosage accordingly.
7) Probable Mechanism: decreased imipramine metabolism, increased imipramine AUC

3.5.1.CS Levomethadyl
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Any drug known to have the potential to prolong the QT interval should not be used with levom pharmacodynamic interactions can occur between levomethadyl and potentially arrhythmogenic agents such prolong the QT interval (Prod Info Orlaam(R), 2001).
3) Severity: contraindicated
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Levomethadyl is contraindicated in patients being treated with imipramine as it may prolongation and interact with levomethadyl.
7) Probable Mechanism: unknown

3.5.1.CT Lidoflazine
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Tricyclic antidepressants (TCAs) and lidoflazine have been shown to prolong the QTc interval a recommended therapeutic dose (Hanley & Hampton, 1983; Marshall & Forker, 1982r). Even though no forma studies have been done, the coadministration of tricyclic antidepressants and other drugs known to prolong tl such as lidoflazine, is not recommended (Prod Info Elavil(R), 1999i).
3) Severity: major

4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of lidoflazine and tricyclic antidepressants is not reco
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.CU Linezolid

1) Interaction Effect: increased risk of serotonin syndrome (hyperthermia, hyperreflexia, myoclonus, mental s
2) Summary: Concomitant use of linezolid and a tricyclic antidepressant, such as imipramine, is contraindica of monitoring for serotonin syndrome. If symptoms occur, consider discontinuation of either one or both of the is a reversible, nonselective inhibitor of monoamine oxidase and may therefore interact with tricyclic antidepr Spontaneous reports of serotonin syndrome associated with the co-administration of linezolid and serotonerg been reported (Prod Info ZYVOX(R) IV injection, oral tablets, oral suspension, 2008).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concurrent use of linezolid and tricyclic antidepressants, such as imipramine, is cor unless patient is closely observed for signs and/or symptoms of serotonin syndrome. If concomitant use is cli monitor for signs and symptoms of serotonin syndrome, such as neuromuscular abnormalities (including hyp muscle rigidity, clonus, peripheral hypertonicity, and shivering), autonomic hyperactivity (including tachycardi diaphoresis, the presence of bowel sounds, and diarrhea), and mental status changes (including agitation an Serotonin syndrome can be life-threatening. If serotonin syndrome develops, discontinue the offending agent supportive care and other therapy as necessary (Boyer & Shannon, 2005; Prod Info ZYVOX(R) IV injection, o suspension, 2008).
7) Probable Mechanism: linezolid inhibition of monoamine oxidase resulting in an increased concentration of

3.5.1.CV Lisdexamfetamine

1) Interaction Effect: hypertension, other cardiac effects, and CNS stimulation
2) Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been reporte enhanced amphetamine effects from the release of norepinephrine (Beaumont, 1973d; Raisfeld, 1972). A sim also occur with all drugs that have amphetamine-like effects. Acute elevations in blood pressure have been n (Flemenbaum, 1971a). Some amphetamine-like drugs may inhibit the metabolism of TCAs, although most co not been studied. When amphetamine analogs are being used to treat obesity, it should be noted that TCAs f moderate weight gain (Russ & Ackerman, 1988). False positive urine tests for amphetamines have been repo therapy with some TCAs (Merigian & Browning, 1993). Caution is advised when concurrent administration of agents and TCAs is warranted. The patient should be closely monitored for increased cardiovascular effects dysrhythmias).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other sympatho could lead to hypertension, increased cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) o Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral t Flemenbaum, 1972). Use caution if such therapy is warranted. Monitor the patient closely for hypertension ar
7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission
8) Literature Reports

a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agen coadministration of d-amphetamine with TCAs such as desipramine or protriptyline results in sustained i amphetamine concentration in the brain (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info DEXE sustained-release oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006).

b) Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism o antidepressants, such as imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transde 2006).

c) Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases i such that the hypotensive effects induced by TCAs may lead to blood pressures as high as 170/120 mm of combined therapy. Discontinuation of the methylphenidate usually results in the blood pressure return normotensive levels; reinstitution of the methylphenidate resulted in further blood pressure elevation (Fle Flemenbaum, 1972).

d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine g four weeks, were given fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transi clinical improvement. However, fenfluramine more than doubled steady-state plasma levels of desipramin 1990).

e) There have been claims based on uncontrolled studies that a better antidepressant response may oc therapy (Garrettson et al, 1969). However, a systemic review of stimulants in the treatment of depressior although uncontrolled studies were generally positive, the ten placebo-controlled studies of stimulant dru depression, with one exception, indicated little advantage of drug over placebo and did not appear to be conventional antidepressants in primary depression (Satel & Nelson, 1989).

3.5.1.CW Lorcainide

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Class I antiarrhythmics have been shown to prolong the QTc interval at the recommended ther
Even though no formal drug interaction studies have been done, the coadministration of Class I antiarrhythmi
known to prolong the QTc interval, including tricyclic antidepressants, is not recommended (Prod Info Tambo
acetate, 1998; Larochelle et al, 1984; Scagliotti et al, 1982).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of a Class I antiarrhythmic and a tricyclic antidepress
recommended.
7) Probable Mechanism: additive effects on QT prolongation
8) Literature Reports
a) EKG effects reported in patients receiving therapeutic doses of tricyclic antidepressants include incre
prolonged PR interval, intraventricular conduction delays, increased corrected QT interval (QTc) and flat
(Marshall & Forker, 1982q).
b) A 68-year-old man suffering from agitated major depression was begun on a dose of desipramine 12
produced a subtherapeutic serum level of 442 nmol/L (therapeutic range = 500 to 1000 nmol/L). An incre
mg daily produced excellent clinical response with no side effects. He developed atrial fibrillation and flut
mg daily was added to his therapy, and desipramine was discontinued. His arrhythmia was suppressed v
propafenone 150 mg twice daily and 300 mg at bedtime. Desipramine 150 mg daily was again begun, at
experienced dry mouth, sedation, and shakiness; the desipramine serum level was measured at 2092 nr
desipramine was discontinued for five days, the side effects ceased, and desipramine therapy was resur
The desipramine serum level was measured at 1130 nmol/L (Katz, 1991).

3.5.1.CX Lumefantrine

1) Interaction Effect: an increased risk of QT interval prolongation
2) Summary: Lumefantrine is a CYP2D6 inhibitor and may cause QT interval prolongation. Concomitant use
artemether/lumefantrine and a CYP2D6 substrate (eg, amitriptyline, clomipramine, flecainide, and imipramine
elevated drug levels of the CYP2D6 substrate. As some CYP2D6 substrates can also prolong the QT interva
for additive QT prolongation. Therefore, artemether/lumefantrine should not be coadministered with CYP2D6
possess cardiac effects (Prod Info COARTEM(R) oral tablets, 2009).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Artemether/lumefantrine should not be administered concomitantly with CYP2D6 su
amitriptyline, clomipramine, flecainide, and imipramine, due to the potential additive effect on QT interval prol
Info COARTEM(R) oral tablets, 2009).
7) Probable Mechanism: additive effects on QT interval prolongation

3.5.1.CY Mazindol

1) Interaction Effect: hypertension, other cardiac effects, and CNS stimulation
2) Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been reporte
enhanced amphetamine effects from the release of norepinephrine (Beaumont, 1973d; Raisfeld, 1972). A sim
also occur with all drugs that have amphetamine-like effects. Acute elevations in blood pressure have been n
(Flemenbaum, 1971a). Some amphetamine-like drugs may inhibit the metabolism of TCAs, although most co
not been studied. When amphetamine analogs are being used to treat obesity, it should be noted that TCAs f
moderate weight gain (Russ & Ackerman, 1988). False positive urine tests for amphetamines have been repo
therapy with some TCAs (Merigian & Browning, 1993). Caution is advised when concurrent administration of
agents and TCAs is warranted. The patient should be closely monitored for increased cardiovascular effects
dysrhythmias).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other sympatho
could lead to hypertension, increased cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) o
Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral t
Flemenbaum, 1972). Use caution if such therapy is warranted. Monitor the patient closely for hypertension ar
7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission
8) Literature Reports
a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agen
coadministration of d-amphetamine with TCAs such as desipramine or protriptyline results in sustained in
amphetamine concentration in the brain (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info DEXE
sustained-release oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006).
b) Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism o
antidepressants, such as imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transde
2006).
c) Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases in
such that the hypotensive effects induced by TCAs may lead to blood pressures as high as 170/120 mm

of combined therapy. Discontinuation of the methylphenidate usually results in the blood pressure return normotensive levels; reinstitution of the methylphenidate resulted in further blood pressure elevation (Fle Flemenbaum, 1972).

d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine g four weeks, were given fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transie clinical improvement. However, fenfluramine more than doubled steady-state plasma levels of desiprami 1990).

e) There have been claims based on uncontrolled studies that a better antidepressant response may oc therapy (Garrettson et al, 1969). However, a systemic review of stimulants in the treatment of depressior although uncontrolled studies were generally positive, the ten placebo-controlled studies of stimulant dru depression, with one exception, indicated little advantage of drug over placebo and did not appear to be conventional antidepressants in primary depression (Satel & Nelson, 1989).

3.5.1.CZ Mephentermine

1) Interaction Effect: hypertension, other cardiac effects, and CNS stimulation

2) Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been reporte enhanced amphetamine effects from the release of norepinephrine (Beaumont, 1973d; Raisfeld, 1972). A sin also occur with all drugs that have amphetamine-like effects. Acute elevations in blood pressure have been n (Flemenbaum, 1971a). Some amphetamine-like drugs may inhibit the metabolism of TCAs, although most co not been studied. When amphetamine analogs are being used to treat obesity, it should be noted that TCAs f moderate weight gain (Russ & Ackerman, 1988). False positive urine tests for amphetamines have been repo therapy with some TCAs (Merigian & Browning, 1993). Caution is advised when concurrent administration of agents and TCAs is warranted. The patient should be closely monitored for increased cardiovascular effects dysrhythmias).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other sympatho could lead to hypertension, increased cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) o Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral t Flemenbaum, 1972). Use caution if such therapy is warranted. Monitor the patient closely for hypertension ar

7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission

8) Literature Reports

a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agen coadministration of d-amphetamine with TCAs such as desipramine or protriptyline results in sustained i amphetamine concentration in the brain (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info DEXE sustained-release oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006).

b) Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism c antidepressants, such as imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transde 2006).

c) Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases i such that the hypotensive effects induced by TCAs may lead to blood pressures as high as 170/120 mm of combined therapy. Discontinuation of the methylphenidate usually results in the blood pressure return normotensive levels; reinstitution of the methylphenidate resulted in further blood pressure elevation (Fle Flemenbaum, 1972).

d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine g four weeks, were given fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transie clinical improvement. However, fenfluramine more than doubled steady-state plasma levels of desiprami 1990).

e) There have been claims based on uncontrolled studies that a better antidepressant response may oc therapy (Garrettson et al, 1969). However, a systemic review of stimulants in the treatment of depressior although uncontrolled studies were generally positive, the ten placebo-controlled studies of stimulant dru depression, with one exception, indicated little advantage of drug over placebo and did not appear to be conventional antidepressants in primary depression (Satel & Nelson, 1989).

3.5.1.DA Mephobarbital

1) Interaction Effect: possible decreased tricyclic antidepressant serum concentrations and possible additive

2) Summary: Concomitant barbiturate and tricyclic antidepressant (TCA) therapy may result in increased me TCA. There have been scattered reports of individuals with decreased serum levels of TCAs in the presence (Moody et al, 1977; Silverman & Braithwaite, 1972; Burrows & Davies, 1971). In addition, TCAs can worsen s reducing the seizure threshold (Brodie, 1992). These drugs also have additive CNS and respiratory depressa

3) Severity: minor

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Monitor for efficacy of antidepressant effect. Increases in tricyclic antidepressant dc required. Additionally, monitor for toxicity when either drug is added to or withdrawn from therapy. Serum con be of value in determining appropriate dosage.

7) Probable Mechanism: increased tricyclic antidepressant metabolism

8) Literature Reports

a) The pharmacokinetics of a single oral dose of desipramine (100 mg) were studied in eight epileptic pa treated with phenobarbital and in eight drug-free healthy controls (Spina et al, 1996). All subjects were e metabolizers with respect to the genetically determined CYP2D6-related metabolic polymorphism. Comp epileptic patients exhibited lower peak plasma desipramine concentrations (74 nmol/L vs. 107 nmol/L), s area under the concentration-time curve values (1943 nmol/L/h vs. 3234 nmol/L/h), and shorter desipran half-lives (15.1 h vs. 20.6 h). All barbiturates are believed to have similar effects leading to induction of h and the 2D6 isozyme is believed to be important in the metabolism of most or all TCAs. Thus, similar eff expected with any combination of TCA and barbiturate.

3.5.1.DB Mesoridazine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Although citing no data, the manufacturer of mesoridazine states that concomitant use with oth prolong the QT interval is contraindicated (Prod Info Serentil(R), 2001). Tricyclic antidepressants (TCAs) at th can cause QT prolongation (Marshall & Forker, 1982e).

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concurrent administration of a tricyclic antidepressant and mesoridazine is contrain

7) Probable Mechanism: additive effect on QT interval

3.5.1.DC Mestranol

1) Interaction Effect: possible attenuation of antidepressant effectiveness; tricyclic toxicity (drowsiness, hypo

2) Summary: In isolated cases, the pharmacologic effects of tricyclic antidepressants may be increased or de estrogens (Somani & Khurana, 1973i), with paradoxical loss of antidepressant effect yet tricyclic toxicity being simultaneously (Prange, 1972i). The effects of the interaction appear to be estrogen dose-related (Khurana, 1 of clinical importance primarily in patients previously stabilized on tricyclic therapy who are being started on e (Krishnan et al, 1984i).

3) Severity: minor

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: If signs or symptoms of altered tricyclic response are noted, dose adjustment down estrogen or tricyclic component may be successful in restoring effectiveness or resolving toxicity. However, d may be required.

7) Probable Mechanism: possible inhibition of hepatic metabolism of the tricyclic antidepressant

8) Literature Reports

a) Some studies evaluated the qualitative effects of concomitant administration of estrogen and TCAs. I depressed female prisoners were randomly assigned to 4 treatment groups. Ten patients received place imipramine (150 milligrams/day) and placebo, 5 patients received imipramine (150 milligrams/day) and e micrograms/day), while 5 patients received imipramine (150 milligrams/day) and ethinyl estradiol (25 mic 10 patients that received placebo did not improve over the 6 weeks of the study. The 10 patients taking e imipramine demonstrated a significantly greater improvement in symptoms than did the 10 patients takin alone. However, after 2 weeks, the 5 patients that received imipramine and high-dose estrogen had not i as the patients receiving imipramine and low-dose estrogen. The only side-effect reported was drowsine affected the patients taking imipramine. Following the discontinuation of ethinyl estradiol, a time period o required for the high-dose estrogen group to do as well as the low-dose group. This effect was attributed residual estrogen in the high-dose group. In another group, 5 women received imipramine 150 milligrams estradiol 50 micrograms daily did not improve as much as 10 patients receiving only imipramine. Also, th combination had severe side-effects including lethargy, coarse tremor and systolic hypotension (Prange,

b) A case report demonstrated an interaction in a 32-year-old female taking conjugated estrogens 2.5 m imipramine 100 milligrams (Khurana, 1972h). The patient developed lethargy, tremors, and signs of depe After 2 years of therapy, the patient increased her estrogen dose to 5 milligrams and then 7.5 milligrams became nauseated, had constant headaches, and low normal blood pressure. All lab work was normal. U the estrogen, the side-effects abated. Some investigators have proposed that the side effects resulted fr effects secondary to estrogen inhibition of hepatic microsomal enzymes (Somani & Khurana, 1973h).

c) In a study women received clomipramine and oral contraceptives or clomipramine alone. At the begin there were 30 women taking the combination, but 12 subsequently dropped out. The 18 patients on the matched with 18 patients taking clomipramine alone. No significant difference was noted in the patients' clomipramine. It was proposed that there was no significant difference in side-effects between the groups groups were matched after patients had dropped out of the study. Had the patients been matched prior t different conclusions may have been drawn (Beaumont, 1973e).

d) The effects of oral contraceptives on clomipramine was studied in 42 women between the ages of 18 three women took clomipramine 25 milligrams at bedtime while 19 took clomipramine 25 milligrams at be contraceptives. Over the 4-week study, 3 control patients (2 due to side-effects) and 5 in the experimenta side-effects) dropped out. Venous blood samples were drawn at weekly intervals for measurement of se concentrations. No difference in serum concentrations was noted between the groups. However, this res due to the low dose of clomipramine given (Luscombe & John, 1980d).

e) The onset of akathisia was reported in 3 patients receiving conjugated estrogens and tricyclic antidep

concurrently. A 24-year-old patient receiving clomipramine 120 milligrams/day for anorexia nervosa and estrogens 1.25 milligrams/day for amenorrhea developed restless legs and a constant desire to move co Estrogen was discontinued and benztropine 2 milligrams was administered, resulting in marked reductio within 48 hours. Akathisia and disorientation developed in a 55-year-old patient on conjugated estrogens milligrams/day who was prescribed amitriptyline 50 milligrams/day for depression. Within hours of amitrip was confused, restless, and possessed an inner desire to move continuously. Symptoms disappeared af amitriptyline. Positive rechallenge at one week with doxepin 100 milligrams, with resolution following disc doxepin. A third case of akathisia was reported in a 35-year-old patient who received conjugated estroge milligrams/day and amitriptyline 50 milligrams/day. Akathisia developed within a few hours after taking th amitriptyline and resolved within 48 hours following discontinuation of the antidepressant (Krishnan et al,

f) The absolute bioavailability of imipramine increased in women who received low-dose oral contracept micrograms or less of ethinyl estradiol) from 27 to 44% (p less than 0.05) as evident by an increase in th plasma concentration time curve (Abernethy et al, 1984e).

g) Estrogens may inhibit the oxidation of TCAs by affecting hepatic microsomal enzymes (John et al, 19 are metabolized via oxidation and conjugation pathways. Inhibition of the oxidation of TCAs could result and toxicity due to decreased clearance. Estrogens are suspected of possessing other effects on the cer system resulting in an antidepressant effect (Oppenheim, 1983d).

3.5.1.DD Methamphetamine

1) Interaction Effect: hypertension, other cardiac effects, and CNS stimulation

2) Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been reporte enhanced amphetamine effects from the release of norepinephrine (Beaumont, 1973d; Raisfeld, 1972). A sim also occur with all drugs that have amphetamine-like effects. Acute elevations in blood pressure have been n (Flemenbaum, 1971a). Some amphetamine-like drugs may inhibit the metabolism of TCAs, although most co not been studied. When amphetamine analogs are being used to treat obesity, it should be noted that TCAs f moderate weight gain (Russ & Ackerman, 1988). False positive urine tests for amphetamines have been repo therapy with some TCAs (Merigian & Browning, 1993). Caution is advised when concurrent administration of agents and TCAs is warranted. The patient should be closely monitored for increased cardiovascular effects dysrhythmias).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other sympatho could lead to hypertension, increased cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) o Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral t Flemenbaum, 1972). Use caution if such therapy is warranted. Monitor the patient closely for hypertension ar

7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission

8) Literature Reports

a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agen coadministration of d-amphetamine with TCAs such as desipramine or protriptyline results in sustained in amphetamine concentration in the brain (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info DEXE sustained-release oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006).

b) Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism o antidepressants, such as imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transde 2006).

c) Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases in such that the hypotensive effects induced by TCAs may lead to blood pressures as high as 170/120 mm of combined therapy. Discontinuation of the methylphenidate usually results in the blood pressure return normotensive levels; reinstitution of the methylphenidate resulted in further blood pressure elevation (Fle Flemenbaum, 1972).

d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine g four weeks, were given fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transie clinical improvement. However, fenfluramine more than doubled steady-state plasma levels of desipramin 1990).

e) There have been claims based on uncontrolled studies that a better antidepressant response may oc therapy (Garrettson et al, 1969). However, a systemic review of stimulants in the treatment of depressior although uncontrolled studies were generally positive, the ten placebo-controlled studies of stimulant dru depression, with one exception, indicated little advantage of drug over placebo and did not appear to be conventional antidepressants in primary depression (Satel & Nelson, 1989).

3.5.1.DE Methohexital

1) Interaction Effect: possible decreased tricyclic antidepressant serum concentrations and possible additive

2) Summary: Concomitant barbiturate and tricyclic antidepressant (TCA) therapy may result in increased me TCA. There have been scattered reports of individuals with decreased serum levels of TCAs in the presence (Moody et al, 1977; Silverman & Braithwaite, 1972; Burrows & Davies, 1971). In addition, TCAs can worsen s reducing the seizure threshold (Brodie, 1992). These drugs also have additive CNS and respiratory depressa

3) Severity: minor

4) Onset: delayed

5) Substantiation: probable
6) Clinical Management: Monitor for efficacy of antidepressant effect. Increases in tricyclic antidepressant do required. Additionally, monitor for toxicity when either drug is added to or withdrawn from therapy. Serum con be of value in determining appropriate dosage.
7) Probable Mechanism: increased tricyclic antidepressant metabolism
8) Literature Reports
a) The pharmacokinetics of a single oral dose of desipramine (100 mg) were studied in eight epileptic pa treated with phenobarbital and in eight drug-free healthy controls (Spina et al, 1996). All subjects were e metabolizers with respect to the genetically determined CYP2D6-related metabolic polymorphism. Comp epileptic patients exhibited lower peak plasma desipramine concentrations (74 nmol/L vs. 107 nmol/L), s area under the concentration-time curve values (1943 nmol/L/h vs. 3234 nmol/L/h), and shorter desipran half-lives (15.1 h vs. 20.6 h). All barbiturates are believed to have similar effects leading to induction of h and the 2D6 isozyme is believed to be important in the metabolism of most or all TCAs. Thus, similar effe expected with any combination of TCA and barbiturate.

3.5.1.DF Methoxamine

1) Interaction Effect: hypertension, cardiac arrhythmias, and tachycardia
2) Summary: Clinical trials have demonstrated a 2- to 8-fold increase in the effects of intravenous infusions d drugs to volunteers on tricyclic antidepressants. Arrhythmias and other severe adverse effects have also bee 1980; Avery, 1973a; Boakes et al, 1973a; Boakes, 1973; Mitchell et al, 1970; Stone et al, 1964a). Local use (anesthesia) of epinephrine in concentrations of 1:100,000 or less is less likely to precipitate clinically significa changes (Steinberg & Block, 1971).
3) Severity: major
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: The vasoconstriction and other alpha-adrenergic effects of sympathomimetic drugs enhanced in the presence of tricyclic antidepressants (TCAs). Concomitant use should be avoided. If these d together, careful monitoring and a dose reduction of the sympathomimetic is required. Patients should be inst their doctor or dentist that they are taking a tricyclic antidepressant prior to any surgery or procedure.
7) Probable Mechanism: inhibition of norepinephrine reuptake
8) Literature Reports
a) Four healthy volunteers received intravenous infusions of various sympathomimetic amines (epineph norepinephrine, phenylephrine, and isoproterenol) before and after imipramine (25 mg three times daily f showed an increased pressor response to epinephrine (2- to 4-fold), norepinephrine (4- to 8-fold), and ph 3-fold) after imipramine, but no difference was observed in the response to isoproterenol. Thus, the incre response appeared to occur only for alpha adrenergic effects. All four subjects demonstrated changes in with epinephrine and imipramine consisting of sinus arrhythmia in three subjects and multiple ectopic be rhythm in the fourth subject (Boakes et al, 1973).
b) A review of spontaneous reports of adverse reactions to vasoconstrictors in local anesthetics found th receiving a local anesthetic with norepinephrine (1:25,000) had severe reactions (severe headaches, che subarachnoid hemorrhage). The drug history was incomplete, but at least three had been taking a tricycl at the time (Anon, 1972).

3.5.1.DG Methylphenidate

1) Interaction Effect: hypertension, other cardiac effects, and CNS stimulation
2) Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been reporte enhanced amphetamine effects from the release of norepinephrine (Beaumont, 1973d; Raisfeld, 1972). A sim also occur with all drugs that have amphetamine-like effects. Acute elevations in blood pressure have been n (Flemenbaum, 1971a). Some amphetamine-like drugs may inhibit the metabolism of TCAs, although most co not been studied. When amphetamine analogs are being used to treat obesity, it should be noted that TCAs f moderate weight gain (Russ & Ackerman, 1988). False positive urine tests for amphetamines have been repo therapy with some TCAs (Merigian & Browning, 1993). Caution is advised when concurrent administration of agents and TCAs is warranted. The patient should be closely monitored for increased cardiovascular effects dysrhythmias).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other sympatho could lead to hypertension, increased cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) o Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral t Flemenbaum, 1972). Use caution if such therapy is warranted. Monitor the patient closely for hypertension ar
7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission
8) Literature Reports
a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agen coadministration of d-amphetamine with TCAs such as desipramine or protriptyline results in sustained in amphetamine concentration in the brain (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info DEXE sustained-release oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006).
b) Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism o

antidepressants, such as imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transde 2006).

c) Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases i such that the hypotensive effects induced by TCAs may lead to blood pressures as high as 170/120 mm of combined therapy. Discontinuation of the methylphenidate usually results in the blood pressure return normotensive levels; reinstitution of the methylphenidate resulted in further blood pressure elevation (Fle Flemenbaum, 1972).

d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine g four weeks, were given fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transi clinical improvement. However, fenfluramine more than doubled steady-state plasma levels of desiprami 1990).

e) There have been claims based on uncontrolled studies that a better antidepressant response may oc therapy (Garrettson et al, 1969). However, a systemic review of stimulants in the treatment of depressior although uncontrolled studies were generally positive, the ten placebo-controlled studies of stimulant dru depression, with one exception, indicated little advantage of drug over placebo and did not appear to be conventional antidepressants in primary depression (Satel & Nelson, 1989).

3.5.1.DH Mibefradil

1) Interaction Effect: an increased risk of imipramine toxicity (drowsiness, hypotension, akathisia)

2) Summary: Imipramine is metabolized by cytochrome P450 2D6 and has a high first-pass effect. When mib inhibitor of CYP450 2D6) and imipramine were coadministered, the area under the concentration-time curve (imipramine was increased seven- to eight-fold (Prod Info Posicor(R), 1997).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Monitor patients for excessive imipramine adverse effects (drowsiness, hypotensior dosage adjustment of imipramine may be necessary.

7) Probable Mechanism: inhibition of imipramine metabolism

3.5.1.DI Midodrine

1) Interaction Effect: hypertension, cardiac arrhythmias, and tachycardia

2) Summary: Clinical trials have demonstrated a 2- to 8-fold increase in the effects of intravenous infusions c drugs to volunteers on tricyclic antidepressants. Arrhythmias and other severe adverse effects have also bee 1980; Avery, 1973a; Boakes et al, 1973a; Boakes, 1973; Mitchell et al, 1970; Stone et al, 1964a). Local use (anesthesia) of epinephrine in concentrations of 1:100,000 or less is less likely to precipitate clinically significa changes (Steinberg & Block, 1971).

3) Severity: major

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: The vasoconstriction and other alpha-adrenergic effects of sympathomimetic drugs enhanced in the presence of tricyclic antidepressants (TCAs). Concomitant use should be avoided. If these d together, careful monitoring and a dose reduction of the sympathomimetic is required. Patients should be inst their doctor or dentist that they are taking a tricyclic antidepressant prior to any surgery or procedure.

7) Probable Mechanism: inhibition of norepinephrine reuptake

8) Literature Reports

a) Four healthy volunteers received intravenous infusions of various sympathomimetic amines (epineph norepinephrine, phenylephrine, and isoproterenol) before and after imipramine (25 mg three times daily f showed an increased pressor response to epinephrine (2- to 4-fold), norepinephrine (4- to 8-fold), and ph 3-fold) after imipramine, but no difference was observed in the response to isoproterenol. Thus, the incre response appeared to occur only for alpha adrenergic effects. All four subjects demonstrated changes in with epinephrine and imipramine consisting of sinus arrhythmia in three subjects and multiple ectopic be rhythm in the fourth subject (Boakes et al, 1973).

b) A review of spontaneous reports of adverse reactions to vasoconstrictors in local anesthetics found th receiving a local anesthetic with norepinephrine (1:25,000) had severe reactions (severe headaches, che subarachnoid hemorrhage). The drug history was incomplete, but at least three had been taking a tricycl at the time (Anon, 1972).

3.5.1.DJ Moclobemide

1) Interaction Effect: neurotoxicity, seizures, or serotonin syndrome (hypertension, hyperthermia, myoclonus changes)

2) Summary: Concomitant TCA and MAOI use has resulted in hyperpyrexia, convulsions, and death. Concur and TCAs has also been reported to result in a condition termed serotonin syndrome (Insel et al, 1982c; Spig Brodribb et al, 1994c; Neuvonen et al, 1993a). Serotonin syndrome is a rare but potentially fatal condition of s hyperstimulation characterized by hypertension, hyperthermia, myoclonus, and changes in mental status (Ste Subsequently, the concomitant use of TCAs and MAOIs is contraindicated in most cases. If TCAs and MAOIs concurrently, avoid large doses, use only oral TCAs, avoid imipramine, clomipramine, desipramine, and trany monitor patients closely (Schuckit et al, 1971c; White & Simpson, 1984b).

3) Severity: contraindicated

4) Onset: delayed
5) Substantiation: established
6) Clinical Management: Concomitant use of moclobemide and imipramine is contraindicated. If imipramine i
treatment with moclobemide, a minimum of 2 weeks should elapse after moclobemide is discontinued and im
is begun (Prod Info imipramine hydrochloride oral tablet, 2003). However, the manufacturer of moclobemide
short washout period of 2 days after discontinuation of moclobemide and before imipramine is initiated (Prod
2001). There is no specific washout period for replacing imipramine treatment with moclobemide. However, it
gradually taper the tricyclic antidepressant dosage before starting treatment with an MAOI (Remick, 2002).
7) Probable Mechanism: altered catecholamine uptake and metabolism
8) Literature Reports

a) Concomitant administration of monoamine oxidase inhibitors (MAOIs) with tricyclic antidepressants (T
considered an absolute contraindication in the past and still is listed as such by the manufacturers. Repo
hyperpyrexia, convulsions, and possible death have been attributed to the combination (Prod Info imipra
oral tablet, 2003; Lockett & Milner, 1965a; Brachfeld et al, 1963; Winston, 1971a; Schuckit et al, 1971b; S
Spiker & Pugh, 1976a). The mechanism may relate to the combined inhibition of catecholamine reuptake
nervous system and inhibition of catecholamine metabolism (Sjoqvist, 1965a).

b) A clinical study designed to detect an interaction between moclobemide and a tricyclic antidepressan
resulted in severe adverse effects, and the study was terminated. Information about interactions with mo
other tricyclic antidepressants is limited (Prod Info Manerix(R), 2001).

c) A 39-year old woman with bipolar disorder developed serotonin syndrome after imipramine was adde
The patient was taking moclobemide 300 mg twice daily when imipramine was started at 50 mg daily, fol
dosage increases of imipramine to 200 mg and a reduction of moclobemide dosage to 150 mg twice dail
the increase in imipramine to 200 mg per day, the patient developed symptoms of serotonin syndrome, i
shivering, confusion, fever, and spasms in the extremities. The patient was treated with chlorpromazine a
resolved over the next few days without further complications (Brodribb et al, 1994b).

d) A drug interaction occurred in which a 76-year old woman who had been taking clomipramine 50 mg
months prior to switching to moclobemide 300 mg daily.The patient experienced somnolence, confusion,
then progressed to further mental impairment, muscle stiffness, myoclonus, and convulsive attacks. The
symptoms were described as fulfilling the diagnostic criteria for serotonin syndrome and were resolved a
after discontinuing all antidepressant medications (Spigset et al, 1993c).

e) A clinical study designed to detect an interaction between moclobemide and a tricyclic antidepressan
resulted in severe adverse effects, and the study was terminated. Information about interactions with mo
other tricyclic antidepressants is limited (Prod Info Manerix(R), 2001).

f) Administration of a TCA after MAOI therapy may result in the development of serotonin syndrome. In
crossover study examining the effects of clorgyline and clomipramine for the treatment of obsessive-com
two subjects developed severe reactions characteristic of serotonin syndrome. During the study, patients
clorgyline therapy, followed by a washout period of approximately four weeks and subsequent clomipram
taking the first 100 mg dose of clomipramine, one patient developed coarse myoclonic jerking in both leg
diaphoresis, and arrhythmia. Another patient developed a similar reaction after the first dose, with upper
symptoms, myoclonic movements, and cardiac irritability. Both patient's symptoms resolved several hou
patients were later treated successfully with clomipramine without adverse effects (Insel et al, 1982b).

g) Three patients with bipolar disorder developed manic symptoms while undergoing concurrent therapy
isocarboxazid and amitriptyline. In all three cases the patients had been given MAOIs and TCAs alone w
complications. It was only when the drugs were used in combination that symptoms of mania emerged, s
synergistic effect (de la Fuente et al, 1986).

h) In one case, clomipramine 10 mg twice daily was added to a stable regimen of tranylcypromine in a p
34-year old man. After taking several doses, the patients developed symptoms of nausea and profuse sv
by pyrexia, dyspnea, and agitation. The hyperpyrexical state led to disseminated intravascular coagulatic
death (Tackley & Tregaskis, 1987b).

i) There is evidence that MAOIs and TCAs can be given concomitantly in patients previously unrespons
TCA alone. A few precautions must be followed including: a) avoidance of large doses (no more than 15
or its equivalent, 45 mg phenelzine, or 60 mg isocarboxazid) b) oral administration c) avoidance of clomi
imipramine, desipramine, and tranylcypromine in any combination, and d) close monitoring of patients (K
Winston, 1971a; Schuckit et al, 1971b; White & Simpson, 1984a; Rom & Benner, 1972). The combinatio
in one of two ways. Most frequently, the recommendation is to stop all previous antidepressants (five to t
and 14 days for MAOIs); the combination is then simultaneously started (Perry et al, 1991a). Alternatively
previously receiving a TCA, small doses of the MAOI may be slowly added (Schoonover, 1983). Some s
that the combination of amitriptyline and isocarboxazid is preferred (Perry et al, 1991a). Numerous studie
refractory depression or phobic anxiety states have successfully used the combination of MAOIs and TC
1977a; Schuckit et al, 1971b; Ashcroft, 1975a).

3.5.1.DK Moxifloxacin

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Moxifloxacin has been shown to prolong the QT interval in some patients and should be avoide
receiving agents that also prolong the QT interval, such as tricyclic antidepressants. Although pharmacokinet
moxifloxacin and other drugs which prolong the QT interval have not been performed, an additive effect cann
Therefore, moxifloxacin should be used with caution when given concurrently with a tricyclic antidepressant (
(TM), 2000).

3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Moxifloxacin should be used with caution when given concurrently with a tricyclic ar
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.DL Nefopam

1) Interaction Effect: an increased risk of seizures
2) Summary: Nefopam inhibits the neuronal uptake of norepinephrine and serotonin and increases the risk o especially in patients with a history of a convulsive disorder. Tricyclic antidepressants also lower the seizure t Therefore, the manufacturer of nefopam advises caution in patients on concurrent tricyclic antidepressant the Woods, 1995).
3) Severity: major
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Because of the increased risk of seizures, extreme caution should be exercised in p nefopam and a tricyclic antidepressant. An alternative analgesic may be considered.
7) Probable Mechanism: additive lowering of seizure threshold

3.5.1.DM Nialamide

1) Interaction Effect: neurotoxicity, seizures, or serotonin syndrome (hypertension, hyperthermia, myoclonus changes)
2) Summary: Concomitant TCA and MAOI use has resulted in hyperpyrexia, convulsions, and death. Concur and TCAs has also been reported to result in a condition termed serotonin syndrome (Insel et al, 1982k; Spig Brodribb et al, 1994j; Neuvonen et al, 1993e). Serotonin syndrome is a rare but potentially fatal condition of s hyperstimulation characterized by hypertension, hyperthermia, myoclonus, and changes in mental status (Ste TCAs and MAOIs must be used concurrently, avoid large doses, use only oral TCAs, avoid imipramine, clom desipramine, and tranylcypromine, and monitor patients closely (Schuckit et al, 1971j; White & Simpson, 198
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Concomitant use of a tricyclic antidepressant (TCA) and a monoamine oxidase inhi should be done only with close monitoring and where the clinical benefit outweighs the potential risk. Other a therapy should first be considered. If deemed clinically necessary, avoid large doses and use agents other th clomipramine, desipramine, and tranylcypromine.
7) Probable Mechanism: altered catecholamine uptake and metabolism
8) Literature Reports

a) Concomitant administration of monoamine oxidase inhibitors (MAOIs) with tricyclic antidepressants (T considered an absolute contraindication in the past. Reports of excitation, hyperpyrexia, convulsions, and have been attributed to the combination (Lockett & Milner, 1965e; Winston, 1971e; Schuckit et al, 1971i; 1976e). The mechanism may relate to the combined inhibition of catecholamine reuptake into the centra and inhibition of catecholamine metabolism (Sjoqvist, 1965e).

b) In a double-blind, crossover study examining the effects of clorgyline and clomipramine for the treatm compulsive disorder, two subjects developed severe reactions characteristic of serotonin syndrome. Dur patients had received clorgyline therapy, followed by a washout period of approximately four weeks and clomipramine therapy. After taking the first 100 mg dose of clomipramine, one patient developed coarse in both legs, hyperreflexia, diaphoresis, and arrhythmia. Another patient developed a similar reaction afte with upper motor neuron symptoms, myoclonic movements, and cardiac irritability. Both patient's sympto several hours later, and both patients were later treated successfully with clomipramine without adverse 1982j).

c) A drug interaction occurred in a 76-year old woman who had been taking clomipramine 50 mg daily fo prior to switching to moclobemide 300 mg daily. The patient experienced somnolescence, confusion, and progressed to further mental impairment, muscle stiffness, myoclonus, and convulsive attacks. The patie were described as fulfilling the diagnostic criteria for serotonin syndrome and were resolved a few days l discontinuing all antidepressant medications (Spigset et al, 1993k).

d) In one case, clomipramine 10 mg twice daily was added to a stable regimen of tranylcypromine in a p 34-year old man. After taking several doses, the patients developed symptoms of nausea and profuse sw by pyrexia, dyspnea, and agitation. The hyperpyrexical state led to disseminated intravascular coagulatio death (Tackley & Tregaskis, 1987f).

e) There is evidence that MAOIs and TCAs can be given concomitantly in patients previously unresponsi TCA alone. The combination may be utilized in one of two ways. Most frequently, the recommendation is previous antidepressants (five to ten days for TCAs and 14 days for MAOIs); the combination is then sim started (Perry et al, 1991e). Alternatively, in a patient previously receiving a TCA, small doses of the MA added (Schoonover, 1983). Numerous studies in patients with refractory depression or phobic anxiety st successfully used the combination of MAOIs and TCAs (Ponto et al, 1977e; Schuckit et al, 1971i; Ashcro

3.5.1.DN Norepinephrine

1) Interaction Effect: hypertension, cardiac arrhythmias, and tachycardia

2) Summary: Clinical trials have demonstrated a 2- to 8-fold increase in the effects of intravenous infusions o drugs to volunteers on tricyclic antidepressants. Arrhythmias and other severe adverse effects have also bee 1980; Avery, 1973a; Boakes et al, 1973a; Boakes, 1973; Mitchell et al, 1970; Stone et al, 1964a). Local use (anesthesia) of epinephrine in concentrations of 1:100,000 or less is less likely to precipitate clinically significa changes (Steinberg & Block, 1971).
3) Severity: major
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: The vasoconstriction and other alpha-adrenergic effects of sympathomimetic drugs enhanced in the presence of tricyclic antidepressants (TCAs). Concomitant use should be avoided. If these d together, careful monitoring and a dose reduction of the sympathomimetic is required. Patients should be inst their doctor or dentist that they are taking a tricyclic antidepressant prior to any surgery or procedure.
7) Probable Mechanism: inhibition of norepinephrine reuptake
8) Literature Reports
a) Four healthy volunteers received intravenous infusions of various sympathomimetic amines (epineph norepinephrine, phenylephrine, and isoproterenol) before and after imipramine (25 mg three times daily f showed an increased pressor response to epinephrine (2- to 4-fold), norepinephrine (4- to 8-fold), and ph 3-fold) after imipramine, but no difference was observed in the response to isoproterenol. Thus, the incre response appeared to occur only for alpha adrenergic effects. All four subjects demonstrated changes in with epinephrine and imipramine consisting of sinus arrhythmia in three subjects and multiple ectopic be rhythm in the fourth subject (Boakes et al, 1973).
b) A review of spontaneous reports of adverse reactions to vasoconstrictors in local anesthetics found th receiving a local anesthetic with norepinephrine (1:25,000) had severe reactions (severe headaches, che subarachnoid hemorrhage). The drug history was incomplete, but at least three had been taking a tricycl at the time (Anon, 1972).

3.5.1.DO Octreotide

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Tricyclic antidepressants (TCAs) and octreotide have been shown to prolong the QTc interval a recommended therapeutic dose (Prod Info Sandostatin(R), 1999; Marshall & Forker, 1982). Even though no f interaction studies have been done, the coadministration of tricyclic antidepressants and other drugs known t interval, such as octreotide, is not recommended (Prod Info Elavil(R), 1999).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of octreotide and tricyclic antidepressants is not reco
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.DP Oxilofrine

1) Interaction Effect: hypertension, cardiac arrhythmias, and tachycardia
2) Summary: Clinical trials have demonstrated a 2- to 8-fold increase in the effects of intravenous infusions o drugs to volunteers on tricyclic antidepressants. Arrhythmias and other severe adverse effects have also bee 1980; Avery, 1973a; Boakes et al, 1973a; Boakes, 1973; Mitchell et al, 1970; Stone et al, 1964a). Local use (anesthesia) of epinephrine in concentrations of 1:100,000 or less is less likely to precipitate clinically significa changes (Steinberg & Block, 1971).
3) Severity: major
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: The vasoconstriction and other alpha-adrenergic effects of sympathomimetic drugs enhanced in the presence of tricyclic antidepressants (TCAs). Concomitant use should be avoided. If these d together, careful monitoring and a dose reduction of the sympathomimetic is required. Patients should be inst their doctor or dentist that they are taking a tricyclic antidepressant prior to any surgery or procedure.
7) Probable Mechanism: inhibition of norepinephrine reuptake
8) Literature Reports
a) Four healthy volunteers received intravenous infusions of various sympathomimetic amines (epineph norepinephrine, phenylephrine, and isoproterenol) before and after imipramine (25 mg three times daily f showed an increased pressor response to epinephrine (2- to 4-fold), norepinephrine (4- to 8-fold), and ph 3-fold) after imipramine, but no difference was observed in the response to isoproterenol. Thus, the incre response appeared to occur only for alpha adrenergic effects. All four subjects demonstrated changes in with epinephrine and imipramine consisting of sinus arrhythmia in three subjects and multiple ectopic be rhythm in the fourth subject (Boakes et al, 1973).
b) A review of spontaneous reports of adverse reactions to vasoconstrictors in local anesthetics found th receiving a local anesthetic with norepinephrine (1:25,000) had severe reactions (severe headaches, che subarachnoid hemorrhage). The drug history was incomplete, but at least three had been taking a tricycl at the time (Anon, 1972).

3.5.1.DQ Pargyline

1) Interaction Effect: neurotoxicity, seizures, or serotonin syndrome (hypertension, hyperthermia, myoclonus

changes)
2) Summary: Concomitant TCA and MAOI use has resulted in hyperpyrexia, convulsions, and death. Concu
and TCAs has also been reported to result in a condition termed serotonin syndrome (Insel et al, 1982a; Spig
Brodribb et al, 1994; Neuvonen et al, 1993). Serotonin syndrome is a rare but potentially fatal condition of se
hyperstimulation characterized by hypertension, hyperthermia, myoclonus, and changes in mental status (Ste
TCAs and MAOIs must be used concurrently, avoid large doses, use only oral TCAs, avoid imipramine, clom
desipramine, and tranylcypromine, and monitor patients closely (Schuckit et al, 1971a; White & Simpson, 198
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Concomitant use of a tricyclic antidepressant (TCA) and a monoamine oxidase inhi
should be done only with close monitoring and where the clinical benefit outweighs the potential risk. Other a
therapy should first be considered. If deemed clinically necessary, avoid large doses and use agents other th
clomipramine, desipramine, and tranylcypromine.
7) Probable Mechanism: altered catecholamine uptake and metabolism
8) Literature Reports
a) Concomitant administration of monoamine oxidase inhibitors (MAOIs) with tricyclic antidepressants (T
considered an absolute contraindication in the past. Reports of excitation, hyperpyrexia, convulsions, an
have been attributed to the combination (Lockett & Milner, 1965; Winston, 1971; Schuckit et al, 1971; Sp
1976). The mechanism may relate to the combined inhibition of catecholamine reuptake into the central
and inhibition of catecholamine metabolism (Sjoqvist, 1965).
b) Administration of a TCA after MAOI therapy may result in the development of serotonin syndrome. In
crossover study examining the effects of clorgyline and clomipramine for the treatment of obsessive-com
two subjects developed severe reactions characteristic of serotonin syndrome. During the study, patients
clorgyline therapy, followed by a washout period of approximately four weeks and subsequent clomipram
taking the first 100 mg dose of clomipramine, one patient developed coarse myoclonic jerking in both leg
diaphoresis, and arrhythmia. Another patient developed a similar reaction after the first dose, with upper
symptoms, myoclonic movements, and cardiac irritability. Both patient's symptoms resolved several hou
patients were later treated successfully with clomipramine without adverse effects (Insel et al, 1982).
c) A drug interaction occurred in a 76-year old woman who had been taking clomipramine 50 mg daily fo
prior to switching to moclobemide 300 mg daily. The patient experienced somnolescence, confusion, an
progressed to further mental impairment, muscle stiffness, myoclonus, and convulsive attacks. The patie
were described as fulfilling the diagnostic criteria for serotonin syndrome and were resolved a few days l
discontinuing all antidepressant medications (Spigset et al, 1993).
d) In one case, clomipramine 10 mg twice daily was added to a stable regimen of tranylcypromine in a p
34-year old man. After taking several doses, the patients developed symptoms of nausea and profuse sv
by pyrexia, dyspnea, and agitation. The hyperpyrexical state led to disseminated intravascular coagulatio
death (Tackley & Tregaskis, 1987).
e) There is evidence that MAOIs and TCAs can be given concomitantly in patients previously unrespons
TCA alone. The combination may be utilized in one of two ways. Most frequently, the recommendation is
previous antidepressants (five to ten days for TCAs and 14 days for MAOIs); the combination is then sim
started (Perry et al, 1991). Alternatively, in a patient previously receiving a TCA, small doses of the MAO
added (Schoonover, 1983). Numerous studies in patients with refractory depression or phobic anxiety st
successfully used the combination of MAOIs and TCAs (Ponto et al, 1977; Schuckit et al, 1971; Ashcroft

3.5.1.DR Paroxetine
1) Interaction Effect: imipramine toxicity (dry mouth, sedation, urinary retention)
2) Summary: Paroxetine coadministered with desipramine or imipramine produced higher serum concentrati
antidepressant (TCA) in some patients (Prod Info Paxil CR(TM), 2003; Hartter et al, 1994; Brosen et al, 1993
effect on TCAs may resemble that of fluoxetine (another selective serotonin reuptake inhibitor), which is knov
metabolism (Aranow et al, 1989b; Vaughan, 1988; Goodnick, 1989b). With coadministration, monitor patients
toxicity. Imipramine doses may need to be reduced.
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Coadministration of paroxetine with other drugs that are metabolized by cytochrom
(CYP2D6) should be approached with caution. When paroxetine is coadministered with imipramine, monitor
and symptoms of imipramine toxicity (dry mouth, sedation, urinary retention, blurred vision). Imipramine dose
reduced.
7) Probable Mechanism: decreased cytochrome P450 2D6-mediated imipramine metabolism
8) Literature Reports
a) The effect of paroxetine on desipramine metabolism was studied in nine extensive metabolizers (EM)
metabolizers (PM) of desipramine. Subjects took a single oral dose of desipramine before starting paroxe
dose after 11 days of paroxetine use. After the addition of paroxetine, EMs experienced a 5-fold decreas
desipramine, indicating that paroxetine inhibits oxidation reactions catalyzed by CYP2D6. PMs had a slig
clearance of desipramine with paroxetine. With concurrent administration of desipramine and paroxetine
two drugs may result in a need for dosage adjustments, especially in extensive metabolizers of desipram
1993).

3.5.1.DS Pemoline

1) Interaction Effect: hypertension, other cardiac effects, and CNS stimulation

2) Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been reporte enhanced amphetamine effects from the release of norepinephrine (Beaumont, 1973d; Raisfeld, 1972). A sin also occur with all drugs that have amphetamine-like effects. Acute elevations in blood pressure have been n (Flemenbaum, 1971a). Some amphetamine-like drugs may inhibit the metabolism of TCAs, although most co not been studied. When amphetamine analogs are being used to treat obesity, it should be noted that TCAs f moderate weight gain (Russ & Ackerman, 1988). False positive urine tests for amphetamines have been repo therapy with some TCAs (Merigian & Browning, 1993). Caution is advised when concurrent administration of agents and TCAs is warranted. The patient should be closely monitored for increased cardiovascular effects dysrhythmias).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other sympatho could lead to hypertension, increased cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) o Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral t Flemenbaum, 1972). Use caution if such therapy is warranted. Monitor the patient closely for hypertension ar

7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission

8) Literature Reports

a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agen coadministration of d-amphetamine with TCAs such as desipramine or protriptyline results in sustained i amphetamine concentration in the brain (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info DEXE sustained-release oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006).

b) Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism o antidepressants, such as imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transde 2006).

c) Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases i such that the hypotensive effects induced by TCAs may lead to blood pressures as high as 170/120 mm of combined therapy. Discontinuation of the methylphenidate usually results in the blood pressure return normotensive levels; reinstitution of the methylphenidate resulted in further blood pressure elevation (Fle Flemenbaum, 1972).

d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine g four weeks, were given fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transie clinical improvement. However, fenfluramine more than doubled steady-state plasma levels of desipramin 1990).

e) There have been claims based on uncontrolled studies that a better antidepressant response may oc therapy (Garrettson et al, 1969). However, a systemic review of stimulants in the treatment of depressior although uncontrolled studies were generally positive, the ten placebo-controlled studies of stimulant dru depression, with one exception, indicated little advantage of drug over placebo and did not appear to be conventional antidepressants in primary depression (Satel & Nelson, 1989).

3.5.1.DT Pentamidine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Tricyclic antidepressants (TCAs) and pentamidine have been shown to prolong the QTc interva recommended therapeutic dose (Lindsay et al, 1990; Marshall & Forker, 1982i). Even though no formal drug have been done, the coadministration of tricyclic antidepressants and other drugs known to prolong the QTc pentamidine, is not recommended (Prod Info Elavil(R), 1999e).

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of pentamidine and tricyclic antidepressants is not re

7) Probable Mechanism: additive effects on QT prolongation

3.5.1.DU Pentobarbital

1) Interaction Effect: possible decreased tricyclic antidepressant serum concentrations and possible additive

2) Summary: Concomitant barbiturate and tricyclic antidepressant (TCA) therapy may result in increased me TCA. There have been scattered reports of individuals with decreased serum levels of TCAs in the presence (Moody et al, 1977; Silverman & Braithwaite, 1972; Burrows & Davies, 1971). In addition, TCAs can worsen s reducing the seizure threshold (Brodie, 1992). These drugs also have additive CNS and respiratory depressa

3) Severity: minor

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Monitor for efficacy of antidepressant effect. Increases in tricyclic antidepressant do required. Additionally, monitor for toxicity when either drug is added to or withdrawn from therapy. Serum con be of value in determining appropriate dosage.

7) Probable Mechanism: increased tricyclic antidepressant metabolism

8) Literature Reports

a) The pharmacokinetics of a single oral dose of desipramine (100 mg) were studied in eight epileptic pa treated with phenobarbital and in eight drug-free healthy controls (Spina et al, 1996). All subjects were ex metabolizers with respect to the genetically determined CYP2D6-related metabolic polymorphism. Comp epileptic patients exhibited lower peak plasma desipramine concentrations (74 nmol/L vs. 107 nmol/L), s area under the concentration-time curve values (1943 nmol/L/h vs. 3234 nmol/L/h), and shorter desipran half-lives (15.1 h vs. 20.6 h). All barbiturates are believed to have similar effects leading to induction of h and the 2D6 isozyme is believed to be important in the metabolism of most or all TCAs. Thus, similar effe expected with any combination of TCA and barbiturate.

3.5.1.DV Phendimetrazine

1) Interaction Effect: hypertension, other cardiac effects, and CNS stimulation

2) Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been reported enhanced amphetamine effects from the release of norepinephrine (Beaumont, 1973d; Raisfeld, 1972). A sin also occur with all drugs that have amphetamine-like effects. Acute elevations in blood pressure have been n (Flemenbaum, 1971a). Some amphetamine-like drugs may inhibit the metabolism of TCAs, although most co not been studied. When amphetamine analogs are being used to treat obesity, it should be noted that TCAs f moderate weight gain (Russ & Ackerman, 1988). False positive urine tests for amphetamines have been repo therapy with some TCAs (Merigian & Browning, 1993). Caution is advised when concurrent administration of agents and TCAs is warranted. The patient should be closely monitored for increased cardiovascular effects dysrhythmias).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other sympatho could lead to hypertension, increased cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) o Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral t Flemenbaum, 1972). Use caution if such therapy is warranted. Monitor the patient closely for hypertension ar

7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission

8) Literature Reports

a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agen coadministration of d-amphetamine with TCAs such as desipramine or protriptyline results in sustained in amphetamine concentration in the brain (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info DEXE sustained-release oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006).

b) Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism o antidepressants, such as imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transde 2006).

c) Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases in such that the hypotensive effects induced by TCAs may lead to blood pressures as high as 170/120 mm of combined therapy. Discontinuation of the methylphenidate usually results in the blood pressure return normotensive levels; reinstitution of the methylphenidate resulted in further blood pressure elevation (Fle Flemenbaum, 1972).

d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine g four weeks, were given fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transie clinical improvement. However, fenfluramine more than doubled steady-state plasma levels of desipramin 1990).

e) There have been claims based on uncontrolled studies that a better antidepressant response may oc therapy (Garrettson et al, 1969). However, a systemic review of stimulants in the treatment of depressior although uncontrolled studies were generally positive, the ten placebo-controlled studies of stimulant dru depression, with one exception, indicated little advantage of drug over placebo and did not appear to be conventional antidepressants in primary depression (Satel & Nelson, 1989).

3.5.1.DW Phenelzine

1) Interaction Effect: neurotoxicity, seizures, or serotonin syndrome (hypertension, hyperthermia, myoclonus changes)

2) Summary: Concomitant TCA and MAOI use has resulted in hyperpyrexia, convulsions, and death. Concur and TCAs has also been reported to result in a condition termed serotonin syndrome (Insel et al, 1982r; Spig Brodribb et al, 1994q; Neuvonen et al, 1993i). Serotonin syndrome is a rare but potentially fatal condition of s hyperstimulation characterized by hypertension, hyperthermia, myoclonus, and changes in mental status (Ste Consequently, coadministration of TCAs and MAOIs is contraindicated in most cases (Prod Info imipramine h tablet, 2003). If TCAs and MAOIs must be used concurrently, avoid large doses, use only oral TCAs, avoid in clomipramine, desipramine, and tranylcypromine, and monitor patients closely (Schuckit et al, 1971t; White &

3) Severity: contraindicated

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: Concomitant use of imipramine with an monoamine oxidase inhibitor (MAOI) is con imipramine is replacing treatment with phenelzine, a minimum of 2 weeks should elapse after phenelzine is d therapy with imipramine begins (Prod Info imipramine hydrochloride oral tablet, 2003). The manufacturer of p

recommends that at least 10 days should elapse before imipramine therapy is replaced by phenelzine (Prod
Tablets, USP, 2005).

7) Probable Mechanism: altered catecholamine uptake and metabolism

8) Literature Reports

a) Concomitant administration of monoamine oxidase inhibitors (MAOIs) with tricyclic antidepressants (T considered an absolute contraindication in the past and still is listed as such by the manufacturers (Prod hydrochloride oral tablet, 2003). Reports of excitation, hyperpyrexia, convulsions, and possible death hav to the combination (Lockett & Milner, 1965j; Brachfeld et al, 1963f; Winston, 1971j; Schuckit et al, 1971s Spiker & Pugh, 1976j). The mechanism may relate to the combined inhibition of catecholamine reuptake nervous system and inhibition of catecholamine metabolism (Sjoqvist, 1965j).

b) Administration of a TCA after MAOI therapy may result in the development of serotonin syndrome. In crossover study examining the effects of clorgyline and clomipramine for the treatment of obsessive-com two subjects developed severe reactions characteristic of serotonin syndrome. During the study, patients clorgyline therapy, followed by a washout period of approximately four weeks and subsequent clomipram taking the first 100 mg dose of clomipramine, one patient developed coarse myoclonic jerking in both leg diaphoresis, and arrhythmia. Another patient developed a similar reaction after the first dose, with upper symptoms, myoclonic movements, and cardiac irritability. Both patient's symptoms resolved several hou patients were later treated successfully with clomipramine without adverse effects (Insel et al, 1982q).

c) A drug interaction was reported in a 76-year old woman who had been taking clomipramine 50 mg da months was switched to moclobemide 300 mg daily. The patient experienced somnolence, confusion, ar progressed to further mental impairment, muscle stiffness, myoclonus, and convulsive attacks. The patie were described as fulfilling the diagnostic criteria for serotonin syndrome and were resolved a few days l discontinuing all antidepressant medications (Spigset et al, 1993r).

d) A 39-year old woman with bipolar disorder developed serotonin syndrome after imipramine was adde The patient was taking moclobemide 300 mg twice daily when imipramine was started at 50 mg daily, fol dosage increases of imipramine to 200 mg and a reduction of moclobemide dosage to 150 mg twice dail the increase in imipramine to 200 mg per day, the patient developed symptoms of serotonin syndrome, i shivering, confusion, fever, and spasms in the extremities. The patient was treated with chlorpromazine a resolved over the next few days without further complications (Brodribb et al, 1994p).

e) Three patients with bipolar disorder developed manic symptoms while undergoing concurrent therapy isocarboxazid and amitriptyline. In all three cases the patients had been given MAOIs and TCAs alone w complications. It was only when the drugs were used in combination that symptoms of mania emerged, s synergistic effect (de la Fuente et al, 1986e).

f) In one case, clomipramine 10 mg twice daily was added to a stable regimen of tranylcypromine in a pl 34-year old man. After taking several doses, the patient developed symptoms of nausea and profuse sw pyrexia, dyspnea, and agitation. The hyperpyrexical state led to disseminated intravascular coagulation a (Tackley & Tregaskis, 1987i).

g) There is evidence that MAOIs and TCAs can be given concomitantly in patients previously unrespons TCA alone. A few precautions must be followed including: a) avoidance of large doses (no more than 15 or its equivalent, 45 mg phenelzine, or 60 mg isocarboxazid) b) oral administration c) avoidance of clomi imipramine, desipramine, and tranylcypromine in any combination, and d) close monitoring of patients (K Winston, 1971j; Schuckit et al, 1971s; White & Simpson, 1984n; Rom & Benner, 1972e). The combinatio in one of two ways. Most frequently, the recommendation is to stop all previous antidepressants (five to t and 14 days for MAOIs); the combination is then simultaneously started (Perry et al, 1991i). Alternatively previously receiving a TCA, small doses of the MAOI may be slowly added (Schoonover, 1983). Some s that the combination of amitriptyline and isocarboxazid is preferred (Perry et al, 1991i). Numerous studie refractory depression or phobic anxiety states have successfully used the combination of MAOIs and TC 1977j; Schuckit et al, 1971s; Ashcroft, 1975i).

3.5.1.DX Phenindione

1) Interaction Effect: increased risk of bleeding

2) Summary: Tricyclic antidepressants (TCAs) may increase the half-life and bioavailability of oral anticoagul 1970g; Williams et al, 1976g). Considerable interindividual differences may be found (Pond et al, 1975g).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: In patients receiving tricyclic antidepressants and oral anticoagulant therapy, the pr ratio or INR (international normalized ratio) should be closely monitored with the addition and withdrawal of th and should be periodically reassessed during concurrent therapy. Achieving a stable dosage regimen which p desired level of anticoagulation may be difficult in patients on this combination, and frequent adjustments of t dose may be required.

7) Probable Mechanism: decreased phenindione metabolism; increased phenindione absorption

8) Literature Reports

a) In a study of healthy volunteers, the concurrent use of nortriptyline or amitriptyline resulted in an incre levels and an increase in the plasma half-life of dicumarol, although the effect was not consistent in all su 1975f). This effect was not observed with warfarin.

b) A single oral dose of bishydroxycoumarin after 8 days of nortriptyline resulted in a significantly prolon decreased volume of distribution of the coumarin anticoagulant in 6 healthy volunteers (Vesell et al, 197(

mechanism of action was suggested to be reduced bishydroxycoumarin metabolism and/or altered coum
c) Drug dosing was studied in 16 patients on long-term anticoagulant therapy who used concurrent TCA
1976f). TCAs affected the stability of anticoagulant control leading to frequent changes in the doses of a
Inhibition of coumarin metabolism was the postulated mechanism.

3.5.1.DY Phenmetrazine

1) Interaction Effect: hypertension, other cardiac effects, and CNS stimulation

2) Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been reporte
enhanced amphetamine effects from the release of norepinephrine (Beaumont, 1973d; Raisfeld, 1972). A sim
also occur with all drugs that have amphetamine-like effects. Acute elevations in blood pressure have been n
(Flemenbaum, 1971a). Some amphetamine-like drugs may inhibit the metabolism of TCAs, although most co
not been studied. When amphetamine analogs are being used to treat obesity, it should be noted that TCAs f
moderate weight gain (Russ & Ackerman, 1988). False positive urine tests for amphetamines have been repo
therapy with some TCAs (Merigian & Browning, 1993). Caution is advised when concurrent administration of
agents and TCAs is warranted. The patient should be closely monitored for increased cardiovascular effects
dysrhythmias).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other sympatho
could lead to hypertension, increased cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) o
Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral t
Flemenbaum, 1972). Use caution if such therapy is warranted. Monitor the patient closely for hypertension ar

7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission

8) Literature Reports

a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agen
coadministration of d-amphetamine with TCAs such as desipramine or protriptyline results in sustained i
amphetamine concentration in the brain (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info DEXE
sustained-release oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006).

b) Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism o
antidepressants, such as imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transde
2006).

c) Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases i
such that the hypotensive effects induced by TCAs may lead to blood pressures as high as 170/120 mm
of combined therapy. Discontinuation of the methylphenidate usually results in the blood pressure return
normotensive levels; reinstitution of the methylphenidate resulted in further blood pressure elevation (Fle
Flemenbaum, 1972).

d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine g
four weeks, were given fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transi
clinical improvement. However, fenfluramine more than doubled steady-state plasma levels of desipramin
1990).

e) There have been claims based on uncontrolled studies that a better antidepressant response may oc
therapy (Garrettson et al, 1969). However, a systemic review of stimulants in the treatment of depressio
although uncontrolled studies were generally positive, the ten placebo-controlled studies of stimulant dru
depression, with one exception, indicated little advantage of drug over placebo and did not appear to be
conventional antidepressants in primary depression (Satel & Nelson, 1989).

3.5.1.DZ Phenobarbital

1) Interaction Effect: possible decreased tricyclic antidepressant serum concentrations and possible additive

2) Summary: Concomitant barbiturate and tricyclic antidepressant (TCA) therapy may result in increased me
TCA. There have been scattered reports of individuals with decreased serum levels of TCAs in the presence
(Moody et al, 1977; Silverman & Braithwaite, 1972; Burrows & Davies, 1971). In addition, TCAs can worsen s
reducing the seizure threshold (Brodie, 1992). These drugs also have additive CNS and respiratory depressa

3) Severity: minor

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Monitor for efficacy of antidepressant effect. Increases in tricyclic antidepressant do
required. Additionally, monitor for toxicity when either drug is added to or withdrawn from therapy. Serum con
be of value in determining appropriate dosage.

7) Probable Mechanism: increased tricyclic antidepressant metabolism

8) Literature Reports

a) The pharmacokinetics of a single oral dose of desipramine (100 mg) were studied in eight epileptic pa
treated with phenobarbital and in eight drug-free healthy controls (Spina et al, 1996). All subjects were e
metabolizers with respect to the genetically determined CYP2D6-related metabolic polymorphism. Comp
epileptic patients exhibited lower peak plasma desipramine concentrations (74 nmol/L vs. 107 nmol/L), s
area under the concentration-time curve values (1943 nmol/L/h vs. 3234 nmol/L/h), and shorter desipram
half-lives (15.1 h vs. 20.6 h). All barbiturates are believed to have similar effects leading to induction of h
and the 2D6 isozyme is believed to be important in the metabolism of most or all TCAs. Thus, similar eff

expected with any combination of TCA and barbiturate.

3.5.1.EA Phenprocoumon

1) Interaction Effect: increased risk of bleeding

2) Summary: Tricyclic antidepressants (TCAs) may increase the half-life and bioavailability of oral anticoagul 1970i; Williams et al, 1976i). Considerable interindividual differences may be found (Pond et al, 1975i).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: In patients receiving tricyclic antidepressants and oral anticoagulant therapy, the pr ratio or INR (international normalized ratio) should be closely monitored with the addition and withdrawal of th and should be periodically reassessed during concurrent therapy. Achieving a stable drug regimen which pro level of anticoagulation may be difficult in patients on this combination, and frequent adjustments of the antic be required.

7) Probable Mechanism: decreased phenprocoumon metabolism; increased phenprocoumon absorption

8) Literature Reports

a) In a study of healthy volunteers, the concurrent use of nortriptyline or amitriptyline resulted in an incre levels and an increase in the plasma half-life of dicumarol, although the effect was not consistent in all su 1975h). This effect was not observed with warfarin.

b) A single oral dose of bishydroxycoumarin after 8 days of nortriptyline resulted in a significantly prolon decreased volume of distribution of the coumarin anticoagulant in 6 healthy volunteers (Vesell et al, 197(mechanism of action was suggested to be reduced bishydroxycoumarin metabolism and/or altered coum

c) Drug dosing was studied in 16 patients on long-term anticoagulant therapy who used concurrent TCA 1976h). TCAs affected the stability of anticoagulant control leading to frequent changes in the doses of a Inhibition of coumarin metabolism was the postulated mechanism.

3.5.1.EB Phentermine

1) Interaction Effect: hypertension, other cardiac effects, and CNS stimulation

2) Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been reporte enhanced amphetamine effects from the release of norepinephrine (Beaumont, 1973d; Raisfeld, 1972). A sim also occur with all drugs that have amphetamine-like effects. Acute elevations in blood pressure have been n (Flemenbaum, 1971a). Some amphetamine-like drugs may inhibit the metabolism of TCAs, although most co not been studied. When amphetamine analogs are being used to treat obesity, it should be noted that TCAs f moderate weight gain (Russ & Ackerman, 1988). False positive urine tests for amphetamines have been repo therapy with some TCAs (Merigian & Browning, 1993). Caution is advised when concurrent administration of agents and TCAs is warranted. The patient should be closely monitored for increased cardiovascular effects dysrhythmias).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other sympatho could lead to hypertension, increased cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) o Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral t Flemenbaum, 1972). Use caution if such therapy is warranted. Monitor the patient closely for hypertension ar

7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission

8) Literature Reports

a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agen coadministration of d-amphetamine with TCAs such as desipramine or protriptyline results in sustained in amphetamine concentration in the brain (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info DEXE sustained-release oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006).

b) Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism o antidepressants, such as imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transde 2006).

c) Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases in such that the hypotensive effects induced by TCAs may lead to blood pressures as high as 170/120 mm of combined therapy. Discontinuation of the methylphenidate usually results in the blood pressure return normotensive levels; reinstitution of the methylphenidate resulted in further blood pressure elevation (Fle Flemenbaum, 1972).

d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine g four weeks, were given fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transie clinical improvement. However, fenfluramine more than doubled steady-state plasma levels of desipramin 1990).

e) There have been claims based on uncontrolled studies that a better antidepressant response may oc therapy (Garrettson et al, 1969). However, a systemic review of stimulants in the treatment of depressior although uncontrolled studies were generally positive, the ten placebo-controlled studies of stimulant dru depression, with one exception, indicated little advantage of drug over placebo and did not appear to be conventional antidepressants in primary depression (Satel & Nelson, 1989).

3.5.1.EC Phenylephrine

1) Interaction Effect: hypertension, cardiac arrhythmias, and tachycardia

2) Summary: Clinical trials have demonstrated a 2- to 8-fold increase in the effects of intravenous infusions c drugs to volunteers on tricyclic antidepressants. Arrhythmias and other severe adverse effects have also bee 1980; Avery, 1973a; Boakes et al, 1973a; Boakes, 1973; Mitchell et al, 1970; Stone et al, 1964a). Local use (anesthesia) of epinephrine in concentrations of 1:100,000 or less is less likely to precipitate clinically significa changes (Steinberg & Block, 1971).

3) Severity: major

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: The vasoconstriction and other alpha-adrenergic effects of sympathomimetic drugs enhanced in the presence of tricyclic antidepressants (TCAs). Concomitant use should be avoided. If these d together, careful monitoring and a dose reduction of the sympathomimetic is required. Patients should be inst their doctor or dentist that they are taking a tricyclic antidepressant prior to any surgery or procedure.

7) Probable Mechanism: inhibition of norepinephrine reuptake

8) Literature Reports

a) Four healthy volunteers received intravenous infusions of various sympathomimetic amines (epineph norepinephrine, phenylephrine, and isoproterenol) before and after imipramine (25 mg three times daily f showed an increased pressor response to epinephrine (2- to 4-fold), norepinephrine (4- to 8-fold), and ph 3-fold) after imipramine, but no difference was observed in the response to isoproterenol. Thus, the incre response appeared to occur only for alpha adrenergic effects. All four subjects demonstrated changes in with epinephrine and imipramine consisting of sinus arrhythmia in three subjects and multiple ectopic be rhythm in the fourth subject (Boakes et al, 1973).

b) A review of spontaneous reports of adverse reactions to vasoconstrictors in local anesthetics found th receiving a local anesthetic with norepinephrine (1:25,000) had severe reactions (severe headaches, che subarachnoid hemorrhage). The drug history was incomplete, but at least three had been taking a tricycl at the time (Anon, 1972).

3.5.1.ED Phenytoin

1) Interaction Effect: an increased risk of phenytoin toxicity (ataxia, hyperreflexia, nystagmus, tremors)

2) Summary: A few case reports have indicated that imipramine inhibits phenytoin metabolism resulting in in phenytoin concentration (Petti & Campbell, 1975a; Perucca & Richens, 1977a). Tricyclic antidepressants (TC seizure threshold in epileptic patients stabilized on anticonvulsants. Theoretically, because phenytoin is an en metabolism of antidepressants may be increased resulting in reduced TCA serum levels.

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Consider phenytoin serum levels if a tricyclic antidepressant is added to therapy or begins to exhibit signs of toxicity; lower doses of phenytoin may be required. If phenytoin is added to tricyclic therapy, monitor for clinical efficacy of the tricyclic agent.

7) Probable Mechanism: inhibition of phenytoin metabolism

3.5.1.EE Pimozide

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Although citing no data, the manufacturer of pimozide states that concomitant use with other dr the QT interval is contraindicated (Prod Info Orap(R), 1999a). Tricyclic antidepressants (TCAs) at therapeutic QT prolongation (Prod Info Norpramin(R), 2000; Marshall & Forker, 1982ad).

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Because of the potential to prolong the QT interval, concurrent administration of a tr antidepressant and pimozide is contraindicated.

7) Probable Mechanism: additive effects on QT interval

8) Literature Reports

a) Electrocardiogram (ECG) changes seen during clinical trials of pimozide in Tourette's syndrome and s patients include prolongation of the QT interval, flattening, notching, and inversion of the T wave, and the waves. Sudden, unexpected deaths have occurred at doses greater than 20 milligrams/day (Prod Info O 1999).

3.5.1.EF Pirmenol

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Class Ia antiarrhythmics and tricyclic antidepressants have been shown to prolong the QTc inte recommended therapeutic dose. Even though no formal drug interaction studies have been done, the coadm Ia antiarrhythmics and other drugs known to prolong the QTc interval, including tricyclic antidepressants, is n (Prod Info Elavil(R), 1999g; Prod Info Quinaglute(R), 1999; Marshall & Forker, 1982n).

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: The concurrent administration of a Class IA antiarrhythmic agent and a tricyclic anti
recommended.
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) Quinidine is an inhibitor of the cytochrome P450 isoenzyme responsible for the 2-hydroxylation of imi
desipramine (Brosen & Gram, 1989). Inhibition of this enzyme system can result in a 35% decrease in im
clearance and 85% decrease in desipramine clearance. Demethylation of imipramine by the cytochrome
unaffected by this interaction. Until more information is available all patients having quinidine added to di
containing imipramine or desipramine should be monitored for increased antidepressant serum concentr
potential toxicity.
b) An increased incidence in sudden death was observed in six out of 53 patients with cardiac disease r
amitriptyline, compared to 0 out of 53 in the control group. It was recommended that amitriptyline be avo
with underlying cardiac disease except when depression was debilitating and no other drugs were helpfu
Coull et al, 1970).
c) In a placebo controlled study, imipramine 3.5 mg/kg was administered daily for seven patients with se
and titrated doses to obtain therapeutic plasma concentrations. Two patients displayed premature atrial c
and premature ventricular depolarizations before therapy. On patient had 33 premature atrial depolarizat
premature ventricular depolarizations (PVD) per hour, which decreased to 0.4 PAC and zero PVC per ho
The other patient had 12 PAD and 169 PVD per hour before treatment and 1.8 PAD and 28.1 PVD per h
The authors also cautioned that the incidence of cardiotoxicity may increase if tricyclic antidepressants a
with Type I antiarrhythmics. It was also recommended that quinidine and procainamide not be used to tre
of a tricyclic overdose. The similarities between these agents may exacerbate the cardiotoxicity (Kantor e

3.5.1.EG Prajmaline

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Class Ia antiarrhythmics and tricyclic antidepressants have been shown to prolong the QTc inte
recommended therapeutic dose. Even though no formal drug interaction studies have been done, the coadm
Ia antiarrhythmics and other drugs known to prolong the QTc interval, including tricyclic antidepressants, is n
(Prod Info Elavil(R), 1999g; Prod Info Quinaglute(R), 1999; Marshall & Forker, 1982n).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: The concurrent administration of a Class IA antiarrhythmic agent and a tricyclic anti
recommended.
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) Quinidine is an inhibitor of the cytochrome P450 isoenzyme responsible for the 2-hydroxylation of imi
desipramine (Brosen & Gram, 1989). Inhibition of this enzyme system can result in a 35% decrease in im
clearance and 85% decrease in desipramine clearance. Demethylation of imipramine by the cytochrome
unaffected by this interaction. Until more information is available all patients having quinidine added to di
containing imipramine or desipramine should be monitored for increased antidepressant serum concentr
potential toxicity.
b) An increased incidence in sudden death was observed in six out of 53 patients with cardiac disease r
amitriptyline, compared to 0 out of 53 in the control group. It was recommended that amitriptyline be avo
with underlying cardiac disease except when depression was debilitating and no other drugs were helpfu
Coull et al, 1970).
c) In a placebo controlled study, imipramine 3.5 mg/kg was administered daily for seven patients with se
and titrated doses to obtain therapeutic plasma concentrations. Two patients displayed premature atrial c
and premature ventricular depolarizations before therapy. On patient had 33 premature atrial depolarizat
premature ventricular depolarizations (PVD) per hour, which decreased to 0.4 PAC and zero PVC per ho
The other patient had 12 PAD and 169 PVD per hour before treatment and 1.8 PAD and 28.1 PVD per h
The authors also cautioned that the incidence of cardiotoxicity may increase if tricyclic antidepressants a
with Type I antiarrhythmics. It was also recommended that quinidine and procainamide not be used to tre
of a tricyclic overdose. The similarities between these agents may exacerbate the cardiotoxicity (Kantor e

3.5.1.EH Primidone

1) Interaction Effect: possible decreased tricyclic antidepressant serum concentrations and possible additive
2) Summary: Concomitant barbiturate and tricyclic antidepressant (TCA) therapy may result in increased me
TCA. There have been scattered reports of individuals with decreased serum levels of TCAs in the presence
(Moody et al, 1977; Silverman & Braithwaite, 1972; Burrows & Davies, 1971). In addition, TCAs can worsen s
reducing the seizure threshold (Brodie, 1992). These drugs also have additive CNS and respiratory depressa
3) Severity: minor
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor for efficacy of antidepressant effect. Increases in tricyclic antidepressant do
required. Additionally, monitor for toxicity when either drug is added to or withdrawn from therapy. Serum con
be of value in determining appropriate dosage.
7) Probable Mechanism: increased tricyclic antidepressant metabolism

8) Literature Reports

a) The pharmacokinetics of a single oral dose of desipramine (100 mg) were studied in eight epileptic pa treated with phenobarbital and in eight drug-free healthy controls (Spina et al, 1996). All subjects were ex metabolizers with respect to the genetically determined CYP2D6-related metabolic polymorphism. Comp epileptic patients exhibited lower peak plasma desipramine concentrations (74 nmol/L vs. 107 nmol/L), s area under the concentration-time curve values (1943 nmol/L/h vs. 3234 nmol/L/h), and shorter desipran half-lives (15.1 h vs. 20.6 h). All barbiturates are believed to have similar effects leading to induction of h and the 2D6 isozyme is believed to be important in the metabolism of most or all TCAs. Thus, similar effe expected with any combination of TCA and barbiturate.

3.5.1.EI Procainamide

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Class Ia antiarrhythmics and tricyclic antidepressants have been shown to prolong the QTc inte recommended therapeutic dose. Even though no formal drug interaction studies have been done, the coadm Ia antiarrhythmics and other drugs known to prolong the QTc interval, including tricyclic antidepressants, is n (Prod Info Elavil(R), 1999g; Prod Info Quinaglute(R), 1999; Marshall & Forker, 1982n).

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: The concurrent administration of a Class IA antiarrhythmic agent and a tricyclic anti recommended.

7) Probable Mechanism: additive cardiac effects

8) Literature Reports

a) Quinidine is an inhibitor of the cytochrome P450 isoenzyme responsible for the 2-hydroxylation of imi desipramine (Brosen & Gram, 1989). Inhibition of this enzyme system can result in a 35% decrease in im clearance and 85% decrease in desipramine clearance. Demethylation of imipramine by the cytochrome unaffected by this interaction. Until more information is available all patients having quinidine added to dr containing imipramine or desipramine should be monitored for increased antidepressant serum concentr potential toxicity.

b) An increased incidence in sudden death was observed in six out of 53 patients with cardiac disease r amitriptyline, compared to 0 out of 53 in the control group. It was recommended that amitriptyline be avo with underlying cardiac disease except when depression was debilitating and no other drugs were helpfu Coull et al, 1970).

c) In a placebo controlled study, imipramine 3.5 mg/kg was administered daily for seven patients with se and titrated doses to obtain therapeutic plasma concentrations. Two patients displayed premature atrial c and premature ventricular depolarizations before therapy. On patient had 33 premature atrial depolarizat premature ventricular depolarizations (PVD) per hour, which decreased to 0.4 PAC and zero PVC per ho The other patient had 12 PAD and 169 PVD per hour before treatment and 1.8 PAD and 28.1 PVD per h The authors also cautioned that the incidence of cardiotoxicity may increase if tricyclic antidepressants a with Type I antiarrhythmics. It was also recommended that quinidine and procainamide not be used to tre of a tricyclic overdose. The similarities between these agents may exacerbate the cardiotoxicity (Kantor e

3.5.1.EJ Procarbazine

1) Interaction Effect: neurotoxicity, seizures

2) Summary: Concomitant tricyclic antidepressant and more potent MAOI use has resulted in hyperpyrexia, c death. Procarbazine has relatively weak MAOI actions, so while the potential for drug interactions between tri antidepressants and procarbazine exists, clinical data are lacking at this time (Schuckit et al, 1971r; White & S Concurrent use is not recommended (Prod Info Matulane(R), 1997).

3) Severity: major

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: Concomitant use is not recommended and should probably be initiated only under c supervision, and then only if other antidepressant class agents have proven unsuccessful. With more potent I recommendations for concurrent use of TCAs have included avoiding large doses of the TCA, using only oral avoiding imipramine, clomipramine, and desipramine. Procarbazine therapy should not begin until seven day discontinuation of tricyclic antidepressants and 14 days following the discontinuation of other MAO inhibitors.

7) Probable Mechanism: altered catecholamine uptake and metabolism

8) Literature Reports

a) Procarbazine is primarily used as an antineoplastic agent, but was originally investigated as a monoa inhibitor (Gilman et al, 1985a). Animal studies have indicated that procarbazine is a monoamine oxidase (DeVita et al, 1965) but appears to be a relatively weak MAOI in man (Gilman et al, 1985a). Hypertensiv still result from concomitant administration of tricyclic antidepressants, sympathomimetics, and tyramine (Gilman et al, 1985a; Ponto et al, 1977i).

b) Concomitant administration of monoamine oxidase (MAO) inhibitors with tricyclic antidepressants has an absolute contraindication in the past and still is listed as such by the manufacturers. Reports of excita convulsions, and possible death have been attributed to the combination (Lockett & Milner, 1965i; Brach Winston, 1971i; Schuckit et al, 1971q; Sargent, 1965e; Spiker & Pugh, 1976i). Careful examination of su unusual circumstances in most cases such as parenteral administration of a tricyclic. The mechanism ma

combined inhibition of catecholamine reuptake into the central nervous system and inhibition of catechol (Sjoqvist, 1965i).

c) Procarbazine therapy should not begin until 7 days following discontinuation of tricyclic antidepressar following the discontinuation of other MAO inhibitors (AMA Department of Drugs, 1992; Gilman et al, 198

3.5.1.EK Prochlorperazine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Q and T wave distortions have been observed in patients taking phenothiazines (Prod Info Cor Prod Info Stelazine(R), 2002; Prod Info Thorazine(R), 2002). Other phenothiazines may have similar effects, are available. Tricyclic antidepressants (TCAs) at therapeutic doses can cause QT prolongation (Marshall & F Case reports have described increased plasma levels and adverse effects when phenothiazines and tricyclic were taken together, likely due to inhibition of their metabolism (Ghaemi & Kirkwood, 1998; Geller et al, 1985 Loga et al, 1981).

3) Severity: major

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: Concurrent administration of a phenothiazine and a tricyclic antidepressant is not re

7) Probable Mechanism: additive effect on QT interval

3.5.1.EL Propafenone

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Class I antiarrhythmics have been shown to prolong the QTc interval at the recommended ther Even though no formal drug interaction studies have been done, the coadministration of Class I antiarrhythmi known to prolong the QTc interval, including tricyclic antidepressants, is not recommended (Prod Info Tambo acetate, 1998; Larochelle et al, 1984; Scagliotti et al, 1982).

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of a Class I antiarrhythmic and a tricyclic antidepress recommended.

7) Probable Mechanism: additive effects on QT prolongation

8) Literature Reports

a) EKG effects reported in patients receiving therapeutic doses of tricyclic antidepressants include increa prolonged PR interval, intraventricular conduction delays, increased corrected QT interval (QTc) and flat (Marshall & Forker, 1982q).

b) A 68-year-old man suffering from agitated major depression was begun on a dose of desipramine 12 produced a subtherapeutic serum level of 442 nmol/L (therapeutic range = 500 to 1000 nmol/L). An increa mg daily produced excellent clinical response with no side effects. He developed atrial fibrillation and flut mg daily was added to his therapy, and desipramine was discontinued. His arrhythmia was suppressed v propafenone 150 mg twice daily and 300 mg at bedtime. Desipramine 150 mg daily was again begun, at experienced dry mouth, sedation, and shakiness; the desipramine serum level was measured at 2092 nr desipramine was discontinued for five days, the side effects ceased, and desipramine therapy was resur The desipramine serum level was measured at 1130 nmol/L (Katz, 1991).

3.5.1.EM Propranolol

1) Interaction Effect: increased imipramine concentrations

2) Summary: One report of 2 cases of children receiving imipramine and propranolol was suggestive of inter metabolism of imipramine with this combination (Gillette & Tannery, 1994). In one case, imipramine levels ros when the propranolol dose was increased following admission to the hospital. No toxicity was noted. The pos compliance prior to admission might have played a role was not considered by the authors, and no rechalleng The other case involved several changes in dose of both drugs. Prospective study is needed to determine the interaction.

3) Severity: minor

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Monitor for an enhanced effect of imipramine. A dosage adjustment may be require

7) Probable Mechanism: decreased imipramine metabolism

3.5.1.EN Propylhexedrine

1) Interaction Effect: hypertension, other cardiac effects, and CNS stimulation

2) Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been reported enhanced amphetamine effects from the release of norepinephrine (Beaumont, 1973d; Raisfeld, 1972). A sim also occur with all drugs that have amphetamine-like effects. Acute elevations in blood pressure have been n (Flemenbaum, 1971a). Some amphetamine-like drugs may inhibit the metabolism of TCAs, although most co not been studied. When amphetamine analogs are being used to treat obesity, it should be noted that TCAs f moderate weight gain (Russ & Ackerman, 1988). False positive urine tests for amphetamines have been repo therapy with some TCAs (Merigian & Browning, 1993). Caution is advised when concurrent administration of agents and TCAs is warranted. The patient should be closely monitored for increased cardiovascular effects

dysrhythmias).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other sympatho could lead to hypertension, increased cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) o Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral t Flemenbaum, 1972). Use caution if such therapy is warranted. Monitor the patient closely for hypertension ar
7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission
8) Literature Reports
a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agen coadministration of d-amphetamine with TCAs such as desipramine or protriptyline results in sustained i amphetamine concentration in the brain (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info DEXE sustained-release oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006).
b) Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism c antidepressants, such as imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transde 2006).
c) Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases i such that the hypotensive effects induced by TCAs may lead to blood pressures as high as 170/120 mm of combined therapy. Discontinuation of the methylphenidate usually results in the blood pressure return normotensive levels; reinstitution of the methylphenidate resulted in further blood pressure elevation (Fle Flemenbaum, 1972).
d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine g four weeks, were given fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transi clinical improvement. However, fenfluramine more than doubled steady-state plasma levels of desiprami 1990).
e) There have been claims based on uncontrolled studies that a better antidepressant response may oc therapy (Garrettson et al, 1969). However, a systemic review of stimulants in the treatment of depressior although uncontrolled studies were generally positive, the ten placebo-controlled studies of stimulant dru depression, with one exception, indicated little advantage of drug over placebo and did not appear to be conventional antidepressants in primary depression (Satel & Nelson, 1989).

3.5.1.EO Quetiapine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod 1999), haloperidol (O'Brien et al, 1999), risperidone (Duenas-Laita et al, 1999), sertindole (Agelink et al, 2001 (Owens, 2001b), sultopride (Lande et al, 1992), and zotepine (Sweetman, 2003). Even though no formal drug studies have been done, the coadministration of a tricyclic antidepressant and an antipsychotic is not recomm Pamelor(R), 2001; Marshall & Forker, 1982t).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of a tricyclic antidepressant and an antipsychotic is n
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) Electrocardiographic changes that have occurred during clinical trials with pimozide have included pr corrected QT interval, flattening, notching, and inversion of the T wave and the appearance of U waves. studies, sudden, unexpected deaths have occurred while patients were receiving pimozide doses of 1 m proposed mechanism for these deaths is prolongation of the QT interval predisposing patients to ventricu (Prod Info Orap(R), 1999).

3.5.1.EP Quinestrol

1) Interaction Effect: attenuation of antidepressant effectiveness; tricyclic toxicity (drowsiness, hypotension, a
2) Summary: In isolated cases, the pharmacologic effects of tricyclic antidepressants may be increased or de estrogens (Somani & Khurana, 1973m), with paradoxical loss of antidepressant effect yet tricyclic toxicity bei simultaneously (Prange, 1972m). The effects of the interaction appear to be estrogen dose-related (Khurana, be of clinical importance primarily in patients previously stabilized on tricyclic therapy who are being started o (Krishnan et al, 1984m).
3) Severity: minor
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: If signs or symptoms of altered tricyclic response are noted, dose adjustment down estrogen or tricyclic component may be successful in restoring effectiveness or resolving toxicity. However, d may be required.
7) Probable Mechanism: possible estrogen-enhanced hepatic metabolism of the tricyclic
8) Literature Reports
a) Some studies evaluated the qualitative effects of concomitant administration of estrogen and TCAs. I depressed female prisoners were randomly assigned to 4 treatment groups. Ten patients received place

imipramine (150 milligrams/day) and placebo, 5 patients received imipramine (150 milligrams/day) and e micrograms/day), while 5 patients received imipramine (150 milligrams/day) and ethinyl estradiol (25 mic 10 patients that received placebo did not improve over the 6 weeks of the study. The 10 patients taking e imipramine demonstrated a significantly greater improvement in symptoms than did the 10 patients takin alone. However, after 2 weeks, the 5 patients that received imipramine and high-dose estrogen had not i as the patients receiving imipramine and low-dose estrogen. The only side-effect reported was drowsine affected the patients taking imipramine. Following the discontinuation of ethinyl estradiol, a time period o required for the high-dose estrogen group to do as well as the low-dose group. This effect was attributed residual estrogen in the high-dose group. In another group, 5 women received imipramine 150 milligrams estradiol 50 micrograms daily did not improve as much as 10 patients receiving only imipramine. Also, th combination had severe side-effects including lethargy, coarse tremor and systolic hypotension (Prange,

b) A case reported by (Khurana, 1972l) demonstrated an interaction in a 32-year-old female taking conju 2.5 milligrams and imipramine 100 milligrams. The patient developed lethargy, tremors, and signs of dep After 2 years of therapy, the patient increased her estrogen dose to 5 milligrams and then 7.5 milligrams became nauseated, had constant headaches, and low normal blood pressure. All lab work was normal. U the estrogen, the side-effects abated. Some investigators have proposed that the side effects resulted fr effects secondary to estrogen inhibition of hepatic microsomal enzymes (Somani & Khurana, 1973l).

c) In a study women received clomipramine and oral contraceptives or clomipramine alone. At the begir there were 30 women taking the combination, but 12 subsequently dropped out. The 18 patients on the matched with 18 patients taking clomipramine alone. No significant difference was noted in the patients' clomipramine. It was proposed that there was no significant difference in side-effects between the groups groups were matched after patients had dropped out of the study. Had the patients been matched prior t different conclusions may have been drawn (Beaumont, 1973g).

d) The effect of oral contraceptives on clomipramine was studied in 42 women between the ages of 18 a three women took clomipramine 25 milligrams at bedtime while 19 took clomipramine 25 milligrams at be contraceptives. Over the 4-week study, 3 control patients (2 due to side-effects) and 5 in the experimenta side-effects) dropped out. Venous blood samples were drawn at weekly intervals for measurement of se concentrations. No difference in serum concentrations was noted between the groups. However, this res due to the low dose of clomipramine given (Luscombe & John, 1980f).

e) The onset of akathisia was reported in 3 patients receiving conjugated estrogens and tricyclic antidep concurrently. A 24-year-old patient receiving clomipramine 120 milligrams/day for anorexia nervosa and estrogens 1.25milligrams/day for amenorrhea developed restless legs and a constant desire to move co Estrogen was discontinued and benztropine 2 milligrams was administered, resulting in marked reductio within 48 hours. Akathisia and disorientation developed in a 55-year-old patient on conjugated estrogens milligrams/day who was prescribed amitriptyline 50 milligrams/day for depression. Within hours of amitrip was confused, restless, and possessed an inner desire to move continuously. Symptoms disappeared a amitriptyline. Positive rechallenge at one week with doxepin 100 milligrams, with resolution following disc doxepin. A third case of akathisia was reported in a 35-year-old patient who received conjugated estroge milligrams/day and amitriptyline 50 milligrams/day. Akathisia developed within a few hours after taking th amitriptyline and resolved within 48 hours following discontinuation of the antidepressant (Krishnan et al,

f) The absolute bioavailability of imipramine increased in women who received low-dose oral contracept micrograms or less of ethinyl estradiol) from 27 to 44% (p less than 0.05) as evident by an increase in th plasma concentration time curve (Abernethy et al, 1984g).

g) Estrogens may inhibit the oxidation of TCAs by affecting hepatic microsomal enzymes (John et al, 19 are metabolized via oxidation and conjugation pathways. Inhibition of the oxidation of TCAs could result and toxicity due to decreased clearance. Estrogens are suspected of possessing other effects on the cer system resulting in an antidepressant effect (Oppenheim, 1983f).

3.5.1.EQ Quinidine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Class Ia antiarrhythmics and tricyclic antidepressants have been shown to prolong the QTc inte recommended therapeutic dose. Even though no formal drug interaction studies have been done, the coadm Ia antiarrhythmics and other drugs known to prolong the QTc interval, including tricyclic antidepressants, is n (Prod Info Elavil(R), 1999g; Prod Info Quinaglute(R), 1999; Marshall & Forker, 1982n).

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: The concurrent administration of a Class IA antiarrhythmic agent and a tricyclic anti recommended.

7) Probable Mechanism: additive cardiac effects

8) Literature Reports

a) Quinidine is an inhibitor of the cytochrome P450 isoenzyme responsible for the 2-hydroxylation of imi desipramine (Brosen & Gram, 1989). Inhibition of this enzyme system can result in a 35% decrease in im clearance and 85% decrease in desipramine clearance. Demethylation of imipramine by the cytochrome unaffected by this interaction. Until more information is available all patients having quinidine added to d containing imipramine or desipramine should be monitored for increased antidepressant serum concentr potential toxicity.

b) An increased incidence in sudden death was observed in six out of 53 patients with cardiac disease r

amitriptyline, compared to 0 out of 53 in the control group. It was recommended that amitriptyline be avo with underlying cardiac disease except when depression was debilitating and no other drugs were helpfu Coull et al, 1970).

c) In a placebo controlled study, imipramine 3.5 mg/kg was administered daily for seven patients with se and titrated doses to obtain therapeutic plasma concentrations. Two patients displayed premature atrial and premature ventricular depolarizations before therapy. On patient had 33 premature atrial depolarizat premature ventricular depolarizations (PVD) per hour, which decreased to 0.4 PAC and zero PVC per ho The other patient had 12 PAD and 169 PVD per hour before treatment and 1.8 PAD and 28.1 PVD per h The authors also cautioned that the incidence of cardiotoxicity may increase if tricyclic antidepressants a with Type I antiarrhythmics. It was also recommended that quinidine and procainamide not be used to tre of a tricyclic overdose. The similarities between these agents may exacerbate the cardiotoxicity (Kantor e

3.5.1.ER Quinidine

1) Interaction Effect: imipramine toxicity (dry mouth, sedation) and an increased risk of cardiotoxicity (QT pro torsades de pointes, cardiac arrest)

2) Summary: Two studies have demonstrated that concomitant use of quinidine and imipramine or desipram increased serum concentrations of these antidepressants (Brosen & Gram, 1989b; Steiner et al, 1987). Due t cardiac effects, the incidence of cardiotoxicity (increased PR interval, QRS complex, and QTc interval) may a tricyclic antidepressants are administered with Type I antiarrhythmics (Kantor et al, 1978b; Bigger et al, 1977

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: The concurrent use of imipramine and quinidine is not recommended. Monitor for in antidepressant side effects with concurrent therapy; lower doses of the tricyclic agent may be required in som monitor the patient for signs and symptoms of additive cardiac effects, including any changes in the EKG.

7) Probable Mechanism: decreased imipramine metabolism, additive cardiac effects

8) Literature Reports

a) Quinidine is an inhibitor of the cytochrome P450 isoenzyme responsible for the 2-hydroxylation of imi desipramine. Inhibition of this enzyme system can result in a 35% decrease in imipramine clearance and desipramine clearance. Demethylation of imipramine by the cytochrome P450 system is unaffected by th more information is available all patients having quinidine added to a drug regimen containing imipramin should be monitored for increased antidepressant serum concentrations and potential toxicity (Brosen &

b) One study reported the cardiac effects of imipramine in two patients with depression and cardiac arrh week single-blind protocol of imipramine 3.5 mg/kg daily. The PR interval, QRS complex, and QTc interv significantly in both cases, producing EKG changes similar to those of Type I antiarrhythmics (quinidine, disopyramide). Each patient showed a decrease in both atrial and ventricular premature depolarizations The first patient decreased from 33.4 atrial and 30.1 ventricular premature depolarizations per hour to 0. ventricular premature depolarizations per hour. A second patient had 12.3 atrial and 169 ventricular pren depolarizations per hour prior to drug treatment which decreased to 1.8 atrial and 28.1 ventricular prema depolarizations per hour during imipramine therapy. The investigators concluded that the doses of antiar should be adjusted downward when used concurrently with tricyclic antidepressants due to an increased cardiotoxicity (Bigger et al, 1977).

c) A placebo controlled study administered imipramine 3.5 mg/kg daily to seven patients with severe de titrated doses to obtain therapeutic plasma concentrations. Two patients displayed premature atrial depo premature ventricular depolarizations before therapy. On patient had 33 premature atrial depolarizations premature ventricular depolarizations (PVD) per hour, which decreased to 0.4 PAC and zero PVC per ho The other patient had 12 PAD and 169 PVD per hour before treatment and 1.8 PAD and 28.1 PVD per h The authors also cautioned that the incidence of cardiotoxicity may increase if tricyclic antidepressants a with Type I antiarrhythmics. It was also recommended that quinidine and procainamide not be used to tre of a tricyclic overdose. The similarities between these agents may exacerbate the cardiotoxicity (Kantor e

3.5.1.ES Rasagiline

1) Interaction Effect: severe CNS toxicity

2) Summary: Concomitant use of rasagiline and tricyclic antidepressants should be avoided. Concurrent adm overlapping therapy with tricyclic antidepressants and non-selective MAOIs has been reported to cause serio fatal, reactions; the mechanisms of these reactions are not fully understood. Signs and symptoms include sev (behavioral and mental status changes, diaphoresis, muscular rigidity, hypertension, and syncope) associate hyperpyrexia and death. Data from clinical studies, where rasagiline-treated patients (n=115) were concomita tricyclic antidepressants, are insufficient to rule out an interaction. At least 14 days should elapse after discon before initiating therapy with a tricyclic antidepressant (Prod Info AZILECT(R) oral tablets, 2006).

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concurrent use of rasagiline and a tricyclic antidepressant is not recommended. Wa after discontinuing rasagiline before initiating therapy with a tricyclic antidepressant (Prod Info AZILECT(R) o

7) Probable Mechanism: unknown

3.5.1.ET Risperidone

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod I 1999), haloperidol (O'Brien et al, 1999), risperidone (Duenas-Laita et al, 1999), sertindole (Agelink et al, 2001 (Owens, 2001b), sultopride (Lande et al, 1992), and zotepine (Sweetman, 2003). Even though no formal drug studies have been done, the coadministration of a tricyclic antidepressant and an antipsychotic is not recomm Pamelor(R), 2001; Marshall & Forker, 1982t).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of a tricyclic antidepressant and an antipsychotic is n
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) Electrocardiographic changes that have occurred during clinical trials with pimozide have included pr corrected QT interval, flattening, notching, and inversion of the T wave and the appearance of U waves. studies, sudden, unexpected deaths have occurred while patients were receiving pimozide doses of 1 m proposed mechanism for these deaths is prolongation of the QT interval predisposing patients to ventricu (Prod Info Orap(R), 1999).

3.5.1.EU Ritonavir
1) Interaction Effect: increased imipramine serum concentrations and potential toxicity (anticholinergic effects confusion, cardiac arrhythmias)
2) Summary: Coadministered ritonavir may increase serum concentrations of imipramine, resulting in imipra Info Norvir(R), 1999). Therapeutic concentration monitoring is recommended for tricyclic antidepressants whe with ritonavir (Prod Info Invirase(R), 2003).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor patients for signs and symptoms of tricyclic antidepressant toxicity (anticho sedation, confusion, cardiac arrhythmias). Reduce doses of imipramine as required.
7) Probable Mechanism: decreased imipramine metabolism

3.5.1.EV Ropivacaine
1) Interaction Effect: increased plasma levels of ropivacaine
2) Summary: Ropivacaine is metabolized in the liver by the cytochrome P4501A enzyme system to 3-hydrox major metabolite. Drugs which are metabolized by P4501A2 via competitive inhibition, such as imipramine, w interact with the metabolism of ropivacaine. This would result in decreased renal clearance and increased pla concentrations of ropivacaine (Prod Info Naropin(TM), 1996).
3) Severity: moderate
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Care must be taken to monitor the patient for signs of local anesthetic toxicity with t coadministration of ropivacaine and other drugs which are known to be metabolized by cytochrome P4501A2 inhibition, such as imipramine.
7) Probable Mechanism: inhibition of ropivacaine metabolism

3.5.1.EW S-Adenosylmethionine
1) Interaction Effect: an increased risk of serotonin syndrome (hypertension, hyperthermia, myoclonus, ment
2) Summary: A single case has been reported of serotonin syndrome likely resulting from the combination of adenosylmethionine (SAMe) and clomipramine (Iruela et al, 1993a). SAMe was shown to hasten the onset of response of imipramine in a clinical trial involving 40 patients, without serotonergic side effects (Berlanga et a is initiated with SAMe and a tricyclic antidepressant, the patient should be monitored closely for early signs of syndrome. Serotonin syndrome is a condition of serotonergic hyperstimulation and manifests as restlessness changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. If the syndrome is not recognized treated, death can result (Sternbach, 1991).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: S-adenosylmethionine (SAMe) used concomitantly with imipramine was found to de symptoms sooner than imipramine alone (Berlanga et al, 1992). One case has been reported of serotonin sy resulting from concomitant use of SAMe and clomipramine (Iruela et al, 1993). If SAMe and a tricyclic antidep together, use low doses of each and titrate upward slowly, while monitoring closely for early signs of serotoni as increasing anxiety, confusion, and disorientation.
7) Probable Mechanism: additive pharmacologic effects resulting in excessive serotonergic stimulation
8) Literature Reports
a) A 71 year-old female was hospitalized with anxiety, agitation, confusion, and symptoms of serotonin s been taking S-adenosylmethionine 100 milligrams (mg) intramuscularly daily and clomipramine 25 mg da which was then increased to 75 mg/day. Within 48-72 hours of the increased clomipramine dosage, she progressively anxious, agitated, and confused. On admission she was verbally unresponsive and stupor

130 beats/minute, respiratory rate 30 breaths/minute, temperature 40.5 degrees Celsius, diarrhea, myoc tremors, rigidity, hyperreflexia, shivering, diaphoresis, and dehydration. Temperature increased to 43 de during her hospital stay, with no documented infection. White blood cell count (WBC) was 13,040 mm3, dehydrogenase was 662 units/liter (U/L), creatine phosphokinase was 8920 U/L, serum potassium 2.7 m (mEq/L), creatinine 1.1 mg/100 milliliter (mL) (laboratory reference values were not provided). A cranial c tomography (CT) scan was normal. The patient was not taking neuroleptics. Serum benzodiazepine and antidepressant levels were normal. Symptoms resolved gradually with 4 days of hydration and supportiv interaction was proposed to be a result of synergistic activity of S-adenosylmethionine and clomipramine 1993).

3.5.1.EX Salmeterol

1) Interaction Effect: an increased risk of cardiovascular excitation

2) Summary: Salmeterol should be administered with extreme caution to patients who are being treated with antidepressant, or within two weeks of the discontinuation of a tricyclic antidepressant (Prod Info SEREVENT inhalation powder, 2006). Clinically significant changes in systolic and diastolic blood pressure, pulse rate, ar electrocardiograms have been seen with the use of salmeterol, and these changes may be exacerbated by th antidepressant.

3) Severity: moderate

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: Close observation for adverse cardiovascular effects is warranted when these ager administered concurrently or if salmeterol is given within two weeks of discontinuation of a tricyclic antidepres

7) Probable Mechanism: potentiation of vascular effects

3.5.1.EY Secobarbital

1) Interaction Effect: possible decreased tricyclic antidepressant serum concentrations and possible additive

2) Summary: Concomitant barbiturate and tricyclic antidepressant (TCA) therapy may result in increased me TCA. There have been scattered reports of individuals with decreased serum levels of TCAs in the presence (Moody et al, 1977; Silverman & Braithwaite, 1972; Burrows & Davies, 1971). In addition, TCAs can worsen s reducing the seizure threshold (Brodie, 1992). These drugs also have additive CNS and respiratory depressa

3) Severity: minor

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Monitor for efficacy of antidepressant effect. Increases in tricyclic antidepressant dc required. Additionally, monitor for toxicity when either drug is added to or withdrawn from therapy. Serum con be of value in determining appropriate dosage.

7) Probable Mechanism: increased tricyclic antidepressant metabolism

8) Literature Reports

a) The pharmacokinetics of a single oral dose of desipramine (100 mg) were studied in eight epileptic pa treated with phenobarbital and in eight drug-free healthy controls (Spina et al, 1996). All subjects were e metabolizers with respect to the genetically determined CYP2D6-related metabolic polymorphism. Comp epileptic patients exhibited lower peak plasma desipramine concentrations (74 nmol/L vs. 107 nmol/L), s area under the concentration-time curve values (1943 nmol/L/h vs. 3234 nmol/L/h), and shorter desipran half-lives (15.1 h vs. 20.6 h). All barbiturates are believed to have similar effects leading to induction of h and the 2D6 isozyme is believed to be important in the metabolism of most or all TCAs. Thus, similar eff expected with any combination of TCA and barbiturate.

3.5.1.EZ Selegiline

1) Interaction Effect: neurotoxicity, seizures, or serotonin syndrome (hypertension, hyperthermia, myoclonus changes)

2) Summary: Coadministration of imipramine and selegiline is contraindicated (Prod Info imipramine hydroch 2003; Prod Info EMSAM(R) transdermal patch, 2006). Concomitant tricyclic antidepressants (TCAs) and MA in hyperpyrexia, convulsions, and death. Concurrent use of MAOIs and TCAs has also been reported to resu termed serotonin syndrome (Insel et al, 1982i; Spigset et al, 1993j; Brodribb et al, 1994i; Neuvonen et al, 199 syndrome is a rare but potentially fatal condition of serotonergic hyperstimulation characterized by hypertensi myoclonus, and changes in mental status (Sternbach, 1991e). A minimum of 14 days should elapse after dis selegiline before initiating therapy with imipramine. A time period of 4 to 5 half-lives, approximately 1 week, s discontinuing imipramine prior to initiating therapy with selegiline (Prod Info EMSAM(R) transdermal patch, 2

3) Severity: contraindicated

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: Concomitant use of imipramine with selegiline is contraindicated. A minimum of 14 elapse after discontinuing selegiline before initiating therapy with imipramine. A time period of 4 to 5 half-lives week, should elapse after discontinuing imipramine prior to initiating therapy with selegiline.

7) Probable Mechanism: altered catecholamine uptake and metabolism

8) Literature Reports

a) Concomitant administration of monoamine oxidase inhibitors (MAOIs) with tricyclic antidepressants (T considered an absolute contraindication in the past and still is listed as such by the manufacturers. Repo

hyperpyrexia, convulsions, and possible death have been attributed to the combination (Prod Info imipra oral tablet, 2003; Lockett & Milner, 1965d; Brachfeld et al, 1963c; Winston, 1971d; Schuckit et al, 1971h; Spiker & Pugh, 1976d). The mechanism may relate to the combined inhibition of catecholamine reuptake nervous system and inhibition of catecholamine metabolism (Sjoqvist, 1965d).

b) Coadministration of selegiline with TCAs such as protriptyline or amitriptyline has resulted in severe C hyperpyrexia and death. Combination of selegiline with various other tricyclic antidepressants has cause effects, including hypertension, syncope, and muscular rigidity (Prod Info selegiline hydrochloride oral tal

c) Administration of a TCA after MAOI therapy may result in the development of serotonin syndrome. In crossover study examining the effects of clorgyline and clomipramine for the treatment of obsessive-com two subjects developed severe reactions characteristic of serotonin syndrome. During the study, patients clorgyline therapy, followed by a washout period of approximately four weeks and subsequent clomipram taking the first 100 mg dose of clomipramine, one patient developed coarse myoclonic jerking in both leg diaphoresis, and arrhythmia. Another patient developed a similar reaction after the first dose, with upper symptoms, myoclonic movements, and cardiac irritability. Both patient's symptoms resolved several hou patients were later treated successfully with clomipramine without adverse effects (Insel et al, 1982h).

d) A drug interaction occurred in a 76-year old woman who had been taking clomipramine 50 mg daily f prior to switching to moclobemide 300 mg daily. The patient experienced somnolence, confusion, and fe progressed to further mental impairment, muscle stiffness, myoclonus, and convulsive attacks. The patie were described as fulfilling the diagnostic criteria for serotonin syndrome and were resolved a few days l discontinuing all antidepressant medications (Spigset et al, 1993i).

e) A 39-year old woman with bipolar disorder developed serotonin syndrome after imipramine was adde The patient was taking moclobemide 300 mg twice daily when imipramine was started at 50 mg daily, fol dosage increases of imipramine to 200 mg and a reduction of moclobemide dosage to 150 mg twice dail the increase in imipramine to 200 mg per day, the patient developed symptoms of serotonin syndrome, i shivering, confusion, fever, and spasms in the extremities. The patient was treated with chlorpromazine a resolved over the next few days without further complications (Brodribb et al, 1994h).

f) Three patients with bipolar disorder developed manic symptoms while undergoing concurrent therapy and amitriptyline. In all three cases the patients had been given MAOIs and TCAs alone without complica when the drugs were used in combination that symptoms of mania emerged, suggesting a synergistic ef et al, 1986c).

g) In one case, clomipramine 10 mg twice daily was added to a stable regimen of tranylcypromine in a p 34-year old man. After taking several doses, the patient developed symptoms of nausea and profuse sw pyrexia, dyspnea, and agitation. The hyperpyrexical state led to disseminated intravascular coagulation a (Tackley & Tregaskis, 1987e).

h) There is evidence that MAOIs and TCAs can be given concomitantly in patients previously unrespons TCA alone. A few precautions must be followed including: a) avoidance of large doses (no more than 15 or its equivalent, 45 mg phenelzine, or 60 mg isocarboxazid) b) oral administration c) avoidance of clomi imipramine, desipramine, and tranylcypromine in any combination, and d) close monitoring of patients (K Winston, 1971d; Schuckit et al, 1971h; White & Simpson, 1984g; Rom & Benner, 1972c). The combinati in one of two ways. Most frequently, the recommendation is to stop all previous antidepressants (five to t and 14 days for MAOIs); the combination is then simultaneously started (Perry et al, 1991d). Alternativel previously receiving a TCA, small doses of the MAOI may be slowly added (Schoonover, 1983). Some s that the combination of amitriptyline and isocarboxazid is preferred (Perry et al, 1991d). Numerous studie refractory depression or phobic anxiety states have successfully used the combination of MAOIs and TC 1977d; Schuckit et al, 1971h; Ashcroft, 1975d).

3.5.1.FA Sematilide

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Cases of QTc prolongation and/or torsades de pointes have been reported with all Class III ant agents, including acecainide (Chow et al, 1984), amiodarone (Faggiano et al, 1996), azimilide (Corey et al, 1 (Gilman et al, 1985), ibutilide (Rodriguez et al, 2001), sematilide (Singh, 1996), dofetilide (Allen et al, 2002), a & Runge, 2001). Even though no formal drug interaction studies have been done, the coadministration of Cla antiarrhythmics and other drugs known to prolong the QTc interval, including tricyclic antidepressants, is not (Yamreudeewong et al, 2003a; Prod Info Corvert(R), 2000).

3) Severity: major

4) Onset: rapid

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of a Class III antiarrhythmic and a tricyclic antidepres recommended.

7) Probable Mechanism: additive QT prolongation

8) Literature Reports

a) EKG effects reported in patients receiving therapeutic doses of tricyclic antidepressants include incre prolonged PR interval, intraventricular conduction delays, increased corrected QT interval (QTc) and flat (Marshall & Forker, 1982ab).

b) Concurrent use of Class III antiarrhythmic agents, and other drugs that can prolong the QT interval, s antidepressants, is not recommended. Dofetilide should be stopped for at least 2 days before any interac initiated. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised (Yam 2003).

3.5.1.FB Sertindole

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod I 1999), haloperidol (O'Brien et al, 1999), risperidone (Duenas-Laita et al, 1999), sertindole (Agelink et al, 2001 (Owens, 2001b), sultopride (Lande et al, 1992), and zotepine (Sweetman, 2003). Even though no formal drug studies have been done, the coadministration of a tricyclic antidepressant and an antipsychotic is not recomm Pamelor(R), 2001; Marshall & Forker, 1982t).

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of a tricyclic antidepressant and an antipsychotic is n

7) Probable Mechanism: additive cardiac effects

8) Literature Reports

a) Electrocardiographic changes that have occurred during clinical trials with pimozide have included pr corrected QT interval, flattening, notching, and inversion of the T wave and the appearance of U waves. studies, sudden, unexpected deaths have occurred while patients were receiving pimozide doses of 1 m proposed mechanism for these deaths is prolongation of the QT interval predisposing patients to ventricu (Prod Info Orap(R), 1999).

3.5.1.FC Sertraline

1) Interaction Effect: modest elevations in imipramine serum levels or possible serotonin syndrome (hyperter hyperthermia, myoclonus, mental status changes)

2) Summary: There is limited evidence suggesting that sertraline may inhibit tricyclic antidepressant (TCA) m resulting in higher TCA serum concentrations. Sertraline inhibits cytochrome P450 2D6 enzyme activity and r plasma concentrations of coadministered drugs that are metabolized by this pathway, including the tricyclic a (Preskorn et al, 1994c; Lydiard et al, 1993; Prod Info Zoloft(R), 1999). Effects of the interaction may have littl impact, however. Increases in TCA serum levels associated with sertraline coadministration were modest cor found when fluoxetine (another selective serotonin reuptake inhibitor) was combined with desipramine (von M Monitor patients on imipramine-sertraline therapy for TCA toxicity (dry mouth, urinary retention, CNS depress doses may need to be reduced.

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: The combined use of tricyclic antidepressants (TCAs) and selective serotonin reupt (SSRIs) may result in the inhibition of the TCA metabolism. A few cases of serotonin syndrome have also be concurrent TCA and SSRI therapy. Caution should be observed when drugs in these two classes are used to

7) Probable Mechanism: inhibition of imipramine metabolism

8) Literature Reports

a) Desipramine pharmacokinetics was studied in 18 healthy male volunteers. Study subjects received o (50 mg daily) for 7 days followed by desipramine with sertraline (50 mg daily) for 21 days. When sertralin desipramine therapy, the mean maximum concentration of desipramine increased by 34% and the area concentration-time curve increased by 26%. Trough concentrations of desipramine were close to baselin sertraline was discontinued. The changes in desipramine concentrations were modest and the interactio clinically significant (Preskorn et al, 1994b).

3.5.1.FD Sotalol

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Cases of QTc prolongation and/or torsades de pointes have been reported with all Class III ant agents, including acecainide (Chow et al, 1984), amiodarone (Faggiano et al, 1996), azimilide (Corey et al, 1 (Gilman et al, 1985), ibutilide (Rodriguez et al, 2001), sematilide (Singh, 1996), dofetilide (Allen et al, 2002), a & Runge, 2001). Even though no formal drug interaction studies have been done, the coadministration of Cla antiarrhythmics and other drugs known to prolong the QTc interval, including tricyclic antidepressants, is not (Yamreudeewong et al, 2003a; Prod Info Corvert(R), 2000).

3) Severity: major

4) Onset: rapid

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of a Class III antiarrhythmic and a tricyclic antidepres recommended.

7) Probable Mechanism: additive QT prolongation

8) Literature Reports

a) EKG effects reported in patients receiving therapeutic doses of tricyclic antidepressants include incre prolonged PR interval, intraventricular conduction delays, increased corrected QT interval (QTc) and flat (Marshall & Forker, 1982ab).

b) Concurrent use of Class III antiarrhythmic agents, and other drugs that can prolong the QT interval, s antidepressants, is not recommended. Dofetilide should be stopped for at least 2 days before any interac initiated. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised (Yam 2003).

3.5.1.FE Sparfloxacin

1) Interaction Effect: prolongation of the QTc interval and/or torsades de pointes

2) Summary: Torsades de pointes has been reported in patients receiving sparfloxacin concomitantly with di amiodarone. The use of sparfloxacin is contraindicated with drugs which produce an increase in the QTc inte torsades de pointes, including tricyclic antidepressants. Sparfloxacin is also contraindicated in persons with k prolongation (Prod Info Zagam(R), 1998a).

3) Severity: contraindicated

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: Sparfloxacin is contraindicated in individuals with known QTc prolongation or in pat concurrently with drugs that are known to increase the QTc interval and/or cause torsades de pointes.

7) Probable Mechanism: additive effects on QTc prolongation

8) Literature Reports

a) In clinical trials involving 1489 patients with a baseline QTc measurement, the mean prolongation of t sparfloxacin steady-state was 10 msec (2.5%). Of these subjects, 0.7% had a QTc interval greater than steady-state. However, no arrhythmic effects were seen in any of the patients. The magnitude of the QT increase with repeated administration of sparfloxacin, and the QTc interval returns to baseline within 48 discontinuation of sparfloxacin (Prod Info Zagam(R), 1998).

b) A case of sparfloxacin-induced torsades de pointes is described (Dupont et al, 1996). A 47-year old v for suppurative otitis media and mastoiditis was treated with sparfloxacin due to an allergy to betalactam six of treatment she felt dizzy and lost consciousness. This was attributed to torsades de pointes on the was followed by cardiac arrest which required cardiopulmonary resuscitation. Her pre-treatment electroc QT and QTc intervals of 0.34 and 0.46 seconds, respectively. An electrocardiogram post-arrest revealed intervals of 0.35 and 0.60 seconds, respectively. A 24-hour continuous electrocardiography confirmed nu of torsades de pointes occurring after episodes of sino-auricular block. Sparfloxacin was discontinued ar returned to baseline within a week. Upon further testing, it was determined that the patient suffered from long QT syndrome. Due to the onset of symptoms with administration of sparfloxacin and the relief of sy discontinuation of the drug, it is highly probable that sparfloxacin contributed to the torsades de pointes.

3.5.1.FF Spiramycin

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Tricyclic antidepressants (TCAs) and spiramycin have been shown to prolong the QTc interval recommended therapeutic dose (Stramba-Badiale et al, 1997; Marshall & Forker, 1982c). Even though no for interaction studies have been done, the coadministration of tricyclic antidepressants and other drugs known t interval, such as spiramycin, is not recommended (Prod Info Elavil(R), 1999b).

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of spiramycin and tricyclic antidepressants is not rec

7) Probable Mechanism: additive effects on QT prolongation

3.5.1.FG St John's Wort

1) Interaction Effect: an increased risk of serotonin syndrome (hypertension, hyperthermia, myoclonus, ment

2) Summary: Theoretically, since St. John's Wort is thought to inhibit serotonin reuptake and may have mild oxidase inhibitory activity (Singer et al, 1999; Thiede & Walper, 1994), serotonin syndrome could result when taken along with a tricyclic antidepressant. This theoretical risk of serotonin syndrome is also based on case serotonin syndrome resulting from concomitant use of selective serotonin reuptake inhibitors with tricyclic ant (Alderman & Lee, 1996), as well as concomitant use of monoamine oxidase inhibitors with tricyclic antidepres al, 1994a; Spigset et al, 1993b; Tackley & Tregaskis, 1987a). Coadministration of amitriptyline and St. John's the area under the concentration-time curve of amitriptyline and its metabolite nortriptyline (Roots et al, 2000) antidepressants are similarly affected by St. John's Wort, the risk of serotonin syndrome may be reduced, yet the tricyclic antidepressant may also be reduced. To maintain maximal effectiveness of the tricyclic antidepre avoid any potential risk of serotonin syndrome, avoid concomitant use of St. John's Wort and tricyclic antidep

3) Severity: moderate

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: Avoid concomitant use of St. John's Wort with tricyclic antidepressants.

7) Probable Mechanism: additive pharmacologic effects resulting in excessive serotonergic stimulation

3.5.1.FH Sulfamethoxazole

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Tricyclic antidepressants (TCAs) and cotrimoxazole have been shown to prolong the QTc inter recommended therapeutic dose (Lopez et al, 1987; Marshall & Forker, 1982s). Even though no formal drug in have been done, the coadministration of tricyclic antidepressants and other drugs known to prolong the QTc cotrimoxazole, is not recommended (Prod Info Elavil(R), 1999j).

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable
6) Clinical Management: The concurrent administration of cotrimoxazole and tricyclic antidepressants is not r
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.FI Sultopride
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod I 1999), haloperidol (O'Brien et al, 1999), risperidone (Duenas-Laita et al, 1999), sertindole (Agelink et al, 2001 (Owens, 2001b), sultopride (Lande et al, 1992), and zotepine (Sweetman, 2003). Even though no formal drug studies have been done, the coadministration of a tricyclic antidepressant and an antipsychotic is not recomm Pamelor(R), 2001; Marshall & Forker, 1982t).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of a tricyclic antidepressant and an antipsychotic is n
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) Electrocardiographic changes that have occurred during clinical trials with pimozide have included pro corrected QT interval, flattening, notching, and inversion of the T wave and the appearance of U waves. studies, sudden, unexpected deaths have occurred while patients were receiving pimozide doses of 1 m proposed mechanism for these deaths is prolongation of the QT interval predisposing patients to ventricu (Prod Info Orap(R), 1999).

3.5.1.FJ Tapentadol
1) Interaction Effect: increased risk of serotonin syndrome (hypertension, hyperthermia, myoclonus, mental s
2) Summary: Concurrent use of tapentadol and a tricyclic antidepressant may result in serotonin syndrome, v threatening. Symptoms of serotonin syndrome may include restlessness, hallucinations, loss of coordination, rapid changes in blood pressure, increased body temperature, overreactive reflexes, nausea, vomiting, and d tapentadol immediate release oral tablets, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of tapentadol and a tricyclic antidepressant may result in a life-thr called serotonin syndrome. If these agents are used together, monitor the patient closely for symptoms of ser (restlessness, hyperthermia, hyperreflexia, incoordination), especially during treatment initiation and dose inc tapentadol immediate release oral tablets, 2008).
7) Probable Mechanism: additive serotonergic effect

3.5.1.FK Tedisamil
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Cases of QTc prolongation and/or torsades de pointes have been reported with all Class III ant agents, including acecainide (Chow et al, 1984), amiodarone (Faggiano et al, 1996), azimilide (Corey et al, 1 (Gilman et al, 1985), ibutilide (Rodriguez et al, 2001), sematilide (Singh, 1996), dofetilide (Allen et al, 2002), a & Runge, 2001). Even though no formal drug interaction studies have been done, the coadministration of Cla antiarrhythmics and other drugs known to prolong the QTc interval, including tricyclic antidepressants, is not r (Yamreudeewong et al, 2003a; Prod Info Corvert(R), 2000).
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of a Class III antiarrhythmic and a tricyclic antidepres recommended.
7) Probable Mechanism: additive QT prolongation
8) Literature Reports
a) EKG effects reported in patients receiving therapeutic doses of tricyclic antidepressants include incre prolonged PR interval, intraventricular conduction delays, increased corrected QT interval (QTc) and flat (Marshall & Forker, 1982ab).
b) Concurrent use of Class III antiarrhythmic agents, and other drugs that can prolong the QT interval, s antidepressants, is not recommended. Dofetilide should be stopped for at least 2 days before any interac initiated. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised (Yam 2003).

3.5.1.FL Telithromycin
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Telithromycin may prolong the QT interval in some patients (Owens, 2001d). Because tricyclic may also prolong the QT interval and increase the risk of arrhythmias, the concurrent administration of telithr tricyclic antidepressants is not recommended (Marshall & Forker, 1982af).
3) Severity: major
4) Onset: unspecified

5) Substantiation: theoretical
6) Clinical Management: Because of the potential for additive QT interval prolongation, the concurrent admin telithromycin and a tricyclic antidepressants is not recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.FM Terfenadine
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Tricyclic antidepressants (TCAs) have been shown to prolong the QTc interval at the recomme dose (Marshall & Forker, 1982ae). Even though no formal drug interaction studies have been done, the coad terfenadine and other drugs known to prolong the QTc interval, including tricyclic antidepressants, is contrain Elavil(R), 1999k; Anon, 1997).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of terfenadine with any drug that prolongs the QT int tricyclic antidepressants, is contraindicated.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.FN Thiopental
1) Interaction Effect: possible decreased tricyclic antidepressant serum concentrations and possible additive
2) Summary: Concomitant barbiturate and tricyclic antidepressant (TCA) therapy may result in increased me TCA. There have been scattered reports of individuals with decreased serum levels of TCAs in the presence (Moody et al, 1977; Silverman & Braithwaite, 1972; Burrows & Davies, 1971). In addition, TCAs can worsen s reducing the seizure threshold (Brodie, 1992). These drugs also have additive CNS and respiratory depressa
3) Severity: minor
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor for efficacy of antidepressant effect. Increases in tricyclic antidepressant dc required. Additionally, monitor for toxicity when either drug is added to or withdrawn from therapy. Serum con be of value in determining appropriate dosage.
7) Probable Mechanism: increased tricyclic antidepressant metabolism
8) Literature Reports
a) The pharmacokinetics of a single oral dose of desipramine (100 mg) were studied in eight epileptic pa treated with phenobarbital and in eight drug-free healthy controls (Spina et al, 1996). All subjects were e metabolizers with respect to the genetically determined CYP2D6-related metabolic polymorphism. Comp epileptic patients exhibited lower peak plasma desipramine concentrations (74 nmol/L vs. 107 nmol/L), s area under the concentration-time curve values (1943 nmol/L/h vs. 3234 nmol/L/h), and shorter desipran half-lives (15.1 h vs. 20.6 h). All barbiturates are believed to have similar effects leading to induction of h and the 2D6 isozyme is believed to be important in the metabolism of most or all TCAs. Thus, similar eff expected with any combination of TCA and barbiturate.

3.5.1.FO Thioridazine
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Although citing no data, the manufacturer of thioridazine states that concomitant use with other prolong the QT interval is contraindicated (Prod Info Mellaril(R), 2001). Tricyclic antidepressants (TCAs) at th can cause QT prolongation (Marshall & Forker, 1982k).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concurrent administration of a tricyclic antidepressant and thioridazine is contraindi
7) Probable Mechanism: additive effect on QT interval

3.5.1.FP Tibolone
1) Interaction Effect: attenuation of antidepressant effectiveness; tricyclic toxicity (drowsiness, hypotension, a
2) Summary: In isolated cases, the pharmacologic effects of tricyclic antidepressants may be increased or de estrogens (Somani & Khurana, 1973a), with paradoxical loss of antidepressant effect yet tricyclic toxicity beir simultaneously (Prange, 1972a). The effects of the interaction appear to be estrogen dose-related (Khurana, be of clinical importance primarily in patients previously stabilized on tricyclic therapy who are being started o (Krishnan et al, 1984a).
3) Severity: minor
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: If signs or symptoms of altered tricyclic response are noted, dose adjustment down estrogen or tricyclic component may be successful in restoring effectiveness or resolving toxicity. However, d may be required.
7) Probable Mechanism: possible estrogen-enhanced hepatic metabolism of the tricyclic
8) Literature Reports
a) Some studies evaluated the qualitative effects of concomitant administration of estrogen and TCAs. I

depressed female prisoners were randomly assigned to 4 treatment groups. Ten patients received place imipramine (150 milligrams/day) and placebo, 5 patients received imipramine (150 milligrams/day) and e micrograms/day), while 5 patients received imipramine (150 milligrams/day) and ethinyl estradiol (25 mic 10 patients that received placebo did not improve over the 6 weeks of the study. The 10 patients taking e imipramine demonstrated a significantly greater improvement in symptoms than did the 10 patients takin alone. However, after 2 weeks, the 5 patients that received imipramine and high-dose estrogen had not i as the patients receiving imipramine and low-dose estrogen. The only side-effect reported was drowsine affected the patients taking imipramine. Following the discontinuation of ethinyl estradiol, a time period o required for the high-dose estrogen group to do as well as the low-dose group. This effect was attributed residual estrogen in the high-dose group. In another group, 5 women received imipramine 150 milligrams estradiol 50 micrograms daily did not improve as much as 10 patients receiving only imipramine. Also, th combination had severe side-effects including lethargy, coarse tremor and systolic hypotension (Prange,

b) A case reported by (Khurana, 1972) demonstrated an interaction in a 32-year-old female taking conju 2.5 milligrams and imipramine 100 milligrams. The patient developed lethargy, tremors, and signs of dep After 2 years of therapy, the patient increased her estrogen dose to 5 milligrams and then 7.5 milligrams became nauseated, had constant headaches, and low normal blood pressure. All lab work was normal. U the estrogen, the side-effects abated. Some investigators have proposed that the side effects resulted fr effects secondary to estrogen inhibition of hepatic microsomal enzymes (Somani & Khurana, 1973).

c) In a study women received clomipramine and oral contraceptives or clomipramine alone. At the begin there were 30 women taking the combination, but 12 subsequently dropped out. The 18 patients on the matched with 18 patients taking clomipramine alone. No significant difference was noted in the patients' clomipramine. It was proposed that there was no significant difference in side-effects between the groups groups were matched after patients had dropped out of the study. Had the patients been matched prior t different conclusions may have been drawn (Beaumont, 1973).

d) The effect of oral contraceptives on clomipramine was studied in 42 women between the ages of 18 a three women took clomipramine 25 milligrams at bedtime while 19 took clomipramine 25 milligrams at be contraceptives. Over the 4-week study, 3 control patients (2 due to side-effects) and 5 in the experimenta side-effects) dropped out. Venous blood samples were drawn at weekly intervals for measurement of se concentrations. No difference in serum concentrations was noted between the groups. However, this res due to the low dose of clomipramine given (Luscombe & John, 1980).

e) The onset of akathisia was reported in 3 patients receiving conjugated estrogens and tricyclic antidep concurrently. A 24-year-old patient receiving clomipramine 120 milligrams/day for anorexia nervosa and estrogens 1.25 milligrams/day for amenorrhea developed restless legs and a constant desire to move co Estrogen was discontinued and benztropine 2 milligrams was administered, resulting in marked reductio within 48 hours. LI Akathisia and disorientation developed in a 55-year-old patient on conjugated estroge milligrams/day who was prescribed amitriptyline 50 milligrams/day for depression. Within hours of amitrip was confused, restless, and possessed an inner desire to move continuously. Symptoms disappeared a amitriptyline. Positive rechallenge at one week with doxepin 100 milligrams, with resolution following disc doxepin. A third case of akathisia was reported in a 35-year-old patient who received conjugated estroge milligrams/day and amitriptyline 50 milligrams/day. Akathisia developed within a few hours after taking th amitriptyline and resolved within 48 hours following discontinuation of the antidepressant (Krishnan et al,

f) The absolute bioavailability of imipramine increased in women who received low-dose oral contracept micrograms or less of ethinyl estradiol) from 27 to 44% (p less than 0.05) as evident by an increase in th plasma concentration time curve (Abernethy et al, 1984).

g) Estrogens may inhibit the oxidation of TCAs by affecting hepatic microsomal enzymes (John et al, 19 are metabolized via oxidation and conjugation pathways. Inhibition of the oxidation of TCAs could result and toxicity due to decreased clearance. Estrogens are suspected of possessing other effects on the cer system resulting in an antidepressant effect (Oppenheim, 1983).

3.5.1.FQ Toloxatone

1) Interaction Effect: neurotoxicity, seizures, or serotonin syndrome (hypertension, hyperthermia, myoclonus changes)

2) Summary: Concomitant TCA and MAOI use has resulted in hyperpyrexia, convulsions, and death. Concu and TCAs has also been reported to result in a condition termed serotonin syndrome (Insel et al, 1982p; Spig Brodribb et al, 1994o; Neuvonen et al, 1993h). Serotonin syndrome is a rare but potentially fatal condition of hyperstimulation characterized by hypertension, hyperthermia, myoclonus, and changes in mental status (Ste TCAs and MAOIs must be used concurrently, avoid large doses, use only oral TCAs, avoid imipramine, clom desipramine, and tranylcypromine, and monitor patients closely (Schuckit et al, 1971p; White & Simpson, 198

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Concomitant use of a tricyclic antidepressant (TCA) and a monoamine oxidase inhi should be done only with close monitoring and where the clinical benefit outweighs the potential risk. Other a therapy should first be considered. If deemed clinically necessary, avoid large doses and use agents other th clomipramine, desipramine, and tranylcypromine.

7) Probable Mechanism: altered catecholamine uptake and metabolism

8) Literature Reports

a) Concomitant administration of monoamine oxidase inhibitors (MAOIs) with tricyclic antidepressants (T

considered an absolute contraindication in the past. Reports of excitation, hyperpyrexia, convulsions, an have been attributed to the combination (Lockett & Milner, 1965h; Winston, 1971h; Schuckit et al, 1971o 1976h). The mechanism may relate to the combined inhibition of catecholamine reuptake into the centra and inhibition of catecholamine metabolism (Sjoqvist, 1965h).

b) There is minimal risk of a clinically significant pharmacokinetic interaction between amitriptyline and t MAOI-A (Vandel et al, 1993). Seventeen inpatients being treated for major depressive illness were admi amitriptyline 125 mg once daily for two weeks, and the following two weeks they received amitriptyline 12 toloxatone 600 mg daily. With combined therapy there was a small, nonsignificant increase in amitriptylir The availability and urinary excretion of amitriptyline and its metabolites were not significantly affected.

c) There is evidence that MAOIs and TCAs can be given concomitantly in patients previously unrespons TCA alone. The combination may be utilized in one of two ways. Most frequently, the recommendation is previous antidepressants (five to ten days for TCAs and 14 days for MAOIs); the combination is then sim started (Perry et al, 1991h). Alternatively, in a patient previously receiving a TCA, small doses of the MA added (Schoonover, 1983). Numerous studies in patients with refractory depression or phobic anxiety st successfully used the combination of MAOIs and TCAs (Ponto et al, 1977h; Schuckit et al, 1971o; Ashcr

d) Serotonin syndrome has been reported with the use of moclobemide, a reversible inhibitor of monoar a TCA. A 39-year old woman with bipolar disorder developed serotonin syndrome after imipramine was a moclobemide. The patient was taking moclobemide 300 mg twice daily when imipramine was started at 5 followed by two dosage increases of imipramine to 200 mg and a reduction of moclobemide dosage to 1 Five days after the increase in imipramine to 200 mg per day, the patient developed symptoms of seroto including sweating, shivering, confusion, fever, and spasms in the extremities. The patient was treated w and symptoms resolved over the next few days without further complications (Brodribb et al, 1994n).

3.5.1.FR Tramadol

1) Interaction Effect: an increased risk of seizures

2) Summary: Seizures have been reported in patients using tramadol. Some medications, including tricyclic a (TCAs), are known to reduce the seizure threshold. The risk of seizures may be enhanced when imipramine a therapy are combined (Prod Info Ultram(R), 1998).

3) Severity: major

4) Onset: rapid

5) Substantiation: theoretical

6) Clinical Management: Caution should be used if tramadol is to be administered to patients receiving conc therapy. If possible, avoid this combination, especially in patients with underlying conditions that might predis

7) Probable Mechanism: unknown

3.5.1.FS Tranylcypromine

1) Interaction Effect: neurotoxicity, seizures, or serotonin syndrome (hypertension, hyperthermia, myoclonus changes)

2) Summary: Concomitant TCA and MAOI use has resulted in hyperpyrexia, convulsions, and death. Concu and TCAs has also been reported to result in a condition termed serotonin syndrome (Insel et al, 1982m; Spi Brodribb et al, 1994l; Neuvonen et al, 1993f). Serotonin syndrome is a rare but potentially fatal condition of se hyperstimulation characterized by hypertension, hyperthermia, myoclonus, and changes in mental status (Ste Consequently, coadministration of TCAs and MAOIs is contraindicated in most cases. If TCAs and MAOIs mu concurrently, avoid large doses, use only oral TCAs, avoid imipramine, clomipramine, desipramine, and trany monitor patients closely (Schuckit et al, 1971l; White & Simpson, 1984j).

3) Severity: contraindicated

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: Concomitant use of imipramine with a monoamine oxidase inhibitor (MAOI), such a is contraindicated. If imipramine is replacing treatment with tranylcypromine, a minimum of 14 days should el tranylcypromine is discontinued before therapy with imipramine begins (Prod Info imipramine hydrochloride o The manufacturer of tranylcypromine recommends that at least 7 days should elapse before tranylcypromine replaced by imipramine. Similarly, if imipramine therapy is substituted by tranylcypromine, there should be a period. Tranylcypromine should then be given using half the normal starting dosage for, minimally, the first w (Prod Info Parnate(R), 2001).

7) Probable Mechanism: altered catecholamine uptake and metabolism

8) Literature Reports

a) Concomitant administration of monoamine oxidase inhibitors (MAOIs) with tricyclic antidepressants (T considered an absolute contraindication in the past and still is listed as such by the manufacturers (Prod hydrochloride oral tablet, 2003). Reports of excitation, hyperpyrexia, convulsions, and possible death hav to the combination (Lockett & Milner, 1965f; Brachfeld et al, 1963d; Winston, 1971f; Schuckit et al, 1971k Spiker & Pugh, 1976f). The mechanism may relate to the combined inhibition of catecholamine reuptake nervous system and inhibition of catecholamine metabolism (Sjoqvist, 1965f).

b) Administration of a TCA after MAOI therapy may result in the development of serotonin syndrome. In crossover study examining the effects of clorgyline and clomipramine for the treatment of obsessive-com two subjects developed severe reactions characteristic of serotonin syndrome. During the study, patients clorgyline therapy, followed by a washout period of approximately four weeks and subsequent clomipram taking the first 100 mg dose of clomipramine, one patient developed coarse myoclonic jerking in both leg

diaphoresis, and arrhythmia. Another patient developed a similar reaction after the first dose, with upper symptoms, myoclonic movements, and cardiac irritability. Both patient's symptoms resolved several hou patients were later treated successfully with clomipramine without adverse effects (Insel et al, 1982l).

c) A drug interaction occurred in a 76-year old woman who had been taking clomipramine 50 mg daily fo prior to switching to moclobemide 300 mg daily. The patient experienced somnolence, confusion, and fe progressed to further mental impairment, muscle stiffness, myoclonus, and convulsive attacks. The patie were described as fulfilling the diagnostic criteria for serotonin syndrome and were resolved a few days l discontinuing all antidepressant medications (Spigset et al, 1993m).

d) A 39-year old woman with bipolar disorder developed serotonin syndrome after imipramine was adde The patient was taking moclobemide 300 mg twice daily when imipramine was started at 50 mg daily, fol dosage increases of imipramine to 200 mg and a reduction of moclobemide dosage to 150 mg twice dail the increase in imipramine to 200 mg per day, the patient developed symptoms of serotonin syndrome, i shivering, confusion, fever, and spasms in the extremities. The patient was treated with chlorpromazine a resolved over the next few days without further complications (Brodribb et al, 1994k).

e) Three patients with bipolar disorder developed manic symptoms while undergoing concurrent therapy isocarboxazid and amitriptyline. In all three cases the patients had been given MAOIs and TCAs alone w complications. It was only when the drugs were used in combination that symptoms of mania emerged, s synergistic effect (de la Fuente et al, 1986d).

f) In one case, clomipramine 10 mg twice daily was added to a stable regimen of tranylcypromine in a pl 34-year old man. After taking several doses, the patient developed symptoms of nausea and profuse sw pyrexia, dyspnea, and agitation. The hyperpyrexical state led to disseminated intravascular coagulation a (Tackley & Tregaskis, 1987g).

g) There is evidence that MAOIs and TCAs can be given concomitantly in patients previously unrespons TCA alone. A few precautions must be followed including: a) avoidance of large doses (no more than 15 or its equivalent, 45 mg phenelzine, or 60 mg isocarboxazid) b) oral administration c) avoidance of clomi imipramine, desipramine, and tranylcypromine in any combination, and d) close monitoring of patients (K Winston, 1971f; Schuckit et al, 1971k; White & Simpson, 1984i; Rom & Benner, 1972d). The combinatio one of two ways. Most frequently, the recommendation is to stop all previous antidepressants (five to ten and 14 days for MAOIs); the combination is then simultaneously started (Perry et al, 1991f). Alternatively previously receiving a TCA, small doses of the MAOI may be slowly added (Schoonover, 1983). Some s that the combination of amitriptyline and isocarboxazid is preferred (Perry et al, 1991f). Numerous studie refractory depression or phobic anxiety states have successfully used the combination of MAOIs and TC 1977f; Schuckit et al, 1971k; Ashcroft, 1975f).

3.5.1.FT Trifluoperazine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Q and T wave distortions have been observed in patients taking phenothiazines (Prod Info Cor Prod Info Stelazine(R), 2002; Prod Info Thorazine(R), 2002). Other phenothiazines may have similar effects, are available. Tricyclic antidepressants (TCAs) at therapeutic doses can cause QT prolongation (Marshall & F Case reports have described increased plasma levels and adverse effects when phenothiazines and tricyclic were taken together, likely due to inhibition of their metabolism (Ghaemi & Kirkwood, 1998; Geller et al, 1985 Loga et al, 1981).

3) Severity: major

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: Concurrent administration of a phenothiazine and a tricyclic antidepressant is not re

7) Probable Mechanism: additive effect on QT interval

3.5.1.FU Trimethoprim

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Tricyclic antidepressants (TCAs) and cotrimoxazole have been shown to prolong the QTc inter recommended therapeutic dose (Lopez et al, 1987; Marshall & Forker, 1982s). Even though no formal drug in have been done, the coadministration of tricyclic antidepressants and other drugs known to prolong the QTc cotrimoxazole, is not recommended (Prod Info Elavil(R), 1999j).

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: The concurrent administration of cotrimoxazole and tricyclic antidepressants is not r

7) Probable Mechanism: additive effects on QT prolongation

3.5.1.FV Vasopressin

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Tricyclic antidepressants and vasopressin have been shown to prolong the QTc interval at the therapeutic dose (Prod Info Vivactil(R), 1999; McCue et al, 1989; Munger & Effron, 1988; Mauro et al, 1988; I 1982j; Goldstein & Claghorn, 1980; Buckhardt et al, 1978; Pinder et al, 1977; Thorstrand, 1976; Singh, 1972) formal drug interaction studies have been done, the coadministration of drugs known to prolong the QTc inter recommended.

3) Severity: major

4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of drugs that prolong the QT interval, such as tricycli and vasopressin, is not recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.FW Venlafaxine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest) effects of both drugs
2) Summary: Tricyclic antidepressants (TCAs) and venlafaxine have been shown to prolong the QTc interval recommended therapeutic dose (Prod Info Effexor(R) XR, 2003; Marshall & Forker, 1982d). Even though no interaction studies have been done, the coadministration of tricyclic antidepressants and other drugs known t interval, such as venlafaxine, is not recommended (Prod Info Elavil(R), 1999c). In addition, venlafaxine and tr antidepressants (TCAs) may competitively inhibit each other's metabolism which may increase side effects o 2000; Prod Info Effexor(R) XR, 2003; Ellingrod & Perry, 1994). Venlafaxine increased the AUC, Cmax, and C desipramine by approximately 35%. The AUCs of 2-OH-desipramine increased by 2.5 and 4.5 fold when adm venlafaxine 37.5 mg and 75 mg every 12 hours, respectively. The pharmacokinetics of imipramine and the 2- were not affected (Prod Info venlafaxine extended release oral tablets, 2008).
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Due to the potential for additive effects on the QT interval, the concurrent administra venlafaxine and tricyclic antidepressants is not recommended.
7) Probable Mechanism: decreased TCA and venlafaxine metabolism; additive effects on QT prolongation
8) Literature Reports
a) When administered with imipramine, the pharmacokinetics of imipramine and the 2-hydroxy metaboli affected. Venlafaxine increased the area under the concentration-time curve (AUC), maximum concentra minimum concentration (Cmin) of desipramine by approximately 35%. The 2-OH-desipramine AUCs incr (venlafaxine 37.5 mg every 12 hours) and by 4.5-fold (venlafaxine 75 mg every 12 hours). The clinical si finding is unknown (Prod Info venlafaxine extended release oral tablets, 2008).

3.5.1.FX Verapamil

1) Interaction Effect: imipramine toxicity (dry mouth, sedation, urinary retention)
2) Summary: Verapamil decreased imipramine clearance by 25% (statistically significant) compared with pla controlled, single-dose study in 12 healthy volunteers (Hermann et al, 1992a). Imipramine bioavailability was by verapamil (15% greater than with placebo). The clinical significance of this interaction and whether it occu tricyclic antidepressants has yet to be determined.
3) Severity: minor
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Monitor for anticholinergic side effects of imipramine if verapamil is added to therap imipramine may be appropriate. Conversely, if verapamil is discontinued, monitor continued clinical efficacy c adjust dosage accordingly.
7) Probable Mechanism: decreased imipramine clearance

3.5.1.FY Warfarin

1) Interaction Effect: an increased risk of bleeding
2) Summary: Tricyclic antidepressants (TCAs) may increase the half-life and bioavailability of oral anticoagul 1970a; Williams et al, 1976a). Considerable interindividual differences may be found (Pond et al, 1975a).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: In patients receiving imipramine and warfarin, closely monitor prothrombin time ratio warfarin doses accordingly.
7) Probable Mechanism: decreased warfarin metabolism; increased warfarin absorption
8) Literature Reports
a) In a study of healthy volunteers, the concurrent use of nortriptyline or amitriptyline resulted in an incre levels and an increase in the plasma half-life of dicumarol, although the effect was not consistent in all su 1975). This effect was not observed with warfarin.
b) A single oral dose of bishydroxycoumarin after eight days of nortriptyline resulted in a significantly pro and decreased volume of distribution of the coumarin anticoagulant in six healthy volunteers (Vesell et a mechanism of action was suggested to be reduced bishydroxycoumarin metabolism and/or altered coum
c) Drug dosing was studied in 16 patients on long-term anticoagulant therapy who used concurrent TCA 1976). TCAs affected the stability of anticoagulant control leading to frequent changes in the doses of an Inhibition of coumarin metabolism was the postulated mechanism.

3.5.1.FZ Ziprasidone

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Ziprasidone use is associated with dose-related prolongation of the QTc interval. Even though interaction studies have been done, it is recommended that concurrent use with other agents that may prolon avoided (Prod Info GEODON(R) oral capsules, IM injection, 2007; Marshall & Forker, 1982ah).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Due to the potential for additive QTc interval prolongation, avoid the concurrent adr ziprasidone and agents that can prolong the QTc interval (Prod Info GEODON(R) oral capsules, IM injection,
7) Probable Mechanism: additive cardiac effects

3.5.1.GA Zolmitriptan

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Tricyclic antidepressants (TCAs) and zolmitriptan have been shown to prolong the QTc interva recommended therapeutic dose (Prod Info Zomig(R), 2001; Marshall & Forker, 1982l). Even though no forma studies have been done, the coadministration of tricyclic antidepressants and other drugs known to prolong tl such as zolmitriptan, is not recommended (Prod Info Elavil(R), 1999f).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of zolmitriptan and tricyclic antidepressants is not rec
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.GB Zotepine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod 1999), haloperidol (O'Brien et al, 1999), risperidone (Duenas-Laita et al, 1999), sertindole (Agelink et al, 2001 (Owens, 2001b), sultopride (Lande et al, 1992), and zotepine (Sweetman, 2003). Even though no formal drug studies have been done, the coadministration of a tricyclic antidepressant and an antipsychotic is not recomm Pamelor(R), 2001; Marshall & Forker, 1982t).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of a tricyclic antidepressant and an antipsychotic is n
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) Electrocardiographic changes that have occurred during clinical trials with pimozide have included pr corrected QT interval, flattening, notching, and inversion of the T wave and the appearance of U waves. studies, sudden, unexpected deaths have occurred while patients were receiving pimozide doses of 1 m proposed mechanism for these deaths is prolongation of the QT interval predisposing patients to ventricu (Prod Info Orap(R), 1999).

3.5.2 Drug-Food Combinations

3.5.2.A Ethanol

1) Interaction Effect: enhanced drowsiness; impairment of motor skills
2) Summary: Ethanol in combination with antidepressants may alter behavior, with the predominant effect be impairment in psychomotor performance. Almost all studies to date have evaluated the effects of the combina skills, driving behavior and psychomotor skills (Landauer et al, 1969; Patman et al, 1969; Milner & Landauer, al, 1975; Seppala, 1977). There are no studies evaluating respiratory response with the combination.
3) Severity: moderate
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Encourage abstention from alcohol during at least the first few weeks of tricyclic ad allow patient accommodation to potential CNS depressant effects of the tricyclic.
7) Probable Mechanism: additive CNS depressant activity; impaired hepatic metabolism of the tricyclic antide
8) Literature Reports
a) The studies available indicate that the interaction between amitriptyline (and other antidepressants) ir ethanol is unpredictable. They indicate that antidepressants may enhance, prevent, or not affect the CNS actions of ethanol. The most significant effect reported is enhanced CNS depression. However, there are tricyclic antidepressants may actually antagonize the sedative effects of ethanol (Milner & Landauer, 197
b) The propensity for interaction may be related to the inherent CNS depressant action of the tricyclic ar listed in one series in descending order as amitriptyline, doxepin, imipramine, nortriptyline, desipramine, (Marco & Randels, 1981).
c) Imipramine and amitriptyline are the best documented examples of disruptions of metabolism. Cleara was 3-fold higher in alcoholics compared with healthy volunteers (Ciraulo et al, 1988).
d) Individual case reports have documented "blackouts" following modest amounts of alcohol in combina amitriptyline or imipramine (Hudson, 1981), and reversible extrapyramidal effects (parkinsonian effects, a amoxapine (Shen, 1984).

3.5.4 Drug-Tobacco Combinations

3.5.4.A Tobacco

1) Interaction Effect: decreased imipramine concentrations
2) Summary: The administration of oral imipramine 3.5 mg/kg to tobacco smokers (15 cigarettes daily) result lower mean plasma levels of combined imipramine and desmethylimipramine (160 ng/mL) when compared to ng/mL) (Perel et al, 1975). Tobacco smoking may alter the response to antidepressants (Linnoila et al, 1981;
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Patients who smoke may require larger doses of imipramine than non-smokers. Mo receiving imipramine for antidepressant efficacy.
7) Probable Mechanism: increased hepatic metabolism

3.5.5 Intravenous Admixtures

3.5.5.1 Drugs

Doxapram

Haloperidol

3.5.5.1.A Doxapram

1) Compatible
a) Doxapram (400 mg/20 mL with imipramine 12.5 mg/1 mL physically compatible and no loss of dc imipramine stability not described) (Trissel, 1990)
b) Imipramine (12.5 mg/1 mL with doxapram 400 mg/20 mL physically compatible in syringe with nc decomposition in 24 hours; temperature not specified) (Trissel, 1990a)

3.5.5.1.B Haloperidol

1) Conflicting Data
a) Incompatible
1) Haloperidol in a 1:1 or 1:2 mixture with imipramine, compatibility is questionable because the no visual changes in 1 hour, was slightly cloudy and viscous in 2 hours, was clear and very visc room temperature, but no haloperidol decomposition was observed in a 4 hour study period; dru not specified (Pers Comm, 1990)
b) Compatible
1) Haloperidol in a 1:1 or 1:2 mixture with imipramine, compatibility is questionable because the no visual changes in 1 hour, was slightly cloudy and viscous in 2 hours, was clear and very visc room temperature, but no haloperidol decomposition was observed in a 4 hour study period; dru not specified (Pers Comm, 1990)

4.0 Clinical Applications

Monitoring Parameters

Patient Instructions

Place In Therapy

Mechanism of Action / Pharmacology

Therapeutic Uses

Comparative Efficacy / Evaluation With Other Therapies

4.1 Monitoring Parameters

A) Imipramine Hydrochloride
1) Therapeutic
a) Laboratory Parameters

1) MHPG Urinary Concentration
a) Patients with urinary levels of 3-methoxy-4-hydroxy-phenyl glycol (MHPG) less than 1950 mcg/d antidepressant (TCA) therapy, respond to imipramine, and other TCAs, more predictably than patier urinary levels greater than 1950 mcg/day (Rosenbaum et al, 1980); (Beckmann & Goodwin, 1975)(M
b) Newer data (Maas et al, 1982) confirm some of the earlier data and hypotheses while failing to c fact that a low cerebrospinal fluid (CSF) 5-HIAA (5-hydroxyindoleacetic acid) or low urinary MHPG v pretreatment period is associated with a favorable response to amitriptyline therapy was not confirm study showed no significant relationships between pre-treatment urinary MHPG, CSF MHPG, 5-HIA (homovanillic acid) values and subsequent amitriptyline efficacy.
c) Low urinary NE and MHPG values are associated with a greater incidence of response to amitrip imipramine therapy in bipolar affective disorder patients, but not in unipolar patients (Maas et al, 198
2) Dexamethasone Suppression Test (DST)
a) The DST has been reported to be a useful tool in predicting whether or not a patient would respo antidepressant therapy (Brown et al, 1979, Brown et al, 1980). Eighty percent of patients with a posi responded to therapy versus a 37% response rate in patients with a negative DST (Brown et al, 197 of DST results as an indicator of tricyclic antidepressant therapy efficacy in the treatment of depress confirmed in one study (Peselow et al, 1983a).
b) Depressed patients with abnormal DST may respond better to imipramine or desipramine therap or clomipramine therapy (Brown et al, 1980). The result of this study must be considered with cautio investigator made a single evaluation of efficacy after 2 weeks of therapy. These results were not re imipramine and amitriptyline therapy (Greden et al, 1981). Therefore, DST results may not be a usef selection of a particular antidepressant.
3) Platelet Monoamine Oxidase Activity
a) Measurements of platelet MAO activity with serotonin reveals that unmedicated depressed patier significantly higher degree of activity compared to controls. This degree of activity decreases progre imipramine therapy and falls within normal limits at the time the patient is classified as recovered (Q Whether platelet MAO activity is useful as a monitoring parameter remains to be determined.
4) Platelet Binding
a) Imipramine has been shown to have specific high-affinity binding sites on human platelet membr McChesney, 1985). These binding sites appear to be similar to those found in the human brain. Rec indicates that platelet membrane binding may be decreased in some depressed patients (Lewis & M Pecknold et al, 1987; De Leo et al, 1991); (Ambrusini et al, 1992). The exact value of this finding is s however, it may be of value in predicting which depressed patients are more likely to respond to ant therapy.
b) The ability of the platelet to bind imipramine decreases with age. Whether this decrease in platel related to decreases in the density or number of receptors or an alteration in membrane microenviro Even though the decrease in platelet binding is significant, whether the changes effects the efficacy unknown (Marazziti et al, 1987).
c) Significant reductions in platelet imipramine binding have been observed in depressed patients. I diagnosed with panic disorders or panic disorders concurrent with depression and patients with a pr depression have normal platelet imipramine binding compared to controls. The reason for this differ but may indicate that the 2 syndromes differ neurochemically (Pecknold et al, 1987).
5) Serum Concentrations
a) Indications for determination of serum imipramine concentration (Hollister, 1982):
1) Utilization of adequate doses without experience clinical effect;
2) Side effects uncertainly related to imipramine therapy;
3) Monitoring high dose imipramine therapy;
4) Assess the influence of intercurrent illness on imipramine serum concentrations;
5) Evaluating a patient suspected of intentional or unintentional overdose of imipramine.

b) Physical Findings
1) Depression
a) Clinical improvement of the signs and symptoms of depression.
2) Enuresis
a) Decreased frequency of nocturnal wetting episodes.
3) Attention Deficit Hyperactivity Disorder (ADHD)
a) Improvement in mental and behavioral symptoms, including inappropriate inattention, impulsivity cognitive performance.

2) Toxic
a) Laboratory Parameters
1) Obtain WBC and differential cells in patients with fever, sore throat, or other signs of infection (Prod I oral tablets, 2007).

b) Physical Findings
1) Obtain baseline ECG in patients with cardiac disease, elderly, or if initiating larger-than-usual doses. during therapy if clinically warranted (Prod Info imipramine hcl oral tablets, 2007).
a) Depression
1) Monitor patients receiving antidepressants for worsening of depression, suicidality, or unusu behavior, especially at the initiation of therapy or when the dose increases or decreases. Such include at least weekly face-to-face contact with patients or their family members or caregivers

weeks of treatment, then visits every other week for the next 4 weeks, then at 12 weeks, and th indicated beyond 12 weeks. Families and caregivers should be advised of the need for close ob observation) of patients and communication with the prescriber (Anon, 2004).

2) Patients who experience symptoms of anxiety, agitation, panic attacks, insomnia, irritability, impulsivity, akathisia, hypomania, or mania may be at an increased risk for worsening depressi these symptoms are observed, therapy should be reevaluated and it may be necessary to disco medications when symptoms are severe, sudden in onset, or were not part of the patient's initia 2004).

b) Attention Deficit Hyperactivity Disorder (ADHD)

1) The American Academy of Pediatrics (AAP) does not recommend the routine use of electroc (ECGS) or routine subspecialty cardiology evaluations (which were previously recommended by Heart Association (AHA) scientific statement to detect cardiac conditions that might place the ch sudden cardiac death) before initiating stimulant therapy to treat attention-deficit/hyperactivity d most children. The APA cited specific reasons for changing the recommendation including: lack establishing a relationship between stimulant drugs used to treat ADHD and sudden cardiac de frequency of sudden unexpected deaths among patients taking stimulant drugs is not higher tha general population of children, and lack of cost-effective analysis to support ECG screening or s by pediatric cardiologist (Perrin et al, 2008).

2) Based on the American Academy of Pediatrics (AAP) and the American Heart Association (A statements, the following cardiac monitoring recommendations have been established to assist evaluation of children treated with stimulant drugs, including imipramine, for ADHD (Perrin et al, 2008):

- Conduct a thorough examination prior to initiating imipramine therapy for a diagnosis of A attention should be given to symptoms indicative of a cardiac condition, including palpitatio or syncope.
- Obtain a complete family and patient history for conditions associated with SCD, and dete of any other prescription or over-the-counter medications.
- Conduct a complete physical evaluation of the patient for hypertension, cardiac murmurs, associated with Marfan syndrome, and signs of irregular cardiac rhythms. Prolongation of C tachycardia, and rarely sudden death have all been reported with imipramine use.
- Perform further evaluation if family history, patient history or physical exam is suggestive during initial visit or at follow up visits, and if indicated, consult pediatric cardiologist .
- Continue to assess the patient for cardiac symptoms and any changes in family history at
- Blood pressure and heart rate should be evaluated at baseline, at dose increases, during within 1 to 3 months, and at follow up visits every 6 to 12 months.

B) Imipramine Pamoate

1) Therapeutic

a) Laboratory Parameters

1) Dexamethasone Suppression Test (DST)

a) The DST has been reported to be a useful tool in predicting whether or not a patient would respo antidepressant therapy (Brown et al, 1979, Brown et al, 1980). Eighty percent of patients with a posi responded to therapy versus a 37% response rate in patients with a negative DST (Brown et al, 197 of DST results as an indicator of tricyclic antidepressant therapy efficacy in the treatment of depress confirmed in one study (Peselow et al, 1983a).

b) Depressed patients with abnormal DST may respond better to imipramine or desipramine therap or clomipramine therapy (Brown et al, 1980). The result of this study must be considered with cautio investigator made a single evaluation of efficacy after 2 weeks of therapy. These results were not re imipramine and amitriptyline therapy (Greden et al, 1981). Therefore, DST results may not be a usef selection of a particular antidepressant.

2) Platelet Monoamine Oxidase Activity

a) Measurements of platelet MAO activity with serotonin reveals that unmedicated depressed patie significantly higher degree of activity compared to controls. This degree of activity decreases progre imipramine therapy and falls within normal limits at the time the patient is classified as recovered (Q Whether platelet MAO activity is useful as a monitoring parameter remains to be determined.

3) Serum Concentrations

a) Indications for determination of serum imipramine concentration (Hollister, 1982):

1) Utilization of adequate doses without experience clinical effect;
2) Side effects uncertainly related to imipramine therapy;
3) Monitoring high-dose imipramine therapy;
4) Assess the influence of intercurrent illness on imipramine serum concentrations;
5) Evaluating a patient suspected of intentional or unintentional overdose of imipramine.

4) Platelet Binding

a) Imipramine has been shown to have specific high-affinity binding sites on human platelet membr McChesney, 1985). These binding sites appear to be similar to those found in the human brain. Rec indicates that platelet membrane binding may be decreased in some depressed patients (Lewis & M Pecknold et al, 1987; De Leo et al, 1991); (Ambrusini et al, 1992). The exact value of this finding is s however, it may be of value in predicting which depressed patients are more likely to respond to ant therapy.

b) The ability of the platelet to bind imipramine decreases with age. Whether this decrease in platel related to decreases in the density or number of receptors or an alteration in membrane microenviro Even though the decrease in platelet binding is significant, whether the changes effects the efficacy unknown (Marazziti et al, 1987).

c) Significant reductions in platelet imipramine binding have been observed in depressed patients. I diagnosed with panic disorders or panic disorders concurrent with depression and patients with a pr depression have normal platelet imipramine binding compared to controls. The reason for this differ but may indicate that the 2 syndromes differ neurochemically (Pecknold et al, 1987).

b) Physical Findings

1) Depression

a) Clinical improvement of the signs and symptoms of depression.

2) Attention Deficit Hyperactivity Disorder (ADHD)

a) Improvement in mental and behavioral symptoms, including inappropriate inattention, impulsivity cognitive performance.

2) Toxic

a) Laboratory Parameters

1) Obtain WBC and differential cells in patients with fever, sore throat, or other signs of infection (Prod I (R) oral capsules, 2007).

b) Physical Findings

1) Obtain baseline ECG in patients with cardiac disease, elderly, or if initiating larger-than-usual doses. during therapy if clinically warranted (Prod Info TOFRANIL-PM(R) oral capsules, 2007).

2) Monitor patients receiving antidepressants for worsening of depression, suicidality, or unusual chang especially at the initiation of therapy or when the dose increases or decreases. Such monitoring should i weekly face-to-face contact with patients or their family members or caregivers during the initial 4 weeks visits every other week for the next 4 weeks, then at 12 weeks, and then as clinically indicated beyond 1 and caregivers should be advised of the need for close observation (ie, daily observation) of patients and with the prescriber (Anon, 2004).

3) Patients who experience symptoms of anxiety, agitation, panic attacks, insomnia, irritability, hostility, akathisia, hypomania, or mania may be at an increased risk for worsening depression or suicidality. If the observed, therapy should be reevaluated and it may be necessary to discontinue medications when sym sudden in onset, or were not part of the patient's initial symptoms (Anon, 2004).

a) Attention Deficit Hyperactivity Disorder (ADHD)

1) The American Academy of Pediatrics (AAP) does not recommend the routine use of electroc (ECGS) or routine subspecialty cardiology evaluations (which were previously recommended by Heart Association (AHA) scientific statement to detect cardiac conditions that might place the ch sudden cardiac death) before initiating stimulant therapy to treat attention-deficit/hyperactivity d most children. The APA cited specific reasons for changing the recommendation including: lack establishing a relationship between stimulant drugs used to treat ADHD and sudden cardiac de frequency of sudden unexpected deaths among patients taking stimulant drugs is not higher tha general population of children, and lack of cost-effective analysis to support ECG screening or s by pediatric cardiologist (Perrin et al, 2008).

2) Based on the American Academy of Pediatrics (AAP) and the American Heart Association (statements, the following cardiac monitoring recommendations have been established to assist evaluation of children treated with stimulant drugs, including imipramine pamoate, for ADHD (P Vetter et al, 2008):

- Conduct a thorough examination prior to initiating imipramine pamoate therapy for a diagn Special attention should be given to symptoms indicative of a cardiac condition, including p syncope, or syncope.
- Obtain a complete family and patient history for conditions associated with SCD, and dete of any other prescription or over-the-counter medications.
- Conduct a complete physical evaluation of the patient for hypertension, cardiac murmurs, associated with Marfan syndrome, and signs of irregular cardiac rhythms. Prolongation of C tachycardia, and rarely sudden death have all been reported with imipramine pamoate use
- Perform further evaluation if family history, patient history or physical exam is suggestive during initial visit or at follow up visits, and if indicated, consult pediatric cardiologist .
- Continue to assess the patient for cardiac symptoms and any changes in family history at
- Blood pressure and heart rate should be evaluated at baseline, at dose increases, during within 1 to 3 months, and at follow up visits every 6 to 12 months.

4.2 Patient Instructions

A) Imipramine (By mouth)

Imipramine

Treats depression. May also be used to treat bedwetting in children. This medicine is a tricyclic antidepressant.

When This Medicine Should Not Be Used:
You should not use this medicine if you have had an allergic reaction to imipramine or to related medicines such a (Elavil®), carbamazepine (Tegretol®), maprotiline (Ludiomil®), or nortriptyline (Aventyl®). You should not use this

have had a recent heart attack or have taken an MAO inhibitor such as isocarboxazid (Marplan®), phenelzine (Na
(Eldepryl®), or tranylcypromine (Parnate®) in the past 14 days.

How to Use This Medicine:
Capsule, Tablet

Your doctor will tell you how much of this medicine to use and how often. Your dose may need to be changed
order to find out what works best for you. Do not use more medicine or use it more often than your doctor tell
You may take this medicine with or without food.
Do not crush or chew the capsules. You may open the capsules and mix the medicine beads with soft food (p
applesauce). Swallow the mixture without chewing.
If you are taking this drug for depression, it may take 2 to 3 weeks before you start to feel better.
This medicine should come with a Medication Guide. Read and follow these instructions carefully. Ask your d
pharmacist if you have any questions. Ask your pharmacist for the Medication Guide if you do not have one.
ask you to sign some forms to show that you understand this information.

If a Dose is Missed:

If you miss a dose or forget to use your medicine, use it as soon as you can. If it is almost time for your next d
then to use the medicine and skip the missed dose. Do not use extra medicine to make up for a missed dose
If you take one dose a day at bedtime, you should not use the missed dose the next morning. Wait until your
bedtime dose.

How to Store and Dispose of This Medicine:

Store the medicine in a closed container at room temperature, away from heat, moisture, and direct light.
Ask your pharmacist, doctor, or health caregiver about the best way to dispose of any leftover medicine after
your treatment. You will also need to throw away old medicine after the expiration date has passed.
Keep all medicine away from children and never share your medicine with anyone.

Drugs and Foods to Avoid:
Ask your doctor or pharmacist before using any other medicine, including over-the-counter medicines, vitamins, a
products.

Make sure your doctor knows if you are using atropine, benztropine (Cogentin®), cimetidine (Tagamet®), gua
(Ismelin®), methylphenidate (Ritalin®), scopolamine, medicine for high blood pressure (such as clonidine or
certain medicine for heart rhythm problems (such as quinidine, flecainide, propafenone, Quinaglute®, Tambo
Rythmol®), medicine to treat seizures (such as phenobarbital, phenytoin, or Dilantin®), a phenothiazine med
chlorpromazine, perphenazine, prochlorperazine, promethazine, thioridazine, Compazine®, Mellaril®, Phene
Thorazine®, or Trilafon®), or other medicines to treat depression (such as fluoxetine, paroxetine, sertraline, P
Zoloft®).
Tell your doctor if you are using any medicines that make you sleepy. These include sleeping pills, cold and a
narcotic pain relievers, and sedatives.
Do not drink alcohol while you are using this medicine.

Warnings While Using This Medicine:

Make sure your doctor knows if you are pregnant, planning to become pregnant, or breastfeeding. Tell your d
glaucoma, trouble urinating, mental problems, stomach problems, seizures, heart disease, liver disease, kidn
thyroid disease.
For some children, teenagers, and young adults, this medicine can increase thoughts of suicide. Tell your do
doctor right away if you or your child start to feel more depressed and have thoughts about hurting yourselves
unusual thoughts or behaviors that trouble you or your child, especially if they are new or are getting worse q
the doctor knows if you or your child have trouble sleeping, get upset easily, have a big increase in energy, o
reckless. Also tell the doctor if you or your child have sudden or strong feelings, such as feeling nervous, ang
violent, or scared. Let the doctor know if you, your child, or anyone in your family has bipolar disorder (manic-
tried to commit suicide.
Do not give this medicine to a child unless directed to do so by the child's doctor.
This medicine may raise or lower your blood sugar, or it may cover up symptoms of very low blood sugar (hyp
Make sure any doctor or dentist who treats you knows that you are using this medicine. You may need to sto
medicine several days before having surgery or medical tests.
Do not stop using this medicine suddenly without asking your doctor. You may need to slowly decrease your
stopping it completely.
This medicine may make your skin more sensitive to sunlight. Use a sunscreen when you are outdoors. Avoi
tanning beds.
This medicine may cause dizziness and vision changes. Avoid driving, using machines, or doing anything els
dangerous if you are not alert or able to see well.
Your doctor will need to check your progress at regular visits while you are using this medicine. Be sure to ke
appointments.

Possible Side Effects While Using This Medicine:
Call your doctor right away if you notice any of these side effects:

Allergic reaction: Itching or hives, swelling in your face or hands, swelling or tingling in your mouth or throat, d

trouble breathing.
Anxiety, restlessness, nervousness, or mood or mental changes.
Change in how much or how often you urinate, or problems with urination.
Changes in behavior, or thoughts of hurting yourself or others.
Chest pain, shortness of breath, cold sweats, and bluish-colored skin.
Fast, pounding, or irregular heartbeat.
Lightheadedness or fainting when getting up suddenly from a lying or sitting position.
Numbness or tingling in the hands and feet.
Numbness or weakness in your arm or leg, or on one side of your body.
Seizures or tremors.
Sudden or severe headache, problems with vision, speech, balance, or walking.
Swelling in your hands, ankles, or feet.
Trouble sleeping.
Twitching or muscle movements you cannot control.
Unexplained fever or sore throat.
Unusual bleeding or bruising.
Unusual tiredness or weakness.
Yellowing of your skin or the whites of your eyes.

If you notice these less serious side effects, talk with your doctor:
Breast swelling or discharge.
Changes in vision.
Changes in weight.
Dizziness or drowsiness.
Dry mouth.
Nausea, vomiting, diarrhea, constipation, or upset stomach.
Problems having sex.
Ringing in the ears.
Skin rash or itching.
Swelling of the breast or testicles in men.

If you notice other side effects that you think are caused by this medicine, tell your doctor.

4.3 Place In Therapy

A) Depression is a complicated disorder and consequently this disease's treatment regimens are diverse. The two mc diagnostic syndromes among affective disorders are major depression and bipolar disorders. The tricyclic antidepress the monoamine oxidase inhibitors (MAOIs) are considered the most effective agents for treating major depression. Fo disorders, lithium is considered the standard of therapy over TCAs, MAOIs and other agents such as carbamazepine

B) Imipramine and amitriptyline, along with the selective sorotonin reuptake inhibitors (SSRI) antidepressants, are cor standard of therapy for endogenous or typical depression. In addition, imipramine may be employed for treating agora has also been used adjunctively for pediatric enuresis, adult urinary incontinence associated with neurogenic bladder, incontinence, and geriatric spontaneous unstable detrusor contractions. Some studies indicate that chronic pain and d neuropathies may also be alleviated with imipramine. Although TCAs reportedly lower seizure threshold, imipramine h demonstrated to reduce the frequency of absence and myoclonic seizures. When an epileptic patient is refractory to o antidepressants and a TCA is deemed necessary for treatment, imipramine should be considered.

C) Imipramine and amitriptyline still have a place in therapy as the standards for the treatment of major depression al antidepressants. Newer classes of antidepressants are not more effective than imipramine for typical depression, but alternatives for treating patients intolerant of TCAs or exhibiting atypical depression. Being versatile, imipramine may b therapy of other disorders besides depression and should be included on hospital formularies. Institutions that commo depression should consider a diverse formulary with agents from each antidepressant class.

4.4 Mechanism of Action / Pharmacology

A) MECHANISM OF ACTION

1) DEPRESSION

a) The antidepressant mechanism of action of imipramine has not been completely determined but appears interaction with biogenic amines. Imipramine, like other tricyclic antidepressants, blocks the re-uptake of nore hydroxy-tryptamine at nerve terminals preventing their degradation and increasing their availability. This resu turnover of these amines in selective neurons but the relation of this effect to anti-depressant activity has not demonstrated (Gilman et al, 1990). Effects on the D1 dopamine receptor may also be important in the mediat antidepressant activity (Gambarana et al, 1995).

2) ENURESIS

a) Why imipramine works in the treatment of enuresis is not well understood. It beneficial effects do not appe changes in sleep architecture, anticholinergic properties, antiadrenergic properties, or effects on thyroid relea induced urinary urgency. In patients with nocturnal polyuria, imipramine had a vasopressin-independent antic attributed primarily to increased tubular reabsorption of urea and to a lesser extent to decreased sodium and excretion (Hunsballe et al, 1997). The drug improves functional bladder capacity during chronic administratio 1992; Prod Info Tofranil(R), 1995a).

B) REVIEW ARTICLES

1) A Consensus Statement on Panic Disorder is available from the International Consensus Group on Depressio
(Ballenger et al, 1998). Also an excellent review is available on the treatment of panic disorder (Bennett et al, 199
2) Drug-interactions of antidepressants are reviewed in German language (Zapotoczky & Simhandl, 1995).

4.5 Therapeutic Uses

Imipramine

Imipramine Hydrochloride

Imipramine Pamoate

4.5.A Imipramine

Anorexia nervosa

Cataplexy - Narcolepsy

Ophthalmoplegic migraine

Severe major depression with psychotic features

4.5.A.1 Anorexia nervosa
See Drug Consult reference: ANOREXIA NERVOSA - DRUG THERAPY

4.5.A.2 Cataplexy - Narcolepsy
See Drug Consult reference: NARCOLEPSY AND CATAPLEXY - DRUG THERAPY

4.5.A.3 Ophthalmoplegic migraine
See Drug Consult reference: THERAPY OF HEADACHE IN CHILDREN

4.5.A.4 Severe major depression with psychotic features
See Drug Consult reference: PSYCHOTIC DEPRESSION - DRUG THERAPY

4.5.B Imipramine Hydrochloride

Agoraphobia

Anorexia nervosa

Attention deficit hyperactivity disorder, predominantly inattentive type

Binging

Bulimia nervosa

Cardiac dysrhythmia

Depression

Diabetic neuropathy

Disorder of ejaculation

Drug dependence

Gardner-Diamond syndrome

Globus hystericus

Mood swings

Nocturnal enuresis

Obsessive-compulsive disorder

Pain

Panic disorder

Posttraumatic stress disorder

Schizophrenia; Adjunct

Separation anxiety disorder of childhood

Sexual disorder

Sleep disorder

Social phobia

Trichotillomania

Urinary incontinence

4.5.B.1 Agoraphobia

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Effective in the treatment of agoraphobia (Deltito et al, 1991)
Efficacy appears to be dose-related and usually requires doses of 150 milligrams or greater per day

c) Adult:

1) Imipramine and placebo were equally effective in the treatment of agoraphobia in a double-blind clinic drug therapy with brief psychological treatment (Cohen et al, 1984a). The drugs were started 2 weeks pr of the psychological therapy. At week 6 the mean dose of IMIPRAMINE was 124 milligrams and at week mg/day. During week 2 to week 12 each treatment group received 6 fortnightly sessions of therapist-aide addition each patient was given a leaflet describing the nature of agoraphobia and ways to cope with it. A requested to complete systematic self-exposure homework and record these activities in a diary. Drug th gradually withdrawn over weeks 26 to 28 of therapy. At the 2-year follow-up only 40 subjects were availa had dropped out of the study (2 refused follow-up, 1 died, 1 moved out of the country, and 1 was untrace of the patients remained improved with regards to their phobias. There was no significant difference betv patients treated with imipramine or placebo therapy. Nor was there a superior effect of therapist-aided ex therapist-aided relaxation.

2) The plasma IMIPRAMINE levels, but not DESIPRAMINE, correlated with the improvement in agoraph (Mavissakalian et al, 1984), which may indicate that the antiphobic effects of IMIPRAMINE therapy are m post-synaptic serotonergic neurotransmitter system and not the noradrenergic system.

3) IMIPRAMINE therapy plus programmed in vivo exposure practice was superior to IMIPRAMINE thera (Mavissakalian & Michelson, 1986; Mavissakalian et al, 1983).

4.5.B.2 Anorexia nervosa

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class III

Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:
Has resulted in some improvement in patients with anorexia nervosa

c) Adult:
1) Imipramine treatment resulted in some improvement in 7 patients with anorexia nervosa treated seria antidepressants (tricyclics, MAOIs, and triazolopyridines) including imipramine. Three of the patients rec imipramine; the treatment trials ranged from 6 to 14 weeks. Four of the patients had some improvement symptoms, 2 experienced some weight gain, and 3 of 3 who had bulimic symptoms reported improveme anorexic symptoms (3 to 6 weeks) was slower than the improvement observed in depression and anxiet following tricyclic therapy (Hudson et al, 1985). Significant weight gain generally began after 2 to 3 montl with IMIPRAMINE tended to tolerate the drug poorly and appeared to have an extraordinary sensitivity to anticholinergic side effects when compared to patients treated with trazodone or MAOIs (Hudson et al, 1 extraordinary sensitivity to the drug's side effects may be associated with their low body weight.

4.5.B.3 Attention deficit hyperactivity disorder, predominantly inattentive type

a) Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Pediatric, Evidence is inconclusive
Recommendation: Pediatric, Class III
Strength of Evidence: Pediatric, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:
Stimulants (eg, amphetamine, methylphenidate) are the drugs of choice in the treatment of attention defi

c) Pediatric:
1) Imipramine therapy should be considered an alternative or adjunctive agent when these agents fail o unable to tolerate them (Hilton et al, 1991; Rancurello, 1985a). The dose used ranges from 25 to 100 mi tends to be lower than those needed to treat depression. Children tend to respond within 24 hours after i The monitoring of serum imipramine and desipramine levels may be useful. The serum levels associate responses have been 10 to 54 ng/ml of imipramine and 10 to 65 ng/ml of desipramine (Linnoila et al, 197
2) A 6-year-old retarded child with Fragile X syndrome and attention deficit disorder responded to IMIPR (Hilton et al, 1991). IMIPRAMINE improved the boy's insomnia, enuresis, and attention deficit disorder, w therapy with METHYLPHENIDATE had caused a deterioration in behavior.
3) A 12-year-old boy with a history of severe attention deficit disorder and stimulant-induced Tourette's s responded well to IMIPRAMINE therapy (50 milligrams/d). During the course of IMIPRAMINE therapy th disorder substantially improved and the Tourette's symptomatology was not affected (Dillon et al, 1985).
4) Ten hyperactive children were treated with IMIPRAMINE 75 to 150 milligrams/day and no response w of the patients (Winsberg et al, 1980).
5) Fifty-two children, 3 to 14 years of age, were enrolled in an open clinical study to evaluate the efficac in the treatment of CHILDHOOD HYPERACTIVITY (Huessy & Wright, 1970). Thirty-five of the 52 childre marked improvement in behavior. The average daily dose of IMIPRAMINE was 50 mg (25 to 125 mg). S (11/17) of the children failing to respond to IMIPRAMINE therapy subsequently responded to METHYLPI therapy.

4.5.B.4 Binging

a) Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:
May be beneficial for weight loss when added to diet counseling and psychological support in obese bing

c) Adult:
1) A short course of low dose imipramine added to diet counseling and psychological support helped ob to lose weight and maintain their weight loss. In a double-blind study, binge eaters (as defined by DSM-I body mass index of greater than 27.5-kilograms (kg)/square meter randomly received imipramine 25 mil daily (n=15) or placebo (n=16) for 8 weeks. Diet counseling and psychological support were provided du phase and continued for 6 months thereafter. Imipramine- treated patients experienced a weight loss of placebo group remained stable (p=0.0002). The occurrence of depression was low for both groups; how on the Hamilton Depression scale declined in the imipramine group (p less than 0.001) but not in the pla eating episodes declined from 7.1 episodes/week to 2.8 episodes for the imipramine group (p less than episodes to 5.4 episodes in the placebo group (p not significant). After the active treatment phase, imipra continued their weight loss by a mean of 1.9 kg (p less than 0.001) while placebo- treated patients regai significant) (Laederach-Hofmann et al, 1999).

4.5.B.5 Bulimia nervosa

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Approximately 75% of patients show at least a moderate response (reduction of binge eating by 50% antidepressant therapy
Monoamine oxidase inhibitors also appear effective in bulimia, and may be superior to tricyclic antid et al, 1983)

c) Adult:

1) Twenty bulimic subjects were followed for a period of up to 2 years to assess the long term efficacy o therapy (Pope et al, 1985). At the end of the follow-up period, 95% had at least partial improvement and experienced a complete remission. Over the course of the study period 85% had either maintained or im quality of their initial response. The one patient that failed to respond discontinued her medication and pr her original frequency of binge eating.

2) A retrospective study of 22 patients with bulimia treated with antidepressants (AMITRIPTYLINE, IMIP DESIPRAMINE, DOXEPIN, TRAZODONE, TRANYLCYPROMINE, or PHENELZINE) showed a decreas bingeing and/or an improvement in depression (Brotman et al, 1984). During a 3-month follow-up period relapsed despite continuation of their antidepressant therapy, while others continued to benefit from drug

4.5.B.6 Cardiac dysrhythmia

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class III
Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Some patients with ventricular tachycardia or premature ventricular contractions may benefit from imipra

c) Adult:

1) IMIPRAMINE was included in a double-blinded crossover pilot study to evaluate the efficacy of ventri complex (VPC) suppression after acute myocardial infarction as a means to improve survival (Anon, 198 was assigned to ENCAINIDE, FLECAINIDE, IMIPRAMINE, MORICIZINE, or placebo. The dose of the m adjusted to achieve 70% or greater reduction of VPC and greater than 90% reduction in unsustained ver tachycardia. If the patient failed to achieve an adequate response or was unable to tolerate the drug, the discontinued and they were crossed over to a different antiarrhythmic class (class 1C to class 1A or clas ENCAINIDE (79%) and FLECAINIDE (83%) were superior to IMIPRAMINE (52%), MORICIZINE (66%), as first line-drugs. In patients failing IMIPRAMINE or MORICIZINE therapy, ENCAINIDE was 68% and F effective. It would appear that IMIPRAMINE is not the drug of choice for the prevention of VPC following myocardial infarction. In addition, changes in therapy secondary to the development or worsening of con failure occurred in 26% of the treatment groups compared to 18% in the placebo group (Greene et al, 19

2) IMIPRAMINE in doses of 50 to 400 milligrams/day (mean = 210 +/- 103 mg/day) and NORTRIPTYLIN to 150 mg/day (mean = 100 +/- 29 mg/day) were effective in the reduction of PVCs (Giardina et al, 1985a percent of the patients had a greater than 80% suppression of their PVCs. Neither drug significantly cha ejection fraction or peak systolic pressure end-systolic volume ratio. Both drugs produced a reduction in blood pressure.

3) Twenty-two patients with 30 or more ventricular premature complexes (PVCs) per hour were treated IMIPRAMINE 1 milligrams/kilogram/day (in two divided doses), increasing by 1 mg/kg/day every other da suppressed by at least 80% (or until adverse effects were observed or a daily dose of 5 mg/kg/day was a Eighteen patients (82%) exhibited antiarrhythmic effects from IMIPRAMINE therapy. All patients treated psychological depression. The elimination half-life was approximately 8 hours, however, duration of actio much longer and antiarrhythmic effects were observed over at least a 12 hour period, which suggests tha IMIPRAMINE may contribute to the duration of antiarrhythmic efficacy (Giardina & Bigger, 1982).

4) In patients with premature ventricular contractions, IMIPRAMINE was noted to suppress arrhythmias 90% in 10 of 11 patients. IMIPRAMINE shortens action potential duration and decreases conduction velo velocity and therefore is classified as a class 1 antiarrhythmic drug. Since the half-life of IMIPRAMINE is to 18 hours) it may be dosed on a twice daily regimen. Antiarrhythmic doses appear to be similar to antic (3.5 mg/kg/day). The antiarrhythmic activity of IMIPRAMINE is partially attributed to its metabolites, desm and 2-hydroxyimipramine. Due to complications, IMIPRAMINE should not be used in patients with pre-ex defects (Thase & Perel, 1982).

4.5.B.7 Depression

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes; Pediatric, no
Efficacy: Adult, Effective; Pediatric, Evidence is inconclusive
Recommendation: Adult, Class IIb; Pediatric, Class IIb

Strength of Evidence: Adult, Category B; Pediatric, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:
Indicated for the relief of symptoms of depression (Prod Info TOFRANIL(R) tablets, 2005)
Endogenous depression may be more likely to respond to imipramine therapy than other depressive
TOFRANIL(R) tablets, 2005)

c) Adult:
1) Various depressive illnesses have responded to treatment with IMIPRAMINE in daily doses of 75 to 2
(Prod Info Tofranil(R), 1995b; Kocsis et al, 1989; Kocsis et al, 1988; Battistini et al, 1980a; Eilenberg, 19
1979a); (Lindberg et al, 1979)(Amin et al, 1978). Patients suffering from endogenous depression (Fabre
endogenous depression (Lindberg et al, 1979), depression of myotonic dystrophy (Brumback & Carlson,
depression (Finnerty et al, 1978a) alcoholic patients with primary depression (McGrath et al, 1996), and
patients with depressive disorders (Nunes et al, 1998) may benefit from IMIPRAMINE therapy. However
of IMIPRAMINE and a neuroleptic are effective in the treatment of delusional depression (Kaskey et al, 1
2) High dose tricyclic antidepressant therapy (IMIPRAMINE 150 to 200 milligrams/d, DESMETHYLIMIPI
500 mg/d) was effective in only a small portion of elderly patients with delusional depression. The dropou
to side effects was 58% and the overall success rate was only 25% (Brown et al, 1984).

d) Pediatric:
1) IMIPRAMINE is efficacious in the treatment of depression in children (Rancurello, 1985a; Petti & Con
general overview of the treatment of childhood behavioral and emotional disorders has been published (
1985a).
2) IMIPRAMINE therapy in adolescents with major depressive illness was less effective than in adults in
of 35 patients (Strober et al, 1990). Twenty-four females and 11 male depressed patients between 13 an
with a Hamilton Rating Scale for Depression scores of 16 or greater were enrolled in the study. Followinç
period, patients received IMIPRAMINE 5 milligrams/kilogram/day (up to a maximum of 300 mg) for 6 wee
adolescents completed the trial. The average daily dose was 222 mg/day. Overall efficacy was low, with
with delusional subtypes responding more poorly than the nondelusional patients. Eight of the 24 nondel
displayed delayed onset of response, followed by sustained improvement. Only one delusional patient d
clinical improvement. Steady state plasma levels did not vary between responders and nonresponders. T
study suggest that imipramine may be less efficacious in the treatment of major depression in adolescen
as has previously been suggested for other tricyclic antidepressants, and raises questions about age diff
neurotransmitter and neuroregulatory system responses to specific antidepressant agents.
3) Twenty-one children (ages 5.8 to 10.25 years) with various types of depression were treated with IMI
67% of the children showing some improvement (Conners & Petti, 1983). The dose of IMIPRAMINE was
at bedtime and slowly increased over a period of 7 to 14 days to a maximum dosage of 5 milligrams/kilog
mg/day (one older child was treated with 225 mg/d (4.9 mg/kg/day). Seven (33%) of the children experie
worsening or no significant change in any of the areas monitored. In fact, 2 children showed a significant
and hostility during the IMIPRAMINE therapy.
4) Imipramine was efficacious in the treatment of 20 prepubertal children hospitalized for major depressi
III) with imipramine (Preskorn et al, 1982). IMIPRAMINE therapy consisted of 75 milligrams/day, adminis
for the first 3 weeks and increased to a maximum of 5 milligrams/kilogram if no response. Serum IMIPRA
DESIPRAMINE levels were drawn during each phase of the study. During phase I, none of the 15 childre
tricyclic antidepressant (TCA) plasma concentration outside the 125 to 225 ng/mL range showed a remis
improvement in their condition. Eighty percent of those children with serum levels between 125 to 225 ng
a remission. During phase II, 12 of the 16 children achieved steady-state total TCA plasma concentration
ng/mL and 11 (92%) of them had experienced a remission by the end of the treatment period. Based on
be concluded that IMIPRAMINE is effective in the treatment of depression in prepubertal children and its
concentration-dependent.

4.5.B.8 Diabetic neuropathy

a) Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:
Effective for diabetic neuropathy in selected patients

c) Adult:
1) In most patients, an imipramine plasma drug concentration of 400 to 500 nmol/L was sufficient to ach
in the treatment of diabetic neuropathy (Sindrup et al, 1990a). All patients were diabetic and had one or
(pain, paresthesia, dysesthesia, and hypesthesia) and signs (reduction of sensibility, strength, or tendon
peripheral neuropathy. One patient demonstrated no significant improvement even with IMIPRAMINE plu
levels below 400 nmol/L. In the other eleven patients doses of 125 to 350 milligrams/day were required t
levels to about 400 mmol/L. One patient required a blood level of 730 mmol/L to achieve maximal relief.
2) A double-blind, cross-over comparison of IMIPRAMINE with placebo was conducted in nine patients
peripheral diabetic neuropathy (Sindrup et al, 1989). The dose of IMIPRAMINE was adjusted to achieve
IMIPRAMINE plus DESIPRAMINE level of 300 to 750 nmol (125 to 225 milligrams/day) during the first w

treatment period was three weeks and no washout phase was used between treatment periods. Efficacy
the end of each treatment period based on symptoms and measurement of peripheral and autonomic ne
IMIPRAMINE provided significant beneficial symptomatic improvement in all patients, but not beneficial c
peripheral or autonomic nerve function.
3) IMIPRAMINE in doses of 50 milligrams (mg) daily for one week, then 100 mg daily for 4 weeks, was e
producing improvement in 7 of 12 patients with severe diabetic neuropathy of the lower extremities in a c
over study (Kvinesdal et al, 1984). IMIPRAMINE had beneficial effects on pain, paresthesia, dysesthesia
nocturnal aggravation.

4.5.B.9 Disorder of ejaculation

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class III
Strength of Evidence: Adult, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

In case reports, imipramine has been effective in treating ejaculatory disorders

c) Adult:

1) IMIPRAMINE 25 milligrams three times/day corrected RETROGRADE EJACULATION of 18 months
duration in 2 adult diabetics. One patient had normal gonadotropin levels; the other had low plasma testo
testosterone therapy did not correct retrograde ejaculation (Brooks et al, 1980).
2) A 29-year-old male with ASPERMIA of 4 years duration secondary to lymphadenectomy noted ejacul
volume and consistency 1 day after beginning IMIPRAMINE 50 milligrams daily for depression. Motile sp
seen on microscopic examination and sperm count was 115,600,000/mm(3). Aspermia returned within 2
discontinuing IMIPRAMINE therapy. These results recurred on 3 separate occasions (Kelly & Needle, 19

4.5.B.10 Drug dependence

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Has little effect in the treatment of drug addiction
Does improve mood in drug-addicted patients with depressive disorders

c) Adult:

1) Treatment of depressed METHADONE-MAINTENANCE OPIATE ADDICTS with IMIPRAMINE or a p
similar subjective results in one study (Kleber et al, 1983). At the end of 8 weeks of therapy both groups
reduction in depressive symptoms. However, a 12-week, double-blind trial that excluded initial placebo r
pre-randomization period found significantly improved depression rating scores after treatment with imipr
compared to placebo (n=42) (p less than 0.001). Imipramine doses were titrated based on response to a
of 268 milligrams daily (Nunes et al, 1998).
2) Imipramine had little effect in the treatment of COCAINE DEPENDENCE and METHAMPHETAMINE
patients (151 cocaine dependent and 32 methamphetamine dependent) seen at the Haight-Ashbury Fre
et al, 1994). Patients were randomly assigned to treatment with imipramine 10 or 150 milligrams/day for
this double-blind study. In addition, all subjects were given intensive drug abuse counseling during the co
treatment. Efficacy was based on negative urine samples, self reporting of abstinence, craving, and Bec
inventory. The longest retention in the program occurred with the group receiving the higher imipramine
retention 34 days vs 17 days). No differences in craving or depressive symptoms were observed and the
scores in both groups decreased after the start of therapy. Positive urine analyses were less in the high
group (5% vs 14%) at 14 days, but were no different at 28 or 90 days. Based on these results it appears
of limited value in the treatment of cocaine or methamphetamine dependent patients who do not have a
disorder.

4.5.B.11 Gardner-Diamond syndrome

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Effective only for short-term therapy of autoerythrocyte sensitization

c) Adult:

1) A 20-year-old female with autoerythrocyte sensitization and depression was treated with IMIPRAMIN
1983). One week later the bleeding resolved and after 2 weeks the depression began to resolve. In 3 to

symptoms had resolved. Six weeks later, while still receiving therapeutic doses of IMIPRAMINE, the dep
recurred and 10 days later bleeding restarted. Compared to previous episodes the severity of depressior
less severe. The bleeding resolved in 10 days and the depressive symptoms were gone within 6 weeks.
subsequent relapse in therapy the IMIPRAMINE was discontinued and AMITRIPTYLINE therapy (300 m
Since the start of AMITRIPTYLINE therapy the patient has been free of depression and bleeding for 10 r

4.5.B.12 Globus hystericus

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Efficacy demonstrated in case reports only

c) Adult:

1) Globus hystericus syndrome is a condition in which the individual develops a fear that he/she is interr
and unable to breathe. If the condition is left untreated the patient may become profoundly disabled or m
threatening weight loss. Case reports of three patients have shown that psychoactive drugs may be effe
this condition. IMIPRAMINE therapy was effective in the treatment of one case, PHENELZINE in anothe
TRANYLCYPROMINE in the other case (Brown et al, 1986). Two additional cases of successful imipram
globus hystericus syndrome were reported (Kaplan, 1987; Rosenthal, 1987).

4.5.B.13 Mood swings

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Possibly effective for PATHOLOGICAL CRYING/LAUGHING

c) Adult:

1) Heightened tendency for crying or laughing in frequency and inappropriate circumstances (pathologic
laughing) and emotional lability unrelated to depression can occur in individuals with brain damage (eg, s
Small doses of IMIPRAMINE (30 to 60 milligrams) may partially or completely control the emotionalism v
(Allman, 1992).

4.5.B.14 Nocturnal enuresis

FDA Labeled Indication

a) Overview

FDA Approval: Adult, no; Pediatric, yes (6 years and older)
Efficacy: Pediatric, Effective
Recommendation: Pediatric, Class IIa
Strength of Evidence: Pediatric, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Indicated as temporary adjunctive therapy for the reduction of enuresis in children 6 years and older
TOFRANIL(R) tablets, 2005)

c) Pediatric:

1) Numerous double-blind, crossover, placebo-controlled studies have demonstrated IMIPRAMINE's eff
adjunct treatment of enuresis in pediatric patients. Most studies report the use of doses ranging from 10
administered at bedtime although doses as high as 100 mg have been utilized. The application of pharm
Bayesian methods) may improve the individualization of IMIPRAMINE dosing in the treatment of enuresi
1994a; Tamayo et al, 1992; Fernandez de Gatta et al, 1989). Most studies report only minor side effects
mouth, constipation, irritability, anorexia, and sleep disturbances (Prod Info Tofranil(R), 1995b; Fernande
1990; Fournier et al, 1987; Wagner et al, 1982; Jorgenson et al, 1980; Rapoport et al, 1980b; Lake et al,
et al, 1974; Maxwell & Seldrup, 1971; Alderton, 1970).

2) Follow-up of 29 young adults, 10 years after IMIPRAMINE therapy for enuresis, suggests that no psy
results from this therapy; these patients showed no psychological decompensation, inhibition of learning
to drug abuse (Bindelglas & Dee, 1978).

4.5.B.15 Obsessive-compulsive disorder

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class III
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Questionable efficacy in the treatment of obsessive-compulsive disorder

c) Adult:

1) Imipramine was ineffective in treating obsessive- compulsive disorder (OCD) in a double-blind, placel study that evaluated the efficacy of IMIPRAMINE in the treatment of depression and obsessive-compulsi patients (Foa et al, 1987). Nineteen (10 women and 9 men) were treated with IMIPRAMINE and 18 (9 w were treated with a placebo. Each placebo patient received 10 tablets per day. The IMIPRAMINE group increased by 25 mg every other day until clinical response, side effects, or a maximum daily dose of 250 daily IMIPRAMINE dose was 233 mg (150 to 250 mg). At the end of 6 weeks the IMIPRAMINE was effec symptoms associated with depression, but had little to no effect on their obsessive-compulsive symptom

2) Four patients with obsessive-compulsive bowel obsessions were treated with IMIPRAMINE (3) or DO patients were free of their bowel obsession within 30 days (10, 14, 14, 30) of starting drug therapy (Jenik

4.5.B.16 Pain

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Pain has occasionally resolved with imipramine therapy

c) Adult:

1) Patients with chest pain, but normal coronary angiograms, may respond to imipramine therapy (Cann The dose of medications used in the study were imipramine 50 milligrams at night and placebo in the mo 0.1 milligrams twice daily, and placebo twice daily. The incidence of chest pain was decreased by 52 +/- with 1 +/- 86% with placebo and 39 +/- 51% with clonidine therapy (data is presented as means +/- SD). associated with imipramine use was statistically significant (p=0.03). A follow-up evaluation of these pati average of 21 months, indicated that none of the patients had been seen in an emergency room or had b because of chest pain. Seventeen patients have had the imipramine therapy discontinued and 16 asked imipramine therapy because of recurrent chest pain symptoms (Cannon, 1994b). The mechanism of this unknown, but may be a result of a visceral analgesic effect and not dependent on cardiac, esophageal, c characteristics or gender. Another possible mechanism for this effect may be an increased pain threshol reduction in psychological depression (Hare, 1994).

2) A survey of Italian oncology centers revealed that 43% of their patients were given antidepressants. T frequently utilized drugs were AMITRIPTYLINE, CLOMIPRAMINE, IMIPRAMINE, and TRAZODONE. Mo that the antidepressants were useful in controlling pain and were most efficacious in depressed patients 1987).

3) A case report of a 26-year-old graduate student being treated with IMIPRAMINE for suicidal thoughts esteem noted an improvement in her chronic pelvic pain (induced by endometriosis four years earlier) wl IMIPRAMINE therapy (Beresin, 1986).

4.5.B.17 Panic disorder

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Similar in efficacy to alprazolam

c) Adult:

1) GENERAL INFORMATION

a) The clinical response to IMIPRAMINE in the treatment of panic disorder is independent of the pre depression or dysphoria (Deltito et al, 1991). Patients with high baseline depression scores have ter poorest outcomes (Rosenberg et al, 1991aa; Rosenberg et al, 1991c; Zitrin, 1983; Nurnberg & Cocc Maintenance with half-dose IMIPRAMINE therapy may be useful in providing patients with a protecti relapses (Mavissakalian & Perel, 1992a; Mavissakalian & Perel, 1992b). The use of IMIPRAMINE in panic disorder may not be as safe as other anxiolytics in patients with cardiovascular disease (Roth

2) Combination imipramine and cognitive-behavioral therapy (CBT) was of limited value initially but prov during maintenance therapy in patients with panic disorder. Patients with panic disorder randomly receiv (n=77), imipramine alone (n=83), placebo alone (n=24), CBT with imipramine (n=65), or CBT alone (n=6 acute treatment phase. Thereafter, responders entered a 6-month maintenance phase. Patient response following the 12- week acute treatment phase, the 6-month maintenance phase, and 6-months after ther discontinuation; assessment tools included the Panic Disorder Severity Scale (PDSS) and the Clinical G Scale (CGI). Initial imipramine doses were 10 milligrams (mg)/day slowly increased over 5 weeks to 200 increased to 300 mg if symptoms continued. Following acute treatment, responses for the PDSS were 4

alone, 45.8% for imipramine alone, 21.7% for placebo alone, 60.3% for CBT with imipramine, and 57.1% placebo. Both CBT alone and imipramine alone were significantly better than placebo (p=0.03 and p=0.0 however, combination therapy provided no greater response rate over each treatment alone (p not signif during the acute phase, none of the therapies were significantly better than the others. Following mainter responses on the PDSS were 39.5% for CBT alone, 37.8% for imipramine alone, 13% for placebo alone, with imipramine, and 46.8% for CBT plus placebo. Responses on both the PDSS and the CGI were sign imipramine versus placebo (p=0.02 for both) and CBT versus placebo (p=0.02, p=0.01, respectively). Us combination therapy was significantly better than either CBT alone (p=0.04) and better than imipramine a the CGI, combination therapy was only significantly better than imipramine alone (p=0.03) and not better not significant). Following treatment discontinuation after the 6-month maintenance phase, the only statis was the PDSS scores in the CBT group compared to the placebo group (p=0.05) (Barlow et al, 2000).

3) Maintenance treatment with imipramine had a significant protective effect against relapse in patients and agoraphobia. Patients who had shown an initial good and stable response to imipramine therapy ov randomly received same-dose imipramine continuation (n=29) or placebo discontinuation (n=27). Patient initial imipramine at a target dose of 2.25 milligrams/kilogram or discontinued their imipramine by decrea 25% each week (substituted with placebo). During this study, no patient received behavioral or cognitive a crisis-type intervention was needed. During the study, if relapse was confirmed the patient exited the s defined as a worsening of their condition (measured as a 33% decline in the End- State Function scale s accompanied by insistent requests for therapeutic action. After 12 months, the study population consiste the imipramine group and 10 patients in the placebo group. This resulted in a 92.5% lower hazard rate o imipramine as compared to placebo (Mavissakalian & Perel, 1999).

4) In a double-blind study, an 8-month therapy period for panic disorder with either alprazolam or imipra (Rickels & Schweizer, 1998). Patients received alprazolam (n=37), imipramine (n=34), or placebo (n=35) period of short-term treatment, a 6-month maintenance period, and then a 15-month follow-up period. Pa alprazolam began at 1 milligram (mg) daily and were titrated up to 10 mg. Those receiving imipramine be were increased to 250 mg. Alprazolam patients had notable reductions in panic attacks during the first 2 while imipramine patients showed improvement over placebo patients after 3 to 4 weeks. Drop-out rates were 11% in the alprazolam group, 41% in the imipramine group, and 57% in the placebo group (p less t alprazolam versus the other groups). In the remaining patients it was noted that tolerance developed to a during the maintenance phase. After the 6-month maintenance phase, doses were titrated off over 3 wee 62% of the alprazolam and 26% of the imipramine groups were panic-free (p less than 0.01). During the patients could be treated with non-study medications. Regardless of medication, patients who completed treatment were more likely to be panic-free than those who had dropped out, even if they received non-s (85% versus 55%, p less than 0.01). Remission rates were higher in younger patients, those with a histo or intense panic attacks, those with a lower initial phobia score, and those with an initial lower score of in self-confidence, and passivity (Minnesota Multiphasic Personality Inventory Dependency Scale).

5) A comparison of cognitive therapy, applied relaxation, and imipramine found that at 3 months cognitiv superior to both applied relaxation and imipramine therapy (Clark et al, 1994). At 6 months the cognitive imipramine treatment produced similar results and were better than applied relaxation. However, betwee months of therapy, several of the imipramine patients relapsed while the patients treated with cognitive th to do better than with imipramine and relaxation therapy.

4.5.B.18 Posttraumatic stress disorder

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Resulted in improvement in positive symptoms of post-traumatic stress disorder

c) Adult:

1) Imipramine treatment resulted in improvement in positive symptoms of post-traumatic stress disorder patients (Burstein, 1984). Therapy was initiated at a low dose and increased over the following 7 days to tolerable dose (mean 260 milligrams/day; range 50 to 350 mg/d). After 2 to 3 weeks of therapy, there wa decrease in the severity of forced recollection, sleep and dream disturbances, and a cessation or reducti Most avoidance items, eg, staying away from reminders of the event, trying not to talk about the event, a remove it from their memory, did not decrease significantly in severity. Based on these results it would a IMIPRAMINE, in combination with psychotherapy, may be an effective treatment for patients.

2) Treatment of 3 patients with acute post-traumatic stress disorder (PTSD) with either DOXEPIN or IMI in an improvement in PTSD symptoms (Blake, 1986). Whether or not tricyclic antidepressant therapy is s equivalent, or inferior to psychotherapy or other means of treatment remains to be determined.

4.5.B.19 Schizophrenia; Adjunct

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive; Pediatric, Evidence is inconclusive
Recommendation: Adult, Class IIb; Pediatric, Class III

Strength of Evidence: Adult, Category B; Pediatric, Category C
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:
May be effective as adjunct therapy in depressed schizophrenic patients
Ineffective for schizophrenia itself

c) Adult:
1) Schizophrenic or schizoaffective patients with POSTPSYCHOTIC DEPRESSION may benefit from th IMIPRAMINE to their neuroleptic therapy. Favorable results were observed in 27 patients previously trea FLUPHENAZINE DECANOATE and BENZTROPINE after the addition of IMIPRAMINE to their drug regi beneficial effects continued in those patients with postpsychotic depression that initially responded to the IMIPRAMINE to their regimen and were monitored for an additional six months on the triple drug regimer patients that did not complete the six-month observation period were discontinued for administrative reas a relapse in either psychosis or depression (Siris et al, 1992). A one-year follow-up study documented th maintaining imipramine therapy in the treatment of postpsychotic depression (Siris et al, 1994).
2) A preliminary study indicates that imipramine may be an effective adjunctive agent in the acute treatn abusing dysphoric schizophrenic or schizoaffective patients (Siris et al, 1993). The importance of these r proven.

d) Pediatric:
1) A pilot study in 10 autistic and schizophrenic children age 2 to 6 years found IMIPRAMINE therapy to (Campbell et al, 1971). The drug did decrease affective blunting, anergy, and withdrawal and stimulated in several children, but increased psychotic speech, behavioral disorganization, and excitation in other cl

4.5.B.20 Separation anxiety disorder of childhood

a) Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Pediatric, Evidence is inconclusive
Recommendation: Pediatric, Class III
Strength of Evidence: Pediatric, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:
Routine use of tricyclic antidepressants is not recommended for separation anxiety in children
Behavioral therapy may be just as effective as imipramine

c) Pediatric:
1) The combination of imipramine and nonpharmacologic therapies (eg, parent management training, be and family therapy) may improve subjective comfort, reduce anxiety and somatic symptoms in 70% of th experiencing separation-anxiety disorder (Rancurello, 1985a). This disorder is associated with a high rat recovery, therefore the routine use of tricyclic antidepressants is not recommended (Rancurello, 1985a).
2) Both IMIPRAMINE and placebo therapy were equally effective for separation anxiety. A small, double placebo-controlled study was conducted with 21 children with separation anxiety disorder (Klein et al, 19 children were first given a month of vigorous behavioral treatment, then randomly assigned to IMIPRAMI therapy for six weeks. Both treatments were approximately 50% effective.

4.5.B.21 Sexual disorder

a) Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category C
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:
Effective in case reports only

c) Adult:
1) IMIPRAMINE may be useful, alone or in combination with LITHIUM, in the treatment of men with PAF NONPARAPHILIC SEXUAL ADDICTIONS (Kafka, 1991). Two patients with sexual disorders improved f IMIPRAMINE therapy. Whether IMIPRAMINE and other antidepressants are useful in the treatment of al paraphilias or nonparaphilic sexual addictions or just specific types remains to be determined.

4.5.B.22 Sleep disorder

a) Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:
Used successfully in the treatment of NIGHT TERRORS, SOMNABULISM, NARCOLEPSY, and CATAP

c) Adult:
1) IMIPRAMINE therapy (50 to 100 milligrams at bedtime) resulted in a dramatic reduction in frequency

night terrors in 2 patients unresponsive to DIAZEPAM therapy (Cooper, 1987).
2) IMIPRAMINE therapy resulted in a significant reduction (242 +/- 156 to 142.8 +/- 120.1) in the total nu episodes in 41.9% of the patients tested (Rubin et al, 1986). Based on these results it appears that IMIPI may be an alternative form of therapy for some nonoverweight patients with negative ear, nose and throa and for some patients who had not responded to weight reduction or ENT surgery.
3) A 62-year-old female had suppression of night terrors with IMIPRAMINE 50 milligrams at bedtime; 75 completely suppressed night terrors but caused daytime drowsiness (Beitman & Carlin, 1979).

4.5.B.23 Social phobia

a) Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class III
Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:
No studies currently support the use of imipramine for social phobia

c) Adult:
1) Imipramine was not useful in the treatment of social phobia in an 8-week, open-trial of 15 patients (Si 1998). Imipramine was started at 50 milligrams (mg) for 3 nights and increased at weekly intervals to a m 300 mg by the fourth week. Only 9 patients were able to complete the study as the others dropped out di effects. Only 2 patients responded to imipramine therapy as determined by the Liebowitz Social Anxiety Liebowitz Social Phobia Disorders Scale-Overall Severity. They were also unable to continue further ther developed urinary hesitancy and the other became hypomanic.

4.5.B.24 Trichotillomania

a) Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Pediatric, Evidence is inconclusive
Recommendation: Pediatric, Class IIb
Strength of Evidence: Pediatric, Category C
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:
Used successfully in a case of trichotillomania and depression in a pediatric patient (Weller et al, 1989).

4.5.B.25 Urinary incontinence

a) Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy; Pediatric, Evidence is inconclusive
Recommendation: Adult, Class IIb; Pediatric, Class IIb
Strength of Evidence: Adult, Category B; Pediatric, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:
Used alone or in combination with other anticholinergic medications, can improve urinary continence
May not be better than bladder training in some patients
May help to achieve continence in children with myelodysplasia alone or in combination with oxybut

c) Adult:
1) Imipramine was useful for genuine stress continence. In a prospective study, women with genuine str received imipramine 25 milligrams 3 times daily for 3 months. A urodynamic assessment was done with test to determine the amount of urine leakage. A cure was defined as a pad weight that resulted in 0 gra After 3 months, 35% of women were cured, 25% showed an improved pad weight result of 50% or bette therapy. The women that were cured or improved had a higher urethral closure pressure than those that 0.001). The authors note that a high pre-treatment urethral closure pressure may serve as a predictor fo success (Lin et al, 1999).
2) IMIPRAMINE 75 milligrams orally daily for four weeks was reported effective in the treatment of fema INCONTINENCE in 21 of 30 women (71%). The drug was reported to extend the functional urethral leng independent of stress factors in women who are continent after therapy. These data support that a short result in urinary incontinence and lengthening of the urethra by IMIPRAMINE treatment or vesicopexy wi dysfunction (Gilja et al, 1984).
3) Bladder drill is more effective than drug therapy in the treatment of incontinence due to idiopathic det women. Fifty women with urinary incontinence due to DETRUSOR INSTABILITY were randomly assigne patient bladder drill training or out-patient drug therapy (FLAVOXATE HYDROCHLORIDE 200 mg three IMIPRAMINE 25 milligrams three times/day) for 4 weeks (Jarvis, 1981). At the completion of the study 8 patients treated with bladder drill were continent and 76% were symptom free. Fifty-six percent (14/25) o with medication were continent and 48% were symptom-free. Side effects occurred in 56% of the patient therapy and 5 patients discontinued drug therapy on their own secondary to side effects.
4) Six of 10 elderly patients (x=80 year old, 63 to 88 years) with urinary incontinence associated with sp unstable detrusor contractions were successfully treated with IMIPRAMINE. The dose of IMIPRAMINE w

mg at bedtime and increased every third day by 25 mg, until the patient was continent, experienced side reached 150 mg/day. At the completion of the study 60% of the patients were continent. No correlation b plasma concentrations of desmethylimipramine and clinical or urodynamic effects could be found (Castle

d) Pediatric:

1) Children and adolescents with myelodysplasia and incontinence (i.e. wet between their clean intermit times performed 3 to 5 times daily) benefited from imipramine therapy. Children (n=19, 4- to 12-years-old imipramine 10 milligrams (mg) daily increased to a maximum of 20 mg twice daily. Combination therapy was used in 10 patients. Eight of the children had also failed therapy with oxybutynin, flavoxate, or ephed imipramine, 15 children developed at least partial continence (dry 50% to 80% of the time) with 9 achievi continence (dry at least 80% of the time). The authors suggest low-dose imipramine alone or in combina oxybutynin for children with myelodysplasia to help achieve continence (Hurley et al, 2000).

4.5.C Imipramine Pamoate

Agoraphobia

Anorexia nervosa

Bulimia nervosa

Cardiac dysrhythmia

Depression

Diabetic neuropathy

Gardner-Diamond syndrome

Globus hystericus

Obsessive-compulsive disorder

Pain

Panic disorder

Posttraumatic stress disorder

Separation anxiety disorder of childhood

Sexual disorder

Sleep disorder

Trichotillomania

4.5.C.1 Agoraphobia

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Effective in the treatment of agoraphobia (Deltito et al, 1991)
Efficacy appears to be dose-related and usually requires doses of 150 milligrams or greater per day

c) Adult:

1) Imipramine and placebo were equally effective in the treatment of agoraphobia in a double-blind clinic drug therapy with brief psychological treatment (Cohen et al, 1984a). The drugs were started 2 weeks pr

of the psychological therapy. At week 6 the mean dose of IMIPRAMINE was 124 milligrams and at week
mg/day. During week 2 to week 12 each treatment group received 6 fortnightly sessions of therapist-aide
addition each patient was given a leaflet describing the nature of agoraphobia and ways to cope with it. A
requested to complete systematic self-exposure homework and record these activities in a diary. Drug th
gradually withdrawn over weeks 26 to 28 of therapy. At the 2-year follow-up only 40 subjects were availa
had dropped out of the study (2 refused follow-up, 1 died, 1 moved out of the country, and 1 was untrace
of the patients remained improved with regards to their phobias. There was no significant difference betv
patients treated with imipramine or placebo therapy. Nor was there a superior effect of therapist-aided ex
therapist-aided relaxation.
2) The plasma IMIPRAMINE levels, but not DESIPRAMINE, correlated with the improvement in agoraph
(Mavissakalian et al, 1984), which may indicate that the antiphobic effects of IMIPRAMINE therapy are m
post-synaptic serotonergic neurotransmitter system and not the noradrenergic system.
3) IMIPRAMINE therapy plus programmed in vivo exposure practice was superior to IMIPRAMINE thera
(Mavissakalian & Michelson, 1986; Mavissakalian et al, 1983).

4.5.C.2 Anorexia nervosa

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class III
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Has resulted in some improvement in patients with anorexia nervosa

c) Adult:

1) Imipramine treatment resulted in some improvement in 7 patients with anorexia nervosa treated seria
antidepressants (tricyclics, MAOIs, and triazolopyridines) including imipramine. Three of the patients rec
imipramine; the treatment trials ranged from 6 to 14 weeks. Four of the patients had some improvement
symptoms, 2 experienced some weight gain, and 3 of 3 who had bulimic symptoms reported improveme
anorexic symptoms (3 to 6 weeks) was slower than the improvement observed in depression and anxiety
following tricyclic therapy (Hudson et al, 1985). Significant weight gain generally began after 2 to 3 montl
with IMIPRAMINE tended to tolerate the drug poorly and appeared to have an extraordinary sensitivity to
anticholinergic side effects when compared to patients treated with trazodone or MAOIs (Hudson et al, 1
extraordinary sensitivity to the drug's side effects may be associated with their low body weight.

4.5.C.3 Bulimia nervosa

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Approximately 75% of patients show at least a moderate response (reduction of binge eating by 50%
antidepressant therapy
Monoamine oxidase inhibitors also appear effective in bulimia, and may be superior to tricyclic antid
et al, 1983)

c) Adult:

1) Twenty bulimic subjects were followed for a period of up to 2 years to assess the long term efficacy o
therapy (Pope et al, 1985). At the end of the follow-up period, 95% had at least partial improvement and
experienced a complete remission. Over the course of the study period 85% had either maintained or im
quality of their initial response. The one patient that failed to respond discontinued her medication and pr
her original frequency of binge eating.
2) A retrospective study of 22 patients with bulimia treated with antidepressants (AMITRIPTYLINE, IMIP
DESIPRAMINE, DOXEPIN, TRAZODONE, TRANYLCYPROMINE, or PHENELZINE) showed a decreas
bingeing and/or an improvement in depression (Brotman et al, 1984). During a 3-month follow-up period
relapsed despite continuation of their antidepressant therapy, while others continued to benefit from drug

4.5.C.4 Cardiac dysrhythmia

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class III
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Some patients with ventricular tachycardia or premature ventricular contractions may benefit from imipra

c) Adult:

1) IMIPRAMINE was included in a double-blinded crossover pilot study to evaluate the efficacy of ventri complex (VPC) suppression after acute myocardial infarction as a means to improve survival (Anon, 198 was assigned to ENCAINIDE, FLECAINIDE, IMIPRAMINE, MORICIZINE, or placebo. The dose of the m adjusted to achieve 70% or greater reduction of VPC and greater than 90% reduction in unsustained ver tachycardia. If the patient failed to achieve an adequate response or was unable to tolerate the drug, the discontinued and they were crossed over to a different antiarrhythmic class (class 1C to class 1A or clas ENCAINIDE (79%) and FLECAINIDE (83%) were superior to IMIPRAMINE (52%), MORICIZINE (66%), as first line-drugs. In patients failing IMIPRAMINE or MORICIZINE therapy, ENCAINIDE was 68% and F effective. It would appear that IMIPRAMINE is not the drug of choice for the prevention of VPC following myocardial infarction. In addition, changes in therapy secondary to the development or worsening of con failure occurred in 26% of the treatment groups compared to 18% in the placebo group (Greene et al, 19

2) IMIPRAMINE in doses of 50 to 400 milligrams/day (mean = 210 +/- 103 mg/day) and NORTRIPTYLIN to 150 mg/day (mean = 100 +/- 29 mg/day) were effective in the reduction of PVCs (Giardina et al, 1985a percent of the patients had a greater than 80% suppression of their PVCs. Neither drug significantly cha ejection fraction or peak systolic pressure end-systolic volume ratio. Both drugs produced a reduction in blood pressure.

3) Twenty-two patients with 30 or more ventricular premature complexes (PVCs) per hour were treated IMIPRAMINE 1 milligrams/kilogram/day (in two divided doses), increasing by 1 mg/kg/day every other da suppressed by at least 80% (or until adverse effects were observed or a daily dose of 5 mg/kg/day was a Eighteen patients (82%) exhibited antiarrhythmic effects from IMIPRAMINE therapy. All patients treated psychological depression. The elimination half-life was approximately 8 hours, however, duration of actio much longer and antiarrhythmic effects were observed over at least a 12 hour period, which suggests tha IMIPRAMINE may contribute to the duration of antiarrhythmic efficacy (Giardina & Bigger, 1982).

4) In patients with premature ventricular contractions, IMIPRAMINE was noted to suppress arrhythmias 90% in 10 of 11 patients. IMIPRAMINE shortens action potential duration and decreases conduction velo velocity and therefore is classified as a class 1 antiarrhythmic drug. Since the half-life of IMIPRAMINE is to 18 hours) it may be dosed on a twice daily regimen. Antiarrhythmic doses appear to be similar to antic (3.5 mg/kg/day). The antiarrhythmic activity of IMIPRAMINE is partially attributed to its metabolites, desm and 2-hydroxyimipramine. Due to complications, IMIPRAMINE should not be used in patients with pre-ex defects (Thase & Perel, 1982).

4.5.C.5 Depression

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes; Pediatric, no
Efficacy: Adult, Effective; Pediatric, Evidence is inconclusive
Recommendation: Adult, Class IIb; Pediatric, Class IIb
Strength of Evidence: Adult, Category B; Pediatric, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Indicated for the relief of symptoms of depression (Prod Info TOFRANIL-PM(R) capsules, 2005)
Endogenous depression may be more likely to respond to imipramine therapy than other depressive TOFRANIL-PM(R) capsules, 2005)

c) Adult:

1) Intramuscular S-adenosyl-L-methionine 1,4-butanedisulphonate (SAMe) was found to be as efficacio imipramine (IMI) for the treatment of depression. In a randomized, double-blind, comparative trial, patien of major depressive episode according to DSM-IV criteria received SAMe 400 milligrams (mg) by intramu once daily (n=146) or oral IMI 150 mg per day in 3 divided doses. Blinding was maintained by a double d IMI dose was titrated over the first week to reach the full dose by day 8. Both treatments were given for 4 preestablished criteria (final score on the Hamilton Depression Rating Scale (HAMD), difference betwee HAMD scores, percentage of responders defined as those with a Clinical Global Impression (CGI) endpo less, and percentage of responders defined as those with a drop of at least 50% from baseline in HAMD treatments were equivalent. By the CGI criterion, 68% of patients in the SAMe group and 66% in the IMI responders; by the HAMD criterion, 59% of the SAME group and 50% of the IMI were responders. Drug reactions occurred in significantly fewer subjects of the SAMe group than of the IMI group: 9.5% vs 33% relevant differences were observed in laboratory measures, vital signs, or ECG parameters (Pancheri et

2) Various depressive illnesses have responded to treatment with IMIPRAMINE in daily doses of 75 to 2 (Prod Info Tofranil(R), 1995b; Kocsis et al, 1989; Kocsis et al, 1988; Battistini et al, 1980a; Eilenberg, 19 1979a); (Lindberg et al, 1979)(Amin et al, 1978). Patients suffering from endogenous depression (Fabre endogenous depression (Lindberg et al, 1979), depression of myotonic dystrophy (Brumback & Carlson, depression (Finnerty et al, 1978a) alcoholic patients with primary depression (McGrath et al, 1996), and patients with depressive disorders (Nunes et al, 1998) may benefit from IMIPRAMINE therapy. However, of IMIPRAMINE and a neuroleptic are effective in the treatment of delusional depression (Kaskey et al, 1

3) High dose tricyclic antidepressant therapy (IMIPRAMINE 150 to 200 milligrams/d, DESMETHYLIMIPI 500 mg/d) was effective in only a small portion of elderly patients with delusional depression. The dropou to side effects was 58% and the overall success rate was only 25% (Brown et al, 1984).

d) Pediatric:

1) IMIPRAMINE is efficacious in the treatment of depression in children (Rancurello, 1985a; Petti & Con

general overview of the treatment of childhood behavioral and emotional disorders has been published (
1985a).
2) Twenty-one children (ages 5.8 to 10.25 years) with various types of depression were treated with IMI
67% of the children showing some improvement (Conners & Petti, 1983).
3) Imipramine was efficacious in the treatment of 20 prepubertal children hospitalized for major depressi
III) with imipramine (Preskorn et al, 1982). IMIPRAMINE therapy consisted of 75 milligrams/day, adminis
for the first 3 weeks and increased to a maximum of 5 milligrams/kilogram if no response. Serum IMIPRA
DESIPRAMINE levels were drawn during each phase of the study. During phase I, none of the 15 childre
tricyclic antidepressant (TCA) plasma concentration outside the 125 to 225 ng/mL range showed a remis
improvement in their condition. Eighty percent of those children with serum levels between 125 to 225 ng
a remission. During phase II, 12 of the 16 children achieved steady-state total TCA plasma concentratior
ng/mL and 11 (92%) of them had experienced a remission by the end of the treatment period. Based on
be concluded that IMIPRAMINE is effective in the treatment of depression in prepubertal children and its
concentration-dependent.

4.5.C.6 Diabetic neuropathy

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Effective for diabetic neuropathy in selected patients

c) Adult:

1) In most patients, an imipramine plasma drug concentration of 400 to 500 nmol/L was sufficient to ach
in the treatment of diabetic neuropathy (Sindrup et al, 1990a). All patients were diabetic and had one or
(pain, paresthesia, dysesthesia, and hypesthesia) and signs (reduction of sensibility, strength, or tendon
peripheral neuropathy. One patient demonstrated no significant improvement even with IMIPRAMINE plu
levels below 400 nmol/L. In the other eleven patients doses of 125 to 350 milligrams/day were required t
levels to about 400 mmol/L. One patient required a blood level of 730 mmol/L to achieve maximal relief.
2) A double-blind, cross-over comparison of IMIPRAMINE with placebo was conducted in nine patients
peripheral diabetic neuropathy (Sindrup et al, 1989). The dose of IMIPRAMINE was adjusted to achieve
IMIPRAMINE plus DESIPRAMINE level of 300 to 750 nmol (125 to 225 milligrams/day) during the first w
treatment period was three weeks and no washout phase was used between treatment periods. Efficacy
the end of each treatment period based on symptoms and measurement of peripheral and autonomic ne
IMIPRAMINE provided significant beneficial symptomatic improvement in all patients, but not beneficial c
peripheral or autonomic nerve function.
3) IMIPRAMINE in doses of 50 milligrams (mg) daily for one week, then 100 mg daily for 4 weeks, was e
producing improvement in 7 of 12 patients with severe diabetic neuropathy of the lower extremities in a c
over study (Kvinesdal et al, 1984). IMIPRAMINE had beneficial effects on pain, paresthesia, dysesthesia
nocturnal aggravation.

4.5.C.7 Gardner-Diamond syndrome

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Effective only for short-term therapy of autoerythrocyte sensitization

c) Adult:

1) A 20-year-old female with autoerythrocyte sensitization and depression was treated with IMIPRAMINE
1983). One week later the bleeding resolved and after 2 weeks the depression began to resolve. In 3 to
symptoms had resolved. Six weeks later, while still receiving therapeutic doses of IMIPRAMINE, the dep
recurred and 10 days later bleeding restarted. Compared to previous episodes the severity of depressior
less severe. The bleeding resolved in 10 days and the depressive symptoms were gone within 6 weeks.
subsequent relapse in therapy the IMIPRAMINE was discontinued and AMITRIPTYLINE therapy (300 m
Since the start of AMITRIPTYLINE therapy the patient has been free of depression and bleeding for 10 r

4.5.C.8 Globus hystericus

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:
Efficacy demonstrated in case reports only

c) Adult:

1) Globus hystericus syndrome is a condition in which the individual develops a fear that he/she is interr and unable to breathe. If the condition is left untreated the patient may become profoundly disabled or m threatening weight loss. Case reports of three patients have shown that psychoactive drugs may be effec this condition. IMIPRAMINE therapy was effective in the treatment of one case, PHENELZINE in anothe TRANYLCYPROMINE in the other case (Brown et al, 1986). Two additional cases of successful imipram globus hystericus syndrome were reported (Kaplan, 1987; Rosenthal, 1987).

4.5.C.9 Obsessive-compulsive disorder

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class III
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:
Questionable efficacy in the treatment of obsessive-compulsive disorder

c) Adult:

1) Imipramine was ineffective in treating obsessive- compulsive disorder (OCD) in a double-blind, placel study that evaluated the efficacy of IMIPRAMINE in the treatment of depression and obsessive-compulsi patients (Foa et al, 1987). Nineteen (10 women and 9 men) were treated with IMIPRAMINE and 18 (9 w were treated with a placebo. Each placebo patient received 10 tablets per day. The IMIPRAMINE group increased by 25 mg every other day until clinical response, side effects, or a maximum daily dose of 250 daily IMIPRAMINE dose was 233 mg (150 to 250 mg). At the end of 6 weeks the IMIPRAMINE was effec symptoms associated with depression, but had little to no effect on their obsessive-compulsive symptom

2) Four patients with obsessive-compulsive bowel obsessions were treated with IMIPRAMINE (3) or DO patients were free of their bowel obsession within 30 days (10, 14, 14, 30) of starting drug therapy (Jenik

4.5.C.10 Pain

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:
Pain has occasionally resolved with imipramine therapy

c) Adult:

1) Patients with chest pain, but normal coronary angiograms, may respond to imipramine therapy (Cann The dose of medications used in the study were imipramine 50 milligrams at night and placebo in the mo 0.1 milligrams twice daily, and placebo twice daily. The incidence of chest pain was decreased by 52 +/- with 1 +/- 86% with placebo and 39 +/- 51% with clonidine therapy (data is presented as means +/- SD). associated with imipramine use was statistically significant (p=0.03). A follow-up evaluation of these pati average of 21 months, indicated that none of the patients had been seen in an emergency room or had b because of chest pain. Seventeen patients have had the imipramine therapy discontinued and 16 asked imipramine therapy because of recurrent chest pain symptoms (Cannon, 1994b). The mechanism of this unknown, but may be a result of a visceral analgesic effect and not dependent on cardiac, esophageal, c characteristics or gender. Another possible mechanism for this effect may be an increased pain threshol reduction in psychological depression (Hare, 1994).

2) A survey of Italian oncology centers revealed that 43% of their patients were given antidepressants. T frequently utilized drugs were AMITRIPTYLINE, CLOMIPRAMINE, IMIPRAMINE, and TRAZODONE. Mo that the antidepressants were useful in controlling pain and were most efficacious in depressed patients 1987).

3) A case report of a 26-year-old graduate student being treated with IMIPRAMINE for suicidal thoughts esteem noted an improvement in her chronic pelvic pain (induced by endometriosis four years earlier) wh IMIPRAMINE therapy (Beresin, 1986).

4.5.C.11 Panic disorder

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:
Similar in efficacy to alprazolam

c) Adult:

1) GENERAL INFORMATION

a) The clinical response to IMIPRAMINE in the treatment of panic disorder is independent of the pre depression or dysphoria (Deltito et al, 1991). Patients with high baseline depression scores have ter poorest outcomes (Rosenberg et al, 1991aa; Rosenberg et al, 1991c; Zitrin, 1983; Nurnberg & Cocc use of IMIPRAMINE in the treatment of panic disorder may not be as safe as other anxiolytics in pat cardiovascular disease (Roth et al, 1992a).

2) Combination imipramine and cognitive-behavioral therapy (CBT) was of limited value initially but prov during maintenance therapy in patients with panic disorder. Patients with panic disorder randomly receiv (n=77), imipramine alone (n=83), placebo alone (n=24), CBT with imipramine (n=65), or CBT alone (n=6 acute treatment phase. Thereafter, responders entered a 6-month maintenance phase. Patient response following the 12- week acute treatment phase, the 6-month maintenance phase, and 6-months after ther discontinuation; assessment tools included the Panic Disorder Severity Scale (PDSS) and the Clinical G Scale (CGI). Initial imipramine doses were 10 milligrams (mg)/day slowly increased over 5 weeks to 200 increased to 300 mg if symptoms continued. Following acute treatment, responses for the PDSS were 48 alone, 45.8% for imipramine alone, 21.7% for placebo alone, 60.3% for CBT with imipramine, and 57.1% placebo. Both CBT alone and imipramine alone were significantly better than placebo (p=0.03 and p=0.0 however, combination therapy provided no greater response rate over each treatment alone (p not signif during the acute phase, none of the therapies were significantly better than the others. Following mainter responses on the PDSS were 39.5% for CBT alone, 37.8% for imipramine alone, 13% for placebo alone, with imipramine, and 46.8% for CBT plus placebo. Responses on both the PDSS and the CGI were sign imipramine versus placebo (p=0.02 for both) and CBT versus placebo (p=0.02, p=0.01, respectively). Us combination therapy was significantly better than either CBT alone (p=0.04) and better than imipramine a the CGI, combination therapy was only significantly better than imipramine alone (p=0.03) and not better not significant). Following treatment discontinuation after the 6-month maintenance phase, the only statis was the PDSS scores in the CBT group compared to the placebo group (p=0.05) (Barlow et al, 2000).

3) Maintenance treatment with imipramine had a significant protective effect against relapse in patients and agoraphobia. Patients who had shown an initial good and stable response to imipramine therapy ov randomly received same-dose imipramine continuation (n=29) or placebo discontinuation (n=27). Patient initial imipramine at a target dose of 2.25 milligrams/kilogram or discontinued their imipramine by decrea 25% each week (substituted with placebo). During this study, no patient received behavioral or cognitive a crisis-type intervention was needed. During the study, if relapse was confirmed the patient exited the s defined as a worsening of their condition (measured as a 33% decline in the End- State Function scale s accompanied by insistent requests for therapeutic action. After 12 months, the study population consiste the imipramine group and 10 patients in the placebo group. This resulted in a 92.5% lower hazard rate o imipramine as compared to placebo (Mavissakalian & Perel, 1999).

4) In a double-blind study, an 8-month therapy period for panic disorder with either alprazolam or imipra (Rickels & Schweizer, 1998). Patients received alprazolam (n=37), imipramine (n=34), or placebo (n=35) period of short-term treatment, a 6-month maintenance period, and then a 15-month follow-up period. Pa alprazolam began at 1 milligram (mg) daily and were titrated up to 10 mg. Those receiving imipramine be were increased to 250 mg. Alprazolam patients had notable reductions in panic attacks during the first 2 while imipramine patients showed improvement over placebo patients after 3 to 4 weeks. Drop-out rates were 11% in the alprazolam group, 41% in the imipramine group, and 57% in the placebo group (p less t alprazolam versus the other groups). In the remaining patients it was noted that tolerance developed to a during the maintenance phase. After the 6-month maintenance phase, doses were titrated off over 3 wee 62% of the alprazolam and 26% of the imipramine groups were panic-free (p less than 0.01). During the patients could be treated with non-study medications. Regardless of medication, patients who completed treatment were more likely to be panic-free than those who had dropped out, even if they received non-s (85% versus 55%, p less than 0.01). Remission rates were higher in younger patients, those with a histo or intense panic attacks, those with a lower initial phobia score, and those with an initial lower score of in self-confidence, and passivity (Minnesota Multiphasic Personality Inventory Dependency Scale).

5) A comparison of cognitive therapy, applied relaxation, and imipramine found that at 3 months cognitiv superior to both applied relaxation and imipramine therapy (Clark et al, 1994). At 6 months the cognitive imipramine treatment produced similar results and were better than applied relaxation. However, betwee months of therapy, several of the imipramine patients relapsed while the patients treated with cognitive th to do better than with imipramine and relaxation therapy.

4.5.C.12 Posttraumatic stress disorder

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Resulted in improvement in positive symptoms of post-traumatic stress disorder

c) Adult:

1) Imipramine treatment resulted in improvement in positive symptoms of post-traumatic stress disorder

patients (Burstein, 1984). Therapy was initiated at a low dose and increased over the following 7 days to tolerable dose (mean 260 milligrams/day; range 50 to 350 mg/d). After 2 to 3 weeks of therapy, there wa decrease in the severity of forced recollection, sleep and dream disturbances, and a cessation or reducti Most avoidance items, eg, staying away from reminders of the event, trying not to talk about the event, a remove it from their memory, did not decrease significantly in severity. Based on these results it would a IMIPRAMINE, in combination with psychotherapy, may be an effective treatment for patients.

2) Treatment of 3 patients with acute post-traumatic stress disorder (PTSD) with either DOXEPIN or IMI in an improvement in PTSD symptoms (Blake, 1986). Whether or not tricyclic antidepressant therapy is s equivalent, or inferior to psychotherapy or other means of treatment remains to be determined.

4.5.C.13 Separation anxiety disorder of childhood

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Pediatric, Evidence is inconclusive
Recommendation: Pediatric, Class III
Strength of Evidence: Pediatric, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Routine use of tricyclic antidepressants is not recommended for separation anxiety in children
Behavioral therapy may be just as effective as imipramine

c) Pediatric:

1) The combination of imipramine and nonpharmacologic therapies (eg, parent management training, be and family therapy) may improve subjective comfort, reduce anxiety and somatic symptoms in 70% of th experiencing separation-anxiety disorder (Rancurello, 1985a). This disorder is associated with a high rat recovery, therefore the routine use of tricyclic antidepressants is not recommended (Rancurello, 1985a).

2) Both IMIPRAMINE and placebo therapy were equally effective for separation anxiety. A small, double placebo-controlled study was conducted with 21 children with separation anxiety disorder (Klein et al, 19 children were first given a month of vigorous behavioral treatment, then randomly assigned to IMIPRAMI therapy for six weeks. Both treatments were approximately 50% effective.

4.5.C.14 Sexual disorder

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Effective in case reports only

c) Adult:

1) IMIPRAMINE may be useful, alone or in combination with LITHIUM, in the treatment of men with PAR NONPARAPHILIC SEXUAL ADDICTIONS (Kafka, 1991). Two patients with sexual disorders improved f IMIPRAMINE therapy. Whether IMIPRAMINE and other antidepressants are useful in the treatment of al paraphilias or nonparaphilic sexual addictions or just specific types remains to be determined.

4.5.C.15 Sleep disorder

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Used successfully in the treatment of NIGHT TERRORS, SOMNABULISM, NARCOLEPSY, and CATAP

c) Adult:

1) IMIPRAMINE therapy (50 to 100 milligrams at bedtime) resulted in a dramatic reduction in frequency night terrors in 2 patients unresponsive to DIAZEPAM therapy (Cooper, 1987).

2) IMIPRAMINE therapy resulted in a significant reduction (242 +/- 156 to 142.8 +/- 120.1) in the total nu episodes in 41.9% of the patients tested (Rubin et al, 1986). Based on these results it appears that IMIP may be an alternative form of therapy for some nonoverweight patients with negative ear, nose and throa and for some patients who had not responded to weight reduction or ENT surgery.

3) A 62-year-old female had suppression of night terrors with IMIPRAMINE 50 milligrams at bedtime; 75 completely suppressed night terrors but caused daytime drowsiness (Beitman & Carlin, 1979).

4.5.C.16 Trichotillomania

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Pediatric, Evidence is inconclusive

Recommendation: Pediatric, Class IIb
Strength of Evidence: Pediatric, Category C
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:
Used successfully in a case of trichotillomania and depression in a pediatric patient (Weller et al, 1989).

4.6 Comparative Efficacy / Evaluation With Other Therapies

Adinazolam

Alprazolam

Amineptine

Amisulpride

Amitriptyline

Amoxapine

Binedaline

Brofaromine

Bromocriptine

Bupropion

Buspirone

Butylscopolamine

Chlordiazepoxide

Chlorprothixene

Citalopram

Clomipramine

Clonazepam

Delorazepam

Desipramine

Desmopressin

Diazepam

Dibenzepin

Diclofenac

Dothiepin

Doxepin

Electroconvulsive therapy

Encainide

Flecainide

Fluoxetine

Fluvoxamine

Gepirone

Haloperidol

Lithium

Lofepramine

Maprotiline

Melitracen

Methscopolamine

Mianserin

Milnacipran

Moclobemide

Moricizine

Nefazodone

Nomifensine

Nortriptyline

Paroxetine

Phenelzine

Reboxetine

Ritanserin

Rolipram

Sertraline

Sotalol

Tranylcypromine

Trazodone

Trimipramine

Tryptophan

Venlafaxine

Viloxazine

Zimeldine

4.6.A Adinazolam

4.6.A.1 Depression

a) SUMMARY: In several small controlled studies, adinazolam has been as effective as imipramine in depres including patients with melancholic depression.

b) Several controlled studies have reported the similar efficacy of adinazolam and imipramine in the treatme depressive disorder in outpatients (Amsterdam et al, 1986; Feighner, 1986). Equivalent efficacy has also bee patients with more severe melancholic depression (Amsterdam et al, 1986). However, all studies have emplo numbers of patients, lending themselves to a type II error. Larger studies of adequate duration, incorporating needed to adequately compare these two agents. In addition, compliance is always a problem in outpatient s involving depressed patients. Either a well-controlled inpatient study or the use of serum drug levels in future required.

c) Adinazolam and imipramine had similar efficacy in the treatment of major depressive disorder, with or with symptoms, in a double-blind study involving 43 outpatients (Amsterdam et al, 1986). Following a 1-week, sing period, patients were randomized to receive either adinazolam 10 milligrams (mg) three times daily initially, ir mg by day 14 of treatment if needed, or imipramine 25 mg three times day initially, increasing up to 225 mg b of therapy, if required. Hamilton Depression Rating (HDR) scores and clinical global impression scale scores similar efficacy of both agents; there was trend toward lower HDR scores in the imipramine group at week 12 improvement in the adinazolam group by week 1. Further analysis revealed the comparable efficacy of the 2 with the more severe, melancholic, subtype of depression. Anticholinergic adverse effects of dry mouth, cons blurred vision occurred more frequently in the imipramine group, as did lightheadedness, agitation and nervo sedation or drowsiness was more prevalent in adinazolam patients. Mood swings into hypomania and worser were more frequent in the adinazolam group, with total episodes during study being 4 versus 1 and 3 versus Other adverse effects occurred to a similar degree in each group.

4.6.B Alprazolam

Anxiety

Depression

Panic disorder

4.6.B.1 Anxiety

a) A six-week, double-blind, parallel study was conducted in 60 patients with generalized anxiety disorder to efficacy of alprazolam and imipramine (Hoehn-Saric et al, 1988). After a three-week washout period, patients divided and randomly assigned to alprazolam 0.5 milligram or imipramine 25 milligrams three times daily for s the first week the dose of the medication could be increased by one capsule daily up to a maximum of 12 cap the end of the study the average dose was for the alprazolam-treated group was 2.2 mg/day (0.5 to 6 mg/day imipramine group 91 mg/day (25 to 200 mg/day). During the first two weeks, alprazolam was superior to imip weeks both drugs were effective based on psychic and somatic parameters, but imipramine predominantly af symptoms (eg, negative anticipatory thinking and dysphoria) as alprazolam was superior in attenuating soma

b) Alprazolam and imipramine might be useful in the treatment of school refusal (school phobia); however, fu need to be conducted to document their usefulness (Bernstein et al, 1991).

4.6.B.2 Depression

a) Alprazolam was as effective as imipramine in the treatment of primary depression (Fabre & McLendon, 19 effective doses of alprazolam in the study were 2.6 milligrams daily in divided doses, as compared with 128.4 for imipramine. The onset of action with alprazolam was more rapid than that observed with imipramine; antic were more evident with alprazolam during the first week of therapy. A similar incidence of side effects occurre medication, with the main side effects being drowsiness, insomnia, nervousness, constipation and lightheade alprazolam was reported to have less anticholinergic side effects (confusion, tachycardia, palpitations, dry mo

retention). Imipramine was reported to cause fewer headaches than alprazolam. However, a detailed descrip in these patients was not provided in this study. In addition, specific data regarding the onset of effects of eac also not provided satisfactorily. More importantly, the patient population ("primary" depression) is unclear in t difficult to evaluate which types of depression were being treated.

b) Alprazolam was compared with imipramine in a 6-week, double-blind study on 723 outpatients (Feighner, were selected with moderate to severe symptoms of a unipolar major depressive disorder of at least one mor Patients were given imipramine 25 milligrams two or three times daily or alprazolam 0.5 milligram two to thre initially, followed by increases in doses at one-week intervals to a maximum of 4.5 mg alprazolam and 225 m Both drugs were more effective than placebo in alleviating depression, with alprazolam being at least as effec imipramine. Alprazolam was reported more effective in relieving somatic symptoms and the data suggested a effect in some evaluated parameters, but the significance of this is questionable. Toxicity, primarily anticholin was reported in patients receiving imipramine; drowsiness was the main side effect reported with alprazolam. suggests benefits of alprazolam in the treatment of unipolar depression as defined by the Feighner Diagnosti primary depression (similar to the DMS-III Criteria for major depression). However, this study was performed basis, and even the best blinding techniques are useless if patients are taking other medications. The author other psychotropic medications were not to be used except for "emergencies". Evaluation of drug response ir difficult at best, especially on an outpatient basis with several investigators doing the evaluation. Alprazolam antidepressant effects.

c) Alprazolam, imipramine, and a placebo were compared in a 6-week, double-blind study of 175 patients wi depressive disorder (DSM-III) (Rickels et al, 1982a). Patients were randomly assigned to alprazolam (N=58), or placebo (N=57) therapy. Dosage increases were allowed during the course of treatment and the mean dos and imipramine during the last 2 weeks of treatment were 3 milligrams/day and 150 milligrams/day, respectiv indicate that alprazolam was more effective than imipramine and placebo therapy. However it should be note placebo response rate was observed at 2 weeks (53% compared to 75% for alprazolam and 64% for imipram placebo response rate may be attributed to the fact that a high percentage of the patient were of the anxious depression subtypes. (Note: The data supplied in the figure comparing clinical improvement over time on the drug therapy is for 171 different patients, which is interesting since only 153 patients completed at least 4 we No information is supplied regarding the study dropouts other than the fact that the dropout rates were not sig between the 3 treatment groups.) Imipramine therapy was associated with a higher incidence of drowsiness a alprazolam or placebo therapy.

d) The efficacy of alprazolam and imipramine were evaluated in the inpatient treatment of depressive illness 1984). Patients were randomly assigned to either alprazolam or imipramine therapy. Dosage was individualiz response. Patients receiving alprazolam therapy improved over the first 10 days of therapy and then reached whereas the patients treated with imipramine continued to improve in vegetative and cognitive symptomology examination of the HAM-D scale indicated that the initial improvements seen with alprazolam is predominantl vegetative features of the illness.

e) Both drugs administered once daily were efficacious in the treatment of outpatients with major depressive (Mendels & Schless, 1986). Fifty percent of the alprazolam treatment group had a greater than 50% improve D scores, compared to the 38% success rate observed in the imipramine treatment group and 18% in the pla groups.

f) Patients who can be classified as DSM-III - major depressive episode but fail to satisfy more restrictive crit depression disorder appear to respond better to alprazolam therapy than imipramine therapy. Patients satisfy criteria for primary depression also appear to tolerate and respond better to alprazolam therapy initially. How appeared to be more efficacious during long term therapy. In addition, patients with biologic depression (eg, r positive DST, and shortened REM latency) tended to respond better to imipramine therapy (Overall et al, 198

g) An 8-week, double-blind, controlled study compared the efficacy of alprazolam (58 patients), diazepam (5 imipramine (63 patients), and placebo (61 patients) in 241 outpatients with a DSM-III diagnosis of major depr was a washout period with all patients receiving placebo. Week 2 through 7, the patients received their assig and during week 8 the dose of the medication was reduced by half for 3 days and discontinued for the remair end of the study the mean daily doses were 143 milligrams imipramine, 3.1 milligrams alprazolam, 24 milligra 6.8 capsules of placebo. Attrition rates were significant, 23% by week 4 of treatment and 39% by week 6. By the study, 41% of the imipramine group had withdrawn, 23% of the alprazolam group, 44% of the diazepam g the placebo group. The main reason given for attrition was side effects with the active compounds and ineffe placebo. Alprazolam and imipramine were both significantly better than placebo in treating depression, but di effective. The clinical effects of imipramine and alprazolam were equivalent, and overall the frequency of side similar. Imipramine produced less drowsiness and more anticholinergic effects than both alprazolam and diaz al, 1987a).

4.6.B.3 Panic disorder

a) Summary: Alprazolam and imipramine appear to be equally efficacious in the treatment of panic disorder i The onset of action is faster with alprazolam, but by the end of four weeks their effectiveness is similar (Ricke 1998)(Taylor et al, 1990; Rosenberg et al, 1991; Rosenberg et al, 1991a; Anon, 1992; Roth et al, 1992; Schw Pollack et al, 1994). The decision to use imipramine over alprazolam should be based on patient-related cha concurrent depression, anxiety disorders, cardiovascular disease), potential drug interactions, and side effect

b) In a double-blind study, an 8-month therapy period for panic disorder with either alprazolam or imipramine (Rickels & Schweizer, 1998). Patients received alprazolam (n=37), imipramine (n=34), or placebo (n=35) duri period of short-term treatment, a 6- month maintenance period, and then a 15-month follow-up period. Patien alprazolam began at 1 milligram (mg) daily and were titrated up to 10 mg. Those receiving imipramine began

were increased to 250 mg. Alprazolam patients had notable reductions in panic attacks during the first 2 wee
imipramine patients showed improvement over placebo patients after 3 to 4 weeks. Drop-out rates during this
the alprazolam group, 41% in the imipramine group, and 57% in the placebo group (p less than 0.001 for alpr
other groups). In the remaining patients it was noted that tolerance developed to adverse effects during the m
After the 6-month maintenance phase, doses were titrated off over 3 weeks. At this point, 62% of the alprazo
the imipramine groups were panic-free (p less than 0.01). During the follow-up period, patients could be treat
medications. Regardless of medication, patients who completed 8 months of treatment were more likely to be
those who had dropped out, even if they received non-study medications (85% versus 55%, p less than 0.01)
were higher in younger patients, those with a history of more frequent or intense panic attacks, those with a l
score, and those with an initial lower score of inadequacy, low self-confidence, and passivity (Minnesota Mult
Inventory Dependency Scale).

c) Seventy-nine patients were enrolled in a placebo controlled, double-blind trial comparing the efficacy and
effects of imipramine, alprazolam, and placebo in patients with panic disorders (Taylor et al, 1990). Doses ra
alprazolam 1 to 8 milligrams/day and imipramine 30 to 270 milligrams/day. In terms of global improvement, th
with alprazolam or imipramine experienced significantly greater improvement than the placebo patients. Alpra
rapid onset of effect, but after four weeks of therapy no significant differences in efficacy were apparent betw
and imipramine treated patients. Imipramine did have a number of significant effects on the cardiovascular sy
the heart rate was significantly increased at resting and standing, and the systolic and diastolic blood pressur

d) Cerebrospinal fluid levels of homovanillic acid, 5-hydroxyindoleacetic acid, 3-methoxy-4-hydroxyphenylgly
somatostatin and beta-endorphin were measured in 12 patients with panic disorders who had been treated w
imipramine for seven months. Seven patients treated with alprazolam (mean dose 4.7 mg, range 2 to 6 mg) a
therapy. Four of the five imipramine-treated patients (mean dose 135 mg, range 100 to 150 mg) benefited. C
levels of the monoamine metabolites and neuropeptides remained unchanged during therapy in both treatme
were similar to levels measured in a control group, suggesting the antipanic activities of alprazolam and imipr
involve the monoamine or neuropeptide systems as was previously believed (Lepola et al, 1989).

e) A double-blind, placebo-controlled trial comparing the effects of imipramine and alprazolam in patients wit
revealed both agents were significantly more effective than placebo, however the patients treated with alpraz
fear than the patients in the imipramine and placebo groups after eight weeks of therapy (Taylor et al, 1990).

f) The Cross-National Collaborative Panic Study compared alprazolam, imipramine, and placebo in the treat
disorder (Anon, 1992). The study used in this evaluation was a double-blind, placebo-controlled, multicenter s
1168 patients with a diagnosis of panic disorder based on DSM-III criteria. Prior to the start of drug treatment
drugs were discontinued during a one- to two-week washout period. Patients were then randomly assigned to
alprazolam 1 milligram, imipramine 25 milligrams, or placebo (1 tablet). The initial starting dose was increase
alprazolam, 150 mg imipramine, and 6 placebo tablets by day 19. Subsequently the dosage could be adjuste
response. Formal psychotherapy and behavioral treatment sessions were to be avoided during the eight wee
Efficacy was assessed by using global improvement scores, a panic attach scale, phobia scale, frequency of
anxiety, 14-item Hamilton Rating Scale for Anxiety, 21-item Hamilton Rating scale for Depression, and Hopki
self-rating scale. The treatment-cohort (anyone completing three weeks of therapy) consisted of 1010 patient
completed the entire eight-week study. Reasons for dropping-out were side effects (alprazolam 3.4%, imipra
placebo 3.1%), lack of efficacy (alprazolam 3.1%, imipramine 2.6%, and placebo 12.8%), treatment refusal (1
reasons (alprazolam 7%, imipramine 7.7%, and placebo 11.8%); percentage are expressed as the number o
divided by number of patients enrolled in that treatment group. Onset of therapeutic benefits was noted by we
alprazolam and week 4 with imipramine. By week 8 there was no difference between the alprazolam and imip
and both groups were statistically superior to placebo.

g) Alprazolam was more effective than imipramine and placebo on anticipatory anxiety and phobic symptom
Scandinavian multicenter study in 41 patients with panic disorder (Andersch et al, 1991). Alprazolam had a m
action than imipramine on all symptoms. Patients receiving alprazolam had more drowsiness and those recei
had more anticholinergic effects.

h) In a study of 123 Scandinavian patients with panic disorder, alprazolam had an early effect on variables re
attacks, such as severity of spontaneous attacks and avoidance, whereas imipramine showed a more delaye
measures (Mellergard et al, 1991).

i) Patients with mild-to-moderate depression and panic disorder will respond equally to either alprazolam (av
milligrams/day) or imipramine (avg dose = 159 milligrams/day) therapy. Both drugs are more effective than pl
treatment of patients with mild-to-moderate depression and panic disorder (Keller et al, 1993).

4.6.C Amineptine

4.6.C.1 Depression

a) A controlled, double-blind study compared the efficacy and safety of amineptine (100 to 200 milligrams (m
imipramine (50 to 100 mg/day) for two months in 33 patients who fulfilled the Diagnostic and Statistical Manu
(DSM-III) criteria for major depressive disorders. Amineptine produced steady improvement of the symptoms
during treatment, according to the Hamilton (p = 0.001) and Montgomery and Asberg (p = 0.002) Depression
Clinical Global Impression Scale (p = 0.002). Imipramine produced a significant improvement in the overall sc
less than 0.001). No statistical differences were found between the two drugs; depressive symptoms improve
of treatment for both amineptine and imipramine. The incidence of anticholinergic adverse effects with amine
lower than with imipramine (Mendis et al, 1989).

4.6.D Amisulpride

4.6.D.1 Dysthymia

a) A double-blind, parallel group study compared the efficacy of amisulpride 50 milligrams (mg) daily versus mg daily and placebo in the treatment of dysthymia. No significant difference was found between the two dru whereas amisulpride showed a tendency to generate fewer adverse effects (Lecrubier et al, 1992).

b) A double-blind study, six months in duration, compared the therapeutic effects of amisulpride (50 milligran imipramine (200 mg daily) and placebo (Boyer & Lecrubier, 1996). The active drugs differed significantly from according to the Clinical Global Impression scale (CGI), Montgomery and Asberg Depressive Rating Scale (M Scale for the Assessment of Negative Symptoms (SANS) global score. Difference in efficacy between the act minimal.

4.6.E Amitriptyline

4.6.E.1 Depression

a) Of 11 studies in which amitriptyline and imipramine were directly compared, 5 reported amitriptyline super imipramine superior and 4 reported no difference between the 2 drugs in efficacy (Hutchinson & Smedberg, 1 1966; Snow & Rickels, 1964; Sandifer et al, 1965; Richmond & Roberts, 1964; Hordern, 1963; Burt, 1962).

b) In another study, imipramine (mean 157 milligrams/day) was compared with amitriptyline (mean 186 millig post-psychotic depressed patients who were also receiving one of several neuroleptics (mean chlorpromazin 795 milligrams/day). Thirteen of 14 patients on imipramine improved, while 8 of 11 on amitriptyline improved

4.6.F Amoxapine

4.6.F.1 Depression

a) SUMMARY: Clinical studies have demonstrated that amoxapine is at least as effective as imipramine in th depression (Sathananthan et al, 1973b; Gelenberg et al, 1984; Wilson et al, 1977; Fabre, 1977; Holden et al, Okerson, 1979; Bagadia et al, 1979; Takahashi et al, 1979; Dominguez et al, 1981; Rickels et al, 1981). Side are comparable in type, frequency, and intensity to imipramine (Dugas & Weber, 1982; Kinney & Evans, 198

b) Maprotiline (mean, 165 mg daily) and amoxapine (mean, 230 mg daily) showed similar efficacy in the trea moderate-to-severe depression in a 4-week, double-blind study involving 76 outpatients. Amoxapine is report rapid onset of action than maprotiline as evidenced by a greater improvement at days 4 and 7 (Fabre, 1985).

c) Equivalent doses of amoxapine and imipramine were equally effective in depressed outpatients during 5- blind clinical trials (Rickels et al, 1981; Gelenberg et al, 1984). Amoxapine produced improvement in a 6-wee study involving 90 depressed outpatients more rapidly than did imipramine; however, the dose of amoxapine milligrams/day) was double that of imipramine (105 milligrams/day) (Kiev & Okerson, 1979).

d) Imipramine and amoxapine were comparable in the treatment of depression in inpatients in a controlled st mean doses of 165 milligrams daily was reported comparable with imipramine 175 milligrams daily in manage depressive illness; however, the imipramine-treated patients had slightly more cardiovascular side effects. An patients reportedly had slightly more neurological toxicity (Ahlfors, 1981).

e) Amoxapine and imipramine were comparable in 90 adult outpatients with mixed depressive illnesses in a controlled, double-blind study. Patients received amoxapine 145 to 265 milligrams daily (mean 235 mg) or im milligrams daily (mean 122.5 mg). Amoxapine and imipramine were both significantly superior to placebo as the Hamilton Rating Scale for depression, Zung Self- Rating Scale, and Clinical Global Impression Scale sco there were no significant differences between the 2 drugs (Fabre, 1977).

4.6.F.2 Efficacy

a) Continuous Performance Test (CPT), a visual vigilance test, of amoxapine and imipramine show several d performance and brain function (Buchsbaum et al, 1988). Amoxapine enhanced N120 amplitude in midline pa parietal cortex. Both amoxapine and imipramine enhanced the P200 area, with amoxapine's greatest effect b midline parietal locations. The clinical importance of these differences in brain activity remains to be determin

4.6.G Binedaline

4.6.G.1 Depression

a) Binedaline, a bicyclic antidepressant, was evaluated against imipramine therapy in the treatment of 50 hos endogenously depressed patients (Faltus & Geerling, 1984). Patients were either treated with 150 mg/d of im mg/d of binedaline in 3 equally divided doses. There was no psychiatric, clinical or statistical differences betw treatment groups. Binedaline efficacy was slightly higher than imipramine utilizing the clinical global impressio Frequency of side effects was less in the binedaline treatment group.

4.6.H Brofaromine

4.6.H.1 Depression

a) Brofaromine is a selective and reversible monoamine oxidase inhibitor (MAOI). In addition, the drug may b inhibitor. A comparison of brofaromine with imipramine was made in 216 outpatients with depression. Patient assigned to brofaromine and imipramine therapy in a 2:1 ratio. Both medications were started at a daily dose milligrams. The average dose of medication at the end of eight weeks was brofaromine 93.1 mg/day and imip mg/day. This phase of the study lasted eight weeks. Baseline HAMD scores were 29.4 in the brofaromine gro imipramine group. At the end of the study period the HAMD scores were 9.34 and 12.31 (p=0.01), respective

of adverse reactions was 27.8% in the brofaromine group (eg, headache, sleep disturbances, palpitation, nau the imipramine group (eg, dryness of mouth accommodation disturbances, impaired vision, and sweating). Du phases of the study only those patients receiving brofaromine were followed for up to 52 weeks. The lower H continued to be maintained, with the exception of a slight increase between weeks 28 to 36, and the drug wa (Moller & Volz, 1992).

4.6.I Bromocriptine

4.6.I.1 Depression

a) No significant differences were observed in 33 outpatients with endogenous depression treated with eithe imipramine. Sixteen patients received bromocriptine 10 to 60 milligrams (mg)/day (mean, 34 mg/day) and sev received imipramine 75 to 250 mg/day (mean, 143 mg/day) for a period of 6 weeks. Based on the Hamilton ra total score of the bromocriptine-treated patients decreased from 19.9 to 7.8 and the imipramine-treated patie 20.1 to 6.1. Side effects associated with bromocriptine included nausea, dizziness and headache and those s imipramine included dryness of mouth, dizziness, and sweating. Although bromocriptine has an antidepressa on anxiety, agitation, and insomnia are less pronounced than that of imipramine (Waehrens & Gerlach, 1981)

b) Bromocriptine (15 milligrams (mg) daily) was as effective as imipramine (75 mg/day daily) in a 10-week, d in patients with endogenous depression. However, only 9 patients were evaluated and more studies are nece definite effects of the drug (Bouras & Bridges, 1982).

4.6.J Bupropion

4.6.J.1 Depression

a) A meta-analysis of published studies between 1980 and 1990 comparing imipramine and bupropion in the major depression indicates that both medications are equally effective (Workman & Short, 1993).

b) Bupropion and imipramine were equally efficacious in a double-blind, 5-week, multicenter trial in 63 elderl patients (Branconnier et al, 1983a). Patients were given either bupropion 150 milligrams/day (18 patients), bu 450 milligrams/day (18 patients), imipramine 150 milligrams/day or less (18 patients), or placebo (9 patients). treatment efficacy utilized depression and anxiety scales. All 3 drug treatment groups were more effective tha 7 to 35.

4.6.J.2 Adverse Effects

a) Bupropion may be safer than imipramine in treating depressed patients with congestive heart failure (Roo The cardiovascular effects of imipramine and bupropion were compared in 10 depressed patients with conge Neither drug had an effect on left ventricular ejection fraction or left ventricular function. Hypotension, severe discontinuation, was a problem in 50% of the imipramine patients but did not occur with bupropion.

4.6.K Buspirone

Depression

Panic disorder

4.6.K.1 Depression

a) Imipramine was more effective than placebo (p less than 0.01) while buspirone trended towards being mo placebo (p less than 0.1) for the treatment of major depression in elderly outpatients. The 8-week, randomize placebo-controlled study involved 177 patients aged 65 years and over. Beginning dosages were imipramine twice daily or buspirone 10 mg twice daily, increased to imipramine 25 mg three times daily and buspirone 10 daily after one week. If tolerated after the second week, imipramine was increased to 100 mg/day and buspir in divided doses. A daily maximum dose of 150 mg of imipramine and 60 mg of buspirone could be reached b response, with the mean optimal dose of 89 mg/day for imipramine and 38 mg/day for buspirone. Following 8 treatment, moderate to marked global improvement occurred in 61% of buspirone patients, 70% of imipramin 42% of placebo patients (Schweizer et al, 1998).

4.6.K.2 Panic disorder

a) A placebo-controlled, double-blind study of outpatients with panic disorder or agoraphobia with panic attac any significant differences in total biweekly numbers of panic attacks, decreases in number of attacks, and ev psychopathology and of global improvement over an eight-week period between patients treated with buspirc placebo. All groups improved. The inconclusive results may have been due to a number of factors, including sizes, the episodic nature of the illness, a possible therapeutic effect of the diagnosis for the subjects (many c diagnosed for the first time during the study), and the limited study duration (Pohl et al, 1989). Somewhat bet seen for both active treatments in a study using higher doses (Robinson et al, 1988).

4.6.L Butylscopolamine

4.6.L.1 Nocturnal enuresis

a) Imipramine was significantly superior to butylscopolamine, which was no better than placebo in 14 childre enuresis (Korczyn & Kish, 1979). Imipramine 10 or 20 milligrams was compared to butylscopolamine 10 or 2(investigators concluded that antimuscarinic activity is not sufficient to inhibit detrusor contraction and that ora is not absorbed to any significant extent.

4.6.M Chlordiazepoxide

4.6.M.1 Depression

a) Imipramine was more effective and better tolerated at assessments made at 4 weeks, 6 weeks, and 8 wee with primary depression who completed a double-blind comparison of imipramine, chlordiazepoxide, and plac 1986). At the end of 2 weeks of therapy the therapeutic advantages associated with imipramine therapy were apparent. By weeks 6 and 8, the imipramine- treated group had a marked superior therapeutic advantage in i symptoms of depression, anxiety, anger-hostility, interpersonal sensitivity, and global improvement. Chlordiaz an advantage in patients with sleep difficulties, but these patients did significantly worse on anger-hostility an sensitivity.

4.6.N Chlorprothixene

4.6.N.1 Depression

a) Imipramine 75 to 225 milligrams/day and chlorprothixene 45 to 135 milligrams/day had comparable efficac double-blind, randomized, crossover study involving 32 patients with depressive disorders. The investigators both drugs were equally efficacious and safe, although the side effect profiles varied (Lodge-Patch et al, 196

4.6.O Citalopram

4.6.O.1 Depression

a) Unpublished studies involving small numbers of patients suggest the comparable efficacy of imipramine a depression, although imipramine has tended to be more effective in improving sleep disturbances (Milne & G well-controlled comparisons of these agents are needed.

4.6.P Clomipramine

Depression

Obsessive-compulsive disorder

4.6.P.1 Depression

a) Clomipramine was as effective as imipramine in treating depression in 24 patients during a 44-day, rando blind study (McClure et al, 1973). The patients were diagnosed with psychotic depression independently by 2 imipramine or oral clomipramine was administered 3 times daily in 50 milligrams doses. Throughout the study assessments using the Hamilton Depression Rating Scale and the Beck Depression Inventory demonstrated reduction in depression from baseline for both drugs; however, a significant difference in antidepressant effec could not be seen. Minor and transient anticholinergic adverse effects were noted in all patients and included mouth, increased sweating, hand tremor, and dizziness. Three patients dropped out of the study, but none of adverse effects.

4.6.P.2 Obsessive-compulsive disorder

a) SUMMARY: Clomipramine is superior to imipramine in the treatment of obsessive-compulsive disorder.

b) Oral clomipramine was slightly superior to oral imipramine in improving symptoms of obsessive-compulsiv (Volavka et al, 1985). A 12-week, double-blind study of 23 patients according to DSM-III with secondary depr was conducted to compare the 2 drugs. Both drugs were started at 50 milligrams/day; this was gradually incr mg/day as tolerated. Seven patients did not complete the study: 4 because of adverse effects (2 from each g of unsatisfactory therapeutic response with imipramine, and 1 for no apparent reason. Both drugs produced i depressive symptoms; however, only clomipramine demonstrated improvement in obsessive symptoms wher baseline. Typical anticholinergic adverse effects were experienced by both treatment groups with no significa between the two. It is difficult to accurately evaluate the clinical response in this study because of the small n and the methods used for statistical analysis.

c) Both oral clomipramine and oral imipramine were effective in improving symptoms in obsessive-compulsiv who met DSM-III criteria (Mavissakalian et al, 1985). The study was a 12-week, double-blind trial that compar clomipramine and imipramine in treating obsessive-compulsive disorders. Both drugs were begun at 25 to 50 this was increased to 300 mg/day as tolerated. At the end of the trial, the mean daily dose of both drugs was clomipramine-treated patients and 2 of 5 imipramine-treated patients were classified as responders. For both improvement in depression was evident at 4 weeks, while maximal improvement in obsessive-compulsive sy seen until 8 weeks. The responders also had higher pretreatment depression scores than did nonresponders corresponded with the results of another study (Marks et al, 1980). Because of the small sample size, differe

efficacy between clomipramine and imipramine could not be determined.
d) The relationship between the antiobsessional and antidepressant effects of tricyclic drugs was studied in p
compulsive disorder. Study 1 consisted of a controlled 12-week trial with clomipramine (n=7) and placebo (n=
analyzed the pooled data from 15 uniformly selected patients who were treated with either clomipramine or in
Although the antiobsessional and antidepressant effects of the drugs covaried, antidepressant action was not
antiobsessional effects. Clomipramine, and probably imipramine, possess specific antiobsessive effects that
partially independent of the antidepressant effects (Mavissakalian et al, 1985).

4.6.Q Clonazepam

4.6.Q.1 Panic disorder
a) Preliminary results from an ongoing double blind study comparing imipramine and clonazepam in the treat
disorders in twelve patients have been reported (Svebak et al, 1990). Six patients received imipramine and si
clonazepam, and all were treated for a total of six months. Clonazepam treated patients required an average
(range 1 to 3 mg/day) to achieve relief of symptoms; imipramine patients required 62.5 mg/day) (range 25 to
During the final four months of the study no patients required more than 2 mg/day of clonazepam or 50 mg/da
Over the course of the first two weeks of treatment a substantial drop in the incidence of panic attacks occurr
Mean scores in global improvement were significantly improved in both groups, as were patients assessed sc
physician assessed scores. These early results demonstrate the efficacy of both imipramine and clonazepam
panic disorders.

4.6.R Delorazepam

4.6.R.1 Anxiety
a) Delorazepam 3 to 6 milligrams (mg) was compared to imipramine 50 to 100 mg/day and paroxetine 20 mg
weeks in 81 patients with generalized anxiety disorders according to DSM-IV criteria. Delorazepam produced
improvement in anxiety ratings during the first two weeks of treatment, but both paroxetine and imipramine w
by the fourth week of treatment. At study end, reduction of at least 50% in the Hamilton Rating Scale for Anxi
reported in 55% of the delorazepam patients, compared with 68% and 72% for paroxetine and imipramine, re
Delorazepam affects predominantly somatic symptoms, whereas paroxetine and imipramine affect psychic sy
al, 1997a).

4.6.S Desipramine

4.6.S.1 Depression
a) Desipramine has been evaluated in comparison with imipramine with most open or double-blind trials indi
drugs are equally effective with similar time of onset and side effects and that no significant differences or ad
apparent with either drug (Rose & Westhead, 1964; Waldron & Bates, 1965; Lafave et al, 1965; St Jean et al
& Maxwell, 1967; Rose & Westhead, 1967). However, other limited data indicates that imipramine may be su
being more active (Edwards, 1965; Heller et al, 1971) or, conversely, that desipramine has the advantage of
and earlier clinical response (Agin et al, 1965).

4.6.T Desmopressin

4.6.T.1 Nocturnal enuresis
a) Patients treated with oral imipramine followed by intranasal desmopressin therapy (n=28) experienced ad
compared to those who received desmopressin followed by imipramine (n=29) in an open label, cross-over st
with nocturnal enuresis (Vertucci et al, 1997). Following a 2 week observation period, patients were randomiz
either desmopressin 30 micrograms per day (mcg/day) (3 puffs per nostril) for 3 weeks followed by oral imipra
milligrams per kilogram (mg/kg) for 3 weeks followed by 2 more weeks of follow up, or imipramine therapy firs
desmopressin. Both patient groups experienced significant reductions in the number of wet nights in the first
compared to the first observation period (p value not specified). Irrespective of which agent was administered
desmopressin therapy significantly increased the number of dry nights per week compared to imipramine (p l
Overall, desmopressin was associated with 20% wet nights while imipramine was associated with 37% wet n
up, patient who received desmopressin last had fewer weekly wet nights than those who received imipramine
suggest the results of this study indicate desmopressin is long acting and is safe for long-term treatment of n
Both agents were well tolerated with few adverse events reported. One imipramine patient experienced pallo
and cold extremities. One desmopressin patient reported inflammation of nasal mucosal.

4.6.U Diazepam

4.6.U.1 Depression
a) An 8-week, double-blind, controlled study compared the efficacy of alprazolam (58 patients), diazepam (5
imipramine (63 patients), and placebo (61 patients) in 241 outpatients with a DSM-III diagnosis of major depr
was a washout period with all patients receiving placebo. Week 2 through 7, the patients received their assig
and during week 8 the dose of the medication was reduced by half for 3 days and discontinued for the remair
end of the study the mean daily doses were 143 mg imipramine, 3.1 mg alprazolam, 24 mg diazepam, and 6.
placebo. Attrition rates were significant, 23% by week 4 of treatment and 39% by week 6. By the completion

of the imipramine group had withdrawn, 23% of the alprazolam group, 44% of the diazepam group, and 40%
group. The main reason given for attrition was side effects with the active compounds and ineffectiveness wit
Alprazolam and imipramine were both significantly better than placebo in treating depression, but diazepam v
The clinical effects of imipramine and alprazolam were equivalent, and overall the frequency of side effects w
Imipramine produced less drowsiness and more anticholinergic effects than both alprazolam and diazepam (
1987).

4.6.V Dibenzepin

4.6.V.1 Depression

a) Dibenzepin and imipramine are both well tolerated and equally effective in the treatment of depression. In
comparative trial, depressed patients (n=22) were administered either dibenzepin (160 milligrams (mg) three
imipramine (50 mg three times daily) for 4 weeks. Both drugs were effective and no significant differences we
patients taking dibenzepin and those taking imipramine (Fielding, 1969).

4.6.W Diclofenac

Cancer pain

Depression

4.6.W.1 Cancer pain

a) In a 1-week study, diclofenac plus placebo was as effective as diclofenac plus imipramine or diclofenac pl
cancer pain. This double-blind study enrolled 180 patients who were randomly assigned to receive diclofenac
(mg) 4 times daily with placebo, diclofenac with imipramine 10 or 25 mg 3 times daily (determined by patient
greater than 65 years), or diclofenac with codeine 40 mg 4 times daily. Efficacy was assessed at baseline an
100 millimeter(mm) visual analogue scale (VAS) (0=no pain; 100=worst possible pain); patients with acceptal
continued treatment for the remainder of the study. Significant differences were NOT detected between the 3
Results of this study are limited by the short duration of treatment which may have been insufficient to detect
of imipramine, lack of dose titration for codeine, concomitant use of morphine in 30 patients, and inclusion of
different cancer pain etiologies. Additional studies which address the limitations of this study are needed (Mir

4.6.W.2 Depression

a) Diclofensine is a isoquinoline derivative, structurally similar to nomifensine, that is a potent inhibitor of 5-hy
dopamine, and norepinephrine reuptake (Capponi et al, 1985). In a double-blind comparison with imipramine
dose = 65 milligrams/day) and high dose (average dose = 97.6 milligrams/day) diclofensine therapy was sho
effective as imipramine therapy (average dose = 102.9 milligrams/day) during the 6-week study period. Durin
weeks of therapy diclofensine therapy was more effective, but by the completion of the 6-week study period t
difference between the treatment groups. Whether or not a difference in onset of action would have been obs
initial doses of imipramine were used is unknown. Diclofensine therapy was better tolerated than the imipram
even if higher doses of imipramine were used it would have resulted in an even higher incidence of side effec

4.6.X Dothiepin

4.6.X.1 Depression

a) Dothiepin and imipramine appear to be equally efficacious in the treatment of depression. In a double-blin
patients with existing depression received either dothiepin or imipramine. Therapy was initiated with 25 milligi
which was increased to a maximum of 250 milligrams/day based on clinical response. Although both dothiepi
groups showed similar improvement, dothiepin was associated with fewer adverse effects, including dry mou
(Eilenberg, 1980). Similar results were seen in another study (Sheth et al, 1979).

4.6.Y Doxepin

4.6.Y.1 Depression

a) Imipramine may be slightly more effective than doxepin in the treatment of depression. Ninety-nine patien
depression received imipramine 100 to 200 milligrams/day or doxepin 100 to 200 milligrams/day for 4 weeks
study. Imipramine was superior in 24 of 27 parameters. Imipramine was shown to be superior to doxepin in ir
symptoms of anxiety/depression; global evaluations showed improvement in 39 of 48 (81%) of imipramine pa
49 (69%) of doxepin patients (Finnerty et al, 1978).
b) In a study involving 79 patients, a higher socioeconomic status and shorter duration of illness were indicat
response to imipramine, whereas a higher response rate to doxepin was found in male patients (Finnerty & G
c) Amitriptyline was superior to imipramine and doxepin in relation to their effects on interpersonal learning ir
inpatients (Gillis, 1981). All subjects performed better, according to quantitative indices of learning tasks, thar
received antipsychotic or neuroleptic drugs but no antidepressants. Amitriptyline patients scored significantly
imipramine or doxepin patients.

d) No significant differences in overall efficacy of the 2 drugs was reported in one study (Kimura, 1972), but
mg daily was superior to imipramine 150 mg daily in neurotic depression, whereas imipramine appeared to b
doxepin in endogenous depression (Pinder et al, 1977a).
e) Similar antidepressant effects of doxepin and imipramine were reported; however, imipramine had a more
action. Doxepin appeared to have more sustained effects (Hasan & Akhtar, 1971).

4.6.Y.2 Efficacy

a) In elderly patients doxepin produces less orthostatic effects than imipramine (10.5 mmHg vs 25.9 mmHg).
effect observed with imipramine was weakly related to dose and did not correlate with pretreatment orthostati
with duration of treatment (Neshkes et al, 1985).

4.6.Z Electroconvulsive therapy

4.6.Z.1 Depression

a) A double-blind, randomized, controlled trial compared electroconvulsive therapy (ECT) with imipramine th
patients suffering from depression (Gangadhar et al, 1982). Group I received modified bilateral ECT using thi
250 mg, succinylcholine 20 to 30 mg, and atropine 0.65 mg during the procedure. ECT was administered eve
during the first 2 weeks for a total of 6 treatments and then once a week for the next 2 weeks. Following this
maintenance ECTs were administered in the next 8 weeks. During the course of this treatment the patients re
identical to the imipramine group. Group II received imipramine 75 milligrams/day during week one and 150 r
second through the eleventh week. The dose was reduced to 75 mg/day during the twelfth week. During the
each patient received a simulated course of ECT therapy at the same frequency as the ECT-treated group. T
patients completed the study period (5 patients in the ECT group and 3 patients in the imipramine group were
the study during the first 6 weeks). Both treatments produced equally significant improvement which was mai
6-month follow-up period. The rate of improvement was quicker in those patients receiving ECT therapy. ECT
fewer side effects than imipramine therapy. There was no lasting organic brain dysfunction associated with th
previously thought.

4.6.AA Encainide

4.6.AA.1 Cardiac dysrhythmia - Myocardial infarction with complication, Post

a) Encainide and flecainide were more effective in suppressing ventricular arrhythmias than moricizine, imipr
placebo during the dose titration phase of a 1-year, multicenter, randomized, double-blind, placebo-controllec
patients (Anon, 1988a). Patients were eligible for this study if they had an acute myocardial infarction within 6
entrance to the study, were less than 75 years of age and demonstrated either an average of 10 or more ven
complexes (VPCs) per hour, or 5 or more episodes of unsustained ventricular tachycardia during a 24-hour a
recording. The total daily doses of the study drugs were encainide 105 to 180 milligrams, flecainide 200 to 40
150 to 375 milligrams, and moricizine 600 to 900 mg. Efficacy was defined as 70% or more suppression in VI
more than 90% suppression of runs of VPC when compared with baseline. The efficacy rates were 83% for fl
encainide, 66% for moricizine, 52% for imipramine, and 37% for placebo during the dose titration phase of th
incidence of adverse effects was 49% for encainide, 55% for flecainide, 67% for imipramine, 64% for moricizi
placebo. Imipramine was the drug most associated with patient withdrawal due to adverse effects. This study
VPC suppression efficacy at the 1-year follow-up.

4.6.AB Flecainide

4.6.AB.1 Cardiac dysrhythmia - Myocardial infarction with complication, Post

a) Encainide and flecainide were more effective in suppressing ventricular arrhythmias than moricizine, imipr
placebo during the dose titration phase of a 1-year, multicenter, randomized, double-blind, placebo-controllec
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incidence of adverse effects was 49% for encainide, 55% for flecainide, 67% for imipramine, 64% for moricizi
placebo. Imipramine was the drug most associated with patient withdrawal due to adverse effects. This study
VPC suppression efficacy at the 1-year follow-up.

4.6.AC Fluoxetine

4.6.AC.1 Depression

a) SUMMARY: Fluoxetine has been as effective as imipramine in the treatment of depression, while producii
incidence of side effects. Overall cost of therapy, clinical efficacy, and patient quality of life have been shown
after six months of treatment.
b) In a double-blind, randomized, parallel group study, fluoxetine was better tolerated although not more effe
imipramine in the treatment of major depression with atypical features. A total of 154 patients (age 18 to 65 y
DSM-IV criteria for major depression for at least 1 month and also met the Columbia criteria for atypical depre

randomized to receive fluoxetine, imipramine, or placebo for 10 weeks. Fluoxetine was administered as 20 m for 4 weeks, 40 mg daily for week 5, and 60 mg daily for the remaining weeks. Imipramine was administered the first week, increasing by 50 mg/day each week until a maximum of 300 mg daily was reached. Mean daily of the study were 51.4 mg/day for fluoxetine and 204.9 mg/day for imipramine. Fluoxetine and imipramine did one another based on the Clinical Global Impression (CGI) scale improvement scores following 10 weeks of t Fluoxetine and imipramine were significantly more effective than placebo in the intention-to-treat (p less than respectively) and completer groups (p less than 0.03 and 0.001, respectively). Imipramine-treated patients de significantly higher dropout rate than fluoxetine-treated patients (p=0.04). In the intention-to-treat group, depr measures including the 17-item and 28-item Hamilton Depression Rating Scale and Patient Global Improvem no differences between fluoxetine and imipramine and a consistent clinical benefit of both treatment groups c placebo. Adverse effects significantly more common for imipramine than for fluoxetine included dry mouth (8 respectively), somnolence (42% versus 24%, respectively), and dizziness (44% versus 25%, respectively); co pain occurred at a significantly higher incidence in fluoxetine- versus imipramine-treated patients (McGrath et

c) For the initial treatment of depression, imipramine and fluoxetine are equivalent in terms of overall treatme and quality of life. In a randomized, controlled trial, patients with newly diagnosed depression (n=536) were p fluoxetine or a tricyclic antidepressant (imipramine or desipramine) and assessed at 1, 3, and 6 months for bo antidepressant regimen as measured by the Hamilton Depression Rating Scale and the Hopkins Symptom C of life. Drug cost and total health care costs were also measured. Clinical efficacy and quality of life were sim two groups; however, patients treated with fluoxetine had fewer adverse effects, were less likely to require a medication, and had less outpatients visits. Although drug costs were higher, total treatment costs were sligh fluoxetine group; however, this difference was not statistically significant (Simon et al, 1996).

d) Controlled studies have demonstrated that oral fluoxetine in doses of 40 to 80 milligrams daily is as effect 150 to 250 milligrams daily in the treatment of major depression (Cohn & Wilcox, 1985; Stark & Hardison, 198 1987a). Fluoxetine was as effective as imipramine doses of 150 to 300 milligrams/day (Byerly et al, 1988). He report (Bremner, 1984), fluoxetine was reported superior to imipramine in several depression scales in a 5-we study involving 40 depressed outpatients. In all studies, the incidence of side effects (anticholinergic effects, drowsiness, dry mouth, cardiovascular effects) was less with fluoxetine as compared with imipramine; fluoxet associated with a greater incidence of anxiety or nervousness, insomnia, and excessive sweating. In another sweating (as well as nausea) was higher with fluoxetine than imipramine (Stark & Hardison, 1985). Of signific has occurred during fluoxetine therapy, as compared to generally no change in body weight or increases in w imipramine. The onset of antidepressant action of each drug has been similar, generally within one week.

e) Imipramine and fluoxetine had similar efficacy in multicenter, double-blind, placebo-controlled, outpatient s the treatment of major depressive disorder (Stark & Hardison, 1985). Five hundred forty patients were randor receive either fluoxetine 60 to 80 milligrams daily, imipramine 150 to 300 milligrams daily (the majority of pati Patients were treated for up to 6 weeks in double-blind fashion. Imipramine and fluoxetine were both superior measures (Hamilton Psychiatric Rating Scale for Depression total, Raskin Severity of Depression Scale, Clin Impressions Severity of Illness Scale, Global Improvement and secondary symptom measures). Fluoxetine a were similarly effective on all general measures of improvement. Anorexia and nausea occurred to a significa in fluoxetine-treated patients; constipation, dizziness, drowsiness, dry mouth, somatosensory disturbances, a sweating were reported more frequently with imipramine.

f) The efficacy and safety of fluoxetine and imipramine was compared in 40 depressed outpatients in a doub parallel trial (Bremner, 1984). Fluoxetine was given in doses increasing from 20 to 40 milligrams daily, then to daily, during the first week; imipramine doses were increased from 75 to 100 milligrams daily, then to 125 mil During the second and third weeks, the maintenance dose of each drug was determined, with fluoxetine bein up to 80 milligrams daily and imipramine up to 300 milligrams daily. During the fourth and fifth weeks of the st maintenance dose was achieved; the maintenance dose for most fluoxetine patients was 60 milligrams daily, milligrams daily for imipramine. Fluoxetine was reported superior to imipramine in the total Hamilton Psychiat Depression, as well as the HAM-D scales for anxiety/somatization, retardation and sleep disturbance. Fluoxe reported more beneficial than imipramine in the Raskin Severity of Depression Scale and Covi Anxiety Scale. HAM-D total score, and the Raskin and Covi scales, fluoxetine was statistically superior to imipramine only du of the study (week 5). The Clinical Global Impressions demonstrated the superiority of fluoxetine over imipran depression but not global improvement. Weight loss (average, 3.8 pounds) occurred with fluoxetine during tre increase in weight being seen with imipramine (average, 0.7 pounds). Heart rate increased significantly with i compared to slight decreases with fluoxetine. Blood pressure decreased with fluoxetine as compared with inc imipramine, and fluoxetine was associated with a lesser degree of gastrointestinal disturbances, dizziness, an mouth occurred in one of 20 fluoxetine patients and in 9 of 20 imipramine-treated patients, with nervousness fluoxetine-treated patients and in two imipramine-treated patients.

4.6.AD Fluvoxamine

4.6.AD.1 Depression

a) SUMMARY: Fluvoxamine and imipramine appear to be equally efficacious in the treatment of depression 1987; Guelfi et al, 1983; Guy et al, 1984; Itil et al, 1983); (March, 1990)(Lydiard et al, 1989).

b) Fluvoxamine demonstrated a trend toward superiority over imipramine in treating 63 patients with major d 4- to 6-week, randomized, placebo-controlled, double-blind study (Lapierre et al, 1987). All drugs were starte milligrams/day, and were gradually increased to a maximum of 300 mg/day. The mean daily dose of fluvoxam of the study was 207 mg, and 192 mg for imipramine. At the end of the study, the total Hamilton Rating Scale (HAM-D) score had decreased by 75%, 55%, and 6% in the fluvoxamine-, imipramine-, and placebo-treated g

respectively. At the end of the study there were 8, 3, and 1 responders from the fluvoxamine, imipramine, and
respectively. Only 1 patient in each active treatment group withdrew from the study because of adverse effec
c) Fluvoxamine was comparable to imipramine in antidepressant activity during a 4-week, double-blind, mult
151 patients (Guelfi et al, 1983). Drug therapy was administered in twice daily dosing in the range of 100 to 3
for fluvoxamine and 50 to 200 milligrams daily for imipramine. At the end of the study there was a mean impr
Hamilton Rating Scale for Depression (HAM-D) of 67.2% in the fluvoxamine-treated group and a 62.1% impr
imipramine-treated group. A similar improvement was detected with both drugs on the Clinical Global Impress
end of the study, the mean daily dose of fluvoxamine was 221 mg and 112 mg for imipramine. A total of 37 pa
from the study prematurely; 19 on fluvoxamine and 18 on imipramine. The reasons for early withdrawal appe
between both drugs.
d) Fluvoxamine and imipramine were comparable in efficacy for the treatment of depression in 36 patients di
unipolar or bipolar depression during a 4- to 6-week, randomized, double-blind study (Guy et al, 1984). Both
administered at bedtime with a maximal dosage range between 150 to 225 milligrams/day. In the unipolar de
fluvoxamine-treated patients, 92% were judged "improved" at the end of the study compared to 81% of the im
However, the imipramine-treated group appeared to have a higher percent of patients rated as "much" or "ve
improved, 75% compared to 54% of the fluvoxamine group.
e) A double-blind comparative study of fluvoxamine and imipramine was carried out in 20 outpatients with de
Patients received randomly-assigned medication over a 4-week period in a dosage range of 50 of 300 mg giv
doses. There was a significant symptom severity reduction in both groups at the end of 4 weeks, and fluvoxa
effective than imipramine in reducing suicidal ideas and anxiety/somatic symptoms. Anticholinergic-type adve
predominated for imipramine and gastrointestinal effects for fluvoxamine (Gonella et al, 1990).
f) In a 6-week, double-blind, placebo-controlled, variable-dose study assessing the comparative antidepressa
fluvoxamine (FLU), imipramine (IMI), and placebo (PBO), 45 patients with major depressive disorder were ev
response and side effects. Dosage ranged between 100 to 300 milligrams/day for active medications. No stat
differences between either the FLU (N=17) and PBO or the FLU and IMI groups were found. Side effects wer
three groups: IMI(N=18): constipation (83%), dry mouth (55%), and sweating, dizziness, and nausea, all 39%
diarrhea, headache, dry mouth, all 41%, nausea (35%), and flatus (29%). PBO(N=18): pruritus (29%, nausea
(18%), asthenia and somnolence, both 12%. This study revealed a high placebo response, with a 50% impro
Thus, it is difficult to show differences from active medication unless the study is carried out for a longer time.
numbers of patients are too small to detect a true difference. Second, patients seemed to either respond or n
while the response to IMI appeared to be more graded. This may reflect a subgroup of depressed patients th
serotonin-deficient type of depression (Lydiard et al, 1989).
g) Other double-blind, placebo-controlled studies comparing imipramine and fluvoxamine have only demons
improvement in depression with either drug when compared with placebo (Dominguez et al, 1985; Norton et a

4.6.AD.2 Adverse Effects

a) SUMMARY: Fluvoxamine produces less cardiovascular and anticholinergic adverse effects than imipramin
nausea and vomiting are more common with fluvoxamine therapy (Benfield & Ward, 1986; Roos, 1983; Salet
et al, 1993).
b) Adverse effects data was pooled from the results of 10 double-blind, placebo-controlled trials comparing f
(n=222) with imipramine (n=221) (Benfield & Ward, 1986). Anticholinergic effects such as dry mouth, dizzines
sweating, and abnormal accommodation were much more prevalent in patients receiving imipramine. Nausea
only adverse effect to be much more prevalent in the fluvoxamine-treated patients.
c) The cardiac effects of tricyclic antidepressants were compared with fluvoxamine. The major cardiac adver
observed with tricyclic antidepressants include postural hypotension, heart rate increase, and slight prolongat
intraventricular conduction time and QT interval. The only cardiac effect observed with fluvoxamine was a sta
clinically, significant slowing of heart rate (Roos, 1983).
d) Fluvoxamine produced less psychomotor impairment than imipramine. Fluvoxamine was superior to imipr
milligrams in regards to concentration, reaction time, mood, psychomotor activity, and affectivity. Following th
fluvoxamine 75 milligrams to 10 healthy volunteers, psychometric tests demonstrated a tendency towards an
psychomotor activity, concentration, attention, after-effect, and mood and a significant increase in critical flick
frequency when compared to placebo (Saletu et al, 1980).

4.6.AE Gepirone

4.6.AE.1 Depression

a) Gepirone extended-release 10 to 60 mg daily was only marginally superior to placebo at some time points
and tended to be less effective than imipramine 50 to 300 mg daily in one double-blind study involving patien
depression (Feiger, 1996).

4.6.AF Haloperidol

4.6.AF.1 Schizophrenia

a) Haloperidol was compared with placebo, chlorpromazine, diazepam, and imipramine as prophylactic ager
relapse of schizophrenic patients. At the end of the three-year trial, haloperidol and chlorpromazine significan
remission as compared to the other three treatments. Daily doses of haloperidol were 3 milligrams; chlorprom
75 mg (Nishikawa et al, 1982).

4.6.AG Lithium

4.6.AG.1 Depression

a) Lithium was more effective in the treatment of unipolar and bipolar depression in 63 female in-patients in a controlled study. The patients received either lithium in doses producing serum levels of 0.8 to 1.2 mmole/L o milligrams/day in divided doses. Improvement occurred more quickly with imipramine (between days 1 and 8) (days 8 to 22); however, all patients treated with lithium improved, but not all imipramine-treated patients did 1979).

4.6.AH Lofepramine

4.6.AH.1 Depression

a) A meta-analysis of 7 studies comparing lofepramine (n=372) with imipramine (n=372) concluded that lofep comparable with imipramine in efficacy and superior in tolerance (Kerihuel & Dreyfus, 1991). Overall, there w difference between the number of lofepramine-treated patients (64%) and imipramine-treated patients (58%) during the trials that ranged from 4 to 8 weeks. Significantly fewer patients reported side effects with lofepram imipramine (55% vs 68%; p less than 0.0001). Lofepramine doses ranged from 25 to 225 milligrams/d, and in ranged from 25 to 150 milligrams/d.

b) Lofepramine is a tricyclic antidepressant that is structurally similar to imipramine, but has an improved lipo et al, 1982).

c) Lofepramine and imipramine had similar efficacy in a randomized, double-blind, placebo-controlled clinica al, 1982). Of the 139 patients initially enrolled in the study, 89 completed the full 6 weeks of treatment (34 lofe imipramine, and 21 placebo). Dropout rates for the lofepramine and imipramine group were similar when com treatment failures and side effects. There was a significantly high placebo dropout rate, with the majority of pa out due to a lack of clinical efficacy. Lofepramine and imipramine were both significantly better than placebo i primary depression. There was no significant difference between the imipramine and lofepramine group with Lofepramine therapy was associated with significantly lower incidence of severe and/or moderate side effects with 66.7% observed in the imipramine group), and a lower incidence of side effects in general.

d) Lofepramine and imipramine were compared in a double-blind placebo-controlled study involving 158 dep outpatients. Both drugs were equally efficacious and superior to placebo therapy. Lofepramine therapy produ incidence of sedation and anticholinergic effects than imipramine therapy (Rickels et al, 1982).

4.6.AI Maprotiline

4.6.AI.1 Depression

a) SUMMARY: Maprotiline is considered very similar to imipramine in therapeutic efficacy (VanderVelde, 198 1977; Lehmann et al, 1976; Singh et al, 1976; Levine, 1975; Middleton, 1975; Rieger et al, 1975; Balestrieri e Maprotiline therapy may be associated with a quicker onset of action (VanderVelde, 1981); (Clayhorn, 1977).

b) Maprotiline 50 milligrams orally 3 times/day was administered to a maximum of 300 mg/day or imipramine milligrams orally per day to 341 patients with manic depressive illness. Patients ranged in age from 19 to 64 y treatment for 4 weeks. Improvement was based on Hamilton's and Self-Rating scales. Sixty-seven percent of receiving maprotiline were reported as improved compared with 66% of the patients who received imipramine system effects, dry mouth, tremor, blurred vision, and gastrointestinal effects were reported but were significa maprotiline-treated group (Logue et al, 1979).

c) Maprotiline was superior to imipramine in a double-blind, randomized controlled trial of 25 inpatients with p disorder (Rieger et al, 1975). The dose of maprotiline and imipramine was 50 milligrams three times a day for by a flexible dosing schedule for three weeks. Results of the 16 patients completing the trial showed the Ham Scores for the maprotiline group to be significantly better (p less than 0.05) than those for the imipramine gro the trial. The Zung Depression Scale favored maprotiline (p less than 0.01) on day seven and at the end of th than 0.10). Overall rating of global impression (p less than 0.05) and global improvement at endpoint (p less t indicated maprotiline to be superior to imipramine. Dropouts from the study included five maprotiline patients, hospital against medical advice, one improving so as to warrant discontinuation of therapy, and one due to in response. Two patients from the imipramine group dropped out due to toxicity, one due to deterioration after treatment, and one because of physician intervention. Side effects were prevalent on day three but decrease day 14. Common complaints in both groups were dry mouth, blurred vision, drowsiness, and nasal congestio reported only in the imipramine group.

4.6.AJ Melitracen

4.6.AJ.1 Depression

a) Four-week, double-blind trial; 29 patients with chronic schizophrenic or neurotic depression; melitracen 75 (mg)/day vs imipramine 50 to 150 mg/day. Brief Psychiatric Rating Scale, Hamilton Psychiatric Rating Scale Impression: some improvement in both treatment groups, efficacy of imipramine superior to melitracen (not s significant). Melitracen better tolerated than imipramine: 46 adverse effects (drowsiness, dry mouth, increase tinnitus, agitation) for melitracen vs 69 for imipramine. Quicker average onset of therapeutic effect for melitra 2.2 weeks (Biros et al, 1969).

4.6.AK Methscopolamine

4.6.AK.1 Nocturnal enuresis

a) Methscopolamine is ineffective in the treatment of enuresis. In a study with 40 severely enuretic boys, me bromide was used to determine whether some subgroups of enuretic children might respond to the peripher muscarinic receptors. The effects of treatment with imipramine, desipramine, methscopolamine bromide, and compared; the tricyclic antidepressants were superior to methscopolamine and placebo (Rapoport et al, 198

4.6.AL Mianserin

Depression

Nocturnal enuresis

4.6.AL.1 Depression

a) Studies to date suggest that there is no significant difference in overall efficacy between imipramine and n treatment of depression in both inpatients and outpatients (Pichot et al, 1978; Murphy et al, 1976; Murphy, 19 several deficiencies are apparent in clinical trials to date, and 1 study has indicated that improvements seen imipramine were equivalent to those observed with placebo (Perry et al, 1978). (However, these patients wer weeks, which may have been insufficient time for therapeutic effects from either drug to occur).

b) Mianserin therapy (20 to 60 milligrams/day) in elderly depressed patients (n=50, age 60 to 80 years) is as imipramine therapy (75 to 150 milligrams/day) (Eklund et al, 1985). The incidence of dry mouth, dizziness, fa weakness was greater in the imipramine group than in the mianserin group, however the total number of side by each group was not significantly different. From these results the authors concluded that mianserin may b imipramine in the treatment of depression in elderly patients because of its lower incidence of side effects. H number of mianserin treated patients withdrew from the study due to confusion, worsening of the condition, o Considering this, it is to early to conclude that mianserin is superior to imipramine in the treatment of depress

4.6.AL.2 Nocturnal enuresis

a) Imipramine was superior to mianserin and placebo in achieving dry nights and reducing wetness scores (mianserin was not superior to placebo. This was a multicenter, randomized, double-blind study involving 80 c al, 1996).

4.6.AM Milnacipran

4.6.AM.1 Depression

a) SUMMARY: Milnacipran offers no efficacy advantage over tricyclic antidepressants

b) Milnacipran 50 to 100 mg twice daily has been comparable to or less effective than imipramine 100 to 15 amitriptyline 150 mg daily, and clomipramine 75 to 150 mg daily in the treatment of major depressive disorde endpoints were improvements on the Hamilton and Montgomery-Asberg scales (Tignol et al, 1998; Leinonen Kasper et al, 1996; Anon, 1997a; Von Frenckell et al, 1990; Ansseau et al, 1989). A more rapid onset of actio observed with clomipramine and amitriptyline (Leinonen et al, 1997; Ansseau et al, 1989).

c) Greater improvement of CGI-3 scores (therapeutic index, incorporating efficacy and tolerance) was report milnacipran in a manufacturer-prepared meta analysis of tricyclic antidepressant comparative trials (Anon, 19 1996), and this appears in manufacturer product information. However, statistical significance between treatm demonstrated (Anon, 1997a).

4.6.AN Moclobemide

4.6.AN.1 Depression

a) SUMMARY: Moclobemide and imipramine have been similarly effective in the treatment of depression; ac generally been greater with imipramine.

b) Moclobemide 300 to 600 milligrams orally daily has been as effective as imipramine 100 to 200 milligrams treatment of endogenous and non-endogenous depression in controlled clinical trials (Baumhackl et al, 1989; 1990; Versiani et al, 1989a; Versiani et al, 1989; Versiani et al, 1990a; Stabl et al, 1989; Lecrubier & Guelfi, 1 1990). However, a trend (not statistically significant) toward the superiority of imipramine over moclobemide i or neurotic depression has been observed by some investigators (Biziere & Berger, 1990; Versiani et al, 198 rapid response was reported with moclobemide in 1 study (Udabe et al, 1990).

c) In 1 study, the response rate to imipramine and moclobemide was similar in both males and females. How tended to be less effective in depressed patients over 60 years of age as compared with patients under 60 (E 1990).

d) Moclobemide and imipramine were equally efficacious in a placebo-controlled, 6-week study (Versiani et the largest trials to date (n=490) involving patients with a major depressive episode (50% with endogenous d reduction in the average Hamilton Rating Scale for Depression (HRSD) was observed with moclobemide 300 daily, as compared with 28% with placebo, during 6 weeks of treatment. Imipramine (100 to 200 milligrams d for comparison in this study, and was as effective as moclobemide, producing a 56% reduction in HRSD scor final assessments of efficacy by the investigators, good to very good responses were reported in 70% of pati

moclobemide, 70% treated with imipramine, and 28% treated with placebo. When subgroups of patients with non-endogenous depression were analyzed, both drugs were similarly effective and superior to placebo in ea Overall tolerability assessments favored moclobemide over imipramine (Versiani et al, 1989).

4.6.AN.2 Adverse Effects

a) Adverse effects have generally been less with moclobemide compared to imipramine, particularly dry mou tremor, sweating, and blurred vision (Stabl et al, 1989).

4.6.AO Moricizine

4.6.AO.1 Cardiac dysrhythmia - Myocardial infarction with complication, Post

a) Encainide and flecainide were more effective in suppressing ventricular arrhythmias than moricizine, imipr placebo during the dose titration phase of a 1-year, multicenter, randomized, double-blind and placebo-contro patients (Anon, 1988b). Patients were eligible for this study if they had an acute myocardial infarction within 6 entrance to the study, were less than 75 years of age and demonstrated either an average of 10 or more ven complexes (VPCs) per hour or 5 or more episodes of unsustained ventricular tachycardia (3 to 9 consecutive of 100/minute or more) during a 24-hour ambulatory ECG recording. The total daily doses of the study drugs to 180 milligrams for encainide, from 200 to 400 milligrams for flecainide, from 150 to 375 milligrams for imipr 600 to 900 milligrams for moricizine. Efficacy was defined as 70% or more suppression in VPC frequency and suppression of runs of VCP when compared to baseline. The efficacy rates were 83% for flecainide, 79% for moricizine, 52% for imipramine, and 37% for placebo during the dose titration phase of the study. The incider effects was 49% for encainide, 55% for flecainide, 67% for imipramine, 64% for moricizine, and 60% for place was the drug most associated with patient withdrawal due to adverse effects. This study did not address VPC efficacy at the 1-year follow-up.

4.6.AP Nefazodone

4.6.AP.1 Depression

a) Nefazodone was comparable overall to imipramine in a 6-week double-blind, placebo-controlled study inv with major depression. Average doses at the end of 6 weeks were 180 and 158 milligrams daily, respectively drugs were not always significantly superior to placebo in improving Hamilton Rating Scale for Depression (H imipramine tended to be superior to nefazodone on the visit-wise (observed case) analysis of HAM-D; in this imipramine was statistically superior to placebo at weeks 4 through 6 of treatment, whereas nefazodone was effective only at week 5. Neither agent proved statistically more effective than placebo on the Clinical Global (clinician's rating). Although adverse effects tended to be less with nefazodone, specific effects induced by ei not presented. This study did not provide a direct statistical comparison of imipramine and nefazodone (Feigh

b) Meta-analysis of 6 placebo-controlled, double blind studies showed that nefazodone and imipramine were treating major depression and the accompanying symptoms of anxiety, and nefazodone was superior to imipr treatment of agitation (Fawcett et al, 1995). Nefazodone (100 to 600 milligrams/day; mean endpoint dose=39 n=184), imipramine (25 to 300 milligrams/day; mean endpoint dose=178 milligrams; n=288), and placebo (n= compared in four 6-week and two 8-week studies. Both agents were significantly better than placebo in treati Anxiety symptoms were significantly improved by both agents compared with placebo; nefazodone resulted i both psychic anxiety and somatic anxiety as measured by the HAM-D scale, whereas imipramine had no effe anxiety. Nefazodone was significantly better than placebo in relieving agitation at weeks 1 and 3 through end showed a significant difference from placebo only at endpoint.

c) In a randomized, double-blind, placebo-controlled trial, nefazodone and imipramine were compared in 180 depression (Fontaine et al, 1994). Nefazodone was comparable in antidepressant efficacy to imipramine; sign improvement was evident in self-report anxiety symptoms as early as week 1 for nefazodone patients in eithe therapeutic dose range of nefazodone was found to be 100 to 500 milligrams/day, with most patients ultimate 500 milligrams/day. In this trial, nefazodone-treated patients experienced significantly fewer adverse events t The dose of imipramine ranged from 50 to 250 milligrams/day with the average dose being 214.4 milligrams/

4.6.AP.2 Adverse Effects

a) With acute phase- or long-term use of therapeutic doses of nefazodone or imipramine for depression, sign imipramine-treated patients than nefazodone-treated patients experienced clinically significant weight gain (g body weight). A retrospective analysis of pooled data from 3 studies comparing nefazodone (n=225) and imip showed that, at some time during the long-term phase of treatment, 9.5% of those taking nefazodone and 24 imipramine had clinically significant weight gain. At study endpoint, 2.9% and 19.7%, respectively (p=0.001) s gain. Percentages of patients with weight gain during acute-phase treatment were 0.9% for nefazodone and 4 imipramine (p=0.02) (Sussman et al, 2001).

4.6.AQ Nomifensine

4.6.AQ.1 Depression

a) SUMMARY: Nomifensine and imipramine appear similarly effective in the treatment of depression in inpat outpatients, including the elderly; comparative doses for each have been 75 to 150 milligrams/day. In genera nomifensine is less than imipramine (Merideth et al, 1984; Bremner et al, 1984; Cohn et al, 1984; Amin et al, 1978b; Forrest et al, 1977).

b) Nomifensine was as effective as imipramine in 20 patients with endogenous over-reactive depression (An Patients received 147.9 milligrams (mean) nomifensine daily or 158.3 milligrams (mean) imipramine daily in a

controlled, double-blind study. The incidence of anticholinergic side effects was lower with nomifensine than i
Nomifensine and imipramine, each in doses of 75 to 150 mg/day for 6 weeks, were equally effective in the tre
depressed patients. Autonomic side effects with nomifensine occurred less frequently than with imipramine (A
c) Nomifensine was equally efficacious as imipramine in 28 patients who received a daily dose of 150 to 200
period of 20 to 30 days. Side effects associated with nomifensine were lower than those associated with imip
al, 1974).
d) Based on the Hamilton rating scale and the Beck depression inventory, nomifensine and imipramine were
efficacious in the treatment of 30 outpatients with depression. Side effects of nomifensine and imipramine we
(Forrest et al, 1977).
e) Nomifensine in average doses of 150 milligrams orally daily was reported similarly effective as imipramine
the treatment of depression in outpatients in a 4-week controlled study (Bremner et al, 1984). However, toxici
mouth and sedation) was more frequent in imipramine patients.

4.6.AR Nortriptyline

4.6.AR.1 Depression

a) Most studies have indicated that there are no significant differences between nortriptyline and other antide
the tricyclic category such as amitriptyline (Rose et al, 1965; Leahy & Martin, 1967; Mendels, 1968; Martin &
Malitz & Kanzler, 1971), desipramine (Levy, 1966; Arieff, 1966; Stewart & Mitchell, 1968; Haider, 1968), protr
1966), and imipramine (Kessell & Holt, 1970).

4.6.AR.2 Efficacy

a) The effects of imipramine and nortriptyline on left ventricular function and blood pressure were studied du
ranging study of 20 patients with ventricular arrhythmias. Ten consecutive patients with more than 30 ventricu
depolarizations (VPDs) were treated with imipramine starting at 1 milligram/kilogram/day, increased by 1 mg/
second day, to a maximum dose of 5 mg/kg/day. Nortriptyline was administered to 10 similar patients beginni
milligram/kilogram/day, increased by 0.5 mg/kg/day every third day to a maximum of 3.5 mg/kg/day. The 2 gr
in terms of age, sex distribution, etiology of heart disease and NYHA functional class. At a mean effective dos
imipramine suppressed VPDs by 74%; VPDs were suppressed 85% by a maximally effective nortriptyline dos
Ejection fraction was slightly decreased with imipramine (from 33% to 31%) and with nortriptyline (from 43 to
decreases in orthostatic systolic pressure were greater following imipramine (26 mmHg) than after nortriptylin
significant change in supine systolic or diastolic blood pressure was noted after either drug. No significant rel
change in standing systolic blood pressure and daily dose, plasma drug concentration, or NYHA functional cl
demonstrated with either drug. Changes in standing systolic pressure were related to patient age with patient
old experiencing greater reductions in systolic pressure following administration of both drugs. To determine i
exist between imipramine and nortriptyline in terms of antiarrhythmic efficacy, studies in cardiac patients who
crossed-over, and randomized to double-blind treatment are needed (Giardina et al, 1985).

4.6.AS Paroxetine

Anxiety

Bipolar disorder, depressed phase

Depression

4.6.AS.1 Anxiety

a) In an uncontrolled trial, paroxetine and imipramine were as effective as 2- chlordesmethyldiazepam, a ben
treating generalized anxiety disorder (Rocca et al, 1997). Patients (n=81) received paroxetine 20 milligrams(r
imipramine 50 to 100 mg/day, or 2-chlordesmethyldiazepam 3 to 6 mg/day for 8 weeks. Over the first 2 week
with 2-chlordesmethyldiazepam showed greater improvement; however, after 4 weeks for paroxetine and 8 w
imipramine, the anti-depressants were more effective. Adverse effects consisted primarily of anticholinergic e
imipramine, nausea for paroxetine, and drowsiness for 2-chlordesmethyldiazepam. Larger, blinded, controlle
needed to confirm the results of this study.

4.6.AS.2 Bipolar disorder, depressed phase

a) Neither paroxetine nor imipramine was more effective than placebo in treating BIPOLAR DEPRESSION ir
stabilized on lithium if their serum lithium levels were above 0.8 milliequivalents per liter (meq/L). However, pa
serum lithium concentration was less than 0.8 meq/L showed greater improvement with 8 weeks of antidepre
than with placebo treatment (p=0.05 for paroxetine, p=0.04 for imipramine). In a double-blind study, patients
according to serum lithium concentration and then randomized to receive paroxetine (n=35), imipramine (n=3
(n=43) for 10 weeks. Among all completers of the study, therapeutic response (Hamilton depression scale sc
was achieved by 56%, 48%, and 54% of patients receiving paroxetine, imipramine, and placebo, respectively
accounted for study discontinuation in 1 patient in the paroxetine group (3%), 12 in the imipramine group (30
placebo group (12%). No patient in the paroxetine group experienced induction to mania, whereas 3 patients
imipramine and 1 treated with placebo developed treatment-emergent mania (Nemeroff et al, 2001).

4.6.AS.3 Depression

a) SUMMARY: Paroxetine, a selective serotonin reuptake inhibitor, and imipramine appear to be similarly eff treatment of major depression. The decision as to which drug to use should be based on patient-related char anxiety disorders, sleep disturbances, cardiovascular disease), potential drug interactions, and side effects.

b) Paroxetine, imipramine, and placebo were compared in 120 outpatients with moderate-to-severe major de (Feighner & Boyer, 1989). Following a 4- to 14-day single-blind, placebo washout period, patients were assig either paroxetine, imipramine, or placebo for 6 weeks. The dose of paroxetine and imipramine could be incre maximum of 50 milligrams and 275 milligrams daily, respectively. Paroxetine was superior to placebo in 5 of evaluated (HAMD scale, Raskin depression scale, MADRS, CGI scale, Covi anxiety scale); no improvement compared to placebo in the 56-item Symptom Checklist (SCL-56). Imipramine was also statistically superior t HAMD, Raskin, MADRS, and the CGI scale, but not on the Covi anxiety scale or the SCL-56. The only outco improved to a significantly greater degree with paroxetine was the HAMD total score. A high number of patie therapy (approximately 50%), which limits evaluation of efficacy. If only the patients completing the study are imipramine and paroxetine appear to be equally effective. Based upon the number of dropouts due to advers paroxetine appeared to be better tolerated than imipramine: 10% versus 30%. The most common adverse ef paroxetine were sedation and gastrointestinal effects, whereas anticholinergic adverse effects (dry mouth, co symptoms) were the most common with imipramine. However, a detailed incidence of all adverse effects was making it difficult to fully compare these agents.

c) Paroxetine was more effective than placebo in the short-term (6-week) treatment of depression; however, less effective than imipramine. The study was double-blinded and 122 patients with a major depressive disor randomized to receive either paroxetine (dose range 20 to 50 milligrams/day), imipramine (dose range 65 to milligrams/day) or placebo. At the end of the study, the imipramine-treated patients demonstrated consistentl both objective and subjective, on all depression rating scales when compared to paroxetine. Overall there wa rate to imipramine, a 48% response rate to paroxetine, and a 33% response rate to placebo (Peselow et al, 1

d) A multicenter, double-blind, placebo-controlled evaluation of paroxetine and imipramine in the outpatient t depression was conducted (Dunbar et al, 1991). After a 4- to 14-day placebo run-in period, patients were ran treatment groups; 240 to the paroxetine group, 237 to the imipramine group, and 240 to the placebo group. T started at 20 milligrams paroxetine and 80 milligrams imipramine. Dosage adjustment, if necessary, was don intervals over the six-week treatment phase. Drop-out rates were high for all groups; paroxetine 42.5%, imipr placebo 53.6%. Lack of efficacy (10%, 7%, and 33%, respectively) and side effects (23%, 36%, and 9%, resp most common reasons stated for dropping out of the study. Imipramine and paroxetine were equally superior produced similar efficacy results. However, paroxetine therapy was associated with less sedation, cardiovasc anticholinergic side effects.

e) Newer clinical trials have continued to support the previous findings that imipramine and paroxetine are si effectiveness. The major differences between the two compounds are the frequency of side effects, types of frequency of patients withdrawing from the clinical trials secondary to side effects from the study medications paroxetine therapy is better tolerated and associated with lower withdrawal rates (Ohrberg et al, 1992; Feighr (Arminen et al, 1994).

f) A 6-week, double-blind study was continued for 1 year by crossing over all patients who had failed to resp treatment to the other drug (Peselow et al, 1989a). Patients first treated with placebo were crossed over to pa total of 15 patients initially treated with paroxetine switched to imipramine, while 10 imipramine patients were paroxetine. Of the patients who initially failed on paroxetine, 73% responded to imipramine, while 50% of the initially failed on imipramine responded to paroxetine. Similar studies have shown paroxetine to be at least as imipramine with fewer side effects (Fabre, 1992; Cohn & Wilcox, 1992; Shrivastava et al, 1992; Feighner & B

4.6.AT Phenelzine

Depression

Posttraumatic stress disorder

4.6.AT.1 Depression

a) SUMMARY: Phenelzine and imipramine have been found to be equally effective in treating depression an imipramine was more effective in the treatment of hostility and paranoia, whereas phenelzine was more effec panic attacks (Davidson et al, 1981; Davidson et al, 1987; Isberg, 1981). Phenelzine therapy is superior to im treatment of atypical depression (Liebowitz et al, 1984; Stewart et al, 1989; Quitkin et al, 1988; Quitkin et al, 1990; Quitkin et al, 1993; McGrath et al, 1991). In one case report, phenelzine treatment was found to relieve obsessive-compulsive disorder (OCD) when treatment with amitriptyline and imipramine had failed.

b) Imipramine (median, 150 milligrams daily) had comparable efficacy with phenelzine (median, 75 milligram treatment of major depression in a 5-week, controlled, outpatient study. However, phenelzine was reported s imipramine in patients also presenting with panic attacks (Davidson et al, 1987).

c) Phenelzine, imipramine, and placebo were compared in a double-blind study in 74 patients with probable depression (Quitkin et al, 1988). Sixty patients completed the study. Dropout was similar among treatment gr weeks, 28% of the placebo-treated group, 50% of imipramine group, and 71% of the phenelzine group were

responders. Patients with reactive mood and only one associated symptom appeared to get more benefit with
During the next 6 weeks of the study, 41% of the placebo patients, 21% of the imipramine patients, and 7% o
patients experienced a relapse, despite continued drug therapy. Patients with definite atypical depression and
attacks responded well to drug therapy; after 6 weeks, response was observed in 60% of the placebo patient
imipramine patients, and 64% of the phenelzine patients. Patients with definite atypical depression without a
attacks did not respond as well; after 6 weeks, response was observed in 7% of the placebo group, 44% in th
group, and 83% in the phenelzine group.

d) A comparison of the results of one study were contrasted with previously published data from 180 patients
depression (Quitkin et al, 1988; Quitkin et al, 1989). Both imipramine and phenelzine were equally effective in
simple mood reactive depressive patients. Patients with atypical depression tended to respond better to phen
imipramine and 66% that had failed imipramine therapy responded with phenelzine therapy.

e) Replication of a previous study (Quitkin et al, 1988) substantiated the previous finding that phenelzine is s
imipramine and placebo in the treatment of atypical depression (Quitkin et al, 1990). This study used the sam
minor changes in dose schedule as in the 1988 study and included 90 patients with atypical depression which
included in the previous study population. Comparison of both groups found no significant difference between
population.

f) A six-week comparison of imipramine, phenelzine, and placebo was conducted in 194 nonmelancholic dep
with features of atypical depression (Stewart et al, 1989). The overall response rates was 71% with phenelzin
73 milligrams/day), 48% with imipramine (mean dose was 265 milligrams/day), and 26% with placebo (mean
tablets/day). Patients with dysrhythmic disorder tended to respond better than those with major depression. A
relationship was found in the placebo group between response and chronicity of the disorder.

g) Double-blind trials demonstrated that some patients may require chronic treatment with antidepressants to
remission from atypical depression. Patients who improved after 6 months of imipramine therapy were rando
either placebo or their same imipramine dose for a further 6 months in a double-bind fashion. A similar double
done in patients who had been maintained successfully on phenelzine. In the imipramine trial (n=32), the recu
continued imipramine (41%) and placebo (47%) was not significantly different. However, in the phenelzine tri
recurrence rate of 87% in the placebo treated patients was significantly higher (p=0.001) than those continue
(23%). Comparison of the results between imipramine and phenelzine is limited by the absence of blinding be
and baseline differences, with earlier onset and longer history of depressive illness in the phenelzine group p
to the high recurrence in those switched from phenelzine to placebo (Stewart et al, 1997).

4.6.AT.2 Posttraumatic stress disorder

a) A double-blind, placebo-controlled study of 60 male veterans found phenelzine to be better than imipramin
of combat-induced post-traumatic stress disorder (Kosten et al, 1991). Patients were treated with an average
milligrams imipramine and 68 milligrams phenelzine for 8 weeks. Dropout rates were high in all three groups
placebo, 60.9% with imipramine, and 21.1% with placebo, 60.9% with imipramine, and 21.1% with phenelzine
common reason being failure to return for clinic visits (50%, 50%, and 25%, respectively). At the end of 8 wee
and phenelzine produced greater improvement than placebo and phenelzine was demonstrated more effectiv
in improving Impact of Event Scale scores and post-traumatic stress disorder symptoms.

4.6.AU Reboxetine

4.6.AU.1 Depression

a) Reboxetine exhibited similar efficacy to, better tolerability than, and earlier onset of effect than imipramine
of major depression in a short-term study (6 weeks) (Berzewski et al, 1997). Patients (n=256) were randomiz
with reboxetine 4 milligrams (mg) twice daily or imipramine 50 mg twice daily with the evening dose increased
weeks of treatment. According to scores on the Hamilton Depression rating scale (HAM-D), response rates fo
with reboxetine or imipramine were 68.5% and 56.2% (statistically significant difference) respectively, and re
last assessment were 52% and 45.5%, respectively. On the Clinical Global Impression Severity of Illness and
Improvement scales (CGI-SI and CGI-GI), the percentage of reboxetine-treated patients classified as "norma
increased more rapidly than the group treated with imipramine, indicating an earlier onset of response. The M
Asberg Depression Rating Scale (MADRS) demonstrated no difference between the two treatment groups. In
adverse events described as probably or definitely related to treatment were 31.9% and 39% for patients trea
reboxetine or imipramine, respectively.

4.6.AV Ritanserin

4.6.AV.1 Depression

a) Ritanserin, a serotonin-2 antagonist, was compared with imipramine in a double-blind, placebo-controlled
patients with mild chronic depression (dysthymic disorder). At the end of the study imipramine was slightly mo
ritanserin based on the Hamilton Depression Rating Scale and the Zerssen Self-Rating Scale but was associ
frequency of side effects and a greater attrition rate (Bakish et al, 1994).

4.6.AW Rolipram

4.6.AW.1 Depression

a) Imipramine was superior to rolipram in patients with major depressive disorder in one double-blind study (
et al, 1989).

4.6.AX Sertraline

Depression

Dysthymia

Mixed anxiety and depressive disorder

4.6.AX.1 Depression

a) More than 50% of chronically depressed patients who were nonresponders to an antidepressant responde to an antidepressant of another class. Patients who had completed a randomized, 12-week, double-blind trial sertraline or imipramine for treatment of chronic depression and had failed to respond were switched to the a for 12 more weeks of double-blind treatment. Fifty-one patients were switched from imipramine to sertraline a sertraline to imipramine. Mean dosages at study end were 221 milligrams (mg) per day for imipramine and 16 sertraline. Ten percent of those switched to sertraline and 25% of those switched to imipramine dropped out. dropout rate was mainly due to intolerable adverse effects of imipramine. Those who switched to imipramine significant reductions in 3 adverse effects but significant increases in 8 adverse effects, whereas those who s sertraline had significant decreases in 6 adverse effects and significant increases in one:

	SERTRALINE TO IMIPRAMINE	IMIPRAMINE TO SE
DECREASED INCIDENCE		
	Insomnia	Dry mout
	Diarrhea	Somnolen
	Abdominal Pain	Increased sw
		Constipati
		Dizzines
		Urinary comp
INCREASED INCIDENCE		
	Dry mouth	Insomnia
	Increased sweating	
	Constipation	
	Dizziness	
	Tremor	
	Abnormal taste	
	Increased appetite	
	Urinary complaints	

b) The intent-to-treat response rates were 60% for sertraline and 44% for imipramine (p=0.03). Among comp response rates were 63% and 55%, respectively (p=0.16). After averaging across the study weeks and adjus status, depression type, and baseline value, there were no significant differences between groups in outcome improvement over time did not differ for the 2 groups (Thase et al, 2002).
c) In a double-blind study of major depression with or without dysthymia, response to sertraline was highest response with imipramine was highest in men. Patients meeting DSM III-R criteria for chronic major depressi

400 women) were randomized to 12-week treatment with sertraline or imipramine in a 2:1 ratio. Both drugs w milligrams (mg) daily and titrated to a maximum of 300 mg for imipramine and 200 mg for sertraline. Althoug response to sertraline was similar to imipramine, a statistically significant gender and treatment interaction wa highest response rates occurred in women taking sertraline and in men taking imipramine. More women resp (147/260; 57%) than to imipramine (61/133; 46%); and more men responded to imipramine (43/69; 62%) tha (73/161; 45%). Gender differences also occurred in the types of adverse events reported, and more women v imipramine group than from the sertraline group; however, withdrawal rates by men were not significantly diff drugs. A significant interaction was also seen between menopausal status and treatment. Withdrawal from tre highest in premenopausal women taking imipramine and postmenopausal women taking sertraline. The mecl these gender differences is unknown, and may relate to interaction of female sex hormones and serotonin ac al, 2000)

4.6.AX.2 Dysthymia

a) Sertraline and imipramine are equally effective for the treatment of dysthymia; however, sertraline is bette randomized trial, sertraline and imipramine were compared and evaluated in a group of 416 patients with ear dysthymia. Outcome was based on response based on clinical evaluation (Hamilton Rate Scale for Depressi Asberg Depression Rating Scale, Hopkins Symptom Checklist) and patient-rated version of the Inventory of D Symptoms. Improvement of scores of Clinical Global Impressions of 1 or 2 (very much or much improved) de response rates of 59% for sertraline, 64% for imipramine, and 44% for placebo. The mean dose of required f was 89.5 milligrams (mg) for sertraline and 159.7 milligrams for imipramine (Thase et al, 1996).

b) Of the 416 patients described in the study above by Thase et al, 355 had completed the Tridimensional P Questionnaire before and after treatment, and the results revealed that temperament scores improved with in dysthymia. At baseline, temperament in dysthymic patients was abnormal, with higher mean harm avoidance Tridimensional Personality Questionnaire than that reported for a community population. After 12 weeks of tr avoidance scores decreased significantly, with no significant differences between the sertraline, imipramine, Scores decreased for those achieving remission and those who did not; however, decreases were significant the remitters. Thus, improvement in temperament was mainly related to disease improvement regardless of t results revealed some gender and treatment effects, and further studies using multiple measures, rather than measure used in this study, would be needed to determine treatment effects on temperament and personality 2000).

4.6.AX.3 Mixed anxiety and depressive disorder

a) Imipramine and sertraline were equally effective in the treatment of anxiety and depression in patients witl disorder and major depressive disorder. In an randomized, multicenter, double-blind study, patients with full A disorder with concurrent major depressive disorder with a minimum of 4 panic attacks in the 4 weeks prior to baseline Montgomery-Asberg Depression Rating Scale (MADRS) score of at least 20 received either sertralir 100 milligrams (mg), mean dose, 65.4 mg/day) or imipramine (n=69; 100 to 200 mg, mean dose 144.2 mg/da Sertraline was given at an initial dose of 25 mg/day for 1 week, then titrated to 50 mg/day for 4 weeks, at whi could be increased to 100 mg, if needed. The initial dose of imipramine was 25 mg/day, increased at weekly 100 mg, and 150 mg. If needed, the dose could be increased again to 200 mg or reduced to 100 mg. Primary measures were weekly panic attack frequency and MADRS score. Sertraline and imipramine produced simila the mean baseline (28.5 vs 28.7, respectively) to endpoint (11.1 vs 11.2, respectively) total MADRS score an baseline (7.1 vs 7, respectively) to endpoint (2.9 vs 2.3, respectively) weekly panic attack frequency. Howeve treated patients reported significantly fewer adverse effects as compared with imipramine-treated patients (23 respectively; p=0.005) and fewer discontinued treatment (11% vs 22%, respectively; p=0.04). Nausea and dia frequently reported with sertraline treatment, while dizziness, dry mouth, sweating, tremor, and constipation w with imipramine administration (Lepola et al, 2003).

4.6.AY Sotalol

4.6.AY.1 Ventricular arrhythmia

a) Sotalol has been shown to be superior to procainamide, quinidine, mexiletine, propafenone, pirmenol, and ability to prevent death and the recurrence of ventricular arrhythmias in selected patients with ventricular tach Patients with a history of ventricular fibrillation or flutter with inducible, sustained ventricular tachyarrhythmias study drugs in random order until one was predicted effective by either Holter monitor assessment or progran stimulation (PES). Long-term therapy with the first effective drug was followed to one of three primary endpoi recurrence, sudden death, or unmonitored syncope. By PES, sotalol was predicted effective in 35% of a total compared to 16% for all other drugs. Although not significant, Holter assessment predicted sotalol effective fo suppression in 41% versus 45% for all other drugs combined. After two years of follow-up on chronic therapy pooled data for all the other drugs, sotalol had the lowest mortality rate (13% to 22%), lowest VT recurrence r and lowest drug withdrawal rate (38% compared to 75% to 80%). Since there was no control group, it is unkn sotalol improved survival or identified a population with a good prognosis (Prod Info Betapace(R), 1996; Mas 1989b).

4.6.AZ Tranylcypromine

4.6.AZ.1 Depression

a) Tranylcypromine is superior to imipramine in the treatment of patients with anergic bipolar depression (Hir

1991). Fifty-six patients with bipolar depression (with 73% meeting the criteria for anergic depression) were ra
to treatment with tranylcypromine 20 to 80 milligrams or imipramine 100 to 400 milligrams/day in a double-bli
study. The mean dose at the end of six weeks was 36.8 mg of tranylcypromine and 245.5 mg of imipramine.
anergic bipolar depression who did not respond to therapy in the initial phase (n=16) were then enrolled in a
with the same doses of each drug (Thase et al, 1992). Nine of the 12 patients who were switched to tranylcyp
to therapy and only one out of four patients switched to imipramine improved. Hypomania and mania develop
drugs, but occurred earlier (5.8 weeks vs 9.2 weeks) in those receiving imipramine.
b) In a double-blind study of 137 patients with psychotic depression, tranylcypromine 10 milligrams three tim
administered for an average of 22 weeks. Patients were also randomly allocated to receive phenelzine or imi
weeks of therapy, 47% of tranylcypromine patients were improved, and after termination of the study 44% we
Tranylcypromine was slightly less effective than imipramine, but more effective than phenelzine (Haydu et al,

4.6.BA Trazodone

4.6.BA.1 Depression

a) Trazodone is not therapeutically superior to imipramine, but its side effects are less troublesome (Fabre e
Feighner, 1980; Gerner et al, 1980; Escobar et al, 1980; Workman & Short, 1993a; Gershon, 1984). Anticholi
occurred more frequently in patients treated with imipramine than those treated with trazodone in a multi-cent
Newton, 1980).
b) A multicenter trial involving 379 patients treated with trazodone 200 to 600 milligrams (mg) per day imipra
mg/day or placebo for 21 to 24 days demonstrated imipramine and trazodone to be of equal efficacy (Gersho
1980). Another study involving 28 patients with endogenous depression receiving an average trazodone dose
an average imipramine dose of 140 mg/day for 28 days also demonstrated equal effectiveness between the 2
al, 1979). The results of a double-blind study involving 45 patients suggested that trazodone 200 to 600 mg/d
more rapid and prolonged improvement than did imipramine 100 to 300 mg/day (Feighner, 1980). In a double
study of 40 patients with endogenous depression, imipramine (maximum daily dose 300 mg) produced more
Hamilton depression scale scores on days 14 and 28 than trazodone (maximum daily dose 600 mg) (Escoba
c) Seventy-four patients were enrolled in a nonrandomized study with placebo baseline treatment to evaluate
imipramine, alprazolam, and trazodone in the treatment of agoraphobia (Charney et al, 1986). Twenty-nine p
assigned to imipramine, 28 to trazodone, and 26 to alprazolam treatment. All patients were treated with place
and then blindly switched to active treatment for clinical response and side effects. Both imipramine and alpra
effective in controlling the agoraphobia, however, alprazolam had a faster onset of action. Clinical responses
within one week with alprazolam therapy and were generally not observed in imipramine treated patients unti
week of therapy. Trazodone therapy was considered not effective in the treatment of agoraphobia.
d) In a double-blind controlled study, imipramine and placebo were compared with trazodone in the treatmer
patients with primary depression. The mean doses received during this study were 6.26 capsules/day of 50 m
trazodone, 6.37 capsules/day of imipramine 25 mg or 10.67 capsules/day of placebo. Three of 17 patients in
groups experienced a 50% reduction in the Hamilton total score on or before day 7 of therapy. On day 14, 8 p
trazodone group achieved this level of improvement. Of the imipramine- treated patients, no one in the group
improvement at day 7. However, by day 14, eight patients in the group had also experienced at least a 50% r
Hamilton differences in the subjects tested through the structured clinical interview. Clinical global impression
significant difference between trazodone and placebo in the proportion of improved patients at the end of 28
Global ward behavior indicated that trazodone was significantly (p less than 0.01) better than placebo for tens
inwardly distressed behavior and difficulty in sleeping. It was significantly (p less than 0.05) better for tired, w
energy behavior and anxious, worried, afraid behavior and concern for bodily health. Trazodone was slightly
0.10) for irritable, annoyed, impatient or angry behavior. Drowsiness was the most frequent side effect experi
trazodone treated patients. Anticholinergic effects were the most common effects in the imipramine group (Fe
e) Ten institutions participated in a multi-center, double-blind, placebo-controlled evaluation of either trazodo
in 263 in-patients. Inclusion criteria included primary depression of the endogenous type, minimum score of 1
Rating Scale for depression (HAM-D) and at least 7 of 21 symptoms in 3 of 5 categories of the symptom prof
Initial doses were 200 mg and 100 mg daily for trazodone or imipramine. At the end of 28 days, 113 patients
lack of efficacy or side effects. Drop out rates were 37% each for imipramine and trazodone and 58% for plac
were statistically superior to placebo in improvement of HAM- D and clinical global interview. There was no si
difference between trazodone and imipramine. Both trazodone and placebo caused statistically significantly f
anticholinergic side effects, 19% and 14% compared WITH imipramine 52% (Gershon, 1981).

4.6.BB Trimipramine

4.6.BB.1 Depression

a) One study showed trimipramine to be slightly superior to imipramine. Thirty-nine inpatients with endogeno
received either imipramine or trimipramine increased over 14 days to a maximum of 300 milligrams at bedtim
another 2 weeks. There were fewer adverse reactions (tremor, drowsiness, insomnia and dry mouth) than wi
however, nasal congestion occurred more frequently during trimipramine therapy (Rifkin et al, 1980).
b) Imipramine was compared with trimipramine in 44 patients with psychotic depression (average duration o
year) (Burns, 1965). Trimipramine was administered in doses of 25 mg three times daily for 1 week followed
times daily for 2 more weeks. Overall recovery was reported in 18 patients receiving trimipramine (in 8.7 days
10 patients receiving imipramine (8.9 days). In addition, anxiety and insomnia responded much better in patie
trimipramine. Similar results have been reported by others (Salzmann, 1965).

4.6.BC Tryptophan

4.6.BC.1 Depression

a) L-tryptophan 6 grams and imipramine 150 milligrams/day were effective in relieving endogenous and non-
depression in 59 patients. Imipramine improved agitation, while L-tryptophan improved work and activities in
endogenous depression. Imipramine therapy improved suicidal feelings in patients with non-endogenous dep
et al, 1979).

4.6.BD Venlafaxine

4.6.BD.1 Depression

a) Venlafaxine and imipramine resulted in similar improvement in depression with melancholia in hospitalize
weeks; however, venlafaxine produced an earlier response than imipramine on 1 test (Benkert et al, 1996). C
dose of venlafaxine was rapidly increased from 75 to 375 milligrams(mg)/day; this dose was continued until d
then decreased to 150 mg/day. The dose of imipramine was increased from 50 to 200 mg/day over 5 days ar
at this dose for the remainder of the study. The time to a 50% response rate was similar for the Montgomery-
Depression Rating Scale (MADRS), but for the 21-item Hamilton Rating Scale for Depression (HAM-D), the ti
was 1 week earlier with venlafaxine than imipramine (p=0.036). Adverse effects were reported in 69% and 76
treated with venlafaxine and imipramine, respectively. Statistically significant differences in dry mouth and tre
for imipramine (p less than 0.05) and nausea for venlafaxine (p=0.011). While this study enrolled 167 patients
than planned, and only 115 patients completed the 6-week study. Additional studies are needed to provide co
for a more rapid onset of effect with venlafaxine.

b) Venlafaxine was found to have antidepressant efficacy comparable to imipramine in outpatients with mod
depression. Venlafaxine was compared to imipramine in a 6 week, double-blind placebo controlled study in 2
depression of moderate to marked severity. Baseline and weekly efficacy measurements were obtained utiliz
Hamilton Rating Scale for Depression (HAM-D), the Montgomery-Asberg Depression Rating Scale (MADRS)
Global Impression severity and improvement scales (CGI). The mean maximal total daily dose of venlafaxine
48 milligrams and the mean maximal total daily dose of imipramine was 176 milligrams and +/- 56 mg. All stu
were administered in a three times a day schedule after meals. Venlafaxine showed a significant clinical adva
imipramine at the week 6 endpoint on the Ham-D total score. It was noted that this effect was probably due to
attrition rate for imipramine as compared to venlafaxine. Attrition rates due to adverse effects were 25% and
imipramine and venlafaxine respectively. Nausea, sedation, dry mouth, and dizziness were the most promine
adverse effects for venlafazine (Schweizer et al, 1994).

4.6.BE Viloxazine

Depression

Nocturnal enuresis

4.6.BE.1 Depression

a) SUMMARY: Several controlled studies have reported the equivalent efficacy of viloxazine 150 to 450 milli
imipramine 75 to 225 milligrams daily in the treatment of depression in inpatients and outpatients (Santonasta
Davies et al, 1977; McEvoy et al, 1982; Battistini et al, 1980; Nair & Schwartz, 1982; Floru et al, 1976; Bayliss
Side effects in some of these reports, primarily anticholinergic, were less with viloxazine; however, others hav
similar incidence as imipramine (McEvoy et al, 1982).

b) At least 2 studies have reported a similar clinical response to placebo as with viloxazine and imipramine ir
neurosis (Petrie et al, 1980; Guy et al, 1982). These data do not necessarily indicate the inefficacy of viloxazi
in this patient group, but rather reflect the methodological problems of placebo responsiveness in neurotic po
effects may also explain the reported early onset of effects with viloxazine in some clinical studies, both neur
endogenous depression.

c) Better scores were reported on the Hamilton Depression Scale in patients treated with viloxazine 50 millig
times/day compared to those treated with imipramine 25 milligrams three times/day (Elwin, 1980). The double
involved 59 depressed patients. However, this data was not reproduced in 40 depressed patients treated with
mg/day or imipramine 150 mg/day (Battistini et al, 1980), nor in 28 depressed patients (Santonastaso et al, 1

d) Viloxazine was compared with imipramine in the treatment of endogenous depression in a double-blind st
patients (McEvoy et al, 1982). Patients were randomly assigned to viloxazine 150 to 450 milligrams (mg) dail
to 225 milligrams daily (10 patients in each group). Flurazepam or chloral hydrate were given for sleep as nee
global impressions indicated that 7 viloxazine patients (70%) and 7 imipramine patients (70%) improved durir
patients receiving viloxazine and 3 receiving imipramine remained unchanged and 1 patient receiving viloxaz
Hamilton Psychiatric Rating Scale for Depression indicated improvement with both drugs with no differences
Imipramine had a faster onset of action for depression (1 week versus 2 weeks). The Hamilton Psychiatric Ra
Anxiety also showed similar degrees of improvement, however, viloxazine had a more rapid onset (1 week ve
Viloxazine had no effect on improving sleep disturbances as determined by the Hamilton Depression Scale, a

compared with other reports. Side effects were similar for both drugs with 1 patient in each group developing treatment (both patients had abnormal EKGs at initiation of treatment).

e) Viloxazine and imipramine has similar efficacy in a 5-week study involving 49 patients with endogenous d Schwartz, 1982). Viloxazine was initiated in oral doses of 50 milligrams (mg) three times a day with meals, wi being given at 5 p.m. Imipramine was given initially in doses of 25 milligrams orally three times a day in a sim dose was increased starting in the second week of the study to a maximum of viloxazine 400 mg daily and im daily by the fourth and fifth weeks. The mean daily dosage by the fifth week of the study was 380 mg daily fo 192 mg daily for imipramine. Both drugs resulted in improvement based upon Clinical Global Impressions, the Scale for Depression, the Hamilton Rating Scale for Anxiety, and the Brief Psychiatric Rating Scale. Based u Impressions, 12 of 24 viloxazine patients were very much improved, with 5 much improved; 13 of 25 imipram very much improved, with 7 being much improved. Side effects occurred more frequently in imipramine patie side effects of dry mouth, constipation, blurred vision, sweating, and sedation occurred more frequently in the However, nausea and vomiting occurred only in viloxazine patients.

4.6.BE.2 Nocturnal enuresis

a) Viloxazine was evaluated in the treatment of nocturnal enuresis in a controlled study with imipramine and children (Attenburrow et al, 1984). The drugs were randomly assigned for a 7-week period. Viloxazine 100 m bedtime was administered to children between 5 and 10 years of age. Imipramine was given in doses of 50 a respectively. At week 7, significantly more dry nights occurred with both viloxazine and imipramine as compa with no statistically significant difference between the two active agents. Toxicity was greater in the imipramin consisting of, primarily anticholinergic effects. These data suggest the efficacy of viloxazine in enuretic childre prove to be a useful alternative to imipramine in children who develop side effects during imipramine therapy.

4.6.BE.3 Adverse Effects

a) The most frequent side effects associated with viloxazine therapy are nausea and vomiting (Elwan, 1980; 1980), and the incidence of anticholinergic side effects is much lower than with imipramine.

b) Viloxazine appears to cause less impairment of psychomotor performance than imipramine. The driving o was tested after multiple doses of viloxazine 50 milligrams three times/day, imipramine 25 milligrams three tir or nothing. The group treated with imipramine demonstrated significantly worse performance in the gap acce subsidiary task responses. There was no effect on driving skills noted 2 hours after the first dose of each drug 1977).

4.6.BF Zimeldine

Agoraphobia

Depression

4.6.BF.1 Agoraphobia

a) A double-blind comparison of zimeldine, imipramine, and placebo in the treatment of 44 patients with agor attacks revealed that zimeldine was better, (not statistically significant), than imipramine and placebo therapy 1986). In fact, the imipramine therapy was not considered to be superior to placebo. Previous positive results (Mavissakalian & Perel, 1985; Cohen et al, 1984) would indicate that the dose of imipramine used in this stud mmilligrams/day) or the group of patients studied is not indicative of all patients with agoraphobia and panic a further studies are conducted the utilization of zimeldine in the treatment of agoraphobia should be limited to

4.6.BF.2 Depression

a) Zimeldine 100 milligrams orally twice a day was compared with oral imipramine 50 milligrams three times treatment of primary major depressive disorders (endogenous) in 95 patients in a controlled study (Hiramatsu During the 4-week study, zimeldine produced similar antidepressant activity as imipramine as evaluated on th Depression Scale. Zimeldine was reported more effective in patients over the age of 40, patients whose initia over 40 years, patients with mild-to-moderate depression and patients who had previously failed to show an a response to other antidepressants. Zimeldine was less toxic than imipramine, primarily with regard to anticho

b) Zimeldine demonstrated significantly lower Hamilton Depression scale total scores compared with imipran forty depressed patients were administered zimeldine, imipramine, and matching placebo in doses of 50 milli Fewer adverse effects were reported in the zimeldine group (Merideth & Feighner, 1983).

4.6.BF.3 Adverse Effects

a) Zimeldine did not differ in psychomotor or cognitive function tests in 18 healthy volunteers. In a double-bli fashion, each subject received zimeldine 100 milligrams, imipramine 50 milligrams, or matching placebo. A ba not exhibit a significant difference between active drugs (Ferris et al, 1980).

b) Zimeldine in therapeutic doses (200 milligrams/day) produces more pronounced anticholinergic effects, as accommodation width and salivary secretion rate, than imipramine in therapeutic doses (75 milligrams/day) (V 1981).

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Last Modified: May 04, 2009

DRUGDEX® Evaluations

OXCARBAZEPINE

0.0 Overview

1) Class

a) This drug is a member of the following class(es):

Anticonvulsant

Dibenzazepine Carboxamide

2) Dosing Information

a) Adult

1) Partial seizure, monotherapy

a) initiation of monotherapy, 300 mg ORALLY twice a day, then increas by 300 mg/day every third day to 1200 mg/day OR 2400 mg/day in patie from other antiepileptic drug therapy to oxcarbazepine monotherapy (Pr TRILEPTAL(R) oral tablets, oral suspension, 2005)

b) conversion to monotherapy, initial, 300 mg ORALLY twice a day; ma dosage by up to 600 mg/day at weekly intervals to 2400 mg/day reache weeks while simultaneously reduce the dose of concomitant antiepilepti 3-6 weeks (Prod Info TRILEPTAL(R) oral tablets, oral suspension, 2005

2) Partial seizure; Adjunct

a) initial, 300 mg ORALLY twice a day; may increase dosage by up to 6 weekly intervals to 1200 mg/day (Prod Info TRILEPTAL(R) oral tablets, suspension, 2005)

b) Pediatric

1) with adjunctive therapy, children 2 to less than 4 years of age may require the oxcarbazepine dose per body weight compared to adults; and children 4 equal to 12 years of age may require a 50% higher oxcarbazepine dose per compared to adults (Prod Info TRILEPTAL(R) oral tablets, oral suspension, 2

a) Partial seizure, monotherapy

1) 4 to 16 year old, initiation of monotherapy, 8-10 mg/kg/day ORA divided doses; may increase dose by 5 mg/kg/day every 3 days to t recommended maintenance dose (Prod Info TRILEPTAL(R) oral tab suspension, 2005)

2) 4 to 16 year old, conversion to monotherapy, initial, 8-10 mg/kg/ in 2 divided doses; may increase doses by up to 10 mg/kg/day at w to the recommended maintenance dose; simultaneously reduce the concomitant antiepileptic drugs over 3-6 weeks (Prod Info TRILEPT tablets, oral suspension, 2005)

3) 4 to 16 year old, maintenance, 600 to 900 mg/day for 20 kg chil 1200 mg/day for 25 to 30 kg; 900 to 1500 mg/day for 35 to 40 kg ch 1500 mg/day for 45 kg children; 1200 to 1800 mg/day for 50 to 55 k 1200 to 2100 mg/day for 60 to 70 kg children (Prod Info TRILEPTA tablets, oral suspension, 2005)

b) Partial seizure; Adjunct

1) 4 to 16 years old, initial, 8-10 mg/kg/day ORALLY in 2 divided d 600 mg/day(Prod Info TRILEPTAL(R) oral tablets, oral suspension,

2) 4 to 16 years old, maintenance, target maintenance dose of oxc should be achieved over 2 weeks, and is dependent upon patient w 29 kg, 900 mg/day); (29.1 to 39 kg, 1200 mg/day); and (greater tha mg/day) (Prod Info TRILEPTAL(R) oral tablets, oral suspension, 20

3) 2 to less than 4 years old, initial, 8-10 mg/kg/day ORALLY in 2 d MAX: 600 mg/day; patients under 20 kg, consider initial dose of 16- in 2 divided doses (Prod Info TRILEPTAL(R) oral tablets, oral suspe

4) 2 to less than 4 years old, maintenance, should be titrated over 2
MAX: 60 mg/kg/day in 2 divided doses (Prod Info TRILEPTAL(R) or
suspension, 2005)

3) Contraindications
a) hypersensitivity to oxcarbazepine, or to any product component (Prod Info TR
oral tablets, suspension, 2007)

4) Serious Adverse Effects
a) Anaphylaxis
b) Angioedema
c) Hyponatremia
d) Immune hypersensitivity reaction, multiorgan
e) Stevens-Johnson syndrome
f) Toxic epidermal necrolysis

5) Clinical Applications
a) FDA Approved Indications
1) Partial seizure, monotherapy
2) Partial seizure; Adjunct

1.0 Dosing Information

1.1 Drug Properties

A) Information on specific products and dosage forms can be obtained by referri
Tradename List (Product Index)

B) Synonyms
Oxcarbazepine

C) Physicochemical Properties
1) Molecular Weight
a) 252.27 (Prod Info Trileptal™, 00)
2) Solubility
a) Systemic: Oxcarbazepine is slightly soluble in acetone, chloroform,
dichloromethane, and methanol. It is practically insoluble in ethanol, eth
(Prod Info Trileptal™, 00)

1.2 Storage and Stability

A) Oral route
1) Oral suspension of oxcarbazepine should be stored between 15 and 30 d
Celsius (59 and 86 degrees Fahrenheit) (Prod Info Trileptal(R), 2003).

1.3 Adult Dosage

1.3.1 Normal Dosage

Oral route

Trigeminal neuralgia

1.3.1.A Oral route

Partial seizure, monotherapy

Partial seizure; Adjunct

1.3.1.A.1 Partial seizure, monotherapy

a) Conversion

1) For conversion of therapy from other antiepileptic drugs (AE
oxcarbazepine monotherapy, oxcarbazepine therapy should be
a dose of 600 milligrams/day (mg/day) in two divided doses; sir
reduction of the dosage of the concomitant AEDs should begin.
oxcarbazepine dose may be increased at weekly intervals, as c
indicated, by a maximum of 600 mg/day to achieve a daily dose
mg/day. The maximum dose of oxcarbazepine should be reach
approximately 2 to 4 weeks while therapy with concomitant AEI
terminated gradually over approximately 3 to 6 weeks. Close m
the patient is recommended during the transition phase (Prod I
TRILEPTAL(R) oral tablets, oral suspension, 2005).

b) Initiation

1) In patients not currently treated with any antiepileptic drugs,
oxcarbazepine therapy should be initiated at a dose of 600 milli
(mg/day) in two divided doses. This dose is then increased eve
300 mg/day to achieve a dose of 1200 mg/day (Prod Info TRILI
tablets, oral suspension, 2005).

c) Withdrawal

1) Withdrawal of oxcarbazepine therapy should be gradual (Pr
TRILEPTAL(R) oral tablets, oral suspension, 2005).

1.3.1.A.2 Partial seizure; Adjunct

a) Oxcarbazepine should be initiated with a dose of 600 milligrams
(mg/day), in two divided doses. This dose may be increased at wee
as clinically indicated, by a maximum of 600 mg/day. The recomme
maintenance dose of oxcarbazepine for adjunctive use is 1200 milli
(mg/day) in 2 divided doses. Although daily doses greater than 120
more effective, most patients are not able to tolerate the 2400 mg/d
to adverse central nervous system effects. Close monitoring of the p
plasma concentrations of concomitant antiepileptic drugs is recomm
the titration phase, especially at doses greater than 1200 mg/day (P
TRILEPTAL(R) oral tablets, oral suspension, 2005).

1.3.1.B Trigeminal neuralgia

1) Effective oral doses of oxcarbazepine in the treatment of trigeminal n
been 300 milligrams 2 to 4 times daily initially, with the dose increased w
adequate pain control was achieved (Zakrzewska & Patsalos, 1989b).

2) Daily maintenance doses associated with pain relief have ranged fro
milligrams/day (Zakrzewska & Patsalos, 1989b; Farago, 1987b). In one
required for effective relief of pain were less than 10 milligrams/kilogram
patients, 11 to 20 milligrams/kilogram/day in 46%, and greater than 20
milligrams/kilogram/day in 31% (Farago, 1987b).

1.3.1.C Equivalent Doses

1) Oxcarbazepine oral suspension and film-coated tablets may be interc
equal doses (Prod Info TRILEPTAL(R) oral tablets, oral suspension, 200

1.3.2 Dosage in Renal Failure

A) For patients with impaired renal function (creatinine clearance less than 3
milliliters/minute), oxcarbazepine therapy should be initiated at 300 milligram
half the usual starting dose, and increased at a slower rate than usual based
response (Prod Info TRILEPTAL(R) oral tablets, oral suspension, 2005).

1.3.3 Dosage in Hepatic Insufficiency

A) Dose adjustments are generally not required in patients with mild to mode impairment (Prod Info TRILEPTAL(R) oral tablets, oral suspension, 2005).

1.3.4 Dosage in Geriatric Patients

A) No specific guidelines exist for oxcarbazepine dosing in the elderly. Maxi concentrations and values for area under the concentration-time curve were higher in elderly volunteers (60 to 82 years of age) than in younger volunteer years of age). Differences are presumed to be due to age-related reductions clearance (Prod Info TRILEPTAL(R) oral tablets, oral suspension, 2005). Be oxcarbazepine is initiated at a low dosage and titrated until a maintenance d reached, these pharmacokinetic differences are felt to have no significant cli implications (van Heiningen et al, 1991).

1.3.6 Dosage in Other Disease States

A) Pregnancy

1) Dose-normalized plasma concentrations of oxcarbazepine and mono carbazepine (MHD), the active metabolite, decreased during pregnancy to return to prepregnancy levels during the postpartum period in a pharm study in 5 pregnant women on oxcarbazepine monotherapy. Although p concentrations were not available in any of the women, plasma concent MHD and oxcarbazepine were measured during each trimester in 4 wom the last trimester in 1 woman, and at least once during the 3 months afte all women. The lowest dose-normalized concentrations were noted after gestation-week. Furthermore, postpartum dose-normalized plasma conc MHD and oxcarbazepine increased between 1.7 to 2.9 fold compared w trimester in 4 of the 5 pregnant women. The postpartum increase was ob soon as 7 to 8 days after delivery. In 1 out of the 5 women no increase i postpartum concentrations were noted (Tomson & Battino, 2007).

1.4 Pediatric Dosage

Normal Dosage

Dosage in Renal Failure

Dosage in Hepatic Insufficiency

1.4.1 Normal Dosage

1.4.1.A Oral route

Partial seizure, monotherapy

Partial seizure; Adjunct

1.4.1.A.1 Partial seizure, monotherapy

a) Conversion

1) For conversion of therapy from other antiepileptic drugs (AE oxcarbazepine monotherapy in children 4 to 16 years, oxcarba should be initiated with a dose of 8 to 10 milligrams/kilogram/da in two divided doses; simultaneously, reduction of the dosage c concomitant AEDs should begin. The oxcarbazepine dose may at weekly intervals, as clinically indicated, by a maximum of 10 achieve the recommended daily dose. Concomitant AEDs shou terminated gradually over approximately 3 to 6 weeks. Close m the patient is recommended during the transition phase. The re total daily dose of oxcarbazepine is as follows (Prod Info Trilep

Patient Weight (in kg)	Target Maintenance Dose Range
20	600 to 900
25	900 to 1200

30	900 to 1200
35	900 to 1500
40	900 to 1500
45	1200 to 1500
50	1200 to 1800
55	1200 to 1800
60	1200 to 2100
65	1200 to 2100
70	1500 to 2100

b) Initiation

1) In children 4 to 16 years not currently treated with any antiep oxcarbazepine therapy should be initiated at 8 to 10 milligrams/ (mg/kg/day) in two divided doses. Doses should be increased b mg/kg/day every 3 days until the recommended daily dose is re recommended total daily dose of oxcarbazepine is as follows (F Trileptal(R), 2003a):

Patient Weight (in kg)	Target Maintenance Dose Rang (mg/day)
20	600 to 900
25	900 to 1200
30	900 to 1200
35	900 to 1500
40	900 to 1500
45	1200 to 1500
50	1200 to 1800
55	1200 to 1800
60	1200 to 2100
65	1200 to 2100
70	1500 to 2100

1.4.1.A.2 Partial seizure; Adjunct

a) 4 to 16 Year Olds

For adjunctive therapy in pediatric patients aged between 4 to oxcarbazepine should be initiated at a daily dose of 8 to 10 milligrams/kilogram/day (mg/kg/day) in two divided doses, usua exceed 600 mg/day. The target maintenance dose, according t below, should be attained within 2 weeks. The median dose rea clinical trials was 31 mg/kg/day (6 to 51 mg/kg/day) (Prod Info T (R) oral tablets, oral suspension, 2005):

Patient Weight (in kg)	Target Maintenance Dose (mg/day)
20 to 29	900
29.1 to 39	1200
greater than 39	1800

Children 4 to less than or equal to 12 years of age may require oxcarbazepine dose per body weight compared to adults. Child higher dose per body weight relative to adults because the app clearance increases with decreasing age (Prod Info TRILEPTA tablets, oral suspension, 2005).

b) 2 to 4 Year Olds

1) For adjunctive therapy in pediatric patients 2 years old to les years old, oxcarbazepine should be initiated at a daily dose of 8 milligrams/kilogram/day (mg/kg/day) in two divided doses, usua exceed 600 mg/day. For patients under 20 kilogram, a starting 20 mg/kg/day in 2 divided doses may be considered. The maxi maintenance dose of oxcarbazepine should be achieved over 2 and should not exceed 60 mg/kg/day in two divided doses. The reached during clinical trials in children 2 to 4 years of age was (Prod Info TRILEPTAL(R) oral tablets, oral suspension, 2005).

2) Children 2 to less than 4 years of age may require up to twic oxcarbazepine dose per body weight compared to adults. Child

higher dose per body weight relative to adults because the app clearance increases with decreasing age (Prod Info TRILEPTA tablets, oral suspension, 2005).

3) Children 2 to 4 years of age may require up to twice the oxc dose per body weight compared to adults. Children require a hi body weight relative to adults because the apparent clearance decreasing age (Prod Info TRILEPTAL(R) oral tablets, oral sus 2005).

c) In children beginning oxcarbazepine therapy, doses have been t 30 milligrams/kilogram/day (mg/kg/day) over 1 to 3 weeks (Gaily et those switching from carbamazepine, an overnight change of 1.5 tin carbamazepine dose has been utilized. The mean effective dose fo achieving at least a 50% decrease in seizures has been 47 mg/kg/d range of 21 to 75 mg/kg/day.

1.4.1.B Equivalent Doses

1) Oxcarbazepine oral suspension and film-coated tablets may be interc equal doses (Prod Info TRILEPTAL(R) oral tablets, oral suspension, 200

1.4.2 Dosage in Renal Failure

A) For patients with impaired renal function (creatinine clearance less than 3 milliliters/minute), oxcarbazepine therapy should be initiated at one-half the u dose, and increased slowly according to the clinical response (Prod Info TRIL oral tablets, oral suspension, 2005).

1.4.3 Dosage in Hepatic Insufficiency

A) Dose adjustments are generally not required in patients with mild to mode impairment (Prod Info TRILEPTAL(R) oral tablets, oral suspension, 2005).

2.0 Pharmacokinetics

Onset and Duration

Drug Concentration Levels

ADME

2.1 Onset and Duration

A) Onset

1) Initial Response

a) Trigeminal neuralgia, oral: 24 hours (Zakrzewska & Patsalos, 1989).

2.2 Drug Concentration Levels

A) Therapeutic Drug Concentration

1) Epilepsy, not established (Zakrzewska & Patsalos, 1989).

B) Time to Peak Concentration

1) Oral: 4.5 hours (tablets), 6 hours (suspension) (Prod Info TRILEPTAL(R) oral suspension, 2005).

a) After the administration of a single dose of oxcarbazepine tablets, un conditions, in healthy, male volunteers, the median time to peak concent was 4.5 hours (range 3 to 13 hours). The median Tmax was 6 hours in h volunteers administered a single-dose of oxcarbazepine suspension, un conditions (Prod Info TRILEPTAL(R) oral tablets, oral suspension, 2005) metabolite, 10-hydroxy-carbazepine, reaches peak levels at 4.5 to 8 hou 1990; Kristensen et al, 1983; Theisohn & Heimann, 1982a).

b) After the administration of a single dose of oxcarbazepine oral suspe fasted conditions, in healthy, male volunteers, the median time to peak c (Tmax) was 6 hours (Prod Info Trileptal(R), 2003b).

2) Steady-state plasma concentrations of 10-hydroxy-carbazepine, the activ are achieved within 2 to 3 days with twice-a-day dosing (Prod Info TRILEPTA tablets, oral suspension, 2005).

3) Maximum serum concentrations of the S- and R- enantiomers of 10-hydro carbazepine were 4.49 and 0.99 mg/L, respectively, but the median time to p concentration was similar for both (Volosov et al, 1999).

C) Area Under the Curve

1) 129.8 mg/L/hr (S-enantiomer); 26.3 mg/L/hr (R-enantiomer) (Volosov et a
a) Approximately 5-fold greater AUC for S-10-hydroxy-carbazepine thar hydroxy-carbazepine (Volosov et al, 1999).
b) AUC values were 30% to 60% higher in elderly volunteers (60 to 82 y than in younger volunteers (18 to 32 years of age). Differences are presi due to age-related reductions in creatinine clearance (Prod Info Trileptal
c) Dose adjusted AUC values were 30% to 40% lower in children below years than in children above 8 years of age (Prod Info Trileptal(R), 2003

2.3 ADME

Absorption

Distribution

Metabolism

Excretion

Elimination Half-life

2.3.1 Absorption

A) Bioavailability
1) Oral: rapidly absorbed (Anon, 1990; Theisohn & Heimann, 1982a).
B) Effects of Food
1) none (Prod Info TRILEPTAL(R) oral tablets, oral suspension, 2005).

2.3.2 Distribution

A) Distribution Sites
1) Protein Binding
a) 40% to 60% (Prod Info TRILEPTAL(R) oral tablets, oral suspens Patsalos et al, 1990a).
1) Approximately 33% to 40% of 10-hydroxy-carbazepine is bc proteins, predominantly albumin (Prod Info TRILEPTAL(R) oral suspension, 2005; Patsalos et al, 1990a).
2) Serum concentration within the therapeutically relevant rang influence protein binding (Prod Info TRILEPTAL(R) oral tablets, suspension, 2005).
3) No difference in binding between males and females was ob (Patsalos et al, 1990a).
2) OTHER DISTRIBUTION SITES
a) SALIVA, correlates to serum concentrations (Kristensen et al, 19
1) A good correlation between saliva and serum concentration hydroxy-carbazepine has been reported from 8 to 72 hours follc administration of oxcarbazepine (Kristensen et al, 1983).
B) Distribution Kinetics
1) Volume of Distribution
a) 49 L (10-hydroxy-carbazepine) (Prod Info Trileptal(R), 2003b)

2.3.3 Metabolism

A) Metabolism Sites and Kinetics
1) LIVER, rapid and extensive metabolism (Faigle & Menge, 1990; Anor Schutz et al, 1986a; Theisohn & Heimann, 1982a).
a) Metabolized via stereoselective reduction by cystolic enzymes o group in position 10 of oxcarbazepine (Faigle & Menge, 1990; Anon Schutz et al, 1986a; Theisohn & Heimann, 1982a).
b) Lacks auto-inducing properties (Anon, 1990; Brodie et al, 1989a
c) Dose-dependent enzyme induction has been reported with highe producing effects similar to carbamazepine (Patsalos et al, 1990d).
B) Metabolites
1) 10-monohydroxy-carbazepine, active (Prod Info TRILEPTAL(R) oral suspension, 2005; Faigle & Menge, 1990; Anon, 1990; Schutz et al, 198 & Heimann, 1982a).
a) Primarily responsible for the therapeutic effects of oxcarbazepine

TRILEPTAL(R) oral tablets, oral suspension, 2005; Faigle & Menge
Patsalos et al, 1990d; Anon, 1990; Anon, 1989; Theisohn & Heimar
b) The metabolite 10-hydroxy-carbazepine is primarily excreted in t
the glucuronide conjugate (Dickinson et al, 1989; Anon, 1989; Schu
1986a; Theisohn & Heimann, 1982a).

2) Two isomeric 10,11-diols, inactive (Dickinson et al, 1989; Anon, 1989
1986a; Theisohn & Heimann, 1982a).

a) The trans-diol (10,11-dihydro-10,11-trans-dihydroxy-carbamazep
predominates (Dickinson et al, 1989; Anon, 1989; Schutz et al, 1986
& Heimann, 1982a).

3) Other minor metabolic pathways include direct O-glucuronidation and
with the enol form (Anon, 1990).

2.3.4 Excretion

A) Kidney

1) Renal Excretion (%)

a) 95% to 96% (Prod Info TRILEPTAL(R) oral tablets, oral suspens
Schutz et al, 1986a).

2) Only small amounts of unchanged oxcarbazepine are recovered (less
and the majority of renal excretion is accounted for by 10-hydroxy-carba
80%), primarily as the glucuronide conjugate. Only negligible amounts o
and cis-10,11-diol are found in the urine (approximately 3%) (Prod Info T
oral tablets, oral suspension, 2005; Anon, 1990; Schutz et al, 1986a).

B) Total Body Clearance

1) The younger and lower in weight the faster the weight-adjusted clear
monohydroxy-carbazepine (MHD). In children 2 years to less than 4 yea
weight-adjusted clearance is approximately 80% higher on average than
adults. When treated with a similar weight-adjusted dose, the correspon
exposure in these children is expected to be about 50% of adult exposu
4 to 12 years of age, weight-adjusted clearance is approximately 40% hi
average than that of adults. When treated with a similar weight-adjusted
corresponding MHD exposure in these children is expected to be about
exposure. The weight-adjusted MHD clearance in children 13 years and
expected to reach that of adults (Prod Info TRILEPTAL(R) oral tablets, o
suspension, 2005).

C) Other

1) OTHER EXCRETION

a) FECES, less than 4% (Prod Info TRILEPTAL(R) oral tablets, ora
2005).

2.3.5 Elimination Half-life

A) Parent Compound

1) ELIMINATION HALF-LIFE

a) 1 to 2.5 hours (Prod Info TRILEPTAL(R) oral tablets, oral suspen
Dickinson et al, 1989).

1) The half-life is prolonged to 19 hours in patients with renal in
(creatinine clearance less than 30 mL/min) (Prod Info TRILEPT
tablets, oral suspension, 2005).

B) Metabolites

1) 10-hydroxy-carbazepine, 8 to 11 hours (Prod Info TRILEPTAL(R) ora
suspension, 2005; Anon, 1990; Dickinson et al, 1989; Theisohn & Heima

a) The half-life of 10-monohydoxy-carbazepine was 9 hours (Prod I
TRILEPTAL(R) oral tablets, oral suspension, 2005).

b) Half-lives of the R- and S- enantiomers were 11.9 and 13 hours,
(Volosov et al, 1999).

3.0 Cautions

Contraindications

Precautions

Adverse Reactions

Teratogenicity/Effects in Pregnancy/Breastfeeding

Drug Interactions

3.1 Contraindications

A) hypersensitivity to oxcarbazepine, or to any product component (Prod Info TR oral tablets, suspension, 2007)

3.2 Precautions

A) anaphylaxis and angioedema of larynx, glottis, lips, and eyelids may occur; in fatalities if laryngeal involvement (Prod Info TRILEPTAL(R) oral tablets, suspensi
B) concomitant alcohol consumption; may cause additive sedative effect (Prod Ir TRILEPTAL(R) oral tablets, suspension, 2007)
C) concomitant medications known to decrease serum sodium levels; hyponatre Info TRILEPTAL(R) oral tablets, suspension, 2007)
D) concomitant use with hormonal contraceptives; therapy renders hormonal cor less effective (Prod Info TRILEPTAL(R) oral tablets, suspension, 2007)
E) decreases in T4 may occur; without decreases in T3 or TSH (Prod Info TRILE tablets, suspension, 2007)
F) hypersensitivity to carbamazepine (25% to 35% of those hypersensitive to car also have hypersensitivity reaction to oxcarbazepine) (Prod Info TRILEPTAL(R) c suspension, 2007)
G) hyponatremia (sodium less than 125 mmol/L); especially during the first 3 mo therapy, but may occur more than 1 year after therapy initiation (Prod Info TRILE tablets, suspension, 2007)
H) multiorgan hypersensitivity reactions have occurred; median time to detection (Prod Info TRILEPTAL(R) oral tablets, suspension, 2007)
I) rapid withdrawal of oxcarbazepine therapy; may result in increased seizure fre Info TRILEPTAL(R) oral tablets, suspension, 2007)
J) renal impairment (creatinine clearance less than 30 mL/minute); elimination of metabolite is slowed resulting in a 2-fold increase in exposure (Prod Info TRILEP tablets, suspension, 2007)
K) serious skin reactions, including Stevens-Johnson syndrome and toxic epider necrolysis, have occurred (median time to onset 19 days) (Prod Info TRILEPTAL tablets, suspension, 2007)
L) suicidality, increased risk of; based on data analysis of 199 placebo-controllec antiepileptic drugs, small elevated risk occurred as early as 1 week after starting continued to at least 24 weeks (US Food and Drug Administration, 2008)

3.3 Adverse Reactions

Dermatologic Effects

Endocrine/Metabolic Effects

Gastrointestinal Effects

Hematologic Effects

Hepatic Effects

Immunologic Effects

Neurologic Effects

Ophthalmic Effects

Psychiatric Effects

Renal Effects

Reproductive Effects

Respiratory Effects

Other

3.3.2 Dermatologic Effects

Cutaneous hypersensitivity

Dermatological finding

Erythema multiforme

Rash

Stevens-Johnson syndrome

Toxic epidermal necrolysis

3.3.2.A Cutaneous hypersensitivity

1) Summary

a) Allergic skin reactions are described with the administration of ox
(Dam et al, 1989a; Dam, 1990a; Houtkooper et al, 1987c); (Zakrzev
1988)(Houtkooper et al, 1987c; Zakrzewska & Patsalos, 1989a; And
Watts & Bird, 1991).

2) LITERATURE REPORTS

a) Desensitization to oxcarbazepine, following the development of a
pruritic rash, was accomplished using a dose of 0.1 milligram (mg) o
doubling the dose every 2 days until a therapeutic dosage was reac
Bird, 1991).

b) Allergic skin reactions have been reported less frequently with ox
as compared to carbamazepine in some clinical studies (Dam et al,
1990a; Houtkooper et al, 1987c).

c) There is evidence that oxcarbazepine can be used safely as an a
some patients with carbamazepine induced hypersensitivity (Zakrze
Ivanni, 1988)(Houtkooper et al, 1987c; Zakrzewska & Patsalos, 198

d) In 1 Danish study, a cross-reaction to oxcarbazepine was seen i
47 patients (25%) with allergic skin reactions to carbamazepine (An

3.3.2.B Dermatological finding

1) Skin rash, Stevens-Johnson syndrome, toxic epidermal necrolysis, u
allergic skin reactions have been reported with the administration of oxc

3.3.2.C Erythema multiforme

1) Summary

a) Although not observed in controlled clinical trials, erythema multi
been observed in post-marketing studies or named patient program
oxcarbazepine (Prod Info Trileptal(R), 2003).

3.3.2.D Rash

1) Summary

a) Skin rash has been a frequently described adverse effect of oxc
therapy, also occurring with the discontinuation of oxcarbazepine th
may be associated with a mild eosinophilia, and was reported in 7%
on oxcarbazepine monotherapy in one study (Prod Info Trileptal(R),
al, 1993a; Watts & Bird, 1991).

3.3.2.E Stevens-Johnson syndrome

1) A 9-year-old Taiwanese boy developed Stevens-Johnson syndrome
14 days of initiating oxcarbazepine for treatment of seizures. The patient
of seizures first occurring at the age of 6 months and was treated with pl
several months and then the phenytoin was discontinued without recurre

seizures until he was 9 years old. Upon presentation, the patient's seizu
characterized by clonic movement of his hands and legs, with loss of co
The results of the electroencephalogram and physical examination were
unremarkable. The patient was started on oxcarbazepine 300 milligrams
and the dose was increased to 600 mg daily after one week. Fourteen d
beginning therapy with oxcarbazepine, the patient developed maculopap
his face and thigh along with high fever. Two days later, he developed b
thigh, multiple oral ulcers and hyperemic conjunctivae. The patient was
the emergency department with the diagnosis of presumed SJS. Labora
revealed leukocytosis (white blood cell (WBC) 13,930/mcL; normal rang
10,000/mcL), elevated C-reactive protein (50.59 mcg/mL; range, 0 to 5 r
Human leukocyte antigen (HLA) genotyping showed HLA-B*1518/B*400
pathology finding revealed lymphohistiocytic infiltration around the blood
scanty eosinophils, which was consistent with SJS. The patient improve
and antihistamine treatment for 7 days and was discharged 12 days late
concluded that similar to carbamazepine-induced SJS, the role of the HL
may be associated with the development of oxcarbazepine-induced SJS
2009).

2) Serious, sometimes life-threatening, cases of Stevens-Johnson synd
been reported with the use of oxcarbazepine in children and adults. Som
have required hospitalization, and rare cases of death have been report
Additionally, re-challenge with the drug has resulted in recurrence of the
reactions. The rate at which these dermatologic events have been repor
association with oxcarbazepine use exceeds the rate at which these eve
reported in the general population by 3- to 10-fold. The median time of o
reported cases was 19 days. Discontinuation of oxcarbazepine should b
in any patient who develops a skin reaction while using the drug (Prod Ir
TRILEPTAL(R) oral tablets, suspension, 2007).

3.3.2.F Toxic epidermal necrolysis

1) Serious, sometimes life-threatening, cases of toxic epidermal necroly
reported with the use of oxcarbazepine in children and adults. Some pat
required hospitalization, and rare cases of death have been reported. Ac
challenge with the drug has resulted in recurrence of the dermatologic re
rate at which these dermatologic events have been reported in associati
oxcarbazepine use exceeds the rate at which these events are reported
population by 3- to 10-fold. The median time of onset in reported cases
Discontinuation of oxcarbazepine should be considered in any patient w
skin reaction while using the drug(Prod Info TRILEPTAL(R) oral tablets,
2007).

3.3.3 Endocrine/Metabolic Effects

Abnormal thyroid hormone

Acute intermittent porphyria

Body temperature above normal

Hormone level - finding, Reproductive

Hyperlipidemia

Hyponatremia

Hypothermia

Weight gain

3.3.3.A Abnormal thyroid hormone

1) Summary

a) Use of oxcarbazepine has been associated with decreases in T4

or thyroid stimulating hormone (TSH) (Prod Info TRILEPTAL(R) ora suspension, 2007).

2) LITERATURE REPORTS

a) One study found that carbamazepine and oxcarbazepine both de serum thyroxine (T4) and free thyroxine (FT4) in girls with epilepsy. were reversible upon discontinuation of therapy. Patients, between and 18 years, were compared to 54 age-matched controls. Mean T4 levels in patients receiving carbamazepine (n=19) was 11.5 nM and compared to 14.4 nM and 96.6 nM in the control group (p less than 0.001, respectively). Mean T4 and FT4 in patients receiving oxcarba (n=18) were 11.3 nM and 74.9 nM (p less than 0.001 for both meas compared control). Thyrotropin and free triiodothyronine levels were significantly different. A second evaluation, taken a mean of 5.8 yea performed. Thyroid hormone levels in patients who had discontinue carbamazepine patients and 10 oxcarbazepine patients) did not sig from the controls. Patients had been off therapy for a mean of 5 and respectively (Vainionpaa et al, 2004).

3.3.3.B Acute intermittent porphyria

See Drug Consult reference: DRUGS CONSIDERED UNSAFE- ACUTE PORPHYRIAS

3.3.3.C Body temperature above normal

1) Case report- Despite several changes in drug therapy, a fever was re 20-year-old female which persisted for a follow-up period of approximate following the initial occurrence during oxcarbazepine therapy. The autho that the patient had actually experienced a change in "set point" for body regulation rather than having a febrile reaction. The oxcarbazepine dose milligrams (mg) twice a day for 2 weeks then increased to 300 milligrams times a day. The patient's body temperature had steadily ranged betwee 36.8 degrees Celsius (C) for several years. After oxcarbazepine treatme achieved good seizure control, but her temperature rose to over 37 degr oxcarbazepine was gradually reduced and valproate 1500 milligrams (m substituted resulting into a gradual return to pre-treatment temperature b increase in simple seizures. After a return to temperatures over 37 degre 37.6 degrees C) 4 months later, the valproate was reduced to 800 milligr (mg/day) and vigabatrin 1500 mg was added. Eventually, good seizure c achieved with doses of lamotrigine up to 150 mg/day and vigabatrin 200 however, the patient's temperature never returned to the pre-treatment r mechanism for this effect was hypothesized to be the influence of antiep on ion concentration, as the inherent ratio of sodium to calcium ions in th hypothalamus has been suggested as the physiological basis for the "se temperature control (Gatzonis et al, 1999).

3.3.3.D Hormone level - finding, Reproductive

1) LITERATURE REPORTS

a) Antiepileptic agents have been associated with changes in serur concentrations of male reproductive hormones. When compared to controls (n=41), carbamazepine treated men with partial epilepsy (n lower serum dehydroepiandrosterone sulfate concentrations (3068 r controls versus 1952 ng/mL for carbamazepine; p less than 0.001). statistically significant differences in dehydroepiandrosterone levels detected between controls and oxcarbazepine treated (n=18) or valp treated (n=27) men with generalized epilepsy. It was also found that valproic acid group had higher androstendione levels (5.9 ng/mL) w to the control group (2.2 ng/mL; p less than 0.001) whereas the othe not. Serum testosterone, sex hormone binding globulin, free androg luteinizing hormone, follicle stimulating hormone, prolactin and inhib measurements were not statistically significantly different between a Whether the differences in reproductive hormones are epilepsy-indu or antiepileptic agent-induced changes remains to be determined (Is 2004).

b) Reproductive hormone levels in men with epilepsy may be affec valproic acid or carbamazepine, with some effect shown by oxcarba doses. In valproate-treated men (n=21), androstenedione levels we increased compared with controls (n=25) (p less than 0.001), and m of the cohort taking valproate (57%) had serum concentrations of te

androstenedione, or dehydroepiandrosterone (DHEA) above the ref
(p less than 0.001). Follicle stimulating hormone levels were abnorm
valproate- treated men (p less than 0.05). Among carbamazepine-tr
(n=40), serum concentrations of DHEA were low (p less than 0.001)
hormone-binding globulin (SHBG) levels were high (p less than 0.05
taking high doses of oxcarbazepine (900 milligrams/day (mg/day) o
concentrations of testosterone, luteinizing hormone, and SHBG wer
(p=0.008, p=0.02, p=0.005, respectively). The authors noted that se
levels were high across all groups (Rattya et al, 2001).

3.3.3.E Hyperlipidemia

1) Case report - increased serum lipids, specifically low-density lipoprot
serum cholesterol were reported in 16-year-old girl. High-density lipopro
triglycerides, and liver function tests remained within normal limits. Oxca
metabolized primarily by ketone reductase and glucuronosyltransferase
minimal hepatic enzyme-induction in humans. An increase in lipid levels
previously in the patient when she was treated with carbamazepine, but
to be less probable with oxcarbazepine. The authors suggest monitoring
patients treated with oxcarbazepine as well as in those treated with carb
(Papacostas, 2000).

3.3.3.F Hyponatremia

1) Summary

a) Significant hyponatremia (sodium less than 125 mmol/L) genera
during the first 3 months of therapy, but may occur more than one y
therapy initiation. Dose reduction, therapy discontinuation, or restric
intake may be required. In patients who discontinued therapy in clin
sodium levels normalized within a few days without further treatmen
of serum sodium should be considered especially in patients at risk
who develop symptoms of hyponatremia. Patients are at risk if they
concomitant medications known to decrease serum sodium levels (
TRILEPTAL(R) oral tablets, suspension, 2007).

b) Hyponatremia has occurred with the administration of oxcarbaze
associated with a greater incidence of hyponatremia as compared w
carbamazepine (Dong et al, 2005). The mechanism is thought to be
antidiuretic hormone-like action on the kidney. HYPONATREMIC C
been described with oxcarbazepine use. Some investigators feel tha
hyponatremia from oxcarbazepine may severely limit its use as an a
Most patients with hyponatremia remain asymptomatic but some ma
drowsiness, increase in seizure frequency, and impaired consciousn
Hyponatremia with oxcarbazepine occurs most commonly in elderly
during administration of high doses of the drug (Kloster et al, 1998;
Amelsvoort et al, 1994; Steinhoff et al, 1992; Anon, 1990b; Pendleb
1989; Houtkooper et al, 1987c; Anon, 1989b; Zakrzewska & Patsalo
Johannessen & Nielson, 1987; Nielson et al, 1988).

2) Incidence: 2.5% to 29.9% (Dong et al, 2005; Prod Info TRILEPTAL(P
suspension, 2007)

3) LITERATURE REPORTS

a) The results of one study indicate that oxcarbazepine use is asso
greater incidence of hyponatremia as compared with the use of carb
In a cross-sectional study, the sodium levels of patients receiving tre
either oxcarbazepine (n=97; mean age, 36.3 years) or carbamazepi
mean age, 38.2 years) were evaluated for the presence of hyponatr
Hyponatremia was defined as a sodium level less than or equal to 1
milliequivalents/liter (mEq/L); severe hyponatremia was defined as a
less than or equal to 128 mEq/L. Hyponatremia was observed in a s
greater number of oxcarbazepine-treated patients, as compared wit
receiving carbamazepine therapy (29.9% (29/97) vs 13.5% (61/451)
p less than 0.0001). The incidence of severe hyponatremia was also
oxcarbazepine group as compared with the carbamazepine group (
vs 2.8%(13/451), respectively). Severe hyponatremia accounted for
(12/29) of all hyponatremia cases in oxcarbazepine-treated patients
accounting for 21.3% (13/61) of all hyponatremia cases reported in
receiving carbamazepine therapy (p less than 0.0001). The investig
found that, for both groups, hyponatremia was more likely to occur i
patients. Hyponatremia was observed in 62.2% and 20.6% of oxcar
carbamazepine-treated patients 40 years of age or older, as compa

and 7.9% of oxcarbazepine- and carbamazepine-treated patients le
years of age, respectively (p less than 0.0001, both values) (Dong e
b) In controlled epilepsy clinical studies, 38 of 1524 patients (2.5%)
oxcarbazepine developed clinically significant hyponatremia (sodiur
125 millimoles/liter (mmol/L), generally within the first 3 months of tr
patients who developed the condition were asymptomatic, but patie
frequently monitored and some had their oxcarbazepine dose reduc
discontinued or had their fluid intake restricted. When oxcarbazepin
discontinued, serum sodium concentrations generally returned to nc
few days without additional treatment (Prod Info Trileptal(R), 2003).
c) Hyponatremia, defined as at least one serum sodium measurem
micromoles/liter (mcmol/L), was observed in 8 of 34 children (24%)
intellectual disability given oxcarbazepine (Gaily et al, 1998).
d) Two cases of impaired water homeostasis and death after inges
oxcarbazepine are reported (Kloster et al, 1998).
e) In a study involving children, hyponatremia occurred in 7 out of 5
given oxcarbazepine (Gaily et al, 1997).
f) Hyponatremia was reported in 80 of 350 (23%) patients whose s
concentrations were monitored during oxcarbazepine therapy. Ten
patients had low serum sodium prior to receiving oxcarbazepine tre
et al, 1993a).
g) Hyponatremic coma, with a serum sodium level of 115 millimole
(mmol/L), was reported in a 50-year-old female following almost one
therapy with oxcarbazepine 2100 milligrams/day (mg/day). On disc
the drug, serum sodium levels improved after 2 days, with resolutio
somnolence and coma (Steinhoff et al, 1992).
h) Significant reductions in mean serum sodium levels (less than 1
millimoles/liter (mmol/L) have been reported in 50% to 80% of patie
studies. Available data suggests that the incidence of hyponatremia
oxcarbazepine may be greater than that observed with carbamazep
(Pendlebury et al, 1989; Nielson et al, 1988).

3.3.3.G Hypothermia

1) Transient hypothermia has been reported rarely during administratio
oxcarbazepine (Sillanpaa & Pihlaja, 1989).

3.3.3.H Weight gain

1) Weight gain has been reported as a relatively frequent adverse effec
oxcarbazepine therapy (Anon, 1990b).

3.3.4 Gastrointestinal Effects

Diarrhea

Gastrointestinal tract finding

Nausea and vomiting

3.3.4.A Diarrhea

1) Summary

a) Diarrhea is described with the administration of oxcarbazepine ir
patients, which stopped as therapy continued (Anon, 1990b; Farago
Sillanpaa & Pihlaja, 1989; Philbert et al, 1986a; Steinhoff et al, 1992
et al, 1989).

3.3.4.B Gastrointestinal tract finding

1) Summary

a) CONSTIPATION, ANOREXIA and a sensation of heat in the sto
described with the administration of oxcarbazepine (Steinhoff et al,
1990b; Pendlebury et al, 1989; Sillanpaa & Pihlaja, 1989; Farago, 1
et al, 1986a).

2) Nausea and vomiting, diarrhea, constipation, anorexia, and a sensati
the stomach are described with the administration of oxcarbazepine.

3.3.4.C Nausea and vomiting

1) Summary

a) Nausea and vomiting are described with the use of oxcarbazepi series, nausea and vomiting occurred with the discontinuation of ox therapy. In another trial, nausea and vomiting occurred with oxcarb at the maximum dosage (2400 mg/day) (Prod Info Trileptal(R), 200

3.3.5 Hematologic Effects

3.3.5.A Thrombocytopenia

1) A case report described thrombocytopenia in a 63-year-old woman a treated with oxcarbazepine. The patient, who had a history of depressio psychotic features and multiple psychiatric hospitalizations, presented to with increasingly disorganized behavior and paranoid ideation. Platelet c of admission was 300,000/microliter. Initial treatment with nortriptyline a was unsuccessful, and the patient was switched to aripiprazole and venl an inadequate response, oxcarbazepine 300 milligrams twice daily was ongoing treatment of aripiprazole and venlafaxine. The patient responde displaying an improvement in mood and energy levels. Following oxcarb therapy for a few days, the patient developed a low-grade fever and plat dropped to 208,000/microliter. Idiopathic thrombocytopenic purpura was partial thromboplastin time, prothrombin time, and international normaliz within normal limits. Platelet count continued to drop and was 18,000/mi 10 of treatment. Oxcarbazepine was discontinued and 4 days later, plate increased to 250,000/microliter and was within normal limits 7 days after oxcarbazepine (Mahmud et al, 2006).

3.3.6 Hepatic Effects

Increased liver function test

Liver finding

3.3.6.A Increased liver function test

1) Summary

a) Elevations in serum gamma-glutaryl transpeptidase (GGT) have observed in some patients treated with oxcarbazepine or 10-hydrox (Farago, 1987b). Although no severe hepatotoxic reactions have be monitoring of liver function tests is advised during therapy.

3.3.6.B Liver finding

1) Elevated liver function tests are described with the administration of oxcarbazepine.

3.3.7 Immunologic Effects

Anaphylaxis

Cross sensitivity reaction

Immune hypersensitivity reaction, multiorgan

3.3.7.A Anaphylaxis

1) Rare cases of anaphylaxis have been reported in patients following i subsequent oxcarbazepine use. In the event of this reaction, therapy sh discontinued and the patient should not be rechallenged with oxcarbaze Info TRILEPTAL(R) oral tablets, suspension, 2007).

3.3.7.B Cross sensitivity reaction

1) Summary

a) Cross-sensitivity reactions are described with the administration oxcarbazepine (Anon, 1990b; Prod Info Trileptal(R), 2003; Beran, 1

2) LITERATURE REPORTS

a) In 1 Danish study, a cross-reaction to oxcarbazepine was seen i patients (25%) with allergic skin reactions to carbamazepine (Anon,

b) Caution is advised in using oxcarbazepine in patients with a hist sensitivity to carbamazepine (Prod Info Trileptal(R), 2003).

c) Although only a 25% cross-sensitivity has been reported betwee oxcarbazepine and carbamazepine, dermatological reactions occur patients treated with oxcarbazepine who had previously discontinue carbamazepine because of the development of skin reactions. Two developed a pruritic skin rash and 1 patient developed exfoliative de following 2 or 3 doses of oxcarbazepine (Beran, 1993).

3.3.7.C Immune hypersensitivity reaction, multiorgan

1) Although the number of cases has been limited, multiorgan hypersen disorders, often considered life-threatening and resulting in hospitalizatic reported in association with the initiation of oxcarbazepine therapy (med detection 13 days, range 4-60 days). Multiorgan hypersensitivity reactior characterized by features such as rash, fever, lymphadenopathy, abnorr function tests, hepatitis, thrombocytopenia, neutropenia, eosinophilia, pr nephritis, oliguria, hepato-renal syndrome, asthenia, and arthralgia. Oxc treatment should be discontinued and replaced with an alternative thera hypersensitivity reaction is suspected. Although there are no reports tha sensitivity with other agents (ie, carbamazepine) has caused this reactio possibility cannot be ruled out (Prod Info TRILEPTAL(R) oral tablets, sus 2007).

3.3.9 Neurologic Effects

Encephalopathy

Neurological finding

Seizure

3.3.9.A Encephalopathy

1) Summary

a) Metabolic encephalopathy has been reported in a patient due to oxcarbazepine-induced hyponatremia (Rosendahl & Friis, 1991).

3.3.9.B Neurological finding

1) Summary

a) Severe HEADACHE (2.9%), DROWSINESS, DIZZINESS (6.4% (5.2%), TREMOR (1.8%), ABNORMAL GAIT (1.7%), and FATIGUE the most frequent adverse effects observed during therapy with oral oxcarbazepine and oral 10-hydroxy carbazepine and were among tl most commonly associated with discontinuation of oxcarbazepine ir studies. Sedation, DIFFICULTY IN CONCENTRATION, and MEMO IMPAIRMENT are also described with the administration of oxcarba is some evidence that the incidence and severity of central nervous effects, including sedation, is less with oxcarbazepine than with carl (Prod Info Trileptal(R), 2003; Anon, 1990b; Dam, 1990a; Sillanpaa & 1989; Farago, 1987b; Houtkooper et al, 1987c; Bulau et al, 1987a; I 1986a; Dickinson et al, 1988; Anon, 1989b; Farago, 1987b; Zakrzev Patsalos, 1989a; Curran & Java, 1993).

2) Headache, drowsiness, dizziness, ataxia, tremor, abnormal gait, fatig encephalopathy, and oculogyric crises are described with the administra oxcarbazepine. Psychomotor slowing, concentration difficulties, speech problems, somnolence or fatigue and coordination abnormalities such as disturbances have also been associated with oxcarbazepine use.

3) LITERATURE REPORTS

a) The incidence of dizziness, drowsiness, headache, and ataxia ha similar with oxcarbazepine as compared to carbamazepine in other 1990a; Houtkooper et al, 1987c).

b) In one study, substitution of carbamazepine with oxcarbazepine

receiving polytherapy was associated with increased alertness and to concentrate (Anon, 1990b).

3.3.9.C Seizure

1) Summary

a) In a case report, a 9-year-old female developed absence-like sei after initiating oxcarbazepine therapy. The patient had been diagnos benign focal epilepsy of childhood with centrotemporal spikes and h language delay. Her seizures were activated by drowsiness and we generalized tonic-clonic or hemi-clonic seizures with occasional pos paralysis. Over a 6-month period, she had 3 nocturnal seizures follc multiple nocturnal seizures over 3 days. She was then prescribed o monotherapy. Soon after, she developed multiple daily episodes of fluttering with loss of awareness. A 30-minute electroencephalogran recorded 6 seizures and benign focal epileptiform discharges of chil (BFEDC) occurring at a rate of 9 per minute. Oxcarbazepine was th discontinued and a 24-hour EEG was performed. BFEDC decrease minute and no seizures were recorded. The patient remained off an medications for 6 months and did not experience a recurrence of ab seizures (Chapman et al, 2003).

3.3.10 Ophthalmic Effects

Eye / vision finding

Oculogyric crisis

3.3.10.A Eye / vision finding

1) Summary

a) DIPLOPIA and ABNORMAL VISION were among the adverse ef frequently associated with discontinuation of oxcarbazepine therapy trials. Diplopia has been a relatively frequent adverse effect of oxca clinical trials abnormal vision and diplopia have been reported in 14 respectively, of patients treated with oxcarbazepine (n=86) (Prod In (TM), 2002)(Anon, 1990b).

2) Visual changes including diplopia, abnormal vision, and oculogyric cr described with the administration of oxcarbazepine.

3.3.10.B Oculogyric crisis

1) Summary

a) CASE REPORT - Oculogyric crisis, which occurred with carbam ceased following its discontinuance, recurred following onset of ther oxcarbazepine in a 31-year-old male. The oculogyric crisis occurrec related event, with as many as 30 episodes daily at higher oxcarbaz of 1800 milligrams/day (mg/day). Following implantation of a vagus stimulator, oculogyric crisis ceased, although oxcarbazepine therap continued (Gatzonis et al, 1999).

b) Dose-related oculogyric crisis has been described with the admi oxcarbazepine (Gatzonis et al, 1999).

3.3.12 Psychiatric Effects

3.3.12.A Suicidal thoughts

1) Data reviewed by the US Food and Drug Administration suggest an i of suicidal behavior or ideation may exist in patients receiving therapy w antiepileptic drugs (AEDs). The analysis included 199 placebo-controllec studies covering 11 different AEDs used for several different indications epilepsy, selected psychiatric illnesses, and other conditions, including n neuropathic pain syndromes. The analysis included 27,863 patients trea and 16,029 patients who received placebo, and patients were aged 5 ye There were 4 completed suicides among patients in the AED treatment g (vs) none in the placebo groups. Suicidal behavior or ideation occurred i patients in the AED treatment groups compared to 0.22% of patients in t groups. This corresponded to an estimated 2.1 per 1000 (95% confidenc to 4.2) more patients in the AED treatment groups having suicidal behav

than the placebo groups. The increased risk of suicidality was noted at 1 starting an AED and continued to at least 24 weeks. When compared to results were generally consistent among the drugs and were seen in all subgroups. Patients treated for epilepsy, psychiatric disorders, or other were all at an increased risk for suicidality compared to placebo. Closely patients treated with AEDs for emergence or worsening of depression, s other unusual changes in behavior, which may include symptoms such a agitation, hostility, mania, and hypomania (US Food and Drug Administr

3.3.13 Renal Effects

3.3.13.A Urogenital finding

1) When compared to healthy controls (n=41), valproic acid treated mer generalized epilepsy (n=27) had smaller testicular volumes (p=0.01). Wi study however, the testicular volumes of carbamazepine treated men wi epilepsy (n=15) or oxcarbazepine treated men with partial epilepsy (n=1 differ from controls. When further examined, valproic acid treated men w sperm morphology had smaller testicular volumes than control whereas volumes of valproic acid treated men with normal sperm were similar to (Isojarvi et al, 2004).

3.3.14 Reproductive Effects

3.3.14.A Semen exam: abnormal

1) Antiepileptic agents have been associated with changes in sperm mo motility. A lower frequency of morphologically normal sperm was found i carbamazepine treated men with partial epilepsy (n=15), in valproic acid with generalized epilepsy and in oxcarbazepine treated men with genera (n=18) (p less than 0.01 for carbamazepine and valproic acid and p less oxcarbazepine) compared to healthy controls (n=41). A statistically signi decrease in the frequency of motile sperm was also found with all treatm combined when compared to the healthy controls (p less than 0.05). Wit various treatment groups, valproic acid treated patients had a statisticall decrease in the frequency of motile sperm than in the control group (p le Carbamazepine treated men had high frequencies of abnormally low spe concentration (p less than 0.001) and poorly motile sperm (p less than 0 compared to controls (Isojarvi et al, 2004).

3.3.15 Respiratory Effects

Respiratory finding

Respiratory tract infection

3.3.15.A Respiratory finding

1) Upper respiratory tract infection has been reported with the administr oxcarbazepine.

3.3.15.B Respiratory tract infection

1) Summary

a) Upper respiratory tract infection has been reported in 7% of patie clinical trials (Prod Info Trileptal(TM), 2002).

3.3.16 Other

Angioedema

Withdrawal sign or symptom

3.3.16.A Angioedema

1) Rare cases of angioedema involving the larynx, glottis, lips, and eyel reported in patients following initial or subsequent oxcarbazepine use ar fatalities in cases with laryngeal involvement . In the event of this reactio

should be discontinued and the patient should not be rechallenged with oxcarbazepine (Prod Info TRILEPTAL(R) oral tablets, suspension, 2007

3.3.16.B Withdrawal sign or symptom

1) Rapid withdrawal of antiepileptic drugs including oxcarbazepine may increased seizure frequency (Prod Info TRILEPTAL(R) oral tablets, susp 2007).

3.4 Teratogenicity/Effects in Pregnancy/Breastfeeding

A) Teratogenicity/Effects in Pregnancy

1) U.S. Food and Drug Administration's Pregnancy Category: Category C (P TRILEPTAL(R) oral tablets, suspension, 2007a) (All Trimesters)

a) Either studies in animals have revealed adverse effects on the fetus (embryocidal or other) and there are no controlled studies in women or st women and animals are not available. Drugs should be given only if the benefit justifies the potential risk to the fetus.

2) Australian Drug Evaluation Committee's (ADEC) Category: D (Australian Department of Health and Ageing Therapeutic Goods Administration, 2006)

a) Drugs which have caused, are suspected to have caused, or may be cause an increased incidence of human fetal malformations or irreversib These drugs may also have adverse pharmacological effects. Accompar should be consulted for further details.

See Drug Consult reference: PREGNANCY RISK CATEGORIES

3) Crosses Placenta: Unknown

4) Clinical Management

a) There are no adequate and well-controlled clinical studies in pregnar Limited data on the safety of oxcarbazepine during pregnancy demonstr evidence of toxicity (Gentile, 2003; Friis et al, 1993). Animal studies hav demonstrated developmental toxicities in the offspring at oral oxcarbaze similar to the maximum recommended human dose. Because oxcarbaze structurally similar to carbamazepine, which is considered to be teratoge humans, it is likely that oxcarbazepine is a human teratogen. Use oxcarb during pregnancy only if the potential benefit outweighs the potential risk (Prod Info TRILEPTAL(R) oral tablets, suspension, 2007a).

5) Literature Reports

a) In a case report of a 34-year-old woman with a 2-year history of idiop (subtype partial seizures evolving to secondary generalized seizures), tr oxcarbazepine 600 mg twice daily before and during pregnancy resulted spontaneous, uncomplicated vaginal delivery of a female infant without a effects. The patient began oxcarbazepine treatment after her diagnosis a seizure-free following the first month of therapy. During week 4 of the 39 gestation and 13 months after she started oxcarbazepine, pregnancy wa According to the patient, there was no other drug intake, no history of sm alcohol or caffeine use or infections during pregnancy. Obstetrical findin fetoprotein concentration, and three ultrasounds at weeks 22, 26, and 3(were all normal. Oxcarbazepine therapy was continued. The patient gav spontaneous and uncomplicated vaginal delivery to a female infant weig and measuring 49 cm with Apgar scores of 8 and 9 at one minute and 5 respectively, and no adverse effects. There was no exacerbation of seiz delivery (Gentile, 2003)

b) No congenital malformations were reported in 9 infants born to mothe oxcarbazepine during the first trimester of pregnancy (Friis et al, 1993).

c) Fetal structural abnormalities and other developmental toxicities were the offspring of rats and rabbits treated with either oral oxcarbazepine or monohydroxy metabolite during pregnancy at doses similar to the maxim recommended human dose. Maternal toxicity was also reported in the ra oxcarbazepine use during pregnancy (Prod Info TRILEPTAL(R) oral tabl suspension, 2007a). In mice, a malformation incidence of 8% was report pregnant mice were given the highest tolerable oxcarbazepine dose of 1 mg/kg/day on days 6 through 18 of gestation compared with a 5% incide mice given no drugs (Bennett et al, 1996)

d) .

B) Breastfeeding

1) Thomson Lactation Rating: Infant risk cannot be ruled out.

a) Available evidence and/or expert consensus is inconclusive or is inac determining infant risk when used during breastfeeding. Weigh the poter of drug treatment against potential risks before prescribing this drug duri

breastfeeding.

2) Clinical Management

a) Oxcarbazepine and its active metabolite, 10-hydroxy metabolite (MH excreted in human breast milk. The milk-to-plasma concentration ratio w be 0.5 for both drug and metabolite. Due to the potential for serious adv the nursing infant, a decision should be made to discontinue oxcarbazep discontinue nursing taking into consideration the importance of the drug mother (Prod Info TRILEPTAL(R) oral tablets, suspension, 2007a; Genti

3) Literature Reports

a) In a case report of a 34-year-old woman with a 2-year history of idiop (subtype partial seizures evolving to secondary generalized seizures), tr oxcarbazepine 600 mg twice daily before and during pregnancy and lact demonstrated no developmental abnormalities in the nursing infant after breast-feeding. The patient began oxcarbazepine treatment after her dia was seizure-free following the first month of therapy. During week 4 of th gestation and 13 months after she started oxcarbazepine, pregnancy wa Oxcarbazepine treatment was maintained throughout gestation. The pat via spontaneous and uncomplicated vaginal delivery to a female infant w kg and measuring 49 cm with Apgar scores of 8 and 9 at one minute an respectively, and no adverse effects. There was no exacerbation of seiz delivery and breast-feeding was successfully initiated with concomitant c treatment. During the first four months of nursing, the infant's developme normal (Gentile, 2003).

3.5 Drug Interactions

3.5.1 Drug-Drug Combinations

Carbamazepine

Clopidogrel

Cyclosporine

Ethinyl Estradiol

Etonogestrel

Evening Primrose

Felodipine

Fosphenytoin

Ginkgo

Lamotrigine

Levonorgestrel

Mestranol

Norelgestromin

Norethindrone

Norgestrel

Phenobarbital

Phenytoin

Selegiline

Simvastatin

Tolvaptan

Valproic Acid

Verapamil

3.5.1.A Carbamazepine

1) Interaction Effect: decreased plasma concentration of the active 10-n
metabolite of oxcarbazepine

2) Summary: Concurrent administration of oxcarbazepine and carbama
has resulted in a 40% decrease in the plasma concentration of the active
monohydroxy derivative (MHD) of oxcarbazepine (Prod Info TRILEPTAL
tablets, oral suspension, 2005). Although the exact mechanism for this c
unknown, it is believed to be partially due to the potential induction of ox
metabolism by CBZ, which is strong inducer of cytochrome P450 enzym
al, 1994). Although, the clinical significance of this interaction is unknow
plasma MHD concentrations may result in a potential loss of oxcarbazep
oxcarbazepine and carbamazepine are administered concurrently, clinic
oxcarbazepine may need to be monitored.

3) Severity: moderate

4) Onset: delayed

5) Substantiation: established

6) Clinical Management: Coadministration of oxcarbazepine and carbar
result in a decreased concentration of the active 10-monohydroxy metab
oxcarbazepine. Monitor patients for clinical response to oxcarbazepine.

7) Probable Mechanism: potential induction of cytochrome P450-mediat
oxcarbazepine metabolism

8) Literature Reports

a) In a randomized, double-blind, placebo-controlled trial in adults,
coadministration of carbamazepine (CBZ) and oxcarbazepine result
decreased levels of the pharmacologically active 10-monohydroxy c
(MHD) of oxcarbazepine. Patients (n=12) being treated with a mear
1025 milligrams (mg) (range 400 to 2000 mg) were administered a s
oral dose of oxcarbazepine and were randomized, a week later, to r
300 mg oxcarbazepine three times daily or matched placebo for 3 w
controls (n=7) were untreated patients who received the single 600
oxcarbazepine dose and 3 weeks active treatment. Study results sh
area under the concentration-time curve (AUC) for MHD at steady s
reduced by 40% (90% confidence interval: 17% decrease, 57% dec
CBZ-treated group compared to the active controls (p less than 0.05
for CBZ did not alter significantly. Although the exact mechanism fo
decrease is unknown, it was partially attributed to a potential inducti
oxcarbazepine metabolism by carbamazepine, a strong inducer of c
P450 enzymes (McKee et al, 1994; Prod Info TRILEPTAL(R) oral ta
suspension, 2005).

3.5.1.B Clopidogrel

1) Interaction Effect: reduction in clinical efficacy of clopidogrel

2) Summary: Clopidogrel is metabolized to its active metabolite by CYP
Concomitant use of CYP2C19 inhibitors, such as oxcarbazepine, would
to result in reduced levels of the active metabolite, and therefore a reduc
clinical efficacy of clopidogrel. Concomitant use of CYP2C19 inhibitors w
clopidogrel is discouraged (Prod Info PLAVIX(R) oral tablet, 2009).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concomitant use of clopidogrel and oxcarbaze
discouraged (Prod Info PLAVIX(R) oral tablet, 2009).

7) Probable Mechanism: inhibition of CYP2C19- mediated clopidogrel m
oxcarbazepine

3.5.1.C Cyclosporine

1) Interaction Effect: decreased cyclosporine concentrations
2) Summary: Cyclosporine is extensively metabolized by CYP3A isozyn
Coadministration with oxcarbazepine, a CYP3A inducer, may result in de
cyclosporine concentrations. If concomitant therapy is required, the clinic
monitor circulating cyclosporine levels and make appropriate cyclosporin
adjustments (Prod Info ESTRADERM(R) transdermal system, 2005).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of cyclosporine and oxcarbaz
result in decreased cyclosporine plasma concentrations. If concurrent th
required, monitor circulating cyclosporine levels and make appropriate d
adjustments as necessary (Prod Info ESTRADERM(R) transdermal syst
Monitor the patient for decreased response to cyclosporine.
7) Probable Mechanism: induction of CYP3A-mediated cyclosporine me

3.5.1.D Ethinyl Estradiol

1) Interaction Effect: decreased contraceptive effectiveness
2) Summary: In studies conducted with oral contraceptives, concurrent
of oxcarbazepine with an oral contraceptive has decreased plasma conc
2 hormonal components: ethinyl estradiol (EE) and levonorgestrel (LNG)
TRILEPTAL(R) oral tablets, oral suspension, 2005). Contraceptive effec
be reduced when hormonal contraceptives (oral, transdermal, or vaginal
coadministered with some drugs, such as oxcarbazepine, that increase t
metabolism of contraceptive steroids. This could result in unintended pre
breakthrough bleeding. Caution is advised when oxcarbazepine is admi
concurrently with hormonal contraceptives (Prod Info ORTHO EVRA(R)
system, 2005). Patients should be advised about using additional contra
methods (Prod Info NUVARING(R) vaginal ring, 2005).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Concurrent use of oxcarbazepine with hormon
contraceptives (oral, transdermal, or vaginal ring) may result in decrease
contraceptive efficacy, leading to unintended pregnancy or breakthrough
Use caution if oxcarbazepine is administered concomitantly with a comb
contraceptive.
7) Probable Mechanism: increased metabolism of contraceptive steroid
8) Literature Reports
a) The effects of oxcarbazepine (OCBZ) on the pharmacokinetics o
estradiol (EE) and levonorgestrel (LNG) were studied in 10 healthy
had taken triphasic oral contraceptives for at least three menstrual c
300 mg was administered once on day 16 of the first study cycle, tw
day 17, and three times daily from day 18 of the first cycle through c
second cycle. Combined use resulted in a significant decrease in th
the concentration-time curve (AUC) for both EE (3 +/- 1.2 vs 1.6 +/-
and LNG (29.3 +/- 94.6 vs 189.5 +/- 71.7 nmol/h) (p = 0.006 for both
not a significant change in mean maximum concentration (Cmax) va
EE or LNG. Progesterone levels were low throughout the study indi
anovulation, but one subject had prolonged menstrual bleeding and
experienced breakthrough bleeding which indicates a potential loss
contraceptive efficacy (Klosterskov-Jensen et al, 1992).
b) The effects of oxcarbazepine (OCBZ) on the pharmacokinetics o
estradiol (EE) and levonorgestrel (LN) were studied on 16 healthy w
18 to 44 years in a randomized double-blind cross-over design. Dur
different menstrual cycles, each woman was given placebo or 1200
in random sequence for 26 consecutive days with a one cycle wash
between. An oral contraceptive containing 50 mcg EE and 250 mcg
for the first 21 days of each cycle. Plasma concentrations of EE and
measured at regular intervals on days 21 to 23 of each cycle. Comp
placebo, a 47% decrease in area under the concentration-time curv
both EE and LN was seen during OCBZ treatment. Peak plasma EE
concentrations decreased from 180 pg/ml to 117 pg/ml during the p

OCBZ cycle, respectively (p less than 0.01) and the LN concentratic
from 10.2 to 7.7 ng/ml (p less than 0.01). In addition, the half-lives o
decreased from 13.6 to 7.9 hours (p less than 0.01) and from 28.8 t
respectively (p less than 0.01) (Fattore et al, 1999).
c) Concurrent administration of oxcarbazepine with an oral contrac
affected plasma concentrations 2 hormonal components: ethinyl est
and levonorgestrel (LNG). In studies conducted with oral combinatic
contraceptives, the mean area under the concentration-time curve (
for EE were reduced by 48% (90% confidence interval (CI): 22 to 65
and 52% (90% CI: 38 to 52) in another study. The mean AUC value
were reduced by 32% (90% CI: 20 to 45) in one study and 52% (90
52) in another study (Prod Info TRILEPTAL(R) oral tablets, oral sus
2005).

3.5.1.E Etonogestrel

1) Interaction Effect: decreased contraceptive effectiveness
2) Summary: In studies conducted with oral contraceptives, concurrent
of oxcarbazepine with an oral contraceptive has decreased plasma conc
2 hormonal components: ethinyl estradiol (EE) and levonorgestrel (LNG)
TRILEPTAL(R) oral tablets, oral suspension, 2005). Contraceptive effec
be reduced when hormonal contraceptives (oral, transdermal, or vaginal
coadministered with some drugs, such as oxcarbazepine, that increase
metabolism of contraceptive steroids. This could result in unintended pre
breakthrough bleeding. Caution is advised when oxcarbazepine is admi
concurrently with hormonal contraceptives (Prod Info ORTHO EVRA(R)
system, 2005). Patients should be advised about using additional contra
methods (Prod Info NUVARING(R) vaginal ring, 2005).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Concurrent use of oxcarbazepine with hormon
contraceptives (oral, transdermal, or vaginal ring) may result in decrease
contraceptive efficacy, leading to unintended pregnancy or breakthrough
Use caution if oxcarbazepine is administered concomitantly with a comb
contraceptive.
7) Probable Mechanism: increased metabolism of contraceptive steroid
8) Literature Reports
a) The effects of oxcarbazepine (OCBZ) on the pharmacokinetics c
estradiol (EE) and levonorgestrel (LNG) were studied in 10 healthy
had taken triphasic oral contraceptives for at least three menstrual c
300 mg was administered once on day 16 of the first study cycle, tw
day 17, and three times daily from day 18 of the first cycle through c
second cycle. Combined use resulted in a significant decrease in th
the concentration-time curve (AUC) for both EE (3 +/- 1.2 vs 1.6 +/-
and LNG (29.3 +/- 94.6 vs 189.5 +/- 71.7 nmol/h) (p = 0.006 for both
not a significant change in mean maximum concentration (Cmax) va
EE or LNG. Progesterone levels were low throughout the study indi
anovulation, but one subject had prolonged menstrual bleeding and
experienced breakthrough bleeding which indicates a potential loss
contraceptive efficacy (Klosterskov-Jensen et al, 1992).
b) The effects of oxcarbazepine (OCBZ) on the pharmacokinetics c
estradiol (EE) and levonorgestrel (LN) were studied on 16 healthy w
18 to 44 years in a randomized double-blind cross-over design. Dur
different menstrual cycles, each woman was given placebo or 1200
in random sequence for 26 consecutive days with a one cycle wash
between. An oral contraceptive containing 50 mcg EE and 250 mcg
for the first 21 days of each cycle. Plasma concentrations of EE and
measured at regular intervals on days 21 to 23 of each cycle. Comp
placebo, a 47% decrease in area under the concentration-time curv
both EE and LN was seen during OCBZ treatment. Peak plasma EE
concentrations decreased from 180 pg/ml to 117 pg/ml during the p
OCBZ cycle, respectively (p less than 0.01) and the LN concentratic
from 10.2 to 7.7 ng/ml (p less than 0.01). In addition, the half-lives o
decreased from 13.6 to 7.9 hours (p less than 0.01) and from 28.8 t
respectively (p less than 0.01) (Fattore et al, 1999).
c) Concurrent administration of oxcarbazepine with an oral contrac
affected plasma concentrations 2 hormonal components: ethinyl est

and levonorgestrel (LNG). In studies conducted with oral combinatic contraceptives, the mean area under the concentration-time curve (for EE were reduced by 48% (90% confidence interval (CI): 22 to 6 and 52% (90% CI: 38 to 52) in another study. The mean AUC value were reduced by 32% (90% CI: 20 to 45) in one study and 52% (90 52) in another study (Prod Info TRILEPTAL(R) oral tablets, oral sus 2005).

3.5.1.F Evening Primrose

1) Interaction Effect: reduced anticonvulsant effectiveness

2) Summary: Theoretically, evening primrose oil may reduce the effecti anticonvulsants by lowering the seizure threshold. Evening primrose oil i contraindicated in patients with epilepsy (Barber, 1998; Newall et al, 199

3) Severity: moderate

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: Avoid concomitant use of evening primrose oil anticonvulsants.

7) Probable Mechanism: evening primrose oil may reduce the seizure th

3.5.1.G Felodipine

1) Interaction Effect: decreased felodipine exposure

2) Summary: Oxcarbazepine and its active 10-monohydroxy metabolite subgroup of cytochrome P450 3A family of enzymes which are utilized ir metabolism of felodipine. A small study indicated that repeated coadmin felodipine and oxcarbazepine decreased exposure to felodipine; howeve plasma concentrations remained within the recommended therapeutic ra et al, 1993; Prod Info TRILEPTAL(R) oral tablets, oral suspension, 2005 and oxcarbazepine are coadministered, it is advisable to monitor clinical felodipine.

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Coadministration of felodipine and oxcarbazep resulted in decreased exposure to felodipine. If felodipine and oxcarbaze administered concurrently, monitor clinical response to felodipine.

7) Probable Mechanism: induction of cytochrome P450-mediated felodi metabolism

8) Literature Reports

a) A pharmacokinetic study was conducted with seven healthy subj were given felodipine 10 mg daily for 13 days; on day 6 oxcarbazep was given and was increased to 450 mg twice daily from day 7 to 1 dose of oxcarbazepine had no effect on felodipine pharmacokinetic compared with felodipine alone, but the week-long coadministration decrease of felodipine area under the concentration-time curve (AU (110.2 +/- 35.9 vs 79.2 +/- 25.7; p less than 0.05) and maximum pla concentration by 34% (9.7 +/- 3.2 vs 6.4 +/- 2 nmol/L). Similar result obtained for the inactive felodipine pyridine metabolite. Despite thes in felodipine AUC and Cmax, the felodipine plasma concentrations r within the recommended therapeutic range (Zaccara et al, 1993).

3.5.1.H Fosphenytoin

1) Interaction Effect: an increased risk of phenytoin toxicity (ataxia, hype nystagmus, tremor)

2) Summary: Fosphenytoin is a prodrug of phenytoin and the same inte occur with phenytoin are expected to occur with fosphenytoin (Prod Info 1999). When phenytoin in doses of 250 mg to 500 mg daily was combin oxcarbazepine in doses of 600 mg to 1800 mg daily, there was less thar change in the concentration of phenytoin. Additionally, concentrations of monohydroxy metabolite (MHD) of oxcarbazepine, which possesses pha activity, were decreased by 30%. This effect is most likely due to inducti cytochrome P450 enzyme system by phenytoin. When the same doses were combined with oxcarbazepine in doses greater than 1200 mg daily to a 40% increase in plasma phenytoin concentrations (Prod Info Trilept

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Patients should be monitored for phenytoin tox
receiving oxcarbazepine concurrently, especially when oxcarbazepine d
1200 mg daily. A decrease in the phenytoin dose may be required.
7) Probable Mechanism: inhibition of cytochrome P450 2C19-mediated
metabolism
8) Literature Reports
a) In polypharmacy studies employing add-on oxcarbazepine and
carbamazepine, increased serum levels of valproic acid and phenyt
observed with patients receiving oxcarbazepine. This was attributec
enzyme induction (Bulau et al, 1987; Houtkooper et al, 1987). Alterr
dependent enzyme induction has been reported by some investigat
doses of oxcarbazepine produced enzyme induction that was simila
carbamazepine (Patsalos et al, 1990a). Further studies are requirec
if oxcarbazepine will offer a significant advantage over carbamazep
regard to enzyme induction.

3.5.1.l Ginkgo

1) Interaction Effect: decreased anticonvulsant effectiveness
2) Summary: In a case report, 2 patients with epilepsy previously well c
valproate sodium developed a recurrence of seizures after ingesting ginl
Seizure control was regained after ginkgo was withdrawn (Granger, 200
developed seizures after exposure to 4'-O-methylpyridoxine arising from
ginkgo seeds (Yagi et al, 1993a). The compound 4'-O-methylpyridoxine,
is found in ginkgo seeds (used as food in Japan) as well as in leaves, th
component from which commercially available extracts are derived (Arer
1996a). The majority of ginkgo leaf products should not contain sufficien
4'-O-methylpyridoxine to cause seizures. However, ginkgo products are
assayed to assure that 4'-O-methylpyridixone is not contained in the con
product. Of concern are those instances where, depending on the harve
the potential introduction of contamination, 4'-O-methylpyridoxine may b
sufficient amounts to be problematic in vulnerable populations (eg, infan
with known seizure disorders).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Avoid concomitant use of ginkgo and anticonv
patients with epilepsy. If seizures occur for the first time or recur in patie
controlled by anticonvulsant medication, inquire about the use of ginkgo
extract. If possible, an assay should be conducted on the specific produc
if 4'-O-methylpyridoxine is present.
7) Probable Mechanism: neurotoxin 4'-O-methylpyridoxine (found in lea
seeds of ginkgo biloba) may cause seizures
8) Literature Reports
a) The serum of a 21-month-old patient with gin-nan food poisoning
for 4'-O-methylpyridoxine levels. The serum concentration was 0.9
micrograms/milliliter (mcg/mL) at 8.5 hours after ingesting ginkgo se
decreasing to 0.05 mcg/mL at 15.5 hours. The authors concluded th
methylpyridoxine content was responsible for the tonic/clonic convu
loss of consciousness observed. They further observed that infants
particularly vulnerable (Yagi et al, 1993).
b) Four to six milligrams of the neurotoxin 4'-O-methylpyridoxine ha
isolated from 2 kilograms of Ginkgo biloba leaves which is the sourc
commercially-available products. Highest amounts were found in se
micrograms (mcg)/seed) and leaves (5 mcg/leaf) derived from the tr
of July and beginning of August. The albumen of the seed can conta
mcg/gram dry weight, but this is reduced to 0.75-1.32 mcg/gram dry
boiled. The unprocessed seed coats contain from 5.44-7.15 mcg/gr
The neurotoxin in ginkgo leaf was detected in medications and it wa
detectable in homeopathic preparations. Specifically, 8.13 mcg/mL
methylpyridoxine was found in Tebonin Forte(R), 9.77 mcg/mL in R
mcg/mL in Kaveri Forte(R), and 7.18 mcg/mL in Gingium(R). Based
recommended daily intake, this translates into a maximum daily inta
methylpyridoxine of 48.78 mcg, 58.62 mcg, 11.40 mcg, and 43.08 m
Tebonin Forte(R), Rokan(R), Kaveri Forte(R), and Gingium(R), resp
Among the homeopathic products, Ginkgo biloba Urtinktur Hanosar
Ginkgo biloba Urtinktur DHU(R) contained 0.301 mcg/mL and 0.589
4'-O-methylpyridoxine, respectively. However, the authors note that

contained in medicinal extracts of ginkgo leaves may be too low to b
significance. Concern remains with the variance in 4'-O-methylpyrid
depending on the season during which the ginkgo was harvested (A
1996).

c) Seizures recurred in 2 patients, both with epilepsy that was well
prior to ingesting ginkgo biloba (Gb). The patients (an 84-year-old w
78-year-old man) had been free of seizures for at least 18 months p
beginning therapy with Gb 120 milligrams daily to treat cognitive de
patients developed seizures within 2 weeks of beginning Gb therapy
remained seizure-free (without changing anticonvulsant therapy) aft
discontinuing Gb (Granger, 2001).

3.5.1.J Lamotrigine

1) Interaction Effect: reduced lamotrigine concentrations and possible lo
control

2) Summary: Oxcarbazepine is structurally similar to carbamazepine bu
form an epoxide metabolite, which is considered responsible for the neu
of carbamazepine. When lamotrigine and oxcarbazepine were administe
concurrently to 14 epileptic patients, plasma concentrations of lamotrigin
decreased 28.7% compared to lamotrigine monotherapy (May et al, 199
patients who had received lamotrigine and oxcarbazepine concurrently,
occurred several weeks after oxcarbazepine discontinuation or dose red
Induction of lamotrigine metabolism by oxcarbazepine was postulated to
mechanism, such oxcarbazepine discontinuation or a dose reduction ma
resulted in a slow increase in lamotrigine levels, thereby increasing its to
& deLeon, 2007). Concomitant use of lamotrigine and oxcarbazepine ma
monitoring the patient closely for seizure control and increasing the lamo
as necessary. Conversely, in patients receiving these agents concurrent
oxcarbazepine is discontinued or its dose is reduced, lamotrigine doses
be reduced. Additionally, the patient may need to be monitored over sev
signs/symptoms of lamotrigine toxicity.

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Monitor seizure control and anticipate a possib
increase lamotrigine doses if oxcarbazepine is added to therapy. Conver
oxcarbazepine is withdrawn from therapy or if dosage is reduced, lamotr
may need to be reduced and the patient may need to be monitored over
weeks for symptoms of lamotrigine toxicity.

7) Probable Mechanism: hepatic induction by oxcarbazepine of lamotrig
metabolism

8) Literature Reports

a) Two patients, receiving lamotrigine and oxcarbazepine concurre
experienced oral ulcers several weeks after oxcarbazepine discontin
dose reduction. In the first case, a 35-year-old woman being treated
disorder (BD II), hypothyroidism, gastritis, migraines, and asthma w
after experiencing one week of worsening depression and two days
thoughts and treated with oxcarbazepine 600 mg/day, topiramate, fl
aripiprazole, quetiapine, lithium, naproxen, pantoprazole, amoxicillin
levothyroxine. On day 2, lamotrigine 50 mg/day was initiated and titr
200 mg/day by day 6. Oxcarbazepine dose was decreased and stop
and she was discharged on day 8 with lamotrigine 200 mg, topirama
aripiprazole, escitalopram, naproxen, pantoprazole, levothyroxine, a
hydroxyzine. On day 42 (41 days after starting lamotrigine and 39 d
stopping oxcarbazepine), she developed painful tongue ulcers. Sub
lamotrigine was stopped and the ulcers resolved in 4 days. In the se
36-year-old man with BD II, hypertension, and GERD was admitted
suicide attempt and prescribed oxcarbazepine 600 mg/day, phenyto
venlafaxine, mirtazapine, metoprolol, and famotidine. Lamotrigine 5
initiated on day 11 and titrated up to 100 mg/day by day 14. He was
on day 14 with lamotrigine 100 mg and oxcarbazepine 1200 mg (alo
medications); however, he reduced the oxcarbazepine dose to 600
discharge. On day 44 (22 days after oxcarbazepine dose decrease)
developed several painful mouth sores on his lips, gums, and tongu
lamotrigine and oxcarbazepine were discontinued and the ulcers res
completely (O'Neill & deLeon, 2007).

b) Lamotrigine serum concentrations from 222 patients receiving la

monotherapy (n = 64) or combination therapy with another antiepile
were evaluated. Fourteen patients were being treated with lamotrigi
oxcarbazepine. In the lamotrigine monotherapy group, the lamotrigi
concentration was 7.14 mcg/mL while the mean dose was 7.27 mg/
lamotrigine level-to-dose ratio (LDR) in this group calculated out to
mcg/mL/mg/kg. In the subjects receiving oxcarbazepine in addition
the plasma concentration was 4.73 mcg/mL while the mean dose w
mg/dose/kg. The lamotrigine LDR in this group was 0.71 mcg/mL/m
demonstrating the inducing properties of oxcarbazepine on lamotrig
metabolism (May et al, 1999).

3.5.1.K Levonorgestrel

1) Interaction Effect: decreased contraceptive effectiveness

2) Summary: In studies conducted with oral contraceptives, concurrent
of oxcarbazepine with an oral contraceptive has decreased plasma conc
2 hormonal components: ethinyl estradiol (EE) and levonorgestrel (LNG)
TRILEPTAL(R) oral tablets, oral suspension, 2005). Contraceptive effec
be reduced when hormonal contraceptives (oral, transdermal, or vaginal
coadministered with some drugs, such as oxcarbazepine, that increase
metabolism of contraceptive steroids. This could result in unintended pre
breakthrough bleeding. Caution is advised when oxcarbazepine is admi
concurrently with hormonal contraceptives (Prod Info ORTHO EVRA(R)
system, 2005). Patients should be advised about using additional contra
methods (Prod Info NUVARING(R) vaginal ring, 2005).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Concurrent use of oxcarbazepine with hormon
contraceptives (oral, transdermal, or vaginal ring) may result in decrease
contraceptive efficacy, leading to unintended pregnancy or breakthrough
Use caution if oxcarbazepine is administered concomitantly with a comb
contraceptive.

7) Probable Mechanism: increased metabolism of contraceptive steroid

8) Literature Reports

a) The effects of oxcarbazepine (OCBZ) on the pharmacokinetics o
estradiol (EE) and levonorgestrel (LNG) were studied in 10 healthy
had taken triphasic oral contraceptives for at least three menstrual c
300 mg was administered once on day 16 of the first study cycle, tw
day 17, and three times daily from day 18 of the first cycle through c
second cycle. Combined use resulted in a significant decrease in th
the concentration-time curve (AUC) for both EE (3 +/- 1.2 vs 1.6 +/-
and LNG (29.3 +/- 94.6 vs 189.5 +/- 71.7 nmol/h) (p = 0.006 for both
not a significant change in mean maximum concentration (Cmax) va
EE or LNG. Progesterone levels were low throughout the study indi
anovulation, but one subject had prolonged menstrual bleeding and
experienced breakthrough bleeding which indicates a potential loss
contraceptive efficacy (Klosterskov-Jensen et al, 1992).

b) The effects of oxcarbazepine (OCBZ) on the pharmacokinetics o
estradiol (EE) and levonorgestrel (LN) were studied on 16 healthy w
18 to 44 years in a randomized double-blind cross-over design. Dur
different menstrual cycles, each woman was given placebo or 1200
in random sequence for 26 consecutive days with a one cycle wash
between. An oral contraceptive containing 50 mcg EE and 250 mcg
for the first 21 days of each cycle. Plasma concentrations of EE and
measured at regular intervals on days 21 to 23 of each cycle. Comp
placebo, a 47% decrease in area under the concentration-time curv
both EE and LN was seen during OCBZ treatment. Peak plasma EE
concentrations decreased from 180 pg/ml to 117 pg/ml during the p
OCBZ cycle, respectively (p less than 0.01) and the LN concentratio
from 10.2 to 7.7 ng/ml (p less than 0.01). In addition, the half-lives o
decreased from 13.6 to 7.9 hours (p less than 0.01) and from 28.8 t
respectively (p less than 0.01) (Fattore et al, 1999).

c) Concurrent administration of oxcarbazepine with an oral contrac
affected plasma concentrations 2 hormonal components: ethinyl est
and levonorgestrel (LNG). In studies conducted with oral combinatio
contraceptives, the mean area under the concentration-time curve (
for EE were reduced by 48% (90% confidence interval (CI): 22 to 65

and 52% (90% CI: 38 to 52) in another study. The mean AUC value were reduced by 32% (90% CI: 20 to 45) in one study and 52% (90 52) in another study (Prod Info TRILEPTAL(R) oral tablets, oral sus 2005).

3.5.1.L Mestranol

1) Interaction Effect: decreased contraceptive effectiveness

2) Summary: In studies conducted with oral contraceptives, concurrent of oxcarbazepine with an oral contraceptive has decreased plasma conc 2 hormonal components: ethinyl estradiol (EE) and levonorgestrel (LNG) TRILEPTAL(R) oral tablets, oral suspension, 2005). Contraceptive effec be reduced when hormonal contraceptives (oral, transdermal, or vaginal coadministered with some drugs, such as oxcarbazepine, that increase t metabolism of contraceptive steroids. This could result in unintended pre breakthrough bleeding. Caution is advised when oxcarbazepine is admi concurrently with hormonal contraceptives (Prod Info ORTHO EVRA(R) system, 2005). Patients should be advised about using additional contra methods (Prod Info NUVARING(R) vaginal ring, 2005).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Concurrent use of oxcarbazepine with hormon contraceptives (oral, transdermal, or vaginal ring) may result in decrease contraceptive efficacy, leading to unintended pregnancy or breakthrough Use caution if oxcarbazepine is administered concomitantly with a comb contraceptive.

7) Probable Mechanism: increased metabolism of contraceptive steroid

8) Literature Reports

a) The effects of oxcarbazepine (OCBZ) on the pharmacokinetics o estradiol (EE) and levonorgestrel (LNG) were studied in 10 healthy had taken triphasic oral contraceptives for at least three menstrual c 300 mg was administered once on day 16 of the first study cycle, tw day 17, and three times daily from day 18 of the first cycle through c second cycle. Combined use resulted in a significant decrease in th the concentration-time curve (AUC) for both EE (3 +/- 1.2 vs 1.6 +/- and LNG (29.3 +/- 94.6 vs 189.5 +/- 71.7 nmol/h) (p = 0.006 for both not a significant change in mean maximum concentration (Cmax) va EE or LNG. Progesterone levels were low throughout the study indi anovulation, but one subject had prolonged menstrual bleeding and experienced breakthrough bleeding which indicates a potential loss contraceptive efficacy (Klosterskov-Jensen et al, 1992).

b) The effects of oxcarbazepine (OCBZ) on the pharmacokinetics o estradiol (EE) and levonorgestrel (LN) were studied on 16 healthy w 18 to 44 years in a randomized double-blind cross-over design. Dur different menstrual cycles, each woman was given placebo or 1200 in random sequence for 26 consecutive days with a one cycle wash between. An oral contraceptive containing 50 mcg EE and 250 mcg for the first 21 days of each cycle. Plasma concentrations of EE and measured at regular intervals on days 21 to 23 of each cycle. Comp placebo, a 47% decrease in area under the concentration-time curv both EE and LN was seen during OCBZ treatment. Peak plasma EE concentrations decreased from 180 pg/ml to 117 pg/ml during the p OCBZ cycle, respectively (p less than 0.01) and the LN concentratio from 10.2 to 7.7 ng/ml (p less than 0.01). In addition, the half-lives o decreased from 13.6 to 7.9 hours (p less than 0.01) and from 28.8 t respectively (p less than 0.01) (Fattore et al, 1999).

c) Concurrent administration of oxcarbazepine with an oral contrac affected plasma concentrations 2 hormonal components: ethinyl est and levonorgestrel (LNG). In studies conducted with oral combinatio contraceptives, the mean area under the concentration-time curve (for EE were reduced by 48% (90% confidence interval (CI): 22 to 65 and 52% (90% CI: 38 to 52) in another study. The mean AUC value were reduced by 32% (90% CI: 20 to 45) in one study and 52% (90 52) in another study (Prod Info TRILEPTAL(R) oral tablets, oral sus 2005).

3.5.1.M Norelgestromin

1) Interaction Effect: decreased contraceptive effectiveness
2) Summary: In studies conducted with oral contraceptives, concurrent
of oxcarbazepine with an oral contraceptive has decreased plasma conc
2 hormonal components: ethinyl estradiol (EE) and levonorgestrel (LNG)
TRILEPTAL(R) oral tablets, oral suspension, 2005). Contraceptive effec
be reduced when hormonal contraceptives (oral, transdermal, or vaginal
coadministered with some drugs, such as oxcarbazepine, that increase
metabolism of contraceptive steroids. This could result in unintended pre
breakthrough bleeding. Caution is advised when oxcarbazepine is admi
concurrently with hormonal contraceptives (Prod Info ORTHO EVRA(R)
system, 2005). Patients should be advised about using additional contra
methods (Prod Info NUVARING(R) vaginal ring, 2005).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Concurrent use of oxcarbazepine with hormon
contraceptives (oral, transdermal, or vaginal ring) may result in decrease
contraceptive efficacy, leading to unintended pregnancy or breakthrough
Use caution if oxcarbazepine is administered concomitantly with a comb
contraceptive.
7) Probable Mechanism: increased metabolism of contraceptive steroid
8) Literature Reports
a) The effects of oxcarbazepine (OCBZ) on the pharmacokinetics o
estradiol (EE) and levonorgestrel (LNG) were studied in 10 healthy
had taken triphasic oral contraceptives for at least three menstrual c
300 mg was administered once on day 16 of the first study cycle, tw
day 17, and three times daily from day 18 of the first cycle through c
second cycle. Combined use resulted in a significant decrease in th
the concentration-time curve (AUC) for both EE (3 +/- 1.2 vs 1.6 +/-
and LNG (29.3 +/- 94.6 vs 189.5 +/- 71.7 nmol/h) (p = 0.006 for both
not a significant change in mean maximum concentration (Cmax) va
EE or LNG. Progesterone levels were low throughout the study indi
anovulation, but one subject had prolonged menstrual bleeding and
experienced breakthrough bleeding which indicates a potential loss
contraceptive efficacy (Klosterskov-Jensen et al, 1992).
b) The effects of oxcarbazepine (OCBZ) on the pharmacokinetics o
estradiol (EE) and levonorgestrel (LN) were studied on 16 healthy w
18 to 44 years in a randomized double-blind cross-over design. Dur
different menstrual cycles, each woman was given placebo or 1200
in random sequence for 26 consecutive days with a one cycle wash
between. An oral contraceptive containing 50 mcg EE and 250 mcg
for the first 21 days of each cycle. Plasma concentrations of EE and
measured at regular intervals on days 21 to 23 of each cycle. Comp
placebo, a 47% decrease in area under the concentration-time curv
both EE and LN was seen during OCBZ treatment. Peak plasma EE
concentrations decreased from 180 pg/ml to 117 pg/ml during the p
OCBZ cycle, respectively (p less than 0.01) and the LN concentratio
from 10.2 to 7.7 ng/ml (p less than 0.01). In addition, the half-lives o
decreased from 13.6 to 7.9 hours (p less than 0.01) and from 28.8 t
respectively (p less than 0.01) (Fattore et al, 1999).
c) Concurrent administration of oxcarbazepine with an oral contrac
affected plasma concentrations 2 hormonal components: ethinyl est
and levonorgestrel (LNG). In studies conducted with oral combinatio
contraceptives, the mean area under the concentration-time curve (
for EE were reduced by 48% (90% confidence interval (CI): 22 to 65
and 52% (90% CI: 38 to 52) in another study. The mean AUC value
were reduced by 32% (90% CI: 20 to 45) in one study and 52% (90
52) in another study (Prod Info TRILEPTAL(R) oral tablets, oral sus
2005).

3.5.1.N Norethindrone

1) Interaction Effect: decreased contraceptive effectiveness
2) Summary: In studies conducted with oral contraceptives, concurrent
of oxcarbazepine with an oral contraceptive has decreased plasma conc
2 hormonal components: ethinyl estradiol (EE) and levonorgestrel (LNG)
TRILEPTAL(R) oral tablets, oral suspension, 2005). Contraceptive effec
be reduced when hormonal contraceptives (oral, transdermal, or vaginal

coadministered with some drugs, such as oxcarbazepine, that increase t
metabolism of contraceptive steroids. This could result in unintended pre
breakthrough bleeding. Caution is advised when oxcarbazepine is admi
concurrently with hormonal contraceptives (Prod Info ORTHO EVRA(R)
system, 2005). Patients should be advised about using additional contra
methods (Prod Info NUVARING(R) vaginal ring, 2005).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Concurrent use of oxcarbazepine with hormon
contraceptives (oral, transdermal, or vaginal ring) may result in decrease
contraceptive efficacy, leading to unintended pregnancy or breakthrough
Use caution if oxcarbazepine is administered concomitantly with a comb
contraceptive.

7) Probable Mechanism: increased metabolism of contraceptive steroid

8) Literature Reports

a) The effects of oxcarbazepine (OCBZ) on the pharmacokinetics c
estradiol (EE) and levonorgestrel (LNG) were studied in 10 healthy
had taken triphasic oral contraceptives for at least three menstrual c
300 mg was administered once on day 16 of the first study cycle, tw
day 17, and three times daily from day 18 of the first cycle through c
second cycle. Combined use resulted in a significant decrease in th
the concentration-time curve (AUC) for both EE (3 +/- 1.2 vs 1.6 +/-
and LNG (29.3 +/- 94.6 vs 189.5 +/- 71.7 nmol/h) (p = 0.006 for both
not a significant change in mean maximum concentration (Cmax) va
EE or LNG. Progesterone levels were low throughout the study indi
anovulation, but one subject had prolonged menstrual bleeding and
experienced breakthrough bleeding which indicates a potential loss
contraceptive efficacy (Klosterskov-Jensen et al, 1992).

b) The effects of oxcarbazepine (OCBZ) on the pharmacokinetics c
estradiol (EE) and levonorgestrel (LN) were studied on 16 healthy w
18 to 44 years in a randomized double-blind cross-over design. Dur
different menstrual cycles, each woman was given placebo or 1200
in random sequence for 26 consecutive days with a one cycle wash
between. An oral contraceptive containing 50 mcg EE and 250 mcg
for the first 21 days of each cycle. Plasma concentrations of EE and
measured at regular intervals on days 21 to 23 of each cycle. Comp
placebo, a 47% decrease in area under the concentration-time curv
both EE and LN was seen during OCBZ treatment. Peak plasma EE
concentrations decreased from 180 pg/ml to 117 pg/ml during the p
OCBZ cycle, respectively (p less than 0.01) and the LN concentratio
from 10.2 to 7.7 ng/ml (p less than 0.01). In addition, the half-lives o
decreased from 13.6 to 7.9 hours (p less than 0.01) and from 28.8 t
respectively (p less than 0.01) (Fattore et al, 1999).

c) Concurrent administration of oxcarbazepine with an oral contrac
affected plasma concentrations 2 hormonal components: ethinyl est
and levonorgestrel (LNG). In studies conducted with oral combinatio
contraceptives, the mean area under the concentration-time curve (
for EE were reduced by 48% (90% confidence interval (CI): 22 to 65
and 52% (90% CI: 38 to 52) in another study. The mean AUC value
were reduced by 32% (90% CI: 20 to 45) in one study and 52% (90
52) in another study (Prod Info TRILEPTAL(R) oral tablets, oral sus
2005).

3.5.1.O Norgestrel

1) Interaction Effect: decreased contraceptive effectiveness

2) Summary: In studies conducted with oral contraceptives, concurrent
of oxcarbazepine with an oral contraceptive has decreased plasma conc
2 hormonal components: ethinyl estradiol (EE) and levonorgestrel (LNG)
TRILEPTAL(R) oral tablets, oral suspension, 2005). Contraceptive effec
be reduced when hormonal contraceptives (oral, transdermal, or vaginal
coadministered with some drugs, such as oxcarbazepine, that increase t
metabolism of contraceptive steroids. This could result in unintended pre
breakthrough bleeding. Caution is advised when oxcarbazepine is admi
concurrently with hormonal contraceptives (Prod Info ORTHO EVRA(R)
system, 2005). Patients should be advised about using additional contra
methods (Prod Info NUVARING(R) vaginal ring, 2005).

3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Concurrent use of oxcarbazepine with hormon contraceptives (oral, transdermal, or vaginal ring) may result in decrease contraceptive efficacy, leading to unintended pregnancy or breakthrough Use caution if oxcarbazepine is administered concomitantly with a comb contraceptive.
7) Probable Mechanism: increased metabolism of contraceptive steroid
8) Literature Reports
a) The effects of oxcarbazepine (OCBZ) on the pharmacokinetics c estradiol (EE) and levonorgestrel (LNG) were studied in 10 healthy had taken triphasic oral contraceptives for at least three menstrual c 300 mg was administered once on day 16 of the first study cycle, tw day 17, and three times daily from day 18 of the first cycle through c second cycle. Combined use resulted in a significant decrease in th the concentration-time curve (AUC) for both EE (3 +/- 1.2 vs 1.6 +/- and LNG (29.3 +/- 94.6 vs 189.5 +/- 71.7 nmol/h) (p = 0.006 for both not a significant change in mean maximum concentration (Cmax) va EE or LNG. Progesterone levels were low throughout the study indi anovulation, but one subject had prolonged menstrual bleeding and experienced breakthrough bleeding which indicates a potential loss contraceptive efficacy (Klosterskov-Jensen et al, 1992).
b) The effects of oxcarbazepine (OCBZ) on the pharmacokinetics c estradiol (EE) and levonorgestrel (LN) were studied on 16 healthy w 18 to 44 years in a randomized double-blind cross-over design. Dur different menstrual cycles, each woman was given placebo or 1200 in random sequence for 26 consecutive days with a one cycle wash between. An oral contraceptive containing 50 mcg EE and 250 mcg for the first 21 days of each cycle. Plasma concentrations of EE anc measured at regular intervals on days 21 to 23 of each cycle. Comp placebo, a 47% decrease in area under the concentration-time curv both EE and LN was seen during OCBZ treatment. Peak plasma EE concentrations decreased from 180 pg/ml to 117 pg/ml during the p OCBZ cycle, respectively (p less than 0.01) and the LN concentratic from 10.2 to 7.7 ng/ml (p less than 0.01). In addition, the half-lives o decreased from 13.6 to 7.9 hours (p less than 0.01) and from 28.8 t respectively (p less than 0.01) (Fattore et al, 1999).
c) Concurrent administration of oxcarbazepine with an oral contrac affected plasma concentrations 2 hormonal components: ethinyl est and levonorgestrel (LNG). In studies conducted with oral combinatic contraceptives, the mean area under the concentration-time curve (for EE were reduced by 48% (90% confidence interval (CI): 22 to 65 and 52% (90% CI: 38 to 52) in another study. The mean AUC value were reduced by 32% (90% CI: 20 to 45) in one study and 52% (90 52) in another study (Prod Info TRILEPTAL(R) oral tablets, oral sus 2005).

3.5.1.P Phenobarbital
1) Interaction Effect: decreased concentration of the active 10-monohyc metabolite of oxcarbazepine and potential loss of oxcarbazepine efficacy
2) Summary: Concurrent administration of oxcarbazepine (600 to 1,800 (mg)/day) in patients receiving treatment with phenobarbital (100 to 150 resulted in a 25% decrease (90% confidence interval (CI), 12% decrease decrease) in the plasma concentration of oxcarbazepine's 10-monohydr (MHD) and a 14% increase (90% confidence interval (CI), 2% increase t increase) in the phenobarbital concentration (Prod Info TRILEPTAL(R) c oral suspension, 2005). Although the clinical significance of this interacti unknown, MHD is the pharmacologically active metabolite of oxcarbazep decreased plasma MHD concentrations may result in potential loss of ox efficacy. If oxcarbazepine and phenobarbital are administered concurrer response to oxcarbazepine may need to be monitored.
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Coadministration of oxcarbazepine and pheno resulted in decreased concentrations of the active 10-monohydroxy met

oxcarbazepine. Monitor patients for clinical response to oxcarbazepine.
7) Probable Mechanism: potential induction of cytochrome P450-mediat oxcarbazepine metabolism

3.5.1.Q Phenytoin

1) Interaction Effect: an increased risk of phenytoin toxicity (ataxia, hype nystagmus, tremor)
2) Summary: Coadministration of phenytoin and oxcarbazepine (600 to milligrams (mg)/day) resulted in decreased levels of the pharmacologica monohydroxy derivative (MHD) of oxcarbazepine while oxcarbazepine d 1200 to 2400 mg/day resulted in increased levels of phenytoin plasma c Patients should be monitored for signs of phenytoin toxicity (ataxia, hype nystagmus, tremor) when receiving oxcarbazepine concurrently, especia oxcarbazepine doses exceed 1200 mg daily. A decrease in the phenytoi be required (Prod Info TRILEPTAL(R) oral tablets, oral suspension, 200
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Concurrent administration of oxcarbazepine ar have resulted in increased plasma levels of phenytoin. Monitor patients f phenytoin toxicity (ataxia, hyperreflexia, nystagmus, tremor) when receiv oxcarbazepine concurrently, especially when oxcarbazepine doses exce daily. A decrease in the phenytoin dose may be required.
7) Probable Mechanism: potential inhibition of cytochrome P450 -media metabolism
8) Literature Reports
a) Administration of phenytoin in doses of 250 to 500 milligrams (m patients concurrently receiving oxcarbazepine in doses of 600 to 18 resulted in a less than 10% change in the concentration of phenytoi concentrations of the active 10-monohydroxy derivative (MHD) of ox were decreased by 30% (90% confidence interval (CI): 3% decreas decrease). When the same doses of phenytoin were combined with oxcarbazepine in doses greater than 1200 to 2400 mg daily, there v 40% increase (90% CI: 12% increase to 60% increase) in phenytoir concentrations (Prod Info TRILEPTAL(R) oral tablets, oral suspensi
b) In polypharmacy studies employing add-on oxcarbazepine and carbamazepine, increased serum levels of valproic acid and phenyt observed with patients receiving oxcarbazepine. This was attributec enzyme induction (Bulau et al, 1987; Houtkooper et al, 1987a). Alte dose-dependent enzyme induction has been reported by some inve higher doses of oxcarbazepine produced enzyme induction that was carbamazepine (Patsalos et al, 1990b). Further studies are required if oxcarbazepine will offer a significant advantage over carbamazep regard to enzyme induction.

3.5.1.R Selegiline

1) Interaction Effect: an increase in selegiline plasma concentration
2) Summary: In subjects who had received carbamazepine 400 mg/day slightly increased levels of selegiline and its metabolites were seen after application of selegiline transdermal patch 6 mg/24 hr. Changes in the s plasma levels were nearly 2-fold and variable across the subject populat EMSAM(R) transdermal patch, 2008). Although not studied with oxcarba similar interaction would be expected. Concomitant use of oxcarbazepin selegiline is contraindicated. It is recommended that selegiline be discor minimum of 14 days prior to initiation of oxcarbazepine when necessary EMSAM(R) transdermal patch, 2008).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of oxcarbazepine and selegil contraindicated. Selegiline should be discontinued for a minimum of 14 d oxcarbazepine therapy is initiated (Prod Info EMSAM(R) transdermal pa
7) Probable Mechanism: unknown

3.5.1.S Simvastatin

1) Interaction Effect: reduced simvastatin exposure
2) Summary: Oxcarbazepine is a molecular derivative of carbamazepin

a similar ability to induce cytochrome P450/3A4. Theoretically, oxcarbaz
expected to induce the metabolism of simvastatin, a cytochrome P450/3
In a controlled study, the concurrent administration of carbamazepine wi
significantly reduced maximum serum concentration, serum half-life, and
the concentration-time curve for both simvastatin and its active metaboli
acid (Ucar et al, 2004).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor cholesterol levels in patients receiving
therapy with oxcarbazepine and simvastatin. Simvastatin dose may nee
adjusted.
7) Probable Mechanism: induction of CYP3A4-mediated first-pass meta
simvastatin by oxcarbazepine
8) Literature Reports
a) Concurrent administration of simvastatin with carbamazepine (a
anticonvulsant chemically related to oxcarbazepine) significantly rec
simvastatin exposure. In a randomized, crossover study with a 2-we
period, healthy subjects (n=12) received either no drug or carbamaz
milligrams (mg) once daily for 2 days, after which the active drug gr
carbamazepine 300 mg twice daily for the next 12 days. On day 15
after the last carbamazepine dose), subjects fasted for 2 hours prio
single dose of simvastatin 80 mg. Serial blood samples were obtain
immediately prior to and for 24 hours after simvastatin administratio
Carbamazepine co-administration significantly reduced the mean m
serum concentration for both simvastatin and its active metabolite s
acid (from 18.7 nanograms/milliliter (ng/mL) to 6.0 ng/mL and from
1.1 ng/mL, respectively; p less than 0.01, both values). Simvastatin
simvastatin acid mean areas under the concentration-time curves (A
declined from 88.8 ng/mL x hour to 22.6 ng/mL x hour and from 33.
hour to 6.8 ng/mL x hour, respectively (p less than 0.001, both value
Concurrent administration with carbamazepine also significantly red
simvastatin acid serum mean half-life (from 5.9 hours to 3.7 hours, p
0.01) (Ucar et al, 2004).

3.5.1.T Tolvaptan

1) Interaction Effect: decreased tolvaptan plasma concentrations
2) Summary: Concomitant use of tolvaptan (primarily metabolized by CY
oxcarbazepine (a CYP3A inducer) may reduce tolvaptan exposure and s
avoided. If concomitant use is required, tolvaptan dose increases may b
to achieve the same clinical effect (Prod Info SAMSCA(TM) oral tablets,
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of oxcarbazepine and tolvapt
avoided due to a risk of reduced plasma concentrations of tolvaptan. If c
use is required, the dose of tolvaptan may need to be increased to achie
clinical effect (Prod Info SAMSCA(TM) oral tablets, 2009).
7) Probable Mechanism: induction of CYP3A-mediated tolvaptan metab
oxcarbazepine

3.5.1.U Valproic Acid

1) Interaction Effect: decreased plasma concentration of the active 10-m
metabolite of oxcarbazepine
2) Summary: Concurrent administration of oxcarbazepine (600 to 1,800
(mg)/day) in patients receiving treatment with valproic acid (400 to 2,800
resulted in a 18% decrease (90% confidence interval, 13% decrease to
decrease) in the plasma concentration of oxcarbazepine's 10-monohydr
(MHD) and a less than 10% change in the valproic acid concentration (P
TRILEPTAL(R) oral tablets, oral suspension, 2005). Although, the clinica
of this interaction is unknown, decreased plasma MHD concentrations m
potential loss of oxcarbazepine efficacy. If oxcarbazepine and valproic a
administered concurrently, clinical response to oxcarbazepine may neec
monitored.
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable

6) Clinical Management: Coadministration of oxcarbazepine and valproi result in a decreased concentration of the active 10-monohydroxy metab oxcarbazepine. Monitor patients for clinical response to oxcarbazepine.
7) Probable Mechanism: unknown

3.5.1.V Verapamil

1) Interaction Effect: decreased plasma levels of the active 10-monohyc metabolite of oxcarbazepine and potential loss of oxcarbazepine efficacy
2) Summary: Concurrent administration of oxcarbazepine (OCBZ) and v resulted in a 20% decrease in the plasma concentration of 10-monohydr (MHD) (Prod Info TRILEPTAL(R) oral tablets, oral suspension, 2005; Ba 1994). Although the clinical significance of this interaction is unknown, M active metabolite of OCBZ and decreased plasma MHD concentrations r potential loss of OCBZ efficacy. If OCBZ and verapamil are administered clinical response to OCBZ may need to be monitored.
3) Severity: moderate
4) Onset: delayed
5) Substantiation: established
6) Clinical Management: Coadministration of oxcarbazepine and verapa in decreased plasma levels of the active 10-monohydroxy metabolite of oxcarbazepine. Although the clinical significance of this interaction is unl oxcarbazepine and verapamil are coadministered, monitor clinical respo oxcarbazepine.
7) Probable Mechanism: unknown
8) Literature Reports
a) Concurrent administration of oxcarbazepine (OCBZ) and verapa decreased plasma concentration of the 10-monohydroxy derivative active metabolite of OCBZ. In healthy volunteers (n=10), upon titrati to 900 milligrams/day (mg/day), verapamil (240 mg/day) was admin week. The area under the concentration-time curve (AUC) of MHD c 20%; however, AUC was unchanged for OCBZ. The mechanism for in MHD plasma concentration and its clinical significance are unkno al, 1994).

4.0 Clinical Applications

4.1 Monitoring Parameters

A) Therapeutic

1) Laboratory Parameters

a) In patients with epilepsy, therapeutic serum levels have not been ade established.
b) In women who plan on becoming pregnant, obtaining concentrations oxcarbazepine and mono-hydroxy-carbazepine (MHD) before becoming during the pregnancy may be beneficial. Although, therapeutic concentra not been established, prepregnancy concentrations in an optimally-treat provide a reference concentration for comparison to concentrations duri when concentrations decrease due to changes in the pharmacokinetic c of oxcarbazepine. Possible sampling times could be once monthly, with in patients with mild and stable epilepsy, and every 3 to 4 days for 2 wee delivery in patients who had their dosage adjusted during pregnancy (To Battino, 2007).

c) In patients with trigeminal neuralgia, therapeutic serum concentration metabolite of oxcarbazepine (10-hydroxy-carbazepine) have ranged fror micromoles/L (Zakrzewska & Patsalos, 1989a).

2) Physical Findings

a) In patients with epilepsy, seizure frequency and electroencephalogra

b) A reduction or elimination of pain is indicative of a therapeutic respor with trigeminal neuralgia.

B) Toxic

1) Laboratory Parameters

a) Serum sodium, during maintenance treatment, particularly if the patie receiving other medications known to decrease serum sodium levels or i hyponatremia (nausea, malaise, headache, lethargy, confusion, obtunda increase in seizure frequency or severity) (Prod Info TRILEPTAL(R) oral suspension, 2005)

b) Liver function tests

c) Blood counts

d) Serum lipid levels

e) Serum levels of concomitant antiepileptic drugs (AEDs) during oxcarb titration. Levels of AEDs may change, especially at oxcarbazepine doses than 1200 milligrams/day (Prod Info TRILEPTAL(R) oral tablets, oral sus 2005)

2) Physical Findings

a) Body weight

b) Temperature

c) Blood pressure

d) Data reviewed by the US Food and Drug Administration suggest an i of suicidal behavior or ideation may exist in patients receiving therapy w antiepileptic drugs (AEDs). The increased risk of suicidality was noted at starting an AED and continued to at least 24 weeks. Patients treated for psychiatric disorders, or other conditions were all at an increased risk for compared to placebo. Closely monitor patients treated with AEDs for em worsening of depression, suicidality, and other unusual changes in beha may include symptoms such as anxiety, agitation, hostility, mania, and h (US Food and Drug Administration, 2008).

4.2 Patient Instructions

A) Oxcarbazepine (By mouth)

Oxcarbazepine

Treats seizures caused by epilepsy in adults and children.

When This Medicine Should Not Be Used:
You should not use this medicine if you have had an allergic reaction to oxca

How to Use This Medicine:
Tablet, Liquid

Your doctor will tell you how much of this medicine to use and how often may need to be changed several times in order to find out what works be not use more medicine or use it more often than your doctor tells you to.
You may take this medicine with or without food.
Measure the oral liquid medicine with a marked measuring spoon, oral s medicine cup.
Shake the oral liquid well just before using. You can take the medicine d the oral syringe, or you can mix the medicine in a glass with a small amo
If you mix the medicine, drink the mixture right away. Do not save any m later.

If a Dose is Missed:

If you miss a dose or forget to use your medicine, use it as soon as you almost time for your next dose, wait until then to use the medicine and s dose. Do not use extra medicine to make up for a missed dose.

How to Store and Dispose of This Medicine:

Store the medicine in a closed container at room temperature, away fror moisture, and direct light.
Ask your pharmacist, doctor, or health caregiver about the best way to d outdated medicine or medicine no longer needed. Dispose of any leftove

medicine 7 weeks after you open the bottle.
Keep all medicine away from children and never share your medicine wi

Drugs and Foods to Avoid:
Ask your doctor or pharmacist before using any other medicine, including ov
medicines, vitamins, and herbal products.
Make sure your doctor knows if you are also using any other medicines
seizures. Seizure medicine includes carbamazepine (Tegretol®), phenol
phenytoin (Dilantin®), or valproic acid (Depakote®).
Tell your doctor if you also use felodipine (Plendil®) or verapamil (Calan
Do not drink alcohol while you are using this medicine.

Warnings While Using This Medicine:
Make sure your doctor knows if you are pregnant or breast feeding.
Tell your doctor if you have kidney disease, or if you have ever had an a
reaction to carbamazepine (Tegretol®).
Birth control pills may not work while you are using oxcarbazepine. To k
getting pregnant, use another form of birth control. Other forms include c
diaphragm, or contraceptive foam or jelly.
This medicine may make you dizzy or drowsy. Avoid driving, using mach
anything else that could be dangerous if you are not alert.
Do not stop using this medicine suddenly without asking your doctor. Yo
slowly decrease your dose before stopping it completely.

Possible Side Effects While Using This Medicine:
Call your doctor right away if you notice any of these side effects:
Allergic reaction: Itching or hives, swelling in your face or hands, swellin
your mouth or throat, chest tightness, trouble breathing.
Blistering, peeling, red skin rash.
Blurred vision or double vision.
Change in how much or how often you urinate.
Confusion, weakness, and muscle twitching.
Fast, slow, or pounding heartbeat.
Fever with rash, swollen glands in your neck.
Nausea, vomiting, loss of appetite, pain in your upper stomach.
Rapid eye movements (especially in children).
Seizures.
Trouble walking, speaking, or controlling body movement.
Uncontrollable shaking.
Unusual bleeding, bruising, or weakness.
Visual changes.

If you notice these less serious side effects, talk with your doctor:
Dizziness or drowsiness.
Headache.
Joint pain.
Mild nausea, vomiting, stomach pain, belching, or gas.
Stomach pain or indigestion

If you notice other side effects that you think are caused by this medicine, tel

4.3 Place In Therapy

A) Oxcarbazepine appears to be as effective as carbamazepine in the treatment and slightly better tolerated. It should be considered an alternative in epileptic pat to tolerate carbamazepine, including those with hypersensitivity, although caution these patients.

B) In the treatment of trigeminal neuralgia, oxcarbazepine has been effective in p unresponsive to, or intolerant of, carbamazepine, which is currently the drug of ch superiority of oxcarbazepine over carbamazepine has been suggested, but these employed small numbers of patients and were not adequately controlled.

C) Dose-dependent enzyme induction has been reported by some investigators, doses of oxcarbazepine producing effects similar to carbamazepine (Patsalos et the optimal dose of oxcarbazepine remains undefined, further studies will also be determine if the drug will offer a significant advantage in regard to enzyme induct autoinduction.

D) Hyponatremia is a concern with oxcarbazepine therapy, and may limit its use anticonvulsant and antineuralgic. The use of oxcarbazepine in diabetes insipidus

suggested, although data is not available for this indication (Pendlebury et al, 198

4.4 Mechanism of Action / Pharmacology

A) MECHANISM OF ACTION

1) Oxcarbazepine, an anticonvulsant, is the 10-keto derivative of carbamaze Chemically, oxcarbazepine is 10,11-dihydro-10-oxo-5H-dibenz(b,f)azepine 5 (Prod Info TRILEPTAL(R) oral tablets, oral suspension, 2005; Anon, 1989; A The metabolite 10-hydroxy-carbazepine is primarily responsible for the pharr activity of oxcarbazepine. However, the exact mechanism of action for its ant is unknown. In vitro electrophysiological studies suggest that drug-induced bl voltage-sensitive sodium channels may prevent repetitive neuronal firing and stabilization of hyperexcited neural membranes and the diminution of synapti propagation. Increased potassium conductance and high-voltage calcium cha modulation may also play a role (Prod Info TRILEPTAL(R) oral tablets, oral s 2005).

2) Animal studies have demonstrated that the mechanism of action of oxcarl similar to that of carbamazepine, which is inhibition of seizure propagation via posttetanic potentiation of synaptic transmission (Baltzer & Schmutz, 1978; A Anon, 1990). The spectrum of antiepileptic activity of each agent is also simil Schmutz, 1978; Anon, 1989). Antineuralgic properties of oxcarbazepine have demonstrated (Farago, 1987; Zakrzewska & Patsalos, 1989).

B) REVIEW ARTICLES

1) Dosages and formulations of antiepileptic drugs used to treat pediatric ep been reviewed (Bourgeois, 2002).

2) The pharmacology and therapeutic use of oxcarbazepine has been reviev 1999; Grant & Faulds, 1992; Bulau & Froscher, 1991; Perucca, 1993; Benete

3) A review of newer antiepileptic medications, including a summary of clinic and recommendations for use, has been published (Dichter & Brodie, 1996).

4) The pharmacokinetic interaction profile of oxcarbazepine and its importan has been reviewed (Baruzzi et al, 1993).

4.5 Therapeutic Uses

Antineoplastic adverse reaction - Peripheral neuropathy; Prophylaxis

Bipolar disorder

Panic disorder

Partial seizure, monotherapy

Partial seizure; Adjunct

Spasticity

Trigeminal neuralgia

4.5.A Antineoplastic adverse reaction - Peripheral neuropathy; Prophylaxis

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RA

2) Summary:

A randomized, open-label trial (n=40) found that oxcarbazepine may oxaliplatin-induced peripheral neuropathy symptoms (Argyriou et al,

3) Adult:

a) A randomized, open-label trial found that oxcarbazepine may preven induced peripheral neuropathy symptoms. Adult patients (age 61.8 years deviation (SD) +/- 9.1) with advanced colon cancer were randomly assig chemotherapy with the FOLFOX-4 regimen plus oxcarbazepine (150 mil (mg) /day initially, doubled weekly for 4 weeks to a maximum dose of 60

daily), or the FOLFOX-4 regimen alone. The oxcarbazepine titration peri
followed by a 20-week maintenance period. The primary endpoint meas
incidence of peripheral neuropathy. Investigators also evaluated differen
total neuropathy scores (TNS; 1-11 = mild, 12-23 = moderate, greater th
severe), neurologic disability scores (NDS) and neurologic symptom sco
The incidence of oxaliplatin-induced neuropathy among the patients who
the trial (n=32) was 5 of 16 patients receiving oxcarbazepine (31.2%) , w
incidence of oxaliplatin-induced neuropathy occurred in 12 of 16 of the c
(75%). This represents a relative risk of 0.42 (95% confidence interval (C
0.91, p=0.033). The intention-to-treat analysis (n=40) also demonstrated
significant results favoring oxaliplatin (p=0.05). The mean TNS scores w
in the patients treated with oxacarbazepine vs 11.2 +/- 9.05 in the patien
with oxcarbazepine (p=0.016). The mean NDS (5.1 +/- 8.2 vs 20 +/- 23.1
and the mean NSS (0.6 +/- 0.9 vs 1.5 +/- 1.3, p=0.025) were both lower
treated with oxcarbazepine. Adverse effects were mild to moderate in se
occurred at similar rates in both treatment groups; the most common effe
diarrhea, myelosuppression, dizziness, nausea, vomiting, and headache
Two patients in the oxcarbazepine group experienced acute headache a
during the titration period that caused them to withdraw from the study; t
symptoms improved shortly after oxcarbazepine discontinuation (Argyric

4.5.B Bipolar disorder

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RA

2) Summary:

Comparable results to other mood stabilizing agents (Ghaemi et al,
et al, 1983)
Limited data on usefulness as add-on therapy to lithium (Vieta et al,
Benedetti et al, 2004; Vieta et al, 2008)

3) Adult:

a) In a 52-week, multicenter, double-blind, randomized, placebo-control
prophylaxis trial (n=55), the addition of oxcarbazepine as adjunctive trea
maintenance lithium therapy of bipolar I and II disorder did not significan
onset of first relapse. Patients (aged 43.5 +/- 12 years, 65% female) with
of bipolar I or II disorder, who were not in an acute phase, but had at lea
episodes in the past year (with the last episode over 6 months prior to en
study) and receiving concomitant lithium (lithium levels greater than or e
milliequivalents/liter) during the past year were assigned to adjunctive ox
(n=26) treatment or placebo (n=29). Oxcarbazepine was started at 300 m
(mg) once a day for 3 days and titrated up by 300 mg increments every
administered twice a day, to a total daily dose of 1200 mg per day. After
week titration, the dose was maintained until the end of the study. Lithiu
administered open label throughout the study with levels monitored for a
months. Patients were required to stop all psychoactive, antipsychotic an
antidepressant medications 72 hours before the start of the study. Loraz
allowed as a concomitant medication up to 5 mg per day for insomnia or
primary efficacy variable was the length of the remission period (time to
manic or depressive episode). Based on an intent-to-treat analysis, the a
until first relapse of any type was not significantly different with the additi
oxcarbazepine compared with placebo (19.2 weeks vs 18.6 weeks; p=0.
of 38.5% and 58.6% patients in the oxcarbazepine and placebo arm, res
relapsed (p=0.1354). The number needed to treat (NNT) with oxcarbaze
any kind of relapse was 5 (odds ratio 0.44; 95% confidence interval, 0.1
study showed a statistically significant difference on the Barratt Impulsiv
Scale (BIS) (p=0.044) with a positive effect of oxcarbazepine in preventi
impulsivity. Overall, oxcarbazepine was well tolerated with no statistical
incidence of adverse events between the 2 groups. Larger trials are nee
evaluating oxcarbazepine in bipolar disorder (Vieta et al, 2008).

b) Adjunctive oxcarbazepine may be useful in the treatment of bipolar d
satisfactorily controlled by lithium. In an open-label study, patients with b
disorder taking lithium for at least 1 month (lithium levels ranging from 0.
milliequivalents/liter) were prescribed oxcarbazepine 300 milligrams/day
Doses of oxcarbazepine were increased to a maximum dose of 2400 mg

maintenance dose 919 mg/day). Patients had bipolar I (n=16) or bipolar
had a Clinical Global Impression Severity score of 4 to 6 at baseline. Oth
psychotropic agents were allowed but were not modified or changed dur
weeks of study. Sedation (66.7%), increased appetite (50%), weight gai
tremors (27.8%), constipation (16.7%), nausea/vomiting (16.7%), dry mo
and insomnia (11.1%) were reported with the use of oxcarbazepine. The
Clinical Global Impression-Bipolar Version Improvement (CGI-BP-I) scor
significantly from baseline at week 2, 4 and 8 (p less than 0.0001). Of th
61.1% were considered to be "responders" (CGI-BP-I score of 2 or 1 at
(Benedetti et al, 2004).

c) Authors of a retrospective chart review concluded that adjunctive or
oxcarbazepine was useful as a mood stabilizer in patients with bipolar di
Charts of patients treated with either adjunctive (n=31) or monotherapy
oxcarbazepine in a private practice clinic were reviewed. The mean oxca
dose was 1056.6 milligrams/day (mg/day) (range 150 to 2400 mg/day).
length ranged from 1 to 71 weeks (mean 16.2 weeks). Clinical response
assessed retrospectively using the Clinical Global Impressions-Improver
the patients receiving monotherapy oxcarbazepine, 36% experienced no
worsening of their symptoms, and 64% experienced mild to marked impr
patients receiving adjunctive oxcarbazepine, 39% experienced a worser
effect, and 61% experienced mild to marked improvement. Overall, 52%
discontinued treatment; 29% due to side effects and 24% due to lack of
Reported side effects included: sedation (40%), dizziness (7%), headacl
cognitive difficulty (5%), paresthesia, twitching, tactile impairment, diplop
nausea, weight gain and leg edema (2% each) (Ghaemi et al, 2003).

d) Comparable results to other mood stabilizing agents was found with
oxcarbazepine in 6 patients with acute mania (Emrich et al, 1983). Dose
2100 milligrams daily produced average decreases in the mania rating o
Multidimensional Psychiatric Scale of 50%.

4.5.C Panic disorder

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RA

2) Summary:

Effective in one case report (Windhaber et al, 1997)

3) Adult:

a) A 23-year-old man with alcohol-related seizures developed panic dis
was successfully treated with an increased dose of oxcarbazepine (Winc
1997). The patient was already receiving oxcarbazepine 600 milligrams
this was increased to 900 mg/day. The patient remained symptom-free o
month follow-up period.

4.5.D Partial seizure, monotherapy

FDA Labeled Indication

1) Overview

FDA Approval: Adult, yes; Pediatric, yes (4 years and older)
Efficacy: Adult, Effective; Pediatric, Effective
Recommendation: Adult, Class IIa; Pediatric, Class IIa
Strength of Evidence: Adult, Category B; Pediatric, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RA

2) Summary:

Indicated for use as monotherapy in the treatment of partial seizures
children 4 years and older (Prod Info TRILEPTAL(R) oral tablets, or
2005)

In an observational study (n=673; mean age 42.5 years) of adult ma
with partial epilepsy, oxcarbazepine improved sexual dysfunction in
preexisting sexual function disorders at baseline (Luef et al, 2009).

3) Adult:

a) Oxcarbazepine (OXC) was an effective monotherapeutic substitute w
to replace antiepileptic drugs (AED) used to maintain patients with medi
refractory partial epilepsy, in a randomized, double-blind, multicenter clir
compared two doses of oxcarbazepine (OXC 300 milligrams (mg)/day a
mg/day). Patients with a history of 2 to 40 seizures per 28-day period re

OXC 300 mg/day (n=46), or OXC 2400 mg/day (n=41) throughout a 126
treatment phase; all prior AED's were tapered and discontinued by day 4
receiving 2400 mg/day were titrated from an initial dose of 1200 mg up t
dose in 600 mg weekly increments; those patients unable to tolerate the
dose were adjusted to either 2100 mg or 1800 mg daily. Efficacy was me
the number of patients meeting one of 4 protocol-defined exit criteria (pr
variable) and the time required to meet one of the exit criteria (secondar
The number of patients meeting one of the 4 exit criteria was significantl
OXC 2400 mg cohort compared with the OXC 300 mg cohort (41.2% ve
less than 0.0001), while significantly greater time was required by the OX
group to meet an exit criterion compared with the OXC 300 mg group (p
intent-to-treat analysis revealed at least a 50% reduction in seizure incid
of OXC 2400 mg-treated patients (12% rendered seizure-free) compared
patients receiving OXC 300 mg (none seizure-free). Dizziness, headach
somnolence, nausea, and vomiting were the adverse events most freque
most were transient, and mild or moderate in severity (Beydoun et al, 20
b) Oxcarbazepine, 2400 milligrams/day (mg/day) in 2 divided doses, wa
monotherapy for the treatment of refractory partial seizures in 102 patien
62 years of age) in a placebo-controlled, double-blind trial. The primary e
variable was time to meet one of the exit criteria, defined as: completion
treatment phase; 4 partial seizures; 2 new-onset secondarily generalized
serial seizures; or status epilepticus. This variable was statistically signif
of oxcarbazepine (p=0.0001; by day 2.5 of the study period, 75% of the p
treated patients had met one of the exit criteria versus (vs) 25% of the pa
with oxcarbazepine. The secondary efficacy variable was the percentage
meet one of the exit criteria and was also statistically significantly lower (
0.0001) for the patients treated with oxcarbazepine (47%) vs 84% for the
treated group (Schachter et al, 1999).
c) Oxcarbazepine initiated at 600 milligrams/day, titrated to 1200 milligr
dosages in 2 daily divided doses), and maintained at the higher dose for
statistically significantly superior to placebo (p=0.046) in previously untre
(n=67; 8 to 69 years of age). The primary efficacy measure was a compa
to first seizure (Prod Info Trileptal(R), 2003a).
d) In 2 trials comparing oxcarbazepine in daily doses of 300 or 2400 mil
in patients previously treated with carbamazepine or other antiepileptic d
higher dose of oxcarbazepine was statistically significantly superior to th
(p=0.0001). Primary efficacy measures differed between the 2 studies; th
to meet exit criteria in 1 study and percentage of patients meeting exit cr
other (Prod Info Trileptal(R), 2003a).
e) Seizure frequency decreased in 32% to 48% of patients treated with
oxcarbazepine in a multicenter trial conducted over 10 years in 947 patie
al, 1993b). Patients were diagnosed with simple partial or complex partia
with or without secondary generalization and primary generalized seizur
daily doses employed were 30 milligrams/kilogram/day in children and 1
milligrams/kilogram/day in adults, usually given in 2 or 3 divided doses. (
patients experienced adverse reactions such as dizziness, sedation, fati
hyponatremia. Oxcarbazepine was used as monotherapy in 63% of the p
as part of polytherapy in 37%.
f) Similar decreases in seizure frequency were seen in a double-blind st
oxcarbazepine and carbamazepine in 16 epileptic patients inadequately
at least 1 anticonvulsant (other than carbamazepine) (Bulau et al, 1987b
patient had experienced at least 1 tonic-clonic or complex partial seizure
Oxcarbazepine or carbamazepine were added sequentially in randomize
during a 1-month titration period; therapy was continued for an additiona
Mean doses were 1111.5 and 788.5 milligrams daily for oxcarbazepine a
carbamazepine, respectively. Concomitant anticonvulsants were continu
the study. Seizure frequency was reduced by 90% during therapy with b
with 28% of all patients becoming seizure-free. Adverse effects were les
treated with oxcarbazepine. Increases in serum levels of valproic acid, p
primidone were observed in the oxcarbazepine group, presumably secon
lesser degree of enzyme induction as compared to carbamazepine.

1) Sexual Dysfunction Improvement in Male Patients with Epilepsy

a) In an observational study (n=673; mean age 42.5 years) of a
patients with partial epilepsy, oxcarbazepine improved sexual c
patients with preexisting sexual function disorders at baseline. I
received oxcarbazepine monotherapy either as initial treatment
changed from other antiepileptic drug (AED) pretreatment to ox

monotherapy; doses were titrated to the optimal therapeutic do
patients were assessed regarding their sexual dysfunction at ba
again 12 weeks later at the final examination. Seizure occurren
ratings of efficacy, and tolerability were also assessed. At base
dysfunction was reported in 228 (34%) patients, with 27 patient
antiepileptic pretreatment, 168 patients receiving enzyme-induc
pretreatment, and 33 patients receiving non-enzyme inducing A
pretreatment. Sexual dysfunction improvement was reported in
(n=181/228) of patients with preexisting sexual function disorde
months of treatment with oxcarbazepine, with no impairment re
10.1% (n=23/228) of patients at final assessment. The improve
most significant in patients receiving enzyme-inducing AED pre
Seizure occurrence per 28 days decreased during the retrospe
from a mean of 1.8 +/- 4.9 (95% CI, 1.43 to 2.17) to 0.4 +/- 1.8
to 0.54) after 3 months of therapy. Carbamazepine-treated pati
were excluded from results; however, in the patients who repor
dysfunction (n=147) with carbamazepine, 110 (75%) patients ir
switched to oxcarbazepine (Luef et al, 2009).

4) Pediatric:

a) An open-label study (n=92) failed to demonstrate the effectiveness o
oxcarbazepine monotherapy for children (1 month to 16 years of age) wi
inadequately-controlled or new-onset partial seizures; however, based o
pharmacokinetic and pharmacodynamic parameters, oxcarbazepine mo
was approved for children 4 years and older. Hospitalized children were
to either oxcarbazepine 10 milligrams/kilogram/day (mg/kg/day) or were
40 to 60 mg/kg/day within 3 days while withdrawing the previous antiepil
the second day of oxcarbazepine therapy. From day 3 to day 5, seizures
monitored by continuous video-electroencephalogram monitoring. The p
efficacy outcome was either completed the 5 day treatment or met one c
criteria. The exit criteria were: 1) 3 study specific seizures (ie, electrogra
seizures with a behavioral correlate) 2) a prolonged study specific seizu
children from both dose groups completed the 5-day study without exitin
between group comparison of the time to meet exit criteria was not statis
significant (p=0.904 for the difference between the curves). The manufa
the results were uninterpretable because of study limitations (no placebo
treatment and assessment period, and inadequate washout period) (Pro
TRILEPTAL(R) oral tablets, oral suspension, 2005).

b) Oxcarbazepine initiated at 600 milligrams/day, titrated to 1200 milligr
dosages in 2 daily divided doses), and maintained at the higher dose for
statistically significantly superior to placebo (p=0.046) in previously untre
(n=67; 8 to 69 years of age). The primary efficacy measure was a compa
to first seizure (Prod Info TRILEPTAL(R) oral tablets, oral suspension, 2

c) Oxcarbazepine, 2400 milligrams/day (mg/day) in 2 divided doses, wa
monotherapy for the treatment of refractory partial seizures in 102 patier
62 years of age) in a placebo-controlled, double-blind trial. The primary e
variable was time to meet one of the exit criteria, defined as: completion
treatment phase; 4 partial seizures; 2 new-onset secondarily generalized
serial seizures; or status epilepticus. This variable was statistically signif
of oxcarbazepine (p=0.0001; by day 2.5 of the study period, 75% of the
treated patients had met one of the exit criteria versus (vs) 25% of the pa
with oxcarbazepine. The secondary efficacy variable was the percentage
meet one of the exit criteria and was also statistically significantly lower
0.0001) for the patients treated with oxcarbazepine (47%) vs 84% for the
treated group (Schachter et al, 1999).

d) Oxcarbazepine was found to be useful in both adjunctive use and mo
children with seizures during a chart review (Gaily et al, 1997a). Children
3.9 years, range 0.6 to 6.9 years) had either localization-related seizures
generalized epilepsy (n=9) with the main seizure types being complex pa
simple partial (n=4), epileptic spasm (n=9), and generalized tonic-clonic
children, an overnight change was made from carbamazepine to oxcarb
times their previous carbamazepine dose. The other children were titrate
milligrams/kilogram/day (mg/kg/day) over 1 to 3 weeks. Out of the childr
localization-related seizures, 12 of 44 became seizure-free while 16 ach
reduction in seizures. No child with generalized seizures became seizure
9 had a 50% reduction in seizures. In children who had previously had a
response to carbamazepine, 4 of 30 children become seizure-free while
reduction in seizures of at least 50%. Of the 23 children receiving monot

became seizure-free, and 7 had a 50% reduction in seizures. The mean
for children achieving at least a 50% decrease in seizures was 47 mg/kg
Hyponatremia occurred in 7 of the 53 children.

4.5.E Partial seizure; Adjunct

FDA Labeled Indication

1) Overview

FDA Approval: Adult, yes; Pediatric, yes (2 years and older)
Efficacy: Adult, Effective; Pediatric, Effective
Recommendation: Adult, Class IIa; Pediatric, Class IIa
Strength of Evidence: Adult, Category B; Pediatric, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RA

2) Summary:

Indicated for use as adjunctive therapy in the treatment of partial se
adults and children 2 years and older (Prod Info TRILEPTAL(R) ora
suspension, 2005)
No evidence that oxcarbazepine was effective in children less than
(n=75) in an open-label, multicenter, rater-blind, randomized, paralle
(Prod Info TRILEPTAL(R) oral tablets, oral suspension, 2005)
During adjunctive therapy studies, median reductions in partial seizu
frequencies from baseline were 26% to 50% for oxcarbazepine and
placebo in adults, and 35% for oxcarbazepine and 9% for placebo i
(Prod Info TRILEPTAL(R) oral tablets, oral suspension, 2005)
No important differences in response due to gender were identified
adjunctive therapy trials (Prod Info TRILEPTAL(R) oral tablets, oral
2005)

3) Adult:

a) Efficacy for oxcarbazepine as adjunctive therapy for partial seizures i
demonstrated in a multicenter, double-blind, placebo-controlled trial (n=6
years of age). Patients who experienced 1 to 4 partial seizures per mont
baseline phase were randomized to receive placebo or fixed oxcarbazep
600, 1200, or 2400 milligrams/day (mg/day) in conjunction with 1 to 3 otl
antiepileptic drugs. A comparison between treatment groups of the perc
change in partial seizure frequency was the primary measure of efficacy
of oxcarbazepine were statistically significantly superior to placebo (p=0
high dose group, however, over 65% of patients discontinued treatment
adverse events (Prod Info TRILEPTAL(R) oral tablets, oral suspension,

b) Seizure frequency decreased in 32% to 48% of patients treated with
oxcarbazepine in a multicenter trial conducted over 10 years in 947 patie
al, 1993b). Patients were diagnosed with simple partial or complex partia
with or without secondary generalization and primary generalized seizur
daily doses employed were 30 milligrams/kilogram/day in children and 1
milligrams/kilogram/day in adults, usually given in 2 or 3 divided doses.
patients experienced adverse reactions such as dizziness, sedation, fati
hyponatremia. Oxcarbazepine was used as monotherapy in 63% of the
as part of polytherapy in 37%.

4) Pediatric:

a) Efficacy for oxcarbazepine as adjunctive therapy for inadequately-co
seizures in children was demonstrated in a multicenter, rater-blind, rand
parallel-group, open-label trial (n=128; 1 month to less than 4 years of a
criteria were at least 2 study specific seizures (ie, partial seizures identifi
electrograph with a behavioral correlate) during the 72 hour baseline pe
were randomized to either 10 milligrams/kilogram/day (mg/kg/day) or we
to 60 mg/kg/day within 26 days. After 9 days on their randomized target
seizures were monitored by continuous video-electroencephalogram mo
during the last 72 hours of the maintenance period. A between group co
the change in seizure frequency per 24 hours compared to the seizure f
baseline was statistically better (results and p value not provided) in the
group vs 10 mg/kg/day group. No evidence that oxcarbazepine was effe
children less than 2 years of age (n=75) (Prod Info TRILEPTAL(R) oral t
suspension, 2005).

b) Oxcarbazepine (OXC) was safe and effective when used as an adjur
antiepileptic agent in the treatment of partial seizures in children, in a ra
double-blind, parallel-group study. Pediatric patients (ages 3 to 17 years
inadequately controlled partial seizures treated with one or two antiepile
(AED) were assigned to receive 98-day regimens of either OXC (titrated
of 30 to 46 milligrams (mg)/kilogram (kg)/day) two times a day (n=138) o

(n=129) in addition to their pre-established AED regimen. Patients in the experienced a baseline median partial seizure frequency of 12 per 28-da median OXC dose administered was 31.4 mg/kg/day. The addition of OX preexisting AED regimen produced a significantly greater median percer from baseline in 28-day partial seizure frequency compared with placebo 9%, respectively; p=0.0001). Forty-one percent of patients OXC-group p recorded a seizure frequency reduction from baseline of 50% or more pe period compared with 22% of patients receiving placebo (p=0.0005), and group patients were seizure- free throughout the double-blind treatment compared with 1 patient receiving placebo. OXC-treated patients also ex significantly greater median percentage reduction in the occurrence of s generalized seizures compared with patients receiving placebo (78% ve respectively; p=0.0012). The frequency of adverse events was similar be groups; somnolence, headache, dizziness, nausea and vomiting were m reported, with the majority being considered mild to moderate in severity TRILEPTAL(R) oral tablets, oral suspension, 2005; Glauser et al, 2000).

c) Oxcarbazepine, in a mean dose of 56.7 milligrams/kilogram/day (mg/ found to be efficacious for adjunctive therapy in epilepsy in a retrospecti review of 46 children and adolescents (mean age 10.3 years; range 1.3 Oxcarbazepine doses ranged from 19 to 123 mg/kg twice a day, valproic most common co-medication (32 of 46 patients) and no patients were m more than one other drug besides oxcarbazepine. After follow-up for 1 y oxcarbazepine was found to be of some benefit in 50% of the patients. S children experienced an exacerbation of seizures and 17 children exhibi change, but 4 children became seizure-free, 18 experienced a 75% to 9 in seizures, and 1 had a 50% to 74% reduction in seizures; 4 patients we follow-up. Adverse effects tended to occur in patients with blood serum c of 35 to 40 mg/L 10-hydroxy-carbazepine, the active metabolite of oxcar (Borusiak et al, 1998).

d) In a small study (n=40) in children with intellectual disability and intra epilepsy, seizure frequency was reduced by at least 50% in 48% (19) of treated with oxcarbazepine 49 milligrams/kilogram/day (mg/kg/day) (mea dosage), given in 2 or 3 divided doses. Nine of the children received oxc monotherapy and 31 received it concomitantly with other antiepileptic dr including vigabatrin, benzodiazepines, valproate, lamotrigine, phenytoin, acetazolamide. Oxcarbazepine therapy was initiated using several strate Oxcarbazepine was initiated in 10 children as an overnight change from carbamazepine (at 1.5 times the carbamazepine dosage). In the remaini who weighed under 40 kg, the oxcarbazepine dose was titrated over 1 to 30/mg/kg/day and then increased as necessary. For the other children w 40 kg, oxcarbazepine was initiated at 20/mg/kg/day and titrated accordir response. A greater than 50% response was reported in 14 of 28 childre localization-related epilepsy and 5 of 12 children (42%) with generalized Oxcarbazepine dose reduction or discontinuation occurred in 8 children adverse effects and at least one adverse effect was reported in 40% of p Hyponatremia occurred in 24% (Gaily et al, 1998a).

e) Oxcarbazepine was found to be useful in both adjunctive use and mo children with seizures during a chart review (Gaily et al, 1997a). Children 3.9 years, range 0.6 to 6.9 years) had either localization-related seizures generalized epilepsy (n=9) with the main seizure types being complex pa simple partial (n=4), epileptic spasm (n=9), and generalized tonic-clonic children, an overnight change was made from carbamazepine to oxcarb times their previous carbamazepine dose. The other children were titrate milligrams/kilogram/day (mg/kg/day) over 1 to 3 weeks. Out of the childr localization-related seizures, 12 of 44 became seizure-free while 16 ach reduction in seizures. No child with generalized seizures became seizure 9 had a 50% reduction in seizures. In children who had previously had a response to carbamazepine, 4 of 30 children become seizure-free while reduction in seizures of at least 50%. Of the 30 children receiving polyth became seizure free and seizure reduction occurred in 14. The mean eff for children achieving at least a 50% decrease in seizures was 47 mg/kg Hyponatremia occurred in 7 of the 53 children.

4.5.F Spasticity

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive

Recommendation: Adult, Class III
Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RA

2) Summary:
Suggested efficacy in the treatment of spasticity related to cerebral lesions (Bittencourt & Silvado, 1985)

3) Adult:
a) Limited data have suggested the efficacy of oral oxcarbazepine in the spasticity related to cerebral epileptogenic lesions. Oxcarbazepine has b doses up to 3900 milligrams daily (Bittencourt & Silvado, 1985). Controll studies are needed to more fully evaluate the efficacy of the drug in spas

4.5.G Trigeminal neuralgia

1) Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category C
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RA

2) Summary:
Effective in the treatment of trigeminal neuralgia in patients unrespo intolerant of, carbamazepine (Zakrzewska & Patsalos, 1989b)

3) Adult:
a) Oxcarbazepine was effective in 6 patients with trigeminal neuralgia re carbamazepine therapy (Zakrzewska & Patsalos, 1989b). Oxcarbazepin administered in a dose of 300 milligrams 2 to 4 times daily, with prior me withdrawn over a 2-day period. The dose was adjusted weekly until adeq control was achieved, then patients were examined at 2 to 4 weekly inte were considered optimally managed after a pain free 2-week period; at t dose was reduced by 1 dose per week (300 milligrams). Re-titration was the event of relapse. Pain control was achieved in all patients, with onse effect being observed within 24 hours. Daily doses ranged from 600 to 2 milligrams. Both oxcarbazepine and 10-hydroxy-carbazepine serum leve with the dose and therapeutic effects. Effective pain relief was seen in al when serum levels of 10-hydroxy-carbazepine were between 50 and 11(micromoles/liter, corresponding to 1200 to 2400 milligrams daily of oxca

4.6 Comparative Efficacy / Evaluation With Other Therapies

Carbamazepine

Haloperidol

Lithium

Surgical procedure

4.6.A Carbamazepine

Epilepsy

Trigeminal neuralgia

4.6.A.1 Epilepsy

a) SUMMARY: Oxcarbazepine appears to be as effective as carbamaze treatment of epilepsy; severe adverse effects have occurred to a lesser oxcarbazepine in some studies. Further studies are needed to investigat inducing effects, particularly at higher doses.

b) Oxcarbazepine is similar in efficacy to carbamazepine as monothera therapy in epileptic patients (Dam et al, 1989; Reinikainen et al, 1987); (1987)(Houtkooper et al, 1987b; Houtkooper et al, 1984; Dam, 1990; Phil 1986; Anon, 1990a; Jensen, 1990). There is some evidence of efficacy i

unresponsive to carbamazepine. Doses associated with therapeutic equ
some studies have been 200 mg carbamazepine and 300 to 400 mg oxc
(Houtkooper et al, 1987b), however the ratio has been closer to 1:1 in ot
al, 1987).
c) Oxcarbazepine is at least as effective as carbamazepine in patients r
polytherapy, and oxcarbazepine may be better tolerated in some patient
efficacy of oxcarbazepine and carbamazepine was compared in 48 epile
poorly controlled on polytherapy, including carbamazepine, in a double-
crossover study (Houtkooper et al, 1987b). The types of seizures were g
patients), partial (10 patients), or both generalized and partial (29 patien
had at least 2 seizures/week despite therapy with 2 to 4 antiepileptic age
were randomly allocated to oxcarbazepine 300 mg/day or carbamazepir
mg/day. Following a titration period, where the dose of each was increas
optimal seizure control, therapy was continued for 12 weeks (steady- sta
trial period. As compared to carbamazepine, therapy with oxcarbazepine
total number of seizures by 9%; tonic-clonic and tonic seizures were furt
by 20% and 31%, respectively. In 5 patients, a shift from complex partial
partial seizures or atypical absence seizures was observed during oxcar
therapy. Other differences reported during oxcarbazepine therapy were
alertness and greater ability to concentrate in 5 patients and remission o
carbamazepine related allergic skin reactions in 2. Serum levels of valpr
phenytoin were higher in oxcarbazepine treated patients, and serum soc
concentration were lower. Other adverse effects were similar with each a
d) In a double-blind study, the efficacy of oxcarbazepine and carbamaz
epileptic patients inadequately controlled on at least 1 anticonvulsant (ot
carbamazepine) was evaluated (Bulau et al, 1987). Each patient had exp
least 1 tonic-clonic or complex partial seizure per month. Oxcarbazepine
carbamazepine were added sequentially in randomized fashion during a
titration period; therapy was continued for an additional 3 months. Mean
1111.5 and 788.5 mg daily for oxcarbazepine and carbamazepine, respe
Concomitant anticonvulsants were continued throughout. Seizure freque
reduced by 90% during therapy with both agents, with 28% of all patient
seizure-free. Adverse effects were less in oxcarbazepine treated patient
serum levels of valproic acid, phenytoin, and primidone were observed i
oxcarbazepine group, presumably secondary to a lesser degree of enzy
as compared to carbamazepine.

4.6.A.2 Trigeminal neuralgia

a) Oxcarbazepine and its 10-hydroxy-metabolite (10-hydroxy-carbazepi
dihydro-10-hydroxy carbamazepine) were compared with carbamazepin
patients with trigeminal neuralgia (Farago, 1987a). All patients had eithe
trigeminal neuralgia or other idiopathic facial neuralgias for at least 2 we
patients had been treated previously with carbamazepine. Oxcarbazepir
administered to 13 of the 24 patients for a mean of 11 months (mean ma
of 1100 milligrams daily), resulting in an adequate clinical response in 1(
moderate response in 3. Symptom recurrence, however, was seen in 1 p
months of treatment. Eleven patients were treated with the 10-hydroxy-n
oxcarbazepine (GP 47779) for a mean of 3.5 months (mean maximal do
milligrams daily), with 7 achieving alleviation of symptoms and 4 noticing
improvement. However, recurrence of symptoms occurred in 2 patients
and 2 months of treatment, respectively. In the 14 patients treated previc
carbamazepine, therapy with either oxcarbazepine or its metabolite was
be more effective than carbamazepine in 12; efficacy was considered ec
and worse in another. These overall results suggest the potential superi
oxcarbazepine over carbamazepine in trigeminal neuralgia. However, pl
controlled trials are required to confirm these findings.

4.6.A.3 Efficacy

a) The primary difference between oxcarbazepine and carbamazepine i
pharmacokinetic properties, which in turn affect the propensity of these a
adverse effects. Following absorption, oxcarbazepine is rapidly and exte
converted via reduction to 10-hydroxy-carbazepine, the active metabolite
excreted in the urine as the glucuronide conjugate. A portion of the 10-h
metabolite is hydroxylated to isomeric 10,11-diols, the trans-diol predom
(Theisohn & Heimann, 1982; Schutz et al, 1986; Anon, 1989a).
b) In contrast, carbamazepine is oxidized to the active carbamazepine-
epoxide; a portion of this metabolite is also converted to the inactive 10,
(Eichelbaum et al, 1985; Anon, 1989a; Anon, 1990a). The 10,11-epoxid

carbamazepine is responsible for dose-dependent adverse effects (Anon Anon, 1989a). Because an epoxide is not produced during oxcarbazepir metabolism, this drug is expected to be better tolerated than carbamaze 1990a).

4.6.A.4 Adverse Effects

a) A trend toward a lower incidence of severe adverse effects has been with oxcarbazepine as compared to carbamazepine in some studies (Bu 1987)(Dam, 1990; Houtkooper et al, 1987b), which at times reached sta significance (Dam, 1990).

b) Oxcarbazepine appears less likely than carbamazepine to influence processes, as the metabolism of oxcarbazepine is facilitated primarily by Studies have reported that oxcarbazepine lacks autoinducing properties carbamazepine, a feature which may decrease the incidence of breakthr (Anon, 1989a; Brodie et al, 1989; Anon, 1990a).

c) In some studies, oxcarbazepine has not influenced antipyrine kinetics an advantage with regard to drug interactions (Anon, 1989a). However, dependent enzyme induction has been reported by other investigators, v doses producing effects similar to carbamazepine (Patsalos et al, 1990c optimal dose of oxcarbazepine remains undefined, further studies will be determine if the drug will offer a significant advantage in regard to enzym and autoinduction.

4.6.B Haloperidol

4.6.B.1 Bipolar disorder

a) Oxcarbazepine has been compared with with haloperidol in 42 patien mania; mean doses used were 2400 mg/day and 42 mg/day respectively the response to oxcarbazepine was slower, by the end of the second we treatment, results were similar in both treatment groups. Haloperidol-trea had a significantly higher incidence of adverse effects (Emrich, 1990).

4.6.C Lithium

4.6.C.1 Bipolar disorder

a) In a review of the results of a double-blind multicenter trial comparing oxcarbazepine with lithium in 58 acutely manic patients, oxcarbazepine be equally effective but with a higher incidence of side effects. Onset wa slower with oxcarbazepine (Grant & Faulds, 1992a).

b) Conversely, a 3-year randomized study of oxcarbazepine vs lithium p 18 patients with bipolar disorder demonstrated no clear responders in th oxcarbazepine-treated group. A reduction in relapses was clearly seen i treated group. This study was flawed by poor patient selection and the tr lithium nonresponders with oxcarbazepine (Wildegrube, 1990).

4.6.D Surgical procedure

4.6.D.1 Trigeminal neuralgia

a) Oxcarbazepine was initially efficacious for relieving pain of intractable neuralgia, but eventually surgery was necessary in most patients. Fifteen had not found relief of trigeminal neuralgia pain or had experienced adve with carbamazepine, phenytoin, and baclofen, either as monotherapy or combination, were transferred from their current medication to oxcarbaz followed for 13 years. Over a period of 3 days, oxcarbazepine 300 millig was substituted for each 200 mg dose of carbamazepine or 100 mg dos phenytoin. Patients were free to discontinue medication during remissior patients used oxcarbazepine continuously, and 7 stopped during remiss periods of 2 to 7 months and, in one case, for 26 months. The mean dail 17.9 mg/kilogram (range 3.9 to 46.5 mg/kg). The mean duration of treatr years (range 2.4 months to 10.8 years). Oxcarbazepine gave pain relief, surgery was considered necessary in 12 of the 13 surviving patients. Su immediately successful in 8 of those patients but had to be repeated in 3 because of pain recurrence or complete failure. Repeat surgery was suc 2 with pain recurrence, but the one whose initial surgery completely faile medication for pain relief after the second surgery. Three of the patients underwent surgery had numbness and one had deafness as a conseque mean time for recurrence of pain after oxcarbazepine treatment was 10 (median 7 months); the mean time for recurrence after surgery was 28 n

time of this report, 8 patients continued to be pain free. Most patients fel
have had surgery earlier (Zakrzewska & Patsalos, 2002).

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Last Modified: July 20, 2009

DRUGDEX® Evaluations

LISDEXAMFETAMINE

0.0 Overview

1) Class
- **a)** This drug is a member of the following class(es):
  Amphetamine (class)
  CNS Stimulant

2) Dosing Information
- **a)** Lisdexamfetamine Dimesylate
  - **1)** Adult
    - **a)** safety and efficacy have not been evaluated in the geriatric population (Prod Info VYVANSE(R) oral capsu
      - **1)** Attention deficit hyperactivity disorder
        - **a)** initial (lisdexamfetamine naive or switching from another medication): 30 mg ORALLY once daily capsules, 2008)
        - **b)** maintenance: may increase dose in increments of 10 mg or 20 mg ORALLY per day at approxim ORALLY per day (Prod Info VYVANSE(R) oral capsules, 2008)
  - **2)** Pediatric
    - **a)** long-term use of amphetamines has not been established in pediatric patients; effectiveness of lisdexamfe weeks duration (Prod Info VYVANSE(R) oral capsules, 2008)
    - **b)** lisdexamfetamine dimesylate has not been studied in children under the age of 6 years or adolescents; ar children under 3 years of age (Prod Info VYVANSE(R) oral capsules, 2008).
      - **1)** Attention deficit hyperactivity disorder
        - **a)** initial (lisdexamfetamine naive or switching from another medication): 30 mg ORALLY once daily capsules, 2008)
        - **b)** maintenance: may increase dose in increments of 10 mg or 20 mg ORALLY per day at approxim ORALLY per day (Prod Info VYVANSE(R) oral capsules, 2008)

3) Contraindications
- **a)** Lisdexamfetamine Dimesylate
  - **1)** cardiovascular disease, symptomatic (Prod Info VYVANSE(TM) oral capsules, 2007)
  - **2)** drug dependence, history of; potential for abuse (Prod Info VYVANSE(TM) oral capsules, 2007)
  - **3)** advanced arteriosclerosis (Prod Info VYVANSE(TM) oral capsules, 2007)
  - **4)** agitated states; may aggravate symptoms (Prod Info VYVANSE(TM) oral capsules, 2007)
  - **5)** concomitant use of monoamine oxidase inhibitors (MAOI), or within 14 days of MAOI use; hypertensive crisis r capsules, 2007)
  - **6)** glaucoma (Prod Info VYVANSE(TM) oral capsules, 2007)
  - **7)** hypersensitivity/idiosyncrasy to sympathomimetic amines (Prod Info VYVANSE(TM) oral capsules, 2007)
  - **8)** hypertension, moderate to severe (Prod Info VYVANSE(TM) oral capsules, 2007)
  - **9)** hyperthyroidism (Prod Info VYVANSE(TM) oral capsules, 2007)

4) Serious Adverse Effects
- **a)** Lisdexamfetamine Dimesylate
  - **1)** Cerebrovascular accident
  - **2)** Chest pain
  - **3)** Dead - sudden death
  - **4)** Gilles de la Tourette's syndrome
  - **5)** Myocardial infarction
  - **6)** Palpitations
  - **7)** Seizure
  - **8)** Stevens-Johnson syndrome
  - **9)** Tachycardia
  - **10)** Toxic epidermal necrolysis due to drug
  - **11)** Ventricular hypertrophy

5) Clinical Applications
- **a)** Lisdexamfetamine Dimesylate
  - **1)** FDA Approved Indications
    - **a)** Attention deficit hyperactivity disorder

1.0 Dosing Information

Drug Properties

Storage and Stability

Adult Dosage

Pediatric Dosage

1.1 Drug Properties

A) Information on specific products and dosage forms can be obtained by referring to the Tradename List (Product In

B) Synonyms

Lisdexamfetamine

Lisdexamfetamine Dimesylate

C) Physicochemical Properties

1) Lisdexamfetamine Dimesylate

a) Molecular Weight

1) 455.6 (Prod Info VYVANSE(TM) oral capsules, 2007)

b) Solubility

1) Lisdexamfetamine is soluble in water at 792 mg/mL (Prod Info VYVANSE(TM) oral capsules, 2007)

1.2 Storage and Stability

A) Lisdexamfetamine Dimesylate

1) Preparation

a) Oral route

1) Lisdexamfetamine dimesylate should be administered once daily in the morning. The dose may be ta swallowed whole, or the capsule may be opened and the entire contents dissolved in a glass of water to (Prod Info VYVANSE(R) oral capsules, 2008).

B) Lisdexamfetamine Dimesylate

1) Oral route

a) Capsule

1) Store at controlled room temperature, 25 degrees Celsius (77 degrees Fahrenheit); excursions permi 86 degrees Fahrenheit) (Prod Info VYVANSE(TM) oral capsules, 2007).

1.3 Adult Dosage

1.3.1 Normal Dosage

1.3.1.A Lisdexamfetamine Dimesylate

1.3.1.A.1 Oral route

1.3.1.A.1.a Attention deficit hyperactivity disorder

1) The recommended initial dose in lisdexamfetamine-naive patients or in patients switching from a once daily in the morning. According to therapeutic need and patient response, the initial dose may orally per day at approximately weekly intervals to a maximum of 70 mg orally per day. The lowest e should be periodically interrupted to determine the need for continued treatment (Prod Info VYVANS

2) Lisdexamfetamine dimesylate has not been studied in the geriatric population (Prod Info VYVANSE(R) ora

1.4 Pediatric Dosage

1.4.1 Normal Dosage

1.4.1.A Lisdexamfetamine Dimesylate

1.4.1.A.1 Oral route

1.4.1.A.1.a Attention deficit hyperactivity disorder

1) The recommended initial dose in lisdexamfetamine-naive patients or in patients switching from a once daily in the morning. According to therapeutic need and patient response, the initial dose may orally per day at approximately weekly intervals to a maximum of 70 mg orally per day. The lowest e should be periodically interrupted to determine the need for continued treatment (Prod Info VYVANS

2) The long-term effects of amphetamine use in the pediatric population have not been established. In clinica dimesylate was established for up to 4 weeks duration. Lisdexamfetamine dimesylate has not been studied ir adolescents. Amphetamines are not recommended for use in children under 3 years of age (Prod Info VYVAl

2.0 Pharmacokinetics

Drug Concentration Levels

ADME

2.2 Drug Concentration Levels

A) Lisdexamfetamine Dimesylate

1) Peak Concentration

a) When the dose of lisdexamfetamine dimesylate was normalized based on weight, the Cmax was 12% low
70 milligrams/day (mg/day) for 7 days. The weight/dose normalized Cmax were the same for girls and boys f
VYVANSE(TM) oral capsules, 2007).

2) Time to Peak Concentration

a) Oral, dextroamphetamine: 3.5 hours (Prod Info VYVANSE(TM) oral capsules, 2007)

b) Oral, lisdexamfetamine dimesylate: 1 hour (Prod Info VYVANSE(TM) oral capsules, 2007)

1) The Tmax of dextroamphetamine after a single oral 30, 50, or 70 milligram dose of lisdexamfetamine
(n=18; aged 6 to 12 years) after an 8-hour fast was approximately 3.5 hours. The Tmax of lisdexamfetan
Info VYVANSE(TM) oral capsules, 2007).

3) Area Under the Curve

a) After lisdexamfetamine dimesylate was administered as a solution and as capsules after an 8-hour fast, th
(Prod Info VYVANSE(TM) oral capsules, 2007).

b) When the dose of lisdexamfetamine dimesylate was normalized based on weight, the AUC was 22% lowe
70 milligrams/day (mg/day) for 7 days. The weight/dose normalized AUC were the same for girls and boys fo
VYVANSE(TM) oral capsules, 2007).

2.3 ADME

Absorption

Metabolism

Excretion

Elimination Half-life

2.3.1 Absorption

A) Lisdexamfetamine Dimesylate

1) Effects of Food

a) Increases Tmax by approximately 1 hr (Prod Info VYVANSE(TM) oral capsules, 2007).

b) Food has no effect on AUC or Cmax but does prolong the Tmax of dextroamphetamine by approxima
dose of lisdexamfetamine dimesylate was given to healthy adults after a high fat meal, the Tmax was 4.7
fasted state (Prod Info VYVANSE(TM) oral capsules, 2007).

2) Following oral administration, lisdexamfetamine dimesylate is rapidly absorbed from the gastrointestinal tr
2007).

2.3.3 Metabolism

A) Metabolism Sites and Kinetics

1) Lisdexamfetamine Dimesylate

a) Liver and/or intestinal metabolism (Prod Info VYVANSE(TM) oral capsules, 2007).

1) After oral administration, lisdexamfetamine dimesylate is converted to dextroamphetamine and L
intestinal and/or hepatic metabolism. Lisdexamfetamine dimesylate is not metabolized by CYP450 e
capsules, 2007).

B) Metabolites

1) Lisdexamfetamine Dimesylate

a) Dextroamphetamine, (active) (Prod Info VYVANSE(TM) oral capsules, 2007).

1) After oral administration, lisdexamfetamine dimesylate is converted to dextroamphetamine and L
intestinal and/or hepatic metabolism (Prod Info VYVANSE(TM) oral capsules, 2007).

b) L-lysine, (inactive) (Prod Info VYVANSE(TM) oral capsules, 2007)

1) After oral administration, lisdexamfetamine dimesylate is converted to dextroamphetamine and L
intestinal and/or hepatic metabolism (Prod Info VYVANSE(TM) oral capsules, 2007).

2.3.4 Excretion

A) Kidney

1) Lisdexamfetamine Dimesylate

a) Renal Excretion (%)

1) 96% (Prod Info VYVANSE(TM) oral capsules, 2007).

a) Following administration of a single 70 milligram dose of lisdexamfetamine dimesylate to 6 h

dose was recovered in the urine; 42% of which was amphetamine, 25% hippuric acid, and 2% i
(TM) oral capsules, 2007).

B) Feces
1) Lisdexamfetamine Dimesylate
a) 0.3% (Prod Info VYVANSE(TM) oral capsules, 2007).
1) Following administration of a single 70 milligram dose of lisdexamfetamine dimesylate to 6 healt
was recovered in the feces (Prod Info VYVANSE(TM) oral capsules, 2007).

2.3.5 Elimination Half-life

A) Parent Compound
1) Lisdexamfetamine Dimesylate
a) less than 1 hour (Prod Info VYVANSE(TM) oral capsules, 2007)
1) The elimination half-life of lisdexamfetamine dimesylate averaged less than one hour in studies i
VYVANSE(TM) oral capsules, 2007).

3.0 Cautions

Contraindications

Precautions

Adverse Reactions

Teratogenicity/Effects in Pregnancy/Breastfeeding

Drug Interactions

3.0.A Black Box WARNING
1) Lisdexamfetamine Dimesylate
a) Oral (Capsule)
1) Amphetamines have a high potential for abuse. Administration of amphetamines for prolonged periods of
attention should be paid to the possibility of subjects obtaining amphetamines for non-therapeutic use or distr
prescribed or dispensed sparingly.
2) Misuse of amphetamines may cause sudden death and serious cardiovascular adverse events (Prod Info

3.1 Contraindications

A) Lisdexamfetamine Dimesylate
1) cardiovascular disease, symptomatic (Prod Info VYVANSE(TM) oral capsules, 2007)
2) drug dependence, history of; potential for abuse (Prod Info VYVANSE(TM) oral capsules, 2007)
3) advanced arteriosclerosis (Prod Info VYVANSE(TM) oral capsules, 2007)
4) agitated states; may aggravate symptoms (Prod Info VYVANSE(TM) oral capsules, 2007)
5) concomitant use of monoamine oxidase inhibitors (MAOI), or within 14 days of MAOI use; hypertensive crisis r
capsules, 2007)
6) glaucoma (Prod Info VYVANSE(TM) oral capsules, 2007)
7) hypersensitivity/idiosyncrasy to sympathomimetic amines (Prod Info VYVANSE(TM) oral capsules, 2007)
8) hypertension, moderate to severe (Prod Info VYVANSE(TM) oral capsules, 2007)
9) hyperthyroidism (Prod Info VYVANSE(TM) oral capsules, 2007)

3.2 Precautions

A) Lisdexamfetamine Dimesylate
1) long duration of use; may lead to dependence (Prod Info VYVANSE(TM) oral capsules, 2007)
2) amphetamine misuse; may cause sudden death and serious cardiovascular events (Prod Info VYVANSE(TM)
3) bipolar disorder, comorbid; may precipitate a mixed/manic episode (Prod Info VYVANSE(TM) oral capsules, 2
4) cardiovascular conditions which may be compromised by increases in blood pressure or heart rate (eg, preexis
myocardial infarction, or ventricular arrhythmia) (Prod Info VYVANSE(TM) oral capsules, 2007)
5) EEG abnormalities, especially with history of; may lower convulsive threshold (Prod Info VYVANSE(TM) oral c
6) psychosis, preexisting; may exacerbate symptoms of behavior disturbance and thought disorder (Prod Info VY
7) seizures, especially with a history of; may lower convulsive threshold (Prod Info VYVANSE(TM) oral capsules,
8) structural cardiac abnormalities/conditions, serious, especially in children and adolescents; sudden death has
(Prod Info VYVANSE(TM) oral capsules, 2007)
9) tics, motor and phonic, history of; risk of exacerbation (Prod Info VYVANSE(TM) oral capsules, 2007)
10) Tourette's syndrome, history of; risk of exacerbation (Prod Info VYVANSE(TM) oral capsules, 2007)

3.3 Adverse Reactions

3.3.1 Cardiovascular Effects

3.3.1.A Lisdexamfetamine Dimesylate

3.3.1.A.1 Chest pain

a) In a retrospective review of poison center databases in 8 states during the initial 10 months of produc
28) of patients between 4 and 44 years of age (median, 8 years) experiencing adverse events with lisde
reliably determined as concomitant drugs or conditions were not evaluated (Spiller et al, 2008).

3.3.1.A.2 Dead - sudden death

a) Incidence: rare

b) Children and Adolescents - With Preexisting Cardiac Risk

1) Following administration of CNS stimulant drugs at usual doses, sudden death has been reporte
cardiac abnormalities or other serious heart problems and adults being treated for ADHD . Sudden d
administration of amphetamines (Prod Info VYVANSE(TM) oral capsules, 2007).

c) Children and Adolescents - Healthy

1) A retrospective, case-controlled study examines the association between stimulant medication, i

unexplained sudden death in healthy children and adolescents. In a collection of data from state vita States, 564 cases of sudden death in children and adolescents between the ages of 7 to 19 years w who died as passengers in motor vehicle accidents. The study determined that 1.8% (n=10) of youth were taking stimulant medication compared with only 0.4% (n=2) of youths in the motor vehicle acci 74.9; p=0.02). Limitations to this study included the time lag between the youths stimulant medicatio recall of information regarding clinical diagnoses, inconsistent postmortem inquiry, and the exclusion authors stated that this finding should be considered when evaluating the overall risk and benefit of adolescents (Gould et al, 2009). Given the limitations of this study, the U.S. Food and Drug Adminis and benefits associated with stimulant medications (US Food and Drug Administration, 2009).

3.3.1.A.3 Increased blood pressure

a) Incidence: adult patients, 3% (Prod Info VYVANSE(R) oral capsules, 2008)

b) Blood pressure increases were reported in 3% of adult patients who received lisdexamfetamine in fin compared with 0% of patients who received placebo (n=62) in a 4-week, double-blind, randomized, place patients diagnosed with ADHD (Prod Info VYVANSE(R) oral capsules, 2008).

c) Elevation of blood pressure has been reported following administration of amphetamines. Modest inc mmHg), and average heart rate (about 3 to 6 bpm) are associated with stimulant medications, but larger (R) oral capsules, 2008).

3.3.1.A.4 Increased heart rate

a) Incidence: adult patients, 2% (Prod Info VYVANSE(R) oral capsules, 2008)

b) Heart rate increases were reported in 2% of adult patients who received lisdexamfetamine in final dos compared with 0% of patients who received placebo (n=62) in a 4-week, double-blind, randomized, place patients diagnosed with ADHD (Prod Info VYVANSE(R) oral capsules, 2008).

3.3.1.A.5 Myocardial infarction

a) Myocardial infarction (MI) has been reported in adults being treated with CNS stimulant drugs at usua following administration of amphetamines (Prod Info VYVANSE(TM) oral capsules, 2007).

3.3.1.A.6 Palpitations

a) Palpitations have been reported following administration of amphetamines (Prod Info VYVANSE(R) o

3.3.1.A.7 Summary

a) Serious cardiovascular events, including sudden cardiac death, myocardial infarction, and stroke hav including lisdexamfetamine. It is recommended that stimulant drugs not be used in patients who have kn serious heart rhythm irregularities, coronary artery disease, or other serious heart problems. Blood press regular intervals in patients receiving lisdexamfetamine (Prod Info VYVANSE(TM) oral capsules, 2007).

3.3.1.A.8 Tachycardia

a) Tachycardia led to discontinuation of therapy in 1% (3/358) of adult patients receiving lisdexamfetami rate compared with those receiving placebo (Prod Info VYVANSE(R) oral capsules, 2008).

b) Tachycardia has been reported following administration of amphetamines or lisdexamfetamine dimes 2008).

c) In a retrospective review of poison center databases in 8 states during the initial 10 months of produc of 28) of patients between 4 and 44 years of age (median, 8 years) experiencing adverse events with lisd reliably determined as concomitant drugs or conditions were not evaluated (Spiller et al, 2008).

3.3.1.A.9 Ventricular hypertrophy

a) Ventricular hypertrophy led to discontinuation of therapy in 1% (2/218) of pediatric patients receiving l discontinuation rate compared with those receiving placebo (Prod Info VYVANSE(R) oral capsules, 2008

3.3.2 Dermatologic Effects

3.3.2.A Lisdexamfetamine Dimesylate

Rash

Stevens-Johnson syndrome

Toxic epidermal necrolysis due to drug

Urticaria

3.3.2.A.1 Rash

a) Incidence: pediatric patients, 3% (Prod Info VYVANSE(R) oral capsules, 2008)
b) During a 4-week, double-blind, randomized, placebo-controlled, parallel-group clinical trial of pediatric (n=290), rash was reported in 3% of pediatric patients receiving lisdexamfetamine (n=218) compared wit the most frequent adverse events leading to discontinuation of therapy was rash with an incidence of 1% which was at least twice the rate compared with placebo (Prod Info VYVANSE(R) oral capsules, 2008).

3.3.2.A.2 Stevens-Johnson syndrome
a) Stevens-Johnson syndrome has been reported following administration of amphetamines (Prod Info V

3.3.2.A.3 Toxic epidermal necrolysis due to drug
a) Toxic epidermal necrolysis has been reported following administration of amphetamines (Prod Info V

3.3.2.A.4 Urticaria
a) Urticaria has been reported following administration of amphetamines (Prod Info VYVANSE(R) oral c

3.3.3 Endocrine/Metabolic Effects

3.3.3.A Lisdexamfetamine Dimesylate

Decreased body growth

Diaphoresis

Problem of growth and development

Sexual dysfunction

Weight decreased

3.3.3.A.1 Decreased body growth
a) Suppression of growth has been reported with long-term use of stimulants in children and adolescent
b) It is recommended that pediatric patients being treated with lisdexamfetamine be monitored for growt (R) oral capsules, 2008).

3.3.3.A.2 Diaphoresis
a) Incidence: adult patients, 3% (Prod Info VYVANSE(R) oral capsules, 2008)
b) Hyperhidrosis was reported in 3% of adult patients who received lisdexamfetamine in final doses of 3 0% of patients who received placebo (n=62) in a 4-week, double-blind, randomized, placebo-controlled, diagnosed with ADHD (Prod Info VYVANSE(R) oral capsules, 2008).

3.3.3.A.3 Problem of growth and development
a) In patients receiving lisdexamfetamine 7 days per week for 1 year, there was a decrease in growth ra from baseline in percentile of -13.4 over 1 year. The average percentile at baseline was 60.6, and at 1 ye (R) oral capsules, 2008).
b) It is recommended that pediatric patients being treated with lisdexamfetamine be monitored for growt (R) oral capsules, 2008).

3.3.3.A.4 Sexual dysfunction
a) Changes in libido have been reported following administration of amphetamines (Prod Info VYVANSE

3.3.3.A.5 Weight decreased
a) Incidence: pediatric patients, 9% (Prod Info VYVANSE(R) oral capsules, 2008)
b) During a 4-week, double-blind, randomized, placebo-controlled, parallel-group clinical trial of pediatric (n=290), a decrease in weight was reported in 9% of pediatric patients receiving lisdexamfetamine (n=21 (n=72) (Prod Info VYVANSE(R) oral capsules, 2008).
c) In a controlled trial in pediatric patients age 6 to 12 years, the mean weight loss from baseline after 4 pounds for patients receiving 30, 50, and 70 mg of lisdexamfetamine, respectively, compared with a 1 pc Higher doses of lisdexamfetamine were associated with greater weight loss during the 4 weeks of therap per week for 1 year, there was a decrease in growth rate (measured by body weight) from mean change The average percentile at baseline was 60.6, and at 1 year was 47.2 (Prod Info VYVANSE(R) oral capsu
d) In a 4-week, double-blind, randomized, placebo-controlled, parallel group trial of 420 adult patients di baseline after 4 weeks of therapy was 2.8, 3.1, and 4.3 pounds in adult patients who received lisdexamfe (n=358), respectively, compared with a mean weight gain of 0.5 pound in patients who received placebo 2008).

3.3.4 Gastrointestinal Effects

3.3.4.A Lisdexamfetamine Dimesylate

Constipation

Diarrhea

Loss of appetite

Nausea

Taste sense altered

Upper abdominal pain

Vomiting

Xerostomia

3.3.4.A.1 Constipation

a) Constipation has been reported following administration of amphetamines (Prod Info VYVANSE(R) o

3.3.4.A.2 Diarrhea

a) Incidence: adult patients, 7% (Prod Info VYVANSE(R) oral capsules, 2008)

b) Diarrhea was reported in 7% of adult patients who received lisdexamfetamine in final doses of 30 mg patients who received placebo (n=62) in a 4-week, double-blind, randomized, placebo-controlled, paralle ADHD (Prod Info VYVANSE(R) oral capsules, 2008).

3.3.4.A.3 Loss of appetite

a) Incidence: pediatric patients, 39%; adult patients, 27% (Prod Info VYVANSE(R) oral capsules, 2008)

b) During a 4-week, double-blind, randomized, placebo-controlled, parallel-group clinical trial of pediatric (n=290), a decreased appetite was reported in 39% of pediatric patients receiving lisdexamfetamine (n=2 placebo (n=72) (Prod Info VYVANSE(R) oral capsules, 2008).

c) Decreased appetite was reported in 27% of adult patients who received lisdexamfetamine in final dos compared with 3% of patients who received placebo (n=62) in a 4-week, double-blind, randomized, place patients diagnosed with ADHD. In the same study, anorexia was reported in 5% of patients receiving lisc receiving placebo (Prod Info VYVANSE(R) oral capsules, 2008).

3.3.4.A.4 Nausea

a) Incidence: pediatric patients, 6%; adult patients, 7% (Prod Info VYVANSE(R) oral capsules, 2008)

b) During a 4-week, double-blind, randomized, placebo-controlled, parallel-group clinical trial of pediatric (n=290), nausea was reported in 6% of pediatric patients receiving lisdexamfetamine (n=218) compared Info VYVANSE(R) oral capsules, 2008).

c) Nausea was reported in 7% of adult patients who received lisdexamfetamine in final doses of 30 mg, patients who received placebo (n=62) in a 4-week, double-blind, randomized, placebo-controlled, paralle ADHD (Prod Info VYVANSE(R) oral capsules, 2008).

3.3.4.A.5 Taste sense altered

a) Unpleasant taste has been reported following administration of amphetamines (Prod Info VYVANSE(

3.3.4.A.6 Upper abdominal pain

a) Incidence: pediatric patients, 12%; adults, 5% or greater (Prod Info VYVANSE(R) oral capsules, 2008

b) During a 4-week, double-blind, randomized, placebo-controlled, parallel-group clinical trial of pediatric (n=290), upper abdominal pain was reported in 12% of pediatric patients receiving lisdexamfetamine (n= placebo (n=72). Abdominal pain was also reported in at least 5% or more adults patients receiving lisdex VYVANSE(R) oral capsules, 2008).

c) Further, in a retrospective review of poison center databases in 8 states during the initial 10 months c in 7% (2 of 28) of patients between 4 and 44 years of age (median, 8 years) experiencing adverse event not be reliably determined as concomitant drugs or conditions were not evaluated (Spiller et al, 2008).

3.3.4.A.7 Vomiting

a) Incidence: pediatric patients, 9% (Prod Info VYVANSE(R) oral capsules, 2008)
b) During a 4-week, double-blind, randomized, placebo-controlled, parallel-group clinical trial of pediatric (n=290), vomiting was reported in 9% of pediatric patients receiving lisdexamfetamine (n=218) compared Vomiting led to discontinuation of therapy in 1% (2/218) of pediatric patients receiving lisdexamfetamine, rate compared with those receiving placebo (Prod Info VYVANSE(R) oral capsules, 2008).
c) In a retrospective review of poison center databases in 8 states during the initial 10 months of produc of patients between 4 and 44 years of age (median, 8 years) experiencing adverse events with lisdexam determined as concomitant drugs or conditions were not evaluated (Spiller et al, 2008).

3.3.4.A.8 Xerostomia

a) Incidence: pediatric patients, 5%; adult patients, 26% (Prod Info VYVANSE(R) oral capsules, 2008)
b) During a 4-week, double-blind, randomized, placebo-controlled, parallel-group clinical trial of pediatric (n=290), dry mouth was reported in 5% of pediatric patients receiving lisdexamfetamine (n=218) compar (Prod Info VYVANSE(R) oral capsules, 2008).
c) Dry mouth was reported in 26% of adult patients who received lisdexamfetamine in final doses of 30 of patients who received placebo (n=62) in a 4-week, double-blind, randomized, placebo-controlled, para with ADHD (Prod Info VYVANSE(R) oral capsules, 2008).

3.3.8 Musculoskeletal Effects

3.3.8.A Lisdexamfetamine Dimesylate

3.3.8.A.1 Muscle fasciculation

a) In a retrospective review of poison center databases in 8 states during the initial 10 months of produc 28) of patients between 4 and 44 years of age (median, 8 years) experiencing adverse events with lisdex reliably determined as concomitant drugs or conditions were not evaluated (Spiller et al, 2008).

3.3.9 Neurologic Effects

3.3.9.A Lisdexamfetamine Dimesylate

Cerebrovascular accident

Confusion, acute

Dizziness

Dystonia

Gilles de la Tourette's syndrome

Headache

Insomnia

Seizure

Somnolence

Tic

Tremor

3.3.9.A.1 Cerebrovascular accident

a) Stroke has been reported in adults being treated with CNS stimulant drugs at usual doses for ADHD. administration of amphetamines (Prod Info VYVANSE(TM) oral capsules, 2007).

3.3.9.A.2 Confusion, acute

a) In a retrospective review of poison center databases in 8 states during the initial 10 months of produc of patients between 4 and 44 years of age (median, 8 years) experiencing adverse events with lisdexam determined as concomitant drugs or conditions were not evaluated (Spiller et al, 2008).

3.3.9.A.3 Dizziness

a) Incidence: pediatric patients, 5% (Prod Info VYVANSE(TM) oral capsules, 2007)

b) During a 4-week, double-blind, randomized, placebo-controlled, parallel-group clinical trial of pediatric (n=290), dizziness was reported in 5% of pediatric patients receiving lisdexamfetamine (n=218) compare (Prod Info VYVANSE(TM) oral capsules, 2007).

c) Further, in a retrospective review of poison center databases in 8 states during the initial 10 months c (2 of 28) of patients between 4 and 44 years of age (median, 8 years) experiencing adverse events with be reliably determined as concomitant drugs or conditions were not evaluated (Spiller et al, 2008).

3.3.9.A.4 Dystonia

a) Incidence: 29% (Spiller et al, 2008)

b) In a retrospective review of poison center databases in 8 states during the initial 10 months of produc 28) of patients between 4 and 44 years of age (median, 8 years) experiencing adverse events with lisde reliably determined as concomitant drugs or conditions were not evaluated (Spiller et al, 2008).

3.3.9.A.5 Gilles de la Tourette's syndrome

a) Exacerbation of Tourette's syndrome has been reported following administration of amphetamines. P be evaluated for Tourette's syndrome (Prod Info VYVANSE(R) oral capsules, 2008).

3.3.9.A.6 Headache

a) Incidence: adult patients, 5% or greater (Prod Info VYVANSE(R) oral capsules, 2008)

b) Headache occurred in at least 5% or more patients receiving lisdexamfetamine during clinical trials, l (2/358) of adult patients , which was at least twice the discontinuation rate compared with those receiving capsules, 2008).

3.3.9.A.7 Insomnia

a) Incidence: pediatric patients, 19%; adult patients, 27% (Prod Info VYVANSE(R) oral capsules, 2008;

b) During a 4-week, double-blind, randomized, placebo-controlled, parallel-group clinical trial of pediatric (n=290), insomnia was reported in 19% of pediatric patients receiving lisdexamfetamine (n=218) compar (Prod Info VYVANSE(R) oral capsules, 2008).

c) Insomnia was reported in 27% of adult patients who received lisdexamfetamine in final doses of 30 m of patients who received placebo (n=62) in a 4-week, double-blind, randomized, placebo-controlled, para with ADHD. In the same trial, initial insomnia was reported in 4% of adult patient receiving lisdexamfetam placebo (Prod Info VYVANSE(R) oral capsules, 2008).

d) Insomnia led to discontinuation of therapy in 1% (2/218) of pediatric patients and 2% (8/358) of adult at least twice the discontinuation rate compared with those receiving placebo (Prod Info VYVANSE(R) o

e) Further, in a retrospective review of poison center databases in 8 states during the initial 10 months c (8 of 28) of patients between 4 and 44 years of age (median, 8 years) experiencing adverse events with be reliably determined as concomitant drugs or conditions were not evaluated (Spiller et al, 2008).

3.3.9.A.8 Seizure

a) Incidence: 4% (Spiller et al, 2008)

b) In a retrospective review of poison center databases in 8 states during the initial 10 months of produc patients between 4 and 44 years of age (median, 8 years) experiencing adverse events with lisdexamfet concomitant trazodone and imipramine, but had not experienced any other seizures prior to the initiation

3.3.9.A.9 Somnolence

a) Incidence: pediatric patients, 2% (Prod Info VYVANSE(R) oral capsules, 2008)

b) During a 4-week, double-blind, randomized, placebo-controlled, parallel-group clinical trial of pediatric (n=290), somnolence was reported in 2% of pediatric patients receiving lisdexamfetamine (n=218) comp (Prod Info VYVANSE(TM) oral capsules, 2007).

3.3.9.A.10 Tic

a) Incidence: pediatric patients, 2% (Prod Info VYVANSE(R) oral capsules, 2008)

b) During a 4-week, double-blind, randomized, placebo-controlled, parallel-group clinical trial of pediatric (n=290), tics were reported in 2% of pediatric patients receiving lisdexamfetamine (n=218) compared wit the most frequent adverse events leading to discontinuation of therapy was exacerbation of motor and pl patients receiving lisdexamfetamine, which was at least twice the rate compared with placebo (Prod Info

c) Tics led to discontinuation of therapy in 1% (2/218) of pediatric patients receiving lisdexamfetamine, v compared with those receiving placebo (Prod Info VYVANSE(R) oral capsules, 2008).

d) Exacerbation of motor and phonic tics has been reported following administration of amphetamines. I should be evaluated for tics (Prod Info VYVANSE(R) oral capsules, 2008).

3.3.9.A.11 Tremor

a) Incidence: adult patients, 2% (Prod Info VYVANSE(R) oral capsules, 2008)

b) Tremor was reported in 2% of adult patients who received lisdexamfetamine in final doses of 30 mg, patients who received placebo (n=62) in a 4-week, double-blind, randomized, placebo-controlled, paralle ADHD (Prod Info VYVANSE(R) oral capsules, 2008).

c) Further, in a retrospective review of poison center databases in 8 states during the initial 10 months c of 28) of patients between 4 and 44 years of age (median, 8 years) experiencing adverse events with lisc reliably determined as concomitant drugs or conditions were not evaluated (Spiller et al, 2008).
d) Tremor has been reported following administration of amphetamines (Prod Info VYVANSE(R) oral ca

3.3.10 Ophthalmic Effects

3.3.10.A Lisdexamfetamine Dimesylate

3.3.10.A.1 Blurred vision
a) In a retrospective review of poison center databases in 8 states during the initial 10 months of produc 28) of patients between 4 and 44 years of age (median, 8 years) experiencing adverse events with lisde reliably determined as concomitant drugs or conditions were not evaluated (Spiller et al, 2008).

3.3.12 Psychiatric Effects

3.3.12.A Lisdexamfetamine Dimesylate

Agitation

Anxiety

Dysphoric mood

Euphoria

Feeling nervous

Hallucinations

Irritability

Labile affect

Psychotic disorder

Restlessness

Summary

3.3.12.A.1 Agitation
a) Incidence: adult patients, 3% (Prod Info VYVANSE(R) oral capsules, 2008)
b) Agitation was reported in 3% of adult patients who received lisdexamfetamine in final doses of 30 mg patients who received placebo (n=62) in a 4-week, double-blind, randomized, placebo-controlled, paralle ADHD (Prod Info VYVANSE(R) oral capsules, 2008).
c) In a retrospective review of poison center databases in 8 states during the initial 10 months of produc 28) of patients between 4 and 44 years of age (median, 8 years) experiencing adverse events with lisde reliably determined as concomitant drugs or conditions were not evaluated (Spiller et al, 2008).

3.3.12.A.2 Anxiety
a) Incidence: adult patients, 6% (Prod Info VYVANSE(R) oral capsules, 2008)
b) Anxiety was reported in 6% of adult patients who received lisdexamfetamine in final doses of 30 mg, patients who received placebo (n=62) in a 4-week, double-blind, randomized, placebo-controlled, paralle ADHD. This led to a 1% discontinuation rate of lisdexamfetamine therapy (Prod Info VYVANSE(R) oral c

3.3.12.A.3 Dysphoric mood
a) Dysphoria has been reported following administration of amphetamines (Prod Info VYVANSE(R) oral

3.3.12.A.4 Euphoria
a) Euphoria has been reported following administration of amphetamines (Prod Info VYVANSE(R) oral c

3.3.12.A.5 Feeling nervous

a) Incidence: adult patients, 4% (Prod Info VYVANSE(R) oral capsules, 2008)
b) Feeling jittery was reported in 4% of adult patients who received lisdexamfetamine in final doses of 3
0% of patients who received placebo (n=62) in a 4-week, double-blind, randomized, placebo-controlled,
diagnosed with ADHD (Prod Info VYVANSE(R) oral capsules, 2008).
c) In a retrospective review of poison center databases in 8 states during the initial 10 months of produc
(3 of 28) of patients between 4 and 44 years of age (median, 8 years) experiencing adverse events with
be reliably determined as concomitant drugs or conditions were not evaluated (Spiller et al, 2008).

3.3.12.A.6 Hallucinations

a) Incidence: 11% (Spiller et al, 2008)
b) In a retrospective review of poison center databases in 8 states during the initial 10 months of produc
of 28) of patients between 4 and 44 years of age (median, 8 years) experiencing adverse events with lisc
reliably determined as concomitant drugs or conditions were not evaluated (Spiller et al, 2008).

3.3.12.A.7 Irritability

a) Incidence: pediatric patients, 10%; adults, 5% or greater (Prod Info VYVANSE(R) oral capsules, 2008
b) During a 4-week, double-blind, randomized, placebo-controlled, parallel-group clinical trial of pediatric
(n=290), irritability was reported in 10% of pediatric patients receiving lisdexamfetamine (n=218) compar
(Prod Info VYVANSE(R) oral capsules, 2008).
c) Irritability was also reported in at least 5% or more adults patients receiving lisdexamfetamine during
1% (Prod Info VYVANSE(R) oral capsules, 2008).

3.3.12.A.8 Labile affect

a) Incidence: pediatric patients, 3% (Prod Info VYVANSE(R) oral capsules, 2008)
b) During a 4-week, double-blind, randomized, placebo-controlled, parallel-group clinical trial of pediatric
(n=290), labile affect was reported in 3% of pediatric patients receiving lisdexamfetamine (n=218) compa
(Prod Info VYVANSE(TM) oral capsules, 2007).

3.3.12.A.9 Psychotic disorder

a) In multiple short term, placebo-controlled studies, psychotic episodes have been reported in 0.1% of
with recommended doses of methylphenidate or amphetamines compared with no patients receiving pla
2008).
b) Psychotic or manic symptoms may occur among patients without prior history of psychosis, or may w
(Prod Info VYVANSE(R) oral capsules, 2008).

3.3.12.A.10 Restlessness

a) Incidence: adult patients, 3% (Prod Info VYVANSE(R) oral capsules, 2008)
b) Restlessness was reported in 3% of adult patients who received lisdexamfetamine in final doses of 3
0% of patients who received placebo (n=62) in a 4-week, double-blind, randomized, placebo-controlled,
diagnosed with ADHD (Prod Info VYVANSE(R) oral capsules, 2008).

3.3.12.A.11 Summary

a) The use of stimulants may result in new-onset or worsening of existing psychotic disorders, even in p
aggressive behavior and evaluating the patient for bipolar disorder prior to stimulant use is recommende

3.3.14 Reproductive Effects

3.3.14.A Lisdexamfetamine Dimesylate

3.3.14.A.1 Impotence

a) Impotence has been reported following administration of amphetamines (Prod Info VYVANSE(R) oral

3.3.15 Respiratory Effects

3.3.15.A Lisdexamfetamine Dimesylate

3.3.15.A.1 Dyspnea

a) Incidence: adult patients, 2% (Prod Info VYVANSE(R) oral capsules, 2008)
b) Dyspnea was reported in 2% of adult patients who received lisdexamfetamine in final doses of 30 mg
patients who received placebo (n=62) in a 4-week, double-blind, randomized, placebo-controlled, paralle
ADHD. This led to a 1% discontinuation rate of lisdexamfetamine therapy (Prod Info VYVANSE(R) oral c

3.3.16 Other

3.3.16.A Lisdexamfetamine Dimesylate

3.3.16.A.1 Fever

a) Incidence: pediatric patients, 2% (Prod Info VYVANSE(R) oral capsules, 2008)

b) During a 4-week, double-blind, randomized, placebo-controlled, parallel-group clinical trial of pediatric (n=290), pyrexia was reported in 2% of pediatric patients receiving lisdexamfetamine (n=218) compared Info VYVANSE(TM) oral capsules, 2007).
c) Further, in a retrospective review of poison center databases in 8 states during the initial 10 months c 28) of patients between 4 and 44 years of age (median, 8 years) experiencing adverse events with lisdex reliably determined as concomitant drugs or conditions were not evaluated (Spiller et al, 2008).

3.4 Teratogenicity/Effects in Pregnancy/Breastfeeding

A) Teratogenicity/Effects in Pregnancy
1) U.S. Food and Drug Administration's Pregnancy Category: Category C (Prod Info VYVANSE(TM) oral capsule
a) Either studies in animals have revealed adverse effects on the fetus (teratogenic or embryocidal or other) studies in women and animals are not available. Drugs should be given only if the potential benefit justifies th
See Drug Consult reference: PREGNANCY RISK CATEGORIES
2) Crosses Placenta: Unknown
3) Clinical Management
a) There are no adequate and well-controlled studies with lisdexamfetamine in humans or animals. Studies v animals have shown adverse maternal and fetal effects. Until further data are available, it is recommended th only if the potential benefit justifies the potential risk to the fetus (Prod Info VYVANSE(TM) oral capsules, 200
4) Literature Reports
a) Reproduction studies with lisdexamfetamine (prodrug of dextroamphetamine) have not been conducted in of premature delivery and low birth weight in infants born to mothers dependent on amphetamine. Additionall agitation, and significant lassitude, may be present in such infants (Prod Info VYVANSE(TM) oral capsules, 2
b) In pregnant rats and rabbits, orally administered amphetamine (D to L enantiomer ratio of 3:1) at doses up not affect embryofetal development or survival. However, parenteral administration of dextroamphetamine at mice resulted in severe maternal toxicity and fetal malformations and death. Additionally, in several studies in clinically relevant amphetamine doses led to long-term neurochemical and behavioral effects, such as learnin activity, and changes in sexual function (Prod Info VYVANSE(TM) oral capsules, 2007).

B) Breastfeeding
1) Thomson Lactation Rating: Infant risk cannot be ruled out.
a) Available evidence and/or expert consensus is inconclusive or is inadequate for determining infant risk wh potential benefits of drug treatment against potential risks before prescribing this drug during breastfeeding.
2) Clinical Management
a) As amphetamines are excreted in human milk, breast-feeding women receiving lisdexamfetamine should VYVANSE(TM) oral capsules, 2007).

3.5 Drug Interactions

3.5.1 Drug-Drug Combinations

Amitriptyline

Amoxapine

Clomipramine

Clorgyline

Desipramine

Dothiepin

Doxepin

Furazolidone

Imipramine

Iproniazid

Isocarboxazid

Lofepramine

Moclobemide

Nialamide

Nortriptyline

Opipramol

Pargyline

Phenelzine

Procarbazine

Protriptyline

Rasagiline

Selegiline

Toloxatone

Tranylcypromine

Trimipramine

3.5.1.A Amitriptyline

1) Interaction Effect: hypertension, other cardiac effects, and CNS stimulation

2) Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been reporte from the release of norepinephrine (Beaumont, 1973; Raisfeld, 1972). A similar reaction might also occur wit Acute elevations in blood pressure have been noted (Flemenbaum, 1971a). Some amphetamine-like drugs m most combinations have not been studied. When amphetamine analogs are being used to treat obesity, it sh moderate weight gain (Russ & Ackerman, 1988). False positive urine tests for amphetamines have been repo & Browning, 1993). Caution is advised when concurrent administration of amphetamine-like agents and TCA monitored for increased cardiovascular effects (hypertension and dysrhythmias).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other sympatho increased cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Inf capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006; Flemenbaum, 1972). Use caution if closely for hypertension and dysrhythmias.

7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission

8) Literature Reports

a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agen amphetamine with TCAs such as desipramine or protriptyline results in sustained increases in d-amphet VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tab 2006).

b) Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transdermal system, 2006).

c) Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases i effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of comb methylphenidate usually results in the blood pressure returning to normotensive levels; reinstitution of th pressure elevation (Flemenbaum, 1971; Flemenbaum, 1972).

d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical doubled steady-state plasma levels of desipramine (Price et al, 1990).

e) There have been claims based on uncontrolled studies that a better antidepressant response may oc 1969). However, a systemic review of stimulants in the treatment of depression concluded that although ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated litt appear to be as effective as the conventional antidepressants in primary depression (Satel & Nelson, 19

3.5.1.B Amoxapine

1) Interaction Effect: hypertension, other cardiac effects, and CNS stimulation

2) Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been reporte from the release of norepinephrine (Beaumont, 1973; Raisfeld, 1972). A similar reaction might also occur wit Acute elevations in blood pressure have been noted (Flemenbaum, 1971a). Some amphetamine-like drugs m most combinations have not been studied. When amphetamine analogs are being used to treat obesity, it sh moderate weight gain (Russ & Ackerman, 1988). False positive urine tests for amphetamines have been repo & Browning, 1993). Caution is advised when concurrent administration of amphetamine-like agents and TCAs monitored for increased cardiovascular effects (hypertension and dysrhythmias).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other sympatho increased cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Inf capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006; Flemenbaum, 1972). Use caution if closely for hypertension and dysrhythmias.

7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission

8) Literature Reports

a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agen amphetamine with TCAs such as desipramine or protriptyline results in sustained increases in d-amphet VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tab 2006).

b) Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism o imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transdermal system, 2006).

c) Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases i effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of comb methylphenidate usually results in the blood pressure returning to normotensive levels; reinstitution of th pressure elevation (Flemenbaum, 1971; Flemenbaum, 1972).

d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine g fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical doubled steady-state plasma levels of desipramine (Price et al, 1990).

e) There have been claims based on uncontrolled studies that a better antidepressant response may oc 1969). However, a systemic review of stimulants in the treatment of depression concluded that although ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated litt appear to be as effective as the conventional antidepressants in primary depression (Satel & Nelson, 19

3.5.1.C Clomipramine

1) Interaction Effect: hypertension, other cardiac effects, and CNS stimulation

2) Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been reporte from the release of norepinephrine (Beaumont, 1973; Raisfeld, 1972). A similar reaction might also occur wit Acute elevations in blood pressure have been noted (Flemenbaum, 1971a). Some amphetamine-like drugs m most combinations have not been studied. When amphetamine analogs are being used to treat obesity, it sh moderate weight gain (Russ & Ackerman, 1988). False positive urine tests for amphetamines have been repo & Browning, 1993). Caution is advised when concurrent administration of amphetamine-like agents and TCAs monitored for increased cardiovascular effects (hypertension and dysrhythmias).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other sympatho increased cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Inf capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006; Flemenbaum, 1972). Use caution if closely for hypertension and dysrhythmias.

7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission

8) Literature Reports

a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agen amphetamine with TCAs such as desipramine or protriptyline results in sustained increases in d-amphet VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tab 2006).

b) Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism o imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transdermal system, 2006).

c) Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases i effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of comb methylphenidate usually results in the blood pressure returning to normotensive levels; reinstitution of th pressure elevation (Flemenbaum, 1971; Flemenbaum, 1972).

d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine g fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical doubled steady-state plasma levels of desipramine (Price et al, 1990).

e) There have been claims based on uncontrolled studies that a better antidepressant response may oc
1969). However, a systemic review of stimulants in the treatment of depression concluded that although
ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated litt
appear to be as effective as the conventional antidepressants in primary depression (Satel & Nelson, 19

3.5.1.D Clorgyline

1) Interaction Effect: hypertensive crisis (headache, hyperpyrexia, hypertension)
2) Summary: Use of lisdexamfetamine during or within 14 days following the administration of a monoamine
Amphetamines stimulate the release of norepinephrine, and the use of MAOIs slows down amphetamine met
norepinephrine and other monoamines from adrenergic nerve ending. This could result in hypertensive crisis,
hyperpyrexia (Prod Info VYVANSE(TM) oral capsules, 2007).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Lisdexamfetamine use during or within 14 days following the administration of a mo
hypertensive crises may occur (Prod Info VYVANSE(TM) oral capsules, 2007).
7) Probable Mechanism: increased norepinephrine availability

3.5.1.E Desipramine

1) Interaction Effect: hypertension, other cardiac effects, and CNS stimulation
2) Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been reported
from the release of norepinephrine (Beaumont, 1973; Raisfeld, 1972). A similar reaction might also occur with
Acute elevations in blood pressure have been noted (Flemenbaum, 1971a). Some amphetamine-like drugs m
most combinations have not been studied. When amphetamine analogs are being used to treat obesity, it sho
moderate weight gain (Russ & Ackerman, 1988). False positive urine tests for amphetamines have been repo
& Browning, 1993). Caution is advised when concurrent administration of amphetamine-like agents and TCAs
monitored for increased cardiovascular effects (hypertension and dysrhythmias).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other sympatho
increased cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Inf
capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006; Flemenbaum, 1972). Use caution if
closely for hypertension and dysrhythmias.
7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission
8) Literature Reports

a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agen
amphetamine with TCAs such as desipramine or protriptyline results in sustained increases in d-amphet
VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tab
2006).

b) Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism o
imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transdermal system, 2006).

c) Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases in
effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of comb
methylphenidate usually results in the blood pressure returning to normotensive levels; reinstitution of th
pressure elevation (Flemenbaum, 1971; Flemenbaum, 1972).

d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine g
fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical
doubled steady-state plasma levels of desipramine (Price et al, 1990).

e) There have been claims based on uncontrolled studies that a better antidepressant response may oc
1969). However, a systemic review of stimulants in the treatment of depression concluded that although
ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated litt
appear to be as effective as the conventional antidepressants in primary depression (Satel & Nelson, 19

3.5.1.F Dothiepin

1) Interaction Effect: hypertension, other cardiac effects, and CNS stimulation
2) Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been reported
from the release of norepinephrine (Beaumont, 1973; Raisfeld, 1972). A similar reaction might also occur with
Acute elevations in blood pressure have been noted (Flemenbaum, 1971a). Some amphetamine-like drugs m
most combinations have not been studied. When amphetamine analogs are being used to treat obesity, it sho
moderate weight gain (Russ & Ackerman, 1988). False positive urine tests for amphetamines have been repo
& Browning, 1993). Caution is advised when concurrent administration of amphetamine-like agents and TCAs
monitored for increased cardiovascular effects (hypertension and dysrhythmias).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other sympatho
increased cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Inf

capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006; Flemenbaum, 1972). Use caution if closely for hypertension and dysrhythmias.

7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission

8) Literature Reports

a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agen amphetamine with TCAs such as desipramine or protriptyline results in sustained increases in d-amphet VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tab 2006).

b) Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism c imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transdermal system, 2006).

c) Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases i effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of comb methylphenidate usually results in the blood pressure returning to normotensive levels; reinstitution of th pressure elevation (Flemenbaum, 1971; Flemenbaum, 1972).

d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine g fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical doubled steady-state plasma levels of desipramine (Price et al, 1990).

e) There have been claims based on uncontrolled studies that a better antidepressant response may oc 1969). However, a systemic review of stimulants in the treatment of depression concluded that although ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated litt appear to be as effective as the conventional antidepressants in primary depression (Satel & Nelson, 19

3.5.1.G Doxepin

1) Interaction Effect: hypertension, other cardiac effects, and CNS stimulation

2) Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been reporte from the release of norepinephrine (Beaumont, 1973; Raisfeld, 1972). A similar reaction might also occur wit Acute elevations in blood pressure have been noted (Flemenbaum, 1971a). Some amphetamine-like drugs m most combinations have not been studied. When amphetamine analogs are being used to treat obesity, it sh moderate weight gain (Russ & Ackerman, 1988). False positive urine tests for amphetamines have been repo & Browning, 1993). Caution is advised when concurrent administration of amphetamine-like agents and TCAs monitored for increased cardiovascular effects (hypertension and dysrhythmias).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other sympatho increased cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Inf capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006; Flemenbaum, 1972). Use caution if closely for hypertension and dysrhythmias.

7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission

8) Literature Reports

a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agen amphetamine with TCAs such as desipramine or protriptyline results in sustained increases in d-amphet VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tab 2006).

b) Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism c imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transdermal system, 2006).

c) Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases i effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of comb methylphenidate usually results in the blood pressure returning to normotensive levels; reinstitution of th pressure elevation (Flemenbaum, 1971; Flemenbaum, 1972).

d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine g fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical doubled steady-state plasma levels of desipramine (Price et al, 1990).

e) There have been claims based on uncontrolled studies that a better antidepressant response may oc 1969). However, a systemic review of stimulants in the treatment of depression concluded that although ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated litt appear to be as effective as the conventional antidepressants in primary depression (Satel & Nelson, 19

3.5.1.H Furazolidone

1) Interaction Effect: hypertensive crisis (headache, hyperpyrexia, hypertension)

2) Summary: Use of lisdexamfetamine during or within 14 days following the administration of a monoamine Amphetamines stimulate the release of norepinephrine, and the use of MAOIs slows down amphetamine me norepinephrine and other monoamines from adrenergic nerve ending. This could result in hypertensive crisis, hyperpyrexia (Prod Info VYVANSE(TM) oral capsules, 2007). Furazolidone has significant MAOI activity (Pet Therefore, concurrent use of furazolidone with lisdexamfetamine should be avoided.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Lisdexamfetamine use during or within 14 days following the administration of a mo contraindicated as hypertensive crises may occur (Prod Info VYVANSE(TM) oral capsules, 2007). As furazoli concurrent use with lisdexamfetamine.
7) Probable Mechanism: increased norepinephrine availability

3.5.1.I Imipramine

1) Interaction Effect: hypertension, other cardiac effects, and CNS stimulation
2) Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been reporte from the release of norepinephrine (Beaumont, 1973; Raisfeld, 1972). A similar reaction might also occur wit Acute elevations in blood pressure have been noted (Flemenbaum, 1971a). Some amphetamine-like drugs n most combinations have not been studied. When amphetamine analogs are being used to treat obesity, it sh moderate weight gain (Russ & Ackerman, 1988). False positive urine tests for amphetamines have been repo & Browning, 1993). Caution is advised when concurrent administration of amphetamine-like agents and TCA monitored for increased cardiovascular effects (hypertension and dysrhythmias).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other sympatho increased cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Inf capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006; Flemenbaum, 1972). Use caution if closely for hypertension and dysrhythmias.
7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission
8) Literature Reports
a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agen amphetamine with TCAs such as desipramine or protriptyline results in sustained increases in d-amphet VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tab 2006).
b) Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transdermal system, 2006).
c) Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases i effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of comb methylphenidate usually results in the blood pressure returning to normotensive levels; reinstitution of th pressure elevation (Flemenbaum, 1971; Flemenbaum, 1972).
d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical doubled steady-state plasma levels of desipramine (Price et al, 1990).
e) There have been claims based on uncontrolled studies that a better antidepressant response may oc 1969). However, a systemic review of stimulants in the treatment of depression concluded that although ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated litt appear to be as effective as the conventional antidepressants in primary depression (Satel & Nelson, 19

3.5.1.J Iproniazid

1) Interaction Effect: hypertensive crisis (headache, hyperpyrexia, hypertension)
2) Summary: Use of lisdexamfetamine during or within 14 days following the administration of a monoamine Amphetamines stimulate the release of norepinephrine, and the use of MAOIs slows down amphetamine me norepinephrine and other monoamines from adrenergic nerve ending. This could result in hypertensive crisis hyperpyrexia (Prod Info VYVANSE(TM) oral capsules, 2007).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Lisdexamfetamine use during or within 14 days following the administration of a mo hypertensive crises may occur (Prod Info VYVANSE(TM) oral capsules, 2007).
7) Probable Mechanism: increased norepinephrine availability

3.5.1.K Isocarboxazid

1) Interaction Effect: hypertensive crisis (headache, hyperpyrexia, hypertension)
2) Summary: Use of lisdexamfetamine during or within 14 days following the administration of a monoamine Amphetamines stimulate the release of norepinephrine, and the use of MAOIs slows down amphetamine me norepinephrine and other monoamines from adrenergic nerve ending. This could result in hypertensive crisis hyperpyrexia (Prod Info VYVANSE(TM) oral capsules, 2007).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Lisdexamfetamine use during or within 14 days following the administration of a mo hypertensive crises may occur (Prod Info VYVANSE(TM) oral capsules, 2007).
7) Probable Mechanism: increased norepinephrine availability

3.5.1.L Lofepramine

1) Interaction Effect: hypertension, other cardiac effects, and CNS stimulation
2) Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been reporte from the release of norepinephrine (Beaumont, 1973; Raisfeld, 1972). A similar reaction might also occur wit Acute elevations in blood pressure have been noted (Flemenbaum, 1971a). Some amphetamine-like drugs n most combinations have not been studied. When amphetamine analogs are being used to treat obesity, it sh moderate weight gain (Russ & Ackerman, 1988). False positive urine tests for amphetamines have been rep & Browning, 1993). Caution is advised when concurrent administration of amphetamine-like agents and TCA monitored for increased cardiovascular effects (hypertension and dysrhythmias).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other sympatho increased cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Inf capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006; Flemenbaum, 1972). Use caution if closely for hypertension and dysrhythmias.
7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission
8) Literature Reports
a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agen amphetamine with TCAs such as desipramine or protriptyline results in sustained increases in d-amphet VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tab 2006).
b) Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transdermal system, 2006).
c) Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases i effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of comb methylphenidate usually results in the blood pressure returning to normotensive levels; reinstitution of th pressure elevation (Flemenbaum, 1971; Flemenbaum, 1972).
d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical doubled steady-state plasma levels of desipramine (Price et al, 1990).
e) There have been claims based on uncontrolled studies that a better antidepressant response may oc 1969). However, a systemic review of stimulants in the treatment of depression concluded that although ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated litt appear to be as effective as the conventional antidepressants in primary depression (Satel & Nelson, 19

3.5.1.M Moclobemide

1) Interaction Effect: hypertensive crisis (headache, hyperpyrexia, hypertension)
2) Summary: Use of lisdexamfetamine during or within 14 days following the administration of a monoamine Amphetamines stimulate the release of norepinephrine, and the use of MAOIs slows down amphetamine me norepinephrine and other monoamines from adrenergic nerve ending. This could result in hypertensive crisis hyperpyrexia (Prod Info VYVANSE(TM) oral capsules, 2007).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Lisdexamfetamine use during or within 14 days following the administration of a mo hypertensive crises may occur (Prod Info VYVANSE(TM) oral capsules, 2007).
7) Probable Mechanism: increased norepinephrine availability

3.5.1.N Nialamide

1) Interaction Effect: hypertensive crisis (headache, hyperpyrexia, hypertension)
2) Summary: Use of lisdexamfetamine during or within 14 days following the administration of a monoamine Amphetamines stimulate the release of norepinephrine, and the use of MAOIs slows down amphetamine me norepinephrine and other monoamines from adrenergic nerve ending. This could result in hypertensive crisis hyperpyrexia (Prod Info VYVANSE(TM) oral capsules, 2007).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Lisdexamfetamine use during or within 14 days following the administration of a mo hypertensive crises may occur (Prod Info VYVANSE(TM) oral capsules, 2007).
7) Probable Mechanism: increased norepinephrine availability

3.5.1.O Nortriptyline

1) Interaction Effect: hypertension, other cardiac effects, and CNS stimulation
2) Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been reporte from the release of norepinephrine (Beaumont, 1973; Raisfeld, 1972). A similar reaction might also occur wit Acute elevations in blood pressure have been noted (Flemenbaum, 1971a). Some amphetamine-like drugs n most combinations have not been studied. When amphetamine analogs are being used to treat obesity, it sh moderate weight gain (Russ & Ackerman, 1988). False positive urine tests for amphetamines have been rep

& Browning, 1993). Caution is advised when concurrent administration of amphetamine-like agents and TCAs monitored for increased cardiovascular effects (hypertension and dysrhythmias).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other sympatho increased cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Inf capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006; Flemenbaum, 1972). Use caution if closely for hypertension and dysrhythmias.
7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission
8) Literature Reports
a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agen amphetamine with TCAs such as desipramine or protriptyline results in sustained increases in d-amphet VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tab 2006).
b) Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism c imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transdermal system, 2006).
c) Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases i effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of comb methylphenidate usually results in the blood pressure returning to normotensive levels; reinstitution of th pressure elevation (Flemenbaum, 1971; Flemenbaum, 1972).
d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine g fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical doubled steady-state plasma levels of desipramine (Price et al, 1990).
e) There have been claims based on uncontrolled studies that a better antidepressant response may oc 1969). However, a systemic review of stimulants in the treatment of depression concluded that although ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated litt appear to be as effective as the conventional antidepressants in primary depression (Satel & Nelson, 19

3.5.1.P Opipramol
1) Interaction Effect: hypertension, other cardiac effects, and CNS stimulation
2) Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been reporte from the release of norepinephrine (Beaumont, 1973; Raisfeld, 1972). A similar reaction might also occur with Acute elevations in blood pressure have been noted (Flemenbaum, 1971a). Some amphetamine-like drugs m most combinations have not been studied. When amphetamine analogs are being used to treat obesity, it sh moderate weight gain (Russ & Ackerman, 1988). False positive urine tests for amphetamines have been repo & Browning, 1993). Caution is advised when concurrent administration of amphetamine-like agents and TCAs monitored for increased cardiovascular effects (hypertension and dysrhythmias).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other sympatho increased cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Inf capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006; Flemenbaum, 1972). Use caution if closely for hypertension and dysrhythmias.
7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission
8) Literature Reports
a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agen amphetamine with TCAs such as desipramine or protriptyline results in sustained increases in d-amphet VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tab 2006).
b) Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism c imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transdermal system, 2006).
c) Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases i effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of comb methylphenidate usually results in the blood pressure returning to normotensive levels; reinstitution of th pressure elevation (Flemenbaum, 1971; Flemenbaum, 1972).
d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine g fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical doubled steady-state plasma levels of desipramine (Price et al, 1990).
e) There have been claims based on uncontrolled studies that a better antidepressant response may oc 1969). However, a systemic review of stimulants in the treatment of depression concluded that although ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated litt appear to be as effective as the conventional antidepressants in primary depression (Satel & Nelson, 19

3.5.1.Q Pargyline
1) Interaction Effect: hypertensive crisis (headache, hyperpyrexia, hypertension)
2) Summary: Use of lisdexamfetamine during or within 14 days following the administration of a monoamine

Amphetamines stimulate the release of norepinephrine, and the use of MAOIs slows down amphetamine met
norepinephrine and other monoamines from adrenergic nerve ending. This could result in hypertensive crisis,
hyperpyrexia (Prod Info VYVANSE(TM) oral capsules, 2007).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Lisdexamfetamine use during or within 14 days following the administration of a mo
hypertensive crises may occur (Prod Info VYVANSE(TM) oral capsules, 2007).
7) Probable Mechanism: increased norepinephrine availability

3.5.1.R Phenelzine
1) Interaction Effect: hypertensive crisis (headache, hyperpyrexia, hypertension)
2) Summary: Use of lisdexamfetamine during or within 14 days following the administration of a monoamine
Amphetamines stimulate the release of norepinephrine, and the use of MAOIs slows down amphetamine met
norepinephrine and other monoamines from adrenergic nerve ending. This could result in hypertensive crisis,
hyperpyrexia (Prod Info VYVANSE(TM) oral capsules, 2007).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Lisdexamfetamine use during or within 14 days following the administration of a mo
hypertensive crises may occur (Prod Info VYVANSE(TM) oral capsules, 2007).
7) Probable Mechanism: increased norepinephrine availability

3.5.1.S Procarbazine
1) Interaction Effect: hypertensive crisis (headache, hyperpyrexia, hypertension)
2) Summary: Use of lisdexamfetamine during or within 14 days following the administration of a monoamine
Amphetamines stimulate the release of norepinephrine, and the use of MAOIs slows down amphetamine met
norepinephrine and other monoamines from adrenergic nerve ending. This could result in hypertensive crisis,
hyperpyrexia (Prod Info VYVANSE(TM) oral capsules, 2007).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Lisdexamfetamine use during or within 14 days following the administration of a mo
hypertensive crises may occur (Prod Info VYVANSE(TM) oral capsules, 2007).
7) Probable Mechanism: increased norepinephrine availability

3.5.1.T Protriptyline
1) Interaction Effect: hypertension, other cardiac effects, and CNS stimulation
2) Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been reported
from the release of norepinephrine (Beaumont, 1973; Raisfeld, 1972). A similar reaction might also occur with
Acute elevations in blood pressure have been noted (Flemenbaum, 1971a). Some amphetamine-like drugs m
most combinations have not been studied. When amphetamine analogs are being used to treat obesity, it sho
moderate weight gain (Russ & Ackerman, 1988). False positive urine tests for amphetamines have been repo
& Browning, 1993). Caution is advised when concurrent administration of amphetamine-like agents and TCAs
monitored for increased cardiovascular effects (hypertension and dysrhythmias).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other sympatho
increased cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Inf
capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006; Flemenbaum, 1972). Use caution if
closely for hypertension and dysrhythmias.
7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission
8) Literature Reports
a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agen
amphetamine with TCAs such as desipramine or protriptyline results in sustained increases in d-amphet
VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tab
2006).
b) Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism o
imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transdermal system, 2006).
c) Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases in
effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of comb
methylphenidate usually results in the blood pressure returning to normotensive levels; reinstitution of th
pressure elevation (Flemenbaum, 1971; Flemenbaum, 1972).
d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine g
fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical
doubled steady-state plasma levels of desipramine (Price et al, 1990).
e) There have been claims based on uncontrolled studies that a better antidepressant response may oc

1969). However, a systemic review of stimulants in the treatment of depression concluded that although ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated litt appear to be as effective as the conventional antidepressants in primary depression (Satel & Nelson, 19

3.5.1.U Rasagiline

1) Interaction Effect: hypertensive crisis (headache, hyperpyrexia, hypertension)
2) Summary: Use of lisdexamfetamine during or within 14 days following the administration of a monoamine Amphetamines stimulate the release of norepinephrine, and the use of MAOIs slows down amphetamine me norepinephrine and other monoamines from adrenergic nerve ending. This could result in hypertensive crisis, hyperpyrexia (Prod Info VYVANSE(TM) oral capsules, 2007).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Lisdexamfetamine use during or within 14 days following the administration of a mo hypertensive crises may occur (Prod Info VYVANSE(TM) oral capsules, 2007).
7) Probable Mechanism: increased norepinephrine availability

3.5.1.V Selegiline

1) Interaction Effect: hypertensive crisis (headache, hyperpyrexia, hypertension)
2) Summary: Use of lisdexamfetamine during or within 14 days following the administration of a monoamine Amphetamines stimulate the release of norepinephrine, and the use of MAOIs slows down amphetamine me norepinephrine and other monoamines from adrenergic nerve ending. This could result in hypertensive crisis, hyperpyrexia (Prod Info VYVANSE(TM) oral capsules, 2007).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Lisdexamfetamine use during or within 14 days following the administration of a mo hypertensive crises may occur (Prod Info VYVANSE(TM) oral capsules, 2007).
7) Probable Mechanism: increased norepinephrine availability

3.5.1.W Toloxatone

1) Interaction Effect: hypertensive crisis (headache, hyperpyrexia, hypertension)
2) Summary: Use of lisdexamfetamine during or within 14 days following the administration of a monoamine Amphetamines stimulate the release of norepinephrine, and the use of MAOIs slows down amphetamine me norepinephrine and other monoamines from adrenergic nerve ending. This could result in hypertensive crisis, hyperpyrexia (Prod Info VYVANSE(TM) oral capsules, 2007).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Lisdexamfetamine use during or within 14 days following the administration of a mo hypertensive crises may occur (Prod Info VYVANSE(TM) oral capsules, 2007).
7) Probable Mechanism: increased norepinephrine availability

3.5.1.X Tranylcypromine

1) Interaction Effect: hypertensive crisis (headache, hyperpyrexia, hypertension)
2) Summary: Use of lisdexamfetamine during or within 14 days following the administration of a monoamine Amphetamines stimulate the release of norepinephrine, and the use of MAOIs slows down amphetamine me norepinephrine and other monoamines from adrenergic nerve ending. This could result in hypertensive crisis, hyperpyrexia (Prod Info VYVANSE(TM) oral capsules, 2007).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Lisdexamfetamine use during or within 14 days following the administration of a mo hypertensive crises may occur (Prod Info VYVANSE(TM) oral capsules, 2007).
7) Probable Mechanism: increased norepinephrine availability

3.5.1.Y Trimipramine

1) Interaction Effect: hypertension, other cardiac effects, and CNS stimulation
2) Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been reporte from the release of norepinephrine (Beaumont, 1973; Raisfeld, 1972). A similar reaction might also occur wit Acute elevations in blood pressure have been noted (Flemenbaum, 1971a). Some amphetamine-like drugs n most combinations have not been studied. When amphetamine analogs are being used to treat obesity, it sh moderate weight gain (Russ & Ackerman, 1988). False positive urine tests for amphetamines have been rep & Browning, 1993). Caution is advised when concurrent administration of amphetamine-like agents and TCA monitored for increased cardiovascular effects (hypertension and dysrhythmias).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical

6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other sympatho increased cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Inf capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006; Flemenbaum, 1972). Use caution if closely for hypertension and dysrhythmias.
7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission
8) Literature Reports
a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agen amphetamine with TCAs such as desipramine or protriptyline results in sustained increases in d-amphet VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tab 2006).
b) Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism c imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transdermal system, 2006).
c) Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases i effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of comb methylphenidate usually results in the blood pressure returning to normotensive levels; reinstitution of th pressure elevation (Flemenbaum, 1971; Flemenbaum, 1972).
d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine g fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical doubled steady-state plasma levels of desipramine (Price et al, 1990).
e) There have been claims based on uncontrolled studies that a better antidepressant response may oc 1969). However, a systemic review of stimulants in the treatment of depression concluded that although ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated litt appear to be as effective as the conventional antidepressants in primary depression (Satel & Nelson, 19

4.0 Clinical Applications

Monitoring Parameters

Patient Instructions

Place In Therapy

Mechanism of Action / Pharmacology

Therapeutic Uses

4.1 Monitoring Parameters

A) Lisdexamfetamine Dimesylate
1) Therapeutic
a) Improvement in mental and behavioral symptoms of attention deficit hyperactivity disorder (ADHD), includ hyperactivity, and cognitive performance.
2) Toxic
a) Physical Findings
1) The American Academy of Pediatrics (AAP) does not recommend the routine use of electrocardiogra evaluations (which were previously recommended by the American Heart Association (AHA) scientific st place the child at risk for sudden cardiac death) before initiating stimulant therapy to treat attention-defici The APA cited specific reasons for changing the recommendation including: lack of evidence establishin treat ADHD and sudden cardiac death (SCD), the frequency of sudden unexpected deaths among patier in the general population of children, and lack of cost-effective analysis to support ECG screening or spe al, 2008).
2) Based on the American Academy of Pediatrics (AAP) and the American Heart Association (AHA) con monitoring recommendations have been established to assist clinicians in the evaluation of children treat lisdexamfetamine, for ADHD (Perrin et al, 2008; Vetter et al, 2008):
- Conduct a thorough examination prior to initiating lisdexamfetamine therapy for a diagnosis of ADH symptoms indicative of a cardiac condition, including palpitations, near syncope, or syncope.
- Obtain a complete family and patient history for conditions associated with SCD, and determine cu counter medications.
- Conduct a complete physical evaluation of the patient for hypertension, cardiac murmurs, physical signs of irregular cardiac rhythms.
- Perform further evaluation if family history, patient history or physical exam is suggestive of cardiac and if indicated, consult pediatric cardiologist .
- Continue to assess the patient for cardiac symptoms and any changes in family history at follow up
- Blood pressure and heart rate should be evaluated at baseline, during routine follow-up within 1 to months. Increases in blood pressure and heart rate have been reported with stimulant use.

b) It is not conclusive whether chronic use of stimulants in children may be associated with suppression of g during treatment (Prod Info VYVANSE(TM) oral capsules, 2007).

4.2 Patient Instructions

A) Lisdexamfetamine Dimesylate (By mouth)

Lisdexamfetamine Dimesylate

Treats attention deficit hyperactivity disorder (ADHD). This medicine is a stimulant.

When This Medicine Should Not Be Used:

You should not use this medicine if you or your child have had an allergic reaction to lisdexamfetamine dimesylate glaucoma, an overactive thyroid, high blood pressure, heart disease, or blood vessel problems. Do not use this m you are very nervous, tense, or agitated most of the time. You should not use this medicine if you have used a dru (MAOI), such as Eldepryl®, Marplan®, Nardil®, or Parnate®, in the past 14 days. Do not give this medicine to a c

How to Use This Medicine:

Capsule

Your doctor will tell you how much of this medicine to use and how often. Your dose may need to be changed best for you. Do not use more medicine or use it more often than your doctor tells you to.

This medicine should come with a Medication Guide. Read and follow these instructions carefully. Ask your d Ask your pharmacist for the Medication Guide if you do not have one. Your doctor might ask you to sign som information.

You may take this medicine with or without food.

It is best to take this medicine in the morning. Taking this medicine in the afternoon or evening could make it

If you cannot swallow the capsule whole, you may open it and pour the medicine into a glass of water. Stir thi

This medicine is part of an ADHD treatment program that may also include counseling or special education. C all treatment measures.

If a Dose is Missed:

If you miss a dose or forget to use your medicine, use it as soon as you can. If it is almost time for your next d the missed dose. Do not use extra medicine to make up for a missed dose.

How to Store and Dispose of This Medicine:

Store the medicine in a closed container at room temperature, away from heat, moisture, and direct light.

Ask your pharmacist, doctor, or health caregiver about the best way to dispose of any leftover medicine after need to throw away old medicine after the expiration date has passed.

Keep all medicine away from children and never share your medicine with anyone.

Drugs and Foods to Avoid:

Ask your doctor or pharmacist before using any other medicine, including over-the-counter medicines, vitamins, a

Make sure your doctor knows if you are also using blood pressure medicines (such as atenolol, lisinopril, met medicines (such as meperidine, propoxyphene, Demerol®, or Darvon®), chlorpromazine (Thorazine®), cold haloperidol (Haldol®), lithium carbonate (Lithobid®), certain medicines for depression (such as amitriptyline, methenamine (Hiprex, Urex®), phenobarbital, or phenytoin (Dilantin®).

Warnings While Using This Medicine:

Make sure your doctor knows if you are pregnant or breastfeeding, or if you or your child have heart problems

Tell your doctor if you or your child have muscle tics or Tourette's syndrome, a condition that causes you to h not able to control.

Your doctor should know if you or your child have epilepsy, or a history of seizures, depression, or mental illn problems. Also tell your doctor if you or anyone in your family has tried to commit suicide.

This medicine may be habit-forming. If you feel that the medicine is not working as well, do not use more thar instructions.

This medicine may cause slow growth. If your child is using this medicine, the doctor will need to keep track o your child is growing properly.

This medicine may cause blurred vision or make you drowsy or dizzy. If any of these occur, do not drive, use dangerous if you are not alert or not able to see well.

Your doctor will need to check your progress at regular visits while you are using this medicine. Be sure to ke

Possible Side Effects While Using This Medicine:

Call your doctor right away if you notice any of these side effects:

Allergic reaction: Itching or hives, swelling in your face or hands, swelling or tingling in your mouth or throat, o

Blistering, peeling, red skin rash.

Blurred vision or trouble seeing.

Chest pain, shortness of breath, or fainting.

Fast, pounding, or irregular heartbeat.

Mood or mental changes, or unusual or disturbing thoughts.

Numbness or weakness in your arm or leg, or on one side of your body.

Seeing, hearing, or feeling things that are not there.
Seizures.
Tremors or shaking.
Uncontrollable muscle movements or twitching.

If you notice these less serious side effects, talk with your doctor:
Constipation, diarrhea, or upset stomach.
Dry mouth or bad taste in your mouth.
Feeling restless or nervous.
Headache or dizziness.
Loss of appetite or weight loss.
Nausea, vomiting, or stomach pain.
Problems having sex.
Trouble sleeping.

If you notice other side effects that you think are caused by this medicine, tell your doctor.

4.3 Place In Therapy

A) Lisdexamfetamine Dimesylate

1) Lisdexamfetamine dimesylate is a pro-drug of dextroamphetamine, approved for the treatment of Attention-De placebo-controlled trials, lisdexamfetamine dimesylate showed improvement in behavior in children aged 6 to 12 v combined type or hyperactive-impulsive type. The long-term (greater than 4 weeks) efficacy of lisdexamfetamine assessed in controlled trials (Prod Info VYVANSE(TM) oral capsules, 2007).

4.4 Mechanism of Action / Pharmacology

A) Lisdexamfetamine Dimesylate

1) After oral administration, lisdexamfetamine dimesylate is rapidly absorbed in the gastrointestinal tract and conv responsible for the drug's activity. The mechanism of action of dextroamphetamine in the treatment of attention-de Amphetamines may block the reuptake of norepinephrine and dopamine at the presynaptic neuron and thus increa dopamine into the extraneuronal space (Prod Info VYVANSE(TM) oral capsules, 2007).

4.5 Therapeutic Uses

4.5.A Lisdexamfetamine Dimesylate

4.5.A.1 Attention deficit hyperactivity disorder

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes; Pediatric, yes (age 6 to 12 years)
Efficacy: Adult, Evidence favors efficacy; Pediatric, Effective
Recommendation: Adult, Class IIb; Pediatric, Class IIa
Strength of Evidence: Adult, Category B; Pediatric, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Approved for the treatment of Attention-Deficit/Hyperactivity Disorder in children aged 6 to 12 and ac 2008)
In a 4-week, randomized, double-blind, placebo-controlled, parallel-group study (n=420), lisdexamfe in the treatment of adults meeting Diagnostic and Statistical Manual of Mental Disorders-Fourth Edit VYVANSE(R) oral capsules, 2008)
In a 4-week, multicenter, randomized, double-blind, fixed-dose study (n=290), lisdexamfetamine dim treatment of children aged 6 to 12 meeting Diagnostic and Statistical Manual of Mental Disorders-Fo or hyperactive-impulsive type ADHD (Biederman et al, 2007)

c) Adult:

1) Lisdexamfetamine mesylate was effective and well tolerated in the treatment of adult ADHD in a rand parallel-group study. Adults meeting the Diagnostic and Statistical Manual of Mental Disorders-Fourth Ed to receive fixed doses of either 30 milligrams (mg), 50 mg, or 70 mg of lisdexamfetamine (n=358) or plac Lisdexamfetamine was initiated at 30 mg and titrated in weekly increments of 20 mg to achieve the 50 ar ratings on the ADHD Rating Scale (ADHD-RS), significant improvements occurred for all lisdexamfetami Treatment-emergent adverse events occurring commonly and more frequently than placebo included dry nausea (7% vs 0%), decreased appetite (27% vs 3%), insomnia (27% vs 8%), and anxiety (6% vs 0%) (

d) Pediatric:

1) Lisdexamfetamine was effective and well tolerated for the treatment of children with combined type o Deficit/Hyperactivity Disorder (ADHD) in a multicenter, randomized, double-blind, fixed-dose study of 4 w 1.8 years) were included if their ADHD Rating Scale version IV (ADHD-RS-IV) was 28 or greater. Childre dimesylate 30 milligrams (mg) once in the morning for 4 weeks (n=71), 50 mg once in the morning (30 m to 4) for 4 weeks (n=74), 70 mg once in the morning (30 mg for 1 week, then titrated to 50 mg for week 2 (n=73), or placebo for 4 weeks (n=72). The primary efficacy endpoint was the mean change from baselir ADHD-RS-IV rated 18 symptoms on a scale of 0 (no symptoms) to 3 (severe symptoms) based on the in

and child. The majority of patients were male (69%), treatment-naive (59.2% to 69.9%), and diagnosed v
ADHD-RS-IV score improved 4- to 5-fold for each lisdexamfetamine dose group relative to the placebo (
improvement was demonstrated in the 70-mg dose group (-26.7 (standard deviation (SD), 1.54)) compar
0.001). Improvement was noticed for all dose groups during the first week with continued improvement th
Conners' Parent Rating Scale-Revised: Short Form (CPRS-R), a 27-question parent rating of the childs's
and ADHD index, at three times through the day (up to 6 PM). Compared with the placebo group, the CP
(morning, afternoon, and evening) improved significantly starting at week 1 through week 4 for all dose g
mg dose group experiencing the greatest improvement. Adverse events were primarily mild to moderate
mostly in the first week. The most common adverse events experienced in the lisdexamfetamine and pla
appetite (39% and 4%, p less than or equal to 0.05), insomnia (19% and 3%, p less than or equal to 0.05
significant), headache (12% and 10%, p = not significant), irritability (10% and 0%, p less than or equal t
significant), weight decrease (9% and 1%, p less than or equal to 0.05), and nausea (6% and 3%, p = no
demonstrated in mean ECG parameters (including QT intervals), laboratory values, or blood pressure fo
2007).

2) Treatment with lisdexamfetamine mesylate led to a significant difference in patient behavior compare
crossover design, analog classroom study in children aged 6 to 12 years (n=52) meeting the Diagnostic
Fourth Edition criteria for ADHD (combined type or hyperactive-impulsive type). Subsequent to a 3-week
amphetamine/dextroamphetamine (Adderall XR(R)) 10 to 30 milligrams (mg) daily, patients were randon
amphetamine/dextroamphetamine, lisdexamfetamine mesylate (30, 50, or 70 mg/day), or placebo once
lasted for 1 week. Efficacy was assessed as the mean of investigator ratings on the Swanson, Kotkin, Al
scores over 8 sessions of a 12 hour treatment day (Prod Info VYVANSE(R) oral capsules, 2008).

6.0 References

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Last Modified: June 18, 2009

DRUGDEX® Evaluations

SERTRALINE

0.0 Overview

1) Class
- **a)** This drug is a member of the following class(es):
  Antidepressant
  Central Nervous System Agent
  Serotonin Reuptake Inhibitor

2) Dosing Information
- **a)** Sertraline Hydrochloride
  - **1)** Adult
    - **a)** Major depressive disorder
      - **1)** 50 mg/day ORALLY as a single dose in the morning or the evening; dosage may be increased at inte
    - **b)** Obsessive-compulsive disorder
      - **1)** 50 mg/day ORALLY as a single dose in the morning or the evening; dosage may be increased at inte
    - **c)** Panic disorder
      - **1)** 25 mg/day ORALLY for 1 week, then increase to 50 mg/day; dosage may then be increased at interv
    - **d)** Posttraumatic stress disorder
      - **1)** 25 mg/day ORALLY for 1 week, then increase to 50 mg/day; dosage may then be increased at interv
    - **e)** Premenstrual dysphoric disorder
      - **1)** daily dosing, 50 mg/day ORALLY as a single dose in the morning or the evening throughout the men
        150 mg/day (Prod Info Zoloft(R), 2002)
      - **2)** luteal phase dosing, 50 mg/day ORALLY only during the luteal phase; dosage may be increased to 1
        cycle should begin with 50 mg/day for 3 days before increasing the dosage to 100 mg/day (Prod Info Zol
    - **f)** Social phobia
      - **1)** 25 mg/day ORALLY for 1 week, then increase to 50 mg/day; dosage may then be increased at interv
  - **2)** Pediatric
    - **a)** Obsessive-compulsive disorder
      - **1)** children 6-12 yr, 25 mg/day ORALLY as a single dose in the morning or the evening; dosage may be
        (R), 2002)
      - **2)** children 13-17 yr, 50 mg/day ORALLY as a single dose in the morning or the evening; dosage may b
        Zoloft(R), 2002)

3) Contraindications
- **a)** Sertraline Hydrochloride
  - **1)** concomitant use of disulfiram (oral concentrate) (Prod Info ZOLOFT(R) concentrate, oral tablets, 2009)
  - **2)** concomitant use of monoamine oxidase inhibitors (MAOIs) or pimozide (Prod Info ZOLOFT(R) concentrate, or
  - **3)** hypersensitivity to sertraline or any other component of the product (Prod Info ZOLOFT(R) concentrate, oral ta

4) Serious Adverse Effects
- **a)** Sertraline Hydrochloride
  - **1)** Bleeding, Abnormal
  - **2)** Depression, exacerbation
  - **3)** Hypomania
  - **4)** Hyponatremia
  - **5)** Mania
  - **6)** Seizure
  - **7)** Serotonin syndrome
  - **8)** Suicidal thoughts
  - **9)** Suicide

5) Clinical Applications
- **a)** Sertraline Hydrochloride
  - **1)** FDA Approved Indications
    - **a)** Major depressive disorder
    - **b)** Obsessive-compulsive disorder
    - **c)** Panic disorder
    - **d)** Posttraumatic stress disorder
    - **e)** Premenstrual dysphoric disorder
    - **f)** Social phobia

1.0 Dosing Information

Drug Properties

Storage and Stability

Adult Dosage

Pediatric Dosage

1.1 Drug Properties

A) Information on specific products and dosage forms can be obtained by referring to the Tradename List (Product In

B) Synonyms

Sertraline
Sertraline HCl
Sertraline Hydrochloride

C) Physicochemical Properties

1) Molecular Weight

a) Sertraline hydrochloride: 342.7 (Fleeger, 1996)

2) Solubility

a) Systemic: Sertraline hydrochloride is slightly soluble in water and sparingly soluble in ethyl alcohol (Prod I

1.2 Storage and Stability

A) Sertraline Hydrochloride

1) Preparation

a) Oral route

1) The oral concentrate formulation of sertraline should be diluted in 4 ounces (½ cup) using only water, (Prod Info ZOLOFT(R) tablets and oral concentrate, 2005).

B) Oral route

1) Tablets and oral concentrate should be stored at a controlled room temperature of 25 degrees Celsius (77 deg are permitted (Prod Info Zoloft(R), 2002).

1.3 Adult Dosage

Normal Dosage

Dosage in Renal Failure

Dosage in Hepatic Insufficiency

Dosage in Geriatric Patients

1.3.1 Normal Dosage

1.3.1.A Sertraline Hydrochloride

1.3.1.A.1 Oral route

Dysthymia

Major depressive disorder

Obsessive-compulsive disorder

Panic disorder

Posttraumatic stress disorder

Premenstrual dysphoric disorder

Social phobia

1.3.1.A.1.a Dysthymia

1) A dose of sertraline 50 milligrams (mg) daily orally as a single dose in the morning or the evening controlled trial. Dose increases up to a maximum of 200 mg/day were allowed (Ravindran et al, 200

1.3.1.A.1.b Major depressive disorder

1) The initial recommended dosage is 50 milligrams daily as a single dose in the morning or the eve recommended dosage of 200 milligrams daily (Prod Info Zoloft(R), 2002).

2) Sertraline oral concentrate contains 20 milligrams/milliliter (mg/mL). Immediately before taking se lemon/lime soda, lemonade, or orange juice. After mixing, a slight haze may appear; this is normal. contains dry natural rubber (Prod Info Zoloft(R), 2002).

a) DURATION OF THERAPY

1) Clinical trials have suggested that depressed patients responding during the first 8 weel term studies of sertraline efficacy have not been completed, treatment of depression gener unknown whether the dose of sertraline required to maintain euthymia is the same as that r

1.3.1.A.1.c Obsessive-compulsive disorder

1) The initial dosage is 50 milligrams once daily in the morning or evening. If 50 milligrams does not daily at intervals of at least 1 week (Prod Info Zoloft(R), 2002).

2) Sertraline oral concentrate contains 20 milligrams/milliliter (mg/mL). Immediately before taking se lemon/lime soda, lemonade, or orange juice. After mixing, a slight haze may appear; this is normal. contains dry natural rubber (Prod Info Zoloft(R), 2002).

a) DURATION OF THERAPY

1) Efficacy of sertraline therapy in obsessive compulsive disorder has not been documente disorder, therapy should be continued for responding patients. Periodic determination of th provide the patient with the lowest effective dose (Prod Info Zoloft(R), 2002).

1.3.1.A.1.d Panic disorder

1) The initial recommended dosage is 25 milligrams (mg) once daily, taken in the morning or evenir still inadequate, the dosage may be increased at intervals of 1 week to a maximum of 200 mg/day (

2) Sertraline oral concentrate contains 20 milligrams/milliliter (mg/mL). Immediately before taking se lemon/lime soda, lemonade, or orange juice. After mixing, a slight haze may appear; this is normal. contains dry natural rubber (Prod Info Zoloft(R), 2002).

a) DURATION OF THERAPY

1) Efficacy of sertraline therapy in panic disorder has not been documented for longer thar therapy should be continued for responding patients. Periodic determination of the need fo patient with the lowest effective dose (Prod Info Zoloft(R), 2002).

1.3.1.A.1.e Posttraumatic stress disorder

1) The initial recommended dosage is 25 milligrams (mg) once daily, taken in the morning or evenir still inadequate, the dosage may be increased at intervals of 1 week to a maximum of 200 mg/day (

2) Sertraline oral concentrate contains 20 milligrams/milliliter (mg/mL). Immediately before taking se lemon/lime soda, lemonade, or orange juice. After mixing, a slight haze may appear; this is normal. contains dry natural rubber (Prod Info Zoloft(R), 2002).

1.3.1.A.1.f Premenstrual dysphoric disorder

1) CONTINUOUS DOSING

a) Premenstrual dysphoric disorder (PMDD) may be treated with sertraline either throughout th dosing). For continuous dosing, sertraline should be started at 50 milligrams (mg) per day (mor day. Dosage adjustments, if needed, should be made in 50 mg increments at the onset of each

2) LUTEAL PHASE DOSING

a) Premenstrual dysphoric disorder (PMDD) may be treated with sertraline either throughout th dosing). For luteal phase dosing, sertraline should be started at 50 milligrams (mg) per day (mo day. For doses higher than 50 mg, use a 50 mg/day titration step for three days at the beginnin

1.3.1.A.1.g Social phobia

1) The initial recommended dosage is 25 milligrams (mg) once daily, taken in the morning or evenir still inadequate, the dosage may be increased at intervals of 1 week to a maximum of 200 mg/day (

a) DURATION OF THERAPY

1) Sertraline in doses of 50 to 200 milligrams per day was effective in the treatment of adu trials. Dosages should be adjusted to the lowest effective dose and periodic determinations

1.3.1.A.2 MAXIMUM DOSE

a) Recommended maximum is 200 milligrams daily (Prod Info Zoloft(R), 2002).

1.3.2 Dosage in Renal Failure

A) Sertraline Hydrochloride

1) In patients with renal impairment, dosage adjustment is NOT necessary. Sertraline is extensively metabol Zoloft(R), 2002).

1.3.3 Dosage in Hepatic Insufficiency

A) Sertraline Hydrochloride

1) Sertraline is extensively metabolized in the liver. In patients with hepatic impairment or cirrhosis, a lower c

1.3.4 Dosage in Geriatric Patients

A) Sertraline Hydrochloride

1) Although no specific dosage adjustments have been recommended for sertraline use in geriatric patients, patients treated with a dose of 100 milligrams daily for 14 days. Steady-state clearance is achieved in 2-3 we but not in females (Prod Info Zoloft(R), 2002). Since steady state may take longer to achieve in elderly, dose

1.4 Pediatric Dosage

Normal Dosage

Dosage in Hepatic Insufficiency

1.4.1 Normal Dosage

1.4.1.A Sertraline Hydrochloride

1.4.1.A.1 Oral route

1.4.1.A.1.a Obsessive-compulsive disorder

1) The initial recommended dose is 25 milligrams (mg) once daily in children 6 to 12 years of age o 200 mg/day in clinical trials which established efficacy in the pediatric population; however, dosage may be administered in the morning or evening (Prod Info Zoloft(R), 2002).

2) Sertraline oral concentrate contains 20 milligrams/milliliter (mg/mL). Immediately before taking se lemon/lime soda, lemonade, or orange juice. After mixing, a slight haze may appear; this is normal. contains dry natural rubber (Prod Info Zoloft(R), 2002).

1.4.3 Dosage in Hepatic Insufficiency

A) Sertraline Hydrochloride

1) In patients with hepatic impairment, a lower or less frequent dosage interval should be used (Prod Info Zo

2.0 Pharmacokinetics

Onset and Duration

Drug Concentration Levels

ADME

2.1 Onset and Duration

A) Onset

1) Initial Response

a) Depression, regular release: 2 weeks (Reimherr et al, 1988).

2) Peak Response

a) Depression, regular release: 6 weeks (Amin et al, 1989a; Doogan & Caillard, 1988).

2.2 Drug Concentration Levels

A) Time to Peak Concentration

1) Oral, regular release: 4 to 8 hours (Prod Info Zoloft(R), 2002w; Doogan & Caillard, 1988; Saletu et al, 1986).

a) The Cmax after continuous administration of sertraline 200 mg/day was 165 ng/mL (children 6 to 12 years

b) A study of 22 young (less than 45 years) and elderly (greater than 65 years) healthy male and female volu and elderly groups after continuous administration of 200 mg for 21 days (Ronfeld et al, 1997).

c) The time of administration (morning versus evening) did NOT affect mean peak plasma sertraline concent single doses of 100 mg. Although no specific recommendation can be made, it appears that sertraline may b 1997a).

d) A mean peak plasma sertraline concentration of 54.5 ng/mL was observed 4 hours after a single 100-milli were 105.4 and 253.2 ng/mL, respectively, at 6 hours post-dosing (Saletu et al, 1986).

B) Area Under the Curve

1) 2296 to 3107 ng-hr/mL (Prod Info Zoloft(R), 2002w).

a) The AUC was 3107 ng-hr/mL (children 6 to 12 years), 2296 ng-hr/mL (adolescents 13 to 17 years), and 2

2002w).

2.3 ADME

Absorption

Distribution

Metabolism

Excretion

Elimination Half-life

Extracorporeal Elimination

2.3.1 Absorption

A) Bioavailability

1) Oral, regular release: complete (Prod Info Zoloft(R), 2002w; Doogan & Caillard, 1988).

a) Single dose bioavailability studies have shown that the tablets and oral solution are approximately eq

b) The time of day of administration (morning versus evening) did NOT affect the area under the curve (mean terminal elimination half-life, or mean elimination rate constant, in 22 healthy male volunteers who appears that sertraline may be administered in the morning or evening without bioavailability differences

B) Effects of Food

1) small (Prod Info Zoloft(R), 2002w).

a) For the tablet, food increased the mean peak plasma concentration by 25%, and it decreased the tim (Prod Info Zoloft(R), 2002w).

2.3.2 Distribution

A) Distribution Sites

1) Protein Binding

a) 99% (Doogan & Caillard, 1988).

B) Distribution Kinetics

1) Volume of Distribution

a) 20 L/kg (Doogan & Caillard, 1988).

2.3.3 Metabolism

A) Metabolism Sites and Kinetics

1) Liver, extensive (Prod Info Zoloft(R), 2002w).

a) Sertraline undergoes extensive first-pass metabolism (Prod Info Zoloft(R), 2002w).

b) Sertraline is primarily metabolized via N-demethylation to desmethylsertraline, which is weakly active hydroxylated. The alpha-hydroxy ketone metabolite is excreted in the urine and feces (Doogan & Caillard

B) Metabolites

1) Desmethylsertraline, weakly active (Doogan & Caillard, 1988).

2) Alcohol metabolites, inactive (Doogan & Caillard, 1988).

3) Oxime metabolites, inactive (Doogan & Caillard, 1988).

2.3.4 Excretion

A) Kidney

1) Renal Excretion (%)

a) 40% to 45% (Prod Info Zoloft(R), 2002w).

2) None of the dose is recovered as unchanged sertraline (Prod Info Zoloft(R), 2002w). The alpha-hydroxy k

B) Other

1) OTHER EXCRETION

a) Feces, 40% to 45% (Prod Info Zoloft(R), 2002w).

b) About 12-14% of sertaline is found unchanged in the feces along with the alpha-hydroxy ketone meta

2.3.5 Elimination Half-life

A) Parent Compound

1) ELIMINATION HALF-LIFE

a) 24 hours (Doogan & Caillard, 1988; Saletu et al, 1986).

1) The half-life after continuous administration of sertraline 200 mg/day was 26.2 hours (children 6 t 2002w).

2) A study of 22 young (less than 45 years) and elderly (greater than 65 years) healthy male and fe

exhibited a 50% shorter half-life (mean 22 hours) compared to the other groups (32 to 36 hours) (Rc
3) The time of day of administration (morning versus evening) did NOT affect mean terminal elimina
single doses of 100 mg (Ronfeld et al, 1997a).

B) Metabolites

1) Desmethylsertraline, 62 to 104 hours (Doogan & Caillard, 1988; Saletu et al, 1986; Prod Info Zoloft(R), 20

2.3.6 Extracorporeal Elimination

A) Hemodialysis

1) Dialyzable: No (Schwenk et al, 1995).

a) In 2 patients undergoing hemodialysis with a Baxter CA-110 hollow fiber dialysis filter, no sertraline w
the dialysis time was 4 and 3.63 hours for patient 1 and 2, respectively (Schwenk et al, 1995).

3.0 Cautions

Contraindications

Precautions

Adverse Reactions

Teratogenicity/Effects in Pregnancy/Breastfeeding

Drug Interactions

3.0.A Black Box WARNING

1) Sertraline Hydrochloride

a) Oral (Solution; Tablet)

Suicidality and Antidepressant Drugs
Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in child
(MDD) and other psychiatric disorders. Anyone considering the use of sertraline hydrochloride or any other a
need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to
compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are ther
started on antidepressant therapy should be monitored appropriately and observed closely for clinical worser
advised of the need for close observation and communication with the prescriber. Sertraline hydrochloride is
disorder (OCD) (Prod Info ZOLOFT(R) concentrate, oral tablets, 2009).

3.1 Contraindications

A) Sertraline Hydrochloride

1) concomitant use of disulfiram (oral concentrate) (Prod Info ZOLOFT(R) concentrate, oral tablets, 2009)
2) concomitant use of monoamine oxidase inhibitors (MAOIs) or pimozide (Prod Info ZOLOFT(R) concentrate, or
3) hypersensitivity to sertraline or any other component of the product (Prod Info ZOLOFT(R) concentrate, oral ta

3.2 Precautions

A) Sertraline Hydrochloride

1) suicidal ideation and behavior or worsening depression; increased risk, particularly in children, adolescents, ar
(Prod Info ZOLOFT(R) concentrate, oral tablets, 2009)
2) abnormal bleeding has been reported, including life-threatening hemorrhages (Prod Info ZOLOFT(R) concentr
3) abrupt withdrawal; serious discontinuation symptoms have been reported (Prod Info ZOLOFT(R) concentrate,
4) bipolar disorder; increased risk of precipitation of a mixed/manic episode (Prod Info ZOLOFT(R) concentrate, c
5) Concomitant use of NSAIDs, aspirin, warfarin, or other drugs that affect coagulation; monitoring recommended
tablets, 2009)
6) concomitant use of serotonergic drugs (serotonin precursors (tryptophan), SSRIs, serotonin-norepinephrine re
tablets, 2009)
7) conditions or diseases that may affect metabolism or hemodynamic response (Prod Info ZOLOFT(R) concentr
8) latex allergy; oral concentrate dropper dispenser contains dry natural rubber (Prod Info ZOLOFT(R) concentra
9) liver disease or impairment; risk of drug toxicity; lower or less frequent dose may be required (Prod Info ZOLO
10) mania, history; risk of activation of mania/hypomania (Prod Info ZOLOFT(R) concentrate, oral tablets, 2009)
11) seizures, history (Prod Info ZOLOFT(R) concentrate, oral tablets, 2009)
12) serotonin syndrome has been reported, including cases that are life-threatening or that resemble neuroleptic
tablets, 2009)
13) use of sertraline within 14 days of MAOI discontinuation (Prod Info ZOLOFT(R) concentrate, oral tablets, 200
14) use of MAOIs within 14 days after sertraline discontinuation (Prod Info ZOLOFT(R) concentrate, oral tablets,
15) volume-depleted, elderly, or concurrent diuretic therapy; hyponatremia, syndrome of inappropriate antidiuretic
concentrate, oral tablets, 2009)

3.3 Adverse Reactions

Cardiovascular Effects

Dermatologic Effects

Endocrine/Metabolic Effects

Gastrointestinal Effects

Hematologic Effects

Hepatic Effects

Immunologic Effects

Musculoskeletal Effects

Neurologic Effects

Ophthalmic Effects

Psychiatric Effects

Renal Effects

Reproductive Effects

Respiratory Effects

Other

3.3.1 Cardiovascular Effects

3.3.1.A Sertraline Hydrochloride

Angina

Cardiac dysrhythmia

Cardiovascular finding

EKG finding

Syncope

3.3.1.A.1 Angina

a) Summary

1) CASE REPORT - A case report notes the occurrence angina along with shortness of breath and were severe enough to warrant hospitalization and withdrawal of treatment. Authors postulate that ir vasoconstriction. This results from the inability of the endothelium to produce sufficient endothelium- al, 1997).

b) LITERATURE REPORTS

1) An 81-year-old woman developed nausea and severe, crushing, retrosternal chest pain with sho milligrams. The pain worsened over the subsequent 2 hours and required hospitalization. The cardio were also normal. The electrocardiogram revealed normal sinus rhythm with nonspecific ST-T wave

acetylsalicylic acid, intravenous (IV) heparin, IV nitroglycerin, and diltiazem; sertraline was stopped. coronary artery and circumflex artery, respectively. Although it is difficult to attribute angina to sertra atherosclerotic coronary arteries causes vasoconstriction. This results from the inability of the endot vasoconstriction caused by serotonin (Sunderji et al, 1997).

3.3.1.A.2 Cardiac dysrhythmia

a) Summary

1) In postmarketing evaluation, AV BLOCK and VENTRICULAR TACHYCARDIA, including TORSA sertraline (Prod Info Zoloft(R), 2002).

3.3.1.A.3 Cardiovascular finding

a) Summary

1) Sertraline has been associated with PALPITATIONS, CHEST PAIN, HYPERTENSION, HYPOTE

b) Arrhythmias, palpitations, electrocardiogram changes, chest pain, hypertension, hypotension, edema

c) In a large cohort study including 481,744 persons and 1487 cases of SUDDEN CARDIAC DEATH oc associated with an increased risk of sudden cardiac death (rate ratio, 0.95; 95% CI, 0.42 to 2.15). In con equivalent) had a 41% increased rate of sudden cardiac death (rate ratio, 1.41; 95% CI, 1.02 to 1.95) (R

3.3.1.A.4 EKG finding

a) Summary

1) Electrocardiographic abnormalities were noted in 2 of 8 patients taking sertraline, 200 milligrams clinically significant Q-T INTERVAL PROLONGATION. Additional data are necessary to establish a

3.3.1.A.5 Syncope

a) Three patients with neurally mediated syncope, which was exacerbated following the use of sertraline

3.3.2 Dermatologic Effects

3.3.2.A Sertraline Hydrochloride

Dermatological finding

Night sweats

Stevens-Johnson syndrome

3.3.2.A.1 Dermatological finding

a) Summary

1) Infrequently, RASH, ACNE, PRURITUS, ALOPECIA, DERMATITIS, and PHOTOSENSITIVITY F

b) Infrequently, rash, acne, pruritus, alopecia, dermatitis, and photosensitivity reaction have been assoc have also been noted.

3.3.2.A.2 Night sweats

a) Summary

1) CASE REPORT - Progressively worse night sweats developed in a young woman treated with se with progressive worsening of night sweats. The patient stopped sertraline abruptly and noted resolu noted mild daytime sweating. After switching sertraline to fluoxetine, she had no further episodes of

3.3.2.A.3 Stevens-Johnson syndrome

a) Summary

1) CASE REPORT - A 96-year-old woman developed cutaneous and mucosal eruptions 3 weeks a atypical flat lesions were found on the face, trunk, and proximal limbs. Painful, oral erosions and cor days after sertraline and arginine chlorhydrate were stopped, the skin lesions disappeared. The auth distribution, atypical flat appearance, and total necrolysis of the epidermis. Other medications or dis

3.3.3 Endocrine/Metabolic Effects

3.3.3.A Sertraline Hydrochloride

Decreased uric acid level

Disorder of fluid AND/OR electrolyte

Endocrine finding

Galactorrhea

Gynecomastia

Hyperglycemia

Hyponatremia

Hypothyroidism

Metabolic finding

Syndrome of inappropriate antidiuretic hormone secretion

3.3.3.A.1 Decreased uric acid level

a) Summary

1) A small decrease in serum uric acid (7%) has been occasionally associated with sertraline therap

3.3.3.A.2 Disorder of fluid AND/OR electrolyte

a) Hyponatremia, which in some cases may be related to syndrome of inappropriate antidiuretic hormon

3.3.3.A.3 Endocrine finding

a) A small decrease in serum uric acid has been occasionally associated with therapeutic sertraline use reported. Syndrome of inappropriate antidiuretic hormone (SIADH) has also been reported in patients of

3.3.3.A.4 Galactorrhea

a) Summary

1) Sertraline therapy has been associated with galactorrhea. The probable mechanism for SSRI-inc stimulation of postsynaptic serotonin receptors in the hypothalamus or presynaptic serotonin recepto

b) LITERATURE REPORTS

1) Galactorrhea associated with sertraline was reported in a 37-year-old woman with a 1-year histo intolerable nausea developed, she was switched to sertraline 50 mg daily. After 2 weeks, the dosag beginning treatment. Sertraline was discontinued, and lactation ceased 21 days later. She was rece Stahl, 1993). Sixteen anecdotal cases of galactorrhea associated with sertraline have been reported have been reported in approximately 36 patients (Pers Comm, 1994).

3.3.3.A.5 Gynecomastia

a) Summary

1) Gynecomastia has been reported with sertraline use (Prod Info Zoloft(R), 2002). BREAST PAIN,

3.3.3.A.6 Hyperglycemia

a) Summary

1) Hyperglycemia was reported following the administration of sertraline for the treatment of depres Following the initiation of sertraline (12.5 milligrams (mg)/day, titrated weekly to 50 mg/day), the wor 116.3 mg/deciliter (dL) to 180.3 mg/dL. Laboratory studies revealed an increase in fasting serum glu treatment. During sertraline therapy, the patient lost 4 pounds and reported a reduction in carbohydr

3.3.3.A.7 Hyponatremia

a) Summary

1) The use of sertraline by elderly patients has been associated with cases of clinically significant h antidiuretic hormone secretion (SIADH) has also been reported following therapy. This effect has be frequently in patients over 65 years of age (Pecora et al, 1997)(Jackson et al, 1995; Leung & Remic Resch, 1995).

b) Incidence: rare

3.3.3.A.8 Hypothyroidism

a) Summary

1) Patients with thyroid disease who are also receiving treatment for depression should have thyroi levels and small increases in serum thyrotropin levels after starting treatment with sertraline and oth

3.3.3.A.9 Metabolic finding

a) Summary

1) HYPOGLYCEMIA, or HYPERCHOLESTEROLEMIA, and HYPERTRIGLYCERIDEMIA have bee DECREASED WEIGHT was also reported in at least 2% of pediatric patients during clinical trials of

b) Weight loss, hypoglycemia, hypercholesterolemia, hyperglycemia, and hypertriglyceridemia has occu

3.3.3.A.10 Syndrome of inappropriate antidiuretic hormone secretion

a) Summary

1) Sertraline has been associated with syndrome of inappropriate antidiuretic hormone secretion (S occurs between 3 days and 4 month after beginning therapy (Woo & Smythe, 1997; Bradley et al, 1

b) LITERATURE REPORTS

1) Of the 25 case reports of selective serotonin reuptake inhibitor (SSRI)-induced SYNDROME OF published, the majority occurred in patients over 70 years of age. Based on published reports, the o included confusion, lethargy, dizziness, fatigue, anorexia, delirium, and abdominal pain. Abnormal la (milliosmole/liter) mOsm/L; range 214 to 272 mOsm/L), decreased serum sodium concentration (me (median 392.5 mOsm/L; 229 to 613 mOsm/L). In all but 1 case, the selective serotonin reuptake inh patient was also treated with sodium chloride 3%. Patients in their fifties generally recovered in 2 to the 6 patients rechallenged with an SSRI, 3 developed a decrease in serum sodium consistent with adequately report symptoms, laboratory results, and exclusion of other causes making it difficult to a

2) Three days after starting sertraline 50 milligrams daily, a 78-year-old woman was diagnosed with encephalopathic and had myoclonus. Her serum sodium decreased from 136 milliequivalents/liter (n 125 mEq/L and 474 milliosmoles/kilogram (mOsm/kg), respectively, compared to a plasma osmolali mL of sodium chloride 3%, (3) restricting fluid intake to 1000 mL/day, and (4) initiating demeclocyclin sodium returned to 138 mEq/L within 3 days. Other drugs and medical conditions were considered u reported although symptoms occurred later, after 5 days and 4 months; discontinuation of sertraline 1996).

3.3.4 Gastrointestinal Effects

3.3.4.A Sertraline Hydrochloride

Gastrointestinal hemorrhage

Gastrointestinal tract finding

Grinding teeth

Nausea and vomiting

Pancreatitis

Xerostomia

3.3.4.A.1 Gastrointestinal hemorrhage

See Drug Consult reference: CONCOMITANT USE OF SSRIs AND NSAIDs - INCREASED RISK OF GA

3.3.4.A.2 Gastrointestinal tract finding

a) Summary

1) During placebo-controlled clinical trials, the following were reported in adults at an incidence grea FLATULENCE (Prod Info Zoloft(R), 2002). Infrequently, sertraline has been reported to cause INDIG

b) Infrequently, sertraline has been reported to cause diarrhea, indigestion, dry mouth, abdominal pain, flatulence, nausea and vomiting have occurred more frequently. Minimal weight loss (mean 1-2 pounds)

3.3.4.A.3 Grinding teeth

a) Sertraline-induced bruxism has occurred after exposure to daily doses ranging from 6.25 to 150 mg, v Stanziani, 1993). Dose reduction from 25 mg/day to 6.25 mg/day failed to relieve symptoms in one 36-ye with longstanding anxiety disorder and depression had her 100 mg/day sertraline discontinued, with an 1 patient's mood deteriorated. Replacement of paroxetine with fluvoxamine (dosage not reported) resulted failed to alleviate her bruxism (Fitzgerald & Healy, 1995).

3.3.4.A.4 Nausea and vomiting

a) Summary

1) During placebo-controlled clinical trials, nausea, and vomiting were reported in adults with sertral vomiting were noted 4 to 6 hours after single doses of 100 milligrams in one study, and were reporte

b) LITERATURE REPORTS

1) The selective serotonin reuptake inhibitors (SSRIs) produce nausea and vomiting in 20% to 25% decreases or resolves over approximately 3 weeks. However, in others, reduction of the dose or dis for a few weeks may facilitate continued treatment with the SSRI. Limited data suggest that ondanse

with careful monitoring for arrhythmias may be more cost effective than ondansetron. The proposed the chemoreceptor trigger zone and area postrema in the brainstem, the primary areas within the br

3.3.4.A.5 Pancreatitis

a) Summary

1) Pancreatitis has been temporally associated with the use of sertraline (Prod Info Zoloft(R), 2002)

3.3.4.A.6 Xerostomia

a) Summary

1) Several studies have reported XEROSTOMIA as an occasional adverse effect of sertraline in the

3.3.5 Hematologic Effects

3.3.5.A Sertraline Hydrochloride

Disorder of hemostatic system

Hematology finding

3.3.5.A.1 Disorder of hemostatic system

a) Summary

1) Rare occurrences (incidence less than 0.1%) of BRUISING, ECCHYMOSES, EPISTAXIS, PROL therapy. The majority of cases have been reported in patients taking fluoxetine but case reports are

b) LITERATURE REPORTS

1) INCIDENCE

a) Rare (incidence less than 0.1%). The majority of cases have been reported in patients takin (Berk & Jacobson, 1998).

2) OUTCOME

a) Mild (treatment continued with/without other management) (Berk & Jacobson, 1998).

3) ASSOCIATED SYMPTOMS

a) Symptoms include: bruising, ecchymoses, epistaxis, prolonged bleeding time, rectal bleedin

4) CLINICAL MANAGEMENT

a) PHARMACOLOGIC - For minor bleeding diatheses (ie, bruising), treatment is usually unnec clinically significant, occurs with other underlying medical illnesses, or fails to improve with time

5) PREDISPOSING RISK FACTORS

a) DOSE-RELATED

1) Yes. Many cases have occurred in patients taking doses at the higher end of the dose r

b) DISEASE STATES

1) Yes. More common in patients with underlying diseases; 1 case occurred in a patient w

6) PROBABLE MECHANISM

a) PHARMACOLOGIC (extension of the expected effects of the drug). Selective serotonin reup storage of serotonin is observed. Serotonin-mediated platelet aggregation may be decreased (E

7) DOCUMENTATION QUALITY

a) Fair

8) CASE REPORT

a) A case of prolonged bleeding time associated with ecchymoses and normal prothrombin and resolved spontaneously with drug cessation (Calhoun & Calhoun, 1996a).

3.3.5.A.2 Hematology finding

a) Summary

1) AGRANULOCYTOSIS, APLASTIC ANEMIA, and THROMBOCYTOPENIA have been reported a

b) Sertraline therapy has been associated with bruising, ecchymoses, epistaxis, prolonged bleeding tim thrombocytopenia. Rare cases of impaired platelet aggregation have been reported.

c) Purpura has been reported in at least 2% of pediatric patients treated with sertraline (Prod Info Zoloft

3.3.6 Hepatic Effects

3.3.6.A Sertraline Hydrochloride

Increased liver enzymes

Liver failure

Liver finding

3.3.6.A.1 Increased liver enzymes

a) Summary

1) Asymptomatic elevations in serum transaminases have been reported within the first 9 weeks of (Prod Info Zoloft(R), 2002).

3.3.6.A.2 Liver failure

a) Summary

1) Liver failure has been temporally associated with the use of sertraline (Prod Info Zoloft(R), 2002)

3.3.6.A.3 Liver finding

a) Elevated liver enzymes and liver failure have been noted occasionally with therapeutic sertraline use.

3.3.7 Immunologic Effects

3.3.7.A Sertraline Hydrochloride

3.3.7.A.1 Anaphylaxis

a) Summary

1) In postmarketing surveillance, ANAPHYLACTOID REACTIONS have been associated with use c

3.3.8 Musculoskeletal Effects

3.3.8.A Sertraline Hydrochloride

Arthralgia

Fracture of bone

Fracture of bone, Nonvertebral

Muscle weakness

Myalgia

Summary

3.3.8.A.1 Arthralgia

a) Incidence: 0.1% to 1% (Prod Info ZOLOFT(R) concentrate, oral tablets, 2009)

b) Arthralgia was reported in 0.1 to 1% of over 4000 adult patients exposed to multiple doses of sertralir concentrate, oral tablets, 2009).

3.3.8.A.2 Fracture of bone

a) In a case-control study including fracture cases (n=124,655) during the year 2000 and age- and gend participants who were using an average standard daily dose of sertraline (adjusted odds ratio (OR), 1.25 use was associated with an increased risk of hip fracture (adjusted OR, 1.76; 95% CI, 1.52 to 2.03), fore 1.74; CI, 1.26 to 2.41) (Vestergaard et al, 2008)

b) In a population-based, randomly selected, prospective cohort study adjusted for potential covariates, years of age and older who used daily SSRIs (n=137; mean age of 65.1 years), including sertraline, com use was associated with a significant 2.1-fold increased risk of fragility fracture (95% confidence interval fragility fracture (95% CI, 1.1 to 2.1). Daily SSRI users who were recurrent (ie, treated with SSRIs at bas (95% CI, 1.1 to 4.0). Fractures were reported at the following sites: forearm (40%), ankle and foot (21%), or fingers (Richards et al, 2007).

3.3.8.A.3 Fracture of bone, Nonvertebral

a) In a prospective, population-based, cohort study (n=7983) with a mean follow-up of 8.4 years, there w age (mean age of 77.5 years) who were currently using an SSRI (citalopram, escitalopram, fluoxetine, flu antidepressants. Current SSRI use was associated with an increased risk of nonvertebral fracture (adjus antidepressant use. Current SSRI use was also associated with an increased risk of nonvertebral fractur (n=1217). In addition, duration of SSRI use showed a 9% increase in fracture risk per extra month on an humerus, and pelvis were reported (Ziere et al, 2008).

3.3.8.A.4 Muscle weakness

a) Incidence: 0.1% to 1% (Prod Info ZOLOFT(R) concentrate, oral tablets, 2009)

b) Muscle weakness was reported in 0.1 to 1% of over 4000 adult patients exposed to multiple doses of (R) concentrate, oral tablets, 2009).

3.3.8.A.5 Myalgia

a) Incidence: 1% or greater (Prod Info ZOLOFT(R) concentrate, oral tablets, 2009)

b) Myalgia was reported in at least 1% of over 4000 adult patients exposed to multiple doses of sertralin concentrate, oral tablets, 2009).

3.3.8.A.6 Summary

a) Sertraline has been frequently associated with myalgia, and infrequently associated with arthralgia ar was associated with an increased risk of hip, forearm, and spine fracture in a case-controlled study (Ves prospective cohort study of SSRIs, including sertraline (Richards et al, 2007). An increased risk of nonve paroxetine, in adult participants older than 55 years of age (Ziere et al, 2008).

3.3.9 Neurologic Effects

Sertraline

Sertraline Hydrochloride

3.3.9.A Sertraline

3.3.9.A.1 Seizure

See Drug Consult reference: COMPARATIVE INCIDENCE OF SEIZURES FROM ANTIDEPRESSANTS

3.3.9.B Sertraline Hydrochloride

Agitation

Cognitive function finding

Dizziness

Dystonia

Dystonia, Mandibular

Extrapyramidal sign

Headache

Hyperactive behavior

Impaired psychomotor performance

Insomnia

Parkinsonism

Restless legs syndrome

Seizure

Sleep walking disorder

Somnolence

Summary

Tic

Tremor

3.3.9.B.1 Agitation

a) Agitation is one of the most frequently reported adverse effects of sertraline (incidence greater than 5

3.3.9.B.2 Cognitive function finding

a) Summary

1) Increases in objective measurements of alertness were observed with sertraline in doses of 50, 7 (critical flicker fusion and choice reaction time tests) were performed on 10 patients after single dose 7.5 hours post-dosing. However, subjective drowsiness was reported with these doses (Hindmarch

3.3.9.B.3 Dizziness

a) Dizziness is one the most frequently reported adverse effects of sertraline (incidence greater than 5%

3.3.9.B.4 Dystonia

a) Incidence: rare (Prod Info Zoloft(R), 2002)

b) Sertraline has been infrequently associated with muscle dystonia (Prod Info Zoloft(R), 2002).

3.3.9.B.5 Dystonia, Mandibular

a) Summary

1) Mandibular dystonia has been noted in several case reports during therapeutic sertraline use. W abatement. Patients on multiple drug therapies should be carefully monitored for interactions or pote 1996b).

b) LITERATURE REPORTS

1) "Sneering" movements developed in the upper mouth area 7.5 months after sertraline was initiat painful pulling sensation of the upper lip. Other dyskinesias or tics were not identified. Symptoms re reappearance of the sneering movement 24 hours later. Two days after stopping sertraline, the abn after identification of this movement disorder (Stanislav & Childs, 1999).

2) A case of mandibular dystonia was reported two days after the addition of metoclopramide 10 mi months with sertraline 100 mg/day (Wilks, 1998b).

3) In a case report, DYSTONIA was reported in a 24-year-old man treated for posttraumatic stress then this dose was increased to 50 mg. Three days after starting the higher dosages, he presented jaw stiffness and feeling as if his face was "frozen." The symptoms were relieved by administration was noted over a year later after he began treatment with sertraline 25 mg, which was increased to common to both drugs, possibly associated with enhancement of serotonergic neurotransmission th

4) A 22-year-old woman developed mandibular dystonia characterized by periauricular pain, jaw tig (mg) daily. Symptoms were relieved by diphenhydramine 50 mg. A third dose of sertraline was admi taking metoclopramide 15 mg four times daily for gastroesophageal reflux which had caused no adv effect of sertraline and metoclopramide resulting in dystonia. This case is intended to alert clinicians (Christensen & Byerly, 1996b).

5) TORTICOLLIS and JAW STIFFNESS responsive to treatment with diphenhydramine, and akathi

3.3.9.B.6 Extrapyramidal sign

a) Summary

1) Extrapyramidal reactions (EPRs) including acute DYSTONIC REACTIONS, NEUROLEPTIC MA selective serotonin reuptake inhibitors (SSRI). The majority of case reports involve fluoxetine; howe

b) LITERATURE REPORTS

1) Extrapyramidal reactions occurred more frequently in women (about 75%) possibly due to more reports, the dose of the SSRI was increased to the maximum recommended dose within 7 days or during the second to fourth week of treatment. Possible mechanisms by which SSRIs cause Extrapy activity resulting in clinically significant effects; and (2) Concurrent use of an SSRI and antipsychotic combination of the two (Caley, 1997).

2) TREATMENT - The majority of extrapyramidal reactions (EPRs) occur within the first few days to during the first 4 weeks of treatment with selective serotonin reuptake inhibitors (SSRIs) and periodi stopping the SSRI (Caley, 1997; Gill et al, 1997). In a limited number of case reports, propranolol a to 90 milligrams (mg) daily, and the dose of clonazepam was 1.5 mg daily (Gill et al, 1997). In single trihexyphenidyl or diphenhydramine 50 mg. Parkinsonism characterized by increasing rigidity and tr a neuroleptic agent. In all cases, symptoms disappeared after reducing the dose or stopping the SS spontaneously over days to weeks after the SSRI is stopped (Gill et al, 1997).

3.3.9.B.7 Headache

a) Headache is one of the most frequently reported adverse effects of sertraline (incidence greater than

3.3.9.B.8 Hyperactive behavior

a) Hyperkinesia has been reported in at least 2% of pediatric patients treated with sertraline (Prod Info Z

3.3.9.B.9 Impaired psychomotor performance

a) Summary

1) Subjective drowsiness was reported with sertraline in a study testing psychomotor function, but t
chart review, nursing home patients treated with fluoxetine and other selective serotonin-reuptake in
risk of falls compared to patients who are not on antidepressants (Thapa et al, 1998).

b) LITERATURE REPORTS

1) A retrospective chart review of 2428 nursing home residents treated with antidepressants assess
were then compared to those not treated (n=847). Antidepressant treatment included tricyclic antide
treated patients was higher than that for patients who were not treated, both before and after the init
or related conditions are at a greater risk of falls than those without such conditions. Patients on TC
(CI), 1.8 to 2.2). The SSRIs had a adjusted rate ratio of 1.8 (1.6 to 2, p=0.001) and trazodone had a
among medications of the same class. It was, however, noted that patients receiving a dose of 20 m
significant increase in the incidence of falls than those receiving lower doses (Thapa et al, 1998).

2) The acute effects of single doses of sertraline 100 milligrams (mg), amitriptyline 50 mg, and plac
double-blind, placebo-controlled crossover study. While performance was clearly impaired by amitri
objective measures of alertness. Although subjective DROWSINESS was reported with both drugs,

3.3.9.B.10 Insomnia

a) Insomnia is one of the most frequently reported adverse effects of sertraline (incidence greater than 5

3.3.9.B.11 Parkinsonism

a) Summary

1) CASE REPORT - A case report notes the development of parkinsonism with symptoms of pill-rol
two weeks after his sertraline dose was increased. A rapid decrease of the dose resolved symptoms
Parkinsonism; therefore, the authors attribute the reaction to sertraline although no rechallenge at a

b) LITERATURE REPORTS

1) Two weeks after the dose of sertraline was increased to 150 milligram (mg) daily, a 90-year-old r
bradykinesia, and festinating gait; he fell twice. The dose of sertraline was rapidly tapered to 50 mg/
sertraline, mental and neurologic examination was normal. The only other medical conditions were s
treated with furosemide and enalapril. In this case, other medical conditions and medications were r
sertraline although rechallenge with the higher dose was not performed (Schechter & Nunes, 1997).

3.3.9.B.12 Restless legs syndrome

a) In a prospective, naturalistic study of patients (median age, 46 years; range, 18 to 87 years) treated v
syndrome (RLS) or worsening of preexisting RLS as a side effect related to treatment. Antidepressants i
duloxetine, reboxetine, and mirtazapine. Mirtazapine led to a marked decline of RLS in 28% of subjects
symptoms (newly occurred or deteriorated) at the rate of 5% to 10%. Subjects stated symptoms occurre

3.3.9.B.13 Seizure

a) Summary

1) CASE REPORT - A 34-year-old woman had a severe TONIC-CLONIC SEIZURE when her sertra
depression. Initial computerized tomography (CT) head scan and electroencephalogram (EEG) were
consistent with a postictal disturbance rather than epilepsy. Sertraline was switched to citalopram, a
predisposing risk factors for seizures such as previous seizures or sedative or alcohol abuse. For m
patient (Saraf & Schrader, 1999).

b) Incidence: rare

3.3.9.B.14 Sleep walking disorder

a) Summary

1) CASE REPORT - A 34-year-old HIV-positive woman developed somnambulism while being treat
milligram (mg) daily dose of paroxetine was gradually increased over 2 weeks to 20 mg daily. Three
according to witnesses. The somnambulism disappeared completely 1 week after the daily dose wa
increasing the dose to 20 mg/day, the sleepwalking reappeared. Paroxetine was discontinued and s
100 mg/day, she again began to sleepwalk. Her symptoms of depression and anxiety improved at th
(Alao et al, 1999).

3.3.9.B.15 Somnolence

a) Somnolence is one of the most frequently reported adverse effects of sertraline (incidence greater tha

3.3.9.B.16 Summary

a) Some of the most frequently reported adverse effects of sertraline are insomnia, headache, dizziness
in 0.4% of patients during clinical studies. Extrapyramidal reactions (EPRs) including acute dystonic reac
been associated with therapeutic use. Nursing home patients have an increased risk of falls compared to

3.3.9.B.17 Tic

a) Exacerbation of TICS in a patient with Tourette's Syndrome that responded to cessation of sertraline

3.3.9.B.18 Tremor

a) Tremor is one of the most frequently reported adverse effects of sertraline (incidence greater than 5%

3.3.10 Ophthalmic Effects

3.3.10.A Sertraline Hydrochloride

Eye / vision finding

Oculogyric crisis

3.3.10.A.1 Eye / vision finding

a) Summary

1) XEROPHTHALMIA, or DIPLOPIA, PHOTOPHOBIA, accommodation changes and CONJUNCTI evaluation, OPTIC NEURITIS and CATARACTS have been temporally associated with use of sertra

b) Rare reports of xerophthalmia, diplopia, photophobia, anterior chamber eye hemorrhage, accommod neuritis and cataracts have also been reported.

3.3.10.A.2 Oculogyric crisis

a) Summary

1) In postmarketing evaluation, oculogyric crisis has been temporally associated with use of sertrali

3.3.12 Psychiatric Effects

3.3.12.A Sertraline Hydrochloride

Depression, exacerbation

Hypomania

Psychiatric sign or symptom

Suicidal thoughts

3.3.12.A.1 Depression, exacerbation

a) Incidence: rare

b) Adult and pediatric patients who experience symptoms of anxiety, agitation, panic attacks, insomnia, hypomania, or mania may be at risk of worsening of their depression. This same concern applies to treat observed, therapy should be reevaluated and it may be necessary to discontinue medications when sym (Anon, 2004).

3.3.12.A.2 Hypomania

a) Summary

1) Two cases of hypomania were reported; one occurred after 5 weeks of sertraline 200 milligrams discontinuation of sertraline and treatment with short-term clonazepam or lithium (Laporta et al, 198

b) Incidence: rare

3.3.12.A.3 Psychiatric sign or symptom

a) Summary

1) Abnormal dreams, AGGRESSIVE BEHAVIOR, delusions, HALLUCINATIONS, EMOTIONAL LAI Info Zoloft(R), 2002; Reimherr et al, 1988b).

2) Aggressive reactions have been reported in at least 2% of pediatric patients treated with sertralir

b) Abnormal dreams, agitation, aggressive behavior, delusions, hallucinations, emotional lability, paranc associated with sertraline therapy.

c) LITERATURE REPORTS

1) Complex, colorful visual hallucinations have been reported less than 3 weeks after initiation of se seconds after awakening and resolved following discontinuation of sertraline (Bourgeois et al, 1998)

3.3.12.A.4 Suicidal thoughts

a) Summary

1) Adult and pediatric patients being treated with antidepressants for major depressive disorder wh

(aggressiveness), impulsivity, akathisia (psychomotor restlessness), hypomania, or mania may be a
treating patients with other psychiatric and nonpsychiatric disorders. If these symptoms are observe
when symptoms are severe, sudden in onset, or were not part of the patient's initial symptoms. Patie
this drug (Anon, 2004; Anon, 2004).
2) A causal role for antidepressants in inducing suicidality has been established in pediatric patients
this risk with the clinical need. In pooled analyses of 24 short-term, placebo-controlled trials of nine a
mirtazapine, nefazodone, and venlafaxine extended-release) including over 4400 pediatric patients
disorders, a greater risk of suicidal behavior or ideation during the first few months of therapy was d
respectively). The risk of suicidality was most consistently observed in the trials that included patient
psychiatric indications, such as obsessive compulsive disorder and social anxiety disorder. No suici
several months) in pediatric patients is not known. It is also unknown whether this risk extends to ad

b) Incidence: rare

3.3.13 Renal Effects

3.3.13.A Sertraline Hydrochloride

Renal failure

Urinary incontinence

Urinary tract infectious disease

Urogenital finding

3.3.13.A.1 Renal failure

a) Summary

1) Acute renal failure has been reported in temporal association with use of sertraline (Prod Info Zo

3.3.13.A.2 Urinary incontinence

a) Urinary incontinence has been reported in at least 2% of pediatric patients treated with sertraline (Pro

3.3.13.A.3 Urinary tract infectious disease

a) Summary

1) In placebo-controlled clinical trials with geriatric patients, the incidence of urinary tract infections
placebo (Anon, 2001).

3.3.13.A.4 Urogenital finding

a) Infrequent reports of dysmenorrhea, intermenstrual bleeding, amenorrhea, leukorrhea, and atrophic v
failure have occasionally been associated with sertraline therapy. Male sexual dysfunction and priapism

3.3.14 Reproductive Effects

Sertraline

Sertraline Hydrochloride

3.3.14.A Sertraline

3.3.14.A.1 Sexual dysfunction

See Drug Consult reference: DRUG-INDUCED SEXUAL DYSFUNCTION
See Drug Consult reference: SELECTIVE SEROTONIN REUPTAKE INHIBITOR-INDUCED SEXUAL D

3.3.14.B Sertraline Hydrochloride

Disorder of menstruation

Priapism

Sexual dysfunction

3.3.14.B.1 Disorder of menstruation

a) Summary

1) Sertraline may cause infrequent DYSMENORRHEA, INTERMENSTRUAL BLEEDING, AMENOF

3.3.14.B.2 Priapism

a) Summary

1) Therapeutic use of sertraline has resulted in rare case occurrence of priapism. The Adverse Eve 46 reports of priapism associated with sertraline (Rand, 1998) One case report noted a 47-year-old resolution occurred after tapering the patient off sertraline. The patient was started on nefazodone t

b) LITERATURE REPORTS

1) INCIDENCE

a) Rare (incidence less than 0.1%). The Adverse Events Reporting System maintained by the sertraline (Rand, 1998).

2) OUTCOME

a) Severe (hospitalization required for treatment) (Rand, 1998).

3) ASSOCIATED SYMPTOMS

a) Pain.

4) ONSET/DURATION

a) DURATION OF SYMPTOMS (with treatment)

1) Several weeks (1 case) (Rand, 1998).

5) CLINICAL MANAGEMENT

a) PHARMACOLOGIC

1) Initial treatment consisted of repeated intracorporeal injection of methoxamine which wa cavernosa and a Winter's shunt procedure which was partially effective. After several week (Rand, 1998).

6) PROBABLE MECHANISM

a) Pharmacologic (extension of the expected effects of a drug).

1) The proposed mechanism for this adverse effect is alpha- 1-adrenergic blockade. Amor alpha-1-adrenergic activity (Rand, 1998).

7) DOCUMENTATION QUALITY

a) Poor.

8) CASE REPORT

a) A 47-year-old man treated with sertraline 200 milligram (mg)/day and dextroamphetamine 1(several brief episodes over the past month. He came to the emergency department (ED) due to injection of methoxamine appeared effective; however, he returned to the ED and was admitted with injection of dilute epinephrine and a Winter's shunt procedure. At follow-up, several weeks was started on nefazodone (Rand, 1998).

3.3.14.B.3 Sexual dysfunction

a) Summary

1) During clinical trials, DELAYED EJACULATION (14%) and DECREASED LIBIDO (6%) were rep & Caillard, 1988c).

2) .FMI DC9691

3.3.15 Respiratory Effects

3.3.15.A Sertraline Hydrochloride

Pulmonary hypertension

Respiratory finding

3.3.15.A.1 Pulmonary hypertension

a) Summary

1) Pulmonary hypertension has been temporally associated with the use of sertraline (Prod Info Zol

3.3.15.A.2 Respiratory finding

a) Summary

1) BRONCHOSPASM, DYSPNEA, and COUGH have occasionally been associated with sertraline

b) Occasional bronchospasm, dyspnea, and cough have been noted with sertraline therapy. Temporary

c) Sinusitis and epistaxis have been reported in at least 2% of pediatric patients treated with sertraline (

3.3.16 Other

Sertraline

Sertraline Hydrochloride

3.3.16.A Sertraline

3.3.16.A.1 Drug withdrawal
See Drug Consult reference: WITHDRAWAL SYNDROME OF SELECTIVE SEROTONIN REUPTAKE I

3.3.16.B Sertraline Hydrochloride

Drug dependence

Drug withdrawal

Fatigue

Fever

Serotonin syndrome

3.3.16.B.1 Drug dependence
a) Summary
1) In a placebo-controlled study designed to assess abuse potential, patients treated with sertraline

3.3.16.B.2 Drug withdrawal
a) Summary
1) Premarketing studies did not report withdrawal reaction to sertraline (Prod Info Zoloft(R), 2002). I
sertraline therapy. Symptoms have included: fatigue, nausea, abdominal cramps, diarrhea, shortnes
tinnitus, ataxia, abnormal sensations ("electric shocks", skin tingling sensations, and involuntary mo
reinstatement of sertraline therapy (Wolfe, 1997; Zajecka et al, 1997; Leiter et al, 1995; Louie et al,
b) LITERATURE REPORTS
1) PEDIATRIC
a) On the fourth day, following the abrupt discontinuation of sertraline (200 milligrams (mg) per
tremor, irritability, and insomnia. The patient was treated with paroxetine 20 mg/day (sertraline
resolved within 30 hours (Diler & Avci, 2002).
b) Withdrawal symptoms in a neonate after maternal sertraline therapy has been reported. Sym
enhanced startle reaction. The child had been well until one day postpartum and symptoms res
Laidlaw, 1995).

3.3.16.B.3 Fatigue
a) Fatigue is one of the most frequently reported adverse effects of sertraline (incidence greater than 5%

3.3.16.B.4 Fever
a) Fever has been reported in at least 2% of pediatric patients treated with sertraline (Prod Info Zoloft(R

3.3.16.B.5 Serotonin syndrome
a) Serotonin syndrome, including life-threatening cases, or neuroleptic malignant syndrome (NMS)-like
serotonin syndrome include mental status changes (eg, agitation, hallucination, coma), autonomic instab
hyperreflexia, incoordination) and/or gastrointestinal symptoms (eg, nausea, vomiting, diarrhea). Severe
rigidity, autonomic instability with possible rapid fluctuation of vital signs, and mental status changes. Se
including triptans, with drugs that impair metabolism of serotonin, including MAOIs, or with antipsychotics
b) Sertraline, a selective serotonin reuptake inhibitor, is capable, as other drugs in this class, of inducing
more drugs capable of enhancing CNS (central nervous system) serotonin activity. Often, patients with s
(Horowitz & Mullins, 1999; Lane & Baldwin, 1997).
c) A 43-year-old woman with severe mental retardation experienced serotonin syndrome (palpitations, c
hypertonicity of the lower limbs, diffuse hyperreflexia, hyperthermia, and leukocytosis) after taking 2 sub-
recovery for hospital discharge on the second day (Bhanji, 2000).

3.4 Teratogenicity/Effects in Pregnancy/Breastfeeding
A) Teratogenicity/Effects in Pregnancy
1) U.S. Food and Drug Administration's Pregnancy Category: Category C (Prod Info Zoloft(R), 2003a) (All Trimes

a) Either studies in animals have revealed adverse effects on the fetus (teratogenic or embryocidal or other) available. Drugs should be given only if the potential benefit justifies the potential risk to the fetus.

2) Australian Drug Evaluation Committee's (ADEC) Category: C(Australian Drug Evaluation Committee, 1999)

a) Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing harmfu be reversible. Accompanying texts should be consulted for further details.

See Drug Consult reference: PREGNANCY RISK CATEGORIES

3) Crosses Placenta: Yes

4) Clinical Management

a) A population-based study found no increased risk of malformations, but the exposed infants were more lik SSRIs, including sertraline, after 20 weeks of gestation has been associated with an increased risk of persist significant association between the use of SSRIs in early pregnancy and the risks of birth defects, including c al, 2007). Sertraline is generally well tolerated in pregnancy and does not appear to pose an unusually high ri and in each case, these dangers must be weighed against the potential for teratogenic effects (Lamberg, 199

5) Literature Reports

a) Data from the case-controlled National Birth Defects Prevention Study (NBDPS), which included data from (defined as treatment with any SSRI from 1 month before to 3 months after conception) to SSRIs was associ confidence interval (CI), 1.1 to 5.1; P=0.02), craniosynostosis in 24 exposed infants out of 432 (adjusted OR 181 (adjusted OR 2.8; 95% CI, 1.3 to 5.7; P=0.005). However, early exposure did not significantly increase th SSRIs reported by control mothers were sertraline, fluoxetine, paroxetine, and citalopram (Alwan et al, 2007)

b) A case-control study found that the use of selective serotonin reuptake inhibitors (SSRIs) after 20 weeks o the newborn (PPHN). Fluoxetine, paroxetine, and sertraline were the specific SSRIs studied to carry this incr and their infants. Assessment of exposure was determined by telephone interview within 6 months of birth. A with an odds ratio of 6.1 (95% CI 2.2 to 16.8; p=0.001) of delivering an infant with PPHN relative to no use du antidepressants use at any gestation time was not associated with increased risk of PPHN development. The study, infants exposed to SSRIs after 20 weeks of gestation have a PPHN incidence of 0.6 to1.2% (Chamber

c) A population-based study of 1782 pregnant women exposed to selective serotonin reuptake inhibitors (SS neonatal intensive or special care unit, particularly with third trimester exposure. Using 1996-2001 data derive who had at least one purchase (a 3-months' supply) of an SSRI during the period of one month before pregn drug purchases during the same peripartum period. The mean age of both cohorts was 30 years (+/- 7). Ther artificial reproductive techniques in the SSRI group compared to controls (p less than 0.001), and mean lengt Malformations, however, were not more common in the SSRI group (p = 0.4). Purchases of SSRIs (citoprar trimester than later in pregnancy, with 118 women purchasing sertraline during the first trimester, 31 during th first trimester exposure, treatment in a special or intensive care unit was more common for the infants expose adjusting for confounding variables, this difference remained statistically significant (OR 1.6; 95% CI 1.1 to 2.

d) In a prospective, multicenter, controlled cohort study of 267 pregnant women taking 3 different SSRIs, 14 group (267 pregnant women exposed only to nonteratogens) no differences between the two groups were re stillbirth, prematurity, birth weight, and gestational age (Kulin et al, 1998).

e) A prospective study through the California Teratogen Information Service compared the outcomes of 112 teratogens. The rate of major anomalies in the two groups was similar (3.8% and 1.9%, respectively). Wome (16.3%) and their infants were more often admitted to the special care nursery (Chambers et al, 1999).

B) Breastfeeding

1) American Academy of Pediatrics Rating: Drugs for which the effect on nursing infants is unknown but may be

2) Thomson Lactation Rating: Infant risk is minimal.

a) The weight of an adequate body of evidence and/or expert consensus suggests this drug poses minimal r

3) Clinical Management

a) The selective serotonin-reuptake inhibitors, including sertraline, are lipid soluble and therefore excreted in manufacturer recommends that sertraline not be used by women while breastfeeding (Prod Info Zoloft(R), 20 should be monitored for anorexia, weight loss, irritability and insomnia.

4) Literature Reports

a) Low or undetectable levels of sertraline in human breast milk have been reported. A study of 3 nursing inf sertraline and the metabolite norsertraline were reported (Mammen et al, 1997). No adverse effects in the inf sertraline; neither drug was detectable in the infant serum (Altshuler et al, 1996).

b) One study involved 12 nursing infants whose mothers used sertraline while breastfeeding (Llewellyn & St adverse effects were noted. Similarly, sertraline was not detectable in the serum of 6 nursing infants whose m as reported by the mothers. The authors suggest that breastfeeding should generally not be discouraged in m

c) Although the clinical data suggest that the absolute dose of sertraline and the metabolite N-desmethylsert adverse outcomes, the effects of perinatal infant exposure to sertraline on long-term cognitive development o

d) Non-quantifiable (0 ng/mL to 2 ng/mL) concentrations of sertraline were detected in 7 of 9 nursing infants; ng/mL. The infant with a sertraline concentration of 64 ng/mL had an N-desmethylsertraline concentration of The infant did not experience any adverse events related to the high concentrations. Two infants had non-qua ng/mL to 6 ng/mL), and one infant had a level of 24 ng/mL, despite a low serum sertraline level. Because N-d Researchers could not conclude why the 1 infant had such high concentrations. Maternal doses of sertraline

e) Three and 6 infants had detectable serum concentrations of sertraline and desmethylsertraline, respective sertraline and desmethylsertraline were highest 7 to 8 hours and 5 to 11 hours, respectively, after the dose. C breast milk 7 to 8 hours after the maternal dose for an infant feeding every 3 hours. Breast milk concentration higher with higher maternal doses. This study was conducted in 12 mother-infant pairs; exposure to sertraline 150 mg daily (Stowe et al, 1997).

5) Drug Levels in Breastmilk

a) Parent Drug
1) Milk to Maternal Plasma Ratio
a) 1.0-3.6 (Buist & A, 2001)
b) Active Metabolites
1) Desmethylsertraline (Stowe et al, 1997)

3.5 Drug Interactions

Drug-Drug Combinations

Drug-Food Combinations

3.5.1 Drug-Drug Combinations

Abciximab

Aceclofenac

Acemetacin

Acenocoumarol

Alclofenac

Almotriptan

Alprazolam

Amitriptyline

Amoxapine

Anagrelide

Ancrod

Anisindione

Antithrombin III Human

Ardeparin

Aspirin

Astemizole

Benoxaprofen

Bivalirudin

Bromfenac

Bufexamac

Bupropion

Cannabis

Carbamazepine

Carprofen

Celecoxib

Certoparin

Cilostazol

Cimetidine

Clomipramine

Clonixin

Clopidogrel

Clorgyline

Clozapine

Dalteparin

Danaparoid

Darunavir

Defibrotide

Dehydroepiandrosterone

Dermatan Sulfate

Desipramine

Desirudin

Desvenlafaxine

Dexfenfluramine

Dexketoprofen

Diclofenac

Dicumarol

Diflunisal

Dipyridamole

Dipyrone

Dothiepin

Doxepin

Droperidol

Droxicam

Duloxetine

Efavirenz

Eletriptan

Enoxaparin

Epoprostenol

Eptifibatide

Erythromycin

Etodolac

Etofenamate

Etoricoxib

Felbinac

Fenbufen

Fenfluramine

Fenoprofen

Fentiazac

Flecainide

Floctafenine

Flufenamic Acid

Fluphenazine

Flurbiprofen

Fondaparinux

Fosphenytoin

Frovatriptan

Furazolidone

Ginkgo

Heparin

Hydroxytryptophan

Ibuprofen

Iloprost

Imipramine

Indomethacin

Indoprofen

Iproniazid

Isocarboxazid

Isoxicam

Ketoprofen

Ketorolac

Lamifiban

Lamotrigine

Levomethadyl

Lexipafant

Linezolid

Lithium

Lofepramine

Lornoxicam

Meclofenamate

Mefenamic Acid

Meloxicam

Methadone

Methylphenidate

Metoclopramide

Milnacipran

Moclobemide

Morniflumate

Nabumetone

Nadroparin

Naproxen

Naratriptan

Nialamide

Niflumic Acid

Nimesulide

Nortriptyline

Oxaprozin

Oxycodone

Parecoxib

Pargyline

Parnaparin

Pentosan Polysulfate Sodium

Phenelzine

Phenindione

Phenprocoumon

Phenylbutazone

Phenytoin

Pimozide

Pirazolac

Piroxicam

Pirprofen

Procarbazine

Propafenone

Propranolol

Propyphenazone

Proquazone

Protriptyline

Rasagiline

Reviparin

Rifampin

Rizatriptan

Rofecoxib

Selegiline

Sibrafiban

Sibutramine

St John's Wort

Sulfinpyrazone

Sulindac

Sulodexide

Sumatriptan

Suprofen

Tapentadol

Tenidap

Tenoxicam

Terfenadine

Tiaprofenic Acid

Ticlopidine

Tinzaparin

Tipranavir

Tirofiban

Tolmetin

Toloxatone

Tramadol

Tranylcypromine

Triazolam

Trimipramine

Valdecoxib

Warfarin

Xemilofiban

Zolmitriptan

Zolpidem

Zomepirac

3.5.1.A Abciximab

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and
been associated with an increased risk of bleeding. Bleeding events reported have included epistaxis, ecchy
tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an antiplatelet agent are given concurrently, monitor patient for
PROZAC(R) oral capsules, delayed-release capsules, solution, 2008)
7) Probable Mechanism: unknown

3.5.1.B Aceclofenac

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and
associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hemator
suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solu
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent
were searched among 26,005 users of antidepressant medications and compared with the number of ho
amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 t
12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The
SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with

3.5.1.C Acemetacin

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and
associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hemator
suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solu
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent

were searched among 26,005 users of antidepressant medications and compared with the number of ho
amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 t
12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The
SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with

3.5.1.D Acenocoumarol

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and
anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp e
reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Alter
coadministration of SSRIs with warfarin (Prod Info ZOLOFT(R) oral tablets, concentrate, 2008). Prothrombin
1997a).

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: When sertraline and an anticoagulant are given concurrently, monitor patient for sig
closely for altered anticoagulant effects, including increased bleeding, when sertraline therapy is initiated or d

7) Probable Mechanism: unknown

8) Literature Reports

a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bl
fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patien
with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopram
bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experie
corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. T
(95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experienci
addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respe
patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other tha

b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoum
increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospit
for abnormal bleeding and compared them with 5818 control subjects who were also taking a coumarin.
on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OI
bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).

c) Sertraline 50 mg to 200 mg daily for 21 days produced an 8% increase in prothrombin time in subject
given prior to sertraline; this compared with a 1% decrease with placebo. Normalization of the prothromb
findings is unknown (Prod Info ZOLOFT(R) oral tablets, concentrate, 2008).

d) In a non-blinded, randomized, placebo-controlled trial involving 12 healthy volunteers, the effect of se
study, all participants received warfarin 0.75 mg/kg. Beginning on day 11, each volunteer was randomize
mg/day to 200 mg/day. Prothrombin time was measured prior to each dose of warfarin and periodically th
enhanced by sertraline to a clinically significant degree, despite the fact that sertraline was given in a hig

3.5.1.E Alclofenac

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and
associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematon
suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solu

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent
were searched among 26,005 users of antidepressant medications and compared with the number of ho
amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 t
12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The
SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton

b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with

3.5.1.F Almotriptan

1) Interaction Effect: an increased risk of serotonin syndrome

2) Summary: Concomitant use of almotriptan and selective serotonin reuptake inhibitors (SSRI's) has been r
Concurrent use of a triptan and an SSRI may result in serotonin syndrome which may be life-threatening. Sy
coordination, fast heart beat, rapid changes in blood pressure, increased body temperature, overreactive refl
commonly used intermittently and that either the triptan or the SSRI may be prescribed by a different physicia
combination and monitor them closely for symptoms of serotonin syndrome (US Food and Drug Administratio

3) Severity: major

4) Onset: delayed

5) Substantiation: theoretical
6) Clinical Management: Coadministration of a triptan, such as almotriptan, and an SSRI may result in a life-
used intermittently and that either the triptan or the SSRI may be prescribed by a different physician. If these
monitor closely for symptoms of serotonin syndrome (restlessness, hyperthermia, hyperreflexia, incoordinatic
7) Probable Mechanism: additive pharmacologic effects resulting in excessive serotonergic stimulation
8) Literature Reports
a) Concomitant administration of fluoxetine and almotriptan is well tolerated and fluoxetine has only a m
pharmacokinetics are not significantly affected. A randomized, open-label, two-way crossover study invo
treatments with a minimum 3-week washout between periods: (1) three 20 mg fluoxetine capsules on da
on day 8 with no treatment on days 1 through 7. Peak almotriptan concentrations were 18% higher follov
This difference was statistically significant (p equal 0.023). Mean almotriptan area under the concentratic
treatment groups. Mean half-life was not statistically different between the treatment groups. During fluo
almotriptan may have been increased by fluoxetine. The author concludes that based on the results of th
and fluoxetine can be safely used concomitantly in migraine management (Fleishaker et al, 2001).

3.5.1.G Alprazolam

1) Interaction Effect: an increased risk of psychomotor impairment and sedation
2) Summary: To date, limited information is available related to the effects of coadministered alprazolam and
metabolism (Von Moltke et al, 1994). It is theoretically possible that an interaction might occur because alpra
inhibit one or more P450 isoenzymes (DeVane, 1994). Current evidence indicates that alprazolam is metabol
inhibiting the CYP3A4 isoenzyme. However, a study involving ten healthy volunteers failed to show an alterat
sertraline (Hassan et al, 2000a).
3) Severity: moderate
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Caution is warranted if alprazolam and sertraline are to be coadministered. Monitor
may need to be reduced.
7) Probable Mechanism: inhibition of cytochrome P450 3A-mediated alprazolam metabolism
8) Literature Reports
a) Ten healthy white volunteers (eight women and two men) participated in a randomized, double-blind,
potential to impair alprazolam metabolism and to assess whether any potential impairment is dependent
sertraline 50 mg, 100 mg, or 150 mg daily. The alprazolam maximum concentration (Cmax), time to max
were not clinically significantly altered in the presence of sertraline. No pharmacodynamic interactions, a
recall, were detected between sertraline and alprazolam at any dose of sertraline. These in vivo findings
via cytochrome P450 3A4 enzymes (Hassan et al, 2000).

3.5.1.H Amitriptyline

1) Interaction Effect: elevated amitriptyline serum levels or possible serotonin syndrome (hypertension, hype
2) Summary: There is limited evidence suggesting that sertraline may inhibit tricyclic antidepressant (TCA) m
P450 2D6 enzyme activity and may increase the plasma concentrations of coadministered drugs that are me
2002o; Preskorn et al, 1994s; Lydiard et al, 1993i). There have been several reports of serotonin syndrome d
antidepressants, including one case report due to sertraline and amitriptyline coadministration (George & Goo
rare but potentially fatal condition of serotonergic hyperstimulation characterized by changes in mental status
1991k). Further clinical studies or case reports are necessary to determine the incidence and implications of
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: The combined use of tricyclic antidepressants (TCAs) and selective serotonin reupt
serotonin syndrome have also been reported with concurrent TCA and SSRI therapy. Caution should be obse
7) Probable Mechanism: inhibition of amitriptyline metabolism
8) Literature Reports
a) A 40-year old woman was admitted to the hospital after developing symptoms of serotonin syndrome
amitriptyline 75 mg was added to a regimen of sertraline 40 mg twice daily. Other medications at time of
examination, the patient had a fever of 38.0 degrees Celsius, was diaphoretic and showed signs of hype
resolved rapidly (Alderman & Lee, 1996).
b) Desipramine pharmacokinetics were studied in 18 healthy male volunteers. Study subjects received
mg daily) for 21 days. When sertraline was added to desipramine therapy, the mean maximum concentra
increased by 26%. Trough concentrations of desipramine were close to baseline one week after sertralin
interaction may not be clinically significant (Preskorn et al, 1994r).

3.5.1.I Amoxapine

1) Interaction Effect: modest elevation in amoxapine serum levels or possible serotonin syndrome (hypertens
2) Summary: There is limited evidence suggesting that sertraline may inhibit tricyclic antidepressant (TCA) m
P450 2D6 enzyme activity and may increase the plasma concentrations of coadministered drugs that are me
2002p; Preskorn et al, 1994u; Lydiard et al, 1993j). Effects of the interaction may have little or no clinical impa
were modest compared with those found when fluoxetine (another selective serotonin reuptake inhibitor) was
sertraline therapy for TCA toxicity (dry mouth, urinary retention, CNS depression). Amoxapine doses may nee
3) Severity: major

4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: The combined use of tricyclic antidepressants (TCAs) and selective serotonin reupt serotonin syndrome have also been reported with concurrent TCA and SSRI therapy. Caution should be obs
7) Probable Mechanism: inhibition of amoxapine metabolism
8) Literature Reports
a) The pharmacokinetics of desipramine have been studied in 18 healthy male volunteers. Study subjec sertraline (50 mg daily) for 21 days. When sertraline was added to desipramine therapy, the mean maxi concentration-time curve increased by 26%. Trough concentrations of desipramine were close to baseli were modest and the interaction may not be clinically significant (Preskorn et al, 1994t).

3.5.1.J Anagrelide

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control an been associated with an increased risk of bleeding. Bleeding events reported have included epistaxis, ecchy tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an antiplatelet agent are given concurrently, monitor patient for PROZAC(R) oral capsules, delayed-release capsules, solution, 2008)
7) Probable Mechanism: unknown

3.5.1.K Ancrod

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control an anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Alte coadministration of SSRIs with warfarin (Prod Info ZOLOFT(R) oral tablets, concentrate, 2008). Prothrombin 1997a).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When sertraline and an anticoagulant are given concurrently, monitor patient for sig closely for altered anticoagulant effects, including increased bleeding, when sertraline therapy is initiated or d
7) Probable Mechanism: unknown
8) Literature Reports
a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bl fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patie with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopra bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experie corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experienci addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respe patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other th
b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocou increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospi for abnormal bleeding and compared them with 5818 control subjects who were also taking a coumarin. on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (O bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).
c) Sertraline 50 mg to 200 mg daily for 21 days produced an 8% increase in prothrombin time in subject given prior to sertraline; this compared with a 1% decrease with placebo. Normalization of the prothromb findings is unknown (Prod Info ZOLOFT(R) oral tablets, concentrate, 2008).
d) In a non-blinded, randomized, placebo-controlled trial involving 12 healthy volunteers, the effect of se study, all participants received warfarin 0.75 mg/kg. Beginning on day 11, each volunteer was randomize mg/day to 200 mg/day. Prothrombin time was measured prior to each dose of warfarin and periodically t enhanced by sertraline to a clinically significant degree, despite the fact that sertraline was given in a hig

3.5.1.L Anisindione

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control an anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Alte coadministration of SSRIs with warfarin (Prod Info ZOLOFT(R) oral tablets, concentrate, 2008). Prothrombin 1997a).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable

6) Clinical Management: When sertraline and an anticoagulant are given concurrently, monitor patient for sig closely for altered anticoagulant effects, including increased bleeding, when sertraline therapy is initiated or d
7) Probable Mechanism: unknown
8) Literature Reports
a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bl fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patien with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopran bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experie corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. T (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experienci addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respe patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other th
b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoum increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospit for abnormal bleeding and compared them with 5818 control subjects who were also taking a coumarin. on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (O bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).
c) Sertraline 50 mg to 200 mg daily for 21 days produced an 8% increase in prothrombin time in subject given prior to sertraline; this compared with a 1% decrease with placebo. Normalization of the prothromb findings is unknown (Prod Info ZOLOFT(R) oral tablets, concentrate, 2008).
d) In a non-blinded, randomized, placebo-controlled trial involving 12 healthy volunteers, the effect of se study, all participants received warfarin 0.75 mg/kg. Beginning on day 11, each volunteer was randomize mg/day to 200 mg/day. Prothrombin time was measured prior to each dose of warfarin and periodically th enhanced by sertraline to a clinically significant degree, despite the fact that sertraline was given in a hig

3.5.1.M Antithrombin III Human

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Alter coadministration of SSRIs with warfarin (Prod Info ZOLOFT(R) oral tablets, concentrate, 2008). Prothrombin 1997a).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When sertraline and an anticoagulant are given concurrently, monitor patient for sig closely for altered anticoagulant effects, including increased bleeding, when sertraline therapy is initiated or d
7) Probable Mechanism: unknown
8) Literature Reports
a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bl fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patien with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopran bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experie corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. T (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experienci addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respe patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other th
b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoum increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospit for abnormal bleeding and compared them with 5818 control subjects who were also taking a coumarin. on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (O bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).
c) Sertraline 50 mg to 200 mg daily for 21 days produced an 8% increase in prothrombin time in subject given prior to sertraline; this compared with a 1% decrease with placebo. Normalization of the prothromb findings is unknown (Prod Info ZOLOFT(R) oral tablets, concentrate, 2008).
d) In a non-blinded, randomized, placebo-controlled trial involving 12 healthy volunteers, the effect of se study, all participants received warfarin 0.75 mg/kg. Beginning on day 11, each volunteer was randomize mg/day to 200 mg/day. Prothrombin time was measured prior to each dose of warfarin and periodically th enhanced by sertraline to a clinically significant degree, despite the fact that sertraline was given in a hig

3.5.1.N Ardeparin

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Alter coadministration of SSRIs with warfarin (Prod Info ZOLOFT(R) oral tablets, concentrate, 2008). Prothrombin 1997a).
3) Severity: major

4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When sertraline and an anticoagulant are given concurrently, monitor patient for sig closely for altered anticoagulant effects, including increased bleeding, when sertraline therapy is initiated or d
7) Probable Mechanism: unknown
8) Literature Reports
a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bl fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patien with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopram bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experie corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experienci addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respe patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other th
b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoum increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospit for abnormal bleeding and compared them with 5818 control subjects who were also taking a coumarin. on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (O bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).
c) Sertraline 50 mg to 200 mg daily for 21 days produced an 8% increase in prothrombin time in subject given prior to sertraline; this compared with a 1% decrease with placebo. Normalization of the prothromb findings is unknown (Prod Info ZOLOFT(R) oral tablets, concentrate, 2008).
d) In a non-blinded, randomized, placebo-controlled trial involving 12 healthy volunteers, the effect of se study, all participants received warfarin 0.75 mg/kg. Beginning on day 11, each volunteer was randomize mg/day to 200 mg/day. Prothrombin time was measured prior to each dose of warfarin and periodically th enhanced by sertraline to a clinically significant degree, despite the fact that sertraline was given in a hig

3.5.1.O Aspirin

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and been associated with an increased risk of bleeding. Bleeding events reported have included epistaxis, ecchy tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an antiplatelet agent are given concurrently, monitor patient for PROZAC(R) oral capsules, delayed-release capsules, solution, 2008)
7) Probable Mechanism: unknown

3.5.1.P Astemizole

1) Interaction Effect: cardiotoxicity (QT interval prolongation, torsades de pointes, cardiac arrest)
2) Summary: Coadministered sertraline may inhibit astemizole metabolism, thereby leading to increased ast administration of astemizole and sertraline should be avoided (Prod Info Hismanal(R), 1998).
3) Severity: major
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Concomitant use of astemizole and sertraline is not recommended.
7) Probable Mechanism: inhibition of cytochrome P450-mediated metabolism of astemizole

3.5.1.Q Benoxaprofen

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematom suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solu
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent were searched among 26,005 users of antidepressant medications and compared with the number of ho amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with

3.5.1.R Bivalirudin

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Alter coadministration of SSRIs with warfarin (Prod Info ZOLOFT(R) oral tablets, concentrate, 2008). Prothrombin 1997a).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When sertraline and an anticoagulant are given concurrently, monitor patient for sig closely for altered anticoagulant effects, including increased bleeding, when sertraline therapy is initiated or d
7) Probable Mechanism: unknown
8) Literature Reports
a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bl fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patien with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopram bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experie corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experienci addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respe patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other th
b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoum increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospit for abnormal bleeding and compared them with 5818 control subjects who were also taking a coumarin. on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (O bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).
c) Sertraline 50 mg to 200 mg daily for 21 days produced an 8% increase in prothrombin time in subject given prior to sertraline; this compared with a 1% decrease with placebo. Normalization of the prothromb findings is unknown (Prod Info ZOLOFT(R) oral tablets, concentrate, 2008).
d) In a non-blinded, randomized, placebo-controlled trial involving 12 healthy volunteers, the effect of se study, all participants received warfarin 0.75 mg/kg. Beginning on day 11, each volunteer was randomize mg/day to 200 mg/day. Prothrombin time was measured prior to each dose of warfarin and periodically t enhanced by sertraline to a clinically significant degree, despite the fact that sertraline was given in a hig

3.5.1.S Bromfenac

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hemator suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solu
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent were searched among 26,005 users of antidepressant medications and compared with the number of ho amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with

3.5.1.T Bufexamac

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hemator suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solu
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent were searched among 26,005 users of antidepressant medications and compared with the number of ho amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton

b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with

3.5.1.U Bupropion

1) Interaction Effect: increased plasma levels of sertraline

2) Summary: It is recommended that sertraline, an antidepressant metabolized by the cytochrome P450 2D6 concomitantly with bupropion (Prod Info Wellbutrin XL(TM), 2003; Prod Info Zyban(R), 2000).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Coadministration of bupropion and sertraline should be approached with caution an to the treatment regimen of a patient already receiving sertraline, consider decreasing the dose of sertraline.

7) Probable Mechanism: inhibition of cytochrome P450 2D6-mediated sertraline metabolism

3.5.1.V Cannabis

1) Interaction Effect: manic symptoms

2) Summary: One case of mania following use of marijuana with fluoxetine therapy has been reported (Stoll symptoms could have resulted from the fluoxetine or marijuana alone. Caution is advised for patients using m

3) Severity: moderate

4) Onset: rapid

5) Substantiation: theoretical

6) Clinical Management: Caution patients taking selective serotonin reuptake inhibitors to avoid concomitant

7) Probable Mechanism: additive serotonergic stimulation

8) Literature Reports

a) A 21-year-old female presented with mania, agitation, and grandiose delusions following use of mariju reported smoking 2 "joints" during a 36-hour period. Over the next 24 hours, she developed increased en perphenazine were given for agitation and excitement which gradually resolved over 4 days. She remain prior to discharge. One week after discharge, she discontinued fluoxetine due to insomnia and feeling "h rapid switch to mania after smoking marijuana with fluoxetine, the manic symptoms were associated with from either fluoxetine or marijuana alone (Stoll et al, 1991).

3.5.1.W Carbamazepine

1) Interaction Effect: an increased risk of carbamazepine toxicity (ataxia, nystagmus, diplopia, headache, vo

2) Summary: Coadministration of sertraline and carbamazepine may cause reduced carbamazepine clearan possibly blood dyscrasias (Joblin & Ghose, 1994a). Similar interactions have been reported between carbam fluvoxamine (Pearson, 1990; Fritze et al, 1991). However, in two separate in vivo studies, coadministration of concentrations of carbamazepine (Prod Info Zoloft(R), 2002j). Two case reports of coadministration of carbar sertraline (Khan et al, 2000).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Due to the potential for elevated carbamazepine levels, patients should be closely f Consider measuring carbamazepine serum concentrations within two to three weeks of adding or discontinui metabolism of sertraline, sertraline levels may be lower than expected, which may result in lack of efficacy of

7) Probable Mechanism: inhibition of carbamazepine metabolism, increase in sertraline CYP3A4-mediated m

8) Literature Reports

a) A 24-year-old woman received maintenance carbamazepine 600 mg daily and flecainide 100 mg dail increased from 4.7 to 8.5 mg/L (normal range, 4 to 10 mg/L), and her blood counts were normal. Two mo white blood cell counts were abnormally low. Postoperatively her blood counts remained low, despite blo had missed one or more doses. On bone marrow examination, erythroid hyperplasia with megaloblastic counts began to improve five days after withdrawal of sertraline and carbamazepine; she was not rechall to inhibition of cytochrome P450 isoenzymes and carbamazepine protein binding displacement (Joblin &

b) Sertraline is suspected of inhibiting cytochrome P450IIIA4 (CYP3A4) enzyme activity (DeVane, 1994 have a potentially significant interaction with sertraline. Conversely, carbamazepine is also a known pote decreased sertraline concentrations (Spina et al, 1996).

c) Two cases have been reported in which concomitant use of sertraline and carbamazepine resulted in schizoaffective disorder who had been successfully treated with haloperidol and carbamazepine for 3 ye mg/day. A plasma level for carbamazepine and sertraline was obtained after sertraline initiation. Sertralin male diagnosed with posttraumatic stress disorder who had been successfully treated with carbamazepi disorder. Plasma levels were obtained for sertraline and carbamazepine during therapy. Sertraline levels mg/day (Kahn et al, 2000).

3.5.1.X Carprofen

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hemator suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solu

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent were searched among 26,005 users of antidepressant medications and compared with the number of ho amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 t 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with

3.5.1.Y Celecoxib
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hemator suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solu
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent were searched among 26,005 users of antidepressant medications and compared with the number of ho amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 t 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with

3.5.1.Z Certoparin
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp e reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Alter coadministration of SSRIs with warfarin (Prod Info ZOLOFT(R) oral tablets, concentrate, 2008). Prothrombin 1997a).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When sertraline and an anticoagulant are given concurrently, monitor patient for sig closely for altered anticoagulant effects, including increased bleeding, when sertraline therapy is initiated or d
7) Probable Mechanism: unknown
8) Literature Reports
a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bl fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patien with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopram bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experie corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. T (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experienci addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respe patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other tha
b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoum increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospit for abnormal bleeding and compared them with 5818 control subjects who were also taking a coumarin. on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OI bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).
c) Sertraline 50 mg to 200 mg daily for 21 days produced an 8% increase in prothrombin time in subject given prior to sertraline; this compared with a 1% decrease with placebo. Normalization of the prothromb findings is unknown (Prod Info ZOLOFT(R) oral tablets, concentrate, 2008).
d) In a non-blinded, randomized, placebo-controlled trial involving 12 healthy volunteers, the effect of se study, all participants received warfarin 0.75 mg/kg. Beginning on day 11, each volunteer was randomize mg/day to 200 mg/day. Prothrombin time was measured prior to each dose of warfarin and periodically th enhanced by sertraline to a clinically significant degree, despite the fact that sertraline was given in a hig

3.5.1.AA Cilostazol
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and been associated with an increased risk of bleeding. Bleeding events reported have included epistaxis, ecchyr

tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an antiplatelet agent are given concurrently, monitor patient for
PROZAC(R) oral capsules, delayed-release capsules, solution, 2008)
7) Probable Mechanism: unknown

3.5.1.AB Cimetidine
1) Interaction Effect: elevated sertraline serum concentrations and increased risk of adverse side effects
2) Summary: Coadministration of cimetidine with sertraline may result in inhibition of sertraline metabolism, l
clinical significance of this effect is as yet undefined. Adjustments in sertraline doses may be required when c
3) Severity: moderate
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Closely follow patients for signs of sertraline toxicity (nausea, diarrhea, tremor, dizz
cimetidine.
7) Probable Mechanism: inhibited cytochrome P450 metabolism of sertraline
8) Literature Reports
a) When sertraline 100 mg was given on the second day of an 8-day regimen of cimetidine 800 mg daily
curve (AUC), a 24% in the maximum concentration (Cmax), and a 26% increased in the half-life as comp
interaction is unknown.

3.5.1.AC Clomipramine
1) Interaction Effect: modest elevations of clomipramine serum levels or possible serotonin syndrome (hyper
2) Summary: There is limited evidence suggesting that sertraline may inhibit tricyclic antidepressant (TCA) m
P450 2D6 enzyme activity and may increase the plasma concentrations of coadministered drugs that are me
2002h; Preskorn et al, 1994k; Lydiard et al, 1993e). Effects of the interaction may have little or no clinical imp
were modest compared with those found when fluoxetine (another selective serotonin reuptake inhibitor) was
sertraline therapy for TCA toxicity (dry mouth, urinary retention, CNS depression). Clomipramine doses may
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: The combined use of tricyclic antidepressants (TCAs) and selective serotonin reupt
serotonin syndrome have also been reported with concurrent TCA and SSRI therapy. Caution should be obse
7) Probable Mechanism: inhibition of clomipramine metabolism
8) Literature Reports
a) The pharmacokinetics of desipramine were studied in 18 healthy male volunteers. Study subjects rec
sertraline (50 mg daily) for 21 days. When sertraline was added to desipramine therapy, the mean maxin
concentration-time curve increased by 26%. Trough concentrations of desipramine were close to baselin
were modest and the interaction may not be clinically significant (Preskorn et al, 1994j).

3.5.1.AD Clonixin
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and
associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hemator
suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solu
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent
were searched among 26,005 users of antidepressant medications and compared with the number of ho
amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 t
12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The
SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with

3.5.1.AE Clopidogrel
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and
been associated with an increased risk of bleeding. Bleeding events reported have included epistaxis, ecchyr
tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable

6) Clinical Management: When an SSRI and an antiplatelet agent are given concurrently, monitor patient for
PROZAC(R) oral capsules, delayed-release capsules, solution, 2008)
7) Probable Mechanism: unknown

3.5.1.AF Clorgyline

1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental sta
2) Summary: Concurrent administration or overlapping therapy with sertraline and a monoamine oxidase (MA
characterized by symptoms such as restlessness, myoclonus, changes in mental status, hyperreflexia, diaph
Zoloft(R), 2002g; Lappin & Auchincloss, 1994e; Graber et al, 1994e; Bhatara & Bandettini, 1993b; Suchowers
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Concurrent use of sertraline and a MAO inhibitor is contraindicated. Wait at least 14
least 14 days after discontinuing sertraline before initiating therapy with a MAO inhibitor.
7) Probable Mechanism: inhibition of serotonin metabolism by monoamine oxidase
8) Literature Reports

a) Concomitant use of serotonin specific reuptake inhibitors and monoamine oxidase inhibitors can prod
syndrome is a condition of serotonergic hyperstimulation and manifests as restlessness, myoclonus, cha
not recognized and correctly treated, death can result.

b) A 26-year old woman who had been taking isocarboxazid for eight weeks stopped taking the drug for
the patient became restless and developed leg twitches. The patients was later admitted to the emergen
disturbances. The patient did not improve after treatment with diazepam and propranolol. The patient wa
in symptoms after the second dose (Lappin & Auchincloss, 1994d).

c) A drug interaction was reported in a 61-year old woman in which sertraline 100 mg twice daily was ac
taking the first sertraline dose, the patient was found in a semicomatose state, with elevated body tempe
mmHg. After transportation to the hospital, the patient was misdiagnosed as having neuroleptic malignar
between sertraline and phenelzine. The authors suggest that MAO inhibitor therapy should be discontinu
inhibitor (SSRI) and that before starting a MAOI, SSRI therapy should be discontinued for at least 5 half-

d) Two cases reports suggested a possible interaction between fluoxetine and selegiline (Suchowersky
approximately one month after adding selegiline to fluoxetine therapy. The patient improved 2 months af
involved diaphoresis, vasoconstriction, and cyanosis of the hands which occurred in close temporal relat
quick resolution of symptoms. Rechallenge with fluoxetine alone occurred without incident.

3.5.1.AG Clozapine

1) Interaction Effect: an increased risk of clozapine toxicity (sedation, seizures, hypotension)
2) Summary: Coadministration of clozapine with sertraline has been reported to result in increased clozapine
Chong et al, 1997a; Centorrino et al, 1996a). Clozapine is metabolized by the cytochrome P450 2D6 isoenzy
addition to being metabolized by CYP2D6 itself (Prod Info Zoloft(R), 1999g; DeVane, 1994e). Cytochrome P4
CYP3A4 (Chong & Remington, 1998).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor the therapeutic efficacy of clozapine and for any evidence of toxicity, partic
dosage may be required in some clinical situations.
7) Probable Mechanism: decreased clozapine metabolism
8) Literature Reports

a) Two case reports revealed the exacerbation of psychotic symptoms with the addition of a selective se
schizophrenia, had been taking clozapine 175 mg per day. Other medications included propranolol for ta
symptoms but continued compulsive behavior, sertraline 50 mg per day was added. Within four weeks, t
clozapine concentrations increased from 325 ng/mL before sertraline therapy to 695 ng/mL after sertralir
of clozapine 500 mg per day which was later increased to 600 mg per day. After fluvoxamine 50 mg per
ng/mL before fluvoxamine treatment to 2750 ng/mL after 28 days of fluvoxamine treatment. During this ti
worsened. The authors postulated that the worsening of psychotic symptoms could be due to SSRI inhib
serotonergic and dopaminergic blockade caused by coadministration of the two drugs (Chong et al, 1997

b) A study evaluated the serum concentrations of clozapine and norclozapine, the major metabolite, wh
paroxetine, and sertraline. Eighty outpatients receiving clozapine all had been diagnosed with schizophre
combination with clozapine. Of these 40 patients, 14 were receiving fluoxetine, 10 were receiving sertrali
serum concentrations of clozapine and norclozapine were 41.1% and 44.8% higher, respectively, than in
norclozapine concentration to dose was also 37.7% higher in patients receiving SSRIs, indicating clozap
study groups were too limited for an accurate statistical comparison between the individual SSRIs (Cento

3.5.1.AH Dalteparin

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and
anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp
reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Alter
coadministration of SSRIs with warfarin (Prod Info ZOLOFT(R) oral tablets, concentrate, 2008). Prothrombin
1997a).

3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When sertraline and an anticoagulant are given concurrently, monitor patient for sig closely for altered anticoagulant effects, including increased bleeding, when sertraline therapy is initiated or d
7) Probable Mechanism: unknown
8) Literature Reports
a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bl fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patien with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopram bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experie corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. T (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experienci addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respe patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other th
b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoum increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospit for abnormal bleeding and compared them with 5818 control subjects who were also taking a coumarin. on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (O bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).
c) Sertraline 50 mg to 200 mg daily for 21 days produced an 8% increase in prothrombin time in subject given prior to sertraline; this compared with a 1% decrease with placebo. Normalization of the prothromb findings is unknown (Prod Info ZOLOFT(R) oral tablets, concentrate, 2008).
d) In a non-blinded, randomized, placebo-controlled trial involving 12 healthy volunteers, the effect of se study, all participants received warfarin 0.75 mg/kg. Beginning on day 11, each volunteer was randomize mg/day to 200 mg/day. Prothrombin time was measured prior to each dose of warfarin and periodically th enhanced by sertraline to a clinically significant degree, despite the fact that sertraline was given in a hig

3.5.1.AI Danaparoid

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Alter coadministration of SSRIs with warfarin (Prod Info ZOLOFT(R) oral tablets, concentrate, 2008). Prothrombin 1997a).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When sertraline and an anticoagulant are given concurrently, monitor patient for sig closely for altered anticoagulant effects, including increased bleeding, when sertraline therapy is initiated or d
7) Probable Mechanism: unknown
8) Literature Reports
a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bl fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patien with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopram bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experie corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. T (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experienci addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respe patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other th
b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoum increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospit for abnormal bleeding and compared them with 5818 control subjects who were also taking a coumarin. on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (O bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).
c) Sertraline 50 mg to 200 mg daily for 21 days produced an 8% increase in prothrombin time in subject given prior to sertraline; this compared with a 1% decrease with placebo. Normalization of the prothromb findings is unknown (Prod Info ZOLOFT(R) oral tablets, concentrate, 2008).
d) In a non-blinded, randomized, placebo-controlled trial involving 12 healthy volunteers, the effect of se study, all participants received warfarin 0.75 mg/kg. Beginning on day 11, each volunteer was randomize mg/day to 200 mg/day. Prothrombin time was measured prior to each dose of warfarin and periodically th enhanced by sertraline to a clinically significant degree, despite the fact that sertraline was given in a hig

3.5.1.AJ Darunavir

1) Interaction Effect: decreased sertraline exposure and plasma concentrations
2) Summary: Coadministration of darunavir/ritonavir with sertraline has resulted in significantly decreased se sertraline dose should be carefully titrated based on clinical response. When darunavir/ritonavir is initiated in sertraline (Prod Info PREZISTA(TM) oral tablets, 2006).

3) Severity: moderate
4) Onset: unspecified
5) Substantiation: established
6) Clinical Management: Concurrent administration of sertraline with darunavir/ritonavir significantly decreas carefully titrate the sertraline dose based on clinical response. When darunavir/ritonavir is initiated in patients
7) Probable Mechanism: unknown
8) Literature Reports
a) In a pharmacokinetics study, concurrent administration of sertraline and darunavir/ritonavir significant administered sertraline 50 mg orally once daily concurrently with darunavir 400 mg/ritonavir 100 mg orall mean ratio % 0.56; 90% confidence interval (CI), 0.49 to 0.63), a 49% decreased in sertraline AUC (LS r mean ratio % 0.51; 90% CI, 0.45 to 0.57). Darunavir pharmacokinetics were not significantly altered (Pro

3.5.1.AK Defibrotide

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Alter coadministration of SSRIs with warfarin (Prod Info ZOLOFT(R) oral tablets, concentrate, 2008). Prothrombin 1997a).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When sertraline and an anticoagulant are given concurrently, monitor patient for sig closely for altered anticoagulant effects, including increased bleeding, when sertraline therapy is initiated or d
7) Probable Mechanism: unknown
8) Literature Reports
a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bl fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patien with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopram bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experie corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experienci addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respe patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other th
b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoum increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospit for abnormal bleeding and compared them with 5818 control subjects who were also taking a coumarin. on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (O bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).
c) Sertraline 50 mg to 200 mg daily for 21 days produced an 8% increase in prothrombin time in subject given prior to sertraline; this compared with a 1% decrease with placebo. Normalization of the prothromb findings is unknown (Prod Info ZOLOFT(R) oral tablets, concentrate, 2008).
d) In a non-blinded, randomized, placebo-controlled trial involving 12 healthy volunteers, the effect of se study, all participants received warfarin 0.75 mg/kg. Beginning on day 11, each volunteer was randomize mg/day to 200 mg/day. Prothrombin time was measured prior to each dose of warfarin and periodically t enhanced by sertraline to a clinically significant degree, despite the fact that sertraline was given in a hig

3.5.1.AL Dehydroepiandrosterone

1) Interaction Effect: development of manic symptoms
2) Summary: A case has been reported in which concomitant dehydroepiandrosterone (DHEA) and sertralin disorder (Dean, 2000a). DHEA was also noted to cause mania in a patient with no previous personal or famil found in patients with mental disorders; DHEA suppression has lead to improvement in psychotic symptoms to manic episodes (Majewska, 1995). DHEA is a precursor to androgenic steroids, which in high doses may p patients with a personal and/or family history of bipolar disorder should not take DHEA until further data is av serotonin reuptake inhibitors (SSRIs) should be avoided due to the potential additive precipitation of mania.
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Avoid concomitant use of dehydroepiandrosterone (DHEA) and selective serotonin irritability, aggressive behavior), determine if the patient is using DHEA and discontinue DHEA.
7) Probable Mechanism: serotonergic activity of dehydroepiandrosterone, possibly increased androgen level
8) Literature Reports
a) A 31-year-old male was admitted following threats to commit suicide and injure family members. He h depression. Sertraline had been prescribed 3 years prior when he was diagnosed with bipolar disorder, v 300 mg to 500 mg daily for the previous 2 months apparently for weight training. Following use of DHEA female friend and family members. He also drank alcohol occasionally and reportedly had difficulty contr valproic acid with the dose titrated to 500 mg twice daily. The combination of DHEA, sertraline, and alcol

3.5.1.AM Dermatan Sulfate

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Alter coadministration of SSRIs with warfarin (Prod Info ZOLOFT(R) oral tablets, concentrate, 2008). Prothrombin 1997a).

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: When sertraline and an anticoagulant are given concurrently, monitor patient for sig closely for altered anticoagulant effects, including increased bleeding, when sertraline therapy is initiated or d

7) Probable Mechanism: unknown

8) Literature Reports

a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bl fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patien with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopram bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experie corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experienci addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respe patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other th

b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoum increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospit for abnormal bleeding and compared them with 5818 control subjects who were also taking a coumarin. on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (O bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).

c) Sertraline 50 mg to 200 mg daily for 21 days produced an 8% increase in prothrombin time in subject given prior to sertraline; this compared with a 1% decrease with placebo. Normalization of the prothromb findings is unknown (Prod Info ZOLOFT(R) oral tablets, concentrate, 2008).

d) In a non-blinded, randomized, placebo-controlled trial involving 12 healthy volunteers, the effect of se study, all participants received warfarin 0.75 mg/kg. Beginning on day 11, each volunteer was randomize mg/day to 200 mg/day. Prothrombin time was measured prior to each dose of warfarin and periodically th enhanced by sertraline to a clinically significant degree, despite the fact that sertraline was given in a hig

3.5.1.AN Desipramine

1) Interaction Effect: modest elevation of desipramine serum levels or possible serotonin syndrome (hyperte

2) Summary: There is limited evidence suggesting that sertraline may inhibit tricyclic antidepressant (TCA) m P450 2D6 enzyme activity and may increase the plasma concentrations of coadministered drugs that are me Lydiard et al, 1993d; Prod Info Zoloft(R), 1999c). Effects of the interaction may have little or no clinical impact were modest compared with those found when fluoxetine (another selective serotonin reuptake inhibitor) was

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: The combined use of tricyclic antidepressants (TCAs) and selective serotonin reupt serotonin syndrome have also been reported with concurrent TCA and SSRI therapy. Caution should be obse

7) Probable Mechanism: inhibition of desipramine metabolism

8) Literature Reports

a) Desipramine pharmacokinetics was studied in 18 healthy male volunteers. Study subjects received o mg daily) for 21 days. When sertraline was added to desipramine therapy, the mean maximum concentra increased by 26%. Trough concentrations of desipramine were close to baseline one week after sertralin interaction may not be clinically significant (Preskorn et al, 1994h).

3.5.1.AO Desirudin

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Alter coadministration of SSRIs with warfarin (Prod Info ZOLOFT(R) oral tablets, concentrate, 2008). Prothrombin 1997a).

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: When sertraline and an anticoagulant are given concurrently, monitor patient for sig closely for altered anticoagulant effects, including increased bleeding, when sertraline therapy is initiated or d

7) Probable Mechanism: unknown

8) Literature Reports

a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bl

fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patien with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopran bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experie corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experienci addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respe patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other th

b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoum increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospit for abnormal bleeding and compared them with 5818 control subjects who were also taking a coumarin. on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (O bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).

c) Sertraline 50 mg to 200 mg daily for 21 days produced an 8% increase in prothrombin time in subject given prior to sertraline; this compared with a 1% decrease with placebo. Normalization of the prothromb findings is unknown (Prod Info ZOLOFT(R) oral tablets, concentrate, 2008).

d) In a non-blinded, randomized, placebo-controlled trial involving 12 healthy volunteers, the effect of se study, all participants received warfarin 0.75 mg/kg. Beginning on day 11, each volunteer was randomize mg/day to 200 mg/day. Prothrombin time was measured prior to each dose of warfarin and periodically t enhanced by sertraline to a clinically significant degree, despite the fact that sertraline was given in a hig

3.5.1.AP Desvenlafaxine

1) Interaction Effect: increased risk of serotonin syndrome (hypertension, hyperthermia, myoclonus, mental s

2) Summary: Concurrent use of desvenlafaxine and a selective serotonin reuptake inhibitor (SSRI) may resu may include restlessness, hallucinations, loss of coordination, fast heart beat, rapid changes in blood pressur (Prod Info PRISTIQ(TM) oral extended-release tablets, 2008).

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Coadministration of desvenlafaxine and an SSRI may result in a life-threatening co serotonin syndrome with the patient and monitor closely for symptoms of serotonin syndrome (restlessness, increases (Prod Info PRISTIQ(TM) oral extended-release tablets, 2008).

7) Probable Mechanism: additive serotonergic effect

3.5.1.AQ Dexfenfluramine

1) Interaction Effect: serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)

2) Summary: Dexfenfluramine is a nonspecific serotonin agonist that both enhances the release of serotonin selective serotonin reuptake inhibitor, such as sertraline, has the potential to cause serotonin syndrome (Sch by symptoms such as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shiverir Dexfenfluramine should not be used in combination with sertraline (Prod Info Redux(R), 1997).

3) Severity: major

4) Onset: rapid

5) Substantiation: theoretical

6) Clinical Management: Concurrent use of dexfenfluramine and sertraline may result in an additive increase (hypertension, hyperthermia, myoclonus, mental status changes). Dexfenfluramine should not be used in co

7) Probable Mechanism: additive serotonergic effects

3.5.1.AR Dexketoprofen

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control anc associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hemator suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solu

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent were searched among 26,005 users of antidepressant medications and compared with the number of ho amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton

b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with

3.5.1.AS Diclofenac

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control anc associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hemator

suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solu
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent were searched among 26,005 users of antidepressant medications and compared with the number of ho amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with

3.5.1.AT Dicumarol

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Alter coadministration of SSRIs with warfarin (Prod Info ZOLOFT(R) oral tablets, concentrate, 2008). Prothrombin 1997a).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When sertraline and an anticoagulant are given concurrently, monitor patient for sig closely for altered anticoagulant effects, including increased bleeding, when sertraline therapy is initiated or d
7) Probable Mechanism: unknown
8) Literature Reports
a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bl fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patien with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopram bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experie corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experienci addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respe patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other th
b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoum increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospit for abnormal bleeding and compared them with 5818 control subjects who were also taking a coumarin. on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (O bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).
c) Sertraline 50 mg to 200 mg daily for 21 days produced an 8% increase in prothrombin time in subject given prior to sertraline; this compared with a 1% decrease with placebo. Normalization of the prothromb findings is unknown (Prod Info ZOLOFT(R) oral tablets, concentrate, 2008).
d) In a non-blinded, randomized, placebo-controlled trial involving 12 healthy volunteers, the effect of se study, all participants received warfarin 0.75 mg/kg. Beginning on day 11, each volunteer was randomize mg/day to 200 mg/day. Prothrombin time was measured prior to each dose of warfarin and periodically t enhanced by sertraline to a clinically significant degree, despite the fact that sertraline was given in a hig

3.5.1.AU Diflunisal

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hemator suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solu
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent were searched among 26,005 users of antidepressant medications and compared with the number of ho amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with

3.5.1.AV Dipyridamole

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and
been associated with an increased risk of bleeding. Bleeding events reported have included epistaxis, ecchy
tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an antiplatelet agent are given concurrently, monitor patient for
PROZAC(R) oral capsules, delayed-release capsules, solution, 2008)
7) Probable Mechanism: unknown

3.5.1.AW Dipyrone

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and
associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hemator
suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solu
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent
were searched among 26,005 users of antidepressant medications and compared with the number of ho
amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 t
12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The
SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with

3.5.1.AX Dothiepin

1) Interaction Effect: modest elevations in dothiepin serum levels or possible serotonin syndrome (hypertens
2) Summary: There is limited evidence suggesting that sertraline may inhibit tricyclic antidepressant (TCA) m
P450 2D6 enzyme activity and may increase the plasma concentrations of coadministered drugs that are me
2002c; Preskorn et al, 1994a; Lydiard et al, 1993). Effects of the interaction may have little or no clinical impa
were modest compared with those found when fluoxetine (another selective serotonin reuptake inhibitor) was
sertraline therapy for TCA toxicity (dry mouth, urinary retention, CNS depression). Dothiepin doses may need
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: The combined use of tricyclic antidepressants (TCAs) and selective serotonin reupt
serotonin syndrome have also been reported with concurrent TCA and SSRI therapy. Caution should be obse
7) Probable Mechanism: inhibition of dothiepin metabolism
8) Literature Reports
a) Desipramine pharmacokinetics were studied in 18 healthy male volunteers. Study subjects received c
daily) for 21 days. When sertraline was added to desipramine therapy, the mean maximum concentration
increased by 26%. Trough concentrations of desipramine were close to baseline one week after sertralin
interaction may not be clinically significant (Preskorn et al, 1994).

3.5.1.AY Doxepin

1) Interaction Effect: modest elevations in doxepin serum levels or possible serotonin syndrome (hypertensio
2) Summary: There is limited evidence suggesting that sertraline may inhibit tricyclic antidepressant (TCA) m
P450 2D6 enzyme activity and may increase the plasma concentrations of coadministered drugs that are me
2002f; Preskorn et al, 1994e; Lydiard et al, 1993b). Effects of the interaction may have little or no clinical impa
were modest compared with those found when fluoxetine (another selective serotonin reuptake inhibitor) was
sertraline therapy for TCA toxicity (dry mouth, urinary retention, CNS depression). Doxepin doses may need t
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: The combined use of tricyclic antidepressants (TCAs) and selective serotonin reupt
serotonin syndrome have also been reported with concurrent TCA and SSRI therapy. Caution should be obse
7) Probable Mechanism: inhibition of doxepin metabolism
8) Literature Reports
a) Desipramine pharmacokinetics was studied in 18 healthy male volunteers. Study subjects received or
daily) for 21 days. When sertraline was added to desipramine therapy, the mean maximum concentration
increased by 26%. Trough concentrations of desipramine were close to baseline one week after sertralin
interaction may not be clinically significant (Preskorn et al, 1994d).

3.5.1.AZ Droperidol

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Any drug known to have the potential to prolong the QT interval should not be used together w potentially arrhythmogenic agents such as antidepressants that prolong the QT interval (Prod Info Inapsine(R
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Droperidol should be administered with extreme caution in the presence of risk fact
7) Probable Mechanism: additive cardiac effects

3.5.1.BA Droxicam

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hemator suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solu
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent were searched among 26,005 users of antidepressant medications and compared with the number of ho amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with

3.5.1.BB Duloxetine

1) Interaction Effect: an increased risk of serotonin syndrome
2) Summary: Duloxetine is a selective serotonin and norepinephrine reuptake inhibitor. The concomitant use due to the potential for serotonin syndrome (Prod Info CYMBALTA(R) delayed-release oral capsules, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concomitant use of duloxetine and sertraline is not recommended due to the po oral capsules, 2008).
7) Probable Mechanism: additive serotonergic effects

3.5.1.BC Efavirenz

1) Interaction Effect: decreased sertraline plasma concentrations
2) Summary: Coadministration of efavirenz and sertraline resulted in significantly decreased concentrations sertraline doses based on clinical response (Prod Info SUSTIVA(R) oral capsules, tablets, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: established
6) Clinical Management: The concomitant use of efavirenz and sertraline resulted in significantly reduced ex sertraline are coadministered. Sertraline doses may need to be increased based on clinical response (Prod In
7) Probable Mechanism: induction of CYP3A4-mediated sertraline metabolism by efavirenz
8) Literature Reports
a) In a pharmacokinetics study, concurrent administration of efavirenz and sertraline significantly decrea sertraline 50 mg orally once daily concurrently with efavirenz 600 mg orally once daily for 14 days. Resul 40%), a 39% decrease in sertraline AUC (90% CI, 27% to 50%), and a 46% decrease in sertraline Cmin was a mean 11% (90% CI, 6% to 16%) increase in efavirenz Cmax (Prod Info SUSTIVA(R) oral capsules

3.5.1.BD Eletriptan

1) Interaction Effect: an increased risk of serotonin syndrome
2) Summary: There have been case reports of weakness, hyperreflexia, and incoordination following concon specific reuptake inhibitor (SSRI) (Prod Info Imitrex(R) Nasal Spray, 2003). Because eletriptan is a 5HT 1B/1 (R), 2003). Concurrent use of a triptan and an SSRI may result in serotonin syndrome which may be life-threa of coordination, fast heart beat, rapid changes in blood pressure, increased body temperature, overreactive r commonly used intermittently and that either the triptan or the SSRI may be prescribed by a different physicia combination and monitor them closely for symptoms of serotonin syndrome (US Food and Drug Administratio
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Coadministration of a triptan, such as eletriptan, and an SSRI may result in a life-th used intermittently and that either the triptan or the SSRI may be prescribed by a different physician. If these monitor closely for symptoms of serotonin syndrome (restlessness, hyperthermia, hyperreflexia, incoordinatio

7) Probable Mechanism: additive pharmacologic effects resulting in excessive serotonergic stimulation

3.5.1.BE Enoxaparin

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Alter coadministration of SSRIs with warfarin (Prod Info ZOLOFT(R) oral tablets, concentrate, 2008). Prothrombin 1997a).

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: When sertraline and an anticoagulant are given concurrently, monitor patient for sig closely for altered anticoagulant effects, including increased bleeding, when sertraline therapy is initiated or d

7) Probable Mechanism: unknown

8) Literature Reports

a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bl fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patien with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopram bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experie corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experienci addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respe patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other th

b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoum increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospit for abnormal bleeding and compared them with 5818 control subjects who were also taking a coumarin. on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (O bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).

c) Sertraline 50 mg to 200 mg daily for 21 days produced an 8% increase in prothrombin time in subject given prior to sertraline; this compared with a 1% decrease with placebo. Normalization of the prothromb findings is unknown (Prod Info ZOLOFT(R) oral tablets, concentrate, 2008).

d) In a non-blinded, randomized, placebo-controlled trial involving 12 healthy volunteers, the effect of se study, all participants received warfarin 0.75 mg/kg. Beginning on day 11, each volunteer was randomize mg/day to 200 mg/day. Prothrombin time was measured prior to each dose of warfarin and periodically t enhanced by sertraline to a clinically significant degree, despite the fact that sertraline was given in a hig

3.5.1.BF Epoprostenol

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and been associated with an increased risk of bleeding. Bleeding events reported have included epistaxis, ecchy tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an antiplatelet agent are given concurrently, monitor patient for PROZAC(R) oral capsules, delayed-release capsules, solution, 2008)

7) Probable Mechanism: unknown

3.5.1.BG Eptifibatide

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and been associated with an increased risk of bleeding. Bleeding events reported have included epistaxis, ecchy tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an antiplatelet agent are given concurrently, monitor patient for PROZAC(R) oral capsules, delayed-release capsules, solution, 2008)

7) Probable Mechanism: unknown

3.5.1.BH Erythromycin

1) Interaction Effect: an increased risk of serotonin syndrome (hypertension, hyperthermia, myoclonus, ment

2) Summary: Serotonin syndrome was precipitated in a pediatric patient taking sertraline when erythromycin status had significantly improved. Erythromycin induces cytochrome P450 3A (CYP3A), becomes demethylat formation of this inactive complex is associated with decreased CYP3A activity both in the liver and the small route of metabolism may result in elevated sertraline levels (Lee & Lee, 1999a).

3) Severity: major

4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: All patients receiving a serotonergic medication should be monitored for signs and s
7) Probable Mechanism: inhibition by erythromycin of cytochrome P450 3A4-mediated sertraline metabolism
8) Literature Reports
a) Sertraline 37.5 mg daily was prescribed for a 12-year-old boy with severe obsessive-compulsive diso adverse effects before erythromycin 200 mg twice daily was initiated. Within four days of concurrent ther restlessness, paresthesias, tremulousness, and confusion. Erythromycin and sertraline were both discon

3.5.1.BI Etodolac

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematon suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solu
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent were searched among 26,005 users of antidepressant medications and compared with the number of ho amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 t 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with

3.5.1.BJ Etofenamate

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematon suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solu
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent were searched among 26,005 users of antidepressant medications and compared with the number of ho amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 t 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with

3.5.1.BK Etoricoxib

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematon suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solu
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent were searched among 26,005 users of antidepressant medications and compared with the number of ho amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 t 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with

3.5.1.BL Felbinac

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematon suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solu

3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent were searched among 26,005 users of antidepressant medications and compared with the number of ho amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 t 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with

3.5.1.BM Fenbufen
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hemator suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solu
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent were searched among 26,005 users of antidepressant medications and compared with the number of ho amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 t 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with

3.5.1.BN Fenfluramine
1) Interaction Effect: serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)
2) Summary: Fenfluramine is a nonspecific serotonin agonist that both enhances the release of serotonin an serotonin reuptake inhibitor, such as sertraline, has the potential to cause serotonin syndrome (Schenck & M symptoms such as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, more data are available, fenfluramine should not be used in combination with sertraline.
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Concurrent use of fenfluramine and sertraline may result in an additive increase in s (hypertension, hyperthermia, myoclonus, mental status changes). Fenfluramine should not be used in combi
7) Probable Mechanism: additive serotonergic effects

3.5.1.BO Fenoprofen
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hemator suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solu
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent were searched among 26,005 users of antidepressant medications and compared with the number of ho amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 t 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with

3.5.1.BP Fentiazac
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hemator suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solu
3) Severity: moderate

4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent were searched among 26,005 users of antidepressant medications and compared with the number of ho amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 t 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with

3.5.1.BQ Flecainide
1) Interaction Effect: an increased risk of flecainide toxicity (cardiac arrhythmia)
2) Summary: No data are currently available related to concomitant flecainide - sertraline administration. Fle al, 1994). Sertraline inhibits the CYP2D6 isoenzyme (Prod Info Zoloft(R), 2002k; DeVane, 1994c). With flecai higher flecainide serum levels and possible flecainide toxicity. Controlled studies are needed to investigate th
3) Severity: major
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Coadministration of these agents should be approached with caution. Monitor the E need to be reduced.
7) Probable Mechanism: inhibition of flecainide metabolism

3.5.1.BR Floctafenine
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hemator suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solu
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent were searched among 26,005 users of antidepressant medications and compared with the number of ho amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 t 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with

3.5.1.BS Flufenamic Acid
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hemator suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solu
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent were searched among 26,005 users of antidepressant medications and compared with the number of ho amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 t 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with

3.5.1.BT Fluphenazine
1) Interaction Effect: an increased risk of developing acute parkinsonism
2) Summary: The development of acute, severe parkinsonism has been observed in a patient receiving fluph sertraline, the parkinsonism resolved. A similar interaction has been observed when fluphenazine was given
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Patients receiving concurrent therapy with fluphenazine and sertraline should be m

need to be discontinued.
7) Probable Mechanism: inhibition of cytochrome P450-mediated fluphenazine metabolism by sertraline
8) Literature Reports
a) A 45-year-old male with chronic, multiple motor and vocal tics since childhood was successfully contr
discontinued, and fluphenazine was instituted without an improvement in the patient's mood. Sertraline 1
parkinsonism after eight weeks. When fluphenazine was discontinued, the parkinsonism resolved, but th

3.5.1.BU Flurbiprofen
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and
associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematon
suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solu
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent
were searched among 26,005 users of antidepressant medications and compared with the number of ho
amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 t
12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The
SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with

3.5.1.BV Fondaparinux
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and
anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp e
reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Alter
coadministration of SSRIs with warfarin (Prod Info ZOLOFT(R) oral tablets, concentrate, 2008). Prothrombin
1997a).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When sertraline and an anticoagulant are given concurrently, monitor patient for sig
closely for altered anticoagulant effects, including increased bleeding, when sertraline therapy is initiated or d
7) Probable Mechanism: unknown
8) Literature Reports
a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bl
fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patien
with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopram
bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experie
corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. T
(95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experienci
addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respe
patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other tha
b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoum
increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospit
for abnormal bleeding and compared them with 5818 control subjects who were also taking a coumarin.
on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OI
bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).
c) Sertraline 50 mg to 200 mg daily for 21 days produced an 8% increase in prothrombin time in subject
given prior to sertraline; this compared with a 1% decrease with placebo. Normalization of the prothromb
findings is unknown (Prod Info ZOLOFT(R) oral tablets, concentrate, 2008).
d) In a non-blinded, randomized, placebo-controlled trial involving 12 healthy volunteers, the effect of se
study, all participants received warfarin 0.75 mg/kg. Beginning on day 11, each volunteer was randomize
mg/day to 200 mg/day. Prothrombin time was measured prior to each dose of warfarin and periodically th
enhanced by sertraline to a clinically significant degree, despite the fact that sertraline was given in a hig

3.5.1.BW Fosphenytoin
1) Interaction Effect: an increased risk of phenytoin toxicity (ataxia, hyperreflexia, nystagmus, tremor)
2) Summary: Fosphenytoin is a prodrug of phenytoin and the same interactions that occur with phenytoin are
sertraline with phenytoin has been reported to result in elevated serum phenytoin levels in two elderly patient
verify the extent of this interaction.
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable

6) Clinical Management: Caution is warranted if fosphenytoin and sertraline are to be coadministered. Serun therapy or changing the sertraline dose. Monitor patients for signs and symptoms of phenytoin toxicity (ataxia downward.
7) Probable Mechanism: sertraline inhibition of phenytoin metabolism by cytochrome P450 isoenzymes
8) Literature Reports
a) Sertraline is known to be a moderate to weak inhibitor of the cytochrome P450IID6 isoenzyme (CYP2 metabolism of phenytoin may involve the cytochrome P450IID6 (Murray, 1992) and the CYP2C9 hepatic activity and pathways, it seems theoretically possible that concurrent sertraline may act to inhibit metabo
b) Two cases in which elderly patients developed elevated serum phenytoin concentrations during coad phenytoin 300 mg per day in addition to several other medications. After sertraline 25 mg every night for to 12.3 mcg/mL. After serial increases in the sertraline dose to 75 mg per day, the patient's serum pheny restarted at a dose of 200 mg per day. Sertraline 100 mg per day was also administered without further a levels (from 15.6 mcg/mL to 20 mcg/mL) after the addition of sertraline 25 mg every other day to phenyto within one week after starting sertraline therapy or initiating a change in sertraline dose (Haselberger et a

3.5.1.BX Frovatriptan
1) Interaction Effect: an increased risk of serotonin syndrome
2) Summary: There have been case reports of weakness, hyperreflexia, and incoordination following concon specific reuptake inhibitor (SSRI) (Prod Info Imitrex(R) Nasal Spray, 2003). Because frovatriptan is a 5HT 1B/ Frova(R), 2004). Concurrent use of frovatriptan and an SSRI may result in serotonin syndrome which may be hallucinations, loss of coordination, fast heart beat, rapid changes in blood pressure, increased body tempera that triptans may be commonly used intermittently and that either the triptan or the SSRI may be prescribed b prescribed this combination and monitor them closely for symptoms of serotonin syndrome (US Food and Dru
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Coadministration of a triptan, such as frovatriptan, and an SSRI may result in a life- used intermittently and that either the triptan or the SSRI may be prescribed by a different physician. If these monitor closely for symptoms of serotonin syndrome (restlessness, hyperthermia, hyperreflexia, incoordinatio
7) Probable Mechanism: additive pharmacologic effects resulting in excessive serotonergic stimulation

3.5.1.BY Furazolidone
1) Interaction Effect: weakness, hyperreflexia, and incoordination
2) Summary: Although not its primary mechanism of action, furazolidone has monoamine oxidase inhibitor a receiving selective serotonin reuptake inhibitors (SSRI) in combination with monoamine oxidase inhibitors (M fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium a SSRI, or within a minimum of 14 days of discontinuing therapy with a MAOI (Prod Info Furoxone(R), 1999).
3) Severity: contraindicated
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: If concurrent therapy with furazolidone and a selective serotonin reuptake inhibitor (excess (mental status changes, diaphoresis, fever, weakness, hyperreflexia, incoordination).
7) Probable Mechanism: additive pharmacologic effects resulting in excessive serotonergic stimulation

3.5.1.BZ Ginkgo
1) Interaction Effect: increased risk of serotonin syndrome (hypertension, hyperthermia, myoclonus, mental s
2) Summary: The addition of Ginkgo biloba and/or St. John's Wort to therapy with buspirone and fluoxetine r is unclear if Ginkgo or St. John's Wort, the combination of both, or other patient factors, contributed to the effe selective serotonin reuptake inhibitors (SSRIs). Caution is advised, especially when ginkgo is taken to counte (Sloley et al, 2000; White et al, 1996), and has demonstrated serotonergic activity in animals (Ramassamy et with SSRIs. The potential MAO inhibitory activity of ginkgo is questionable. A human study did not show MAO extract inhibited MAO-A/MAO-B in the rat brain in vitro (Sloley et al, 2000; White et al, 1996) and MAO-B in h following oral consumption (Porsolt et al, 2000).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor patients closely for symptoms of serotonin syndrome if ginkgo is combined
7) Probable Mechanism: additive pharmacologic effects resulting in excessive serotonergic stimulation
8) Literature Reports
a) A 42-year-old female experienced symptoms consistent with a mixed hypomanic episode following co symptoms resolved following discontinuation of Ginkgo and St. John's Wort. The patient was being treate twice daily and buspirone 15 mg twice daily. Several weeks prior to presentation, buspirone was increase melatonin, and St. John's Wort in unspecified doses. Melatonin was considered unlikely to have contribu since they may potentiate antidepressants, and considering the temporal relationship between the use o symptoms. However, the brain injury was considered a possible contributor (Spinella & Eaton, 2002).

3.5.1.CA Heparin
1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and
anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp
reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Alter
coadministration of SSRIs with warfarin (Prod Info ZOLOFT(R) oral tablets, concentrate, 2008). Prothrombin
1997a).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When sertraline and an anticoagulant are given concurrently, monitor patient for sig
closely for altered anticoagulant effects, including increased bleeding, when sertraline therapy is initiated or d
7) Probable Mechanism: unknown
8) Literature Reports
a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bl
fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patien
with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopram
bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experie
corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively.
(95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experienci
addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respe
patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other th
b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoum
increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospit
for abnormal bleeding and compared them with 5818 control subjects who were also taking a coumarin.
on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (O
bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).
c) Sertraline 50 mg to 200 mg daily for 21 days produced an 8% increase in prothrombin time in subject
given prior to sertraline; this compared with a 1% decrease with placebo. Normalization of the prothromb
findings is unknown (Prod Info ZOLOFT(R) oral tablets, concentrate, 2008).
d) In a non-blinded, randomized, placebo-controlled trial involving 12 healthy volunteers, the effect of se
study, all participants received warfarin 0.75 mg/kg. Beginning on day 11, each volunteer was randomize
mg/day to 200 mg/day. Prothrombin time was measured prior to each dose of warfarin and periodically th
enhanced by sertraline to a clinically significant degree, despite the fact that sertraline was given in a hig

3.5.1.CB Hydroxytryptophan

1) Interaction Effect: an increased risk of serotonin syndrome (hypertension, hyperthermia, myoclonus, ment
2) Summary: Hydroxytryptophan (5-HTP) may potentiate the serotonergic effect of selective serotonin reupta
when combined with an SSRI, the serotonin level may be increased sufficiently to produce serotonin syndron
3) Severity: moderate
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: No cases have been reported of serotonin syndrome resulting from this combinatio
inhibitor (SSRI) are used concomitantly. Monitor the patient for early signs of serotonin syndrome such as an
7) Probable Mechanism: additive serotonergic effect
8) Literature Reports
a) Hydroxytryptophan (5-HTP) (200 milligrams (mg) orally) as a single dose increased plasma cortisol a
obsessive compulsive disorder (OCD). These responses were greater if the patient was also taking fluox
mg/day,and for OCD patients it was 60 mg/day. Cortisol or prolactin (PRL) levels in patients taking 5-HT
significantly different from each other. A measurement of serotonergic effects of antidepressants can be
clinical manifestations of serotonin syndrome were reported in patients taking 5-HTP concomitantly with

3.5.1.CC Ibuprofen

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and
associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematom
suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solu
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent
were searched among 26,005 users of antidepressant medications and compared with the number of ho
amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7
12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The
SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with

3.5.1.CD Iloprost

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and
been associated with an increased risk of bleeding. Bleeding events reported have included epistaxis, ecchy
tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an antiplatelet agent are given concurrently, monitor patient for
PROZAC(R) oral capsules, delayed-release capsules, solution, 2008)

7) Probable Mechanism: unknown

3.5.1.CE Imipramine

1) Interaction Effect: modest elevations in imipramine serum levels or possible serotonin syndrome (hyperter

2) Summary: There is limited evidence suggesting that sertraline may inhibit tricyclic antidepressant (TCA) m
P450 2D6 enzyme activity and may increase the plasma concentrations of coadministered drugs that are me
Lydiard et al, 1993g; Prod Info Zoloft(R), 1999f). Effects of the interaction may have little or no clinical impact
modest compared with those found when fluoxetine (another selective serotonin reuptake inhibitor) was coml
therapy for TCA toxicity (dry mouth, urinary retention, CNS depression). Imipramine doses may need to be re

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: The combined use of tricyclic antidepressants (TCAs) and selective serotonin reupt
serotonin syndrome have also been reported with concurrent TCA and SSRI therapy. Caution should be obse

7) Probable Mechanism: inhibition of imipramine metabolism

8) Literature Reports

a) Desipramine pharmacokinetics was studied in 18 healthy male volunteers. Study subjects received o
daily) for 21 days. When sertraline was added to desipramine therapy, the mean maximum concentratio
increased by 26%. Trough concentrations of desipramine were close to baseline one week after sertralin
interaction may not be clinically significant (Preskorn et al, 1994n).

3.5.1.CF Indomethacin

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and
associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hemator
suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solu

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent
were searched among 26,005 users of antidepressant medications and compared with the number of ho
amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 t
12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The
SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton

b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with

3.5.1.CG Indoprofen

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and
associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hemator
suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solu

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent
were searched among 26,005 users of antidepressant medications and compared with the number of ho
amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 t
12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The
SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton

b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with

3.5.1.CH Iproniazid

1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental sta
2) Summary: Concurrent administration or overlapping therapy with sertraline and a monoamine oxidase (MA characterized by symptoms such as restlessness, myoclonus, changes in mental status, hyperreflexia, diaph concomitant use of serotonin specific reuptake inhibitors and MAO inhibitors (Prod Info Zoloft(R), 1999e; Lap & de Vries, 1990e). Concomitant use is contraindicated.
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Concurrent use of sertraline and a MAO inhibitor is contraindicated. Wait at least 14 least 14 days after discontinuing sertraline before initiating therapy with a MAO inhibitor.
7) Probable Mechanism: inhibition of serotonin metabolism by monoamine oxidase
8) Literature Reports
a) Concomitant use of SSRIs and monoamine oxidase inhibitors can produce a toxic reaction known as hyperstimulation and manifests as restlessness, myoclonus, changes in mental status, hyperreflexia, dia fatality can result.
b) A 26-year old woman who had been taking isocarboxazid for eight weeks stopped taking the drug for the patient became restless and developed leg twitches. The patients was later admitted to the emergen disturbances. After treatment with diazepam and propranolol the patient did not improve. The patient was symptoms after the second dose (Lappin & Auchincloss, 1994f).
c) A drug interaction was reported in a 61-year old woman in which sertraline 100 mg twice daily was ad taking the first sertraline dose, the patient was found in a semicomatose state, with elevated body tempe Hg. After transportation to the hospital, the patient was misdiagnosed as having neuroleptic malignant sy sertraline and phenelzine. The authors suggest that monoamine oxidase inhibitor (MAOI) therapy should serotonin reuptake inhibitor (SSRI) and that before starting a MAOI, SSRI therapy should be discontinue 1994f).
d) Two cases reports suggested a possible interaction between fluoxetine and selegiline (Suchowersky approximately one month after adding selegiline to fluoxetine. The patient improved two months after bot involved diaphoresis, vasoconstriction, and cyanosis of the hands which occurred in close temporal relat quick resolution of symptoms. Rechallenge with fluoxetine alone occurred without incident.

3.5.1.CI Isocarboxazid

1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental sta
2) Summary: Concurrent administration or overlapping therapy with sertraline and a monoamine oxidase (MA characterized by symptoms such as restlessness, myoclonus, changes in mental status, hyperreflexia, diaph Zoloft(R), 2002l; Lappin & Auchincloss, 1994i; Graber et al, 1994i; Bhatara & Bandettini, 1993d; Suchowersky
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Concurrent use of sertraline and a MAO inhibitor is contraindicated. Wait at least 14 least 14 days after discontinuing sertraline before initiating therapy with a MAO inhibitor.
7) Probable Mechanism: inhibition of serotonin metabolism by monoamine oxidase
8) Literature Reports
a) Concomitant use of serotonin specific reuptake inhibitors and monoamine oxidase inhibitors can prod syndrome is a condition of serotonergic hyperstimulation and manifests as restlessness, myoclonus, cha not recognized and correctly treated, death can result.
b) A 26-year old woman who had been taking isocarboxazid for eight weeks stopped taking the drug for the patient became restless and developed leg twitches. The patients was later admitted to the emergen disturbances. The patient did not improve after treatment with diazepam and propranolol. The patient wa in symptoms after the second dose (Lappin & Auchincloss, 1994h).
c) A drug interaction was reported in a 61-year old woman in which sertraline 100 mg twice daily was ad taking the first sertraline dose, the patient was found in a semicomatose state, with elevated body tempe mmHg. After transportation to the hospital, the patient was misdiagnosed as having neuroleptic malignar between sertraline and phenelzine. The authors suggest that MAO inhibitor therapy should be discontinu inhibitor (SSRI) and that before starting a MAOI, SSRI therapy should be discontinued for at least 5 half-
d) Two cases reports suggested a possible interaction between fluoxetine and selegiline (Suchowersky approximately 1 month after adding selegiline to fluoxetine therapy. The patient improved 2 months after involved diaphoresis, vasoconstriction, and cyanosis of the hands which occurred in close temporal relat quick resolution of symptoms. Rechallenge with fluoxetine alone occurred without incident.

3.5.1.CJ Isoxicam

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hemator suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solu
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in

7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent were searched among 26,005 users of antidepressant medications and compared with the number of ho amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 t 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with

3.5.1.CK Ketoprofen
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hemator suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solu
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent were searched among 26,005 users of antidepressant medications and compared with the number of ho amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 t 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with

3.5.1.CL Ketorolac
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hemator suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solu
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent were searched among 26,005 users of antidepressant medications and compared with the number of ho amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 t 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with

3.5.1.CM Lamifiban
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and been associated with an increased risk of bleeding. Bleeding events reported have included epistaxis, ecchyr tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an antiplatelet agent are given concurrently, monitor patient for PROZAC(R) oral capsules, delayed-release capsules, solution, 2008)
7) Probable Mechanism: unknown

3.5.1.CN Lamotrigine
1) Interaction Effect: an increased risk of lamotrigine toxicity (fatigue, sedation, confusion, decreased cognitic
2) Summary: Two case reports describe epileptic patients who experienced lamotrigine toxicity when sertrali sertraline relies on N-demethylation, hydroxylation, oxidative deamination, and glucuronidation. It is hypothes glucuronidation (Kaufman & Gerner, 1998a).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Caution should be exercised when combining sertraline and lamotrigine therapy. La
7) Probable Mechanism: inhibition of lamotrigine glucuronidation
8) Literature Reports

a) A 39-year-old female with epilepsy was maintained on lamotrigine 200 mg daily with a baseline lamot
25 mg daily was initiated. Six weeks later, the lamotrigine level was 5.1 mcg/mL and the patient complair
lamotrigine was decreased to 100 mg daily. This lower lamotrigine dose eliminated the patient's confusic
(Kaufman & Gerner, 1998).
b) Lamotrigine 450 mg daily was not controlling seizures in a 17-year-old female with mixed epileptic dis
any side effects. Lamotrigine was also increased to 600 mg daily, and six weeks later, the patient compla
mcg/mL at this time. The sertraline dose was decreased to 50 mg daily while the lamotrigine level was in
In this case report, the lamotrigine blood level decreased to approximately 50% with a 33% decrease in t
(Kaufman & Gerner, 1998).

3.5.1.CO Levomethadyl

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Any drug known to have the potential to prolong the QT interval should not be used with levom
potentially arrhythmogenic agents such as sertraline that prolong the QT interval (Prod Info Orlaam(R), 2001)
3) Severity: contraindicated
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Levomethadyl is contraindicated in patients being treated with sertraline as it may p
7) Probable Mechanism: unknown

3.5.1.CP Lexipafant

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and
been associated with an increased risk of bleeding. Bleeding events reported have included epistaxis, ecchyr
tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an antiplatelet agent are given concurrently, monitor patient for
PROZAC(R) oral capsules, delayed-release capsules, solution, 2008)
7) Probable Mechanism: unknown

3.5.1.CQ Linezolid

1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental sta
2) Summary: Linezolid is a reversible, nonselective inhibitor of monoamine oxidase. Concurrent administratio
result in CNS toxicity or serotonin syndrome, a hyperserotonergic state characterized by symptoms such as r
and tremor. Serious, even fatal, reactions have been reported. There have been spontaneous reports of sero
(Prod Info ZYVOX(R) IV injection, oral tablets, oral suspension, 2008; Prod Info Zoloft(R) sertraline HCl table
of serotonin syndrome. Serotonin syndrome can be life-threatening. If serotonin syndrome develops, disconti
(Boyer & Shannon, 2005).
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Unless carefully monitored for serotonin syndrome, linezolid should not be administ
suspension, 2008). If linezolid and sertraline are used concomitantly, monitor closely for symptoms of serotor
muscle rigidity, clonus, peripheral hypertonicity, and shivering), autonomic hyperactivity (including tachycardi
and delirium). Serotonin syndrome can be life-threatening. If serotonin syndrome develops, discontinue the o
Shannon, 2005).
7) Probable Mechanism: inhibition of serotonin metabolism by monoamine oxidase
8) Literature Reports

a) A case of serotonin syndrome occurred in a patient who was prescribed linezolid and sertraline. A 45
service after an acute suicide attempt that resulted in a T6 level spinal cord injury and paraplegia. Pharm
after the patient was diagnosed with acute depression and psychosis. Bupropion 75 mg twice daily, trazo
patient underwent sacral flap closure with a bilateral gluteal myocutaneous flap and then developed a de
for several days. Culture of the ulcer revealed a vancomycin-resistant enterococcus fecalis. He was start
hours. Lithium was discontinued after the patients lithium carbonate level was found to be elevated at 1.
increasing tremor, nausea, vomiting, diarrhea, and dry mouth. Sertraline, bupropion and trazodone were
sodium, bisacodyl, megestrol, lansoprazole, and risperidone. The following day the patient became deliri
elevated to 100.1 degrees Fahrenheit, pulse 101, respirations 20/min, and blood pressure 100/71 mm Hg
minimally reactive. A diagnosis of serotonin syndrome was considered. Symptoms of serotonin syndrom
b) A retrospective chart review identified one highly probable case of serotonin syndrome in a patient wh
Charts of 72 inpatients who received linezolid and an SSRI or venlafaxine within 14 days of each other w
Hunter Serotonin Toxicity criteria. Of these patients, 52 (72%) were treated concomitantly with linezolid a
probability of SS. Of these, one case involved an 81-year-old woman who was diagnosed with a high pro
citalopram. Linezolid was given for a vancomycin-resistant Enterococcus urinary tract infection. When th
shouting. Although she appeared to have met 6 of the Sternbach criteria and 4 of the Hunter criteria for S
Hg with a heart rate of 120 beats/min, and a respiratory rate of 50 breaths/min. The following day, she ba
twitching and jerking, eyes rolled back in her head, and labored breathing. Linezolid was discontinued, a

after linezolid was stopped, she was extubated and had returned to baseline mental status with the abilit
c) In one case report, a 36-year-old male experience symptoms of serotonin syndrome after concomitar transplant after receiving high-doses of cyclophosphamide, total body irradiation, and antihymocyte globu versus-host disease, thrombotic thrombocytic purpura, renal failure, and multiple pulmonary infections. C medications consisted of tacrolimus, corticosteroids, thalidomide 100 mg daily, sertraline 50 mg daily, mo restlessness, delirium and agitation. He developed hypertension and a high fever (40 degrees Celsius). V all medications with neurological effects were discontinued, including sertraline, thalidomide, alprazolam, and morphine were reinstated with no reoccurrence of symptoms (Hachem et al, 2003).

3.5.1.CR Lithium

1) Interaction Effect: possible increased lithium concentrations and/or an increased risk of SSRI-related sero
2) Summary: Concomitant use of lithium and various SSRIs has been associated with enhanced side effects resulted in neurotoxicity and increased lithium levels in one case report (Salama & Shafey, 1989a). Signs and who demonstrated therapeutic serum lithium levels while on concurrent fluoxetine and lithium (Muly et al, 199 interaction between lithium and citalopram (Gram et al, 1993a; Baumann et al, 1996a). Combined administra significant effect on the pharmacokinetics of citalopram or lithium. However, plasma lithium levels should be m clinical practice. Lithium may enhance the serotonergic effects of citalopram, therefore caution should be exe Concurrent use of fluvoxamine and lithium has led to case reports of increased lithium levels and neurotoxicit Spigset, 1993a; Evans & Marwick, 1990; Burrai et al, 1991a). No pharmacokinetic interference was apparent (TM), 2003). If these two agents are to be given concomitantly, the manufacturer suggests that caution be us have been reported when lithium was coadministered with fluoxetine and fluvoxamine (both in the same phar Spigset, 1993a; Salama & Shafey, 1989a).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: established
6) Clinical Management: Monitor patients on concurrent lithium and selective serotonin reuptake inhibitor the and symptoms associated with serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status c
7) Probable Mechanism: unknown
8) Literature Reports
a) Concomitant administration of oral lithium carbonate and oral fluoxetine resulted in increased lithium s (Salama & Shafey, 1989). Fluoxetine 20 mg daily was added to a regimen of lithium 1200 mg daily follow morning awakening. Lithium serum levels increased to 1.7 mEq/L from a range of 0.75 to 1.15 mEq/L pri resulted in a decrease in the lithium serum level within 48 hours to 1.2 mEq/L. The neurologic symptoms contribution of fluoxetine to lithium toxicity in this patient was obscured by the fact that the lithium was re
b) A 53-year old woman who had been taking fluoxetine 20 mg daily and lorazepam 0.5 mg four times d order to augment her response to fluoxetine. Within 48 hours, the patient became confused, ataxic, and degrees F, and laboratory values were normal except for an elevated leukocyte count and slightly elevat resolved over the next four days. At no point did the lithium levels reach a toxic level, suggesting that the et al, 1989).
c) Serotonin syndrome was precipitated when lithium 300 mg twice daily was added to a three-month re measured at 0.65 mEq/L and the dose was increased to 300 mg three times daily. Two days after this do tremor, diarrhea, and incoordination. After discontinuation of lithium and initiation of cyproheptadine thera of fluoxetine 40 mg per day without further symptoms of serotonin syndrome (Muly et al, 1993).
d) Eight healthy male volunteers completed three phases of an interaction study to determine the effects sparteine, indicating normal cytochrome P450 2D6 enzyme activity. Although lithium is not influenced by subject received citalopram 40 mg alone as a single daily dose for 10 days, lithium 30 mmol (1980 mg) a two weeks separated each treatment phase. Results showed that the concurrent administration of citalo 1993).
e) Twenty-four patients experiencing depression (DSM III criteria) were randomized under double-blind daily) or placebo. All of the subjects had failed to respond to four weeks of citalopram monotherapy. Lithi between lithium and citalopram was noted, and cotherapy was well tolerated (Baumann et al, 1996).
f) Serotonin syndrome was described in a 53-year-old patient who was stabilized on lithium 1400 mg da period the fluvoxamine dose was increased to 200 mg daily; tremor and difficulty with fine hand moveme bilateral hyperreflexia of biceps and knee jerks, and clonus in both ankles were seen. After 12 weeks of daily replaced fluvoxamine, and the neuromuscular symptoms abated over a 2-week period. After four w
g) Three cases of mania were reported in patients who were treated with lithium and fluvoxamine. The r begun. Fluvoxamine was discontinued and, in two of the three patients, the mania resolved, and success depression reappeared within a month of fluvoxamine discontinuation (Burrai et al, 1991).
h) In an open-labeled, placebo-controlled study, lithium 600 mg was administered to 16 subjects orally t sertraline 100 mg or placebo was given twice, ten hours and two hours prior to lithium dosing on day nin renal clearance increased by 6.9% (0.11 L/hour) when sertraline was coadministered. Seven subjects ex subjects who ingested placebo and lithium experienced side effects (Wilner et al, 1991).

3.5.1.CS Lofepramine

1) Interaction Effect: modest elevations in lofepramine serum levels or possible serotonin syndrome (hyperte
2) Summary: There is limited evidence suggesting that sertraline may inhibit tricyclic antidepressant (TCA) m P450 2D6 enzyme activity and may increase the plasma concentrations of coadministered drugs that are me 2002i; Preskorn et al, 1994m; Lydiard et al, 1993f). Effects of the interaction may have little or no clinical impa

were modest compared with those found when fluoxetine (another selective serotonin reuptake inhibitor) was sertraline therapy for TCA toxicity (dry mouth, urinary retention, CNS depression). Lofepramine doses may ne

3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Concurrent use of lofepramine and sertraline may result in an additive increase in s (hypertension, hyperthermia, myoclonus, mental status changes). Lofepramine should not be used in combin
7) Probable Mechanism: inhibition of lofepramine metabolism
8) Literature Reports

a) Desipramine pharmacokinetics were studied in 18 healthy male volunteers. Study subjects received d daily) for 21 days. When sertraline was added to desipramine therapy, the mean maximum concentration increased by 26%. Trough concentrations of desipramine were close to baseline one week after sertralin interaction may not be clinically significant (Preskorn et al, 1994l).

3.5.1.CT Lornoxicam

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematom suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solu
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent were searched among 26,005 users of antidepressant medications and compared with the number of ho amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 t 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with

3.5.1.CU Meclofenamate

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematom suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solu
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent were searched among 26,005 users of antidepressant medications and compared with the number of ho amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 t 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with

3.5.1.CV Mefenamic Acid

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematom suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solu
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent were searched among 26,005 users of antidepressant medications and compared with the number of ho amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 t 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with

3.5.1.CW Meloxicam

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hemator suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solu

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent were searched among 26,005 users of antidepressant medications and compared with the number of ho amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton

b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with

3.5.1.CX Methadone

1) Interaction Effect: increased serum methadone levels

2) Summary: Coadministration of methadone and sertraline may result in increased or prolonged opioid effe these agents are coadministered, consider reducing the methadone dosage. Additionally, monitor patients fo METHADOSE(R) oral concentrate, sugar-free oral concentrate, 2005).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Coadministration of methadone and sertraline may result in increased serum metha coadministered, consider reducing the methadone dosage. Also, monitor patients for increased methadone a concentrate, sugar-free oral concentrate, 2005).

7) Probable Mechanism: potential inhibition of CYP3A4-mediated methadone metabolism

3.5.1.CY Methylphenidate

1) Interaction Effect: increased selective serotonin reuptake inhibitor plasma concentrations

2) Summary: Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metab the SSRI may be necessary when it is used concurrently with methylphenidate. Additionally, when initiating o Info METADATE CD(R) extended-release oral capsules, 2007).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Use caution when prescribing methylphenidate to patients who take an selective se cause elevated SSRI plasma concentrations. Consider a decrease in the dose of SSRI when these agents ar initiating or discontinuing methylphenidate therapy (Prod Info METADATE CD(R) extended-release oral caps

7) Probable Mechanism: inhibition of selective serotonin reuptake inhibitor metabolism by methylphenidate

3.5.1.CZ Metoclopramide

1) Interaction Effect: an increased risk of developing extrapyramidal symptoms

2) Summary: In a case report, a 23-year old woman developed extrapyramidal symptoms after sertraline wa report describes a 14-year old female who experienced mandibular dystonia five days after starting metoclop controlled studies are necessary to confirm the clinical implications of this interaction.

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Clinicians should be alerted to the possibility that patients may have an increased ri metoclopramide. Close patient monitoring is warranted.

7) Probable Mechanism: synergistic dopaminergic inhibition

8) Literature Reports

a) A 23-year-old woman developed mandibular dystonia after sertraline was added to a chronic regimen for six months when she was admitted to the hospital with depression. After two 50 mg doses of sertralin periauricular pain, jaw tightness, and the sensation of teeth clenching and grinding. After diphenhydrami recurrence of symptoms after her third dose of sertraline. After sertraline was discontinued the patient ex (Christensen & Byerly, 1996).

b) A 14-year-old patient stabilized on sertraline 100 mg for the previous two months presented to her ph times daily. Five days later, the patient was taken to the emergency room because of mandibular dyston

c) A risk of serotonin syndrome with serious extrapyramidal reactions may occur with the concomitant u 18 months for depression and agoraphobia. Other medications were celecoxib and hydrocortisone. After Metoclopramide was initiated on postoperative day 2 because of nausea. Two hours after the first metoc shoulders, twitching of the lips, stiffness of the tongue and jaw and difficulties in controlling tongue move Symptoms resolved in 4 hours after administration of diazepam. Upon reinstitution of metoclopramide, th

concentrations rose to 535 U/L, but CK MB fraction, troponin concentrations and ECG remained normal. normal the following day. Two days later a similar pattern of clinical features occurred 1.5 hours after she there was no recurrence of the previous symptoms. According to the Naranjo probability scale, the comb syndrome (Fisher & David, 2002).

3.5.1.DA Milnacipran

1) Interaction Effect: increased risk of serotonin syndrome (hypertension, hyperthermia, myoclonus, mental s
2) Summary: Concurrent use of milnacipran and an SSRI may result in hypertension, coronary artery vasocc syndrome may include restlessness, hallucinations, loss of coordination, fast heart beat, rapid changes in blo diarrhea (Prod Info SAVELLA(R) oral tablets, 2009).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of milnacipran and an SSRI may result in hypertension and coron used together, discuss the risks of serotonin syndrome with the patient and monitor closely for symptoms of s during treatment initiation and dose increases (Prod Info SAVELLA(R) oral tablets, 2009).
7) Probable Mechanism: additive serotonergic effect

3.5.1.DB Moclobemide

1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental sta
2) Summary: Concurrent administration or overlapping therapy with sertraline and a monoamine oxidase (MA characterized by symptoms such as restlessness, myoclonus, changes in mental status, hyperreflexia, diaph Zoloft(R), 2002b; Lappin & Auchincloss, 1994c; Graber et al, 1994c; Neuvonen et al, 1993a; Bhatara & Band similar reaction may occur. Concomitant use is contraindicated.
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Concurrent use of sertraline and a MAO inhibitor is contraindicated. Wait at least 14 least 14 days after discontinuing sertraline before initiating therapy with a MAO inhibitor.
7) Probable Mechanism: inhibition of serotonin metabolism by monoamine oxidase
8) Literature Reports
a) Concomitant use of selective serotonin reuptake inhibitors and monoamine oxidase inhibitors can pro syndrome is a condition of serotonergic hyperstimulation and manifests as restlessness, myoclonus, cha not recognized and correctly treated, death can result.
b) A 26-year old woman who had been taking isocarboxazid for 8 weeks stopped taking the drug for 11 patient became restless and developed leg twitches. The patients was later admitted to the emergency r disturbances. The patient did not improve after treatment with diazepam and propranolol. The patient wa in symptoms after the second dose (Lappin & Auchincloss, 1994b).
c) A drug interaction was reported in a 61-year old woman in which sertraline 100 mg twice daily was ac taking the first sertraline dose, the patient was found in a semicomatose state, with elevated body tempe mmHg. After transportation to the hospital, the patient was misdiagnosed as having neuroleptic malignar between sertraline and phenelzine. The authors suggest that MAO inhibitor therapy should be discontinu inhibitor (SSRI) and that before starting a MAOI, SSRI therapy should be discontinued for at least five ha
d) Five fatal cases of serotonin syndrome following overdoses have been reported. In three of the five c selective monoamine oxidase inhibitor, and citalopram. Of these three patients, moclobemide blood conc concentrations ranged from normal to five times the therapeutic level (Neuvonen et al, 1993).

3.5.1.DC Morniflumate

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hemator suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solu
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent were searched among 26,005 users of antidepressant medications and compared with the number of ho amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 t 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with

3.5.1.DD Nabumetone

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and

associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hemator
suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solu
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent
were searched among 26,005 users of antidepressant medications and compared with the number of ho
amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 t
12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The
SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with

3.5.1.DE Nadroparin

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and
anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp e
reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Alter
coadministration of SSRIs with warfarin (Prod Info ZOLOFT(R) oral tablets, concentrate, 2008). Prothrombin
1997a).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When sertraline and an anticoagulant are given concurrently, monitor patient for sig
closely for altered anticoagulant effects, including increased bleeding, when sertraline therapy is initiated or d
7) Probable Mechanism: unknown
8) Literature Reports
a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bl
fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patien
with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopram
bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experie
corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. T
(95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experienci
addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respe
patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other th
b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoum
increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospit
for abnormal bleeding and compared them with 5818 control subjects who were also taking a coumarin.
on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (O
bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).
c) Sertraline 50 mg to 200 mg daily for 21 days produced an 8% increase in prothrombin time in subject
given prior to sertraline; this compared with a 1% decrease with placebo. Normalization of the prothromb
findings is unknown (Prod Info ZOLOFT(R) oral tablets, concentrate, 2008).
d) In a non-blinded, randomized, placebo-controlled trial involving 12 healthy volunteers, the effect of se
study, all participants received warfarin 0.75 mg/kg. Beginning on day 11, each volunteer was randomize
mg/day to 200 mg/day. Prothrombin time was measured prior to each dose of warfarin and periodically th
enhanced by sertraline to a clinically significant degree, despite the fact that sertraline was given in a hig

3.5.1.DF Naproxen

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and
associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hemator
suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solu
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent
were searched among 26,005 users of antidepressant medications and compared with the number of ho
amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 t
12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The
SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with

3.5.1.DG Naratriptan

1) Interaction Effect: an increased risk of serotonin syndrome

2) Summary: Rare incidences of weakness, hyperreflexia, and incoordination have been reported with the co 1 (5HT-1) agonist (Prod Info Amerge(TM), 2002). Concurrent use of a triptan and an SSRI may result in sero include restlessness, hallucinations, loss of coordination, fast heart beat, rapid changes in blood pressure, in Clinicians should be aware that triptans may be commonly used intermittently and that either the triptan or th syndrome with patients who are prescribed this combination and monitor them closely for symptoms of seroto

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Coadministration of a triptan, such as naratriptan, and an SSRI may result in a life-t used intermittently and that either the triptan or the SSRI may be prescribed by a different physician. If these monitor closely for symptoms of serotonin syndrome (restlessness, hyperthermia, hyperreflexia, incoordinatic

7) Probable Mechanism: additive pharmacologic effects resulting in excessive serotonergic stimulation

3.5.1.DH Nialamide

1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental st

2) Summary: Concurrent administration or overlapping therapy with sertraline and a monoamine oxidase (M characterized by symptoms such as restlessness, myoclonus, changes in mental status, hyperreflexia, diaph concomitant use of serotonin specific reuptake inhibitors and MAO inhibitors (Prod Info Zoloft(R), 1999h; Lap & de Vries, 1990i). Concomitant use is contraindicated.

3) Severity: contraindicated

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: Concurrent use of sertraline and a MAO inhibitor is contraindicated. Wait at least 1 least 14 days after discontinuing sertraline before initiating therapy with a MAO inhibitor.

7) Probable Mechanism: inhibition of serotonin metabolism by monoamine oxidase

8) Literature Reports

a) Concomitant use of SSRIs and monoamine oxidase inhibitors can produce a toxic reaction known as hyperstimulation and manifests as restlessness, myoclonus, changes in mental status, hyperreflexia, dia fatality can result.

b) A 26-year old woman who had been taking isocarboxazid for eight weeks stopped taking the drug for the patient became restless and developed leg twitches. The patients was later admitted to the emergen disturbances. After treatment with diazepam and propranolol the patient did not improve. The patient wa symptoms after the second dose (Lappin & Auchincloss, 1994j).

c) A drug interaction was reported in a 61-year old woman in which sertraline 100 mg twice daily was ac taking the first sertraline dose, the patient was found in a semicomatose state, with elevated body tempe Hg. After transportation to the hospital, the patient was misdiagnosed as having neuroleptic malignant sy sertraline and phenelzine. The authors suggest that monoamine oxidase inhibitor (MAOI) therapy should serotonin reuptake inhibitor (SSRI) and that before starting a MAOI, SSRI therapy should be discontinue 1994j).

d) Two cases reports suggested a possible interaction between fluoxetine and selegiline (Suchowersky approximately one month after adding selegiline to fluoxetine. The patient improved two months after bo involved diaphoresis, vasoconstriction, and cyanosis of the hands which occurred in close temporal relat quick resolution of symptoms. Rechallenge with fluoxetine alone occurred without incident.

3.5.1.DI Niflumic Acid

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control anc associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hemator suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solu

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent were searched among 26,005 users of antidepressant medications and compared with the number of ho amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton

b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with

3.5.1.DJ Nimesulide

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control anc associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hemator

suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solu
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent were searched among 26,005 users of antidepressant medications and compared with the number of ho amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with

3.5.1.DK Nortriptyline
1) Interaction Effect: elevated nortriptyline serum levels or possible serotonin syndrome (hypertension, hyper
2) Summary: There is limited evidence suggesting that sertraline may inhibit tricyclic antidepressant (TCA) m cytochrome P450 2D6 enzyme activity and may increase the plasma concentrations of coadministered drugs al, 1994q; Lydiard et al, 1993h). Effects of the interaction may have little or no clinical impact, however. Incre compared with those found when fluoxetine (another selective serotonin reuptake inhibitor) was combined wi therapy for TCA toxicity (dry mouth, urinary retention, CNS depression). Nortriptyline doses may need to be r
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: The combined use of tricyclic antidepressants (TCAs) and selective serotonin reupt serotonin syndrome have also been reported with concurrent TCA and SSRI therapy. Caution should be obs concentrations as the dose of TCA may need to be reduced.
7) Probable Mechanism: inhibition of nortriptyline metabolism
8) Literature Reports
a) Desipramine pharmacokinetics were studied in 18 healthy male volunteers. Study subjects received daily) for 21 days. When sertraline was added to desipramine therapy, the mean maximum concentratio increased by 26%. Trough concentrations of desipramine were close to baseline one week after sertralin interaction may not be clinically significant (Preskorn et al, 1994p).
b) Fourteen elderly depressed patients were retrospectively studied to determine the effect that sertralin and increased up to 150 mg daily. Overall, sertraline caused a median increase of only 2% in nortriptylin clinical implications. In patients taking sertraline in doses of 100 mg or 150 mg daily, the nortriptyline leve in the change of nortriptyline levels, careful monitoring of nortriptyline concentrations should be practiced

3.5.1.DL Oxaprozin
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hemator suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solu
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent were searched among 26,005 users of antidepressant medications and compared with the number of ho amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with

3.5.1.DM Oxycodone
1) Interaction Effect: an increased risk of serotonin syndrome (tachycardia, hyperthermia, myoclonus, menta
2) Summary: Coadministration of oxycodone and sertraline has resulted in the development of symptoms su Caution is advised if oxycodone and sertraline are coadministered. Monitor patients for signs and symptoms
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Concomitant administration of oxycodone and sertraline may increase the risk of de symptoms of serotonin syndrome (tachycardia, hyperthermia, myoclonus, mental status changes).
7) Probable Mechanism: additive pharmacologic effects resulting in excessive serotonergic stimulation
8) Literature Reports
a) Symptoms of serotonin syndrome developed in an 86-year-old woman following concurrent administr

resulted in a sacral fracture. Prior to hospitalization, medications included extended-release oxycodone 1
20 mg twice daily for pain control and following a brief hospital stay, she was transferred to a long-term c
increased muscle tone in lower extremities, truncal ataxia, and coarse tremors, with myoclonic jerks, in b
decreased which resolved the myoclonus, rigidity, and tremors within 2 days. It was postulated that the i
(Gnanadesigan et al, 2005).

b) A 34-year-old bone marrow transplant male patient experienced visual hallucinations and tremors foll
presentation, the patient had been discharged from the hospital, following extensive evaluation (includin
of sertraline 50 mg once daily, oxycodone 10 mg as needed (average daily dose 10 to 20 mg/day), and c
omeprazole, folinic acid, acyclovir, fluconazole, and trimethoprim/sulfamethoxazole. Within 48 hours afte
biopsy-site related pain and during this interval, he experienced severe tremors and visual hallucinations
year ago and his current cyclosporine level was 467 ng/mL, cyclosporine was believed to be the offendir
discontinued and hydromorphone (maximum 6 mg/day) was initiated for pain control. However, 72 hours
cyclosporine level had decreased to 128 ng/mL. It was postulated that increased oxycodone doses in co
Subsequently, sertraline was discontinued and oral cyproheptadine 8 mg was administered, which resol

3.5.1.DN Parecoxib

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control anc
associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hemator
suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solu

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent
were searched among 26,005 users of antidepressant medications and compared with the number of ho
amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 t
12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The
SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton

b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with

3.5.1.DO Pargyline

1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental sta

2) Summary: Concurrent administration or overlapping therapy with sertraline and a monoamine oxidase (MA
characterized by symptoms such as restlessness, myoclonus, changes in mental status, hyperreflexia, diaph
concomitant use of serotonin specific reuptake inhibitors and MAO inhibitors (Prod Info Zoloft(R), 1999; Lapp
de Vries, 1990a). Concomitant use is contraindicated.

3) Severity: contraindicated

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: Concurrent use of sertraline and a MAO inhibitor is contraindicated. Wait at least 14
least 14 days after discontinuing sertraline before initiating therapy with a MAO inhibitor.

7) Probable Mechanism: inhibition of serotonin metabolism by monoamine oxidase

8) Literature Reports

a) Concomitant use of SSRIs and monoamine oxidase inhibitors can produce a toxic reaction known as
hyperstimulation and manifests as restlessness, myoclonus, changes in mental status, hyperreflexia, dia
fatality can result.

b) A 26-year old woman who had been taking isocarboxazid for eight weeks stopped taking the drug for
the patient became restless and developed leg twitches. The patients was later admitted to the emergen
disturbances. After treatment with diazepam and propranolol the patient did not improve. The patient wa
symptoms after the second dose (Lappin & Auchincloss, 1994).

c) A drug interaction was reported in a 61-year old woman in which sertraline 100 mg twice daily was ac
taking the first sertraline dose, the patient was found in a semicomatose state, with elevated body tempe
Hg. After transportation to the hospital, the patient was misdiagnosed as having neuroleptic malignant sy
sertraline and phenelzine. The authors suggest that monoamine oxidase inhibitor (MAOI) therapy should
serotonin reuptake inhibitor (SSRI) and that before starting a MAOI, SSRI therapy should be discontinue
1994).

d) Two cases reports suggested a possible interaction between fluoxetine and selegiline (Suchowersky
approximately one month after adding selegiline to fluoxetine. The patient improved two months after bo
involved diaphoresis, vasoconstriction, and cyanosis of the hands which occurred in close temporal relat
quick resolution of symptoms. Rechallenge with fluoxetine alone occurred without incident.

3.5.1.DP Parnaparin

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control anc
anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp

reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Alter coadministration of SSRIs with warfarin (Prod Info ZOLOFT(R) oral tablets, concentrate, 2008). Prothrombin 1997a).

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: When sertraline and an anticoagulant are given concurrently, monitor patient for sig closely for altered anticoagulant effects, including increased bleeding, when sertraline therapy is initiated or d

7) Probable Mechanism: unknown

8) Literature Reports

a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bl fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patien with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopram bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experie corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. T (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experienci addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respe patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other tha

b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoum increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospit for abnormal bleeding and compared them with 5818 control subjects who were also taking a coumarin. on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (O bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).

c) Sertraline 50 mg to 200 mg daily for 21 days produced an 8% increase in prothrombin time in subject given prior to sertraline; this compared with a 1% decrease with placebo. Normalization of the prothromb findings is unknown (Prod Info ZOLOFT(R) oral tablets, concentrate, 2008).

d) In a non-blinded, randomized, placebo-controlled trial involving 12 healthy volunteers, the effect of se study, all participants received warfarin 0.75 mg/kg. Beginning on day 11, each volunteer was randomize mg/day to 200 mg/day. Prothrombin time was measured prior to each dose of warfarin and periodically tl enhanced by sertraline to a clinically significant degree, despite the fact that sertraline was given in a hig

3.5.1.DQ Pentosan Polysulfate Sodium

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Alter coadministration of SSRIs with warfarin (Prod Info ZOLOFT(R) oral tablets, concentrate, 2008). Prothrombin 1997a).

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: When sertraline and an anticoagulant are given concurrently, monitor patient for sig closely for altered anticoagulant effects, including increased bleeding, when sertraline therapy is initiated or d

7) Probable Mechanism: unknown

8) Literature Reports

a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bl fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patien with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopram bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experie corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. T (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experienci addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respe patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other tha

b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoum increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospit for abnormal bleeding and compared them with 5818 control subjects who were also taking a coumarin. on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (O bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).

c) Sertraline 50 mg to 200 mg daily for 21 days produced an 8% increase in prothrombin time in subject given prior to sertraline; this compared with a 1% decrease with placebo. Normalization of the prothromb findings is unknown (Prod Info ZOLOFT(R) oral tablets, concentrate, 2008).

d) In a non-blinded, randomized, placebo-controlled trial involving 12 healthy volunteers, the effect of se study, all participants received warfarin 0.75 mg/kg. Beginning on day 11, each volunteer was randomize mg/day to 200 mg/day. Prothrombin time was measured prior to each dose of warfarin and periodically tl enhanced by sertraline to a clinically significant degree, despite the fact that sertraline was given in a hig

3.5.1.DR Phenelzine

1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental sta

2) Summary: Concurrent administration or overlapping therapy with sertraline and a monoamine oxidase (MA
characterized by symptoms such as restlessness, myoclonus, changes in mental status, hyperreflexia, diaph
Zoloft(R), 2002q; Lappin & Auchincloss, 1994q; Graber et al, 1994q; Bhatara & Bandettini, 1993h; Suchowers
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Concurrent use of sertraline and a MAO inhibitor is contraindicated. Wait at least 14
least 14 days after discontinuing sertraline before initiating therapy with a MAO inhibitor.
7) Probable Mechanism: inhibition of serotonin metabolism by monoamine oxidase
8) Literature Reports
a) Concomitant use of serotonin specific reuptake inhibitors and monoamine oxidase inhibitors can prod
syndrome is a condition of serotonergic hyperstimulation and manifests as restlessness, myoclonus, cha
not recognized and correctly treated, death can result.
b) A 26-year old woman who had been taking isocarboxazid for eight weeks stopped taking the drug for
the patient became restless and developed leg twitches. The patients was later admitted to the emergen
disturbances. The patient did not improve after treatment with diazepam and propranolol. The patient wa
in symptoms after the second dose (Lappin & Auchincloss, 1994p).
c) A drug interaction was reported in a 61-year old woman in which sertraline 100 mg twice daily was ad
taking the first sertraline dose, the patient was found in a semicomatose state, with elevated body tempe
mmHg. After transportation to the hospital, the patient was misdiagnosed as having neuroleptic malignar
between sertraline and phenelzine. The authors suggest that MAO inhibitor therapy should be discontinu
inhibitor (SSRI) and that before starting a MAOI, SSRI therapy should be discontinued for at least 5 half-
d) Two cases reports suggested a possible interaction between fluoxetine and selegiline (Suchowersky
approximately 1 month after adding selegiline to fluoxetine therapy. The patient improved 2 months after
involved diaphoresis, vasoconstriction, and cyanosis of the hands which occurred in close temporal relat
quick resolution of symptoms. Rechallenge with fluoxetine alone occurred without incident.

3.5.1.DS Phenindione

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and
anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp e
reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Alter
coadministration of SSRIs with warfarin (Prod Info ZOLOFT(R) oral tablets, concentrate, 2008). Prothrombin
1997a).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When sertraline and an anticoagulant are given concurrently, monitor patient for sig
closely for altered anticoagulant effects, including increased bleeding, when sertraline therapy is initiated or d
7) Probable Mechanism: unknown
8) Literature Reports
a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bl
fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patien
with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopram
bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experie
corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. T
(95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experienci
addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respe
patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other tha
b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoum
increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospit
for abnormal bleeding and compared them with 5818 control subjects who were also taking a coumarin.
on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR
bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).
c) Sertraline 50 mg to 200 mg daily for 21 days produced an 8% increase in prothrombin time in subject
given prior to sertraline; this compared with a 1% decrease with placebo. Normalization of the prothromb
findings is unknown (Prod Info ZOLOFT(R) oral tablets, concentrate, 2008).
d) In a non-blinded, randomized, placebo-controlled trial involving 12 healthy volunteers, the effect of se
study, all participants received warfarin 0.75 mg/kg. Beginning on day 11, each volunteer was randomize
mg/day to 200 mg/day. Prothrombin time was measured prior to each dose of warfarin and periodically th
enhanced by sertraline to a clinically significant degree, despite the fact that sertraline was given in a hig

3.5.1.DT Phenprocoumon

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and
anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp e
reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Alter
coadministration of SSRIs with warfarin (Prod Info ZOLOFT(R) oral tablets, concentrate, 2008). Prothrombin

1997a).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When sertraline and an anticoagulant are given concurrently, monitor patient for sig closely for altered anticoagulant effects, including increased bleeding, when sertraline therapy is initiated or d
7) Probable Mechanism: unknown
8) Literature Reports
a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bl fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patien with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopram bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experie corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. T (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experienci addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respe patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other th
b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoum increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospit for abnormal bleeding and compared them with 5818 control subjects who were also taking a coumarin. on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (O bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).
c) Sertraline 50 mg to 200 mg daily for 21 days produced an 8% increase in prothrombin time in subject given prior to sertraline; this compared with a 1% decrease with placebo. Normalization of the prothromb findings is unknown (Prod Info ZOLOFT(R) oral tablets, concentrate, 2008).
d) In a non-blinded, randomized, placebo-controlled trial involving 12 healthy volunteers, the effect of se study, all participants received warfarin 0.75 mg/kg. Beginning on day 11, each volunteer was randomize mg/day to 200 mg/day. Prothrombin time was measured prior to each dose of warfarin and periodically th enhanced by sertraline to a clinically significant degree, despite the fact that sertraline was given in a hig

3.5.1.DU Phenylbutazone
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematom suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solu
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent were searched among 26,005 users of antidepressant medications and compared with the number of ho amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 t 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with

3.5.1.DV Phenytoin
1) Interaction Effect: an increased risk of phenytoin toxicity (ataxia, hyperreflexia, nystagmus, tremor)
2) Summary: Coadministration of sertraline with phenytoin has been reported to result in elevated serum phe controlled studies are needed to verify the extent of this interaction.
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Caution is warranted if phenytoin and sertraline are to be coadministered. Serum pl therapy or changing the sertraline dose. Monitor patients for signs and symptoms of phenytoin toxicity (ataxia downward.
7) Probable Mechanism: sertraline inhibition of phenytoin metabolism by cytochrome P450 isoenzymes
8) Literature Reports
a) Sertraline is known to be a moderate to weak inhibitor of the cytochrome P450IID6 isoenzyme (CYP2 metabolism of phenytoin may involve the cytochrome P450IID6 (Murray, 1992a) and the CYP2C9 hepati activity and pathways, it seems theoretically possible that concurrent sertraline may act to inhibit metabo
b) Two elderly patients developed elevated serum phenytoin concentrations during coadministration wit addition to several other medications. After sertraline 25 mg every night for depression was added to his increases in the sertraline dose to 75 mg per day, the patient's serum phenytoin level rose to 30.9 mcg/m per day. Sertraline 100 mg per day was also administered without further adverse effects. Patient 2, an 8 mcg/mL) after the addition of sertraline 25 mg every other day to phenytoin 260 mg per day. The authors sertraline therapy or initiating a change in sertraline dose (Haselberger et al, 1997b).

3.5.1.DW Pimozide

1) Interaction Effect: an increase in plasma pimozide levels
2) Summary: Due to the narrow therapeutic index of pimozide and due to the interaction noted at low dose o Info Zoloft(R), 2002s).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Concomitant use of sertraline in patients taking pimozide is contraindicated.
7) Probable Mechanism: unknown
8) Literature Reports
a) In a controlled trial of a single 2 mg dose of pimozide, sertraline 200 mg daily coadministration to stea time curve (AUC) and maximum plasma concentrations (Cmax) of about 40%, but was not associated w been evaluated in combination with sertraline, the effect on QT interval and pharmacokinetic parameters and observed interaction data with low doses, the combination should be avoided (Prod Info Zoloft(R), 2

3.5.1.DX Pirazolac

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hemator suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solu
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent were searched among 26,005 users of antidepressant medications and compared with the number of ho amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with

3.5.1.DY Piroxicam

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hemator suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solu
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent were searched among 26,005 users of antidepressant medications and compared with the number of ho amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with

3.5.1.DZ Pirprofen

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hemator suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solu
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent were searched among 26,005 users of antidepressant medications and compared with the number of ho amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton

b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with

3.5.1.EA Procarbazine

1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental sta
2) Summary: Concurrent administration or overlapping therapy with sertraline and a monoamine oxidase (MA characterized by symptoms such as restlessness, myoclonus, changes in mental status, hyperreflexia, diaph concomitant use of serotonin specific reuptake inhibitors and MAO inhibitors (Prod Info Zoloft(R), 1999j; Lapp & de Vries, 1990q). Concomitant use is contraindicated.
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Concurrent use of sertraline and a MAO inhibitor is contraindicated. Wait at least 14 least 14 days after discontinuing sertraline before initiating therapy with a MAO inhibitor.
7) Probable Mechanism: inhibition of serotonin metabolism by monoamine oxidase
8) Literature Reports

a) Concomitant use of SSRIs and monoamine oxidase inhibitors can produce a toxic reaction known as serotonergic hyperstimulation and manifests as restlessness, myoclonus, changes in mental status, hype correctly treated, fatality can result.

b) A 26-year old woman who had been taking isocarboxazid for eight weeks stopped taking the drug for the patient became restless and developed leg twitches. The patients was later admitted to the emergen disturbances. After treatment with diazepam and propranolol the patient did not improve. The patient was symptoms after the second dose (Lappin & Auchincloss, 1994r).

c) A drug interaction was reported in a 61-year old woman in which sertraline 100 mg twice daily was ac taking the first sertraline dose, the patient was found in a semicomatose state, with elevated body tempe Hg. After transportation to the hospital, the patient was misdiagnosed as having neuroleptic malignant sy sertraline and phenelzine. The authors suggest that monoamine oxidase inhibitor (MAOI) therapy should serotonin reuptake inhibitor (SSRI) and that before starting a MAOI, SSRI therapy should be discontinue 1994r).

d) Two cases reports suggested a possible interaction between fluoxetine and selegiline (Suchowersky approximately one month after adding selegiline to fluoxetine. The patient improved two months after bot involved diaphoresis, vasoconstriction, and cyanosis of the hands which occurred in close temporal relat quick resolution of symptoms. Rechallenge with fluoxetine alone occurred without incident.

3.5.1.EB Propafenone

1) Interaction Effect: an increased risk of propafenone toxicity (cardiac arrhythmias)
2) Summary: No data are currently available related to concomitant propafenone - sertraline administration. I 2000). Sertraline inhibits the CYP2D6 isoenzyme (Prod Info Zoloft(R), 1999d). With propafenone - sertraline propafenone serum levels and possible propafenone toxicity. Controlled studies are needed to investigate the
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Coadministration of these agents should be approached with caution. Monitor the E may need to be reduced.
7) Probable Mechanism: inhibition of propafenone metabolism

3.5.1.EC Propranolol

1) Interaction Effect: an increased risk of chest pain
2) Summary: Sertraline is a moderate to weak inhibitor of the hepatic cytochrome P450IID6 isoenzyme (CYP report describes sudden chest pain when sertraline was added to existing propranolol therapy (Iruela, 1994a)
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor patients receiving propranolol and sertraline cotherapy for an increased inc coronary artery disease.
7) Probable Mechanism: endothelium vasoconstriction caused by serotonin
8) Literature Reports

a) A 53-year-old male physician was maintained on propranolol 160 mg daily and aspirin 200 mg daily fo depression, he experienced sudden precordial chest pain that was responsive to 2 mg of sublingual glyc occurred on the electrocardiogram. The next day, a similar reaction happened soon after the administrat nortriptyline 50 mg daily with no further episodes of chest pain. Possible mechanisms for this interaction artery disease (Iruela, 1994).

3.5.1.ED Propyphenazone

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hemator suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solu
3) Severity: moderate

4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent were searched among 26,005 users of antidepressant medications and compared with the number of ho amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 t 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with

3.5.1.EE Proquazone

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hemator suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solu
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent were searched among 26,005 users of antidepressant medications and compared with the number of ho amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 t 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with

3.5.1.EF Protriptyline

1) Interaction Effect: modest elevations in protriptyline serum levels or possible serotonin syndrome (hyperte
2) Summary: There is limited evidence suggesting that sertraline may inhibit tricyclic antidepressant (TCA) m P450 2D6 enzyme activity and may increase the plasma concentrations of coadministered drugs that are me Lydiard et al, 1993a; Prod Info Zoloft(R), 1999a). Effects of the interaction may have little or no clinical impac were modest compared with those found when fluoxetine (another selective serotonin reuptake inhibitor) was sertraline therapy for TCA toxicity (dry mouth, urinary retention, CNS depression). Protriptyline doses may ne
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: The combined use of tricyclic antidepressants (TCAs) and selective serotonin reupt serotonin syndrome have also been reported with concurrent TCA and SSRI therapy. Caution should be obse
7) Probable Mechanism: inhibition of protriptyline metabolism
8) Literature Reports
a) Desipramine pharmacokinetics were studied in 18 healthy male volunteers. Study subjects received c daily) for 21 days. When sertraline was added to desipramine therapy, the mean maximum concentration increased by 26%. Trough concentrations of desipramine were close to baseline one week after sertralin interaction may not be clinically significant (Preskorn et al, 1994b).

3.5.1.EG Rasagiline

1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental sta
2) Summary: Concurrent administration or overlapping therapy with selective serotonin reuptake inhibitors, in has been reported to cause serious, sometimes fatal reactions. Signs and symptoms included hyperthermia, status changes progressing to extreme agitation, delirium, and coma. Similar reactions have been reported w selegiline. Rasagiline clinical trials did allow concomitant use of sertraline in doses less than or equal to 100 m adequate to rule out the possibility of adverse events from the combination of rasagiline and sertraline, and s initiating therapy with sertraline (Prod Info AZILECT(R) oral tablets, 2006).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Concurrent use of sertraline and rasagiline Should be avoided. Wait at least 14 day
7) Probable Mechanism: inhibition of serotonin metabolism by monoamine oxidase
8) Literature Reports
a) Concomitant use of serotonin specific reuptake inhibitors and monoamine oxidase inhibitors can prod syndrome is a condition of serotonergic hyperstimulation and manifests as restlessness, myoclonus, cha not recognized and correctly treated, death can result.

3.5.1.EH Reviparin

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Alter coadministration of SSRIs with warfarin (Prod Info ZOLOFT(R) oral tablets, concentrate, 2008). Prothrombin 1997a).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When sertraline and an anticoagulant are given concurrently, monitor patient for sig closely for altered anticoagulant effects, including increased bleeding, when sertraline therapy is initiated or d
7) Probable Mechanism: unknown
8) Literature Reports
a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bl fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patien with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopram bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experie corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experienci addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respe patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other th
b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoum increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospit for abnormal bleeding and compared them with 5818 control subjects who were also taking a coumarin. on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (O bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).
c) Sertraline 50 mg to 200 mg daily for 21 days produced an 8% increase in prothrombin time in subject given prior to sertraline; this compared with a 1% decrease with placebo. Normalization of the prothromb findings is unknown (Prod Info ZOLOFT(R) oral tablets, concentrate, 2008).
d) In a non-blinded, randomized, placebo-controlled trial involving 12 healthy volunteers, the effect of se study, all participants received warfarin 0.75 mg/kg. Beginning on day 11, each volunteer was randomize mg/day to 200 mg/day. Prothrombin time was measured prior to each dose of warfarin and periodically th enhanced by sertraline to a clinically significant degree, despite the fact that sertraline was given in a hig

3.5.1.EI Rifampin

1) Interaction Effect: loss of sertraline efficacy
2) Summary: Sertraline is metabolized by cytochrome P450 3A4 enzymes, which are induced by rifampin the of selective serotonin reuptake inhibitor (SSRI) withdrawal syndrome following seven days of concurrent rifam
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor patients for sertraline efficacy and signs of selective serotonin reuptake inh rifampin is given concomitantly.
7) Probable Mechanism: induction of cytochrome P450 3A4-mediated sertraline metabolism
8) Literature Reports
a) Rifampin administration was thought to precipitate selective serotonin reuptake inhibitor withdrawal sy concurrent therapy. The patient had been stabilized on sertraline 200 mg nightly for generalized anxiety mg was started for a methicillin-resistant Staphylococcus aureus skin infection. Seven days later, the pat a blood sample was drawn to determine the plasma sertraline concentration. Laboratory analysis reveale ng/mL. The patient finished the remainder of the 10-day course of rifampin. Seven days after rifampin wa an N-desmethylsertraline concentration of 136 ng/mL. Anxiety was still persistent in this patient, so sertra (Markowitz & DeVane, 2000).

3.5.1.EJ Rizatriptan

1) Interaction Effect: an increased risk of serotonin syndrome
2) Summary: There have been case reports of weakness, hyperreflexia, and incoordination following concon specific reuptake inhibitor (SSRI) (Prod Info Imitrex(R), 1998). Because rizatriptan is a 5HT 1B/1D receptor a 1998a). Concurrent use of a triptan and an SSRI may result in serotonin syndrome which may be life-threate coordination, fast heart beat, rapid changes in blood pressure, increased body temperature, overreactive refl commonly used intermittently and that either the triptan or the SSRI may be prescribed by a different physicia combination and monitor them closely for symptoms of serotonin syndrome (US Food and Drug Administratio
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Coadministration of a triptan, such as rizatriptan, and an SSRI may result in a life-th used intermittently and that either the triptan or the SSRI may be prescribed by a different physician. If these monitor closely for symptoms of serotonin syndrome (restlessness, hyperthermia, hyperreflexia, incoordinatio
7) Probable Mechanism: additive pharmacologic effects resulting in excessive serotonergic stimulation

8) Literature Reports
a) Twelve healthy volunteers received paroxetine 20 mg daily for two weeks and a single dose of rizatrip paroxetine (Prod Info Maxalt(R), 1998).

3.5.1.EK Rofecoxib
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hemator suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solu
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent were searched among 26,005 users of antidepressant medications and compared with the number of ho amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with

3.5.1.EL Selegiline
1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental sta
2) Summary: Concurrent administration or overlapping therapy with sertraline and a monoamine oxidase (MA characterized by symptoms such as restlessness, myoclonus, changes in mental status, hyperreflexia, diaph Zoloft(R), 2002u; Lappin & Auchincloss, 1994u; Graber et al, 1994u; Bhatara & Bandettini, 1993j; Suchowers contraindicated, and a minimum of 14 days should elapse after discontinuing selegiline before initiating thera before initiating therapy with selegiline (Prod Info EMSAM(R) transdermal patch, 2006).
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Concurrent use of sertraline and selegiline is contraindicated. Wait at least 14 days after discontinuing sertraline before initiating therapy with selegiline.
7) Probable Mechanism: inhibition of serotonin metabolism by monoamine oxidase
8) Literature Reports
a) Concomitant use of serotonin specific reuptake inhibitors and monoamine oxidase inhibitors can prod syndrome is a condition of serotonergic hyperstimulation and manifests as restlessness, myoclonus, cha not recognized and correctly treated, death can result.
b) A 26-year old woman who had been taking isocarboxazid for eight weeks stopped taking the drug for the patient became restless and developed leg twitches. The patients was later admitted to the emergen disturbances. The patient did not improve after treatment with diazepam and propranolol. The patient wa in symptoms after the second dose (Lappin & Auchincloss, 1994t).
c) A drug interaction was reported in a 61-year old woman in which sertraline 100 mg twice daily was ac taking the first sertraline dose, the patient was found in a semicomatose state, with elevated body tempe mmHg. After transportation to the hospital, the patient was misdiagnosed as having neuroleptic malignar between sertraline and phenelzine. The authors suggest that MAO inhibitor therapy should be discontinu inhibitor (SSRI) and that before starting a MAOI, SSRI therapy should be discontinued for at least 5 half-
d) Two case reports suggested a possible interaction between fluoxetine and selegiline (Suchowersky & approximately 1 month after adding selegiline to fluoxetine therapy. The patient improved 2 months after involved diaphoresis, vasoconstriction, and cyanosis of the hands which occurred in close temporal relat quick resolution of symptoms. Rechallenge with fluoxetine alone occurred without incident.

3.5.1.EM Sibrafiban
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and been associated with an increased risk of bleeding. Bleeding events reported have included epistaxis, ecchyr tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an antiplatelet agent are given concurrently, monitor patient for PROZAC(R) oral capsules, delayed-release capsules, solution, 2008)
7) Probable Mechanism: unknown

3.5.1.EN Sibutramine
1) Interaction Effect: an increased risk of serotonin syndrome (hypertension, hyperthermia, myoclonus, ment
2) Summary: Sibutramine inhibits the reuptake of norepinephrine, dopamine, and serotonin. In addition, the t

neurotransmitters. A hyperserotonergic state, termed serotonin syndrome, may result if sibutramine is given c
and selective serotonin reuptake inhibitors is not recommended (Prod Info Meridia(R), 1997).
3) Severity: major
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Sibutramine should not be administered with serotonergic agents, including selectiv
7) Probable Mechanism: additive pharmacologic effects resulting in excessive serotonergic stimulation
8) Literature Reports
a) Serotonin syndrome is a condition of serotonergic hyperstimulation and manifests as restlessness, m
the syndrome is not recognized and correctly treated, death can result (Sternbach, 1991b).

3.5.1.EO St John's Wort
1) Interaction Effect: an increased risk of serotonin syndrome (hypertension, hyperthermia, myoclonus, ment
2) Summary: Case reports describe the onset of serotonin syndrome-like symptoms, mania, and hypomania
(Spinella & Eaton, 2002c; Barbanel et al, 2000a; Waksman et al, 2000a; Lantz et al, 1999a). A patient exhibit
paroxetine therapy (Gordon, 1998a). St. John's Wort is thought to inhibit serotonin reuptake and may have m
which when added to selective serotonin reuptake inhibitors may result in serotonin syndrome.
3) Severity: major
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Patients should be advised to wait two weeks after stopping St. John's Wort before
selective serotonin reuptake inhibitor (SSRI) therapy with St. John's Wort, the half-life of the specific SSRI sh
metabolized out of the body.
7) Probable Mechanism: additive serotonergic effect
8) Literature Reports
a) Five cases have been reported of serotonin syndrome in the elderly after combining prescription antic
headache 4 days after starting St. John's Wort 300 milligrams (mg) three times daily combined with sertr
2 developed nausea, epigastric pain and anxiety 3 days after starting St. John's Wort 300 mg twice daily
discontinuing both medications, and he resumed sertraline use without complications. The third case dev
mg twice daily combined with sertraline 50 mg daily. His symptoms improved in 4 to 5 days after stoppin
nausea, anxiety, restless, and irritability 2 days after starting St. John's Wort 300 mg three times daily co
seven days, and his symptoms improved in 1 week after stopping the medication. Cases 1 through 4 res
Case 5 developed nausea, vomiting and restlessness 3 days after starting St. John's Wort 300 mg three
John's Wort but discontinued the nefazodone and over 1 week her symptoms Improved. She refused to
moderate symptoms of depression and anxiety returned (Lantz et al, 1999).
b) A 50-year-old female taking St. John's Wort 600 mg daily experienced symptoms of sedative intoxica
slow-moving, and complained of nausea and weakness. Prior to starting St. John's Wort, she had been r
sleep, she returned to her baseline mental status (Gordon, 1998).
c) A 61-year-old female experienced restlessness and involuntary movements of her extremities after be
mg daily. The patient reported agitation and akathisia 8 hours after taking the first dose of paroxetine. Sh
hyperreflexia and rigidity. Blood pressure, heart rate, and temperature were normal. After admission, blo
minute. Creatine kinase increased from 212 units/liter (U/L) initially to 1024 U/L. The patient was manage
2000).
d) A 28-year-old male developed a manic syndrome following comedication with St. John's Wort and se
orchidectomy 2 years earlier, but testosterone levels were subtherapeutic. The patient was prescribed se
patient preference (dose not specified). Before sertraline was started, the patient was instructed to disco
improved mood so did not see his physician, believing that he did not need further treatment. Over 2 mo
afford, and was ultimately arrested for stealing fuel for the car. On arrest, he was referred to psychiatric s
distractible, have flight of ideas, and grandiose delusions, leading to a diagnosis of a manic episode. The
that St. John's Wort may have increased the risk as a result of monoamine oxidase inhibition. Since the
state was considered low. However, the patient had elevated gonadotropin levels (luteinizing hormone a
(Barbanel et al, 2000).
e) A 42-year-old female experienced symptoms consistent with a mixed hypomanic episode following co
symptoms resolved following discontinuation of Ginkgo and St. John's Wort. The patient was being treat
twice daily and buspirone 15 mg twice daily. Several weeks prior to presentation, buspirone was increas
melatonin, and St. John's Wort in unspecified doses. Melatonin was considered unlikely to have contribu
since they may potentiate antidepressants, and considering the temporal relationship between the use o
symptoms. However, the brain injury was considered a possible contributor (Spinella & Eaton, 2002b).

3.5.1.EP Sulfinpyrazone
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and
been associated with an increased risk of bleeding. Bleeding events reported have included epistaxis, ecchy
tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an antiplatelet agent are given concurrently, monitor patient for

PROZAC(R) oral capsules, delayed-release capsules, solution, 2008)
7) Probable Mechanism: unknown

3.5.1.EQ Sulindac
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and
associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hemator
suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solu
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent
were searched among 26,005 users of antidepressant medications and compared with the number of ho
amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7
12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The
SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with

3.5.1.ER Sulodexide
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and
been associated with an increased risk of bleeding. Bleeding events reported have included epistaxis, ecchy
tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an antiplatelet agent are given concurrently, monitor patient for
PROZAC(R) oral capsules, delayed-release capsules, solution, 2008)
7) Probable Mechanism: unknown

3.5.1.ES Sumatriptan
1) Interaction Effect: an increased risk of serotonin syndrome
2) Summary: There have been case reports of weakness, hyperreflexia, and incoordination following concon
Zoloft(R), 2002t; Prod Info Imitrex(R), 2002). Concurrent use of a triptan and an SSRI may result in serotonin
restlessness, hallucinations, loss of coordination, fast heart beat, rapid changes in blood pressure, increased
should be aware that triptans may be commonly used intermittently and that either the triptan or the SSRI ma
patients who are prescribed this combination and monitor them closely for symptoms of serotonin syndrome
3) Severity: major
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Coadministration of a triptan, such as sumatriptan, and an SSRI, such as sertraline
triptans may be commonly used intermittently and that either the triptan or the SSRI may be prescribed by a
syndrome with the patient and monitor closely for symptoms of serotonin syndrome (restlessness, hypertherr
7) Probable Mechanism: additive pharmacologic effects resulting in excessive serotonergic stimulation

3.5.1.ET Suprofen
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and
associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hemator
suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solu
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent
were searched among 26,005 users of antidepressant medications and compared with the number of ho
amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7
12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The
SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with

3.5.1.EU Tapentadol
1) Interaction Effect: increased risk of serotonin syndrome (hypertension, hyperthermia, myoclonus, mental s

2) Summary: Concurrent use of tapentadol and a selective serotonin reuptake inhibitor (SSRI) may result in s
include restlessness, hallucinations, loss of coordination, fast heart beat, rapid changes in blood pressure, inc
Info tapentadol immediate release oral tablets, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of tapentadol and an SSRI may result in a life-threatening conditio
closely for symptoms of serotonin syndrome (restlessness, hyperthermia, hyperreflexia, incoordination), espe
release oral tablets, 2008).
7) Probable Mechanism: additive serotonergic effect

3.5.1.EV Tenidap
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and
associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematom
suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solu
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent
were searched among 26,005 users of antidepressant medications and compared with the number of ho
amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 t
12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The
SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with

3.5.1.EW Tenoxicam
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and
associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematom
suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solu
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent
were searched among 26,005 users of antidepressant medications and compared with the number of ho
amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 t
12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The
SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with

3.5.1.EX Terfenadine
1) Interaction Effect: cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: In two in vivo studies, no pharmacokinetic interaction between terfenadine and sertraline was c
likely to be of any clinical significance (Prod Info Zoloft(R), 2002a). However, the manufacturer of terfenadine
Seldane(R), 1997).
3) Severity: major
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Concomitant use of terfenadine and sertraline should be avoided.
7) Probable Mechanism: inhibition of cytochrome P450-mediated metabolism of terfenadine

3.5.1.EY Tiaprofenic Acid
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and
associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematom
suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solu
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown

8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent were searched among 26,005 users of antidepressant medications and compared with the number of ho amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 t 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with

3.5.1.EZ Ticlopidine
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and been associated with an increased risk of bleeding. Bleeding events reported have included epistaxis, ecchyr tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an antiplatelet agent are given concurrently, monitor patient for PROZAC(R) oral capsules, delayed-release capsules, solution, 2008)
7) Probable Mechanism: unknown

3.5.1.FA Tinzaparin
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp e reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Alter coadministration of SSRIs with warfarin (Prod Info ZOLOFT(R) oral tablets, concentrate, 2008). Prothrombin 1997a).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When sertraline and an anticoagulant are given concurrently, monitor patient for sig closely for altered anticoagulant effects, including increased bleeding, when sertraline therapy is initiated or d
7) Probable Mechanism: unknown
8) Literature Reports
a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bl fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patien with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopran bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experie corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. T (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experienci addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respe patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other th
b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoum increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospit for abnormal bleeding and compared them with 5818 control subjects who were also taking a coumarin. on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (O bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).
c) Sertraline 50 mg to 200 mg daily for 21 days produced an 8% increase in prothrombin time in subject given prior to sertraline; this compared with a 1% decrease with placebo. Normalization of the prothromb findings is unknown (Prod Info ZOLOFT(R) oral tablets, concentrate, 2008).
d) In a non-blinded, randomized, placebo-controlled trial involving 12 healthy volunteers, the effect of se study, all participants received warfarin 0.75 mg/kg. Beginning on day 11, each volunteer was randomize mg/day to 200 mg/day. Prothrombin time was measured prior to each dose of warfarin and periodically th enhanced by sertraline to a clinically significant degree, despite the fact that sertraline was given in a hig

3.5.1.FB Tipranavir
1) Interaction Effect: increased sertraline plasma concentrations
2) Summary: Although the drug interaction between sertraline and tipranavir/ritonavir has not been studied, c plasma concentrations. Sertraline doses may need to be adjusted when tipranavir/ritonavir therapy is initiated
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concurrent administration of sertraline and tipranavir/ritonavir may increase sertrali consider adjusting the sertraline dose as needed upon initiation of tipranavir/ritonavir (Prod Info APTIVUS(R)
7) Probable Mechanism: unknown

3.5.1.FC Tirofiban
1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and
been associated with an increased risk of bleeding. Bleeding events reported have included epistaxis, ecchy
tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an antiplatelet agent are given concurrently, monitor patient for
PROZAC(R) oral capsules, delayed-release capsules, solution, 2008)
7) Probable Mechanism: unknown

3.5.1.FD Tolmetin

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and
associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hemator
suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solu
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent
were searched among 26,005 users of antidepressant medications and compared with the number of ho
amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 t
12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The
SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with

3.5.1.FE Toloxatone

1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental sta
2) Summary: Concurrent administration or overlapping therapy with sertraline and a monoamine oxidase (MA
characterized by symptoms such as restlessness, myoclonus, changes in mental status, hyperreflexia, diaph
concomitant use of serotonin specific reuptake inhibitors and MAO inhibitors (Prod Info Zoloft(R), 1999i; Lapp
& de Vries, 1990m). As a reversible and selective monoamine oxidase inhibitor, toloxatone may not potentiat
duration observed with other MAOIs. However, until further studies confirm the safety and efficacy of this con
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Concurrent use of sertraline and a MAO inhibitor is contraindicated. Wait at least 14
least 14 days after discontinuing sertraline before initiating therapy with a MAO inhibitor.
7) Probable Mechanism: inhibition of serotonin metabolism by monoamine oxidase
8) Literature Reports
a) Concomitant use of SSRIs and monoamine oxidase inhibitors can produce a toxic reaction known as
hyperstimulation and manifests as restlessness, myoclonus, changes in mental status, hyperreflexia, dia
fatality can result.
b) A 26-year old woman who had been taking isocarboxazid for eight weeks stopped taking the drug for
the patient became restless and developed leg twitches. The patients was later admitted to the emergen
disturbances. After treatment with diazepam and propranolol the patient did not improve. The patient was
symptoms after the second dose (Lappin & Auchincloss, 1994n).
c) A drug interaction was reported in a 61-year old woman in which sertraline 100 mg twice daily was ad
taking the first sertraline dose, the patient was found in a semicomatose state, with elevated body tempe
Hg. After transportation to the hospital, the patient was misdiagnosed as having neuroleptic malignant sy
sertraline and phenelzine. The authors suggest that monoamine oxidase inhibitor (MAOI) therapy should
serotonin reuptake inhibitor (SSRI) and that before starting a MAOI, SSRI therapy should be discontinue
1994n).
d) Two cases reports suggested a possible interaction between fluoxetine and selegiline (Suchowersky
approximately one month after adding selegiline to fluoxetine. The patient improved two months after bot
involved diaphoresis, vasoconstriction, and cyanosis of the hands which occurred in close temporal relat
quick resolution of symptoms. Rechallenge with fluoxetine alone occurred without incident.

3.5.1.FF Tramadol

1) Interaction Effect: an increased risk of seizures and serotonin syndrome (hypertension, hyperthermia, myo
2) Summary: Seizures and serotonin syndrome have been reported in patients using tramadol. Some medica
and serotonin syndrome may be enhanced when sertraline and tramadol therapy are combined (Prod Info UL
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Caution should be used if tramadol is to be administered to patients receiving conc

underlying conditions that might predispose to seizures. Observe the patient closely for signs and symptoms
7) Probable Mechanism: increased concentration of serotonin in the nervous system and periphery

3.5.1.FG Tranylcypromine
1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental sta
2) Summary: Concurrent administration or overlapping therapy with sertraline and a monoamine oxidase (MA characterized by symptoms such as restlessness, myoclonus, changes in mental status, hyperreflexia, diaph Zoloft(R), 2002n; Lappin & Auchincloss, 1994m; Graber et al, 1994m; Bhatara & Bandettini, 1993f; Suchowe
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Concurrent use of sertraline and a MAO inhibitor is contraindicated. Wait at least 14 least 14 days after discontinuing sertraline before initiating therapy with a MAO inhibitor.
7) Probable Mechanism: inhibition of serotonin metabolism by monoamine oxidase
8) Literature Reports
a) Concomitant use of serotonin specific reuptake inhibitors and monoamine oxidase inhibitors can prod syndrome is a condition of serotonergic hyperstimulation and manifests as restlessness, myoclonus, cha not recognized and correctly treated, death can result.
b) A 26-year old woman who had been taking isocarboxazid for eight weeks stopped taking the drug for the patient became restless and developed leg twitches. The patients was later admitted to the emergen disturbances. The patient did not improve after treatment with diazepam and propranolol. The patient wa in symptoms after the second dose (Lappin & Auchincloss, 1994l).
c) A drug interaction was reported in a 61-year old woman in which sertraline 100 mg twice daily was ac taking the first sertraline dose, the patient was found in a semicomatose state, with elevated body tempe mmHg. After transportation to the hospital, the patient was misdiagnosed as having neuroleptic malignar between sertraline and phenelzine. The authors suggest that MAO inhibitor therapy should be discontinu inhibitor (SSRI) and that before starting a MAOI, SSRI therapy should be discontinued for at least 5 half-
d) Two cases reports suggested a possible interaction between fluoxetine and selegiline (Suchowersky approximately 1 month after adding selegiline to fluoxetine therapy. The patient improved 2 months after involved diaphoresis, vasoconstriction, and cyanosis of the hands which occurred in close temporal relat quick resolution of symptoms. Rechallenge with fluoxetine alone occurred without incident.

3.5.1.FH Triazolam
1) Interaction Effect: increased serum concentrations of triazolam and risk of adverse effects (excessive sed
2) Summary: To date, no information is available related to the effects of coadministered triazolam and sertra sertraline was a moderate inhibitor in vitro of alprazolam metabolism (Von Moltke et al, 1994a). It is theoretica cytochrome P450 system and sertraline is thought to inhibit one or more P450 isoenzymes (DeVane, 1994f). family of isoenzymes and sertraline is suspected of inhibiting the CYP3A4 isozyme. Until further information i
3) Severity: minor
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Caution is warranted if triazolam and sertraline are to be coadministered. Monitor p Triazolam doses may need to be reduced.
7) Probable Mechanism: decreased triazolam metabolism

3.5.1.FI Trimipramine
1) Interaction Effect: modest elevations in trimipramine serum levels or possible serotonin syndrome (hyperte
2) Summary: There is limited evidence suggesting that sertraline may inhibit tricyclic antidepressant (TCA) m P450 2D6 enzyme activity and may increase the plasma concentrations of coadministered drugs that are me Lydiard et al, 1993c; Prod Info Zoloft(R), 1999b). Effects of the interaction may have little or no clinical impact were modest compared with those found when fluoxetine (another selective serotonin reuptake inhibitor) was sertraline therapy for TCA toxicity (dry mouth, urinary retention, CNS depression). Trimipramine doses may n
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: The combined use of tricyclic antidepressants (TCAs) and selective serotonin reupt serotonin syndrome have also been reported with concurrent TCA and SSRI therapy. Caution should be obse
7) Probable Mechanism: inhibition of trimipramine metabolism
8) Literature Reports
a) Desipramine pharmacokinetics were studied in 18 healthy male volunteers. Study subjects received c daily) for 21 days. When sertraline was added to desipramine therapy, the mean maximum concentration increased by 26%. Trough concentrations of desipramine were close to baseline one week after sertralin interaction may not be clinically significant (Preskorn et al, 1994f).

3.5.1.FJ Valdecoxib
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hemator

suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solu
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent were searched among 26,005 users of antidepressant medications and compared with the number of ho amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with

3.5.1.FK Warfarin

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Alter coadministration of SSRIs with warfarin (Prod Info ZOLOFT(R) oral tablets, concentrate, 2008). Prothrombin 1997a).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When sertraline and an anticoagulant are given concurrently, monitor patient for sig closely for altered anticoagulant effects, including increased bleeding, when sertraline therapy is initiated or d
7) Probable Mechanism: unknown
8) Literature Reports
a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bl fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patien with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopram bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experie corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experienci addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respe patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other th
b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoum increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospit for abnormal bleeding and compared them with 5818 control subjects who were also taking a coumarin. on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (O bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).
c) Sertraline 50 mg to 200 mg daily for 21 days produced an 8% increase in prothrombin time in subject given prior to sertraline; this compared with a 1% decrease with placebo. Normalization of the prothromb findings is unknown (Prod Info ZOLOFT(R) oral tablets, concentrate, 2008).
d) In a non-blinded, randomized, placebo-controlled trial involving 12 healthy volunteers, the effect of se study, all participants received warfarin 0.75 mg/kg. Beginning on day 11, each volunteer was randomize mg/day to 200 mg/day. Prothrombin time was measured prior to each dose of warfarin and periodically t enhanced by sertraline to a clinically significant degree, despite the fact that sertraline was given in a hig

3.5.1.FL Xemilofiban

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and been associated with an increased risk of bleeding. Bleeding events reported have included epistaxis, ecchy tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an antiplatelet agent are given concurrently, monitor patient for PROZAC(R) oral capsules, delayed-release capsules, solution, 2008)
7) Probable Mechanism: unknown

3.5.1.FM Zolmitriptan

1) Interaction Effect: an increased risk of serotonin syndrome
2) Summary: There have been case reports of weakness, hyperreflexia, and incoordination following concon specific reuptake inhibitor (SSRI) (Prod Info Imitrex(R), 1998a; Prod Info Zomig(TM), 1997). Because zolmitri occur (Prod Info Zomig(TM), 1997). Concurrent use of zolmitriptan and an SSRI may result in serotonin synd restlessness, hallucinations, loss of coordination, fast heart beat, rapid changes in blood pressure, increased should be aware that triptans may be commonly used intermittently and that either the triptan or the SSRI ma

patients who are prescribed this combination and monitor them closely for symptoms of serotonin syndrome
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Coadministration of a triptan, such as zolmitriptan, and an SSRI may result in a life-
used intermittently and that either the triptan or the SSRI may be prescribed by a different physician. If these
monitor closely for symptoms of serotonin syndrome (restlessness, hyperthermia, hyperreflexia, incoordinatic
7) Probable Mechanism: additive pharmacologic effects resulting in excessive serotonergic stimulation
8) Literature Reports
a) The pharmacokinetics of a single 10 mg dose of zolmitriptan were not altered by four weeks of fluoxe
pressure were also not changed by fluoxetine therapy (Prod Info Zomig(R), 2002).

3.5.1.FN Zolpidem
1) Interaction Effect: an increased risk of hallucinations
2) Summary: The publication of five case reports from the Washington Poison Center elucidates potential int
reported hallucinations after concurrent use of zolpidem and antidepressant medication. The hallucination ep
1998a).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Observe patients for hallucinatory activity. Alternative anti-insomnia medication may
7) Probable Mechanism: unknown
8) Literature Reports
a) The Washington Poison Center reports that they received five different calls from patients experiencir
the five reports came from patients taking serotonin-reuptake inhibitors in addition to zolpidem. The antid
and bupropion. In each case, the hallucinatory activity lasted longer than one hour, but the patients' sym
which zolpidem might cause hallucinations has not been firmly established (Elko et al, 1998).

3.5.1.FO Zomepirac
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and
associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hemator
suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solu
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent
were searched among 26,005 users of antidepressant medications and compared with the number of ho
amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 t
12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The
SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with

3.5.2 Drug-Food Combinations

Ethanol

Grapefruit Juice

3.5.2.A Ethanol
1) Interaction Effect: an increased risk of impairment of mental and motor skills
2) Summary: In experiments with healthy subjects, sertraline did not potentiate cognitive or psychomotor effe
manufacturer of sertraline recommends that depressed patients be advised to avoid alcohol while using sertr
3) Severity: moderate
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Patients receiving sertraline should be advised to avoid the use of alcohol.
7) Probable Mechanism: unknown

3.5.2.B Grapefruit Juice
1) Interaction Effect: elevated sertraline serum concentrations and an increased risk of adverse side effects
2) Summary: In a small study, grapefruit juice was shown to inhibit the metabolism of sertraline, resulting in i

cytochrome P450 3A4 (CYP3A4) enzymes, and sertraline relies on CYP3A4 for metabolism to its metabolite, this interaction (Lee et al, 1999a).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Counsel patients to avoid grapefruit juice while taking sertraline. Orange juice may metabolism.
7) Probable Mechanism: inhibition of cytochrome P450 3A4-mediated sertraline metabolism
8) Literature Reports
a) Five depressed patients stabilized on sertraline for more than six weeks participated in a prospective, pharmacokinetics of sertraline. During the first seven days of the study, each patient received their usual mL of grapefruit juice. The mean sertraline trough levels increased from 13.6 mcg/L to 20.2 mcg/L during effects reported between the two periods. Grapefruit juice had minimal effects on sertraline metabolism i activity. A larger study is needed to substantiate the clinical significance of the interaction between grape

4.0 Clinical Applications

Monitoring Parameters

Patient Instructions

Place In Therapy

Mechanism of Action / Pharmacology

Therapeutic Uses

Comparative Efficacy / Evaluation With Other Therapies

4.1 Monitoring Parameters

A) Sertraline Hydrochloride
1) Therapeutic
a) DEPRESSION
1) Improvement in target symptoms (depressed mood, suicidal thoughts or intent, change in appetite, la of excessive guilt/worthlessness, psychomotor retardation or agitation, difficulties in thinking/concentratic
2) Patients with thyroid disease who are also receiving treatment for depression should have thyroid fun and small increases in serum thyrotropin levels after starting treatment with sertraline and other antidepr
b) OBSESSIVE-COMPULSIVE DISORDER
1) Reduction or resolution of recurrent and persistent impulses, ideas or thoughts that are intrusive and
2) Reduction or resolution of repetitive and intentional behaviors performed in response to obsessive th
c) PANIC DISORDER
1) Reduction or resolution of signs/symptoms consistent with panic disorder (dyspnea, palpitations, trem experiencing an uncontrolled feeling).
2) Toxic
a) Physical Findings
1) Since EXTRAPYRAMIDAL REACTIONS including dystonic reactions, parkinsonian-like movement di weekly during the first 4 weeks of therapy is recommended (Gill et al, 1997).
2) Gastrointestinal adverse effects (nausea, vomiting) are common during initiation of therapy but usuall
3) Monitor patients receiving antidepressants for worsening of depression, suicidality, or unusual change decreases. Such monitoring should include at least weekly face-to-face contact with patients or their fam week for the next 4 weeks, then at 12 weeks, and then as clinically indicated beyond 12 weeks. Families observation) of patients and communication with the prescriber (Anon, 2004; Anon, 2004).
4) Patients who experience symptoms of anxiety, agitation, panic attacks, insomnia, irritability, hostility, depression or suicidality. If these symptoms are observed, therapy should be re-evaluated and it may be were not part of the patient's initial symptoms (Anon, 2004; Anon, 2004).

4.2 Patient Instructions

A) Sertraline (By mouth)
Sertraline

Treats depression, obsessive-compulsive disorder (OCD), posttraumatic stress disorder (PTSD), premenstrual dy is an antidepressant called a selective serotonin reuptake inhibitor (SSRI).

When This Medicine Should Not Be Used:

You should not use this medicine if you have had an allergic reaction to sertraline or if you are also using pimozid
such as Eldepryl®, Marplan®, Nardil®, or Parnate® within the past 14 days. Do not use the liquid form of sertralir

How to Use This Medicine:
Tablet, Liquid
Your doctor will tell you how much of this medicine to use and how often. Do not use more medicine or use it
Measure the oral liquid medicine with a marked measuring spoon, oral syringe, or medicine cup. The oral liqu
with 1/2 cup (4 ounces) of water, ginger ale, lemon-lime soda, lemonade, or orange juice. Do not mix this me
liquid until you are ready to take your dose. It is okay if the mixture looks hazy.
This medicine should come with a Medication Guide. Read and follow these instructions carefully. Ask your d
Guide if you do not have one. Your doctor might ask you to sign some forms to show that you understand this

If a Dose is Missed:
If you miss a dose or forget to use your medicine, use it as soon as you can. If it is almost time for your next d
medicine to make up for a missed dose.

How to Store and Dispose of This Medicine:
Store the medicine in a closed container at room temperature, away from heat, moisture, and direct light.
Ask your pharmacist, doctor, or health caregiver about the best way to dispose of any leftover medicine after
expiration date has passed.
Keep all medicine away from children and never share your medicine with anyone.

Drugs and Foods to Avoid:
Ask your doctor or pharmacist before using any other medicine, including over-the-counter medicines, vitamins, a
Make sure your doctor knows if you are also using cimetidine (Tagamet®), diazepam (Valium®), digitoxin, lin
sumatriptan (Imitrex®), tolbutamide, tramadol (Ultram®), tryptophan, or valproate (Depacon®). Tell your doct
depression such as amitriptyline, nortriptyline, Elavil®, Pamelor®, or Sinequan®. Your doctor will need to knc
Rythmol®, or Tambocor®.
Make sure your doctor knows if you are using a pain or arthritis medicine (sometimes called “NSAIDs”) such
Motrin®. Tell your doctor if you have used an MAO inhibitor such as Eldepryl®, Marplan®, Nardil®, or Parnat
Tell your doctor if you are using any medicines that make you sleepy. These include sleeping pills, cold and a
using this medicine.

Warnings While Using This Medicine:
Make sure your doctor knows if you are pregnant or breastfeeding, or if you have seizures, liver disease, blee
For some children, teenagers, and young adults, this medicine can increase thoughts of suicide. Tell your do
have thoughts about hurting yourselves. Report any unusual thoughts or behaviors that trouble you or your cl
you or your child have trouble sleeping, get upset easily, have a big increase in energy, or start to act reckles
nervous, angry, restless, violent, or scared. Let the doctor know if you, your child, or anyone in your family ha
This medicine may cause hyponatremia (low sodium in the blood). This is more common in elderly patients, t
decreased amounts of fluids in the body due to severe diarrhea or vomiting. Stop taking this medicine and ch
problems, confusion, weakness, or unsteadiness.
Tell your doctor if you are allergic to latex rubber. The oral liquid form of this medicine has a latex rubber drop
This medicine may make you dizzy or drowsy. Avoid driving, using machines, or doing anything else that cou
Do not stop using this medicine suddenly without asking your doctor. You may need to slowly decrease your
Your doctor will need to check your progress at regular visits while you are using this medicine. Be sure to ke

Possible Side Effects While Using This Medicine:
Call your doctor right away if you notice any of these side effects:
Allergic reaction: Itching or hives, swelling in your face or hands, swelling or tingling in your mouth or throat, d
Blistering, peeling, red skin rash.
Change in how much or how often you urinate.
Chest pain.
Fast or pounding heartbeat.
Headache, trouble concentrating, memory problems, weakness, or unsteadiness.
Muscle stiffness, twitching, shaking, or uncontrolled muscle movements.
Painful, prolonged erection of your penis, or trouble having sex.
Severe confusion, sweating, diarrhea, or fever.
Unusual bleeding or bruising.
Unusual thoughts, behavior, restlessness, nervousness, aggressive behavior, or anger.

If you notice these less serious side effects, talk with your doctor:
Decreased interest in sex.
Dizziness or drowsiness.
Dry mouth.
Loss of appetite.
Mild diarrhea, constipation, nausea, vomiting, or stomach pain.
Tiredness.

Trouble sleeping.
Weight loss.

If you notice other side effects that you think are caused by this medicine, tell your doctor.

4.3 Place In Therapy

A) SUMMARY

1) Sertraline has received approval by the United States Food and Drug Administration for treating depression, o numerous other psychiatric disorders.

B) DEPRESSION

1) All of the selective serotonin reuptake inhibitors (SSRIs) are effective for treating depression although selected NOT have any major therapeutic benefits over other SSRIs; however, it has less potential for drug interactions an an SSRI is dependent on clinical judgement and response of patients to previous therapy (Edwards & Anderson,

2) Preliminary data suggest that a trial of a second serotonin reuptake inhibitor (SSRI) is a viable clinical alternati (Joffe et al, 1996). In a retrospective review of 55 patients who had failed to respond to at least five weeks of thera dosages), 51% did respond to a trial of an alternative agent. The choice of the second agent was based on clinicia

4.4 Mechanism of Action / Pharmacology

A) MECHANISM OF ACTION

1) Sertraline is a potent and selective inhibitor of synaptosomal serotonin reuptake in the brain. It has a higher de including clomipramine, fluoxetine, fluvoxamine, and zimeldine (Heym & Koe, 1988a). It appears to have little effe

2) Like most other antidepressants (except fluoxetine), sertraline also causes an indirect down-regulation of posts therapeutic effect and for its delay in clinical efficacy (Doogan & Caillard, 1988; Heym & Koe, 1988a).

B) REVIEW ARTICLES

1) A comparison of selective serotonin reuptake inhibitors with a guide to selection is provided (Edwards & Ander

2) Two reviews provide a discussion of the efficacy of selective serotonin reuptake inhibitors and other antidepres

3) The efficacy of antidepressants in reducing panic attack frequency, symptoms of depression, social avoidance

4) A review article discusses the rational treatment of depression and each class of antidepressants (Cohen, 199

5) A review article describes the treatment of panic disorder, including the role of selective serotonin reuptake inh

6) Treatment of elderly patients with selective serotonin reuptake inhibitors is discussed with emphasis on improv

7) Pharmacological and therapeutic information about sertraline has been summarized (Peruche & Schulz, 1997

8) Drug-interactions of antidepressants are reviewed in German language (Zapotoczky & Simhandl, 1995).

4.5 Therapeutic Uses

4.5.A Sertraline Hydrochloride

Aggressive behavior

Alcoholism

Alzheimer's disease; Adjunct

Alzheimer's disease - Depression

Anorexia nervosa

Binging - Eating disorder

Cerebrovascular accident, Post - Depression; Prophylaxis

Cerebrovascular accident, Post - Mood swings

Clozapine adverse reaction - Obsessive-compulsive disorder

Complication of hemodialysis - Hypotensive episode

Depression - Myocardial infarction, Post

Drug-induced depressive state

Dysthymia

Flashbacks

Generalized anxiety disorder

Intermittent explosive disorder

Major depressive disorder

Myocardial infarction; Prophylaxis

Night eating syndrome

Non-cardiac chest pain

Obsessive-compulsive disorder

Panic disorder

Pathological laughing

Posttraumatic stress disorder

Premature ejaculation

Premenstrual dysphoric disorder

Respiratory obstruction

Schizophrenia

Severe major depression with psychotic features

Social phobia

4.5.A.1 Aggressive behavior

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Sertraline has been effective in the treatment of severe aggressiveness and self-injurious behavior a
reports (Ranen et al, 1996; Hellings et al, 1996)

c) Adult:

1) Sertraline has been effective in the treatment of severe aggressiveness and self-injurious behavior as
reports (Ranen et al, 1996; Hellings et al, 1996). Because serotonergic mechanisms have been implicate
was attempted after multiple pharmacologic interventions had failed. Dosages in these cases ranged fro
mg to avoid akathisia or irritability. Marked improvement to complete cessation of aggressive behaviors
sertraline for this indication.

4.5.A.2 Alcoholism

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Helpful in alcoholic patients without lifetime depression but not in alcoholic patients with lifetime dep

c) Adult:

1) Sertraline treatment was more effective than placebo in reducing alcohol intake of alcoholic subjects were currently experiencing or had previously experienced depression ("lifetime depression"). One hund (n=53) and those without (n=47) before being randomly assigned to receive sertraline 200 milligrams/da noted for frequency of drinking; however, the interaction between lifetime depression status and treatme never-depressed groups (p=0.33), whereas placebo was favored over sertraline in the lifetime-depressio never-depressed groups; there was no difference between treatments in the lifetime depression groups. adverse reactions (sexual disturbance, fatigue, and headache) were significantly more frequent in the se 2001).

4.5.A.3 Alzheimer's disease; Adjunct

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class III
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

May be effective as an adjunctive therapy in the treatment of behavioral and psychological symptom severe symptoms (Finkel et al, 2004)

c) Adult:

1) Sertraline therapy was not effective in the treatment of behavioral and psychological symptoms in the analysis of a subgroup of patients with moderate to severe symptoms. In a randomized, double-blind, pla received 8 weeks of open label treatment with donepezil (5 to 10 milligram (mg)/day) followed by 12 wee dose, 125.7 mg/day) or placebo (n=120). Primary endpoints included scores for the Neuropsychiatric Inv (CGI-S) scale. In the initial analyses, no significant improvements were found for any of the primary endp However, in a post hoc analyses of a subgroup of patients with moderate to severe behavioral and psych sertraline treatment was associated with a significant improvement on the mean NPI Behavioral and Psy significantly more patients in the donepezil-plus-sertraline group were rated as responders on the NPI Be placebo group (60% vs 33%, respectively; p=0.006). Sertraline was well tolerated with only diarrhea occu

4.5.A.4 Alzheimer's disease - Depression

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIa
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Reduced depressive symptoms in patients with Alzheimer's disease in double-blind, placebo-control

c) Adult:

1) Sertraline therapy effectively reduced depressive symptoms in patients with Alzheimer's disease. In a disorder and probable Alzheimer's disease received sertraline (n=24; initial, 25 milligrams (mg)/day for 1 or placebo (n=20) for 12 weeks following a one-week placebo run-in phase. Response to treatment was Depression Rating Scale (HDRS). Significantly more sertraline-treated patients were full or partial respon Patients in the sertraline group also had significantly greater improvements on CSDD and HDRS scores Although not significant, sertraline-treated patients showed a stronger statistical trend toward stabilizatio Depression Rating Scale-ADL subscale, as compared with placebo. There was no difference between tr dizziness and gastrointestinal symptoms being the most frequently reported adverse events (Lyketsos et

2) Sertraline was more effective than placebo in reducing DSM-IV diagnosed major depressive disorder Alzheimer's disease and major depression were randomized to receive either sertraline (n=12) or placeb over 6 weeks to 150 mg/day or the maximum tolerated dose. Three of the 12 patients receiving sertraline response occurring by the third week of treatment. In the placebo group, there was one full responder an less than 0.05). Mean reductions in scores on the Cornell Scale for Depression were significantly greater placebo group reported nervous system side effects (tremor, restlessness) (Lyketsos et al, 2000).

4.5.A.5 Anorexia nervosa

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Pediatric, Evidence is inconclusive
Recommendation: Pediatric, Class III
Strength of Evidence: Pediatric, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Not better than non-drug treatment for anorexia nervosa (Santonastaso et al, 2001)

c) Pediatric:

1) Addition of sertraline to a multidisciplinary treatment of anorexia nervosa was not more effective than

DSM-IV criteria for restricting-type anorexia nervosa, were treated with open-label sertraline 50 milligram whose response had been unsatisfactory. Eleven other similar subjects were given no medication. All pa per week. At 14 weeks, 6 patients in each group (55%) still had a diagnosis of a full eating disorder. Bod months, rates of full remission were 54% in the sertraline group and 27% in the control group (not signifi headache, and insomnia. No subject interrupted treatment because of side effects (Santonastaso et al, 2

4.5.A.6 Binging - Eating disorder

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

A small double-blind study found sertraline to decrease the frequency of binges compared to placeb

c) Adult:

1) Sertraline reduced the frequency of binges, global clinical severity scores, and body mass index to a met DSM-IV criteria for binge eating disorder and had binge episodes at least 3 times weekly for 6 month placebo; doses were adjusted based on response up to 200 mg daily. Estimated mean weight loss was an underlying condition in most of the study patients. Of the 18 patients treated with sertraline, 11 had a disorder. In the 16 placebo-treated patients, 7 had a lifetime diagnosis and 3 had a current diagnosis of

4.5.A.7 Cerebrovascular accident, Post - Depression; Prophylaxis

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Sertraline was more effective than placebo in the prevention of post-stroke depression (Rasmussen

c) Adult:

1) Sertraline treatment appeared to be more effective than placebo in the prevention of depression follo post-stroke patients received sertraline (n=70; initial, 50 milligrams (mg)/day for 2 weeks then titrated up months. The incidence rate of depression (assessed by the total score on the Hamilton Depression Scal placebo group (8.2% vs 22.8%, respectively). The depression occurrence rate as measured by scores o (11.5% vs 28%, respectively). Fewer sertraline-treated patients had Clinical Global Impression (CGI) sev given placebo (18% vs 29.8%, respectively; p=0.12). Sertraline was well tolerated and there were no sig

4.5.A.8 Cerebrovascular accident, Post - Mood swings

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

In a small study (n=28), sertraline reduced emotional lability after a stroke (Burns et al, 1999)

c) Adult:

1) More patients treated with sertraline than placebo experienced a reduction in emotional lability (Burns randomly assigned to receive placebo or sertraline 50 milligrams/day for 8 weeks. At 8 weeks, 93% of pa Clinician's Interview-based impression of change and the emotionalism/lability of mood questions (p=0.0 to placebo (p=0.041). Four patients did NOT complete the study; 2 patients receiving sertraline experien suggest that sertraline is useful for reducing emotional lability after stroke.

4.5.A.9 Clozapine adverse reaction - Obsessive-compulsive disorder

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

In a single case, sertraline effectively treated obsessive-compulsive behavior induced by clozapine(

c) Adult:

1) Addition of sertraline to clozapine reduced obsessive compulsive behavior without adversely affecting effectively reduced treatment-refractory psychosis, the patient developed obsessive compulsive behavio to risperidone and clomipramine which were ineffective so treatment with clozapine was reinstituted alon

plasma concentrations which were likely due to competitive inhibition of cytochrome P450 isoenzymes b
regimen, his psychotic and obsessive-compulsive symptoms were well controlled (Rahman et al, 1998).

4.5.A.10 Complication of hemodialysis - Hypotensive episode

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class III
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Reduced the severity of hypotension during and after hemodialysis sessions (Yalcin et al, 2002)

c) Adult:

1) Sertraline treatment raised the systolic and diastolic nadirs during hemodialysis sessions and increas
hypotension. Of 12 patients selected for treatment, 3 were unable to tolerate sertraline at 100 milligrams
before sertraline treatment were compared to data from a 4-week sertraline period. The sertraline period
before data collection. Dry weights of the patients, ultrafiltration volumes, dialysate composition, dialysat
and diastolic blood pressure (DBP) were the same in the sertraline period as in the pre-sertraline period.
the pre-sertraline period to 87 in the sertraline period (p less than 0.05); the nadir of DSP rose from 51 to
than 0.005). Post-dialysis DPB did not change significantly (59 to 62). The need for therapeutic intervent
0.001) (Yalcin et al, 2002).

4.5.A.11 Depression - Myocardial infarction, Post

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Sertraline relieved depression without causing adverse cardiac effects (Shapiro et al, 1999)
Heart rate variability recovery following acute MI was facilitated by sertraline (McFarlane et al, 2001)

c) Adult:

1) Sertraline improved depressive symptoms in patients with a recent myocardial infarction (MI). In this
milligrams daily beginning a mean of 30 days after the MI. At 16 weeks, 74% of patients had a positive re
Hamilton rating decreased from 19.7 to 7.8 (p less than 0.001). Fifteen (78.9%) of 19 patients who comp
completely resolved" by the Clinical Global Impression Scale. There were no significant changes in cardi
controlled study is underway to evaluate efficacy and safety of sertraline in this patient population (Shapi
2) Depressed, post-myocardial infarction (MI) patients treated with sertraline 50 milligrams (mg) daily ha
to a matched placebo group. Thirty-eight depressed patients were entered into a randomized, double-bli
sertraline) leaving 27 patients (16 males, average age 62 +/- 11 (SD) years) to complete the 22 week stu
and was composed of 11 age-matched, non-depressed, post MI patients (9 males). All three groups had
of mortality within the first year of an acute (MI), 2 weeks following the MI before sertraline or placebo wa
normal sinus-conducted N-N interbeat intervals, the average heart rate, and the standard deviation of all
sertraline group increased by 5% compared to a 28% increase in the reference group and a 9% decreas
depression (IDD) score for the sertraline group compared to the placebo group (p less than 0.05). The au
theoretically improve clinical outcomes (McFarlane et al, 2001).

4.5.A.12 Drug-induced depressive state

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Relieved depression caused by interferon-alfa therapy in a small study (n=10) (Schramm et al, 2000

c) Adult:

1) Sertraline relieved symptoms of interferon-alfa (IA)-induced depression without the necessity of disco
who met the DSM-IV criteria for substance (interferon-alfa)-induced depressive disorder were treated wit
improvement in depressed mood and irritability, with 7 reporting complete resolution of symptoms. Mild a
8 weeks, 1 patient experienced erectile dysfunction, and his medication was changed to moclobemide (S

4.5.A.13 Dysthymia

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:
Sertraline was effective in the treating dysthymia, based upon improvement in psychiatric rating sco

c) Adult:
1) Sertraline was more effective than placebo in improving psychiatric rating scores in patients meeting concomitant diagnosis of major depressive disorder and who were not taking any other psychotropic dru mg or placebo daily. Dose adjustments up to 200 mg daily were allowed during the 12-week treatment p reductions in Structured Interview Guide for the Hamilton Depression Rating Scale-Seasonal Affective D Clinical Global Impressions-Severity of Illness scale (CGI-S), and Hospital Anxiety and Depression Scale achieving response, defined as reduction in SIGH-SAD or MADRS scores by 50%, or a CGI-Improvemer and 60.1% based on the 3 respective scales), compared with response rates in the placebo group (33.8% significantly higher with sertraline (33.8%) than with placebo (21.6%). Quality of life rating scores also im

4.5.A.14 Flashbacks

a) Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category C
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:
In a single patient, sertraline was effective for eliminating flashbacks associated with lysergic acid di

c) Adult:
1) Sertraline treatment, started at 25 milligrams (mg) daily and slowly titrated to a target dose of 100 mg and depressive symptoms in a single patient with an 8-month history of LSD intake and daily flashbacks days after each dose increase but then subsided. This patient had no history of seizures or migraines. H experience at a later time of the original effects of the hallucinogenic drug. The hallucinogen, LSD, is bel Sertraline decreased the typical physiologic responses to serotonergic agonists as well as attenuated the LSD which present as flashbacks (Young, 1997).

4.5.A.15 Generalized anxiety disorder

a) Overview
FDA Approval: Adult, no;
Efficacy: Adult, Evidence favors efficacy;
Recommendation: Adult, Class IIb;
Strength of Evidence: Adult, Category B; Pediatric, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:
Sertraline-treated adults had significant decreases in the total Hamilton Rating Scale for Anxiety sco dose study of 326 adults with moderate to severe primary generalized anxiety disorder (Brawman-M Sertraline therapy in combination with cognitive behavioral therapy (CBT) was shown to be superior were both superior to placebo in a randomized, controlled trial among children and adolescents with Reduced psychic and somatic symptoms in children with generalized anxiety disorder (Rynn et al, 2

c) Adult:
1) Sertraline-treated adult outpatients had significant decreases in the total Hamilton Rating Scale for An double-blind, flexible-dose study of 326 evaluable adults with moderate to severe, primary generalized a GAD, had a total HAM-A symptom score of 20 or greater, a score of 2 or greater on item 1 of the HAM-A Scale score. There was no placebo run-in phase, but patients could not receive psychotropic drugs withi baseline. Patients were randomized to receive either placebo (n=162), or sertraline 25 milligrams/day (m and 7, up to a maximum of 200 mg/day. Decreases in dose were permitted at any time with only one sub was 149.1 mg +/- 59 mg. The mean age of patients was approximately 40 years, including 8.3% of patie measurement, the mean change in total HAM-A at 10 weeks compared with baseline was -12.71 +/- 7.1 between groups of -1.8 +/- 0.8 (95% CI, -3.4 to -0.2, p=0.032). There were significant improvements in to 6 and lasting through week 10. An analysis of the HAM-A somatic subscale in sertraline-treated patients subscale did demonstrate significant improvements (p=0.011). The response rate (at least 50% reductio (p=0.05). Significant adverse events (p less than 0.001) in the sertraline group (n=165) compared with pl libido 17.6% vs 2.4%. Diastolic blood pressure increases of 1.59 mmHg +/- 8.83 mmHg occurred in the s (p=0.0204) (Brawman-Mintzer et al, 2006).

d) Pediatric:
1) Sertraline therapy) was shown to be superior t both superior to placebo in a randomized, controlled trial among children and adolescents with childhood 10.7 years; 74.2% under the age of 13), with a primary diagnosis of social phobia, separation or generali receive sertraline plus CBT (n=140), sertraline alone (n=133), CBT alone (n=139) or placebo (n=76). Sul subjects receiving sertraline alone and placebo therapy were not aware which therapy they were receivir titrated on a fixed-flexible schedule beginning with 25 mg per day and adjusted upward in the absence o sessions which included anxiety-management skills and behavioral exposure to anxiety-provoking situati +/- 59.8 mg and the mean daily dose for sertraline-only patients was 146 +/- 60.8 mg. The primary outco

improvement on the Clinical Global Impression-Improvement scale (a scale of 1 to 7 with lower scores in included all patients randomized. At week 12, a Clinical Global Impression-Improvement scale of 1 or 2 (86.4) of patients receiving sertraline in combination with CBT, 54.9% (95% CI, 46.4 to 63.1) of patients re 23.7% (95% CI, 15.5 to 34.5) of patients receiving placebo therapy (all p less than 0.001 vs placebo). Pa either sertraline alone (OR 3.4; 95% CI, 2 to 5.9; p less than 0.001) or CBT alone (OR 2.8; 95% CI, 1.6 t patients receiving sertraline alone or CBT alone (p=0.41). In the number needed to treat (NNT) analysis, event; treating 3 patients with sertraline alone or CBT alone prevented 1 additional event. The incidence in the sertraline group compared to the placebo group. There were no suicide attempts (Walkup et al, 20

2) Sertraline was safe and efficacious in the treatment of generalized anxiety disorder in children and ac DSM-IV diagnosis of generalized anxiety disorder were randomly assigned to receive sertraline or placel first week and 50 mg/day thereafter. Significant treatment differences in favor of sertraline were evident f Anxiety Rating Scale, as well as the psychic factor score, was significantly better in the sertraline group t factor). Ten of 11 patients receiving sertraline were rated as improved, while only 1 of the placebo patien marked improvement. There was no depression-by-treatment interaction effect, indicating that the obser age effects on treatment were observed. Patients receiving sertraline reported less dizziness, nausea, a and restlessness occurred more frequently among those treated with sertraline than among those receiv

4.5.A.16 Intermittent explosive disorder

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Three patients treated with sertraline noted a decrease in explosive behavior (Feder, 1999)

c) Adult:

1) Three patients (age range, 29 to 51 years old) who met DSM-IV diagnostic criteria for intermittent exp sertraline. Two patients received sertraline 50 milligrams daily while the third required sertraline 100 milli months to 2 years with continued treatment; family members and friends also observed the change. The which is corrected with sertraline (Feder, 1999).

4.5.A.17 Major depressive disorder

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes; Pediatric, no
Efficacy: Adult, Effective; Pediatric, Evidence favors efficacy
Recommendation: Adult, Class I;
Strength of Evidence: Adult, Category B; Pediatric, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

More effective than placebo in relieving acute depression
In comparison to placebo, reduced recurrence of chronic depression in 18-month study of responde
Sertraline has more favorable adverse effect profile than amitriptyline
Possibly efficacious in adolescents with major depression
Safe and effective in the treatment of moderate to severe depression in children and adolescents ag
Sertraline was safe and effective in reducing depressive symptoms in elderly patients
In elderly patients with depression, sertraline did not provide protection against relapse when given

c) Adult:

1) Treatment with sertraline effectively reduced depressive symptoms in patients with late-life depressio (n=752), elderly patients (60 years and older) with major depressive disorder and with or without comorb included in the comorbid illness group (n=442) had a vascular morbidity (ie, cardiovascular, cerebrovasc endpoint, significantly greater score improvements for the Hamilton Depression scale (p=0.02), Clinical G (p=0.001) were seen in sertraline-treated patients as compared with patients who received placebo. Sign effective in the treatment of depression regardless of medical comorbidity. Sertraline was generally well t

2) Sertraline therapy following remission of depressive symptoms did not provide prophylaxis against re major depressive disorder (mean age, 77.6 years of age) received open-label treatment with sertraline (r achieving remission of depressive symptoms entered a randomized, double-blind, placebo- controlled, m received sertraline (at their final therapeutic dose; range, 50 to 100 mg/day) or placebo. Increases in dos in the prevention of recurrence of depression (Wilson et al, 2003).

3) Sertraline therapy was more effective than placebo in the treatment of symptoms associated with maj controlled study, geriatric patients (mean age, 69.8 years; range, 59 to 97 years) with major depressive d score of at least 18 received sertraline (n=371; initial, 50 milligrams (mg)/day for 4 weeks, then titrated to period of 4 to 14 days. From baseline to endpoint, sertraline treatment produced significantly greater cha p=0.01) and the Clinical Global Impressions (CGI) Severity score (-1 vs -0.8, respectively; p=0.009). Ser endpoint as compared with placebo (2.7 vs 2.9, respectively; p=0.02). The CGI response rate (defined as 35% for those taking placebo (p=0.005). The HAM-D response rate (defined as at least a 50% reduction placebo (35% vs 26%, respectively; p=0.007). Diarrhea, headache, somnolence, tremor, nausea, fatigue

(Schneider et al, 2003).

4) At the end of a 20-week continuation study, more patients receiving sertraline than placebo had a per sertraline-treated and 49% of placebo-treated patients withdrew or failed to complete the study. In this co with major depression. One hundred seven responders (66 sertraline; 41 placebo) from a 6-week acute p only responders had been entered into the continuation phase, a prospectively defined Clinical Global Im persistence of a treatment effect in this period (Olie, 1997).

5) After 6 weeks, sertraline produced significant improvement in depression compared to placebo at all compared to placebo in a double-blind, parallel study of 289 patients with depression.

6) In an 18-month continuation study of patients with chronic depression or dysthymic disorder with majo placebo. Following treatment for depression and a short continuation period, patients (n=161) who respo weeks; the maximum allowable dose was 200 milligrams (mg). The recurrence rate was 6% and 23% for recurrence of depressive symptoms compared to placebo. Of the 161 patients enrolled in the continuatio the patients treated with sertraline, the major reason for discontinuation was adverse effects, whereas in sertraline is useful for preventing recurrence or reemergence of depression in patients with chronic depre

d) Pediatric:

1) Sertraline therapy effectively treated depressive symptoms in children and adolescents with moderate placebo- controlled trials, pediatric patients (n=376; ages 6 to 17 years) with major depressive disorder c sertraline (50 to 200 milligrams (mg)/day; mean dose, 131 mg/day) or placebo for 10 weeks. Psychotrop allowed during the study. Response was defined as a 40% or greater reduction in the adjusted total scor Impression-Improvement (CGI-I) score of 2 or less ("very much" or "much" improved). From baseline to e significantly better for sertraline-treated patients as compared with placebo-treated patients (-22.84 vs -2 sertraline group as compared with placebo for both the CDRS-R (69% vs 59%, respectively; p=0.05) and with insomnia, diarrhea, anorexia, vomiting, agitation, purpura, and urinary incontinence being reported r ideation (3 patients) and aggressive reaction (1 patient) (Wagner et al, 2003).

2) In an uncontrolled, open-label study of adolescents (ages 12 to 18 years) with DSM-IV major depress depressive symptoms, although response patterns differed for MDD and DD. Patients (n=21) received se 200 mg/day. Response to treatment, as indicated by a 50% or greater improvement in the Hamilton-Dep was sustained to the end of the study (24 weeks). In the DD group (n=8), the HAM-D response rate was of a score of 2 or less on the Clinical Global Impression-Improvement Scale (CGI-I), the response rate re the end of the study. In the DD group, the CGI-I maximal response rate was 75% at week 6. That maxim were the most common adverse events, with of the DD group and 30% of the M of the MDD group. Two obese patients were withdrawn from the study for elevations in blood pressure a efficacious in the acute treatment of MDD and DD and in the continued treatment of MDD in adolescents

4.5.A.18 Myocardial infarction; Prophylaxis

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class III
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Associated with decreases in platelet/endothelial activation in depressed, post-acute coronary syndr
May confer a protective effect against first myocardial infarction (Sauer et al, 2001)

c) Adult:

1) Sertraline therapy was associated with a decrease in platelet/endothelial activation in patients experie placebo-controlled sub-study of the Sertraline Antidepressant Heart Attack Randomized Trial (SADHART placebo for 24 weeks. The use of aspirin, anticoagulants, and ADP- receptor inhibitors was allowed throu platelet/endothelial activation as compared with placebo and may offer further advantage for this patient et al, 2003).

2) In a case-control study comprised of 653 cases of first myocardial infarction (MI) and 2990 control sul protective effect against first MI. The subjects in this study were smokers, between the ages of 30 to 65 y SSRIs investigated in this study were fluoxetine, fluvoxamine, paroxetine, and sertraline; doses taken by first MI compared to controls (after adjustment for potential confounders) was 0.35 (95% CI 0.18, 0.68; p inhibitory effect on serotonin-medicated platelet activation or amelioration of other factors associated with

4.5.A.19 Night eating syndrome

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Treatment with sertraline reduced the symptoms of night eating syndrome compared to placebo in a (O'Reardon et al, 2006)

c) Adult:

1) In an 8-week, randomized, double-blind, placebo-controlled study (n=34), treatment with sertraline re

Patients meeting the standard criteria for night eating syndrome and with a body mass index of greater tl
depression, a lifetime diagnosis of bipolar disorder or any psychotic disorder, or who lacked awareness c
sertraline 50 milligrams (mg; n=17) or placebo (n=17) orally once daily for 8 weeks. Sertraline was adjus
conducted every other week. No other psychotropic medications were allowed during the study period. A
Inventory, and the Quality of Life Enjoyment and Satisfaction Questionnaire, and a physician administere
Hamilton Depression Rating scale. The primary outcome was the CGI-improvement scores, where patie
improved) were considered to have responded and remitted, respectively. An intent-to-treat analysis reve
achieved remission (p less than 0.001). Three of 17 patients (18%) in the placebo group responded (p le
In the sertraline group, the CGI severity scale decreased from 4.2 at baseline (moderate severity) to 2.2
decreased from 4.2 at baseline to 3.4 at week 8 (p=0.004). Among secondary endpoints, the night eating
the sertraline and placebo groups, respectively (p less than 0.0001). Although a significant correlation be
(r=0.68; p=0.01) indicated that early improvement with sertraline was predictive of ultimate response, 50
8. The number of nocturnal ingestions decreased from a baseline mean (+/- standard deviation) value of
to a decrease from the baseline mean of 6.4 +/- 4.9 per week to 5.5 +/- 4.9 per week at week 8 in the pla
placebo, improvements also occurred for patients treated with sertraline in the number of awakenings, ca
patients. Both groups had a modest level of depressive symptoms at baseline, and reductions in depress
symptom scores. Sertraline was well-tolerated, only mild side effects that included dry mouth, fatigue, dir

4.5.A.20 Non-cardiac chest pain

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

A small double-blind study found sertraline to significantly reduce noncardiac chest pain (Varia et al,

c) Adult:

1) Sertraline significantly reduced pain scores compared to placebo in patients with chest pain determin
30 patients were randomized to either sertraline 50 milligrams (mg) or placebo, with dose adjustments up
decreased significantly in the sertraline group compared with the placebo group. Sertraline's effect did no
were excluded and no effect was seen on the Beck Depression Inventory in these patients. Sertraline wa

4.5.A.21 Obsessive-compulsive disorder

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes; Pediatric, yes ((6 years or older))
Efficacy: Adult, Effective; Pediatric, Effective
Recommendation: Adult, Class I; Pediatric, Class I
Strength of Evidence: Adult, Category B; Pediatric, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Considered a first-line agent for treating obsessive-compulsive disorder (OCD)
Cognitive behavior therapy alone or in combination with sertraline was more effective in the treatme
placebo

c) Adult:

1) Effectiveness of sertraline for treatment of obsessive-compulsive disorder (OCD) was sustained with
Patients who had responded successfully to sertraline (final mean dose 189 milligrams/day) in a 52-weel
sertraline (n=109) or with placebo (n=114) for an additional 28 weeks. Study discontinuation due to relap
(9% vs 24%, p=0.006). Experiences of acute exacerbation (not resulting in study discontinuation) were a
groups in discontinuation due to adverse events. During the double-blind trial, patients in the sertraline g
decreases. During the entire 80 weeks of treatment, fewer than 20% of patients taking sertraline dropped
patients receiving placebo and 4.6% of those receiving sertraline dropped out because of adverse event
upper respiratory infection, headache, and malaise. The only notable difference in rates of adverse even
et al, 2002).

2) Sertraline was more effective than placebo for treatment of obsessive-compulsive disorder (OCD). In
were randomly assigned to receive placebo or sertraline 50 milligrams/day titrated to a maximum dose o
significantly more effective than placebo based on the Yale-Brown Obsessive Compulsive Scale (p less
less than 0.05), and the Clinical Global Impression Scale (p less than 0.01). Forty-one percent of sertrali
placebo-treated patients (p=0.01). Thirteen patients stopped treatment due to adverse effects primarily s
completed by 71% and 69% of patients treated with sertraline and placebo, respectively. Sertraline is an

3) Of the selective serotonin reuptake inhibitors (SSRIs) (ie, fluoxetine, sertraline, paroxetine, fluvoxamin
Limited clinical studies also suggest that the SSRIs are comparable to clomipramine; however, results of
& Bisserbe, 1997; Leonard, 1997). Selection of initial treatment is often based on the side effect profile o
(Leonard, 1997). Early studies used near maximal doses of an SSRI which resulted in a high incidence c
response in some patients and better tolerance in most (Leonard, 1997). While the optimal duration of tr
studies have shown relapse rates between 65% and 90% when pharmacologic treatment was stopped (I
doses of an SSRI and/or behavioral therapy are considered refractory to treatment. In about 20% of this

therapy with haloperidol or clonazepam may be beneficial (Rasmussen & Eisen, 1997).

4) Results of a study demonstrated significant improvement of obsessive compulsive disorder (OCD) on multicenter trial in 87 patients with OCD who did not meet criteria for depression, sertraline 200 milligram symptoms as measured by the Yale-Brown Obsessive-Compulsive Scale and the NIMH Scale. The Mau although there was a trend toward greater improvement in the sertraline-treated group; the physician-rat some improvement as compared with 26% of the placebo-treated group (Chouinard et al, 1990).

d) Pediatric:

1) Cognitive behavior therapy (CBT) either alone or in combination with sertraline was more effective in compared with sertraline monotherapy or placebo. In the randomized, controlled, multicenter Pediatric O age, 11.7 years) with a primary diagnosis of OCD and a Children's Young-Brown Obsessive-Compulsive over a 12-week period. Equal numbers of patients received either CBT alone, sertraline therapy alone, c titration schedule (25 to 200 milligrams/day over 6 weeks, after which no further dosage adjustments wer the 12-week study period. At 12 weeks, significantly greater reductions in CYBOCS scores were observe placebo (p less than 0.001). Monotherapy with sertraline or CBT was not significantly different when com scores as compared with placebo (p=0.007 and p=0.003, respectively). Significantly higher rates of clinic combination therapy (53.6%; 95% CI, 36% to 70%) as compared with sertraline (21.4%, 95% CI, 10% to differ from CBT alone (39.3%; 95% CI, 24% to 58%) (p=ns). As with reductions in CYBOCS scores, sert remission rates, however, CBT was superior to placebo (p=0.002) while sertraline was not (p=ns). Sertra attempt during the study. Common adverse effects included decreased appetite, diarrhea, enuresis, mot Team, 2004).

2) Sertraline was shown to be effective in a 12-week, multicenter, placebo-controlled, parallel group stud open extension study of 137 outpatients (ages 6 to 18) for the treatment of obsessive-compulsive disord score of 22 on the Children's Yale-Brown Obsessive-Compulsive Scale (CYBOCS). Children ages 6 to 1 to 17) were started on 50 mg/day. Doses were increased over the next four weeks to a maximum dose o sertraline group had a mean reduction of approximately 7 units on the CYBOCS total score which was si Response to treatment was not altered by either age or gender (Prod Info Zoloft(R), 2003a).

4.5.A.22 Panic disorder

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes; Pediatric, no
Efficacy: Adult, Effective
Recommendation: Adult, Class IIa
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Sertraline has reduced the frequency of panic attacks in blinded studies (Pohl et al, 1998; Londborg

c) Adult:

1) Sertraline is an effective therapy for panic disorder. In a 10-week, double-blind, multicenter study, 166 titration to a maximum dose of 200 mg daily; at study endpoint, the mean sertraline dose was 126 mg/da number of panic attacks per week decreased by 77% and 51% in the sertraline and placebo groups, resp (62%) than placebo (46%) were free of panic attacks (p=0.04). Investigators also noted significant impro (severity and improvement: p less than 0.001). Adverse effects resulted in study discontinuation in 9% a effects had a mild-to-moderate severity rating (Pohl et al, 1998).

2) Sertraline was significantly more effective than placebo in the treatment of panic disorder. Patients we 200 mg daily (n=44), or placebo (n=44) for 12 weeks. The primary measure of efficacy was the number o the number of weekly panic attacks compared to a 39% reduction with placebo. There were no significar decreased the frequency of situational and unexpected panic attacks, anticipatory anxiety, and limited sy After 12 weeks, more patients were panic-free with sertraline than placebo, 57% and 41%, respectively. 200 mg group, and 31% of the placebo group discontinued the study. A significantly greater number of p placebo. Because efficacy was independent of plasma concentrations, 50 mg of sertraline daily is the re (Londborg et al, 1998).

4.5.A.23 Pathological laughing

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Relieved pseudobulbar laughter in one patient (Okun et al, 2002)

c) Adult:

1) Sertraline resolved pseudobulbar laughter within 48 hours in a 46-year-old man who had suffered inju Parkinson's disease), the man underwent right gamma knife thalamotomy, targeting the ventral intermed numbness in his lip, which resolved, and numbness in his left hand, which persisted over the following ye symptoms of depression or elated mood. He was given sertraline 50 milligrams/day, which resolved the follow-up (Okun et al, 2002).

4.5.A.24 Posttraumatic stress disorder

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes; Pediatric, no
Efficacy: Adult, Effective
Recommendation: Adult, Class I
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Effective for treating posttraumatic stress disorder (Rapaport et al, 2002)
Effectiveness maintained during extended treatment (Londborg et al, 2001)
Some nonresponders to acute treatment respond to longer treatment (Londborg et al, 2001)

c) Adult:

1) Quality of life (QOL) was significantly improved in patients with posttraumatic stress disorder (PSTD) In a manufacturer-funded study, 359 patients meeting DSM-III-R criteria for PTSD for at least 6 months v milligrams (mg) per day or placebo for 12 weeks. Completers of the acute phase (n=275), whether or not (n=234). Responders during the continuation phase (n=172) were eligible for a 28-week, randomized, do maintenance phase. In comparison to placebo treatment, acute sertraline treatment resulted in significan (Q-LES-Q) of patients without comorbid depression. Improvement in scores of those with comorbid depr measures of psychological functioning and well-being were significant (relative to placebo) for sertraline- occupational impairment scores were significantly better with sertraline than with placebo. During the cor the double-blind, maintenance phase, QOL and functioning scores deteriorated somewhat for both group

2) Effectiveness of sertraline for treating posttraumatic stress disorder (PTSD) was maintained in most p Furthermore, half of the nonresponders to acute treatment became responders during the 6 months of c the acute phase of 2 double-blind, placebo-controlled trials of sertraline for treatment of severe DSM-III-R during the acute phase. Blinding to acute-phase treatment was maintained throughout the open label stu (mg) daily for the first week. The dose was then increased to 50 mg/day, which was titrated on an individ sustained their initial response. Average scores on various investigator-completed and patient-completed patients who were nonresponders during the acute phase who became responders during the continuati response time was having a high baseline severity score (higher than 75) on the Clinician Administered I frequent moderate-to-severe treatment-related adverse events were headache, insomnia, dry mouth, an vital signs attributed to sertraline during the 24 weeks. Body weight increased by a mean of 0.8 kilogram

3) Sertraline was more effective than placebo in prevention of posttraumatic stress disorder (PTSD) rela for posttraumatic stress disorder (PTSD), were enrolled in this 28-week, double-blind, multicenter, placeb biweekly and were classified as relapsed if their Clinical Global Impression (CGI) improvement score inc increased by at least 30%, and there was significant worsening of the patient's clinical condition on two c relapse than the patients treated with sertraline (mean endpoint dose=137 milligrams). Forty percent of t 28-week trial (Davidson et al, 2001).

4) Sertraline was more effective than placebo for treating patients with chronic post-traumatic stress dis randomly assigned to sertraline 25 milligrams (mg)/day or placebo; after the first week, the sertraline dos patients who received treatment, 65 and 68 patients assigned to sertraline and placebo completed the tri follow-up. In patients completing the study, the mean daily dosage of sertraline was 151.3 mg. For 3 of th Clinical Global Impression-Severity scale (CGI-S), and the Clinical Global Impression-Improvement Scal 33 versus (vs) -23.2, p=0.02; CGI-S -1.2 vs -0.8, p=0.01; CGI-I 2.5 vs 3, p=0.01). In addition, a trend tow treated with sertraline versus placebo. About 70% of the reduction on the CAPS-2 and IES was achieved

4.5.A.25 Premature ejaculation

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Sertraline effectively increased time to ejaculation during a randomized, placebo-controlled trial (n=3

c) Adult:

1) Thirty-seven men were successfully treated with sertraline 50 mg daily for premature ejaculation. Dur (n=19) for 4 weeks. Patients then underwent a 4-week washout period and entered phase 2 which consi open-label trial to evaluate the long-term effects of sertraline on premature ejaculation and the effects of significantly compared to those in the placebo group, from a mean of 0.3 minutes to 3.2 minutes (P less drug, efficacy was lost after 6 to 13 days. This suggests that long-term treatment with sertraline may be r

4.5.A.26 Premenstrual dysphoric disorder

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes; Pediatric, no
Efficacy: Adult, Effective

Recommendation: Adult, Class I
Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:
Sertraline is effective for premenstrual dysphoric disorder (PMDD) (Prod Info Zoloft(R), 2002; Pearls
Administration during the luteal phase was as effective as continuous sertraline and more effective t
& Smoller, 1997)

c) Adult:
1) Women with PMDD demonstrated greater improvement in psychosocial function after treatment with
the psychosocial functioning results reported here. All women (n=243) completed the Daily Record of Se
form of the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q) before and after treatme
enrolled in this study showed impairment of psychosocial functioning during the luteal phase compared v
phase of 3 menstrual cycles versus placebo resulted in significant improvement on the SAS total score (
reduction of productivity, interference of hobbies and social activities, and interference with relationships
second menstrual cycle on (Pearlstein et al, 2000).
2) Sertraline produced greater improvement in symptoms associated with premenstrual dysphoric disor
50 mg or placebo daily during the first cycle; if needed, the sertraline dose was titrated to 100 mg in cycl
Severity of Problems (DRSP) showed a 32% versus 11% decrease in total scores (p less than 0.001) aft
beneficial effects of sertraline. This study also demonstrated significant improvement in productivity and
8% and 2% of patients treated with sertraline and placebo withdrew from treatment. Sertraline is an effec
3) Sertraline administered during the luteal phase was as effective as continuous sertraline and more ef
(Halbreich & Smoller, 1997). In this study, patients were initially treated with sertraline 100 milligrams (m
assigned to receive placebo or sertraline 100 mg daily for 2 weeks during the luteal phase; each treatme
Scale for Depression (HAM-D), Clinical Global Impressions scale (CGI), and Daily Rating Forms (DRF))

4.5.A.27 Respiratory obstruction

a) Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class III
Strength of Evidence: Adult, Category C
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:
Low doses of sertraline were effective in the treatment of patients with obstructive airway disease (n

c) Adult:
1) Sertraline 25 milligrams (mg) to 100 mg daily was effective in decreasing breathlessness and increas
Sertraline, however, had little effect on measures of forced expiratory volume at 1 second (FEV1). Only 3
experienced anxiety during attacks of dyspnea. Sertraline may decrease the anxiety associated with bre
patients did not have mood/anxiety disorders, sertraline may work on respiratory, rather than psychiatric
decreasing patient sensitivity to carbon dioxide concentrations. Further studies are needed to confirm the

4.5.A.28 Schizophrenia

a) Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Ineffective
Recommendation: Adult, Class III
Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:
Sertraline had no effect on positive or negative symptoms of schizophrenia when added to an antips

c) Adult:
1) Addition of sertraline to haloperidol therapy had no effect on the positive or negative symptoms of sch
for an average of 10 years and required institutional care. Patients were randomly assigned to placebo o
differences between treatments on the Positive and Negative Syndrome Scale, the Clinical Global Impre
shown beneficial effects of adding a selective serotonin reuptake inhibitor to an anti-psychotic. In this stu
the study population, the short duration of treatment, and the fixed, low-dose of sertraline. Further studie

4.5.A.30 Social phobia

FDA Labeled Indication

a) Overview
FDA Approval: Adult, yes; Pediatric, no
Efficacy: Adult, Effective
Recommendation: Adult, Class I
Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:
Effectively treated social phobia in short-term (12-20 weeks) and longer-term clinical trials (44 week
c) Adult:
1) Treatment with sertraline was more effective than placebo in reducing symptoms of severe generalize
controlled, flexible-dose study, patients (n=415) with a least a 2-year history of generalized social phobia
to 200 milligrams (mg) daily (mean dose, 158.8 mg/day) or placebo for 12 weeks. Response was define
Impressions-Improvement Scale (CGI-I). At endpoint, the CGI-I responder rate was significantly higher f
than 0.001). Additionally, the mean change in the LSAS score showed significantly greater reductions wi
and endpoint (p less than 0.001). The most commonly reported adverse events with sertraline treatment
mouth (14.4%), sweating (11.5%), and ejaculatory dysfunction (men, 14.3%) (Liebowitz et al, 2003).
2) Sertraline in doses of 50 to 200 milligrams per day was effective in the treatment of adult outpatients
also demonstrated a statistically significant lower relapse rate in a 24-week continuation study when com

4.6 Comparative Efficacy / Evaluation With Other Therapies

Amisulpride

Amitriptyline

Bupropion

Desipramine

Fluoxetine

Fluvoxamine

Imipramine

Mianserin

Mirtazapine

Nortriptyline

Paroxetine

Sildenafil

St John's Wort

Venlafaxine

4.6.A Amisulpride

Burning mouth syndrome

Dysthymia

4.6.A.1 Burning mouth syndrome

a) Amisulpride, sertraline, and paroxetine were all effective in reducing the symptoms of burning mouth synd
serotonin reuptake inhibitors (SSRIs). In a randomized, single-blind study, 76 patients with BMS and without
mg/day, or sertraline 50 mg/day for 8 weeks. Pain scores decreased significantly in all groups, as did depres
Anxiety), by week 8. The only difference among treatments was the shorter latency to response in the amisul
paroxetine and 6% with sertraline) (Maina et al, 2002a).

4.6.A.2 Dysthymia

a) Although amisulpride and sertraline were equally effective for treatment of dysthymia at 12 weeks of treat

amisulpride than with sertraline. In a 12-week, randomized, double-blind study, patients between the ages of depression, were given amisulpride (n=156) or sertraline (n=150), each drug at a starting dose of 50 milligran were eventually increased to 100 mg/day). The median time to onset of partial response (corresponding to a score) was significantly shorter with amisulpride: 11 days versus 15 days (p less than 0.0091). Percentages c sertraline (p less than 0.01). Patients reported perceiving improvement earlier with amisulpride: 8.4 days vs 1 HAMD score) also occurred earlier with amisulpride. By week 4, 63% of patients in the amisulpride group and corresponding values were 82% and 69% (p=0.009). By week 12, the percentage of responders did not differ percentage of patients reporting adverse events was about 45% for both groups but the adverse events were sertraline and endocrine adverse events with amisulpride (Amore & Jori, 2001).

4.6.B Amitriptyline

4.6.B.1 Depression

a) SUMMARY: Five clinical studies have reported similar efficacy between amitriptyline and sertraline in the Doogan & Caillard, 1988b; Reimherr et al, 1988a). Sertraline has had a higher incidence of gastrointestinal si with anticholinergic effects, sedation, dizziness, and hypotension (Cohen et al, 1990)(Reimherr et al, 1990).
b) In an 8-week, double-blind, parallel-group study (n=385), sertraline and amitriptyline were comparable for (Lydiard et al, 1997). Patients were randomly assigned to receive placebo, sertraline 50 milligrams (mg), or a in the protocol. Selected sections of Profile of Mood States (POMS) showed greater improvement in patients similar between treatments. Significantly more patients reported adverse effects (71.8%) and dropped out of adverse effects, blinding may have been inadequate in this study. Long-term studies are needed to compare
c) In an 8-week, double-blind placebo-controlled parallel study of 379 patients with major depression, sertral amitriptyline 50 to 150 mg/day. However, both drugs produced significant improvement over placebo. Patient Global Impressions (CGI) measurement (Doogan & Caillard, 1988b). Similar results were reported in 77 patie controlled trial, the investigators found that sertraline caused fewer adverse reactions than did amitriptyline.
d) However, in another study, patients receiving sertraline had a significantly higher incidence of gastrointest treated group. The amitriptyline-treated group had a high incidence of anticholinergic effects, sedation and di (mean dose 145 milligrams), amitriptyline (mean dose 104 milligrams), or placebo. As measured by both the groups showed significantly greater improvement than placebo (Reimherr et al, 1990).
e) In 241 elderly depressed patients, amitriptyline 50 to 150 milligrams daily or sertraline 50 to 200 milligrams effects varied greatly. A higher proportion of amitriptyline-treated patients (38%) withdrew from the study due compared with a 28% incidence of treatment-withdrawal with sertraline. Sertraline-treated patients had a high

4.6.C Bupropion

4.6.C.1 Depression

a) In a randomized, double-blind comparison trial between sustained- release bupropion (bupropion SR) and treated patients (Segraves et al, 2000). In the study, 248 patients diagnosed with moderate to severe major d dose of bupropion SR was 100 milligrams/day (mg/day). If indicated, the dose was increased to 200 mg/day was increased to 100 mg/day on day 8, 150 mg/day on day 15, and 200 mg/day on day 22, if clinically indicat dysfunction compared with bupropion SR (men: 63% and 15%, respectively, p less than 0.001; women: 41% disorder, sexual arousal disorder, orgasm dysfunction, decreased satisfaction with sexual functioning, and wo treated patients reported instances of premature ejaculation; however, this difference was not statistically sign determine the extent of influence of the natural course of depression. This data does suggest, however, that whom sexual dysfunction is of concern.
b) In an 8-week, double-blind trial, sertraline and bupropion produced similar antidepressant effects while bu received bupropion sustained release 150 to 400 milligrams (mg)/day (n=120), sertraline 50 to 200 mg/day (r were bupropion SR 293 mg/day and sertraline 121 mg/day. Both active treatment groups responded better th bupropion SR 66%, sertraline 68%, placebo 47%, p=0.002). At baseline, sexual desire disorder was reported patients. At the end of 8 weeks this problem decreased to only 19% of bupropion patients versus 31% receivi the disorder (not significant as compared to placebo). More sertraline patients also experienced orgasmic dys 0.001). Somnolence, insomnia, nausea, and diarrhea also occurred more often in the sertraline group than in
c) In a randomized, double-blind trial, bupropion sustained release (SR) and sertraline were similarly effectiv received either bupropion SR 100 to 300 milligrams (mg) daily in 2 doses (n=119) or sertraline 50 to 200 mg and sertraline 114 mg/day. Patients improved similarly on several scales including the Hamilton Rating Scale Scale for Severity of Illness and for Improvement. Nausea, diarrhea, somnolence and sweating were experie Orgasm delay and/or failure was also experienced more often in the sertraline group (p less than 0.001).

4.6.D Desipramine

Depression - Obsessive-compulsive disorder

Premenstrual dysphoric disorder

4.6.D.1 Depression - Obsessive-compulsive disorder

a) Sertraline was more effective than desipramine for reducing symptoms of major depressive disorder (MDD assigned to receive desipramine 50 milligrams (mg) per day or sertraline 50 mg per day for 12 weeks. The do desipramine was 300 mg/day. At study end-point, the mean dosage of sertraline and desipramine was 160.1 Rating Scale for Depression (HAM-D) and Yale-Brown Obsessive Compulsive Scale (Y-BOCS), sertraline wa treated with sertraline than desipramine had a 40% or greater reduction in the Y-BOCS (p=0.01); remission o patients in the sertraline than desipramine groups (p=0.04). Discontinuation due to adverse effects occurred i p=0.009). For patients with OCD and MDD, sertraline is an effective treatment (Hoehn-Saric et al, 2000).

4.6.D.2 Premenstrual dysphoric disorder

a) Sertraline more effectively reduced symptoms and improved functioning in women with premenstrual dysp al, 1999). After a 3-month screening period, patients (n=189) were randomly assigned to sertraline 50 milligra intervals to a maximum of 150 mg/day were allowed. Significantly more patients assigned to desipramine dis resulted in a significantly greater decrease from baseline to endpoint in the Premenstrual Daily Symptom Rep 17-item Hamilton Depression Rating Scale (p less than 0.001). Direct comparison of a sertraline and desipra

b) In an open-label trial of 32 women with a history of severe premenstrual symptoms, sertraline and desipra months treatment, 78% of sertraline-treated patients and 75% of desipramine-treated patients experienced a more sertraline-treated patients (68%) reported a 50% or more reduction in premenstrual symptoms than des the study, but this difference may not apply to long-term therapy. Long-term, placebo-controlled trials are nee syndrome.

4.6.E Fluoxetine

Depression

Obsessive-compulsive disorder

Weight gain

4.6.E.1 Depression

a) Paroxetine, fluoxetine, and sertraline were equally effective for the treatment of depression and for improv label trial (the ARTIST trial), depressed patients, whose symptoms warranted antidepressant treatment, acco (n=184) or sertraline (n=182). Starting doses were paroxetine 20 milligrams (mg), fluoxetine hydrochloride 20 response and could switch the treatment to one of the other study drugs. Final average doses were 23.5 mg substantial improvement in depressive symptoms and quality of life. Overall, the percentage of patients categ and 26% at 9 months. No significant differences were evident among the 3 groups. When data from subgrou assigned) were analyzed separately, still no differences among the drug treatments was evident. Patient satis to show improvement for all drug treatments. The drugs were associated with similar incidences of adverse e

b) An eight-week, double-blind, randomized study evaluated the efficacy and safety of fluoxetine vs sertralin with major depression entered into the study, but only 88 (48 sertraline and 40 fluoxetine) were evaluable. Th treatment groups showed a statistically significant improvement from baseline at one week, and this was mai between the two treatment groups on the primary efficacy variables measured by Hamilton Rating Scale for D Asberg Depression Rating Scale (MADRS), Leeds Sleep Score scale and Zung Anxiety Rating Scale. The in common were gastrointestinal (nausea and abdominal pain) and central nervous system (irritability, headach tolerated than fluoxetine overall; 9.6% of sertraline-treated patients discontinued treatment, compared with 19 population is warranted to definitively establish the comparative efficacy and safety of the two drugs (Aguagli

4.6.E.2 Obsessive-compulsive disorder

a) Both fluoxetine and sertraline were effective and well tolerated in the treatment of patients with obsessive- per day (mean 139.5 +/- 58.5 mg; N=76), or fluoxetine, 20 to 80 mg/day (mean 56.7 +/- 23.0 mg; N=72), in a matched patient populations. Safety and efficacy measures were taken at the end of study weeks 1, 2, 4, 6, 8 the study. Primary efficacy measures included the Yale-Brown Obsessive- Compulsive Scale (Y-BOCS), the the Clinical Global Impression Severity and Improvement scales (CGI-S and CGI-I). Secondary measures inc Anxiety Scale (CAS). By the end of the 24 week study, both medications were effective and there were no sig measures showed similar amounts of improvement. The time-course of improvement was also similar for bot measures (Y-BOCS change score and global severity of illness score) during some of the early assessments differences between the drug treatments during this time period. Adverse drug effects were described as mild sertraline or fluoxetine (Bergeron et al, 2002).

4.6.E.3 Weight gain

a) Weight gain is a common complaint during antidepressant therapy, and weight gain was significantly grea meeting DSM-IV criteria for major depressive disorder were randomized to double-blind treatment with sertra daily (n=96) for 4 weeks. Patients responding to this dose continued for an additional 6 weeks, and those not 60 mg fluoxetine, and 60 mg paroxetine, and then maintained at their optimal doses for 6 weeks. After this tre consecutive weeks) continued for 16 additional weeks. The number of responders participating in the 16 addi paroxetine. However, among these responders, the mean increase in weight in the paroxetine group (3.6%) v

with fluoxetine (-0.2%). A gain of 7% or greater in weight occurred in 25.5% of paroxetine patients, 4.2% of se
2000a).

4.6.F Fluvoxamine

4.6.F.1 Depression

a) In a small study (n=64), the incidence of recurrent depression was similar between patients treated prophy
received either sertraline 100 milligrams(mg)/day or fluvoxamine 200 mg/day for 2 years; increases in dose w
fluvoxamine-treated patients had a new episode of depression (p=0.88). Adverse effects were minor and tran
were effective for preventing recurrent depression episodes, but are limited by the absence of a placebo cont
b) The pharmacology, pharmacokinetics, adverse effects, drug interactions, efficacy, and dosage of fluvoxar
review (Grimsley & Jann, 1992b). All three agents have large volumes of distribution and are highly protein-b
lives (approximately 24 hours) and are metabolized to clinically-inactive compounds. These agents, therefore
commonly reported adverse effect for all three agents. Other reported adverse effects include sedation, head
be superior to placebo and equivalent to imipramine, clomipramine, desipramine, mianserin, and maprotiline
placebo in the treatment of obsessive-compulsive disorder (OCD). PRX has been found to be superior to pla
treatment of depression while SRT has been found to be superior to placebo and equivalent to amitriptyline.
depression. They may be especially useful in elderly patients, in those who cannot tolerate alternate treatmer

4.6.G Imipramine

Depression

Dysthymia

Mixed anxiety and depressive disorder

4.6.G.1 Depression

a) More than 50% of chronically depressed patients who were nonresponders to an antidepressant responde
randomized, 12-week, double-blind trial with either sertraline or imipramine for treatment of chronic depressic
double-blind treatment. Fifty-one patients were switched from imipramine to sertraline and 117 from sertraline
imipramine and 163 mg/day for sertraline. Ten percent of those switched to sertraline and 25% of those switc
intolerable adverse effects of imipramine. Those who switched to imipramine experienced significant reductio
switched to sertraline had significant decreases in 6 adverse effects and significant increases in one:

	SERTRALINE TO IMIPRAMINE	IMIPRAMINE TO SI
DECREASED INCIDENCE		
	Insomnia	Dry mout
	Diarrhea	Somnolen
	Abdominal Pain	Increased swe
		Constipati
		Dizzines
		Urinary comp
INCREASED INCIDENCE		
	Dry mouth	Insomnia
	Increased sweating	
	Constipation	
	Dizziness	

	Tremor
	Abnormal taste
	Increased appetite
	Urinary complaints

b) The intent-to-treat response rates were 60% for sertraline and 44% for imipramine (p=0.03). Among comp
averaging across the study weeks and adjusting for completion status, depression type, and baseline value, t
improvement over time did not differ for the 2 groups (Thase et al, 2002).
c) In a double-blind study of major depression with or without dysthymia, response to sertraline was highest
III-R criteria for chronic major depression (235 men and 400 women) were randomized to 12-week treatment
daily and titrated to a maximum of 300 mg for imipramine and 200 mg for sertraline. Although the overall resp
treatment interaction was observed. The highest response rates occurred in women taking sertraline and in n
imipramine (61/133; 46%); and more men responded to imipramine (43/69; 62%) than to sertraline (73/161; 4
women withdrew from the imipramine group than from the sertraline group; however, withdrawal rates by mer
between menopausal status and treatment. Withdrawal from treatment was highest in premenopausal womer
these gender differences is unknown, and may relate to interaction of female sex hormones and serotonin ac

4.6.G.2 Dysthymia

a) Sertraline and imipramine are equally effective for the treatment of dysthymia; however, sertraline is bette
in a group of 416 patients with early-onset primary dysthymia. Outcome was based on response based on cli
Rating Scale, Hopkins Symptom Checklist) and patient-rated version of the Inventory of Depressive Sympton
improved) demonstrated response rates of 59% for sertraline, 64% for imipramine, and 44% for placebo. The
159.7 milligrams for imipramine (Thase et al, 1996).
b) Of the 416 patients described in the study above by Thase et al, 355 had completed the Tridimensional P
temperament scores improved with improvement in dysthymia. At baseline, temperament in dysthymic patien
Personality Questionnaire than that reported for a community population. After 12 weeks of treatment, harm a
sertraline, imipramine, and placebo group. Scores decreased for those achieving remission and those who di
improvement in temperament was mainly related to disease improvement regardless of treatment. The result
measures, rather than the single measure used in this study, would be needed to determine treatment effects

4.6.G.3 Mixed anxiety and depressive disorder

a) Imipramine and sertraline were equally effective in the treatment of anxiety and depression in patients witl
double-blind study, patients with full Axis I panic disorder with concurrent major depressive disorder with a mi
Asberg Depression Rating Scale (MADRS) score of at least 20 received either sertraline (n=138; 50 to 100 m
144.2 mg/day) for 26 weeks. Sertraline was given at an initial dose of 25 mg/day for 1 week, then titrated to 5
The initial dose of imipramine was 25 mg/day, increased at weekly intervals to 50 mg, 100 mg, and 150 mg. I
outcome measures were weekly panic attack frequency and MADRS score. Sertraline and imipramine produ
(11.1 vs 11.2, respectively) total MADRS score and in the mean baseline (7.1 vs 7, respectively) to endpoint
patients reported significantly fewer adverse effects as compared with imipramine-treated patients (23% vs 4
p=0.04). Nausea and diarrhea was more frequently reported with sertraline treatment, while dizziness, dry mo
administration (Lepola et al, 2003).

4.6.H Mianserin

1) Adverse Effects
a) In a double-blind, placebo-controlled crossover study in elderly patients, sertraline doses of 100 to 200 mg
tests. The addition of alcohol did not affect these results. Conversely, mianserin doses of 10 to 30 mg daily pr
from the study (Hindmarch et al, 1990).

4.6.I Mirtazapine

4.6.I.1 Depression

a) The onset of response was faster with mirtazapine orally disintegrating tablets than with sertraline capsule
Rating Scale (HAM-D) scores were observed with both drugs by day 4, however, and dose titration schedules

4.6.J Nortriptyline

4.6.J.1 Depression

a) Sertraline and nortriptyline were equally effective in treating depression in elderly outpatients; however, se
In this double-blind study, 210 patients ages 60 years and older, and who met DSM III-R criteria for major dep
randomized to 12 weeks of sertraline or nortriptyline. Sertraline was given as 50 milligrams (mg) daily titrated
titrated weekly as needed to 100 mg daily. At 12 weeks, improvements in HAM-D scores were similar for the
72 (72.4%) sertraline-treated and in 43 of 70 (61.4%) nortriptyline-treated patients; this difference was not sig

those of patients younger than 70 years after treatment with nortriptyline, whereas sertraline decreased HAM
energy, and quality of life improved significantly with sertraline compared to scores with nortriptyline. (Bondar

4.6.K Paroxetine

Burning mouth syndrome

Depression

Weight gain

4.6.K.1 Burning mouth syndrome

a) Amisulpride, sertraline, and paroxetine were all effective in reducing the symptoms of burning mouth synd
serotonin reuptake inhibitors (SSRIs). In a randomized, single-blind study, 76 patients with BMS and without
mg/day, or sertraline 50 mg/day for 8 weeks. Pain scores decreased significantly in all groups, as did depress
Anxiety), by week 8. The only difference among treatments was the shorter latency to response in the amisul
paroxetine and 6% with sertraline) (Maina et al, 2002).

4.6.K.2 Depression

a) Paroxetine, fluoxetine, and sertraline were equally effective for the treatment of depression and for improv
label trial (the ARTIST trial), depressed patients, whose symptoms warranted antidepressant treatment, acco
(n=184) or sertraline (n=182). Starting doses were paroxetine 20 milligrams (mg), fluoxetine hydrochloride 20
response and could switch the treatment to one of the other study drugs. Final average doses were 23.5 mg
substantial improvement in depressive symptoms and quality of life. Overall, the percentage of patients categ
and 26% at 9 months. No significant differences were evident among the 3 groups. When data from subgroup
assigned) were analyzed separately, still no differences among the drug treatments was evident. Patient satis
to show improvement for all drug treatments. The drugs were associated with similar incidences of adverse e
b) Sertraline and paroxetine were equally effective in treating major depression, although side effects may b
criteria for major depression and having a score of at least 21 on the Montgomery-Asberg Depression Rating
randomized to receive 24 weeks of treatment with either sertraline 50 milligrams (mg) or paroxetine 20 mg. D
sertraline and 40 mg paroxetine. No significant differences were observed in the improvement of MADRS and
the 176 patients taking sertraline, 64% completed 24 weeks of treatment, and 65 % of 177 treated with parox
less than 7)was achieved in 80.2% of the sertraline and in 73.7% of the paroxetine-treated patients. Quality o
Comparable improvements also occurred for the 2 groups in measures of personality. Both treatments were
constipation, fatigue, decreased libido in women, and micturition problems significantly more common with pa
compared with sertraline (1.3 pound) (Aberg-Wistedt et al, 2000)

4.6.K.3 Weight gain

a) Weight gain is a common complaint during antidepressant therapy, and weight gain was significantly grea
meeting DSM-IV criteria for major depressive disorder were randomized to double-blind treatment with sertra
daily (n=96) for 4 weeks. Patients responding to this dose continued for an additional 6 weeks, and those not
60 mg fluoxetine, and 60 mg paroxetine, and then maintained at their optimal doses for 6 weeks. After this tre
consecutive weeks) continued for 16 additional weeks. The number of responders participating in the 16 addi
paroxetine. However, among these responders, the mean increase in weight in the paroxetine group (3.6%)
with fluoxetine (-0.2%). A gain of 7% or greater in weight occurred in 25.5% of paroxetine patients, 4.2% of s
al, 2000).

4.6.L Sildenafil

4.6.L.1 Premature ejaculation

a) According to a double-blind, randomized, cross-over study (n=31), as-needed SILDENAFIL was superior
SERTRALINE, and PAUSE-SQUEEZE technique. Clomipramine, paroxetine, and sertraline had generally sir
pause-squeeze, while efficacy and satisfaction were similar to pause-squeeze for clomipramine and sertraline
(min), 4 min, 3 min, 15 min, and 3 min from baseline 1 min for clomipramine, paroxetine, sertraline, sildenafil,
pause-squeeze with respect to IVELT (p=0.04) and sexual satisfaction (p=0.025). A significant positive correl
differences in adverse effects were found among the 4 drugs. Three patients dropped out due to side effects,
additional patients dropped out due to lack of efficacy related to clomipramine, paroxetine, sertraline, and/or
intercourse and not more than twice a week. Doses were clomipramine 25 milligrams (mg), paroxetine 20 mg

4.6.M St John's Wort

4.6.M.1 Depression

a) In a randomized, double-blind, 12-week study, there was no difference in improvement in depression scor
St. John's Wort (SJW). Eighty-seven subjects with major depression according to DSM-IV criteria and a score
to receive sertraline 50 to 100 milligrams (mg) per day (n=43) or SJW 900 to 1800 mg/day (n=44). The Hyper

patients in the sertraline group and 29 in the SJW group completed the study. In the intent-to-treat analysis, b
weeks . Scores on the self-rated Beck Depression Inventory (BDI) declined similarly for the 2 groups. Mean r
sertraline. Thereafter, differences between the groups were not statistically significant. One serious adverse r
required hospitalization. One-third of the subjects of each group dropped out before completion of the study,
efficacy; from the sertraline group, 7 withdrew because of side effects and 1 for lack of efficacy (van Gurp et a

4.6.N Venlafaxine

Bipolar disorder, depressed phase

Depression

Depression, Elderly

4.6.N.1 Bipolar disorder, depressed phase

a) There were no significant differences between bupropion, sertraline, and venlafaxine with regard to respo
switching into hypomania or mania was significantly higher with venlafaxine compared with bupropion and se
outpatients diagnosed with bipolar depression. All patients were receiving at least one mood stabilizer with in
bupropion 75 to 450 milligrams (mg)/day (n=51), sertraline 50 to 200 mg/day (n=58), or venlafaxine 37.5 to 3
Depression Symptomatology (IDS), the Young Mania Rating Scale (YMRS), and the Clinical Global Impressi
antidepressant response (defined as either a 50% or greater improvement in IDS score or a decrease of at le
IDS score less than 12 and/or a CGI-BP depression score of 1 at study endpoint), and antidepressant-relatec
score during any point of the trial or a CGI-BP manic severity score of 3 or more or a YMRS score above 13 a
were 49%, 53%, and 51%, respectively, while remission rates were 41%, 36%, and 34%, respectively. Differe
reported. Controlling for lithium use did not alter the results. Based on CGI-BP score, switching to mania or h
and sertraline (9%; p less than 0.01 overall). During post hoc analysis, it was demonstrated that the switch ef
venlafaxine and sertraline (p=0.01, adjusted for lithium) and bupropion (p less than 0.01, adjusted for lithium)
Based on YMRS score, switching occurred in 4%, 7%, and 15% of patients receiving bupropion, sertraline, a
(31%) and bupropion (14%) and sertraline (16%) treatment groups remained significant when the combinatio
for lithium; p=0.02 when controlled for lithium). Post hoc analysis results again showed that the difference wa
history of rapid cycling was also higher with venlafaxine (43%) compared to bupropion (14%) and sertraline (
for any reason were 31%, 41%, and 45% in the bupropion, sertraline and venlafaxine groups, respectively (P

4.6.N.2 Depression

a) An 8-week, randomized, double-blind, active-control study of outpatient adults with major depressive diso
not significantly different than that of venlafaxine XR (n=76). Patients were randomized to receive capsules c
to 3 capsules/day. Primary outcome measure was the change in Quality of Life Enjoyment and Satisfaction Q
endpoint (8-weeks). Secondary outcome measures were the changes from baseline to endpoint in the scores
Impressions - Severity of Illness scale (CGI-S), the Clinical Global Impressions - Improvement scale (CGI-I),
1 (very much improved) or 2 (much improved) on the CGI-I scale, or a reduction of HAM-D-17 score by at lea
less. There were no significant differences between study groups with any outcome measures, including rem
most common reported adverse effects during active treatment (10% or greater occurrence) were diarrhea, h
scores, response rates, and remission rates for the outcome measures (Shelton et al, 2006):

Endpoint Scores, Response Rates and Remiss	
Measure/Sample	Sertraline (n=82)
Q-LES-Q score, mean (SD)	0.69 (0.12)
HAM-D-17 score, mean (SD)	10.8 (6.4)
HAM-D-17 response rate, (N/N)	55%(45/82)
HAM-D-17 remission rate, (N/N)	38% (31/82)
CGI-S score, mean (SD)	2.6 (1.1)
CGI-I score, mean (SD)	2.3 (1.1)
HAM-A score, mean (SD)	9.1 (5.4)
CGI-I = Clinical Global Impressions-Improvement scale; CGI-S = Clinical Global Impressions-Severity of Rating Scale for Depression; Q-LES-Q = Quality of Life Enjoyment and Satisfaction Questionnaire; XR =	

b) In patients with major depressive disorder, almost twice as many experienced a remission with venlafaxin
depressive disorder randomly received venlafaxine 37.5 mg twice daily (n=75) or sertraline 50 mg daily (n=72
or the sertraline increased to 50 mg twice daily on day 15. After 8 weeks, patients in both groups showed sig
Montgomery- Asberg Depression Rating Scale (p less than 0.05). In the venlafaxine group 83% were respon
the venlafaxine group and in 45% of the sertraline group (p=0.008). The most common adverse events were
with sertraline (Mehtonen et al, 2000).

4.6.N.3 Depression, Elderly

a) Treatment with venlafaxine had a lower tolerability, but was equally effective to sertraline therapy in elderl study, fifty-two elderly patients (mean age, 82.5 years) with depression received either sertraline (initial, 25 m mg/day, titrated to 150 mg/day) for 10 weeks. No significant differences were found in Hamilton Rating Scale groups. However, early termination and withdrawal rates due to serious adverse events were higher in venlaf tract infection, cerebrovascular accident, hypertension, decreased renal function, rapid atrial fibrillation, anem were observed in both treatment groups. From baseline to endpoint, heart rate increased in the venlafaxine g bpm to 70.9 bpm, respectively). The authors suggest that the lowered tolerability of venlafaxine may be relate

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Last Modified: May 20, 2009

DRUGDEX® Evaluations

OLANZAPINE

0.0 Overview

1) Class
- **a)** This drug is a member of the following class(es):
  Antipsychotic
  Thienobenzodiazepine

2) Dosing Information
- **a)** Adult
  - **1)** Agitation - Bipolar I disorder
    - **a)** initial, 10 mg INTRAMUSCULARLY; lower dose of 5 mg or 7.5 mg may be used if indicated; usual effectiv ZYPREXA(R) oral tablets, IM injection, ZYPREXA(R) ZYDIS(R) orally disintegrating tablets, 2006)
    - **b)** subsequent doses may be given INTRAMUSCULARLY in doses up to 10 mg; maximal dosing, three 10 n orthostatic hypotension prior to the administration of repeated doses) (Prod Info ZYPREXA(R) oral tablets, IM disintegrating tablets, 2006)
  - **2)** Agitation - Schizophrenia
    - **a)** initial, 10 mg INTRAMUSCULARLY; lower dose of 5 mg or 7.5 mg may be used if indicated; usual effectiv ZYPREXA(R) oral tablets, IM injection, ZYPREXA(R) ZYDIS(R) orally disintegrating tablets, 2006)
    - **b)** subsequent doses may be given INTRAMUSCULARLY in doses up to 10 mg; maximal dosing, three 10 n orthostatic hypotension prior to the administration of repeated doses) (Prod Info ZYPREXA(R) oral tablets, IM disintegrating tablets, 2006)
  - **3)** Bipolar I disorder, Acute mixed or manic episodes
    - **a)** monotherapy: 10 to 15 mg/day ORALLY, dose adjustments should be made in 5 mg increments in interva (Prod Info ZYPREXA(R) oral tablets, IM injection, ZYPREXA(R) ZYDIS(R) orally disintegrating tablets, 2006)
    - **b)** combination therapy (with lithium or valproate): 10 mg/day ORALLY, dose adjustments should be made ir hours, MAX dose is 20 mg/day (Prod Info ZYPREXA(R) oral tablets, IM injection, ZYPREXA(R) ZYDIS(R) ora
  - **4)** Bipolar I disorder, Maintenance therapy
    - **a)** (monotherapy) 5 to 20 mg ORALLY per day (after achieving a responder status for an average duration o IM injection, ZYPREXA(R) ZYDIS(R) orally disintegrating tablets, 2006)
  - **5)** Schizophrenia
    - **a)** 5 to 10 mg/day orally with a target dose of 10 mg/day within several days; further dose adjustments shoul MAX dose is 20 mg/day (Prod Info ZYPREXA(R) oral tablets, IM injection, ZYPREXA(R) ZYDIS(R) orally disi
- **b)** Pediatric
  - **1)** safety and effectiveness in pediatric patients have not been established

3) Contraindications
- **a)** specific contraindications have not been determined (Prod Info ZYPREXA(R) oral tablets, orally disintegrating table

4) Serious Adverse Effects
- **a)** Cerebrovascular disease
- **b)** Death
- **c)** Diabetic ketoacidosis
- **d)** Status epilepticus
- **e)** Sudden cardiac death

5) Clinical Applications
- **a)** FDA Approved Indications
  - **1)** Agitation - Bipolar I disorder
  - **2)** Agitation - Schizophrenia
  - **3)** Bipolar I disorder, Acute mixed or manic episodes
  - **4)** Bipolar I disorder, Maintenance therapy
  - **5)** Schizophrenia

1.0 Dosing Information

Drug Properties

Storage and Stability

Adult Dosage

Pediatric Dosage

1.1 Drug Properties

A) Information on specific products and dosage forms can be obtained by referring to the Tradename List (Product In

B) Synonyms

Olanzapine

C) Physicochemical Properties

1) Molecular Weight

a) 312.44 (Prod Info Zyprexa(R), 2004)

2) Solubility

a) Practically insoluble in water (Prod Info Zyprexa(R), 2004)

1.2 Storage and Stability

A) Preparation

1) Intramuscular route

a) For intramuscular use only. Do not administer intravenously or subcutaneously (Prod Info ZYPREXA(R) ir 2004).

b) For the preparation of solution for intramuscular injection containing approximately 5 milligrams/milliliter (r supplied vial using 2.1 mL of Sterile Water for Injection. The resulting solution should appear clear and yellow (within 1 hour) after reconstitution and any unused portion should be discarded (Prod Info ZYPREXA(R) injec

2) Oral route

a) Orally Disintegrating Tablets

1) For administration of orally disintegrating tablets, peel back foil on blister pack to expose tablet; do N hands to remove the tablet from the blister unit and immediately place the entire tablet in the mouth. Tab swallowed with or without liquid (Prod Info Zyprexa(R), Zyprexa(R) Zydis(R), Zyprexa(R) IntraMuscular C

B) Oral route

1) Store at controlled room temperature, 20 to 25 degrees C (68 to 77 degrees F) (Prod Info Zyprexa(R), Zyprexa Olanzapine, 2004a). Protect from light and moisture

C) Extemporaneous Formulation - Oral route

1) Olanzapine is practically insoluble in water. A 1-milligram per milliliter (mg/mL) suspension prepared from crus syrup, carboxymethylcellulose and parabens) was found to be stable for 14 days when stored in a refrigerator and preparation and administration is advised as olanzapine may be irritating to the eye and can cause contact derma it is recommended to wear gloves and wash hands before and after exposure (Personal Communication, 2001).

1.3 Adult Dosage

Normal Dosage

Dosage in Renal Failure

Dosage in Hepatic Insufficiency

Dosage in Geriatric Patients

Dosage Adjustment During Dialysis

Dosage in Other Disease States

1.3.1 Normal Dosage

Intramuscular route

Oral route

Chemotherapy-induced nausea and vomiting; Treatment and Prophylaxis

Parkinson's disease - Psychotic disorder

1.3.1.A Intramuscular route

Agitation - Bipolar I disorder

Agitation - Schizophrenia

1.3.1.A.1 Agitation - Bipolar I disorder

a) The recommended intramuscular dose for the treatment of agitation associated with bipolar mania is may be used when clinically indicated. Efficacy of intramuscular olanzapine has been demonstrated in a ZYPREXA(R) oral tablets, IM injection, ZYPREXA(R) ZYDIS(R) orally disintegrating tablets, 2006).

b) The efficacy of repeated doses of intramuscular olanzapine in agitated patients has not been evaluat persists after the initial dose and additional intramuscular doses are warranted, subsequent doses up to total daily doses greater than 30 mg, or 10 mg injections given more frequently than 2 hours after the init not been evaluated in clinical trials. Maximal dosing of intramuscular olanzapine (ie, three 10 mg doses a with an increased risk of orthostatic hypotension. It is recommended that patients requiring subsequent i hypotension prior to the administration of any subsequent doses of intramuscular olanzapine for injectior patient with a clinically significant postural change in systolic blood pressure. If ongoing olanzapine thera a range of 5 to 20 mg/day as soon as clinically appropriate (Prod Info ZYPREXA(R) oral tablets, IM injec tablets, 2006).

c) Intramuscular olanzapine for injection is intended for intramuscular use only; do NOT administer intra into the muscle mass (Prod Info ZYPREXA(R) oral tablets, IM injection, ZYPREXA(R) ZYDIS(R) orally di

1.3.1.A.2 Agitation - Schizophrenia

a) The recommended intramuscular dose for the treatment of agitation associated with schizophrenia is mg may be used when clinically indicated. Efficacy of intramuscular olanzapine has been demonstrated ZYPREXA(R) oral tablets, IM injection, ZYPREXA(R) ZYDIS(R) orally disintegrating tablets, 2006).

b) The efficacy of repeated doses of intramuscular olanzapine in agitated patients has not been evaluat persists after the initial dose and additional intramuscular doses are warranted, subsequent doses up to total daily doses greater than 30 mg, or 10 mg injections given more frequently than 2 hours after the init not been evaluated in clinical trials. Maximal dosing of intramuscular olanzapine (ie, three 10 mg doses a with an increased risk of orthostatic hypotension. It is recommended that patients requiring subsequent i hypotension prior to the administration of any subsequent doses of intramuscular olanzapine for injectior patient with a clinically significant postural change in systolic blood pressure. If ongoing olanzapine thera a range of 5 to 20 mg/day as soon as clinically appropriate (Prod Info ZYPREXA(R) oral tablets, IM injec tablets, 2006).

c) Intramuscular olanzapine for injection is intended for intramuscular use only; do NOT administer intra into the muscle mass (Prod Info ZYPREXA(R) oral tablets, IM injection, ZYPREXA(R) ZYDIS(R) orally di

1.3.1.B Oral route

Agitation - Bipolar I disorder

Agitation - Schizophrenia

Bipolar I disorder, Acute mixed or manic episodes

Bipolar I disorder, Maintenance therapy

Schizophrenia

1.3.1.B.1 Agitation - Bipolar I disorder

a) In one study, rapid initial dose escalation of oral olanzapine was effective in the treatment of acute ag disorder. Investigators used a dosing regimen of 20 to 40 milligrams (mg)/day for 2 days, then 20 to 30 n days. Also effective was the more conventional dosing regimen of olanzapine 10 mg daily with adjunctive olanzapine 5 to 20 milligrams for 3 days (Baker et al, 2003).

1.3.1.B.2 Agitation - Schizophrenia

a) In one study, rapid initial dose escalation of oral olanzapine was effective in the treatment of acute ag disorder. Investigators used a dosing regimen of 20 to 40 milligrams (mg)/day for 2 days, then 20 to 30 n days. Also effective was the more conventional dosing regimen of olanzapine 10 mg daily with adjunctive olanzapine 5 to 20 milligrams for 3 days (Baker et al, 2003).

1.3.1.B.3 Bipolar I disorder, Acute mixed or manic episodes

a) Monotherapy

1) In clinical trials evaluating the short-term (3 to 4 weeks) effects of olanzapine in acute mania, effi to 20 mg daily. The recommended initial dosage of olanzapine is 10 or 15 milligrams (mg) once daily less than 24 hours, by 5 mg daily. Doses above 20 mg/day have not been evaluated for safety in cli

injection, ZYPREXA(R) ZYDIS(R) orally disintegrating tablets, 2006).

b) Combination Therapy

1) In clinical trials evaluating the short-term (6 weeks) effects of olanzapine in acute mania, efficacy (mg) daily. The recommended initial dosage of olanzapine in combination with lithium or valproate is not been evaluated for safety in clinical trials (Prod Info Zyprexa(R), Zyprexa(R) Zydis(R), Zyprexa(R

1.3.1.B.4 Bipolar I disorder, Maintenance therapy

a) Monotherapy

1) Bipolar patients responding to initial olanzapine therapy for an average period of two weeks have monotherapy at a dose of 5 to 20 milligrams/day. The long-term usefulness of olanzapine for the ind olanzapine is used for extended periods of time (Prod Info ZYPREXA(R) oral tablets, IM injection, Z 2006).

1.3.1.B.5 Schizophrenia

a) Initial dosages are 5 to 10 milligrams administered on a once-a-day schedule without regard to meals several days of initiation of therapy is recommended. If dosage adjustments are needed, decrease or inc adjustments should typically occur at intervals of not less than 1 week (Prod Info ZYPREXA(R) oral table disintegrating tablets, 2006).

b) In clinical trials, antipsychotic efficacy occurred at a dosage range of 10 to 15 milligrams/day. Doses a be more efficacious than the 10 milligrams/day dose. The safety of doses above 20 milligrams/day has n ZYPREXA(R) oral tablets, IM injection, ZYPREXA(R) ZYDIS(R) orally disintegrating tablets, 2006).

c) Effective doses of olanzapine in the treatment of schizophrenia have ranged from 7.5 to 40 milligrams al, 1996)(Beasley et al, 1996aa; Anon, 1994b; Anon, 1994aa). Clinical trials have shown that 10 milligrar dose may have greater efficacy in relieving negative symptoms; further studies are needed (Nemeroff, 1

1.3.1.C Chemotherapy-induced nausea and vomiting; Treatment and Prophylaxis

See Drug Consult reference: CHEMOTHERAPY AND RADIOTHERAPY TREATMENT GUIDELINES FOR N

1.3.1.D Parkinson's disease - Psychotic disorder

See Drug Consult reference: THERAPY OF PSYCHOTIC DISTURBANCES IN PARKINSONIAN PATIENTS

1.3.1.E Switching to Olanzapine

1) Schizophrenic and schizophreniform patients may be successfully transitioned from clozapine to olanzapi a stable dose of clozapine (Henderson et al, 1998). Olanzapine is increased by 2.5 to 5 mg weekly to a maxi doses should be gradually decreased by increments of 25 to 50 mg per week.

2) Switching patients to olanzapine from conventional antipsychotic therapy or risperidone was most succes implemented at the full therapeutic dose and other antipsychotics were gradually discontinued. In a study of 2 schizophrenia or schizoaffective disorder, 4 treatment strategies were used. Patients were randomized to unc antipsychotic drug and immediate or stepwise initiation of olanzapine. Olanzapine was administered in doses stepwise fashion (1 week of placebo, followed by 1 week of olanzapine 5 mg daily and then 1 week of olanza assessed using the Clinical Global Impressions (CGI) Improvement scale, Patient's Global Impressions (PGI) Syndrome Scale (PNSS). These scoring systems showed that immediate initiation of olanzapine with gradua the safest and most effective approach. However, all strategies were effective; by week 3, the majority of pati clinically unchanged without increased risk of relapse or of drug withdrawal symptoms. Patients who abruptly gradually implemented olanzapine had a significantly greater incidence of sleep disorders than those using o more often in when antipsychotic medication was abruptly discontinued with immediate implementation of ola et al, 2000).

1.3.2 Dosage in Renal Failure

A) Patients with renal impairment DO NOT require a dosage adjustment. The pharmacokinetic parameters were impairment and normal patients. Only 7% of olanzapine is excreted in the urine as unchanged drug (Prod Info Zyp IntraMuscular Olanzapine, 2004b). However, a lower initial dose of 5 milligrams daily should be considered (Prod

1.3.3 Dosage in Hepatic Insufficiency

A) Olanzapine is extensively metabolized, however, no change in dosage is needed. In patients with significant li A and B), little effect was seen on the pharmacokinetics of olanzapine (Prod Info Zyprexa(R), Zyprexa(R) Zydis(R

1.3.4 Dosage in Geriatric Patients

A) Caution should be used when oral olanzapine is administered to the elderly, especially if there are other factor pharmacodynamic parameters (Prod Info Zyprexa(R), Zyprexa(R) Zydis(R), Zyprexa(R) IntraMuscular Olanzapine

B) The recommended intramuscular dose for elderly patients is 5 milligrams per injection (Prod Info Zyprexa(R) I

1.3.5 Dosage Adjustment During Dialysis

A) Hemodialysis

1) Olanzapine is not removed by dialysis (Prod Info Zyprexa(R), Zyprexa(R) Zydis(R), Zyprexa(R) IntraMusc

B) Peritoneal Dialysis

1) Olanzapine is not removed by dialysis (Prod Info Zyprexa(R), Zyprexa(R) Zydis(R), Zyprexa(R) IntraMusc

1.3.6 Dosage in Other Disease States

A) Special Populations
1) The recommended starting oral dose is 5 milligrams in the following populations: patients who are debilita reactions, who exhibit a combination of factors that may cause a slower metabolism of olanzapine (eg, nonsn pharmacodynamically sensitive to olanzapine (Prod Info Zyprexa(R), Zyprexa(R) Zydis(R), Zyprexa(R) IntraM
2) The recommended intramuscular dose is 2.5 milligrams per injection for patients who are debilitated, have be pharmacodynamically sensitive to olanzapine (Prod Info Zyprexa(R) IntraMuscular, 2004).
3) No dosage modification is needed but the manufacturer reports that the clearance of olanzapine is 30% lo Zydis(R), Zyprexa(R) IntraMuscular Olanzapine, 2004b).
4) No dosage modification is needed but the manufacturer reports that the clearance of olanzapine is 40% h Zyprexa(R), Zyprexa(R) Zydis(R), Zyprexa(R) IntraMuscular Olanzapine, 2004b).
5) The combined effects of age, smoking, and gender could cause substantial pharmacokinetic differences i male smokers may be 3 times higher than that in elderly nonsmoking females (Prod Info Zyprexa(R), Zyprexa Olanzapine, 2004b). Age over 65, gender, or smoking status alone does NOT require dosage modification.

1.4 Pediatric Dosage

1.4.1 Normal Dosage

1.4.1.A Anorexia nervosa
See Drug Consult reference: ANOREXIA NERVOSA - DRUG THERAPY

2.0 Pharmacokinetics

Onset and Duration

Drug Concentration Levels

ADME

2.1 Onset and Duration
A) Onset
1) Initial Response
a) Schizophrenia: 1 week (Beasley et al, 1996).

2.2 Drug Concentration Levels
A) Therapeutic Drug Concentration
1) Schizophrenia, greater than 9 ng/ml (Perry et al, 1997).
a) In acutely schizophrenic patients receiving olanzapine (n=79), 45% of patients with a trough level above 9 versus only 15% of patients with concentrations less than 9.3 ng/ml responding (Perry et al, 1997).
B) Time to Peak Concentration
1) Oral: 6 hours (Prod Info Zyprexa(R), Zyprexa(R) Zydis(R), Zyprexa(R) IntraMuscular Olanzapine, 2004). Oral: (R), Zyprexa(R) IntraMuscular Olanzapine, 2004).
a) In an open-label, inpatient trial involving 8 patients (ages 10 to 18 years) receiving olanzapine 2.5 to 20 m plasma concentration was 115.6 +/- 26.7 nanograms/milliliter. The mean time to maximum concentration was these adolescent patients are similar to the concentrations observed in nonsmoking adult patients being treat twice the average concentrations in smokers (Grothe et al, 2000).
2) Intramuscular: 15 to 45 minutes (Prod Info Zyprexa(R), Zyprexa(R) Zydis(R), Zyprexa(R) IntraMuscular Olanza

2.3 ADME

Absorption

Distribution

Metabolism

Excretion

Elimination Half-life

2.3.1 Absorption

A) Bioavailability
1) Oral: Well-absorbed (Prod Info Zyprexa(R), Zyprexa(R) Zydis(R), Zyprexa(R) IntraMuscular Olanzapine, 2
a) Extensively eliminated by first-pass metabolism; 40% of dose metabolized before reaching systemic
(R), Zyprexa(R) IntraMuscular Olanzapine, 2004; Bever & Perry, 1998a).
B) Effects of Food
1) None (Prod Info Zyprexa(R), Zyprexa(R) Zydis(R), Zyprexa(R) IntraMuscular Olanzapine, 2004).

2.3.2 Distribution
A) Distribution Sites
1) Protein Binding
a) 93% (Prod Info Zyprexa(R), Zyprexa(R) Zydis(R), Zyprexa(R) IntraMuscular Olanzapine, 2004).
1) The primary binding sites are albumin and alpha-1- acid glycoprotein (Prod Info Zyprexa(R), Zyp
Olanzapine, 2004).
B) Distribution Kinetics
1) Volume of Distribution
a) 1000 L (Prod Info Zyprexa(R), Zyprexa(R) Zydis(R), Zyprexa(R) IntraMuscular Olanzapine, 2004).

2.3.3 Metabolism
A) Metabolism Sites and Kinetics
1) Liver, extensively metabolized (Prod Info Zyprexa(R), Zyprexa(R) Zydis(R), Zyprexa(R) IntraMuscular Ola
a) The primary metabolic pathways for olanzapine are direct glucuronidation and oxidation mediated by
monooxigenase system. CYP2D6 appears to be a minor pathway (Prod Info Zyprexa(R), Zyprexa(R) Zy
2004).
b) Forty percent is metabolized via first pass metabolism (Prod Info Zyprexa(R), Zyprexa(R) Zydis(R), Z
B) Metabolites
1) 10-N-glucuronide, (inactive) (Prod Info Zyprexa(R), Zyprexa(R) Zydis(R), Zyprexa(R) IntraMuscular Olanz
2) 4'-N-desmethyl olanzapine, (inactive) (Prod Info Zyprexa(R), Zyprexa(R) Zydis(R), Zyprexa(R) IntraMuscu

2.3.4 Excretion
A) Kidney
1) Renal Excretion (%)
a) 57% (Prod Info Zyprexa(R), Zyprexa(R) Zydis(R), Zyprexa(R) IntraMuscular Olanzapine, 2004; Anon
B) Total Body Clearance
1) 26.1 L/hr (Kando, 1997).
a) Clearance ranges from 12 to 47 L/hour (Prod Info Zyprexa(R), Zyprexa(R) Zydis(R), Zyprexa(R) Intra
b) In 8 pediatric and adolescent patients (ages 10 to 18 years) receiving 2.5 to 20 milligrams olanzapine
9.6 +/- 2.4 liters/hour (Grothe et al, 2000).
C) Other
1) OTHER EXCRETION
a) Feces, 30% (Prod Info Zyprexa(R), Zyprexa(R) Zydis(R), Zyprexa(R) IntraMuscular Olanzapine, 2004

2.3.5 Elimination Half-life
A) Parent Compound
1) ELIMINATION HALF-LIFE
a) 21 to 54 hours (mean = 30 hours) (Prod Info Zyprexa(R), Zyprexa(R) Zydis(R), Zyprexa(R) IntraMusc
1) In 8 pediatric and adolescent patients (ages 10 to 18 years) receiving 2.5 to 20 milligrams olanza
life was 37.2 +/- 5.1 hours (Grothe et al, 2000).
2) Although the mean elimination half-life of olanzapine is prolonged in the elderly (young patients:
renal clearance is reduced from 18.2 Liters/hour (L/h) in the young to 17.5 L/h in those 65 years and
than in young patients. Thus, a dose reduction is not necessary in otherwise healthy elderly patients

3.0 Cautions

Contraindications

Precautions

Adverse Reactions

Teratogenicity/Effects in Pregnancy/Breastfeeding

Drug Interactions

3.0.A Black Box WARNING
1) Intramuscular (Powder for Solution)

Increased Mortality in Elderly Patients with Dementia-Related Psychosis

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of d
trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of d
times the risk of death in placebo-treated patients. Over the course of a typical 10-week controlled trial, the ra
4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, mos
cardiovascular (eg, heart failure, sudden death) or infectious (eg, pneumonia) in nature. Observational studie
drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findin
may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear. C
patients with dementia-related psychosis (Prod Info ZYPREXA(R) oral tablets, orally disintegrating tablets, IM

2) Oral (Tablet; Tablet, Disintegrating)

Increased Mortality in Elderly Patients with Dementia-Related Psychosis

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of d
trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of d
times the risk of death in placebo-treated patients. Over the course of a typical 10-week controlled trial, the ra
4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, mos
cardiovascular (eg, heart failure, sudden death) or infectious (eg, pneumonia) in nature. Observational studie
drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findin
may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear. C
patients with dementia-related psychosis (Prod Info ZYPREXA(R) oral tablets, orally disintegrating tablets, IM

3.1 Contraindications

A) specific contraindications have not been determined (Prod Info ZYPREXA(R) oral tablets, orally disintegrating tabl

3.2 Precautions

A) elderly patients with dementia-related psychosis (unapproved use); increased risk of death; most deaths were attri
sudden death) or infections (eg, pneumonia) (Prod Info ZYPREXA(R) oral tablets, orally disintegrating tablets, IM injec
B) elderly patients with dementia-related psychosis (unapproved use); cerebrovascular events (eg, stroke, transient is
(Prod Info ZYPREXA(R) oral tablets, orally disintegrating tablets, IM injection, 2009)
C) cardiovascular or cerebrovascular disease or conditions that predispose patients to hypotension (eg, dehydration,
increased risk of orthostatic hypotension (Prod Info ZYPREXA(R) oral tablets, orally disintegrating tablets, IM injection
D) concomitant use of parenteral benzodiazepine and intramuscular olanzapine is not recommended (Prod Info ZYPF
IM injection, 2009)
E) conditions that may contribute to elevated body temperature (eg, strenuous exercise, extreme heat exposure, dehy
disrupt body temperature regulation (Prod Info ZYPREXA(R) oral tablets, orally disintegrating tablets, IM injection, 200
F) diabetes mellitus or risk factors for diabetes mellitus; increased risk of severe hyperglycemia (Prod Info ZYPREXA(
injection, 2009)
G) diseases or conditions affecting hemodynamic response, preexisting (Prod Info ZYPREXA(R) oral tablets, orally di
H) elderly patients, especially elderly women, are at increased risk of tardive dyskinesia (Prod Info ZYPREXA(R) oral
2009)
I) glaucoma, narrow angle; condition may be exacerbated due to anticholinergic properties (Prod Info ZYPREXA(R) o
2009)
J) hepatic impairment, significant, preexisting conditions associated with limited hepatic functional reserve, or concom
hepatic impairment (Prod Info ZYPREXA(R) oral tablets, orally disintegrating tablets, IM injection, 2009)
K) hyperglycemia (some extreme cases associated with ketoacidosis or hyperosmolar coma or death) has been repo
disintegrating tablets, IM injection, 2009)
L) hyperlipidemia, hypercholesterolemia, and significantly elevated triglycerides have been reported (Prod Info ZYPRI
injection, 2009)
M) increased duration of therapy and/or higher cumulative doses; increased risk of tardive dyskinesia (Prod Info ZYPI
IM injection, 2009)
N) neuroleptic malignant syndrome, potentially fatal; has been reported in association with olanzapine therapy; immed
oral tablets, orally disintegrating tablets, IM injection, 2009)
O) paralytic ileus, history; condition may be exacerbated due to anticholinergic properties (Prod Info ZYPREXA(R) ora
2009)
P) prostatic hypertrophy; condition may be exacerbated due to anticholinergic properties (Prod Info ZYPREXA(R) ora
2009)
Q) seizure disorder, history, or conditions that may lower seizure threshold; may increase seizure risk (Prod Info ZYPI
IM injection, 2009)
R) tardive dyskinesia, potentially irreversible, may occur (Prod Info ZYPREXA(R) oral tablets, orally disintegrating tab

3.3 Adverse Reactions

Cardiovascular Effects

Dermatologic Effects

Endocrine/Metabolic Effects

Gastrointestinal Effects

Hematologic Effects

Hepatic Effects

Immunologic Effects

Musculoskeletal Effects

Neurologic Effects

Ophthalmic Effects

Psychiatric Effects

Renal Effects

Reproductive Effects

Respiratory Effects

Other

3.3.1 Cardiovascular Effects

Bradyarrhythmia

Chest pain

Hypertension

Hypotension

Orthostatic hypotension

Peripheral edema

Sudden cardiac death

Tachyarrhythmia

3.3.1.A Bradyarrhythmia

1) A 24-year-old, healthy, non-smoking, woman volunteer experienced hypotension (70/30 mmHg) and brad
taking a single oral dose of olanzapine 5 mg. Lying down with feet elevated brought both pulse and blood pre
The maximum plasma concentration of olanzapine in this subject (13 nanograms/mL) was unusually high and
reported range for Tmax (5 to 6 hours). Her Cmax was in the range expected for a single dose of 10 to 15 mg

3.3.1.B Chest pain

1) Incidence: 3% (Prod Info Zyprexa(R), Zyprexa(R) Zydis(R), Zyprexa(R) IntraMuscular Olanzapine, 2004a)
2) Chest pain has been reported in 3% of patients treated with olanzapine (Prod Info Zyprexa(R), Zyprexa(R
2004a).

3.3.1.C Hypertension

1) Incidence: 2% (Prod Info Zyprexa(R), Zyprexa(R) Zydis(R), Zyprexa(R) IntraMuscular Olanzapine, 2004a)
2) Hypertension has been reported in 2% of patients treated with olanzapine (Prod Info Zyprexa(R), Zyprexa
Olanzapine, 2004a).

3.3.1.D Hypotension

1) A 24-year-old, healthy, non-smoking, woman volunteer experienced hypotension (70/30 mmHg) and brad
taking a single oral dose of olanzapine 5 mg. Lying down with feet elevated brought both pulse and blood pre
The maximum plasma concentration of olanzapine in this subject (13 nanograms/mL) was unusually high and
reported range for Tmax (5 to 6 hours). Her Cmax was in the range expected for a single dose of 10 to 15 mg

3.3.1.E Orthostatic hypotension

1) Incidence: 3% to 5% (Prod Info Zyprexa(R), Zyprexa(R) Zydis(R), Zyprexa(R) IntraMuscular Olanzapine,
2) Postural hypotension has been reported in 3% to 5% of patients treated with olanzapine (Prod Info Zyprex
IntraMuscular Olanzapine, 2004a).
3) Orthostatic hypotension has been observed in greater than 5% of patients participating in olanzapine clini
beats per minute has been reported in clinical trials with tachycardia occurring in greater than 5% of the patie
orthostatic hypotensive changes (Bronson & Lindenmayer, 2000).
4) Small reductions in orthostatic blood pressure have been reported in olanzapine-treated patients during cl

3.3.1.F Peripheral edema

1) Incidence: 3% (Prod Info Zyprexa(R), Zyprexa(R) Zydis(R), Zyprexa(R) IntraMuscular Olanzapine, 2004a)
2) Peripheral edema has been reported in 3% of patients treated with olanzapine (Prod Info Zyprexa(R), Zyp
Olanzapine, 2004a).

3.3.1.G Sudden cardiac death

1) In a large, retrospective, cohort study that included a primary cohort of 93,300 users of antipsychotic drug
there was an increased risk of sudden cardiac death in adult participants 30 to 74 years of age (mean age of
to those who were not using antipsychotic drugs (incidence-rate ratio, 2.04; 95% confidence interval (CI), 1.5
treated with atypical antidepressants (clozapine, olanzapine, quetiapine, risperidone), the incidence-rate ratio
(95% CI, 1.03 to 2.46) for those using low doses to 2.86 (95% CI, 2.25 to 3.65) for those using high doses (p=

3.3.1.H Tachyarrhythmia

1) Incidence: 3% (Prod Info Zyprexa(R), Zyprexa(R) Zydis(R), Zyprexa(R) IntraMuscular Olanzapine, 2004a)
2) Tachycardia has been reported in 3% of patients treated with olanzapine (Prod Info Zyprexa(R), Zyprexa(
2004a).

3.3.2 Dermatologic Effects

Dermatological finding

Sweating symptom

3.3.2.A Dermatological finding

1) Summary
a) A 36-year-old African-American man developed a PUSTULAR SKIN ERUPTION 2 weeks after begin
began on his face and spread to his hips and buttocks. One day later he developed ERYTHEMATOUS P
no lymphadenopathy or fever. Olanzapine was discontinued and warm compresses were applied. The e
1999).
2) Pustular eruptions, sweating and erythematous plaques are reported with olanzapine administration.

3.3.2.B Sweating symptom

1) Summary
a) The manufacturer reports that sweating has been associated with olanzapine therapy (Prod Info Zypr
IntraMuscular Olanzapine, 2004a).

3.3.3 Endocrine/Metabolic Effects

Diabetes mellitus

Diabetic ketoacidosis

Galactorrhea

Hypercholesterolemia

Hyperglycemia

Hypoglycemia

Hypothermia

Increased appetite

Increased body temperature

Metabolic syndrome

Prolactin level raised

Serum triglycerides raised

Summary

Weight gain

Weight loss

3.3.3.A Diabetes mellitus

1) Summary

a) Diabetic mellitus was reported infrequently (0.1% to 1%) in clinical trials (n=8661) representing 4165 multiple doses of oral olanzapine at doses 1 mg/day or more (Prod Info ZYPREXA(R) oral tablets, IM inj tablets, 2008).

b) As with other atypical antipsychotics, hyperglycemia has been reported in patients on olanzapine. Th nonfasting levels, from baseline to the average of the 2 highest serum concentrations was 15 mg/dL, dur Effectiveness in patients treated for a median olanzapine-exposure duration of 9.2 months. Olanzapine i difficult to assess the relationship because of an increased risk of diabetes mellitus in patients with schiz mellitus in the general population. In general, epidemiological studies show that atypical antipsychotics ir hyperglycemia. Olanzapine appears to have a greater risk of glucose abnormalities compared with other oral tablets, IM injection, ZYPREXA(R) ZYDIS(R) orally disintergating tablets, 2008).

c) The risks and benefits of olanzapine should be considered prior to prescribing in patients with an esta with borderline increased blood glucose levels (fasting 100 to 126 mg/dL or nonfasting 140 to 200 mg/dL recommended. For patients with risk factors for diabetes mellitus (obesity, family history of diabetes), fas initiation and periodically during olanzapine therapy. All patients should be monitored for signs and symp polyphagia, and weakness). Fasting blood glucose should be tested if symptoms of hyperglycemia devel discontinuation of olanzapine; however, some patients may continue to need antidiabetic therapy despite ZYPREXA(R) oral tablets, IM injection, ZYPREXA(R) ZYDIS(R) orally disintergating tablets, 2008).

2) Incidence: 0.1% to 1% (Prod Info ZYPREXA(R) oral tablets, IM injection, ZYPREXA(R) ZYDIS(R) orally di

3) New onset diabetes mellitus (DM) has been reported with the administration of olanzapine. At least 25 fat olanzapine-induced diabetic ketoacidosis (Torrey & Swalwell, 2003; Goldstein et al, 1999; Lindenmayer & Pa

4) A 51-year-old woman with schizoaffective disorder and type 2 diabetes (stabilized on metformin 1 gram tw developed hyperglycemia, without weight gain, when an episode of elevated mood and psychosis was treate risperidone for 4 weeks but did not respond. Chlorpromazine also was not effective. Olanzapine, titrated to 3(symptoms. Her blood glucose then began to increase, although her diet was controlled by the hospital. Oral h maximum and she was started on actrapid insulin. Glucose levels remained unstable until olanzapine was ta hypoglycemic medications were reduced to previous levels and actrapid insulin was discontinued. Zuclopenth schizoaffective disorder. The patient showed no significant weight gain during treatment with olanzapine, whi effect on glucose regulation (Ramankutty, 2002).

5) A 27-year-old man developed signs of diabetes mellitus (polydipsia, polyphagia, nausea and vomiting, hyp olanzapine for treatment of schizophrenia. He was treated with insulin, and his dose of olanzapine was increa valproic acid, which he had taken for 3 years. After 3 months, insulin therapy was replaced by pioglitazone 3(control. Olanzapine therapy was not discontinued because of the risk of psychotic worsening (Seaburg et al,

6) A 45-year-old obese man developed elevated fasting glucose 1 year after his treatment for schizophrenia 25 mg/day). Six months later, he was treated with glyburide 1.25 mg/day. Over the next 6 months, his glycos weight began to increase. Five months later, he complained of diarrhea and weight loss. His glyburide dose v symptoms (polyuria, polydipsia, and diaphoresis), his glyburide dosage was increased to 10 mg twice daily, i replaced by risperidone. Six weeks after discontinuation of olanzapine, the patient's glycosylated hemoglobin glyburide was reduced to 1.25 mg/day, and his weight stabilized. Five months later, his diabetes was well-co

7) Olanzapine-induced glucose dysregulation has been reported as an adverse effect, possibly due to drug-i with a severe exacerbation of type 2 diabetes in a 51-year-old woman with a major depressive disorder and s

with sertraline and haloperidol decanoate. After 4 weeks, sertraline was replaced by fluoxetine due to continu haloperidol was replaced by olanzapine due to persistent auditory and visual hallucinations. Prior to initiation well-controlled by diet (glycosylated hemoglobin 6.5%, baseline fasting blood glucose 89 to 132 mg/dL). Twe control diminished and continued to worsen despite treatment with glipizide, metformin, and diet. At week 26, due to inadequate antidepressant response. At week 35 (fasting blood glucose 120 to 461 mg/dL, glycosylate was initiated and titrated to 70 units per day. Olanzapine was tapered during weeks 39 and 40 and discontinu stopped, the patient's fasting blood glucose levels had decreased to within 85 and 163 mg/dL. By the time of units/day NPH 70/30 (Bettinger et al, 2000).

8) Cases of new-onset diabetes mellitus (DM) were reported that developed after initiation of olanzapine trea months (mean 26 weeks; median 20 weeks) after olanzapine initiation. Two cases presented with diabetic ke and 4 patients experienced weight gain while on olanzapine. Olanzapine was eventually discontinued in all ca DM was still required (Goldstein et al, 1999).

See Drug Consult reference: ATYPICAL ANTIPSYCHOTIC AGENTS - EFFECT ON GLUCOSE AND RISK C

3.3.3.B Diabetic ketoacidosis

1) Summary

a) Diabetic acidosis was reported rarely (less than 0.1%) in clinical trials (n=8661) representing 4165 pa multiple doses of oral olanzapine at doses 1 mg/day or more (Prod Info ZYPREXA(R) oral tablets, IM inje tablets, 2008).

b) As with other atypical antipsychotics, diabetic ketoacidosis or hyperosmolar coma, including death, ha Olanzapine is implicated in glucose abnormalities; however, it is difficult to assess the relationship becau patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. In atypical antipsychotics increase the risk of treatment-emergent hyperglycemia. Olanzapine appears to ha compared with other atypical antipsychotics (Prod Info ZYPREXA(R) oral tablets, IM injection, ZYPREXA

c) The risks and benefits of olanzapine should be considered prior to prescribing in patients with an esta with borderline increased blood glucose levels (fasting 100 to 126 mg/dL or nonfasting 140 to 200 mg/dL recommended. For patients with risk factors for diabetes mellitus (obesity, family history of diabetes), fas initiation and periodically during olanzapine therapy. All patients should be monitored for signs and symp polyphagia, and weakness). Fasting blood glucose should be tested if symptoms of hyperglycemia devel discontinuation of olanzapine; however, some patients may continue to need antidiabetic therapy despite ZYPREXA(R) oral tablets, IM injection, ZYPREXA(R) ZYDIS(R) orally disintergating tablets, 2008).

2) Incidence: less than 0.1% (Prod Info ZYPREXA(R) oral tablets, IM injection, ZYPREXA(R) ZYDIS(R) orall

3) A case report described a near fatal case of olanzapine-induced ketoacidosis in a 44-year-old African Am for approximately one month (Straker et al, 2002).

4) Diabetic ketoacidosis following 3 months of olanzapine therapy was reported in a 31-year-old man with no was started on insulin and olanzapine was discontinued. Fifteen days later, his insulin requirements decrease has remained metabolically stable, free of diabetic symptoms (Gatta et al, 1999).

5) At least 25 fatalities have been reported in association with olanzapine-induced diabetic ketoacidosis (Tor Lindenmayer & Patel, 1999).

6) A 50-year-old African American man developed diabetic ketoacidosis after receiving 8 months of olanzapi olanzapine 30 mg daily with divalproex 750 mg twice daily. He began insulin therapy and after olanzapine wa (Lindenmayer & Patel, 1999).

7) A 39-year-old man developed diabetic ketoacidosis after receiving olanzapine 10 mg for a treatment-refra laboratory evidence of diabetes. His BMI was 40 kg/m(2). He was admitted with asthenia, polyuria, dehydrati His HbA1C was 14.7%. He was maintained on insulin 3 times daily. When olanzapine was discontinued, insu blood glucose and HbA1C became normal (Gatta et al, 1999).

3.3.3.C Galactorrhea

1) A case of galactorrhea with elevated serum prolactin levels was reported in a 33-year-old woman after rec treatment of schizophreniform disorder. During the fifth week of olanzapine therapy, the patient developed sp reported missing her menstrual period. Her serum prolactin level was 146.55 nanograms (ng)/mL (normal ran and replaced with quetiapine (25 to 100 mg/day). Symptoms of galactorrhea resolved within 3 weeks of stopp to decrease. Quetiapine therapy was continued without recurrence of galactorrhea (Mendhekar et al, 2004).

3.3.3.D Hypercholesterolemia

1) Summary

a) Increases in total cholesterol have been observed during treatment with olanzapine. The mean increa lipoprotein (LDL) from baseline were 5.3 mg/dL and 3 mg/dL, respectively, in olanzapine-treated patients mg/dL and 4.3 mg/dL, respectively, in placebo-treated patients (statistically significant), in an analysis of 12-weeks duration. There were no statistically significant differences between olanzapine-treated and pla lipoprotein cholesterol. Patients with lipid dysregulation at baseline experienced greater increases in fast compared to patients without these factors. Lipid dysregulation was defined as patients diagnosed with c treated with lipid-lowering agents, or patients with high baseline lipid levels. Baseline and follow-up lipid r olanzapine (Prod Info ZYPREXA(R) oral tablets, IM injection, ZYPREXA(R) ZYDIS(R) orally disintergatin

2) Incidence: up to 24% (Prod Info ZYPREXA(R) oral tablets, IM injection, ZYPREXA(R) ZYDIS(R) orally dis

3) In an analysis of 5 placebo-controlled monotherapy studies of up to 12-weeks duration, the fasting total ch olanzapine-treated patients compared with up to 12% of placebo-treated patients. The fasting low density lipo approximately 24% of olanzapine-treated patients compared with up to 14% of placebo-treated patients. The

increase of fasting cholesterol and LDL cholesterol (Prod Info ZYPREXA(R) oral tablets, IM injection, ZYPRE 2008):

Fasting Total Cholesterol In Adults

Change from Baseline	Treatment Arm	N	Portion of Patients
Increase by 40 mg/dL or more	olanzapine	745	21.6% *
	placebo	402	9.5%
Increase from Normal (less than 200 mg/dL) to High (240 mg/dL or more)	olanzapine	392	2.8%
	placebo	207	2.4%
Increase from Borderline (200 mg/dL to less than 240 mg/dL) to High (240 mg/dL or more)	olanzapine	222	23% *
	placebo	112	12.5%
KEY: mg/dL = milligrams/deciliter; * = statistically significant compared to placebo			

Fasting Low-Density-Lipoprotein Cholesterol In Adults

Change from Baseline	Treatment Arm	N	Portion of Patients
Increase by 30 mg/dL or more	olanzapine	536	23.7% *
	placebo	304	14.1%
Increase from Normal (less than 100 mg/dL) to High (160 mg/dL or more)	olanzapine	154	0%
	placebo	82	1.2%
Increase from Borderline (100 mg/dL to less than 160 mg/dL) to High (160 mg/dL or more)	olanzapine	302	10.6%
	placebo	173	8.1%
KEY: mg/dL = milligrams/deciliter; * = statistically significant compared to placebo			

4) In an analysis of 3 placebo-controlled monotherapy studies of up to 6 weeks duration in adolescents, the f approximately 39% of olanzapine-treated patients compared with up to 8% of placebo-treated patients. The f in up to approximately 49% of olanzapine-treated patients compared with up to 11% of placebo-treated patie degree of increase of fasting total cholesterol and LDL cholesterol (Prod Info ZYPREXA(R) oral tablets, IM in disintergating tablets, 2008):

Fasting Total Cholesterol In Adolescents

Category Change from Baseline	Treatment Arm	N	Portion of Patients
Increase by 40 mg/dL or more	olanzapine	138	14.5% *
	placebo	66	4.5%
Increase from Normal (less than 170 mg/dL) to High (200 mg/dL or more)	olanzapine	87	6.9%
	placebo	43	2.3%
Increase from Borderline (170 mg/dL to less than 200 mg/dL) to High (200 mg/dL or more)	olanzapine	36	38.9% *
	placebo	13	7.7%
KEY: mg/dL = milligrams/deciliter; * = statistically significant compared to placebo			

Fasting Low-Density-Lipoprotein Cholesterol In Adolescents

Category Change from Baseline	Treatment Arm	N	Portion of Patients
Increase by 30 mg/dL or more	olanzapine	137	17.5%
	placebo	63	11.1%
Increase from Normal (less than 110 mg/dL) to High (130 mg/dL or more)	olanzapine	98	5.1%
	placebo	44	4.5%
Increase from Borderline (110 mg/dL to less than 130 mg/dL) to High (130 mg/dL or more)	olanzapine	29	48.3% *
	placebo	9	0%
KEY: mg/dL = milligrams/deciliter; * = statistically significant compared to placebo			

5) Random cholesterol levels of 240 mg/dL or more has been reported during postmarketing reports (Prod Ir ZYPREXA(R) ZYDIS(R) orally disintergating tablets, 2008).

6) Patients receiving olanzapine (n=25) were found to have increases in their weight and serum triglycerides receiving olanzapine (mean dose 13.8 mg) had their weight, cholesterol, and triglycerides measured at basel mean of 5.4 kg. Cholesterol levels increased by only 3 mg/dL while triglyceride levels increased by 60 mg/dL with weight change (p less than 0.02).

7) After an average of 16 months of olanzapine therapy, 9 patients had marked increases in triglyceride leve 170 mg/dL to a mean of 240 mg/dL. Five patients had at least a 50% increase in levels. Cholesterol levels re mean weight gain of 10 kg (Sheitman et al, 1999).

3.3.3.E Hyperglycemia

1) Summary

a) As with other atypical antipsychotics, hyperglycemia has been reported in patients on olanzapine. Th nonfasting levels) from baseline to the average of the 2 highest serum concentrations was 15 mg/dL, du Effectiveness in patients treated for a median olanzapine-exposure duration of 9.2 months. Olanzapine i difficult to assess the relationship because of an increased risk of diabetes mellitus in patients with schiz

mellitus in the general population. In general, epidemiological studies show that atypical antipsychotics ir hyperglycemia. Olanzapine appears to have a greater risk of glucose abnormalities compared with other oral tablets, IM injection, ZYPREXA(R) ZYDIS(R) orally disintergating tablets, 2008).

b) The risks and benefits of olanzapine should be considered prior to prescribing in patients with an esta with borderline increased blood glucose levels (fasting 100 to 126 mg/dL or nonfasting 140 to 200 mg/dL recommended. For patients with risk factors for diabetes mellitus (obesity, family history of diabetes), fas initiation and periodically during olanzapine therapy. All patients should be monitored for signs and symp polyphagia, and weakness). Fasting blood glucose should be tested if symptoms of hyperglycemia devel discontinuation of olanzapine; however, some patients may continue to need antidiabetic therapy despite ZYPREXA(R) oral tablets, IM injection, ZYPREXA(R) ZYDIS(R) orally disintergating tablets, 2008).

2) Incidence: 0.1% to 17.4% (Prod Info ZYPREXA(R) oral tablets, IM injection, ZYPREXA(R) ZYDIS(R) orall

3) The mean increases in fasting glucose levels were 2.76 mg/dL in olanzapine-treated adults compared witl analysis of 5 placebo-controlled trials of adults treated with monotherapy olanzapine up to 12 weeks. Patients were patients with glucose dysregulation at baseline defined as: diagnosis with diabetes mellitus or related a baseline random glucose concentrations of 200 mg/dL or greater, and/or a baseline fasting glucose level of 1 glucose levels (less than 100 mg/dL) and baseline borderline fasting glucose levels (100 mg/dL or greater an 2.2% (n=543) and 17.4% (n=178), respectively, had high glucose levels of 126 mg/dL or greater. In comparis of the placebo-treated patients had high glucose levels (Prod Info ZYPREXA(R) oral tablets, IM injection, ZYI 2008).

4) The mean changes in fasting glucose levels were an increase of 2.68 mg/dL in olanzapine-treated adoles placebo-treated children (statistically significant), in an analysis of 3 placebo-controlled trials of adolescents t of 6 weeks in schizophrenia trials or 3 weeks in bipolar disorder trials. In adolescents with normal fasting gluc borderline fasting glucose levels (100 mg/dL to less than 126 mg/dL) treated with olanzapine, 0% (0 out of 12 glucose levels of 126 mg/dL or greater. In comparison, 1.9% (1 out of 53) and 0% (0 out of 13), respectively, levels (Prod Info ZYPREXA(R) oral tablets, IM injection, ZYPREXA(R) ZYDIS(R) orally disintergating tablets,

5) Hyperglycemia was reported infrequently (0.1% to 1%) in clinical trials (n=8661) representing 4165 patien doses of oral olanzapine at doses 1 mg/day or more (Prod Info ZYPREXA(R) oral tablets, IM injection, ZYPR 2008).

6) An 89-year-old man with a two-year history of mixed dementia with psychosis and behavioral disturbance olanzapine for psychotic symptoms and agitation. The patient received olanzapine 2.5 mg twice daily for 2 da increase, fasting glucose levels had increased from a baseline of 114 mg/dL to 138 mg/dL, with a fasting fing patient also experienced worsening renal function, including increased BUN (37 to 45 mg/dL) and creatinine to 125 mg/dL 2 days after discontinuing olanzapine and starting aripiprazole 5 mg/day. Due to worsening agit 2.5 mg twice daily and the hyperglycemia returned, with fasting blood glucose levels increasing from 97 mg/d discontinuation, fasting blood glucose levels returned to normal (104 mg/dL) (Kohen et al, 2008).

7) A 15-year-old African American boy developed hyperglycemia, along with weight gain and hypertriglyceric behavior disorders. At baseline, when the boy had been taking olanzapine for 3 months and valproic acid for normal ranges. His BMI was 28.7 kg/m(2). Four months later, buspirone was added to his treatment. Within 2 Three months later, he had experienced weight loss (BMI=27.5 kg/m(2)) and developed polyuria and polydips Olanzapine was discontinued. Without hypoglycemic drugs, insulin treatment, or dietary changes, his serum did his serum triglyceride and cholesterol levels. Twenty weeks after the discontinuation of olanzapine, his BM

3.3.3.F Hypoglycemia

1) Incidence: 0.1% to 1% (Prod Info ZYPREXA(R) oral tablets, IM injection, ZYPREXA(R) ZYDIS(R) orally di

2) Hypoglycemia was reported infrequently (0.1% to 1%) in clinical trials (n=8661) representing 4165 patient doses of oral olanzapine at doses 1 mg/day or more (Prod Info ZYPREXA(R) oral tablets, IM injection, ZYPR 2008).

3) Hypoglycemic coma was reported in a frail, 95-year-old woman following olanzapine administration for the associated with Alzheimer's dementia. Three days after the initiation of olanzapine at a dose of 2.5 mg daily, sleepy, and she could not be woken by verbal or tactile stimulation. She was treated with 33% glucose and re however, hypoglycemia was noted again the following day. Olanzapine was withdrawn and the blood glucose administration of 33% glucose. A direct cause and effect correlation could not be established because the pa been documented to possibly induce hypoglycemia. While a drug interaction between enalapril and olanzapir that there was a correlation between enalapril and hypoglycemia because the patient had been receiving ena et al, 2003).

3.3.3.G Hypothermia

1) Hypothermia developed in a 54-year-old hemodialysis patient with end-stage renal disease following the u day course of oral olanzapine 2.5 mg daily for the treatment of sudden-onset night delirium with visual halluci delirium resolved, but then reappeared 7 days later. He was given olanzapine again at the same dose for 10 medication, his body temperature suddenly decreased to less than 34 degrees Celsius. Hypothermia persiste administration, and did not resolve until 6 days after olanzapine was discontinued (Fukunishi et al, 2003).

3.3.3.H Increased appetite

1) Incidence: 24% (Tollefson et al, 1997a)

2) Excessive appetite was seen more commonly with olanzapine therapy than with haloperidol (24% vs 12.4 associated with a clinically significant greater increase in weight over haloperidol therapy (p less than 0.001). mass index was the predominant predictor of weight gain. Patients with a low pre-study body mass index wer

treatment. Treatment effect on weight change was consistent between male and female patients (Tollefson e

3.3.3.I Increased body temperature

1) Disruption of the body's ability to reduce core body temperature may occur with antipsychotic agents. Elev following therapeutic doses in clinical trials. Patients experiencing conditions that may contribute to an elevat strenuously, exposure to extreme heat, or dehydration) should use appropriate care (Prod Info ZYPREXA(R) orally disintergating tablets, 2008).

3.3.3.J Metabolic syndrome

See Drug Consult reference: ANTIPSYCHOTIC AGENTS - METABOLIC SYNDROME

3.3.3.K Prolactin level raised

1) Summary

a) Prolactin levels are modestly-elevated and persist during treatment with olanzapine. The clinical signi however, galactorrhea, amenorrhea, gynecomastia, and impotence have been reported in patients on pr elevating potential of olanzapine should be considered in patients with prolactin-dependent breast cance ZYPREXA(R) ZYDIS(R) orally disintergating tablets, 2008).

b) A dose-related increase in prolactin elevation occurred in 31.2% to 61.1% of olanzapine-treated patie in an 8-week randomized, double-blind, fixed-dose study (n=599). Elevated prolactin levels (greater than 18.77 ng/mL in males) occurred in 31.2% in patients on 10 mg/day; 42.7% in patients on 20 mg/day; and significant differences between 10 mg/day and 40 mg/day and between 20 mg/day and 40 mg/day (Seab

2) Incidence: 31.2% to 61.1% (Prod Info ZYPREXA(R) oral tablets, IM injection, ZYPREXA(R) ZYDIS(R) ora

3) A case of galactorrhea with elevated serum prolactin levels was reported in a 33-year-old woman after rec treatment of schizophreniform disorder. During week 5 of olanzapine therapy, the patient developed spontane reported missing her menstrual period. Her serum prolactin level was 146.55 nanograms (ng)/mL (normal rar and replaced with quetiapine (25 to 100 mg/day). Symptoms of galactorrhea resolved within 3 weeks of stopp to decrease. Quetiapine therapy was continued without recurrence of galactorrhea (Mendhekar et al, 2004).

4) High dose olanzapine was associated with mild extrapyramidal symptoms (EPS), elevated serum prolactin an average weight gain of 8 kg in 8 men with schizophrenia and schizoaffective disorder. These patients, who risperidone or clozapine at adequate doses, were dosed with olanzapine 20 to 40 mg for a mean of 40 weeks

5) Olanzapine has produced small elevations in serum prolactin (about 0.1 to 0.2 nanomoles (nmol)/L), that a greater increases have occurred with haloperidol (Anon, 1994a; Beasley et al, 1996). Cases of unwanted pre conventional neuroleptic medications to olanzapine, possibly due to a normalization of prolactin levels and a 1998).

3.3.3.L Serum triglycerides raised

1) Summary

a) Elevations in serum triglycerides have been observed, at times a greater than 500 mg/dL increase, du increase in fasting triglyceride from baseline was 20.8 mg/dL in olanzapine-treated patients compared wi placebo-treated patients (statistically significant), in an analysis of 5 placebo-controlled monotherapy stu lipid dysregulation at baseline experienced greater increases in fasting triglyceride levels compared to pa was defined as patients diagnosed with dyslipidemia or related adverse events, patients treated with lipid lipid levels. Baseline and follow-up lipid monitoring of lipids is recommended in patients on olanzapine (P ZYPREXA(R) ZYDIS(R) orally disintergating tablets, 2008).

2) Incidence: up to 40% (Prod Info ZYPREXA(R) oral tablets, IM injection, ZYPREXA(R) ZYDIS(R) orally dis

3) In an analysis of 5 placebo-controlled monotherapy studies of up to 12-weeks duration, the fasting triglyce olanzapine-treated patients compared with up to 26% of placebo-treated patients. The table below provides t triglycerides (Prod Info ZYPREXA(R) oral tablets, IM injection, ZYPREXA(R) ZYDIS(R) orally disintergating ta

Fasting Triglycerides In Adults

Category Change from Baseline	Treatment Arm	N	Portion of Patients
Increase by 50 mg/dL or more	olanzapine	745	39.6% *
	placebo	402	26.1%
Increase from Normal (less than 150 mg/dL) to High (200 mg/dL or more)	olanzapine	457	9.2%*
	placebo	251	4.4%
Increase from Borderline (150 mg/dL to less than 200 mg/dL) to High (200 mg/dL or more)	olanzapine	135	39.3% *
	placebo	65	20%
KEY: mg/dL = milligrams/deciliter; * = statistically significant compared to placebo			

4) In an analysis of 3 placebo-controlled monotherapy studies of up to 6 weeks duration in adolescents, the f approximately 60% of olanzapine-treated patients compared with up to 35% of placebo-treated patients. The increase of fasting triglycerides (Prod Info ZYPREXA(R) oral tablets, IM injection, ZYPREXA(R) ZYDIS(R) ora

Fasting Triglycerides In Adolescents

Category Change from Baseline	Treatment Arm	N	Portion of Patients
Increase by 50 mg/dL or more	olanzapine	138	37% *
	placebo	66	15.2%
Increase from Normal (less than 150 mg/dL)	olanzapine	67	26.9%

to High (200 mg/dL or more)	placebo	28	10.7%
Increase from Borderline (150 mg/dL to less than 200 mg/dL) to High (200 mg/dL or more)	olanzapine	37	59.5%
	placebo	17	35.3%
KEY: mg/dL = milligrams/deciliter; * = statistically significant compared to placebo			

5) Random triglyceride levels of 1000 mg/dL or more has been reported during postmarketing reports (Prod ZYPREXA(R) ZYDIS(R) orally disintergating tablets, 2008).

6) Patients receiving olanzapine (n=25) were found to have increases in their weight and serum triglycerides receiving olanzapine (mean dose 13.8 mg) had their weight, cholesterol, and triglycerides measured at basel mean of 5.4 kg. Cholesterol levels increased by only 3 mg/dL while triglyceride levels increased by 60 mg/dL with weight change (p less than 0.02).

7) After an average of 16 months of olanzapine therapy, 9 patients had marked increases in triglyceride leve 170 mg/dL to a mean of 240 mg/dL. Five patients had at least a 50% increase in levels. Cholesterol levels re mean weight gain of 10 kg (Sheitman et al, 1999).

3.3.3.M Summary

1) In clinical trials of olanzapine, diabetes mellitus (0.1% to 1%), diabetic ketoacidosis (0.1%), elevated serur to 24%), hyperglycemia (0.1% to 17.4%), hypoglycemia (0.1% to 1%), increased body temperature, and weig ZYPREXA(R) oral tablets, IM injection, ZYPREXA(R) ZYDIS(R) orally disintergating tablets, 2008). There hav and diabetic ketoacidosis following olanzapine use. Elevated prolactin levels have been observed in case rep clinical trials (Prod Info ZYPREXA(R) oral tablets, IM injection, ZYPREXA(R) ZYDIS(R) orally disintergating ta trial of 22 patients where olanzapine orally disintegrating tablets were substituted for standard oral tablets, sig Luxton-Andrew, 2008). In a trial comparing haloperidol and olanzapine, increased appetite was reported at a (Tollefson et al, 1997a). A case report described galactorrhea (not associated with childbirth) in a female pati 2004). A case of hypothermia was reported in a 54-year-old man with end-stage renal disease. The hypother (Fukunishi et al, 2003).

3.3.3.N Weight gain

1) Summary

a) Weight gain (greater than 7% of their baseline weight) occurred in 56% of patients treated with olanza with an average weight gain of 5.4 kg. Regular monitoring of weight should be performed. Before initiatin potential consequences of weight gain (Prod Info ZYPREXA(R) oral tablets, IM injection, ZYPREXA(R) Z

2) Incidence: up to 57% (Prod Info ZYPREXA(R) oral tablets, IM injection, ZYPREXA(R) ZYDIS(R) orally dis

3) An average weight gain of 2.6 kg in olanzapine-treated patients compared with a loss of 0.3 kg in placebo observed in an analysis of 13 monotherapy trials with a median exposure of 6 weeks. After a median duration compared with 3% of placebo-treated patients (statistically significant) gained at least 7% of their baseline we olanzapine-treated compared with 0.3% of placebo-treated patients (statistically significant) gained at least 1 index did not make a difference in the amount gained. The discontinuation rate due to weight gain was 0.2% patients, respectively. The table below provides the weight gain observed in olanzapine-treated patients from tablets, IM injection, ZYPREXA(R) ZYDIS(R) orally disintergating tablets, 2008) :

Amount Gained	6 weeks	6 months	12 months	24 months
	n=2976	n=1536	n=778	n=442
0 kg gain or weight loss	27%	21%	20%	22%
0 to 5 kg (0 to 11 lb)	57%	34%	25%	22%
5 to 10 kg (11 to 22 lb)	15%	26%	25%	22%
10 to 15 kg (22 to 23 lb)	2%	12%	16%	18%
greater than 15 kg (greater than 33 lb)	0%	6%	14%	16%
Key: kg = kilograms; lb = pounds				

4) An average weight gain of 4.6 kg in olanzapine-treated adolescents and 0.3 kg in placebo-treated adolesc analysis of 4 placebo-controlled trials of adolescents (ages 13 to 17 years) treated with monotherapy olanzap or 3 weeks in bipolar disorder trials. After a median duration of 4 weeks, 40.6% of olanzapine-treated compar (statistically significant) gained at least 7% of their baseline weight. After a median duration of 19 weeks, 7.1% placebo-treated patients gained at least 15% of their baseline weight. Baseline body mass index (BMI) did nc however, mean changes in weight were greater in adolescents with BMI above normal at baseline. The disco in the olanzapine and placebo treated patients, respectively. .(Prod Info ZYPREXA(R) oral tablets, IM injectio tablets, 2008).

5) Weight gain was more frequent compared to placebo during short-term trials (6 weeks) of monotherapy ol in combination with lithium or valproate. The frequency of weight gain was 6% and 1% in olanzapine-treated (n=118), respectively, in 6-week, placebo-controlled schizophrenia trials. The frequency of weight gain was 5 and placebo-treated patients (n=294), respectively, in short-term, placebo-controlled clinical trials. When use frequency was 26% and 7% in olanzapine-treated patients (n=229) and placebo-treated patients (n=115), res bipolar mania trials of 6 weeks duration. (Prod Info ZYPREXA(R) oral tablets, IM injection, ZYPREXA(R) ZYD

6) A dose-related increase in weight gain of 1.9 kg to 3 kg occurred in olanzapine-treated patients with schiz randomized, double-blind, fixed-dose study (n=599). The mean baseline-to-endpoint increase in weight was 1 on 20 mg/day, and 3 kg in patients on 40 mg/day. There were statistically significant differences among the 3

IM injection, ZYPREXA(R) ZYDIS(R) orally disintergating tablets, 2008).
7) Adolescent patients taking olanzapine experienced greater weight gain and increased in body mass index retrospective study involving 103 patients younger than 18 years of age. Patients received olanzapine (n=50, mean daily dose 510.9 mg) for at least 2 weeks. Weight and height were measured at baseline and 14 or mo baseline in the olanzapine group was 3.8 kg (p less than 0.001) compared to 0.03 kg in the quetiapine group. showed slight, but significant, increases in height from baseline (0.006 meters, p=0.042 and 0.006 meters, p baseline differences, the mean weight change between groups was significant (3.4 kg, p less than 0.001). BM olanzapine group (p less than 0.001) compared to a decrease of 0.2 kg/m(2) in the quetiapine group. After co difference in change in BMI was significant (0.9 kg/m(2), p=0.008) (Patel et al, 2004).
8) Excessive appetite was seen more commonly with olanzapine therapy than with haloperidol (24% versus also associated with a clinically significant greater increase in weight over haloperidol therapy (p less than 0.0 body mass index was the predominant predictor of weight gain. Patients with a low pre-study body mass inde olanzapine treatment. Treatment effect on weight change was consistent between male and female patients
9) In a continuing day-treatment program, 15 out of 16 patients receiving olanzapine gained weight. The mea olanzapine dose of 14 mg and mean treatment duration of 7 months (Gupta et al, 1999).
10) A prospective, multicenter, observational study showed that olanzapine treatment of outpatients (n=2128 group of patients (n=821) receiving a variety of other antipsychotic drug therapies. Drugs used in the control zuclopenthixol, fluphenazine, thioridazine, perphenazine, pimozide, clozapine, pipotiazine, sulpiride, chlorpro lorazepam. Overall, olanzapine had a significantly lower incidence of adverse events than the control group (weight gain occurred significantly more frequently in olanzapine-treated patients. Over a 6-month period, few concomitant anticholinergic medication in comparison to patients in the control group (36% vs 58%, p less tha

3.3.3.O Weight loss

1) Weight loss was reported when the formulation of olanzapine was changed from standard oral tablets (SO open-label, prospective study of 22 adult patients with schizophrenia and a BMI of 25 kg/m(2) or greater who relapses requiring hospitalization within 3 months of study recruitment and no changes in medication required minimum of 1 year. Olanzapine ODT (mean dose of 13.9 mg) was substituted for SOT. Participants' weights months. At 3, 6, and 12 months, the mean changes in weight compared with baseline were -2.5 +/- 0.8 kg (p= kg (p=0.01), respectively. At 12 months, the average decrease in BMI was 1 +/- 0.3 kg/m(2) (p=0.001) and th Patients who received a 20-mg or greater dose of olanzapine ODT lost a greater percentage of their body we less than 20 mg (5.6 +/- 1.2% vs 1.9 +/- 0.9%; p=0.04). (Chawla & Luxton-Andrew, 2008).

3.3.4 Gastrointestinal Effects

Constipation

Excessive salivation

Gastrointestinal tract finding

Nausea and vomiting

Pancreatitis

Xerostomia

3.3.4.A Constipation

1) Summary
a) The manufacturer reports that constipation (9-11%) has occurred with olanzapine therapy (Prod Info IntraMuscular Olanzapine, 2004a). A relatively common adverse gastrointestinal effect of olanzapine is c which appears to be dose-related (Anon, 1995); (Beasley et al, 1996). In patients receiving a mean of 12 incidences of constipation were 8% and 15% (Beasley et al, 1996). The incidence of constipation with ol greater than observed with haloperidol 10 to 20 mg daily (Beasley et al, 1996). Anticholinergic effects, wh effects of olanzapine therapy (Isbister et al, 2001); (Beasley et al, 1996)(Prod Info Zyprexa(R), Zyprexa(R 2004a).
2) Incidence: 5-6%

3.3.4.B Excessive salivation

1) Summary
a) Hypersalivation has occurred with olanzapine therapy. A 20-year-old woman experienced morning gr sleep while receiving olanzapine 10 milligrams/day (mg/d). Her symptoms worsened with an increased d salivation has been reported in premarketing clinical trials and in an accidental pediatric ingestion (Prod IntraMuscular Olanzapine, 2004a; Yip & Graham, 1997).

3.3.4.C Gastrointestinal tract finding

1) Summary

a) The manufacturer reports that INCREASED SALIVATION, THIRST and DYSPEPSIA (7-11%) have o DYSMOBILITY has been associated with antipsychotic therapy. (Prod Info Zyprexa(R), Zyprexa(R) Zydis 2004a). Dyspepsia is not dose-related. (Beasley et al, 1996). ANTICHOLINERGIC EFFECTS, including adverse effects of olanzapine therapy. These effects are dose-related (Isbister et al, 2001); (Beasley et a also been one case report of acute hemorrhagic pancreatitis (Doucette et al, 2000).

2) The manufacturer reports that constipation, increased salivation, vomiting, thirst, dry mouth, dyspepsia, ar Dry mouth and nausea appear to be dose-related. Esophageal dysmobility has been associated with antipsy

3.3.4.D Nausea and vomiting

1) Summary

a) Vomiting (4%) and nausea (greater than or equal to 2%) have occurred with olanzapine therapy. Nau nausea tends to increase with dose (2% with 12 milligrams (mg) daily, 9% with 16 mg daily) and in highe observed with haloperidol 10 to 20 mg daily (Beasley et al, 1996)(Prod Info Zyprexa(R), Zyprexa(R) Zydi 2004a).

3.3.4.E Pancreatitis

1) Summary

a) ACUTE HEMORRHAGIC PANCREATITIS has been reported as a probable adverse event of olanza onset of symptoms. Other concomitant drugs were ruled out as contributing to pancreatitis. Death due to case (Doucette et al, 2000). This is a rare adverse effect of olanzapine.

b) In one study of reported cases (n=192) of antipsychotic-induced pancreatitis, 33% of the cases were daily dose of 15 milligrams. In most patients, time to onset of pancreatitis was within 6 months after initia

c) Olanzapine was the probable cause of acute hemorrhagic pancreatitis in a 72-year-old female admitt verapamil overdose. Past medical history included multiple sclerosis, left temporal cerebral infarct (2 wee and drug abuse. Prior to admission she was taking ketorolac, morphine, and temazepam. Olanzapine (5 prior to admission for recent cognitive decline. The patient's chief complaint of abdominal pain began 24 ingested 10 of her husband's verapamil 240 mg sustained release tablets. Laparotomy revealed hemorr patient died due to peritonitis related to pancreatitis. Using the Naranjo Probability Scale, olanzapine was pancreatitis in this patient (Doucette, 2000). Other authors have pointed out possible discrepancies in th medications and chronic alcoholism which they believe could have contributed to the acute pancreatitis (

3.3.4.F Xerostomia

1) Summary

a) The manufacturer reports that dry mouth (9-22%) has occurred with olanzapine therapy. Dry mouth a Zyprexa(R) Zydis(R), Zyprexa(R) IntraMuscular Olanzapine, 2004a). A relatively common adverse gastr (secondary to anticholinergic activity), which appears to be dose-related (Anon, 1995); (Beasley et al, 19 (mg) daily and 16 mg daily, respective incidences of dry mouth were 5% and 13% (Beasley et al, 1996). higher doses (12.5 to 17.5 mg daily) is greater than observed with haloperidol 10 to 20 mg daily (Beasley dry mouth, are common adverse effects of olanzapine therapy (Isbister et al, 2001); (Beasley et al, 1996 Zyprexa(R) IntraMuscular Olanzapine, 2004a).

2) Incidence: 5-15%

3.3.5 Hematologic Effects

Agranulocytosis

Leukopenia

Neutropenia

Pancytopenia

3.3.5.A Agranulocytosis

1) Summary

a) Agranulocytosis has not been reported with administration of olanzapine either during clinical studies was given to the hematologic parameters during premarketing studies of olanzapine and no evidence of ZYPREXA(R) oral tablets, orally disintegrating tablets, IM injection, 2007).

b) Unlike clozapine, a structurally related drug, olanzapine has not been shown in preclinical trials to ca 1997a); (Beasley et al, 1996)(Anon, 1994a; Anon, 1995). However, due to the structural similarities of th hematologic reactions. Subsequently, however, there have been reports of agranulocytosis with olanzap (Fachinfo, Zyprexa(R), 1998)(Naumann et al, 1999). There have also been several cases of olanzapine clozapine-induced granulocytopenia reported (Konakanchi et al, 2000).

2) LITERATURE REPORTS

a) Fifteen days after starting olanzapine (5 milligrams daily), a 46-year-old male presented to the hospita concurrently taking cyanamide. A white blood cell count of 0.5 x 10(9)/liter (L) with a neutrophil count of (cyanamide were stopped and antibiotic therapy was initiated. By the sixth hospital day, his white blood c between olanzapine therapy and new onset agranulocytosis was noted (Tolosa-Vilella et al, 2002).

b) Neutropenia was reported in a 39-year-old African American woman receiving olanzapine for paranoi received clozapine for 7 years, but this was discontinued due to the development of granulocytopenia. C 1000 milligrams (mg) three times daily, nifedipine 60 mg daily, metformin 1000 mg three times daily, insu evening) and lorazepam 2 mg once daily. Her absolute neutrophil count (ANC) was 3110/millimeter (mm millimeter (/mm) at the time clozapine was switched to olanzapine (10 mg once daily). After 7 days of ola day 14, it had decreased to 1050 cells/mm. Olanzapine was reintroduced 6 months later without incident therapy in patients with clozapine-induced granulocytopenia until the patient's hematologic status has no

c) During clozapine-induced agranulocytosis in 2 patients with schizophrenia, olanzapine [doses greater safe and effective treatment. Additionally, olanzapine did not worsen the severe neutropenia or agranulo Semaan, 2000).

d) A 27-year-old man who had been previously treated with clozapine therapy and had a normal leukocy olanzapine. Five months after discontinuing clozapine therapy, olanzapine therapy was begun and rapidl days his white blood cell (WBC) count decreased to 3.4 x 10(9)/Liter (L). Olanzapine therapy was discon decreased to 2.3 x 10(9)/L. His neutrophil count also decreased to 0.39 x 10(9)L. He was successfully tr micrograms/kilogram (mcg/kg)(Naumann et al, 1999).

3.3.5.B Leukopenia

1) Summary

a) Leukopenia was reported infrequently in clinical trials (n=8661) representing 4165 patient-years of ex olanzapine at doses 1 mg/day or more. Careful attention was given to the hematologic parameters during evidence of neutropenia was demonstrated (Prod Info ZYPREXA(R) oral tablets, orally disintegrating tab

b) Unlike clozapine, a structurally related drug, olanzapine has not been shown in preclinical trials to ca (Anon, 1994a; Anon, 1995). However, due to the similarities of the two drugs, there may be a potential fo of olanzapine adversely prolonging the recovery time of clozapine-induced granulocytopenia have been

2) Incidence: 0.1% to 1% (Prod Info ZYPREXA(R) oral tablets, orally disintegrating tablets, IM injection, 200

3) LITERATURE REPORTS

a) Two patients treated with olanzapine for levodopa-induced psychosis developed leukopenia. A 56-ye (2400 microliters) after 4 months of therapy. She was tapered off olanzapine and recovered over 4 week similar reaction. In the other case, a 58-year-old man who had previously had a decline in his white blood decline in his WBC (2100 microliters) 13 months after starting olanzapine therapy. After discontinuation o after 2 weeks (Meissner et al, 1999).

3.3.5.C Neutropenia

1) Summary

a) Neutropenia was reported during postmarketing surveillance. Careful attention was given to the hema olanzapine and no evidence of neutropenia was demonstrated (Prod Info ZYPREXA(R) oral tablets, oral

b) Significant hematologic abnormalities have not been reported during olanzapine therapy in available 1996)(Anon, 1994a; Anon, 1995). However, neutropenia has been reported with olanzapine therapy (Oy 1998; Benedetti et al, 1999). Unlike clozapine, a structurally related drug, olanzapine has not been show leukopenia or agranulocytosis. However, due to the similarities of the two drugs, there may be a potentia cases of olanzapine adversely prolonging the recovery time of clozapine-induced granulocytopenia have

2) LITERATURE REPORTS

a) A patient previously treated with clozapine developed neutropenia associated with olanzapine therap schizoaffective disorder (bipolar type), chronic paranoid schizophrenia, and schizoid personality disorder (mg) daily for over 1 year. His white blood cell (WBC) count ranged from 4000 to 6000 cells per cubic mi discontinued, however, when the absolute neutrophil count (ANC) fell below 1000 cells/mm(3). After 11 7300 cells/mm(3) (ANC not reported). Olanzapine therapy was initiated at 10 mg once daily and titrated week (olanzapine dose 15 mg at bedtime), WBC fell to 5500 cells/(mm(3) At 30 mg/day, the WBC count (3)). Olanzapine was discontinued and the patient's WBC count slowly began to return to normal, and th patients who have previously taken clozapine may have an increased risk for neutropenia with olanzapin

b) A 60-year-old African American male with chronic undifferentiated schizophrenia had been treated wi gallbladder surgery. While receiving clozapine, his WBC counts ranged between 4000 and 6000 cells/m course of olanzapine (30 mg once daily), which was discontinued due to hyperglycemia and weight gain. over a 17-month period, the patient's WBC count declined to 3100 cells/mm(3) with an ANC of 1023 cell after 5 days, the patient's WBC count had risen to 4500 cells/mm(3) with an ANC of 1986 cells/ mm(3). hematologic monitoring performed every other day. Within 1 week, the patient's WBC count again declin mm(3). Olanzapine was continued with intensive monitoring. The patient's WBC ranged between 4000 a patients who have previously taken clozapine may have an increased risk for neutropenia with olanzapin

c) During clozapine-induced agranulocytosis in 2 patients with schizophrenia, olanzapine [doses greater safe and effective treatment. Additionally, olanzapine did not worsen the severe neutropenia or agranulo Semaan, 2000).

d) A 31-year-old woman who had previously experienced neutropenia with clozapine, experienced neut 1999). Olanzapine was introduced 5 days after clozapine withdrawal; the neutrophil count had normalize

(mg) was given on the first day and 10 mg daily starting on the second day. After 1 week, her neutrophil discontinued and the neutrophil count normalized after 4 weeks.
e) Thirty-two patients with a history of clozapine-induced neutropenia or agranulocytosis did not experie treatment (Prod Info Zyprexa(R), 1998). However, clinical experience with olanzapine, especially with lor

3.3.5.D Pancytopenia

1) LITERATURE REPORTS

a) A case report describes a 36-year-old male who experienced olanzapine-induced pancytopenia. Rele delusions, starvation and abuse of suppositories to purge himself. Upon admission, his RBC 4.67 x 10(1 4.52 x 10(9)/L were within normal range. On day 2, he started olanzapine 10 mg daily. By day 8 of olanz indicative of pancytopenia (values provided in the following table). On day 9, olanzapine was discontinue began to recover. He started risperidone on day 20. On day 29, his RBC, WBC and neutrophils continue He did not experience recurrence of pancytopenia while taking risperidone (Pattichis et al, 2008).

Day	Olanzapine dose	Red Blood Cells	White Blood Cells	Ne
Normal Ranges		4.5 to 6 x 10(12)/L	4 to 11 x 10(9)/L	1.8
Baseline		4.67	6.48	4.5
8	10 mg	4.65	6.67	3.9
9	discontinued			
10	0	4.11	3.57	1.7
11				1.7
15		3.95	2.79	1.6
17		3.78	2.8	1.8
19		3.81	3.16	2.4
23		3.6	3.61	2.6
25		3.82	4.83	3.2
29		3.75	6.12	4.8
KEY: mg = milligrams				

b) Olanzapine was associated with pancytopenia and exacerbated motor disability in a 67-year-old man (mg) daily was added to a regimen of levodopa 1.1 grams (g) and benserazide 275 mg once daily to trea paranoid delusions. After 1 week, the dose was increased to 10 mg/day. Complete blood count (CBC) va therapy, visual hallucinations and delusions decreased in frequency, but motor symptoms, neck rigidity, worsened. Levodopa was increased to 1.3 g/day and benserazide was increased to 325 mg/day. After 4 modest reduction in white blood cells (WBC), red blood cells (RBC), and platelets. One week later the he olanzapine was discontinued. Subsequently, WBC, RBC, and platelet counts increased. Within 4 weeks normal limits and remained normal for the following year. This report suggests that olanzapine should be disease and that hematologic monitoring may be necessary (Onofrj and Thomas, 2001).

3.3.6 Hepatic Effects

Cholestatic hepatitis

Hepatitis

Increased liver function test

3.3.6.A Cholestatic hepatitis

1) Incidence: rare (Prod Info ZYPREXA(R) oral tablets, IM injection, ZYPREXA(R) ZYDIS(R) orally disintegra
2) In the postmarketing period, there have been rare reports of hepatitis and very rare cases of cholestatic o tablets, IM injection, ZYPREXA(R) ZYDIS(R) orally disintegrating tablets, 2006a).

3.3.6.B Hepatitis

1) Incidence: rare (Prod Info ZYPREXA(R) oral tablets, IM injection, ZYPREXA(R) ZYDIS(R) orally disintegra
2) In the postmarketing period, there have been rare reports of hepatitis and very rare cases of cholestatic o tablets, IM injection, ZYPREXA(R) ZYDIS(R) orally disintegrating tablets, 2006a).

3.3.6.C Increased liver function test

1) Summary

a) Increases in serum alanine aminotransferase (ALT) above 200 International Units/Liter (IU/L) occurre tablets, IM injection, ZYPREXA(R) ZYDIS(R) orally disintegrating tablets, 2006a). Elevations of aspartate glutamyl transferase (GGT) have been observed in approximately 10% of patients. These changes appe withdrawal of therapy. Close monitoring of liver function is advised, especially with use of higher doses a (Bronson & Lindenmayer, 2000; Beasley et al, 1996; Beasley et al, 1996a; Prod Info ZYPREXA(R) oral t disintegrating tablets, 2006a).

2) Incidence: 2% to 10% (Prod Info ZYPREXA(R) oral tablets, IM injection, ZYPREXA(R) ZYDIS(R) orally dis

3) LITERATURE REPORTS

a) In placebo-controlled premarketing trials, ALT (SGPT) elevations (greater than or equal to 3 times the 2% (6/243) of patients exposed to olanzapine compared to none (0/115) of the placebo patients. This dif six olanzapine-treated patients experienced jaundice. In two olanzapine-treated patients, liver enzymes r patients in the treatment group discontinued olanzapine therapy. Liver enzymes normalized in 2 of these determine the outcome and the other patient, seropositive for hepatitis C, had persistent enzyme elevatic (Prod Info ZYPREXA(R) oral tablets, IM injection, ZYPREXA(R) ZYDIS(R) orally disintegrating tablets, 2

b) Within the larger olanzapine premarketing database of about 2400 patients with baseline SGPT less elevation to greater than 200 IU/L was 2% (50/2381). None of these patients experienced jaundice or oth most had transient changes that tended to normalize while olanzapine treatment was continued. Among approximately 1% (23/2500) discontinued treatment due to transaminase increases (Prod Info ZYPREXA (R) orally disintegrating tablets, 2006a).

c) High dose olanzapine was associated with mild extrapyramidal symptoms (EPS), elevated serum pro and an average weight gain of 8 kilograms (kg) in 8 men with schizophrenia and schizoaffective disorder neuroleptics and risperidone or clozapine at adequate doses, were dosed with olanzapine 20 to 40 millig experienced increases in serum ALT concentrations; in one patient also taking pravastatin, ALT rose fro 2000a).

d) In another trial, the incidence of TRANSAMINASEMIA was comparable to that seen with haloperidol

e) Elevations of aspartate and alanine aminotransferases and gamma-glutamyl transferase (GGT) have (Beasley et al, 1996a) . These changes appear to be dose-dependent and are reversible upon withdrawa have not been reported in available trials. However, close monitoring of liver function is advised, especia prolonged therapy.

f) The incidence of aminotransferase elevations was greater with olanzapine than with haloperidol in on

3.3.7 Immunologic Effects

3.3.7.A Immunology finding

1) Summary

a) FLU SYNDROME (greater than 1%) has occurred with olanzapine therapy (Prod Info Zyprexa(R), Zy Olanzapine, 2004a). Olanzapine-induced HYPERSENSITIVITY syndrome, consisting of fever, rash, eos 34-year-old man 60 days after initiation of olanzapine therapy. Symptoms resolved following the disconti confirmed drug-induced hypersensitivity syndrome (Raz et al, 2001).

2) Hypersensitivity syndrome and flu syndrome have occurred with olanzapine therapy.

3.3.8 Musculoskeletal Effects

3.3.8.A Musculoskeletal finding

1) Summary

a) The manufacturer reports that BACK PAIN, JOINT PAIN (5%), EXTREMITY PAIN (5%), and TWITCH olanzapine therapy (Prod Info Zyprexa(R), Zyprexa(R) Zydis(R), Zyprexa(R) IntraMuscular Olanzapine, 2 PHOSPHOKINASE (CPK) have been reported during clinical trials (Prod Info Zyprexa(R), Zyprexa(R) Zy 2004a). Marked elevation of serum creatine kinase (CK) associated with olanzapine therapy, with no oth syndrome, has been reported. No psychomotor agitation was present. Drug discontinuation resulted in re

2) Back pain, joint pain, extremity pain, elevated creatine phosphokinase and twitching are reported with ola

3.3.9 Neurologic Effects

Akathisia

Asthenia

Cerebrovascular disease

Disturbance in speech

Dizziness

Extrapyramidal disease

Insomnia

Neurological finding

Parkinsonism

Restless legs syndrome

Seizure

Somnolence

Status epilepticus

Tardive dyskinesia

Tremor

3.3.9.A Akathisia

1) Incidence: 1% to 27% (Prod Info ZYPREXA(R) oral tablets, IM injection, ZYPREXA(R) ZYDIS(R) orally dis

2) Akathisia has been reported in 1% (IM injection) to 27% (oral) of patients treated with olanzapine compare ZYPREXA(R) oral tablets, IM injection, ZYPREXA(R) ZYDIS(R) orally disintergating tablets, 2008).

3.3.9.B Asthenia

1) Incidence: 2% to 20% (Prod Info ZYPREXA(R) oral tablets, IM injection, ZYPREXA(R) ZYDIS(R) orally dis

2) Asthenia has been reported in 2% to 20% of patients treated with olanzapine compared with patients treat tablets, IM injection, ZYPREXA(R) ZYDIS(R) orally disintergating tablets, 2008).

3.3.9.C Cerebrovascular disease

1) The manufacturer has reported cerebrovascular adverse events (ie, stroke transient ischemic attack) in ol Placebo-controlled trials revealed a significantly higher incidence of cerebrovascular adverse events in elderl were treated with olanzapine as compared with placebo (Prod Info ZYPREXA(R) oral tablets, IM injection, ZY 2008; Pers Comm, 2004).

3.3.9.D Disturbance in speech

1) Four older patients (70 to 86 years old) presented with speech dysfunction or general decreases in functio (mg/d). Within 3 days to 4 weeks patients developed the inability to articulate clearly or unintelligible slurred s functioning in the presence of increased or new incontinence, inability to feed oneself, and unsteady gait. Pat once the olanzapine was discontinued (Gail & Noviasky, 1998).

3.3.9.E Dizziness

1) Incidence: 4% to 18% (Prod Info ZYPREXA(R) oral tablets, IM injection, ZYPREXA(R) ZYDIS(R) orally dis

2) Dizziness was reported in 4% (IM injection) to 18% (oral) of patients treated with olanzapine compared wi ZYPREXA(R) oral tablets, IM injection, ZYPREXA(R) ZYDIS(R) orally disintergating tablets, 2008).

3.3.9.F Extrapyramidal disease

1) The manufacturer reports that extrapyramidal events occurred in 15% to 32% of patients, specific occurre to 11%, dystonic events 2% to 3%, dyskinesia, tardive dyskinesia, and other residual events (movement diso ZYPREXA(R) oral tablets, IM injection, ZYPREXA(R) ZYDIS(R) orally disintergating tablets, 2008). Extrapyra olanzapine therapy of schizophrenia (Glazer, 2000a; Tollefson et al, 1997a); (Beasley et al, 1996)(Anon, 199 have been reported in less than 9% of patients treated, with parkinsonian tremor occurring in approximately 5 (Tollefson et al, 1997a; Anon, 1995); (Beasley et al, 1996)(Anon, 1994a).

2) A prospective, multicenter, observational study showed that olanzapine treatment of outpatients (n=2128) group of patients (n=821) receiving a variety of other antipsychotic drug therapies. Drugs used in the control g zuclopenthixol, fluphenazine, thioridazine, perphenazine, pimozide, clozapine, pipotiazine, sulpiride, chlorpro lorazepam. Overall, olanzapine had a significantly lower incidence of adverse events than the control group (and weight gain occurred significantly more frequently in olanzapine-treated patients. Akathisia, dystonia, ext were significantly higher in the control group. Abnormal ejaculation and impotence occurred significantly mor month period, fewer olanzapine-treated patients received a concomitant anticholinergic medication in compar 58%, p less than 0.001) (Gomez et al, 2000).

3) High dose olanzapine was associated with mild extrapyramidal symptoms (EPS), elevated serum prolacti
an average weight gain of 8 kilograms (kg) in 8 men with schizophrenia and schizoaffective disorder. These p
and risperidone or clozapine at adequate doses, were dosed with olanzapine 20 to 40 milligrams (mg) for a n
rigidity alone or combined with cogwheeling of the elbow, wrist, or shoulder joints (Bronson & Lindenmayer, 2
4) The incidence of extrapyramidal symptoms (EPS) as a result of antipsychotic treatment was less in olanza
patients. This finding was confirmed in an international, multicenter, double-blind, prospective study involving
doses of olanzapine 17 milligrams/day (mg/d) or risperidone 7 milligrams/day (mg/d) for 28 weeks. The use o
of anticholinergic medications. Data suggests that the therapeutic dose threshold for EPS may be wider for o
needed for verification (Glazer, 2000a).
5) Extrapyramidal effects have occurred in clinical trials and appear to be dose-related (greater than 20 mg/d
appear to be more sensitive to extrapyramidal side effects of olanzapine (Granger & Hanger, 1999).
6) An 81-year-old woman treated with olanzapine 5 mg daily developed rigidity and hypertonicity. She had n
were normal. She had been independent but over several weeks declined, eventually requiring the assistanc
and within 1 week, she was totally independent again (Granger & Hanger, 1999).
7) A rate of 1.4% has been reported for acute dystonic reactions in patients taking olanzapine. Two case rep
woman who had severe torticollis and lingual dystonia with dysarthria, respectively. Both were controlled with
1998).
8) In one comparative trial, akathisia, tremor, and dystonia were reported in 16%, 15%, and 13% of schizoph
[mean, 16 milligrams (mg) daily]. Corresponding incidences in those treated with olanzapine in higher doses
studies, olanzapine has produced numeric improvements relative to baseline in the Simpson-Angus scale (fo
akathisia) during treatment, whereas numerical worsening of these scales occurred in haloperidol-treated pat
See Drug Consult reference: NEUROLEPTIC-INDUCED EXTRAPYRAMIDAL REACTIONS

3.3.9.G Insomnia

1) Incidence: 1% to 12% (Prod Info ZYPREXA(R) oral tablets, IM injection, ZYPREXA(R) ZYDIS(R) orally dis
2) Insomnia has been reported in 1% (IM injection) to 12% (oral) of patients treated with olanzapine compare
ZYPREXA(R) oral tablets, IM injection, ZYPREXA(R) ZYDIS(R) orally disintergating tablets, 2008).

3.3.9.H Neurological finding

1) Olanzapine has been shown to have acute central nervous system depressant effects in humans during c
frequent adverse effect, occurring at an incidence of 26%, and appears to be dose-related. asthenia and dizz
patients, respectively, in clinical trials (Beasley et al, 1996).

3.3.9.I Parkinsonism

1) Contrary to common belief, the results of a retrospective cohort study suggest that atypical antipsychotics
dose and potency are considered (Rochon et al, 2005).
2) In a retrospective review of 12 Parkinson's disease patients receiving olanzapine, only 1 patient was able
disease (Molho & Factor, 1999). Several other studies also reported a worsening of Parkinson's disease sym
1999; Rudolf et al, 1999; Jimenez-Jimenez et al, 1998).
3) The results of a cohort study indicate that high-dose atypical antipsychotic therapy carries a similar risk fo
antipsychotic therapy. In a population-based, retrospective cohort study, adults (aged 66 years and older) wit
year for the development of parkinsonism symptoms associated with typical or atypical antipsychotic use. As
antipsychotic therapy (ie, olanzapine, risperidone, quetiapine), incident parkinsonism was 30% more likely to
chlorpromazine, haloperidol, perphenazine) (adjusted HR, 1.3; 95% CI, 1.04 to 1.58), and 60% less likely to d
(HR, 0.4; 95% CI, 0.29 to 0.43). Older adults using higher potency typical antipsychotics had almost a 50% g
compared with patients prescribed atypical antipsychotics (all were considered lower potency) (HR, 1.44; 95%
lower potency typical antipsychotics, the risk of developing parkinsonism was no different from that in adults t
0.48 to 1.15). In addition, a positive dose-related relationship was observed between the occurrence of incide
antipsychotics. The risk for developing parkinsonism was more than twice as great in patients using a high-do
those prescribed a low-dose atypical antipsychotic agent (HR, 2.07; 95% CI, 1.42 to 3.02). Furthermore, patie
have a similar risk for the development of parkinsonism as patients receiving high-dose atypical antipsychotic
antipsychotics may not be safer than typical antipsychotics when dose and potency are considered (Rochon
4) In a retrospective review of 12 Parkinson's disease patients receiving olanzapine, only 1 patient was able
disease. Nine out of 12 patients had their psychosis improve with olanzapine therapy. Nine out of 12 also had
available Unified Parkinson's Disease Rating Scale scores, average declines in scores were 9 points. Only 1
Factor, 1999).
5) A 72-year-old man had his Parkinson's disease worsen with olanzapine treatment for hallucinations. The d
became very rigid. He was unable to stand or walk. After discontinuing olanzapine, his functioning returned o
6) A 68-year-old man with Parkinson's disease developed a severe akinetic-rigid syndrome after receiving ol
was later successfully treated with clozapine (Rudolf et al, 1999).
7) Parkinson's disease was reported to worsen in 2 patients after olanzapine was substituted for clozapine. C
hematological assessments. However, after 4 to 7 days, olanzapine 5 milligrams/day (mg/d) resulted in worse
(Jimenez-Jimenez et al, 1998).

3.3.9.J Restless legs syndrome

1) A 41-year-old man developed restless legs syndrome while receiving olanzapine therapy for schizophreni
and increased to 20 mg daily after 6 weeks. At that time, he began to experience paresthesias of both legs oc
He experienced some relief by applying cold packs and walking around. A sleep lab evaluation also showed

dose was decreased to 10 mg daily with only a slight decrease in symptoms. Nine days later the patient disc immediately (Kraus et al, 1999).

3.3.9.K Seizure

1) Seizures have been reported in only 0.9% of patients in pre- marketing clinical trials of olanzapine. Patien the seizure threshold may be more prone to seizures following olanzapine therapy (Lee et al, 1999; Prod Info (R) ZYDIS(R) orally disintergating tablets, 2008).

2) Drug interactions with other drugs that lower the seizure threshold, such as clomipramine, have been repo olanzapine (Deshauer et al, 2000a).

3) A 31-year-old woman with schizoaffective disorder, organic mental disorder due to anoxic brain injury, and generalized tonic-clonic seizures 13 days after starting olanzapine. Previously, she had been seizure-free for haloperidol 40 milligrams (mg) twice daily to olanzapine 5 mg twice daily. Her other medications included lithi nitrofurantoin, and docusate. Multiple confounding factors may have contributed to her seizures (Lee et al, 19

3.3.9.L Somnolence

1) Incidence: 2% to 52% (Prod Info ZYPREXA(R) oral tablets, IM injection, ZYPREXA(R) ZYDIS(R) orally dis

2) Somnolence was reported in 6% to 52% of patients treated with olanzapine compared with patients treate tablets, IM injection, ZYPREXA(R) ZYDIS(R) orally disintergating tablets, 2008).

3) During five placebo-controlled trials, somnolence was reported in at least 2% of elderly patients (n=1184) olanzapine, at a rate significantly greater than placebo-treated patients (Prod Info ZYPREXA(R) oral tablets, I disintergating tablets, 2008).

3.3.9.M Status epilepticus

1) A 48-year-old female with psychotic disorder experienced status epilepticus within 2 days following antips olanzapine and dose increase of mirtazapine. A brain MRI 10 days prior revealed no pathological findings, ar head trauma. Laboratory tests at hospital admission for psychogenic vomiting and anorexia showed no bioch was prescribed quetiapine 600 mg which was abruptly discontinued due to the lack of efficacy and suspicion tablets found). Therefore, the patient was switched to orodispersible olanzapine 10 mg, and the dose was qu initiated 4 days prior to the seizure and then increased to 60 mg 2 days prior to the incident. On day 16 of hos tonic-clonic seizure which progressed to status epilepticus. CT tomography revealed no abnormalities, and n neurological signs. Olanzapine and mirtazapine were discontinued and IV phenytoin was initiated. Phenytoin complications and the patient remained seizure-free (Spyridi et al, 2009).

2) Fatal status epilepticus associated with olanzapine therapy in a woman with no underlying cause or predis had been on olanzapine therapy for 5 months prior to the seizures. Subsequent to the seizures she died from intravascular coagulation. The authors classified this as a probable adverse event due to olanzapine (Wyders

3.3.9.N Tardive dyskinesia

1) Incidence: rare

2) Tardive dyskinesia may occur occasionally with olanzapine (Glazer, 2000a; Ananth & Kenan, 1999; Herra Tardive dyskinesia has been reported during clinical trials (Prod Info ZYPREXA(R) oral tablets, IM injection, 2 2008).

3) A 40-year-old woman developed tardive dystonia with olanzapine therapy for her psychosis. She had prev therapy. After beginning olanzapine 10 mg at bedtime, she developed severe, frequent torticollis. She also di She was switched to clozapine and her dystonia decreased by 50% after 4 months (Dunayevich & Strakowsk

4) Two cases of tardive dyskinesia associated with olanzapine therapy were described. A 30-year-old woma months after beginning olanzapine 10 milligrams/day (mg/d). She had previously experienced parkinsonism v developed athetoid movements of the tongue and chewing movements of the jaw after 7 months of olanzapir the tardive dyskinesia continued (Herran & Vazquez-Barquero, 1999).

5) Tardive dyskinesia may occur occasionally with olanzapine. A patient diagnosed with paranoid schizophre daily. Five years later, the patient developed abnormal movements of his upper extremities and neck. A diagn dystonia was made after ruling out all other causes. The patient continued to receive olanzapine with improve in his tardive dyskinesia (Ananth & Kenan, 1999).

6) A long-term follow-up study, which utilized results from 3 other studies, reported that haloperidol-treated p incidence rate/year 12 times higher than that of olanzapine-treated patients (n=513). Both medications were i 2000a). (Tollefson, 1997a)

7) Data combined from 3 studies evaluating patients treated with olanzapine (n=707) or haloperidol (n=197) lower incidence of tardive dyskinesia. At any visit after baseline, 7.1% of patients in the olanzapine group and manifested treatment-emergent tardive dyskinesia (p less than 0.001). At the last study visit, 2.3% of olanzap manifested tardive dyskinesia (p equal to 0.001) (Tollefson, 1997a).

3.3.9.O Tremor

1) Incidence: 1% to 23% (Prod Info ZYPREXA(R) oral tablets, IM injection, ZYPREXA(R) ZYDIS(R) orally dis

2) Tremors have been reported in 1% (IM injection) to 23% (oral) of patients treated with olanzapine compar ZYPREXA(R) oral tablets, IM injection, ZYPREXA(R) ZYDIS(R) orally disintergating tablets, 2008).

3.3.10 Ophthalmic Effects

Esotropia

Eye / vision finding

3.3.10.A Esotropia

1) Esotropia developed in a 14-year-old African American female with psychotic depression, who received ol fluoxetine 40 mg/d) for 6 months. The patient, who had no history of strabismus, complained of a severe hea A neurologic examination revealed no focal neurologic findings. Computed tomography and magnetic resona week of discontinuation of olanzapine, diplopia and headache had cleared, with reported resolution of esotro

3.3.10.B Eye / vision finding

1) Summary

a) The manufacturer reports that AMBLYOPIA (3%) and CONJUNCTIVITIS (greater than 1%) have bee Zyprexa(R), Zyprexa(R) Zydis(R), Zyprexa(R) IntraMuscular Olanzapine, 2004a). Esotropia with diplopia olanzapine and fluoxetine therapy. When olanzapine was discontinued, symptoms cleared within one we

2) Amblyopia, diplopia, esotropia and conjunctivitis are reported with olanzapine therapy.

3.3.12 Psychiatric Effects

Aggressive behavior

Mania

Obsessive-compulsive disorder

Panic attack

Psychiatric sign or symptom

3.3.12.A Aggressive behavior

1) Summary

a) Two cases of patients developing AGITATION, CONFUSION, PARANOID BEHAVIOR and aggressic cases of aggression in patients beginning olanzapine were reported. The aggressive behavior worsened Agitation has been reported in up to 23% of olanzapine-treated patients in clinical trials, as compared to nervousness may be a part of the disease process as opposed to a pharmacologic effect of the drug (Pr

3.3.12.B Mania

1) Summary

a) Mania and hypomania have been described following olanzapine Administration (Aubrey et al, 2000)(1998).

2) LITERATURE REPORTS

a) A review of the literature identified 10 cases of mania or hypomania related to olanzapine therapy. Pa schizophrenia (n=6), schizoaffective disorder (n=2), pervasive developmental disorder (n=1), or an unsp development of manic symptoms ranged between 2 days and 35 days. Six of 10 patients were receiving patients, the use of concomitant medications makes causality difficult to assess. Remission of symptoms olanzapine (n=6). In the other 4 patients, hypomania or mania resolved with a decrease in olanzapine do

b) A 31-year-old woman with psychotic disorder experienced hypomania after receiving olanzapine 20 m second day of olanzapine therapy, she developed pressured speech, social disinhibition, and euphoric m her symptomatology remitted.

c) Two schizophrenic patients experienced manic-like activation after the start of olanzapine treatment. but had never experienced mania. In one case the mania resolved with a decrease in olanzapine dose fr second case olanzapine was discontinued (Lindenmayer & Klebanov, 1998).

3.3.12.C Obsessive-compulsive disorder

1) Summary

a) Two cases of patients experiencing olanzapine-induced OBSESSIVE-COMPULSIVE DISORDER (O 1999). A 35-year-old woman developed obsessive-compulsive disorder (OCD) after having olanzapine a 35-year-old man with schizophrenia and obsessive- compulsive disorder (OCD), had his OCD symptoms al, 1998).

2) LITERATURE REPORTS

a) Two cases of patients experiencing olanzapine-induced obsessive-compulsive disorder (OCD) were switched to olanzapine 15 to 25 milligrams (mg). The first man developed OCD 14 days after beginning

head and the compulsion to check doors. This disappeared with fluoxetine therapy. The second develop isolation, repeated hand-washing, checking doors and the alarm system. He also had impulsion phobias (Mottard & De La Sablonniere, 1999).

b) A 35-year-old woman developed obsessive-compulsive disorder (OCD) after having olanzapine 10 m major depression with psychotic features, borderline personality, and bulimia. After 1 week she develope changed to venlafaxine which successfully treated her OCD (Al-Mulhim et al, 1998).

c) A 35-year-old man with schizophrenia and obsessive-compulsive disorder (OCD), had his OCD symp (Morrison et al, 1998). His fluvoxamine was increased from 200 to 300 milligrams/day (mg/d) which help

3.3.12.D Panic attack

1) Summary

a) CASE REPORT - A 36-year-old woman with schizophrenia began experiencing panic attacks after be Olanzapine was started at 5 milligrams (mg) twice daily and increased to 3 times daily after 18 days. Par were successfully treated with alprazolam 0.5 mg as needed (Mandalos & Szarek, 1999).

3.3.12.E Psychiatric sign or symptom

1) Summary

a) The manufacturer reports that the following adverse reactions have occurred with olanzapine therapy (Prod Info Zyprexa(R), Zyprexa(R) Zydis(R), Zyprexa(R) IntraMuscular Olanzapine, 2004a). Relapse of p olanzapine administration (Kostakoglu et al, 1999). The manufacturer reports that INTENTIONAL INJUR olanzapine therapy. (Prod Info Zyprexa(R), Zyprexa(R) Zydis(R), Zyprexa(R) IntraMuscular Olanzapine, administration (Ramos & Budman, 1998).

2) Hostility, anxiety, aggression, koro and personality disorder are reported with olanzapine administration.

3) LITERATURE REPORTS

a) Two cases are reported where patients initially responded to olanzapine therapy and then relapsed a to 20 milligrams (mg) over 2 to 3 weeks for chronic paranoid schizophrenia. A 38-year-old man showed a fourth week through the sixth week. After 7 weeks, he had reemergence of the paranoid hallucinations, h old woman also had an increase in paranoid delusions and reemergence of auditory hallucinations, lack weeks. The authors conclude that a rapid displacement of these drugs due to loose binding could play a

b) A 19-year-old schizophrenic man developed KORO after having his olanzapine abruptly stopped to b sudden overwhelming fear that his penis and left testicle were shrinking and receding into his abdomen d days, the olanzapine was restarted with his symptoms resolving (Ramos & Budman, 1998). Hostility and have been reported in approximately 15% and 10% of patients treated, respectively, although the freque patients (Beasley et al, 1996).

3.3.13 Renal Effects

Urinary incontinence

Urogenital finding

3.3.13.A Urinary incontinence

1) Summary

a) There has been one reported case of urinary incontinence successfully treated with ephedrine followi

2) LITERATURE REPORTS

a) Ephedrine successfully counteracted urinary incontinence associated with olanzapine in a 61-year-old patient developed urinary incontinence when olanzapine (dose not reported) was added to lithium (dose mania, psychosis, agitation, and verbalized homicidal thoughts. Incontinence remitted 24 hours after eph regimen. (Vernon, 2000).

3.3.13.B Urogenital finding

1) Summary

a) The manufacturer reports that AMENORRHEA (1%), HEMATURIA (1%), METRORRHAGIA (1%), UR INFECTION (2%), and VAGINITIS (greater than 1%) have been associated with olanzapine therapy (Pro (R) IntraMuscular Olanzapine, 2004a).

b) A prospective, multicenter, observational study showed that olanzapine treatment of outpatients (n=2 group of patients (n=821) receiving a variety of other antipsychotic drug therapies. Drugs used in the cor sertindole, zuclopenthixol, fluphenazine, thioridazine, perphenazine, pimozide, clozapine, pipotiazine, su clothiapine, and lorazepam. Overall, olanzapine had a significantly lower incidence of adverse events tha 0.001). Somnolence and weight gain occurred significantly more frequently in olanzapine-treated patient hypertonia, and tremor were significantly higher in the control group. Abnormal ejaculation and impotenc the control group. Over a 6-month period, fewer olanzapine-treated patients received a concomitant anti the control group (36% versus 58%, p less than 0.001) (Gomez et al, 2000).

2) Amenorrhea, hematuria, metrorrhagia, urinary incontinence, urinary tract infection, vaginitis and priapism

3.3.14 Reproductive Effects

3.3.14.A Priapism

1) Summary

a) Priapism and instances of PAINFUL ERECTIONS have been reported with Olanzapine (Kuperman et et al, 1998; Heckers et al, 1998).

2) LITERATURE REPORTS

a) Priapism developed in a 26-year-old man treated with olanzapine 10 milligrams per day for disorganiz sexually overactive, he had previously taken varied psychotropic medications (including risperidone) with hours of discontinuation of olanzapine, priapism disappeared (Kuperman, 2000).

b) There are reports of men with painful erections occurring 1 to 3 days after beginning olanzapine. One symptoms of sexual dysfunction receiving olanzapine 15 mg nightly (Gordon & De Groot, 1999). The oth involving the spinal cord and a history of prostate surgery receiving olanzapine 5 mg daily. Both required return (Heckers et al, 1998).

c) One report of an African-American man with a history of hypersexual behavior receiving olanzapine 1 increased frequency and duration of erections (up to 2 hours). Within 1 week of olanzapine discontinuati (Deirmenjian et al, 1998).

3.3.15 Respiratory Effects

Cough

Dyspnea

Pharyngitis

Pulmonary aspiration

Pulmonary embolism

Rhinitis

Summary

3.3.15.A Cough

1) Incidence: 6% (Prod Info ZYPREXA(R) oral tablets, IM injection, ZYPREXA(R) ZYDIS(R) orally disinterga

2) Increased cough was reported in 6% of patients treated with oral olanzapine at doses of 2.5 mg/day or gre with placebo (n=294) in the acute phase of short-term, placebo controlled trials (Prod Info ZYPREXA(R) oral disintergating tablets, 2008).

3.3.15.B Dyspnea

1) Incidence: 3% (Prod Info ZYPREXA(R) oral tablets, IM injection, ZYPREXA(R) ZYDIS(R) orally disinterga

2) Dyspnea was reported in 3% of patients treated with oral olanzapine at doses of 5 mg/day or greater plus those treated with lithium or valproate alone (n=115) in the acute phase of short-term, placebo-controlled, co oral tablets, IM injection, ZYPREXA(R) ZYDIS(R) orally disintergating tablets, 2008).

3.3.15.C Pharyngitis

1) Incidence: 4% (Prod Info ZYPREXA(R) oral tablets, IM injection, ZYPREXA(R) ZYDIS(R) orally disinterga

2) Pharyngitis was reported in 4% of patients treated with oral olanzapine at doses of 2.5 mg/day or greater placebo (n=294) in the acute phase of short-term, placebo controlled trials. Pharyngitis was also reported in 4 of 5 mg/day or greater plus lithium or valproate (n=229) compared with 1% of those treated with lithium or val term, placebo-controlled, combination, clinical trials (Prod Info ZYPREXA(R) oral tablets, IM injection, ZYPRE 2008).

3.3.15.D Pulmonary aspiration

1) Aspiration has been associated with antipsychotic therapy. Aspiration pneumonia has resulted in morbidit Alzheimer's disease. Olanzapine should be used cautiously in patients at increased risk for aspiration pneum injection, ZYPREXA(R) ZYDIS(R) orally disintergating tablets, 2008).

3.3.15.E Pulmonary embolism

1) A case report described 3 episodes of pulmonary embolism in a 25-year-old man after treatment with olan schizoaffective disorder. His physical health was generally good and there was no personal or family history or physical activity level changed under neuroleptic medication. Smoking a pack of cigarettes per day was his

antipsychotic therapy included olanzapine 20 mg/day, paroxetine 20 mg/day and oral valproate 2000 mg/day treatment, the patient presented with a complaint of sudden back pain radiating to the left front part of his tho breath and experienced an episode of hemoptysis. CT scan revealed bilateral pulmonary embolism. Ultrasou DVT. His coagulopathy workup did not demonstrate any abnormalities. Olanzapine was discontinued and ora of 2 to 3) was initiated and maintained for 6 months. Twelve weeks after olanzapine was discontinued, he wa of psychotic symptoms. After 3 weeks of risperidone treatment, the patient presented with chest pain, cough, pulmonary emboli were observed on a chest spiral CT scan. Concomitant DVT in lower extremities was ruled (evidenced by low INR) appeared to be the cause of this second episode of pulmonary embolism. Therefore, confirm adherence. Sixteen weeks later, the patient presented with thoracic pain and dyspnea. Spiral chest C indicated bilateral pulmonary embolism with no DVT in the lower limbs. Because antipsychotic agents appear the patient was administered anticoagulant therapy and amisulpride 400 mg/day which resulted in improveme valproate 2 g/day therapy was continued after being maintained throughout the 3 episodes of pulmonary emb
2) A case report described a pulmonary embolism in a 28-year-old male patient after beginning olanzapine tl Olanzapine therapy was initiated at 10 mg/day and gradually increased to 30 mg/day. Following 10 weeks of spiral CT, which was performed after the patient complained of respiratory pain and experienced two episode discontinued and the patient's symptoms resolved with anticoagulant therapy. Because tests for possible coa risks factors for this patient, olanzapine was believed to be the causal effect for the development of the pulmo

3.3.15.F Rhinitis

1) Incidence: 7% (Prod Info ZYPREXA(R) oral tablets, IM injection, ZYPREXA(R) ZYDIS(R) orally disinterga
2) Rhinitis was reported in 7% of patients treated with oral olanzapine at doses of 2.5 mg/day or greater (n=5 placebo (n=294) in the acute phase of short-term, placebo controlled trials (Prod Info ZYPREXA(R) oral table disintergating tablets, 2008).

3.3.15.G Summary

1) Cough, dyspnea, pharyngitis, and rhinitis were reported at a higher incidence with olanzapine treatment c controlled trials. Additionally, antipsychotic therapy has been associated with aspiration. Aspiration pneumoni with advanced Alzheimer's disease. Therefore, caution should be used when olanzapine is administered in th tablets, IM injection, ZYPREXA(R) ZYDIS(R) orally disintergating tablets, 2008). Two case reports described man and a 29-year-old man following oral olanzapine therapy. Both patients experienced improvement after therapy was initiated (Borras et al, 2008; Waage & Gedde-Dahl, 2003).

3.3.16 Other

Summary

Death

Drug withdrawal

Extrapyramidal disease

Neuroleptic malignant syndrome

3.3.16.A Summary

1) OTHER EFFECTS
a) In a large trial comparing haloperidol and olanzapine in schizophrenic patients, discontinuation of ther with olanzapine. Withdrawal syndrome has been reported with olanzapine therapy.
2) OTHER FINDINGS
a) In a large trial comparing haloperidol and olanzapine in schizophrenic patients (n=1996), discontinuat less often with olanzapine (3.6% versus 7.4% of patients) (Anon, 1995).

3.3.16.B Death

1) Results of a population-based, retrospective cohort study demonstrated that the use of conventional antip for death than atypical antipsychotics when administered to elderly patients (aged 66 years and older) with de conventional versus atypical antipsychotic use pair-wise comparisons were made. A total of 27,259 matched stratified based on place of residence (community versus long-term care facilities). In order to adjust for differ matching was used. The primary outcome of the study was all-cause mortality. The risk for death was evalua antipsychotic medications were initially dispensed. There was a statistically significant increase in the risk for atypical antipsychotic medications compared with nonuse in both the community-dwelling cohort (adjusted ha 1.02 to 1.70); absolute risk difference, 0.2 percentage point) and long-term care cohort (adjusted HR, 1.55 (9 percentage points). For both cohorts, the risk associated with atypical antipsychotics appeared to persist to 1 conventional antipsychotics was even greater than the risk identified with atypical antipsychotics. At 30 days, was 1.55 (95% CI, 1.19 to 2.02) and 1.26 (95% CI, 1.04 to 1.53) for the long-term care cohort (adjusted risk c

risk appeared to persist to 180 days for both groups. Some important limitations to the study include unknown results and cause of death could not be examined (Gill et al, 2007).
2) Results of a population-based, retrospective cohort study demonstrated comparable to possibly greater ris antipsychotic medications in the elderly (aged 65 years and older) compared with atypical antipsychotic medi and included only new users of antipsychotic medications. The primary study outcome was 180-day all-cause measured based on healthcare utilization data within 6 months before the initiation of antipsychotic medicatio and 24,359 received conventional and atypical antipsychotic medications, respectively. The risk of death in th was 14.1% compared with 9.6% in the atypical drug group (unadjusted mortality ratio, 1.47; 95% confidence analysis which controlled for potential confounders, the adjusted mortality ratio for the risk of death within 180 was 1.32 (95% CI, 1.23 to 1.42). When the most frequently prescribed conventional antipsychotic drugs were associated with haloperidol was 2.14 (95% CI, 1.86 to 2.45) and loxapine was 1.29 (95% CI, 1.19 to 1.40), wh olanzapine. The increased mortality risk for conventional versus atypical drug therapy was greatest when dos (mortality ratio 1.67; 95% CI, 1.5 to 1.86) and also during the first 40 days of therapy (mortality ratio 1.6; 95% of multi-variable Cox regression, propensity score, and instrumental variable estimation confirmed the results
3) The findings of one meta-analysis suggest that there may be a small increased risk of death associated w treatment of dementia in elderly patients. The study analysis (n=5110), including 15 randomized, double-blind antipsychotic use (ie, aripiprazole (n=3), olanzapine (n=5), quetiapine (n=3), risperidone (n=5)) in elderly pati dementia, found that death occurred more often in patients receiving atypical antipsychotic therapy as compa respectively). The overall odds ratio, as assessed by meta-analysis, for death in elderly patients receiving aty 1.54 (95% confidence interval (CI), 1.06 to 2.23; p=0.02), and the risk difference was 0.01 (95% CI, 0.004 to with atypical antipsychotic use was 1.65 (95% CI, 1.19 to 2.29; p=0.003); however this increased risk was on analysis; meta-analyses of individual drugs did not show a statistically significant increased risk. A similar dro and placebo-treated patients (32.2% vs 31.4%, respectively), with no significant difference in dropouts found
4) The results of a retrospective cohort study indicate that conventional antipsychotic agents are at least as l the risk of death among elderly patients 65 years of age or older. The study included 9,142 new users of conv 13,748 new users of atypical agents (mean age, 83.5 years). A higher adjusted relative risk of death was ass as compared with atypical antipsychotics at all timepoints studied after beginning therapy (within 180 days: re 1.27 to 1.49; less than 40 days: RR, 1.56; 95% CI, 1.37 to 1.78; 40 to 79 days: RR, 1.37; 95% CI, 1.19 to 1.5 In addition, the adjusted risks of death observed in patients with dementia (RR, 1.29; 95% CI, 1.15 to 1.45), w a nursing home (RR, 1.26; 95% CI, 1.08 to 1.47), or not in a nursing home (RR, 1.42; 95% CI, 1.29 to 1.56) w antipsychotic therapy as compared with atypical antipsychotic use. This risk appeared to be dose-related and greater than the median) conventional antipsychotics (RR, 1.73; 95% CI, 1.57 to 1.90). Additional studies whi elderly patients requiring antipsychotic therapy are needed so that appropriate guidance regarding therapeuti

3.3.16.C Drug withdrawal

1) Summary

a) CASE REPORT - Within 3 days of stopping olanzapine therapy, a 33- year-old female developed myo depression, restlessness, and blurred vision. Because myoclonus is consistent with serotonergic hyperac represented a SEROTONERGIC REBOUND phenomena (Nayudu & Scheftner, 2000).

3.3.16.D Extrapyramidal disease

See Drug Consult reference: NEUROLEPTIC-INDUCED EXTRAPYRAMIDAL REACTIONS

3.3.16.E Neuroleptic malignant syndrome

1) Summary

a) Neuroleptic malignant syndrome (NMS), due to dopaminergic blockade, associated with olanzapine th taking concomitant or recently discontinued neuroleptics appear to be more susceptible to drug-induced myoglobin levels may be elevated; and high fever and rigidity are present. Generally after stopping the d NMS resolves (Stanfield & Privette, 2000; Nyfort-Hansen & Alderman, 2000; Sierra-Biddle et al, 2000; M 1999); (Burkhard et al, 1999)(Apple & Van Hauer, 1999; Cohen et al, 1999); (Johnson & Brusner, 1998)(
b) Symptoms have begun as early as 2 to 4 days and as late as 1 year. Patients have presented with ty muscle rigidity, mental status changes, and autonomic instability. Increases in serum creatine kinase hav 41,900 international units/L. Some patients previously had NMS with other neuroleptics including risperic discontinuation of olanzapine and with treatments including dantrolene, bromocriptine, or benzodiazepine however, the patient was also receiving clozapine and no rigidity was noted (Moltz & Coeytaux, 1998).

2) LITERATURE REPORTS

a) A case report describes a 56-year-old male who experienced neuroleptic malignant syndrome (NMS) history included sleep disturbances, preoccupied and hallucinatory behaviors and persecutory thoughts. treatments with thioridazine, then trifluperazine with chlordiazepoxide, which caused extrapyramidal sym year, he was noncompliant with treatments of fluoxetine, clonazepam, escitalopram and olanzapine befo schizophrenia based on ICD-10 criteria. Upon admission, he started olanzapine 5 mg twice daily and alp olanzapine was increased to 15 mg/day. On day 5, his perspiration and blood pressure (BP, 150/86 mmH EPS or dehydration. On day 6, he experienced fever (102 degrees Farenheit), confusion, diaphoresis, ta tremors, upper and lower limb rigidity, leucocytosis, uremia and elevated creatinine phosphokinase. He v olanzapine and alprazolam were discontinued and he received amoxicillin 500 mg three times daily and his sensorium improved and the rigidity and tremors resolved. After 7 days, he was discharged on loraze he started amisulpride 50 mg nightly. He has continued success with amisulpride 100 mg and clonazepa
b) Atypical neuroleptic malignant syndrome, also described as fever- delirium-autonomic instability synd

30-year-old man developed fever, difficulty swallowing, sinus tachycardia, delirium, elevated white blood
olanzapine (10 milligrams/day) was initiated for the treatment of violent behavior. No rigidity, hyperreflexi
observed. Olanzapine was discontinued and symptoms completely resolved within 2 days (Robinson et a
c) A 23-year-old woman developed clinical features consistent with neuroleptic malignant syndrome (NM
daily for schizoaffective disorder. Other medications included lithium and fluoxetine. After 40 days of olar
admission to the hospital, her trunk and limbs were hypertonic and hyperextended, with generalized trem
blood pressure fluctuations, and an elevated body temperature of 38.6 degrees Celsius. Laboratory data
metabolic acidosis, hypernatremia, hypokalemia, a lithium levels of 0.7 milliequivalents per liter (mEq/L),
Cultures of cerebrospinal fluid and blood were negative. A urine toxicology screen was consistent with ar
intensive care unit, the patient recovered fully (Sierra-Biddle et al, 2000).
d) A 42-year-old man with a history of schizophrenia developed symptoms consistent with neuroleptic m
olanzapine therapy. At the onset of symptoms, the patient was also taking ranitidine, benztropine mesyla
respiratory distress, intermittent apnea, decreased mental status, fever (rectal temperature of 41 degrees
stimulus, rigid muscle tone, and dry mucous membranes. On admission, vital signs included a pulse of 1
111/79. Respiratory effort was absent. Laboratory tests revealed a serum creatinine phosphokinase (CP
hemoglobin 12.4 grams%, hematocrit 35%, serum sodium 141 millimoles/liter (mmol/L), blood urea nitro
creatinine 0.8 mg/dL. Olanzapine was discontinued. The patient was intubated and mechanically ventilat
bromocriptine and empiric antibiotic therapy. The patient's hospital course was complicated by pneumon
discharge, he demonstrated obvious cognitive deficits and left hemiplegia (Stanfield & Privette, 2000).
e) Other cases have reported only elevations in serum creatine kinase without other symptoms of NMS

3.4 Teratogenicity/Effects in Pregnancy/Breastfeeding

A) Teratogenicity/Effects in Pregnancy

1) U.S. Food and Drug Administration's Pregnancy Category: Category C (Prod Info ZYPREXA(R) oral tablets, IM
disintergating tablets, 2008) (All Trimesters)

a) Either studies in animals have revealed adverse effects on the fetus (teratogenic or embryocidal or other)
studies in women and animals are not available. Drugs should be given only if the potential benefit justifies th

2) Australian Drug Evaluation Committee's (ADEC) Category: B3(Australian Drug Evaluation Committee, 1999)

a) Drugs which have been taken by only a limited number of pregnant women and women of childbearing ag
malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in a
occurrence of fetal damage, the significance of which is considered uncertain in humans.

See Drug Consult reference: PREGNANCY RISK CATEGORIES

3) Crosses Placenta: Yes

4) Clinical Management

a) There is insufficient evidence to clearly establish the safety of olanzapine during pregnancy and it is recon
the potential benefit justifies the potential risk to the fetus (Prod Info ZYPREXA(R) oral tablets, IM injection, Z
2008). Limited data to date do not suggest an increased risk of major malformation (Aichhorn et al, 2008; Ern
notably, schizophrenic women may have higher prevalence rates of social and lifestyle behaviors (e.g. smoki
status) associated with risky neonatal outcomes (Patton et al, 2002). Patients with histories of chronic psycho
maintained on medication therapy throughout gestation, as these patients and their fetuses represent a high

5) Literature Reports

a) A prospective, observational study of 54 women (mean age, 30.7 years), recruited from the Emory Wome
antipsychotic medication during pregnancy, showed permeability of the placental barrier. Outcomes were det
samples taken at delivery and through data collected from maternal reports and medical records. Placental p
to maternal plasma concentrations) showed a significant difference between antipsychotic medications, with
the highest, followed by haloperidol 65.5% (95% CI, 40.3%-90.7%), risperidone 49.2% (95% CI, 13.6%-84.8%
showing the lowest placental passage ratio. There was a greater frequency of pre-term deliveries (21.4%, p=
than 0.07), and neonatal intensive care admission (30.8%, p=less than 0.09) in infants exposed to olanzapine
b) There are no adequate and well-controlled studies with olanzapine use during pregnancy. Seven pregnan
which resulted in 2 normal births, 1 neonatal death due to cardiovascular defect, 3 therapeutic abortions and
oral tablets, IM injection, ZYPREXA(R) ZYDIS(R) orally disintergating tablets, 2008). However, in 23 prospec
in risk of spontaneous abortion, stillbirth, prematurity, or major malformation in those infants exposed to olanz
expanded data from this latter report produced similar conclusions; data included 96 pregnancies, among wh
spontaneous abortions, 2.1% in premature deliveries, 3.1% in stillbirths, and 1% in major malformation (Ernst
assess the fetal safety of atypical antipsychotics, interim results from 32 exposures to risperidone, olanzapine
births with no malformations, 3 spontaneous abortions, 2 stillbirths, and 7 therapeutic abortions (McKenna et
c) Occasional spontaneous case reports of in utero exposure to olanzapine have produced viable newborns,
established (Mendhekar et al, 2002; Nagy et al, 2001; Littrell et al, 2000; Kirchheiner et al, 2000). A case repo
blood) level of 11 nanograms (ng)/mL compared with 34 ng/mL in the maternal plasma drawn before birth in a
mg during pregnancy. During gestation, the maternal olanzapine plasma levels were between 25 and 34 ng/m
only complication being gestational diabetes which was resolved with diet. Delivery was uncomplicated and h
normally during the first 6 months (Aichhorn et al, 2008).
d) In another case report, a 37-year-old woman with a 7-year history of paranoid schizophrenia gave birth to
25 mg/day starting at week 8 until week 32 when she discontinued it against medical advice. She had not be
preceding her pregnancy (Lim, 2001). An isolated case of maternal use of up to 20 mg of olanzapine and 2 m
gestation until 10 days prior to delivery has been reported. In this case, a healthy baby was delivered with Ap
minutes; at 3 months of age, the infant showed age-appropriate milestones (Mendhekar et al, 2002). A single
the 18th week of pregnancy through delivery and during breastfeeding also exists. Delivery was uncomplicate

months of age, the infant showed no abnormal findings at 11 months of age (Kirchheiner et al, 2000).

B) Breastfeeding

1) Thomson Lactation Rating: Infant risk cannot be ruled out.

a) Available evidence and/or expert consensus is inconclusive or is inadequate for determining infant risk wh benefits of drug treatment against potential risks before prescribing this drug during breastfeeding.

2) Clinical Management

a) Limited data from studies of nursing mothers treated with olanzapine have demonstrated that olanzapine i ZYPREXA(R) oral tablets, IM injection, ZYPREXA(R) ZYDIS(R) orally disintergating tablets, 2008; Gardiner e described jaundice, cardiomegaly, somnolence, and a heart murmur in the infant of a mother receiving olanza after bottle-feeding was initiated on day 7 of life. Another case from the same report demonstrated no advers olanzapine doses at 2 months of age (Goldstein et al, 2000a). Undetectable infant olanzapine plasma levels (32.8 to 39.5 nanograms/mL were reported in another case (Kirchheiner et al, 2000a). Because olanzapine ha it is recommended that women treated with olanzapine should not breast-feed (Prod Info ZYPREXA(R) oral t disintergating tablets, 2008).

3) Literature Reports

a) In a study of healthy, nursing women, olanzapine was excreted in breast milk. The estimated mean infant olanzapine dose (Prod Info ZYPREXA(R) oral tablets, IM injection, ZYPREXA(R) ZYDIS(R) orally disintergati to 20 mg/day of olanzapine, the median infant dose ingested through breast milk was approximately 1% (Gar plasma samples from five nursing mothers treated with olanzapine 2.5 mg to 10 mg daily, milk-to-plasma rati theoretical value of 0.38 that was determined using the known pharmacokinetic parameters of the drug. Base and assuming 100% bioavailability, relative infant dose was estimated to be 0% to 2.5% of the weight-adjuste report, breast milk was collected by an electric pump and olanzapine concentrations were measured by gas c olanzapine was excreted in the breast milk in relatively small amounts. Breast milk/plasma concentration ratio

b) Limited data from cases of olanzapine exposure via breast milk fail to affirm or eliminate the potential for a described an infant exposed in utero to olanzapine (maternal dose 5 mg/day) who was born with cardiomega However, jaundice and sedation continued despite the initiation of bottle-feeding on day seven of life. In the s months of age (maternal dose 10 mg/day) had no adverse effects (Goldstein et al, 2000a). Another case repo plasma levels (less than 2 ng/mL) despite maternal steady-state trough levels of 32.8 to 39.5 nanograms/mL throughout pregnancy and during breastfeeding (Kirchheiner et al, 2000a).

4) Drug Levels in Breastmilk

a) Parent Drug

1) Milk to Maternal Plasma Ratio

a) 0.2 to 0.84 (mean 0.46) (Buist & A, 2001; Croke et al, 2002)

3.5 Drug Interactions

Drug-Drug Combinations

Drug-Food Combinations

3.5.1 Drug-Drug Combinations

Activated Charcoal

Belladonna

Belladonna Alkaloids

Betel Nut

Carbamazepine

Ciprofloxacin

Clomipramine

Dehydroepiandrosterone

Eszopiclone

Fluvoxamine

Haloperidol

Levodopa

Levomethadyl

Lithium

Mirtazapine

Phenylalanine

Ritonavir

St John's Wort

Tetrabenazine

Tramadol

3.5.1.A Activated Charcoal

1) Interaction Effect: decreased bioavailability of olanzapine
2) Summary: Activated charcoal reduces the maximum concentration and area under the concentration-time Zyprexa(R), 1999b). This drug interaction may make activated charcoal useful in cases of olanzapine overdo
3) Severity: minor
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Do not administer activated charcoal and olanzapine concomitantly.
7) Probable Mechanism: binding of olanzapine in the gut

3.5.1.B Belladonna

1) Interaction Effect: excessive anticholinergic activity (severe dry mouth, constipation, decreased urination,
2) Summary: The anticholinergic activity of the active alkaloids present in belladonna may predispose the pa with olanzapine. Belladonna contains L-hyoscyamine, atropine, and scopolamine with a total alkaloid content (Blumenthal et al, 1998). Because belladonna is typically available as a homeopathic preparation, the clinical unknown. Caution is advised.
3) Severity: minor
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Excessive anticholinergic activity may be manifested by dry mouth, constipation, ur mydriasis, blurred vision, elevated temperature, muscular weakness, and sedation. If such effects are noted, severe cases, paralytic ileus, confusion, psychoses, agitation, delusions, delirium, and paranoia may be encc hypertension. In severe cases, immediate medical attention should be obtained.
7) Probable Mechanism: additive anticholinergic effect

3.5.1.C Belladonna Alkaloids

1) Interaction Effect: excessive anticholinergic activity (severe dry mouth, constipation, decreased urination,
2) Summary: The anticholinergic activity of the active alkaloids present in belladonna may predispose the pa with olanzapine. Belladonna contains L-hyoscyamine, atropine, and scopolamine with a total alkaloid content (Blumenthal et al, 1998). Because belladonna is typically available as a homeopathic preparation, the clinical unknown. Caution is advised.
3) Severity: minor
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Excessive anticholinergic activity may be manifested by dry mouth, constipation, ur mydriasis, blurred vision, elevated temperature, muscular weakness, and sedation. If such effects are noted, severe cases, paralytic ileus, confusion, psychoses, agitation, delusions, delirium, and paranoia may be encc hypertension. In severe cases, immediate medical attention should be obtained.
7) Probable Mechanism: additive anticholinergic effect

3.5.1.D Betel Nut

1) Interaction Effect: increased extrapyramidal side effects of olanzapine (difficulty with movement or abnorm

2) Summary: Case reports have described increased extrapyramidal side effects when betel nut was chewe for schizophrenia (Deahl, 1989a). The extrapyramidal effects were not improved with anticholinergic therapy discontinuation (Deahl, 1989a). A similar effect may occur if betel nut is chewed with concomitant olanzapine been attributed to the arecoline content. When given with peripheral anticholinergics, arecoline increased the (Nutt et al, 1978a). Case reports suggest the onset of betel nut activity to be within 3 weeks with resolution w 1989a).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: It is unclear to what extent the cholinergic effect of betel nut may increase the incid especially if patients are treated with anticholinergic agents to control these side effects. Deterioration in sym extrapyramidal movement disorders may be expected. Persons who have been chewing betel nut have a cha the clinician discover betel nut use.
7) Probable Mechanism: cholinergic effect of betel nut
8) Literature Reports
a) Within 3 weeks of initiating betel nut chewing, a 51-year-old Indian man experienced marked rigidity, been stabilized for the previous 2 years on fluphenazine decanoate depot 50 milligrams (mg) every 3 we daily for a mild Parkinsonian tremor. Within one week of discontinuation of betel nut chewing, the patient appears to demonstrate decreased anticholinergic effects of procyclidine when coadministered with bete
b) Following betel nut ingestion, a 45-year-old Indian man developed akathisia, tremor and stiffness whi 20 mg daily of procyclidine. This patient had been previously stabilized on fluphenthixol 60 mg depot eve schizoaffective disorder without extrapyramidal side effects. His symptoms resolved over 4 days after dis anticholinergic effects of procyclidine were diminished when betel nut was chewed concomitantly (Deahl
c) High doses (5 mg, 10 mg, and 20 mg) of subcutaneous (SC) arecoline given one hour after SC admi agent methscopolamine increased the heart rate and blood pressure of six patients with Huntington's dis occurred at doses of 5 mg, 10 mg (p less than 0.01) and 20 mg (p less than 0.05). Heart rate increased 10 mg (p less than 0.05). Subjective effects in some patients included tremor, flushing or pallor at the tim mental changes at the higher doses. No peripheral cholinergic effects were noted. The results indicated 1978).
d) A low dose (0.5 mg) of arecoline given intravenously 3 minutes after the peripheral anticholinergic ag depressive disorder increased their heart rates. The peak heart rate increase in a non-REM portion of th period was 6.75 +/- 12.9 beats per minute for placebo and 25 +/- 10.3 beats per minute for arecoline. Th the arecoline infusion, and the mean heart rate was significantly elevated over placebo from 2 to 10 minu (Abramson et al, 1985).
e) Though chewing betel nut alone does not significantly increase catecholamine levels, a popular betel chewing betel nut, 4 subjects had only a moderate increase in plasma noradrenaline from 266.2 +/- 105. pg/mL (p equal to 0.0607). Combining betel nut with lime, catechu and Piper betel flower as is commonly norepinephrine in nine subjects from 292.2 +/- 59.5 pg/mL to 375.1 +/- 130.0 pg/mL (p equal to 0.0244) a +/- 45.0 pg/mL (p equal to 0.0226). In this group dopamine was also elevated in 8 of 9 subjects, but the

3.5.1.E Carbamazepine

1) Interaction Effect: reduced olanzapine efficacy
2) Summary: Carbamazepine induces CYP1A2 mediated oxidation. Concomitant administration of olanzapin increased the clearance of olanzapine by 50% (Prod Info Zyprexa(R), 1999a). Higher daily doses of carbama olanzapine clearance. In a study of 11 healthy volunteers, concurrent administration of olanzapine and carba clearance (Lucas et al, 1998). Because patients respond to a relatively wide range of olanzapine serum conc patterns and changes is necessary whenever carbamazepine is added to or withdrawn from olanzapine thera most likely be highly patient specific (Licht et al, 2000a).
3) Severity: moderate
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Monitor patients for olanzapine efficacy. Doses of olanzapine may need to be adjus
7) Probable Mechanism: induction of cytochrome P450 1A2-mediated olanzapine metabolism
8) Literature Reports
a) A 23-year-old paranoid schizophrenic female was admitted to the hospital for treatment of hallucinati admission was perphenazine 12 mg daily, but carbamazepine 600 mg daily was initiated for aggressive risperidone 6 mg daily due to akathisia, rigidity, and tremor, but risperidone was also discontinued due to daily was started and her psychiatric symptoms improved over the next three weeks. Because her aggre was discontinued due to lack of efficacy. She had received cotherapy with olanzapine 15 mg daily and c weeks. The day prior to carbamazepine discontinuation, the patient's olanzapine serum concentration wa weeks, her olanzapine concentration increased by 114% to 45 ng/mL. The dose of olanzapine was decre olanzapine level occurred. This case report suggests that carbamazepine induces the metabolism of ola 1A2 enzyme system (Licht et al, 2000).

3.5.1.F Ciprofloxacin

1) Interaction Effect: an increased risk of olanzapine toxicity (increased sedation, orthostatic hypotension)
2) Summary: Ciprofloxacin was suspected of inhibiting the metabolism of olanzapine in a 54-year-old female 1A2 (CYP1A2) has been shown in vitro to be responsible for the formation of some of the metabolites of olan

inhibitor of CYP1A2. Although olanzapine has a wide therapeutic range and a correlation between plasma co established, this interaction may be clinically significant (Markowitz & DeVane, 1999a).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Patients receiving olanzapine and ciprofloxacin concurrently should be monitored fo increased sedation and orthostatic hypotension.
7) Probable Mechanism: inhibition by ciprofloxacin of cytochrome P450 1A2-mediated olanzapine metabolis
8) Literature Reports
a) A 54-year-old female was admitted to the hospital with suicidal ideation and lacerations to her wrists. 10 mg at bedtime, nefazodone 100 mg twice daily, atenolol 25 mg daily, levothyroxine 0.25 mg daily, and tapered off prior to electroconvulsive therapy, and ciprofloxacin 250 mg twice daily for seven days was in Immediately before her last dose of ciprofloxacin, the plasma olanzapine concentration was 32.6 ng/mL. her olanzapine concentration had decreased by more than 50% to 14.6 ng/mL. Although this patient did increased olanzapine level, higher doses of ciprofloxacin could potentially cause more inhibition of olanz

3.5.1.G Clomipramine

1) Interaction Effect: an increased risk of seizures
2) Summary: Psychotropic drugs have been shown to reduce the seizure threshold. A case report describes who received treatment with olanzapine and clomipramine concomitantly. This combination resulted in seizur olanzapine and clomipramine. It is advised to use caution when administering olanzapine concomitantly with seizure threshold (Deshauer et al, 2000a).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: It is advised to use caution when administering olanzapine concomitantly with clom seizure threshold.
7) Probable Mechanism: unknown
8) Literature Reports
a) A 34-year-old male with schizophrenia and obsessive-compulsive disorder (OCD) without any underly following long-term noncompliance. Inpatient olanzapine treatment (20 mg/day) was initiated and positive Patient was discharged and readmitted because of inability to control symptoms. Clomipramine 250 mg myoclonic jerks were reported which quickly progressed to general motor seizures and postictal somnole paroxysmal slowing on the EEG was consistent with seizure activity. Clomipramine and olanzapine were controlled with diazepam 30 mg per day for three days. This pattern repeated upon re-challenge with the Presumably from the temporal relationship between clomipramine and olanzapine administration and sei adverse event is due to an interaction between these two drugs. Clomipramine and olanzapine are both 1A2 and 2D6. One theory is that coadministration may result in elevated levels of both compounds. Altho occurs is not yet known, it is advised to use caution when administering olanzapine concomitantly with cl seizure threshold (Deshauer et al, 2000).

3.5.1.H Dehydroepiandrosterone

1) Interaction Effect: reduced effectiveness of olanzapine
2) Summary: Dehydroepiandrosterone (DHEA) levels within the normal range of 100 to 400 microgram/decil patients with psychosis (Howard, 1992a). In case reports, patients have been resistant to antipsychotics whe Patients being treated with olanzapine should avoid DHEA supplementation.
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Avoid concomitant use of dehydroepiandrosterone (DHEA) and olanzapine. If DHE orally per day may be used to normalize DHEA levels.
7) Probable Mechanism: elevated dehydroepiandrosterone (DHEA) blood levels may reduce responsiveness
8) Literature Reports
a) A 24-year-old female diagnosed with schizophrenia was resistant to daily doses of haloperidol 20 mill carbonate 1200 mg, and lithium carbonate 900 mg plus thioridazine 300 mg. The patient appeared Cush hair, and a 40 pound weight gain in the previous 8 months. Dehydroepiandrosterone (DHEA) measured micrograms/deciliter (mcg/dL) (normal: 100 to 400 mcg/dL). Dexamethasone 1 mg orally at bedtime resu The patient appeared calmer, more alert with improved psychotic symptoms and ability to concentrate. A normal range (328 mcg/dL). The author concluded that elevated DHEA levels were associated with seve therapy (Howard, 1992).
b) A 13-year-old male decompensated with a subsequent two-year period of emotional problems accom and alcohol. His mental status included bizarre, disorganized, delusional thinking, auditory and visual ha hygiene, agitation, and combativeness. He was diagnosed with chronic paranoid schizophrenia; schizopl schizoaffective disorder, excited type. He was resistant to daily doses of trifluoperazine 40 mg, chlorpron also resistant to combination therapy with chlorpromazine 400 mg with thiothixene 80 mg, thioridazine 1(1200 mg, clonazepam 4 mg, and carbamazepine 1200 mg daily. Baseline DHEA level exceeded 900 mc dexamethasone 1 mg orally at bedtime resulted in a normal DHEA level of 200 mcg/dL. By day 5, psych conversational, and was making good eye contact. Once dexamethasone was discontinued, rapid decor

"substantial amounts of psychotropic medications". DHEA increased to 536 mcg/dL. The author conclud florid psychosis resistant to conventional antipsychotic therapy (Howard, 1992).

3.5.1.I Eszopiclone

1) Interaction Effect: decreased psychomotor function

2) Summary: Coadministration of 3 mg eszopiclone and 10 mg olanzapine resulted in the pharmacodynamic Substitution Test scores, a measurement of psychomotor function. No pharmacokinetic interactions were obs function (Prod Info LUNESTA(TM), 2004).

3) Severity: minor

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Monitor patients for decreased psychomotor function. Adjust dose accordingly or co

7) Probable Mechanism: unknown

3.5.1.J Fluvoxamine

1) Interaction Effect: an increased risk of olanzapine adverse effects

2) Summary: Fluvoxamine inhibits cytochrome P450 1A2 enzymes and may inhibit olanzapine elimination (P significance of this interaction is unknown since olanzapine is metabolized by multiple enzyme systems.

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Monitor patients for excessive olanzapine adverse effects (orthostatic hypotension,

7) Probable Mechanism: inhibition of olanzapine elimination

8) Literature Reports

a) A patient experienced elevated olanzapine plasma levels during coadministration of fluvoxamine. The several months for schizophrenia and secondary depression. She appeared to move rigidly, had a slight concentration was 120 mcg/L and fluvoxamine concentration was 70 mcg/L. Olanzapine was decreased Fourteen days after the last decrease in dose, olanzapine plasma levels were 38 mcg/L. Tremor and rigi Fluvoxamine was replaced by paroxetine which resulted in paroxetine concentration of 0.027 mg/L and c al, 2001).

b) Addition of fluvoxamine to olanzapine therapy may result in olanzapine-induced side effects or intoxic being treated for not less than 3 months with 10-20 mg/day of olanzapine. The dose of olanzapine was u study and remained stable throughout the study period. Fluvoxamine 100 mg/day was added to olanzapi continued for 8 weeks. Olanzapine concentrations increased during fluvoxamine treatment 1.58-fold from 4, and 1.81-fold from week 0 to week 8. Percentage change from week 0 to week 8 ranged from 12% to metabolite were not significantly changed. Even though all eight patients had higher olanzapine blood se ratio of increase of olanzapine blood serum concentrations from week 0 to week 8 did not correlate signi than 0.05). This study confirmed that the addition of fluvoxamine to a stable dose of olanzapine increase Combined olanzapine and fluvoxamine should be used cautiously and controlled clinically and by therap side effects or intoxication (Hiemke et al, 2002).

3.5.1.K Haloperidol

1) Interaction Effect: an increased risk of parkinsonism (cogwheeling rigidity, unstable gait)

2) Summary: A patient receiving haloperidol experienced extreme parkinsonism following the addition of olar pharmacokinetic interaction between olanzapine, a weak cytochrome P450 2D6 (CYP2D6) inhibitor, and halo Pharmacodynamically, the small amount of dopamine (D2) blockade from olanzapine may have been enough 1999a).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Patients should be closely monitored for signs and symptoms of increased parkinso haloperidol therapy. Doses of haloperidol may need to be decreased.

7) Probable Mechanism: competitive inhibition of cytochrome P450 2D6-mediated haloperidol metabolism; ir

8) Literature Reports

a) A 67-year-old hospitalized male with bipolar disorder who had stopped taking his medications was re mg nightly, and valproate 750 mg twice daily. He had been experiencing some mild parkinsonian sympto worsen when haloperidol was reinstituted. Following stabilization on this regimen, it was decided to chan minimize any parkinsonism that was a result of his medications. While tapering the haloperidol and initiat parkinsonism that resulted in an inability to walk. His mental status remained unchanged. Haloperidol wa and two days later the patient's parkinsonism side effects had resolved back to baseline. Benztropine wa symptoms did not reoccur while on olanzapine (Gomberg, 1999).

3.5.1.L Levodopa

1) Interaction Effect: decreased levodopa effectiveness

2) Summary: Concurrent use of olanzapine may antagonize the pharmacological effects of levodopa (Prod I this interaction is unknown.

3) Severity: moderate

4) Onset: rapid

5) Substantiation: theoretical
6) Clinical Management: Monitor patients for levodopa efficacy.
7) Probable Mechanism: pharmacological antagonism

3.5.1.M Levomethadyl

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Any drug known to have the potential to prolong the QT interval should not be used with levom can occur between levomethadyl and potentially arrhythmogenic agents such as olanzapine that prolong the
3) Severity: contraindicated
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Levomethadyl is contraindicated in patients being treated with olanzapine as it may levomethadyl.
7) Probable Mechanism: additive cardiac effects

3.5.1.N Lithium

1) Interaction Effect: weakness, dyskinesias, increased extrapyramidal symptoms, encephalopathy, and brai
2) Summary: An encephalopathic syndrome followed by irreversible brain damage has occurred in a few pat antagonist, particularly haloperidol. A causal relationship between these events and the concomitant adminis not been established (Prod Info LITHOBID(R) slow-release oral tablets, 2005). Coadministration of lithium an wide variety of encephalopathic symptoms, brain damage, extrapyramidal symptoms, and dyskinesias in isol have occurred with therapeutic lithium levels (Amdisen, 1982; Prakash, 1982; Addonizio et al, 1988a). Howev such combinations with no severe adverse consequences (Goldney & Spence, 1986). The mechanism is not decreases neostriatal dopaminergic activity, probably through a direct action on the G protein and the capaci adenyl cyclase (Carli et al, 1994). Hyperglycemic reactions have also occurred during combined phenothiazir
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor patients closely for any signs of toxicity or extrapyramidal symptoms, espec particularly haloperidol, and lithium are used. Serum lithium levels should be monitored periodically. Some cli therapeutic range.
7) Probable Mechanism: unknown
8) Literature Reports

a) Concomitant haloperidol and lithium therapy has resulted in symptoms of encephalopathy, confusion, patients with mania (Cohen & Cohen, 1974; Loudon & Waring, 1976; Thomas, 1979). Irreversible neurol Hurwitz, 1983; Keitner & Rahman, 1984).

b) Seizures, encephalopathy, delirium, and abnormal EEG occurred in four patients during combined lit Serum lithium levels were below 1 mEq/L at the time of the toxic reaction in all cases. All patients had pr another phenothiazine. Three of these patients developed symptoms within eight days of initiating combi

c) The addition of lithium to neuroleptic therapy exacerbated extrapyramidal symptoms (EPS) in a small received at least five days of treatment with either oral thiothixene, haloperidol, or fluphenazine in mean initiation of the lithium and were experiencing drug-induced extrapyramidal symptoms. Oral lithium was a achieve a therapeutic serum concentration. The maximum levels attained were 0.65 to 1.27 mEq/L. The the addition of lithium. However, only three patients developed marked symptoms and no patient develo symptoms included gait, shoulder shaking, elbow rigidity, and tremor.

d) Ten patients treated with clozapine and lithium were studied (Blake et al, 1992). Of the ten patients, f including jerking of limbs, facial spasms and tics, tremor of hands and arms, tongue twitching, and stumb These effects reversed when lithium was discontinued or given at a lower dose. On rechallenge, one of t keeping serum lithium no greater than 0.5 mEq/L, clozapine could be safely coadministered.

e) Chlorpromazine serum levels can be significantly reduced in the presence of lithium treatment. If use result in rebound elevation of chlorpromazine levels, resulting in chlorpromazine toxicity. In patients on a withdrawal of the lithium may precipitate chlorpromazine cardiotoxicity. In this report, such toxicity was m associated with prolongation of the QTc interval. Hypotension and EPS are also possible in this situation

f) However, other data do not support that such adverse events are frequent or indeed causally related antagonist antipsychotic drugs and lithium have been used successfully in many patients with manic-dep interaction may only become significant with very high doses of one or both drugs or with failure to disco (Miller & Menninger, 1987).

g) A 69-year-old patient with oxygen-dependent chronic obstructive pulmonary disorder and a 25-year h 3 mg for the treatment of new-onset auditory and visual hallucinations. She had also been maintained or 10 years. In addition, she was given amantadine (100 mg twice daily) for tremor. Three weeks after the s decline in mental status in addition to dizziness, worsening tremors, nausea and vomiting, polyuria, depr was then admitted to the hospital for delirium. Her lithium serum level was 1.36 mEq/L at the time of the Although her lithium level decreased to 0.41 mEq/L, she continued to experience profound delirium, trem week. After she started to respond to commands, she was restarted on lithium (300 mg at bedtime) beca later, she was discharged with a regimen of lithium and low-dose lorazepam for treatment of insomnia. It by the concurrent use of lithium and risperidone. Other factors could also have caused delirium, such as pulmonary pathology. In addition, amantadine, which facilitates the release of presynaptic dopamine and contributed (Chen & Cardasis, 1996).

3.5.1.O Mirtazapine

1) Interaction Effect: an increased risk of serotonin syndrome

2) Summary: Concurrent use of olanzapine with mirtazapine and tramadol in a 53-year-old male resulted in s
Fetchko, 2002). If olanzapine is used concomitantly with mirtazapine and/or tramadol, monitor closely for sym
can be life-threatening. If serotonin syndrome develops, discontinue the offending agents and provide suppor
Shannon, 2005).

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: A case of serotonin syndrome was reported with coadministration of olanzapine, mi
If 2 or more of these drugs are are used concomitantly, monitor closely for symptoms of serotonin syndrome
hyper-reflexia, tremor, muscle rigidity, clonus, peripheral hypertonicity, and shivering), autonomic hyperactivit
the presence of bowel sounds, and diarrhea), and mental status changes (including agitation and delirium). S
serotonin syndrome develops, discontinue the offending agents and provide supportive care and other therap

7) Probable Mechanism: additive serotonergic pharmacologic effects

8) Literature Reports

a) A 53-year-old male on mirtazapine and tramadol experienced serotonin syndrome 8 days after olanza
mirtazapine 45 mg/day for depression and tramadol 150 mg/day for chronic back pain. Olanzapine 10 m
admitted 8 days later after being found by the police wandering the streets in inappropriate dress and in
tachycardic (120 bpm), and had flushing, twitching of his face, tremors, myoclonus, hyperreflexia, and ar
spoke with a stutter. He had marked derailment, appeared perplexed, had prominent perceptual abnorm
The creatine phosphokinase was normal. All medications were discontinued and within 12 hours he sign

3.5.1.P Phenylalanine

1) Interaction Effect: increased incidence of tardive dyskinesia

2) Summary: Taking phenylalanine concomitantly with certain neuroleptic drugs may exacerbate tardive dysl
phenylalanine metabolism in certain patients may lead to phenylalanine accumulation in the brain and in turn
amino acids. This may interfere with the synthesis of catecholamines (Gardos et al, 1992a).

3) Severity: moderate

4) Onset: rapid

5) Substantiation: theoretical

6) Clinical Management: Caution is advised if phenylalanine is administered with a neuroleptic agent. Monito

7) Probable Mechanism: reduced brain availability of other large neutral amino acids and interference with ca

8) Literature Reports

a) Phenylalanine tended to increase the incidence of tardive dyskinesia in patients taking neuroleptics ir
studied: (1) patients with unipolar depression with tardive dyskinesia (n=11), (2) patients with no tardive
than or equal to 100 milligrams (mg) of a chlorpromazine equivalent for at least 3 months (n=10), and (3)
exposed to a neuroleptic drug (n=10). Neuroleptic agents were taken during the study by 6 patients in gr
powdered phenylalanine 100 mg/kilogram dissolved in orange juice after an overnight fast. Blood sample
administration and 2 hours after administration. Three patients in group 1 (with tardive dyskinesia) had th
this group as a whole had higher (though nonsignificant) mean phenylalanine levels than the other group
Abnormal Involuntary Movements Scale (AIMS)) nonsignificantly increased in group 1. Postloading phen
significantly positively correlated in group 1 (rs=0.347, p less than 0.05; Spearman correlation coefficient
phenylalanine level and baseline AIMS scores demonstrated a trend toward correlation (rs=0.246, p=0.0
than 0.05). In all patients, phenylalanine loading increased plasma phenylalanine levels approximately ei
as a result of conversion of phenylalanine to tyrosine. Plasma levels of competing large neutral amino ac
et al, 1992).

3.5.1.Q Ritonavir

1) Interaction Effect: reduced olanzapine effectiveness

2) Summary: An open-label study involving 14 healthy volunteers revealed a significant alteration in pharma
exposure of olanzapine when administered in the presence of ritonavir. Baseline blood samples were drawn
mg tablet. Venous blood samples were then obtained at specified times. After a 14-day washout period, subj
400 mg BID for 4 days, then 500 mg BID for 4 days. Blood samples were again drawn at specified times. On
follows: Statistically significant reductions in the mean olanzapine area under the plasma concentration-time
hr/mL) (p less than 0.001); the half-life by 50% (from 32 hr to 16 hr) (p less than 0.00001) and the peak plasm
ng/mL) (p less than 0.002). The oral clearance of olanzapine increased by 115% (from 20 L/hr to 43 L/hr) (p l
well-tolerated and a clear relationship between plasma concentrations and toxicity has not been defined, the
study (Penzak et al, 2002).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: Monitor patients for olanzapine efficacy. Doses of olanzapine may need to be adjus
Patients stabilized on olanzapine and ritonavir, who have their ritonavir discontinued, should have be monitor
systemic exposure to olanzapine.

7) Probable Mechanism: induction or CYP1A2- and glucuronosyl transferase-mediated metabolism of olanza

3.5.1.R St John's Wort

1) Interaction Effect: reduced olanzapine efficacy

2) Summary: This interaction is based on in vitro information that St. John's Wort induced CYP1A2 enzymes reduced blood theophylline concentrations and loss of efficacy (Nebel et al, 1999). Since olanzapine is metab olanzapine may be similarly affected. If St. John's Wort and olanzapine are taken together, their dosages sho increased dosages of olanzapine may be required. Discontinuation of St. John's Wort should be done careful dose reduction may be required.

3) Severity: moderate

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: Avoid concomitant use of olanzapine with St. John's Wort. If patients elect to remai consistent dosing. Olanzapine dosage may need to be increased. Patients should not discontinue St. John's downward adjustments in olanzapine dose may be necessary as well as monitoring for increased side effects constipation, dry mouth, asthenia).

7) Probable Mechanism: induction of cytochrome P450 1A2 enzymes by St. John's Wort

3.5.1.S Tetrabenazine

1) Interaction Effect: increased risk of QT interval prolongation, neuroleptic malignant syndrome, extrapyram

2) Summary: Tetrabenazine causes a small increase in the correct QT interval. As the degree of prolongatio torsade de pointes-type VT. The concomitant use of tetrabenazine with other drugs known for QT prolongatic randomized, double-blind, placebo controlled crossover study of healthy subjects, the effect of a single 25 mg was studied with moxifloxacin as a positive control. The 50 mg dose of tetrabenazine caused an approximate XENAZINE(R) oral tablets, 2008). In addition to QT prolongation, tetrabenazine may also cause adverse reac extrapyramidal disorders, which may be exaggerated when coadministered with neuroleptic drugs (eg, olanz

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Coadministration of tetrabenazine with olanzapine or other neuroleptic drugs may ir QT interval prolongation and increased risk of torsade de pointes. Other adverse reactions, such as neurolep disorders may be enhanced when given with a dopamine agonist such as olanzapine (Prod Info XENAZINE(

7) Probable Mechanism: increased dopamine levels; additive effects on QT interval prolongation

3.5.1.T Tramadol

1) Interaction Effect: an increased risk of serotonin syndrome

2) Summary: Concurrent use of olanzapine with mirtazapine and tramadol in a 53-year-old male resulted in s Fetchko, 2002). If olanzapine is used concomitantly with mirtazapine and/or tramadol, monitor closely for sym can be life-threatening. If serotonin syndrome develops, discontinue the offending agents and provide suppor Shannon, 2005).

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: A case of serotonin syndrome was reported with coadministration of olanzapine, mi If 2 or more of these drugs are are used concomitantly, monitor closely for symptoms of serotonin syndrome hyper-reflexia, tremor, muscle rigidity, clonus, peripheral hypertonicity, and shivering), autonomic hyperactivit the presence of bowel sounds, and diarrhea), and mental status changes (including agitation and delirium). S serotonin syndrome develops, discontinue the offending agents and provide supportive care and other therap

7) Probable Mechanism: additive serotonergic pharmacologic effects

8) Literature Reports

a) A 53-year-old male on mirtazapine and tramadol experienced serotonin syndrome 8 days after olanz mirtazapine 45 mg/day for depression and tramadol 150 mg/day for chronic back pain. Olanzapine 10 m admitted 8 days later after being found by the police wandering the streets in inappropriate dress and in tachycardic (120 bpm), and had flushing, twitching of his face, tremors, myoclonus, hyperreflexia, and ar spoke with a stutter. He had marked derailment, appeared perplexed, had prominent perceptual abnorm The creatine phosphokinase was normal. All medications were discontinued and within 12 hours he sign

3.5.2 Drug-Food Combinations

3.5.2.A Ethanol

1) Interaction Effect: excessive central nervous system depression

2) Summary: Coadministration of olanzapine and ethanol will potentiate the orthostatic hypotension observe ethanol (45 mg/70 kg) had no effect on olanzapine pharmacokinetics, these drugs should not be taken conco depressive effects of both drugs (Prod Info Zyprexa(R), 1999d).

3) Severity: moderate

4) Onset: rapid

5) Substantiation: theoretical

6) Clinical Management: Concurrent use of olanzapine and ethanol should be avoided if at all possible. If the should be used.

7) Probable Mechanism: additive central nervous system depression

4.0 Clinical Applications

Monitoring Parameters

Patient Instructions

Place In Therapy

Mechanism of Action / Pharmacology

Therapeutic Uses

Comparative Efficacy / Evaluation With Other Therapies

4.1 Monitoring Parameters

A) Therapeutic

1) Physical Findings

a) Improvement of schizophrenic symptoms on standard examination/testing

1) Positive symptoms (distortion of normal function) include hallucinations, irritability, delusions, incoher

2) Negative symptoms (loss or diminution of function) include blunted affect, emotional or social withdra

B) Toxic

1) Laboratory Parameters

a) Fasting blood glucose at beginning of treatment and periodically thereafter for patients with diabetes melli obesity, family history of diabetes) (Prod Info ZYPREXA(R) oral tablets, orally disintegrating tablets, IM inject

b) Fasting blood glucose for any patient who develops symptoms of hyperglycemia (Prod Info SYMBYAX(R)

c) Baseline and follow-up lipid panels are suggested (Prod Info ZYPREXA(R) oral tablets, orally disintegratin

d) Liver function tests periodically during therapy for patients with significant hepatic disease (Prod Info ZYP IM injection, 2007).

e) ECG at baseline and periodically during treatment (Pacher & Kecskemeti, 2004)

2) Physical Findings

a) Examination/questioning to detect extrapyramidal effects (ie, continuous pacing, restlessness, fine tremor Info ZYPREXA(R) oral tablets, orally disintegrating tablets, IM injection, 2007).

b) Temperature

c) Vital signs, especially during initial dose titration (Prod Info ZYPREXA(R) oral tablets, orally disintegrating

d) Assess for orthostatic hypotension, bradycardia, and hypoventilation, especially prior to subsequent intrar tablets, orally disintegrating tablets, IM injection, 2007).

e) Monitor body weight regularly during treatment (Prod Info ZYPREXA(R) oral tablets, orally disintegrating t

f) Monitor all patients for signs and symptoms of hyperglycemia (ie, polydipsia, polyuria, polyphagia, and wea hyperglycemia during atypical antipsychotic treatment should undergo fasting blood glucose testing. In some atypical antipsychotic was stopped; however, some patient required ongoing anti- diabetic treatment despite Info ZYPREXA(R) oral tablets, orally disintegrating tablets, IM injection, 2007).

g) Monitor patients for signs and symptoms of neuroleptic malignant syndrome (ie, hyperpyrexia, muscle rigi autonomic instability) (Prod Info ZYPREXA(R) oral tablets, orally disintegrating tablets, IM injection, 2007).

4.2 Patient Instructions

A) Olanzapine (By mouth)

Olanzapine

Treats psychotic mental disorders, such as schizophrenia or bipolar disorder (manic-depressive illness).

When This Medicine Should Not Be Used:
You should not use this medicine if you have had an allergic reaction to olanzapine.

How to Use This Medicine:
Tablet, Dissolving Tablet

Your doctor will tell you how much of this medicine to use and how often. Your dose may need to be changed for you. Do not use more medicine or use it more often than your doctor tells you to.
You may take this medicine with or without food.
If you are using the disintegrating tablet, make sure your hands are dry before you handle the tablet. Do not o you are ready to take it. Remove the tablet from the blister pack by peeling back the foil, then taking the table the tablet in your mouth. It should melt quickly. After the tablet has melted, swallow or take a drink of water.

If a Dose is Missed:

If you miss a dose or forget to use your medicine, use it as soon as you can. If it is almost time for your next d
the missed dose. Do not use extra medicine to make up for a missed dose.

How to Store and Dispose of This Medicine:

Store the medicine in a closed container at room temperature, away from heat, moisture, and direct light. Kee
until you are ready to take it.
Ask your pharmacist, doctor, or health caregiver about the best way to dispose of any leftover medicine after
need to throw away old medicine after the expiration date has passed.
Keep all medicine away from children and never share your medicine with anyone.

Drugs and Foods to Avoid:

Ask your doctor or pharmacist before using any other medicine, including over-the-counter medicines, vitamins, a

You must be careful if you are also using other medicine that might cause similar side effects as olanzapine.
pressure, overheating, or liver problems. Make sure your doctor knows about all other medicines you are usi
Make sure your doctor knows if you are also using carbamazepine (Tegretol®), fluoxetine (Prozac®), fluvoxa
omeprazole (Prilosec®), or rifampin (Rifadin®).
Make sure your doctor knows if you are also using medicine to treat high blood pressure (such as atenolol, h
quinapril, Accupril®, Cozaar®, Diovan®, Lotrel®, Norvasc®, Toprol®, Zestril®).
Make sure your doctor knows if you are using medicine to treat anxiety (such as alprazolam, diazepam, Valiu
medicines that make you sleepy. These include sleeping pills, cold and allergy medicine, narcotic pain relieve
Do not drink alcohol while you are using this medicine.
Tell your doctor if you smoke. You might need a different amount of this medicine if you smoke.

Warnings While Using This Medicine:

Make sure your doctor knows if you are pregnant or breastfeeding, or if you have diabetes, liver disease, pro
have a history of seizures, breast cancer, or severe constipation.
Make sure your doctor knows about any heart or blood problems you have now or have had in the past. This
Tell your doctor if you have ever had neuroleptic malignant syndrome (NMS) caused by any medicine for psy
This medicine may increase your cholesterol and fats in the blood. If this condition occurs, your doctor may g
of cholesterol and fats in the blood.
This medicine may increase your weight. Your doctor may need to check your weight regularly during treatm
This medicine may raise or lower your blood sugar, or it may cover up symptoms of very low blood sugar (hy
Your doctor will need to check your blood at regular visits while you are using this medicine. Be sure to keep
This medicine may make you dizzy or drowsy. Avoid driving, using machines, or doing anything else that cou
until you no longer feel dizzy. Get up slowly.
This medicine might reduce how much you sweat. Your body could get too hot if you do not sweat enough. If
tired, or confused. You might vomit or have an upset stomach. Do not get too hot while you are exercising. A
are too hot and cannot cool down.
Some side effects are more likely to happen in elderly people who have memory problems or other reduced r
person who will be using this medicine has Alzheimer's disease or similar problems (often called "dementia").
Zyprexa® Zydis® contains phenylalanine (aspartame). This is only a concern if you have a disorder called ph
have this condition, talk to your doctor before using this medicine.

Possible Side Effects While Using This Medicine:

Call your doctor right away if you notice any of these side effects:

Allergic reaction: Itching or hives, swelling in your face or hands, swelling or tingling in your mouth or throat, d
Blurred or other changes in vision.
Change in how much or how often you urinate.
Fast or uneven heartbeat.
Fever, sweating, confusion, muscle stiffness.
Increased restlessness or excessive movements.
Jerky muscle movement you cannot control (often in your face, tongue, or jaw).
Lightheadedness or fainting.
Numbness or weakness in your arm or leg, or on one side of your body.
Severe sleepiness, slurred speech, trouble breathing.
Shakiness, problems with balance or walking.
Swelling in your hands, ankles, or feet.
Swollen breasts, or liquid discharge from your nipples (men or women).
Trouble swallowing.

If you notice these less serious side effects, talk with your doctor:

Back pain.
Constipation, upset stomach.
Dry mouth, increased thirst, watering of mouth.
Increased appetite.
Missed menstrual period.
Redness or swelling in your eye.
Sleepiness or unusual drowsiness.

Stuffy or runny nose.
Trouble sleeping.
Weakness.
Weight gain.

If you notice other side effects that you think are caused by this medicine, tell your doctor.

B) Olanzapine (Injection)

Olanzapine

Treats an episode of agitation (being overexcited, tense, hostile, or anxious) in a person who has schizophrenia o

When This Medicine Should Not Be Used:
You should not use this medicine if you have had an allergic reaction to olanzapine.

How to Use This Medicine:
Injectable
Your doctor will prescribe your exact dose and tell you how often it should be given. This medicine is given as
A nurse or other trained health professional will give you this medicine.
If your doctor wants you to keep using this medicine, you will need to change to the oral (tablet) form.

Drugs and Foods to Avoid:
Ask your doctor or pharmacist before using any other medicine, including over-the-counter medicines, vitamins, a
You must be careful if you are also using other medicine that might cause similar side effects as olanzapine.
pressure, overheating, or liver problems. Make sure your doctor knows about all other medicines you are usi
Make sure your doctor knows if you are also using carbamazepine (Tegretol®), fluoxetine (Prozac®), fluvoxa
omeprazole (Prilosec®), or rifampin (Rifadin®).
Make sure your doctor knows if you are also using medicine to treat high blood pressure (such as atenolol, h
quinapril, Accupril®, Cozaar®, Diovan®, Lotrel®, Norvasc®, Toprol®, Zestril®).
Make sure your doctor knows if you are using medicine to treat anxiety (such as alprazolam, diazepam, Valiu
medicines that make you sleepy. These include sleeping pills, cold and allergy medicine, narcotic pain relieve
Do not drink alcohol while you are using this medicine.
Tell your doctor if you smoke. You might need a different amount of this medicine if you smoke.

Warnings While Using This Medicine:
Make sure your doctor knows if you are pregnant or breastfeeding, or if you have diabetes, liver disease, pro
have a history of seizures, breast cancer, or severe constipation.
Make sure your doctor knows about any heart or blood problems you have now or have had in the past. This
Tell your doctor if you have ever had neuroleptic malignant syndrome (NMS) caused by any medicine for psy
This medicine may increase your cholesterol and fats in the blood. If this condition occurs, your doctor may g
of cholesterol and fats in the blood.
This medicine may increase your weight. Your doctor may need to check your weight regularly during treatm
This medicine may raise or lower your blood sugar, or it may cover up symptoms of very low blood sugar (hy
Your doctor will need to check your blood at regular visits while you are using this medicine. Be sure to keep
This medicine may make you dizzy or drowsy. Avoid driving, using machines, or doing anything else that cou
until you no longer feel dizzy. Get up slowly.
This medicine might reduce how much you sweat. Your body could get too hot if you do not sweat enough. If
tired, or confused. You might vomit or have an upset stomach. Do not get too hot while you are exercising. A
are too hot and cannot cool down.
Some side effects are more likely to happen in elderly people who have memory problems or other reduced r
person who will be using this medicine has Alzheimer's disease or similar problems (often called "dementia")

Possible Side Effects While Using This Medicine:
Call your doctor right away if you notice any of these side effects:
Allergic reaction: Itching or hives, swelling in your face or hands, swelling or tingling in your mouth or throat, d
Blurred or other changes in vision.
Change in how much or how often you urinate.
Fast or uneven heartbeat.
Fever, sweating, confusion, muscle stiffness.
Increased restlessness or excessive movements.
Jerky muscle movement you cannot control (often in your face, tongue, or jaw).
Lightheadedness or fainting.
Numbness or weakness in your arm or leg, or on one side of your body.
Severe sleepiness, slurred speech, trouble breathing.
Shakiness, problems with balance or walking.
Swelling in your hands, ankles, or feet.
Swollen breasts, or liquid discharge from your nipples (men or women).
Trouble swallowing.

If you notice these less serious side effects, talk with your doctor:
Back pain.
Constipation, upset stomach.
Dry mouth, increased thirst, watering of mouth.
Increased appetite.
Missed menstrual period.
Pain where the shot is given.
Redness or swelling in your eye.
Sleepiness or unusual drowsiness.
Stuffy or runny nose.
Trouble sleeping.
Weakness.
Weight gain.

If you notice other side effects that you think are caused by this medicine, tell your doctor.

4.3 Place In Therapy

A) Current users of atypical antipsychotic drugs (including olanzapine) and typical antipsychotic drugs had a similar d according to a retrospective cohort of 93,300 adult users of antipsychotic drugs and 186,600 matched controls. The st 45.7 +/- 11.8 years) with similar cardiovascular risk at baseline who had at least one filled prescription and had 1 outpa cardiac death was defined as occurring in the community and excluded deaths of patients admitted to the hospital, no causes not related to ventricular tachyarrhythmia. Current use was defined as the interval between the time the prescr Low and high doses was defined as comparable to less than 100 milligrams (mg) of chlorpromazine, and doses compa respectively. The adjusted rate of sudden cardiac death (incidence-rate ratio) in current users of atypical antipsychotic 1.88 to 2.72, p less than 0.001) which was similar to the risk in current users of typical antipsychotic drugs in 86,735 p p less than 0.001). The risk of sudden cardiac death in current olanzapine users in 27,257 person-years was 2.04 (95 sudden cardiac death significantly increased with increasing dose in both the typical and atypical antipsychotic drug gr rate ratio increased from 1.59 (95% CI, 1.03 to 2.46) in low-dose use to 2.86 (95% CI, 2.25 to 3.65) in high-dose use. results, there was a secondary analysis performed in a cohort of patients matched by propensity score, which resulted cohort analysis (Ray et al, 2009). In an editorial in The New England Journal of Medicine, it has been suggested that a with clear evidence of benefit, but in vulnerable populations with cardiac risk profiles (eg, elderly patients), there shoul administration. It has also been suggested (although not formally tested) that ECGs be performed before and shortly a existing or emergent QT interval prolongation (Schneeweiss & Avorn, 2009).

B) Clinical effects of olanzapine appear similar to those of clozapine in schizophrenic patients. Olanzapine when com symptoms and is associated with a lower incidence of extrapyramidal effects. Olanzapine has been shown to be supe suggest the possibilities that maintenance of long-term response may be better than haloperidol (Beasley et al, 1997; more expensive than haloperidol, however, savings have been demonstrated that make the 2 agents approximately e These include olanzapine's reduced need for medical services due to lower relapse rates and its greater efficacy in all

C) Olanzapine offers a potential advantage over clozapine as it does not appear to cause severe neutropenia or agra clozapine are a lower propensity to induce orthostatic hypotension, tachycardia, seizures, and hyperthermia, although clinical trials. Clozapine is primarily indicated in severely disturbed patients who are refractory to typical antipsychotics symptoms (including tardive dyskinesia) related to other agents. Olanzapine may have a similar role, although further imposed by a risk of agranulocytosis, indications for olanzapine may be extended (eg, first-line therapy in some types psychosis are needed (eg, schizoaffective disorders, psychotic mood disorders, major depression with psychotic featu Olanzapine is effective for treating schizophrenia and has a favorable adverse effect profile (Bever & Perry, 1998).

See Drug Consult reference: CHEMOTHERAPY AND RADIOTHERAPY TREATMENT GUIDELINES FOR NAUSEA A
See Drug Consult reference: FIRST- VS SECOND-GENERATION ANTIPSYCHOTIC AGENTS FOR SCHIZOPHREN

4.4 Mechanism of Action / Pharmacology

A) MECHANISM OF ACTION

1) Olanzapine is an antipsychotic agent (thienobenzodiazepine derivative) structurally similar to clozapine. Pharm those of clozapine, and both agents are classified as "atypical" antipsychotic agents mainly by virtue of their effica schizophrenia and lower propensity for extrapyramidal effects compared to conventional or typical antipsychotics A disadvantage of clozapine is its ability to induce agranulocytosis in up to 2% of patients; olanzapine was primari alternative (Anon, 1994; AMA Department of Drugs, 1994).

2) Similar to clozapine, olanzapine is both a dopamine (D) and serotonin (5-HT) antagonist; both compounds hav mediated than D-mediated responses (Moore et al, 1992; Fuller & Snoddy, 1992). Receptor binding studies have D4, 5-HT2A, and 5-HT2C receptors, as well as histamine-1, alpha-1 adrenergic, and muscarinic (particularly M1) 1994a; Higgins, 1993). The drug binds more potently to the 5-HT2A receptor than the D2 receptor (3-fold); greate been reported (Tollefson et al, 1994; Fuller & Snoddy, 1992; Beasley et al, 1996). Results of neuroendocrine stud potent than clozapine with respect to blockade of 5-HT2 and D2 receptors (Fuller & Snoddy, 1992).

3) Olanzapine induces near saturation of the 5-HT(2) receptor at all doses (Kapur et al, 1998). Even a dose of 5 m (2) occupancy, however, is dose-related:

DOSE	D(2) RECEPTOR OCCUPANCY
5 mg/day	55%
10 mg/day	73%

15 mg/day	75%
20 mg/day	76%
20 mg/day	83%

4) D(2) receptor occupancy was measured at 88% in a single patient taking olanzapine 40 mg/day.

B) REVIEW ARTICLES

1) A review of the side effects of antipsychotic medications, including olanzapine, in the elderly is available. Of pa incidence of sedation and abnormal gait which can lead to falls and other accidents (Masand, 2000).

2) Reviews of the adverse effects related to olanzapine are available. The management of these side effects, inc appetite, and weight gain is discussed (Zarate, 2000). Safety data from comparative clinical trials is also available

3) Comprehensive reviews on olanzapine have been published (Tollefson & Kuntz, 1999; Falsetti, 1999; Bever &

4) The pharmacologic properties and therapeutic efficacy of olanzapine in the management of psychoses are rev

5) An indepth overview of the efficacy of olanzapine in clinical trials has been published (Beasley et al, 1997).

6) A review of clinical trails evaluating olanzapine dosing is available (Nemeroff, 1997).

7) A study reviewing the safety profile of olanzapine has been published (Beasley et al, 1997a).

8) The use of atypical antipsychotic medications in adults (Markowitz et al, 1999; Brown et al, 1999), older adults 1999; Lewis, 1998; Toren et al, 1998) has been reviewed.

9) The mechanisms of neuroleptic-induced extrapyramidal symptoms and tardive dyskinesia and their relationshi (Glazer, 2000).

10) A review of atypical antipsychotics in the treatment of drug-induced psychosis in Parkinson's disease was co

4.5 Therapeutic Uses

Adverse reaction to cannabis - Induced psychotic disorder

Agitation, acute - Psychotic disorder

Agitation - Bipolar I disorder

Agitation - Schizophrenia

Alzheimer's disease - Psychotic disorder

Anorexia nervosa

Anxiety - Dementia

Bipolar I disorder, Acute mixed or manic episodes

Bipolar I disorder, Maintenance therapy

Borderline personality disorder

Cancer - Nausea - Pain

Catatonia

Chemotherapy-induced nausea and vomiting; Prophylaxis

Chemotherapy-induced nausea and vomiting; Treatment and Prophylaxis

Cocaine dependence

Delirium

Dementia

Depressed bipolar I disorder

Depression, Treatment-resistant

Essential tremor

Fibromyalgia

Gilles de la Tourette's syndrome

Headache, Chronic, refractory

Huntington's disease

Obsessive-compulsive disorder, Refractory

Parkinson's disease - Psychotic disorder

Pervasive developmental disorder

Posttraumatic stress disorder

Repetitive self-excoriation

Schizophrenia

Schizophrenia, Refractory

Schizophrenic prodrome

Senile dementia of the Lewy body type

Severe major depression with psychotic features

Tardive dyskinesia

Trichotillomania

4.5.A Adverse reaction to cannabis - Induced psychotic disorder

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

As effective as haloperidol for the treatment of cannabis-induced psychotic disorder (Berk et al, 1999b)

3) Adult:

a) Olanzapine was as effective as haloperidol in the treatment of cannabis-induced psychotic disorder. In a c episode associated with cannabis use were randomized to receive either olanzapine 10 milligrams (n=15) or a significant improvement in both groups as compared to baseline measured on the Brief Psychiatric Rating S haloperidol). There was no significant difference between the 2 groups. Olanzapine was associated with fewe

4.5.B Agitation, acute - Psychotic disorder

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Olanzapine orally disintegrating tablets (ODT) and risperidone oral solution (OS) yielded similar improve
Negative Syndrome Scale (PANSS-EC) and the Clinical Global Impression (CGI) scale in 87 patients tre
emergency setting, according to an open-label, flexible-dose study(Hatta et al, 2008).

3) Adult:

a) Olanzapine orally disintegrating tablets (ODT) and risperidone oral solution (OS) yielded similar improvem
Negative Syndrome Scale (PANSS-EC) and the Clinical Global Impression (CGI) scale in 87 patients treated
emergency setting, according to an open-label, flexible-dose study. Patients with a baseline PANSS-EC scor
were assigned to receive initial doses of either olanzapine ODT 10 milligram (mg) (n=34) or risperidone OS 3
based on previous effective treatments, or monthly assignments to olanzapine or risperidone according to the
continued agitation could be re-dosed at any time, and after 1 hour could receive adjunctive drug therapy. PA
time. The mean CGI change from baseline was similar between the olanzapine and risperidone group (2.8 vs
PANSS-EC score over time ANOVA (at baseline and every 15 minutes for 1 hour) revealed no significant ma
treatment over time (p=0.09 and p=0.41, respectively). There was a significant mean change in heart rate in t
risperidone OS group (-9.2 vs 1.1 beats/minute, p=0.03). There were no significant differences between the t
extrapyramidal symptoms (Hatta et al, 2008).

4.5.C Agitation - Bipolar I disorder

FDA Labeled Indication

1) Overview

FDA Approval: Adult, yes (intramuscular formulation only); Pediatric, no
Efficacy: Adult, Effective
Recommendation: Adult, Class IIa
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Intramuscular olanzapine is indicated for the treatment of acute AGITATION ASSOCIATED WITH BIPOL
IM injection, ZYPREXA(R) ZYDIS(R) orally disintegrating tablets, 2006)

3) Adult:

a) Intramuscular olanzapine effectively reduced symptoms of agitation in patients with schizophrenia or bipol
trials. The primary efficacy measure in these trials was the change in the Positive and Negative Syndrome Sc
2 hours post-injection. The mean baseline PANSS Excited Component score was 18.4 (range, 13 to 32) out
moderate levels of agitation. The first trial included agitated inpatients meeting DSM-IV criteria for schizophre
doses (2.5 mg, 5 mg, 7.5 mg and 10 mg) were evaluated and all doses were significantly better as compared
2 hours post-injection. However, the effect was larger and more consistent for the 5 mg, 7.5 mg, and 10 mg d
inpatients with schizophrenia (n=311), received a fixed 10 mg dose of intramuscular olanzapine or placebo. A
placebo on the PANSS Excited Component at 2 hours post-injection. In the third trial, agitated inpatients with
episode with or without psychotic features) (n=201), received one fixed intramuscular olanzapine dose of 10 r
as compared with placebo on the primary outcome measure. Examination of population subsets such as age
responsiveness on the basis of these sub-groupings (Prod Info Zyprexa(R) IntraMuscular, 2004).

b) Rapid initial dose escalation (RIDE) of orally administered olanzapine was effective in the treatment of acu
bipolar disorder. In a randomized, double-blind, multicenter study, acutely agitated patients (n=148) received
milligrams (mg)/day for 2 days, then 20 to 30 mg/day for 2 days) or "usual clinical practice" (UCP) therapy (ol
4 days of blinded treatment before entering an open-label phase in which all patients received olanzapine 5 t
therapies produced significant mean reductions in the Positive and Negative Syndrome Scale-Excited Compo
(mean reduction, -7.01 and -5.51, respectively, p less than 0.001, both values). However, patients in the RIDI
those in the UCP group on days 2, 3, and 4 as measured by mean changes in PANSS-EC scores (p=0.03, p=
similar in both groups with headache, somnolence, dizziness, nervousness, and insomnia being reported mo

4.5.D Agitation - Schizophrenia

FDA Labeled Indication

1) Overview

FDA Approval: Adult, yes (intramuscular formulation only); Pediatric, no
Efficacy: Adult, Effective
Recommendation: Adult, Class IIa
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Intramuscular olanzapine is indicated for the treatment of agitation associated with schizophrenia (Prod I
ZYPREXA(R) ZYDIS(R) orally disintegrating tablets, 2006)

In a multicenter, double-blind, placebo-controlled study (n=270), intramuscular (IM) olanzapine was more
agitation among patients with schizophrenia, but there was no significant differences in efficacy between
2002).

Treatment with olanzapine intramuscular (IM) injection was no different from IM haloperidol in reducing a
schizophrenia in a multicenter, double-blind, placebo-controlled study (n=311) (Wright et al, 2001).

3) Adult:

a) Intramuscular

1) Intramuscular olanzapine effectively reduced symptoms of agitation in patients with schizophrenia or
trials. The primary efficacy measure in these trials was the change in the Positive and Negative Syndrom

baseline to 2 hours post-injection. The mean baseline PANSS Excited Component score was 18.4 (rang
suggesting mostly moderate levels of agitation. The first trial included agitated inpatients meeting DSM-I
intramuscular olanzapine doses (2.5 mg, 5 mg, 7.5 mg and 10 mg) were evaluated and all doses were si
PANSS Excited Component at 2 hours post-injection. However, the effect was larger and more consister
second placebo-controlled trial, agitated inpatients with schizophrenia (n=311), received a fixed 10 mg d
olanzapine was statistically superior to placebo on the PANSS Excited Component at 2 hours post-inject
I Disorder (and acute manic or mixed episode with or without psychotic features) (n=201), received one f
placebo. Olanzapine was significantly better as compared with placebo on the primary outcome measure
race, and gender did not show any differential responsiveness on the basis of these sub-groupings (Proc
2) In a multicenter, double-blind, placebo-controlled study (n=270), intramuscular (IM) olanzapine was n
of agitation among patients with schizophrenia, but there was no significant differences in efficacy betwe
agitated patients (mean age, 36.3 +/- 10.7 years (yr), range 18 to 73 yr) diagnosed with schizophrenia, s
disorder underwent 5:1 randomization of active treatment to placebo to olanzapine 2.5 milligram (mg) (m
Excited Component (PANSS-EC) score, 18.3 +/-2.4; n=48), olanzapine 5 mg (mean PANSS-EC score, 1
PANSS-EC score, 18.9 +/- 2.6; n=46), olanzapine 10 mg (mean PANSS-EC score, 19.3 +/- 2.6; n=46) in
injection (mean PANSS-EC score, 19.3 +/- 3.1; n=40) or placebo IM injection (mean PANSS-EC score, 1
allowed to receive a maximum of 3 injections within the 24-hour treatment period. Concomitant benzodia
after the administration of the first injection. The primary endpoint was the mean change in Positive and
(PANSS-EC) score from baseline to 2 hours after the first IM injection. Response was defined as a 40%
the first injection, there was a dose-response correlation across all IM olanzapine doses in reducing agita
change in PANSS-EC was -5.5 +/- 4.6 in the olanzapine 2.5-mg arm, -8.1 +/-5.3 in the olanzapine 5-mg
+/- 4.9 in the olanzapine 10-mg arm, -7.5 +/- 5.9 in the haloperidol 7.5-mg compared with -2.9 +/- 4.7 in t
rates were 50%, 62.6%, 73.9% and 80.4% in patients who received IM olanzapine 2.5 mg, 5 mg, 7.5 mg
patients who received IM haloperidol was 60% compared to 20% in the placebo arm (all p=0.003 or less
the differences in mean change on the PANSS-EC (last observation carried forward) was significant in th
the remaining 5-mg, 7.5-mg or 10-mg arms (p=0.12 or higher). The most common adverse effect reporte
hypotension (range, 2.2% to 4.4%) while no patients reported hypotension in the haloperidol or placebo
reported acute dystonia compared to zero patients in the olanzapine and placebo arms. IM olanzapine w
parkinsonism (0.7% vs 16.7%; p=0.03 or less) and akathisia (1.2% vs 7.9%) than IM haloperidol (Breier
3) In a multicenter, double-blind, placebo-controlled study (n=311), treatment with olanzapine intramusc
haloperidol in reducing agitation in patients with schizophrenia. Patients (mean age, 38.2 +/- 11.6 years
with a diagnosis of schizophrenia, schizophreniform disorder or schizoaffective disorder were randomize
IM injection (mean Positive and Negative Syndrome Scale Excited Component (PANSS-EC) score, 18.4
(mean PANSS-EC score, 18.2 +/-3.2; n=126) or placebo IM injection (mean PANSS-EC score, 18.4 +/-3
carried-forward response rate was defined as a 40% reduction in the PANSS-EC scores at 2 hours follov
hours following the first injection, the mean change in the PANSS-EC scores (primary endpoint) was -7.7
+/- 5 for patients who received haloperidol, and -3.6 +/- 5.2 for patients who received placebo (p not repo
better response rates than a 33.3% response rate with placebo (p less than 0.001), there was no signific
olanzapine and haloperidol arms (73.3% vs 69%; p=0.52). Acute dystonia was reported in 7.1% of patier
olanzapine arm. Extrapyramidal side effects were reported more frequently in the haloperidol compared
Significantly more patients (20.6%) who received haloperidol required anticholinergics compared with 4.6
who received placebo (all p=0.003 or less) (Wright et al, 2001).

b) Oral

1) Rapid initial dose escalation (RIDE) of oral olanzapine was effective in the treatment of acute agitatio
In a randomized, double-blind, multicenter study, acutely agitated patients (n=148) received either RIDE
for 2 days, then 20 to 30 mg/day for 2 days) or "usual clinical practice" (UCP) therapy (olanzapine 10 mg
blinded treatment before entering an open-label phase in which all patients received olanzapine 5 to 20 r
therapies produced significant mean reductions in the Positive and Negative Syndrome Scale-Excited Co
hours (mean reduction, -7.01 and -5.51, respectively, p less than 0.001, both values). However, patients
in agitation those in the UCP group on days 2, 3, and 4 as measured by mean changes in PANSS-EC sc
Adverse events were similar in both groups with headache, somnolence, dizziness, nervousness, and in
(Baker et al, 2003).

4.5.E Alzheimer's disease - Psychotic disorder

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class III
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk
Drug Administration, 2009).
Olanzapine doses of 5 or 10 mg daily were shown to be safe and effective in decreasing behavioral and
disease in elderly patients in a 6-week, multicenter, double-blind, placebo-controlled trial (n=206) (Street
Somnolence and gait disturbances increased in olanzapine-treated patients (Street et al, 2000)

3) Adult:

a) Low doses of olanzapine (5 milligrams (mg) or 10 mg daily) were safe and significantly superior to placebo

symptoms associated with Alzheimer's disease in elderly patients. In a 6-week, multicenter, double-blind, pla
were randomized to receive a fixed daily dose of olanzapine 5, 10, or 15 mg or placebo. Efficacy was measu
aggression, hallucinations, and delusion items ("Core Total") of the Neuropsychiatric Inventory-Nursing Home
Disruptiveness score, to assess patient-related caregiver distress. Core Totals were significantly improved in
Occupational Disruptiveness scores were significantly reduced in those receiving 5 mg doses. Somnolence o
receiving olanzapine than placebo. Gait disturbances were more common in those receiving olanzapine 5 or
impairment, increased extrapyramidal symptoms, and central anticholinergic effects in olanzapine-treated pa
patients (Street et al, 2000). In an 18-month, open extension of this trial with 105 patients, behavioral and psy
final average Core Total score having decreased to 6 from 7.9 at the start of the open trial (p=0.002). Nearly
additional reduction in Core Total score. Measures of cognitive status showed no change. Levels of akathisia
symptoms and parkinsonian symptoms did not increase. Although weight did not change significantly for the
weight gain (average, 4.3 kilograms) or weight loss (average, 4.4 kilograms). Somnolence and accidental inju
events. Five milligrams was the modal dose (the dose prescribed for a patient for the most number of days) f
(Street et al, 2001).

4.5.F Anorexia nervosa

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Significantly improved body mass index and obsessive symptoms compared to placebo in patients with a
trial (n=34) (Bissada et al, 2008)

Associated with a mean weight gain of 8.75 pounds in a small, 10-week, open-label trial in patients with

See Drug Consult reference: ANOREXIA NERVOSA - DRUG THERAPY

3) Adult:

a) Treatment with olanzapine resulted in greater weight gain and decreased obsessive symptoms compared
10-week, double-blind clinical trial. Women (n=34) with DSM-IV criteria for anorexia nervosa (restricting or bi
17.5 kilograms/square meter (kg/m(2)) or less attended a day hospital program at the Ottawa Hospital for eat
group therapy 4 days a week for 12 to 14 weeks. In addition, patients were randomized to receive olanzapine
milligrams (mg) daily, increased by 2.5 mg/week up to a maximum dose of 10 mg/day, or placebo (n=18; mea
started after a 2-week baseline period, continued for 10 weeks, and was followed by a 1-week posttreatment
6.61 +/- 2.32 mg/day for study completers (n=14). A significant (p less than 0.001) increase in BMI occurred f
significantly (p=0.03) greater rate of increase occurred in the olanzapine group (16.39 +/- 1.13 at baseline (n=
to the placebo group (15.93 +/- 1.39 at baseline (n=18) to 19.66 +/- 1.32 at week 13 (n=12)). Weight restorati
kg/m(2), occurred in 87.5% of olanzapine patients and 55.6% of placebo patients (p=0.02) with mean time to
interval (CI) 6.74-9.39) for the olanzapine group and 10.06 weeks (95% CI 8.75-11.36) for the placebo group
significant reductions in depression (p less than 0.001) and anxiety (p=0.02), as measured by the Personality
in obsessions (p=0.003) and compulsions (p=0.001), as measured by the Yale-Brown Obsessive Compulsive
in these scores in the olanzapine group compared to the placebo group was in obsessive symptoms (p=0.02)
tolerance or development of diabetes mellitus, were observed (Bissada et al, 2008).

b) Weight gain occurred in patients with anorexia nervosa when treated with olanzapine. In a small, open-lab
or binge/purge subtype) without schizophrenia, schizoaffective disorder or bipolar disorder received olanzapi
(n=18). Patients attended weekly group psychoeducational sessions. Of the 14 patients that completed the st
pounds and 4 patients lost an average of 2.25 pounds. Of these patients, those that gained weight had signifi
compared to both week 5 and week 10 (p=0.0195 and p=0.0092, respectively). Three patients attained their i
event was sedation. Controlled studies are needed to substantiate these findings (Powers et al, 2002).

c) A 49-year-old woman with anorexia nervosa and obsessive-compulsive symptoms improved with olanzap
obsessive-compulsive problems were mainly fear of food contamination, preoccupation with nutritional issues
She had no insight into her problems and was depressed. She weighed 31.2 kilograms when she was started
following months, her confusion cleared and her insight changed markedly. Approximately 6 months later her

4.5.G Anxiety - Dementia

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Reduced anxiety in elderly dementia patients (Mintzer et al, 2001)

3) Adult:

a) Olanzapine treatment reduced anxiety in elderly patients with Alzheimer's-type dementia independently of
somnolence, or benzodiazepine use. A post hoc analysis was performed on a subset of patients (n=120) from
evaluated the efficacy of olanzapine (3 dosages) versus placebo for 6 weeks for the treatment of psychosis a
disease. The subgroup (mean age 83 years) was selected for exhibiting clinically significant anxiety, defined

Neuropsychiatric Inventory/Nursing Home instrument (NPI/NH). Anxiety scores of patients receiving olanzapi more than scores of patients receiving placebo (p=0.034). Improvement in anxiety with olanzapine 5 mg/day for improvement in hallucinations. With higher doses of olanzapine (10 and 15 mg/day), improvement in anxie with placebo. Somnolence was the only adverse effect that occurred significantly more frequently with olanza peripheral or central potential anticholinergic adverse events occurred more frequently with olanzapine than v effects collectively occurred more frequently with olanzapine 15 mg/day than with placebo (26% vs 6%, p=0.(and placebo treatments in the occurrence of extrapyramidal symptoms (Mintzer et al, 2001).

4.5.H Bipolar I disorder, Acute mixed or manic episodes

FDA Labeled Indication

1) Overview

FDA Approval: Adult, yes (oral formulations only); Pediatric, no
Efficacy: Adult, Effective; Pediatric, Evidence is inconclusive
Recommendation: Adult, Class IIa; Pediatric, Class IIa
Strength of Evidence: Adult, Category B; Pediatric, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Indicated for the treatment of acute manic or mixed episodes associated with bipolar I disorder (Prod Info (R) ZYDIS(R) orally disintegrating tablets, 2006)
The combination of olanzapine with lithium or valproate is indicated for the short-term treatment of acute (Prod Info ZYPREXA(R) oral tablets, IM injection, ZYPREXA(R) ZYDIS(R) orally disintegrating tablets, 2

3) Adult:

a) Monotherapy

1) In a small open-label study, olanzapine was found to be somewhat effective as an adjunctive treatme three, severely ill, BPD patients (10 men) with a history of poor response or intolerance to therapeutic co were enrolled in this long-term study (mean 303 days). The Clinical Global Impressions Scale for use in olanzapine effectiveness. The depression subscale decreased by 0.9 (p less than 0.006), the mania sub score decreased by 1.3 (p less than 0.0003). Ten of the 23 patients had a decrease of at least 2 points o rated as in remission. There were 6 dropouts in the study, 2 due to adverse effects, 2 due to lack of resp follow-up. The mean final dose of olanzapine was 8.2 milligrams (mg) per day with 16 patients taking lith and one each taking gabapentin and lamotrigine concurrently. The most common adverse events were s cases of tardive dyskinesia were reported during the study (Vieta et al, 2001).

2) Olanzapine was more effective than placebo in the treatment of patients with acute bipolar mania. In patients were assigned to receive olanzapine 5 to 20 milligrams (mg) daily (n=55) or placebo (n=60) for 4 significantly greater mean improvement in symptoms over placebo, as determined by the total Young-Ma clinically evident within the first week of treatment and was maintained throughout the study. Significantly 50% or more decrease in total YMRS score from baseline (65% versus 43%, p=0.02) and euthymia as m endpoint) (61% versus 36%, p=0.01). The incidence of extrapyramidal symptoms was similar between ol weight gain, treatment-emergent somnolence, and elevations in aspartate aminotransferase (AST) and a significantly more often in olanzapine-treated patients (Tohen et al, 2000).

3) Olanzapine exhibited superior efficacy over placebo in the treatment of acute mania (Tohen et al, 199 study, patients with manic or mixed episodes associated with bipolar disorder were randomized to receiv placebo (n=69). The olanzapine dose could be adjusted between a range of 5 to 20 mg daily. At the end was 14.9 mg daily. The olanzapine group had a significantly greater improvement in total scores on the Y 0.02). Olanzapine was well-tolerated with no dropouts due to adverse effects.

4) In 2 case reports, olanzapine effectively augmented mood stabilizers in 2 patients with nonpsychotic first was a 34-year-old male with bipolar I disorder that entered a nonpsychotic mixed mood state after in previously been euthymic on lithium and divalproex. Olanzapine 10 milligrams (mg) was added at bedtim the first time in over 2 weeks. He reported complete remission of his symptoms by the next morning. A 4 to a mixed mood state after previously taking divalproex, lorazepam, and levothyroxine. Olanzapine 10 m first time in 10 days. Her mood was also improved by the next morning. Both of these patients had rapid been an indirect benefit of improved sleep with olanzapine or may have actually been due to a direct mo

b) Combination Therapy

1) In patients with bipolar manic or mixed episodes who do not respond adequately to lithium or valproa treatment. In a randomized, double-blind, placebo-controlled trial, patients with bipolar disorder who had therapy (ie, maintaining a score of 16 or more on the Young Mania Rating Scale (YMRS)) received eithe milligrams/day) (n=229) or placebo (n=115). Both groups improved during the course of treatment, but th YMRS score from baseline, while the monotherapy group improved by 40% (p=0.003). Particular items c were irritability, speech, language/thought disorder, and disruptive/aggressive behavior. Sixty-eight perce or greater improvement in YMRS score), compared to 45% of the monotherapy group (p=0.01). Median 28 days with monotherapy. Patients in the co-therapy group showed significantly greater improvement in monotherapy group (p less than 0.001). Among patients experiencing a mixed episode with moderate to Hamilton Depressive scale from baseline to 6 weeks was 10.3 for co-therapy and 1.6 for monotherapy (p adverse events in the co-therapy group were somnolence, dry mouth, weight gain, increased appetite, tr significant changes from baseline were observed in extrapyramidal symptoms (Tohen et al, 2002a).

2) Combination therapy with olanzapine and lithium or valproate was effective in the treatment of acute with manic or mixed episodes. In two 6-week, randomized, placebo-controlled trials, patients (n=175, n= uncontrolled manic or mixed symptoms and with a score of 16 or higher on the Young Mania Rating scal

of 5 to 20 milligrams (mg) once daily, starting at 10 mg/day) or placebo, in combination with their original milliequivalents/liter (mEq/L) to 1.2 mEq/L) or valproate (in a therapeutic range of 50 micrograms/milliliter olanzapine in combination with lithium or valproate was more effective than either lithium or valproate alo Zyprexa(R), Zyprexa(R) Zydis(R), Zyprexa(R) IntraMuscular Olanzapine, 2004b).

4) Pediatric:

a) Monotherapy

1) Olanzapine monotherapy effectively treated symptoms of psychosis, depression, and mania in a grou disorder (BPD). In this open-label, 8-week study, 23 youths, 5 to 14 years old, discontinued their current 2.5 milligrams (mg) per day. Olanzapine was increased by 2.5 mg/day every 3 days to a maximum dose 4.3 mg per day). Lorazepam (up to 4 mg/day) and benztropine (up to 2 mg/day) were allowed as needed symptoms respectively. Patients taking guanfacine or clonidine for attention deficit hyperactivity disorder medications, but could not adjust the dose during the study. Psychiatric symptoms were assessed at bas Rating Scale (YMRS), the Clinical Global Impressions Severity Scale (CGI-S), the Brief Psychiatric Ratin Rating Scale (CDRS). Extrapyramidal symptoms were assessed on the same schedule using the Simps the Abnormal Involuntary Movement Scale (AIMS). Significant improvement from baseline to endpoint w (38%, p less than 0.001), and BPRS (62%, p less than 0.001). The most frequently reported adverse effe (n=10), abdominal pain (n=7) and weight gain (n=7). There was no significant difference in extrapyramid had treatment-emergent akathisia. There were small statistically significant decreases in hematocrit, hem significant increases in alanine transferase (ALT) and prolactin levels. One patient dropped out of the stu symptoms (Frazier et al, 2001).

4.5.I Bipolar I disorder, Maintenance therapy

FDA Labeled Indication

1) Overview

FDA Approval: Adult, yes (oral formulations only); Pediatric, no
Efficacy: Adult, Effective
Recommendation: Adult, Class IIa
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Indicated for maintenance monotherapy in bipolar patients who have responded to initial treatment with o injection, ZYPREXA(R) ZYDIS(R) orally disintegrating tablets, 2006)

3) Adult:

a) Continuation olanzapine therapy was more effective than placebo in delaying the time to relapse in patien blind, placebo-controlled trial, bipolar patients with a mixed or manic episode who responded to initial, open-l (mg)/day for approximately two weeks) received either continuation of olanzapine at their same dose (n=225) Response during the initial phase of the study was defined as a decrease in the Young Mania Rating Scale (the Hamilton Depression Rating Scale (HAM-D) score to 8 or less. Relapse was defined as an increase of the hospitalization for either mania or depression. Patients treated with olanzapine showed a significantly longer placebo (Prod Info Zyprexa(R), Zyprexa(R) Zydis(R), Zyprexa(R) IntraMuscular Olanzapine, 2004b).

4.5.J Borderline personality disorder

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Improved symptoms in all 4 cores areas of BPD in a 6-month study (Zanarini & Frankenburg, 2001)

3) Adult:

a) Olanzapine was superior to placebo for reducing symptoms of borderline personality disorder (BPD) in a s for BPD and did not meet criteria for major depression were randomized in a 2:1 ratio to receive olanzapine o The starting dose of olanzapine was 1.25 milligrams/day and was adjusted according to perceived response was 5.3 mg. Olanzapine was significantly more effective than placebo in the affective area of anxiety (p=0.00 area of paranoia (p=0.003), and in the area of trouble relationships (p=0.016). Subjects in the olanzapine gro subjects in the placebo group (p=0.012). However, average weight gain of olanzapine- treated subjects was s movement disorders were observed (Zanarini & Frankenburg, 2001).

4.5.K Cancer - Nausea - Pain

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Preliminary data indicated safety and efficacy in patients with moderate nausea related to advanced can

study (n=15) (Passik et al, 2002)

3) Adult:

a) In an open-label, pilot study of 15 patients with advanced cancer and associated pain, the administration c nausea. Patients with nausea due to chemotherapy were excluded. Patients (female, n=11; male, n=4) aged primarily breast, lung, and ovarian cancers were receiving opioid analgesics for stable cancer pain and had m nausea) to 10 (worst nausea imaginable)). Patients received olanzapine 2.5 milligrams (mg), 5 mg, and 10 m washout and placebo run-in period. Nausea was measured using the nausea item (scale of 0 (no nausea) to Assessment of Cancer Treatment-General (FACT-G) scale. The proportion of patients who reported scores c decreased from 60% at baseline, to 40% in the 2.5-mg group (p less than 0.04 compared to baseline), and 6. 0.0001 compared to baseline). It could not be determined if efficacy was a dose-response or cumulative effec scores, was highest at the 5-mg dose level (79.5) and differed significantly from baseline (66.6; p < 0.005). A Simpson Angus Scale, and the Mini Mental Status Exam, adverse effects related to olanzapine were minimal baseline (Passik et al, 2002).

4.5.L Catatonia

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Olanzapine was effective in the treatment of catatonia in one case report (DelBello et al, 2000)

3) Adult:

a) A 16-year-old African American male was successfully treated for catatonia with a combination of lorazepa admission, the patient had become increasingly noncommunicative and had not slept for 1 week. He was una incontinent of urine and feces. An electroencephalogram (EEG) showed diffuse mild slowing without any evic a dose of 1 milligram (mg) four times daily (QID) and increased to 2 mg three times daily (TID) without improv started, and 3 days later, olanzapine was added and titrated to 10 mg twice daily (BID). Over the next 14 day and attempted to wash and dress himself. On day 21, lorazepam was tapered and discontinued due to exces Valproic acid was discontinued on day 28 By day 42, the patient was interacting with peers and communicati the patient was discharged, experiencing only an occasional auditory hallucination. Olanzapine therapy was c year (DelBello et al, 2000).

4.5.M Chemotherapy-induced nausea and vomiting; Prophylaxis

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Effectively prevented acute chemotherapy-induced nausea and vomiting in combination with standard ar vomiting when continued alone, in patients receiving moderately and highly emetogenic chemotherapy ir et al, 2007)

Effective, in combination with granisetron and dexamethasone, for the prevention of acute and delayed c patients receiving moderately and highly emetogenic chemotherapy in a single-arm, phase 2 clinical trial

3) Adult:

a) Use of olanzapine, in combination with palonosetron and dexamethasone, effectively prevented acute che continued monotherapy with olanzapine prevented most cases of delayed nausea and vomiting in patients re chemotherapy in a single-arm, phase 2 clinical trial. Patients (n=40; median age, 61 years; range, 36-84 year cancer (n=12), colon cancer (n=7), small cell lung cancer (n=2), lymphoma (n=2), and bladder cancer (n=2), meter (mg/m(2)) or greater) or moderately (carboplatin area under the curve (AUC) 5 or greater, irinotecan, c doxorubicin 25 mg/m(2) or greater) emetogenic chemotherapy were scheduled to receive antiemetic prophyla and olanzapine on day 1 of their first cycle of chemotherapy. Doses consisted of 8 mg of dexamethasone giv emetogenic chemotherapy or 20 mg orally or IV for highly emetogenic chemotherapy, 0.25 mg of palonosetro and 10 mg of olanzapine orally. On days 2 through 4, only olanzapine 10 mg orally daily was administered. A chemotherapy up to 6 cycles. Rescue antiemetics were administered per physician discretion. For the 8 patie in cycle 1, 100% had complete responses (no emesis and no rescue medication) in the acute (0 to 24 hours) the delayed (24 to 120 hours) and overall (0 to 120 hours) periods. For the 32 patients who received moderat complete responses in the acute period, 75% in the delayed period, and 72% in the overall period. Nausea, v M.D. Anderson Symptom Inventory (MDASI), occurred in 11 patients in the delayed period (highly emetogeni Results in subsequent cycles were not significantly different from those in the first cycle. No grade 3 or 4 adv (Navari et al, 2007).

b) The combination of olanzapine, granisetron, and dexamethasone were effective for the prevention of acut vomiting in patients receiving moderately and highly emetogenic chemotherapy in a single-arm, phase 2 clini range, 25-84 years) with breast cancer (n=16), small cell lung cancer (n=4), non-small cell lung cancer (n=3), (n=4), receiving highly (cisplatin 70 milligrams/square meter (mg/m(2)) or greater) or moderately (carboplatin,

mg/m(2), or doxorubicin 25 mg/m(2) or greater) emetogenic chemotherapy were scheduled to receive antiem orally each morning for 2 days prior to chemotherapy (days -2 and -1), then dexamethasone (20 mg orally or micrograms/kilogram IV or 2 mg orally 30 to 60 minutes prior to chemotherapy) on day 1. In addition, olanzap through day 4, and dexamethasone 8 mg twice daily for days 2 and 3 and 4 mg twice daily on day 4. Antieme chemotherapy up to 6 cycles. Rescue antiemetics were administered per physician discretion. For the 10 pat chemotherapy in cycle 1, 100% had complete responses (no emesis and no rescue medication) in the acute responses each in the delayed (24 to 120 hours) and overall (0 to 120 hours) periods. For the 20 patients wh 100% had complete responses in the acute period and 85% had complete responses each in the delayed an daily by patients using the M.D. Anderson Symptom Inventory (MDASI), occurred only in patients receiving m (15%), delayed (35%), and overall (35%) periods. Results in subsequent cycles were not significantly differer adverse events due to the study drugs were observed (Navari et al, 2005).

4.5.N Chemotherapy-induced nausea and vomiting; Treatment and Prophylaxis

See Drug Consult reference: CHEMOTHERAPY AND RADIOTHERAPY TREATMENT GUIDELINES FOR NAUS

4.5.O Cocaine dependence

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Ineffective
Recommendation: Adult, Class III
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Olanzapine was ineffective in the treatment of cocaine dependence (Kampman et al, 2003)

3) Adult:

a) Olanzapine was not an effective therapy for the treatment of cocaine dependence. In a randomized, place dependent patients (n=30) received olanzapine (initial, 2.5 milligrams (mg)/day, titrated to 10 mg/day) or plac phase. Urine benzoylecgonine tests (UBT) were obtained twice a week. A significant time by medication grou results whereby the estimated odds of a positive UBT went up by 4% between visits for olanzapine-treated pa by 6% for patients in the placebo group (95% CI, 0.92 to 0.968) (p=0.01). In addition, treatment retention was olanzapine group. Patients in the placebo group attended a significantly greater median number of treatment vs 18, respectively; p=0.029). Finally, olanzapine was not superior to placebo in any of the secondary outcom anxiety symptoms, and self-reported cocaine use. The most common adverse effects reported during the stu constipation (13%), dizziness (10%), dry mouth (7%), nausea (7%), restlessness (7%), and urticaria (3%) (Ka

4.5.P Delirium

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

May produce significant improvement in patients with delirium (Kim et al, 2001; Sipahimalani & Masand,
Attenuated delirium in hospitalized cancer patients, with no report of any extrapyramidal effects (Breitbar

3) Adult:

a) A 7-day course of oral olanzapine produced resolution of delirium or reduction of symptom severity in hos (DSM-IV), according to an open-label observational study (n=79). Enrollees (mean age 60.6 years) had a me from mild (17%) to moderate (61%) to severe (23%). Mean olanzapine starting dose was 3 milligrams (mg), v mean 6.3 mg at days 4 to 7. Subjects were given olanzapine as a single dose at bedtime or in 2 divided dose patients (76%) achieved complete resolution of delirium (defined as a Memorial Delirium Assessment Scale (decreased from baseline 19.85 to 12.73 at day 2/3 (p=0.001) and to 10.78 at study endpoint (days 4 to 7) (p= strongly associated with a poor response were age above 70 years, central nervous system spread of cancer factors which tended to correlate with less successful outcomes were a history of dementia, severe delirium a Side effects were few and relatively mild; sedation was the most commonly reported adverse effect (30% inci cohort. Olanzapine was withdrawn in 2 subjects whose delirium seemed to worsen when taking the drug (Bre

b) Fourteen patients given olanzapine demonstrated a 50% or greater reduction in delirium scores in an ope females), patients (mean age 46 years) with varying etiologies of delirium. Mean olanzapine treatment doses occurring in an average of 3.8 days. The pretreatment Delirium Rating Scale (DRS) score showed a significa following a mean duration of 6.6 days. Eleven of the 14 patients that had a 50% or greater decrease in DRS v brain injury had a DRS score that increased from 19 to 21. None of the patients had comorbid psychiatric dia medications during this study. The authors said that adverse effects due to olanzapine were minimal althoug placebo control group for comparison (Kim et al, 2001).

c) In an open-label study of 22 adult patients (mean age approximately 64 years) with varying etiologies of d of 11 patients given haloperidol showed marked improvement in the Delirium Rating Scale (DRS; greater tha were 8.2 milligrams (mg) with olanzapine and 5.1 mg with haloperidol. Pretreatment DRS were similar in both haloperidol group. Mean improvement in the DRS was 7.6 with olanzapine and 10 with haloperidol. Peak resp agents. Some of the patients in each group had comorbid psychiatric diagnoses and were taking other psych

olanzapine experienced side effects, while 3 haloperidol patients experienced extrapyramidal symptoms and Masand, 1998).

d) A 59-year-old cancer patient with delirium was successfully treated with olanzapine (Passik & Cooper, 19 patient's symptoms and she was started on olanzapine 5 milligrams (mg) daily. She improved dramatically wi olanzapine 10 mg with 2.5 mg as needed during the day. Her mental status returned to normal over 72 hours

4.5.Q Dementia

See Drug Consult reference: BEHAVIORAL AND PSYCHOLOGICAL SYMPTOMS OF DEMENTIA

4.5.R Depressed bipolar I disorder

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Olanzapine monotherapy and olanzapine plus fluoxetine combination therapy reduced depressive sympt al, 2003)

3) Adult:

a) Both olanzapine monotherapy and olanzapine plus fluoxetine combination therapy were more effective tha In a randomized, double-blind, placebo-controlled, multi- center, international study, patients with bipolar I dis Montgomery-Asberg Depression Rating Scale (MADRS) received olanzapine (n=370; 5 to 20 milligrams (mg) plus fluoxetine (n=86; 6 and 25 mg/day, 6 and 50 mg/day, or 12 and 50 mg/day; mean dose, 7.4 and 39.3 mg objective of the study compared olanzapine monotherapy versus placebo with regard to change in the MADR all 8 weeks of the study, treatments with both olanzapine and olanzapine-fluoxetine combination produced sig symptoms (as measured by the MADRS) as compared with placebo (p less than 0.001, all values). Also, a si MADRS score at weeks 4, 6, and 8 were observed with olanzapine-fluoxetine combination therapy as compa p=0.01, respectively). The rate of response (defined as at least a 50% improvement in the MADRS total score significantly higher in olanzapine-treated patients as compared with placebo (39% vs 30.4%, respectively; p= significantly higher in the olanzapine-fluoxetine group as compared with both the placebo (56.1% vs 30.4%, r groups (56.1% vs 39%, respectively; p=0.006). There were no statistically significant differences between gro mania. Adverse events were similar between the combination therapy and monotherapy groups, however, the higher rate of nausea and diarrhea (Tohen et al, 2003).

4.5.S Depression, Treatment-resistant

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Ineffective as a single agent in resistant depression
Possibly effective as augmentation therapy with antidepressants (Parker, 2002)

3) Adult:

a) Some patients experiencing a recurrence of depression while under medical treatment responded very qu regimen. In a case series of 10 patients, 4 patients, all of whom had unipolar depression, were judged to be r treatment. Of the 6 responders, 5 had bipolar conditions and were receiving venlafaxine, desipramine, anafra taking lithium. Each received olanzapine augmentation of 2.5 milligrams (mg) or 5 mg each night. Daily rating the first day, 73% by day 4, and 89% by day 6. Anxiety and insomnia scores, in particular, showed notable im showed linear improvement over the week. Two patients emerged with what they described as a "high." Beca majority, it is uncertain whether the improvement with olanzapine was through an effect on a switching mecha

b) Patients with treatment-resistant, nonpsychotic, unipolar depression treated with olanzapine combined wit improvement than either agent alone across a variety of measures. In an 8-week, double-blind study, 28 patie treatment groups: olanzapine plus placebo, fluoxetine plus placebo or olanzapine plus fluoxetine. The mean r and 13.5 mg for the monotherapy and combined therapy groups, respectively. The mean modal dose of fluox and combination group. Patients receiving combination therapy experienced greater improvements over base Scale scores than with either agent alone and in total Hamilton Depression scale scores than olanzapine trea (at least 50% improvement in Montgomery-Asberg Depression Rating Scale score) in the combination therap olanzapine alone (60% versus 0%). Both drugs were well tolerated alone or in combination. Adverse effects i weight gain, headache, dry mouth, and nervousness. Increased appetite and weight gain occurred significant (Shelton,et al, 2001).

4.5.T Essential tremor

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive

Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:
May be effective in the treatment of essential tremor (Yetimalar et al, 2003)

3) Adult:
a) Results of an open-label study suggest that olanzapine may be effective in the treatment of essential trem with essential tremor received divided, oral doses of olanzapine 5 to 20 milligrams daily. Six months following significantly reduced from 3.3 (baseline) to 1.12 (scale, 1 to 4; p=0.0001). Mild, transient sedation was the mo studies are needed to further substantiate these findings (Yetimalar et al, 2003).

4.5.U Fibromyalgia

1) Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:
Treatment with olanzapine led to reduction in pain symptoms and improvement in daily life functioning in review (n=51); treatment discontinuation was high (53%), mostly due to weight gain (30%), somnolence/ (Freedenfeld et al, 2006)

3) Adult:
a) A retrospective chart review showed that treatment with olanzapine led to reduction in pain symptoms and (n=51) with fibromyalgia. Records of all fibromyalgia patients 18 to 65 years of age (mean age, 44 years; fem during a 3-year period at one center were reviewed. Comorbid psychiatric conditions were present in 88% of treated being major depressive disorder (81%) and anxiety disorder (42%). At the time of treatment with olan Patients with a history olanzapine use prior to receiving treatment for fibromyalgia were excluded. While olan for treatment of fibromyalgia symptoms, it was also used for relief of other symptoms, such as anxiety and sle Inventory (BPI) were evaluated separately, and results from 1 month pretreatment and posttreatment with ola was determined to be when the patient had reached the maximal therapeutic dose, defined as when then pat physician and/or when the olanzapine dose was unchanged for a month. Pretreatment ratings on pain and in pain variables, significant improvements occurred in the mean current pain level, worst pain level, least pain l scales measuring pain interference with daily functioning, significant improvements occurred in interference v enjoyment, and concentration. For patients with dosing information in their records (n=41), the majority (80.5% milligrams or less per day. Based on physician rating data (n=29), the majority experienced at least moderate (62%). Treatment discontinuation occurred in 53% (27/51) of patients, with the most common reasons being and no treatment benefit (11%). Overall, weight gain occurred in 24% and somnolence/sedation occurred in 2

4.5.V Gilles de la Tourette's syndrome

1) Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:
Effective in a small study of 14 patients (Stamenkovic et al, 2000)

3) Adult:
a) Olanzapine was found to be a safe and effective alternative to other antipsychotics for the treatment of To olanzapine was initiated at 10 milligrams daily with a maximum dose of 20 milligrams daily. The mean dose a Yale Global Tic Severity Scale (YGTSS) and the Clinical Global Impression Severity Scale (CGI) scores sign day 0 (p less than 0.005). The definition of treatment success (60% reduction in YGTSS score) was achieved observed between the groups. The only side-effect observed was mild sedation which resolved as treatment The data suggests that olanzapine is safe and effective for the treatment of Tourette's disorder but more doul (Stamenkovic et al, 2000).

4.5.W Headache, Chronic, refractory

1) Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:
Effectively treated patients with chronic refractory headache who had failed previous therapies (Silberste

3) Adult:
a) The results of a retrospective review indicate that olanzapine was effective in the treatment of patients wit

unblinded review of 50 patient charts was conducted to assess the effectiveness of olanzapine treatment in p
had failed at least 4 previous preventative medication trials. Olanzapine doses ranged from 2.5 to 35 milligrar
mg (n=19) or 10 mg (n=17) per day. The mean number of headache days was significantly reduced from 27.5
following treatment (p less than 0.001). Average headache severity scores were also significantly lower after
8.7, respectively; p less than 0.001). The most common adverse events were weight gain and somnolence. C
findings (Silberstein et al, 2002).

4.5.X Huntington's disease

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Lessens involuntary movements (Bonelli et al, 2002; Dipple, 1999)
Decreases agitation, aggression, and delusions (Grove et al, 2000)

3) Adult:

a) High dose olanzapine (30 milligrams (mg) per day) greatly improved chorea in a 30-year-old woman with
6 years and in 2 days had a severe worsening of her chorea. She could not eat or dress without help and did
dysfunction or psychiatric abnormality. Her major deficits were in fine motor tasks, oral functions, chorea, and
first day and 30 mg/day thereafter. The chorea nearly stopped in the next 2 days, and she was able to eat an
improvement in fine motor tasks and gait. Her mild parkinsonism was not improved. Four months later, her im
2002).

b) Olanzapine improved cognition and function as measured by the Abnormal Involuntary Movement Scale (
in a 49-year-old man with dementia resulting from Huntington's disease. Prior to admission, treatment with ha
10 mg/d, and tiapride 200 mg/d had been unsuccessful. Olanzapine 5 mg/d decreased the patient's impulsivi
10 mg/d was associated with improvement in chorea movements and ability to perform activities of daily living
score dropped from 40 to 22, MMSE improved from 20 to 26. At 5 months, the cessation of irritability and agg
movement disorders, cognitive ability and functional ability suggested therapeutic benefit was related to olanz
serotonergic or dopaminergic receptor is theorized as a reason for these effects (Bogelman et al, 2001).

c) Olanzapine was used in combination with valproate in a 39-year-old man and 52-year-old woman to treat
with Huntington's disease of 8 and 13 years duration, respectively. In the year prior to hospitalization, the pat
severe neither could walk or assist in their care. Prior haloperidol treatment had been unsuccessful. Initially b
milligrams (mg) daily and valproate 125 mg twice daily. Subsequently, the olanzapine dose was reduced to 5
valproate was increased to 500 mg three times daily (plasma concentrations from 60 to 80 micrograms per m
discharged to nursing homes, able to walk with assistance, cooperative with eating, bathing, and social activi
movements decreased (Grove et al, 2000).

d) A man in his early 50's had marked improvement of his movement disorder associated with Huntington's d
been treated with sulpiride, which was ineffective, and risperidone, which caused hypotension. Olanzapine 5
improvement in his involuntary movements within 1 week. He experienced slowed thinking but adjusting the t
maintained his improvement in involuntary movements over the next 6 months. The authors hypothesized tha
associated with Huntington's disease, the D2 antagonist properties of olanzapine may be beneficial in the imp

4.5.Y Obsessive-compulsive disorder, Refractory

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Partially effective as an augmentation strategy with serotonin-reuptake inhibitors in studies with small nu
1999)
One study showed no additional benefit in the addition of olanzapine to fluoxetine therapy in the treatmer
compulsive disorder (Shapira et al, 2004)
Adjunctive therapy of risperidone or olanzapine with serotonin-reuptake inhibitors (SRI) were equally effe
in SRI monotherapy-resistant outpatients, according to an 8-week, single-blind, randomized trial (Maina

3) Adult:

a) General Information

1) Information regarding the efficacy of olanzapine for the treatment of patients with refractory obsessive
studies with small numbers of patients have reported that olanzapine therapy (1.25 to 20 milligrams (mg)
strategy with selective serotonin-reuptake inhibitors (SSRI), while the findings of a controlled study indica
additional benefit when added to SSRI therapy in patients with fluoxetine-refractory obsessive compulsiv
determine the role of olanzapine as an augmentation therapy in this patient population (Shapira et al, 20
et al, 1998).

b) Adjunctive therapy of risperidone or olanzapine with serotonin-reuptake inhibitors (SRI) were equally effec
in SRI monotherapy-resistant outpatients, according to an 8-week, single-blind, randomized trial; however thi

placebo arm, single-arm design, and underpowered nature of the trial. Following a 16-week prospective, ope who were treatment-resistant (defined as less than 35% improvement in the total score of Yale-Brown Obses Global Impression Severity (CGI-S) score greater than 2, entered an 8-week single-blind phase (n=50). Patie doses of clomipramine 200 to 225 mg, citalopram 50 to 80 mg, fluoxetine 60 mg, fluvoxamine 200 to 300 mg, were randomized to receive either risperidone 1 to 3 mg/day (n=25), or olanzapine 2.5 to 10 mg/day (n=25) i personnel and assessor-blinding constituted the single-blind study design; patients were not blinded. In an int analysis of the primary endpoints, both treatments significantly improved Y-BOCS and CGI-S scores by week mean Y-BOCS total scores, CGI-S scores, and responder rates (35% or greater improvement in Y-BOCS sc was similar between groups (Maina et al, 2008).

Primary Efficacy Endpoints at 8 Weeks		
	Risperidone (n=25)	Olanzapine (n=25)
Responder rates*	44% (11/25)	48% (12/25)
Mean end-point Y-BOCS score	22.6 +/- 7.2	22.2 +/- 7.4
Change in mean Y-BOCS score from baseline	-7.5; p less than 0.001	-8.4; p less than 0.0
Mean end-point CGI-S score	3.2 +/- 1.7	3.1 +/- 1.8
Change in mean CGI-S score from baseline	-1.7; p less than 0.001	-1.9; p less than 0.0
* p=1; Y-BOCS=Yale-Brown Obsessive Compulsive Scale; CGI-S=Clinical Global Impression Severity s		

(Maina et al, 2008)

1) Adverse effects of risperidone compared with olanzapine-treated patients included tension/inner unre 52%, p=0.016), and amenorrhea (66.7% vs 10%, p=0.02), respectively. The small sample size and the a contributed to the limitations of this study (Maina et al, 2008).

c) The addition of olanzapine to ongoing fluoxetine therapy did not provide additional benefit in the treatment refractory to fluoxetine. In a double-blind, placebo-controlled study, patients (n=44) with obsessive-compulsiv partial or non- responders to 8 weeks of open-label treatment with fluoxetine (up to 40 milligrams (mg)/day) re (initial, 5 mg/day, titrated up to 10 mg/day) or placebo for 6 weeks. Mean scores for the Yale-Brown Obsessiv improved for patients in both the fluoxetine-plus- olanzapine (decrease of 5.1) and fluoxetine-plus-placebo (d However, the treatment x time interaction was not significant for olanzapine (mean, 6.1 mg) versus placebo (treatment groups, 9 (41%) patients showed a 25% or greater improvement in Y-BOCS score. In addition, a 3 patients in the fluoxetine-plus-olanzapine group and in 4 (18%) patients in the fluoxetine-plus-placebo group. fluoxetine was generally well tolerated, however patients receiving add-on therapy with olanzapine gained mo placebo (mean, 2.8 kilograms vs 0.5 kilograms, respectively) (Shapira et al, 2004).

d) Olanzapine augmentation was partially effective in the treatment of 10 patients with obsessive-compulsive milligrams per day (mg/d) for at least 10 weeks). Olanzapine 2.5 mg/d was added and titrated to 10 mg daily additional 4 weeks. Patients were assessed for improvement of symptoms using the Yale-Brown Obsessive- therapy was defined as a greater than or equal to 25% decrease in Y-BOCS score. Three patients responded and 2 only minimally improved. Seven of 10 patients had comorbid conditions, including major depression, dy disorder, and schizotypal personality disorder with tics. Two patients with comorbid conditions showed improv markedly improved mood symptoms but not OCD, and another patient with dysthymia and OCD showed rapi common adverse effects were weight gain, drowsiness, dry mouth, and increased appetite (Koran, et al, 200

e) Olanzapine may be effective in augmenting selective serotonin reuptake inhibitor (SSRI) treatment for sor disorder (OCD) refractory to SSRI therapy. Ten patients diagnosed with OCD and who had completed at leas were given open- label olanzapine augmentation for a minimum of 8 additional weeks. Prior to initiating olanz at the end of SSRI treatment and only 4 demonstrated a partial response. Olanzapine augmentation was initi indicated (mean dose was 7.3 +/- 7.3 milligrams/day). Within 8 weeks, 4 patients were responders and 3 wer changes in their OCD symptoms. Symptomatic improvement generally began within the first 2 weeks of olanz tolerated with 2 patients discontinuing olanzapine due to sedation. Further studies are warranted to determine therapy in the treatment of SSRI-refractory OCD (Weiss et al, 1999).

f) A 24-year-old woman with refractory obsessive-compulsive disorder benefited from the addition of olanzap She had previously failed a trial of clomipramine with risperidone. She was being maintained on fluoxetine 80 Obsessive Compulsive Scale (Y-BOCS) score of 18. Olanzapine was titrated up to 20 mg daily over 3 months decreased to 10. She has maintained this response for 6 months, however, she has gained 18 pounds.

4.5.Z Parkinson's disease - Psychotic disorder

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class III
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Decreases psychotic symptoms in nondemented, Parkinson's patients with drug-induced psychosis

May also worsen Parkinsonian symptoms
See Drug Consult reference: THERAPY OF PSYCHOTIC DISTURBANCES IN PARKINSONIAN PATIENTS

3) Adult:

a) The results of a prospective, open-label, uncontrolled study of 21 elderly patients (mean age 74.4 +/- 6.4 y concluded olanzapine improved delusions and hallucinations while not worsening parkinsonism or cognition. milligrams/day. Due to frequent side effects (primarily drowsiness), the starting dose was reduced to 2.5 milli milligrams/day. After 8 weeks of treatment, the summed score of the Neuropsychiatric Inventory (NPI) for del 85%, and 80% of those who completed the 8 weeks were considered much or very much improved, accordin scores. Twenty-nine percent of patients withdrew due to side effects (primarily drowsiness). Larger controlled

b) In a case series of patients suffering hallucinations and vivid dreams secondary to treatment of their parki improved, however, their motor symptoms declined (Graham et al, 1998a). Five outpatients with idiopathic Pa were started on olanzapine 5 milligrams (mg) nightly. Two patients were increased to 7.5 mg. Hallucinations to discontinue olanzapine while the other 3 also had declines in their motor function and "on" time. The autho been as problematic if a smaller initial dosage form were available (less than 5 mg).

c) Olanzapine was well-tolerated and effective in an open study of 15 Parkinson's disease patients with drug Criteria) (Wolters et al, 1996a). The initial dose was 1 milligram (mg) daily, titrated up to a maximum of 15 mg Brief Psychiatric Rating Scale (BPRS), the Unified Parkinson's Disease Rating Scale (UPDRS), and a sleep s BPRS scores by 65% (p less than 0.05), significantly reduced UPDRS total scores by 21% (p less than 0.01) than 0.01).

d) In a letter to the editor, one physician's experiences with olanzapine, in patients with drug-induced psycho Parkinson's disease, were not encouraging (Friedman, 1998). He described only 9 of 19 patients remaining c other 10 all experienced worsening of their parkinsonism despite 7 patients also improving in their psychoses

4.5.AA Pervasive developmental disorder

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive; Pediatric, Evidence is inconclusive
Recommendation: Adult, Class IIb; Pediatric, Class IIb
Strength of Evidence: Adult, Category B; Pediatric, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Some improvement in one small open-label study in patients with autism or pervasive developmental dis
Only 3 of 12 pediatric patients benefited in a small retrospective chart review (Demb & Roychoudhury, 2

3) Adult:

a) In a 12-week open-label pilot study of eight children, adolescents, and adults with pervasive development were rated as much improved or very much improved on the Clinical Global Impression Scale. Patients range criteria for pervasive developmental disorder (autistic disorder, n=5; not otherwise specified, n=3). Mean olan changes from baseline were observed on the Vineland Maladaptive Behavior Scale, Rivto-Freeman Real-life Questionnaire, and portions of the Clinician-Rated Visual Analog Scale (all p less than 0.001). One patient dr patients experienced weight gain, and three patients reported sedation (Potenza et al, 1999).

4) Pediatric:

a) A retrospective chart review demonstrated that olanzapine therapy (2.5 to 15 milligrams per day (mg/d)) w and hallucinations in only 3 of 12 pediatric patients (aged 5 to 17 years) with developmental disabilities or psy efficacy reporting improvement or worsening of symptoms. Ten of the 12 studied had previously failed other p mentally retarded. Eight of the 12 children discontinued olanzapine after a mean duration of 50 days due to a exacerbated target symptoms or a combination of these issues (2). The most frequent side effects were an ir tremulousness, drooling, and suicidal ideation were also reported (Demb & Roychoudhury, 2000). In another olanzapine due to weight gain despite a positive response to therapy, while adult responders continued thera groups may exhibit diverse responses to olanzapine treatment (Potenza & McDougle, 2001).

b) In a 12-week open-label pilot study of eight children, adolescents, and adults with pervasive development were rated as much improved or very much improved on the Clinical Global Impression Scale. Patients range criteria for pervasive developmental disorder (autistic disorder, n=5; not otherwise specified, n=3). Mean olan changes from baseline were observed on the Vineland Maladaptive Behavior Scale, Rivto-Freeman Real-life Questionnaire, and portions of the Clinician-Rated Visual Analog Scale (all p less than 0.001). One patient dr patients experienced weight gain, and three patients reported sedation (Potenza et al, 1999).

4.5.AB Posttraumatic stress disorder

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category C
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Improved all types of symptoms of PTSD in combat veterans (Petty et al, 2001)
Effective in reducing sleep disturbance and nightmares secondary to PTSD in one case report (Labbate,

3) Adult:

a) Adjunctive olanzapine therapy was more effective than placebo in the treatment of patients with selective

posttraumatic stress disorder (PTSD). In a randomized, double-blind, placebo-controlled study, patients with
responsive to at least 12 weeks of SSRI treatment received 8 weeks of adjunctive therapy with either placebo
(mg)/day then titrated to 20 mg/day as necessary; mean dose, 15 mg/day). Concurrent SSRI medications inc
paroxetine (median dose 40 mg/day), and sertraline (median dose 200 mg/day). Olanzapine-treated patients
symptoms (p less than 0.05), sleep disturbances (p=0.01), and depressive symptoms (p less than 0.03) as co
clinical global improvement were not significantly different between the two treatment groups. Patients treate
during treatment as compared with placebo (mean, 13.2 pounds (lb) vs -3 lb, respectively; p=0.001). In this re
olanzapine as an adjunctive treatment to an SSRI should be weighed against the potential health risks assoc
b) Olanzapine treatment improved all outcome measures of post- traumatic stress syndrome (PTSD) in a gro
PTSD. In an 8-week, open-label, uncontrolled study, all patients (n=46) were initially given olanzapine 5 milli
in 5 mg/week increments to a maximum of 20 mg/day. Mean dose at study end was 14 mg/day. By the end o
PTSD Scale (CAPS) decreased by approximately 30%. Symptom clusters were reduced: intrusive by 31%, a
Adverse event included increased appetite (49%), dry mouth (45%), insomnia (23%), weight gain (22%), drow
(13%), dizziness (10%), constipation (10%), and tremor (10%). Only 30 patients completed the study (Petty e
c) Nightmares and hallucinations experienced by a 58-year-old male combat veteran with posttraumatic stre
initiation of olanzapine therapy (5 milligrams at bedtime). The patient, who had a 20-year history of PTSD had
disturbances with psychotherapy and numerous psychotropics including amitriptyline, imipramine, doxepin, d
fluoxetine, bupropion, sertraline, and trazodone. Although his depression and anxiety improved, nightmares a
and anxiety were reasonably well controlled with sertraline 200 mg daily, bupropion 150 mg daily, and diazep
this regimen, sleep quality improved after 2 nights. A trial dose of 10 mg caused daytime drowsiness and har
Nightmares did not recur during the next 4 months (Labbate, 2000).

4.5.AC Repetitive self-excoriation

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Effective in self-induced dermatoses in isolated cases (Gupta & Gupta, 2000)

3) Adult:

a) Self-excoriation of acne lesions was significantly reduced in a 28-year-old high school teacher by treatmer
14 and had begun excoriating her acne at age 16. At age 18 her acne was successfully treated with isotretino
of stress, and she resumed self- excoriation. Under stress at age 28 and performing excoriation, she was give
Improvement in her excoriating behavior was evident in 2 weeks, with further improvement at 4 weeks. She c
psychotherapy. As of 4 months after the discontinuation of olanzapine, she had maintained the improvement
b) Three patients with self-inflicted dermatoses were successfully treated with olanzapine 2.5 to 5 milligrams
acne, self-induced skin ulcers, and trichotillomania within 2 to 4 weeks of initiating olanzapine therapy. Durati
Improvement was maintained in 1 patient by taking 2.5 mg once or twice weekly as required (Gupta & Gupta,

4.5.AD Schizophrenia

FDA Labeled Indication

1) Overview

FDA Approval: Adult, yes (oral formulations only); Pediatric, no
Efficacy: Adult, Effective; Pediatric, Evidence favors efficacy
Recommendation: Adult, Class IIa; Pediatric, Class IIb
Strength of Evidence: Adult, Category B; Pediatric, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Indicated for the management of schizophrenia (Prod Info ZYPREXA(R) oral tablets, IM injection, ZYPRI
2006).
Produced significant reductions in both positive and negative symptoms in schizophrenic and schizophre
Effective for positive and negative symptoms of schizophrenia in Japanese patients (Ishigooka et al, 200
Olanzapine and quetiapine were both effective in reduction of symptomatology, but a significant weight g
population, according to a 6-month, randomized, open-label study in 51 patients with first episode psych

3) Adult:

a) General Information

1) Oral olanzapine has produced significant reductions in both positive and negative symptoms in schizo
uncontrolled and placebo-controlled studies, with a low propensity for extrapyramidal effects (Prod Info Z
al, 1996)(Anon, 1995; Anon, 1994b; Anon, 1994aa). The drug has been more effective than haloperidol f
(Beasley et al, 1996)(Anon, 1995). In one review of medical records, olanzapine was more likely to be ef
also have a diagnosis of bipolar disorder (Zarate et al, 1998). In 1 case, it was successfully used for the s
associated with coproporphyria (Strauss & DiMartini, 1999).

b) Short-term Treatment

1) Olanzapine and risperidone were equally safe and effective therapies in the treatment of schizophren
multicenter, double-blind study, 175 elderly patients (mean age, 71 years) were randomized to receive e
(mg)/day) or olanzapine (mean dose, 11.1 mg/day) for 8 weeks following a 1 week washout period of all

was 36.5 years and Positive and Negative Syndrome Scale (PANSS) scores were between 50 and 120 a decrease of at least 20% in the total PANSS score. Both treatment groups showed significant reductions points (p less than 0.005) and significant differences were not observed between groups. Fifty-eight perc olanzapine-treated patients achieved clinical improvement as defined by the study. Both groups also exh PANSS factor scores (p less than 0.001). The greatest mean change in the total PANSS score occurred antipsychotic medications in the thirty days prior to entering the study (p less than 0.001). The rate of ext the risperidone and olanzapine treatment groups (9.2% vs 15.9%, respectively, p=ns). The severity of EP baseline to endpoint with no significant difference between groups. A 7% or higher increase in weight oc patients as compared with those who received risperidone (14.8% vs 5.1%, p=0.043). No new cardiovas population and mean QT-c changes were not considered clinically relevant (Jeste et al, 2003a).

2) Olanzapine was safe and effective for the treatment of schizophrenia in Japanese patients. Eighty-on of Diseases, 9th edition, criteria for schizophrenia were given olanzapine 1 milligram (mg) per day to a m optional 4 week extension. The mean dose during the study was 7.9 mg/day. Prior to the study, 67% of p medications, whereas during the study, only 14% used anticholinergics, suggesting that the frequency o with olanzapine than with their prior antipsychotic medications. Moderate and remarkable improvement v Psychiatric Rating Scale showed statistically significant improvement (p less than 0.05) from week 1 to w anergia; from week 2 to week 9 on activation and thought disturbances; and from week 4 to week 8 on h effects were insomnia, weight increase, excitement, sleepiness, and anxiety. Serum prolactin levels, whi endpoint (Ishigooka et al, 2001a).

3) In one case report, high doses (40 milligrams/day) of olanzapine appeared to be more effective for tre milligrams/day (Alao, 2000). The patient, who had a history of schizophrenia, initiated olanzapine therapy was continued for 3 weeks with no significant clinical improvement. The dose was then increased to 40 r improvements in thought process, agitation, and behavior. Additionally, there was no evidence of extrapy dose. Complete blood counts, liver function tests, electrocardiogram, vital signs, and clinical evaluations distinguish the benefits and weaknesses of high-dose olanzapine therapy in treatment- resistant schizop

4) Olanzapine combined with sulpiride, a selective dopamine-2-receptor blocker, significantly improved s schizophrenia (n=5) and acute psychosis (n=1). Olanzapine doses were titrated to 20 milligrams (mg) da Sulpiride doses ranged from 60 to 600 mg daily. Treatment response, defined by improvement in the Bri and Negative Syndrome Scale (PANSS), and the Clinical Global Impression Scale (CGI), occurred betw adverse effects were reported (Raskin et al, 2000).

5) Five patients who experienced refractory psychosis attributed to noncompliance with clozapine therap to tolerate olanzapine therapy (Weiss, 1999). On admission, all patients were drug-free, highly symptom (BPRS) score of 47. At discharge, all patients were responding well to olanzapine treatment (10 to 20 mi Upon interview, 2 patients reported mild dizziness and weight gain, while 1 patient reported akathisia. M olanzapine in patients with treatment-refractory psychosis who are intolerant of clozapine.

6) A successful transition from clozapine to olanzapine was attained in 8 out of 19 schizophrenic or schi clozapine (Henderson et al, 1998). In an open study, olanzapine 5 milligrams (mg) daily was added to ea weekly to a maximum of 30 mg/day. After the first week, clozapine doses were gradually decreased by ir transition was defined as maintaining a stable clinical status on olanzapine treatment alone for at least 2 and mean final olanzapine dose was 17.1 mg/day. Eight patients successfully transitioned, 7 patients de hospitalization, and an additional 4 patients showed worsening of clinical status. Scores on the Brief Psy increases for the negative symptoms subscale (p=0.002) and the depressive symptoms subscale (p=0.0 clinical status stabilize after 4 to 8 weeks. Those that responded had been treated for a significantly shor receiving a lower dose of clozapine (p=0.05).

7) In an open study, some patients with refractory schizophrenia or schizoaffective disorder responded t (mg)/day (Fanous & Lindenmayer, 1999). Seven treatment-refractory patients received olanzapine titrate Brief Psychiatric Rating Scale was achieved at a dose of 25 mg in 3 of 7 patients; they had only achieved was achieved by a fourth patient at 30 mg/day while only attaining a 14% reduction at lower doses. Only mg/day. Three of the 4 responders were also receiving typical neuroleptics. The 2 nonresponders were r were well-tolerated with only weight gain and diarrhea reported as adverse effects.

8) In an open trial of olanzapine in 16 patients with treatment-refractory psychosis, only two patients sho Improvement score of 1 to 3) over the 12 week study period. Patients were between 31 and 49 years old patients had failed therapy with at least 2 antipsychotics previously and were taken off all psychotropics, patient taking valproic acid. Two patients were taken off olanzapine after one week; one due to mania an behavior and paranoia. Two additional patients did not finish 12 weeks of treatment. Based on the Positiv Global Impression scale, no significant changes were seen over the 12 week period. Mean daily benzodi period; however, benztropine use decreased (p less than 0.05). No patient discontinued olanzapine due

9) Olanzapine showed a superior and broader spectrum of efficacy over haldol in the treatment of schizo profile (Tollefson et al, 1998a; Tollefson et al, 1997b). In a large international, multicenter double-blind tri haloperidol (n=660) over 6 weeks. Starting doses were 5 milligrams (mg) for both drugs which could be i discretion to a maximum of 20 mg/day. Olanzapine was significantly superior to haldol on the Brief Psych and Negative Syndrome Scale (p=0.05), the Clinical Global Impression severity score (p less than 0.03), Scale total score (p=0.001). Significant advantages were also seen in the extrapyramidal profiles and eff subsequently criticized (Capehart & Holsinger, 1998; Barbui, 1998; Mattes, 1998). Some of the criticisms participants, mismatched doses of haloperidol and olanzapine, and questionable blinding procedures.

10) In an open, pilot study, olanzapine was effective and well-tolerated in neuroleptic-resistant patients ((subtypes: 18 paranoid type, 4 disorganized, 3 undifferentiated) with a documented lack of response to 2 week study with olanzapine 15 to 25 milligrams. At the end of the study, the patients showed a statistical

positive and negative symptoms (p less than 0.05). Overall 35% of the patients met the criteria for treatm total score of less than 18 on the Brief Psychiatric Rating Scale and a rating of less than 3 on the Clinica report also documents the effectiveness of olanzapine in a patient that was treatment-resistant to typical clozapine due to tachycardia (Thomas & Labbate, 1998).

11) With olanzapine in mean doses of 11.6 and 16.3 milligrams daily for a period of 6 weeks, reductions scores by 13 and 15 (from baseline of approximately 42), respectively, were reported in schizophrenic pa exacerbation) in a relatively large trial (n=335). For positive symptoms (BPRS-positive), such as concept suspiciousness, both doses were of similar efficacy (decreased by 4.5 points), whereas the higher dose (BPRS-negative) (-3 versus -1.4 points), including emotional withdrawal and motor retardation. The Scal also revealed trends for the superiority of the higher dose. Although decreases in the BPRS-total and BP compared to placebo, significance was achieved for negative symptoms on both SANS and BPRS-negat A lower dose of olanzapine (mean, 6.6 milligrams/day) did, however, result in significant reductions in ne flaw in the trial or the need for additional dose-ranging studies. The percentage of patients demonstrating improvement, 80% improvement) did not always reach a level of significance for olanzapine over placeb

12) In a placebo-controlled study (n=152), olanzapine 10 milligrams (mg) daily was significantly superior Psychiatric Rating Scale total and Positive and Negative Syndrome Scale (PANSS) total scores) in chron refractory to prior therapy. Some patients had shown refractoriness to clozapine (Beasley et al, 1996aa). also superior to placebo with regard to core psychotic symptoms (PANSS positive scores and PANSS ne was comparable to placebo on all measures of efficacy.

c) Long-term Treatment

1) Olanzapine is also approved for long-term therapy and maintenance treatment of schizophrenia. Auth concluded that olanzapine demonstrated efficacy and long-term safety in the maintenance treatment res stable schizophrenia or schizoaffective disorder were randomized to receive olanzapine (10 to 20 milligra olanzapine improved on all quality of life measures while the patients receiving placebo worsened. Olanz 15 or 20 milligrams daily) (Anon, 2000).

2) Two other studies were presented that demonstrated olanzapine's superiority to placebo and to a sub maintenance therapy of schizophrenia (Dellva & Tran Tollefson, 1997). In a 46 week double-blind, multic schizophrenia with an acute exacerbation and who had previously responded to acute therapy were enro olanzapine (n=45) or placebo (n=13), and in the second study patients received either olanzapine (n=48) the first study, patients in the olanzapine group experienced a significantly lower relapse risk (p equal to study, patients in the olanzapine group again experienced a significantly lower relapse risk (p equal to 0. dose of olanzapine.

4) Pediatric:

a) Olanzapine and quetiapine were both effective in reducing the symptomatology of first episode psychosis, olanzapine in the adolescent population, according to a 6-month, prospective, randomized, open-label study 1.25 years (range 12 to 18 years), a diagnosis of schizophrenia or any other psychotic disorder according to before the age of 18, lasting less than 1 year were included in the study. Patients were randomized to receive milligrams/day (mg/day), n=24), or olanzapine (mean dose 9.7 +/- 6.5 mg/day, n=26) for 6 months (mean, 14 antipsychotics, such as benzodiazepines, antidepressants, antiepileptics, were permitted. The results of the p published. Based on the intent-to-treat analysis of secondary outcomes, both the olanzapine and quetiapine g months from baseline in the Positive and Negative symptoms scale (PANSS) total score (-2.201, p=0.028 an positive subscale (-2.366; p=0.018 and -2.028, p=0.042, respectively). The negative PANSS subscale scores p=0.011), but the reduction did not reach statistical significance in the olanzapine arm (-0.21, p=0.833). Patie the Strengths and Difficulties Questionnaire (SDQ), but the improvements did reach statistical significance ex between-group comparisons of improvement in secondary endpoints were nonsignificant except patient-repo 15.5 kilograms (kg) (p less than 0.001) was seen in the olanzapine group, and a 5.4 kg gain was seen in the adverse events associated with quetiapine and olanzapine throughout the study included concentration diffic fatigability (79% vs 73%), and sleepiness/sedation (79% vs 84%). At the study conclusion at 6 months, 16 pa study. The results were limited by the open-label study design, small sample size, variety of concomitant med 2009).

4.5.AE Schizophrenia, Refractory

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive; Pediatric, Evidence is inconclusive
Recommendation: Adult, Class IIb; Pediatric, Class IIb
Strength of Evidence: Adult, Category B; Pediatric, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Improved symptoms sufficiently for hospital discharge in about half of patients in small study (Dinakar et
May be effective in the treatment of children with drug-resistant childhood-onset schizophrenia (Mozes e

3) Adult:

a) Among patients who had been hospitalized for schizophrenia for longer than 5 years and who were consid showed sufficient clinical improvement after 3 months of treatment with olanzapine or risperidone to be disch suited to treatment with clozapine either because of medical contraindications or because of unwillingness to were given olanzapine 10 to 30 milligrams (mg) per day or risperidone 4 to 10 mg/day. Treatments were titrat continued for 3 months. Mean scores on the Brief Psychiatric Rating Scale decreased from 67 to 53 for the o risperidone group (n=47) (p less than 0.001 for both groups). Of the 34 patients who were discharged from th

the 90-day follow-up. No significant side effects (such as weight change) were observed during the 3 months

4) Pediatric:

a) Olanzapine seemed to be effective in the treatment of children with drug-resistant schizophrenia. In an op (mean age, 12.5 years), with childhood-onset schizophrenia refractory to previous treatment with at least two 2.5 milligrams (mg)/day, titrated to doses of 10, 15, or 20 mg per day; mean dose, 15.56 mg/day) for 12 week reductions were observed at week 12 as compared with baseline in the mean scores for the Brief Psychotic R p=0.03) and the Clinical Global Impression scale (decreased from 6.09 to 4.7; p less than 0.005). The Positiv mean score was reduced from 123.56 at baseline as compared with 96.7 at week 12 (p=0.026). In addition, t significant reductions at week 12 as compared with baseline (p=0.048 and p=0.05, respectively). The most co and weight gain (100%; mean weight gain, 6.1 kilograms). No extrapyramidal side effects, dystonias, elevate electrocardiogram or electroencephalogram abnormalities were observed. Larger, controlled studies are neec olanzapine for the treatment of childhood-onset schizophrenia (Mozes et al, 2003).

4.5.AF Schizophrenic prodrome

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

May be effective in the treatment schizophrenic prodromal syndrome (Woods et al, 2003)

3) Adult:

a) The results of one study suggest that olanzapine may be effective in the treatment of patients experiencin randomized, double-blind, placebo-controlled, multicenter study, patients with prodromal syndrome received mean dose, 8 mg/day) or placebo (n=29) for 8 weeks. Results of the study were inconsistent across analyses olanzapine-treated patients showed a significant improvement from baseline to endpoint in total score for the x time interaction), as compared with placebo (p less than 0.005). However, when a last observation carried f favored olanzapine but did not reach statistical significance. Significantly more patients taking olanzapine exp baseline body weight as compared with placebo (56.7% vs 3.4%, respectively, p less than 0.001). Larger, lon clinical efficacy (Woods et al, 2003).

4.5.AG Senile dementia of the Lewy body type

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Effective in low doses (5 milligrams/day) but not at high doses (15 mg/day) (Cummings et al, 2002)

3) Adult:

a) Olanzapine at low doses significantly reduced delusions and hallucinations in patients with dementia with were a subset of patients with Alzheimer's disease being treated for psychosis with various doses of olanzapi controlled trial. Within the DLB subset, 10 patients were treated with placebo, 5 with olanzapine 5 milligrams with olanzapine 15 mg/day. In comparison to scores with placebo treatment, final scores on the delusions sul Home (NPI/NH) after 12 weeks of olanzapine treatment were significantly better for the 5 mg group (p=0.009) mg group. Scores on the hallucinations subscale were significantly better for the 5 mg group only. Olanzapine symptoms of parkinsonism or any decrease in cognition. The 5-mg dose also diminished disruptiveness of pa

b) Olanzapine (2.5 to 7.5 milligrams daily) showed little advantage over conventional neuroleptics in 8 patien (DLB). Only 2 patients demonstrated clear improvement in psychotic and behavioral symptoms. Three patien remaining 3 patients could not tolerate olanzapine, even at the lowest dose. The data suggests that benzodia methods should be considered prior to olanzapine for treatment of DLB (Walker et al, 1999).

4.5.AH Severe major depression with psychotic features

See Drug Consult reference: PSYCHOTIC DEPRESSION - DRUG THERAPY

4.5.AI Tardive dyskinesia

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Improvements seen in tardive dyskinesias after switching to olanzapine in case reports (Soutullo et al, 19

See Drug Consult reference: TARDIVE DYSKINESIA - DRUG THERAPY

3) Adult:

a) Tardive dyskinesia improved in 2 patients after being switched to olanzapine (Soutullo et al, 1999a). The f
Abnormal Involuntary Movement Scale (AIMS) which improved after 4 weeks. His AIMS score was 9 at 2 mo
maintained on olanzapine 15 milligrams (mg). The second had a score of 31 which improved to 3 after 1 wee
a score of 9. Other cases of significant improvement have been reported (Almeida, 1998).
b) Four cases of patients with tardive dyskinesias showing marked improvements on the Abnormal Involunta
al, 1998). All cases involved patients on long-term neuroleptic therapy that were switched to olanzapine and t
therapy tardive dyskinesias had decreased.

4.5.AJ Trichotillomania

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Effective in several cases, either alone or as adjunct therapy with fluoxetine or citalopram (Gupta & Gupt
Effectively reduced symptoms of hair pulling during small, open-label trial (Stewart & Nejtek, 2003)

3) Adult:

a) Olanzapine therapy reduced symptoms of hair pulling, depression, and anxiety in patients with trichotillom
(n=17) diagnosed with trichotillomania received 12 weeks of treatment with olanzapine (initial, 2.5 milligrams
mg at bedtime by week 8; mean dose at week 12, 8.5 mg/day). A significant reduction in the mean score for t
Scale (MGH) was observed from baseline to weeks 4, 6, 8, and 12 (weeks 4 and 6, p less than or equal to 0.
From baseline to endpoint, hair pulling was reduced by 66% (MGH), anxiety levels decreased by 63% as mea
less than or equal to 0.05) and depressive symptoms shrunk by 43% as measured by the Hamilton Rating Sc
events were sedation and weight gain. Randomized, controlled trials are needed to confirm these findings (St
b) In 3 of 4 patients with trichotillomania as well as other psychiatric disorders, olanzapine in addition to citalo
trichotillomania had failed to respond to various regimens of SSRIs (selective serotonin reuptake inhibitors). E
milligrams (mg) per day. The dose used by the patient whose trichotillomania did not respond was 1.25 mg/d
mg/day (Ashton, 2001).
c) Three patients with self-inflicted dermatoses were successfully treated with olanzapine 2.5 to 5 milligrams
acne, self-induced skin ulcers, and trichotillomania within 2 to 4 weeks of initiating olanzapine therapy. Durati
Improvement was maintained in 1 patient by taking 2.5 mg once or twice weekly as required (Gupta & Gupta,
d) A 22-year-old woman with trichotillomania improved when olanzapine was added to her fluoxetine regime
trichotillomania and obsessive-compulsive disorder. She had failed trials with multiple selective serotonin reu
perphenazine. She did have a response to fluvoxamine with risperidone but developed severe hyperprolactin
milligrams (mg)/day and then had olanzapine 10 mg added. After 7 weeks, her Massachusetts General Hosp
and the Yale-Brown Obsessive Compulsive Scale compulsion subscale from 13 to 4. Due to sedation, her ola
Thereafter, she tolerated olanzapine well but gained 8 pounds.

4.6 Comparative Efficacy / Evaluation With Other Therapies

Aripiprazole

Chlorpromazine

Clozapine

Haloperidol

Lithium

Olanzapine/Fluoxetine Hydrochloride

Perphenazine

Quetiapine

Risperidone

Valproic Acid

Ziprasidone

4.6.A Aripiprazole

4.6.A.1 Schizophrenia

a) A trend toward greater improvement in some areas of neurocognitive function (eg, verbal learning, workin daily compared to olanzapine 15 mg daily in a randomized study (n=256) (Kern et al, 2001). However, a plac unavailable (unpublished).

4.6.B Chlorpromazine

Schizophrenia

Schizophrenia, Treatment-resistant

4.6.B.1 Schizophrenia

a) Based upon comparisons of minimum effective dosages identified in placebo-controlled, fixed-dose and fi schizophrenic patients, the minimum effective dose of olanzapine was 10 milligrams/day (equivalent to chlorp

4.6.B.2 Schizophrenia, Treatment-resistant

a) Olanzapine 25 milligrams (mg) daily and chlorpromazine 1200 mg daily plus benztropine 4 mg daily show randomized trial of 84 patients with treatment-resistant schizophrenia. No significant differences were seen b Scale (BPRS), Scale for the Assessment of Negative Symptoms, or the Clinical Global Impression (CGI) Sco of the chlorpromazine patients met response criteria of at least a 20% reduction in baseline BPRS score and post-treatment BPRS score of less than 35. Dry mouth, orthostatic changes, and unsteady gait were more co 0.01), as was extrapyramidal symptoms (p less than 0.05) (Conley et al, 1998).

4.6.C Clozapine

Bipolar disorder

Drug-induced psychosis

Hostile behavior

Schizophrenia

Schizophrenia - Suicidal intent

4.6.C.1 Bipolar disorder

a) In a retrospective study of 50 consecutive patients treated for bipolar disorder with atypical antipsychotic r and risperidone (n=25), along with standard mood stabilizers, showed similar efficacy. Overall, 68% of patien Clinical Global Impressions assessment over the 12-week study. Mean dosages were 210 milligrams (mg) pe and 1.7 mg day for risperidone. The only serious adverse event to occur during the study was a seizure in a p (EPS) were reported in 12 of 42 subjects (28.6%). Parkinsonism occurred in 4 of 25 patients taking risperidor clozapine. Weight gain was more extreme in patients taking clozapine and olanzapine than in those taking ris reported in other studies, may have been affected by concurrent mood enhancing medications (Guille et al, 2

4.6.C.2 Drug-induced psychosis

a) In a small (n=18), open study, clozapine and olanzapine were both effective in reducing symptoms of dop Parkinson's disease. However, olanzapine and not clozapine caused worsening of Parkinsonian symptoms. T milligrams (mg) per day and was increased at weekly intervals as necessary to optimize clinical status. The fi week study was 16.9 mg /day (range: 6.25 to 37.5 mg/day). Olanzapine was started at 2.5 to 5 mg/day. The f completing the study was 4.7 mg/day (range: 2.5 to 10 mg/day). Three patients dropped out of the study after for 2 patients, 5 mg for 1 patient) because of worsening of parkinsonism. All patients in the clozapine group c somnolence, falls, orthostatic hypotension, and syncope. Neuropsychiatric symptoms markedly improved with Neuropsychiatric Inventory global scores for clozapine and olanzapine, respectively). Parkinsonian motor scc group and worsened by 25% in the olanzapine group. It is possible that the differences observed were due to of olanzapine was excessive (Gimenez-Roldan & Mateo D Navarro, 2001).

4.6.C.3 Hostile behavior

a) Clozapine reduced hostility in patients with schizophrenia and was superior to haloperidol and risperidone with a diagnosis of schizophrenia or schizoaffective disorder and a history of poor response to drug treatmen

olanzapine, risperidone, or haloperidol in cross-titration with the antipsychotic drug used prior to the start of th antidepressants had been phased out earlier. Daily doses of olanzapine, risperidone, and haloperidol were es 20, 8, and 20 milligrams (mg), respectively. Patients receiving clozapine were scheduled to achieve the targe fixed for the remainder of the initial 8-week period. In a second (6-week) period, doses were allowed to vary: olanzapine, 4 to 16 mg for risperidone, and 10 to 30 mg for haloperidol. Hostility, measured by the hostility ite (PANSS), improved significantly (in comparison to baseline) in the clozapine group only (p=0.019). This effec symptoms (delusional thinking, hallucinations) or on sedation. The effect of clozapine on hostility was superic (p=0.012) but not to that of olanzapine (Citrome et al, 2001).

4.6.C.4 Schizophrenia

a) Olanzapine and risperidone improved neurocognitive deficits more than did haloperidol or clozapine in pat that was refractory to treatment with typical antipsychotics. In a randomized, double-blind study, inpatients we (mg) per day, olanzapine (n=26) 10 to 40 mg/day, risperidone (n=26) 4 to 16 mg day, or haloperidol (n=25) 1(treatment (target doses: olanzapine 20 mg/day, risperidone 8 mg/day, haloperidol 20 mg/day, clozapine 500 week study; during the last 6 weeks, dosages were adjusted individually (generally increased if response was adverse effects). Improvement over time in global neurocognitive score was seen for olanzapine and risperid organization and in processing speed and attention, improvement was seen with olanzapine. In simple motor Changes in global neurocognitive performance with olanzapine and risperidone were of medium magnitude (enough to be clinically significant. Beneficial changes with clozapine were modest. Despite cognitive gains, p ability and social/vocational functioning. Improvements in neurocognitive deficits were associated with improv

4.6.C.5 Schizophrenia - Suicidal intent

a) In the International Suicide Prevention Trial (InterSePT), clozapine was shown to be more effective than o adult, patients with schizophrenia or schizoaffective disorder. Men and women between the ages of 18 to 65 recruited to participate in this 2-year, prospective, randomized, international, parallel group, study. The endpo attempts (including completed suicides) or hospitalization due to imminent suicide risk (type 1 events) or ratin Clinical Global Impression of Suicide Severity (CGI-SS) scale (type 2 events). Of the total sample of 980 pati diagnosed as having schizophrenia and 38% (371) were diagnosed with schizoaffective disorder. Twenty-sev treatment resistant. The patients were divided into two treatment groups (clozapine or olanzapine) and did no diagnosis, treatment resistance, number of previous suicide attempts, or baseline concomitant medications. E Dropout rates for the two groups were similar with 192 discontinuing treatment with clozapine and 187 with ol (95% CI, 0.58-0.97) for type 1 events (p=.03) and 0.78 (95% CI, 0.61-0.99) for type 2 events (p=.04) compare adverse events for the olanzapine group were weight gain, somnolence, dry mouth, and dizziness, while saliv dizziness were the most frequently reported adverse events reported for the clozapine group. The overall nur between the two groups. Decreased white blood cell counts occurred in 5.8% of clozapine-treated patients ar were no reports of agranulocytosis or deaths due to granulocytopenia in either group. There was a total of 8 s olanzapine). The mean daily olanzapine dosage was 16.6 +/- 6.4 mg and the mean daily clozapine dosage w

4.6.C.6 Adverse Effects

a) The results of one study suggest that patients receiving atypical antipsychotics have a higher incidence of conventional antipsychotic medication. In a retrospective, pharmacovigilance study, 192 cases of pancreatitis dose, 306.7 milligrams (mg)/day), olanzapine (mean dose, 15 mg/day), risperidone, (mean dose, 4 mg/day) c identified cases, 40%, 33%, and 16% were related to treatment with the atypical antipsychotic medications cl as compared with 12% of the cases which were related to the conventional neuroleptic, haloperidol. In most p months after initiation of treatment (Koller et al, 2003b).

b) Results of a retrospective analysis showed that olanzapine treatment was associated with a lower rate of but was similar to rates occurring with risperidone and clozapine therapy. In a pooled analysis of 23 randomiz schizophrenia, frequency and severity of EPS associated with olanzapine therapy (2.5 to 20 milligrams (mg)/(mg/day), risperidone (4 to 12 mg/day), clozapine (25 to 625 mg/day), and placebo. Dystonic events (ie, dysto occurred in significantly fewer patients during olanzapine treatment as compared with haloperidol (0.5% vs 5. (1% vs 3.2%, respectively; p=0.047) treatment, while no significant difference was found between olanzapine olanzapine-treated patients, a significantly higher percentage of haloperidol-treated patients experienced parl extrapyramidal syndrome, hypertonia, hypokinesia, masked facies, and tremor) (9.3% vs 28.3%, respectively akathisia, hyperkinesia) (6.7% vs 20.4%, respectively; p less than 0.001) during therapy. However, no signific olanzapine group as compared with the placebo, risperidone, or clozapine groups in regard to the occurrence occurred in significantly more patients treated with haloperidol as compared with olanzapine (44.4% vs 16.2% patients treated with clozapine as compared with olanzapine (2.6% vs 6.8%, respectively; p=0.047). The over and risperidone groups as compared with olanzapine. Significantly fewer patients received anticholinergic me with the haloperidol (p less than 0.001) or risperidone (p=0.018) groups. No difference was found between ol placebo or clozapine in regard to percentage of patients given anticholinergic drugs during therapy (Carlson e

c) In an open-label trial (n=24), olanzapine-treated patients had significantly lower levels of serum anticholine to enrollment, subjects were stabilized on therapeutic doses, averaging 15 milligrams (mg)/day and 444 mg/d mean serum anticholinergic levels were 0.96 and 5.47 picomoles/atropine equivalents in the olanzapine and (Scores assessing clinical anticholinergic effects were significantly higher for salivation, constipation, micturitic clozapine versus olanzapine recipients (p less than 0.05). Dry mouth was more problematic with olanzapine t differ cognitively with respect to Mini Mental State Exam scores. Although efficacy was not a primary endpoin clozapine (p=0.002), with no statistical difference in Clinical Global Impression Scale, Severity subscale score due to adverse effects (Chengappa et al, 2000).

4.6.D Haloperidol

Adverse reaction to cannabis - Drug-induced psychosis

Mania

Schizophrenia

Tardive dyskinesia

4.6.D.1 Adverse reaction to cannabis - Drug-induced psychosis

a) Olanzapine was as effective as haloperidol in the treatment of cannabis-induced psychotic disorder (Berk
a psychotic episode associated with cannabis use were randomized to receive either olanzapine 10 milligram
weeks there was a significant improvement in both groups as compared to baseline measured on the Brief Ps
p=0.0001 for haloperidol). There was no significant difference between the 2 groups. Olanzapine was associa

4.6.D.2 Mania

a) Olanzapine and haloperidol therapies were similarly effective in the treatment of acute mania in patients w
study, patients with bipolar I disorder, mixed or manic episode and a Young-Mania Rating Scale (Y-MRS) sco
milligram (mg)/day) or haloperidol (3 to 15 mg/day) at flexible doses for 6 weeks. Patients showing symptom
in which they received ongoing treatment. Symptomatic remission was defined as a Y-MRS score of 12 or les
score (HAM-D) of 8 or less at week 6. Symptomatic remission rates for patients in the olanzapine group were
at week 6 (52.1% vs 46.1%, respectively; p=NS) and week 12 (51.7% vs 43.8%, respectively; p=NS). Howev
improvements in health- related quality of life factors as compared with haloperidol treatment (Shi et al, 2002)

4.6.D.3 Schizophrenia

a) SUMMARY: Olanzapine is more effective than haloperidol for the treatment of negative symptoms of schiz
managing positive symptoms. Olanzapine is less likely to induce extrapyramidal reactions or elevation of seru
b) Olanzapine and risperidone improved neurocognitive deficits more than did haloperidol or clozapine in pa
that was refractory to treatment with typical antipsychotics. In a randomized, double-blind study, inpatients we
(mg) per day, olanzapine (n=26) 10 to 40 mg/day, risperidone (n=26) 4 to 16 mg day, or haloperidol (n=25) 1
treatment (target doses: olanzapine 20 mg/day, risperidone 8 mg/day, haloperidol 20 mg/day, clozapine 500
week study; during the last 6 weeks, dosages were adjusted individually (generally increased if response was
adverse effects). Improvement over time in global neurocognitive score was seen for olanzapine and risperid
organization and in processing speed and attention, improvement was seen with olanzapine. In simple motor
Changes in global neurocognitive performance with olanzapine and risperidone were of medium magnitude (
enough to be clinically significant. Beneficial changes with clozapine were modest. Despite cognitive gains, p
ability and social/vocational functioning. Improvements in neurocognitive deficits were associated with improv
c) Olanzapine was at least as effective as and safer than haloperidol for the treatment of schizophrenia in a l
and negative symptoms resistant to treatment with typical antipsychotics. In a randomized, double-blind trial,
milligrams (mg) per day and increased to a maximum of 15 mg/day, or haloperidol, starting at 4 mg/day and i
daily doses were 10.5 mg for olanzapine and 8 mg for haloperidol. The proportion of olanzapine-treated patie
improvement was 44.5%, compared to 40.5% of haloperidol-treated patients. The 95% confidence interval wa
olanzapine was not inferior to haloperidol in efficacy. Total and subscale scores on the Positive and Negative
in the olanzapine group than in the haloperidol group, but only on the negative symptoms subscale did the di
Eighty-one percent of olanzapine-treated patients and 66% of haloperidol-treated patients finished the study,
because of adverse events or abnormal laboratory values (8 vs 22). Olanzapine-treated patients showed an
whereas haloperidol-treated patients showed a worsening (p less than 0.001). Treatment-emergent parkinsor
18.8% of the haloperidol group. By the end of treatment, parkinsonism had resolved in all patients in the olan
haloperidol group. There was a significantly greater incidence of insomnia, akathisia, tremor, anorexia, increa
nausea, and weight decrease in haloperidol-treated patients than in olanzapine-treated patients. Only weight
kilogram vs -0.71 kilogram, p less than 0.001). Thirty-two percent of olanzapine-treated patients showed no a
abnormality, compared to 15.5% of haloperidol-treated patients (p=0.008) (Ishigooka et al, 2001).
d) Olanzapine has been at least as effective as haloperidol, each given for six weeks, in the treatment of sch
1996)(Anon, 1996; Anon, 1995). Overall improvement, based on Brief Psychiatric Rating Scale (BPRS) total s
reached significance in the largest trial (Anon, 1996). Both agents have produced similar decreases in positiv
with olanzapine is attributed to a greater reduction in negative symptoms in these patients, particularly in high
negative symptoms have been significantly greater with olanzapine on the Scale for the Assessment of Nega
Syndrome Scale (PANSS), although significance was not achieved on the BPRS-negative scale in one study
have demonstrated greater than 80% improvement in BPRS-total scores with olanzapine, whereas the perce
always differed significantly between drugs.
e) Intramuscular (IM) olanzapine successfully treated acutely agitated patients with schizophrenia in 3 clinica
evaluated 108 patients receiving fixed or variable doses of 2.5, 5.0, 7.5, or 10.0 milligram (mg) given as 1 to 4
20 mg orally (PO) QD for 2 days. Response was assessed using the Brief Psychiatric Rating Scale (BPRS); t

PO Administration (no statistical analysis was performed). The third study was a multicenter, double-blind, pla with IM haloperidol in the treatment of acute agitation. Patients (n=311) received up to 3 doses of olanzapine hours. Thereafter, patients were treated with oral olanzapine (5 to 20 mg QD) or oral haloperidol (5 to 20 mg or haloperidol showed significantly greater improvement over placebo at 2 and 24 hours as measured by the observed between olanzapine- and haloperidol-treated patients. Patients treated with intramuscular olanzapi significant difference between patients treated with IM drug between baseline and day 5 (Jones et al, 2000)

f) In a study of 300 patients with schizoaffective disorder, olanzapine treated patients showed significantly gr patients on the Brief Psychiatric Rating Scale (BPRS) total (p=0.002), Positive and Negative Syndrome Scale (p=0.006), and Montgomery-Asberg Depression Rating Scale (MADRS) total (p less than 0.001). Patients we study. Patients were assessed weekly for a six week acute phase with responders followed for up to 1-year. olanzapine (5 to 20 milligrams) was superior to haloperidol (5 to 20 milligrams) in the BPRS (p=0.012), PANS MADRS (p less than 0.001); however, in depressed subtype patients, no significant differences were seen wh During the double-blind extension phase, the only significant difference between treatment groups was in the (p=0.045). Extrapyramidal symptoms were less severe among olanzapine treated patients (p=0.016), but wei al, 1997).

g) In a 6-week randomized study of 83 patients with first-episode psychosis (schizophrenia, schizophreniform receiving olanzapine showed significantly greater improvement on the Brief Psychiatric Rating Scale (BPRS) (PANSS) as compared to patients receiving haloperidol. Patients greater than 45 years of age at onset of syr years received olanzapine or haloperidol 5 milligrams (mg) per day and adjusted every 7 days within the rang olanzapine treated patients experienced a 40% or greater improvement from baseline compared to 29.2% of treated patients also improved more on the PANSS total score (p=0.02) and positive symptom score (p=0.03 the Simpson-Angus scale, olanzapine patients showed improvement in extrapyramidal symptoms, whereas h 0.001). Somnolence was more common in olanzapine treated patients, whereas akathisia and hypertonia we 1999).

h) Olanzapine showed a superior and broader spectrum of efficacy over haloperidol in the treatment of schiz profile (Tollefson et al, 1997). In a large international, multicenter double-blind trial, olanzapine (N=1336) was Starting doses were 5 milligrams (mg) for both drugs which could be increased by 5 mg increments at the inv Olanzapine was significantly superior to haloperidol on the Brief Psychiatric Rating Scale (p less than 0.02), t (p=0.05), the clinical Global Impression severity score (p less than 0.03), and the Montgomery-Asberg Depre Significant advantages were also seen in the extrapyramidal profiles and effects on prolactin levels. Further *a* symptoms were also better controlled with olanzapine therapy (Tollefson et al, 1998). On the Montgomery-As significantly more effective than haloperidol (p = 0.001).

i) In multiple clinical trials of olanzapine, the incidence of self-directed aggression among patients receiving o significantly different (Keck et al, 2000a). These trials indicated a significantly greater improvement in suicida with haloperidol-treated patients. Another analysis demonstrated a 2.3-fold reduction in the annual suicide att receiving olanzapine versus haloperidol.

4.6.D.4 Tardive dyskinesia

a) Olanzapine was associated with a lower incidence of tardive dyskinesia when compared to haloperidol (T and blinded studies evaluating patients with schizophrenia, schizophreniform disorder, or schizoaffective disc (n=197) were compared. Patients had no evidence of tardive dyskinesia at baseline. At any visit after baselin 16.2% of patients in the haloperidol group manifested treatment-emergent tardive dyskinesia (p less than 0.0 patients and 7.6% of haloperidol patients manifested tardive dyskinesia (p equal to 0.001). Similar results hav

4.6.D.5 Efficacy

a) Results of a retrospective analysis showed that olanzapine treatment was associated with a lower rate of but was similar to rates occurring with risperidone and clozapine therapy. In a pooled analysis of 23 randomiz schizophrenia, frequency and severity of EPS associated with olanzapine therapy (2.5 to 20 milligrams (mg)/ mg/day), risperidone (4 to 12 mg/day), clozapine (25 to 625 mg/day), and placebo. Dystonic events (ie, dysto occurred in significantly fewer patients during olanzapine treatment as compared with haloperidol (0.5% vs 5. (1% vs 3.2%, respectively; p=0.047) treatment, while no significant difference was found between olanzapine olanzapine-treated patients, a significantly higher percentage of haloperidol-treated patients experienced par extrapyramidal syndrome, hypertonia, hypokinesia, masked facies, and tremor) (9.3% vs 28.3%, respectively akathisia, hyperkinesia) (6.7% vs 20.4%, respectively; p less than 0.001) during therapy. However, no signific olanzapine group as compared with the placebo, risperidone, or clozapine groups in regard to the occurrence occurred in significantly more patients treated with haloperidol as compared with olanzapine (44.4% vs 16.2% patients treated with clozapine as compared with olanzapine (2.6% vs 6.8%, respectively; p=0.047). The over and risperidone groups as compared with olanzapine. Significantly fewer patients received anticholinergic me with the haloperidol (p less than 0.001) or risperidone (p=0.018) groups. No difference was found between ol placebo or clozapine in regard to percentage of patients given anticholinergic drugs during therapy (Carlson e

b) Pooled safety results from 3 large double-blind, controlled trials in 2606 patients demonstrated that olanza extrapyramidal symptoms (EPS) occurring versus haloperidol (p less than 0.001) (Tran et al, 1997). Also stat discontinued the study because of EPS (p less than 0.001). This suggests that the use of olanzapine may be fewer adverse effects.

c) The risk of extrapyramidal adverse effects is lower with olanzapine compared to haloperidol, especially dy been significantly less with olanzapine (Tollefson et al, 1997); (Beasley et al, 1996)(Anon, 1996; Anon, 1995)

4.6.D.6 Adverse Effects

a) The results of one study suggest that patients receiving atypical antipsychotics have a higher incidence of conventional antipsychotic medication. In a retrospective, pharmacovigilance study, 192 cases of pancreatitis

dose, 306.7 milligrams (mg)/day), olanzapine (mean dose, 15 mg/day), risperidone, (mean dose, 4 mg/day) c
identified cases, 40%, 33%, and 16% were related to treatment with the atypical antipsychotic medications cl
as compared with 12% of the cases which were related to the conventional neuroleptic, haloperidol. In most p
months after initiation of treatment (Koller et al, 2003).

4.6.E Lithium

4.6.E.1 Mania

a) A review of 3 randomized, double-blinded, placebo-controlled studies concluded that a more rapid antima
loading of divalproex than with standard titration divalproex, lithium or placebo. In these short-term studies, o
30 milligrams/kilogram/day (mg/kg/day) for the first 2 days and maintained at 20 mg/kg/day or it was initiated
increased to a maximum of 20 mg/kg/day plus 1000 mg by day 6. This regimen was compared to divalproex
to serum levels of 40 to 150 micrograms/milliliter (mcg/mL), lithium (n=54) initiated at 300 mg 3 times a day a
and olanzapine (n=55) initiated at 10 mg/day and titrated to a maximum of 20 mg/day and placebo (n=72). Pa
assessed using the change from baseline measurement of the Mania Rating Scale (MRS), the Manic Syndro
Scale (BIS). Intent-to-treat analyses showed that MRS measurements from oral-loaded divalproex patients w
patients. However, it showed significant differences from standard titration divalproex and placebo by day 5 a
Similar results were found for MSS and BIS measurements. Dry mouth and increased appetite was more con
standard titration (p less than 0.05). However, standard titration divalproex was associated with an increased
(p less than 0.05). Divalproex overall was associated with greater decreases in platelet counts than other gro
greater reports of headache and fever (p less than 0.05) and olanzapine was associated with greater adverse
speech disorder, rhinitis, increases in total cholesterol and increases in serum alanine aminotransferase) ove
b) Olanzapine was found to be at least as effective as lithium in the treatment of mania. In a 4-week, double-
were randomized to receive olanzapine 10 milligrams daily or lithium carbonate 400 milligrams twice daily. Th
two treatment groups on any primary outcome measures. However, olanzapine was significantly (p equal to 0
Global Impression severity scale at week 4 (lithium 2.83, olanzapine 2.29). The two medications did not differ
symptoms (Berk et al, 1999a).

4.6.F Olanzapine/Fluoxetine Hydrochloride

4.6.F.1 Depression - Schizophrenia

a) Results of an 8-week, double-blind trial demonstrated that patients receiving both olanzapine and fluoxeti
improvement in Montgomery-Asberg Depression Rating Scale (MADRS) and Clinical Global Impression (CGI
medication alone. Twenty-eight patients with nonpsychotic treatment-refractory depression received olanzapi
60 milligrams/day). In addition, there were no significant differences in adverse events among the 3 different

4.6.G Perphenazine

4.6.G.1 Chronic schizophrenia

a) When newer antipsychotic medications (olanzapine, quetiapine, risperidone, and ziprasidone) were comp
perphenazine, the majority of patients in each group discontinued their antipsychotic study medication before
schizophrenia were randomized to receive olanzapine 7.5 to 30 milligrams/day (mg/day), perphenazine 8 to 3
risperidone 1.5 to 6.0 mg/day, or ziprasidone 40 to 160 mg/day for up to 19 months. Overall, 74% of patients
months; discontinuation rates ranged from 64 to 82%. Time to discontinuation ranged from 3.5 months for zip
to discontinuation was significantly longer in the olanzapine group as compared with the quetiapine (hazard r
to 0.76; p less than 0.001) or risperidone groups (HR, 0.75; 95% CI, 0.62 to 0.90; p=0.002). Time to discontin
all groups, but the rates ranged from 10% for risperidone to 19% for olanzapine (p=0.04). More patients disco
(average of 0.9 kilograms/month) and greater increases in glycosylated hemoglobin, total cholesterol, and trig

4.6.H Quetiapine

4.6.H.1 Chronic schizophrenia

a) When newer antipsychotic medications (olanzapine, quetiapine, risperidone, and ziprasidone) were comp
perphenazine, the majority of patients in each group discontinued their antipsychotic study medication before
schizophrenia were randomized to receive olanzapine 7.5 to 30 milligrams/day (mg/day), perphenazine 8 to 3
risperidone 1.5 to 6.0 mg/day, or ziprasidone 40 to 160 mg/day for up to 19 months. Overall, 74% of patients
months; discontinuation rates ranged from 64 to 82%. Time to discontinuation ranged from 3.5 months for zip
to discontinuation was significantly longer in the olanzapine group as compared with the quetiapine (hazard r
to 0.76; p less than 0.001) or risperidone groups (HR, 0.75; 95% CI, 0.62 to 0.90; p=0.002). Time to discontin
all groups, but the rates ranged from 10% for risperidone to 19% for olanzapine (p=0.04). More patients disco
(average of 0.9 kilograms/month) and greater increases in glycosylated hemoglobin, total cholesterol, and trig

4.6.I Risperidone

Agitation, acute - Psychotic disorder

Bipolar disorder

Chronic schizophrenia

Dementia - Problem behavior

Extrapyramidal disease

Obsessive-compulsive disorder, Refractory

Schizophrenia

4.6.I.1 Agitation, acute - Psychotic disorder

a) Olanzapine orally disintegrating tablets (ODT) and risperidone oral solution (OS) yielded similar improvem Negative Syndrome Scale (PANSS-EC) and the Clinical Global Impression (CGI) scale in 87 patients treated emergency setting, according to an open-label, flexible-dose study. Patients with a baseline PANSS-EC scor were assigned to receive initial doses of either olanzapine ODT 10 milligram (mg) (n=34) or risperidone OS 3 based on previous effective treatments, or monthly assignments to olanzapine or risperidone according to the continued agitation could be re-dosed at any time, and after 1 hour could receive adjunctive drug therapy. PA time. The mean CGI change from baseline was similar between the olanzapine and risperidone group (2.8 vs PANSS-EC score over time ANOVA (at baseline and every 15 minutes for 1 hour) revealed no significant ma treatment over time (F=2.94, p=0.09 and F=0.88, p=0.41, respectively). There was a significant mean change compared with risperidone OS group (-9.2 vs 1.1 beats/minute, p=0.03). There were no significant differences including extrapyramidal symptoms (Hatta et al, 2008).

4.6.I.2 Bipolar disorder

a) In a retrospective study of 50 consecutive patients treated for bipolar disorder with atypical antipsychotic r and risperidone (n=25), along with standard mood stabilizers, showed similar efficacy. Overall, 68% of patien Clinical Global Impressions assessment over the 12-week study. Mean dosages were 210 milligrams (mg) pe and 1.7 mg day for risperidone. The only serious adverse event to occur during the study was a seizure in a p (EPS) were reported in 12 of 42 subjects (28.6%). Parkinsonism occurred in 4 of 25 patients taking risperidor clozapine. Weight gain was more extreme in patients taking clozapine and olanzapine than in those taking ris reported in other studies, may have been affected by concurrent mood enhancing medications (Guille et al, 2

4.6.I.3 Chronic schizophrenia

a) When newer antipsychotic medications (olanzapine, quetiapine, risperidone, and ziprasidone) were compa perphenazine, the majority of patients in each group discontinued their antipsychotic study medication before schizophrenia were randomized to receive olanzapine 7.5 to 30 milligrams/day (mg/day), perphenazine 8 to 3 risperidone 1.5 to 6.0 mg/day, or ziprasidone 40 to 160 mg/day for up to 19 months. Overall, 74% of patients months; discontinuation rates ranged from 64 to 82%. Time to discontinuation ranged from 3.5 months for zip to discontinuation was significantly longer in the olanzapine group as compared with the quetiapine (hazard r to 0.76; p less than 0.001) or risperidone groups (HR, 0.75; 95% CI, 0.62 to 0.90; p=0.002). Time to discontin all groups, but the rates ranged from 10% for risperidone to 19% for olanzapine (p=0.04). More patients disco (average of 0.9 kilograms/month) and greater increases in glycosylated hemoglobin, total cholesterol, and trig

4.6.I.4 Dementia - Problem behavior

a) Risperidone and olanzapine were equally effective in the treatment of dementia-related behavioral disturb facilities. In a double-blind, parallel study, patients (mean age, 83 years) with dementia received oral olanzap titrated to maximum dose of 10 mg/day) or risperidone (n=19, initial dose 0.5 mg/day, titrated to maximum do a 3-day washout period of psychotropic drugs. Antidepressants and mood stabilizers were allowed at stable d medication at doses of 0.5 to 1 mg as needed for acute agitation. The mean daily doses for olanzapine and ri 1.47 mg (range, 0.5 to 2 mg), respectively. Lorazepam was utilized a median of 3.5 days (range 1-12 days) a mg). Primary outcome measures were the Neuropsychiatric Inventory (NPI) and the Clinical Global Impressio lowered CGI scores and total NPI scores from baseline to endpoint (p less than 0.0001, both values), howeve Adverse events were frequent in this elderly population, with the most common including drowsiness, falls, ar

4.6.I.5 Extrapyramidal disease

a) Results of a retrospective analysis showed that olanzapine treatment was associated with a lower rate of but was similar to rates occurring with risperidone and clozapine therapy. In a pooled analysis of 23 randomiz schizophrenia, frequency and severity of EPS associated with olanzapine therapy (2.5 to 20 milligrams (mg)/ mg/day), risperidone (4 to 12 mg/day), clozapine (25 to 625 mg/day), and placebo. Dystonic events (ie, dysto occurred in significantly fewer patients during olanzapine treatment as compared with haloperidol (0.5% vs 5. (1% vs 3.2%, respectively; p=0.047) treatment, while no significant difference was found between olanzapine olanzapine-treated patients, a significantly higher percentage of haloperidol-treated patients experienced parl extrapyramidal syndrome, hypertonia, hypokinesia, masked facies, and tremor) (9.3% vs 28.3%, respectively akathisia, hyperkinesia) (6.7% vs 20.4%, respectively; p less than 0.001) during therapy. However, no signific

olanzapine group as compared with the placebo, risperidone, or clozapine groups in regard to the occurrence occurred in significantly more patients treated with haloperidol as compared with olanzapine (44.4% vs 16.2% patients treated with clozapine as compared with olanzapine (2.6% vs 6.8%, respectively; p=0.047). The over and risperidone groups as compared with olanzapine. Significantly fewer patients received anticholinergic me with the haloperidol (p less than 0.001) or risperidone (p=0.018) groups. No difference was found between ol placebo or clozapine in regard to percentage of patients given anticholinergic drugs during therapy (Carlson e

4.6.I.6 Obsessive-compulsive disorder, Refractory

a) Adjunctive therapy of risperidone or olanzapine with serotonin-reuptake inhibitors (SRI) were equally effec in SRI monotherapy-resistant outpatients, according to an 8-week, single-blind, randomized trial; however thi placebo arm, single-arm design, and underpowered nature of the trial. Following a 16-week prospective, oper who were treatment-resistant (defined as less than 35% improvement in the total score of Yale-Brown Obses Global Impression Severity (CGI-S) score greater than 2) entered an 8-week single-blind phase (n=50). Patie doses of clomipramine 200 to 225 mg, citalopram 50 to 80 mg, fluoxetine 60 mg, fluvoxamine 200 to 300 mg, were randomized to receive either risperidone 1 to 3 mg/day (n=25), or olanzapine 2.5 to 10 mg/day (n=25) i personnel and assessor-blinding constituted the single-blind study design; patients were not blinded. In an int analysis of the primary endpoints, both treatments significantly improved Y-BOCS and CGI-S scores by week mean Y-BOCS total scores, CGI-S scores, and responder rates (35% or greater improvement in Y-BOCS sco was similar between groups.

Primary Efficacy Endpoints at 8 Weeks		
	Risperidone (n=25)	Olanzapine (n=25)
Responder rates*	44% (11/25)	48% (12/25)
Mean end-point Y-BOCS score	22.6 +/- 7.2	22.2 +/- 7.4
Change in mean Y-BOCS score from baseline	-7.5; t=7.588, df=21, p less than 0.001	-8.4; t=7.456, df=20 0.001
Mean end-point CGI-S score	3.2 +/- 1.7	3.1 +/- 1.8
Change in mean CGI-S score from baseline	-1.7; t=7.022, df=21, p less than 0.001	-1.9; t=7.707, df=20 0.001
* p=1; Y-BOCS=Yale-Brown Obsessive Compulsive Scale; CGI-S=Clinical Global Impression Severity s		

b) Adverse effects of risperidone compared with olanzapine-treated patients included tension/inner unrest (2 p=0.016), and amenorrhea (66.7% vs 10%, p=0.02), respectively. The small sample size and the absence of to the limitations of this study (Maina et al, 2008).

4.6.I.7 Schizophrenia

a) Olanzapine and risperidone were equally safe and effective therapies in the treatment of schizophrenia in double-blind study, 175 elderly patients (mean age, 71 years) were randomized to receive either risperidone (mean dose, 11.1 mg/day) for 8 weeks following a 1 week washout period of all psychotropic medications. Me and Negative Syndrome Scale (PANSS) scores were between 50 and 120 at baseline. Clinical improvement total PANSS score. Both treatment groups showed significant reductions from baseline in the total PANSS sc significant differences were not observed between groups. Fifty-eight percent of risperidone-treated patients clinical improvement as defined by the study. Both groups also exhibited significant improvement in four of th The greatest mean change in the total PANSS score occurred in the 93 patients who had received conventio to entering the study (p less than 0.001). The rate of extrapyramidal symptoms (EPS) was similar between th (9.2% vs 15.9%, respectively, p=ns). The severity of EPS symptoms was reduced in both groups from baseli between groups. A 7% or higher increase in weight occurred in significantly more olanzapine-treated patients (14.8% vs 5.1%, p=0.043). No new cardiovascular events were observed in this patient population and mean relevant (Jeste et al, 2003).

b) Olanzapine and risperidone improved neurocognitive deficits more than did haloperidol or clozapine in pa that was refractory to treatment with typical antipsychotics. In a randomized, double-blind study, inpatients we (mg) per day, olanzapine (n=26) 10 to 40 mg/day, risperidone (n=26) 4 to 16 mg day, or haloperidol (n=25) 1 treatment (target doses: olanzapine 20 mg/day, risperidone 8 mg/day, haloperidol 20 mg/day, clozapine 500 week study; during the last 6 weeks, dosages were adjusted individually (generally increased if response was adverse effects). Improvement over time in global neurocognitive score was seen for olanzapine and risperid organization and in processing speed and attention, improvement was seen with olanzapine. In simple motor Changes in global neurocognitive performance with olanzapine and risperidone were of medium magnitude (enough to be clinically significant. Beneficial changes with clozapine were modest. Despite cognitive gains, p ability and social/vocational functioning. Improvements in neurocognitive deficits were associated with improv

c) In a prospective, multicenter, double-blind trial, olanzapine was more cost-effective than risperidone in pa or schizophreniform disorder. One hundred fifty patients were randomized to either olanzapine (10 to 20 milli mg/d) (n=75) treatment for a period of 28 weeks. During the study, olanzapine- treated patients were significa

throughout the course of therapy than risperidone- treated patients (p=0.048). However, the proportion of pat
significantly different between groups. Overall, the incidence of side effects was similar between groups, but
required an anticholinergic to control treatment-emergent extrapyramidal effects than did those receiving olar
costs were significantly higher for olanzapine-treated patients than those treated with risperidone ($2513 vers
52% reduction in inpatient and outpatient service costs ($3516 vs $7291 US) (Edgell et al, 2000).

d) In an open-label study of patients with DSM-IV schizophrenia, olanzapine (n=21) was shown to be as effe
6 months, risperidone was more effective for treatment of psychotic symptoms. However, olanzapine was ass
At discharge the average doses of olanzapine and risperidone were 14.4 and 5.7 milligrams (mg) daily, respe
risperidone was significantly greater than with olanazapine. The dose of drug was uncontrolled and adjusted
response, tolerability of side effects, and manufacturer recommendations. Measures of effectiveness include
(BPRS), Global Assessment Scale (GAS) and quality of life measures. (Ho et al, 1999). Larger studies are ne

e) Olanzapine (10 to 20 milligrams (mg) daily) was superior to risperidone (4 to 12 mg daily) in the treatment
international, multicenter, double-blind, parallel-group 28-week prospective study of 339 patients with DSM-iv
disorder, or schizoaffective disorder, the olanzapine group had a significantly better overall response rate (gre
Negative syndrome Scale) and was significantly superior to risperidone in the treatment of negative symptom
curves, a significantly greater number of the olanzapine patients maintained their response at 28 weeks com
reactions were significantly less with olanzapine, in particular extrapyramidal side effects, hyperprolactinemia
weight gain; suicide attempts occurred significantly less in the olanzapine group (Tran et al, 1997a). The use
been subsequently criticized (Schooler, 1998; Gheuens & Grebb, 1998).

4.6.I.8 Adverse Effects

a) The results of one study suggest that patients receiving atypical antipsychotics have a higher incidence of
conventional antipsychotic medication. In a retrospective, pharmacovigilance study, 192 cases of pancreatitis
dose, 306.7 milligrams (mg)/day), olanzapine (mean dose, 15 mg/day), risperidone, (mean dose, 4 mg/day) c
identified cases, 40%, 33%, and 16% were related to treatment with the atypical antipsychotic medications cl
as compared with 12% of the cases which were related to the conventional neuroleptic, haloperidol. In most p
months after initiation of treatment (Koller et al, 2003a).

4.6.J Valproic Acid

4.6.J.1 Mania

a) A review of 3 randomized, double-blinded, placebo-controlled studies concluded that a more rapid antima
loading of divalproex than with standard titration divalproex, lithium or placebo. In these short-term studies, o
30 milligrams/kilogram/day (mg/kg/day) for the first 2 days and maintained at 20 mg/kg/day or it was initiated
increased to a maximum of 20 mg/kg/day plus 1000 mg by day 6. This regimen was compared to divalproex
to serum levels of 40 to 150 micrograms/milliliter (mcg/mL), lithium (n=54) initiated at 300 mg 3 times a day a
and olanzapine (n=55) initiated at 10 mg/day and titrated to a maximum of 20 mg/day and placebo (n=72). Pa
assessed using the change from baseline measurement of the Mania Rating Scale (MRS), the Manic Syndro
Scale (BIS). Intent-to-treat analyses showed that MRS measurements from oral-loaded divalproex patients w
patients. However, it showed significant differences from standard titration divalproex and placebo by day 5 a
Similar results were found for MSS and BIS measurements. Dry mouth and increased appetite was more con
standard titration (p less than 0.05). However, standard titration divalproex was associated with an increased
(p less than 0.05). Divalproex overall was associated with greater decreases in platelet counts than other gro
greater reports of headache and fever (p less than 0.05) and olanzapine was associated with greater adverse
speech disorder, rhinitis, increases in total cholesterol and increases in serum alanine aminotransferase) ove

b) Olanzapine was superior to divalproex for the treatment of acute mania in a 3-week, randomized, double-
bipolar I disorder, manic or mixed episode, and with or without psychotic features, were given flexibly dosed c
divalproex (500 to 2500 mg/day). Modal doses were 17.4 mg/day for olanzapine and 1401 mg/day for divalpr
(mcg/L) or greater (the targeted therapeutic range) was attained by approximately 87% of divalproex-treated
Mania Rating Scale total score was 13.4 points for the olanzapine group and 10.4 points for the divalproex gr
difference was significant (in favor of olanzapine) among patients without psychotic features (p=0.06), but the
patients with psychotic features. Clinical response (50% or greater improvement in they Young Mania Rating
treated patients and 43% of divalproex-treated patients (p=0.058). Time-to- remission was significantly shorte
0.04). There were more adverse events with olanzapine, mainly somnolence, dry mouth, and weight gain. Na
group (Tohen et al, 2002).

4.6.K Ziprasidone

Chronic schizophrenia

Schizophrenia

4.6.K.1 Chronic schizophrenia

a) When newer antipsychotic medications (olanzapine, quetiapine, risperidone, and ziprasidone) were comp
perphenazine, the majority of patients in each group discontinued their antipsychotic study medication before
schizophrenia were randomized to receive olanzapine 7.5 to 30 milligrams/day (mg/day), perphenazine 8 to 3

risperidone 1.5 to 6.0 mg/day, or ziprasidone 40 to 160 mg/day for up to 19 months. Overall, 74% of patients months; discontinuation rates ranged from 64 to 82%. Time to discontinuation ranged from 3.5 months for zip to discontinuation was significantly longer in the olanzapine group as compared with the quetiapine (hazard r to 0.76; p less than 0.001) or risperidone groups (HR, 0.75; 95% CI, 0.62 to 0.90; p=0.002). Time to discontin all groups, but the rates ranged from 10% for risperidone to 19% for olanzapine (p=0.04). More patients disco (average of 0.9 kilograms/month) and greater increases in glycosylated hemoglobin, total cholesterol, and trig

4.6.K.2 Schizophrenia

a) In a randomized, double-blind trial (n=269), six-week courses of OLANZAPINE and ZIPRASIDONE had c or schizoaffective disorder (DSM-IV), while the side effects profile of ziprasidone appeared to be more favora favorable related to QT interval prolongation. Enrollees were acutely ill, recently admitted inpatients. During th study drugs: olanzapine 5 milligrams (mg) on days 1 and 2 and 10 mg/day on days 3 to 7 (n=133); ziprasidon twice daily on days 3 to 7 (n=136). Dosing was flexible over weeks 2-6 (olanzapine 5 to 15 mg/day; ziprasido doses were 12.4 mg for olanzapine and 138.6 mg for ziprasidone (the latter in 2 divided doses daily). Efficacy Scale (BPRS), Clinical Global Impression (CGI) severity and improvement scales, Positive and Negative Syn for Schizophrenia. At study end, there were no significant differences on any rating scale between improveme ziprasidone group. At endpoint, 36.8% of the olanzapine group and 48.5% of the ziprasidone group had disco olanzapine and ziprasidone groups, respectively, had experienced adverse events that were considered treat seen related to dyskinesia, dystonia, or extrapyramidal symptoms. Weight gain amounted to approximately 3 ziprasidone-treated patients, respectively (p less than 0.0001). Total cholesterol, low- density lipoprotein chol approximately 10%, 13%, and 25%, respectively, in the group receiving olanzapine; all the same measures d than 0.0001; p=0.0004; p less than 0.003, respectively). Fasting serum insulin increased by median 3.3 and 0 ziprasidone groups, respectively (p=0.051). Prolongation of the QTc interval amounted to 0.52 and 6.08 millis than 0.05) (Simpson et al, 2004).

b) A multicenter, randomized, double-blind, parallel-group, 28 week study (n=548) found that olanzapine the psychopathology improvement and higher response and completion rates compared to ziprasidone, while zip and lipid profile. Patients with schizophrenia were randomized to receive olanzapine (n=277) 10 to 20 mg/day primary efficacy measure, the Positive and Negative Syndrome Scale total score, showed that the olanzapine the ziprasidone group (p less than 0.001). The olanzapine group also showed significant improvement from b Positive and Negative Syndrome subscales: positive symptoms, negative symptoms, general psychopatholog except for negative symptoms p=0.003). Patients were allowed to take benzodiazepines or hypnotic monothe study if they required more than two concurrent benzodiazepine hypnotic medications. Significantly more pati dose of a benzodiazepine compared to the olanzapine group (53.5% versus 40.4%; p=0.003). Response was Negative Syndrome Scale total score at endpoint, and the rate was significantly higher for the olanzapine gro versus 42.5%) (p less than 0.001). There was no significant difference in exacerbation of symptoms between in the Positive and Negative Syndrome Scale total score by 20% or more and a decrease in the Clinical Glob more after week 8 (14.6% olanzapine and 25.3% ziprasidone; p=0.06). Significantly more patients in the olan group (42.4%) completed the study (p less than 0.001). Reasons for discontinuation were only significant for ziprasidone 13.7%; p=0.02) and aggravation of psychosis (olanzapine 1.4% versus ziprasidone 4.4%; p=0.05 body weight and levels of total cholesterol, low-density lipoprotein cholesterol, and triglycerides (all p less tha high-density lipoprotein cholesterol (p=0.001) in the olanzapine group than in the ziprasidone group (Breier et

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Last Modified: June 26, 2009

DRUGDEX® Evaluations

FLUOXETINE HYDROCHLORIDE/OLANZAPINE

0.0 Overview

1) Class
- **a)** This drug is a member of the following class(es):
  Antidepressant
  Antipsychotic

2) Dosing Information
- **a)** Adult
  - **1)** Bipolar disorder, depressed phase
    - **a)** initial, olanzapine 6 mg/ fluoxetine 25 mg ORALLY once daily each evening (Prod Info SYMBYAX(R) oral
    - **b)** usual range, olanzapine 6 to 12 mg/fluoxetine 25 to 50 mg ORALLY once daily each evening (Prod Info S
  - **2)** Major depressive disorder, Treatment resistant
    - **a)** initial, olanzapine 6 mg/ fluoxetine 25 mg ORALLY once daily each evening (Prod Info SYMBYAX(R) oral
    - **b)** usual range, olanzapine 6 to 18 mg/fluoxetine 25 to 50 mg ORALLY once daily each evening (Prod Info S

3) Contraindications
- **a)** concomitant use of pimozide, MAOIs, or thioridazine (Prod Info SYMBYAX(R) oral capsule, 2009)

4) Serious Adverse Effects
- **a)** Death
- **b)** Depression, Worsening
- **c)** Diabetic ketoacidosis
- **d)** Dyskinesia
- **e)** Hyponatremia
- **f)** Mania
- **g)** Neuroleptic malignant syndrome
- **h)** Pulmonary eosinophilia
- **i)** Seizure
- **j)** Suicidal thoughts
- **k)** Suicide
- **l)** Violent behavior

5) Clinical Applications
- **a)** FDA Approved Indications
  - **1)** Bipolar disorder, depressed phase
  - **2)** Major depressive disorder, Treatment resistant

1.0 Dosing Information

1.1 Drug Properties

A) Information on specific products and dosage forms can be obtained by referring to the Tradename List (Product In

1.2 Storage and Stability

A) Preparation
- **1)** Oral
  - **a)** The combination of olanzapine/fluoxetine should be administered in the evening. While food has no appre
    fluoxetine given individually, the effect of food on the absorption of the combination has not been studied (Pr

B) Symbyax(TM) capsules should be stored at 25 degrees Celsius (77 degrees Fahrenheit); excursions permitted to
Fahrenheit). Keep tightly closed and protect from moisture (Prod Info Symbyax(TM), 2003b).

1.3 Adult Dosage

Normal Dosage

Dosage in Renal Failure

Dosage in Hepatic Insufficiency

Dosage in Geriatric Patients

Dosage in Other Disease States

1.3.1 Normal Dosage

1.3.1.A Oral route

Bipolar disorder, depressed phase

Major depressive disorder, Treatment resistant

1.3.1.A.1 Bipolar disorder, depressed phase

a) The recommended initial dose for the acute treatment of depressive episodes associated with bipolar (mg)/fluoxetine 25 mg orally once daily each evening. The usual dose range is olanzapine 6 to 12 mg/flu oral capsule, 2009).

1.3.1.A.2 Major depressive disorder, Treatment resistant

a) The recommended initial dose in the acute treatment of treatment-resistant major depressive disorde previous trials of antidepressant therapy is olanzapine 6 milligrams (mg)/fluoxetine 25 mg orally once dai olanzapine 6 to 18 mg/fluoxetine 25 to 50 mg (Prod Info SYMBYAX(R) oral capsule, 2009).

B) The safety of doses greater than olanzapine 18 milligrams (mg) and fluoxetine 75 mg per day have not been e capsule, 2009).

1.3.2 Dosage in Renal Failure

A) Dose adjustments based upon renal impairment is not routinely required, although the possibility exists that pa accumulate higher levels of fluoxetine metabolites (Prod Info SYMBYAX(R) oral capsule, 2009).

1.3.3 Dosage in Hepatic Insufficiency

A) A reduced starting dose of olanzapine 3 to 6 milligrams (mg)/ fluoxetine 25 mg should be considered for patier individual pharmacokinetic profiles of olanzapine and fluoxetine, the pharmacokinetics of olanzapine/fluoxetine ma (Prod Info SYMBYAX(R) oral capsule, 2009).

1.3.4 Dosage in Geriatric Patients

A) Based on the individual pharmacokinetic profiles of olanzapine and fluoxetine, the pharmacokinetics of the cor Caution should be used in dosing the elderly, especially if there are other factors that might additively influence dr sensitivity (female gender, geriatric age, nonsmoking status). Dose escalation should be performed with caution ir capsule, 2009).

B) In a study involving 24 healthy subjects, the mean elimination half- life of olanzapine was about 1.5 times grea age) than in non-elderly subjects (65 years of age or under) (Prod Info SYMBYAX(R) oral capsule, 2009).

1.3.6 Dosage in Other Disease States

A) A reduced starting dose of olanzapine 3 to 6 milligrams (mg)/ fluoxetine 25 mg should be used for patients wit patients with hepatic impairment, or in slow CYP2D6 metabolizers, patients who exhibit a combination of factors t (female gender, geriatric age, nonsmoking status). Dose escalation should be performed with caution in these pat 2009).

B) A reduced dose is recommended in women during the third trimester of pregnancy due to the risk of adverse e Info SYMBYAX(R) oral capsule, 2009).

1.4 Pediatric Dosage

1.4.1 Normal Dosage

1.4.1.A Oral route

1) Safety and effectiveness of the combination of olanzapine and fluoxetine in pediatric patients have not be capsule, 2009).

2.0 Pharmacokinetics

Drug Concentration Levels

ADME

2.2 Drug Concentration Levels

A) Therapeutic Drug Concentration

1) Bipolar disorder, plasma concentrations are not used clinically.

B) Time to Peak Concentration

1) ORAL, capsule: olanzapine, 4 hours, fluoxetine, 6 hours (Prod Info Symbyax(TM), 2003a).

a) Following a single oral 12 mg/50 mg dose of olanzapine/fluoxetine, peak plasma concentrations of olanza 6 hours, respectively (Prod Info Symbyax(TM), 2003a).

2.3 ADME

Absorption

Distribution

Metabolism

Excretion

Elimination Half-life

2.3.1 Absorption

A) Bioavailability

1) Oral, capsule: Olanzapine, 60%; fluoxetine 100% (Lemberger et al, 1985a; Prod Info Symbyax(TM), 2003

a) Olanzapine: extensive first-pass metabolism, with approximately 40% of the dose metabolized before Symbyax(TM), 2003a).

B) Effects of Food

1) none (Prod Info Symbyax(TM), 2003a).

a) The effect of food on the absorption and bioavailability of the combination of olanzapine and fluoxetin olanzapine of fluoxetine were not affected by food. It is unlikely that there would be a significant food effe Info Symbyax(TM), 2003a). The absorption of fluoxetine is delayed but not decreased in the presence of

2.3.2 Distribution

A) Distribution Sites

1) Protein Binding

a) Olanzapine, 93%; fluoxetine 94.5% (Prod Info Symbyax(TM), 2003a).

1) Olanzapine is 93% bound to plasma proteins over the concentration range of 7 to 1100 ng/mL, b glycoprotein (Prod Info Symbyax(TM), 2003a).

2) Over the concentration range from 200 to 1000 ng/mL, approximately 94.5% of fluoxetine is bou albumin and alpha-1-glycoprotein (Prod Info Symbyax(TM), 2003a; Lemberger et al, 1985a; Aronoff

B) Distribution Kinetics

1) Volume of Distribution

a) Olanzapine, 1000 L (Prod Info Symbyax(TM), 2003a); fluoxetine, 1000 to 7200 L (Aronoff et al, 1984)

1) The corresponding volume of distribution for norfluoxetine ranged from 700 to 5,700 L. No relatio fluoxetine or its metabolite and renal function has been observed (Aronoff et al, 1984).

2.3.3 Metabolism

A) Metabolism Sites and Kinetics

1) LIVER, extensive for both olanzapine and fluoxetine (Prod Info Symbyax(TM), 2003a).

a) Olanzapine: extensive first-pass metabolism, with approximately 40% of the dose metabolized before Symbyax(TM), 2003a).

B) Metabolites

1) OLANZAPINE

a) 10-N-glucuronide is present at steady state at 44% of the olanzapine concentration (Prod Info Symby

b) 4'-N-desmethyl olanzapine (inactive) is present at steady state at 31% of the olanzapine concentratio

2) FLUOXETINE

a) Fluoxetine is metabolized primarily via N-demethylation to the active metabolite, norfluoxetine (Lemb Glucuronide conjugates are also found but in small quantities (Lemberger et al, 1985a).

b) Extensive metabolizers with respect to cytochrome P450 2C19 (CYP2C19) showed lower maximum

levels of norfluoxetine (p less than 0.001) after a 40 milligram dose of fluoxetine than did poor metabolize
Oral clearance by poor metabolizers was 55% lower than oral clearance by extensive metabolizers (p les

2.3.4 Excretion

A) Kidney

1) Renal Excretion (%)

a) Olanzapine, 57% (Prod Info Symbyax(TM), 2003a); fluoxetine, 60% (Lemberger et al, 1985a)

1) OLANZAPINE: About 7% of the olanzapine dose was recovered in the urine as unchanged drug, (Prod Info Symbyax(TM), 2003a)

2) FLUOXETINE: The primary route of fluoxetine elimination appears to be hepatic metabolism to i Info Symbyax(TM), 2003a)

3) Only 2.5 to 5.0% of an oral fluoxetine dose is recovered as unchanged drug; 10% is excreted as Aronoff et al, 1984). Conjugated metabolites, fluoxetine glucuronide and norfluoxetine glucuronide, (Lemberger et al, 1985a).

B) Other

1) PLASMA CLEARANCE

a) 25 L/hr (Prod Info Symbyax(TM), 2003a)

1) The apparent plasma clearance ranges from 12 to 47 L/hr (Prod Info Symbyax(TM), 2003a)

2) OTHER EXCRETION

a) Feces: olanzapine 30% (Prod Info Symbyax(TM), 2003a); fluoxetine, 12% (Lemberger et al, 1985a)

2.3.5 Elimination Half-life

A) Parent Compound

1) ELIMINATION HALF-LIFE

a) olanzapine, 30 hours (Prod Info Symbyax(TM), 2003a); fluoxetine, 4 to 6 days, chronic administration (R), 2001ai; Lemberger et al, 1985a).

1) OLANZAPINE

a) The olanzapine half-life ranges from 21 to 54 hours (mean 30 hours) (Prod Info Symbyax(TM

2) FLUOXETINE

a) Following acute administration, the elimination half-life of fluoxetine is 1 to 3 days (Prod Info 2002).

b) The mean half-life of fluoxetine among extensive metabolizers with respect to cytochrome P450 2C19 among poor metabolizers with the CYP2C19*2 or CYP2C19*3 mutation, mean half-life was 62 hours (Liu

B) Metabolites

1) Norfluoxetine, 4 to 16 days (Prod Info Prozac(R), 2001ai; Lemberger et al, 1985a).

3.0 Cautions

Contraindications

Precautions

Adverse Reactions

Teratogenicity/Effects in Pregnancy/Breastfeeding

Drug Interactions

3.0.A Black Box WARNING

1) Oral (Capsule)

Suicidality and Antidepressant Drugs -

Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in child studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of fl antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk w adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with ages who are started on antidepressant therapy should be monitored appropriately and observed closely for changes in behavior. Families and caregivers should be advised of the need for close observation and comm hydrochloride/olanzapine is not approved for use in pediatric patients.

Increased Mortality in Elderly Patients with Dementia-Related Psychosis - .

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of d 1.7 times the risk of death in placebo-treated patients. Over the course of a typical 10-week controlled trial, th about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varie cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Observational stu

drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findin
may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear. F
approved for the treatment of patients with dementia-related psychosis (Prod Info SYMBYAX(R) oral capsule

3.1 Contraindications

A) concomitant use of pimozide, MAOIs, or thioridazine (Prod Info SYMBYAX(R) oral capsule, 2009)

3.2 Precautions

A) elderly with dementia-related psychosis (unapproved use); increased risk of death; most deaths were attributed to sudden death) or infections (eg, pneumonia) (Prod Info SYMBYAX(R) oral capsule, 2009)
B) suicidal ideation and behavior or worsening depression; increased risk, particularly in children, adolescents, and y during the first few months of therapy or following changes in dosage (Prod Info SYMBYAX(R) oral capsule, 2009)
C) abnormal bleeding has been reported, including life-threatening hemorrhages; increased risk with concomitant use affect coagulation (Prod Info SYMBYAX(R) oral capsule, 2009)
D) abrupt withdrawal; serious discontinuation symptoms have been reported (Prod Info SYMBYAX(R) oral capsule, 2
E) allergic reactions including anaphylaxis, rash, and systemic reactions possibly related to vasculitis may occur; may SYMBYAX(R) oral capsule, 2009)
F) body weight increases may occur; monitoring recommended (Prod Info SYMBYAX(R) oral capsule, 2009)
G) bipolar disorder; increased risk of precipitation of a mixed/manic episode (Prod Info SYMBYAX(R) oral capsule, 2
H) cardiovascular or cerebrovascular disease, conditions that predispose patients to hypotension (eg, dehydration, h concomitant antihypertensive drug use; increased risk of orthostatic hypotension, bradycardia, and syncope (Prod Info
I) concomitant serotonergic drug use (serotonin precursors (tryptophan), SSRIs, serotonin-norepinephrine reuptake in Info SYMBYAX(R) oral capsule, 2009)
J) conditions that may contribute to elevated body temperature (eg, strenuous exercise, extreme heat exposure, dehy disrupt body temperature regulation and increase risk of hyperthermia (Prod Info SYMBYAX(R) oral capsule, 2009)
K) diabetes mellitus, preexisting disease or risk factors, or patients with borderline increased blood glucose level; incr recommended (Prod Info SYMBYAX(R) oral capsule, 2009)
L) dyslipidemia (abberations in cholesterol, triglycerides, HDL, and LDL) has been reported; monitoring recommende
M) elderly patients, especially elderly women are at increased risk of tardive dyskinesia (Prod Info SYMBYAX(R) oral
N) glaucoma, narrow-angle; condition may be exacerbated due to cholinergic antagonism (Prod Info SYMBYAX(R) or
O) hepatic impairment, preexisting conditions associated with limited hepatic functional reserve, or concomitant use o impairment and reduce fluoxetine clearance (Prod Info SYMBYAX(R) oral capsule, 2009)
P) hyperglycemia (some extreme cases associated with ketoacidosis or hyperosmolar coma or death) has been repo SYMBYAX(R) oral capsule, 2009)
Q) hyponatremia may occur; elderly or volume-depleted patients, and concomitant diuretic use may increase risk; dis develops (Prod Info SYMBYAX(R) oral capsule, 2009)
R) increased duration of therapy and/or higher cumulative doses; increased risk of tardive dyskinesia (Prod Info SYM
S) neuroleptic malignant syndrome, potentially fatal; has been reported in association with olanzapine therapy; immed oral capsule, 2009)
T) paralytic ileus, history; condition may be exacerbated due to cholinergic antagonism (Prod Info SYMBYAX(R) oral
U) prostatic hypertrophy; condition may be exacerbated due to cholinergic antagonism (Prod Info SYMBYAX(R) oral
V) seizure disorder, history, or conditions which lower seizure threshold (Prod Info SYMBYAX(R) oral capsule, 2009)
W) serotonin syndrome has been reported, including fatalities; monitoring recommended (Prod Info SYMBYAX(R) ora
X) tardive dyskinesia, potentially irreversible, may occur (Prod Info SYMBYAX(R) oral capsule, 2009)
Y) use of fluoxetine/olanzapine within 14 days of MAOI discontinuation (Prod Info SYMBYAX(R) oral capsule, 2009)
Z) use of MAOI or thioridazine within 5 weeks of fluoxetine/olanzapine discontinuation (Prod Info SYMBYAX(R) oral c
AA) volume-depleted, elderly, or concurrent diuretic therapy; increased risk of hyponatremia (Prod Info SYMBYAX(R)

3.3 Adverse Reactions

Cardiovascular Effects

Dermatologic Effects

Endocrine/Metabolic Effects

Gastrointestinal Effects

Hematologic Effects

Hepatic Effects

Immunologic Effects

Musculoskeletal Effects

Neurologic Effects

Ophthalmic Effects

Psychiatric Effects

Renal Effects

Reproductive Effects

Respiratory Effects

Other

3.3.1 Cardiovascular Effects

Bradyarrhythmia

Cardiovascular finding

Edema

Orthostatic hypotension

Peripheral edema

QT interval - finding

Tachycardia

3.3.1.A Bradyarrhythmia

1) In a clinical pharmacology study of olanzapine/fluoxetine, 3 healthy subjects were discontinued from the tr hypotension and bradycardia that occurred 2 to 9 hours following a single 12-mg/50-mg dose of olanzapine/fl combination of hypotension and bradycardia (and also accompanied by sinus pause) have been observed in various formulations of olanzapine (one oral, two intramuscular) (Prod Info SYMBYAX(R) oral capsule, 2009)

3.3.1.B Cardiovascular finding

1) Olanzapine/fluoxetine should be used with particular caution in patients with known cardiovascular diseas heart failure, or conduction abnormalities), cerebrovascular disease, or conditions that would predispose pati and treatment with antihypertensive medications) (Prod Info SYMBYAX(R) oral capsule, 2009).

3.3.1.C Edema

1) Incidence: 3% (Prod Info SYMBYAX(R) oral capsule, 2009)

2) In short-term, controlled studies including depressive episodes associated with Bipolar I Disorder and trea 3% of patients who received fluoxetine/olanzapine (n=771) compared with 0% of patients who received place capsule, 2009).

3.3.1.D Orthostatic hypotension

1) Incidence: 4% (Prod Info SYMBYAX(R) oral capsule, 2009)

2) In the olanzapine/fluoxetine-controlled clinical studies across all indications, there were no significant diffe receiving combination therapy compared to olanzapine, fluoxetine, and placebo groups. Orthostatic systolic b occurred in 4% (28/705), 2.3% (19/831), 4.5% (18/399), and 1.8% (8/442) of the olanzapine/fluoxetine, olanz respectively. In controlled clinical studies, the incidence of patients with a decrease in orthostatic pulse of 20 with a decrease in orthostatic systolic blood pressure of 20 mmHg or greater was 0.3% (2/706) in the olanzap olanzapine group, 0% in the fluoxetine group, and 0.2% (1/445) in the placebo group. The incidence of synco 0.4% (3/771) compared to placebo (0.2%, 1/477)(Prod Info SYMBYAX(R) oral capsule, 2009).

3) In a clinical pharmacology study of olanzapine/fluoxetine, 3 healthy subjects were discontinued from the tr

hypotension and bradycardia that occurred 2 to 9 hours following a single 12-mg/50-mg dose of olanzapine/fl
combination of hypotension and bradycardia (and also accompanied by sinus pause) have been observed in
various formulations of olanzapine (one oral, two intramuscular) (Prod Info SYMBYAX(R) oral capsule, 2009)

3.3.1.E Peripheral edema

1) Incidence: 9% (Prod Info SYMBYAX(R) oral capsule, 2009)

2) In short-term, controlled studies including depressive episodes associated with Bipolar I Disorder and trea
occurred in 9% of patients who received fluoxetine/olanzapine (n=771) compared with 0% of patients who re
oral capsule, 2009).

3.3.1.F QT interval - finding

1) The mean increase in QTc interval for olanzapine/fluoxetine-treated patients (4.4 msec) in clinical studies
treated (-0.8 msec), olanzapine-treated patients (-0.3 msec), and fluoxetine-treated patients (1.7 msec). Ther
patients treated with olanzapine/fluoxetine, placebo, olanzapine, or fluoxetine in the incidence of QTc outliers
(R) oral capsule, 2009).

3.3.1.G Tachycardia

1) Tachycardia has occurred in olanzapine/fluoxetine-treated patients in premarketing clinical studies (Prod I

3.3.2 Dermatologic Effects

3.3.2.A Erythema multiforme

1) Erythema multiforme has been reported with olanzapine or fluoxetine monotherapy, but was not observed
premarketing clinical studies (Prod Info SYMBYAX(R) oral capsule, 2009).

3.3.3 Endocrine/Metabolic Effects

Bicarbonate level - finding

Body temperature above normal

Diabetes mellitus

Diabetic ketoacidosis

Hypercholesterolemia

Hyperglycemia

Hyperprolactinemia

Hypoalbuminemia

Hyponatremia

Hypophosphatemia

Serum triglycerides raised

Weight gain

3.3.3.A Bicarbonate level - finding

1) Incidence: 14.1% (Prod Info SYMBYAX(R) oral capsule, 2009)

2) In olanzapine/fluoxetine clinical studies (including treatment resistant depression, depressive episodes as
depressive disorder with psychosis, or sexual dysfunction), low bicarbonate level occurred at a greater freque
olanzapine/fluoxetine-treated patients compared to placebo (14.1% vs 8.8%) (Prod Info SYMBYAX(R) oral ca

3.3.3.B Body temperature above normal

1) Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic drugs
olanzapine/fluoxetine for patients who will be experiencing conditions which may contribute to an elevation in
strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity, or bein

(R) oral capsule, 2009).

3.3.3.C Diabetes mellitus

1) Summary

a) As with other atypical antipsychotics, hyperglycemia has been reported in patients on olanzapine. Th nonfasting levels, from baseline to the average of the 2 highest serum concentrations was 15 mg/dL, dur Effectiveness in patients treated for a median olanzapine-exposure duration of 9.2 months. Olanzapine i is difficult to assess the relationship because of an increased risk of diabetes mellitus in patients with sch diabetes mellitus in the general population. In general, epidemiological studies show that atypical antipsy hyperglycemia. Olanzapine appears to have a greater risk of glucose abnormalities compared with other oral capsule, 2009).

b) The risks and benefits of olanzapine/fluoxetine hydrochloride should be considered prior to prescribin diabetes mellitus or in patients with borderline increased blood glucose levels (fasting 100 to 126 mg/dL monitoring of blood glucose is recommended. For patients with risk factors for diabetes mellitus, fasting l initiation and periodically during olanzapine/fluoxetine therapy. All patients should be monitored for signs polyuria, polyphagia, and weakness). Fasting blood glucose should be tested if symptoms of hyperglyce discontinuation of olanzapine/fluoxetine; however, some patients may continue to need antidiabetic thera Info SYMBYAX(R) oral capsule, 2009).

2) New onset diabetes mellitus (DM) has been reported with the administration of olanzapine. At least 25 fat olanzapine-induced diabetic ketoacidosis (Torrey & Swalwell, 2003; Goldstein et al, 1999; Lindenmayer & Pa

3) A 51-year-old woman with schizoaffective disorder and type 2 diabetes (stabilized on metformin 1 gram tw developed hyperglycemia, without weight gain, when an episode of elevated mood and psychosis was treate risperidone for 4 weeks but did not respond. Chlorpromazine also was not effective. Olanzapine, titrated to 3(symptoms. Her blood glucose then began to increase, although her diet was controlled by the hospital. Oral h maximum and she was started on actrapid insulin. Glucose levels remained unstable until olanzapine was ta hypoglycemic medications were reduced to previous levels and actrapid insulin was discontinued. Zuclopenth schizoaffective disorder. The patient showed no significant weight gain during treatment with olanzapine, whi effect on glucose regulation (Ramankutty, 2002).

4) A 27-year-old man developed signs of diabetes mellitus (polydipsia, polyphagia, nausea and vomiting, hy olanzapine for treatment of schizophrenia. He was treated with insulin, and his dose of olanzapine was increa valproic acid, which he had taken for 3 years. After 3 months, insulin therapy was replaced by pioglitazone 3(control. Olanzapine therapy was not discontinued because of the risk of psychotic worsening (Seaburg et al,

5) A 45-year-old obese man developed elevated fasting glucose 1 year after his treatment for schizophrenia to 25 mg/day). Six months later, he was treated with glyburide 1.25 mg/day. Over the next 6 months, glycosy weight began to increase. Five months later, he complained of diarrhea and weight loss. His glyburide dose v symptoms (polyuria, polydipsia, and diaphoresis), his glyburide dosage was increased to 10 mg twice daily, i replaced by risperidone. Six weeks after discontinuation of olanzapine, the patient's glycosylated hemoglobin glyburide was reduced to 1.25 mg/day, and his weight stabilized. Five months later, his diabetes was well-co

6) Olanzapine-induced glucose dysregulation has been reported as an adverse effect, possibly due to drug-i with a severe exacerbation of type 2 diabetes in a 51-year-old woman with a major depressive disorder and s with sertraline and haloperidol decanoate. After 4 weeks, sertraline was replaced by fluoxetine due to continu haloperidol was replaced by olanzapine due to persistent auditory and visual hallucinations. Prior to initiation well-controlled by diet (glycosylated hemoglobin 6.5%, baseline fasting blood glucose 89 to 132 mg/dL). Twe control diminished and continued to worsen despite treatment with glipizide, metformin, and diet. At week 26, due to inadequate antidepressant response. At week 35 (fasting blood glucose 120 to 461 mg/dL, glycosylate 70/30) was initiated and titrated to 70 units per day. Olanzapine was tapered during weeks 39 and 40 and dis therapy was stopped, the patient's fasting blood glucose levels had decreased to within 85 and 163 mg/dL. B been reduced to 45 units/day NPH 70/30 (Bettinger et al, 2000).

7) Cases of new-onset diabetes mellitus (DM) were reported that developed after initiation of olanzapine trea months (mean 26 weeks; median 20 weeks) after olanzapine initiation. Two cases presented with diabetic ke DM and 4 patients experienced weight gain while on olanzapine. Olanzapine was eventually discontinued in treatment for DM was still required (Goldstein et al, 1999).

3.3.3.D Diabetic ketoacidosis

1) Summary

a) As with other atypical antipsychotics, diabetic ketoacidosis or hyperosmolar coma, including death, ha Olanzapine is implicated in glucose abnormalities; however, it is difficult to assess the relationship becau patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. I atypical antipsychotics increase the risk of treatment-emergent hyperglycemia. Olanzapine appears to ha compared with other atypical antipsychotics (Prod Info SYMBYAX(R) oral capsule, 2009).

b) The risks and benefits of olanzapine/fluoxetine hydrochloride should be considered prior to prescribin diabetes mellitus or in patients with borderline increased blood glucose levels (fasting 100 to 126 mg/dL monitoring of blood glucose is recommended. For patients with risk factors for diabetes mellitus, fasting l initiation and periodically during olanzapine/fluoxetine therapy. All patients should be monitored for signs polyuria, polyphagia, and weakness). Fasting blood glucose should be tested if symptoms of hyperglyce discontinuation of olanzapine/fluoxetine; however, some patients may continue to need antidiabetic thera Info SYMBYAX(R) oral capsule, 2009).

2) Diabetic coma has been reported with olanzapine or fluoxetine monotherapy, but was not observed in ola

premarketing clinical studies (Prod Info SYMBYAX(R) oral capsule, 2009).
3) Olanzapine-induced ketoacidosis has been reported, including one near-fatal case in a 44-year-old Africa patient had taken olanzapine 25 mg/day for approximately 1 month (Straker et al, 2002).
4) Diabetic ketoacidosis following 3 months of olanzapine therapy was reported in a 31-year-old man with nc patient was started on insulin and olanzapine was discontinued. Fifteen days later his insulin requirements de the patient has remained metabolically stable, free of diabetic symptoms (Gatta et al, 1999).
5) Diabetic ketoacidosis has been reported with the administration of olanzapine. At least 25 fatalities have b induced diabetic ketoacidosis (Torrey & Swalwell, 2003; Goldstein et al, 1999; Lindenmayer & Patel, 1999).
6) A 50-year-old African American man developed diabetic ketoacidosis after receiving 8 months of olanzapi olanzapine 30 mg daily with divalproex 750 mg twice daily. He began insulin therapy but after the olanzapine normal (Lindenmayer & Patel, 1999).
7) A 39-year-old man developed diabetic ketoacidosis after receiving olanzapine 10 mg for a treatment-refra previous laboratory evidence of diabetes. His body mass index was high at 40 kg/m(2). He was admitted with hyperglycemia (6 mmol/L), and acidosis. His HbA1c was 14.7%. He was maintained on insulin 3 times daily. requirements decreased after 15 days. His blood glucose and HbA1c became normal (Gatta et al, 1999).

3.3.3.E Hypercholesterolemia

1) Summary
a) Significant increases in total cholesterol have been observed during treatment with olanzapine/fluoxe total cholesterol from baseline was 12.1 mg/dL in olanzapine/fluoxetine-treated patients compared with 4 patients and a decrease of 5.5 mg/dL in placebo-treated patients (statistically significant), in an analysis duration. Baseline and follow-up lipid monitoring of lipids is recommended in patients on olanzapine (Pro
2) Incidence: up to 36% (Prod Info SYMBYAX(R) oral capsule, 2009)
3) In an analysis of 7 placebo-controlled monotherapy studies of up to 12 weeks duration, the mean increase 12.1 mg/dL in olanzapine/fluoxetine-treated patients compared with 4.8 mg/dL in olanzapine monotherapy-tre placebo-treated patients. The table below provides the frequency and degree of increase of nonfasting chole with treatment up to 12 weeks(Prod Info SYMBYAX(R) oral capsule, 2009):

Nonfasting Total Cholesterol In Adults With Treatment Up to 12 weeks			
Change from Baseline	Treatment Arm	N	Portion of Patients
Increase by 40 mg/dL or more	olanzapine/fluoxetine	685	35% *
	olanzapine	749	22.7%
	placebo	390	9%
Normal to High	olanzapine/fluoxetine	256	8.2% *
	olanzapine	279	2.9%
	placebo	175	1.7%
Borderline to High	olanzapine/fluoxetine	213	36.2% *
	olanzapine	261	27.6%
	placebo	111	9.9%
KEY: mg/dL = milligrams/deciliter; Normal = less than 200 mg/dL; Borderline = 200 mg/dL to less than 240 mg/dL; High = 240 mg/dL or greater; * = statistically significant compared to placebo and olanzapine			

4) In long-term olanzapine/fluoxetine studies of at least 48 weeks, changes in nonfasting total cholesterol fro (n=150) and changes from borderline to high occurred in 56.6% (n=143) of patients. The mean change in nor (Prod Info SYMBYAX(R) oral capsule, 2009).
5) In an analysis of 5 placebo-controlled monotherapy studies of up to 12 weeks duration, olanzapine-treate fasting total cholesterol of 5.3 mg/dL compared to decreases from baseline of 6.1 mg/dL for placebo-treated least 48 weeks, patients had increases from baseline in mean fasting total cholesterol of 5.6 mg/dL. In an ana therapy, the mean nonfasting total cholesterol did not increase further after approximately 4 to 6 months. The of increase of fasting cholesterol and LDL cholesterol (Prod Info SYMBYAX(R) oral capsule, 2009):

Fasting Total Cholesterol In Adults					
		Up to 12 weeks exposure		At least 48 weeks exposure	
Change from Baseline	Treatment Arm	N	Portion of Patients	N	Portion of Patients
Increase by 40 mg/dL or more	olanzapine	745	21.6%	489	32.9%
	placebo	402	9.5%	NA	NA
Normal to High	olanzapine	392	2.8%	283	14.8%
	placebo	207	2.4%	NA	NA
Borderline to High	olanzapine	222	23%	125	55.2%
	placebo	112	12.5%	NA	NA
KEY: mg/dL = milligrams/deciliter; Normal = less than 200 mg/dL; Borderline = 200 mg/dL to less than 240 mg/dL; High = 240 mg/dL or greater; NA = Not Applicable					
Fasting Low-Density-Lipoprotein Cholesterol In Adults					

		Up to 12 weeks exposure		At least 48 weeks exposure	
Change from Baseline	Treatment Arm	N	Portion of Patients	N	Portion of Patients
Increase by 30 mg/dL or more	olanzapine	536	23.7% *	483	39.8%
	placebo	304	14.1%	NA	NA
Normal to High	olanzapine	154	0%	123	7.3%
	placebo	82	1.2%	NA	NA
Borderline to High	olanzapine	302	10.6%	284	31%
	placebo	173	8.1%	NA	NA
KEY: mg/dL = milligrams/deciliter; Normal = less than 100 mg/dL; Borderline = 100 mg/dL to less than 160 mg/dL; High = 160 mg/dL or greater; NA = Not Applicable					

6) In an analysis of 3 placebo-controlled monotherapy studies of up to 6 weeks duration in adolescents, olan baseline in mean fasting total cholesterol of 12.9 mg/dL and LDL cholesterol compared to increases from bas cholesterol of 1.3 mg/dL and 1 mg/dL for placebo-treated patients, respectively. In long-term olanzapine stud increases from baseline in mean fasting total cholesterol and LDL cholesterol of 5.5 mg/dL and 5.4 mg/dL, re cholesterol of 4.5 mg/dL. The tables below provide the frequency and degree of increase of fasting total chol (R) oral capsule, 2009):

Fasting Total Cholesterol In Adolescents					
		Up to 6 weeks exposure		At least 24 weeks exposure	
Category Change from Baseline	Treatment Arm	N	Portion of Patients	N	Portion of Patients
Increase by 40 mg/dL or more	olanzapine	138	14.5%	122	14.8%
	placebo	66	4.5%	NA	NA
Normal to High	olanzapine	87	6.9%	78	7.7%
	placebo	43	2.3%	NA	NA
Borderline to High	olanzapine	36	38.9%	33	57.6
	placebo	13	7.7%	NA	NA
KEY: mg/dL = milligrams/deciliter; Normal = less than 170 mg/dL; Borderline = 170 mg/dL to less than 200 mg/dL; High = 200 mg/dL or greater ; NA = Not Applicable					

Fasting Low-Density-Lipoprotein Cholesterol In Adolescents					
		Up to 6 weeks exposure		At least 24 weeks exposure	
Category Change from Baseline	Treatment Arm	N	Portion of Patients	N	Portion of Patients
Increase by 30 mg/dL or more	olanzapine	137	17.5%	121	22.3%
	placebo	63	11.1%	NA	NA
Normal to High	olanzapine	98	5.1%	92	10.9%
	placebo	44	4.5%	NA	NA
Borderline to High	olanzapine	29	48.3% *	21	47.6%
	placebo	9	0%	NA	NA
KEY: mg/dL = milligrams/deciliter; Normal = less than 110 mg/dL; Borderline = 110 mg/dL to less than 130 mg/dL; High = 130 mg/dL or greater; NA = Not Applicable					

7) Patients (n=25) receiving olanzapine were found to have increases in body weight and serum triglyceride receiving olanzapine (mean dose 13.8 mg) had their weight, cholesterol, and triglycerides measured at basel mean of 5.4 kg. Cholesterol levels increased by only 3 mg/dL while triglyceride levels increased by 60 mg/dL with weight change (p less than 0.02).

8) After an average of 16 months of olanzapine therapy, 9 patients had marked increases in triglyceride leve increased from a mean of 170 mg/dL to a mean of 240 mg/dL. Five patients had at least a 50% increase in le unchanged. The patients had a mean weight gain of 10 kg.

3.3.3.F Hyperglycemia

1) Summary

a) As with other atypical antipsychotics, hyperglycemia has been reported in patients on olanzapine. In a which were placebo-controlled, with treatment duration up to 12 weeks, olanzapine/fluoxetine was assoc glucose compared to placebo (8.65 mg/dL vs -3.86 mg/dL) . The mean increase of serum glucose (fastin average of the 2 highest serum concentrations was 15 mg/dL, during Clinical Antipsychotic Trials of Inte median olanzapine-exposure duration of 9.2 months. Olanzapine is implicated in glucose abnormalities; because of an increased risk of diabetes mellitus in patients with schizophrenia and the increasing incide population. In general, epidemiological studies show that atypical antipsychotics increase the risk of trea

appears to have a greater risk of glucose abnormalities compared with other atypical antipsychotics (Pro
b) The risks and benefits of olanzapine/fluoxetine hydrochloride should be considered prior to prescribin
diabetes mellitus or in patients with borderline increased blood glucose levels (fasting 100 to 126 mg/dL
monitoring of blood glucose is recommended. For patients with risk factors for diabetes mellitus, fasting l
initiation and periodically during olanzapine/fluoxetine therapy. All patients should be monitored for signs
polyuria, polyphagia, and weakness). Fasting blood glucose should be tested if symptoms of hyperglycer
discontinuation of olanzapine/fluoxetine; however, some patients may continue to need antidiabetic thera
Info SYMBYAX(R) oral capsule, 2009).

2) Incidence: baseline normal, 2.3%; baseline borderline-normal, 34.1% (Prod Info SYMBYAX(R) oral capsu

3) The mean changes in random glucose concentrations were an increase of 8.65 mg/dL in olanzapine/fluox
3.86 mg/dL (statistically significant), in an analysis of 7 controlled clinical studies, 2 of which were placebo-co
In patients with normal random glucose levels (less than 140 mg/dL) and baseline borderline random glucose
mg/dL) treated with olanzapine/fluoxetine, 2.3% and 34.1% (statistically significant compared with placebo), r
greater. In comparison, 0.3% and 3.6%, respectively, of the placebo-treated patients had high glucose levels.
concentration increases were patients with glucose dysregulation at baseline defined as: diagnosis with diabe
with antidiabetic agents, or baseline random glucose concentrations of 200 mg/dL or greater, and/or a baseli
These patients had a greater mean increase in glycosylated hemoglobin (Prod Info SYMBYAX(R) oral capsu

4) In a study of healthy volunteers, patients who received olanzapine (n=22) for 3 weeks had a mean increas
compared to baseline . Placebo-treated patients (n=19) had a mean increase in fasting blood glucose compa
SYMBYAX(R) oral capsule, 2009).

5) Data for fasting glucose are limited for olanzapine/fluoxetine. However for olanzapine monotherapy the m
mg/dL in olanzapine-treated adults compared with 0.17 mg/dL in placebo-treated patients, in an analysis of 5
to 12 weeks (Prod Info SYMBYAX(R) oral capsule, 2009).

6) The mean change in fasting glucose for olanzapine-treated patients was 4.2 mg/dL (n=487), and mean ch
at least 48 weeks was 5.9 mg/dL (n=425). In analyses of patients who completed 9 to 12 months of olanzapir
nonfasting glucose levels continue to increase over time (Prod Info SYMBYAX(R) oral capsule, 2009).

7) The mean changes in fasting glucose levels were an increase of 2.68 mg/dL in olanzapine-treated adoles
placebo-treated adolescents (statistically significant), in an analysis of 3 placebo-controlled trials of adolescer
duration of 6 weeks in schizophrenia trials or 3 weeks in bipolar disorder trials. The mean change in fasting g
weeks was 3.1 mg/dL. In adolescents with normal fasting glucose levels (less than 100 mg/dL) and baseline
less than 126 mg/dL) treated with olanzapine, 0% (0 out of 124) and 14.3% (2 out of 14), respectively, had hi
comparison, 1.9% (1 out of 53) and 0% (0 out of 13), respectively, of the placebo-treated patients had high gl
capsule, 2009).

3.3.3.G Hyperprolactinemia

1) Incidence: up to 61.1% (Prod Info SYMBYAX(R) oral capsule, 2009)

2) Olanzapine/fluoxetine elevates prolactin levels as with other drugs that antagonize dopamine D2 receptor
impotence have been reported in patients receiving prolactin-elevating compounds. In clinical studies of olan
concentrations were observed in 27.6% of the olanzapine/fluoxetine-treated adults compared to 4.8% of plac
plasma prolactin concentrations were reported in 34% of adults treated with olanzapine compared to 13.1% c
from clinical studies including 8136 adults treated with olanzapine, potentially associated clinical manifestatio
gynecomastia of males was 0.2% (8/4896), and breast enlargement of females were 0.06% (2/3240) (Prod In

3) In a single 8-week randomized, double-blind, fixed-dose study comparing olanzapine 10 mg/day (n=199),
incidence of treatment-emergent prolactin elevation greater than 24.2 ng/mL in females or greater than 18.77
31.2% at 10 mg, 42.7% at 20 mg, and 61.1% at 40 mg per day (Prod Info SYMBYAX(R) oral capsule, 2009).

4) In placebo-controlled olanzapine monotherapy studies in adolescent patients with schizophrenia or bipola
compared to baseline occurred in 47.4% of the adolescents treated with olanzapine compared to 6.8% of pla
adolescents, gynecomastia occurred in 2.4% of males (7/286) and galactorrhea occurred in 1.8% of females
2009).

3.3.3.H Hypoalbuminemia

1) Incidence: 2.7% (Prod Info SYMBYAX(R) oral capsule, 2009)

2) In olanzapine/fluoxetine clinical studies (including treatment resistant depression, depressive episodes as
depressive disorder with psychosis, or sexual dysfunction), low albumin level occurred at a greater frequency
olanzapine/fluoxetine-treated patients compared to placebo (2.7% vs 0.3%) (Prod Info SYMBYAX(R) oral cap

3.3.3.I Hyponatremia

1) Hyponatremia (headache, difficulty concentrating, memory impairment, confusion, weakness, and unstead
use, with some serious or acute cases resulting in hallucination, syncope, seizure, coma, respiratory arrest, a
110 mmol/L, which was reversible upon discontinuation, have been reported with olanzapine/fluoxetine. The
secretion may have been one possible etiology. Older patients and patients taking diuretics or who were othe
hyponatremia. Drug discontinuation is recommended in patients who develop symptomatic hyponatremia (Pr

3.3.3.J Hypophosphatemia

1) Incidence: 1.9% (Prod Info SYMBYAX(R) oral capsule, 2009)

2) In olanzapine/fluoxetine clinical studies (including treatment resistant depression, depressive episodes as
depressive disorder with psychosis, or sexual dysfunction), low inorganic phosphorus level occurred at a grea
olanzapine/fluoxetine-treated patients compared to placebo (1.9% vs 0.3%) (Prod Info SYMBYAX(R) oral cap

3.3.3.K Serum triglycerides raised

1) Summary

a) Elevations in serum triglycerides have been observed, at times a greater than 500 mg/dL increase, du hydrochloride. Baseline and follow-up lipid monitoring of lipids is recommended in patients on olanzapine capsule, 2009).

2) Incidence: up to 70% (Prod Info SYMBYAX(R) oral capsule, 2009)

3) The table below provides the frequency and degree of increase of nonfasting triglycerides in adults on ola of up to 12 weeks(Prod Info SYMBYAX(R) oral capsule, 2009):

Nonfasting Triglycerides In Adults on Olanzapine/Fluoxetine			
Category Change from Baseline	Treatment Arm	N	P
Increase by 50 mg/dL or more	olanzapine/fluoxetine	174	6
	olanzapine	172	7
Normal to High	olanzapine/fluoxetine	57	0
	olanzapine	58	0
Borderline to High	olanzapine/fluoxetine	106	1
	olanzapine	103	8
KEY: mg/dL = milligrams/deciliter; Normal = less than 150 mg/dL; borderline = 150 mg/dL to less than 5(mg/dL or greater			

4) In an analysis of 5 placebo-controlled olanzapine monotherapy studies of up to 12 weeks duration, the me by 20.8 mg/dL in olanzapine-treated patients compared to decreases from baseline of 10.7 mg/dL for placebo studies of at least 48 weeks, patients had increases from baseline in mean fasting triglycerides of 18.7 mg/dL who had at least one change in triglycerides from normal or borderline to high was greater in long-term studie median exposure of 9.2 months in phase 1 of the Clinical Antipsychotic Trials of Intervention Effectiveness (C olanzapine-treated patients was 40.5 mg/dL. The table below provides the frequency and degree of increase SYMBYAX(R) oral capsule, 2009):

Fasting Triglycerides In Adults on Olanzapine-Monotherapy					
		Up to 12 weeks exposure		At least 48 weeks exposure	
Category Change from Baseline	Treatment Arm	N	Portion of Patients	N	Portion of Patients
Increase by 50 mg/dL or more	olanzapine	745	39.6%	487	61.4%
	placebo	402	26.1%	NA	NA
Normal to High	olanzapine	457	9.2%	293	32.4%
	placebo	251	4.4%	NA	NA
Borderline to High	olanzapine	135	39.3%	75	70.7%
	placebo	65	20%	NA	NA
Increase by 40 mg/dL or more	olanzapine	745	21.6%	489	32.9
	placebo	402	9.5%	NA	NA
KEY: mg/dL = milligrams/deciliter; Normal = less than 150 mg/dL; Borderline = 150 mg/dL to less than 200 mg/dL; High = 200 mg/dL or greater; NA = Not Applicable					

5) In an analysis of 3 placebo-controlled olanzapine monotherapy studies of up to 6 weeks duration in adoles increases from baseline in mean fasting triglycerides of 28.4 mg/dL compared to a decrease of 1.1 mg/dL for olanzapine studies of at least 24 weeks, adolescents had increases from baseline in mean fasting triglyceride frequency and degree of increase of fasting triglycerides(Prod Info SYMBYAX(R) oral capsule, 2009):

Fasting Triglycerides In Adolescents					
		Up to 6 weeks exposure		At least 24 weeks exposure	
Category Change from Baseline	Treatment Arm	N	Portion of Patients	N	Portion of Patients
Increase by 50 mg/dL or more	olanzapine	138	37%	122	45.9%
	placebo	66	15.2%	NA	NA
Normal to High	olanzapine	67	26.9%	66	36.4%
	placebo	28	10.7%	NA	NA
Borderline to High	olanzapine	37	59.5%	31	64.5
	placebo	17	35.3%	NA	NA
KEY: mg/dL = milligrams/deciliter; Normal = Normal = less than 90 mg/dL; Borderline = 90 mg/dL to less than 130 mg/dL; High = 130 mg/dL or greater; NA = Not Applicable					

6) Random triglyceride levels of 1000 mg/dL or more have been reported during postmarketing reports with c

SYMBYAX(R) oral capsule, 2009).
7) Patients (n=25) receiving olanzapine were found to have increases in body weight and serum triglycerides receiving olanzapine (mean dose 13.8 mg) had their weight, cholesterol, and triglycerides measured at basel mean of 5.4 kg. Cholesterol levels increased by only 3 mg/dL while triglyceride levels increased by 60 mg/dL with weight change (p less than 0.02).
8) After an average of 16 months of olanzapine therapy, 9 patients had marked increases in triglyceride leve increased from a mean of 170 mg/dL to a mean of 240 mg/dL. Five patients had at least a 50% increase in le unchanged. The patients had a mean weight gain of 10 kg.

3.3.3.L Weight gain

1) Summary
a) Weight gain is associated with olanzapine use. Weight gain (greater than 7% of their baseline weight) olanzapine/fluoxetine long term (median days of exposure, 448) with the mean weight gain of 6.7 kg. For change was +4 kg and -0.3 kg for olanzapine/fluoxetine and placebo-treated patients, respectively, in an which were placebo-controlled. Regular monitoring of weight should be performed. Before initiating olanz to the potential consequences of weight gain (Prod Info SYMBYAX(R) oral capsule, 2009).
2) Incidence: 25% (Prod Info SYMBYAX(R) oral capsule, 2009)
3) In short-term, controlled studies including depressive episodes associated with Bipolar I Disorder and trea occurred in 25% of patients who received fluoxetine/olanzapine (n=771) compared with 3% of patients who re (R) oral capsule, 2009).
4) In a single 8-week randomized, double-blind, fixed-dose study comparing olanzapine 10 mg/day (n=199), mean baseline to endpoint increase in weight was 1.9 kg, 2.3 kg, and 3 kg, respectively, with significant differ SYMBYAX(R) oral capsule, 2009).
5) The mean weight change was +4 kg and -0.3 kg for olanzapine/fluoxetine and placebo-treated patients, re studies, 2 of which were placebo-controlled. After a median duration of 6 weeks, 22% of olanzapine/fluoxetin patients (statistically significant) gained at least 7% of their baseline weight. After a median duration of 8 wee compared with 0% of placebo-treated patients (statistically significant) gained at least 15% of their baseline w difference in the amount gained. The discontinuation rate due to weight gain was 2.5% and 0% in the olanzap respectively.(Prod Info SYMBYAX(R) oral capsule, 2009).
6) The table below provides the adult weight gain observed in olanzapine treated patients from 86 clinical ola capsule, 2009) :

	Olanzapine-Monotherapy Trials in Adults		
Amount Gained	6 weeks	6 months	12 months
	n=7465	n=4162	n=1345
0 kg gain or loss of weight	26.2%	24.3%	20.8%
0 to 5 kg (0 to 11 lb)	57%	36%	26%
greater than 5 to 10 kg (11 to 22 lb)	14.9%	24.6%	24.2%
greater than 10 to 15 kg (22 to 33 lb)	1.8%	10.9%	14.9%
greater than 15 to 20 kg (33 to 44 lb)	0.1%	3.1%	8.6%
greater than 20 to 25 kg (44 to 55 lb)	0%	0.9%	3.3%
greater than 25 to 30 kg (55 to 66 lb)	0%	0.2%	1.4%
greater than 30 kg (greater than 66 lb)	0%	0.1%	0.8%
Key: kg = kilograms; lb = pounds			

7) Weight gain (greater than 7% of their baseline weight) occurred in 66% of patients treated with olanzapine 448) with the mean weight gain of 6.7 kg. Discontinuation due to weight gain in long-term exposure (48 week olanzapine/fluoxetine-treated patients. In long-term olanzapine monotherapy studies, the mean weight gain w 64% of patients who gaining at least 7% of their baseline weight. Discontinuation due to weight gain occurred long-term olanzapine monotherapy studies (Prod Info SYMBYAX(R) oral capsule, 2009).
8) An average weight gain of 4.6 kg in olanzapine-treated adolescents and 0.3 kg in placebo-treated adolesc controlled trials of adolescents (under the age of 18 years) treated with monotherapy olanzapine for a mediar 4 weeks, 40.6% of olanzapine-treated compared with 9.8% of placebo-treated patients gained at least 7% of 19 weeks, 7.1% of olanzapine-treated compared with 2.7% of placebo-treated patients gained at least 15% o due to weight gain was 1% and 0% in the olanzapine and placebo treated patients, respectively (Prod Info SY
9) In long-term (24 weeks or more) olanzapine studies, 89% of adolescents gained at least 7% of their basel the mean weight gain of 11.2 kg. Baseline body mass index (BMI) did not affect the amount gained. Discontir occurred in 2.2% of olanzapine-treated patients(Prod Info SYMBYAX(R) oral capsule, 2009).
10) The table below provides the adolescent weight gain with olanzapine treated patients from 6 clinical olan capsule, 2009) :

Olanzapine-Monotherapy Trials in Adolescents	
Amount Gained	6 weeks
	n=243
0 kg gain or loss of weight	2.9%
0 to 5 kg (0 to 11 lb)	47.3%
greater than 5 to 10 kg (11 to 22 lb)	42.4%
greater than 10 to 15 kg (22 to 33 lb)	5.8%
greater than 15 to 20 kg (33 to 44 lb)	0.8%
greater than 20 to 25 kg (44 to 55 lb)	0.8%
greater than 25 to 30 kg (55 to 66 lb)	0%
greater than 30 to 35 kg (66 to 77 lb)	0%
greater than 35 to 40 kg (77 to 88 lb)	0%
greater than 40 kg (greater than 88 lb)	0%
Key: kg = kilograms; lb = pounds	

11) Weight gain (39.8%) and increased appetite (32%) were reported following the administration of olanzap and 46.1 mg/day, respectively (Corya et al, 2003a).
12) Adolescent patients taking olanzapine experienced greater weight gain and increased in body mass inde retrospective study involving 103 patients younger than 18 years of age. Patients received olanzapine (n=50, mean daily dose 510.9 mg) for at least 2 weeks. Weight and height were measured at baseline and 14 or mo baseline in the olanzapine group was 3.8 kg (p less than 0.001) compared to 0.03 kg in the quetiapine group. showed slight, but significant, increases in height from baseline (0.006 meters, p=0.042 and 0.006 meters, p for baseline differences, the mean weight change between groups was significant (3.4 kg, p less than 0.001). the olanzapine group (p less than 0.001) compared to a decreased of 0.2 kg/m(2) in the quetiapine group. Af difference in change in BMI was significant (0.9 kg/m(2), p=0.008) (Patel et al, 2004).
13) Excessive appetite was seen more commonly with olanzapine therapy than with haloperidol (24% versus was also associated with a clinically significant greater increase in weight over haloperidol therapy (p less tha that body mass index was the predominant predictor of weight gain. Patients with a low prestudy body mass olanzapine treatment. Treatment effect on weight change was consistent between male and female patients
14) A prospective, multicenter, observational study showed that olanzapine treatment of outpatients (n=2128 group of patients (n=821) receiving a variety of other antipsychotic drug therapies. Drugs used in the control sertindole, zuclopenthixol, fluphenazine, thioridazine, perphenazine, pimozide, clozapine, pipotiazine, sulpirid clothiapine, and lorazepam. Overall, olanzapine had a significantly lower incidence of adverse events than th 0.001). Somnolence and weight gain occurred significantly more frequently in olanzapine-treated patients. Ak hypertonia, and tremor were significantly higher in the control group. Abnormal ejaculation and impotence oc control group. Over a 6-month period, fewer olanzapine-treated patients received a concomitant anticholinerg control group (36% versus 58%, p less than 0.001) (Gomez et al, 2000).

3.3.4 Gastrointestinal Effects

Abdominal distension

Constipation

Diarrhea

Dysphagia

Flatulence

Gastrointestinal hemorrhage

Increased appetite

Nausea

Xerostomia

3.3.4.A Abdominal distension
1) Incidence: 2% (Prod Info SYMBYAX(R) oral capsule, 2009)

2) In short-term, controlled studies including depressive episodes associated with Bipolar I Disorder and trea occurred in 2% of patients who received fluoxetine/olanzapine (n=771) compared with 0% of patients who re oral capsule, 2009).

3.3.4.B Constipation

1) Constipation was associated with olanzapine/fluoxetine in premarketing clinical studies (Prod Info SYMBY

3.3.4.C Diarrhea

1) Incidence: 12.5% (Corya et al, 2003a)

2) Dry mouth (37.1%), nausea (15.7%), and diarrhea (12.5%) have occurred following the administration of o of 7.5 and 46.1 milligrams/day, respectively (Corya et al, 2003a).

3.3.4.D Dysphagia

1) Antipsychotic drug use has been associated with esophageal dysmotility and aspiration. Olanzapine/fluox Alzheimer's disease due to the risk of aspiration pneumonia, a common cause of morbidity and mortality in th SYMBYAX(R) oral capsule, 2009).

3.3.4.E Flatulence

1) Incidence: 3% (Prod Info SYMBYAX(R) oral capsule, 2009)

2) In short-term, controlled studies including depressive episodes associated with Bipolar I Disorder and trea in 3% of patients who received fluoxetine/olanzapine (n=771) compared with 1% of patients who received pla capsule, 2009).

3.3.4.F Gastrointestinal hemorrhage

1) Serotonin norepinephrine reuptake inhibitors (SNRIs) and SSRIs, including fluoxetine, may increase the ri aspirin, NSAIDs, warfarin and other anticoagulants may increase this risk. Case reports and epidemiological design, have demonstrated an association between use of drugs that interfere with serotonin reuptake and th anticoagulant effects, including increased bleeding, have been reported with SNRIs or SSRIs when given cor warfarin 20 mg did not affect olanzapine pharmacokinetics. Likewise, single doses of olanzapine did not affec reactions associated with SNRIs and SSRIs use have ranged from ecchymoses, hematomas, epistaxis and p Patients receiving warfarin therapy should be carefully monitored when olanzapine/fluoxetine is initiated or di capsule, 2009).

2) Case reports have documented the occurrence of bleeding episodes in patients treated with psychotropic Subsequent epidemiological studies, both of the case-control and cohort design, have demonstrated an asso interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding. The same epidemiolo a nonsteroidal anti-inflammatory drug (NSAID) or aspirin potentiated the risk of bleeding. Patients should be associated with the concomitant use of olanzapine/fluoxetine with NSAIDs, aspirin, or other drugs that affect capsule, 2009).

3.3.4.G Increased appetite

1) Incidence: 20% (Prod Info SYMBYAX(R) oral capsule, 2009)

2) In short-term, controlled studies including depressive episodes associated with Bipolar I Disorder and trea occurred in 20% of patients who received fluoxetine/olanzapine (n=771) compared with 4% of patients who re (R) oral capsule, 2009).

3.3.4.H Nausea

1) Incidence: 15.7% (Corya et al, 2003a)

2) Dry mouth (37.1%), nausea (15.7%), and diarrhea (12.5%) have occurred following the administration of o of 7.5 and 46.1 milligrams/day, respectively (Corya et al, 2003a).

3.3.4.I Xerostomia

1) Incidence: 15% to 37.1%(Prod Info SYMBYAX(R) oral capsule, 2009; Corya et al, 2003a)

2) In short-term, controlled studies including depressive episodes associated with Bipolar I Disorder and trea in 15% of patients who received fluoxetine/olanzapine (n=771) compared with 6% of patients who received p capsule, 2009).

3) Dry mouth (37.1%), nausea (15.7%), and diarrhea (12.5%) have occurred following the administration of o of 7.5 and 46.1 milligrams/day, respectively (Corya et al, 2003a).

3.3.5 Hematologic Effects

Aplastic anemia

Decreased hemoglobin

Lymphocytopenia

Neutropenia

3.3.5.A Aplastic anemia

1) Aplastic anemia has been reported with olanzapine or fluoxetine monotherapy, but was not observed in ol premarketing clinical studies (Prod Info SYMBYAX(R) oral capsule, 2009).

3.3.5.B Decreased hemoglobin

1) Incidence: 2.6% (Prod Info SYMBYAX(R) oral capsule, 2009)

2) In olanzapine/fluoxetine clinical studies (including treatment resistant depression, depressive episodes as depressive disorder with psychosis, or sexual dysfunction), low hemoglobin level occurred at a greater freque olanzapine/fluoxetine-treated patients compared to placebo (2.6% vs 0%) (Prod Info SYMBYAX(R) oral caps

3.3.5.C Lymphocytopenia

1) Incidence: 1.9% (Prod Info SYMBYAX(R) oral capsule, 2009)

2) In olanzapine/fluoxetine clinical studies (including treatment resistant depression, depressive episodes as depressive disorder with psychosis, or sexual dysfunction), low lymphocytes level occurred at a greater frequ olanzapine/fluoxetine-treated patients compared to placebo (1.9% vs 0%) (Prod Info SYMBYAX(R) oral caps

3.3.5.D Neutropenia

1) Neutropenia has been reported with olanzapine or fluoxetine monotherapy, but was not observed in olanz premarketing clinical studies (Prod Info SYMBYAX(R) oral capsule, 2009).

3.3.6 Hepatic Effects

Cholestatic hepatitis

Decreased bilirubin level

Hepatitis

Increased liver function test

3.3.6.A Cholestatic hepatitis

1) Incidence: rare (Prod Info SYMBYAX(R) oral capsule, 2009)

2) In the postmarketing period, there have been rare reports of hepatitis and very rare cases of cholestatic o capsule, 2009).

3) Jaundice and cholestatic jaundice have been reported with olanzapine or fluoxetine monotherapy, but was patients during premarketing clinical studies (Prod Info SYMBYAX(R) oral capsule, 2009).

3.3.6.B Decreased bilirubin level

1) Incidence: 15.3% (Prod Info SYMBYAX(R) oral capsule, 2009)

2) In olanzapine/fluoxetine clinical studies (including treatment resistant depression, depressive episodes as depressive disorder with psychosis, or sexual dysfunction), low total bilirubin level occurred at a greater frequ olanzapine/fluoxetine-treated patients compared to placebo (15.3% vs 3.9%) (Prod Info SYMBYAX(R) oral ca

3.3.6.C Hepatitis

1) Incidence: rare (Prod Info SYMBYAX(R) oral capsule, 2009)

2) In the postmarketing period, there have been rare reports of hepatitis and very rare cases of cholestatic o capsule, 2009).

3.3.6.D Increased liver function test

1) Incidence: 2% to 3.4% (Prod Info SYMBYAX(R) oral capsule, 2009)

2) As with olanzapine, asymptomatic elevations of hepatic transaminases (ALT (SGPT), AST (SGOT), and G observed with olanzapine/fluoxetine. In the olanzapine/fluoxetine-controlled database, ALT (SGPT) elevation of the normal range) were observed in 3.4% (20/586) of patients exposed to olanzapine/fluoxetine compared 3.5% (23/665) of olanzapine-treated patients. The difference between olanzapine/fluoxetine and placebo was olanzapine/fluoxetine patients who started normal at baseline and had increases in ALT 5 times or more of th jaundice and 4 had transient elevations greater than 200 IU/L (Prod Info SYMBYAX(R) oral capsule, 2009).

3) In olanzapine placebo-controlled studies, clinically significant ALT elevations (3 times the upper limit or gr (6/243) of patients exposed to olanzapine compared with 0% (0/115) of the placebo patients. None of these p patients, liver enzymes decreased toward normal despite continued treatment, and in 2 others, enzymes dec remaining 2 patients, one, seropositive for hepatitis C, had persistent enzyme elevations for 4 months after di follow-up to determine if enzymes normalized (Prod Info SYMBYAX(R) oral capsule, 2009).

4) Within the larger olanzapine premarketing database of about 2400 patients with baseline ALT less than or to greater than 200 international units/L was 2% (50/2381). None of these patients experienced jaundice or o and most had transient changes that tended to normalize while olanzapine treatment was continued. Among approximately 1% (23/2500) discontinued treatment due to transaminase increases (Prod Info SYMBYAX(R)

3.3.7 Immunologic Effects

3.3.7.A Immune hypersensitivity reaction

1) In premarketing controlled clinical studies, the overall incidence of rash or allergic events in treated patien (5.2% (25/477)). The majority of the cases of rash and/or urticaria were mild; however, three patients disconti severity, and two due to allergic events, one of which included face edema). In fluoxetine US clinical studies, developed various types of rashes and/or urticaria (Prod Info SYMBYAX(R) oral capsule, 2009).

2) Among the cases of rash and/or urticaria reported in premarketing clinical studies, almost a third were witl and/or systemic signs or symptoms associated with the rash. Clinical findings reported in association with ras carpal tunnel syndrome, respiratory distress, lymphadenopathy, proteinuria, and mild transaminase elevation discontinuation of fluoxetine and/or adjunctive treatment with antihistamines or steroids, and all patients expe completely (Prod Info SYMBYAX(R) oral capsule, 2009).

3) In fluoxetine premarketing clinical studies, 2 patients are known to have developed a serious cutaneous s unequivocal diagnosis, but 1 was considered to have a leukocytoclastic vasculitis, and the other, a severe de variously to be a vasculitis or erythema multiforme. Other patients have had systemic syndromes suggestive fluoxetine, systemic events, possibly related to vasculitis, have developed in patients with rash. Although thes the lung, kidney, or liver. Death has been reported to occur in association with these systemic events (Prod In

4) Anaphylactoid events, including bronchospasm, angioedema, and urticaria alone and in combination, hav inflammatory processes of varying histopathology and/or fibrosis, have been reported rarely. These events ha symptom. Whether these systemic events and rash have a common underlying cause or are due to different Furthermore, a specific underlying immunologic basis for these events has not been identified. Upon the app phenomena for which an alternative etiology cannot be identified, the drug should be discontinued (Prod Info

3.3.8 Musculoskeletal Effects

Arthralgia

Muscle rigidity

Pain, Extremity

3.3.8.A Arthralgia

1) Incidence: 4% (Prod Info SYMBYAX(R) oral capsule, 2009)

2) In short-term, controlled studies including depressive episodes associated with Bipolar I Disorder and trea 4% of patients who received fluoxetine/olanzapine (n=771) compared with 1% of patients who received place capsule, 2009).

3.3.8.B Muscle rigidity

1) Incidence: 2% (Prod Info SYMBYAX(R) oral capsule, 2009)

2) In short-term, controlled studies including depressive episodes associated with Bipolar I Disorder and trea stiffness occurred in 2% of patients who received fluoxetine/olanzapine (n=771) compared with 1% of patient SYMBYAX(R) oral capsule, 2009).

3.3.8.C Pain, Extremity

1) Incidence: 3% (Prod Info SYMBYAX(R) oral capsule, 2009)

2) In short-term, controlled studies including depressive episodes associated with Bipolar I Disorder and trea occurred in 3% of patients who received fluoxetine/olanzapine (n=771) compared with 1% of patients who re oral capsule, 2009).

3.3.9 Neurologic Effects

Asthenia

Central nervous system finding

Dizziness

Dyskinesia

Hypersomnia

Impaired cognition

Lethargy

Sedated

Seizure

Somnolence

Tremor

3.3.9.A Asthenia

1) Incidence: 3% (Prod Info SYMBYAX(R) oral capsule, 2009)

2) In short-term, controlled studies including depressive episodes associated with Bipolar I Disorder and trea 3% of patients who received fluoxetine/olanzapine (n=771) compared with 1% of patients who received place capsule, 2009).

3.3.9.B Central nervous system finding

1) Cerebrovascular adverse events (eg, stroke, transient ischemic attack), including fatalities, were reported patients with dementia-related psychosis. In placebo-controlled trials, there was a significantly higher inciden treated with olanzapine compared to patients treated with placebo. Olanzapine is not approved for the treatm (Prod Info SYMBYAX(R) oral capsule, 2009).

2) Somnolence (47.7%), headache (22.3%), asthenia (19.3%), tremor (18.8%), anxiety (13.9%), dizziness (1 (11.6%) were reported following the administration of olanzapine/fluoxetine combination at mean doses of 7.5 al, 2003a).

3.3.9.C Dizziness

1) Incidence: 1.6% to 6.6%

2) In a single 8-week randomized, double-blind, fixed-dose study comparing olanzapine 10 mg/day (n=199), dizziness was reported at 2.6%, 1.6%, and 6.6%, respectively, with significant differences between 20 vs 40 2009).

3.3.9.D Dyskinesia

1) A syndrome of potentially irreversible, involuntary, dyskinetic movements (tardive dyskinesia) may develo Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndr in their potential to cause tardive dyskinesia is unknown. The risk of developing tardive dyskinesia and the lik believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs adminis syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses or treatment (Prod Info SYMBYAX(R) oral capsule, 2009).

2) The incidence of dyskinetic movement in olanzapine/fluoxetine-treated patients was infrequent. The mean Scale (AIMS) across clinical studies involving olanzapine/fluoxetine-treated patients decreased from baseline prescribed in a manner that is most likely to minimize the risk of tardive dyskinesia. If signs and symptoms of olanzapine/fluoxetine, drug discontinuation should be considered. However, some patients may require treatr presence of the syndrome. The need for continued treatment should be reassessed periodically (Prod Info S

3) Dyskinesia has been reported with olanzapine or fluoxetine monotherapy, but was not observed in olanza premarketing clinical studies (Prod Info SYMBYAX(R) oral capsule, 2009).

3.3.9.E Hypersomnia

1) Incidence: 5% (Prod Info SYMBYAX(R) oral capsule, 2009)

2) In short-term, controlled studies including depressive episodes associated with Bipolar I Disorder and trea occurred in 5% of patients who received fluoxetine/olanzapine (n=771) compared with 1% of patients who rec oral capsule, 2009).

3.3.9.F Impaired cognition

1) Sedation-related adverse events were commonly reported with olanzapine/fluoxetine treatment, occurring olanzapine/fluoxetine patients compared with 10.9% in placebo patients. Sedation-related adverse events (sc discontinuation in 2% (15/771) of patients during controlled clinical studies. As with any CNS-active drug, olar judgment, thinking, or motor skills. Patients should be cautioned about operating hazardous machinery, inclu certain that olanzapine/fluoxetine therapy does not affect them adversely (Prod Info SYMBYAX(R) oral capsu

3.3.9.G Lethargy

1) Incidence: 3% (Prod Info SYMBYAX(R) oral capsule, 2009)

2) In short-term, controlled studies including depressive episodes associated with Bipolar I Disorder and trea 3% of patients who received fluoxetine/olanzapine (n=771) compared with 1% of patients who received place capsule, 2009).

3.3.9.H Sedated

1) Incidence: 8% (Prod Info SYMBYAX(R) oral capsule, 2009)

2) In short-term, controlled studies including depressive episodes associated with Bipolar I Disorder and trea 8% of patients who received fluoxetine/olanzapine (n=771) compared with 4% of patients who received place capsule, 2009).

3.3.9.I Seizure

1) Incidence: 0.2% (Prod Info SYMBYAX(R) oral capsule, 2009)

2) Seizures occurred in 0.2% (4/2547) of olanzapine/fluoxetine-treated patients during open-label clinical stu olanzapine/fluoxetine studies. Seizures have also been reported with both olanzapine and fluoxetine monothe used cautiously in patients with a history of seizures or with conditions that potentially lower the seizure thres may be more prevalent in a population of greater than or equal to 65 years of age (Prod Info SYMBYAX(R) o

3) There have been rare reports of prolonged seizures in patients on fluoxetine receiving electroconvulsive tl studies establishing the benefit of the combined use of ECT and fluoxetine (Prod Info SYMBYAX(R) oral caps

3.3.9.J Somnolence

1) Incidence: 14% (Prod Info SYMBYAX(R) oral capsule, 2009)

2) In short-term, controlled studies including depressive episodes associated with Bipolar I Disorder and trea occurred in 14% of patients who received fluoxetine/olanzapine (n=771) compared with 6% of patients who re (R) oral capsule, 2009).

3.3.9.K Tremor

1) Incidence: 9% (Prod Info SYMBYAX(R) oral capsule, 2009)

2) In short-term, controlled studies including depressive episodes associated with Bipolar I Disorder and trea 9% of patients who received fluoxetine/olanzapine (n=771) compared with 3% of patients who received place capsule, 2009).

3.3.10 Ophthalmic Effects

3.3.10.A Blurred vision

1) Incidence: 5% (Prod Info SYMBYAX(R) oral capsule, 2009)

2) In short-term, controlled studies including depressive episodes associated with Bipolar I Disorder and trea occurred in 5% of patients who received fluoxetine/olanzapine (n=771) compared with 2% of patients who rec oral capsule, 2009).

3.3.12 Psychiatric Effects

Depression, Worsening

Disturbance in thinking

Disturbance of attention

Feeling nervous

Mania

Restlessness

Suicidal thoughts

Suicide

Violent behavior

3.3.12.A Depression, Worsening

1) All patients being treated with antidepressants for any indication should be monitored appropriately and ol and unusual changes in behavior, in particular during the first few months or at times of dose increase or dec 2009).

3.3.12.B Disturbance in thinking

1) Incidence: 2% (Prod Info SYMBYAX(R) oral capsule, 2009)

2) In short-term, controlled studies including depressive episodes associated with Bipolar I Disorder and trea occurred in 2% of patients who received fluoxetine/olanzapine (n=771) compared with 1% of patients who re oral capsule, 2009).

3.3.12.C Disturbance of attention

1) Incidence: 5% (Prod Info SYMBYAX(R) oral capsule, 2009)

2) In short-term, controlled studies including depressive episodes associated with Bipolar I Disorder and trea attention occurred in 5% of patients who received fluoxetine/olanzapine (n=771) compared with 1% of patient SYMBYAX(R) oral capsule, 2009).

3.3.12.D Feeling nervous

1) Incidence: 2% (Prod Info SYMBYAX(R) oral capsule, 2009)

2) In short-term, controlled studies including depressive episodes associated with Bipolar I Disorder and trea occurred in 2% of patients who received fluoxetine/olanzapine (n=771) compared with 1% of patients who re oral capsule, 2009).

3.3.12.E Mania

1) In the two controlled bipolar depression studies there was no statistically significant difference in the incid depressive reaction) between olanzapine/fluoxetine- and placebo-treated patients. In one of the studies, the i olanzapine/fluoxetine-treated patients compared to (3% (5/184)) in placebo-treated patients. In the other stud in olanzapine/fluoxetine-treated patients compared to (8% (15/193)) in placebo-treated patients. This limited olanzapine/fluoxetine in the treatment of bipolar depression makes it difficult to interpret these findings until a the cyclical nature of bipolar disorder, patients should be monitored closely for the development of symptoms olanzapine/fluoxetine (Prod Info SYMBYAX(R) oral capsule, 2009).

3.3.12.F Restlessness

1) Incidence: 4% (Prod Info SYMBYAX(R) oral capsule, 2009)

2) In short-term, controlled studies including depressive episodes associated with Bipolar I Disorder and trea occurred in 4% of patients who received fluoxetine/olanzapine (n=771) compared with 1% of patients who re oral capsule, 2009).

3.3.12.G Suicidal thoughts

1) Adult and pediatric patients being treated with antidepressants for major depressive disorder (MDD) and o who experience symptoms of anxiety, agitation, panic attacks, insomnia, irritability, hostility (aggressiveness) restlessness), hypomania, or mania may be at risk of suicidal ideation and behavior (suicidality). In pooled an of 9 antidepressants including over 4400 pediatric patients with MDD, obsessive compulsive disorder (OCD), suicidal behavior or ideation during the first few months of therapy was demonstrated in children, adolescents receiving antidepressants as compared with placebo. However, pooled analyses of 295 short-term (median d 11 antidepressants including over 77,000 adults with MDD or other psychiatric disorders did not demonstrate antidepressants compared to placebo in adults beyond age 24 years. Further, there was a reduction in risk of placebo in adults aged 65 years and older. The risk of suicidality was most consistently observed in the trials signs of risk emerging from trials in other psychiatric indications, such as OCD and social anxiety disorder. N however, there were suicides in the adult trials. The risk of suicidality during longer-term use (ie, beyond seve known. However, placebo-controlled maintenance trials in adults with depression indicate that antidepressant Info SYMBYAX(R) oral capsule, 2009).

3.3.12.H Suicide

1) The possibility of a suicide attempt is inherent in bipolar disorder and may persist until significant remissio should accompany drug therapy. Prescriptions for olanzapine/fluoxetine should be written for the smallest qu in order to reduce the risk of overdose. There were reports of suicides during clinical trials in adults, but the n about drug effect on suicide (Prod Info SYMBYAX(R) oral capsule, 2009).

3.3.12.I Violent behavior

1) Violent behaviors have been reported with olanzapine or fluoxetine monotherapy, but was not observed in premarketing clinical studies (Prod Info SYMBYAX(R) oral capsule, 2009).

3.3.13 Renal Effects

Glycosuria

Increased uric acid level

Serum blood urea nitrogen raised

3.3.13.A Glycosuria

1) Incidence: 4.4% (Prod Info SYMBYAX(R) oral capsule, 2009)

2) In an analysis of 6 controlled clinical studies, glycosuria were reported at 4.4% in patients treated with ola receiving placebo (Prod Info SYMBYAX(R) oral capsule, 2009).

3.3.13.B Increased uric acid level

1) Incidence: 2.9% (Prod Info SYMBYAX(R) oral capsule, 2009)

2) In olanzapine/fluoxetine clinical studies (including treatment resistant depression, depressive episodes as depressive disorder with psychosis, or sexual dysfunction), elevated uric acid level occurred at a greater freq olanzapine/fluoxetine-treated patients compared to placebo (2.9% vs 0.5%) (Prod Info SYMBYAX(R) oral cap

3.3.13.C Serum blood urea nitrogen raised

1) Incidence: 2.8% (Prod Info SYMBYAX(R) oral capsule, 2009)

2) In olanzapine/fluoxetine clinical studies (including treatment resistant depression, depressive episodes as depressive disorder with psychosis, or sexual dysfunction), elevated urea nitrogen level occurred at a greater olanzapine/fluoxetine-treated patients compared to placebo (2.8% vs 0.8%) (Prod Info SYMBYAX(R) oral cap

3.3.14 Reproductive Effects

Erectile dysfunction

Sexual dysfunction

3.3.14.A Erectile dysfunction

1) Incidence: 2% (Prod Info SYMBYAX(R) oral capsule, 2009)

2) In short-term, controlled studies including depressive episodes associated with Bipolar I Disorder and trea occurred in 2% of patients who received fluoxetine/olanzapine (n=771) compared with 1% of patients who re oral capsule, 2009).

3.3.14.B Sexual dysfunction

1) In the pool of controlled olanzapine/fluoxetine studies, there were higher rates of treatment-emergent adv anorgasmia, impotence and abnormal ejaculation in the olanzapine/fluoxetine group than in the placebo grou discontinuation in the olanzapine/fluoxetine group. In the controlled studies that contained a fluoxetine arm, t ejaculation in the olanzapine/fluoxetine group were less than the rates in the fluoxetine group. None of the di study (n=560), decreased libido occurred in 11.4% of patients following the administration of olanzapine/fluox milligrams/day, respectively (Prod Info SYMBYAX(R) oral capsule, 2009; Corya et al, 2003a).

2) Sexual dysfunction, including priapism, has been reported with all SSRIs. While it is difficult to know the p the use of SSRIs, physicians should routinely inquire about such possible side effects (Prod Info SYMBYAX(

3.3.15 Respiratory Effects

Pulmonary eosinophilia

Respiratory finding

Sinusitis

3.3.15.A Pulmonary eosinophilia

1) Eosinophilic pneumonia has been reported with olanzapine or fluoxetine monotherapy, but was not obser during premarketing clinical studies (Prod Info SYMBYAX(R) oral capsule, 2009).

3.3.15.B Respiratory finding

1) Pharyngitis (10.4%), rhinitis (22.1%), and dyspnea have been reported in olanzapine/fluoxetine-treated pa

3.3.15.C Sinusitis

1) Incidence: 2% (Prod Info SYMBYAX(R) oral capsule, 2009)

2) In short-term, controlled studies including depressive episodes associated with Bipolar I Disorder and trea 2% of patients who received fluoxetine/olanzapine (n=771) compared with 1% of patients who received place capsule, 2009).

3.3.16 Other

Death

Fatigue

Fever

Neuroleptic malignant syndrome

Pain

Serotonin syndrome

3.3.16.A Death

1) Incidence: 3.5% (Prod Info SYMBYAX(R) oral capsule, 2009)

2) In olanzapine placebo-controlled clinical trials of elderly patients with dementia-related psychosis, the inci
significantly higher than the placebo group (3.5% vs 1.5%, respectively)(Prod Info SYMBYAX(R) oral capsule

3) Sudden unexpected death has been reported with olanzapine or fluoxetine monotherapy, but was not obs
during premarketing clinical studies (Prod Info SYMBYAX(R) oral capsule, 2009).

4) Results of a population-based, retrospective cohort study demonstrated that the use of conventional antip
risk for death than atypical antipsychotics when administered to elderly patients (aged 66 years and older) wi
and conventional versus atypical antipsychotic use pair-wise comparisons were made. A total of 27,259 matc
cohort was stratified based on place of residence (community versus long-term care facilities). In order to adj
propensity score matching was used. The primary outcome of the study was all-cause mortality. The risk for
days after the antipsychotic medications were initially dispensed. There was a statistically significant increase
new use of atypical antipsychotic medications compared with nonuse in both the community-dwelling cohort
confidence interval (CI), 1.02 to 1.70); absolute risk difference, 0.2 percentage point) and long-term care coh
absolute risk difference, 1.2 percentage points). For both cohorts, the risk associated with atypical antipsycho
death associated with conventional antipsychotics was even greater than the risk identified with atypical antip
community-dwelling cohort was 1.55 (95% CI, 1.19 to 2.02) and 1.26 (95% CI, 1.04 to 1.53) for the long-term
was 1.1 percentage points). The risk appeared to persist to 180 days for both groups. Some important limitati
unmeasured confounders may influence the results and cause of death could not be examined (Gill et al, 200

5) Results of a population-based, retrospective cohort study demonstrated comparable to possibly greater ris
conventional antipsychotic medications in the elderly (aged 65 years and older) compared with atypical antips
patients with cancer and included only new users of antipsychotic medications. The primary study outcome w
confounders was measured based on healthcare utilization data within 6 months before the initiation of antips
patients identified, 12,882 and 24,359 received conventional and atypical antipsychotic medications, respecti
group within the first 180 days was 14.1% compared with 9.6% in the atypical drug group (unadjusted mortali
to 1.56). In the multi-variable analysis which controlled for potential confounders, the adjusted mortality ratio f
conventional versus atypical drug therapy was 1.32 (95% CI, 1.23 to 1.42). When the most frequently prescri
compared with risperidone, the mortality ratio associated with haloperidol was 2.14 (95% CI, 1.86 to 2.45) an
there was no difference associated with olanzapine. The increased mortality risk for conventional versus atyp
higher (above median) doses were used (mortality ratio 1.67; 95% CI, 1.5 to 1.86) and also during the first 40
1.42 to 1.8). Confirmatory analyses consisting of multi-variable Cox regression, propensity score, and instrum
the study (Schneeweiss et al, 2007).

3.3.16.B Fatigue

1) Incidence: 12% (Prod Info SYMBYAX(R) oral capsule, 2009)

2) In short-term, controlled studies including depressive episodes associated with Bipolar I Disorder and trea
12% of patients who received fluoxetine/olanzapine (n=771) compared with 2% of patients who received plac
capsule, 2009).

3) In a single 8-week randomized, double-blind, fixed-dose study comparing olanzapine 10 mg/day (n=199),
fatigue was reported at 1.5%, 2.1%, and 6.6%, respectively, with significant differences between 10 vs 40 an
capsule, 2009).

3.3.16.C Fever

1) Incidence: 2% (Prod Info SYMBYAX(R) oral capsule, 2009)

2) In short-term, controlled studies including depressive episodes associated with Bipolar I Disorder and trea
2% of patients who received fluoxetine/olanzapine (n=771) compared with 1% of patients who received place
capsule, 2009).

3.3.16.D Neuroleptic malignant syndrome

1) Neuroleptic malignant syndrome (NMS) has been reported in association with administration of antipsych manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic in tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatinine phosph acute renal failure. Management of NMS should include immediate discontinuation of antipsychotic drugs and therapy, intensive symptomatic treatment and medical monitoring, and treatment of any concomitant serious are available. There is no general agreement about specific pharmacological treatment regimens for NMS (P

3.3.16.E Pain

1) Incidence: 2% (Prod Info SYMBYAX(R) oral capsule, 2009)

2) In short-term, controlled studies including depressive episodes associated with Bipolar I Disorder and trea of patients who received fluoxetine/olanzapine (n=771) compared with 1% of patients who received placebo (2009).

3.3.16.F Serotonin syndrome

1) The development of a potentially life-threatening serotonin syndrome or neuroleptic malignant syndrome (serotonin norepinephrine reuptake inhibitor (SNRIs) and SSRIs alone but particularly with concomitant use of drugs which impair metabolism of serotonin (including MAOIs), or with antipsychotics or other dopamine anta include mental status changes (eg, agitation, hallucinations, coma), autonomic instability (eg, tachycardia, lab neuromuscular aberrations (eg, hyperreflexia, incoordination) and/or gastrointestinal symptoms (eg, nausea, most severe form can resemble NMS, which includes hyperthermia, muscle rigidity, autonomic instability with mental status changes. Patients should be monitored for the emergence of serotonin syndrome or NMS-like s olanzapine/fluoxetine with MAOIs for depression is contraindicated. Further, concomitant use of olanzapine/fl agonist (triptans) is clinically warranted, and its use is not recommended with SNRIs, SSRIs, or tryptophan. T concomitant serotonergic or antidopaminergic agents, including antipsychotics, should be discontinued imme supportive symptomatic treatment should be initiated (Prod Info SYMBYAX(R) oral capsule, 2009).

3.4 Teratogenicity/Effects in Pregnancy/Breastfeeding

A) Teratogenicity/Effects in Pregnancy

1) Fluoxetine

a) U.S. Food and Drug Administration's Pregnancy Category: Category C (Prod Info PROZAC(R) oral capsu (All Trimesters)

1) Either studies in animals have revealed adverse effects on the fetus (teratogenic or embryocidal or ot women or studies in women and animals are not available. Drugs should be given only if the potential be

b) Australian Drug Evaluation Committee's (ADEC) Category: C(Batagol, 1999)

1) Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing ha without causing malformations. These effects may be reversible. Accompanying texts should be consulte

See Drug Consult reference: PREGNANCY RISK CATEGORIES

c) Crosses Placenta: Yes

d) Clinical Management

1) A large, population-based study found no increased risk of malformations in infants exposed to select exposed infants were more likely to require treatment in a special or intensive care unit (Malm et al, 2005 20 weeks of gestation has been associated with an increased risk of persistent pulmonary hypertension (of prospectively collected data suggests antenatal use of selective serotonin-reuptake inhibitor (SSRI) ar prolongation in exposed neonates (Dubnov-Raz et al, 2008). There was no significant association betwe risks of birth defects, including congenital heart defects, according to a later population-based case-cont to fluoxetine and other SSRI and selective serotonin and norepinephrine reuptake inhibitors (SNRI), late symptoms of SSRI and SNRI toxicity or withdrawal syndrome (Prod Info PROZAC(R) oral capsules, dela the dangers of failing to treat major depression are obvious, and in each case, these dangers must be w effects (Nulman et al, 1997; Lamberg, 1999). In pregnant patients diagnosed with obsessive compulsive behavioral therapy has proven inadequate (Anon, 2000; Altshuler et al, 1996a).

e) Literature Reports

1) A study of prospectively collected data suggests antenatal use of selective serotonin-reuptake inhibito interval prolongation in exposed neonates. Between January 2000 and December 2005, researchers co antidepressants (paroxetine (n=25), citalopram (n=13), fluoxetine (n=12), fluvoxamine (n=1), and venlafa 52 matched neonates with no exposure. Prolonged QTc is defined as an interval of greater than 460 mill cited by authorities in both pediatric cardiology and neonatology). A pediatric cardiologist blinded to drug (ECGs) using standard statistical analyses. ECG recordings revealed markedly prolonged mean QTc int unexposed neonates (mean; 409 +/- 42 msec versus 392 +/- 29 msec, p=0.02). The mean uncorrected C neonates (mean; 280 +/- 31 msec versus 261 +/- 25 msec, p less than 0.001). Ten percent (n=5) of expo interval prolongation (greater than 460 msec) compared to none of the unexposed neonates. The longes Raz et al, 2008).

2) Data from the case-controlled National Birth Defects Prevention Study (NBDPS), which included data 2002, indicated that early maternal exposure (defined as treatment with any SSRI from 1 month before t associated with anencephaly in 9 exposed infants out of 214 (adjusted odds ratio (OR), 2.4; 95% confide craniosynostosis in 24 exposed infants out of 432 (adjusted OR 2.5; 95% CI, 1.5 to 4.0; P less than 0.00 181 (adjusted OR 2.8; 95% CI, 1.3 to 5.7; P=0.005). However, early exposure did not significantly increa other birth defects. The most commonly used SSRIs reported by control mothers were sertraline, fluoxet 2007).

3) In a prospective longitudinal study (n=201), discontinuation of antidepressant medication in women w
euthymic at the start of pregnancy increased the chance for relapse of major depression compared to wo
However, neonatal exposure, particularly in the third trimester, to fluoxetine and other selective serotonir
norepinephrine reuptake inhibitors (SNRIs) has led to complications requiring prolonged hospitalization,
findings have included cyanosis, apnea, seizures, tremor, and constant crying, and the clinical scenario i
careful assessments of potential risks and benefits of treatment must be conducted prior to using fluoxet
trimester (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).

4) A case-control study found that the use of selective serotonin reuptake inhibitors (SSRIs) after 20 we
increased risk of persistent pulmonary hypertension of the newborn (PPHN). Fluoxetine, paroxetine, and
carry this increased risk. A total of 377 women who had infants with PPHN were matched to 836 women
determined by telephone interview within 6 months of birth. After adjusting for other covariates, SSRI use
an odds ratio of 6.1 (95% CI 2.2-16.8; p=0.001) of delivering an infant with PPHN relative to no use durir
gestation and non-SSRI antidepressants use at any gestation time was not associated with increased ris
in the general population is about 0.1 to 0.2%. According to this study, infants exposed to SSRIs after 20
0.6 to 1.2% (Chambers et al, 2006).

5) A population-based study of 1782 pregnant women exposed to selective serotonin reuptake inhibitors
perinatal outcome except for treatment in the neonatal intensive or special care unit, particularly with thir
derived from a government project involving 4 birth or medication registries in Finland, women who had a
SSRI during the period of one month before pregnancy and the day pregnancy ended were compared to
purchases during the same peripartum period. The mean age of both cohorts was 30 years (+/- 7). There
times as many pregnancies induced by artificial reproductive techniques in the SSRI group compared to
gestation and birth weight were lower (p less than 0.001) in the SSRI group. Malformations, however, we
0.4). Purchases of SSRIs (citalopram, fluoxetine, paroxetine, sertraline and fluvoxamine) were more com
with 525 women purchasing fluoxetine during the first trimester, 232 during the second trimester, 239 du
When compared to first trimester exposure, treatment in a special or intensive care unit was more comm
trimester (11.2% and 15.7%, respectively; p = 0.009). Even after adjusting for confounding variables, this
1.6; 95% CI 1.1 to 2.2) (Malm et al, 2005).

6) In a prospective clinical trial designed to evaluate the pharmacokinetics of fluoxetine and norfluoxetin
pregnancy outcomes were found to be similar in both the control and treated groups. The study compare
50 mg per day during pregnancy and lactation to 10 women in the control group who were not exposed t
hepatic blood flow, increased volume of distribution and decreased binding to plasma proteins, trough pl
norfluoxetine were low. At delivery, umbilical vein concentrations were 65% and 72% of the maternal cor
postnatal period, plasma concentrations of fluoxetine and norfluoxetine were still elevated, likely due to t
capacity and CYP2D6 enzyme activity. There were no fetal malformations or difference in birth weights b
at fifteen minutes were lower in the fluoxetine group (Heikkinen et al, 2003).

7) In one study assessing the direct effects of fluoxetine on infant outcome at birth (Chambers et al, 199
to fluoxetine in the third trimester may be at an increased risk for perinatal complications such as respira
jitteriness. These neonates may have had difficulty clearing the drug due to its long half-life. Depending c
and patient may consider tapering the dose of fluoxetine to discontinue 10 to 14 days prior to delivery to
1999).

8) Based on analyses of independently collected data and that obtained through the Motherisk Program
function, temperament and general behavior in children exposed prenatally to fluoxetine as compared to
Nulman & Koren, 1996; Nulman et al, 1997). However, among infants who were exposed to either fluoxe
gestation, those born to mothers with uncontrolled depressive symptoms showed lower cognitive and lar
who were well-controlled (Nulman et al, 2002).

9) An increased risk for central nervous system serotonergic symptoms was observed during the first fo
selective serotonin reuptake inhibitors (SSRI) during the third trimester of pregnancy. In a controlled, pro
milligrams/day of either citalopram (n=10) or fluoxetine (n=10) while pregnant were compared to a contro
ranged from 7 to 41 weeks. Newborns in the SSRI group had a lower Apgar score at 15 minutes as com
The only significant difference observed in the vital signs of the newborns was a higher heart rate in the
controls (mean, 153 vs 141 beats per minute; p=0.049). Serotonergic symptom scores in the first 4 days
group than in the control group (total score, 121 vs 30, respectively; p=0.008). Tremor, restlessness, and
Myoclonus was reported in one infant exposed to fluoxetine. Significantly lower cord blood 5-hydroxyindo
in the SSRI-exposed infants as compared with the control group (mean, 63 mmol/L vs 77 mmol/L; p=0.0
was observed between the serotonergic symptom score and the umbilical vein 5-HIAA concentrations in
control group (p=0.007). Although not statistically significant, mean umbilical cord serum prolactin conce
infants than in control infants at the time of birth (Laine et al, 2003).

2) Olanzapine

a) U.S. Food and Drug Administration's Pregnancy Category: Category C (Prod Info ZYPREXA(R) oral table
disintergating tablets, 2008) (All Trimesters)

1) Either studies in animals have revealed adverse effects on the fetus (teratogenic or embryocidal or ot
women or studies in women and animals are not available. Drugs should be given only if the potential be

b) Australian Drug Evaluation Committee's (ADEC) Category: B3(Australian Drug Evaluation Committee, 19

1) Drugs which have been taken by only a limited number of pregnant women and women of childbearir
malformation or other direct or indirect harmful effects on the human fetus having been observed. Studie
increased occurrence of fetal damage, the significance of which is considered uncertain in humans.

See Drug Consult reference: PREGNANCY RISK CATEGORIES

c) Crosses Placenta: Yes

d) Clinical Management

1) There is insufficient evidence to clearly establish the safety of olanzapine during pregnancy and it is r only if the potential benefit justifies the potential risk to the fetus (Prod Info ZYPREXA(R) oral tablets, IM disintergating tablets, 2008). Limited data to date do not suggest an increased risk of major malformatior Goldstein et al, 2000); notably, schizophrenic women may have higher prevalence rates of social and life drug use, low socioeconomic status) associated with risky neonatal outcomes (Patton et al, 2002). Patie bipolar disorder should be maintained on medication therapy throughout gestation, as these patients and (Altshuler et al, 1996).

e) Literature Reports

1) A prospective, observational study of 54 women (mean age, 30.7 years), recruited from the Emory W antipsychotic medication during pregnancy, showed permeability of the placental barrier. Outcomes were blood samples taken at delivery and through data collected from maternal reports and medical records. F umbilical cord to maternal plasma concentrations) showed a significant difference between antipsychotic 46.8%-97.5%) being the highest, followed by haloperidol 65.5% (95% CI, 40.3%-90.7%), risperidone 49. 24.1% (95% CI, 18.7%-29.5%), showing the lowest placental passage ratio. There was a greater frequer 0.23), low birth weights (30.8%, p=less than 0.07), and neonatal intensive care admission (30.8%, p=less (Newport et al, 2007).

2) There are no adequate and well-controlled studies with olanzapine use during pregnancy. Seven preg olanzapine, which resulted in 2 normal births, 1 neonatal death due to cardiovascular defect, 3 therapeut Info ZYPREXA(R) oral tablets, IM injection, ZYPREXA(R) ZYDIS(R) orally disintergating tablets, 2008). F pregnancies, there was no increase in risk of spontaneous abortion, stillbirth, prematurity, or major malfo utero (Goldstein et al, 2000). Analysis of expanded data from this latter report produced similar conclusic 71.9% resulted in normal births, 12.5% in spontaneous abortions, 2.1% in premature deliveries, 3.1% in Goldberg, 2002). From an ongoing study to assess the fetal safety of atypical antipsychotics, interim resu olanzapine, or quetiapine had the following outcomes: 20 live births with no malformations, 3 spontaneou abortions (McKenna et al, 2003).

3) Occasional spontaneous case reports of in utero exposure to olanzapine have produced viable newb established (Mendhekar et al, 2002; Nagy et al, 2001; Littrell et al, 2000; Kirchheiner et al, 2000). A case (cord blood) level of 11 nanograms (ng)/mL compared with 34 ng/mL in the maternal plasma drawn befo olanzapine 15 mg during pregnancy. During gestation, the maternal olanzapine plasma levels were betw development with the only complication being gestational diabetes which was resolved with diet. Delivery score of 10/10/10) developed normally during the first 6 months (Aichhorn et al, 2008).

4) In another case report, a 37-year-old woman with a 7-year history of paranoid schizophrenia gave birt olanzapine 25 mg/day starting at week 8 until week 32 when she discontinued it against medical advice. 3 months preceding her pregnancy (Lim, 2001). An isolated case of maternal use of up to 20 mg of olanz 23rd week of gestation until 10 days prior to delivery has been reported. In this case, a healthy baby was and 9-10 at 5 minutes; at 3 months of age, the infant showed age-appropriate milestones (Mendhekar et day exposure from the 18th week of pregnancy through delivery and during breastfeeding also exists. De suspicious motor development at 7 months of age, the infant showed no abnormal findings at 11 months

B) Breastfeeding

1) Fluoxetine

a) American Academy of Pediatrics Rating: Drugs for which the effect on nursing infants is unknown but may

b) Thomson Lactation Rating: Infant risk cannot be ruled out.

1) Available evidence and/or expert consensus is inconclusive or is inadequate for determining infant ris potential benefits of drug treatment against potential risks before prescribing this drug during breastfeedi

c) Clinical Management

1) Fluoxetine and its active metabolite, norfluoxetine, appear in breast milk and the oral dose available t mcg/kg/day for fluoxetine (Burch & Wells, 1992), and 40 mcg/kg/day for fluoxetine plus norfluoxetine (Ta recommendation that fluoxetine not be used by women while breastfeeding (Prod Info PROZAC(R) oral 2008), many women choose to do so. The American Academy of Pediatrics considers antidepressants to (Anon, 2001). There is insufficient data available to safely recommend use of fluoxetine by nursing moth infant should be monitored for anorexia, weight loss, irritability, and insomnia. The long-term effects of ex (SSRIs) via breast milk on the cognitive development of the infant have not been determined.

d) Literature Reports

1) A number of cases have been reported in which fluoxetine was used to treat postpartum depression i or composition was observed. While increased infant irritability during maternal fluoxetine treatment has after exposure to fluoxetine during nursing (Epperson et al, 2003; Burch & Wells, 1992; Isenberg, 1990).

2) In a study of 14 mother-infant pairs, the mean total infant exposure was estimated as 6.81% (3.36% f 9 infants with blood samples, 5 and 7 had detectable concentrations of fluoxetine and norfluoxetine, resp had withdrawal symptoms described as uncontrollable crying, irritability, and poor feeding. Symptoms in plasma concentrations of fluoxetine and/or norfluoxetine. One mother also used methadone, and 4 infan authors recommend caution especially during the early neonatal period and in infants exposed in utero to

3) A 1996 cohort study involved 11 infants nursed by 10 mothers. Although limited by maternal perceptio infants were reported by the mothers (Taddio et al, 1996).

4) One study described 4 nursing mothers, taking 20 to 40 mg of fluoxetine per day, in which the Bayley development of the infants. None of the infants exhibited any neurological abnormality (Taddio et al, 199

5) The manufacturer reports a maternal plasma concentration of 295 nanograms/mL for fluoxetine plus concentration of 70.4 nanograms/mL. No adverse effects in the nursing infant were reported. In another

340 nanograms/mL of fluoxetine and 208 nanograms/mL of norfluoxetine on the second day of breastfee not reported. The infant developed crying, sleep disturbance, vomiting, and watery stools (Prod Info PRO capsules, solution, 2008).

6) No clinically significant changes in platelet 5-hydroxytryptamine (5-HT) transport were reported in 11 the study) exposed to fluoxetine through maternal breast milk. Determinations of whole-blood 5-HT, fluox both infants and mothers prior to initiating fluoxetine doses of 20 mg to 40 mg per day. Post-exposure lev maternal plasma concentrations of fluoxetine were 125 nanograms/mL, and norfluoxetine were 142 nanc fluoxetine levels below 1 nanograms/mL, and the mean infant plasma concentration of norfluoxetine was post-fluoxetine 5-HT levels were 157 nanograms/mL and 23 nanograms/mL, respectively. The mean infa were 217 nanograms/mL and 230 nanograms/mL, respectively. Baley Scale scores were determined for revealing that 6 infants were within one standard deviation of the mean on mental and motor developmer most exclusively breastfed infants will not likely experience changes in platelet 5-HT levels upon materna

2) Olanzapine

a) Thomson Lactation Rating: Infant risk cannot be ruled out.

1) Available evidence and/or expert consensus is inconclusive or is inadequate for determining infant ris potential benefits of drug treatment against potential risks before prescribing this drug during breastfeedi

b) Clinical Management

1) Limited data from studies of nursing mothers treated with olanzapine have demonstrated that olanzap ZYPREXA(R) oral tablets, IM injection, ZYPREXA(R) ZYDIS(R) orally disintergating tablets, 2008; Gardi report described jaundice, cardiomegaly, somnolence, and a heart murmur in the infant of a mother rece remained after bottle-feeding was initiated on day 7 of life. Another case from the same report demonstra maternal olanzapine doses at 2 months of age (Goldstein et al, 2000a). Undetectable infant olanzapine p olanzapine levels of 32.8 to 39.5 nanograms/mL were reported in another case (Kirchheiner et al, 2000a excreted in human breast milk, it is recommended that women treated with olanzapine should not breast injection, ZYPREXA(R) ZYDIS(R) orally disintergating tablets, 2008).

c) Literature Reports

1) In a study of healthy, nursing women, olanzapine was excreted in breast milk. The estimated mean in maternal olanzapine dose (Prod Info ZYPREXA(R) oral tablets, IM injection, ZYPREXA(R) ZYDIS(R) ora mothers receiving 5 to 20 mg/day of olanzapine, the median infant dose ingested through breast milk wa analysis of milk and plasma samples from five nursing mothers treated with olanzapine 2.5 mg to 10 mg 0.84. This compared to a theoretical value of 0.38 that was determined using the known pharmacokinetic consumption of 0.15 L/kg/day and assuming 100% bioavailability, relative infant dose was estimated to b dose (Croke et al, 2002). In a case report, breast milk was collected by an electric pump and olanzapine chromatography. The findings indicated that olanzapine was excreted in the breast milk in relatively sma ratio was 0.42 at steady state (Ambresin et al, 2004).

2) Limited data from cases of olanzapine exposure via breast milk fail to affirm or eliminate the potential case described an infant exposed in utero to olanzapine (maternal dose 5 mg/day) who was born with ca murmur. However, jaundice and sedation continued despite the initiation of bottle-feeding on day seven exposed at two months of age (maternal dose 10 mg/day) had no adverse effects (Goldstein et al, 2000a infant olanzapine plasma levels (less than 2 ng/mL) despite maternal steady-state trough levels of 32.8 t olanzapine doses of 10 mg daily throughout pregnancy and during breastfeeding (Kirchheiner et al, 2000

3.5 Drug Interactions

Drug-Drug Combinations

Drug-Food Combinations

3.5.1 Drug-Drug Combinations

Abciximab

Acecainide

Aceclofenac

Acemetacin

Acenocoumarol

Activated Charcoal

Ajmaline

Alclofenac

Almotriptan

Alprazolam

Amiodarone

Amisulpride

Amitriptyline

Amoxapine

Anagrelide

Ancrod

Anisindione

Antithrombin III Human

Aprindine

Ardeparin

Aripiprazole

Arsenic Trioxide

Aspirin

Astemizole

Atomoxetine

Azimilide

Belladonna

Belladonna Alkaloids

Benoxaprofen

Bepridil

Betel Nut

Bivalirudin

Bretylium

Bromfenac

Bufexamac

Bupropion

Buspirone

Cannabis

Carbamazepine

Carbamazepine

Carprofen

Celecoxib

Certoparin

Chloral Hydrate

Chloroquine

Chlorpromazine

Cilostazol

Ciprofloxacin

Clarithromycin

Clomipramine

Clonixin

Clopidogrel

Clopidogrel

Clorgyline

Clozapine

Cyclobenzaprine

Cyproheptadine

Dalteparin

Danaparoid

Defibrotide

Dehydroepiandrosterone

Dehydroepiandrosterone

Delavirdine

Dermatan Sulfate

Desipramine

Desirudin

Desvenlafaxine

Dexfenfluramine

Dexketoprofen

Dextromethorphan

Diazepam

Dibenzepin

Diclofenac

Dicumarol

Diflunisal

Digitoxin

Digoxin

Dihydroergotamine

Dipyridamole

Dipyrone

Disopyramide

Dofetilide

Dolasetron

Doxepin

Droperidol

Droxicam

Duloxetine

Eletriptan

Enflurane

Enoxaparin

Epoprostenol

Eptifibatide

Ergoloid Mesylates

Ergonovine

Ergotamine

Erythromycin

Eszopiclone

Etodolac

Etofenamate

Etoricoxib

Felbinac

Fenbufen

Fenfluramine

Fenoprofen

Fentiazac

Flecainide

Floctafenine

Fluconazole

Flufenamic Acid

Fluphenazine

Flurbiprofen

Fluvoxamine

Fondaparinux

Foscarnet

Fosphenytoin

Frovatriptan

Furazolidone

Galantamine

Gemifloxacin

Ginkgo

Halofantrine

Haloperidol

Haloperidol

Halothane

Heparin

Hydroquinidine

Hydroxytryptophan

Ibuprofen

Ibutilide

Iloperidone

Iloprost

Imipramine

Indomethacin

Indoprofen

Insulin Aspart, Recombinant

Insulin Detemir

Insulin Glargine, Recombinant

Insulin Glulisine

Insulin Human Inhaled

Iproniazid

Isocarboxazid

Isoflurane

Isoxicam

Isradipine

Ketoprofen

Ketorolac

Lamifiban

Levodopa

Levomethadyl

Levomethadyl

Lexipafant

Lidoflazine

Linezolid

Lithium

Lithium

Lorcainide

Lornoxicam

Meclofenamate

Mefenamic Acid

Mefloquine

Meloxicam

Meperidine

Mesoridazine

Methylergonovine

Methylphenidate

Methysergide

Metoprolol

Milnacipran

Mirtazapine

Mirtazapine

Moclobemide

Morniflumate

Nabumetone

Nadroparin

Naproxen

Naratriptan

Nebivolol

Nialamide

Niflumic Acid

Nimesulide

Nortriptyline

Octreotide

Oxaprozin

Parecoxib

Pargyline

Parnaparin

Paroxetine

Pentamidine

Pentazocine

Pentosan Polysulfate Sodium

Phenelzine

Phenindione

Phenprocoumon

Phenylalanine

Phenylbutazone

Phenytoin

Pimozide

Pirazolac

Pirmenol

Piroxicam

Pirprofen

Prajmaline

Probucol

Procainamide

Procarbazine

Prochlorperazine

Propafenone

Propranolol

Propyphenazone

Proquazone

Quetiapine

Quinidine

Rasagiline

Reviparin

Risperidone

Ritonavir

Ritonavir

Rizatriptan

Rofecoxib

Selegiline

Sematilide

Sertindole

Sibrafiban

Sibutramine

Sotalol

Spiramycin

St John's Wort

St John's Wort

Sulfamethoxazole

Sulfinpyrazone

Sulindac

Sulodexide

Sultopride

Sumatriptan

Suprofen

Tamoxifen

Tamsulosin

Tapentadol

Tedisamil

Telithromycin

Tenidap

Tenoxicam

Terfenadine

Tetrabenazine

Tetrabenazine

Thioridazine

Tiaprofenic Acid

Ticlopidine

Tinzaparin

Tipranavir

Tirofiban

Tolmetin

Toloxatone

Tramadol

Tramadol

Tranylcypromine

Trazodone

Trifluoperazine

Trimethoprim

Trimipramine

Tryptophan

Valdecoxib

Vasopressin

Venlafaxine

Warfarin

Xemilofiban

Ziprasidone

Zolmitriptan

Zolpidem

Zomepirac

Zotepine

3.5.1.A Abciximab

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and use of SSRIs and antiplatelet agents has been associated with an increased risk of bleeding. Bleeding events hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008; release capsules, solution, 2008).

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an antiplatelet agent are given concurrently, monitor patient for oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 200

7) Probable Mechanism: unknown

3.5.1.B Acecainide

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Even though no formal drug interaction studies have been done, the coadministration of Class prolong the QTc interval is not recommended (Allen et al, 2002; Prod Info Tikosyn(TM) dofetilide capsules, 1 been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Prozac(R), 2001a).

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of class III antiarrhythmic agents and agents that pro recommended.

7) Probable Mechanism: additive effects on QT prolongation

3.5.1.C Aceclofenac

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have incl petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info L CELEXA (R) oral tablet, solution, 2005).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in

7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressar hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of u than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin inc
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with TORADOL(R) oral tablets, 2007).

3.5.1.D Acemetacin

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control anc use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have incl petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info L CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressar hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of u than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin inc
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with TORADOL(R) oral tablets, 2007).

3.5.1.E Acenocoumarol

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control anc use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2 (R) oral capsules, delayed-release capsules, solution, 2008). Bleeding events reported have included epistax threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported wi (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When fluoxetine and an anticoagulant are given concurrently, monitor patient for sig taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, wl (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
7) Probable Mechanism: unknown
8) Literature Reports
a) Fluoxetine is thought to inhibit the cytochrome P450 2C9 isoenzyme (CYP2C9). This is the enzyme b warfarin, is metabolized (Riesenman, 1995). In addition, both fluoxetine and warfarin are tightly bound to protein-binding displacement of either drug is present (Prod Info Coumadin(R), 1999).
b) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bl patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks followi mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected p SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. T treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model
c) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoum reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal blee hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal b subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interva gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekam
d) In 6 reported cases, INR increased during combined fluoxetine and warfarin therapy. In a seventh ca a woman initially treated with fluoxetine and, secondarily, started on warfarin (Woolfrey et al, 1993; Claire

e) An 83-year-old man died from cerebral hemorrhage secondary to increased warfarin concentrations. week for atrial fibrillation with a target INR between 2 and 3. The patient's other drugs included lisinopril, acetaminophen. After being seen for symptoms of depression, anxiety, and insomnia, the patient was giv mg 3 to 4 times per day. Eight days later, the patient's INR increased to 4.8, and the dose of warfarin wa was later seen for symptoms of drug delirium, including confusion, incoherence, and speaking irrationally was discontinued. The next day the patient presented to the hospital with left-sided weakness and later c interparenchymal hemorrhage. The authors proposed that the addition of fluoxetine to the patient's regim warfarin and diazepam, resulting in delirium and loss of anticoagulant control (Dent & Orrock, 1997).

3.5.1.F Activated Charcoal

1) Interaction Effect: decreased bioavailability of olanzapine
2) Summary: Activated charcoal reduces the maximum concentration and area under the concentration-time Zyprexa(R), 1999b). This drug interaction may make activated charcoal useful in cases of olanzapine overdo
3) Severity: minor
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Do not administer activated charcoal and olanzapine concomitantly.
7) Probable Mechanism: binding of olanzapine in the gut

3.5.1.G Ajmaline

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, the coadministration of Class prolong the QTc interval is not recommended (Prod Info Quinaglute Dura-tabs(R), 1999). Fluoxetine has dem (Prod Info Prozac(R), 2001z).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of class Ia antiarrhythmic agents and agents that pro recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.H Alclofenac

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have incl petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info L CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressar hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of up than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin inc
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with TORADOL(R) oral tablets, 2007).

3.5.1.I Almotriptan

1) Interaction Effect: an increased risk of serotonin syndrome
2) Summary: Concomitant use of almotriptan and selective serotonin reuptake inhibitors (SSRI's) has been r incoordination (Prod Info Axert(TM), 2001). Concurrent use of a triptan and an SSRI may result in serotonin s Symptoms of serotonin syndrome may include restlessness, hallucinations, loss of coordination, fast heart be body temperature, overreactive reflexes, nausea, vomiting, and diarrhea. Clinicians should be aware that trip that either the triptan or the SSRI may be prescribed by a different physician. Discuss the risks of serotonin s combination and monitor them closely for symptoms of serotonin syndrome (US Food and Drug Administratic
3) Severity: major
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Coadministration of a triptan, such as almotriptan, and an SSRI may result in a life- Be aware that triptans may be commonly used intermittently and that either the triptan or the SSRI may be pr are used together, discuss the risks of serotonin syndrome with the patient and monitor closely for symptoms hyperthermia, hyperreflexia, incoordination).
7) Probable Mechanism: additive pharmacologic effects resulting in excessive serotonergic stimulation

8) Literature Reports

a) Concomitant administration of fluoxetine and almotriptan is well tolerated and fluoxetine has only a m concentration (Cmax). Other almotriptan pharmacokinetics are not significantly affected. A randomized, healthy volunteers has been conducted. Subjects received each of the following treatments with a minim 20 mg fluoxetine capsules on day 1 to 8 and one dose almotriptan 12.5 mg on day 8, (2) one dose of alm days 1 through 7. Peak almotriptan concentrations were 18% higher following concomitant administratio administration alone. This difference was statistically significant (p equal 0.023). Mean almotriptan area u oral clearance were borderline statistically different between treatment groups. Mean half-life was not sta During fluoxetine coadministration, Tmax was shorter, suggesting that the absorption rate of almotriptan author concludes that based on the results of this study and the lack of effect of fluoxetine on almotriptar can be safely used concomitantly in migraine management (Fleishaker et al, 2001).

3.5.1.J Alprazolam

1) Interaction Effect: an increased risk of alprazolam toxicity (somnolence, dizziness, ataxia, slurred speech,

2) Summary: Coadministered fluoxetine increases alprazolam serum concentrations (Greenblatt et al, 1992a interaction is thought to be inhibition by fluoxetine of the cytochrome P453A4 isoenzyme (CYP3A4), which is metabolism. Some benzodiazepines (lorazepam, oxazepam) are metabolized by glucuronidation rather than choice for fluoxetine and benzodiazepine cotherapy.

3) Severity: moderate

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: Monitor patients for signs and symptoms of alprazolam intoxication (somnolence, d psychomotor impairment). Alprazolam doses may need to be reduced. Alternatively, consider substituting a b oxazepam) that has less potential for interacting with fluoxetine.

7) Probable Mechanism: inhibition of cytochrome P450 3A-mediated alprazolam metabolism

8) Literature Reports

a) Alprazolam serum concentrations were analyzed in a double-blind, placebo-controlled study involving Concurrent administration of alprazolam 1 mg four times a day and fluoxetine 60 mg each morning for fo alprazolam levels and a 21% decrease in the alprazolam elimination rate. The elevated alprazolam conc impairment, but did not affect mood status or sedation.

b) The effect of fluoxetine on the pharmacokinetics of alprazolam was analyzed in a 31-day, double-blin included a 10-day washout period (Greenblatt et al, 1992). Twelve healthy male volunteers were given fl single dose of alprazolam 1 mg on days 3 and 24. Fluoxetine significantly increased the half-life of alpraz decreased its clearance from 61 mL/min to 48 mL/min.

c) Inhibition of alprazolam metabolism by fluoxetine occurs via cytochrome P450 3A4. A randomized, do design was used to assess this potential interaction. Twenty healthy volunteers attended four study sess absence of an SSRI in the first two study sessions; alprazolam/placebo while at steady-state with either was given in the last two study sessions. At each session they received alprazolam 1 mg orally or placeb of alprazolam by 16% and increased the area under the concentration-time curve by 32%. Citalopram di alprazolam were not altered by either SSRI. These findings suggest that citalopram and fluoxetine differe 2002).

3.5.1.K Amiodarone

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest

2) Summary: Even though no formal drug interaction studies have been done, the coadministration of Class prolong the QTc interval is not recommended (Allen et al, 2002; Prod Info Tikosyn(TM) dofetilide capsules, 1 been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Prozac(R), 2001a).

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of class III antiarrhythmic agents and agents that pro recommended.

7) Probable Mechanism: additive effects on QT prolongation

3.5.1.L Amisulpride

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest

2) Summary: Fluoxetine has been shown to prolong the QTc interval at the recommended therapeutic dose formal drug interaction studies have been done, the coadministration of antipsychotics and other drugs know fluoxetine, is not recommended. Several antipsychotic agents have demonstrated QT prolongation including quetiapine (Owens, 2001b), sertindole (Agelink et al, 2001), sultopride (Lande et al, 1992), and zotepine (Sw

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of fluoxetine and antipsychotics is not recommended

7) Probable Mechanism: additive effects on QT prolongation

3.5.1.M Amitriptyline

1) Interaction Effect: tricyclic antidepressant toxicity (dry mouth, urinary retention, sedation) and an increase

de pointes, cardiac arrest)
2) Summary: Tricyclic antidepressants (TCAs) and fluoxetine have been shown to prolong the QTc interval a Prozac(R), 2001h; Marshall & Forker, 1982). Even though no formal drug interaction studies have been done coadministration of tricyclic antidepressants and other drugs known to prolong the QTc interval, such as fluox 1999). In addition, concurrent use of fluoxetine and TCAs such as desipramine, nortriptyline, and imipramine concentrations (Preskorn et al, 1994a; Preskorn et al, 1994a; Aranow et al, 1989a; Downs et al, 1989a; Gooc
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: The concurrent administration of fluoxetine and a tricyclic antidepressant is not recc
7) Probable Mechanism: decreased tricyclic antidepressant metabolism; additive effects on QT prolongation
8) Literature Reports
a) Fluoxetine increased the level of tricyclic antidepressants (nortriptyline, imipramine, desipramine) in 4 ratio of antidepressant level to dose increased by 109% to 486% in the patients. Three patients develope constipation, urinary hesitancy, sedation, unstable gait) as a result of the increased levels (Aranow et al,
b) Fluoxetine statistically and clinically significantly increased desipramine concentrations in 18 healthy added to desipramine (50 mg daily), the mean maximum concentration of desipramine increased by 278 curve increased by 342%. Desipramine trough concentrations continued to be 198% above baseline thre same study compared pharmacokinetics of desipramine when combined with sertraline. The impact of se short-term increases in desipramine plasma concentrations (Preskorn et al, 1994).
c) A 75-year-old female experienced symptomatic increases in her desipramine serum concentrations w levels ranged from 109 to 150 ng/mL with oral doses of 300 mg at bedtime prior to fluoxetine therapy. Fo to the regimen, the desipramine serum level increased to 212 ng/mL within five days. The fluoxetine dos and the desipramine serum level was 419 ng/mL after four days. A worsening of depression and severe desipramine serum levels. Withdrawal of fluoxetine and reduction in the desipramine dose to 200 mg dai ng/mL within two weeks (Bell & Cole, 1988).
d) A 33-year-old depressed male developed adverse effects of dry mouth, tinnitus, and difficulties with a 40 mg daily and desipramine 150 mg daily for five weeks; fluoxetine was discontinued and the blood leve ng/mL with resolution of clinical symptoms (Goodnick, 1989).
e) A 39-year-old female experienced symptomatic increases in her desipramine levels with concomitant the patient's measured levels of desipramine had ranged from 148 to 160 ng/mL on a regimen of 300 mg 20 mg daily, she reported anticholinergic symptoms, sedation, and confusion with a desipramine level of to 200 mg/day; eleven days later, the level was 244 ng/mL; the patient reported decreased energy, impa speech, as well as an episode of nausea, dizziness, and syncope. The desipramine dose was reduced t days. Eight days later, the desipramine level was 122 ng/mL (Downs et al, 1989).
f) Concomitant administration of fluoxetine and desipramine was reported to result in an increased desip year-old male within 10 days of the addition of fluoxetine to the patient's regimen (Preskorn et al, 1990).

3.5.1.N Amoxapine
1) Interaction Effect: tricyclic antidepressant toxicity (dry mouth, urinary retention, sedation) and an increase de pointes, cardiac arrest)
2) Summary: Tricyclic antidepressants (TCAs) and fluoxetine have been shown to prolong the QTc interval a Prozac(R), 2001h; Marshall & Forker, 1982). Even though no formal drug interaction studies have been done coadministration of tricyclic antidepressants and other drugs known to prolong the QTc interval, such as fluox 1999). In addition, concurrent use of fluoxetine and TCAs such as desipramine, nortriptyline, and imipramine concentrations (Preskorn et al, 1994a; Preskorn et al, 1994a; Aranow et al, 1989a; Downs et al, 1989a; Gooc
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: The concurrent administration of fluoxetine and a tricyclic antidepressant is not recc
7) Probable Mechanism: decreased tricyclic antidepressant metabolism; additive effects on QT prolongation
8) Literature Reports
a) Fluoxetine increased the level of tricyclic antidepressants (nortriptyline, imipramine, desipramine) in 4 ratio of antidepressant level to dose increased by 109% to 486% in the patients. Three patients develope constipation, urinary hesitancy, sedation, unstable gait) as a result of the increased levels (Aranow et al,
b) Fluoxetine statistically and clinically significantly increased desipramine concentrations in 18 healthy added to desipramine (50 mg daily), the mean maximum concentration of desipramine increased by 278 curve increased by 342%. Desipramine trough concentrations continued to be 198% above baseline thre same study compared pharmacokinetics of desipramine when combined with sertraline. The impact of se short-term increases in desipramine plasma concentrations (Preskorn et al, 1994).
c) A 75-year-old female experienced symptomatic increases in her desipramine serum concentrations w levels ranged from 109 to 150 ng/mL with oral doses of 300 mg at bedtime prior to fluoxetine therapy. Fo to the regimen, the desipramine serum level increased to 212 ng/mL within five days. The fluoxetine dos and the desipramine serum level was 419 ng/mL after four days. A worsening of depression and severe desipramine serum levels. Withdrawal of fluoxetine and reduction in the desipramine dose to 200 mg dai ng/mL within two weeks (Bell & Cole, 1988).
d) A 33-year-old depressed male developed adverse effects of dry mouth, tinnitus, and difficulties with a 40 mg daily and desipramine 150 mg daily for five weeks; fluoxetine was discontinued and the blood leve

ng/mL with resolution of clinical symptoms (Goodnick, 1989).
e) A 39-year-old female experienced symptomatic increases in her desipramine levels with concomitant the patient's measured levels of desipramine had ranged from 148 to 160 ng/mL on a regimen of 300 mg 20 mg daily, she reported anticholinergic symptoms, sedation, and confusion with a desipramine level of to 200 mg/day; eleven days later, the level was 244 ng/mL; the patient reported decreased energy, impa speech, as well as an episode of nausea, dizziness, and syncope. The desipramine dose was reduced t days. Eight days later, the desipramine level was 122 ng/mL (Downs et al, 1989).
f) Concomitant administration of fluoxetine and desipramine was reported to result in an increased desip year-old male within 10 days of the addition of fluoxetine to the patient's regimen (Preskorn et al, 1990).

3.5.1.O Anagrelide

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and use of SSRIs and antiplatelet agents has been associated with an increased risk of bleeding. Bleeding events hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008; release capsules, solution, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an antiplatelet agent are given concurrently, monitor patient for oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 200
7) Probable Mechanism: unknown

3.5.1.P Ancrod

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2 (R) oral capsules, delayed-release capsules, solution, 2008). Bleeding events reported have included epistax threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported wi (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When fluoxetine and an anticoagulant are given concurrently, monitor patient for sig taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, wh (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
7) Probable Mechanism: unknown
8) Literature Reports
a) Fluoxetine is thought to inhibit the cytochrome P450 2C9 isoenzyme (CYP2C9). This is the enzyme b warfarin, is metabolized (Riesenman, 1995). In addition, both fluoxetine and warfarin are tightly bound to protein-binding displacement of either drug is present (Prod Info Coumadin(R), 1999).
b) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bl patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks followi mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected p SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. T treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model
c) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoum reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal blee hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal b subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interva gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekam
d) In 6 reported cases, INR increased during combined fluoxetine and warfarin therapy. In a seventh cas a woman initially treated with fluoxetine and, secondarily, started on warfarin (Woolfrey et al, 1993; Claire
e) An 83-year-old man died from cerebral hemorrhage secondary to increased warfarin concentrations. week for atrial fibrillation with a target INR between 2 and 3. The patient's other drugs included lisinopril, acetaminophen. After being seen for symptoms of depression, anxiety, and insomnia, the patient was giv mg 3 to 4 times per day. Eight days later, the patient's INR increased to 4.8, and the dose of warfarin wa was later seen for symptoms of drug delirium, including confusion, incoherence, and speaking irrationally was discontinued. The next day the patient presented to the hospital with left-sided weakness and later c interparenchymal hemorrhage. The authors proposed that the addition of fluoxetine to the patient's regim warfarin and diazepam, resulting in delirium and loss of anticoagulant control (Dent & Orrock, 1997).

3.5.1.Q Anisindione

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2((R) oral capsules, delayed-release capsules, solution, 2008). Bleeding events reported have included epistax threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported wi (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: When fluoxetine and an anticoagulant are given concurrently, monitor patient for sig taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, wh (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).

7) Probable Mechanism: unknown

8) Literature Reports

a) Fluoxetine is thought to inhibit the cytochrome P450 2C9 isoenzyme (CYP2C9). This is the enzyme b warfarin, is metabolized (Riesenman, 1995). In addition, both fluoxetine and warfarin are tightly bound to protein-binding displacement of either drug is present (Prod Info Coumadin(R), 1999).

b) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bl patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks followi mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected p SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. T treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model

c) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoum reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal blee hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal b subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interva gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekam

d) In 6 reported cases, INR increased during combined fluoxetine and warfarin therapy. In a seventh ca a woman initially treated with fluoxetine and, secondarily, started on warfarin (Woolfrey et al, 1993; Claire

e) An 83-year-old man died from cerebral hemorrhage secondary to increased warfarin concentrations. week for atrial fibrillation with a target INR between 2 and 3. The patient's other drugs included lisinopril, acetaminophen. After being seen for symptoms of depression, anxiety, and insomnia, the patient was giv mg 3 to 4 times per day. Eight days later, the patient's INR increased to 4.8, and the dose of warfarin wa was later seen for symptoms of drug delirium, including confusion, incoherence, and speaking irrationally was discontinued. The next day the patient presented to the hospital with left-sided weakness and later c interparenchymal hemorrhage. The authors proposed that the addition of fluoxetine to the patient's regim warfarin and diazepam, resulting in delirium and loss of anticoagulant control (Dent & Orrock, 1997).

3.5.1.R Antithrombin III Human

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2((R) oral capsules, delayed-release capsules, solution, 2008). Bleeding events reported have included epistax threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported wi (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: When fluoxetine and an anticoagulant are given concurrently, monitor patient for sig taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, wh (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).

7) Probable Mechanism: unknown

8) Literature Reports

a) Fluoxetine is thought to inhibit the cytochrome P450 2C9 isoenzyme (CYP2C9). This is the enzyme b warfarin, is metabolized (Riesenman, 1995). In addition, both fluoxetine and warfarin are tightly bound to protein-binding displacement of either drug is present (Prod Info Coumadin(R), 1999).

b) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bl patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks followi mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected p SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4

corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. T
treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only
bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI
dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding
exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model
c) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoum
reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal blee
hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal b
subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690
for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interva
gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekam
d) In 6 reported cases, INR increased during combined fluoxetine and warfarin therapy. In a seventh ca
a woman initially treated with fluoxetine and, secondarily, started on warfarin (Woolfrey et al, 1993; Claire
e) An 83-year-old man died from cerebral hemorrhage secondary to increased warfarin concentrations.
week for atrial fibrillation with a target INR between 2 and 3. The patient's other drugs included lisinopril,
acetaminophen. After being seen for symptoms of depression, anxiety, and insomnia, the patient was giv
mg 3 to 4 times per day. Eight days later, the patient's INR increased to 4.8, and the dose of warfarin wa
was later seen for symptoms of drug delirium, including confusion, incoherence, and speaking irrationally
was discontinued. The next day the patient presented to the hospital with left-sided weakness and later d
interparenchymal hemorrhage. The authors proposed that the addition of fluoxetine to the patient's regim
warfarin and diazepam, resulting in delirium and loss of anticoagulant control (Dent & Orrock, 1997).

3.5.1.S Aprindine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, the coadministration of Class
prolong the QTc interval is not recommended (Prod Info Tambocor(R) flecainide acetate, 1998). Fluoxetine h
recommended therapeutic dose (Prod Info Prozac(R), 2001w).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of class I antiarrhythmic agents and agents that prolo
recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.T Ardeparin

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and
use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2
(R) oral capsules, delayed-release capsules, solution, 2008). Bleeding events reported have included epistax
threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported wi
(Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When fluoxetine and an anticoagulant are given concurrently, monitor patient for sig
taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, wh
(Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
7) Probable Mechanism: unknown
8) Literature Reports
a) Fluoxetine is thought to inhibit the cytochrome P450 2C9 isoenzyme (CYP2C9). This is the enzyme b
warfarin, is metabolized (Riesenman, 1995). In addition, both fluoxetine and warfarin are tightly bound to
protein-binding displacement of either drug is present (Prod Info Coumadin(R), 1999).
b) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bl
patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks followi
mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected p
SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients
treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4
corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. T
treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only
bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI
dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding
exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model
c) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoum
reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal blee
hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal b
subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690
for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interva
gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekam

d) In 6 reported cases, INR increased during combined fluoxetine and warfarin therapy. In a seventh ca
a woman initially treated with fluoxetine and, secondarily, started on warfarin (Woolfrey et al, 1993; Clair
e) An 83-year-old man died from cerebral hemorrhage secondary to increased warfarin concentrations.
week for atrial fibrillation with a target INR between 2 and 3. The patient's other drugs included lisinopril,
acetaminophen. After being seen for symptoms of depression, anxiety, and insomnia, the patient was gi
mg 3 to 4 times per day. Eight days later, the patient's INR increased to 4.8, and the dose of warfarin wa
was later seen for symptoms of drug delirium, including confusion, incoherence, and speaking irrationall
was discontinued. The next day the patient presented to the hospital with left-sided weakness and later
interparenchymal hemorrhage. The authors proposed that the addition of fluoxetine to the patient's regi
warfarin and diazepam, resulting in delirium and loss of anticoagulant control (Dent & Orrock, 1997).

3.5.1.U Aripiprazole

1) Interaction Effect: increased aripiprazole levels
2) Summary: Aripiprazole is partly metabolized by cytochrome P450 2D6 (CYP2D6) enzymes. Coadministra
may inhibit aripiprazole elimination causing increased blood concentrations. Consider a dosage reduction for
coadministered. If therapy with fluoxetine is discontinued, the dose of aripiprazole should then be increased (
2005).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Increased aripiprazole plasma levels may result if used concomitantly with fluoxetin
when these agents are coadministered. If therapy with fluoxetine is discontinued, the dose of aripiprazole sh
7) Probable Mechanism: inhibition of cytochrome P450 2D6-mediated metabolism of aripiprazole

3.5.1.V Arsenic Trioxide

1) Interaction Effect: cardiotoxicity (QT interval prolongation, torsades de pointes, cardiac arrest)
2) Summary: Arsenic trioxide and fluoxetine have been shown to prolong the QTc interval at the recommend
2001a; Prod Info Prozac(R), 2001u). Even though no formal drug interaction studies have been done, arseni
drugs which are also known or have the potential to prolong the QTc interval, including fluoxetine (Prod Info
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of arsenic trioxide and fluoxetine is not recommende
7) Probable Mechanism: additive effects on QT prolongation
8) Literature Reports

a) QT/QTc prolongation should be expected during treatment with arsenic trioxide and torsade de pointe
reported. Over 460 ECG tracings from 40 patients with refractory or relapsed APL treated with arsenic tri
Sixteen of 40 patients (40%) had at least one ECG tracing with a QTc interval greater than 500 msec. Pr
and 5 weeks after arsenic trioxide infusion, and then returned towards baseline by the end of 8 weeks af
evaluations, women did not experience more pronounced QT prolongation than men, and there was no
2001).

b) QT Prolongation was observed on the electrocardiogram (ECG) of a 52- year-old man who had been
followed by 40 milligrams/day thereafter) for depression for 3 months. An ECG just before the start of flu
The QT interval returned to normal within 10 days of discontinuing fluoxetine treatment (Varriale, 2001).

3.5.1.W Aspirin

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control an
use of SSRIs and antiplatelet agents has been associated with an increased risk of bleeding. Bleeding event
hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008;
release capsules, solution, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an antiplatelet agent are given concurrently, monitor patient for
oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 200
7) Probable Mechanism: unknown

3.5.1.X Astemizole

1) Interaction Effect: cardiotoxicity (QT interval prolongation, torsades de pointes, cardiac arrest)
2) Summary: It is theoretically possible that an interaction might occur between astemizole and fluoxetine be
cytochrome P450 system. Astemizole is metabolized by CYP3A4. Fluoxetine is known to be a potent inhibito
P450 enzymes, including CYP3A4 (Riesenman, 1995a). Coadministered fluoxetine may inhibit astemizole cl
serum concentrations and potential astemizole toxicity. The manufacturer of astemizole recommends avoidin
Hismanal(R), 1998). In addition, fluoxetine has been shown to prolong the QTc interval at the recommended
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical

6) Clinical Management: Concomitant use of astemizole and fluoxetine is not recommended.
7) Probable Mechanism: possible inhibition of astemizole P450 metabolism by fluoxetine and/or additive effe
8) Literature Reports
a) Astemizole has been shown to prolong the QTc interval at the recommended therapeutic dose (Prod drug interaction studies have been done, the coadministration of astemizole and other drugs known to pr not recommended.

3.5.1.Y Atomoxetine
1) Interaction Effect: an increase in atomoxetine steady-state plasma concentrations
2) Summary: Atomoxetine is primarily metabolized by the cytochrome P450 2D6 (CYP 2D6) pathway to 4-hy atomoxetine steady-state plasma concentrations are increased with selective inhibitors of CYP2D6, such as f observed in poor metabolizers. In extensive metabolizers treated with fluoxetine, the area under the concentr 6- to 8-fold greater, and maximum plasma concentration at steady-state is about 3- to 4-fold greater than atoı
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Dosage adjustment of atomoxetine may be necessary when coadministered with flu
7) Probable Mechanism: inhibition of cytochrome P450 2D6-mediated metabolism of atomoxetine by fluoxeti

3.5.1.Z Azimilide
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, the coadministration of Class prolong the QTc interval is not recommended (Allen et al, 2002; Prod Info Tikosyn(TM) dofetilide capsules, 1 been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Prozac(R), 2001a).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of class III antiarrhythmic agents and agents that pro recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.AA Belladonna
1) Interaction Effect: excessive anticholinergic activity (severe dry mouth, constipation, decreased urination,
2) Summary: The anticholinergic activity of the active alkaloids present in belladonna may predispose the pa with olanzapine. Belladonna contains L-hyoscyamine, atropine, and scopolamine with a total alkaloid content roots (Blumenthal et al, 1998). Because belladonna is typically available as a homeopathic preparation, the c is unknown. Caution is advised.
3) Severity: minor
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Excessive anticholinergic activity may be manifested by dry mouth, constipation, ur mydriasis, blurred vision, elevated temperature, muscular weakness, and sedation. If such effects are noted, In severe cases, paralytic ileus, confusion, psychoses, agitation, delusions, delirium, and paranoia may be er and hypertension. In severe cases, immediate medical attention should be obtained.
7) Probable Mechanism: additive anticholinergic effect

3.5.1.AB Belladonna Alkaloids
1) Interaction Effect: excessive anticholinergic activity (severe dry mouth, constipation, decreased urination,
2) Summary: The anticholinergic activity of the active alkaloids present in belladonna may predispose the pa with olanzapine. Belladonna contains L-hyoscyamine, atropine, and scopolamine with a total alkaloid content roots (Blumenthal et al, 1998). Because belladonna is typically available as a homeopathic preparation, the c is unknown. Caution is advised.
3) Severity: minor
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Excessive anticholinergic activity may be manifested by dry mouth, constipation, ur mydriasis, blurred vision, elevated temperature, muscular weakness, and sedation. If such effects are noted, In severe cases, paralytic ileus, confusion, psychoses, agitation, delusions, delirium, and paranoia may be er and hypertension. In severe cases, immediate medical attention should be obtained.
7) Probable Mechanism: additive anticholinergic effect

3.5.1.AC Benoxaprofen
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have incl petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info L CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate

4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressar hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of u than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin inc
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with TORADOL(R) oral tablets, 2007).

3.5.1.AD Bepridil

1) Interaction Effect: cardiotoxicity (QT interval prolongation, torsades de pointes, cardiac arrest)
2) Summary: Both bepridil and fluoxetine have been shown to prolong the QTc interval at therapeutic doses (R), 2000). Even though no formal drug interaction studies have been done, the coadministration of bepridil a Vascor(R), 2000).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of bepridil and fluoxetine is contraindicated.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.AE Betel Nut

1) Interaction Effect: increased extrapyramidal side effects of olanzapine (difficulty with movement or abnorm
2) Summary: Case reports have described increased extrapyramidal side effects when betel nut was chewe fluphenthixol for schizophrenia (Deahl, 1989a). The extrapyramidal effects were not improved with anticholine betel nut discontinuation (Deahl, 1989a). A similar effect may occur if betel nut is chewed with concomitant ol betel nut has been attributed to the arecoline content. When given with peripheral anticholinergics, arecoline muscarinic agonist activity (Nutt et al, 1978a). Case reports suggest the onset of betel nut activity to be withir discontinuation (Deahl, 1989a).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: It is unclear to what extent the cholinergic effect of betel nut may increase the incid especially if patients are treated with anticholinergic agents to control these side effects. Deterioration in sym other extrapyramidal movement disorders may be expected. Persons who have been chewing betel nut have help the clinician discover betel nut use.
7) Probable Mechanism: cholinergic effect of betel nut
8) Literature Reports
a) Within 3 weeks of initiating betel nut chewing, a 51-year-old Indian man experienced marked rigidity, been stabilized for the previous 2 years on fluphenazine decanoate depot 50 milligrams (mg) every 3 we twice daily for a mild Parkinsonian tremor. Within one week of discontinuation of betel nut chewing, the p report appears to demonstrate decreased anticholinergic effects of procyclidine when coadministered wi
b) Following betel nut ingestion, a 45-year-old Indian man developed akathisia, tremor and stiffness whi to 20 mg daily of procyclidine. This patient had been previously stabilized on fluphenthixol 60 mg depot e schizoaffective disorder without extrapyramidal side effects. His symptoms resolved over 4 days after dis anticholinergic effects of procyclidine were diminished when betel nut was chewed concomitantly (Deahl
c) High doses (5 mg, 10 mg, and 20 mg) of subcutaneous (SC) arecoline given one hour after SC admi anticholinergic agent methscopolamine increased the heart rate and blood pressure of six patients with H blood pressure occurred at doses of 5 mg, 10 mg (p less than 0.01) and 20 mg (p less than 0.05). Heart less than 0.01), and 10 mg (p less than 0.05). Subjective effects in some patients included tremor, flushi nausea, weakness, and mental changes at the higher doses. No peripheral cholinergic effects were note effect for arecoline (Nutt et al, 1978).
d) A low dose (0.5 mg) of arecoline given intravenously 3 minutes after the peripheral anticholinergic ag major depressive disorder increased their heart rates. The peak heart rate increase in a non-REM portio infusion period was 6.75 +/- 12.9 beats per minute for placebo and 25 +/- 10.3 beats per minute for arec minutes after the arecoline infusion, and the mean heart rate was significantly elevated over placebo fror than 0.05) (Abramson et al, 1985).
e) Though chewing betel nut alone does not significantly increase catecholamine levels, a popular betel chewing betel nut, 4 subjects had only a moderate increase in plasma noradrenaline from 266.2 +/- 105. pg/mL (p equal to 0.0607). Combining betel nut with lime, catechu and Piper betel flower as is commonly norepinephrine in nine subjects from 292.2 +/- 59.5 pg/mL to 375.1 +/- 130.0 pg/mL (p equal to 0.0244) a 102.2 +/- 45.0 pg/mL (p equal to 0.0226). In this group dopamine was also elevated in 8 of 9 subjects, bu

3.5.1.AF Bivalirudin

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2 (R) oral capsules, delayed-release capsules, solution, 2008). Bleeding events reported have included epistax threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported wi (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When fluoxetine and an anticoagulant are given concurrently, monitor patient for sig taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, wh (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
7) Probable Mechanism: unknown
8) Literature Reports
a) Fluoxetine is thought to inhibit the cytochrome P450 2C9 isoenzyme (CYP2C9). This is the enzyme b warfarin, is metabolized (Riesenman, 1995). In addition, both fluoxetine and warfarin are tightly bound to protein-binding displacement of either drug is present (Prod Info Coumadin(R), 1999).
b) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bl patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks followi mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected p SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. T treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model
c) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoum reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal blee hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal b subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interva gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekam
d) In 6 reported cases, INR increased during combined fluoxetine and warfarin therapy. In a seventh ca a woman initially treated with fluoxetine and, secondarily, started on warfarin (Woolfrey et al, 1993; Claire
e) An 83-year-old man died from cerebral hemorrhage secondary to increased warfarin concentrations. week for atrial fibrillation with a target INR between 2 and 3. The patient's other drugs included lisinopril, acetaminophen. After being seen for symptoms of depression, anxiety, and insomnia, the patient was giv mg 3 to 4 times per day. Eight days later, the patient's INR increased to 4.8, and the dose of warfarin wa was later seen for symptoms of drug delirium, including confusion, incoherence, and speaking irrationally was discontinued. The next day the patient presented to the hospital with left-sided weakness and later d interparenchymal hemorrhage. The authors proposed that the addition of fluoxetine to the patient's regim warfarin and diazepam, resulting in delirium and loss of anticoagulant control (Dent & Orrock, 1997).

3.5.1.AG Bretylium

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, the coadministration of Class prolong the QTc interval is not recommended (Allen et al, 2002; Prod Info Tikosyn(TM) dofetilide capsules, 19 been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Prozac(R), 2001a).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of class III antiarrhythmic agents and agents that pro recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.AH Bromfenac

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have incl petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info L CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent
Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressar
hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of u
than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose
confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of
upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin inc
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with
TORADOL(R) oral tablets, 2007).

3.5.1.AI Bufexamac

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control anc
use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have incl
petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info L
CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent
Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressar
hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of u
than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose
confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of
upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin inc
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with
TORADOL(R) oral tablets, 2007).

3.5.1.AJ Bupropion

1) Interaction Effect: increased plasma levels of fluoxetine
2) Summary: Because bupropion inhibits CYP2D6-mediated metabolism it is recommended that fluoxetine, a
cytochrome P450 2D6 isoenzyme, be initiated at the lower end of the dose range when administered concom
(TM), 2003; Prod Info Zyban(R), 2000). Increased plasma concentrations of fluoxetine may result in increase
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Coadministration of bupropion and fluoxetine should be approached with caution ar
range of fluoxetine. If bupropion is added to the treatment regimen of a patient already receiving fluoxetine, c
Monitor for increased adverse effects including weight gain or loss, anxiety, weakness, or sleeping disturbanc
7) Probable Mechanism: inhibition of cytochrome P450 2D6-mediated fluoxetine metabolism
8) Literature Reports

a) The concomitant administration of fluoxetine and bupropion was associated with a hyperactive libido
depression. The patient, a 35-year-old woman, initially received treatment with fluoxetine 40 milligrams (
therapy due to suboptimal therapeutic effect. She experienced a diminished libido from the onset of clom
conversion to fluoxetine. Three months after the conversion to fluoxetine, bupropion 100 mg/day was ad
antidote for the sexual dysfunction. Sexual function appeared to normalize 1 month after the start of bup
beginning bupropion, the patient complained of having an exaggerated increase in libido, causing her to
to normal within 2 months of stopping all medication, accompanied by a recurrence of depressive sympt
same time period, producing another reduction in libido yet accompanied by a full remission from depres

3.5.1.AK Buspirone

1) Interaction Effect: worsening of psychiatric symptoms
2) Summary: In a number of case reports, the concomitant use of buspirone and fluoxetine has been reporte
underlying anxiety/or obsessive-compulsive disorder (Bodkin & Teicher, 1989; Tanquary & Masand, 1990; M
patient maintained on fluoxetine who presented with symptoms of serotonin syndrome, including confusion, d
myoclonus after buspirone was added to his drug regimen (Manos, 2000a).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: If possible, the combination of fluoxetine and buspirone should be avoided; howeve
worsening of psychiatric symptoms.
7) Probable Mechanism: possible inhibition of buspirone serotonergic effects
8) Literature Reports

a) One of 10 patients with obsessive-compulsive disorder experienced anorgasmia after buspirone (mea
fluoxetine therapy (mean maximum dose, 78 mg daily). The anorgasmia could not be definitely attributed
the two agents. Both fluoxetine and buspirone have reported a low incidence of sexual dysfunction when

1999d; Prod Info Buspar(R), 1994; Jenike et al, 1991).
b) Three cases of potentiation of the antidepressant effects of fluoxetine by buspirone have been report
treatment-resistant symptoms of depression, obsessional traits, anxiety, and a history of eating disorder
regimen.
c) A case report describes a 37-year-old male patient maintained on fluoxetine 20mg per day who bega
augment the actions of fluoxetine. The starting dose of buspirone was gradually increased from 5mg twic
five weeks. After five days at this dose, the patient complained of confusion, diaphoresis, incoordination,
be serotonin syndrome. The patients symptoms resolved shortly after discontinuation of buspirone (Man

3.5.1.AL Cannabis
1) Interaction Effect: manic symptoms
2) Summary: One case of mania following use of marijuana with fluoxetine therapy has been reported (Stoll
proposed, the authors also state the manic symptoms could have resulted from the fluoxetine or marijuana al
marijuana and taking fluoxetine or other serotonin reuptake inhibitors.
3) Severity: moderate
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Caution patients taking selective serotonin reuptake inhibitors to avoid concomitant
7) Probable Mechanism: additive serotonergic stimulation
8) Literature Reports
a) A 21-year-old female presented with mania, agitation, and grandiose delusions following use of mariju
taking fluoxetine 20 mg daily for 4 weeks and reported smoking 2 "joints" during a 36-hour period. Over t
energy, hypersexuality, pressured speech, and grandiose delusions. Lorazepam and perphenazine were
gradually resolved over 4 days. She remained hospitalized for 36 days. Fluoxetine 20 mg every other da
One week after discharge, she discontinued fluoxetine due to insomnia and feeling "hyper". These symp
fluoxetine. Due to the rapid switch to mania after smoking marijuana with fluoxetine, the manic symptoms
fluoxetine and marijuana, though mania could have developed from either fluoxetine or marijuana alone

3.5.1.AM Carbamazepine
1) Interaction Effect: reduced olanzapine efficacy
2) Summary: Carbamazepine induces CYP1A2 mediated oxidation. Concomitant administration of olanzapin
increased the clearance of olanzapine by 50% (Prod Info Zyprexa(R), 1999a). Higher daily doses of carbama
olanzapine clearance. In a study of 11 healthy volunteers, concurrent administration of olanzapine and carba
olanzapine clearance (Lucas et al, 1998). Because patients respond to a relatively wide range of olanzapine
of symptom patterns and changes is necessary whenever carbamazepine is added to or withdrawn from olar
adjustments will most likely be highly patient specific (Licht et al, 2000a).
3) Severity: moderate
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Monitor patients for olanzapine efficacy. Doses of olanzapine may need to be adjus
carbamazepine.
7) Probable Mechanism: induction of cytochrome P450 1A2-mediated olanzapine metabolism
8) Literature Reports
a) A 23-year-old paranoid schizophrenic female was admitted to the hospital for treatment of hallucinatic
admission was perphenazine 12 mg daily, but carbamazepine 600 mg daily was initiated for aggressive
risperidone 6 mg daily due to akathisia, rigidity, and tremor, but risperidone was also discontinued due to
daily was started and her psychiatric symptoms improved over the next three weeks. Because her aggre
carbamazepine was discontinued due to lack of efficacy. She had received cotherapy with olanzapine 15
three consecutive weeks. The day prior to carbamazepine discontinuation, the patient's olanzapine serur
Over the next few weeks, her olanzapine concentration increased by 114% to 45 ng/mL. The dose of ola
corresponding fall in the olanzapine level occurred. This case report suggests that carbamazepine induc
through the cytochrome P450 1A2 enzyme system (Licht et al, 2000).

3.5.1.AN Carbamazepine
1) Interaction Effect: carbamazepine toxicity (ataxia, nystagmus, diplopia, headache, vomiting, apnea, seizur
2) Summary: The addition of fluoxetine to carbamazepine therapy has increased carbamazepine concentrati
vision, dizziness, and tremors in some reports (Grimsley et al, 1991a; Gernaat et al, 1991a; Pearson, 1990a)
carbamazepine levels have been reported with the addition of fluoxetine (Spina et al, 1993a). Symptoms of s
myoclonus, mental status changes) have also been reported with this combination (Dursun et al, 1993a).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Due to the potential to increase carbamazepine levels, patients should be monitore
fluoxetine is added to therapy. Carbamazepine levels should be considered within two to three weeks of addi
adjustments made as indicated.
7) Probable Mechanism: decreased carbamazepine metabolism
8) Literature Reports
a) An interaction between fluoxetine and carbamazepine was reported in six normal volunteers (Grimsle

days, and fluoxetine was added to the regimen on day 7. The addition of fluoxetine 20 mg daily to carbar
the area under the concentration-time curve for both carbamazepine and carbamazepine-epoxide and a
significant changes were observed in absorption, volume of distribution or elimination rate constant, indic
carbamazepine.
b) The effect of fluoxetine 20 mg daily was studied for three weeks in eight epileptic patients who were s
1993). Steady-state plasma levels of carbamazepine and its epoxide metabolite were not significantly ch
results differ from previous reports. The authors speculate that chronic carbamazepine administration ma
decreased levels of fluoxetine, thereby lowering the chances of a metabolic interaction. Unfortunately flu
c) An interaction between fluoxetine and carbamazepine was reported in two patients receiving chronic
daily respectively. Within 7 to 10 days of initiation of fluoxetine 20 mg daily, both patients developed sym
disappeared within two weeks in one patient following carbamazepine dosage reduction by 200 mg daily
with symptom resolution within two weeks (Pearson, 1990).
d) Two cases of parkinsonism were reported after fluoxetine was added to an existing carbamazepine re
developed symptoms three days after fluoxetine 20 mg per day was added to an existing 12-month regin
patient developed cogwheel rigidity, a mask-like face, and a parkinsonian gait. After discontinuation of flu
patient showed only a slight hypertonia of the arms 17 days later. The other patient, a 53-year old woma
fluoxetine 20 mg per day was added to an existing regimen of carbamazepine 200 mg twice daily. The p
per day which was stopped when fluoxetine was added. The patient developed cogwheel rigidity and a n
fluoxetine therapy (Gernaat et al, 1991).
e) A female patient experienced a drug interaction 14 days after she had fluoxetine 20 mg added to a re
patient presented with symptoms of serotonin syndrome, such as uncontrollable shivering, agitation, inco
diaphoresis. The patient also had leukopenia and thrombocytopenia. After discontinuation of fluoxetine, a
hematological abnormalities resolved over the next 72 hours (Dursun et al, 1993).

3.5.1.AO Carprofen

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control anc
use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have incl
petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info L
CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent
Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressar
hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of u
than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose
confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of
upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin inc
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with
TORADOL(R) oral tablets, 2007).

3.5.1.AP Celecoxib

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control anc
use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have incl
petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info L
CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent
Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressar
hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of u
than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose
confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of
upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin inc
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with
TORADOL(R) oral tablets, 2007).

3.5.1.AQ Certoparin

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2 (R) oral capsules, delayed-release capsules, solution, 2008). Bleeding events reported have included epistax threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported wi (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When fluoxetine and an anticoagulant are given concurrently, monitor patient for sig taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, wi (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
7) Probable Mechanism: unknown
8) Literature Reports
a) Fluoxetine is thought to inhibit the cytochrome P450 2C9 isoenzyme (CYP2C9). This is the enzyme b warfarin, is metabolized (Riesenman, 1995). In addition, both fluoxetine and warfarin are tightly bound to protein-binding displacement of either drug is present (Prod Info Coumadin(R), 1999).
b) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bl patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks followi mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected p SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. T treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model
c) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoum reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal blee hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal b subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interva gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekam
d) In 6 reported cases, INR increased during combined fluoxetine and warfarin therapy. In a seventh ca a woman initially treated with fluoxetine and, secondarily, started on warfarin (Woolfrey et al, 1993; Claire
e) An 83-year-old man died from cerebral hemorrhage secondary to increased warfarin concentrations. week for atrial fibrillation with a target INR between 2 and 3. The patient's other drugs included lisinopril, acetaminophen. After being seen for symptoms of depression, anxiety, and insomnia, the patient was giv mg 3 to 4 times per day. Eight days later, the patient's INR increased to 4.8, and the dose of warfarin wa was later seen for symptoms of drug delirium, including confusion, incoherence, and speaking irrationally was discontinued. The next day the patient presented to the hospital with left-sided weakness and later d interparenchymal hemorrhage. The authors proposed that the addition of fluoxetine to the patient's regim warfarin and diazepam, resulting in delirium and loss of anticoagulant control (Dent & Orrock, 1997).

3.5.1.AR Chloral Hydrate

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Chloral hydrate and fluoxetine have been shown to prolong the QTc interval at the recommend 2001ac; Young et al, 1986). Even though no formal drug interaction studies have been done, the coadministr is not recommended.
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of chloral hydrate and fluoxetine is not recommended.
7) Probable Mechanism: additive effects on QT prolongation
8) Literature Reports
a) QT Prolongation was observed on the electrocardiogram (ECG) of a 52- year-old man who had been followed by 40 milligrams/day thereafter) for depression for 3 months. An ECG just before the start of flu The QT interval returned to normal within 10 days of discontinuing fluoxetine treatment (Varriale, 2001a)

3.5.1.AS Chloroquine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Chloroquine and fluoxetine have been shown to prolong the QTc interval at the recommended Prod Info Aralen(R), 2001). Even though no formal drug interaction studies have been done, the coadministra is not recommended.
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of chloroquine and fluoxetine is not recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.AT Chlorpromazine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Although citing no data, the manufacturers of some phenothiazines state that concomitant use
not recommended. Q and T wave distortions have been observed in patients taking phenothiazines (Prod Inf
2002; Prod Info Thorazine(R), 2002) . Other phenothiazines may have similar effects, though no reports are a
the QTc interval at the recommended therapeutic dose (Prod Info Prozac(R), 2003).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of fluoxetine and a phenothiazine is not recommende
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.AU Cilostazol

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and
use of SSRIs and antiplatelet agents has been associated with an increased risk of bleeding. Bleeding events
hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008;
release capsules, solution, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an antiplatelet agent are given concurrently, monitor patient for
oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 200
7) Probable Mechanism: unknown

3.5.1.AV Ciprofloxacin

1) Interaction Effect: an increased risk of olanzapine toxicity (increased sedation, orthostatic hypotension)
2) Summary: Ciprofloxacin was suspected of inhibiting the metabolism of olanzapine in a 54-year-old female
1A2 (CYP1A2) has been shown in vitro to be responsible for the formation of some of the metabolites of olan
inhibitor of CYP1A2. Although olanzapine has a wide therapeutic range and a correlation between plasma co
established, this interaction may be clinically significant (Markowitz & DeVane, 1999a).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Patients receiving olanzapine and ciprofloxacin concurrently should be monitored fo
increased sedation and orthostatic hypotension.
7) Probable Mechanism: inhibition by ciprofloxacin of cytochrome P450 1A2-mediated olanzapine metabolis
8) Literature Reports
a) A 54-year-old female was admitted to the hospital with suicidal ideation and lacerations to her wrists.
olanzapine 10 mg at bedtime, nefazodone 100 mg twice daily, atenolol 25 mg daily, levothyroxine 0.25 m
Nefazodone was tapered off prior to electroconvulsive therapy, and ciprofloxacin 250 mg twice daily for s
tract infection. Immediately before her last dose of ciprofloxacin, the plasma olanzapine concentration wa
was discontinued, her olanzapine concentration had decreased by more than 50% to 14.6 ng/mL. Althou
effects from her increased olanzapine level, higher doses of ciprofloxacin could potentially cause more ir
DeVane, 1999).

3.5.1.AW Clarithromycin

1) Interaction Effect: delirium and psychosis
2) Summary: Delirium and psychosis were reported in a 53-year-old male after clarithromycin was added to t
effects are most likely due to accumulation of fluoxetine (Pollak et al, 1995a).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Clarithromycin should be avoided in patients treated with fluoxetine.
7) Probable Mechanism: fluoxetine toxicity due to decreased metabolism
8) Literature Reports
a) Delirium and psychosis were reported in a 53-year-old male after clarithromycin was added to therapy
most likely due to accumulation of fluoxetine, because these symptoms have been associated with fluox
patient had previously tolerated an inadvertent overdose of nitrazepam without symptoms of delirium and

3.5.1.AX Clomipramine

1) Interaction Effect: an increased risk of seizures
2) Summary: Psychotropic drugs have been shown to reduce the seizure threshold. A case report describes
who received treatment with olanzapine and clomipramine concomitantly. This combination resulted in seizur
olanzapine and clomipramine. It is advised to use caution when administering olanzapine concomitantly with
seizure threshold (Deshauer et al, 2000a).
3) Severity: major

4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: It is advised to use caution when administering olanzapine concomitantly with clom seizure threshold.
7) Probable Mechanism: unknown
8) Literature Reports
a) A 34-year-old male with schizophrenia and obsessive-compulsive disorder (OCD) without any underly following long-term noncompliance. Inpatient olanzapine treatment (20 mg/day) was initiated and positive Patient was discharged and readmitted because of inability to control symptoms. Clomipramine 250 mg and myoclonic jerks were reported which quickly progressed to general motor seizures and postictal som and paroxysmal slowing on the EEG was consistent with seizure activity. Clomipramine and olanzapine were controlled with diazepam 30 mg per day for three days. This pattern repeated upon re-challenge wi clomipramine. Presumably from the temporal relationship between clomipramine and olanzapine adminis suspected that this adverse event is due to an interaction between these two drugs. Clomipramine and o cytochrome P450 isoenzymes 1A2 and 2D6. One theory is that coadministration may result in elevated l mechanism by which this interaction occurs is not yet known, it is advised to use caution when administe clomipramine, or other agents known to lower the seizure threshold (Deshauer et al, 2000).

3.5.1.AY Clonixin

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have incl petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info L CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressar hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of u than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin inc
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with TORADOL(R) oral tablets, 2007).

3.5.1.AZ Clopidogrel

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and use of SSRIs and antiplatelet agents has been associated with an increased risk of bleeding. Bleeding events hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008; release capsules, solution, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an antiplatelet agent are given concurrently, monitor patient for oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 200
7) Probable Mechanism: unknown

3.5.1.BA Clopidogrel

1) Interaction Effect: reduction in clinical efficacy of clopidogrel
2) Summary: Clopidogrel is metabolized to its active metabolite by CYP2C19. Concomitant use of CYP2C19 expected to result in reduced levels of the active metabolite, and therefore a reduction the clinical efficacy of inhibitors with clopidogrel is discouraged (Prod Info PLAVIX(R) oral tablet, 2009).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of clopidogrel and fluoxetine is discouraged (Prod Info PLAVIX(R)
7) Probable Mechanism: inhibition of CYP2C19- mediated clopidogrel metabolism by fluoxetine

3.5.1.BB Clorgyline

1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental st
2) Summary: Concurrent administration or overlapping therapy with fluoxetine and a monoamine oxidase (M serotonin syndrome, a hyperserotonergic state characterized by symptoms such as restlessness, myoclonus diaphoresis, shivering, and tremor. Serious, even fatal, reactions have been reported (Prod Info Prozac(R), 1

1993t; Feighner et al, 1990t; Kline et al, 1989u; Suchowersky & de Vries, 1990u). Concomitant use is contrai
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Concurrent use of fluoxetine and a MAO inhibitor is contraindicated. Wait at least tw
before initiating fluoxetine therapy. In addition, wait at least five weeks after discontinuing fluoxetine before in
7) Probable Mechanism: inhibition of serotonin metabolism by monoamine oxidase
8) Literature Reports
a) Concomitant use of serotonin specific reuptake inhibitors and monoamine oxidase inhibitors can prod
syndrome (Sternbach, 1991v). Serotonin syndrome is a condition of serotonergic hyperstimulation and m
mental status, hyperreflexia, diaphoresis, shivering, and tremor (Sternbach, 1991v). If the syndrome is n
result.
b) It has been suggested that fluoxetine therapy be discontinued for five weeks before beginning therap
one case report describes a 28-year old woman who had discontinued a 2-year fluoxetine regimen for si
tranylcypromine. Over the next few days the patient developed fever, paresthesias, confusion, abdomina
Upon discontinuation of tranylcypromine, the patient's symptoms began to resolve. Blood samples taken
tranylcypromine revealed no presence of fluoxetine; however, the norfluoxetine level was 84 ng/mL (Cop
c) Adverse reactions reported when fluoxetine was given concomitantly with phenelzine (n=9) or tranylc
restlessness (42%), mental status changes (42%), myoclonus (33%), diarrhea (33%), and blood pressur
one of the patients were taking other medications (ie, benzodiazepines, neuroleptics, anticonvulsants, ar
adverse reactions.
d) Ten hours after her last dose of fluoxetine, a 45-year-old woman began tranylcypromine therapy (Klir
insomnia, and unsteady gait were reported on the second day. Thioridazine and tryptophan were added
rigidity of the arms and legs, and hyperreflexia. She died in the intensive care unit of a hospital 44 hours
e) Two cases suggestive of an interaction between fluoxetine and selegiline were reported (Suchowersk
episode of mania being observed approximately one month after adding selegiline to fluoxetine therapy.
drugs were discontinued, and no further details were provided. The second case involved diaphoresis, v
occurred in close temporal relationship to adding fluoxetine and selegiline. Both drugs were discontinuec
Rechallenge with fluoxetine alone occurred without incident.

3.5.1.BC Clozapine
1) Interaction Effect: an increased risk of clozapine toxicity (sedation, seizures, hypotension)
2) Summary: With concurrent administration of fluoxetine, increased serum clozapine concentrations have b
Centorrino et al, 1994a; Centorrino et al, 1996a; Spina et al, 1998a). Certain adverse effects associated with
sedation (Ayd, 1974) and seizures (Haller & Binder, 1990), and might be expected to occur with concurrent u
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor the therapeutic efficacy of clozapine and for any evidence of toxicity, partic
mg or 3.5 mg/kg. Lower clozapine dosage may be required in some clinical situations.
7) Probable Mechanism: inhibition by fluoxetine of N-dealkylation and N-oxidation of clozapine via the cytoch
8) Literature Reports
a) Subjects receiving concurrent clozapine and fluoxetine had 76% higher serum clozapine concentratio
average compared with controls receiving only clozapine. The mean ratio of total drug level (clozapine pl
mean ratio of concentrations to dose was 75% higher in patients receiving clozapine and fluoxetine com
clozapine alone (Centorrino et al, 1994).
b) A study evaluated the serum concentrations of clozapine and norclozapine, the major metabolite, wh
serotonin reuptake inhibitors (SSRIs) fluoxetine, paroxetine, and sertraline. Eighty outpatients receiving c
schizophrenia or major affective disorder, and 40 of these patients were receiving an SSRI in combinatio
receiving fluoxetine, 10 were receiving sertraline, and 16 were receiving paroxetine therapy. Among the
of clozapine and norclozapine were 41.1% and 44.8% higher, respectively, than in matched patients wh
clozapine plus norclozapine concentration to dose was also 37.7% higher in patients receiving SSRIs, in
differences between the three SSRIs were minor, and the study groups were too limited for an accurate
SSRIs (Centorrino et al, 1996).
c) A 44-year-old male receiving fluoxetine and clozapine was found dead in his yard. The dates of the p
remained indicated that he had been taking his medications as prescribed. Autopsy results showed a hig
mcg/mL) and also a high therapeutic norfluoxetine concentration (0.6 mcg/mL). Fluoxetine found in his g
was being taken as directed. The clozapine blood concentration was in the lethal concentration range (4
contents suggested that the clozapine was being taken as prescribed and that the patient had not consu
Other pathological findings included pulmonary edema, visceral vascular congestion, paralytic ileus, gas
consistent with clozapine toxicity. The combined central nervous system, respiratory, and cardiovascular
sufficient to result in the death of this patient, and his death was ruled to be a clozapine overdose due to
d) Ten institutionalized schizophrenic patients stabilized on clozapine therapy for at least one month par
effect of fluoxetine on clozapine pharmacokinetics. Fluoxetine 20 mg once daily was administered for eig
concentrations increased from 348 ng/mL to 550 ng/mL (58%) at week 8. Plasma levels of norclozapine
381 ng/mL). Clozapine N-oxide levels rose from 89 ng/mL at baseline to 128 ng/mL, representing a 38%
and metabolite plasma concentrations were not associated with significant changes in efficacy or safety

3.5.1.BD Cyclobenzaprine

1) Interaction Effect: an increased risk of QT prolongation

2) Summary: Fluoxetine and cyclobenzaprine caused asymptomatic QT prolongation in a female patient. Ho preoperatively to this patient resulted in torsades de pointes and cardiac arrest. The authors of this case repo cyclobenzaprine, which is structurally similar to the tricyclic antidepressants, was inhibited by fluoxetine. Cyto by fluoxetine, and cyclobenzaprine may also be metabolized via this pathway (Michalets et al, 1998a).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Clinicians should monitor patients receiving cyclobenzaprine and fluoxetine for card who receive these two agents concurrently should avoid other drugs which are also known to prolong the QT

7) Probable Mechanism: inhibition of cyclobenzaprine metabolism by fluoxetine via the cytochrome P450 he

8) Literature Reports

a) A 59-year-old female patient was receiving fluoxetine 30 mg daily, cyclobenzaprine 10 mg daily, amlo triamterene 37.5 mg/hydrochlorothiazide 25 mg daily. Five days prior to elective Achilles tendon surgery, this finding, she was premedicated for surgery with intravenous droperidol 0.625 mg and metoclopramid surgery, the patient developed ventricular tachycardia consistent with torsades de pointes which progres Immediately following cardioversion, the patient's QTc was 500 msec. All preadmission medications wer postoperative day 1, the QTc was 440 msec and an electrocardiogram showed normal sinus rhythm (Mi

3.5.1.BE Cyproheptadine

1) Interaction Effect: decreased fluoxetine efficacy

2) Summary: Coadministration of cyproheptadine with fluoxetine may result in reduced fluoxetine effectivene postsynaptic serotonin. Concomitant use of cyproheptadine with drugs that possess serotonergic activity (suc or SSRIs) might be expected to result in a pharmacodynamic interaction. Lack of antidepressant efficacy has concomitantly with fluoxetine and paroxetine (Katz & Rosenthal, 1994a; Feder, 1991a; Goldbloom & Kennedy

3) Severity: moderate

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: Monitor patients for a reduction in fluoxetine efficacy. When cyproheptadine is coad might need to be adjusted upward. In some cases, it may be necessary to withdraw cyproheptadine.

7) Probable Mechanism: unknown; because cyproheptadine is a serotonin antagonist, it may oppose effects

8) Literature Reports

a) Although not consistently reported, decreased antidepressant effects were found in some patients wh therapy (Katz & Rosenthal, 1994; Feder, 1991; Goldbloom & Kennedy, 1991). A 42-year-old woman usir depression, subsequently started cyproheptadine (4 mg per dose) for its antihistaminic properties (Katz & and after four doses of cyproheptadine, she experienced dysphoria, irritability, and suicidal ideation. She On rechallenge, her feelings of dysphoria returned.

b) A 54-year-old woman was using paroxetine 20 mg per day for the treatment of nonpsychotic major de mg twice a day was added to her therapy. Two days later, her depression worsened and she experience psychotic symptoms resolved two days after cyproheptadine was discontinued. She declined to be recha

3.5.1.BF Dalteparin

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2 (R) oral capsules, delayed-release capsules, solution, 2008). Bleeding events reported have included epistax threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported wi (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: When fluoxetine and an anticoagulant are given concurrently, monitor patient for sig taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, wh (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).

7) Probable Mechanism: unknown

8) Literature Reports

a) Fluoxetine is thought to inhibit the cytochrome P450 2C9 isoenzyme (CYP2C9). This is the enzyme b warfarin, is metabolized (Riesenman, 1995). In addition, both fluoxetine and warfarin are tightly bound to protein-binding displacement of either drug is present (Prod Info Coumadin(R), 1999).

b) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bl patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks followi mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected p SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. T treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI

dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model
c) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoum reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal blee hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal b subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interva gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekam
d) In 6 reported cases, INR increased during combined fluoxetine and warfarin therapy. In a seventh ca a woman initially treated with fluoxetine and, secondarily, started on warfarin (Woolfrey et al, 1993; Claire
e) An 83-year-old man died from cerebral hemorrhage secondary to increased warfarin concentrations. week for atrial fibrillation with a target INR between 2 and 3. The patient's other drugs included lisinopril, acetaminophen. After being seen for symptoms of depression, anxiety, and insomnia, the patient was giv mg 3 to 4 times per day. Eight days later, the patient's INR increased to 4.8, and the dose of warfarin wa was later seen for symptoms of drug delirium, including confusion, incoherence, and speaking irrationally was discontinued. The next day the patient presented to the hospital with left-sided weakness and later c interparenchymal hemorrhage. The authors proposed that the addition of fluoxetine to the patient's regim warfarin and diazepam, resulting in delirium and loss of anticoagulant control (Dent & Orrock, 1997).

3.5.1.BG Danaparoid

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2 (R) oral capsules, delayed-release capsules, solution, 2008). Bleeding events reported have included epistax threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported wi (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When fluoxetine and an anticoagulant are given concurrently, monitor patient for sig taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, wh (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
7) Probable Mechanism: unknown
8) Literature Reports
a) Fluoxetine is thought to inhibit the cytochrome P450 2C9 isoenzyme (CYP2C9). This is the enzyme b warfarin, is metabolized (Riesenman, 1995). In addition, both fluoxetine and warfarin are tightly bound to protein-binding displacement of either drug is present (Prod Info Coumadin(R), 1999).
b) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bl patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks followi mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected p SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. T treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model
c) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoum reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal blee hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal b subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interva gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekam
d) In 6 reported cases, INR increased during combined fluoxetine and warfarin therapy. In a seventh ca a woman initially treated with fluoxetine and, secondarily, started on warfarin (Woolfrey et al, 1993; Claire
e) An 83-year-old man died from cerebral hemorrhage secondary to increased warfarin concentrations. week for atrial fibrillation with a target INR between 2 and 3. The patient's other drugs included lisinopril, acetaminophen. After being seen for symptoms of depression, anxiety, and insomnia, the patient was giv mg 3 to 4 times per day. Eight days later, the patient's INR increased to 4.8, and the dose of warfarin wa was later seen for symptoms of drug delirium, including confusion, incoherence, and speaking irrationally was discontinued. The next day the patient presented to the hospital with left-sided weakness and later c interparenchymal hemorrhage. The authors proposed that the addition of fluoxetine to the patient's regim warfarin and diazepam, resulting in delirium and loss of anticoagulant control (Dent & Orrock, 1997).

3.5.1.BH Defibrotide

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2

(R) oral capsules, delayed-release capsules, solution, 2008). Bleeding events reported have included epistax
threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported wi
(Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When fluoxetine and an anticoagulant are given concurrently, monitor patient for sig
taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, wh
(Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
7) Probable Mechanism: unknown
8) Literature Reports
a) Fluoxetine is thought to inhibit the cytochrome P450 2C9 isoenzyme (CYP2C9). This is the enzyme b
warfarin, is metabolized (Riesenman, 1995). In addition, both fluoxetine and warfarin are tightly bound to
protein-binding displacement of either drug is present (Prod Info Coumadin(R), 1999).
b) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bl
patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks followi
mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected p
SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients
treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4
corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively.
treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only
bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI
dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding
exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model
c) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoum
reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal blee
hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal b
subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690
for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interva
gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekam
d) In 6 reported cases, INR increased during combined fluoxetine and warfarin therapy. In a seventh ca
a woman initially treated with fluoxetine and, secondarily, started on warfarin (Woolfrey et al, 1993; Claire
e) An 83-year-old man died from cerebral hemorrhage secondary to increased warfarin concentrations.
week for atrial fibrillation with a target INR between 2 and 3. The patient's other drugs included lisinopril,
acetaminophen. After being seen for symptoms of depression, anxiety, and insomnia, the patient was giv
mg 3 to 4 times per day. Eight days later, the patient's INR increased to 4.8, and the dose of warfarin wa
was later seen for symptoms of drug delirium, including confusion, incoherence, and speaking irrationally
was discontinued. The next day the patient presented to the hospital with left-sided weakness and later c
interparenchymal hemorrhage. The authors proposed that the addition of fluoxetine to the patient's regim
warfarin and diazepam, resulting in delirium and loss of anticoagulant control (Dent & Orrock, 1997).

3.5.1.BI Dehydroepiandrosterone
1) Interaction Effect: reduced effectiveness of olanzapine
2) Summary: Dehydroepiandrosterone (DHEA) levels within the normal range of 100 to 400 microgram/decil
of patients with psychosis (Howard, 1992a). In case reports, patients have been resistant to antipsychotics w
1992a). Patients being treated with olanzapine should avoid DHEA supplementation.
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Avoid concomitant use of dehydroepiandrosterone (DHEA) and olanzapine. If DHEA
mg orally per day may be used to normalize DHEA levels.
7) Probable Mechanism: elevated dehydroepiandrosterone (DHEA) blood levels may reduce responsiveness
8) Literature Reports
a) A 24-year-old female diagnosed with schizophrenia was resistant to daily doses of haloperidol 20 mill
carbonate 1200 mg, and lithium carbonate 900 mg plus thioridazine 300 mg. The patient appeared Cush
abdominal hair, and a 40 pound weight gain in the previous 8 months. Dehydroepiandrosterone (DHEA)
micrograms/deciliter (mcg/dL) (normal: 100 to 400 mcg/dL). Dexamethasone 1 mg orally at bedtime resu
The patient appeared calmer, more alert with improved psychotic symptoms and ability to concentrate. A
normal range (328 mcg/dL). The author concluded that elevated DHEA levels were associated with seve
antipsychotic therapy (Howard, 1992).
b) A 13-year-old male decompensated with a subsequent two-year period of emotional problems accom
barbiturates, and alcohol. His mental status included bizarre, disorganized, delusional thinking, auditory
attention to personal hygiene, agitation, and combativeness. He was diagnosed with chronic paranoid sc
undifferentiated type, and schizoaffective disorder, excited type. He was resistant to daily doses of trifluo
imipramine 100 mg. He was also resistant to combination therapy with chlorpromazine 400 mg with thiot
perphenazine 48 mg with lithium carbonate 1200 mg, clonazepam 4 mg, and carbamazepine 1200 mg d
A seven-day suppression test with dexamethasone 1 mg orally at bedtime resulted in a normal DHEA lev
and the patient was well-oriented, conversational, and was making good eye contact. Once dexamethas

and florid psychosis ensued despite "substantial amounts of psychotropic medications". DHEA increased elevated DHEA levels were associated with florid psychosis resistant to conventional antipsychotic thera

3.5.1.BJ Dehydroepiandrosterone

1) Interaction Effect: development of manic symptoms

2) Summary: A case has been reported in which concomitant dehydroepiandrosterone (DHEA) and sertralin episode in a patient with a history of bipolar disorder (Dean, 2000a). DHEA was also noted to cause mania in history of bipolar disorder (Markowitz et al, 1999). Elevated DHEA levels have been found in patients with me improvement in psychotic symptoms (Howard, 1992b). DHEA possesses proserotonergic activity which may (Majewska, 1995). DHEA is a precursor to androgenic steroids, which in high doses may precipitate mania (M for bipolar disorder or patients with a personal and/or family history of bipolar disorder should not take DHEA drug-herb interaction. Concomitant use of DHEA with selective serotonin reuptake inhibitors (SSRIs) should b precipitation of mania.

3) Severity: moderate

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: Avoid concomitant use of dehydroepiandrosterone (DHEA) and selective serotonin symptoms (i.e. agitation, anger, irritability, aggressive behavior), determine if the patient is using DHEA and c

7) Probable Mechanism: serotonergic activity of dehydroepiandrosterone, possibly increased androgen level

8) Literature Reports

a) A 31-year-old male was admitted following threats to commit suicide and injure family members. He h daily for the previous 2 to 3 weeks for depression. Sertraline had been prescribed 3 years prior when he discontinued after 2 weeks. He had also taken dehydroepiandrosterone (DHEA) 300 mg to 500 mg daily training. Following use of DHEA for a short time, he became more irritable, was not sleeping well, and be members. He also drank alcohol occasionally and reportedly had difficulty controlling his anger when into was treated with valproic acid with the dose titrated to 500 mg twice daily. The combination of DHEA, ser for the developing of the manic episode (Dean, 2000).

3.5.1.BK Delavirdine

1) Interaction Effect: increased trough delavirdine concentrations

2) Summary: Population pharmacokinetic data in 36 patients suggested that coadministration of delavirdine increase in trough delavirdine concentrations (Prod Info Rescriptor(R), 1999). The clinical significance of this

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Concurrent use of delavirdine with fluoxetine should be coadministered with caution delavirdine adverse effects.

7) Probable Mechanism: unknown

3.5.1.BL Dermatan Sulfate

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2 (R) oral capsules, delayed-release capsules, solution, 2008). Bleeding events reported have included epistax threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported wi (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: When fluoxetine and an anticoagulant are given concurrently, monitor patient for sig taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, wh (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).

7) Probable Mechanism: unknown

8) Literature Reports

a) Fluoxetine is thought to inhibit the cytochrome P450 2C9 isoenzyme (CYP2C9). This is the enzyme b warfarin, is metabolized (Riesenman, 1995). In addition, both fluoxetine and warfarin are tightly bound to protein-binding displacement of either drug is present (Prod Info Coumadin(R), 1999).

b) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bl patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks followi mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected p SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. T treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model

c) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoum

reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal blee
hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal b
subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690
for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interva
gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekam
d) In 6 reported cases, INR increased during combined fluoxetine and warfarin therapy. In a seventh ca
a woman initially treated with fluoxetine and, secondarily, started on warfarin (Woolfrey et al, 1993; Claire
e) An 83-year-old man died from cerebral hemorrhage secondary to increased warfarin concentrations.
week for atrial fibrillation with a target INR between 2 and 3. The patient's other drugs included lisinopril,
acetaminophen. After being seen for symptoms of depression, anxiety, and insomnia, the patient was giv
mg 3 to 4 times per day. Eight days later, the patient's INR increased to 4.8, and the dose of warfarin wa
was later seen for symptoms of drug delirium, including confusion, incoherence, and speaking irrationally
was discontinued. The next day the patient presented to the hospital with left-sided weakness and later c
interparenchymal hemorrhage. The authors proposed that the addition of fluoxetine to the patient's regim
warfarin and diazepam, resulting in delirium and loss of anticoagulant control (Dent & Orrock, 1997).

3.5.1.BM Desipramine

1) Interaction Effect: tricyclic antidepressant toxicity (dry mouth, urinary retention, sedation) and an increase
de pointes, cardiac arrest)

2) Summary: Tricyclic antidepressants (TCAs) and fluoxetine have been shown to prolong the QTc interval a
Prozac(R), 2001h; Marshall & Forker, 1982). Even though no formal drug interaction studies have been done
coadministration of tricyclic antidepressants and other drugs known to prolong the QTc interval, such as fluox
1999). In addition, concurrent use of fluoxetine and TCAs such as desipramine, nortriptyline, and imipramine
concentrations (Preskorn et al, 1994a; Preskorn et al, 1994a; Aranow et al, 1989a; Downs et al, 1989a; Gooc

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: The concurrent administration of fluoxetine and a tricyclic antidepressant is not recc

7) Probable Mechanism: decreased tricyclic antidepressant metabolism; additive effects on QT prolongation

8) Literature Reports

a) Fluoxetine increased the level of tricyclic antidepressants (nortriptyline, imipramine, desipramine) in 4
ratio of antidepressant level to dose increased by 109% to 486% in the patients. Three patients develope
constipation, urinary hesitancy, sedation, unstable gait) as a result of the increased levels (Aranow et al,

b) Fluoxetine statistically and clinically significantly increased desipramine concentrations in 18 healthy
added to desipramine (50 mg daily), the mean maximum concentration of desipramine increased by 278
curve increased by 342%. Desipramine trough concentrations continued to be 198% above baseline thre
same study compared pharmacokinetics of desipramine when combined with sertraline. The impact of se
short-term increases in desipramine plasma concentrations (Preskorn et al, 1994).

c) A 75-year-old female experienced symptomatic increases in her desipramine serum concentrations w
levels ranged from 109 to 150 ng/mL with oral doses of 300 mg at bedtime prior to fluoxetine therapy. Fo
to the regimen, the desipramine serum level increased to 212 ng/mL within five days. The fluoxetine dos
and the desipramine serum level was 419 ng/mL after four days. A worsening of depression and severe
desipramine serum levels. Withdrawal of fluoxetine and reduction in the desipramine dose to 200 mg dai
ng/mL within two weeks (Bell & Cole, 1988).

d) A 33-year-old depressed male developed adverse effects of dry mouth, tinnitus, and difficulties with a
40 mg daily and desipramine 150 mg daily for five weeks; fluoxetine was discontinued and the blood leve
ng/mL with resolution of clinical symptoms (Goodnick, 1989).

e) A 39-year-old female experienced symptomatic increases in her desipramine levels with concomitant
the patient's measured levels of desipramine had ranged from 148 to 160 ng/mL on a regimen of 300 mg
20 mg daily, she reported anticholinergic symptoms, sedation, and confusion with a desipramine level of
to 200 mg/day; eleven days later, the level was 244 ng/mL; the patient reported decreased energy, impa
speech, as well as an episode of nausea, dizziness, and syncope. The desipramine dose was reduced to
days. Eight days later, the desipramine level was 122 ng/mL (Downs et al, 1989).

f) Concomitant administration of fluoxetine and desipramine was reported to result in an increased desip
year-old male within 10 days of the addition of fluoxetine to the patient's regimen (Preskorn et al, 1990).

3.5.1.BN Desirudin

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and
use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2
(R) oral capsules, delayed-release capsules, solution, 2008). Bleeding events reported have included epistax
threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported wi
(Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: When fluoxetine and an anticoagulant are given concurrently, monitor patient for sig
taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, wh

(Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
7) Probable Mechanism: unknown
8) Literature Reports
a) Fluoxetine is thought to inhibit the cytochrome P450 2C9 isoenzyme (CYP2C9). This is the enzyme b warfarin, is metabolized (Riesenman, 1995). In addition, both fluoxetine and warfarin are tightly bound to protein-binding displacement of either drug is present (Prod Info Coumadin(R), 1999).
b) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bl patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks followi mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected p SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. T treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model
c) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoum reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal blee hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal b subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interva gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekam
d) In 6 reported cases, INR increased during combined fluoxetine and warfarin therapy. In a seventh ca a woman initially treated with fluoxetine and, secondarily, started on warfarin (Woolfrey et al, 1993; Claire
e) An 83-year-old man died from cerebral hemorrhage secondary to increased warfarin concentrations. week for atrial fibrillation with a target INR between 2 and 3. The patient's other drugs included lisinopril, acetaminophen. After being seen for symptoms of depression, anxiety, and insomnia, the patient was giv mg 3 to 4 times per day. Eight days later, the patient's INR increased to 4.8, and the dose of warfarin wa was later seen for symptoms of drug delirium, including confusion, incoherence, and speaking irrationally was discontinued. The next day the patient presented to the hospital with left-sided weakness and later c interparenchymal hemorrhage. The authors proposed that the addition of fluoxetine to the patient's regim warfarin and diazepam, resulting in delirium and loss of anticoagulant control (Dent & Orrock, 1997).

3.5.1.BO Desvenlafaxine

1) Interaction Effect: increased risk of serotonin syndrome (hypertension, hyperthermia, myoclonus, mental s
2) Summary: Concurrent use of desvenlafaxine and a selective serotonin reuptake inhibitor (SSRI) may resu threatening. Symptoms of serotonin syndrome may include restlessness, hallucinations, loss of coordination, increased body temperature, overreactive reflexes, nausea, vomiting, and diarrhea (Prod Info PRISTIQ(TM) c
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of desvenlafaxine and an SSRI may result in a life-threatening co agents are used together, discuss the risks of serotonin syndrome with the patient and monitor closely for sy hyperthermia, hyperreflexia, incoordination), especially during treatment initiation and dose increases (Prod I 2008).
7) Probable Mechanism: additive serotonergic effect

3.5.1.BP Dexfenfluramine

1) Interaction Effect: serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)
2) Summary: Dexfenfluramine is a nonspecific serotonin agonist that both enhances the release of serotonin therapy with dexfenfluramine and another selective serotonin reuptake inhibitor, such as fluoxetine, has the p & Mahowald, 1996). Serotonin syndrome is a hyperserotonergic state characterized by symptoms such as re status, hyperreflexia, diaphoresis, shivering, and tremor. Serious, even fatal, reactions have been reported (S be used in combination with fluoxetine (Prod Info Redux(R), 1997).
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Concurrent use of dexfenfluramine and fluoxetine may result in an additive increase system, and could result in serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status chan combination with fluoxetine or other serotonin specific reuptake inhibitors.
7) Probable Mechanism: additive serotonergic effects

3.5.1.BQ Dexketoprofen

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have incl petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info L CELEXA (R) oral tablet, solution, 2005).

3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressar hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of u than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin inc
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with TORADOL(R) oral tablets, 2007).

3.5.1.BR Dextromethorphan

1) Interaction Effect: possible dextromethorphan toxicity (nausea, vomiting, blurred vision, hallucinations) or myoclonus, mental status changes)
2) Summary: Fluoxetine strongly inhibits hepatic cytochrome P450IID6 (CYP2D6), the isoenzyme known to & Wrighton, 1993). Fluoxetine inhibits dextromethorphan metabolism (Otton et al, 1993a). With concomitant competitively inhibit each others metabolism, increasing serum levels of both drugs. Serotonin syndrome, cha changes in mental status (Sternbach, 1991e), is a possibility with the combined use of dextromethorphan and reports of serotonin syndrome associated with concurrent paroxetine and dextromethorphan therapy (Skop e
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Caution patients taking fluoxetine that an interaction could occur with dextromethor may be necessary.
7) Probable Mechanism: competitively inhibited metabolism of both agents
8) Literature Reports
a) Therapeutic doses of fluoxetine were found to potently inhibit the metabolism of dextromethorphan, a function (Otton et al, 1993). A 30 mg dose of dextromethorphan hydrobromide was given to 19 patients t addition, dextromethorphan was given to 208 known extensive metabolizers and to 15 known poor meta dextromethorphan metabolism was reduced in the fluoxetine-treated patients, it was more significantly a indicates that patients who are slow metabolizers may be at greater risk for experiencing dextromethorp fluoxetine.
b) A 32-year-old woman experienced visual hallucinations after concomitant use of fluoxetine and dextr fluoxetine 20 mg daily for 18 days prior to taking two doses of dextromethorphan. After each dose of dex and saw bright colors. These effects continued for six to eight hours. Fluoxetine was withdrawn and she
c) A 51-year old male patient with vascular disease following concurrent use of dextromethorphan and p days after self-medication with a dextromethorphan-containing cold product, the patient experienced sho confusion. Upon arrival to the hospital, the patient presented with diaphoresis, tremor, confusion, abdom administration of benzodiazepines and discontinuation of paroxetine, the patient's condition improved an 1994).

3.5.1.BS Diazepam

1) Interaction Effect: higher serum concentrations of diazepam
2) Summary: During coadministration of fluoxetine with diazepam, the fluoxetine area under the concentratio not associated with increased impairment (Lemberger et al, 1988a). Conversely, a controlled study observed performance when diazepam was added to fluoxetine (Moskowitz & Burns, 1988a). The metabolism of diaze may be inhibited by fluoxetine (Riesenman, 1995c; Shen, 1995a; Nemeroff et al, 1996b). Further case report appropriately define the pharmacokinetic effects as well as the degree of psychomotor impairment resulting f
3) Severity: minor
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Although dose adjustments are thought not to be necessary when fluoxetine and di patients for signs and symptoms of excessive diazepam concentrations (sedation, dizziness, ataxia, decreas patients, such as the elderly, it may be safer to give a lower dose of diazepam during combination therapy.
7) Probable Mechanism: inhibition of the hepatic P450 metabolism of diazepam
8) Literature Reports
a) Coadministration of fluoxetine and diazepam resulted in prolonged half-life, reduced plasma clearanc diazepam 10 mg was given alone, after a single dose of oral fluoxetine 60 mg, and after 8 daily doses of demonstrated no effect of fluoxetine on the psychomotor response to diazepam. Thus, although fluoxetir does not appear to be of clinical relevance and dosing adjustments are not required during combined the
b) Combined therapy with diazepam and fluoxetine caused an increase in the half-life of the metabolite clinically significant. Diazepam had no effect on the disposition of fluoxetine or norfluoxetine (Lemberger
c) To date, in-vitro studies have found that diazepam demethylation occurs via P450 1A2, 3A4, 2C9, an metabolized by these enzymes suggests that fluoxetine strongly inhibits 2C9, moderately inhibits 2C19 a

1995b; Nemeroff et al, 1996a; Shen, 1995).

d) In a controlled study of performance of 90 healthy volunteers, the effects of fluoxetine, amitriptyline, c Volunteers received one of six treatment combinations, and were given performance tests including a cri search task, memory test, and vigilance test. Fluoxetine alone did not affect performance, but when fluox significant increase in the divided attention tracking error and significant impairment on the vigilance test coadministration with diazepam, significant impairment was observed. On most tests, the combination of effects. The authors concluded that the combination of diazepam and an antidepressant may increase a performing other complex tasks (Moskowitz & Burns, 1988).

e) A case was reported in which an 83-year old man developed delirium after the addition of fluoxetine a furosemide, potassium, digoxin, and acetaminophen. The patient was given fluoxetine 20 mg per day an for symptoms of depression, anxiety, and insomnia. The patient then developed symptoms of drug deliriu irrational speaking. The patient also developed an increased international normalized ratio (INR), after w presented to the hospital with left-sided weakness and later died from complications of a large interparer the addition of fluoxetine to the patient's regimen resulted in increased serum levels of both warfarin and and loss of anticoagulant control (Dent & Orrock, 1997a).

3.5.1.BT Dibenzepin

1) Interaction Effect: tricyclic antidepressant toxicity (dry mouth, urinary retention, sedation) and an increase de pointes, cardiac arrest)

2) Summary: Tricyclic antidepressants (TCAs) and fluoxetine have been shown to prolong the QTc interval a Prozac(R), 2001h; Marshall & Forker, 1982). Even though no formal drug interaction studies have been done coadministration of tricyclic antidepressants and other drugs known to prolong the QTc interval, such as fluox 1999). In addition, concurrent use of fluoxetine and TCAs such as desipramine, nortriptyline, and imipramine concentrations (Preskorn et al, 1994a; Preskorn et al, 1994a; Aranow et al, 1989a; Downs et al, 1989a; Gooc

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: The concurrent administration of fluoxetine and a tricyclic antidepressant is not recc

7) Probable Mechanism: decreased tricyclic antidepressant metabolism; additive effects on QT prolongation

8) Literature Reports

a) Fluoxetine increased the level of tricyclic antidepressants (nortriptyline, imipramine, desipramine) in 4 ratio of antidepressant level to dose increased by 109% to 486% in the patients. Three patients develope constipation, urinary hesitancy, sedation, unstable gait) as a result of the increased levels (Aranow et al,

b) Fluoxetine statistically and clinically significantly increased desipramine concentrations in 18 healthy added to desipramine (50 mg daily), the mean maximum concentration of desipramine increased by 278 curve increased by 342%. Desipramine trough concentrations continued to be 198% above baseline thre same study compared pharmacokinetics of desipramine when combined with sertraline. The impact of se short-term increases in desipramine plasma concentrations (Preskorn et al, 1994).

c) A 75-year-old female experienced symptomatic increases in her desipramine serum concentrations w levels ranged from 109 to 150 ng/mL with oral doses of 300 mg at bedtime prior to fluoxetine therapy. Fc to the regimen, the desipramine serum level increased to 212 ng/mL within five days. The fluoxetine dos and the desipramine serum level was 419 ng/mL after four days. A worsening of depression and severe desipramine serum levels. Withdrawal of fluoxetine and reduction in the desipramine dose to 200 mg dai ng/mL within two weeks (Bell & Cole, 1988).

d) A 33-year-old depressed male developed adverse effects of dry mouth, tinnitus, and difficulties with a 40 mg daily and desipramine 150 mg daily for five weeks; fluoxetine was discontinued and the blood leve ng/mL with resolution of clinical symptoms (Goodnick, 1989).

e) A 39-year-old female experienced symptomatic increases in her desipramine levels with concomitant the patient's measured levels of desipramine had ranged from 148 to 160 ng/mL on a regimen of 300 mg 20 mg daily, she reported anticholinergic symptoms, sedation, and confusion with a desipramine level of to 200 mg/day; eleven days later, the level was 244 ng/mL; the patient reported decreased energy, impa speech, as well as an episode of nausea, dizziness, and syncope. The desipramine dose was reduced t days. Eight days later, the desipramine level was 122 ng/mL (Downs et al, 1989).

f) Concomitant administration of fluoxetine and desipramine was reported to result in an increased desip year-old male within 10 days of the addition of fluoxetine to the patient's regimen (Preskorn et al, 1990).

3.5.1.BU Diclofenac

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control anc use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have incl petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info L CELEXA (R) oral tablet, solution, 2005).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent
Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressar
hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of u
than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose
confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of
upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin inc
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with
TORADOL(R) oral tablets, 2007).

3.5.1.BV Dicumarol

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control anc
use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2
(R) oral capsules, delayed-release capsules, solution, 2008). Bleeding events reported have included epistax
threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported wi
(Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When fluoxetine and an anticoagulant are given concurrently, monitor patient for sig
taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, wi
(Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
7) Probable Mechanism: unknown
8) Literature Reports

a) Fluoxetine is thought to inhibit the cytochrome P450 2C9 isoenzyme (CYP2C9). This is the enzyme b
warfarin, is metabolized (Riesenman, 1995). In addition, both fluoxetine and warfarin are tightly bound to
protein-binding displacement of either drug is present (Prod Info Coumadin(R), 1999).

b) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bl
patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks followi
mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected p
SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients
treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4
corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively.
treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only
bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI
dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding
exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model

c) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoum
reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal blee
hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal b
subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690
for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interva
gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekam

d) In 6 reported cases, INR increased during combined fluoxetine and warfarin therapy. In a seventh ca
a woman initially treated with fluoxetine and, secondarily, started on warfarin (Woolfrey et al, 1993; Claire

e) An 83-year-old man died from cerebral hemorrhage secondary to increased warfarin concentrations.
week for atrial fibrillation with a target INR between 2 and 3. The patient's other drugs included lisinopril,
acetaminophen. After being seen for symptoms of depression, anxiety, and insomnia, the patient was giv
mg 3 to 4 times per day. Eight days later, the patient's INR increased to 4.8, and the dose of warfarin wa
was later seen for symptoms of drug delirium, including confusion, incoherence, and speaking irrationally
was discontinued. The next day the patient presented to the hospital with left-sided weakness and later c
interparenchymal hemorrhage. The authors proposed that the addition of fluoxetine to the patient's regim
warfarin and diazepam, resulting in delirium and loss of anticoagulant control (Dent & Orrock, 1997).

3.5.1.BW Diflunisal

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control anc
use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have incl
petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info L
CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent
Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressar

hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of u
than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose
confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of
upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin inc
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with
TORADOL(R) oral tablets, 2007).

3.5.1.BX Digitoxin

1) Interaction Effect: an increased risk of digitoxin toxicity (nausea, vomiting, arrhythmias)
2) Summary: The administration of fluoxetine to a patient taking digitoxin, also tightly bound to plasma protei
digitoxin (Prod Info Prozac(R), 1999c).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Patients receiving fluoxetine and digitoxin therapy concomitantly should be monitor
signs and symptoms of digitoxin toxicity.
7) Probable Mechanism: unknown

3.5.1.BY Digoxin

1) Interaction Effect: an increased risk of digoxin toxicity (nausea, vomiting, arrhythmias)
2) Summary: One case report describes a 93-year-old female stabilized on digoxin who experienced toxic le
her regimen for depression. Rechallenge with fluoxetine again caused her digoxin levels to increase dramatic
not clear, it could be related to displacement of digoxin from binding sites or reduced clearance of digoxin (Le
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Patients receiving fluoxetine and digoxin therapy concomitantly should be monitore
signs and symptoms of digoxin toxicity, including anorexia.
7) Probable Mechanism: unknown
8) Literature Reports
a) Digoxin 0.125 mg daily was being administered to a 93-year-old female for congestive heart failure ar
ranged from 1.0 to 1.4 nmol/L during the two months preceding the initiation of fluoxetine 10 mg daily. W
anorexia. Her digoxin level measured 4.2 nmol/L, while renal function and potassium levels remained un
discontinued, and her digoxin level returned to normal in five days with resolution of the anorexia. During
ranged from 0.9 nmol/L to 1.4 nmol/L. Because the symptoms of depression persisted, fluoxetine was ag
serum level was closely monitored. After two days of fluoxetine therapy, the digoxin level increased to 2.
Renal function remained unchanged, as did serum electrolytes. The patient again experienced anorexia,
(Leibovitz et al, 1998).

3.5.1.BZ Dihydroergotamine

1) Interaction Effect: an increased risk of ergotism (nausea, vomiting, vasospastic ischemia)
2) Summary: Because of the potential for serious toxicity including vasospasm that can occur with increased
concurrent use of fluoxetine and ergot derivatives is contraindicated. Fluoxetine and ergot derivatives are bot
enzymes, and the competition for metabolism could result in an increased plasma concentration of the ergot
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: The concurrent use of fluoxetine and ergot derivatives is contraindicated.
7) Probable Mechanism: inhibition of cytochrome P450 3A4- mediated ergot metabolism by fluoxetine

3.5.1.CA Dipyridamole

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and
use of SSRIs and antiplatelet agents has been associated with an increased risk of bleeding. Bleeding events
hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008;
release capsules, solution, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an antiplatelet agent are given concurrently, monitor patient for
oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 200
7) Probable Mechanism: unknown

3.5.1.CB Dipyrone

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and
use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have incl
petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info L

CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressar hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of u than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin inc
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with TORADOL(R) oral tablets, 2007).

3.5.1.CC Disopyramide

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, the coadministration of Class prolong the QTc interval is not recommended (Prod Info Quinaglute Dura-tabs(R), 1999). Fluoxetine has dem (Prod Info Prozac(R), 2001z).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of class Ia antiarrhythmic agents and agents that pro recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.CD Dofetilide

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, the coadministration of Class prolong the QTc interval is not recommended (Allen et al, 2002; Prod Info Tikosyn(TM) dofetilide capsules, 1 been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Prozac(R), 2001a).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of class III antiarrhythmic agents and agents that pro recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.CE Dolasetron

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Though citing no data, the manufacturer of dolasetron recommends caution if dolasetron is adr the QTc interval (Prod Info Anzemet(R), 1997). Fluoxetine has been shown to prolong the QTc interval at the Prozac(R), 2001y).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of fluoxetine and dolasetron is not recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.CF Doxepin

1) Interaction Effect: tricyclic antidepressant toxicity (dry mouth, urinary retention, sedation) and an increase de pointes, cardiac arrest)
2) Summary: Tricyclic antidepressants (TCAs) and fluoxetine have been shown to prolong the QTc interval a Prozac(R), 2001h; Marshall & Forker, 1982). Even though no formal drug interaction studies have been done coadministration of tricyclic antidepressants and other drugs known to prolong the QTc interval, such as fluox 1999). In addition, concurrent use of fluoxetine and TCAs such as desipramine, nortriptyline, and imipramine concentrations (Preskorn et al, 1994a; Preskorn et al, 1994a; Aranow et al, 1989a; Downs et al, 1989a; Gooc
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: The concurrent administration of fluoxetine and a tricyclic antidepressant is not rec
7) Probable Mechanism: decreased tricyclic antidepressant metabolism; additive effects on QT prolongation
8) Literature Reports
a) Fluoxetine increased the level of tricyclic antidepressants (nortriptyline, imipramine, desipramine) in 4 ratio of antidepressant level to dose increased by 109% to 486% in the patients. Three patients develope constipation, urinary hesitancy, sedation, unstable gait) as a result of the increased levels (Aranow et al,

b) Fluoxetine statistically and clinically significantly increased desipramine concentrations in 18 healthy added to desipramine (50 mg daily), the mean maximum concentration of desipramine increased by 278 curve increased by 342%. Desipramine trough concentrations continued to be 198% above baseline thre same study compared pharmacokinetics of desipramine when combined with sertraline. The impact of s short-term increases in desipramine plasma concentrations (Preskorn et al, 1994).
c) A 75-year-old female experienced symptomatic increases in her desipramine serum concentrations w levels ranged from 109 to 150 ng/mL with oral doses of 300 mg at bedtime prior to fluoxetine therapy. Fo to the regimen, the desipramine serum level increased to 212 ng/mL within five days. The fluoxetine dos and the desipramine serum level was 419 ng/mL after four days. A worsening of depression and severe desipramine serum levels. Withdrawal of fluoxetine and reduction in the desipramine dose to 200 mg dai ng/mL within two weeks (Bell & Cole, 1988).
d) A 33-year-old depressed male developed adverse effects of dry mouth, tinnitus, and difficulties with a 40 mg daily and desipramine 150 mg daily for five weeks; fluoxetine was discontinued and the blood leve ng/mL with resolution of clinical symptoms (Goodnick, 1989).
e) A 39-year-old female experienced symptomatic increases in her desipramine levels with concomitant the patient's measured levels of desipramine had ranged from 148 to 160 ng/mL on a regimen of 300 mg 20 mg daily, she reported anticholinergic symptoms, sedation, and confusion with a desipramine level of to 200 mg/day; eleven days later, the level was 244 ng/mL; the patient reported decreased energy, impa speech, as well as an episode of nausea, dizziness, and syncope. The desipramine dose was reduced t days. Eight days later, the desipramine level was 122 ng/mL (Downs et al, 1989).
f) Concomitant administration of fluoxetine and desipramine was reported to result in an increased desip year-old male within 10 days of the addition of fluoxetine to the patient's regimen (Preskorn et al, 1990).

3.5.1.CG Droperidol

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Droperidol has been shown to prolong the QTc interval at the recommended therapeutic dose. have been done, the coadministration of droperidol and other drugs known to prolong the QTc interval, includ Inapsine(TM), 2001; Prod Info Prozac(R), 2001ab).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of droperidol and fluoxetine is not recommended.
7) Probable Mechanism: additive cardiac effects

3.5.1.CH Droxicam

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have incl petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info L CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressar hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of u than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin inc
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with TORADOL(R) oral tablets, 2007).

3.5.1.CI Duloxetine

1) Interaction Effect: increased duloxetine and fluoxetine serum concentrations and an increased risk of sero
2) Summary: Duloxetine is a selective serotonin and norepinephrine reuptake inhibitor (SSNRI). The concom is not recommended due to the potential for serotonin syndrome. In addition, the coadministration of duloxeti bioavailability of either drug, increasing the risk of serious adverse events. Duloxetine and fluoxetine are both of CYP2D6. Coadministration of duloxetine 40 mg once daily with another SSRI (the potent CYP2D6 inhibitor increase in the serum concentration of duloxetine (Prod Info CYMBALTA(R) delayed-release oral capsules, 2
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: The concomitant use of duloxetine and fluoxetine is not recommended due to the p Additionally, concomitant use has resulted in increased duloxetine and fluoxetine serum levels (Prod Info CY 2008).

7) Probable Mechanism: fluoxetine inhibition of CYP2D6-mediated duloxetine metabolism; additive serotone

3.5.1.CJ Eletriptan

1) Interaction Effect: an increased risk of serotonin syndrome

2) Summary: There have been case reports of weakness, hyperreflexia, and incoordination following concon 1 (5HT-1) agonist, and a serotonin specific reuptake inhibitor (SSRI) (Prod Info Imitrex(R) Nasal Spray, 2003) similar interaction between SSRIs and eletriptan may occur (Prod Info Relpax(R), 2003). Concurrent use of a syndrome which may be life-threatening. Symptoms of serotonin syndrome may include restlessness, halluci rapid changes in blood pressure, increased body temperature, overreactive reflexes, nausea, vomiting, and c may be commonly used intermittently and that either the triptan or the SSRI may be prescribed by a different syndrome with patients who are prescribed this combination and monitor them closely for symptoms of seroto Administration, 2006).

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Coadministration of a triptan, such as eletriptan, and an SSRI may result in a life-th Be aware that triptans may be commonly used intermittently and that either the triptan or the SSRI may be pr are used together, discuss the risks of serotonin syndrome with the patient and monitor closely for symptoms hyperthermia, hyperreflexia, incoordination).

7) Probable Mechanism: additive pharmacologic effects resulting in excessive serotonergic stimulation

3.5.1.CK Enflurane

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Even though no formal drug interaction studies have been done, enflurane should be coadmini known to prolong the QTc interval, including fluoxetine (Owens, 2001c; Prod Info Prozac(R), 2001n).

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of enflurane with other agents that can prolong the Q recommended.

7) Probable Mechanism: additive effects on QT prolongation

3.5.1.CL Enoxaparin

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2 (R) oral capsules, delayed-release capsules, solution, 2008). Bleeding events reported have included epistax threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported wi (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: When fluoxetine and an anticoagulant are given concurrently, monitor patient for sig taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, wh (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).

7) Probable Mechanism: unknown

8) Literature Reports

a) Fluoxetine is thought to inhibit the cytochrome P450 2C9 isoenzyme (CYP2C9). This is the enzyme b warfarin, is metabolized (Riesenman, 1995). In addition, both fluoxetine and warfarin are tightly bound to protein-binding displacement of either drug is present (Prod Info Coumadin(R), 1999).

b) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bl patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks followi mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected p SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. T treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model

c) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoum reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal blee hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal b subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interva gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekam

d) In 6 reported cases, INR increased during combined fluoxetine and warfarin therapy. In a seventh ca a woman initially treated with fluoxetine and, secondarily, started on warfarin (Woolfrey et al, 1993; Claire

e) An 83-year-old man died from cerebral hemorrhage secondary to increased warfarin concentrations. week for atrial fibrillation with a target INR between 2 and 3. The patient's other drugs included lisinopril, acetaminophen. After being seen for symptoms of depression, anxiety, and insomnia, the patient was giv mg 3 to 4 times per day. Eight days later, the patient's INR increased to 4.8, and the dose of warfarin wa was later seen for symptoms of drug delirium, including confusion, incoherence, and speaking irrationally was discontinued. The next day the patient presented to the hospital with left-sided weakness and later c interparenchymal hemorrhage. The authors proposed that the addition of fluoxetine to the patient's regim warfarin and diazepam, resulting in delirium and loss of anticoagulant control (Dent & Orrock, 1997).

3.5.1.CM Epoprostenol

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and use of SSRIs and antiplatelet agents has been associated with an increased risk of bleeding. Bleeding events hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008; release capsules, solution, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an antiplatelet agent are given concurrently, monitor patient for oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 200
7) Probable Mechanism: unknown

3.5.1.CN Eptifibatide

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and use of SSRIs and antiplatelet agents has been associated with an increased risk of bleeding. Bleeding events hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008; release capsules, solution, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an antiplatelet agent are given concurrently, monitor patient for oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 200
7) Probable Mechanism: unknown

3.5.1.CO Ergoloid Mesylates

1) Interaction Effect: an increased risk of ergotism (nausea, vomiting, vasospastic ischemia)
2) Summary: Because of the potential for serious toxicity including vasospasm that can occur with increased concurrent use of fluoxetine and ergot derivatives is contraindicated. Fluoxetine and ergot derivatives are bot enzymes, and the competition for metabolism could result in an increased plasma concentration of the ergot
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: The concurrent use of fluoxetine and ergot derivatives is contraindicated.
7) Probable Mechanism: inhibition of cytochrome P450 3A4- mediated ergot metabolism by fluoxetine

3.5.1.CP Ergonovine

1) Interaction Effect: an increased risk of ergotism (nausea, vomiting, vasospastic ischemia)
2) Summary: Because of the potential for serious toxicity including vasospasm that can occur with increased concurrent use of fluoxetine and ergot derivatives is contraindicated. Fluoxetine and ergot derivatives are bot enzymes, and the competition for metabolism could result in an increased plasma concentration of the ergot
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: The concurrent use of fluoxetine and ergot derivatives is contraindicated.
7) Probable Mechanism: inhibition of cytochrome P450 3A4- mediated ergot metabolism by fluoxetine

3.5.1.CQ Ergotamine

1) Interaction Effect: an increased risk of ergotism (nausea, vomiting, vasospastic ischemia)
2) Summary: Because of the potential for serious toxicity including vasospasm that can occur with increased concurrent use of fluoxetine and ergot derivatives is contraindicated. Fluoxetine and ergot derivatives are bot enzymes, and the competition for metabolism could result in an increased plasma concentration of the ergot
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: The concurrent use of fluoxetine and ergot derivatives is contraindicated.
7) Probable Mechanism: inhibition of cytochrome P450 3A4- mediated ergot metabolism by fluoxetine

3.5.1.CR Erythromycin

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Erythromycin significantly increased the mean QTc interval versus baseline in a retrospective s Erythromycin has demonstrated QTc prolongation in combination with other drugs that prolong the QT interva associated with QT prolongation (Prod Info Prozac(R), 2003a). Caution is advised with coadministration of dr

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Caution is advised if erythromycin and fluoxetine are used concomitantly. Monitor Q treatment.

7) Probable Mechanism: additive effects on QT prolongation

8) Literature Reports

a) Erythromycin significantly increased the QTc interval compared with baseline in a retrospective study milligrams or 1 gram four times daily, with a mean of 15 doses received. Patients (n equal to 9) who rece increases in QT interval of 15% or greater. For all patients, the mean QTc interval increased from 432 m less than 0.01). In patients with delayed repolarization at baseline (n equal to 9), the QTc interval increas 0.01). In patients with heart disease (n equal to 30), all experienced an increase in QTc interval (mean o patients without heart disease (p less than 0.05). In 5 patients (10%), the QTc interval was severely prol pointes attributed to erythromycin. Of 16 patients receiving cotrimoxazole concomitantly, 8 developed QT Bauman, 1995).

3.5.1.CS Eszopiclone

1) Interaction Effect: decreased psychomotor function

2) Summary: Coadministration of 3 mg eszopiclone and 10 mg olanzapine resulted in the pharmacodynamic Substitution Test scores, a measurement of psychomotor function. No pharmacokinetic interactions were obs psychomotor function (Prod Info LUNESTA(TM), 2004).

3) Severity: minor

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Monitor patients for decreased psychomotor function. Adjust dose accordingly or co

7) Probable Mechanism: unknown

3.5.1.CT Etodolac

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have incl petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info L CELEXA (R) oral tablet, solution, 2005).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressar hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of up than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin inc

b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with TORADOL(R) oral tablets, 2007).

3.5.1.CU Etofenamate

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have incl petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info L CELEXA (R) oral tablet, solution, 2005).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressar hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of up

than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose
confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of
upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin inc
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with
TORADOL(R) oral tablets, 2007).

3.5.1.CV Etoricoxib

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control anc
use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have incl
petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info L
CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent
Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressar
hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of u
than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose
confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of
upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin inc
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with
TORADOL(R) oral tablets, 2007).

3.5.1.CW Felbinac

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control anc
use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have incl
petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info L
CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent
Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressar
hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of u
than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose
confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of
upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin inc
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with
TORADOL(R) oral tablets, 2007).

3.5.1.CX Fenbufen

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control anc
use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have incl
petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info L
CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent
Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressar
hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of u
than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose
confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of
upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin inc
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with
TORADOL(R) oral tablets, 2007).

3.5.1.CY Fenfluramine

1) Interaction Effect: serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)
2) Summary: Fenfluramine is a nonspecific serotonin agonist that both enhances the release of serotonin an therapy with fenfluramine and another selective serotonin reuptake inhibitor, such as fluoxetine, has the pote Mahowald, 1996a). Serotonin syndrome is a hyperserotonergic state characterized by symptoms such as res hyperreflexia, diaphoresis, shivering, and tremor. Serious, even fatal, reactions have been reported (Sternba fenfluramine should not be used in combination with fluoxetine.
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Concurrent use of fenfluramine and fluoxetine may result in an additive increase in and could result in serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes). Fe with fluoxetine or other serotonin specific reuptake inhibitors.
7) Probable Mechanism: additive serotonergic effects

3.5.1.CZ Fenoprofen

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control anc use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have incl petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info L CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressar hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of u than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin inc
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with TORADOL(R) oral tablets, 2007).

3.5.1.DA Fentiazac

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control anc use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have incl petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info L CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressar hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of u than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin inc
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with TORADOL(R) oral tablets, 2007).

3.5.1.DB Flecainide

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, the coadministration of Class prolong the QTc interval is not recommended (Prod Info Tambocor(R) flecainide acetate, 1998). Fluoxetine h recommended therapeutic dose (Prod Info Prozac(R), 2001w).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of class I antiarrhythmic agents and agents that prolc recommended.

7) Probable Mechanism: additive effects on QT prolongation

3.5.1.DC Floctafenine

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have incl petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info L CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressar hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of u than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin inc
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with TORADOL(R) oral tablets, 2007).

3.5.1.DD Fluconazole

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Case reports have described QT prolongation and torsades de pointes associated with flucona 1999). Fluoxetine has been shown to prolong the QTc interval at the recommended therapeutic dose (Prod In drug interaction studies have been done, caution is advised if drugs known to prolong the QT interval are use
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Caution is advised if fluconazole and fluoxetine are used concomitantly.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.DE Flufenamic Acid

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have incl petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info L CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressar hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of u than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin inc
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with TORADOL(R) oral tablets, 2007).

3.5.1.DF Fluphenazine

1) Interaction Effect: an increased risk of developing acute parkinsonism
2) Summary: The development of acute, severe parkinsonism has been observed in a patient receiving fluph for depression. Upon discontinuation of fluoxetine, the parkinsonism resolved. A similar interaction has been combination with paroxetine or sertraline (Kurlan, 1998a).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor patients receiving concurrent therapy with fluphenazine and fluoxetine for t Therapy with fluoxetine may need to be discontinued.
7) Probable Mechanism: inhibition of cytochrome P450-mediated fluphenazine metabolism by fluoxetine
8) Literature Reports
a) A 63-year-old female with chronic, multiple motor and vocal tics was successfully treated with fluphen

for depression failed, the patient was started on fluoxetine 20 mg daily. After two weeks, she developed
resting tremor, rigidity, bradykinesia, postural imbalance, and stooped posture. The parkinsonism resolve
fluphenazine and the fluoxetine, but the tics reappeared (Kurlan, 1998).

3.5.1.DG Flurbiprofen

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and
use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have incl
petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info L
CELEXA (R) oral tablet, solution, 2005).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent
Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressar
hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of u
than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose
confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of
upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin inc

b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with
TORADOL(R) oral tablets, 2007).

3.5.1.DH Fluvoxamine

1) Interaction Effect: an increased risk of olanzapine adverse effects

2) Summary: Fluvoxamine inhibits cytochrome P450 1A2 enzymes and may inhibit olanzapine elimination (P
significance of this interaction is unknown since olanzapine is metabolized by multiple enzyme systems.

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Monitor patients for excessive olanzapine adverse effects (orthostatic hypotension,

7) Probable Mechanism: inhibition of olanzapine elimination

8) Literature Reports

a) A patient experienced elevated olanzapine plasma levels during coadministration of fluvoxamine. The
for several months for schizophrenia and secondary depression. She appeared to move rigidly, had a sli
Olanzapine concentration was 120 mcg/L and fluvoxamine concentration was 70 mcg/L. Olanzapine was
mg/day. Fourteen days after the last decrease in dose, olanzapine plasma levels were 38 mcg/L. Tremor
persisted. Fluvoxamine was replaced by paroxetine which resulted in paroxetine concentration of 0.027 r
(de Jong et al, 2001).

b) Addition of fluvoxamine to olanzapine therapy may result in olanzapine-induced side effects or intoxic
being treated for not less than 3 months with 10-20 mg/day of olanzapine. The dose of olanzapine was u
study and remained stable throughout the study period. Fluvoxamine 100 mg/day was added to olanzapi
and continued for 8 weeks. Olanzapine concentrations increased during fluvoxamine treatment 1.58-fold
week 4, and 1.81-fold from week 0 to week 8. Percentage change from week 0 to week 8 ranged from 1
demethylated metabolite were not significantly changed. Even though all eight patients had higher olanz
than on week 1, the ratio of increase of olanzapine blood serum concentrations from week 0 to week 8 d
serum levels (p greater than 0.05). This study confirmed that the addition of fluvoxamine to a stable dose
concentrations in the blood serum. Combined olanzapine and fluvoxamine should be used cautiously an
monitoring to avoid olanzapine-induced side effects or intoxication (Hiemke et al, 2002).

3.5.1.DI Fondaparinux

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and
use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2
(R) oral capsules, delayed-release capsules, solution, 2008). Bleeding events reported have included epistax
threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported wi
(Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: When fluoxetine and an anticoagulant are given concurrently, monitor patient for sig
taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, wh
(Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).

7) Probable Mechanism: unknown

8) Literature Reports

a) Fluoxetine is thought to inhibit the cytochrome P450 2C9 isoenzyme (CYP2C9). This is the enzyme b

warfarin, is metabolized (Riesenman, 1995). In addition, both fluoxetine and warfarin are tightly bound to protein-binding displacement of either drug is present (Prod Info Coumadin(R), 1999).
b) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bl patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks followi mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected p SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. T treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model
c) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoum reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal blee hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal b subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interva gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekam
d) In 6 reported cases, INR increased during combined fluoxetine and warfarin therapy. In a seventh ca a woman initially treated with fluoxetine and, secondarily, started on warfarin (Woolfrey et al, 1993; Claire
e) An 83-year-old man died from cerebral hemorrhage secondary to increased warfarin concentrations. week for atrial fibrillation with a target INR between 2 and 3. The patient's other drugs included lisinopril, acetaminophen. After being seen for symptoms of depression, anxiety, and insomnia, the patient was giv mg 3 to 4 times per day. Eight days later, the patient's INR increased to 4.8, and the dose of warfarin wa was later seen for symptoms of drug delirium, including confusion, incoherence, and speaking irrationally was discontinued. The next day the patient presented to the hospital with left-sided weakness and later c interparenchymal hemorrhage. The authors proposed that the addition of fluoxetine to the patient's regim warfarin and diazepam, resulting in delirium and loss of anticoagulant control (Dent & Orrock, 1997).

3.5.1.DJ Foscarnet

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Foscarnet can prolong the QT interval in some patients, which may result in ventricular tachyca pointes. Because fluoxetine may also prolong the QT interval and increase the risk of arrhythmias, the concu not recommended (Prod Info Prozac(R), 2001t; Prod Info Foscavir(R), 1998).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of foscarnet and fluoxetine is not recommended.
7) Probable Mechanism: additive cardiac effects

3.5.1.DK Fosphenytoin

1) Interaction Effect: an increased risk of phenytoin toxicity (ataxia, hyperreflexia, nystagmus, tremor)
2) Summary: Fosphenytoin is a prodrug of phenytoin and the same interactions that occur with phenytoin are Cerebyx(R), 1999). Several case reports indicate that concurrent use of fluoxetine and phenytoin can result in leading to toxicity (FDA, 1994c; Jalil, 1992c; Woods et al, 1994a). Alternatively, patients who are stabilized on experience subtherapeutic concentrations of phenytoin and loss of seizure control when fluoxetine is disconti
3) Severity: moderate
4) Onset: delayed
5) Substantiation: established
6) Clinical Management: Monitor phenytoin serum levels with the addition of fluoxetine and periodically there dosage may be required with concomitant therapy. Serum levels of phenytoin should be monitored following because of the long half-life of fluoxetine, decreases in phenytoin levels may not be clinically significant for a
7) Probable Mechanism: decreased phenytoin metabolism
8) Literature Reports
a) Twenty-three reported cases of fluoxetine-phenytoin interactions that resulted in large increases in se phenytoin toxicity were evaluated. On the average, the adverse effects began within 2 weeks after fluoxe The average increase in plasma levels in 9 evaluable cases was 161% (range 75 to 309%) and the maxi evaluable cases ranged from 22 to 53.5 mcg/mL (therapeutic level, 10 to 20 mcg/mL) (FDA, 1994b).
b) An 84-year-old woman was stabilized on phenytoin 300 mg daily; after two months of treatment, fluox increased to 40 mg daily after 10 days (Jalil, 1992b). Within five days of starting fluoxetine, she develope mental status; her phenytoin serum level had increased from 15 to 35 mcg/mL. Both phenytoin and fluox symptoms of toxicity abated. Four weeks later she was rechallenged with the same dose of fluoxetine wi
c) In another case, a 57-year-old woman who had been stabilized on phenytoin 400 mg/d for a year (se mg/d (Jalil, 1992b). Ten days later she developed vomiting, vertigo, trunk ataxia, limb dysmetria, and mu serum level was 47 mcg/mL. Fluoxetine was discontinued and all signs and symptoms of toxicity disappe fluoxetine, the phenytoin serum level was 20 mcg/mL.
d) A 42-year-old male with a history of grand mal seizures and aggressive behavior was receiving pheny daily without resolution of his problems. His phenytoin level was 2.0 ng/mL and his dose was subsequen

daily was added for aggression, and the patient experienced resolution of his behavioral problems and a level ranged between 10.9 ng/mL and 15.7 ng/mL during fluoxetine therapy. However, the patient discon experienced a recurrence of problems. Phenytoin concentration was measured at 6.6 ng/mL six weeks a change in his phenytoin dose. This case report illustrates the need for close monitoring of phenytoin leve since subtherapeutic levels of phenytoin may result if doses of phenytoin are not readjusted following the 1999b).

3.5.1.DL Frovatriptan

1) Interaction Effect: an increased risk of serotonin syndrome

2) Summary: There have been case reports of weakness, hyperreflexia, and incoordination following concon 1 (5HT-1) agonist, and a serotonin specific reuptake inhibitor (SSRI) (Prod Info Imitrex(R) Nasal Spray, 2003) similar interaction between SSRIs and frovatriptan may occur (Prod Info Frova(R), 2004). Concurrent use of f syndrome which may be life-threatening. Symptoms of serotonin syndrome may include restlessness, halluci rapid changes in blood pressure, increased body temperature, overreactive reflexes, nausea, vomiting, and c may be commonly used intermittently and that either the triptan or the SSRI may be prescribed by a different syndrome with patients who are prescribed this combination and monitor them closely for symptoms of seroto Administration, 2006).

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Coadministration of a triptan, such as frovatriptan, and an SSRI may result in a life- Be aware that triptans may be commonly used intermittently and that either the triptan or the SSRI may be pr are used together, discuss the risks of serotonin syndrome with the patient and monitor closely for symptoms hyperthermia, hyperreflexia, incoordination).

7) Probable Mechanism: additive pharmacologic effects resulting in excessive serotonergic stimulation

3.5.1.DM Furazolidone

1) Interaction Effect: weakness, hyperreflexia, and incoordination

2) Summary: Although not its primary mechanism of action, furazolidone has monoamine oxidase inhibitor a reactions have been reported in patients receiving selective serotonin reuptake inhibitors (SSRI) in combinati Hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mer progressing to delirium and coma have been reported. Furazolidone should not be used in combination with a discontinuing therapy with a MAOI (Prod Info Furoxone(R), 1999).

3) Severity: contraindicated

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: If concurrent therapy with furazolidone and a selective serotonin reuptake inhibitor (monitor the patient for signs of serotonergic excess (mental status changes, diaphoresis, fever, weakness, hy

7) Probable Mechanism: additive pharmacologic effects resulting in excessive serotonergic stimulation

3.5.1.DN Galantamine

1) Interaction Effect: increased galantamine plasma concentrations

2) Summary: Based upon in vitro studies, the major enzymes involved in galantamine metabolism are CYP3 of CYP2D6. In a population pharmacokinetic analysis using a database of 852 Alzheimer's disease patients, fluoxetine (N=48), demonstrated a 25-33% decrease in galantamine clearance. The resulting plasma concen caution when it is coadministered with fluoxetine. Monitor for galantamine toxicity including anorexia, nausea, gastrointestinal bleeding (Prod Info RAZADYNE(R) ER extended release oral capsules, oral tablets, oral solu

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: Increased galantamine plasma concentrations may result from fluoxetine inhibition (Monitor for galantamine toxicity including anorexia, nausea, vomiting, dizziness, arrhythmias, or gastrointestin extended release oral capsules, oral tablets, oral solution, 2007).

7) Probable Mechanism: inhibition of cytochrome CYP2D6-mediated galantamine metabolism

3.5.1.DO Gemifloxacin

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Gemifloxacin should be avoided in patients receiving fluoxetine. Gemifloxacin has the potential (Prod Info Factive(R), 2003). Additive effects on QT prolongation may occur with the concomitant use of fluox

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: The concurrent administration of two drugs that prolong the QT interval, such as ge

7) Probable Mechanism: additive effects on QT prolongation

3.5.1.DP Ginkgo

1) Interaction Effect: increased risk of serotonin syndrome (hypertension, hyperthermia, myoclonus, mental s

2) Summary: The addition of Ginkgo biloba and/or St. John's Wort to therapy with buspirone and fluoxetine r

case report (Spinella & Eaton, 2002a). It is unclear if Ginkgo or St. John's Wort, the combination of both, or o
Theoretically, Ginkgo may increase the risk of serotonin syndrome when taken with selective serotonin reupta
especially when ginkgo is taken to counteract sexual dysfunction associated with SSRIs. Ginkgo may inhibit
al, 1996), and has demonstrated serotonergic activity in animals (Ramassamy et al, 1992) which might increa
is combined with SSRIs. The potential MAO inhibitory activity of ginkgo is questionable. A human study did n
consumption (Fowler et al, 2000). Ginkgo biloba extract inhibited MAO-A/MAO-B in the rat brain in vitro (Slole
human platelets in vitro (White et al, 1996). No significant MAO inhibition was found in mice following oral cor

3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor patients closely for symptoms of serotonin syndrome if ginkgo is combined
(SSRIs).
7) Probable Mechanism: additive pharmacologic effects resulting in excessive serotonergic stimulation
8) Literature Reports
a) A 42-year-old female experienced symptoms consistent with a mixed hypomanic episode following co
biloba, and St. John's Wort. The symptoms resolved following discontinuation of Ginkgo and St. John's V
depression following a mild traumatic brain injury with fluoxetine 20 milligrams (mg) twice daily and busp
presentation, buspirone was increased to 20 mg twice daily for persistent anxiety and the patient began
Wort in unspecified doses. Melatonin was considered unlikely to have contributed to her symptoms. Gink
possible contributors since they may potentiate antidepressants, and considering the temporal relationsh
symptoms and discontinuation of the herbs and resolution of symptoms. However, the brain injury was c
Eaton, 2002).

3.5.1.DQ Halofantrine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Halofantrine can prolong the QT interval in some patients, which may result in ventricular tachy
pointes. Because fluoxetine has demonstrated QT prolongation at therapeutic doses and may increase the ris
of halofantrine with fluoxetine is not recommended (Prod Info Prozac(R), 2001i; Prod Info Halfan(R), 1998).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of halofantrine and fluoxetine is not recommended.
7) Probable Mechanism: additive cardiac effects

3.5.1.DR Haloperidol

1) Interaction Effect: an increased risk of parkinsonism (cogwheeling rigidity, unstable gait)
2) Summary: A patient receiving haloperidol experienced extreme parkinsonism following the addition of olan
pharmacokinetic interaction between olanzapine, a weak cytochrome P450 2D6 (CYP2D6) inhibitor, and halo
Pharmacodynamically, the small amount of dopamine (D2) blockade from olanzapine may have been enough
(Gomberg, 1999a).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Patients should be closely monitored for signs and symptoms of increased parkinso
to haloperidol therapy. Doses of haloperidol may need to be decreased.
7) Probable Mechanism: competitive inhibition of cytochrome P450 2D6-mediated haloperidol metabolism; ir
8) Literature Reports
a) A 67-year-old hospitalized male with bipolar disorder who had stopped taking his medications was re
1 mg nightly, and valproate 750 mg twice daily. He had been experiencing some mild parkinsonian symp
worsen when haloperidol was reinstituted. Following stabilization on this regimen, it was decided to chan
minimize any parkinsonism that was a result of his medications. While tapering the haloperidol and initiat
parkinsonism that resulted in an inability to walk. His mental status remained unchanged. Haloperidol wa
and two days later the patient's parkinsonism side effects had resolved back to baseline. Benztropine wa
symptoms did not reoccur while on olanzapine (Gomberg, 1999).

3.5.1.DS Haloperidol

1) Interaction Effect: haloperidol toxicity (pseudoparkinsonism, akathisia, tongue stiffness) and an increased
de pointes, cardiac arrest)
2) Summary: Haloperidol is associated with QTc prolongation and torsade de pointes (Hassaballa & Balk, 20
been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Prozac(R), 2001x).
drugs that potentially prolong the QTc interval. In addition, several case reports describe development of extr
haloperidol were taken together, possibly due to inhibition of haloperidol metabolism (Benazzi, 1996a; Goff et
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: The concurrent administration of fluoxetine and haloperidol is not recommended.
7) Probable Mechanism: inhibition of haloperidol metabolism by fluoxetine; theoretical additive effects on QT
8) Literature Reports

a) Fluoxetine increased plasma concentrations of haloperidol in 8 outpatients. Patients received fluoxeti doses of haloperidol (average dose, 14 mg per day). After ten days, mean plasma concentrations of halo symptom scores did not change appreciably after the addition of fluoxetine although one patient develop tremors. Extrapyramidal symptoms were expected to increase because of indirect inhibition of dopamine
b) A 39-year-old male experienced tardive dyskinesia with concomitant fluoxetine and haloperidol thera months, then haloperidol 2 mg twice daily was started and later lowered to 1 mg per day. Five months la dyskinesia was diagnosed. The suggested mechanism was the down-regulation of dopamine activity (St
c) A 39-year-old female developed tardive dyskinesia associated with concomitant fluoxetine and halope to 5 mg a day for two years (both with and without benztropine) with occasional mild, reversible extrapyra haloperidol, she started taking fluoxetine, which was increased over several days to 40 mg twice a day. A 5 mg each on two consecutive days (along with continuation of fluoxetine). She then experienced severe Both fluoxetine and haloperidol were withdrawn. During the next seven days her extrapyramidal symptor
d) A 40-year-old male developed urinary retention while taking fluoxetine and haloperidol. During a recu with fluoxetine 20 mg per day, alprazolam 1.5 mg per day, and haloperidol 1 mg per day. The patient ha without incident. Approximately one week after beginning therapy, the patient developed difficulty in void restlessness, hand tremors, and insomnia. After discontinuation of haloperidol and alprazolam, side effe postulated that the interaction was due to fluoxetine inhibition of cytochrome CYP2D6, which metabolizes

3.5.1.DT Halothane

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, halothane should be administ known to prolong the QTc interval, including fluoxetine (Owens, 2001; Prod Info Prozac(R), 2001).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of halothane with other agents that can prolong the Q recommended.
7) Probable Mechanism: additive effect on QT interval

3.5.1.DU Heparin

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2 (R) oral capsules, delayed-release capsules, solution, 2008). Bleeding events reported have included epistax threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported wi (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When fluoxetine and an anticoagulant are given concurrently, monitor patient for sig taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, wh (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
7) Probable Mechanism: unknown
8) Literature Reports

a) Fluoxetine is thought to inhibit the cytochrome P450 2C9 isoenzyme (CYP2C9). This is the enzyme b warfarin, is metabolized (Riesenman, 1995). In addition, both fluoxetine and warfarin are tightly bound to protein-binding displacement of either drug is present (Prod Info Coumadin(R), 1999).
b) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bl patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks followi mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected p SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. T treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model
c) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoum reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal blee hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal b subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interva gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekam
d) In 6 reported cases, INR increased during combined fluoxetine and warfarin therapy. In a seventh ca a woman initially treated with fluoxetine and, secondarily, started on warfarin (Woolfrey et al, 1993; Claire
e) An 83-year-old man died from cerebral hemorrhage secondary to increased warfarin concentrations. week for atrial fibrillation with a target INR between 2 and 3. The patient's other drugs included lisinopril, acetaminophen. After being seen for symptoms of depression, anxiety, and insomnia, the patient was giv

mg 3 to 4 times per day. Eight days later, the patient's INR increased to 4.8, and the dose of warfarin wa
was later seen for symptoms of drug delirium, including confusion, incoherence, and speaking irrationally
was discontinued. The next day the patient presented to the hospital with left-sided weakness and later c
interparenchymal hemorrhage. The authors proposed that the addition of fluoxetine to the patient's regim
warfarin and diazepam, resulting in delirium and loss of anticoagulant control (Dent & Orrock, 1997).

3.5.1.DV Hydroquinidine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, the coadministration of Class
prolong the QTc interval is not recommended (Prod Info Quinaglute Dura-tabs(R), 1999). Fluoxetine has dem
(Prod Info Prozac(R), 2001z).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of class Ia antiarrhythmic agents and agents that pro
recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.DW Hydroxytryptophan

1) Interaction Effect: an increased risk of serotonin syndrome (hypertension, hyperthermia, myoclonus, ment
2) Summary: Hydroxytryptophan (5-HTP) may potentiate the serotonergic effect of selective serotonin reupta
Since 5-HTP increases serotonin levels, when combined with an SSRI, the serotonin level may be increased
Caution is advised with concomitant use of 5-HTP and SSRIs.
3) Severity: moderate
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: No cases have been reported of serotonin syndrome resulting from this combinatio
HTP) and a selective serotonin reuptake inhibitor (SSRI) are used concomitantly. Monitor the patient for early
confusion, and disorientation.
7) Probable Mechanism: additive serotonergic effect
8) Literature Reports
a) Hydroxytryptophan (5-HTP) (200 milligrams (mg) orally) as a single dose increased plasma cortisol a
unmedicated patients with major depression or obsessive compulsive disorder (OCD). These responses
fluoxetine (n = 16) (p less than 0.0001). Mean fluoxetine dose for depressed patients was 44 mg/day,and
prolactin (PRL) levels in patients taking 5-HTP with tricyclic antidepressants (n = 14) or those receiving n
different from each other. A measurement of serotonergic effects of antidepressants can be evaluated by
(HPA) axis or PRL response. No clinical manifestations of serotonin syndrome were reported in patients
(Meltzer et al, 1997).

3.5.1.DX Ibuprofen

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and
use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have incl
petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info L
CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent
Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressar
hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of u
than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose
confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of
upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin inc
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with
TORADOL(R) oral tablets, 2007).

3.5.1.DY Ibutilide

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, the coadministration of Class
prolong the QTc interval is not recommended (Allen et al, 2002; Prod Info Tikosyn(TM) dofetilide capsules, 1
been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Prozac(R), 2001a).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of class III antiarrhythmic agents and agents that pro recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.DZ Iloperidone
1) Interaction Effect: increased plasma concentrations of iloperidone
2) Summary: Coadministration of iloperidone and fluoxetine results in increased plasma levels of iloperidone iloperidone (Prod Info FANAPT(TM) oral tablets, 2009).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: established
6) Clinical Management: If administered with fluoxetine, reduce iloperidone doses by one-half. Upon withdra resume the previous iloperidone dose (Prod Info FANAPT(TM) oral tablets, 2009).
7) Probable Mechanism: inhibition of the CYP2D6-mediated metabolism of iloperidone
8) Literature Reports
a) Coadministration of fluoxetine 20 mg twice daily for 21 days and iloperidone 3 mg (single doses) in 2 classified as CYP2D6 extensive metabolizers, increased the AUC of iloperidone and the P88 metabolite P95 metabolite by one-half (Prod Info FANAPT(TM) oral tablets, 2009).

3.5.1.EA Iloprost
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and use of SSRIs and antiplatelet agents has been associated with an increased risk of bleeding. Bleeding events hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008; release capsules, solution, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an antiplatelet agent are given concurrently, monitor patient for oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 200
7) Probable Mechanism: unknown

3.5.1.EB Imipramine
1) Interaction Effect: tricyclic antidepressant toxicity (dry mouth, urinary retention, sedation) and an increase de pointes, cardiac arrest)
2) Summary: Tricyclic antidepressants (TCAs) and fluoxetine have been shown to prolong the QTc interval a Prozac(R), 2001h; Marshall & Forker, 1982). Even though no formal drug interaction studies have been done coadministration of tricyclic antidepressants and other drugs known to prolong the QTc interval, such as fluox 1999). In addition, concurrent use of fluoxetine and TCAs such as desipramine, nortriptyline, and imipramine concentrations (Preskorn et al, 1994a; Preskorn et al, 1994a; Aranow et al, 1989a; Downs et al, 1989a; Gooc
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: The concurrent administration of fluoxetine and a tricyclic antidepressant is not rec
7) Probable Mechanism: decreased tricyclic antidepressant metabolism; additive effects on QT prolongation
8) Literature Reports
a) Fluoxetine increased the level of tricyclic antidepressants (nortriptyline, imipramine, desipramine) in 4 ratio of antidepressant level to dose increased by 109% to 486% in the patients. Three patients develope constipation, urinary hesitancy, sedation, unstable gait) as a result of the increased levels (Aranow et al,
b) Fluoxetine statistically and clinically significantly increased desipramine concentrations in 18 healthy added to desipramine (50 mg daily), the mean maximum concentration of desipramine increased by 278 curve increased by 342%. Desipramine trough concentrations continued to be 198% above baseline thre same study compared pharmacokinetics of desipramine when combined with sertraline. The impact of s short-term increases in desipramine plasma concentrations (Preskorn et al, 1994).
c) A 75-year-old female experienced symptomatic increases in her desipramine serum concentrations w levels ranged from 109 to 150 ng/mL with oral doses of 300 mg at bedtime prior to fluoxetine therapy. Fo to the regimen, the desipramine serum level increased to 212 ng/mL within five days. The fluoxetine dos and the desipramine serum level was 419 ng/mL after four days. A worsening of depression and severe desipramine serum levels. Withdrawal of fluoxetine and reduction in the desipramine dose to 200 mg dai ng/mL within two weeks (Bell & Cole, 1988).
d) A 33-year-old depressed male developed adverse effects of dry mouth, tinnitus, and difficulties with a 40 mg daily and desipramine 150 mg daily for five weeks; fluoxetine was discontinued and the blood leve ng/mL with resolution of clinical symptoms (Goodnick, 1989).
e) A 39-year-old female experienced symptomatic increases in her desipramine levels with concomitant the patient's measured levels of desipramine had ranged from 148 to 160 ng/mL on a regimen of 300 mg 20 mg daily, she reported anticholinergic symptoms, sedation, and confusion with a desipramine level of to 200 mg/day; eleven days later, the level was 244 ng/mL; the patient reported decreased energy, impa speech, as well as an episode of nausea, dizziness, and syncope. The desipramine dose was reduced t

days. Eight days later, the desipramine level was 122 ng/mL (Downs et al, 1989).
f) Concomitant administration of fluoxetine and desipramine was reported to result in an increased desip year-old male within 10 days of the addition of fluoxetine to the patient's regimen (Preskorn et al, 1990).

3.5.1.EC Indomethacin
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have incl petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info L CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressar hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of up than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin inc
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with TORADOL(R) oral tablets, 2007).

3.5.1.ED Indoprofen
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have incl petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info L CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressar hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of up than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin inc
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with TORADOL(R) oral tablets, 2007).

3.5.1.EE Insulin Aspart, Recombinant
1) Interaction Effect: hypoglycemia
2) Summary: Fluoxetine may increase the blood glucose-lowering effect of insulin and the susceptibility to hy powder inhaler, 2006; Prod Info NOVOLOG(R), 2005; Prod Info LEVEMIR(R) injection, 2005; Prod Info LANT Apidra(TM), 2004).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Blood glucose levels should be closely monitored when fluoxetine is added or disco doses of insulin may be required with concomitant therapy.
7) Probable Mechanism: additive hypoglycemia

3.5.1.EF Insulin Detemir
1) Interaction Effect: hypoglycemia
2) Summary: Fluoxetine may increase the blood glucose-lowering effect of insulin and the susceptibility to hy powder inhaler, 2006; Prod Info NOVOLOG(R), 2005; Prod Info LEVEMIR(R) injection, 2005; Prod Info LANT Apidra(TM), 2004).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Blood glucose levels should be closely monitored when fluoxetine is added or disco doses of insulin may be required with concomitant therapy.

7) Probable Mechanism: additive hypoglycemia

3.5.1.EG Insulin Glargine, Recombinant

1) Interaction Effect: hypoglycemia
2) Summary: Fluoxetine may increase the blood glucose-lowering effect of insulin and the susceptibility to hy powder inhaler, 2006; Prod Info NOVOLOG(R), 2005; Prod Info LEVEMIR(R) injection, 2005; Prod Info LANT Apidra(TM), 2004).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Blood glucose levels should be closely monitored when fluoxetine is added or discc doses of insulin may be required with concomitant therapy.
7) Probable Mechanism: additive hypoglycemia

3.5.1.EH Insulin Glulisine

1) Interaction Effect: hypoglycemia
2) Summary: Fluoxetine may increase the blood glucose-lowering effect of insulin and the susceptibility to hy powder inhaler, 2006; Prod Info NOVOLOG(R), 2005; Prod Info LEVEMIR(R) injection, 2005; Prod Info LANT Apidra(TM), 2004).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Blood glucose levels should be closely monitored when fluoxetine is added or discc doses of insulin may be required with concomitant therapy.
7) Probable Mechanism: additive hypoglycemia

3.5.1.EI Insulin Human Inhaled

1) Interaction Effect: hypoglycemia
2) Summary: Fluoxetine may increase the blood glucose-lowering effect of insulin and the susceptibility to hy powder inhaler, 2006; Prod Info NOVOLOG(R), 2005; Prod Info LEVEMIR(R) injection, 2005; Prod Info LANT Apidra(TM), 2004).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Blood glucose levels should be closely monitored when fluoxetine is added or discc doses of insulin may be required with concomitant therapy.
7) Probable Mechanism: additive hypoglycemia

3.5.1.EJ Iproniazid

1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental sta
2) Summary: Concurrent administration or overlapping therapy with fluoxetine and a monoamine oxidase (M serotonin syndrome, a hyperserotonergic state characterized by symptoms such as restlessness, myoclonus diaphoresis, shivering, and tremor. Serious, even fatal, reactions have been reported (Prod Info Prozac(R), 1 1993i; Feighner et al, 1990i; Kline et al, 1989i; Suchowersky & de Vries, 1990i). Concomitant use is contrainc
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Concurrent use of fluoxetine and iproniazid is contraindicated. Wait at least two wee initiating fluoxetine therapy. In addition, wait at least five weeks after discontinuing fluoxetine before initiating
7) Probable Mechanism: inhibition of serotonin metabolism by monoamine oxidase
8) Literature Reports

a) Concomitant use of serotonin specific reuptake inhibitors and monoamine oxidase inhibitors can prod syndrome (Sternbach, 1991j). Serotonin syndrome is a condition of serotonergic hyperstimulation and m mental status, hyperreflexia, diaphoresis, shivering, and tremor (Sternbach, 1991j). If the syndrome is nc result.

b) It has been suggested that fluoxetine therapy be discontinued for at least five weeks before beginning 28-year old woman discontinued fluoxetine for six weeks before starting therapy with tranylcypromine. O fever, paresthesias, confusion, abdominal cramping, and various other CNS symptoms. Upon discontinu began to resolve. Blood samples taken three days after discontinuation of tranylcypromine revealed no p level was 84 ng/mL (Coplan & Gorman, 1993h).

c) Adverse reactions reported when fluoxetine was given concomitantly with phenelzine (n=9) or tranylc restlessness (42%), mental status changes (42%), myoclonus (33%), diarrhea (33%), and blood pressur one of the patients were taking other medications (ie, benzodiazepines, neuroleptics, anticonvulsants, ar adverse reactions.

d) Ten hours after her last dose of fluoxetine, a 45-year-old woman began tranylcypromine therapy (Klir insomnia, and unsteady gait were reported on the second day. Thioridazine and tryptophan were added rigidity of the arms and legs, and hyperreflexia. She died in the intensive care unit of a hospital 44 hours

e) Two cases suggestive of an interaction between fluoxetine and selegiline have been reported. One ca

observed approximately one month after adding selegiline to fluoxetine therapy. The patient improved tw
and no further details were provided. The second case involved diaphoresis, vasoconstriction, and cyanc
temporal relationship to adding fluoxetine and selegiline. Both drugs were discontinued, with relatively qu
fluoxetine alone occurred without incident (Suchowersky & de Vries, 1990h).

3.5.1.EK Isocarboxazid

1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental sta
2) Summary: Concurrent administration or overlapping therapy with fluoxetine and a monoamine oxidase (M
serotonin syndrome, a hyperserotonergic state characterized by symptoms such as restlessness, myoclonus
diaphoresis, shivering, and tremor. Serious, even fatal, reactions have been reported (Prod Info Prozac(R), 1
1993o; Feighner et al, 1990o; Kline et al, 1989o; Suchowersky & de Vries, 1990o). Concomitant use is contra
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Concurrent use of fluoxetine and a MAO inhibitor is contraindicated. Wait at least tw
before initiating fluoxetine therapy. In addition, wait at least five weeks after discontinuing fluoxetine before in
7) Probable Mechanism: inhibition of serotonin metabolism by monoamine oxidase
8) Literature Reports

a) Concomitant use of serotonin specific reuptake inhibitors and monoamine oxidase inhibitors can prod
syndrome (Sternbach, 1991p). Serotonin syndrome is a condition of serotonergic hyperstimulation and n
mental status, hyperreflexia, diaphoresis, shivering, and tremor (Sternbach, 1991p). If the syndrome is n
result.

b) It has been suggested that fluoxetine therapy be discontinued for five weeks before beginning therap
one case report describes a 28-year old woman who had discontinued a 2-year fluoxetine regimen for si
tranylcypromine. Over the next few days the patient developed fever, paresthesias, confusion, abdomina
Upon discontinuation of tranylcypromine, the patient's symptoms began to resolve. Blood samples taken
tranylcypromine revealed no presence of fluoxetine; however, the norfluoxetine level was 84 ng/mL (Cop

c) Adverse reactions reported when fluoxetine was given concomitantly with phenelzine (n=9) or tranylc
restlessness (42%), mental status changes (42%), myoclonus (33%), diarrhea (33%), and blood pressur
one of the patients were taking other medications (ie, benzodiazepines, neuroleptics, anticonvulsants, ar
adverse reactions.

d) Ten hours after her last dose of fluoxetine, a 45-year-old woman began tranylcypromine therapy (Klir
insomnia, and unsteady gait were reported on the second day. Thioridazine and tryptophan were added
rigidity of the arms and legs, and hyperreflexia. She died in the intensive care unit of a hospital 44 hours

e) Interactions between fluoxetine and selegiline were suggested in two case reports (Suchowersky & d
episode of mania being observed approximately one month after adding selegiline to fluoxetine therapy.
drugs were discontinued, and no further details were provided. The second case involved diaphoresis, v
occurred in close temporal relationship to adding fluoxetine and selegiline. Both drugs were discontinued
Rechallenge with fluoxetine alone occurred without incident.

3.5.1.EL Isoflurane

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, isoflurane should be administ
known to prolong the QTc interval, including fluoxetine (Owens, 2001a; Prod Info Prozac(R), 2001k).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of isoflurane with other agents that can prolong the Q
recommended.
7) Probable Mechanism: additive effect on QT interval

3.5.1.EM Isoxicam

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and
use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have incl
petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info L
CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent
Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressar
hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of u
than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose
confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of

upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin inc
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with
TORADOL(R) oral tablets, 2007).

3.5.1.EN Isradipine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Isradipine can prolong the QT interval in some patients, which may result in ventricular tachyca
pointes. Because fluoxetine may also prolong the QT interval and increase the risk of arrhythmias, the concu
not recommended (Prod Info DynaCirc(R), 2000).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of isradipine and fluoxetine is not recommended.
7) Probable Mechanism: additive cardiac effects

3.5.1.EO Ketoprofen

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and
use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have incl
petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info L
CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent
Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressar
hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of u
than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose
confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of
upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin inc
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with
TORADOL(R) oral tablets, 2007).

3.5.1.EP Ketorolac

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and
use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have incl
petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info L
CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent
Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressar
hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of u
than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose
confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of
upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin inc
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with
TORADOL(R) oral tablets, 2007).

3.5.1.EQ Lamifiban

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and
use of SSRIs and antiplatelet agents has been associated with an increased risk of bleeding. Bleeding events
hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008;
release capsules, solution, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an antiplatelet agent are given concurrently, monitor patient for
oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 200

7) Probable Mechanism: unknown

3.5.1.ER Levodopa

1) Interaction Effect: decreased levodopa effectiveness
2) Summary: Concurrent use of olanzapine may antagonize the pharmacological effects of levodopa (Prod I
of this interaction is unknown.
3) Severity: moderate
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Monitor patients for levodopa efficacy.
7) Probable Mechanism: pharmacological antagonism

3.5.1.ES Levomethadyl

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest
2) Summary: Any drug known to have the potential to prolong the QT interval should not be used with levom
can occur between levomethadyl and potentially arrhythmogenic agents such as olanzapine that prolong the
3) Severity: contraindicated
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Levomethadyl is contraindicated in patients being treated with olanzapine as it may
levomethadyl.
7) Probable Mechanism: additive cardiac effects

3.5.1.ET Levomethadyl

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest
2) Summary: Any drug known to have the potential to prolong the QT interval should not be used with levom
can occur between levomethadyl and potentially arrhythmogenic agents such as fluoxetine that prolong the Q
3) Severity: contraindicated
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Levomethadyl is contraindicated in patients being treated with fluoxetine as it may p
levomethadyl.
7) Probable Mechanism: unknown

3.5.1.EU Lexipafant

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and
use of SSRIs and antiplatelet agents has been associated with an increased risk of bleeding. Bleeding events
hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008;
release capsules, solution, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an antiplatelet agent are given concurrently, monitor patient for
oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 200
7) Probable Mechanism: unknown

3.5.1.EV Lidoflazine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest
2) Summary: Lidoflazine and fluoxetine have been shown to prolong the QTc interval at the recommended th
Hanley & Hampton, 1983). Even though no formal drug interaction studies have been done, the coadministra
not recommended.
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of lidoflazine and fluoxetine is not recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.EW Linezolid

1) Interaction Effect: increased risk of serotonin syndrome (hypertension, hyperthermia, myoclonus, mental s
2) Summary: Linezolid is a reversible, nonselective monoamine oxidase inhibitor (MAOI). Concurrent admini
and a MAOI may result in CNS toxicity or serotonin syndrome, a hyperserotonergic state characterized by sy
changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. Serious, even fatal, reactions hav
reports of serotonin syndrome associated with concomitant use of linezolid and serotonergic agents, includin
Morin, 2007; Prod Info ZYVOX(R) IV injection, oral tablets, oral suspension, 2008; Prod Info PROZAC(R) ora
are used concomitantly, monitor for serotonin syndrome effects, including confusion, delirium, restlessness, t
If symptoms occur, consider discontinuation of either one or both of the agents (Prod Info ZYVOX(R) IV injec
washout period of 2 weeks is usually recommended following discontinuation of an MAOI and initiation of fluo

washout period of 5 weeks is usually recommended prior to initiation of an MAOI (Prod Info PROZAC(R) oral
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Unless carefully monitored for serotonin syndrome, linezolid should not be administ ZYVOX(R) IV injection, oral tablets, oral suspension, 2008). A washout period of 2 weeks is usually recomme initiation of fluoxetine. Following discontinuation of fluoxetine, a washout period of 5 weeks is usually recomm PROZAC(R) oral capsules, oral solution, 2006). If fluoxetine and linezolid are used concomitantly, monitor clo as neuromuscular abnormalities (including hyper-reflexia, tremor, muscle rigidity, clonus, peripheral hyperton (including tachycardia, mydriasis, diaphoresis, and diarrhea), and mental status changes (including agitation threatening. If serotonin syndrome develops, discontinue the offending agents and provide supportive care a Shannon, 2005).
7) Probable Mechanism: inhibition of serotonin metabolism by monoamine oxidase
8) Literature Reports
a) A 4-year-old female patient, weighing 12.8 kg, experienced serotonin syndrome-like symptoms follow Eleven days after receiving fluoxetine 5 mg daily for acute stress disorder in response to a burn injury, th hours. Two days later, she was premedicated with oral fentanyl 200 mcg prior to a wound debridement p agitated and had myoclonus in her arms and legs. She also had mydriasis, was unable to visually track a lower left quadrant. Discontinuation of fluoxetine and initiation of oral diphenhydramine 25 mg led to part linezolid was discontinued and replaced with an alternate antibiotic. Symptoms of agitation, myoclonic m 2 days (Thomas et al, 2004).
b) The concomitant administration of fluoxetine and linezolid was associated with mild symptoms of sero described in a case report. The patient, who had recently achieved complete remission of acute myeloge maintenance chemotherapy, routinely received treatment with oral fluoxetine 60 mg once daily, oral meth mg twice daily, transdermal nicotine patch 21 mg (changed daily), oral lorazepam 2 mg twice daily (with quetiapine 200 mg every evening. On day 9 of admission, the fluoxetine dose was increased to 80 mg da every 12 hours was initiated on day 43. Within 12 hours of initiating linezolid, the patient experienced phy (described as feeling like a "runner's cramp" and making it "difficult to breathe"). The discomfort continue next day. On day 47, linezolid was discontinued, after a total of 6 linezolid doses, and the pain and other linezolid therapy, vital signs and laboratory results were unremarkable, except for chemotherapy-induced (Steinberg & Morin, 2007).
c) A retrospective chart review identified one highly probable case of serotonin syndrome in a patient wh and venlafaxine, followed by citalopram. Charts of 72 inpatients who received linezolid and an SSRI or v reviewed for a diagnosis of serotonin syndrome (SS) using the Sternbach and the Hunter Serotonin Toxi treated concomitantly with linezolid and an SSRI or venlafaxine. Four patients met the criteria for having one case involved an 81-year-old woman who was diagnosed with a high probability of having SS after r followed by citalopram. Linezolid was given for a vancomycin-resistant Enterococcus urinary tract infecti eat, was confused as to time and place, and began shouting. Although she appeared to have met 6 of th for SS, a diagnosis of SS was not documented in her chart. Her blood pressure was 180 mm Hg with a h of 50 breaths/min. The following day, she barely spoke and could not be aroused; additional symptoms i eyes rolled back in her head, and labored breathing. Linezolid was discontinued, and she was sedated a symptoms and 2 days after linezolid was stopped, she was extubated and had returned to baseline ment et al, 2006).
d) In one case report, a 39-year-old female experienced symptoms of serotonin syndrome after concom was admitted to the emergency room after being found unresponsive at home. This patient had a history dependency. Before admission, her medications consisted of disulfiram, fluoxetine, buspirone, cyclobenz discontinued upon admission. The patient was given two doses of physostigmine for anticholinergic sym cyclobenzaprine overdose. Two days after admission, the patient became sedated, developed tachycard alcohol withdrawal. She was given lorazepam and haloperidol for the alcohol withdrawal and agitation. C depression thought to be from either pneumonia or respiratory suppression from lorazepam. The patient staphylococcus aureus (sputum) and on day thirteen, was extubated and her mental status improved. O linezolid. Immediate changes in her mental status were apparent. She experienced convulsions, tremors linezolid, the patient had a temperature of 98 degrees, blood pressure of 140/90, a heart rate of 170, and and the vancomycin regimen restarted. The patient was diagnosed with benzodiazepine withdrawal, neu serotonin syndrome. Serotonin syndrome was diagnosed as a likely drug interaction between linezolid a

3.5.1.EX Lithium

1) Interaction Effect: weakness, dyskinesias, increased extrapyramidal symptoms, encephalopathy, and brai
2) Summary: An encephalopathic syndrome followed by irreversible brain damage has occurred in a few pat antagonist, particularly haloperidol. A causal relationship between these events and the concomitant adminis has not been established (Prod Info LITHOBID(R) slow-release oral tablets, 2005). Coadministration of lithiu caused a wide variety of encephalopathic symptoms, brain damage, extrapyramidal symptoms, and dyskines effects have occurred with therapeutic lithium levels (Amdisen, 1982; Prakash, 1982; Addonizio et al, 1988a) using such combinations with no severe adverse consequences (Goldney & Spence, 1986). The mechanism treatment decreases neostriatal dopaminergic activity, probably through a direct action on the G protein and t stimulate adenyl cyclase (Carli et al, 1994). Hyperglycemic reactions have also occurred during combined ph
3) Severity: major
4) Onset: delayed

5) Substantiation: probable
6) Clinical Management: Monitor patients closely for any signs of toxicity or extrapyramidal symptoms, espec particularly haloperidol, and lithium are used. Serum lithium levels should be monitored periodically. Some cli therapeutic range.
7) Probable Mechanism: unknown
8) Literature Reports
a) Concomitant haloperidol and lithium therapy has resulted in symptoms of encephalopathy, confusion, patients with mania (Cohen & Cohen, 1974; Loudon & Waring, 1976; Thomas, 1979). Irreversible neurol Hurwitz, 1983; Keitner & Rahman, 1984).
b) Seizures, encephalopathy, delirium, and abnormal EEG occurred in four patients during combined lith Serum lithium levels were below 1 mEq/L at the time of the toxic reaction in all cases. All patients had pr another phenothiazine. Three of these patients developed symptoms within eight days of initiating combi
c) The addition of lithium to neuroleptic therapy exacerbated extrapyramidal symptoms (EPS) in a small received at least five days of treatment with either oral thiothixene, haloperidol, or fluphenazine in mean to initiation of the lithium and were experiencing drug-induced extrapyramidal symptoms. Oral lithium wa doses to achieve a therapeutic serum concentration. The maximum levels attained were 0.65 to 1.27 mE patients following the addition of lithium. However, only three patients developed marked symptoms and Significantly increased symptoms included gait, shoulder shaking, elbow rigidity, and tremor.
d) Ten patients treated with clozapine and lithium were studied (Blake et al, 1992). Of the ten patients, f including jerking of limbs, facial spasms and tics, tremor of hands and arms, tongue twitching, and stumb delirium. These effects reversed when lithium was discontinued or given at a lower dose. On rechallenge symptoms. By keeping serum lithium no greater than 0.5 mEq/L, clozapine could be safely coadministere
e) Chlorpromazine serum levels can be significantly reduced in the presence of lithium treatment. If use result in rebound elevation of chlorpromazine levels, resulting in chlorpromazine toxicity. In patients on a withdrawal of the lithium may precipitate chlorpromazine cardiotoxicity. In this report, such toxicity was m associated with prolongation of the QTc interval. Hypotension and EPS are also possible in this situation
f) However, other data do not support that such adverse events are frequent or indeed causally related dopamine antagonist antipsychotic drugs and lithium have been used successfully in many patients with that the interaction may only become significant with very high doses of one or both drugs or with failure symptoms (Miller & Menninger, 1987).
g) A 69-year-old patient with oxygen-dependent chronic obstructive pulmonary disorder and a 25-year h risperidone 3 mg for the treatment of new-onset auditory and visual hallucinations. She had also been m for more than 10 years. In addition, she was given amantadine (100 mg twice daily) for tremor. Three we experienced a decline in mental status in addition to dizziness, worsening tremors, nausea and vomiting, hallucinations. She was then admitted to the hospital for delirium. Her lithium serum level was 1.36 mEq/ were discontinued. Although her lithium level decreased to 0.41 mEq/L, she continued to experience pro hallucinations for almost one week. After she started to respond to commands, she was restarted on lithi mild hypomania. Five days later, she was discharged with a regimen of lithium and low-dose lorazepam delirium could have been caused by the concurrent use of lithium and risperidone. Other factors could al serum lithium level and the underlying pulmonary pathology. In addition, amantadine, which facilitates th mild anticholinergic effect, may have contributed (Chen & Cardasis, 1996).

3.5.1.EY Lithium
1) Interaction Effect: possible increased lithium concentrations and/or an increased risk of SSRI-related sero myoclonus, mental status changes)
2) Summary: Concomitant use of lithium and various SSRIs has been associated with enhanced side effects elevated lithium levels. The combination has resulted in neurotoxicity and increased lithium levels in one case symptoms of lithium toxicity and serotonin syndrome have also been reported in patients who demonstrated t concurrent fluoxetine and lithium (Muly et al, 1993a; Noveske et al, 1989a). Two studies have failed to identif and citalopram (Gram et al, 1993a; Baumann et al, 1996a). Combined administration of citalopram (40 mg da days) had no significant effect on the pharmacokinetics of citalopram or lithium. However, plasma lithium leve adjustment to the lithium dose in accordance with standard clinical practice. Lithium may enhance the serotor should be exercised when citalopram and lithium are coadministered (Prod Info Celexa(R), 2004). Concurren reports of increased lithium levels and neurotoxicity, serotonin syndrome, somnolence, and mania (Salama & Evans & Marwick, 1990; Burrai et al, 1991a). No pharmacokinetic interference was apparent during a multiple paroxetine (Prod Info Paxil CR(TM), 2003). If these two agents are to be given concomitantly, the manufactur clinical experience is available. Drug interactions leading to lithium toxicity have been reported when lithium w fluvoxamine (both in the same pharmacological class as paroxetine, eg, selective serotonin reuptake inhibitor 1989a).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: established
6) Clinical Management: Monitor patients on concurrent lithium and selective serotonin reuptake inhibitor the lithium. In addition, monitor patients for signs and symptoms associated with serotonin syndrome (hypertensi changes).
7) Probable Mechanism: unknown
8) Literature Reports
a) Concomitant administration of oral lithium carbonate and oral fluoxetine resulted in increased lithium s

woman with a bipolar affective disorder (Salama & Shafey, 1989). Fluoxetine 20 mg daily was added to a patient complaints of weakness, tiredness, decreased concentration, and early morning awakening. Lithi range of 0.75 to 1.15 mEq/L prior to fluoxetine. Fluoxetine was discontinued and the dose of lithium decr serum level within 48 hours to 1.2 mEq/L. The neurologic symptoms subsided within seven days as the l contribution of fluoxetine to lithium toxicity in this patient was obscured by the fact that the lithium was re

b) A 53-year old woman who had been taking fluoxetine 20 mg daily and lorazepam 0.5 mg four times d 900 mg per day added to her regimen in order to augment her response to fluoxetine. Within 48 hours, th developed a coarse tremor in her right arm. Vital signs showed a rectal temperature of 101 degrees F, a elevated leukocyte count and slightly elevated bilirubin level. After discontinuation of lithium and fluoxetir four days. At no point did the lithium levels reach a toxic level, suggesting that the patient's symptoms we and lithium (Noveske et al, 1989).

c) Serotonin syndrome was precipitated when lithium 300 mg twice daily was added to a three-month re later, the patient's lithium level was measured at 0.65 mEq/L and the dose was increased to 300 mg thre change, the patient experienced akathisia, myoclonus, hyperreflexia, shivering, tremor, diarrhea, and inc initiation of cyproheptadine therapy, the patient's symptoms began to improve. The patient was discharg without further symptoms of serotonin syndrome (Muly et al, 1993).

d) Eight healthy male volunteers completed three phases of an interaction study to determine the effects subjects were extensive metabolizers of sparteine, indicating normal cytochrome P450 2D6 enzyme acti oxidation, citalopram metabolites are excreted by the kidney, as is lithium. Each subject received citalopr days, lithium 30 mmol (1980 mg) alone daily for five days, and lithium coadministered with citalopram on treatment phase. Results showed that the concurrent administration of citalopram and lithium did not sig (Gram et al, 1993).

e) Twenty-four patients experiencing depression (DSM III criteria) were randomized under double-blind daily) and lithium carbonate (800 mg daily) or placebo. All of the subjects had failed to respond to four w coadministered on days 29 to 42. No evidence of a pharmacokinetic interaction between lithium and cita tolerated (Baumann et al, 1996).

f) Serotonin syndrome was described in a 53-year-old patient who was stabilized on lithium 1400 mg da fluvoxamine 50 mg daily. Over a 10-day period the fluvoxamine dose was increased to 200 mg daily; tre developed. After two weeks, tremor, impaired motor function coordination, marked bilateral hyperreflexia ankles were seen. After 12 weeks of continued therapy, during which time no further deterioration occurr fluvoxamine, and the neuromuscular symptoms abated over a 2-week period. After four weeks the patier Spigset, 1993).

g) Three cases of mania were reported in patients who were treated with lithium and fluvoxamine. The r weeks, respectively, after cotherapy was begun. Fluvoxamine was discontinued and, in two of the three treatment of depression occurred with lithium alone. The third patient improved, but depression reappear (Burrai et al, 1991).

h) In an open-labeled, placebo-controlled study, lithium 600 mg was administered to 16 subjects orally t the morning on day nine. In addition, oral sertraline 100 mg or placebo was given twice, ten hours and tw steady-state lithium level was only decreased by 1.4% (0.01 mEq/L) and the lithium renal clearance incre coadministered. Seven subjects experienced side effects, mainly tremors, after receiving lithium and sert placebo and lithium experienced side effects (Wilner et al, 1991).

3.5.1.EZ Lorcainide

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Even though no formal drug interaction studies have been done, the coadministration of Class prolong the QTc interval is not recommended (Prod Info Tambocor(R) flecainide acetate, 1998). Fluoxetine h recommended therapeutic dose (Prod Info Prozac(R), 2001w).

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of class I antiarrhythmic agents and agents that prolo recommended.

7) Probable Mechanism: additive effects on QT prolongation

3.5.1.FA Lornoxicam

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have incl petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info L CELEXA (R) oral tablet, solution, 2005).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressar

hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of u
than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose
confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of
upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin inc
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with
TORADOL(R) oral tablets, 2007).

3.5.1.FB Meclofenamate

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control anc
use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have incl
petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info L
CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent
Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressar
hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of u
than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose
confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of
upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin inc
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with
TORADOL(R) oral tablets, 2007).

3.5.1.FC Mefenamic Acid

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control anc
use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have incl
petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info L
CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent
Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressar
hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of u
than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose
confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of
upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin inc
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with
TORADOL(R) oral tablets, 2007).

3.5.1.FD Mefloquine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Fluoxetine has been shown to prolong the QTc interval at the recommended therapeutic dose
formal drug interaction studies have been done, caution is advised if mefloquine is used with other drugs whi
(R), 1999).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of fluoxetine and mefloquine is not recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.FE Meloxicam

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control anc
use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have incl
petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info L
CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified

5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressar hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of u than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin inc
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with TORADOL(R) oral tablets, 2007).

3.5.1.FF Meperidine
1) Interaction Effect: an increased risk of serotonin syndrome
2) Summary: A 43-year-old male on fluoxetine every other day experienced serotonin syndrome immediatel (Tissot, 2003). If fluoxetine and meperidine are used concomitantly, monitor closely for symptoms of serotoni threatening. If serotonin syndrome develops, discontinue the offending agents and provide supportive care a Shannon, 2005).
3) Severity: major
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: A case of serotonin syndrome was reported with coadministration of fluoxetine and discouraged (Tissot, 2003). If fluoxetine and meperidine are used concomitantly, monitor closely for symptom abnormalities (including hyper-reflexia, tremor, muscle rigidity, clonus, peripheral hypertonicity, and shivering mydriasis, diaphoresis, the presence of bowel sounds, and diarrhea), and mental status changes (including a be life-threatening. If serotonin syndrome develops, discontinue the offending agents and provide supportive Shannon, 2005).
7) Probable Mechanism: additive pharmacologic effects
8) Literature Reports
a) A 43-year-old male on fluoxetine every other day experienced serotonin syndrome immediately after other medications were rosiglitazone and fenofibrate. His medical history includes type 2 diabetes, dysli Prior to this adverse event he received meperidine and midazolam, while not on fluoxetine, without any s administered intravenous midazolam and 50 mg of intravenous meperidine. He immediately became agi verbal commands because of confusion. Blood pressure (180/100 mm Hg) and heart rate (130 bpm) inc He had diaphoresis and dilated pupils. Within 10 minutes his blood pressure started to decrease. He ha minutes, his agitation subsided, he remained sleepy and confused, and blood pressure and heart contin 98.4 degrees Farenheit. After 60 to 90 minutes his sensorium appeared to clear and diaphoresis resolve signs over the next 24 hours. He was treated with hydromorphone for abdominal pain without any adver fentanyl, midazolam, and propofol pre-endoscopy without any event, but had not taken fluoxetine for 2 w

3.5.1.FG Mesoridazine
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Fluoxetine has been shown to prolong the QTc interval at the recommended therapeutic dose data, the manufacturer of mesoridazine states that concomitant use with other drugs which prolong the QT in 2000).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of fluoxetine and mesoridazine is contraindicated.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.FH Methylergonovine
1) Interaction Effect: an increased risk of ergotism (nausea, vomiting, vasospastic ischemia)
2) Summary: Because of the potential for serious toxicity including vasospasm that can occur with increased concurrent use of fluoxetine and ergot derivatives is contraindicated. Fluoxetine and ergot derivatives are bot enzymes, and the competition for metabolism could result in an increased plasma concentration of the ergot
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: The concurrent use of fluoxetine and ergot derivatives is contraindicated.
7) Probable Mechanism: inhibition of cytochrome P450 3A4- mediated ergot metabolism by fluoxetine

3.5.1.FI Methylphenidate
1) Interaction Effect: increased selective serotonin reuptake inhibitor plasma concentrations
2) Summary: Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metab (SSRIs). Downward dose adjustments of the SSRI may be necessary when it is used concurrently with meth discontinuing methylphenidate, the SSRI dose may need to be adjusted as needed (Prod Info METADATE C

3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Use caution when prescribing methylphenidate to patients who take an selective se use of methylphenidate and an SSRI may cause elevated SSRI plasma concentrations. Consider a decrease coadministered. Additionally, consider adjusting the SSRI dose if necessary when initiating or discontinuing n CD(R) extended-release oral capsules, 2007).
7) Probable Mechanism: inhibition of selective serotonin reuptake inhibitor metabolism by methylphenidate

3.5.1.FJ Methysergide
1) Interaction Effect: an increased risk of ergotism (nausea, vomiting, vasospastic ischemia)
2) Summary: Because of the potential for serious toxicity including vasospasm that can occur with increased concurrent use of fluoxetine and ergot derivatives is contraindicated. Fluoxetine and ergot derivatives are bot enzymes, and the competition for metabolism could result in an increased plasma concentration of the ergot
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: The concurrent use of fluoxetine and ergot derivatives is contraindicated.
7) Probable Mechanism: inhibition of cytochrome P450 3A4- mediated ergot metabolism by fluoxetine

3.5.1.FK Metoprolol
1) Interaction Effect: an increased risk of metoprolol adverse effects (shortness of breath, bradycardia, hypot
2) Summary: To date, little information is available related to the effects of combined fluoxetine and metopro between metoprolol and fluoxetine resulting in bradycardia (Walley et al, 1993a). Fluoxetine is a potent inhibi isoenzyme that catalyzes metoprolol metabolism (DeVane, 1994). Additional research is needed to further as pharmacokinetics.
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Atenolol should be considered for fluoxetine-treated patients who require a beta blo coadministered, monitor patients for metoprolol adverse effects. A reduction in the metoprolol dose may be n
7) Probable Mechanism: inhibition of hepatic metabolism of metoprolol
8) Literature Reports
a) A case report described a possible interaction between metoprolol and fluoxetine resulting in bradyca with metoprolol 100 mg daily developed lethargy and bradycardia within two days after fluoxetine 20 mg was discontinued and metoprolol was replaced with sotalol 80 mg twice daily. A week later fluoxetine wa bradycardia. Fluoxetine is known to inhibit hepatic metabolism. Metoprolol is extensively metabolized via and possibly CYP3A). Sotalol does not undergo significant hepatic metabolism (Walley et al, 1993).

3.5.1.FL Milnacipran
1) Interaction Effect: increased risk of serotonin syndrome (hypertension, hyperthermia, myoclonus, mental s
2) Summary: Concurrent use of milnacipran and an SSRI may result in hypertension, coronary artery vasocc life-threatening. Symptoms of serotonin syndrome may include restlessness, hallucinations, loss of coordinat pressure, increased body temperature, overreactive reflexes, nausea, vomiting, and diarrhea (Prod Info SAV
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of milnacipran and an SSRI may result in hypertension and coron serotonergic effects. If these agents are used together, discuss the risks of serotonin syndrome with the patie syndrome (restlessness, hyperthermia, hyperreflexia, incoordination), especially during treatment initiation an tablets, 2009).
7) Probable Mechanism: additive serotonergic effect

3.5.1.FM Mirtazapine
1) Interaction Effect: an increased risk of serotonin syndrome
2) Summary: Concurrent use of olanzapine with mirtazapine and tramadol in a 53-year-old male resulted in s Fetchko, 2002). If olanzapine is used concomitantly with mirtazapine and/or tramadol, monitor closely for sym syndrome can be life-threatening. If serotonin syndrome develops, discontinue the offending agents and prov necessary (Boyer & Shannon, 2005).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: A case of serotonin syndrome was reported with coadministration of olanzapine, mi 2002). If 2 or more of these drugs are are used concomitantly, monitor closely for symptoms of serotonin syn (including hyper-reflexia, tremor, muscle rigidity, clonus, peripheral hypertonicity, and shivering), autonomic h diaphoresis, the presence of bowel sounds, and diarrhea), and mental status changes (including agitation an threatening. If serotonin syndrome develops, discontinue the offending agents and provide supportive care a Shannon, 2005).

7) Probable Mechanism: additive serotonergic pharmacologic effects
8) Literature Reports
a) A 53-year-old male on mirtazapine and tramadol experienced serotonin syndrome 8 days after olanza
mirtazapine 45 mg/day for depression and tramadol 150 mg/day for chronic back pain. Olanzapine 10 m
was admitted 8 days later after being found by the police wandering the streets in inappropriate dress an
afebrile, tachycardic (120 bpm), and had flushing, twitching of his face, tremors, myoclonus, hyperreflexi
agitated. He spoke with a stutter. He had marked derailment, appeared perplexed, had prominent percep
hallucinations. The creatine phosphokinase was normal. All medications were discontinued and within 12
Fetchko, 2002).

3.5.1.FN Mirtazapine
1) Interaction Effect: an increased risk of serotonin syndrome
2) Summary: Concurrent use of fluoxetine and mirtazapine resulted in serotonin syndrome in a 75-year-old v
nausea, dry mouth, intense anxiety and agitation with suicidal ideas. Other symptoms were difficulty walking,
insomnia (Benazzi, 1998). If fluoxetine and mirtazapine are used together, monitor closely for symptoms of se
life-threatening. If serotonin syndrome develops, discontinue the offending agents and provide supportive car
Shannon, 2005).
3) Severity: major
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: A case of serotonin syndrome was reported with concomitant use of fluoxetine and
discouraged (Benazzi, 1998). If fluoxetine and mirtazapine are used together, monitor closely for symptoms c
abnormalities (including hyper-reflexia, tremor, muscle rigidity, clonus, peripheral hypertonicity, and shivering
mydriasis, diaphoresis, the presence of bowel sounds, and diarrhea), and mental status changes (including a
be life-threatening. If serotonin syndrome develops, discontinue the offending agents and provide supportive
Shannon, 2005).
7) Probable Mechanism: potentially additive pharmacologic effects
8) Literature Reports
a) Within a few hours of starting mirtazapine and shortly after stopping fluoxetine, a 75-year-old woman
syndrome. Besides fluoxetine 20 mg/day, she was on chlorpromazine 75 mg/day, and lorazepam 2.5 mg
fluoxetine was discontinued and soon afterward mirtazapine 30 mg/day was started and the dose of chlo
a few hours of starting mirtazapine, she experience dizziness, headache, nausea, dry mouth, intense an
symptoms were difficulty walking, marked resting tremor of the hands, and insomnia. Over the next 3 da
discontinued on day 5. Her symptoms improved the following day. Fluoxetine 20 mg/day was restarted o
nausea, headache, and agitation resolution over the following days. Over the next 10 days, tremor, anxie
improved (Benazzi, 1998).

3.5.1.FO Moclobemide
1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental sta
2) Summary: Concurrent administration or overlapping therapy with fluoxetine and a monoamine oxidase (M
serotonin syndrome, a hyperserotonergic state characterized by symptoms such as restlessness, myoclonus
diaphoresis, shivering, and tremor. Serious, even fatal, reactions have been reported (Prod Info Prozac(R), 1
1993r; Feighner et al, 1990r; Kline et al, 1989s; Suchowersky & de Vries, 1990s). Although not reported spec
similar interaction may occur. Concomitant use is contraindicated.
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Concurrent use of fluoxetine and a MAO inhibitor is contraindicated. Wait at least tw
before initiating fluoxetine therapy. In addition, wait at least five weeks after discontinuing fluoxetine before in
7) Probable Mechanism: inhibition of serotonin metabolism by monoamine oxidase
8) Literature Reports
a) Concomitant use of serotonin specific reuptake inhibitors and monoamine oxidase inhibitors can prod
syndrome (Sternbach, 1991t). Serotonin syndrome is a condition of serotonergic hyperstimulation and m
mental status, hyperreflexia, diaphoresis, shivering, and tremor. If the syndrome is not recognized and c
b) Ten hours after her last dose of fluoxetine, a 45-year-old woman began tranylcypromine therapy (Klin
insomnia, and unsteady gait were reported on the second day. Thioridazine and tryptophan were added
rigidity of the arms and legs, and hyperreflexia. She died in the intensive care unit of a hospital 44 hours
c) Two cases suggestive of an interaction between fluoxetine and selegiline, a selective monoamine oxi
(Suchowersky & de Vries, 1990r). One case involved a first episode of mania being observed approxima
fluoxetine therapy. The patient improved two months after both drugs were discontinued, and no further
diaphoresis, vasoconstriction, and cyanosis of the hands which occurred in close temporal relationship to
were discontinued, with relatively quick resolution of symptoms. Rechallenge with fluoxetine alone occur
d) In three of five cases of serotonin syndrome following overdoses, the drug combination that induced t
selective monoamine oxidase inhibitor, and citalopram. Of these three patients, moclobemide blood conc
therapeutic level, and citalopram concentrations ranged from normal to 5 times the therapeutic level (Ne
e) Moclobemide is a selective and reversible inhibitor of monoamine oxidase A (MAO-A). Based on anim
and MAO-B are essential for the development of serotonin syndrome. In an effort to assess the safety ar
fluoxetine and moclobemide, 18 healthy subjects participated in a randomized, placebo-controlled, parall

dose of moclobemide 300 mg on days 1 and 24, fluoxetine 40 mg on days 2 through 8, and fluoxetine 20
were randomized to receive either placebo or moclobemide on an ascending dose schedule. Doses of m
increased to 200 mg on day 17, 300 mg on day 18, and 600 mg on days 19 through 23. Steady-state flu
achieved when moclobemide therapy was initiated, and did not change with the addition or increasing do
serotonin syndrome or any kind of a pharmacodynamic interaction between these two agents. Additional
platelets almost completely as expected, but moclobemide had no effect on serotonin uptake during sing
suggest that a long wash-out period between treatment with moclobemide and fluoxetine is not necessar
f) An 82-year-old woman developed various serotonin syndrome symptoms after changing from fluoxeti
period in between. She experienced agitation, confusion, and tremor, progressing to inability to answer q
After treatment with 4 mg cyproheptadine, her condition improved significantly (Chan et al, 1998a).

3.5.1.FP Morniflumate

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and
use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have incl
petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info L
CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent
Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressar
hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of u
than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose
confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of
upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin inc
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with
TORADOL(R) oral tablets, 2007).

3.5.1.FQ Nabumetone

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and
use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have incl
petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info L
CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent
Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressar
hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of u
than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose
confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of
upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin inc
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with
TORADOL(R) oral tablets, 2007).

3.5.1.FR Nadroparin

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and
use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2
(R) oral capsules, delayed-release capsules, solution, 2008). Bleeding events reported have included epistax
threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported wi
(Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When fluoxetine and an anticoagulant are given concurrently, monitor patient for sig
taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, wh
(Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
7) Probable Mechanism: unknown
8) Literature Reports

a) Fluoxetine is thought to inhibit the cytochrome P450 2C9 isoenzyme (CYP2C9). This is the enzyme b warfarin, is metabolized (Riesenman, 1995). In addition, both fluoxetine and warfarin are tightly bound to protein-binding displacement of either drug is present (Prod Info Coumadin(R), 1999).
b) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bl patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks followi mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected p SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. T treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model
c) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoum reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal blee hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal b subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interva gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekam
d) In 6 reported cases, INR increased during combined fluoxetine and warfarin therapy. In a seventh ca a woman initially treated with fluoxetine and, secondarily, started on warfarin (Woolfrey et al, 1993; Claire
e) An 83-year-old man died from cerebral hemorrhage secondary to increased warfarin concentrations. week for atrial fibrillation with a target INR between 2 and 3. The patient's other drugs included lisinopril, acetaminophen. After being seen for symptoms of depression, anxiety, and insomnia, the patient was giv mg 3 to 4 times per day. Eight days later, the patient's INR increased to 4.8, and the dose of warfarin wa was later seen for symptoms of drug delirium, including confusion, incoherence, and speaking irrationally was discontinued. The next day the patient presented to the hospital with left-sided weakness and later c interparenchymal hemorrhage. The authors proposed that the addition of fluoxetine to the patient's regim warfarin and diazepam, resulting in delirium and loss of anticoagulant control (Dent & Orrock, 1997).

3.5.1.FS Naproxen

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have incl petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info L CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressar hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of up than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin inc
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with TORADOL(R) oral tablets, 2007).

3.5.1.FT Naratriptan

1) Interaction Effect: an increased risk of serotonin syndrome
2) Summary: Rare incidences of weakness, hyperreflexia, and incoordination have been reported with the co inhibitor (SSRI) and a 5-hydroxytryptamine-1 (5HT-1) agonist (Prod Info Amerge(TM), 2002). Concurrent use syndrome which may be life-threatening. Symptoms of serotonin syndrome may include restlessness, halluci rapid changes in blood pressure, increased body temperature, overreactive reflexes, nausea, vomiting, and c may be commonly used intermittently and that either the triptan or the SSRI may be prescribed by a different syndrome with patients who are prescribed this combination and monitor them closely for symptoms of seroto Administration, 2006).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Coadministration of a triptan, such as naratriptan, and an SSRI may result in a life-t Be aware that triptans may be commonly used intermittently and that either the triptan or the SSRI may be pr are used together, discuss the risks of serotonin syndrome with the patient and monitor closely for symptoms hyperthermia, hyperreflexia, incoordination).
7) Probable Mechanism: additive pharmacologic effects resulting in excessive serotonergic stimulation

3.5.1.FU Nebivolol

1) Interaction Effect: increased nebivolol exposure and plasma levels

2) Summary: Nebivolol is partially metabolized by the CYP2D6 isozyme. Coadministration of a single 10 mg receiving fluoxetine, a CYP2D6 inhibitor, at a dose of 20 mg/day for 21 days led to 8- and 3-fold increases in (pharmacologically active isomer). Closely monitor blood pressure in patients receiving fluoxetine and nebivo of nebivolol may be necessary (Prod Info BYSTOLIC(TM) oral tablets, 2007).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: established

6) Clinical Management: Coadministration of fluoxetine, a CYP2D6 inhibitor, and nebivolol led to increased e nebivolol, the pharmacologically active isomer. In patients receiving these agents concomitantly, closely mon may be necessary (Prod Info BYSTOLIC(TM) oral tablets, 2007).

7) Probable Mechanism: inhibition of CYP2D6-mediated nebivolol metabolism

3.5.1.FV Nialamide

1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental sta

2) Summary: Concurrent administration or overlapping therapy with fluoxetine and a monoamine oxidase (M serotonin syndrome, a hyperserotonergic state characterized by symptoms such as restlessness, myoclonus diaphoresis, shivering, and tremor. Serious, even fatal, reactions have been reported (Prod Info Prozac(R), 1 1993g; Feighner et al, 1990g; Kline et al, 1989g; Suchowersky & de Vries, 1990g). Concomitant use is contra

3) Severity: contraindicated

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: Concurrent use of fluoxetine and nialamide is contraindicated. Wait at least two we initiating fluoxetine therapy. In addition, wait at least five weeks after discontinuing fluoxetine before initiating

7) Probable Mechanism: inhibition of serotonin metabolism by monoamine oxidase

8) Literature Reports

a) Concomitant use of serotonin specific reuptake inhibitors and monoamine oxidase inhibitors can prod syndrome (Sternbach, 1991h). Serotonin syndrome is a condition of serotonergic hyperstimulation and m mental status, hyperreflexia, diaphoresis, shivering, and tremor (Sternbach, 1991h). If the syndrome is n result.

b) It has been suggested that fluoxetine therapy be discontinued for at least five weeks before beginning 28-year old woman discontinued fluoxetine for six weeks before starting therapy with tranylcypromine. O fever, paresthesias, confusion, abdominal cramping, and various other CNS symptoms. Upon discontinu began to resolve. Blood samples taken three days after discontinuation of tranylcypromine revealed no p level was 84 ng/mL (Coplan & Gorman, 1993f).

c) Adverse reactions reported when fluoxetine was given concomitantly with phenelzine (n=9) or tranylc restlessness (42%), mental status changes (42%), myoclonus (33%), diarrhea (33%), and blood pressur one of the patients were taking other medications (ie, benzodiazepines, neuroleptics, anticonvulsants, ar adverse reactions.

d) Ten hours after her last dose of fluoxetine, a 45-year-old woman began tranylcypromine therapy (Klin insomnia, and unsteady gait were reported on the second day. Thioridazine and tryptophan were added rigidity of the arms and legs, and hyperreflexia. She died in the intensive care unit of a hospital 44 hours

e) Two cases reports suggested a possible interaction between fluoxetine and selegiline (Suchowersky episode of mania being observed approximately one month after adding selegiline to fluoxetine therapy. drugs were discontinued, and no further details were provided. The second case involved diaphoresis, v occurred in close temporal relationship to adding fluoxetine and selegiline. Both drugs were discontinued Rechallenge with fluoxetine alone occurred without incident.

3.5.1.FW Niflumic Acid

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have incl petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info L CELEXA (R) oral tablet, solution, 2005).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressar hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of u than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin inc

b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with TORADOL(R) oral tablets, 2007).

3.5.1.FX Nimesulide

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have incl petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info L CELEXA (R) oral tablet, solution, 2005).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressar hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of u than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin inc

b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with TORADOL(R) oral tablets, 2007).

3.5.1.FY Nortriptyline

1) Interaction Effect: tricyclic antidepressant toxicity (dry mouth, urinary retention, sedation) and an increase de pointes, cardiac arrest)

2) Summary: Tricyclic antidepressants (TCAs) and fluoxetine have been shown to prolong the QTc interval a Prozac(R), 2001h; Marshall & Forker, 1982). Even though no formal drug interaction studies have been done coadministration of tricyclic antidepressants and other drugs known to prolong the QTc interval, such as fluox 1999). In addition, concurrent use of fluoxetine and TCAs such as desipramine, nortriptyline, and imipramine concentrations (Preskorn et al, 1994a; Preskorn et al, 1994a; Aranow et al, 1989a; Downs et al, 1989a; Gooc

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: The concurrent administration of fluoxetine and a tricyclic antidepressant is not rec

7) Probable Mechanism: decreased tricyclic antidepressant metabolism; additive effects on QT prolongation

8) Literature Reports

a) Fluoxetine increased the level of tricyclic antidepressants (nortriptyline, imipramine, desipramine) in 4 ratio of antidepressant level to dose increased by 109% to 486% in the patients. Three patients develope constipation, urinary hesitancy, sedation, unstable gait) as a result of the increased levels (Aranow et al,

b) Fluoxetine statistically and clinically significantly increased desipramine concentrations in 18 healthy added to desipramine (50 mg daily), the mean maximum concentration of desipramine increased by 278 curve increased by 342%. Desipramine trough concentrations continued to be 198% above baseline thre same study compared pharmacokinetics of desipramine when combined with sertraline. The impact of s short-term increases in desipramine plasma concentrations (Preskorn et al, 1994).

c) A 75-year-old female experienced symptomatic increases in her desipramine serum concentrations w levels ranged from 109 to 150 ng/mL with oral doses of 300 mg at bedtime prior to fluoxetine therapy. Fo to the regimen, the desipramine serum level increased to 212 ng/mL within five days. The fluoxetine dos and the desipramine serum level was 419 ng/mL after four days. A worsening of depression and severe desipramine serum levels. Withdrawal of fluoxetine and reduction in the desipramine dose to 200 mg dai ng/mL within two weeks (Bell & Cole, 1988).

d) A 33-year-old depressed male developed adverse effects of dry mouth, tinnitus, and difficulties with a 40 mg daily and desipramine 150 mg daily for five weeks; fluoxetine was discontinued and the blood leve ng/mL with resolution of clinical symptoms (Goodnick, 1989).

e) A 39-year-old female experienced symptomatic increases in her desipramine levels with concomitant the patient's measured levels of desipramine had ranged from 148 to 160 ng/mL on a regimen of 300 mg 20 mg daily, she reported anticholinergic symptoms, sedation, and confusion with a desipramine level of to 200 mg/day; eleven days later, the level was 244 ng/mL; the patient reported decreased energy, impa speech, as well as an episode of nausea, dizziness, and syncope. The desipramine dose was reduced t days. Eight days later, the desipramine level was 122 ng/mL (Downs et al, 1989).

f) Concomitant administration of fluoxetine and desipramine was reported to result in an increased desi year-old male within 10 days of the addition of fluoxetine to the patient's regimen (Preskorn et al, 1990).

3.5.1.FZ Octreotide

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Octreotide and fluoxetine have been shown to prolong the QTc interval at the recommended th Prod Info Sandostatin(R), 1999). Even though no formal drug interaction studies have been done, the coadm

interval is not recommended.
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of octreotide and fluoxetine is not recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.GA Oxaprozin
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have incl petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info L CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressar hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of u than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin inc
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with TORADOL(R) oral tablets, 2007).

3.5.1.GB Parecoxib
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have incl petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info L CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressar hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of u than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin inc
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with TORADOL(R) oral tablets, 2007).

3.5.1.GC Pargyline
1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental st
2) Summary: Concurrent administration or overlapping therapy with fluoxetine and a monoamine oxidase (M serotonin syndrome, a hyperserotonergic state characterized by symptoms such as restlessness, myoclonus diaphoresis, shivering, and tremor. Serious, even fatal, reactions have been reported (Prod Info Prozac(R), 1 1993m; Feighner et al, 1990m; Kline et al, 1989m; Suchowersky & de Vries, 1990m). Concomitant use is cor
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Concurrent use of fluoxetine and pargyline is contraindicated. Wait at least two wee initiating fluoxetine therapy. In addition, wait at least five weeks after discontinuing fluoxetine before initiating
7) Probable Mechanism: inhibition of serotonin metabolism by monoamine oxidase
8) Literature Reports
a) Concomitant use of serotonin specific reuptake inhibitors and monoamine oxidase inhibitors can prod syndrome (Sternbach, 1991n). Serotonin syndrome is a condition of serotonergic hyperstimulation and n mental status, hyperreflexia, diaphoresis, shivering, and tremor (Sternbach, 1991n). If the syndrome is n result.
b) It has been suggested that fluoxetine therapy be discontinued for at least five weeks before beginning 28-year old woman discontinued fluoxetine for six weeks before starting therapy with tranylcypromine. O

fever, paresthesias, confusion, abdominal cramping, and various other CNS symptoms. Upon discontinu began to resolve. Blood samples taken three days after discontinuation of tranylcypromine revealed no p level was 84 ng/mL (Coplan & Gorman, 1993l).

c) Adverse reactions reported when fluoxetine was given concomitantly with phenelzine (n=9) or tranylc restlessness (42%), mental status changes (42%), myoclonus (33%), diarrhea (33%), and blood pressur one of the patients were taking other medications (ie, benzodiazepines, neuroleptics, anticonvulsants, ar adverse reactions.

d) Ten hours after her last dose of fluoxetine, a 45-year-old woman began tranylcypromine therapy (Klir insomnia, and unsteady gait were reported on the second day. Thioridazine and tryptophan were added rigidity of the arms and legs, and hyperreflexia. She died in the intensive care unit of a hospital 44 hours

e) Two cases reports suggested a possible interaction between fluoxetine and selegiline (Suchowersky episode of mania being observed approximately one month after adding selegiline to fluoxetine therapy. drugs were discontinued, and no further details were provided. The second case involved diaphoresis, v occurred in close temporal relationship to adding fluoxetine and selegiline. Both drugs were discontinuec Rechallenge with fluoxetine alone occurred without incident.

3.5.1.GD Parnaparin

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control anc use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2 (R) oral capsules, delayed-release capsules, solution, 2008). Bleeding events reported have included epistax threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported wi (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: When fluoxetine and an anticoagulant are given concurrently, monitor patient for sig taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, wl (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).

7) Probable Mechanism: unknown

8) Literature Reports

a) Fluoxetine is thought to inhibit the cytochrome P450 2C9 isoenzyme (CYP2C9). This is the enzyme b warfarin, is metabolized (Riesenman, 1995). In addition, both fluoxetine and warfarin are tightly bound to protein-binding displacement of either drug is present (Prod Info Coumadin(R), 1999).

b) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bl patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks followi mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected p SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. T treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model

c) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoum reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal blee hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal b subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interva gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekam

d) In 6 reported cases, INR increased during combined fluoxetine and warfarin therapy. In a seventh cas a woman initially treated with fluoxetine and, secondarily, started on warfarin (Woolfrey et al, 1993; Claire

e) An 83-year-old man died from cerebral hemorrhage secondary to increased warfarin concentrations. week for atrial fibrillation with a target INR between 2 and 3. The patient's other drugs included lisinopril, acetaminophen. After being seen for symptoms of depression, anxiety, and insomnia, the patient was giv mg 3 to 4 times per day. Eight days later, the patient's INR increased to 4.8, and the dose of warfarin wa was later seen for symptoms of drug delirium, including confusion, incoherence, and speaking irrationally was discontinued. The next day the patient presented to the hospital with left-sided weakness and later d interparenchymal hemorrhage. The authors proposed that the addition of fluoxetine to the patient's regim warfarin and diazepam, resulting in delirium and loss of anticoagulant control (Dent & Orrock, 1997).

3.5.1.GE Paroxetine

1) Interaction Effect: fluoxetine toxicity (dry mouth, sedation, urinary retention)

2) Summary: Coadministration of paroxetine with drugs that are metabolized by cytochrome P450 2D6 (CYP with caution (Prod Info Paxil CR(TM), 2002).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: When paroxetine is coadministered with fluoxetine monitor patients for signs and sy
sedation, urinary retention, blurred vision). Fluoxetine doses may need to be reduced.
7) Probable Mechanism: decreased cytochrome P450 2D6-mediated fluoxetine metabolism

3.5.1.GF Pentamidine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Pentamidine and fluoxetine have been shown to prolong the QTc interval at the recommended
Lindsay et al, 1990). Even though no formal drug interaction studies have been done, the coadministration of
recommended.
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of pentamidine and fluoxetine is not recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.GG Pentazocine

1) Interaction Effect: hypertension, diaphoresis, ataxia, flushing, nausea, dizziness, and anxiety
2) Summary: A case of neurologic effects associated with concomitant use of fluoxetine and pentazocine has
1990a).
3) Severity: moderate
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Until more data are available, concomitant use of fluoxetine and pentazocine should
7) Probable Mechanism: unknown
8) Literature Reports
a) One study reported a case in which coadministration of fluoxetine and pentazocine was associated w
male taking fluoxetine 40 mg daily was administered oral pentazocine 50 mg for a severe headache. App
pentazocine, the patient became hypertensive, diaphoretic, flushed, ataxic, paresthetic, nauseated, lightl
between fluoxetine and pentazocine may have occurred, a hypersensitivity to pentazocine alone was not
b) Fluoxetine administered seven days before surgery had no effect on kappa-opiate pentazocine analg
produced by morphine (p less than 0.05), a mu-opiate. The duration of action of morphine analgesia was
authors point out that the effect of chronic fluoxetine administration on mu-opiate analgesia is not clear a
1994).

3.5.1.GH Pentosan Polysulfate Sodium

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and
use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2
(R) oral capsules, delayed-release capsules, solution, 2008). Bleeding events reported have included epistax
threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported wi
(Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When fluoxetine and an anticoagulant are given concurrently, monitor patient for sig
taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, wh
(Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
7) Probable Mechanism: unknown
8) Literature Reports
a) Fluoxetine is thought to inhibit the cytochrome P450 2C9 isoenzyme (CYP2C9). This is the enzyme b
warfarin, is metabolized (Riesenman, 1995). In addition, both fluoxetine and warfarin are tightly bound to
protein-binding displacement of either drug is present (Prod Info Coumadin(R), 1999).
b) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bl
patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks followi
mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected p
SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients
treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4
corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively.
treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only
bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI
dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding
exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model
c) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoum
reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal blee
hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal b
subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690
for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interva
gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekam

d) In 6 reported cases, INR increased during combined fluoxetine and warfarin therapy. In a seventh ca
a woman initially treated with fluoxetine and, secondarily, started on warfarin (Woolfrey et al, 1993; Claire
e) An 83-year-old man died from cerebral hemorrhage secondary to increased warfarin concentrations.
week for atrial fibrillation with a target INR between 2 and 3. The patient's other drugs included lisinopril,
acetaminophen. After being seen for symptoms of depression, anxiety, and insomnia, the patient was giv
mg 3 to 4 times per day. Eight days later, the patient's INR increased to 4.8, and the dose of warfarin wa
was later seen for symptoms of drug delirium, including confusion, incoherence, and speaking irrationally
was discontinued. The next day the patient presented to the hospital with left-sided weakness and later c
interparenchymal hemorrhage. The authors proposed that the addition of fluoxetine to the patient's regim
warfarin and diazepam, resulting in delirium and loss of anticoagulant control (Dent & Orrock, 1997).

3.5.1.GI Phenelzine

1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental sta
2) Summary: Concurrent administration or overlapping therapy with fluoxetine and a monoamine oxidase (M
serotonin syndrome, a hyperserotonergic state characterized by symptoms such as restlessness, myoclonus
diaphoresis, shivering, and tremor. Serious, even fatal, reactions have been reported (Prod Info Prozac(R), 1
1993e; Feighner et al, 1990e; Kline et al, 1989e; Suchowersky & de Vries, 1990e). Concomitant use of phene
least five weeks between discontinuation of fluoxetine and initiation of phenelzine and at least 10 days betwe
fluoxetine, or other serotoninergic agents (Prod Info Nardil(R), 1995).
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Concurrent use of fluoxetine and phenelzine is contraindicated. Wait at least 14 day
fluoxetine therapy. In addition, wait at least five weeks after discontinuing fluoxetine before initiating therapy v
7) Probable Mechanism: inhibition of serotonin metabolism by monoamine oxidase
8) Literature Reports
a) Concomitant use of serotonin specific reuptake inhibitors and monoamine oxidase inhibitors can prod
syndrome (Sternbach, 1991f). Serotonin syndrome is a condition of serotonergic hyperstimulation and m
mental status, hyperreflexia, diaphoresis, shivering, and tremor. If the syndrome is not recognized and c
b) It has been suggested that fluoxetine therapy be discontinued for five weeks before beginning therap
one case report describes a 28-year old woman who had discontinued a 2-year fluoxetine regimen for si
tranylcypromine. Over the next few days the patient developed fever, paresthesias, confusion, abdomina
Upon discontinuation of tranylcypromine, the patient's symptoms began to resolve. Blood samples taken
tranylcypromine revealed no presence of fluoxetine; however, the norfluoxetine level was 84 ng/mL (Cop
c) Adverse reactions reported when fluoxetine was given concomitantly with phenelzine (n=9) or tranylc
restlessness (42%), mental status changes (42%), myoclonus (33%), diarrhea (33%), and blood pressur
one of the patients were taking other medications (ie, benzodiazepines, neuroleptics, anticonvulsants, ar
adverse reactions.
d) Ten hours after her last dose of fluoxetine, a 45-year-old woman began tranylcypromine therapy (Klin
insomnia, and unsteady gait were reported on the second day. Thioridazine and tryptophan were added
rigidity of the arms and legs, and hyperreflexia. She died in the intensive care unit of a hospital 44 hours
e) Two cases suggestive of an interaction between fluoxetine and selegiline were reported (Suchowersk
episode of mania being observed approximately one month after adding selegiline to fluoxetine therapy.
drugs were discontinued, and no further details were provided. The second case involved diaphoresis, v
occurred in close temporal relationship to adding fluoxetine and selegiline. Both drugs were discontinuec
Rechallenge with fluoxetine alone occurred without incident.

3.5.1.GJ Phenindione

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and
use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2
(R) oral capsules, delayed-release capsules, solution, 2008). Bleeding events reported have included epistax
threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported wi
(Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When fluoxetine and an anticoagulant are given concurrently, monitor patient for sig
taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, wh
(Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
7) Probable Mechanism: unknown
8) Literature Reports
a) Fluoxetine is thought to inhibit the cytochrome P450 2C9 isoenzyme (CYP2C9). This is the enzyme b
warfarin, is metabolized (Riesenman, 1995). In addition, both fluoxetine and warfarin are tightly bound to
protein-binding displacement of either drug is present (Prod Info Coumadin(R), 1999).
b) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bl
patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks followi
mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected p

SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients
treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4
corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively.
treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only
bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI
dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding
exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model
c) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoum
reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal blee
hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal b
subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690
for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interva
gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekam
d) In 6 reported cases, INR increased during combined fluoxetine and warfarin therapy. In a seventh ca
a woman initially treated with fluoxetine and, secondarily, started on warfarin (Woolfrey et al, 1993; Claire
e) An 83-year-old man died from cerebral hemorrhage secondary to increased warfarin concentrations.
week for atrial fibrillation with a target INR between 2 and 3. The patient's other drugs included lisinopril,
acetaminophen. After being seen for symptoms of depression, anxiety, and insomnia, the patient was giv
mg 3 to 4 times per day. Eight days later, the patient's INR increased to 4.8, and the dose of warfarin wa
was later seen for symptoms of drug delirium, including confusion, incoherence, and speaking irrationally
was discontinued. The next day the patient presented to the hospital with left-sided weakness and later d
interparenchymal hemorrhage. The authors proposed that the addition of fluoxetine to the patient's regim
warfarin and diazepam, resulting in delirium and loss of anticoagulant control (Dent & Orrock, 1997).

3.5.1.GK Phenprocoumon

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and
use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2
(R) oral capsules, delayed-release capsules, solution, 2008). Bleeding events reported have included epistax
threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported wi
(Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When fluoxetine and an anticoagulant are given concurrently, monitor patient for sig
taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, wh
(Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
7) Probable Mechanism: unknown
8) Literature Reports

a) Fluoxetine is thought to inhibit the cytochrome P450 2C9 isoenzyme (CYP2C9). This is the enzyme b
warfarin, is metabolized (Riesenman, 1995). In addition, both fluoxetine and warfarin are tightly bound to
protein-binding displacement of either drug is present (Prod Info Coumadin(R), 1999).
b) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bl
patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks followi
mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected p
SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients
treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4
corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively.
treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only
bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI
dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding
exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model
c) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoum
reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal blee
hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal b
subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690
for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interva
gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekam
d) In 6 reported cases, INR increased during combined fluoxetine and warfarin therapy. In a seventh ca
a woman initially treated with fluoxetine and, secondarily, started on warfarin (Woolfrey et al, 1993; Claire
e) An 83-year-old man died from cerebral hemorrhage secondary to increased warfarin concentrations.
week for atrial fibrillation with a target INR between 2 and 3. The patient's other drugs included lisinopril,
acetaminophen. After being seen for symptoms of depression, anxiety, and insomnia, the patient was giv
mg 3 to 4 times per day. Eight days later, the patient's INR increased to 4.8, and the dose of warfarin wa
was later seen for symptoms of drug delirium, including confusion, incoherence, and speaking irrationally
was discontinued. The next day the patient presented to the hospital with left-sided weakness and later d
interparenchymal hemorrhage. The authors proposed that the addition of fluoxetine to the patient's regim
warfarin and diazepam, resulting in delirium and loss of anticoagulant control (Dent & Orrock, 1997).

3.5.1.GL Phenylalanine

1) Interaction Effect: increased incidence of tardive dyskinesia

2) Summary: Taking phenylalanine concomitantly with certain neuroleptic drugs may exacerbate tardive dysk phenylalanine metabolism in certain patients may lead to phenylalanine accumulation in the brain and in turn amino acids. This may interfere with the synthesis of catecholamines (Gardos et al, 1992a).

3) Severity: moderate

4) Onset: rapid

5) Substantiation: theoretical

6) Clinical Management: Caution is advised if phenylalanine is administered with a neuroleptic agent. Monito dyskinesia.

7) Probable Mechanism: reduced brain availability of other large neutral amino acids and interference with ca

8) Literature Reports

a) Phenylalanine tended to increase the incidence of tardive dyskinesia in patients taking neuroleptics ir studied: (1) patients with unipolar depression with tardive dyskinesia (n=11), (2) patients with no tardive greater than or equal to 100 milligrams (mg) of a chlorpromazine equivalent for at least 3 months (n=10), previously exposed to a neuroleptic drug (n=10). Neuroleptic agents were taken during the study by 6 pa Patients received powdered phenylalanine 100 mg/kilogram dissolved in orange juice after an overnight phenylalanine administration and 2 hours after administration. Three patients in group 1 (with tardive dys phenylalanine plasma levels, this group as a whole had higher (though nonsignificant) mean phenylalani dyskinesia score (measured using the Abnormal Involuntary Movements Scale (AIMS)) nonsignificantly i level and postloading AIMS scores were significantly positively correlated in group 1 (rs=0.347, p less tha p less than 0.05). Postloading phenylalanine level and baseline AIMS scores demonstrated a trend towa correlation coefficient 0.679, p less than 0.05). In all patients, phenylalanine loading increased plasma ph plasma tyrosine increased 2.5 times as a result of conversion of phenylalanine to tyrosine. Plasma levels tryptophan decreased slightly (Gardos et al, 1992).

3.5.1.GM Phenylbutazone

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have incl petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info L CELEXA (R) oral tablet, solution, 2005).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressar hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of up than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin inc

b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with TORADOL(R) oral tablets, 2007).

3.5.1.GN Phenytoin

1) Interaction Effect: an increased risk of phenytoin toxicity (ataxia, hyperreflexia, nystagmus, tremor)

2) Summary: Several case reports indicate that concurrent use of fluoxetine and phenytoin can result in sign leading to toxicity (FDA, 1994a; Jalil, 1992a; Woods et al, 1994). Alternatively, patients who are stabilized on experience subtherapeutic concentrations of phenytoin and loss of seizure control when fluoxetine is disconti vitro study, the inhibitory effects of fluoxetine on cytochrome P450 2C9 were evaluated using p-hydroxylation reflecting CYP2C9 activity. In vivo, p-hydroxylation of phenytoin depends on the formation of 5-(p-hydroxy-ph specifically the R-component of the racemic fluoxetine mixture, impaired the formation of HPPH, which can le levels (Schmider et al, 1997).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Monitor phenytoin serum levels with the addition of fluoxetine and periodically there may be required with concomitant therapy. Serum levels of phenytoin should be monitored following the disc the long half-life of fluoxetine, decreases in phenytoin levels may not be clinically significant for a few weeks.

7) Probable Mechanism: decreased phenytoin metabolism

8) Literature Reports

a) Twenty-three reported cases of fluoxetine-phenytoin interactions have resulted in large increases in s phenytoin toxicity. On the average, the adverse effects began within two weeks after fluoxetine was adde increase in plasma levels in nine evaluable cases was 161% (range 75 to 309%) and the maximum pher

ranged from 22 to 53.5 mcg/mL (therapeutic level, 10 to 20 mcg/mL) (FDA, 1994).
b) An 84-year-old woman was stabilized on phenytoin 300 mg daily. After two months of treatment, fluox
increased to 40 mg daily after 10 days (Jalil, 1992). Within five days of starting fluoxetine, she developec
status; her phenytoin serum level had increased from 15 to 35 mcg/mL. Both phenytoin and fluoxetine w
symptoms of toxicity abated. Four weeks later she was rechallenged with the same dose of fluoxetine wi
c) In another case, a 57-year-old woman who had been stabilized on phenytoin 400 mg daily for a year
20 mg daily (Jalil, 1992). Ten days later she developed vomiting, vertigo, trunk ataxia, limb dysmetria, an
serum level was 47 mcg/mL. Fluoxetine was discontinued and all signs and symptoms of toxicity disappe
post-fluoxetine, the phenytoin serum level was 20 mcg/mL.
d) A 42-year-old male with a history of grand mal seizures and aggressive behavior was receiving pheny
daily without resolution of his problems. His phenytoin level was 2.0 ng/mL and his dose was subsequen
daily was added for aggression, and the patient experienced resolution of his behavioral problems and a
level ranged between 10.9 ng/mL and 15.7 ng/mL during fluoxetine therapy. However, the patient discon
experienced a recurrence of problems. Phenytoin concentration was measured at 6.6 ng/mL six weeks a
change in his phenytoin dose. This case report illustrates the need for close monitoring of phenytoin leve
since subtherapeutic levels of phenytoin may result if doses of phenytoin are not readjusted following the
1999).

3.5.1.GO Pimozide

1) Interaction Effect: bradycardia, somnolence, and potentially increased risk of cardiotoxicity (QT prolongati
2) Summary: One case of bradycardia and somnolence resulting from concomitant fluoxetine and pimozide t
Although a specific interaction study has not been conducted with these agents, due to the potential for additi
of fluoxetine and pimozide is contraindicated (Prod Info PROZAC(R) oral capsule, oral pulvule, oral solution,
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Due to the possibility of additive effects on the QT interval, the concurrent administr
contraindicated.
7) Probable Mechanism: additive effects on QT prolongation
8) Literature Reports
a) One case has been reported in which concurrent use of pimozide 5 mg daily and fluoxetine 20 mg da
bradycardia and somnolence. The pulse rate gradually returned to normal after discontinuation of pimozi
a higher fluoxetine dose also resulted in bradycardia (Ahmed et al, 1993).

3.5.1.GP Pirazolac

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control anc
use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have incl
petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info L
CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent
Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressar
hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of u
than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose
confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of
upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin inc
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with
TORADOL(R) oral tablets, 2007).

3.5.1.GQ Pirmenol

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, the coadministration of Class
prolong the QTc interval is not recommended (Prod Info Quinaglute Dura-tabs(R), 1999). Fluoxetine has dem
(Prod Info Prozac(R), 2001z).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of class Ia antiarrhythmic agents and agents that pro
recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.GR Piroxicam

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have incl petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info L CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressar hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of u than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin inc
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with TORADOL(R) oral tablets, 2007).

3.5.1.GS Pirprofen

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have incl petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info L CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressar hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of u than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin inc
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with TORADOL(R) oral tablets, 2007).

3.5.1.GT Prajmaline

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, the coadministration of Class prolong the QTc interval is not recommended (Prod Info Quinaglute Dura-tabs(R), 1999). Fluoxetine has dem (Prod Info Prozac(R), 2001z).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of class Ia antiarrhythmic agents and agents that pro recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.GU Probucol

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Fluoxetine and probucol have been shown to prolong the QTc interval at the recommended the Gohn & Simmons, 1992; Prod Info Lorelco(R), 1991). Even though no formal drug interaction studies have be prolong the QTc interval is not recommended.
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of fluoxetine and probucol is not recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.GV Procainamide

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, the coadministration of Class prolong the QTc interval is not recommended (Prod Info Quinaglute Dura-tabs(R), 1999). Fluoxetine has dem

(Prod Info Prozac(R), 2001z).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of class Ia antiarrhythmic agents and agents that pro
recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.GW Procarbazine
1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental sta
2) Summary: Concurrent administration or overlapping therapy with fluoxetine and a monoamine oxidase (M
serotonin syndrome, a hyperserotonergic state characterized by symptoms such as restlessness, myoclonus
diaphoresis, shivering, and tremor. Serious, even fatal, reactions have been reported (Prod Info Prozac(R), 1
1993a; Feighner et al, 1990a; Kline et al, 1989a; Suchowersky & de Vries, 1990a). Concomitant use is contra
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: established
6) Clinical Management: Concurrent use of fluoxetine and procarbazine is contraindicated. Wait at least two
initiating fluoxetine therapy. In addition, wait at least five weeks after discontinuing fluoxetine before initiating
7) Probable Mechanism: inhibition of serotonin metabolism by monoamine oxidase
8) Literature Reports
a) Concomitant use of serotonin specific reuptake inhibitors and monoamine oxidase inhibitors can prod
syndrome (Sternbach, 1991a). Serotonin syndrome is a condition of serotonergic hyperstimulation and n
mental status, hyperreflexia, diaphoresis, shivering, and tremor (Sternbach, 1991a). If the syndrome is n
result.
b) It has been suggested that fluoxetine therapy be discontinued for at least five weeks before beginning
28-year old woman discontinued fluoxetine for six weeks before starting therapy with tranylcypromine. O
fever, paresthesias, confusion, abdominal cramping, and various other CNS symptoms. Upon discontinu
began to resolve. Blood samples taken three days after discontinuation of tranylcypromine revealed no p
level was 84 ng/mL (Coplan & Gorman, 1993).
c) Adverse reactions reported when fluoxetine was given concomitantly with phenelzine (n=9) or tranylc
restlessness (42%), mental status changes (42%), myoclonus (33%), diarrhea (33%), and blood pressur
one of the patients were taking other medications (ie, benzodiazepines, neuroleptics, anticonvulsants, ar
adverse reactions.
d) Ten hours after her last dose of fluoxetine, a 45-year-old woman began tranylcypromine therapy (Klin
insomnia, and unsteady gait were reported on the second day. Thioridazine and tryptophan were added
rigidity of the arms and legs, and hyperreflexia. She died in the intensive care unit of a hospital 44 hours
e) Two cases reports suggested a possible interaction between fluoxetine and selegiline (Suchowersky
episode of mania being observed approximately one month after adding selegiline to fluoxetine therapy.
drugs were discontinued, and no further details were provided. The second case involved diaphoresis, v
occurred in close temporal relationship to adding fluoxetine and selegiline. Both drugs were discontinued
Rechallenge with fluoxetine alone occurred without incident.

3.5.1.GX Prochlorperazine
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Although citing no data, the manufacturers of some phenothiazines state that concomitant use
not recommended. Q and T wave distortions have been observed in patients taking phenothiazines (Prod Inf
2002; Prod Info Thorazine(R), 2002) . Other phenothiazines may have similar effects, though no reports are a
the QTc interval at the recommended therapeutic dose (Prod Info Prozac(R), 2003).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of fluoxetine and a phenothiazine is not recommende
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.GY Propafenone
1) Interaction Effect: increased serum propafenone concentrations and an increased risk of cardiotoxicity (QT
arrest)
2) Summary: Propafenone has been shown to prolong the QTc interval (Larochelle et al, 1984). Fluoxetine h
recommended therapeutic dose (Prod Info Prozac(R), 2001e). Even though no formal drug interaction studies
known to prolong the QT interval are used concomitantly. In addition, fluoxetine may inhibit cytochrome P450
propafenone (Cai et al, 1999a).
3) Severity: major
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Caution is advised if fluoxetine and propafenone are used concomitantly.
7) Probable Mechanism: inhibition of cytochrome P450 2D6-mediated propafenone metabolism; theoretical a
8) Literature Reports

a) The metabolism of propafenone enantiomers was altered after fluoxetine treatment in 9 healthy Chine CYP2D6 metabolizers. Subjects received a single oral dose of propafenone 400 mg both before and afte clearance of both S- and P- enantiomers of propafenone decreased from approximately 75 L/hr to 50 L/h Compared to baseline, the elimination half life, peak concentration, and area under the curve for both en significantly increased (Cai et al, 1999).

3.5.1.GZ Propranolol

1) Interaction Effect: an increased risk of complete heart block
2) Summary: Metabolism of propranolol occurs in the liver and is thought to involve cytochrome P450IID6 (C CYP2D6 (DeVane, 1994a). It is theoretically possible that coadministered fluoxetine could inhibit propranolol concentrations of this beta blocker and possible toxicity. One case report describes a man who developed co was added to propranolol therapy (Drake & Gordon, 1994a).
3) Severity: minor
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Fluoxetine should be prescribed cautiously to patients on propranolol therapy. A ba prior to the initiation of fluoxetine.
7) Probable Mechanism: impaired atrioventricular conduction
8) Literature Reports
a) A 53-year-old male experienced a loss of consciousness two weeks after fluoxetine 20 mg daily was included propranolol 40 mg twice daily for anxiety. He had no previous cardiac history. An electrocardiog fluoxetine and propranolol were both discontinued. Two days later, the patient reverted to sinus rhythm v heart block was attributed to the fluoxetine-propranolol combination, since sinus rhythm returned two day patient had no previous complications from propranolol therapy. Because 5-hydroxytryptamine (5-HT) re fluoxetine may have potentiated the action of 5-HT, causing impaired atrioventricular conduction (Drake

3.5.1.HA Propyphenazone

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have incl petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info L CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressar hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of u than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin inc
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with TORADOL(R) oral tablets, 2007).

3.5.1.HB Proquazone

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have incl petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info L CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressar hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of u than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin inc
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with TORADOL(R) oral tablets, 2007).

3.5.1.HC Quetiapine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Fluoxetine has been shown to prolong the QTc interval at the recommended therapeutic dose (formal drug interaction studies have been done, the coadministration of antipsychotics and other drugs known fluoxetine, is not recommended. Several antipsychotic agents have demonstrated QT prolongation including quetiapine (Owens, 2001b), sertindole (Agelink et al, 2001), sultopride (Lande et al, 1992), and zotepine (Swe
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of fluoxetine and antipsychotics is not recommended
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.HD Quinidine

1) Interaction Effect: an increased risk of fluoxetine and quinidine toxicity and an increased risk of cardiotoxic cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, the coadministration of Class drugs known to prolong the QTc interval is not recommended (Prod Info Quinaglute Dura-tabs(R), 1999a). Fl therapeutic doses (Prod Info Prozac(R), 2001af). In addition, quinidine inhibits CYP2D6 which may reduce flu 1993b) and fluoxetine inhibits CYP3A4, which may reduce quinidine metabolism (Nemeroff et al, 1996).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of Class Ia antiarrhythmic agents, such as quinidine, fluoxetine, is not recommended.
7) Probable Mechanism: altered fluoxetine or quinidine metabolism; additive effects on QT prolongation
8) Literature Reports
a) In vitro studies found that quinidine, a potent inhibitor of CYP2D6, inhibited fluoxetine N-demethylatio indicating that fluoxetine is, in part, metabolized by CYP2D6, this study showed that much of fluoxetine n

3.5.1.HE Rasagiline

1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental sta
2) Summary: Concurrent administration or overlapping therapy with selective serotonin reuptake inhibitors, in the selective MAO-B inhibitor selegiline, has been reported to cause serious, sometimes fatal reactions. Sign myoclonus, autonomic instability with rapid vital sign fluctuations, and mental status changes progressing to e reactions have been reported with serotonin-norepinephrine reuptake inhibitors (SNRIs) and non-selective M not allow concomitant use of fluoxetine; the combination of rasagiline and fluoxetine should be avoided. Wait before initiating fluoxetine therapy. Wait at least five weeks or more, especially if fluoxetine has been used ch fluoxetine before initiating therapy with rasagiline (Prod Info AZILECT(R) oral tablets, 2006).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Concurrent use of fluoxetine and rasagiline should be avoided. Wait at least two we fluoxetine therapy. Wait at least five weeks or more, especially if fluoxetine has been used chronically and/or before initiating therapy with rasagiline.
7) Probable Mechanism: inhibition of serotonin metabolism by monoamine oxidase
8) Literature Reports
a) Concomitant use of serotonin specific reuptake inhibitors and monoamine oxidase inhibitors can prod syndrome (Sternbach, 1991l). Serotonin syndrome is a condition of serotonergic hyperstimulation and m mental status, hyperreflexia, diaphoresis, shivering, and tremor (Sternbach, 1991l). If the syndrome is nc result.

3.5.1.HF Reviparin

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2 (R) oral capsules, delayed-release capsules, solution, 2008). Bleeding events reported have included epistax threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported wi (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When fluoxetine and an anticoagulant are given concurrently, monitor patient for sig taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, wh (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
7) Probable Mechanism: unknown
8) Literature Reports
a) Fluoxetine is thought to inhibit the cytochrome P450 2C9 isoenzyme (CYP2C9). This is the enzyme b warfarin, is metabolized (Riesenman, 1995). In addition, both fluoxetine and warfarin are tightly bound to

protein-binding displacement of either drug is present (Prod Info Coumadin(R), 1999).
b) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bl patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks followi mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected p SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. T treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model
c) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoum reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal blee hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal b subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interva gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekam
d) In 6 reported cases, INR increased during combined fluoxetine and warfarin therapy. In a seventh ca a woman initially treated with fluoxetine and, secondarily, started on warfarin (Woolfrey et al, 1993; Claire
e) An 83-year-old man died from cerebral hemorrhage secondary to increased warfarin concentrations. week for atrial fibrillation with a target INR between 2 and 3. The patient's other drugs included lisinopril, acetaminophen. After being seen for symptoms of depression, anxiety, and insomnia, the patient was giv mg 3 to 4 times per day. Eight days later, the patient's INR increased to 4.8, and the dose of warfarin wa was later seen for symptoms of drug delirium, including confusion, incoherence, and speaking irrationally was discontinued. The next day the patient presented to the hospital with left-sided weakness and later c interparenchymal hemorrhage. The authors proposed that the addition of fluoxetine to the patient's regim warfarin and diazepam, resulting in delirium and loss of anticoagulant control (Dent & Orrock, 1997).

3.5.1.HG Risperidone

1) Interaction Effect: increased plasma concentrations of risperidone
2) Summary: Concomitant use of fluoxetine (CYP2D6 inhibitor) and risperidone (CYP2D6 substrate) has res concentrations and an increased risk of risperidone adverse effects such as serotonin syndrome, QT prolong mechanism of action is inhibition of CYP2D6-mediated metabolism of risperidone by fluoxetine. One study de patients treated concurrently with fluoxetine and risperidone (Prod Info RISPERDAL(R) oral tablets, oral solut al, 2002). Monitoring the patient for increased risperidone plasma levels side effects may be necessary (Spin reevaluated if fluoxetine is initiated or discontinued (Prod Info RISPERDAL(R) oral tablets, oral solution, orally 2002a).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Concomitant use of fluoxetine and risperidone has resulted in increased risperidone risperidone side effects (Prod Info RISPERDAL(R) oral tablets, oral solution, orally disintegrating tablets, 200 plasma risperidone levels and side effects (serotonin syndrome, extrapyramidal symptoms, and cardiotoxicity risperidone (Spina et al, 2002). Reevaluate the dose of risperidone when concomitant fluoxetine is initiated or tablets, oral solution, orally disintegrating tablets, 2008).
7) Probable Mechanism: inhibition of CYP2D6-mediated metabolism of risperidone
8) Literature Reports
a) Fluoxetine (a CYP2D6 inhibitor) 20 mg/day has been shown to increase the plasma concentration of fold. Fluoxetine did not affect the concentration of 9-hydroxyrisperidone. The dosage of risperidone shou discontinued (Prod Info RISPERDAL(R) oral tablets, oral solution, orally disintegrating tablets, 2008).
b) Fluoxetine, an inhibitor of cytochrome CYP2D6, may impair the elimination of risperidone, primarily b hydroxylation and, to a lesser extent, by simultaneously affecting the further metabolism of 9-hydroxyrisp risperidone biotransformation. In an open, 4-week, pharmacokinetic study including 9 patients with schiz type, risperidone concentrations increased when fluoxetine was coadministered with risperidone. Patient to 6 mg/day for at least four weeks and received adjunctive fluoxetine therapy 20 mg/day for the manage risperidone concentrations increased from 12 ng/mL at baseline to 49 nanograms (ng)/mL (p less than 0 at week 4. Plasma concentrations of 9-hydroxyrisperidone (9-OH-risperidone) showed no significant incr weeks of concurrent therapy, the active moiety (risperidone plus 9-OH-risperidone) was increased by 75 compared with baseline. The mean plasma risperidone to 9-OH-risperidone ratio also increased significa symptoms during week 2 of concomitant therapy and were treated with anticholinergic medication. The a risperidone levels may be warranted in patients receiving concomitant fluoxetine and risperidone treatme

3.5.1.HH Ritonavir

1) Interaction Effect: reduced olanzapine effectiveness
2) Summary: An open-label study involving 14 healthy volunteers revealed a significant alteration in pharma exposure of olanzapine when administered in the presence of ritonavir. Baseline blood samples were drawn 10 mg tablet. Venous blood samples were then obtained at specified times. After a 14-day washout period, s then 400 mg BID for 4 days, then 500 mg BID for 4 days. Blood samples were again drawn at specified times

were as follows: Statistically significant reductions in the mean olanzapine area under the plasma concentrati 235 (ng)hr/mL) (p less than 0.001); the half-life by 50% (from 32 hr to 16 hr) (p less than 0.00001) and the pe to 9 ng/mL) (p less than 0.002). The oral clearance of olanzapine increased by 115% (from 20 L/hr to 43 L/hr usually well-tolerated and a clear relationship between plasma concentrations and toxicity has not been defin needs further study (Penzak et al, 2002).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Monitor patients for olanzapine efficacy. Doses of olanzapine may need to be adjus Patients stabilized on olanzapine and ritonavir, who have their ritonavir discontinued, should have be monitor increased systemic exposure to olanzapine.
7) Probable Mechanism: induction or CYP1A2- and glucuronosyl transferase-mediated metabolism of olanza

3.5.1.HI Ritonavir
1) Interaction Effect: alterations in cardiac and/or neurologic function
2) Summary: Coadministration of fluoxetine 30 mg twice daily for eight days and ritonavir 600 mg as a single in the area under the concentration-time curve (AUC) of ritonavir but no changes in the ritonavir maximum co experience has revealed reports of cardiac and neurologic events when ritonavir and fluoxetine have been co
3) Severity: moderate
4) Onset: delayed
5) Substantiation: established
6) Clinical Management: Monitor the patient for changes in cardiac and/or neurologic function.
7) Probable Mechanism: unknown

3.5.1.HJ Rizatriptan
1) Interaction Effect: an increased risk of serotonin syndrome
2) Summary: There have been case reports of weakness, hyperreflexia, and incoordination following concon 1 (5HT-1) agonist, and a serotonin specific reuptake inhibitor (SSRI) (Prod Info Imitrex(R), 1998). Because ri similar interaction between SSRIs and rizatriptan may occur (Prod Info Maxalt(R), 1998a). Concurrent use of syndrome which may be life-threatening. Symptoms of serotonin syndrome may include restlessness, halluci rapid changes in blood pressure, increased body temperature, overreactive reflexes, nausea, vomiting, and c may be commonly used intermittently and that either the triptan or the SSRI may be prescribed by a different syndrome with patients who are prescribed this combination and monitor them closely for symptoms of seroto Administration, 2006).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Coadministration of a triptan, such as rizatriptan, and an SSRI may result in a life-th Be aware that triptans may be commonly used intermittently and that either the triptan or the SSRI may be pr are used together, discuss the risks of serotonin syndrome with the patient and monitor closely for symptoms hyperthermia, hyperreflexia, incoordination).
7) Probable Mechanism: additive pharmacologic effects resulting in excessive serotonergic stimulation
8) Literature Reports
a) Twelve healthy volunteers received paroxetine 20 mg daily for two weeks and a single dose of rizatrip were not altered by the administration of paroxetine (Prod Info Maxalt(R), 1998).

3.5.1.HK Rofecoxib
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have incl petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info L CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressar hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of u than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin inc
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with TORADOL(R) oral tablets, 2007).

3.5.1.HL Selegiline

1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental sta
2) Summary: Concurrent administration or overlapping therapy with fluoxetine and selegiline may result in Cl hyperserotonergic state characterized by symptoms such as restlessness, myoclonus, changes in mental sta tremor. Serious, even fatal, reactions have been reported (Prod Info Prozac(R), 1999g; Sternbach, 1991m; C Kline et al, 1989k; Suchowersky & de Vries, 1990k). Concomitant use is contraindicated. A minimum of 14 da before initiating therapy with fluoxetine. At least five weeks should elapse after discontinuing fluoxetine prior t EMSAM(R) transdermal patch, 2006).
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Concurrent use of fluoxetine and selegiline is contraindicated. Wait at least two wee fluoxetine therapy. In addition, wait at least five weeks after discontinuing fluoxetine before initiating therapy v
7) Probable Mechanism: inhibition of serotonin metabolism by monoamine oxidase
8) Literature Reports
a) Concomitant use of serotonin specific reuptake inhibitors and monoamine oxidase inhibitors can prod syndrome (Sternbach, 1991l). Serotonin syndrome is a condition of serotonergic hyperstimulation and m mental status, hyperreflexia, diaphoresis, shivering, and tremor (Sternbach, 1991l). If the syndrome is nc result.
b) It has been suggested that fluoxetine therapy be discontinued for five weeks before beginning therap one case report describes a 28-year old woman who had discontinued a 2-year fluoxetine regimen for si tranylcypromine. Over the next few days the patient developed fever, paresthesias, confusion, abdomina Upon discontinuation of tranylcypromine, the patient's symptoms began to resolve. Blood samples taken tranylcypromine revealed no presence of fluoxetine; however, the norfluoxetine level was 84 ng/mL (Cop
c) Adverse reactions reported when fluoxetine was given concomitantly with phenelzine (n=9) or tranylc restlessness (42%), mental status changes (42%), myoclonus (33%), diarrhea (33%), and blood pressur one of the patients were taking other medications (ie, benzodiazepines, neuroleptics, anticonvulsants, ar adverse reactions.
d) Ten hours after her last dose of fluoxetine, a 45-year-old woman began tranylcypromine therapy (Klin insomnia, and unsteady gait were reported on the second day. Thioridazine and tryptophan were added rigidity of the arms and legs, and hyperreflexia. She died in the intensive care unit of a hospital 44 hours
e) Two cases suggestive of an interaction between fluoxetine and selegiline were reported (Suchowersk episode of mania being observed approximately one month after adding selegiline to fluoxetine therapy. drugs were discontinued, and no further details were provided. The second case involved diaphoresis, v occurred in close temporal relationship to adding fluoxetine and selegiline. Both drugs were discontinued Rechallenge with fluoxetine alone occurred without incident.

3.5.1.HM Sematilide
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, the coadministration of Class prolong the QTc interval is not recommended (Allen et al, 2002; Prod Info Tikosyn(TM) dofetilide capsules, 19 been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Prozac(R), 2001a).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of class III antiarrhythmic agents and agents that pro recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.HN Sertindole
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Fluoxetine has been shown to prolong the QTc interval at the recommended therapeutic dose formal drug interaction studies have been done, the coadministration of antipsychotics and other drugs know fluoxetine, is not recommended. Several antipsychotic agents have demonstrated QT prolongation including quetiapine (Owens, 2001b), sertindole (Agelink et al, 2001), sultopride (Lande et al, 1992), and zotepine (Sw
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of fluoxetine and antipsychotics is not recommended
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.HO Sibrafiban
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and use of SSRIs and antiplatelet agents has been associated with an increased risk of bleeding. Bleeding events hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008; release capsules, solution, 2008).
3) Severity: major
4) Onset: unspecified

5) Substantiation: probable
6) Clinical Management: When an SSRI and an antiplatelet agent are given concurrently, monitor patient for oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 200
7) Probable Mechanism: unknown

3.5.1.HP Sibutramine
1) Interaction Effect: an increased risk of serotonin syndrome (hypertension, hyperthermia, myoclonus, ment
2) Summary: Sibutramine inhibits the reuptake of norepinephrine, dopamine, and serotonin. In addition, the t M2, also inhibit the reuptake of these neurotransmitters. A hyperserotonergic state, termed serotonin syndror concurrently with a selective serotonin reuptake inhibitor. Coadministration of sibutramine and selective serot (Prod Info Meridia(R), 1997).
3) Severity: major
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Sibutramine should not be administered with serotonergic agents, including selectiv increased risk of serotonin syndrome.
7) Probable Mechanism: additive pharmacologic effects resulting in excessive serotonergic stimulation
8) Literature Reports
a) Serotonin syndrome is a condition of serotonergic hyperstimulation and manifests as restlessness, m hyperreflexia, diaphoresis, shivering, and tremor. If the syndrome is not recognized and correctly treated

3.5.1.HQ Sotalol
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest
2) Summary: Even though no formal drug interaction studies have been done, the coadministration of Class prolong the QTc interval is not recommended (Allen et al, 2002; Prod Info Tikosyn(TM) dofetilide capsules, 1 been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Prozac(R), 2001a).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of class III antiarrhythmic agents and agents that pro recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.HR Spiramycin
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest
2) Summary: Spiramycin and fluoxetine have been shown to prolong the QTc interval at the recommended t Stramba-Badiale et al, 1997). Even though no formal drug interaction studies have been done, the coadminis interval is not recommended.
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of spiramycin and fluoxetine is not recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.HS St John's Wort
1) Interaction Effect: reduced olanzapine efficacy
2) Summary: This interaction is based on in vitro information that St. John's Wort induced CYP1A2 enzymes reduced blood theophylline concentrations and loss of efficacy (Nebel et al, 1999). Since olanzapine is metab olanzapine may be similarly affected. If St. John's Wort and olanzapine are taken together, their dosages sho that increased dosages of olanzapine may be required. Discontinuation of St. John's Wort should be done ca increase and dose reduction may be required.
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Avoid concomitant use of olanzapine with St. John's Wort. If patients elect to remai consistent dosing. Olanzapine dosage may need to be increased. Patients should not discontinue St. John's downward adjustments in olanzapine dose may be necessary as well as monitoring for increased side effects constipation, dry mouth, asthenia).
7) Probable Mechanism: induction of cytochrome P450 1A2 enzymes by St. John's Wort

3.5.1.HT St John's Wort
1) Interaction Effect: an increased risk of serotonin syndrome (hypertension, hyperthermia, myoclonus, ment
2) Summary: Case reports describe the onset of serotonin syndrome-like symptoms, mania, and hypomania sertraline, fluoxetine, and paroxetine therapy (Spinella & Eaton, 2002c; Barbanel et al, 2000a; Waksman et a a syndrome resembling sedative/hypnotic intoxication after adding St. John's Wort to paroxetine therapy (Go serotonin reuptake and may have mild monoamine oxidase inhibitory activity (Singer et al, 1999; Thiede & W serotonin reuptake inhibitors may result in serotonin syndrome.
3) Severity: major

4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Patients should be advised to wait two weeks after stopping St. John's Wort before therapy. If a patient plans to replace selective serotonin reuptake inhibitor (SSRI) therapy with St. John's Wor taken into consideration, waiting at least 5 half-lives for the SSRI to be metabolized out of the body.
7) Probable Mechanism: additive serotonergic effect
8) Literature Reports

a) Five cases have been reported of serotonin syndrome in the elderly after combining prescription antic developed dizziness, nausea, vomiting and a headache 4 days after starting St. John's Wort 300 milligra sertraline 50 mg daily. Her symptoms resolved 2 to 3 days after stopping all medications. Case 2 develo after starting St. John's Wort 300 mg twice daily combined with sertraline 75 mg daily. His symptoms res medications, and he resumed sertraline use without complications. The third case developed nausea, vo starting St. John's Wort 300 mg twice daily combined with sertraline 50 mg daily. His symptoms improve and taking cyproheptadine 4 mg three times daily. Case 4 developed nausea, anxiety, restless, and irrita three times daily combined with sertraline 50 mg daily. Cyproheptadine 4 mg twice daily was administere 1 week after stopping the medication. Cases 1 through 4 resumed their prescriptive sertraline after symp Case 5 developed nausea, vomiting and restlessness 3 days after starting St. John's Wort 300 mg three twice daily. She continued to take St. John's Wort but discontinued the nefazodone and over 1 week her therapy with nefazodone, but continued therapy with St. John's Wort and mild to moderate symptoms of 1999).

b) A 50-year-old female taking St. John's Wort 600 mg daily experienced symptoms of sedative intoxica paroxetine 20 mg. She was incoherent, groggy, slow-moving, and complained of nausea and weakness. receiving paroxetine 40 mg daily for eight months without adverse effects. After a night of sleep, she retu 1998).

c) A 61-year-old female experienced restlessness and involuntary movements of her extremities after b after discontinuing St. John's Wort 600 mg daily. The patient reported agitation and akathisia 8 hours aft presented with diaphoresis and involuntary movement of all extremities with hyperreflexia and rigidity. Bl normal. After admission, blood pressure increased to 200/116 mmHg and heart rate increased to 145 be 212 units/liter (U/L) initially to 1024 U/L. The patient was managed with supportive care and lorazepam a 2000).

d) A 28-year-old male developed a manic syndrome following comedication with St. John's Wort and se replacement therapy following bilateral orchidectomy 2 years earlier, but testosterone levels were subthe 50 milligrams daily for depression following a 2 week trial of St. John's Wort per patient preference (dose patient was instructed to discontinue St. John'sWort, but continued it despite this advice. The patient exp physician, believing that he did not need further treatment. Over 2 months, the patient had elated mood, could not afford, and was ultimately arrested for stealing fuel for the car. On arrest, he was referred to ps disinhibition. He was observed to be over-aroused, distractible, have flight of ideas, and grandiose delus The authors state the possibility of the manic state resulting from sertraline therapy alone, and that St. Jo result of monoamine oxidase inhibition. Since the patient's testosterone level was subnormal, the possibi considered low. However, the patient had elevated gonadotropin levels (luteinizing hormone and follicle- predisposed the patient to mania (Barbanel et al, 2000).

e) A 42-year-old female experienced symptoms consistent with a mixed hypomanic episode following co biloba, and St. John's Wort. The symptoms resolved following discontinuation of Ginkgo and St. John's V depression following a mild traumatic brain injury with fluoxetine 20 milligrams (mg) twice daily and busp presentation, buspirone was increased to 20 mg twice daily for persistent anxiety and the patient began t Wort in unspecified doses. Melatonin was considered unlikely to have contributed to her symptoms. Gink possible contributors since they may potentiate antidepressants, and considering the temporal relationsh symptoms and discontinuation of the herbs and resolution of symptoms. However, the brain injury was c Eaton, 2002b).

3.5.1.HU Sulfamethoxazole

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Cotrimoxazole and fluoxetine have been shown to prolong the QTc interval at the recommende 2001ah; Lopez et al, 1987). Even though no formal drug interaction studies have been done, the coadministra is not recommended.
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of cotrimoxazole and fluoxetine is not recommended
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.HV Sulfinpyrazone

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and use of SSRIs and antiplatelet agents has been associated with an increased risk of bleeding. Bleeding events hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008; release capsules, solution, 2008).
3) Severity: major

4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an antiplatelet agent are given concurrently, monitor patient for oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 200
7) Probable Mechanism: unknown

3.5.1.HW Sulindac
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have incl petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info L CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressar hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of u than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin inc
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with TORADOL(R) oral tablets, 2007).

3.5.1.HX Sulodexide
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and use of SSRIs and antiplatelet agents has been associated with an increased risk of bleeding. Bleeding events hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008; release capsules, solution, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an antiplatelet agent are given concurrently, monitor patient for oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 200
7) Probable Mechanism: unknown

3.5.1.HY Sultopride
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Fluoxetine has been shown to prolong the QTc interval at the recommended therapeutic dose formal drug interaction studies have been done, the coadministration of antipsychotics and other drugs know fluoxetine, is not recommended. Several antipsychotic agents have demonstrated QT prolongation including quetiapine (Owens, 2001b), sertindole (Agelink et al, 2001), sultopride (Lande et al, 1992), and zotepine (Sw
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of fluoxetine and antipsychotics is not recommended
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.HZ Sumatriptan
1) Interaction Effect: an increased risk of serotonin syndrome
2) Summary: There have been case reports of weakness, hyperreflexia, and incoordination following concon reuptake inhibitor (SSRI) (Prod Info Imitrex(R), 2002). Concurrent use of a triptan and an SSRI may result in threatening. Symptoms of serotonin syndrome may include restlessness, hallucinations, loss of coordination, increased body temperature, overreactive reflexes, nausea, vomiting, and diarrhea. Clinicians should be awa intermittently and that either the triptan or the SSRI may be prescribed by a different physician. Discuss the ri prescribed this combination and monitor them closely for symptoms of serotonin syndrome (US Food and Dr
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Coadministration of a triptan, such as sumatriptan, and an SSRI, such as fluoxetine serotonin syndrome. Be aware that triptans may be commonly used intermittently and that either the triptan o physician. If these agents are used together, discuss the risks of serotonin syndrome with the patient and mo (restlessness, hyperthermia, hyperreflexia, incoordination).
7) Probable Mechanism: additive pharmacologic effects resulting in excessive serotonergic stimulation

8) Literature Reports
a) In the Canadian post-marketing surveillance program of fluoxetine, six cases of suspected drug intera these cases, two are strongly suggestive of a drug interaction. Patients demonstrated symptoms consist 1997).

3.5.1.IA Suprofen
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have incl petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info L CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressar hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of u than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin inc
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with TORADOL(R) oral tablets, 2007).

3.5.1.IB Tamoxifen
1) Interaction Effect: decreased tamoxifen efficacy
2) Summary: A retrospective analysis revealed a 1.9-fold higher breast cancer recurrence rate in patients re tamoxifen than those receiving tamoxifen alone (Aubert, Stanek, and Yao, 2009). Coadministration of tamoxi fluoxetine, may inhibit the CYP2D6-mediated metabolism of tamoxifen to the active metabolite, endoxifen. M concomitantly with tamoxifen closely for loss of tamoxifen efficacy.
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of fluoxetine and tamoxifen may result in decreased concentratior thereby decreasing tamoxifen efficacy. If administered concurrently, monitor closely for decreased tamoxifen
7) Probable Mechanism: inhibition of CYP2D6-mediated tamoxifen metabolism to endoxifen (active metaboli
8) Literature Reports
a) A retrospective analysis of breast cancer patients revealed a 1.9-fold higher 2-year recurrence rate of therapy with tamoxifen and a CYP2D6 inhibitor compared with those receiving tamoxifen therapy alone. 1928 patients who were new to tamoxifen therapy in a 30-month period and who had follow-up data for a Among these patients, 353 (median age, 53 years) received tamoxifen concurrently with a CYP2D6 inhib tamoxifen alone. Disease recurrence was identified by diagnosis and insurance billing codes for mastect radiation therapy, occurring at least 6 months after initiation of tamoxifen therapy. The 2-year breast can receiving concomitant tamoxifen and CYP2D6 inhibitor therapy compared with 7.5% in women receiving hazard ratio, 1.92). Intervention procedures in the tamoxifen/CYP2D6 inhibitor group to treat breast canc (36%), and radiation therapy (47%); corresponding intervention rates in the tamoxifen only group were 5 and Yao, 2009).

3.5.1.IC Tamsulosin
1) Interaction Effect: an increase in tamsulosin plasma exposure
2) Summary: In vitro data have shown that tamsulosin is primarily metabolized by CYP2D6 and CYP3A4 hep a mild inhibitor of CYP450 enzymes, resulted in moderate increases in tamsulosin plasma exposure. Althoug conducted with moderate or strong CYP2D6 inhibitors, such as fluoxetine, use caution if these agents are co tamsulosin doses exceeding 0.4 mg (Prod Info FLOMAX(R) oral capsules, 2007). Patients should be monitor as postural hypotension, dizziness, and syncope.
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Due to the potential for increased tamsulosin plasma exposures, use caution when fluoxetine, are coadministered with tamsulosin, particularly at tamsulosin doses higher than 0.4 mg (Prod Info patients for increased tamsulosin adverse effects (postural hypotension, dizziness, and episodes of syncope)
7) Probable Mechanism: potential inhibition of CYP2D6-mediated tamsulosin metabolism

3.5.1.ID Tapentadol
1) Interaction Effect: increased risk of serotonin syndrome (hypertension, hyperthermia, myoclonus, mental s
2) Summary: Concurrent use of tapentadol and a selective serotonin reuptake inhibitor (SSRI) may result in

threatening. Symptoms of serotonin syndrome may include restlessness, hallucinations, loss of coordination, increased body temperature, overreactive reflexes, nausea, vomiting, and diarrhea (Prod Info tapentadol imm
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of tapentadol and an SSRI may result in a life-threatening conditic used together, monitor the patient closely for symptoms of serotonin syndrome (restlessness, hyperthermia, l treatment initiation and dose increases (Prod Info tapentadol immediate release oral tablets, 2008).
7) Probable Mechanism: additive serotonergic effect

3.5.1.IE Tedisamil
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, the coadministration of Class prolong the QTc interval is not recommended (Allen et al, 2002; Prod Info Tikosyn(TM) dofetilide capsules, 19 been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Prozac(R), 2001a).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of class III antiarrhythmic agents and agents that pro recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.IF Telithromycin
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, telithromycin should be coadn also known to prolong the QTc interval, including fluoxetine (Owens, 2001d; Prod Info Prozac(R), 2001o).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of telithromycin with other agents that can prolong th recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.IG Tenidap
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have incl petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info L CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressar hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of up than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin inc
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with TORADOL(R) oral tablets, 2007).

3.5.1.IH Tenoxicam
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have incl petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info L CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressar

hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of u
than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose
confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of
upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin inc
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with
TORADOL(R) oral tablets, 2007).

3.5.1.II Terfenadine

1) Interaction Effect: cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Although 2 cases have been reported in which concomitant terfenadine and fluoxetine resulted
heart disease, a study of 12 healthy males demonstrated no significant pharmacokinetic or pharmacodynami
(Swims, 1993a; Marchiando & Cook, 1995a; Bergstrom et al, 1997a). Terfenadine and fluoxetine have been
doses. The administration of terfenadine with any other medication that may prolong the QT interval is contra
3) Severity: contraindicated
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: The concomitant administration of fluoxetine and terfenadine is contraindicated.
7) Probable Mechanism: decreased terfenadine metabolism
8) Literature Reports
a) In a study of 12 healthy male volunteers, fluoxetine did not inhibit the metabolism of terfenadine. Fluo
Terfenadine 60 mg was given alone and after eight days of the nine-day fluoxetine regimen. A high dose
interaction rigorously. Subject were monitored for changes in terfenadine pharmacokinetics and adverse
slight decrease in terfenadine plasma concentration. In addition, the area under the plasma concentratio
decreased by fluoxetine. No change in blood pressure, heart rate, or cardiac electrographic tracings (EK
dizziness after taking terfenadine alone and one subject had an abnormal EKG at baseline and during al
1997).
b) A 39-year old woman experienced cardiac toxicity due to a possible interaction of terfenadine and flu
patient's medications included acyclovir, beclomethasone, pseudoephedrine, and ibuprofen. During hosp
program, the patient was started on fluoxetine 40 mg daily, terfenadine 60 mg twice daily, and disulfiram
patient underwent a routine electrocardiogram (ECG) study that revealed a prolonged QT interval of 550
had no prior history of heart disease. Terfenadine was discontinued, and an ECG taken one week later r
c) A case report describes a possible interaction with terfenadine and fluoxetine in a 41-year-old male w
beats, and shortness of breath a month after institution of fluoxetine 20 mg daily; he had no previous hist
fluoxetine, terfenadine 60 mg twice daily, ibuprofen 800 mg three times daily, misoprostol 100 mcg four t
dichloralphenazone 100 mg, isometheptene mucate 65 mg) as needed, and ranitidine 150 mg twice daily
frequent sinus tachycardia, three isolated atrial premature contractions, and three couplets. Terfenadine
symptoms did not reoccur. Fluoxetine is a known enzyme inhibitor and may have inhibited terfenadine m
seen in this patient (Swims, 1993).

3.5.1.IJ Tetrabenazine

1) Interaction Effect: increased risk of QT interval prolongation, neuroleptic malignant syndrome, extrapyram
2) Summary: Tetrabenazine causes a small increase in the correct QT interval. As the degree of prolongatio
torsade de pointes-type VT. The concomitant use of tetrabenazine with other drugs known for QT prolongatic
randomized, double-blind, placebo controlled crossover study of healthy subjects, the effect of a single 25 mg
interval was studied with moxifloxacin as a positive control. The 50 mg dose of tetrabenazine caused an appr
(Prod Info XENAZINE(R) oral tablets, 2008). In addition to QT prolongation, tetrabenazine may also cause ac
syndrome and extrapyramidal disorders, which may be exaggerated when coadministered with neuroleptic dr
oral tablets, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of tetrabenazine with olanzapine or other neuroleptic drugs may ir
as QT interval prolongation and increased risk of torsade de pointes. Other adverse reactions, such as neuro
disorders may be enhanced when given with a dopamine agonist such as olanzapine (Prod Info XENAZINE(I
7) Probable Mechanism: increased dopamine levels; additive effects on QT interval prolongation

3.5.1.IK Tetrabenazine

1) Interaction Effect: increased exposure to tetrabenazine
2) Summary: Caution should be used when administering a strong CYP2D6 inhibitor (eg, fluoxetine, paroxet
substrate), and the daily dose of tetrabenazine should be halved if fluoxetine and tetrabenazine are used con
tetrabenazine given after 10 days of daily administration of paroxetine 20 mg, an increase in tetrabenazine ex
When compared with tetrabenazine alone, coadministration with paroxetine caused an approximately 30% in
of the alpha-HTBZ metabolite of tetrabenazine. Subjects given paroxetine prior to tetrabenazine alone experi
increase in the AUC of the beta-HTBZ metabolite of tetrabenazine. The elimination half-life for both metabolit
tetrabenazine was coadministered with paroxetine (Prod Info XENAZINE(R) oral tablets, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable

6) Clinical Management: Use caution when prescribing fluoxetine to patients who take tetrabenazine. Patient tetrabenazine should have their daily dose of tetrabenazine decreased by half if coadministration with fluoxet and tetrabenazine may cause elevated tetrabenazine levels. Monitor for increased tetrabenazine side effects depression, anxiety, akathisia, and nausea (Prod Info XENAZINE(R) oral tablets, 2008).
7) Probable Mechanism: inhibition of CYP2D6-mediated tetrabenazine metabolism by fluoxetine

3.5.1.IL Thioridazine
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Fluoxetine inhibits the metabolism of thioridazine through inhibition of CYP2D6. The resulting e prolongation (Prod Info Mellaril(R), 2000). Fluoxetine has been shown to prolong the QTc interval at the reco 2001ae). Although citing no data, the manufacturer of thioridazine states that concomitant use with other drug contraindicated (Prod Info Mellaril(R), 2000).
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: The concurrent administration of fluoxetine and thioridazine is contraindicated.
7) Probable Mechanism: inhibition of cytochrome P450 2D6-mediated thioridazine metabolism; additive effec

3.5.1.IM Tiaprofenic Acid
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have incl petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info L CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressar hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of up than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin inc
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with TORADOL(R) oral tablets, 2007).

3.5.1.IN Ticlopidine
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and use of SSRIs and antiplatelet agents has been associated with an increased risk of bleeding. Bleeding events hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008; release capsules, solution, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an antiplatelet agent are given concurrently, monitor patient for oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 200
7) Probable Mechanism: unknown

3.5.1.IO Tinzaparin
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2 (R) oral capsules, delayed-release capsules, solution, 2008). Bleeding events reported have included epistax threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported wi (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When fluoxetine and an anticoagulant are given concurrently, monitor patient for sig taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, wh (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
7) Probable Mechanism: unknown
8) Literature Reports
a) Fluoxetine is thought to inhibit the cytochrome P450 2C9 isoenzyme (CYP2C9). This is the enzyme b

warfarin, is metabolized (Riesenman, 1995). In addition, both fluoxetine and warfarin are tightly bound to protein-binding displacement of either drug is present (Prod Info Coumadin(R), 1999).
b) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bl patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks followi mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected p SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. T treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model
c) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoum reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal blee hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal b subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interva gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekam
d) In 6 reported cases, INR increased during combined fluoxetine and warfarin therapy. In a seventh ca a woman initially treated with fluoxetine and, secondarily, started on warfarin (Woolfrey et al, 1993; Claire
e) An 83-year-old man died from cerebral hemorrhage secondary to increased warfarin concentrations. week for atrial fibrillation with a target INR between 2 and 3. The patient's other drugs included lisinopril, acetaminophen. After being seen for symptoms of depression, anxiety, and insomnia, the patient was giv mg 3 to 4 times per day. Eight days later, the patient's INR increased to 4.8, and the dose of warfarin wa was later seen for symptoms of drug delirium, including confusion, incoherence, and speaking irrationally was discontinued. The next day the patient presented to the hospital with left-sided weakness and later c interparenchymal hemorrhage. The authors proposed that the addition of fluoxetine to the patient's regim warfarin and diazepam, resulting in delirium and loss of anticoagulant control (Dent & Orrock, 1997).

3.5.1.IP Tipranavir
1) Interaction Effect: increased fluoxetine plasma concentrations
2) Summary: Although the drug interaction between fluoxetine and tipranavir/ritonavir has not been studied, tipranavir/ritonavir may result in increased fluoxetine plasma concentrations. Fluoxetine doses may need to b initiated (Prod Info APTIVUS(R) oral capsules, solution, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concurrent administration of fluoxetine and tipranavir/ritonavir may increase fluoxet these agents are coadministered and consider adjusting the fluoxetine dose as needed upon initiation of tipra capsules, solution, 2008).
7) Probable Mechanism: unknown

3.5.1.IQ Tirofiban
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and use of SSRIs and antiplatelet agents has been associated with an increased risk of bleeding. Bleeding events hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008; release capsules, solution, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an antiplatelet agent are given concurrently, monitor patient for oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 200
7) Probable Mechanism: unknown

3.5.1.IR Tolmetin
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have incl petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info L CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent

Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressar hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of u than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin inc

b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with TORADOL(R) oral tablets, 2007).

3.5.1.IS Toloxatone

1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental st

2) Summary: Concurrent administration or overlapping therapy with fluoxetine and a monoamine oxidase (M serotonin syndrome, a hyperserotonergic state characterized by symptoms such as restlessness, myoclonus diaphoresis, shivering, and tremor. Serious, even fatal, reactions have been reported (Prod Info Prozac(R), 1 1993c; Feighner et al, 1990c; Kline et al, 1989c; Suchowersky & de Vries, 1990c). As a reversible and selecti not potentiate the effects of selective serotonin reuptake inhibitors to the same frequency, extent, and duratio further studies confirm the safety and efficacy of this combined therapy, concomitant use is contraindicated.

3) Severity: contraindicated

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: Concurrent use of fluoxetine and toloxatone is contraindicated. Wait at least two we initiating fluoxetine therapy. In addition, wait at least five weeks after discontinuing fluoxetine before initiating

7) Probable Mechanism: inhibition of serotonin metabolism by monoamine oxidase

8) Literature Reports

a) Concomitant use of serotonin specific reuptake inhibitors and monoamine oxidase inhibitors can prod syndrome (Sternbach, 1991c). Serotonin syndrome is a condition of serotonergic hyperstimulation and m mental status, hyperreflexia, diaphoresis, shivering, and tremor (Sternbach, 1991c). If the syndrome is n result.

b) It has been suggested that fluoxetine therapy be discontinued for at least five weeks before beginnin 28-year old woman discontinued fluoxetine for six weeks before starting therapy with tranylcypromine. O fever, paresthesias, confusion, abdominal cramping, and various other CNS symptoms. Upon discontinu began to resolve. Blood samples taken three days after discontinuation of tranylcypromine revealed no p level was 84 ng/mL (Coplan & Gorman, 1993b).

c) Adverse reactions reported when fluoxetine was given concomitantly with phenelzine (n=9) or tranylc restlessness (42%), mental status changes (42%), myoclonus (33%), diarrhea (33%), and blood pressur one of the patients were taking other medications (ie, benzodiazepines, neuroleptics, anticonvulsants, ar adverse reactions.

d) Ten hours after her last dose of fluoxetine, a 45-year-old woman began tranylcypromine therapy (Klir insomnia, and unsteady gait were reported on the second day. Thioridazine and tryptophan were added rigidity of the arms and legs, and hyperreflexia. She died in the intensive care unit of a hospital 44 hours

e) Two cases reports suggested a possible interaction between fluoxetine and selegiline (Suchowersky episode of mania being observed approximately one month after adding selegiline to fluoxetine therapy. drugs were discontinued, and no further details were provided. The second case involved diaphoresis, v occurred in close temporal relationship to adding fluoxetine and selegiline. Both drugs were discontinuec Rechallenge with fluoxetine alone occurred without incident.

3.5.1.IT Tramadol

1) Interaction Effect: an increased risk of serotonin syndrome

2) Summary: Concurrent use of olanzapine with mirtazapine and tramadol in a 53-year-old male resulted in s Fetchko, 2002). If olanzapine is used concomitantly with mirtazapine and/or tramadol, monitor closely for sym syndrome can be life-threatening. If serotonin syndrome develops, discontinue the offending agents and prov necessary (Boyer & Shannon, 2005).

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: A case of serotonin syndrome was reported with coadministration of olanzapine, mi 2002). If 2 or more of these drugs are are used concomitantly, monitor closely for symptoms of serotonin syn (including hyper-reflexia, tremor, muscle rigidity, clonus, peripheral hypertonicity, and shivering), autonomic h diaphoresis, the presence of bowel sounds, and diarrhea), and mental status changes (including agitation an threatening. If serotonin syndrome develops, discontinue the offending agents and provide supportive care a Shannon, 2005).

7) Probable Mechanism: additive serotonergic pharmacologic effects

8) Literature Reports

a) A 53-year-old male on mirtazapine and tramadol experienced serotonin syndrome 8 days after olanza mirtazapine 45 mg/day for depression and tramadol 150 mg/day for chronic back pain. Olanzapine 10 m was admitted 8 days later after being found by the police wandering the streets in inappropriate dress an afebrile, tachycardic (120 bpm), and had flushing, twitching of his face, tremors, myoclonus, hyperreflexi agitated. He spoke with a stutter. He had marked derailment, appeared perplexed, had prominent percep hallucinations. The creatine phosphokinase was normal. All medications were discontinued and within 1

Fetchko, 2002).

3.5.1.IU Tramadol

1) Interaction Effect: an increased risk of seizures and serotonin syndrome (hypertension, hyperthermia, myo concentrations of tramadol and decreased concentrations of tramadol active metabolite, M1

2) Summary: Seizures and serotonin syndrome have been reported in patients using tramadol. Some medica the seizure threshold. The risk of seizures and serotonin syndrome may be enhanced when fluoxetine and tra (R), 2001). Fluoxetine is also an inhibitor of CYP2D6, and concomitant administration with tramadol may resu decreases in active metabolite, M1, concentrations. This may cause an increase in side effects or a reduction ULTRAM(R)ER extended-release oral tablets, 2005).

3) Severity: major

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: Caution should be used if tramadol is to be administered to patients receiving conc combination, especially in patients with underlying conditions that might predispose to seizures. Observe the serotonin syndrome. Also, monitor patients for signs and symptoms of narcotic toxicity (extreme sedation, res analgesic effect of tramadol.

7) Probable Mechanism: increased concentration of serotonin in the nervous system and periphery; inhibitio active metabolite by quinidine

8) Literature Reports

a) The combination of tramadol and fluoxetine may result in serotonin syndrome and mania. A 72-year-o treated with fluoxetine for the past 10 years. She was prescribed tramadol 150 mg daily for articular pain began to feel nervous, had a temperature of 37.2 C, piloerection, and muscular contractions. She discon symptoms disappeared. She was still agitated, euphoric, hyperactive, had rapid speech, paranoid ideatic hospitalized and haloperidol treatment was initiated, however, her symptoms continued. She was readm olanzapine was initiated. Two weeks later she became euthymic and continued olanzapine therapy after for inducing mania and serotonergic syndrome when using tramadol combined with SSRIs must be cons

3.5.1.IV Tranylcypromine

1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental sta

2) Summary: Concurrent administration or overlapping therapy with fluoxetine and a monoamine oxidase (M serotonin syndrome, a hyperserotonergic state characterized by symptoms such as restlessness, myoclonus diaphoresis, shivering, and tremor. Serious, even fatal, reactions have been reported (Prod Info Prozac(R), 1 1993q; Feighner et al, 1990q; Kline et al, 1989q; Suchowersky & de Vries, 1990q; Sternbach, 1988a). Conco

3) Severity: contraindicated

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: Concurrent use of fluoxetine and tranylcypromine is contraindicated. Wait at least tw before initiating fluoxetine therapy. In addition, wait at least five weeks after discontinuing fluoxetine before in

7) Probable Mechanism: inhibition of serotonin metabolism by monoamine oxidase

8) Literature Reports

a) Concomitant use of serotonin specific reuptake inhibitors and monoamine oxidase inhibitors can prod syndrome (Sternbach, 1991r). Serotonin syndrome is a condition of serotonergic hyperstimulation and m mental status, hyperreflexia, diaphoresis, shivering, and tremor (Sternbach, 1991r). If the syndrome is no result.

b) It has been suggested that fluoxetine therapy be discontinued for five weeks before beginning therapy one case report describes a 28-year old woman who had discontinued a 2-year fluoxetine regimen for six tranylcypromine. Over the next few days the patient developed fever, paresthesias, confusion, abdomina Upon discontinuation of tranylcypromine, the patient's symptoms began to resolve. Blood samples taken tranylcypromine revealed no presence of fluoxetine; however, the norfluoxetine level was 84 ng/mL (Cop

c) Adverse reactions reported when fluoxetine was given concomitantly with phenelzine (n=9) or tranylc restlessness (42%), mental status changes (42%), myoclonus (33%), diarrhea (33%), and blood pressur one of the patients were taking other medications (ie, benzodiazepines, neuroleptics, anticonvulsants, ar adverse reactions.

d) Ten hours after her last dose of fluoxetine, a 45-year-old woman began tranylcypromine therapy (Klin insomnia, and unsteady gait were reported on the second day. Thioridazine and tryptophan were added rigidity of the arms and legs, and hyperreflexia. She died in the intensive care unit of a hospital 44 hours

e) Two cases suggestive of an interaction between fluoxetine and selegiline were reported (Suchowersk episode of mania being observed approximately one month after adding selegiline to fluoxetine therapy. drugs were discontinued, and no further details were provided. The second case involved diaphoresis, va occurred in close temporal relationship to adding fluoxetine and selegiline. Both drugs were discontinued Rechallenge with fluoxetine alone occurred without incident.

f) A 31-year-old female received fluoxetine 20 mg daily for 14 days, and was subsequently discontinued 1988). The administration of tranylcypromine 10 mg daily commenced two days following the discontinua increased tranylcypromine to 20 mg daily and developed a serotonin-like syndrome two to three hours la tranylcypromine, all signs and symptoms resolved within 24 hours.

3.5.1.IW Trazodone

1) Interaction Effect: trazodone toxicity (sedation, dry mouth, urinary retention) or serotonin syndrome (hyper changes)
2) Summary: When given concurrently, trazodone and fluoxetine have been reported to be therapeutically ef Shader, 1990; Swerdlow & Andia, 1989; Neirenberg et al, 1992; Maes et al, 1997a). Coadministration of traz in speech dysfunction in a 43-year old man following traumatic brain injury (Patterson et al, 1997a). There ha syndrome due to interactions between selective serotonin reuptake inhibitors and antidepressants (George & Alderman & Lee, 1996). Serotonin syndrome is a rare but potentially fatal condition of serotonergic hyperstim hyperthermia, myoclonus and changes in mental status (Sternbach, 1991y). Further clinical studies are nece of serotonin syndrome associated with this drug combination.
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Due to the potential for impairment in trazodone metabolism, patients should be mo Occasional dosage reductions of trazodone may be required. Serotonin syndrome, characterized by hyperter status changes, may also occur during concomitant therapy.
7) Probable Mechanism: decreased trazodone clearance
8) Literature Reports
a) Five cases of elevated antidepressant levels, four involving tricyclic antidepressants (nortriptyline, imi trazodone, have been reported. After the addition of fluoxetine, the ratio of antidepressant level to dose i tricyclics and by 31% in the patient on trazodone. The trazodone-treated patient developed sedation and
b) A 44-year-old man developed symptoms characteristic of serotonin syndrome due to a possible inter patient had been taking fluoxetine 40 mg daily and trazodone 100 mg daily for approximately two months experienced disorientation, tremor, diaphoresis, and anxiety, followed by uncontrollable shaking and loss with cyproheptadine 4 mg orally, symptoms resolved over the next 30 minutes. Trazodone was discontin 40 mg daily without further complications (George & Godleski, 1996).
c) Serotonin syndrome was also reported in a 29-year-old woman taking trazodone and paroxetine. The at bedtime for approximately three months for depression and insomnia. The patient's depressive sympt trazodone was subsequently decreased to 50 mg daily at bedtime for two weeks before paroxetine 20 m after the first dose of paroxetine, the patient became agitated, confused, shaky, and diaphoretic. Upon e concentration, intermittent myoclonus in all extremities, hyperreflexia, tremor, and diaphoresis. After disc patient's symptoms resolved (Reeves & Bullen, 1995).
d) A 43-year-old male with traumatic brain injury developed speech dysfunction during therapy with fluo treated with trazodone 150 mg at bedtime for chronic pain as a result of a fall. After undergoing a compre rehabilitation, fluoxetine 20 mg every morning was added to the patient's regimen for treatment of sympt therapy with fluoxetine, the patient began to slur his speech and later exhibited a slow rate of speech, inc phonemes, and word-finding difficulties. After discontinuation of fluoxetine and tapering of trazodone the speech difficulty and returned to normal over the next week (Patterson et al, 1997).
e) The pharmacokinetic effect of trazodone and fluoxetine cotherapy was studied in 27 inpatients with a trazodone 100 mg daily, followed one week later with the addition of fluoxetine 20 mg daily, pindolol 7.5 placebo had no significant effect on the plasma concentrations of trazodone or its active metabolite, met when fluoxetine was combined with trazodone, levels of mCPP increased from a mean baseline value of increase was also associated with an improvement in the clinical response to the antidepressants (Maes

3.5.1.IX Trifluoperazine
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest
2) Summary: Although citing no data, the manufacturers of some phenothiazines state that concomitant use not recommended. Q and T wave distortions have been observed in patients taking phenothiazines (Prod Inf 2002; Prod Info Thorazine(R), 2002) . Other phenothiazines may have similar effects, though no reports are a the QTc interval at the recommended therapeutic dose (Prod Info Prozac(R), 2003).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of fluoxetine and a phenothiazine is not recommende
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.IY Trimethoprim
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest
2) Summary: Cotrimoxazole and fluoxetine have been shown to prolong the QTc interval at the recommende 2001ah; Lopez et al, 1987). Even though no formal drug interaction studies have been done, the coadministra is not recommended.
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of cotrimoxazole and fluoxetine is not recommended
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.IZ Trimipramine
1) Interaction Effect: tricyclic antidepressant toxicity (dry mouth, urinary retention, sedation) and an increase

de pointes, cardiac arrest)
2) Summary: Tricyclic antidepressants (TCAs) and fluoxetine have been shown to prolong the QTc interval a Prozac(R), 2001h; Marshall & Forker, 1982). Even though no formal drug interaction studies have been done coadministration of tricyclic antidepressants and other drugs known to prolong the QTc interval, such as fluox 1999). In addition, concurrent use of fluoxetine and TCAs such as desipramine, nortriptyline, and imipramine concentrations (Preskorn et al, 1994a; Preskorn et al, 1994a; Aranow et al, 1989a; Downs et al, 1989a; Gooc
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: The concurrent administration of fluoxetine and a tricyclic antidepressant is not recc
7) Probable Mechanism: decreased tricyclic antidepressant metabolism; additive effects on QT prolongation
8) Literature Reports
a) Fluoxetine increased the level of tricyclic antidepressants (nortriptyline, imipramine, desipramine) in 4 ratio of antidepressant level to dose increased by 109% to 486% in the patients. Three patients develope constipation, urinary hesitancy, sedation, unstable gait) as a result of the increased levels (Aranow et al,
b) Fluoxetine statistically and clinically significantly increased desipramine concentrations in 18 healthy added to desipramine (50 mg daily), the mean maximum concentration of desipramine increased by 278 curve increased by 342%. Desipramine trough concentrations continued to be 198% above baseline thre same study compared pharmacokinetics of desipramine when combined with sertraline. The impact of se short-term increases in desipramine plasma concentrations (Preskorn et al, 1994).
c) A 75-year-old female experienced symptomatic increases in her desipramine serum concentrations w levels ranged from 109 to 150 ng/mL with oral doses of 300 mg at bedtime prior to fluoxetine therapy. Fc to the regimen, the desipramine serum level increased to 212 ng/mL within five days. The fluoxetine dos and the desipramine serum level was 419 ng/mL after four days. A worsening of depression and severe desipramine serum levels. Withdrawal of fluoxetine and reduction in the desipramine dose to 200 mg dai ng/mL within two weeks (Bell & Cole, 1988).
d) A 33-year-old depressed male developed adverse effects of dry mouth, tinnitus, and difficulties with a 40 mg daily and desipramine 150 mg daily for five weeks; fluoxetine was discontinued and the blood leve ng/mL with resolution of clinical symptoms (Goodnick, 1989).
e) A 39-year-old female experienced symptomatic increases in her desipramine levels with concomitant the patient's measured levels of desipramine had ranged from 148 to 160 ng/mL on a regimen of 300 mg 20 mg daily, she reported anticholinergic symptoms, sedation, and confusion with a desipramine level of to 200 mg/day; eleven days later, the level was 244 ng/mL; the patient reported decreased energy, impa speech, as well as an episode of nausea, dizziness, and syncope. The desipramine dose was reduced t days. Eight days later, the desipramine level was 122 ng/mL (Downs et al, 1989).
f) Concomitant administration of fluoxetine and desipramine was reported to result in an increased desip year-old male within 10 days of the addition of fluoxetine to the patient's regimen (Preskorn et al, 1990).

3.5.1.JA Tryptophan
1) Interaction Effect: serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)
2) Summary: Tryptophan is metabolized to serotonin, and fluoxetine, a selective serotonin reuptake inhibitor & Fontaine, 1986a; Boyer & Blumhardt, 1992). It is possible that combining these agents may result in excess "serotonin syndrome".
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: If tryptophan and fluoxetine are coadministered, monitor patients for signs of seroto myoclonus, mental status changes). It may be necessary to reduce doses of one or both agents or to discont
7) Probable Mechanism: additive adverse effects
8) Literature Reports
a) In a case series, the concurrent use of fluoxetine 50 to 100 mg daily and L-tryptophan 1 to 4 g daily re nervous system toxicity (agitation, poor concentration, nausea, diarrhea, paresthesias, palpitations, chills insomnia) within a few days. Tryptophan was discontinued and the symptoms disappeared (Steiner & Fc
b) Concurrent paroxetine (another SSRI) and tryptophan have been linked to headache, nausea, sweati tryptophan administration increases serotonin concentration in the central nervous system and paroxetin receive potent serotonin reuptake inhibitors should be advised not to take L-tryptophan.

3.5.1.JB Valdecoxib
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have incl petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info L CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown

8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent
Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressar
hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of u
than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose
confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of
upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin inc
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with
TORADOL(R) oral tablets, 2007).

3.5.1.JC Vasopressin

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Fluoxetine and vasopressin have been shown to prolong the QTc interval at the recommended
Jacoby & Wiegman, 1990). Even though no formal drug interaction studies have been done, the coadministra
is not recommended.
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of fluoxetine and vasopressin is not recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.JD Venlafaxine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
(hypertension, hyperthermia, myoclonus, mental status changes)
2) Summary: Venlafaxine and fluoxetine have been shown to prolong the QTc interval at the recommended
Prod Info Effexor(R) XR, 2000). Even though no formal drug interaction studies have been done, the coadmi
interval is not recommended. In addition, the concurrent use of venlafaxine and fluoxetine may result in serot
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of venlafaxine and fluoxetine is not recommended.
7) Probable Mechanism: additive effects on QT prolongation; additive serotonergic effect

3.5.1.JE Warfarin

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and
use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2
(R) oral capsules, delayed-release capsules, solution, 2008). Bleeding events reported have included epistax
threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported wi
(Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When fluoxetine and an anticoagulant are given concurrently, monitor patient for sig
taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, wh
(Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
7) Probable Mechanism: unknown
8) Literature Reports
a) Fluoxetine is thought to inhibit the cytochrome P450 2C9 isoenzyme (CYP2C9). This is the enzyme b
warfarin, is metabolized (Riesenman, 1995). In addition, both fluoxetine and warfarin are tightly bound to
protein-binding displacement of either drug is present (Prod Info Coumadin(R), 1999).
b) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bl
patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks followi
mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected p
SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients
treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4
corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively.
treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only
bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI
dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding
exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model
c) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoum
reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal blee
hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal b
subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690
for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interva
gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekam
d) In 6 reported cases, INR increased during combined fluoxetine and warfarin therapy. In a seventh ca

a woman initially treated with fluoxetine and, secondarily, started on warfarin (Woolfrey et al, 1993; Claire
e) An 83-year-old man died from cerebral hemorrhage secondary to increased warfarin concentrations.
week for atrial fibrillation with a target INR between 2 and 3. The patient's other drugs included lisinopril,
acetaminophen. After being seen for symptoms of depression, anxiety, and insomnia, the patient was giv
mg 3 to 4 times per day. Eight days later, the patient's INR increased to 4.8, and the dose of warfarin wa
was later seen for symptoms of drug delirium, including confusion, incoherence, and speaking irrationally
was discontinued. The next day the patient presented to the hospital with left-sided weakness and later c
interparenchymal hemorrhage. The authors proposed that the addition of fluoxetine to the patient's regim
warfarin and diazepam, resulting in delirium and loss of anticoagulant control (Dent & Orrock, 1997).

3.5.1.JF Xemilofiban

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and
use of SSRIs and antiplatelet agents has been associated with an increased risk of bleeding. Bleeding events
hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008;
release capsules, solution, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an antiplatelet agent are given concurrently, monitor patient for
oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 200
7) Probable Mechanism: unknown

3.5.1.JG Ziprasidone

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, ziprasidone should not be coa
known to prolong the QTc interval, including fluoxetine (Prod Info Geodon(TM), 2002; Prod Info Prozac(R), 2
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of ziprasidone with other agents that can prolong the
recommended.
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) It has been shown that ziprasidone prolongs the QTc and that this represents a risk of potentially fata
prolongation is dose-related. It is not yet known whether ziprasidone will cause torsades de pointes or in
ziprasidone increased the QTc interval, compared to placebo, by approximately 10 milliseconds (msec) a
QTc interval increased 9 to 14 msec more with ziprasidone than with risperidone, olanzapine, quetiapine
less than that observed with thioridazine (Prod Info Geodon(R), 2002).

3.5.1.JH Zolmitriptan

1) Interaction Effect: an increased risk of serotonin syndrome and an increased risk of cardiotoxicity (QT prol
2) Summary: Zolmitriptan and fluoxetine have been shown to prolong the QTc interval at the recommended t
Prod Info Zomig(R), 2001). Even though no formal drug interaction studies have been done, the coadministra
is not recommended. Additionally, concurrent use of a triptan and an SSRI may result in serotonin syndrome
serotonin syndrome may include restlessness, hallucinations, loss of coordination, fast heart beat, rapid chan
temperature, overreactive reflexes, nausea, vomiting, and diarrhea. Clinicians should be aware that triptans r
either the triptan or the SSRI may be prescribed by a different physician. Discuss the risks of serotonin syndr
combination and monitor them closely for symptoms of serotonin syndrome (US Food and Drug Administratio
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of a triptan, such as zolmitriptan, and an SSRI, such as fluoxetine
serotonin syndrome. Be aware that triptans may be commonly used intermittently and that either the triptan o
physician. If these agents are used together, discuss the risks of serotonin syndrome with the patient and mo
(restlessness, hyperthermia, hyperreflexia, incoordination). Additionally, concurrent administration of zolmitrip
risk of cardiotoxicity due to additive QT prolongation effects.
7) Probable Mechanism: additive pharmacologic effects resulting in excessive serotonergic stimulation; addit
8) Literature Reports
a) The pharmacokinetics of zolmitriptan were unaffected by 4 weeks of pretreatment with fluoxetine 20 r

3.5.1.JI Zolpidem

1) Interaction Effect: an increased risk of hallucinations
2) Summary: Short-term combined therapy with fluoxetine and zolpidem was determined to be safe by a stu
dose of zolpidem followed by one washout day, the subjects were given a daily dose of fluoxetine on days thr
evening on days 28 through 32. There were no significant changes in either fluoxetine or zolpidem plasma co
tolerated well, either individually or combined (Allard et al, 1998a). However, the publication of five case repo
elucidates potential interactions between zolpidem and various antidepressant medications. Five patients rep

zolpidem and antidepressant medication. The hallucination episodes all lasted longer than one hour, but resc
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Observe patients for hallucinatory activity. Alternative anti-insomnia medication may
7) Probable Mechanism: unknown
8) Literature Reports
a) A study conducted by Lorex Pharmaceuticals and Boston Research and Science Consulting demonst therapy with fluoxetine and zolpidem. In this study, 29 healthy female volunteers were given a single eve washout day. This was followed by a daily morning dose of fluoxetine 20 mg on days 3 through 27. On d zolpidem was added. Steady state plasma concentrations of fluoxetine and norfluoxetine were reached c serial venous blood sampling. There were no significant differences in area under concentration curve (A reach peak concentration (Tmax) after one or five consecutive doses of zolpidem in conjunction with fluo pharmacokinetic mean parameters were observed for zolpidem: AUC 917.04 ng/hr/mL on day 28, 978.7 day 28, 175.91 ng/mL on day 32, Tmax 1.67 hr on day 28, 1.54 hr on day 32. For fluoxetine the following 2879.63 ng/hr/mL on day 32, Cmax 133.48 ng/mL on day 27, 142.23 ng/mL on day 32, Tmax 8.28 hr on significant difference was a higher half-life value for zolpidem on day 32, the fifth consecutive dose of zol 1998).
b) The Washington Poison Center reports that they received five different calls from patients experienci zolpidem and antidepressant medication. Four of the five reports came from patients taking serotonin reu antidepressant medications being taken were desipramine, fluoxetine, sertraline, venlafaxine, and bupro lasted longer than one hour, but the patients' symptoms resolved without further sequelae. The authors c might cause hallucinations has not been firmly established (Elko et al, 1998).

3.5.1.JJ Zomepirac

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have incl petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info L CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressar hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of up than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin inc
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with TORADOL(R) oral tablets, 2007).

3.5.1.JK Zotepine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Fluoxetine has been shown to prolong the QTc interval at the recommended therapeutic dose formal drug interaction studies have been done, the coadministration of antipsychotics and other drugs known fluoxetine, is not recommended. Several antipsychotic agents have demonstrated QT prolongation including quetiapine (Owens, 2001b), sertindole (Agelink et al, 2001), sultopride (Lande et al, 1992), and zotepine (Swe
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of fluoxetine and antipsychotics is not recommended
7) Probable Mechanism: additive effects on QT prolongation

3.5.2 Drug-Food Combinations

3.5.2.A Ethanol

1) Interaction Effect: excessive central nervous system depression
2) Summary: Coadministration of olanzapine and ethanol will potentiate the orthostatic hypotension observed of ethanol (45 mg/70 kg) had no effect on olanzapine pharmacokinetics, these drugs should not be taken con depressive effects of both drugs (Prod Info Zyprexa(R), 1999d).
3) Severity: moderate
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Concurrent use of olanzapine and ethanol should be avoided if at all possible. If the

caution should be used.
7) Probable Mechanism: additive central nervous system depression

4.0 Clinical Applications

Monitoring Parameters

Patient Instructions

Place In Therapy

Mechanism of Action / Pharmacology

Therapeutic Uses

Comparative Efficacy / Evaluation With Other Therapies

4.1 Monitoring Parameters

A) Therapeutic

1) Physical Findings

a) Signs of improvement in bipolar symptoms.

1) Positive symptoms (distortion of normal function) include hallucinations, irritability, delusions, incoher

2) Negative symptoms (loss or diminution of function) include blunted affect, emotional or social withdra

b) Improvement in target symptoms associated with depression (depressed mood, suicidal thoughts or inten sleep patterns, lack of pleasure/interest in usual activities, feeling of excessive guilt/worthlessness, psychomo thinking/concentration/memory).

B) Toxic

1) Laboratory Parameters

a) Fasting blood glucose levels should be assessed in any patient who exhibits symptoms of hyperglycemia. treatment and regularly thereafter in patients with diabetes mellitus, with borderline increased blood glucose l 200 mg/dL), or with risk factors for diabetes mellitus (i.e., obesity, family history of diabetes) (Prod Info SYME

b) Lipid profile evaluations should be done at the beginning of treatment and periodically during therapy to m triglycerides, LDL, and HDL (Prod Info SYMBYAX(R) oral capsule, 2009)

c) ECG at baseline and periodically during treatment (Pacher & Kecskemeti, 2004)

d) Serum sodium levels should be monitored (levels lower than 110 mmol/L have been reported). There is a the syndrome of inappropriate antidiuretic hormone secretion) in patients receiving concomitant diuretics, pat hyponatremia is confirmed, fluoxetine/olanzapine should be discontinued and medical management may be r

2) Physical Findings

a) Abnormal bleeding should be monitored for ecchymoses, hematomas, epistaxis and petechiae especially NSAIDs, warfarin or other anticoagulants.

b) Allergic reactions including anaphylaxis and rash should be monitored. Systemic reactions possibly relate If an etiology for these reactions cannot be identified, fluoxetine/olanzapine therapy should be discontinued (F

c) Body temperature dysregulation should be monitored for signs of dehydration, excessive or lack of sweati able to produce urine. Activities such as exercising strenuously, extreme heat exposure, concomitant anticho body temperature.

d) Body weight should be monitored regularly during treatment (Prod Info SYMBYAX(R) oral capsule, 2009).

e) Hyperglycemia symptoms should be monitored regularly in all patients for signs of polydipsia, polyuria, po symptoms of hyperglycemia during atypical antipsychotic treatment should undergo fasting blood glucose tes resolved when the atypical antipsychotic was stopped; however, some patient required ongoing anti- diabetic (Prod Info SYMBYAX(R) oral capsule, 2009).

f) Hyponatremia (as a result of SIADH) should be monitored including symptoms of headache, difficulty conc weakness, and unsteadiness. More severe symptoms include hallucination, syncope, seizure, coma, and res increased risk of hyponatremia in patients receiving concomitant diuretics, patients who are volume depleted, fluoxetine/olanzapine therapy should be discontinued and medical management may be necessary.

g) If intolerable withdrawal symptoms occur following a decrease in dose or when therapy is being discontinu previously prescribed dose and taper the dose at a more gradual rate. Symptoms may include dysphoric moo disturbances, anxiety, confusion , headache, lethargy, emotional lability, insomnia, and hypomania (Prod Info

h) Involuntary, dyskinetic movements should be monitored periodically. There is an increased incidence of ta females with some irreversible cases. Risk benefit of continued treatment should be assessed if symptoms d 2009).

i) Mania/hypomania may be activated in patients with undiagnosed bipolar disorder. Monitoring is recommen (Prod Info SYMBYAX(R) oral capsule, 2009).

j) Orthostatic hypotension, including dizziness, tachycardia, bradycardia, and syncope should be monitored e patients with cardiovascular or cerebrovascular disease, or conditions which might predispose patients to hyp

concomitant antihypertensive drugs) (Prod Info SYMBYAX(R) oral capsule, 2009)
k) Monitor patients receiving antidepressants for worsening of depression, suicidality, or unusual changes in 2009) especially at the initiation of therapy or during dose adjustment. Such monitoring should include at leas their family members or caregivers during the initial 4 weeks of treatment, then visits every other week for the clinically indicated beyond 12 weeks. Families and caregivers should be advised of the need for close observ communication with the prescriber (US Food and Drug Administration, 2004).
l) Patients who experience symptoms of anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggre mania may be at an increased risk for worsening depression or suicidality. If these symptoms are observed, t necessary to discontinue medications when symptoms are severe, sudden in onset, or were not part of the pa Administration, 2004).
m) Seizures should be monitored, especially in patients with a history of seizure disorder or with comorbiditie
n) Serotonin syndrome or neuroleptic malignant syndrome-like reactions should be monitored including men (tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (muscle rigidity, hyperreflexia, symptoms. There may be an increased risk of this reaction with concomitant use of serotonergic drugs (inclu serotonin, or antipsychotics or dopamine antagonists, all of which are not recommended during fluoxetine/ola discontinued if serotonin syndrome or neuroleptic malignant syndrome-like reactions occur (Prod Info SYMBY

4.2 Patient Instructions

A) Olanzapine/Fluoxetine (By mouth)
Fluoxetine Hydrochloride/Olanzapine

Treats depression that is a part of bipolar disorder or that does not respond to other antidepressants. This medicir inhibitor (SSRI) antidepressant.

When This Medicine Should Not Be Used:
You should not use this medicine if you have had an allergic reaction to olanzapine (Zyprexa®) or fluoxetine (Proz have used an MAO inhibitor (MAOI) such as Eldepryl®, Marplan®, Nardil®, or Parnate® within the past 14 days. for at least 5 weeks after you stop using Symbyax®. You should not use this medicine if you are using pimozide (

How to Use This Medicine:
Capsule
Your doctor will tell you how much of this medicine to use and how often. Do not use more medicine or use it This medicine should come with a Medication Guide. Read and follow these instructions carefully. Ask your d Ask your pharmacist for the Medication Guide if you do not have one. Your doctor might ask you to sign some information.
You may take this medicine with or without food.

If a Dose is Missed:
If you miss a dose or forget to use your medicine, use it as soon as you can. If it is almost time for your next d the missed dose. Do not use extra medicine to make up for a missed dose.

How to Store and Dispose of This Medicine:
Store the medicine in a closed container at room temperature, away from heat, moisture, and direct light.
Ask your pharmacist, doctor, or health caregiver about the best way to dispose of any leftover medicine after need to throw away old medicine after the expiration date has passed.
Keep all medicine away from children and never share your medicine with anyone.

Drugs and Foods to Avoid:
Ask your doctor or pharmacist before using any other medicine, including over-the-counter medicines, vitamins, a
Make sure your doctor knows if you are using digitoxin, linezolid (Zyvox®), omeprazole (Prilosec®), rifampin (Imitrex®), tramadol (Ultram®), tryptophan, or vinblastine. Tell your doctor if you are using a blood thinner (su for mental illness (such as clozapine, fluvoxamine, haloperidol, lithium, tryptophan, Clozaril®, Haldol®, or Luv levodopa, Sinemet®, or Stalevo®), phenothiazine medicine (such as prochlorperazine, Compazine®, Mellaril medicine for heart rhythm problems (such as flecainide, propafenone, Rythmol®, or Tambocor®).
Make sure your doctor knows if you are also using a pain or arthritis medicine (such as aspirin, diclofenac, ibu Daypro®, Motrin®, Orudis®, Relafen®, or Voltaren®), medicine for seizures (such as carbamazepine, pheny depression (such as amitriptyline, desipramine, imipramine, nortriptyline, Aventyl®, Elavil®, Norpramin®, Par as alprazolam, diazepam, Librium®, Valium®, or Xanax®), or blood pressure medicine (such as atenolol, hyd Cozaar®, Diovan®, Lotrel®, Norvasc®, Prinivil®, Toprol®, or Zestril®).
Do not drink alcohol while you are using this medicine.
Tell your doctor if you are using any medicines that make you sleepy. These include sleeping pills, cold and a sedatives.
Tell your doctor if you are also using any other medicine that contains olanzapine or fluoxetine. Some other b Prozac®, Prozac Weekly™, or Sarafem®.

Warnings While Using This Medicine:
Make sure your doctor knows if you are pregnant, or if you have diabetes, seizures, bleeding problems, liver glaucoma, trouble swallowing, or a history of neuroleptic malignant syndrome (NMS), breast cancer, or sever

have any kind of heart or circulation problems, including heart disease, low blood pressure, high blood pressu
history of heart attack or stroke.
Do not breastfeed while you are using this medicine.
For some children, teenagers, and young adults, this medicine can increase thoughts of suicide. Tell your do
your child start to feel more depressed and have thoughts about hurting yourselves. Report any unusual thou
especially if they are new or are getting worse quickly. Make sure the doctor knows if you or your child have t
increase in energy, or start to act reckless. Also tell the doctor if you or your child have sudden or strong feeli
violent, or scared. Let the doctor know if you, your child, or anyone in your family has bipolar disorder (manic-
This medicine may raise or lower your blood sugar, or it may cover up symptoms of very low blood sugar (hy
Your doctor will need to check your blood at regular visits while you are using this medicine. Be sure to keep
This medicine may increase your cholesterol and fats in the blood. If this condition occurs, your doctor may g
amount of cholesterol and fats in the blood.
This medicine may increase your weight. Your doctor may need to check your weight regularly during treatme
If you develop new hives or a skin rash, even a mild one, stop using this medicine and call your doctor right a
This medicine may cause a serious condition called serotonin syndrome when it is taken with certain medicin
other medicines.
Tardive dyskinesia (a movement disorder) may occur and may not go away after you stop using the medicine
your child have any of the following symptoms while taking this medicine: lip smacking or puckering, puffing c
the tongue, uncontrolled chewing movements, or uncontrolled movements of the arms and legs.
You might get overheated while using this medicine. Drink plenty of water during hot weather, while exercisin
gets too hot, you might feel dizzy, weak, tired, or confused. You might have an upset stomach or vomit. Call y
away from the heat does not cool you down.
Some side effects are more likely to happen in elderly people who have memory problems or other reduced r
person who will be using this medicine has forgetfulness or confusion related to aging (such as Alzheimer's d
This medicine may make you dizzy or drowsy. Avoid driving, using machines, or doing anything else that cou
also feel lightheaded when getting up suddenly from a lying or sitting position, so stand up slowly.
Do not stop using this medicine suddenly without asking your doctor. You may need to slowly decrease your
If your symptoms do not improve or if they get worse, call your doctor.

Possible Side Effects While Using This Medicine:
Call your doctor right away if you notice any of these side effects:
Allergic reaction: Itching or hives, swelling in your face or hands, swelling or tingling in your mouth or throat, c
Bloody or black, tarry stools.
Change in how much or how often you urinate.
Changes in behavior, or thoughts of hurting yourself or others.
Chest pain, shortness of breath, or coughing up blood.
Confusion, weakness, and muscle twitching.
Fast, slow, uneven, or pounding heartbeat.
Feeling very thirsty or hungry.
Fever, unusual sweating, or feeling too hot.
Lightheadedness or fainting.
Muscle pain, tenderness, or weakness.
Muscle stiffness, spasms, or other muscle movements you cannot control (especially in your face or mouth).
Pain in your lower leg (calf).
Seizures or tremors.
Severe stomach pain, or vomiting of blood or material that looks like coffee grounds.
Sudden or severe headache, problems with vision, speech, or walking.
Swelling in your hands, ankles, or feet.
Trouble breathing or swallowing.
Trouble sleeping, racing thoughts, feeling very nervous, energetic, or restless.
Unusual bleeding or bruising.
Yellowing of your skin or the whites of your eyes.

If you notice these less serious side effects, talk with your doctor:
Blurred vision.
Diarrhea.
Dry mouth, sore throat, or hoarseness.
Increase in appetite.
Joint pain or swelling.
Sleepiness or unusual drowsiness.
Tiredness.
Trouble concentrating.
Trouble having sex.
Weight gain.

If you notice other side effects that you think are caused by this medicine, tell your doctor.

4.3 Place In Therapy

A) Depression Associated with Bipolar I Disorder

1) The combination of olanzapine and fluoxetine is effective for the treatment of depressive episodes associated established guidelines for the length of time patients with bipolar disorder experiencing a major depressive episod chronic illness requiring chronic treatment. The use olanzapine/fluoxetine for extended periods should periodically continued therapy(Prod Info SYMBYAX(R) oral capsule, 2009).

B) Treatment-Resistent Depression

1) Combination olanzapine and fluoxetine is effective for the acute treatment of treatment-resistant major depress 2 separate previous trials of antidepressant therapy. There are no established guidelines for the length of time pat treated; however, it is considered a chronic illness requiring chronic treatment. The use olanzapine/fluoxetine for e reevaluated for benefits and risks of continued therapy (Prod Info SYMBYAX(R) oral capsule, 2009).

4.4 Mechanism of Action / Pharmacology

A) MECHANISM OF ACTION

1) Although the exact mechanism of the combination of olanzapine and fluoxetine is unknown, the enhanced anti serotonin, norepinephrine, and dopamine activation. Increased norepinephrine and dopamine release in the prefr well as increases in serotonin, have been demonstrated in animal studies (Prod Info SYMBYAX(R) oral capsules,

2) Olanzapine is a psychotropic agent and fluoxetine is an antidepressant. Fluoxetine is an inhibitor of the seroto norepinephrine and dopamine transporters. The following list provides the binding affinity of olanzapine to neurotr capsules, 2007):

High affinity:
- serotonin 5HT2A/2C
- 5HT6
- dopamine D1-4
- histamine H-1
- adrenergic alpha-1

Moderate affinity
- serotonin 5HT3
- muscarinic M1-5

Weak affinity
- GABA-A
- benzodiazepine
- beta-adrenergic

3) The therapeutic and adverse effects of olanzapine may be due to its antagonism of certain receptors, such as M1-5 receptor antagonism, somnolence effects related to histamine H-1 receptor antagonism, and orthostatic hyp histamine H-1 receptor antagonism. Fluoxetine does not contribute to the above effects because of its relatively lo histamine H-1 receptors (Prod Info SYMBYAX(R) oral capsules, 2007).

4.5 Therapeutic Uses

Bipolar disorder, depressed phase

Major depressive disorder, Treatment resistant

4.5.A Bipolar disorder, depressed phase

FDA Labeled Indication

1) Overview

FDA Approval: Adult, yes; Pediatric, no
Efficacy: Adult, Effective
Recommendation: Adult, Class IIa
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Indicated in adults for the acute treatment of depressive episodes associated with bipolar I disorder (Pro Efficacy of olanzapine/fluoxetine was established in 2 identically designed, 8-week, randomized, double- Info Symbyax(TM), 2003).

3) Adult:

a) Both olanzapine monotherapy and olanzapine plus fluoxetine combination therapy were more effective tha In a randomized, double-blind, placebo-controlled, multi- center, international study, patients with bipolar I dis the Montgomery-Asberg Depression Rating Scale (MADRS) received olanzapine (n=370; 5 to 20 milligrams (olanzapine plus fluoxetine (n=86; 6 and 25 mg/day, 6 and 50 mg/day, or 12 and 50 mg/day; mean dose, 7.4 a weeks. The primary objective of the study compared olanzapine monotherapy versus placebo with regard to to 8 weeks. Throughout all 8 weeks of the study, treatments with both olanzapine and olanzapine-fluoxetine c reductions in depressive symptoms (as measured by the MADRS) as compared with placebo (p less than 0.0 improvement in the mean MADRS score at weeks 4, 6, and 8 were observed with olanzapine-fluoxetine comb monotherapy (p=0.01, p=0.02, p=0.01, respectively). The rate of response (defined as at least a 50% improv

of at least 4 weeks of study) was significantly higher in olanzapine-treated patients as compared with placebo
Additionally, the response rate was significantly higher in the olanzapine-fluoxetine group as compared with b
p less than 0.001) and olanzapine groups (56.1% vs 39%, respectively; p=0.006). There were no statistically
regard to rates of treatment-emergent mania. Adverse events were similar between the combination therapy
olanzapine-fluoxetine group had a significantly higher rate of nausea and diarrhea (Tohen et al, 2003).

b) The efficacy of olanzapine/fluoxetine for the treatment of depressive episodes associated with bipolar disc
week, randomized, double-blind, controlled studies (n=403, n=385) of patients who met Diagnostic and Statis
Bipolar I Disorder, Depressed utilizing flexible dosing of olanzapine/fluoxetine (6/25, 6/50, or 12/50 mg/day), c
studies included patients (greater than or equal to 18 years of age) with or without psychotic symptoms and v
primary rating instrument used to assess depressive symptoms in these studies was the Montgomery-Asberg
clinician-rated scale with total scores ranging from 0 to 60. The primary outcome measure of these studies wa
MADRS total score. In both studies, SYMBYAX was statistically significantly superior to both olanzapine mon
MADRS total score (Prod Info Symbyax(TM), 2003).

4.5.B Major depressive disorder, Treatment resistant

FDA Labeled Indication

1) Overview

FDA Approval: Adult, yes; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Indicated for the acute treatment of treatment-resistant major depressive disorder in adults who experien
antidepressant therapy (Prod Info SYMBYAX(R) oral capsule, 2009).
Reduced symptoms of major depressive disorder in patients with non-treatment resistant and treatment-

3) Adult:

a) Combination therapy with olanzapine/fluoxetine resulted in significantly greater reductions in the mean tot
(MADRS) scores when compared with olanzapine or fluoxetine alone, according to 3 clinical trials of 579 adu
did not respond to 2 antidepressant therapies of adequate dose and duration, including a randomized, double
patients received olanzapine 6 to 18 milligrams (mg) plus fluoxetine 25 to 50 mg (Prod Info SYMBYAX(R) ora

b) Combination treatment with olanzapine and fluoxetine effectively reduced symptoms of major depressive
and treatment-resistant depression. In an open-label, multicenter, 76-week study, patients (n=560) with majo
resistant depression, received combination therapy with olanzapine and fluoxetine at mean doses of 7.5 milli
Efficacy was assessed by mean change from baseline in the Montgomery-Asberg Depression Rating Scale (
Impression-Severity of Illness scale (CGI-S) score. At 76 weeks, there was a 67.7% (21.8 points) mean reduc
mean score was reduced by 49.3% (2.2.points). Mean change scores for both the MADRS and CGI-S were s
points (p=0.0001). At endpoint, 61.6% of patients were considered responders (defined as at least a 50% dec
endpoint) and throughout the study period, 56.3% of patients achieved remission (defined as 2 consecutive M
However, 14.8% of patients who remitted, relapsed by endpoint. Patients with treatment-resistant depression
patients with non-treatment-resistant depression. Somnolence (47.7%), weight gain (39.8%), dry mouth (37.1
(22.3%), rhinitis (22.1%), asthenia (19.3%), and tremor (18.8%) were the most commonly reported adverse e
2003).

4.6 Comparative Efficacy / Evaluation With Other Therapies

Fluoxetine

Olanzapine

4.6.A Fluoxetine

4.6.A.1 Depression - Schizophrenia

a) Results of an 8-week, double-blind trial demonstrated that patients receiving both olanzapine and fluoxetir
improvement in Montgomery-Asberg Depression Rating Scale (MADRS) and Clinical Global Impression (CGI
medication alone. Twenty-eight patients with nonpsychotic treatment-refractory depression received olanzapi
to 60 milligrams/day). In addition, there were no significant differences in adverse events among the 3 differe

4.6.B Olanzapine

4.6.B.1 Depression - Schizophrenia

a) Results of an 8-week, double-blind trial demonstrated that patients receiving both olanzapine and fluoxetir
improvement in Montgomery-Asberg Depression Rating Scale (MADRS) and Clinical Global Impression (CGI
medication alone. Twenty-eight patients with nonpsychotic treatment-refractory depression received olanzapi
to 60 milligrams/day). In addition, there were no significant differences in adverse events among the 3 differe

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Last Modified: June 26, 2009

DRUGDEX® Consults

RECOMMENDATION, EVIDENCE AND EFFICACY RATINGS

RESPONSE

The Thomson Efficacy, Strength of Evidence and Strength of Recommendation definitions are outlined below:

Table 1. Strength Of Recommendation		
Class I	Recommended	The given test or treatment has been proven to be useful, and should be performed or administered.
Class IIa	Recommended, In Most Cases	The given test, or treatment is generally considered to be useful, and is indicated in most cases.
Class IIb	Recommended, In Some Cases	The given test, or treatment may be useful, and is indicated in some, but not most, cases.
Class III	Not Recommended	The given test, or treatment is not useful, and should be avoided.
Class Indeterminant	Evidence Inconclusive	

Table 2. Strength Of Evidence	
Category A	Category A evidence is based on data derived from: Meta-analyses of randomized controlled trials with homogeneity with regard to the directions and degrees of results between individual studies. Multiple, well-done randomized clinical trials involving large numbers of patients.
Category B	Category B evidence is based on data derived from: Meta-analyses of randomized controlled trials with conflicting conclusions with regard to the directions and degrees of results between individual studies. Randomized controlled trials that involved small numbers of patients or had significant methodological flaws (e.g., bias, drop-out rate, flawed analysis, etc.). Nonrandomized studies (e.g., cohort studies, case-control studies, observational studies).
Category C	Category C evidence is based on data derived from: Expert opinion or consensus, case reports or case series.
No Evidence	

Table 3. Efficacy		
Class I	Effective	Evidence and/or expert opinion suggests that a given drug treatment for a specific indication is effective
Class IIa	Evidence Favors Efficacy	Evidence and/or expert opinion is conflicting as to whether a given drug treatment for a specific indication is effective, but the weight of evidence and/or expert opinion favors efficacy.
Class IIb	Evidence is Inconclusive	Evidence and/or expert opinion is conflicting as to whether a given drug treatment for a specific indication is effective, but the weight of evidence and/or expert opinion argues against efficacy.
Class III	Ineffective	Evidence and/or expert opinion suggests that a given drug treatment for a specific indication is ineffective.

Subject: RE: Updated DRUGDEX Monographs
From: "Torgerson, James E." <JETORGERSON@stoel.com>
Date: Sun, 14 Mar 2010 09:02:49 -0700
To: "Jim Gottstein" <jim.gottstein@psychrights.org>

Hi Jim:

I will pass your request on to my client and get back to you with its response as soon as I have it.

Regards,

Jim

From: Jim Gottstein [mailto:jim.gottstein@psychrights.org]
Sent: Saturday, March 13, 2010 12:24 PM
To: Torgerson, James E.
Cc: Jim Gottstein
Subject: Updated DRUGDEX Monographs

Hi Jim,

I am working on a motion for a preliminary injunction I expect to file shortly after everyone's responses to the complaint are in and in working through that it has become apparent the most recent DRUGDEX® monographs are extremely relevant. For example, the FDA approved Seroquel and Zyprexa for limited pediatric uses on December 4, 2009, which is not reflected in the DRUGDEX monographs I have. The injunction which I will be seeking would, of course, not prohibit causing or presenting claims to Medicaid for those newly approved indications. Additions to medically accepted indications as a result of new FDA approval is easy enough for me to pick up, but DRUGDEX also updates its monographs pertaining to indications that have not received FDA approval.

It seems likely the judge would order your client to provide them in the context of the motion for preliminary injunction and I can certainly subpoena them to a hearing (subject to your possible objection), but I would prefer not to have to go to the court. Therefore, I am writing to ask if your client would voluntarily provide me with copies of the most recent monographs, and updates as they occur, for the drugs included in the Medically Accepted Indications Chart, plus the following drugs which I intend to add to the chart:

- alprazolam (Xanax®)
- Clonazepam (Klonopin®)
- clorazepate (Tranxene®)
- diazepam (Valium®)
- flurazepam (Dalmane®)
- lorzepam (Ativan®)

- temazepam (Restoril®)
- zaleplon (Sonata®)
- Zolpidem (Ambien®)

Granting me access to DRUGDEX would certainly be acceptable to me and presumably easier for your client, but I know your client closely guards access to DRUGDEX. Perhaps your client can grant me access to just the drugs of interest. Again, these would be the drugs included in the Medically Accepted Indications Chart as well as those listed above.

Please let me know.
--

James B. (Jim) Gottstein, Esq.
President/CEO

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PsychRights®
Law Project for
Psychiatric Rights

The Law Project for Psychiatric Rights is a public interest law firm devoted to the defense of people facing the horrors of forced psychiatric drugging. We are further dedicated to exposing the truth about these drugs and the courts being misled into ordering people to be drugged and subjected to other brain and body damaging interventions against their will. Extensive information about this is available on our web site, http://psychrights.org/. Please donate generously. Our work is fueled with your IRS 501(c) tax deductible donations. Thank you for your ongoing help and support.

JAMES B. GOTTSTEIN, ABA # 7811100
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Attorney for Law Project for Psychiatric Rights

IN THE UNITED STATES DISTRICT COURT
DISTRICT OF ALASKA

UNITED STATES OF AMERICA *Ex rel.* Law Project for Psychiatric Rights, an Alaskan non-profit corporation, Plaintiff, vs. OSAMU H. MATSUTANI, MD, *et al*., Defendants.	)	Case No. 3:09-CV-00080-TMB

(Proposed) ORDER GRANTING PRELIMINARY INJUNCTION

Qui tam relator Law Project for Psychiatric Rights (PsychRights®) has moved for a preliminary injunction prohibiting defendants William Hogan and William Streur, their agents, servants, employees and attorneys, and any persons who are in active concert or participation with them, from presenting claims or causing claims to be presented to Medicaid for reimbursement or payment of the United States Government's federal

financial participation (FFP) share[1] of outpatient prescriptions for psychotropic drugs to anyone under 18 (children and youth) that are not for a medically accepted indication. After hearing from PsychRights, Defendants Hogan and Streur, and all other parties wishing to be heard, for the reasons that follow, PsychRights' motion for preliminary injunction is **GRANTED.**

I. REASONS FOR ISSUANCE

1. Background

This is a case under the federal False Claims Act, 31 U.S.C. §3729, et seq., to recover for false claims presented to and paid by Medicaid for outpatient psychiatric drugs prescribed to children and youth that were not for a "medically accepted indication," and for an injunction prohibiting the defendants from presenting or causing the presentment of such claims to Medicaid. The parties which the motion seeks to enjoin are Defendants William Hogan and William Streur, their agents, servants, employees and attorneys, and any persons who are in active concert or participation with them. Defendant Hogan is the Commissioner of the Alaska Department of Health and Social Services (DHSS), and William Streur is the Director of the Division of Health Care Services (HCS) within DHSS. Defendant Streur is in charge of the administration of the Medicaid program by the State of Alaska under the direction and supervision of Defendant Hogan.

Through 42 USC § 1396r-8(k)(3); 42 USC § 1396r-8(k)(6), and 42 USC § 1396r-8(g)(1)(B)(i), Congress restricted payment for outpatient drugs by the federal government under Medicaid to those that are for "medically accepted indications," defined as indications approved by the Food and Drug Administration (FDA), or the use of which is supported by one or more citations included or approved for inclusion in (i) American Hospital Formulary Service Drug Information, (ii) United States Pharmacopeia-Drug

[1] "FFP" stands for "Federal Financial Participation," which means "the Federal Government's share of a State's expenditures under the Medicaid program." 42 CFR §400.203.

Information (or its successor publications), or (iii) DRUGDEX Information System (Compendia).

The State of Alaska, under the direction of Defendants Hogan and Streur, continues to approve or present claims for payment or reimbursement by Medicaid of the United States Government's federal financial participation (FFP) share of outpatient prescriptions for psychotropic drugs to children and youth that are not for a medically accepted indication, and thus not covered under the federal portion of the Medicaid program. This preliminary injunction prohibits this continued violation of federal law.

II. STANDARDS FOR PRELIMINARY INJUNCTIONS

In Order to prevail on its motion for a preliminary injunction, PsychRights must establish, (1) it is likely to succeed on the merits, (2) irreparable harm in the absence of preliminary relief, (3) the balance of equities tips in favor of such injunction, and (4) the injunction is in the public interest. *California Pharmacists Ass'n v. Maxwell-Jolly*, 563 F.3d 847, 849 (9th Cir. 2009), citing to *Winter v. Natural Res. Def. Council, Inc.*, --- U.S. ----, 129 S.Ct. 365, 376, 172 L.Ed.2d 249 (2008).

III. DISCUSSION

2. Likelihood of Success on the Merits

PsychRights has demonstrated it is likely to succeed on the merits. Medicaid is only permitted by Congress to reimburse the states for expenditures on outpatient drugs for "medically accepted indications," defined as indications approved by the FDA or "supported" by a citation in one or more of the three Compendia. *US ex rel Rost v. Pfizer*, 253 F.R.D. 11, 13-14 (D.Mass 2008); and *U.S. ex rel. Franklin v. Parke-Davis*, 147 F.Supp. 2d 39, 44,45 (D.Mass 2001).

Under 42 USC §1396r-8 (g)(1)(A) the State of Alaska is required to have a drug use review program (DUR) "designed to educate physicians and pharmacists to identify and reduce the frequency of patterns of fraud." Under 42 CFR §456.703 & 705, the DUR

is required to include "prospective drug review" that confirms each prescription is properly reimbursable by Medicaid before such prescription is filled or delivered to a Medicaid recipient.

Injunctive relief to enjoin a state official from violating a federal statute is proper and not barred by the 11th Amendment to the United States Constitution. *Armstrong v. Wilson*, 124 F.3d 1019 (9th Cir. 1997); *Independent Living Center of Southern California, Inc., v Maxwell-Jolly*, 572 F.3d 644 (9th Cir. 2009). Where a district court has the power to issue a permanent injunction, it also has authority to issue preliminary injunctions. *F.T.C. v. H. N. Singer, Inc.*, 668 F.2d 1107, 1111 (9th Cir. 1982).

Defendants Hogan and Streur are violating 42 USC § 1396r-8(k)(3); 42 USC § 1396r-8(k)(6), and 42 USC § 1396r-8(g)(1)(B)(i) by presenting or causing the presentment of claims to Medicaid for psychotropic drug prescriptions to children and youth that are not for a medically accepted indication. Defendants Hogan and Streur are also violating 42 USC §1396r-8 (g)(1)(A), 42 CFR §456.703 & 705, which require the State of Alaska to perform a prospective review to confirm eligibility before each prescription is filled or delivered to a recipient.

The court concludes PsychRights is likely to succeed on the merits.

3. Irreparable Harm

To the extent the State of Alaska is immune from an award of money damages for its presenting false claims to Medicaid, or causing the presentment of such false claims, irreparable harm is established as a matter of law. *California Pharmacists, supra*., 563 at 852. However, under *Stoner v. Santa Clara County Office of Education*, 502 F.3d 1116, 1123 (9th Cir. 2007), the Ninth Circuit left open the possibility that the State of Alaska could be held liable under the False Claims Act. Because the Court finds that the continued violation of federal law constitutes irreparable harm, the Court does not decide at this time whether the State of Alaska is immune from an award of money damages under the False Claims Act through suing Defendants Hogan and Struer.

New Motor Vehicle Bd. v. Orrin W. Fox Co., 434 U.S. 1345, 1351, 98 S.Ct. 359, 363, 54 L.Ed.2d 439 (1977) (Rehnquist, J., in chambers); *Coalition for Economic Equity v. Wilson*, 122 F.3d 718, 719 (9th Cir. 1997); and *Independent Living Center of Southern California, Inc., v Maxwell-Jolly*, 572 F.3d 644 (9th Cir. 2009), hold that enjoining a state statute constitutes irreparable harm as a matter of law. The Court concludes that if enjoining a state statute constitutes irreparable harm as a matter of law, the continued violation of a federal law also constitutes irreparable harm as a matter of law. Therefore, PsychRights has established irreparable harm if the preliminary injunction is not granted.

4. The Balance of Equities and Public Interest

Under *California Pharmacists*, *supra*., 563 at 852-853, the balance of equities tips in favor of the plaintiff and a prospective preliminary injunction is in the public interest if, as here, the requested preliminary injunction is to enjoin continuing violation of federal law.

For these reasons, the Court finds the preliminary injunction should be granted.

IV. BOND

Under F.R.C.P. 65(c) the United States is not required to give security. Therefore, no security is being required because the United States is the real party in interest. *Stoner, supra*, 502 F.3d at 1126.

V. INJUNCTION

IT IS ORDERED that Defendants William Hogan and William Streur, their agents, servants, employees and attorneys, and any persons who are in active concert or participation with them (Enjoined Parties), are enjoined and prohibited from presenting claims or causing claims to be presented to Medicaid for reimbursement or payment of the United States Government's federal financial participation (FFP) share of outpatient prescriptions for psychotropic drugs to Medicaid recipients under 18 years of age that are not for a medically accepted indication.

IT IS FURTHER ORDERED, that subject to modification pursuant to the provisions set forth below, the Enjoined Parties, are prohibited from approving for

payment or reimbursement by Medicaid of the United States Government's federal financial participation (FFP) share of outpatient prescriptions for psychiatric drugs to anyone under 18 as follows:

1. The following drugs are prohibited entirely:

    a. Clozaril (clozapine)
    b. Cymbalta (duloxetine)
    c. Desyrel (trazadone)
    d. Effexor (venlafaxine)
    e. Geodon (ziprasidone)
    f. Invega (paliperidone)
    g. Paxil (paroxetine)
    h. Symbyax (fluoxetine hydrochloride/olanzapine)

2. All but the following indications are enjoined and prohibited for the following drugs:

Drug	Medically Accepted Indication	Notes
Abilify (Aripiprazole)		
	Bipolar I Disorder - Adjunctive therapy with lithium or valproate for Acute Manic or Mixed Episodes	10 yrs old and up
	Bipolar I Disorder, monotherapy, Manic or Mixed Episodes	10-17 years old for acute therapy
	Schizophrenia	13-17 years old
Adderall (amphetamine/dextroamphetamine)		
	Attention Deficit Hyperactivity Disorder (ADHD)	3 years old and up for immediate-release and 6 years old and up for extended-release
	Narcolepsy	6 years old and up for immediate release
Anafranil (clomipramine)		
	Obsessive-Compulsive Disorder	10 years and up
Concerta (methylphenidate)		
	Attention Deficit Hyperactivity Disorder (ADHD)	6 years old to 12 years old
	Attention Deficit Hyperactivity Disorder (ADHD)	6 years old and up for ConcertaR
Depakote (valproic acid)		
	Absence Seizure, Simple and Complex	10 years and older

Drug	Medically Accepted Indication	Notes
	and/or Complex Partial Epileptic Seizure	
Dexedrine (dextroamphetamine)		
	Attention Deficit Hyperactivity Disorder (ADHD)	3 years to 16 years old (immediate-release) and age 6 years to 16 years old (sustained-release))
	Narcolepsy	6 years old and up
Focalin (dexmethylphenidate)		
	Attention Deficit Hyperactivity Disorder (ADHD)	6 years and older
Haldol (haloperidol)		
	Hyperactive Behavior, (Short-term treatment) after failure to respond to non-antipsychotic medication and psychotherapy	3 years old and up
	Problematic Behavior in Children (Severe), With failure to respond to non-antipsychotic medication or psychotherapy	3 years old and up
	Psychotic Disorder	3 years old and up but ORAL formulations only
	Schizophrenia	3 years old and up but ORAL formulations only
Lamictal (lamotrigine)		
	Epilepsy, Refractory	
Lexapro (escitalopram)		
	Major Depressive Disorder	12 years old and up
Luvox (fluvoxamine)		
	Obsessive-Compulsive Disorder	8 years old and up and immediate release formula only
Mellaril (thioridazine)		
	Schizophrenia, Refractory	
Neurontin (gabapentin)		
	Partial Seizure; Adjunct	3-12 years old
Orap (pimozide)		
	Gilles de la Tourette's syndrome	12 years and older
Prozac (fluoxetine)		
	Major Depressive Disorder	8 years old and up

Drug	Medically Accepted Indication	Notes
	Obsessive-Compulsive Disorder	7 years old and up
Ritalin (methylphenidate)		
	Attention Deficit Hyperactivity Disorder (ADHD)	6 years to 12 years old (extended release)
	Attention Deficit Hyperactivity Disorder (ADHD)	6 years old and up (immediate release)
	Narcolepsy	6 years and up, and Ritalin(R) -SR only
Risperdal (risperidone)		
	Autistic Disorder – Irritability	5 years old and up
	Bipolar I Disorder	10 years old and up
	Schizophrenia	13 years old and up (Orally)
Seroquel (quetiapine)		
	Manic episodes associated with bipolar disorder	10 years old to 17 years old
	Schizophrenia	13 years old to 17 years old
Sinequan (doxepin)		
	Alcoholism - Anxiety – Depression	12 years old and up
	Anxiety – Depression	12 years old and up
	Anxiety - Depression - Psychoneurotic personality disorder	12 years old and up
Strattera (atomoxetine)		
	Attention Deficit Hyperactivity Disorder (ADHD)	6 years old and up
Tegretol (carbamazepine)		
	Epilepsy, Partial, Generalized, and Mixed types	
Tofranil (imipramine)		
	Nocturnal enuresis	6 years old and up
Trileptal (*oxcarbazepine*)		
	Partial Seizure, monotherapy	4 years old and up
	Partial seizure; Adjunct	2 years old and up
Vyvanse (lisdexamfetamine)		
	Attention Deficit Hyperactivity Disorder (ADHD)	6 years old to 12 years old
Zoloft (sertraline)		

Drug	Medically Accepted Indication	Notes
	Obsessive-Compulsive Disorder	6 years old and up
Zyprexa (olanzapine)		
	Schizophrenia	13 years old to 17 years old
	manic or mixed episodes associated with bipolar I disorder	13 years old to 17 years old

IT IS FURTHER ORDERED, that for psychotropic drugs not listed in paragraphs 1 or 2 above, the Enjoyed Parties are prohibited and enjoined from approving for payment or reimbursement by Medicaid of the United States Government's federal financial participation (FFP) share of outpatient prescriptions for psychiatric drugs to anyone under 18 unless (a) it is for an indication approved by the FDA, or (b) upon application to the court with notice to the other parties to determine whether such use is for a medically accepted indication.

IT IS SO ORDERED,

This ____ day of _____, 2010.

By: _____
TIMOTHY M. BURGESS
UNITED STATES DISTRICT JUDGE